

ETHICAL ISSUES ARISING IN THE USE OF GENOMICS IN CANCER

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Abstract

This paper examines ethical issues in relation to genomics that arise in connection with their use in cancer, focusing primarily on the clinical context. The role of genomics in cancer is investigated through the lens of 'personalised medicine' or 'precision medicine', and the implementation of contemporary genomics into mainstream clinical practice. The paper explores the impact that 'next generation sequencing' (high throughput sequencing) is having, including whole genome sequencing, exome sequencing and the use of cancer panel testing. It also examines a number of ethical-legal issues which regularly arise in the context of next generation sequencing technologies, in particular: consent; privacy; management of clinical findings and results back; and the scope of a physician's/doctor's duty to a patient over time and whether there is a duty to recontact. This is an area where medical technology is rapidly developing and ethical, as well as legal principles need to be reassessed from time to time so we can recalibrate to take account of these advancements. While next generation sequencing holds remarkable potential, some caution in its deployment is warranted so that there is good preparedness for the outcomes. To this end, cancer panel tests appear to be a good compromise to address the clinical questions at hand while avoiding the problem of too much information.

This paper will examine ethical issues in relation to genomics that arise in connection with their use in cancer. The focus will primarily be on the clinical context, although it must be acknowledged that there are many clinicians who are also involved in genomic research and therefore the boundaries between clinical practice and research can become blurred. This exploration of the role of genomics in cancer must be understood in the broader context of the 'personalised medicine' era,¹ now referred to as 'precision medicine', and the implementation of contemporary genomics into mainstream clinical practice, including its use for diagnosis and treatment. Advancements in precision medicine are opening up new medical possibilities around personalised health care, that is, care tailored to the individual patient's genetic characteristics and medical history.³ Also to be noted is the related field of pharmacogenomics, a form of genetic testing that determines the influence of genetic variation on drug response. This has seen the emergence of targeted therapies that provide benefit to particular cancer patients as illustrated with the targeted use of Herceptin (trastuzumab),² a targeted therapy for HER2 positive metastatic breast cancer and HER2 positive gastric cancer.⁴

Developments in genetic testing: single gene tests to gene sequencing

The technological capacity for genetic testing to reveal changes in a person's genes, or gene mutations, to

determine the risk of cancer and appropriate care strategies, has increased significantly over recent years. Predictive gene testing is usually undertaken where there is a family history of disease which suggests that there may be an inherited mutation. For example, where there is a family history of breast cancer, testing for BRCA1 and BRCA2 mutations may be recommended. Genetic testing may also be undertaken for people who already have a cancer diagnosis in an attempt to confirm a suspected gene mutation in the family which may influence the course of treatment. There is now also capacity for testing of cancer cells from a cancer tumour of a person with cancer, which may assist in determining prognosis and also inform treatment decisions. Genetic testing, facilitated with a genetic counsellor, enables better understanding of disease risk; identification of a gene mutation can ensure closer surveillance, with the likelihood of detecting the disease earlier, at a time when treatment is more likely to be effective.

Numerous hereditary cancers have been identified involving mutations inherited in a dominant fashion, including hereditary breast and ovarian cancer, Lynch syndrome (hereditary nonpolyposis colorectal and endometrial cancer) and familial adenomatous polyposis. Predictive genetic testing for a range of cancers has been available for decades, initially taking the form of single gene tests using Sanger DNA sequencing. More recently, there has been a move away from single gene testing to high throughput sequencing – referred to as 'next generation

sequencing' (NGS) involving massively parallel sequencing of exomes or even whole genome sequencing (WGS). This has occurred as a direct consequence of the dramatic decrease in the cost of NGS,^{4,5} to the extent that it is becoming cheaper to undertake WGS than undertake a number of the individual genetic tests, although in practice, most laboratories are still targeting specific genes rather than using WGS. In January 2014, a media release announced that Sydney's Garvan Institute of Medical Research was one of the first in the world to acquire machines that can sequence a whole human genome at a base cost below \$US1000.⁶ Commentators have suggested that using NGS to identify the complete DNA sequence of cancer genomes has the potential to provide significant breakthroughs in understanding the origin and evolution of cancer.^{4,7} The current trend towards NGS however, gives rise to questions about whether the availability of a more comprehensive, but less targeted form of testing, should be undertaken simply because it is more economical to do so. This is particularly the case for WGS given its far reaching scope, with potential for information overload, and greater likelihood of 'incidental findings' that is, unanticipated discoveries unrelated to the condition being treated or for which tests are performed, and the resulting legal and ethical challenges in relation to which results should be disclosed. At the heart of the problem is the reality that the capacity to generate data through massively parallel sequencing has outpaced our capacity to determine its functional significance.⁸ There is high demand for bioinformatics in the implementation of NGS and anticipated workforce shortages.⁴

Cancer panel testing

Currently, the main focus of WGS in relation to cancer mutation detection is in the context of research. For clinical purposes, the preferred approach is the use of cancer panel testing. Cancer gene panels use next generation sequencing technology to assess inherited mutations in multiple genes simultaneously,⁹ but seek to contain their analysis by focusing on a specific clinical question. Prior to next generation sequencing, genetic testing usually started with the most commonly involved genes and proceeded to less likely genes only when clinical suspicion was very high. However, cancer panels allow testing of all genes in parallel without substantially increasing the cost, leading to a different clinical algorithm in which all known contributing genes can be assayed at first evaluation.⁹ Cancer gene panels can vary in size from just a few genes (e.g. BRCA1 and BRCA2) to panels comprising 50 or more genes. In June 2013, in a case involving Myriad Genetics, the United States Supreme Court overruled the Myriad patent for detection of breast and ovarian cancer, holding that merely isolating genes that are found in nature does not make them patentable.¹⁰ Since that decision, there has been a rapid expansion of the clinical options for genetic testing and of commercial providers of cancer panel tests, and incorporation of this sequencing technology into a range of clinical oncologic settings. More recently, the Australian High Court, in the

case of *D'Arcy v Myriad Genetics Inc and Anor*, also found the Myriad patent to be invalid on the basis that claims were not patentable subject matter,¹¹ however, as the patent had already expired this decision will not have an impact on the availability of BRCA1 testing in Australia.

There are limitations as well as advantages of the cancer gene panels, and there is considerable debate surrounding the clinical, ethical, legal and counselling aspects associated with NGS and gene panels. This contemporary technology presents challenges, as the clinical value of multiple gene panels for cancer susceptibility is not yet fully understood. One of the major drawbacks is the increased complexity of results. A major concern is the increased likelihood of identifying variants of unknown significance. The more genes subject to tests, the greater the chances that there will be uncertain results. For many genes, clear risk reduction strategies for mutation carriers are not established and there is, therefore, increased scope for misinterpretation of uncertain results, possibly leading to unnecessary interventions.⁹ Learned commentators have taken different views as to the appropriateness of WGS in preference to gene cancel panels in a given scenario.¹² Mark Robson lays down the following challenge:

*"The rapid pace of technological innovation has driven multiple panel testing into the clinic, perhaps a bit before we have built a responsible framework to accommodate it. Counselling and clinical management paradigms that were developed to support single gene testing are not adequate to address the disruptive challenges presented by NGS and panel testing. The clinical cancer genetic community needs to respond to these challenges with a systematic program of collaborative research and clinical trials to realise the potential and minimise the risks of this exciting new technology."*¹³

However, cancer panel testing also represents something of a compromise because compared with WGS, it is a far more targeted form of testing, thereby reducing the risk of revealing excess, extraneous information regarding, for example, untreatable conditions unrelated to that which is under investigation, or information which is not understood e.g. variants of unknown significance. This helps to reduce the risk of misinterpretation of uncertain results.

What is encouraging is that early research into patient experiences with gene panel tests based on exome sequencing found that most adults accepted and were satisfied with gene panels based on diagnostic exome sequencing, few reporting distress regardless of mutations found within known disease causing gene panels.¹⁴ The authors suggest that there should be continued evaluation of patient experiences following exome-wide analysis.

There are a number of particular ethical-legal issues which regularly arise in the context of NGS technologies and which are the focus of the discussion which follows: consent; privacy, including the issue of sharing genomic test information with genetic relatives; management of clinical findings and results back; and the scope of a

physician's/doctor's duty to a patient over time and whether there is a duty to recontact.

Consent

The vastness and complexity of data from high throughput technologies creates challenges in ensuring adequate understanding of what is involved and in particular, in securing 'informed consent' from patients. The consenting process could potentially take a number of hours if everything is gone through comprehensively due to the sheer scale of NGS sequencing.¹⁵ The extensive nature of counseling required for NGS has been confirmed in practice due to the extent of the information to be covered in order for participants to make informed decisions, in particular in relation to return of incidental findings.¹⁶ Yet consent is crucial to clarify expectations about the scope of the test, return of results, and the extent of clinicians' duty to disclose. Before testing is undertaken, there needs to be a clear understanding in regards to these matters and this all needs to be clearly communicated to the patient at the time of consent.

Relatively speaking, a key advantage of cancer panel testing over WGS, is its more limited scope, which reduces the potential of information that will be available. This makes the process of providing information to patients and obtaining consent less complex than is the case for WGS, but even with the more targeted approach of cancer gene panels, there are still challenges and the potential for difficult issues with regard to the return of incidental findings.

Ideally, as much as possible should be dealt with in the first instance so that patients know the range of testing undertaken and what results will potentially be available, and how these will be managed. Only then can they make a well-informed decision about whether to proceed with the genetic test.¹⁷ Individual preferences regarding the return of incidental findings should be dealt with as part of the consent process, although questions have legitimately been raised as to whether patients can really appreciate the nature of this information and decide what they want.¹⁸ Biesecker refers to 'informational saturation' with respect to return of results,¹⁶ and argues that there is a difference between what patients want and what they can cope with in the context of a maximum of 20-40 minutes of counselling. In any event, various sources support the view that the patient's right of autonomy is not absolute and may have to give way to the clinician's fiduciary duty or professional responsibilities to the patient as indicated by United States Presidential Commission for the Study of Bioethical Issues Report, *Anticipate and Communicate: Ethical Management of Incidental and Secondary Findings in Clinical Research, and Direct-to-Consumer Contexts* December 2013,¹⁹ or with reference to the patient's relatives. If there is potential for enforced disclosure of certain information, patients should be advised about this at the outset so that they can make an informed decision about whether to proceed with the testing.

Privacy

Genetic and genomic information is, of its nature, sensitive information. Clinicians may seek to share information from WGS/NGS in order to maximise understanding of the patient's data and informing clinical advice, but data sharing inevitably has privacy implications, particularly if the patient's raw genomic sequencing data is to be placed in the public domain. Combining high throughput sequencing with the capacity of electronic health records creates unique opportunities to understand the genetic determinants of disease,²⁰ however the use of electronic health records in this context also raises concerns about privacy and data security.²¹

There are times where tensions arise in families regarding the extent to which genetic information about an inheritable mutation such as BRCA1 and BRCA2 mutations should be shared with other genetic relatives who may benefit from this knowledge by undertaking prophylactic measures or regular screening. Guidelines in a number of jurisdictions, including Australia and the United Kingdom, help to guide the decision-making of clinicians in circumstances where a patient declines to consent for information to be shared with genetic relatives, but the clinician takes the view that the information should be disclosed.^{22,23}

Management of clinical findings and results back/or 'return of incidental findings'

There has been evolving debate across clinical genetics specialities about the management of clinical findings. The American College of Medical Genetics and Genomics (ACMG) has issued guidelines, initially in 2013, and revised in 2014,^{24,25} regarding what laboratories undertaking clinical sequencing should test for and report on. The initial 2013 recommendations required laboratories, regardless of the indication for which clinical sequencing was ordered, to explicitly seek and report on a minimum list of variants - 57 in total later revised down to 56, including for specific cancers.²² Under the original recommendations, it was recommended that patients not be given the option of opting out of this information, and it was also recommended that this approach should be taken regardless of the age of the patient. This was justified on the grounds that many of the conditions could be prevented, treated or risk reduced and it was anticipated that approximately 1% of sequencing reports would include a variant from the list. The recommendations of the ACMG came under strong criticism from a range of sources, particularly in relation to overriding patient autonomy, also because it was in conflict with established guidelines on the genetic testing of children for late onset disorders. In April 2014, revised recommendations were announced, allowing patients to opt out of receiving certain incidental results before the test was undertaken, and where the patient was a child, parents would have the option of opting out of such analysis.²³

In contrast, the European Society of Human Genetics (ESHG) has recommended a more conservative

approach,²⁴ suggesting that whenever possible, testing should be targeted to genome regions linked to the indication and that wider testing requires a justification in terms of necessity, defined as the need to solve a clinical problem and proportionality, understood to be the balance of benefits and drawbacks for the patient. According to the ESHG, adding screening targets to a diagnostic test violates the criterion of necessity. The ESHG was of the view that imposing this extra testing on patients who need an answer to a clinical problem is at odds with respect for autonomy; people have the right to decline testing on the basis of their own assessment of the burdens and benefits.²⁶ Similarly, in Canada, a cautious approach has been recommended by the Canadian College of Medical Geneticists.²⁷ The college position paper states that until the benefits of reporting incidental findings are established, the college does not endorse the intentional clinical analysis of disease-associated genes other than those linked to the primary indication.

In Australia, the Human Genetics Society of Australasia had expressed concerns in relation to the initial ACMG recommendations, in particular, in relation to the ethical principal of autonomy and testing in minors, which have since been amended.²⁸ The Royal College of Pathologists of Australasia, in the updated Massively Parallel Sequencing Implementation Guidelines, revised May 2015, notes that there is as yet no consensus on whether and what incidental findings should be reported to the patient. The guidelines recommend that patients should receive a clear written record of the policy regarding the reporting of incidental findings.²⁹

The quite prescriptive nature of the proposed approach of the ACMG has fuelled debate in relation to the management of clinical findings and return of incidental findings to the patient. This has, in turn, had implications for the research context, where there appears to be growing support for the return of 'incidental findings' that meet certain threshold criteria - analytical validity, clinical validity and clinical utility,^{30,31} and even, more controversially, suggestions that researchers may have an obligation to actively look for genetic incidental findings.³² However, this area is by no means settled, and some commentators caution about the risks associated with return of incidental findings,³³ and others highlight the importance of recognising the difference between clinical and research contexts.³⁴

Scope of duty of disclosure: duty to recontact?

When incidental information arising from genomic testing reveals a significant health risk for which a preventative or therapeutic intervention is available, the law may well require its disclosure by the laboratory to the clinician, who must then inform the patient. It should be noted that the United States and Canada recognise a legal duty to warn, which potentially extends also to relatives. This concept does not have direct authority to support it in Australia

or the United Kingdom,³⁵ however general common law principles in relation to duty of care apply.

Accepting that there may be circumstances where a clinician is under a duty to disclose pertinent genomic findings, the question then arises as to the scope and duration of this duty, in particular, if the clinical relevance of incidental findings changes over time in light of new information? Is there an obligation to recontact the patient to share that new information, even though some time may have passed since the patient saw the clinician? Commentators have suggested that it is unlikely that liability would accrue for information, that was not known or knowable during the existence of the doctor patient relationship; once that relationship has ceased, that duty is generally concluded.³⁶ Ideally, the possibility of new information later coming to light should be raised with the patient at the time that consent for testing is obtained; if the dynamic nature of this area is explained, the patient can be empowered to be proactive and recontact the clinician after a year or two to see if there is any relevant new information. This seems a more reasonable course than proposing that clinicians should have an ongoing duty to the patient, particularly given the vast amount of information involved with NGS and the rapid pace of change, which would very quickly render any such duty unmanageable.

Conclusion

The shift from single gene testing to clinical use of NGS has presented a range of ethical challenges which have demanded fresh thinking on key ethical principles. At a very practical level, a lack of genomic expertise in the health system generally has been highlighted, and the difficulty of interpreting the clinical implications of highly complex genomic data indicated. Education will inevitably be part of the solution – continuing education for clinicians to ensure that they are enabled to serve the interests of their patients in this fast moving area, as well as helping to improve the genetic literacy of the broader public.

In the application of genomics to cancer, the use of gene panel testing seems a reasonable compromise, focused on obtaining the information that is needed and managing the risk of too much information. Continued monitoring of patient experience and satisfaction with this form of testing will be important. Above all, it is vital that decisions about clinical care are evidenced-based.

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