

**Duchenne Muscular Dystrophy and  
Reproductive Decision-making:  
Implications of Newborn Screening**

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**A Thesis Submitted for the degree of Doctor of Philosophy**

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## Summary

Newborn screening programmes once focused on identifying treatable conditions. In recent years, increasing numbers of untreatable genetic conditions have been included in newborn screening programmes, on the premise that families will benefit from the provision of information, support and reproductive choice. However, there is a paucity of research documenting families' experiences of newborn screening and the implications of screening for untreatable conditions.

This study focuses on one untreatable condition, Duchenne muscular dystrophy (DMD). Using both quantitative and qualitative methods, this study explores the implications of two different diagnostic pathways for reproductive decision-making; newborn screening and a later clinical diagnosis (which occurs when the child is an average age of 4.5 years). Quantitative data on reproductive behaviour were collected from 72 families; 38 families who received a later clinical diagnosis (LCD) in the west of Scotland, and 34 families in Wales, who received a diagnosis through newborn screening (NBS), between 1990 and 2006. Qualitative data (in-depth interviews) were collected from a subset of 19 families to explore reproductive decision-making; 8 families from the LCD cohort, and 11 families from the NBS cohort.

The quantitative data highlighted varied effects of providing families with an earlier awareness of risk. Families in the newborn screening cohort were more likely to continue family building, and significantly more likely to use prenatal testing ( $p=0.05$ ). However, there was no association between carrier risk and reproductive behaviour and little difference in the number of second affected boys.

Participants in the qualitative interviews were often ambivalent about the provision of reproductive choice. Mothers' descriptions of the importance of "choice" were juxtaposed against accounts of "ignorant bliss", profound appreciation of the "carefree years", and relief at the avoidance of "difficult decisions". The medical information provided to families was often perceived to lack experiential validity. In addition, few families felt supported. The findings suggest a need for greater consideration of the true value of providing information, "choice" and support.

## Abbreviations

AMCG	American College of Medical Genetics
BMD	Becker muscular dystrophy
CDM	Classical Decision-Making
cDNA	Complementary deoxyribonucleic acid
CF	Cystic fibrosis
CHT	Congenital hypothyroidism
CK	Creatine kinase
ddNTP	Dideoxynucleotide
dHPLC	Denaturing high performance liquid chromatography
DMD	Duchenne muscular dystrophy
dNTP	Deoxynucleotide
ENMC	European Neuromuscular Committee
EUT	Expected Utility Theory
FISH	Fluorescent in situ hybridization
GRO	General Register Office
LCD	Later clinically diagnosed
MCADD	Medium chain acyl CoA dehydrogenase deficiency
MLPA	Multiplex ligation-dependent probe amplification
mRNA	Messenger ribonucleic acid
MS/MS	Tandem mass-spectrometry
NARC	National Association for Retarded Citizens
NBS	Newborn screening
NSC	National Screening Committee
ONS	Office for National Statistics
PFGE	Pulsed field gel electrophoresis
PGD	Pre-implantation genetic diagnosis
PKU	Phenylketonuria
PCR	Polymerase chain reaction
PTT	Protein truncation technique
QUAL	Qualitative
QUAN	Quantitative
RFLP	Restriction fragment length polymorphism
RNA	Ribonucleic acid
SCD	Sickle cell diseases
TOP	Termination of pregnancy
UK	United Kingdom
USA	United States of America
VOC	(The theory of the)Value of Children
WHO	World Health Organisation

## Introduction

This thesis explores the implications of newborn screening and a later clinical diagnosis for reproductive decision-making. One of the main arguments used to support the expansion of newborn screening for untreatable conditions is the provision of reproductive choice. The first three chapters of this thesis provide the background on three key aspects of this study. Chapter One explores the changing interpretations of “reproductive choice” through examining the social and political response to newborn screening, reproductive technologies and genetic counselling. Chapter Two provides a historical overview of the technologies that have enabled the diagnosis, and subsequent assessment of carrier risk, in families affected by Duchenne muscular dystrophy (DMD). Chapter Three explores the literature on reproductive behaviour and the implications of increasing sophistication of technologies, for reproductive behaviour in families affected by DMD.

Chapter Four provides the rationale for using both quantitative and qualitative methods, to examine the implications of two different diagnostic pathways for DMD. The findings of the quantitative data are explored in Chapter Five. Considerable differences in reproductive behaviour were found between the two cohorts, particularly in relation to family size, birth interval and the uptake of prenatal testing. Qualitative data analysis explores the differences between the two cohorts in greater depth in Chapters Six, Seven and Eight. Differences were apparent in families’ experiences of the diagnosis and the early few years of their child’s life, which had important implications for reproductive decision-making. In the final Chapter, the findings of both the quantitative and qualitative sections are discussed.

# Chapter One

## Defining Reproductive Choice: Changing the provision of newborn screening, prenatal testing and genetic counselling

### Introduction

Newborn screening programmes were traditionally implemented to detect treatable genetic conditions; early identification was followed by a treatment regime to improve the health of the newborn (Wilson & Jungner 1968). The development of sophisticated diagnostic technologies has enabled the detection of an increasing number of genetic conditions, many of which are untreatable. In recent years there has been a rapid expansion of newborn screening programmes for untreatable conditions, across much of Europe and the United States of America. However, there remains a considerable lack of concordance between local, national and international policies.

Social and political forces have determined the application of technologies and the purpose of newborn screening. During the 1970s and 1980s, proponents of newborn screening for untreatable conditions argued that early identification of affected individuals would reduce the burden of disease (Beckmann *et al.* 1978, den Dunnen *et al.* 1989, Gardner-Medwin *et al.* 1978, Greenberg *et al.* 1988). Contemporary proponents of newborn screening for untreatable conditions argue that programmes should be implemented to provide families with information, choice and support (Pollitt 1999, Therrell 2001, Fearing & Levy 2003).

The expansion of newborn screening highlights a number of pertinent questions that lie at the heart of this thesis. First, technological capacity has led to a reassessment of the meaning of “health” and the role of (genetic) health services. Acquisition of knowledge about ways to diagnose genetic conditions is far outpacing the capacity to provide therapeutic treatment (Wood-Harper & Harris 2000). However, diagnostic technologies have provided the potential to offer families broader, but possibly more moderate “lifestyle” benefits (Bailey *et al.* 2005). Should (genetic)

health services focus on providing medical benefit to the individual, or should they reflect a broader definition of “health”, which encompasses information, choice and support?

Second, one of the most prominent justifications for the rapid expansion of newborn screening programmes, for untreatable conditions, has been the provision of reproductive choice. Families are offered genetic counselling and the option of an increasing range of reproductive technologies in subsequent pregnancies, but what does “reproductive choice” choice mean? Does the provision of “reproductive choice” reflect a societal desire to increase individual autonomy, or to reduce the burden of disease? Can genetic counsellors provide sufficient information to enable families to make autonomous, informed reproductive decisions?

To explore the foundations of these questions and the trajectory of the socio-political response to newborn screening, from a focus on “births avoided” to “reproductive choice”, this chapter is divided into three sections. First, medical and social models of health are described. The subsequent sections address the extent to which incorporation of the differing models of health into healthcare has influenced the changing provision of newborn screening and reproductive choice. The second section addresses the early years of newborn screening for treatable conditions, prenatal testing and genetic counselling. The third section addresses the contemporary approach to newborn screening, reproductive technologies and genetic counselling<sup>1</sup>.

## **1. Defining health**

Preoccupation with our own health and the health of others is a central facet of humankind. Throughout history significant changes have occurred in the way we define “health” and the degree of autonomy individuals exert over their own health. The etymology of the word “health” has routes in “wholeness” and is reflected,

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<sup>1</sup> It should be noted that the “early” and “contemporary” approaches of newborn screening, prenatal testing and genetic counselling are presented as discrete “moments”; aimed at portraying mainstream views found in the literature, rather than the vast variety of views that actually existed during each “moment”.

albeit disparately, in two core theories of health in contemporary Western societies: the biomedical model and the social model.

The biomedical model emerged during the eighteenth and nineteenth centuries as a result of the rise of scientific enquiry, aimed at identifying aetiological agents that cause disease (Bowling 2002). The model is based on the premise of scientific rationality, which focuses on the structure and functions of the body and the eradication of illness through diagnosis and effective treatment. The focus on biological and chemical structures reflects the Cartesian philosophy of the human body as a mechanistic structure, whose malfunctioning parts can be repaired or replaced. Essentially the biomedical model defines health as the absence of disease (Jones 1994, Bowling 2002); to heal is to make whole (Townsend & Davidson 1982).

One of the criticisms of the medical model is that the structure of health care becomes oriented towards individual presentation of signs and symptoms of a condition, rather than tackling the broader determinants of health (Gabe *et al.* 2007). The social model provides a broader definition of health, which emphasises social and environmental determinants of health, as well as the biological and medical factors. However, although the interpretation of health in the social model has broader foundations, it also highlights the expertise of the individual in assessing the range of factors that contribute towards quality of life. The absence of disease is just one factor amongst many.

The encompassment of wider social factors and the role of an autonomous decision maker in interpretations of health are not new. In ancient Greece, followers of the goddess Hygeia symbolised health as “rational individual behaviour, socially organised to focus not only on freedom from pain and discomfort, but on the engagement of individuals with their own well-being in relation to their environment and their community” (Townsend & Davidson 1982). In contemporary societies the social model is perhaps best encapsulated by the World Health Organisation’s (1946) definition of health as a “state of complete physical, mental and social well-being and not merely the absence of disease and mortality”.



The relevance of different interpretations of “health” should not be underestimated; social and cultural definitions are reflected in political frameworks of health service delivery. In industrialised nations, the medical model remains the prevailing paradigm in modern health care systems (Bury 2005). Health policies and services are broadly divided into two categories, those which attempt to preserve the health of society through ‘public health’ measures, defined as the “science and art of preventing disease, prolonging life and promoting health through the organised efforts of society” (Acheson 1998), and those which serve to identify the aetiology of disease in individuals and to provide treatment or palliative care. Although the public health approach focuses on broader determinants of health, the measurement of health still relies on medical explanations of health and illness (Bury 2005).

Although the social and medical models of health can be presented as discrete and opposing approaches to health and health care, it should be noted that areas of overlap have always existed. Some health practitioners have always recognised wider social influences on health, and many proponents of the social model of health recognise the medical advances achieved through a narrow focus on the body (Bury 2005). In recent decades, however, there have been increasing areas of overlap between the two models. Alongside the WHO’s bold recognition of broader determinants of health, significant changes have occurred in relation to the role and responsibility of the individual in health related decision making.

The development of newborn screening and prenatal testing, together with the changing provision of genetic counselling, provide an interesting arena, to explore the changing influence of medical and social models of health on health care. The following sections explore the foundations of newborn screening, prenatal testing and genetic counselling and address the extent to which social models of health care have changed the provision of reproductive choice.

## **2. Early years of newborn screening, prenatal testing and genetic counselling: preventing disease**

Despite the differing foundations of newborn screening, prenatal testing and genetic counselling, the development of the three processes reflects changing approaches to the delivery of health care. The following sections focus on the development and initial socio-political response to newborn screening for treatable conditions, prenatal testing, genetic counselling and newborn screening for one untreatable condition, Duchenne muscular dystrophy.

### **2.1 Newborn screening and public health; improving the health of mankind**

Newborn screening has traditionally been rooted in the discipline of public health (Khoury 1996, Holtzman 1997, Carlson 2004, Ross 2006). Public health has been concerned with threats to population health; focusing on prevention, rather than cure. During the nineteenth and twentieth centuries, the public health discipline focused on controlling the threat of communicable diseases. Responses to infectious disease epidemics employed extensive population measures, with a focus on protecting the unaffected either through immunisation or the process of diagnosis, isolation, localisation and treatment. For example, polio epidemics in the USA and Canada during the first half of the twentieth century were dealt with through mass immunisation programmes. Over two million children across the United States, and parts of Canada and Finland were involved in the trial of the Salk polio vaccine (Meldrum 1998). Once the vaccine was licensed in 1954, several hundred million children in industrialised nations were immunised (Shiffman *et al.* 2002). The success of such programmes paved the way for the implementation of population screening programmes, to enable the prevention of a wider range of conditions.

Newborn screening began in the early 1960s, after Guthrie and Susi developed a method of detecting phenylketonuria (PKU) from a blood spot dried on filter paper (Guthrie & Susi 1963). PKU is an inborn error of metabolism resulting in deficiency of the enzyme phenylalanine hydroxylase, which causes progressive developmental delay and severe learning difficulties if not recognised soon after birth. Early implementation of low-phenylalanine dietary interventions had already been shown

to ameliorate the morbidity and mortality associated with PKU (Bickel *et al.* 1954). The development of a simple method of screening, applicable to whole populations, heralded the potential to “improve the prevention of severe handicaps” (Dhondt 2007:418).

The technological potential was not immediately met with widespread support, because of the relative rarity of PKU (Therrell 2001). However, after significant pressure from interest groups in the USA, such as the National Association for Retarded Citizens (NARC), the public health benefits of testing gained political support. Mandated national newborn screening programmes for PKU were established across many industrialised nations during the late 1960s (Therrell 2001, McCabe *et al.* 2002, Kemper & Wake 2007).

In 1967, the World Health Organisation (WHO) Scientific Group on Screening convened in Geneva to discuss “whether and how newborn screening programmes could improve the health of mankind” (WHO 1968). One of the most influential reports considered by the Scientific Group was Wilson and Jungner’s (1968) “Principles of Early Disease Detection”, which defined the fundamental purpose of screening as providing “treatment for those with previously undetected disease” while “avoiding harm to those persons not in need of treatment.” The success of NBS programmes in ameliorating the medical effects of PKU, combined with Wilson and Jungner’s focus on avoiding morbidity and mortality in treatable conditions, served to consolidate the emerging field of newborn screening firmly in the realms of a disease-focused interpretation of ‘public health’; for the common good.

During the 1970s and 1980s, new technologies enabled detection of an increasing number of conditions. Newborn screening for congenital hypothyroidism (CHT) was initiated using the “Guthrie test” in the mid-1970s after Raiti & Newns (1971) and Klein *et al.* (1972) demonstrated that early treatment avoided intellectual impairment. In the 1970s automated punching machines were developed, capable of punching and distributing four samples from a single blood spot (McCabe *et al.* 2002).

By the mid-1980s it was possible to extract DNA from newborn blood samples and by the end of the decade screening for haemoglobinopathies, such as sickle cell disease and thalassaemia, had been adopted in many regions. Technology provided the potential, Guthrie set the precedent for gaining political support and Wilson & Jungner consolidated newborn screening as a valid public health measure. The expansion of newborn screening programmes for treatable conditions became inevitable.

The capacity to detect increasing numbers of conditions far outreached the capacity to treat those conditions. The foundations of newborn screening lay firmly in the realms of public health, which traditionally aimed to prevent the effect of a condition being realised in an individual. However, the genetic nature of the conditions identified created the possibility of pursuing the preventative focus of the public health discipline, by preventing the birth of individuals affected by genetic conditions. The development of newborn screening had been mirrored by significant changes in both reproductive technologies and statutory laws governing the rights of the unborn child. First cases of a genetic condition could be identified through newborn screening; secondary cases could be avoided by offering families prenatal testing and termination in subsequent pregnancies.

## **2.2 Prenatal testing and termination; creating the inextricable link**

Prior to the discovery of sex-linked chromosomes, Barr and Bertram (1949) reported the discovery of a technique capable of distinguishing between male and female cells. Identification of the Barr body was subsequently used to establish the sex of human fetuses from cells extracted from amniotic fluid (Serr *et al.* 1955, Fuchs & Riis 1956, Makowski *et al.* 1956, Shettles 1956). Amniocentesis involves obtaining a sample of amniotic fluid from the pregnancy sac using a needle inserted through the woman's abdomen. Due to the risk of miscarriage, fetal talipes and an increased failure rate in cell culture (Royal College of Obstetricians and Gynaecologists 2005) amniocentesis is rarely performed before 15-18 weeks gestation. Living cells are removed from the fluid and cultured for 1-2 weeks before diagnostic procedures can be performed.

Amniocentesis provided the potential to inform pregnant mothers of the sex of their child, which was deemed a significant advance for families with a history of sex-linked genetic conditions. However, although the procedure gained widespread acceptance during the 1950s (Ullman *et al.* 1985), amniocentesis and foetal sexing were not immediately integrated into the health service.

Until the late 1960s, in the United Kingdom, terminations of pregnancies were only permitted for the sole purpose of preserving the life of the mother (Infant Life Preservation Act 1929). The Abortion Act (1967) legalised the termination of foetuses up to birth if two doctors agree that “there is a substantial risk that if the child were born it would suffer from such physical or mental abnormalities as to be seriously handicapped” or up to 24 weeks if two doctors agree that “the continuance of the pregnancy would involve risk greater than if the pregnancy were terminated, of injury to the physical and mental health of the pregnant woman or existing children of her family”<sup>2</sup>. The integration of amniocentesis and foetal sexing into antenatal care only occurred after the legalisation of abortion; suggesting that the provision of information alone, regarding the health status of the foetus, was not considered to constitute a sufficiently significant benefit to families.

Initially few physicians were able to safely conduct the procedure and few laboratories were equipped to culture amniotic samples. Amniocentesis was therefore only offered to families with a known family history of congenital abnormalities, for whom “management decisions would be changed by the data obtained” (Evans *et al.* 1993). High-risk families were required to demonstrate a prior commitment to terminating affected foetuses as a precondition of being offered testing (Statham 2002). In practice, limited resources and expertise created an inextricable link between prenatal testing and termination (Evans *et al.* 1993).

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<sup>2</sup> The Abortion Act 1967 (as amended by the Human Fertilisation and Embryology Act 1990) also reaffirmed and expanded on earlier legislation (the Infant Life Preservation Act 1929) (BMA Medical Ethics Committee 2007). The legislation highlights significant ethical dilemmas. First, pregnancy will always involve a greater risk to the physical health of the pregnant woman than if she was not pregnant and second, it highlights significant tensions between the rights of the mother and rights of the unborn child.

### **2.3 Genetic counselling; assisting decisions to minimise burden of disease**

The increasing availability of amniocentesis meant genetic counsellors became increasingly involved with offering at-risk families the option of prenatal testing. Kessler (1980) highlighted the growing importance of decision-making in genetic counselling to ensure that individuals are informed about their genetic risks and the options available through genetic technologies, in order to make informed reproductive decisions. To ensure that the procedure of providing prenatal testing and genetic information was standardised, a normative, analytic and rational model of genetic counselling was derived from classical decision-making theory (Shiloh 2000, Anderson 2007).

Classical decision-making (CDM) theory evolved from the field of economics in an attempt to understand our ability to process alternative options and choose an alternative course of action (Sanfey 2007). Although a number of theories fall under the rubric of CDM theory (see Lipshitz *et al.* 2001), Expected Utility Theory (EUT) has been the most commonly used theory in relation to genetic decision-making (Shiloh 2000). In EUT, an 'optimal decision' maximises 'expected utility', which is computed as the product of the probability and value of each potential outcome (Shiloh 2000, Sanfey *et al.* 2006). Various alterations have been made to the model, to include subjective assessment of probabilities (Savage 1954), and to replace "expected utility" with "expected burden" (Cote 1983). However, the underlying premise remains; people weigh up their objective risk against the value of the outcome.

The early approach of many genetic counsellors reflected a paternalistic approach to decision-making, derived from the medical model (Emery 2001). Foucault (1973) argues modern medicine is based on the notion that medical science, and those trained in the profession, merely sees what was already there. From this perspective, the medical model of health care entails a paternalistic drive within which only a privileged few are able to 'see' or grasp the mechanics of health. The individual may not have access to relevant factual information, and may not always reason in ways conducive to rational choice (Harsanyi 1982), in essence: doctor knows best.

In an attempt to distance the discipline from any association with the eugenics movement, genetic counsellors espoused a non-directive approach to counselling (Clarke 1997, Statham 2002). After individuals and couples at-risk of genetic disorders had been provided information on recurrence risks, they were expected to assign weight and meaning to each potential option to reach an optimal decision. An 'optimal decision' maximised expected utility (Antley 1979, Pauker & Pauker 1987 in Shiloh 2000), or minimised expected burden (Cote 1983).

Genetic counsellors routinely communicated the complexities of genetic risk to families, in an attempt to facilitate their decision-making. However, at the time, risk was defined as the "probability of occurrence of a negative genetic outcome" (Shiloh 2000:91) and disability was predominantly defined as a "constant menace" to be desperately avoided (Fraser 1974:642). In addition, increasing technical capacity and acceptability of prenatal testing and termination rested on a drive to prevent the "negative genetic outcome". Termination was perceived as a solution to the problem of an 'abnormal' foetus (Statham 2002) and the elimination of disease was largely disassociated from the elimination of fetuses with the disease (Cunningham-Burley & Kerr 1999).

The possibility of avoiding the birth of children affected by genetic conditions, relied on the assumption that families, after genetic counselling, would choose either to cease family building or to utilise increasingly available reproductive technologies to diagnose and terminate affected fetuses. The primary focus of genetic counselling was therefore to equip people with appropriate information on genetic risk, "believing that if they understood scientific explanation, they would use it to make rational or logical reproductive choices (i.e. ones that made sense to the provider)" (Biesecker 2001:323). During the 1970s and 1980s, 'minimising expected burden' through the prevention of birth defects and genetic disorders was often cited as the primary aim of genetic counselling (Wendt 1979, Moser 1983, Kelly 1986).

## 2.4 Prenatal testing; reducing the psychological burden of termination

For some families, the capacity to prevent the birth of an affected foetus was a valued resource. High-risk couples, who had previously avoided family building, were more likely to attempt to have the healthy child they wanted, after the introduction of prenatal testing and termination (Laurence & Morris 1981). However, although the process of amniocentesis and foetal sexing was considered a significant improvement on the reproductive options previously available to women at increased risk of genetic conditions (to either cease reproducing or to continue a pregnancy unaware of the sex or disease status of the foetus), major shortcomings remained.

In 1975, Blumberg *et al.* (1975) reported that families undergoing termination of the pregnancy after amniocentesis experienced significant depression and guilt-ridden stress periods after the event. Mothers facing a second-trimester termination had already felt foetal movements and the pregnancy was usually visually obvious to friends and family. Even if families considered a baby with a foetal abnormality to be a 'problem', "the decision to terminate was difficult, the experience harrowing and the psychological impact significant" (Statham 2002:215). One proposed solution to the psychological impact of second trimester termination was to conduct prenatal testing and subsequent termination in the first trimester. This approach was deemed to be more acceptable to women (Hodgson and Bobrow 1989, Norman *et al.* 1989, Emery & Muntoni 2003).

The first technique for early foetal diagnosis was proposed by Mohr (1968) and subsequent publications reported developments and refinements of the original technique (Department of Obstetrics and Gynaecology, Tietung Hospital of Ansham Iron and Steel Company 1975, Kazy *et al.* 1982). In 1982, Ward and Modell (1982) introduced chorionic villus sampling (CVS), performed at 10-12 weeks gestation, into clinical practice. By 1983, Simoni *et al.* (1983) had developed a direct cytogenetic technique for analysis of CVS samples allowing karyotyping within a few hours of sampling (Holzgreve *et al.* 1984). The technique for chorionic villus sampling involves the insertion of a flexible cannula /catheter, either through the cervix or transabdominally, into the uterine cavity, to extract chorionic villi which



are of foetal origin. Sufficient foetal material can be obtained through CVS at ten weeks gestation.

The development of CVS mirrored increasingly sophisticated genetic testing techniques, enabling DNA studies and diagnosis of a wider range of genetic conditions in the first trimester. For some, the capacity to offer reproductive choice, to an increasing numbers of families, added impetus to implement newborn screening for untreatable conditions. The focus on prevention was mirrored in the development of newborn screening for one untreatable condition, Duchenne muscular dystrophy.

### **2.5 Newborn screening for Duchenne muscular dystrophy; reducing incidence**

The development of a cheap and reliable assay for creatine kinase (CK) testing for Duchenne muscular dystrophy (DMD) resulted in the introduction of pilot newborn screening programmes for DMD in 1975 in Lyon, France (Plauchu *et al.* 1989); Antwerp, Belgium; Iowa, USA (Zellweger & Antonik 1975); and the Federal Republic of Germany (Beckmann *et al.* 1978). The following year a pilot programme was set up in Edinburgh, Scotland (Skinner *et al.* 1982) and in 1978 in Auckland, New Zealand (Drummond & Veale 1978). The main arguments for newborn screening for DMD focused on preventing the birth of second affected males (Rosenberg *et al.* 1993, Jacobs *et al.* 1989, Emery & Muntoni 2003).

Early literature on newborn screening for DMD defined reproductive “choice” in terms of enabling families to avoid the birth of second affected boys before the diagnosis of the first. Due to the delay in clinical diagnosis of DMD, many families were known to have more than one affected boy prior to the diagnosis of the first. The proportion of boys who had an affected brother was variously reported to be around 13%-18% (Zellweger & Antonik, 1975, Scheuerbrandt & Beckmann 1977, Gardwin-Medwin *et al.* 1978), between 15% and 30% (Zellweger *et al.* 1982, Worton 1990) and 30%-40% (Greenberg *et al.* 1988).

Numerous authors suggested that mass neonatal screening with subsequent detection of carriers and provision of genetic counselling would reduce the

incidence of DMD (Beckmann *et al.* 1978, den Dunnen *et al.* 1989, Gardner-Medwin *et al.* 1978, Greenberg *et al.* 1988, Emery & Muntoni 2003). For some, the potential to avoid second affected boys was the main aim and purpose of screening. Beckmann *et al.* (1980:156) argued that “reduction of the number of DMD cases to one-third or less even in the absence of an effective medication is the main goal and promise of neonatal screening”. Rosenberg (1993:541) stated that “the primary objective of DMD screening is to avoid repeat cases in families and not early diagnosis *per se.*”

Interestingly, the widespread implementation of newborn screening for DMD was not hindered by ethical concerns regarding the focus on avoiding second affected boys. Initially concerns focused on practical and financial issues. Gilboa & Swanson (1976) and Wharton (1976) argued that the CK test would not be sensitive enough to be used in a neonatal screening programme. Roses *et al.* (1977) argued that screening for DMD would “create huge costs in manpower and money”. Gardner-Medwin *et al.* (1978) argued that parents would oppose the test. Later on, Gardner-Medwin (1979), Al-Jader *et al.* (1990) and Andrews *et al.* (1994) raised concerns about the effect of an earlier diagnosis on the mother-baby relationship and some questioned the wisdom of screening for an untreatable disease (Dubowitz 1976).

A number of studies were conducted to assess whether screening could be performed at an alternative time. Gardner-Medwin *et al.* (1978) proposed an alternative approach of using the CK test to screen boys at 18 months who are not walking and/or who demonstrate delayed gross motor skills. Gardner-Medwin and colleagues argued that this procedure would require fewer tests, would be less likely to cause parents anxiety as their concern would already be aroused, and would identify the vast majority of cases. However, Rosenberg (1993), argued that many cases could be missed by screening at 18 months, that repeat pregnancies may already have occurred and that a significant number of DMD children start walking earlier than this age. Screening at 18 months was eventually trialled in Wales (Smith *et al.* 1989) and “though it did detect half of affected cases, logistical difficulties in community health care made the rate of detection unacceptably low”.

Advances in molecular genetics throughout the 1980s enabled more accurate diagnosis of carriers and detection of affected fetuses. Subsequently, pilot newborn screening programmes for DMD were established in 1986 in Manitoba, Canada (Jacobs *et al.* 1989) and Western Pennsylvania, USA (van Ommen & Scheuerbrandt 1993) and in 1990 in Wales (Bradley *et al.* 1993).

Many of the earlier concerns regarding newborn screening were challenged by subsequent research. Reports from the screening programme in France (Dellamonica *et al.* 1983) and Germany (Scheuerbrandt *et al.* 1986) proved the sensitivity of CK testing to be high. Rosenberg *et al.* (1993:541) evaluated cost effectiveness of newborn screening in Canada and concluded that “earlier predictions of inordinate costs of screening from DMD are refuted”. Parsons *et al.* (2002) study showed that there was no evidence of any long term disruption to the mother-baby relationship.

In addition, Firth *et al.* (1983) argued that the majority of families were in favour of an early diagnosis. Firth *et al.* (1983) interviewed 53 parents in three regions of England, who had received a later clinical diagnosis of DMD. The average age of the boy at diagnosis was 5.9 years and some parents discussed “with some bitterness the long delays they had experienced in obtaining a diagnosis” (Firth *et al.* 1983:467). Parents were asked whether they thought screening for DMD would be best a) close to birth, b) at 18 months or c) at some other time. There were eight families who were undecided, 40 who preferred newborn screening and four with a preference for ‘some other time’. Firth *et al.* (1983:468) conclude that the “majority of parents (75%) were in favour of neonatal screening”, to avoid the diagnostic delay, to prevent the birth of further affected boys and to enable practical and emotional preparation. Parents also felt that they had a “right to be informed” (Firth *et al.* 1983:486).

However, the study by Firth *et al.* (1983) also highlighted some contradictions between parents’ response to the questions about screening and their experience of a later clinical diagnosis. Parents were asked about whether they felt the later clinical diagnosis had been made at the best possible time, and only 37.7% (n=20) felt that it had not. The same proportion (37.7%, n=20) felt that the diagnosis had been made

at the best possible time, and a further 24.6% (n=13) of families were undecided. The findings of Firth *et al.*'s (1983) study suggest that there may be a difference between actual experience of the diagnosis and a hypothetical view on the best possible time to receive a diagnosis.

Studies conducted by Crisp *et al.* (1982), Firth *et al.* (1983), Firth & Wilkinson (1983) and Smith *et al.* (1990) and Parsons *et al.* (2002) also concluded that the majority of affected families would favour early diagnosis. However, all of the studies, bar one (Parsons *et al.* 2002) relied on parents' hypothetical preferences, rather than their actual experience.

### **3. Current approach to newborn screening, prenatal testing and genetic counselling: providing “reproductive choice”**

Earlier concerns regarding the ethics of prenatal testing and the role of genetic counselling have become significantly more prevalent. In particular, the disability rights movement and feminists have mounted an ever more vocal critique of the expanding use of prenatal testing. The following sections explore the arguments presented by the disability rights critique, the development and promise of prenatal genetic diagnosis, the changing approach to genetic counselling and current debates surrounding the expansion of newborn screening programmes. Lastly, the current provision of newborn screening for the untreatable condition, Duchenne muscular dystrophy, is addressed.

#### **3.1 Disability rights critique: level the field, not the players**

The way in which disability is perceived is important for the way society responds to disability. In particular, the concept of disability affects the provision of health services aimed at managing disability. Views of disability have typically been dominated by the medical model conception of disease (Scott 2005, Bury 2005). In the medical model, disability is defined as an attribute of the individual; an impairment that alters the structure or function of the human body, resulting in an inability to perform tasks that a non-impaired person carries out (Bury 2005).

In recent years there has been increasing recognition of the conceptual difficulty of defining disability. Unlike disease, 'disability' is "less categorical and more 'relational' in character" (Bury 1996:21). Oliver (1990) argues that disability should be perceived as a product of the physical and social environment, rather than an attribute of the individual. The focus on the environment, rather than the individual, reflects a social model interpretation of disability and calls for attention to be paid to "what is wrong with society, rather than what is wrong with the individual" (Bury 2005:73).

Debates on the social and medical models of disability have become increasingly sophisticated. Despite important differences, some degree of common ground has been found between the opposing perceptions of disability. Proponents of the medical model largely accept that there are "social dimensions" to disability (Harris 2000:95). Many proponents of the social model accept that "not all problems of disability are socially created [...] disability itself limits some options" (Asch 1990:73). Arguably, some combination of the medical and social models of disability "is best placed to capture the reality of impairment and disability" (Scott 2005:77).

Despite the increasing areas of overlap in the definition of disability, the disability rights movement continues to raise considerable concerns about the routine practice of prenatal testing and termination for foetal abnormality. One of the most fervent arguments presented by the disability rights movement is the "expressivist objection"; that "prenatal testing and selective abortion communicate that disability is so terrible, it warrants not being alive" (Asch 1999:387). The use of prenatal testing has profound implications for the way people with impairments are viewed, and also for how they view themselves (Clarke 1991).

Proponents of the disability rights critique also argue that the focus on the elimination of disability may lead to a loss of support for existing people with disabilities. The technological imperative of prenatal diagnosis may use up resources that could otherwise be used to support families with a disabled child (Parens and Asch 2003). In addition, the birth of fewer people with a certain condition may lead to a loss of support. Research may focus on treatment for more

prevalent conditions and the political visibility of people with impairments may be reduced (Scott 2005).

The interpretation of “reproductive choice” has moved away from an explicit focus on “births avoided”, but the notion of “choice” remains the source of considerable debate. Clarke (1990:1146) argues that social and political pressures exert influence on couples’ decisions to test and terminate pregnancies:

“If there is no confidence in the willingness of society to care for their child once they are unable to do so, parents may choose to terminate a pregnancy against their own wishes and beliefs.”

In addition, a number of feminists have argued that the medical focus of clinicians coerces women into accepting prenatal testing and termination (Lippman 1991, Rothman 1994).

### **3.2 Genetic counselling: is non-directiveness possible?**

The increasingly unacceptable nature of linking prenatal testing with termination and the changing views on disability, initiated a more widespread desire to provide a less directive approach to prenatal testing and genetic counselling. Nondirective counselling increasingly focused on psychological well-being and educational elements of decision-making. Nondirectiveness was presented as a “guiding principle for genetic counselling that promotes the autonomy of the self-determination and personal control of the client” (Biesecker 2001).

Emery (2001) argues that genetic counsellors now endeavour to view counsees as consumers, who are supplied with sufficient information to reach a decision alone. Emery (2001:81) suggests that the doctor/patient relationship is “slowly evolving from a paternalistic one towards a partnership, where health professionals share their biomedical viewpoint with patients’ personal values and experiences in order to meet a mutual decision”. Although the degree to which “shared decision-making” is feasible remains controversial, the recognition of differing perspectives highlights a significant shift in the approach of the medical profession. Aspects of the social model of health, which highlights the expertise of the individual in assessing the

range of factors that contribute towards quality of life, are increasingly being integrated with the medical model approach.

However, the degree to which nondirectiveness is achievable, or even desirable, has remained the source of considerable debate (Clarke 1991, Clarke 1997, Michie *et al.* 1997a, Statham 2002). The provision of 'sufficient' information to enable autonomous decision-making requires assessment of the amount of information and the content of such information. Lippman and Wilfond (1992:936) argue that it is impossible to tell more than one story at one time; "communication about genetic disorders will always require choice; no single story, however balanced, can be neutral, or value free". In addition, a number of studies have shown that patients attending genetic counselling expect to be offered advice (Michie *et al.* 1997a) and consultations often included attempts by the counsellor to influence patients' decisions (Michie *et al.* 1997b). In relation to reproductive decision-making, the offer of prenatal testing may, in itself, be perceived to be promoting acceptance; an implicit directiveness (Clarke 1997).

The influence of genetic counselling on reproductive decision-making has been the subject of much debate. Numerous studies have explored the cognitive processes through which genetic counselees subjectively appraise their risk (Shiloh & Sagi 1989, Rothman 1993, Shiloh *et al.* 2002, Marteau & Weinman 2006). The framing of risk information has an important influence on perceptions of risk (Edwards *et al.* 2001). However, counselees' perception of risk *prior* to counselling remains more closely associated with reproductive behaviour (Shiloh & Saxe 1989).

There is no empirical evidence from any studies to suggest that genetic counselling influences reproductive decision-making. After reviewing the literature on genetic counselling and reproductive decision-making, Kessler (1989:352) concluded that "the role of counselling largely is to confirm or reinforce a decision already taken, rather than to shape a reproductive decision from the outset". Sorenson *et al.* (1987) found that counselling appeared to increase the likelihood of at-risk couples having more children, particularly in low risk couples. Beeson & Golbus (1985) argue families' reproductive decisions focus on social meanings and consequences of having an affected child, rather than on the quantitative analysis of risk.

### **3.3 Pre-implantation genetic diagnosis; avoiding the psychological impact of termination**

Amniocentesis and CVS carry a risk of miscarriage (1% and 2% respectively) (Royal College of Obstetricians and Gynaecologists 2005). In both procedures, the only course of action, to ensure that an unaffected child is not born, is to undergo elective termination of all affected fetuses. Numerous studies have shown the significant psychological burden accrued from termination, regardless of whether it is conducted in the first or second trimester (Rothman 1994, Rapp 1999). White-Van Mourik *et al.* (1992) found that, two years after a termination, 27% of women felt angry, 60% sad and 33% guilty. Many feminists have argued that the paradoxical lack of choice presented by termination makes a mockery of choosing (Rothman 1994, Chandler & Smith 1998).

The first real possibilities of avoiding terminations through pre-implantation genetic diagnosis (PGD) of human X-linked genetic conditions were demonstrated in 1989 (Handyside *et al.* 1989). The procedure works by removing ova by laparoscopy from a carrier female, fertilizing them with her husband's sperm, and allowing them to develop in vitro. Initially embryos obtained in vitro were tested to ascertain the existence of the Y-chromosome; only female embryos would be transferred. Increasingly sophisticated molecular and cytogenetic techniques have enabled the analysis of disease status; only female or unaffected male conceptuses are reimplanted in the uterus to undergo further development (Raeburn 1995, Vergeer *et al.* 1998, Emery & Muntoni 2003).

Laboratories have now been set up in many countries to perform PGD (Klipstein 2005). Arguably if the technique was easy and inexpensive it would supplant prenatal diagnosis for DMD (Raeburn 1995). However, although PGD has been performed regularly since the late 1990s, it is still fraught with difficulties. PGD is technically very demanding and consequently prohibitively expensive. In the UK, few families meet the criteria for funding set by local health administrations of the NHS; of those that do only around 20% of families give birth to an unaffected child as a result of PGD (Soini *et al.* 2006). In addition, the process of PGD can be a stressful experience for couples. Although couples often perceive PGD to be



morally less problematic than termination (Katz *et al.* 2002), Lavery *et al.* (2002) found that 41% of patients undergoing PGD described the experience as stressful and anxiety-ridden.

### **3.4 Newborn screening: technological promise and the arrival of a varied political response**

Although the development of tests, during the 1970s and 1980s, reflected the political focus on treatable conditions, the introduction of tandem mass-spectrometry (MS/MS) in the late 1990s introduced new considerations and ethical dilemmas. MS/MS technology enabled the detection of “over fifty disorders simultaneously from a 3mm dried blood spot, in around two minutes per sample” (Wilcken 2008: 173), facilitating cheap and reliable screening for a range of rare inborn errors of metabolism. There is evidence that screening for one of these conditions, medium chain acyl CoA dehydrogenase deficiency (MCADD) may be beneficial for an affected individual, but for the majority of detectable conditions there is limited clinical evidence on the natural history of the condition, the effectiveness of treatments and the sensitivity and specificity of MS/MS to justify implementation of nationally mandated screening programmes (Stuart 2006).

Technological development has transformed screening potential from one condition to over fifty and it is now estimated that around a quarter of the world’s newborns are screened for at least one condition (Wilcken 2007). Newborn screening policies throughout industrialised nations are nominally founded on Wilson & Jungner’s ten principles (Therrell 2001, Pollitt 2006, Wilcken 2007) and consistently affirm the “necessity of treatment potential and proven benefit to the infant” (Bailey *et al.* 2005:1889). However, there has been significant international debate on whether traditional criteria should be expanded to include screening for untreatable conditions (Pollitt 1999, Therrell 2001, Fearing & Levy 2003).

There is a lack of even broad concordance in national policies. In the United States of America (USA), newborn screening programmes have been implemented “sometimes as a result of scientific findings (e.g. new testing technologies, automated punching), sometimes due to financial incentives (e.g. federal support of

sickle cell testing) and sometimes due to consumer advocacy and accompanying political pressures” (Therrell 2001:64). In the United Kingdom (UK), newborn screening programmes have been implemented as the result of scientific findings, or personal research interests (Downing & Pollitt 2008). Different justifications for implementing newborn screening programmes highlight the disparate and highly varied influence of interest groups and political interpretation of traditional criteria.

Increasing technological sophistication in the field of medical genetics has fuelled ethical tensions. Acquisition of knowledge about genetic conditions is far outpacing the capacity to provide therapeutic treatment (Wood-Harper & Harris 2000). Technology has confronted health care systems with the imperative to decide, by default if not deliberately, as to whether or not to implement assorted genetic screening programmes. Although political and social bodies have often provided support, relevant guiding principles have not been sufficiently developed to direct contemporary practice (Parsons and Bradley 2003).

The disparate implementation of newborn screening programmes in the UK and the USA highlights very different interpretations of traditional criteria. In 1996, the National Screening Committee (NSC) was established in the UK to unify approaches to the implementation of screening programmes by developing national policies and regulatory strategies (Downing & Pollitt 2008). The NSC developed a set of 19 screening criteria based on the Wilson and Jungner’s 10 criteria and recommended that “there should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment” (NSC 2003). The NSC currently recommends newborn screening for five conditions: phenylketonuria (PKU), congenital hypothyroidism (CHT), sickle cell diseases (SCD), cystic fibrosis (CF) and medium chain acyl CoA dehydrogenase deficiency (MCADD) (National Screening Committee 2005).

In contrast, the American College of Medical Genetics (AMCG) highlight the potential of newborn screening to identify conditions even when improved clinical outcomes may be not be substantial or relevant to the affected individual, noting however that “the nature of genetic disease is such that knowledge of its presence

can be of value to other family members". In 2005, the ACMG proposed that 29 conditions should be included in uniform newborn screening programmes, despite the lack of evidence that early treatment leads to better disease-related outcomes in all conditions (Grosse *et al.* 2006).

### **3.5 Newborn screening; expanding interpretations of "benefit"**

The acknowledgement of a broader interpretation of benefits of screening, beyond 'treatability', has been welcomed by many (see Bailey *et al.* 2005, Pollitt 2006, Kemper & Wake 2007). Although the broad spectrum of non-medical benefits may vary for each condition, those which are most generalisable include the avoidance of the often difficult and time-consuming process of establishing a diagnosis for relatively rare conditions (Kemper & Wake 2007); access to supportive, educational and therapeutic services (Bailey *et al.* 2005); and the provision of information on genetic risk to inform reproductive decision-making (Bailey *et al.* 2005, Pollitt 2006, Kemper & Wake 2007). Bailey *et al.* (2005) also argue that the expansion of newborn screening could provide other societal benefits by increasing knowledge about the incidence, developmental patterns and range of effects of particular conditions, as well as encouraging the research agenda for the development of new treatments.

Grosse *et al.* (2006) and Dhondt (2007) suggest that expanding interpretations of 'benefit' marks a shifting paradigm in newborn screening; a gradual yet distinct move away from the "Guthrie age", characterised by the prevention of morbidity and mortality to a "genetic age", which justifies screening on the basis of "broader but possibly more moderate benefits" (Bailey *et al.* 2006:270). Although newborns are essentially screened for genetic conditions, the foundations of contemporary newborn screening policy clearly lie firmly in the realms of public health (Khoury 1996, Holtzman 1997, Carlson 2004, Ross 2006), which conflicts with the traditional remit of genetic testing, whose foundations are historically rooted in "principles of individual choice, informed consent and autonomy" (Parsons and Bradley 2003:336).

The broader interpretation of benefit mirrors a more social approach to health care. However, the increasing focus on individualism and the requirement for informed choice creates both logistical and ethical difficulties. Medicine is becoming more technologically sophisticated and simultaneously less paternalistic (Hunt *et al.* 2005). At risk families are frequently presented with ever deeper and more encompassing problem explorations, and expected to make deliberate choices about whether to conceive, test and terminate wanted pregnancies. There has been considerable debate regarding the capacity for informed decision making for both prenatal testing (Marteau & Dormandy 2001, Michie *et al.* 2003), and newborn screening (Clarke 1997, Parsons *et al.* 2002).

Historically, state regulation of health care has reflected the need to monitor and control individual action which may conflict with the preservation of societal health. Arguably modern political and health care systems are founded on the philosophy of utilitarianism: the ‘greatest good for the greatest number’ (Mooney 2003), but the rise of prevailing ethical paradigms “predominantly concerned with individualism and choice” (Chadwick 2004:162) have resulted in increasing ethical tensions. Mooney (2003:62) argues that the tension between social and individualistic ethics creates significant problems in medicine and health care: “first in determining what is common good and, second, in devising appropriate institutional arrangements to allow it to prosper alongside the individualistic ethics of virtue and duty.”

The shifting paradigm raises three crucial questions: first, do families actually value the avoidance of diagnostic delay, access to supportive services and the provision of information on reproductive risk? Second, is it feasible for public health services to provide sufficient information to enable autonomous informed decision-making? Finally, pending a positive response to the first two questions, should newborn screening programmes be expanded to reflect a social model which recognises a broader interpretation of health, beyond the absence of disease?

Although in the United States and many European nations newborn screening programmes are expanding, on the implicit understanding that there is inherent value in providing access to information and reproductive choice, there is a paucity of evidence to justify this assumption. The lack of evidence is due to the recent

development of the new MS/MS technology and the changing value commitments of industrialised societies, which are increasingly reflecting individualised ethical paradigms and - albeit tentatively - a social model of health. However, due to the early implementation of newborn screening programmes for the untreatable condition, DMD, there is potential to address the implications of an earlier diagnosis for reproductive decision-making.

### **3.6 Current provision of newborn screening for DMD; providing information, choice and support**

The fourteenth European Neuromuscular Committee (ENMC) workshop focused on neonatal screening for DMD (van Ommen & Scheuerbrandt 1993). The consensus recommendation of the ENMC concluded that a number of benefits were accrued as a result of newborn screening. Firstly, the avoidance of diagnostic delay through newborn screening reduced the anxiety and stress experienced during the manifestation of the disease “especially, the retrospective regret, reported by many families about their lack of tolerance for their child’s earlier clumsiness and difficulties walking”. Secondly, female relatives are offered the options of carrier detection and prenatal diagnosis before embarking upon future pregnancies, enabling genetic counselling “in an atmosphere of relative calm reflection, rather than hasty decisions being made in anxiety, under pressure of last minute information”. Lastly, the earlier diagnosis allows parents time to “prepare for decisions related to their future life with a handicapped child, e.g. selection of proper housing, timely education and assistance, provisions for early nursery etc”.

The consensus report concluded that the aim of neonatal screening for DMD should be to provide optimal information, choice and support to families afflicted by DMD. Arguably this conclusion marks a move away from screening as a public health focus on prevention of affected males, towards offering parents the option of testing and the option of prenatal diagnosis in subsequent pregnancies.

Despite the technical capacity to screen babies for DMD, evidence to refute some of the earlier concerns and support the suggestion that families may benefit from an earlier diagnosis, the implementation of programmes has remained controversial.

Nearly all the original pilot programmes ceased before the recent interest in expanding the benefit of newborn screening. Within Europe, the only programmes remaining are in Antwerp, in Belgium, and Wales. Various reasons have been provided for ending the programmes<sup>3</sup>. The majority cite technical and financial issues. However, programmes that were implemented on the basis of avoiding second affected boys found that success was limited. In addition, the programme in Lyon reported a high proportion of families suffering from psychological disturbances, as a result of the early diagnosis.

In the United Kingdom, persistent reticence to screen for an untreatable condition, combined with the perception that families would benefit from an earlier diagnosis (Firth *et al.* 1983) has resulted in a continued quest to find alternative ways of reducing the diagnostic delay. Mohamed *et al.* (2000) proposed screening boys who demonstrated any of the following criteria; not walking by 18 months, delayed speech and global developmental delay, awkward gait, inability to run or painful legs under the age of four years. However, the study by Parsons *et al.* (2004), on a cohort of 18 affected boys diagnosed through newborn screening, demonstrated that five out of the six criteria would have limited effectiveness in detecting DMD. The only criterion that was apparent in the majority of affected boys (94%) was awkward gait under four years of age. Parsons *et al.* (2004) argue that concerns regarding awkward gait would not be triggered until the child was two to three years old, and the problem may be easily mistaken as orthopaedic, rather than neuromuscular.

One possible explanation for the continued use of newborn screening for DMD in Wales is that the primary purpose of the programme did not rest on the ethically dubious aim of preventing second affected boys. Uniquely, newborn screening was introduced in Wales as an “opt-in” programme, in addition to the routine tests for PKU and hypothyroidism. The programme aimed “to provide families with reproductive choice in future pregnancies, to enable them to plan for the future with a child with a disability; to avoid the experience of a prolonged diagnosis; and to

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<sup>3</sup> Personal correspondence via Don Bradley, Director of Newborn Screening in Wales

identify a presymptomatic cohort who may benefit from future treatments” (Bradley *et al.* 1993).

In addition, newborn screening for DMD in Wales has been hailed as the only programme that “provides a systematic, integrated psychological and social assessment of the effects of the screening program” (van Ommen & Scheuerbrandt 1993). The programme also provides a systematic approach to disclosure of diagnosis, by working “closely with each child’s primary health care team, a network of paediatricians in each district and the Muscular Dystrophy Group family care officers” (van Ommen & Scheuerbrandt 1993).

Continued evaluation of the newborn screening programme in Wales has shown that the majority of families were happy with the way the diagnosis was disclosed. In addition, families expressed a favourable attitude towards newborn screening, as it provided them with reproductive choice and time to prepare emotionally and practically (Parsons *et al.* 1996, Parsons *et al.* 2002).

#### **4. Summary**

The social and political response to diagnostic and reproductive technologies highlights the varying influence of medical and social models of health on the delivery of health care. Early implementation of newborn screening, prenatal testing and genetic counselling reflected the medical focus on disease prevention. Newborn screening programmes for treatable conditions focused on preventing the realisation of genetic conditions in individuals, while screening for one untreatable condition, Duchenne muscular dystrophy focused on preventing second affected cases.

The genetic nature of the conditions identified through newborn screening meant that families were offered genetic counselling and prenatal testing. Genetic counsellors communicated the complexities of genetic risk to at-risk couples, with the aim assisting the counselee to make an “optimal” decision. However, the main aim of genetic counselling was often described as reducing the burden of disease and many have argued that an optimal decision was one that made sense to the

provider. In addition, prenatal testing was initially limited to at-risk couples who demonstrated a commitment to terminating an affected foetus; creating an inextricable link between testing and termination.

Changing views on disability and the increasingly unacceptable nature of linking prenatal testing with termination initiated a desire to provide a less directive approach to prenatal testing and counselling. Genetic counsellors, in an attempt to disassociate genetic health care from the spectre of eugenics, have shifted away from the traditional paternalistic approach to decision-making. In recent years there has been greater acknowledgement of the role of the individual in health-related decision making. Individuals and families affected by genetic disorders have, to an extent, become responsible for negotiating their own ethical dilemmas and reproductive decisions. However, concerns remain about the social and political pressures exerted on at-risk couples offered prenatal testing. The very offer of prenatal testing may imply a recommendation to accept the test and proceed to termination in the event of a positive diagnosis.

The foundations of newborn screening lie firmly in the realms of public health, which has traditionally focused on population-wide preventative measures. The capacity to detect untreatable conditions through newborn screening has also raised questions about the role of newborn screening. Screening for conditions to provide families with broader, but possibly more moderate benefits such as information, choice and support raises some critical questions. Do families value the provision of information? Do families receive support? Furthermore, what are the implications of newborn screening for reproductive decision-making?

Implementing newborn screening programmes to provide families with reproductive choice remains controversial. There is now a greater range of reproductive options (amniocentesis, chorionic villus sampling and preimplantation genetic diagnosis), but each is associated with psychological burdens. In addition, the disability rights critique and feminists have questioned whether reproductive “choice” is really a choice. Considering the explicit focus on “births avoided”, from early proponents of newborn screening programmes for one untreatable condition, DMD, the lingering



concerns regarding the real meaning of “reproductive choice” are entirely justifiable.

Assessment of all potential benefits of early identification for all untreatable conditions is beyond the scope of this thesis. However, one of the most prevalent justifications for screening for untreatable conditions is the provision of information on genetic risk to inform reproductive decision-making. In Wales, newborn screening for one untreatable condition, Duchenne muscular dystrophy (DMD) has been available since 1990. The programme has been continuously monitored and reviewed, providing a unique opportunity to utilise a significant body of data to assess the implications of newborn screening for reproductive decision-making. This thesis focuses on an analysis of reproductive decision-making in families in Wales after their sons were diagnosed with DMD through newborn screening compared to families in the West of Scotland<sup>4</sup> whose sons were diagnosed later through traditional clinical diagnosis.

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<sup>4</sup> Justification of the use of families from the West of Scotland as a comparative cohort is provided in Chapter Four: Methodology.

# Chapter Two

## Duchenne Muscular Dystrophy

### Introduction

Duchenne muscular dystrophy (DMD) is an X-linked condition, affecting around 1:3500 males worldwide<sup>5</sup>. DMD is one of the most severe forms of muscular dystrophy. Progressive muscle weakness results in wheelchair dependency by the age of twelve years. Subsequent deterioration in lung and heart function limits an affected male's lifespan; the majority die in their early twenties.

Significant developments in respiratory care have, to date, had considerably more impact on extending life expectancy of affected males than genetic therapies. There is considerable potential in recent advances, to suggest that genetic therapies may provide the possibility of treatment for some patients (depending on the location and size of the gene deletion). However, for the majority a cure remains a distant promise; potentially beyond their lifetimes.

Although a cure remains elusive, during the last fifty years, increasing technological sophistication has created the potential to provide families affected by DMD with reproductive choice. Providing families with reproductive choice depends on two factors; ensuring families are aware of their risk and offering families reproductive options. The previous chapter showed how the development of newborn screening has provided some families with an earlier awareness of their risk, and reproductive technologies have provided risk-aware families with a greater range of options in subsequent pregnancies. This chapter focuses on the development of carrier testing procedures that have provided families with an increasingly accurate awareness of genetic risk.

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<sup>5</sup> Mean incidence from neonatal screening and several exhaustive population studies is estimated to be 1:3500 but single study estimations range from 1:3000 to 1:7000 (Emery & Muntoni 2003, Walton 1974, Zellweger and Antonik 1975).

The aim of this chapter is to provide a historical overview of the technologies that have enabled the diagnosis, and subsequent assessment of carrier risk, in families affected by DMD. This chapter is divided into four sections. First, the causes, effects and nature of the condition are described. Second, the tools used to clinically diagnose DMD are explored; from early clinical observations to developments in histological tools and the identification of specific testable biochemical defects. The third section explores the advent of cytogenetics and recombinant DNA techniques, the localisation of the DMD gene, and the subsequent development of highly predictive tests to either confirm or exclude diagnosis of DMD. The final section summarises the implications of increasingly sophisticated technologies for reproductive options.

This chapter needs to be presented with a caveat; for the non-geneticist, it may appear - at best - a little dense. However, it is deemed essential to convey the technological developments for two key reasons. First, whilst the drive to increase our knowledge about the genome may have emerged from a desire to develop gene therapies (Marteau & Richards 2000), in practice, the developments have served primarily to increase the accuracy of information used in reproductive decision-making. Second, if risk awareness and choice are so valuable – as proponents of expanded newborn screening programmes often profess – technological developments have had significant implications for the degree of awareness and the degree of choice.

## **1. Overview of Duchenne muscular dystrophy**

Duchenne muscular dystrophy (DMD) affects smooth muscle, skeletal muscle and cardiac muscle (Korf 2000). Around 5-10% of female carriers demonstrate some degree of muscle weakness, but the majority of carriers are asymptomatic (Emery 2002). Affected boys are phenotypically normal at birth and frequently little clinical weakness can be detected before 3-5 years of age (Kunkel & Hoffman 1989, Dubowitz 1995, Emery & Muntoni 2003). Due to the delayed manifestation of signs and symptoms of the condition, it is often difficult to detect and diagnose the condition for some years after birth. The mean age at which boys are clinically

diagnosed in the UK is 4.5 years (range: 3 months to 8.5 years) (Appleton & Nicolaides 1995, Bushby *et al.* 1999).

During the early symptomatic stages progressive weakness of muscles of the pelvis, knee and hip extensors may cause delayed walking, abnormal gait, toe walking, frequent falls, and difficulty climbing stairs. Often affected males demonstrate difficulty rising from the floor. Some boys may also present delayed intellectual milestones, in particular a delay in speech development. Some degree of intellectual impairment occurs in 20% of cases but, unlike muscle weakness, it is not progressive (Emery 2002).

As the disease progresses, muscle tissue degenerates and is replaced by fat and connective tissue. Fifty percent of boys lose ambulation by 8.5 years (Emery 1993). Once a wheelchair is required many boys develop progressive scoliosis and other deformities thought to be related to their increasing immobility. Many develop contractures of the flexors of the elbows and pronators of the forearms resulting in loss of antigravity function in their upper arms.

Around half way through the course of the disease weakness of intercostal and associated muscles cause a gradual deterioration in lung function. Episodes of respiratory failure and pneumonia are the primary cause of death in 70-80% of affected boys with the remaining deaths thought to be caused by progressive weakness of cardiac muscle, resulting in dilated cardiomyopathy (Heckmatt *et al.* 1989). Until the early 1990s, 90% of boys died before twenty years of age; improvements in respiratory and supportive care have now resulted in survival into the mid-20s (Emery & Muntoni 2003). However, DMD remains an incurable condition.

## **2. Development of clinical diagnosis for DMD**

Before the discovery of a biochemical marker in the 1970s, clinical diagnosis of DMD relied on two factors; the ability to recognise signs and symptoms as indicative of Duchenne muscular dystrophy and the ability to distinguish between

DMD and other forms of muscular dystrophy, using muscle biopsies. In recent decades clinical observations and histological tools have been complemented by the capacity to detect muscle enzymes, found to be raised in patients with muscular dystrophy, and the advent of cytogenetics and recombinant DNA techniques. Development of the capacity to recognise signs and symptoms and conduct muscle biopsies are explored in the first subsection. The capacity to detect muscle enzymes is explored in the second subsection. The advent of cytogenetics and recombinant DNA techniques is explored later on, in section four.

## **2.1 Signs, symptoms and muscle biopsies**

Cont and Gioga were the first to recognise DMD as a specific clinical disorder in 1836 (Emery & Muntoni 2003). Further developments were made in the mid-nineteenth century by an English physician, Edward Meryon and a French physician, Guillaume Benjamin Amand Duchenne. Meryon studied the physical effects of the condition in affected males and conducted post-mortem microscopic examinations of muscle tissue. Meryon described the condition as a disease of the nervous system, primarily causing destruction of muscle tissue and noted that DMD was a family disorder with a predilection for males.

Guillaume Duchenne characterised the disease by progressive weakness of movement, starting with the lower limbs and progressing to the upper limbs. He described a gradual increase in size of many affected muscles (pseudohypertrophy) and the production of abundant fibrous and adipose tissue in the later stages (Emery & Muntoni 2003). Duchenne's name became most closely associated with the pseudohypertrophic muscular dystrophy studied by both himself and Meryon, leading to the now commonly used name Duchenne or Duchenne's muscular dystrophy.

Meryon and Duchenne's work on muscular dystrophy enabled a diagnosis of the condition to be made based on the clinical manifestation of signs and symptoms. However, in the early 20<sup>th</sup> century Willheim Heinrich Erb, a German neurologist suggested the existence of multiple forms of muscular dystrophy. The hypothesis was confirmed in 1955 by the German human geneticist, Peter Emil Becker, who

proved that there were clearly two separate, but related clinical manifestations of progressive muscular dystrophy, namely DMD and another milder version, now known as Becker muscular dystrophy (BMD).

BMD is rarer than DMD with an incidence of 1:18500 males. BMD also has a later onset, around the age of twelve years (although sometimes as late as 40-50 years), and a slower disease progression (Emery 2002, Lai *et al.* 2006). However, males affected with severe forms of BMD demonstrate similar characteristics to those with DMD. Reliance on the recognition of clinical manifestations to distinguish between milder forms of DMD and more severe cases of BMD is problematic.

One of the most commonly used techniques to differentiate between DMD and BMD is the muscle biopsy. Developments in histological procedures provided means of analysing microscopic structure of muscle. Muscle biopsies from young boys demonstrating severe degeneration, with marked variation in muscle fibre size and the presence of connective tissue and fat separating muscle fibre, is usually indicative of the more severe form of muscular dystrophy; DMD. Since the discovery of the protein product 'dystrophin'<sup>6</sup> analysis of the presence of dystrophin in muscle biopsies has enabled a more definitive differentiation between the two conditions.

## 2.2 Biochemical markers

In 1949, Sibling & Lehninger noted that a serum enzyme, adolase, could be raised in patients with muscular dystrophy. In subsequent experiments several other serum enzymes were found to be raised in muscular dystrophy and other muscle disorders, namely aminotransferases, lactate dehydronase and creatine kinase (Dubowitz 1995).

Ebashi *et al.* (1959) were the first to show that creatine kinase (CK) activity is raised in muscular dystrophy patients and the finding was confirmed in the following year by Dreyfus *et al.* (1960). Creatine kinase proved to be the most

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<sup>6</sup> The identification of dystrophin is explored in greater detail, later in this chapter, in the section on cytogenetics and recombinant DNA techniques.

sensitive and easily detectable serum enzyme. Boys affected by DMD demonstrate a marked elevation of CK of up to 100 times higher than an unaffected boy (Dubowitz 1995, Specht & Kunkel 1993, Emery & Muntoni 2003). In 1960, Schapira and colleagues introduced the CK test into clinical practice, allowing a boy presenting with symptoms of DMD to immediately undergo a diagnostic test (Schapira *et al.* 1960).

The current process of providing a clinical diagnosis for boys affected by DMD in the UK occurs in four stages. First, signs and symptoms of the condition must be recognised as being indicative of DMD. Second, creatine kinase tests are conducted. Third, genetic tests are conducted to identify the exact location of the genetic deletion or duplication. Lastly, if a mutation cannot be detected, families are offered the option of a muscle biopsy to determine whether the child has BMD or DMD.

The creatine kinase test also enabled newborn screening for DMD and was later used to identify carriers of the condition. One of the key justifications for providing newborn screening for DMD has been the capacity to provide mothers with some awareness of their genetic risk in subsequent pregnancies. The following section explores the considerable changes in cytogenetic and recombinant DNA techniques, which have increased the capacity to provide families with an accurate awareness of their genetic risk.

### **3. Cytogenetics and recombinant DNA techniques; increasing the accuracy of carrier testing techniques**

The hereditary nature of DMD has been suspected since the mid-nineteenth, when Meryon described DMD as a family condition. Subsequent developments have radically changed our understanding of the processes involved in the genetic inheritance of DMD. This section is divided into three subsections; Mendelian principles, the role of creatine kinase, and the evolution of genetic testing techniques, which have enabled detection of specific gene deletions and mutations in an affected boy and subsequent identification of same mutations in carrier mothers.

### 3.1. Mendelian Principles

In the late 19<sup>th</sup> century a Moravian monk, Gregor Mendel, began the first scientific study of heredity; his observations became the foundations of the modern discipline of genetics. Mendel argued that particulate properties did not combine when passed on to the next generation; some were dominant, whilst others recessive. He made the distinction between the observable properties (phenotype) and specific genetic constitution (genotype) of an organism. Through analysis of dominant and recessive traits Mendel reasoned that 'parents' must have two alternative forms (alleles) of a gene, which can be distinguished from other alleles by their phenotypic effects.

Mendel developed two key laws of heredity: segregation and independent assortment. In the first law on the principle of segregation, Mendel reasoned that in order to avoid gene pairs doubling, in each successive generation, they must segregate during gamete formation. Mendel's second law, on the principle of independent assortment, describes how the segregation of one gene pair (in one gamete) occurs independently of the other pair in a separate gamete. Mendel's laws describe the separation of what we now refer to as chromosomes, during a process called meiosis (see Box 1).

#### **Box 1 – Meiosis**

Each individual has two copies of each of the 23 chromosomes in every cell, 46 chromosomes in all. Genetic information is inherited from the parents in the gametes, the sperm and the egg. These gametes are produced from the germ cells in the testes and the ovary in a process termed 'meiosis'. During meiosis each pair of chromosomes replicates and then separates, forming four cells which contain 23 chromosomes (each chromosome is represented in an unpaired condition). Fertilisation of two gametes to form a zygote restores the chromosome number to 46 and provides a full set of genetic information. The combination of genes carried on the chromosomes is a unique selection of the genes present in the two parents of each individual. Individuals that carry two identical alleles of a given trait are referred to as 'homozygous', whilst those that carry two different alleles are 'heterozygous'.



### 3.2 Genetic linkage for pedigree analysis

Walter Sutton and Theodore Boveri proposed the idea that genes are carried on chromosomes in 1903. In 1915 Thomas Hunt Morgan described the principle of genetic “linkage”; alleles located relatively close together on a chromosome tend to be inherited together. Morgan and colleagues studied the distance between a number of traits on the same chromosome and the frequency with which traits are inherited together, to create the first linkage map.

In 1956, Tjio and Levan revealed the number of chromosomes in humans to be forty six. Subsequent experiments have estimated the number of genes carried on chromosomes to be around 25,000 in humans. The majority of chromosomes are called autosomes, apart from one pair involved in sex determination, known as sex chromosomes. Through numerous studies on Turner and Klinefelter syndromes, females were found to have two X chromosomes and males to have one Y and one X chromosome (Christie & Tansey 2003).

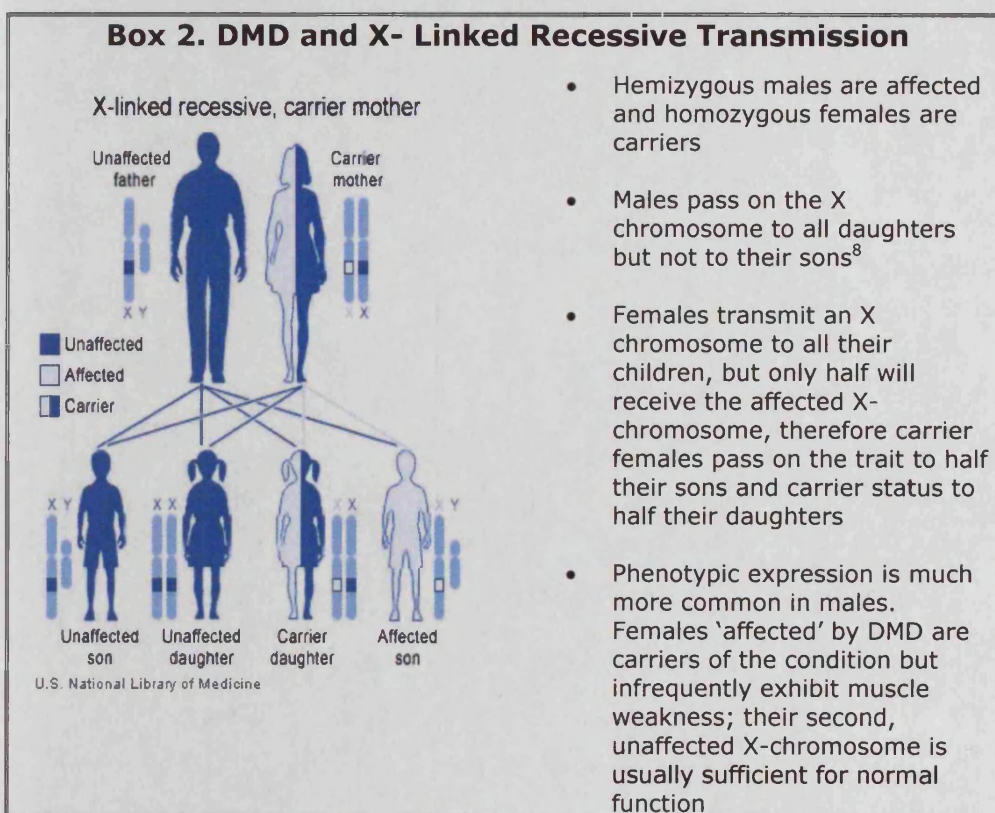
Although the gene responsible for DMD had not yet been located, Mendelian principles could be used to study a family tree, referred to as a pedigree chart. A particular trait could be tracked through generations to determine whether the trait had a dominant or recessive pattern of inheritance and to assess whether the gene causing the trait was located on an autosome or sex chromosome. BMD and DMD were both found to be X-linked recessive disorders (see Box 2), enabling clinical geneticists to track the affected x-chromosome through generations.

Following the pattern of X-linked transmission through generations, once an affected male had been diagnosed with DMD, enabled carrier risk assessment of females related to the proband. If a female had an affected son as well as another known affected maternal male relative, it was assumed<sup>7</sup> that she was an obligate carrier, with a 1:4 risk of having an affected boy in subsequent pregnancies.

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<sup>7</sup> Although this assumption was usually correct new mutations have occurred in families with a known family history (Douglas Wilcox, Personal correspondence).

Frequently the condition occurs in families with no known history of the condition. If the mother of an affected boy had few male relatives or little information on distant male relatives, the probability that she was a carrier had to be statistically assessed. Bayes theorem, a mathematical formula used for calculating conditional probabilities, enabled the inclusion of information on all unaffected male relatives to provide a female with a numerical carrier risk. At risk females would either be provided with a numerical risk or be designated to a “high”, “intermediate” or “low” risk category by clinicians. The complexity and influence of external factors in pedigree analysis often resulted in unsatisfactorily uncertain risk estimations.



### 3.3. The role of creatine kinase

The establishment of basic genetic inheritance, combined with the identification of a testable biochemical indicator of DMD (creatine kinase), provided a breakthrough in the identification of female carriers. Although creatine kinase (CK) tests enabled

<sup>8</sup> Due to the clinical progression of DMD affected males rarely reproduce.

the development of newborn screening for DMD, Pennington (1980) argued that the most important application of CK measurements in muscular dystrophy was the identification of female carriers. Although female carriers do not demonstrate such a marked elevation of serum CK activity, it was possible to combine pedigree analysis with CK test results, to assess a female's carrier risk (Hodgson & Bobrow 1989, Emery & Muntoni 2003).

Analysis of CK levels quickly became the most widely used method of carrier detection, but the test did not prove to be reliably precise. A number of factors were shown to affect detected levels of CK. Serum CK activities were shown to fall during pregnancy (Blyth & Hughes 1971, Emery & King 1971, King *et al.* 1972, Emery 1980), be raised due to physical activity (Emery 1980, Pennington 1980) and to lower with progressive age (Moser & Vogt 1974, Skinner & Emery 1974, Bunday *et al.* 1979, Nicholson *et al.* 1979). Consequently only 70-75% of carriers demonstrate raised CK (Thompson *et al.* 1967, Walton *et al.* 1969, Dubowitz 1995).

Due to the variability in different samples it became general practice to calculate the mean of samples taken on three separate occasions. Logarithms of CK values in healthy individuals and carrier females were developed to enable statistical analysis of the probability that a female, with a given mean, was a carrier (Pennington 1980, Emery 1980, Hodgson & Bobrow 1989). However, questions regarding reliability remained. Bullock *et al.* (1979) conducted a survey to assess whether clinical geneticists obtained the same carrier risk after analysis of CK results and pedigree data. The results revealed a serious lack of precision. Nevertheless, carrier risk assessed using a combination of pedigree analysis and CK results remained significantly more accurate than pedigree analysis alone.

During the late 1970s, it was hoped that CK analysis could be used to detect at-risk fetuses. Mahoney *et al.* (1977), Stengel-Rutowski *et al.* (1977) and Dubowitz (1995) all reported the successful diagnosis of at-risk fetuses using CK testing. However, Mahoney *et al.* (1977) had also reported normal fetal serum CK and the subsequent birth of an affected male. Ionasescu *et al.* (1978) and Golbus *et al.* (1979) reported further false negative results. The process was later abandoned amidst fears of unreliability (see Edwards *et al.* 1984a, 1984b, 1984c).

### 3.4. Evolution of genetic testing techniques

Increasingly sophisticated genetic technologies have rapidly transformed the ability to identify specific gene deletions and duplications in affected males. Once a deletion or duplication was identified, many of the same technologies could be used to identify whether the mother was a carrier of the condition. Each technology is explored in subsequent sections, in relation to the order in which they became available.

#### *3.4.1 Genetic linkage using linked DNA markers*

During the 1960s and 1970s, there were significant developments in understanding genetic processes. Chromosomes were known to be carried in the nucleus of every cell and DNA had been identified as the substance within chromosomes that carries genetic information. In 1953, Frances Crick and James Watson discovered the double helix structure of the DNA molecule (see Box 3) and a few years later Brenner, Jacob and Meselson determined the role of mRNA, as the messenger molecule that carries genetic information from DNA in the cell nucleus out to the cytoplasm; the cell ultimately uses mRNA to make specific proteins (see Box 4).

#### **Box 3. Basic DNA structure**

The outer rails of the double helix consist of phosphate molecules and sugar (deoxyribose) molecules. The rungs that weakly bind the outer rails together are made up of molecules consisting of bases. There are four different bases which always pair in the same way: adenine (A) always pairs with thymine (T) and guanine (G) always pairs with cytosine (C). A single strand of DNA is made up of letters representing the bases (e.g. ATGCTCGAATAAATGTGAATTTGA etc). A sequence of three **nucleotides** constitutes one codon, which encodes information for one of twenty different amino acids (e.g. ATG CTC GAA TAA ATG TGA ATT TGA etc). A chain of amino acids may constitute a particular gene product (protein) (e.g. < ATG CTC GAA TAA>).

In 1966, Marshall Nirenburg and H. Gobind Khorana demonstrated the triplet nature of genetic code; each of the 20 amino acids is coded by a sequence of three nucleotide bases, called codons. In 1978, David Botstein and colleague discovered a

useful type of DNA polymorphism called restriction fragment length polymorphisms (RFLPs), which provided a breakthrough in gene mapping.

Restriction enzymes digest specific fragments of DNA. DNA probes, each consisting of a length of DNA from a specific segment of the human genome, recognise their complementary sequences in DNA from a patient or family member. The length of DNA recognised by a probe varies, depending upon the pattern of the restriction enzyme sites around the sequence of DNA that is recognised by the probe. The variation can be used to track the restriction site and probe through a family to ascertain whether the disease tracks with the probe and restriction site (Emery & Muntoni 2003, Cummings 2003).

Analysis of rare individuals with chromosome translocations indicated that the gene responsible for DMD was located on the short arm of the X-chromosome. The exact position of the DMD gene was finally located on the short arm at Xp21 in 1983 (Kunkel and Hoffman 1989, Dubowitz 1995, Korf 2000, Emery & Muntoni 2003) and a linkage map became available. Initially the most commonly used intragenic probes (pERT and XJ1.1) were used to detect polymorphic RFLPs within the gene and were able to detect deletions in about 10% of patients (Hodgson & Bowbrow 1989). Use of multiple probes, including flanking markers used at both the proximal and distal ends of the dystrophin gene locus, increased the proportion of cases showing deletions to over 25% (Hodgson & Bowbrow 1989).

Despite the increased accuracy, obtained through use of multiple probes, there was still a chance that crossing-over (recombination), during gamete formation, could have moved the RFLP to the healthy allele. As even the closest markers were located some distance from each other, recombination occurred in approximately 5% of cases, making interpretation difficult. If an actual deletion was identified in an affected boy the risk of recombination could be circumvented (Hodgson & Bowbrow 1989, Dubowitz 1995).

The advent of linked markers enabled more precise identification of carriers. Once a boy was suspected of having DMD, DNA would be collected from as many family members as possible and linked markers used to track the affected gene through the

family. If a deletion was detected in an index case this provided a direct marker for antenatal diagnosis or carrier detection. If a deletion was not detected, carrier detection was significantly more complex.

If a mother of an affected boy was found to have different polymorphic marker alleles on her two x-chromosomes (i.e. she is heterozygous), it was possible to ascertain that if the allele inherited by her affected son was also inherited by her other children, they would also inherit the DMD mutation (affected male or carrier female), unless recombination had occurred. If the mother of an isolated case of DMD also had a normal son(s), the presence of the same x-chromosome in both normal and affected boys increased the probability that the affected boy had the condition as a result of a new mutation, and that she was therefore not a carrier. If her sons had inherited different x-chromosomes, her carrier risk would be increased (Hodgson & Bobrow 1989).

In practice, the risk of recombination meant that the use of linked markers alone was an unreliable assessment of carrier risk. It became standard practice to combine pedigree analysis, biochemical tests of carrier status (CK), and linkage analysis, assessed in a Bayesian calculation, to provide an integrated risk figure. Despite these efforts many families still received uncertain results; the quest for more powerful diagnostic tools able to directly detect gene mutations began.

A few years after the discovery of the gene locus the entire gene had been cloned and the protein product of the gene discovered and named “dystrophin” (see Box 4). The dystrophin gene was found to be the largest genetic locus characterised to date, containing over 2 million base pairs and at least 79 exons (Kunkel & Hoffman 1989, Emery & Muntoni 2003). Extracting mRNA from the leucocytes and cloning as complementary DNA (cDNA) provided a means of examining in more detail the location and extent of deletions identified with genomic probes. Approximately 70% of mutations in DMD and BMD patients could be identified using cDNA probes, as deletions (Love *et al.* 1989:666). Around 7% of boys were found to have duplications and the remainder were presumed to have point mutations, not detectable by existing techniques (Dubowitz 1995, Yau *et al.* 1996).

Certain deletions were found to result in the production of virtually no dystrophin, causing the more severe clinical phenotype of DMD, while other overlapping and often larger deletions could result in the production of abnormal dystrophin resulting in the milder clinical phenotype of BMD (Kunkel & Hoffman 1989, Dubowitz 1995).

#### **Box 4. Genes and protein production – the basics**

Gene expression leads to protein synthesis. The action of the protein is responsible for specific hereditary traits. Within most human genes there are nucleotide sequences that are transcribed but not translated into the amino acid sequence of a protein; these are called **introns**. The nucleotide sequences that are transcribed and translated into protein are called **exons**. Gene expression has two stages, transcription and translation.

**Transcription** begins when a section of DNA unwinds. An enzyme, RNA polymerase, binds to a particular nucleotide sequence just outside the gene, called the promoter region. The RNA polymerase then moves along the DNA strand adding nucleotides to their complementary RNA strand. The rules of base pairing are the same as in DNA replication except that RNA contains Uracil (U) which replaces Thymine (T). When the RNA polymerase reaches a specific nucleotide sequence known as the terminator region, the newly formed single strand of RNA detaches from the DNA strand and the DNA strand re-forms to make a double helix.

During **translation** messenger RNA in the cytoplasm binds to the ribosome. A second RNA molecule, transfer RNA, carries its specific amino acid from the cytoplasm and transports it to the ribosome, to produce a specific amino acid chain, called a polypeptide, which corresponds to the mRNA. Once formed the polypeptide folds into a three dimensional shape, determined by its amino acid sequence. Mutations in genes can alter folding and lead to genetic disorders. Once a polypeptide is folded, modified and functional it is called a protein.

To explain the variation in clinical severity, Monaco *et al.* (1988) proposed a hypothesis of 'in frame/out of frame' mutations. A deletion in DMD, irrespective of size, leads to frame shift of the triplet codons for amino acids, resulting in a 'non-sense' type of mutation and a severely truncated non-functional protein, whereas in Becker dystrophy the nucleotides remain in frame, resulting in mRNA molecules capable of directing the translation of a semi-functional protein. The hypothesis

proved to be correct in over 90% of cases with deletions (Kunkel & Hoffman 1989, Specht & Kunkel 1993, Dubowitz 1995).

The dystrophin gene was also found to have a very high mutation rate, thought to be related to the enormous size of the gene. The high rate of new mutations redefined the types of known carriers (Table 2.1). New mutations are now thought to account for approximately one third of all affected males and can occur in the egg cell that produced the affected boy or the sperm or egg that produced his mother (Korf 2000). In the latter case the woman is likely to be a carrier with a 1:4 risk of having another affected boy.

A mutation occurring in the egg cell that produced the boy is referred to as germ-line, germinal, or gonadal mosaicism; mothers are not genetic carriers but are at risk of transmitting a mutation to more than one child due to somatic mutation.

Estimates of frequency of germ-line mosaicism among families with DMD have been variously calculated to be between 12% and 20% (Emery & Muntoni 2003).

**Table 2.1 Types of carriers**

<b>Type of carrier</b>	<b>Description</b>	<b>Risk in subsequent pregnancies</b>
Carrier	Female "carries" a mutation in the dystrophin gene	1:4
Non-carrier (at risk of germline mosaicism)	New mutation occurred in mother's egg which resulted in affected boy	Estimated to be approximately 1:20

Localisation of the dystrophin gene and the potential to identify mutations in individual cases, through linked markers and gene specific cDNA probes, further extended the sensitivity of carrier detection and male diagnosis. In the first decade following the identification of the dystrophin gene the most commonly used mutation detection technique was the Southern blot, involving the transfer of DNA after digestion with restriction enzymes, followed by hybridisation with fragments of relevant genomic DNA (probes).



Once the gene was isolated and sequenced, a series of cDNA probes were made available to laboratories around the world, which made possible the screening of probands for deletion of individual exons with the gene. Plauchu *et al.* (1989:669) argued that “neonatal screening programmes for DMD now have an increasing place among preventive programmes for genetic disorders.”

### ***3.4.2 Polymerase Chain Reaction***

Polymerase chain reaction (PCR) was invented in 1986 and revolutionised the diagnosis of affected boys and detection of female carriers. PCR works by firstly separating the double strand of DNA (denaturation). The nucleotides of interest on a single strand are then marked or “primed” by the addition of two short strands of nucleotides (oligonucleotides), designed to bind at specific points on either side of the chosen nucleotides. A copy of the desired area of the strand is then produced using the enzyme Taq polymerase to form a new double strand. After every round of replication the double stranded products are separated and used as templates. The process of amplification is then repeated, to create thousands or millions of copies of the desired area of DNA. Amplification increases the size of the PCR products, making it possible to visualise them by running them on a gel, followed by staining with ethidium bromide. Deletions result in products which are smaller than that of a corresponding normal allele, whilst duplications generate products which are larger (Tyrrell 1997, Cummings 2003, Korf 2000, Young 2005). Deletions and duplications cluster in the 5 prime and 3 prime hotspots and therefore not all mutations needed to be analysed for identifying most mutations (Dubowitz 1995, Emery & Muntoni 2003).

In the late 1980s, Jeff Chamberlain and his colleagues (1988) and Alan Beggs *et al.* (1990) developed a modification of the PCR process known as the ‘multiplex method’, in which multiple pairs of primers are used to bind to a number of regions, which are known to be deletion susceptible. Amplification of more than one exon in a gene allowed “hot spot” regions to be simultaneously analysed (Emery & Muntoni 2003:65). Multiplex PCR proved to be significantly less time consuming than linkage and Southern blot and required a considerably smaller amount of DNA (Korf 2000).

By studying 19 exons in two multiplex PCR assays, over 98% of deletions can be detected (Chamberlain *et al.* 1988). Although the procedure is rapid, reliable and accurate, in practice multiplex PCR can only detect gene deletions in about 70% of cases. Of the remaining cases, around 10-15% of duplications can be detected; the rest carry point mutations that are spread throughout the entire gene, some of which occur outside of the 'hot spot' regions analysed by multiplex PCR (Emery & Muntoni 2003).

Multiplex PCR is not sensitive enough to detect deletions or duplications in females, due to the activation of their second X chromosome. If a deletion or duplication has been identified in a male, female DNA is assessed for the amount of PCR product produced at the site of the mutation through a process called 'quantitative PCR', or 'dosage'. The use of automated and quantitative fluorescent PCR system facilitated the detection of deletions, making it possible to assign the carrier status of females related to an affected male with a known mutation (Emery & Muntoni 2003).

### ***3.4.3 Identifying point mutations***

Various techniques have been used to identify mutations which escape detection following the multiplex PCR approach; only those used regularly in laboratories today are reviewed in this section. During the 1990s the most commonly used test was the protein truncation technique (PTT), developed in the early 1990s by Roberts *et al.* (1991 in Dubowitz 1995). PTT requires an RNA sample from a blood sample, or preferably a muscle biopsy which is amplified and translated into protein using an in vitro system. The proteins are run on a gel and analysed; if a fragment carries a mutation the resulting protein will be truncated. The cDNA corresponding to the truncated fragment can then be sequenced to identify the mutation (Emery & Muntoni 2003:191)

Bennett *et al.* (2001) described a PCR-based scanning method, referred to as 'denaturing high performance liquid chromatography' (DHPLC) or WAVE technology. DHPLC is based on the differential separation of mismatched heteroduplexes that form after normal and mutant DNA strands are bonded back

together. DHPLC is an extremely sensitive method for detecting base substitutions and small deletions or insertions (Young 2005).

#### ***3.4.4 Multiplex litigation-dependent probe amplification and sequencing***

Schouten *et al.* (2002) described a new technique to screen the entire DMD gene for duplications and deletions. Multiplex litigation-dependent probe amplification (MLPA) analyses all 79 exons in one assay which allows detection of large genetic rearrangements by simultaneous amplification of nucleic acid sequences. Each MLPA probe consists of two target-specific oligonucleotides and a PCR primer binding sequence, which hybridize to the target sequence at sites immediately adjacent to each other. After hybridisation to the target DNA, the two halves of each probe are joined together by a ligation reaction, which can be amplified by PCR. The quantity of the PCR products appears in different lengths allowing peak areas to be identified (Lai *et al.* 2006). MLPA has been shown to be considerably more sensitive and accurate than PCR, enabling detection of all known deletions and duplications.

Sequencing of the entire dystrophin gene is the 'gold standard' method for detecting deletions and duplications. The initial stages of sequencing follow the PCR method: strands of DNA are denatured and a single strand acts as a template for the synthesis of a complementary strand using Taq polymerase. In sequencing the Taq polymerase is combined with a mixture of deoxynucleotide (dNTP) in four separate reactions in each of which a specific dideoxynucleotide (ddNTP) is incorporated. Each reaction generates a series of different sized fragments. The fragment from each reaction are then analysed enabling the position of each fragment to be compared and the sequence of the complementary strand to be read (Young 2005). Sequencing is both time-consuming and expensive (Young 2005). Occasionally sequencing will be used for a particular exon if a suspected point mutation has been highlighted through PCR.

#### **4. Summary of implications of testing techniques for reproductive options**

During the last fifty years there have been considerable changes in the techniques used to diagnose boys and identify carriers. Table 2.2 shows how diagnostic procedures, carrier testing and reproductive technologies have transformed the reproductive options available for families affected by DMD. It should be noted that throughout all these stages families could – of course – choose to continue with family building without intervention; the third column merely indicates the alternatives options available in each decade.

The developments are complex, remarkable and hugely significant. Only in recent years has it become possible to provide mothers with a reasonably accurate assessment of their carrier status. The drive to increase the accuracy of genetic testing techniques initially occurred in an era when prevention of genetic abnormality was a paramount feature of the genetic discourse. In more recent years there has been increasing recognition of the difficulty families face, in trying to decipher complex risk assessments (Parsons & Atkinson 1993).

The trajectory of risk-awareness began with recognition of the familial nature of DMD and the simultaneous realisation that not all family members will be affected by the condition. The reproductive options available to families were to either cease, or continue, family building. In recent decades mothers have been provided with ever more complex (and at times unreliable) assessments of their carrier risk. Capacity to detect the sex of the foetus occurred in an era when disability was overtly defined as tyranny to be desperately avoided. Families were offered the desperately difficult decision: to terminate all male foetuses, without knowing whether or not they were affected, or to risk the birth of an affected male.

**Table 2.2 Impact of technological developments on reproductive options**

Decade	Technological Developments	Reproductive options
1950s	Pedigree analysis	No more children – based on estimation of risk
1960s	Amniocentesis Foetal sexing, (UK Abortion Act)	Test pregnancy at 16-18 weeks and terminate if foetus male
1970s	Creatine kinase (CK)	Test pregnancy at 16-18 weeks and terminate if foetus male
1980s	Linkage Southern blotting with cDNA probes Chorionic villus sampling	Test pregnancy at 10-12 weeks and terminate if male foetus affected – not always possible or accurate
1990s	PCR Multiplex Pre-implantation genetic diagnosis (PGD)	Test pregnancy at 10-12 weeks and terminate if male foetus affected – available for more families and more accurate  OR  Avoid testing and termination through PGD – limited availability and low success rate
2000s	dHPLC MLPA Sequencing	Test pregnancy at 10-12 weeks and terminate if male foetus affected – available for all families with increased accuracy

In recent years technological sophistication has perhaps reached the ‘gold-standard’; finally, it has become possible to inform a mother whether she carries the genetic ‘mutation’ responsible for DMD (and therefore has a 1 in 4 risk of having an affected child), or has a risk of ‘germline mosaicism’ (and therefore has a 1 in 20 risk of having an affected child). It is now highly unlikely that a family would have to face the option of termination, unaware of the disease status of the foetus. However, as noted in chapter one, there are still significant psychological issues associated with terminating a wanted pregnancy on the basis of foetal abnormality.

Increasing technological sophistication has radically changed the reproductive options available to families at risk of DMD. However, it is unlikely that technology is the only consideration in the reproductive decision-making process. The following chapter explores literature on the determinants of fertility; the motivations and considerations that form the reproductive decision-making process, in the general public and in families affected by DMD.

# Chapter Three

## Reproductive Behaviour: A review of the literature

### Introduction

The aim of this chapter is to address the literature on the key contextual and subjective aspects of reproductive decision-making for families affected by Duchenne muscular dystrophy (DMD). It is possible that the genetic condition may not be the only consideration in reproductive decision-making and it was therefore deemed necessary to explore the determinants of fertility in families who are not faced with the additional consideration of genetic risk. Therefore, the chapter is divided into three sections. The first section explores the determinants of fertility in relation to having a child without a disability. The second section addresses the influence of perceptions of disability on fertility in the general population. The final section explores the literature on reproductive behaviour in families affected by DMD.

### 1. Determinants of fertility; theoretical contributions from demography, sociology and psychology

This section explores the development of key theoretical approaches to fertility, to address questions that lie at the very heart of our understanding of human reproduction: what motivates people to have or not have a child, and to have the number of children they have? (Miller 1992). Contributions from demography, sociology and psychology are used, to develop an integrated framework of the determinants of fertility<sup>9</sup>. Literature from the field of demography focuses on fertility at the population level, and utilises economic theories of cost-benefit

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<sup>9</sup> It should be noted that demography and medicine use two disparate definitions of 'fertility', which reflect two facets of the human experience of sexual reproduction. Medicine is concerned with the biological *processes* affecting an individual's capacity to conceive. In contrast, demography examines the *product* of fertility: population. My concern here is not with assessment of biological determinants of (in)fertility, nor with the measurement of global trends. However, it is important to note that my use of the term 'fertility' draws upon both notions. In this chapter I use 'fertility' to refer to the constituents of 'fertility behaviour', which include an individual's capacity to conceive, and the wider context that influences fertility trends.

analysis to explain the decline in fertility. Sociological theories address the benefit aspect of the cost-benefit analysis, by focusing on the social value of children. Psychological theories address individual motivation and lifestyle factors that influence reproductive decision-making.

### **1. 1 Demography and Transition Theory: aggregate analysis of changing populations**

Demography involves statistical analysis of population parameters and dynamics, and the causes and consequences of population structures and change (Marshall 1998). The focus of demography is the examination of changing facets of populations, such as mortality, fertility and migration, primarily through the collection and analysis of survey data and population censuses. Critics argue that survey data generates abstract data (Pfeffer 1999), and creates logistical and interpretative issues associated with both inputting values and assessing the relationship between listed values (Friedman *et al.* 1994, Schoen *et al.* 1999). Demography is criticised for being “all methods and no theory” (McNicoll 1980:441). However, until recently, fertility was the most studied topic in the discipline (Greehalgh 1996). The extensive collection and subsequent presentation of data provides substantial foundations for subsequent theoretical contributions on the determinants of fertility.

The production of demographic data enables recognition of the significant changes in fertility trends in the UK. Firstly, the average age of mothers at first pregnancy has risen. In 1977, women aged 25-29 were twice as likely to give birth as a women aged 30-34, whereas in 2007 women aged 30-34 had the highest fertility rate (ONS 2008). Secondly, demographic data demonstrates a decrease in average family size. In the 1960s, the average completed family size was 2.46 children, compared to 1.74 children today and the proportion of families with three or more children has fallen by almost half (ONS 2008). Lastly, the median birth interval has increased; in 1972 the second child was born 31 months after the first, compared to 35 months in 2007. The increase in birth interval between the second and third child is less marked; 39 months in 1972, compared to 40 months in 2007 (ONS 2008).



The recent decline in fertility in the UK reflects a broader trend in industrialised nations. Fertility decline in Western societies, during the late nineteenth and early twentieth centuries, was matched by substantial increases in the population size of many pre-industrialised, ex-colonial nations (Hirschman 1994). To explain such patterns, Thompson (1929) and later Nonestein (1945) developed the theory of fertility transition. Transition theory attributes the decline in fertility to “urbanisation, industrialisation, rising levels of living, popular education, and popular participation in political life” (Nonestein 1945:52).

Henry (1961) argued that Westernisation had enabled individuals to exert deliberate control over their own fertility. Henry (1961) presented the concept of “natural fertility” to refer to fertility controlled through social norms that prescribe, for example, the number of partners and frequency of coital activity. Henry (1961) proposed that “natural fertility” occurred in societies where people make no conscious attempts to limit their fertility. In contrast, “controlled fertility”, refers to the conscious parental limitation of fertility when desired family size had been reached. Henry (1961) also argued that fertility behaviour in Western cultures had shifted from “natural fertility” to “controlled fertility”.

Two key points emerge from demographic data on fertility. First, the gradual decline in fertility suggests that the provision of reproductive choice, for families affected by DMD, may have become a less pressing issue when newborn screening for DMD first became available, thirty years ago. Families are now more likely to have fewer children. However, the average birth interval is around three years and families receive a later clinical diagnosis of DMD, on average, 4.5 years after their child’s birth. Although less people are having large families, many of those who do continue family building remain unaware of their risk.

Secondly, the focus on fertility decline and transition theory in demography has resulted in micro-level descriptions of individual behaviour (Greenhalgh 1996). In demography, society is no longer viewed as “integrated and cohesive system”, but as an “atomistic collection of individuals” (Greenhalgh 1996:40); each endowed with the capacity to deliberately plan and control their own fertility (Pfeffer 1999).

The focus on the individual has had substantial implications for subsequent theoretical assessments of fertility.

## 1.2 Economic theories of fertility; assessing the cost of children

The prominence of economic development in transition theory, and the new-found focus on the individual, paved the way for the application of economic theories to fertility. Becker (1960) applied price theory to fertility. The economic theory of fertility classified children as “durable consumption and production goods” (Becker 1960:210); children, like any other material object, were thought to provide utility to the consumer. The determinants of fertility, therefore, were defined as “the relative cost of children versus other goods, the couples’ income, and their preference for children versus competing forms of consumption” (Mason 1997:444).

Subsequent reformulations of Becker’s (1960) microeconomic theory of fertility attempted to convey broader determinants of fertility. Easterlin (1975) argued for the inclusion of sociological variables, and proposed that facets of “natural fertility” were still applicable to Western democracies. Cultural beliefs, for example, “that sexual intercourse should be avoided while a mother is nursing” or practical considerations such as the “physical separation of partners due to such events as civil strife or seasonal migration for employment purposes” may still influence fertility behaviour (Easterlin 1975:56).

Although the approach taken by Easterlin (1975) lacked in-depth sociological theory, it provided some counterbalance to the dominant demographic theories of the time. Even when direct measures of “controlled fertility” could not be determined, patterns of sustained declines in fertility were often interpreted as conscious parental planning (Hirschman 1994). Despite recognition of sociological variables, economic theories maintained a monopolistic position in the explanation of fertility behaviour (Nauck 2007). Couples were “*assumed* to maximise utility” (Bagozzi 1978:302, emphasis in original) and *assumed* to consciously plan. The varying forms of economic theory detached the decision-making process from the

socio-cultural and political contexts within which reproductive decisions are made, and motivational aspects of fertility were entirely ignored (Price & Hawkins 2002).

### **1.3 The theory of the Value of Children; assessing the benefit of children**

During the 1970s, attention turned to why families in industrialised nations were still having children, since they had become an “economic liability” (Hoffman and Hoffman 1973:19). In an attempt to explore cross-cultural differences in fertility behaviour Hoffman and Hoffman (1973) developed the theory of the Value of Children (VOC) to explore the motivations for parenting. VOC complemented economic theories of fertility by addressing cultural factors and the subjective value of children (Nauck 2007). Whilst economic theory offered “fresh insights into neglected aspects of the demand for children” (Greenhalgh 1996:54) the value of children approach emphasised the supply side (Hoffman & Hoffman 1973).

Hoffman & Hoffman’s approach to the concept of ‘value’ was “anchored in psychological needs, tied to the social structure and subject to cultural variation” (Hoffman and Hoffman 1973:20), enabling consideration of both the personality of the individual and structures of the social environment (Buhler 2008). Through empirical studies, Hoffman and Hoffman (1973) showed that children satisfy a broad range of psychological and economic needs. Having children signifies adult status, expands the identity of the parents into a larger social entity and demonstrates the fulfilment of social norms. Parenthood may strengthen existing family ties and simplify parental access to supportive resources. Having children may also provide couples with the opportunity for new experiences, can expand their prestige and status, and may provide fun and stimulation.

Although the theory of the Value of Children emerged from the discipline of psychology, the incorporation of economic, social and cultural dimensions enhanced its interdisciplinary appeal. The theory of the Value of Children has continued to be influential throughout recent decades (Michaels and Goldberg 1989, Friedman *et al.* 1994, Nauck 2007). By focusing on the values, or benefits, parents hope to accrue from having a child, VOC provided a “substantial contribution to the

understanding of the processes of declining fertility and to explanations of why people in modern societies still want to have children” (Buhler 2008:570)

#### **1.4 The theory of the social value of children: assessing the social benefit of children**

A number of sociologists have re-conceptualised the theory of the value of children in relation to theories of social structure. Nauck (2007:616) proposed a revised version of the VOC approach, which “deduces VOC from a general social theory”. According to the theory of social production functions, human actors aim to maximise social esteem and physical well-being, by seeking social reinforcement and physical survival, in his or her social context. Social esteem and well-being are achieved through context-specific production factors. Production factors govern whether parenthood is an efficient strategy to achieve social esteem by determining the (positive) value of children.

Nauck (2007:617) argues that children help to improve parent’s physical well-being “if they actively contribute to household production and thus function as productive, not just consumptive goods” and by providing “physical and psychological stimulation”. Children may optimise parents self esteem indirectly, by intensifying existing relations and initiating new relations, or directly, through the creation of an intimate, life-long social relationship between parent and child (Nauck 2007).

Buhler (2008) uses theories of social networks, interpersonal exchange and social capital to address the structural value of children. Social capital refers to how individuals access, and utilise, resources embedded in social networks (Portes 1998, Lin 1999). The general determinants of fertility behaviour are identified in relation to interpersonal relationships between parents and children, and the extended family or local community perception of parenthood (Buhler 2008). A universal element of relationships is that they are created and maintained under the expectation of attaining either personal benefit (Coleman 1990), or mutual benefit (Buhler 2008).

Opportunities to access direct or indirect exchanges of “information, goods, services, emotions, affection or recognition” (Buhler 2008:573) are defined by

social networks. The location of an actor within a specific network defines opportunities, and interpersonal exchange focuses on individuals' intentions to profit from their activities, by creating and maintaining personal relationships which will provide access to social capital (Coleman 1990, Buhler 2008).

Buhler (2008) argues that social networks influence fertility behaviour by defining preferences and opportunities. However, having a child also changes parents' social networks:

“The child becomes a new and highly significant network member and it alters its parents' personal relationships and social environments. It affects the nature of the tie between mother and father, their relationships with relatives, friends, or neighbours, and changes the parents' status in the local community or society” (Buhler 2008:572)

Buhler (2008) suggests that by changing the parents' social networks, children also alter exchange relationships, which constitute the building blocks of the social network. Parents invest time and financial and emotional resources, in the expectation of eventually receiving love, support at old age, or material benefit from their children. The reaction of relatives or other members of the parents' social network, to the birth of a child, may initiate changes in the parents' social status and induce greater access to both family and social support.

Social capital emerges as an “unintended bi-product of existing relationships and group memberships or as an outcome of purposeful investments in existing or new relationships” (Buhler 2008:575). In the structural approach to the value of children, value is defined as direct or indirect consequences of having children, which alter interpersonal exchange relationships and social networks.

Theories of social production functions, social networks, interpersonal exchange and social capital all focus on the primacy of social interaction in creating social structure, thereby providing an interesting and comprehensive sociological approach to the socially constructed determinants of fertility. However, sociological theories do not address the subjective mechanisms through which costs and benefits are perceived, nor how the group values relate to individual differences in attitudes, intentions, or personality (von der Lippe 2006).

## **1.5 Psychological determinants of fertility; personality traits and the influence of individual experience**

Fertility behaviour reflects the salience of individual agency and purposeful human action; theoretical elements which are lost in demography's aggregate analysis of numbers (Schoen *et al.* 1999), and reviewed as a cumulative product by sociological theories. In response to the methodological limitations of demographic research, psychologists have sought to move beyond "merely listing the values and costs of having children, to incorporating intentions and attitudes into parenthood decision-making" (Purewal & van der Akker 2007:79).

Three core concepts of fertility behaviour lie at the heart of psychological analysis of fertility: motivations, desires and intentions. Miller (1992) argues that motivations are antecedent to desires, and in turn desires are antecedent to intentions. According to Miller (1992:281), fertility motivation emerges from "biologically based human traits" that "govern the human tendency to form attachments and perform care-taking". Miller's (1992) study revealed that two personality traits affected fertility motivation; nurturance and affiliation. Two more recent studies have presented similar findings. Langdridge *et al.* (2005) found that the most popular reasons for wanting a child were to "give love" and "receive love", to "become a family" and to "have a child that is biologically related to both members of the dyad". Three related themes emerged from Purewal & van der Akker's (2007) qualitative study on the meaning of parenting: "parenting as selfless", the "fulfilling role of parenting", and the "importance of genetic ties".

Miller (1992) argues that when motivations to have a child are activated, they are experienced as the desire for a child, or for a specific number of children. Desires do not lead directly to action, until they are converted, through personal commitment to act, into intentions. Only when the situational conditions are conducive, and the intentions reach sufficient intensity, is intention translated into behaviour (Miller 1992).

In their theory of reasoned action, Fishbein and Azjen (1975) regard intention as the principal predictor of behaviour; the stronger the intention, the more likely the

intention will be translated into action. Ajzen (1985:29-30) developed a more complex assessment of intentions in the theory of planned behaviour, by redefining intention as “intention to try” and performance as “attempt to perform”. To emphasise the mediating affect of context and circumstance, Azjen (1985) introduced a number of intervening variables between intention and behaviour, including the strength of the attempt to perform and the degree of control that the individual has over their behaviour.

Control is a central aspect in the psychological approach to fertility behaviour. Motivation, desire and intention to have a(nother) child may be apparent, but the transformation of intention into behaviour may not be possible due to constraints, which are out of the individual’s control. Constraints may be internal (e.g. infertility) or external (e.g. absence of a willing partner) (Schoen *et al.* 1999).

Schoen *et al.* (1999) argue for the inclusion of the ‘life course perspective’ in the assessments of external constraints. Significant life events, such as “the formation and dissolution of sexual relationships and entries into and exits from both education and employment”, generate external constraints on fertility behaviour (Schoen *et al.* 1999:791). Miller and Pasta (1995) present three categories of constraints: spouses intentions (whether the couple’s intentions concur): life cycle factors (such as age, marital duration, parity, gender and age of previous children), and changes related specifically to reproduction (such as unplanned pregnancy and divorce).

The combination of personality traits and life events provides a useful addition to social and economic theories of fertility. Although every individual is part of a social network and an economic and cultural context, analysis of an individual’s subjective experience of specific life events helps to elucidate the differences between individuals located in the same context.

## **1.6 Summary of the determinants of fertility**

The common thread between theories of the determinants of fertility is the cost/benefit analysis, whereby people weigh up the advantages and disadvantages of

having children in order to reach a reproductive decision. Using an integrated framework, consolidating the most salient aspects of theories from each discipline, an individual “evaluates the economic and psychological costs and benefits of children, taking into account personal factors and social context to reach a subjective opinion regarding a preference toward having a(nother) child” (Lawson 2001:74). Fertility behaviour therefore results from complex interactions between biological forces, ideology, cultural representations of gender roles, normative expectations presented by family, friends and role models (Sonsenstein *et al.* 1997) as well as economic considerations, personality traits and life experience.

## **2. Disability and the determinants of fertility**

This section addresses the determinants of fertility in relation to disability. Perception of the type and magnitude of the costs and rewards of parenting a child with a disability may differ from those perceived in relation to parenting a child with no disability. There may be “economic factors”, such as medical care and equipment, and “psychological costs”, such as “higher rates of marital dissolution elevated levels of maternal depression, restricted mobility and poor social relationships” Lawson (2001:74). Two studies were identified (Lawson 2001 and 2006), which used an integrated framework of economic, sociological and psychological theories, to explore the perceived costs and rewards of parenting a child with or without a disability.

In the first study, Lawson (2001) conducted a survey of 165 women to examine the perceptions of raising a child with Down’s syndrome, spina bifida and cystic fibrosis and attitudes toward using prenatal testing. Over half of the participants (n=92) had personal experience with disability. However, the degree of experience was not noted (i.e. whether participants knew of a person with a disability, had a relative or child with a disability). In addition, despite differences between Down’s syndrome, spina bifida and cystic fibrosis, perceptions of the three different conditions were amalgamated.



The findings showed that the dominant view of raising a child with a disability (compared to raising a child without a disability) was negative, especially in relation to three key factors: 67.9% (n=112) mentioned financial expense, 66.7% (n=110) mentioned time commitment and 65.5% (n=108) mentioned the emotional toll of raising a child with a disability. The author notes “that these three factors were generated with such a high frequency suggests that both psychological and economic concerns are relevant when women are evaluating the potential experience of parenting a disabled child” (Lawson 2001:79). However, it should be noted that the financial concerns may have been less prevalent in a sample from the United Kingdom, due to the nationalised provision of free health care.

In the second study, Lawson (2006) conducted a survey of 335 university employees to explore how perceptions of parenting a child with Down’s syndrome differed from attitudes toward parenting a child with muscular dystrophy, and toward parenting a child with no disability. The type of muscular dystrophy was not explicitly noted. However, the vignette provided to participants, described a condition that appeared to be DMD: “your child will gradually lose muscle use [...] the muscle weakness will making walking very difficult and a wheelchair will likely be necessary” (Lawson 2006:47). A large proportion of participants indicated that they had no personal familiarity with someone with either mental disabilities (61.4%) or physical disabilities (49.3%).

The study measured a number of factors relating to the perception of parenting a child with a disability; personal enrichment, continuity of self and family, social isolation, commitment, and tangible instrumental costs. All factors were found to be significantly associated with less positive perceptions of parenting a child with a disability. However, loss of anticipated parenting rewards appeared to have a greater influence than expectation of heightened costs. The findings suggested that perceptions of parenting a child with Down’s syndrome were significantly less positive than those of parenting a child with no disability ( $p < 0.001$ ), and marginally less positive than that of parenting a child with muscular dystrophy ( $p = 0.062$ ). The perception of parenting a child with muscular dystrophy was also significantly less positive than those of parenting a non-disabled child ( $p < 0.001$ ).

Both of Lawson's studies (2001, 2006) reviewed perceptions of disability in relation to perceived willingness to consider termination. Lawson (2001, 2006) concluded that perceptions of the costs and rewards associated with raising a child with a disability are predictive of stated willingness to undertake prenatal testing and termination. Both studies reviewed hypothetical decision-making. However, the studies provide interesting insight into the general perception of the costs and rewards associated with parenting a child with a disability.

### **3. Reproductive behaviour in families at-risk of Duchenne muscular dystrophy**

Numerous studies have tried to assess reproductive behaviour in families at-risk of genetic disorders, who already have a child, or relative, with a disability. Studies have focused on different genetic conditions and the findings are varied and often conflicting. It is often difficult to ascertain whether the different findings are due to different study designs, different settings, or different conditions. A number of studies have shown that the severity of the condition affects reproductive decision-making (Verp *et al.* 1988 Evans *et al.* 1993, Eggers & Zatz 1998, Lerman *et al.* 2002). Therefore, this section only addresses literature on reproductive decision-making in families affected by Duchenne muscular dystrophy<sup>10</sup>.

A total of ten studies were identified which addressed varying aspects of reproductive decision-making in families affected by DMD. The studies are explored in three sections. First, literature on reproductive behaviour in DMD families after a later clinical diagnosis is explored. Second, literature on reproductive behaviour in families whose sons had been diagnosed through newborn screening is addressed. Third, literature on the way women make sense of their carrier risk of DMD is explored. Although the final section does not directly address reproductive behaviour, the studies highlight the difficulty individuals experienced in retaining complex mathematical probabilities of risk.

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<sup>10</sup> Although some studies include families at-risk of other genetic conditions (e.g. Beeson & Golbus 1985, Kay & Kingston 2002), when possible, data is presented only from families affected by DMD.

### 3.1 Reproductive behaviour after later clinical diagnosis of DMD

Six studies were identified that explored reproductive behaviour in families affected by DMD, after receiving a later clinical diagnosis: Hutton & Thompson (1976), Beeson and Golbus (1985), Cole *et al.* (1988), Parsons and Atkinson (1993), Eggers *et al.* (1999) and Kay and Kingston (2002). The studies are addressed in chronological order, to explore the reproductive behaviour as different testing procedures became available.

Hutton & Thompson (1976) study was published after creatine kinase testing had been introduced to assess mothers' carrier risks. Hutton and Thompson address families' attitudes towards family planning after a later clinical diagnosis and assess whether "reproductive performance correlated inversely with their genetic risk" (Hutton & Thompson 1976:749). Questionnaires were sent to 336 female relatives of boys with DMD, one year after genetic counselling, to assess their future family planning.

All women invited to participate in the study were at reproductive age and had already had their carrier status assessed using creatine kinase and pedigree analysis. Women were divided into four categories of carrier risk: "high", "doubtful", "moderate" or "low". Although 256/336 (76%) responded, only 105 (31%) were included. The rest were excluded due to being "single, separated, divorced, infertile, sterile or family complete", or because they had failed to complete the whole questionnaire (Hutton & Thompson 1976:749).

A total of 24 women suggested that they would like one or more subsequent pregnancies; 58% (n=14) of whom had been informed that they were low risk. None of the 42 high risk carriers expressed a desire to have subsequent pregnancies. The findings showed that 81% (n=34) of high risk carriers indicated that they were deterred from having subsequent pregnancies as a result of their carrier risk. Of those who had been deterred, 55% (n=19) had sought sterilisation. In contrast, among the women who had been informed that they had a low risk of having an affected child, only one indicated that she was deterred from having subsequent pregnancies by her genetic risk.

Although the study reviewed future, and therefore potentially hypothetical decisions, the larger numbers of high risk carriers undergoing sterilisation suggests that families at this time were keen to avoid reproducing altogether. Families described their family planning in relation to their carrier risk. Hutton & Thompson conclude that “the decision by the majority of proven carriers to prevent the birth of further male offspring was reflected in the recent decline in the frequency of a known family history of DMD among newly ascertained cases”.

Beeson and Golbus (1985) reviewed reproductive behaviour in 26 families at-risk of X-linked conditions; 11 of whom were at-risk of DMD. Details were not provided on carrier testing techniques. However, it was noted that all families were “high-risk” (Beeson & Golbus 1985:108). Families were offered amniocentesis in subsequent pregnancies.

Beeson and Golbus (1985) proposed that people at risk of DMD often did not consider themselves to be engaged in decision-making as only one course of action appeared tenable. The authors found that only 3 of 11 couples, at risk of DMD, were willing to risk the birth of a child affected by DMD; all three of whom who had no exposure to the later stages of the condition. For those who had lived with muscular dystrophy, the experience of caring for an affected child appeared to increase motivation to use prenatal testing and termination.

The study by Cole *et al.* (1988) reports on the outcome of 53 pregnancies after the use of DNA restriction length polymorphisms (RFLPs) was introduced into clinical practice. The 53 pregnancies occurred in 34 women at risk of DMD and 6 women at risk of Becker muscular dystrophy (BMD). No differentiation was made between reproductive decision-making in families affected by the two different conditions, perhaps suggesting that the severity of the condition was not deemed an important consideration. After carrier tests were carried out, families chose not to test 8 pregnancies; one was terminated, 4 miscarried and 3 mothers “no longer wanted chorionic villus sampling following reduction in their carrier risk estimates” (Cole *et al.* 1988:265).

After carrier tests had been performed 45 (85%) chose to have chorionic villus sampling (CVS) and 25 male foetuses were identified. The study highlights the complexity of using restriction fragment length polymorphisms (RFLPs); DNA analysis had to be conducted on numerous family members in order to provide mothers with an estimated risk of carrying an affected child. Foetal risk estimates were calculated based on the sex of the foetus and the risk of a male foetus carrying either a high or low risk maternal chromosome. The authors defined a high risk foetus as 6-99%.

DNA analysis was not possible in two pregnancies; both of which were terminated. Fourteen male foetuses were identified as high risk; of which 11 were terminated. Three male foetuses identified in high risk women were carried to term and one was diagnosed with DMD. Nine male foetuses were identified in low risk mothers, eight of which were carried to term: the remaining pregnancy miscarried. The authors conclude that "DNA analysis of at-risk pregnancies seems to be an acceptable and effective form of diagnosis, providing a means of preventing the births of boys affected with this disease" (Cole *et al.* 1988:265). The study by Cole and colleagues highlights the complexity of using RFLPs for foetal diagnosis; it is highly likely that a number of the 13 terminated foetuses were not affected by either DMD or BMD.

Parsons and Atkinson (1993) report findings from in-depth interviews with 54 women at-risk of DMD; 22 mothers, whose sons had received a later clinical diagnosis and 32 sisters of affected boys. A total of 113 pregnancies had occurred in the 54 women. The study focused on reproductive decision-making and outcomes of 40 pregnancies, occurring in 22 risk-aware women. Details of specific tests used to assess genetic risk were not included. However, it is clear that the majority of women had been provided with estimates of their carrier risk and reproductive risk; at the time it was only possible to inform a few mothers that they were definitely carriers.

Parsons and Atkinson (1993) divide women into three categories: risk takers (women who consistently chose not to have PND), risk refusers (women who consistently, either tested and terminated male pregnancies or terminated pregnancies prior to PND) and risk modifiers (women whose reproductive decisions

were not consistent in all subsequent pregnancies). Nineteen (48%) pregnancies were untested, resulting in 2 affected males, 8 unaffected males and 9 females. Sixteen pregnancies were tested resulting in 5 terminations of males, one miscarriage and the births of 10 females. Five further pregnancies were terminated prior to PND.

The authors note that risk refusers generally had a higher carrier risk (mean risk of 67%), compared to risk takers (mean risk of 23%), suggesting families behaviour reflected an important association between carrier risk and reproductive behaviour. However, it should be noted that not all risk refusers were high risk carriers and not all risk takers were low risk. Parsons and Atkinson (1993) highlight the complexity of factors influencing reproductive decision-making; namely the desire to have children regardless of the risks, experience of living with an affected boy, attitudes towards abortion and prior experience of late terminations.

Eggers *et al.* (1999) review the impact of genetic counselling in 263 young women at-risk of DMD; 64% sisters and 36% cousins, aunts or nieces of affected males. Reproductive outcomes and plans, requests for DNA tests for carrier detection and prenatal diagnosis were analysed according to genetic risk, comprehension of genetic counselling issues, family and personal history, socio-educational level and opinion on abortion.

Genetic risk was estimated using pedigree analysis, creatine kinase levels and (undefined) DNA tests. Women's risk was classified as very low (1-4%), low (5-9%), intermediate (10-24%) or high (>25%). However, the authors note that the allocated risk categories did "not reflect counselees' opinion about the magnitude of the risk" (Eggers *et al.* 1999:448). Genetic counselling included at least one session when the aetiology, prognosis and management of the condition and the counselees' genetic risk, carrier detection and options for prenatal and preclinical diagnosis were discussed. Reproductive plans were simplistically classified as "wants children" or "doesn't want children" depending on whether participants expressed a hypothetical wish for biological children. Requests for both carrier tests and prenatal diagnosis tests were analysed together, despite potentially significant differences in influence on reproductive decision-making.

Findings showed that 65% of women had not had children at the time of the study. The mean number of children in those who already had children was less than mean observed in general population, with comparable age and socio-economic status. However, it was not clear whether women in the study were refraining from having more children or merely delaying reproduction. Genetic risk magnitude was not found to have a significant influence on reproductive plans or outcome:

“Women with a greater reproductive risk >25% did not reproduce significantly less after genetic counselling, did not request DNA tests more frequently, and did not express fewer reproductive plans than those with genetic risks ( $\leq 24\%$ ), even considering only those who showed a good comprehension of information received during genetic counselling” (Eggers *et al.* 1999:448)

There was no difference between sisters, aunts, cousins and nieces despite significantly more sisters having intermediate to high risk ( $p < 0.01$ ).

The only factor found to be significantly associated with reduction in the number of subsequent pregnancies was good comprehension of genetic counselling issues, which was significantly correlated with socio-educational levels. DNA tests were more frequently requested by counselees from higher socio-economic backgrounds and with more than one DMD relative.

Kay and Kingston (2002) conducted in depth interviews with 14 known carriers of X-linked conditions; nine of whom were carriers of DMD. None of the 14 women had affected children of their own, but all had either an affected sibling or distant male relative. All but one of the women in the study intended to make, or had made decisions, to avoid having a child affected by the condition by opting for prenatal testing and termination if the foetus was found to be affected. The one woman, who would not consider termination of an affected pregnancy, had no personal experience of her relative with DMD.

The seven women who had grown up with brother(s) affected by DMD were certain that they could not knowingly allow a boy with DMD to be born. In contrast, women with less direct, or no, personal experience of the affected relative appeared less sure about their intentions to avoid having an affected child. The authors conclude that “it seems that prospective decisions made to terminate an affected

baby were easier in a sense for women 'with personal experience' since they saw no alternative." (Kay & Kingston 2002:176). Kay and Kingston's (2002) study reflected the findings of Beeson and Golbus (1985); individuals at-risk of DMD were more likely to test and terminate pregnancies if they had personal experience of the condition.

### **3.2 Reproductive behaviour after newborn screening diagnosis of DMD**

There is a significant paucity of studies that address reproductive decision-making after newborn screening for DMD. Only two studies were identified: Hildes *et al.* (1993) and Parsons *et al.* (2002). The studies are addressed in chronological order.

Hildes *et al.* (1993) report on reproductive decision-making in families after a family member had been diagnosed with DMD through newborn screening, in Manitoba, Canada. Separate questionnaires were sent to both parents of 8 boys, two high probability carriers aunts and one high probability carrier sister (n=17), three to six years after the diagnosis of the proband. Data were collected on demographics, knowledge of DMD, reproductive outcome and attitude to prenatal diagnosis and newborn screening for DMD. Responses from fathers were excluded due to a low response rate so results were analysed from questionnaires returned from 10 at-risk women and interview data from a mother who had not completed the questionnaire.

Results showed that 7 of the 8 families had no family history of DMD; in one family the maternal uncle of the proband had died from the condition. Carrier status was defined as high risk (>95%), low risk (<5%) or obligate. All respondents were aware that the condition was severe, fatal and inheritable. However, only 7 of the 11 had correct recall of their carrier status. Six of the 11 women or their partners had undergone elective sterilisation; in 4 of the 6 cases sterilisation had occurred prior to genetic counselling and "seemed largely based on previous perceptions of ideal family size and maternal age" (Hildes *et al.* 1993:671). Seven pregnancies had occurred in 6 women after the diagnosis of the proband, of which 6 were in women who had been defined as high risk (>95%) carriers. Prenatal testing was utilised in only two pregnancies, both of which were found to be female. The remaining



untested pregnancies resulted in the birth of two females, one unaffected male and two affected males.

Hildes *et al.* (1993) note that the previous reproductive history combined with older mean maternal age may have had an impact on the low uptake of prenatal testing. However, the authors also suggest that the lack of clinical symptoms in newborn boys may account for the low uptake; four requests for PND were made by families whose sons had been clinically diagnosed in the same period. Hildes *et al.* (1993:672) conclude that “identification of DMD males in population screening programmes may not be an effective way of decreasing the number of repeat cases of DMD within families or the overall population frequency of DMD”.

There are three key drawbacks to the study by Hildes *et al.* (1993). First, the study appeared to focus on whether newborn screening reduced the incidence of DMD, rather than how it influenced the reproductive behaviour of families affected by DMD. Second, the sample size was extremely small, and as the authors themselves note “the amount of social chaos in the lives of the four high risk women who did not request prenatal diagnosis seems disproportionately high for our small number of index cases”. [...] The socially disrupted lives of these four women appear to be one important factor in their reproductive decision-making.” Lastly, it is possible that more recent developments in carrier testing techniques may influence families’ response to newborn screening.

The study by Parsons *et al.* (2002) study reviewed reproductive behaviour in 20 families who had received a diagnosis of DMD through the newborn screening programme in Wales, and 16 who had received a later clinical diagnosis. Greater sophistication of genetic testing techniques used at this time meant that the majority of mothers were informed whether or not they were carriers, rather than provided with complicated risk assessments.

The Institute of Medical Genetics was informed about 27 subsequent pregnancies in the 20 newborn screening families. Four pregnancies were terminated prior to testing; the relationship between the diagnosis and the decision to terminate was unknown. A total of 19 (83%) of pregnancies “were tested or identified as being at

minimal risk” (i.e. 1 in 20 germline mosaicism risk). The outcome of the pregnancies was 7 unaffected boys, 7 girls, termination of 4 fetuses affected by DMD and a further termination of a foetus with a chromosomal abnormality. Of the 16 families in the later clinically diagnosed cohort, 10 had subsequent pregnancies prior to the diagnosis of the first affected child. The outcome of the 10 pregnancies was 5 unaffected boys and 5 girls.

Parsons *et al.* (2002) report that reproductive behaviour had changed in 80% (n=16) of families who had received newborn screening (n=16). Fifteen families stated that they had wanted more children but, after the diagnosis, 4 had decided against another pregnancy and 11 had delayed. The mean birth interval in the 20 families between the first and second child was 41 months, compared to 21 months in the general population.

The authors conclude that “most families modified their reproductive decisions and used prenatal testing”. In addition, the majority of those who received either a later clinical diagnosis or a diagnosis through newborn screening expressed a favourable attitude towards newborn screening “on the grounds of gaining time to prepare emotionally and practically”. Families who received a later clinical diagnosis “perceived the advantage of avoiding diagnostic delay and expressed regret about misunderstanding their sons’ early symptoms”.

### **3.3 Making sense of being ‘at-risk’ of DMD**

Two studies were identified that focused on the way women at-risk of DMD make sense of their risk: Parsons and Atkinson (1992), Parsons and Clarke (1993).

Parsons and Atkinson (1992) report the findings of interviews conducted with 44 women (22 mothers and 32 daughters) in families affected by DMD. The study focused on women’s constructions of genetic risk. The authors conclude that women at risk of DMD turned probabilistic assessments of risk into definitive, descriptive categories. Although the vocabulary of percentages or ratios was still employed, women tended to use a simplistic format, such as fifty-fifty, or ‘high risk’ or ‘low risk’; “the probabilistic was expressed as a matter of certainty” (Parsons & Atkinson 1992: 454). There was also evidence to suggest that for

women at risk of DMD, their genetic risks garnered differing degrees of relevance, depending “critical junctures in the life course” (Parsons & Atkinson 1992: 454).

Parsons and Clarke (1993) report a study of 48 women (16 mothers and 32 daughters representing 28 families) in families affected by DMD. Women in the study had been provided with information regarding their carrier risk and their reproductive risk. Carrier risk was generally assessed using a Bayesian calculation of linkage and creatine kinase results; few families were provided with an exact assessment of their risk (i.e. that they were carriers and had a 1 in 4 risk in subsequent pregnancies or that they had a germline mosaicism risk of 1 in 20).

Parsons and Clarke’s (1993) study found that a number of women, when quoting their mathematical risk, confused reproductive risks with their carrier risks. In addition, there was “evidence that several of the women did not retain their risk in a mathematical form but had translated it into a descriptive category which resolved their risk into greater certainty” (Parsons and Clarke 1993: 562). The findings suggest that providing women with a less complex assessment of their risk may facilitate understanding of risk awareness.

### **3.4 Summary of literature on genetic risk and reproductive behaviour in families affected by DMD**

The ten studies addressing the assessment of carrier risk information and/or reproductive behaviour provide a useful starting point for this study. Although the number of studies is relatively low, a number of salient points emerged. Firstly, increasingly sophisticated diagnostic and carrier testing techniques potentially reduced the number of fetuses terminated. Prior to genetic analysis, many families who were informed of being at high risk of having a child with DMD refrained from family building. After the introduction of genetic testing techniques, families often continued family building, using prenatal testing.

Cole *et al.*’s (1988) study demonstrated that when the only genetic test available to families was RFLPs, the majority of families chose to terminate high risk fetuses; many of which may not have been affected. Although the study by Cole *et al.*

(1988) included a similar number of families (n=53) as Parsons and Atkinson's (1993) study (n=40), the uptake of prenatal testing was considerably lower in the latter study; 85% compared to 52%. In addition, the number of terminations was considerably lower in the latter study (13 compared to 5).

The studies did not report a uniform response to carrier risk. Hutton & Thompson (1976), Cole *et al.* (1988) and Parsons and Atkinson (1993) suggest women are either deterred from reproduction or choose to use prenatal testing in subsequent pregnancies. However, Eggers *et al.* (1999) and Hildes *et al.* (1993) report no association between carrier risk and reproductive behaviour. Beeson and Golbus (1985) and Kay and Kingston (2002) argue that experience of the condition has a notable impact on reproductive behaviour; mothers with experience of DMD were more likely to avoid the risk of having an affected boy.

Parsons and Atkinson (1993) and Parsons and Clarke (1993) highlight mothers' difficulty of making sense of complex assessments of risk, particularly in defining the difference between carrier risk and reproductive risk. Risk was found to be relevant at different points in women's lives. Probabilities were redefined as certainties; families often perceived risk to be either high or low. It is possible that subsequent developments in carrier testing techniques have reduced the degree of confusion resulting from complex assessments of carrier risk and reproductive risks.

Only two studies addressed reproductive behaviour after diagnosis of DMD through newborn screening. Hildes *et al.* (1993) and Parsons *et al.* (2002) reached considerably different conclusions. The study by Hildes *et al.* (1993) showed a limited uptake of prenatal testing in families identified through newborn screening, compared to families who had received a later clinical diagnosis. However, the study size was small. Parsons *et al.* (2002) concluded that newborn screening had a significant influence on reproductive behaviour, with the majority of families choosing to either cease family building, delay subsequent pregnancies and/or test subsequent pregnancies.

The studies explored in this chapter provide a useful background to address how families, at risk of DMD, have previously made sense of their carrier and

reproductive risks to inform reproductive behaviour. However, increasingly sophisticated technologies have had considerable impact on the capacity to provide families with a more accurate assessment of their carrier risk; few of the studies reviewed were conducted after these technologies became available. In addition, only two studies have been published on reproductive behaviour following a newborn screening diagnosis and they present conflicting findings. The rapid acceleration of technological capacity calls for a contemporary assessment of the implications of carrier testing techniques, diagnostic pathway and reproductive options for reproductive behaviour in families affected by DMD.

# Chapter Four

## Methodology

### Introduction

This chapter provides the rationale for using both quantitative and qualitative methods to answer the following research question:

**What are the implications of newborn screening for Duchenne Muscular Dystrophy for reproductive decision making?**

The chapter is divided into five sections. First, the background and context of the study, the research sites and the sample population are addressed. Second, the rationale for using mixed methods is provided. Third, the practicalities of collecting and analysing quantitative data are addressed. Fourth, the practicalities of the collecting and analysing qualitative data are addressed. Lastly, the theoretical approach to data analysis is explored. Disparities between the positivist (quantitative) and interpretivist (qualitative) paradigms are addressed, followed by an exploration of the practical and conceptual difficulties and advantages of combining methods.

### 1. Background and context of the study

The purpose of exploring the implications of newborn screening for Duchenne muscular dystrophy (DMD) for reproductive decision-making was addressed in Chapters One, Two and Three. In summary, newborn screening policies were initially limited to testing for treatable conditions. However, increasingly sophisticated technologies enabled the detection of increasing numbers of untreatable genetic conditions. Newborn screening programmes have rapidly expanded and there is now little consensus on the number and type of conditions that programmes should include. The primary justifications for screening for untreatable conditions are to avoid the diagnostic delay (Kemper & Wake 2007); provide access to supportive, educational and therapeutic services (Bailey *et al.*

2005); and to provide information on genetic risk to inform reproductive decision-making (Bailey *et al.* 2005, Pollitt 2006, Kemper & Wake 2007).

However, there is a paucity of research addressing any of the proposed benefits of newborn screening; data on implications for reproductive decision making are limited and conflicting. Thus, a comparative mixed methods design was utilised. The first part of the study involved a review of medical files for the collection and analysis of quantitative data on reproductive behaviour. The second part of the study involved in-depth qualitative interviews with a subset of families, from the sample used for quantitative section. The aim of collecting qualitative data was to explore families' experience of reproductive decision-making. Details of the research sites, the mixed method design and the quantitative and qualitative aspects of the study are provided in subsequent sections.

### **1.1 The research sites: Wales and the west of Scotland**

In most of the United Kingdom, DMD is diagnosed clinically when the child is on average 4.5 years old (range: 3 months to 8.5 years) (Appleton & Nicolaides 1995, Bushby *et al.* 1999). However, a newborn screening programme for the untreatable condition DMD was implemented in Wales in 1990. The programme has been continuously monitored and reviewed, providing a unique opportunity to utilise a significant body of data, to assess the implications of newborn screening (NBS) for reproductive decision-making.

Funding was limited and therefore only one region in the UK could be selected to provide comparative analysis of families who had received a later clinical diagnosis (LCD). The west of Scotland was an obvious candidate. The west of Scotland Regional Genetics Centre in Glasgow provides services for Duchenne families living in Argyll and Clyde, Ayrshire and Arran, Forth Valley, Greater Glasgow, Highland and Lanarkshire. The Institute of Medical Genetics in Cardiff provides services for Duchenne families throughout Wales. The population size between the areas is very similar; 2,703,876 in the west of Scotland (General Register Office for Scotland 2005) and 2,958,600 in Wales (Office for National Statistics 2005). Both

areas have a similar urban/rural divide with a concentration of people living in the major cities of Glasgow and Cardiff.

## **1.2 Sample population**

One of the main justifications for implementing the newborn screening programme in Wales was to ensure that families received information on their reproductive risk, prior to having subsequent pregnancies. Obviously the provision of reproductive risk information is aimed at families who are not already aware of their risk. Some families have an affected relative and are therefore already aware of their risk, prior to having an affected child of their own. However, there is a high rate of new mutations in the dystrophin gene, which is thought to be related to the particularly large size of the gene. Approximately one third of cases are a result of a new mutation and therefore families are unaware of their risk of the condition until their child is diagnosed. In addition, occasionally mothers are unaware of having a family history of DMD; affected relatives may not have been alive in the mothers' lifetime, or family communication with a distant relative may have been minimal.

In order to address the proposed benefit of providing families with an earlier awareness of their risk through newborn screening, it was essential to ensure that families included in the study were not already aware of a family history of the condition. Families were therefore divided into two categories: those with a known family history of the condition and those for whom the diagnosis was a new and unexpected event. Any family who was aware of the condition in family was aware, to some degree, of their risk in subsequent pregnancies prior to the diagnosis and were therefore excluded from analysis.

The newborn screening programme for DMD began in Wales in 1990 and data collection took place between 2006 and 2007. The study population for the quantitative section of the study was therefore families:

- With a child affected by Duchenne muscular dystrophy
- Who had no known family history of the condition



- Who had received a diagnosis between 1990 and 2006, either through newborn screening in Wales or a later clinical diagnoses in the west of Scotland

The sample for the qualitative aspect of the study was drawn from the study population used for the quantitative aspect of the study.

Thirty-four families in Wales, who had no known family history of DMD, had their sons diagnosed through newborn screening between 1990 and 2006. Forty-three families in west Scotland with no known family history of DMD were identified as having had their sons diagnosed clinically with DMD between 1990 and 2006. The average 4.5 year delay in making a clinical diagnosis means it is quite possible that some cases born since 2000 have not yet been diagnosed in the west of Scotland. It is also possible that some cases may not have been diagnosed in Wales, due to parents opting out of newborn screening, or receiving a false-negative diagnosis.

## **2. Using mixed methods to address the research question**

The aim of this section is to describe the rationale for using a mixed methods approach, as well as a description of the typology of mixed method used for this study.

### **2.1 Rationale for using mixed methods to address the research question**

The selection of a particular research method (or methods) depends on finding the most appropriate method for answering the research question. This study required assessment of two factors; reproductive outcomes and reproductive decision-making. In simplistic terms: what is happening and why is it happening? Therefore mixed methods were chosen as an appropriate approach for this study.

The term “mixed methods” has been used to describe many different types of methodologies, from using two or more quantitative methods, two or more qualitative methods, or the use of both quantitative and qualitative methods. Around 40 mixed method designs have been reported in the literature (Teddlie &

Tashakkori 2003), with four major purposes or rationales: “enhanced validity and credibility”; “greater comprehensiveness of findings”; “more insightful understandings”; and “increased value consciousness and diversity” (Greene *et al.* 2001:30).

This study used both quantitative and qualitative methods. Quantitative methods were used to address and outline the overall reproductive ‘picture’: the number of children in each family/cohort, whether the affected boy had been diagnosed prior to subsequent pregnancies, the provision and uptake of prenatal testing and the outcome of each pregnancy. Qualitative methods were used to explore the decision-making behind the outcomes through an exploration of the factors families felt had influenced their reproductive decision-making. Factors were explored that could not be addressed through quantitative data, such as contextual factors (e.g. change of partner, infertility issues etc), and psycho-social responses to the diagnosis (e.g. perception of risk, view of disability etc). The rationale for using mixed methods in this study was therefore to provide more insightful understanding.

### ***2.1.1 Exploring the ‘patient voice’ through qualitative methods***

An additional advantage of using qualitative methods is that it offers the potential to explore the patient voice. There is growing recognition of the importance of exploring patients’ experiences of health services. ‘Health’ is increasingly recognised as not just the absence of disease. A person with cancer, for example, is also a person with other priorities and a particular approach to life; each of us may respond quite differently to the diagnosis. In addition, technological capacity is leading to the implementation of healthcare programmes that may not provide families with medical benefit. To ensure that proposed “lifestyle” benefits of providing information, choice and support are reflected in practice, it is imperative to explore families’ experiences of such health services.

In recent decades there has been a growing call for greater public participation in health policy, in line with democratic ideals (Rowe & Frewer 2000). Increasingly complex decision-making processes require a more informed policy process, to assess how individuals define, interpret and experience health services. In academic

fields, the drive for research to inform policy has led to an increasing emphasis on employing an appropriate mix of methods, to address the complex mix of social-economic, environmental, and political factors that affect health (Baum 1995, Brannen 2005).

Quantitative methods provide a way of addressing what people 'do' in response to health services. Qualitative methods provide a way of exploring the explanations people provide for what they 'do'. The patient voice is an essential resource to counteract the 'technological imperative'. This study explores families' experiences of two very different health policies. In addition to providing health policy decision-makers with evidence of the implications of their policies, this study provided a platform from which families could communicate their experiences of the diagnostic procedure and subsequent reproductive decision-making.

## **2.2 Mixed method design**

There are a number of mixed method typologies that define whether priority is given to quantitative or qualitative methods; whether data is collected simultaneously or sequentially; and whether the methods are integrated during data collection, analysis or interpretation (Teddlie & Tashakkori 2003). These issues are explored in the following paragraphs. Detailed description of the quantitative and qualitative procedures used is provided in subsequent sections.

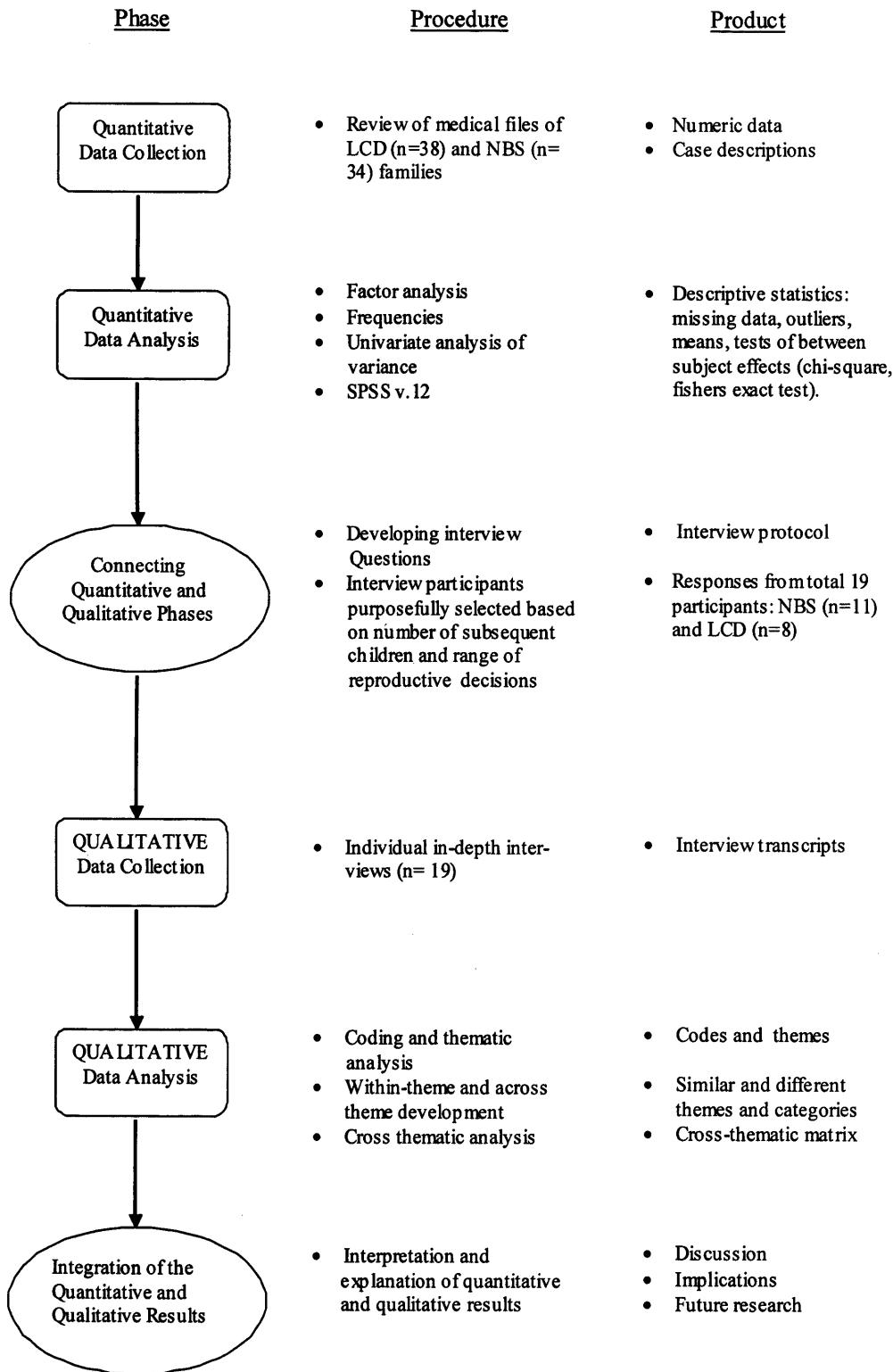
Often mixed methods grant priority to either the quantitative or qualitative approach (Teddlie & Tashakkori 2003). In this study, the quantitative data collection aimed to provide an outline of reproductive outcomes, which would inform the qualitative data collection process. Before data collection and analysis commenced, it was thought that the quantitative and qualitative aspects of the study would be given equal priority.

Initially, it was assumed that the overall size of the cohort (n=72) would be large enough to conduct effective statistical analysis. However, during the process of analysing the quantitative data it became apparent that there were a number of potential factors that may influence reproductive decision-making (e.g. carrier

status, number of pregnancies occurring prior to the birth of the index). The sample size proved to be too small to conduct multivariate analysis of all the disparate factors. It was therefore decided that the quantitative data was more likely to provide descriptive statistics, rather than statistically significant results. Priority was therefore given to the qualitative aspect of the study.

There are also a number of different mixed methods typologies that refer to the order in which data is collected. Morse (1991) developed a notational system to describe the sequence of data collection and the priority given to either the quantitative or qualitative approach. For example QUAN + qual indicates that quantitative and qualitative data was collected simultaneously with priority given to quantitative data, while quan → QUAL indicates data collected sequentially, with priority given to qualitative data. In this study, quantitative data collection occurred first, followed by qualitative data collection. The quan → QUAL design, which was used in this study, has been described as the “sequential explanatory design” (Cresswell 2003, Ivankova *et al.* 2006). Figure 1 provides an outline of the sequential explanatory design used in this study.

**FIGURE 4.1**  
**Visual Model for Mixed Methods**  
**Sequential Explanatory Design Procedures**



### **3. Quantitative data collection and analysis**

This section describes the quantitative aspect of the study. The aims and objectives are described, followed by a description of the data collection methods, the subsequent sample and methods used for analysis.

#### **3.1 Aims and objectives**

The aim of the collecting quantitative data was to identify reproductive outcomes.

In order to achieve the aim it was necessary to execute the following objectives:

1. To determine the number of children born before and after diagnosis of first affected male in the family (index)
2. To ascertain the number of pregnancies occurring between the birth and diagnosis of the index
3. To determine the number of families who accepted the offer of prenatal testing (chorionic villus sampling or amniocentesis)
4. To examine the pregnancy outcome:
  - a. Number of males/females born
  - b. Number of affected/unaffected males born
  - c. Number of pregnancies terminated as result of DMD diagnosis through prenatal testing (TOPs)
  - d. Other (e.g. stillbirth, miscarriage, social terminations<sup>11</sup>)

#### **3.2 Data collection and sample included for analysis**

Although the final sample for the quantitative aspect of this study included 72 families (LCD=38, NBS=34), data was initially collected from 77 families (LCD=38, NBS=34), as well as their relatives. This section provides details of the data collection methods and justification for the subsequent decision to exclude relatives and five families from the LCD cohort.

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<sup>11</sup> Defined as terminations of pregnancies occurring for reasons other than a positive diagnosis of DMD

Families' medical files were held at the West of Scotland Regional Genetics Centre in Glasgow, or the Institute of Medical Genetics in Cardiff. Files of families who had no known family history of the condition, and who had an affected boy diagnosed between 1990 and 2006, were reviewed (west of Scotland = 43, Wales =34). To achieve the objectives of the research, data was collected on the following fields:

- Affected male (index)
  - o Date of birth of affected male
  - o Age of affected male at diagnosis
  - o Index diagnostic tests and results (creatine kinase, muscle biopsy, linkage, polymerase chain reaction multiplex, point analysis techniques, multiplex ligation-dependent probe amplification)
  - o Affected exons
- Mother of affected male
  - o Date of birth of mother
  - o Carrier testing for mother and subsequent risk given to her after each test/assessment (family history, creatine kinase, linkage, polymerase chain reaction (PCR) multiplex, PCR dosage, point analysis techniques, multiplex ligation-dependent probe amplification, sequencing)
- Reproductive behaviour
  - o Previous pregnancies (date of birth, sex and DMD status)
  - o Subsequent pregnancies (tested or not, terminations, date of birth, sex and DMD status)
- Key points from genetic counselling sessions/letters to families/doctors
  - o Details of risk information provided to parents
  - o Miscellaneous information (e.g. mother pregnant when receiving diagnosis/mother sterilised etc)

Data was also collected on reproductive behaviour of all female relatives of the index to assess the implications of the diagnosis on the wider family. However, since the data appeared to be incomplete it was decided to exclude data from relatives. In some files, the pedigree chart showed the existence of at-risk female relatives, but not further information was available. Although the data on relatives

provided anecdotal evidence of the wider implications<sup>12</sup> of a later clinical diagnosis, it was not possible to collect data on all female relatives. In addition, the carrier tests had often been conducted at laboratories in other regions and it was therefore not possible to check the file information with laboratory data. Rather than include incomplete and potentially incorrect data on female relatives, they were excluded from analysis.

Often there was data missing from medical files on the affected male and their immediate family (e.g. no test results). Collecting data from files held at the west of Scotland Regional Genetics Centre in Glasgow proved to be particularly problematic. A flood in the department in 2002 had destroyed many of the files and although the department had created new files, often letters and test results had not been replaced. It was therefore necessary to search for original copies of test results, kept in the laboratory.

Thorough searches were also conducted of laboratory records stored on computerised databases, paper files and patient cards. Reviewing data from a number of different sources enabled triangulation and increased the breadth and validity of data. The same process of triangulation was used in both Wales and the west of Scotland. Each file was subsequently discussed in depth with an Associate Specialist in Medical Genetics in Cardiff and with an Honorary Consultant in Medical Genetics in Glasgow, both of whom were closely involved with families affected by DMD in their area throughout the 1990-2006 period of the study. Any anomalies found between the medical files and laboratory data were addressed. The medical geneticists were usually able to provide either copies of missing letters, genetic counselling notes, or verbal confirmation of the risk information provided to families. Data were not included for analysis unless it had been double checked and confirmed.

Files were excluded if they did not include a sufficient amount of data to warrant analysis after the checks. Files which still had some fields missing were retained but

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<sup>12</sup> A number of pregnancies occurred in at-risk female relatives prior to the diagnosis (all of which were unaffected). In addition, a number of female relatives chose to test pregnancies after becoming aware of the diagnosis.



excluded from analysis of particular aspects (i.e. if the age of mother was missing the file would not be included in overall analysis of ages of mothers). A total of five files were excluded from analysis from the later clinically diagnosed cohort. No files were excluded from the newborn screening cohort. Final analysis was conducted on 38 families who had received a later clinical diagnosis and 34 families who had received a newborn screening diagnosis.

Ensuring the medical files included up to date reproductive data required further measures. It was possible that families had chosen not to inform medical genetics of subsequent pregnancies and if no cytogenetic tests had been conducted there would obviously be no laboratory records. Letters were therefore sent out from medical genetics to all families, who had not had contact with the department for some years, to offer them a clinic appointment. As a result, many families either telephoned the geneticist or were seen in clinic, enabling collection of up to date reproductive information. It should be noted, however, that it was not possible to contact all families and therefore it is possible that a minimal number of subsequent pregnancies may have been missed. Due to use of the same thorough data collection methods and a similar response rate from families in both Scotland and Wales it is fair to assume that any pregnancy data missing from the files would be roughly equal in both cohorts.

### **3.3 Quantitative data analysis**

The primary aim of collecting quantitative data from medical files was to analyse any differences in reproductive behaviour resulting from the diagnostic procedure. However, as already noted, during the process of data collection and analysis a broad and varied range of confounding factors<sup>13</sup> were identified and therefore any assessment of any potential association between diagnostic procedure and reproductive behaviour proved to be complex.

To avoid either falsely demonstrating an apparent association between the diagnostic procedure and reproductive behaviour (type I error), or masking an actual

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<sup>13</sup> Variables which may also be related to the outcome measures; reproductive behaviour

association (type II error), it was essential to control for confounding factors. However, the sample size proved to be too small to conduct multivariate analysis. In addition, some of the confounding factors that may have affected reproductive behaviour could not be measured quantitatively (see Table 4.1). The small sample size and the existence of residual confounding meant that only a few statistical tests could be conducted to provide evidence of the influence of diagnostic procedure on reproductive behaviour. Data was analysed using SPSS version 12, to assess frequencies, and to conduct analysis of variance.

**Table 4.1 Confounding variables**

<b>Measured quantitatively</b>	<b>Explored qualitatively</b>
<ul style="list-style-type: none"> <li>• Age of mother</li> <li>• Number of previous children/index position</li> <li>• Carrier status</li> </ul>	<ul style="list-style-type: none"> <li>• Desire for children/ideal family size</li> <li>• Experience of condition</li> <li>• Knowledge of condition</li> <li>• Perceived risk</li> <li>• View on pregnancy termination</li> <li>• Life situation (work commitments, financial constraints etc)</li> <li>• Parental relationship (together/ separated/ divorced)</li> </ul>

In addition to the difficulties arising from potential confounding factors, grouping people into neat categories (e.g. risk aware families) proved to be inherently complex. For example, how do you decide from numerical data what equates to being “risk aware”? Were families aware of their risk as soon as they received the diagnosis, when the first carrier test was conducted (e.g. creatine kinase test), or after mothers received (genetic) confirmation of their carrier status?

Further problems ensued when addressing families’ reproductive decision-making. For example, one family received a later clinical diagnosis while pregnant with another child. Should they be defined as risk aware or should risk-awareness only refer to families who received the diagnosis prior to conceiving? The pregnant mother received the diagnosis in the second trimester of her pregnancy and chose to have an ultrasound to find out the sex of the foetus; the foetus was female, so the

family chose not to have an amniocentesis. Would they have chosen to have amniocentesis if the foetus was male? Does ultrasound equate to testing the foetus? If so, should it be included with the data on families who had chorionic villus sampling or amniocentesis?

Quantitative data can be manipulated by defining and redefining categories, to ‘prove’ what the researcher is aiming to demonstrate. For example, including the use of ultrasound in the category of a “tested pregnancy” would have increased the statistical significance of the difference in the uptake of prenatal testing between the two cohorts. However, the aim of this study was not to ‘prove’ that newborn screening had either a positive or negative effect on reproductive behaviour. The aim was to address the implications of the diagnostic procedure. Therefore, every attempt was made to ensure families were categorised with the utmost attention to detail. Table 4.2 shows how each factor was defined.

**Table 4.2 Definition of categories used in quantitative analysis**

<b>Factor</b>	<b>Definition</b>
Risk awareness	All three possible points of risk awareness were assessed to address which one had the most impact on reproductive behaviour: <ul style="list-style-type: none"> <li>- diagnosis</li> <li>- first carrier test</li> <li>- confirmation of carrier status</li> </ul>
Carrier status	Tests conducted and evidence in file that mother is informed of the results.
Pregnancies	All pregnancies (rather than life-births). Details provided on miscarriages, stillbirths and terminations.
Prenatal testing	Amniocentesis or chorionic villus sampling (not ultrasound)

#### 4. Qualitative data collection and analysis

This section describes the qualitative aspect of the study. Firstly, the aim of the qualitative section and the rationale for using in-depth qualitative interviews is described. Secondly, the sample population and experience of collecting qualitative data is explored. In the final section, the practical issues of analysing the qualitative

data are described. However, the theoretical underpinnings of the analysis are explored in the second part of this chapter.

#### **4.1 Aim and rationale for using in-depth qualitative interviews**

The aim of collecting qualitative data was to explore family accounts of the lived experience of reproductive decision making and the benefits and burdens of reproductive choice. The qualitative data method used was in-depth qualitative interviews.

In-depth semi-structured interviews were deemed the most appropriate method for a number of reasons. Firstly, observation of families would be inappropriate as there were a set of specific questions that needed to be asked about past and present reproductive behaviour and future reproductive plans. Secondly, it was necessary to ask a number of potentially sensitive questions, such as views and experiences of testing and terminating pregnancies. Sensitive issues are best addressed in more intimate, one-to-one settings, rather than through focus group discussions. Lastly, semi-structured in-depth interviews were chosen over structured or narrative interviews because it was necessary to provide families with the opportunity to expand on questions, to talk about the issues that were important to them, whilst still obtaining specific information about their reproductive decision-making process.

#### **4.2 Sample population**

The aim was to invite each of the 72 families (NBS=34, LCD=38) to participate in the qualitative aspect of the study, to obtain a purposive sample (i.e. maximum variation). However, to ensure that the letter would not arrive at an inappropriate time for the family (e.g. a death in the family or a recent termination), health professionals, who were closely involved with the families, were asked to provide their view on whether the families may be upset by receiving a letter about the study. It was felt that this method of contact provided additional safeguards for the families. No issues were identified and therefore letters inviting all 72 families to participate in the study were sent out by the All Wales Medical Genetics Service and the West of Scotland Regional Genetics Centre. Families were asked to

complete and return an "expression of interest" form if they were willing to be contacted by myself to discuss the research further.

An initial round of letters resulted in expression of interest forms being returned by eight families in Wales and three in the west of Scotland; the majority of whom had chosen not to have subsequent pregnancies. A second round of letters was therefore sent out to specifically to families who had pregnancies after the birth of the index. A further three families in Wales and four in the west of Scotland returned forms.

I was approached by another family who were keen to be involved in the study, during a family meeting in Glasgow. Although their son had been diagnosed shortly after the cut off date, it was felt that their experience of the diagnosis and subsequent reproductive decision-making added relevant and valuable insights. A total of eight families, from the later clinically diagnosed cohort, were therefore interviewed, one of whom was not in the original cohort. A total of 11 families, from the newborn screening cohort, were interviewed, all of whom were from the original cohort.

#### **4.3 Qualitative data collection**

After expression of interest forms had been returned, families were contacted to discuss any questions they had regarding the study. All families, who returned the form, were keen to be involved and arrangements were made for a suitable time to conduct the interview, either at the medical genetics centre or in their homes. All participants chose to be interviewed in their homes. The majority of interviews were conducted with mothers. However on three occasions, the husbands were present for part or all of the interview process. All participants were provided with a consent form, which they signed to indicate whether they were willing to allow me to review their medical genetics files and record the interview. All families consented.

The topics addressed during interview were as follows:

- The impact of the diagnostic process on the participant, their partner, their immediate family and their wider family – especially in relation to their perceptions of having more children
- The effect of living with the disease, DMD, on “family life” in a broad sense and also in relation to their perceptions of having more children
- Reproductive plans before the diagnosis
- The experience of making decisions regarding the following both before and after diagnosis:
  - family planning methods
  - prenatal testing
- Whether the outcome of reproductive plans matched their intention (i.e. had they had more children even though they had planned not to, or vice versa)

I conducted all 19 interviews. Each interview started with the same question “Can you tell me a bit about how [name of son] was diagnosed?” From that point onwards the order in which questions were addressed differed in each interview.

I wrote field notes immediately after each interview. Usually the field notes recorded aspects of the environment, my feelings about how well I had managed to ‘connect’ with the participant, and an outline of their main points. However, on one occasion the tape recorder failed to record and on another occasion there was so much background noise that I was concerned the mothers’ voice would be indecipherable on the recording. On both of these occasions I left their homes, drove a short distance away and then immediately recorded everything I could remember about the conversations.

I attended a number of qualitative interview courses prior to starting interviewing and I practiced my newfound skills by conducting a small pilot study. However, courses and practice do not necessarily prepare you for the real thing. As a novice interviewer I found the process of keeping field notes an extremely useful learning tool. I recorded what had worked and what had not and changed my approach to interviewing accordingly. For example, during my first real interview I asked the participant whether she had found health professionals interfering. She replied that she had found them very interfering and used the word ‘interfering’ in much of her

subsequent descriptions. In subsequent interviews, I asked “how did you find your involvement with health workers?” and avoided the use of any other leading questions.

I also realised the potential impact of subtle changes in interaction between myself and interviewee. The following extract is taken from my field notes after the first few interviews had been conducted and demonstrates my changing approach to the interview process.

I didn't think that I would need to learn much to conduct qualitative interviews: it's just chatting to a stranger about something personal and I'd had plenty of conversations like that over the years. How wrong I was! There are a few fundamental issues that make an interview entirely different from a random conversation, namely:

1. You are collecting data
2. You don't need to talk to make people feel comfortable
3. You have to learn when it is time to speak, when it is time for silence and how best to make a conversation flow around the topics you want addressed.

By getting better at doing interviews I've overcome the issue I had with data. I saw the families as data and then felt guilty about manipulating it out of them and worried about judging them and being judged. Now I see it as having the skills to enable a flowing conversation, in which you give nothing away, make no judgements, listen and direct.

I have also learnt that you can make people feel comfortable without saying very much. To me a conversation is about reciprocity, but in an interview situation, it is neither necessary, nor wise to share your views. I learnt to use non-verbal signs of encouragement, empathy and understanding (e.g. nodding, smiling etc). After reading the transcripts from the first few interviews I realised that I occasionally interrupted people with a new question. It is frustrating to think that I may not have allowed enough time for people to say everything they wanted, so I have learnt to take things slower, to try to assess from their demeanour, whether they have finished or still have more to say (Field notes from 9<sup>th</sup> September 2007).

Focusing on the participants became considerably easier as I became more familiar with the interview questions. I always avoided sitting down with a list of questions in front of me, because I was concerned that it would make the situation seem clinical. I wanted the participants to feel that we were having a cup of tea and a chat, rather than me firing endless questions at them from a clipboard. I also learnt to say as little as possible, to listen as hard as I could and to respond in ways which

encouraged participants to elaborate – even on issues where it was easy to assume a shared interpretation.

#### **4.4 Qualitative data analysis – practicalities**

I transcribed the first four interviews; the remaining 15 were transcribed by a professional company. After I received each transcript I checked them for accuracy by listening to the recordings again. This was particularly useful for the interviews with participants with strong Scottish accents. I had become accustomed to the deciphering the Scottish accent and, having participated in the interview, I was more aware of the topics addressed.

I took an iterative approach to data analysis; alternating between analyses of transcripts and conducting interviews. This process enabled me to reflect on ‘what was going on’ and then use that information to guide my thoughts during the next interview. After I had carried out preliminary analysis of the first three transcripts, three of my fellow students also read and coded the transcripts. The aim of the exercise was to ascertain whether my interpretation of the data would be replicated by others. We discussed emergent themes, which highlighted a considerable degree of overlap, but also helped to highlight some aspects I had not considered. I used my colleagues’ thoughts to inform further analysis. I also combined transcripts with my field notes and with information from the families’ medical file, to provide a more complete picture of each family’s situation.

When all of the interviews had been completed, I conducted detailed coding of each transcript. To inform the coding process, I drew upon a simplified version of Strauss and Corbin’s (1990, 1998) process of coding. However, for two key reasons, I do not claim that this study was conducted with a grounded theory approach. Firstly, grounded theory, as outlined by Glaser and Strauss (1967) has been criticised for its failure to acknowledge the influence of implicit theories which guide research at the early stage (Bryman 1988, Silverman 2000). Conducting a mixed methods study, with a sequential explanatory design, further undermines the possibility of being devoid of implicit theories. Secondly, I used the process of open coding, axial coding and selective coding, as outlined by grounded theory, as a way of guiding



the analysis process. Rather than adhering to the strict tenets of grounded theory, I use the process to develop categories of information, to interconnect the categories and to build a story that connected the categories.

During the open coding stage, I created a list of ten headings and cut and pasted the data from each interview under each heading (see Box 4.1). This process was extremely simplistic. My aim was to organise the data into headings in order to become familiar with the data and to get an overall picture of the variety of views held.

I then went through all the data under each heading and organised them under subheadings (see Box 4.2). For example, to explore whether and why people chose to have or not have subsequent children, I cut and pasted all extracts using hyperlinks (so that clicking on the extract would take me back to the exact position within the original transcript). Again, this was a simplistic approach aimed at becoming familiar with the data. It also served as a useful organisational tool; before I became familiar with exactly who had said a particular thing, I could refer to the main document and simply click on the relevant extract to find the original transcript.

#### **Box 4.1 Example of open coding**

1. Positive experience of NBS (Negative LCD)
2. Negative experience of NBS (Positive LCD)
3. Experience of LCD
4. General experience of living with boys with DMD
5. General understanding of genetics and risk
6. Feelings associated with being a carrier
7. To have or not to have children
8. General view of PND/TOP/PGD
9. General experience of disability
10. Effect on relationship

#### **Box 4.2 Example of coding of one category**

##### **To have or not to have children**

1. Diagnosis complicates decision-making
2. Diagnosis changes number of children and/or birth spacing
  - 2.1 Replacement child
  - 2.2 Good for affected sibling
  - 2.3 Hard for unaffected sibling
  - 2.4 Unaffected sibling provides 'welcome taste of normality'
  - 2.5 Need to devote time to affected boy
3. Diagnosis does not change number of children and/or birth spacing

After completing the process of open coding, it was possible to address how the some of the categories were interconnected through axial coding. Strauss and Corbin (1990, 1998) suggest that the researcher identifies a single category from the open coding list, which is extensively discussed by participants. I chose the category of 'to have or not have children' as the core category and began the process of examining the connections between the different sub-headings. It quickly became clear that families often provided the same reason for different decisions. For example, some families described their decision to have more children in relation to how another child would provide resources for their affected boy (e.g. companionship and care). In contrast, other families described their decision not to have more children, in relation to how another child would take away resources otherwise focused on the affected boy (e.g. parental time and financial resources). Through cross-category analysis, it became clear that the justification provided for having or not having more children required more in-depth analysis.

Examining similar justifications for the disparate decisions formed the third stage of coding, 'selective coding'. I developed propositions that connected the different decisions by addressing the way families described their decisions. Rather than focusing on 'factors' (e.g. resources), I reanalysed the data in relation to the way each factor was described (e.g. prioritising responsibility towards existing child, rather than future, unborn child). I reanalysed the extracts in the coding system, with

a deeper level of analytical and interpretative thought. A number of cross-cutting themes emerged, such as responsibility, perception of disability and desire for children. For the final analysis I therefore once again reviewed each transcript in its entirety, and assessed the range of contextual factors individually for each family.

## **5. Theoretical considerations**

Historically, quantitative and qualitative methods have been understood to reflect two disparate and opposing paradigms: positivism and interpretivism. Simplistically speaking, the two paradigms represent dualistic notions: objectivity versus subjectivity, deduction versus induction, generality versus context, realism versus relativism. Due to the dichotomous divide between the two paradigms, there has been considerable debate about the feasibility of combining quantitative and qualitative methods. The aims of this theoretical section of the chapter are to explore the proposed differences between the two paradigms, describe my own experience of the practical and conceptual difficulties of combining methods, and lastly, to explore my theoretical approach to the methodology.

### **5. 1 Ontological, epistemological and methodological disparities between the positivist and interpretivist paradigms**

This section will present the disparities between the positivist and interpretivist paradigms. To address the extremes of each paradigm, I draw upon the arguments commonly presented in text books on methodology. Although this is an unconventional approach for a PhD thesis, it serves two main purposes. Firstly, it enables me to present the key disparities between the two paradigms in their simplest form. Secondly, (and perhaps in paradoxical contrast to the first point) it highlights the oversimplification of the dichotomies between the two paradigms, which are used to educate emerging academics and further solidify a disputable notion of the incompatibility of quantitative and qualitative methods.

**5.1.1. Disparities between the positivist and interpretivist paradigms**

The positivist and interpretivist (often combined with constructivist) paradigms encompass disparities at three levels of the research process: ontological, epistemological and methodological. Simplistically speaking, at the ontological level, positivists argue for the existence of an objective, apprehensible reality, whilst interpretivists argue that there are multiple, subjective realities (Guba & Lincoln 2005). At the epistemological level, positivists take an objectivist stance, believing that phenomena can be reduced to their constituent parts, and inductively tested and measured using scientific methods (Baum 1995). In contrast, interpretivists argue that phenomena cannot be irreducible. Interpretivists argue that all knowledge is subjective; a matter of context-specific interpretation, and therefore research findings are created (Baum 1995, Guba & Lincoln 2005, Morgan 2007).

At the methodological level, quantitative research uses deductive experimental methods adopted from the natural sciences, which are used to test the relationship between variables from predetermined hypotheses, to explain and predict an ordered universe (Baum 1995, Guba and Lincoln 2005). In contrast, qualitative methods are designed to help researchers deductively understand the human dimension; to explore meanings and perspectives, through observation, interviews and documents (Silverman 2006). Qualitative methods are deemed to produce micro, context-specific findings, whereas quantitative methods seek objective, macro, context-free generalisations (Johnson & Onwuegbuzie 2004). Table 4.3 summarises the disparities between the two paradigms.

**Table 4.3 Quantitative and qualitative approaches to methodology<sup>14</sup>**

	Qualitative Approach	Quantitative Approach
Connection of theory and data	Induction	Deduction
Relationship to research process	Subjectivity	Objectivity
Inference from data	Context	Generality

<sup>14</sup> Adapted from Morgan (2007:71)

### *5.1.2 Oversimplification of dichotomous divides?*

Discussions about the differences between quantitative and qualitative research have oscillated between philosophical and technical levels (Baum 1995, Bryman 2006). The disparate philosophical concepts in each paradigm and assumptions about how we define and theorize notions of reality have been viewed as incommensurable (Kuhn, 1970), and the technical methods employed, as “incompatible” (Teddlie and Tashakkori 2003). Although many purists still argue that the disparities cannot be overcome (see Howe 1988, Green *et al.* 2001, Guba & Lincoln 2005, Johnson & Onwuegbuzie 2004), closer examination of the two paradigms highlights considerable areas of overlap.

Positivism was dislodged from its prominent position after World War II and replaced by postpositivism. Many of the tenets of postpositivism were defined by Karl Popper, who argued that scientific inquiry is influenced by the values, theories and the ontological position of the investigators (Teddlie & Tashakkori 2003, Stokes 2006). Quine (1951) also attacked the assumptions of positivism, arguing that no hypothesis can be tested in isolation from the web of beliefs and ideas of which it forms a part. In addition, Heisenberg’s (1958) Theory of Uncertainty highlighted that “science alters and refashions the object of investigation. In other words, method and object can no longer be separated”. ‘Reality’ cannot be apprehended.

Postpositivists essentially reject positivist claims that a hypothesis can be proven; instead postpositivists indicate a failure to reject the null hypothesis (Cresswell 2003). Although many aspects of positivism have remained in postpositivism (Guba & Lincoln 2005), the recognition that observation does not provide a direct window on reality removes one of the fundamental disparities between the paradigms. Science, once the arbiter of objective Truth, now provides us with one truth amongst many.

Disparities can also be seen within the interpretivist/constructivist paradigm. Guba and Lincoln (2005) define the ontological position of the constructivist paradigm as relativist, but there is a considerable variety of ontological views within the

constructivist paradigm. Taking social constructionism, a subset of the interpretivist paradigm, as an example, it is clear that there is simply no single feature, or adequate description, which defines the social constructionist position (Burr 2003). Rather, writers referred to as social constructionists share a “family resemblance” (Burr 2003:2), or “shared consciousness” (Gergen 1985:266).

Social constructionists are called upon to “absolutely believe” (Burr 2003:2) in the central tenets, such as taking a critical stance toward taken for granted knowledge, acknowledgement of historical and cultural specificity, acceptance that knowledge is sustained by social processes, and recognition that knowledge and social action are inherently intertwined (Gergen 1985, Burr 2003). However, there is little consensus in beliefs on the limits of social constructionism (Cromby & Nightingale 1999). In essence, there are two broad schools of thought; a divide between realism and relativism, which reflect the extent to which writers reject or accept essentialist notions of reality.

The relativist account of reality argues that our experience of the world and of ourselves is defined by social processes, and therefore we cannot reach beyond our representations of the world to access an external reality (Edwards *et al.* 1995, Burr 2003, Burkitt 2003,). Edwards *et al.* (1995:36) posit that “relativists have no problem with reality as the practical and commonplace ground for everyday living”, but to closely examine taken-for-granted reality draws attention to the “workings of consensual agreement”. Edwards *et al.* (1995:2) provide support for Derrida’s (1988) (albeit contested<sup>15</sup>) claim that “there is nothing beyond the text” through their assertion that the world, like texts “all has to be represented and interpreted” (1995:2).

Edwards *et al.* (1995:41) present relativism as a “non position, as critique or scepticism, not as a positive statement opposed to realism”. Gergen (1994:72) proposes that “constructionism is ontologically mute”; as soon as we attempt to articulate ‘reality’ we are drawn into the world of discourse, and “at that moment

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<sup>15</sup> According to Searle (1995:160) all that Derrida meant “by the apparently spectacular declaration that there is nothing outside of *texts* is the banality that everything exists in some *context* or other”. Also see Derrida (1988: 136).

the processes of construction commences, and this is inextricably woven into processes of social interchange and into history and culture” (Gergen 1994:72). For relativists there is no possibility of reaching an objective and universal human science; taken-for-granted reality, whether physical or social, is essentially a product of discourse and rhetoric (Harre & Langenhove 1999, Burkitt 2003).

In contrast, realists argue that our representations of the world are underpinned by a physical reality (Burr 2003). Searle (1995) examines the relation between physical and social reality and argues that intrinsic (physical) features of the world should be distinguished from “observer-relative” (social) features.

“Some features of the world exist regardless of our feelings and attitudes [...] They include such things as force, mass, gravitation attraction, photosynthesis, etc. Other things are dependent on us because they are our creations. These include money, property, government, hammers, cars, and tools generally.” (Searle 2005:325)

For Searle (1995:19), the assignment of functions to objects and other phenomena, such as money and property, is the “first feature we need to note in our discussion of the capacity of conscious agents to create social facts”. Searle expands on these notions considerably. Categories and sub-categories are created to describe complex social processes. However, some fundamental premises remain; physical “brute” facts exist independently of social facts, and social reality is a complex reaction to the physical world.

Harre (1990:352) seems to accept the existence of both a physical and social reality as two ontological positions “that do not mesh”. One reality emphasises a physical reality; “as embodied beings we are located in physical space-time and have such powers as our material embodiment endows us with”. The other reality emphasises a social reality: “that as psychological and social beings we are located in another world”, the world of discourse (Harre 1990:352). Although Harre (1990) claims there are conditions of reality that stand outside of discourse, Harre fails to reconcile how external conditions “inform meaningful human activity in the world and vice versa” (Burkitt 2003:321). Physical and social realities remain discrete entities.

The three stances outlined above represent the range of ontological views held by researchers within the interpretivist paradigm, and highlight the continuum between

relativist and realist stance. Little is known about actual views of those who identify themselves within the postpositivist paradigm, because qualitative, rather than quantitative, researchers have spent considerably more time defining the ontological and epistemological position of quantitative researchers (Bryman 1984). However, the increasing range of theoretical approaches used by those who are posited by others to “belong” to the postpositivist paradigm, suggest that there is a similar continuum between the relativist and realist stances (Grbich 1999).

Arguably, qualitative purists (and the authors of methods text books) have created a rather monolithic version of the postpositivist paradigm that does not accurately reflect the true diversity and complexity of views. Although it would be unwise to suggest that there is a complete convergence of views between the interpretivist and postpositivist paradigms, the differences have clearly been overemphasised (Grbich 1999, Mason 2006). Even Kuhn (1970), who claimed that the paradigms were incommensurable, in a later postscript (1996:198-204) described “incommensurability” as a “breakdown of communication” between paradigm purists, rather than a fundamental incompatibility of the two paradigms.

The “paradigm wars” are still being waged, but perhaps only by those who posit themselves at the extreme ends of the two paradigms. Many researchers, particularly in the field of public health and nursing, have long been successfully mixing quantitative and qualitative methods (Teddlie & Tashakkori 2003). Although there remain some practical and conceptual difficulties, perhaps it is time to move away from a narrow focus on postpositivism and interpretivism to develop a third paradigm; to turn our attention to the area where the two extremes converge. In the following section I address the practical and conceptual difficulties I experienced during the collection and analysis of quantitative and qualitative data. Subsequently, I explore the possibility of reaching a ‘middle ground’ between the ontological and epistemological divides.

## **5.2 From quantitative to qualitative: practical and conceptual difficulties**

Although the disparities between the two paradigms appear to have been overplayed and overemphasised, there is no doubt that collecting and analysing both



quantitative and qualitative data can initiate both practical and conceptual difficulties. In this section I explore my own experience of mixing methods, and the critical demands of moving sequentially from a quantitative to a qualitative approach to data collection and analysis.

Moving from one data collection method to another required a process of transition. Inherent to the practice of analysing quantitative data is the desire to find predictable, regular patterns; numbers to be “crunched” into an informative, uniform picture. Alas, my numbers demonstrated a profound resistance to crunching. Neatly envisaged categories proved to have inherently porous boundaries. Every time I created another rubric to encompass the category (e.g. “risk aware”), another ill-fitting family emerged; a round brick in a dam of data squares. I reassured myself that the collection of qualitative data would silence the cacophony of confounding factors; neatly folding misshaped entities into distinct categories... and so the process of qualitative data collection began.

I started conducting interviews with an implicit intention to obtain factual data on the key factors that participants felt had influenced their reproductive decision-making. A number of problems arose. First, mothers did not appear to have a ‘shopping list’ of factors that had affected their decisions; instead I was presented with reconstituted memories – more akin to glancing at a kitchen cupboard, often years after the ‘shopping’ had been done. There was no reassurance that the items on display were ever on the ‘reproductive decision-making list’, nor that factors, once paramount, had not been gobbled away; dissipating with the passing of time. Second, many of the factors I had spent a considerable amount of time collecting quantitative data on (e.g. carrier risk information), rarely appeared as primary considerations in the reproductive decision-making process. Lastly, expected items were replaced by unexpected influential factors, such as change of partner, desire for children and perception of disability; a veritable can of worms.

The culmination of problems initially proved frustrating. My expectations that the qualitative data would clarify the quantitative data, or provide a neatly categorised package of “factors affecting reproductive decision-making”, were not realised. In fact, the qualitative data seemed only to exacerbate the complexity and highlight the

phenomenal variety of lived experience. However, the more interviews I conducted, the more I realised that the point of the study was not to arbitrarily simplify the complexity; indeed it was the very nature of the complexity that proved to be the most fascinating aspect of the study. Taking a positivist approach to qualitative data only served to eclipse the breadth and depth of lived experience; the qualities of which were at the very heart of reproductive decision-making.

To recover a sense of the qualities of lived experience required going beyond the traditional empiricist approach of collecting (numerical) 'facts'. First, I had to recognise the temporality of experience and the complex interaction of presentation and memory. Each interview lasted 1-3 hours; experience is a boundless process. The very act of recounting events in our lives, in the presence of others, constitutes a process of renegotiating our experience of those events. Each time we describe a past experience to a new acquaintance, our memory serves to polish the representation.

“Objectively, stories and ritual scenarios seldom tell the truth about what actually happened. They tell a truth that enables people to live in the here and now with what happened to them in the past. In this sense the scenarios are expedient lies; they prioritise the existential urge to remaster experience rather than the epistemological need to preserve an exact record of it.” (Jackson 1998:24)

In effect we fail to describe the reality of the event, to preserve an exact record of how it was experienced at the time; we can only deliver a remastered version, morphed by memory and congruent with our present day persona.

Second, I learnt to recognise that direct, pre-reflective experience is no less significant than experience that comes from ratiocination or analytical reflection. Often families had not analysed the factors that had influenced their decisions; frequently only one reaction, one course of action, had appeared tenable. The decision-making process, therefore, was rarely presented as a process of extensive deliberation, but as an inevitable response to a tapestry of subconscious motivations.

Lastly, it was necessary to recognise my own influence on the process of data collection. In a rather overt sense, my positivist approach to data collection had initially blinded me to the complexity of qualitative data collection. However,

recognition of the need to employ reflective strategies, to recover the qualities of lived experience, does not and cannot imply that I was subsequently able to comprehend the complexity of an “other”. This problem is perhaps best encapsulated by Merleau-Ponty (1964:348):

“How can the word ‘I’ be put into the plural, how can a general idea of the *I* be formed, how can I speak of an *I* other than my own, how can I know that there are other *I*s, how can consciousness which, by its nature, and as self-knowledge, is in the mode of the *I*, be grasped in the mode of Thou, and through this, in the world of ‘One’.”

The question of whether we can *know* the inner experience of an “other” is one of the central dilemmas of human coexistence. Our ability to ‘recognise’ each other is at once intuitive and fallible. Schutz (1973:11) regarded intersubjective understanding as a product of “the natural attitude of common-sense thinking in daily life”. Although we are products of differing biographies, for the most part we take for granted that we have much in common. We retain a capacity to comprehend much an ‘other’s’ experience:

“...there is always some aspect of oneself, however well hidden, that corresponds, albeit obliquely, to the beliefs and behaviours one sees in others. Methodologically, therefore, one proceeds from the latent in self to the manifest in other, and from the manifest in self to the latent in other in a demanding series of essays at recognition” (Jackson 1998:15).

This is not to suggest that we are capable of truly empathetic understanding of another. The “outward facts and bodily movements are [...] indications of the lived experiences”, representations, rather than the essence of experience itself (Schutz 1967:111).

Schutz (1967) suggests that genuine understanding of another person comes from focusing on what lies behind the indications; the intersubjective meaning. In essence, there are aspects of human interaction that suggest that the “other” is not the aspect that needs to be known. The other, like the self, is essentially a product of intersubjective engagement, not a given property of existence (Husserl 1970). My “self”, without others to be myself with/against/in relation to, is difficult to comprehend. Likewise, the other is a “self”, not defined by me, or by their ‘self’ but by the intersubjective interaction between our ‘selves’ (and ‘others’).

My own influence on the interpretation of the data turned from an explicit desire to collect 'objective' facts, to recognition of my implicit influence on the findings. The data collected was not a window onto a world of another, but a window onto the world we share; a focus on the intersubjective construction of meaning. The collection of qualitative data also served to highlight the subjective nature of quantitative data analysis and had a considerable influence on my interpretation of the quantitative data.

Although I had initially felt frustrated by the perceived lack of statistical evidence, I realised that the quantitative data *did* provide a useful picture. It was not the expected uniform presentation of neat categories, but a fascinatingly complex representation of life; many kitchen cupboards, containing many different items. In essence, through collecting both quantitative and qualitative data, I developed a far greater understanding of the complexity of the reproductive decision-making process.

In summary, moving sequentially from one data collection method to another required the use of significantly different practical and conceptual skills. However, the process also illuminated the complimentary nature of quantitative and qualitative methods. The collection and analysis of quantitative data actually provided a greater understanding of the importance of recognising the temporality of experience, the complex interaction of presentation and memory, as well as the value of hearing direct, pre-reflective voices. Having access to families medical records highlighted the chasm between the factors assumed to be paramount in the reproductive decision-making process (e.g. timing of diagnosis and carrier status) and those which families described (e.g. experience of living with a child with DMD, desire for children, life-event factors such as infertility or a change of partner).

### **5.3 Dichotomous dualisms: finding solace in the place in between**

Rather than instigating a conflict between the traditional dualisms of the positivist and interpretivist paradigms, the collection and analysis of quantitative and qualitative data served to bring my theoretical thinking to a place in between. In this

section, I draw upon the works of Schutz, Merleau-Ponty, Dewey, James and Sartre, to clarify my theoretical position. Although these theorists have emerged from diverse fields of pragmatism, existentialism and phenomenology, they are all united in a rejection of the traditional dualisms, found in the positivist and interpretivist paradigms. In this section I describe my focus on intersubjectivity (rather than objectivity or subjectivity), transferability (rather than generalisability or context-specific data) and abduction (rather than induction or deduction).

Schutz, Merleau-Ponty, Dewey, James and Sartre all focus on the practical realities of an individual's experience; the common-sense understanding of lived experience is the framework from within which all inquiry should begin and return. Focusing on the practical realities enables us to approach the ontological and epistemological disputes of postpositivism and interpretivism from a different perspective. James (1995) and Dewey (1958), in particular, called for attention to be paid to the practical consequences and significance of metaphysical positions. To find the meaning of an idea, we must "try to interpret each notion by tracing its respective practical consequences" (James 1995: 18). For example, if two opposing ontological positions on whether brute physical facts actually exist, or are socially constructed, have no bearing on the way we conduct our study, then the distinction has no practical purpose.

In this thesis, I focus on the *lived reality* of reproductive decision-making. Families affected by DMD did not debate the possibility that their experience of living with DMD might be a social construct. For families in this study, their son's condition, the progressive muscle weakness, wheelchair dependency and premature death are just some of the practical realities of their life. Setting aside questions regarding the ontological status of various modes of comprehending and experiencing practical realities enabled me to explore the behavioural consequences of these modes of understanding.

I also set aside debates on the relationship between the individual and the socio-cultural. While some argue for the existence of an external, imposed social order, others perceive individual actors as the creators of social meaning. I felt it was necessary to describe both the social order *and* individual action. Drawing on

Sartre's (1982) progressive-regressive method, I used the introductory chapters in this thesis to describe both the pre-existing social and historical factors that constitute the human situation (practico- inert), in relation to reproductive choice. The data chapters explore the ways in which human action (praxis) reinforces and develop prior conditions, in relation to reproductive decision-making.

Exploring the way in which people negotiate the boundary between the human situation and purposeful human action serves to illuminate the paths between what is given and what is chosen. Although there are inherent difficulties in defining reproductive "choice" amidst complex theories of political power, paternalistic health care systems, and anti-disability social structures, it is necessary to bracket out any distinctions between real and imaginary choice and control, to address people's experience of the world as an active subject and "not solely as a contingent predicate" (Jackson 1998:21). The exclusion of circumscriptive notions of power is not to deny the potential for their existence, but to emphasise the phenomenal world of immediate, lived experience; the notion that choice exists, within constraints.

Through the process of data collection, I drew upon Dewey's (1958) notion that researcher must reject claims of both objectivity and subjectivity; theories, values, and motives cannot be discarded in order to impartially collect independent facts. In addition, Dewey argued that meaning is not entirely dependent on context. Claims that quantitative research is generalisable, while qualitative research is context specific, are overly simplistic (Brannen 2005). It is difficult to comprehend research results that are either so unique as to have no relevance for any other actors in similar situations, or so generalisable as to be applicable in every possible historical and cultural setting (Morgan 2007). I therefore focused on the transferability of the findings of this study.

Quantitative and qualitative methods have traditionally focused on either side of the dichotomous divides between structure and agency, socio-cultural and individual, object and subject, macro and micro, and yet the world we live in inevitably contains both (Mason 2006). Every human is "at once a subject for himself or herself – a who – and an object for others – a what" (Jackson 1998:8). Rejecting the forced dichotomy between subjective and objective is achieved by emphasising the

intersubjective experience. A focus on intersubjectivity helps us to focus on the experience of life as enacted on simultaneous scales of macro and micro, socio-cultural and individual. In essence, lived experience traverses dualisms (Mason 2006).

I also found it was necessary to reject the forced dichotomy between inductive and deductive reasoning. The actual process of data collection and analysis involved moving between theory and data, which never operated in only one direction. In practice, “it is impossible to operate in either an exclusively theory or data-driven fashion” (Morgan 2007:70-71). As Bateson (1973:60) suggests, rather than attempting to achieve the unachievable:

“We ought to accept and enjoy this dual nature of scientific thought and be willing to value the way in which the two processes work together to give us advances in understanding the world. We ought not to frown too much on either process, or at least to frown equally on either process when it is unsupplemented by the other.”

In our quest for knowledge, perhaps it is time we acknowledged that ways of knowing are at once physical, cultural, innate and learned; the constant moving back and forth between induction and deduction, an inevitable process of abductive reasoning (Morgan 2007). As Dewey (1958) suggests, inquiry should focus on a naturalistic and process-oriented organism-environment transaction.

In summary, rather than starting with an (unproven and disputed) ontological assumption that would have imposed epistemological limitations on the study, I started with what I perceived to be the most fundamental aspect of the research process: the research question. The process of collecting and analysing both quantitative and qualitative data illuminated potential disparities between the two paradigms. However, although there was a transitional period between the two methods, the process actually appeared to initiate a more thoughtful approach to the ontological, epistemological and methodological disparities between the two paradigms. Through exploring the work of Schutz, Merleau-Ponty, Dewey, James and Sartre, I was able to find solace in their rejection of traditional dualisms and found a way to elicit specific issues related to mixing methods, namely: abduction, intersubjectivity and transferability (see Table 4.4).

**Table 4.4 An Approach to Mixed Methods<sup>16</sup>**

	Qualitative Approach	Quantitative Approach	Pragmatic Approach
Connection of theory and data	Induction	Deduction	Abduction
Relationship to research process	Subjectivity	Objectivity	Intersubjectivity
Inference from data	Context	Generality	Transferability

### 5.5 Conclusions, caveats and contentions

In this final section I address some of the caveats and contentions that may emerge from this study. When analysing data, it is necessary to recognise that the drive to find conceptual order in our representations of the world, is at best a process of wishful thinking. The concepts we use to describe and represent lived experience can never truly reflect the complexity, nor symbolize the character of human existence, without serious distortions. Lived experience, in Sartre's (1969) terms, is "dialectically irreducible".

Nonetheless, behind of the curtain of academic endeavour, lies an unerring urge to find patterns in our data, to create order in our world. Dewey (1958) and James (1995) suggest that our preoccupation with pattern and order is a form of instrumental rationality, a historical drive to control nature and the human condition. At best, the drive to find order is an attempt to make sense of an unstable world; a "consoling illusion" (Jackson 1989), rather than an "accurate representation of reality" (Rorty 1979:10). At worst, it serves to create conceptual obligations; a need to legitimise research as unproblematic and 'real'.

Throughout this chapter I have attempted to present the practical and conceptual difficulties of both quantitative and qualitative research. I have described my own influence on the collection and analysis of data and theoretical difficulties of truly comprehending another's experience. Despite the inherently problematic nature of

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<sup>16</sup> Adapted from Morgan (2007:71)



comprehending another through either quantitative or qualitative data, I have, as you will see, categorised, summarised and possibly even simplified a cacophony of data.

Recognising our inability to apprehend reality is not to suggest we can just ‘make it up’; it merely serves to acknowledge that “there is no constant, substantive “self”, which can address a constant, substantive “others” as objects of knowledge”

(Jackson 1989). For James (1950:296-297) the “*fons et origo* of all reality, whether from the absolute or the practical point of view, is [...] subjective, is ourselves”.

This is not to suggest that I have been consumed by solipsism, but it does serve to highlight that the “truth” of this thesis is not an objective truth. Rather than presenting my data as an objective Truth, I seek alternative solace in the presentation of a small truth; an R.D Laing (1970) worthy<sup>17</sup> representation of families’ representations of their experiences to me.

In conclusion, the categories, summaries and simplifications of the vast complexity of reproductive decision-making have emerged from a reflective account of both quantitative and qualitative data. Current beliefs and research conclusions cannot be perfect, certain or absolute. Truth, when addressed pragmatically, is temporal, provisional; truth is “what *happens* to an idea. It *becomes* true, is *made* true by events. Its verity *is* in fact an event, a process” (James 1995:77) and therefore, as with all research findings, we must “be ready tomorrow to call it a falsehood” (James 1995:86).

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<sup>17</sup> In RD Laing describes the human condition as an interactive reflection of ourselves in others and others in ourselves. In his (1970) book “Knots” the complexity of human action is defined through a number of *ad finitum* examples of reflective interaction, such as “Jill thinks she can’t see what she thinks Jack can see, and that Jack himself thinks that, Jill does not see it. Jack sees Jill *does* see it and she thinks that she does not, and that she thinks, he thinks, she does not”... etc

## Chapter Five

### Implications of diagnostic pathway, carrier testing techniques and reproductive technologies for reproductive behaviour

#### Introduction

Reproductive behaviour in families affected by genetic conditions may be influenced by the provision of reproductive choice. Providing families with reproductive choice depends on two factors; ensuring families are aware of their risk and offering families reproductive options. Increasing technological sophistication has changed a number of aspects of reproductive choice. The development of newborn screening procedures has provided some families with an *earlier* awareness of their genetic risk. The development of carrier testing procedures has provided families with an increasingly *accurate* awareness of genetic risk. The development of reproductive technologies has provided risk-aware families with a broader range of reproductive options in subsequent pregnancies.

The aim of this chapter is to explore the implications of diagnostic pathways, carrier testing techniques and reproductive technologies for reproductive behaviour in families affected by Duchenne muscular dystrophy (DMD). Quantitative data on reproductive behaviour is presented from 72 families affected by DMD; of whom, 38 received a later clinical diagnosis (LCD) in the west of Scotland and 34 received a diagnosis through newborn screening (NBS) in Wales, between 1990 and 2006.

Reproductive behaviour is a complex phenomenon. Families' decision-making may be influenced by the awareness of genetic risk. "Risk awareness" may be defined either as the point at which families received the diagnosis, or the time at which they received confirmation of their carrier status. In addition, reproductive behaviour after the diagnosis of an affected child may be influenced by reproductive behaviour occurring prior to the birth of an affected child (e.g. a family who already have three children prior to the birth of the index, may be less likely to have subsequent pregnancies).

To determine how to define “risk awareness” (as either the point at which families received the diagnosis, or the point at which mothers received confirmation of their carrier status) and to disentangle the varying influences of increasing technological sophistication and previous reproductive behaviour, the chapter is divided into six sections. The first section outlines the different diagnostic pathways and the different carrier testing and reproductive technologies available to families, in the LCD and NBS cohorts. The remaining five sections focus on the implications of the different diagnostic pathways, carrier testing techniques and reproductive options for risk awareness and reproductive behaviour at various points in time. Table 5.1 outlines the aims and objectives of the five sections on the implications of technologies for risk awareness and reproductive behaviour.

**Table 5.1 Aims and objectives of the five sections on risk awareness and reproductive behaviour**

Time period	Aims	Objectives (variables measured)
Prior to birth of index	To explore whether the cohorts are comparable	<ul style="list-style-type: none"> <li>- Number of children born prior to index</li> <li>- Age of mother</li> </ul>
Prior to diagnosis of index	To explore implications of diagnostic pathway for risk awareness	<ul style="list-style-type: none"> <li>- Number of pregnancies occurring between birth and diagnosis</li> <li>- Outcome of pregnancies</li> </ul>
Prior to confirmation of carrier status	To explore the implications of carrier testing techniques for risk awareness	<ul style="list-style-type: none"> <li>- Number of pregnancies occurring between diagnosis and confirmation of carrier status</li> </ul>
After diagnosis of index	To explore the implications of the timing of the diagnosis on subsequent reproductive behaviour	<ul style="list-style-type: none"> <li>- Number of pregnancies occurring after diagnosis</li> <li>- Uptake of prenatal testing</li> <li>- Birth interval</li> </ul>
Overall	To highlight outcome of differences explored in previous sections	<ul style="list-style-type: none"> <li>- Family size</li> <li>- Fertility rate pre/post diagnosis</li> </ul>

Section two focuses on reproductive behaviour occurring prior to the birth of the affected male, to address whether the cohorts had a similar family structure prior to

the birth of the index. Section three focuses on reproductive behaviour occurring between the birth of the affected male and the diagnosis, to address the implications of diagnostic pathway for risk awareness. Section four explores reproductive behaviour occurring after the diagnosis, but before confirmation of carrier status, to address the implications of carrier testing techniques for risk awareness. Section five addresses reproductive behaviour in families after they have received the diagnosis. The final section explores the overall differences in reproductive behaviour, occurring before and after the diagnosis of the affected male.

## **1. Technological opportunities for families in the LCD and NBS cohorts**

The aim of this section is to describe the different technologies available to 38 families in the west of Scotland and 34 families in Wales, who had a son diagnosed with DMD between 1990 and 2006. First, the differences between the two diagnostic pathways are addressed. Second, the differing provision of carrier testing techniques is explored, across time and between regions. Finally, details of the reproductive technologies offered during 1990 and 2006 in the west of Scotland and Wales, are provided.

### **1.1 Differences between later clinical diagnosis in the west of Scotland and newborn screening diagnosis in Wales**

Newborn screening for DMD was introduced in Wales in 1990. Unlike many newborn screening programmes for untreatable conditions, the programme in Wales requires families to opt for screening. A systematic approach to testing and disclosing results was established (Bradley *et al.* 1993), and the programme aimed to work closely with each family's primary health care team, a local network of paediatricians and family care officers (van Ommen & Scheuerbrandt 1993, Parsons *et al.* 1996).

Newborn screening for DMD is offered to families when the midwife visits their home, six or seven days after the child's birth. A blood sample is taken from a heel

prick, to test for other conditions screened for in the UK<sup>18</sup>. Families are offered the opportunity to 'opt-in' for an extra test for DMD. Informed consent is sought. If the test demonstrates grossly elevated creatine kinase (CK) levels, the health visitor or family practitioner is contacted when the baby is about six weeks old. An appointment is made with a paediatrician before the family are contacted, to ensure the family will be seen within a day of being approached by the primary health care team.

The paediatrician offers families a second CK test to ensure the first result was not a false positive. If parents accept, blood is taken and another appointment arranged to give the results, usually on the same day, to minimise the period of uncertainty and anxiety. If the second test confirms grossly elevated CK levels, the family are offered genetic counselling and the opportunity to further the diagnostic process, initially by genetic analysis and subsequently by muscle biopsy and dystrophin analysis.

In the west of Scotland diagnosis relies on presentation and recognition of clinical symptoms. Affected boys are phenotypically normal at birth and frequently little clinical weakness can be detected before 3-5 years of age. During the early symptomatic stages progressive weakness of muscles of the pelvis, knee and hip extensors may cause delayed walking, abnormal gait, toe walking, frequent falls and difficulty climbing stairs. Often affected males demonstrate difficulty rising from the floor. Some boys may also present delayed intellectual milestones, in particular a delay in speech development.

In young boys, the cause of their slow development is often not recognised as indicative of DMD. However, once DMD is suspected, a CK test is conducted and families are referred to a genetic counsellor. If the test demonstrates grossly elevated CK levels, families in the west of Scotland are offered the opportunity to further the diagnostic process, initially by genetic analysis and subsequently by

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<sup>18</sup> As already noted in Chapter One, in the UK, the Newborn Screening Committee currently recommend newborn screening for five conditions: phenylketonuria (PKU), congenital hypothyroidism (CHT), sickle cell diseases (SCD), cystic fibrosis (CF) and medium chain acyl CoA dehydrogenase deficiency (MCADD) (National Screening Committee 2005).

muscle biopsy and dystrophin analysis. Table 5.2 highlights the differences between the two diagnostic procedures.

**Table 5.2 Differences between the diagnostic procedures**

Cohort:	LCD	NBS
Method of diagnosis:	Clinical diagnosis	Population screening
Child's condition:	Symptomatic	Pre-symptomatic
Age of child when parents informed of diagnosis	17 to 96 months	1.5 months

The different diagnostic pathways had important implications for the timing of the diagnosis. Families received a later clinical diagnosis (LCD) when the affected boy was aged, on average, 56 months; nearly four years and four months. Some families received the diagnosis before their child's second birthday. However, some families did not receive a diagnosis, until their child was eight years old. In comparison, families in the newborn screening (NBS) cohort received a diagnosis around six weeks after their child's birth. The timing of the diagnosis obviously has significant implications for families' risk awareness in subsequent pregnancies.

### **1.2 Carrier testing techniques used in the west of Scotland and Wales between 1990 and 2006**

In relation to reproductive behaviour, families may perceive themselves to be "risk aware" after receiving the diagnosis, or after they have received confirmation of their carrier status. The diagnosis of an affected child provides families with awareness that their child has a genetic condition, which may be passed on to subsequent children. However, to provide families with an exact awareness of their risk in subsequent pregnancies, it is necessary to conduct carrier tests on the mother.

To explore the differences between the cohorts in the provision of carrier testing techniques, this section is divided into two subsections. First, the different carrier testing techniques available to families in Wales and the west of Scotland are

described. Second, the differences between the cohorts in the time taken to provide mothers with confirmation of their carrier status are explored.

### *1.2.1 Provision of carrier testing techniques*

Chapter Two highlighted the increasing sophistication of techniques used to diagnose affected boys and identify carriers. Families living in Wales, and the west of Scotland, relied on the testing procedures used in laboratories in Cardiff and Glasgow, respectively. Table 5.3 highlights the different procedures used in laboratories in Glasgow and Cardiff between 1990 and 2006.

The first test offered to a mother after her child was diagnosed with Duchenne muscular dystrophy in Wales or the west of Scotland between 1990 and 2006, was the creatine kinase test and/or linkage. The results of these tests provided some mothers with some awareness of their carrier risk. However, for most families the results of CK and linkage are inconclusive; it was often necessary to conduct further genetic tests. There was a gradual change in the specific tests used to identify genetic deletions and mutations between 1990 and 2006, enabling the identification of an increasing number of deletions and duplications.

Once a gene deletion or duplication has been identified in the affected boy, it is possible to test the mother to ascertain whether she is a carrier or has a risk of germline mosaicism (GM). A carrier of the condition has a 1 in 4 (25%) risk of having an affected boy in each pregnancy, whereas a mother with a GM risk, will be informed that she has a 1 in 20 (5%) risk of having an affected boy in each pregnancy. However, it is only in recent years that it has become possible to detect all known deletions, duplications and point mutations. During the period of data collection, 1990 to 2006, it was not always possible to inform families whether the mother was a carrier or had a GM risk.

**Table 5.3 Diagnostic and carrier testing procedures used in Glasgow and Cardiff between 1990 and 2006**

<b>Time</b>	<b>Glasgow</b>	<b>Cardiff</b>
Early 1990s	Creatine Kinase Linkage FISH cDNA PFGE PCR – confirmed by Southern Blotting (initially on 8 exons, then 11, then 17 exons: 3 Prime: 42, 43, 44, 45, 47, 48, 50, 51, 52, 53, 60 5 Prime: 3,4,6,8,13,19)	Creatine Kinase Linkage  cDNA PFGE (conducted in Oxford) PCR – not confirmed by Southern Blotting (initially 11 exons, then 17 exons: 3 Prime: 42, 43, 44, 45, 47, 48, 50, 51, 52, 53, 60 5 Prime: 3,4,6,8,13,19)
Mid-late 1990s	Creatine Kinase Linkage PCR (17 exons)	Creatine Kinase Linkage PCR (17 exons) PTT (conducted in London)
Early 2000s	Creatine Kinase Linkage PCR (17 exons)  dHPLC	Creatine Kinase Linkage PCR (17 exons) PTT (Conducted in London) dHPLC Sequencing (Conducted in London)
Mid 2000s	Creatine Kinase Linkage PCR (17 exons)  dHPLC MLPA	Creatine Kinase Linkage PCR (17 exons) PTT dHPLC MLPA Sequencing

During the early 1990s, laboratories in Glasgow and Cardiff used complementary deoxyribonucleic acid (cDNA) probes to detect deletions and duplications.

Approximately 70 percent of deletions could be identified using cDNA probes, and around seven percent of boys were found to have duplications. If a deletion or duplication was identified in the child, it was possible to test the mother and inform her whether she had a 1 in 4 risk, or a 1 in 20 risk, in subsequent pregnancies.

When a deletion or duplication could not be identified, the affected boy was assumed to have a point mutation, which was undetectable by cDNA. In these families, the mother's carrier risk was calculated by combining pedigree analysis,



creatine kinase results, and linkage analysis, in a Bayesian calculation. Rather than providing a mother with information on whether she was a carrier, or had a GM risk, she would be provided with information on her “carrier risk” (e.g. that the mother had a percentage risk of being a carrier).

In 1993, laboratories in both Glasgow and Cardiff started using polymerase chain reaction (PCR), to identify deletions and mutations in 17 exons at the 3’ and 5’ “hot-spot” regions of the dystrophin gene. Although PCR increased the reliability and accuracy of detecting deletions and duplications, it was still only possible to detect gene deletions in about 70 percent of cases, and duplications in around seven percent of cases. In the remaining families, the mothers’ risk of being a carrier was assessed using pedigree analysis, creatine kinase results, and linkage.

In the early 1990s, in an attempt to identify point mutations, the laboratory in Wales started sending samples to a laboratory in Guys Hospital, London, to carry out protein truncation tests (PTT). In Scotland, the laboratory was unable to detect point mutations until the early 2000s, when denaturing high performance liquid chromatography (dHPLC) was introduced. The ability to identify point mutations further increased the proportion of mothers who could be informed of their carrier status, rather than their “carrier risk”. By the mid-2000s both laboratories, in Glasgow and Cardiff, were using multiplex ligation-dependent probe amplification (MLPA). The procedure is capable of detecting all known deletions and duplications. In Cardiff, if a mutation was not detected, sequencing was conducted.

### ***1.2.2 Time taken to provide mothers with confirmation of carrier status***

The use of different carrier testing techniques in Wales and the west of Scotland, combined with differing administrative procedures, led to considerable differences in the provision of carrier status information. Table 5.4 highlights the difference between the two cohorts in the time taken to confirm carrier status, through cDNA, PCR, PTT, dHPLC, MLPA, or sequencing.

**Table 5.4 Number of months between diagnosis and confirmation of carrier status**

<b>Time Period</b>	<b>NBS (range)</b>	<b>LCD (range)</b>	<b>Overall (range)</b>
<b>1990-1995</b>	77.60 (5 to 169)	85.30 (35 to 118)	79.38 (5 to 118)
<b>1996-2000</b>	26.67 (4 to 89)	7.94 (0 <sup>19</sup> to 44)	13.05 (0 to 89)
<b>2001-2006</b>	17.10 (3 to 44)	9.53 (0 to 54)	13.88 (0 to 54)

Families who received a diagnosis of DMD before 1995 had to wait, on average, over six and a half years before receiving confirmation of their carrier status (range = 5 years to 14 years). The difference between the three time periods highlights the impact of increasingly sophisticated carrier testing techniques on the capacity to provide families with prompt confirmation of their carrier status. After the introduction of PCR for 17 exons, the time taken to provide confirmation of carrier status reduced dramatically. However, during the period 1996 to 2006, families who received a newborn screening diagnosis had to wait over twice as long to receive confirmation of their carrier status, than families in the LCD cohort.

Although there are clearly differences between the two regions, the range of time taken to provide families with confirmation of their carrier status also indicates differences between families. In some families, the gene deletion or duplication was easy to identify; in others, a variety of tests had to be conducted before the mutation could be found. In Wales, samples often had to be sent to Oxford for PFGE, or London for PTT. In the west of Scotland, families had to wait until more sophisticated techniques had been introduced in the laboratory in Glasgow. The delay resulting from sending samples, or waiting for the introduction of more sophisticated techniques, often lasted for a considerable number of years. The implications of the different carrier testing procedures, for reproductive behaviour, are addressed in section four.

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<sup>19</sup> Carrier testing was conducted and results were received within a month of the diagnosis

### **1.3 Reproductive technologies**

Once families were aware of the diagnosis, it was possible to offer them prenatal testing in subsequent pregnancies, using either amniocentesis, performed at 15-18 weeks gestation, or chorionic villus sampling (CVS), performed at 10-12 weeks gestation. If a gene deletion or duplication had been identified in the affected boy, it was possible to determine whether the foetus carried the same mutation. If the gene deletion or duplication was found in the foetus, families were provided with the option of termination. The majority of families, who opted for prenatal testing, chose to use CVS. Although some families used amniocentesis, no difference could be found between those who opted for either test. There were also no differences between the regions in the provision of prenatal testing.

By the early 2000s, a number of parents in both cohorts were expressing interest in using pre-implantation genetic diagnosis (PGD). However, data could only be found on one family who been through the process of PGD. Unfortunately the family's attempts to conceive had not been successful. Due to the lack of subsequent pregnancies occurring as a result of PGD, only the use of prenatal testing is addressed in this chapter.

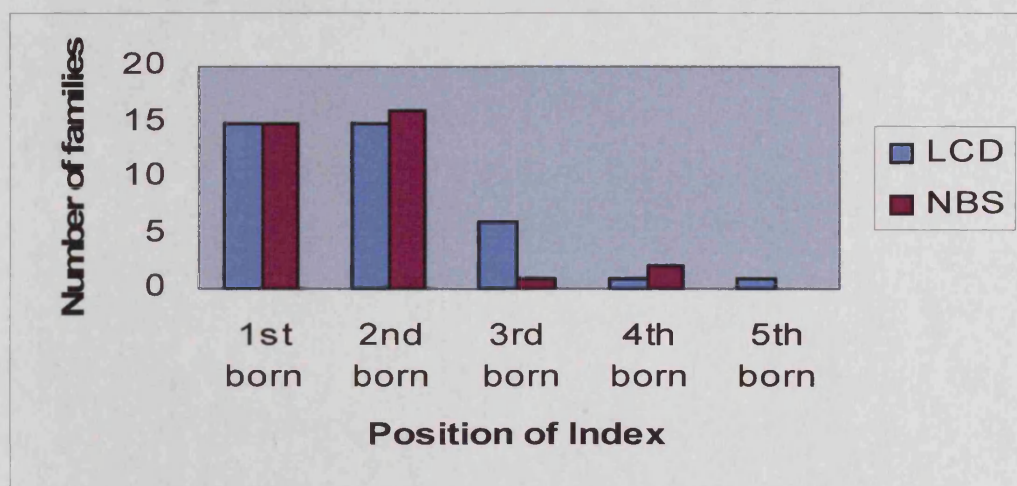
## **2. Reproductive behaviour prior to the birth of the index**

Before comparing the influence of diagnostic pathway, carrier testing techniques and reproductive technologies on reproductive behaviour, it was essential to ensure the possibility of comparative analysis. If the underlying family structure of each cohort differed significantly prior to the diagnosis, it would be difficult to address the influence of technological developments on reproductive behaviour after the diagnosis. Two quantifiable variables were identified, which may also have influenced subsequent reproductive behaviour; the position of the index (whether the first affected child was first/second/third born etc), and the age of the mother. These two variables are explored in the next two sections.

## 2.1 Index position

A total of 58 pregnancies (LCD=34, NBS=24) occurred in 42 families (LCD=23, NBS=19), prior to the birth of the index. According to national data collected by the Office of National Statistics (ONS 2008a) and the General Registrars Office Scotland (GRO-Scotland 2006), the most common family size is two children in both Scotland and Wales. Therefore, families, in which the index was the third born child, might be less likely to have subsequent pregnancies, than families in which the index was the first born child. Figure 5.1 shows the position of the index in each cohort.

Figure 5.1 Position of index by cohort



The index was the first or second born child in a very similar proportion of families in both cohorts. The index was born third or more in a slightly higher number of LCD families ( $n=8$ ), than NBS families ( $n=3$ ). However, table 5.5 shows that the difference was not statistically significant. However, the slightly higher number of previous pregnancies in the LCD cohort might result in a slightly higher number of subsequent pregnancies in the NBS cohort. Index position cannot be ruled out as a potential confounding factor.

**Table 5.5 Confidence interval for difference in proportion of index by position**

	Families (n=72)		Difference between proportions	95% Confidence interval for difference
	LCD (n=38)	NBS (n=34)		
No. with index position	n (%)	n (%)		
First	15 (39.5)	15 (44.1)	-0.046	-0.262 to 0.173
Second	15 (39.5)	16 (47.1)	-0.076	-0.289 to 0.146
Third or more	8 (21.1)	3 (8.8)	-0.122	-0.051 to 0.286

## 2.2 Age of mothers

The age of mothers has important implications for reproductive behaviour. The probability of being able to conceive is twice as high for women aged 19-26 years compared with women aged 35-39 years (Dunson *et al.* 2002). Therefore, any significant difference between cohorts in the age of mother at first pregnancy, or the age of mother at the birth of the index, may have considerable implications for the number of subsequent pregnancies.

National data shows that the mean age<sup>20</sup> of mothers at childbirth in Scotland and Wales<sup>21</sup> has remained fairly consistent between the regions. The mean age of mother at first birth has gradually increased from around 26 years in 1977, to 27 years in 1991, to 29 years in 2005 (ONS 2008a, GRO-Scotland 2006). National data on mothers' age are separated for each birth; first, second, third or more, on a yearly basis. Due to the relatively small numbers in each cohort it was not possible to directly compare the mean age of mothers, for each pregnancy, on yearly basis. However, the overall similarity between the regions suggests that there should be no significant difference between the cohorts in the mean age at childbirth.

Table 5.6 demonstrates the difference between cohorts in the mean age of mothers at first pregnancy and at the birth of the index. The range of ages in the LCD cohort, were 16 to 38 years at both first pregnancy and birth of index, compared to 18 to 35 years in the NBS cohort. The difference between the cohorts in both the range of

<sup>20</sup> Standardised ages are used to take into account the different age structures of the populations

<sup>21</sup> ONS data on age of mother is amalgamated for England and Wales and therefore not possible to extract relevant data for Wales only.

ages and the mean age is consistently small, suggesting that the age of mother is unlikely to be a confounding factor in subsequent reproductive behaviour.

**Table 5.6 Confidence interval for difference in mean age of mothers**

	<b>Mothers (n=72)</b>		<b>Difference between means</b>	<b>95% Confidence Interval</b>
	<b>LCD (n=38)</b>	<b>NBS (n=34)</b>		
Data missing	0	3		
Mean age of mother at 1 <sup>st</sup> pregnancy	24.55	25.00	-0.45	-2.09 to 2.99
Mean age of mother at birth of index	27.71	27.69	0.02	-2.39 to 2.43

### **3. Reproductive behaviour between birth of index and diagnosis**

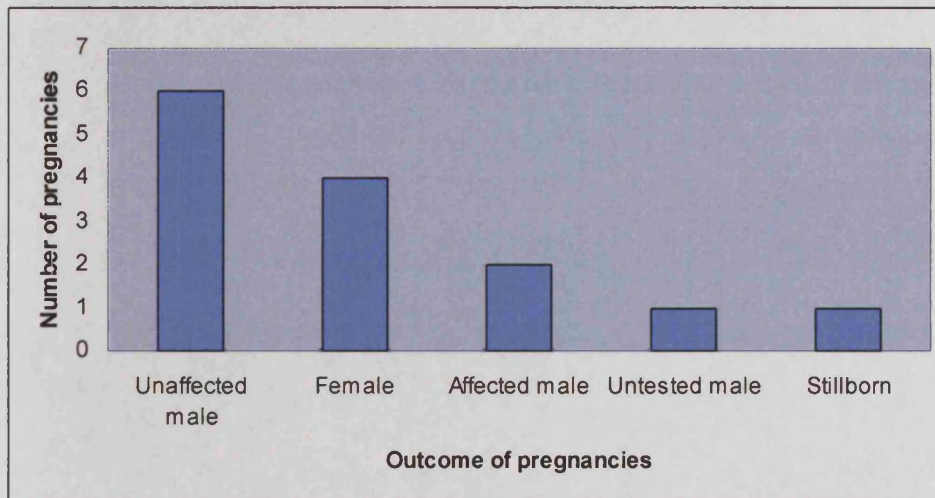
The aim of this section is to explore the implications of diagnostic pathway for risk awareness in subsequent pregnancies. All families received a newborn screening diagnosis within weeks of their child’s birth. As it was not possible for NBS families to conceive prior to the diagnosis, this section only explores reproductive behaviour in the LCD cohort, occurring between birth and diagnosis.

In the LCD cohort, affected boys were diagnosed clinically between the age of 17 months and eight years. The average age was four years and four months. Seventeen LCD families had 29 subsequent pregnancies after the birth of the index. Ten of the 17 families had 13 pregnancies before the diagnosis of the first affected male, and therefore 44.8% of subsequent pregnancies in the LCD cohort occurred prior to the diagnosis. Figure 5.2 shows the outcome of the 14<sup>22</sup> births.

<sup>22</sup> One pregnancy resulted in the birth of twins



**Figure 5.2 Outcome of subsequent pregnancies in LCD cohort, occurring between birth and diagnosis of index**



The majority of the 14 births, occurring prior to the diagnosis of the index, resulted in the birth of unaffected males or females (n=10). However, only four of the 13 pregnancies occurred in carriers; two of which resulted in the birth of a second affected male. The proportion of mothers who were carriers was 53% in both cohorts. However, the proportion of carriers in the LCD cohort, who had subsequent pregnancies prior to the diagnosis, was only 44%. If the proportion of carriers having subsequent pregnancies prior to the diagnosis was representative of the total LCD cohort, it is possible that there may have been a greater number of second affected boys.

#### **4. Reproductive behaviour between diagnosis and confirmation of carrier status**

The aim of this section is to explore the implications of carrier testing for risk awareness. To address whether reproductive behaviour is affected by the provision of more accurate carrier testing techniques, this section addresses the number of pregnancies occurring after families received the diagnosis, but before mothers received confirmation of their carrier status.

Chapter two and section one of this chapter highlighted the significant technological developments that have enabled an increasingly prompt provision of more accurate

carrier testing. Before the introduction of more sophisticated diagnostic and carrier testing techniques, many mothers were provided with a probability of being a carrier (carrier risk) and a probability of having an affected boy (reproductive risk). As noted in Chapter Three, a number of studies highlight the difficulty mothers' encounter when trying to make sense of complex assessments of risk, particularly in defining the difference between carrier risk and reproductive risk (Parsons & Atkinson 1993, Parsons & Clarke 1993).

Section two of this chapter highlighted the decreasing length of time taken to provide mothers with confirmation of their carrier status, over the three time periods; 1990 to 1995, 1996 to 2000 and 2001 to 2006. Table 5.7 shows the number of pregnancies occurring between the diagnosis and confirmation of carrier status, during these three time periods.

**Table 5.7 Number of pregnancies between diagnosis and confirmation of carrier status**

<b>Time Period</b>	<b>NBS</b>	<b>LCD</b>	<b>Overall</b>
<b>1990-1995</b>	14	3	17
<b>1996-2000</b>	1	1	2
<b>2001-2006</b>	0	5	5
<b>Total</b>	<b>15</b>	<b>9</b>	<b>24</b>

The data from this study suggests that the accuracy of carrier tests may not be a primary consideration in reproductive decision-making; of the 50 pregnancies occurring after the diagnosis of the index, nearly half (n=24) occurred before mothers had received confirmation of their carrier status.

Table 5.7 shows considerable differences, between the cohorts, in the number of pre-confirmation pregnancies occurring in each time period. In the NBS cohort, the majority of pre-carrier confirmation pregnancies (14/15) occurred between 1990 and 1995, when the average time taken to confirm carrier status was 6.5 years. In contrast, between 1996 and 2006, only one pregnancy occurred before NBS families had received confirmation of their carrier status. However, the data suggests that the fewer pre-confirmation pregnancies were a result of families having less time to conceive, rather than waiting for confirmation of their carrier status. During 1996



and 2006, the average time between diagnosis and confirmation of carrier status had reduced dramatically to 27 months (range = 4 months to 7.4 years) and the average birth interval<sup>23</sup> was 38.5 months (range = 11 to 6 years).

In the LCD cohort, pre-carrier confirmation pregnancies were more evenly spread throughout 1990 and 2006. However, the data does not suggest that families in the LCD cohort were more likely to wait for confirmation of carrier status. Although 16 boys affected by DMD were born in the west of Scotland between 1990 and 1995, only three received a diagnosis during this period. The majority of the 16 families in the LCD cohort (13/16) received a diagnosis when the average length of time taken to provide mothers with confirmation of their carrier status had reduced from seven years to eight months. It was therefore unlikely that families would conceive between receiving the diagnosis and obtaining confirmation of their carrier status.

Although mothers did not appear to wait for confirmation of their carrier status, many chose to use prenatal testing; 14 of the 24 pregnancies occurring prior to receiving confirmation of carrier status were tested. One possible interpretation of the data is that the availability of prenatal testing had a greater influence on reproductive behaviour than the availability of accurate carrier testing techniques. Due to the lack of evidence to suggest families waited for confirmation of their carrier status before proceeding with subsequent pregnancies, from this point onwards “risk awareness” is defined as the point at which families received the diagnosis.

## **5. Reproductive behaviour after the diagnosis**

The aim of this section is to explore the differences in reproductive behaviour in risk aware families who received a later clinical diagnosis, and those who received a newborn screening diagnosis. The section is divided into three subsections to address the following reproductive factors, occurring after the diagnosis:

- Number of subsequent pregnancies
- Outcome of subsequent pregnancies

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<sup>23</sup> Birth interval is explored in greater depth in section five

- Uptake of prenatal testing
- Birth interval between the index and each subsequent pregnancy

### 5.1 Number of pregnancies after the diagnosis

The focus of this section is on reproductive behaviour in risk-aware families (i.e. families who have received the diagnosis). However, defining the influence of risk awareness in LCD families who chose not to have subsequent pregnancies is inherently problematic. The decision to cease family building may have been affected by the diagnosis, or families may have already completed family building prior to receiving the diagnosis. Although it is not possible to assess the influence of risk awareness on the decision to cease family building, families' decisions *not* to have subsequent children are as relevant as their decisions about how to proceed with subsequent pregnancies. The first part of this section therefore addresses the number of subsequent pregnancies in all LCD families, including those who may not have been risk aware at the time of the decision.

Over half of the 72 families (51.4%) in the LCD and NBS cohorts, chose not to have subsequent pregnancies after the birth of their affected child (LCD=21, NBS=16). Table 5.8 shows that the proportion of families choosing to not to have subsequent pregnancies was higher in the LCD cohort (55.3%) compared to the NBS cohort (47.1%). However, the difference was not statistically significant.

National data shows that the average family in Wales and the west of Scotland is two children. Of the 72 families in the total cohort, 42 (58.3%) had reached family size of two, at the birth of their affected child. It is therefore possible that many families had already completed family building after the birth of their affected child. The lower proportion of LCD families having subsequent pregnancies may be related to the slightly higher number of previous pregnancies, which was highlighted in section three.

**Table 5.8 Number of subsequent pregnancies after birth of index**

Number of subsequent pregnancies	No. of Families (n=72)		Difference between proportions	Confidence Interval
	LCD (n=38) (%)	NBS (n=34) (%)		
<b>0</b>	21 (55.3)	16 (47.1)	0.082	-0.143 to 0.296
<b>1</b>	9 (23.7)	10 (29.4)	-0.057	-0.256 to 0.143
<b>2</b>	5 (13.2)	4 (11.8)	0.014	-0.152 to 0.172
<b>3 or more</b>	3 (7.8)	4 (11.8)	-0.039	-0.196 to 0.109

A total of 63 pregnancies occurred after the *birth* of the first affected male in the family; 29 pregnancies in 17 LCD families and 34 pregnancies in 18 NBS families. A total of 50 pregnancies (LCD=16, NBS=34) occurred in 27 women (LCD=9, NBS=18) after the *diagnosis* of the first affected male. Table 5.9 demonstrates the difference between risk-aware families in the two cohorts in relation to carrier status and number of subsequent pregnancies.

**Table 5.9 Number of subsequent pregnancies in risk aware families by carrier status**

Carrier status	No. of Pregnancies (n=50)		Difference between proportions	95% confidence Interval
	LCD (n=16) N (%)	NBS (n=34) N (%)		
Carrier	8 (50.0)	23 (67.7)	-0.177	-0.433 to 0.100
GM	6 (37.5)	9 (26.5)	0.110	-0.143 to 0.377
Unknown	2 (12.5)	2 (5.8)	0.066	-0.094 to 0.305

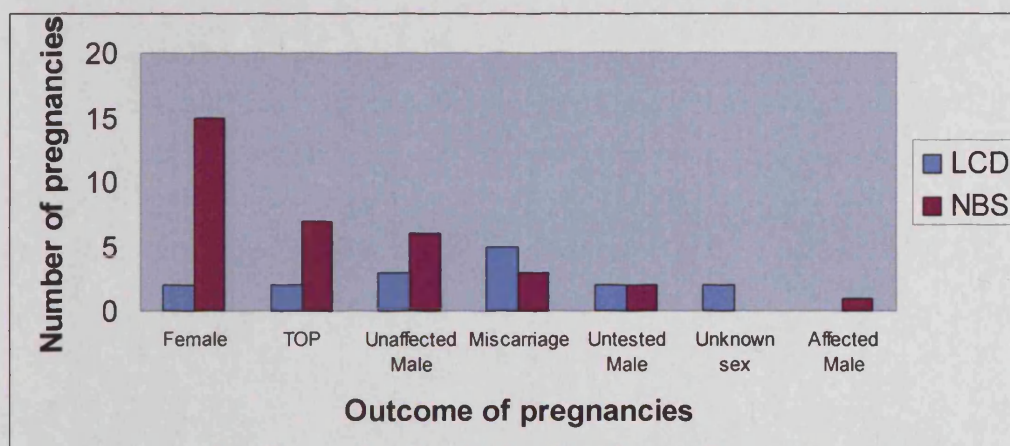
In the NBS cohort, 11 risk aware carriers had 23 subsequent pregnancies and 8 mothers with a germline mosaicism (GM) risk had 9 subsequent pregnancies. In contrast, in the LCD cohort, only four risk aware carriers had eight subsequent pregnancies and five women with a GM risk had 6 subsequent pregnancies. A greater proportion of pregnancies occurred in carriers in the NBS cohort (67.7%), than in the LCD cohort (50.0%). However, the confidence intervals show that there were no significant associations between cohort and carrier status, in the number of subsequent pregnancies. The data suggests that the difference between a 25% carrier risk and a 5% GM risk may have not been a primary consideration in the reproductive decision-making process.

## 5.2 Outcome of subsequent pregnancies after diagnosis

Figure 5.3 highlights considerable differences in the outcome of the 50 pregnancies occurring in risk aware families. In the NBS cohort, the most frequent outcome of subsequent pregnancies was the birth of a female. In the LCD cohort there were no similar trends. The most frequent outcome of pregnancies in the LCD was a miscarriage. However, it should be noted that this figure is skewed by one woman, who experienced three miscarriages.

Seven pregnancies were terminated in the NBS cohort; five of which occurred after prenatal testing identified a foetus affected by DMD. One pregnancy was terminated after prenatal diagnosis identified another condition and one was terminated prior to prenatal testing. In contrast, only two pregnancies were terminated in the LCD cohort, both of which were males affected by DMD. Interestingly, in risk-aware families, there was one second affected child born to a NBS family, but none to LCD families.

Figure 5.3 Outcome of 50 subsequent pregnancies in risk aware families



## 5.3 Uptake of prenatal testing

A number of interesting findings emerged from the data on the uptake of prenatal testing. First, there was a significant difference in the uptake of prenatal testing between cohorts, suggesting that the diagnostic pathway influences reproductive behaviour. Second, there was a marked decline in the uptake of prenatal testing



between 1990 and 2006, across both cohorts. Third, some families did not demonstrate consistency in their decision to use prenatal testing. These findings are explored in the sections below.

### 5.3.1 Comparison of uptake of prenatal testing between cohorts

To assess the uptake of prenatal testing, it was necessary to exclude families who were not provided with the option of prenatal testing. Obviously families who had not received the diagnosis were not offered prenatal testing for DMD. In addition, eight risk-aware families miscarried prior to prenatal testing (LCD=5, NBS=3), and two risk-aware families chose to terminate prior to testing (LCD=1, NBS=1). Therefore data were analysed from a total of 40 pregnancies (LCD=10, NBS=30). Figure 5.4 illustrates the considerable differences between the cohorts in the uptake of prenatal testing.

**Figure 5.4 Proportion of tested pregnancies by cohort**

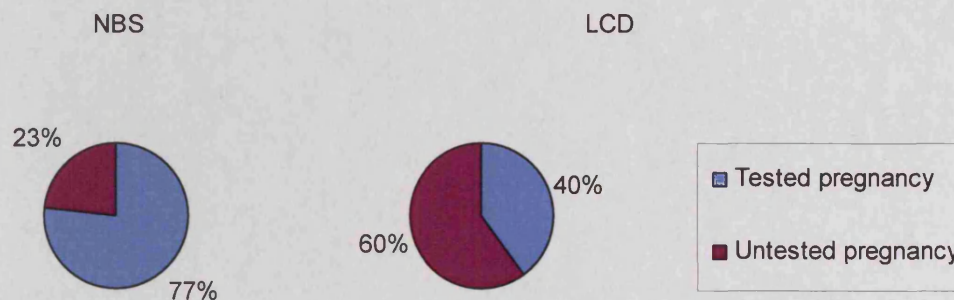


Table 5.10 shows a contingency table of the difference between the two cohorts. In the LCD cohort, only 40% (n=4) of pregnancies occurring in risk aware women were tested. In contrast, 77% (n=23) of pregnancies were tested in the NBS cohort. There was a significant association between cohort and whether or not subsequent pregnancies were tested;  $p=0.05^{24}$ . Families who received a later clinical diagnosis were significantly less likely to opt for prenatal testing in subsequent pregnancies.

<sup>24</sup> Calculated using Fishers exact test

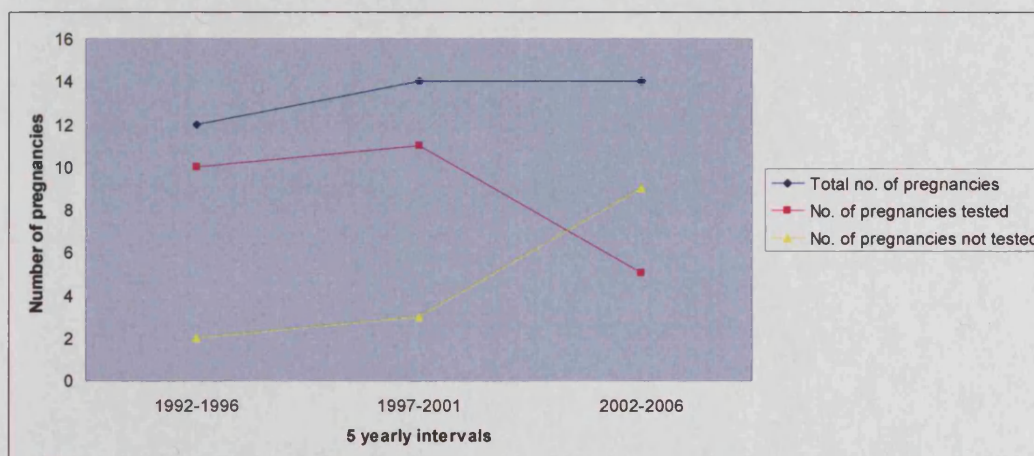
Table 5.10 Contingency table for difference in uptake of prenatal testing

	Number of pregnancies in risk aware women		Total
	LCD	NBS	
<b>Tested</b>	4	23	<b>27</b>
<b>Not tested</b>	6	7	<b>13</b>
<b>Total</b>	<b>10</b>	<b>30</b>	<b>40</b>

### 5.3.2 Comparison of uptake of prenatal testing between 1990 and 2006

In addition to the significant difference in the uptake of prenatal testing between the two cohorts, there was also a marked difference over time. Figure 5.5 highlights the gradual decline in the uptake of prenatal testing in both cohorts. Between 1992 and 1996, 83% (n=10) pregnancies were tested, compared to only 36% (n=5) between 2002 and 2006. The majority of untested pregnancies occurred between 2002 and 2006; four of the seven untested pregnancies in the NBS cohort and five of the six untested pregnancies in the LCD cohort occurred during this period.

Figure 5.5 Number of tested/untested pregnancies between 1992<sup>25</sup> and 2006



The data collection finished in 2006 and therefore it is not possible to assess whether the decline in the uptake of prenatal testing is a temporary or lasting change. However, it is possible that families are becoming less inclined to use invasive prenatal testing.

<sup>25</sup> There were no subsequent pregnancies prior to 1992

### ***5.3.3 Consistency of decision to use prenatal testing***

Another important factor in the uptake of prenatal testing is whether families consistently made the same decision, in each subsequent pregnancy. Nine families (LCD=2, NBS=7) gave birth to more than one child after the diagnosis of the index. Both LCD families, and the majority of NBS families (n=5) were consistent in their decisions whether or not to test each pregnancy (i.e. if they tested the first pregnancy after the index, they also tested subsequent pregnancies).

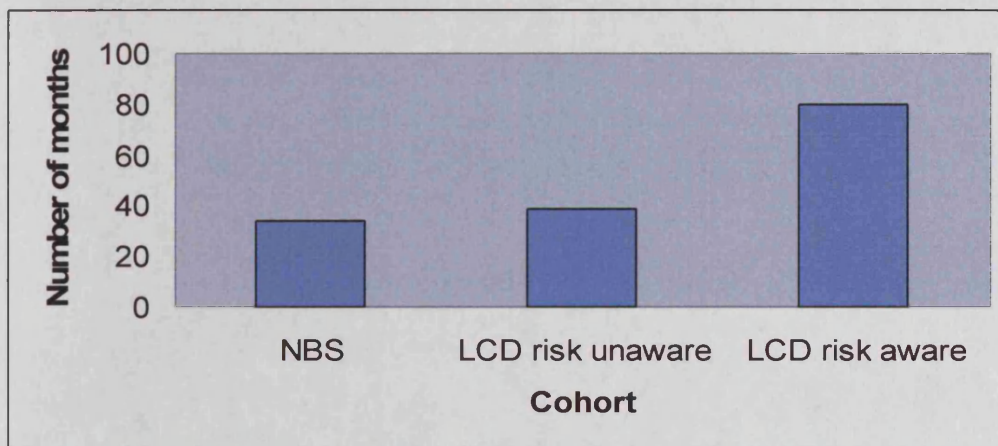
However, two of the seven families in the NBS cohort did not demonstrate consistency in their decisions about prenatal testing. One NBS family chose not to test their first pregnancy, but tested their second subsequent pregnancy. Another NBS family chose to test and terminate her first pregnancy, tested the second pregnancy, but chose not to test her third pregnancy. The genetic counselling notes in the family's medical file suggested that the mother "could not cope" with the prospect of terminating another pregnancy. The lack of consistency suggests that the influences on reproductive behaviour, and perceptions of the benefit of testing and terminating, may change over time.

### **5.4 Birth interval**

Another important aspect of reproductive decision-making in families affected by DMD is whether families choose to delay having subsequent children after receiving the diagnosis. National data for the whole of the UK shows that the median birth interval between first and second child, ranged from 33 months in 1990 to 38 months in 2006. Birth interval between second and third child remained consistently higher than birth interval between first and second, and ranged from 37 months in 1990 and 42 months in 2006. The birth interval between third and fourth child was similar to that between first and second child (ONS 2008b). The data from this study showed a marked difference in birth interval between the two cohorts. Figure 5.6 shows the average birth interval, between the index and the first subsequent pregnancy, in both cohorts.



Figure 5.6 Mean birth interval between index and first subsequent pregnancy



Due to the relatively low numbers in each cohort, it was not possible to directly compare the birth interval by both year and index position. However, the mean birth interval found in NBS families (33.5 months) and LCD risk-unaware families (38.5 months) is roughly equivalent to that found in the general population. The slightly lower birth interval in the NBS cohort may be related to the position of the index (i.e. birth interval between first and second, and third and fourth child, is generally found to be lower than the birth interval between second and third child). The index was the first or third born child in a higher proportion of families in the NBS cohort (55.5%), than LCD cohort (33%).

The mean birth interval in risk aware families in the LCD cohort was 79.6 month (range 35 to 136 months); considerably higher than either the 33.5 months (range 11 to 66 months) in the NBS cohort, or the 38.5 months (range 11 to 72 months) in families who were unaware of their risk in the LCD cohort. One possible explanation is that families in the LCD cohort, who had not had subsequent pregnancies prior to the diagnosis, deliberately delayed further child-bearing for some years after the diagnosis. However, the considerable range in birth intervals suggest that the diagnostic pathway may not be the only influence on whether or not to delay childbearing; there was no statistically significant difference between the two cohorts.



## 6. Overall reproductive behaviour

The aim of this section is to summarise the outcome of all the differences between the cohorts, which were explored in previous sections. To achieve this, two factors are addressed: the fertility rate before and after the diagnosis, and the overall family size at the end of data collection.

### 6.1 Fertility rate pre/post diagnosis

To assess the implications of diagnostic pathway on risk awareness, the overall fertility rate was calculated in families, before and after they received the diagnosis. The fertility rate was calculated by dividing the number of pregnancies by number of woman-years, when women were aged between 16 and 45. Although this calculation is extremely crude, it provides an overview of reproductive behaviour both prior to and following the diagnosis of the index.

Table 5.11 highlights the mean number of woman-years in each cohort in which a woman is fertile and either risk-unaware (prior to diagnosis of son) or risk-aware (after diagnosis of son), as well as the fertility rate during each risk awareness category. There was a marked difference between the cohorts in the fertility rate after the diagnosis, suggesting that diagnostic pathway may influence reproductive behaviour. However, in both cohorts, the fertility rate was higher prior to than following the diagnosis.

**Table 5.11 Crude fertility rate before and after diagnosis**

	<b>LCD (n=38)</b>	<b>NBS (n=34)</b>
Mean no. of fertile years per woman, prior to diagnosis	16.70	12.19
Crude fertility rate prior to diagnosis	0.13	0.14
Mean no. of fertile years between diagnosis and end of data collection (2006)	6.08	9.44
Crude fertility rate after diagnosis	0.07	0.11
Mean no. fertile years remaining (after 2006)	6.86	7.93

The fertility rate prior to the diagnosis is similar between the cohorts (LCD=0.13, NBS=0.14). In both cohorts, the fertility rate is higher prior to the diagnosis. One possible explanation for the higher fertility rate prior to the diagnosis is that families chose to deter or defer child bearing after receiving the diagnosis. However, it is also possible that many families may have already completed family building prior to the diagnosis.

The fertility rate after the diagnosis is higher in the NBS cohort (0.11), than the LCD cohort (0.07). One possible explanation is that families in the LCD cohort delayed childbearing and may have more children in the future. However, mothers in the LCD cohort had a lower mean number of fertile years remaining, before they reached the age of 45, which suggests that LCD families are more likely to have completed family building.

## 6.2 Overall family size

The data on overall family size highlighted some interesting differences between the two cohorts. As previously noted, the most common number of children born to families in both Wales and Scotland, is two. The number of one-child families has remained fairly consistent during the last three decades. However, the proportion of families having three or more children has fallen. It is difficult to directly compare national data to data collected during this study, not least because families may not have completed family building<sup>26</sup>. However, it is clear from figure 5.7 that the family size in the NBS cohort broadly reflects national data. In contrast, family size in the LCD cohort bears no resemblance to national data.

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<sup>26</sup> Data in this study was collected and analysed on the total number of pregnancies, whereas national data shows the total number of live births. National data on family size is collated when mother is over 45 years old and assumed to have finished family building. In the LCD and NBS cohorts only 6 of 72 mothers were over the age of 45 when data collection finished in 2006.

Figure 5.7 Total family size in the LCD and NBS cohorts

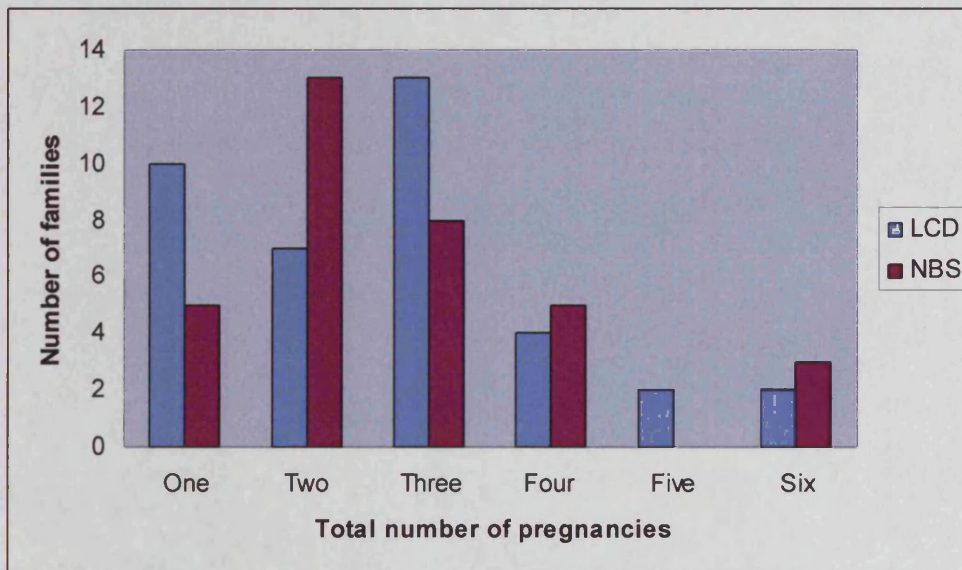


Figure 5.7 shows a clear disparity between the cohorts in the most common family size. In the NBS cohort the most common number of pregnancies in each family was two, compared to three in the LCD cohort, closely followed by one pregnancy. Of the 13 LCD families who had a total of three children, the index was the third born in four families. A further four families were aware of their risk before reaching a family size of three. However, five LCD families were unaware of their risk in seven pregnancies, before reaching family size of three children.

One possible explanation for the higher number of families in the LCD cohort who had only one child might have been that the LCD mothers were younger, and therefore more likely to have subsequent children after data collection finished. However, the mean number of fertile years remaining in each woman, after data collection completed in 2006, highlighted that LCD families had less time left, in which to conceive subsequent pregnancies. Only three of the 10 mothers in the LCD cohort, who only had one pregnancy, were under 40 years of age in 2006, compared to nearly all the NBS women (4/5). The age of the mothers suggests that LCD mothers, with only one child, were less likely to have subsequent children.

The data presented in this section highlights two key points. First, when addressing the overall implications of diagnostic procedure on reproductive behaviour, it is important to consider the number of families who have pregnancies prior to the birth of their affected child. Many families will have completed family building when the index is born, and therefore the provision of reproductive choice may be irrelevant. However, it should be noted that the risk-awareness may be relevant to at-risk female relatives.

Second, the fertility rate after the diagnosis was higher in the NBS cohort, despite the similarities in crude fertility rate prior to the diagnosis. Data on family size demonstrated considerable differences between the two cohorts. Family size in the NBS cohort was more likely to reflect the national average, whereas family size in the LCD cohort demonstrates an unusual pattern. One possible explanation is that NBS families, and in particular carriers, feel more confident in attempting to reach their ideal family size. The significantly lower uptake of prenatal testing in the LCD cohort suggests that families, who received a later clinical diagnosis, were less comfortable with the prospect of testing and terminating a subsequent child.

## **7. Summary of findings**

During the period of data collection, 1990 to 2006, the provision of reproductive technologies remained fairly consistent between the two regions. However, different diagnostic pathways and carrier testing techniques had significant implications for families who received a diagnosis of DMD in Wales, or the west of Scotland. Affected males received a later clinical diagnosis at an average age of 4 years and 4 months (range 17 months to 8 years). In contrast, newborn screening families predominantly received a diagnosis for their affected child at around six weeks, after the birth.

The use of particular carrier testing techniques differed across time and between regions. Between 1990 and 1995, families in both cohorts had to wait an average of 79 months before receiving confirmation of their carrier status. After the introduction of more accurate and less time consuming testing procedures, there was

a significant reduction in the time taken to confirm a mothers' carrier status. However, variations in administrative procedures and testing techniques used in laboratories in Glasgow and Cardiff, led to considerable differences in the time taken to provide confirmation. Between 1996 and 2006, families in the NBS cohort had to wait around two years for confirmation; over twice as long as their LCD counterparts.

The implications of increasing technological sophistication, for reproductive behaviour, varied between families. Table 5.12 highlights how the data presented met the aims and objectives outlined at the beginning of this chapter, by defining the different reproductive behaviour between cohorts at varying times.

**Table 5.12 Reproductive behaviour by time**

<b>Time period</b>	<b>Difference between cohorts</b>
Prior to birth of index	The underlying family structure was not significantly different.
Prior to diagnosis of index	Diagnostic pathway had considerable implications for the number of pregnancies occurring between the birth and diagnosis of index in the LCD cohort. However, there was little difference between the cohorts in the number of second affected boys born.
Prior to confirmation of carrier status	Families did not appear to wait for confirmation of carrier status, before proceeding with subsequent pregnancies.
After diagnosis	Families in the NBS cohort were more likely to have subsequent pregnancies, and were significantly more likely to use prenatal testing. Birth interval in the NBS and risk-unaware LCD families reflected the national average. In contrast, risk aware LCD families who had not conceived prior to the diagnosis, appeared to delay family building.
Overall	Fertility rate in families prior to the diagnosis is similar in both cohorts. Fertility rate after the diagnosis is higher in NBS cohort. Overall family size in NBS cohort reflects national average. Considerably more LCD families have either three or only one child.

Over half of the 72 families (51.3%) in the LCD and NBS cohorts, chose not to have subsequent pregnancies. Quantitative data does not allow an assessment of

whether the decision to cease family building was related to the diagnosis.

However, national data shows that the average family has two children. In the total cohort, 58.3% of the families already had at least two children at the birth of the affected child; suggesting that, for many families, the decision to cease family building may not have been related to the diagnosis.

Diagnostic pathway had considerable implications for the number of pregnancies occurring between the birth and diagnosis of the first affected male. However, there was little difference in the number of second affected children born. In the LCD cohort, nearly half of the subsequent pregnancies (44.8%) occurred prior to the diagnosis. Two LCD families had a second affected child before the diagnosis of the first<sup>27</sup>. In contrast, all NBS families had received the diagnosis prior to embarking on subsequent pregnancies. However, one NBS family chose not to have prenatal testing and had a second affected child.

Carrier testing did not appear to have a notable influence on reproductive behaviour. Nearly half of the pregnancies after the diagnosis (48.0%) occurred before families had received confirmation of their carrier status. The majority of families, who had to wait a considerable amount of time before receiving confirmation of their carrier status, proceeded with subsequent pregnancies regardless. There was a reduction in the number of pre-carrier confirmation pregnancies after more sophisticated technologies were introduced in the early to mid 1990s. However, the average birth interval after families received the diagnosis was considerably greater than the time taken to provide families with confirmation. It is therefore not possible to address whether families *chose* to wait for confirmation, or just happened to conceive after carrier confirmation had been provided.

Once families had received the diagnosis, families in the NBS cohort were more likely to have subsequent pregnancies. There were a slightly higher number of previous pregnancies in the LCD cohort, which may have had some influence on the number of subsequent pregnancies. However, the overall fertility rate in the NBS and LCD cohorts suggests that NBS families are more likely to have more children,

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<sup>27</sup> It is possible that the number of second affected boys may have been higher, if the proportion of mothers, who were carriers, was representative of the total cohort.

regardless of the number of previous children. It is possible that a newborn screening diagnosis increased families desire to have more children.

The overall family size in the NBS cohort closely resembled that of families in the general population. In contrast, families who received a later clinical diagnosis were more likely to have only one child, or three children. Risk aware families, who chose to have subsequent pregnancies, made significantly different decisions regarding prenatal testing, depending on which diagnostic procedure they had received ( $p=0.05$ ). This raises an important question: why are families who receive a newborn screening diagnosis, significantly more likely to use prenatal testing in subsequent pregnancies? This question is explored in the qualitative section of the study.

There were also notable differences in the birth interval. In families, who had received a newborn screening diagnosis and LCD families who were unaware of their risk, the birth interval broadly reflected the birth interval found in the general population. In contrast, risk aware families in the LCD cohort who had not had subsequent pregnancies prior to the diagnosis, appeared to wait considerably longer before proceeding with subsequent pregnancies.

In conclusion, a newborn screening diagnosis appears to “normalise” reproductive behaviour. Families who received a newborn screening diagnosis were more likely to have subsequent pregnancies, were more likely to use prenatal testing, and were more likely to reach a family size that reflected the national average. Interestingly, risk aware families in the LCD cohort did not appear to respond to the provision of reproductive choice in the same way. Many LCD families chose not to have prenatal testing. In addition, the slightly higher number of families choosing not to have subsequent pregnancies may suggest that some families chose to cease family building, as a result of the diagnosis.

## Chapter Six

### Living with Duchenne Muscular Dystrophy

#### Introduction

Families' experiences of living with Duchenne muscular dystrophy (DMD) altered in relation to the progression of the condition, and the severity of symptoms.

Affected children are phenotypically normal at birth, and frequently, little clinical weakness can be detected before the child is three to five years of age. As the condition progresses, affected boys find walking increasingly difficult; most become wheelchair dependent between the ages of eight and ten years. In the interview cohort, the age of the affected boy ranged from five to fifteen years in the LCD cohort, and one to sixteen years in the NBS cohort. Families had therefore experienced quite different aspects of the condition at the time of the interview.

Family descriptions of their experience of living with DMD can be divided into three stages: the early, middle, and late years. The 'early years' describe the period in which parents received the diagnosis. For families in the newborn screening (NBS) cohort, the diagnosis was received soon after birth and the affected child remained asymptomatic for a number of years. Families in the later clinically diagnosed (LCD) cohort received the diagnosis after signs and symptoms of the condition become apparent. The middle years are characterised by the child's decreasing mobility. Families described the process of adapting lifestyles and family homes to children's emerging needs. The final stage, described by families, was the experience of living with disability: the time after children have become wheelchair dependent.

There was considerable variation in families' experiences. First, not all families had experienced all three stages. All families had received a diagnosis and therefore had some experience of the early years, and seventeen out of nineteen families had started making practical adaptations to their homes. However, only seven families had a child who was wheelchair dependent at the time of the interview (NBS = 4, LCD = 3). Second, families' descriptions of the different stages highlighted



considerable disparity between the two different diagnostic procedures, particularly during the early years. This chapter is divided into three sections, to explore the stages of living with DMD, in relation to the diagnostic pathway.

## 1. The early years

Families' experiences of the early years highlighted both similarities and disparities between the two diagnostic pathways. Eleven families received the diagnosis when their child was around six weeks old and eight families received a diagnosis when their child was an average age of 3.9 years (range 3 to 5.75 years)<sup>28</sup>. The disparate experiences of the early years are explored under two themes: 'from confirmation of concerns to stunned devastation' and 'uncertain identity and parental competency'. The similarities, in families' experiences of the two diagnostic procedures, are explored under two subsequent themes: 'disrupting relationships; the role of communication' and 'resuming normal life and seeking explanations; the role of responsibility'.

### 1. 1. From confirmation of concerns to stunned devastation; the variable role of diagnostic pathway

Receiving a diagnosis of DMD generated multiple responses. For some, it meant long sought confirmation of parental concerns, or the end of blissful ignorance. For others, the diagnosis meant the acquisition of an unexpected disease label for a seemingly healthy baby, or the creation of unsolicited anxiety. In all cases, the meaning of the diagnosis emerged from preceding events, which had profound implications for subsequent experiences.

Families who received a later clinical diagnosis described the early years as moving from the carefree years, to the recognition of signs and symptoms, to the eventual confirmation of their concerns through the diagnosis. In contrast, families who

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<sup>28</sup> It is important to note that families in the interview cohort received the diagnosis, on average, over 6 months earlier than the total LCD cohort. In the total LCD cohort the average age at diagnosis was 4.5 years (range 1.4 to 8 years) and therefore LCD families in the interview cohort were less likely to have experienced a particularly delayed diagnosis.

received a diagnosis through newborn screening in the NBS cohort described the early years quite differently; focusing on the diagnosis as the point at which their concerns were created, and the years immediately after the diagnosis as the “lost years”. Experiences of the diagnostic pathways are explored under four headings. The first two, ‘the carefree years’ and ‘recognising signs’, refer to the experiences of families who had received a later clinical diagnosis. The remaining two, ‘creating concerns’ and ‘the lost years’ refer to the experiences of families who had received a newborn screening diagnosis.

### *1.1.1 The carefree years*

Without fail, every family, who had received a later clinical diagnosis, described the value of receiving a later clinical diagnosis. Families felt that the later diagnosis had enabled them to enjoy precious, carefree years with their child, without the stress and worry induced by the diagnosis. For some families, the thought of receiving the diagnosis at birth would have been simply unbearable.

I think it would have been awful. I think it would have been awful, I thought, well thinking back I thought I had two perfectly healthy kids. You know and for that to be taken away like that would have been... I think that would have been a big one. I had six years not to worry about anything like that. Thinking well, he’s alright. [If you knew earlier] you’d still have had six years more worrying about them and thinking what’s going to happen to them and you have enough years of that worrying about them because you do it every day of your life. There’s not a day in your life that you don’t think about it. (Pamela, first child diagnosed clinically after birth of second affected child)

Families’ immediate response to the prospect of receiving the diagnosis at birth always focused on the loss of the carefree years; the loss of happiness and blissful ignorance. During the carefree years, Lesley, like many mothers, described bonding with her child, enjoying spending time with him without worry or fear of the prognosis.

I think we enjoyed him more because we didn't know. We enjoyed him more in the five years. I think if we had have known it would have changed things. We wouldn't have changed towards him but we would have - I don't think we would have been - it would have felt very happy. We'd have just looked at him and knew that's what he had, but he's not - we didn't know for five years and we enjoyed him and he was happy. (Lesley, first child diagnosed clinically after conception of second child)

Both Pamela and Lesley received a clinical diagnosis later than the 4.5 year average, and both had conceived their second son prior to the diagnosis of their first. Pamela had two affected boys. Lesley had decided not to test her second boy until he was older because, as Lesley noted, she would “rather enjoy him before [she] found out”.

Providing information and choice has become a common rationale for expanding newborn screening programmes, but for families who had not had the opportunity to benefit from such information, the prospect was entirely bleak. Families often described their lives after the clinical diagnosis as haunted by worry, unhappiness, and fear of the prognosis. For them, therefore, receiving an earlier diagnosis was perceived as merely reducing, or eliminating, precious carefree years.

### *1.1.2 Recognising signs*

However, the years prior to the diagnosis were not entirely care-free. All families had noticed some of the physical attributes of the condition, from enlarged calf muscles, to slow development, mobility difficulties, or a tendency toward clumsiness. Often families sought justifications from within existing frameworks of understanding, as a way of defining symptoms within a familiar context.

The level of concern garnered by early symptoms was dependent on whether families were able to find reassuring justifications. Families who remained relatively unconcerned by the symptoms were those who could find simple explanations from within their own experience. For example, one mother assumed the premature birth of their son would inevitably lead to slower development; another assumed her son’s enlarged calf muscles were merely a sign that he had inherited his father’s large build. In the following extract Maureen demonstrates how her initial assessment of her son’s symptoms focused on considerations of her own physical abilities.

Well, Daniel was always – well, he was fifteen months when he started walking but he was quite clumsy and he kept falling quite a lot. And he’s our only child so we had nothing to compare it to. At nursery he kept on falling and I kept saying to the health visitor, he’s really, really clumsy. I don’t know if it’s – my husband was working away at the time. And so he was only home at the

weekends and I'm left handed and quite clumsy as a result. And I thought maybe it's because I was going about everything in a left handed way and he's right handed. (Maureen, first child diagnosed clinically, aged 4.5 years)

The most common approach to the symptoms was to search for a simple explanation; there was often nothing in the families' biographical experience that made them think that the signs and symptoms were a product of illness.

Some families used their experience of watching other children's progression, to compare their son's development. However, families without previous children described the difficulty of accessing such information.

[My son] was like quite hesitant - I mean he was what, two and a half, just before he turned three, he was kind of a hesitant getting up and down kerbs and really wasn't getting anywhere with going up and down stairs. So I did have some concerns. And the way he ran wasn't quite - I knew there was something. But then I didn't have any other children to compare him with and people kept saying oh, they develop at different stages so I kept thinking oh, it's nothing. It's nothing. (Mary, first child diagnosed clinically)

Giving birth and raising a first child extends families' biography into uncharted territory. Without recourse to comparative experiences on the development of an unaffected child, concern about the aetiology of symptoms was often mitigated by assumptions of normal development. When parental concerns were voiced to health professionals, reassurance was often provided that the symptoms merely demonstrated slow, but normal progression.

A few children were diagnosed after concerns were brought to the attention of medical professionals. One child, for example, fell over and was slow to recover; another was admitted to hospital for liver problems; another referred for speech delay. However, many families experienced no such catalyst. Previously assuaged concerns only became prominent again once the affected child was in regular contact with children of a similar age. Many families found their attention drawn to their son's development after their children had joined nursery or school.

Me and his dad always noticed he was a wee bit stiff. But we just put it down to... he was just normal. A lot of kids are like that. But it was the school that had noticed. I think somebody goes round the schools just to keep an eye on the kids. And somebody had noticed that there were some things Jonathon couldn't do in the gym. So the head teacher got me down and explained to me and I told her I'd make an appointment with the doctor. So then I got referred up to the paediatricians. And we done a blood test and

had to do another one and it confirmed that he had Duchenne muscular dystrophy. (Lesley, first child diagnosed clinically when Lesley was pregnant with second child)

Parents reported that midwives and health visitors tended to provide families with reassurance, while nursery staff and teachers often noted discrepancies in physical abilities. The tendency to mistake early signs for slow development became progressively more difficult as children grew older, and could be visually compared to their contemporaries.

Families who had received a later clinical diagnosis tended to spend more time describing the gradual progression towards the diagnosis, than vivid descriptions of the actual diagnosis. For many families, the reality of their child's difficulties had already become apparent. Their accounts spoke of a gradual realisation, a slow ebbing away of belief in the prospect of having a "normal", healthy child.

Although none of the families described the diagnosis as a relief, there was an unerring sense that the diagnosis had at least vindicated, what others had assumed to be, excessive worry. One mother, Pamela, noted that "everyone had laughed" at her anxiety about her child's slow development. Another mother described people's dismissive responses to her concerns:

[My mum] used to think... I think she said, "I actually thought you were mollycoddling him". And when they found out at the nursery they said to me do you know you've been telling us this all along and nobody's really been listening to you. Like you always said when he came in with new shoes Scott's got new shoes today, keep an eye on him now, he'll trip over and he always done that and he couldn't just join in anything like a birthday party when all of his friends go to get on a trampoline and everything. Oh, there's no way Scott would be going on a trampoline and I remember him, the staircase was in the living room and he crawled up the stairs and I remember thinking that, it's just things. You just go back and think right, I knew it wasn't ever, you know, mollycoddling him at all but everybody else thought that... (Nicola, first affected boy diagnosed clinically, after birth of second affected boy)

Many mothers, in both cohorts, mentioned hearing stories of families who had taken their children back and forth to doctors for years, before their concerns were taken seriously. In this cohort, although many had been given false reassurances from health professionals, every family expressed relief that they had not received a diagnosis through newborn screening. Although some mothers felt their concerns

had been dismissed as excessive worry or mollycoddling, none expressed discontent with receiving a later clinical diagnosis.<sup>29</sup>

### ***1.1.3 Creating concerns***

In contrast to experiencing the gradual progression of the condition and diminishing belief in the idea of having a “normal”, healthy child, families who had received a positive newborn screening result were less prepared for the diagnosis. Many mothers who had received a diagnosis through newborn screening, described their sons as “normal babies”; they had no cause for concern prior to the diagnosis.

There wasn't anything... to say... that that there was going to be anything wrong. It was a perfectly normal birth. You know? There was nothing... (Anne, second child diagnosed through newborn screening)

For newborn screening families, the diagnosis occurred after families had chosen to have their child screened for the condition. However, only seven of the eleven NBS families interviewed had some recollection of ticking a box, or signing a form to consent for testing for DMD. The remaining four families did not appear to be aware that testing for DMD was optional. Even the families who remembered choosing to have the test did not recall making a considered decision.

#### **Do you remember being told about the condition before, you know, the heel prick?**

(Shakes head) because it was, I suppose, you go to the clinic don't you with a screaming baby and they say they're going to do so and so, and such and such and you just think yeh, just do it, do what needs to be done. You don't think at the time, do you? That something's going to come back. So... it's not really something I thought through. (Fiona, second child diagnosed through NBS)

The test is conducted when the baby is six days old, when most families are in the midst of adjusting to the phenomenal changes a baby induces in daily routines.

Mothers described themselves as sleep-deprived and somewhat oblivious. As one mother noted:

...in fairness whatever they would have told me ... I can hardly remember what they said now, I would never have remembered what I'd just been told anyhow. (Lauren, second child diagnosed through NBS)

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<sup>29</sup> It should be noted that five of the eight families interviewed had received the diagnosis considerably earlier than the national average of 4.5 years.

The test for DMD is an extra, optional test that is conducted alongside routine newborn screening tests. For the majority of newborn screening families, the test for DMD was perceived to be part of routine care. The decision to opt-in seemed to be influenced by the timing and availability of the test.

I suppose we just thought at the time well, it's just another one to check. And of course we didn't, you know, it wasn't – we weren't there thinking oh, but what if it comes – you know, it – it didn't really – it was just like oh well, it's there. We should have it, type of thing really I thought. Well, that's what I thought anyway. But I didn't really think too much about it. It was just a test that was offered and we just decided to – to have it done because it was you know, available, as I say with the others anyway that were normally done, so. (Jess, first child diagnosed through NBS)

None of the families considered the consequences of testing; all assumed the results would be negative, and most had forgotten having the tests by the time they received the diagnosis. In Lauren's words:

"I completely dismissed what could come out of it. I didn't think it was anything to worry about I was completely calm, I forgot that I'd even had it done" (Lauren, second child diagnosed through newborn screening).

In the NBS cohort, babies were too young to demonstrate any detectable clinical weakness. For some families, the lack of signs and symptoms made the diagnosis harder to accept.

...if they're 4 or 5 you can actually see the effects, you know, they are falling over more and they can't run as fast as the other children and – and things like that. So ... you know, you – you probably dwell on it a lot more then because every little thing they do you're thinking, oh of course, that's why he's doing that and that's why he's doing this. Whereas, when Jamie was so young he was just like any other ten week old baby [...] That does make it difficult to accept because you look at Jamie and you say well it can't be true, look at him, he's just perfect. Erm ... and – and, you know, I still think that every day: well there can't be anything wrong with him. Look at him, he's perfect. But erm... you know it does make it a little harder to accept I suppose when you can't see the actual signs there. (Sue, first child diagnosed through NBS)

Newborn screening diagnoses provided families with the opportunity to avoid the diagnostic delay. However, by eliminating the opportunity for the gradual progression of signs and symptoms, families who had received a diagnosis through newborn screening, were often left stunned by the diagnosis.

### 1.1.4 *The lost years*

Descriptions of the diagnosis revealed the depth of devastation felt by families. Many parents took time off work; homes became places of tears and depression, whilst families dealt with what many described as a “terrible bereavement”. Many families, who had received a diagnosis through newborn screening, described how they “lost” the first few years of their child’s life. Some mothers felt that receiving the diagnosis so soon after the birth was particularly traumatic, due to the heightened emotions experienced during the newborn period. One mother, through tears, and obvious distress, described her devastation:

I can always remember saying at the time ‘you can’t just tell some young mother that! That their son is going to be dead. (*Crying*)  
What? You know? They could just slip, you know just go into postnatal depression and I’ve got to be honest, yeh... we lost the first year of Gethin, you know? It went... a year... just worrying [...] We took hundreds of photos of Jim when he was a baby... Gethin’s just... went. (Anne, second child diagnosed through NBS)

Parents who received a positive newborn screen, tended to provide slightly lengthier descriptions of the trauma and devastation caused by the diagnosis. For newborn screening families, coming to terms with the initial devastation of the diagnosis often took years.

The first – I think the first two years it – you know, I – I had to take anti-depressants, I was – it was hard, but after the first two years yeah – yeah things do get easier and you know, you – you do see light at the end of the tunnel so – and now, we – we just – I mean I still have days but we – we try and look on the bright side and you know, and we get on with things now... (Louise, second child diagnosed through NBS)

In contrast, families who had received a later clinical diagnosis tended to spend more time describing the gradual progression towards the diagnosis, and described the length of time spent in tears and depression, in months, rather than years.

For some parents, a positive test for DMD confirmed suspicions, or brought to the fore some half-conscious concerns, but for others the diagnosis arrived without warning, and was met with stunned devastation. Parents, who received a positive newborn screening result for a seemingly healthy baby, appeared less prepared. Tests, nonchalantly chosen, were promptly forgotten; lost in sleepless wonderment in the early days of newborn life. For these parents, there was no gradual progression, no slow deterioration to spark concerns, just an unsolicited visit from



the doctor to announce their child's "death sentence before they'd started their life" (Rebecca, second child diagnosed through NBS).

## **1.2 Uncertain identity and parental competency; negotiating the medical label**

This section explores families' experiences of the early years, after their child had been diagnosed. Receiving the diagnosis marked the beginning of a new life. For some families the carefree years were replaced by an endless stream of appointments, "and every time you have a hospital appointment", as Maureen explained "it's another reminder and it's never good news, it's never progress". Other families were presented with the diagnosis long before physical deterioration was apparent or medical intervention was necessary. These families often described either a battle to assert authority over their child's upbringing, or a sense of isolation and doubt about the appropriate way to raise their child.

Many families spoke of the difficulty of distinguishing the aspects of their child's character, which emanated from their condition, and those which were simply personality traits. Negotiating medical information, and experience of their child, created a sense of uncertain identity; a quest to disentangle characteristics of 'disease' from 'child'. Experiences of families who had received a later clinical diagnosis are explored under the theme 'receiving a label', and experiences of those who had received a newborn screening diagnosis, are explored under the theme 'living with a label'.

### ***1.2.1 Receiving a label***

All families, who had received a later clinical diagnosis, had recognised that their child had some mobility difficulties, or was slow to develop, even if they had not realised symptoms were indicative of DMD. The diagnosis, therefore, often provided an explanation for previously recognised behaviours. Many LCD families described how the diagnosis had merely provided a label for such behaviours; nothing else had changed.

I think it was to our – you know, the whole family's benefit because the only thing that had changed at that point was the diagnosis; the

label that had been put on it, because he was the same boy. [...] I think that probably if Daniel had been diagnosed as a baby our expectations of him and for him would have been less. Because, you know, he went to nursery there weren't any immediate problems and whatever. He goes to a mainstream school; you know and he's very much – well, my life's like more work – but there's nothing wrong in here [pointing to head], you know, and yes, he's bright. He's in the top groups, [...] he – goes to boys' brigade. He's had loads of trophies and you know, he's – he really has got a very good quality of life. But I think maybe if he'd been diagnosed as a baby we'd have thought well, that's it. You know, we can't expect him to go to boys brigade – we can't expect this. Whereas I expect him to have everything in his life that able-bodied boys of his age have. And he has, so... (Maureen, first child diagnosed clinically)

For this family, and many others, the later diagnosis had enabled parents to develop a personal awareness of their child's abilities. When parents received a diagnosis, they received a label for some, but not all, aspects of their child's behaviour. During the early carefree years parents began to have expectations for their child, which some felt would have been diminished by receiving a medically defined label at birth.

Many families articulated the benefit of getting to know their child, before the weight of uncertain identity was placed on their shoulders; defining the line between “normal” childhood behaviour and attributes of the condition was inherently problematic.

People have got perceptions of disability and I wouldn't have liked to have thought that - I know another woman who's got a wee boy and I think he was a baby, he was a baby when he was diagnosed. And talking to her, everything was to do with muscular dystrophy. Everything about this wee boy was to do with muscular dystrophy, do you know what I mean? If he had problems on the potty, it was because he had muscular dystrophy. He had problem - whatever he had a problem with, it was muscular dystrophy, and I wouldn't have wanted to be like that. I mean I wanted - because I think I'm a wee bit like that with him as well sometimes because you'll read things and you'll see, you know, they can have behavioural problems and things and I'm going is it him or is that what other children are like? Do you know what I mean? I'm sometimes - I mean my sister's got wee girls and my sister-in-law's got wee boys, and I'm always saying to them, you know, what are they like? What are they like? And I think it would have been worse if he'd been a wee baby. I wouldn't have wanted - and even my parents in law, they're obviously - they're older, and they've been very upset by it as well, and they don't understand it. And I just think it annoys you sometimes when they put it down to muscular dystrophy and you feel like saying it's not that. He's a perfectly normal wee boy in all respects other than that. (Mary, first child diagnosed clinically)

Mary illustrates the difficulty of distinguishing between the aspects of their child's identity that resulted from the condition, from those which merely reflected their child's character. The diagnosis provided a label for a medical condition that was outside parental experiences. However, parents who had received a later clinical diagnosis often spoke of the mitigating effect of the carefree years; parents had grown to know their child, without a diagnostic label. Defining the line between behaviour relating to the condition and behaviour relating to the child, whilst still problematic, was perceived to be an easier task as a result of the later diagnosis.

### *1.2.2 Living with a label*

For the eleven NBS families interviewed, the diagnosis marked the end of their experience of having a "normal" child, and the beginning of their lives with a child with special health needs. Receiving a diagnosis radically changed families' perceptions of private family life. The slow ebb and flow of involvement with medical professionals subsided after the birth, only to be replaced, for some families, by a tidal wave of involvement. Although one mother, Jennifer, felt that it was useful to "be in the system", many others articulated a sense of invasion.

I found it very interfering in the beginning. Really, really interfering in the beginning because... there was nothing wrong with them. So all I wanted was the practical things done and they were all fussing over the other things and I just wanted the practical things done. Um... there was nothing you could do for them. There was nothing wrong with them for all these people to come in and say you know, you should be doing this or you shouldn't be doing that and I was thinking just let them get on with being boys please. You know? When this comes it will come. So I found it annoying. I must admit. (Anne, second child diagnosed through NBS. First child subsequently diagnosed)

Although Anne's youngest child was diagnosed after the introduction of newborn screening, she had experienced the slow development of the condition in her eldest child. Anne articulated her confidence in defining her children's needs and the travesty of being told how to care for asymptomatic boys.

...it's the plonkers out there that try to tell you... what you should be doing. That is the worst. And it's terrible I can always remember the first meeting after they were diagnosed. I was told I had to go to a meeting, so I thought right, I'll go to this meeting and how many were they? There was about 12 of them, you know? The school, psychologist, midwife and they were all... giving me this. And I could see me sitting there thinking woh, woh. So I just looked at them and said hang on now, these are my sons! This is what I want for them.

And I thought, you know, Anne that's you, because that's the sort of person I am. What about the thousands out there that can't do what I want to do. You know? That haven't, that aren't eloquent enough or confident enough or whatever who will sit there and take it. It must be heartbreaking! For all these people to tell you what they think is best for your children. I thought I'm not having this. You know? (Anne, second child diagnosed through newborn screening; first child subsequently diagnosed)

Many descriptions of the battle between the medical world and the private family home emanated from families who had received a diagnosis during the early years of the newborn screening programme. In contrast, many NBS families, who had received a diagnosis in more recent years, described their feelings of isolation.

The first year, I - I felt that there was nobody to talk to at all, only my family, you know. I - we - we've seen Scott's specialist and I mean all she did was tell us about the condition and you go and see her you know, that's it. There was no support or anything at all, you know. [...] In the first year or two there was nothing and it was like we had to do it all ourselves, you know, there was nobody there to say, "well why do you not do this, why do you do that?" (Louise, second child diagnosed through newborn screening)

Louise, like many NBS mothers, articulated a profound sense of doubt about the appropriate way to care for her asymptomatic child. Presented with a baby and a disease label, many described a desperate search for information, which medical professionals were often unable, or unwilling to provide.

To be honest, we haven't had all that much ... contact with - with people in the Health Service. I mean the health visitor was absolutely fantastic. I mean she's such a lovely woman, but she - she'd never dealt with - she'd never had a, you know, a child with Duchenne before and the same with GP, erm ... my GP I've known since I moved down to Wales, but he - he, you know, he's lovely but he never had a patient with Duchenne before. So they obviously don't know that much about it so they couldn't be of that much help really. Erm ... and ... we haven't really had contact with anyone else apart from [the consultant] but that was only to do the tests and for - to tell us that she didn't really have anything to tell us. So it's, you know, it's not been ideal. (Sue, first child diagnosed through NBS)

The presentation of diagnostic label, to parents who are just discovering how to care for their baby, appeared to undermine parents' belief in their ability to care for their child. Contact with health professionals was perceived to be a vital connection to expertise and advice on appropriate caring techniques. However, the disengaged approach of the health professionals often left families with a sense of isolation and abandonment.

Five of the eleven newborn screening families interviewed had received a diagnosis during the first five years, after the implementation of the newborn screening programme. Six of the eleven families had received a diagnosis since the year 2000. There was a resounding sense that the level of support provided to families was felt to be overbearing during the first few years of the programme. However, families who had received a newborn screening diagnosis since the year 2000 often described feeling unsupported and isolated. One mother, Jacky, noted with some disdain that their family care officer had informed them that “we can’t do anything until he is five years old, so just enjoy him as you would any other child”. For the majority of newborn screening families, the knowledge that their child had a medical condition, elicited a belief that medical professionals should be involved in their child’s life.

Some families seemed to make a conscious decision to try to ignore the diagnosis until house adaptations became a necessity. One way of setting aside the diagnosis was to keep news of the condition away from the public domain, until the signs and symptoms of the condition became more prominent.

*I mean when we first, you know, we didn’t tell anybody for a long, long time -*

*No, we just kept it to ourselves -*

*We were -*

*Told our mothers. My father and my mother.*

*Wanted people to enjoy him... Because people tend to see him differently don’t they, if - and we didn’t want that to happen. So then I don’t know if we’re perhaps protecting him.*

*No, we just thought he - you know, might as well not say anything because you know -*

*Well, that’s it. Nobody would know.*

*No one would know. And - You know, we just thought there’s no point saying until there’s a need to. (Neil and Jess, first child diagnosed through newborn screening)*

For some families, the diagnosis was a closely guarded secret; a desire to protect their child’s identity from the connotations of a disease label. No one needed to know, and - whilst their child remained in the early stages of the condition - no one would know.

After the initial diagnosis, some families felt that the lack of contact with health professionals provided them with the opportunity to pretend life was normal. These families often attempted to keep life undisturbed by the realities of the diagnosis, and avoided facing their child’s future. Families often mentioned actively avoiding

sources of information, such as the internet or access to other families' experiences through support groups.

[The progression of the condition is] something that gradually happens... its something you could pretend isn't happening for quite a long time. So even though you can see it and you know it's there, even with other children and stuff, it's something you can't sort of well you know...I've never really been that involved in... um the groups and stuff you see so... it wasn't... at that point you know when he was walking and stuff it wasn't in my face all the time and he was going to school up the road and they were wonderful you know... so... you can pretty much get on with things and pretend... Not that you are really pretending because you know that, you know it's there but... you can be as normal as you can which is nice I think. I liked it, I liked... pretending that it was all quite normal because um... I didn't... I wanted to be as normal for as long as we could really. (Fiona, second child diagnosed through NBS)

NBS families presented the reality of living with a child in the early stages of the condition, as a no-man's land. Although children stumbled a little more than others, they were still capable of being a "normal" child. Before the routine of regular hospital appointments began, and mobility difficulties signalled the need for house adaptations, families were able to continue life as they would have done without the diagnosis. For some families the lack of support was frustrating and isolating; for others, it was an opportunity to regain some sense of the carefree years.

### **1.3 Disrupting relationships; the role of communication**

Many families in the NBS and LCD cohorts did describe a number of similar experiences during those early years. Whether the affected child was diagnosed at birth, or after signs and symptoms of the condition became apparent, the diagnosis often had a considerable effect on the mother and father's relationship. For some couples, the diagnosis strengthened their relationship.

[The diagnosis] probably brought us closer. You know, it's – because – and actually a lot of the times you know, Daniel's in bed, we've just sat and cried. You know, but we've got a better understanding of each other I think. So, and I think it's brought us closer. [Maureen, LCD, son diagnosed aged 5]

Many parents noted that, through sharing a traumatic experience, they had become more emotionally aware of each other, and their relationship had been strengthened as a result.

In contrast, some families felt that the diagnosis had a negative effect on their relationship. Sue discussed the reasons why she and her husband had separated within a year of their son's birth.

Gary's the type of person who doesn't ... he's - it's as if nothing bothers him, you know, he - he's just - doesn't worry about anything and it - for that reason he doesn't really talk about things either. So it probably does bother him but he hasn't really ... he doesn't open up about things like that and it, you know, and I got really down about it obviously and ... found it hard to talk to him because he didn't really want to talk about it. So it - it did put a massive strain - you know, I don't know if that's the reason we split up because you know these things happen, but it definitely didn't help.

Rather than causing the relationship to end, the diagnosis introduced new requirements from each partner, particularly in the techniques used to cope and communicate.

Sue was not the only mother who had once questioned whether her husband's laid back and easy going appearance reflected a lack of concern with the diagnosis.

Esther felt that her relationship with her husband was strong, but still commented on their different styles of coping:

I think a lot of the time men just get on with it, they just - he says - it sometimes maybe seems as if they're not as upset but they are, they've got different ways of coping.

For families whose relationship suffered after the diagnosis, the primary source of contention was how each partner coped with and communicated about their feelings. Many mothers, like Esther, commented on how differently their husbands had dealt with the diagnosis.

Although many mothers felt that their relationship with their partner had been irrevocably changed by the diagnosis of their son, whether the change was positive or negative was specific to each family. Some mothers had separated from their partners, either temporarily or permanently, whilst others felt that their relationship had been solidified and strengthened following the diagnosis.

## **1.4 Resuming normal life and seeking explanations; the role of responsibility**

Responsibility emerged as a dominant feature in many families' stories. Parents from both cohorts presented two facets of responsibility in relation to the diagnosis. First, many families described a sense of duty to cope with the diagnosis, to resume normal life, for the sake of their children. Second, mothers described their sense of responsibility for causing the condition. The two themes 'resuming normal life' and 'seeking explanations' are addressed in subsequent sections.

### ***1.4.1 Resuming normal life***

As already noted, descriptions of the diagnosis revealed the depth of devastation felt by families. However, many mothers noted a sense of urgency to deal with the diagnosis; to resume their roles as the responsible parent.

Looking back at my childhood, I think I went through bouts of depression, my mum would say "how could a child be depressed?", but I think I was depressed. Fixated on death and things [...] And I remember going through stages that I could hardly function for thinking about that, I'd be paralysed with fear. But when he was diagnosed, I thought oh my god, you know, if I went into a bout like that, where would that leave him? He needs us to be strong. (Mary, first child diagnosed clinically)

No matter how traumatic families found the diagnosis, few felt in a position to break down. Many mothers made a conscious decision to act positively, to care for their children, rather than become someone who needed to be cared for.

We had the other two boys and we had him and you have to get on with a normal life. Because if we didn't cope, they wouldn't cope. Because I think like – because if we didn't cope they'd maybe want to protect you or look after you, and like they would just think there was nothing but despair. And I just think we had to cope and be positive, for them to be positive. (Esther, third child diagnosed clinically)

Interestingly, the perceived responsibility to resume "normal life" seemed most prevalent in parents of older children, and consequently occurred more frequently in LCD families.

In the NBS cohort, many families described how the earlier diagnosis had enabled them to grieve whilst their children were still too young to notice.

Because Kirsten was so young, she wasn't aware of how bad things were, you know there was a bit of a depressed feeling in



the house but because she was so young she wasn't aware, whereas now at eight and a half to nine she would have been very aware of us all being upset and Jack as well, I think the thing about him being a baby he didn't, you know he was completely unaware of what was going on and how we were feeling and us crying and sobbing around the place all the time. (Rebecca, second child, Jack, diagnosed through NBS)

Parents who had received a diagnosis through newborn screening tended to provide slightly lengthier descriptions of the trauma and devastation caused by the diagnosis. One possible explanation is that newborn screening families were not beset with the urgent responsibility to resume normal life, for children who are old enough to be aware of their parents' grief.

### *1.4.2 Seeking explanations*

After receiving the diagnosis, the majority<sup>30</sup> of mothers had undergone carrier testing. The provision of a carrier status label had a noticeable impact on mother's sense of responsibility for the condition. The majority of carriers described how they had felt guilty for passing on the condition. Some carrier mothers presented the sense of guilt as a fleeting experience:

I said "oh my god," at the beginning I can't believe it's my fault. I grew out of that in a couple of weeks. It was weird first off, I was oh god, but then I grew out of that... (Lauren, carrier, second child diagnosed through NBS)

Other carrier mothers experienced genetic responsibility as a constant, unerring sense of guilt.

The main feeling every day is... you know... it's my fault. It's a horrible, sick feeling I think but... how can you not feel that when you, when you find out that, you know, it's your family that's carried this thing down and... I don't know that you... It's your decision isn't it? When you have kids it's your decision to have them... and it's your decision and it's then your responsibility to ensure that they're safe... no matter what you can do and, and make sure everything, I know I did, you know, I know I did, I know I did everything I could do you know, it's not my fault... but without me he wouldn't be here so... what... I, I don't... I can't see how I couldn't feel... responsible... because I feel like I am... (Fiona, carrier, second child diagnosed through NBS)

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<sup>30</sup> In the NBS cohort, a deletion/duplication had not been detected in the boy and therefore genetic carrier testing was unfeasible. In the LCD cohort, one mother had chosen to delay carrier testing.

Although all carrier mothers described how they could not have known their risk prior to giving birth, receiving the carrier label provided them with a previously unknown sense of “being genetic”.

I try and look at it, and I think, well genes, you know, I mean we have a cancer a gene, you have this, you have that – it’s just one of these things. It’s just the way you are, you know... it is – you’ve genes for everything and some of them aren’t quite right and... you know, if your child has cancer or this or that, I mean ... So I try and look at it in that way, rather than, you know ... In the end then I start saying, well, you know, at the end of the day, I’ve not got the illness, I don’t have to cope with it; I have to watch it, which is hard. But I try not to bog myself down with that because I need to focus on Sean. He’s the one that’s suffering, not me. You know, erm, although I’m suffering, but not to the same extent, if you know what I mean. So I try not to go down that way because you could go into self pity, you know ... and that wouldn’t be good. That’s not good for anybody, is it, you know? (Pamela, carrier, second child diagnosed clinically)

For some mothers, feeling genetically responsible had to be addressed in relation to their sense of responsibility to deal with the diagnosis. Feeling guilty was perceived as a distraction from the role of the responsible parent.

Many mothers, who had been told that they were not carriers of the condition, expressed their relief and yet were not relieved from feeling responsible. For some mothers, the elimination of genetic responsibility merely created other avenues of guilt. In the extract below, Tracey describes her difficulty with understanding the medical description of the cause of the condition.

We went up [to the hospital] and asked to be tested. When we went up [the consultant] had the results and he just says congratulations, you’re not, you know, a carrier. I says well, actually it doesn’t make me feel me any better, how has it happened? And that’s then when he goes on and calls it a spontaneous mutation of the genes. I says but how does that happen? Basically - I think to this day you just don’t know how it’s happened because you try to read it up on the internet and it’s all like technical stuff, eh. And there’s no – place like writes it a way like makes you understand, I even tried to... like when we found out like it was deletion 3 to 17. It was like - it showed you like a normal DNA build up – for someone who didn’t have muscular dystrophy. And suddenly like someone who had deletion 3 to 17 it was just all these shades of colours was different. So I thought – again they say like the cat sat on the mat, in the genetic books and stuff like that, but like I say I just couldn’t get round it... (Tracey, GM risk, second child diagnosed clinically)

Tracey, like many GM mothers, found the genetic explanation for the condition unsatisfactory. Left without a comprehensible explanation of the cause of the

condition, many mothers sought alternative justifications. Common health promotion messages, particularly those surrounding appropriate behaviour during pregnancy, emerged in many mother's accounts.

**How did it make you feel, not being a carrier?**

I was going to say relieved as an initial thing. Relief that I hadn't passed it on [...] but then you still want to know where it's come from and you never do know do you? It's still an unanswered question. You always think, did I do something wrong? Did I eat something while I was pregnant or did I do something? Was my lifestyle wrong before I conceived? (Rebecca, GM risk, second child diagnosed through newborn screening)

Although parents had been informed that spontaneous mutations "just happened", mothers often perceived ill-health to be a result of specific behaviours. Mothers therefore claimed responsibility for their sick child through analysing their actions during pregnancy, which they perceived to be inappropriate.

...maybe it's like – I know when you're expecting, they say don't eat soft cheeses and I won't eat anything like that. And my pregnancy well, was – I was out cycling my bike [...] I smoked when I was pregnant [...] And I spoke to [the genetic consultant], I says, was it because I smoked? I says maybe if I had of – I know I fell when I was cleaning a window because the window came down and had it been that that caused it, I don't know. But he says no, he says it's just – it just happens. (Tracey, GM risk, second child diagnosed clinically)

Family accounts demonstrate a wavering belief that the condition must have happened for a reason. Although tempered by genetic explanations, these rarely dampened the sense of responsibility. Many mothers were still searching through their lives, to find answers to the unanswerable.

For mothers who are carriers, the sense of responsibility is imbued with guilt; it was them, their families who had caused their child's condition. Previously unknown aspects of their bodies become illuminated. A carrier becomes genetic, becomes genetically responsible, genetically at fault, and yet, as one carrier mother, Jacky, stated "at least I know where it came from". For mothers who have a risk of germline mosaicism, there is considerably less comprehension of the origin of the condition. Although they often present themselves as absolved from genetic responsibility, this merely leaves them with the unanswered question of causation. Mothers with a germline mosaicism risk often assumed responsibility by referring to health promotion messages regarding appropriate behaviour during pregnancy.

## **2. The middle years**

The middle years refers to the time when signs and symptoms of the condition became more apparent. Affected children often struggle to negotiate common features in the family home, such as steps, stairs, baths and toilets. In anticipation of their future needs and wheelchair dependency, family homes and lifestyles must be adapted. Families who had received a newborn screening diagnosis often spoke at length of the value of having time to prepare for the future.

Although many NBS families felt that a later diagnosis would have caused delay in starting the process of house adaptations, the average age of the affected boy when families started house adaptations was six years in both cohorts. In the NBS cohort, one family started the process when their son was two years old, and two families started when the boy was four years old, but others delayed until their child was ten, or in one case twelve years old. In contrast, families in the LCD cohort started the process of house adaptations when their child was between five and seven years old.

Families in both cohorts noted a number of factors that affected the time at which house adaptations were commenced. First, many families found the process of house adaptations an incredibly distressing experience. Choosing to start the process was sometimes experienced as a disruption of normality, which many parents, particularly in the NBS cohort, chose to delay. Second, the majority of families, in both cohorts, had felt that their attempts to start adaptations had been hindered by the lack of necessary information and support from social services. Families' experiences of adapting life to disability are explored in three subsequent themes: 'lifestyle preparations', 'disrupting normality' and 'seeking assistance/fighting the system'.

### **2.1 Lifestyle preparations**

Without fail, every family who had received a newborn screening diagnosis expressed gratitude for the provision of time to prepare, practically, rather than emotionally. However, the degree to which NBS parents made practical

preparations for life with a disabled child differed significantly between families. Some families had made considerable changes to their lifestyles, whilst others waited until they were struggling to cope with their child's progressive weakness, before addressing the condition. Despite the differences, all families felt that they had benefited from knowing earlier, although for many, the reasons were difficult to elucidate.

It's just that finding out before, I've been able to plan things, but not an awful lot – you know we bought a bungalow. Just thinking more about the future... But then again, saying that I suppose you know, if they are, you know, diagnosed at five, seven, then you know that's going to hit then anyway because it's a slow progressing thing anyway, it's not as if, you know, they're going to get really ill overnight or anything, but... I don't know, I can't really say, just – I feel that I think that you know, I'd prefer that it happened, we found out then rather than, rather than later on. (Jess, first child diagnosed through NBS)

A number of families simply felt that it was better to know; forewarned is forearmed. NBS families rarely perceived any benefit of receiving a later diagnosis. Families described the view that if they were to receive a diagnosis sooner or later, sooner was surely better than later.

A few families had made significant changes to their lives as a result of the diagnosis.

With work and things we've made choices. We've stayed round the area so we can be closer to friends and family because we need that support network and I think that, whereas we might have flitted round the other side of the world or we might... and we do things like we try and pack in as much as we can now. You know so that he'll have memories and he'll have... and as a family we do as much as we can because I don't want to say, 'oh I wish we'd done that' or 'we could have done that' and you know? So now I think it was good. At the time, no it was devastating, but it would be devastating whatever age they are to find out. But I think we've definitely been able to make choices for things with other children. You know Jack could have been our first child and I could have been a carrier. (Rebecca, second child diagnosed through newborn screening)

Many families had chosen to stay, or move closer to friends and relatives, in an attempt to access networks of support. Mothers, in particular, often changed career plans to ensure flexible hours, or work patterns which fitted in with school holidays. Numerous families felt that they would make more of their years with their child, before he became wheelchair dependent.

Many families felt that the newborn screening diagnosis had provided time to emotionally prepare for their child's prognosis. One mother, Lauren, described the benefit of being able to introduce her children to the equipment required, before her son actually needed it.

I think being told early on for us... we've had seven years to get used to the idea without any of them... nobody realising. You're always one step ahead of the kids, and you're always in control as much as you can possibly be; you're organised. You, like for instance when the lift went in the kids thought it was for ... so that I didn't have to carry the hoover up the stairs [...] I didn't want the kids to figure out that all the gadgets, as they call them, that we've got were for Ryan. I wanted them to grow up with them and see them everyday, I didn't want them to be brought in at the wrong time. (Lauren, second child diagnosed through newborn screening)

Lauren had moved house and completed adaptations within a few years of the diagnosis. It should be noted, however, that the approach taken by Lauren and her family was unusual in the newborn screening cohort. The majority of families did not introduce equipment into the family home until it was required by their child.

For many parents, a profound sense of loss at learning their child's prognosis at birth, co-existed with heart-felt gratitude for the early provision of life-changing information.

I can remember being offered [the test]... And choosing to take it!  
(laughing)

**Do you regret doing that?**

No. No. I think at the time when he was diagnosed yes, because you felt like your child had died. It was like the death sentence you know before they'd started their life but now no because we've been able to make choices that will benefit him long-run whereas I think we would probably be banging on doors now - we might not even have had a definitive diagnosis (Rebecca, second child diagnosed through newborn screening)

Although many families found the newborn screening diagnosis devastating, many described how, with hindsight, they felt they had benefited. Some families felt that they had been provided with the opportunity to make early preparations for their child, their families, and their future.

## 2.2 Disrupting normality

Many families found themselves living in houses that were unsuitable for adaptation and were therefore forced to uproot from their family home. Families who had older children often found this a very disruptive experience for their children, who had to be moved away from their schools and friends.

**So did you have this house before –**

No, we moved. We moved, we were up hill. And I think that was probably – made it very hard. It was at that time. We were going to stay over there because it was such a – the kids loved it and we had all our friends. (Esther, third child diagnosed clinically)

In contrast, some NBS families felt that the earlier diagnosis had enabled them to avoid disrupting their older children, by moving before they had settled into a particular neighbourhood.

Our house wasn't adaptable. You know we'd had plans done but it wasn't adaptable. So it meant the other children would have been uprooted. Well they might have got settled and had friends where they were. So we were able to make that choice to move before the kids all got to the point. (Rebecca, second child diagnosed through newborn screening)

Once a suitable house had been found, the process of adapting the house for wheelchair use could begin. For many families, starting the process of house adaptations was the point at which the diagnosis, and prognosis, became a living reality. The condition, quite literally, had to become part of the family home; many families described this as an emotionally distressing experience.

My husband's certainly been affected by it more than me. Quite a sensitive person and I think - I do think about it every day, but it doesn't always upset me. Sometimes when I talk about the extension, talk about things like that, it's not for that. When I talk about even wheelchairs or hoists and that, it's like it's not him, it's like I'm just talking about it, whereas my husband can't disassociate it. I'm not saying he's upset all the time, but he definitely hasn't slept properly since [the diagnosis], definitely more stressed and he's still struggling to accept it. (Mary, first child diagnosed clinically. House adaptations started when affected child aged seven)

Some parents presented a pragmatic approach to the adaptations and were able to disassociate them from their child's condition. Other parents found the prospect of having their homes filled with equipment incredibly distressing.

For some of the NBS families who had chosen to delay house adaptations, the decision seemed to be related to a desire to maintain a sense of normality.

I remember once three people just turning up out of the blue on the doorstep basically saying that I was, you know when I said I could pretend, there was a nice quiet time when I could just pretend that things were normal and it was you know it was nice, well they turned up, three of them, to have a look around the house, to talk about an extension and I think he could have only been about four... to talk about an extension and I didn't even know they were coming and they, they just came and said... along the lines of, now these weren't their words but along the lines of 'you're pretending this isn't happening, therefore we've turned up, we're going to have a look at an extension being done and... you know... we've come to... wake you up' really. And I was, I was so upset [...] Um... they were awful. They had no idea what they were talking about and they were, they said they'd make the garage into a room for him and then they'd have tracking all the way round and out and going into the bathroom so we'd share... one bathroom... and um... have all this equipment in it that we were all going to have to be in there with it... all and you know I was so worried about it I thought this is just ridiculous. So... I didn't do anything about it for a long time because I thought I just can't bear to see them again. (Fiona, second child diagnosed through newborn screening. House adaptations started when affected child aged twelve)

Some families were keen to have the equipment in the house before their child actually needed it. Others chose to avoid the emotional strain of adaptations until the physical strain of lifting their child, on and off the toilet, in and out of bed, simply became unfeasible.

### **2.3 Seeking support/fighting the system**

In addition to the emotional strain placed on families by the need to have their homes adapted, the majority of families felt completely unsupported by social services. One mother succinctly described their experiences:

To be honest, coping with Daniel having muscular dystrophy would be a lot easier if there wasn't so much bureaucracy and red tape and fighting to be done for what he needs. (Maureen, first child clinically diagnosed)

Families were left to decide exactly what their child might require during each stage of the condition, and forced to fight every step of the way.

Stories of short-term measures abounded. Families often described how social services were only willing to provide equipment and adaptations that were required at that particular stage of the condition. A few years later, when the child's mobility had decreased further, families were forced to fight for another set of adaptations.



We couldn't have a handrail we had to put our own handrail in for them to start with and then they wanted to put... the stair lift in. They wanted to do in stages as they were going. Oh it was rubbish if I'm honest. It was just not on. You know, you just can't do this, I said one day he's just not going to be able to do it. What am I supposed to do then? You know? (Anne, second child diagnosed through newborn screening)

Family accounts demonstrated the exceptional determination required, to avoid constant disruption to the family home, and family life.

Many families felt completely unsupported when deciding what adaptations might be required in the future.

**So the extension, are you getting somebody in to help out with plans and things for that?**

Well, to be honest with you the social, they don't seem to actually help, you know, it's like I know it's a private dwelling and it's up to you, if you get an extension done, it's up to you to get builders and architects and that. But I just thought because there has to be certain things in the extension, it has to be - I don't know about disabled adaptations and I thought they would give me further information. And that's why I've got this big manual. And that's the muscular dystrophy campaign's manual. I don't think there's anything else available. (Mary, first child diagnosed clinically)

Families felt they were expected to become experts on suitable adaptations for a DMD child, before they had any experience of the later stages of their child's condition.

One NBS family had moved to a bungalow within a few years of the diagnosis, and had adapted their new house "with their son in mind". The adaptations transpired to be incorrect and at the time of the interview they were facing the prospect of re-adapting their home. In the extract below, Neil describes the process that he thought should have taken place.

*I think the system is wrong. I think it should all change. It should be a case of Lewis is diagnosed, this what you need, this is what you're having, this is when it's - when you're having it but - It should all be automatic. It should be a process [...] It should be like this is what you've got. You know, or it's in we go, change the house ready, it's all done. Or - or say well, right. You need maybe wheelchair access for the back door and maybe you need a bathroom with aids. So you know, they build a bathroom with aids. You know. They could do it bit by bit or they could come in and do it in one go. They say it's cheaper to do it in one go don't they, it's easier; you know, just do a - to me it's like when the diagnosis is made you should, to me, you should have a doctor, social worker you know, and someone to tell you about these are the things you're going to need. May - maybe not so much on the day of diagnosis because we can't take it*

*in but... Within a couple of days. [Neil and his wife Jess continue to discuss the issue and eventually conclude that a couple of months would be a more appropriate time than a couple of days] (Neil, first child diagnosed through newborn screening)*

The majority of families, in both cohorts, described the lack of information and support, and the constant need to fight for every change that needed to be made. Many NBS families felt that an earlier diagnosis had enabled them to start preparing for adaptations, and was therefore beneficial. However, an equal proportion of families, from both cohorts, had not completed house adaptations by the time their child became wheelchair dependent. Families in the NBS cohort either described an emotional reluctance to start the process, or a lack of support from social services. In the LCD cohort, families perceived the delay as resulting from a lack of support.

One family, who had not received a diagnosis for their eldest child until he was nearly six years old, had struggled to complete house adaptations before their child became wheelchair dependent. The mother, Nicola, was particularly outspoken about the value of having carefree years with her children. However, Nicola also described the difficult and delayed process of completing house adaptations. When asked if she would have swapped the carefree years for more time to prepare, Nicola replied:

*Aye, I probably would because you see at the end of the day if it's in and it's in place then they think nothing of it and they're used to it and I think before that you would have thought, oh, I don't want them seeing all that equipment and I've read that about folk but, see if it's there, and you use it and you let other folk use it then it's not scary. You know and it's mainly the kids that come in here and go, Wow! Could I do that? Do you want a wee shot? Do you want to go in the hoist? Because I think you've got to do that. No probably not, probably you don't need all; that stress that's a lot of tears and heartache and anger and frustration with folk just passing the buck and you don't need that because when that is happening, that's happening when your child is off his feet and that's a big thing in your life. (Nicola, first child diagnosed after birth of second affected boy)*

Preparing for a future with a child with a disability requires considerable time and effort. Families who had received a later clinical diagnosis often began the process of house adaptations within a few years. Most families felt that they had plenty of time to adapt their houses, whilst others struggled to complete by the time their child required the adaptations. In contrast, families who had received a newborn screening diagnosis expressed gratitude for the extra years to prepare for the future.

Some parents made many decisions about their families' future, but others actively avoided the diagnosis, resulting in delayed adaptation.

### **3. The later years**

Children affected by DMD became wheelchair dependent between the age of eight and ten years. The experience of living with a wheelchair-dependent child did not vary between cohorts, but it varied considerably between families. Some families described a gradual progression from fearing the day their child would require a wheelchair, to discovering that the wheelchair provided their child with a renewed sense of freedom. Many families presented living with their son in a wheelchair, as a normal life. In contrast, other families described their child's frustration as their freedom became limited by the wheelchair. Many families described their sense of isolation from social networks, generated by the sheer number of locations that were physically inaccessible to wheelchair users. However, many families felt that their relationship with their immediate family had been strengthened as a result of living with DMD. The four themes: 'from fear to freedom', 'from freedom to frustration', 'diminishing social networks' and 'strengthened family ties' are explored below.

#### **3.1 From fear to freedom**

Many parents described an emotional progression, from fearing their child's wheelchair dependency, to realisation of the sense of liberation the wheelchair provided their son. Parents, who had watched them stumbling, falling and unable to run, often described how the wheelchair had provided him with a new lease of life.

I think when – I think like going into the chair actually was better for him because he could keep up with his friends because I think – because I did, I said to him about steroids and he says he wanted something to keep him walking for longer and I don't know if he would have – well, he liked walking but I think he always felt he was always at the end and he was never at the front of the queue and he was just all – he just felt always to slow and he couldn't keep up with anybody. And so I think when he went into the chair and his pals pushing him, brought him back into the kind of fore of it. And then when he got his first electric chair, kind of like – the people would stand at the back of it and riding on it and all, and you know. So I think – because sometimes what he'll say it's like he doesn't – he would rather but he doesn't – he doesn't mind not being able – he could cope with not being able to walk but he wishes he wouldn't

lose everything else because he knows the full prognosis so –  
(Esther, third child diagnosed through newborn screening)

Rather than confining the child's mobility, some families had found their children felt more secure and mobile in a wheelchair.

Many families were keen to present the normality of their child's life. Parents often mentioned that their children attended mainstream school and had been provided the opportunity to 'do what other children do'.

I suppose...we're lucky. I've got good social work... good network... They've never missed out. [...] You know we've been on holiday with everyone else, They've always attended mainstream school. You know? They've always done what everyone else has. In fact, a friend, a little girl, one of the little girls when I was in school because I used to help in school and she was doing something and she said well why is he called disabled Miss? And I said well, he's like, you know, in a wheelchair and she said 'he's not disabled, he's in a wheelchair!'. (Anne, second child diagnosed through newborn screening)

A few mothers, who also had unaffected children, described their attempts to treat their affected son the same as their other children. For some parents, it was not just the wheelchair that provided freedom. Some parents described negotiating their responsibility for caring for their child, with the sense of responsibility to let them get on and be teenagers.

I do know that there's people, that they... wouldn't leave them like. But I just think I'm not – I'm not the only one that can look after him and he's old enough now to tell people what he needs. And I'd say that he's probably getting better at other people helping him because I think he realises if other people don't help it limits his world. Because he was actually taken to Lourdes last Easter and like that, he knew that I wasn't going to be doing his care and if he hadn't – if he doesn't let people do that then his world's going to shrink. So he has – well, I say and he – he's got a wee friend, he stays down the road with and his chair gets parked in the garage and they carry him in. But he always – he sleeps in his clothes and comes back in his clothes, and he just – but if he needs to do, like have his brother could take him to the loo, do you know what I mean, so – (Esther, third child diagnosed clinically)

For some families, the wheelchair had provided their child with a sense of freedom. However, a few families also described a conscious effort to stand back from the caring role during the teenage years, in an attempt to provide freedom by not limiting their child's world.

### 3.2 From freedom to frustration

In contrast, some families described the frustration their child had experienced, as a result of becoming wheelchair dependent.

It just got to that point that he was more comfortable, felt safer being in his chair, so that's the way it went. But then, that comes with other problems that you don't think about. So you think that he feels safe in his chair and what have you and... um... it brings on this other sort of train of thought that you've got to have and things like when ur... little things happen all the time. We went on holiday with fourteen of us... and we were all walking somewhere to get lunch and next thing you suddenly hear this screaming and you're so busy chatting and stuff that he's got stuck on the kerb! (laughs) And you've got to back and get him you know and he thinks you're all going to walk off and leave him and he's just stuck and it must be an awful feeling. Absolutely terrible. I couldn't imagine myself, you know, the feeling. He's quite young for his age... so um... being a child and being stuck somewhere thinking that everybody is just going to go and leave you there, must be awful. And we never would. We'd never get more than a couple of paces and he'd scream but it makes you feel awful because it's little things because when you're busy and that you do forget, the smallest things that do count and you feel awful because of it. Funny how... you... can't possibly imagine... (pause) how it's going to be. You know you think you know... the things you're going to have to do and you see people in wheelchairs in the supermarket and you think yeh, you know, not too bad, you know. But it's all these little things that you just couldn't even imagine... (Fiona, second child diagnosed through newborn screening)

Fiona, in particular, provided numerous examples of society's impatience with wheelchair users; from people in restaurants complaining about moving to let her child pass, to people in supermarket car parks, impatiently honking their horn as she tried to push her child's wheelchair up the ramp, into the car. For Fiona, living with a child with a disability was the source of considerable distress and frustration.

Although few families described so many negative experiences, many expressed a sense of isolation from society.

### 3.3 Diminished social networks

Many families described how their son's wheelchair dependency had placed physical limitations on his social networks.

...obviously really most people have to come to us. Ben's got – rather than go to friend's houses because often they aren't very – it's very difficult to get – get in there with electric chairs – And not everybody's got enough room or – he's got one – one of his best friends he can go

there. They – they put a little ramp up for him to go [Jennifer, son, Ben, aged 12]

Many mothers mention that the houses of their friends, or their son's friends, were rarely wheelchair accessible; most social interaction took place within their own homes.

Many parents articulated diminution of their own social networks, through practical considerations or social exclusion. Nicola and Stuart's first child was diagnosed with DMD after they had already given birth to a second affected son. Both boys are now wheelchair dependent. Nicola felt that their friends excluded them from parent/child activities:

You know, I just think, having two is not just as easy as going joining things and you know it's like, like last night we were round at a friends' and all the guys had obviously been at the golfing. They're all taking their kids golfing you know and Stuart's dying to go golfing, Stuart's got a golf set you know and you think, folk just don't think and you get left out quite a lot as a family I would say. It always has to be here and you can get in other houses but folk just, if it's not happened to you, you don't need to make that effort and I'm probably one that always makes the effort. And it probably hurts more now because folk don't make the effort. I think that's probably the hardest thing.

Parents described their feelings of exclusion from social networks, caused either by physical limitations of wheelchair manoeuvrability, or other families' tendency to exclude families with DMD from physical activities.

Families often moved, or had chosen to stay, close to family support networks. However, as the affected boys' condition progressed, many families found that access to family support diminished. As each boy grew less mobile and more reliant on others to deal with his own physical needs, grandparents were often simultaneously facing their own physical limitations.

It's since um... since Ben's gone off his feet now (Fiona gets up to get a tissue).Um...there's um....there's no one else that can....sort him out...so, ur...it's up to us to be here really. I don't know who else would put him on the loo and um...and who could, it's not that they wouldn't it's who could manage to do it you know. My mum's got a bad back she couldn't do it, my Dad's got bad knees, you know they're all getting older now... [Fiona, second child diagnosed through newborn screening]

Fiona and Paul, like many other parents, felt they had little access to family support. In the middle to late stages of the condition, affected boys need to be assisted from

their bed to their wheelchair, from their wheelchair to the toilet, to the bath, to the car. The physical demands required to deal with an affected child were often presented as the reason for the limited support provided by family networks.

### 3.4 Strengthened family ties

Social networks may decrease, family support may become less feasible, but the interpersonal exchange relationships within the family may simultaneously be strengthened. Many families noted that their relationship with their immediate family had been enriched by the diagnosis.

I think it's made us better people, much better parents and a better family because you appreciate ... because you go out and you see members of your family and you look and you think god what's wrong with you, why don't you take those kids down the park, why don't you do this, why haven't you done this, why, why and they're all just me, me, me. They don't appreciate their children. [Lauren, NBS, affected boy aged 8]

Like many mothers, Lauren expressed a profound sense of having gained perspective on life. Families often spoke of making the most of the time they have with their children.

Families often found that the medical description of the condition had not matched the reality of living with, and loving, an affected child.

Daniel's got muscular dystrophy but things are not as bad as you think they're going to be. That's our experience you know, because you don't – you – you don't understand what a child with muscular dystrophy can give apart from what they – you know, you – you've just not get any – Any concept of how that is. You know, I said that to Daniel. I says you know, Daniel, you're the best thing that's ever happened to me and dad. [Maureen, LCD, affected boy aged 11]

Maureen highlights the unexpected value of having an affected child; a sentiment expressed by many families. Although access to social networks may diminish, the intensity of interpersonal relations is increased.

There was simply no unified experience of living with child in a wheelchair. While some families were keen to present the normality of their child's life, others concentrated on the limitations induced by wheelchair dependency. The diagnostic procedure did not appear to influence the experience of the later years. Disparate

experiences appeared to be related to the parental approach to disability, and their ability to access supportive social networks.

#### **4. Summary of experiences of living with DMD**

Families' experiences of living with Duchenne muscular dystrophy varied considerably, depending on the stage of the condition and the severity of symptoms. The role of the diagnostic pathway also had considerable influence on families' experiences, particularly during the early years, and to some extent, the middle years. There was considerable variation in families experiences in the later years, but this appeared to be unrelated to the diagnostic pathway.

Exploring families' experiences of the early years of the condition offers rich insight into the influence of diagnostic procedure on the relationship between two sources of knowledge: personal experience and medical information. Parents who accepted the offer of newborn screening received a disease label for their asymptomatic baby; those who received a later clinical diagnosis, acquired confirmation of half-conscious concerns. Parents were propelled forward on a journey of learning, disentangling their sons' character from the character of the disease label.

Families, who received a later clinical diagnosis, expressed the value of having carefree years with their child. These families had come to know their child and had developed expectations of their child's abilities, which some felt would have been diminished by an earlier diagnosis. The gradual progression towards the diagnosis often meant the disease label provided confirmation of half-conscious concerns; a justification for their worries. In addition, families who had older children often felt a sense of responsibility to resume normal life.

In contrast, families who received a newborn screening diagnosis are presented with a baby and a disease label. Many families articulated their devastation, and described the benefit of being able to grieve for their child whilst their children were too young to be aware. Some expressed doubt about whether they were treating



their child appropriately, and often felt abandoned when health professionals seemed unable, or unwilling, to impart information or advice. For these families, the weight of uncertain identity characterised their early years with their child, as they struggled to define aspects of the condition from their child's personality. Families, who had more involvement with health professionals during the early years, described the difficulty of negotiating authority over their child's upbringing.

During the middle stage of the condition, families who had received an earlier diagnosis expressed gratitude for the provision of extra time to prepare. However, the average age of the boy when house adaptations commenced was six years in both cohorts, and the range of ages much greater in the NBS cohort. Although some NBS families made life-changing decisions and early preparations as a result of the diagnosis, others chose to ignore the reality of the condition, until faced with their child's increasing immobility. Most families, in both cohorts, described the difficulty of obtaining support from social services, and the need to fight for both information and practical assistance.

Descriptions of the later stages of the condition highlighted the different experiences of families living with the same condition. Some families felt that their child's wheelchair dependency was 'better than expected' as it provided a renewed sense of freedom. However, other families described the limitation of freedom, and a sense of isolation from social networks.

## Chapter Seven

### Dealing with what is done; choosing what is to become

#### Introduction

The previous chapter illustrated the diversity in families' experiences of living with a child with Duchenne muscular dystrophy (DMD). Families' approaches to their reproductive future were characterised by equal variation. The different experiences of dealing with the diagnosis and living with DMD provided the context, within which families chose to defer, deter from or continue family building. It should be noted from the outset that there was no simple recipe for reproductive decision-making. No single variable was identified, such as the number of previous children, or awareness of genetic risk, which had a direct and unambiguous effect on reproductive decision-making. Families in similar situations often made strikingly disparate decisions.

The aim of this chapter is to explore the factors that families discussed in relation to reproductive decision-making. There was considerable variation in the choices families made about their reproductive future and a range of factors families felt had influenced their decisions. First and foremost, the majority of families described the formation of fertility intentions prior to having any children, which often remained paramount in subsequent reproductive decision-making. Second, mothers described their aspirations for the future, in relation to their sense of responsibility towards their partners, their existing children and their future unborn child. Third, many families described their perception of risk, either risk of having a second affected child, or risk of miscarriage, in relation to reproductive decisions. Lastly, families described their reproductive decision-making in relation to their perceived ability to cope with a number of aspects of the condition.

The four themes: 'planning the family', 'reproductive responsibility', 'negotiating risk' and 'coping with today, coping with tomorrow' are explored after the background demographics of the cohorts are addressed. The first section outlines the situational aspects of reproductive behaviour, to provide information on the

context of reproductive decision-making. The background demographics of both cohorts are explored; the number of children prior to and post diagnosis, the age of mother and affected child, awareness of genetic risk and the uptake of prenatal testing.

## 1. Reproductive characteristics of the LCD and NBS cohorts

Families were at quite different stages in the reproductive decision-making process. In some families, the children were teenagers, and family building appeared to have been completed some years previously. In other families, children were still toddlers. Some expressed belief that their families were complete, whilst others were still considering, or trying for more children. Table 1.1 shows the age of mothers and the age of the affected male at the time of interview, as well as the age of mothers at the birth of their affected son. Mothers and sons, in the LCD cohort, tended to be a little older at the time of the interview, but the age of mothers at the birth of their affected son was very similar between the cohorts.

**Table 1.1 Age of mother and sons in interview cohort**

<b>Mean age of:</b>	<b>LCD</b>	<b>NBS</b>
Mother at time of interview	40 (range 28-50)	38 (range 30-49)
Mother at birth of affected male	30 (range 23-38)	30 (range 21-35)
Affected male at time of interview	9.5 (range 5-15)	7.6 (range 1-16)

Another factor that may affect reproductive decision-making is the number of children born prior to the affected boy. Table 2 demonstrates that the position of the index (whether he was the parents first, second, or third-born child).

**Table 1.2 Position of index in interview cohort**

<b>Position of index</b>	<b>LCD (n=8)</b>	<b>NBS (n=11)</b>	<b>Total n=19)</b>
First	4	4	8
Second	3	7	10
Third	1	0	1

A slightly higher proportion of families had one or more children prior to the birth of their affected son in the NBS cohort (64%, n=7), compared to the LCD cohort

(50%, n=4), suggesting that LCD families might be more likely to have more subsequent pregnancies. In families in which the index was the first born, the same proportion of families in both cohorts, were trying, or had tried for more children (75% n=3). However, in families in which the index was second or third born, less than half of the families in the newborn screening cohort (44%, n=3) had tried, or were trying for more children. In contrast, the majority of families in the LCD cohort, in which the index was second or third born (75%, n=3), were either trying for another child, or had another child

Differences in reproductive behaviour were also apparent. Two LCD families had subsequent children before the diagnosis of their first affected child, whereas all NBS families were aware of their risk, prior to embarking on subsequent pregnancies. After receiving the diagnosis, five NBS families had subsequent children, compared to only one LCD family. In contrast, three LCD families had tried or were trying to conceive, compared to only one NBS family. The data suggests that five out of six NBS families had been successful in their attempts to conceive after the diagnosis, compared to only one out of four LCD families. Possible reasons for the differences are explored in subsequent sections.

Of the remaining nine families, who had not had children after the diagnosis, five families (NBS=3, LCD=2) had either considered, or were still deliberating about whether to have more children. Four families (NBS=2, LCD=2) described their families as complete prior to receiving the diagnosis and chose not to have subsequent pregnancies.

Families' decisions, and views, on how to proceed with having subsequent children also varied considerably. Of the six, risk aware, families who had more children, four had opted for prenatal testing (NBS=4, LCD=0), and two opted for no intervention (NBS=1, LCD=1). Of the five families who had considered or were trying for more children, most expressed a desire to opt for prenatal testing, some expressed interest in, or had tried, pre-implantation genetic diagnosis (PGD), and others had considered adoption.

Table 1.3 shows the offer and uptake of prenatal testing in nine families that had subsequent pregnancies. As already noted, only two of the four LCD families were aware of their genetic risk at the time of conception; one of whom chose not to have prenatal testing and gave birth to an unaffected male, and the other family had a number of miscarriages prior to reaching 10-12 weeks gestation period in which prenatal testing is offered. In the NBS cohort, all five families were aware of their genetic risk and all were offered prenatal testing. Four families chose to test their pregnancies, two of which were found to be carrying girls, one was found to be carrying an unaffected boy and one chose to terminate a foetus with a different condition before continuing to conceive a girl. One family chose not to test their pregnancy and had a girl.

**Table 1.3 Subsequent pregnancies in the interview cohort: offer and uptake of prenatal testing**

	LCD (n=4)	NBS (n=5)	Total
No. of families aware of genetic risk	2	5	7
No. of families offered PND	1	5	6
No. of families who had PND	0	4	4

Although the number of families in the interview cohort who had subsequent children was small, their decisions regarding the number of subsequent children, and the uptake of prenatal testing, reflected the data from the quantitative section of the study. Factors which families discussed in relation to their reproductive decision-making are discussed in subsequent sections.

## 2. Planning the family

Families often described forming fertility intentions prior to starting a family. Original fertility intentions were presented as a paramount feature in the decision-making process after the diagnosis. For example, if a family spoke of “always wanting two children”, they were likely to have acted in accordance with their stated desires. A family who already had two children prior to the diagnosis usually ceased family building; a family that only had one child, usually continued family building, albeit with redefined justifications.

Although families tended to act in accordance with their stated desires, following original fertility intentions was often described as problematic. Families who presented themselves as having completed their families, often deliberated about whether to change original plans in light of the diagnosis. Families who chose to continue family building often considered a variety of reproductive options before proceeding, such as adoption, prenatal testing, and pre-implantation genetic diagnosis. In the following two sections parents' fertility intentions are addressed, followed by an exploration of the reproductive options families considered when assessing their reproductive future.

## 2.1 Forming fertility intentions

Each of the 19 families interviewed were asked whether they had discussed their fertility intentions prior to starting a family. The majority of families (n=13) described their considerations of their ideal family size, prior to having children. Intentions were sometimes presented as a desire for a specific number of children, for example:

I – I think it was always two, a boy and a girl. I think that's what really, you know - That's what we always wanted really. (Louise, NBS second child affected)

Other families expressed fertility intentions as a general desire for children, rather than for a specific number:

We both knew we wanted children and we both - and I think we both thought we wouldn't want only one, but we hadn't really discussed it further. In my head it probably would have been just the two. I don't think he would have wanted any more than that. He's not really said. No, I think he'd have been happy with two as well. (Mary, LCD, first child diagnosed aged three)

Some families presented their reproduction as a *fait accompli*, with no indication that fertility intentions had been considered prior to having children. In these families, fertility intentions were often superseded by unplanned pregnancies:

We didn't discuss any children before Mike was born. Mike just happened and then about five years went by before we tried for another child. The gap was just... the years had just flown by.<sup>31</sup> (Sandra, NBS, second child diagnosed)

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<sup>31</sup> All extracts from the interview with Sandra and John are paraphrased, due a technical fault with the voice recorder

Many families expressed their fertility intentions as a desire to replicate their own experiences of childhood family life. Notions of ideal family size appeared to be socially, if not biologically, inherited.

I've always wanted at least two because I've got two sisters and a brother and I've, you know, I've loved growing up with brothers and sisters. I think it's really important, so I, you know, I'd like – I've always wanted to have more, more than one. [Sue, first child diagnosed through newborn screening]

Family trees often showed clear associations between the parent's family size (number of siblings), and their choices about their own family size (number of children). However, transforming intentions into behaviour was often met by biological obstacles, such as infertility; or social obstacles, such as separation from a partner. Although Sue expressed the desire to replicate her own family life, like a number of mothers in both cohorts, she had separated from her partner shortly after the diagnosis.

In contrast, some families chose to avoid replicating their childhoods. Rebecca and James' second child had been diagnosed with DMD through newborn screening. They chose to have a subsequent pregnancy to reach their ideal family size of three children:

We always wanted more children. We always wanted three.  
[Rebecca, NBS]

James had come from a large family, and all his siblings had since created their own large families, whereas Rebecca felt she'd had a lonely childhood:

I think it's important to have, I've got one brother and there is ten years between us so I grew up mainly as an only child so I really missed not having brothers and sisters and you know there is always somebody here to play with. [Rebecca, NBS]

For Rebecca and James, the decision to have more children after the diagnosis of their affected son, represented a continuation of their original intentions; formed in childhood, followed in adulthood.

Other families described a selection of disparate factors that had influenced their fertility intentions. Anne and David's second child was diagnosed through newborn screening. Their decision not to have more than two children did not seem to occur as the result of the diagnosis, nor as a result of the trying to replicate their own childhood experiences:

...it's just me and two brothers. David comes from, he's one of four. His mother lost a few in between, but no, no just one of three I am. It's just that I'd worked, I was thirty, I was getting married, I wanted to just give them the best and when you've got a houseful you just can't do it. I'm not that maternal to be honest. My mother was shocked that I had one.

Anne expressed a multiplicity of factors that had influenced their decision to limit family size, including age, a desire to focus resources on two children, a lack of maternal instinct, and the demands of paid employment.

Lauren, like Anne, chose not to replicate her own experiences of childhood and expressed a desire to retain autonomy and to exercise control over her fertility behaviour.

I thought it would be nice to have two because I like to be in control. I like to be organised, I couldn't stand a house full of kids, you know. I love the people who say I want four, why? ... I just don't understand why people would want more. I couldn't cope."

Both Lauren and Anne express an explicit desire to deal effectively with the responsibilities of motherhood, and chose the limitation of family size as a way of achieving their goal.

The majority of families had considered their ideal family size, prior to starting a family. Often families attempted to replicate their own experience of childhood family life. Other families described other factors which had influenced the formation of fertility intentions, such as age, a desire to focus resources by limiting family size, or an expressed need to retain autonomy and control in the family home. Families frequently presented their reproductive decisions after the diagnosis, in relation to their original fertility intentions, albeit with reformulated justifications and deliberation of a wider range of reproductive options.

## **2.2 Deliberating reproductive options**

Many families described how the diagnosis had complicated reproductive decision-making; original intentions had to be reassessed.

I think you've got to be more careful about things, your choices, you've got to, I've got to think about things a bit more... but... we definitely waited and thought about things really, really hard before deciding well we'll just give it one chance... and we'll see what happens and then if it doesn't work out...you know we've given it a



try sort of thing rather than just giving up completely. (Fiona, second child diagnosed through newborn screening)

For many families, the diagnosis created new complications, and a wider variety of reproductive options, which had to be carefully deliberated.

Families, who considered having, or had children after the diagnosis, often reviewed a range of reproductive options, from adoption, to prenatal testing, and pre-implantation genetic diagnosis. Families presented their deliberations about whether to have subsequent children, in relation to their fertility intentions, biological and social circumstances, and views on the available options. Few families addressed all available options; the majority only presented those which were perceived to be potentially suitable and acceptable. For example, a family who had moral objections to prenatal testing and termination considered adoption and pre-implantation genetic diagnosis. A family who had difficulty conceiving considered adoption.

Some families presented themselves as unwilling to negotiate the new-found complications presented by reproductive options.

I did think about [having more children], but the risk was just – it's just too high, I think to take that risk – I mean I would have my eggs sorted out but I think "Oh god it's just – this takes so long" and I – you know, I'm 35 now, I don't – but I don't think I can – I don't think I want to go down that road – Two is enough and they're hard work anyway! I don't know if I want to start all over again, you know. (Louise, second child diagnosed through newborn screening)

Louise had moral objections to prenatal testing and termination and did not discuss the possibility of adoption. The remaining option – pre-implantation genetic diagnosis – was perceived to be too time-consuming. It is important to note that the majority of families, who presented themselves as being discouraged from having more children, also described themselves as having already met their original fertility intentions.

A number of families in both cohorts had considered adoption. However, the reasons for adopting varied considerably. One set of parents, Jennifer and Tom, went quite far through the process of adoption whilst they waited for confirmation of their genetic risk. However, once they had been informed that they were "low risk" the adoption process was abandoned, in favour of prenatal testing.

We did go ahead and sort of go through the adoption process and go on, sort of, a course and – and go through the process, you know,

seeing people and – and going on training, you know, sort of that type of thing. So we did go, you know, when it got as far as that and then I – I had a result – it would – came back to say that I was – I should have got the things out – the documents but I was sort of relatively low risk [...] and so – in that case then we thought we would try then. (Jennifer, GM risk, first child diagnosed through newborn screening)

Other families, who were unsure about prenatal testing, considered adoption as a way of avoiding the risk of having another affected child.

[My husband] would rather adopt I think because, only because he thinks it would be a lot of work, I think it would be a lot of work probably at the beginning being up through the night yes, but, **So he wants to miss out on the sort of first months?** Aye, I think only because of that I think, and because of fear of it having it. Having another one with [DMD] I think. (Nicola, carrier, second child diagnosed clinically, after birth of second affected child)

Another family, who had received a later clinical diagnosis, had considered adopting a child, after the mother had experienced a number of miscarriages. Rather than considering adoption as a way of avoiding the risk of having a second affected child, this family considered adopting a child affected by DMD.

[My husband] Kevin was a bit like, well, you know, we're all set up, you know, we could have another boy with Duchenne. I'm thinking ... well maybe - I began to sort of come round to his way of thinking, so that's strange, isn't it? In fact, I was looking at a magazine, it must have been the Muscular Dystrophy magazine, there was a wee boy in it who had Duchenne and he was looking to be adopted and Kevin said we should adopt him. And I was thinking? – but I just don't know if I could do anything like that, but, you know, it is one ... you know ... I don't know. I don't know. (Pamela, second child diagnosed clinically)

Although Pamela expressed doubts about adopting an affected child, presenting their consideration of the option suggested that families are not always averse to the possibility of caring for another boy with DMD. As another mother stated:

You don't always ... you don't always you don't like to think 'oh gosh I don't want to have another baby with Duchenne'. You know, you don't – tend – you tend not to think like that. (Sue, first child diagnosed through newborn screening)

Many families felt that their reproductive plans had been complicated by the diagnosis and as a result deliberated about a wider range of reproductive options. However, their deliberations did not always result from attempts to avoid a second affected child; many described positive experiences of living with a child with DMD.

### 3. Responsibility

Mothers presented their experiences of the diagnosis, and their subsequent reproductive decision-making, as a negotiation of a network of responsibility. The diagnosis and carrier testing instigated specific feelings of responsibility towards existing children. Views on future children, and the renegotiation of fertility intentions, emerged in relation to the mothers' responsibility to their partners, to their children, and to their extended family. Mothers negotiation of their reproductive responsibility is explored in the following three sections: 'providing a healthy child', 'providing for children', and 'protecting the future, unborn child'.

#### 3.1 Providing a healthy child

The negotiation of fertility intentions between partners varied considerably. Some mothers felt that their partners had handed them responsibility for reproductive decision making.

[My husband] just says, "it's up to you". That's all he ever said, yeah, "up to you". He – he, you know, if I said to him "shall we have another baby?" He'd say "well it's up to you", you know. (Louise, second child diagnosed through NBS)

Other mothers briefly mentioned discrepancies between their own fertility intentions and their partners. However, mothers usually expressed a belief that their own fertility intentions had been followed.

In contrast, families who had embarked on new relationships seemed to dwell on their different intentions. Fiona separated from her husband after their second child was diagnosed with DMD, and did not consider having more children. Some years later Fiona began a new relationship and described having to renegotiate her reproductive plans.

I think settling down with Paul was the thing that...and being so happy was the thing that... made us think about [having children] more I suppose. I think it was something that I probably wouldn't have done anyway... although it... how can I put it? [The diagnosis] just confirmed it a bit more you know, definitely I was definitely not going to have anymore, that was it you know. I'd got my hands full, that was plenty and then of course Paul didn't have any of his own. (Fiona, second child diagnosed through NBS)

Fiona presented the decision to have a third child, not as her ideal choice, but as a sense of responsibility to provide her partner with his own, biological family, which was exacerbated by his parents.

I kind of felt pressured as well from his parents point of view because they...obviously everything being so complicated they... weren't exactly impressed that we were going to get married... and... they've always... always made excuses to get him on his own... and... to... every time I was out the way 'well are you sure, you know, she might never want to have a child with you' and you know, that made me furious and that... kind of felt like a bit of pressure as well (Fiona, second child diagnosed through NBS)

Another mother, Tracey, who already had one child with another partner before her second child, with a new partner was diagnosed, highlighted her own sense of responsibility to provide her partner with an unaffected child.

I'm hoping to try and have another one, yeah. I know that the age gaps is big but Connor is the only child that Tony's got anyway so – it's a decision I've got to come round to. (Tracey, second child diagnosed clinically)

Mothers, especially those with new partners, presented themselves as responsible for providing their partners with (unaffected) children. Fertility emerged as a responsibility; a need to negotiate conflicting desires. In nuclear families, resolving disparate fertility intentions was presented only briefly, suggesting relatively easy resolution of conflict. However, mothers with new partners often presented themselves as responsible for providing their partners with a healthy child.

### **3.2 Providing for children**

Mothers often presented a sense of responsibility to provide a suitable family environment. Parents combined their sense of responsibility towards their children, with their original fertility intentions, reformulating them in light of the diagnosis. Although most parents seemed to follow their stated fertility intentions, families often presented fertility behaviour as a responsible consideration of the families' new needs.

Many mothers, who presented themselves as having already decided not to have more children prior to the diagnosis, reevaluated their circumstances in light of the diagnosis and considered having more children. Most decided, in Maureen's words, that the diagnosis was "the wrong reason to have another baby". However, many

mothers shelved previous plans to be sterilised, in anticipation of future technological developments, which may mean a subsequent child could provide a cure.

I went in to be sterilised and then I changed my mind. Because I felt – what – what made me change my mind really was thinking, you know when you see people having babies and it helps the brother or sister if they've got some sort of – I feel what if something like that happens? You know, and I wouldn't think twice about it then, I mean I'd have another one straightaway – If it was going to help Scott, you know. So I think that stopped me then, I thought "no I can't go and be sterilised". I want to leave my options open. (Louise, second child diagnosed through NBS)

Many mothers presented retaining fecundity, not as a desire for subsequent children, but as an obligation to their affected child.

For some families, the diagnosis elicited a desire to focus all attention and resources on the affected child. Lesley, whose first child was diagnosed clinically when she was seven months pregnant with her second, doubted whether they would have had another child if they had known.

If I wasn't pregnant when I found out about Jonathon - I had, I'd have just had Jonathon and that would have been it, just to give him the time and everything because of what he's got. He'll still get all the time and everything, right enough, but for that reason I wouldn't have had another one so I could be there for him and help him more than anything. (Lesley, first child diagnosed clinically)

Lesley's second son was still young, and as yet undiagnosed at the time of the interview. Throughout the interview Lesley expressed difficulty with bonding with her newborn. The birth of an unaffected child was perceived as a distraction from the parental responsibility towards the affected child.

Families who wanted more children before the diagnosis, presented their decision to have more as a responsibility towards their affected child, or towards the as-yet unborn child. Many families presented their decision to have more children as beneficial for their affected child.

**Do you think Michael's diagnosis has changed your reasoning for wanting another child?**

Well, yeah, slightly because I did get fixated on the future and how my husband's quite a quiet person. He likes the house. He doesn't bother about socialising or anything. And I just thought for the future, what would it mean for Michael if he was kind of isolated in the house with just us two, being a bit older. I just thought it would be nice that we have a younger sibling in the family just to keep things a wee bit kind of lighter and brighter. Who knows? You

don't know. It might not have worked out like that anyway. But I just wanted for the future that he would have somebody. And again, with our ages, you thought well is he going to be left with nobody, you know, and be disabled. That worries me as well. Not that I thought another child should take that responsibility, but just for him to feel that there was somebody there, do you know what I mean? (Mary, first child diagnosed clinically)

Like many mothers, Mary worried about her son's future. Although they had always wanted "more than one" child, the decision to try for a second was reformulated as a responsibility to provide company, and support, for their affected son.

The decision to provide an unaffected child with siblings was not infinite. Some families felt that two unaffected siblings would be ideal, but most decided that one would suffice. Jacky provided justification for having another child.

I would have been unhappy with one. I always wanted two regardless, and I just thought you know with Joe I thought it'd be good for him to have a sibling. I think for us and also for Rowan as well because you know its knowing somebody with a disability, I think it's good for her as well to know that but you know there's differences and so on. (Jacky, first child diagnosed through NBS)

However, after Jacky had reached her ideal family size, her reasons for not having more children were formulated in relation to her responsibility towards her existing children.

I did feel my family was complete once I had Rowan. I don't regret never having anymore, you know if we'd started a bit earlier maybe, but I think when you've got one child with a disability you want to give them as much as possible, and again you've got to think about the room in your house, that extra room is going to be for ... you know the biggest room has got to be for the child with disability, and you've got to think how accessible that can be for him, and about extensions. And I just don't think it would be fair to Joe if we had more children because I wouldn't be able to devote so much time to him. (Jacky, first child diagnosed through NBS)

Prior to reaching the ideal family size, the diagnosis was presented as an influential factor in continuing family building. Once ideal family size was reached, reproductive decision-making was formulated as a responsibility to focus resources on existing children.

### **3.3 Protecting the potential future child**

A number of mothers expressed surprise at hearing other families had chosen to take the risk of having a second affected child. The sense of surprise ranged from

wondering how people would cope when their children died, to wondering how families could choose to put another child through the same condition.

I've heard, I'm sure I've heard of it...in fact in might have been [Cardiff based researcher] that actually said that... some of the, some family members have said well my brother had it and he was wonderful and I chose not to have tests done and what have you and to me, my personal opinion and I know that's their choice I just think it's absolutely horrendous to think that... I watch Sam every day you know and I think how upset he gets... and how much he'd want to be able to do things and I can't see how somebody would want to ever put somebody through that... (Fiona, second child diagnosed through newborn screening)

The extracts from Fiona in the previous chapter highlighted the family's difficult experiences of living with a child with a disability. Some mothers, like Fiona, who had negative perceptions or experiences of living with a child with DMD, expressed a sense of responsibility to ensure that they had no further children with the condition.

Some families, who described their decision not to have more children as occurring before the diagnosis, reformulated their decision as a responsibility towards the possible future child.

I don't think I could subject that to a sister, who would've ended up looking after them because basically your life revolves round them. I don't think it would have been fair on her, personally. I don't think it's fair on another child because you just basically (unclear). What would they do if we was off to appointments or well, we can't do this because they can't do it. You know? And I don't think I would've subjected my child to that, personally. (Anne, second child diagnosed through NBS)

In this instance, the mother perceived subjecting an unaffected child to life with affected siblings as unfair. Many mothers presented their responsibility to their existing children as paramount; life with an affected child was perceived to be unsuitable for unaffected children.

Reproductive responsibility took many guises. Some mothers described retaining their fertility as a responsibility toward their affected child, in the event that a future child may provide a cure. Others presented a sense of responsibility towards their existing child, to ensure resources were focused on their affected child, or, in contrast, to provide their affected son with siblings. Some families felt that it would be unfair to subject an unaffected child to life with an affected boy, whilst others

expressed a desire to prevent another child from experiencing the trauma of being affected by DMD. In the majority of cases, families presented a reformulation of their original fertility intentions, with the diagnosis providing an extra incentive to follow original intentions.

#### **4. Negotiating risk**

Many mothers discussed their reproductive decision-making in relation to their perceived risk. Although some discussed the risk of miscarriage when choosing to test a pregnancy, most mothers focused on their genetic risk and the consequent risk of having a second affected child. Interpretations of genetic risk varied considerably between families; statistics were deciphered in many different ways.

In addition, families articulated a change in their perception of risk. Many families described their decision not to undergo routine testing procedures for conditions such as Down's syndrome and Spina Bifida, in pregnancies prior to the diagnosis, as a willingness to "take a chance". In pregnancies after the diagnosis, "chance" became a "risk"; an external tyranny to be desperately avoided. Families' descriptions of risk are explored in the following sections under three themes: 'relevant risk', 'deciphering statistics', and 'from taking a "chance" to avoiding a "risk"'.

##### **4.1 Relevant risk**

The relevance of genetic risk in reproductive decision-making varied considerably between families. Some mothers waited for their carrier risk to be confirmed before proceeding with subsequent pregnancies, whilst others described their reproductive decision-making as unaffected by genetic risk. The majority families noted their genetic risk of having a second affected boy when discussing their reproductive intentions. For most families, genetic risk was described as just one factor amongst many, which had influenced their reproductive decisions.

After we had Daniel we decided we didn't want anymore anyway. I had quite a lot of back problems during my pregnancy and quite a difficult labour and my blood pressure had gone up towards the end of my pregnancy, so I wasn't all that well when he was born anyway.



And he was nine and a half pounds, or nine pounds three. But we were just quite happy with – you know, with the one. And my husband, he's had asthma, but it was contract work he was doing so he maybe had three months work here, six months work there and – And in reality it costs a lot of money to bring up a child. You know, so we were just quite happy, plus I was twenty nine when he was born and I just felt you know, quite happy. With the one.

**So did the diagnosis make you re-think about it all?**

No. I'm a carrier of muscular dystrophy. (Maureen, carrier, first child diagnosed clinically)

Frequently families described genetic risk as one factor amongst many, as an extra reason for not having more children. This was particularly prevalent in families who presented themselves as having already reached their ideal family size. Parents rarely described a single reason for choosing to have, or not to have, more children. Reproductive decision-making involved a complex negotiation of circumstances, in which the diagnosis became just one more factor amongst many.

For families who felt that they had not yet reached their ideal family size, genetic risk often became a prominent factor in decision-making. A few families described their unwillingness to proceed with subsequent pregnancies, until they had been informed of their genetic risk.

We had to wait. We – we, you know, we were hoping that we could be given some help on this to, you know, to help us make a decision really [...] I had a result – it would – came back to say that I was – I should have got the things out – the documents, but I was sort of relatively low risk – It didn't come back to say I was a high risk. But it – it sort of gave a relatively low risk. But this mutation had happened somewhere along the line, and so – in that case then we thought we would try then. (Jennifer, GM, first child diagnosed through newborn screening)

For some, genetic risk was a key aspect of the reproductive decision-making process. Trying for another child was occasionally delayed until the parents had received reassurance that their risk of a second affected boy was low.

In contrast, other families, who had proceeded with subsequent pregnancies, did not mention their genetic risk as an influential factor in decision-making.

**So did you have any tests during your pregnancy?**

No just in case it gave me a miscarriage and stuff like that. I thought I didn't want to take that chance I'd rather wait until he's born and if he's got the same condition he's got the same condition. (Lisa, carrier, second child diagnosed clinically)

For this family the risks associated with prenatal testing, were more relevant to decision-making than genetic risk, and the consequent risk of having a second affected child.

#### 4.2 Deciphering statistics

Despite families' frequent assessment that genetic risk influenced their reproductive decisions, the variety of interpretations of risk highlighted the disparate ways families' deciphered statistical risk. Some families described the difficulty of gaining meaningful interpretations of numerical risk.

**Do you remember, were you given a sort of number?**

I – I think I was given a percentage. Yes.

**What – what did that mean to you?**

It's very – it is really difficult to – because whatever you do you're taking a risk. You are – and my husband, he was really keen to have more children. I was more cautious but giving me this, it did – it did help a little bit – To think well if – it would have been a different matter if, you know, if it had said you are a high risk, it falls in a high risk category that you're going to – if it's a boy, you're going to have this – (Jennifer, GM, first child diagnosed through newborn screening)

Quantifying risk was often reported as problematic; as Jennifer noted, whatever was decided involved risk. Rather than focusing on numerical risk assessments, some families described their risk in terms of “low” or “high”.

Some families appeared to have been confused by numerical statements. Jessica, who had a 1 in 20 risk of having an affected boy in subsequent pregnancies, described her risk:

I had a test as well to see if I was a – carrier, which wasn't identified – But they said I still – so it was like, what was it, twenty – still 20% chance. [Jessica, NBS, germline mosaicism risk]

Jessica and Neil's first child was diagnosed through newborn screening and they had decided to have a second child. They chose not to have prenatal testing. Neil felt that their decision might have been different if Jessica had been a carrier:

*... if Jess had been the carrier I think the choice would have been the opposite to what we done wouldn't it because I mean we were down if – if it had been a boy it's 50-50 isn't it? Then you got the – the 50-50 chance if it's a boy or a girl. You know, and then because Jess wasn't a carrier we went down to a 20% chance. [Neil, NBS, wife, Jess has GM risk]*

A germline mosaicism risk of having an affected boy is 1 in 20, or 5% in each pregnancy and a carrier has a risk of 1:4 or 25%. It is unclear from the extracts from Jess and Neil whether they felt their risk of having an affected boy was 20% overall or 20% if it was a boy. Either way, they had grossly overestimated their risk and yet were still unwilling to test the pregnancy; implying that a 5% reduction in risk was an adequate reduction in risk, enabling them to proceed with a subsequent pregnancy without prenatal testing.

One newborn screening family, Christine and Mark, had ceased family building, after being informed that it was “dangerous to have anymore children, because if you have a boy it will definitely have the Duchenne”. Christine and her husband, Mark had decided against having subsequent children and consequently Mark had a vasectomy. After a recent visit from a genetic counsellor, Christine had been reassured that it was possible to have an unaffected child. However, Christine still believed that all male children would be affected.

...of course then it's got to be a girl, it's – it can't be a boy, so I'll have to have a special test done at the hospital [...] if I did find out, if it – if I was carrying a – you know, a boy, I would have to have a termination. [Christine, NBS, carrier, trying to conceive after diagnosis of second child]

With a newfound belief that it was only dangerous to have boys, Christine expressed her desire to continue family building, and her husband Mark was hoping to have the vasectomy reversed.

Some families described how their assessment of numerical risk had become imbued with reflections from real-life experience. Nicola, whose first child was diagnosed after her second affected boy had been born, was asked to describe her risk in each pregnancy. She replied:

One in four and I've got two already. Oh that doesn't mean two out of four you know what I mean? But there's not many folk have two so I just think, what's the chances? [Nicola, LCD, second affected boy born before diagnosis of first]

Nicola understood that the risk was 1 in 4 and that having two already did not make the risk 1 in 2. However, her personal experience of having two affected boys led to a sense of distrust of purely mathematical risk. Genetic risk was interpreted in relation to families' experiences and situations.

Although families often discussed their risk of having a second affected child in relation to their reproductive decisions, there was no correlation between actual risk and uptake of prenatal testing. Of the six families in the interview cohort who were offered prenatal testing, a total of two families (NBS=1, LCD=1) chose not to test; the NBS mother had a germline mosaicism risk and the LCD mother was a carrier. Of the four families who chose to test their pregnancy (NBS=4, LCD=0), two were carriers and two had a germline mosaicism risk.

### 4.3 From taking a “chance” to avoiding a “risk”

Many mothers noted that they had chosen not to have any routine prenatal tests in pregnancies prior to the diagnosis. However, after the diagnosis these mothers had often accepted, or felt that they would accept, all available prenatal tests in future pregnancies. Some mothers presented their changed decision in relation to their perceived ability to cope with whatever condition might occur. Mary had chosen not to have routine prenatal tests in her first and only pregnancy. In the extract below Mary describes her reasons for wanting to test subsequent pregnancies.

If I was - if I was to fall pregnant I would want [prenatal testing for Down's syndrome] because I - having said that I know - I don't know. I think the first time I thought I'll take what life throws at me. If I have a Down's syndrome baby, we'll cope with it, or any other disability. But, with Michael, knowing that the future's going to be difficult, I don't know that I would - I don't know. But I'd find it very difficult to make the decision. But I think I'd rather know beforehand than not know. So I would get a test before it.

#### **So it's - what made you sort of change your mind?**

Well, just the fact that I would have two disabled children. I just think, you know, if he's in later stages he's going to be quite disabled, then how could I cope with another if it was Down's syndrome, something that takes a lot of support and a lot of parenting, I just wouldn't want to consider it. I wouldn't want to think that that - life would just be difficult. But people manage with a lot worse, you know what I mean? You see people - even people that foster like three or four disabled children and they're doing that through choice. I'm not that big-hearted, I think. I think if it was my baby and yeah, I would, I would love it and I would look after it. But to make the decision beforehand to do it, no, I'm not that selfless. (Mary, first child clinically diagnosed)

Families described the changed context of the reproductive decision; from having no children, or healthy children, to having a child with DMD. Whilst a chance is willingly taken prior to the diagnosis, afterwards the risk of another disabled child becomes an external tyranny to be desperately avoided.

After the diagnosis, families present their decision to test subsequent pregnancies in relation to two key contextual factors. First, many families highlighted the difference between dealing with what is done and choosing what is to become. Second, the decision to test a subsequent pregnancy was made in relation to families' perceived ability to cope with *another* disabled child. Many families presented the perceived burden of coping with two disabled children, to be beyond their capacity.

## 5. Coping with tomorrow, coping with today

Families' aspirations for the future were frequently presented as a negotiation of their perceived ability to cope with two key aspects of the condition. First, a number of families discussed the prospect of facing a child-less future, once their affected child had died. Second, families articulated the difficulties of family building when faced with the immediate demands of caring for a child with DMD. The two themes, 'facing the future' and 'coping with the present' are explored in subsequent sections.

### 5.1 Facing the future

A number of mothers described their fear of being left childless. For some, the prospect of losing their child had induced a brief, but meaningful consideration of their reproductive options.

I do sometimes think, you know, is - is he going to die young which and we know that they do die younger and I think, "oh, you know, do I - do I want to be left with one child" and think - that did used to enter my head. But I - I don't - I try not to think of that anymore because you don't know what's around the corner so I, you know, I don't think of him dying young anymore. I just, you know, you've just got to hope for the best, haven't you, so - but I did used to think like that in the beginning but now I - I think, you know, you've got to deal with that when it comes haven't you and you don't know what's around the corner as my mother keeps telling me, so, and that's what keeps us going really so you've - you've got to have a little bit of something to cling to. So it doesn't - that doesn't come into it now with - with children. It did in the beginning but it doesn't now. (Louise, second child diagnosed through newborn screening)

While some families chose to direct their focus on the possibility of finding a cure for the condition, others described how the thought of losing their child had influenced their decision to have more.

I mean it wasn't until like I saw this thing on television, it was about the Liverpool disaster at the football stadium... where all these fans got killed and there was like a - this family had lost two children, and I was thinking well you know where am I going to be if I lose Joe and I haven't got anybody else. And I suppose that was a selfish thing so partly I was thinking well I need something else to focus on, I mean [when] Joe is not here I need another child. I just ... I couldn't then be childless. I just don't think I could have coped with it.  
(Jacky, first child diagnosed through newborn screening).

Although some families described how the diagnosis, and prognosis, had induced a desire for another child, fertility intentions appeared to play a greater role in reproductive behaviour. If families described that they had always wanted more children, the diagnosis was described as adding an extra incentive to have a replacement child. For families who had not planned to have any more children, consideration of having another child was eventually replaced by their original fertility intentions.

## 5.2 Coping with the present

When parents discussed their aspirations for the future, they often described aspects of living with the condition which had influenced their reproductive decisions. Parenting a child with DMD was presented as both a physically and emotionally demanding role. Parents present themselves as responsible for the practical, day to day, management of their child's condition, from helping them on the toilet, to ensuring that they are turned over regularly during the night. In addition, parents often described the emotional distress caused by watching their child's slow progression towards immobility.

Families with one affected child often expressed doubts about their ability to cope with more children. Some families felt an increased sense of fear of having another child after the diagnosis, as demonstrated by Lauren:

We always wanted two, I'm talking ... we've had a couple of scares and I've been practically suicidal, I've really been practically suicidal because even the thought of having ... not just because of Ryan I don't think that, but because I was so ill I don't think I could go through another nine months of feeling like that and the after, plus

Hannah and Ryan on top do you know what I mean, and I think everything else you're supposed to be, to do... superwoman you know. I don't think I could cope. [Lauren, NBS, second child diagnosed through NBS]

However, as Lauren notes, they had only-ever wanted two children. Lauren's fear of having another was related to her experience of having a difficult pregnancy, Ryan's diagnosis, and her perceived inability to cope with more children.

Interestingly, a family with two affected boys described their ability to cope with two, but expressed doubt about their ability to cope with three affected children.

...you start thinking well if you'd known earlier would you have had Jamie so then you think well, obviously you would have wanted to have Jamie so, I don't know. But then now, I wouldn't have a third, I couldn't cope with a third one, another. Well maybe if that happened you would change your mind and that. That's why these things I think just have to happen but I wouldn't like to have to do that. I don't think I could watch that again. It's too cruel to watch I think to be honest. But, it's too much hard work as well. I mean you can only cope with so much and you've got to stop haven't you? You know, as they get older and they're very active you know they want to do this that and the next thing. (Nicola, first child diagnosed clinically, after birth of second affected child)

Parents often presented themselves as capable of coping with the life they had, but when choosing what was to become, parents were faced with incredibly difficult dilemmas. For Nicola, coping with the life they had, with the diagnosis, her children's day to day needs and the house adaptations, had acted as a distraction from following her original reproductive intentions.

I always wanted another and I think with them having that has made it worse because I did want another one and obviously things aren't the same now to have another one. There's a lot of ifs and buts there and I think that makes it more definite but, why haven't I done it in the last ten years? That's strange now looking back but you were dealing with your worst scenario. You know you were dealing with that, you were dealing with the house. You know we done everything straight away so that you know to be sitting in this position now kind of thing. And I, where we were ten years ago I don't know but, you know. I think as years go on it gets, as the clock ticks away I think you start thinking, I should have done that because it's all I've ever wanted to do. (Nicola, first child diagnosed clinically, after birth of second affected child)

Throughout the interview, Nicola presents numerous reasons for and against having more children. Her fear of having another affected child or having to cope with a baby and two wheelchair bound sons undermined her desire to have another, and yet her fear of regret remained excruciatingly palpable.

A number of families from both cohorts had experienced difficulties either conceiving or carrying to term (NBS=1, LCD=3). The NBS family eventually carried to term and reached their ideal family size. However, all of the LCD families in the interview cohort were still trying. All three families, who had received a later clinical diagnosis, had stopped trying for children immediately after their sons' diagnosis. Mary and Chris's son was three and half years old when he was clinically diagnosed.

We had been trying for another baby before he was diagnosed, but as soon as we heard about it we stopped right away. And when the geneticist was telling us there was a one in four chance, I mean my age was a factor. I mean I was already 40, 41 then, he said that if I'd wanted another child, not to hesitate. [Mary, LCD, affected boy diagnosed aged 3]

Mary felt that if she had received an earlier diagnosis, she would have tried to have more children before the years progressed.

I would have tried right away for another - if I'd been - if he'd been diagnosed right away and I got my diagnosis right away [Mary, LCD, affected boy aged 6]

At the time of the interview, Mary was going through her third round of pre-implantation genetic diagnosis.

For many LCD families the diagnosis delayed the continuation of family building for some years. Families were often dealing with the emotional aspects of the diagnosis, alongside practical demands of getting their houses adapted. Often, by the time they felt ready to have another child, mothers were in their late thirties and had difficulty conceiving or carrying to term

I had Sean when I was 31 so, say, I was 33 when diagnosed, yeah I might have thought two years after that, at 35, I would have had one. But then the delay went on so long because... I - I wasn't in a - you know, I was upset for a - for all these years, so erm... so I might have. But then when I was 38, you know ... although they've said the miscarriage isn't - that they're just one of these things, it's purely basically unlucky for three of them. [...] Erm, but you know, I think now ... erm, you know, looking back, I probably would have had children closer together and more of them. [Pamela, LCD, affected boy diagnosed aged 3]

Although a number of NBS families had miscarriages after the birth of their affected son, all families who had tried to have more children had eventually given birth to a healthy child.



Many parents, who had received a later clinical diagnosis, had simply put aside fertility decisions, in the midst of coping with the diagnosis, and going through the process of house adaptations. In contrast, families who had received a newborn screening diagnosis often proceeded with their original fertility intentions, prior to starting house adaptations.

## **6. Summary of factors families discussed in relation to reproductive decision-making**

Families presented a number of factors in relation to their reproductive decisions. First and foremost families often felt that they had already deliberated about their ideal family size, prior to commencing family building. Frequently, fertility intentions were influenced by parental experiences of their own childhood family life. For example, if parents had come from a large family, they were often keen to replicate their own experiences. However, parents also presented a number of reasons for limiting family size, such as a desire to focus resources on fewer children, or an expressed need to maintain autonomy and control in the family home. Families presented their original fertility intentions as a paramount feature in reproductive decision-making.

Although families often sought to reach their ideal family size, regardless of the diagnosis, many described how their reproductive decision-making had been complicated by the diagnosis. Families often deliberated about a number of reproductive options, from prenatal testing and termination, to pre-implantation genetic diagnosis and adoption. Families' experiences of the decisions regarding testing and terminating and the experience of pre-implantation genetic diagnosis are explored in greater depth in the following chapter. Reasons families articulated for accepting or rejecting different reproductive options varied considerably. Some families focused on avoiding the risk of a second affected child, whilst others considered themselves as well-placed to have a second affected child.

Responsibility emerged as a key theme in the reproductive decision-making process. Some mothers presented their decisions in relation to their responsibility to provide their (new) partner with an (unaffected) child. Others spoke of their

responsibility to provide for their children. For some mothers this involved retaining fertility, in the event that a future technological development might mean another child could provide a cure for their affected child. For other mothers, providing for their child involved avoiding having subsequent children, which may distract resources from their affected son. Others described feeling a sense of responsibility to provide their affected child with a sibling, for company and support. In contrast, some presented the decision to have another (affected) child as irresponsible.

Many mothers discussed their reproductive decision-making in relation to their perceived risk. However, there was some difference in the aspects that were described as risky. Although most mothers focused on the risk of having a second affected boy, some did not express the prospect as a risk, and others focused on the risks of miscarriage, associated with prenatal testing. Despite families' assessment that genetic risk had often been an important consideration in their decision-making, many families had an incorrect awareness of their risk. Families often described the difficulty of gaining meaningful interpretations of genetic risk; numerical probabilities were imbued with personal experiences or perceptions of disability.

Many families described their decision not to have routine prenatal tests on previous pregnancies as a 'chance willingly taken'. However, in subsequent pregnancies, families often expressed a desire to test for a number of conditions, alongside Duchenne muscular dystrophy. Negotiation of the new family situation often led parents to express concern about their ability to cope with another disabled child. A chance willingly taken became a risk actively avoided.

Negotiation of the families' new situation and the prospect of a future, childless life, occasionally enhanced families' desires for more children. However, a number of families who had received a later clinical diagnosis expressed a sense of missed opportunity to have more children. Whilst dealing with the diagnosis and the consequent upheaval of the family home, many had delayed reproductive decisions. By the time house adaptations had been completed, many mothers in the LCD cohort were met with biological obstacles to transforming their fertility intentions into behaviour. In contrast, families who had received a newborn screening

diagnosis had often continued family building immediately and were consequently more likely to be successful in transforming intentions into behaviour.

# Chapter Eight

## Living with choice

### Introduction

One of the main arguments that has been used to support newborn screening programmes for untreatable conditions, and of course, the primary focus of this thesis, is the early provision of reproductive choice. Inevitably, choice creates the necessity to decide between competing options. The aim of this chapter is to explore families' descriptions of living with choice, which highlighted the complex and highly emotional context of reproductive decision-making for Duchenne muscular dystrophy (DMD).

Families' descriptions highlighted the difference between two contexts of decision-making. Families who had received a later clinical diagnosis articulated their experiential knowledge of their child and his condition. In contrast, families who received a diagnosis through newborn screening described the influence of medical information on reproductive decisions. Families who chose to use prenatal testing in subsequent pregnancies articulated their hopes and fears, in their quest to seek reassurance of a 'normal' pregnancy. For those who had followed their original fertility intentions, chosen prenatal testing and given birth to a healthy child, the experience was described with immense joy, and yet most expressed profound trepidation at the prospect of repeating the process. Those who were unsuccessful in their attempts to follow original intentions and give birth to a healthy child described an intoxicating process; driven by hope and dashed by disappointment.

Family accounts spoke of the value of choice, and yet, those who had already completed family building, or did not have choice, expressed a profound sense of relief at having avoided being compelled to choose. Some articulated the value of choice for others, but not for themselves. Families' experiences of living with choice are explored under four themes: 'knowing my child, knowing his condition', 'prenatal testing; hope, fear and the quest for reassurance', 'testing intentions and the limitations of choice' and 'oscillating between the public and private domain'.

## 1. Knowing my child, knowing his condition; the variable role of diagnostic pathway

Once families received the diagnosis, they were then offered the option of prenatal testing and termination of subsequent affected foetuses. Families described using different sources of knowledge to inform the reproductive decision-making process. Families with older children spoke at length of the immense ethical dilemma of choosing to test and terminate an affected foetus, which had the same condition as the child they had come to know and love. Families with younger children often described the difference between medical information and experiential knowledge of the condition. Families' experiences are explored under two themes: 'ethical dilemmas' and 'medical information and experiential knowledge'.

### 1.1 Ethical dilemmas

Families' descriptions of the decision to test and terminate a subsequent pregnancy highlighted the exceptional distress caused by even considering terminating a future child, which had the same condition as their existing child. Many families, who had received a later clinical diagnosis, were sure that they would find a termination unacceptable.

Lesley and Mick's son was diagnosed when Lesley was seven months pregnant with her second son. Lesley had been offered prenatal testing, but they had decided that would prefer to "enjoy their son", before finding out whether he had the same condition as his elder brother. When asked if she had considered or would ever consider terminating a pregnancy, Lesley replied:

No, not at all. Never. No, I don't agree with. I wouldn't do it at all. No, that's - no, I don't agree with that. I would never. Never even entered my head. No, I wouldn't have done that. No.

#### **Is that for religious reasons or -?**

No, it's just - it's nothing to do with religion, it's just I would never terminate a pregnancy, my own pregnancy at all. I would never. It's just something I wouldn't do, you know, even if I'd got - if I knew that he had it before he was born I wouldn't have, no. No matter what was wrong. [Lesley, LCD, carrier status unknown, second boy conceived before first child was diagnosed]

Lesley articulated her responsibility as a mother, to love and care for any child, regardless of “what was wrong”. A number of families in the LCD cohort described a strong ethical standpoint against termination, and associated prenatal testing with termination. Prenatal testing, therefore, was not a feasible option.

Some mothers noted disparity between their ethical beliefs and their potential decisions regarding prenatal testing and termination. Pamela described her views on termination, in relation to her decision not to have prenatal testing, on pregnancies prior to the diagnosis.

I don't actually agree with [abortion]... on – it's against my principles, erm, I don't – I don't judge though. I'm not a person that would say, you know, personally, for myself, I just wouldn't do it. When I had Jemma and Sean I didn't have any of the blood tests at all. Because erm, because the doctor said to me: 'Do you want a blood test or not?' And I said: 'Uh, I don't know'. And he said, well, he said: 'What would you do if the test came back and says it was Downs' Syndrome?' And I said: 'I don't – I don't know'. He said: 'Well, would you have a termination? And I said: 'No'. And he said: 'Well don't have the test'. And I didn't. Erm, you know, because ... you know, I – I don't – I just don't believe in it and I don't know how much I could live with myself ... if I was to do it. (Pamela, second child diagnosed clinically)

Pamela went on to explain that her view on abortion was not influenced by religion, but was part of her moral outlook on life. Although Pamela had chosen not to have routine prenatal testing for other conditions, due to her moral standpoint against termination, in subsequent pregnancies she had decided to use prenatal testing for DMD. Sadly, all subsequent pregnancies miscarried before ten weeks gestation; the decision to test therefore remained hypothetical. In the following extract, Pamela describes the prospect of negotiating her moral standpoint with the prospect of having a second affected child.

...saying that, obviously if the – the tests had come back at ten weeks ... what would I have done? I don't know. For the first time I would need to have thought very carefully about that [pause] So it's not right for that time, but, you know, would I have considered it? Probably yes [pause] But I don't believe in it. But I just don't know if I would have been able to... have another child with Duchenne. But... I would never swap Sean. Ever. You know, I would never go back and – and swap that. That's what's done is done. Erm, and he's a great boy and he's brought so many things to our lives that probably wouldn't have been there. We've met people and ... I – I just – I just wouldn't change it. But would I go through it again? ... And I've not even been through anything yet, I don't think. Apart from knowing what's going to happen we've not actually lived through it. (Pamela, second child diagnosed clinically)

Many mothers described the difficulty of negotiating previously held beliefs with the prospect of having a second affected child. Families expressed their love for their child, and the benefits that they had gained from his existence. However, parents love for their children was harshly juxtaposed against the prospect of watching another child's slow progression to immobility.

Many families articulated the belief that the decision to test and terminate a future pregnancy undermined the value of their child's existence.

[The consultant] said that if I'd wanted another child, not to hesitate and that they would test, well, if I fell pregnant they would test the foetus and abort if there was a - part of me I think I did want another child and part of me said yeah, I was prepared to do that. But my husband couldn't. He said no. He said he knew right away if he was faced with it he wouldn't go through an abortion. Well, not that he would, I would go through it, but he didn't want to face that. So he said no, no, that wasn't an option.

**Was that for religious reasons or - ?**

Well, not strongly, just his own moral reasons, his own feelings on it that he didn't want - and I think as well it was kind of a feeling that there's something wrong with him [their son], and look at him, he's a perfectly able, capable wee boy, but obviously in future if you had two children the same it could be very, very difficult. So I think that's how he felt that it was really saying, thinking about him, would we have done it and he didn't want to think about all the issues. And I think I would have - I think I would have found it very, very difficult myself. And in the end up, I'd probably went through with the pregnancy no matter what the outcome was. But we decided not to take the risk. (Mary, first child diagnosed clinically)

Mary and her husband had decided to avoid the ethical complexity of choosing to test and terminate an affected foetus, by opting for pre-implantation genetic diagnosis.

One possible explanation for the lower uptake of prenatal testing, in families who received a later clinical diagnosis, was the age of their affected child at the time they were considering further pregnancies. For the LCD families, the option of testing and terminating an affected foetus was often wrought with emotional complexity. Although many families felt that they could not cope with a second affected child, the decision to test and terminate a child for a particular condition was being made in the context of already knowing a person with that condition. The decision-making process included experiential knowledge of living with a child affected by DMD.

## 1.2 Medical information and experiential knowledge

Many families felt that the medical information provided at the time of diagnosis provided a stark and distressing outlook for their child. A number of families, who had received a later clinical diagnosis, described their experience of the condition as more positive than they had originally imagined.

They said that he can't ... he can't ride a bike, he can't do horse riding, he can't this, you assume he can't do anything and it's funny this little one is crawling around and you're thinking hang on a minute. So, whatever they do then it's a surprise to you, and you're not thinking well ... that gives you, not hope, but you think well yeah actually so he can't ride a bike, so? So he can't go horse riding, so? He can do that, he can do this. He can't play football, he hates football he 'don't wanna play it anyway, it's a stupid game' you know [...] but when you're first told it's devastation, and if you see the later on stages it frightens you to death. 'Cos you're thinking oh my god I'm going to be wheeling him around, and he's got a standing frame ... starts off as a little thing and it grows as he does, like you grow in your thoughts and ideas, but when you look at it you see something and you think they've got him strapped up from his feet to his head and he's on this plank of wood with wheels on... have I got to wheel my son round like that because you're expecting from day one, he's strapped together and that's what you expect ... you expect it because you don't know (Lauren, second child diagnosed through newborn screening)

The medical description of the condition was often found to be lacking in experiential validity. As the affected child grew older, families who had received a newborn screening diagnosis realised that medical knowledge did not fully describe the reality of living with a boy with DMD.

Anne, whose second child was diagnosed through newborn screening, described the medical information that they had received at the time of the diagnosis:

You know they say a wheelchair but you know to me a wheelchair was not the end of the world. You know? But, I mean [unclear]... they were going to grow up to accept it... it was the prognosis that you know, by the time they were 16, 17 that everything would start to go and you think well what was the point... of them being born? But of course it's not been like that. It's not been like that at all. It's been really positive, I've got to be honest. (Anne, second child diagnosed through newborn screening. First child subsequently diagnosed)

Anne's family was already complete at the time of the diagnosis, but she felt that if she had tried to have more children she would have tested and terminated on the basis of the medical information provided.



I think sort of time you know, from what the things they'd told me, what sort of life and what a life span... I really think I would have had an abortion. Just for their sake really, you know? You know? I mean not now but that's with hindsight isn't it? But I couldn't blame anybody on what they were told to take that decision. You know? I really couldn't. (Anne, affected boys aged 16 and 19 years)

Another newborn screening family had chosen to test a subsequent pregnancy for DMD. The foetus had been diagnosed with another condition, and the parents had decided to terminate. Jacky and her husband decided to have another pregnancy and chose to use prenatal testing; they had a girl and named her Rowan. However, now her son, Joe, was older, Jacky felt that her decision regarding prenatal testing and termination would be quite different.

I don't think I probably really thought about [having prenatal testing] as deeply... If I would have known what I know now I might not have gone for the tests. I mean if I ever got pregnant accidentally I don't think I would go for any testing at all ...because I now know I would never have terminated. I don't know what I would have done then... if anything.

**So, what's changed?**

Well knowing Joe I think has ... and what you're doing, I mean when they're young, 'cos Joe was only four then you know he wasn't in a wheelchair then, he was able bodied, I just didn't know what to expect, I didn't know erm you know if he had ... would have learning difficulties, if erm you know how he would cope with it, you know no sort of idea. But then once you've grown up with it ... like with Rowan I was really surprised when she said "well, I wouldn't mind if I had a boy like Joe," because she's used to it, she can see Joe as a normal person but I think because I had no idea what Joe was going to be like I was always scared of what... I didn't think I could cope with it. I think now well yes, I could, if I had another boy, you know I would cope with it because I've seen other families with two boys and they've managed. I think I would cope less having to terminate the pregnancy... you know if I had to terminate it because of Duchennes it would be obviously like saying that Joe's existence, he shouldn't be here ... [Jacky, NBS, carrier, affected boy aged 12 years]

This extended extract from Jacky highlights a number of key factors in the decision-making process about prenatal testing. First, like many mothers who had older children, Jacky felt that the decision to test and terminate an affected foetus essentially conveyed the message that a life with Duchenne was not worth living. Second, their original decision to test their pregnancy was in effect born out of fear of the unknown. Now that they had got to know their son, realised that he could

cope with his condition and they could cope with him, their decision would have been based on experience, rather than medical information.

## **2. Prenatal testing; hope, fear and the quest for reassurance**

Families who had experienced prenatal testing often described an incremental process of decision-making. Rather than deciding whether they would choose to terminate an affected child, families described the decision to test as a quest for reassurance; hoping for an unaffected child.

### **So what was – what did you – what did you want to gain from the amniocentesis?**

I suppose to ease – to feel more at ease. I suppose the only thing I would possibly gain from it is if it was a girl then I would know you're not going to go through the same sort of thing. So it – that was the only thing I gained through it because I don't know whether I could have terminated the pregnancy... even if they'd have said it was a boy [...] but I suppose it was to ease really, hopefully that was the outcome. That would help me feel more at ease for the rest of the pregnancy you know. (Jennifer, first affected child diagnosed through newborn screening)

Many families hoped that the tests would show that they were carrying a female, so that they “didn't have to make any decisions” (Pamela, second child diagnosed clinically).

Those who chose to use prenatal testing rarely described the decision as synonymous with the decision to terminate. Families viewed decision-making as an incremental process, whereby immediate options were addressed (i.e. shall we test the pregnancy?), rather than deliberating about possibilities that may not transpire (i.e. would we terminate an affected child if the tests come back positive?).

For many mothers, enjoyment of the pregnancy was postponed until reassurance had been provided that the foetus was unaffected. All of the families who had prenatal testing described safeguarding news of their pregnancy from becoming public knowledge. Informing the wider family, and friends, portrayed happiness with the pregnancy, which families described as absent.

I had no enjoyment of being pregnant. I was happy to be pregnant but I couldn't really feel fully happy about it until I'd gone through all the tests. So, it stopped that initial feel of enjoyment until you knew

everything was going to be okay. So, you couldn't really bond, you couldn't really feel happy and tell everybody until you'd had all the results back. So, it did spoil that initial bit, but when you did get the results back and like you know, you knew Rowan was going to be a girl then it was absolutely fantastic, you know elation and I just had a really, really you know enjoyable pregnancy after that, as much as I enjoyed Joe. (Jacky, first affected child diagnosed through newborn screening)

Many mothers spoke of the difficulty of bonding with their future child, until receiving reassurance that no further decisions needed to be made. After receiving reassurance, 'normal' enjoyment of the pregnancy could be resumed.

Families often described their anxiety, whilst they waited for the test and then waited again for the results. During this time some mothers, who had avoided the prospect of deciding whether to terminate, felt compelled to reassess the decision.

Once I had the CVS test I was quite worried because it seemed to take a long time to have the test. I think I was told it could be between about ten to thirteen weeks and I think I was almost fourteen – fifteen weeks when they did the test and of course by that time I was feeling him moving and so I was really stressed about - if it did come back with him having Duchenne how would I cope with that and what would I do? We talked about it and said that we would abort. I don't know whether push came to shove if I could do that so no, that was quite stressful and a relief when the tests came through and said that no, he was fine. (Rebecca, second child diagnosed through newborn screening)

Many mothers described an active disassociation from the decision to terminate, and consequently with their pregnancy. However, for those who had begun to feel the foetus moving, the avoidance of bonding with their child was described as an increasingly difficult endeavour.

Some mothers highlighted the end of the tentative pregnancy; once reassurance had been provided, enjoyment of the pregnancy could commence. However, others described a lasting sense of fear and trepidation.

[The hospital] phoned us at about 5 o'clock I don't know how they'd done it so quick... um... yeh and said you know it was a little girl and I had to say well you know... please, please carry on, um, doing all the other tests that you can do... because as much as you say things are OK from... this particular side of things I still won't be able to cope with another child if there's anything else wrong, please do everything you can, you know. So, which they did do and they phoned back a couple of weeks later then and said you know we've done everything we can and everything is OK. So, which was, it was dead exciting then you know... what a relief, unbelievable um... it was

quite a horrendous... (Fiona, second child diagnosed through newborn screening)

For Fiona, the quest for reassurance was not simply a quest for a child without DMD. Although Fiona described her relief when 'all the other tests' came back clear, she subsequently explained that her heightened sense of fear that something else might be wrong, lasted throughout her pregnancy.

Until I had her as well, until she came out and I could see that she was OK I worried the whole time. I worried the whole way through until I actually had her and she was out safely and everything was fine, I worried the whole time. Anything could have happened, you know, even during birth or whatever you know... you know it does make you worry more. I don't know whether you worry about how you'd cope or the fact that you know you can't take everything for granted that everything's going to be OK... but you know it was - it was... a big worry all the way through. (Fiona, second child diagnosed through newborn screening)

Not only had her son's diagnosis removed a previously taken for granted belief that her child would be healthy, Fiona described her concern about her capacity to cope with another child with any other disability. Testing the pregnancy for reassurance was not just focused on gaining reassurance that the foetus was unaffected with DMD.

### **3. Testing intentions and the limitations of choice**

Seven of the eleven newborn screening families in the interview cohort felt that they had not reached their ideal family size; four of whom chose to have prenatal testing on subsequent pregnancies and eventually gave birth to a girl or unaffected boy.

Families often described the value of having an unaffected child. Jacky and Richard had a second child, Rowan, after Joe was diagnosed, and found that having a healthy child provided them access to an otherwise inaccessible world.

I said "I've just got to have another child." And I did, and it's the best thing I ever did because you know Rowan makes us focus on something different - you can have the same hopes and dreams and aspirations for them, what they would do for the future. Where Joe, yes you can have the same dreams for them but it gets cut short. So... and then you know everything's very focused when you have a child with a disability, around OT, Physio, wheelchairs and you just get fixed in. With Rowan then you've got that little reprieve where you can go and watch her play football, you know Joe can come with us but we wouldn't have that... have that opportunity, we couldn't have done that. (Jacky, first child diagnosed through newborn screening)

Jacky's description of living with a child with DMD, highlights the constant rigmarole of hospital appointments; the medicalisation of life with a child DMD. Rowan had provided access to a 'normal' life, unhindered by immobility issues. For Jacky, an unaffected child provided the opportunity to have aspirations for her child's future, which lasted - as most parents hope for - beyond her own lifetime.

None of the parents interviewed had more than one subsequent pregnancy after the diagnosis of their son. Many families described the decision in relation to having already reached their ideal family size. However, for some parents, the prospect of going through the process of testing another pregnancy was decidedly unappealing.

I think my husband would have liked to [have more children] but I felt I wanted - I thought I was pushing my luck. I felt we were lucky and we had Rosie [...] you know - be thankful that you've got two and, you know, I didn't really want to think "I want to do it" - you know, go through that again, you know. (Jennifer, first child diagnosed through newborn screening)

Jennifer and Tom had previously described their desire to have a large family. However, undergoing prenatal testing during her pregnancy with Rosie, was described as a quest to be put "at ease"; Jennifer articulated doubts about whether she would have been able to terminate an affected foetus. Rather than following their original reproductive intentions, Jennifer expressed her desire not to 'push her luck'.

Not every family was successful in their attempts to have another child. In an attempt to avoid the immense ethical dilemma of whether to test and terminate an affected child, Mary and Chris had opted for pre-implantation genetic diagnosis. During the interview, Mary described the captivating fear of missing an opportunity.

They've offered me this chance and it's my only chance. I can't change my mind. Next year I couldn't change my mind, I'm getting older. And I thought I'll go along with it to the end, whatever they offer me I'll take it.

At the time of the interview, Mary had already had two unsuccessful rounds of pre-implantation genetic diagnosis, and was about to commence a third attempt. Mary spoke at length of the rollercoaster ride of pre-implantation genetic diagnosis; sickness, hope and disappointment. When asked whether she would undergo a fourth round, her response oscillated between resignation and lingering hope.

You'd like to think - you have to be able to say I tried, and you have to be able to say no, that's where it ends and you get on with your life. I don't know though. It's very - every time you convince yourself you're happy with what you got, you know, having a baby, you think oh god, disrupts you life again. Do you really want that? And then you start this process, you get so caught up in it and then they reimplant the egg, you feel as if you're pregnant. I mean it's just the same as if they told you you were pregnant, you kind of have a bond with this wee egg that probably doesn't exist, you know, when they put it back nothing happens to it. But you do bond with it and when it doesn't work, no matter what you thought before, it's - I wouldn't say devastating, as such. I would imagine it would be for women that maybe don't have a child and are fairly desperate, I wouldn't say I was devastated, but I was very upset. Even the last time I was quite upset. (Mary, first affected child clinically diagnosed)

Despite pondering whether she really wanted another child, Mary describes the intoxicating process of being provided with a small chance that they might. When each fertilised egg was implanted, previous doubts were swept away in contemplation of the future child; only for brief bonding to be replaced by grief. Deciding to “get on with your life” was described as another choice not easily taken.

#### **4. Oscillating between public and private domains**

Although the preceding sections and chapters have focused on the implications of diagnostic procedure for reproductive decision-making, it is essential to note that a number of families described their reproductive decision-making as unaffected by the diagnosis. Many families had already completed family building, prior to receiving the diagnosis.

In the interview cohort a number of families, who had received a newborn screening diagnosis or a later clinical diagnosis, described having already met their reproductive intentions, prior to the diagnosis. These families often spoke of their relief at having avoided the complexity of reproductive decision-making, after the diagnosis.

I'm very lucky in that, the position in the family where Iain was that I didn't have all those - I don't have a lot of the - the worries and things that maybe people have if it's their oldest child. Whereas they then have to - seriously think about having any more and going through genetics and that and everything else. [Esther, third child clinically diagnosed]

The sense of relief was also expressed by a family who had two affected children. Anne's first son was born prior to the implementation of the newborn screening programme; he was diagnosed after her second child received a diagnosis through newborn screening. Whilst discussing whether she might have considered prenatal testing, Anne announced:

In some ways I've been lucky because I've had all those choices taken from me... because I really don't know... (Anne, second child diagnosed through newborn screening)

Many families who had not required, or had not experienced the early provision of choice, expressed an unerring sense that they had escaped from being faced with difficult reproductive decisions.

However, when families were asked to describe the perceived benefit of newborn screening, many mentioned the provision of reproductive choice. For families who had already completed their families, the provision of choice was described as valuable for others, but not for themselves.

I don't know if we'd want – I don't know if I would have wanted to know when he was a baby because we had those three years when we were oblivious to that, and then when he was three it was then, it's a –, like it's a terrible bereavement. So I don't know if I would have wanted to. But then that was, I had my family, like I had my children, the boys and I had one. I think it'd probably be different if he had been the first because there's about three years of a gap. So I could have been pregnant with another child and so you can see why [newborn screening] is controversial. I personally wouldn't have wanted to know but I think there's – I think there's benefits in people knowing that – because there's so many families that have it, they're pregnant with their second child or their sister's having a child and she's a carrier as well. [Esther, affected boy diagnosed aged three]

Like many families who had received a later clinical diagnosis, Esther described having received greater value from the carefree years with their child, than they might have received from the provision of reproductive choice. However, Esther recognised that the provision might be valuable for others.

For newborn screening families who had continued to family build after the diagnosis, the provision of choice had enabled them to proceed with subsequent pregnancies with an awareness of their genetic risk. One family in the newborn screening cohort described the provision of reproductive choice as the greatest

benefit of newborn screening. The father, Neil, described how a newborn screening programme would inevitably reduce the incidence of the condition.

*I think [newborn screening for DMD] really should be world wide, I've got to be honest and having been in the position and I think it's – you know, definitely because it gives people an option doesn't it? And it may – I mean Duchene on a whole then may reduce maybe. Well, not so much reduce then but it won't grow as fast will it, like families having one and having a second one, all of a sudden they have two, might even have three or four by the time they're found but if – if those families knew perhaps they'd only have one child and then there's only one boy out there with Duchenne's, not four boys then isn't there? So it – it's reducing the number of people with it (Neil, first child diagnosed through newborn screening)*

Despite Neil's fervent expression of the value of reproductive choice, to reduce the incidence of DMD, Neil and Jess decided to have another child after the diagnosis, and chose not to test the pregnancy.

*But we had that option and you know, and – and we – we couldn't make that decision. (Neil, first child diagnosed through newborn screening)*

Parents often presented different views, depending on whether they were discussing the public, or private, domains of reproductive choice. In the public domain, reproductive choice is valued. Choice is presented as an asset, an entitlement, which each and every family deserves. However, in the private domain, the domain where individual families make real decisions, the value of reproductive choice must be negotiated. For some, reproductive choice was irrelevant. For others, who chose to continue family building, choosing was either anxiety ridden and stressful, or the complexity of the decision was simply rejected.

## 5. Summary

The timing of the provision of reproductive choice appeared to have significant implications for families' reproductive behaviour. Numerous families, who received a later clinical diagnosis, had continued family building, unaware of their genetic risk. Some families had a second affected child, prior to the diagnosis of their first. Others had ceased family building immediately after receiving the diagnosis, only to be faced with fertility difficulties once efforts to conceive were resumed. In contrast, newborn screening provided families with an earlier awareness of their



genetic risk, and many families had successfully continued family building to reach their ideal family size.

However, with reproductive choice comes responsibility. Families' accounts highlighted the complex and highly emotional context of reproductive decision-making for Duchenne muscular dystrophy. Many families who had already completed family building expressed gratitude that they had avoided being faced with such complex decisions. For those who desired to continue family building, previous fertility intentions were set into turmoil as families wrestled with ethical dilemmas. Families that had received a later clinical diagnosis discussed a range of reproductive options; prenatal testing, adoption and pre-implantation genetic diagnosis. In contrast newborn screening families rarely mentioned any options other than prenatal testing and termination.

There was considerable variation in families' views on, and approach to prenatal testing. Often families, who had chosen not to have prenatal testing, associated the testing procedure with termination (i.e. if they were not willing to terminate the pregnancy, there was no perceived benefit of testing). The majority of families who used prenatal testing were seeking reassurance; hoping for a positive outcome, fearing the possibility of being faced with another decision. All families who underwent prenatal testing described the initial weeks of the pregnancy as bereft of enjoyment; unable to bond with the child they may choose to terminate. For some the fear that 'something else might be wrong' permeated the entire experience of pregnancy.

Despite the often difficult experience of prenatal testing, many families, who were successful in their attempts to have another child, spoke of the value of having an unaffected child. Not only had they reached their ideal family size, living with an unaffected child served to mitigate the medicalised lifestyle, associated with living with a child with Duchenne muscular dystrophy. However, after one experience of prenatal testing, nearly all families in the interview cohort had reached their ideal family size. Only one family who had received a diagnosis through newborn screening cohort suggested that they may not have followed their original reproductive intentions. This family presented the prospect of going through the

stressful process of prenatal testing and termination, as a paramount feature in the decision to cease family building.

In the newborn screening cohort, families often spoke of the impact of medical information, received around the diagnosis, on their perception of their future life with a child with DMD. Many families, who received a newborn screening diagnosis, chose to have prenatal testing in subsequent pregnancies. As children grew older, families often described their experience of living with a child with DMD, as considerably more positive than they had anticipated.

Some families described how decisions to test and terminate in the early years of their child's life, were made before they had come to know their child, know how he would cope with the condition, and know how they would cope with him. Once families had experiential knowledge of their child, they often described the immense ethical dilemma of choosing to test and terminate a child with the same disability. Decisions were no longer based on factual descriptions, but experiential evidence; knowledge of person with a disability, rather than information on the disability alone.

In an attempt to avoid the emotional complexity of choosing to test and terminate, one family, who had received a later clinical diagnosis, had opted to undergo pre-implantation genetic diagnosis. Their experience of reproductive choice was described as rollercoaster ride of hope and disappointment. This mother expressed the difficulty of saying 'no' to choice, when the possibility of having another child remained.

When families discussed the public domain, the provision of reproductive choice was often described as having value. Choice was perceived as an advantage that all should have. However, in the individual domain, the value of reproductive choice must be negotiated. For families who had already completed family building, the potential values of other competing attributes of the newborn screening programme, such as the provision of time to prepare, must be addressed in relation to the detrimental aspects of an earlier diagnosis. Families who received a newborn screening diagnosis, lost the carefree years and the opportunity to get to know their

child before receiving a diagnostic label. Despite the perceived value of reproductive choice for families who wished to continue family building, the reality of living with choice was constituted by hope, fear and disappointment; a process some were unwilling to bear.

# Chapter Nine

## Discussion

### Introduction

Early newborn screening programmes for Duchenne muscular dystrophy (DMD) were implemented with a focus on enabling families to avoid the birth of a second affected child. However, the newborn screening programme in Wales aimed to provide families with “reproductive choice” in future pregnancies, to enable them to plan for the future with a child with a disability; to avoid the diagnostic delay; and to identify a presymptomatic cohort who may benefit from future treatments (Bradley *et al.* 1993).

The focus on providing information, support and choice is reflected in a growing drive to expand the remit of newborn screening programmes, to include untreatable conditions. Newborn screening for treatable conditions aims to improved the health of the newborn, whereas screening for untreatable conditions may provide with families “broader, but possibly more moderate benefits” (Bailey *et al.* 2006:270). There is a paucity of research documenting families’ experience of, and response to, the early provision of information, support and “reproductive choice”.

This study reviewed the implications of two different diagnostic pathways for reproductive decision-making, in families affected by DMD. This chapter summarises the findings from the quantitative and qualitative data. The chapter is divided into seven sections. The first explores the limitations of the findings and the unexpected consequences of conducting a mixed methods study. The second section explores the literature on illness narratives, in order to contextualise the findings of this study. The remaining sections discuss the findings of this study in relation to relevant literature. Section three explores the determinants of fertility in families affected by DMD. Section four addresses the role of risk in reproductive decision-making. Section five explores the role of diagnostic pathway in changing the type of information accessible to families during the reproductive decision-making process, from experiential knowledge to medical information. The sixth section describes the

experience and outcome of providing families with reproductive choice. The final section provides a summary and conclusion of both the quantitative and qualitative data, as well as policy recommendations for newborn screening for untreatable conditions.

## **1. Methodological considerations**

Methodological issues are often addressed after discussion of the key findings. However, in this study, the experience of combining quantitative and qualitative methods had a considerable impact on interpretation of the data. Therefore, it is deemed necessary to address interpretative issues at the outset, in order to place the discussion of the findings firmly within the methodological framework. The following sections explore the methodological limitations of the study and address the unforeseen depth and potency of the qualitative data.

### **1.1 The limitations of methodology; reliability and validity**

There are many threats to the reliability and validity of any investigation. Biases and errors can occur in the conceptualisation of the research idea, and the design, sampling and processes of a study (Bowling 2002). As already noted in Chapter Four, this study was designed to explore reproductive outcomes, through the collection and analysis of quantitative data, and reproductive decision-making, through the collection and analysis of qualitative data. The difficulties associated with combining methods are explored in the following section. First, the reliability and validity of the findings is explored in relation to the comparability of the samples used, in both the quantitative and qualitative sections of this study.

Quantitative data was collected from nearly all of the families who had received a later clinical diagnosis of DMD in the west of Scotland, and all families who had received a diagnosis of DMD through newborn screening diagnosis in Wales, between 1990 and 2006. Unfortunately, it was not possible to assess whether the five families, excluded from analysis in the west of Scotland, had different experiences of reproductive decision-making. The reason for their exclusion - incomplete

medical files – hindered the possibility of addressing potential disparities. In addition, the comparable nature of the two cohorts rested on similarities drawn from national data on reproductive behaviour; no data was collected on family-specific influences, such as the socio-economic status of each family. Although these issues raise potential questions about the validity of the comparison, it should be noted that the cohorts included the majority of the “DMD population”, diagnosed during that time. The cohorts were not selected samples.

In contrast, the participants in the qualitative part of the study were a sample of the total “DMD population”. There are two key issues associated with the qualitative sample used in this study. First, the sample size was relatively small compared to the total cohort (only 26% of the total cohort was interviewed). Second, the qualitative sample was selected on the basis of providing maximum variation of reproductive behaviour. It is not known whether selection based on another variable, such as socio-economic status, would have provided different results.

Ideally, the qualitative sample should have reflected a diversity of factors that may have influenced reproductive behaviour. However, the focus of the study was to review reproductive behaviour and the selected sample included a range of experiences and responses to reproductive technologies. In addition, the sample reflected differences in the total cohort in relation to the age of the affected male, the stage of his condition, the age of mothers, and decisions regarding whether or not to continue family building and whether or not to have prenatal testing. The sample also included a range of people with different socio-economic backgrounds. It would be a misnomer to call the qualitative sample “representative” of the total cohort, and the myriad of variables that may have influenced reproductive behaviour. However, from a pragmatic perspective it is difficult to envisage a sampling procedure that could have truly reflected the considerable diversity of factors, affecting reproductive decision-making.

## **1.2 Unexpected consequences of conducting a mixed methods study**

The original aim of the study was to compare the reproductive behaviour of families after receiving a diagnosis of DMD through two different diagnostic pathways. It

was assumed that the quantitative data would provide a neat list of “factors affecting reproductive behaviour”, which could be explored in greater depth during the qualitative interviews. Neither the quantitative nor qualitative data provided simplistic factors to compare and contrast. The quantitative data highlighted the arbitrary nature of porous categories; the qualitative data added unexpected depth and complexity. An intentional strategy used to ease participants into the interview process<sup>32</sup> had unexpected consequences; participants expressed and articulated their experiences of the diagnosis and living with DMD in and through narratives.

Using a narrative approach to qualitative data collection and analysis was unintentional and unforeseen. The collection and analysis of quantitative data instigated an urge to find predictable, regular patterns in the qualitative data; an approach that was frustratingly fruitless. After a considerable amount of re-analysis, the depth and breadth of the qualitative data was finally recognised. Instead of “shopping lists” of “factors affecting reproductive decision-making”, there were powerful narrative accounts; stories that illuminated the influence of context, and emphasised the diversity of experience.

## **2. Illness narratives; contextualising the qualitative data**

There is now a significant body of work on chronic illness and disability that has used the narrative approach. The use (and meaning) of “illness narratives” has varied considerably (for example, see Hyden 1997 for a description of the differences between “illness as narrative”, “narratives about illness” and “narrative as illness”). One of the most popular distinctions between narrative types is presented by Bury (2001), who describes three forms of illness narrative; contingent narratives, moral narratives and core narratives.

“Contingent narratives” reflect Hyden’s (1997) concept of “illness as narrative”; the personal experience of illness that draws upon biographical and social contexts. However, Bury (2001:268) adds a temporal dimension to personal experience of chronic illness, focusing on the “beliefs and knowledge about factors that influence

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<sup>32</sup> Asking people “to tell me a little about how [their] son was diagnosed”, before delving into more personal and potentially more sensitive issues of reproductive decision-making.

the onset of a disorder; its emergent symptoms, and its immediate or “proximate” effects on the body, self and others”. The “moral narrative” draws upon notions of shame and blame, and reflects moral or religious contingencies used to inform personalised concepts of aetiology. In contrast to both contingent and moral narratives, “core narratives” focus on form; language and symbols are explored to identify narrative structures, such as “tragic, comic, romantic” (Pierret 2003:11).

The narratives presented in this study were authored by both narrator (the interview participant) and researcher (myself) and focused on both contingent and moral narratives. Families provided accounts that highlighted the complexity of reproductive decision-making, and reflected the salience of contextual factors in the reproductive decision-making process. Stories were presented that enabled families to make sense of the past in order to live in the present, and address their future.

There is a striking resemblance between the narratives presented in this study and previous work on illness narratives. In subsequent sections, I explore the factors described by families, such as original fertility intentions prior to the diagnosis; responsibility toward partners, existing children and the future unborn child; perception of risk in relation to perceived capacity to cope with another affected child; willingness to undergo prenatal testing and termination; and underlying views on, and experience of, disability. Where appropriate, I draw upon previous studies on illness narratives to facilitate an exploration of the subjective experiences of disability, and to enable an interpretation of the data that is “sensitive to a broad range of micro- and macro-contextual influences” (Lawton 2003:23).

### **3. Determinants of fertility in families affected by DMD**

Many of the determinants of fertility in families affected by DMD reflected those described in the literature review in Chapter Three. Families presented a broad range of economic, social and psychological factors that influenced the formation of fertility intentions and the transformation intentions into behaviour; many of which were unrelated to the diagnosis. Families discussed the desire to access the perceived psychological and social benefits associated with having a healthy child.



However, families also described the perceived value of living with a child with DMD. In addition to the desire for children, families presented their reproductive behaviour as a negotiation of responsibility. Before motivations were transformed into intentions, families considered the potential impact of their motivations and redefined justifications for their decisions, in light of the diagnosis. The four issues, forming and transforming fertility intentions, the perceived value of a child with DMD, the perceived value of a child without a disability and the role of responsibility, are addressed in separate sections below.

### **3.1 Forming fertility intentions and transforming intention into behaviour**

The data from this study highlighted a number of similarities between the determinants of fertility in families living with DMD and those outlined in the literature review. The majority of families in the interview cohort (n=13) described forming a notion of their ideal family size, prior to having children. Couples often expressed a desire to replicate their own experience of childhood. Family trees often showed clear associations between the parent's family size (number of siblings), and their choices about their own family size (number of children). Few families were explicit about the social factors that had influenced the formation of intentions. However, like families in the general population, families affected by DMD appeared to form intentions through an evaluation of "the economic and psychological costs and benefits of children, taking into account personal factors and social context" (Lawson 2001:74). The age of the mothers and the number of children desired broadly reflected national data.

Original fertility intentions were presented as a paramount feature in the decision-making process after the diagnosis. Families who felt that they had already reached their ideal family sized ceased family building, and those felt that they had not yet reached their ideal family size continued family building, albeit with redefined and reformulated justifications.

Around half of the total cohort (51.3%, n=37) chose not to have subsequent children after the birth of the first affected male. Families in the interview cohort, who presented themselves as having completed their families, sometimes deliberated

about whether to change original plans in light of the diagnosis, but there was no evidence to suggest that the decision to cease family building was entirely a result of the diagnosis. It is not possible to determine the influence of the diagnosis on the decision to cease family building in the total cohort. However, 58.3% (n=42) of families already had at least one child before the birth of the index and the average number of children in the general population is two, suggesting that many families may have already ceased family building prior to the diagnosis.

Families, who described themselves as wanting more children prior to the diagnosis, often proceeded with subsequent pregnancies after the diagnosis. A total of 35 (48.7%) of the 72 families in the total cohort had at least one subsequent pregnancy after the birth of the affected male, suggesting that many families had not yet reached their ideal family size. However, following original fertility intentions was often described as problematic and families reformulated original intentions in light of the diagnosis. Families who chose to continue family building often considered a variety of reproductive options before proceeding, such as adoption, prenatal testing, and pre-implantation genetic diagnosis.

Some of the constraints families encountered, when attempting to transform fertility intentions into behaviour, were similar to those found in the literature on the determinants of fertility in the general population. Mothers' reproductive behaviour was influenced by the three types of constraints outlined by Miller and Pasta (1995); her partners fertility intentions; life cycle factors (such as age, marital duration, parity, gender and age of previous children); and changes related specifically to reproduction (such as unplanned pregnancy and divorce/separation).

The diagnosis of DMD appeared to influence the experience of the three types of constraints. Receiving a later clinical diagnosis appeared to cause families to delay family building. By the time families, who received a later clinical diagnosis (LCD), felt in a position to continue family building, many were faced with age-related fertility issues. Mothers, in both cohorts, who had separated from their partners felt that the diagnosis had influenced the separation. In addition, mothers who had formed new relationships often felt under pressure to conform to her new partners'

fertility intentions, to have a (healthy) child. These issues are explored in greater depth in subsequent sections.

One of the key factors that emerged in the literature on the determinants of fertility was the influence of the perceived value of children. Families who received a diagnosis of DMD described the perceived value of living with a boy with DMD and living with a child without a disability. These two factors are explored in the next two sections.

### **3.2 The perceived value of living with a child with DMD**

Families' narrative accounts highlighted considerable variation in perceptions and experience of living with DMD. Some families felt that their social networks and access to social support had diminished as a result of having a child with a disability. However, many families described the value of having a child with a disability. Some families described how their interpersonal relationships had been strengthened and intensified, and their lives enriched by the experience.

However, despite the general view that there were positive attributes of living with DMD, the possibility of having a second affected child was met with varying degrees of enthusiasm. Families who described their experience of the condition in predominantly negative terms expressed a desire to avoid the birth of a second affected child. Families who described a more positive experience varied in their degree of willingness to contemplate life with a second affected child. One family had considered adopting another child with DMD, as they were 'already set up' for living with a child with a disability. However, another mother, Mary, commenting on other people fostering disabled children, described herself as "not that big-hearted". Mary felt that loving a child with a disability was an easy task, but *choosing* to have a child with a disability required a 'selflessness', which she felt she lacked.

The perceived value of living with a child with a disability varied considerably between families. In addition, there was considerable variation in the relationship between perceived value and reproductive behaviour. Families who perceived value in living with a child with DMD were not necessarily willing to repeat the

experience. However, it is important to note that some families – who had been provided with the opportunity to get to know their child, prior to making reproductive decisions – described their experience of already caring for a child with a disability as a positive asset for facing a future with a second affected child. It is possible that the newborn screening diagnosis removes families' opportunity to assess the value of living with a child with DMD, before making reproductive decisions; contributing to a higher uptake of prenatal testing. This point is explored in greater depth in a later section.

Many families interviewed in this study spoke at length of the lack of support received from social services, medical professionals and their communities. It is possible that the perceived lack of support and access to care was integral to their perception of disability and their subsequent reproductive decision-making. Brookes (2001) interviewed twenty women who were either affected by a genetic condition and making reproductive decisions, already mothering children with a genetic condition, or had recently made a decision during pregnancy to accept or decline prenatal testing. For some, the perceived lack of care was integral to their reproductive decision-making and resulted in an increased desire to use prenatal testing and termination. Brookes (2001:137-138) notes that “it is the social context that frames women’s decision-making and within which a child’s access to care is a central influence on women’s decision-making.”

A crucial consideration in reproductive decision-making is the level of acceptance of disability families perceive in their community (Brookes 2001). Clarke (1990:1146) notes that “if there is no confidence in the willingness of society to care for their child once they are unable to do so, parents may choose to terminate a pregnancy against their own wishes and beliefs. This is an external pressure on couples that is exerted by social and political decisions.” The very offer of prenatal testing creates a social pressure to accept it (Lippman 1991). The perceived consequences of having an affected child may therefore be imbued with feelings of responsibility and guilt (Kay & Kingston 2002).

### **3.3 The perceived value of a child without a disability**

A number of families in the interview cohort described the perceived value of having a child without a disability. Although living with a child with a disability was rarely perceived in purely negative terms, there was a clear perception that a child without a disability may provide a different type of value. A number of families mentioned that their unaffected child had provided them with access to different social networks. In addition, parents had the opportunity to develop hopes, dreams and aspirations for an unaffected child, which reached beyond the parents' lifetime. While living with a child with a disability was often perceived to have value in the private domain, in the social domain the value of a child with a disability was less apparent. Few friends or relatives had wheelchair accessible houses and families often felt isolated with diminished social networks.

A number of families in the LCD cohort presented a similar desire to access the values and benefits associated with having a child without a disability. However, for those who had not conceived again prior to the diagnosis, the emotional distress caused by the diagnosis, and immediate practical upheaval associated with house adaptations, often led to a considerable delay in family building. The birth interval between the affected boy and the next subsequent pregnancy in risk aware families was considerably longer in the LCD cohort, than the NBS cohort. By the time mothers' felt in a position to face the upheaval associated with having a baby, many were in their late thirties or early forties and facing age-related fertility issues.

Although the later clinical diagnosis may have provided families with the opportunity to assess the value of living with a child with a disability, it did not diminish the perception of the value of having an unaffected child. However, for many families, the later clinical diagnosis appeared to hinder their attempts to reach their ideal family size and access the perceived rewards associated with living with a child without a disability.

### **3.4 The role of responsibility**

Responsibility emerged as a key factor in many families' discussions of their reproductive decision-making. Families described the need to negotiate the desire for children with their sense of responsibility to partners, existing children and the

future unborn child. Often the way responsibility was negotiated depended on which relationships were prioritised, which supports the findings of Downing's (2005) study on reproductive behaviour in families at risk of Huntington disease.

In this study, some mothers had formed new relationships and felt responsible for providing their new partner with an (unaffected) child. Others worried about the effect another (affected) child might have on their existing family, and expressed the need to focus emotional and financial resources on their existing children. Many of the families who had chosen to have subsequent pregnancies spoke of a sense of responsibility to provide their affected child with unaffected sibling(s).

Some presented the desire for a healthy child as a desire to provide the affected child with company. Others felt a responsibility to provide the existing child with a sibling to care for them if and when the parents were no longer able. A few families, who had already reached their ideal family size, chose not to be sterilised. Fertility was presented as a responsibility to the existing child in case some future development provided an opportunity for a sibling to provide a cure.

The association between responsibility and prenatal testing also varied depending on which relationship was prioritised and how motherhood was perceived. Some families felt that a mother should love her child no matter what and therefore prenatal testing and termination were unacceptable. However, other families who had previously rejected prenatal testing on moral grounds reassessed their position after the diagnosis. Often families who had previously decided not to use routine prenatal testing for Downs' and Spina Bifida felt that their decisions would be different in subsequent pregnancies. A chance, once willingly taken, became a risk – an external tyranny to be desperately avoided. The existing child was presented as the paramount consideration in the reproductive decision-making process.

Moral narratives emerged in descriptions of responsibility and reproductive decision-making. Choosing to continue or cease family were decisions imbued with perceptions of the severity and consequences of the condition; on emotional and financial resources, in relation to both family and society. Previously held beliefs about the morality of abortion sometimes wavered in the spotlight of new

considerations. The desire for another child was juxtaposed against questions about the morality of abortion versus the moral and practical consequences of having another child with Duchenne.

A few mothers presented a moral obligation to avoid the birth of a second affected child. Often these mothers were carriers who were beset with profound feelings of guilt. Williams *et al.* (2002a) note that in many people's minds, responsibility is linked with the avoidance of disabled births. The offer of prenatal testing may sometimes be perceived "not so much as being about trying to give greater control to couples as to the circumstances in which they become pregnant, but rather as a feature of good parenting" (Williams *et al.* 2002a:751). Brookes (2001:143) also argues that "a child with a genetic condition has become socially constructed as women's lack of care towards their child, as well as an indication of a lack of social responsibility".

The moral implications of reproductive decisions reflect potential gender dimensions (Chadwick 2009). Although couples may discuss reproductive decisions together, "the impact of the decision falls predominantly on the woman, who has to either carry a foetus to term or undergo a termination" (Chadwick 2009:10). In addition, in many societies, it is the mother who is responsible for the day to day caring of a child, with or without a disability.

In this study, the role of gender was particularly salient. The mothers in this study described reproductive decisions in relation to feelings of guilt and responsibility; reflecting previous studies on maternal feelings associated with carrier mothers of x-linked conditions (Kay & Kingston 2002). Interestingly, the perceptions of guilt and responsibility pervaded many of the narratives presented in this study; regardless of whether the mother "carried" the DMD gene. As an x-linked genetic condition, carrier mothers often drew upon concepts of genetic responsibility to apportion (self) blame, whilst those at risk of germline mosaicism sought alternative explanations, which reflected popular health promotion messages surrounding appropriate behaviour during pregnancy. In addition, mothers often presented themselves as the primary arbiter of subsequent reproductive decisions; the one who must live with the consequences of termination, or having another affected child.

## **4. Risk and reproduction**

A number of salient factors emerged from the quantitative and qualitative data regarding the importance of risk in reproduction, and the understanding of how risk is defined. The interpretation of risk is paramount feature in reproductive decision-making and may be affected by a number of factors. First, genetic counsellors have played an important role in informing families of their genetic risk and there is a significant body of literature documenting the potential influence of genetic counselling on subsequent decisions. The first subsection therefore explores the potential influence of genetic counselling. The second subsection explores the influence of diagnostic pathway and increasingly sophisticated carrier testing techniques on awareness of risk. The final subsection explores the perception of risk in relation to reproductive decision-making.

### **4.1 Genetic counselling; framing risk and informing decision-making**

The role of genetic counselling in reproductive decision-making has been the subject of much debate (Michie & Marteau 2000). Many authors note that counsellors' communication of risk and counselees' consideration of risk are fundamental aspects of decision-making about the use of prenatal testing (Gates 2004, Emery 2001). The following sections explore the way in which genetic counsellors present risk information and the potential influence genetic counselling has on reproductive decision-making.

#### ***4.1.1 Genetic counselling; framing risk information***

In Chapter One, it was noted that genetic counsellors have traditionally employed classical decision-making theories, derived from the field of economics. Classical decision-making theories reflect an analytical, rational model of decision-making. As a result genetic counsellors have traditionally provided risk information “in the language of rational thinking, explanations, comparisons, logical propositions, and problem-solving, or problem prevention” (Anderson 2007:14). Professionals have tended to focus on the provision of probabilities (Shiloh 2000).



The applicability and appropriateness of applying rational decision-making theories to genetic-related decisions has long been questioned (Lippman-Hand & Fraser 1979c, Kessler 1980, Beeson and Golbus 1985). Economic theories were developed in relation to “simple choice decisions where decision implementation was easy to accomplish and thus easy to overlook” (Kendzierski 1990:27). Observed decision-making in complex social situations typically deviates, “quite substantially”, from the models’ predictions (Sanfey 2007:599). Early decision-making theorists largely ignored the influence of emotions (Sanfey 2007), or claimed that “good decision-making could be derailed by emotions” (Anderson 2007:13).

The degree to which genetic counsellors still use classical decision-making theories to inform their genetic counselling sessions is both debateable and dependant on the individual genetic counsellor. However, even if genetic counsellors recognise the important role of emotions in decision-making, numerous studies have shown that the counsellors and counselees often have quite different expectations of the role of genetic counselling.

Mishler (1984) argued that the doctor-patient relationship reflects a transaction between two distinct worlds: the biomedical world of physicians and the socio-psychological world of patients. Studies examining communication between clinicians and patients in prenatal decision-making often emphasise the biomedical perspective by highlighting the completeness of information provided to patients (Bernhardt et al. 1998, Marteau et al. 1993, Marteau & Dormandy 2001) or describing the means by which clinicians impart information (Pauker & Pauker 1987, d’Ydewalle & Kiebooms 1987, Michie & Marteau 1996).

Sorenson *et al.*’s (1981) quantitative study of 628 patients attending 47 genetics clinics found that patients reported that genetic counselling provided a large amount of medical and technical information and spent little time discussing emotional and social issues. These results were replicated in a number of subsequent studies (Michie *et al.* 1996, 1997, Williams *et al.* 2002b, Hunt *et al.* 2005).

Clinicians have been found to have different goals, purposes and values regarding testing, which affect their clinical interactions. Hunt *et al.* (2005:302) state that “the

information clinicians provide patients reflects their clinical interest in identifying and controlling pathophysiology, while patients, in contrast are most concerned with protecting and nurturing their pregnancy". Michie and Marteau (2000) suggest that the focus on the provision of probabilistic information has eclipsed the provision of information about the actual condition.

Latimer (2007) argues that Western ideas of knowledge are based on the notion of having perspective, of being distant, objective. Genetic counsellors attempt to provide this sense of perspective to assist families to make an informed reproductive decision:

“...by giving parents objective information about their child’s troubles they will be given a more ‘correct’ perspective on these troubles and will therefore be able to make better (i.e., more rational) reproductive choices” (Latimer 2007:15)

In genetic counselling the focus has been on equipping people with appropriate information on genetic risk, “believing that if they understood scientific explanation, they would use it to make rational or logical reproductive choices (i.e. ones that made sense to the provider)” (Biesecker 2001:323).

#### ***4.1.2 Genetic counselling and reproductive decision-making***

The framing of risk information has an important influence on perceptions of risk (Tversky & Kahneman 1974, Edwards & Elwyn 2001, Shiloh *et al.* 2002). However, counselees’ perception of risk *prior* to counselling remains more closely associated with reproductive behaviour (Shiloh & Saxe 1989). After reviewing the literature on genetic counselling and reproductive decision-making, Kessler (1989:352) concluded that “the role of counselling largely is to confirm or reinforce a decision already taken, rather than to shape a reproductive decision from the outset”.

Frets *et al.* (1990) interviewed 164 couples two to three years after genetic counselling, and developed a model to study factors related to reproductive decision-making. The key factors found to be related to reproductive decision-making were reproductive outcome before counselling, desire for children, and interpretation of genetic counselling information. The model enabled identification of reproductive decisions in 96% of cases.

Several studies have since demonstrated that counselees interpret risk information in a personalised manner; perceived risk appears more salient to decision-making than actual genetic risk (Lippman-Hand & Fraser 1979a,b,c, Wertz *et al.* 1984, Shiloh & Saxe 1989, Kraus & Brettler 1988, Parsons & Atkinson 1993, Denayer *et al.* 1997, Lerman *et al.* 2002). Perceived risk is often associated with the severity of the condition (Lippman-Hand & Fraser 1979b, Verp *et al.* 1988, Ekwo *et al.* 1987) or social meanings (Beeson & Golbus 1985, Sorenson *et al.* 1987, Bostrom & Ahlstrom 2005). Rather than focusing on probabilities, at-risk couples tend to categorise their risk as either high, or low (Lippman-Hand & Fraser 1979a, Parsons & Atkinson 1993, Denayer *et al.* 1997). Couples at-risk of genetic conditions, who are facing reproductive decisions, often focus on the meaning of the pregnancy and their attitudes towards both disability and termination (Rothman 1993, Rapp 1999, Biesecker 2001).

Despite a pervasive enthusiasm to tar genetic counsellors with a eugenic brush, evidence suggests that families are actually more likely to continue a pregnancy after receiving information from a genetic counsellor than an obstetrician (Sorenson *et al.* 1981, Michie & Marteau 2000). The issue is perhaps less about genetic counselling *per se*, than the general concept of receiving information from someone who has no experience – and is unlikely to ever have experience – of living with a child with a particular genetic condition. A family, who has no experience of a condition, and looks to the future with a disabled child with fearful anticipation, is likely to find that the medical professional who provided the information has the same fearful concept of disability. This does not reflect a paternalistic, eugenic-driven health care system; this reflects the negative view of disability found throughout society. Perhaps we are all tarred with the eugenic brush.

#### **4.2 The influence of diagnostic and carrier testing techniques on risk awareness**

The diagnostic procedure had considerable influence on families who had not yet reached their ideal family size. A total of 35 families (48.7%) had subsequent pregnancies after the birth of the first affected child in the family. For these families, the diagnostic pathway had important implications for awareness of genetic risk. Of the 17 families in the LCD cohort, who chose to continue family

building, 58.8% (n=10) were unaware of their risk in 13 subsequent pregnancies, resulting in the birth of two second affected males, prior to the diagnosis of the first. However, awareness of risk does not necessarily correlate with an overriding desire to avoid the birth of a second affected child; one risk-aware family in the newborn screening cohort chose not to have prenatal testing and had a second affected child.

#### *4.2.1 The role of genetic risk*

Significant advances in carrier testing techniques have enabled the provision of less complex risk assessments for mothers at risk of DMD. Before the introduction of more sophisticated technologies, mothers were often provided with a separate figure for carrier risk and reproductive risk. Previous research has shown that mothers often confused the two probabilities (Parsons & Clarke 1993, Parsons & Atkinson 1993). In addition, families may have struggled to make sense of carrier risk figures. In recent years, rather than providing families with a carrier risk, (e.g. a 66% or 37% risk of being a carrier), it has become possible to provide families with information on whether they do or do not carry the same genetic mutation as their child. It is now possible to tell a mother that she is either a carrier, with a 1 in 4 risk of having an affected child in each subsequent pregnancy, or she has a germline mosaicism risk of 1 in 20 in each subsequent pregnancy.

Despite these developments, information on carrier status does not appear to have a direct influence on reproductive behaviour. The quantitative data demonstrated that when families had to wait a considerable amount of time to receive more accurate confirmation of their carrier status, many chose to proceed with subsequent pregnancies regardless. Overall, there was little difference in the proportion of carriers or women with a germline mosaicism risk who chose to have subsequent pregnancies; 53% (n=38) of mothers in the total cohort were carriers and 52% (n=14) of risk-aware women who had subsequent pregnancies were carriers. The proportion of pregnancies occurring in carriers was higher in the NBS cohort (72%, n=23) than in the LCD cohort (58%, n=8). However, the difference was not statistically significant.

There was also no association between carrier status and uptake of prenatal testing. A slightly higher proportion of women with germline mosaicism risk (77%, n=7), who were aware of their carrier status, had a subsequent pregnancy and were offered prenatal testing, chose to test the pregnancy, compared with only 61% (n=8) of carriers. However, there was a significant difference between the two cohorts in the uptake of prenatal testing ( $p<0.05$ ). Mothers in the newborn screening cohort were significantly more likely to opt for prenatal testing than mothers in the LCD cohort. Potential reasons for the differences are explored in subsequent sections.

#### **4.3 Perception of risk; perceived burden and the capacity to cope**

Findings from both the quantitative and qualitative data suggested that actual genetic risk does not necessarily correspond with subjective perceptions of risk. None of the families in the interview cohort presented themselves as having ceased family building because of the genetic risk in subsequent pregnancies. However, those who had continued family building often presented genetic risk as an important factor in their decisions regarding prenatal testing and termination.

Many families had an incorrect awareness of their genetic risk, and drew upon numerical risk assessment that did not correspond with their actual risk. Risk appeared to be related to the perception of the outcome: the burden of having a second affected child. This finding suggests that it is not just the severity of the condition that informs reproductive behaviour (which was obviously the same for each family in this cohort), but the subjectively perceived burden of the condition and families perceived capacity to cope. Often the perceived inability to cope with another child with a genetic condition is the deciding factor in the uptake of prenatal testing and subsequent termination (Brookes 2001). The following two sections review the literature on the role of the perceived burden of the condition on reproductive decision-making and families' perceived ability to cope with a second affected child.

#### ***4.3.1 The influence of the perceived burden of disability; reviewing the literature***

Numerous studies have tried to assess the influence of experience of living with a condition on the perception of burden; the findings are varied and often conflicting. Two studies on reproductive behaviour in families affected by DMD, which were reviewed in Chapter Three, highlighted an association between experience of the condition and desire to avoid having a child with DMD (Beeson & Golbus 1985, Kay & Kingston 2002). Both studies found that the experience of caring for an affected sibling appeared to increase motivation to use prenatal testing and termination.

The studies conducted by Beeson and Golbus, and Kay and Kingston, also addressed reproductive decision-making in other x-linked conditions. Beeson and Golbus (1985) reviewed 15 families at risk for haemophilia and Kay and Kingston reviewed three families at risk of Lesch-Nyhan syndrome, one at risk of Menkes syndrome and one at risk of Fabry disease. Despite the difference in severity of these conditions, there was little difference between families in relation to reproductive decision-making. Both studies found that the experience of caring for an affected sibling appeared to increase motivation to use prenatal testing and termination.

The difference between the findings from both Beeson and Golbus' (1985) and Kay and Kingston's (2002) studies, and this study highlight the importance of the relationship with the affected individual and the perceived severity of the condition. Participants in this study had an affected child, whereas participants in the studies conducted by Beeson and Golbus (1985) and Kay and Kingston (2002) had an affected sibling or distant male relative. The differences between reproductive behaviour in mothers of children with disabilities and those at risk of having a child with a disability is reflected in other studies. Meryash (1989) found that women without a child affected by Fragile-X perceived the burden of the condition to be higher than mothers of affected children.

Brookes (1991) conducted interviews with 20 women who were already living with a child with a genetic condition, or were themselves affected by a condition to

explore families' response to the offer of prenatal testing. Brookes (2001) found that the experience with people with disabilities did not have a predictable relationship with reproductive decision-making. Brookes (2001) found that some women perceived themselves to be "at risk" of a genetic condition. However, others "saw the experience of already caring for a child with a genetic condition and their increased maturity as positive asset for engaging in further caring" (Brookes 2001:140). Experience of living with an affected child enabled mothers to assess their capacity to cope with another affected child. Experience was found to be a more useful asset in the reproductive decision-making process than the information provided by medical practitioners.

Frets *et al.* (1991) conducted in depth interviews with 23 families who had either a child, sibling or spouse affected by physical or mental disabilities and had chosen to have subsequent pregnancies. The authors assessed how "receptive" participants were to genetic counselling information regarding reproductive options. Frets and colleagues note that "most couples (16/23) appeared to be receptive to information". However, couples with an affected sibling were significantly more receptive than couples who had an affected child ( $p < 0.005$ ). Although the study did not address the uptake of prenatal testing, the findings suggest that experience of living with an affected child may contradict the information provided by genetic counsellors, resulting in the appearance of being "less receptive".

Ferguson *et al.* (2000:81) cumulated research on parents' experience of living with disability and concluded that "there is a level of agreement that the overall adaptation profile of families who have children with disabilities basically resembles the overall profile for families in general (including children with and without disabilities)." In addition, research shows that "family responses to disability are immensely variable". Considering the variability in families' experiences of disability, it would be unwise to view the decision to terminate as always right or always wrong; the individual context of decision-making has significant bearings.

Despite the significant amount of research suggesting that parents adapt to life with a disabled child as well as they might to life with a child without disabilities, there

remains a dominant view that “a child with a disability poses substantial heartache, difficulty and burden to families that far exceed in kind and degree, the stresses modern parents typically face” (Asch 2000:22). Lawson’s (2001, 2006) two studies on the perception of disability, reviewed in Chapter Three, reflect this view.

Perceptions of disability may be reflected in the uptake of prenatal testing. The findings from this study showed a general decline in the use of prenatal testing. Between 1992 and 1996, 83% (n=10) of pregnancies were tested, compared to only 36% (n=5) between 2002 and 2006. A recent study on families at-risk of Fragile X found similar results; between 1991 and 1995, 93% of those counselled opted for prenatal testing compared to only 33% of those counselled between 2001 and 2005 (Nelson *et al.* 2009). A study reviewing changes in the utilisation of prenatal diagnosis for Down syndrome in the United States found that “the number of women receiving amniocentesis or CVS declined more than 50% from 1,988 in 1991 to 933 in 2002 ( $P < .001$ ), despite an increase in the number of women of advanced maternal age in the population served” (Benn *et al.* 2004) There was a 68% decline in the number of women who underwent invasive prenatal testing solely on the basis of their age (1,314 in 1991 to 423 in 2002,  $P < .001$ ).

The findings of these studies suggest that a decline in prenatal testing is occurring across conditions, regardless of severity. It is possible that changing views on disability and social norms regarding what is deemed an acceptable choice may be influencing a gradual decline in the uptake of prenatal testing (Shiloh 2000).

The findings from these studies pay testament to the complexity of trying to explore the factors people associate with reproductive decision-making. However, three key issues emerge. First, the social context of decision-making may influence the uptake of prenatal testing. Second, the majority of the studies demonstrate that families, who are risk of a particular condition and have an affected relative, perceive the burden of the condition to be high. In contrast, many families who have lived with a child with a particular condition perceive the burden of the condition to be reduced. Third, families who have direct experience of living with a child with a disability may be “less receptive” to medical discourse about the genetic risk of a condition. However, not all families who have direct experience of living with a child with a



disability perceive themselves as able to cope. The following section reviews literature on the perceived ability to cope.

#### ***4.3.2 The influence of the perceived capacity to cope: reviewing the literature***

Chapter Three explored the social context of the desire for children and the predominantly negative perceptions of living with a child with a disability.

Klitzman et al. (2007:359) state that “sociological interactions and relationships can involve a broad array of dynamic, complex pressures and input that individuals can accept, resist or negotiate”. However, the capacity and drive of an individual to resist social pressures depends on their degree of confidence in ‘swimming against the tide’. Bandura’s theory of self-efficacy defines four factors that influence our confidence in decision-making: 1) Have I coped with something like this before? 2) Have I seen other people cope with it? 3) Has anyone else convinced me I can cope? 4) Am I calm when I make the decision?

The four factors in the theory of self-efficacy have particular salience for reproductive decision-making in families affected by DMD. First, a number of families mentioned that their perceived capacity to cope with the condition had strengthened as they had got to know their child. For some families this introduced the idea that they would be able to cope with another affected child. Second, families who had the opportunity to get to know other families with two affected boys, sometimes felt that seeing others coping increased their perceptions of their own capacity to cope. Third, few families felt that they received information or support from either the medical profession, or society, to suggest that they could cope with another. Fourth, some families who received a later clinical diagnosis were already pregnant and were therefore forced to make a stressful, time-limited decision on the future of the pregnancy.

Although the latter factor negatively affected the perceived capacity of a few families who received a later clinical diagnosis, the first two factors potentially have a more negative impact on all families who received a newborn screening diagnosis. Few families – if any – will have any concept of either their ability to cope with the condition, or the opportunity (or desire) to meet any other families with the

condition immediately after the diagnosis. Many families who received a newborn screening diagnosis found meeting other families, whose affected children demonstrated greater degrees of muscle weakness, incredibly distressing. In contrast, families whose knowledge and experience of the condition had grown with their child, often seemed better placed to assess their own capacity to deal with another affected child.

Langer (1975) synthesized an impressive body of data documenting how people respond to chance by creating an “illusion of control”; behaving as though chance elements may be controlled. Langer argues that people develop the illusion of control for a number of key reasons. Firstly people are motivated to master their environment. Secondly, no one likes to feel that they do not have control. Thirdly, people introduce skill elements to assist with coping and lastly, the illusion of control tends to help us more emotionally, than it harms us practically. Langer concludes that “when an individual is actually in the situation, the more similar the chance situation is to a skill situation in outcome-independent ways, the greater will be the illusion of control [...] people are more confident and more likely to take risks”.

Reviewing Langer’s findings in relation to reproductive decision-making, families who perceive that they are able to cope with living with an affected child have in a sense learnt to develop an illusion of control over their situation. To learn to cope with what we already have, we “seek to make that which is given and inevitable seem chosen” (Jackson 1998:26). As Nikos Kazantzakis (1961:274) observed “to say yes to necessity and change the inevitable into something done of [one’s] own free will...is perhaps the only human way to deliverance. It is a pitiable way, but there is no other”.

We cannot provide families, who already have a child affected by DMD, with the choice to avoid the condition altogether. Offering families the opportunity to avoid another child with the same condition therefore presents them with an existential dilemma. Families learning to make the most of what they have often find benefit and pleasure from their child, but faced with prenatal testing, must simultaneously reconcile efforts to say “yes to necessity” with the option of saying “no, we don’t

want a(nother) child affected by this condition”. Of course some families are simply not able to cope, emotionally nor financially, with the prospect of a second affected child and it is entirely justifiable for these families to attempt to avoid that which is perceived to be negative, but let us not forget – our capacity to accept is often far greater than our capacity to control.

The supposedly transformative properties of genetic technologies may have changed clinical understandings, and abilities to detect particular genetic deletions and duplications, but has done little to change families’ experience of living with the condition. More accurate carrier testing techniques do not appear to have increased the accuracy of individual interpretation of risk. Risk is a complex, highly emotional, personal and socially complex phenomenon. Accuracy does not mean that a mother with a 1 in 4 risk is more likely to avoid risk by opting for prenatal testing, than a mother with a 1 in 20 risk.

It is not the technological capacity to provide accurate awareness of risk that influences reproductive behaviour; it is the perceived burden of the outcome that affects decision-making. The perception of burden is not influenced by the probability of occurrence, but the social context of decision-making, and the individuals’ perceived capacity to cope. The perceived capacity to cope is affected by psychological factors specific to each individual and family, but also by the opportunity to experience the capacity to cope; the opportunity to live with and get to know a child with DMD.

## **5. Diagnostic pathway; delayed diagnosis and medical information**

Two key factors emerged from the qualitative data on the experience of the diagnosis. First, the diagnostic pathway had considerable implications for the experience of the diagnosis. Second, the timing of the diagnosis had significant implications for the decision-making process, by changing the role of personal experience and medical information in subsequent reproductive decision-making. These two factors are explored in greater detail in the next two sections.

## 5.1 Experience of the diagnosis: lost years versus carefree years

Previous studies have shown that families are in favour of receiving a diagnosis of DMD through newborn screening (Crisp *et al.* 1982, Firth *et al.* 1983, Firth & Wilkinson 1983, Smith *et al.* 1990, Parsons *et al.* 1992). However, only one study (Parsons *et al.* 1992) addressed actual experience, rather than hypothetical views. In this study, the majority of families who received a diagnosis through newborn screening expressed relief that they had learnt of their child's condition at an early stage. However, the majority of families who had received a later clinical diagnosis expressed relief that they had *not* found out earlier.

The findings reflect the contradiction found in Firth *et al.*'s (1983) study; although 75% (n=40) of families who had received a later clinical diagnosis were in favour of an earlier diagnosis, only 37.7% (n=20) felt that the later clinical diagnosis had *not* been made at the best time. Some LCD families in this study, felt that the provision of an earlier awareness of risk may benefit other families, but were personally glad to have received a later clinical diagnosis. It is possible that families, when asked hypothetically, value the provision of choice for others. However, families' actual experience of the later clinical diagnosis and the early years of their child's life often outweighed the potential value of choice.

The diagnostic pathway had particular implications for the experience of the early years of a child's life. An unprompted diagnosis for an asymptomatic baby devastated families, often to the extent that they felt they "lost" the first few years of their babies' life. Although families who received a later clinical diagnosis appeared equally devastated, considerably more time was devoted to describing the gradual progression of signs and symptoms. For some, the later clinical diagnosis vindicated what others had assumed to be excessive worry. The "lost" time was described in months, rather than years.

Various studies have reviewed the process of parental adjustment to the diagnosis of disabling condition in their child (see Meryash 1989:20 for a review of literature). Many conclude that adjustment to the diagnosis occurs in three stages. The first stage is characterised by crisis responses in the form of shock, denial and disbelief.

The second stage entails emotional disorganisation as families experience guilt, disappointment, anger and lowered self-esteem. The final stage of adjustment to the diagnosis involves emotional organisation, acceptance and adjustment (Meryash 1989). Although the division of adjustment into stages may be overly simplistic (Sorenson *et al.* 1981), it is clear that it takes time to adjust to the diagnosis, regardless of the age of the child.

Although the diagnosis may be equally devastating to NBS and LCD families, the process of diagnosis differs substantially. NBS families are presented with a baby and a diagnosis, whereas LCD families experience a transition from recognising “trivial symptoms” to acknowledgement of a “developing and persisting disability” (Bury 1982:170).

There is a striking resemblance between the narratives presented in this study and previous work conducted on beliefs and knowledge about emergent symptoms and subsequent moral dimensions of understanding. For example, Bury (1982) explored how and when first signs of rheumatoid arthritis were recognised, and highlighted the complex layers of uncertainty associated with the medical knowledge and the individuals’ concept of self. Like many families who had experienced a later clinical diagnosis, the participants in Bury’s study drew upon existing frameworks of understanding as a way of defining symptoms within a familiar context. Symptoms were often mistaken for “normal” development, or inevitable “wear and tear”, rather than indicative of a persistent and developing disability. As Bury (1982:171) suggests, “there is often nothing in the individual’s biography which provides an immediate basis for recognition of illness *as* illness”.

Uncertainty is a key aspect of the disruptive experience; early signs of DMD are often mistaken for slow development, making the problem of diagnosis particularly difficult. Uncertainty is a well recognised concept in the experience of chronic illness involving both “uncertain knowledge about the impact and course of the condition and of appropriate behaviour in the face of its effects” (Bury 1982:172). For some families, access to medical knowledge offers an “opportunity to conceptualise the disease as separate from the individual’s self” (Bury 1982:172). Little research has been conducted on how a presymptomatic diagnosis may affect

the development of child identity. For families raising a child who has received a diagnosis, but is yet to show symptoms, attempts to separate aspects of the condition from 'normal' child behaviour can be problematic.

The age of the boy at diagnosis clearly has significant implications for how people perceive their child and cope with the diagnosis. For families who receive a later clinical diagnosis, their understanding of the medical information about the condition is combined with their own experience of their child. In relation to decision-making about prenatal testing, two key factors are apparent: the role of experiential knowledge and the influence of medical information.

## **5.2 The role of experiential knowledge and medical information**

Many families felt that the medical information provided at the time of diagnosis provided a stark and distressing outlook for their child. Consequently, a number of NBS screening families felt that their experience of the condition had 'not been as bad as they had expected it to be'. The medical description of the condition was often found to be lacking in experiential validity. As the affected child grows older, families realise that medical knowledge is incomplete. As Bury (1982:174) suggests, "the search for a more comprehensive level of explanation, a more certain basis of coping" indicates the "need to *complete* knowledge gained from specialist sources; a need to tie in formal knowledge with the person's total biography".

Receiving a diagnostic label for a seemingly healthy baby had an insidious effect on families' perception of their capacity to care for their child. As one NBS mother, Sharon noted, "there was nobody there to say, "well why do you not do this, why do you do that?". Although many families found involvement with health professionals, in the early years, overbearing or interfering, many others felt isolated and abandoned during a time in which they felt the need for reassurance about the appropriate way to care for their affected child.

For families who received a diagnosis through newborn screening, the difficulty of disentangling aspects of the condition from their child's developing personality was exacerbated. Families who received a later clinical diagnosis presented themselves

as more competent at defining their child's identity, in relation to aspects of the condition. Describing the impact of the later clinical diagnosis, one LCD mother, Maureen, noted: "I think it was to our – you know, the whole family's benefit because the only thing that had changed at that point was the diagnosis; the label that had been put on it, because he was the same boy". LCD families had developed expectations of their child's abilities, which they often felt would have been negatively affected by receiving an earlier diagnosis.

Numerous studies have suggested that the provision of medical information alone is not enough (Curtis *et al.* 1994, Vehmas 2001, Marteau & Dormandy 2001), or that the medical information provided is too negative (Asch 1999). Health professionals tended to focus on information regarding the "worst case scenario" of the medical aspects of the condition, rather than the reality of living with, and caring for, an affected child (Brookes 2001). However, it may not be possible to provide families with a 'balanced' view of the condition. Even families living with a child affected by DMD demonstrated some reticence to hear about, or see, the later stages of the condition. As a number of families noted, information that families living with a child with more progressive weakness may perceive to be positive, may be devastating to families coming to terms with the early stages of the condition.

The interview data suggest that, although emotion-based reproductive decisions may not be better, they are not necessarily less rational decisions. While NBS families often decide about whether to use prenatal testing on the basis of medical information alone, LCD families are able to access both medical information and their own biographical repertoire of experience. One possible explanation for the significantly higher uptake of prenatal testing in the newborn screening cohort is that an earlier diagnosis increases susceptibility to medical discourses about the importance of risk (Grob 2008).

Many of the findings of this study are corroborated by two recently published articles on the experience of newborn screening (Grob 2006, 2008). Grub's (2008) study focused on the implications of newborn screening for families' perception of disease and illness. Semi-structured interviews were conducted with a total of 35 parents of children who received a diagnosis of cystic fibrosis either through

newborn screening (n=16), a later clinical diagnosis (n=11), an early clinical diagnosis, within days or weeks of the birth of a symptomatic child (n=4), or through prenatal testing (n=4). The research aimed to explore how families experienced receiving a positive screen for a genetic disease while their child was still asymptomatic, and to compare families' experiences with those who received a diagnosis after the emergence of symptoms.

The findings of Grob's (2008) study highlight a number of potent consequences associated with affixing a disease label to an asymptomatic baby. A newborn screening diagnosis "deeply affects parents' feelings of competence to care for their newborn and their sense of who the child is, and places the disease – rather than the process of "falling in love with" the new baby – at centre stage during the child's early weeks and months; and causes health professionals to loom very large in the family's life at this formative time." The consequences of an early diagnosis on the development of the identity of an affected child are not known. Furthermore, Sanders (2006) argues that lowered expectation of people with disabilities has a pervasive effect on their development, confidence and perception of worth.

Grob (2006:168) explored the experience of newborn screening from the perspective of mothers and called for the expansion of newborn screening programmes to "proceed with caution". The participants in Grob's (2006) study highlighted the "cursed blessing on newborn screening". An early diagnosis may provide some families with a welcome opportunity to address the practical and emotional consequences of a condition, but for many it profoundly alters the experience of new motherhood. The dramatic rescue of a small number of children from tragic outcomes must be juxtaposed against the far reaching effects of "automatic classification and diagnosis of newborn babies".

## **6. The experience and outcome of reproductive choice**

The desire for children and the perceived burden of the condition, whether influenced by social perceptions of disability or individual assessments of the capacity to cope were the defining factors in the decision to continue family



building and use prenatal testing. None of the eight families in the LCD cohort had experienced prenatal testing or termination. The experiences of families in the NBS cohort pays testament to the incredible levels of stress and anxiety caused by the experience. The following sections explore the difference between choosing to test and choosing to terminate, and the experience of prenatal testing.

### **6.1 Prenatal testing and termination; often discrete entities**

The literature shows that there remains an inextricable link between prenatal testing and termination; the majority of individuals who actually receive a positive diagnosis through prenatal testing choose to terminate (Rapp 1988, Edwards *et al.* 1989, Palomaki 1996). However, the interview data suggested that, at the outset, the decision to test a pregnancy is not always synonymous with the decision to terminate.

Qualitative data from this study and others (Garcia *et al.* 2008) suggest that families with strong ethical views against termination tended to associate the decision to use prenatal testing with the decision to terminate. However, not all families considered their views on termination prior to undergoing prenatal testing, and some families chose to have prenatal testing even if they felt that they were ethically opposed to termination. Although some people who choose to use prenatal testing have a more favourable outlook on termination (Tercyak *et al.* 2001), many do not decide whether they would terminate until faced with a positive diagnosis. Often families chose to undergo prenatal testing in the hope of receiving reassurance of a 'normal' pregnancy (Laurence 1981, Kraus & Brettler 1988, Sagi *et al.* 1992, Santalahti 1998).

The lack of perceived association between prenatal testing and termination, for some families, suggests a 'step by step' approach to decision-making, which has some similarities with Simon's (1978) concept of "bounded rationality". Rather than following the tenets of classical decision making, individuals reduce options to a limited number (e.g. whether or not to have prenatal testing) and make decisions which appear reasonable, rather than optimal (e.g. not thinking through to the next

level of decision-making until faced with that option). Under “bounded rationality” thorough processing of all possible options is exhausting and potentially futile.

Orasanu & Conelly (1993:9) suggest that in complex real-world situations, people “think a little, act a little, and then evaluate the outcomes and think and act some more”. Leach-Schully (2007) suggests that the series of micro-decisions occurs as a result of the relationship between ethical choice and time. Decisions regarding genetic testing require people to contemplate an imagined future:

“When the patient asks, *How will I live with this decision?* she is struggling to make sense of a past which has not yet happened” (Leach-Schully 2007:209)

The difficulty of imagining an unknown future often leads to people deliberately limiting their mental projection into the future during the decision-making process. Families, who are faced with the option of prenatal testing, often hope that they will not be faced with the option of termination. Avoidance of an ethically and emotionally difficult decision, until that decision has to be made, can be viewed as an entirely legitimate response.

## **6.2 Experience of prenatal testing and termination**

During the qualitative interviews, many families described the experience of prenatal testing as incredibly stressful. All mothers who had experienced prenatal testing felt that the first few months of their pregnancy had been bereft of enjoyment. After receiving confirmation that they were carrying a healthy child, the majority felt that the pregnancy could be enjoyed as any other. However, for some the fear and anxiety that ‘something else might be wrong’ permeated their whole experience of pregnancy. Until they held their (healthy) child in their hands, they worried.

None of the families in the interview cohort had received a positive prenatal diagnosis of DMD. However, receiving a positive diagnosis through prenatal testing has been shown to entail a variety of losses for couples “including the loss of joy of pregnancy, possibilities inherent in pregnancy, the dream child, innocence, and the world as they knew it” (Sandelowski & Barosso 2005:311).

In addition, couples experience selective termination as a traumatic life-event, regardless of the stage in pregnancy in which termination occurred (Kolker & Burke 1993). A number of authors have drawn upon William Styron's (1979) novel "Sophie's Choice"<sup>33</sup> to describe the paradoxical lack of choice presented by termination, which makes a mockery of choosing (Rothman 1994, Chandler & Smith 1998). Rapp (1999:225) refers to the irony of choosing to terminate a wanted child as a "chosen loss".

Only one of the families in the interview cohort had experienced termination. However, they had terminated a child with a chromosomal abnormality. Although they had obviously found the experience traumatic, the mother noted that the decision was made easier by knowing that the particular condition meant the child would not survive long after birth. This particular mother felt the burden of terminating a child with DMD would far outweigh the burden of living with another affected child; if she ever became pregnant again, she explained, she would never terminate a foetus with DMD.

Another family in the NBS cohort, who was not interviewed, tested and terminated her first subsequent pregnancy, tested her second subsequent pregnancy, but chose not to test her third. The genetic counselling notes highlighted that the mother felt unable to cope with the terminating another pregnancy. Over time, the risk of having a second affected child had become less important than the burden of terminating.

Preimplantation genetic diagnosis (PGD) is often presented as a way of avoiding the traumatic ethical decision of termination. However, while it might be argued that it is "advantageous to women to be able to make selection decisions that do not involve a termination", in practice the decision-making context of PGD arguably accrues more power to the practitioner than to the woman involved, "as the object of the decision is now located outside her body" (Chadwick 2009:11).

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<sup>33</sup> In the novel, a Nazi officer offers Sophie the opportunity of going free, rather than being sent to a concentration camp. The condition of the offer was that she must choose which of her two children would join her and which would be sent to a concentration camp. With only a few seconds to choose and knowing that the choice was between all three of them dying, or one of them dying, Sophie chose to escape with her daughter. However, the rest of her life was destroyed by that choice.

PGD had only been experienced by one mother, Mary, in the interview cohort and although it clearly changed the circumstances of her choice, it was not clear whether her choice had been enhanced. Despite pondering whether she really wanted another child, Mary described the intoxicating process of being provided with a small chance that they might. When each fertilised egg was implanted, previous doubts were swept away in contemplation of the future child; only for brief bonding to be replaced by grief. Deciding to “get on with your life” was described as another choice not easily taken. The low uptake of PGD may reflect limited availability, as well as parental recognition of the considerable practical and emotional resources required, in an attempt to avoid a “risk”.

Risk is subjective and the perception of risk may change over time. A bad outcome is an external tyranny to be desperately avoided. Families who have a positive experience of DMD may not always perceive the negative aspects of the condition to outweigh the positive attributes of their experience. While few wish their children to have the condition, the alternative options – to have no more children, to terminate all affected foetuses, or to embark on the emotional and time-consuming process of PGD – may bring more anguish than a life with an(other) affected child could ever bring. The risk of a lost pregnancy, the risk of a lost life may far outweigh the risk of having a second affected child. When the risk of one potentially negative outcome far outweighs another, the lesser risk becomes a chance to be willingly taken. If the chance results in another affected child, this may be preferable to no child at all.

## **7. Summary and conclusion**

Conducting a mixed-methods study provided disparate insights into the implications of two different diagnostic pathways, for families affected by Duchenne muscular dystrophy. The quantitative data demonstrated the nebulous affect of providing risk information; there was no association between carrier status and reproductive behaviour. Providing an earlier awareness of risk had varied effects. Families in the newborn screening cohort were more likely to continue family building, and significantly more likely to use prenatal testing ( $p=0.05$ ). In contrast, families who

received a later clinical diagnosis were more likely to cease or delay family building after the diagnosis; consequently, family size and birth interval differed considerably from the national average. There was little difference in the number of second affected boys.

The qualitative data illustrated depth and complexity. Receiving a diagnosis of DMD (regardless of the diagnostic pathway) marked a “biographical disruption” (Bury 1982); a disruption of structures of meaning, relationships, social networks and access to resources. In light of the diagnosis, the personal narrative was reformulated, reconstructed, “in order to understand the illness in terms of past social experience and to reaffirm the impression that life has a course and the self has a purpose or *telos*” (Williams 1984). The meaning of the diagnosis lay in the consequences for the individual and the significance of varying connotations associated with DMD. Rather than providing a list of “factors affecting reproductive decision-making”, reproductive decisions were presented as relative to – and imbedded in – illness narratives.

The data presented in this study raises important questions about the purpose, meaning and consequences of providing families with reproductive choice. The following sections explore three key questions, before considering the implications of this study in relation to current newborn screening policies.

### **7.1 Why provide choice?**

During the 1980s, Margaret Thatcher developed national policies around the notion of free individuals, consumers, able to choose how to live their lives between competing market options. Subsequent governments have maintained an emphasis on individual choice, and as a result “the UK has become closer to the American ideal of competitive individualism and choice has become enshrined as a central ethic” (Kerr & Shakespeare 2002:120). Newborn screening for untreatable conditions is increasingly presented as a pragmatic response to consumer demand, which rests on implicit assumptions that families’ value choice and/or will choose to avoid the birth of a second affected male.

## 7.2 Are newborn screening and reproductive technologies a real choice?

Disability rights activists have done much in recent decades to dislodge and deconstruct the dominant medical model of disability. Highlighting the social dimensions of disability has enabled recognition of the aspects of society that actively create, or reinforce, discriminatory attitudes towards those with impairments. However, both the medical and social model of disability fall prey to the pitfalls of reductionism, whether cultural or biological (Danermark & Gellerstedt 2004); neither model, alone, provides an adequate reflection of the lived experience of disability. The narrative accounts provided in this study highlight the ways in which people are disabled by both society and their bodies (Shakespeare 2008).

Encompassing aspects of both social and medical models of disability enables discussion of the practical implications of disability, alongside the influence of dominant attitudes towards disability on the provision of genetic services. Kerr and Shakespeare (2002:179) argue that attitudes towards disabled people are still “largely based on a mixture of fear, suspicion and pity”. Despite increasing sophistication of genetic technologies, reproductive interventions far outweigh the possibilities for treatments or cures. Overt coercion to participate in reproductive interventions is rare, but the widespread view amongst clinicians, scientists and policy-makers is that “the birth of a disabled child is a tragedy best avoided” (Kerr & Shakespeare 2002:180).

There are still “subtle and not so subtle ways in which people are pressurised to comply with genetic testing, particularly screening programmes” (Kerr & Shakespeare 2002:180). For example, newborn screening for DMD in Wales is presented as an “opt-in” programme, and yet in practice few mothers were aware that they had “chosen” to have screening. The few mothers, who had actively decided to opt for newborn screening, presented the decision as inevitable; the very offer of the test, alongside other routine tests, implied a benefit of testing.

For those who received a positive result, the consequences of an inadvertent decision were significant. Families were hoisted onto a conveyor belt of genetic

information and risk management. In the field of genetics, information has become imbued with exceptional significance. Newborns are tested so that families may know; may be informed; may have choice. Genetic information is perceived to be the cornerstone of human existence, the key to individual identity and health (Samerski 2006). It is presented with gravitas, as the foundation of informed decision-making; but genetic information is complex and its relevance to each family is subjective, opaque, and questionable.

Information is provided to enable autonomous, informed decisions, but reliance on the notion of individual choice is inherently problematic. In practice, choices are constrained and knowledge may be uncertain (Kerr & Shakespeare 2002). The participants in this study demonstrated a wavering ambivalence toward the provision of choice. Mothers' descriptions of the importance of "choice" were juxtaposed against accounts of "ignorant bliss", profound appreciation of the "carefree years", and relief at the avoidance of "difficult decisions". Choice was not always valued and knowledge was not always empowering, especially as nothing could be done to alleviate or cure the condition being tested.

### **7.3 What are the consequences of choice?**

Increasing emphasis has been placed on the need to "educate" or "empower" the public to make "informed choices" about health and healthcare. However, the very notion of "informed choice" raises questions about information and questions about choice (Kerr & Shakespeare 2002). Parents received genetic counselling in order to educate them about the scientific, biological and genetic facts of their existence, and inform them of their risk of DMD, and the risk of miscarriage. This "unleashing of genetic terminology" (Samerski 2006) had considerable implications for mothers' perceptions of themselves, and their experience of pregnancy. By informing mothers about inherited, physical faults, which constituted a real risk to the health of their family, they were left with an unerring sense of responsibility for an unchangeable past. By informing mothers of their carrier and reproductive risk, mothers became responsible for their families' future.

Mothers' accounts of reproductive decision-making highlight the subjective nature of genetic risk and the influence of other considerations, such the desire for children, practical considerations of work and finances, and responsibility toward partners and existing children. Abstract concepts of risk had to be reconciled with other considerations. No matter how mothers accommodated conflicting demands and responsibilities, the decision they were urged to make had "real consequences, which women experienced physically" (Samerski 2006:199). Abstract facts competed with kicking foetuses and emotional consequences. Prenatal testing transformed the "state of happy expectation into one of foreboding" (Samerski 2006:205).

The difference between providing families with risk information at birth, and after a gradual progression of signs and symptoms had led to a diagnosis, was significant. The narrative accounts from this study suggest that the carefree years, experienced by families who received a later clinical diagnosis, provided fertile ground in which to develop experiential knowledge. When making reproductive decisions, families drew upon both medical information and their own experience of their child and his condition. In contrast, newborn screening affixed a disease label to a seemingly healthy baby. At best, the early provision of information created new dilemmas; a choice between unknowable futures. At worst, genetic information had cataclysmic effects; displacing the seeds of experiential knowledge with powerful information on prognosis, risk, and responsibility. Many mothers questioned the experiential validity of shallow clinical descriptions of the condition; some of whom had tested their pregnancies on the basis of such information. Newborn screening stripped away the opportunity to "know my child, know his condition", and paved the way for medical discourses on disease and prevention to take unwarranted prominence in reproductive decision-making.

#### **7.4 Recommendations**

Many studies describe peoples' positive perceptions of newborn screening. However, the majority focus on hypothetical views of the general public (e.g. Bailey *et al.* 2005, Fanos *et al.* 2006, Plass *et al.* 2009), or hypothetical views of affected families (i.e. asking families who had received a later diagnosis if they



would like to have known earlier) (e.g. Firth 1983). There are few studies that explore the actual experience of newborn screening (Grob 2006, 2008).

The studies that have addressed newborn screening for DMD often focus on unjustified or outdated notions of benefit; the dramatic rescue of a small number of families from the “tragedy” of a second affected boy; the supposed value of providing families the opportunity to prepare for the future, practically and emotionally; or the avoidance of diagnostic delay (e.g. Parsons *et al.* 2001). In this study, none of the families had experienced a particularly delayed diagnosis. Only a few families who received a diagnosis through newborn screening made early practical preparations; most lost the first few years to grief<sup>34</sup>. Families who had watched the slow development of signs and symptoms often appeared more emotionally prepared, than families who received an unsolicited, and devastating, diagnosis at birth.

The hypothetical value of “choice” remains relatively undisputed; few are willing to deny others access to a notion so imbued with connotations of freedom and individuality. The value of choice also has experiential validity; it has undoubtedly led to the “dramatic rescue of a small number of families from tragic outcomes” (Grob 2006:161). However, hypothetical views and dramatic accounts of the value of choice are problematic when they become – as they have done – meta-narratives that dominate the political landscape (Grob 2006). In this study, families’ accounts of the experience of disability touched on notions of tragedy, but so did the accounts of living with choice. The complexity of the experiential value of “choice” is missing from contemporary political debates.

Explanations for the oversimplification, or deliberate selection of specific experiential evidence, can be found in both philosophical debates about methodological issues, and pragmatic considerations of the practical implications of policy development. Firstly, the influence of researchers’ values and theories cannot be underestimated; we are unable to escape the web of beliefs and ideas that inform our academic endeavours. As members of a society that places exponential value on

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<sup>34</sup> The average age of the affected boy at the time at which house adaptations commenced was 6 years in both cohorts.

choice, and simultaneously views disability with a mixture of fear, suspicion and pity, we are more likely to recognise – and emphasise - aspects of others that correspond to our own beliefs and hypothetical behaviours (Jackson 1989). Secondly, the very nature of political frameworks calls for the development of “one fits all” policies. It is in part the recognition of the diversity of human experience, and the fallibility of prescribing an overt solution to the “problem” of disability, that has led to increasing emphasis on individual choice.

Disability rights activists have provided an essential platform from which to view the subtle and not so subtle influences on the provision of, and response to, genetic services. Arguably, however, the technological imperative keeps marching on. Newborn screening programmes are expanding to include an ever greater array of non-treatable conditions. Prenatal testing is presented as a simple solution to the “problem” of foetal abnormality (Statham 2000). Couples and families are faced with terminating wanted pregnancies; decisions informed by pervasive nuances of fear, suspicion and pity, rather than experience of the disability in question.

Individual choice is viewed as a progression; a new, nominally democratic version of “one fits all” policies. In practice, the promise of “individual choice” fails to recognise implicit restraints and practical considerations. The justification for newborn screening for DMD has undoubtedly moved away from the explicit emphasis on the avoidance of second affected boys, but the emphasis on reproductive choice creates new dilemmas. The findings from this study highlight the need for a more considered approach to policy-making. The “opt-in” screening programme for DMD proved to be only nominally optional; few remembered choosing to test. In addition, families did not always choose to avoid the birth of second affected males. Families experienced significant distress and desolation, and were faced with desperate decisions and existential dilemmas. Is the provision of choice really in the best interest of parents?

Newborn screening policies for DMD need to take into account the minority who are “rescued from tragedy”, as well as the majority for whom newborn screening inflicts broader, but (arguably) more moderate harm. If policy-makers choose to privilege the minority, they must also recognise that the minority is ever-decreasing.

Changing social dynamics have resulted in smaller family sizes and longer birth intervals; fewer families are “at risk” of having a second affected child before the first receives a later clinical diagnosis. In addition, increasing acceptance of disability and slow improvements in social support also suggest that the experience of disability may be less tragic than once assumed.

If newborn screening for untreatable conditions is to continue, the privileging of the minority must be made explicit; it should be clear to families that only a few are likely to benefit. In addition, considerable improvements are required in the provision of information, choice and support. A nominally optional programme is not acceptable. Negative information or information “limited to a shallow description of the features of impairment” (Shakespeare 2008:100) will not suffice. Abandoning families in the early years of their child’s life ‘until something practical can be done’ is a dereliction of duty. If the premise of avoiding second affected children still remains an implicit drive, it is my hope that the cost of essential improvements to the provision of newborn screening will initiate a desperately needed discussion, about the true value of choice.

## References

- Acheson D (1998) *Independent Inquiry into Inequalities in Health Report* [Online]. Available at: <http://www.archive.official-documents.co.uk/document/doh/ih/ih.htm> [Accessed: 21<sup>st</sup> July 2008]
- Al-Jader L N, Goodchild M C, Ryley H C and Harper P S (1990) Attitudes of parents of cystic fibrosis children towards neonatal screening and antenatal diagnosis. *Clinical Genetics* 38 (6) 460-465.
- American College of Medical Genetics. Newborn screening: towards a uniform screening panel and system – report for public comment. [Online] Available at: [http://www.acmg.net/resources/policies/NBS/NBS\\_Main\\_Report\\_01.pdf](http://www.acmg.net/resources/policies/NBS/NBS_Main_Report_01.pdf) [Accessed 29<sup>th</sup> August 2007]
- Anderson G (2007) Patient decision-making for clinical genetics. *Nursing Inquiry* 14 (1) 13-22.
- Andrews L B, Fullarton J E, Holtzman M A and Motulsky A G (1994) Assessing genetic risks: implications for health and social policy. Washington DC: National Institute of Sciences.
- Antley R M (1979) "The genetic counsellor as facilitator of the counslee's decision process". In Capron A M, Lappe M, Murray M, Powledge T M, Twiss
- Appleton R E and Nicolaides P (1995) Early diagnosis of Duchenne muscular dystrophy. *Lancet* 345 (8959) 1243-1244.
- Asch A (1990) "Reproductive technology and disability". In Cohen S and Taub, N. (eds). *Reproductive Laws for the 1990s*. Clifton, N.J. : Humana Press.
- Asch A (1999) "Can aborting "imperfect" children be immoral?" From Asch A. Real Moral Dilemmas, *Christianity and Crisis*, 46(10):237. Reprinted in Arras J and Steinbock B. *Ethical Issues in Modern Medicine*, Fifth edition. Mountain View, CA: Mayfield
- Asch A (2000) "Why I haven't changed my mind about prenatal diagnosis: reflections and refinements". In Parens E, Asch A (eds) *Prenatal Testing and Disability Rights*. Washington: Georgetown University Press.
- Azjen I (1985) "From intentions to actions: A theory of planned behavior". In Kuhl J and Beckmann J. (eds). *Action control: From cognition to behavior*. New York: Springer-Verlag.
- Bagozzi R P and Van Loo M F (1978) Toward a general theory of fertility: a causal modeling approach. *Demography* 15 (3) 301-320.
- Bailey D B, Jr., Beskow L M, Davis A M and Skinner D (2006) Changing perspectives on the benefits of newborn screening. *Mental Retardation and Developmental Disability Research Reviews* 12 (4) 270-279.

- Bailey D B, Jr., Skinner D and Warren S F (2005) Newborn screening for developmental disabilities: reframing presumptive benefit. *American Journal of Public Health* 95 (11) 1889-1893.
- Barr M L and Bertram E G (1949) A Morphological Distinction between Neurones of the Male and Female, and the Behaviour of the Nucleolar Satellite during Accelerated Nucleoprotein Synthesis. *Nature* 163 (4148) 676-677.
- Bateson G (1973) *Steps to an Ecology of Mind*. Frogmore: Paladin
- Baum F (1995) Researching Public-Health: Behind the Qualitative Quantitative Methodological Debate. *Social Science & Medicine* 40 (4) 459-468.
- Becker, G S (1960) An economic analysis of fertility. In Coale A J. (ed). *Demographic and Economic Change in Developed Countries*. Princeton: Princeton University Press.
- Beckmann R, Sauer M, Ketelsen U P and Scheuerbrandt G (1978) Early diagnosis of Duchenne muscular dystrophy. *Lancet* 2 (8080) 105.
- Beeson D and Golbus M S (1985) Decision making: whether or not to have prenatal diagnosis and abortion for X-linked conditions. *American Journal of Human Genetics* 20 (1) 107-114.
- Beggs A H, Koenig M, Boyce F M and Kunkel L M (1990) Detection of 98-Percent of Dmd/Bmd Gene Deletions by Polymerase Chain-Reaction. *Human Genetics* 86 (1) 45-48.
- Benn PA, Egan JF, Fang M, Smith-Bindman R (2004) Changes in the use of prenatal diagnosis, *Obstetrics and Gynaecology* 103 (6) 1255-1260
- Bennett R R, den Dunnen J, O'Brien K F, Darras B T and Kunkel L M (2001) Detection of mutations in the dystrophin gene via automated DHPLC screening and direct sequencing. *BMC Genetics* 2 17.
- Bernhardt B A, Geller G, Doksum T, Larson S M, Roter D and Holtzman N A (1998) Prenatal Genetic Testing: Content of Discussions Between Obstetric Providers and Pregnant Women. *Obstetrics and Gynecology* 91 (5, Part 1) 648-655.
- Bickel H J, Gerard J and Hickmans E M (1954) The influence of phenylalanine intake on the chemistry and behaviour of a phenylketonuric child. *Acta Paediatrica* 43 64-88.
- Biesecker B B (2001) Goals of genetic counseling. *Clinical Genetics* 60 (5) 323-330.
- Blumberg B D, Golbus M S and Hanson K H (1975) The psychological sequelae of abortion performed for a genetic indication. *American Journal of Obstetrics & Gynecology*. 122 (7) 799-808.

- Blyth H and Hughes BP (1971). Pregnancy and serum C.P.K. levels in potential carriers of severe X-linked muscular dystrophy. *Lancet*. Apr 24 1(7704) 855–856.
- BMA Medical Ethics Committee (2007) The law and ethics of abortion. [Online:] Available at: [http://www.bma.org.uk/images/lawethicsabortionnov07\\_tcm41-146867.pdf](http://www.bma.org.uk/images/lawethicsabortionnov07_tcm41-146867.pdf) [Accessed 12<sup>th</sup> August 2007]
- Bostrom K and Ahlstrom G (2005) Living with a hereditary disease: persons with muscular dystrophy and their next of kin. *American Journal of Medical Genetics A* 136 (1) 17-24.
- Bourdieu P (1985) “The forms of capital”. In Richardson J. (ed). *Handbook of theory and research for the sociology of education*. New York: Greenwood.
- Bowling A (2002) *Research Methods in Health, Investigating Health and Health Services*. Second Edition. Maidenhead: Open University Press.
- Bradley D M, Parsons E P and Clarke A J (1993) Experience with screening newborns for Duchenne muscular dystrophy in Wales. *British Medical Journal* 306 (6874) 357-360.
- Brannen J (2005) Mixing methods: The entry of qualitative and quantitative approaches into the research process. *International Journal of Social Research Methodology* 8(3) 173-184.
- Brookes A (2001) Women's voices: prenatal diagnosis and care for the disabled. *Health Care Analysis* 9 (2) 133-150.
- Bryman A (1984) The debate about quantitative and qualitative research: a question of method or epistemology? *British journal of Sociology* 35 75-92.
- Bryman A (1988) *Quantity and Quality in Social Research*. London: Unwin and Hyman.
- Bryman A (2006) Integrating quantitative and qualitative research: How is it done? *Qualitative Research* 6(1) 97-113.
- Buhler C (2008) On the structural value of children and its implication on intended fertility in Bulgaria. *Demographic Research* 18 (20) 569-610.
- Bullock D G, Mcsweeney F M, Whitehead T P and Edwards J H (1979) Serum Creatine-Kinase Activity and Carrier Status for Duchenne Muscular-Dystrophy. *Lancet* 2 (8156) 1370-1370.
- Bunday S, Crawley J M, Edwards J H and Westhead R A (1979) Serum creatine kinase levels in pubertal, mature, pregnant, and postmenopausal women. *Journal of Medical Genetics* 16 (2) 117-121.
- Burkitt I (2003) Psychology in the field of being: Merleau-Ponty, ontology and social constructionism. *Theory and Psychology* 13 319–338.

- Burr V (2003) *Social constructionism*. Second Edition. London: Routledge.
- Bury M (1982) Chronic illness as biological disruption *Sociology of Health and Illness* 4 (2) 167-182.
- Bury M (1996) "Defining and Researching Disability: Challenges and Responses". In Barnes C and Mercer, G. (eds). *Exploring the Divide*. Leeds: The Disability Press.
- Bury M (2005) *Health and Illness*. Cambridge: Polity Press.
- Bushby K M, Hill A and Steele J G (1999) Failure of early diagnosis in symptomatic Duchenne muscular dystrophy. *Lancet* 353 (9152) 557-558.
- Carlson M D (2004) Recent advances in newborn screening for neurometabolic disorders. *Current Opinion in Neurology* 17 (2) 133-138.
- Chadwick R (2004) Nutrigenomics, individualism and public health. *Proceedings of the Nutrition Society* 63 (1) 161-166.
- Chamberlain J S, Gibbs R A, Ranier J E, Nguyen P N and Caskey C T (1988) Deletion Screening of the Duchenne Muscular-Dystrophy Locus Via Multiplex DNA Amplification. *Nucleic Acids Research* 16 (23) 11141-11156.
- Chandler M, Smith A (1998) Prenatal screening and women's perception of infant disability: A Sophie's Choice for every mother. *Nursing Inquiry* (5) 71-76.
- Christie D.A, Tansey E M (2003) *Genetic testing: the transcript of a Witness Seminar held by the Wellcome Trust Centre for the History of Medicine at UCL, London, on 13 July 2001*. London: Wellcome Trust Centre for the History of Medicine at UCL.
- Clarke A (1990) Genetics, Ethics, and Audit. *Lancet* 335 (8698) 1145-1147.
- Clarke A (1991) Is non-directive genetic counselling possible? *Lancet* 338 (8773) 998-1001.
- Clarke A J (1997) "Newborn Screening". In *Genetics, Society and Clinical Practice*. Harper P S and Clarke A J. (eds). Oxford: Bios Scientific Publishers Ltd.
- Clarke A J (1997) The Process of Genetic Counselling. In Harper P S and Clarke A J. (eds). *Genetics, Society and Clinical Practice*. Oxford: BIOS Scientific Publishers.
- Cole C G, Walker A, Coyne A, Johnson L, Hart K A, Hodgson S, Sheridan R and Bobrow M (1988) Prenatal testing for Duchenne and Becker muscular dystrophy. *Lancet* 1 (8580) 262-266.
- Coleman J S (1990) *Foundations of social theory*. Cambridge, MA: Harvard University Press.

- Cote G B (1983) Reproductive drive and genetic counselling. *Clinical Genetics* 23 359-362.
- Cresswell J W (2003) *Research Design: Qualitative, Quantitative and Mixed Methods Approaches*. Second Edition. London: Sage
- Crisp D E, Ziter F A and Bray P F (1982) Diagnostic delay in Duchenne's muscular dystrophy. *Journal of the American Medical Association* 247 (4) 478-480.
- Cromby J and Nightingale D J (1999) "What's wrong with social constructionism?". In Nightingale D J and Cromby J. (eds). *Social Constructionist Psychology: A Critical Analysis of Theory and Practice*. Buckingham: Open University Press.
- Cummings M R (2003) *Human Heredity: principles and issues*. Sixth Edition. Thomson: London.
- Cunningham-Burley S and Kerr A (1999) Defining the 'social': towards an understanding of scientific and medical discourses on the social aspects of the new human genetics. *Sociology of Health & Illness* 21 (5) 647-668.
- Curtis G, Dennis N and MacPherson J (1994) The impact of genetic counselling on females in fragile X families. *Journal of Medical Genetics* 31 (12) 950-952.
- d'Ydewalle G and Evers-Kiebooms G (1987) Experiments on genetic risk perception and decision making: explorative studies. *Birth Defects Original Article Series* 23 (2) 209-225.
- Danermark, B. And Gellerstedt, L.C. (2004) Social justice; redistribution and recognition – a non-reductionist perspective on disability, *Disability and Society*, 19 (4), 339-353
- Dellamonica C, Collombel C, Cotte J and Addis P (1983) Screening for neonatal Duchenne muscular dystrophy by bioluminescence measurement of creatine kinase in a blood sample spotted on paper. *Clinical Chemistry* 29 (1) 161-163.
- den Dunnen J T, Bakker E, van Ommen G J and Pearson P L (1989) The DMD gene analysed by field inversion gel electrophoresis. *British Medical Bulletin* 45 (3) 644-658.
- Denayer L, Welkenhuysen M, Evers-Kiebooms G, Cassiman J J and Van den Berghe H (1997) Risk perception after CF carrier testing and impact of the test result on reproductive decision making. *American Journal of Medical Genetics* 69 (4) 422-428.
- Department of Obstetrics and Gynaecology, Tietung Hospital of Anshan Iron and Steel Company, Anshan (1975). Fetal sex prediction by sex chromatin of chorionic villi cells during early pregnancy. *Chinese Medical Journal* (1) 117-126.
- Derrida J (1988) *Limited, Inc*. Evanston: Northwestern University Press
- Dewey J (1958) *Experience and Nature*. New York: Dover



- Dhondt J L (2007) Neonatal screening: from the 'Guthrie age' to the 'genetic age'. *Journal of Inherited Metabolic Disease* 30 (4) 418-422.
- Downing C (2005) Negotiating responsibility: case studies of reproductive decision-making and prenatal genetic testing in families facing Huntington disease. *Journal of Genetic Counseling* 14 (3) 219-234.
- Downing M and Pollitt R (2008) Newborn bloodspot screening in the UK: past, present and future. *Annals of Clinical Biochemistry* 45 (1) 11-17.
- Dreyfus J C, Schapira G and Demos J (1960) Etude De La Creatine-Kinase Serique Chez Les Myopathes Et Leurs Familles. *Revue Francaise D Etudes Cliniques Et Biologiques* 5 (4) 384-386.
- Drummond L M and Veale A M O (1978) Muscular-Dystrophy Screening. *Lancet* 1 (8076) 1258-1259.
- Dubowitz V (1976) Screening for Duchenne muscular dystrophy. *Archives of Disease in Childhood* 51 (4) 249-251.
- Dubowitz V (1995) *Muscle Disorders in Childhood*. Second edition. London: W. B. Saunders.
- Dunson D B, Colombo B and Baird D D (2002) Changes with age in the level and duration of fertility in the menstrual cycle. *Human Reproduction* 17 (5) 1399-1403.
- Easterlin R A (1975) An Economic Framework for Fertility Analysis. *Studies in Family Planning* 6(3) 54-63.
- Ebashi S, Toyokura Y, Momoi H and Sugita H (1959) High Creatine Phosphokinase Activity of Sera of Progressive Muscular Dystrophy. *Journal of Biochemistry* 46 (1) 103-104.
- Edwards A, Elwyn G, Covey J, Matthews E and Pill R (2001) Presenting risk information: a review of the effects of "framing" and other manipulations on patient outcomes. *Journal of Health Communication* 6 (1) 61-82.
- Edwards D, Ashmore A and Potter J. (1995). Death and furniture : The rhetoric, politics and theology of bottom line arguments against relativism. *History of the Human Sciences* 8 25- 49.
- Edwards J G, Rothstein W and Young S R (1989) Elective termination of chromosomally abnormal pregnancies: psychosocial effects and experience in genetic counselling. *Women and Health* 14 21-36.
- Edwards R J, Rodeck C H and Watts D C (1984a) False elevation of amniotic fluid enzymes of relevance for prenatal diagnosis: creatine kinase measurement in relation to Duchenne muscular dystrophy. *Prenatal Diagnosis* 4 (1) 35-42.

- Edwards R J, Rodeck C H and Watts D C (1984b) The diagnostic value of plasma myoglobin levels in the adult and fetus at-risk for Duchenne muscular dystrophy. *Journal of Neurological Science* 63 (2) 173-182.
- Edwards R J, Watts D C, Watts R L and Rodeck C H (1984c) Creatine kinase estimation in pure fetal blood samples for the prenatal diagnosis of Duchenne muscular dystrophy. *Prenatal Diagnosis* 4 (4) 267-277.
- Eggers S, Pavanello, R C, Passos-Bueno M R and Zatz M. (1999) Genetic counseling for childless women at risk for Duchenne muscular dystrophy. *American Journal of Medical Genetics* 86(5) 447-453.
- Eggers S and Zatz M. Social adjustment in adult males affected with progressive muscular dystrophy. *American Journal of Medical Genetics* 1998 81 4-12
- Ekwo E E, Kim J O and Gosselink C A (1987) Parental perceptions of the burden of genetic disease. *American Journal of Medical Genetics* 28 (4) 955-963.
- Emery A E (2002) The muscular dystrophies. *Lancet* 359 (9307) 687-695.
- Emery A E H (1980) Duchenne muscular dystrophy: genetic aspects. *British Medical journal* 36 (2) 117-122.
- Emery A E H (1993) *Duchenne Muscular Dystrophy*, Second Edition. Oxford Monographs on Medical Genetics, No. 24. Oxford University Press.
- Emery A E H and King B (1971) Pregnancy and serum creatine kinase levels in potential carriers of Duchenne x-linked muscular dystrophy. *Lancet* (1) 1013.
- Emery J (2001) Is informed choice in genetic testing a different breed of informed decision-making? A discussion paper. *Health Expectations* 4 (2) 81-86.
- E. Emery and F. Muntoni (2003) *Duchenne muscular dystrophy*. Third Edition. New York: Oxford University Press.
- Evans M I, Pryde P G, Evans W J and Johnson M P (1993) The choices women make about prenatal diagnosis. *Fetal Diagnosis and Therapy* 8 (Supplement. 1) 70-80.
- Fanos, JH., Spagner, KA., Musci, TJ. (2006) Attitudes toward prenatal screening and testing for Fragile X *Genetics in Medicine* 8 (2):129-133
- Farrant W (1985) "Who's for amniocentesis? The politics of prenatal screening". In Homans H. (ed). *The sexual politics of reproduction*. London: Gower.
- Fearing M K and Levy H L (2003) Expanded newborn screening using tandem mass spectrometry. *Advanced Pediatrics* 50 81-111.
- Ferguson P M, Gartner A, Lipsky D K (2000) The experience of disability in families: a synthesis of research and patient narratives. In Parens E, Asch A (eds) *Prenatal Testing and Disability Rights*. Washington: Georgetown University Press.

Firth M A and Wilkinson E J (1983) Screening the newborn for Duchenne muscular dystrophy: parents' views. *British Medical Journal Clinical Research Ed.* 286 (6382) 1933-1934.

Firth M, Gardner-Medwin D, Hosking G and Wilkinson E (1983) Interviews with parents of boys suffering from Duchenne muscular dystrophy. *Developmental Medicine & Child Neurology* 25 (4) 466-471.

Fishbein M and Azjen I (1975) Belief, attitude, intention and behaviour: An introduction to theory and research. Reading: Addison-Wesley.

Foucault M (1973) *The Birth of the Clinic*. London: Tavistock.

Fraser F C (1974) Current Issues in Medical Genetics: Genetic-Counseling. *American Journal of Human Genetics* 26 (5) 636-659.

Frets P G and Niermeijer M F (1990) Reproductive planning after genetic counselling: a perspective from the last decade. *Clinical Genetics* 38 (4) 295-306.

Frets P G, Duivenvoorden H J, Verhage F, Ketzer E and Niermeijer M F (1990) Model identifying the reproductive decision after genetic counseling. *American Journal of Medical Genetics* 35 (4) 503-509.

Friedman D, Hechter M and Kanazawa S (1994) A Theory of the Value of Children. *Demography* 31 (3) 375-401.

Fuchs F and Riis P (1956) Antenatal sex determination. *Nature* 177 (4503) 330.

Gabe J, Bury M and Elston MA (2007) *Key Concepts in Medical Sociology*. London: Sage.

Garcia E, Timmermans D R and van Leeuwen E (2008) The impact of ethical beliefs on decisions about prenatal screening tests: Searching for justification. *Social Science and Medicine* 66 (3) 753-764.

Gardner-Medwin D (1979) Controversies about Duchenne muscular dystrophy. (1) Neonatal screening. *Developmental Medicine and Child Neurology* 21 (3) 390-393.

Gardner-Medwin D, Bunday S and Green S (1978) Early diagnosis of Duchenne muscular dystrophy. *Lancet* 1 (8073) 1102.

Gates E (2004) Communicating risk in prenatal genetic testing. *Journal of Midwifery & Women's Health*, 49 (3) 220-227.

General Register Office for Scotland (2005) Mid-2005 Population Estimates Scotland. [Online]. Available at: <http://www.gro-scotland.gov.uk/statistics/publications-and-data/population-estimates/mid-2005-population-estimates/index.html> [Accessed 7<sup>th</sup> January 2006]

General Register Office for Scotland (2006) Registrar General's Annual Review of Scotland's Population. [Online]. Available at: <http://www.gro->

scotland.gov.uk/press/2006-news/registrar-generals-annual-review-of-scotlands-population.html [Accessed on 10th January 2006].

Gergen K J (1994) *Realities and relationships: Soundings in social construction*. Cambridge: Harvard University Press.

Gergen K J (1985) "Social pragmatics and the origins of psychological discourse". In Gergen K J. (ed). *The social construction of the person*. New York: Springer-Verlag.

Gilboa N and Swanson J R (1976) Serum creatine phosphokinase in normal newborns. *Archives of Disease in Childhood* 51 (4) 283-285.

Glaser B and Strauss A (1967) *The discovery of grounded theory: Strategies for qualitative research*. Chicago: Aldine

Golbus M S, Stephens J D, Mahoney M J, Hobbins J C, Haseltine F P, Caskey C T and Banker B Q (1979) Failure of fetal creatine phosphokinase as a diagnostic indicator of Duchenne muscular dystrophy. *New England Journal of Medicine* 300 (15) 860-861.

Grbich C (1999) *Qualitative Research in Health: An Introduction*. Sydney: Allen and Unwin.

Greenberg C R, Rohringer M, Jacobs H K, Averill N, Nylén E, van Ommen G J and Wrogemann K (1988) Gene studies in newborn males with Duchenne muscular dystrophy detected by neonatal screening. *Lancet* 2 (8608) 425-427.

Greene J. C, Benjamin L and Goodyear L (2001) The Merits of Mixing Methods in Evaluation. *Evaluation* 7(1) 25-44.

Greenhalgh S (1996) The social construction of population science: an intellectual, institutional, and political history of twentieth century demography. *Comparative Studies in Society and History* 38 26- 66.

Grob R (2006) Parenting in the genomic age: the 'cursed blessing' of newborn screening *New Genomics and Society* 25 (2) 159-170

Grob R (2008) Is my sick child healthy? Is my healthy child sick? Changing parental experiences of cystic fibrosis in the age of expanded newborn screening. *Social Science and Medicine* 67 1056-1064.

Grosse S D, Boyle C A, Kenneson A, Khoury M J and Wilfond B S (2006) From public health emergency to public health service: the implications of evolving criteria for newborn screening panels. *Pediatrics* 117 (3) 923-929.

Guba E and Lincoln Y (2005) "Paradigmatic controversies, contradictions, and emerging confluences". In Denzin N and Lincoln Y. (eds). *The Handbook of Qualitative Research*. Thousand Oaks, CA: Sage

Guthrie R and Susi A (1963) A Simple Phenylalanine Method for Detecting Phenylketonuria in Large Populations of Newborn Infants. *Journal of Pediatrics* 32 338-343.

Handyside A H, Pattinson J K, Penketh R J, Delhanty J D, Winston R M and Tuddenham E G (1989) Biopsy of human preimplantation embryos and sexing by DNA amplification. *Lancet* 1 (8634) 347-349.

Harre R (1990) "Exploring the human *Umwelt*". In Bhaskar R. (ed). *Harre and his critics*. Oxford: Blackwell.

Harre R and Langenhove L. Van (1999) "The Dynamics of Social Episodes". In Harre R and Langenhove L. Van. (eds). *Positioning Theory: The Moral Contexts of Intentional Action*. Oxford: Blackwell

Harris J (2000) Is there a coherent social conception of disability? *Journal of Medical Ethics* 26 (2) 95-100.

Harsanyi J C (1982) "Mortality and the theory of rational behaviour". In Sen A and Williams B. (eds). *Utilitarianism and Beyond*. Cambridge: Cambridge University Press.

Heckmatt J, Rodillo E and Dubowitz V (1989) Management of children: pharmacological and physical. *British Medical Bulletin* 45 (3) 788-801.

Heisenberg W (1958) *Physics and Philosophy: The Revolution in Modern Science*. New York: Harper & Row.

Henry L (1961) Some data on natural fertility *Eugenics Quarterly* (8) 81-91

Hildes E, Jacobs H K, Cameron A, Seshia S S, Booth F, Evans J A, Wrogemann K and Greenberg C R (1993) Impact of genetic counselling after neonatal screening for Duchenne muscular dystrophy. *Journal of Medical Genetics* 30 (8) 670-674.

Hirschman C (1994) Why fertility changes. *Annual Review of Sociology* 20 203-233.

Hodgson S V and Bobrow M (1989) Carrier detection and prenatal diagnosis in Duchenne and Becker muscular dystrophy. *British Medical Bulletin* 45 (3) 719-744.

Hoffman L W and Hoffman M L (1973) The value of children to parents. In Fawcett J T. (ed.) *Psychological Perspectives on Population*. New York: Basic Books.

Holtzman N A (1997) Genetic screening and public health.[comment]. *American Journal of Public Health* 87 (8) 1275-1277.

Holzgreve W, Hogge W A and Golbus M S (1984) Chorion villi sampling (CVS) for prenatal diagnosis of genetic disorders: first results and future research. *European Journal of Obstetrics, Gynaecology, & Reproductive Biology* 17 (2-3) 121-130.

Howe K R (1988). Against the quantitative-qualitative incompatibility thesis, or, Dogmas die hard. *Educational Researcher* 17 10-16.

Hunt L M, de Voogd K B and Castaneda H (2005) The routine and the traumatic in prenatal genetic diagnosis: does clinical information inform patient decision-making? *Patient Education and Counselling* 56 (3) 302-312.

Husserl E (1970) *Cartesian Meditations*. The Hague: Martinus Nijhoff.

Hutton E M and Thompson M W (1976) Carrier detection and genetic counselling in Duchenne muscular dystrophy: a follow-up study. *Canadian Medical Association Journal* 115 (8) 749-752.

Hyden, LC (1997) Illness and narrative *Sociology of Health and Illness* 19 (1) 48-69

Ionasescu V, Zelleger H and Cancilla P (1978) Fetal serum-creatine-phosphokinase not a valid predictor of Duchenne muscular dystrophy. *Lancet* 2 (8102) 1251.

Ivankova N V, Creswell J W, and Stick S L (2006). Using mixed methods sequential explanatory design: From theory to practice. *Field Methods* 18(1) 3–20.

Jackson M (1998) *Minima ethnographica: Intersubjectivity and the anthropological project*. Chicago: University of Chicago Press.

Jackson M. 1989. *Paths Toward a Clearing: Radical Empiricism and Ethnographic Inquiry*. Bloomington: University Press.

Jacobs H K, Wrogemann K, Greenberg C R, Seshia S S and Cameron A I (1989) Neonatal Screening for Duchenne Muscular-Dystrophy: the Canadian Experience. *Current Trends in Infant Screening* 848 361-366.

James W (1950) *The Principles of Psychology*. New York: Dover.

James W (1995) *Pragmatism*. Ontario: Dover.

Johnson R B and Onwuegbuzie A J (2004). Mixed methods research: A research paradigm whose time has come. *Educational Researcher* 33 (7) 14-26.

Jones L J (1994) *The Social Context of Health and Health Work*. Basingstoke: Macmillan.

Katz M G, Fitzgerald L, Bankier A, Savulescu J and Cram D S (2002) Issues and concerns of couples presenting for preimplantation genetic diagnosis (PGD). *Prenatal Diagnosis* 22 (12) 1117-1122.

Katzantzakis N (1961) *Zorba the Greek*. London: Faber and Faber.

Kay E and Kingston H (2002) Feelings Associated with Being a Carrier and Characteristics of Reproductive Decision Making in Women Known to be Carriers of X-linked Conditions. *Journal of Health Psychology* 7 (2) 169-181.

Kazy Z, Rozovsky I S and Bakharev V A (1982) Chorion Biopsy in Early-Pregnancy: a Method of Early Prenatal-Diagnosis for Inherited Disorders. *Prenatal Diagnosis* 2 (1) 39-45.

Kelly T E (1986) "Genetic counseling". In *Clinical Genetic Counseling*. Chicago: Year Book Medical Publishers.

Kemper A R and Wake M A (2007) Duchenne muscular dystrophy: issues in expanding newborn screening. *Current Opinion in Pediatrics* 19 (6) 700-704.

Kendzierski D (1990) Decision-Making Versus Decision Implementation: an Action Control Approach to Exercise Adoption and Adherence. *Journal of Applied Social Psychology* 20 (1) 27-45.

Kerr A, Shakespeare T (2002) *Genetic politics* London: New Clarion Press.

Kessler S (1980) The psychological paradigm shift in genetic counselling. *Social Biology* 27 165-185.

Kessler S (1989) Psychological aspects of genetic counseling: VI. A critical review of the literature dealing with education and reproduction. *American Journal of Human Genetics* 34 (3) 340-353.

Khoury M J (1996) From genes to public health: the applications of genetic technology in disease prevention. Genetics Working Group.[see comment]. *American Journal of Public Health* 86 (12) 1717-1722.

King B, Spikesman A and Emery A E (1972) The effect of pregnancy on serum levels of creatine kinase. *Clinica Chimica Acta* 36 (1) 267-269.

Klein A H, Meltzer S and Kenny F M (1972) Improved prognosis in congenital hypothyroidism treated before age three months. *Journal of Pediatrics* 81 (5) 912-915.

Klipstein S (2005) Preimplantation genetic diagnosis: technological promise and ethical perils. *Fertility and Sterility* 83 (5) 1347-1353.

Klitzman R, Thorne D, Williamson J, Chung W & Marder K (2007) Decision-making about reproductive choices among individuals at-risk for Huntington's Disease. *Journal of Genetic Counseling* 16(3) 347-362.

Kolker A and Burke B M (1993) Grieving the wanted child: ramifications of abortion after prenatal diagnosis of abnormality. *Health Care for Women International* (14) 513-526.

Korf B R (2000) *Human Genetics: A problem based approach*. Second Edition. Oxford: Blackwell Science.

Kraus E M and Brettler D B (1988) Assessment of reproductive risks and intentions by mothers of children with hemophilia. *American Journal of Medical Genetics* 31 (2) 259-267.

Kuhn T (1996) *The Structure of Scientific Revolutions*. Third Edition. Chicago: University of Chicago Press.

Kuhn T S (1970) *The structure of scientific revolutions*. Chicago: University of Chicago Press.

Kunkel L M and Hoffman E P (1989) Duchenne/Becker muscular dystrophy: a short overview of the gene, the protein, and current diagnostics. *British Medical Bulletin* 45 (3) 630-643.

Lai K K S, Lo I F M, Tonga T M F, Lydia L Y L and Lam S T S (2006) Detecting exon deletions and duplications of the DMD gene using Multiplex Ligation-dependent Probe Amplification (MLPA). *Clinical Biochemistry* 39 (4) 367-372.

Laing R (1970) *Knots*. New York: Pantheon.

Langdrige D, Sheeran P and Connolly K (2005) Understanding the reasons for parenthood. *Journal of Reproductive and Infant Psychology* 23 (2) 121-133.

Langer E J (1975) Illusion of Control. *Journal of Personality and Social Psychology* 32 (2) 311-328.

Latimer J (2007) Becoming in-formed: genetic counselling, ambiguity and choice. *Health Care Analysis* 15 (1) 13-23.

Laurence K M and Morris J (1981) The effect of the introduction of prenatal diagnosis on the reproductive history of women at increased risk from neural tube defects. *Prenatal Diagnosis* 1 (1) 51-60.

Lavery S A, Aurell R, Turner C, Castello C, Veiga A, Barri P N and Winston R M (2002) Preimplantation genetic diagnosis: patients' experiences and attitudes. *Human Reproduction*. 17 (9) 2464-2467.

Lawson K L (2001) Contemplating selective reproduction: the subjective appraisal of parenting a child with a disability. *Journal of Reproductive and Infant Psychology* 19 (1) 73-82.

Lawson K L (2006) Expectations of the parenting experience and willingness to consider selective termination for Down Syndrome. *Journal of Reproductive and Infant Psychology* 24 (1) 43-59.

Lawton J (2003) Lay experience of health and illness: past research and future agendas *Sociology of Health and Illness* 25, 23-40



- Leach-Scully J, Porz R and Rehmann-Sutter C (2007) You don't make genetic test decisions from one day to the next: Using time to preserve moral space. *Bioethics* 21 (4) 208-217.
- Lerman C, Croyle R T, Tercyak K P and Hamann H (2002) Genetic testing: psychological aspects and implications. *Journal of Consulting and Clinical Psychology* 70 (3) 784-797.
- Lin N (1999) Building a network theory of social capital. *Connections* 22(1) 28-51.
- Lippman A (1991) Prenatal Genetic Testing and Screening: Constructing Needs and Reinforcing Inequities. *American Journal of Law & Medicine* 17 (1-2) 15-50.
- Lippman A and Wilfond B S (1992) Twice-told tales: stories about genetic disorders. *American Journal of Human Genetics* 51 (4) 936-937.
- Lippman-Hand A and Fraser F C (1979a) Genetic counseling -- the postcounseling period: II. Making reproductive choices. *Am J Med Genet* 4 (1) 73-87.
- Lippman-Hand A and Fraser F C (1979b) Genetic counseling: parents' responses to uncertainty. *Birth Defects Orig Artic Ser* 15 (5C) 325-339.
- Lippman-Hand A and Fraser F C (1979c) Genetic counseling: provision and reception of information. *Am J Med Genet* 3 (2) 113-127.
- Lipshitz R, Klein G, Orasanu J and Salas E (2001) Focus article: Taking stock of naturalistic decision making. *Journal of Behavioral Decision Making* 14 (5) 331-352.
- Love D R, Forrest S M, Smith T J, England S, Flint T, Davies K E and Speer A (1989) Molecular analysis of Duchenne and Becker muscular dystrophies. *British Medical Bulletin* 45 (3) 659-680.
- Mahoney M J, Haseltine F P, Hobbins J C, Banker B Q, Caskey C T and Golbus M S (1977) Prenatal diagnosis of Duchenne's muscular dystrophy. *New England Journal of Medicine* 297 (18) 968-973.
- Makowski E L, Prem K A and Kaiser I H (1956) Detection of sex of fetuses by the incidence of sex chromatin body in nuclei of cells in amniotic fluid. *Science* 123 (3196) 542-543.
- Marshall G (1998) *Oxford Dictionary of Sociology*. Oxford: Oxford University Press.
- Marteau T M and Dormandy E (2001) Facilitating informed choice in prenatal testing: how well are we doing? *American Journal of Medical Genetics* 106 (3) 185-190.
- Marteau T and Richards M (2000) *The troubled helix: social and psychological consequences of the new human genetics*. Cambridge: Cambridge University Press.

Marteau T M and Weinman J (2006) Self-regulation and the behavioural response to DNA risk information: a theoretical analysis and framework for future research. *Social Science and Medicine* 62 (6) 1360-1368.

Marteau T M, Plenicar M, Kidd J (1993) Obstetricians presenting amniocentesis to pregnant women: practice observed. *Journal of Reproductive and Infant Psychology* 11 3-10.

Mason J (2006) Mixing methods in a qualitatively driven way. *Qualitative Research* 6(1) 9-25.

Mason K O (1997) Explaining fertility transitions. *Demography* 34 (4) 443-454.

McCabe L L, Therrell B L, Jr. and McCabe E R (2002) Newborn screening: rationale for a comprehensive, fully integrated public health system. *Molecular Genetics & Metabolism* 77 (4) 267-273.

McNicoll G (1980) Institutional determinants of fertility change. *Population and Development Review* 1 (1) 441-462.

Meldrum M (1998) "A Calculated Risk": the Salk polio vaccine field trials of 1954. *British Medical Journal* 317 1233-1256.

Merleau-Ponty M (1964) *The Primacy of Perception*. Evanston E J. (ed). Illinois: North-western University Press.

Meryash D L (1989) Perception of burden among at-risk women of raising a child with fragile-X syndrome. *Clinical Genetics* 36 (1) 15-24.

Michaels G, Goldberg W (1989) *The Transition to Parenthood: Current Theory and Research*. New York: Cambridge University Press.

Michie S and Marteau T (2000) "Genetic counselling: some issues of theory and practice". In Marteau T and Richards M. (eds). *The troubled Helix: social and psychological implications of the new human genetics*. Cambridge: Cambridge University Press.

Michie S, Bron F, Bobrow M and Marteau T M (1997a) Nondirectiveness in genetic counseling: an empirical study. *American Journal of Human Genetics* 60 (1) 40-47.

Michie S, Marteau T M and Bobrow M (1997b) Genetic counselling: the psychological impact of meeting patients' expectations. *Journal of Human Genetics* 34 (3) 237-241.

Michie S, Dormandy E and Marteau T M (2003) Informed choice: understanding knowledge in the context of screening uptake. *Patient Education and Counselling* 50 (3) 247-253.

Miller W and Pasta D (1995) Behavioral Intentions: Which ones predict fertility behavior in married couples? *Journal of Applied Social Psychology* 25 (6) 530-555.

Miller W B (1992) Personality traits and developmental experiences as antecedents of childbearing motivation. *Demography* 29 (2) 265-285.

Mishler E G (1984) The discourse of medicine: dialectics of medical interviews. Norwood, NJ: Ablex.

Mohamed K, Appleton R and Nicolaidis P (2000) Delayed diagnosis of Duchenne muscular dystrophy. *European Journal of Paediatrics and Neurology* 4 (5) 219-223.

Mohr J (1968) Foetal genetic diagnosis: development of techniques for early sampling of foetal cells. *Acta Pathologica et Microbiologica Scandinavica* 73 (1) 73-77.

Monaco A P, Bertelson C J, Liechti-Gallati S, Moser H and Kunkel L M (1988) An explanation for the phenotypic differences between patients bearing partial deletions of the DMD locus. *Genomics* 2 (1) 90-95.

Mooney, G (2003) *Economics, Medicine and Health Care*. Essex: Pearson Education Ltd.

Morgan D L (2007) Paradigms lost and pragmatism regained: Methodological implications of combining qualitative and quantitative methods. *Journal of Mixed Methods Research* 1(1) 48-76.

Morse J M (1991) Approaches to Qualitative-Quantitative Methodological Triangulation. *Nursing Research* 40 (2) 120-123.

Moser H (1983) Genetische Familienberatung. Ethische Gesichtspunkte. *Z Allg Medizin* 59 967-978.

Moser H and Vogt J (1974) Follow-up Study of Serum-Creatine-Kinase in Carriers of Duchenne Muscular-Dystrophy. *Lancet* 2 (7881) 661-662.

National Screening Committee (2003) Criteria for appraising the viability, effectiveness and appropriateness of a screening programme. [Online]. Available at: <http://www.library.nhs.uk/SCREENING/ViewResource.aspx?resID=314462&tabID=288> [Accessed 12<sup>th</sup> August 2008].

National Screening Committee (2005) Newborn screening [Online]. Available at: [http://www.ich.ucl.ac.uk/newborn/download/FullGuideline\\_website010208.pdf](http://www.ich.ucl.ac.uk/newborn/download/FullGuideline_website010208.pdf) [Accessed 11<sup>th</sup> August 2006].

National Screening Committee (2006) Newborn Screening Criteria. [Online]. Available at: <http://www.nsc.nhs.uk/pdfs/criteria.pdf> [Accessed 10<sup>th</sup> August 2006].

Nauck B (2007) Value of children and the framing of fertility: results from a cross-cultural comparative survey in 10 societies. *European Sociological Review* 23 (5) 615-629.

Nelson F, Tolmie J, van Mourik M (2009 Publication in progress) Fragile X Syndrome in pregnancy: Trends in Prenatal Diagnosis. Ferguson Smith Centre for Clinical Genetics, Yorkhill Hospitals. Glasgow. Scotland.

Nicholson G A, Pennington R J T, Gardnermedwin D and Walton J N (1979) Carrier Detection in Duchenne Muscular-Dystrophy: Assessment of the Effect of Age on Detection-Rate with Serum-Creatine-Kinase-Activity. *Lancet* 1 (8118) 692-694.

Nonestein F W (1945) "Population – the long view". In Schultz T. (ed). *Food for the World*. Chicago: University of Chicago Press.

Norman A M, Rogers C, Sibert J R and Harper P S (1989) Duchenne muscular dystrophy in Wales: a 15 year study, 1971 to 1986. *Journal of Medical Genetics* 26 (9) 560-564.

Office for National Statistics (2005) Mid-2005 Population Estimates. [Online]. Available at: <http://www.statistics.gov.uk/StatBase/ssdataset.asp?vlnk=9394&Pos=&ColRank=2&Rank=288> [Accessed 7<sup>th</sup> January 2006].

Office for National Statistics (2005) Rise in UK Fertility Continues. [Online]. Available at: [www.statistics.gov.uk/cci/nugget.asp?ID=951](http://www.statistics.gov.uk/cci/nugget.asp?ID=951) [Accessed 10th January 2006].

Office for National Statistic (2008) Social Trends. [Online]. Available at: [http://www.statistics.gov.uk/downloads/theme\\_social/Social\\_Trends37/Social\\_Trends\\_37.pdf](http://www.statistics.gov.uk/downloads/theme_social/Social_Trends37/Social_Trends_37.pdf) [Accessed on 10<sup>th</sup> January 2006].

Office for National Statistics (2008a) Fertility. [Online] Available at: <http://www.statistics.gov.uk/cci/nugget.asp?ID=951> [Accessed 10<sup>th</sup> January 2006]

Office for National Statistics (2008b) Birth interval between third and fourth child similar to that between first and second child. [Online]. Available at: <http://www.statistics.gov.uk/STATBASE/ssdataset.asp?vink=9555> [Accessed 10th January 2006].

Oliver M (1990) *The Politics of Disablement*. London: Macmillan.

Orasanu, J., Connolly, T. (1993), "The reinvention of decision making", in Klein, G.A., Orasanu, J., Calderwood, R., Zsombok, C.E. (Eds), *Decision Making in Action: Models and Methods*, Ablex Publishing Corporation, NJ, pp.3-21")

Palomaki G, Haddow J and Beauregard L (1996) Prenatal testing for Downs syndrome in Maine: 1980-1993. *New England Journal of Medicine* 334 1409-1410.

Parens E and Asch A (2003) Disability rights critique of prenatal genetic testing: reflections and recommendations. *Mental Retardation and Developmental Disability Research Reviews* 9 (1) 40-47.

- Parsons E and Atkinson P (1993) Genetic Risk and Reproduction. *Sociological Review* 41 (4) 679-706.
- Parsons E and Atkinson P (1992) Lay constructions of genetic risk. *Sociology of Health and Illness* 14 (4) 437-455.
- Parsons E P and Clarke A J (1993) Genetic risk: women's understanding of carrier risks in Duchenne muscular dystrophy. *Journal of Medical Genetics* 30 (7) 562-566.
- Parsons E P, Clarke A J and Bradley D M (2004) Developmental progress in Duchenne muscular dystrophy: lessons for earlier detection. *European Journal of Paediatrics and Neurology* 8 (3) 145-153.
- Parsons E P, Clarke A J, Hood K, Lycett E and Bradley D M (2002) Newborn screening for Duchenne muscular dystrophy: a psychosocial study. *Archives of Disease in Childhood Fetal & Neonatal Edition* 86 (2) F91-95.
- Parsons E P, Moore C, Israel J, Hood K and Bradley D M (2005) Emphasizing parental choice on newborn screening. *British Journal of Midwifery*. 13 (3) 165-168.
- Parsons E, Bradley D and Clarke A (1996) Disclosure of Duchenne muscular dystrophy after newborn screening. *Archive of Diseases in Childhood* 74 (6) 550-553.
- Parsons, E P, Clarke, A J, Bradley, D M (2003) Implications of carrier identification in newborn screening for cystic fibrosis. *Archive of Diseases in Childhood (Fetal Neonatal Edition)* 88 F467-471.
- Pauker S G and Pauker S P (1987) Prescriptive models to support decision making in genetics. *Birth Defects Original Article Series* 23 (2) 279-296.
- Pennington RJT (1980) Clinical biochemistry of muscular dystrophy. *British Medical Bulletin* 36 (2) 123-126 .
- Pfeffer N (1999) Who counts? Prepared for the seminar on Social Categories in Population Health, organised by the Committee on Anthropological Demography of the International Union for the Scientific Study of Population, 15-18 September 1999, Cairo, Egypt.
- Pierret, J (2003) The illness experience: state of knowledge and perspectives for research *Sociology of Health and Illness* 25, 4-22
- Plass, AMC., van El, CG., Pieters, T., Cornel, C (2009) Neonatal Screening for Treatable and Untreatable Disorders: Prospective Parents' Opinions *Paediatrics* 125 (1) e99-e106
- Plauchu H, Dorche C, Cordier M P, Guibaud P and Robert J M (1989) Duchenne muscular dystrophy: neonatal screening and prenatal diagnosis. *Lancet* 1 (8639) 669.
- Pollitt R J (1999) Principles and performance: assessing the evidence. *Acta Paediatrica Supplement* 88 (432) 110-114.

- Pollitt R J (2006) International perspectives on newborn screening. *Journal of Inherited Metabolic Disease* 29 (2-3) 390-396.
- Portes A (1998) Social capital: its origins and applications in modern sociology. *Annual Review of Sociology* 22 1- 24.
- Price N and Hawkins K (2002) Researching sexual and reproductive behaviour: a peer ethnographic approach. *Social Science & Medicine* 55 (8) 1325-1336.
- Purewal S and van den Akker O (2007) The socio-cultural and biological meaning of parenthood. *J Psychosom Obstetrics and Gynaecology* 28 (2) 79-86.
- Quine (1951) Two Dogmas of Empiricism. *Philosophical Review* 60 20–43.
- Raeburn J A (1995) Commentary: Preimplantation diagnosis raises a philosophical dilemma.[comment]. *British Medical Journal* 311 (7004) 540.
- Raiti S and Newns G H (1971) Cretinism: early diagnosis and its relation to mental prognosis. *Archives of Disease in Childhood* 46 (249) 692-694.
- Rapp (1999) *Testing Women, Testing the Fetus: The Social Impact of Amniocentesis in America*. London: Routledge.
- Rapp R (1988) “Moral pioneers: women, men and fetuses on a frontier of reproductive technology”. In Hoffman-Baruch E, D’Adamo A and Seager J. (eds). *Embryos, ethics and women’s rights: exploring new reproductive technologies*. New York: Harrington Park.
- Roberts R G, Barby T F, Manners E, Bobrow M and Bentley D R (1991) Direct detection of dystrophin gene rearrangements by analysis of dystrophin mRNA in peripheral blood lymphocytes. *American Journal of Human Genetics* 49 (2) 298-310.
- Rorty R (1979) *Philosophy and the Mirror of Nature*. Princeton: Princeton University Press.
- Rosenberg T, Jacobs H K, Thompson R and Horne J M (1993) Cost-effectiveness of neonatal screening for Duchenne muscular dystrophy: How does this compare to existing neonatal screening for metabolic disorders? *Social Science and Medicine* 37 (4)541-547.
- Roses A D, Nicholson G A and Roe C R (1977) Screening for Duchenne muscular dystrophy. *Pediatrics* 60 (2) 248-251.
- Ross L F (2006) Screening for conditions that do not meet the Wilson and Jungner criteria: the case of Duchenne muscular dystrophy. *American Journal of Medical Genetics. Part A* 140 (8) 914-922.
- Rothman (1994) *The Tentative Pregnancy: Amniocentesis and the sexual politics of motherhood*. London: Pandora.

Rothman A J, Salovey P, Antone C, Keough K and Martin C D (1993) The Influence of Message Framing on Intentions to Perform Health Behaviors. *Journal of Experimental Social Psychology* 29 (5) 408-433.

Rowe G and Frewer L J (2000) Public participation methods: A framework for evaluation. *Science Technology & Human Values* 25 (1) 3-29.

Royal College of Obstetricians and Gynaecologists (2005) Guideline No. 8: Amniocentesis and Chorionic Villus Sampling. [Online]. Available at: <http://www.rcog.org.uk/files/rcog-corp/uploaded-files/GT8AminiocentesisChorionicVillus2005.pdf> [Accessed 29<sup>th</sup> July 2009].

Sagi M, Shiloh S and Cohen T (1992) Application of the Health Belief Model in a study on parents' intentions to utilize prenatal diagnosis of cleft lip and/or palate. *American Journal of Medical Genetics* 44 (3) 326-333.

Samerski, S (2006) The unleashing of genetic terminology: how genetic counselling mobilizes for risk management *New Genetics and Society* 25 (2) 197-208

Sandelowski M and Barroso J (2005) The Travesty of Choosing After Positive Prenatal Diagnosis. *Journal of Obstetrics and Gynecology and Neonatal Nursing* 34 (3) 307-318.

Sanders K Y (2006) Overprotection and lowered expectations of persons with disabilities: the unforeseen consequences. *Work* 27 (2) 181-188.

Sanfey A G (2007) Social decision-making: insights from game theory and neuroscience. *Science* 318 (5850) 598-602.

Sanfey A G, Loewenstein G, McClure S M and Cohen J D (2006) Neuroeconomics: cross-currents in research on decision-making. *Trends in Cognitive Sciences* 10 (3) 108-116.

Santalahti P, Aro A R, Hemminki E, Helenius H and Ryyanen M (1998) On what grounds do women participate in prenatal screening? *Prenatal Diagnosis* 18 (2) 153-165.

Sartre J P (1969) Itinerary of a Thought. *New Left Review* 58 43-66.

Sartre J P (1982) *Critique of Dialectic Reason 1: Theory of Practical Ensembles*. London: Verso.

Savage L J (1954) *The Foundations of Statistics*. New York: Wiley.

Schapira F, Dreyfus J C, Schapira G and Demos J (1960) Etude De Laldolase Et De La Creatine Kinase Du Serum Chez Les Meres De Myopathes. *Revue Francaise D Etudes Cliniques Et Biologiques* 5 (10) 990-994.

Scheuerbrandt G, Lundin A, Lovgren T and Mortier W (1986) Screening for Duchenne Muscular-Dystrophy: an Improved Screening-Test for Creatine-Kinase and Its Application in an Infant Screening-Program. *Muscle & Nerve* 9 (1) 11-23.

Scheuerbrandt G, Beckmann R and Pongratz D (1977) Prenatal diagnosis of Duchenne's muscular dystrophy. *Lancet* i 1359-1360

Schoen R, Astone N M, Kim Y J, Nathanson C A and Fields J M (1999) Do fertility intentions affect fertility behaviour? *Journal of Marriage and the Family* 61 (3) 790-799.

Schouten J P, McElgunn C J, Waaijer R, Zwijnenburg D, Diepvens F and Pals G (2002) Relative quantification of 40 nucleic acid sequences by multiplex ligation-dependent probe amplification. *Nucleic Acids Research* 30 (12) e57.

Schutz A (1967) *The Phenomenology of the Social World*. Illinois: Northwestern University Press.

Schutz A (1973) *Collected Papers*. Volume 1. Natanson M (ed). The Hague: Martinus Nijhoff.

Scott R (2005) Prenatal testing, reproductive autonomy and disability interests. *Cambridge Quarterly of Healthcare Ethics* 14 (1) 65-82.

Searle J (1995) *The construction of social reality*. New York: The Free Press.

Serr D M, Sachs L and Danon M (1955) The diagnosis of sex before birth using cells from the amniotic fluid (a preliminary report). *Bulletin of the Research Council of Israel* 5B (2) 137-138.

Shakespeare, T (2008) *Disability Rights and Wrongs*. Cornwall: Routledge.

Shettles L B (1956) Nuclear morphology of cells in human amniotic fluid in relation to sex of infant. *American Journal of Obstetrics & Gynecology* 71 (4) 834-838.

Shiffman J, Beer T and Wu Y (2002) The emergence of global disease control priorities. *Health Policy Planning*, 17(3) 225-234.

Shiloh S (2000) "Decision-making in the context of genetic risk". In Marteau T, Richards M. (eds). *The troubled helix: social and psychological consequences of the new human genetics*. Cambridge: Cambridge University Press.

Shiloh S and Sagi M (1989) Effect of framing on the perception of genetic recurrence risks. *American Journal of Human Genetics* 33 (1) 130-135.

Shiloh S, Salton E and Sharabi D (2002) Individual differences in rational and intuitive thinking styles as predictors of heuristic responses and framing effects. *Personality and Individual Differences* 32 (3) 415-429.

Shiloh S, Saxe L (1989) Perception of recurrence risks by genetic counselees. *Psychology and Health* 3: 45-61.



Silverman D (2000) *Doing Qualitative Research: a Practical Handbook*. London: Sage

Silverman D (2006) "Introducing Qualitative Research". In Silverman D. (ed). *Qualitative Research: Theory, Method and Practice*. London: Sage.

Simon H A (1978) Rationality as a process and as a product of thought. *American Economic Association* (68) 1-16

Simoni G, Brambati B, Danesino C, Rossella F, Terzoli G L, Ferrari M and Fraccaro M (1983) Efficient direct chromosome analyses and enzyme determinations from chorionic villi samples in the first trimester of pregnancy. *Journal of Human Genetics* 63 (4) 349-357.

Skinner R and Emery A E (1974) Letter: Serum-creatine-kinase levels in carriers of Becker muscular dystrophy. *Lancet* 2 (7887) 1023-1024.

Skinner R, Emery A E, Scheuerbrandt G and Syme J (1982) Feasibility of neonatal screening for Duchenne muscular dystrophy. *Journal of Medical Genetics* 19 (1) 1-3.

Smith R A, Sibert J R, Wallace S J and Harper P S (1989) Early diagnosis and secondary prevention of Duchenne muscular dystrophy. *Archive of Diseases in Childhood* 64 (6) 787-790.

Smith R A, Williams D K, Sibert J R and Harper P S (1990) Attitudes of mothers to neonatal screening for Duchenne muscular dystrophy. *British Medical Journal* 300 (6732) 1112.

Soini S, Ibarreta D, Anastasiadou V, Ayme S, Braga S, Cornel M, Coviello D A, Evers-Kiebooms G, Geraedts J, Gianaroli L, Harper J, Kosztolanyi G, Lundin K, Rodrigues-Cerezo E, Sermon K, Sequeiros J, Tranebjaerg L and Kaariainen H (2006) The interface between assisted reproductive technologies and genetics: technical, social, ethical and legal issues. *European Journal of Human Genetics* 14 (5) 588-645.

Sonsenstein F, Goldberg H, Lamberty G, Newcomer S, Miller W (1997) Fertility motivation, decision-making, and intention to engage in sex, contraception, pregnancy, abortion and birth. Prepared for the NICHD workshop *Improving Data on Male Fertility and Family Formation*, at the Urban Institute, Washington DC, January 16-17. [Online] Available at <http://fatherhood.hhs.gov/cfsforum/apend.htm> [accessed 16th December 2006]

Sorenson J, Kavanagh C, Mucatel M (1981) Client learning of risk and diagnosis in genetic counselling. *Birth Defects: Original Articles Series* 17: 215-218

Sorenson J R, Scotch N A, Swazey J P, Wertz D C and Heeren T C (1987) Reproductive Plans of Genetic-Counseling Clients Not Eligible for Prenatal-Diagnosis. *American Journal of Medical Genetics* 28 (2) 345-352.

Specht L A, Kunkel L M (1993) Duchenne and Becker Muscular Dystrophies, In Rosenberg Prusiner SB, DiMauro S, Barchi RL, Kunkel LM, (eds). *The Molecular and Genetic Basis of Neurological Disease*. Boston: Butterworth-Heinemann.

- Statham H (2002) Prenatal diagnosis of fetal abnormality: the decision to terminate the pregnancy and the psychological consequences. *Fetal and Maternal Medicine Review* 13 (4) 213-247.
- Stengel-Rutowski L, Scheuerbrandt G, Beckmann R, and Pongratz D (1977) Prenatal diagnosis of Duchenne muscular dystrophy. *Lancet* 2 (8048) 1115-1116.
- Stokes P (2006) *Philosophy: 100 Essential Thinkers*. London: Arcturus.
- Strauss A and Corbin J (1990) *Basics of qualitative research: Grounded theory procedures and techniques*. Newbury Park, CA: Sage.
- Strauss A and Corbin J (1998) *Basics of qualitative research: Techniques and procedures for developing grounded theory*. Second Edition. Thousand Oaks, CA: Sage.
- Stuart F (2006) Ethics of newborn screening *Current Paediatrics* (16) 216-220
- Styron W (1979) *Sophies Choice*. New York: Random House.
- Teddlie C and Tashakkori A (2003) "Major issues and controversies in the use of mixed methods in the social and behavioural sciences". In Tashakkori A and Teddlie C. (eds). *Handbook of Mixed Methods in Social and Behavioural Research*. London: Sage.
- Tercyak K P, Johnson S B, Roberts S F and Cruz A C (2001) Psychological response to prenatal genetic counseling and amniocentesis. *Patient Education and Counselling* 43 (1) 73-84.
- Therrell B L, Jr. (2001) U.S. newborn screening policy dilemmas for the twenty-first century. *Molecular Genetics & Metabolism* 74 (1-2) 64-74.
- Thompson M W, Murphy E G and McAlpine P J (1967) An assessment of the creatine kinase test in the detection of carriers of Duchenne muscular dystrophy. *Journal of Pediatrics* 71 (1) 82-93.
- Thompson W (1929) Population. *American Journal of Sociology* 34 (6) 969-975.
- Townsend P and Davidson N (1982) *Inequalities in Health: The Black Report*. Harmondsworth: Penguin Books Ltd.
- Tversky A and Kahneman D (1974) Judgment under Uncertainty: Heuristics and Biases. *Science* 185 (4157) 1124-1131.
- Tyrrell D A (1997) Polymerase chain reaction. *British Medical Journal* 314 (7073) 5-6.
- Ullman S, Nelson L B and Jackson L G (1985) Prenatal diagnostic techniques: Chorionic villus sampling. *Survey of Ophthalmology* 30 (1) 33-40.

Van Ommen G J and Scheuerbrandt G (1993) Neonatal screening for muscular dystrophy: Consensus recommendation of the 14th workshop sponsored by the European Neuromuscular Center (ENMC). *Neuromuscular Disorders* 3 (3) 231-239.

Vehmas S (2001) Just ignore it? Parents and genetic information. *Theoretical Medicine and Bioethics* 22 (5) 473-484.

Vergeer M M, van Balen F and Ketting E (1998) Preimplantation genetic diagnosis as an alternative to amniocentesis and chorionic villus sampling: psychosocial and ethical aspects. *Patient Education and Counselling* 35 (1) 5-13.

Verp M S, Bombard A T, Simpson J L and Elias S (1988) Parental decision following prenatal diagnosis of fetal chromosome abnormality. *American Journal of Medical Genetics* 29 (3) 613-622.

Von der Lippe H (2006). On the psychological determinants of fertility: A panorama of concepts and approaches, and evidence from eastern Germany. MPIDR Working Paper WP-2006-050. Rostock: Max-Planck-Institut für demografische Forschung.

Walton J N (1969) Carrier detection in X-linked muscular dystrophy. *Journal of Human Genetics*. 17 (3) 497-510.

Walton J N (1974) *Disorders of Voluntary Muscle*, 3rd ed, London: Churchill Livingstone.

Ward R H, Modell B, Petrou M, Karagözü F and Douratsos E (1983). Method of sampling chorionic villi in first trimester of pregnancy under guidance of real time ultrasound. *British Medical Journal (Clin Res Ed)*. May 14 1983 286 (6377) 1542-1544.

Wendt L V (1979) Nonketotic hyperglycinemia: A genetic study of 13 Finnish families. *Clinical Genetics* 15 (5) 411-417.

Wharton B A (1976) Duchenne muscular dystrophy: early diagnosis, and screening. *Archives of Disease in Childhood* 51 (12) 982-986.

White-Van Mourik M C, Connor J M and Ferguson-Smith M A (1990) Patient care before and after termination of pregnancy for neural tube defects. *Prenatal Diagnosis* 10 (8) 497-505.

Wilcken B (2007) Recent advances in newborn screening. *Journal of Inherited Metabolic Disease* 30 (2) 129-133.

Wilcken B (2008) The consequences of extended newborn screening programmes: Do we know who needs treatment? *Journal of Inherited Metabolic Disease* 31 (2) 173-177.

Williams C, Alderson P and Farsides B (2002a) Too many choices? Hospital and community staff reflect on the future of prenatal screening. *Social Science & Medicine* 55 (5) 743-753.

Williams C, Alderson P and Farsides B (2002b) What constitutes 'balanced information in the practitioners portrayals of Down's syndrome? *Midwifery* (18) 230-270

Williams G (1984) The genesis of chronic illness: narrative reconstruction *Sociology of Health and Illness* 6 (2) 175-199

Wilson JMG and Jungner G (1968) Principles and practice of screening for disease. Public health papers no. 34. Geneva: World Health Organization

Wood Harper and Harris J (2000) "Ethics of human genome analysis: some virtues and vices" in In Marteau T, Richards M. (eds). *The troubled helix: social and psychological consequences of the new human genetics*. Cambridge: Cambridge University Press.

World Health Organisation (1948) Preamble to the Constitution of the World Health Organisation as adopted by the International Health Conference, New York, 19 June-22 July 1946; signed on 22<sup>nd</sup> July 1946 by the representatives of 61 States (Official Records of the World Health Organisation, no.2, p.100) and entered into force on 7<sup>th</sup> April 1948. [Online]. Available from: [www.who.int/suggestions/faq/en/index.html](http://www.who.int/suggestions/faq/en/index.html) [Accessed 2<sup>nd</sup> September 2007].

World Health Organization (1968) Scientific Group on Screening for Inborn Errors of Metabolism: Screening for inborn errors of metabolism. *World Health Organization Technical Report Series* 401 1-57.

Worton R G (1990) Does Research Success in Duchenne-Becker Muscular-Dystrophy Now Warrant Neonatal Mass-Screening: the Perspective of a Molecular Biologist. *Genetic Screening from Newborns to DNA Typing* 901 197-202.

Yau S C, Bobrow M, Mathew C G and Abbs S J (1996) Accurate diagnosis of carriers of deletions and duplications in Duchenne/Becker muscular dystrophy by fluorescent dosage analysis. *Journal of Medical Genetics* 33 (7) 550-558.

Young I D (2005) *Medical Genetics*. Oxford: Oxford University Press.

Zellweger H and Antonik A (1975) Newborn screening for Duchenne muscular dystrophy. *Pediatrics* 55 (1) 30-34.

Zellweger H, Simpson J and Ionasescu V (1982) Twenty years-Iowa muscle clinic: reminiscences and prospects. *European Journal of Pediatrics* 138 (1) 17-22.