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EDITORIAL

Editorial to special issue on Ethics in Genetics

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It is a pleasure and honour to introduce this special issue on 'Ethics in Genetics', co-edited by myself and Professor Angus Clarke, a clinical geneticist and Professor of Clinical Genetics at Cardiff University, Wales.

We are in the midst of a technological revolution in terms of our ability to identify and potentially treat genetic disease. Whilst the *nature* of the ethical considerations at play with respect to genetic technologies and testing have not changed, the scope of these ethical issues has expanded dramatically with genomic technologies such as next-generation (high-throughput, massively parallel) sequencing. Risk is inherent: and the levels of risk that individuals, families, and societies will tolerate will often depend upon the perceptions and experiences of benefit. Yet, those perceptions and experiences may not be achieved without broader use. There is an urgent need rapidly but also thoroughly to assess the potential ethical challenges, without discarding the potential benefits. These ethical considerations must extend beyond the traditional pillars of autonomy, beneficence, and non-maleficence, encompassing justice and a public health ethics approach.

Indeed, one key theme running throughout these contributions is justice: how can we support and inform a just genomic revolution? Health inequality has been exacerbated by the recent coronavirus epidemic, with inequity seemingly impervious to interventions, such as universal healthcare, to reduce its impact on the health of the most disadvantaged. The ways in which genomics exacerbates and extends notions of inequity are clear to see—testing remains the preserve of high-functioning, high-investment health systems, and genomic therapies even more so. Adequately addressing the public health ethical considerations—creating a genomic revolution with solidarity and justice at its core—will be key to how the ethics of the genomic revolution play out in the near and the distant future.

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A number of articles focus on the considerations that arise in prenatal testing, with respect to both reproductive decision-making and the foetus as patient. **Dive and colleagues** describe the evolution of carrier screening in reproductive decision-making, from one aimed at individuals at known increased risk of having offspring affected by disease, to a commercially viable entity in assisted reproduction or indeed a public health level intervention. Again, justice is at play—inequity due to the financial means to access testing and the knowledge of families who may benefit from this testing that it is indeed an option. The paper draws on three genes which exemplify the challenges in gene selection, namely CFTR, GALT and SERPINA1, with a particular focus on how the seriousness of a disease, and issues around incomplete penetrance, variable expressivity, and the ability to provide screening at a public health level may impact decisions about what should be included in screening.

Bryant gives us a personal account of her complex, even entangled, relationship with Down's syndrome. This is a rich reflection upon the tension between respect for individual women and the decisions they make about reproduction, on the one hand, and the respect due to people with Down's syndrome both individually and at the broader societal level. There are no easy answers but it is important to be aware of the tensions and, indeed, to make effective use of the tension to enhance the quality of care for both groups.

Prenatal medicine has been revolutionised by genomic technologies, and remains the field in which concerns about the ethical, social, and legal impact of genetics have been most comprehensively considered and explored. **Schmitz and Henn** explore the implications of the age of the genome for foetal medicine, from both a diagnostic and interventional perspective. Future autonomy is key to this exploration—how can the implications of technologies which assist reproductive decision-making and choice be rendered congruent with the (potential) rights of (future) children? Defining the unborn foetus as a separate moral subject, rather than one in unique physical connection with the pregnant woman, acts as a barrier rather than a support to characterising the moral quandaries and asserting the

moral boundaries that underpin the practice of foetal medicine. Here, perspectives on justice encompass the assignment of significant financial resource to prenatal genomic testing, as well as the long term societal implications of 'screening out' variation such as trisomy 21.

The application of next-generation sequencing in the newborn intensive care nursery is examined by **Lantos and colleagues**, who present a cautious account of the potential role of genomic technologies for acutely unwell infants. This challenges the notion of what a more timely diagnosis, achieved through genetic testing, *does* for both their clinical care, and the early experiences of families coming to terms with an uncertain diagnosis. The paper describes how quicker diagnosis may not necessarily be better, if the management remains unchanged. There is a critique of accounts in the literature about how the value, or impact, or a genetic diagnosis made through NGS can be measured, asserting that many of the claims of genetic diagnosis impacting on clinical care are, at best, overstated and, at worst, misleading. Yet, there is also an account of the solidarity a diagnosis of rare disease can provide to parents, through ending a diagnostic Odyssey and moving on to a place of knowing. It calls on practitioners to remain humble about what genomic technologies can hope to achieve for patients and families, and recognises how recently this field has been born and is already applied in neonatal care.

Newson extends on and contrasts with these concepts by looking at how newborn preventative genomic sequencing, presented as a form of precision medicine, can be framed as a collective endeavour through the lens of public health ethics. She calls again for the ethics underpinning public health—built on notions of justice—to fuel future considerations of the ethics of genomic medicine through a focus on populations, collectives, and shared values. New perspectives from patients and genetic services within and beyond the UK support precision medicine at population scale, which is possible only because of the new genomic technologies. This is a call to the next phase of bioethics scholarship in genetic medicine, as we explore what a moral genomics means at the collective level beyond that of individuals and families.

Next, we move to practical considerations around information use within the clinical setting. As genomic knowledge develops constantly, what obligations do we have to patients and families who have had testing in the past, for whom new genetic understanding may be relevant? **Doheny** explores this question, taking the narrative beyond one of professional consensus by considering the ethical and practical imperatives, as well as perspectives from patients using genetic services within and beyond the UK. The action of re-contacting becomes contingent on the 'duty to reinterpret' (Applebaum, 2020) which is poorly defined and unregulated. Is there an ethical obligation which flows from the production of new knowledge? How can this be practically managed in the context of already-overwhelmed systems of healthcare, and how do considerations such as patient autonomy come into play?

In their paper, 'In the Family—access to and communication of family information in clinical practice', **Clarke and Luccassen** go head-to-head to consider 'who' genetic information belongs to. They are agreed on the need for information generated in testing with potential consequences for health to be used—at the laboratory level—for testing family members, which may help in the diagnosis of disease, or potential disease. However, they remain opposed in their accounts of whether genotypic information should be regarded as belonging to individuals or to family groups. They sometimes agree as to what needs to happen but differ in their justification as to why. The paper draws on real-world conflicts in disclosure practices, with respect to the case of *St Georges versus ABC*, and the 'right to know' familial information in the context of both personal and reproductive risk. Considering molecular information as distinct from diagnostic labels (and the implication of these labels), whilst a seemingly straightforward concept, is challenging in the reality of integrated systems of healthcare, where notions of confidentiality and indeed 'who is the patient' at a particular time, in a particular place, are in flux. They conclude with a topical account of contact tracing in the coronavirus pandemic, and the apparent public acceptance of knowing about exposure, without knowing where or how exposure happened—an interesting parallel around notions of acceptable information sharing.

The inherent risk of generating off-target, secondary information, or variants of uncertain and unknown significance, provide challenges for all those involved in genome-based testing. How such information is managed, in both the research and clinical settings, is addressed by **Vears.** She argues for increasing familial autonomy when considering unsolicited findings through the concept of establishing zones of parental discretion within the consenting process, drawing on empirical examples from practice. This concept maximises parental autonomy even where there is no expected benefit, provided that there is no evidence of serious harm. From an equity point of view, this supports patients in receiving information about potentially life-saving information and provides a method for mitigating the current vast variety in practices regarding the reporting of unsolicited findings.

We then turn to two papers that relate to treatment, i.e. active patient management. The first paper is by Austen, who outlines her approach to the use of genetic testing for copy number variants (CNVs) in the context of developmental delays in childhood and psychiatric disorders in adults. The same chromosomal changes are often associated with both types of disorder but it is less clear that genetic testing is

of equal value in both settings. This is part of an important dialogue that we need to pursue as genome sequencing comes to reveal changes associated with a risk of psychiatric disease. Under what circumstances will genetic testing be helpful in terms of diagnosis, therapeutic guidance or stratifying the degree of individual susceptibility to such problems? What potential difficulties—stigmatisation, the scope for self-fulfilling prophecies—will result from genetic testing for psychiatric conditions? While genetic research in psychiatric disease is clearly of importance, will it be of value in a more routine clinical context?

In the second paper, **FitzPatrick and Bird** provide a comprehensive account of potential genetic therapies for neurological disease, examining the mechanisms and challenges of moving from bench to bedside. Some of these arise from the risk of undesirable side effects, where an intervention might reverse or ameliorate symptoms of disease, recognising that the severity of the disease in question may influence the risk that individuals, families and indeed society at large, may be willing to take. Whilst editing in germline cells remains ethically contentious, and indeed illegal, what constitutes adequate consideration of the potential consequences of gene editing in somatic cells remains poorly defined, and statutory guidance is lacking. The theme of justice arises again, in terms of the cost of interventions limiting their use to a chosen few.

Janssens and Penders explore the notion of 'doing polygenic risk scores', challenging the credibility of PRS-based knowledge claims. There is a particular focus on how our language as professionals—be it in clinical practice or research—renders elements of practice more or less visible or certain, and that for polygenic risk scores, this contributes to their credibility as much more than formal inferences. It describes the need for the language of genomics to move away from 'black box' thinking, which implies acceptance, to a more critical and nuanced frame of description which acknowledges the limits of inference and computation. Recognising that we use words and numbers to describe the world, we have come to appreciate how these language practices shape the world as well as describing it. The article calls on practitioners to be critical of how languages of discovery can easily be conflated with those of expertise and skill.

Finally, there is a paper with an explicit focus on issues of justice. **Clarke and van El** consider the notion of justice with respect to the potential harms and inequities of genomic medicine. In this critique, there is recognition of how hopeful perspectives of the potential of genomic technologies fail to recognise its potential in contributing to, and indeed exacerbating, inequity and injustice at the individual level and at the broader, societal level. It builds on the account of FitzPatrick and Bird, who described therapeutic interventions in neurological disease as being limited to a chosen group due to their cost. Clarke and van El provide an ambitious account of the potential for injustice arising in the implementation of genomics in medicine. This paper provides a wide-ranging account of potential harms; it serves as a call-to-arms for those working in genomics to recognise their own potential for generating or amplifying injustice and, especially, their potential for conflicts-of-interest. These arise in relation to the promises and potential pitfalls of genomic technologies in clinical work, and the world beyond the clinic, including public health and population screening, reproduction, and direct-to-consumer testing.

The intention in coordinating this special issue was to commission a broad range of articles of universal interest to those working in genetics—be that in the clinic, the laboratory or in academia. We could not cover all areas, not even all areas of topical interest, but believe that this collection will be of interest both within the community of genetics professionals and more generally within society.

The timing of this special issue has been impacted enormously by the coronavirus epidemic, with it having been some 3 years in the making. We would like to thank the contributors for their thoughtful, energetic contributions. We hope you enjoy, and are challenged by, these perspectives. It has been a privilege to commission them and see them gradually assembled to become this collection. We believe that these articles serve as a reminder of the ever-changing scope and scale of the ethical considerations arising in genomic practice within and beyond the clinic. We hope that you agree.