Ethics and logistics of using archival pathological material

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It seems that almost every day heralds a new 'breakthrough' in our understanding of, or ability to treat, diseases such as cancer. However history has shown us that the majority of these are in reality relatively minor incremental advances in our knowledge, with few emerging as significant in improving healthcare. Much of this is due to overzealous reporting and overstatement for funding purposes, and it is clear that there is much to be done to make good on the promises of rapid advances in medicine through molecular biology.

Most recently, alongside the preliminary completion of the Human Genome Project, DNA array technology has been predicted to revolutionise our understanding of the natural history of disease by providing a means to examine several thousand genes in any individual at a single time. However, it is already clear that any practical applications of data from microarrays will utilise only a handful of the several thousand genes present on such arrays. Moreover, many gene array studies have been limited in using small numbers of samples and are biased towards cases from which spare tissue, excess to that required for a diagnosis, may be obtained. The potential for limited application of any findings is a real concern and therefore attention is already turning to validation of any such gene candidates in larger and broader patient series. This translational research may be carried out using archival pathology material and the following outlines some pressing issues with using this, as well as how this is currently being carried out in Perth.

Pathology archives

The supply of quality human tissue for validation of new prognostic and predictive markers is dependent on pathology services whose primary objective is to provide diagnoses and not to provide a suitable archive for research. Moreover, access to these archives is limited by stringent ethical considerations, there are issues regarding the number of cases available and how representative these are of a general population, and great care has to be taken to ensure some element of consistency in the handling of the tissue. As important as access to the pathological material itself is the breadth and quality of associated clinical information such as staging, treatment and outcome.

In recent years there has been some debate on who 'owns' archival pathology material. The various State and Territory Human Tissue and Transplant Acts do not extend to tissue taken as part of elective surgery and in the WA Act (1982) section 32 (1) (a) goes so far as to say:

"Nothing in this Ordinance applies to or in relation to:

(a) the removal of tissue from the body of a living person in the course of a procedure or operation carried out, in the interests of the health of the person, by a medical practitioner with the consent, express or implied, given by or on behalf of the person or in circumstances necessary for the preservation of the life of the person;

(b) the use of tissue so removed;"

This has led to the adoption of the common law principle of ownership such that those who have done 'work' on the samples 'own' them, ie tissues fixed and processed become the property of the pathology service. The recent Australian Law Reform Commission (ALRC)

and Australian Human Ethics Committee (AHEC) Discussion Paper 66 (DP66) entitled Protection of Human Genetic Information[1] re-affirms this and states in proposal 17-1 that:

"The common law right to possession of preserved samples, which is currently enjoyed by hospitals and others, should continue to be upheld, but full property rights in genetic samples should not be granted"

This recommendation ensures the continued use of this material for medical research and for teaching.

Consent for using archival material

It is important to understand that consent for use of archival pathology material is almost never obtained. However, the NHMRC National Statement on Ethical Conduct in Research Involving Humans —June 1999[2], provides specific guidelines on "where the requirement for consent could be waived" under sections 15.8 (tissue) and 16.13 (genetic samples). The decision to allow consent to be waived is given to a Human Research Ethics Committee (HREC) and requires that they carefully consider items such as the difficulty or obtrusive nature of obtaining consent, as well as the likely risk to benefit ratio of permitting a restricted and carefully monitored invasion of an individuals privacy. Although it is commonly ignored, the National Statement goes on under section 16.14 to recommend that institutes permitting waiver of consent put in place some formal system of prospective consent. It would seem sensible to follow this guideline.

Privacy

Beginning in 2001 the Australian Law Reform Commission (ALRC) together with the Australian Human Ethics Committee (AHEC) undertook a joint program to obtain submissions on the issue of protecting human genetic privacy. In their document, DP66, they make two key recommendations. The first, proposal 7.1 identifies that the current Privacy Act (Commonwealth and Private Sector) permits great inconsistency in the way in which privacy is protected across state/federal or public/private domains, and so seeks the harmonisation of health privacy legislation as it relates to human genetic information to provide nationally consistent rules. It then goes on under proposal 7.2 to amend the privacy act expressly to "a) define bodily samples as personal information, b) define a record to include a bodily sample". This follows then that tissue and blood samples become legislatively covered by the Privacy Act.

This is, in substance, similar to some legal interpretations made in the UK in regard to the Data Protection Act (1998), which stated that "Human tissue contains DNA, and DNA represents data". However, whereas legal interpretation of the UK Act demands consent from the individual for each and every use of this "data", there are several provisions within the Australian Privacy Act (1988, 2001) that permit waiver of consent. In the section 95a guidelines on the Privacy Act published by the NHMRC, section 10.3 outlines ways in which non-consented secondary uses of health information, other than the original purpose to which they were collected, are permitted, such as if the subsequent research is relevant to public health or public safety, and it is impracticable for the organisation to seek the individual's consent to the collection.

As one can see this not only covers the use of existing health information about the person from whom the sample was obtained, but also the potential for tissue samples to come under the privacy act as recommended by DP66, and avoids the devastating effect such provisions have had in the UK and US.

Tissue microarrays

The chronic shortage of archival pathology material and the difficulties with abiding by ethical and privacy guidelines requires optimal management of existing samples and tissue microarrays (TMAs). Containing hundreds of tissue samples on a single glass slide represent the means to achieve this. The advantages include speed of analysis, throughput, standardisation and conservation of material. Their use is analogous to the use of DNA microarrays and already there are 300-400 academic groups worldwide who are working with TMAs. Like their DNA cousins, TMAs have a 'garbage in: garbage out' principle and many of the current groups are working with widely heterogenous collections that cannot be used for systematic evaluation of disease.

The National Cancer Institute has a Tissue Array program[3] that makes available breast, prostate, ovary, lung, colon and brain specimens with 600 samples per slide at a cost of US$20 each. A limit of 10 slides per investigator is levied and there is limited clinical

information made available, with many samples not having information on sex of the patient or any pathological diagnosis. This is similar for the multi-tumour tissue microarrays[4] made available by the National Human Genome Research Institute's Tissue Array Research Program (TARP)[5].

Within WA we have established, under the WA Research Tissue Network (WARTN)[6], a program of accessing archived pathology material from all pathology services, both public and private, that provides a unique population-based collection of samples. Ethics approval has been sought and obtained at each hospital individually for the construction of the TMAs, as well as linkage to health information. Each project requesting sections will need to go through only one ethics application in WA, and reciprocal approval will be sought from other Perth institutes by the WARTN. The existence of the WA Health Data Linkage Unit (DLU) has enabled us to create a TMA relational database of all cases put into TMAs that can then search the DLU databases electronically for treatment and outcome data and produce this as anonymised output for researchers. Moreover, this provides a means to carry out quality assurance between databases as a quid pro quo. For instance, the WA State Cancer Registry provides mortality data to the TMA colorectal database, which in turn provides staging data on all its cases. This exchange is facilitated by the WARTN being governed and wholly owned by the WA Government.

To identify cases in WA is relatively simple involving either the creation of a list of all cases from the WA State Cancer Registry or a search by ICD0 code (WHO) of the respective pathology database (pathology records are in electronic form from 1995 onward in most institutes in Perth). A data extract is made of all cases into the TMA database. This database has been developed alongside the Data Linkage Unit and existing clinical databases to ensure it is compliant for data exchanges. Blocks and slides are retrieved from the pathology archives using a system that includes card labelling for facilitated tracking and return of these items.

A pathologist reviews slides and marks areas of normal and malignant tissue for punching on the H&E section. A consultant histopathologist can mark up to 12 cases per hour, or approximately 500 cases per week full-time. However, finding a willing pathologist is less difficult than finding one with sufficient time available over and above diagnostic demands to do such work. It is likely that pathology review will provide the rate-limiting step in TMA production. Marked slides are matched to their paraffin block and cores taken. Two malignant and one normal core of tissue is taken wherever possible, and at least two replica blocks are made for each tissue type.

The precise location of each sample is entered into a database during TMA manufacture. Once completed, sections may be cut from TMAs in the routine way on a microtome and depending on core depth up to 200 5mm section may be cut from one TMA. Blocks so created are constructed separately for each institution so that not only is there internal quality assurance and consistency of all cases on any single TMA, but also so that each stakeholder retains ownership of their own blocks. Sections can then be processed for techniques such as immunohistochemistry to look for protein expression patterns associated with specific disease processes, and the resulting data extrapolated back to the database. We are collaborating with the Burnham Institute in San Diego for high throughput automated scanning of slides using robotic techniques. As with DNA arrays, bioinformatics and the ability to handle large data sets is likely to demand high-level computational and statistical support.

Conclusion

Pathology archives represent a valuable resource for translational oncology but the real challenge will be to establish prospective collections of samples from all patients with their informed consent, both from clinical trial and otherwise, in order that these may be used for molecular analysis. In a recent paper, Betensky et al[7] have clearly illustrated that a major confounder in any clinical trial is molecular heterogeneity, and point toward the necessity of obtaining appropriate samples from clinical trials in order to evaluate these potential confounders. Moreover, moves to establish national networks of biospecimen banks such as the Australian Biospecimen Network, will be vital in increasing the attractiveness of conducting Australian oncology trials for both industry and trials groups.

References

1. www.austlii.edu.au/au/other/alrc/publications/dp/66/

2. www.nhmrc.gov.au/publications/pdf/e35.pdf

3. http://resresources.nci.nih.gov/database.cfm?id=521

4. http://resresources.nci.nih.gov/tarp/

5. http://research.nhgri.nih.gov/tma/TARP.shtml

6. Details on the WARTN may be obtained from N Zeps at nikolajs.zeps@health.wa.gov.au

7. RA Betensky, DN Louis, JG Cairncross. “Influence of unrecognized molecular heterogeneity on randomized clinical trials.” J Clin Oncol, 20 (2002): 2495-9.

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