Ethics in action: Approving and improving medical research with human subjects

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TUMOUR TISSUE: WHO IS IN CONTROL?1

Guidelines on tissue banking for clinical and research purposes

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Abstract

Recent developments in genomics have resulted in the increased availability of gene profiles for early diagnostics and prognostics in breast cancer. We expect that genetic analysis of a patient’s (tumour) tissue will, in time, become a standard part of cancer treatment. A request from a Dutch woman to have her tumour tissue tested years after treatment confronted the Netherlands Cancer Institute (NKI) and its staff with legal, ethical and practical questions regarding patients’ rights in relation to residual tissue storage and its use for clinical purposes. Was her tissue still available? If so, could she (and her relatives) demand that the test be carried out? Or, could she demand that the tissue be transferred to another hospital? As it became apparent that appropriate guidance was lacking in this area, the NKI arranged for a group of professionals with legal and ethical expertise to develop a guideline within the framework of a Technology Assessment project. Subsequently, the relevant stakeholders, including oncologists, pathologists, medical researchers and patient representatives, were invited to reflect on the guideline, including its practical implications. Consensus was reached on the

guideline, including its main practical implications and the preservation of a sufficient amount of a patient’s residual tissue: exclusively for future use in diagnostics and prognostics. Finally, the staff of the pathology department was asked to report on the feasibility of the guideline given its current tissue banking procedures.

5.1 Introduction

A promising technology in the treatment of breast cancer is the introduction of genomic profiling for prognostics and (early) diagnostics. This development puts the availability of tissue for clinical care in the spotlight. We expect that both hospitals and medical professionals will increasingly be confronted with legal and ethical questions concerning the rights of patients regarding their tissue. Can a patient expect that enough suitable tissue is stored for his future treatment or that of his relatives? Should a patient, after initial treatment, be informed about newly introduced diagnostic or prognostic tests, and if so, to what extent? Can a patient demand that a test be performed and/or that his tissue be transferred to another hospital? Likewise, what are the rights of a patient’s relatives with regard to that patient’s tissue?

While a number of issues concerning the storage and use of tissue for research purposes, such as ownership and informed consent, have already been extensively discussed in the literature, little focus has been placed on patients’ rights regarding tissue banking for clinical purposes (Hansson et al. 2006, McHale et al. 2007). Against that background, the Netherlands Cancer Institute (NKI) initiated a research project covering these questions. The project resulted in a guideline on tissue storage and use for clinical purposes, specifically focusing on patients’ rights. This paper concentrates on the guideline, its underlying principles, its main provisions and the feasibility of its application in clinical practice. In the following, first the background to the guideline is briefly described. Then we address the fundamental legal and ethical principles underlying the guideline and its main provisions, which should, in our opinion, form the basis for more detailed institutional regulations. Finally, we make some observations about the feasibility of applying the guideline in hospital practice, making reference to the first experiences of the NKI’s pathology department.
5.2 Background to the guideline

5.2.1 Promising developments in genomics
Gene-expression profiling is an important development that is likely to predict the diagnosis and prognosis of malignant disease more accurately than existing clinicopathological parameters (Bertucci et al. 2001). Although gene-expression profiling is not yet routine procedure, several tests are currently under investigation. In the United States for example, the prognostic and predictive accuracy of a genomic profile for breast cancer patients (called the 21-gene recurrence score), based on paraffin embedded tumour tissue is currently being studied in a randomized trial (Paik et al. 2004). In Europe, a 70-gene signature (MammaPrint), which uses microarrays on fresh frozen tumour tissue, is being tested in a multicenter randomized trial (MINDACT) for its prognostic and predictive accuracy (Bueno-de-Mesquita et al. 2007, van ’t Veer et al. 2002, van de Vijver et al. 2002). Although genomic profiling will in the first place help make cancer treatment more effective, in the future genetic profiling will probably be used for many other diseases and for other goals than prognostics, such as for establishing the presence or absence of a disease or its responsiveness to therapy. For the successful performance of these tests tissue should be available, both in a proper form and in sufficient quantity.

5.2.2 Developing a guideline
In the course of the feasibility and technology assessment study of the 70-gene-signature in the Netherlands, it became apparent that implementation of these new diagnostic and prognostic technologies generates new legal and ethical questions concerning the storage and use of a patient’s tissue for clinical purposes (Douma et al. 2007). We refer here to the questions addressed in the introduction. Further encouraged by an actual request by a Dutch woman previously treated for breast cancer to have her tumour tissue tested with the 70-gene test, the hospital appointed a group of lawyers and ethicists to study the new questions, together with the professionals concerned, i.e. physicians of the departments of oncology and pathology and researchers in the field of genomic profiling. Following the exploratory phase, a draft guideline was written and discussed with professionals and patient representatives.
during two subsequent meetings. Finally, the hospital’s department of pathology was asked to explore the feasibility of applying the guideline in daily clinical practice.

5.3 The guideline’s underlying principles

The literature addresses tissue banking for clinical purposes much less than tissue banking for research purposes (Hansson et al. 2006). Since tissue banking for clinical purposes must also comply with international legislation and guidelines, we had to look at related legal and ethical documents. On an international level, our research included the Council of Europe’s Convention on Human Rights and Biomedicine and its additional protocols on Biomedical Research and Genetic Testing for Health Purposes, the Recommendation of the Council of Europe on research on biological materials of human origin and UNESCO’s International Declaration on Human Genetic Data; and on a national level we looked at regulations on patients’ rights, privacy protection and the use of tissue for research purposes (Council of Europe 1997, Council of Europe 2005, Council of Europe 2008, Council of Europe, Committee of Ministers 2006, Federation of Biomedical Scientific Societies 2001, UNESCO 2003, Wet bescherming persoonsgegevens 2000, Wet op de geneeskundige behandelingsovereenkomst 1994).

From these documents, we distinguish four general principles, which should be taken into account. First, care providers have a moral and legal obligation to protect the clinical interests of their patients (World Medical Association 1948). In light of emerging technologies, we think that good clinical care should include securing the availability of sufficient tissue for future clinical care and access for patients (and ultimately their relatives) to generally accepted diagnostic or prognostic tests on that tissue.

Second, irrespective of whether they can be considered “owners” of their removed tissue in their own jurisdiction, patients have personal rights regarding their removed bodily material (Charo 2006). We primarily aim to take into account the right of patients to consent or object to the storage and use of their tissue for other purposes than that for which it was removed, such as research (Council of Europe 1997). This implies that patients should be informed about the consequences of storage-and-use
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As patients have the final say over their residual tissue, a patient should always be able to request its destruction, unless he has agreed with its storage and use for research. As care providers are likely to differ in their policies on the availability of tests and the conditions under which they are accessible to patients, patients should also be entitled to request tissue transfer in order to have their tissue tested elsewhere.

A third principle concerns the position of the patient’s relatives. Here, the underlying question is whether a physician’s duty to provide good clinical care involves the protection of the relatives’ medical interests too. From the perspective of a physician’s duty to provide good clinical care, the mere fact that stored tissue can also serve health interests of genetically related relatives justifies protection of their position (Haites et al. 2001). Receiving genetic information of clinical relevance is an example of such an interest. Article 17 of the United Nations International Covenant on Civil and Political Rights (United Nations 1966) and Article 8 of the European Convention on Human Rights (Council of Europe 1950) point in this direction too, while they connect the constitutional right to private life with the recognition of the family as the basic unit. The Council of Europe’s Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research in Articles 13-15 specifically refers to situations in which tests could benefit relatives while the patient himself cannot provide consent (Council of Europe 2005). Finally, we refer to one of the conclusions of the Icelandic Supreme Court in its internationally discussed decision of November, 27 2003 (i.e. that not only patients themselves, but also their children or other relatives in the first line deserve privacy protection whenever their genetic data are being collected, stored and used) (Gevers 2004, Guðmundsdóttir v Iceland 2004). On the other hand, it is generally acknowledged that physicians have less extensive obligations to patients’ relatives than to patients themselves, as they are primarily responsible for the care of the persons who were seeking their assistance (Council of Europe 2008). This implies that as long as patients are capable of giving authorization, they should decide whether their tissue is tested or transferred in the interest of relatives.

The final principle that can be derived from international documents concerns the situation in which a patient’s interests conflict with the general interest of medical science. We refer to Article 2 of the Biomedicine Convention stating that “the interests of
and welfare of the human being shall prevail over the sole interest of society or science” (Council of Europe 1997). A similar article is incorporated in UNESCO’s Declaration on the Human Genome: “No research or research application concerning the human genome (...) should prevail over respect for the human rights, fundamental freedoms and human dignity of individuals or, where applicable, of groups of people” (UNESCO 1997). Therefore, in situations in which tissue has been stored for the purpose of medical care as well as scientific research and is insufficient to serve both purposes, the medical interest of the patient overrides the general interest of doing scientific research. Only if a patient has been asked, has agreed and can oversee the consequences of his decision to donate his or her material specifically for research, does it seem reasonable that it may be used exclusively for that purpose (Winickoff and Winickoff 2003).

5.4 Main provisions of the guideline

5.4.1 Duties of hospitals and professionals
Primarily, excised tissue is sent to the pathologist for diagnostic purposes. In a number of cases it is difficult to obtain sufficient tissue and discussions on patient rights or scientific storage regulations should always take this into account. Once there is residual tissue, it should be acknowledged that patients have legitimate health interests in the availability of proper tissue.

The hospital’s primary responsibility in our opinion is to ensure that, as far as is reasonably possible, enough of a patient’s tissue is available for present or future clinical use. This implies that the practitioners responsible (i.e. surgeons and pathologists) should therefore ensure that sufficient tissue is stored and preserved in such a way – fresh-frozen or otherwise – that it is suitable for testing, even many years after initial diagnosis or treatment. In addition, the tissue should be stored as long as is necessary to serve the patient’s clinical interest, unless during that period the patient explicitly requests the destruction, donation or transfer of his tissue to another hospital. Because Dutch law does not regulate the storage period of human tissue, its length depends on professional and local guidelines. However, this may be different in other countries.
Second, after expiration of the required storage period, a hospital may destroy the tissue, but only if at that moment the medical interest of the patient, his relatives or the general interest of medical science no longer requires its retention.

Third, where the legal relationship between a patient and a hospital has come to an end and the patient or his relatives request that his tissue be transferred for diagnostic purposes, the hospital should cooperate with the transfer of the tissue to a different hospital. The right to have one’s tissue transferred to a different hospital should also apply when the attending practitioner refuses to do the requested test.

A final, but crucial, responsibility of the hospital is to develop local guidelines that cover all the relevant administrative aspects concerning tissue banking for clinical purposes, not in the least to be able to provide clear information to patients about their rights.

Apart from their previously cited responsibilities, physicians, who are primarily responsible for patient care, should consider it their duty to keep the patient informed about new clinically relevant tests that can be done on stored tissue as soon as these tests, according to local or national medical standards, can be considered an element of evidence based, good clinical care. We feel that it is a responsibility of professional organizations together with patient representatives to develop more detailed standards on what the responsibilities of physicians should entail in this respect. Making an exception only seems justified when it would be reasonably impossible for the physician to provide such information. This appears to be the case when the physician-patient relationship has ended or a patient is no longer traceable, or if he has invoked his right not to know. Once a test is generally accepted as standard practice and relevant, it should be offered to patients, or at least be carried out when patients demand it. If a situation occurs in which a patient and a physician disagree about the usefulness of a test, and a different physician is prepared to perform it, the tissue should be transferred at the patient’s request.

5.4.2 Rights of patients and their relatives
To ensure that patients are aware that their tissue is being stored for a long time and that they have an important say about what happens to it, they should receive adequate information on the storage period and use of their tissue, their personal rights and those
of their relatives. Without such information, the legal recognition of a patient's position with respect to his tissue remains theoretical. The rights of patients can further be incorporated in local rules for tissue banking (see the section above), and should include a right to the destruction or donation of the tissue and a right to have the tissue transferred to a different hospital. The latter right can be particularly instrumental in a situation where patients (or their relatives) are treated by a physician working in a different hospital, or when the attending practitioner refuses to perform the requested test.

With regard to the position of relatives, their interests should be protected to at least some extent. Subject to the condition that the patient concerned consents to it, relatives should also be able to request tissue transfer and testing related to their legitimate health interests. When a patient has died or is incapable of giving consent but the tissue is still available, relatives, in our view, have the right to request continuation of storage, transfer of the tissue to a different medical center, and testing of the tissue.

5.5 Some observations from practice

After all parties involved committed themselves to the guideline, the NKI's pathology department assessed the feasibility of incorporating the requirements of the guideline in their present tissue banking procedures.

The department reported that it is already NKI policy to store tissue for a practically limitless period. In situations of scarcity of the available tissue, it is not permitted to use it for research purposes, unless the patient consents to the donation of the tissue for that purpose. As to the actual application of the guideline's provisions, the department notes that it also has responsibilities towards researchers and has to support and facilitate tissue storage and use for clinical and retrospective research. From that perspective, it would be helpful to appoint a “tissue bank manager”, responsible for matters such as the further automatization of the record keeping of specimens and the assessment and handling of tissue. Furthermore, the actual selection, division and
preparation of the tissue should be conducted by well-trained pathologists and/or (senior) technicians.

Finally, provided it is reasonably possible, it would be preferable to store a “control piece” in a separate tissue bank, reserved exclusively for patient usage. These measures can have financial implications that should be taken into account.

A number of other issues remain to be addressed. Priority is currently given to the storage of paraffin embedded tissue, whereas fresh-frozen tissue could be more informative and promising for the future. However, this should not be an individual pathologist’s or hospital’s choice, but is an issue that should be discussed within the framework of professional and institutional obligations and of the principles set out above.

A different question is how long the obligation to store tissue should extend. In our view, this is primarily a matter of professional medical judgment as it depends on both the type of tissue and the significance and the expression modes of related prognostic or genomic factors. Genetic counselors are likely to advise a lengthy period, as relatives may benefit from a comprehensive “tissue-history” in future situations. On the other hand, pathology departments may consider limitless storage obligations neither reasonable nor feasible. Apart from this, privacy considerations could play a role, for instance with regard to minors (Gurwitz et al. 2009).

Although this guideline is primarily developed to inform storage policy on tumour tissue, we expect that it is also relevant to the storage of other types of tissue. We are aware that the presented elements require further reflection and debate. It is obvious that tissue storage for clinical purposes urgently needs further attention from medical, ethical, legal and practical perspectives. Hopefully, the guidance we propose will contribute to the discussion of this important issue.
References


Council of Europe Committee of Ministers (2006) Recommendation of the Committee of Ministers to member states on research on biological materials of human origin.


