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Regulatory aspects of genetic research with residual human tissue: Effective and efficient data coding

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ABSTRACT

In a large retrospective cohort of breast cancer patients, *BRCA1* and *BRCA2* germline mutations were analysed in DNA isolated from residual paraffin-embedded tissue samples. Because it was not feasible to ask individual for informed consent, a data and DNA coding protocol, based on the Dutch 'Code of Conduct', was developed. The corner stone of the protocol is that a trusted third party, in our case a notary, keeps the coding keys of clinical data and DNA. Because (re)linkage of the combined coded clinical and genotyping data (*BRCA1/2*) is only possible through the notary's keys, these can be considered to be comparable to anonymised data at the level of the researcher. Issues around retrospective genotyping of allegedly high-risk mutations and the coding procedure itself are discussed. Our protocol is an appropriate solution to safeguard the privacy of patients when using residual tissue or DNA of patients. Importantly, the coding procedure also allows re-linkage of new genotyping data or extended patient follow-up data to the valuable coded dataset.

1. Introduction

Important clinical questions regarding the influence of germline variants on the prognosis of (hereditary) cancer can be efficiently addressed if stored human materials can be retrospectively genotyped and combined with long-term follow-up data of the patients concerned.[1] However, governance issues usually preclude retrospective genotyping of patients for allegedly high-risk germline mutations, for example in *BRCA1* and *BRCA2*, unless informed consent has been given or patient identifiers are irretrievably destroyed.[2,3]

Nowadays, retrospective analysis of germline mutations can be performed on residual, stored, formalin-fixed, paraffin-embedded tissue of breast cancer patients, obtained during earlier clinical procedures. This development raises a number of issues, e.g. patient privacy and the right of self-determination, which need to be addressed. These issues become even more relevant in the case of retrospective determination of high-risk germline mutations. *BRCA1* and *BRCA2* mutation carriership predisposes for a strongly increased risk of disease[4] and possibly for a different disease prognosis compared to non-*BRCA* mutation carriers.[5] The results of a *BRCA* mutation analysis may not only have consequences for the patient herself (if still alive), but also concern her relatives who do not (yet) know if they are a carrier. The consequences primarily include dealing with the knowledge of a genetic disease with implications for breast cancer screening, prophylactic oophorectomy, and prophylactic bilateral or contralateral mastectomy.

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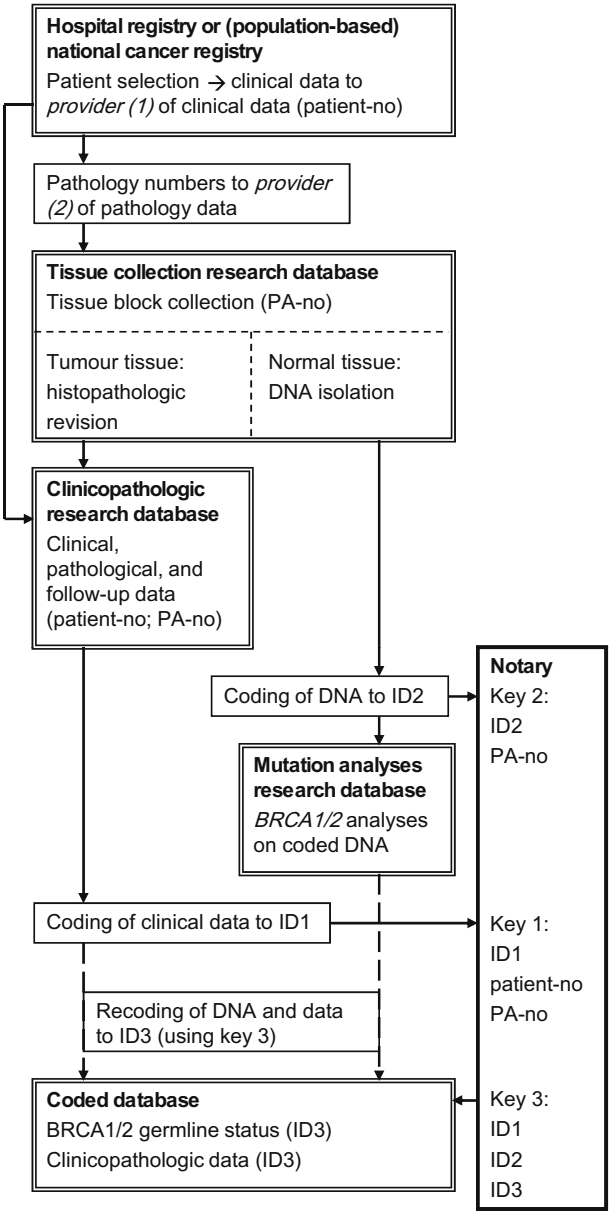

Fig. 1 – Flow diagram of coding procedure. Breast cancer patients are selected through the hospital registry and/or cancer registries. In the present study, clinical data, such as treatment and medical follow-up, are collected using the hospital registries, patient records and cancer registries. These data are submitted under supervision of *provider (1)*. Mutation analysis is performed on DNA from non-tumour formalin-fixed paraffin-embedded tissue blocks that are retrieved from Pathology archives under supervision of *provider (2)*. In principle the protocol calls for a provider of clinical data and paraffin blocks, who should be the physician who treated the patients. However, the patients in our study were diagnosed before 2003 and since then many specialists have left the hospital. Therefore, the chairman of The Breast Cancer Working Party, Head of Surgery or the head of the Cancer Registry and the head of the Pathology Department (in each of the hospitals) acted as the providers 1 and 2 of clinical data and tissue blocks, respectively. All databases mentioned in the figure are separated (i.e. in different folders belonging to different departments) and user-name linked and password protected. Tumour blocks are used for collection of additional histopathologic data while normal paraffin-embedded tissue blocks are collected for DNA isolation and subsequent *BRCA1/2* mutation analysis. The researcher and research assistants are involved in the process of tissue block selection and manage a tissue collection research database for administration of blocks used for tumour revision and DNA isolation. Tissue slices from paraffin-embedded blocks are used for DNA isolation (using PA-no). After DNA has been checked for quality and concentration, a batch of DNA is coded to ID2 by a data manager or research assistant, who is involved in the study but not involved in the mutation analysis. DNA is then moved to the containers labelled with ID2 by the research technicians, using a paper list which contains both PA-no and ID2, this list is destroyed after DNA has been contained by ID2. The key is given to the notary before the start of mutation analysis of that batch. Results of the mutation analysis are kept in the mutation analyses research database accessible only for the research technicians. Histopathologic data, together with the

We feel that such research, including genotyping for high-risk germline mutations, should take place if the invasion of privacy and personal integrity is minimised and security of mutation analyses results is maximised. Clearly, research aiming to improve knowledge, prevention and therapy of disease is in the interest of researchers, patients and the population as a whole. However, there is insufficient regulation in Dutch and European law regarding the secondary use of residual human materials.[6] In the Netherlands, self-regulation led to a 'Code of Conduct for proper secondary use of human tissue in research' by the Dutch Federation of Biomedical Scientific Societies, together with the Royal Dutch Medical Association and several patient groups in 2002 (http://www.federa.org/?s=1&m=78&p=&v=4).

In case it is not feasible or desirable to ask for informed consent, the general rule is that patient data have to be either anonymised or coded. However, truly anonymised data mean that the use of these data is severely limited for use in future research.[7,8] To address this problem for our ongoing research project on the prognosis of *BRCA1/2* germline mutation carriers, a special coding procedure based on the above-mentioned Code of Conduct was developed.

2. Methodology and results

2.1. *Research project on the prognosis of breast cancer according to germline mutations: using residual, stored human tissue*

The main research question in the project concerned is whether *BRCA* mutation carriers have a different course of disease compared to non-carriers. Eligible women were diagnosed with breast cancer below age 50 in several hospitals in the Netherlands, in the period 1970–1995. Recently, we have extended this period of diagnosis to 2002. For all women ($n \sim 5000$), the presence of a *BRCA1* or *BRCA2* germline mutation is being determined using DNA from formalin-fixed, paraffin-embedded, normal (non-tumour) tissue. For this type of research, a prospective cohort study, including a large, unselected sample of incident breast cancer cases, would be preferable, also because informed consent could be asked at the start of the study. However, when studying prognosis of breast cancer a follow-up of at least 10–15 years is needed to adequately investigate survival differences. We considered that such a time span was not desirable given the importance of the clinical questions. In addition, recent changes in the intensity of screening of *BRCA1/2* carriers by mammography and MRI, and prophylactic surgeries would bias a prospective cohort.

2.2. *Patient privacy regarding the use of residual human material: regulations and guidelines*

It is outside the scope of this paper to give a complete overview of world-wide regulations and guidelines for the use of patient data and tissue or DNA for research purposes; others have discussed these issues already.[1,6,9–11] We will briefly describe the Dutch situation, to explain the framework in which our coding procedure was developed. We emphasise that the regulations described are those applicable to the use of *residual* human materials and clinical data for research. If a human sample would specifically be collected for research, different regulations would apply, i.e. an informed consent procedure.

The Dutch general act on patients rights, which came into force in 1995, stipulates that (clinical) patient data can be used for scientific research without informed consent, if asking for informed consent is judged to be not realistically possible (Dutch Data Protection Act and Dutch Medical Treatment Contract Act; info via: http://www.dutchdpa.nl/indexen/en_ind_wetten_wbp.shtml and http://www.dutchdpa.nl/documenten/en_inf_subj_Confidentiality_Medical_Data.shtml). The act states that patients should be notified that their residual tissue can be used for research and should have the possibility to opt-out. However, the act only mentions the use of patient data and *anonymised* residual human material. Anonymised is defined in such a way that the coding key between patient identifiers and human material must be

clinical data collected, are transported to a clinicopathologic research database which does not contain patient names or addresses, just patient identifiers such as hospital (patient-no) and pathology numbers. These data are coded to ID1 before being used in statistical analyses by an independent data manager (meaning a data manager not directly involved in the study). Upon coding also other patient identifying variables are removed from the database and dates are reduced to years. Clinical data may also be coded directly to ID3, but we choose to include an additional step in the coding to extra safeguard the non-coded clinical data not to be linked to the DNA. In case the clinical data and tissue are delivered from another hospital to the hospital where the researcher is placed, even one coding key instead of two could be maintained, in which case the other hospital should send the key directly to the notary. If the researcher wants to analyse the clinical/pathological data by *BRCA1/2* stratification, a data manager, who is not directly involved in the study, links both databases and replaces ID1 and ID2 by ID3, under supervision of the notary who also retains the keys of this linkage procedure. The role of the notary is to witness each linkage procedure and to summarise the procedure in official minutes. The notary does not keep the actual data, but just the coding keys (paper prints and CD's). A data manager performs these data coding procedures and gives the keys to the notary. ID2 codes are random numbers from a list of 15 000 numbers generated before the start of the study. ID1 and ID3 are random numbers generated upon coding the clinicopathologic data. All databases are Access database and all procedures are run by the standardised queries. The IDs used are random numbers (non-overlapping numbers or, e.g. pre-fixes distinguishing the three keys could be used), but encryption methods could be used as well. PA-no: pathology number (the number of the pathology reports and tissue blocks); patient-no: the unique number under which a patient is registered at the hospital or cancer registry; and ID: unique identification number (a meaningless code).

irreversibly destroyed, so that the test results can never be traced back to the patient concerned. The Dutch law has not yet regulated the use of *coded* residual patient material, i.e. material that could (theoretically) be traced back to the individual concerned. The use of residual tissue has also not (yet) been regulated by the European Union.[6,11,12]

Ahead of new regulations, self-regulation of researchers in the Netherlands led to the 'Code of Conduct' for proper secondary use of human tissue (http://www.federa.org/?s=1&m=78&p=&v=4). This Code postulates that both anonymised *and coded* patient materials obtained during a clinical procedure may be used for scientific research, as long as the patient did not object to such use (opt-out). It is based on the assumption that appropriate general information is given to all patients in the hospital, e.g. a leaflet stating that patients can opt-out from the rule that allows their material to be used in coded form for scientific research. In addition, each research protocol using residual human tissue should be approved by a medical ethical committee or by an Institutional Review Board (IRB). Also, the Code specifies the terms under which the material can be used and provides rules for informing patients in case of unexpected findings with clinical relevance.

One difficulty is that patients whose tissue was removed before 1995 were not made aware of the fact that they should object if they did not want their residual tissue to be used for scientific research. In retrospective cohort studies, with large numbers of patients of whom many have already died, have moved or are otherwise unattainable, asking for informed consent retrospectively is difficult, if not impossible.[13] Even if asking for informed consent is possible, it is questionable whether this is always desirable.[14] Therefore, the Code of Conduct included a transitional regulation, allowing the use of coded material from before 1995.

2.3. The coding procedure

In our retrospective study, we did not consider it feasible to ask for informed consent because in the large cohort ($n = 5000$) ~50% of the patients had already died while an additional ~25% were no longer under medical surveillance in the hospitals concerned and thus would be difficult to trace. We also considered the right of patients to remain uninformed of the results of such analyses (as indicated in the Dutch Medical Treatment Contract Act). In addition, we wondered whether it would be desirable to contact patients diagnosed such a long time ago, or their families, as we did not know their current (health) condition. On the other hand, anonymising the data would mean that the use of our valuable data collection in further research would we severely limited. In terms of effort, time and money spent to assemble this large cohort this would have been a waste. Therefore, we developed a coding protocol, which was approved by the IRBs of all centres involved in the project, including the Netherlands Cancer Institute and two large University hospitals.

The coding procedure is extensively described in Fig. 1.[15] In short, for clinicopathologic data and for DNA mutation analyses data (*BRCA1/2* carriership), different coding keys are used. To foster patient privacy and to decrease the risk of accidental 'abuse' of data, the clinical data are in a database which is separated from the mutation analysis database while collection of medical follow-up data is ongoing. DNA has already been coded before mutation analysis, while the clinical data are coded upon linkage with the *BRCA1/2* germline mutation results or at the start of any analysis. Unique identifiers, which may link the DNA or data back to the individual patient without unreasonable effort, are removed upon coding. The coding procedure makes use of a trusted third party, in our case a notary, to keep the keys that contain identifiers for linkage of the clinical and pathological data with the *BRCA1/2* mutation analysis results. For statistical analyses, genotyping results are linked to the clinicopathologic data and the linked dataset is returned to the researcher under a third code. This is performed by a data manager who is not directly involved in the project and under supervision of the notary who keeps all coding keys. Hence, all data, including the *BRCA1/2* mutation analysis results, can are only be traced back to identifiable persons through the notary.

In terms of time investment, once the databases (in our case SQL and Access) and procedures were established, each coding session with the notary took about 1 h. At the start of the project we performed a pilot to check whether patients could be uniquely coded indeed and to develop a standard set of 'queries' to run the coding procedures.

3. Discussion

3.1. Coding procedure

There is still a fierce ongoing debate on the possibilities of using anonymised and coded stored tissue, with or without asking for informed consent. To the advantage of both researchers and patients, we and others[1,14,16,17] feel that usage of stored human tissue should be allowed without (informed) consent, provided that approval of an IRB has been obtained and the privacy of the patients can be ensured. Important international reports support this view, e.g. the Council of Europe's Recommendation on research on biological materials of human origin (http://wcd.coe.int/ViewDoc.jsp?id=977859); the recommendation of the European Society of Human Genetics[18]; the World Health Organisation Guideline for obtaining informed consent for the procurement and use of human tissue, cells and fluids in research (http://www.who.int/reproductive-health/hrp/tissue.pdf); and comment 137 of the explanatory report of Convention on Human Rights and Biomedicine (http://conventions.coe.int/Treaty/en/Reports/Html/164.htm) states that in some cases 'express consent of an individual to the use of parts of his body is not systematically needed'.

The use of anonymised data avoids (in theory) ethical problems related to patient identifiable data, but puts enormous restraints on research possibilities.[1] Anonymous data render it impossible to extent patient follow-up and also pose difficulties when the researcher wishes to include the data in meta-analyses (i.e. the risk of including patients several times). Furthermore, anonymisation precludes prevention of fraud by archiving of traceable data. This is especially true for research including germline mutations analysis and for research in which it is not feasible or desirable to contact patients or families (of deceased patients) to ask for informed consent. Interestingly, a review in 1999 on studies using

human tissue showed that studies which included germline mutation analyses were more likely to be reviewed by an IRB 'suggesting that these (and perhaps investigators) perceive genetics studies as posing more than minimal risks to subjects'.[19] Using a coding procedure with a trusted third party to keep the coding keys is in our view an appropriate solution, and is in line with what others have suggested (e.g. Ref. [20]). In our study we used a notary firstly because of the sensitivity of the data concerned (*BRCA1/2* carriership) and because our study involves multiple centres, which made the choice for an external third party seem logical. With the approval of the IRB, a comparable procedure using another third trusted party instead of a notary could be used, for example an institution where the researcher is not based (e.g. a National Cancer Registry), or the chairman of the IRB. We feel that this could assure an equally appropriate coding procedure while costs would be largely reduced.

A difficult point to consider in this discussion is whether the coding suffices to truly exclude the possibility that an individual patient can be traced back. Probably if we would include many variables this may become possible, but that would be quite an effort and only be possible by linking to databases which are on different locations while names or addresses would only be retrievable through the hospital registries, which seems only to be a relevant, hypothetical threat for patients diagnosed in the hospital where the database is located. However, this point of discussion holds equally true for anonymous data, which may also be traced back to an individual patient if enough variables are used, especially in the new era of genome sequencing.[21,22] We think that the relevant point here is that data are not traceable to the individual patient without unreasonable effort and time. As in any research project, an important pillar is the integrity of the researcher not to make misuse of data. The obligation to report every linkage of data with the presence of a notary (or another third party) certainly may help to sustain optimal awareness of this fact.

Although the privacy of the patient is optimally protected in our coding procedure, we had to consider two remaining important issues. Firstly, the use of coded material without asking for informed consent implies that the research findings cannot be reported directly to the patients (through their treating physicians). Secondly, is it indeed justified, from an ethical point of view and the right of self-determination of patients, to use stored tissue under a (postulated) opt-out regime without informing patients? These issues will be discussed below. Of course there are also important technical issues that need to be considered when using formalin-fixed, paraffin-embedded tissue (see e.g. Ref. [23]) which we considered beyond the scope of this paper.

Yet another debatable issue when using anonymous and coded materials is the possibility of unnecessary repeated analyses of, e.g. germline mutations on the same material. Though this is a discussion which may need a separate paper as well we would like to make two remarks. Firstly, in our opinion each institute should advocate exchange of information and collaboration between researchers, assuring to the most possible extent that materials are not used unnecessarily. Secondly, data linkage between databases should be made possible whenever acceptable from an ethical and regulatory perspective, to avoid (re)analyses of known information. For example, we recently extended our study cohort with NKI-AVL patients diagnosed between 1995 and 2002. Our IRB agreed that we used data from our Clinical Genetic Laboratory to avoid re-analyses of *BRCA1/2* mutation status for patients diagnosed in this period (i.e. in this case about 140 of 800 patients).

3.2. *Research findings: implication for patients and their relatives*

The Code of Conduct states that, in general, new research findings will not directly lead to changes in clinical protocols. Therefore it is undesirable to confront persons with information about a possible high risk of disease or worse prognosis. If the results of a study (combined with the findings of others) would have implications for the treatment or diagnosis of patients, then in practice *all* patients and not just the population included in the study should benefit from this change in protocol. This includes results of genetic research. Hence, if our present study, and other research, show that young breast cancer patients with a *BRCA1* or *BRCA2* mutation have an unfavourable prognosis or different treatment response, then *all* young breast cancer patients who are at high risk to carry a *BRCA1/2* mutation (based on family history or other indicators) should be counselled and recommended to undergo DNA testing.

Apart from potential relevance of new research findings for the study participants, a study involving *BRCA1/2* mutation testing has an additional dilemma. The *BRCA1/2* test results itself could be relevant and have consequences for the patient herself or her relatives. In case of stored tissue dated before 1995, this will concern patients who were unaware of potential *BRCA1/2* carriership at that time, but who may have undergone mutation testing later on. We expected that patients who are still under surveillance in the hospitals participating in our study would already have been informed by their treating physicians of the possibilities of counselling where applicable (guideline available from http://www.oncoline.nl/). Likely, such patients made a well-funded decision to undergo or not undergo mutation testing. We also assumed that relatives of the deceased patients in our study, for whom *BRCA1/2* mutation screening would be indicated according to the current guidelines, would have been informed by their general practitioner or via the lay press.

The literature shows that *BRCA1/2* may also be found in (young) breast cancer patients *without* a family history of breast cancer.[4,24] Such patients may be less informed about *BRCA1/2* screening, but especially in those families the impact and relevance of *BRCA1/2* carriership are still unclear, and other genetic or non-genetic factors may play a role. Careful evaluation of the benefits and harms in decision making by clinicians for *BRCA1/2* screening is needed.[25] The consequences of *BRCA1/2* testing and the influence on behaviour and well being of breast cancer patients and unaffected women should not be taken lightly.[26,27] Life-time risk estimates from population-based studies are lower than those from family-based studies,[4] while so far one study, specifically investigating Ashkenazi Jewish *BRCA* mutations, found that the risk of breast cancer in *BRCA* carriers was similar in families with and without a history of breast cancer.[24]

Another argument against communicating *BRCA1/2* results to our study population is that the mutation analysis in our study comprises ~75% of the known *BRCA1/2* mutations in the Netherlands. As such it cannot be considered a diagnostic test in which the whole genes would be screened. Therefore, in case we had asked for the patients' consent and promised to report the test results to those indicating they wanted to receive it, a negative test result would not exclude a *BRCA1* or *BRCA2* mutation. Hence, families with indications for *BRCA1/2* mutations screening, e.g. breast cancer at very young age or a family history of breast cancer, should be referred to clinical genetic centres, irrespective of the test result in our study. In a related study, in which we asked breast cancer patients whether they would consent or not for research including *BRCA1/2* germline mutation analyses with their stored tissue, 97% consented, even though most understood that results would not be communicated to them.[28] Nevertheless the reporting back of such mutation analysis results remains a difficult decision. We know of at least one prospective study that decided differently than we did and invited participants for genetic counselling upon the detection of a *BRCA1/2* mutation.[3]

3.3. *Use of stored tissue: self-determination of the patient*

Although there may be agreement on the usefulness and importance of stored human tissue for research purposes, issues of ownership are still debatable, and are becoming more difficult in the light of the development of genetic research, e.g. the discovery of low-risk single nucleotide polymorphisms.[1,16,29,30] The question of disclosure of mutation analyses results to research participants and the *informed* consent process in research with newly collected material, especially now that whole-genome sequencing is possible, remain under discussion.[17,31–34] We consider that with a careful definition of research questions and protocol approval by an IRB, tissue (and medical data) should be stored for as long as possible to be available for future research, as new techniques may lead to novel research opportunities that may benefit the diagnosis and treatment of future patients. In addition, we would argue that excluding paraffin tissue blocks from the definition of human material, as stated by Jones and colleagues,[30] ignores recent and future technical possibilities. Although the emotional significance relevant for whole organs may not apply, the possibility to isolate DNA from paraffin-embedded tissue has placed this material in a possibly even more complex context, whether this being justifiable or not.[35]

In our specific case we did not consider it feasible to approach all patients (only about 25% of patients were still under medical surveillance in the hospital where the breast cancer surgery was performed). Though we took care of privacy issues, we may not have given patients enough possibilities to claim their self-determination of the residual tissue.[36] A possibility would have been to inform patients through major newspapers to give them the possibility to opt-out from the research project. It would have been difficult, however, to explain all the issues involved in the study as briefly as needed for such an advertisement.

3.4. *Conclusion*

The described coding procedure is an appropriate solution for research involving germline mutation testing in stored, residual materials of patients who may or may not have had the possibility to opt-out. It may be applicable for other researchers, who would lose valuable information by anonymising their data, in most (European) countries depending on whether the national legislation allows the use of coded data and coded human materials.[6] Recently, it has been argued that under certain conditions the coded data may be considered as anonymous data in the sense of the European Data Directive.[11] Though European legislation widely varies, in many countries coding of data may be allowed, for example within the context of the Human Tissue Act for researchers in the United Kingdom.[6,8,11] The described procedure is also applicable to research into other diseases (e.g. diabetes mellitus and heart disease). Hopefully, our coding procedure may guide other researchers who wish to use archived human tissue to address medical research questions.

Conflict of interest statement

None declared.

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