Personalizing healthcare: from genetics through payment to improving care?

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Interindividual variability in patients' responses to medicines, including the likelihood of toxicity, is commonly due to differences in their genetics.[1] Both problems present adverse care and resource issues, with non-response rates as high as 30–60%.[2] Resource issues include the cost of adverse reactions which increase the number of emergency hospital admission at an estimated cost of GB£2 billion per annum.[3] Such resource issues are an increasing concern among health authorities with pharmaceutical expenditure growing faster than other components of ambulatory care, driven by ageing populations, rising patient expectations and the continued launch of new expensive drugs.[4] New premium-priced medicines are being launched at over US$300,000 per year, often with only limited health gain versus current standards.[4,5]

Targeting valuable resources through personalization is empirically an attractive proposition for health authorities or health insurers as it reduces the numbers needed to treat (NNT) and increases the numbers needed to harm (NNH), thereby improving the health gain for patients within available resources. It claims to deliver the right treatment to the right patient at the right time.[6] However, there are barriers that need to be addressed before personalized medicine becomes a reality. This article aims to stimulate this ongoing debate and provide guidance for the future.

Personalized medicine is not new. For instance, GPs in the UK do not prescribe non-steroidal antiinflammatory drugs (NSAIDs) to patients with asthma as a matter of course. The guidelines for antihypertensives are predicated on knowledge of a patient's race, age and co-morbidities. When there are a few examples, physicians can memorize and integrate these into routine practice. However, as we dissect diseases beyond such phenotypic stratification, we find increasing examples of genetic differences in therapeutic responses, some of which are already being exploited.[1,7–9] This is resulting in a more heterogeneous spectrum of disease referred to by the recently coined 'precision medicine'.[6] Ultimately, full personalization of medicines will require a better understanding of the systems of genetic pathways rather than just single gene association, as demonstrated by the disappointing predictive yield of genome-wide association studies (GWAS). New technologies for whole genome sequencing and new approaches for combining information from a panel of biological variables will have a profound impact on the way in which drugs and diagnostic tests are being and will be developed, as well as the way physicians will practise medicine in the future.[2]

As this field of systems biology evolves with greater clinical utility in personalizing therapy, the funding and policy environment must also evolve to facilitate the expediency with such therapies that are introduced, used and evaluated in routine care.[2] Currently, there are only relatively few clinical examples of personalized medicine

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being integrated into routine care, a phenomenon that has not been helped by the current controversies surrounding the testing of patients prescribed clopidogrel or warfarin.[7–9] However, this is changing with recent research suggesting that 50% of the variability in the dosing of anticoagulant therapy can be explained by genetic factors.[10] Overall, greater integration of personalized medicine into routine care will require new clinical trial structures, and innovative funding strategies that make it easier to fund new diagnostic drugs and any additional facilities along with potentially 'valued' drug therapy. Patient education will also be needed as the range of therapeutic options increases and becomes more complicated to navigate.

Barriers

However, for personalized medicine to become a greater reality, the current barriers need to be appraised and addressed.

The fragmentation of the pharmaceutical market into ever smaller subpopulations is an understandable threat to the traditional business model of the pharmaceutical industry. However, the development and funding of new 'blockbusters' is becoming increasingly difficult as more existing drugs lose their patents, with the cost of generics as low as 2–3% of originator prices.[11] Increasing pressure on resources will also mean that the value of new drugs will come under greater scrutiny, especially if they are adding to choices rather than targeting real unmet need.[12]

Occasionally, events precipitate a retrospective search for personalization, which was the case for the 'Coxibs'.[4] The commercial value of identifying a genetic subgroup in which the pendulum swings towards a favourable outcome precipitated a search for single nucleotide polymorphisms (SNPs) to help predict therapeutic response. However, launching strategies appeared not to have been directed towards such an approach, ultimately contributing to the demise of the drug class. If such practices increasingly become the norm, it will be essential to develop policies that prevent, for example, the development of drugs whose effectiveness is maximal in ethnic groups that are enriched in affluent populations.

A major concern among health authorities and health insurance agencies is that increased targeting of new drugs, will lead to more and more new drugs being considered as 'orphan drugs'. As a result, companies will seek very high acquisition costs for their new drugs increasing the cost burden alongside the cost of the tests. This appears already to be happening with crizotinib and vermurafenib being launched at US$10,000 month excluding the cost of diagnostic tests, administration costs and other drugs to treat these patients, and US$25,000 for new drugs to treat a small cohort of cystic fibrosis patients again excluding the costs of other treatments.[5] This at a time when the funding of cancer care is increasingly challenging for all countries. Consequently, pharmaceutical companies should seek to moderate their price expectations as without targeting, the value proposition of their new drugs would be appreciably reduced making it unlikely that high prices will be reimbursed especially in Europe.

The burgeoning field of genetic diagnostics is also becoming attractive commercially. However, their integration into traditional models of care is currently not commonplace. This has resulted in private enterprises offering direct-to-consumer genetic testing. While their penetration would historically be restricted to a small cadre of health seekers, such services are increasingly accessible via mobile software. Ashley and co-workers recently demonstrated that personalized sequencing does yield clinically useful information.[13] However, while companies such as deCodeme, 23 and me and Navigenetics could be considered the pragmatic vanguards of this phenomenon, and a case made for their role in driving this field into the clinic, there have been concerns regarding the lack of clinical utility of their outputs, discordance of results between companies and test-related anxiety.[14] This mismatch between clinically interesting information, and its clinical utility, again demonstrates the major barriers that need to be addressed before their routine use in clinical practice. Further, the lack of clarity around the route to reimbursement for innovative diagnostics remains an incitement to caution among investors. Equally for commercial organisations, the incentives for developing their own diagnostics are limited by the risk of eroding existing profits through market segmentation.

At a health systems level, population health remains the critical driver of policy development. Health authorities are interested in drugs that are effective in an appreciable proportion of patients with a given disease, that is, those with low NNTs, whereas individual patients wish for therapies that have a high chance of working on them. Consequently in the short term, the costs and associated infrastructure to instigate large-scale diagnostic facilities and testing may well be a barrier, and outsourcing may be a short-term possibility for new tests with proven clinical utility. This will also help address the current deficiencies in staff training.

Lastly, patients can be forgiven for having an incomplete understanding of how to steer through the plethora of genetic developments. Where once longevity drove medical advance, and then a more focused measure taking into account patient-reported outcomes in terms of for instance quality-adjusted life years (QALYs), patients may soon have to navigate decisions based on their own personalized QALYs; for example which putative genetic risk do I want to mitigate against and at what cost? Unregulated, this could be the source of major anxiety.[14] However, if appropriately implemented, it could usher in a new development giving people the opportunity to live the life they choose.[15]

Next steps – benefits of personalized medicine

What benefits could personalized medicine bring to commercial organizations, health systems, patients and practitioners? Despite the many challenges, the benefits for all key stakeholders are clear. For pharmaceutical companies, personalization prior to the first phase III trials will reduce the likelihood of failure in drug development.[1] As such, there may need to be a rebalancing in the parameters in the current equation of drug development. If personalization means less failure, then market fragmentation becomes less hazardous. Furthermore, the *a priori* use of pharmacogenomic approaches may reduce the costs of development by reducing the risk of not showing a clinically useful treatment. The model of effective medicines for niche markets was the foundation of Genzyme's success, whose original orphan drug Ceredase was used to treat Gaucher's disease, before being acquired by Sanofi-Aventis in 2011 for approximately US$20.1 billion.[16] Where *personalized medicine* is gradually seeping into healthcare delivery, i.e. BRCA status in breast and ovarian cancer, epidermal growth factor receptor (EGFR) mutation status testing in lung cancer or the BCR-ABL fusion protein in chronic myelogenous leukaemia, cautious lessons can increasingly be drawn on the indirect impact of outcomes and economics at a system level.

As discussed, adverse drug reactions account for between 5% and 10% of all acute hospital admissions at an estimated cost to UK NHS of £2 billion annually.[3] In the USA, admissions related to the complications of warfarin alone cost on average $10,819.[17] The cost implications of prescribing drugs to patients with limited therapeutic effect also offer incentives to health systems to address this alongside reducing the costs of toxicity. However, this must be balanced against the resources in manpower and funding necessary for increased testing, as well as the concerns that new drugs for targeted subpopulations will increasingly be considered as orphan drugs with higher associated costs.[5]

For individuals, improvements in effectiveness and reductions in toxicity should help to reduce anxiety with drug taking, and potentially improve compliance where toxicity is a concern.[18] Furthermore, improvements in personalized care is a frequently demanded value by patient groups.[19]

For practitioners, frequent therapeutic failure could lead to work stress and ultimately a more disenfranchized workforce.[20] Appropriate training in the delivery of personalized medicine, coupled with effective and appropriate system-wide analysis, would limit the current lottery of clinical effectiveness and adverse events. The fall in NNTs would reduce the number of prescriptions and associated costs before a single patient benefits, a phenomenon that would be favoured by patients and providers alike.

Conclusions

There are causes for concern with the move towards personalized medicine; genetic prejudice, commercial monopolies of the care of specific patient groups and escalating costs, especially if

targeted therapies are priced similar to current orphan drugs. However, progress in a manifestly ethical direction, with an eye on the systemic implications, and the potential to appreciably improve health within available resources should provide a stimulus to develop an environment in which the patient orientated and value driven personalization of medicine can flourish.

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