

# Predictive tests and personalised medicine

Acceptance of the personalised medicines paradigm is strictly dependent on this approach clearly benefiting patients with minimal effects on the actual delivery of healthcare. The use of molecular diagnostics to predict how an individual will respond to a particular medicine, in terms of safety or effectiveness, offers considerable benefits over the current practices of prescribing and monitoring patient responses. This brief article examines the real value of predictive tests based on molecular diagnostic technologies, in part by citing two cases studies, one examining drug safety and the other drug efficacy. However, the impact of present forms of disease management through molecular diagnostics also impacts on the requirements that may evolve in terms of future healthcare provision.

**W**ith the increasing number of ‘blockbuster’ drugs, ie, those individual entities that reach global sales of more than \$1 billion per annum, being marketed and prescribed, it has become apparent that many of these drugs only benefit part of the intended patient cohort, with estimates suggesting that overall effectiveness ranges from 80% to as low as 20% depending on the disease area addressed<sup>1</sup>. These observations about the relative effectiveness of medicines, equally fuelled by concerns about safety of medicines, the rising costs of supplying medicines and other macroeconomic factors affecting healthcare budgets, are leading to new models of how medicines are prescribed. Such new models of prescribing increasingly involve health technology assessments, undertaken by agencies modelled on the UK National Institute of Clinical Excellence (NICE) and now prevalent across Europe and the United States, two of the largest geographic pharmaceutical markets.

Among the many activities of these agencies, there lies a role in the decision-making around

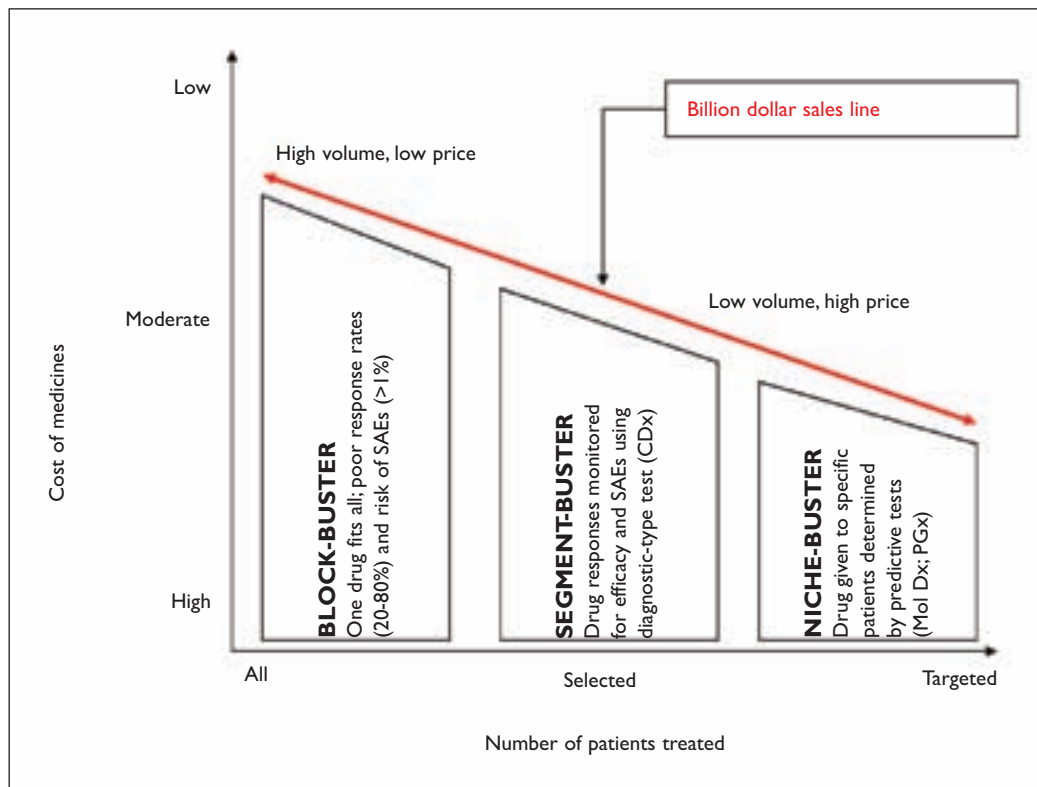
reimbursement for medicines, and indeed the level and timing of reimbursement. The timing of reimbursement in particular is interesting and begins to touch on the potential role of molecular diagnostics in how medicines are supplied to appropriate

**By Dr Eddie Blair**



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**Figure 1:** Migration from block-buster treatments to high-value targeted treatments (SAE = severe adverse event; CDx = companion diagnostic; PGx = pharmacogenetics)



patients. For example, two years ago, UK NICE ruled that the UK National Health Service (NHS) should only pay for a ubiquitin proteasome inhibitor, bortezomib (Velcade) when it had been proven effective, as measured by the response of a single validated biomarker, Serum M Protein (SMP)<sup>2</sup>. There is now open discussion that this model of 'proven efficacy preceding reimbursement' is the preferred model for regulators, payors and healthcare providers in all major pharmaceutical markets. What this model then does is to

remove the perceptual barrier that protected the block-buster mentality and heralds the opportunity for segment-buster and niche-buster<sup>3</sup> medicines, ie, medicines based on higher response rates with minimised side-effects (Figure 1).

The segment-buster opportunity extends the healthcare tool-kit to include companion diagnostics and monitoring tests. Such tests will tend to use traditional diagnostic technologies based on protein and/or small molecule detection, although the increasing use of molecular diagnostics in

## Box 1: Predictive vs prognostic tests

The Genomics Health Oncotype Dx test<sup>4</sup> commands a substantial and fully reimbursable price of about \$3,500 because it identifies patients likely to suffer a relapse and/or metastasis of primary breast cancer. It is known to have a very high prognostic value in determining the likelihood of an individual to experience a particular outcome, ie, recurrence-free survival.

The various tests that indicate the likelihood of an individual responding to trastuzumab (Herceptin) or to imatinib (Gleevec) are known as predictive tests because they predict with reasonable confidence whether the particular form of breast cancer present is likely to be sensitive to treatment. As many of these tests use relatively simple technologies to conduct the predictive diagnosis, they do not command a high reimbursable price, despite offering high value information.

It is possible for predictive tests to also have prognostic value and vice versa, but it is the primary application of the test that determines its real value and positioning. In addition, such tests may also be used for response monitoring but generally their pricing means that alternate platforms will be used for this purpose.

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nearer-patients settings may extend the tool-kit somewhat. The niche-buster model is predicated upon the careful definition of the responder population during drug development and then the careful identification of individual responders in the marketplace; it is this predictive role that is a key

benefit of molecular diagnostics in the personalised medicine offering.

Predictive tests (see **Box 1** to understand the differences between prognostic and predictive tests) are now available for guiding the metabolic potential of individuals and the often-linked propensity to suffer serious adverse events, as well as tests that robustly identify those that are most likely to respond to specific medicines, either as individual entities (cetuximab) or as part of a specific drug class (EGFR kinase inhibitors)<sup>5</sup>. Case study examples of these types of tests – predictive tests of safety or effectiveness – are discussed in **Boxes 2 and 3**, by way of illustrating the real value that these tests offer.

### Box 2: Case study 1 – Kras-based efficacy prediction<sup>6</sup>

It has been known to molecular oncologists for many years that the signalling cascade, initiated by occupancy of the epidermal growth factor receptors (EGFRs), continued downstream via the *ras* transducer molecular to result in the nuclear activation of gene expression and DNA replication. This cascade is managed by a series of on-off switches – actually mediated by the opposing processes of phosphorylation and dephosphorylation – which ensure that signal transduction operates in a controlled and environmentally-responsive way. Equally, molecular oncologists have known for many years that the *ras* family of proteins can be altered by gene mutations such that they remain in a permanently activated form resulting in permanent downstream activation that manifests itself as the unregulated growth of cancer cells. Thus when exciting new EGFR-modulating products, such as panitumumab (Vectibix) and cetuximab (Erbix), reached the marketplace, it was reasonable to expect that individuals with activating mutations in *ras* might respond less well. This sadly has indeed proven to be the case. Individuals expressing a normal *Kras* molecule, on the basis of *Kras* genotyping, show substantial benefit, in terms of improved survival (overall and ‘progression-free’) while those with ‘activating’ mutations in the *Kras* gene show no benefit from cetuximab treatment<sup>6</sup>. *Kras* mutation tests, offered by several vendors, are now featured on drug labels in the EU and are likely to be approved for full reimbursement by UK NICE, such is the predictive value of these molecular diagnostic tests.

#### What’s the future situation?

The role of molecular diagnostics in the future delivery of healthcare is not as simple as guiding the right treatment to the right patient at the right dose and at the right time, but also impacts on health economics by delivery benefit at the right price. As a general consequence, the prediction of response and the early treatment of disease is likely to have a more favourable outcome on the health to individuals. This, however, has two long term effects: firstly, individuals may be on therapies for considerably longer treatment periods and, secondly, individuals are likely to stay functionally well for much longer. In terms of health economics, costs may well switch from expensive primary, secondary and/or tertiary care provision, such as hospital beds, mechanical interventions, etc, to the costs of providing long-term treatments to many more symptomatically well individuals. In fact, the scenario above is one that many healthcare systems as moving to; they are supplanting symptom-based reactive medicine with objective testing-based predictive medicine. Thus it is clear that molecular

### Box 3: Case study 2 – abacavir hypersensitivity safety prediction<sup>7</sup>

The nucleoside-based reverse transcriptase inhibitor, abacavir (Ziagen), became an important component of multi-drug HIV therapies following clinical development in the mid- to late-1990s. However, its role at the vanguard of successful HIV management was compromised by a rare but potentially fatal hypersensitivity reaction in AIDS patients. Following a genome-wide genetic association study by several independent groups, it was found that mutations at a major histocompatibility locus, ie a part of the genome that expressed regulators of immune response and tolerance, appeared to be retrospectively associated with the majority of hypersensitivity reactions. Prospective studies confirmed the association of this single-nucleotide polymorphism (SNP) locus, called HLA-B\*5701, with hypersensitivity and established a clinical utility for the test. The test, offered by a number of clinical lab organisations, now appears in the label of all abacavir-containing drug formulations, and since its introduction there have been no reported SAEs associated with abacavir hypersensitivity. In essence, this predictive test has rescued a whole disease-management strategy for HIV/AIDS.



diagnostics tests as guides to prescribing tailored (or personalised) medicines have an impact way beyond the current scenarios described in Figure 1. Indeed, the use of molecular testing to offer better medicines at earlier times with more favourable outcomes may well have longer-term effects on societies as a whole.

Many healthcare commentators, particularly those with a predilection for the problems of the pharmaceutical industry, can get very pre-occupied by issues such as dry development pipelines, inexorably increasing costs for medicines R&D and the difficulties in getting medicines approved and reimbursed at an economically fair rate. However, the real challenges for the future of healthcare are readily summed up by two words – ‘ageing population’. In almost all countries globally, life expectancy is increasing – driven in part by basics such as clean water, better sanitation and plentiful food supplies – with effective medicines playing a considerable role; at the same time the quality of life is not increasing<sup>7</sup>. Indeed, in India, dietary changes are causing a huge rise in the levels of Type 2 Diabetes (T2D) and in China the affordability of cigarettes is seeding respiratory problems, particularly chronic obstructive pulmonary disease (COPD). In Western populations, the management of previously lethal disease conditions, including some, but not all, cancers, is allowing all members of societies to live longer; however, the rise of degenerative disease, particularly associated with the central nervous system (CNS), is substantially reducing the quality of life in later years for many

individuals. Thus some care must be taken in assessing benefit over perhaps inappropriately short timeframes.

### In conclusion

Rationally developed therapies used diligently in the healthcare marketplace can undoubtedly benefit society, and the role of good quality predictive and diagnostic molecular tests is unambiguously a great advance for pharmaceutical medicine. The increased use of predictive tests will surpass the benefits already seen by traditional companion diagnostics to the point that earlier interventions will herald the rise of predictive medicines. However, disease will not become a thing of the past; disease will remain and will manifest in different forms from that observed and so-well managed today. It is clear that in ensuring a healthier future, we should be careful about what we ask for and be careful about what we deliver. **DDW**

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