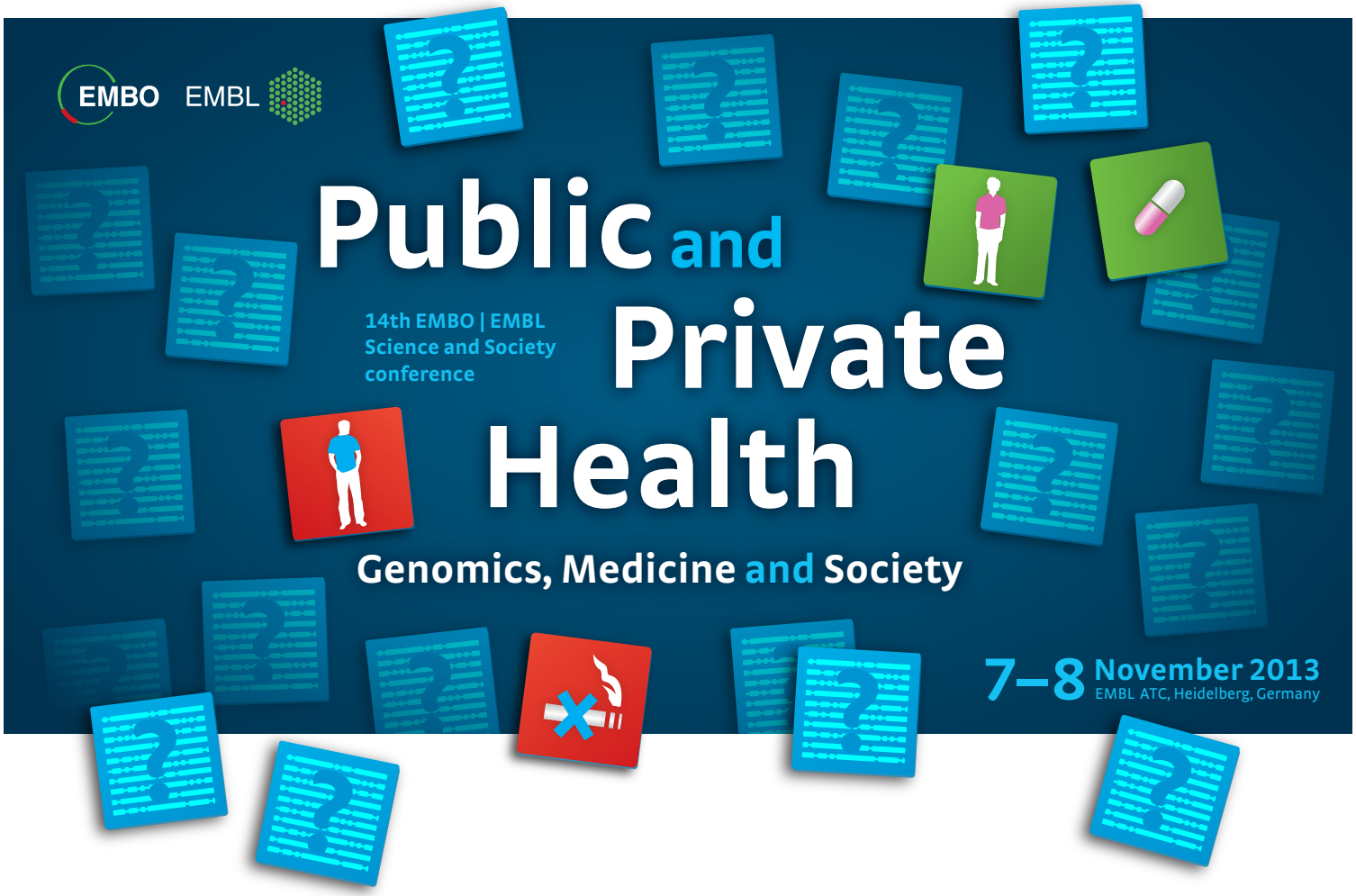

Introduction

The 14th EMBO|EMBL Science and Society conference focused on the use of genomic information to benefit individual and public health.

18 speakers and more than 250 participants from many countries and disciplines gathered in the EMBL Advanced Training Centre to learn about and discuss the status of genomic research; the obstacles to using genomics for the advancement of human health; and the ethical, legal, economic and social implications of applying genomics to biomedicine.

Three main challenges to the use of genomics to benefit medical practice were identified in the talks and discussions:

- → Scientific, technological and computational challenges
- → Work force and educational challenges
- → Policy challenges

One of the main messages from the conference was that human genomics will not bring a dramatic revolution to medicine in the very near future. Rather, it will result in notable improvements in specific areas in the short term, perhaps most notably in cancer diagnosis and treatment, but the full impact will take a long time to be realized.

Scientific challenges

Eric D. Green, Director of the US National Human Genome Research Institute, NIH, described genomics research as a journey from understanding the basic structure of the human genome to genomic medicine: the emerging medical discipline based on using individuals' genomic information as part of their clinical care.

The beginning of that journey was the end of the Human Genome Project (HGP), an international effort that took over 10 years. Since then, research into understanding how the human genome works and research into the biology of disease have become predominant in human genomics research.

In the effort to understand the function of the genome, one of the main achievements has been the discovery of a large number of *non-protein-coding functional regions*, which are thought to play an important role in health and disease. More efforts are needed to better understand the exact role and function of these vast regions in the human genome.

Much progress has been made in understanding the role of genomic variants among individuals: when the HGP started, about 4000 variants were known to exist; now, 50–60 million variants have been catalogued in public databases (resulting from large-scale projects such as the 1000 Genomes Project), although the functional significance of most of them is still not known.

Some significant progress has also been made in understanding the biology of genetic diseases, in particular of rare, simple, or *monogenic diseases* (for example, cystic fibrosis and sickle cell anaemia). In 1990, the genes mutated in only 61 rare disorders were known; by 2012, scientists had discovered the relevant gene for almost 5000 such diseases. However, there are

upwards of 4000 other simple disorders for which the underlying genetic defect is still not understood.

In the case of common, complex, or *multigenic diseases* (for example, hypertension, diabetes, autism, Alzheimer's disease, different forms of mental diseases) that represent the major healthcare burden worldwide, progress has been much slower. Large-scale genome-wide association studies (GWAS) comparing the genomes of people with and people without a disease have led to statistical associations between regions of the human genome harboring specific variants and inherited complex disease. As Eric Green explained, one of the first successful studies of this kind was on age-related macular degeneration, which identified a specific gene in 2005. There have now been more than 1600 successful GWASs, although these have largely allowed the identification of regions of the genome associated with an increased risk of disease development and not yet the genes themselves.

As Jan Korbel from the EMBL in Heidelberg and Anne-Lise Børresen-Dale from Oslo University Hospital discussed, *cancer research* is the area that has benefitted most by the introduction of human genome sequencing, and cancer genomics has already improved clinical treatment. Another positive result of sequencing has been a better understanding of the role played by environmental factors on the genetic mechanisms of some tumours, e.g. in lung and skin cancers.

In particular in breast cancer, DNA sequencing has allowed the identification of a much larger number of genes involved, which are now being used to classify patients into different categories so they receive targeted and more effective treatment. But several factors make these classifications difficult: DNA mutations evolve over the lifespan of a tumour, variation exists within a single tumour and between different tumours, and many mutations are present in the still not-understood non-protein-coding regions of the genome. Moreover, there is a lack of harmonisation of the criteria for classification of patients in different studies, making statistical analyses very difficult.

What is also lacking is a comprehensive understanding of the molecular mechanisms involved in different kinds of cancer. The need to merge data from different studies has been addressed by the International Cancer Consortium, which aims at sequencing and comparing the full genomes of 2000 patients for 50 kinds of cancer. The Cancer Genome Atlas run by the U.S. National Cancer Institute and National Human Genome Research Institute is also looking at about 30 different types of tumours. Eventually a holistic view of these data will lead to improved prognoses. Meanwhile, development of tools to understand the data remains a significant gap. As Anne-Lise Børresen-Dale stressed, a better understanding of tumour development will depend on a better understanding of the function of the genome in healthy individuals, and, as with "disease," "health" is not a single entity.

Epigenetics, the heritable changes in gene expression that are independent of changes in the genome, has been identified as being critical in both health and disease. *Epigenetic factors*, triggered by environmental exposure, play an important role in the overall changes of genome function. Geneviève Almouzni from the Institut Curie explained that genomic tools will need to be applied to epigenetics, and collaborations between genomic researchers and epigeneticists need to intensify to understand the complex interactions between the different factors at play.

An area that has developed dramatically with the developments in human genome sequencing is *prenatal* and *newborn diagnosis*. The advent of whole genome sequencing in combination with extracting foetal DNA in a non-invasive manner makes it possible to obtain the genetic information of an unborn child, and identify possible genetic mutations. As genetic counselor Wolfram Henn from Saarland University described in his talk, this is not yet routinely done in the clinic, but it will probably be introduced in the near future. While this will represent an advance for some childhood preventable diseases, for most other conditions the meaning of variations in the genome is still unknown, making any kind of decisions very difficult.

Although the scientific progress made since the start of the HGP is evident, all speakers agreed that the journey towards genomic medicine has just started, and that we are a long way from the goal of changing clinical practice with the application of genomics.

Technological challenges

Genomic research is strongly driven by technology. The first decade after the Human Genome Project saw major developments in DNA sequencing technologies that allowed scientists to progress rapidly from the sequencing of one genome in 2001, to the 1000 Genomes Project in 2008 and a variety of projects producing a huge amount of genetic data. There are even plans to sequence the entire populations of small countries (e.g. the Faroe Islands), or to sequence every child born or every person with cancer.

In order to be able to collect more data we need to develop faster and cheaper technologies. As Jan Korbel from EMBL pointed out, after a dramatic drop in the prices of sequencing in the years after the HGP, prices have plateaued at a point above where several sequencing projects had projected, thus compromising these projects. The promised development of nanopore-based technologies in the near future gives hope that the prices will drop even further. Moreover, as Eric Green pointed out, we need to develop better technologies to be able to routinely sequence non-protein-coding areas of the genome, which scientists barely understand, but that are thought to play

a central role in the development of common, complex genetic disorders.

As Paul Flicek, a bioinformatician at the EMBL-EBI, described, a big challenge is also presented by the ever-growing volume of genomic data generated by DNA sequencing centres that produce as much information in seconds as the HGP did in a decade. Also all the data need to be stored, transferred and analysed. But genomic data are produced much more quickly than they can be analysed. As Eric Green said, *"The largest bottleneck in genetics is that we are analysis limited, no longer data limited."* Increased investments in infrastructures are necessary to be able to store and analyse data on an even larger scale. The cost of building and maintaining these infrastructures is already a significant portion of the cost of genome sequencing.

Work force and education

Now that genomics is moving from understanding the structure and biology of genomes to understanding the biology of diseases, it has become relevant for health-care providers and, increasingly, for patients and their relatives and friends. From a public health perspective, this means that all stakeholders need to understand the role of genomic information, which has implications for the relevant workforce.

Biomedical researchers need to learn about the most recent technologies, and how to interpret the data. As noted by several speakers, clinicians and other healthcare providers need to be able to understand how genomic information is relevant for their patients. New or better clinical genomics information systems to support healthcare providers need to be developed.

Better cooperation and communication are needed between biomedical researchers and healthcare providers to make sure that the relevant information needed in clinical settings is readily available. Another major challenge is the standardization of the reporting of biomedical research in a way that is useful in clinical settings.

Helena Kääriäinen, a medical geneticist from Helsinki, noted that the imminent introduction of routine clinical whole genome sequencing requires *genetic counselors* who need to be trained to be able to understand and explain the interactions of many genes and their effects not only to patients but also their families.

As Buddug Cope from Genetic Alliance UK explained, patients suffering from genetic disorders and their families see genomics as the only way to obtain a diagnosis for their often rare diseases. Therefore, an increasing number of *patients* and *citizens* are willing to contribute to genomic research projects, and will have to learn some of the lexicon and the concepts of genomics and risk susceptibility. How this new kind of education should be introduced in the general population (in school, through the internet) will have to be discussed by all stakeholders.

Policy challenges

The analysis of the ethical, legal and societal implications (ELSI) of genomics has been an important aspect of this research since the beginning of the HGP. As noted by Timothy Caulfield, from the University of Alberta, Canada, in parallel with genomic research—from understanding the basic structure of the human genome towards implementation into the clinic—the focus of the ELSI issues has also evolved, and some of the ethical and legal concerns that were seen as main obstacles to the use of genomic technologies (genetic discrimination, health insurance issues, some consent issues) have now diminished or changed. As Jane Kaye, University of Oxford and Bartha Knoppers, McGill University, each discussed, new issues have emerged:

- → the need to harmonize research ethics and regulation globally to enable international cooperation;
- → the need for a global consensus of how to deal with incidental findings; that is, health information that is discovered serendipitously: what findings to return, who should return them, and when;
- → data protection regulations and their effect on research and medical practice. Serious concerns have been noted about the proposed revision of the EC Directive on Data Protection (Directive 95/46/EC), which, in the current version, could limit the use of genomic data in research;
- → a need for oversight or regulation of whole human genome sequencing in the clinic. For example, there may be a need for an international consensus on which prenatal and postnatal identifiable traits must /must not /may be disclosed to parents;
- → data sharing and data handling procedures in biomedical research. The data from genomic research will be useful to understand disease development only if they are globally available. As Bartha Knoppers pointed out, this calls for a data sharing code of conduct for international genomic research. An example of an effort to harmonize data storing practices is the Global Alliance Initiative, involving over 70 leading healthcare, research, and disease advocacy organizations in more than 40 countries.

New approaches to ELSI issues are also emerging, such as in the ELSI 2.0 initiative presented by Jane Kaye, to integrate this kind of research globally, avoid repetition of efforts, offer capacity building and involve more stakeholders (including patients and families).

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Conclusion

The conference highlighted the technical and policy problems for advancing genomic research to genomic medicine. One of the difficulties is that these problems constantly evolve. As genomics is something that is personal to everyone, it is our responsibility as a research community and as people interested in policy to understand the science and to be involved in crafting policies to make best use of the technologies. These policies should be sufficiently flexible to be changed as necessary and should be informed by rigourous analyses and public dialogue.

Thanks to all speakers and chairs for their contribution to the conference:

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Peter Goodfellow, University of Kent, Canterbury, UK
Eric D. Green, National Human Genome Research Institute, NIH, USA
Ernst Hafen, ETH Zurich, CH
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For more information on the conference, videos of the talks and interviews of the speakers:
http://events.embo.org/science-society-conference/index.html

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Further reading:

Human Genome Project: *www.genome.gov/10001772*
1000 Genomes Project: *www.1000genomes.org*
International Cancer Consortium: *http://icgc.org*
US Cancer Genome Atlas: *http://cancergenome.nih.gov*
FarGen Faroe Genome Project: *www.fargen.fo/en/*
Genetic Alliance UK: *www.geneticalliance.org.uk*
EC Directive on Data Protection: *http://ec.europa.eu/justice/data-protection/*
Global Alliance initiative: *www.genomicsandpolicy.org/Ressources/130605-white-paper.pdf*
ELSI 2.0 initiative: *www.p3g.org/programmes/elsi-20*

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