Waiver of individual patient consent in research: when do potential benefits to the community outweigh private rights?

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ABSTRACT

- Health services research is important to ensure continued best quality of care, but often uses data obtained without explicit consent for this purpose.
- Obtaining consent may be difficult for many reasons, but excluding individuals may introduce biases that alter the significance of studies.
- Approval by ethics committees of a waiver of the need for consent allowed our study to proceed and provide evidence that has led to the implementation of a population-based screening policy for the prospective detection of hereditary non-polyposis colorectal cancer.
- This screening policy has resulted in more cases being detected routinely with better management for affected patients and their at-risk families.
- A need for consent would have prohibited this study, and the development of a more efficient screening policy could have been delayed for several more years.
- Ethics committees can effectively manage the need to uphold basic ethical principles without unnecessarily impeding socially useful research. Committees need to be familiar with the guidelines approved under sections 95 and 95A of the *Privacy Act 1988* (Cwlth) in addition to the National Health and Medical Research Council *National statement on ethical conduct in research involving humans*.

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Informed consent, based on the need to respect an individual's autonomy, is the gold standard for the ethical conduct of human research studies. The right to choose to participate in research or not is a fundamental cornerstone of ethical behaviour in a civilised society. However, there are considerable merits in performing research on datasets and tissue samples that were obtained as part of routine management. Indeed, it is reasonable to propose that such research may be in the best interests of the broader community, and hence consistent with situations in which individual autonomy might justifiably be sacrificed. While there has been some recent debate on whether autonomy is "first among equals" in terms of ethical principles,[1] there are practical issues in medicine that mean individual autonomy is not always upheld. Nevertheless, the principle of non-maleficence to the individual must always be borne in mind when autonomy is not upheld.

Australian ethics committees may provide a "waiver" of the need for consent, in accordance with the relevant guidelines in the 1999 National Health and Medical Research Council (NHMRC) *National statement on ethical conduct in research involving humans*,[2] and in the guidelines under section 95 of the *Privacy Act 1988* (Cwlth) and the guidelines approved under Section 95A (private sector amendment effective from 21 December 2001) of this Act.[3] However, complex legislation and state or federal guidelines, as well as constraints at the institutional level, provide significant disincentives for conducting some types of research that are potentially beneficial to the community.

In view of the potential controversy over the use of human genetic material for research, institutional-based human research ethics committees (HRECs) may take a conservative approach to the waiver of consent guidelines and thus retard the progress of studies with potential value to the community. This problem is compounded by the dearth of literature on practical examples of research that employ waiver of consent, and so might assist the ethics committees.

In this article, we present a case study involving a heritable disease for which there is a preventive and effective course of treatment available. Like a great deal of research today, the distinction between basic research and refining clinical practice was somewhat blurred. We suggest this work is "health services" research, as it seeks to analyse and provide a means to improve on a clinical service already in existence. Two major issues arise from this work:

- the need for waiver of consent to perform screening of colorectal cancer cases for a marker of risk of disease; and
- the mechanism by which to contact patients or their families who fall within a "high-risk" category.

We will use our case study to discuss how we went about addressing the ethical issues arising from this work in the hope that this commentary will provide some useful guidance for those intending to carry out similar work.

Case study

Hereditary non-polyposis colorectal cancer

Hereditary non-polyposis colorectal cancer (HNPCC) syndrome accounts for 0.3%–3.0% of colorectal cancer cases, and arises because of defects in one of the mismatch repair (MMR) gene products. Identification of colorectal cancers associated with HNPCC syndrome depends on physicians and surgeons making use of internationally agreed clinical and pathological criteria that include family history of cancer, age at diagnosis and morphological tumour features (Amsterdam criteria).[4,5]

Analysis of tumour DNA for somatic variation in microsatellite markers and loss of MMR gene expression provides further supporting evidence for a possible germline MMR mutation. These analyses are complicated by the occurrence of both allelic and non-allelic heterogeneity, and a preliminary screening process is necessary to ascertain families at likely high risk of an MMR gene mutation, and hence of having HNPCC.

In light of epidemiological data on the prevalence of HNPCC, the anecdotal evidence in Western Australia suggested that few at-risk families were being referred to the state's only familial cancer program run by Genetic Services of Western Australia (GSWA). A study was therefore conducted to estimate the ascertainment of HNPCC families by GSWA at the population level.[6] The investiga-

tors made use of tissue microarrays comprising 1050 consecutive colorectal cancers diagnosed in Western Australia over 10 years. Twenty-four individuals at risk of HNPCC, by virtue of their young age (< 60 years at diagnosis) and loss of expression of MMR genes, were identified, of whom only four were known to the Familial Cancer Program. Eighteen of the remaining 20 at-risk individuals, or their next of kin, were successfully contacted and offered an appointment for consultation. Of these, 17 agreed to attend the clinic for further discussion.

Only one of all the people contacted, including those who declined a clinic appointment, expressed negative sentiments about research being done on his or her tissue specimen without consent or about having been contacted. The dissenting person expressed serious objections about lack of contact and prior consent, but did elect to receive the result. Most people, however, were grateful for the follow-up, perceived it as a valuable extension of primary health care, and were pleasantly surprised that a public service was sufficiently concerned about their wellbeing to embark on an investigation of this nature. No specific psychosocial studies were done on this cohort to formally document a potential change in psychological parameters before and after receiving the new information.

Following discussion with stakeholders on the implications of the results, it was agreed by the state familial colorectal cancer committee that detection of MMR loss by immunohistochemistry should be adopted as a primary screening tool for all patients with a diagnosis of colorectal cancer at age < 60 years. This represented a substantial change from the < 45-years cutoff advocated previously, in response to international recommendations.

Justification for waiver of consent

In the example described above, we presented a case to each of three ethics committees covering institutions involved in the care of the patients. We suggested that, under Section 15.8 of the NHMRC national statement, we fulfilled the need to consider "the justification presented for seeking waiver of consent including the extent to which it is impossible or difficult or intrusive to obtain specific consent". Considering that only 0.3%–3.0% of all colorectal cancers are HNPCC-related (3–32 patients in this cohort), between 1018 and 1047 patients who were not at increased risk of the condition would have received counselling on the nature of the study and aspects of HNPCC that were not relevant to their own clinical situation. This would have been a considerable administrative burden, but we argued that a more important concern was that these individuals would have been unnecessarily presented with the prospect of a potentially worrying medical condition that the statistics indicated they would almost certainly not have. There was therefore the very real prospect of causing undue harm if the need to uphold the autonomy of each individual were to be exercised to the fullest extent. We considered this harm (maleficence) to be greater than the risk of harm arising from potential misuse of patients' personal information. Because the study was conducted by health care workers within a public system bound by confidentiality requirements, and the identity of patients was not going to be made public, we argued that the risk of harm from invasion of privacy was outweighed by the potential benefits from the study.

We argued that, as 313 patients had died by the time we initiated the study, identifying and contacting their next of kin would have been a major undertaking, and would have introduced potential bias into the study if they had to be excluded. We further argued that a prospective study requiring informed consent would take several years to accrue a statistically significant sample. In the meantime, many patients who could potentially benefit from a simple screening method would not have their cancers detected under current practice. Moreover, these patients and their family members could present with more advanced, potentially incurable disease than if screened earlier.

Finally, we argued that the process of obtaining informed consent from each of the 1050 individuals whose tumours were screened would have imposed a prohibitive cost burden and required significant counselling resources. In times of major economic rationalisation of health care services, the use of valuable resources required to obtain individual consent for this project could in itself be seen as unethical.

Justification for informing high-risk individuals

The second ethical issue we were required to address involved making contact with individuals whose tests indicated they were at a higher risk of having HNPCC. The failure to inform people that there may be additional relevant information about their disease was identified as a potential failure to meet a basic duty of care. However, it was clear that a negative test result would provide no relevant health information to those individuals (the majority) and there was therefore no purpose in giving them this information. We acknowledged there was a possibility that a person may be upset that a test had been performed without their permission, that inconclusive germline mutation results could create anxiety for the patient or their family, or that revealing the results could lead to financial problems or social stigmatisation. However, predictive testing for HNPCC differs from other adult-onset genetic conditions in that carriers of MMR gene mutations can be offered effective surveillance programs.[7] The clear pathway established for contacting, counselling and managing at-risk individuals satisfied the ethics committees that there was potential benefit to those identified as being at risk and their families. In this matter, the HRECs were convinced because the organisation involved in the study (GSWA) was also committed to managing the at-risk individuals, as they provided the only state familial cancer genetic counselling and testing service.

Ethics committee responses

Of the three HRECs to which the application was submitted, one approved the study based on the initial application, and two asked for further clarification of the impracticability argument. One of the two approved the study after a written response, and the other required a personal presentation by the investigators. It emerged that this committee had not previously considered the issue, had no point of reference from which to work, and was not entirely familiar with the relevant sections of the NHMRC national statement or the guidelines approved under section 95A of the Privacy Act.

Discussion

If individual informed consent had been a fundamental requirement for the case study presented here, this retrospective screening for HNPCC could not have proceeded. Obtaining consent from and providing counselling for all individuals would have required

large-scale funding, and would have delayed the study by several years. The study provided data that have changed the policy for colorectal cancer management in patients aged under 60 years. Newly identified patients with germline mutations and their at-risk family members can now receive potentially life-saving surveillance that was not previously offered because their cancers had gone undetected.

Our study involved a well described hereditary condition with a well established management strategy. It is important to examine how the waiver-of-consent model would operate in less well defined instances. We suggest that it would not be appropriate to grant a waiver of consent for studies involving the identification of gene mutations for which there were no available management strategies.

A broad range of standards is present within HRECs, and there is currently no benchmarking of how reviews are conducted or how decisions are reached. There is an element of "pot luck" with regard to where the application is sent in terms of local expertise and opinions. This can result in some projects being deemed ethical by one committee while being rejected as unethical by another.

It could be argued that releasing the names and addresses of patients to obtain consent is in itself an invasion of privacy in the strictest sense of the "right to be let alone".[8] It has been suggested that routine "opt-out" type consent could be offered to all patients so there is a means to record patient preferences from the outset, with the possibility of recontacting patients for additional consent in the future if need be.[9,10] We believe this to be a useful strategy that could be adopted as part of routine medical practice.

We propose that the criteria used to evaluate the risks and benefits involved in human genetic research, with or without consent, should be made clearer so both HRECs and researchers can work toward adhering to the highest standards of research governance, including ethics, while at the same time facilitating this potentially valuable research.

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Competing interests

None identified.

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