

# What do we mean by 'genetic testing' in 2013?

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Until recently – until roughly 'now' – genetic testing has had two broad meanings. It has meant either the focused testing of one gene (or a few genes) for a specific diagnostic entity or a screening test in pregnancy for chromosome anomalies such as Down's syndrome. The nature of 'genetic testing' is changing rapidly, however, and the issues and concerns it raises are also changing. It will be important that those who study these social and ethical issues acquire a nuanced understanding of these developments in clinical practice. In this personal assessment of the current state of genomic diagnostics, I argue that it may be best to keep only those items of sequence information that are clearly interpretable at the time in the patient's records and not the full results.

Talk of the impact of radical change in technology on the ethical issues it raises will often elicit the comment that nothing fundamental has altered. In a sense that is true. What is new is the scope and scale of the ethical and social issues raised by genetic tests, while the principles at stake are not strictly novel. A word used to characterise the new developments in testing is 'genomic': instead of a genetic test that examines one gene or a specific part of one chromosome, we have technologies that can simultaneously examine the whole genome – all 46 or so chromosomes – in great detail. Already in regular diagnostic practice in many countries are the hybridisation-based array tests that assess the number of copies of each section of each chromosome. So-called Copy Number Variants (CNVs) detected by this technology – array-based comparative genomic hybridisation (aCGH) – may identify the deletion or duplication of anything from a few kilobases to a whole chromosome, largely bridging the gap between molecular and cytogenetics.

There has now been enough clinical familiarity with aCGH results to have given a flavour of the likely much greater impact of Next Generation Sequencing (NGS) on clinical practice. NGS takes two principal forms, Whole Exome Sequencing (WES) and Whole Genome Sequencing (WGS). The exome represents those portions of each gene (amounting to some 1% of the genome) that are transcribed into mRNA, much of which will then be translated into protein. Sequencing a patient's exome is possible now for research projects and will soon be feasible within standard laboratory diagnostics as the cost has fallen rapidly; this will soon apply also to (re)sequencing the whole genome. It is the reduced cost of sequencing that is driving these appli-

cations of genetics into mainstream medicine as there are large potential savings to be made through identifying the cause of a disorder early in the process of investigation. Such savings are especially important if the information produced can usefully guide therapy, as is now the case with many cancers, whose underlying causal mutations can indicate which (expensive and often toxic) treatments will or will not be effective. The fall in cost of DNA sequencing enables new questions to be asked both in research and in diagnosis. One clearly helpful development is the ability to sequence clusters of genes, any one or two of which may be responsible for a particular disease phenotype (the disease being investigated). If we think of conditions like retinitis pigmentosa, deafness, muscular dystrophy, bowel cancer or hypertrophic cardiomyopathy, there are many candidate genes known in which mutation can produce rather similar clinical problems, so that the investigation of many gene loci in parallel, rather than slowly and laboriously in series, will lead to great savings. In practice it will often be cheaper to sequence the entire exome or genome rather than a set of 50 or 100 specific genes, especially if the full set of relevant genes is probably not (yet) known. Then, once we have switched to sequencing the exome or genome, we find that we are generating much more information than we have asked for. This has two large categories of consequences: (i) we are given answers to questions we have not asked, and (ii) we uncover lots of information whose significance is uncertain, i.e. that we cannot readily interpret.

These two problematic categories of 'too much information' – Incidental Findings (IFs) and Variants of Uncertain Significance (VUS) – are not novel; they have been familiar in cytogenetics from its earliest diagnostic applications, and also in imaging. Indeed, the karyotype could be regarded as the first 'whole genome technology' regularly generating uncertainty. Similarly, stumbling across unsought information – the IFs – has become familiar in cytogenetics and also, again, in imaging.

Antenatal chromosome tests have often generated information incidental to the question being asked. When a fetal trisomy is suspected from findings on ultrasound scan, such as Down's syndrome or Edward syndrome, but a different anomaly is found on testing, this may be an IF. This will often be of little diagnostic significance but the uncertainty may still generate much concern and distress in the setting of a preg-

nancy and the pregnant woman will be faced with questions and decisions with which most people would prefer not to be confronted. Examples of such IFs include XYY syndrome or an apparently balanced chromosome translocation, when there may be real uncertainty as to whether the finding will impact on the welfare of the future child.

Moving from karyotypes and single gene tests to genome-wide tests, aCGH or NGS, confronts us with a number of policy decisions that need to be considered. If we do not take these decisions deliberately, we will find that the decisions have been made by default, which is likely to mean by large commercial pressure groups thinly disguised as the voice of the public. Surely a public process of rational deliberation must be preferable.

Examples of the decisions to be made include (i) whether to store the results of exome or genome sequencing, (ii) what type of consent process will be appropriate for these studies and (iii) under what circumstances should stored sequence information be made available for purposes other than the original diagnostic question. These issues will be particularly challenging when information is to be generated about children: (iv) what items of sequence should NOT be looked at but left for the <child> to think about when older? An additional question would concern the cascading of the offer of secondary genetic tests out into the immediate and then the extended family of anyone in whom a risk was identified: (v) what obligation will there be on health services to track down other family members and offer them testing for the risky variant identified in their relative? This question may have to be re-considered after every fresh re-interpretation of the sequence information.

Another important consideration is the cost of storing genomic data; it requires active maintenance and the switch to new systems in line with the inevitable developments in both software and hardware over the course of an individual's life. Given that the accuracy of sequencing is likely to improve progressively, and that additional information is likely to be generated by genomic approaches within 5–10 years – such as the methylation profile and chromatin configuration – the information stored so expensively may soon be regarded as woefully inadequate. Repeat sequencing when a reanalysis is deemed appropriate seems a policy far superior to the effort and expense entailed in data storage. Destroying sequence data after it has been analysed for the original diagnostic question may seem an absurd or appalling suggestion but it may be the most sensible approach. The data produced concerning variation in the genome, which is of public value, could still be released to the appropriate databases but not in the form of an entire genome; this would not require storage of the patients' full sequences as part of their medical record.

Finally, what type of information would it be appropriate to discuss at the initial clinical decision to offer genome testing? And how should consent for this be negotiated or <taken>?

It must be explained to the patient and/or family that such testing has the potential to achieve a diagnosis that would answer the immediate clinical question but, in doing so, it will generate additional information. While that fact is not unanticipated – it is inevitable – any particular <incidental finding> will itself be unanticipated. Of all the sequence variants that will be identified in a patient's exome or their WGS, which should the clinical team pass to the patient/family? One possibility would be to give each person a copy of their sequence information on disk and leave them to seek to interpret it as best they can, perhaps with commercial software. Another extreme position would be to impart no information, apart from putative answers to the diagnostic question being tackled. This would be a logically defensible position but perhaps not sustainable for health care professionals. An intermediate position that informs patients, parents or families of variants that have health implications, for the patient as an individual or for their close relatives, could be developed in which health risks, for which an individual could make some useful intervention (e.g. surveillance for risk of cancer or cardiac dysrhythmia), would be notified but not those for which no intervention is known to help (e.g. polyglutamine expansion in the gene for Huntington's disease – HD). Variants that indicated a reproductive risk – such as carrier status for autosomal recessive or sex-linked disease – could also be passed to the patient.

Such a <solution> may appear neat and tidy but, even with such a framework, there will be many problems of interpretation and many VUSs that challenge the drive for clarity and certainty, such as how to note the transition of a disease from untreatable to being treatable. In summary, I argue that there is a strong case for not storing the results of diagnostic exome or WGS data as part of the patient's medical record. Given the uncertainties of interpretation that will persist for many years and the burden that will otherwise be placed on genetic services, this may be the most appropriate policy for the circumstances of today.

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