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Managing the ethical challenges of next-generation sequencing in genomic medicine

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Abstract

Introduction: Next-generation sequencing (NGS) is transforming the conduct of genetic research and diagnostic investigation. This creates new challenges as it generates additional information, including unsought and unwanted information. Nevertheless, this information must be deliberately managed—interpreted, disclosed and then either stored or destroyed.

Areas of agreement: Handling the process of consent to exome or genome sequencing should include discussion about the possible detection of variants of uncertain significance (VUSs) or incidental findings (IFs) that the patient may prefer not to hear about. A plan should be drawn up that specifies whether and how the patient would be recontacted in the future with new interpretations.

Areas of controversy: There is an active debate about which IFs or VUSs should be disclosed to the patient when an exome or genome sequence has been performed, or whether all findings of any possible relevance should always be disclosed. How this is managed has important implications for the initial explanation of the test to the patient and the process of consent. The assumption is often made that all sequence information should be stored, but this may not be sustainable or useful.

Growing points: Efforts are being made to build a consensus on what 'incidental' information should be disclosed. These policy questions are being addressed in many centres and practices are evolving rapidly.

Areas timely for developing research: Those interested in genetics, public health, bioethics and medical ethics may wish to debate these issues and influence future practice in both genetic research and genetic diagnostic services.

Key words: incidental findings, variants of uncertain significance, genetic testing, next-generation sequencing, genetic testing of children, foetal genome, consent

Genomics

The enhanced capacity of the new DNA sequencing technologies is not only reducing the cost of sequencing but is also enabling entirely new questions to be asked, both for research and for clinical practice. In the context of clinical medicine, genetic investigations are giving way to the genomic: instead of generating sequence information about specific gene loci one at a time, 'in series', all loci in which mutations are known to cause the disorder in question can be examined together, 'in parallel'. If we have no prior, plausible suspects to examine then all transcribed sequences can be examined together (the exome), or the whole genome can be sequenced.

This blurs or even collapses the distinction between a focussed diagnostic investigation and a nonspecific 'screening' test, because an investigation that has been initiated to answer a specific health question will generate much more information, that has not been deliberately sought although it could, perhaps, be relevant to the patient's future well-being. The same investigation entails both a targeted inquiry and a much broader health-related screen. It is this generation of unsought and redundant information that raises potential difficulties.

The first 'genetic investigation' to be established was taking the family history and the first real genetic investigation was the karyotype, which could be seen as genomic in that it examined the entire genome through the light microscope. Since then genetic investigations have focussed more and more on less and less but now the precision of DNA sequencing is attainable across all genes simultaneously with genomic methods. Instead of likely causes of a genetic disorder being suggested on the basis of clinical acumen, and these hypotheses then being tested by sequencing plausible candidate genes one at a time, the laboratory produces a torrent of information that has to be interrogated with the aid of bioinformatic tools to recognize the patterns it contains.

Familial factors other than DNA sequence are going to remain important in medicine for a long time and markers of gene activity, such as DNA methylation and chromatin configuration, will become included along with DNA sequencing as a natural part of genomic analysis. Taking a family history may then reveal little about an individual's biological propensity to disease that is not revealed by 'testing', although taking a family history will still often reveal a great deal about the personality and background of the individual patient, including relationships within the family.

Perhaps a focus on genetic factors as causes of disease will downplay other important influences, a phenomenon known as 'geneticization'. However, genomics could also be seen as giving us the tools to dissect out—to distinguish—the environmental and life course contributions to disease from the inherited ones: it is up to us to choose in what spirit to pursue genomics within medicine. Geneticization not only removes responsibility for disease from the individual, when each person's behaviour may in fact be a powerful factor, but it also distracts attention from collective and public health measures that may make a real difference to community health. Geneticization is therefore attractive to those who wish to diminish the scope of public and collective action for the common good; it comes with a political agenda.[1]

Genomic diagnostics

Genomic investigations, like any to be adopted into health care practice, must be assessed for their validity and utility.[2,3] A framework has emerged of evaluating genetic tests for their analytic validity and clinical utility; this has bolstered resistance to the alliance of 'overenthusiastic' professionals and commercial interests, who argued for the uncritical adoption of genetic and genomic investigations by health services, when such genetic associations between single nucleotide polymorphisms (SNPs) and complex

disorders were weak and, although of potential research value, of no clinical applicability in the individual case. The ability of SNP-based testing to assess genetic influences on the common, complex diseases is poor, much less than the high values of heritability might lead one to expect, because of genetic and gene–environment interactions and the inflation of heritability estimates (in some disorders) by new mutations.[4]

Another major objection to SNP-based risk assessments of disease susceptibility is that the relative risks of disease given on the basis of these tests may be actively misleading in the context of an unrecognized mutation in a Mendelian gene of major effect, perhaps giving false reassurance in the presence of a high genetic risk . . . or the converse.

The introduction of exome sequencing (ES) and genome sequencing (GS) into clinical practice, however these technologies are accessed, raises ethical questions and social issues on a scale far beyond those familiar from previous genetic investigations. How can we approach these?

The most appropriate way to tackle these questions is to consider three key issues that clinical geneticists have had to confront for some years but where the scale and scope of the issue have been transformed by the shift to data-rich biology. These are the questions of (i) variants of uncertain significance (VUSs), (ii) incidental findings (IFs) and (iii) the genetic testing of children. Space does not permit us to address other important issues, such as reproduction more generally, although we consider parallels between genetic testing of the child and of the foetus.

Variants of uncertain significance

Clinical geneticists have become familiar with genetic variants of uncertain significance while handling conventional DNA sequence data, from Sanger sequencing of single genes, such as *BRCA1* and *BRCA2*. These are large genes with many rare variants, whose pathogenetic significance may be unclear. Systems have been developed for classifying variants into categories of greater or lesser likelihood of pathogenicity[5,6] and the bioinformatic tools are becoming progressively more accurate. The incorporation of structural biology into modelling the impact of mutations promises further to enhance the interpretation of newly recognized variants.

The ways in which patients interpret the information given to them about a VUS found in these genes have been assessed over some years; while some women can accept the uncertainty others conclude that they are (or are not) carriers of a disease-associated mutation and some will base major decisions (such as prophylactic mastectomy) on a subjective interpretation which their professionals might not share.[7] Uncertainty of interpretation also makes it more difficult for patients to pass information about the genetic testing to family members.

Many of the VUSs found in individuals at high familial risk when gene testing was first available have since been reclassified, although in one series more than 20% remain of uncertain significance.[8] An approach to updating any result given to a patient or family should be built into the clinical process from the beginning.

The arrival of high throughput technologies

The first high-throughput genetic technology to impact on clinical diagnostics was microarray-based comparative genomic hybridization (aCGH). This indicates the relative copy number of each section of the genome. From a knowledge of the genes included within a copy number variant (CNV), a deletion or duplication, it may be possible to predict with high confidence that an individual (and perhaps their relatives) will be at risk of a previously unsuspected, adult-onset, autosomal-dominant or sex-linked disease, especially a malignancy. Such findings may be completely incidental to the initial trigger for the investigation, so that the findings may be regarded as IFs. Professional bodies have issued guidance on the interpretation of aCGH results: caution is required to avoid either exaggerating the causal significance of particular CNVs or downplaying a CNV as irrelevant on the grounds that it is found in healthy individuals, when in fact it may exhibit variable penetrance and/or contribute to a disorder through a

two-hit mechanism, a gene–gene or gene–environment interaction or a more complex mechanism.[9,10]

High-throughout 'next-generation' sequencing

The experience gained with VUSs through conventional sequencing and with IFs through aCGH has been helpful, but there is still much disagreement about how to tackle the 'practical ethics' of genomic investigations. The issues interlock, extending from the initial explanation of testing, then the process of consent, through the reporting of results, the storage of samples and data, the communication of results to the patient and family members and then the arrangements to be made for reviewing or reinterpreting the sequence and passing these updates to the patient.

One positive perspective is to accept a patient's genome sequence as a lifetime resource rather than a single 'test'.[11] The cost of ES or GS is now less than the cost of conventional analysis of some single genes, so that cost pressures will ensure that this switch to data-rich medicine continues. The cost of genome analysis, however, is not merely the cost of the sequence generation but also includes the cost of the data analysis and sometimes the cost of validating the findings by replication or by using an independent laboratory method. Errors in the sequencing will be inevitable if the read depth of sequence accepted for clinical reporting is set inappropriately low (if those reporting the sequence are too tolerant of genomic areas where the read depth achieved is inadequate). This reduces to a matter of cost and of willingness to compromise on quality before sufficient experience has been gained. The cost pressures are complex and the fall in cost of the sequencing, when viewed in isolation, could be misleading if the quality of the sequence generated and of its interpretation are not incorporated into the assessment.[12]

By the same token, however, the continuing fall in price of sequencing means that it becomes feasible to delete genome sequence data after its interpretation. Indeed, this may have advantages as the long-term storage of data is expensive given changes in IT software and hardware, is liable to being superseded by new developments in genome analysis (such as incorporating assessments of DNA methylation, chromatin configuration and gene expression), requires expensive data security and may impose a legal and/or ethical obligation to continue regular re-interpretations of the sequence.[13]

One way to minimize the problems of VUSs and IFs is only to sequence those genes that have already been associated with the disease phenotype that is the indication for testing—the 'phenotypic bundle' of relevant genes. This will not eliminate these problems of practical policy but will minimize them. Alternatively, one could sequence the exome or genome but restrict the bioinformatic analysis to the 'phenotypic bundle'; this may raise legal questions about the status of the sequence information that has been generated and stored but not interpreted but it does minimize many of the problems arising from the potentially open-ended commitment to patients and families that could otherwise arise in genomic practice. Such approaches allow professionals to accumulate experience and skill in tackling these issues[14,15] and policy can then evolve reflexively rather than being developed with excessive haste.

A system is required for assessing the available evidence in order to make a collective, consensual, professional decision about how to act upon finding a specific variant in a particular patient. A system of 'tiers' or 'bins' can be defined, into which each known genetic variant is placed on the basis of the (current) evidence. These categories will define the situations in which these genetic variants are acted upon; new evidence may accumulate and lead to a variant being moved from one category to another.[16,17]

Another practical question concerns regions of homozygosity identified by sequencing or by SNP-based aCGH. This may be helpful in identifying an autosomal recessive disease locus and recognizing regions of uniparental disomy. However, the same information may also indicate previously unrecognized cases of incest and sexual abuse. How should genetics services respond to these IFs of a social or criminal rather than narrowly medical nature?

Accumulating experience of sequence interpretation

The first report of a whole genome sequence interpretation was published in 2010 of a patient with a family history of early sudden death;[18] this included genome-wide association study-based disease associations, 752 CNVs, a few variants of potential pharmacogenetic relevance and rare variants in three genes associated with sudden cardiac death. Subsequent reports have demonstrated the value of next-generation sequencing (NGS) approaches to the clinical diagnosis of disorders of development, psychiatric diagnoses and unexplained disease. There are two principal lessons apparent from these reports: (i) the need to establish a robust and integrated 'pipeline', involving scientists and clinicians, that can manage each stage of the process so that all decisions are explicit and justified, especially variant annotation, report generation and clinical interpretation, and (ii) the need for clinical judgement at entry to the process and again with the return to the patient of the results and the planning of future care.

Sufficient experience of ES in populations of European and African origin has accumulated to confirm the widespread variation, both of single nucleotides and of segmental copy numbers, with most variants being rare, novel and population specific. On average, an individual has >13 500 SNVs, of which >85% are rare and >300 are predicted to impact on protein function.[19] The chance of identifying the knockout of a tumour suppressor gene, resulting in a predisposition to cancer, has been reported as 1–2%.[20]

As the ability to interpret genome sequence data improves, will we acquire an obligation to reinterpret the sequence of patients whose samples were interpreted some time ago? How often should we conduct such re-analyses? Should we also repeat the sequence generation, once the accuracy of the techniques has improved or once it has become standard practice to generate not only the bare DNA sequence but also epigenetic data of functional significance, such as methylation patterns? Laboratory genetic service providers will want to answer these questions in the negative; to take on the burden of regular reinterpretation (and perhaps re-analysis) would have a major impact on the cost of genomic studies, which would inhibit the development of services and consume an exponentially increasing fraction of health care costs. These questions are already being addressed with the aim of developing consensus policies and setting appropriate performance standards.

Genome sequencing in tumours

In addition to sequencing a patient's constitutional DNA, it may also be of interest to examine the genome of their cancer. Genetic testing of tumours holds out the promise of the rational design of therapeutic opportunities, such as the use of poly adenosine diphosphate-ribose polymerase inhibitors and other drugs in the treatment of breast cancers arising in those with constitutional BRCA gene mutations.[21,22] There will always be difficulties with the interpretation of genome sequence in tumours because of their internal heterogeneity and the opportunities for divergent clonal evolution, although even limited knowledge of the variation within a tumour may be useful in selecting the appropriate treatment. The extent to which tumour DNA shed into the patient's plasma is representative of the tumour itself will be an important object of study.

It is becoming clear that a knowledge of the cancer patient's constitutional genomic background may be useful in order to optimize treatment. Raising the possibility of an inherited basis for their cancer in someone just given a diagnosis has been avoided in the past because of concern that it might add to their distress. However, this will inevitably change as a knowledge of a patient's genetic predispositions becomes important in guiding the immediate treatment of their cancer; we will have to learn how to manage this altered pattern of service delivery.[23] Furthermore, in addition to determining each cancer patient's pattern of predisposition to malignancy, their genomic analysis will inevitably identify additional, unsought information: not only the VUSs in the genes of interest but also the full range of IFs.

Achieving the most benefit from the improved understanding of the genetic basis of cancer in the population as a whole—not only in rare, high-risk

subgroups—will require the proactive identification of those at risk of common cancers, such as colon cancer and breast cancer, and the use of genomic data to stratify the population into risk groups with tailored screening programmes.[24]

Managing uncertainties and incidentals: are you a Techno-enthusiast, a Fabian, a Luddite or a Genomic Libertarian?

Coping with the uncertainties of genomic analysis and interpretation requires careful thought but is not as difficult as managing the decisions about potentially important IFs.

The frequent finding of VUSs requires a systematic approach to the reporting of genomic analyses, with clarity as to whether or not the service provider (the laboratory and clinician together) will conduct periodic reanalyses of an individual's ES or GS. If regular reanalysis is provided—where that is feasible—then the uncertainties will (one hopes) diminish over time; in the interim, patients and professionals will have to avoid overinterpreting their findings and laboratory professionals will have to decide which VUSs to disclose to the requesting clinician, and which not even to report.

While IFs have been familiar in genetic laboratory diagnostics from the early days of chromosome testing, it is the scale of the problem that makes them such an important factor in the delivery of genome diagnostics. Every GS performed reveals many thousands of novel variants and hundreds of nonsynonymous (protein coding) variants. Of the novel SNVs, >250 will be disruptive variants in a gene and 50–100 will occur in disease-associated genes, with ~20 expected to be completely inactivated by the variant. The process of fully assessing the significance of each of these would consume far more time and resource than could possibly be devoted to it. Developing intelligent bioinformatic systems that permit the sharing of genotypic and phenotypic data internationally, between different laboratories and different health care systems, is the only coherent approach to tackling this. Any other strategy will entail the wasteful duplication of effort or block the implementation of genomics. Even with effective bioinformatic systems in place, it seems likely that this will be a globally shared task extending over a decade or two.

There are very different approaches being recommended for the handling of IFs as genomic diagnostics come to be incorporated into mainstream medical practice. At the risk of dealing in caricature, one can recognize four principal 'opinion groupings'. Three positions are clearly unreasonable while one (the third) is the wise path of moderation recommended to the reader:

(i) Techno-enthusiasts, who wish all results that are both important and 'actionable', i.e. leading to useful medical interventions, to be given both to patients and to research participants. This concern to enable action on the basis of potentially useful results overrides issues of consent, such as whether the research participants had or had not agreed to such a policy when they consented to the research. The concern of these hyper-enthusiasts is both to maximize the benefits for the individuals and simultaneously to learn from the accumulating experience of genomics as rapidly as possible in the form of publicly accessible, collective knowledge. Techno-enthusiasts will generally wish to insist on disclosing 'important' IF results so as to collect further data about these patients' outcomes. They will not be so concerned about the errors (of sequencing and of interpretation) that are inevitable in the early stages of application to clinical practice; pushed to the extreme, the concern to collect further data and advance our collective knowledge trumps concern for the welfare of the individual patient or research participant.

(ii) A second group of enthusiasts wishes to maximize autonomy; they wish to treat everyone (who can afford these investigations) as responsible adults (grown-ups) who should be allowed to generate whatever information about themselves that they wish;[25] the consequences are for the individuals to sort out. These are the Genomic Libertarians. Their motto is '*caveat emptor*'; they are reluctant to establish social

mechanisms to protect the incompetent and the vulnerable.

(iii) Those in the third group are more cautious than the two above and would like to see an evaluation of each step along the road. They are supported by the socially concerned, who aim to recognize the contextual factors that work against the sick, the poor and the disadvantaged and to give them a voice; these include Bevan and colleagues, who approach IFs from the perspective of critical social theory.[26] In addition, those trained in public health and the management of population screening programmes will wish to monitor and evaluate interventions such as NGS; they will not want the 'technological imperative' to drive the uncritical introduction of such a potentially transformative technology. The PHG Foundation and comparable bodies may be seen as enthusiastic but critical friends of GS. Those, who wish to ensure that individuals have a choice as to whether to receive their IF results, will often be in this category of Genomic Fabians, to borrow a term from Roman history.

(iv) A fourth grouping exists of those completely opposed to the new genetic technologies. However, we will not discuss them any further except to label them 'Luddite'. [This term describes workers who smashed textile-producing machines in the English industrial revolution and is commonly used (as here) to discredit the conservative views of those with whom one disagrees].

Sequence and interpretation

The challenge of delivering genomic tests *along with a coherent (genomic) interpretation* is recognized even by the techno-enthusiasts as a major challenge—demanding on multiple fronts, including the financial—but as the only feasible way to proceed.[27] A useful set of definitions, distinguishing incidental from pertinent findings and setting out a default approach to disclosure of test results has been developed.[28] Several systematic approaches to categorizing test results, defining the type of clinical action to be taken, have been recommended (see above).[29,30]

IFs generated in a research context, such as a biobank that has an archive of samples and data collected in advance of NGS methods, may raise some problems additional to those of genomic tests carried out in a service setting or with consent obtained in the light of experience with GS; this is because the original terms of consent may be inadequate to the context of today. It has been argued that, where feasible, biobanks should endeavour to return clinically useful and important results to the sample contributor (the professional involved) so that decisions about return of results to the research participant can be taken in the local setting,[31] although this may require breaking the anonymity of biobank samples and will sometimes not be feasible.

While a system of categorizing genomic findings as a guide to clinical practice and the return of results to patients is helpful, the difficulty of gathering and assessing the evidence and keeping it under review should be recognized as a major task; tackling this task will make apparent the many gaps of evidence that will need to be addressed. One framework for assessing the benefits of the incidental recognition of the well-known condition, Klinefelter syndrome, could be modified for other findings;[32,33] this approach incorporates a temporal perspective that can be important in weighing the potential advantages and disadvantages of making a diagnosis at different ages.

A strong lead has recently been given by the (generally techno-enthusiastic) American College of Medical Genetics and Genomics (ACMG), which has recommended a framework within which IFs may be—indeed, should be—reported to patients (or parents) whether the genomic analysis has been undertaken in a diagnostic or a research context.[34] These recommendations include a list of 56 (originally 57) genes, in which they recommend the active return of results when a likely disease-causing mutation is identified in adult or paediatric (but not foetal) samples. These are genes in which mutation causes a serious health problem for which early diagnosis and intervention can make a major difference to outcomes; these genes are associated with either tumours, a cardiac dysrhythmia or cardiomyopathy, or malignant hyperthermia.

The vigorous international reception accorded this document led to the publication of a clarificatory note some months later but without retraction of the original suggestion.[34] As a step towards defining those genes, in which a mutation should be disclosed to the individual concerned, the ACMG's policy statements have indeed been most constructive. However, perhaps the strongest objections centre on the strength of the obligation to return the specified set of IF results even when neither the patient nor the physician wish this or has agreed to it: should it be mandatory? Many will answer 'No',[35] while others agree with ACMG that such information should be returned to the ordering physician, even if not always passed to the patient or family.[36] The College's view has since been softened to incorporate the offer of patient choice, recorded when the test is explained and the patient agrees to have the investigation.[37] Particular concerns have also been raised about the document's approach to consent and the position of children; we will address both issues below.

There are two important but not necessarily decisive objections to the ACMG's policy. First, this may lead to the definition of a new standard of care that makes it increasingly difficult for many diagnostic laboratories, without major resources behind them, to enter the field of genomic analysis from fear of litigation.[38,39] However, the very fact that the ACMG-recommended return of results applies to such a circumscribed list of genes should turn their policy from a disadvantage to a real boon for laboratories: it serves to 'contain' the problem. The other serious objection to the ACMG's approach—with the policy having been steered by the enthusiasts—is that of the Reverend Bayes. 'The pretest probability of a true positive result in a disease gene that fits the symptoms of an ill child is high. In this setting, false-positive results are uncommon and there is usually physician and family support for further confirmatory tests to weed out the few that do occur. In contrast, the pretest probability of a true positive result in these 57 genes in the general US population is less than 1 in 1000. In this setting, there are likely to be 20 false-positive results per true positive'.[40] In the context of a strong (Mendelian) family history, the finding of a pathogenic variant in one of the plausibly relevant loci is highly likely to be a true disease-causing variant; a similar, novel finding in someone without a family history is much more difficult to interpret.

The competing approaches to handling the problem of IFs may be a site of struggle among different interest groups over the next 5–10 years. Some are cautious—Fabian—and emphasize that knowledge is growing and we can reassess in a few years. In the context of research, there will be a particularly vigorous debate about how to handle the results from analysing the genomic sequence of research participants recruited with the expectation of no feedback of results. While problems that have been anticipated can be avoided in the future by careful discussion at the time of recruitment, those recruited in the past will need to be included in our plans for many years, as their samples will remain in the biobanks. Should the previous understanding (of no feedback) be put to one side on the grounds that the scope of useful results had not been envisaged on the scale available today?

The genome of children

In addition to those already discussed, there are additional concerns about the application of NGS to the health care of children. To the extent that NGS may be the most efficient and effective approach to diagnosis for a rare and possibly genetic disorder, it will often be of great value. In the context of a sick child with an elusive diagnosis, GS analysis may give the best opportunity to attain a diagnosis. However, there may be grounds for building in additional protection beyond that appropriate when the patient is a competent adult, especially for handling VUSs and IFs.

Professional practice in many countries is not to generate or disclose to families genetic information about a child that is not relevant to their health care now or that will not reveal itself before the child becomes able to have a voice in the decision about testing. Predictive testing for adult-onset disease is generally avoided unless there are health benefits to be gained from testing in childhood; testing for carrier status would usually be deferred until the

child could be involved in the discussion, although this may be seen as a less weighty matter in which some family-led flexibility is not unreasonable, as less is at stake. The policies of the British Society for Genetic Medicine[41] and the European Society of Human Genetics[42,43] largely concur. The joint policy of the American Academy of Pediatrics and the ACMG [44,45] gives similar guidance, although it is substantially weaker: it could be interpreted as expressing both a preference for not testing under these circumstances and at the same time a willingness to do so on no stronger grounds than insistent parental request.

The return of possibly important IFs from genomics research involving children has been widely and sensitively discussed. Nuanced—and therefore complex—guidance has been presented by paediatric researchers with an awareness of (i) the potential emotional harm of labelling a child as being destined to develop a condition years into the future, (ii) the potential medical benefits to the child's parents of receiving certain categories of information (e.g. cancer predispositions) and (iii) the need to preserve the child's future ability not to have information about her genetic constitution circulated to her disadvantage.[46] We approach this topic with a commitment to preserve the child's right to an open future.[47,48] One approach is to accept the disclosure of a minimum 'default' package of important information (as per ACMG recommendations) but no more than that until the 'child' can make her own decisions as an adult.[49]

Decisions that will have to be made, but about which consensus has yet to emerge, relate to newborn screening and the generation of 'difficult' information about children: for psychiatric disorders, cardiac disorders associated with sudden death and later-onset neurodegenerative disease.

Newborn screening exists to bring direct benefits to children through early diagnosis, when awaiting a clinical presentation is too late for the treatment to be effective, as with congenital hypothyroidism and phenylketonuria. There are other disorders where the family unit may find it helpful to know the diagnosis early but where the child does not benefit directly. For those conditions, it may be important for health professionals involved in newborn screening to help families decide whether they would or would not want to know, at an early stage, if their child had a serious but untreatable disorder. However, this is not necessarily a straightforward decision as new 'liminal' categories of children who become 'patients in waiting'[50] may be created, and the screening programme will need to work out how to support parents making such decisions.[51,52] Finally, there are those disorders where an early knowledge of the child's genetic status is not itself beneficial unless the family would otherwise be unaware of their (the family's) risk of a serious inherited condition.[53,54] If they are unaware of that risk, however, then other considerations may apply, as proposed in the ACMG guidelines.[55] However, care should be taken that ES/GS testing does not pre-empt previously made decisions about when to test a child already known to be at risk.

It can be especially difficult for parents to adapt to knowing that their child has a condition predisposing to sudden cardiac death.[56–58] When a child is at risk of inheriting such a condition, it may be important to perform the genetic testing at some stage but it may be possible to defer this by monitoring a child phenotypically. Knowing that a child is at high risk of a psychotic illness, such as schizophrenia, is another very difficult matter for parents to deal with. While CNVs (including 22q11 microdeletions) are known to contribute to the development of schizophrenia and autism—the two conditions share a number of causal factors—it has recently become clear from ES that *de novo* mutations in a number of different genes can also make an important contribution in from 20 to 50% of cases.[58–61] At the same time, it is clear that the penetrance of the contributing genetic variants is far from complete and a new framework for understanding schizophrenia alongside the neurodevelopmental problems of childhood is required.[62]

Part of the difficulty of the situation can be the parents' guilt at having transmitted the risk to the child but there is also the concern about how to live as a family in such a way as to minimize the risk of the child developing a psychosis. Must one always concede to the child so as to avoid conflict? Of course not, as managing conflict must be learned

within the relatively safe context of the family, if a child is to negotiate the outside world with any success. But then what should the family do 'differently' to take this risk into account? There may be a heavy expectation of guilt arising if a psychosis develops in the child, either a 'genetic guilt' or a 'behavioural guilt', from the perceived failure to have been 'good enough' parents to protect the child from the trigger factor(s). This oppressive anxiety could lead to the identified risk of psychosis operating as a self-fulfilling prophecy.

Those families that do not spontaneously achieve the 'firm but kind consistency' that will be recommended are perhaps unlikely to be able to learn this very readily in response to instruction. They may have their own psychiatric difficulties, if the predisposition in the child has been inherited. Even without parental psychopathology—with entirely normal parents in a well-functioning family—the potential for complex interactions between genetic predisposition, parental knowledge of the genetic predisposition and parental behaviours is striking. The limited experience with this so far has arisen in the relatively uncommon context of chromosome 22q11 microdeletions, which carry a one in four risk of psychosis; parents describe the anxiety of their situation and the difficulty of learning about this risk through self-guided Internet searches.[63] Finding ways to support these families will be important and may yield guidance relevant to the more general context of predisposition to schizophrenia.

Another difficult context is that of the (usually) adult-onset, incurable neurodegenerative disorders including Huntington's disease (HD), early-onset Alzheimer's disease, the frontotemporal dementias and several other polyglutamine (CAG triplet repeat) expansion diseases. In the context of these disorders, where there is no medical intervention to defer the onset of the disease or slow its progression, the considerations are rather different to familial cancers and cardiac conditions and the ACMG recommendations do not include these disorders in the list of IFs to be disclosed. The one set of professional recommendations that is not firmly opposed to the testing of young children at risk for HD at the request of their parents are the recent joint recommendations of the American Academy of Pediatrics (AAP) and ACMG (2013). While suggesting that the deferral of testing is to be preferred, these guidelines are disappointingly open to professional weakness; they fail to challenge the practitioner willing to test a young child at risk of HD and could undermine attempts to maintain high ethical standards in genetic counselling practice.

The foetus as a child

There are clear parallels between the genetic testing of a foetus and of a child. Genetic tests of a foetus may, if the pregnancy continues, generate information about the child born a few months later. Predictive testing of a child for an untreatable, adult-onset, neurodegenerative disorder will usually be regarded as inappropriate: she will be raised by parents who know her genetic status and who may have shared this with friends or family from before her birth. This knowledge is likely to be a burden for the parents and may distort the child's upbringing. This situation does arise occasionally, when a pregnant woman has prenatal diagnosis for HD (usually with the intention of terminating the pregnancy if the foetus is affected) but then changes her mind and continues the pregnancy. Professional experience with the outcomes of these situations, however, is limited; such families often drop out of contact with genetics professionals. This context of prenatal diagnosis for such late-onset conditions as HD is the one setting in prenatal genetic counselling where practitioners will often be somewhat directive; they want the woman to be as clear in herself as she can be that, if the result is adverse, then she will terminate the pregnancy. They wish, if at all possible, to avoid the situation of a child being born who is already known from prenatal testing to carry a disease-causing expansion in the HD gene.

The other aspect of foetal genetic testing is the determination of foetal DNA sequence, including whole genome sequencing of the foetus, by the application of NGS methods to the free DNA in maternal plasma.[64] While only a modest fraction of this plasma DNA is foetal in origin, the foetal sequence can be inferred if sufficient read depth is obtained of

the total cell-free DNA circulating in the mother's plasma. The amount of information generated about the foetus from a single, maternal blood sample can range from the recognition of whole chromosome aneuploidy (e.g. trisomy[21]) to a complete foetal genome sequence. The ethical issues raised are much as for prenatal diagnosis by 'conventional' prenatal tests (chorionic villus biopsy or amniocentesis), but there are reservations about the technical progress that this represents. The principal reservations arise from the very advantages of the procedure: the safety of the test for the foetus and the fact that results can be obtained from as early as 7–8 weeks of gestation.

There are several concerns. The safety of the test for the foetus means that women, who might in the past have used the risk to the pregnancy of an invasive diagnostic method as a reason for declining such tests, can no longer shield behind that objection and may feel coerced into having prenatal diagnosis performed. Further, the ease with which more and more information can be generated means that NGS of maternal plasma DNA may generate large quantities of information about a child from before birth and this information might be to the disadvantage of the baby as s/he grows up, especially if the information has been circulated widely. It is not only information about HD but about a host of other disease and non-disease traits that might be better not generated, until the foetus is adult and has made his/her own decision to do so.

The possibility of terminating the pregnancy in response to information about the foetal genome triggers two additional concerns. Terminations may be triggered by uncertainties of interpretation of the genome sequence; we have already considered such VUSs and IFs but these may now influence practice in a way that would disturb many professionals, especially as society is only beginning to adjust to the uncertainties of interpretation of genomic information. Basing serious and irreversible decisions on such provisional interpretations, which are so liable to shift in significance, could lead patients to make decisions that they later bitterly regret.

Finally, the application of maternal plasma DNA to antenatal screening programmes for Down syndrome could lead to the firm diagnosis of almost all cases of Down syndrome by about 10 weeks of pregnancy. The decision about whether to terminate or continue the pregnancy, when Down syndrome has been diagnosed at 10 weeks, is likely to be more often a decision to terminate the pregnancy when the diagnosis is made so early. It has been suggested that Down syndrome may then almost be eliminated[65] and that this would not necessarily be a helpful development. What would it say about our society's attitudes towards and valuation of people with Down syndrome in particular but also those with intellectual disability more generally?

Conclusion

The principle of autonomy is perhaps the key ethical issue in contemporary health care and is usually protected through an insistence on 'informed consent'. The weight placed upon this concept is vast and perhaps unsustainable.[66] We cannot do without this concept but we need the rhetoric and the reality at least to engage with instead of talking past each other. The difficulty in genomic medicine is that the information likely to emerge from genomic investigations can often not be predicted in advance; it can only be explained with hindsight that may not emerge for some years into the future, if repeat interpretations of sequence information are performed. We have to locate consent for genomic analysis within the on-the-ground ethos of consent-in-practice, as a process of communication rather than a legalistic debate about the interpretation of consent forms. The development of consensual approaches in this difficult area, with an explanation and a corresponding acceptance of the provisional nature of the 'information' required for 'consent', demands a reorientation of bioethical discussion towards the under-explored area of patients' understandings of the communicative process that is consent-in-action.[67,68]

The question of consent in the context of genomic medicine has been addressed but raising more questions than supplying answers.[69] Experience is accumulating and most would now agree that consent for genomic analysis should be explicit, with reference made in the consent process to the possibility of IFs and VUSs. The 2013 ACMG guidance about

reporting IFs[34] has been very helpful in setting limits to the obligation to disclose IFs, although the list of genes drawn up will doubtless be subject to change. Additional safeguards need to be developed to protect children when they are tested. In the fields of cancer and cardiology, the importance of a genetic diagnosis will grow and management decisions will be influenced by a knowledge of genotype–phenotype relationships, although a thorough knowledge of the natural history of many disorders may take years, or even decades, to acquire. In the meantime, we must make sure that we take every opportunity consistent with good professional practice to glean useful knowledge from our clinical experience and to share it with the community of practitioners and researchers. We must also learn how to approach subtle issues of communication, the spirit and not merely the letter of the law.

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