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Personalising medicine: feasibility and future implications from a payers' perspective

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ABSTRACT

There are considerable differences in how patients respond to treatments due to a number of factors calling for personalised approaches to care, which is happening. However, the early promise of personalised medicine has not always translated into improved care for patients. Payers have concerns that current tests can be costly, requests for funding specific tests have subsequently been reversed as more information becomes available, and there is currently fragmentation in the funding of diagnostic tests. Payers also have concerns that pharmaceutical companies are exploiting the situation by seeking orphan status for their new targeted medicines driving up requested prices. It is also not clear who should fund biomarkers that accompany new expensive medicines. This is changing as the cost of tests come down, and payers develop new models to optimise the managed entry of new medicines as well as evaluate potential prices for new medicines for orphan diseases. There are also developments with 'big data' offering new understanding of disease complexity to enhance pipeline productivity and diagnosis as well as ongoing developments with drug resistance testing and research into the role of microbiomes to improve future health. Current challenges and concerns are being addressed. This will continue to improve patient care.

Introduction

Patients respond differently to medicines due to a variety of factors including biologic, environment and genetic factors^{1,2}. A patient's genomes account for 20-95% of the variation in response to drug disposition^{2,3}, translating into considerable differences in response to treatments^{2,4,5}.

Some treatments are already targeted, e.g. tamoxifen for patients with breast cancer with oestrogen receptor (ER) sensitivity and trastuzumab for HER2 positive patients^{2,6}. Until recently, treatment for patients with hepatitis C was dependent on their genotype⁷. This is changing with the development of second generation direct-acting antiviral agents⁸.

However, the complexity of the various biological systems involved in different diseases^{2,9} helps explain why there are a high number of non-responders to certain medicines^{1,2,6}, and why an appreciable number of medicines fail to progress beyond Phases II or III despite early promise¹⁰. These issues put into doubt Adaptive Licensing approaches until better targeting of medicines can be achieved¹¹.

As knowledge of biological systems grows, drug pipelines should become more productive and patient care improve². This helps explain why the European Commission is one of the leading drivers in personalised medicine in Europe and beyond^{2,12}. The collection of 'big data' offering new understanding of disease complexity^{13,14} should further enhance pipeline productivity. However, there are continuing concerns that the concept of personalised treatments in for instance cancer will be difficult to achieve due to inherent limitations including Darwinian evolution resulting in intratumour heterogeneity⁶.

Resource issues are important especially in Europe with payers increasingly unable to fund all new premium priced medicines¹⁵. This includes new cancer medicines and those for orphan diseases at ever increasing prices^{2,6,16-18}. Consequently, new effective medicines or genomic tests that offer better targeting and reduced overall costs should be welcomed by all key stakeholder groups.

Objectives and definitions

Personalised medicine and personalised healthcare are not new concepts². Greater targeting of treatments has the potential to revolutionise healthcare delivery through improved effectiveness, reducing the numbers needed to treat (NNT), reducing side-effects increasing the numbers needed to harm (NNH), as well as potentially reducing costs^{2,19}.

However, as in many growing fields, the promises of pharmacogenomics have not always translated into appreciable improvements in patient care². In addition, some tests have been advocated to improve patient selection; however, subsequent caution is preached as more data becomes available². There are also concerns that pharmaceutical companies are seeking orphan status for new targeted medicines driving up prices costs^{2,20,21}.

Consequently, the objective of this mini review is to appraise current knowledge about the value and concerns of personalised medicine principally from a payer's perspective to debate potential ways forward.

Key considerations

General considerations

Greater knowledge of genomics increases the possibility for defining patient subgroups for medicines to enhance their effectiveness and/ or reduce their toxicity. However, there are concerns that currently only a few geno- or phenotyping tests are being used routinely in clinical practice, exacerbated by ongoing debates². Pharmacogenomics has been effective in predicting toxicities to treatments, e.g. abacavir in HIV type 1 patients. However there are concerns with the sensitivity and specificity of testing for dihydropyrimidine dehydrogenase

(DPD) deficiency in patients prior to starting 5-Fluorouracil (infusion or oral tablets) for the management of their GI cancer².

In cancer, Poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors have shown promise in a subgroup of breast cancer patients with triple negative breast cancer (TNBC) who have inherent defects in DNA repair². However, there is ongoing debate whether the addition of PARP1 inhibitors to platinum agents or other agents, including mTOR inhibitors, will improve survival in TNBC patients^{22,23}. In addition, the results from different targeted approaches to managing patients with cancer have generally been disappointing apart from a few well-known cases⁶.

Biomarkers

The National Cancer Institute in the US defines a biomarker as a biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease². They are increasingly being used in the field of cancer to improve treatment effectiveness². This is illustrated by gefitinib for NSCLC, which the FDA initially restricted because of toxicity concerns. Following this, it became apparent that patients with tumours that have EGFR activating mutations could significantly benefit from treatment (10 – 26% of NSCLC cancers), leading to label changes².

Research has also centred on identifying easy to use biomarkers, which along with increasing knowledge of gene expression and aberrant signalling pathways, should increase the number of medicines that can be rationally prescribed and dosed². However, this is proving problematic⁶.

Challenges and concerns for routine use of diagnostic tests

There are ongoing controversies and concerns regarding the routine use and funding of some pharmacogenetic tests. The EGAPP (Evaluation of Genomic Applications in Practice and Prevention) group in the US^{2,24} had concerns with 3 out of the first 4 tests they initially evaluated.

There are also continuing controversies surrounding genetic testing prior to initiation with either clopidogrel or warfarin² as well as ongoing debates about funding of BRCA testing and Oncotype DX testing for patients with breast cancer in terms of their associated costs and cost-effectiveness. This should change with costs falling for pharmacogenetic testing². These issues increase concerns among payers with funding new personalised medicine approaches including tests. This needs to be addressed.

Future developments may include improved translation of single and combined biomarker test information as well

as developments in technology platforms, mathematical models, and systems biology. This may mean more complex and costly clinical studies posing organisational and ethical problems especially if multiple subgroups with different treatment strategies are included^{2,25}. One way forward could be to have studies combined with systems biology modelling including big data^{2,14}.

Big data is characterised and defined by the volume, velocity, variety and veracity of complex data, combining the generation, storage and analysis of data from health records, biological samples, imaging, environmental factors, digital biomarkers and known biological mechanisms, with statistical, mathematical and computational analyses¹⁴. The objective is to identify disease specific factors and associations. Knowledge, predictive models and decision support systems developed from these analyses could potentially be applied to data from an individual patient to allow for more personalisation in the research and discovery process, more precise diagnosis, and more personalised preventative and therapy strategies²⁶. However, still concerns in patients with cancer⁶.

Genetic data is being generated in ever escalating volumes at faster speeds as a consequence of the rapidly evolving sequencing technology. However, a gulf has evolved between the speculated potential of genomic data and the yields that it was delivering clinically²⁷. To help address this, the systems available are undergoing a revolution with for instance IBM Watson working with a number of institutions to use cognitive computing capability to develop OncoKB, an Oncology knowledge base²⁸ to generate new understanding, diagnostic and treatment options for individual cancer patients.

In addition to genetic biomarkers, high volume, high frequency digital biomarkers defined as “consumer-generated physiological and behavioural measures”²⁹ are becoming increasingly available and are being exploited in primary research. For example, the myHeartCounts study is a global cardiovascular research study using technology built on the Apple ResearchKit Platform. This is using a combination of mobile phone sensors and short questionnaires to collect data on over 50,000 participants. The study is now collaborating with 23andMe and participants have the option of sharing their genetic data with myHeartCounts researchers^{30,31}.

It will also become increasingly important for regulatory agencies to collaborate on the development and establishment of harmonised guidelines for genotyping and biomarker testing. However, it is acknowledged there are many challenges and difficulties achieving this.

Key issues for healthcare and funding bodies

Key issues for payers include clearer co-ordination between the various bodies responsible for funding of

care and those evaluating new treatment approaches. Companies also need strategies that address concerns among payers regarding personalised medicine to enhance future use².

These concerns resulted in a number of medical, ethical, legal, social, economic and organisational issues that need to be considered by organisation when commercialising new personalised medicine approaches². Key funding issues from a payers’ perspective include current high prices for new orphan medicines, with a number now reaching blockbuster status as a result^{2,32}. We are already seeing new medicines for orphan diseases funded at up to €15million/ QALY following pressure on governments, and this cannot continue^{21,33}.

Social issues include potential stigmatisation of certain subpopulations as well as reimbursement issues. Reimbursement issues include who should fund accompanying tests for new medicines if there are resource concerns².

Future

There are a number of potential ways forward for all key stakeholder groups to enhance utilisation and funding for new diagnostic or prognostic tests as well as targeted treatment approaches, which have been summarised in a recent publication². Suggested activities include re-defining orphan status for new medicines as well as new pricing approaches, seeking more information about the sensitivity and specificity of diagnostic tests before reimbursement, and developing new models to optimise the management of new personalised treatments starting pre-launch and continuing post launch^{2,21,34}.

Patient and physician education will also be an increasing challenge as the range of therapeutic options increase and become more complicated to navigate. For instance, a recent survey suggested only 10% of physicians in the US believed they were adequately informed about pharmacogenomic testing³⁵, and this will grow with greater sophistication and more options unless addressed. However, this is likely to change as targeted therapies become more commonplace coupled with developments in decision support tools and technology platforms.

Personalised medicine for infection – Drug resistance testing

Conventional lab culture techniques can take several weeks and may not accurately capture all pathogenic strains. Specific resistant genes can be assayed using rapid polymerase chain reaction (PCR) methods, amplifying pre-selected resistance genes if they are present. Such tests can reduce diagnosis time to <1 day³⁶. However, one limitation of such methods is that they are currently unable to detect novel resistance genes. Recent advances in Whole

Genome Sequencing (WGS) should help address this³⁷, allowing the tracking of resistant outbreaks in hospitals³⁸ and the community. WGS may also allow early warning of resistance before it emerges³⁹. Further research to identify the genotypes that lead to phenotypic resistance will be essential for the potential of WGS to be fulfilled to reduce resistance development. This is increasingly essential to reduce resistance rates, which is a global concern increasing morbidity, mortality and costs^{40,41}. Alongside this, the development of new bioinformatics tools capable of improving data analysis⁴².

The role of the microbiome in personalised medicine

The role of the microbiome is also becoming increasingly apparent in human health^{43,44} especially as the microbiome can be cheaply and, in some cases, relatively easily, manipulated, in a non-invasive manner^{45,46}. The microbiome has the potential to be used both to profile disease risk, e.g. obesity⁴⁷ which is another growing global public health issue⁴⁸, and as a non-invasive biomarker, e.g. diagnosis of Crohn's disease⁴⁹. Drug-microbiota interactions have also been shown to affect the efficacy and safety of medicines⁵⁰. Large-scale studies such as the Human Microbiome Project have extensively mapped the composition of the microbiome during disease states and shown the role of microbial species present by association. However a greater understanding of the mechanism of interaction between host and microbe will be required to apply these findings therapeutically to aid payers improve patient care efficiently⁵¹.

Funding and other issues

Successful funding by payers of new developments will need to address their key concerns following the early disappointing findings of the EGAPP studies². There will also be greater scrutiny over the value of new personalised medicines including new cancer medicines given ever increasing costs^{16-18,52,53}, leading to discussions on minimum effectiveness criteria for these medicines^{16,17}. There will also increasingly be discussions on who should fund companion diagnostic tests for new premium priced developments starting pre-launch.

Conclusions

Personalised medicines, including targeted treatments, should bring considerable benefits to patients and healthcare systems with increasing knowledge of genomics and pharmacogenomics⁶.

To attain this, there must be greater co-ordination of bodies including payers to fund new medicines and diagnostic tests of value. Alongside this, greater scrutiny over requested prices for new targeted medicines especially for cancer and orphan diseases^{16-18,21,52}. Pharmaceutical companies should also consider more realistic pricing for new targeted treatments to enhance reimbursement

with reduced need for extensive marketing including advertising^{2,53}.

We hope this short review has stimulated further debate about personalised medicine and potential ways forward for all key stakeholder groups.

Conflicts of Interest

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