Commentary

Managing the Ethical Issues of Genomic Research using Pathology Specimens

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Abstract
Biobanks of human biospecimens involving tissue taken from surgery require close relationships with diagnostic pathology practices. As most of the tissue will be analysed using genetic or genomic technologies there is the possibility that new information is created that could be of relevance to the donors. Although attention has been recently focused on the responsibilities that may arise from researchers and biobanks in terms of giving back individual genetic research results (IGRRs) to research participants, little has been said in relation to the role of pathology services. In this Commentary, we summarise the issues with respect to pathology services and what guidelines and professional practice documents say about their responsibilities. We also provide points to consider in the development of an ethically defensible plan for giving back individual research results.

Introduction
Pathology is of central importance to medical care in making the diagnosis of most diseases, helping define the care to be given and monitoring the outcomes for an individual to maintain their wellbeing. Besides this central role in routine care, pathology is also central for medical research infrastructure because it provides an essential source of research biospecimens that are derived from human tissue taken during surgery or from biopsies. Indeed, the role of pathologists in medical research and medicine is now more critical than ever. This is in large part due to the advent of ‘personalised medicine’, which is predicated on information derived from molecular analysis of human biospecimens. Whole genome sequencing (WGS), which has been enabled through the advent of high throughput Massively Parallel Sequencing platforms (MPS), is already being introduced into clinical practice in place of traditional approaches such as Sanger sequencing, to define whether a patient will respond to certain treatments or not. The initiation and validation of these approaches has been made through the collaboration of pathology practices that supply clinically annotated human biospecimens with medical researchers who perform the analyses. This collaboration underpins discovery and validation of molecular pathways that can be exploited for therapeutic purposes and continues a long-standing tradition of research within and with pathology services.

It has always been a possibility that research performed on a sample originally used for making a diagnosis may result in a challenge to the original diagnostic finding, for instance showing that a tissue sample contains a more malignant type of cancer than previously thought. If the biospecimen could be linked back to the person it came from and they were still alive then there may be a duty of care to ensure that this information be provided back to that person through that individual’s primary physician. However, the ability to fulfil any such a duty is limited in practice by several important factors that include the way the research test was done (analytical validity), the extent to which the finding is based upon any consensus of medical importance (clinical validity) whether anything could be done in light of the finding (clinically actionable), and how practical it would be to provide information back. The practicability is also affected by time such that some patients may have died since their surgery and in some instances it may be difficult to locate the patient and/or the treating physicians as they may have moved on or retired.

Whilst there have been a few articles discussing real life examples of returning research results including some of our own, there are almost none that we could find that related to the role of pathology practices. Although Lockhart et al. have recently described the issues regarding discrepant pathologic
diagnoses that may arise from biospecimens obtained from biobanks, none have looked at the role of pathologists in returning findings from genomic research. Instead, the focus has been on the obligations of researchers and biobanks to return genomic findings without any reference to pathology practices. Any research use of pathology-derived biospecimens must be approved by an ethics committee but in addition they are governed by professional practice standards that include commentary on research activity. For genomic sequencing in Australia the Royal College of Pathologists of Australasia (RCPA) have issued a guideline produced by their genetic advisory committee that covers the implementation of MPS in clinical practice. Whilst this focuses on clinical practice and not research, it does discuss return of incidental findings (IFs) suggesting that patients should be informed about the policies prior to testing and notes that if patients decline to know about potential IFs then doctors will often seek alternative diagnostic pathways other than MPS. In the research context any study using MPS that could generate IFs must be approved by an ethics committee and whether or how any results will be given back must be approved by that committee. In Australia the criteria regarding whether to give back results is outlined in section 3.4.10 of the National Statement (see Appendix) and researchers must develop and obtain approval for an ‘ethically defensible plan’ (EDP) based upon these. In this commentary we examine some of the key criteria used to underpin an EDP and how these relate to pathology practices that supply biospecimens for research purposes.

Is this a New Issue?
Prior to the advent of more affordable WGS it was extremely unlikely that research on human pathology specimens would reveal something about a person that was unrelated to their original disease. For example, looking at a cancer under a microscope wouldn’t be likely to provide any useful information about the risk of heart disease. WGS is a transformative technology that by its very nature will reveal information about far more than just the area under study. For instance, one may be intending only to look at one molecular pathway altered in cancer, but WGS will generate data on all genetic variants present including other conditions and potentially those that are germ line. The data thus generated has been referred to as the ‘incidentalome’ being similar to IFs that arise in other clinical settings such as those that occur during review of radiological scans. These IFs are now indistinguishable in any practical sense from ‘Research Results’. For this reason we will adopt the convention of referring to them as Individual Genetic Research Results (IGRR) for the remainder of this commentary. Some may argue that the attention given to the return of genetic findings is genetic exceptionalism, that is, that genetic information is somehow more important than other health information. However, the reality is that some of these IGRRs may be of significance to the health of both the person from whom the biospecimens came from as well as their blood relatives and so the need to address this issue may be more significant in some ways than non-genomic research.

Although little has been written regarding best practices for pathology services in return of genetic research results, the American College of Medical Genetics and Genomics (ACMG) recently published a position paper proposing best practice for those employing WGS in clinical practice. In this article they proposed that there are 57 genes considered medically actionable that should be actively screened for and reported to people who may not have given their consent for that purpose. This led to a number of point/counterpoint papers that were both for and against the proposal. However, it is important to note that this list of genes that should be returned was developed for use in clinical practice, not for medical research. Indeed, unlike the ACMG report, the Presidential Commission for the Study of Bioethical Issues suggested that there is no similar duty to look for mutations in the research context. Nevertheless, it is impossible to ignore the fact that WGS enables analysis of the entire genome and therefore whilst researchers may not be seeking to look at anything beyond their gene or pathway of interest, the assay they employ may in fact turn up findings in other genes. Some have argued that it is therefore impossible for researchers to disregard what the analyses may or may not be able to reveal, and that they too must consider their WGS data in a similar way to the ACMG and at the very least have a plan regarding whether and how to give back certain results.

Recent discussions have focused on whether biobanks have a duty to establish a framework that enables the potential to give back IGRRs. This raises the issue of whether the pathology practices that supply them must also be included in any such framework since they were a primary source for the biospecimens. We and others have argued that a mandate to return research results from all biobanks creates several problems including a possibility that many biobanks would have to discontinue operations because of logistical and other concerns and therefore have an unintended consequence of reducing the amount of medical research done. An alternative way to approach this is that proposed by Beskow and Burke, who have proposed the application of an ancillary care framework to the return of IGRRs. To determine whether such obligations exist they proposed that one must consider the relationship between the researchers and participants as well as the participants’ vulnerability and degree of dependence. Using this framework, they suggest that there may be only a weak obligation to return IGRRs in the context of the use of pathology material originally collected for diagnostic
purposes for research. This was particularly so if the samples were not re-identifiable by the researchers in any practical sense (that is, they would have to take extraordinary steps to re-identify an individual such as hacking into a database or breaking a code). One of the results of such a framework could be that researchers seek to make sure that their biospecimens are not re-identifiable and so avoid any obligations. However, there are sound arguments as to why this would not be a good outcome. Firstly, the value of biospecimens is linked to their clinical annotation in most instances, and this may require ongoing updates of information such as clinical treatment and outcome. It would also be undesirable if research were curtailed simply to avoid creating an obligation that was perceived to be logistically problematic.

It is also important to bear in mind that the primary purpose of research is not to provide a benefit to research participants but to generate generalisable new knowledge. Another argument against giving back IGRRs is that it would create a therapeutic misconception; that is, it would place the research endeavour within a context of also being tagged closely to clinical care. It has been argued that this may undermine the whole basis upon which research is based and place unreasonable expectations on researchers. In contrast, others suggest that an obligation exists and therefore any cost must be accepted, even if it means that fewer research projects are funded adequately to do this.  

Considerations for Pathology Practices in Developing an EDP for Returning IGRRs

A number of ethical guidelines regarding when individual research results should be given back to participants or their physicians have previously been published. These guidelines include a number of factors to be considered in the decision of when to return individual research results, including analytic validity, clinical validity and actionability. In addition, the Australian National Statement on Ethical Conduct in Human Research (NS) addresses return of individual research results through specific considerations outlined in the revised section 3.4 which form the basis of an EDP, which must also take into account the relationship between the researchers and the person, if any, and the reliability and utility of any result. The option for an individual research participant to refuse to be given any information has been framed as an important pillar of any such EDP. The EDP must be approved by an ethics committee with authority to do so (e.g. Institutional Review Board (IRB) in the US and Human Research Ethics Committee (HREC) in Australia) The US Presidential Commission for the Study of Bioethical Issues in their report ‘Anticipate and Communicate’ published in December 2013 came to similar conclusions regarding the need for such plans.

Developing an EDP

Taking into account the recent ethical guidelines and professional practice guidelines described above we provide a commentary below on the considerations that can be used to develop an EDP that will enable access to biospecimens whilst balancing any obligations that may arise to deal with IGRRs.

1) Was the possibility and process regarding the return of IGRRs disclosed as part of patient consent?

One issue to consider in developing an EDP for return of IGRRs is whether the consent process addressed this issue. It is a pillar of commonly accepted ethical frameworks that consent should be obtained when humans are involved in research and with their consent given freely and on the basis of sufficient information. In practice most patients are not aware of the specifics of how their samples are being tested, or indeed how they are distributed for analysis and ultimately used. The majority of people would not be aware that any tissue samples taken from them might be stored as a requirement of legislation or best practice guidelines governing pathology practice. Whilst purpose built biobanks that obtain patient consent have emerged over the last 10-20 years, the vast majority of pathology samples available today for use in research would not have consent for such use.

Whilst Australian ethical guidelines and legislation such as the Privacy Acts make consent a strict requirement to collect and use personal medical information, in practice this requirement may be breached if a properly constituted HREC endorses a request to waive the need for consent. The HREC must apply criteria such as public interest of the research, the practicability of obtaining consent and the level of risk to the people who are not being asked for their consent. In the US, the Federal Policy for the Protection of Human Subjects (the ‘Common Rule’) currently allows a similar waiver of consent if certain conditions have been met. In Australia, institutions that allow waivers are required to look at introducing prospective consent processes where they identify that there will likely be a need for this as identified during the review to grant the waiver.

Given the high probability of generating IGRRs from genomic research it would seem reasonable to expect a more robust process to govern patient preferences than those exercised through ethics committees granting of a waiver. Introducing such a consent system in routine pathology has been considered unrealistic and it is fairly obvious that were it to be introduced in a manner similar to many biobanks it would be financially unsustainable. Nevertheless, less onerous processes are used in one of the author’s own pathology services, which includes mention of IGRRs and
how they will or will not be disclosed, and by others using ‘front door consents’ to allow future contact with potential research participants. It may be useful for pathology practices engaged in supplying human biospecimens for research to examine such processes in the future and in our own practice we have demonstrated this is practical and cost effective.24

2) Is the testing to be performed as part of the research likely to be ‘analytically valid’

Another very important factor to consider when developing an EDP is whether the testing was analytically valid. Pathology services are well versed in the potential for errors that can arise in clinical practice. In Australia the National Pathology Accreditation Advisory Council (NPAAC) set standards for pathology services that are evaluated by the National Association for Testing Authorities, Australia (NATA). Similarly in the US the Clinical Laboratories Improvement Amendments (CLIA) are the basis for pathology service accreditation performed by the Division of Laboratory Services, within the Survey and Certification Group, under the Center for Clinical Standards and Quality (CCSQ). These accreditation processes ensure pathology services follow strict protocols with comprehensive documentation to minimise the margin of error as well as ensuring the tests done are fit for purpose. Whilst researchers must comply with guidelines and institutional policies that cover good laboratory practice, they are not subject to the rigorous auditing required for clinical services. It is therefore an additional criterion in the EDP that the reliability of any research finding be ascertained; either performing the tests in a certified facility under ‘clinical-grade’ conditions or that it is repeated in such a facility under those conditions. More recently standards for ensuring accurate genomic sequencing have been presented for clinical services so there are now additional standards for laboratory accreditation.26,27 Nevertheless, it is unclear that research facilities will seek or obtain such certification unless they intend to provide diagnostic services as the costs involved in doing this may be prohibitive. The question then remains whether or not one can trust an individual result generated in a research setting? One would certainly hope so but a recent article in the Lancet has identified significant shortcomings in research enterprises that limit reproducibility.28 Thus, whilst we would hope that research results are reliable it would be unwise to rely upon them as a primary source of clinical decision-making.

3) Are the genetic findings important from a health perspective (clinically valid)?

The problem with many genetic mutations/variants is that they are still of uncertain consequence. Whilst Berg et al. have provided some guidance for how such variants could be identified and managed,12 the ACMG paper proposing how to manage results arising from genomic sequencing in the clinical setting stated that:

“The Working Group recognized that there is no single database currently available that represents an accurately curated compendium of known pathogenic variants, nor is there an automated algorithm to identify all novel variants meeting criteria for pathogenicity. Therefore, evaluation and reporting of positive findings in these genes may require significant manual curation.”18

It is possible that a research project will in fact employ analyses of well validated genetic variations such as Kras, braf and HER2 and it would be a clear possibility that this data could be useful in the future management of patients. Given that this could arise, researchers should discuss with pathology practices whether they will be performing these tests in a analytically valid manner such that they would be available for return for future clinical use (see also point 2 above). This may become increasingly important in the light of the increasing likelihood of multi-gene analyses becoming a part of routine cancer care.

In addition to having clear criteria for what is and what is not clinically valid, in many instances use of pathology derived biospecimens involves use of tissue which may harbour significant genetic variation from that seen in the germ line. Extrapolation from the tumour with respect to potential inheritable risk factors should be treated with extreme caution and it would be necessary to make contact with a person to obtain a fresh germ line sample and only after appropriate genetic counselling. The pathway for doing this should be spelled out in the EDP and should include sample letters to be sent to patients from the relevant clinical services that have been developed together with those services.

4) Is there an intervention (medically actionable)?

An additional issue to consider in the development of an EDP is whether or not the findings are medically actionable, i.e. there is an intervention that would be recommended by a health practitioner as a direct result of this new information. This is a potentially highly contentious criterion that depends greatly on there being publicly available, well established clinical standards to refer to. The NS identifies this as a criterion when establishing an EDP for returning IGRRs and in practice most will argue that by definition IGRRs that are not related to a primary condition for which there is a clear clinical treatment plan should not be regarded as actionable. Berg et al. have outlined how one may determine what is and what is not medically ‘actionable’,12 although this leaves as many questions as it does answers. In the case where a finding is analytically and clinically valid and medically actionable
and will be returned to individuals, extensive counselling is required. Individuals would need to be informed about the meaning of the test results and about the pros and cons of available treatments and be provided with guidance in making an appropriate decision; this is not dissimilar to screening tests already in routine practice.

Another factor in some healthcare systems will be equity of access to appropriate treatments or follow up care that may be required in response to the IGRRs. That is, it is one thing to say that a disease linked to a gene has a treatment and another to actually provide that treatment freely to a person. Is it ethical to tell someone they have a disease that requires treatment with a very expensive drug if they cannot afford that drug and have no insurance to access it? Whilst this is an ethical debate not limited to this situation, it is important that it is included in formulating the EDP. Moreover, it may not be clear who should have the obligation to fund any clinical follow-ups. For instance, an IGRR may require corroboration using an independent sample performed by a pathology laboratory and follow up radiological scans. Who should pay for these tests? If they are not requested by a physician then it will have to be paid for either by the researchers or the participants. The EDP should include a discussion of what mechanisms and resources will be available to return results to patients in an ethically defensible way.

**Conclusion**

Pathology services that provide specimens to researchers may find themselves unwittingly caught up in having to commit time and resources to giving back IGRRs to participants. Requirements to recontact participants with all IGRRs would place an extraordinary burden on clinical practices and we propose that at this stage it would be an unethical diversion of essential resources to require the return of all IGRRs generated in a research setting.

Instead, a set of genetic variations could be defined as part of a carefully constructed EDP based upon clinical and analytical validity and actionability. Once established only these would be required to be analysed and possibly returned to participants. However, we argue that there is no duty of researchers or clinicians to constantly revise prior diagnoses or data generated from several years prior for renewed clinical significance. The EDP should clearly demarcate responsibilities and should be based on a careful balance of practical considerations together with duties that arise toward participants.

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**References**

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1 The content of this paper represents the authors’ personal perspectives and should not be taken as formal legal or policy opinions or advice. Investigators must check with their local institutional officials and research ethics committees regarding official interpretations of regulatory and other local requirements for their work.
2 While the Common Rule at the time of writing this article allows for a waiver of consent by an IRB if certain conditions have been met, modifications to the Common Rule are currently under consideration that could change the consent requirements for human biospecimens.
Appendix. Extract from the National Statement on ethical conduct in human research relating to return of research results using human biospecimens. Reproduced with permission from the National Health and Medical Research Council.5

3.4.10 Where proposed research involving the use of human biospecimens may reveal information that may be important for the health of the donor(s), their blood relatives or their community, whether anticipated or incidental to the scope of the research, researchers should prepare an ethically defensible plan to describe the management of any proposed disclosure or non-disclosure of that information. This plan must be approved by an HREC and should include consideration of the following:

(a) The circumstances in which the biospecimens were obtained, including the type of consent provided (see paragraph 2.2.14) and the manner in which the consent was obtained;
(b) the likelihood of the research generating information that may be important for the health of the donor(s), their blood relatives or their community;
(c) whether a recognised intervention exists that can benefit or reduce the risk of harm to the donor(s), their blood relatives or their community from any health impact revealed by this information;
(d) the resource requirements and infrastructure in place to support the return of information of the kind referred to in (b) and (c) in an ethically appropriate manner;
(e) whether participants will be given a choice to receive such information;
(f) whether there is a pathway to identify and recontact the donor(s), their blood relatives or their community, taking into account the relationship between the researchers and the donor(s), if any;
(g) the potential for sampling or coding errors that may compromise the certainty that the biospecimens came from a particular donor;
(h) whether the findings of specific tests being undertaken as part of the research have been produced or validated in an accredited laboratory; and
(i) who will take responsibility for any subsequent care requirements.