Key challenges for next-generation pharmacogenomics

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The “post-genomic revolution” has advanced our understanding of the molecular etiology of a range of human genetic diseases, which might lead to improved disease prognosis and treatment. Over the past decade, genomics research has revealed the genomic variants underlying diseases, from single nucleotide variations to complex genome rearrangements, and/or altered gene expression patterns that lead directly to pathogenesis. These findings have enormous potential to guide physicians in their task of estimating disease risk and deciding on the most efficient and safe treatment options. More generally, genomic research could catalyze the maturation of individualized healthcare by considering each person’s genomic profile alongside his or her clinical condition to personalize therapeutic interventions.

These developments have been enabled by the rapid technological progress from the low- and medium-throughput genetic screening methods of yesteryear to the new high-throughput genome-wide approaches of today, including microarray assays and next-generation sequencing. In particular, as the costs for sequencing are steadily decreasing and the data analysis tools are constantly improving, whole-genome sequencing is an attractive and potentially very efficient method to determine an individual’s pharmacogenomic profile. In several cases, whole exome and whole-genome re-sequencing has helped researchers to correlate specific genomic variants with disease predisposition and other clinical features or physiological traits.

However, such developments have yet to make their way into clinical practice, as various factors slow down the transition from research into patient care and public health benefits. Most notably, healthcare professionals still lack sufficient education and training to make better use of genomics services. Furthermore, patients and the general public tend to have low genetic literacy, which impedes their ability to meaningfully integrate their genomic information into their lifestyle and health decisions. Lastly, there are legislative gaps, ethical concerns and a dearth of economic studies into their lifestyle and health decisions.

At present, approximately 150 drugs have pharmacogenomics information on their labels, mostly to avoid adverse drug reactions. In addition, pharmacogenomic-based techniques are widely used as diagnostic tools to select and/or dose therapeutics based on the genomic characteristics of the individual patient. Pharmacogenomic approaches are used to identify biomarkers and the targets of currently prescribed medications for drug development; ideally, pharmacogenomic tests would be developed for existing drugs and new drug candidates to increase their efficacy and safety.

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of 47 HapMap DNA samples and found 3,558 genetic variants of which 449 were novel [1]. Similar applications of next-generation sequencing could also be envisaged for detecting germline cancer susceptibility and for individualized cancer treatment.

By way of example, whole-genome sequencing was performed for seven members of a family in order to delineate the differential response rate to anticoagulation treatment in two members who suffered from atrial fibrillation. One family member responded well to acenocoumarol, while the other did not. Whole-genome sequencing revealed the pharmacogenomic variants that caused the different responses to acenocoumarol treatment. It also predicted the outcome of an alternative treatment, clopidogrel, based on the presence of several novel variants in pharmacogenes involved in the clopidogrel pathway. However, there are still numerous drugs, particularly in the fields of oncology and psychiatry, for which pharmacogenic information, albeit available, is still missing from their labels, which clearly illustrates how far we still are from attaining the goals of personalized medicine.

Despite the advances in research and the advent of next-generation sequencing, there are numerous challenges that hinder the translation of research into medical application. These cut across the research phase itself to the translation of knowledge into clinical practice and its integration into health policy. Existing ethical and legal frameworks are ill-equipped to respond to these challenges. Furthermore, societal trends, such as easy access to genetic information, the proliferation of online networks, self-tracking and so on, are likely to affect advances in pharmacogenomics and the quest for precision medicine, while adding new layers of ethical complexity. These developments take place in a climate in which the public’s genomic literacy is still rather low and their expectations of genomic medicine in general, and pharmacogenomics in particular, are likely to be somewhat inflated. Further research will require genetic data from large numbers of individuals, while professionals and the lay public will have to be able to deal with genetic information in and beyond the clinical context. Ultimately, financial cost will remain a critical consideration in integrating genomics in health care.

The issue of informed consent is crucial for the further development of genomics medicine for at least two reasons: it is a key ethical and legal requirement in biomedical research, originally put in place in order to protect individual autonomy; and there is increasing evidence that the concept of informed consent and the practical procedures to obtain consent have severe weaknesses, especially when it comes to genomic research.

Informed consent requires that patients and participants in clinical and other studies are provided with adequate information to make an informed—and entirely voluntary—
decision regarding their participation in research, and that they are aware of their right to revoke their consent at any time. The theoretical ideal of informed consent is difficult to achieve in practice [2]. The context of genomics and pharmacogenomics has special challenges for the informed consent process: the research projects are often complex, the data generated can be used for multiple projects in many different ways, including projects that were not originally envisaged by the investigators. In these cases, participants are usually asked to give “broad consent” to future uses of their data that are, at the time of asking, not only unknown to them but also to the researchers. Given the low genomic literacy of the broader public and frequent misconceptions about the potential and the achievements of genetics and/or genomics, these nuances and complexities are hard to communicate. It is therefore necessary to develop informed consent models that take such constraints into account and are directly relevant to the specific context of genomic research, especially because the information derived from genomics and pharmacogenomics research is so complex.

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There are currently some interesting proposals about consent processes that might address at least some of these issues. One example is the “portable legal consent” (PLC) model, which takes participants through a rigorous information session before they are invited to give their broad consent for their own data to be used by any research team that fulfills certain stringent requirements ([3]; http://weconsent.us). Another proposal is the “dynamic consent” model, which allows participants to track the uses of their data and the option to make changes to their original consent if they so desire [4]. While such efforts are laudable and need to be further explored, the question remains whether genomic research requires a different model of governance that does not rely so heavily on informed consent; one where protecting genomic data is a matter of shared responsibility and stewardship and one that strikes a fair balance between the risks and benefits to individuals and/or patients. This way of thinking also includes more active public participation in research governance itself to promote accountability and transparent practices.

Public attitudes are generally favourable towards genetic testing. However, when it comes to real-life decisions in relation to undergoing a genetic test, decisions are influenced by perceived potential risks. The general public appears to conflate other types of testing with genetic testing, and to expect that genetic tests may provide definite answers regarding their health conditions [5]. Given that direct-to-consumer (DTC) genetic tests, including pharmacogenomics tests, are becoming increasingly available, the public requires a better understanding of what answers genetic tests can and cannot provide about potential health risks and benefits.

There are two important issues that are crucial to the public understanding of genetics. The first one is the perception of science, and of the knowledge it produces, particularly when it comes to genetics. This is especially important given that popular TV series often advance an entirely unrealistic view of what science laboratories can achieve [6,7]. Notably, there is evidence that TV shows that promote a view of certainty in science enhance laypersons’ interest in it, whereas those shows which present science as uncertain do not have such an impact [8]. If TV and other media generally portray the conclusions of genetic/genomic testing as definitive and certain, the public will be more likely to develop unrealistic expectations and inaccurate perceptions [8].

The second issue relates to how people perceive the role of DNA and genes in human health. The idea of genetic determinism appears to be widespread, at least in formal education. A common view held by the public is that there are genes for traits and that single gene defects often determine complex traits. The roots of such misconceptions may be partly found in the way biology is taught in school, as textbooks often present genetic concepts without relating them to the complexities of development. Interestingly, even biology teachers may hold simplistic and inaccurate views of genetic determinism [9]. It is therefore unsurprising that students might complete their high school education with a naive deterministic view of genetics [10].

One important step forward would be to provide the general public with a more accurate portrayal of how scientific research works and what type of knowledge it produces: sometimes generating inconclusive results, sometimes hampered by conflicts of interest and often giving rise to more questions than answers. This education should begin in schools and researchers should become more involved to convey a more accurate view of how genes function and emphasizing the complexities of inheritance and development. Exploring the psychological roots of naive genetic determinism could also improve education.

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Improving health professionals’ knowledge about genomics is also critically important for integrating pharmacogenomics into clinical practice. However, recent data show that the typical practicing physician has very limited training in genetics: A US national survey of 10,303 physicians indicated that although 97.6% of them agreed that genetic variation may influence drug response, only 29.0% of them had received any education in pharmacogenomics and only 10.3% felt adequately informed about pharmacogenomic testing. Fewer than 40% of them had recently ordered a test or anticipated ordering a test in the near future [11]. Another study, involving 597 primary care physicians in the USA, found that although the majority of respondents had heard of pharmacogenomics testing and anticipated that it would be useful to their patients, only 13% felt comfortable ordering such tests and 22% reported that they had not received any education in pharmacogenomics [12]. A recent survey of Greek pharmacists showed that they do not feel sufficiently competent to explain the results of pharmacogenomic tests to their clients [13].

Finally, and most interestingly, a study with 516 clinical geneticists and genetic counselors indicated that even they might not be adequately prepared for pharmacogenomics counseling. Twelve percent of genetic counselors and 41% of clinical geneticists indicated that they had ordered
or coordinated patient care for pharmacogenomics testing [14]. However, despite the fact that almost all respondents had received some education in pharmacogenomics, only 28% of counselors and 58% of clinical geneticists indicated they felt well-informed [14].

Healthcare professionals should therefore be encouraged—or even required by their respective professional bodies—to obtain continuous genetics education. This could be provided as accredited seminars organized by local universities and/or international organizations, for example. Such continuous genetics education would be especially important for those healthcare professionals who have not acquired sufficient knowledge in genetics during their undergraduate studies.

In recent years, individuals have increasingly sought access to their personal genetic information—personal genomes—outside the normal clinical context. Online DTC genetic testing is probably the best known example of this, although other movements, such as the “Quantified Self”, have also been catching up. The proliferation of mobile devices and applications that allow measuring, sharing and assessing data have contributed to this phenomenon. DTC genetic testing has been received with scepticism by most physicians, bioethicists and regulators. At the center of the highly polarised debate is the continuing uncertainty about the clinical validity and utility of the information these tests generate.

Critics of DTC genetic testing have called for strict regulation and even a ban of such services, primarily on the grounds that the information can be misleading. Recently, the US Food and Drug Administration (FDA) ordered the company 23andMe to cease offering health-related services, because the company had not complied with the agency’s requirement for prior approval of its services. It is noteworthy that one of the main arguments was the risk of harm posed to consumers related to pharmacogenomic information. The FDA warning letter to 23andMe suggested that consumers might opt to change their dosage or stop taking their medication on the basis of information that had not been properly understood, or had not been put into the context of their condition by a medical professional, thereby endangering their health (http://www.fda.gov/iceci/enforcementactions/warningletters/2013/ucm376296.htm).

However, it could be argued that consumers already have access to unfiltered and misleading information online that could lead to them drawing incorrect conclusions and making potentially dangerous adjustments to their own medication dosages. Why, then, did the FDA single out the genetic information provided by 23andMe in this context? Ultimately, this relates to concerns about the limited public literacy in genetics and genomics. However, it may also reflect a more general trend at the regulatory level to take exceptional measures in the name of protecting individual rights. Given that it is becoming increasingly easy and affordable to generate genetic data, the question we are facing is whether this “genetic exceptionalism” achieves its goal of protecting our rights, and if so, at what cost. Instead of accepting low rates of genetics/genomics literacy as inevitable, we should instead aim to increase literacy to enable people to make appropriate use of their genetic information. With sequencing costs continuing to plummet, it is possible that there will be a corresponding increase in both the supply of and demand for genetic/genomic services. On the other hand, as Caulfield has observed, the public image of commercial genetics—and of genetics in general—has shifted from enthusiasm to skepticism, with the pendulum swinging from uncritical euphoria about the tremendous benefits that genetics might yield to disappointment about how little it has so far delivered [15]. It is quite possible that this increasingly skeptical attitude could influence further uptake of genetic services.

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The over-the-counter (OTC) provision of private molecular genetic testing services in the form of saliva and buccal swab collection kits is a variation of the DTC theme. Genetic testing laboratories enter into partnerships with pharmacies to provide their services to the public. Although this situation is somewhat different from the DTC genetic testing model—since pharmacists are, in most Western countries, qualified healthcare professionals—there are still several shortcomings. The first, as noted above, is that pharmacists also have limited training in genomics. A second is that regulatory issues come into play, as illustrated by the example of the Walgreen-Pathway Genomics partnership, which was put on hold by the FDA in May 2010 owing to the lack of clearance for the DNA collection kit, which the FDA regarded as a medical device.

Two types of concern are usually raised in relation to the cost of pharmacogenomics testing: the first refers to the large investment needed to eventually bring a drug to market; the second is the cost that pharmacogenomics will eventually impose on health care systems. Skeptics are concerned that integrating pharmacogenomics testing and drugs into healthcare will be both unfair and unsustainable because their availability will be population-stratified and health care systems are already strained [16]. Limited resources will be spent on targeted drugs that are effective—or even marginally effective—for a small number of patients. Expensive drugs are likely to end up being available only to those who are able to afford them, thereby further exacerbating health inequalities. On a more positive note, it has been argued that costs will eventually come down as other costs are significantly reduced, such as those associated with treating adverse events or patient non-adherence. Furthermore, sequencing will soon be possible at significantly low cost, which will further reduce prices.

Whether pharmacogenomics will be integrated into the clinic will inevitably depend on costs. What constitutes an acceptable cost is ultimately a societal and policy decision, which should be based on evidence and concerned with social justice. Currently, one hurdle for this decision-making process is the lack of cost-effectiveness data. The economic evaluation of pharmacogenomics—understood both in terms of cost-effectiveness and cost-utility analyses—is therefore important, since it must take into account not only individual treatment costs but also overall nationwide healthcare expenditure. Such an analysis will require new assessment tools and eventually new rationing models.

 Genomics research has made significant advances over the past years, but is still not fully exploited in the clinic. The issues described here—the need to increase genetics literacy among the
general public, enrich the genomic education of healthcare professionals, economically evaluate genomic medicine, and address genethics—all require urgent attention. If genomics research is the foundation on which genomic medicine will be based, we need to build strong pillars to hold the whole edifice. Although the scientific foundations of genomic medicine are becoming stronger, the pillars on which the smooth transition of this knowledge to public healthcare benefits will stand are still under construction. These pillars must also be carefully crafted and supported so that genomic medicine can ultimately benefit the global community.

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Conflict of interest
The authors declare that they have no conflict of interest.

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