Personalized medicine: hope or hype

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This editorial refers to ‘Personalized medicine: hope or hype?’ by K. Salari et al., on page 1564

As Salari et al. state in their recent study, medicine has always been personalized. As more is learnt about diseases, their causes, and how they can be treated, diseases become better characterized. The definitions of diseases become more specific and treatments more tailored to achieve improved outcomes in those who stand to benefit. At the same time, potentially toxic or expensive treatments are avoided in those who do not. The genetic characterization of diseases and response to treatments is no different from this process of improving the classification and treatment of disease that has been part of the development of medicine for over a hundred years. Improving the specificity of disease recognition and treatment in a rational way is neither hope nor hype. It is simply good medicine. The cost of sequencing a human genome has tumbled from about US$1 billion in 2001 to less than US$10 000 in 2011 and soon it is expected to be less than US$1000. This reduction in cost will create intense pressure to move such testing from research into clinical medicine. Before being adopted, the value of such testing will need to be assessed critically and will need to satisfy the criteria for a worthwhile screening or diagnostic test.

Salari et al. consider individual genetic treatments under three categories: pharmacogenomics, genetic predisposition to common diseases, and the identification of rare disease-causing genetic variants. Examples are given where pharmacogenomics may be useful in determining treatment, such as the categorization of people according to their different responses to the anticoagulant warfarin. The recognition of people with a genetic sensitivity to statins, with an increased risk of statin-induced myopathy, is another example. Acknowledging the differential responses to medicines is important, but the extent to which the ability to distinguish susceptible and non-susceptible individuals is of clinical value is still uncertain. The value of statins in lowering LDL cholesterol and reducing the risk of heart attacks and ischaemic strokes is great, and it may be a mistake to create a barrier to treatment by genotyping all people before they receive treatment. Adjusting treatment on the basis of reported clinical side effects may be better, by changing or reducing the dose of a statin in individuals who have persistent muscle pain. The choice of drugs in the treatment of cancer, some of which are expensive, offers a place for such genetic testing. The authors give an interesting set of examples that clinicians need to be aware of in the general practice of medicine, but judgement is needed over what tests should be used and when they should be done.

In the second category, common disease risk assessment, there is little scope for genetic testing in the prediction of common disease; it is an area where hope unfortunately trumps the negative evidence. Risk factors that can make a significant contribution to the burden of a disease are, within a population, usually too weakly associated with the disease they cause to be useful predictors of who will become affected. Genome-wide association studies have identified thousands of statistically significant associations of little or no clinical significance. Common diseases occur commonly, and it is usually not useful to screen for something that is common. In such circumstances, a population-wide approach is needed that is simple, effective, and safe. Screening based on age alone may be enough in these circumstances, the use of more complex assessments can be a distraction and unfruitful. A plot of detection rate (sensitivity) against false-positive rate (1 – specificity) is the appropriate way of assessing disease prediction, not the prediction of a person’s absolute risk of disease. The authors express the view that the clinical utility of determining genetic variance of disease may be at least comparable with that seen with established risk factor measurement. This is probably optimistic, but, even if true, the established risk factors are themselves poor predictors of disease.

In the third category considered by the authors, rare disease genetic variant discovery, the enormous heterogeneity that is emerging from the application of whole-genome sequencing stretches the imagination. There may be useful clinical applications of this technology, but these may well be more limited than many people suspect. An example of its valid use is pre-implantation genetic diagnosis. An area where it is abused is direct-to-consumer genetic testing; this is often promoted, perhaps disingenuously, as an information-gathering exercise, when in reality it services the anxieties of the worried well, and offers risk assessments of little or no practical value. Often there is no remedy, or if there is it could be offered using simple information such as the presence of existing disease, or just age.
Salari et al. are correct in suggesting caution and focusing on the first of their three application categories. It is commendable that these authors, who have worked in this field, have been candid in recognizing the strengths and limitations of our increasing knowledge of identification of genetic determinants of disease.

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References

CARDIOVASCULAR FLASHLIGHT

Cholesterol pericarditis with massive pericardial cholesterol cyst

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A 63-year-old male presented with exertional dyspnoea, chest pain, and dizziness. He had a cardiac history of coronary artery disease with a percutaneous coronary intervention of the left descending artery. Furthermore, a pericarditis with a small pericardial cyst was observed 8 years ago. The general history revealed rheumatoid arthritis. On admission, central venous pressure was elevated and an apical systolic murmur was heard. Transthoracic echocardiography showed a large pericardial mass with compression of the right ventricle (Panels A and B). Magnetic resonance (MR) showed a large inhomogeneous mass of 9 × 8 cm, suspected to be a pericardial cyst (Panel C). The patient was discussed with our cardiac surgeons and accepted for cystectomy. During operation, the pericard was very fibrotic. The cyst was filled with small crystals (Panel D). Despite careful removing of the cyst the right ventricle could not unfold properly due to local constriction. Only after local epicardectomy, the right ventricle could visually unfold again. Pathology showed a fibrotically thickened pericard with extensive bleeding and cholesterol crystals, all of which suit a cholesterol pericarditis. A cholesterol pericarditis is an uncommon form of pericardial disease which is characterized by cholesterol crystals. The occurrence of a cholesterol pericarditis in patients with rheumatoid arthritis has been previously reported. In this unique case of cholesterol pericarditis, a massive cyst was discovered which caused symptoms due to right ventricular compression. To our knowledge, no similar cases have been reported to date in the literature.

Panels A and B. Transthoracic echocardiography of the subcostal view and the apical four-chamber view. Arrow indicates the cyst.
Panel C. MR, arrow indicates the cyst.
Panel D. The surgical view during operation, arrow indicates the edge of the surgically opened cyst.

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