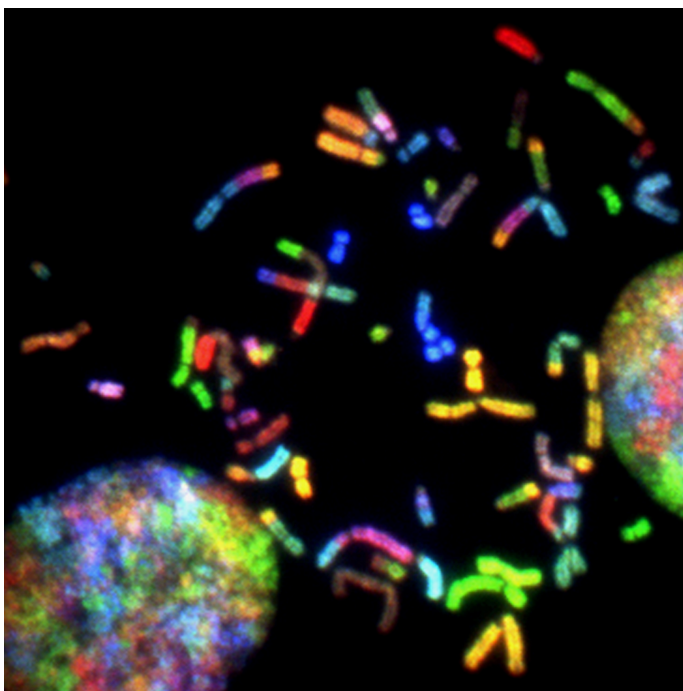


Genetic diagnostics: technology reaches the limits of what is medically reasonable

Rapid progress in sequencing technologies is poised to set the imagination of biomedical researchers on fire. Experts now believe that progress is about to make possible what seemed to be utopian a few years ago – it seems likely that it will soon be possible to sequence the human genome in only a few minutes and store and automatically analyse it using tiny automates. However, is everything that is technically feasible also reasonable?

While basic researchers and technology providers radiate confidence, human geneticists and clinicians are tending to attenuate expectations raised by genomic medicine. The road from genetic/genomic diagnostics into clinical routine is a long one with the one exception to the rule being commercial genetic tests for monogenic diseases. In the foreseeable future, the predictive genetic testing of common diseases will continue to make no medical sense as well as being meaningless.

It's the regulation, stupid!



Symbolic image: The function of only half of the human genome is known. Less than two percent of the DNA (exome) code for proteins.
© National Cancer Institute | unsplash.com

Recent publications by the international genome research community (<https://www.gesundheitsindustrie-bw.de>, www.encodeproject.org/ENCODE/ and www.1000genomes.org/) have disillusioned many researchers. Scientists have discovered that the human genome harbours around four million gene switches in DNA regions that were previously dismissed as “junk”. It is becoming increasingly clear that the 22,000 or so human genes underlie far more complex regulation processes than previously thought. The function of only half of the human genome is known. Less than two percent of the DNA (exome) code for proteins; the remaining and seemingly useless amount of DNA is vast and largely unknown territory.

What implications does this have for genetic diagnostics? Independent experts agree that the application of genetic diagnostics in clinical routine is a pipe dream. As things stand at the moment, genetic diagnostics only makes medical sense for the diagnosis of monogenic diseases and pharmacokinetic applications; genetic diagnostic testing is a long way from becoming standard practice (Harper, A.).

Genome sequencing limited to basic research

Genome sequencing is currently largely limited to basic research. Speaking at the public hearing of the German Ethics Council in March 2012, Karl J. Lackner, director of the Institute of Clinical Chemistry and Laboratory Medicine at the University of Mainz, expressed the opinion that the untargeted sequencing of the entire genome does not make any medical sense at all. “As long as we do not understand how certain genes affect a person’s susceptibility to a certain disease, it is of little use knowing that he or she has a moderately increased genetic disease risk.”

The human geneticist Karsten Held believes that the same applies to prenatal diagnostics: “The higher the resolution, the more nightmarish it can be for a genetic counsellor to deal with. The level we are referring to is not the issue. It will always be

a problem that the more information we have, the more difficult it becomes to communicate it.”

Technological developments at record speed

All experts agree that sequencing technologies have developed at a revolutionary speed over the last five years. The “\$1000 genome” seems just to be around the corner and, according to experts, the trend towards further miniaturisation and cost degression will continue.

Next-generation sequencing (NGS) is currently replacing Frederick Sanger’s method of DNA sequencing developed in the 1980s. Basically, high-throughput DNA analysis methods enable miniaturisation and optimisation, which enables individual sequencing reactions to be carried out in a highly parallel manner. At present, 10^7 to 10^{10} nucleotides can be sequenced per day and system, surpassing the sequencing capacity of existing technologies by several magnitudes.

State-of-the-art NGS systems are able to sequence and compare four human genomes within two weeks, not including data analysis. Experts believe that a 100-fold per-base coverage is required to provide a high enough level of precision. This in turn reduces the throughput rate. The NGS market is currently dominated by three companies offering different though basically comparable technologies. The most innovative approach is single-molecule sequencing.

Norwegian pilot project: genome-wide tumour analysis

State-of-the-art sequencing technologies are already playing a major role in basic research and help to explain the pathogenesis of diseases on the molecular level as well as detecting microbes such as those that caused the EHEC epidemics in Germany in summer 2011. Oncology centres in the USA are looking into several hundred tumour genes in their effort to correlate genomics with therapy response. And yet another example: a pilot programme was recently started in Norway that aims to bring next-generation DNA sequencing into the country’s national healthcare system to personalise cancer treatments and increase the chances of curing cancer (Theurillat, Jean-Philippe).

That said, NGS technologies still suffer from one major drawback in that they produce high false-positive rates (Timmermann, Bernd). All whole-genome sequencers produce their own specific errors. Although these errors are difficult to quantify, their number (error rates of up to one percent) is nevertheless too high for them to be used for medical purposes.

Hope for monogenetic diseases

Experts believe that genome sequencing can have far-reaching consequences for research into and treatment of monogenic diseases. They believe that the determination of the molecular causes of monogenic defects (e.g. Neuromics project at the University of Tübingen) will become easier and cheaper. Modifications in up to two thirds of all human genes can lead to monogenic diseases.

In contrast to multifactorial diseases, monogenic diseases are relatively rare. However, they affect a large number of people worldwide, as Hans-Hilger Ropers from the Max Planck Institute for Molecular Genetics explains. Three to four percent of all newborn babies have a monogenic disease. Around 7000 monogenic diseases have been studied in detail; they are caused by a single modification in a single gene (of a total of 3000 genes known to cause monogenic disease), and are difficult to detect. It is assumed that between 33 and 50% of all monogenic diseases are known. Treatment (e.g. combination of diet and medication) is available for 500 of them.

Brave new world in the USA

A universal heterozygote screening test for 448 autosomal recessive diseases can be bought in the USA for the equivalent of €400. It is not approved for sale in Germany. This test is specifically aimed at couples who want to exclude the possibility of being carriers of a rare but severe hereditary disease and potentially transferring this gene to their children. Relevant medical associations in Germany reject the test.

Ethical issues related to genetic diagnostics become most obvious when dealing with monogenic diseases. There is a high chance of a monogenic disease being passed on during pregnancy and leading to many serious disorders. Moreover, monogenic diseases sometimes run in families and the quality of life of the sufferers is significantly reduced. The ethics associated with the testing of individuals for monogenic diseases was also discussed at a public debate held at the Berlin-Brandenburg Academy of Sciences in September 2012.

Absolutely necessary: the counselling – diagnostics – counselling triad

Human geneticists like Karsten R. Held, the medical director of the Centre of Human Genetics in Hamburg, only consider

genetic diagnostics acceptable on condition that it is an integral part of genetic counselling, which means that advice needs to be given before and after diagnosis. The reason for this is that the increasing sensitivity of the tests is leading to a higher number of erroneous diagnoses and makes the interpretation of data more difficult. Held further highlights that progress in the ability to predict diseases will be fostered by epigenetic analyses and the identification of new biomarkers which not only provide information about a person's genetic make-up, but to an even greater extent on the activity of the genes.

Experts therefore believe that the use of NGS is only reasonable when carried out and discussed in close cooperation with doctors who have special knowledge of human diseases and syndromes. This may prevent patients with a rare disease from having to visit one doctor after another or at least cut back on the number of visits to the doctor.

With regard to monogenic diseases there is always the question as to why one should try to diagnose a disease when causal therapies are (still) lacking for most such diseases. Huntington's disease, an autosomal dominant monogenic disease for which no cure is available, has raised several ethical issues, particularly with regard to the application of genetic tests for diagnosing the disease. For example, German law prohibits prenatal genetic testing for diseases such as Huntington's that manifest themselves only in adulthood. Familial (hereditary) breast cancer is another disease that manifests itself in adulthood.

According to experts, successful prediction of diseases using genetic tests is only achieved in rare cases, for example those in which only one or a few gene variants have an impact on disease predisposition. They believe that predictive genetic diagnostics is only possible for those psychiatric diseases that are linked to copy number variations (CNVs), which are quite rare. Examples of such diseases include early-onset Alzheimer's where three genes have been shown to have a major effect on the risk of people developing the disease in their 30s or 40s, in people at risk of developing diabetes due to mutations in the insulin receptor gene and in people at risk of suffering myocardial infarction due to mutations in genes that code for certain enzymes.

Impossible: predicting the risk of contracting common diseases

The results obtained by the Encode and 1000 Genome projects are a real goldmine for scientists. However, the data are a bitter disappointment for those who believe that genetic analyses are able to predict susceptibility to common diseases such as diabetes, Alzheimer's or cancer. The data show unambiguously that it is impossible to deduce a reasonable risk for developing multifactorial diseases from the human genome.

Numerous scientific studies have come up with similar results (e.g. Roberts, Nicholas J.). Speaking at the public hearing of the German Ethics Council on 3rd May 2012, Thomas Wienker from the Max Planck Institute for Molecular Medicine summarised the outcome of such hallmark studies as follows: "The information that can be deduced from the genetic architecture of many multifactorial diseases is extremely sobering."

Genetic heterogeneity slows down euphoria

The causes of genetic disease can relate to alterations in a large number of gene loci and alleles, all of which can have different effects. According to experts, many people have underestimated this heterogeneity, especially as far as common diseases are concerned. Every individual differs from another in around one thousandth (around 4 million bp) of his or her genome. That said, a person suffering from a disease might only differ from a healthy person in one mutation. The targeted search for such mutations requires access to the information deduced from the genomes of millions of individuals whose diseases would have to be known. In addition, complex diseases can arise as a result of interactions between a person's genes and the environment; however, these interactions are usually unknown or not quantified to the degree that would be necessary to predict susceptibility to disease.

Efforts undertaken by the German National Cancer Plan to develop criteria and conditions that would allow the risk-adapted prevention of diseases based on new genetic risk factors are less ambitious but potentially more successful. The goal of these approaches is to protect patients and people seeking advice against useless and unfounded predictive genetic analyses as well as strengthening cancer prevention efforts (Schmutzler, R. et al.).

Genetic counsellors are urgently needed

The quantity of data related to the human genome is increasing at enormous speed. And this also generates a greater demand for genetic counselling. Or to put it another way: the increasing application of high-tech medicine also requires paid counsellors. In Germany, prenatal diagnostics has been integrated into the Genetic Diagnostic Act. This has serious consequences; far too few human genetics specialists or doctors with in-depth genetic expertise are available to deal with the people undergoing diagnostic testing. It is estimated that around 500,000 prenatal genetic examinations and disease risk assessments are carried out in Germany per year, which means that around one million genetic counselling sessions need to be offered, one prior to and one after the examination. Up until now, human genetics specialists have provided genetic counselling to around 50,000 people per year.

In order to increase the number of human genetics specialists, the German government gave doctors the possibility to attend a course (72 training hours) to undergo further training in genetic counselling (Schwerdtfeger, p. 56, in: Duttge et al.). It did not come as a surprise that the highly controversial Genetic Diagnostics Act was once again heavily criticised. The German Medical Association and the Association of German Human Geneticists called the new regulation "the worst ever legal error", an "inflationary medical service designed by politicians without any consideration for patients and doctors" (Schulze, Bernt).

The law needs to be revised

The German Ethics Council has announced that a comprehensive report on genetic diagnostics is to be published in 2013 and believes that this report will fuel the discussion on genetic testing. In fact, the vast majority of experts believe that the German Genetic Diagnostics Act needs to be amended. Many people have criticised the fact that research that leads to huge quantities of genetic information does not fall under the scope of this law. Another controversial aspect relates to the information study volunteers need to be given before and after testing. Calls for guidelines for researchers, clinicians and patients are getting louder.

In addition to medically questionable lifestyle genetic tests (so-called direct-to-consumer tests), the economic dimension of genetic diagnostics is another controversial issue. So for example the question as to whether insurance companies should pay for genome sequencing services in cases when lifestyle changes might prevent or improve the diagnosed or predicted condition. The Netherlands are evaluating the introduction of a targeted exome test (which comprises 1200 genes) to assess the disease risk of seriously ill children.

Up until the end of the year, the interdisciplinary Genetic Diagnostic Commission will provide information about the current price of genome sequencing. Human geneticists are keen to find out about the counselling requirements associated with newborn hearing disorder screening, which has recently been implemented in all German states. Approximately 50% of all hearing disorders in children have a genetic basis (Henn, in: Duttge et al., p. 27).

And there is yet another unsolved serious problem that needs to be dealt with, namely the problem of quality assurance. A survey on human molecular genetic testing laboratories published in 2012 (Berwouts, S. et al.) concluded that the quality practices vary widely in European genetic testing laboratories and that this is associated with potential risks for patients as well as compromising patient care and treatment. Human geneticists are also calling for measures that ensure the quality of genetic counselling (Henn, in Duttge et al., p. 30) and for the approval of genetic tests that enable people who have been tested to take the necessary steps to improve their health.

Recent genome research results might have disproved the dogma of the exceptionality of genes. However, the bioethical debate needs to be continued as it is governments' responsibility to regulate the use of the flood of genetic data while respecting basic individual rights. However, it is safe to assume that if something is technically feasible, it will be put into practice – now and in the future; the detailed knowledge of a person's genome will not be an exception to this rule.

Publications:

Abecasis, GR: The 1000 Genomes Project Consortium, An integrated map of genetic variation from 1,092 human genomes, *Nature*, 491, 1st November 2012, doi: 10.1038/nature11632.

Berwouts, S. et al.: Quality assurance practices in Europe: a survey of molecular genetic testing laboratories, *European Journal of Human Genetics* (2012), 20, p. 118-1126, doi: 10.1038/ejhg.2012.125 online 27th June 2012.

Goldsmith, L. et al.: Direct-to-consumer genomic testing: systematic review of the literature on user perspectives, *European Journal of Human Genetics* (2012), 20, 811-816, doi:10.1038/ejhg.2012.18.

Harper, A./Topol, E.: Pharmacogenomics in clinical practice and drug development, *Nature Biotechnology*, V. 30, No. 11, Nov. 2012, p. 1117-1124, doi:10.1038/nbt.2424

Kaiser, J.: A Reality Check for Personal Genomes, *Science now*, 24.2012. <https://www.gesundheitsindustrie-bw.denews.sciencemag.org/sciencenow/2012/04/a-reality-check-for-personal-gen.html>

Mullard, A.: Consumer gene tests poised for regulatory green light, *Nature Medicine*, Vol. 18, No. 9, September 2012, p. 1306.

Roberts, Nicholas J.: The Predictive Capacity of Personal Genome Sequencing, *Science Translational Medicine Rapid Publication on April 2 2012*, *Sci. Transl. Med.* DOI: 10.1126/scitranslmed.3003380

Challenges associated with the Encode project, e.g.:

Ward, L./Kellis, M.: Interpreting noncoding genetic variation in complex traits and human disease, in: *Nature Biotechnology*, Vol. 30, No. 11, Nov. 2012, p. 1095-1106, doi: 10.1038/nbt.2422.

Articles in German:

Theurillat, Jean-Philippe, NZZ, 23.5.2012, https://www.gesundheitsindustrie-bw.denz.ch/wissen/wissenschaft/die-krebstherapie-der-zukunft_1.16997844.html

Timmermann, Bernd, MPI for Molecular Genetics, March 2012, public hearing of the German Ethics Council.

Orth, M. et al.: Praktische Umsetzung des Gendiagnostikgesetzes (GenDG) in der Laboratoriumsmedizin, dem humangenetischen Laboratorium und der humangenetischen Beratung/Practical Implications of the German Genetic Diagnostics Act (GenDG) for Laboratory Medicine, the Human Genetics Laboratory for

Genetic Counseling, in: LaboratoriumsMedizin, Vol. 35, H. 5, p. 243ff.

Schulze, Bernd: Gendiagnostikgesetz und genetische Beratung I: Geschichte eines Irrwegs, Dt. Ärzteblatt, H. 16, 20. April 2012

Schmutzler, R. et al.: Hoffnung und Fluch der Genanalyse, in Deutsches Ärzteblatt, H. 26, 29.6.2012, p. 1371ff.

Duttge, G./Engel, W./Zoll, B. (Eds.): Das Gendiagnostikgesetz im Spannungsfeld von Humangenetik und Recht, Göttingen 2012 (Göttinger Schriften zum Medizinrecht Vol. 11).

Klinkhammer, G.: Arbeitskreis medizinischer Ethikkommissionen: Eine klare Vereinbarung treffen, Dt. Ärzteblatt, H. 33-34, 17.8.2012.

Public discussion of the Berlin-Brandenburg Academy of Sciences on genetic diagnostics, German title: 'Schicksal Gendiagnostik', 'Gentechnologiebericht' work group, 10th September 2012, Berlin: (audio recording) https://www.gesundheitsindustrie-bw.de/www.bbaw.de/mediathek/schicksal_gendiagnostik/?searchterm=schicksal_gendiagnostik

Public hearing of the German Ethics Council, 3rd May 2012: Opportunities and limits of predictive genetic diagnostics of multifactorial diseases <https://www.gesundheitsindustrie-bw.de/www.ethikrat.org/veranstaltungen/anhoerungen/praediktive-genetische-diagnostik-multifaktorieller-erkrankungen>

Public hearing of the German Ethics Council, 22nd March 2012: Scientific and technological developments in the field of multiplex and high-throughput diagnostics <https://www.gesundheitsindustrie-bw.de/www.ethikrat.org/veranstaltungen/anhoerungen/multiplex-und-high-throughput-diagnostik>

Opinion of the German Society of Human Genetics on the qualification related to "human genetic diagnostics and consultation" as stipulated in § 7 paragraph 3 of the German Genetic Diagnostics Act, 15th Feb. 2012, and others relating to the GEKO guidelines, <https://www.gesundheitsindustrie-bw.de/www.gfhev.de/de/leitlinien/gfh.htm?Submit2=Liste+anzeigen#GEKO>

German Society of Human Genetics/Association of German Human Geneticists (HG): S2k guideline "Human genetic diagnostics" and genetic counselling, online publication 21st June 2011, doi: 10.1007/s11825-011-0284-x, guideline available through: https://www.gesundheitsindustrie-bw.de/www.awmf.org/uploads/tx_szleitlinien/078-015l_S2k_Humangenetische_Diagnostik_genetische_Beratung.pdf

Genetic Diagnostics Commission at the Robert Koch Institute: https://www.gesundheitsindustrie-bw.de/www.rki.de/DE/Content/Kommissionen/GendiagnostikKommission/GEKO_node.html

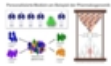
German Academy of Natural Scientists Leopoldina/acatech/Berlin-Brandenburg Academy of Sciences: Opinion on predictive genetic diagnostics as a tool for disease prevention, November 2010

Dossier

26-Nov-2012

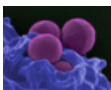
© BIOPRO Baden-Württemberg GmbH

Other dossier articles



16.09.2021

Pharmacogenomics enables individualised drug prescription



07.01.2021

Gene accordions as potential markers for pathogenic properties