The personal genome—the future of personalised medicine?

Doctors have practised personalised medicine since time immemorial, using information about a patient's lifestyle, family history, and environment to inform decisions. Yet we know that this approach is far from perfect—even for evidence-based medicines we need to treat many individuals for years to prevent one event. Similarly, the huge burden of iatrogenic illness caused by drugs stems from our inability to predict side-effects.

Much of the interindividual variation in disease susceptibility, or therapeutic response, is believed to be genetically determined. Hence, since the first demonstration of human DNA variation in the 1970s,[1] and especially since the sequencing of the human genome and subsequent systematic cataloguing of human genetic variation,[2,3] there has been a growing expectation that the association of such variation with disease susceptibility will personalise the delivery of medicine. Indeed, there has been progress already. For example, the finding that rare mutations in *BRCA* genes affect breast cancer risk has provided more accurate risk prediction in some patients.[4] Similarly, studies have shown the potential of genetic tests to better predict responses to, or side-effects from, drugs such as warfarin, statins, and clopidogrel.[5-7] The advent of genome-wide association studies, and the rapidly growing catalogue of variants that affect risk of common diseases,[8,9] has provided further impetus.

Furthermore, the cost of acquiring genetic information has plummeted. The first human genome sequence cost US$2·7 billion. Now, with next-generation rapid-sequencing technology, a human genome can be sequenced for less than $10 000, and in the foreseeable future, the cost could reach $1000.[10]

In *The Lancet* today, Euan Ashley and colleagues[11] illustrate the potential that this rapid-sequencing technology could have for personalised medicine. They evaluated an individual's genome, through whole-genome sequencing, for genetic risk and clinical utility in the context of family history. Their 40-year-old healthy male patient had a family history of premature coronary artery disease, abdominal aortic aneurysm, osteoarthritis, and sudden (presumed cardiac) death. The investigators focused on three types of variants: novel mutations and rare variants in genes for mendelian diseases, variants that could modulate responses to drugs, and variants associated with risk of complex diseases.

The novel mutations and rare variants carried by this individual are consistent with findings in other sequenced genomes.[12,13] It seems that we all carry some potentially adverse mutations, but most do not result in overt disease, either because they act in a recessive way or for other reasons such as presence of modifier genes or absence of environmental triggers. The most compelling findings in today's study relate to drug responses. Ashley and colleagues identified 63 known pharmacogenomic variants that could affect the patient's response to commonly used drugs, including those that might be pertinent in view of this man's family history. For example, he is likely to respond well to a statin and to be at a lower risk of statin-induced myopathy. Were he to need warfarin, his initial doses are likely to be low; by contrast, clopidogrel might be less effective. Although screening for such variants could be done when clinically needed, rather than through a whole-genome sequence, the investigators identified six further novel aminoacid-changing variants in genes important for drug response. These variants could have an equal, if not greater, effect in drug response, and they would have eluded a targeted analysis.

Perhaps the most interesting aspect of today's study is the way the investigators have analysed and incorporated information for their patient on the growing plethora of variants associated with common diseases, such as coronary artery disease and type 2 diabetes. Because most known variants for such diseases have small effect sizes individually (odds ratios 1·1–1·3), clinical translation of these discoveries into personal prediction has been particularly challenging.[14] Rather than just report the

Step	Challenges
Sequencing and assembly	Extremely high accuracy (probably <1 error in 10^{-7} bp) to avoid misclassification
Annotation	Development of automatic algorithms for annotation; functional characterisation of rare mutations and variants and their relevance to causing disease; more complete catalogue of genetic variants affecting risk of common diseases
Presentation	Flagging-up of relevant genetic findings in comprehensible way and tailored to clinical context
Training	Training of broad range of health-care professionals (from general practitioners to specialists to pharmacists) to assess and incorporate genomic information into their daily practice and to communicate findings to patients and their families
Clinical usefulness	Demonstration that data from a personal genome significantly influences clinical management
Cost-effectiveness	Demonstration that health benefits are worth the cost

Table: Challenges that need to be overcome if the use of personal genome is to enter clinical practice

number of risk alleles from known loci for a particular disease carried by this patient, or even their cumulative odds ratio, Ashley and colleagues calculated his pre-test probability for the disease and then a post-test probability integrating the likelihood ratios for each allele carried. This could provide a measure that is much more clinically relevant, although the reliability and value of this approach need further testing.

Even if the direct cost of sequencing whole-individual genomes becomes affordable, there are many practical challenges that will need to be overcome if the personal genome is going to enter clinical practice (table). Arguably of greater importance are ethical issues: who should have their genome sequenced, what counselling should be provided before and after testing and by whom, and who should have access to an individual's genetic information. Whereas these issues are familiar in genetic testing, the scale of the data contained within each personal genome, and the potential implication for so many different aspects of an individual's health (and the health of their relatives), mean that these issues will need to be even more carefully considered (and legislated on where necessary) to prevent misuse. Some of these points are discussed in a Viewpoint by Kelly Ormond and colleagues.[15]

Notwithstanding these challenges, today's elegant analysis shows the huge potential this approach could have for clinical care and takes the notion of personalised medicine one big step forward.

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Lp-PLA$_2$ and risk of atherosclerotic vascular disease

LDL serves a crucial physiological role as a transporter of cholesterol to various tissues. Cellular cholesterol homoeostasis is regulated by the activity of the LDL receptor through negative feedback mechanisms. In industrialised societies, LDL cholesterol concentrations often exceed physiological requirements. This excess in LDL particles promotes transport into the vessel wall where they might be retained through interactions with intimal proteoglycans, and undergo physicochemical modification. Specific modifications in the chemical structure of the LDL particle facilitate their ingress into macrophages through non-regulated pathways, resulting in foam-cell formation.

Conformational changes in apolipoprotein B, the major protein on the surface of LDL and other athero-genic lipoproteins, reduce interactions through the regulated LDL receptor, resulting in diversion of these physicochemically altered LDL particles through non-regulated pathways. The core composition of LDL is altered by a two-step process in which cholesterol ester-transfer protein mediates exchange of cholesterol for triglycerides in VLDL, and the resultant triglyceride-enriched LDL particle undergoes hydrolysis by hepatic lipase or endothelial lipase. Chemical alterations in LDL that alter interactions with the LDL receptor include glycation, oxidation, and immunoglobulin binding.