Getting personal

The possibility of more widespread application of 'personalized medicine', in which therapy is tailored to factors such as an individual's genetic make-up, has been on the horizon for years, but so far, translation of this concept to clinical practice has been limited. What might it take to change this situation?

This year marks the 150th anniversary of the birth of the British doctor Archibald Garrod, who coined the term 'inborn error of metabolism' to refer to monogenic diseases such as alkaptonuria — a disorder characterized by symptoms such as pigmented urine that is now known to be caused by the inheritance of two abnormal copies of the gene that encodes homogentisic acid oxidase. Garrod has also been credited with making the first proposal of a familial component in the variability of the effects of drugs, which might be considered to be the birth of the field of pharmacogenetics.

Now, several decades on from these ground-breaking proposals, it seems that the understanding of the genetic basis of diseases and of the responses to drugs is entering a new era. For example, as discussed in a news feature on page 590 of this issue, the past year has seen a flurry of genome-wide association studies that have identified genetic variants linked with various common complex diseases such as type 2 diabetes, rheumatoid arthritis and prostate cancer. Elucidating the genetic factors underlying such diseases poses a much greater challenge than that for monogenic diseases such as alkaptonuria, as these diseases are related to the complex interaction of multiple genes — each typically with a small effect — and environmental factors. Such challenges, however, are increasingly now being successfully tackled.

The completion of the sequencing of the human genome at the start of this decade has been a key to this success, but it is only recently that several other advances have begun to allow more of the potential of this genomic knowledge to be realized. In the case of genome-wide association studies, important information has also come from the cataloguing of genomic variations in the form of single nucleotide polymorphisms and data on their statistical relatedness from the HapMap project (http://www.hapmap.org). Coupling the availability of such information with increasingly powerful high-throughput technologies for genotyping has made the analysis of the potential linkage of up to 500,000 genetic variants with disease in thousands of subjects practically and financially feasible. As a result, a wide variety of clues — both expected and unexpected — about the genetic basis of disease are being revealed.

As such knowledge is likely to grow rapidly with the completion of further genome-wide association studies, also including those studying variations in drug response, a key question as always is how the knowledge might be translated into therapeutic applications. This question was the basis for a recent symposium entitled *Personalized medicine: prospect or pipedream?* organized by the Institute for Translational Medicine and Therapeutics (http://www.itmat.upenn.edu) in Philadelphia, USA, and supported by *Nature Reviews Drug Discovery*.

One theme of the symposium was the growth in possibilities for the use of disease-related genomic knowledge beyond the long-sought goal of developing and/or using targeted therapies on the basis of the identification of variations in genes linked to disease. For example, data from genome-wide association studies could also be used to enhance systems-biology-oriented disease research (see page 591), which might prove fruitful in a shorter time frame than the many years taken to move from a novel target to a drug.

It was also apparent that significant challenges to achieving the long-term goals of personalized medicine remain. First is the demonstration that the application of a particular aspect of genomic knowledge has a meaningful clinical benefit — a complex task for diseases in which multiple genetic factors, each with a small effect, are involved. Second, even in relatively simple monogenic cases for which the clinical importance is already well established, application of this knowledge is still not as widespread as it might be owing to issues such as the need to demonstrate cost-effectiveness.

However, with the cost of genetic testing set to fall further, and knowledge from studies such as genome-wide associations set to burgeon rapidly, there will be a growing number of opportunities to identify cases in which these challenges can be convincingly addressed. Concerted collaboration between the multiple disciplines engaged in research related to personalized medicine to achieve this would help considerably in addressing a third key challenge: raising awareness further among doctors, health-care providers and patients of the opportunities that personalized medicine offers.