Personalised Medicine: Moving Away from Large Randomised Controlled Trials?

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Randomised, controlled trials (RCTs) have become the gold standard for disease prevention and treatment, both in terms of effect and safety. These necessarily rely on identified epidemiological risk factors and in turn contribute strong recommendations for guidelines.

This extensive use of RCTs as the basis for any medical or scientific advance works well in a homogeneous population and has proved of value in many cases but fails to take into account genetic and biochemical individuality. Furthermore, some RCTs have required tens of thousands of patients in order to achieve sufficient power and a p-value of <0.05. Much is made of these mega-trials, whereas a trial of 100 subjects which produces a p-value of <0.001 is often overlooked due to its small size, although in fact it could be far more specific and predictive. In addition, the lack of homogeneity in the population is perhaps understating the true effect of various treatments in the subset of the population which will respond well but is failing those who are non-responders; the overall effects are further diluted due to large numbers.

Approximately 50% of patients suffer cardiovascular events or end up with triple vessel coronary disease without having any of the conventional risk factors (smoking, type 2 diabetes, obesity, dyslipidaemia, hypertension and family history of cardiovascular disease). This would strongly suggest that at least one significant risk factor is missing and this has been suggested to be genetics. Genes themselves carry numerous variables in terms of single nucleotide polymorphisms (SNPs) and mutations, as well as multiple genes affecting the same condition. For example, for cardiovascular disease, genetic risk seems to be dependent on not only the apolipoprotein E genotype but also on pro- or anti-inflammatory and other genotypes, all representing many additional variables. The state of the organ or tissue on which treatment is intended to act, plus the patient's digestive, absorptive, metabolic and detoxification ability are all factors further affected by genetics. These will also play a large role in the success or otherwise of treatment, providing yet more variables. Remarkable though the sequencing of the human genome has been, all it has achieved so far in practical terms is to increase the possible permutations of risk factors.

A consideration of the mathematics shows that with the five conventional risk factors for atherosclerosis there are a possible 31 different combinations; if genetics as one risk factor is added in, this rises to 63 possible combinations. Nevertheless, individuals at risk are currently put on statins and/or aspirin, whether or not genetics supports this strategy. Those with risk factors but normal cholesterol are urged to take statins, even in the absence of evidence-based support of this practice. Consideration of conventional risk factors merely generates more questions; for example, should patients with a family history of late disease development be treated early as a preventive measure? If they are not carrying the same genotype, the treatment will have no effect but could potentially generate side effects.

Nevertheless, we will soon see large numbers of RCTs that look at genetic markers in order to assess their sensitivity in disease prevention; in a genetically homogeneous population, sample sizes can be significantly smaller and still achieve significance. This would allow specific drugs to be developed for specific genotypes for a particular condition. It would allow a much more narrowly defined normal range for biomarker tests, since the current wide normal ranges are of little help in identifying patients at risk by proximity to the current upper or lower normal limits. This would further enable patients at risk to be more easily identified and accurately stratified. Routine blood test requests could then be sent with notification of the patient's genotypes, in order to obtain the much narrower normal range which would detect both clinical conditions and those which were previously subclinical. It is therefore expected that, at least with respect to cardiovascular disease, a number of 'subdiseases' would emerge within the realm of atherosclerosis and consequently management strategies would be unlikely to remain the same as they are today.

Although this would represent a significant improvement on the present state of diagnosis and treatment, genetics alone is insufficient and cannot account for the 50% of all cardiovascular events not predicted by risk factors. Merely having a predisposing gene variant or series of genes does not necessarily mean that one will succumb to the condition. Epigenetics shows us that diet, lifestyle and exposure to toxins and pollutants will modify the effect of this predisposition, creating yet more possible permutations. Some of these environmental influences may be recent and others may have set in train a pathological or protective process many years ago, such as the reduction in allergy found in children who were breast fed as babies.

The individual genetic approach will take time and is at present expensive, so what is the optimum way of tackling disease and its risks for the present? An individually tailored approach, making greater use of expanded biochemical analysis would take into account any effect of genetic SNPs and nutritional deficiencies, which also to some extent reflects exposure to environmental toxins and pollutants. The assays to test individual nutritional status (vitamins, minerals, essential fatty acids etc) are already widely used in nutritional therapy and greater demand for these tests would increase availability and reduce cost. Correction of nutritional deficiencies and poor lifestyle choices could go a long way towards improving the patient's condition, as has been demonstrated in numerous studies. Many of these trials, however, are published in non-clinical journals and clinicians are frequently unaware of them, suggesting that clinical journals could usefully make more effort to incorporate these studies.

Finally, it is clear that consideration of genetics, nutritional, lifestyle and environmental factors and the patient's internal state will add an almost infinite number of variables to the equation. We cannot hope to allow for all of these factors but acknowledgement of their existence should cast doubt on the slavish adherence to RCTs, 'evidence-based medicine' and a 'one size fits all' approach to testing and treatment. All we can hope for is a reasonable estimate of the patient's individual makeup, while seeking always to improve the usefulness of testing and the quality of care.