

The background of the cover is a repeating pattern of DNA base pairs (A, C, G, T) in various colors (green, blue, red, black). A magnifying glass is positioned over the center, focusing on a specific DNA sequence. The text is overlaid on this background.

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ETHICAL, LEGAL, AND SOCIAL ISSUES IN CLINICAL GENOMICS

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INTRODUCTION

The astonishing development of massively parallel, high-throughput DNA sequencing technologies over the last decade means that sequencing multiple genes or even whole genomes is now becoming a clinical reality with enormous diagnostic potential.^{1,2} This has far-reaching consequences for the practice of clinical genetics as well as mainstream medicine and public health.

Sequencing a genome should not only be regarded as a clinical test, but also as an assay that creates a data resource that has the potential to be repeatedly interrogated with specific analytical questions. Under a model wherein individual genome sequences are stored and linked to personal medical records, each new analysis is essentially free of cost. The clinician will no longer need to decide what laboratory test to order based on a set of clinical phenotypes, but which bioinformatics analyses to perform and when. The challenge will therefore become one of data interpretation rather than data acquisition. Ultimately, both the scope and breadth of testing are likely to expand, from the niche specialty of clinical genetics focused primarily on targeted diagnostic testing of families with inherited disorders and birth defects, to genome sequencing of individuals throughout mainstream medicine to allow increasingly stratified diagnosis and treatment.

Does the shift from genetics to genomics raise any new ethical, legal, or social issues? Although at first sight there might appear to be nothing new beyond the scale and flexibility of genomic testing, the creation of unprecedented amounts of personal, identifiable data with a multiplicity of medical (and other) applications has novel ethical implications,³ particularly for responsible data stewardship. Genome sequencing is not only likely to be the first medical test that could potentially offer everyone a positive result of some clinical value, but is also likely to be one where the vast majority of results will be of little or no value whatsoever.

This change in scale therefore creates enormous challenges in itself, from accurately interpreting variants in individuals, families, and populations, to protecting individual privacy and managing public expectations, to the delineation of the responsibilities and duties of care of clinicians and researchers.

In the first section of this chapter, we review the ethical values and norms at the heart of traditional clinical genetics (often termed “genethics”⁴); in the second section, we outline the key ethical, legal, and social challenges in an era of whole-genome sequencing (which we term “genomethics”). Finally, we discuss the implications for the boundary between clinical practice and research.

GENETHICS

Clinical genetics has traditionally focused on diagnostic and predictive testing for rare, highly penetrant germline genetic variants. These variants are either inherited and are uncovered through family history, or occur spontaneously (*de novo*) and are generally diagnosed in childhood, in relation to reproduction or linked to the inheritance of adult-onset cancer. Therefore, unlike most other areas of medicine, clinical management is generally centered around the family rather than individual patients. Of the thousands of rare disease-causing variants known, many have catastrophic biological and phenotypical effects, and determining the presence (or absence) of a particular genetic variant in an individual is highly predictive of current and future disease both in that individual and their relatives.

Many of the ethical principles and guidelines that have evolved in the practice of clinical genetics stem directly from these properties of rare Mendelian diseases—that variants are extremely predictive, and they may have profound implications that reach beyond the individual being tested. Similarly, many of society’s concerns about genetics

can be traced to the same origin. The perceived power and inescapably deterministic feature of Mendelian genetics has led to a fear of stigmatization and unfair discrimination, which in turn has led to the introduction of genetic non-discrimination legislation and insurance moratoria in many countries. The treatment of genetic information in this way, as needing special protection above and beyond other biomedical data—a practice known as “genetic exceptionalism”—also derives to some extent from the widespread misunderstanding that genetic tests deliver certainty. Although *genetic exceptionalism* has been widely criticised,⁵ and is based on the false belief that most genetic information is deterministic, clinicians must nonetheless address and respond to these preconceptions and worries when working with patients.

The emotion attached to a diagnosis of many Mendelian diseases may be very significant for both the individual and family. The discipline of genetic counselling has developed from the (patient-led) necessity for psychosocial and informational support to help individuals and families cope with the impact of a genetic condition. Genetic counselling for rare, highly penetrant, serious—often life-threatening—conditions is available from specially trained clinical geneticists and genetic counsellors. These professionals use established, evidence-based communication models that offer time and space to individuals and families to consider the emotional and psychological implications of being tested for a family condition. Many recognized ethical, legal, and social issues have emerged from genetic counselling practice over the last 50 years, and any discussion about genethics must involve genetic counselling practice.

CONSENT AND AUTONOMY

A key ethical commitment in clinical genetics is a respect for individual autonomy, which manifests itself in a widely agreed recognition of the importance of providing genetic counselling and ensuring informed consent prior to undertaking testing. This often involves gathering consent for testing from potentially affected relatives, particularly where the individual referred for testing is not himself affected. The obtaining of valid consent (or refusal) is, however, not always a straightforward matter. Individuals may struggle to fully comprehend the future implications of a test result, and obtaining informed consent from family members can sometimes be extremely challenging; for example, due to difficulty in knowing how to communicate genetics to relatives, possible differences in opinion about testing, or simply problems in even making contact due to family breakdown. Moral dilemmas faced

by genetic health professionals occur when individual autonomy conflicts with familial solidarity. Should an individual be able to consent alone to a test that will reveal information about a family member who does not want to know their result?

Maintaining patient confidentiality and an individual's right to privacy is important in clinical genetics and, as such, genetic diagnoses are generally treated no differently from other potentially sensitive personal medical information. However, unlike the case with most other medical data, respecting individual privacy and or choice can be problematic in the context of “at risk” families in which it is possible that individual family members will have different values and conflicting opinions. Does an individual have a right not to know their own genetic makeup,⁶ or to withhold access to it when a family member is in need of the same information?⁷ In such cases, the value of privacy needs to be balanced against the rights and freedoms of others, and in certain circumstances it may be justified to break confidence in order to avoid serious harm to a relative.⁸

Particular difficulties arise around testing those who cannot give consent (minors and those lacking capacity). Testing for preexisting conditions or those where early preventative actions may be taken is usually advised, and offered with consent from a parent or legal guardian. However, most professional guidelines in Europe⁹ recommend that minors should not be tested for adult-onset conditions for which no immediate preventative action exists, which reflects a general consensus that this would infringe on the autonomy of the future adult to make their own decision about genetic testing.¹⁰

REPRODUCTIVE AUTONOMY AND ITS APPROPRIATE LIMITS

The use of preconception, pre-implantation, and prenatal genetic testing to facilitate reproductive autonomy is a critical part of modern clinical genetics, and for many couples who choose this option, it has substantially reduced the burden of serious inherited diseases.¹¹ Individual autonomy, non-directive counselling, and patient empowerment¹² are central to supporting decisions that may include opting for assisted reproduction, destruction of unwanted embryos, or termination of affected pregnancies. Respecting the individual's reproductive autonomy also means supporting and providing appropriate care to women and couples who choose not to opt for these routes—for example, women who, on discovering that their pregnancy is “at risk” or “affected,” opt to continue the pregnancy to term.

Ongoing political debate surrounding embryo research and the ethics of abortion, amplified by the unpleasant historical specter of eugenics, means that developments in this area continue to be somewhat contentious. The scope of individual reproductive choice remains unclear, and the majority of genetic tests available remain within the confines of highly penetrant clinical diseases. Controversies have arisen relating to what constitutes a “disease” and to what extent the autonomous choices of parents—to choose to have a deaf child using preimplantation genetic diagnosis, for example¹³—should be respected. Sex selection for social and cultural reasons or family balancing is generally viewed as unacceptable in most countries and is only permitted to prevent X-linked diseases.

INCIDENTAL FINDINGS

The issue of obtaining informed consent for genetic testing is further complicated by the potential for uncovering incidental findings (IFs)—unexpected results that do not relate to the original clinical inquiry but that may nonetheless have equivalent or greater clinical or personal significance. This is a familiar problem within the medical imaging community, where scans may often reveal unexpected findings of unknown significance, many of which turn out—after further investigation—to be benign.¹⁴ Genetic examples range from discovering an adult-onset cancer-predisposition gene in a child being investigated for developmental disorders,¹⁵ or uncovering misattributed paternity (or maternity)¹⁶ in the course of a routine test. Although the use of targeted molecular testing for specific variants largely mitigates this problem for many conditions, use of genome-wide technologies such as karyotyping and DNA microarrays have made IFs a more frequent clinical occurrence. To date, there is very little consensus on how to handle these findings, and practice tends to vary between services and clinicians, often based on perceived clinical utility.

GENOMETHICS

The move from genetics to genomics will bring about a profound change in the practice of clinical genetics, primarily due to the dramatic fall in costs and the impending data tsunami. Since every individual has around 3 to 4 million genomic variants (versus the reference sequence),¹⁷ data management and interpretation will be an enormous challenge. High-resolution DNA microarrays have already given laboratories and clinicians a glimpse of the problem: a plethora of genetic variants present in every individual,

most of which have unknown clinical significance and are unrelated to the reasons for which these tests were ordered.

In twentieth-century genetics, the majority of variants seen clinically were rare and assumed to be pathogenic; however, twenty-first-century genomics has shown that non-pathogenic genetic variation is far more common. Knowledge of normal population genetic variation is therefore crucial to interpreting genomic data. Whole-genome sequencing has the potential to reveal, not only rare highly predictive variants with heritable consequences, but also novel and common variants with unknown or no clinical or phenotypical consequence. Some variants will be risk factors for common complex diseases; others may play a role in drug metabolism and toxicity; a number will relate to behavioral phenotypes; but many will have no discernable effect. In an era of multi-gene panel testing and clinical whole-genome sequencing, most variants are likely to be assumed to be benign until proven otherwise.

Whilst genetic counselling and the ethical practices developed in the rare-disease-genetics field offer a solid foundation upon which to build, their relevance is weakened when we consider whole-genome testing. The paradigm of genetics as deterministic and familial is unconvincing in the context of common variation, minor genetic risk factors, and somatic mutations. In reality, most human traits and diseases are complex and multifactorial, most variants have variable penetrance due to environmental interactions or other genetic modifiers, and the majority of germline genetic variation has little or no predictive power for individuals or their families. All genomes contain some loss of function variants and recessive alleles,¹⁸ and a whole-genome analysis could yield reams of information pertaining to a multitude of traits, providing risk figures that are either small, weakly predictive, or uninterpretable. One might expect that such benign information will have minimal emotional or psychosocial value for the individual or their family. This contrasts enormously with a single test for a highly predictive, serious, life-threatening condition. Therefore, although the ethical, legal, and social issues around the rare-disease component of genomics are well established, the framework required for genomethics necessarily has a broader scope, due to the unprecedented scale and range of genomic data as well as the seemingly less evocative nature of it.

RESPONSIBLE DATA STEWARDSHIP

The first and most obvious principle in genomethics, stemming from respect for autonomy and the importance

of avoiding, or minimizing, harms, is the need to ensure that individuals' data are handled in an ethical manner. In particular, difficulties arise where respect for an individual's privacy conflicts with public beneficence and the need for data sharing. There is no question that individual medical records, which include genomic data, should be stored securely and protected effectively (like any other sensitive medical data), with access limited to the patient themselves, medical professionals who need access to deliver high-quality clinical care, and the researchers involved in studies to which the patient/participant has consented.

However, there is also no doubt that data-sharing across jurisdictions is crucial for both clinical interpretation of genomic test results, as well as future scientific research and development. Discriminating between classes of variants for different diseases in any individual's genome will rely entirely upon large genotype-phenotype databases of previously sequenced genomes, against which each variant can be compared. These databases will inevitably be the result of international collaboration in many, if not most, cases. How can this be achieved without infringing on an individual's right to medical privacy? What is the just and fair way to treat an individual's genomic data shared across multiple jurisdictions?

Although ethical practice in this area is still evolving,¹⁹ the principle of responsible data stewardship has already been established, and models of good practice are being developed by numerous biobanks and data repositories globally.²⁰ This includes strong protections for individuals, such as explicit consent for inclusion in genomic databases at the point of testing and appropriately de-identifying or anonymizing publicly accessible data, whilst promoting managed data access to those who have a legitimate need for it. Because genome sequences (and some rare phenotype combinations) are uniquely identifiable, it may never be possible to completely remove the chance of re-identifying an individual from within a full dataset; hence limited, aggregate, or pooled datasets may be more suitable for wider release. However, the likelihood of, and harms associated with, this outcome must be appropriately weighed against the certain benefits of data sharing. Genomic databases frequently have different levels of access with alternative security provisions based on professional and institutional responsibility and accountability. However, while managed data sharing amongst academic and medical centers is now commonplace, granting access to commercial organizations—ranging from biotech, diagnostics, and pharmaceutical companies, to insurance, advertising, and employment

agencies—is varied and likely to remain controversial for the foreseeable future.

VALID CONSENT

Although obtaining informed consent remains the cornerstone of good practice, many have pointed out the difficulty of obtaining truly informed consent for whole-genome sequencing.^{21,22} The potential scope and use of the data, both now and in the future, is enormous and unpredictable; hence, the potential benefits and risks of genome sequencing cannot be accurately or comprehensively assessed. This has led to proposals for “open” or “broad” models of consent,²³ which do not attempt to restrict the data to specific uses but keep the dynamic nature of scientific research in mind. For example, using the data from specific individuals or cohorts as control datasets in unrelated research studies is an invaluable method for interpretation and discovery, but it is clearly impossible to predict what future studies will either investigate or uncover. Regardless of the context for testing, depositing data in global databases to facilitate the interpretation of individual variants and for use in future research is absolutely critical to reaping the benefits of genomics for healthcare.

GENOME SCREENING

The issue of consent for multigene testing or whole-genome sequencing is further complicated by the occurrence of IFs. The magnitude of this issue is so vastly increased in whole-genome sequencing versus traditional genetic testing that there are suggestions that IFs should no longer be regarded as incidental or unexpected, but as anticipated secondary findings that will occur regardless of the primary purpose of testing. Everyone carries a number of recessive variants of relevance to reproductive choice, as well as variants relating to drug metabolism, disease susceptibility, ethnicity, and family background. There remains much debate over how to deal with the spectrum of information contained in a genome sequence, ranging from whose responsibility it is to look for and interpret IFs, to what types of IFs should be shared with patients and research participants, and who should have access to the information. Genomic analysis will necessarily be targeted using computational methods, but these analyses could be limited to diagnostically relevant variants or used to facilitate wider genomic screening. In 2013 the American College of Medical Genetics and Genomics recommended that all clinical genomes should be screened for clinically actionable variants in a short list of genes relating to serious genetic conditions.^{23a} Should

individuals be able to consent to receive specific genomic findings, but not others? Do healthcare professionals have a duty to reanalyze individual genomes and re-contact patients in light of new scientific discoveries relating to any clinically important findings?

Although most of the work on dealing with IFs has focused thus far on research participants²⁴—primarily because most genome-sequencing data to date have been generated in a research context—the same conceptual frameworks for thinking about IFs apply equally in the clinic. The main difference, if indeed there is one, is in the responsibility of a clinician to act in the best interests of their patient (although the clinician may actually wear two hats—one as the main clinical caregiver, and one as a clinical researcher). When clinically actionable variants are uncovered, it would be usual for a clinician (wearing her or his clinical hat) to share these with patients, regardless of whether the result relates to the primary purpose for testing or not. Difficulties nonetheless arise around variants with unknown or minor clinical significance, variants associated with diseases for which no therapeutic or preventative actions can be taken, recessive variants that may be relevant to reproductive choice, and so on. Although numerous proposals have been made to group variants into different categories according to their clinical validity and utility, and potentially offer a choice of which variants to analyze and disclose to the patients,²⁵ no consensus has yet been reached. From a public health perspective, trawling through an individual's genome looking for potentially pathogenic variants in the absence of any associated symptoms, phenotypes, or family history is perhaps more akin to screening than diagnostic testing and hence is likely to be prone to false positives and over-diagnosis. Even relatively well-characterized known pathogenic variants have often been studied only in symptomatic individuals and families, so little is known about their frequency and penetrance in the asymptomatic general population.^{25a}

There are specific concerns about IFs and genome screening in relation to prenatal genome sequencing.²⁶ Currently, there are clear guidelines for tests that are offered prenatally, and where possible targeted tests are generally preferred to open-ended genome-wide assays. However, were genome sequencing to be used, and potentially offered non-invasively by testing cell-free fetal DNA circulating in the maternal blood,²⁷ there is a potential to creep outside of the purpose of testing. In addition to their potential for use in reproductive choice beyond those envisaged at the time of testing, such as decisions to terminate pregnancies at very low or uncertain risks, secondary

information from prenatal genome sequencing might be used to inform parents about traits of future interest in the child. This could change the norms and expectations of pregnancy, and undermine the child's future autonomy to choose not to know about their genome, while perpetuating an inappropriately deterministic view of the role of genetics in child-rearing.

A concern often raised over IFs and variants of unknown significance is the potentially unmanageable workload that dealing with large numbers of variants in every patient might bring to the health profession. Although this is unlikely to be problematic if IFs are limited to known clinically actionable variants,²⁸ the informatics infrastructure required to develop and maintain a clinical-grade analysis system to alert clinicians to important genomic findings is currently nonexistent within healthcare services. The possibility that patients might be able to choose what results they wish to receive from a menu of options is highly speculative at this point, and would require substantial investment in informatics, medical training, and public education. Moreover, the economic and legal implications of providing a detailed interpretation of every individual's entire genome sequence have not yet been established, and doing so will be crucial for determining how best to invest limited healthcare resources.

MAINSTREAMING GENETICS

As the science of genomics develops, and more single-gene subsets of common diseases are uncovered, it is likely that genetic or genomic tests will increasingly be ordered and interpreted by medical specialists outside of clinical genetics. The move towards mainstream medicine is likely to be accompanied by a shift away from managing families in favor of testing individual patients—even if it is likely to continue to be the case that at-risk family members will be identified as a consequence of unexpected clinical manifestations of potentially inherited disorders. Consent for testing may become more *laissez-faire*, as a genomic analysis comes to be seen as just another test along with a battery of other standard tests used to diagnose an individual's condition. Indeed, for the vast majority of people who do not have a highly penetrant, heritable genetic condition—where the genetic information will be used primarily to stratify the disease subgroup or choose the most suitable treatment regime—enforcing a model of genetic counselling and informed consent that requires individuals to consider the future implications for family members prior to testing may be unwarranted and possibly unwelcome.

GENOMICS IN PUBLIC HEALTH

There are also potentially far-reaching applications of genomics in public health.²⁹ Existing genetic-screening programs—such as preconception carrier-screening, antenatal screening, and the newborn bloodspot screening test—could potentially be expanded to include more conditions using genome sequencing, without the need for a major reassessment of the overarching ethical context in which these programs are offered. However, it has been suggested in the media that newborn babies will or even should have their genome sequenced at birth and stored for future use, replacing the existing newborn bloodspot and any future requirement for genetic data. Such an enormous change to medical and public health practice is unlikely to be considered seriously until data security and public acceptance can be guaranteed, and clinical utility and cost-effectiveness proven.³⁰

A population database of individuals' genomes would allow a plethora of screening tests to be systematically performed, both for heritable single-gene conditions and for genetic risk factors associated with common diseases. This might allow existing screening programs to be better targeted at populations with the highest risk.³¹ Whether the systematic collection and storage of individual genome sequence would improve population health to an extent that justifies the resources required is currently unclear. Public acceptability of the storage and use of genomic data for such purposes remains largely unexplored, and the clinical impact of specific genomic variants in healthy individuals is largely unknown.

RESEARCH VERSUS CLINICAL CARE

One peculiarity of genetics and genomics is the particularly close relationship between clinicians and researchers, and hence between patients and research participants. Both genomic technologies and scientific understanding have advanced at such a pace over the last decade that the best way to access state-of-the-art technology and knowledge is through research studies. Many patients have become research participants in the hope of finding a genetic diagnosis for their condition, and many clinicians have turned to research for the same reason. This has led to a substantial blurring of traditional boundaries between providing individual clinical care and doing scientific research.

As a consequence, in the genomic era, many of the ethical principles discussed in the previous section are going to become equally applicable within the research and the clinical context. However, unlike clinicians, whose primary responsibility is to their patient, the researchers'

main responsibility of has until now been primarily seen as being to society (or to their funders). The relationship between patients and clinicians, and their respective rights and responsibilities, are well established and enshrined in best-practice guidance, medical regulation, and governance; in contrast, the relationship between research participants and researchers is essentially unregulated (aside from the input of local research ethics committees). What responsibilities does a genomic researcher have towards an individual research participant?

INFORMED AND VOLUNTARY CONSENT

Informed and freely given consent is a vital part of research on human subjects, enshrined in the Declaration of Helsinki,³² which states that "in medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests." Participants should have a good understanding of the research and its implications, and should feel able to refuse to take part or withdraw at any time without penalty. Aside from issues concerning obtaining meaningful informed consent for genome sequencing, discussed earlier, the other key element of informed consent is that it should be given voluntarily. Ensuring true voluntariness in the face of ever blurring boundaries between clinical practice and research is a challenge, and the therapeutic or diagnostic misconceptions that accompany that blurring are potentially important. Individuals may feel they have no choice but to join a study if they want to get a diagnosis, particularly where the clinician and the researcher are one and the same person. Cultural and linguistic barriers, as well as a general ignorance about genetics, may also play a role in whether individuals or families fully understand what they are consenting to and whether they feel able to decline to participate. With respect to samples, consent must detail whether samples will be stored for future use; though again, broad consent may be preferable to allow for future avenues of research. Importantly, there is a developing consensus that unauthorized (unconsented) genome testing should be prohibited,¹⁹ and performing a genetic test on any sample originating from an individual who has not consented ("DNA theft") is illegal in many countries.

RESEARCH FINDINGS

Individuals may participate in medical research for largely altruistic purposes, to contribute to human knowledge, or they may be motivated to enter a research study primarily

for personal reasons, such as access to a new treatment or diagnostic technology. Regardless of their motivations, it has been argued, the ethical principles of autonomy, beneficence, and reciprocity are directly relevant to the relationship between scientific researchers and research participants.³³ This has led to the suggestion that, in addition to publishing the aggregate results of their research in the public interest, researchers should offer to return individual-level research findings to individual participants. Importantly, the policy regarding the return of individual results should be made clear at the consent stage, so that individuals can choose whether they wish to participate.

Once again, the issue of IFs is highly topical here. Unlike clinical testing, there is no requirement or expectation in most research studies to return any individual-level data, even results relating to the specific research purpose. However, the academic debate over returning individual research findings to individual research participants is moving in favor of offering to return a variety of different findings, possibly with an option at the point of consent for an individual to decide what types of results (if any) they would wish to receive.³⁴ Options might range from raw genome data, to data about a wide variety of traits and diseases, to pathogenic variants that cause a specific predefined condition. Non-clinical data, such as consanguinity or misattributed paternity, should be also be explicitly considered and discussed.

Some proponents of this model go further, and suggest there is a moral imperative to return life-saving clinically actionable findings to individuals (or their healthcare providers), arguing that not to do so is tantamount to disregarding the “Rule of Rescue—the perceived duty to save endangered life where possible”³⁵ This implies that researchers have a duty not only to society, to perform the research that they have been funded for, but also to individual research participants—to provide genomic analysis across a wide variety of clinical conditions and re-contact individuals or their clinicians where it is deemed appropriate. In practice, placing this additional burden on research teams or biobanks has enormous resource implications and may ultimately be deemed inappropriate and unnecessary in many cases, particularly where the cohort is simply too large or geographically dispersed to maintain high enough standards of sample-tracking and data quality. In addition to concerns over feasibility, feedback might exacerbate the therapeutic misconception by further blurring the distinction between research and clinical care, and may cause harm through incorrect interpretation of a result by either the researcher, clinician, or research participant themselves.³⁵

CASE STUDY: THE DECIPHERING DEVELOPMENTAL DISORDERS PROJECT

One large genomics study that is pioneering the systematic return of individual research results is the Deciphering Developmental Disorders (DDD) project,³⁵ which aims to improve understanding of the genetic architecture of severe developmental disorders while facilitating the translation of high-throughput genomic technologies into the United Kingdom’s National Health Service (NHS).³⁵ Families have been recruited into the study by regional genetic services across the United Kingdom (starting in 2011 and continuing until 2015), and clinical and phenotype data are entered online by local clinicians. Samples are sent to the Wellcome Trust Sanger Institute, where various high-resolution genomic assays (DNA microarrays and exome sequencing) are performed to attempt to identify the cause of the child’s developmental disorder. When a diagnosis has been made, it is fed back to the family’s referring clinician via a secure-log-in website¹⁵ using a semi-automated system, and the local clinician can then decide whether to contact the family to confirm the result and provide genetic counselling as required.

Because the study is focused on children with severe, undiagnosed developmental disorders, it was felt that returning carrier information or results relating to adult-onset disorders would be inappropriate, so the policy of the project is not to return IFs at all (except where it is unavoidable; e.g., a large deletion removing both a developmental disorder and a cancer-predisposition gene). Crucially, since the study is returning pathogenic changes likely to be pertinent for individuals, the practical requirements for returning genomic variants of any kind have been developed and put in place, including sample tracking, variant filtering algorithms, and informatics pipelines, as well as linked-anonymized patient records. The experience of shifting resources in this project from pure genomics research into providing a translational service should be invaluable in assessing the viability of such an approach in future studies.

CONCLUSIONS

High-throughput multi-gene or whole-genome sequencing is now reaching clinical application. This will bring substantial new challenges to clinical genetics and mainstream medicine if we are to maximize its utility and reap the benefits in terms of healthcare whilst providing appropriate protections for the interests of patients and research participants. Although the principles of genetics will still be relevant in the genomethics era, particularly for the management

of disorders with a strong heritable component, the potential for much wider applicability of whole-genome data may require the development of a new ethical paradigm. Together with this, considerable thought needs to be given to what principles of genetic counselling can also be usefully applied to whole-genome data-sharing. It is unlikely that genetic counselling in its current form—established for serious, often life-threatening genetic conditions—will translate directly to dealing with the data gained from a whole genome. Thus, genomics challenges us to reevaluate the relevance of genetic counselling in its current form, and it is likely that a new model of communication about genomics will emerge.

The defining feature of the genomic world is the generation of data on an unprecedented scale, making ethical data-management crucial. Storage, access, and interpretation of individual genomes will be vastly facilitated by global genotype-phenotype databases, which need governance frameworks that promote responsible data-stewardship and use suitable consent procedures. This will require an appropriate balance between respecting individual autonomy and the right to privacy on one hand, and the benefits of data sharing and the duty to care for family members on the other.

Individual clinical and research teams will need to decide on a policy for the return of incidental or secondary findings and ensure that patients and research participants understand and consent to this policy. Once again, this will require an appropriate balance between individual autonomy and beneficence, versus public beneficence and fair allocation of resources. Against this background, it is our view that there is an urgent need in this area for empirical social science research, critical ethical analysis, and the creation of new conceptual frameworks, to identify and analyze the key ethical issues and to work towards the development of models of good practice.

An interesting and somewhat unexpected result of the decreasing cost of genomic technologies, coupled with scientific and medical uncertainty around their interpretation and implementation, is the rise of consumer genetics. Although many have been quick to criticize this nascent industry and the validity of some of the information provided,³⁶ these companies have provided fertile ground for exploring what sort of information individuals might wish to receive, how best to store and communicate complex probabilistic information, how individuals use the information and what levels of uncertainty consumers are willing to accept in the analysis of genome data. These are the very questions with which the emerging discipline of genomics must concern itself.

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