"The implementation of genomics in healthcare: the challenge of justice".

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ABSTRACT
Many ethical issues have been considered in relation to the implementation of genomics in modern healthcare. However, questions of justice have received less attention than other core ethical topics. When justice has been considered, it has largely focused on questions of 'race', ethnicity and population groups. This topic is of immense importance but there are other important areas where justice also needs to be considered.

We address the numerous other ways in which genomics does or could reinforce or exacerbate current social injustices. We must take great pains to counter misapplications of the science under all these categories:

- access to healthcare in general, the impact of social class and the 'inverse care law'
- management of personal genetic and health data; institutionalised discrimination
- epigenetic effects that reinforce the harmful impact on health of poverty and inequality
- the genetics of intelligence (i.e. IQ) and mental health and the potential for its abuse in public life and harm from unwise clinical applications
- the complex genetics of multifactorial diseases, the drive the individualisation of responsibility for personal health, and the genetics of non-disease traits
- the potential for reproductive genetic screening to drive inequity and discrimination
- dealing with the 'promise' of genomics: maintaining the balance between offering realistic hope versus raising false expectations

There will be no single solution to these difficulties and tensions. The professional responsibility not to inflate achievements or promises will need to be monitored by all genomics professionals, reviewers of grants and papers, and publishers. Professional bodies need to recognise their obligation to set standards. The law may need to be invoked in the realm of private and direct-to-consumer genetic testing. The most important requirement for progress, however, is the growing recognition among genomics practitioners that there is a problem and that we must confront it collectively.

KEYWORDS
Justice, genomics, genetic testing, epigenetics, inequity, discrimination, stigma, bioethics, 'race', expectations, complex genetics, screening

ARTICLE

Technological innovation creates circumstances that are especially challenging for public policy. Questions of fairness and the just distribution of the benefits of innovation arise; there may be opportunities to promote justice but circumstances may change and the effects of intervention

may be difficult to predict (Papaioannou 2021). This chapter aims to focus attention on justice in the context of medical genetics and genomics. We review, in very broad terms, the ways in which bioethics has addressed the questions raised by genetics and genomics. We then identify the potential challenges for genomics that may be raised by a concern for justice. Finally, we consider how those working in medical genetics services can be alert to potential issues of justice and ensure that they do not inadvertently make these problems worse for their patients and society more generally.

CONTEXT

There has been much discussion of the ethical issues around the medical applications of genetics over the past three or four decades, often given the acronym 'ELSI' to represent the Ethical, Legal and Social Implications of this rapidly developing field. Since around 2010 this has often focused specifically on the issues around genomics, as the scale and scope of the genomic approach to genetic research and its clinical applications have been so great as to represent a qualitative change in what is technically possible and what is at stake. These bioethical considerations, however, have focused on some topics much more than others; indeed, some areas have been relatively neglected.

Topics that have been extensively studied and debated include respect for a patient's autonomy, the sharing of genetic information within families, and the management of genetic information in research and diagnostic settings. We will not dwell on these issues here.

At least three other important areas have also been addressed, (i) the processes of information and explanation around consent to genetic testing or research, (ii) the question of ethnic diversity within population genetics research, and (iii) the tension between reproductive autonomy on the one hand and respect for those affected by genetic conditions, intellectual disability and malformation on the other, which may be given the label 'disability rights' although the questions raised are rather broader than that term might suggest and also include issues around the status of the embryo. All of these areas involve considerations of justice as well as other issues.

The way in which consent to genetic testing or research is approached is of great importance, as it is often the ethos of the discussion around consent that shapes decisions and that a patient or participant will recall when the details may be long forgotten. While the importance of consent is in no doubt, it has been addressed in the literature largely through reflections on the principles involved or through empirical studies of attitudes and hypothetical preferences gathered in surveys or interviews involving stakeholders or members of the general public. Occasional studies have collected retrospective accounts of the process of 'information, explanation, decision and (finally) documentation', that we often refer to in brief as 'informed consent', but very few have observed, recorded and evaluated instances of this in the day-to-day practice of genomics (Burke 2018). We can still learn from empirical studies of consent in other areas, such as clinical drug trials (Corrigan 2003), but the dearth of fine-grained empirical studies around consent in genomics, in both healthcare and research, is a major deficit that needs to be addressed. This is because of the central role of personal interaction and inference in shaping the meaning of what is said and understood in communication, which is often subtle and nuanced; it is difficult to elucidate such influences through tick-box survey methods that can work well for other topics.

Indeed, the adjective 'informed' in the phrase 'informed consent' may have done us all a disservice in focusing our attention on what information has been conveyed or can be recalled and away from what it means to people, whether as individuals or in their family context.

The second issue, of the representation of different population groups in genetics research, is not only of great ethical significance but, in addition, of great scientific significance too. This is because the scale of genetic diversity is enormously greater in populations from Africa than from anywhere else, with most of the diversity found outside Africa being only a modest fraction of the diversity within Africa. This has long been understood to confirm the out-of-Africa hypothesis, indicating that the origin of modern humankind took place within Africa and that our ancestors then spread around the globe from there. Details of the process, especially the contribution of other human population groups (e.g. Neanderthalers and Denisovans) to our modern genetic constitution, may remain open to improved understanding but the centrality of our African forebears is not in doubt. The fact that most population biobanks, and the related genetic research, have examined populations consisting largely of white people of European extraction is therefore a scientific problem that needs to be addressed. Thus, a benign genetic variant that is present in some populations within Africa may be difficult to interpret - and may be declared a variant of uncertain significance - if it is identified in a patient before it has been identified in a database of healthy individuals, because so few samples have been collected from healthy members of the relevant group.

Here, the important issues are complex and interconnected: they are practical, social and ethical. The under-representation of African populations in genetic biobanks and population genetic studies is a result of the uneven development of scientific research and healthcare services across the world, with more research and more health care delivery in the more developed and wealthier, western countries. This has arisen because of the greater practical ease of sample and data collection within those countries with the more developed systems, that in turn results from the greater wealth of these countries. The interconnectedness is revealed in the history of colonialism and slavery that boosted the economies of Belgium, France, the Netherlands, the UK and the USA. The context is perhaps more complex in USA than elsewhere, because those wronged include not only slaves but also poor whites, indigenous inhabitants and immigrants from East Asia. The greater present wealth of these western countries can be seen as a legacy of the exploitation of fellow humans used as material resources. The ethical problem that this leaves us with now is that the present gross inequities in health and healthcare are the direct result of this historical legacy of several centuries. How can this be addressed now?

One consequence of this history for genomics is that the interpretation of molecular variants found in white Europeans is simpler, cheaper and more reliable than for variants found today largely in African populations. If a black person - whether in Africa, Europe or USA - can gain access to modern genetic diagnostics, they are less likely to benefit from healthcare based on a clear interpretation of genomic investigations. And they are less likely to have ready access to such investigations if they live in Africa or, if they live in USA, they are less likely to have adequate healthcare insurance. The situation in Europe and Asia is more variable. The social health insurance schemes common in Europe are more equitable but some disadvantaged communities may even be over-represented through specific efforts to collect samples for potential forensic

applications, as with the Roma in parts of Europe and also Turkic communities (such as the Uyghurs) in China.

The poor representation of historically disadvantaged populations in genomic research therefore leads to the persistence of this sad legacy. Efforts are being made to address this problem but it may take many years to achieve a reasonable degree of equity. In the meantime, our ability to work on gene-gene and gene-environment interactions in quantitative traits and complex diseases will remain limited as our knowledge of genomic variation in different populations remains impoverished.

The third issue - of 'disability rights', the tension between reproductive autonomy and respect for those affected by genetic conditions - has received much attention within the rare disease and disability communities but remains less tractable. There is a fundamental asymmetry in this tension, in that both reproductive autonomy and institutional discrimination often need to be addressed primarily through legislation and/or regulation while disrespect ofen plays out in much less formal settings. The remedy for the disrespect sometimes shown to affected individuals entails changing people's patterns of behaviour and thought, especially in micro-level interactions in schools, in clinics and on the streets; this is far from being straightforward.

We have seen the legal developments in Ireland that have opened up autonomy for women after many decades of oppressive, misogynistic control. We - i.e. the global public - have been watching the legal contests addressing reproductive autonomy in the USA, as they worked their way through state legislatures up to the (Federal) Supreme Court, and are now passing back down to legislatures and plebiscites at the level of individual states. In contrast, measures to support respect for those with genetic conditions, intellectual disability and malformation are much less apparent in the public sphere. However, we have seen other important public initiatives relating to respect for individuals. The MeToo movement to support women, and the Black Lives Matter movement after the killing of George Floyd, have both had profound consequences. It remains to be seen whether these social movements will draw attention away from other types of disrespect - stigmatising and offensive behaviours towards people affected by rare diseases and conditions - or whether they will strengthen the social movement towards respect and consideration for all. Let us hope it is the latter. Those of us who live with or work with those affected by rare diseases and conditions do not wish to belittle any efforts to improve the lot of women and those from minority communities. Rather than resenting the attention bestowed on them, we need to add the concern for people with genetic conditions and disabilities to these higher profile debates. This is not a zero sum game; a basic respect for other persons must be seen as indivisible. There is a basic minimum of respect towards other people that is required of us unconditionally.

WHERE GENOMICS ENCOUNTERS QUESTIONS OF JUSTICE

There are several ways in which the implementation of genomics in research, clinical practice and genetic testing outside healthcare may raise questions of justice, even giving rise to injustices. We see the term 'justice' as referring to an abstract entity, while 'an injustice' is a more concrete

exemplar of the lack of justice (Shklar 1990). There are several ways in which injustices can arise in the implementation of genomics, some of them relating to general features of healthcare within society rather than anything specific to genetics. In this account, we adopt and adapt the six-part framework of Clarke and van El (2022).

(i) Access to healthcare

First, there is the question of access to healthcare in general. Inequity in health outcomes is inevitable when healthcare is funded privately by the individual, and access will be restricted on the basis of personal wealth or other characteristics such as group membership (e.g. ethnicity//race). There are likely to be interactions and intersections here, as people of low social status are likely, if employed, to work in low status and less well paid occupations and to be subject to more occupational health hazards while being unable to afford adequate health insurance. Even within a country with a comprehensive, national insurance scheme that should embody equity, it is clear that poverty and low social standing lead to substantial inequities (Tudor Hart 1971) and there is always scope for these to be exacerbated by racial discrimination and other social prejudices. Genetic disease and social disadvantage can also intersect to compound the problems 'synergistically' but unfortunately.

While they may as individuals be unable to alter the local system of healthcare funding, professionals can work with others to make it more equitable; their personal behaviour can also emphasise the respect owed to all in and beyond their professional lives.

(ii) Managing personal data

A second way in which injustice can interact unhelpfully with genomics is in the collection and handling of genomic and other personal data. We have already mentioned the relative underinvestment in the collection and analysis of genomic data from non-European, especially African, populations. In addition, there is the collection of health, social and lifestyle data about individuals and its potential merging for analysis in population biobanks. What is the appropriate balance between tracking a population's health for healthcare and for academic research, on the one hand, and intrusive data collection open to commercial misuse or political abuse on the other hand? Experience in the UK suggests that the public does not like to lose control over how their data are used, with a low level of trust in corporations, and suspicion of the potential abuse of information in forensic genetics, while a focus on ethnicity can open up pathways to even more serious abuse, both in Europe (Lipphardt 2021) and China (Moreau 2019, 2022).

Even without the dimension of race and politics, there is ample scope for unfair social discrimination through the misuse of genetic data alone or in combination with other datasets (Joly et al 2021; Joly and Daplé 2022). In the past, this has focused on the misuse of data in insurance, with implications for employment where insurance and employment are closely associated (as in USA) but the scope for unfairness has since broadened out to include access to education. We consider this further below in the potential application of complex genetics to the context of reproduction.

(iii) Predictive adaptive responses and human disease

Starting with the observation that the prevalence of some complex, degenerative disorders (type 2 diabetes, hypertension, coronary artery disease, stroke) is higher in some populations and communities, Neel (1962) proposed that genetic selection for a "thrifty" gene enabled these groups to withstand prolonged periods of starvation but carried the penalty of degenerative disease after years of an ample calorie intake. From his observation that infants of low birth weight for their gestation were more likely to develop type 2 diabetes and coronary artery disease, Barker proposed that the fetus responds to the maternal environment so as to be better adapted metabolically to the prevailing nutritional circumstances (Barker et al 1989; Hales and Barker 1992). The fetus had acquired a "thrifty phenotype", but with the same penalty as Neel had noted. These competing explanations for degenerative disease under conditions of nutritional plenty have led to research into possible mechanisms. For the Barker effect to operate, there would be non-mutational (epigenetic) changes to the individual's DNA, such as those mediated by methylation of the CpG groups in gene promoters. Such adaptive responses to gene function in response to environmental circumstances are now known as 'predictive adaptive responses', a term coined by Hanson and Gluckman, and can operate across the life-course or even across generations (Hanson et al 2019). Disease occurs when the developmental cues are not matched by subsequent events. From this perspective, Neel's model of a thrifty genotype would cause disease through an evolutionary mismatch between the circumstances operating today in a population and those operating in its past.

While many details remain to be clarified, the implication of these different approaches to questions of public health and political policy have been discussed and differ in important respects (McDermott 1998; Hanson and Gluckman 2015). One feature of note is the differences in political power often experienced by those with a greater or lesser risk of disease. Biological disadvantage seems to affect those who are relatively powerless, especially when an indigenous culture has been overwhelmed and the survivors remain at a major social and political disadvantage, as applies today to some groups within USA, Australia and elsewhere. This raises the possibility that a communal cultural dislocation and powerlessness may interact with the epigenetic disadvantage from metabolic stress in early life to have this effect through a chronic, postnatal stress response.

Work that would promote justice in relation to these biological effects on human populations includes systematic studies of societies in which indigenous or low caste individuals live alongside more privileged groups. The provision of educational, social and nutritional interventions along with equitable access to medical care could reduce health inequities and enable investigation of the biological mechanisms underlying the transgenerational cycles of disadvantage that are only too common in many countries.

(iv) Genetics and the mind

Where cognitive ability is seriously impaired by genetic factors, we are often dealing with chromosomal or Mendelian variants that have major, often damaging, effects. Such conditions, often accompanied by malformation and other hazards to health, clearly fall within the remit of medical genetics and benefit from medical diagnosis when possible.

When we come to variation of intelligence within "the normal range" (i.e. with IQ above 70), the situation is different. We know that both genetic and environmental factors are important in determining cognitive ability. Of the genetic factors, chromosomal alterations may sometimes be relevant and single gene effects may also operate but most of the underlying variation is polygenic, with large numbers of variants exerting individually small effects. From parallels with other complex traits in lower organisms, there may be powerful interactions among these genetic factors, or between specific genetic variants and environmental factors, but our methods for studying these are mostly unable to dissect out these effects. There is still much that we do not understand.

'Intelligence' however is a highly rated trait and often regarded as highly desirable in our children. It is concerns about 'intelligence' that underlie much of the history of eugenics and much of its contemporary residue. There is a debate to be had about the ranking of 'intelligence' among the other human attributes and virtues but this is not the place for that. Much data has been collected on this as there are researchers who find it an irresistable topic for genetic investigation, although its relevance to disease and suffering is unclear. Equally, there are prospective parents who are keen to do all they can to have a child with the highest IQ score feasible. The strength of this parental wish has been recognised, and the wish is being granted by commercial genetic testing concerns in USA, who offer something akin to genetic "prediction" for IQ in the context of IVF and pre-implantation genetic diagnosis (PGD). The scientific basis of this is feeble, with testing able to predict only about 10% of the variance in IQ (von Stumm and Plomin 2021). The ramping up of expectations about genetic testing for IQ and the willingness to exploit parental misunderstandings of genetics and their unrealistic dreams for their children may be abhorrent but they are not illegal, at least in California. The scientific and moral flaws in this process have been discussed (Turley et al 2021; Forzano et al 2022).

Inseparable from these problems are some even larger problems that are an inevitable consequence of such research. These are the misapplication of genetic testing results of individuals for their 'IQ propensity' not only in reproduction but also in education and employment, and the abuse of any differences for 'IQ propensity' between population groups in the service of racism. Any difference in incidence between population groups of genetic variants associated with differences in IQ will inevitably be given a politically motivated interpretation, to add to tensions between ethnic groups within a community or a country. Such abuse of IQ research findings has such a long history (Gould 1981), and this is such a predictable abuse, while the scientific benefits likely to flow from research in this area are so slim or non-existent, that one must question the motives for pursuing such research. Some scientists will simply not have thought of the potential misuse or abuse of their research but they will become fewer in number as the exploitation of this body of research becomes more prominent. One must hope that institutional ethics review bodies and the funders of research will take responsibility to block such proposals at an early stage. There is no case for funding such projects ahead of so much other research that is clearly worthwhile, even urgent, and that is waiting for funds. Simply including some public engagement activities to counter the wilful misinterpretation of findings is not adequate in this context, where the abuse of research is deliberate and wilful and sealed off from any rational assessment.

The other topic to consider in this section on 'the mind' is genomic research into mental illness. Mental illness is of great importance as it is so common and can be devastating in its effects. Research into its causes is necessary and has shown that much mental ill health is of complex causation - a mix of multiple small genetic effects and environmental, including life-course, factors. The questions to consider here are (a) whether or when genetic testing for a general susceptibility to mental illness is appropriate, and (b) whether or when cascade testing within a family for a known genetic variant of major effect - a Mendelian gene variant, or a chromosomal copy number variant - would be appropriate.

The attempts to answer (a) will have much in common with our generally cautious approach to testing for genetic susceptibility, i.e. for polygenic factors that may modify a person's risk of a problem but are unlikely either to generate strongly predictive information or give complete reassurance. Unless there is an intervention to be made on the basis of the test result, there may be little to recommend testing and much to caution against it, especially in the context of mental health. Efforts to avoid psycho-emotional problems and unsatisfactory relationships are better addressed directly rather than through a very limited, detached and abstract form of knowledge about causation. As for other complex traits, there is a strong professional consensus against the use of such testing in prenatal genetics, such as in IVF/PGD.

In the presence of a family history of mental illness, or some other reason to anticipate a high risk of mental illness in an individual, how about question (b)? We know that a moderately strong genetic predisposition to mental illness in a child can be difficult for parents to cope with, as with children identified with 22q11 deletion syndrome, whether or not either parent is known to carry the same cytogenetic feature (Hercher and Bruenner 2008). How does the knowledge of a predisposition to schizophrenia, for example, alter the way in which a child is to be treated by her parents and others? Is this helpful, leading to better strategies for behaviour management, or does it weigh the family down and become a self-fulfilling prophecy? How do other family members respond to the knowledge that they may carry, and even transmit, a predisposition to mental illness? This may not be the best place for a detailed discussion of this area but our knowledge is limited and there are strong grounds for caution in regards to such testing, which should only proceed after reflection on the likely impact on the individual and the family of the various possible test results and with a careful process of genetic counselling (Manzini and Vears 2018).

(v) Complex causation and responsibility for health

We have already discussed some of the difficulties that arise when genetic testing is used to assess susceptibility to the common, complex disorders. There are often good reasons to study the polygenic influences on such conditions, as this can give helpful insights into disease mechanisms, but that does not mean that the clinical application of such research to testing individuals is appropriate or justified (Janssens 2019). Multiple reasons for caution include the usually very modest fraction of the variance in the trait or disease risk that can be examined in this way, our limited understanding of gene-gene interactions that may render our assessments unexpectedly inaccurate, the inequity in test performance depending on a person's ancestry (their population/s of origin), and the potential for unanticipated consequences of reproductive decisions made on the basis of such testing through genetic pleiotropy (Turley et al 2021). Indeed,

reviews of the utility of such testing confirm that it has little to offer in clinical practice, at least for now (PHGF 2021), even when performed by enthusiasts (Polygenic Risk Score Task Force of the International Common Disease Alliance 2021). Furthermore, there is a risk that someone may seek such genetic testing because of an awareness of "something in the family" when the genuine familial risk may not be detectable by the polygene-based genetic tests for complex disease. This can give false reassurance when a more thorough clinical genetic assessment would be needed for the risks to be better defined and the appropriate test to be offered. In other words, the offer of inappropriate genomic tests for common diseases may distract people from seeking the more focused type of genetic testing for Mendelian or chromosomal disorders.

Justice enters into the equation here in several ways. One concern is that genetic testing for susceptibility to complex disorders will often be of very limited clinical utility, so that the promotion of such testing may be based upon an erroneous understanding of disease causation and may actively contribute to the spread of mis- or dis-information. If marketing succeeds in selling tests, this will often be through misleading customers into thinking they are more useful than they are. Positive test results, which are often erroneous (Horton et al 2019), may also lead to additional demands being placed upon under-resourced social or national health care schemes to follow up results indicating specific disease risks or to offer testing to other family members. Such consequences will most likely not be paid for by the genetic testing company and will be born by society at large; this wastes resources and may exacerbate pre-existing health inequities.

For many complex disorders, a person at above average risk of disease has the opportunity to make lifestyle decisions that may - to some extent - reduce their risk. This is, indeed, claimed as one of the benefits of genetic testing for disease susceptibility. Unfortunately, however, this case is weakened by the difficulty in showing that such disease susceptibility test results actually motivate adherence to clinically recommended behaviours. Genetic tests for strongly inherited (usually Mendelian) health risks are often acted upon by those who have sought testing, with behaviours such as taking statin drugs by those with familial hypercholesterolaemia, or disease surveillance and/or risk-reducing surgery for high Mendelian risks of cancer of the breast or bowel. In contrast, however, for the common, complex disorders such as type 2 diabetes, hypertension, coronary artery disease or stroke, the behavioural changes required to modify risks will often not be accepted, in that they may be seen as beneficial but not acted upon in a sustained fashion (McBride et al 2010; Hollands et al 2016). Furthermore, the recommended behaviours are very much the same, whatever one's level of risk and whatever the disease in question. There really is rather little point in performing genome-wide testing for disease susceptibilities when it will often make no difference to the recommendations made, whichever disease is indicated as a risk and whatever the level of risk is thought to be. At best, it would merely provide some additional motivation to lead a generally healthy lifestyle and the evidence that it achieves even that is thin.

Another consequence of genetic testing for disease susceptibility may be to promote an individualised approach to the organisation of healthcare rather than developing community-based systems. While much treatment of disease and surveillance for disease complications needs to be provided to each individual separately, we have already seen that health promotion and enhancing the motivation for behaviour change in the individual is difficult and often

unsuccessful. In contrast, community-wide measures may be simpler to implement and much more effective. The individualisation of responsibility for disease is therefore often encouraged by commercial concerns that stand to gain from direct-to-consumer (DTC) genetic testing, whereas the health of the public may be much better served by community-wide responses to the people's health challenges. Community-based policies in relation to transport and physical exercise, the availability and costs of different types of food, the quality of air and water, tobacco and alcohol consumption are all amenable to public policy interventions that can use 'nudge' as well as taxation and subsidy, regulation, legislation and other policy choices. It is known that these approaches can be implemented in an effective and equitable manner, while the individualised approach to genomic testing as a guide to lifestyle choices is costly, inequitable and largely ineffective.

Related to this area of diseases that have complex causation, including genetic and other factors, is the interest in genetic testing for non-disease traits, including IQ in the normal range [cf (iv) above] but also potential for education, personality type, athleticism, musicality, height etc. We do not consider these further here but the potential for harm in applying tests for such traits is very substantial.

(vi) Genomic screening and reproduction

Having already considered screening for personal health risks, we now turn to screening in the context of reproduction. This covers principally antenatal screening for the autosomal trisomies (including trisomy 21) and for malformation, and preconception carrier screening for recessive disease. Questions of justice arise in these contexts in three principal ways: if the programmes exacerbate inequity, if people's reproductive decisions are shaped by external pressures that are excessive, manipulative or coercive, or if disrespect is shown towards those affected by the conditions that screening is designed to avoid or prevent.

We are not considering here the individual decisions made by families who have sought genetic services in relation to a condition already known about in their family. When people have direct experience such a condition, they will make their decisions informed by their prior knowledge and experience of that condition and they will be less likely to feel or to be steered towards a decision which they feel is wrong for them. They may feel pressure, perhaps from relationships within the family, but this is not externally imposed but a core part of being a human in relationship with others; the notion of autonomy as making decisions in isolation, as if within a social vacuum, is shallow. In the context of population screening, many people will have no direct experience of the condition for which screening is being offered; they may be dependent on the programme for information. The way in which the condition is represented and discussed will therefore be more important and the scope for society to shape people's decisions will be greater.

Respect or Autonomy?

As already referred to in the introductory section, there is a tension within society between the respect due to an affected person and the ability of a pregnant woman to make decisions about her pregnancy, i.e to control her own body, which entails the choice whether to continue or to terminate her pregnancy (Parens and Asch 1999). Those affected by conditions for which screening is offered as a routine part of antenatal care may indeed experience this as a lack of

respect - even hostility - and be greatly saddened as a result. These feelings do not arise from nowhere but as one part of a difficult emotional journey in response to the stigmatisation, abuse and disrespect that they may have had to endure for many years, often from the middle school years through into adult life. Affected individuals can feel great sadness at being part of a group that society at large wishes to dispense with, i.e. to not be bothered by (Alderson 2001; Bryant 2021). Screening programmes that are seen as devaluing affected individuals may reinforce prejudice against those affected. Such stigmatisation can be as severe a problem for those affected as any medical troubles, so that the screening 'for' a condition might contribute to the problems experienced by those affected, thereby establishing a positive-feedback loop that could exacerbate stigma and further drive uptake. These social processes shape the context within which screening operates and make it difficult to arrive at an arrangement acceptable to all parties.

One approach towards finding a resolution is to make antenatal screening available to pregnant women but also to ensure that parents who have a child with additional needs for educational, medical or social support - whatever the cause - are indeed offered enough support. If all prospective parents could have a realistic confidence that, were their child to face problems with their health or development, they would be provided with a decent level of care for the life of the child, then fears for the child's long term welfare would not drive their decision about whether to continue or terminate the pregnancy.

This would mean that society would enable reproductive choice but would then actively welcome every child born, especially those with problems, whether genetic (e.g. Down's syndrome), a malformation or damage from extreme prematurity. Under these conditions, the choices people make about antenatal screening would not have been coerced. These decisions will always be sensitive and difficult; they may often be subject to later regrets. However, if society can instil a 'justified confidence' that children born with problems will be supported collectively by the citizenry, then that society can be said to offer antenatal screening as a free choice. Without this reassurance built into the context within which a pregnancy takes place, the "offer" of antenatal screening will be one that many people feel they cannot afford to decline, so a high uptake will be achieved but at the cost of fear. With this reassurance to pregnant women, those affected by such conditions will also feel that society does not disvalue them. While there may still be problems from stigmatisation and loneliness, these will be simpler to cope with if society at large takes trouble to ensure that affected individuals are well supported.

Pressures to accept screening include simple routinisation, a bureaucratic audit culture, and commercialised packaging and marketing. If audit culture dominates the ethos of a screening programme, the performance of the programme will be judged by inappropriate metrics such as the uptake of the screening. While it will be important to ensure that as many pregnant women as possible accept the offer of some types of screening, such as where the wellbeing of the mother is at stake, this does **not** apply to the offer of antenatal screening as a "quality control" of the fetus. Professional expectations that women will comply with an offer of screening can be very strong, reinforcing multiple other factors that lead women to accept screening (Rapp 2000). The marketing of antenatal screening tests may also drive uptake if there are other social mechanisms

that lead to eugenic consequences, operating through a consumer mentality in which children are seen as products to be chosen or rejected (Duster 1990).

Choice and Commitment

Reproductive genetic screening is sometimes said to be offered with the goal of enabling parental, especially maternal, autonomy for its own sake. However, this is unconvincing as there are numerous other, sometimes trivial decisions that could be made available if the maximisation of autonomous decision-making counted as a valid goal *per se.* That, however, begs the question of what makes choice in itself so important. In the setting of prenatal testing, it must be the nature of the decision that is weighty not the mere fact of a decision. A more convincing explanation of society's wish to make antenatal screening available is that it allows decisions to be made as to which pregnancies - and therefore which fetuses - are continued to term. There is a tension here, between the mother's commitment to her fetus/baby on the one hand and, on the other, society's wish - and her wish too - that she have a healthy baby, who will go on to become a productive member of society.

We should not forget that the offer of screening tests imposes a burden on the pregnant woman. She may feel that she is expected to accept any offer, even if she is told that it is her choice. She is also being forced to make a decision - even by default - on possibilities that she may find it disturbing to consider. One way of describing this is to consider the question of parental (especially maternal) commitment to the pregnancy, fetus or infant. At some point, parents commit to a child and will then do all they can for her. That point may be at the first awareness of a pregnancy, at 'quickening', at birth or even some months after the birth. In some ancient societies, famously including Sparta, there was no automatic 'commitment' to a newborn infant at birth.

The offer of antenatal screening can impact the commitment to a pregnancy, as in the title of Barbara Katz Rothman's famous book, "The Tentative Pregnancy" (Katz Rothman 1986). Such disruption of a woman's relationship with her fetus must have emotional sequelae that play out at some point, and probably not to anyone's advantage. From the point of commitedness, parents accept the fetus or child as McDougall's "virtuous parent" (McDougall 2007). This can be at conception, at some point in the pregnancy - perhaps conditional upon "passing" the antenatal screening tests (Katz Rothman 1988) - or it may be after the birth. One can describe this as a tension between the parental commitment to a wanted fetus/baby and the more general, societal wish to commit to fetuses that will become healthy.

Inequity can be a problem in antenatal screening if only some can afford it and that shapes the pattern of disease in specific parts of society, as those who can't afford screening are more likely to have to face the practical, financial and emotional burden of a child with long-term illness or impairment. Conversely, those with additional resources may feel able to care for a child with a "costly" condition when a poorer family may be more reluctant to take these on; poorer parents may then face the moral hazard of not feeling able to afford to live up to their beliefs.

Compulsion and Carrier Screening

Finally, we can consider the injustice of compulsion. This is most evident when states have applied a eugenics approach, as in Nazi Germany, Communist China (Hesketh 2003), Sweden and some states within USA, where varying degrees and styles of compulsion have been used to impose sterilization, long-term contraception or compulsory abortion. We will not dwell on the details of these programmes here but the dangers and injustices are clear. Differing degrees of coercion or socially imposed obligation have also been used to require carrier screening for recessive diseases before marriage in some Islamic states in North Africa and the Middle East, some Orthodox Jewish communities and the Greek Orthodox church in Cyprus. There are valid debates to be had about the social obligation to have carrier screening as an approach to reducing the birth incidence of some otherwise common disorders. This may be the only way in which a low-income country could afford to provide treatment for their population of patients with, for example, beta-thalassaemia (Modell 2020; Cornel and Clarke 2021).

(vii) The promise of genomics: expectations and the management of hope

In this final section we look at the 'promise' of genomics, whether explicit or merely implicit. There is often an assumption that identifying the underlying cause of a problem will inevitably lead to a treatment, even a cure, within the near future. While entirely understandable, as a measure of hope is important when faced with great sadness and loss, raising false expectations is no kindness. When used to gain professional or commercial advantage, it becomes manipulative and cruel. We need to strike a balance when talking with patients and families: we need to offer and maintain a realistic hope, neither tipping people into despair nor raising false hopes that will only be dashed. One of the core functions of genetic counselling services is to promote adjustment to the reality of disease that affects oneself or a family member; this goal is not achieved by ramping up false expectations.

We will consider two settings within which this economy of hope can play out: recruitment to clinical trials of gene-based treatments for rare diseases, and whole genome sequencing of healthy newborns, leading to a person's whole genome sequence (WGS) being kept as a 'life-long resource'.

Clinical Trials, 'Actionablity' and the Therapeutic Misconception

A clear example is that of calls to identify the underlying genetic basis of essentially untreatable neurodegenerative disorders, such as amyotrophic lateral sclerosis/motor neurone disease (ALS/MND) on the basis that the diagnosis is "actionable" (Mehta et al 2022). Trials of a rational, gene-based but unproven treatment may be in process but there are potential disadvantages to the genetic testing needed to identify the very few families for whom a trial would be available. These potential disadvantages include the possible impact on other family members, who would be put at risk of the same condition - and in *C9ORF72*-disease also at risk of fronto-temporal dementia (FTD) - if a genetic basis was identified. Some patients and families will wish to go through with such investigations and to participate in any trials for which they are eligible but this altruism should not be assumed. Such actions should be undertaken with eyes wide open.

No clearly beneficial treatment has yet been identified for any genetic subtype of ALS/MND and careful discussion with the patient, and preferably the wider family, should take place before

genetic testing for this (Crook and McEwen 2022; Dharmadasa et al 2022; McNeill et al 2022). The fact that a natural history study of a condition is in process, or that a clinical trial is open to recruitment, is far from being the same as the condition being treatable, let alone curable. While the clinician may regard the disease as "actionable" - s/he can refer the patient to researcher colleagues - the patient and their family may well understand it otherwise. This difference in perspective between professionals and patients or parents is well recognised (Horng et al 2003) and may be especially problematic when a child has a rare disease (Woods et al 2014). Parents may be especially vulnerable to feeling the obligation to act - to "do something" - even when this is likely to be futile and may involve the child in discomfort or even a potential for serious harm (Clarke and Abdala 2018).

There are strong parallels with the rare neurodegenerative disorder Huntington disease (HD), where only a modest proportion (<20%) of individuals at risk seek predictive testing (Baig et al 2016) and where clinical trials have been in process for some years without a proven treatment having yet emerged.

Newborn Screening including Whole Genome Sequencing

Questions around the meaning of 'actionability' of genetic findings can also arise in the discussion about the introduction of whole genome sequencing (WGS) to newborn screening programmes.

There is understandable concern to develop newborn screening, so that it can be of benefit to more infants. The simplest, and the conventional, way to do this would be to use two approaches: to expand the range of inherited disorders identified by metabolic testing, that currently uses tandem mass spectroscopy (TMS); and to include other disorders that can be detected by sequencing a panel of genes in which variants lead to serious but treatable conditions, where the treatment is very substantially more effective if it is started before the onset of overt disease. To use WGS in this context is unnecessary; it adds to the costs and generates vastly more data than needed if the aim is simply to improve a 'newborn screening' programme. So why is this being proposed?

The simple reason is that the advocates of WGS in newborn screening have a broader agenda, much wider than merely the improvement of the health of a modest number of babies. The motivation to bring in WGS is a belief, held with great enthusiasm, that the additional data generated will be of great benefit to "the future". It may indeed assist with the interpretation of DNA sequence variants currently of uncertain significance and there will doubtless be long-term benefits to genomic research. In terms of the infants being tested, however, the situation is much less certain.

One likely outcome of such data being available is that there would be institutional pressure to demonstrate direct clinical utility to the WGS data on these healthy infants, by identifying those with sequence variants that might be pathogenic. Given that WGS inevitably finds many VUS in anyone sequenced, there is the potential that variants will be found that trigger interventions, such as contacting families to arrange monitoring and perhaps performing WGS on the parents too (to help interpret the variants) with complex medical, emotional and social consequences.

We must keep in mind that WGS can never replace the metabolic aspects of newborn screening for two reasons: because the commonest diagnosis is congenital hypothyroidism, which is not a (simple) genetic condition, and because the metabolic evidence is generated by TMS much more rapidly than the interpretation of the genome and is much stronger evidence for a diagnosable disease than is the WGS data, because the metabolic measurements on TMS are part of the phenotype.

Horton and Lucassen (2023) have considered the consequences of WGS in newborn screening and shown grounds for doubt about the wisdom of this, unless it is kept very specifically as a research endeavour clearly distinct from the regular newborn screening programme. Perhaps the most contentious aspect is the argument that the WGS could be a lifelong resource to guide a person's healthcare. There are many points at which this concept can be challenged, on both practical and ethical grounds, if it is introduced within the framework of newborn screening. It has been possible for consent for newborn screening to have become largely routinised, as it is so focused on the benefit of each particular child and has not been used to drive any other, larger agenda.

If WGS is 'slipped into' the newborn screening programme, consent will become a major and highly complex issue, with its own potential for adverse effects on uptake. In addition, other difficulties may arise with the 'lifelong resource' concept:

a) the tension between allowing access to information when needed clinically and the security of the data;
b) whether storing WGS data taken today is worthwhile, when the costs will be very substantial and will need to allow for changes in IT software and hardware systems over 80-90 years. Furthermore, the quality of today's WGS data may become woefully inadequate - not worth storing - within a few years. An alternative approach is to perform a WGS when indicated clinically, interpret the data and report it but then destroy the data and retest the individual as and when a further analysis comes to be needed;
c) it will be necessary to transfer the consent for holding and interrogating the WGS data from parent to child over time, so that a practical mechanism for this will need to be established;
d) it will be necessary to have a transparent and defensible policy on the question of whether secondary uses of the data - searching for evidence of pathogenic variants that are relevant to later-onset conditions but not relevant to a child's health - and whether/when/how parents would be given access to this, as it could be relevant to them;
e) the overall difficulty of the initial consent, when parents will need to understand a lot of these issues for that consent to be valid.

Many of these issues also arise when a sick infant in intensive care has WGS performed to help diagnose their acute, severe illness and the decision as to whether or not to perform the testing is forced by an immediate concern for the child. With a healthy child, in contrast, one is walking into the ethical and practical difficulties without the clear obligation to do so and with little expectation of benefit to the child.

The advantage of an early diagnosis for conditions that in the past have faced long delays is a major benefit of genome-based genetic investigations, even where no treatment is available. An

explanation for serious problems can itself be very helpful and even therapeutic in an emotional sense. However, the screening of healthy (so far unaffected) newborn infants for gene variants that it might prove helpful to know about is bound to flag up lots of variants in infants who will develop problems years into the future or perhaps never at all. This is imposing a different type of diagnostic Odyssey to replace the one we have been dealing with until now. This is the lengthy, distressing and (I would expect in many cases) hugely expensive search for a disease phenotype that may or may not ever appear. These will be "patients in waiting" (Timmermans and Buchbinder 2010) and will suffer the psychological sequelae of intense medicalisation as well as being subjected to lots of investigations and monitoring, and with consequences for the parents including much anxiety and sadness that they may resent. Generating predictive health information that does not give access to safe and effective preventive measures or treatments is much less clearly a benefit to families, as considered above in relation to neurodegenerative disorders.

It is the over-selling of unrealistic benefits that brings genomics into disrepute. In newborn screening, there will be a great temptation to over-emphasise the likely clinical utility of WGS by including entry to clinical trials or a natural history study or the ability to offer prenatal diagnosis in a future pregnancy (before pathogenicity has been established) as 'actionable' or 'beneficial'. All those types of actionability may be a good idea in principle, and one could support offering these tests to parents, but only as part of a research programme where there was a real focus on ensuring that parents understood what was and what was not being made available and with the assurance that full support and care would be available to families in the long term. To offer such testing without a high level of parental understanding would not be acceptable. Furthermore, those healthy children identified as likely to develop a serious condition will require monitoring, and their parents will require support, at least until the time that the child develops the anticipated problems. And some of these children may wait a long time before becoming unwell, and some may never become ill. They will undergo medicalisation, and their parents will suffer anxiety, sadness, and disruption to family life for …. nothing.

SUMMARY, CONCLUSION AND ABSTRACT

Many ethical issues have been considered in relation to the implementation of genomics in modern healthcare. However, questions of justice have received less attention than other core ethical topics, such as autonomy and consent, privacy and the handling of genetic information, and the utilitarian balance between benefits and harms. When justice has been considered, it has largely focused on questions of 'race', ethnicity and population groups, which is the complex but still important legacy of historic wrongs, especially the colonialism, slavery and oppression of indigenous peoples by European powers and the USA. This topic is of immense importance but there are other important areas where justice also needs to be considered.

We address the numerous other ways in which genomics does or could reinforce or exacerbate current social injustices. We consider these under seven headings. As the application of genomics within healthcare expands, we must take great pains to counter misapplications of the science under all these categories:

- access to healthcare in general, the impact of social class and the 'inverse care law'
- management of personal genetic and health data; institutionalised discrimination against social groups
- the recognition of biological, epigenetic effects that reinforce the harmful impact on health of poverty, inequality and powerlessness
- the genetics of intelligence (i.e. IQ) and mental health and the potential for its abuse in public life as well as the potential for harm in unwise clinical applications, such as self-fulfilling prophecies
- the complex genetics of multifactorial traits and diseases and the trend for this to undermine collective efforts to improve public health and instead drive the individualisation of responsibility for one's personal health
- the potential for reproductive genetic screening, both antenatal screening and carrier screening for recessive disorders, to drive inequity and perhaps discrimination
- dealing with the 'promise' of genomics: maintaining the balance between offering realistic hope versus raising false expectations in how genomics and genome-based interventions are presented to patients

There will be no single solution to these difficulties and tensions. The professional responsibility not to inflate achievements or promises will need to be monitored by all genomics professionals, reviewers of grants and papers, and publishers. Professional bodies, such as (in the UK) the Royal Colleges and the General Medical Council need to recognise their obligation e to set standards and police them, especially in relation to genetic testing in mainstream specialties and fetal medicine/obstetrics. The law may need to be invoked in the realm of private and direct-to-consumer genetic testing, in addition to professional standards, with additional standards to be set for test providers to ensure understanding of a test prior to consent and honesty in advertising and promoting tests. Furthermore, to avoid the imposition of the costs of follow-on personal or family genetic testing on the national healthcare system, this may need to be charged to the provider of the initial test. These are all steps that will promote the recognition of justice in the implementation of genomics in healthcare and beyond. The most important requirement for progress, however, is the growing recognition among genomics practitioners that there is a problem and that we must confront it collectively.

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