MARSILIUS KOLLEG

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Project EURAT
"Ethical and Legal Aspects of Whole Human Genome Sequencing"

Position Paper

CORNERSTONES FOR AN ETHICALLY AND LEGALLY INFORMED PRACTICE OF WHOLE GENOME SEQUENCING: CODE OF CONDUCT AND PATIENT CONSENT MODELS

Heidelberg, May 2016
2nd, updated edition

UniversitätsKlinikum Heidelberg
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Position Paper

CORNERSTONES FOR AN ETHICALLY AND LEGALLY INFORMED PRACTICE OF WHOLE GENOME SEQUENCING: CODE OF CONDUCT AND PATIENT CONSENT MODELS

ENDORSEMENT TO THE SECOND EDITION OF THE EURAT POSITION PAPER

Progress in the life sciences has made possible many of the achievements in modern medicine. In the quest for better treatments for cancers, whole genome sequencing is one of the particularly promising approaches. The experiences so far have been encouraging. Most assumable, whole genome sequencing will soon be part of the standard repertoire in cancer diagnostics.

As whole genome sequencing is increasingly being used in medical research and health care, the ethical and legal implications associated with this technology also increase significantly. The position paper "Cornerstones for an ethically and legally informed practice of whole genome sequencing" addresses these questions and suggests practical solutions.

The recommendations are the result of inter-disciplinary and inter-institutional cooperation across the scientific community in Heidelberg and within the university's future strategy as part of the Excellence Initiative. The research project "Ethical and Legal Aspects of Whole Human Genome Sequencing" (EURAT) at the Marsilius Kolleg of the Heidelberg University provided a platform and the necessary resources for intensive discussions and sound research. This made it possible for scientists from the University, the Heidelberg University Hospital, the German Cancer Research Center (DKFZ), the European Molecular Biology Laboratory, as well as the Max Planck Institute for Comparative Public Law and International Law

(MPIL) to identify normative challenges associated with whole genome sequencing and to develop possible solutions. Their scientific and clinical expertise in the fields of human genetics, pathology, oncology, bioinformatics, constitutional law, ethics and healthcare economics formed the basis of interdisciplinary exchange and the position paper at hand.

The Heidelberg University as well as the German Cancer Research Center (DKFZ) and the Heidelberg University Hospital have agreed to bind themselves to the code of conduct for researchers presented in the position paper. In doing so they consciously set an example of responsible self-regulation in science.

The position paper was well-received, both in Heidelberg and beyond. To meet demand, and to respond to the extensive feedback received, the project group now presents the second, updated edition. Once again it is emphasised that in Heidelberg, as a center for science and medicine, scientific progress and social responsibility are viewed, and lived, as two sides of the same coin.

Heidelberg, September 2015

Prof. Dr. Bernhard Eitel
Rector of Heidelberg University

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PREFACE TO THE SECOND EDITION

In view of the rapid developments in sequencing technology and bioinformatics, which have reduced the time required to analyse whole genomes of individuals to just a few days, the EURAT Project Group in Heidelberg was established to consider the ethical and legal implications of genome-wide analyses, and to develop practicable recommendations for responsible engagement with the emerging technologies.

The results of the first project phase were published in the position paper entitled "Cornerstones for an ethically and legally informed practice of whole genome sequencing" in June 2013. The "Cornerstones", published in German and English, have been available since then in print and electronic form, free of charge. Since the German print version, in particular, rapidly went out of stock, this second edition of the "Cornerstones" is now being published.

The new edition continues the history of the EURAT project and highlights new trends in the ethical and legal discussions that accompany the application of Next Generation Sequencing (NGS) technologies. This illustrates that EURAT is a dynamic project, characterized by the communicative exchange between the scientists and institutions involved, and their joint effort to shape the developments in the dynamic field of genomic research in terms of good scientific practice.

Currently there are physicians, scientists, bioinformatics specialists, and law and ethics academics from Heidelberg University and its Medical Faculty, the Max Planck Institute for Comparative Law and International Law, the German Cancer Research Center (DKFZ) and the European Molecular Biology Laboratory (EMBL) involved with the EURAT project group. The first phase of the project was financed by the Marsilius Kolleg of Heidelberg University within the framework of the Excellence Initiative; subsequent funding has been provided by the Innovations Fund of the State of Baden-Wuerttemberg.

The publication of the position paper and the presentation at medical and ethics conferences have contributed to the discussion and perception of, and critical engagement with the ethical and legal questions associated with genome sequencing, both in the mainstream media and academic community (see: http://www.uni-heidelberg.de/totalsequenzierung).

We have grasped the opportunity to take up suggestions for improvements and they are reflected in the present second edition. Important changes to the current edition relate in particular to the title of the code of conduct for researchers. Whereas the previous title "Code for non-physician scientists [...]" may have suggested that physicians in the research context were not being addressed, the new title "Code for researchers [...]" should prevent any such misunderstanding. The code also applies to physicians who work outside of the patient care setting as researchers and are therefore not in the position of treating physician for the patient whose genome is being analysed in the research context.

In the patient "Statement of Consent" for "the use of genome-wide analysis for the diagnosis of diseases" we have reframed those passages which did not contain options to choose between different results to be returned into a straightforward statement of consent.

The "Patient Information, Statement of Consent and Patient Statement on Reporting Preferences for 'Genome sequencing in cancer research'" are currently being further developed in a research project at the National Center for Tumor Diseases. Focus groups were carried out with patients in order to take into account their preferences regarding patient education and feedback, and to improve the readability and clarity of the documents. The aim of the project is to establish a procedure in which the patients are well-informed, and supported in their decisions to participate in sequencing studies.

With respect to the original intention of EURAT to organize the practice of genome sequencing in Heidelberg context-sensitively, the code of conduct was adopted by resolution of the senate of Heidelberg University on January 28, 2014 and now applies to all researchers in the field of genome sequencing of the Heidelberg University. Furthermore, the DKFZ gave the code equal status with its existing guidelines on good scientific practice via a letter of the board of directors to all current employees on December 12, 2013, and new employees are now required to sign the code. Through its establishment on this contractual level the code contributes to the employees‘ guidance. Nonetheless, it will only fulfil its full scope if employees are educated about it in further trainings and have the opportunity to engage in the discourse; here the institutions are called upon to provide the respective resources. We learned from the feedback received to date from other universities and research institutes, that the documents from our position paper are being used as reference points for their own policy development.

As a platform for ethically and legally relevant topics EURAT has prompted further policy development in the field of NGS, for example in the areas of data protection.

The questions around data protection in genomic research were already addressed in the first edition of the “Cornerstones” and generic solutions were suggested for the most important ethical questions. Since then a project group at the DKFZ has developed a “Data Security Concept for Personal Data in Cancer Research” for working with personal data specifically for research projects using genomic data and EURAT had an advisory role in this project. With this concept, the DKFZ assumes its responsibility to enable long-term, sustainable research with personal data in the oncology setting, while simultaneously securing the confidentiality of such data and protecting the rights and interests of the data donor. This framework data-protection concept is now adopted within the institution and is discussed in the final chapter on data protection.

A second subject at the core of EURAT’s work right from the start is the responsible handling of additional findings. By the time of publishing the first edition of the “Cornerstones” we expected the number of additional findings to increase with the growing volume of genomic data and research projects. So far this has not been the case, and evidently the reasons relate to methodology, with the filters required to process the data records excluding additional findings. On the other hand, findings with relevance

for the patient's health certainly do occur within the original research question, for example in cancer research, and are reported to the patient in line with the guidelines set out in the "Cornerstones". The Code for Researchers and the Patient Information contribute to a practice in which reporting of such findings is well-prepared and put into effect.

This update of the "Cornerstones" so continues the ethical and legal debate about genome sequencing and ways of self-regulation within the research institutions.

Prof. Dr. Dr. Eva Winkler
(Project spokesperson)

PREFACE TO THE FIRST EDITION

Improvements in technologies for analyzing human genetic information have made it possible to analyze entire genomes of individual people in far less time today than at the conclusion of the Human Genome Project in 2003 (Collins et al. 2003, Levy et al. 2007). We now have access to a highly sophisticated system of computer-based methods with which detailed and comprehensive analyses of genetic information can be completed in a mere few days. The ongoing development and improvement of these analysis methods, often referred to in the context "genome sequencing," "whole genome sequencing," or "next generation sequencing of genomes," (NGS) remains a primary objective for genome research.

In the meantime, the development of sequencing technologies (socalled high-throughput sequencers) has ushered in a new era of technical viability: implementation of sequencing is becoming increasingly feasible both in basic research and in the clinical context. Genetic traits and causes of diseases can now be identified early in order to improve possibilities for prevention and treatment.

The use of "clinical genome sequencing" remains on the rise in Heidelberg's University Hospitals and research institutes, where clinicians and basic researchers continue to explore its potential as a new diagnostic tool. One example for ongoing research in this area are objectives formulated

by the German Cancer Research Center (DKFZ) to enable sequencing of the tumor genomes of all cancer patients treated at the National Center for Tumor Diseases (NCT) within a few years (Wiestler 2012). This goal was the impetus for establishing the Heidelberg Center for Personalized Oncology (DKFZ-HIPO) in 2011 (bio-pro 2013). Information obtained from genetic analyses already helps physicians to tailor chemotherapy treatment more specifically to individual patients. This patient-specific care strategy is part of an ongoing trend in medicine that continues to develop under the umbrella of "personalized medicine", "precision medicine", and/or "stratified medicine" (PHG Foundation 2011, 45ff., German Ethics Council 2012). At the Institute for Human Genetics of Heidelberg University, whole genome sequencing is being used in the diagnosis of rare diseases; and in pediatrics the genomes of minors with brain tumors have likewise been sequenced, in some cases directly influencing treatment decisions (Lichter 2012).

The current state of knowledge does not permit conclusive judgments regarding whether and to what extent genome sequencing will become a routine instrument of clinical diagnostics (Varmus 2010, Evans et al. 2011, Green et al. 2011, 206). The following, however, is certain: physicians who would like to make greater use of this diagnostic tool will have to navigate the attendant ethical, legal, and economic prospects and challenges; and patients who seek treatment in Heidelberg will have to consider these new genome-based diagnostic options and their associated opportunities and risks more extensively as part of the information and consent processes.

The developmental leap in basic research on genome sequencing and its pervasive medical application sparked the initial impulse for putting together an interdisciplinary working-group comprised of medical experts, scientists, bioinformaticians, lawyers, ethicists, and economists in Heidelberg in 2011. The group's contributing members are active scholars and researchers from Heidelberg University, the Max Planck Institute for Comparative Public Law and International Law, the German Cancer Research Center (DKFZ), the European Molecular Biology Laboratory (EMBL), and Hannover University.

The project (EURAT), financed by Heidelberg University's Marsilius Kolleg as part of the Excellence Initiative, has the following objective: to analyze the ethical, legal, and economic dimensions of genome sequencing in clinical application onsite in Heidelberg and to develop practice-based recommendations for dealing with the new technical capabilities and the

larger issues they pose.
The work performed by the project-group produces two different kinds of results. The visible results are the collaboratively developed and jointly formulated documents at hand: a code for non-physician scientists and its explanations, as well as model texts to serve as templates for patient information and consent-statement forms. The second kind of result is less visible. EURAT has initiated communication flows in the participating institutions regarding the normative aspects of genome sequencing. Once established, these flows serve as a basis for bolstering "responsible" and "fiduciary conduct" in local practice.

The analyses and communication flows conducted in connection with Heidelberg's EURAT-Project are guided by the overall principle of "encouraging responsible conduct" and strengthening "fiduciary conduct" (Kirchhof 2002, 29) among the local actors promoting genome sequencing at the interface between basic research and its utilization in patient care. Approached from this position of guiding and reinforcing responsible conduct, the central focus for policy becomes the self-regulatory capacity of medical and research professionals, not the regulatory means of additional state impositions.

The Faculty Council of the University of Heidelberg Faculty of Medicine and the Boards of the University Clinic and Faculty have officially adopted this Position Paper. The German Cancer Research Center (DKFZ) is adopting the Code of Conduct for non-physician scientists.

Prof. Dr. Klaus Tanner
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PREAMBLE

In its collective effort

- to charge the researcher to seek new knowledge in the pursuit of healing patients,
- to oblige the physician to treat patients in accordance with the latest developments in science and technology and to contribute to their advancement,
- to negotiate the necessities of knowing and collecting personal data about patients for treatment and research, of using this knowledge conservatively, and of protecting this information against revelation to unauthorized parties,
- to foster international scientific cooperation, which can only take place within the jurisdiction of differing legal frameworks,
- to learn from, and translate into better approaches, experiences with the insufficiencies of traditional medical law and its measures for diagnosis, education, consent, treatment lege artis, and documentation vis-à-vis the complexities of whole genome sequencing,
- to account for the limited scope of medical law, which applies to clinicians but pertains neither to researchers nor to their colleagues,
- to assume responsibility for developing new legislation effective in clinics and research institutes, and thus to relieve individual clinicians and researchers of such burdens,

the EURAT Group adopts the following documents:

A. *Code for researchers and personnel involved in whole genome sequencing, particularly of patient genomes, and its explanations*

B. *Patient Information and Statement of Consent for "Health services research on the use of genome-wide analysis for the diagnosis of diseases"*

C. *Patient Information, Statement of Consent, and Patient Statement on Reporting Preferences for "Genome sequencing in cancer research"*

A. Code for researchers and personnel involved in whole genome sequencing[1], particularly of patient genomes, and its explanations

Code

Part one: Basic ethical principles

1. Respect for persons and patient autonomy

Every patient is to be regarded and respected as a person. Researchers acknowledge the patient as a person

- when they abide by the preferences of the patient, as expressed in the patient's statement of consent, regarding the management of personal data and samples,
- when they ensure the security of personally identifiable data and samples, and
- when they are careful in handling research results that are medically relevant to the patient.

People who are not in a position to make decisions freely and independently (people incapable of giving consent) are covered by provisions of special protection.

2. Beneficence and Non-maleficence

Genome-wide analyses are only to be conducted after carefully weighing possible risks against benefits. All potential harm to research participants is to be minimized.

Research results that are of medical relevance and linked to an identifiable person should be handled carefully and in the best interest of that patient's well-being. Researchers must safeguard the personal samples and data made available to them against misuse.

3. Non-discrimination and justice

Protection against discrimination requires equal treatment and respect for all people whose genome/genomic data are used in research. The interests and needs of every person must be respected without bias; every person must be protected from harm and treated with care impartially.

4. Privacy protection and confidential stewardship of personal data

Protection of patient privacy must be ensured. Confidential stewardship and non-disclosure of data vis-à-vis unauthorized third-parties are indispensable to that end.

[1] The fields addressed include: total or partial sequencing of the genome, transcriptome, and methylome.

Extensive data of various kinds must often be stored, aggregated, made accessible, or exchanged in order to achieve research goals. All researchers must strictly adhere, in accordance with applicable law, to the regulations on data protection specified within a given research project or institute. All participating researchers have the obligation to report violations of any existing rules and regulations and to work toward the continued improvement (adaptation to evolving conditions) of data protection.

5. No rise to financial gains

The human genome in its natural state shall not give rise to financial gains.

6. Good scientific practice

Good scientific practice includes scientific honesty (professionalism, forth-rightness, transparency) in the stewardship of samples, data, and research results. It is subverted by scientific dishonesty (deception, fraud, illegitimate use of knowledge from other sources).

Research conducted with patient genomes requires special data protection, since it might also include medically pertinent information that may be directly conducive to a patient's health.

7. Public benefit

Genomic research serves the greater well-being of all humankind. Its benefit to society consists in achieving greater insight into the foundations of biology as well as in integrating its findings into clinical care. For the sake of realizing societal benefit, it is necessary to ensure the broadest participation, which includes the general public, in sharing the benefits of scientific advancement.

8. Protection of future generations

Research conducted on the human genome proceeds under obligation to protect future generations, since the genome represents the biological unity and diversity of all the members of the human race.

Concluding remark

The following guidelines are intended to establish good research practices on the basis of these ethical principles and to assist in protecting patients and researchers.

Part two: Guidelines

I. Scope of the guidelines

These guidelines apply to researchers and personnel involved in the analysis and evaluation of patient genomes.

II. Addressees

This code applies to every individual researcher active within the fields addressed, as well as to the steering committees of the institutions involved.

1. The individual researcher

The individual researchers bears personal responsibility for their acts specific to that individual's occupation, based on the research conducted with and on patient genomes and on their knowledge of human genetics.

2. Steering committees of involved institutions

Steering committees bear organizational responsibility.

III. Legal liability

Each individual researcher is solely responsible for complying with existing legal regulations. It is incumbent upon the individual researcher to ascertain which legal regulations are applicable to their activities and to uphold them within their sphere of competence.

Primary investigators and directors of projects, departments, and institutions also bear responsibility – particularly within the legal framework of vicarious liability – for the conditions and practices within the entire organization over which they preside.

This code aims to reinforce researcher rights and responsibilities with greater capacity for facilitating selfregulation and with more

precise formulation in the context of whole genome sequencing of patient genomes in order to protect the patient as well as the researcher.

IV. Individual guidelines

1. Risks

Potential risks are to be assessed before proceeding with research plans. Risks – in particular the potential misuse of research results and of data and samples linked to an identifiable person – are to be minimized. Unavoidable yet prudent risks should be documented and communicated to the patient prior to consent.

2. Patient consent and Ethical Review Board approval

Researchers must make certain that a patient's statement of consent and a vote of approval from the appropriate ethical review board are on file for the sequencing and analysis of each and every genome.

3. Samples

Samples may be preserved beyond the duration of the immediate study or project in pseudonymized manner, provided that the patient has consented to their future use. Otherwise they are to be destroyed upon the project's conclusion.

4. Data

a) Data collection and use

Data may only be used for the purposes identified and permitted within the patient's statement of consent. Their use is subject to the following provisions for data protection.

b) Data security

No research is to be conducted with uncoded datasets linked to identifiable patients. Sequence data are to be stored only in encoded form. Pseudonymization currently offers the best protection against unauthorized reidentification in the case that medically relevant results need to be communicated to a patient's physician (see no. 7).

If additional patient data are transferred to the researcher, they must like-wise be pseudonymized.

The key-holder is prohibited from sharing the code necessary for reidentifying a patient with unauthorized third-parties.

Access to data and their use are regulated by the applicable Data Protection Acts.

Researchers are bound by non-disclosure. Dissemination of data to unauthorized third-parties (insurance companies, employers) is forbidden. Inquiries made by the patient's relatives are to be directed to the patient's physician.

Normally, the question whether the researcher has the right to refuse testimony (evidentiary privilege) vis-à-vis law enforcement does not arise; as researchers work exclusively with pseudonymized data they therefore cannot provide any information regarding identities. If the issue does arise, it must be determined whether the treating physician's evidentiary privilege also extends to the researcher as an exceptional case. In all other instances, precedence goes to the regulations of the German Genetic Diagnostics Act (Art.11 GenDG) concerning the supplementation and concretization of medical confidentiality in reporting the results of genetic examinations and analyses.

c) Data sharing and access to databases

Patient-related datasets must be encrypted before they are permitted to be transmitted to (local, national, or international) databases. If pseudonymized datasets that permit patient reidentification are entered into research databases, their access must be regulated in a manner that is transparent, uniform, and in compliance with the relevant data-protection standards. Public databases with unrestricted access are not permitted to contain data that are linked to individual patients and that make reidentification by genome sequencing possible with the latest technology.

d) Documentation of results and publication

For the sake of good scientific practice, primary data and research results (including interim results) are to be stored securely in the institutions in which they originated.

In order to permit everyone to participate in the benefits of research out-comes, research results should be made accessible to a wide public audience in appropriate fashion.

5. Research findings

Results from genome-wide analyses can lead to patient-specific medical in-sights and the awareness that, in the absence of this knowledge, the patient would be subject to additional harm or increased suffering. In this case it can be imperative that the researcher intervene: if this knowledge pertains to a specific person, it should be communicated to the appropriate authority or to the physician treating that patient, provided that the patient's statement of consent does not state otherwise.

The patient's physician is always the appropriate channel for reporting findings that might be relevant to the patient's health. The physician alone must decide whether routine laboratory diagnostics will be performed as follow-up in order to validate the findings and, depending on the results, communicate them to the patient.

6. The patient's right to withdraw consent

A patient's data and samples are to be destroyed immediately upon with-drawal of consent. In order to be able to comply commensurately with a patient's revocation of consent, it must be documented where the data and tissue samples linked to the withdrawing patient have been transmitted. In cases of anonymous data and tissue samples, or those that have already been processed or transmitted in encrypted form, the physician responsible and the researcher will negotiate with cooperation partners toward securing protection of the data and tissue samples comparable to that provided in Heidelberg.

7. Binding force

The principles and guidelines laid out here are binding for all researchers who are involved in whole genome sequencing, especially of patient genomes. The individual researcher, within the established sphere of the freedom of research, is solely responsible for following the regulations of the law and of this code. Primary investigators and directors of projects, departments, and institutes also bear the responsibility – in particular within the legal framework of vicarious liability – of upholding this code in the organization over which they preside.

Researchers should in the first instance alert the primary investigator or researcher(s) responsible for the given project – and, if the case requires, also the director of the relevant department and, in special cases, the institute's directors – of statutory violations and of ethical concerns, without consequence of incurring any disadvantage for doing so.

8. Implementation

a) Implementing the code and monitoring compliance

The directors of a given research institute must integrate this code into the institution's regulatory framework. They must ensure, through routine courses of instruction and training, that researchers align their scientific practice with the principles and guidelines of this code. Furthermore, they must work toward ensuring that the use of shared data and tissue samples complies with measures and guidelines that correspond to those that are formulated in this code.

b) Updating the code

The steering committees are responsible for ensuring that the code is routinely reviewed in order to improve the code and to keep it continuously up-to-date with new advances in basic research and bioinformatics, as well as ethical and legal developments.

This code was,

- in recalling, emphatically, the Universal Declaration of Human Rights from 10 December 1948 and to the two International Covenants of the United Nations from 19 December 1966 on Civil and Political Rights and on Economic, Social and Cultural Rights;

- in view of the Council of Europe's Convention for the Protection of Human Rights and Fundamental Freedoms from 4 November 1950 and the European Union's Charter of Fundamental Freedoms proclaimed on 7 December 2000;

- in consideration of international and regional agreements in the field of bioethics, including the Council of Europe's Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine (Convention on Human Rights and Biomedicine), and its additional protocols, which opened for signature in 1997 and entered into force in 1999, the Universal Declaration on the Human Genome and Human Rights adopted by the UNESCO General Conference on 11 November 1997 as well as the International Declaration on Human Genetic Data adopted on 16 October 2003 and the Universal Declaration on Bioethics and Human Rights adopted on 19 October 2005, the UNESCO Recommendation on the Status of Scientific Researchers from 20 November 1974 and the Declaration of the UN General Assembly on the Use of Scientific and Technological Progress in the Interests of Peace and for the Benefit of Mankind from 10 November 1975, as well as the Helsinki Declaration of the World Medical Association, adopted in 1964 and last amended in 2008, on Ethical Principles for Medical Research Involving Human Subjects and the International Ethical Guidelines for

Biomedical Research Involving Human Subjects, adopted in 1982 and amended in 1993 and 2002, by the Council for International Organizations of Medical Sciences;

- in consideration also of international and national codes of conduct and guidelines, such as the guidelines of the International Cancer Genome Consortium, the Deutsche Forschungsgemeinschaft (German Research Foundation's) 1998 Proposals for Safeguarding Good Scientific Practice, and the 2010 Guidelines and Rules of the Max Planck Society on a Responsible Approach to Freedom of Research and Research Risks

adopted by the EURAT Project Group.

Explanations of the code

1. Why a code for researchers?

In recent years progressively more complicated research methods and results have prompted emphatic admonition that the practice of scientific inquiry should be guided by basic ethical principles. The sciences are answering this call by autonomously developing their own codes that concretize good scientific practice. But additional steps must be taken to cover the remaining and multiplying issues. For instance, there is science's obligation to inform society about the methods of its research, its aims, and its results, as well as the associated risks. For all research on human subjects there is an additional obligation vis-à-vis the patients or persons who are the object of a study. This obligation also pertains to the persons with whom researchers do not come into immediate contact, hence the need for a code for researchers. One means by which to effect an equivalent to the obligation physicians have towards their patients could be a form of self-commitment for these researchers comparable to the Hippocratic Oath.

2. Scope of application and addressees

The guidelines apply for all researchers and personnel who are involved in the study and analysis of patient genomes. Whereas the conduct of researchers who are entrusted to evaluate patient genomes in clinical diagnostics is more closely bound to the canon of rights and responsibilities for physicians in the clinic, there is no such code for the conduct of researchers and personnel involved in life-sciences research or in "preliminary diagnostic" analysis. This code serves to specify their rights and responsibilities.

A researcher who conducts whole genome sequencing of human genomes in research projects often has extensive knowledge about human genetics and thus occupies a position of expertise in this area superior to that of the greater majority of medical practitioners. When conducting genome-wide analyses, researchers can gain clinically relevant knowledge about a patient, since they

generally have a clear overview of, or sufficient information to recognize, the clinical significance of their findings. In such cases, the researcher is in position to pass this relevant knowledge on to the patient's physician so that the latter can initiate or suggest genetic counseling.

Researchers who are currently utilizing and contributing to the adoption of whole genome sequencing as a clinical diagnostic tool are in a position on par with physicians regarding clinical knowledge and information. They have enough information at their disposal for "preliminary diagnostics," but any preliminary finding must be confirmed by certified (laboratory) diagnostic tests. Scientists trained in human genetics or oncology, on the other hand, can assess the risks and implications of findings from a perspective that is often inaccessible to the physicians (clinicians) treating the patients.

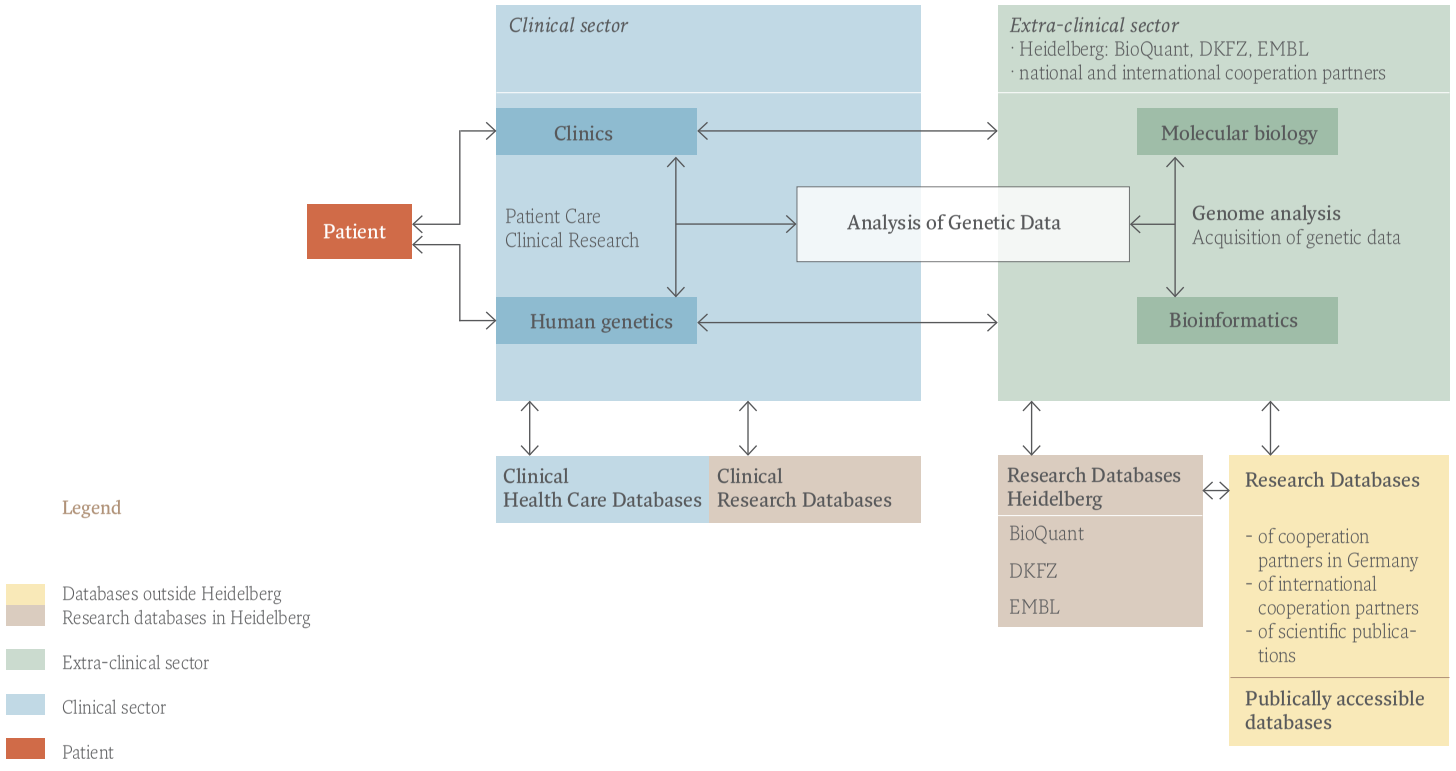
The whole genome is sequenced through highly specialized processes based on the division of labor; the sequencing of one whole genome usually involves a number of different clinics and research institutes.

3. Problem description

Let us consider an example typical of today's cooperative overlap in treatment and research practices, i.e. the utilization of genome sequencing in a clinical study. The patient, Peter, is a little boy receiving treatment at Heidelberg University Hospital, where clinicians discover that he has a brain tumor. The genetic causes of this tumor are as yet uncertain. There happens to be a concurrent clinical study underway – approved by the ethical review committee – with the goal of gaining better insight into the nature of such brain tumors. The physician treating Peter is aware of the study and informs the child's parents about it. After being fully informed about the potential risks and benefits, the parents consent to have Peter's genome sequenced. After the statement of consent has been completed and processed, tissue samples are collected from Peter's tumor and blood samples are taken from the child and both parents. Patient medical records for Peter and

his parents are also prepared in order to provide the researchers with relevant medical data in conjunction with the samples. Because the German Cancer Research Center (DKFZ) houses the necessary infrastructure, it will be the site where the actual whole genome sequencing is conducted. Additionally, the samples are pseudonymized and then placed in the tissuebank for storage under the stewardship of the Institute of Pathology at Heidelberg University Hospital. The statement of consent also included permission to use Peter's material for additional studies on brain tumors in minors. The sequenced genome from Peter's blood and tumor cells is analyzed by molecular biologists and bioinformaticians at the DKFZ in cooperation with experts from the European Molecular Biology Laboratory (EMBL). Since this particular study on brain tumors is not limited to Heidelberg institutions, but part of an international research project, the data (or at least excerpts of the data) collected from sequencing Peter's genome are entered into international databases with additional, non-genetic patient data. All of the data, which might be entered either conjointly or separately, is entered exclusively in pseudonymized form. In order to permit relevant results to be reported back to Peter's parents, a line of communication is secured and maintained with the treating physician.

This complexity of operational procedures must not lead to failures in clearly defining the role-specific obligations and competences for each of the individual actors involved in the stewardship of patient samples and data. Even at first glance it is clear that the process of whole genome sequencing requires a high proportion of researchers and other personnel in order to proceed from the initial tissue samples to sequenced DNA to the evaluation of those sequences. That is why it is an immediate and primary concern to determine which regulations, responsibilities, and obligations pertain to the researchers and personnel involved in genome sequencing. Clear identification of the specific competences and guidelines throughout the complex work flows of whole genome sequencing equally serves to protect and benefit both the researcher and the patient.



Schematic representation of the actors involved in sequencing a genome

4. Research findings and informed consent

When Peter's sequence data is analyzed in the EMBL and at the DKFZ, a finding that poses high clinical relevance comes to light in the context of oncological investigation. The molecular biologists and bioinformaticians involved in Peter's case recognize that this particular finding signals a precarious position for the patient. They are aware, due to the clinical information they received about Peter in conjunction with his samples, that his current treatment will remain ineffective. The gene mutation they discovered is known to inhibit the efficacy of the drugs administered to Peter – in fact they could even cause the boy additional harm. The researchers decide to report this finding to the treating physician. The physician in turn must decide whether to have this finding verified by an accredited laboratory and initiate the necessary steps toward changing the patient's treatment.

Researchers, as this case shows, can find themselves in situations in which they have access to exclusive, clinically relevant knowledge that has resulted from their research and that perhaps only they can interpret. In genome-wide analyses the potential research findings include not only the findings that pertain directly to the sequencing request (primary findings) but also additional findings[2] beyond the context for which the sequencing was ordered. Peter's case above concerns a finding directly related to the specified sequencing task that probably would not have been discovered in a focused genetic analysis of the tissue. However the analysis of sequence data frequently results in additional, unintended findings that fall beyond the scope of the actual investigation and that likely present new knowledge that could be clinically relevant for the affected patient. In some cases researchers intentionally look for additional findings that are not immediately related to the sequencing request. Researchers can expect to encounter clinically relevant research results – whether they be intended primary findings, unexpected secondary findings or additional findings – in every instance of genome sequencing.

[2] We refer to findings that were not intended, but are generally to be expected, as "additional findings" and not "incidental findings".

The researcher is obligated by a duty of care to notify the responsible physician of all findings, including additional findings, that have been recognized as medically relevant for the patient, as long as the patient's statement of consent does not rule out such reporting. The researcher is not obligated to engage in the active or deliberate search for findings beyond the specified context of a sequencing request.

The patient's wishes concerning reporting of non-primary findings should be covered in the statement of consent and with the help of adequate information provided by the responsible physician, such as and including the patient's right not to know.

5. Data protection and risk assessment

The utmost care must be taken in handling personal data in order to offer a justifiable defense of the extensive intrusion into a person's private information that necessarily accompanies the sequencing and analysis of patient genomes. Forms of personal data include clinical data, patient data, and humangenetic data that directly express or permit the discovery of particulars about the personal or material circumstances of identified or identifiable patients or participants.

There is little sense in getting lost in a catalogue of alarming scenarios. Nonetheless one should always be mindful of the risks associated with the storage, transmission, and use of genetic data. Genomic data and the danger of reidentification are inseparable, given that every genome is unique and therefore only and ultimately linked to one specific person. The risk of reidentification increases when additional personal data (e.g. age, gender, country of origin, etc.) are included together with the genomic data and, especially, when these data are entered jointly into semipublic (research-) databases. This situation presents an instance of the so-called "dual-use" problem, in this case the misuse of personal data by others.

In general, research plans should be subjected to a formal risk assessment. Research is ethically most justifiable when the scales weighing the benefits and risks associated with its outcomes are tipped in favor of the project. The ethics committees of hospitals and research communities take on a central role in risk assessment, since their independent status enables these committees to improve the initial impact assessments conducted by the researchers. In basic research, which includes genomic research, assessing benefits and risks proves particularly difficult because results often permit no or at least no clear anticipation. This difficulty however does not relieve the researchers involved of their obligation to determine and to avoid high-probability risks to the greatest extent permitted by the state of available scientific knowledge.

The protection of data is a central field of activity within genomics. Data protection faces difficult challenges here, considering that (at the very least) the principle of data reduction and economy (Art.3a BDSG) is rendered ineffective or jettisoned wherever genome-wide datasets must be examined, e.g. in order to improve understanding of diseases that are associated with multiple genes. Shortcomings in current frameworks thus demonstrate the growing need to elaborate a robust and institutionalized data-protection policy that promotes research in the interest of public health and prevents misuse.

6. Evidentiary privilege (right to refuse testimony) for researchers?

The purpose of evidentiary privilege is to protect the relationship of trust between the practitioners of certain professions and those who enlist their assistance and expertise. Thus in accordance with Art. 53, Sec.1 Nr. 3 StPO (German Code of Criminal Procedure), physicians, dentists, and pharmacists have the right to refuse, whether in court or vis-à-vis other public authorities, to give any information pertaining to knowledge that was entrusted or became known to them in the context of medical exami-

nation or treatment. Since the specific professions within which evidentiary privilege applies to entitled practitioners are listed in the statute, the prevailing opinion is to reject as inadmissible any analogous extension of evidentiary privilege to other occupation groups. However, this evidentiary privilege is indeed expanded in Art. 53 a StPO to include, by extending the privilege of their employers, the professional assistants of persons entitled to refuse testimony on professional grounds.

Since researchers do not fall within the purview of Art. 53 StPO and its specifications, it will have to be determined on a case-by-case basis whether they can be legally regarded as belonging to the support staff of the responsible physician and thereby entitled to refuse testimony in accordance with Art. 53 a StPO. The classification of personnel as support staff does not depend on a (hierarchical) labor relationship that pertains between agents, but exclusively on one's actual involvement in relevant professional activities. Although the researcher conducts sequencing of patient genomes in the context of a task ordered by the responsible physician, the researcher's activities are in no way subordinated to that particular workflow. To be sure, the question of subordination certainly does not apply when the researcher identifies and reports additional findings that are beyond the ordered task. Furthermore, the determining factor for qualifying as a professional assistant entitled to evidentiary privilege is whether one's occupational activities include participation in the relationship of trust between the physician, who has the primary legal obligation of confidentiality, and the patient, who enlists the physician's services. This is categorically not the case for researchers conducting genome sequencing without ever having face-to-face contact with the patient.

Thus, as the law currently stands, Art. 53 and 53 a StPO do not guarantee complete protection for researchers against the coercive

efforts to force testimony delineated in Art. 70 StPO. In order to secure protection for researchers, it would be worth considering new legislation to expand the circle of actors who are entitled to evidentiary privilege in the StPO. Such an amendment would be perfectly consistent with the history of that section, which has been characterized by continual changes and amendments and thus does not suggest a concluding developmental arc.

7. Patenting

The aim of genetic research is to gain generalizable knowledge concerning the confirmation or rejection of suspected genomic causal-links among the more immediate causes, in the onset, and throughout the course of diseases. This large-scale endeavor can act as a catalyst for the formulation and establishment of significant, previously undeveloped ideas and inventions. It is necessary to be able to provide industrial protection for these advancements within the scope of this code for researchers.

However, the human genome in its natural state shall not give rise to financial gains. In accordance with Article 4 of the UNESCO Universal Declaration on the Human Genome and Human Rights, any such attempt to the contrary must always be prohibited. The knowledge that is unlocked by the codes of the human genome should not only be disseminated as widely as possible in order to prevent its monopolization but also free to be used for additional research.

8. Conclusion

A culture of trust is necessary in order to ensure that people are willing to donate their genomic data and that the public sector is willing to provide continued support. Active support and acceptance can only be achieved if people are convinced that adequate measures are in place to protect the personal genomic data collected and utilized in research and medicine. The benefit of whole genome sequencing to society can only be increased by maximally diminishing the potential risks to individual privacy: there is a direct correlation between privacy and progress in medical science.

B. Patient Information and Statement of Consent for "Health services research[3] on the use of genome-wide analysis for the diagnosis of diseases"

Patient information

Dear Patient,

You have a rare disease, the cause of which is not yet fully understood. There is evidence that this disease is caused by a variation or mutation in genetic material and therefore has a genetic basis.

You or your physician initiated contact with the Institute for Human Genetics with a desire to determine the cause of your disease. Thus far conventional tests, including those which have examined genetic material, have not identified a definitive cause. In the following pages we would like to provide information about an additional possibility for investigation, which takes place within the context of a research study.

Please read through these pages carefully. We encourage you to discuss any questions that you have with the physician responsible for your care. You may have questions about our goal in conducting this research, about the study's procedure, about the potential risks and benefits of your participation, or about your rights as a patient. Once we have answered your questions, you will need to decide whether you would like to participate in the study.

If you decide to take part in the study, we will need your written consent on the attached form (Statement of Consent).

[3] Health services research is defined as "observation, analysis, prognosis, assessment, advancement, and evaluation of routine care." "Routine" cannot yet be used to refer to genome-wide analysis; the goal of the research is to prepare genome-wide analysis for implementation within clinical diagnostics. (Deutsche Forschungsgemeinschaft (German Research Foundation), Versorgungsforschung in Deutschland: Stand – Perspektiven – Förderung, 2010, S. 23)

Participation in this study is voluntary. If you decide not to take part in this study, your medical treatment will not be affected negatively in any way. You will continue to receive the best possible medical care.

1. What is the purpose of this study?
Goal of the Study

In the course of this study, we will offer to give you a blood test. Our analysis of this blood test aims to identify the cause of the medical condition that you have specified. In addition, this analysis may be able to assess to what extent other members of your family may be at risk of developing this disease.

Method of the Study

Previous studies of genes aimed either to study individual segments of genetic material (individual genes) or to analyze complete genetic material (the genome) for relatively crude changes (e.g. chromosomal abnormalities). The new study that is being introduced here is fundamentally different in that it employs genome-wide analyses. In this method, all known segments of genetic material that contain information are analyzed. The new genome-wide analyses currently represent the most comprehensive method possible for the workup of diseases that have a genetic basis. The probability that you will understand the genetic cause of your illness is much greater with genome-wide analysis than it would be with conventional analyses of individual genes. The technology continues to develop and improve. In the future, new methods of analysis may arise.

In genome-wide analysis, we look specifically for a possible genetic cause of your illness. It may be that, in doing so, we come across findings that have nothing to do with understanding the cause of your illness (so-called additional findings). Item 6 provides more detailed information about the way that these additional findings are handled.

2. Who is performing the study?

The diagnostic study will be conducted by:

.....
Principal Investigator
{Name, Institution with address, Department}

You may contact the physician with whom you have discussed this information and the consent form, and who will care for you throughout this study, with any question:

.....
{Name, Clinic, Telephone number, Email address, Ward, Stamp, Signature}

This diagnostic study was approved by the Heidelberg Institutional Review Board ..... {Nr.}

3. What does your participation in the study entail?

If you have not yet provided a DNA sample for use, we will request a blood sample of about 10ml for the genetic analysis.

We are looking for a genetic change that has not yet been identified. In order for us to interpret the results, it is often important to have blood samples from your parents or other members of your family. If this is the case, we will need to obtain consent from them individually.

After the study has been completed, your physician

.....
{Name given in item 2}
will explain the findings to you verbally and in writing, and will discuss the next steps with you.

4. What will happen to the removed specimens?

In this study, the samples of your blood and DNA will be used only for the genome-wide analysis that we have described here.

Before and after the genetic analysis, your blood and DNA samples will be stored – separately from your patient information and encrypted with the best available technology – in the Molecular Genetics Laboratory at the Institute for Human Genetics for the specified duration or until you withdraw consent. Only authorized members of the research team will have access to your tissue samples.

In order to safeguard your tissue samples against personal identification, the Institute of Human Genetics will assign a "pseudonym" in place of your name. The pseudonym is a random combination of letters and numbers and is associated with a computer program to a person. Identifying which tissue sample belongs to which patient is only possible by means of a digital key that links the patient name to the corresponding pseudonym. This key will not be made available to any third parties.

Those responsible for these programs, and therefore for decoding your tissue samples, are the physician named in item 2

.....
{Name}

as well as <his/her> three assistants

....
{3 names, institution}

The DNA samples collected in the course of this study will be retained for up to 30 years or until you withdraw consent.

5. What will happen to the findings?

The new research methods have produced a large volume of data. Methods to interpret the collected data must be developed.

Our analyses may yield findings of different kinds:
a) Findings that are relevant to your disease, and
b) Findings that are relevant to other diseases.

a) Findings related to your disease

We will share with you any findings that we are certain are relevant to your disease. We will also inform you of any findings that, based on current knowledge, are involved in causing disease.

b) Findings related to other diseases (additional findings)

It is possible that we will discover findings that are not relevant to your disease, but that are related to other hereditary characteristics. This includes any findings that are implicated, to a greater or lesser degree, in increasing the likelihood that a person will develop other diseases. In the case of some of these predispositions, preventive measures and possibilities for treatment have already been developed, but this is not always the case. An additional finding may also reveal that some diseases are hereditary, which means that, although these findings may not apply to you, they could be significant for your offspring. We will not search actively for additional findings and are not under obligation to collect any.

However if you would like for us to do so, we will share with you any additional findings related to diseases that are likely to occur and for which there are preventive measures and treatment options. Additional findings that may affect health significantly include hereditary breast cancer, hereditary colon cancer, and certain myocardial or metabolic diseases. The examples that will be given during your patient-education session within the consent process will make this clear.

The following will not be further investigated or reported:

- additional findings relating to diseases that medical science is currently unable to treat or for which no preventive measures exist,
- genetic changes that, according to current medical science, have only a slight probability of causing disease,
- genetic changes that, according to current medical science, do not affect you and can only cause hereditary diseases if both partners carry the gene (gene carriage).

Passage regarding information and consent for ***minors and youth***:

- additional findings regarding conditions that, according to current medical science, occur only in adulthood and cannot be treated with preventive measures, will not be investigated. Susceptibility to tumors, as in hereditary breast cancer, falls within this category.

c) Dissemination of findings

The new sequencing techniques have not yet been integrated into routine diagnostics for identifying the causes of diseases. As a result the primary findings and additional findings obtained through the method of genome-wide analysis must be confirmed (validation). In order for these findings to be confirmed, your samples must be transferred to another laboratory in uncoded form, which means they will be labeled with your name and date of birth. The consent form will ask specifically for your written permission to carry out this transfer.

Primary and additional findings that have been validated and are clinically significant will be shared with you during a personal conversation with your physician

..... {Name, see item 2}

and will be given to you in writing. On the consent form, you can indicate whether you would like for us to share the findings with your personal physician as well.

6. What will happen to the collected data?

Genetic data contain a large amount of information about a person. For this reason, it is especially important to protect this information and prevent any misuse. To this end, we have developed a data protection policy. You will find it at

.....
{Homepage}

Everyone involved in this project is under obligation to adhere to and to enforce this policy.

We will collect your personal patient data (name, address, date of birth) and clinical data (diagnosis, disease history). Your genetic data will be the object of this study. In the course of the genome-wide analyses, these data will be collected and saved. In order to protect your privacy, your patient data and your genetic data will be coded and stored in separate databases, and access to each of these databases will be limited.The findings that are shared with you will also be recorded in your medical file. The data collected in the course of this study will be stored for up to 10 years or until you withdraw consent.

We have no plans to perform additional analyses of this data in the future.

Only authorized members of the research team will be able to access the coded data. This ensures that personally identifying information about you cannot be used for any purpose that is not expressly intended. Data will not be shared with unauthorized third parties, for example employers or insurers.

Your data, as well as the results of the analysis, will be used exclusively for the purpose of this study. However, when you fill out the consent form, you can decide whether you will permit your genetic data to be used in other research projects.

Beyond this study, your genetic data may be used in scientific publications, but will appear only in coded form. There is no way that you could be identified personally from the published data.

7. What are the risks to you?

Collecting the blood sample for this study is associated with the same minor risks that are present whenever blood is drawn from a vein. At the site where the needle was inserted, you may experience temporary pain, minor bruising, or, very rarely, an infection or damage to the cutaneous nerve. After the blood sample has been taken, there will be no further health risks to you as a result of your participation.

It is possible that being notified of additional findings will affect your life and the lives of your family and relatives. The consent form permits you to specify how you would like to be notified of additional findings.

8. What benefits will come from this study?

We cannot guarantee that we will be able to identify the cause of your disease. It is possible that we will be able to identify its cause. However, we cannot guarantee that we will.

9. Do I have the right to withdraw from this study?

Your participation in this research study is voluntary. ***You may withdraw your consent at any time without having to provide a reason, and your withdrawal will have no negative impact on your subsequent diagnoses or treatment.*** Upon withdrawal from the study, the samples that have been collected from you will immediately be destroyed and your personal data will be erased. However, if your samples have already been analyzed and your data were already processed or transferred to a third party in

coded form, we will no longer be able to erase all data and destroy all samples because doing so could jeopardize the validity of the research findings. However, the relevant pseudonym key will be destroyed.

Documentation of Patient Questions

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Statement of Consent

I have been informed of the methods, benefits, and risks of the study. I understand that I have the right to withdraw from the study and that the study will require me to have blood drawn.

I agree,

- that my tissue sample will be analyzed and that the data collected during this study will be recorded, evaluated, and stored in coded form for scientific purposes.

- that the compiled results may be used and published in coded form for scientific purposes.

- that my genetic findings and additional findings will be transferred to another laboratory for verification.

- that the additional findings that have been excluded, as stated in item 5), will not be shared with me.

I consent,

- that the verified findings that are considered medically significant will be shared with me:

  ☐ yes
  ☐ no

- that the findings and additional findings will be relayed to my personal physician:

  ☐ yes
  ☐ no

- that my genetic data may be used in other research projects carried out on-site (Heidelberg University Hospital and German Cancer Research Center):

  ☐ yes
  ☐ no

Please indicate your preferences by marking the appropriate response with an x.

I/we waive the right to claim any profits that arise from commercial use of my personal biological or genetic material. My privacy rights, particularly with regard to anonymity and data storage, will be preserved.

....
Place and Date Patient Signature

....
Place and Date Clinician Signature

C. Patient Information, Statement of Consent, and Patient Statement on Reporting Preferences for "Genome sequencing in cancer research"

Patient information

Dear Patient,

You have been diagnosed with a tumor disease. As part of your care, your tumor tissue will be removed and thoroughly analyzed so that you can be treated. After all of the necessary diagnostic analyses have been completed, the tumor tissue that is no longer needed (the residual tissue) will be disposed of. We would like for you to permit us to retain the residual tissue and your data for research and will request your consent for us to do so.

The residual tissue can contribute to scientific research. Scientific research is now working on new molecular and cell-biology methods. Among these new methods are the genome-wide analyses of your genetic material. These methods will be applied to cancer research at the National Center for Tumor Diseases (NCT) Heidelberg. The new studies aim to advance our understanding of tumors so that we can improve diagnostic and therapeutic procedures.

In the following pages we provide you with information about the method and procedure of these analyses. Please read through these pages carefully. We encourage you to discuss any questions about this information or about the Statement of Consent with the responsible physician,

.....
{Name, institution}

You may have questions about our goal in conducting this research, about the study procedure, about potential risks and benefits of your participation, about your rights as a

patient, or about anything else that is unclear to you. Once we have answered your questions, you will need to decide whether you would like to donate your residual tissue to cancer research.

If you decide to contribute to cancer research, we will need your written consent on the attached form (Statement of Consent).

Participation in this study is voluntary. If you decide not to take part in this study, your medical treatment will not be affected negatively in any way. You will continue to receive the best possible medical care at NCT Heidelberg.

1. What is the new research about?
Goal of the Study

We intend to use molecular and cell-biological analyses, in addition to genome-wide analyses of your tumor cells and your healthy cells, in order to investigate genetic changes and the processes that these genes control. By conducting this investigation we want to improve our understanding of the genetic changes in tumor tissue that are responsible for the development and progression of cancer. This information will be used to develop new treatment strategies for future patients and, in the future, enable us to provide cancer treatment that is more personalized. This can be achieved if we can use genetic information to become more and more familiar with a patient's disease, or if we develop therapies that can be adapted to the specific genetic changes in an individual patient's tumor.

Method of the Study

Previous studies of genes aimed either to study individual segments of genetic material (individual genes) or to analyze complete genetic material (the genome) for relatively crude changes (e.g. chromosomal abnormalities). The new method that is being introduced here is fundamentally different in that it employs genome-wide analyses. In this method, all known segments of

genetic material that contain information are analyzed, because the genetic changes that interest us may be located anywhere within the entire genome. The probability of identifying possible causes of cancer is much greater with genome-wide analysis than it would be with conventional analyses of individual genes.

It is possible that these comprehensive analyses will produce findings that do not have to do with your type of cancer (so-called additional findings). Item 6 provides more detailed information about the way that additional findings are handled.

2. Who is performing the analysis in this research project?

The following researchers are involved in leading this study:

· NCT POP Medical Principal Investigator

.....
{Institution with address}

· DKFZ HIPO Principal Investigator

.....
{Institution with address}

· Responsible Party: Bioinformatics

.....
{Institution with address}

This research project was approved by the Heidelberg Institutional Review Board ..... {Nr.}

3. Who is your contact person?

You may contact the oncologist managing your treatment, who will care for you throughout this study, with any questions:

.....
{Name, Clinic, Telephone number, Email address, Ward, Stamp, Signature}

4. What does your participation in the research project involve?

In the course of your treatment, your tumor tissue will be removed (through sampling or through an operation). After this tissue has been removed, it will be analyzed. The pathologist often needs only a part of the resected tissue. The tissue that we do not need for the diagnosis will be used for further genetic testing.

This analysis will not require you to undergo any additional operation, invasive procedure, or puncture. During a routine blood test, an additional 10ml of blood (healthy tissue) will be drawn.

5. What will happen to the tissue that is removed?

We will typically store your tissue samples (tumor tissue and healthy tissue) at the NCT. They will be coded there. Your tissue sample will be stored separately from your patient files and encrypted with the best available technology. The tissues can be stored indefinitely until withdrawal of consent, and will be available for scientific research studies. Only authorized members of the research team will have access to your tissue samples.

In order to code your tissue samples in the NCT, a "pseudonym" will be assigned in place of your name. The pseudonym is a random combination of letters and numbers and is associated with a computer program to a person. Finding out which tissue sample belongs to which patient is only possible with a digital key that links the patient name to the corresponding pseudonym. This key will not be made available to any third parties.

Those responsible for this software, and therefore for decoding your tissue samples, are the two Principal Investigators (see item 2) and the directors in the National Center for Tumor Diseases (NCT POP: Personalized Oncology Program) and in the German Cancer Research Center (DKFZ HIPO: Heidelberg Center for Personalized Oncology) who oversee these research programs.

The genome-wide analyses are generally carried out in Heidelberg (DKFZ, University Clinic, European Molecular Biology Laboratory). However, we conduct research in collaboration with other academic partners within this country and internationally. Tissue samples may be transferred to these partners. If this does occur, samples and data will be transferred only in coded form – that is, without your name or any other information that could identify you.

6. What will happen to the findings?

The new methods of analysis have not yet been integrated into routine diagnostics for identifying the causes of diseases. This method produces a large volume of data. New techniques to interpret the collected data must be developed.

Our analyses may yield findings of different kinds:
a) Findings that are relevant to your type of cancer, and
b) Findings that are relevant to other diseases.

a) Findings related to your type of cancer

It is possible that we will discover findings that are directly related to your type of cancer. We will share these findings with you, provided that these findings can be combined with existing knowledge and methods to provide treatment and care measures tailored to your specific needs. We will also share these findings with you if they enable us to predict the onset or progression of cancers.

A systematic investigation of all of your data for cancerous changes for which targeted treatments have been developed is currently under development but is not yet available.

If we are able to provide you with any findings that are new to your type of cancer, we will contact you again. The Statement of Consent prompts you to specify your preference in this matter.

b) Findings related to other diseases (additional findings)

It is possible that we will discover findings that are not relevant to your type of cancer, but that are related to other hereditary characteristics. We will not search actively for such findings, or for the causes of other diseases, and we are not obligated to collect any.

If you would like, we can inform you of any findings that we do uncover that are related to other diseases for which, according to our current knowledge, targeted treatment options and preventive measures exist, or which may suggest a change in your lifestyle. Examples of findings that might be significant to your health will be given during your consultation and will make this clear. You can indicate your decision about these notifications on the Patient Statement on Reporting Preferences form.

If we identify findings that are hereditary, rather than being located only in the tumor cell, then they could be significant for your offspring as well as for you. In this case, you – and, if applicable, your family – will be offered additional genetic counseling.

During a personal conversation, a qualified specialist will share with you any findings and additional findings about which you wish to be notified.

7. What will happen to the collected data?

Genetic data contain a large amount of information about a person. For this reason, it is especially important to protect this information and prevent any misuse. To this end, we have developed a data protection policy. You will find it at

..... {Homepage}

Everyone involved in this project is under obligation to adhere to and to enforce this policy.

We will collect your personal patient information (name, address, date of birth) and clinical data (diagnosis, disease history). Your genetic data will be the object of this study. In the course of the genome-wide analyses, these data will be collected and saved. In order to protect your privacy, your patient information and your genetic data will be coded and stored in separate databases, and access to each of these databases will be limited. The genetic findings that are necessary for your clinical treatment and that are shared with you will also be recorded in your medical file.

Your genetic data will be collected, analyzed, and stored only in coded form. Only authorized members of the research team will be able to access the coded data. This ensures that personally identifying information about you cannot be used for any purpose that is not expressly intended. Data will not be shared with unauthorized third parties, for example employers or insurers.

It should be noted that international cooperation is common in this kind of research. International scientific research can involve the exchange of data in coded form. External scientists with whom we collaborate will receive your data in coded form only. In addition, all parties with whom we collaborate are committed to comparable security measures: they have pledged that they will not transfer data to third parties, that they will use data only for the specified research purposes, and that they will make no attempt to identify you from your data.

We would also like to advise you that, in the course of scientific evaluation of your genetic data, your data may be entered into extensive international databases. It is essential for the research study that your complete genetic data be entered into the database.

In this case, too, your data will only be transferred in coded form. We will work to ensure that these data are protected to the same degree as they are in Heidelberg, and that it will be impossible for anyone to identify you personally. The Statement of Consent prompts you to specify whether you grant permission for this scientific use of your data.

Beyond this study, we will use the evaluated genetic data only in scientific publications. In order to publish the pseudonymized genetic data that have been evaluated, some of the leading scientific journals first require controlled access to whole-genome data so that they can verify the research results and maintain the scientific quality of their publication. Access to the data will be monitored by special committees. In the Statement of Consent, we will ask for your permission to publish your evaluated genetic data and to make whole-genome data available for quality control by scientific journals.

8. What are the risks to you?

Participation in the study does not put you at any health risk beyond the risk that exists when the tissue and blood samples are removed during your treatment. If your participation in the research study requires an additional blood sample, then there will be the minor risk that accompanies this medical procedure. We assure you that any additional blood tests that are necessary will be conducted by skilled personnel.

It is possible that being notified of additional findings will affect your life and the lives of your family and relatives. This may be particularly significant for you if additional findings indicate a hereditary disease, because hereditary diseases may also affect other members of your family. On the Patient Statement on Reporting Preferences form (attached), you will be able to specify what you would like us to do about notifying you of additional findings.

It is theoretically possible that specific patterns of genetic variation could be used to identify an individual, even if the genetic dataset has been separated from your personal data. By doing so, unauthorized third parties could link you with your genetic data. This risk is particularly large if your personal data (last name, date of birth) is coupled with your genetic data somewhere else, as is sometimes the case in publicly-accessible databases for genealogical research.

The more data that are saved in a comprehensive international database, the greater the possibility becomes that you could be identified personally from your genetic data. We assure you, however, that we will do everything to protect your data and to prevent you from being identified personally. Legislation has made the misuse of your data punishable by law.

9. What benefits will come from this study?

Participating in cancer research often does not benefit you or your treatment directly. We may produce results that are related to tumors, and that are therefore relevant to you. We will then contact you. That could improve your treatment and your care.

We hope and expect that these studies will benefit patients who suffer from cancer in the future. Your tissue donation will contribute to research on the cause of cancer and to the development of new methods of detection and treatment. The greatest medical benefit, therefore, is not expected for several years and will mainly benefit future patients. In this way you are making an important contribution to research and to further improvements in medical care.

10. Do I have the right to withdraw from this study?

Your participation in this research study is voluntary.
You may withdraw your consent at any time without having to provide a reason, and your withdrawal will have no negative impact on your subsequent treatment.

Upon withdrawal of consent, the samples that have been collected from you will be immediately destroyed and your personal data erased. However, if your samples have already been analyzed and your data already processed or transferred (in coded form) to a third party, we will no longer be able to erase all data and destroy all samples because doing so could jeopardize the validity of the research findings. The third parties to which data may be transferred include national and international research partners. However, the relevant key will be destroyed.

Documentation of Patient Questions

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Statement of Consent

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Patient Name

I have been informed about benefits and risks of genome analysis, of the data that will be collected, and of my right to withdraw from the study. I consent to the research on my tissue and on the data that will be collected under the following conditions:

I understand that I can be informed of medically significant findings that are relevant to my type of cancer and for which, according to current knowledge, treatment options and preventive measures exist, or which enable the prediction of the onset or progression of cancers.

I hereby donate my tissue to the National Center for Tumor Diseases (NCT) Heidelberg for cancer research. It will retain its right to use my tissue even after my death.

I consent,

- that my tissue will be analyzed for cancer research and that the data collected will be stored and evaluated in coded form (pseudonym).
- that I can be asked whether I would like to participate in a study to test new treatment possibilities for my disease.
- that my tissue and my coded data, including complete genetic data, will be made available to international cancer research for scientific purposes.
- that my tissue and my coded data, including complete genetic data, will be made available to international cancer research for scientific publications.

I waive claims to any profits that arise from commercial use of my personal biological or genetic material. My privacy rights, particularly with regard to anonymity and data storage, will be preserved.

.....	.....
Place and Date	Patient Signature
.....	.....
Place and Date	Clinician Signature

Patient statement on reporting preferences for additional findings

What is my position on receiving reports of findings not related to my type of cancer (additional findings)?

.....
Patient Name

.....
Physician Name

.....
Date

A) Additional findings for which targeted treatment options or preventive measures exist

I agree,
that I can be informed of verified, medically significant findings that are not related to my type of cancer and for which, according to current knowledge, targeted treatment options or preventive measures exist

☐ yes
☐ no. I do not agree, I do not want to know such findings.

B) Additional findings for which no targeted treatment options or preventive measures exist

I agree,
that I can be informed of verified, medically significant findings that are not related to my type of cancer and for which, according to current knowledge, no targeted treatment options or preventive measures exist, but which could be significant for making life decisions.

☐ yes
☐ no. I disagree, I do not want to know such findings.

1. GUIDING PRINCIPLES UNDERLYING THE DOCUMENTS PREPARED

In the creation of the documents, EURAT group has orientated itself by the following guiding principles:

(1) It is ethically imperative to seize the opportunities which are afforded by the progress in genome research, because they may contribute to improving diagnosis and therapies, thereby increasing life expectancy and quality of life for numerous people.

(2) The complexity of whole genome analysis entails that the patient's decision-making rights cannot be ensured any longer by the traditional model of "informed consent". Clinicians, however, are legally obliged to inform patients or participants about the nature and meaning of possible findings and hazards, and to obtain their consent. Legally, this may be accomplished in the context of a trustee model.

(3) In the written patient-information, the patient receives suggestions on various possibilities regarding the provision of feedback of findings and results arising from the whole genome analysis. In this manner patients are given the opportunity to express their preferences in a differentiated way.

(4) Secondary or additional findings are disclosed to those patients who have expressly stated this wish in the context of the process of patient information.

(5) In research, there exists an ethical duty to also include individuals who are unable to consent for themselves because, otherwise, this group would be excluded from medical progress. For those persons incapable of consent, especially minors, a specific procedure of informed consent is to be designed, in which no feedback shall be given of disease susceptibilities that may result in disease only in adulthood, and for which there are no therapeutic measures available during childhood.

(6) For researchers, new forms of responsibility in dealing with their knowledge about patients and their families will arise. For them, no code of ethics or obligations exists, which would be comparable to those that apply to physicians. It follows that they also are not protected in a comparable manner. To remedy this, a code of obligations and guidelines for researchers is formulated, which is similar to the professional ethics of physicians. This code can exert a protective effect, for those who sign it, as a form of self-commitment.

(7) The work of researchers is not regulated by a list of additional findings to report from sequencing (positive list). However, they are obliged to report to the attending physician any findings and additional findings whose significance for the patient they recognize, provided that the patient's statement about preferences on the return of results does not pre-clude this kind of feedback.

(8) The large amount of sensitive genetic data gathered requires special protection. In a concept for data protection, the needs of both clinical care and of genome research must be taken into consideration simultaneously. This protection is to be guaranteed by special data protection protocols in the participating research institutions and hospitals.

2. EXPLANATIONS ON THE DOCUMENTS PREPARED

The documents prepared are focused on the following problem fields evoked by the "next-generation sequencing of genomes":

(2.1) The potential for cultural change arising from genome sequencing
(2.2) Normative foundations
(2.3) Limitations of the traditional concept of information, consent and advice
(2.4) Dealing with additional findings
(2.5) Research on persons incapable of giving consent
(2.6) Responsibility of researchers in genome research
(2.7) The economic dimension
(2.8) Protection of a person's genetic data
Reference points for a data protection regulation

(2.1) The potential for cultural change arising from genome sequencing

A major objective of genomic research in the coming years will be the identification of those mutations and causative pathways which are relevant for disease. Currently, the significance of genetic information for the lifestyle of individuals cannot be evaluated with certainty in many cases. Genetic

information, on the one hand, constitutes a crucial biological prerequisite of human identity (Habermas, 2001, 44 et seq.). On the other hand, in most cases, only statistical probabilities can be employed for the correlation of genetic changes with the occurrence of a disease. Many changes (mutations) which are ascertainable by genome analyses have no consequences at all, within the human body. Discoveries of genetic traits can provide relief, if they enable improved diagnosis and treatment. However, they can also evoke feelings of uncertainty. A person may be phenotypically asymptomatic, but already might perceive himself as potentially diseased due to predictive genotypic findings (Kenen 1996). Life as a member of the "healthy ill" (Hubbard, 1993) can lead to psychological stress.

Thus, scientific access to this genetic information affects people in the deep layers of their personhood. Because parts of an individual's genetic information simultaneously reveal facts about family members, the significance of this information reaches far beyond said individual and also involves the social context. For researchers, new forms of responsibility arise in dealing with their knowledge about patients and their families. For a person carrying a mutation there may arise obligations of a predictive life style in acknowledgement of the predictive risk factors, for example, by adherence to earlier or more intensive screening schedules (van den Daele, 2007). But also in social relationships, e.g. towards relatives and offspring, there may arise forms of "genetic responsibility" (Kollek et al., 2008, 223 et seq.), for instance, when it comes to any decision about reproduction. Because genome sequencing techniques are changing human lifestyle and culture, they have become the subject of extensive interdisciplinary discussions (Berlin-Brandenburg Academy of Sciences 2009, Leopoldina 2010, Presidential Commission for the Study of Bioethical Issues 2012, American College of Medical Genetics and Genomics 2013, German Ethics Council 2013, Berlin-Brandenburg Academy of Sciences 2013, German Society of Human Genetics, 2013). They have evoked issues concerning respect for the dignity and personhood of the human being and their social relationships, in a new manner.

(2.2) Normative foundations

The guiding principle of respect for the person forms the normative foundation of the project. The problems raised by the "next-generation sequencing of genomes" are not entirely new. The quantity and range of challenges, such as in data protection policy or in dealing with additional

findings, represent a new issue, though. For this reason, in ethical, legal, and health-economical analysis, recourse may be had to proven methods as well as established standards in the form of laws, guidelines and ethical principles.

To perceive the "patient as person" (Ramsey 1970), means to take the multidimensionality of human life into due account. This multidimensionality comprises the patient's physicality and vulnerability, such as it becomes apparent especially in the context of medicine, the patient's inner contradictions between fear and hope, dynamic biographical nature and individuality but also the extent to which a person is embedded within social structures and cultural contexts involving giving and receiving social recognition within which the patient is able to develop personal freedoms. "Person" therefore encompasses more than just the idea of isolated autonomy and self-determination or an aggregate of existing characteristics. Counterbalancing the restriction of a human being merely to "his" disease or to a data record, the orientation at the person as a whole constitutes a barrier against reductive definitions (Plessner 1976, 144). In the quartet of bioethical principles (Beauchamp / Childress 2008) – respect for autonomy, non-maleficence, beneficence and justice – this multidimensionality of personhood is well reflected. This principles-based approach is not targeted at autonomy exclusively. It focuses on both the protection of the person and the person's roots and dependence on other persons within social contexts prestructured by institutions.

"Respect for human dignity" is the short expression in which the comprehensive interest of each and every human being in the protection of their personhood has been formulated summarily. In the German constitution (Grundgesetz, GG), in Article 1, Section 1 GG, as well as in the statute on physical integrity (Art. 2, Sec. 2, sentence 1, GG), and the general personality protection law (Art. 2, Sec. 1 GG, together with Art. 1, Sec. 1, GG), this ethical foundation is formulated in judicial terms. The protection of fundamental rights is substantiated by specific statutory instruments, such as the Genetic Diagnostics Act (Gendiagnostikgesetz, GenDG) and the Federal Data Protection Act (Bundesdatenschutzgesetz, BDSG). Loopholes in these regulations can be ascertained, especially regarding the Genetic Diagnostics Act (Bartram 2012, 167ff.).

Genome sequencing is a highly dynamic field of research. Both analysis techniques and evaluation patterns for genetic information are changing rapidly (Greely 2011, 12). Therefore, it is of little help to formulate abstract

and static catalogues of obligation or prohibition which may be outdated again the very next day. Rather, it is necessary to enhance ethical sensibility, and possibilities of self-commitment to good practice, and to establish structures in which the dynamics of the rapidly changing research and technology can be taken into account. The enhancement of these possibilities can make an important contribution to strengthening patients' confidence. Transparency and confidence are important prerequisites to ensure that patients feel comfortable getting involved in the dynamic and complex field of human genome research projects.

Analysis of the genetic information is performed within highly cross-linked, international research networks, characterized to a high degree by division of labour, such as e.g. the "International Cancer Genome Consortium" (ICGC et al. 2010). These worldwide cooperating research groups are influenced in their work, inter alia, by differing legal cultures and legal protective standards, for example in the fields of data protection, liability law or patent law. Therefore, any individual orientation focusing merely on the German legislative landscape is by far not sufficient. In legal analysis and evaluation, therefore, international standards have also been considered within the EURAT project, as they are set out in their respective form of documents in international law, in particular resolutions of the United Nations (UN) and its special agencies, the Convention on Human Rights and Biomedicine of the European Council, the regulations of the EU and the Helsinki Declaration of the World Medical Association. Such international agreements will increasingly gain in importance.

(2.3) Limitations of the traditional concept of information, consent and advice

First of all, the sequencing of the entire human genome is, in a similar manner to any other medical intervention, also an intervention in the patient's rights. Before performing whole-genome analyses, the informed consent of the patient or participant is required in accordance with established bioethical standards and legal regulations. A prerequisite of any effective statement of consent is that the patient is allowed to form their own judgment about the purpose, meaning, and scope of the intervention and the potential risks associated therewith.

Independently of genome sequencing, the concept of "informed consent" has been extensively criticized as a kind of consenting ritual that only has a

figleaf function for justifying research and medical interventions on human subjects (Brownsword 2004): in focusing on an act of consenting and of signing a form, executed only once, the communicative dimension in the process of informing and consenting (Manson/O'Neill 2007) is said not to receive sufficient consideration. The traditional model is said to be based on a limited understanding of autonomy, in contrast with which the interpersonal conditions of exerting individual self-determination would have to be upvalued (Donchin 2000, Christman 2011, 117).

These critical inquiries are intensified by the specific challenges that have been raised by the emergence of genome sequencing. An exact medical description of any potential danger is not obligatory. Rather, it is necessary to communicate to the patient a general overview of the extent of the risks associated with the intervention (BGH on 03/12/1991, VI ZR 232/90).

It is actually imperative to communicate information about possible additional findings, even if the patient (as a "layperson") may have difficulties in understanding and judging particular aspects properly.

The requirements of this classic model of "informed consent" cannot be satisfied any longer in the case of whole genome sequencing. Instruction of the patient on the multitude of genetic changes and their potential relevance for a disease can no longer be accomplished in a reasonable time frame (Bartram 2012, 165). The significance of the collected data cannot be fully explained to the patient (PHG Foundation 2011, 90, German Ethics Council (Deutscher Ethikrat 2013, 173f.). The structure of largescale research (global data exchange), a large volume of vague knowledge (research is in flux), the nature of genetic information (probability knowledge) and the quantity of possible additional findings (off target results) undermine aspirations towards any comprehensively informed decisionmaking.

Another essential feature distinguishes whole genome sequencing from conventional medical interventions, and complicates informed consent even more. In contrast, for example, with surgery, this procedure requires no substantial physical interventions on the patient. A simple blood sample is often sufficient to decode the entire human genome. In cancer patients, collection of a tumor tissue sample (biopsy) is in general sufficient. But even if the intervention is more severe, and tissue samples are dissected, the following holds true: The low physical burden is disproportionate to the actual focus of the intervention, i.e. the acquisition of data. In research, gradually, more and more information can be obtained from genetic analysis.

Unlike conventional – in most cases physical – medical interventions, whole genome sequencing does not represent an isolated intervention, but rather a permanent intervention in the rights of the person concerned. The possibility of successive acquisition of information makes it difficult to assess the extent and scope of the intervention definitively. The German Genetic Diagnostics Act (GenDG) does not pay sufficient attention to this particular dynamic of said intervention (Molnár-Gábor/Weiland 2013, 5).

Genome sequencing is changing the general conditions for informed consent. Because this research method brings about changes to the understanding of the relationship between genotypic and phenotypic variations, it makes sense to think of the concept of Informed Consent as no longer an event that is completed in a single act. Consequently, the main focus is shifting towards the development of communication procedures and tiered consent models, (Forgó et al. 2010, 17 et seq.) wherein patients will be granted more options to inform themselves, than in a oneoff explanatory discussion and in reading a patient-information brochure. However, this can only be guaranteed if humangenetic counseling is expanded. The oral and written instruction may be supported by graphically and textually appealing brochures, and/or socalled "FAQs" (Frequently Asked Questions) as well as resources on the internet and video documentaries. The scope of the protective function of "Informed Consent" remains limited, nevertheless.

(2.4) Dealing with additional findings

Using the methods of genome sequencing, a huge amount of data is generated in an initial step, which must be interpreted and evaluated for relevance to disease in subsequent, more complex, steps. This methodology will necessarily result in the generation of additional information, which was not explicitly sought. Said information is referred to as "incidental findings" in common practice.

In everyday clinical practice, incidental findings represent those findings, which were not requested in the original diagnostic question (= unintended results) and which were generally not to be foreseen at all (German Bundestag printed papers, BT-Drs. 16/12000, 99). Incidental findings are not only unintended, but are also considered as unexpected. In particular, in the course of imaging procedures, such as X-ray or MRI examinations, such findings may be obtained. As early as in the 1990s, the issue of such

findings, particularly with regard to their disclosure, was addressed in international recommendations (Council of Europe Recommendations in 1992 and 1997, and Human Genome Organization 1996).

While using methods of whole genome sequencing, however, the physician and researchers, must assume that they will encounter additional findings, beyond the original diagnostic question. Since such findings, being unintended but to be expected, can no longer be classified as merely "incidental", they are more appropriately designated as "additional findings". The finding itself, reaching beyond the scope of the original question, remains incidental, but the occurrence of such findings does not.

The foreseeability of additional findings during whole-genome sequencing raises ethical and legal issues, which are only imperfectly addressed by the relevant standards under existing law. Whether the discussion of additional findings should be assigned to the patient-counseling about the benefits or the patient-counseling about the risks, cannot be answered on a general basis. In the written and verbal information provided to the patient, it should be made clear that such findings are neither specifically targeted, nor does there exist any obligation to detect such findings at all. If, however, an additional finding should be detected, the informed consent documents must include a description of the available options for dealing therewith, and of the consequences entailed. The disclosure of additional findings may confront the individual patient involved, and possibly also family members, with a new situation of living. In particular, the possibility of detecting additional findings that indicate hereditary diseases should be explained to the patient, because hereditary diseases may also have consequences for family members. Nevertheless, a detailed instruction on all the additional findings that might be disclosable according to the prevailing state of medical knowledge, cannot be accomplished. According to the current state of knowledge, explanations about the significance of some 6,000 mutations and at least 3,000 genetic diseases would have to be communicated to the patient.

Thus, during the phase of instructing the patient, only exemplary findings can be explained, such as those genetic changes causing hereditary breast cancer, hereditary bowel cancer, and certain myocardial and metabolic diseases. Furthermore, this phase should outline which types of findings generally will not be evaluated and disclosed (see the patient information "Health-services research on the use of genome-wide analysis in the workup of diseases"). On the basis of this instruction, the patient should be

able to tell the physician whether feedback of additional findings is desired, or not.

In the global debate, at present, there is no consensus on how best to deal with excess information of potential medical relevance arising from genome-wide analyses in research and diagnosis.

The range of perspectives extends from the proposal to disclose nothing about additional findings to the patient, up to formulating certain obligations for disclosure, which are guided by so-called "positive lists". The most recent recommendation of the ACMG proposes feedback of additional findings in minors which are not yet manifest and not treatable in childhood, as well as feedback against the patient's will, provided that the findings are registered on a positive list (American College of Medical Genetics and Genomics 2013). The EURAT Panel, however, rejects this solution.

Dealing with additional findings should be regulated on a project-specific basis in each and every application of genome sequencing. In deciding whether feedback on additional findings shall be given, the prerogative of assessment by the physician always plays an important role. Whether and which additional findings are to be reported also depends on the patient's wish. The patient determines these decisions in the context of the statement of consent, having obtained competent advice in advance. As long as genome sequencing is not yet an accredited diagnostic method (but rather a pre-diagnostic measure), additional findings that are to be disclosed must be validated by an accredited diagnostics laboratory beforehand. An interdisciplinary advisory panel will be instituted in Heidelberg to assist with decisions regarding the return of results in difficult cases. The expert panel will document and collect decisions on the disclosure of additional findings. It will develop and update guidelines concerning decisions on which additional findings should be considered medically significant. If no such guidelines exist, the ultimate decision rests with the physician.

(2.5) Research on persons who are incapable of giving consent

Research on persons who are incapable of giving consent, e. g. minors, is an especially sensitive area (Knoppers 2012, Boos et al. 2010, May 2002, 120ff.). For this area, special restrictions are applicable. With minors, additional findings that may result in disease only in adulthood, and for which

there are no therapeutic measures available during childhood, shall not be reported. Here, the EURAT Group follows the regulation as set forth for diagnostics in the German Genetic Diagnostics Act.

If it is not possible to obtain consent, the possible benefit for the person who is incapable of giving consent represents a fundamental justification basis for an examination. This is the case with a medical examination, or medical treatment of the person who is incapable of giving consent. However, in case of research, the distinction between therapeutic and non-therapeutic goals, or between benefit to the patient and the benefits for science cannot always be clearly identified. There is no conclusive definition of the benefit. Genome analyses for thirdparty benefit, such as for the benefit of other family members, are legally disputed, and ethically may only be justified under strict conditions.

Determining the ability to give informed consent is a fundamental difficulty. It can neither be assessed by definite age limits, nor is it possible to define any general and abstract criteria for assessment (BT-Drs. 16/3233, 37; BT-Drs. 16/10532, 30). In fact, the ability to give informed consent must be considered on an individual basis. It is to be determined with regard to the intellectual ability of the affected person, and to the genetic examinations in question (BT-Drs. 16/10532, 30; GEKO 2011, 1257). In case of a temporary incapacity to give informed consent, any decision on genetic examinations should be deferred to a later stage when the ability to give informed consent is recovered, unless there are medical reasons against the deferral (GEKO 2011, 1259).

For persons who are incapable of giving consent, especially minors, a specific procedure of informed consent shall be conceived before carrying out whole genome sequencing. Besides the parents or guardians, this process should also include the person who is incapable of giving consent, in line with their developmental level. A written documentation of the consent shall particularly enable minors to independently avail of their right of withdrawal after they reach adulthood.

In research, there is an ethical obligation to include also those persons who are incapable of giving consent, as in terms of medical progress, any other way would leave this age group even more behind. This was the practice in pharmaceutical research for years with negative consequences, and has only recently been partially corrected with an amendment to the German Medicinal Products Act (Arzneimittelgesetz, AMG).

(2.6) The responsibility of researchers in genome research

Responsible officers and areas of responsibility must be nameable. This is the basic condition for a responsible application of the new technologies of genome sequencing. Compared to a mere fulfilment of obligations, or following of rules, an action is responsible if it is based on a complex risk assessment of one's own intended action. This assessment is required whenever a "correct" solution cannot be achieved by simply following the existing rules (Kaufmann 1992, 41 and 45). In highly specialized processes it is sometimes difficult to recognize the specific responsibilities of each involved person. There is always a risk of diffusion of responsibilities. Everyone relies on their colleagues or partners, presuming they will act responsibly. In order to create more transparency, the project has drawn up the most exact description possible of work flows for obtaining and analyzing genomic data. This description serves as a structuring tool to overview the whole range of specialized work flows pertaining to research and medical applications. It forms the basis for the identification of problems, and for proposals of solutions. For the research context of "genome research" as a whole, the following statement is essential: The whole chain is as strong and as trustworthy as its weakest link. Hence, it is imperative to strengthen all links and all involved persons in terms of acting responsibly when working with human body materials and patient data.

Very often, the work flow begins with a conversation between the patient and a physician. It is the physician's duty to protect the patient, keeping their data confidential and secret. However, the area of a physician's responsibility is rapidly exceeded in genome analysis. Other professional groups then play a decisive role, especially molecular biologists, bioinformatics specialists and computer experts.

For these scientists, no treatment contract exists, and there is no physician-patient relationship. The scientist is bound to the principles of good scientific practice (German Research Foundation (Deutsche Forschungsgemeinschaft, DFG,) 1998, Max Planck Society 2010). Scientific research is a form of realizing freedom, and is constitutionally ensured. Freedom of science, guaranteed by Germany's constitution (Art.5, Sec.3 GG), does not release researchers from obligations, such as the obligation to comply with applicable laws. For non-clinician scientists however, the obligations and protections they are subject to are not equal to those existing for physicians. Physicians may, for example, draw on a long and sophisticated tradition of professional ethics and on a well-established legal position,

e.g. with respect to the right to remain silent. For researchers, there is no established canon of obligations or code of conduct comparable to that applying to physicians.

In genome analysis, results may be found that are to be classified as possibly medically relevant knowledge. The researcher has exclusive knowledge of this. If this knowledge can be referred back to an individual, and if a physician could use this knowledge as the basis of a possibly successful therapy, the question may arise, whether it would be classified as failure to render assistance if this knowledge remains unforwarded. Therefore, repeated calls have been made for a code of conduct to be developed also for researchers, which would be comparable to the professional ethics of physicians (ten Have 2007). Such a code would have an orientating function, and would also disburden and legally secure those who commit themselves to it.

(2.7) The economic dimension

From an economic perspective, the focus is to be set on the costs of whole genome sequencing, as well as on its benefits. For both, more assumptions than facts are available at present.

In public discourse, it is always emphasized that the costs of whole genome sequencing have rapidly decreased, even though no valid estimate of costs for carrying out whole genome sequencing exists so far, as extensive and systematic literature reviews by the EURAT group show. However, one fact is presently certain: A complete whole genome analysis for less than US$1,000 as promoted in public and by many researchers will not be feasible within the next years. This is due to the circumstance that a significant part of the costs pertains to supplies, consumables and human labor – in both cases, a decrease in costs is not to be expected in future. In addition, costs for infrastructure are incurred when exchanging and saving the huge amounts of data. Other costs are associated with human genetics consultation, and with the communication of findings. These costs have to be considered in cost analyses as well.

Even if a sequencing plus the analysis should “only” cost US$1,000 in the future, the use of this method for patient care still has to be justified due to the limited resources in the health care sector. A justification to apply this method depends above all on the additional benefit generated for the

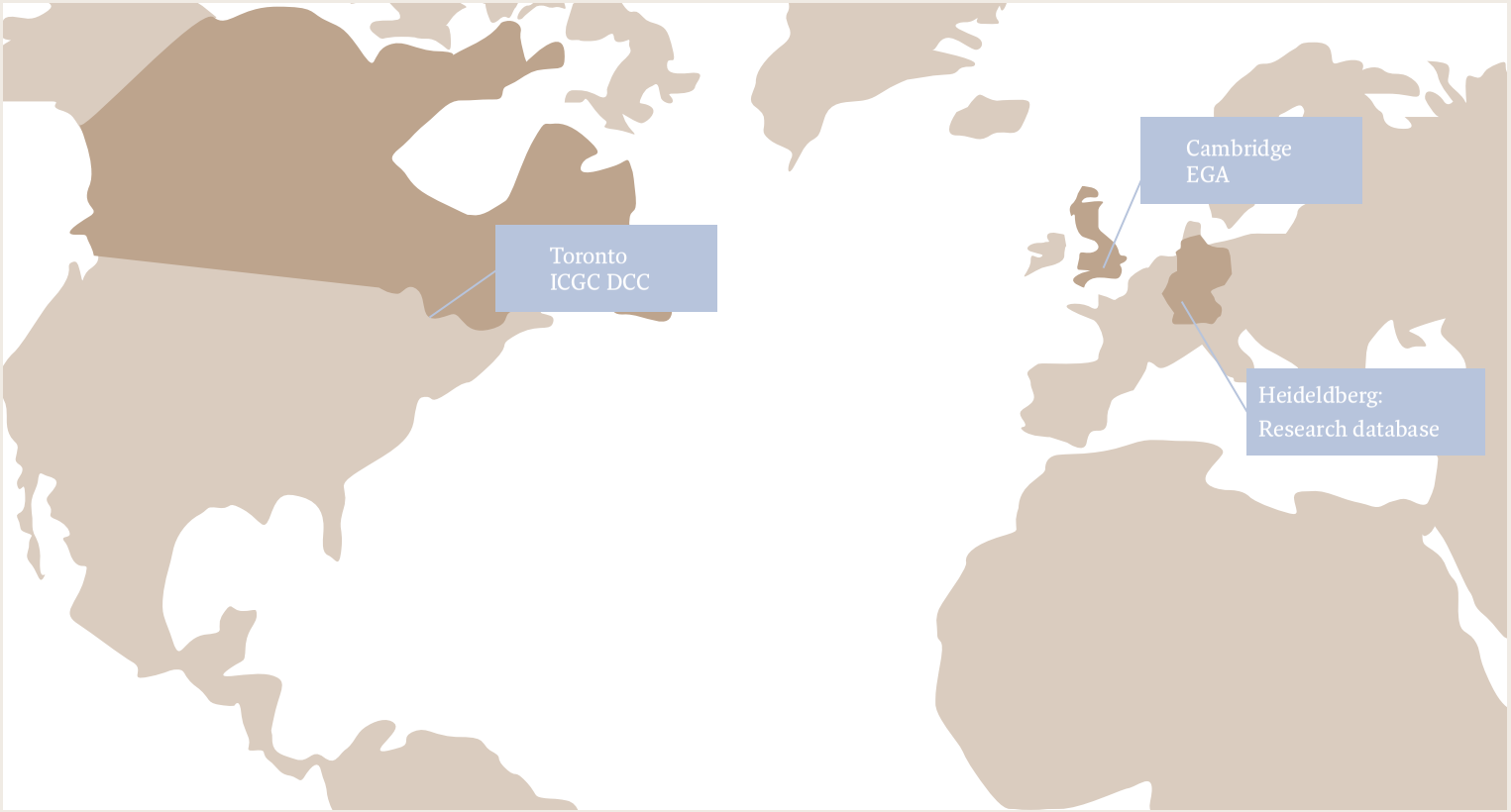
patient. However, so far, there are no valid clinical data regarding the efficacy and/or effectiveness of whole genome sequencing, which must in turn be dependent on the application field and the patient group. At present, it is thus not yet possible to conduct a valid health economic evaluation.

Due to the remaining uncertainty regarding the benefit for the patient, and to the unclear costs of whole genome sequencing, calls for an extensive application of this method in Germany's patient care, which would have to be borne by a mutually supportive community like the German statutory health insurance, must be critically discussed. To start with, valid data need to be obtained by doing more clinical research and some initial economic cost analyses. Then it will be possible to assess the implementation of whole genome sequencing in patient care, and beyond research.

(2.8) Protection of a person's genetic data

Genome research amalgamates the fields of medicine, biology and computer technologies. Sequencing produces enormous amounts of data. Analyzing this genetic information without the help of computer software is impossible. The data is exchanged by worldwide computer networks and saved in various databases. To obtain data about the probability of disease for certain genetic information, this information is linked to the patient's medical data. A digital "picture" of an individual is drawn by this "clinical genome sequencing" with an unprecedented density.

In the computer based science of genome research, data protection represents a key issue. Genetic data are considered a special kind of personal data (Art. 3 Sec.1and 9, BDSG). They are easily available and easy to obtain – with a simple blood or saliva sample, it is possible to isolate the DNA. By means of genetic data, a person can be unequivocally identified. Personality profiles can be created with the help of genetic data (McGuire et al. 2008, by Bose 2011). They also enable a scientist to make statements regarding genetic relatives. The genetic data may be of interest to third parties, in particular for criminal investigation authorities, employers and insurers. In the networks of data exchange and data processing, the boundaries between private and public data can become blurred. It has been shown that the possibility exists to identify an individual on the basis of freely accessible information in databases (Gymrek et al. 2013). The broader accessibility of genetic information in data networks leads to new possibilities of discrimination. (See page 72)



Example of international data exchange:
Heidelberg in the International Cancer Genome Consortium (ICGC)

Data can be protected in the best way by anonymization, as long as no other connections exist between the genetic data of an individual and the identifying personal data. However, with the best possible data protection in form of anonymized research data, patients or participants would no longer be retraceable. In such a case, any feedback of medically relevant findings would be impossible. With longterm studies, retraceability will usually be required to assign additional data to the original data. Pseudonymization means a compromise – replacing the name and other personal identifiers by another mark for the purpose of preventing the identification of the affected person (Art. 3 Sec.6a BDSG). As soon as the data leave the clinical context, they have to be pseudonymized. When pseudonymized data is to be used for research purposes, there is a need for guidelines to determine in which cases a reidentification by a keyholder should take place. The personality rights of the patient or participant need to be considered in this process. The interfaces between clinical practice and research play a decisive role, as this is where the conversion of personal data into pseudonymized data takes place. Genome research may result in the knowledge of diseases or the susceptibility to diseases that requires pseudonymization to be reversed. One proven instrument is to appoint so-called "data-access committees", who then develop rules for such access rights and reidentifications, and who decide in each case whether a pseudonymization will be reversed.

To guard against potential misuse, the EURAT Group has formulated some points of reference for the development of data protection policies. Any institution involved in genome sequencing may use these as a basis for developing data protection policies.

Reference points for a data protection regulation

I. Ethical principles and legal framework of data protection

Genetic data are especially sensitive data. They enable a scientist to obtain knowledge about the state of health of individuals and their relatives. Based on this knowledge, probability statements may be made concerning the future; they may be used for predictions. By means of certain genetic data, a person can be unequivocally identified. Genetic data are of interest for third parties. For these reasons, working with them is subject to

special rules. This refers in particular to those research projects combining clinical data with the genetic data of the patient, obtained through genome sequencing.

I.1 Ethical principles

The work with genetic data in translational medicine is determined by four ethical principles: the principle of respect for patient's autonomy when dealing with patient data; the principle of non-maleficence, the protection of the person and their privacy from abuse, stigma and discrimination; the principle of beneficence, the patient derives a benefit from the results of genetic research, particularly through feedback of findings; the principle of freedom of research and enabling scientific progress. The obligation to comply with all of these principles may often cause tensions. Thus, the principle of non-maleficence may be in conflict with the freedom of research insofar as the protection of privacy implies measures that impede or even prevent research projects. When making use of the right of withdrawal, respect for the patient's volition will be restricted if untraceable data flows prevent the complete deletion of all of the research data that were authorized by the patient. Implementing a quality-assured feedback method for additional findings may be associated with additional costs for scientific projects.

I.2 Legal frame conditions of data protection

The four ethical principles for the treatment of data from translational medicine are strongly connected with data protection law, which developed as a consequence of increased data volumes and a growing need for protection of privacy. This development has taken place in detail on a national and international level since the early nineties.

UNESCO (Declaration on human genetic data, 2003) and various other international organisations have set up uniform regulations for the treatment of data in the international legal area by means of non-binding recommendations, but also by binding conventions (Council of Europe 1981, Council of Europe 1997). In the European legal area, directive 95/46/EG was the decisive basis for national data protection laws for the protection of individual persons in terms of processing personal data and free exchange of data. In Germany, the directive was implemented by the Federal Data Pro-

tection Act (BDSG). In general, gathering, processing, and using data was thereby prohibited unless explicitly permitted by a law or by consent of the affected person (principle of prohibition with the reservation of permission). The BDSG data protection regulations are further specified by the German Genetic Diagnostics Act (e.g. non-discrimination in the insurance and labour sector) as well as on a regional state level in each state's hospital law and cancer registration law. There are special challenges in reconciling freedom of research and scientific progress with the data protection principles of data minimization, the avoidance of accumulation of data (Art. 3a BDSG) and the principle of purpose limitation. Especially in the area of whole genome sequencing, data are gathered on a large scale for the better understanding of the interaction of different genes and diseases for certain projects (genome-wide records). These could even be useful for other research projects, even if they were neither gathered nor intended for this purpose.

On a European level, the protection of the huge amounts of personal data that are gathered especially in the course of human genome sequencing is a fundamental right pursuant to Art. 8.1 of the European Union's Charter of Fundamental Rights, and on a national level pursuant to Art. 2.1 of the German constitution.

The collection, processing and use of genetic information may not lead to disproportionate interference with the general rights of personality, especially the right to informational self-determination of the person concerned (Laufs et al. 2009).

The German Federal Constitutional Court (Bundesverfassungsgericht, BverfG) clearly rejected the use of DNA data gained for the purpose of a secretly initiated DNA paternity analysis, i.e. without active participation of the person concerned (BVerfG 13.02.2007, 1 BvR 421/05). The court also emphasized the need for consent to the collection of data (see also Art. 8.2 sentence 1 of the EU Charter of Fundamental Freedoms).

In particular, the judgment regarding data retention (BverfG 2.3.2010, 1BvR 256/08), which declares a precautional, groundless data retention as incompatible with the Constitution, could in the future affect the biomedical field. Data generated for studies, published in publications or fed into public databases are kept in this way and may possibly be useful years later in another research context. If the purpose cannot be defined in advance, any storage can be considered groundless. However,

it is to be questioned how precisely the purpose of a storage needs to be specified: Is it enough to define the broad area for a later use of the data (e.g. cancer research), or must future research projects be defined as precisely as possible?

In general, the question arises whether it is a legislative task to attend to this problem. The relationship between the physician and the patient, as well as between the researcher and participants are governed by private law. Nevertheless it is assumed that the system of values set forth in the fundamental rights will affect private law (BVerfG 22.11.1951, 1 BvR 400/51, BVerfG 23.04.1986, 2 BvR 487/80) and it follows that the constitutionally ensured basic data protection rights will also affect relationships under private law (Griese 2013, Datenschutz Rn 1). Thus, in the event of a conflict, those applying the law are to reach judgments under consideration of the valuesetting significance of the general, constitutionally ensured rights of an individual, i.e. in conformity with the constitution (Di Fabio 2013, GG Art. 2, Rn 192) – such as those set forth in Art. 242 (if applicable in connection with the principle of positive violation of contractual duty), 138 or 823ff. BGB (German Civil Code).

I.3 Relevant ethical and legal perspectives

To satisfy all four ethical principles and the legal conditions, extensive regulations are required relating to collection, saving, usage, transfer and publication of the records on an institutional level. These regulations are implemented under the following aspects[5]:

1. Data avoidance and purpose limitation of data: Only those data may be gathered, saved and forwarded that serve the specific research purpose.
2. Accessibility of data: The data are to be made available to the scientific community to the greatest extent possible, on one hand to enable the best possible use of the data, on the other hand for the scientific verifiability of results (quality of research)
3. Data protection and data security: Data must not be lost and must be protected from unauthorized access with measures that cannot be bypassed.
4. Transparency: The methods used have to be described and explained fully and made understandable to the public.
5. Responsibility: All participating scientists and institutions have to handle the data in a responsible manner. Competences are to be assigned to all parties involved to prevent conflicts and diffusion of responsibilities.

[5] Based on the concepts of Knoppers et al. 2011 and Krawczaket al. 2011, chapter 7.6.

Clear guidelines facilitate the handling of data by physicians and researchers and ensure data privacy and security for affected persons.

II. Problem description

The data flow in genome sequencing connects different stakeholders and institutions with each other. It links clinics with scientific institutions as well as local and external research contexts. The following diagram is an exemplary illustration of the data flow of a genome sequencing in the Heidelberg Cancer Research: (See page 78)

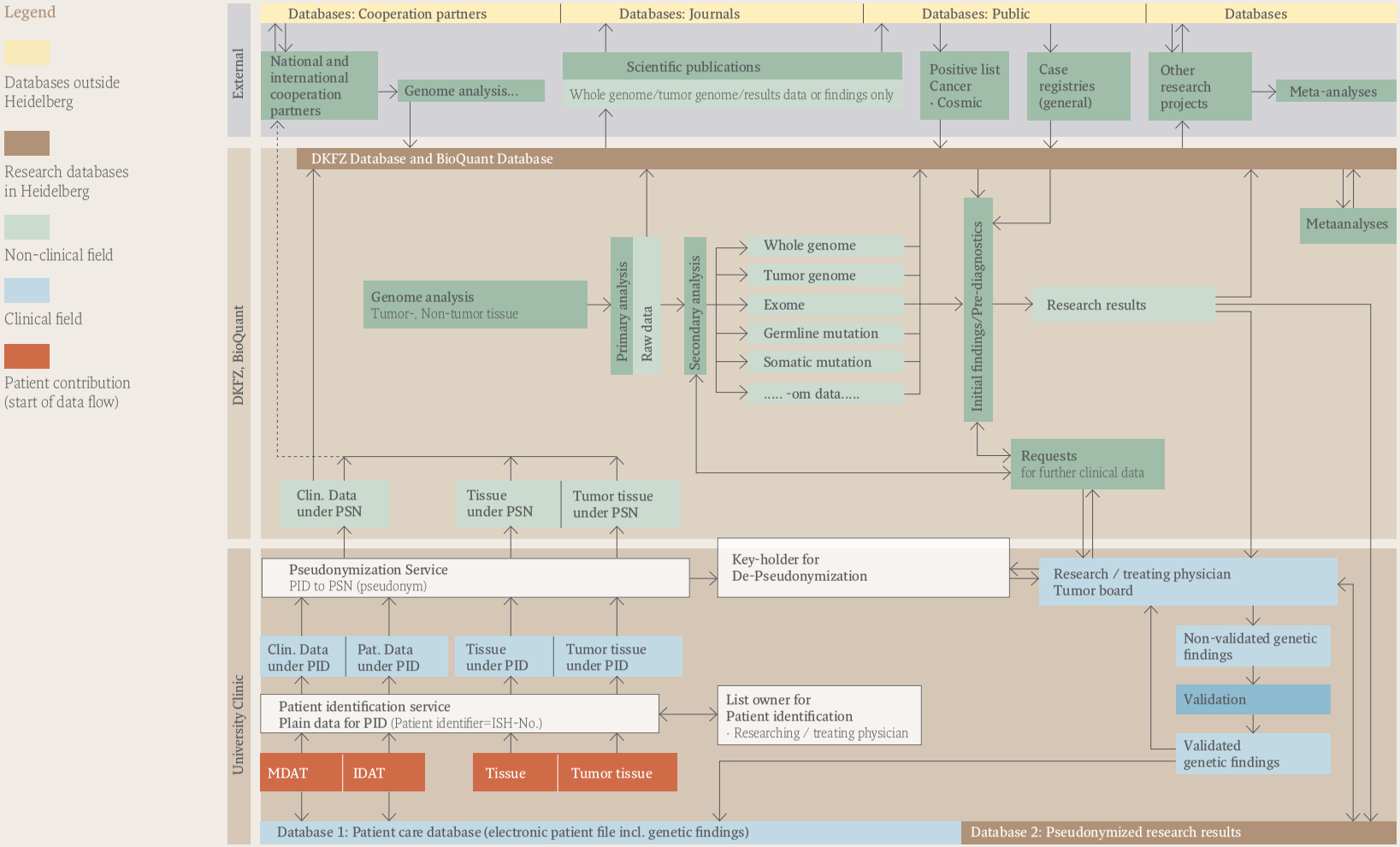
In the current data flow, two problems are identifiable that require a guideline:

1. Pseudonymization and De-Pseudonymization of data
2. Access to and forwarding of data

II.1 Pseudonymization and De-Pseudonymization of data

To protect the patients, personal data and tissue samples must be marked with a pseudonym to be usable in research contexts. Even though anonymization of the data would represent a maximum protection against reidentification, it does not make sense for two reasons. Firstly, anonymity impedes the feedback process of relevant findings (normal and additional medical findings). Secondly, it makes it impossible to forward queries arising from research (request more clinical data). Therefore, the use of pseudonyms is a solution that can contribute to a well-reasoned balance between the interests of patients and research.

The possibilities of the use of pseudonyms in medical research have been widely discussed and generic data protection concepts have been designed elsewhere (Reng et al. 2006, Pommerening et al. 2005). An essential characteristic of scientific research in the field of whole genome sequencing, however, is that in addition to research results, findings with clinical relevance to the person who is the source of the data or to genetically related persons will be generated with high probability. Sometimes it is necessary to gather and transmit more of the patient's clinical data in the course of the research project, which requires the possibility of re-identification. A certain degree of permeability for data between research and clinical practice is therefore desirable in whole genome sequen-



Exemplary illustration of the data flow of a genome sequencing in the Heidelberg Cancer Research

cing; however, this increases the demands on the pseudonymisation and de-pseudonymisation processes. A data protection policy has to prevent access by researching persons to non-pseudonymized patient data, while also enabling de-pseudonymization in case of need.

II.2 Forwarding and access

The following problems are associated with the storage of data in biological databases and with access possibilities to these data, and their dissemination: The research community has a fundamental interest in obtaining access in a way as simple and barrier-free as possible to all of the data relevant for the scientific research questions. In addition, there exists interest, especially in genome research, in generating the widest possible data collections, to be able to identify the diseasespecific differences within the genome. One possibility for being able to generate larger collections of data for very specific purposes consists in networking and sharing of databases and dissemination of data (data sharing). This pooling of data is considered to have a huge potential for gaining knowledge more quickly, particularly in cancer research. Thus, the benefits of individual data records for research will be the greater, the more readily and comprehensively researchers can access these records worldwide. The patients' rights to data privacy and informational self-determination contradict the interests and demands of research. Patients possess the right to have their information used only for the intended purposes (research) for which they had given their consent, and to be protected from misuse of their data. In particular, patients possess a right to have their genetic data not assignable to themselves, i.e. that (outside the medical-therapeutic relationship of trust) there must be no occurrence of re-identification of their data with their own person. The preservation of these patients' rights is in direct conflict with the above mentioned interests of research. The task of regulations, therefore, is to ensure the rights of patients to protection of their data against the interest of research in the widest possible unrestricted access to data.

Regarding the collection and dissemination of data, data can be abstractly classified in three different stages: at first, data are collected and stored by a particular local research group. Secondly, these data can be made accessible to a wider circle of external research groups and cooperating partners. Third, the data can be made available to a wider circle again by granting access rights on it to institutions not directly involved in the research consortium or possibly even to public access databases. With

each expansion of access rights, especially with that to international institutions beyond the jurisdiction of German or European law, it becomes more difficult to track down, prevent and penalise violations of patients' rights to confidential handling of their data.

Owing to the comprehensiveness of data in a sequenced genome, the probability of re-identification is increasing despite pseudonymization or anonymization (German Ethics Council 2010, 11 et seq.). As several recent publications illustrate, the risk of the later re-identification of patients or subjects is indeed real (Gymrek et al. 2013, Rodriguez et al. 2013). The risk of re-identification increases with the expansion of access rights. Therefore, there is a special requirement to regulate any forwarding of data from said first stage into the second and third stage, as well as the expansion of access rights between institutions and associations, and to ensure data security. Patient instruction and informed consent must duly indicate and explain the possible or planned forwarding of data and the risks associated with such disclosure.

III. Considerations on possible solutions

The following proposed solutions follow on from already-existing functions, expanding them, where this proves necessary, by the addition of new regulations and institutions. They build upon the organizational responsibility resting with Directors to define, implement, and supervise the Standards (SOP), on the function of the person entrusted with data protection at the Clinic (in the meaning of Art. 4g of the German Federal Data Protection Act), as well as on the decision-making process of the institution's independent ethics commission.

III.1 Pseudonymization and De-Pseudonymization of the Data

a) Pseudonymization by the Pseudonymization Service

The Pseudonymization Service internal to the Clinic issues a pseudonym (PSN) for those clinical data, patient data, and tissue samples which have been provided with a PID and passes on said data and tissue in pseudonymized form. This Service checks, before passing on these data and tissue samples, whether patient consent has been given in each case and sees to it that only that selection of data defined as necessary for each specific project is passed on to the internal research division. A record is

maintained about any such data transfer into the internal research division, so that the Clinic can comply with any rescission of consent on the part of any patient (type of data and samples, addressees of transferred data, and location/designation of databases).

b) Pseudonymization by the Attending Physician

The attending physician receives a PSN from the Pseudonymization Service whenever it is intended to pass over data from a patient into the sphere of research. All the data concerned must be marked by the physician with this PSN.

c) De-Pseudonymization by the Key-Holder

The key-holder has access to the key which matches up PID and PSN. When instructed to do so, the key-holder proceeds, in certain cases that must be clearly defined, to a de-pseudonymization of the data or samples. The instruction to do so must come from the Director of the clinical institution concerned or from a representative commissioned by this latter. For reasons connected with the legal right to refuse testimony, the key-holder should be a physician employed by the Clinic.

The key-holder is to proceed to a de-pseudonymization if:

1. Clinically relevant results have emerged which make a de-pseudonymization appear advisable on the grounds of continuing investigation of normal and additional medical findings.
2. Further patient data and clinical data from the specific medical-care context concerned are required for the purpose of research, or there exists the possibility of offering the patient a chance to participate in a new clinical study.
3. A de-pseudonymization due to rescission of consent on the part of the patient or of a person authorized to represent the patient, must result in the deleting of all the data concerned. In the case of such a rescission, notification thereof is submitted to the key-holder, who then issues the corresponding PSN to the Pseudonymization Service, so that the request of the affected patient can be complied with.

III.2 Access to and Forwarding of Data

a) In-Principle Approval of Data Access

No accessing of personal data shall take place except under supervision and limitation. An application for such access is made to the Ethics Commission and to the competent person-in-charge within the institution, and

must comply with the terms of the specific project it is required for or, prior to the commencement of such a project, with the framework protocols for same. Such an application must specify who shall enjoy access to which pseudonymized data, under which conditions, and for what period of time. Within the limits of the project, those with right of access to data must protect said data from being accessed by those without said right. The data made available must never be saved or stored on external or portable harddrives. Forwarding said data to unauthorized third parties is forbidden.

All those enjoying right of access – particularly the non-medical staff – are made aware of the sensitive nature of the datasets in question and undertake to sign a Code of Conduct for researchers and to adhere to the legally applicable data-protection guidelines. Employee training sessions should also be organized with signoffs by signature.

b) Access by Medical Staff

Access rights enjoyed by physicians in research projects differ depending upon whether the physician in question is also the attending physician of patients taking part in the study. An attending physician, for example, would have access to all clinical data, while non-attending physicians within the research project would have access only to the pseudonymized data.

c) Access by Non-Medical Staff

The non-medical staff who receive access rights to data include: system administrators, IT staff, and technical personnel; non-physician clinical staff; non-physicians taking part in interdisciplinary panels and committees, and non-physician research project staff. Access rights will vary according to function.

d) Forwarding Data from the Clinical Field into Research

No passing on of clinical data, likewise, shall take place except under supervision and limitation. Here too, an application must be made, in a specifically project-related manner either prior to the commencement of the project or in the form of follow-up research, to the Ethics Commission and to the competent person-in-charge within the institution. This application establishes which data attributes and human-genetic data-sets may be passed on to which databases. Whether the application is accepted is a decision for the Ethics Commission and the competent person-in-charge within the clinical institution. In compliance, however, with the legal principle of minimal use of personal data, no further data may be inspec-

ted along with those for which authorization has been granted. Nor is it permitted to make available outside the Clinic, for research purposes, the entire set of data contained in a patient's medical file.

d.1) Forwarding Data to a Local, Supervised Research Database

If arrangements are requested whereby complete packages of clinical data are to be placed, in pseudonymized form, at the disposal of a local research database, the project-specific use of the data is regulated by applying to the access rights the legal principle of "purpose limitation" or "earmarking" (see a) above).

It is vital that the question be addressed here of whether arrangements involving first the transfer of large packages of data out of the Clinic into the research sphere and then, only afterward, the "gradation" of the granting of rights of access to these data are, with respect to the protection of personal data, as effective as arrangements whereby the transfer of data is itself gradated.

Besides the passing on to supervised local databases three special cases must also be considered:

d.2) Forwarding Data to Supervised External Databases

If data attributes and human genetic data are transferred not only to local databases but also to supervised external databases, then the internal research group makes contractual arrangements regarding this with external cooperation partners. These arrangements guarantee, by including a concrete definition of mechanisms imposing sanctions in case of misuse, that the external partners shall observe the desired rules as regards handling the data. Such contractual arrangements with external databases must meet the data-protection standards applying to local research databases.

d.3) Forwarding Data to Public (Open-Access) Databases

Access to public databases is not limited. They harbour, therefore, greater risks for participants in medical studies. Care must be taken to restrict the scope of the personal and human genetic data which are allowed to be passed on to public databases such that re-identification of the participant in the study is as close as possible to entirely excluded (see, e.g., Document 2 in the Appendix: Example of Clinical Data Attributes and Selection of Human Genetic Data for the Purpose of Transfer to Open-Access Databases and Controlled-Access Databases: ICGC). In establishing which data attributes may and may not be passed on to public databases, it must be

borne in mind that the technical possibilities as regards such re-identification are increasing year by year.

d.4) Forwarding Data in the Case of Professional Journals

Professional journals often require that selected non-genetic data and human genetic data that have been used in the published medical analysis be made available to third parties so that the published results can be checked. These data are only examinable in a non-modifiable database subject to preliminary monitoring of access.

A scientist who wishes to examine and check the research results published in the journal must submit an application for data access, supported by the head of their institute. If the data are stored in a Heidelberg database (or in an associated database on whose body of rules the Heidelberg institutions can exert some influence), the application must include the purpose for which the data will be used and must also give the names of all further individuals (e.g. doctoral candidates) who are to be given access to these sets of data. This application is examined by a responsible person or group of people (generally, by the person who stored the sets of data in the first place). If the application is granted, the applicant receives access to the pseudonymized data for a fixed period of time (generally for a year; application for extension is possible).[6]

III.3 Establishment of a Data Committee

The Data Committee is intended as an advisory committee in which interdisciplinary specialist knowledge is represented from the fields of medicine, bioinformatics, molecular biology, ethics, and the legal sciences (with special emphasis on data protection). The members are appointed by the Directors of the participating institutions as their representatives. The Data Committee should be established at the key-holder institution. In disputed cases where no decision can be arrived at in the usual way, the committee will be advised by the persons-in-charge of the various departments. Examples of such disputable cases might, for example, include: the determination of attributes for the forwarding of data; the approval of the

[6] The ICGC has formulated the following four conditions for requests for access to data:
1. Description, in writing, of the purpose of research,
2. A solemn assurance that no attempt to identify or contact study-participants will be made,
3. An agreement not to pass on the data received,
4. A description of the plans for how the data received can be deleted and destroyed once they are no longer needed.

passing on of data to specific research databases; the granting of rights of access on the basis of research applications; and the establishment and updating of SOPs.

Furthermore, the Data Committee can also operate in an advisory capacity in cases where requests are made to undertake research in collaboration with external research groups, in the course of which personal data would be passed on to external databases.

IV. Implementation in Heidelberg

Since the publication of the first edition of the EURAT position paper, the discussion of its data protection guidelines has been given much consideration by the DKFZ. EURAT members played an advisory role in this process. The recommendations have now been implemented at the DKFZ in form of a Data Security Concept for Personal Data in Cancer Research (DSC), Data Transfer Agreements (DTA) and Data Access Committees (DACO).

Data Security Concept for Personal Data in Cancer Research

Translational research is particularly concerned with research using clinical data from humans. Therefore, data protection requirements are necessary here which do not apply to basic research to the same extent. This is particularly true for genomic data, which on the one hand are personal data, and on the other hand may be of significance for genetically related individuals. In order to account for the specific nature of genomic data, a Data Security Concept for Personal Data in Cancer Research (DSC) was developed at the DKFZ, with the aim of ensuring protection and confidentiality of personal data without hindering research disproportionately (http://www.uni-heidelberg.de/totalsequenzierung/informationen/datenschutz.html). The DSC defines and regulates technical and organisational data protection measures for scientific projects with personal data at the DKFZ and applies to all DKFZ employees working with personal data.

The aim of the DSC is to identify the level of protection required for research with personal data in order to adequately facilitate that protection by applying specific regulations. This process is informed by concepts already developed in the field of risk management. At the core of the DSC stand three security classes, which require different protection measures.

1) A “normal” protection level is required if a risk exists which could

impair the respective persons with regard to their social or economic circumstances.

2) A “high” protection level is required if the risk of a significant impairment exists.
3) A “very high” protection level is required for data if a risk to life or to the personal freedom of the person concerned exists, and data protection is absolutely mandatory.

For every data pool a risk assessment with regard to defined risk events (e.g., data access by unauthorized persons) is carried out and the potential risk is determined. Using a risk matrix, the probability of occurrence (unlikely; possible; likely) and the degree of adverse effects (insignificant; moderate; severe) of each risk event are combined to produce a risk value (2-4 low risk; 6-12 moderate risk; >12 high risk).

Probability of occurrence	Damage effects		
	insignificant (=2)	moderate (=4)	severe (=6)
unlikely (=1)	2	4	6
possible (=2)	4	8	12
likely (=3)	6	12	18

Risk matrix for determination of risk measurement value (probability of occurrence x damage effects)

Based on the risk value, each data set is assigned to one of the three security classes. Because each security class corresponds with certain technical or organisational human resources related measures (including controls on physical and electronic access and storage media), distinct protection measures are ensured.

With the DSC, the DKFZ meets the obligation to protect both new data and data already existing. The DSC will be contractually obligating for DKFZ staff. The leaders of the institute must provide regular training for the staff to ensure that researchers in scientific practice act according to the code. They must also ensure that the use of shared data and tissue samples complies with measures and guidelines equivalent to those that are formulated in this code. With the publication of the DSC, the DKFZ has taken a significant step towards meeting transparency requirements.

Data Transfer Agreement

A Data Transfer Agreement (DTA) is a standard contract that a research institution, in this case the DKFZ, uses to regulate data sharing with other research institutions. The exchange of biomedical data is important for research, yet simultaneously bears risks to the security and confidentiality of patients' or study participants' data. The DTA is used to address this challenge by imposing certain obligations regarding security measures and the engagement with data on the institution receiving data from the DKFZ for purposes of research. The EURAT position paper (Code, II. Guidelines; Section 8) requires research institutes, when sharing and exchanging data, to work toward ensuring that cooperation partners apply security and data-protection rules similar to those laid out by EURAT for the Heidelberg research institutes regarding the handling of shared data.

Data Access Committee

A Data Access Committee (DACO) makes decisions about further sharing of data for subsequent research projects, where data from the security classes "high" and "very high" are exchanged with other organizations using a DTA. The DACO is a compulsory measure for genome sequencing data in particular, where storage of such data in international databases following a "controlled access" model is intended, since these databases require a DACO (e.g., European Genome-Phenome Archive).

Appendices re: Reference Points for a Data Protection Regulation

1. Definitions

1.1 Personal Data

Personal data are individual details regarding the personal or material circumstances of certain determined or determinable individuals, along with their family, companions and other significant others, which may become known in connection with the care of the patient. (Following from Art. 43 Sec. 4 LKHG Baden-Württemberg, Art. 3 Sec. 1 BDSG/ LDSG, Art. 42a BDSG No. 2-4, Art. 3 Sec. 9 BDSG, Art. 33 LDSG)

1.1.1 Data Attributes

a) Patient data (= IDAT)
Patient data are data that are made available by the patient. They make identification

of the patient possible and are independent of medical examinations (family name, first name, former names, day, month and year of birth, sex, address at the time of registration at the institution [postcode and city or district code, street, house-number], month and year of the tumor diagnosis, month and year of death, National Insurance Number, if available in Baden-Württemberg). (Art. 3 Sec. 1 LkrebsRG)

b) Clinical data (= MDAT)
Clinical data are data which arise in the context of the medical diagnosis and therapy (month and year of birth, sex, postcode or district code, month and year of tumor diagnosis, month and year of death, tumor diagnosis, stage, reason for tumor diagnosis, earlier tumor diagnoses, confirmatory diagnosis, type of therapy, cause of death) along with other details regarding the diagnosis, therapy and the course of cancers. (Art. 3 Sec. 4 LkrebsRG)
c) Data of Notifying Party
Source of notification (Surname, first name of notifying physician, address of the notifying institution with postcode, city, street, house number, telephone number at time of notification), time of notification, reference number, transaction number, note of patient's having been informed of their right to rescission. (Art. 3 Sec. 3 LKrebsRG)

1.1.2 Human genetic data

Human genetic data are acquired by molecular-biological and bio-informatic methods from bio-material (primary data, sequence data, result data, OMICS data).

- *Comprehensive sequence data: sum of all the sequence data forming the result of the primary analysis and not yet evaluated. These make possible a reidentification of the individual concerned.*
- *Result data: OMICS data acquired from the primary data along with the genetic findings and research results acquired from the OMICS data, which contain somatic mutations and germline mutations.*
  - *Research results: results relevant to research which, either in themselves or in association with other personal data, make possible a re-identification.*
  - *Genetic findings (=results of examinations): Medical and health-relevant findings which contain manifold pieces of sensitive information about the causes of diseases that have already manifested themselves and about tendencies thereto.*

1.2 Patient Identifiers (PID)

A patient identifier (PID) is something that serves to identify the patient. It consists of a clinic-internal number which makes it possible to trace back tissue samples and data to a particular patient. Thus, each patient file has its own PID. A PID is not a pseudonym, since it allows everyone who enjoys the right of access to it within the

context of the clinic and its care to infer from it the real name of the patient and, where required, the whole corresponding patient file.

1.3 Pseudonym (PSN)

A pseudonym (PSN) is an indicator which assigns a set of data to an individual person without betraying their identity, or that at least makes the determination of the identity of the person in question significantly harder (Art. 3 Sec. 6a BDSG, Art. 3 Sec. 7 LDSG). This indicator should be a randomly generated letternumber combination. The PSN may not be a consecutive number. The PSN prevents any direct inference to the actual name of a patient. It means that patient data and tissue samples can be used for research purposes without (in contrast to anonymized data) re-identification having been rendered absolutely impossible, should one be needed. A key-holder can, in certain cases that need to be clearly defined, proceed, when instructed, to a depseudonymization, which involves converting the PSN back to the PID or the patient name.

2. Example of Clinical Data Attributes and Selection of Human Genetic Data for the Purpose of Transfer to Open-Access Databases and Controlled-Access Databases: ICGC

ICGC Open Access Datasets

- *Cancer pathology*
  - *Histologic type of subtype*
  - *Histologic nuclear grade*
- *Patient/person*
  - *Gender*
  - *Age (single category for ages over 89)*
  - *Vital status*
  - *Age at last follow-up (single category for ages over 89)*
  - *Survival time*
  - *Relapse type*
  - *Relapse interval*
  - *Disease status at last follow-up*
  - *Interval from primary diagnosis to last follow-up*
- *Gene expression (normalized)*
- *DNA methylation*
- *Genotype frequencies*
- *Computed copy numbers and loss of heterozygosity*
- *Newly discovered somatic variants*

ICGC Controlled Access Datasets

- *Detailed Phenotype and Outcome Data*
  - *Region of residence*
  - *Risk factors*
  - *Examination*
  - *Surgery*
  - *Drugs*
  - *Radiation*
  - *Sample*
  - *Slide*
  - *Specific histological features*
  - *Analyte*
  - *Aliquot*
  - *Donor notes*
- *Gene Expression (probe-level data)*
- *Raw genotype calls*
- *Gene-sample identifier links*
- *Genome sequence files*

Fig: Data Categories and Access Restrictions (see ICGC, Updates to Goals, Structure Policies and Guidelines, Section E.1, December 2012, p. 7. See also ICGC Data Submission Manual, Document Version 0.6a, September 2011, p. 41ff.)

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