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The Heidelberg practice of whole-genome sequencing

After two years' work, scientists from Heidelberg have now presented their opinion on the ethical and legal consequences of the total sequencing of the human genome. The paper presents principles and practical recommendations aimed at maintaining the balance between the wellbeing and interests of patients on the one hand and the freedom of research and clinical progress on the other.

Experts believe that the total sequencing of the human genome will become standard practice in diagnostics in the foreseeable future. It is increasingly being assessed as a diagnostic tool at the University Hospital of Heidelberg and the German Cancer Research Center (DKFZ). Whole-genome analysis is used for the diagnosis of rare genetic diseases at the Institute of Human Genetics (Director: Prof. Dr. Claus Bartram). The PedBrain-Tumour research consortium (part of the International Cancer Genome Consortium) led by Prof. Dr. Peter Lichter (DKFZ) and Prof. Dr. Roland Eils (DKFZ and University of Heidelberg) is focussed on the systematic analysis of the genomes of children with brain tumours and the results are taken into account in the formulation of therapeutic recommendations. A research group led by Dr. Jan Korbel at the European Molecular Biology Laboratory (EMBL) also uses whole-genome sequencing for the diagnosis of prostate cancer and lymphoma.

Prof. Dr. Dr. h.c. Otmar Wiestler, chairman of the DKFZ, defined the sequencing of the entire DNA of all tumours of all patients treated at the National Centre for Tumour Diseases as a major objective of the centre. Information derived from genome analyses is already being used for planning the customised treatment of cancer patients using chemotherapeutic drugs and biopharmaceuticals.

Unclarified ethical and legal questions

Whole-genome sequencing raises ethical and legal questions that go far beyond the framework of currently used genetic diagnostics. All medical interventions require patients to give their informed consent. However, this is no longer possible to the same extent with whole-genome sequencing. It is impossible to discuss with a patient the information obtained from his/her blood sample or tumour biopsy material and the potential relevance of the large number of genetic modifications for a disease within the relatively limited period of time available for the purpose.

Encrypting the results is an issue that is of crucial importance for the protection of data and personal rights, as the total sequencing of a person's genome enables a person to be reliably identified and also because the genome analysis involves a large number of people, including non-medical scientists. A set of regulations needs to be agreed upon and put in place.

Members of the EURAT project group presenting their opinion on the ethical and legal consequences of whole-genome sequencing at a press conference. From the left: Prof. Dr. Klaus Tanner, Prof. Dr. Claus R. Bartram, Prof. Dr. Paul Kirchhof, Prof. Dr. Wolfgang Schluchter and Prof. Dr. Peter Lichter.

The way to deal with incidental findings that inevitably arise from the total sequencing and analysis of a human genome needs to be regulated. Although these and other issues related to the total sequencing of the human genome have been discussed by the German Ethics Council and the National Academy of Sciences Leopoldina, they still require further clarification.

To provide clarity, Heidelberg scientists established the cooperative interdisciplinary project “EURAT – ethical and legal aspects of whole-genome sequencing” two years ago (see "The Eurat project at the Marsilius Kolleg in Heidelberg"; link on the right-hand side). The project group brings together 13 well-known researchers from the University of Heidelberg, DKFZ, EMBL, the Max Planck Institute for Comparative Public Law and International Law and the Research Center for Health Economics at the University of Hanover, all experts in various fields including human genetics, bioinformatics, genome sequencing and tumour genetics, oncology, pathology and biobanking, ethics and theology, constitutional law and international law as well as health economy. Prof. Dr. Klaus Tanner, chair of Systematic Theology/Ethics at the Scientific-Theological Seminary at the University of Heidelberg is the chairperson of EURAT.

In June 2013, the EURAT project published its opinion on the ethical and legal consequences of the total sequencing of the human genome. The opinion not only addressed individual issues, but also formulated principles and proposed solutions on all central aspects in the fields of ethics, law, research, medicine and economy. These were published as “Eckpunkte für eine Heidelberger Praxis der Ganzgenomsequenzierung” (Key aspects of the Heidelberg practice of whole-genome sequencing). The opinion can be downloaded as a PDF file from the link in the top right-hand corner (only available in German). Below is a summary of a few, but not all, of the issues addressed in the document.

Prof. Dr. Klaus Tanner, spokesperson of the EURAT project group

Code for non-medical scientists

The Heidelberg scientists stress that it is ethically necessary to use genome research for obtaining new insights that can be directed towards the treatment of patients. Due to their knowledge of human genetics, researchers involved in whole-genome sequencing now face new kinds of responsibility. They not only have the duty to inform the scientific community and the public about their research, the methods used, the objectives and results, but they also have an obligation towards the people who have been examined and their families, an obligation which involves using the data gained for the benefit of such people as well as protecting them against unauthorised knowledge.

This obligation also applies to people with whom the scientist and his/her team have no direct connection; in contrast to treating doctors, this obligation cannot be derived from Medical Law. The EURAT project group has established a number of "key aspects" that amount to a code for non-medical scientists involved in whole-genome sequencing, in particular the sequencing of patient genomes. This code can be seen as a kind of equivalent to the Hippocratic oath taken by doctors. It contains – in addition to general ethical principles in accordance with which the researchers must act (e.g. respect for individuals, self-determination of patients, the prevention of harm, good scientific practice and the protection of future generations) – detailed and binding guidelines for action.

In addition, the project group also agreed on patient information and declarations of consent for this new type of research, which can be used as references and models: (i) for healthcare research relating to the usability of genome-wide analyses for the diagnosis of disease; (ii) for genome

sequencing in cancer research. The documents also come with case studies and comprehensive explanations. The problem of data and information protection is addressed and detailed solutions are presented.

Discussion on how to deal with incidental findings

Samples required for whole-genome sequencing are now becoming smaller and smaller.
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One debate that has not yet reached a conclusion is how to deal with incidental findings. This involves findings that doctors and researchers are not specifically looking for. In whole-genome sequencing, any individual finding that goes beyond the issue investigated remains incidental, but such findings are nevertheless bound to occur. However, doctors are unable, due to the time constraints mentioned above, to provide patients with details about the whole range of findings. This would mean discussing the importance and effect of 6,000 mutations and at least 3,000 genetic diseases.

The way this potentially medically relevant surplus information is to be dealt with is a matter of international dispute. The ACMG (American College of Medical Genetics and Genomics) recently required patients to be informed against their will about any genetic findings that appear on so-called positive lists. The EURAT project group rejects this. Instead, it recommends dealing with incidental findings on the basis of specific projects and according to the assessment of the treating doctor.

At present, whole-genome sequencing is a pre-diagnostic and uncertified method, which is why the findings need to be validated by a certified diagnostics laboratory before they are communicated to the patient. In Heidelberg, an interdisciplinary advisory board, along with an experience registry, will provide support in the forming of judgements relating to the communication of incidental findings to patients.

A delicate situation – genome analyses of people who are unable to give their consent

The situation is particularly delicate with regard to investigations involving people who are unable to give their consent. Basically, the investigation is justified if it is considered to be of benefit to the

person who is unable to give his/her consent; this is similar to a medical examination with a therapeutic goal. But drawing a line between therapeutic and non-therapeutic goals – research for the benefit of patients and research for the benefit of science – is often impossible. However, research has the duty to also include people who are unable to give their consent, as certain age groups would otherwise remain isolated from medical research to a greater extent than has already been the case over many years with the attendant negative consequences.

A genomic analysis conducted for the benefit of family members rather than for the benefit of the person examined is highly controversial from a legal point of view and ethically only justified in exceptional cases. Children are part of the group of people who are unable to give their consent. Incidental findings must not be disclosed if a child will only develop a certain disease in adulthood and for which therapies are not available in childhood. This requirement was agreed by the EURAT group in accordance with a diagnostics regulation stipulated by the Gene Diagnostics Law. Whole-genome sequencing in children and other people who are unable to give their consent requires the creation of a specific process of informed consent which also involves the person in question according to his/her stage of understanding. Written documentation of the consent process is expected to give children the right to exercise the right to retract once they reach adulthood.

The spokesperson of the EURAT project, Prof. Tanner, writes in the forward of the "key aspects" paper that the Heidelberg practice of whole-genome sequencing is based on the lead concept of encouraging responsible action and strengthening the fiduciary action of those who are driving forward whole-genome sequencing at the boundary between basic research and its application in patient care. This makes the capacity of self-regulation of doctors and researchers a central issue in the debate, and moves away from further governmental regulations. These "key aspects" have the potential to be used as a model for the regulations of other institutions involved in the total sequencing of the human genome.

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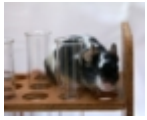

Progress expands bioethical boundaries