A focus on personal genomics

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Since the completion of the human reference genome [1], human geneticists have been using this 'encyclopedia' as a baseline for discovering the variation of the human genome at many levels, from SNPs to copy number variation, to complex structural variation. Such studies have largely focused on characterizing the genomic context of disease or disease susceptibility, initially through genome-wide association studies carried out on SNP arrays of ever-increasing density, with varying levels of success. More recently, by applying next-generation sequencing technology to resequence and characterize entire human genomes, geneticists have set the stage for a revolution in personal genomics that will ultimately progress towards the reality of personalized medicine. Namely genomic data can be collected in a relatively straightforward manner within a matter of hours or days depending upon the technology, yielding a dataset that consists of an individual's genotype (the unique combination of > 1 million single nucleotide variants as identified by a genotyping array) or of each of the approximately 6 billion nucleotide bases comprising the diploid genome. As a result, companies have been founded that offer 'direct-to-consumer' (DTC) genomic profiling and interpretation, individuals have had their own genomes sequenced [2–7] and mutated genes have been discovered in an unbiased fashion by sequencing complete cancer genomes [8,9]. Several scientific meetings have been organized around personal genomics, reflecting the dramatic increase in scientific efforts and interest in this area. The fields of human origins and pharmacogenetics, among others, have been re-energized by the emergence of the personal genome, with the anticipated results improving our understanding of migratory patterns and changing medical practice, respectively.

The aforementioned advances in genomics technology and its applications have had unprecedented impacts on the fields of ethics and governance. The established framework of ethical, legal and social issues (ELSI) in genomics has been shaken to its foundations by something as simple as the emergence of personal genomics. Experts in the areas of ethics, social and political sciences, and governance, have been called to arms in order to restore the steady state that ELSI brought to genomics [10]. There are two tiers to the developments that result from technological progress, each of which confronts the ELSI disciplines with specific challenges.

First, there are the aforementioned spectacular advances in sequencing. We have progressed from gene analysis to whole-genome scans in just half a decade. The availability of information regarding substantial parts of genomes, and even of full human genome sequences, has changed the way we look at such information – the building blocks of the human–organism are no longer hidden and it is becoming ever clearer that integrative personal genomics will enable rational and effective personalized medicine. Increasingly, individualized diagnostics and therapies require a rethinking in terms of justice and equity in healthcare delivery. In addition, new designs and strategies must be developed for both clinical trials and epidemiological studies. This means that substantial innovation in the field of research ethics will be needed.

The integrative 'omics' sciences will not only change our concepts of health and disease, they will also redefine the interactions of the individual–human–organism and the environment.

The second tier consists of the very sudden appearance in the market place of DTC genotyping services that, until recently, mainly provided certain types of selective genome scans. The established disciplines in the field of clinical genetics and in the ELSI area, as well as the various regulatory authorities, have been taken by surprise and, obviously, they are not able to

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control the ongoing developments. Irrespective of questions concerning clinical utility and related issues such as clinical validity and quality assurance, direct access for consumers to a choice of genetic tests and to their own results undermines traditional professional paternalism. This fundamentally shifts the questions regarding responsibility for dealing with the available information from the professional to the individual realm. The traditional protection paradigm of medical ethics gives way to new forms of agency in participatory research, and, for example, to product liability, as a feature of market-place transactions.

> *"The established framework of ethical, legal and social issues ... in genomics has been shaken to its foundations by something as simple as the emergence of personal genomics."*

In this Personal Genomics Special Focus issue of *Personalized Medicine*, we present commentaries, perspectives and research articles that encompass the broad spectrum of science and ethics related to personal genomics. We are especially pleased to begin the issue with an editorial from Dr James Watson (Cold Spring Harbor Laboratory, NY, USA) [11], who was the first individual to have his genome sequenced using next-generation DNA sequencing technology [2]. Another highlight in the 'News and Views' section is an interview [12] with the second cancer patient to have his tumor and normal genome sequenced, analyzed and reported in the literature [8] (the first patient was deceased by the time her genomes were sequenced and reported [9]).

Exploring fixed SNPs in populations

Baye *et al.* [13] present a very innovative research study that explores the presence of fixed rare SNPs in specific populations that may have phenotypic effects. By examining private SNPs that impact proteins in specific biochemical pathways in HapMap samples from geographically separated populations, these authors convincingly demonstrate that fixed SNPs effect variability in cellular differentiation, apoptosis and activation of the transcription factor NF-κB. Moreover, such variability may provide clues that indicate human adaptation to specific environments, perhaps explaining ethnicity-specific responses to drugs or other phenotypes. It will be interesting to see how such analyses are aided by SNPs imputed from low-coverage genomic sequence data, such as is being produced by next-generation sequencing of genomic DNAs obtained from different ethnic groups in the 1000 Genomes Project [101].

Preparing for pharmacogenetics

The research article conclusions are a perfect segue to Michael Wagner's (University of North Carolina at Chapel Hill, NC, USA) review of pharmacogenetics and personal genomes [14]. He effectively argues that the flood of information from personal genotyping and personal genome sequencing will begin to impact our understanding of the genome's variability and its influence on response to medicines. Importantly, Wagner outlines what will be needed in terms of bioinformatics, electronic medical records and other analytical capabilities to effectively manage the new information and to use it to its full predictive advantage.

Personalized cancer genomes

Adding further granularity to the potential impact of personal genome sequencing on disease treatment is a perspective offered by oncologist Timothy Ley (Washington University, MO, USA) and colleagues [15]. Their perspective illustrates how the application of genomic technologies, including the next-generation sequencing of cancer genomes in acute myeloid leukemia, will bring the diagnostic power of examining the cancer genome to its highest resolution that originally began with cytogenetics-based examination. Certainly their work highlights the possibility that, with falling costs for whole-genome sequencing and the proof of its efficacy in treatment decisions, many patients may begin to demand that this information is included as a component of their diagnosis and treatment.

Principles in ethics

In their perspective '*Principled' Personalized Medicine*, Bartha Maria Knoppers and Denise Avard (McGill University and Genome Quebec Innovation Centre, QC, Canada) argue for a shift in ethical principles from the traditional principles of autonomy and individual privacy protection towards the more practical and concrete principles of quality, safety and solidarity [16]. The authors examine the context of both research and medical ethics and find that although the topic is personal genomics, there is a move towards more relational and communitarian concepts. They see an increased need for governance, directed towards quality assurance in particular, while

at the same time they assume that genetic information with increasing availability will become more integrated into our everyday life and thus, 'normalized'.

Need for education

Neil Lamb and Chris Gunter (HudsonAlpha Institute for Biotechnology, AL, USA) address the need for education in personalized genomics-related matters [17]. It is not only the average lay person who needs to be introduced to the dimensions of her or his own genomic universe, but professionals including physicians and science journalists must also be provided with the knowledge required to inform and educate their patients and the public at large, respectively. Lamb and Gunter end with the conclusion that the (traditional) geneticists will need to accept the availability of DTC genetic testing and the fact that others (nongeneticists) will play a pivotal role in the dissemination of genetic knowledge.

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From the eyewitness' point of view

Contributions by Misha Angrist (Duke University Institute for Genome Sciences & Policy, NC, USA) [18] and Darren Platt (Amyris Biotechnologies, CA, USA) [19] are written from the unique expert but personal eyewitness point of view. Both authors are professionals with more than an average expertise in the field of genetics/genomics, and both are, at the same time, actively involved as participants in consumer genetic testing and participatory whole-genome research, respectively. Platt is in a position to simultaneously take the provider's, the client's and the informal 'expert of the family's' point of view. He uses the familial microscope to look at DTC genotyping services. He forecasts the availability of whole-genome sequencing becoming DTC within 5 years and emphasizes the need for a very urgent revision of the way in which science information is communicated to the public.

Misha Angrist gives a very close and personal, and at the same time professional, account of the development of the Personal Genome Project (PGP) [102] and of his personal involvement as a proactive participant. He makes a strong case for 'citizen science' and altruism in order to be able to build, in the public domain, the comprehensive open datasets of genotype and related phenotype data that are needed to advance the biomedical sciences. Open access requires open consent, and Angrist strongly supports the idea, which is fundamental to PGP, that veracity is a precondition for any valid consent.

Conclusion & future perspective

This special focus issue of *Personalized Medicine* appears at a time when the use of individual human genome sequence information has passed the threshold of basic experimentation and speculation, and has entered the early stages of clinical research and diagnostics, beginning to find application in determining treatment strategies. In other words, genome-based personalized medicine is no longer a thought experiment and the course of both disease research and medical practice will be substantially altered as a result.

The ethical, legal and societal implications of the developments in the genomic sciences cannot be ignored and require ongoing assessment. The changing concepts of health and disease impact on the empirical basis of the current mainstream ELSI frameworks that are underlying today's governance. We now see that new information and communication tools are applied in open, 'democratic' networks and that new 'agents' are making their own choices.

As the contributions in this special focus issue illustrate, we are only at the beginning of an exciting future, but it has definitely arrived. We look forward to the challenges and the rewards.

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