Commentary

New hurdles for translational research

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Abstract

New guidelines for the collection and use of human tissues for research will impose new requirements on researchers to seek ethical approval and patient consent. This extends to the use of surplus tissue, such as breast cancer excision biopsies, which, until recently, have been regarded as having been 'abandoned' by the patient. This article argues that some of these new constraints provide hurdles to translational research that are unnecessary for patient protection. This is particularly significant when emerging technologies are expected to elicit major advances in clinical cancer research.

Keywords: consent, ethics, guidelines, translational research

Introduction

Characterization of the molecular constituents of cancer and of the relationship of genotypic and phenotypic features to the clinical behaviour of the disease(s) are of enormous contemporary interest. This activity is fuelled by the exponential rate of discovery of new genes, an increasing understanding of the biological consequences of their expression, and a recognition that application of this knowledge in the clinic should provide the opportunity for individually optimized therapeutic approaches.

Additionally, tumours may be explored as a primary research material in their own right, which is probably best epitomized by the recently announced Cancer Genome Project [1], in which the aim is to establish all of the genotypic defects of a selection of human carcinomas. The rapidly approaching completion of the Human Genome Project may be expected to extend the number of candidate genes for clinical evaluation by several orders of magnitude. Some of the new analytical tools required are already in place (although they need substantial refinement to keep pace) to handle this vast amount of new information in a miniaturized manner (eg DNA arrays and tissue arrays enable the simultaneous analysis of the expression of thousands of genes in a single sample, and of the expression of a small number of genes in several hundred tumours, respectively).

Excitement about the possible advances resulting from molecular pathology has never been greater, and therefore the imposition of restrictions on this work that unnecessarily impede progress is of substantial concern.

Over the past few years there has been a perceived need for official guidelines to ensure that access to and analysis of tissues from patients can occur within a framework that will not damage the individuals from whom the tissues were collected and will free the clinical scientist from

REC = research ethics committee; MRC = Medical Research Council.

concerns of litigation. It is therefore welcome that a number of bodies have considered this matter and that their views are available, at least in provisional or interim form. The guidelines are well described in the accompanying editorial [2], as they affect both the USA and UK. This article argues that some of the guidelines will restrict research activity by the increased number and height of the hurdles imposed, and that it is important to assess whether these restrictions are really necessary to safeguard the public both individually and as a whole.

The driving force behind the derivation of many of these guidelines has been the advent of germline genetic testing. It is clear that genetic research raises several different issues from those for nongenetic analyses. As such it is reasonable to regulate genetic work in a way that addresses the associated special issues. However, it should be possible to apply such regulations without their being an encumbrance to nongenetic research. It is instructive to consider how the guidelines of the UK Medical Research Council (MRC) [3] would impact on one particularly active area of nongenetic clinical laboratory research.

Impact of guidelines on research

To address certain research questions relatively small sets of tumours may be sufficient, and these may usually be readily derived prospectively such that consenting of patients is not a significant problem. However, in many cases analysis of large numbers of tumours together with associated, rigorously documented, full clinical histories is required (eg assessing the clinical importance of new biomarkers). This is particularly pertinent in breast cancer, in which the disease and its treatment are exceptionally heterogeneous. Evaluation of biomarkers is uniquely informative when performed in association with large randomized clinical trials, because this may allow the identification of specific subsets of patients as benefiting or not benefiting from a particular treatment. In these circumstances the tissue to be accessed is that which is surplus to pathological diagnostic procedures.

Data derived from such studies not only assist in developing new criteria for patient–treatment selection, but may also help in the identification of response and resistance mechanisms and thereby direct new approaches to therapy. The widespread recognition of the value of this clinical scenario for such research is illustrated by the fact that almost all clinical trials of a significant size now have an associated correlative science committee dealing with this specific issue.

In principal, it may be argued that the preferred approach is to investigate the role of particular factors prospectively. However, the follow-up time required for the clinical endpoints to mature is generally prohibitive to the conduct of such prospective studies. Additionally, with new potential markers being identified it is inevitable that the selection of analyses will change as a clinical trial progresses. Most modern clinical trials need to be very large to have sufficient statistical power, and as a result are almost always multicentre (and frequently international).

For example, the current Anastrozole and Tamoxifen Alone or Combined trial of adjuvant therapy in postmenopausal breast cancer has recruited from 95 centres around the UK (plus many more outside the UK). This trial has in fact completed recruitment and may be able to collect tissues under the less stringent guidelines relating to retrospective specimens. If such a trial were to be initiated under the new MRC guidance [3], however, then for retrieval of specimens to occur every one of the 95 centres would be required to operate a consent procedure for pathological research on its patients and to record the individual results of that procedure. Additionally, as associated research ideas develop, each of the local research ethics committees (RECs) will need to consider, presumably under the guidance of a multicentre REC, the research analyses to be conducted. As new analytes became assayable, the protocol and ethical approval would need to be revisited by the analyst, the multicentre REC and the local REC. This type of work might be assisted by future clinical trials requesting consent in a general form (eg for ‘biochemical’ analyses) at the time of recruitment, but it is not clear that this general consent will satisfy all authorities. In addition, for many studies associated and correlative research questions are unclear at the time of the study, and the trialists may be reluctant to perform this additional procedure when there appears to be no immediate research goal.

The requirement for patient consent to analysis of this surplus tissue and the involvement of numerous local RECs lead to a substantial encumberance and extra expense. As far as RECs are concerned, would it not be sufficient for the clinical scientist to obtain local REC approval at his/her local site, and presentation of certification of approval be sufficient for the pathologist to release tissue without recourse to each individual local REC?

Consent is such a fundamental component of clinical practice and research that it seems heretical to question its necessity, but it is appropriate to ask whether in this context it is a real necessity or a political nicety. The need for consent appears to derive in part from the recommended change in the way in which we regard this surplus tissue (ie from it being considered as ‘abandoned’ to it being seen as a ‘gift’). For the latter to be the case there has to be documentation demonstrating that the tissue is a gift, in essence a delivery note ‘from me to you’. Is this change in the status of surplus tissue really needed? It seems to me that there should be no public unease if it was clear that an enforceable set of regulations

were in place to guide the use of such tissues. It is likely that the large majority of those patients who would decide not to consent to surplus pathological material being used for research would do so out of ignorance or misunderstanding. It should be sufficient to require that pathology laboratories and other custodians of tissues receive certification of REC approval before release of materials. In the latter circumstances the REC itself would be required to ensure that the approaches of the particular project would cater sufficiently for the individuals concerned, and in particular that issues of confidentiality are dealt with satisfactorily.

Conclusion

Presented above is but one example of a type of study that will be made substantially more difficult by the guidelines of the MRC such that research, which could significantly improve our understanding and treatment of breast cancer, may be discouraged to the degree that it does not occur. This is not to decry the work of the expert committees that have debated these issues at length and provided these guidelines. They have indeed asked for responses before finalization such that modifications may be considered. It is important that individuals and research organizations do not merely accept these provisional guidelines, perhaps in their relief that some have been derived, but examine carefully how they may affect their future research and address any concerns to the respective body.

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