

Array Comparative Genomic Hybridisation and the Newborn Intensive Care Unit: Sociological Perspectives on Mainstreaming Medical Genetics

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This thesis is submitted to Cardiff University in fulfillment for the degree of Doctor of
Philosophy

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Declarations

This work has not been submitted in substance for any other degree or award at this or any other university or place of learning, nor is being submitted concurrently in candidature for any other degree or award.

Signed Katherine Burke

Date 21st June 2019

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This thesis is being submitted in partial fulfillment of the requirements for the degree of PhD

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Abstract

This thesis presents the findings of a UK-based ethnography of the mainstreaming of array comparative genomic hybridisation in the neonatal intensive care unit. Mainstreaming refers to the strategies employed to embed genetic/genomic technologies for patient benefit, incorporating genome-wide methods in everyday, mundane clinical work, beyond the specialist genetic realm. It draws on observations in the laboratory and the clinic alongside interviews with members of the extended bioclinical collective (Bourett, 2005). This constructs an ethnography of the activity of *doing* chromosomal microarray (Mol, 2002). I describe how three important traditions in sociological thought – namely (medical) uncertainty, processes of classification and categorisation and expertise – can be applied to the activity of mainstreaming. In the laboratory, I explore the role of standardisation and how despite calls for rigid adherence to technical rules, it is the subversion of standards – through appeals to expertise – that renders the technology workable for the messy clinical context. I continue by describing the dividing practices of the clinic, which designate infants as (potentially) genetically problematic, demonstrating how discourses between professionals and with parents serve to seek the assent of parents for chromosomal microarray testing through a highly directive process. I show how rhetorical discourse devices are used in ‘consent conversations’ as a tool in information sharing and as a means of persuasion. For the parents of infants having aCGH testing, uncertainty around decisions to test and the information genetic testing can generate are woven into personal narratives of restitution, chaos and quest (Frank, 1995). I conclude by reflecting upon how the ability and means by which uncertainty is tolerated differs vastly between the laboratory, the clinic and the family and the way in which diverging practices enact ontology in medicine as bound to specific sites and situations (Mol, 2002).

Abbreviations

aCGH	Array comparative genomic hybridisation
ADA	American Diabetic Association
ANNP	Advanced neonatal nurse practitioner
ACMGG	American College of Medical Genetics and Genomics
BRCA1/2	Breast Cancer gene 1 and 2 (tumour suppressor gene)
BSHG	British Society Human Genetics
CBAVD	Congenital Bilateral Absence of the Vas Deferens
CEQA(S)	Cytogenetic European Quality Assessment (Service)
CF	Cystic Fibrosis
CFTR	Cystic Fibrosis Transmembrane Conduction Regulator
CG	Clinical geneticist
CMA	Chromosomal microarray
CNV	Copy number variation
CVS	Chorionic villous sampling
DECIPHER	Database of sub-chromosomal imbalances
DGV	Database of Genomic Variants
DNA	Deoxyribonucleic acid
ECF	Extreme Case Formulation
ECS	Extreme Case Scenario
EQ	External Quality
GPwSI	General Practitioner with a Specialist Interest
HDU	High Dependency Unit
IF	Incidental findings
ISCA	International Standard Cytogenomic Array
IUGR	Intrauterine Growth Restriction
ITU	Intensive Care Unit
MG	Medical geneticist
NC	Neonatal Consultant
NE-QAS	National External Quality Assessment Service
NHS	National Health Service
NICU	Neonatal Intensive Care Unit
NIPE	Newborn Infant Physical Examination
NIPT	Non invasive prenatal testing
NR	Neonatal Registrar
NSHO	Neonatal Senior House Officer
PhD	Doctor of Philosophy
PHG	Public Health Genomics Foundation
PMETB	Postgraduate Medical Education and Training Board
QC	Quality Control
QF-PCR	Quantitative Florescence Polymerase Chain Reaction
RCPCH	Royal College of Paediatrics and Child Health
SCOT	Social Construction of Technology
SHO	Senior House Officer
SOP	Standard Operating Procedure
SSK	Sociology of Scientific Knowledge
UK	United Kingdom

UKAS	United Kingdom Accreditation Service
US	United States
VHL	Von Hippel Lindau
VOUS	Variant of unknown or uncertain significance
VUS	Variant of unknown or uncertain significance
WHO	World Health Organisation
WGS	Whole Genome Sequencing
WES	Whole Exome Sequencing

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Chapter One: Introduction

This research considers how 'new' genetic technologies are incorporated in 'non-expert' clinical practice in the National Health Service setting. Using ethnography, it examines the introduction of array comparative genomic hybridisation (aCGH) as a first-line genetic test in the Neonatal Intensive Care Unit. This work largely falls within the constructivist tradition in sociology, and more specifically, the Social Construction of Technology (SCOT), whilst also drawing on literature from the philosophy of science and policy-orientated, cross-disciplinary work on uncertainty.

The introduction outlines my own background as a paediatrician using genetic technologies before outlining the core research questions. I then foreground the empirical data in situating the study within the broader context, particularly with respect to the current status of clinical medical genetics within the National Health Service, and the 'mainstreaming' medical genetics agenda. The particular significance of the work is discussed with respect to genetic testing as a complex social activity. I conclude by providing a justification of the literature included in the empirical foregrounding, before moving on to an outline of the thesis chapters.

Uncertainty is ubiquitous in medicine (Ghosh, 2004). The study of 'medical uncertainty' extends conceptually between disciplinary boundaries: medical sociology, philosophy, linguistics and communication, along with the science and practice of medicine all provide perspectives on the constitution and enactment of 'medical uncertainty'. Many core concepts from the literature on medical uncertainty have been extended seamlessly to encompass genetic - and more recently - genomic¹ uncertainty. Arising from this uncertainty are bioethical, legal, sociological, philosophical and practical empirical perspectives. Uncertainty is characterised as an undesirable side-effect of our increasing testing capabilities and of genetic/genomic knowledge: a property to be characterised, managed and reduced, lest it impede the rate at which innovations can transition from bench to bedside (Khoury et al., 2012).

¹ Though frequently used interchangeably, the terms genetics and genomics have different meanings. Genetics is the study of heredity with its basis in the targeted examination of limited regions of the genome with known function and structure, usually a protein-coding gene (WHO, 2002). Genomics is the study of genes, their functions and related techniques (WHO, 2004, see http://apps.who.int/gb/ebwha/pdf_files/WHA57/A57_R13-en.pdf). This distinction is less useful than considering the notion of genome-wide testing, encompassing aCGH as well as sequencing technologies, albeit at different resolutions. Whilst genetics seeks to scrutinise the function and composition of single genes, genomics addresses all of the genes and their inter-relatedness both within the genome and with complex environmental or non-genetic factors (epigenetics), although the clinical utility of this is yet to be realised. For the purposes of this thesis, I will primarily use 'genetic', in recognition of the vernacular preference for using 'genomic' in relation primarily to sequencing-based – rather than dosage- technologies.

Yet empirical, situated studies of genetic/genomic uncertainty are limited, and the concepts poorly developed. Where does uncertainty arise? How does it manifest? What are the consequences for those populations using the technology? How do organisational and relational structures exacerbate and ease the causes and consequences of uncertainty? Extending methodologies employed by Social Construction of Technology theory, this study is an ethnography of the uncertainty arising from the introduction and use of array comparative genomic hybridisation (aCGH) in a Neonatal Intensive Care Unit. The period of implementation for a new technology into the work of a community is a valuable time during which to explore the role of the technology itself: the articulation of assumptions that accompanies the assimilation of new technologies and ways of working is quickly lost when a technology is routinised in practice (Berg, 1997; De Laet and Mol, 2000; Suchman, 2007).

Being a paediatrician, using genetic tests

My interest in this subject emerged during my employment as a junior doctor in paediatric medicine. The five years I had spent practicing and training as a paediatrician (and the two years prior to that spent in the adult medical setting) had taken me through various places of paediatric 'medical work' (Atkinson, 1995): the neonatal intensive care unit, the children's ward in both small, district general hospitals and large, tertiary referral centres and the out-patient clinics based in both hospitals and 'children's centres', community based, multi-disciplinary clinics for the care and assessment of children with mainly developmental and behavioural pathologies. It was during a placement in a children's center as a very junior paediatrician that my interest in this particular area emerged. In this role, I was responsible for the day-to-day running of an 'assessment nursery'², a novel clinical setting in which children identified as having delayed or disordered development would attend a 'day-care like' environment. Here, they would undergo formal assessment by a range of educational, medical and allied health professionals³, with the aim of establishing a diagnosis and in order to plan and initiate further care, particularly with respect to their educational and developmental needs. My responsibility was to oversee the progress of each child through a series of assessments and investigations in accordance with local protocols, aimed at establishing (or excluding) relevant diagnoses, particularly for children with developmental delay.

² As far as I am aware from further research, the area I worked in at the time was the only region providing this sort of comprehensive service for children presenting with disordered or delayed development. It appeared just like a nursery school, facilitated by early years teaching staff who provided assessments on children's interaction, play, motor skills, social skills and speech and language skills.

³ Those involved included medical staff (paediatricians, neurologists), physiotherapists, occupational therapists, speech and language therapists, parenting support workers, health visitors, educational psychologists and early years practitioners from the Child and Adolescent Mental Health Service, among others.

During my six months in this role, the ‘first line’ genetic investigation offered to these families changed from karyotyping to array comparative genomic hybridization (aCGH)⁴, as aCGH became available through the local genetics service for use by paediatricians, rather than just genetic specialists. Relatively soon after the technology was introduced, a child undergoing the investigation in the assessment nursery was found to have a variant of unknown significance in a cancer predisposition gene, necessitating referral to the local tertiary genetics service for further investigation. This would include assessment by clinical geneticists and, later, the testing of parents and siblings. The paediatrician who had initiated this investigation - and had negotiated consent with the family to perform aCGH - was troubled by this. She felt she had provided inadequate information about the scope of the test and its potential implications. The parents were understandably concerned and confused about how - in the process of investigating the delayed development of their child with autistic-like behaviour - we were now pre-occupied and concerned about the possibility of a cancer predisposition syndrome.

Two things became clear through this case. Firstly, the need for better information provision and professional consensus with respect to what constitutes ‘adequately informed’ (a central tenet of informed consent) when discussing investigations with parents and families. Secondly, the need for clinician education when new technologies, investigations and treatments become available. Following on from this challenging case, I presented a rudimentary assessment of the consent documentation as it related to aCGH testing at a national meeting of paediatricians⁵. For me personally it highlighted the need for maintaining knowledge of new technologies impacting on practice – throughout the professional enculturation of ‘becoming a doctor’, it is often repeated that you ‘don’t ever take consent for a procedure you are not able to perform’, yet this had not been logically extended to taking consent for investigations you may not have much experience or knowledge of. When the opportunity to undertake a structured research project became available, this matter seemed a logical and interesting subject of study – how do non-specialists talk to parents and families about investigations with which they are relatively unfamiliar? It was my insider status that largely served as the ethnographic beginning: prior to formal entry into the field, my whole role was in fact ‘preliminary field-work ... exploration, reflexivity, creativity, mutual exchange and interaction through the establishment of research relationships with local people’ (Caine et al, 2009: 491).

⁴ Comparative genomic hybridization is often abbreviated to ‘array’ or ‘microarray’ or ‘chromosomal microarray’ (‘CMA’), or can be known as ‘CGH’, ‘CGH array’ or ‘array CGH’. The terms and abbreviations will be used interchangeably throughout.

⁵ Presented as an abstract (see Appendix A) - Consent for Genetic Investigations in the Community Paediatric Setting: A Snapshot of Current Practice. Burke, K and Brooks, J., North Bristol NHS Trust, Bristol, UK. Presented at the Royal College of Paediatrics and Child Health Annual Conference, Glasgow, UK, 2012, http://adc.bmj.com/content/97/Suppl_1/A71.2.full.pdf+html?sid=699b592b-1ce1-48ac-89d1-303adb36ccf2

Research Questions

The central aim of this study is to explore experiences of, and responses to, the introduction of a new genetic technology, namely array comparative genomic hybridization, in a novel medical setting – the neonatal intensive care unit. The contribution of this work is to the mainstreaming debate, with the introduction of chromosomal microarray representing an early example of mainstreaming-in-practice. Particularly, I focus on the use of chromosomal microarray technology by a new, non-expert, community of practitioners, namely paediatricians, and their management of uncertainty. Ethnographic observations, and interview accounts (with laboratory staff, clinicians and parents) will broadly address two key questions:

How do professionals and families negotiate the complexities of engaging with a new health technology (chromosomal microarray) as it transitions (mainstreams) from a specialist, expert setting (medical genetics), to a general, non-expert setting (newborn intensive care)?

What are the consequences for the individuals and populations around this technology?

What are the situated responses to uncertainty that arise with the application of aCGH technology in the neonatal setting?

Where does uncertainty arise? How does it manifest?

How do organisational and relational structures exacerbate and ease the cause and consequence of this uncertainty?

Describing the newborn intensive care setting as ‘general’ or ‘non-expert’ refers exclusively to the relationship between this specific place of medical work and the relationship it has with the professional medical specialism of medical genetics. In this sense, it is general as it forms one of a multitude of sites in which ‘mainstreaming’ is underway to embed genetic technology in the routine, every day work of the site.

The Context

What is Comparative Genomic Hybridization?

Cytogenetics is the study of the morphology of chromosomes. Human chromosome visualisation has been an important subject of study for cytogeneticists since the early 20th century. Following the improved techniques that permitted the confirmation of the human chromosome number as 46 (Tijo and Levan, 1956), there was a rapid proliferation in the description of human chromosome aberrations in association with described clinical phenotypes or syndromes such as trisomy 21

(Lejeune et al., 1959) and the sex chromosome abnormalities Turner (Ford et al., 1959) and Klinefelter syndromes (Jacobs et al., 1959). Karyotyping provided the means by which to examine the number and structural appearance of the chromosomes in a species or an individual organism. Cells (usually white blood cells) are arrested during cell division (usually by the application of colchicine to cells in metaphase or prometaphase) when the chromosomes are most condensed and therefore most easily visualised and stained, usually using Giemsa, to allow differentiation. These are then directly visualised using light microscopy with alterations to chromosome structure and number observed and recorded.

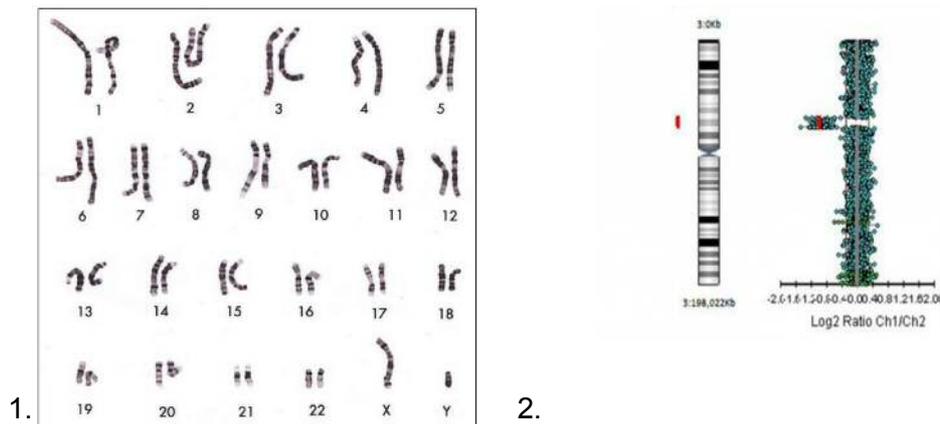


Figure One and Two: Representations of the human chromosome as facilitated through different methods. Image one shows a human karyotype (G banded staining). Image two demonstrates the appearance of a single human chromosome as displayed in chromosomal microarray analysis: the first image a karyogram, displaying the banding patterns with the red line displaying an area of copy number variation (deletion). The corresponding adjacent image displays the same chromosome with each dot representing the position of an oligo, or probe as applied during the microarray analysis.

In comparative genomic hybridization, patient DNA, extracted from white blood cells from whole blood samples, and control DNA are co-hybridized to normal metaphases. Computer-mediated comparisons of the fluorescent intensities at each locus are made in parallel by scanning along each chromosome. Where there is no difference, the patient and control DNA have the gene present in equal number. Where there is a difference in fluorescent intensity, an imbalance may be present. Increases in the copy number of genes are duplications, illustrated in the array by a predominance of subject DNA colour. Decreases in gene copy number – deletions – are identified by a predominance of control DNA colour. Array-CGH (aCGH) is a development of this method where control and test (patient) DNA are hybridized to DNA spotted onto slides (also known as chips). Each of these spots contains DNA from marker sequences on the human genome database, chosen to represent loci along each chromosome – densely packed at points of clinical interest, and more broadly spaced in non-coding regions, which are less likely to contain genes associated with disease.

Microarray testing is limited in its ability to identify balanced structural changes, such as translocations and inversions: as a dosage method, aCGH testing is limited to identifying changes in the amount of genetic material at a particular locus. Where structural changes are balanced in nature, meaning there is no loss or gain of genetic material at a particular locus (as in the case of a translocation or inversion of a region of a chromosome), conventional karyotyping or, sometimes, chromosome painting, may provide the best means by which to make a diagnosis. Similarly, aCGH is limited in its ability to detect mosaicism: the presence of two (or more) populations of cells with different genotypes in one individual.

Practical challenges – likely to reduce with experience and further research – relate to how information about the significance of gene copy number variation (CNV) continues to emerge, requiring a constant – and consistent – balance between over-interpreting the causal significance of copy number variation in association with particular clinical phenotypes on the one hand (Vermeesch et al., 2011), and dismissing the (potential) significance of a copy number variant (which may have variable penetrance) merely because it is found in healthy individuals, on the other. Similarly, copy number variation may contribute to disease or developmental disorder through complex mechanisms not currently understood (Girirajan et al., 2010). These complexities have resulted in guidance around the design of arrays, in addition to the sensitivity and specificity considerations in analysis and the interpretation of results (O’Leary and Zimern, 2010; Manning et al., 2010).

The literature supporting the increased diagnostic yield of aCGH technology developed quickly for a heterogeneous disease group: syndromic mental retardation (Shaw-Smith et al., 2004; de Vries et al., 2005), autism associated with other features, such as intellectual disability (Sebat et al., 2007), isolated heart defects (Erdogan et al., 2008), syndromic craniosynostosis (Krepischi-Santos et al., 2006) and isolated neuropsychiatric conditions including autism and schizophrenia (Weiss et al., 2008). As such, support for array CGH as a first-line diagnostic investigation in the clinical setting quickly gathered pace. The publication by the Public Health Genomics Foundation of the paper ‘Evaluation of aCGH for chromosomal abnormalities in clinical practice’ (Burton et al., 2006) supported the approach of replacing traditional karyotyping with microarray, followed by a consensus statement from the International Standard Cytogenomic Array (Miller et al., 2010). As a high-throughput genetic technology, it is highly automated and less time consuming than conventional karyotyping, ultimately contributing to the cost effectiveness when undertaken at scale.

‘Mainstreaming Medical Genetics’

Fuelled by the successful completion of the Human Genome Project, the 2003 UK government White Paper, 'Our Inheritance, Our Future: realising the potential of genetics in the NHS' (NHS, 2003) provided an outline of how genetic technologies and knowledge could be translated for clinical care. 'Mainstreaming' refers to the strategies employed to most effectively use genomic knowledge and technologies to benefit patients across medical specialties in which they may receive their care, incorporating 'genetic work'⁶ into the standard practices of medicine. Primarily, this involves transferring the responsibility for diagnostic testing⁷ – including the responsibility for financing this – to specialties other than Clinical Genetics, such as Paediatrics.

In 2011, the Public Health Genomics Foundation updated this vision in 'Genetics and Mainstream Medicine: service development and integration' (Burton et al., 2011), which sought to 'set out a strategy for the most effective use of genomic knowledge and technologies to benefit patients in different clinical specialties'. Particularly pertinent was the acknowledgement that 'diffusion' from clinical genetics to other areas would be insufficient, and that mainstream medicine must 'incorporate' genetics into their own standard practices, with regional genetics services taking a leadership role in this. The transfer of expertise from the specialist (genetic) to the general (medical) domain is explicit in policy orientated to realising the potential of genetic medicine. Whilst specialist genetics services often work closely with specialties to provide coordinated patient care - through initiatives such as combined clinics aimed at integrating services - this agenda represents a significant change in the relationships between professions and specialties, resulting in new roles and responsibilities in the organisation of services which cross and merge traditional boundaries and cultures.

The Significance

Genetic testing is 'more than a laboratory procedure; it is a complex social activity' (Arribas-Ayllon et al., 2011:1). This section builds upon the context in which clinical microarray testing is performed, describing the significance of the research undertaken with particular respect to the typologies of results which can be generated by genome-wide methods (and the prevalence of these results in this context), the challenge of consent and the role of genetic expertise.

⁶ The notion of '*genetic work*' presented throughout the thesis unabashedly builds upon and extends the concept of '*medical work*' as described by Atkinson (1995), the intersection of the highly-situated material, social and technical tasks enacted in the provision of clinical care.

⁷ Diagnostic testing refers to testing for individuals who already have signs or symptoms of a medical or developmental condition with the aim of establishing a genetic diagnosis. The testing observed as part of this project was all diagnostic in nature, as the infants all had disordered development or disease of a potential genetic cause. Pre-symptomatic or predictive testing refers to the testing of individuals who are currently healthy, but who are deemed at risk of having a particular condition (usually based on family history information).

The types and categories of 'findings' from aCGH testing

Array comparative genomic hybridization can generate multiple types, or categories, of results, each with their own inherent ethical and social considerations.

Confirmation of a clinical diagnosis: a 'positive result'

Where a phenotype of a patient is suggestive of a particular genetic diagnosis, performing a genetic test is employed to answer a specific clinical question: do the clinical features (the phenotype) correlate with the anticipated genetic mutation (the genotype), confirming a clinical diagnosis? As described earlier, a positive, diagnostic result generated by aCGH means that a duplication or deletion in the gene copy number known to be associated with a specific clinical correlate has been identified. Testing reveals a known pathogenic variant and the clinical diagnosis can be confirmed. An example of this is testing a neonatal patient for 22q deletion when they are known to have congenital cardiac anomalies, palatal abnormalities and hypocalcaemia. Testing, using aCGH, identifies a pathogenic deletion at 22q11.2, confirming the diagnosis.

Making a diagnosis can enable the right treatment to be initiated, prevent other (potentially more invasive) tests and curtail a 'diagnostic Odyssey'. It can however also have unwelcome consequences. It may identify other 'at risk' family members who may not welcome information about genetic risk, resulting in family discord and psychological distress. The diagnosis may involve stigmatisation, from a social perspective, or discrimination, perhaps limiting (health or life) insurance entitlements or employment opportunities.

No mutation identified: a 'negative result'

When 'no mutation' is identified using microarray this means that, when compared to the reference genome, no significant change in the copy number of the genes constituting each chromosome has been detected. The cause of the clinical phenotype cannot be accounted for by copy number variation and array CGH has given a 'negative result'.

This does not mean that the phenotype does not have a genetic aetiology: indeed, whole genome or whole exome sequencing may well reveal a sequence error accounting for the clinical phenotype. Nor does it mean there is an absence of variation, as polymorphisms without known associated health or developmental correlates are not reported routinely in clinical laboratories (owing to their lack of proven clinical significance).

'Incidental findings'

'Incidental findings' are genetic variants with known clinical correlates that are unrelated to the original indication that prompted genetic testing. Such findings are not a new phenomenon for medical practice – the 'incidentaloma' is a common phenomenon in radiology, whereby imaging undertaken for one reason, for example musculoskeletal pain in the shoulder, reveals another potential - or actual - medical problem, such as a lung lesion suggestive of malignancy. An example from genetic practice might mean that in using a genome-wide technology for testing – such as array CGH or whole exome/whole genome sequencing - for the investigation of delayed development, a cancer predisposition gene is identified, with potential implications for the health of the proband and other relatives.

Though not a new challenge for genetic practice, it is the magnitude of scale that makes incidental findings (and variants of uncertain significance) an important consideration when employing genome-wide technologies. Incidental findings in genetic practice provoke particular ethical considerations. Where evidence-based interventions exist to treat, screen or provide prophylaxis (that may favourably alter the outcome of a disease) disclosure of incidental findings by health care professionals, though challenging, is usually preferred. Implications for the health and reproductive decision-making processes of the proband and (potentially affected) family members are then considered. For those mutations where the risk-benefit consequences are less clear-cut, more consideration may be needed: what are the consequences, clinical and psycho-social, of knowing such information or having it withheld?

Pre-symptomatic or predictive testing refers to the testing of individuals who are currently healthy, but who are deemed at risk of having a particular condition, usually based on family history information. Yet diagnostic testing may reveal information of a predictive or pre-symptomatic nature incidentally. Where these types of results are generated for paediatric patients, this counters the well-established norm of deferring testing until the child is able to participate meaningfully in decision-making (BSHG, 2010), preserving their (future) autonomy and the right to an open future (Feinberg, 1980).

Acting in the best interests of children with respect to genetic testing (and the information it can generate) is not necessarily straightforward. What happens when incidental information has potential health implications for a parent? Sharing this information may limit the future autonomy of the child, but withholding it may risk the communitarian benefit of the genetic test. This could pose a threat to the health of the parents (and perhaps other relatives) and ultimately the wellbeing of the child. When a child is unlikely to achieve independence due to serious and permanent cognitive impairment, what constitutes the best interests of the child or the family can be challenging to

untangle (Birchley, 2010). The ethical, legal and social implications of genetic testing are highly situated.

Variants of Uncertain (or Unknown) significance (VUS/VOUS)

The terms “variant of uncertain significance” and “variant of unknown significance” are used interchangeably and such subtle semantic differences are irrelevant clinically. In contrast to a genetic variant with confirmed association with disease, a variant of uncertain significance has an uncertain relationship to disease. This uncertainty has numerous potential sources. Firstly, where there is an unknown or uncertain effect of a specific genetic alteration on gene function. Secondly, where there is insufficient data to confirm that a variant is associated with manifest disease or the future development of disease. Thirdly, a patient may have a variant which is expected to be associated with manifest disease, but be unaffected or have no symptoms: as such a genotype-phenotype correlation is unclear and the consequence of the variant is questioned. Finally, a variant is considered to have uncertain or unknown significance when the phenotype of the patient is different to those expected based on the variant that has been found.

Further challenges are presented in the management of variants of unknown (or uncertain) significance for which there is currently not enough evidence for them to be considered either pathogenic or benign. These differ from polymorphisms in that they are ‘novel’ or rare, or that their location is in a known disease-causing gene. As such, based on current knowledge, there is no known effect in terms of disease or development, but further knowledge may contradict this assumption. As more evidence emerges, these variants may be reclassified as pathogenic (with a diagnostic or predictive implication) or benign. They may also remain as of uncertain diagnostic and prognostic significance.

Variants of uncertain significance present a number of practical and ethical challenges. Laboratories must decide when these variants are reported: distinguishing research from the delivery of clinical care, developing systems that classify ‘uncertain’ variants into categories of likelihood with respect to potential pathogenicity (Easton et al., 2007). These variants may require ‘re-evaluation’ by geneticists over time to consider possible re-classification, meaning there needs to be laboratory, bioinformatic and interpretive processes which support timely review of these variants, in addition to patients and families being aware of the notion that the meaning associated with these variants is potentially subject to change (Murray et al., 2011). Most of the research associated with patient experiences of variants of uncertain significance comes from work with women with VOUS in the breast cancer susceptibility loci *BRCA1* and *BRCA2*. This work demonstrates the variability in experience and expectation: while some women can accept this uncertainty (Cypowyj et al., 2009), substantial numbers undertake decisions such as prophylactic mastectomy based on an

individuated subjective interpretation, which their responsible health care professional may not share (Vos et al., 2008). Where uncertainty of interpretation exists, patients find this information more challenging to share with family members (Cypowyj et al., 2009).

Consent⁸

One of the central problems that can arise in genome-wide testing is that of consent: how can a valid, adequately informed consent be ensured? For the vast quantities of data generated by the new sequencing technologies, this is even more of a problem but consent remains a concern for aCGH too. It may be reasonable to doubt that 'informed consent' is attainable in everyday genetic/genomic practice (Dondorp et al., 2012).

Beauchamp and Childress (2013) define informed consent for medical treatment as having two key normative elements. First, an appropriately qualified individual, prior to testing or treatment, must obtain consent from the patient or their proxies. The foundation for this is respect for autonomy – patients, or their families, must remain authors of their own lives. Children's parents and carers, as proxies, must act in the best interests of their child, exercising both beneficence and respect for autonomy based on their unique knowledge of their family circumstances. This respect for autonomy, when the testing and treatment of children is being considered, must be balanced with the beneficence-based obligation of the clinicians and professionals providing care to the family to take all reasonable steps to arrive at a diagnosis to allow appropriate treatment and care of the child.

Secondly, for consent to be valid, it must be sufficiently informed, meaning the patient or their proxy must be able to understand the potential positive and negative consequences of, and alternatives to, the proposed test or treatment. Professionals must provide this information in an appropriately tailored manner. This means taking into account the specific information needs of the individuals involved in the particular setting, allowing for the educational background of the person and taking appropriate account of their personal values, ideals and preferences. This recognises how attempts to provide exhaustive factual detail about every conceivable finding may lead to 'information overload', which may undermine informed decision-making (Van Zweiten, 2006).

Whole genome sequencing challenges our notions of informed consent even more strongly than aCGH, due to the extensive range of possible outcomes, so that it has been suggested that informed consent for whole genome sequencing may be impossible, given the scale of variants of

⁸ See Article (appendix B) The Challenge of Consent in Clinical Genome Wide Testing. Burke, K and Clarke, AJ. Archives of Disease in Childhood 2016; 101: 1048-1052. <http://dx.doi.org/10.1136/archdischild-2013-304109>

uncertain significance and the unpredictable nature of incidental findings and their potential implications for other relatives and life-long health care. Sufficiently informed consent has been labeled 'generic consent' (Elias and Annas, 1994), and involves providing broad categories of possible health outcomes rather than specific information about all the possible outcomes. Empirical data to support the use of generic consent, in terms of clinicians' and parents' expectations and perceptions, is awaited.

Scale of the problem: the burden of 'uncertain' results

How often are these challenging results encountered when aCGH is undertaken in the neonatal population? Whilst countless individual case reports are available for neonatal patients, a limited body of research looks specifically at the neonatal population undergoing aCGH testing.

Lu and colleagues (2007) published a case series of 2531 infants referred with congenital anomalies and/or dysmorphism for genetic investigation by chromosomal microarray. Using two versions of array over a two year period, 8% of infants were found to have a 'clinically significant' variant. No comment was made about the prevalence of incidental or uncertain information, and indeed the study did not define what constitutes 'clinically significant'.

Ahn and colleagues (2013) reported a case series of 13,412 patients undergoing aCGH testing in a UK public hospital. Though cases of dysmorphic infants and those with congenital anomalies were included in the cohort, they were not considered separately. In this cohort, 25% of patients had a copy number variation in a known pathogenic region or in other regions where imbalances had not been reported in the normal population. 87% of these variants were less than 5Mb in size, meaning they were considered not to be detectable using G-banded karyotyping. The paper did not distinguish between variants in keeping with the clinical phenotype, and those that might be considered incidental or uncertain for the purposes of clinical reporting.

Park and colleagues (2013) reported on a cohort of 20,000 unselected infants in Korea (recruited for 'chromosomal abnormality screening' as part of a whole population study) with a detection rate of 0.43%: 53 cases of aneuploidy (18 autosomal, 35 sex chromosomes), 23 deletions and 11 duplications. There was no means to distinguish between incidental findings, those of uncertain significance and those with a clear phenotypic correlate.

For infants with congenital heart disease in a Canadian neonatal cohort (n=45), three infants had an abnormality detected by classical cytogenetic analysis, and an additional ten had a copy number variation detected by an aCGH (Bachman et al., 2015). Of these copy number variations, 58.3%

were classified as variants of uncertain significance. This study included an assessment of dysmorphology of the infants with syndromic congenital heart disease: while 25% of the infants enrolled were considered to be dysmorphic by a paediatric cardiologist, 75% were noted to have dysmorphic features by a geneticist. This seeks to distinguish between the 'expert' and 'non-expert' in doing genetic work: an important consideration as the responsibility for delivering diagnostic testing is mainstreamed from the specialist or expert (medical genetic) domain, to the general medical domain.

The Local Context

A simple retrospective audit⁹ was undertaken over an 18 month period to assess the burden of incidental findings and variants of uncertain significance in chromosomal microarray testing performed on neonatal patients in the seven neonatal units served by the regional genetics laboratory.

339 arrays were requested, the first inclusion criterion. These cases included all neonatal patients (defined as first 28 days of life for term infant, and term corrected plus 28 days for infants born preterm) where array CGH testing was initiated and carried out by a neonatal physician (rather than another subspecialist, for example, a geneticist). Sixteen infants did not require aCGH testing, due to previous testing having been undertaken and providing a diagnostic result (such as QF-PCR for suspected trisomy). 23 samples were classified as 'failed' samples: 12 were sub-optimal results (failed quality control), 8 had unsuitable DNA, 1 had insufficient DNA on extraction and there were 2 where the DNA was unavailable. 68 results were then manually excluded as the requests were made by professionals other than neonatologists. 194/232 (83.6%) demonstrated no significant chromosomal imbalance. 38/232 results were abnormal, giving an overall diagnostic rate of 16.4%.

Copy number variation was then subdivided into 'pathogenic' or 'VOUS', with the pathogenic group being further subdivided in accordance with either being concordant with the reported phenotype or an apparent incidental finding. 20/232 were pathogenic, giving a pathogenicity rate of 8.62%. Of these, 4/20 were incidental findings, whilst 16/20 (80%) matched the phenotype. Variants of uncertain significance reaching the clinical reporting threshold occurred in 18/232 (7.76%) of neonatal patients, more frequently than the relevant pathogenic results in 16/232 (6.9%).

Experts (and expertise) in genetic medicine

⁹ See Appendix C, a poster presentation: Consent in (dis)array: bioethical and clinical considerations in the use of genome-wide technologies in the neonatal populations. Presented at the British Association of Perinatal Medicine, Birmingham, UK, May 2017.

When considering the role of genomic technologies in healthcare, the recognition and characterisation of clinical medicine – its care, work, participants – as highly heterogeneous is key. Clinical medicine takes place across a variety of contexts and locations (Atkinson, 1995), and as such the impacts and implications of new technical artefacts across contexts and locations may differ. In the local context, prior to being available as a first-line cytogenetic investigation for all clinicians, microarray was available as a clinical investigation to genetic specialists only. As such, patients with a normal karyotype where a high clinical suspicion of a genetic causation exists would need to be referred for clinical assessment by a geneticist who would then consider the need for microarray testing. ‘Mainstreaming’ means that the use of array CGH technology becomes available to more clinicians – in this study, paediatricians and more specifically neonatologists - with differing expertise.

Limited qualitative work has been undertaken to examine clinicians’ experience of using new genetic technologies. Reiff and colleagues (2013) performed an online survey among clinicians requesting microarray testing for patients at one laboratory. This convenience sample of physicians, paediatricians (both general and specialist) and medical geneticists demonstrated (using a non-validated questionnaire) a self-reported need from paediatricians for further information and education to allow them to support patients and families when testing is undertaken, especially with respect to explaining and interpreting particular variants. Further work using interviews with health care professionals (Reiff et al., 2014) supported this, building on a body of work which suggests that non-specialist medical professionals in general (Nippert et al., 2011) - and paediatricians more specifically (Rosas-Blum et al., 2007) - self-report lacking the confidence and expertise to effectively counsel patients and families considering (or undergoing) genetic testing.

Attitudes towards the management of incidental findings – and in particular, how (and indeed if) patients and families are informed about the possibility of incidental information being generated during testing – have formed another subject of enquiry for questionnaire and interview studies. The studies by Reiff and colleagues (2013; 2014) demonstrated variability in the perceived need to discuss the potential for incidental findings prior to testing, ranging from a clear acknowledgement of the pertinence of sharing this potential prior to testing (Reiff et al., 2013), through to the avoidance of the subject altogether as a means of avoiding unnecessary anxiety in the context of a time limited consultation (Reiff et al., 2014). This ambivalence persists regardless of primary specialism, with medical geneticists and paediatricians both reporting similar practices. For variants of uncertain significance, both paediatricians and other practitioners, including genetic specialists, reported a strong preference for sharing uncertain results with patients and families (Turbitt et al, 2015), with paediatricians reporting greater challenge in explaining these types of results to families, particularly *de novo* variants of uncertain significance.

Complementing and building upon self-reported methods, such as surveys and questionnaires, are situated empirical studies which observe (and analyse) the content and form of the communication of genetic information to families, either through observations of consultations (for an overview, see Paul et al., 2015) or through the analysis of documentation such as clinic letters (Paul et al., 2017). A systematic review of studies examining communication in genetic consultations (Paul et al, 2015), found risk communication and adherence to genetic counselling principles of non-directiveness in addition to issues around power and knowledge formed the main focus of analysis in 22 studies. Though some studies included were performed in the paediatric setting, the professionals concerned were specialist genetic health professionals (Ordonez et al., 2013; Zayts et al, 2013; Babul-Hirji et al, 2010; Latimer, 2007; Brooks Howell, 2006). As such, empirical, situated work examining the practices of ‘non-specialists’ undertaking genetic work is limited.

Practically, genetic work is achieved through ‘(bio)clinical collectives’: groups of professionals such as medical geneticists, clinical scientists, bioinformaticians and other clinicians (such as paediatricians or oncologists) involved in clinical care who “combine and co-ordinate the necessary skills and resources, establishing the material conditions required to carry out an activity” (Bourret, 2005: 62). Bourret (2005) explored the collective activities of cancer care services and genetics in their work with breast cancer patients, revealing how the result of collective work constructed the “extended patient, defined by the articulation of clinical data (the disease), biological data (the gene and the mutation) and the social data (family links and degrees of relationship)” (Bourret, 2005: 48). Each of these three aspects draws on differing expertise within the bioclinical collective.

The Response

Considering the Future

Whilst microarray analysis on a tightly defined population of children with autism yields a pathogenic copy number variation in around 10% of cases (Luo et al., 2012), the application of whole genome sequencing to the same population identifies likely causal mutations in almost 50% of cases¹⁰ (Jiang et al., 2013). Genomics England – a commercial entity whose only shareholder is the Department of Health – aims to deliver whole genome sequencing to 50,000 patients (and where possible, parents, forming trio samples) via the 100,000 Genomes Project, delivered through 11 Genome Medicine Centers. The patients eligible for whole genome sequencing fall broadly into three streams: cancer, infectious disease and rare diseases, with ‘gene discovery’ a high priority. This gene discovery has been presented as one means of reducing the uncertainty associated with genomic technologies; by

¹⁰ Functional studies will usually be needed to determine pathogenicity, and these were not performed in this study. This requirement to robustly identify pathogenicity underlies the complexity and enormity of the work facing clinical diagnostic genomics.

enabling more variants of uncertain significance to be 're-classified' as either pathogenic or benign. Reduction of uncertainty is linked with the ability to generate ever-greater quantities of data, inadvertently elevating data quantity to a means of reducing uncertainty (Hacking, 1990). Current empirical considerations of the ethical, legal and social implications of genetic and genomic technologies are largely focused on the role of next generation sequencing technologies – such as whole genome, whole exome and panel sequencing – in the clinical setting. Yet many of the issues associated with these technologies are not new issues *per se*, particularly with respect to the management of uncertainty. Rather, next generation sequencing means these challenges will be encountered at a new scale of magnitude. As such there are practical lessons to be drawn from the situated, empirical study of 'older' genetic technologies, and in particular, their transition from specialist to general use. An empirical, situated approach to non-experts' communication about genetic testing with families builds upon and extends the research performed on interactions between geneticists/genetic counsellors and patients or families contemplating or undergoing genetic testing. In doing this, this research both aligns itself with and seeks to examine the broader agenda seeking to 'mainstream' genetic medicine, embedding it as part-and-parcel of 'everyday' medical work, attempting to describe and define its practice as both similar to, and distinct from, genetic work described previously.

Selecting the literature for review

Here I describe the rationale for selecting the literature examined in chapter three, four and five. Namely, these address the literature in relation to genetic uncertainty (chapter three) and the subsequent management of this uncertainty through practices of division, classification and categorisation (chapter four) and the development or transfer of expertise (chapter five) between and within expert to non-expert communities of practice.

Uncertainty is well defined as a cardinal feature of medical work in a general sense and genetic work as considered more specifically here. Though ubiquitous, the causes and consequences of this uncertainty are realised differently in the various sites in which genetic work is done, namely the laboratory, the clinic and the family. Through exploring the uncertainty literature, I address uncertainty as a material and social feature of genetic work, engaging critically with what is known about its manifestations and implications across the sites of empirical study, which are then considered separately in the data chapters.

Emerging through the 'management' of genetic uncertainty, two practices are considered. Firstly, processes of division, classification and categorisation are employed, rendering the uncertain explicit and then contained. These processes allow for the tolerance of uncertainty, enabling the

promise of genetic technologies to be realised in the clinic. This chapter explores these processes of division, classification and categorisation and the social antecedents and consequences of these practices in (and for) genomic work.

The literature on expertise considers specifically the role and development of expertise in the management of uncertainty. This is particularly apposite as we consider in the analysis how genetic technologies – namely array CGH – embed in new communities of practice. How do clinical scientists develop expertise in the interpretation of array data? How do paediatricians - as non-genetic specialists – develop expertise in the use of this ‘new’ technology?

Thesis Structure

This introduction concludes by outlining the structure of the thesis.

Chapter two positions the study thematically and methodologically as a multi-sited ethnography with a constructivist perspective, using the Social Construction of Technology as a theoretical lens. Here I describe the conduct of and recruitment to the study, introduce the settings in which data collection was conducted, in addition to detailing the analytical strategies employed.

Chapter three introduces the broad concept of medical uncertainty, and more specifically the literature addressing uncertainty as both a material and social phenomenon in genetic practice. Drawing upon literature from a range of disciplines, it outlines an approach to the analysis of the nature of uncertainty. **Chapter four** examines the role of classification and categorisation in creating and maintaining zones of uncertainty, with attention to the social and material implications of this practice. **Chapter five** reviews the theoretical and empirical literature related to expertise more broadly, and the nature of medical expertise and practice in different clinical specialisms, examining how these concepts are enacted in the mainstreaming medical genetics agenda.

Part two contains three analytic chapters drawing on data from three sites of genetic work, namely the laboratory, the clinic and the family. **Chapter six** draws on ethnographic observations and interview data examining the role of the laboratory in managing both the material and social uncertainty of genetic testing. **Chapter seven** uses discourse analysis of 'consent conversations' and interviews with medical professionals in the neonatal intensive care unit, alongside data from ethnographic observations, to describe the processes and challenges of employing microarray testing as a 'new technology' in this setting. More broadly, it investigates portrayals of 'the genetic baby' as a category of patient requiring particular types of problematic work, such as 'consent' for genetic testing. **Chapter eight** examines the consequences of such 'genetic' uncertainty for the families of neonatal patients, exploring how uncertainty is relativised and accounts which render uncertainty as inherently problematic are countered and resisted.

In conclusion, **chapter nine** provides a discussion spanning the analytic chapters, returning to the research questions and providing reflection and commentary as to how effectively these questions have been addressed. Reflecting on both the contributions and limitations of this work - and in particular the challenge of 'insider research' - I conclude with suggestions as to future work in this area.

Chapter Two: Notes on Method

This chapter provides both description and critique of the ontological and epistemological orientation of the work in the constructivist tradition within sociology, and more particularly, the social construction of technology (SCOT). Using Mols' (2002) concept of an ethnography of 'doing' a concept (in this case, aCGH) I describe how this work aims to orientate uncertainty as something manipulated through practices which span the traditional places of genetic work. I describe the rhetorical discourse devices employed during analysis and outline the practical and ethical approvals required for data collection.

Finding (and developing) a 'theoretical lens'

The epistemic perspective with which this work is undertaken is inherently constructivist – “contingent upon human practices, being constructed in and out of interaction between human beings and their world, and developed and transmitted within an essentially social context” (Crotty, 1998: 42). The complexity of developing a coherent theoretical framework reflects, in part, how the multiple identities and the complexity of ‘medical uncertainty’ as applied to genetic work cannot be comprehensively addressed by a single discipline or framework. As such, the methodology builds on the notion of a “toolbox”¹¹, borrowing tools offered and employed in differing theoretical frameworks to make sense of the multiple sites of ‘work’ when microarray is undertaken in the clinical setting. It was clear that the initial proposal which has attracted support from the Wellcome Trust (see appendix D for award letter) – characterised mainly by the observation of clinical consultations and subsequent semi-structured interviews - would not fully capture the emergence of uncertainty, which did not cleave at neat points of observation between the laboratory, clinic and life-world of the families. Rather, the interaction and connectedness between the sites was key, as were the taken-for-granted processes embedded and routinised in the work of the laboratory and the clinic.

¹¹ “All my books... are little toolboxes... if people want to open them up, to use this sentence as a screwdriver or spanner to short-circuit, discredit or smash systems of power, including eventually those from which my books have emerged...so much better!” (Foucault, 1975: Interview with Roger Pol Droit, cited in Paton and Morris, 1979:115)

Epistemology	The theory of knowledge embedded in the theoretic perspective and thereby in the methodology	Constructivism
Theoretical Perspective	The philosophical stance informing the methodology and as such providing a context for the process and grounding the logic and criteria	The Social Construction of Technology
Methodology	The strategy, plan of action, process of design lying behind the choice or use of a particular theory and linking the choice and the use of methods to the desired outcome.	Ethnography Discourse Analysis
Methods	The techniques or procedures used to gather and analyze data, related to some research question or hypothesis	

Table One: Employing the framework by Liamputtong and Ezzy (2005) to describe the epistemology, theoretical perspectives, methodology and methods underpinning this study

The Importance of Timing

Downs' framework of the Issue-Attention Cycle (1972) demonstrates how attention in social contexts over a period of time follows a recurrent pattern.

<p>'Pre-problem stage': an undesirable social condition exists, but has not yet attracted public attention</p> <p>'Alarmed discovery and euphoric enthusiasm': awareness of a particular problem arises (usually quickly). The alarmed discovery is usually accompanied by 'euphoric enthusiasm' regarding society's ability to 'solve the problem' or 'do something effective' within a short time frame</p> <p>'Realising the cost of significant progress': there is a 'gradually spreading realisation that the cost of solving the problem is very high indeed... doing so would take not only a great deal of money but would also require major sacrifice by large groups in the population'</p> <p>'Gradual decline of intense public interest': the high costs of mounting a response or the threat of continuing to consider the problem seriously mean that thoughts of action are suppressed, and others become 'bored' by the issue</p> <p>'Post problem stage': issue moves into a 'prolonged limbo – a twilight realm of lesser attention or spasmodic reoccurrences of interest'.</p>

Figure Three: The Issue-Attention Cycle (Down, 1972)

The timing of this study seeks to capture part, if not all, of this cycle with respect to the adoption and use of chromosomal microarray in the non-expert or non-specialist context. The 'pre-problem' stage was defined in the introduction: there is an increasing evidence base for the use of chromosomal microarray for a range of common neonatal clinical presentations, and the use of this technology has the ability to increase the diagnostic yield for this patient group. Subsequent to this, the following stages encompass the uptake and use of the technology, with the inherent benefits and challenges, and ultimately the mainstreaming of the technology into everyday, mundane practices. The process supporting this embeddedness can be examined using the Social Construction of Technology approach.

Social Construction of Technology (SCOT)

Bloor (1991, 1999) contended that the social sciences should strive to observe scientific knowledge production as subject to the conventions of other social spheres, exploring and questioning the communal belief systems, practices, social conventions and interactions to account for the practices and conclusions it demonstrates. The approaches employed by the Sociology of Scientific Knowledge (SSK) and the Strong Programme were novel in that they considered 'science' as a product of both historical and economic considerations, as well as an active social practice. Case studies emerged examining the production of scientific facts through ethnographic methods (Latour and Woolgar, 1979). Technological innovation was examined from both historical and contemporary perspectives, resulting in the recognition of technological development as non-linear and indeterministic (Pinch and Bijker, 1984).

In their seminal article on the development of the bicycle, Pinch and Bijker (1984) demonstrated how the prevailing design differed enormously from the original intention as a result of conflict emerging around the purpose, or aims, of cycling as an activity. In the 'real-world' application of a technology, negotiation of purpose is an important force, with SCOT providing a mechanism through which the technical artefact itself can be de-essentialised. This emphasises how technologies – far from being 'finished' once invented or implemented – are subject to human influence. Human action ultimately shapes the technology itself.

It is important to note that this is not a social construction of technology study in the conventional sense. Array comparative genomic hybridization is not a new technology or innovation – it is well established in other clinical areas, and in research. Rather this study examines the technology as it is introduced and made available to a new social group, in a new context – paediatricians or, more broadly, doctors who do not have specific expertise in medical genetics. As such, the technology itself is not shaped by the relevant social groups, rather the social and clinical contexts are fluid and changing as the technology embeds and becomes useful to and familiar within a new community.

Though aspects of the use of this technology are contentious, it is validated widely for clinically use, and as such it is not inherently controversial or problematic from a technological perspective.

The social construction of technology describes four key concepts or stages.

Interpretive Flexibility

The configuration of systems and the definition (and realisation) of end goals arise as both subject to, and the consequence of, interpretive flexibility (Pinch and Bijker, 1984). Interpretive flexibility means that the ethical and practical value of a particular technological innovation will vary according to the perspective – the relevant social group – afforded a voice, with the ultimate end-point arising through implicit and explicit negotiation. Pinch and Bijker described how the air tyre of the bicycle constituted a better form of transport for some users, whereas it represented a form of technical nuisance, ugly aesthetics and traction problems for others. The artefacts that come into production can be seen as shaped through controversy (around what is needed and for whom) in addition to considerations of acceptability and function. These processes represent a contest (and ultimately compromise) between relevant social groups.

Relevant Social Groups

'Relevant social group' describes the way in which subgroups are delineated with respect to the technological artefact. These groups are not merely the producers and users of a technological artefact. Rather, they are largely distinguished based on having shared or diverging interpretations of the technology in question. Relevant social groups may not all be visible *a priori*, and may emerge and be (re)defined over time.

When scientific practices and technical artefacts are viewed as constructed (through particular social settings) by the engagement of a relevant social group with a technology, significant importance is attached to the shared epistemologies that exist within these communities of experts (Adler and Haas, 1992; Haas, 1989; Knorr Cetina, 1981, 2009). These epistemic communities are constituted when they display consensus across four types of belief: (i) sharing normative principles and beliefs, (ii) shared causal beliefs, (iii) common validity standards and (iv) an aligned policy agenda. Central to this study is the recognition of paediatricians as an epistemic community (of non-expert practitioners, with respect to genetic work). They are distinct from those of other medical practitioners, and in particular to geneticists and genetic specialists. The medical profession does not form or constitute a coherent epistemic community, in keeping with conceptions of medical practice arising from medical sociology, which recognise medical work as heterogeneous (Atkinson, 1995).

Closure Mechanisms

As consensus emerges over what an artefact should be, the number of interpretations (inherent in the notion of interpretive flexibility) declines. This happens through two main processes: firstly, rhetorical closure, where controversies are redefined. Secondly, through the redefinition of the problem, allowing consensus via a particular technical solution, which develops and emerges from a process of stabilisation.

Framing

In recognising how technology is socially shaped (Mackenzie and Wajcman, 1985), accounts have emerged examining the role of closure mechanisms and interpretive flexibility resulting from a series of processes. These include differing trajectories of development (Collingridge, 1981), the role played by people's expectations of technologies (Bazerman, 2006), the role of public demonstration and complex social interaction in innovation (Geels, 2005). Framing is the process by which the processes of interpretive flexibility, relevant social groups and closure can be situated within the wider socio-cultural milieu. This may recognise differential forms of power between various social groups in terms of the dominant values and interests – with the technological frame being shaped by the meaning and behaviours in relation to particular artefacts.

Interpreting 'the material'

Uncertainty with respect to genetic practice emerges from both the social practices associated with performing genetic work but also from the genetic material itself: from the meaning-making that results from the interpretation of the material. Nancy Cartwright's writing on the philosophy of science (1999) describes how knowledge-generating tools – such as technical artefacts – mediate the material world and our understanding of it.

We must combine both knowledge and technical know-how from a large number of different fields to produce a model that will agree well enough on the matter we are looking to predict, with the method of combination justified at best very locally... The point is that the claims to knowledge we can defend by our impressive scientific successes do not argue for a unified world of universal order, but rather for a dappled world of mottled objects.

Cartwright, 1999: 10

Under idealised conditions, knowledge follows on from assumptions generated in controlled settings or particular populations. As such, we cannot assume that these conditions will necessarily reflect accurately (or completely) all of the possible real-world circumstances. Modeling or assumptions of transferability cannot be assumed: rather, these act as simplifications, which provide a means of cementing abstract relations and forcing constrained observations from phenomena (Hacking, 1983). Genetic/genomic variants are not considered as part of a limitless

spectrum of genetic variation and phenotypic consequence: where identified, variation is sorted into categories – ‘benign’, ‘pathological’ or ‘uncertain’ - and subcategories for sense-making and shared meaning. Cartwright describes this process as the product of a ‘nomological machine’, which is defined as:

..a fixed (enough) arrangement of components or factors with stable (enough) capacities that in the right sort of stable (enough) environment will, with repeated operation, give rise to the kind of regular behaviour which we represent in our scientific laws

Cartwright, 1999: 50

This recognises how situated, real-world practices will not yield ‘law-like’ results, but rather can be considered as instances of regularly occurring natures¹² of some entities under some circumstances. As such, processes of scientific reasoning can be seen as akin to moral reasoning – just as morals are not applied as dogmatic rules, we should consider our perspectives of the relationship between limited observations and general descriptions by adopting this notion of natures. This borrows from the Kuhnian notion of paradigm shifts in science: theories and methods must be open to revision when normal science fails to account for new findings (Kuhn, 1970).

Considering the multiplicity of the material

Clinical medicine takes place across a variety of contexts and locations (Atkinson, 1995), and the impacts and implications of new technical artefacts across contexts and locations may differ. The study borrows from the concepts developed by Annemarie Mol in *The Body Multiple* (2002), in that it attempts to provide an ethnography of a concept, rather than a place, space or process. The heterogeneous nature of genetic work is examined across places and spaces, the methods and implications of uncertainty arising from microarray are followed travelling in multiple directions between the laboratory, the clinic and the family. This allows for the understanding of uncertainty as something manipulated in practices. Foregrounding these practices and acknowledging their cross-boundary consequences, rather than bracketing the practices in which objects are handled, has far reaching effects (Mol, 2002:4).

In *The Body Multiple* (2002), Ann-Marie Mol contends that objects-in-the-world are always multiple, meaning that focus on an artefact or practice allows multiple versions of any entity to be recognised, even when they may be considered (in practice) to be settled through observation and quantification. Enactments of the same phenomena can be recognised and observed according to the perspective of the social actor. Using atherosclerosis as the focus of study, Mol demonstrates how atherosclerosis for the pathologist exists as an observable phenomenon under a microscope, visualising calcified vessels in an amputated limb. For the physiotherapist, it is a discomfort

¹² Nancy Cartwright also refers to these ‘natures’ as ‘capacities’, using the terms interchangeably

associated with exertion, ameliorated through a programme of exercise training. For the radiologist, it is represented characteristically in images collected during angiography and ultrasound imaging. These 'composite realities' rely heavily on multiple perspectives on and concepts of a multiply observable entity – the entity itself being constructed through the multiplicity of these various enactments. The method for this is 'praxiology', the study of the practices surrounding it. For Mol, doctors do not 'treat' and patients do not 'have' atherosclerosis, rather participants, patients and families, doctors, allied health professionals and wider social and political discourses 'do' atherosclerosis through various practices or enactments.

Key for Mol was the recognition that "ontology in medical practice is bound to a specific site and situation" (2002: 53). Yet this multiplicity is not problematic, it merely supports notions of ethics-in-interaction, in so far as ethical considerations are bound in the enactments of each individual case. Further, this approach challenges the dichotomy of 'values' (as the preserves of both patients and caregivers) and 'facts' (traditionally considered as purely biomedical). What if, instead, "values reside inside the facts? Then it may be better to stop shifting the boundary between the domains of professionals and patients, and instead look for new ways of governing the territory together" (2002: 171).

The work of Mol informs this project in two key ways. Firstly, though the recognition that ontology in medicine is bound to specific sites and situations. Genetic 'work' as performed by paediatricians must not be merely accepted as akin to that of medical geneticists or genetic counsellors. The way in which a new technology is employed and enacted in their professional practice, in their enactments of genetic testing, should not be overlooked, rather bound to the sites and situations in which professionals, such as neonatologists, work. Secondly, Mol demonstrates how to examine the way in which expertise and experience impact on enactments. Sociological presentations of biomedicine as 'culturally unified' (Atkinson, 1995: 32) overlook the enormous complexity and interrelatedness of medical sub-specialisms, the role of expertise, both within and beyond the hospital walls: the 'work' of medicine should not be considered as homogenous or culturally uniform.

The case for ethnography

Ethnography is the study of social interactions, behaviours and perceptions that occur within groups, teams, organisations and communities [...] The central aim of ethnography is to provide rich, holistic insights into people's views and actions, as well as the nature of the locations they inhabit, through the collection of observations and interviews.

Reeves et al., 2008: 512

Medical ethnographies have contributed enormously to the understanding of the social in medical settings (Atkinson, 1995; Bosk, 1995; Latimer, 2013; Mol, 2002; Silverman, 1987). Though I had

initially felt that the clinical encounter would be the primary focus, my early observations of clinical conversations demonstrated that the construction of uncertainty was highly fragmented across various places or sites of genetic work. It quickly became apparent that observing just the clinical consultations, even supplemented with paired interview data, would not represent a microcosm of all the aspects of medical work involved in this process (Atkinson, 1995), and indeed, worse still, may represent mistaking a part of the process for the whole (Bosk, 1995).

This fits well with previous descriptions of 'multi-sited' ethnography (Marcus, 1995: 95), in which ethnographic research transitions from the conventional single-site to a multiplicity of sites. Central to this is the convention that the micro- and the macro- are the 'same size' (Callon and Latour, 1981) enabling the macro (i.e. the organisational and institutional) to be considered as just as important as the micro (i.e. the families, professional groups and individuals). It is in this frame of mind that we are able to consider the role of macro (organisational) factors, (big 'D' discourse) such as the classification and categorisation of genetic variants, alongside the 'd'iscourse of the laboratory clinical reporting, or the clinical encounter, with each of the areas contributing meaningfully to the construction of uncertainty (Gee, 2005). The scope of the study expanded from the assessment of the clinical consultation and the life world implications for families to encompass the institutional and organisational aspects of laboratory practice and the clinic.

As such, the classification and categorisation of genetic variation can be seen as a source of power, enacted in the laboratory, the clinic and later in the lived experience of parents, patients and family members. Foucauldian perspectives echo here, in that the power is not concentrated in one space, or possessed by just one person, rather it is highly fragmented or dispersed throughout the sites of work, and with the conduits for this power being the members involved. Power is manifested 'into the very grain and processes of everyday life' (Foucault, 1980: 39), being productive and legitimate, rather than repressive or coercive. This power manifests through 'discourse' (Foucault, 1972) – the language and practices of the members 'composed of ideas, attitudes, courses of action, beliefs and practices that systematically construct the subjects and the worlds of which they speak' (Lessa, 2006: 285). On the macro- level, discourse constructs knowledge and disciplines via the production of categories and assemblages of text (Foucault, 1972). In the micro-discourses of the laboratory and the clinic, discourse contributes to the constitution of categories – 'normal' or 'abnormal', and of 'known' pathogenic/benign or 'unknown' significance. Patients, as subjects, are constituted via these dividing practices (Foucault 1982), with judgment producing classifications – an 'order of things' (Foucault, 1970).

It was apparent from the early observations how much of the work being undertaken in these settings was highly routine and ritualised, both familiar and mundane to those professionals involved – laboratory scientists and clinicians – yet central to the complexities of the use of array

technology in this setting. As such, 'theorising the mundane' (Scott, 2009: 10) would be key to revealing and understanding the process – the taken-for-granted practices which produce and reproduce the order of the settings and process. This knowledge, concealed in the 'most commonplace activities of daily life' (Garfinkel, 1967:1), constructs and controls the 'socially managed production' (Garfinkel, 1967:75) that is central to the ethnographic study of both the laboratory and the clinic.

For the study of consultations, the role of face-to-face interaction is key. Rather than just interviewing professionals about their practices, it is important to observe the interactions, the 'front stage' work (Goffman, 1959). This allows for the assessment of human conduct and engagement with the strategic ways individuals behave in specific situations, in terms of how impressions are managed, performances maintained and identities negotiated: the projection of the self-in-interaction. This is identity-work (Goffman, 1959), the way in which an identity is constructed and altered through interactions with other people. With people sharing a world in which there is ongoing correspondence between the expressed meanings and intended interpretation, the reality of the interaction can only be meaningfully considered with due insight to the influences with respect to both the timing and the social and cultural meanings. Characterising the way in which professionals manage, order, perform and direct interaction exposes how they take account of others, and how they maintain their identity to shape the conventions of the clinic. Goffman's (1959, 1967, 1974) concepts of face, frame and footing provide a useful framework for considering the self-in-interaction.

Face

The term face may be defined as the positive social value a person effectively claims for himself by the line others assume he has taken during a particular contact... The combined effect of the rule of self-respect and the rule of considerateness is that the person tends to conduct himself during an encounter so as to maintain both his own face and the face of the other participants'

Goffman, 1967: 5-11

Face work refers to the way in which participants work to seek appreciation and approval in the social interaction. It involves the maintenance of every participant's face for the duration of the social interaction, serving to counteract 'incidents' – that is, events effective symbolic implications threaten face" (Goffman, 1967: 12). It is in the interests of all the participants to reduce face-threatening behaviour to a minimum, as the maintenance of face is a condition of the interaction rather than its objective (Goffman, 1967:11).

Frame

... no communicative move, verbal or non-verbal, could be understood without reference to a metacommunicative message, about what is going on – that is, what frame of interpretation applies to the move

Tannen, 1993: 3

For Goffman, 'frame' describes the means by which the organisation of the interaction, encounter or situation, is achieved. Frame has been considered in three useful ways. Firstly, as a metaphorical container: a noun defining how communication or discourse is bounded in space and time (physical or imagined), holding different objects and elements. This bounding becomes the 'frame' through which objects and elements are related, forming a story or collective meaning. Frames provide an important structural and cognitive facet for the interpretation of meaning-in-interaction. Frame can also be considered as means of structuring the expectation of an interaction (Goffman, 1974; Tannen, 1993) or finally as a means of shaping opinion (Lakoff, 1973).

Footing

Footing can be simply described as the participant's relation to what is occurring (contrasting frame which relates to what is actually occurring practically and functionally in the interaction). Goffman (1974) describes how there are times when we shift – or attempt to shift – frames within a social interaction. This happens by shifting the footing, stance or alignment participants take up *vis-a-vis* one another and their utterances. Shifts in footing affect the task, tone, social roles and interpersonal alignments achieved in interaction (Goffman, 1981).

No aspect of the interaction can be considered trivial. Conducting interviews, in the comfort of the 'backstage', allows for the assessment of how professionals make sense of their world, and the impact of this impression on their conduct in interaction (Goffman, 1959) and their 'accounts' of their practices (Garfinkel, 1967). These accounting practices refer to the way in which participants describe and justify their conduct as grounded and reasonable from the perspective of others in social interaction. Coupling these accounts with observations of clinical interactions ground the accounts within the realities of practices defining how testing is done (Mol, 2002) by members of the bioclinical collective (Bourret, 2005).

Constructing the site(s)

With ethnography as both the methodology and the broad theoretical lens, the intention became the 'tracking' (Marcus, 1995:95) of the process of doing aCGH: from the laboratory and the office, through the meeting room and various clinical spaces, such as wards and outpatient rooms, and out to the home.

The Laboratory

The laboratory system supporting medical genetics across the whole geographical region is centrally located in Cardiff. This meant that samples for array CGH (no matter where they had been collected across the country) were sent to the cytogenetics department in Cardiff for processing, analysis and reporting. The laboratory receives samples from paediatric patients attending thirteen hospitals and countless community clinics across Wales. Paediatricians, and some specialist nursing staff, are allowed to request aCGH, negotiating consent with parents and families prior to collecting and sending samples to the laboratory for analysis, after completing a standardised form. Observing clinical scientists in laboratories and offices, doing their routine activities formed the first site of the ethnographic research, and is described in further detail in chapter six.

The 'clinic'

The second site was 'the clinic'. As described in the introductory chapter, aCGH is performed as a clinical test across a multiplicity of settings in which children receive medical investigation and care. With ethical and NHS permissions, data could be collected from any of these thirteen hospitals and multiple community clinics as NHS clinical sites. Through a series of letters, emails and invited talks at medical and educational meetings, paediatricians were informed about the study, and asked if they would like to participate. Participation involved attending ward rounds and clinics to observe clinical encounters in which aCGH might be discussed as a potential investigation. Initially, many sites were accessed as clinicians contacted me to express their willingness to be involved. Though privileged, this raised multiple challenges. Firstly, it was possible to travel long distances to clinics at which no data was collected, as the patients and families who appeared to have been referred for reasons that might warrant aCGH testing did not attend or did not need testing once the history taking and clinical examination had been completed. It was clear that trying to observe in so many potential sites would compromise the ability to provide 'thick description' (Geertz, 1973). Secondly, it became clear early on in the process that many of those responding to calls for participants were particularly motivated, confident and informed with respect to the process of consenting and performing aCGH testing. As such, I was increasingly concerned that the data collected did not represent the experience of typical paediatricians in their everyday work. This method also was disproportionately attracting consultants – the most senior paediatricians – to participate. I had little interest from more junior doctors who, based on a recently conducted audit of aCGH testing across Wales (see introduction), appeared to take consent for the procedure most frequently. As such, it was apparent that a change in direction was needed.

I had been especially successful in building a research association with one particular clinical site: a tertiary neonatal intensive care unit at Lakeside Hospital, caring for newborn infants with medical and surgical pathology. Here, many newborn infants presenting with congenital anomalies required aCGH testing, in addition to those thought to be 'dysmorphic' following newborn examination by the paediatrician or midwife¹³. Rather than asking clinicians to contact me as the need for aCGH was identified in patients, I began to attend ward rounds, clinical grand-round meetings, educational meetings and the post-natal wards, being present when conversations about the need for genetic testing took place. I observed naturalistic talk between clinicians at the bedside, in meeting rooms, during lunch-breaks and with colleagues such as nurses, radiologists and specialists from other areas, such as neurologists and surgeons. This subsequently resulted in relationships with professionals at two other neonatal intensive care units where specialists from the base hospital provided support.

The family

The final site in which data was collected was in the homes of families in whom a variant of unknown/uncertain significance or an incidental finding had been identified. These families were identified through the neonatal intensive care unit doctors, who provided families with information leaflets about the study, and details of how to contact me should they wish to participate. Information was offered to all families encountered in routine clinical care (i.e. attending outpatient appointments) that had received a variant of uncertain significance or an incidental finding during microarray testing performed in the neonatal period. Families who contacted me were given further information about the study and invited to participate in an interview at a convenient time in a location of their choosing.

¹³ All newborn infants have a 'first day check' or NIPE (Newborn Infant Physical Examination). This is a physical screening examination performed by a paediatrician or trained midwife which looks for early evidence of disease or disorder. Abnormalities or concerns may lead to further testing or investigation.

Participants

'Relevant Social Group' [Participant and Names]	Role in the process and research
<p>Clinical Scientist (CS)</p> <p><u>Participants</u></p> <p>Susan (Head of Cytogenetic Lab) Anna (Senior CS) Emily Hannah Laura John</p>	<p>Clinical scientists (CS) are National Health Service employees who are based in the clinical genetics laboratory. They are responsible for the processing, analysis and reporting of genetic testing conducted in the laboratory. They have no contact with the patients themselves.</p> <p>Most are graduates of science subjects, with some having postgraduate qualifications, followed by significant training in the specific laboratory setting. Progression is via years of experience and the undertaking of additional training and responsibilities, such as the supervision of junior staff, and the reviewing or validation of the work of other (more junior) clinical scientists.</p> <p><u>Role in research:</u> observation in laboratory, participation in audio recordings, qualitative interviewing during the clinical reporting process</p>
<p>Medical Geneticist (MG)</p> <p><u>Participants</u></p> <p>David</p>	<p>Medical Geneticists (MG) are clinical doctors working specifically in the field of clinical genetics. They provide clinical support to clinicians from other medical specialties (for example paediatricians) when managing patients/ families with suspected or confirmed genetic disease, in addition to seeing patients in dedicated genetic clinics. Genetic registrar doctors' work under the supervision of consultant geneticists.</p> <p><u>Role in research:</u> observed in clinical consultations, participation in qualitative interviews</p>
<p>Consultant Neonatologist</p> <p><u>Participants</u></p> <p>Michael Lizzy Raj Beth</p>	<p>Neonatologists are clinical doctors who work specifically with children and their families. They can be based in a number of sub-specialist settings, for example the neonatal intensive care unit and community clinics. They manage the care of both inpatients and outpatients. Paediatricians may order genetic tests in their practice, however challenging results would usually be managed in conjunction with a geneticist.</p> <p><u>Role in research:</u> observations in clinical consultations, audio recordings, participation in qualitative interviews.</p>
<p>Neonatal Registrar / Senior House Officer</p> <p><u>Participants</u></p> <p>Peter Ben Zoe Laura Claire</p>	<p>Neonatal Registrars (NR) and Neonatal Senior House Officers (NSHO) are doctors-in-training who work under the supervision of consultant neonatologists to provide care to children and their families. Registrar doctors are more senior, having completed 4-8 years of paediatric training. SHOs are in the first 3 years of training.</p> <p><u>Role in research:</u> observations in clinical consultations, audio recordings, participation in qualitative interviews.</p>

<p>Advanced Neonatal Nurse Practitioner (ANNP)</p> <p><u>Participants</u></p> <p>Racheal Kate</p>	<p>ANNPs are nursing staff who have undergone significant (2 year) postgraduate level training to enable them to perform some of the tasks of medical staff in a highly specialized area, in this case, the neonatal intensive care setting.</p> <p><u>Role in research</u>: observations in clinical consultations, audio recordings, participation in qualitative interviews.</p>
<p>Parent / carer of patient</p> <p><u>Participants</u></p> <p>Martha, Amy, Fred, George, Carly, Melanie, James, Tom, Lowri, Lucy, Gareth, Lisa, Ruth, Chris, Charlotte, Duncan, Amy, Judy, Rhodri, Richard, Abi, Sabina</p>	<p>This group of participants includes the parents or legal guardians of children undergoing, or being considered for, genetic testing. These were usually (but not always) the biological parents of the children, who sometimes had to undergo testing to clarify the significance of results in their offspring.</p> <p><u>Role in research</u>: observations in clinical consultations, audio recordings, participation in qualitative interviews.</p>
<p>Family member</p>	<p>Parents/carers attending the clinic often attended with a member of the family as support. Where this was the case, given their genetic relatedness to the child (and therefore the potential implication for their own health), they were also recruited as participants (provided the parent or carer gave consent for this to be the case).</p> <p><u>Role in research</u>: observations in clinical consultations, audio recordings, participation in qualitative interviews.</p>

Table Two: Table summarising the participants in the study, including their background with respect to genetic work and their role in the research.

Collecting the data

Many hours of observations, recorded consultations, semi-structured interviews and document analysis represented an attempt to triangulate the data collection approaches to provide ‘thick description’ (Geertz, 1973). Observing the clinical consultation or laboratory work provides an insight into the ‘front-stage’, however the ‘back-stage’, the offices, informal talk and intra- and inter-professional interactions also provide rich data (Goffman, 1959). Of particular interest here is how spatial ‘sites’ may impact on social role – for example, a doctor may give a confident, assured answer to a parent’s question in the clinical interaction (the ‘front-stage’ performance), only to then check the validity of their response through an internet search - ‘back-stage’ - in the privacy of their office. Through this, I found myself increasingly privileged with respect to participants revealing their own uncertainty, accessing the space in which ‘...the team can run through its performance, checking for offending expressions when no audience is present to be affronted by them. Here the performer can relax; he can drop his front, forgo his speaking lines and step out of character’ (Goffman, 1959: 112). The focus was on participants’ actions, as shaped by routine and institutional discourses rather than as professional failings or omissions (Goffman, 1959). Rather than

comparison to (or measurement against) a proposed ideal of best practice, the focus was on what participants do, why they do these things over others, and how the social and cultural forces that drive what they do can be explained and described (Latimer, 2008). Actors are both free as individual practitioners and, simultaneously, highly constrained by institutional and organisational expectations and forces.

For fieldwork in the clinical setting, it was important to develop a 'cover story' (Bosk, 1979: 194). This was especially important when observing participants who knew of my clinical background and familiarity with the setting. Where possible, I did not reveal my clinical background, saying something like 'I am a PhD student looking at genetic testing in the paediatric setting', revealing more only when asked (rarely). I was often referred to as 'the research student' and 'the student doctor'¹⁴. For those who were familiar with my previous or professional role (mainly nursing staff and consultant doctors), I just asked them not to address me in a clinical capacity, but to remember I was here as a researcher and to treat me as they would other visitors in that capacity. In terms of 'props' (Goffman, 1959), rather than using them as tools to symbolise or legitimise my presence, I was careful not to wear the same badge as I wore in my capacity as a doctor, not to appear dressed like clinical staff and not to pre-empt activities through my knowledge of the practices and rituals of the clinical spaces. Instead of trying to be helpful, I deliberately remained ornamental and extraneous (Bosk, 1979). For many of the observations, I formed part of a group of individuals who are relatively poorly distinguished in settings such as ward rounds and meetings, allowing me to perform fieldwork without limitation much of the time (Silverman, 1987). I avoided data collection and observations alongside people I know socially and only rarely did participants make reference to my role (see chapter nine for a reflection on the notion of researching as an insider).

Similarly, in the laboratory, my observations came to be accepted as a normal part of the departmental work, merely through my being present repeatedly over a prolonged period. In the laboratory, in contrast to the clinical areas, it was quite difficult not to be an active participant. Thus, my engaging in conversations and collecting papers from the printer built rapport with participants and decreased their (often expressed) anxiety about my observing their work. During observations, I often asked participants to speak their thought processes out loud, when they could, having found that refraining from asking questions during observations produced rich accounts from scientists of their work.

I scheduled my presence between settings at various times in the week, partly to avoid exhausting my welcome with particular participants and in part also as certain days represented certain activities in each setting – Thursday and Friday were particularly fruitful days in the laboratory, as

¹⁴ This is in keeping with the usual practice in medical settings, whereby one emphasises the junior status of observers such as medical students and student nurses in order to legitimise their presence

this was when the results of arrays became available and early interpretation was taking place and Wednesdays were a good day in the neonatal intensive care, as the grand-round meetings took place, where numerous clinicians and allied health professionals engaged in explicit reasoning about the management and prognosis of patients. Interviews with families were scheduled on an ad-hoc basis, according to their availability. Ongoing analysis provided an iterative approach to the focus and scope of subsequent observations.

Recording the field

Ethnographic observations

I began by making field notes in a journal - which often felt like an intrusive or threatening process, particularly when in conversation with individuals during semi-structured interviews. The field notes proved most fruitful when describing non-verbal practices, materials, the organisation of a setting alongside personal reflections and responses to the field in observation. I made rough notes and transcribed them soon afterwards into more formal and structured reflections, the content of which could be treated as textual matter for interpretation, as a source which can be read and subjected to (further) interpretation.

Supported and encouraged by the notion that my presence, to some extent, was altering the normal order of the clinical interactions, I increasingly used a tape-recorder to allow the recording and verbatim transcribing of some encounters and observations, such as clinical meetings, educational meetings and laboratory observations. I felt more comfortable using this when recording group talk, or talk based around a task, such as interpretive computer work, where the recordings could be performed unobtrusively. Even when recording, I continued to make field notes to capture events not recorded on tape, such as referencing materials like patient records and images/representations on computer screens.

Clinical consultations

For consultations, I used a voice recorder placed discretely near the clinician to record the consultation, with parents and families always agreeing to this through the consent process. I (usually) observed the consultations, making field notes to complement recordings. However, on a few occasions I recorded consultations without being present. This occurred on two occasions when junior doctors were clearly anxious about my presence, perhaps exacerbated by them knowing my previous clinical role. For these cases, I confirmed that the families were willing to provide consent and set up the equipment prior to them entering the room. I then collected the recorder at the end of the consultation, conducting the interview with the clinician in the usual way at some later date.

Interviews (with professionals)

Interviews with professionals supplement the consultation and observational data in two key ways, supported by the notion that ethnography is enriched through the use of multiple methods for data collection. Firstly, their 'accounts' (Garfinkel, 1967) served as an opportunity to examine 'slippage' between 'informal' ways of working, as captured through consultation recordings and observations, and the 'formal' accounts participants provide of their own working. Secondly, they provided the opportunity to balance and verify observational data. This augments the validity of the ethnographic works, allowing participants to 'speak for themselves' (Atkinson and Delamont, 2006:166), allowing the interview data itself to become 'the reality they purport to describe' (Atkinson and Delamont, 2006:167). The data becomes a topic of study in itself, representing a constructed account away from the ordinary life circumstances or tasks forming the topic of study – in this case, the consultation data and ethnographic observations.

Generally interviews were performed after a number of informal interactions had already taken place, either through ethnographic observations or consultation recordings, at a point where I, and the study, had become a familiar, and more trusted part of their working life – a comfortable part of the 'back-stage' (Goffman, 1959). Previous interactions with the professional concerned allowed for an iterative and situated approach to questioning, developed from an initially rudimentary interview schedule. On some occasions, I referred to particular aspects of transcript data to probe specific areas of practice, encouraging deeper engagement and reflection on particular aspects of their work.

Interviews (with families)

Interviews with families were conducted under a number of circumstances, though were generally focused on the experience of receiving an 'uncertain' result, in the form of a variant of unknown significance or an incidental finding. These were mainly recruited through clinicians, or through observations in clinical areas. These interviews were aimed at describing the parental experience of uncertainty – the processes undertaken to resolve uncertainty, the ways in which uncertainty was understood by the parents and family and its (ongoing) consequences.

Data analysis

...discourse analysis looks at how language constructs professional practice. Recordings of naturally occurring interactions are transcribed and combined with ethnographic knowledge. Analytic themes drawn primarily from sociology and linguistics shed light on how meaning is negotiated in interaction. Detailed features of talk, such as intonation and choice of vocabulary, trigger inferences about what is going on and being talked about. These affect how interactants judge each other and decisions are

made. Interactions also have larger rhetorical patterns used by both patients and doctors to persuade each other.

Roberts and Sarangi, 2005: 632

Site of 'work' / Research site	Methods of data collection	Sources and materials generated	Data analysis methods
<i>Regulation and guidance of classification and categorisation of genetic variants in clinical testing</i>	Analysis of documents, guidelines, regulations governing clinical reporting		Discourse analysis
<i>The Laboratory</i>	Ethnographic observations of laboratory practices, meetings, education sessions	Field notes	Ethnography
	Audio recordings of observations	Transcription of observation Accompanying field notes	Discourse analysis
	Semi-structured interviews with clinical scientists	Transcription of interviews	Discourse analysis
<i>The Clinic</i>	Ethnographic observations of ward rounds, routine clinical care, clinical meetings, educational meetings	Field notes	Ethnography
	Audio recordings of clinical consultations (consent, return of results, discussion of genetic testing)	Transcription of consultations	Discourse analysis
	Semi-structured interviews with clinicians	Transcription of interviews	Discourse analysis
	Audio recordings of observations – clinical meetings, educational meetings	Transcription of observation Accompanying field notes	Ethnography Discourse analysis
<i>The Family / lifeworld</i>	Audio recording of semi structured interviews	Transcription of interviews Accompanying field notes	Thematic analysis Discourse analysis

Table Three: Table summarising data collected in different sites, and the methods of analysis employed.

The methods employed generated an enormous amount of data in various forms: field notes in written and transcribed form, transcriptions of clinical consultations, transcriptions of interviews with

professionals, transcriptions of educational and multidisciplinary meetings, in addition to documents, photographs and diagrams depicting processes, representations of genetic data and numerous other images arising from observations. In this sense the work is founded on a situational analysis of aCGH in clinical settings, with my own role being the mapping the work across time and across settings.

Audio recordings of both consultations and interviews were transcribed verbatim, with identifying features, such as gender, names and places being removed or replaced to ensure anonymity for participants. Field notes were transcribed into more formal records, structured to allow for easier analysis. Audio transcriptions were assembled. Both naturalistic consultation transcript data and interview data were then entered into NVivo 10 (QSR International), a qualitative data analysis software package that allows for the open coding of textual data and the identification of rhetorical devices. Open coding allows responses to be coded inductively without predetermined codes allowing categories and themes to emerge and theories to be developed. Though the computer software package proved useful in providing a structured approach to working through transcripts, much of the analysis was performed using manual methods – colour coding interview transcripts, manually copying-and-pasting quotes and fieldnotes together into themed groups, categories and interpretations. This worked better as a method given the scope of the materials available for interpretation: interview data, consultation data, field notes, recordings from educational meetings.

Rhetorical discourse devices

There are specific circumstances, particularly in the analysis of clinical conversations (chapter seven) and parents' accounts (chapter eight) of focusing on how participants utilise specific rhetorical devices or patterns. Here, I focus on the persuasive use of language: justifications of previous professional and personal behaviours and examples of the categorisations and ethical work that occur in situated encounters.

Character and Event Work

Character work involves a description of conduct (either of self or of others) to allow a particular moral perspective to dominate. Event work functions similarly to (re)present an event (either past or future) to support a current concern or perspective

Reported speech

Reported speech (or constructed dialogue) refers to the way in which a participant quotes or reports the talk of another person. This attempts to move the study of communication away from linguistic analysis to one that is embedded in the context and social life of the participant and discourse. Volosinov (1973: 116, italics in original) describes how “what is expressed in the forms employed for

reporting speech is an *active relation* of one message to another". Through reported speech in accounts, it is possible to recruit different voices with respect to a particular account, and to present, manage and authenticate different versions of events.

Extreme Case Formulation

Extreme case formulations (ECF) are absolute expressions used to enhance the legitimacy of complaints, accusations and justifications (Pomerantz, 1986). Their use is a 'practice of description' (Pomerantz, 1986) with the aim of having a participant in an interaction arrive at a particular conclusion, proposing that a particular action or behaviour is 'acceptable and right or unacceptable and wrong' (Pomerantz, 1986). The common feature of extreme case formulations is that they are semantically extreme – 'always' or 'never' for example – invoking the minimal or maximal properties of projects or events. ECF use has been reported in professional accounts as a means for justifying practices, particularly with respect to childhood (predictive) genetic testing (Arribas-Allyon et al., 2008a). These formulations are extended through the use of extreme case scenarios, employing multiple devices to enhance the legitimacy of a claim through a longer account.

Contrast structures

Smith (1978) describes contrast structures as a means of establishing differing versions of events. Sarangi and Clarke (2002a) describe how the use of contrast structures provides a useful analytic lens through which to explain and contest different states-of-affairs.

Metaphor (chapter seven) and *listing* (chapters four and seven) also feature in the analysis and can be considered as rhetorical devices, particularly where they appear as examples of persuasive talk, or patterns of description or argumentation in institutional encounters.

Ethical issues: approvals and the challenge of 'ethical ethnography'

Here we focus on both the 'ethics in practice' of conducting ethnographic work, just briefly summarising the 'procedural ethics' around gaining formal institutional approvals (Guilleman and Gillam, 2004: 261). Ethical approval was required in order to access NHS clinical sites and the laboratory. Gaining permission to access sites of healthcare delivery for ethnographic research has been depicted as both a difficult, lengthy and complex exercise (Bosk and De Vries, 2004) and contrastingly as straightforward (Hedgecoe, 2012). My previous experience of the clinical setting – knowledge of and respect for the rules and order of the setting - made this process somewhat easier, as did the support of prominent academic clinicians in both paediatrics and genetics who supported the concept of the work and its topical importance. The fact that a substantial award from a prestigious body was funding the work implicitly inferred broader support. Referring to this

frequently formed a large part of the 'art' in gaining formal approval through more local processes. Having been involved in research projects before, I was familiar with the need to 'play the ethics game' (Reed, 2007), and the importance of (apparent) familiarity with the clinical environment I hoped to research, in this case accrued through my personal professional experience, rather than via a gatekeeper. Following the submission of the Research Ethics Committee paperwork (see appendix E for the permissions, information sheets and consent forms), I was asked to attend a meeting. Approval was subsequently given, pending a minor clarification and resubmission.

Ethnography is frequently described as a morally problematic activity (Bosk, 2001): how do we reveal to subjects that they are being observed? How do we disclose our role honestly without compromising our position in the field? How do we have authentic relationships with subjects whilst also collecting data? One particular issue facing ethnography is how individuals in the setting who do not wish to be observed can be alerted and subsequently avoided when observations are undertaken. Informed consent is highly problematic when undertaking such work, and Bosk's claim (2001: 211) that it is impossible to undertake ethnography in clinical areas "without both violating informed consent and without breaking promises made to subjects about confidentiality and anonymity" certainly rings true. Whilst posters were displayed describing the work being undertaken, it was impractical to consent all those using the clinical areas – consenting all individuals would be time consuming, disruptive and socially peculiar (Bosk, 2001).

A key concern of the ethics committee, and the reason for clarification and resubmission, related to my dual status as both a sociological researcher and a clinician. Assuming that (based on experience from my prior clinical role), I would be able to recognise poor or unethical practice, what is my moral obligation with regards to reporting or addressing this? I felt very uncomfortable and deeply compromised by this apparent need to 'police' the practice of clinicians who had generously agreed to have me observe their work. After discussion with the ethics committee and colleagues, I agreed to state in the information leaflet for clinicians that where negligent practice was observed, it would be discussed with my supervisor with respect to the need for further action. This distinction between poor and negligent practice was important, as "...under an ethnographic microscope everyone has warts and anyone can be made to look like a monster.." (Bourgeois, 1996:18). I offered signposting to online resources for clinicians regarding consent processes and testing¹⁵ after I had observed or recorded consultations. It is of great importance to me that this work is not seen as a criticism of laboratory or medical professionals, nor as a record of their limitations in practice. Rather, the aim is to situate their practices and experiences in the context of organizational constraints – to examine the micro-, their 'd'iscourse in the context of the macro- 'D'iscourse (Gee,

¹⁵ I signposted, where needed, to free, open-access, medical education resources – namely, <https://www.genomicseducation.hee.nhs.uk/courses/>

2005). The aims are neither normative nor punitive, rather to provide an accurate and reasoned analytical account of the work of doing aCGH.

Conclusion

This chapter provides both description and critique of the ontological and epistemological orientation of the work in the constructivist tradition within sociology, and more particularly, the social construction of technology (SCOT). I have addressed how the use of aCGH in a new clinical setting can be addressed through attending to the interplay of practice, discourse and materials. Whilst the technology itself is not novel, the focus on the relationships between practices, discourses and technology itself does provide a useful frame with which to examine how a new technology establishes itself in the practices and work of a new community of practitioners, specifically paediatricians and neonatologists.

The study is the story of how array CGH is 'done' (Garfinkel, 1967; Mol, 2002): studying everyday affairs and occurrences through both the 'content' of medical action (Berg, 1992: 151) and through the everyday, mundane work of the laboratory and the clinic, where 'people do (perform, reproduce and occasionally challenge) social life, day to day' (Scott, 2009: 1). More specifically, this is guided by an interest in the interactions, accounts and discourse of the places of genetic work. Encounters are examined as both social and technical accomplishments (Mol, 2002) with appropriate emphasis on making the materiality of peoples' worlds explicit and central, rather than implicit and marginal – allowing the exposure of everyday work and rhythms in the hospital.

The next three chapters address the cross-disciplinary literature relating to uncertainty, processes of classification and categorisation and expertise, foregrounding the data analysis across the three sites of genetic work, namely the laboratory, the family and the clinic.

Chapter Three: Uncertainty in Medicine and Genetics

This chapter explores literature on uncertainty, with specific reference to manifestations of uncertainty in medical and genetic practice. I outline taxonomies of uncertainty from the empirical literature, relating them to the inherent uncertainty of genetic testing and practice. Using the example of the efforts to establish the chromosome number of man, I demonstrate how it is the scope, rather than the nature, of uncertainty that changes with increasing technical capability and knowledge. The chapter concludes by outlining the recent considerations of uncertainty generated through genetic testing technologies for patient identity and experience.

James is born at 32 weeks gestation, with dysmorphic features, including low set ears and a cleft lip. He is small for gestational age. A chromosomal microarray is performed to identify a genetic cause for these features. A deletion of uncertain significance is identified.¹⁶

Uncertainty is ubiquitous in medicine (Ghosh, 2004). It can be considered as both an objective property of medical information itself - that which is not (completely or perfectly) known - or as a subjective experience representing a lack of knowledge, confidence or assuredness. Uncertainty has been a key theme in medical sociology (Fox, 2000). More recently it has emerged as a key a concept in practical and sociological thought within genetic/genomic medicine, with the role of sociotechnical ensembles in generating and attempting to mitigate uncertainty has also formed the subject of discussion and debate (Christakis, 1997). Whilst reasonable to assume that genetic testing has the reduction of uncertainty as one of its aims (Skirton, 2001; Brookes-Howell, 2006), genetic technologies, along with advancing scientific knowledge, have paradoxically increased uncertainty: as medicine becomes more accomplished in its achievements of diagnosis and treatment, expectations rise, as does our awareness (and experience) of risk and uncertainty.

Accounts of uncertainty in medical practice are fragmented and incomplete, existing across numerous disciplines including communication, nursing, health services research and increasingly sociology and bioethics. Accounts of uncertainty have been divergent in focus and have considered uncertainty as a monolithic phenomenon, failing to integrate insights from cross-disciplinary studies, particularly those from bioethics. The result is the failure to construct a shared concept of what constitutes 'medical uncertainty'. Though uncertainty itself may have no ethical quality, the management of uncertainty, especially in the clinical context, may have explicit moral or ethical elements, such as behaviours that change or are adjusted in response to encountering ethical dilemmas, avoiding danger and diminishing risk.

¹⁶ Case example, US Genetics Education Online Resource [<http://www.nchpeg.org/microarray/real>]

How are these forms of uncertainty manifest when array comparative genomic hybridisation is undertaken in a paediatric patient? For James and his family, multiple sources of uncertainty arise. Despite having had a genetic investigation, significant uncertainty remains as to the cause of his medical problems. The prognosis remains uncertain: is this phenotype likely to be associated with other problems with his development and health? For his parents, reproductive risk – in terms of the likelihood of having another child with similar problems – may be important and may remain uncertain. The significance of the variant identified is uncertain. Also unclear is what James's parents were told when consenting for this process: were they told about the possibility of incidental findings and variants of unknown significance? What are the consequences of knowing about a variant of unknown significance for how families experience genetic information and the problems their child is experiencing? Where does medical practice – and more specifically genetic practice – sit on the spectrum of embodying uncertainty in its theories and rituals?

Whilst a full account of the concept of uncertainty remains beyond the scope of this chapter, I seek here to summarise and critique a variety of taxonomies of uncertainty, forming a basis on which to describe uncertainty as it manifests across the sites of empirical study, in the laboratory, clinic and family. Emphasising and demonstrating the normative status of uncertainty, I move on to the literature addressing how uncertainty manifests through innovations that visualise and represent the genome, a process central to laboratory meaning making. Through clinical reporting, this meaning is shared with the clinic and the role of communication is key. The literature with regards to uncertainty in the genetic consultation provides insight into how uncertainty is created and managed in interaction, with consequences for individuals and families experiencing uncertain identities when a variant of uncertain significance is identified.

How can uncertainty be described?

The unknown. As we know, there are known knowns. There are things we know we know. We also know there are known unknowns. That is to say there are some things we do not know. But there are also unknown unknowns. The ones we don't know we don't know.

Donald Rumsfeld, 12th February 2002. US Department of Defense News Briefing (emphasis added)

The variety of typologies available to describe the nature of uncertainty – drawn from a diversity of academic domains including economics, environmental science, philosophy, psychology and more – are possible because of the broad definition of uncertainty, along with the variety of theoretical orientations which exist both between and within academic accounts. Rumsfeld's typology summarised three¹⁷ well-described manifestations or zones of uncertainty¹⁸: a rudimentary

¹⁷ A fourth group, the 'unknown knowns' are considered later when looking at tacit knowledge (unconscious competence) as related to expertise.

classification of uncertainty, with parallels in the uncertainty manifest in genetic work. From a pragmatic standpoint, it is useful to characterise uncertainty within frameworks, as this allows for the explication of uncertainty, and the potential to reduce uncertainty (when possible). Knowing can be seen as a spectrum, extending from ‘known’ to ‘unknown’, with varying degrees of uncertainty and certainty in between.

Extending Rumsfeld’s typology: describing incidental findings and variants of uncertain significance

Divisions of uncertainty based on its nature – that is to say, the general characteristics of the uncertainty – provide a useful typology for describing when uncertainty is either based on inherent variability (aleatory uncertainty) or arises from lack of knowledge or awareness (epistemic uncertainty). Further typologies have emerged with particular reference to the nature of medical or clinical uncertainty.

Kerwin (1993) presents clear parallels with Rumsfeld in distinguishing what is known from what is uncertain. Here, ignorance refers to the unknown as relating to error (Smithson, 1989), rather than its pejorative vernacular use.

		Meta-level	
		<i>Known</i>	<i>Unknown</i>
Primary level	<i>Known</i>	Known knowns	Unknown knowns (tacit knowledge)
	<i>Unknown</i>	Known unknowns (conscious ignorance)	Unknown unknowns (meta-ignorance)

Figure Four: Structuring Uncertainty (Kerwin, 1993) with respect to medical ignorance

The parallels between this matrix and the Rumsfeld typology are clear – there are the known knowns, the known unknowns and the unknown unknowns¹⁹. Unknown knowns, or tacit knowledge, provide a useful lens through which to examine the assessment of social practices with respect to generating or seeking to resolve uncertainty, and this is addressed later through the examination of both classification and categorisation (chapter four) and expertise (chapter five) as a method through which uncertainty can be mitigated and managed. Related to this, and also omitted from

¹⁸ The reference to ‘zones of uncertainty’ extends on the concept of ‘zones of expertise’ as described by Sarangi and Clarke (2002b). Zones of expertise refers to the mechanisms by which genetic professionals enact the limits of their professional knowledge, and maintain a non-directive stance. Zones of uncertainty refer to the limits of ‘certainty’ in genetic testing: the nature and content of these zones is explored throughout the thesis.

¹⁹ One obvious omission is the notion that things can be known incorrectly, resulting in confusion or inaccuracy (Smithson, 1989).

Rumsfeld's typology, is the notion of something that is known but remains (consciously or unconsciously) unknown. This is elaborated upon by the Smithson typology (1989) in the form of 'active ignorance', referring to things that are known, but ignored. Under the umbrella of 'irrelevance', this is divided into ignorance caused through 'untopicality', 'taboo' or 'undecidability'.

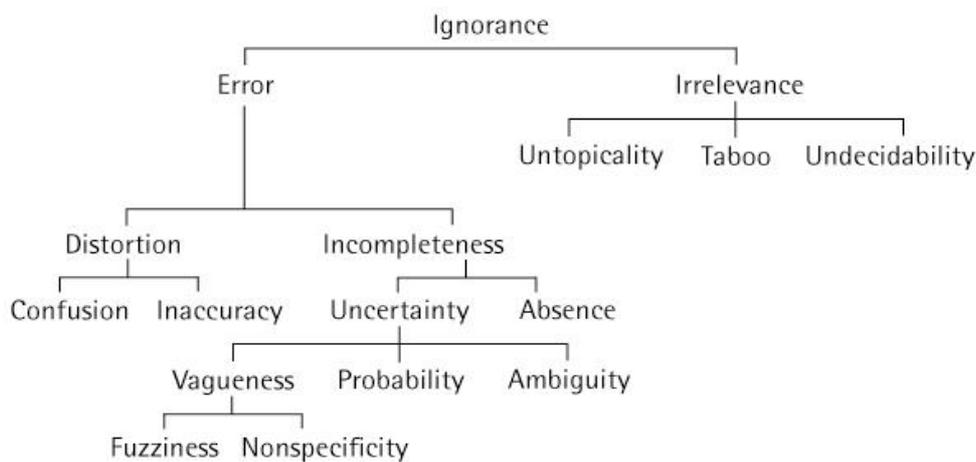


Figure Five: Smithson's taxonomy of medical uncertainty (1989)

The notion of uncertainty as arising secondary to irrelevance is an important and novel perspective for genetic practice. Issues of untopicality, taboo and undecidability may play an often overlooked role. With respect to what constitutes adequately informed consent, for example, medical professionals must identify which facets of testing to make explicit in consent conversations with parents and families. In the absence of standardised guidance, individual clinicians make decisions about what is considered (ir)relevant, or (un)topical prior to testing. Taboo issues, such as the potential for genetic testing to reveal false paternity may be avoided (Lucassen and Parker, 2001). The means to describe uncertainty within genetic work expands by applying notions from Smithson's taxonomy (1989), encompassing the elements of uncertainty related to social activities of information sharing and consent.

In Smithson's taxonomy, 'ignorance' is again related to the unknown as emerging from both error and irrelevance. Error represents a passive ignorance, arising from data and process. Irrelevance is an active form of active ignorance arising from social sources. From a social constructionist perspective, this provides a helpful distinction and emphasises the role of communication in both generating and sustaining uncertainty. The reasons for these 'irrelevances' provide important insights into how uncertainty shapes work and action, and should not be overlooked. These insights create questions such as why practitioners overlook certain features or risks of genetic tests in their accounts. Exploring sources of active ignorance provides important insights into the social construction of uncertainty in consultations about genetic testing.

Ignorance as either active/open or passive/closed also arises in the schematic ‘the igloo of uncertainty’ (Tannert et al., 2007). This represents an attempt to consider both the mathematical (probabilistic) and the moral considerations (usually unaddressed in risk assessments). Here, dangers are defined in terms of the outcomes of a given situation. In knowing there are dangers and risks, such as the risk of uncertain or incidental information, it becomes morally justifiable to reduce gaps in knowledge through research, or to take other steps to avoid ‘harm’ (as in those related to data, process and patient, outlined above). Tannert et al (2007) provide a taxonomy of uncertainty which acknowledges these factors, in addition to the moral component of uncertainty management. Their taxonomy brings us full circle: describing ‘objective uncertainty’ as either epistemological or ontological in nature before moving onto ‘subjective’ uncertainty, consisting of ‘moral’ uncertainty and ‘rule’ uncertainty.

The notion of ‘moral uncertainty’ describes well the current status with respect to the management of incidental information in genomic practice: in the absence of agreed, specific applicable moral rules, decision makers must rely on general moral rules, extending them to infer or deduce guidance for the special situation in question. As the conditions for informed consent in genomics are not yet established, previous criteria for informed consent continue to be applied, despite the acknowledgement of the challenge of summarising or describing meaningfully the potential outcomes of genome-wide testing, which are so broad in scope and implication. Decisions may be guided by intuition rather than knowledge or implicit/explicit moral rules. Here, members of relevant social groups behave on the basis of fundamental preformed moral convictions, in addition to experiential, internalised moral models. This will hold particular relevance to the practice of scientists and clinicians whose practice is deeply ritualised within the social (and scientific) norms of laboratory and clinical practice, and has links to tacit knowledge, addressed more extensively in chapter five when considering the role of expertise.

Uncertainty in Scientific Practice

Uncertainty is inherent in scientific practice: where uncertainty fails to be acknowledged and communicated meaningfully, consumers of science face placing too much (or too little) faith in what is known or described. Wynne (1992) described the four types of uncertainty with manifest consequences for scientific practice.

<i>Uncertainty Type</i>	<i>Description</i>
-------------------------	--------------------

Risk	Uncertainty with known odds
Uncertainty	Parameters of the uncertainty are understood, but the odds are unknown
Ignorance	Uncertainty is unknowable, but frozen under the controlled environment in which scientific practice takes place. This can become more evident when social commitments are made on the basis of such knowledge, and particularly as a science enters the public realm.
Indeterminacy	An open-ended characteristic of proposed causal chains in which it is unclear where the analysis of the natural world ends and where analysis for social commitments begins.

Table Four: Wynne (1992) Classification of Scientific Uncertainty

Wynne elaborates on the nature of indeterminacy, describing how

Indeterminacy exists in the open-ended question of whether knowledge is adapted to fit the mismatched realities of application (in) situations, or whether these (technical and social) situations are reshaped to validate the knowledge

Wynne, 1992:115

Complexity is central in this situated approach to the nature of ‘uncertainty’ in genetic work. Situated within a broader tradition (Collins and Evans, 2007) it aims to counter the narrow realist perspective that commonly overlooks the epistemological distinctions between risk, indeterminacy and uncertainty. This comes to bear in the genetics/genomics context: the information genetic testing can generate has consequences for the downstream deployment and applications of technologies, while demands on knowledge production and expectations for the application of genomic technologies in the clinical context drive social activities. There is an inherent conditionality in the types of knowledge production that are mandated and these are shaped by social policy. The identification of variants that are clearly pathogenic and provide a diagnosis, in correlation with the phenotypic features, is desirable. Microarray superseded karyotyping as the first line investigation for developmental delay owing to the improvement in diagnostic yield in using this technology. Production here is considered to be clinically actionable – or significant - knowledge, which constitutes the basis of clinical reporting: genomic variants that are identified and communicated to clinical staff, and subsequently (usually) to patients. Therefore, we might consider whether it is

always possible to distinguish between facts and values within socio-technical ensembles: where does the science end and the policy begin?

Precautionary Principle

The Precautionary Principle²⁰, emerging from environmental science, provides a strategy for managing risk and uncertainty when scientific knowledge or understanding is incomplete and evolving. As such, it has a practical application in considering both epistemic and ontological uncertainty (Kriebel et al., 2001), particularly for genetic medicine, where new knowledge – with potential clinical actionability and benefit – is always being generated. Application of the principle means that when an activity has the potential to cause morally unacceptable harm, then action should be taken to avoid or diminish the potential harm. Harm is defined broadly, being described as a threat to human life or health or as something resulting in inequality between present and future generations. The risk of harm is increased where conditions are imposed without adequate consideration of the human rights of those affected. This definition of harm has parallels to how harm can be considered in genetic medicine, encompassing consequences for the health and wellbeing of the proband and their relatives, for (potential) reproductive decision-making, as well as intergenerational consequences, impact on the autonomy (and future autonomy) of children in addition to broader considerations around equity of access to genetic testing (and the potential benefits of this). Actions to mitigate uncertainty are chosen as they are proportional to the seriousness of the potential harm, with consideration for the positive and negative consequences and considering the moral implications of both action and inaction. Assessed in this framework, the handling of uncertainty has both practical and ethical dimensions.

How can the application of the Precautionary Principle add to the consideration of uncertainty in genetic clinical practice? With the management of secondary variants being seen as a potential barrier to the mainstreaming of genomic testing in clinical medicine, a variety of research papers, commentaries and professional policies has emerged as a response to the potential harm of secondary variants for individuals and families when diagnostic genomic tests are performed in the clinical setting. For much of this work, the (potential) consequences are portrayed simultaneously as inevitable, yet morally unacceptable. Whilst attempts to address risk, ignorance and uncertainty are needed, they can also decrease public trust and complicate perceptions of an intervention or technology by amplifying unreal risk perceptions. This can manifest through the previously described notion of distortion (Smithson, 1989) that results in confusion and inaccuracy, and in taboo.

²⁰<http://unesdoc.unesco.org/images/0013/001395/139578e.pdf> ,<http://www.precautionaryprinciple.eu/>

Certainty Trough

The consequences of uncertainty – in particular, the extent to which an individual or group is concerned about, or appreciates and experiences uncertainty – have also been described as varying with respect to proximity to the technology in question. Members of different relevant social groups have also been described as having differing experiences of uncertainty in relation to a particular innovation. These differing beliefs are the subject of Donald MacKenzie's 'Certainty Trough' (1990), which compares the experience of uncertainty for three separate groups – developers, users and outsiders - in relation to a particular technological innovation (in this case, the use of so-called smart weapons, or intercontinental ballistic missiles). MacKenzie proposes that experiences of uncertainty are lowest among users - those charged with implementing a technology in practice - and highest among outsiders, who are most skeptical about a technology's particular merits.

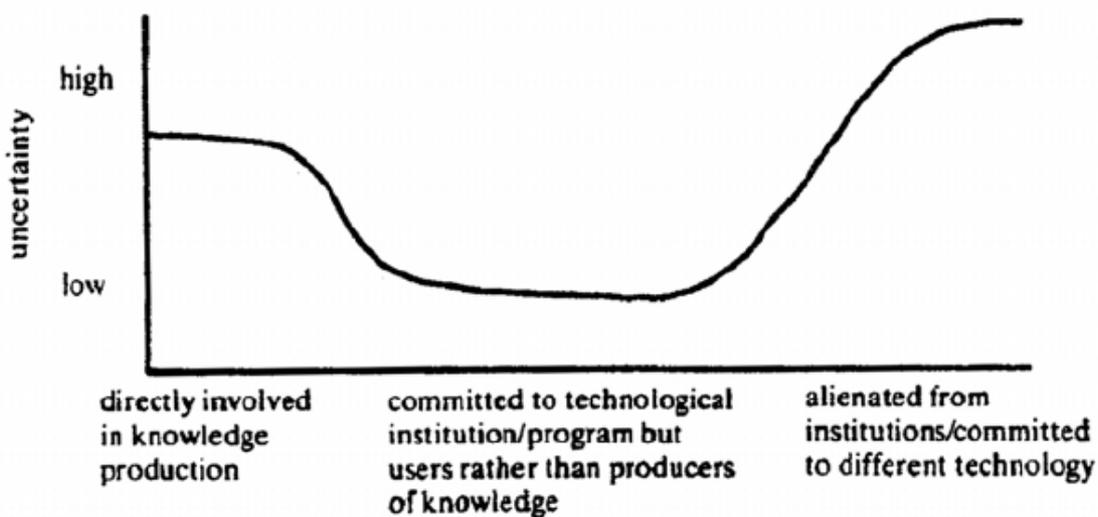


Figure Six: The Certainty Trough (MacKenzie, 1990)

The notion of members of different relevant social groups having radically different experiences of uncertainty (in relation to a particular innovation) is an important notion in considering how technologies and their associated uncertainties 'travel' between settings. As such, I align with Woolgar's suggestion that the uncertainty trough has conceptual value when considering innovations more broadly (Woolgar, 1994), as a heuristic rather than a universal framework for mapping or comparing beliefs. Criticisms of the model relate to the simplistic manner in which group affiliation is typified (Lahson, 2005), alongside the fact that the model fails to capture how scientists – and indeed innovators more generally – express 'excessive' faith and belief in their own research. For this empirical study, these criticisms can be put aside as those directly involved in the

development of aCGH technology are not considered. Rather than considering innovation *per se*, here, we consider the transition of an innovation to a new setting: ‘users’ of knowledge or those committed to technological institution are the clinical geneticists and laboratory cytogeneticists considered in the empirical study of the laboratory; those committed to a different technology might include paediatricians and neonatologists whose primary experience of genetic testing technology is through the use of karyotypes. Similarly, the characterisation within a particular group may prove difficult where paediatricians or neonatologists have a specific interest or expertise in genetics, or at least a specific genetic condition. An alternative approach could involve asking participants to self-define where they ‘lie’ on this spectrum. Regardless, the concept provides a useful means through which to examine how experience of and with a technological innovation shapes experiences of certainty and uncertainty.

Addressing Uncertainty

For data sources, a number of approaches have been advocated. Reducing the amount of data subject to interrogation is a key approach in the reduction of uncertainty, as is setting boundaries as to what is being sought within the available data. The use of gene panel testing, whereby panels of genes are selected for interrogation in light of a particular presenting phenotype, reduces the risk of identifying variants of uncertain significance and incidental findings. Clinical exome, or even whole exome (as opposed to whole genome) methods similarly reduce the risk of off-target variant identification in clinical testing. For dosage methods, the use of targeted testing, such as FISH or MLPA when a particular variant is suspected, again reduces the volume of data available for interrogation, thereby reducing the risk of off-target information being revealed²¹. Often FISH or MLPA is the preferred method of confirming a copy number variant, or family linkage studies may be used to assess a sequence variant. The aim of data-based interventions addressing uncertainty is to minimise the risk of off-target (uncertain) information becoming generated.

Process level interventions address how systems can more holistically approach the issue of uncertainty as it occurs across the sites of genetic work. The ACMGG advocates a highly contentious approach of systematically interrogating all sequencing samples for 56 genes related to 25 disease processes (Green et al, 2013). At least some variants found in the selected genes have analytical validity, clinical significance, and actionability, meaning their early (or pre-symptomatic) identification allows for potential benefit in terms of access to enhanced screening for complications or disease prevention for the proband, in addition to the identification of relatives who are also potentially at risk. The potential harm of unexpected secondary information is diminished as all

²¹ For further information, see article: Genetic and Genomic Investigations in the Neonatal Intensive Care Unit. Burke, KB, Howard, Z and Kamath A. Paediatrics and Child Health 2017; 27 (1): 23-27 <https://doi.org/10.1016/j.paed.2016.08.001>

individuals or families undergoing testing can be informed about this systematic screening, and the potential implications can be shared prior to testing. Knowing about the risk of this information may diminish harm in cases when it is then revealed: uncertainty is decreased by (potentially) increasing the amount of clinically useful information provided to patients and families, and consciously blinding (both healthcare professionals, probands and families) to other information. Despite this approach being advocated by powerful relevant social groups – indeed, by a group constituting part of the core set – it remains contentious. The selection of loci remains contested, as do the variants at each locus which are considered pathogenic: as such, the guidance has not been implemented at many centres.

Other process-based interventions have included attempts to establish a minimum informational requirement for valid (informed) consent when testing is undertaken (Ayuso et al, 2013). This frames the need to provide comprehensive information about the risks of incidental findings and variants of uncertain significance for the proband and the family as a moral duty, making the risk of 'off target' findings morally acceptable when probands and families have been appropriately prepared for this risk, through providing information, negotiating consent and providing support through counselling. Indeed, movements away from 'informed' consent to 'generic' models of consent (Dondorp et al., 2012) have also been suggested, given the broad range of potential outcomes and implications of genome-wide testing that challenge the central notions of informed consent in terms of the (in)ability to address all potential outcomes during the consent process. Deciding what constitutes "adequately informed" consent means that uncertainty itself has an important ethical dimension: which types of uncertainty must be made explicit to patients and proxies prior to testing?

[Uncertain technologies: \(genetic\) science and technology and their relationship to uncertainty](#)

In this section, I discuss how the literature has addressed issues of uncertainty in genetic practice as it emerges from the technical artefacts which facilitate genetic (and genomic) testing and the sociotechnical ensembles emerging from the use of chromosomal microarray in the clinical context.

Uncertainty around both technical artefacts and the socio-technical ensembles they enable can be considered at multiple levels. First, uncertainty as an objective property of the material under examination – the genetic substrate - or the data, or representation of the material that the technology facilitates. Next, uncertainty as related to the technology itself: for example, the resolution, sample or process quality control or the appropriateness of a particular technology's use in a given context. When technologies produce data, subsequent analysis and interpretation of the findings can give rise to further uncertainty arising from the complexity of variant annotation and

interpretation, with the quality and value of comparative and functional genomic information and genotype-phenotype relationships providing both evidence and uncertainty in different informational contexts.

Variants of uncertain significance exist in 'an interpretive void': a midpoint on a spectrum extending from variants known to be benign through degrees of (un)certainty to those variants known to be pathogenic (Richards et al., 2015). The term variant of uncertain significance can itself be subjected to scrutiny. Variants are a difference from the usual base at that position in the reference genome sequence. The use of 'variant' avoids the semantic disputes associated with terms like 'polymorphism' and 'mutation', which have more obvious associations with frequency and disease effect. The use of 'uncertain' is also contentious: implying that 'certainty' is associated with other variants. This is rarely ever the case, particularly with respect to prognosis and penetrance which is often overestimated due to the phenotype-driven ascertainment of individuals and families with a particular disease or disorder (Antoniou et al., 2003). Variants might be classified as pathogenic despite highly uncertain implications for a proband owing to limited understandings of gene x environment interactions modulating their effects²².

Policymakers are often called upon to make decisions when faced with uncertainty. Incrementalist orientations (Lindblom, 1959) embrace how waiting for more data or consensus to emerge is not always feasible and, as such, policy progresses through successive limited comparisons, using the knowledge or norms 'at hand' in relation to a particular technology or method. These observations create a foundation on which to consider the similarity in both the governance and the 'real-world' situated realities of applications of (new) science and technologies when uncertainty is problematic (Collingridge, 1981). Incrementalists employ flexibility as their overriding philosophy: trial-and-error, accompanied by a learning process rooted in responding to error or the unexpected. This has parallels with the Collingridge 'falliballist' approach, accepting uncertainty as inherent and minimising the costs of error whilst optimising opportunities for development or implementation. This shifts the aim from decisions that predict success towards those with a basis in corrigibility, control, flexibility and insensitivity to error (Collingridge, 1981).

The next section explores the uncertainty around establishing the chromosome number in man, seeking to demonstrate the enduring presence of uncertainty in genetics and arguing how it is the scope, rather than the nature of uncertainty, which evolves with new sociotechnical ensembles and knowledge.

²² Mirroring this is the 'polygenic dust' model (International Schizophrenia Consortium), in which many common variants which are proven risk factors for disease remain classified as benign using standard nomenclature because the magnitude of their individual effects is thought to be so minuscule.

Visualisation and Representation: depicting certainty (and uncertainty)

Science depends crucially on its own ontologies, so very different from commonplace ontologies, painstakingly assembled from diverse shards of evidence as a mosaic is assembled from tiny stones of diverse colour and shape. It is observation, grounded in training, collective, cultivated habit that fuses these bits and pieces into a picture – often a literal picture crafted by the techniques of scientific visualisation

Daston, 2008: 110

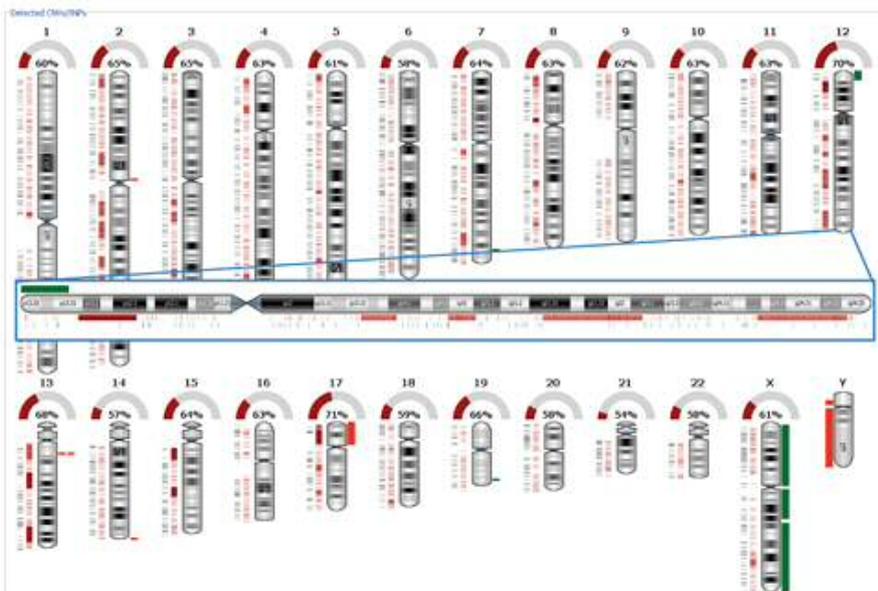
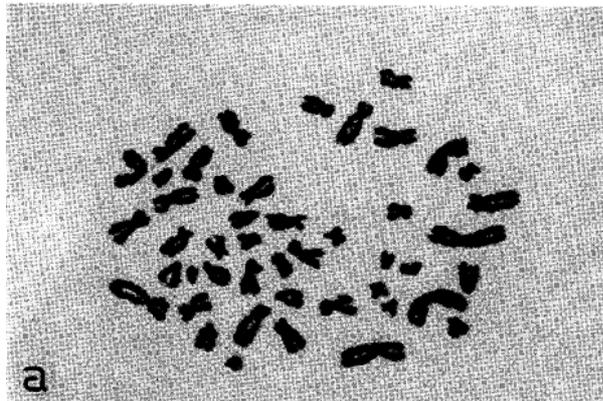
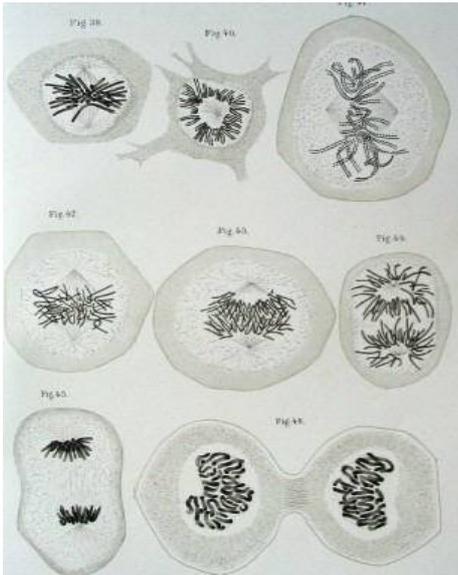


Figure seven, eight and nine: Visualising chromosome material throughout the ages: representations through drawing of the genetic material by hand following visualisation by light microscopy, photographic

representations using light microscopy and photography and digital representation of the chromosomes following microarray analysis.

The role of technological artefacts in how scientists and physicians think about disease is well documented: particularly the role of imaging technologies such as X-Ray, ultrasound and scanning technologies such as computerized tomography and magnetic resonance imaging (Kevlas, 1997). 'Clinical' visualisation – perception of the patient, facilitated through technologies such as the stethoscope and through medical knowledge - has been developed as an extension of the notion of the 'clinical gaze' (Foucault, 1963). Genetic technologies in the clinic have been credited as realizing a new type of 'gaze' – the 'molecular gaze' (Rose, 2007). Through the molecular gaze, there is a need to depict the genome as a standardised scientific object, through which (clinical) meaning is bestowed or acknowledged.

Visual representations of the genetic substrate have a rich history and important role in the field of human cytogenetics. The representational artefacts in use – from the light microscope to the microarray – provide an evolving representation of the chromosome, and the way in which these images are gathered, constructed, arranged, interpreted and subsequently disseminated has been the subject of technically driven development and change. The result of this process is a shared visual ontology for cytogenetic practice. This visual ontology, developed initially through the use of hand-drawn depictions of genetic material viewed with a simple light microscope (see figure seven), was seen as the way in which genetic work could become a more accurate and reliable – a more *certain* means of distinguishing the nature of genetic material and its variation. Later this visual ontology would turn to attempts to account for disease and difference, aligning the visual ontologies of the chromosome with the signs and symptoms described in the clinic, creating a new nosology on which notions of health and illness are based. Visualising variation provided the opportunity to associate genetic disease with a location in the genome, giving it a distinct cytological, or molecular identity.

Advances in laboratory techniques played an important role in the ability to physically 'see' genetic materials at ever improving resolution. The primary aim of early work in cytogenetics was the attempt to ascertain the chromosome number of different species. The ease with which chromosomes could be visualised using early, rudimentary microscope technology contributed to their popularity as a subject of study and examination. As such, the way in which chromosomes could be rendered visible by technological advances was tied to their emerging role as a subject for analysis in the laboratory. Early visualisations of chromosomes occurred through two optical 'instruments', namely the human eye and the early microscope, used in tandem to create hand-drawn graphical representations of chromosomes, as seen via the microscope (see figure seven). These early representations were therefore constituted technically as forms of observation, or gaze.

Dichotomisation of the relationship between these objects – the genetic material itself (the chromosome) and the technology (the microscope) – permitted the characterisation of the genetic material as an objective material, previously interpreted erroneously by the subjective human eye. The representations, or inscriptions (Latour, 1987, 1991), carry deep meaning, and can be transmitted around and between members of relevant social groups. These inscriptions are central to the polemic practice of consensus building, forming a closure mechanism in which the absolutism of the representation becomes challenging to contest. This consensus was key, in a scientific sense: though the inscriptions (at this stage, in the form of drawings) were a rudimentary representational method, cytogeneticists developed mechanisms to mitigate against bias and error, such as the production of drawing based on a single slide by multiple individuals, with this communal agreement serving as an indication that counting was accurate. From a sociological perspective, resemblance, as described here, presumes the centrality of the primary reference, or original – in this case, the genetic material itself. Representations or copies render this material only partially, and often inaccurately, representing a source of interpretive flexibility. For the dark ages of cytology, the selection and circulation of images was an important social activity, highly distinct from image perception, which must be considered as a (largely) individual activity.

Commentators account for the persistent and incorrect assertion of the human chromosome number of 48 through reference to the investigators' preconceptions, crediting methodological and technical improvements for the 'correct' count in 1956. Improved cell culture techniques meant that samples could be more easily acquired from blood and tissue samples, as opposed to from bone marrow alone (Martin, 2004; Lindee, 2005). Colchicine was used to arrest the cell cycle when chromosomes could be visualised best²³, whilst the accidental use of a hypotonic solution – the 'hypotonic miracle' (Martin, 2004) – meant that chromosomes could be 'spread out' within the nucleus, allowing them to be identified and distinguished from one another more easily. As is typical of such techno-scientific progress stories, claims that under these new technical circumstances, there was no need for interpretation and therefore no chance for pre-conception to exert its long-felt effect describe how the technical was seen as a means of overcoming the social and all the inaccuracy it entails: 46 chromosomes had to be counted. Chromosome counters themselves suggested that alignment with the expected counts could operate at the subconscious level: once the number was 'known', it was not possible that it could not influence the technician at work. Error is seen as emerging from interpretive practices, and the inability of the operator to act subjectively. Technologically deterministic perspectives maintain that the twenty years during which an incorrect account was accepted as fact can be explained by ignorance, misconception and self-satisfaction with the familiar, trusted methods. Using perspectives from the sociology of scientific knowledge,

²³ During chromatin condensation at the start of prophase chromosomes are easily discernable (through microscopy) as distinct entities

this argument is weakened by its asymmetry: why would preconception be such an important factor prior to the 1956 discovery, and not afterwards? It is more reasonable to assert that the poor resolution of the method used when chromosome counting first took place allowed for greater interpretive flexibility, allowing cytogeneticists to 'agree' on numbers which, albeit erroneously, became a constant. Corroboration served to close the debate: in the inter-subjective activity of counting, closure was achieved through concordance between socially, and scientifically, independent sources. The more 48 was quoted, the more certain it became.

As an established 'fact', human chromosome counting attracted little attention between 1930 and 1950. Partly this was associated with the failure to recognise (from a social perspective) the medical applications of human cytology, and (from a technical perspective) the fact that the chromosomes of many easily available laboratory animals were larger, fewer and easier to obtain and manipulate. Sociopolitically, this period of decreased interest in the field of human cytology is seen as a period that distanced cytogenetic practices from the popular eugenics of the period.

The variation in the reporting of this 'fact' was accounted for through various means, with justifications around racial differences forming a major part of the discourse. Guyer, an early human cytogeneticist, described how the chromosome number of white subjects was "considerably in excess of those found... in (my) negro material" (Guyer, 1914). Establishing this 'fact' – and replicating it successfully – became important as cytologists attempted to ensure the credibility of their work, demonstrating it to be the product of logical interpretation and rational thinking. Interpretive flexibility was seen as explaining the ever changing accounts of the human chromosome number and was given social justifications, such as those related to race, alongside socio-technical accounts, such as those related to the type or quality of biological sample used. Improvements to the techniques employed, such as those relating to fixation or the use of different cell lines – provided a closure mechanism through which variation was accounted for and then minimised between relevant social groups. The analysis of 'agreement' between scientific communities and the production of inscriptions represents the process of closure: the resulting representations are the products of inherently social activities. These representations and their analysis and description become a rich repository of social action. Interest in eugenics and scientific accounts of ethnicity were gaining increasing attention and, as such, significant attention was devoted by the early chromosome counters to ethnic origin as the basis of variation. The lens through which variation was accounted for was that of race: other cytogeneticists were examining samples from (white) Europeans whilst American cytologists led by Guyer, worked on samples largely acquired from male African-American subjects. Guyer, originally a zoologist, had a strong interest in ethnicity and spoke publically in support of eugenics, lamenting the 'mongrelisation' of

ethnic groups and the (high) rates of reproduction among immigrants in the United States. Ethnicity was used as a closure mechanism accounting for the variation of human chromosome number.

Martin (2004) observes, in his description of how improvements in visualisation allowed for a shift in the ontological orientation of cytogeneticists:

This .. changed the counting game from the question of 'how many?' to the question 'are all members accounted for?'. An analogy would be counting how many people are in a room versus taking attendance.

Martin, 2004: 935-936

This suggests that certainty about the accuracy of the human chromosome number – or the resolution of uncertainty - was important in allowing the ontological concepts to move beyond simple 'counting' to the categorisation of 'normal' from 'pathological' chromosome sets (Canguilhem, 2012). The association between the phenotypic features of trisomy 21 (Down's Syndrome) and the identification of 47, rather than 46 chromosomes in these patients (Lejeune et al, 1959) resulted in the recognition that a standardised way of naming and identifying individual chromosomes was needed. This decision was made at an institutional level, identifying and naming chromosomes by size (Lindee, 2005), providing another closure mechanism with respect to how chromosomes should be ordered, named and identified. This created a common reference for use by relevant social groups. This had real consequences for representation too, as the 'standard karyotype' emerged to represent all chromosomes in one picture. Photographs were developed, and chromosomes cut out and rearranged by size, allowing systematic, standardised representation for the identification of normality and abnormality²⁴.

What does this brief case study into the evolution of cytogenetics tell us? Without being reductionist, it is apparent that 'new' technologies can give rise to a new episteme: in genetics for example, the microscope gave rise to a new and wide range of knowledge. This can be seen through SCOT: through the roles of interpretive flexibility, relevant social groups and closure mechanisms. It also demonstrates clearly how observation and representation are collective practices, through which actors learn and agree through implicit and explicit communication, reasoning and decision-making how to see their object of study in a coordinated and concordant way (Daston, 2008). This has clear parallels with the work of the laboratory, clinic and family as members of an extended bioclinical collective (Bourett, 2005), coordinating how the genetic work will be collectively rendered meaningful.

²⁴ Interview with Malcolm Ferguson-Smith, 5th December 2003 by Peter Harper. 'Interviews with Human and Medical Geneticists' series. Held at Special Collections and Archives, Cardiff University, Cardiff UK.

Each stage of genetic technological development can be characterised as having an early phase of uncertainty, as the ability to interpret what is seen is limited, then subsequently improves and eventually stabilises. Uncertainty persists, but in a new form – the aforementioned zones of uncertainty persist, albeit in contracted form. These zones may shrink and expand even after a sustained and useful stabilisation of knowledge, and how these are characterised, curated and enacted is explored later, through processes of classification (chapter four).

Next we look at the social construction of uncertainty-in-interaction through the work of diagnosis in the clinic.

Uncertain interactions: uncertainty in the genetic consultation

Research into genetic talk in the clinic has taken two main forms. Firstly, interview studies in which the accounts of geneticists and genetic counsellors (and less frequently, patients and service users) are sought to gain insight into the processes of everyday genetic work. Secondly, observations (either audio-recorded, video-recorded or ethnographic) have observed genetic counselling in action. Analysis again has two main approaches: quantitative methodologies in which talk is coded and classified using standardised tools and qualitative methods, which use an inductive approach without a preconceived hypothesis employing methods such as discourse analysis, conversation analysis and ethnography. Within these analyses, uncertainty – as either an objective property of a genetic test or diagnosis or as a subjective experience constructed or negotiated in interaction – is a key theme.

Navigating diagnostic uncertainty in interaction

Dysmorphology, the evaluation of abnormalities of physical form, performed mainly by geneticists and paediatricians, has formed an important site of study for the role of the uncertain in the clinical consultation. Decisions about genetic testing – particularly with regards to the assessment of dysmorphology – involve a particular form of medical examination, perception or ‘medical gaze’ (Foucault, 1963), seeing and assessing physical features in a structured and focused manner. Ethnographic studies of a genetic clinic (Featherstone et al., 2005; Latimer et al., 2006) demonstrate how decisions to look for chromosomal or genetic variants via a cytogenetic or molecular test occurs via a negotiated process, existing alongside other ‘traditional’ means of diagnosis (Brookes-Howell, 2006; Kerr, 2000) employed in the clinic, namely history taking and physical examination, followed by professional deliberation and consideration. Representation is a central concept, as photographs and descriptions are presented, examined by professionals and

discussed, culminating in decisions that seek to resolve uncertainty in diagnosis, usually through the use of genetic testing.

Variants of Uncertain Significance in interaction

With respect to variants of uncertain significance, notions of living between illness and health are captured in numerous ways in the social science literature: the pre-symptomatic person (Konrad, 2003), the partial patient (Greaves, 2000), the perpetual patient (Finkler, 2010) and the patient in waiting (Timmermans and Buchbinder, 2010). Timmermans and Buchbinder (2010) described the consequences of the extended use of newborn screening technologies in the generation of diagnostic uncertainty when results of screening indicate the increased risk, but not necessarily the presence, of disease. Whilst screening for a larger number of diseases is technologically feasible, and justified by the assumption that families would welcome information about rare genetic disease (Bailey et al., 2006), there has been less work on the role of technologies, especially in terms of the nature of communication between families and health care professionals and the consequences for the lived experience of families (Grob, 2006; Grob, 2008). Diagnostic uncertainty is 'hardwired' in both screening and genome wide technologies, and this uncertainty can create interactional dilemmas. Screening results outside the (pre-set) normal range do not always clearly correlate with defined disease categories. This is analogous to variants of unknown significance: with patients existing between pathology and an undistinguished state of normalcy. Questions remain in both instances about whether disease will develop, and also what the condition may actually be. The 'diagnosis' of uncertainty – whilst biologically and socially ambiguous – requires social action. For newborn screening, this may be engagement in further testing, undertaking prophylactic diets or feeding regimens, and undergoing further investigations by medical professionals. For variants of unknown significance, it may involve referral to specialist genetics services for further evaluation, testing of parents and siblings and surveillance for other potential signs and symptoms of disease or disordered development. Both processes involve becoming a 'patient-in-waiting' (Timmermans and Buchbinder, 2010). Both involve a shared 'role' between the parents and the infant or child being tested: parents may be questioned, reassured and supported; later, they may have to submit their own samples for analysis, rendering them patients in some sense, whilst the child is examined as a (potential) patient. Both are subject to the clinical gaze.

For children under medical surveillance following newborn screening, there will most likely have been no cause for enhanced medical surveillance prior to participation in newborn screening. This differs from infants existing as 'patients-in-waiting' after a variant of unknown significance is identified, who may still require observation, monitoring of developmental milestones and monitoring for the recognition of potential symptoms. Both involve further testing, with the ultimate aim of

establishing 'a diagnosis': a process of deliberate judgment, and a pre-existing set of categories (Jutel, 2009), initiating a set of experiences, identities, life strategies and subsequent medical actions.

Timmermans and Buchbinder contest that the, "closest group of people similar to patients in waiting are people who undergo genetic susceptibility testing for conditions such as breast cancer, thrombophilia, Huntington's disease or Alzheimer's disease" (Timmermans and Buchbinder, 2010). In these contexts, patients-in-waiting can be pre-symptomatic or asymptomatic, but with known increased risk for a condition, usually due to information from the family history. They may also be those who are neither sick nor healthy but suffering from 'protodisease states': conditions such as high blood pressure, obesity or hypercholesterolaemia, which represent a risk for future illness, rather than true disease (Novas and Rose, 2000). Children with disordered development are also described by Timmermans and Buchbinder (2010) as 'patients-in-waiting', subject to assessments to determine their eligibility for social and medical care.

Timmermans and Buchbinder (2010) describe four common characteristics associated with the 'patient-in-waiting' status. Patients inhabit a 'liminal space' between pathology and normalcy, often failing to fit the diagnostic category in the absence of the correct complaints. As such, the ontological status of the diagnostic categories, and the patient's 'ability' to fit them, is unclear. This results in a long period of uncertainty – largely as a result of medical bureaucratic factors – the necessity for more testing, observation or monitoring, with the aim of establishing the absence or presence of a diagnosis. This contrasts with the established norm of disposing of patients by treating them efficiently (Berg, 1992), and means that patients remain under surveillance for long periods.

Through this process, the clinic becomes a site of knowledge production. Diagnostic certainty (and uncertainty) represent forms of categorical work (Bowker and Star, 1999). Diagnostic designations and categories are in constant flux, resulting in the criteria for diagnosis being (re)constructed, refined, contested and expanded. Whilst categories can reify diseases, (new) knowledge production means they are constantly changing: with the diseases themselves evolving ontologically (Aronowitz, 1998). Genetic diagnosis can complicate a diagnosis by asserting a 'genetic logic' that may disregard the presence or absence of clinical symptoms, or produce unintended consequences that require ongoing 'bridging work' by professionals (Timmermans and Buchbinder, 2012). For patients, this process may also result in declassification without reclassification: a state in which they are no longer defined as 'healthy' nor 'genetically unwell', rather they hover in an in-between state due to abnormal test results.

These processes demonstrate how clinical work can encompass both old and new styles of professional reasoning. Shaw et al. (2003: 5) describe how clinical decision making is not supplanted by new molecular technologies, but through the existing ‘hierarchies and traditions’ of clinical work. New technologies can extend the diagnostic repertoire of clinical decision making, but the value of testing is usually negotiated in relation to ‘traditional diagnostic techniques of history, observation and examination, investigation and diagnosis (2003: 16).

Imprecision and uncertainty in medical talk

Uncertainty can be socially constructed, and also constructed in the discourse of institutions such as the clinic. Linguistic approaches to medical interaction have also considered how uncertainty and imprecision are manifest in the discourse of the clinical encounter. Even where the frame of the encounter is not that of uncertainty, Dubois (1987) described a taxonomy of modalities deployed in conversation to convey imprecision.

Verbs	think, suggest, guess
Auxillaries	might, may, could
Nouns	estimate
Adverbs	roughly, approximately

Table Five : Dubois (1987) Taxonomy of modalities deployed to convey imprecision

Linguistic manifestations of uncertainty in the clinic can also include ‘approximators’, such as ‘sort of’ and ‘nearly’ and ‘shields’ such as ‘I’m not sure’ and ‘as far as I know’. Often it is the form rather than the content of the discourse which relays important indices of uncertainty and imprecision.

Uncertain identities: consequences for families of an uncertain diagnosis in a child

Having summarised the antecedents of ‘variants of uncertain significance’ in genetic technologies, and their consequences for the clinical consultation and notion of diagnosis, I will now look at the literature related to how parents and families embody variants of uncertain significance in their identities – both individual and familial – in addition to how diagnostic uncertainty impacts on their experience of illness and disease.

Previous examinations of patients’ experiences of uncertainty have focused on the experiences of patients contending with ‘uncertain’ syndromes, or of symptoms and conditions which are not given medical legitimacy (Nettleton, 2006). This literature emphasises the way in which medical

professionals and processes normalise ambiguity and risk, contrasting the patient experience of uncertainty in diagnosis as a problem awaiting resolution. Genetic information which adds to the aetiological explanation of disease or disordered development improves parental coping and adaptation, increasing the sense of control and providing relief from (often misplaced) guilt about other potential causes (often related to maternal behaviours in pregnancy). For families receiving a 'normal' result following chromosomal microarray for children with autistic spectrum disorder, qualitative work describes a 'disappointment' associated with not identifying a clear cause (Giarelli and Reiff, 2015).

Qualitative work with families undergoing chromosomal microarray testing has mainly been conducted as interviews with families who have received a variant of unknown significance (Reiff et al., 2012, 2013, 2014). Further work has been performed combining qualitative data with the use of standardised tools to assess child vulnerability and parental stress when a variant of uncertain significance is identified (Jez et al., 2015).

Reiff et al. (2012) conducted semi-structured interviews with families receiving pathogenic and VUS results following chromosomal microarray testing in the paediatric outpatient setting. Three key themes emerged. In the comprehension of results, families expressed initial difficulty in understanding the meaning and implications of both pathogenic and uncertain results, with understanding improving quickly with the availability of skilled counselling and further information resources. Most families reported that comprehension was often made difficult by communication with non-genetic specialists, who lacked the ability to provide clear information about the nature and implications of findings, and that comprehension was improved through communication with a genetic specialist. Parental understanding of variants of unknown significance was increased through additional counselling and the provision of supplementary information (Jez et al., 2015; Reiff et al., 2012). Long waiting periods to see specialists, and the delivery of results over the phone also had negative consequences for parental experiences of understanding results, allowing misunderstandings to linger and become compounded.

Novas and Rose (2000) described how individuals with a genetic diagnosis are expected to optimise their health by gaining knowledge of what the diagnosis implies. A self-administered questionnaire study examined the parental understanding, perceived value and perceptions of child vulnerability and parental stress after a variant of uncertain significance had been found following chromosomal microarray testing for developmental delay or autistic spectrum disorder (Jez et al., 2015). Many parents drew a causal link between the VUS and their child's disordered development, yet most would not undergo testing again with another child (the reason for this was not elicited). Interestingly, parents framed the test as a 'rule out' exercise: an opportunity to exclude serious,

potentially anxiety-provoking diagnoses, and as such, an uncertain result provided relief that more serious diagnoses had been excluded. No association with parental stress or perceived child vulnerability was established. The enquiry was limited through its use of categorical designations to measure parental perspectives, and through a failure to collect demographic data. Low participation was also noted: potentially those with (more) problematic experiences of uncertain genetic results may not have participated.

Whilst parents primarily expressed relief at finding a causal explanation for their child's medical problems, some also embraced an uncertain result, as the lack of definitiveness meant there was still a possibility of a causal process which might improve, or be reversible, with genetic anomalies being framed as irreparable (Reiff et al., 2012). In the same study, the authors expressed concern about how parents (potentially wrongly) assume that a normal CMA result means the cause is definitely not genetic in origin. A 'result', even when uncertain, provides the opportunity to alleviate misplaced parental guilt about other potential aetiologies, such as embryopathies caused by alcohol or foodstuffs consumed in pregnancy, as well as being empowering with respect to accessing resources, particularly education services.

For the families of children receiving a diagnosis with largely variable or uncertain phenotypic features and disease course (Fragile X, Klinefelter or Turner Syndromes), parents reported ambivalence about the diagnosis, often holding both positive and negative views about the impact of diagnosis simultaneously. Notably, they were comfortable and able to express the inherent uncertainty contingent upon the diagnosis about what the result may mean for the abilities (and inabilities) of their children (Whitmarsh et al., 2007). Multiple studies have demonstrated how parents reject and criticise health professionals who describe children in terms of their genetic diagnosis, preferring the simplicity of (even a complex) diagnosis rather than the multiplicity of the child and their problems (McKeever and Miller, 2004; Jez et al, 2015). This counters the discourse that patients merely seek more detailed prognosis for their condition when testing is undertaken, with parents instead drawing on accomplishments and characteristics of their own child to distance themselves from the (potential) implications of a diagnosis (Landsman, 2003). In this sense, uncertainty is valued, with parents conceptualising even an uncertain diagnosis as 'more than a label'. This has parallels with clinicians, who may doubt a genetic test result on the basis of their clinical judgment (Shaw et al., 2003).

Negative consequences of uncertain results following chromosomal microarray include parental misunderstanding of the value of the test (Reiff et al., 2012, 2013, 2014) and the role of uncertain information in preventing parental and familial adaption to the day-to-day management of a child with complex needs (Biesecker and Erby, 2008). The parents of children without a diagnosis, and

individuals with inconclusive results (as opposed to those with a definitive diagnosis) experience greater levels of stress and additional challenges in the comprehension of results from genetic testing (Ardern-Jones et al., 2010; Maheu et al., 2008).

In summary, the apparent consequences of identifying a variant of uncertain significance for family dynamics and notions of identity are variable. In the paediatric population, these are largely focused on disorders of development such as developmental delay and autistic spectrum disorders in older children, rather than testing in the neonatal period when the phenotype is less well characterised. The timing of interviews and questionnaires in relation to receiving the result of chromosomal microarray testing has been overlooked, and studies have not yet addressed the potential for parent/familial concepts of uncertain information to evolve longitudinally.

Conclusion

In this chapter, I have examined how previous accounts of uncertainty as a problematic, monolithic phenomenon have failed to capture the nuanced complexity of medical uncertainty, and the consequences for the lived experience of families. Typologies of uncertainty – and indeed, empirical descriptions of uncertainty – counter this, providing an engaged means by which to describe the nature of uncertainty as it arises in the places of genetic work, as well as its relation to social and technical practices.

How can a better characterisation of uncertainty be helpful for clinical practice? How much of the backstage (the laboratory) uncertainty of clinical genetic/genomic practice is it reasonable or practical to expect patients to understand? Clear delineation and placing an emphasis on zones of uncertainty when genomic variants are reported is, to some extent, the prevailing trend; it supports an ideology of uncertainty reduction in health care. Zones of uncertainty – extending on Sarangi and Clarke's (2002b) description of zones of expertise – contract and expand as new technologies and practices are enacted in the clinic. These zones are material, interpretive and relational. With respect to the material and the interpretive, the nature of the uncertainties remains the same, and rather it is the scale of magnitude at which they are experienced which is subject to change. There have always been incidental findings in medical and genetic practice, however, the use of higher resolution genetic technologies – sequencing rather than dosage methods – will mean these are rendered visible with greater frequency than before.

Creating and curating clear zones of uncertainty allows doctors, and therefore patients, to be aware of the uncertainties regarding the benefits and harms of particular investigations such as whole exome or whole genome sequencing. Yet uncertainty, in the form of a variant of unknown

significance, may also represent uncertainty as a source of possibility or hope. Where an extensive *diagnostic Odyssey* has failed to yield a cause for a particular phenotype, the identification of a tangible abnormality of any sort may constitute a meaningful event: it has the potential of achieving a diagnosis. Indeed, these are not just zones arising from the material: the extent to which the recognition of zones of uncertainty - as a relational act - occurs between the clinician and the patient when genomic investigations are undertaken has yet to be empirically explored. As a field of scientific practice, genetics has been keen to counter this through the inclusion of social and bioethical expertise: whilst sociologists or bioethicists cannot perform experiments or 'do' science, they have engaged meaningfully in technological discussions and contributed significantly to scientific debate through immersion in the language and ideas of genetic practice, to enormous mutual benefit.

Whilst cognitive, statistical and philosophical conceptualisations of uncertainty are well developed, considering these alone risks abstracting uncertainty away from social and cultural antecedents and consequences. Highly rational models of uncertainty – such as those borrowing from psychological and cognitive frameworks and those focused on risk and decision making abstract uncertainty from actual behaviour, paying insufficient attention to social, cultural and organisational forces. A comprehensive sociology of medical uncertainty will embed the norms, beliefs, rituals and institutional responses within its account, acknowledging imperfect knowledge, incompleteness, inconclusiveness and vagueness in the everyday. Uncertainty does not exist in itself as an abstract entity but, rather, can only be experienced and recognised in relationship to order (Douglas, 1966). More differentiated order creates greater uncertainty: what is ordered and known defines what is not known. As the sphere of knowledge expands, the surface of uncertainty - the boundary of what is known (as far as this can be appreciated) - expands with it.

In the next chapter, I examine this phenomenon with relation to the classification and categorisation of genomic variants. By describing how the sociology and science of classificatory work and categorisation seek to classify genetic variants, I reveal how zones or diagnoses of uncertainty are created in which the contested and unknown can be 'managed' for work in the clinic.

Chapter Four: Classification and Categorisation

In the previous chapter, I explored how uncertainty is characterised both as a concept in medical sociology and more specifically as a social and ethical challenge in genomic medicine. In this chapter, I examine how uncertainty is manifest and accommodated in taxonomies of genomic variants, looking at the emergence and development of categories to rigidly define the uncertain. I explore the literature related to the social function of classification and categorisation, differentiating this process explicitly from issues related to the identification and naming of genomic variation. The expansion of categories to render genomic variants clinically useful is revealed and explored, describing how uncertainty has been 'lumped' (McKusick, 1969). This lumping allows uncertainty to be tolerated within genetic work, with categories constituting boundary objects for the management of uncertainty across the environments examined later in this inquiry, notably the laboratory, the clinic, and the life-world of the family.

We demand rigidly defined areas of doubt and uncertainty.

Vroomfondel, Philosopher

The Hitchhiker's Guide to the Galaxy, Douglas Adams

Setting the scene: categorising genes, classifying people

The development of classificatory systems for genomic variants supports the interpretation of genomic information for clinical use, extending the notion of the clinical gaze (Foucault, 1963) to the 'molecular gaze' (Rose, 2007). Ascribing meaning to genomic variants has scientific, biomedical and social antecedents and consequences. Edward Yoxen (1982) contended that, although medical and scientific conceptions of disease are socially determined, they are grounded in a material reality. This material reality constituting the object of analysis – be that chromosomal and gene copy number in array CGH, or the sequences of bases in the protein coding regions in exome sequencing – exists in and of itself in a 'material reality' (1982:144). The process through which the material reality is observed, mapped, annotated and interpreted is highly social. Yoxen contends that knowledge of the material reality plays but a small part in the construction of disease. Instead, accounts of disease emerge from the structural constraints of the modern healthcare system, economic and professional interests, and the organisation and distribution of genetic expertise within clinical environments. This echoes the description of chromosome counting as a contingent activity.

In conceiving genetic disease as both materially and socially determined, Yoxen's conceptual work underpins Abby Lippman's (1991, 1992, 1994) notion of geneticization: the 'ongoing process by which differences between individuals are reduced to their DNA codes' (1991: 19). Here, the code – the DNA – is material; its consequences are highly, perhaps even primarily, social. Geneticization is a conceptual extension responding to the 'new genetics', emerging from the literature of medicalisation and feminist literature critical of genetic reductionism, determinism and essentialism (Arribas Ayllon, 2016). It has been argued that this reduces the individual to 'a molecular entity, equating all human beings, in all their social, historical and moral complexity, with their genes' (Nelkin and Lindee, 2010: 2). Through this, genetic markers identify and create new categories of people who would otherwise remain undifferentiated, designating populations of risk, such as breast cancer or Alzheimer's disease and designating individuals as being part of a social group of affected persons through genomic designation (Navon, 2011).

The geneticization of human disease and difference emerging from biomedicine was seen as a negative force, and a form of molecular reductionism (Lippman, 1991, 1992). Nelkin and Colleagues (1994) described the potential social power of simple genetic diagnostic tests, with their simplicity and scientific legitimacy meaning that potential social harms could be overlooked prior to implementation. The scientific and social salience of 'gene talk' transformed the molecular into a source of social difference, with potentially destructive ends, driving society's embrace of genetic essentialism, and its status in defining kinship, health (and disease) and responsibility (Nelkin and Lindee, 2010). Symmetry emerged through positive accounts of geneticization (Hedgecoe, 1998, 2001).

Geneticization is both a social phenomenon, a subject for empirical examination (largely by social scientists); and an analytic or conceptual lens, through which the impacts of genetic knowledge and practice can be examined (a position usually assumed by philosophers and bioethicists). Empirical work has challenged the way in which geneticization is actualised in medical and social practice, leading to the criticism that the geneticization concept may in fact oversimplify the individual, social and biomedical impacts of genetic discourses (Kerr, 2004a). The study of geneticization has embraced two key methodological approaches. Firstly, ethnographic analysis has examined the processes around the assessment, diagnosis and management of (potential) genetic disease (Shaw et al., 2003; Featherstone et al., 2005; Latimer et al., 2006). These countered earlier accounts of genetic reductionism in biomedicine (Lippman, 1991; Hedgecoe, 2001) describing how the clinical - rather than the molecular - gaze provides evidence for the diagnosis of disorders, with genetic evidence often providing inconclusive or ambiguous assessments of disease status. Genetic information contributes to, rather than reducing, uncertainties.

Anti-reductionist accounts of genetic diagnostic processes describe how the clinic provides a site for the integration, or triangulation of information about mutations, phenotypes and disease categories, downplays the notion that genetic (molecular) information is somehow epistemologically that (clinical) information generated in the clinic (Rabeharisoa and Bourret, 2009: 701). The diagnostic value of a mutation is linked to pre-existing interpretive models for a particular disorder. Ethnographic studies allow the analysis of the uncertainties associated with making a definitive diagnosis, yet few of these studies have been orientated towards one type of molecular diagnosis, rather limiting themselves to exploring how genotype–phenotype associations are generated, stabilised and subsequently made clinically useful.

The second methodology contributing to empirical conceptualisations of geneticization is the historical documentary analysis related to a particular clinical or molecular aberration. Such analysis is orientated towards how existing disease entities are reframed through a molecular or genetic lens, such as diabetes or schizophrenia (Hedgecoe, 2001; 2002), or how geneticization impacts on the process of establishing a clinical diagnosis. Studies into cystic fibrosis have demonstrated how the process of geneticization has complicated the clinical conceptualisations of a particular pathology, particularly with respect to likely symptoms, prognosis and disease risk (Kerr, 2000; Hedgecoe, 2003; Kerr, 2005). The consequence of this is the expanded phenotypes of cystic fibrosis and the inclusion of previously unrecognised phenotypic features within the disease process. Molecular accounts are implicated in destabilising previously well-circumscribed clinical categories and knowledge, leading to periods of uncertainty whilst molecular genetic conceptions of disease are established through the ‘lumping’ and ‘splitting’ of existing categories of pathology and disease (see later).

Gaudilliere (2000) has argued that as a result of geneticization and the foregrounding of molecular analysis in the process of diagnosis, the laboratory has replaced the clinic as the primary site generating medical knowledge and practice. This, with other accounts, paint an image of a one-directional flow of knowledge from the laboratory to the clinic (Gaudilliere, 2000; Clarke and Fukimura, 2014): acknowledging a central role of technical artefacts and the socio-technical ensembles they create. Countering this, accounts from ethnographic studies of dysmorphology maintain that in the absence of concrete molecular accounts for disorders of physical form, a return to the clinic occurs, downplaying the transformative power of the laboratory in biomedical accounts. Genetic testing technologies do not necessarily provide an ease of diagnosis, or a clearly defined disease category into which patients can be easily placed when a genetic test has been undertaken. The clinic remains the central site of knowledge production, supported but not surpassed by the laboratory and molecular genetic testing (Shaw et al., 2003; Latimer et al., 2006). Keating and

Cambrosio (1995; 2003; 2011) contested that contemporary biomedicine represents the realignment, rather than fusion, or reduction, of the 'pathological' and the 'normal' (Canguilhem, 2012). The development of 'platforms'²⁵ provides a space in which biomedical practices occur collaboratively on both an intellectual and organisational basis. Keating and Cambrosio (2003) demonstrate how historical accounts of the new genetics have misrepresented the interrelated role of the clinic and the laboratory in the production of new knowledge and, importantly here, the resolution of uncertainty: attributing advances in knowledge solely to the work of laboratories and basic science, whilst at best marginalising – at worst ignoring - the contribution of clinical research and practice. This representation of a linear relationship between the generation of 'new' knowledge from research (in the laboratory) and the use of knowledge (in the clinic) occurs across sociological accounts (Fujimura, 1992).

The role of new genetic technologies in facilitating more specific classifications of disease has been considered as “perhaps the single most important contribution of the new genetics to healthcare ... creating a biological ... framework with which to categorise diseases” (Bell, 1998: 618-619). More specifically, this could mean ‘...the subdivision of heterogeneous diseases ... into discrete entities ... Understanding the biological events and pathways identified by genetics as contributing to disease will lead to a clear definition of disease’ (Bell, 1998: 618-619). In part this could be seen as predicting the ‘genomic designation’ (Navon, 2011) of individuals: diseases as constituted by their molecular basis, rather than the manifest illness, phenotype or lived experience of patients and families. Yet there is much to counter the position that genetic information alone can provide us with a clear definition of what disease is, free from clinical expertise. Shaw et al. (2003) describe how clinical decision making processes continue largely unchanged despite the availability and use of molecular technologies, with testing being undertaken in assistance to, rather than instead of traditional techniques of history, observation and examination.

Decisions about genetic testing - be it predictive or pre-symptomatic, diagnostic or carrier testing – in the clinical domain at least, are made in light of a gross categorisation: the designation of a person or their family as having, or potentially having, a problem, manifest or future, with a known genetic aetiology. Information about family history, or from the physical clinical assessment or medical history of an individual, results in the first stage of classification – categorising individuals and families as genetically problematic (or not), and warranting further surveillance, assessment or testing. When testing is initiated, categories are used to classify variants, allowing for diagnosis (and non-diagnosis) to guide clinical care.

[Why classify? The social and practical function of classification and categorisation](#)

²⁵ Platforms being the “benches upon which conventions concerning the biological or the normal are connected with conventions concerning the medical or the pathological” (Keating and Cambrosio, 2000: 368).

Categorisation is the process through which objects are recognised, differentiated and understood. A classification system provides 'boxes' – metaphorical or literal – into which objects can be placed based on commonalities, and is often referred to as the process through which the world is 'segmented' (Bowker and Star, 1999). These boxes are constituted by categories and are infrastructural to organisation (Douglas, 1966), forming the basis through which different users across different settings can render information useful. Subsequent to this ordering - distinguishing, naming and sorting things into kinds and classes - some sort of 'work' can then be performed (Bowker and Star, 1999).

Classification systems typically display three key features. Firstly, consistent, unique classificatory principles are in operation - adhering to a so-called genetic principle of ordering - with genetic here referring to the process of classification by origin or descent (Tort, 1989). Secondly, classificatory systems consist of categories that provide clearly demarcated 'bins', into which objects being sorted will clearly and exclusively fit. As such, within single classificatory systems, categories are mutually exclusive, with most objects fitting into one of a series of categories. Finally, categorisation systems are complete with respect to items, actions and areas under consideration: with this total coverage of the world being described, it is possible for new discoveries to be readily absorbed.

As discussed in the previous chapter, early cytogeneticists were highly preoccupied with 'counting' to establish the chromosome number across various species, as opposed to 'categorising' or 'classifying' based on the absence or presence of phenotypic features. Indeed, categorisation could be seen as confusing the early attempts to establish the human chromosome number. Race and ethnic background as a means of categorising individuals and justify variety in chromosome number was erroneous – with variety in reporting the result of experimental error and technical limitation as described previously.

Early attempts to characterise genetic aberrations were based broadly around changes in two categories: numerical changes, referring to alterations in the chromosome number, and structural changes, referring to duplications and deletions of gene number or translocations, altering the structure of a chromosome at the resolution of microscopy. Later cytogenetic work with phenotypically defined patient populations, such as those with Down's Syndrome, focused on categorising and classifying numerical features – chromosome number - as 'pathological' or 'normal'. Identifying trisomy of chromosome 21 (three copies of the chromosome rather than the expected two) as the genetic basis of Down's Syndrome allowed the clinical entity to be associated with its genetic basis and thereby led to a more accurate phenotypic description of the condition.

Trisomy of chromosome 21 constitutes a pathological category, which can be contrasted with the 'normal' status of having two copies of chromosome 21.

The complications involved in nosology as related to genetic disease are not solely a direct consequence of increasingly sophisticated technologies for visualising and testing the genome. In 1969, Victor McKusick, an eminent geneticist based at John Hopkins University, wrote extensively about the issue of nosology, the study of the classification of disease. He described two main processes through which classifications of genetic diseases were being shaped (McKusick, 1969). 'Lumping' - performed by 'lumpers' - related to pleiotropism²⁶, the multiple effects of a single aetiological factor, such as mutation in a single gene. 'Splitting' occurs where there is genetic heterogeneity, such as two or more fundamentally distinct entities with one and the same phenotype. For McKusick, it was a pragmatic and clear response to have classificatory processes evolving in these two distinct ways, both in terms of the material reality of the genetic in and of itself, and the role of medical genetics within the broader organisational structure of medicine:

In an earlier period medical genetics suffered from excessive and inappropriate splitting, which was at least partly inadvertent, arising as it did from the specialization in medicine. Seeing cases of one and the same entity, physicians in different specialties were concerned mainly with the features falling within their particular purview and often failed to recognise that the feature of particular interest to them was merely part of a syndrome... Thus, medical geneticists have been, and continue to be, lumpers, to the extent that they pull together pleiotropic manifestations of genetic syndromes (indeed, medical geneticists can be the generalists of modern medicine)

McKusick, 1969: 23-24

The role of the context, or medical subspecialism, in which observations are made is key to how the concept of something – as a genetic entity or as having a different aetiology altogether – is defined. Salient features may fail to be recognised and categorised as representing only part of a phenotype. It is interesting that genetics is seen as 'general', reflecting both the origins of medical genetics as a general specialty, and its current position in being 'mainstreamed' or rendered an unexceptional, mundane and everyday part of modern medical practice. In this sense, lumping and splitting processes refer not only to the attribution of meaning to the genetic material itself. Lumping and splitting can also frame an understanding for the way in which medical professionals from different medical specialties 'see' – enact a clinical gaze (Foucault, 1963) - symptoms and signs as part of the Gestalt, and subsequent to this, the way in which knowledge and expertise is distributed between these same groups of medical professionals. For McKusick (1969), lumping and splitting represent ways of classifying which are real, owing mainly to being real in their consequences (Bowker and Star, 1999).

²⁶ Pleiotropism is the process by which a single gene affects a number of phenotypic traits in the same organism. The traits are not necessarily related to one another.

Taking these extended concepts of 'lumping' and 'splitting' and applying them to disease categories allows the exploration of some of the challenges to medical practice and knowledge, when genetic information becomes central to how disease is classified and described.

'Lumping': cystic fibrosis and expanding categories

Cystic fibrosis is a monogenic recessive disease, first described and characterised in the literature in 1938, with further descriptions of the inheritance pattern emerging in 1952 (Super, 1992). The discovery of the CFTR gene²⁷ (and its various mutations) changed the way in which cystic fibrosis, as a disease entity, is diagnosed. As opposed to diagnosis being made on the basis of clinical symptoms (which can be variable in type and severity), imaging, or the results of biochemical testing (the results of which are frequently ambiguous), genetic screening for mutations of the CFTR gene was seen as a potential method for quickly and economically reaching a definitive diagnosis.

Kerr's analysis (2000) of the increasing number of clinical 'disease states' associated with alterations in the CFTR gene demonstrates McKusick's 'lumping' in action. Her focus on male infertility caused by congenital bilateral absence of the vas deferens (CBAVD) demonstrates how in spite of phenotypic heterogeneity in the pathologies associated with CFTR, there was "an epistemological shift from considering CBAVD to be one symptom of cystic fibrosis in men" rendering CBAVD as "a mild or genital form of cystic fibrosis" (Kerr, 2000: 861). The shift towards reclassification was problematic for clinicians, who grappled with "whether all cases of CBAVD as an isolated finding should be uniformly classified within the spectrum of cystic fibrosis, or be defined as CFTR associated, but distinguishable from clinical cystic fibrosis" (Colin et al., 1996: 442).

The answer, from a pragmatic and clinically useful point-of-view, is to concede that "CBAVD and cystic fibrosis exist as extreme forms of a wide nosological spectrum of conditions with a common molecular basis" (Chillon et al., 1995: 1779-1480). The wide-ranging phenotypic spectrum associated with mutations in one gene has resulted in "the definition (of cystic fibrosis) becoming progressively more hazy" (Sharer et al., 198: 645). Application of a molecular gaze has resulted in category expansion – lumping - of the pathologies associated with CFTR. This has increased uncertainty: the availability of the genetic test has led to "the paradoxical situation of having some patients with typical cystic fibrosis in the absence of mutations, and others with CFTR mutations in the absence of clinical features" (Rosenstein, 2002:84).

²⁷ The discovery of the CFTR gene is often cited as an example of 'reverse genetics', whereby a gene is identified, then 'worked forward' in order to identify the gene product.

Splitting: the case of type II diabetes mellitus

In contrast, diabetes mellitus, an overarching term for disorders of glucose metabolism, has been subject to splitting as a result of the identification of a genetic aetiology. Diabetes has been described in literature for over 2000 years. Its heterogeneous manifestations included those described by Bouchart (1875), who contrasted the quick-and-thin 'diabete maigre' with the fat and slow 'diabete gras', differing in their management and prognosis. Binary divisions continued – based on clinical assessments and management - with the disease later being categorised as insulin sensitive and insulin insensitive and between those individuals requiring insulin to survive, and those who do not.

Numerous authors address the creation, evolution and curation of the categories constituting diabetes mellitus (Keen, 1986; Gale, 2001; Hedgecoe, 2002), describing the splitting of diabetes into smaller disease sub-categories. Divisions were increasingly justified by the genetic, particularly, the assumed association of the disease with the human leukocyte antigen. Information from these genetic associations and from phenotypic information was used to constitute nine categories of diabetes mellitus in the National Diabetes Data Group's classification of diabetes mellitus: by 1997, using genetic association data, 57 subcategories of diabetes were discretely constituted (American Diabetes Association, 1997).

Much like the 'lumping' of cystic fibrosis described earlier (Kerr, 2000), this splitting was contentious: with the terms being seen as classifying the patient based on treatment rather than on etiology (ADA, 1997). Whilst potential benefits existed for some patients (in the form of more defined treatment regimens), the consequences for patients identified asymptotically were considered contentious (Hedgecoe, 2002). This mirrored previous work with (asymptomatic) haemochromatosis patients, whose experience of medical intervention prior to the onset of symptoms was largely negative (Seamark et al., 2000). The creation of liminal disease/non-disease identities, much like the 'patients-in-waiting' described by Timmermans and Buchbinder (2012), must be examined in light of which sub-categorisations constitute a disease state, and consequences of these liminal states for individuals facing classification who may not be experiencing disease.

Through these examples, it is clear to see that how disease is classified and categorised – be it molecularly, clinically, or otherwise - can have moral consequences. With respect to the genetic domain, these consequences include issues of genetic discrimination (Ettorre, 2002), the potential risk to future generations and shaping cultural categories relating to identity. Sociological enquiry in the field of genomics differs from medical sociology more broadly, focusing on the social and cultural factors shaping categories (Berg, 1992) rather than the production of medical categories

themselves (Yoxen, 1982). The processes and work of diagnostic categories – be it clinical, biochemical, genetic or otherwise - are real (Bowker and Star, 1999), as they are real in their consequences: for the medical work performed, and the lived experience of those in and between disease states.

Disposal

Another important classificatory process in medical practice is the way in which patients are deemed to no longer be in need of medical attention, care or a particular form of treatment. The action of disposal draws on the work of Silverman (1987), Berg (1992) and Latimer (1997) and Roberts and Latimer (2015), all of which describe processes and practices of disposal in a slightly different way. Across accounts, disposal serves as a 'dividing practice' (Foucault, 1983: 208), constituting persons as no longer in need of medical care and attention. For Silverman (1987), this concentrates on the social constitution of infants with trisomy 21 who may require cardiac surgery. For Roberts and Latimer (2015), it is the way in which an antenatal diagnosis (again trisomy 21) can result in the consideration of both the literal and figurative disposal of fetuses in the antenatal clinic. Silverman's (1987) work on the social constitution of children with trisomy 21 in the clinic provides the most relevant account of disposal for this work, as illness and wellness are constituted in the discourse of the clinic. Children, through clinical assessment and discourse, are constituted as 'social objects', and assessments and discourse can incorporate, shape and transform parental formulations of their own children. Particularly, this attends to the way in which the medical concerns of parents are reframed by medical professionals as social issues, justifying non-intervention and avoiding surgery (Silverman, 1987: 134). Children are constructed in discourses between parents and professionals as having social -rather than medical – problems and subsequently, persuasive discourses allow them to be disposed. For Silverman (1987) disposal occurs in the sense that medical treatment is deemed unnecessary and therefore the patient can be discharged, or disposed from further medical care.

Disposal can occur as an important part of classificatory processes. Fundamentally, it is an action of inclusion/exclusion (Roberts and Latimer, 2015), which can occur prior to or as part of a process of categorisation. Patients can be deemed as being in need of, or not in need of, a particular type of expertise (referral to a specialist) or test. Having been subject to a clinical gaze, they can be disposed (discharged) from further care, or disposed to another specialist or type of testing. The construction of a particular (medical) problem is transformed and through this transformation, there is a requirement for an altered trajectory of care (Berg, 1992).

The work of classification: expanding knowledge, categories and implications

When we establish a considered classification, when we say that a cat and a dog resemble each other less than two greyhounds do, even if both are tame or embalmed.... what is the ground on which we are able to establish the validity of this classification with complete certainty? On which tables, according to which grid of identities, similarities, analogies have we become accustomed to sort out so many different and similar things?... For it is not a question of linking consequences, but of grouping and isolating, of analyzing, of matching and pigeon-holing concrete contents...

Foucault, 1970: xxi

'Identities, similarities, analogies' had proven useful for the early cytogeneticists. Yet advancing technologies, and the processes of lumping and splitting demonstrate how molecular definitions of similarity and difference lead to less dependence or need for (phenotypic) sameness. Yet primacy of the genotype in establishing categories was also problematic, as demonstrated by the case of cystic fibrosis and type II diabetes mellitus. In contrast to the notions of Michel Foucault, who argues that linked consequences should not form the basis of grouping practices, for genetic practice it is the consequences themselves that constitute a key divider in the process of categorisation and classificatory processes.

In response to the enormous quantity of information generated by sequencing technologies²⁸ following the completion of the Human Genome Project, there was an urgent need to develop categories, classifications and taxonomies extending beyond the binary division of variants as 'pathological' or 'benign'. For use in the clinical setting²⁹, it was clear that a common, standardised approach was needed that would coordinate the work of the laboratory and the clinic.

In this clinical context, it is important to recognise how a classification appropriate to a clinician whose concern is diagnosis and treatment may well be inappropriate to a basic scientist, whose concern is research strategy and experimental design (Keen, 1986). Implicit here is the need for classificatory systems which 'work' for different fields of scientific practice involved in coordinating genetic work, and that are able to tolerate uncertainty. The purpose of systems of classification may be different for the various stakeholders in the process, yet "classification schemes and diagnostic criteria should, above all, be utilitarian. They should help physicians select a management programme which is of maximum benefit and minimum harm to individual patients in their offices today" (Genuth, 1982: 1191).

For clinical genetic practice, this utilitarianism is justified as clinical actionability, defined as a known ability to intervene and avert or favorably modify a potential adverse outcome. Clinical actionability

²⁸ Untargeted whole genome sequencing (WGS) would be estimated as generating 3-4 million variants, of which >99.9% 'must be ignored from any reasonable clinical or public health perspective' (Berg et al, 2011)

²⁹ The purposes of reporting for the research or direct-to-consumer setting have different agendas and needs, which are not addressed here.

itself is based on three concepts. Firstly, analytic validity, referring to how accurately or reliably a particular test is able to measure the genotype of interest. Secondly, clinical validity refers to how consistently and accurately a test is able to predict the intermediate or final outcomes of interest. Finally, the clinical utility or actionability, referring to how likely a test is to improve outcomes for patients, either through modifying disease course or allowing prophylaxis (Ramos et al., 2014).

For the laboratory - in between the crudest binary classification of genomic variants as 'pathogenic' or 'benign' - has emerged a complex infrastructure of classification related to both degrees, sources and consequences of uncertainty. These manifest as variants of unknown or uncertain significance and incidental findings – zones of uncertainty. Classificatory mechanisms have emerged have attempted to encompass these zones within spectra of certainty and uncertainty, and of analytic validity, clinical validity and clinical actionability. The initial guidance, issued from the American College of Medical Genetics and Genomics (ACMG) in 2000, stratifies genomic variants 'within a spectrum of interpretation, ranging from those in which the variation is almost certainly of clinical significance, and those in which it is almost certainly not' (Kazazian et al., 2000). The 'spectrum of interpretation' reflects the categorisation of genetic variants across a spectrum of both meaning and certainty/uncertainty.

Category (Kazazian et al, 2000)	Clinical Implication	Degree of uncertainty regarding clinical implications
Sequence variant reported and recognised as a cause of disease	Considered pathogenic (disease causing)	No uncertainty, considered disease causing
Sequence variation unreported and is of type expected to cause a disorder	Probable pathogenicity	Some uncertainty, but likely to be disease causing
Sequence variant previously unreported and is of type which may or may not cause disorder	Variant of unknown or uncertain significance	Uncertainty as to potential implication of variant
Sequence variant unreported and probably not causative of disease	Probably a benign variant	Some uncertainty, but not likely to account for disease
Sequence variant previously recorded and is a recognised common variant	Benign variant	No uncertainty, considered not to be disease causing

Table Six: The Spectrum of Interpretation (Kazazian et al, 2000)

The 'spectrum of interpretation' is created by categorising genomic information according to two factors. The first factor considers whether the particular genomic variant has been reported previously i.e. is it well evidenced in the existing knowledge base. This is potentially problematic for an emergent science of interpretation, as the process of genetic and genomic testing in the clinical setting can be seen, to some extent, as an heuristic endeavour. This means that in the early period of cytogenetic practice, and indeed when new technologies are introduced, clinical reporting is essentially an experience-based technique, good enough for the given goal of producing potentially clinically useful information, but not optimal in terms of the ability to provide standardised, and universally highly-evidenced, information. Emergent expertise and experience in clinical reporting is reflected in the proliferation of guidance over the following few years (representing a process of uncertainty followed by relative stabilisation), reflecting the constructive deliberation of the nature and social operation of expertise. Variants are identified through testing, but their implications or meaning may not be known, i.e. they may be variants of uncertain significance. The use of databases³⁰ to accumulate and compare genotypic information, along with the accumulation of phenotypic information related to variants of uncertain significance, demonstrates the role of the laboratory and the clinic as synergistic sites of knowledge production.

The second factor concerns the locus and nature of genetic information, and the subsequent assessment of whether this is likely to be associated with pathogenicity or disease. Again, such assessments are highly dependent upon replication – the repeated identification of experimental results. In this case, the results are in the form of evidenced genotype-phenotype relations. This process of replication is seen as key when trying to make credible, or to validate, the quality of scientific work, tying it to rational thinking and logical rules. Yet the interpretive flexibility inherent in the activity of reporting genetic and genomic variants for clinical use challenges this notion: there is significant evidence that identifying which genetic variants to report is a highly subjective – or contingent - activity despite the existence of guidance (Tsuchiya et al., 2009). Studies have identified how both deletions and duplications identified through aCGH were subject to differing interpretations (in the absence of published data on the significance of the genomic variant) by thirteen different laboratories, ranging from reporting variants to clinicians as benign, to reporting the same variants as pathogenic (Tsuchiya et al., 2009). As such, the 'bins' provided, though mutually exclusive, are 'filled' as a result of a process that employs substantial subjectivity – contingency of the interpretive task - when ascribing a variant as either pathogenic, benign, or of uncertain significance of varying degrees.

Classification and standards are linked through their use across settings, in the social world or in communities of practice, such as the National Health Service, or medicine more broadly. This

³⁰ ENSEMBL <http://www.ensembl.org/index.html> and DECIPHER <https://decipher.sanger.ac.uk/> for example.

impacts on issues of membership and inclusion, and can link with how objects for classification can be 'taken for granted' (Cambrosio and Keating, 1995). Yet here, the process of both categorizing and classifying genomic information in the clinical setting could also be seen as 'taken for granted', using categorisations and classifications largely borrowed from the research, or non-clinical, laboratory setting yet employed in clinical, medical work: the aims and objectives of clinical work being very different from that of the research context.

As such, new attempts emerged which classify genomic information based upon its 'clinical' rather than 'informational' utility, reflecting the difference in the objectives and obligations of two settings which are different but enmeshed. The research and diagnostic settings can be closely related temporally and spatially and in terms of the professionals and patients involved, yet constitute work whose aims, ideals and objectives are very different. The table presented in appendix G demonstrates some of the classificatory systems that have emerged for the classification of sequence variants. Explicit in the aims of two papers (Kazazian et al., 2000; Richards et al., 2008) is the role of category creation (and curating) in education. Categories exist to "educat[e] them' [health professionals] as to the possible test outcomes, so they can inform patients and families" (Kazazian et al., 2000) in addition to "providing a framework for the interpretation and reporting of test results" (Richards et al., 2008). Categories must demonstrate utility to multiple users.

Categories as boundary objects

In this way, classification systems for genomic findings serve as boundary objects (Star and Griesmar, 1989) – inhabiting several communities of practice (bureaucratic, research and clinical settings) and satisfying the informational requirements of all three. Yet (perhaps wrongfully) they travel across the bench-bedside border and maintaining a constant identity, rather than being tailored to meet the needs of one setting. Frameworks for variant interpretation serve as boundary objects, and consequently as evidence of boundary work:

Boundary objects are objects which are both plastic enough to adapt to local needs and constraints of the several parties employing them, yet robust enough to maintain a common identity across sites. They are weakly structured in common use, and become strongly structured in individual-site use. They may be abstract or concrete. They have different meanings in different social worlds but their structure is common enough to more than one world to make them recognizable, a means of translation. The creation and management of boundary objects is key in developing and maintaining coherence across intersecting social worlds

Bowker and Star, 1999: 393

As boundary objects, classification systems and categories themselves become objects which allow co-ordination without explicit consensus, with individual participants, be they laboratory technicians, clinicians, or indeed patients and their families, able to frame their understanding in an individualised, contextualised way. This is done whilst remaining in the frame of a wider collective activity, in this case the construction of meaning from genetic variants, and the implications of these for the work of each participant. The extent to which variant classifications form boundary objects for probands and family members has yet to be empirically explored. For the association between the laboratory and the clinic, categorisation links both communities of scientists and clinicians, allowing both groups to collaborate on a common task in deriving meaning and guiding further action when the implications of a variant are established. Whilst the categories were established as a means of classifying variants, they manifest in the clinic as a means of making meaning and sense of the types of information genetic and genomic tests can generate.

Classificatory taxonomies themselves - in their role as boundary objects - reflect the instability of variants and their potential to flux from one category to another, so called 'boundary negotiating artifacts' (Lee, 2005, 2007). These are represented explicitly as variants of uncertain significance, and over time, as knowledge and experience emerges, it would be expected that many of these variants would be reclassified as either pathogenic or benign.

[A place for the uncertain: categories of uncertainty](#)

Taxonomies of these 'off-target' genetic results – zones of uncertainty - have started to emerge and are in constant flux as clinicians and scientists grapple with a rapidly evolving genomic knowledge base. The semantics of these findings is also subject to constant revision and alteration, with such findings referred to in the literature under a number of titles: 'incidental', 'pertinent/non-pertinent', 'accidental', 'ancillary', 'secondary' and 'unsolicited' (Christianhusz et al., 2013). The everyday work of establishing whether or not a laboratory variant is pathological, and the relation of this to the process of diagnostic categorisation in the clinic, is seen as key to the understanding of medical power as revolving around the retention and redistribution of discretion. In creating and enacting these categories, clinicians transform themselves into centers of discretion by transferring much of the discretion in diagnosis from the patient to themselves (and indeed to the laboratory systems they use). Further discretion in diagnosis is maintained by disposing with the meaning of laboratory findings when they are not allied with their clinical judgments – for example, in the case of variants of uncertain significance, where the finding may be shared, or not shared, with the patient and family. Attempts to label genetic information which is unrelated to the presenting phenotype has taken little account of the patient or family perspective on the information people hope or expect to

receive, instead focusing on technological capability and clinicians' analysis of moral imperatives about information sharing and the possible prevention of disease.

It is perhaps unsurprising that a homogenous category for lumping 'the uncertain' has arisen, through variants of uncertain significance. Whilst geneticization does not provide a unifying framework to stratify disease along genetic lines, it is also not introducing clarity and continuity into medical classifications. As demonstrated by the case of chromosome counting, and the development of taxonomies beyond pathological and benign divisions, the identity of a variant or finding is always the product of an open-ended process. These processes can be seen as precarious since other processes can easily destabilize this process. In the case of variants of uncertain significance, this may be the availability of new genomic knowledge allowing a variant to be reclassified as either pathological or benign, the availability of new testing methods, or the clarification or emergence of family history information.

ACMG approach: 'Checking a list' versus 'categorising and classifying'

Recently, guidance has recommended increasingly targeted approaches to the genomic variants that laboratories and clinicians are able to identify (see chapter three). Rather than attempting to make meaning of all information, this approach favors a 'minimal requirement' – in fact a list – of variants, which are opportunistically screened for each time a whole genome or whole exome sequence is undertaken. Whilst in this case such a defined, prescribed list has been contentious, list making is frequently described as one of the foundational activities of advanced human societies (Bowker and Star, 1999). Many sociologists have examined the role of lists in modern science, agreeing that the production of lists during the 19th century revolutionised science, and catalysed its evolution to its modern form (Foucault, 1970). Indeed, a similar catalysis of the discussion of ethical, social, legal and practical applications of WGS in the clinical context has been driven by the production of this list of variants.

Creating (and curating) lists serves as a process of hierarchical ordering: an initial stage or tool in the ordering of work, or division of labour. While the standardization of what constitutes a variant aids laboratories, the categorisation allows the responsibility for sense-making to be shared by the laboratory and the clinic, integrating the scientific identification of variants with 'results' for patients and families, which may subsequently become a 'diagnosis'. Latour (1987) described the work of the bureaucrat as compiling lists that can be shuffled and compared, providing the opportunity for control, albeit from a distance. This has parallels with many of the criticisms of the ACMGG guidance (Green et al., 2013), whereby the control is taken from the laboratory or the clinic by the introduction of 'standards' for reporting through the formation of a list of mutations, which must always be reported. This list performs the important function of ensuring consistency of approach

between laboratories and health systems. Yet the list means that control transfers from patients, whose autonomy and preference becomes a secondary consideration, from the clinician-patient dyad, where decisions, preferences and their real-world meanings can be explored and deciphered. The contingent, situated approach with respect to reporting is lost, with discretion being removed from individual laboratories, clinics and ultimately, patients. Notably for clinical genomics, there has been no attempt to vary categories and classifications when children undergo genomic testing, even with the acknowledgement that the ethical challenges differ significantly (Dondorp et al., 2012).

Yet this list of variants, despite criticisms about its scope and implementation, forms an important 'genre of representation' (Yates and Orlikowski, 1992). Such genres are defined as "typified communicative action performed by members of an organizational community in response to a recurrent situation.... Identified by both their socially recognised communicative purpose, and by common characteristics of form" (Yates et al., 1997: 50). From this we can see that when lists are used to co-ordinate work across spatial and temporal borders, correspondingly complex organizational structure and infrastructure must also evolve. As such "genre systems... interlocking and interdependent sets of genres that, by definition, require collaboration" (Yates et al., 1997: 51). Collaboration in this sense spans cultural and physical settings – the focus of study here being the laboratory, the clinic, and the patient experience, all of which have conflicting perspectives and requirements. As such, attempts to standardise, render uniform or remove discretion and contingency from the sites of genetic work are countered and resisted.

Conclusion

Categorisations do not simply hold a mirror to processes of recognition, fitting people into categories of disease or disorder based on their characteristics, physical and otherwise. What emerges from categorisation work - particularly in the genetic domain - is the enactment of the genetic as a prominent domain of classification in and of itself within medicine: a problem is assigned to the category of being, or potentially being, 'genetic'. Individuals' bodies and families, and their patterns of development and disease, are identified or characterised, examined and tested as genetically problematic. Identifying disease or disorder as potentially genetic becomes a classificatory act before any genetic testing has taken place. Whilst this is a classificatory act, it does not constitute a classificatory system: as we will see later, clinicians do not apply the need for genetic testing to patients in an orderly, uniform way even where they present with similar pathologies, meaning that principles are not constant and unique.

The categorisation and classification of genetic and genomic information into variant groups provide an evolving example of how the medical gaze works to create meaning as genetic information becomes medically meaningful, initially in the laboratory, and later in the clinic and on an individual and familial level. Uncertainty relates to the resolution of this gaze, as created in these examples by the microscope in traditional karyotyping, and by the computational representation of the chromosomes through array comparative genomic hybridisation. As our ability to characterize the genome in greater detail evolves – as the gaze increases both in scope and resolution – so does uncertainty. Our ability to see uncertainty through this prosthetic gaze is not always matched by our ability to make genomic information clinically meaningful. Nor should this evolution of the seen (the real) and the understood (the symbolic) be a smooth continuum, occurring in direct relation to one another. It is through the material, the substrate in the form of raw genetic information itself, that the process of deciphering meaning is initiated – both on a research level, as demonstrated by early accounts of cytogenetics, and in the clinical context.

From a molecular perspective, the infinite number of variants it is possible to identify has led to the ‘lumping’ of uncertainty into one category, that of the ‘variant of unknown or uncertain significance’. Testing represents the ontological transformation of the genetic substrate into genetic information and subsequently into ‘disease’, ‘normalcy’ or ‘uncertainty’. For variants of uncertain significance, this allows for heterogeneous, infinitely variable, identified variants to be neatly compartmentalised into a zone of uncertainty. Within this zone exists further probabilistic sub-categories, such as ‘likely pathogenic’ or ‘likely benign’. Whilst knowledge production in genetics is largely iterative – it is only through the association of genotype with phenotype through testing which identifies candidate genes – the need is for a system of classification that renders the uncertain ‘manageable’ in a clinical context. In subsequent chapters, I will examine how actors in the various sites of genetic work, namely the laboratory, the clinic, and the family structure, enact this process.

As such, the uncertainty of genetic variants is dynamic. Zones of uncertainty appear and disappear through reclassification and categorization, through the emergence of new information which moves genetic information from areas of uncertainty to those which can be defined, delineated, and made definite in meaning and consequence. Classifications and categorisations themselves morph to accommodate new zones of uncertainty in an attempt to make genetic variants non-discursive, to create tidy spectra of uncertainty which act as boundary objects as genetic information ‘travels’, attempting to create shared meaning between the laboratory, the clinic and the family.

Chapter Five: Expertise

What do we mean when we talk about expertise in 'genetic work'? Different types of expertise are mobilised and employed in the different sites of genetic work, and different stages in the 'making' (or failure to make) a genetic diagnosis. In the laboratory, clinical scientists perform rapid assessments of representations of genetic data (see chapter six) to assess the quality of the testing, and identifying the presence or absence of important genomic variants. In the clinical space, neonatologists designate which 'genetic work' they can perform, and that which must be disposed of to medical geneticists - 'experts' in the field. Patients and families can also become experts in the clinical aspects and lived experience of disease. The chapter is formed of two sections. The first section explores expertise and (de)professionalisation as a tension latent within mainstreaming. How does (or should) clinical genetics ensure its survival as a specialty whilst distributing its skills to colleagues in other specialties? How can clinical geneticists develop the competence of non-genetic specialists who may not have the same exposure to clinical or laboratory genetics? Ultimately, the answer to these questions will define the future role of clinical geneticists and the work they do. The second section presents an abridged, focussed, account of 'becoming expert' with a particular focus on how expertise is developed and described, with a view to describing how participants across the sites of genetic work become 'expert'.

Defining 'expertise'

Traditionally, genetics has been the **preserve of specialised clinical genetics** services.....Current UK policy is based on **knowledge and expertise spreading out from clinical genetics into different areas of mainstream medicine**. However, research from the PHG Foundation challenges this approach, with increasing evidence that it is not functioning effectively. Although where geneticists work with other specialists, the joint services they provide are typically highly regarded, access is very variable, and too many patients miss out....**Genetics and mainstream medicine presents an alternative paradigm whereby mainstream clinical areas develop and expand to integrate new genetic expertise and genomic technologies into their own clinical pathways, with regional genetics services playing a leading role**. This will deliver the immediate benefits of genetics for patients, whilst building capacity to expand and improve services in the future as new tools emerge.

Genetics and mainstream medicine. PHG Foundation (2011) [emphasis added]

Medical expertise is traditionally considered to be related to the experience of or amount of time spent in, a particular domain. A medical consultant is considered 'expert' in a particular area of knowledge, for example, neonatologists in the care of newborn infants, geneticists in the investigation and management of genetic disease. This expertise is supported and endorsed by academic qualifications, such as undergraduate and postgraduate degrees, professional diplomas

and qualifications and through professional accreditation through membership of professional bodies. Such bodies require evidence of ongoing practice (i.e. through a set 'requirement' for the amount of 'work' a professional must complete over a given time, in order to maintain their skills) and continuing professional development (such as participation in educational activities). This reflects how expertise is developed through both the acquisition of particular knowledge and skills and then later through experience of a given field of work or technique.

Atkinson (1995: 122) describes medical expertise as how "the physician locates the sources and nature of doubt equivocation and the like". As such, expertise is not the absence of uncertainty. *Expertise* is distinct from profession in that it relates not specifically to jurisdiction over a task, rather to the capacity to complete a task competently. Legitimacy strategies – based around jurisdiction over tasks - strongly underpin the sociology of medicine. A central concept in this thesis is the notion that reconfiguring the responsibilities of different professional groups (and indeed intraprofessional groups, as in different medical specialties such as medical genetics and paediatrics) is central to the aim of fully realising the clinical potential of genetic and genomic technologies for patient benefit. As such, it is important to consider to what extent can 'doctors' – with all their differing areas of professional expertise - be considered a single, unified profession, and as such, a single, unified relevant social group? Accounts from the mainstreaming literature challenge the paradigm of medicine as one knowledge community, presenting it rather as a fragmented web of expertise and jurisdiction.

...those in the specialty (cardiology, ophthalmology etc.) need to **develop expertise in genetics**. For example, in cardiovascular genetics this would include professionals in cardiology, clinical genetics, genetic counselling, cardiac nursing, pathology, lipidology (including paediatric lipid care) and the associated investigative professionals such as electrophysiologists. To complement this, **regional genetics services need to continue to include specialists who develop and maintain experience in this particular clinical area. It will be necessary for leaders in each field to work with regulatory bodies, such as the Royal Colleges, and, for medical specialties, the Postgraduate Medical Education and Training Board (PMETB) to develop, where appropriate, highly specialist modules, training programmes and placements and educational resources.**

Genetics and mainstream medicine. PHG Foundation (2011): 29 [emphasis added]

Both new technologies and managerial structures have been described as changing the character of the medical profession (Friedson, 1984; Harrison and Ahmad, 2000), particularly with respect to differentiation and the division of labour between medical specialties. The mainstreaming agenda places medical geneticists as a 'knowledge elite' (Friedson, 1984), setting and policing the standards of conduct for others or '..playing a leading role' as termed by the report Genetics and Mainstream Medicine (PHG, 2011). The availability of new technologies for use within 'mainstream clinical areas' (PHG, 2011), could be seen as enhancing the autonomy of non-expert clinicians with respect to genetic testing, allowing individual doctors to make decisions about how and when the

investigation of disease is conducted, within structured pathways which account for the evidence base with respect to the timely, appropriate care of patients and families. The ability – or expertise - of medical professionals charged with doing this is also an important component. This counters accounts of ‘scientific-bureaucratic medicine’ (Harrison and Ahmed, 2000) in which processes and trends within medical work (for example evidence-based medicine, health technology assessment or managerialisation) fuel fragmentation within the medical profession, ultimately eroding the autonomy of the ‘ordinary medical clinician’ (2000: 138). Rather than fragmenting, the mainstreaming agenda seeks to embed genetic expertise across the medical profession, making clinicians more autonomous with respect to who receives genetic testing, and how it is done.

The Clinical Genetics Society (2015) describes the evolving role of the clinical geneticist:

With their broad based training and ability to deal with all ages, from conception to the end of life, Clinical Geneticists provide a unique role, particularly in the diagnosis and management of multisystem disease. In this area, they are likely to remain key players. In the future however, it is envisaged that for some areas of clinical practice the role of the Clinical Geneticist will move away from making genetic diagnoses and communicating test results to being a multidisciplinary team member providing genetic education and input to complex cases. There will also be a major role in the analysis and interpretation of complex genomic investigations for the wider medical community. As such, Clinical Geneticists will need to develop expertise in certain specialist clinical areas to interact more effectively with mainstream clinicians.

Clayton-Smith et al., Clinical Genetic Society, 2015: 3

Traditionally, professional knowledge has been constituted within an institutional order (Sarangi and Roberts, 1999). Mainstreaming challenges this norm whereby professionals strive to maintain control over specialist knowledge through actions that prevent (their specialist) knowledge from being routinised. For medical genetics, routinisation – or mainstreaming – is a necessary act in order to realise the potential of genomics across medical care: there are too few medical geneticists to do all the genetic work. Yet it is unclear if processes of routinisation and mainstreaming may amount to the de-professionalisation of medical geneticists. Clearly mainstreaming represents a considerable alteration in their jurisdiction – transferring the responsibility for much of testing from the specialist genetic domain into general mainstream medicine. With this comes the responsibility, or jurisdiction, over the education of other medical and clinical professionals, with education and multidisciplinary working becoming a key role and a critical component of expert genetic work.

Next I consider how the sociology of professionals and of expertise provides a sociological frame through which to consider the consequences of mainstreaming for genetic expertise.

[The Sociology of Professionals](#)

Abbot (1988) in *The System of Professions* describes how professions defend their jurisdictions, responding to (perceived and actual) incursions by reasserting the legitimacy of existing boundaries.

Various techniques can be employed by professionals in order to defend knowledge and practices which are perceived as falling within their jurisdiction. Central to this are claims to scientific and specialist expertise: the monopoly over this expertise constitutes what is needed to both practice within and indeed enter the 'profession' (Friedson, 1970). Professional status is achieved when the 'power and persuasive rhetoric are of greater importance than the objective character of knowledge, training and work' (Friedson, 1970:79). Rather than a history of groups of individuals, assembled as professions, Abbott calls for emphasis on the 'tasks and problems' (1988: 314) being addressed, with jurisdiction being defined as 'the link between a profession and its work' (Abbott, 1988:20). Abbotts' perspective is attractive as it allows a lens through which how specific 'tasks and problems' – for example taking consent, or explaining a test or a challenging result - can be identified and addressed as genetic expertise diffuses from the specialist to the general domain.

This links clearly with the sociological work on medicalisation, in which medical systems extend their jurisdiction by rendering social, ethical and legal problems as medical (Zola, 1972). Both the literature on the professions and medicalisation can be seen as failing to consider the division of expert labour: overlooking how conflict around professional jurisdiction occurs not just between professional groups, but *within* them, with particular groups or subgroups claiming expertise on the basis of knowledge or mere control over a technique - or 'crafts' (Abbott, 1988).

Mainstreaming can be seen as an attempt to embed the 'crafts' of clinical genetics within other medical specialties, transferring and disseminating the 'knowledge, training and work' (Friedson, 1970) of medical geneticists to other medical professionals. As such, there is an important role for defining and characterising the 'crafts' – or the expertise - (Abbott, 1988) needed to do 'genetic work' well. What types of expertise are required to do genetic work? How do these disseminate between and within professional groups?

Towards a 'Sociology of Expertise'

Collins and Evans (2002, 2007) consider expertise as an attribution – the recognition in individuals, groups and bodies of the interests, role sets and organisation. This complements and builds upon the sociology of professions laid out by Abbott in that, while the sociology of professions recognises the organisational elements, such as accreditation, formal recognition and the formation of professional organisation, one either *is* or *is not* a professional; the sociology of expertise recognises a typology of expertise including the universality of tacit knowledge as the foundation from which degrees of expertise emerge.

Eyal (2013) extends upon this notion defining how expertise emerges from ‘networks which link together objects, actors, techniques, devices and institutional and spatial arrangements (which) are gradually assembled’ (2002: 824).

	Sociology of Professions	Sociology of Expertise
Scope	Limited to professions and would-be professions	Inclusive of all who can make viable claims to expertise
Mode of analysis	Expertise reducible to the experts’ interests and views	Experts and expertise distinguished as two different modes of analysis
What is privileged?	Organisational and institutional form: credentialing, licensing	The capacity to perform a task better and faster than others
Question	Jurisdiction: who has control over a task	What does it take to accomplish a task
What is expertise	Attribution: a formal quality reducible to interests	A network connecting together actors, devices, concepts and institutional and spatial arrangements.

Table Seven: Contrasting the sociology of expertise and the sociology of professions (adapted from Eyal, 2013)

Becoming an expert? An example from the field

How do broader political agendas regarding the mainstreaming of medical genetics challenge the inter- and intra- professional division of labour, in particular with reference to the medical (and allied health) professionals? Are professions eager to protect their jurisdictions, deploying legitimacy claims familiar from the study of the sociology of professions? Within complex systems such as healthcare delivery, changes to the responsibility of one professional group inevitably impact on those of others (Nancarrow and Borthwick, 2005). Martin and colleagues (2009) examined one such ‘boundary’, namely the interface between medical geneticists and general practitioners with a specialist interest in genetics (GPwSI). The development of this ‘new’ specialist role represented a shift towards staff ‘competencies’ over traditional boundaries of clinical responsibilities and expertise. This occurred as part of a wider agenda to deliver more health care in the primary care setting, but also as an early facet of the mainstreaming medical genetics agenda. Qualitative interviews with both GPwSI and the local medical geneticists revealed two relevant themes. Firstly,

the role played by general practitioners with a special interest: the geneticists involved hoped the focus of the work of GPwSI would be educational work and disseminating genetic knowledge among their primary care peers, rather than the provision of clinical genetics services. Secondly, the role of genetic knowledge, and in particular concerns around whether adequate knowledge can be feasibly achieved by non-specialists. Geneticists saw clinical genetics as a field characterised by its breadth and depth: "...because they [i.e. GPwSI] would have to do paediatrics, adult medicine and four years' training ... so you can only train them to the level of a genetic counsellor, and they make very expensive genetic counsellors" (Martin et al., 2009: 1195). Here, the intra-specialty distinctions, in terms of expertise, are laid bare: the role of being a GPwSI provided insufficient scope to appreciate the nuanced nature of genetic work, as defined by genetic specialists.

What defines 'who does what' in terms of medical subspecialism? In the case of GPwSI, gaining additional expertise provided an opportunity to practice medicine in a field or specialty from which they had previously been excluded, and as such claims to competence were central to legitimising this work (Sanders and Harrison, 2008). This perceived legitimacy of the GPwSI was challenged by geneticists, who felt that immersion in practice was central in achieving both the confidence and competence to do genetic work safely, highlighting the indeterminacy of their (non-specialist) knowledge (Hibbert et al, 2003; McLaughlin and Webster, 1998). Expertise is defined relationally (Foley and Faircloth, 2003), with genetics professionals describing accumulated collective knowledge through embeddedness within a clinical genetics department (Martin et al, 2009): expertise has a highly collective, relational element.

The role of a GPwSI represents the sociology of expertise in action, and in many ways an attempt to employ the principles underpinning mainstreaming. It is inclusive of all those who can make viable claims to expertise through additional training and accreditation, recognising the difference between being an expert and having expertise. The capacity of the GP to perform genetic work well – to a better standard than their peers – is privileged, and there is the recognition of the interplay between individuals with expertise and experts with the institutional privileges this may entail.

'Expert Patients'

Though not entirely relevant for this thesis, it is important to briefly mention 'expert patients' when considering expertise in medical practice and patient care. The expert patient programme was a self-management and peer education program aimed at developing a population of expert patients for a range of chronic health conditions, such as asthma, eczema and diabetes. The theory behind this was that self-management would offer not only economic benefits to the healthcare system more broadly and improve the well-being of individuals with chronic illness through empowerment, improved quality of life and self-esteem, ultimately resulting in a user-driven NHS (Wanlass, 2002).

However, the effectiveness was questioned (Greenhalgh, 2009) and accounts of expert patients programmes described the scheme as poorly evidenced, with the program being positively valued by patients but ultimately failing to produce changes in self-management (Greenhalgh, 2009).

In this second section, I consider sociological accounts of 'becoming expert', with a view to looking at how expertise is demonstrated in the sites of genetic work.

Becoming 'expert': Linear Models of Expertise

'*See one, do one, teach one*' is a common (albeit outdated) mantra in medical education. In its most basic form, it reflects the notion that expertise, or experience, in medical skills as being attained through three sequential stages: seeing, doing and then teaching. This quip for describing a rudimentary linear model of expertise is credited to William Halstead, an American surgeon heavily involved in the education and training of surgeons. The Halstead model of 'see one, do one, teach one'³¹ is based on acquiring increasing amounts of responsibility, from apprenticeship to (near) independence. This relates to Kolb's Model of 'learning by doing', which describes the process of experiential learning through observation, thinking, action and experience (Kolb, 1984). A more applied, explicated account of this is provided through Peyton's four stage approach (1998) to the acquisition of medical procedural skills, through the process of demonstration of the skill, deconstruction, comprehension and then execution.

³¹ The model has faced severe criticism, particularly with respect to patient safety, and the notion that patients are potentially unwillingly being 'practiced' upon prior to the acquisition of total competence (though notions of 'total competence' are also easy to contest).

Demonstration	The teacher performs the skill in real time, without explicit commentary. This provides the benchmark standard for the performance of a given skill.
Deconstruction	The teacher performs every step slowly with commentary to explain what is happening. The task is explicated into smaller sub-tasks.
Comprehension	The student describes every step of the skill whereupon the teacher performs on instruction. The description and execution do not occur simultaneously.
Execution	The student simultaneously narrates and executes step by step.

Table Eight: Peyton's Four Stage Approach (1998)

The linear models emerging from medical practice and education describe the journey through apprenticeship to competence, rather than expertise. Linear models emerging from sociological and philosophical accounts – and based on which the medical accounts emerge - extend the journey from competence to expertise, describing the transition from novice to expert as a journey through a series of predictable 'stages'. Dreyfus and Dreyfus (1980) summarise the acquisition of expertise (through philosophical and phenomenological means) as a series of five stages.

<i>Stage</i>	<i>Description</i>
1. Novice	Novice driver follows explicit rules and the performance is laboured, jerky and unresponsive to change in context. Skills are exercised 'mechanically' and are context-free, as the learner fails to account for the nuances implied by different conditions of the application.
2. Advanced Beginner	More of the skill is 'mastered' and unexplicated features of the situation play a part in the performance, for example responding to loudening revs in the engine by changing gear.
3. Competence	Problem solving is no longer the predominant force: more intuitive than calculating.
4. Proficiency	The proficient driver recognises whole problem situation holistically: some elements of conscious choice and analysis remain to guide decisions.
5. Expertise	The total concept of driving a car in traffic is unselfconsciously recognised and performance is related to this in a fluid way using cues which are impossible to articulate. If articulated, they may contradict the rules as explained to novices. When experts revert to a more self-conscious way of tackling a task, they do it less well.

Table Nine: Five stage model of the acquisition of expertise (Dreyfus and Dreyfus, 1980: 21-36, using the example of learning to drive (example described in Collins and Evans, 2007)

Here, all five stages relate to the 'do-one' stage of the Halstead account. In the novice stage, a person follows rules that are without context, with their primary responsibility (and aim) being strict adherence to these rules. With increasing experience, comes increasing competence. Proficiency is achieved when individuals are able to make decisions with increasing intuition, developing their own rules or schemas – implicit and explicit – to guide activity. Expertise – when and if it is achieved – represents unconscious, automatic function that is fluid and not clearly dependent on explicated knowledge. As such, expertise is characterised as a transition from rigid adherence to rules, to a fluid, implicit mode of practice that reverts to explicit rule only when intuitive approaches are insufficient or failing. Expertise is therefore a transition from the explicit to implicit or from abstract to concrete reasoning.

In further developing the five-stage model, Dreyfus has added two further stages (Dreyfus, 2001): namely 'master' and 'practical wisdom'. The process of becoming expert, and perhaps even acquiring mastery, requires individuals to have access to (and be the apprentice of) 'masters' whose style is manifest on a day-to-day basis. Subsequently, this style is imitated with Dreyfus making it clear that the bodily presence of apprenticeship is the only available technique for encouraging the inheritance of style. Here, style is the characteristics of the master's approach and method of handling challenges, problems and deviations. The aim is not for apprentices to become mere

copies of their masters, rather Dreyfus postulates that only by developing an individual style can an apprentice achieve mastery of their own. The concept of practical wisdom is concerned with an individual's "general ability to do the appropriate thing, at the appropriate time, in the appropriate way" (Dreyfus, 2001: 48). Practical wisdom can only be gained by being apprentice to one's parents and teachers³² and tends to relate to 'everyday life skills', rather than specific skills or crafts: rather, practical wisdom is framed as the generic, overlooked competencies which underpin and form the foundation on which all other skills or crafts are based (this parallels the ubiquitous expertise we see later in the Periodic Table of Expertise, Collins and Evans, 2007).

These final two additional stages appear to have particular relevance to how medical education comprises 'generic skills', akin to practical wisdom, and how these are gained through a process of enculturation within the medical profession. This enculturation is achieved largely through apprenticeship – through exposure to, and reflection on, the practice of other medical professionals, and how they cope with challenges, problems and deviations.

Linear models of expertise acquisition have attracted criticism, especially in the field of health education. Hargreaves and Lane (2001) have argued that the linear model gives insufficient weight to 'the everyday' in supporting learning. This foregrounds other criticisms that argue the model fails to reflect the critical role of social structures and social knowledge in developing expertise (Rudge, 1992). The model has clear parallels with the accepted approaches and norms of medical education, with applications in concrete clinical skills and procedures, for example phlebotomy (the process of taking blood from a patient). Using the driving parallel, this reflects that of knowing how to operate the vehicle, in terms of using the gears, steering, operating the lights and other functions – the 'know how'. Indeed, linear models have been broadly employed as the organising philosophy for many aspects of undergraduate and postgraduate medical education, despite the reservations of those involved in health education.

³² Peers are notably absent from important sources of apprenticeship that can underpin practical wisdom.

The Periodic Table of Expertise

Table 1: The periodic table of expertises

UBIQUITOUS EXPERTISES					
DISPOSITIONS				Interactive ability	Reflective ability
SPECIALIST EXPERTISES	UBIQUITOUS TACIT KNOWLEDGE			SPECIALIST TACIT KNOWLEDGE	
	Beer-mat knowledge	Popular understanding	Primary source knowledge	Interactive expertise	Contributory expertise
			Polimorphic	Mimeomorphic	
META-EXPERTISES	EXTERNAL (Transmuted expertises)		INTERNAL (Non-transmuted expertises)		
	Ubiquitous discrimination	Local discrimination	Technical connoisseurship	Downward discrimination	Referred expertise
META-CRITERIA	Credentials		Experience	Track record	

Figure Ten: The Periodic Table of Expertise (Collins and Evans, 2007:14)

Traditional analyses of expertise are highly preoccupied with the notion of individual expertise. Collins contends that both philosophy and psychology as disciplines treat expertise ‘one dimensionally’, resulting in stage or linear theories, as described earlier. To contrast these highly individualised accounts, in which the critical role of social structures and social knowledge are overlooked, Collins and Evans (2007) developed the Periodic Table of Expertise. The central premise of the table is the notion of tacit knowledge: the acquisition of all expertise depends on tacit knowledge of the expert domain in question, with tacit knowledge gleaned through immersion in the society of those who already possess it.

Tacit Knowledge

Tacit knowledge is described as the ‘chief organising principle’ of the periodic table of expertise (Collins and Evans, 2007). The chemical engineer turned philosopher of science, Michael Polanyi, coined the term ‘tacit knowledge’. This transition from scientist to philosopher was partially born of the notion that philosophers concerned with scientific practice were (wrongly) preoccupied by the way in which scientific knowledge was considered formulaic and propositional, and that analysis had overlooked the skills required to work in a laboratory, doing scientific work. This embodied, hands-on, unwritten knowledge (‘tacit’ knowledge) was overlooked in part as it was difficult to

identify and challenging to study, but also because it was considered as being epistemically less valuable.

Tacit knowledge can be considered as the pre-logical phase of knowing: it cannot be fully captured by language or numbers; rather it is an embodied knowledge that means individuals and groups who are immersed in a particular task or skill know more than they can describe or explicate. Tacit knowledge can be seen through its action: 'the aim of a skillful performance is achieved by the observance of a set of rules which are not known as such to the person following them' (from Polanyi, *Personal Knowledge* 2002 [1958]: 49). There are 'rules', as Polanyi describes them, however he explains:

Rules of art can be useful, but they do not determine the practice of an art; they are maxims which can serve as a guide to the art only if they can be integrated into the practical knowledge of the art. They cannot replace this knowledge

Polanyi, 2002 [1958]: 50

Tacit knowledge has been described as comprising a range of conceptual and sensory information that attempt to make sense of something, meaning it cannot be put into words. This evasion of linguistic encoding means tacit knowledge is difficult – if not impossible – to store and as such it must be passed from person to person.

An art which cannot be specified in detail cannot be transmitted by prescription, since no prescription for it exists [...] it follows that an art which has fallen into disuse for a period of a generation is altogether lost.

Polanyi, 2002 [1958]: 53

This description of knowledge as embedded in the practices of individuals is challenging: without some way of translating the knowledge to a symbolic form, it is unclear how knowledge is transmitted between individuals. Polanyi describes this as happening through apprenticeship.

By watching the master and emulating his efforts in the presence of his example, the apprentice unconsciously picks up the rules of the art

Polanyi, 2002 [1958]: 53

Tacit knowledge is gained in enculturation: social groups and processes develop, maintain and alter complex tacit knowledge in a way that cannot be easily replicated by non-human entities. Expertise becomes inextricably linked with experience: gained through observation, imitation and practice, resulting in enculturation – or *connoisseurship* - as termed by Polanyi. This connoisseurship, Polanyi recognises, could be dismissed as unscientific – the diagnostician's 'instinct' or the 'art' of medicine. As such, Polanyi maintains:

Whenever connoisseurship is found operating within science or technology we may assume that it persists only because it has not been possible to replace it with a measureable grading

Polanyi, 2002 [1958]: 55

This implies that Polanyi recognises in part that connoisseurship arises due to the limitations of tools, and as such, the limitations are likely to be countered and overcome through the development of more accurate measuring tools. Despite Polanyi's call for the recognition of the centrality of personal knowledge and skill, there is acknowledgement that all discernable differences do have a physical explanation, and that in the absence of other means of doing so (instruments, scales and so on) personal knowledge is a means through which these tasks can be understood. There are rules – they are not known as such – but these rules do not necessarily have to be known explicitly in order to work in accordance with them – they are 'unspecifiable' (2002 [1958]: 55). This 'unspecifiable' nature can be understood in two ways, firstly, that rules for action do not need to be specified in order to be useful, or contrarily, that they are in fact categorically unspecifiable as is implicit in the master/apprentice relationship.

Criticisms of tacit knowledge

Gilbert Ryle in his book *The Concept of Mind* (1949) preceded Polanyi's conceptualisation in drawing a distinction between 'knowing that' – the knowledge that something was the case, and 'knowing how' - the ability to execute the task. This distinction – with origins in Plato's account of knowledge - is the precursor to Polanyi's analysis of knowledge types. Fodor, in his critique of this distinction and the concept of tacit knowledge describes how 'there is not one, but a family of distinctions that goes by that name' (Fodor, 1981:70). Fodor lists skills, which may be best 'taught by example' (1981:70) and 'cases where we know how to do X and can give an account of what we do when we do X, but where it seems clear that the ability to give the account is logically and psychologically independent of the abilities involved in X-ing' (1981:70). Fodor considers Polanyi's (and Ryle's) conceptualisations as too simplistic – both 'knowing how' and tacit knowledge fail to distinguish between degrees of competence, describing how 'traits give rise to adverbs, competences to verbs: we exhibit our competences in our activities and our traits in our style' (1981:72). It is possible to know how to do something, but there are also degrees of competency allowing us to do things well to greater and lesser extents. Tacit knowledge, for Fodor, fails to capture this nuance.

Tacit knowledge, specialist and ubiquitous expertise

A full analysis of the Periodic Table of Expertise lies beyond the scope of this thesis, and as such, I limit my description to the sections likely to be of use later in the analysis of genetic work.

Ubiquitous expertise refers to those expertise or skills (such as native language skills) that are required in order to live or participate within a society or social group, and are usually tacit within a given context. Imagine a geneticist working in the UK clinical context without any English language skills – it is impossible to move through the columns of expertise without this basic ubiquitous expertise, the use of language, on which to build. These skills have parallels with Dreyfus' notion of practical wisdom. The second column encompasses *dispositions*. Collins describes these as 'not very important to the conceptual structure of the table' and uses the examples of linguistic fluency and analytical flair. This infers fluency, or the ability to skillfully employ or extend ubiquitous expertise

The categories in the *specialist expertise* column indicate how Collins and Evans (2007) conceive of two types of socialisation, which result in the development of specialist expertise. The first of these – *contributory expertise* – describes the commonly held norms of expertise, that is, the practical skills and/or knowledge that allow an individual to contribute meaningfully to a particular domain of practice. Contributory expertise develops and emerges as a result of working within a particular domain. It is important to consider how a domain is defined: whilst some skills and knowledge could be considered as sitting within a broad 'medical' domain, others might be considered as specific to a particular domain, or subspecialty, practice

Interactional expertise differs in that it can be acquired through immersion in the linguistic discourse of the domain alone. Collins describes this as a subsidiary expertise that ultimately underpins social and collective practices. This mutual understanding of the real worlds of others is what allows cooperation and understanding, and ultimately the sophisticated division of labour in society. Both develop through prolonged social contact: contributory expertise when emerged in a specific domain of practice, underpinned by interactional expertise, which allows the co-operation and understanding which makes the development of further expertise a social/practical possibility.

Interactional expertise

Interactional expertise sits below this, defined as 'expertise in the language of a specialism in the absence of expertise in its practice' (Collins and Evans, 2007: 28). This seemingly contradicts the notion of enculturation, experience or *connoisseurship*, implying that expertise can exist in a specialist form without this process having taken place. Interactional expertise reflects a hinterland between the possession of formal knowledge and having some access to (but insufficient) tacit knowledge: to the 'expert' who has internalised the rules of enculturation, possessing tacit knowledge, the limited expertise of the individual displaying interactional expertise may be obvious, however recognition of these 'rules' can only occur when *sufficient* tacit knowledge is possessed.

[Interactional expertise is] ... needed in some approximate form by successful participatory sociologists, ethnographers, and social anthropologists, mastery of interactional expertise is also the goal of specialist journalists; it is needed by salespersons... it is the medium of interchange within large-scale science projects, where again not everyone can be a contributor to everyone else's narrow specialism: it is, a fortiori, the medium of interchange in properly *interdisciplinary*, as opposed to multidisciplinary, research....

Collins and Evans, 2007: 31-32

To what extent can the work of medicine be considered either (or both) interdisciplinary and multidisciplinary? These terms are ambiguously defined and used interchangeably. Multidisciplinary builds on the central premise of the sociology of the professions, in that knowledge may draw from multiple domains or specialties, yet the boundaries are clear and maintained. Interdisciplinary implies links between disciplines forming a coherent whole: one in which the jurisdictions may become unclear (Choi and Pak, 2006). The way in which the relationship between the work of neonatologists and clinical geneticists in the care of newborn infants with suspected genetic disease is defined or in flux between an interdisciplinary and multidisciplinary state is explored in chapter seven, contending that neonatologists display interactional expertise with respect to the use of array CGH: the transition to interactional expertise accomplished through engagement with the technology and experience of its use, critical components of the mainstreaming of medical genetics.

It is nature of the relationship between neonatologists and geneticists – the progression as Collins and Evans describe from 'interview' to 'discussion' to 'conversation' (Collins and Evans, 2007:33) – which is of interest. There is no identifiable threshold at which interactional expertise is achieved, but it is described as a transition from 'eavesdropping' on the subject of the expertise to actively 'participating' (2007: 34). The process is a parasitic rather than symbiotic one: interactional expertise emerges from interaction with specialist expertise, however it does not benefit specialist expertise even when it is established. Even where interactional expertise is established, they are unlikely to attain contributory expertise, for example, becoming involved in laboratory work, or managing complex genetic disease without the support of a geneticist. These are examples of the genetic work which will render medical genetics relevant and useful as the mainstreaming agenda moves forward.

Specialist knowledge types

The categories to the left hand side of the specialist line are best described as types of specialist 'information', which can be gained through reading, learning or other means not associated exclusively with an association with experts. The capacity to develop explicit knowledge requires 'ubiquitous tacit knowledge': the skills we develop as members of a particular society, with Collins

stating the example of how close we might walk to others when sharing a pavement or the volume and expressivity of speech in particular social situations. More relevant here are examples such as fluency in a particular language, the ability to read, or to access relevant materials such as books or articles. These instances of generic ubiquitous expertise allow for the development of specialist knowledge, which Collins and Evans (2007) describe in three forms.

Specialist knowledge type	Description of knowledge type
'Beer mat knowledge'	Basic, functional, knowledge. Cannot be manipulated or extended due to superficial knowledge only – little meaning.
'Popular understanding'	Akin to understanding from mass media or popular books. Deeper understanding of meaning. Can be an important distinction in the case of conflict or controversy.
'Primary source knowledge'	Knowledge gained from reference to high quality primary resources. Does not require apprenticeship, or <i>connoisseurship</i> immersion in the field.

Table Ten: Types of Specialist Knowledge (Collins and Evans, 2007)

As we move through each of these stages, fewer and fewer people can make claim to the level of specialist knowledge: the expertise becomes more esoteric. Popular understanding is limited to those willing and able to refer to sources such as books and newspapers. Primary source knowledge usually arises from some specific need: a specialist health need or political motivation. Where do the clinicians working in areas where genetics is being mainstreamed (such as oncology, or paediatrics) lie on this spectrum? Most likely, there are professionals existing across the spectrum: for example those such as neonatologists who may have a special interest in developmental disorders (and need high levels of knowledge and expertise of genetics to do their daily work), versus acute paediatricians (who may encounter these pathologies infrequently). But is there a 'minimum standard' we might expect from professionals? There are attempts to enact minimum standards through postgraduate medical qualifications. How individuals and groups become socialised in a domain of practice is demonstrated in the expertise-space model.

[The expertise-space model](#)

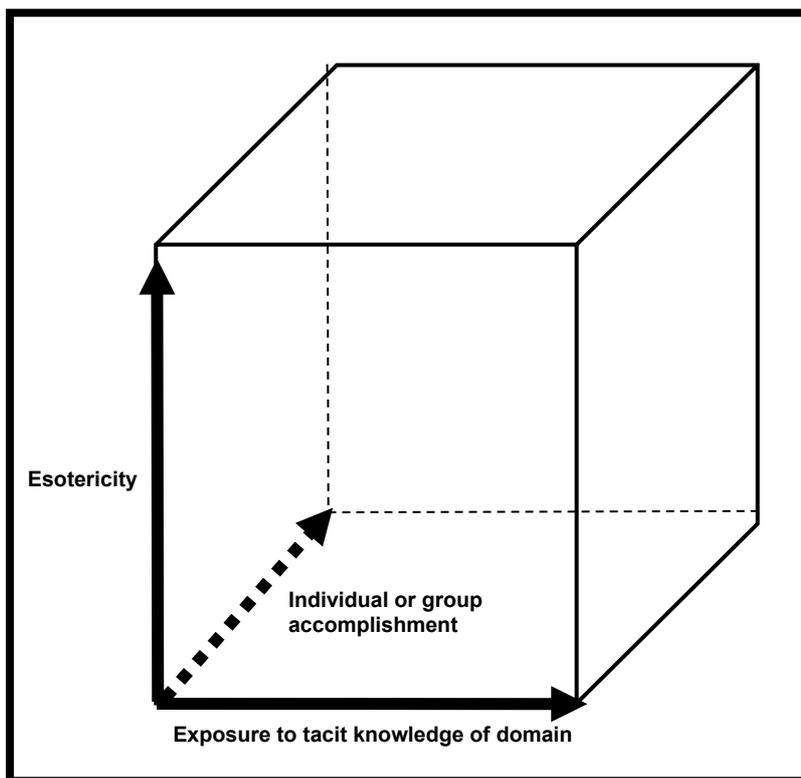


Figure Eleven: the expertise space model

As a counterpoint to one-dimensional conceptions of expertise, Collins has developed the expertise-space model to represent the relationship between exposure to tacit knowledge with reference to both individuals and groups (horizontal axis). The vertical dimension represents the degree to which a domain can be considered esoteric with ubiquitous domains, with the lower axis representing skills considered ubiquitous, such as fluency in a given language, and the upper segment of the axis representing knowledge not considered esoteric. Collins uses the example of gravitational wave physics (Collins 2004, 2016). This diagram borrows from the notion of chemical phase diagrams: emphasising how there can be sudden, discontinuous transitions in the development of expertise, as occurs in chemical changes of state between solid, liquid and gaseous states.

A discontinuous or step-wise notion of expertise development is implicit in the stage theories described earlier and indeed even within the periodic table of expertise, the classes themselves represent discontinuities. Central to the expert-space representation is the notion of a particular domain of practice as consisting of individuals in relation in the topic, rather than a primary reference to the topic itself. Whilst Collins uses the example again of gravitational wave physics, it is useful to think about this with respect to clinicians developing expertise around genetic testing or counselling. Whilst reading a book on a subject does not necessarily place someone in the domain, some social contact and reading may lead to the domain of 'popular understanding' or 'primary

source knowledge', depending upon the type and rigour of the book in question. Collins describes these domains as creating an expertise 'space' instead of an expertise 'line'.

Another important aspect of the expertise-space model is the way in which it emphasises the situated nature of expertise, described by Collins through the (almost) ubiquitous skill of driving a car. Collins contends that the notion of driving as an ubiquitous 'expertise' is highly situated – for example, car driving would not have been considered ubiquitous at the start of the Twentieth century, nor could it be considered ubiquitous in a rural location in a developing society. Different 'levels' emerge in the diagram in order to represent this situatedness: activities can be considered as requiring differing 'levels' of expertise at different times in different places. Expertise becomes highly contingent and situated.

Relevant to the mainstreaming of genetic and genomic medicine is the way in which the esotericism of a particular domain of practice is considered and defined. Whilst the levels figure represents different types of driving as different contingent activities, for example normal care road driving as opposed to racing driving, they could also be considered as instances of the same activity, driving. Here, the notion of gaining experience in difference highly contingent circumstances may not necessarily have wider implications for the development of expertise. Driving a car in normal road conditions might be considered as akin to providing diagnostic genetic testing in straightforward clinical circumstances. Formula one racing – as an expert skill – represents challenging tasks such as predictive testing: medical geneticists will remain the racing car drivers even as technologies are mainstreamed.

Conclusion

The sociological and empirical literature has explored the shifting sands of professional boundaries within health and medicine at different levels. As genetic and genomic technologies become available to non-expert groups, medical genetics – in order to maintain its professional status – must act to ensure that it is not deprofessionalised. Whilst other professionals and clinicians encroach on its territory, or domain of practice (assisted by managerial and technical interventions), medical genetics must mount a politically informed defense of the qualities which make it distinct. Yes this counters the current policy orientation in the UK – the mainstreaming of medical genetics – and demonstrates a key tension. How can clinical geneticists maintain their professional status when the jurisdiction they have over testing is transferred to other medical specialties? As this jurisdiction is transferred, how is the quality of care provided ensured? It appears that one of the core functions of clinical genetics will be the education of other health professionals doing genetic work. This study is one of intra-professional division in medicine – between neonatologists involved

in the care of infants and medical geneticists. Does the availability of aCGH technology to paediatricians represent a new division of labour and knowledge?

Where the education of professionals is considered, it is necessary to understand how expertise is developed, and the levels, or standards, at which it can exist. How does expertise evolve, within individuals and within groups and networks? This provides a useful framework through which to understand the relationship between experts and those developing expertise, and the trajectory of individuals seeking to develop knowledge and experience.

The next three analytic chapters consider and present data from the groups and networks forming the bioclinical collective (Bourett, 2005) in doing chromosomal microarray.

Chapter Six: The Laboratory

This first analytic chapter explores, through ethnography, the interpretive practices of clinical scientists in mapping, annotating, interpreting and ultimately reporting gene copy number variation using array comparative genomic hybridisation. It explores the relationship between the laboratory and the clinic, especially with respect to the use of standards and the role of the 'messy' clinic in disrupting the genetic work of the laboratory.

The laboratory forms a key component of the 'bioclinical collective' (Bourett, 2005). It constitutes an important site in the construction of the 'extended patient, defined by the articulation of clinical data (the disease), biological data (the gene and the mutation) and social data (family links and degrees of relationship) (Bourett, 2005: 48). In this chapter, I explore the role of the laboratory as producers - or generators - of biological data. Subsequent chapters explore the antecedents and consequences of this data: the antecedents in the clinic, and the consequences in the life-world of the patient and family.

Observations in the laboratory were conducted weekly over an eighteen-month period following the introduction of array comparative genomic hybridisation as the first-line clinical test for disordered development and potential genetic disease in the paediatric population. With the introduction of a 'new' technology³³, I was provided with the opportunity to observe during a period in which those performing the work were still unfamiliar with much of it. They gave running commentaries on their activities and tasks as they themselves grappled with the technology before it becomes an unremarkable part of their routine, everyday practice (De Laet and Mol, 2000) – capitalising on the 'anthropological strangeness' (Bowker and Star, 1999) of non-specialist clinicians engaging with this technology. Novel 'hot' issues and entanglements were more frequently encountered and negotiated, providing the opportunity to (more frequently) observe the management of the uncertain and the unfamiliar.

In this chapter, I contend that the clinical laboratory is a site of uncertainty intolerance. For the relevant social groups based in (or proximal to) laboratory work, uncertainty is not experienced as an objective property of microarray technology *per se*: instead, uncertainty is minimised, eliminated or situated through the use of standards. Where standards 'fail', reflexive standardisation draws on expertise to tinker with, repair, subvert or circumvent the standards, in order to allow the technology to 'work' (Lampland and Star, 2009). The process of reflexive standardisation combines the work of

³³ The International Standard Cytogenetic Array (ISCA) consortium advised that array comparative genomic hybridisation was the preferred cytogenetic investigation for developmental disability and congenital anomalies in 2010 (Miller et al, 2010). As such, the use of the technology cannot be described as new *per se*, rather just new in this particular clinical setting.

interpretive flexibility and closure, and is heavily dependent on calls upon expertise. The uncertainty inherent in microarray testing, from the perspective of those in the laboratory, emerges from the (dis)order of the clinic, where standards are more difficult to establish and apply. Narratives of uncertainty problematise the practices of the ‘messy’ clinic, seeking to externalise the challenges associated with aCGH beyond the laboratory.

A note on ‘Laboratory Studies’

The rich array of laboratory work considered by science and technology studies (such as Latour and Woolgar, 1979; Knorr Cetina, 1981) mainly examine the work of research laboratories rather than work occurring in clinical or diagnostic laboratories. The distinction is important: in contrast to examining how generalisable, new facts or knowledge are constituted and made ³⁴, this study, based in a clinical laboratory, focuses on diagnosis as the aim. How are facts about individual patients, and potentially their families, made and justified through the visualisation of genetic material, the rendering of representations and the subsequent meaning making?

The laboratory forms an important site, as it is where the scientific work of genetic testing is rendered visible, examining the indexical nature of scientific action and reasoning. Much of the ‘work’ in the laboratory is not directly visible. In the case of microarray, the process itself occurs obscured from view inside the scanner – the ‘black box’ (Latour, 1999) - at the center of microarray testing. Social constructivist approaches aim to ‘open’ this black box, revealing the internal workings of the system, and countering the way scientific and technical work is rendered invisible by its own success (Latour, 1999).



Figure Twelve: A Microarray Scanner – the ‘black box’

Around the literal black box of the array scanner, the work of the laboratory creates a metaphorical black-boxing of microarray testing:

³⁴ Though this does occasionally, inadvertently occur – so-called scientific knowledge in the making (Latour, 1987)

...the way scientific and technical work is made invisible by its own success. When a machine runs efficiently, when a matter of fact is settled, one need focus only on its inputs and outputs and not on its internal complexity. Thus, paradoxically, the more science and technology succeed, the more opaque and obscure they become

Latour, 1999: 316

The social constructivist approach employed here, aligned with social construction of technology approaches, attempts to 'open' this black box, and understand the work of the laboratory in constituting microarray generally, and specifically the uncertainty inherent in and generated by cytogenetic testing.

Situating the study: The Laboratory

The All Wales Medical Genetics Service provides the clinical and laboratory genetic services for approximately three million people cared for in a range of healthcare settings, ranging from major university hospitals, local district general hospitals, primary care and community based clinics. The genetics service is an integrated service, with laboratory services and a clinical genetics team. Staff working in the laboratory includes technicians and clinical scientists, responsible for the processing of clinical samples – blood and tissues – and the generation of factual 'reports' for use in the clinic. The clinical team consists of genetic counselors and doctors working in clinical genetics ('medical geneticists'), who interface directly with patients and families undergoing testing, as well as providing a 'consulting'-style service to medical professionals in other medical specialties, such as paediatrics, who care for patients with potential or diagnosed genetic disease. Clinical staff work in this building, and in other areas within Wales, taking responsibility for the care of patients in defined geographical areas by holding clinics in local hospitals.

The All Wales Medical Genetics Service is based in a building at the rear of the hospital site – fortuitously - but not deliberately - located opposite both the Maternity Unit and the new Children's Hospital. These clinical areas represent the locations where much of the 'work' of clinical geneticists takes place: seeing antenatal patients when a genetic anomaly is suspected during pregnancy – usually as out-patients in the fetal medicine unit, as well as seeing children with congenital anomalies or disordered development in the neonatal intensive care unit, when complications have required additional support following birth or in the children's hospital, when the complications occur later in childhood. As a junior doctor, I accessed the building many times to 'drop off' precious blood samples taken from neonatal patients, when syndromes - such as trisomy 21 - were suspected. The samples are deemed 'too precious' to be put into the main system of sample transfer – where porters manually collect samples from the unit to be delivered to other hospital areas. They cannot be transported in the airpod system (as being in a separate building,

the genetic laboratory is not accessible from the network). Because of this, and as results are often needed quickly, samples are usually dropped off by a member of staff from the clinical area.

The building is simple and announced by a small, discrete sign placed outside – ‘The All Wales Medical Genetics Service’. The fabric of the building appears worn, having been constructed in the 1980’s: particularly when compared to the new glass fronted research facility for Cancer and Genetics next door, complete with brightly-coloured awnings. Access to the reception is down stairs or a meandering ramp into a dimly lit lobby accessed via two automated doors, adorned with signs familiar from around the hospital site, advising against smoking on hospital grounds.

The reception is not typical of the familiar out-patient clinical spaces of the main hospital. It is darker than most clinical spaces, partially due to dim lighting but also because it is floored with carpet, rather than the high-sheen, wipe-clean flooring preferred for cleanliness in high traffic clinical areas, frequented by the ‘unwell’. It is sparsely decorated, and upon entering, there is a choice of receptions – one for ‘specimens’ and one for ‘patients’, in addition to a small seating area. The ‘Specimen Reception’ consists of a small glass window, staffed in office hours by a laboratory technician assistant – a ‘scientist’, wearing a white laboratory coat - who collects samples passed through the window by a range of staff – couriers, healthcare assistants and clinical staff like doctors and nurses. ‘Specimens’ range from blood samples (the majority of samples are blood) through to tissue samples from skin, tumours or products of conception following miscarriage, upon which genetic investigations will hopefully be performed. Samples are contained in specimen pots of various shapes and sizes, and accompanied are by a request form, issued by the medical genetics service, and completed by the requesting clinician when a test is required. Following delivery to this window, ‘specimens’ are given a unique departmental identifier (‘lab number’) during a process known as ‘booking in’, where patient information, clinical information and request forms are assessed for their completeness. Samples are then grouped according to the type of testing to be undertaken and prepared for transfer to the appropriate laboratory space.

The ‘main’ reception is opposite the specimen reception, staffed during working hours by receptionists dressed in smart office clothing. There are charity appeals, usually related to genetic disease, adorning the countertop, appealing to patients, staff or visitors for donations in return for Christmas cards, ribbons or badges of various colours. Staff at the desk are responsible for directing visitors to the building to the appropriate areas – patients to the small waiting area, to be called to the corridor of consulting rooms directly adjacent to the reception area, deliveries to a small area adjacent to the door and visitors to the laboratory and research spaces on the two floors above.

Behind the desk, an office area deals with paperwork related to clinical consultations and appointments. Patients approach the desk – often with an appointment letter – and their details are verified by the receptionist against clinic lists for that day. Patients are then directed to the small seating area, complete with a small selection of outdated magazines and toys and a noticeboard announcing charity days and support groups. The waiting room is rarely busy and even when patients are waiting, they usually do so quietly. Medical geneticists and genetic counselors emerge into the waiting area via an adjacent door – calling patients to a corridor of clinical consulting rooms in order to be seen.

Adjacent to the specimen reception is a secure door, accessed via code, leading to the two floors of laboratory and research space. The building is unusual in that it houses staff from both the university – working on research projects – and the National Health Service, providing clinical care for patients. In this building areas like laboratories and offices are often dual purpose, housing staff from both areas together, reflecting the overlapping and interweaving of the two spaces and places of clinical work and research work. The dual purpose – and indeed dual nature – of the ‘genetic work’ is emphasised and embedded in these physical and spatial arrangements.

The ‘array lab’

Samples for analysis by aCGH are forwarded for the attention of the cytogenetics³⁵ laboratory. Though termed ‘the lab’ by those working there, the laboratory space consists of a series of rooms on the second floor of the building, emerging either side of a long corridor, with many of the rooms appearing much like conventional offices, equipped with computers and printers, alongside table-top microscopes³⁶, genetics textbooks and other equipment, adjoining more typical white-tiled laboratory spaces, housing staff in white coats working at scientific benches.

During my initial orientation with Emily (a clinical scientist), I was introduced to the ‘array lab’ as a series of three main spaces: the ‘extraction lab’, where DNA is extracted from patient blood samples in a part-manual, part-automated process. The ‘array lab’ housed the small tabletop microarray scanner – a ‘box’ through which microarray analysis is performed. Both spaces were governed by strict standards regarding health and safety, specimen handling and clothing, with scientists being required to ‘put on white coats’ when entering and working in these spaces.

³⁵ Cytogenetics, as mentioned earlier, is a branch of genetics ‘that links the study of inheritance (genetics) with that of cells (cytology), [being] concerned mainly with the study of chromosomes, especially their origin, structure and functions’ (Martin, 2015). Chromosomal microarray is a cytogenetic test.

³⁶ During my twelve months of observations in the laboratory, the table-top microscopes were used vanishingly infrequently. Indeed, at the end of my observations, there were removed and replaced with computers.

Yet despite being competent to perform a task independently there are caveats. Firstly, the ability to perform a task competently is considered as different and distinct from the ability to do it fluently. Tasks are not performed 'automatically' - meaning they are not tacit, or performed with automaticity. Rather there is the observation that junior or inexperienced clinical scientists continue to perform each stage of the task deliberately. Secondly, there is an implication that 'abnormals' – those samples in which a pathological variant is identified – render mere competence inadequate, and there is a need for expertise, even mastery (Deyfus, 2001). When the normal or anticipated order is disrupted, expertise enables order to be restored. Despite the roles of scripts and standards (described later), there was still a role for 'getting to grips' with how reporting is 'done'.

In the next section, I examine how 'calls' are made, before moving onto the central role of standards and scripts in the work of the laboratory.

Analysing 'calls'

The mapping and calling of variants are computer-led, software-driven processes, relating to the array data generated from sample analysis (see appendix H for a full screen view of the software output). As described earlier, array uses a series of probes across the genome to examine gene copy number at different loci. Probes are most densely concentrated in regions with known disease-causing genes: a variant is 'called' by the software when three adjacent probes are 'displaced' on the sample (the patient's) DNA, compared to the reference DNA. This indicates either a gain – a 'dup' or duplication - or a loss – a deletion - of genetic material at a particular location on the chromosome.

We set the algorithm to 50kB for disease regions, 150kB for deletions in the backbone regions and 250kB for duplications in the backbone regions. These are the standard settings for blood samples.

Hannah, Clinical Scientist

The software then categorises these 'calls' into two distinct categories: 'below algorithm' and 'above algorithm' settings. The 'algorithm settings' – or standard settings - refer to numerical parameters, selected by the clinical scientist, which guides the software in attempting to distinguish pathological copy number variation from benign copy number variation, based on the size and location of the material change to the genetic material.



Karyogram display

Each chromosome is displayed independently with its characteristic banding pattern. 'Calls' are made by the software, according to the pre-determined algorithm settings, are displayed as red or green bars adjacent to the region of chromosome. **Red bars** represent a **loss of gene copy number** relative to the reference DNA, and are termed **deletions**. **Green bars** represent a **gain of gene copy number** relative to the reference DNA and are termed **duplications**.

Figure Fourteen: A karyogram presenting 'calls' as red (deletion / loss / reduction in copy number) and green bands (duplication / gain / increase in copy number) across the genome

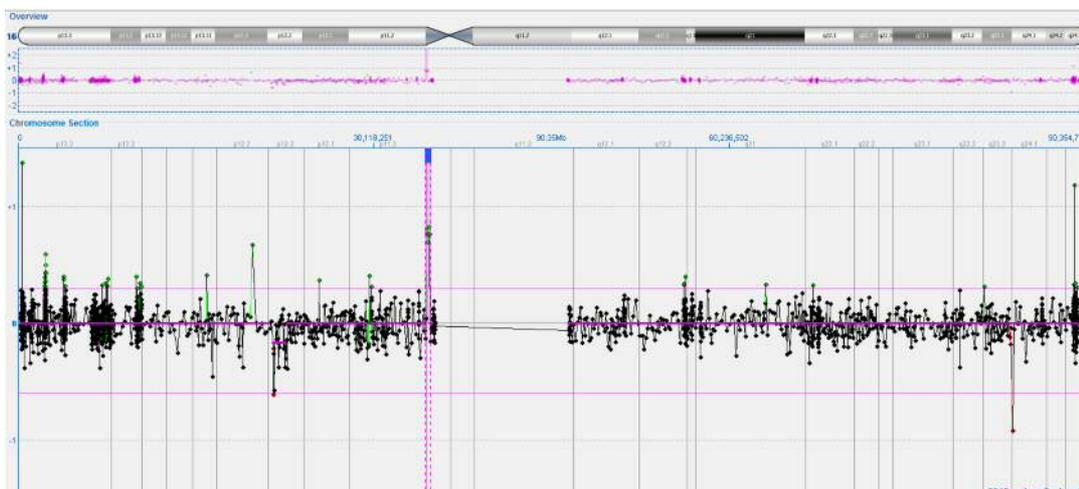


Figure Fifteen: Chromosome 16, passed quality control, no copy number variation

Hannah describes how the initial software generated classification of copy number variation is based on two factors: the size of the loss or gain of genetic material and the location of this change on the chromosome. 'Disease regions' are positions in the chromosome where genes known to be associated with disease are located, the 'backbone' refers to other areas. Smaller aberrations are 'called' - and as such subjected to scrutiny - in the areas of the genome most likely to be associated with disease. In the backbone, parameters are set that aberrations need to be much bigger to generate

'a call': 150kB for deletions, and 250kB for duplications, which are even less likely to be associated with disease.



Figure Sixteen: Chromosome 16, passed quality control, a pathogenic 'call' with probe displacement highlighted

In referring to the 'standard setting', she reveals how the conduct of classifying variants is governed by standards. The initial classification of a call is automated through software, according to a standard defined and set by the clinical scientist. Though the call is highlighted, there is the need for manual curation by the clinical scientist when a variant is in a position, or of a size, which suggests pathogenicity. This numerical sorting by software ensures that variants are addressed and evaluated consistently – drawing human, operator attention to aberrations most likely to be of clinical importance.

Some of these calls will represent pathological changes, however, in practice, these distinctions are not always straightforward, and many calls are quickly disregarded or disposed:

I don't think those are real

I think its probably a false positive, it doesn't look like the most convincing call.

Emily, Clinical Scientist

So there is nothing striking me as likely to be real... There's nothing jumping out as potentially real there.

Hannah, Clinical Scientist

Though 'the call' is real – meaning three adjacent probes have been displaced – the assessment of the likelihood of the variant being of 'real' clinical significance, or indeed not just a mere artefact of the technology and software is made quickly – tacitly - by the analyst. Laboratory staff quickly become familiar with the variants most likely to constitute pathological or benign 'calls', in terms of their size, location and nature. A clear example of this is the observation of 'recurrents': variants that are seen repeatedly, three or more times, within the samples which have been previously processed in the laboratory.

Oh yes this is one of our recurrents (1) see scroll down here we see this one a lot
Emily, Clinical Scientist

That's one of our regulars
Hannah, Clinical Scientist

Tacit knowledge in this sense is highly temporal and local, then verified and confirmed – checked and justified – through reference samples that have been previously analysed. Categorisation is used to group variants requiring no additional attention, allowing deliberative attention to be focused on variants likely to be of clinical significance.

Variants of Uncertain Significance

Variants of uncertain significance are defined as variants with an uncertain relationship to disease. This can arise in multiple ways: when there is an uncertain or unknown effect of a specific genetic alteration on gene function. Next, where there is insufficient data to confirm that a variant is associated with manifest disease or the future development of disease. A patient may have a variant which is expected to be associated with manifest disease, but be unaffected or have no symptoms: as such, the genotype-phenotype correlation is unclear and the consequences of the variant is unknown. Finally, a variant can be considered to have unknown or uncertain significance when the phenotype of the patient is different to that expected based on the variant that has been found.

I think this one will be a VUS (.) it's a large deletion (.) but I've looked through the databases (.) looking through (.) this infant is IUGR [intrauterine growth restriction] there is nothing there to explain that [the growth restriction] and those two in ISCA are larger than our deletion

Anna, Clinical Scientist

Here Anna describes identifying a large deletion of uncertain consequence. A change is identified by the array, the 'call' is made and then cross-referenced with changes recorded in collaborative databases of array data which identify genotype-phenotype correlations.

Yes in this one [ISCA database] its developmental delay and in this one (.) yes developmental delay again [DECIPHER database] (.) but again our deletion isn't quite as big (.) but it is all in there (.) let's put this one to one side for Susan to look at too as I'm not quite sure

Anna, Clinical Scientist

In many cases, uncertain variants required more interrogation, review and deliberation than straightforward 'abnormals'. Anna describes the difference:

With a straightforward abnormal pathogenic variant you have (.) well straight away you have one or more of the databases recording a similar (.) if not identical finding both in terms of location and size and ideally the phenotype too. It's pretty straightforward really

...

with the VUS's it can be more tricky to discern as usually it's around the same location (.) around the same size (.) or completely within another reported VUS or there is a gene in there which has no relation to the phenotype on the form and then you're like (.) well firstly is this uncertainty of any significance (.) is it worth reporting it (.) and is it worth looking at the parents (.) sometimes you report it knowing it's the only way to get the parents in to give the samples or to get the family referred into genetics

Anna, Clinical Scientist

The process of 'diagnosing' or identifying a VOUS is described as inherently more uncertain than making a straightforward pathological diagnosis. This uncertainty manifests in two key ways: firstly, the complexity of the interpretive processes involved in cross-checking sources and secondly, in terms of the potential consequences of reporting something as unknown, for the health of the proband and their relatives, and the potential consequences for information sharing and decision making. In this sense, reporting is tactical. It is concerned with ensuring further samples (parental samples) become available for testing, and at other times, it is to ensure that an individual or family are referred for specialist evaluation and care.

In the next section, I examine how certainty/uncertainty is addressed through the application of an array of standards governing the practices and processes of clinical reporting.

[\(Un\)certainty and solutions: the role of standards and expertise](#)

Throughout observations, there was reference to 'the standards': 'standard operating procedures', 'meeting quality standard', the 'standards' of the clinical information. Standards are means through which uniformities are constructed across time and space through the production of and adherence

to a set of agreed-upon technical rules (Bowker and Star, 1999; Timmermans and Epstein, 2010). Though frequently context dependent, standards are often used to provide a means of making practices uniform across different communities of practice, or activity sites (Timmermans, 2015). They are frequently endorsed by external agencies, which maintain, define and regulate the application of standards. Standards and standardisation play an important role in the transition of technologies from the research to the clinical setting (Thevenot, 2009), with the way in which standards emerge and develop around new practices and techniques having their own contexts of origin, memory practices and limitations and opportunities that circumscribe the types of work that can be easily accomplished (Timmermans, 2015). In this section I describe and examine the enactments of standards as observed in the array laboratory.

Standards as 'scripts'

If the workings of the laboratory are conceptualised as a 'blackbox', then the Standard Operating Procedure (referred to hereafter as the 'SOP') represents an attempt to unpack this box. It does this through rich, staged description of the laboratory task. Standard operating procedures are a common feature of laboratory work, described as

... document(s) which describe(s) the regularly recurring operations relevant to the quality of the investigation. The purpose of a SOP is to carry out the operations correctly and always in the same manner. A SOP should be available at the place where the work is done.

United Nations, 1998

This document was referred to by participants as a 'guide', 'handbook', 'a standards document', 'guideline' and 'manual'. These underline the (supposed) informational utility of the document in performing microarrays. Standardisation is explicit in the aims of the Standard Operating Procedure – supporting laboratory staff in attempting to carry out the task – in this case the reporting of copy number variation, termed by staff as 'calls' – 'correctly' and 'always in the same manner'. Implicit in this is an acknowledgement that the task is highly contingent: it can be subject to variation when performed in different places or by different individuals, and this variation can impact on the quality or accuracy of the investigation being conducted. In being available at the place the work is being performed the SOP can be seen as providing a 'script' (Akrich, 1992) for how arrays are to be interpreted and subsequently reported. Contingency in this process is a threat to quality and accuracy and as such should be minimised at all costs.

With respect to chromosomal microarray, this 'script' is a 28 page document, prepared jointly by the head of the cytogenetics laboratory and the section lead for microarray. The document is available to all of those undertaking the analysis of array data, termed 'the analysts'. Analysts are described

as individuals who 'have read and been trained/demonstrated competence in the procedure as detailed in the SOP', and are usually graduates in biological sciences who have undertaken further training in cytogenetics (clinical scientists). The document states that 'all staff have the responsibility to perform the procedure as detailed in this SOP'. As such, the script becomes more than a series of instructions. The potential negative implications of deviating from this script are emphasised, with adherence to and enacting of these standards being framed as a moral duty for staff undertaking this task.

Quality as standard: quality control

Quality control (QC) represents a standard, in terms of its role as a measure of 'the quality' of the array data. Below Emily describes the notion of QC in both concrete and abstract terms.

...it's basically just a measure of the dispersion of Log2 ratio of all clones on the array, giving an overall picture of the noise in the array. It's a number and a standard that the software produces and assesses (.) but you just know whether it's going to be a pass or fail just by feel... scanning the raw data for how messy it is.

Emily, Clinical Scientist

Quality control here is presented in a number of potentially conflicting ways: as a measure, or numerical value, as a standard produced by computational, bioinformatic processes, and finally, as a 'feeling' - a tacit visual assessment by the clinical scientist of the 'messiness' of the data. Though quality control is initially described as a numeric value represented as a binary 'pass' or 'fail', this is a simplistic representation of the practical task. The quality control of array data refers to an ordinal-scaled assessment of sample quality based on two key measures. Firstly, the 'DLR spread', referring to the probe-to-probe log ratio noise of the array: with high values representing poor quality DNA, Secondly, the 'signal to noise ratio', which divides the signal intensity by the background noise to reveal how clearly probe displacement can be detected against background noise. While both measures have associated numerical values, automated assessments of these values by the software provides the binary, explicit assessment of quality control, with a 'QC pass' indicated in green or orange text, and red text representing a 'QC fail'.

This simplified representation of sample quality means analysts performing the task can, but don't always, process or refer to the absolute associated values. The role these values played in the scientists' assessment was linked with the experience and confidence in the visual inspection of array data. For experienced staff like Emily, this assessment was tacit - 'you just know' - whereas for staff like Hannah, new to the reporting process, the assessment of QC is highly deliberate:

You see some of the girls ... and they can just tell... I still depend on the values though. I mean sometimes you can tell ... when it's completely all over the place... but to be confident I have the computer do the work [laughs] it tells you pass and fail and I just use that still (.) maybe as I get more experience I'll get that sense

Hannah, Clinical Scientist, Observation six

Here Hannah recognises the role of expertise: though proficient, she continues to rigidly adhere to rules, rather than the fluid, implicit mode of practice she sees 'some of the girls' use. Using the Collins and Evans (2007) examples, she is driving the car with some elements of conscious choice and analysis, rather than in complete automaticity. Reverting to the standard appropriately represents an example of this choice and analysis, guiding her practice.

Subverting standards

Emily's description shows how the assessment of sample quality is, in part, tacit: you can assess the sample quality 'by feel' through the visualisation of the karyogram. This representation of the genetic material in association with the array probes can be visually assessed, appearing 'messy' or 'spiky' or 'clean' and 'smooth'.



Figure Seventeen: Chromosome 16, failed quality control – 'spiky' – multiple probes are displaced around the central purple band. The sample quality is poor.

Whilst acknowledging the role of the software in generating an assessment of pass and fail, even where the minimum quality requirements have been exceeded and a sample has achieved a 'QC pass', analysts qualitatively undertake the tacit assessment of sample quality based on the visual

assessment of 'noise' in the images of each chromosome: described by Emily as the process of 'scanning the raw data for how messy it is'. This is a process of moving through the karyogram representations of each chromosome. When samples are 'noisy', there is a greater frequency of one or two probes being displaced, meaning 'true' calls of three or more probes are more challenging to discern on brief visual inspection. This noise was described in terms of 'waves' and 'spikes', distortion in the way in which the probes are displayed relative to the chromosome.

It is very wavy. It isn't just ... spiky. The quality is very poor (1) it's a QC fail and I can see that straight away

Anna, Clinical Scientist

So this is really horrible. It's really wavy, loads of spikes

Emily, Clinical Scientist

Tacit assessments are supported by the numerical assessment of QC. However, even when QC thresholds are not exceeded and the minimum standard for clinical interpretation has not been achieved, 'calls' are still subject to manual scrutiny and examination.

So even though it is QC failed, we'll still have a look... we did have one case where we were able to make an interim report based on something which was clearly abnormal... even (1) even given the poor sample quality and the failed QC ... so even if it's a really bad fail (1) sometimes you can still salvage something...

Anna, Clinical Scientist

Here, Anna describes the process by which a standard is subverted. Though the sample has failed to reach the quality standard required, they are subjected to the scrutiny of a sample that may be reported, in case something can be 'salvaged' – meaning it may still be possible to generate information for a clinical report. This significant deviation from the task as defined in the SOP practices is defended through a turn to expertise. Anna continues:

...I generally wouldn't make that decision (1) it would be passed to someone more senior of course (1) you'd leave that to someone like Susan... she is more senior and more involved with the whole process (1) obviously making a report of a clinical finding on a sample where QC hasn't been met ... it does happen but it's a provisional report and it's the most senior scientists who would make the call if that was appropriate or not (1) you won't find that in there [gestures to SOP on table]

Anna, Clinical Scientist

Anna describes the circumventing of the standard using interpretive flexibility: where it is possible to identify an important variant, even in a sample which fails to reach a standard of quality required for clinical reporting, seniority and expertise can be called upon to consider how, if and when a standard may be bypassed, albeit temporarily.

Further examples of this standard tinkering occurred when a sample was mislabeled. Anna explains:

Normally (.) I mean the rule is that with the wrong name sticker on this sample should just be thrown away (.) you know (.) but it's a very precious baby sample and they need a quick diagnosis for this family (.) so I said just this once we can put it on (.) since the form is filled out right and everything.

Anna, Clinical Scientist

Anna describes how a wrongly labeled sample is received from the ward, with the blood sample having the maternal details attached, rather than the infants. Here, the standard is tinkered: since the form is completed correctly, and because the sample is precious having been taken from an infant, the test is allowed to go ahead. The standard is subverted to ensure that the work of the laboratory can be performed. There is a situated element too, in light of the prematurity and small size of the patient:

Sometimes you get such a tiny volume of blood (.) from a very small unwell baby (.) and the DNA extraction is tricky then the sample quality is poor (.) every stage is a challenge but you want to make it work because potentially it could be a really important result

Anna, Clinical Scientist

This frequently circumventing or bypassing of the standard occurs in order to make the technology work for the clinical context, and is highly situated: achieved through a call to expertise and a tolerance of uncertainty.

Next, I consider how external standards shape the work processes of the laboratory.

Standardising 'between' and 'within'

In order to provide clinical services to patients being cared for within the National Health Service, laboratories require accreditation, providing formal recognition of the laboratory to perform specific processes, activities and tasks in a reliable, accurate and impartial manner. In the UK, this accreditation has been provided since 2009 by the UKAS (United Kingdom Accreditation Service). Over the past seven years, 'Medical Laboratory Accreditation' has replaced 'Clinical Pathology Accreditation' as the mechanism through which standardisation and quality assurance is recognised. Accreditation is open to many types of laboratory spaces: public and private laboratories in health, science and pharmacology and to manufacturers of diagnostic equipment and reagents. Formal accreditation is compulsory for laboratories providing services to the National

Health Service, ensuring standards are enacted to facilitate safe and optimal patient care, and is regularly reassessed to ensure maintained adherence to standards.

In preparing for this accreditation, the laboratory participates voluntarily in externally facilitated, continuous quality control exercises. Since 1983, the National External Quality Assessment Service (NE-QAS) has provided a 'voluntary' scheme in which laboratories are provided with two or three samples for analysis, twice each year. Following this, participating laboratories receive independent, objective, impartial reports on their performance, enabling them to identify weaknesses and take appropriate action, alongside access to a variety of educational resources. In 2014, the NE-QAS scheme for clinical cytogenetics and the Europe wide equivalent the Cytogenetic European Quality Assessment (CEQA) merged forming CEQAS, the Cytogenetic External Quality Assessment Service, with the aim of providing a 'broad, consistent and sustainable range of external quality assessments at reasonable cost to the genetic community worldwide'. The merger recognised the increasing need for international standardisation, as the centralisation of specialist services, and the role of cost effectiveness means samples are increasingly sent between countries for analysis and interpretation.

Though not compulsory, the relationship between participation in such schemes and the process of formal accreditation is intertwined in the experience and definition of quality for the laboratory staff:

When these samples come in, you do see it as a bit of a test. From the quality assurance side, it's getting the right result, on the right specimen, at the right time, using the right reference data. It is coupling up the internal quality control in terms of using... applying the SOP [standard operating procedure] locally, then participating the EQ [external quality] assessment programs to check in in terms of overall accuracy and how we compare to other centers

Susan, Director of Cytogenetic Laboratory

The notion of unified standards of practice for doing microarray therefore exists on two levels: the intra-laboratory level, using standards defined through the SOP and local practices, and the inter-laboratory level, which serve to validate practices and standards within laboratories against a constantly evolving backdrop of evidence, techniques, technologies and standards. Whilst seen as the panacea, and the subject of enormous effort, standardisation between laboratories is frequently problematic, and seemingly not always desirable, as described by Laura:

They shouldn't really vary intra because they should follow the SOP [standard operating procedure] for their particular center, but inter-laboratories you could have completely different settings for analysis and a different pipeline for getting to that answer so it doesn't always happen the same way. We do see reports... we're seen one recently where we were quite surprised that the laboratory reported this particular imbalance. We wouldn't report it at the moment, because there isn't that much evidence to say it is pathogenic. But there are research studies out there and I understand some of the London labs are recruiting patients and they reported it but we didn't. So we had to draft another

report to say we also found that region. We wouldn't usually have given that information in the clinical report because we don't think it is information that could be helpful in the clinical setting. So we know that. We know there are different reporting set ups between different laboratories.

Laura, Clinical Scientist

Laura describes a case in which different members of the same family undergo testing through different clinical genetics services. Different reporting thresholds result in different (initial) clinical reports being issued, despite both family members having the same variant. Laura speculates that the laboratory may have reported this variant as they are recruiting for a study. For the laboratory, this would not normally be reported due to a lack of evidence supporting pathogenicity, however, 'tinkering' occurs in light of the variant already being reported to a relative. The standard of identifying and reporting the variant is made to 'work' (Lampland and Star, 1999). This interpretive flexibility demonstrates how the 'technology is actively shaped by social actors who invest it with meanings and bend it to the desires and interests of (non-technical) forms of collective life' (Kirkpatrick, 2008:25). In this case, the collective consists of both the family members undergoing testing, and the laboratories involved in their care. The closure mechanism employed is that of redefinition of the problem (for the laboratory) from 'is this a pathological variant?' to 'is this variant present in this family group?'

The role of standards is ubiquitous throughout the work of the laboratory. Through standards - as the provision of unambiguous information about how a laboratory, scientific or technical task should be performed - the aim is rendering uniform how tasks are performed, reducing variation and ultimately error. In this sense, strict adherence standards challenge or limit the work it is possible for the laboratory to do. In response, there are examples throughout the genetic work of the laboratory in which standards are tinkered, repaired, subverted or circumvented with the ultimate aim of rendering standards workable, fulfilling where possible the aim of the laboratory as a service which provides accurate clinical reporting. Often these acts of rendering a standard workable depend on a call to expertise: only those with mastery are able to make decisions about which standards can be abandoned and manipulated and in which cases these actions are acceptable. Checking, verification and paperwork provide the evidence that standards are being enacted, as acts of checking allow work to be replicated and verified, what Timmermans describes as 'retracing and duplicating' (Timmermans, 2015: 80).

In the next section, I examine another way in which the order of the laboratory is maintained, through the externalisation of the messy problems associated with aCGH being framed as arising from the clinic.

Problematizing the clinic: conflict in the bioclinical collective

Well, you remember Laura? Her son was born with a heart thing. I don't remember what it was now. Tetralogy of Fallot maybe? Anyway, she was saying how shocking it was. I mean they [clinical neonatal staff] spoke to her about all the tests he needed and she didn't even realise they had apparently consented her for an array. She didn't realise until they handed her the form to sign. Of course she recognised it [the request form] from the lab. She was shocked about how little they explained. She questioned it and of course then they explained it properly.

Emily, Clinical Scientist

In this anecdote, Emily reports on the experience of fellow clinical scientist, Laura. After her child was diagnosed with a congenital cardiac anomaly, she was asked to sign a consent form for an aCGH, seemingly not realising array testing was being proposed until she was asked to sign the consent section of the request form – a form she was able to recognise due to her work in the laboratory. Implicit in this account is the notion that consenting for this test is inadequate – indeed, that someone with a detailed knowledge of aCGH was '*shocked about how little they [medical staff] explained*'. Upon her challenging this, they '*explained it properly*', demonstrating that an acceptable account of microarray testing was achievable, and indeed performed, after she '*questioned it*'.

The account and others demonstrate how laboratory staff experience challenges inherent in microarray testing as arising from the chaotic, inconsistent and irregular practices of the clinic. Two key themes dominated the problem accounts provided by laboratory staff: those related to consent, with these problems transitioning from the clinic to the laboratory via the 'request form' and those arising from the provision of phenotypic information to inform and support variant analysis.

Problematizing consent

In the extract above, Emily describes how consent is rendered problematic: a member of laboratory staff was 'consented' for this test, yet did not realise. This expresses concern about how the aCGH technology is described to parents and families when it is used by clinicians. Indeed, as we see later in chapter seven, a great deal of the bridging work (Timmermans and Buchbinder, 2010) performed by laboratory and clinical genetic staff focused on the need for adequately informed consent. As such, samples would only be accepted into the laboratory for processing when the 'consent form' - which formed a component of the genetic diagnostic request form (see image nineteen) - was 'completed'. Hannah explained:

We need to know the clinicians have spoken to parents about what the test actually is (.) you know (.) so they understand that we might need blood from them (.) that we might get a result which isn't expected or that we can't explain

In this sense, the request form is an enactment of standards. The form becomes a source of institutional authority, as requests can only be legitimately made through the use of the form. It is also an example of the tension between the administrative and the clinical aims, operating as an administrative standard of sorts. Timmermans (2015) describes the notion of an integrated consent and request form as a pragmatic hybrid that combines multiple aims: identifying patients along various clinically relevant demographic dimensions, tracking a blood sample, facilitating payment defining the type of test required, offering a checklist of paperwork required for the test and providing a summary of clinical indications.

Yet the form in use by the neonatologists – indeed by all those in whom aCGH technology had been mainstreamed - was highly rudimentary with respect to the ‘checking’ of consent. The processes differed between the documentation used for consent in the non-specialist genetic setting, in which aCGH was being ‘mainstreamed’ and the specialist genetic setting, where aCGH was in established use.

Clinical Genetics Service for Wales
Park, Cardiff, CF14 4XW

Patient Consent

*I confirm that has explained
(professional's name)
the genetic test that I am about to have done
with respect to
(genetic condition)*

Signature: **Date:**

Health Professional: **Date:**

N.B. For presymptomatic molecular diagnosis - Clinical Genetics referral indicated.

Figure Eighteen: The combined request/consent form in use in ‘mainstreaming’ clinical areas, including the Newborn Intensive Care Unit

conversation through a series of steps – effectively constituting the minimal informational requirements agreed locally. In contrast, paediatricians consent tool merely required the highly subjective confirmation that the clinician had ‘explained the genetic test’.

The stand-alone consent form employs a number of methods in an attempt to ensure the rigour of consent, particularly the use of listing as a means of ordering the work to be performed – an attempt to achieve a consistency of approach. Control for – and indeed responsibility for - the standards of consent are clearly laid out, essentially as a minimal informational requirement. In this sense, the use of listing confirms Latour’s (1987) notion of listing as a means of exerting bureaucratic control, albeit from a distance.

A medical geneticist described the development of the stand-alone consent form:

in fact many aspects of this form [stand alone consent form] were as a result of the problems we had encountered with our own consenting processes (.) what we say (.) how much detail (.) it seemed that what people were saying did vary enormously and so there was a movement towards making it less contingent on who took the consent and on why the test was being done (.) it [informational requirements and consenting process] should be uniform across areas and people (.) it’s the same test so the same rules for consent should apply (1) it doesn’t make any sense at all why we don’t expect (.) or indeed allow (.) our colleagues in other areas to use this [gestures to combined request/consent form] form (.)

David, Medical Geneticist.

For David, it is logical that the artefacts around the technology – particularly those artefacts that develop as a solution to problems previously encountered – should ‘mainstream’ along with the technology, transitioning from the expert to the non-expert setting. However, Emily counters this perspective:

I think we just felt at the time like it would be too much (.) another consideration (.) another different form to complete in addition to all the other demands the introduction [of array CGH] was making (.) probably now we should roll it out as lots of the feedback from users is about the potential consequences of testing laid out on this form (.) you know the uncertain results (.) who the results can be shared with (.) I think that people [non expert clinicians] want something in a more prescriptive format to use with patients so they can be sure they are saying the right thing

Emily, Clinical Scientist

Here, early mainstreaming of the associated artefact is framed as ‘too much’ and another change for clinicians grappling with a new technology. Yet retrospectively, the role of a ‘prescriptive format’ is recognised and valued as a means by which to counter contingency in the consenting process as professionals get to grips with a new type of test. The request form, in travelling between the sites in which array CGH is performed, provides more than a representation of the network – it is an

important facet in the constitution of the network of people, specimens, technologies and experts (Berg and Bowker, 1997). It must not be assumed that the artefacts associated with (and indeed the lessons learned through use of) a particular technology will seamlessly transfer with its availability.

'Quality' of phenotypic information and the decision to test

Another means through which the genetic work of the clinic is problematised is through the notion that the phenotypic information provided is incomplete or poor in quality. Based on the assessment of the phenotypic information as poor quality or inadequate, questions can arise about whether testing is in fact justified. Susan explains:

...the quality of the referrals and the testing requests themselves are still very poor.

...

It varies [standard of phenotypic information provided by clinicians] and it varies hugely. I would say extremely poor. But we are planning a new referral form to prise out the information more carefully and precisely. It does help in making that phenotype-genotype correlation. The sad thing is, I wish we didn't have to do it this way – introducing more exhaustive paperwork, making people tick boxes rather than do free text. It means we get a more accurate in-depth description of any signs and symptoms. Even maybe listing systems, you know... cardiovascular, development and leaning. It makes people realise that features in all these areas... all these features are potentially worthy of note.

Susan, Director of Cytogenetic Laboratory

Here, John describes how a movement away from free text towards listing phenotypes to be selected is seen as a means to '*prise out*' information '*more carefully and precisely*'. Latour (1987) described the work of the bureaucrat as compiling lists that can be shuffled and compared, providing the opportunity for control, albeit from a distance. In moving from free text to lists, the laboratory yields control of the sorts of phenotypic features it expects to be described, in addition to the level of detail expected. In some way, this states a standard of 'abnormality' to be reached and recognised in order to access testing. Moving from free text to lists of phenotypic features represents a transition in the 'genre of representation' of phenotypic features (Yates and Orlikowski, 1992). Such genres are defined as 'typified communicative action performed by members of an organizational community in response to a recurrent situation.... Identified by both their socially recognised communicative purpose, and by common characteristics of form' (Yates et al., 1997: 50). Listing (potentially) important features to be noted (by organ system) lays out the types of physical interrogation – the types of gaze – the laboratory expects clinicians to apply.

Key to this notion was that it is the responsibility of the clinician to provide this information, and that it is beyond the scope of the work of the laboratory to 'chase up' additional information, even when this might be helpful in the interpretation of variants.

Within the routine laboratory it is very, very rarely we've got time to go back. The report just gets issued based on the information we have available, and that's that.

Emily, Laboratory Scientist

Along with the quality of the phenotypic information, the provision of phenotypic information also facilitates laboratory staff in making judgments about when testing is necessary, or indeed justified.

Something I've been very aware of this year is within the neonatal group. There are two types [of problem] we've had this year... ones when they've had babies ... *very slightly* dysmorphic or a single isolated congenital anomaly which is not associated with a genetic cause... and again I think the potential implications of the test are not fully understood. It's potentially not an appropriate test in that situation.

Emily, Laboratory Scientist

Here, the clinical scientist considers how dysmorphic features are evaluated and assessed as meeting a threshold for testing. These judgments are made despite self-professed limits in the understanding of dysmorphology.

Just for my own interest, because I haven't seen a lot of babies... do some of them just look a bit funny? Rather than actually being dysmorphic?

Emily, Laboratory Scientist

In considering when testing is clinically justified, in addition to ensuring it is performed, the role of the laboratory also encompasses a moral one. As the technology becomes available to more medical professionals – and not just genetic specialists – the use of the technology and testing must be policed, ensuring adherence to recognised and established ethical codes and rules, for example the avoidance of testing children for carrier status or adult onset disease. This is similar to the 'rule' about completing the consent form on the request form. John explains:

..another one we've had is if the parents are the carrier of a known genetic disorder. There's been a request for an array and if you do ring up and query it... they'll often say the baby is well in his own right. There's nothing wrong necessarily with the baby, but they are just testing because they know there is a genetic condition in the family. Basically it's a request for carrier status or worse, a predictive test. These are things the geneticists wouldn't even consider doing, or things they would consider very, very carefully. Yes other clinicians just put in the request. So we have to be careful there a few times.

John, Clinical Scientist

Here John, in his role as a clinical scientist differentiates between ‘expert users’ i.e. geneticists and ‘non-expert users’ i.e. neonatologists in their appreciation of the moral, ethical and legal aspects of testing in children. For the laboratory, users of the microarray technology are not considered as one unified relevant social group. The laboratory is described as a line of defense against the unethical – or ill informed – practices of predictive or carrier testing as requested (albeit infrequently) inappropriately. Geneticists, as experts, can be trusted to make sound decisions – ‘very, very careful’ decisions – about when testing might be appropriate. Their expertise again means the standard or rule can be subverted given the individual considerations of a particular case. For non-experts, that trust – that a standard is known, recognised, and purposefully bypassed – cannot be taken for granted. The laboratory must police the actions of non-expert professionals who seek to carry out inappropriate testing.

Case example - The ‘messy’ clinic

Anna	We were really shocked (.) you know to identify a probable VHL as an incidental finding (.) well that’s pretty massive. Massive implications potentially for the patient and the family (.) so we are trying to validate report (.) requesting samples from the parents (.) then next thing you know we’ve got the consultant neonatologist on the phone extremely cross about the array having been done (.) furious (.) I think what it demonstrated to me is that they have <u>no clue</u> about how things work up here
Researcher	No clue in what sense
Anna	How the samples are processed, the fact once the DNA is extracted you can have numerous tests (.) she was cross as she had received the result she wanted and no more blood had been sent so she couldn’t understand why another test had been done (.) well the form said dysmorphic features and intestinal instruction query CF query other cause (.) well it wasn’t CF so we went on to test for other causes (.) one of their doctors okayed it over the phone (.) she didn’t have a clue about any of this (.) it was <u>a mess</u>

This extreme case scenario is presented by Anna to describe a case of an incidental finding in a neonatal patient of an aberration that was thought to potentially confer risk of Von Hippel-Lindau Syndrome³⁷. This was ‘shocking’ and ‘massive’ with real implications for the health and wellbeing of the proband and their relatives, as well as the potential reproductive decision making of the parents with a child in the newborn intensive care unit. Whilst the laboratory were requesting samples (from parents) to validate the finding, it emerged that the consultant responsible for this child’s care was not aware an aCGH had been carried out: having received the results for a (negative) cystic fibrosis screen, she had assumed that the genetic testing was complete. However, based on the clinical information provided, and as per the laboratory protocol, the sample had gone on for aCGH in light of the unexplained dysmorphology³⁸. The consultant was angry this was the case as this

³⁷ <https://ghr.nlm.nih.gov/condition/von-hippel-lindau-syndrome#definition>

³⁸ The aim was to exclude cystic fibrosis, a condition associated with delayed passage of meconium (a problem this infant had). CF is not associated with dysmorphic features.

unnecessary testing had generated a challenging result of potential enormous significance. In the next chapter the extreme case scenario is considered from the perspective of the clinical staff in NICU.

Anna contends that the clinic have 'no clue' about the processes and practices of the laboratory. The case emphasises the core ways in which the clinic is problematized. The consultant is angry (as described later) as the parents have (likely) not given consent for aCGH testing, and have not been adequately informed about the incidental, off-target and uncertain information it can generate. The laboratory staff are frustrated by the fact that the request form does not state the required test, rather lists a phenotype for which aCGH would be reasonable (dysmorphic features): a diagnostic Odyssey is underway, involving multiple genetic tests. Anna is frustrated as the clinicians have not appreciated that this is the standard practice in relation to this test, and indeed, when the laboratory called the clinical area to confirm aCGH would take place, they spoke to a doctor (who could later not be identified) who asserted this was a reasonable course of action.

Anna describes this 'mess' as arising from the practices and understanding of the clinic. The phenotypic information provided guided the testing, yet it is unclear which tests were discussed with the parents. The result is greater bureaucracy: the system is changed so that when the clinic is phoned to discuss a test, the name of the individual spoken to must be checked and recorded, then documented in record book to create an audit trail. This can be seen in two ways: as either a lack of trust in the standard, or as the need for standards which are replicable and verifiable (Timmermans, 2015: 80) and ultimately defensive in orientation.

Conclusion

This chapter explores two key and interrelated aspects of laboratory work. Firstly, the apparent central role of standards in guiding and shaping laboratory practice, and the ways in which standards must be pragmatically employed (and not employed at certain times) in order to do genetic work. Secondly, the way in which as a component of the bioclinical collective (Bourret, 2005), the laboratory problematises the social aspects of testing – the messy world of the clinic and the family. Standards, from the perspective of the laboratory, are distributed unevenly across the landscapes – the places and spaces - of aCGH: concentrated in the laboratory and then largely absent from the work of the clinic. The result is testing which is (from the point of view of the laboratory) problematic or difficult, in that it is either not clinically indicated, not adequately supported by phenotypic information or that is morally problematic (as in the case of requests for predictive testing). The laboratory takes on a role of gatekeeper, guarding the proper and prudent use of a limited, underappreciated and potentially ethical contentious resource.

Where standards are subverted, tinkered or circumvented (Lampland and Star, 2009) what justifications are used? Practices of reflexive standardisation combine interpretive flexibility and closure to allow the technology to work (Timmermans, 2015). Reflexive standardisation relies on expertise: the presentation of 'trust' and 'standard' as existing as opposite ends of the spectrum of scientific validity - diametrically opposed in terms of their equipoise and subjectivity – does not reflect the on-the-ground pragmatic interaction of the ability to apply standards reflexively, usefully and responsibly as a 'hybrid form of expertise' (Timmermans, 2015).

It is important to note that in the process of mainstreaming, the work of the laboratory has not inherently changed. Rather it is the nature of their interactions with non-expert practitioners that has increased in scope and frequency. From the perspective of the laboratory, 'users' of the technology are not defined as a unified relevant social group. Non- experts must be policed and guided in their use of the technology, with the laboratory being the gatekeeper to its prudent use. The laboratory must be insulated from the 'messy' clinic through processes of checking and verification.

The next chapter examines the work of the clinic, as it requests and responds to the information provided by the laboratory. What are the practical, ethical and social issues arising from the mainstreaming of the technology and how do situated responses emerge?

Chapter Seven: The Clinic

This second analytic chapter explores the nature of ‘genetic work’ in the neonatal intensive care unit³⁹. The data draws on both ethnographic observations and interviews with neonatal professionals – doctors (both consultants and junior doctors) and neonatal nurse practitioners – who carry out the ‘most commonplace activities of daily life’ in the clinic (Garfinkel, 1967:1). It contends that the communicative context of consent for genetic testing in the NICU is fundamentally different from those examined previously in the empirical literature. The frame of interactions, despite being described as consent-seeking, is highly directive and is often more akin to information sharing in its nature: assent to testing is elicited rather than consent being sought. Finally, I explore the role of metaphor in the discourses of information sharing, particularly the way in which clinicians use metaphor as a means of explaining complex concepts related to the normal and abnormal structure of genetic material, in addition to the process of testing.

The chapter commences with a brief summary of the issues around communication, decision-making and consent in the Newborn Intensive Care Unit, referring to both the literature and to the observed practices in the places and rituals of the setting. Next, I describe the dividing practices (Foucault, 1983) used to constitute babies as genetically problematic, and the role of uncertainty and expertise in this process. The next two sections use transcripts of naturalistic conversations to examine (i) the genetics education undertaken prior to, and in the support of the introduction of aCGH in the newborn intensive care, and (ii) pre-test counselling – or ‘consent conversations’ as they were referred to by paediatricians – to explore the practices of non-experts undertaking this ethical work.

Notes on decision making in the NICU

Much of the literature around shared-decision making in the neonatal intensive care environment is based around the process of redirecting care from curative to palliative aims and the process through which clinicians gain the consent of parents for this difficult decision. This research has employed ethnographic data (Anspach, 1993; Orfali et al., 2014), recordings of conversations between parents and clinicians (Boss et al., 2016; de Vos et al., 2015; Shaw et al., 2016) and hypothetical scenarios (Coekelbergh and Mesman, 2007). Though naturalistic conversational data

³⁹ Neonatal Intensive Care Unit is frequently abbreviated to NICU, or NIC. NICU is also known as the Special Care Baby Unit, or SCBU.

has featured in these studies (Boss et al., 2016; de Voss et al., 2015; Shaw et al., 2016) such an approach risks viewing conversational discourse as self-representational, without the contextual Discourse framing the shape of the interaction itself. What foregrounds the decision to take a particular clinical decision? What shapes the sort of information presented to patients when a decision is being made? End-of-life decision-making provides a rich source of data for considering the complex interplay between information-giving, decision-making and consent as the consequences of the decision are so profound. Yet other decisions, such as the decision to perform a genetic test, encompass these stages too: decision-making about the proposed benefit of a genetic test by the clinicians, the presentation of information to parents and the decision-making process between parents and clinicians culminating in either parents providing consent to testing, or not. Only by embedding discourse analysis of consent conversations within broader ethnographic data can these processes be revealed. One perspective absent from these accounts is the role of communication and deliberation between professionals, and the multidisciplinary discourses that precede conversations with parents.

Consent

Emerging from the Bristol Inquiry, The Kennedy Report stated that 'processes of consent should apply to all clinical procedures and examinations which include any kind of touching' (Kennedy, 2001:440), or in the case of neonatal patients, proxy consent from parents. For neonatal patients, such rigorous demands face significant challenges: the physical presence of parents when infants are transferred between hospitals for specialist care, complications arising when mothers are in the postnatal period (such as tiredness, pain, illness and anxiety), the pressure of time and concerns about overwhelming parents with information about decisions (even if they seem 'straightforward' to the clinicians) which may cause worry or concern. Yet calls for drastic changes to the culture around consent in the NICU resulted from the findings that in 95% of routine procedures consent was not sought, with 77% of units having no formal guidelines about consent and 73% of units providing no training for junior doctors around informed consent practice (Shenoy, 2003). Whilst a tick-box culture and seeking consent to a great many procedures may not promote genuine consent (Corrigan, 2003), there is a need for a practically applicable and ethically robust approach to how consent is conducted in this setting.

Another suggestion for this is the use of a 'hierarchy' of consent levels, based around the nature of the intervention (Manning, 2005). This means that for emergency procedures, a doctrine of necessity is employed and consent need not necessarily be sought. For 'routine tests and procedures', a 'blanket consent' conducted on admission is suggested, also acknowledging that for some tests a more explicit disclosure and consent might be demanded. In this example, Manning

uses the example of chromosome analysis in an infant suspected to have Down's Syndrome, stating "*if parents were presented with an abnormal result for their infant without prior warning, this could cause great distress and undermine trust in the clinician*", acknowledging the special status of genetic testing. Manning also describes the category of consent associated with "interventions with debatable risk-benefit ratio", stating that formal consent is then appropriate. Here, he draws on the use of steroids for chronic lung disease associated with prematurity, describing how whilst decreasing the length of ventilator dependence, steroids do not reduce mortality and are associated with poor neurodevelopmental outcomes. Microarray could also be considered in this category: balancing the opportunity to make a diagnosis with the potential implications of off-target information, variants of uncertain significance and the health and reproductive decision-making of the proband and family, or indeed merely delaying testing until more phenotypic information is available.

It is practical to consider how the processes that govern how communication, information-sharing and consent take place as an amalgam of the associated or previous practices, meaning that clinical work encompasses both old and new styles of reasoning or work. This can be used to explain some of the inconsistencies that persist in how consent is performed: for example, the same procedure – the insertion of a central venous line - has two grossly differing consent processes associated with it depending on whom it is performed by and where it is performed. When performed by surgeons, in the operating theatre, explicit consent is sought: a formal conversation takes place, facilitating information transfer to parents before they are asked to sign a consent form. For neonatologists doing the same task, no consent form – nor indeed explicit consent conversation – is sought. Applying Manning's maxims (2005), this task falls under blanket consent for one group of clinicians (neonatologists), and in a category necessitating explicit consent for another (surgeons). The reasoning behind this is potentially institutional: surgeons seek written consent for all operations, and as such, extend their same rituals and practices to procedures with a lower associated risk. Neonatologists work within a setting where blanket consent is commonplace and readily extend this to encompass the insertion of central venous access. Whether this is ethically problematic is beyond the scope of this analysis, however it is important to explicate the inconsistency with which the practices and principles of shared decision-making, and indeed informed consent, are applied. As such, the practices of neonatologists in using microarray technologies can be viewed as encompassing aspects of the practice of geneticists – as experts – alongside those hierarchies and traditions of neonatal medicine.

Consent forms – and structured consent conversations with parents based around the completion of forms – occurred for a number of procedures within the NICU: microarray testing, surgical procedures, the use of anaesthesia, vaccination and the use of a pacifier or dummy⁴⁰. Consent is

an actionable task for clinicians. The need to complete a consent form necessitates the clinician and parent sitting together in formal interaction, which (usefully for my research) makes these conversations easy to observe and record. Though 'blanket consent' is often invoked, brief exchanges between parents and clinical staff at the cot-side may also occur. When a parent is visiting and an investigation is proposed, a consent conversation may take place, that may not have happened had the parent not been present. This allows the giving of information and the seeking of (verbal) consent. As such, participation in decision-making in the NICU is a spectrum, ranging from assumed consent, through mere awareness that a decision is being made, through collaborative decision-making between parents and clinicians to parents assuming independence and taking responsibility for the decisions being made (Einarsdottir, 2009; Caeymaex et al., 2011; Rosenthal and Nolan, 2013). Parents report differing perceptions around who 'made' a decision, based on the stage in which their participation about a particular decision commences, for example, presenting a decision to a parent which has already been made, or discussed, by the clinical team (McHaffie et al, 2001).

Evidence suggests that despite guidance advocating shared-decision making in the neonatal setting, many parents report experiencing poor involvement in these processes (POPPY Steering Group, 2009): whilst parents retrospectively report a desire to be active participants in decision making (Gillam and Sullivan, 2011), what constitutes involvement and how it can be achieved remains poorly defined.

Setting the scene: inside the Neonatal Intensive Care Unit

The bureaucratic context in which the care of neonatal patients takes place, both in terms of the places and the people involved shapes much of the medical work, and in particular the genetic work of this clinical space. Neonatal intensive care provides a rich location in which to examine the complex and evolving division of labour – spatially, temporally and in terms of expertise - in contemporary medicine. Next, I describe how the unit is organised providing thick description of the context in which this genetic work is performed.

Places and spaces of Neonatal Care

Lakeside Hospital is a large, tertiary referral hospital, based in the suburbs of a large urban centre. Staff from the maternity service – midwives and obstetric doctors – support around 6000 births per year in three settings: infants born at home, in the midwifery-led unit and in the consultant-led

⁴⁰ This may seem curious but is also shaped by institutional practices. The Baby Friendly Initiative of the World Health Organisation is designed to encourage women to breastfeed, and the use of a pacifier/dummy, is seen as a barrier to establishing breastfeeding. As such, use in the hospital is limited and the introduction of a need for written consent serves as a prompt to consider whether this will limit an infants ability to establishing breastfeeding, and maternal milk supply.

delivery suite. The 'midwife-led unit', situated on the ground floor of the hospital, provides care for women during and after childbirth who are considered 'low risk', meaning there are no features of the maternal health or the pregnancy that would indicate the need for additional medical support or intervention during childbirth or during the postnatal period. The 'consultant-led unit' or 'delivery suite' is a unit equipped with obstetric theatre spaces alongside rooms for deliveries. The majority of the births in the hospital occur here. Women may be transferred to this unit from home, or from the midwife-led unit, when the birth is not progressing as expected or may receive care here when there have been (or continue to be) health issues which complicate or require additional monitoring and care during birth. Following delivery, woman and infants are transferred to the postnatal wards for continuing care. Here, all infants will have a 'baby check' or 'NIPE' (newborn infant physical examination) prior to going home: a multi-system physical screening examination, conducted by a junior doctor, neonatal nurse practitioner or specially trained midwife to look for evidence of abnormality or disease. The time for which mother and baby remain on the postnatal ward depends on physical and social factors, related to the wellbeing of mother and baby⁴¹.

Infants requiring additional medical care, both anticipated and unanticipated, will be looked after by doctors and nurses based in the adjacent Lakeside Neonatal Intensive Care Unit (NICU). When it is known that additional care will be needed following delivery, midwives and obstetric doctors contact staff from the Neonatal Intensive Care Unit to attend the delivery of the baby and provide immediate care. Who responds to this request is dependent upon the anticipated care required: for complex cases, such as extreme preterm birth, and some congenital anomalies requiring significant intervention and support immediately following birth, a team consisting of a neonatal consultant doctor, a registrar, senior house officer or nurse practitioner along with nursing staff will attend. For less complex cases, a smaller team, or even an individual (usually a senior house officer or registrar) will attend, calling for more support if needed. Support from the NICU team can also be requested urgently by obstetric staff attending births for example when a baby is born and (unexpectedly) requires additional care, or when complications arising during the birth indicate that the baby may need resuscitation following delivery.

Infants requiring continuing support or surveillance following birth are 'transferred' to the neonatal intensive care unit for further care. These 'transfers' can occur in one of two ways. Infants born at Lakeside Hospital are taken, by transport incubator, from the midwife-led, consultant-led or postnatal wards to the neonatal intensive care unit. Infants requiring high level or sub-specialty care

⁴¹ Factors which prolong the postnatal stay include the need for antibiotics for the mother or baby when infection is suspected, support with feeding, the need for medical investigations or surveillance in the infant – infants with suspected genetic problems, such as Trisomy 21, may remain here while investigations are conducted.

can be 'transferred' from other neonatal intensive care units in other hospitals by specialist ambulance. This may happen when an infant required assessment or treatment from a paediatric subspecialist, for example a cardiologist or a neurologist, in cases of extreme prematurity⁴² or when an infant requires surgical care⁴³ for a congenital anomaly or a complication arising after birth.

Within the unit, care is provided in one of three dedicated rooms within the unit. 'Intensive Care' provides high-level specialist care for infants requiring 'organ support', usually ventilation. In this room are the most unwell infants, cared for by a registrar doctor, two senior house officers and a team of specialist nurses. Nursing staff care for infants in this space on a one-to-one basis. Each incubator is surrounded by the equipment required to provide care: ventilators, infusion pumps, monitoring equipment to record the heart rate, oxygen saturations, respiratory rate and blood pressure of the baby, in addition to a chair to allow parents to sit near their baby, and a table on which written records are made by staff and stored. Although curtains can be drawn around each incubator space, they are rarely used meaning privacy is limited. The room is noisy, with the noises associated with monitors and equipment resulting in consistent background noise, in addition to conversations between staff and staff and parents.

The 'high dependency' space is adjacent to the 'intensive care' – accessed through a door – and here staff care for infants who require some sort of additional care, usually an intravenous infusion of fluids or medications, or oxygen delivered via a non-invasive method. Infants can be admitted directly to this room, or can be 'stepped down' from the intensive care room as the need for medical care allows. Here, infants are cared for in a mixture of incubators and cots, and parents tend to be more involved in care activities, such as feeding, dressing and washing. Nurses in this space may care for two or three babies at any time. Finally 'low dependency' or 'nursery' provides care for infants who are preparing to be discharged home, with parents taking a significant role in their care. Infants here are often referred to as 'feeding and growing', and may in fact require little medical care.

Adjacent to the clinical areas are a series of rooms: a breastfeeding room, where parents are able to express and store breast milk, a doctors' office, with computers and desk space for administrative work, a series of nursing and administrative offices, along with a staff room for taking breaks and preparing food and drinks. Beyond these rooms is 'the quiet room', used for private discussions with

⁴² Neonatal Intensive Care Units are stratified, based on the 'level' of care they are able to provide for infants. Lakeside is a level 3 surgical unit, meaning it provides the highest level of intensive care available along with surgery for infants. For explanation, see <http://www.bliss.org.uk/different-levels-of-care>

⁴³ Surgical care for neonatal units is provided in a small number of specialist centres: seven units refer their neonatal patients requiring surgery to Lakeside Neonatal Intensive Care Unit.

parents and families and for the provision of bereavement care when a baby has died. This room provides the only space on the unit for confidential conversations, and is decorated simply, with a sofa and chairs. Families are often brought here for 'sensitive' conversations, for example redirection of care conversations, or when discussing test results, though many – indeed most – of these conversations take place at the cot side.

The 'rituals' of the unit

Admissions to the unit can happen at any time, and the ward provides care 24 hours a day, 7 days a week. The days follow a repeating pattern. The main, formal ward round of the day occurs at 9am, and is attended by the 'consultant of the week', registrar doctors, senior house officers, nurse-in-charge and pharmacist. During this ward round, the team move around the intensive care unit, with the registrar or senior house officer who has been 'on shift' overnight 'presenting' each patient. This involves providing a summary of their antenatal, birth and medical history, along with important features of their current care, such as level of support, medications, feeding, the results of investigations and any awaited procedures. Following this, a plan is formulated for that day and any tasks to be completed are recorded and delegated. Patients' medical problems and their care can form the basis of an educational discussion, with (usually junior) medical staff being questioned by consultants on a variety of topics – pathology, pharmacology, and the latest evidence related to newborn care. The round lasts around one hour. Further, abridged ward rounds occur at 4.30pm and 9pm, the first being when the evening 'on-call' staff take over care (and the consultant normally leaves the hospital), the second being at the commencement of the night shift, when the registrars and senior house officers summarize details related mainly to the care provided that day.

Handover happens around the cot or incubator, moving in a highly ritualistic manner from space to space. Artefacts such as the patient medical record, the observation chart and the results of investigations may be called upon and examined. Plans are made for the investigations and treatments to be conducted that day, with the round serving as a time for planning and decision-making regarding infant care. There is also a significant educational component, with consultants calling upon registrars, senior house officers and nurse practitioners to justify why decisions have been made, providing accounts of the rationales – physiological, biochemical and pharmacological – underlying decisions about treatment and investigation. Following the ward round, doctors and nursing staff complete the planned tasks (such as blood tests, ultrasounds, physical examinations), general care (such as feeding, changing and administering medications) and administrative tasks, for example referral to other medical professionals.

Parents are allowed – and indeed encouraged – to visit and spend time at the unit as often as possible. Some mothers will remain inpatients while their infants are being cared for, some will be housed in parent accommodation (available in the hospital) other parents will be at home and visit as and when they can. The only restriction on visiting is around nursing handover, at 7am and 7pm for 30 minutes – parents are asked to wait outside during this time. This is to allow nurses to discuss confidential information freely while handing over to the next member of staff responsible for the care of the infant. Although there is an additional restriction around doctors handover time, at 9am (morning handover), 4.30pm (evening handover) and 9pm (night time handover), this is rarely enforced; with the doctors (attempting, at least) to perform their handovers at the side of each cot at low volume, maintaining confidentiality when possible. Parents may listen to the handover and may be offered the opportunity to ask questions, or doctors may arrange to return later to provide an update on the care of their baby. Often these ‘formal’ updates may be arranged around significant events or transitions, for example as an infant moves from intensive care to high dependency, or in the event of a change in clinical condition, for example the commencement of antibiotics for a suspected infection. Less formal updates, related to the general wellness of the baby will be provided to parents by the nursing staff, who maintain contact with parents through visiting and by phone.

Each week, a series of scheduled meetings take place. On Wednesdays, there is the weekly ‘grand round’ meeting, held away from the clinical area in a meeting room. Here, each baby is discussed, particularly those having long admissions to the unit, to plan their on-going care. This forum is especially useful as, although patients are admitted under the care of a particular consultant, it is the consultant of the week who will be involved in the main decision making regarding treatment and care at a particular time. This meeting provides an opportunity for collegial decision-making, and discussion of more challenging treatment choices. The meeting has purposes for both service provision and education, as each meeting has a period assigned to an educational activity, usually a presentation on a given topic, or an invited external speaker.

It is within these practices and procedures, wards rounds and meetings, that much of the genetic work of the clinic is performed. In the next section I explore the form this work takes.

Dividing and Classifying: ‘the genetic baby’

Classification is inherent in the designation of infants in the care of the neonatal intensive care unit: it is designated in the physical spaces they occupy, with babies described as ‘ITU’, ‘HDU’ or ‘special care’ depending on the level of support they require. It is also designated in the way medical and nursing staff refer to infants who are receiving, or will receive, care: ‘the 24 weeker’, ‘the diaphragm’, ‘the sugar baby’ and ‘*the genetic baby*’.

Kate Delivery suite just called. The lady in room six is pushing. I told them to call the SHO (senior house officer)

Peter Which one is that?

Kate The genetic baby [pauses, refers to paperwork] multiple limb abnormalities, horseshoe kidney. Known to fetal med. Heart okay, lungs okay, head okay.

Peter I'll go up. That one will need to come in

Kate Yes it says plan admit. I'll get Jess to set up HDU 2

Kate, Nurse in Charge and Peter, Neonatal Registrar
 Fieldnote, Neonatal Intensive Care Unit, Lakeside Hospital

This exchange, between Peter (the registrar) and Kate (the nurse-in-charge) demonstrates how infants come to be designated as problematic – specifically in this case, as genetically problematic – through a series of institutional practices. This ‘genetic baby’ has had concerning features identified on antenatal ultrasound scanning and, as such, has received additional antenatal surveillance via the foetal medicine service. Here, obstetricians and specialist midwives provide antenatal care to pregnant women in whom a complication with the foetus is anticipated, likely to occur, or has already been identified. In this clinic, a weekly meeting is conducted jointly with the neonatal intensive care unit, in which the ongoing antenatal investigations are discussed – such as detailed scanning methods like fetal echocardiography, foetal cerebral magnetic resonance imaging scanning, genetic investigations, such as amniocentesis, chorionic villous sampling (CVS) and non-invasive pre-natal testing (NIPT). Following this, a plan for ‘appropriate’ perinatal care is made, such as the location and method for delivery and availability of specialist neonatal care services.

Receiving care, or being deemed as requiring assessment in the foetal medicine unit constitutes an organisational, or bureaucratic, act of classification. The process of being ‘known to foetal med’ renders the pregnancy and antenatal care atypical: (automatically) alerting those who will be responsible for the care of the mother (and subsequently, the infant) to the ‘problematic’ circumstances. The nurse-in-charge alludes to the organ systems known to be abnormal as constituting a further classificatory act guiding a bureaucratic decision – there are ‘multiple limb anomalies ... horseshoe kidney’ but the heart, head and lungs are ‘okay’. As such, the baby can be cared for in the high dependency space, as the need for organ support (provided in intensive care) is not anticipated.

Yet this classification is speculative: the infant may have features suggestive of a genetic aetiology, yet no genetic investigations have been conducted. Following birth, genetic investigations may be indicated, as may the review of the infant by a medical geneticist. The commonality on which an infant is designated as ‘genetic’ is the presence of multiple congenital anomalies: phenotypically ‘lumping’ (McKusick, 1969) this heterogeneous group of infants with congenital anomalies together

in one category even prior to their birth. Many 'genetic babies' – largely those with congenital anomalies – come under the care of the neonatal team.

Other categories of genetically problematic infants included 'dysmorphic babies' and babies with suspected recognised syndromes – 'the suspected Down's' or 'the suspected di George'. The clinicians responsible for their care designated these groups of babies differently. Following the delivery and admission of '*the genetic baby*', we discussed the use of the term.

Researcher It's interesting that we are calling this baby 'the genetic baby'. There are so many babies here [in the neonatal unit] with genetic problems at the moment.
Peter I know. I suppose he's only 'the genetic baby' until we know what the problem is. We know that one is a Down's now. That one has the other syndrome... I've never heard of. The dysmorphic one... it's all soft features. It could be nothing I think. I'm not sure I'd have done the array so soon. He might not have even come here if it wasn't for the sugars [hypoglycaemia]. I suppose that's the genetic baby because his problems are multiple and complex. They must have a genetic cause.

Peter, Neonatal Registrar and Researcher
Interview

The 'lumping' of potential genetic patients together is a pragmatic classificatory task. In this designation or identity work, the objects and subjects of the interactions are made clearer: there will be the need for a full physical examination of infants and the documentation of any abnormalities of form. There will be the potential or anticipated need for genetic testing.

The results of further phenotypic and genotypic characterisation is be the 'splitting' occurs – designating *more specifically* the nature of the 'genetic' problem. This might be dysmorphism, the presence of congenital anomalies, a syndrome with clear phenotypic features. The splitting, whilst often associated with the nature of the phenotype, can also occur as a feature of expertise, as neonatologists decide when to request a microarray themselves, as opposed to seeking the expertise of medical geneticists through a clinical review prior to testing. This is deemed as deserving the expert input of a geneticist, as opposed to the generic skills of a neonatologist.

Michael I think this is one to have genetics see off the bat. They might have even heard about this one antenatally. Don't do the array, let's get them down to see her and speak to Mum. They can have a chat with her about the array and what needs to happen next. It's multisystem, very complex.... I'm sure the array will pick something up. Make sure she's had the echo and renal scan before they come so they have the full picture.

Michael, Neonatal Consultant
Fieldnote

In this case, rather than being assessed by specialist neonatal staff, the doctors responsible for the patient make a formal referral to the genetics service for assessment of the patient and family, usually prior to initiating microarray testing. This process involves contacting the genetics registrar on call, and asking them to attend in order to examine the infant, take a history from the family, and arrange the appropriate investigation to aid in making a diagnosis. Referral to the clinical genetics service for testing – rather than the initiation of testing by neonatal staff – served as an indication that the assessment, likely aetiology and diagnosis of the patient and family was deemed more complex by the neonatal staff.

This can be seen as an act of disposal. A high-risk heuristic is applied by the neonatal consultant: the case is '*multisystem*' and '*complex*', with abnormalities of the airway, gastrointestinal tract and limbs: the consequence being that a problem or sequence of problems is deemed as having a likely genetic cause. As such, the clinician is '*sure the array will pick something up*'. Through the neonatologists brief, initial assessment, the likelihood of an array abnormality is deemed high, and the work is immediately referred – or 'disposed' of - to the specialist genetics team. This process involves the clinician applying a *risk heuristic* with respect to the likelihood of the pattern of anomalies being of genetic cause: the referral is made early, allowing the genetics team to be involved early in the care of the infant. This is framed as both of organisational and patient benefit.

Michael Its best they see them sooner rather than later [*the geneticist*]. That way they can explain the test and follow up with the result, assuming it's abnormal. Speak to them about reproductive risk and so on. It's their first baby. Better than us getting the result and then referring for their [*the family's*] continuity too.

Michael, Neonatal Consultant
Fieldnote

Anticipating infants for early assessment by genetics acts also by anticipating the need for the input of a genetics specialist at a later stage, when the (expected) abnormal result is received. Implicit also is the notion that '*they*' – geneticists – can '*explain the test*' in a way that is different from how this task might, or indeed would, be performed by a neonatologist or other non-specialist. Genetic infants can fall within, or outside, the realm of expertise of non-specialist practices. Clinicians as a group expressed ambivalence about these potential differences in how microarray technology is described with parents when undertaken by either a geneticist or a non-specialist.

Ben It's difficult to know how what they [the geneticists] say could be different. I mean (.) I just say what they told us to say when they did the teaching prior to the roll out of the array CGH. I say it's genome wide, it looks for deletions and duplications, and it might pick up things we don't expect or can't explain. I'm not really sure what else you could say.

Ben, Neonatal Registrar

Interview

Lizzy When you have a strong suspicion that it's going to be abnormal [1] I think it is best that the geneticists handle the family from the start. It provides continuity. It means you're not springing a new person on the family at a time of stress, when an abnormal result has come back. The geneticists have that experience (.) in talking about the test (.) the potential implications (.) in a clearer way that comes with the experience of handling abnormal results.

Lizzy, Neonatal Consultant
Interview

Here, we see neonatal staff acknowledge that despite the responsibility and privilege for the use of the technology transferring to non-specialists, the experience and practices around the technology are not so readily or easily embedded. Yet the accounts diverge: for one doctor, the registrar, it is 'difficult to know how what they say [the geneticists] might be different'. In one sense this conveys some ignorance around the nuances of pre-test counselling – questioning whether a specialist would be any better than a non-specialist in their methods and in their ability to prepare a family for a genetic test. On the certainty trough (MacKenzie, 1990), Ben lies within the area of low uncertainty. He is committed to a technological program, but as a user rather than a producer of knowledge. For the second doctor, a consultant, there is a clear advantage to involving specialist expertise to 'handle' the family, with experience meaning they can prepare patients in a more meaningful way, providing both expertise and continuity of care. Expertise, in the sense of the *confidence and ability* to talk to families about microarray in a meaningful and comprehensive manner, is seen as both knowledge that can be quickly acquired and employed, and an embodied practice or 'experience'. Whilst geneticists have contributory expertise, neonatologists depend on primary source knowledge or interactional expertise to do genetic work with parents.

Alternatively, a low risk heuristic is applied, in which case performing an aCGH is seen as unproblematic and straightforward, meaning it falls comfortably within the remit of a non-expert i.e. the paediatrician:

Michael I don't know (.) I get the feeling this is just an isolated diaphragm (.) he does have an unusual nose and chin (.) but Mum did too (.) did you see/
Peter Shall we just do the array anyway as a screen (.) rule anything else out
Michael I think that's reasonable (.) we're not anticipating anything abnormal so let's just get on and do it [leaves the bedspace]

Michael, Neonatal Consultant and Peter, Neonatal Registrar
Fieldnote

Registrar is he [dysmorphic?]
Consultant his ears are low set and he has a very broad nasal bridge
Registrar is there anything else?

Consultant he has that inguinal hernia doesn't he (.) yeah just do it (.) we do them for less I think (.) let's just rule out any weird and wonderfuls

Lizzy, Neonatal Consultant and Ben, Neonatal Registrar
Fieldnote

'Screening' here refers to the use of the array technology as part of an evaluation or investigation - as part of a methodical survey - to exclude genetic disease. This is not screening in its traditional, population-orientated sense⁴⁴: rather it is the application of a low risk heuristic, a (perhaps inappropriate) attempt to confirm the absence of a genetic causation – the 'weird and wonderfuls' – for a series of features which may be explained otherwise. Here it was important to explore whether this decision about testing arises as part of a process that supports or displaces clinical expertise:

Researcher would you have done a karyotype if the aCGH wasn't available?
Lizzy =probably not (.) I don't have a strong sense of this being something but it would be nice to the family to rule it out (.) there was also the maternal medication too so it would be nice to be able to say there's nothing else (.) genetic (.) going on here

Lizzy, Neonatal Consultant and Researcher
Interview

The clinician maintains the low risk heuristic: he does 'not have a strong sense of this being something' genetic, and the problem is downgraded. This sense is tacit, and the process of undertaking genetic testing is as a process of exclusion and to designate a complex condition as 'not genetic'. This mother was also taking medication in pregnancy, and there is a suggestion that potentially, a genetic diagnosis would serve to either potentially designate or exonerate blame. Of course, this is incoherent in that microarray cannot designate the cause of the deformation as genetic or non-genetic, merely as not associated with a dosage change at the particular level of resolution of a given microarray.

In order to explore this ambivalence, the next section will talk in more detail about the education of clinicians with respect to microarray testing occurring prior to and following the roll out of microarray as a first-line genetic test.

Educating the clinic

See one, do one, teach one

⁴⁴ For a full discussion of 'Genetic Screening', see Katherine Burke and Angus Clark (2016) Genetic Screening, Encyclopedia of Global Bioethics, Springer, 2015. Editor Ten Have, H.

Following a decision by the clinical team to perform a microarray for an infant, a clinician – usually a registrar, nurse practitioner or senior house officer – is called upon to ‘take consent’ or ‘do the consent’ from, or with the family. This explication of the consent process renders the process distinct from other diagnostic tests performed in this environment (such as imaging, biochemical or haematological investigations) as consent is constructed as a key step in the process of ‘performing’ the investigation: without explicit, documented and written parental consent, a sample could not⁴⁵, or should not, be sent for analysis.

Despite this recognised need for parental consent, samples were frequently taken and stored, with the sending off of the sample ‘pending’ the consent of the parents. The reasons for this were frequently practical: infants who had been transferred to Lakeside NICU from other units, whose parents had been unable to visit yet, or where the (potential) need for blood transfusion was identified, a process which (clinicians assumed) could possibly render the interpretation of a microarray more challenging⁴⁶. In these cases, blood samples for microarray would be taken from the infant – usually alongside venous blood sampling – labeled, the request form completed, and stored in the fridge. Later, when parents are able to attend, the ‘consent conversation’ takes place, and the sample is sent for microarray in the genetics laboratory.

Raj	Okay fine, so we’ll do the microarray. Can you speak to the parents today? [to registrar]
Zoe	Yes, that’s fine. Have you done a consent for microarray yet? [to senior house officer]
Claire	No. I saw [registrar] do one though
Zoe	Okay, we can go through it and you can do this one

Raj, Neonatal Consultant, Zoe, Neonatal Registrar and Claire, Neonatal SHO
Fieldnote

Demonstrating the ‘see one, do one, teach one’ traditional medical teaching adage (as discussed in chapter 5) the process of discussing and negotiating consent for microarray testing is framed as a skill to be learned in a linear fashion, rehearsed backstage by the SHO with the registrar (the backstage) then performed in real life – ‘do this one’ – with the parents. Though traditionally applied to craft tasks, having emerged from the education and training of junior surgeons, here, the SHO, having ‘seen’ a registrar do one, is prepared for ‘doing one’ front-stage, in the presence of parents

⁴⁵ The reality of this was that samples frequently were sent to the laboratory without explicit consent having been sought due to procedural failures i.e. the sample being taken before consent had been sought, the sample being sent rather than stored.

⁴⁶ The impact of red packed cell transfusion was potentially overstated by the clinicians on the unit. Though a theoretical risk or misinterpretation existed after blood transfusion, blood for transfusion is leukocyte-depleted, whilst extraction techniques preferentially yield white cell DNA.

and family. As per Goffman's (1959) description, this process affords for a run through of the performance, checking for offending expressions. Reflecting on these interactions provides the backstage, making sense of the interaction, performance and identities.

Implicit here is the notion that consent for microarray is anticipated as being performed in a dependable, repeatable format: that there is a 'right way' to do it. This supports the perspective of David (Medical Geneticist) in Chapter six: the consent form, in use by medical geneticists, supports the 'right' or correct way of doing (Mol, 2002) consent, removing contingency from the practice.

The next section examines how the bioclinical collective (Bourett, 2005) engage in 'bridging work' (Timmermans and Buchbinder, 2012) prior to and following the implementation of aCGH in the neonatal setting.

Reaching out: the laboratory educating the clinic

In contrast to the previous chapter, I here explore the education relating to the roll out of microarray from the perspective of the clinicians in the neonatal intensive care unit, focusing particularly on the content of two educational meetings.

Meeting One: preparing for aCGH

The first meeting was held the week before microarray replaced karyotyping as a first line investigation, and was delivered during the weekly 'grand round' meeting. Here, the head of clinical cytogenetics and a medical geneticist delivered a short presentation lasting fifteen minutes (based around the content of a series of PowerPoint slides) about the differences between microarray and karyotyping, and the special considerations for paediatricians as this test is introduced. In attendance were eighteen members of medical staff (eight consultants, four registrars and six senior house officers/advanced neonatal nurse practitioners). The meeting served as an example of pre-emptive 'bridging work': an activity designed to 'reconcile the promise of technologies with the reality of their implementation' (Timmermans and Buchbinder, 2012)

Consent

- Unexpected findings
- Unclear findings (VOUS)
- Repeat samples
- Phenotypic variability (parents found to be carriers ? Significance)

Figure Twenty: Powerpoint slide from teaching session summarising issues regarding consent

David In terms of consent (.) these are things we really should be telling people prior to testing. Let's avoid surprises [laughs]. So (.) unexpected findings these would be the incidental findings. So the results where we know the meaning but it isn't related to the reason we did the testing. These are things like cancer predisposition and so on. These sorts of results are less of a problem for array but will be a much bigger challenge when sequencing technologies come online (.) so it's important to let people know that we might get a result that has got real clinical implications but might be completely unexpected. The variants of uncertain significance are results which [1] where the implications are unclear. So these are the deletions and duplications which we identify but we can't yet say what they mean. These can be tricky and again we [medical geneticists] would be happy to see these families and (.) and have that conversation. That might mean saying this is very unlikely to be a problem or it might be a problem. Waiting for that information to (.) for the research to be done better linking the CNV to the phenotype (.) repeats (1) well if the sample quality is a problem or if a confirmatory test is needed then we may ask for another sample from baby (.) or for a sample from Mum and Dad if both are available [1] again we would probably ask you [*the paediatricians*] to do that. [Reading from slide] phenotypic variability (.) carrier status. Well (.) I'm not sure that's something we need to mention prior to testing. No not really in the first instance again that's more for the genetics side [moves to next slide]

David, Medical Geneticist
Audio Recording of Education Meeting, Lakeside Hospital

Following an explanation of the aCGH technology, the discussion quickly turned to the practical application of aCGH in the NICU. This brief discussion describes the role of 'consent' in the process, highlighting the 'things we really should be telling people' prior to testing. This is framed as a process aimed at reducing 'surprises': the laughter here is not meaningless, rather it demonstrates discomfort with the notion of uncertainty generated by unexpected outcomes or results. The use of the verb 'should' implies this has a moral component: 'surprises' or unanticipated outcomes are associated with potential distress, and as such, patient preparedness for these outcomes is key.

Interestingly, incidental findings are framed as ‘unexpected findings’ and these are clearly described as having known meaning, unrelated to the initial indication for testing. Multiple versions of the same entity are identified: for the laboratory it is ‘unexpected’ but understood, for the family it is seen as unexpected – a ‘surprise’ – and potentially distressing. The moral element – we ‘should’ tell parents and families about these types of results - aims to pre-empt the distress where these results are revealed. Those responsible for taking consent for aCGH are encouraged to ‘govern the territory together’ (Mol, 2002:171): enrolling families and parents in the challenges of testing.

Variants of uncertain significance are addressed as ‘results which ... where the implications are unclear ... we can’t yet say what they mean’. The language, as with the unexpected results, problematises these outcomes – they are a ‘challenge’ or ‘tricky’. Here, another practice of division is encouraged: problematic cases are disposed of from the paediatric setting to the specialist genetics setting, even in the potential absence of genetic disease. Indeed, there is a process of division explicated by the medical geneticist about what constitutes a reasonable expectation of both the specialist and non-specialist. Carrying out repeat blood samples, or requesting samples from parents, is deemed as falling within the remit of the non-specialist, whilst describing phenotypic variation is an expert task - ‘more for the genetics side’.

These dividing practices have two purposes. Firstly, it insulates paediatricians as non-experts from the messy, unwanted consequences (namely VOUS/IF) of genomic testing – and the process of navigating this uncertainty with families. Secondly, it ensures that geneticists, as experts, maintain jurisdiction over this complex area of practice. Uncertain, challenging and even diagnostic results become the domain of experts, through both the practices encouraged and enacted by laboratory and clinical services⁴⁷.

Meeting two: learning from experiences

This data was recorded during a lunchtime educational meeting, to which all neonatal staff are invited (consultant neonatologists, junior doctors in neonatology, nursing staff and allied health professionals working on the unit, such as physiotherapists). The meeting takes place at a regular time each week, in a meeting room adjacent to the neonatal intensive care unit. Typically, a member of staff leads the discussion, giving a presentation relevant to the care of an infant on the unit at that time. Staff bring along lunch to eat in an informal atmosphere, where questions and

⁴⁷ When a report from an aCGH is issued to an ordering (non-expert) clinician, enclosed with the report is a referral from for the genetics service: implicit in the process of making a genetic diagnosis is the assumption that this would require or necessitate the input of specialist genetics services.

discussions are encouraged. During this particular session, a consultant geneticist was coming to speak about interesting cases arising in patients cared for on the unit since the introduction of array CGH as a clinical test (about six months previously). The meeting was attended by twenty eight people: seven consultants in neonatal medicine, thirteen junior doctors training to be paediatricians, one registrar in genetic medicine, four nurses, a physiotherapist, a medical student and myself. Here I present a series of extracts from the meeting. The discussion begins with the consideration of consent:

David So °erm° pre-test counselling (.) this is something that I do (.) I think in the last meeting or the one before there was a feedback from paediatricians that will be useful to have a leaflet which you can give to a patient (.) <name> has sort of devised a leaflet and we've sort of tried to formalise it (.) but the advice is wait until Quality and Safety have read it so once that is done we can send that to you. There is information on it which can help you too as well as for the families (.) this is what I usually do (.)

David, Medical Geneticist
Audio Recording of Education Meeting, Lakeside Hospital

It is interesting to note how the use of a 'leaflet' is encouraged. The need for the leaflet to be validated as of sufficient standard at the "quality and safety" meeting demonstrates the institutional forces which shape information sharing and consenting processes. The leaflet is a bureaucratically mandates artefact to guide an information-sharing (and ultimately decision-making) process. The medical geneticist then continues to describe his own practice, engaging in deconstruction (Peyton, 1998) of his work:

David so I say that it [aCGH] scans all the chromosomes in high detail to check whether there's a small deletions or duplications (.) and I say that does not check for spelling mistakes within individual genes (.) I say that there are four possible answers which can come out of it (.) one if a definite answer which explains the child's medical features (.) secondly is no answer which is by far the majority (.) about 85% you don't get any answer (.) and then you have these uncertain findings where because it's such a high definition test if you do a test and a thousand people in the general population some people without any problem at all they have small changes on their array CGH which doesn't mean anything (.) so we might find changes reported before but at present we don't know (.) and then there's an unrelated finding so that is unrelated to the question that we're asking but it could have implications (.) so I say if you've got a finding that it's not related to the child's clinical features that may have implications for the child or the family in the future (.) sometimes I have left it there (.) till now and no-one has actually questioned me what it is (.) but if they do ask I'll say that it might could be something like a (.) in terms of a cancer gene that could be identified (.) but that's something that can be useful for them to be able to be aware of (.) then I say that we have parental testing if abnormalities are identified so we would offer testing to the parents to see whether it's inherited or it's happened for the first time in the child (.) first time in the child means it (.) well if it's in the parent and the child it's less likely to be a problem

David, Medical Geneticist

The approach reported here supports the notion of pre-test counselling as a call to ‘govern the terrain together’ (Mol, 2002): meaning the professional and the people giving consent must come to some understanding – together – of what the outcomes, results and consequences might be. This process of ‘outcome listing’ is akin to ‘option listing’ (Toerien et al, 2013): providing typologies of the type of results aCGH can yield. Laying out ‘four possible options’ or potential outcomes here performs three purposes. Firstly, it enrolls the family in the problematic elements of testing: the failure to make a diagnosis in addition to the generation of uncertainty in the form of variants of unknown/uncertain significance and incidental findings. Second, it attempts to create an interactional space in which parents can raise questions and concerns about particular types of results, and have these addressed. Outcome listing used in this way represents the use of the categories created primarily for laboratory processes as boundary objects for and within the clinic. Clinicians are encouraged to inform patients through the provision of a classification, or typology, containing or listing the types of information microarray can yield. Thirdly, it lays out the challenging uncertain results in a clear way, addressing the ethical work of adequately informing parents and families about the outcomes of testing.

Whilst this provides a thorough and systematic approach to pre-test counselling, it perhaps represents a level of candour that the medical geneticist is perhaps uncomfortable describing: with respect to incidental findings describing how ‘it could have implications... sometimes I leave it there’. This – ‘could’, ‘sometimes’ - is evidence of ‘hedging’ (Dubois, 1987), a modality deployed to convey imprecision and uncertainty. The medical geneticist seems comfortable with the notion that no-one would question what this may result in or entail, whilst retreating to the notion of clinical utility and actionability: that an incidental finding is one which it ‘can be useful for them to be able to be aware of’. Indeed, other clinicians expressed this even more clearly during interviews.

Raj At the consent stage (.) I’m still talking about (.) I put them in the same basket and say unexpected results (.) and I don’t differentiate between results of (.) whose clinical significance is incidental or results whose clinical significance is clearly related to the reason for the test (.) they are all results and I just leave it at that (.) you don’t want to put people off having a potentially useful test

Raj, Consultant Neonatologist
Interview

This lays out how despite encouragement from experts (clinical geneticists), some non-expert clinicians deem incidental findings to not form a significant component of pre-test counselling. Again, practices around counselling and testing are contingent: in this case, the decision (by the

clinical team) that an investigation would or may be useful must not be compromised by candour (about the risk of uncertain and incidental information) which might "put people off" testing.

The meeting then re-orientated to a discussion of 'problem cases', to explore issues arising in the practices of performing aCGH. The next section presents a long discussion (fragmented for analysis) around the first of these two problem cases: the first, a case of an infant identified as having a cancer predisposition syndrome on an aCGH.

David So erm unrelated findings I've got two (.) I wanted to highlight on unrelated findings, it just the importance of a pre-test counselling. This is something I don't think we will be able to avoid altogether (.) the unexpected findings (.) it is part of the test and it is part of any other test that you would do as well (.) to doing a full blood count to doing an MRI brain to a lot of other things (.) in genetics we see it more commonly but unlike other incidental findings they may have implications for the wider family so there's a lot more (.) sort of implications there when you're doing a genetic test [1] so I think that's something for us all to think about so, erm

David, Medical Geneticist
Audio Recording of Education Meeting, Lakeside Hospital

David's call to discuss incidental information as an inherent risk of testing counters and calls caution to the previous account by Raj where revealing the risk of incidental information in pre-test counselling could be seen as off-putting and unnecessarily candid. This is presented as a 'food-for-thought' prior to the discussion of the clinical case: framing uncertain and incidental information as an inevitable consequence of testing. In doing this he invokes a form of 'genetic (un)exceptionalism' in two key ways. Firstly, he draws a parallel between the unexpected information generated in genetic tests, and that produced by other medical testing technologies, (though he subsequently does emphasise the potential far-reaching implications for other family members). Secondly, he emphasises the need to consider this as 'something for us all to think about': in using 'all', he aligns expert and the non-expert in having the same responsibilities with respect to the use of this test. Rather than a practice of division between the 'expert' geneticist and 'non-expert' paediatrician he frames the values and practices as universal as they relate to the technology.

Next, the discussion turns to the case previously referenced in Chapter six, where an incidental finding of an variant in the VHL gene was identified in a neonatal patient:

David so this was a baby pre-term IUGR, this is the information that I have at present (.) so I think this baby was born in the peripheral hospital and transferred here because the baby was born there and transferred here with query NEC (.) abdominal distention and erm I think there was a possible family history of CF (.) I think maybe (.) but I don't know and an array CGH was requested

Lizzy =no, that's not right (.) CF panel testing was requested because of the meconium ileus (.) that was negative (.) and that was that I thought. Then I received an array result. I wanted to know why there was an array? Who did they array? Why did they do the array? I thought they [*the laboratory*] might have just done it after the CF

testing. I tried to get to the bottom of it. I think they [*the laboratory*] called the unit and asked if we wanted an array (.) with the IUGR. But it just got added on over the phone on the sample they already had. So when I got this result my concern immediately was what type of counselling had this Mum had? I didn't know was the answer.

David Yeah so basically what have they identified? They identified a very small deletion going to the limits of detection (.) deletion on the short arm of chromosomes so 3p very small deletion (.) basically what they said is that deletion in this region is very rare (.) no reports in DECIPHER (.) therefore the clinical information contained in the form is unlikely to be related to the phenotype (.) but please note that the gene VHL⁴⁸ which is a tumour suppressor gene maps with the region. So that was quite (.) I was thinking gosh!

Lizzy You can imagine when I got this result and I thought mmm [laughs] this baby is in a different hospital and I couldn't not find out who requested the CGH and what information the parents had been given (.) no information in the notes at all (.) I obviously had to pass this information on through another consultant in another hospital (.) and the mum said I didn't know this test was being done

David, Medical Geneticist and Lizzy, Neonatal Consultant
Audio Recording of Education Meeting, Lakeside Hospital

This case was presented earlier in the thesis, when it was cited as typical of the 'messy' entanglements of the clinic that threatened the order and standard to which aCGH could be performed by the laboratory. Here, the clinicians perform event work in discussing the case of an infant with meconium ileus (which is frequently associated with cystic fibrosis). As such, cystic fibrosis panel testing was undertaken to exclude this particular diagnosis. There is misalignment when the medical geneticist suggests that aCGH testing was requested: indeed, the constructed dialogue here seeks to counter the notion that an aCGH was a useful or desired test, using reported speech to authenticate a different version of the event. There is character work with respect to 'the laboratory', as no particular individual is identified. Though not explicitly accusatory, there is a moral element to the description of the conduct, which allows the neonatologists particular ethical perspective to dominate – 'why was there an array....why did they do they array.... It just got added on over the phone'. Repetition of 'why' forms a rhetorical device to persuade the audience about how unreasonable this course of action (the laboratory performing a seemingly unnecessary array) is deemed. The end point of this is to acknowledge concern about the nature of the pre-test counselling the parent may have received. Interestingly, the nature of the problematic result has not yet been revealed in this sequence: however, the event and character work that has taken place clearly frames this as a problematic case. Following a brief description of how the case was resolved, the frame of the conversation changes from describing the problem to discussion of potential solutions to avoid further problem cases:

⁴⁸ Von Hippel Lindau syndrome is a rare multisystem genetic disease associated with visceral cysts and benign tumours that can then undergo malignant transformation. For more information see <https://ghr.nlm.nih.gov/gene/VHL>

- Michael =you know that very nice thing you just showed us with the four things that you explain to parents when you're prenatally testing them? I wonder whether on the forms that we have we clip that in the back saying please ensure you've documented that you've discussed these four things and just stick it in the notes or something?
- Lizzy =yeah we're getting the leaflet.
- Raj =but in this case none of that would of helped (.)
-
- Michael That's just what was nice (.) you know those four points (.) as you say you know (.) you just say to parents (.) there are four possibilities. No answer, a full answer, unrelated, maybe a problem for future.
- David The counselling is really important for this (.) we will never know what happened or what was said to the family.
- Lizzy =but I think we know that the reality is that there isn't that much discussion at all when we do these tests
- Raj =no and that's what worries me and I think...
- Michael =it's the most junior doctors doing the tests as well (.) having been asked to do it by someone else ... the trainees change every six months.
- Lizzy Before the form comes it might be worth sending that slide with the four points. These guys [*geneticists*] have enough to do without constantly having to tell us what to do (.) bearing in mind the juniors come through so quickly (.) you can't catch every single one of them.
- Ben Should we not just have a guideline? Something we can refer to?
- Raj It's just the problem is then are you in the middle of talking to a parent (.) are you then going to go to the portal to refer and check that you've said all the things?
- Lizzy =well it's better than nothing.

Raj, Lizzy and Michael, Neonatal Consultants, Ben, Neonatal Registrar and David, Medical Geneticist
Audio Recording of Education Meeting, Lakeside Hospital

This case is clearly challenging: an (seemingly) unnecessary test has been performed in an infant, without the explicit consent of the parents, generating a challenging result of uncertain significance with potential far-reaching implications for the family. The responsible clinician, Lizzy, is quick to invoke the role of other members of the bioclinical collective (Bourett, 2005) in this incident, problematising the laboratory practices and procedures: why had 'they' called 'us'? Why had 'they' done the test? This counters and opposes the problematisation of the clinic exposed in chapter six. The role of the laboratory, expert genetic services and clinic is called to the fore by Michael, who later contends that despite their 'expert' role, the laboratory has "enough to do without constantly having to tell us what to do".

The recognition of pre-test counselling and indeed testing itself as highly contingent, fuels a reductionist approach of how practical and ethical challenges can be confronted. A guideline, though limited in its practical utility – would be 'better than nothing'. This takes on numerous forms, including the availability of an information leaflet in the earlier extract, which attempts to standardise the informational requirements for both clinicians and families. Whilst not explored in more detail in this discussion, clinicians expressed strong positive opinions about the role of leaflets in information-giving processes.

What you need is a leaflet that explains it all in simple terms (.) that way you know the family have the information in some form (.) it becomes a point of reference

Lizzy, Neonatal Consultant
Interview

Having information 'in some form': whether from pre-test counselling or from the availability of a leaflet, recognises the need and effort by clinicians to provide adequate information – even when, as acknowledged later, this is not always done well. For some clinicians and junior staff, the availability of an information leaflet may also serve as a safety net or topic guide, laying out the minimum important items for discussion in pre-test counselling (and also perhaps preventing too much information being given to parents) and providing a point of reference both prior to and after consent conversations have taken place.

You know information leaflets are useful for doctors too in that they can be used as a guide (.) a touchstone around which to guide the specifics of the conversation (.) and something for parents to come back to later as we are often giving a lot of information at once

Beth, Neonatal Consultant
Interview

Sometimes if you're going to discuss a procedure with a family and it isn't something you're overly familiar with then just reading a patient information leaflet is useful (.) you know they are a vetted source of information (.) more often than not prepared by an expert in the field or someone with a strong interest (.) so they are reliable and straightforward (.) they only have the information that you really need to know

Peter, Neonatal Registrar
Interview

There are repeated references to both the information leaflet and the checklist (listing the categories of result types which can be generated) as a mechanism of 'ensuring' parents are adequately informed. Though recognised as an example of empty ethics, information leaflets, checklists and guidelines are held up in this account as "*a standard*" by paediatricians, or less emphatically, as "*better than nothing*", despite the recognition that "none of this would have helped" in preventing or improving the circumstances of this complex case. Indeed they are abandoned as points of interest in this conversation as the reality of their use is questioned and difficult to reconcile.

Though the 'bridging work' (Timmermans and Buchbinder, 2012) – in the form of education sessions given by laboratory and clinical staff from genetics - performed prior to implementation is acknowledged, commentaries of the practical challenges abound: there is a high staff turnover, the junior staff are largely responsible for pre-test counselling and may be unfamiliar with the

technology. Senior staff acknowledge the system level difficulties, however the inherent uncertainty of the test is used as a means of absolving the clinical team of responsibility for this messy, complex genetic work. Despite this, there is a sense of realisation as Lizzy exclaims "so whenever you find something like this then there really are implications for the whole family": whilst bridging work attempts to foresee and prepare practitioners for the realities of a technology or process, personal experiences – on both an individual and a systems level – remain a powerful way to learn about the real-world challenges and to drive change.

The next extract is a short discussion between a David (Medical Geneticist) and Beth (Consultant neonatologist) about an infant unexpectedly diagnosed with 22q11 microdeletion syndrome:

David So (.) female baby (.) extreme preterm had a lot of problems (.) so it was thought that the external genitalia was a bit unusual (.) and an array was requested. It picked up the 22q11 which is the most common microdeletion syndrome. I was looking at it and because I don't know this baby much and I don't know whether the baby had other features but if you think just of ambiguous genitalia this doesn't explain. But there are probably other features.

Beth Because it was quite late on into their course this was picked up, she was born pre-term (.) and so that on week two have a bit of NEC and made a slow recovery (.) making progress as you might expect her to do (.) but then she sort of had lots of infections and then had seizures and we sort of went back to the books again and cast the net quite wide and she was probably about two months old I think (.) six to eight weeks of age (.) Di George had never (.) had never ever come into my thinking (.) I think the array was just a screen really (.) just to rule anything out

David anything in particular you were thinking of?

Beth I think as she grew (.) she looked more dysmorphic maybe (.) a number of us said she didn't look quite right (.) even given the prematurity (.) we discussed it at grand round (.) there was some Dysmorphism ... It is quite difficult sometimes you know when they're born at 26, 28 weeks its quite difficult to and then sort of grow into it a little bit and for a lot of time it's quite difficult to have a look at their face because of the paraphernalia of being ventilated, then CPAP. But there was a feeling there's something not quite right so we sort of then said right okay then let's go back to the start and sent everything. So it was a quite a shock.

David When the results came in you started looking for 22q signs (.) was there anything

Beth maybe the calcium?

David Okay so I should move that to a definite answer then rather than an incidental (.) in hindsight.

David, Medical Geneticist and Beth, Consultant Neonatologist
Audio Recording at Clinical Meeting

The clinicians here describe the process of ordering the array as part of the process of going 'back to the books' and 'casting the net wide' in the search for a unifying diagnosis: in facing a series of incongruent and unusual clinical features, notably multiple infections and seizures. The array was 'just a screen', it was not requested with any particular clinical diagnosis in mind, rather as another stage in a diagnostic Odyssey which sought to provide a diagnosis. As such, a low risk heuristic was applied. The actual diagnosis – 22q microdeletion – had 'never ever come into my thinking' –

though there were concerns about potential unspecified dysmorphic features, the diagnosis was described as 'quite a shock'. Here, the finding is 'incidental', but only in the sense that any diagnosis would have been incidental, as the test was 'a screen' performed with no particular diagnosis in mind. Retrospectively, with the diagnosis known, the notion that there were dysmorphic features was more broadly elaborated on, and the (low) calcium levels, which had been unproblematic, were cited in support of the diagnosis. In contrast to the first account, the process of coming to a diagnosis – even an unexpected or incidental diagnosis – for a complex patient was not seen as particularly problematic, and was in fact welcomed.

These examples demonstrate the dynamic relationship between the laboratory and medical genetics (as expert perspectives) and the clinic as they grapple with the realities of an unfamiliar technology in a new setting. Both parts of the bioclinical collective (Bourett, 2005) – the laboratory and the clinic – seek to problematise the other, seeing the problems arising from the technology and testing as associated with the practices of their counterpart.

Consent Conversations: 'recruiting' consent

This section uses transcribed data of 'consent conversations' between parents and clinicians when microarray testing is considered to be a potentially useful diagnostic test. The frame for this interaction is that of seeking to gain consent from parents. Frames allow participants to enter social interactions and engage in familiar tasks, with consequences for the form of the interaction. For participants to comprehend the content of an exchange, both must be conscious of the frame in which it was intended. From a linguistic anthropology standpoint, frames are shaped by the socio-cultural considerations (Gumpertz, 1982). Shared socio-cultural norms (or the recognition of difference by those participating in a conversational exchange) allow for the ability for participants to respond in the expected way.

When frames are not shared, misinterpretations and misunderstandings become more likely. Sociological perspectives build upon this in recognizing the potential for multiple frames to emerge and exist within a single event: so-called participation framework (Goffman, 1981). Participants constantly adapt the ways in which they participate in interaction (such as listening, speaking and interacting) based on comprehension of their own and others' involvement in an encounter. This underlies footing as the "alignment we take up to ourselves and others present as expressed in the way we manage the production or reception of an utterance" (Goffman, 1981:128). In this sense, considering interaction as consisting of a speaker and listener is too simple: shifts in footing can allow – even require – the role of the participant to change in the interaction, for example from a

ratified (most frequently for these exchanges, the parents of the infant and the clinician) to an unratified participant, or between principal, author and animator of an utterance or message.

In contrast, the context of these 'consent conversations' is markedly different than others in the neonatal unit. Communication between doctors and parents in the unit is usually unscheduled. As parents are allowed to visit at any time, communication between parents and medical staff (usually registrars and senior house officers) most often takes place at the cot-side when the doctor is providing care to the infant, for example, during physical examinations, medication prescribing or when performing blood sampling. As infants' needs are more closely tended to by nursing staff, nurses often serve as the main providers of information about day-to-day issues in relation to care. When there are questions or queries nurses are unable to address, nursing staff will approach the medical staff to request parents are updated or informed about progress and developments as required. When infants are unstable, or difficult treatment decisions are required, scheduled appointments between parents and consultants may be arranged.

The nature of the 'consent conversations' was as a scheduled, explicit discussion between a parent or parents and a clinician, usually a doctor or nurse practitioner. Consent conversations usually took place at the cot side when the infant was an inpatient on the neonatal unit, though sometimes clinicians would visit mothers who remained inpatients on the postnatal ward. Occasionally, conversations might also take place in the quiet room.

'Getting' consent: non-directive, persuasive or coercive?

In the following extract, Rachel, a neonatal nurse practitioner visits Martha, a mother of an infant born six hours earlier with Gastroschisis, a congenital anomaly of the anterior abdominal wall. The diagnosis was made antenatally, and Rachel has met Martha immediately prior to the birth and was present throughout the birth and immediate postnatal period. She returns to the postnatal ward to speak to Martha about microarray testing.

Rachel	Hello can we talk quickly/ Just two minutes it is not a longwinded thing.
Martha	okay
Rachel	so this is the blood that we have taken from baby [holds up the request form and sample bag containing blood sample from baby] and we're going to send it for genetic testing
Martha	=okay
Rachel	has anyone talked to you about that/
Martha	=no
Rachel	<u>okay</u> so basically we send it off and it goes through erm numerous tests looking for any genetic conditions (1) that could or could not be related to gastroschisis
Martha	=okay
Rachel	so your baby was born with a congenital condition
Martha	=yeah

Rachel Which is often not related to anything else [=yeah] but to be on the safe side we do this test .. we just want to check there is no underlying genetic reason

Martha =you just wanna check

Rachel =why this might have happened. So we need you to consent for them.

Martha so how long will this take then/

Rachel how long does an array take/ Around three weeks but it could be longer

Martha will the results come back to us as well then/

Rachel yeah

Martha so this is quite a rare thing then gastroschisis/

Racheal it is .. but not that rare. We do see quite a bit on .. about the unit because we are a surgical centre.. so all the children in ** born with this condition come to us [hands consent form to M]

Martha just here is it [looking for place to sign on the consent form]

Racheal =yes just there. You need to write my name on it too

Martha what's your name

Racheal [gives name]

Martha [says name] did you say/

Racheal yeah. That's impressive that you know how to spell gastroschisis

Martha do I need to sign as well/

Racheal no we just need one signature [M hands the completed form to N] that's fab. Erm we do see a lot. About twelve to fifteen per year

Fred =not that many then really .. which is a good thing I suppose

Martha have any come back with genetic problems then/ Or not/

Racheal not that I'm aware of [=oh good] as I said this condition is normally an isolated thing. It's normally isolated

Martha it's normally isolated isn't it

Racheal we do this just to be on the safe side and to collect more data

Fred to do research yeah

Racheal =we're learning about these conditions all the time

Martha fab thank you

Racheal great .. thank you [leaves the room]

Martha [to F] send [name] and [name] back in love

Racheal, Advanced Neonatal Nurse Practitioner, Martha, Mother and Fred, Father
 Audio Recording, Consultation (Infant with Gastroschisis)

This conversation is notable in terms of the brevity and form. There is very little introduction or rapport building, reflecting the fact that this (recorded and transcribed) interaction is just a part of a series of closely linked interactions between this professional and family throughout the hours following delivery. Immediately the purpose of the interaction is downplayed through the need to merely 'talk quickly' and the assurance that (unlike other interactions potentially) this will not be a 'longwinded thing'. The blood sample is something 'we' have taken and 'we are going to send off': a pronominal reference to the collegial decision-making characteristic of decisions to test. This contrasts the first 'we' as a superficially collaborative alignment: we being the mother and nurse practitioner in interaction. This demonstrates how pronominal reference is often used to index shared or non-shared perspectives in inclusive and exclusive terms (Arribas-Ayllon et al, 2008b): 'we' as clinicians have decided to do this test, 'we' as a clinician and parent in interaction will now discuss the nature of this. The modal construction frames the suggestion as patterned and predictable and as a course of action that is normative: as such, challenging or questioning the recommendation to test is difficult to achieve.

The interactional style is largely one of the advanced neonatal nurse practitioner explaining her agenda. The early part of the interaction contains very minimal parental responses – mainly just continuers such as ‘yeah’ – which recognise the formation of a lengthy unit of talk, and allow the clinician to continue: the parents are listening, but the clinician maintains interactional control. Backchannels are listener responses – such as ‘okay’ – which alongside continuers define a listener's comprehension and interest. The presentation of the blood sample is a powerful cue that the decision to test has been made: the blood sample has already been taken and the request form completed. As such, rather than obtaining consent, the clinician merely seeks to recruit support for the (already established) decision to test, despite the later assertion that ‘we [the clinicians] need you [the parent] to consent for them’. As such, this interaction is better characterised as assent or a process of agreement – the mere formality of having the parent agree with the statement already made – than consent as a process of allowing, requiring the permission of a parent which might be withheld or denied.

The frame is one of ‘recommending’ testing, which embodies the expert or paternalistic model of the doctor-parent relationship. Resisting the suggestion or recommendation for testing would be more interactionally complex, and as such, we see assent. The default assumption of the clinician here is that ‘we’re going to send it [the blood for aCGH testing]’ and as such the footing is directive with only superficial attempts at alignment.

Multiple frames, multiple aims

Formal introductions of name and status – typical of medical exchanges – did not always form the opening of the conversations. When clinicians had been involved in the clinical care prior to the conversation, the opening usually consisted of an introduction phase, in which interpersonal relationships are negotiated, during which participants seek information about shared experiences and common perspectives (Gumpertz, 1982), often through the use of a common social frame. Despite this social frame, the institutional frame is one of seeking consent.

Zoe Did you have a caesarean/ [assisting M in wheelchair into position at cot-side]
Carly =yeah
Zoe I had a caesarean as well. The contracting afterwards is terrible.. it kills
Carly =yeah.. it's awful
Zoe So again.. I'm Zoe (.) one of the medical doctors here. So we've talked
 about it (.) we're going to do this genetics blood test (.) I'll talk you through it
 anyway

Zoe, Neonatal Registrar and Carly, Mother
Audio Recording, Consultation (Infant with Multiple Congenital Anomalies)

Here, the patients' mother, Carly, and the neonatal registrar, Zoe, commence the conversation in a social frame. This allows for Carly to be positioned next to the cot-side, where the conversation takes place. The social frame allows time for this to take place – without an awkward silence - assisted by a nurse (an unratified participant) and by Zoe. Once in a position, the frame shifts to the more traditional introduction in medical caregiving, with the neonatal registrar introducing herself with the caveat 'so *again*', indicating their familiarity. The rapid transition from the social to the medically orientated frame leaves the psychosocial concern of Carly unattended – in relation to her 'awful' pain, but allows Zoe to re-construct her interpersonal identity in the unfolding talk⁴⁹. Here again, the decision to test is presented as one made collectively by medical professionals involved in the infant's care, 'we've [the medical professionals] (have) talked about it [the utility of genetic testing] (.) we're going to do this genetic test'. 'We've talked about it' here functions as a rhetorical device for eliciting consent: it is a strong medical recommendation, and implicit in this is that any challenge to this decision, let alone disagreement, would be inappropriate and obstructive. The frame then changes to information giving, or 'talking you [the mother] through it anyway', placing the mothers footing as one of a passive recipient of information about testing and implying that testing would take place 'anyway'. For both previous extracts, although the overarching frame is supposedly one of consent-seeking, little is done to confer a sense of truly free choice for the parent in either interaction.

Frames can be multiple, nested and suspended or subordinated within an interaction, either semantically or through the use of other cues, such as gesture, gaze, pauses and prosody. Nested within the frame of information-giving is that of providing a justification for testing, in which the parent is 'informed' of the reasons testing is being proposed. In the earlier section, Racheal (advanced neonatal nurse practitioner) classifies gastroschisis explicitly as a 'congenital anomaly' for the parents and as such 'to be on the safe side' an array is proposed 'to check there is no underlying genetic reason'. Returning to this conversation, Zoe (neonatal registrar) continues with a description of the infant (named James) anomalies, lending support for the decision to test.

Zoe ...so you know James has got this problem with his oesophagus...sometimes that can be associated with other problems. I've explained to you that he also has 13 ribs and that there also appear to be a problem with the shape of the bones in the bottom of his spine... I'll show you the x-ray after [=we've seen it].. oh you've seen it right/ so sometimes genetics can explain these things... in

⁴⁹ Part of this emerges from language variation: the use of 'kills' as a vernacular description of pain is appropriate here, as the women in conversation align their experience of a caesarean birth, whereas to refer to infant discomfort as 'killing' rather than 'painful' elsewhere would be considered inappropriate and insensitive.

that they can all be linked together...so we can explain why they are linked. Is there a problem with the genetic make up of James that's causing him to have all these problems So we do a blood test which shows all the genes that make him up... the genes from you [to Carly] and the genes of Dad and checks it against a normal person to see if there are any differences okay

Zoe, Neonatal Registrar and Carly, Mother
Audio Recording, Consultation (Infant with Multiple Congenital Anomalies)

The explicit presentation – or listing – of James' anomalies by Zoe serves to demonstrate to the parents why testing is needed. The potential 'problem with the genetic make up' of James will be contrasted, through microarray testing, with that of a 'normal person'. The use, or offering of artefacts, such as the radiograph or growth chart (see next section), add further weight to the justification for testing. Yet these artefacts can also provide opportunities for parents to contest the legitimacy of the clinicians' claims about the abnormal physical form of their child.

Zoe. and that could be why the baby has the hernia through the abdominal wall or why the bones in baby's legs are short [pointing to antenatal ultrasound report]. So that's why we look [*do an array*] does that make any sense/
Carly (3) they have never classed the legs as a defect before.. they were just saying oh he's going to be small and oh he's got a small head (4) but I suppose they haven't got the testing there (1) and the studying that they've got here...

Zoe, Neonatal Registrar and Carly, Mother
Audio Recording, Consultation (Infant with Multiple Congenital Anomalies)

Lowri He just said you were going to run some tests...and genetics or something along them lines... something to do with his head not measuring on the chart or something
Peter Because his head is measuring [presents mother with the OFC growth chart] because it's smaller than we would expect it to be and there are loads of causes for this. We've done some earlier blood tests looking for infection and they've all come back negative and that's why we've decided to investigate the genetic causes. So the blood test we are going to send is called an array CGH and it looks at genetic causes of what could be responsible for the baby having this small head
Lowri it's just because my waters broke early and he needed my waters to grow/ [laughs]
Peter it could be one of the reasons yeah .. but sometimes when a baby is born with a small head we just do all these tests together to cover all the bases just to make sure we are not missing out on anything
[later]
Lowri it's the first I heard of it yesterday and they said he had a little head and I said no its big [laughs] I thought he had a big head
Peter Yeah 'cause he is so tiny (1) it looks like everything is tiny so it's hard to know. But when you look at the chart that we showed you earlier on
Lowri =yeah he's never done any of the charts anyway like throughout the pregnancy as well

Lowri, Mother and Peter, Neonatal Registrar
Audio Recording, Consultation (Infant with prematurity and severe IUGR)

The long pauses in the interaction between Zoe and Carly indicates the mother's affective response to the evidencing – by way of an antenatal ultrasound report – that her baby has short long bones,

and that this is 'a defect', rather than an individual (and perhaps cherished) characteristic of potential short height. Despite weakly contesting the doctor's assertion, the mother soon corrects her own narrative of her infant's small size, crediting the (apparent) expertise of Lakeside – the 'testing' and 'studying' available in this specialist unit, as compared to the limited expertise and resources of her local hospital where she received antenatal care. This notion of expertise legitimises the revision of previous classifications of 'the normal' and 'abnormal' to be reformulated, providing further justification for testing. In extract five, an infant growth chart is presented to demonstrate the growth restriction of an infant born prematurely at 26 weeks, who is now 10 weeks old. Despite the evidencing by the growth chart and the concern of the doctor regarding a potential genetic cause, Lowri is quick to dismiss the concern of a potential genetic cause, presenting defensively and emphatically her (lay) reasoning that this is all owing to the premature rupture of membranes. Again, there is an affective consequence of (re)classifying head size as an anomaly, leading to a need for repair by Peter, acknowledging the potential legitimacy of her explanation before moving on to claim that testing is a reasonable course of action. Despite this, Lowri continues to contend that "he's never done any of the charts anyway", and her reasoning remains apparently unchanged.

As demonstrated here, the processes of seeking consent, and justifications for testing, are highly contingent on both individual and organisational practices. Though the perceived frame is one of consent seeking, the actual frame is often that of information sharing and justifying rationales to test. There is a highly directional footing, which makes the suggestion of testing by professionals difficult to resist. In the next section, I explore another rhetorical device used in the process of information sharing – metaphor.

Metaphor and meaning in information sharing

In this section I explore the use of metaphor as a communicative tool arising in the interactions between non-experts and parents discussing genetic testing. Metaphor is defined as a figure of speech in which a word or phrase is applied to an object or action to which it is not literally applicable, using a familiar example or concept as a symbolic representative of something else. Metaphor is a rhetorical device in discourse analysis, and characteristic of persuasive talk. Metaphor in medical talk has received some attention, notably the work of Susan Sontag in *Illness as Metaphor* (1983) and *AIDS and its Metaphors* (1990). Here, she explored how the association of certain metaphors and certain illnesses – drawing largely on her own experience of breast cancer – has consequences for patient experience and public attitudes towards disease. She argued that metaphor exaggerates an unhelpful affective dimension to the experience of and attitudes towards

illness, contending that they should be largely excluded from rational, scientific discussion of health and disease.

She focused on two key 'types' of metaphor. Biomilitary metaphors are those which describe illness, and the response of the body to it: the 'attack' on the body of cancer, and the 'fight' both individuals, systems and drugs can wage against it. These types of metaphors are highly pervasive in descriptions of cancer, and Sontag (1983) contends they frame transitions to palliative care as moral defeats or weakness: unnecessarily adversarial, and binary in terms of defining victory and defeat. In contrast, bioinformationist metaphors describe both health and disease states, configuring the body and its processes as a system of communication consisting of transmitters and receptors. These predominate in accounts of the cardiovascular system as a network of 'plumbing', with mechanistic descriptions downgrading the modifiable nature of much cardiovascular disease, absolving individuals of autonomy and control.

Metaphor use is commonplace in medical talk. As with metaphor itself, the study of medical metaphor centres largely on oncology and palliative care. For medical talk, the aim of a metaphor is to explain, using a familiar, concrete concept to describe something abstract. They provide a focus point around which an information-sharing encounter can be structured and re-referenced.

In the transcripts, three key categories of 'bioinformationist' metaphors were identified, used primarily in the information sharing frame. These categories can be listed as (i) those describing the normal form and structure of genetic material, (ii) those describing aberrations of 'normal', and (iii) metaphorical descriptions of specific genetic technologies and methods of gene testing.

Category of 'Bioinformationist' Metaphor	Examples
<i>Describing the normal form and structure of genetic material</i>	<p>Remember those old style encyclopedias with multiple books yeah (.) well each book is like a chromosome (.) and inside each book at the chapters (.) they would be the genes (.) and what you want is to have all the books and all the chapters in the right order (.) no extra books or extra pages inside each chapter [Community Paediatrician, field note]</p>
<i>Describing aberrations of normal</i>	<p>At the consent stage (.) I'm still talking about (.) I put them in the same basket and say unexpected results (.) and I don't differentiate between results of (.) whose clinical significance is incidental or results whose clinical significance is clearly related to the reason for the test [Consultant Neonatologist, interview]</p> <p>If a page or a couple of pages were missing (.) that would be a deletion (.) if you had lots of extra pages then that would be a duplication [Community Paediatrician, field note]</p> <p>If you zoomed in and saw a house had been bulldozed or knocked down (.) that's the missing gene (.) you might not see that from too far out [Neonatal Registrar, consultation]</p>
<i>Describing technologies and methods of testing</i>	<p>The gene tests are like a newspaper (.) you can read them at different levels of detail (.) The oldest test, the karyotype, is like looking at the headlines only. Then the array is like reading the sub titles too. This test which we can send away looks at the spelling of each word, but focuses especially on the stories we are interested in reading (.) that is the genes which we know about which may cause epilepsy. So it reads all the paper, but pays special attention to the most interesting (.) or relevant stories [Community Paediatrician, field note]</p> <p>I describe it like google maps (.) you can zoom in and out (.) see more detail and see less detail (.) so the karyotype is like looking at the whole road and the array is like looking at whole road but also being able to zoom in and look in more detail (.) better resolution [Neonatal registrar, interview]</p>

Table Eleven: Categories of informational metaphor use in pre-test counselling

Though neatly presented here in three categories, it is clear that metaphorical use can extend between these categories: for example the encyclopedia is used to describe firstly the 'normal' state or structure of the genetic, it is then extended to include aberrations. When 'reading' metaphors are

considered together – both the encyclopedia and the newspaper – then a bioinformationist metaphor is used to encompass all three purposes.

This example demonstrates the use of metaphor in interaction, as a clinician talks to a parent about a normal QF-PCR result, and the need for aCGH to be undertaken.

James oh yeah (.) okay (.) I think you mentioned about this one (.) this is the one you do when the rapid test is normal?
Laura yes, this is the array. Did we explain the test to you?
James no (.) you just said it might be needed
Laura yes, I think we should do it. As I said we know that the chromosomes are there now in the right number. That's good. The chromosomes are like houses, they are big (.) they are easy to see. Now we want to look at the bricks that make the houses (.) those are the genes. So we have counted the houses, now we need to count the bricks and make sure there are not too many or too few. It's a more detailed test.
James okay (.) that makes sense. So we have excluded big things now we look at smaller things
Laura well, we have excluded big number changes. Now we are looking for more subtle changes to the chromosomes. Obviously even smaller changes can cause problems, so we need to make sure we look for those too.

James, Father and Laura, Neonatal Registrar
Audio Recording, Consultation (Infant with dysmorphic features)

As with some of the other metaphors, one function here is comparative, comparing the (resolution of) one technology, QF-PCR and aCGH. To do this, the chromosomes are described as houses – 'big' and 'easy to see', and the QF-PCR has confirmed their presence in the expected number. The aCGH is described as a different level of resolution – a common metaphorical theme here - 'we have counted the houses, now we need to count the bricks and make sure there are not too many or too few', with the bricks being the metaphorical genes. The father uses some of the same words in his response: the neonatal registrar has described the chromosomes as 'big', and although not explicated the genes are implied to be small. The father infers that the normal QF-PCR means the 'big' things have been excluded, and it is unclear if by this he means 'big' structural changes, or things with 'big' (serious, clinical) significance. The neonatal registrar makes an attempt at repair, clarifying that the 'big' refers to chromosome number changes rather than the potential severity of any changes identified describing how 'even smaller changes can cause problems'.

One core issue with metaphor use in this context is whether we can assess when a metaphor has been helpful. Here, we see an attempt by the father to develop the metaphor and demonstrate that it has been understood. The father does however imply that it has been helpful, saying "that makes sense". This dichotomy demonstrates how expert and lay interpretations of meanings and extensions can diverge, meaning the connotation of the metaphor may not necessarily be shared.

Though not demonstrated in the data here, there may also be important cultural factors, in addition to those related to the knowledge and literacy of those in interaction.

What was clear from the observations is the ways in which metaphors can be contagious or inherited: transmitted within and between domains of practice. As demonstrated earlier, the 'see one, do one, teach one' model means that individual practice is often shaped by practices – both good and bad – the trainee professional may have observed. This was demonstrated in an interview with one of the registrars

Researcher how do you describe the array to parents?
Ben I actually went along to a few genetics clinics (.) I was thinking of giving up
paeds [laughs] and they did it really well there (.) explaining the test using the
idea of one of those old encyclopedias (.) it was so clear (.) in terms of what
constitutes normal and abnormal and what the tests actually look for

Ben, Neonatal Registrar and Researcher
Interview

Ben here describes his own immersion in the social world and discourses of specialist genetic practice: his literal 'eavesdropping' (Collins and Evans, 2007) on their ways of work. Ben describes how this insight then informs his own way of working. This underlines why it is important that there is critical reflection on metaphor use. Metaphor does not just describe similarity, it can create it, with cultural methods to in use to simplify or explain complex concepts eventually blurring the lines between the literal and figurative.

Conclusion

This chapter examines how infants are designated as genetically problematic, and the processes that underpin decisions to use aCGH testing in the neonatal intensive care unit. It specifically examines the work of paediatricians as non-expert users of this 'new' technology.

The use of microarray technology is enacted through practices of inclusion/exclusion: who is, and what constitutes, a *genetic baby*? After this lumping of the genetically problematic, there is a process of splitting. Who needs specialist expertise? When problematic results arise how is the care of infants transferred, or disposed, from the general (paediatric) setting to the specialist (genetic) setting? Through the application of a risk heuristic - the process and nature of which is not always explicitly articulated - non-expert paediatricians determine which patients can be assigned to have array CGH performed without expert genetics input (*low risk heuristic*). In this case, neonatologists, as non-experts, perform the genetic work. Some cases will be deemed complex, and of benefiting from expert genetics assessment prior to the laboratory investigation. The application of a high-risk

heuristic means they are 'disposed of' by neonatologists to specialist care. The aims of these processes of inclusion/exclusion and disposal are twofold: (i) they seek to insulate non-specialist practitioners from the complex, uncertain aspects of genetics work. This arises from the acknowledgment that, although the use of the technology is available to them as practitioners, the complexities associated with its use are not as easily transferred. Furthermore, (ii) they ensure that clinical geneticists ultimately maintain professional jurisdiction over the technology as it enters mainstream medicine and becomes part of the work and diagnostic arsenal of the non-expert medical population.

The practices around the technology are highly contingent. Who performs the test? Even among the non-expert paediatricians there is a range of seniority and experience, with mechanisms to pass down or transfer proficiency in this task. Why and when is the test being performed? As 'a screen', to exclude potential genetic disease, or as a diagnostic test in the truest sense, with a high index of suspicion of genetic disease? The use of heuristics which stratify infants as 'high' or 'low' risk shapes the discourse of pre-test counselling. Indeed, more than this, it shapes the deployment or recruitment of expertise, shaping whether it is a geneticist or a paediatrician who 'does' the test and how consent is sought.

Shaw et al (2005: 3) contend that clinical decision-making is not supplanted by new molecular technologies, but through the existing hierarchies and traditions of clinical work. New technologies can extend the diagnostic repertoire of clinical decision making, but the value of testing is negotiated in relation to 'traditional diagnostic techniques of history, observation and examination, investigation and diagnosis' (2003:16). In the use of aCGH as a 'screen' we see evidence that in some sense, clinical decision-making is being shaped by the availability of this technology as it is used to 'exclude' rather than diagnose genetic disease.

Chapter Eight: The Family

This final analytic chapter draws on discourse data generated during nineteen interviews with parents whose children had undergone genetic testing in the neonatal period. These families had received a result considered to be of unknown or uncertain significance, or an incidental finding. The chapter presents a narrative structure from the experience of the parent, focusing on the key events in the process of arriving at a diagnosis of 'uncertainty': through being categorised as a 'genetic baby', the process of testing, receiving results and then the lived experience of (genetic) uncertainty beyond the realm of the clinic in the lifeworld. Using rhetorical discourse analysis of accounts provided by parents, I contend that parents themselves recognise genetic testing as distinctive from other forms – or technologies - of medical investigation commonly encountered in the neonatal period. Despite clinicians' seeming discomfort with the uncertainty associated with off-target information, parents and families embrace uncertainty as mere or more uniqueness: another part of their journey into parenthood which deviates from the expected, anticipated or 'normal'.

The previous two chapters have provided an analytic account of the 'genetic work' undertaken in both the laboratory and the clinical setting when an infant is undergoing genetic investigations using comparative genomic hybridisation. This chapter examines the accounts provided by parents and families of children who receive results considered to be 'uncertain'. These interviews include some families where children had been born after there had been antenatal concerns explored in fetal medicine, and others where the medical problems had not necessarily been anticipated before birth.

Frank (1998) provided a useful framework through which illness narratives are described, providing accounts for how their neonatal experiences, and indeed, their accounts of genetic testing and genetic uncertainty, are integrated into their current narratives. In this process, parents seek to present themselves in the best way, defensive against threats to their face (Goffman, 1959).

Type of Narrative	Description
Restitution	“The plot of the restitution has the basic storyline: “Yesterday I was healthy, today I’m sick, but tomorrow I’ll be healthy again.” This storyline is filled out with talk of tests and their interpretation, treatments and their possible outcomes, the competence of physicians, and alternative treatments.” (Frank, 1998)
Chaos	“Chaos is the opposite of restitution: its plot imagines life never getting better. Stories are chaotic in their absence of narrative and order. Events are told as the storyteller experiences life: without sequence or discernable causality.” (Frank, 1998)
Quest	“Quest stories meet suffering head on; they accept illness and seek to use it. Illness is the occasion of a journey that becomes a quest. What is quested for may never be wholly clear, but the quest is defined by the ill person’s belief that something is to be gained through the experience” (Frank, 1998).

Table Twelve: Frank’s Illness Narrative Typologies (1998)

In this chapter, we will see how narratives, along with reported speech and contrast, are used to ‘foreground’ the ‘practical’ lifeworld considerations of illness and uncertainty.

Being/becoming a patient and parent

It’s not what you expect (.) you know (.) born early (.) no-one can explain why and then next thing it was he having help breathing and with his heart and then suddenly they’re saying about (.) his eyes and his chin (.) we couldn’t see any of it (.) and his x-ray. Then it’s more than just being born early and you can’t take it all in.

Gareth, Father
Interview

Having an infant who requires additional medical care after birth usually represents a deviation from the anticipated: a narrative of chaos (Frank, 1998). Whilst some infants who are admitted to the neonatal intensive care unit will have problems which are diagnosed antenatally – through prenatal genetic testing, or through imaging technologies such as ultrasound or magnetic resonance imaging – the majority will have problems which have not been anticipated or prepared for, including premature birth and congenital anomalies. The postnatal period is immediately medicalised for these infants, and the transition from baby to patient is described in terms of extremes - ‘*sudden*’

and '*not what you expect*'. Harrison was born prematurely with a postnatal diagnosis of congenital heart defect and dysmorphic features, and had array CGH testing on the second day of his life.

- Gareth I think we were both quite shocked when they said about the genetic test [turns to talk to Lucy] was it on the first day?
- Lucy I think it was that first afternoon the day after he was born (.) they were saying about the ventilation and the lines in his tummy (.) then they said about the brain scan (.) the ultrasound and the genetic blood test (.) You think you're just going to have a baby and then all of a sudden it's not that at all. You're a parent and they're a patient (.) and it feels like you're a patient too
- Interviewer A patient in what sense?
- Lucy 5] in the sense that it does feel like you are in hospital too because you're in the neonatal unit all the time and in the sense that [2] not that you are to blame no-one made us feel like that but they are asking all questions (.) were you sick in pregnancy (.) were you taking any medications (.) are there any heart problems in the family (.) is your other boy ok

Lucy and Gareth, Mother and Father of Harrison
Interview

Chaos quickly turns to restitution as Harrison's parents describe a rapid immersion into a world of new and unfamiliar interventions, such as ventilation, vascular access and the administration of fluids and medications ("*lines in his tummy*") and technologies aimed at the assessment and characterisation of this infant with the aim of providing diagnostic and prognostic information. Some of these technologies form a routine part of neonatal care, such as ultrasound, and some which represent a deviation or extension of the usual processes, such as "*the genetic blood test*". Lucy describes how the suggestion that there are (potential) genetic causes for a medical problem places the broader family, and especially her, as the mother, under scrutiny too. Here, Lucy does character work, describing feeling "like a patient too". In the same way Harrison is a subject of medical scrutiny – the 'clinical gaze' - so her pregnancy, personal health and the health and wellbeing of the family more widely become a subject of unanticipated scrutiny. This scrutiny – though the collection of family history and pregnancy information (which form a standard part of the medical assessment of children) - when aligned with the suggestion of potential or actual genetic disease and the notion of genetic testing medicalises the family, leading them further from the normal, anticipated experiences of early parenthood. The interchangeable shifts between 'I', 'you' and 'we' signal authority and vulnerability in differing parts of the experience – as a parent, a patient themselves and as a proxy in decision-making for Harrison.

Talking about testing

In this section, we consider parents event work around the process of genetic testing. Using these accounts, I contend that genetic testing in this domain is clearly distinct from other types of testing from the perspective of parents.

"It seems like there are hundreds of tests but this one was different": recognising genetic testing as distinct

They do a lot of tests in there and most of them you don't even know anything about it (.) they don't even tell you what they're doing half the time. So yeah it was obvious this one was different (.) there was a form to sign and a sit-down chat [laughs]. The doctor brought a chair over and really spoke with us. I mean it seems like there are hundreds of tests but this one was different.

Amy, Mother
Interview

Every day (.) or every hour (.) in those first few days seems to be a different test. A scan of the brain (.) of the kidneys (.) blood tests (.) collecting wee. Most of them you're not even really sure what they are doing and they don't sit down and explain every test most are just a quick mention if anything at all. So I suppose in that way this test [aCGH] was different in that the consultant really explained what it was and made us sign a form.

George, Father
Interview

Parents reported the battery of medical investigations undertaken as part of neonatal medical care. Accounts supported the literature and ethnographic observations in describing how 'consent' – in its traditional form – is not sought for every investigation undertaken. Testing – in the form of fluids such as blood and urine, for haematological, biochemical and metabolic examinations – or in the form of imaging tests, particularly bedside ultrasound imaging – are carried out without explicit discussion and description: they are standard parts of neonatal care. Array comparative genomic hybridisation is distinct in that consent is explicitly sought in verbal and written form⁵⁰. In multiple accounts, parents described a ritual, as previously observed in the ethnographic observations performed in the clinic. These involved the explicit request to speak with parents at a particular time and the sitting down with doctors (as opposed to the bedside communication) and the signing of consent forms.

What I remember was him [consultant] saying (.) "we will come back later to chat to you about the array test (.) explain what you need to know". We spent the whole morning worrying then. It sounds weird but planned conversations like that were normally reserved for special news (.) usually bad news like about something or another. So from the off the genetic test was clearly different in that it needed a special chat like.

⁵⁰ As mentioned in chapter seven, the only other context in which written and verbal consent is sought in this way is prior to surgery and in the use of pacifiers.

In describing the consent conversation as ‘planned’ parents are performing event work: planned conversations are reserved for ‘special’, ‘bad’ or onerous occasions. The use of extreme case formulation – the ‘whole’ morning is spent worrying, augments this concern. In contrast to the consent conversations which frequently present aCGH as ‘just a blood test’, the nature of the consent conversation as explicit – clearly different from other ‘tests’ – meant parents experienced genetic testing as distinct. For many, the mere request for ‘consent conversations’ was anxiety provoking, with intimate conversations between clinicians and parents seen as an occasion for ‘special’ – usually negative – information sharing. The lack of contingency in the form, timing and nature of the interaction - the anticipation of a ‘special chat’ - made genetic testing distinct before it had even taken place – this test became ‘clearly different’. This emphasises how the highly contingent practices around testing: the who, the how, the where and the why have important consequences for the parents’ experiences of genetic testing in particular, and more broadly the practices and technologies of the neonatal intensive care setting.

This notion of a ‘special chat’ invokes the concept of ‘genetic exceptionalism⁵¹’: if genetic information is considered in some way as distinct from other types of health information, then the means by which genetic information is identified may also be considered as exceptional. In the case of diagnostic testing, in the context of a given phenotype, it is challenging to see why it is necessary to treat genetic health information as exceptional: this is not predictive information. However there is the risk it may generate information relevant to the health and reproductive decision making of other individuals, and there is the possibility of a diagnosis with psychological implications for the parents and family, or a diagnosis which might (later) be a source of stigma or discrimination. A key challenge to genetic exceptionalism, relevant here, is the difficulty in defining what is genetic information? Is this just information generated through genetic testing? Or can it also relate to family history information, information generated through biochemical assays (for example those employed in newborn screening)? It is important to consider that invoking genetic exceptionalism may wrongly result in the inappropriate restriction of a potentially beneficial diagnostic technology as mainstreaming becomes commonplace.

Assent or consent for testing: non-directive, persuasive or coercive?

⁵¹ This phrase extends upon the concept of HIV Exceptionalism, first used in the New England Journal of Medicine (Bayer, 1991), exerting the special status of ‘knowing’ the HIV status of an individual. This particularly related to the need for informed consent, which prepares individuals for a positive result, and the potential consequences of this (at this time when prognosis was very poor) for privacy and confidentiality and autonomy as related to issues such as employment and life insurance.

I mean you signed the form but it didn't feel like something that needed (1) that needed like enormous special consideration (.) it was just another part of the puzzle that needed to be completed (.) they had decided this was needed and like everything else you just sort of go along with it which is of course the right thing to do

Melanie, Mother
Interview

Amy They were sort of asking us if they could do it (.) I mean like we had to sign the form so that they could do it (.) but you didn't really feel like it was asking (.) it didn't seem like saying no (2) it didn't feel like we (1) they had decided it was going to be a useful test and they wanted to check we were happy with that

Tom =why would we have said no (.) it was just another test trying to get to the bottom of what was going on

Amy, Mother and Tom, Father
Interview

Accounts from parents lay out how testing was perceived as both an exceptional event, requiring explication and particular rituals, yet also highly routinised: "just another test". These accounts explore how the parents came to understand that testing was being suggested as a useful test by the clinical team. In line with the observations of consent conversations in chapter seven, some parents recognised that decisions about the clinical utility of testing had already been considered prior to 'asking' parents 'if they could do it'. As such, parents did not conceive of the notion of testing as value neutral or non-directive, but rather as driven by an unstated imperative to accept testing, to give their approval. Indeed, as demonstrated here and in the ethnographic observations, the interactions around testing involved clinicians explaining their agenda, as opposed to negotiating a shared agenda: assent to testing is recruited in a way which could be viewed by parents as making the refusal of testing interactionally challenging, meaning they 'sort of go along with it'⁵². Parents take the advice of clinicians around testing decisions at face value and indeed oppose the notion that testing might be refused. Only in retrospect might the impact of testing at this time be questioned.

⁵² This could be considered as a significant statement: what constitutes informed consent in this situation? Is the parental experience of an unstated imperative to accept testing ethically problematic? Agreement in the face of a professional recommendation is not non-directive, but that need not be seen as necessarily inherently problematic, given the context. The contexts of different 'genetic tests' are all very different, and as such, the tradition standards of "informed consent" or "non-directiveness" are going to apply more in some settings than others, reflecting their inherent (potential) moral and ethical implications. Assent may be appropriate, for example, in well-evidenced screening programs, which are low risk for the subject with high potential benefit, for example, in the case of newborn screening programs. Predictive testing – using the example of Huntington's Disease – is inherently problematic as the diagnosis does not alter the disease course and may cause significant psychological distress if undertaken without due consideration of the potential consequences, both for the individual and for other family members. Though a full consideration falls outside the remit of this thesis, clearly other genetic tests, including diagnostic array CGH in the NICU context exist at other points on this assent-consent spectrum. The question for this thesis relates more to the perceptions of expertise which allow consent to be performed in a way that meets the informational and practical needs of the parents, and represents a reasonable transition of the practices that surround a technology (in this case, aCGH) as genetic mainstreaming becomes a practical reality.

In the extract between Amy and Tom, the parents do event work, constructing contrast. Amy describes how 'saying no' did not feel like a valid or reasonable option: testing was presented as the preferred action; they were not 'asking' they were '*sort of asking*'. Tom contrasts this ambivalence with a contrasting certainty 'why would we have said no'. There is misalignment between the mothers' perspective, her implicit internal consideration of whether this test was useful at this time, and the fathers perspective that testing may offer useful, uncontentious and (potentially) diagnostic information. In both accounts, the parents do not share (or appear to share) the notion of medical staff that genetic testing constitutes testing which has unique properties which require due consideration prior to testing being undertaken.

Revealing information about the future

- | | |
|-----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Amy | =well we might of questioned the time it was done (.) I think we still had quite a lot to get our heads around (1) and then when the cardiologist came a few days later he said there might have been another type of test that would have come back quicker if they had done that (1) when they thought it was Williams (1) we spent a lot of time talking about what if it was Williams |
| Tom | =yeah I suppose in some way if we just had more time to take in that first bit (.) take one day at a time instead of all the what ifs for the future (.) we spent time being sad about not only what was happening at the time but then stuff that might happen in the future too (.) then especially when they said there would be no particular treatment for it (.) it did feel (.) just really sad |

Amy, Mother and Tom, Father
Interview

Amy and Tom continue their account with an orientation to restitution. They describe the overwhelming nature of an admission to the neonatal unit: the need to "get our heads around" the deviation from the normal, anticipated experience of new parenthood. Acceptance of this occurs on multiple temporal scales: in the short term, the immediacy of dealing with the clinical, practical and emotional aspects of both separation from your infant and anxiety about their illness. In the longer term, there are also the considerations of the impact of the reason for admission (be this prematurity, congenital anomaly or otherwise) to the neonatal intensive care unit, for future health and development. Genetic testing in this period has an explicit future orientation: parents are 'tak(ing) in that first bit' whilst also being confronted with "'what ifs?' for the future". Parents describe how the temporal implications of testing were either *not considered*, as they were acting responsively in the here-and-now of a stressful and dynamic clinical situation, or *not welcomed*, as considerations of the future felt too tentative in light of a situation where a child may not survive.

A number of parents describe their grief and distress at the potential of both particular and potential genetic causes for disease, especially in light of the results being of little immediate clinical

consequence. The 'sadness' described above relates to the potential diagnosis of Williams Syndrome in an infant with a cardiac defect, and particularly its association with intellectual disability: the 'right not to know', to exist comfortably in diagnostic uncertainty, is limited or removed when testing is undertaken at this early stage⁵³.

I remember Becky (.) we had talked a lot because both of our babies were under cardiology (.) James got his result and whatever gene it was they found explained the heart condition (.) like perfectly (.) it was exactly the right gene for the heart problem he had [2] but then the gene also meant he was going to have problems later too (.) with learning like (.) he would be quite disabled (.) and I don't even think you're thinking about that then (.) about school and learning (.) she was so upset about it because she didn't expect it at all (.) especially because his [cranial] ultrasounds had been normal and he had no bleeds (.) no other problems really [1] we are still in touch now he is a gorgeous boy

Lisa, Mother
Interview

Here, Lisa presents an account of another mother, Becky, formulating an extreme case scenario recognising and characterising the important distinction between incidental and uncertain information, and an incidental or uncertain finding. Though a particular molecular diagnosis may be expected based on a particular phenotype, in the context of the relatively limited (short) lifespan and phenotypic information available for neonatal patients, a molecular diagnosis may reveal more (potential) phenotypic information than is already known. In this case, the finding that the genotype would be associated with intellectual disability was challenging, and ran counter to other, earlier prognostic information (i.e. the absence of intraventricular haemorrhage on cranial ultrasound scanning). Though the purpose of testing is future-oriented, parents and families themselves may not be ready to receive information with far-reaching and unforeseen, or previously unconsidered, consequences. Accounts included distress related to both the unexpectedness of information, and the nature of the information received, in terms of its future-orientation and prognostic nature.

Countering this are accounts where parents describe ambivalence: on one hand, testing appears exceptional and distinct from other investigations, whilst the delay in the availability of results means parents dismiss the potential findings ('answers' - in the short term at least) as irrelevant.

I mean they are doing the test (.) you're signing a form and so on so it feels important and then they are like (.) the results might not be back for months (.) and you think what was the point of that then (.) compared to most other things like the head scan and other bloods where you get an answer straight away

⁵³ It might be reasonable to consider whether it is necessary to know information about a particular diagnosis in the neonatal period. For Williams Syndrome, there is clinical value in knowing the diagnosis, in terms of the opportunity for surveillance for problems and early intervention with respect to delayed and disordered development. An important question is not so much whether the test should be done but rather how to negotiate with the parents as to how much information they want to know about the results, especially where it might only be the responsible clinicians need to know at that stage. There is an absence of research on how acceptable it would be, to both medical professionals and families, to 'know' information about a child, generated through testing, and not share it with and between all parties.

Ruth, Mother
Interview

There is a clear divergence in the experience of parents when a particular diagnosis is anticipated as opposed to those occasions where aCGH is undertaken as a 'screen' (under a low-risk heuristic) for genetic disease (see examples in chapter seven). Knowledge of the anticipated outcome of testing suspends families into 'patients-in-waiting' status, pondering the known-unknown. They are preoccupied with the anxieties of a potential, but as yet unknown result, for a disease or disorder that is increasingly known: a state of conscious ignorance. For those considered at low risk of genetic disease, the absence of an immediate and relevant (potential) diagnosis means the potential impacts are not anticipated and experienced in the same way prior to a result being available: there are too many unknown unknowns to consider, and as such, they exist in a state of meta-ignorance (as characterised in chapter three). More accurately this could be considered as a case of suspended ignorance: whilst meta-ignorance describes a state where there was no awareness of what was unknown, here, the possibility of knowing something is merely suspended until the result arrives. Responses to testing are contingent on whether a diagnosis is anticipated, and how the likelihood of this is communicated with the family.

'It was more involved': enrolling parents in the problems of testing

It did sound like a big deal (.) they said it was best to do it now in case he needed a blood transfusion (.) that the results would take weeks or months to come back

Sarah, Mother
Interview

Duncan ...when that chat did happen it wasn't the consultant it was the registrar but he sat down with us and went through it all like. The different results and the fact we might need a blood test too. It was more involved.

Interviewer What do you mean more involved?

Judy You know in that they clearly wanted you to know what this particular test entailed and what the (.) after-effects (.) repercussions might be. That there might be more involved than just the blood test

Interviewer What types of things?

Judy He did say about the different types of results (.) we definitely knew we might need a blood test (.) I think he said we might find something and we might not (.) we might find something and not understand what it is (.) we might need to see the specialist (.) you need to sign this form

Duncan, Father and Judy, Mother
Interview

Through 'consent conversations' parents experienced recruitment into the uncertainty of aCGH testing. This includes the practical frustrations of the test experienced by the clinic, described as

'after-effects' and 'repercussions': the length time it can take to have a report or result, the role of blood transfusion (a common procedure in neonatal intensive care) in potentially delaying testing or distorting results and the potential need for parental/trio samples. Parents are enrolled in the uncertainty through the discussion of off-target findings, and this was loosely associated with the potential involvement of specialist medical genetics staff, such as genetic counsellors and doctors. The involvement of specialist genetics expertise was described as disposal in action: someone to become involved if there was 'a problem... later'. This is considered here as disposal, rather than division of labour, as the neonatologists conceive of these zones of uncertainty as outside their zone of expertise and as such, prepared parents for this (potential) disposal, rather than rendering all problematic (genetic) work, for example the absence of a diagnosis or a complex phenotype as something for 'the experts'. The notion that a genetics specialist may be involved at a given stage, either prior to testing, or following testing if there was a 'problem', meant parents (potentially) derived a notion of how 'serious' a problem or risk might be: being able to wait to see a genetic specialist until after testing had taken place and a result was available meant 'it' – the nature of the concern necessitating a genetic test take place – 'wasn't that serious', as we see below:

- Chris Initially they said they might ask the genetic doctor to come and see him to see what he thought and talk about testing (.) what might be needed. Then it was all change and [neonatal registrar] just sat us down and said this is the genetic test we are going to do and this is what it involves. They had spoken to the genetic specialist and I suppose that was the test they would recommend (.) then if there was a problem with the test we would see them [the geneticist] later. It made us think it wasn't as serious really (.) didn't it
- Charlotte =I don't know (.) I thought it was that the specialist couldn't come until later in the week so they just decided to do it (.) get on with it when they were doing the other bloods
- Chris =yeah (.) it made me feel like (.) he could wait to see the specialist so it wasn't that serious

Chris, Father and Charlotte, Mother
Interview

Of course you talk about it ... when you're expressing [expressing breastmilk] or when you're passing outside. When [parent of other infant] said the geneticist was coming to see them (.) I know it sounds weird but it made us think that maybe Harrison wasn't so bad (.) so ill. You know he didn't need to see a specialist for the genetic things (.) they could just do the test. He did [need a specialist] for most other things mind [laughs].

Lucy, Mother
Interview

In chapter seven, I described how clinicians defined, experienced and enacted the differences between babies who required the clinical consideration of a geneticist or genetic counselor, and those in whom aCGH could be undertaken by neonatal professionals, later being 'disposed' of to medical genetic services (when 'problems' such as a VUS or IF arose). Parents also experienced

this 'disposal'. Chris describes a feeling of relief at the realisation that other parents of children undergoing genetic testing in the neonatal unit at the same time had been 'disposed' to specialist services, (perhaps falsely) seeing this as a marker of severity, or seriousness, of the (potential) genetic problem. In the absence of an explicit description or reasoning around the practices of genetic testing – the forms of assessment, the involvement of a genetic specialist prior to or after testing – parents construct lay accounts to explain why their infant might be experiencing testing in a different way. For parents, the early involvement of a geneticist makes the risk of a genetic problem greater and the undertaking of testing by a non-specialist means that the stakes of testing are reduced. This contrasts with professionals' accounts, which describe how the likelihood - rather than severity - of a particular set of problems having a genetic cause defines when a referral or disposal is made. Similarly in the account of Amy and Tom not requiring specialist input is seen as demonstrative of the 'downgrading' of a (potential) genetic problem. Rather than the type of test being undertaken – which is the same in every case described – it is a question of which professionals are conducting the test that shapes how the parents understand and perceive the genetic risk.

'Receiving' results

The long delay in getting array-CGH results reported made observing parents receiving results challenging. As the infants in this study were receiving care in tertiary referral neonatal intensive care units, by the time results were available they may have been transferred to other hospitals (for specialist care, or for continuing care closer to home), they may have been discharged from hospital and be under outpatient care, or they may have died. As such, the opportunity to perform ethnographic observations was limited. Instead, I focused on the accounts of parents' subjective experiences of receiving results in both the inpatient and outpatient context.

Indicating uncertainty

They explained that one of us might have the change too and if we did then probably the result (.) didn't matter or wasn't a problem (.) I remember being a bit confused at that stage and saying to the paediatrician if you have found something how can it not mean anything

Rhodri, Father
Interview

It wasn't even mentioned that we would need to give a blood test too so when the paediatrician asked about that it was clear they were on to something (.) though no-one really explained so we just ended up thinking it was definitely something one of us had caused (.) given it to her you know

Judy, Mother
Interview

For the parents in the excerpts above, their first indication of a potential abnormal result was the request for parental samples and the issuing of an interim report. The variability in pre-test counselling means parents may – or may not – have been prepared for the need for a trio sample. Parents describe the initial difficulty in understanding how there is a possibility of "hav(ing) found something" that could "not mean anything". This is in reference to a variant of uncertain significance and the laboratory efforts to establish if this was inherited, and therefore unlikely to be of clinical significance, or having arisen *de novo*, and as such more likely to account for the phenotype. Though the diagnostic Odyssey for neonatal patients is relatively short, it is easy to appreciate the complexity of 'a finding' which is without meaning, as in the case of a variant of unknown/uncertain significance. This uncertainty, about both the (potential) meaning of a variant, and the potential that it was inherited, was described as the source of a sense of guilt for parents, as they grappled with the potential cause for and consequence of a 'finding'.

Parental experience of this process was highly contingent on who was involved in sharing and explaining results:

- | | |
|---------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Abi | We had this phone call from the neonatal unit (.) the consultant there to say they had found this result (.) <u>they</u> didn't know what it meant yet and that genetics would need to be involved and we would get booked into clinic as soon as possible (.) there wasn't really enough information given on the phone except for it was chromosome 8 (.) we were in a tailspin then thinking he had some big genetic problem |
| Richard | =I think we thought after that phone call that <u>he</u> knew what it meant but he felt like (.) he couldn't explain it (.) not actually that it couldn't be explained (.) definitely then when we spoke with the genetic counsellor before the appointment it all became clearer that this result wasn't a big deal at all that this was just normal for them to deal with these uncertain results (.) part and parcel of the test itself (.) so yeah the geneticist just made it feel like it was no big deal (.) just another thing to add on the list of things no-one can explain about Archie |
| Abi | =yeah after the NICU called we had googled something completely wrong, like a whole chromosome 8 and you couldn't survive with that (.) we were beside ourselves |

Abi, Mother and Richard, Father
Interview

In this excerpt the parents do event work: describing how they took a phone call from the neonatal intensive care consultant to inform them about a variant of unknown significance. It is framed by the parents as 'a result': a meaningful finding, regardless of the category of uncertain or unknown as framed by the laboratory reporting processes. Next arises the uncertainty: initially it is unclear whether the presentation of uncertainty relates to the uncertainty of the clinician about these types of results, or uncertainty as arising from the variant itself – it was that 'he couldn't explain it' rather than 'it couldn't be explained' and this distinction for the parent initially obscures the meaning of the result - described in this case as "not knowing what it (the finding) meant yet". There is further ambiguity as it is unclear whether the uncertainty itself is related to prognostic uncertainty: what this

'finding' means in terms of Archie's future health and development or to the categorisation of the variant as of uncertain or unknown significance. Archie's father elaborates further on this, describing how following the phone call the family were left with the impression that the variant could be described and made meaningful, however the paediatrician was unable to do this, and instead this would be done by the genetics clinic i.e the (the paediatrician) was uncertain, rather than the result itself. Understandably this caused significant anxiety, and indeed the sharing of the incomplete information about the genetic locus led to the parents incorrectly researching trisomy 8. Through the interaction with the genetic counsellor the source of the uncertainty was further characterised and ultimately routinised as a predictable, routine or ordinary artefact of aCGH: in contrast to the anticipated "big genetic problem", the finding was in fact "no big deal": "uncertain results" were to be "dealt with" and described as "part and parcel of the test itself". Uncertainty in the form of a variant of uncertain significance exists as a boundary object in a broader uncertainty around the cause, nature and prognosis of Archie's disordered and delayed development.

For other parents, the consequences of an uncertain result represent a significant disruption in an otherwise resolving diagnostic Odyssey.

No one could tell us what it would mean for him (.) it just seemed like another piece of useless information [1] but it was upsetting (.) I suppose because we felt things had been improving and that he wasn't having the problems they said he might have (.) in fact he had been discharged from neurology

Sabina, Mother
Interview

This account describes the experience of a family after an infant had microarray testing following concerns about low tone following birth. For this family, the finding of a VUS was unwelcome and unexpected. Despite initial concerns about his tone, the child had made good clinical progress, and the initial concerns about his tone and behaviour had entirely resolved, meaning he had in fact been discharged from the care of the clinical team responsible for requesting the microarray investigation. For this family, the clinical or prognostic uncertainty was largely reducing: despite his initial low tone, his development was progressing normally for his age, and his tone had improved and was considered normal. A genetic result from a test which could now be considered unwarranted was a disruption, a new, unwelcome, uncertainty which represented a setback in their journey. The *disruption* of a VUS – of molecular uncertainty – represented a further and unanticipated source of uncertainty and the need for more medical scrutiny, at just the time when the family felt that things were returning "to normal". The use of extreme case formulation – 'no one could tell us what it would mean' – no-one referring to the paediatricians involved, is later resolved through the involvement of the geneticists.

Other parents countered this, describing a relief when an uncertain finding was discovered, with uncertainty here conferring prognostic hope:

It's actually better from our point of view to not know what it means (.) the sort of lack of information about what the future will hold is a good thing in that we can assume (.) perhaps naively of course (.) that he will be fine in terms of his development and capacity to learn and so on (2) better than being told when he is just a baby (.) this is it he has this and this is what the future will look like (.) like Becky did

Lisa, Mother
Interview

Earlier this Mother described her experience of another parent's distress having received a genetic diagnosis associated with learning disability. Her own experience contrasts with this in that a variant of uncertain significance – even in light of other sources of uncertainty (particularly diagnostic and prognostic uncertainty) – maintains a sense of hope about the future, particularly with respect to 'development and capacity to learn'. A 'lack of information' – epistemic uncertainty⁵⁴ - or ignorance, is preferable to a known-known, and the negative consequences it entails or predicts.

The affective consequences of incomplete or inaccurate parental understanding when a variant of unknown or uncertain significance is found are clear: Archie's parents formulate an extreme case – they are "in a tailspin" and "beside ourselves", both of which resolved with the better characterisation of the nature of the uncertainty encountered. Archie's Father went on to describe how that affective element had formed an opportunity to feedback during an appointment about the consequences of the way in which the result had been shared and actioned.

His neonatal consultant (.) actually said (.) [turns to talk to partner] he admitted didn't he that he had learned a lot about the genetic test and about what to be prepared for by Archie's result (.) he did say didn't he [to partner] that he described it to parents totally differently now (.) to prepare them like for when they get a result like ours. It was a new test (.) they said that when they were doing it (.) so they were getting used to it too (.) when we told him about the chromosome 8 thing and getting all in a panic he was (.) he was upset that we were upset like

George, Father
Interview

The clinician concerned (Raj) offered further reflection on this case in an earlier interview.

You learn from your mistakes don't you (.) we all do. I had this family who had a VUS in their son (.) whether I explained it poorly or not they ended up with the impression he had something that was incompatible with life (.) total wrong end of the stick. I now really emphasise to parents in the pre-test counselling that we can get these results where we cannot say what it means (.) it's quite an abstract concept to have a finding on a report that might not really (.) probably doesn't (.) mean anything at all for them clinically

⁵⁴ This uncertainty could just as easily have been considered to be aleatory in nature – arising from inherent variability

Here we triangulate the consequences of a variant of uncertain significance for both the family involved, and the clinician managing this complex communication. The case is a restitution narrative: the misconception of the parents is described as a 'mistake' from which lessons can be learned. To counter this, the counselling is made more extensive: more potential outcomes are explored, and variants of uncertain significance as 'an abstract concept' are laid out clearly. This is a subtle justification for the miscommunication because the content is 'abstract' and therefore difficult to explain anyway countering the other lingering possibility is that it might mean something (developmentally) just not loss of life (extreme case)

The paediatrician uses an extreme case formulation: the phrase "report that might not really (.) probably doesn't (.) mean anything at all for them clinically". The acknowledgement of this case as a 'mistake' is a candid acknowledgement of the role of experience in developing expertise in performing counselling and admitting this mistake (and its consequences) shapes future practice. It serves as further evidence that counselling is highly contingent on the motivations, perspectives, beliefs and experiences of the professional conducting the counselling.

Complex cases have real consequences for the practices around counselling: the way in which counselling is performed is contingent on the individual and shared experiences of testing, with the extreme cases being especially formative for professionals.

Meaning and misunderstanding

Whilst some families embody the uncertainty of their uncertain variants, allowing this to cohere with their intrinsic hope, anxiety or acceptance, others focus less on the uncertainty and regard their variant as causally implicated in the problems their child is experiencing:

I mean (.) I know it is uncertain (.) but it's got to be the cause hasn't it? His problems are unique and his gene change is unique so probably (.) eventually that will explain it all I reckon

Lowri, Mother
Interview

Interviewer How do you describe the variant of uncertain significance to other people?
Lucy I just say it's a change (.) you can't really say if it is the cause of his problems or if it isn't (.) it is something though (.) and if that helps people to understand what he has (.) if it gets him help like then that's a useful piece of the puzzle
Interviewer What kind of help?

Lucy you know (.) getting his statement for school (.) getting the portage (.) before it was just he was behind on his milestones and now he also has this gene (.) it makes people listen

Lucy, Mother and Interviewer
Interview

By the ‘reckoning’ of Lowri, the association of her child's rare phenotype, alongside the finding of a variant of uncertain significance has led to a personalised interpretive process, distinct from the account of the medical practitioners involved. In anticipation of an association ‘eventually’ being found, this parent infers causality: the variant is attributed to the child’s unique problems in an (understandable) lay strategy of causal explanation. ‘Knowing’ a variant is uncertain in the face of other uncertainties complicates further the illness narrative and as such, "it must be the cause" and it is effective in supporting the family’s agenda as it “makes people listen”. For other parents, inferred causality not only simplified the illness narrative, it was seen as having real consequences in the lived experience – the life world Odyssey – of disordered and delayed development: rather than just "being behind on development" you "have a gene". There was a belief for this parent that this inferred causation mobilised or eased the challenges of getting practical assistance with schooling – having a finding "makes people listen". This ambiguity allows different versions of a molecular account to be mobilised at different times, with uncertainty existing on a spectrum of interpretation: whilst ‘a diagnosis’ can account for problems and potentially facilitate accessing support, it may also bring unwanted medical scrutiny and it may close down access to some activities and support. Different versions of an uncertain narrative can be mobilised at different times, in response to different needs.

Emphasising ‘uniqueness’

Richard I suppose as time as gone on (.) it matters less and less to have a name for what the problem is [2] At the time though it felt terrible. It felt like not having a name meant there was no treatment (.) no prognosis (.) nothing to look up online to read about. Then of course you speak to various people (.) doctors physiotherapist occupational therapist speech and language therapist and you realise there is lots to do. Lots of areas of potential progress (.) movement forward. Having a name for what Archie has (.) it doesn’t really matter

Abi =it’s unique to him (.) it’s not a bad thing that they can’t explain it (.) it’s just another thing they can’t explain (.) he’s unique

Richard, Father and Abi, Mother
Interview

Abi describes the normalization of molecular difference. In this quest narrative, multiple rhetorical devices are in use. Extreme case formulation is used to produce contrast through event work which considers the ‘now and then’ of an uncertain genetic result. The consequences of uncertainty at the time of a shared result are described as ‘terrible’ with an absence of information (‘nothing to look up

online to read about') to a quest narrative whereby this uncertainty matters 'less and less', and the focus shifts to that of prognosis. Despite the absence of 'a name' or unifying diagnosis for all the problems their child experiences, there is 'lots to do'. Parents become experts in their child, in their needs and abilities and in the challenges they face. In some way, the development of this expertise can be considered as linear, as a clearer concept of their child's abilities and challenges emerges and as parents learn to navigate the complex systems of care.

Valuing and recognising the unique problems faced by these infants was an important part of the character work performed by parents when describing the impact of a variant of uncertain or unknown significance on their child's life and care, their health and development. The multiplicity of technologies encountered on the diagnostic Odyssey, many of which fail to achieve diagnoses for these families (be they imaging technologies such as ultrasound and magnetic resonance imaging or genomic technologies such as array-CGH) represent a stalling in the process of defining problems by coming to a unifying diagnosis. As described by Bosk (1995), this 'impotence' of being unable to make a diagnosis shifts the focus, from making a diagnosis to characterising and addressing the practical challenges it poses through interventions aimed at optimising function rather than achieving a diagnosis or cure. Ultimately the need to achieve a definitive diagnosis, an explanation, is superseded by the desire to furnish their child with the care and resources as need emerge and change.

Conclusion

The data here contributes to the thesis in addressing how parents retrospectively view and reflect upon the processes and practices of testing undertaken in the neonatal period, with an emphasis on the experiences of parents who receive a result classified as a variant of uncertain significance. It is important that these perspectives are not overlooked: whilst analyses of the practices of the laboratory and clinic provide us with insights to the antecedents and consequences of uncertainty played out in these spaces, ultimately they endure longest in the lived experiences of patients and families who receive these results.

Rhetorical devices serve a number of ends in these parental accounts. Extreme case formulation is used throughout the narratives as demonstrating the uniqueness of the individual experience: often contrasting the initial disorientation arising from medical uncertainty with the acceptable lived experience of uncertainty (of diagnosis, prognosis, resource availability and many other aspects of life) in the family and the lifeworld. Event work and character work is used to justify the actions of the parents themselves and the responsible clinicians, making sense of how previous events embed

in the broader narrative or account of their child today. Illness narratives transition from chaos – a disruption – to the variable quest.

Families describe being enrolled in the inherent uncertainty of the process of testing. Parents themselves recognise genetic testing as distinctive from other forms – or technologies – of medical investigation and prognostication commonly encountered in the neonatal period. Despite clinicians' seeming discomfort with the uncertainty associated with off-target information, parents and families embrace uncertainty as mere uniqueness: another part of their journey into parenthood which deviates from the expected, anticipated or 'normal'. Uncertainty is relativised and normalised by parents and accounts which render uncertainty as enduring or inherently problematic are countered and resisted, or attenuated and minimised. Families resist attempts to enroll them into the problematic uncertainty of the laboratory and the clinic. Uncertainty is minimised and ultimately integrated into the clinical or illness narrative. Its utility relates to whether it enables access to practical support, such as education, or (un)welcome medical surveillance.

Uncertainty for parents is paradoxical, in that their 'result' is uncertain, but it is 'a result' nonetheless: a (tentative) finding in a diagnostic Odyssey – a limited category of uncertainty serving as a boundary object around which less circumscribed uncertainties abound, such as the consequences and prognosis of the manifested medical or developmental problems. Uncertainty does not exist in the absolute, and can only be experienced and recognised in relationship to order (Douglas, 1966). For parents, this order is their role as an expert in their child's own unique medical and developmental trajectory.

Just as the process of testing is highly contingent, so are parental lived experiences of uncertainty. What is clear is that the who, the how, the where and the why combine to shape these experiences. In the context of suspicion about a particular genetic disease, parents exist in a state of conscious ignorance, anticipating a particular result. In this context, the impact of a result – even an uncertain result – is mitigated by the preparedness that a result is likely (though unknown). For families in the low risk heuristic described in chapter seven, testing is a screen, anticipated as a way of ruling out potential or manifest genetic disease: these are unknown unknowns – it is uncertain if the problem has a genetic aetiology, and if it is 'genetic' it is not (yet) clear what the diagnosis or prognosis might be. Families exist in meta-ignorance, and as such, an uncertain result adds to anxiety, constituting an outcome they may never have considered. Using Smithson's taxonomy, parents can experience confusion (what does this diagnostic uncertainty represent prognostically?), inaccuracy (when parents perhaps falsely confer meaning), ambiguity (how is this result useful?) and later irrelevance and untopicality or unexceptionalism, as the meaning of genetic uncertainty fades behind the realities of the lived experience of parenting a child with additional – unique - needs.

Chapter Nine: Discussion and Future Directions

This chapter concludes the thesis, discussing the data presented in the previous three chapters in light of the earlier presented empirical literature. I consider this in four parts. Firstly, the original contributions of this work to the academic literature. Secondly, the implications of this work for both the practical delivery of clinical care and more broadly for the policy as they relate to the mainstreaming of genetic/genomic technologies in public healthcare provision. Next, I consider the strengths and limitations of the work, with special reference to the task of being an ‘insider’ when performing ethnography. Finally, I conclude with the future considerations emerging from this situated study, namely the mainstreaming of sequencing technologies such as whole exome and whole genome sequencing, the future of medical genetics as a medical specialism and the role of technologies of prognostication in the clinic.

In this thesis, I have explored how the use of array Comparative Genomic Hybridisation is organised, constituted, negotiated and performed – how it is *done* (Mol, 2002) – across three sites of genetic work, namely the laboratory, the clinic (Newborn Intensive Care Unit) and the family. Taken together, these sites and participants form an extended bioclinical collective (Bourett, 2005). In trying to provide an ethnography of a concept, chromosomal microarray and the inherent uncertainties are demonstrated as manipulated in practices, placing centrally the cross boundary elements. Array CGH represents a ‘new’ technology. In this context, ‘new’ relates to the mainstreaming of aCGH technology in broader medical practice: the process (not act) of this technology mainstreaming from the specialist, expert, genetic domain, to use in the general, clinical domain (represented here by the newborn intensive care unit). The period of implementation for a new technology into the work of a community is a valuable time during which to explore the role of the technology itself: the articulation of assumptions that accompanies the assimilation of new technologies and ways of working is quickly lost once a technology becomes routinised in practice (Berg, 1997; De Laet and Mol, 2000; Suchman, 2007). For mainstreaming, this routinisation represents the aim of the endeavour. Taken together, the thesis demonstrates the complexity of a practice that might be easily overlooked as it emerges from a single highly specialist domain and merges with the everyday routines in more general medical work and talk (Bosk, 1995; Silverman, 1987). Ontology is bound to specific sites and situations: chromosomal microarray as performed by geneticists is not the same as that performed by neonatologists. Medical work - with respect to this task and many others – cannot be considered as culturally uniform or unified.

Contributions to the academic literature

The thesis sought to reveal the situated responses to uncertainty that arise with the application of aCGH technology in the neonatal setting. In table thirteen, a 'patchwork image' (Mol, 2002: 151) of the antecedents and consequences of uncertainty across the sites of genetic work is presented. In this single entity in practice – here, called uncertainty – there are multiple, distinct entities, masquerading under the same name. The zones of uncertainty are material, interpretive and relational. Though bracketed through the places in which uncertainty emerges and is countered around the use of a single technology, the enactments of uncertainty are entangled in every action. Mol (2002) describes this as multiplicity without pluralism. Yet uncertainty is inherent rather than problematic: the explicit aim is not to reduce uncertainty, rather to appraise, adapt and communicate it.

The ethnographic observations sought to reveal enactments of this uncertainty in the practices – or work – of a variety of places and people. In doing this, there is a shift from asking how uncertainty is represented in these practices, to how it intervenes in the processes of doing of chromosomal microarray. In this sense, uncertainty comes to be a practice that ultimately interferes with and shapes other practices, including other practices of uncertainty itself. Thus, it comes to participate in reality. In focusing on practices and enactments, the genetic material itself is not the primary referential, rather the 'practitioners hands become the point of theorizing' (Mol, 2002:152). Rather than an emphasis about knowing *in* medicine (about disease), we focus instead on knowing *about* medicine, understanding how objects (such as a copy number variant, variant of uncertain significance) are enacted. Through this it is possible to understand how the practices of diagnosing and intervening are intertwined.

The nature of this relatedness can be considered through the conceptualisation presented earlier in the thesis, courtesy of Nancy Cartwright, revealing a dappled world of order:

We must combine both knowledge and technical know-how from a large number of different fields to produce a model that will agree well enough on the matter we are looking to predict, with the method of combination justified at best very locally... The point is that the claims to knowledge we can defend by our impressive scientific successes do not argue for a unified world of universal order, but rather for a dappled world of mottled objects

Cartwright, 1999:10

The knowledge and technical know-how here refers to the provision of aCGH technology by the genetic laboratory services. The model refers to the diagnostic yield – the act of diagnosis being the matter we are looking to predict. The locality can be seen on a number of levels. Does local refer to the individual patients i.e. is this test a useful test for a particular patient with these particular features? Or a group of patients with a given phenotype (intrauterine growth restriction, for

example)? Regardless the aim (or indeed, the effect) is not universal order, rather a 'dappled world of mottled objects': in the case of enormous heterogeneity, in terms of the clinical cases and places in which the technology is utilised, aCGH does not lay claims to order, rather to:

A fixed (enough) arrangement of components or factors with stable (enough) capacities that in the right sort of stable (enough) environment will, with repeated operation, give rise to the kind of regular behaviour ...

Cartwright 1999: 50

This notion of the qualifier *enough* represents the contingency in practices around doing aCGH: the aim should not be the direct replication of some 'perfect' experience of testing, or in mainstreaming the technology the aim should not be to merely replicate its 'doing' from the expert to the general domain. The practices and enactments in doing aCGH are highly situated. In mainstreaming, the contingency includes – indeed holds centrally - the behaviours of non-experts with respect to the technology. This contingency emerges as problematic and is seen across the sites of genetic work.. In the next section, I expand upon the issues documented in table thirteen: the 'patchwork image' (Mol, 2002) of uncertainty as emerging and countered in the places of genetic work.

The Laboratory

Does the mainstreaming of chromosomal microarray present a distinct or unique challenge for laboratory practice? Not really. Validity, from the perspective of defining a variant as pathogenic, benign or uncertain, remains unchanged regardless of who requests the chromosomal microarray. The sensitivity, specificity and reporting of the test, and the reporting practices of the laboratory have their own inherent uncertainty, and this remains unchanged. The laboratory (through geneticists using the technology in their everyday, routine work) has already encountered the conceptual and pragmatic challenges involved in providing a clinical aCGH service, which generates valid, significant and actionable reporting. The material and interpretive uncertainty inherent in laboratory work remains unchanged.

For the laboratory, countering this inherent uncertainty occurs primarily through the use of standards. Yet to make the technology workable - to fulfill the ultimate aim of providing a clinical report - these standards can be bypassed, where needed, through calls to expertise and experience. As such, standardisation becomes reflexive in nature. Deviations from standards can be defended through reference to expertise. For the laboratory, mainstreaming necessitates greater reflexivity, to deal with the messy entanglements that arise more frequently from wider, non-expert use of the technology. It is the magnitude - rather than the nature - of issues arising from the

mainstreaming of technology to the non-expert clinical setting of the neonatal intensive care unit that challenge, shape and change how the laboratory *do* array testing. Calls to standards do not appear to be equally distributed across the landscape of testing, rather concentrated around the laboratory and its practices. Standards are created as a means to insulate laboratory work from error and uncertainty. With respect to error, the need for standards is seen as arising from the messy practices of the clinic. Is this the correct sample? From the correct patient? Is this phenotypic information correct and complete? Scientists can only exercise expertise when these basic requirements (be they informational or quality based) are assured.

One clear situated response of the laboratory to mainstreaming is the need to govern the application of the technology when it is in use by non-expert groups. Though the technology is available (on an institutional level) to a new group of medical professionals, there is an expectation that it will or may be used inappropriately. As such, the laboratory adopts a gatekeeper role: limiting access to the resource where testing is seen to be being used inappropriately, and providing teaching and instruction on the use of the technology where it is mainstreamed. Mainstreaming represents a jurisdictional change altering the existing boundary. Rather than jurisdiction over a task, the notion of what it takes to perform a task (well) is valued. In this, what defines expertise transforms, from attribution – a formal quality reducible to interests, to a network emerging from the laboratory and encompassing paediatricians: connecting together actors, devices, concepts and institutional arrangements.

The Clinic

The way in which we talk about genetic technologies is constitutive of how knowledge and expertise is manifest in the scientific, clinical and organisational dimensions of *doing* aCGH. Talk with parents – and indeed most healthcare encounters – can be considered as moral encounters (Goffman, 1961; Silverman, 1987). Rhetorical discourse analysis reveals how talk about decisions to test (both among professionals and between parents and professionals) is persuasive, in the sense that it either seeks to encourage (or discourage) testing. This work adds to the sociological literature on talk and consent in genetic testing in how it considers a diagnostic test undertaken in a mainstreamed domain, and in how it considers genetic work as done by non-expert neonatologists. The work also seeks to explore the role of communication between professionals in the backstage, before (potential) testing is addressed with parents. Much of the uncertainty here is generated relationally, particularly with respect to what constitutes being adequately informed about genetic testing.

Is it possible, or even useful, to offer commentary about how 'well' non-expert neonatologists do consent and counselling for array CGH? Reiff and colleagues (2013, 2014) record the self-reported need for genetic education, particularly the need to develop how findings are interpreted, and how this information should be shared with families. Mainstreaming, in its attempt to quickly realise the potential of these genetic technologies, must consider first the educational needs of those who will be enrolled in its benefits and risks: ensuring they are doing array CGH *well*. What is clear is how mainstreaming parallels the issue-attention cycle (Downs, 1972). The low diagnostic yield represents the 'pre-problem', and the availability of a new technology, aCGH, is met with 'euphoric enthusiasm' by the neonatal staff. Next, come 'the costs': the generation of challenging (incidental and uncertain) results, the challenge of ensuring adequate consent, the long wait time for test results, the frustrations of a failure to make a diagnosis in spite of suspicions of a genetic aetiology for disease. These 'costs' provide opportunities for learning, reflection and changes in practice, and formed the basis of many interactions with medical genetics and the laboratory. These reaches – or disposals - from the clinic to expertise occurred less frequently as the 'post-problem' stage was established, characterised by 'spasmodic reoccurrences of interest' (Downs, 1972) only when challenging cases emerged. In this sense, the way in which clinicians learn is highly situated and highly iterative. Extreme or atypical cases form significant learning experiences for both the individual clinician, the department and the bioclinical collective (Bourett, 2005) more broadly.

What is clear from this enquiry is how the ability to tolerate uncertainty differs vastly between the laboratory, the clinic and the family. Uncertainty, for the laboratory, is diminished through strict adherence to standards, and through the 'lumping' of uncertainty into categories that can then serve as boundary objects – curated, managed, zones of uncertainty. Whilst (genetic) uncertainty is inherently problematic for neonatologists, something to be disposed of to experts, families ably weave accounts of (genetic) uncertainty into their narrative, occasionally (falsely or prematurely) inferring causality, but usually framing uncertainty as another facet of their child's uniqueness, rather than a quirk or limit of a technology and knowledge. In this sense, different members of the bioclinical collective (Bourett, 2005) are enrolled into the (different types of) inherent uncertainty of testing at the different stages in which it emerges. Subsequently, they employ differing strategies to allow them to *do* array, even given the uncertainty it entails.

In the clinic, there is a quieter call for standards to address contingency: a checklist to guide consent, for example. It is important to emphasise here that I do not seek to criticise the practice or knowledge of non-specialist groups with respect to a particular technology, moreover to emphasise the inherent complexity when technologies travel - even short distances - between and within professional groups. The case of the different consent forms demonstrates an important point about the need for diligence: despite the technology being mainstreamed, the artefacts associated with its

use did not just seamlessly transfer. In this case, the same problems had to be *re-lived* by a new group of users in order for the solution to the problem to be mainstreamed too. It must not be taken for granted that as a technology mainstreams the lessons, knowledge and experience gleaned through its use will mainstream too. It is here that medical genetics, as an expert advocate, will play a key role, but it remains unclear whether it is necessary, or indeed desirable, for each domain of practice to learn separately through the mistakes it makes. Though learning is iterative, the places of genetic work, be it the genetics clinic, or sites of mainstreaming (such as the NICU, oncology clinic or other clinical spaces) learn in silos.

The Family

Parental accounts bring this story full circle: ultimately the consequences of illness, uncertainty and genetic testing endure the longest in the lived experiences of patients and families who experience these disruptions. For the family, this technology is done with the aim of providing the greatest (currently available) possibility of providing a clinically 'useful' diagnosis. It is important to ask in this sense: what does 'useful' diagnosis represent for a family? For some, the key aim will be the ability access treatment or social support, care or specialist education. For others, it is defining the reproductive risks in future pregnancies. For some, the diagnosis – the understanding and knowing of why something has happened is central to the process of meaning making. All of these perspectives featured in the parental accounts of doing of chromosomal microarray.

Mol (2002) calls for us to address through enactments the way in which people live with a disease – the psychosocial aspects – as having an indistinct boundary with the physical realities of disease or impairment. This is especially pertinent when considering the group of children who come to have variants of unknown or uncertain significance. This form of genetic uncertainty is tolerated along with what is known about the medical and developmental challenges a child and family experience. The consequence of a VOUS may include undertaking further testing, genetic and otherwise, in both the patient (proband) as well as in other family members. A variant that has a clear classificatory or categorical implication for the laboratory may be enacted differently in family narratives, for example through the false or premature inference of causality when evidence basis for the implication of a variant is lacking. Variants of unknown and uncertain significance for the laboratory represent a shifting source of doubt and confidence (Mol, 2002) as new evidence emerges on their implication and meaning. For parents and families, there is a permanent possibility of alternative configurations (Mol, 2002), and as such, different places and participants in doing chromosomal microarray live with different realities: reality can move (Mol, 2002).

For variants of uncertain significance in the laboratory, this is a consequence of the (scientifically) underdetermined world. As more evidence emerges about particular variants, they might be reclassified as being either benign or pathogenic. For families, the underdetermined nature relates primarily to knowing what (future) life for their child will be like in terms of their health and development: values exist alongside facts (Mol, 2002). Underdetermination is dependent on largely social matters: practicalities of variant interpretation, contingencies and traditions.

In demonstrating the diverging enactments of uncertainty in relation to one test, chromosomal microarray again enacts ontology in medicine as bound to specific sites and situations (Mol, 2002). This must not be overlooked as the mainstreaming agenda moves forward. Both Mol (2002) – through ontology - and Cartwright (1999) – through machines – speak to the capacities and situatedness inherent in *doing* genetic work. Mainstreaming provides an example of how the interferences between the enactments add to the complexity of doing genetic testing or diagnosis through the use of chromosomal microarray.

	The Laboratory	The Clinic	The Family
Uncertainty	<p>The inherent uncertainty of aCGH technology</p> <p>Standards as a means of insulating laboratory work and reporting from problematic uncertainty</p> <p>Uncertainty arising from the practices of the clinic, particularly regarding the provision of (correct, complete) phenotypic information</p>	<p>Uncertainty about diagnosis and prognosis prior to and following aCGH testing</p> <p>Uncertainty about the use of a 'new' technology – what it can/cannot identify, its limitations, when it should be used, how it should be explained to parents</p>	<p>Uncertainty about diagnosis and prognosis prior to and following aCGH testing</p> <p>Tolerating uncertainty in the form of VOUS</p> <p>Assimilating uncertainty (with respect to a genetic result or diagnosis) with what is known (about the child and their medical and developmental capacities and limits)</p>
Classification and Categorisation	<p>Role of categories in producing validated, clinically useful results</p>	<p>Constituting 'the genetic baby'</p> <p>Using the categories of results generated in aCGH as 'boundary objects' in the clinic</p>	<p>'Categories' of results and (falsely) inferring causality when a variant is uncertain</p>
Expertise	<p>The process of scientists acquiring expertise in reporting the results of microarray.</p> <p>Role as 'experts' in process of mainstreaming – educating the clinic</p>	<p>The relationship between 'experts' – medical geneticists – and 'non-expert' neonatologists.</p> <p>Developing 'expertise' in the use of the technology</p> <p>The 'disposal' of problematic cases to 'expert care'</p>	<p>Distinguishing between clinicians level of expertise and experience with aCGH technology and variants of uncertain significance</p> <p>Being an 'expert parent' when diagnosis is uncertain</p> <p>Future orientated uncertainty regarding prognosis and care provision</p>

Table Thirteen: Themes emerging from the spaces of genetic work

Implications for the delivery of care and for broader policy

Genomic technologies have transitioned rapidly from bench to bedside (Khoury et al., 2012). Learning has been largely iterative, and policy development has frequently occurred post hoc; responding to, rather than foreseeing, the challenges associated with the clinical implementation of testing. Most often, this has adopted an incrementalist approach: practice or policy emerges as a series of successive, limited comparisons or attritions. What can be known ultimately shapes what will be known and policy is often playing catch up with technical abilities. For example, initially, incidental information was not reported in research studies, as the primary purpose of the sequencing was research, rather than clinical care. As such, when testing was introduced on a clinical basis, off-target information was also not reported. As this was ethically contentious, reporting was then encouraged, occurring in an ad hoc way between and within centres. To address this, the ACMGG developed a list of off-target variants in sequencing which should be reported, owing to their clinical validity and actionability (Green et al., 2013). Though contentious, this list sought to standardise practice around an evidence base, facilitating laboratory reporting practices which evolve in a coordinated and concordant way.

The 100,000 Genomes Project sought to embed sequencing technologies in routine medical care. Yet this in itself was contentious – the NHS was a partner in a project with significant research and commercial aims, and the nations with devolved healthcare (including Wales) were not included in the early part of the scheme, meaning patients could not easily access testing. It was appointed as a commercial limited company, rather than a more typical arms length body. There have already been multiple contributions emerging from this research with respect to how paediatricians and neonatologists prepare for the impact of genetic/genomic technologies in their work (see appendix B and F). A full consideration of the implications of the genetic/genomic revolution for healthcare practice and policy lies beyond the scope of this thesis, however there are some important considerations emerging in respect to the clinical testing in the newborn intensive care setting which are outlined below, namely the education of non-expert staff and the special status of children.

Educating (non-expert) professionals for the genomic revolution

Mainstreaming is contingent on non-expert medical professionals, such as paediatricians, developing adequate expertise and confidence in the application of genomic technologies to clinical care. Ultimately, this will involve managing not only the straightforward, everyday case, but also the

more practically, ethically and socially challenging aspects of clinical genomic care. In chapter five, I explored the challenge of developing (sufficient) expertise in genetic work. In order to negotiate the complexities of engaging with chromosomal microarray and other genomic technologies emerging for use through mainstreaming, it is essential to consider the educational needs of professionals. Health Education England through the Genomics Education Programme is responsible for *'upskilling existing staff so they can make the most of genomic technologies in their work'*⁵⁵. Little guidance has been issued to medical schools and accrediting medical colleges about what the nature of this 'upskilling' should be. The Royal College of Paediatrics and Child Health has commissioned a project to look – in part – at the role of genomic innovation in the work of the future paediatrician⁵⁶. In recognising that clinician learning is iterative, it is important to recognise that practitioners must not merely be told what to do, but engaged in the process of how their work can be supplemented and enhanced by doing genomics well.

As the scope and limits of the role of paediatricians and other non-genetic clinicians evolves, there will be a need to ensure a policy vision and educational emphasis in both undergraduate and postgraduate education which adequately addresses the needs of the workforce and the work they will encounter. Whilst here the focus is on the role of non-expert clinical staff, the need for an expanded genetic/genomic workforce, in particular for bioinformaticians and genetic/genomic counsellors who work outside of the traditional departmental silos of National Health Service working, bridging the gap between laboratory work, (specialist) genetic/genomic knowledge and (mainstream) clinical practice.

Children as a vulnerable group

The additional considerations with respect to the genetic testing of children are well documented (BSHG, 2010). This relates particularly to the antecedents and consequences of informed consent, with the notion of incidental/off-target and uncertain information being especially pertinent. How can we balance the calls for opportunistic screening (revealing off-target information) to parents and family with the attempts to generate clinically actionable information? How can health systems ensure that the needs of individuals who have had testing continue to be met i.e through the responsibility to re-contact? Meaning-making involves not only addressing material uncertainty

⁵⁵ See <https://www.genomicseducation.hee.nhs.uk/about-the-programme/>

⁵⁶ <https://www.rcpch.ac.uk/work-we-do/paediatrics-2040>. I am currently working as an advisor to the innovations in genomics stream of this work.

through testing and interpreting, but also through relational means. What are the requirements of health systems to ensure parents share important results with children? How can health systems put in place safety nets to ensure significant, actionable results are known to individuals and health systems when needed ?

As sequencing technologies are bringing real clinical benefits, it is now matter of justice that we ensure equity of access to new genetic technologies (McClellan et al 2013). In the context of an unwell infant with a difficult-to-make or elusive diagnosis, whole genome or whole exome sequencing may give the best opportunity to make a timely, important diagnosis. Yet, the decisions about testing and about the disclosure of results will not be taken by the child or by professionals answerable to the child, so there may be grounds for building in additional protection beyond that appropriate when the patient is a competent adult. Standard practice is not to generate or disclose to families genetic information about a child that is not relevant to their health care at that particular time or that will not become apparent before the child has become sufficiently mature to have a voice in the decision about testing. Predictive testing for adult-onset disease is generally avoided unless there are (well-evidenced) health benefits to be gained from treatment, screening or prophylaxis commenced in childhood (BSHG, 2010). This corresponds to respect for a child's right to an open future (Feinberg, 1980). Useful perspectives on the genetic testing of children may gained by assuming a best interests position with respect to the care of the child. The problem then, however, becomes the difficulty in distinguishing the best interests of the child from those of her family, especially when she is very young or if she is affected by a serious and permanent cognitive impairment so that independence is unlikely ever to be achieved (Birchley 2010). Genetic testing in those circumstances may not then act to constrain an 'open future' in so far as it is already severely constrained by other factors.

Challenging incidental / off-target and predictive information

Care should be taken that the use of sequencing technologies do not pre-empt or overlook usual processes of decision-making about testing a child for known familial conditions. Some of the information generated about children as incidental information through genomic testing is especially difficult. Whilst generating such information may be helpful if there is no previous awareness of the disorder in the family (especially for familial cancers and inherited cardiac conditions), it is none the less challenging to know how the disclosure and management of information should be performed and acted upon.

Parents can sometimes regret the decision to test their young children for their family's known autosomal dominant mutation associated with cardiac disease, especially when the child is at risk of sudden death or may have difficulties obtaining life insurance (Hendriks et al 2005; Geelen et al 2011, 2012). It may still be important to perform the genetic testing at some stage but it is often possible to defer this by monitoring a child medically without necessarily testing genetically, although there may be additional health care costs as a result (for example, the echocardiogram that would in hindsight be unnecessary in children without the relevant mutation on testing). Knowing that a child is at substantially increased risk of a psychotic illness, such as schizophrenia, is a challenging matter for parents to deal with. Part of the difficulty can be the guilt of having transmitted the risk to the child - whether it has been inherited or has arisen *de novo* and also the concern about how to live as a family in such a way as to minimise the risk of the child developing psychosis. Must one always concede to the child so as to avoid conflict? Managing conflict must be learned within the relatively safe context of the family, if a child is to negotiate the outside world with any success - but what then should the family do differently to take this risk into account?

As health systems and providers such as the NHS adopt genomic strategies, there must be policy and perhaps more importantly resource to support the additional demands that generating this type of information will necessitate.

Newborn Screening

Tandem mass spectroscopy (TMS) has dramatically expanded the number of conditions it is possible to identify through screening, and the sequencing technologies seem set to transform newborn screening further. The medical benefits of early, pre-symptomatic diagnosis (using newborn screening) have in the past been very clear but early diagnosis of some of the 'newer' disorders (new in that it is possible to make a diagnosis during newborn screening) is perhaps marginal and there is substantial scope for creating new 'liminal' categories of children who are 'patients in waiting' (Timmermans and Buchbinder 2010) and generating distress and anxiety for parents and families. Families' responses to an early diagnosis need to be assessed carefully and, where medical benefits are unlikely, then real parental autonomy of choice must be enabled about whether to include each child in screening for ever-expanding disease categories, for example newborn screening for Duchenne Muscular Dystrophy. Some families will want the early knowledge for its own sake or for reproductive planning, while others would not to know. Policies will be decided along international politically driven preferences, based on what can be achieved, what can be funded, and what public pressure demands. Recognising that existing screening criteria will not neatly apply to what is possible with the expanding and affordable availability of sequencing

technologies, there is an urgent need to consider the implications of this, and policy which supports an evidence-based approach.

Study Strengths and Limitations

The study presents a situated account of mainstreaming a genetic technology in the clinical domain. Lingering in each of the areas of genetic work can be presented as both a strength and limitation of the study. Any single one of these sites (the places of genetic work) or any component of the extended bioclinical collective (Bourett, 2005) would have constituted a data source rich enough to form a whole, if not multiple, doctoral projects. Yet it seemed impossible to consider a cohesive and comprehensive account of the inherent uncertainty of the process without dwelling, for some time at least, in all three. This was supported by Bourret's (2005) notion of the extended patient: defined by the articulation of clinical data (the disease/disorder), the biological data (the genes and their aberrations) and the social data (family links and relationships). Only this holistic consideration would allow the interrelatedness of the issues emerging from uncertainty, processes of classification/categorisation and expertise to 'travel' between these sites and spaces of genetic work: acknowledging how cross-boundary consequences, rather than the bracketing of practices in which objects are handled, can have far reaching effects (Mol, 2002: 4). Yet dividing time and attention between three places and groups limited what could be achieved, seen, recorded and analysed, and indeed perhaps did not do justice to the rich complexity of each site, its members and the interplay with other places of work.

The applied the Social Construction of Technology framework in a novel way, considering a (relatively) non-contentious technology establishing itself in a new context. The Social Construction of Technology also has limitations. One of these is the way in which social constructivist approaches are considered superficial in their focus on how the immediate needs, interests, problems and solutions of chosen social groups influence technological choice, but disregarding any possible deeper cultural, intellectual or economic origins of social choices concerning technology. In this work, chromosomal microarray was the only technology available to the professionals working in the newborn intensive care, and in the face of a lack of a 'choice'; many of the intellectual and economic origins were rendered less important. One voice which is missing in this work is that of the individuals having a genetic test, the children themselves: only in the future will it be possible to study the impacts of incidental information revealed through testing, or the consequences of uncertainty when this endures. It will be an important priority for empirical research to consider the ethical, social and legal aspects of sequencing technologies for children in particular, and the consequences of results generated throughout the life course. Social construction of technology will form a useful framework to consider how and which sequencing technologies (whole exome/whole genome/gene panel testing) are taken up, and in what way, in clinical practice.

The work is an important contribution to the literature on communication in the newborn intensive care environment. Particularly, it addresses the need to move the analysis of communication in the neonatal intensive care setting beyond that of communication about end-of-life decision making, and demonstrates the way in which triangulation of data collection methods, particularly recordings of naturalistic data and interviews, allow for the exploration and justification of practices and perspectives with greater depth. Ethically oriented ethnography provides the ideal means by which to perform these analyses.

Another important consideration is that of how my professional role – as a doctor working in the paediatric setting – shaped the way in which the data was collected and analysed. In the next section, I consider this, in a reflection on the notion of ‘insider research’.

A Reflection on ‘Insider Research’

The qualitative researcher’s perspective is perhaps a paradoxical one: it is to be acutely tuned in to the experiences and meaning systems of others – to indwell – and at the same time to be aware of one’s own biases and preconceptions which may be influencing what one is trying to understand.

Maykut and Morehouse, 1994: 123

There is no neutrality. There is only greater or lesser awareness of one’s biases. And if you do not appreciate the force of what you are leaving out, you are not fully in command of what you are doing.

Rose, 1985: 77

The centrality of the beliefs, values and experiences of the researcher in how qualitative research is conceived, conducted and interpreted has led to the popular judgment that it is best performed by those naïve to or unfamiliar with the social setting in question. Prior knowledge and experience is seen as acting as a barrier to the rigour, legitimacy or trustworthiness of the researcher, despite the methods which exist within the critical analysis of qualitative methodology to enhance reliability, in particular reflexivity, defined as the process of acknowledging and documenting the role of the researcher as an ‘instrument’ in qualitative research. The debate around ‘insider’ and ‘outsider’ roles when performing qualitative research continues to be the source of significant methodological debate, centered on whether qualitative researchers should be members of the population they are studying, or whether they should not. Whilst post-modernist approaches emphasise the importance of the personal context and demographics of the researcher – for example, in terms of their gender, class or ethnicity – the potential impact of membership identity in both the conduct of research and later, narrative interpretations, is of obvious relevance here as my (prior) situational identity in this

context, as a junior doctor, interacts with my (new) situational identity as an observer and qualitative researcher – a challenge described as the ‘ultimate existential dual role’ (Adler and Adler, 1987).

‘Insider’ research refers to performing research with populations of which you are also a member (Kanuha, 2000), such that the identity, language and experiential base of the researcher and subjects are shared (Asselin, 2003). Being an insider provides multiple benefits. Access is easier, as the practices and procedures of the environment and social group under investigation is known. The language is familiar, meaning that focus can readily attend to relevant details, rather than having to decipher which information may be important. Perceptions of shared identity may mean that there is a faster and more complete acceptance of the researcher by the subjects, enhancing the depth and breadth of the data collected. Commonality allows a starting point to conversation, as well as privileged access to opinions, thoughts and vulnerabilities, which might be closed to ‘outsiders’. As a junior doctor working in the paediatric setting, you are frequently asked the question ‘do you have children?’, demonstrating that even as a supposed ‘insider’ in this context, to the parents and families of patients, the perception is that of being on the outside of their experiences, demonstrating that an individual’s position as being on ‘the inside’ or ‘the outside’ can also be fluid within a single setting.

Yet there are also important potential disadvantages. Notions of shared identity as experienced by participants may mean that potential data is seen as mundane and therefore not worthy of expression. Alternatively, assumptions of understanding are made – a supposedly shared membership of a key category means that experiences or decisions may not be fully explained or accounted for.

Ben you understand .. [coughs], you’re one of us ... (pause 8 seconds)
Researcher try to explain?
Ben you’ve faced it yourself on the ward, trying to know ...it’s difficult to unpick and to
 decide how much information is too much [pauses] when trying to explain something
 in depth is just muddying the water for the family ... giving them too much to consider
 at a time when we ought to take some responsibility for deciding what investigations
 are best, what tests will move things forward. You know we don’t always do a good
 job in terms of people being fully informed, you know, informed consent as defined by
 the GMC or a lawyer [...] or an ethics book [...] or you for that matter [both laugh]
 would define them, but we do enough given the circumstances at the time, given our
 assessment.

Ben, Neonatal Registrar and Researcher
Interview

Here the participant, an individual whom I have not worked alongside and do not know socially, but who is also undertaking training in paediatrics assumes a shared understanding whilst also demonstrating ambivalence about my role – in one instance, I am a clinician, experiencing the same

challenges as he does, whilst immediately afterwards, I am a researcher and an enforcer, seen as someone who would have a differing perspective or standard with regard to what defines good practice with respect to informed consent.

Researcher I find it interesting that you would compare me to the GMC [...] or an ethics book
Ben No offence [laughs] ... I just mean you know a lot about it because you are interested in it [laughs] you must think it is something we should do better or differently. I mean that's the point of your research, right? I wouldn't want to tell just anyone that we do this badly ... but you understand how it is with the pressures and the demands with poorly babies. It's not always clear cut as to how much information would be helpful.

Ben, Neonatal Registrar and Researcher
Interview

Here, my role as an insider means this subject is able to (seemingly slightly ashamedly) disclose his own feeling that 'we do this badly'. Whilst as a researcher in this context I risk 'role confusion' – where a researcher responds to participants or analyses data from a perspective other than that of a researcher (Asselin, 2003), participants also experience this same confusion with regard to my role – which acts as both an enabler and barrier to effective data collection. My identity work was both performed and ascribed.

Dichotomist perspectives on the insider / outsider debate are reductionist and fail to acknowledge the challenges and benefits of having a position in both the research world and the social world under examination. Just as holding membership of a group does not mean a complete likeness with the group (which will not be homogeneous in terms of the individuals within it), so the not being in a group does not assure that there will be sufficient difference, or expertise, for the group non-member to characterise the group accurately. As such it is paradoxical that binary alternatives that narrow the opportunity for understanding experiences should be applied. The dualistic approach to these roles represents the powerful and persistent tendency to frame complex issues as a struggle between two opposing sides as opposed to recognising that the relationship, when appropriately managed, need not be one of antagonism, particularly in qualitative research, where reflexivity and an appreciation for the complexity of the human experience is central.

What next? The Future of Discussions and Research

In considering what I have engaged in, it is also possible to see what is left undone (Mol, 2002). For many of the issues I consider here, the character of the problems will remain the same even as new sequencing technologies and applications emerge. The zones of uncertainty will continue to be material, interpretive and relational in nature. Rather, it is the scale of magnitude that will dramatically expand. In concluding this work, a number of important questions emerge in relation to the findings, representing opportunities and challenges for future work.

The clinical use of sequencing technologies

The clinical use of whole genome and whole exome sequencing methods will raise many of the same questions addressed here: how can genomic technologies be best employed for clinical care? How can this care be realised in practice, through mainstreaming or otherwise? The promise of clinical genomics is to curtail the diagnostic Odyssey and indeed, even provide prognostic information to inform screening and potential prophylaxis, and pharmacogenetic information that may guide drug choices and treatment more broadly. The nature of the social, ethical and legal considerations will not change, and these considerations rather will increase in magnitude, so that many of the themes encountered here will remain entirely relevant.

An important question relates to the use of whole genome technologies in the newborn intensive care. The scope of uncertain and off-target genetic information associated with the use of these technologies is an order of magnitude beyond what is currently encountered. How can this be managed in a concordant way? Will whole genome sequencing technologies – even when established as the standard first line genetic investigation – always be appropriate for this particular population, with the inherent challenge of proxy consent and (future) autonomy? This speaks to Mols' (2002) notion of autonomy as challenged by the routine normative decision-making in healthcare. Whilst 'free' or autonomous patient choice between the various genetic tests available – a so-called market model – may not support evidence-based testing, a civic model in which WGS is the preferred or standard test merely because it is the expected first line investigation at an organisational or policy level is also unsatisfactory. As institutional preferences emerge – usually based on cost and speed – the perspectives and vulnerabilities of specific patient groups must not be overlooked. Whilst an ethical and philosophical discussion is beyond the scope of this thesis, the isolation of moments where choices about types of testing are made should not separate decision making from the layered and intertwined histories which inform them.

It is also important to consider the ethical notion of justice. As sequencing technologies are introduced in NICU, they are largely done so through trio methods. Here, samples from both parents are required to 'filter out' the heterozygous inherited variants that are less likely to account for disease presentations in the neonatal period. As a result, when samples are not available from both parents, infants may be excluded from access to sequencing tests on both a clinical and research basis, threatening equity of access.

The future of medical genetics and the professional consequences of mainstreaming

Despite predictions of the stability of the clinic in terms of its cultural forms and practices (Atkinson, 1995), mainstreaming does represent a significant change in the relationships between professionals and specialties, crossing and merging traditional boundaries and professional cultures. As institutional orders change, the ways in which professional knowledge is constituted, deployed and defended will change too (Sarangi and Roberts, 2005). What will this mean for the work of medical genetics? When the potentials of mainstreaming are realised, what work will remain for medical geneticists? How will the education of the non-expert clinicians take place, and how will educationalists and professional bodies respond to and ensure that adequate expertise exists (see above)?

Technologies of prognostication

Genetic technologies can be considered in the broad grouping of technologies that provide – through diagnosis – prognostication about the potential future health, well-being and development of children. How are technologies of prognostication used in the critical care setting? How do parents respond to their use? As sequencing technologies come into clinical use, the diagnostic yield will increase, likely in excess to our ability to understand the consequences and implications of the particular variant for health and well-being. How will this be managed in the clinic? What is it possible (and useful) to know? When known, what clinical advantage is generated through the availability of this knowledge – is it purely economic or are there positive benefits in terms of mortality and morbidity too?

For mainstreaming of the new genetic technologies to be encompassed in the everyday, mundane work of the non-expert, non-specialist clinic, a reasonable approach has to be developed that does not deny patients access to an important diagnostic tool because their parents have difficulty understanding degree-level molecular biology. Equally, it will be important to ensure that the parents (and patients too, where feasible) have a pragmatic understanding that genome wide methods

(including both aCGH, and the high-throughput DNA sequencing technologies) might yield clear diagnostic information, or might add nothing or it might identify a genetic change of uncertain significance. Parents (and patients) should appreciate that further investigations on other members of the family may be needed to assist with interpreting the findings. They should also understand that other findings may arise, unrelated to the reason for testing but potentially important for the health of the child and perhaps others too. The need is to find a position in which the pragmatic and ethical concerns of the laboratory, clinic and patients are central, yet do not inhibit the *doing* of genetic technologies for maximum patient benefit. Ultimately, for the benefits of genomics in health to be realised, genetic and genomic practice will need to become part-and-parcel of every area concerned with the practice of medicine. Spectrums of certainty and utility will enable the work of the sequencing technologies to be rendered applicable and acceptable in everyday medical care, whilst spectrums of expertise will be needed to ensure that all parties do in fact benefit from their application in practice.

So what of the 'rigidly defined areas of doubt and uncertainty' demanded by Vroomfondel? In *The Hitchhikers Guide to the Galaxy*, Link and Fook are using Deep Thought, a supercomputer 'the size of a small city... the greatest most powerful computer in all time'. As they use the computer to try and elucidate the answers to questions of 'life... the universe.... everything', they are interrupted by the philosophers Majikthise and Vroomfondel, who exclaim that the problem is 'demarcation' here, rather than classification. Referring to the roles carried out by people, as opposed to computers, they exclaim 'you just let the machines get on with the adding up.... And we'll take care of the eternal verities'. Whilst data and bioinformatics also underpins the *doing* of genetics and genomics in clinical medicine, it is people, from all parts of the extended bioclinical collective (Bourett, 2005) who will address, enact, manage and tolerate the uncertainties, or 'eternal verities', intrinsic in the messy – necessary - *doing* of genetic work.

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Appendix C

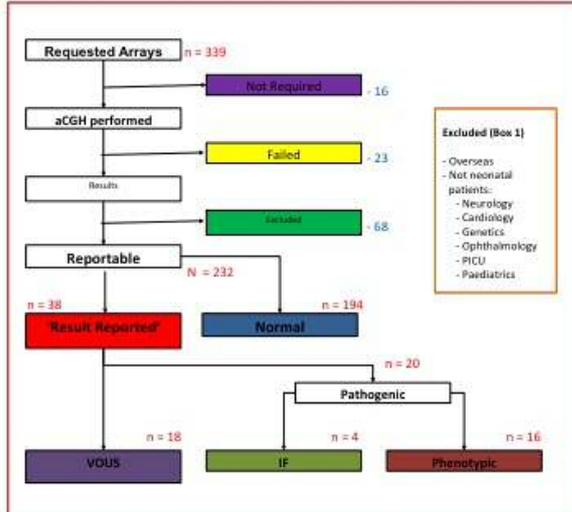
Poster Presentation: Consent in (dis)array: bioethical and clinical considerations in the use of genome-wide technologies in the neonatal populations. Presented at the British Association of Perinatal Medicine, Birmingham, UK, May 2017.

Consent in (dis)array: bioethical and clinical considerations in the use of genome-wide technologies in the neonatal population

Dr Katherine Burke, Wellcome Trust Fellow in Society and Ethics, Cardiff University and Paediatric Registrar, Wales Deanery and Prof. Angus Clarke, Professor of Medical Genetics, Cardiff University. katherine.burke@wales.nhs.uk

Background

Despite recommendations around shared decision-making, parents continue to report a poor experience of participation in decision-making processes when their child is receiving neonatal care (POPPY Steering Group, 2009). Empirical work on informed consent and decision-making in Neonatal Intensive Care Unit has focused almost exclusively on end-of-life decision-making. The use of genome-wide testing methods is now attracting significant bioethical and sociological consideration: given the endless variety of possible outcomes following genome-wide testing (for both the proband and relatives) is informed consent even achievable (Dundorp et al, 2012)? When decisions to perform genetic testing are being considered, how do medical professionals engage parents and carers in processes of 'informed' consent?



Methods

Mixed methods : analysis of typologies of results generated through aCGH in neonatal patients (All Wales Regional Genetics Laboratory), alongside situated empirical study uses transcriptions of real-time audio-recorded consultations between families with infants in the Neonatal Intensive Care Unit (n=22), in which proposed genetic testing was the subject of the interaction. This was supplemented with data from semi-structured interviews with neonatal professionals (n=17) involved in consenting families for genetic testing

Results

- Over 18 months, 339 arrays were requested
- 16 were not required (previous tests sufficient/breach of protocol)
- 23 arrays failed quality control (sub-optimal results/ issues with DNA)
- 68 results were then manually excluded (see **Box 1**)
- This left 232 relevant 'reportable' aCGH results, of which
 - **20/232 were pathogenic, giving a pathogenicity rate of 8.62%.**
 - 4/20 were incidental findings (not 'matching' the phenotypic presentation)
 - 16/20 matched the phenotype (pathogenic results)
 - **Variants of Uncertain Significance accounted for 18/232 (7.76%).**

Discussion

Previous analyses of genetic testing in the neonatal population has been limited not differentiating between subgroups of 'reportable' variants, particularly variants of uncertain significance and incidental findings. These more challenging results have significant life-long implications for patients: the scale of which is set to increase as sequencing technologies replace dosage methods as a first-line genetic investigation in the clinical setting.

Analysis of the 'consent conversations' demonstrated how consent for genetic investigations is *recruited* rather than *negotiated*: decisions around the need for testing are deliberated and conceived in the work of neonatal professionals, and then subsequently proposed to parents. Neonatal professionals use schema emerging from clinical assessments of the risk of genetic abnormality to influence the form and function of the consent conversation. The interaction varies between one in which the purpose is to merely relay basic information (where testing is seen as a 'screen'), to an extended engagement with the potential outcomes of genetic testing (and the implications for the proband and relatives) when the risk of identifying a pathological variant is seen as being high. Professionals see the process of communicating uncertainty as moral work.





Private and Confidential

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Your Ref:
 Our Ref: 101555/Z/13/Z

Friday 21st June 2013

Dear Professor Morgan

I am writing to let you know that the Trust has agreed to award Cardiff University a grant of up to £170,951 to provide a Society and Ethics Research Fellowship for Health Professionals for Dr Katherine B Burke, over 36 months for her study entitled 'Consent in (dis)array? Genome-wide testing in the paediatric setting: bioethical and clinical perspectives on informed consent in practice', under your sponsorship.

The grant has been given a notional start date of 01/09/2013 and is intended to provide support as follows:

RING FENCED FUNDS

	Amount
Basic Fellow	
Dr Katherine B Burke	144,518
Fees	
PhD Student Fees	12,479
Subtotal	£156,997

TRANSFERABLE FUNDS

	Amount
Inflation Allowance	214
Flexible Funding	335
Travel To Meetings	
Allowance	4,500
Training	
Health Communication summer school, Cardiff	500
Intro to Qualitative Interviewing, Oxford	450
Analysing Qualitative interviews, Oxford	450
Intro to Media Content Analysis	275
Research Expenses	
Audio Equipment	200
Transcription Time (@80 hours)	4,560
Computer equipment	1,500
Software (Nvivo 9)	370
Printing (information leaflets etc)	600
Subtotal	£13,954
Grand Total	£170,951

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The Wellcome Trust is a charity registered in England and Wales, no. 210153. Its sole trustee is The Wellcome Trust Limited, a company registered in England and Wales, no. 2711000 (whose registered office is at 215 Euston Road, London NW1 2BE, UK).

Ring-fenced funds may only be used for the purpose stated above. The budgets for transferable funds are indicative only and movement of funds between these budget headings is allowed without prior permission from the Trust. However, prior permission is required if the funds are needed for any other purpose, i.e. for expenditure under any budget heading not specified in this Award Letter.

The ring-fenced funds provided for Dr Burke include a basic starting salary of £36,777 per annum, as set by the Host Organisation, plus inflation.

The grant is cash-limited; supplementary funding will only be provided in specific circumstances (see Information to Note).

The Trust anticipates that Research Training Fellows will be able to focus on their research throughout the duration of their fellowship. Clinical duties should be restricted to a maximum of two programmed activities per week, where appropriate, and only if agreed by the supervisor.

We actively encourage our researchers to interact and collaborate, build networks and engage with people about their research. Whether Dr Burke is new to public engagement or already has expertise, the Wellcome Trust can help. Details can be found at <http://www.wellcome.ac.uk/Education-resources/Engagement-with-your-research/index.htm> or please contact us as engage@wellcome.ac.uk.

We would remind you that with regard to clause 6 (iii) of the Grant Conditions, all research papers that have been accepted for publication in a peer-reviewed journal, and are supported in whole or in part by Wellcome Trust funding, must be made available from Europe PubMed Central as soon as possible, and in any event within six months of publication, in line with our Open Access policy <http://www.wellcome.ac.uk/About-us/Policy/Spotlight-issues/Open-access/>.

It is a condition that the Head of your Host Organisation will administer the grant in accordance with the purposes for which it has been awarded. I should be grateful if your Organisation would confirm, in writing, the acceptance of this grant on the conditions detailed in this letter and the notes. A Grant Start Certificate for this purpose can be downloaded from the Trust's website (see Information to Note). The grant cannot be activated until this confirmation has been received. The Trust will not accept liability for any expenses incurred on the grant until a signed Grant Start Certificate has been returned.

When accepting this Award of Grant, the Organisation recognises that the UNDERTAKINGS given by the Organisation and others at the time of signing the Application Form are "conditions precedent" and the Organisation will ensure that they, their agents, servants, employees and students will continue to abide by the undertakings given throughout the lifetime of the grant.

Copies of this letter and the notes should be forwarded to the Head of your Host Organisation, your Head of Procurement, your Research Grants Office and your Finance Officer. For payment of grant funds see Information to Note.

If you would like to discuss any administrative issues regarding the grant, please contact me at this office.

Yours sincerely



Philomena Gibbons
Head of Operations
Medical Humanities and Engagement Division

Appendix E

Permissions and Project Information

- E1 (a) Approval from Clinical Ethics Committee (Wales C) and (b) Response
- E2 (a) Invitation letter and (b) Participant Information and Consent form for Parents and Guardians
- E3 (a) Invitation letter and (b) Participant Information and Consent form for Medical Professionals

Appendix E1(a)

Part of the research infrastructure for Wales funded by the National Institute for Social Care and Health Research, Welsh Government.
Yn rhan o seilwaith ymchwil Cymru a ariannir gan y Sefydliad Cenedlaethol ar gyfer Ymchwil Gofal Cymdeithasol ac Iechyd, Llywodraeth Cymru



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Wales Research Ethics Committee 1

10 April 2014

Dr Katherine Burke
Academic Clinical Fellow in Paediatrics
Cardiff University
Room 2.25, Institute of Medical Genetics
University Hospital Wales, Heath Park
Cardiff
CF14 4XN

Dear Dr Burke

Study Title: Consent in (dis)array? Genetic and genomic testing in the non-genetic setting
REC reference: 14/WA/0097
Protocol number: SPON 1267-13
IRAS project ID: 142382

The Wales REC 1 reviewed the above application at their meeting held on the 10th April 2014.

Thank you for attending to discuss the study, the clarification that you provided was most helpful.

Documents reviewed

The documents reviewed at the meeting were:

Document	Version	Date
Covering Letter		01 January 2014
Evidence of insurance or indemnity	Cardiff University	26 July 2013
Investigator CV	Dr K. Burke - No date	
Letter from Sponsor	Cardiff University	02 January 2014
Other: CV	Prof A Clarke - No date	
Other: Referee Feedback 1		
Other: Referee Feedback 2		
Other: Welcome Trust letter re funding		21 June 2013
Other: Clinical Vignette	1	01 January 2014



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Cynhelir Cyswethrediad Gwyddor Iechyd Academaidd y Sefydliad Cenedlaethol ar gyfer Ymchwil Gofal Cymdeithasol ac Iechyd gan Fwrdd Addysgu Iechyd Powys
The National Institute for Social Care and Health Research Academic Health Science
Collaboration is hosted by Powys Teaching Health Board



Other: Protocol Flowchart	1	01 January 2014
Other: Invitation Letter - Clinicians managing IF/VUS	1	01 January 2014
Other: Invitation Letter - patient/families undergoing genetic testing	1	01 January 2014
Other: Invitation Letter - clinicians performing genetic testing	1	01 January 2014
Other: Invitation Letter - Patient - Known IF/VUS	1	01 January 2014
Other: Interview Schedule - Clinicians Performing Genetic Testing	1	01 January 2014
Other: Interview Schedule - Families with known IF or VUS	1	01 January 2014
Other: Interview Schedule - Families undergoing genetic testing	1	01 January 2014
Other: Interview Schedule - Clinicians managing IF or VUS	1	01 January 2014
Participant Information Sheet: Information Sheet for Clinicians managing IF/VUS including consent	1	01 January 2014
Participant Information Sheet: Patient Information Leaflet (genetic test) including consent	1	01 January 2014
Participant Information Sheet: Information Sheet for Clinicians Performing genetic tests including consent	1	01 January 2014
Participant Information Sheet: Patient - Known IF/VUS including consent	1	01 January 2014
Protocol	1	01 January 2014
REC application	3.5	26 March 2014

Provisional opinion

The Committee noted that this was a multi-centre qualitative research project which will question how clinicians in the UK, who are not genetic specialists, manage the challenge of genomic technologies in the 'real life' clinical setting, when array comparative genomic hybridisation (aCGH) and more broadly, genome wide investigations, are indicated for a patient or family.

The Committee noted that the study was being carried out as part of an educational qualification for a PhD sponsored by a Wellcome Trust Society and Ethics Grant for Medical Professionals.

The Committee noted that potential participants would initially be identified and approached by healthcare professionals involved in their care.

The Committee noted your clarification that the protocol has been developed with consideration of the NHS guidance on information governance. At no point during the process will the study team access patient information without the express knowledge and consent of the patient/family participant. It was also noted that Clinicians will be informed about the study through publicity, word of mouth, or when a study information leaflet is enclosed with the results of a patient's investigation. It was further noted that through semi structured interviews with clinicians and patients / families, that you will look more closely at the issues around incidental findings and variants of unknown significance, the management of which remains difficult and contentious from a practical, ethical and sociological perspective.

The Committee noted that potential participants will be provided with written information about the purpose of the study, why they have been invited to participate, who is conducting the research, how the data would be used and what participation will require of them. They will also be given the opportunity to ask any questions about the study. Written consent will be obtained prior to participation in the study. It will be made clear throughout the study that participation is entirely voluntary and that they can withdraw at any point for any reason.

The Committee noted that no intervention or procedure, which would normally be considered a part of routine care, would be withheld from participants.

The Committee noted that the Cardiff University would be acting as sponsor for the above study in accordance with the Research Governance Framework.

The Committee noted that the sponsor had signed the declaration in the application form to confirm that an appropriate process of scientific critique had demonstrated that the research proposal is worthwhile and of high scientific quality and that the necessary insurance or indemnity arrangements will be in place prior to commencement of the research.

The Committee also noted that the project has been subject to review by the Wellcome Trust, who are supporting this work via a Society and Ethics Award for Clinicians in training.

The Committee noted your clarification that as you are discussing potentially upsetting diagnosis, such as autistic spectrum disorders or developmental delay, you will have information of relevant support groups available should participants wish to have them. It was also noted that where participants have become distressed in discussing a diagnosis or condition, this will be fed back to the responsible clinician for further consideration and the need for further support.

The Committee noted from Q (A43) of the application form that study data would be stored for less than 3 months after the end of the study. The Committee asked that you ensure that all data is recorded, collected, stored and destroyed in line with the Data Protection Act (1998).

The Committee agreed that they would be content to give a favourable ethical opinion of the research, subject to receiving a complete response to the request for further information set out below. Authority to consider your response and to confirm the Committee's final opinion has been delegated to the Chair.

Further information or clarification required

1. The Committee noted that you had been named as the Chief/Principal Investigator on the application form however Professor Angus Clarke was named as Principal Investigator on the Information Sheets? Please either update the information sheets or provide clarification?
2. The Committee noted your clarification that patients will not be approached on their first appointment and they will be aware that they will require genetic testing and asked that you confirm this.
3. The Committee agreed that information relating to the study should not be sent out in the post to any patients. The Committee was of the view that the invitation letter should be merged with the information sheet to create one new information sheet.
- 3.1 The Committee agreed that once the clinician has discussed the genetic testing with their patients only then should patients be informed about the study.

- 3.2 It was agreed that the clinical team should provide a letter (on NHS headed notepaper) explaining why the study is being carried out, who is carrying out the study and enclosing a copy of the information sheet asking potential participants to contact you (the investigators) if they are interested in participating in the research.
4. The Committee asked that you detail in the patient information sheets that if potential participants were to disclose any sensitive information/inappropriate behaviour/bad practice relating to themselves or others (relating to risk/harm) at any time throughout the study, that confidentiality would have to be broken and explain how this would be managed. Please note that you should have a system in place to deal with this situation at the outset of your research. You should also explain that this may necessitate passing information on to the relevant services/third parties.
 - 4.1 The Committee also asked that you detail in the information sheet for clinicians that if sensitive information about inappropriate behaviour or bad practice relating to them or others arises during data collection period, it would be reported to the relevant third parties.
5. Your CV and Professor Clarke's CV should be dated as required by the Standard Operating Procedures for RECs.

If you would find it helpful to discuss any of the matters raised above or seek further clarification from a member of the Committee, you are welcome to contact Mrs J Sidhu, REC Manager on 02920 376822.

When submitting your response to the Committee, please send revised documentation where appropriate underlining or otherwise highlighting the changes you have made and giving revised version numbers and dates.

If the committee has asked for clarification or changes to any answers given in the application form, please do not submit a revised copy of the application form; these can be addressed in a covering letter to the REC.

The Committee will confirm the final ethical opinion within a maximum of 60 days from the date of initial receipt of the application, excluding the time taken by you to respond fully to the above points. A response should be submitted by no later than 10 May 2014.

Membership of the Committee

The members of the Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

Dr K J Craig / Jagit Sidhu
Sixth Floor, Churchill House
17 Churchill Way
Cardiff CF10 2TW

Thursday 5th June 2014

Dear Dr Craig (Chairperson REC A),

Study Title:	Consent in (dis)array? Genetic and genomic testing in the non-genetic setting
REC reference:	14/WA/0097
Protocol number:	SPON 1267-13
IRAS project ID:	142382

Please accept my sincere thanks for the consideration of my application at the REC A meeting on the 10th April 2014. Further to this meeting, please find enclosed clarifications and amendments as helpfully suggested by the committee [changes to documents are noted in yellow, with version number and date amended as appropriate].

1. I can clarify that I will be the Principal Investigator for this project, with Professor Clarke acting as the supervisor. This has been amended in the protocol and patient and clinician information leaflets.
2. I can confirm that the study will not be discussed with participants in their first appointment with a clinician. This has been amended in the protocol. No information will be sent to patients (who have not been told about the study) through the post.
3. The invitation letters, information sheets and consent forms have been merged to form a single document for patients and clinicians.
4. Issues around disclosures in confidentiality have been addressed in the patient information and clinician information leaflet. For patients, this now reads:

"The information collected in this study is confidential. Rare exceptions may apply if information is given to the researcher during an interview, which suggests you, or a member of your family, are at risk from harm. We can provide details for support groups to help, however where a participant or relative is thought to be at risk, this information will be shared with the doctor looking after you."

The written copies of consultations and interviews only contain a study number. No individual names or details that can identify any children will be included in any future study reports or publications”.

For clinicians, the following clarification is made

“The information collected in this study will be held confidentially. The written copies of interviews only contain a study number. Any information will only be accessible by members of the research team. No individual names or details that can identify any clinicians, patients or children will be included in any future study reports or publications.

Resources, in the form of an online learning module will be available to clinicians taking part to improve and build consent taking skills in clinician genetics. In the rare event of a researcher witnessing inappropriate or negligent clinical behaviour, this will be discussed with the participating clinician and their supervisor”

5. Dates have been added to the accompanying CVs as requested.
6. ‘Sponsored’ has been changed to ‘funded’ in respect to the Wellcome Trust association with the project
7. In the information leaflet, the paragraphs regarding ‘What will be involved if I take part?’ have been simplified.

Please do not hesitate to get in touch if further clarifications are required. Again, please accept my thanks for making the process so insightful and informative.

Best wishes,

Dr Katherine Burke
BA Hons. (Cantab), MB BS (London), DRCOG, MRCPCH
Clinical Research Fellow, Cardiff University



Institute of Medical Genetics
Room 2.25,
University Hospital Wales,
Heath Park, Cardiff, CF14 4XW.

Dear Patient / Family,

Consent in Microarray Genetic Testing

My name is Katherine Burke and I am a doctor working at Cardiff University, looking at the experiences of patients and families who have undergone, or may undergo as part of their medical investigation, a genetic test.

The study is aiming to help doctors and patients going through this process to establish in information they need, and the way in which this information can best be shared. This work is sponsored by the Wellcome Trust.

If you agree to participate, a research fellow will attend your clinic appointment to record your discussion with the doctor. Following this, you will be asked to take part in an interview discussing your consultation with the doctor, and the genetic test you/ your child might have. If you do not need a genetic test, we will not need to conduct this further interview. This interview will last around 30 minutes, and can be arranged at a convenient time and location for you and your family.

Recordings will be held securely, transcribed (written out) with no identifiable information in the text, and then the recordings will be deleted. It will not be possible to identify you from the written documents. There are unlikely to be any direct benefits or consequences for your own / your child's care, though some people may find it helpful to discuss the process in more detail. We can provide information for relevant support groups if you may find this helpful.

You do not need to participate in the study – this will not affect your clinical care.

If you would like to take part, or to discuss this project further, please do not hesitate to contact Katherine Burke, Academic Clinical Fellow at Cardiff University.

Email BurkeKB@cardiff.ac.uk
Telephone 0779 204 0522

If you would like to take part, please contact Katherine on the above number, or by email, to arrange a time to meet, otherwise, bring this letter and consent form along to your next appointment. We have included an information leaflet and consent form for you to read – if you have further questions, please do get in touch.

Best wishes, and many thanks for your consideration of this important project,

Dr Katherine Burke.

Academic Clinical Fellow, Cardiff University.
0779 204 0522 / burkekb@cardiff.ac.uk



Genetic and genomic investigations in the clinical setting

Thank you for reading this information sheet about the study.

We would like to invite you / your family to participate in this study looking at genetic and genomic tests in the clinical setting. Before you decide whether to take part, it is important for you to understand why the study is being performed and what it involves. Please contact Dr Katherine Burke (BurkeKB@cardiff.ac.uk / 0779 204 0522) with any questions you may have.

What is the purpose of this study?

Genetic and genomic tests are a common part of the investigation or diagnosis of many medical problems. This study is looking at how doctors, who are not genetic specialist doctors, talk to patients or parents, and families, about genetic tests and the sorts of results they may give.

Why have I / my family been asked to take part?

You have been invited to take part as either you as a patient, or your child, may be having a genetic test as part of the investigation of your medical problem. After your consultation with a doctor, you may not need a genetic test, in which case you will not need to participate in the study.

Where a genetic test is being considered in a child, we are interested in speaking to the parents / carers, and not the child involved (though they can be present for the discussion if you are happy with this, considering that we will be discussing their testing and assessment during the interview).

Do I have to take part?

You do not have to take part in this study. It will not alter the care you receive from the health professionals responsible for your care.

What will I be asked to do if I take part?

If you have not yet had a genetic investigation

- a researcher, who is not involved in you / your child's clinical care, observing and recording (using a voice recorded) your appointment with your doctor. The researcher will not be actively involved in the appointment with the doctor.
- an interview with you as a patient, or as the parent / carer of a child, about your experience of talking about a genetic test with your doctor, and what you understand about what is involved. This can take place either at the hospital, or a researcher can visit your home, and will be at a time that is convenient for you. It should last around 30 minutes to 1 hour.
- an interview with the doctor responsible for the care of you / your child, to look at their understanding of the process, and the difficulties they may experience.

- where possible, the same researcher may arrange to attend a subsequent appointment when you discuss the results of the test with your doctor

What will happen to the information I provide?

You will be invited to participate in the study by a member of the clinical team looking after you – usually you will receive this information with your appointment letter. If you agree to take part, you will meet the clinical research fellow at your clinic appointment.

Recordings of clinical consultations and interviews will be transcribed (typed) into a written document – at this stage, identifiable data, such as names and dates of birth, will be removed, and it will not be possible to identify, or see, who the information relates to. All data will be held on a secure, password protected computer.

What are the possible risks or disadvantages of taking part?

We do not anticipate any disadvantages in taking part but please do not hesitate to contact us if you have any concerns or questions. Some people may find it distressing to discuss investigations and diagnosis related to them or their child. If this is the case, we can provide contact details for organizations who may be able to help.

What are the possible benefits of taking part?

There are no direct benefits to your child for taking part. The information you provide may help us establish the best way to talk about genetic investigations with patients and families in the future.

Will my taking part in this study be kept confidential?

The information collected in this study will be kept strictly confidential. The written copies of consultations and interviews only contain a study number. Any information will only be accessible by members of the research team. No individual names or details that can identify any children will be included in any future study reports or publications.

What will happen to the results of the study?

The results will be written up as medical papers for publication in journals and for presentations at meetings of professionals involved in genetic tests.

Who is organizing and funding the study?

The study is being organized by Cardiff University, and is funded by a fellowship from the Wellcome Trust.

Who has reviewed the study?

The study has been reviewed and approved by the South East Wales Research Ethics Committee (REC).

What should I do if I have any complaints about the study?

If you have any questions about the study, please contact Dr Katherine Burke using the contact details below. If you remain unhappy and wish to complain formally, you can do this through NHS Complaints Procedure.

Contact details

Dr Katherine Burke
Clinical Research Fellow

Prof Angus Clarke
Principal Investigator

Institute of Medical Genetics
University Hospital Wales
Heath Park, Cardiff,
CF14 4XN

Email BurkeKB@cardiff.ac.uk
Tel 0779 204 0522

Institute of Medical Genetics
University Hospital Wales
Heath Park, Cardiff,
CF14 4XN

clarkeaj@cf.ac.uk

What do I do now?

If you are happy to participate, please bring the signed consent form along to the appointment with your doctor.



Consent form **Genetic and genomic investigations in the clinical setting**

Participant Name[.....]

Researcher Name

Date

I confirm I have read and understand the information sheet for the above study. I have had the opportunity to consider the information, ask questions of a member of the research team and have had these answered satisfactorily.

I agree to the audio recording of my / my child consultation and the subsequent interview. I understand that direct quotations may be used in presentations and publications, but it will not be possible to identify me / my family from these quotes



NHS WALES GIG CYMRU

I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from Cardiff University, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records

I understand that aspects of my own / my child's diagnosis, treatment and medical care will be discussed during the interview. Where my child is present for this, I understand that they are not being asked to participate in the study, but that comments they might make during the interview will be recorded and transcribed,

I can stop participating in the study at any time by informing the doctor looking after me, or by contacting the clinical research fellow organizing the study.

I agree to take part in the above named study

Participant's Name

Date

Signature

Researchers

Date

Signature

Contact Details

--



Institute of Medical Genetics
Room 2.25,
University Hospital Wales,
Heath Park, Cardiff, CF14 4XW.

Dear Doctor,

Consent in Microarray Genetic Testing

My name is Katherine Burke and I am a doctor working at Cardiff University, looking at the experiences of patients and families who have undergone, or may undergo as part of their medical investigation, a genetic test. This work is sponsored by the Wellcome Trust.

The study aims to help doctors and patients going through this process to establish in information they need, and the way in which this information can best be shared. We are contacting you as you are a non-genetic specialist doctor who is involved in arranging genetic tests for patients.

If you agree to participate, we will observe and record a consultation between you and a patient / family where a possible genetic investigation is being discussed. Following this, we will conduct an informal semi-structured interview with you, and later with the patient, about the process of discussing genetic investigations. This interview will last around 30 minutes, and can be arranged at a convenient time and location for you.

Recordings will be held securely, transcribed (written out) with no identifiable information in the text, and then the recordings will be deleted. It will not be possible to identify you from the written documents.

If you are willing to take part, or to discuss this project further, please do not hesitate to contact Katherine Burke, Academic Clinical Fellow at Cardiff University.

Email BurkeKB@cardiff.ac.uk
Telephone 0779 204 0522

If you would like to take part, please contact Katherine on the above number, or by email, to arrange a time to meet. We have included an information leaflet and consent form for you to read – if you have further questions, please do get in touch.

Best wishes, and many thanks for your consideration of this important project,

Dr Katherine Burke.
Academic Clinical Fellow, Cardiff University.
0779 204 0522 / burkekb@cardiff.ac.uk



Information Sheet for clinicians : Genetic and genomic investigations in the clinical setting

Thank you for reading this information sheet about the study.

We would like to invite you to participate in this study looking at genetic and genomic tests in the clinical setting. Before you decide whether to take part, it is important for you to understand why the study is being performed and what it involves. Please contact Dr Katherine Burke (BurkeKB@cardiff.ac.uk / 0779 204 0522) with any questions you may have.

What is the purpose of this study?

This study is looking at how doctors, who are not genetic specialist doctors, talk to patients or parents, and families, about array comparative genomic hybridisation (aCGH) and the sorts of results they may give, particularly with regard to unexpected findings such as incidental findings and variants of unknown significance.

Why have I / my family been asked to take part?

You have been asked to take part as you work in a clinical area where aCGH is performed regularly. We are hoping to also be able to discuss this investigation with the patients and families in your care, when you have suggested that aCGH may be indicated.

Do I have to take part?

You do not have to take part in this study.

What will I be asked to do if I take part?

In taking part, you agree to

- having a clinical encounter with a patient who may need array CGH performed observed by a clinical research fellow, who will also record and create a transcript of the appointment
- take part in a semi structured interview about the process of discussing aCGH, and genomic tests, with patients and families
- in some cases we will also be trying to observe the appointment where results are given to patients and families – this would involve further observation, recording and transcribing of the interaction

What will happen to the information I provide?

Recordings of clinical consultations and interviews will be transcribed (typed) into a written document – at this stage, identifiable data, such as names and dates of birth, will be removed, and it will not be possible to identify, or see, who the information relates to. All data will be held on a secure, password protected computer.

What are the possible risks or disadvantages of taking part?

We do not anticipate any disadvantages in taking part but please do not hesitate to contact us if you have any concerns or questions.

What are the possible benefits of taking part?

The information you provide may help us establish the best way to talk about genetic investigations with patients and families in the future, and also enable us to develop tools to help clinicians who are not genetic specialists improve their knowledge and skill in this complex area.

Will my taking part in this study be kept confidential?

The information collected in this study will be kept strictly confidential. The written copies of consultations and interviews only contain a study number. Any information will only be accessible by members of the research team. No individual names or details that can identify any clinicians, patients or children will be included in any future study reports or publications.

What will happen to the results of the study?

The results will be written up as medical papers for publication in journals and for presentations at meetings of professionals involved in genetic tests.

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Contact details

Dr Katherine Burke
Clinical Research Fellow

Prof Angus Clarke
Principal Investigator

Institute of Medical Genetics
University Hospital Wales
Heath Park, Cardiff,
CF14 4XN

Institute of Medical Genetics
University Hospital Wales
Heath Park, Cardiff,
CF14 4XN

Email BurkeKB@cardiff.ac.uk
Tel 0779 204 0522

clarkeaj@cf.ac.uk

What do I do now?

If you are happy to participate, please sign the consent form. We will contact you to arrange how best to identify potentially suitable patients prospectively.

Date

I confirm I have read and understand the information sheet for the above study. I have had the opportunity to consider the information, ask questions of a member of the research team and have had these answered satisfactorily.

I agree to the audio recording of the consultation and the subsequent interview. I understand that direct quotations may be used in presentations and publications, but it will not be possible to identify me / my family from these quotes

I can stop participating in the study at any time by contacting the clinical research fellow organizing the study.

I agree to take part in the above named study

Participants Name

Date

Signature

Researchers

Date

Signature

Participant Number

Contact Details

Appendix G

Table displaying Classification Systems for Genetic Variants

Kazazian et al (2000)	Richards et al (2008)	Plon et al (2008)	Tavtigian et al (2008)																								
<i>ACMG recommendations of standards for interpretation of sequence variants</i>	<i>ACMG recommendation for standards for reporting and interpreting of sequence variations: revisions 2007</i>	<i>Sequence variant classification and reporting: recommendations for improving the interpretation of cancer susceptibility gene test results.</i>	<i>Assessing pathogenicity: overview of results from IARC unclassified genetic variants group</i>																								
Genetic Medicine 2000; 2:302-303	Genetics in Medicine 2008 10(4): 294-300	Human Mutation 2008 29 1282-1291	Human Mutation 2008 29(11) 1261-1264																								
To provide a framework for interpretation and reporting of test results. To aid referring clinicians by educating them as to possible test outcomes, so they can inform patients and families.	Provide a framework for laboratories for the interpretation and reporting of test results. To aid referring clinicians by educating them as to the possible test outcomes, so they may inform patients and families appropriately.	Attempt to move beyond mere annotation and classification to how clinical management is impacted. Specific application to genetic variants associated with Lynch Syndrome.	Attempt to establish who is responsible for classifications and how information is disseminated to relevant users.																								
5 categories	6 'interpretive categories' of sequence variation for the purposes of clinical reporting		Expectations:																								
<ol style="list-style-type: none"> 1. Sequence variant reported and a recognized cause of disease 2. Sequence variant previously unreported and is of type expected to cause disorder 3. Sequence variant previously unreported and is of type which may or may not cause disorder 4. Sequence variant previously unreported and probably not causative of disease 5. Sequence variant previously reported and is a recognized natural variant 	<ol style="list-style-type: none"> 1. Sequence variation previously reported and recognized cause of disorder 2. Sequence variation previously unreported and of type expected to cause disease 3. Sequence variant unreported and is of type which may / may not cause disease 4. Sequence variant previously reported and probably not causative of disease 5. Sequence variant previously reported as benign variant 6. Sequence variation not known / expected to be causative of disease, but is found to be associated with a clinical presentation 	<table border="1"> <thead> <tr> <th>Variant Type</th> <th>Predicative test for relatives?</th> <th>Surveillance for relatives?</th> <th>Research testing for relatives?</th> </tr> </thead> <tbody> <tr> <td>Pathogenic</td> <td>Yes</td> <td>Yes – full, high risk</td> <td>No</td> </tr> <tr> <td>Likely pathogenic</td> <td>Yes</td> <td>Yes – full high risk</td> <td>Yes</td> </tr> <tr> <td>Uncertain</td> <td>No</td> <td>Yes/No – consider FH, other risk factors</td> <td>Yes</td> </tr> <tr> <td>Likely not pathogenic</td> <td>No</td> <td>Consider FH and other risk factors – consider as having no known mutation for this disorder</td> <td>Yes</td> </tr> <tr> <td>Not pathogenic</td> <td>No</td> <td>As above</td> <td>No</td> </tr> </tbody> </table>	Variant Type	Predicative test for relatives?	Surveillance for relatives?	Research testing for relatives?	Pathogenic	Yes	Yes – full, high risk	No	Likely pathogenic	Yes	Yes – full high risk	Yes	Uncertain	No	Yes/No – consider FH, other risk factors	Yes	Likely not pathogenic	No	Consider FH and other risk factors – consider as having no known mutation for this disorder	Yes	Not pathogenic	No	As above	No	<p>Do expect panels of experts in all facets of a genetic syndrome to 'do' classification</p> <p>Do not expect clinical testing laboratories to independently carry out a full integrated analysis and independently classify variants. Do expect them to gather data in a report 'as best they can' and to faithfully report conclusions made by expert panels in standardized terminology.</p> <p>Do not expect physicians or genetic counselors themselves to carry out full integrated analysis or to independently classify variants. We do expect them to know that data they gather can modify existing classifications, share data with testing laboratories and expert panels with appropriate consent and know how to present a fair summary of the data and conclusions to patients.</p>
Variant Type	Predicative test for relatives?	Surveillance for relatives?	Research testing for relatives?																								
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<p>'The certainty with which any given sequence variation is of clinical significance falls within a spectrum of interpretation, ranging from those in which the variation is almost certainly of clinical significance, and those in which it is almost certainly not'</p> <p>'The purpose of the test report is to state clearly the absence or presence of sequence variation and to set this information into the clinical context, in order to facilitate case management'</p>	<p>The reporting of sequence variants – the process of categorizing and reporting – should not report well known common polymorphisms. Variants of unknown significance (category 3) whether believed to be benign or pathogenic should be reported, followed by a laboratory interpretation of likely clinical significance.</p> <p>'The purpose of test reports is to clearly state presence if detected of any significant sequence change that differs from the consensus wild type sequence and may be of clinical significance.</p>		<p>'Pathogenic' and 'non-pathogenic' reserved only for variants for which multiple lines of evidence have been evaluated, or for which a convincing statistical association with disease is apparent based on large, sound studies of cases and controls (again binary) with a spectrum of uncertainty'.</p> <p>References Goldgar et al (2004) – all variations between 0.1% and 99%, the probability of pathogenicity is unknown.</p>																								

Tsuchiya et al (2009)			Berg et al (2011)																																																																																			
Variability in interpreting and reporting copy number variants detected by array based technologies in clinical laboratories. Genetics in Medicine 11(12): 866			Emory Genetic Laboratory Classification System Definitions Genetics in Medicine 13 (6) : June 2011																																																																																			
To guide the management of further analysis with regard to parental sampling, and to reduce reporting discrepancies among laboratories			Avoidance of 'information overload' of whole genome sequencing by employing a standardized, clinically orientated structured analysis.																																																																																			
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Suggests more nuanced system for evaluation of uncertainty through a weighted scoring system i.e. a deletion is more likely to be pathogenic than duplication. Explicit acknowledgement of uncertainty as a broad category			Ordering in this system is different – not a spectrum from certain – uncertain – certain, but pathogenicity used as primary ordering factor, and degrees of uncertainty as a secondary factor.																																																																																			
			Recognition of incidental / secondary information as 'inherently heterogeneous' – scope of WGS makes this a bigger problem. Therefore a 'scalable approach to the return of incidental information is needed. 'Majority of information generated by WGS will be useless (at least initially) simply because we have no idea of how to accurately interpret it; thus it must be disregarded in the clinical context' Categorisation as 'iterative, centralized, evidence based and consensus driven' Interpretation of sequence data in the diagnostic setting will provide information which is qualitatively similar to current genetic test results: a 'definitive etiology' (positive result), possible etiology and no etiology identified'.																																																																																			

Lindor et al (2012)	Green et al (2013)	Wright et al (2013)
A review of multifactorial probability based models for classification of BRCA 1/2 variants of unknown significance Human Mutation 2012 33:8-21	ACMG recommendations in reporting incidental findings in clinical exome and genome sequencing Genetics in Medicine 15 (7) July 2013 565-574	Policy challenges of clinical genome sequencing BMJ 2013; 347 f68845
To introduce a posterior probability model for assessing variants of unknown significance in BRCA 1/2	State a minimum list of conditions, genes and variants which should be routinely evaluated and reported to the ordering clinician.	Further categorization of secondary variants.
<p>Not classifications per se, but an attempt to better characterize variants of unknown significance (in BRCA 1/2) as pathogenic or benign.</p> <p>Variants of unknown significance are not clinically useful and therefore should not factor in clinical decision making.</p> <p>Recognition of <i>semantic</i> differences with ontological and categorical implications</p> <p>'Uncertain' (implies analysis has been performed, and the variant has a posterior probability between 5 – 95%) and 'Unclassified' (the state of a variant before any attempts at classification).</p> <p>'Non pathogenic' should be used instead of 'neutral', 'benign' or 'polymorphism'</p> <p>'Deleterious' is short for 'evolutionarily deleterious' and is most applicable, as opposed to 'damaging' or 'pathogenic'</p>	<p>Move away from annotation and categorization towards a minimum standard for screening on all samples undergoing WGS / WES, regardless of the indication.</p> <p>Creation of a 'minimum list' of incidental findings to report from clinical sequencing. 'Actively search' for the specified types of mutations in the genes listed in these recommendations, associated with 'common monogenic disorders.</p> <p>Regardless of reason for WGS/WES, regardless of age, regardless of patient preference for receipt of results (though this was later revised to encompass patient right not to know).</p> <p>Minimum list includes:</p>	
	<p>Movement from categorization to listing – a significant shift in sociological approach.</p> <p>Identifying variants has a moral imperative – to prevent future disease.</p>	<p>The 'meaning' of secondary variants interpreted through the lens of LOCATION as well as MEANING. i.e. opportunistic if deliberately searched for at another location, co-incidental if co-located with a finding related to the phenotype under investigation.</p>

Appendix H

Diagram explaining the operator interface when using software to process variants generated in aCGH testing

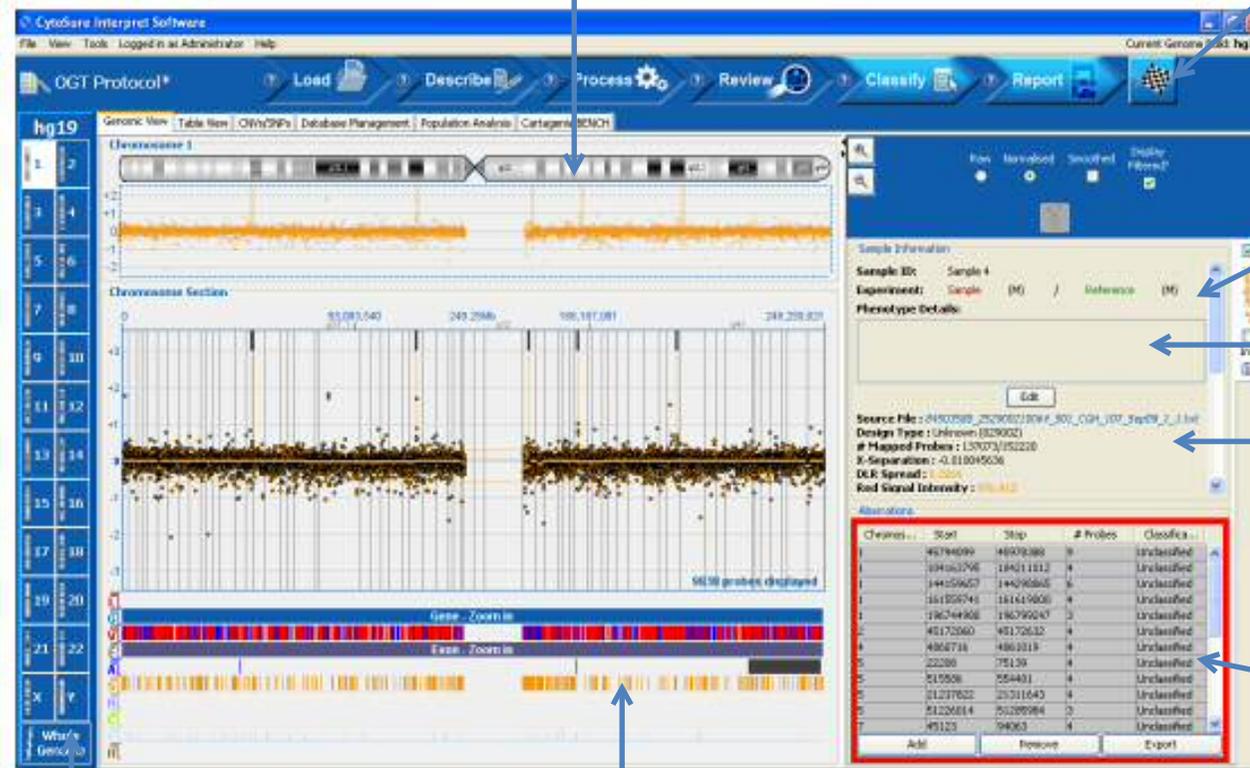
Each of these horizontal displays (**'tracks'**) constitutes a different way of displaying the chromosome. The first is the banded chromosome one as it would be displayed in a karyogram. In yellow is a low-resolution display of the probe distributions, the large spikes demonstrating regions where the probes fall outside the expected range. In the track below, the 'chromosome section' represents an opportunity to 'zoom in' on a smaller area, examining the distribution of individual probes.

This is a series of tabs which enables the analyst to move through the 'work' performed on the array data: the **loading** of the data, the standard driven **description**, the **processing**, referring to the analysts manual curation of 'calls', the **review** of the true variants and finally, their **classification** (pathogenic / benign / variant of uncertain significance) and **reporting**.

Further information including **array settings and build**, and the **numerical data associated with quality control** (pass / fail represented by colour of text – red for fail, yellow and green for pass)

Phenotypic information -transcribed from request form

Sample information – an important part of the checking and verification process



Numbers represent each chromosome, allowing analysts to move between chromosomes. There is also a whole genome view.

These tracks represent data from external genome databases such as the DGV, DECIPHER, allowing the variants identified within the sample to be compared with variants identified through research and clinical databases. There is also a track specific to the laboratory for identifying 'recurrents'

'Calls' i.e. variants identified by the software are displayed in list form, stating the chromosome they appear on, their start and stop position, the number of probes which are displaced, and an automated classification as benign / pathogenic or unclassified.



Final Page