Big Data

Looking at the whole genome raises new questions

Research laboratories around the world have long focused on studying the whole human genome. It is hoped that knowing the whole human genome will improve diagnostics and enable more specific therapies. Although genome analysis has not yet reached routine clinical application, whole genome sequencing has already raised many ethical and legal issues - for researchers, physicians and patients.

The “Cornerstones for an ethically and legally informed practice of whole genome sequencing: code of conduct and patient consent models” provide possible answers. The cornerstones are templates for informing and educating patients about practical healthcare research and scientific research, a research codex and a list of theoretical problems that seek to strike a balance between patient well-being, patient access to information and patient participation, and freedom of research and clinical progress. This Heidelberg position paper is considered ground-breaking for Germany; the German Research Foundation (DFG) has recommended that it be used for orientation (1st August 2016).

You quickly end up with an ethical dilemma

It was the case of a seriously ill patient with a brain tumour that motivated us to write the paper. The patient was also part of an international clinical study,” says Prof. Dr. Eva Winkler, physician, ethicist and spokesperson of the interdisciplinary project group EURAT at the University of Heidelberg (“Ethical and Legal Aspects of Genome Sequencing of the Human Genome”), which has published the cornerstones.

What happens when researchers from a research institute sequence a patient's tumour genome and discover a mutation (accidentally or one that is closely related to the issue they are investigating) that is typical for people who lack gene repair enzymes and are therefore at risk of developing tumours? Radiation and chemotherapy harm more than help such cancer patients.

The researchers suddenly find themselves in an ethical dilemma. Are they obliged to pass on this possibly useful information to the treating physicians? Are they even allowed to do so? “That was the starting point for the cornerstones,” says Eva Winkler. Actually, cases like this should not occur because in research, patient samples are one-fold and even two-fold pseudonymised, sometimes also anonymised, and cannot simply be traced back. This is for data protection reasons. “At the moment, research and clinical application are like two different plants that work separately and according to different rules,” explains Eva Winkler. It is important to know that the sequencing of a person’s whole genome is not done at a single institute or clinic, but rather at different clinical and research institutes.

Equivalent to the Hippocratic Oath

Researchers who are investigating the whole genome of an individual might come across medically relevant information that they were not primarily looking for. Researchers therefore bear new kinds of responsibility in dealing with the knowledge they acquire about patients and their families. The cornerstones, or code of conduct, can be seen as equivalent to the Hippocratic Oath taken by physicians, which is also important as far as employment law is concerned. The code of
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Institutions where researchers are entrusted with the genomic data of patients and volunteers need to take steps to ensure that data misuse is unlikely. The

DKFZ recently adopted a “Data Security Concept for Personal Data in Cancer Research” for working with personal data, particularly in the case of research

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Patient privacy and patient participation in decision-making is important

Prof. Winkler also points out that big data is expected to bring huge medical benefits. For this reason, great care must be taken to protect patient privacy and

patient involvement in deciding right from the start what happens with the data acquired. Honesty with patients is essential, including making them aware that

the total anonymisation of genomic data is not possible (see Gymrek). When a patient is given information, he or she should be involved in the decision as to

whether the risk profile is still reason enough to support research using his or her tissue or data.

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tumours, which is why the tumour genome of young patients or of patients with an unusual disease course is usually sequenced. “Today,” Winkler says, “we

does not take into account a patient’s right to not know.

number of genetic diseases (56). The patient is informed about this prior to the examination. However, this practice, which is also a matter of dispute in the USA,

does not take into account a patient’s right to not know. i.e. giving the patient the freedom to choose whether he/she wants to

know or not.

The “Cornerstones for an ethically and legally informed practice of whole genome sequencing” were published for the first time in 2013 and were followed by an

expanded version in 2015. They have set in motion a debate about ethical and legal issues relating to whole genome sequencing. There is no consensus on how

best to deal with additional information arising from genome-wide analyses in research and diagnosis. Solutions that have been put forward range from the

American College of Medical Genetics and Genomics’ (ACMG) recommendation for formulating obligations for disclosure guided by so-called “positive lists” to

disclosing nothing whatsoever to the patient about additional findings. According to the ACMG’s recommendation, whole genome analysis is also focused on a

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Originally, the experts from Heidelberg also favoured a positive list of important treatable diseases. However, they decided against this in favour of orienting

themselves towards current practice in human genetic diagnostics “not to take too broad a look into the genome” so as not to leave room for any eventuality.

The debate into these issues is still ongoing as Eva Winkler observed at this year’s Annual Meeting of Human Geneticists in a session called “My genome is mine”.

“In oncology, genome sequencing has become an established routine through so-called molecular tumour boards,” says Eva Winkler. In addition to her role as

spokesperson for EURAT, Eva Winkler is a senior physician in the Department of Medical Oncology at the National Center for Tumour Diseases at the University of

Heidelberg. She points out that physicians working in the treatment and care of oncology patients are usually very interested in the molecular makeup of

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Patient statement of consent

The cornerstones aim to counteract such dilemmas with patient statements [see Winkler] in which the patients provide consent as to whether they want to be

informed about an additional, treatable disease or not. The patient can also choose to be informed in the event that the chance find suggests the presence of a

non-treatable disease. EURAT spokesperson Winkler does not see this as the definitive solution to the problem. She does however see it as a way to leave the

doctor open for both the possibility of feedback as well as the patient’s right not to know, i.e. giving the patient the freedom to choose whether he/she wants to

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comparison group, who were treated on the basis of individual molecular recommendations and whose life expectancy was promising.

Many international data needed for evidence validation

“Meanwhile, molecular diagnostics has changed the design of clinical studies,” says Eva Winkler. Basket studies include patients with a specific mutation across different cancers. Winkler believes that although the first step involved in the translation of information into clinical trials is often successful, the second step, i.e. comparing genome diagnostics data with data from conventional diagnostics procedures, will differ in future from current practices as the questions derived from molecular diagnostics will become more and more specific. Nevertheless, evidence validation must go beyond the individual case. As large-scale studies in their present form will no longer be carried out in the future, Winkler points out that researchers will rely on international data on smaller disease subgroups, and that to make this work, a great deal of brainpower, money and structure formation needs to be invested in such adaptive study designs.

Further reading: