The use of *in vitro* diagnostics to define the exact nature of a disease and guide treatment will change the way that new drugs are developed and prescribed.

**IVDs: Transforming the Prospects for Personalised Medicine**

The increased prevalence of chronic disease and the demand for cost-effective therapies is responsible for the rise in prominence of personalised medicine (PM). Today, PM is largely driven by pharmacogenetics and targeted therapy – but PM is more than this, and will need to incorporate the routine utilisation of objective non-genetic testing in treatment decisions for early detection, dosage and efficacy. The use of *in vitro* diagnostic (IVD) testing to define the nature and severity of a disease, and to guide treatment options, is already evident in the oncology and infectious disease therapeutic areas, and the mindset within pharma is quickly switching from PM being a threat to business to becoming an opportunity to gain strategic competitive advantage.

**In Vitro Diagnostics (IVDs)**

IVDs are essential in the quest to improve the treatment of disease by enabling PM – defined as providing the right treatment at the right time to the right patient in the right dose. To provide the best possible outcome, we need to be able to detect the disease or condition as early as possible, and subsequently monitor the efficacy of the therapy.

An IVD is designed to detect the presence of a biomarker that correlates with an aspect of the disease or treatment needed to be measured or monitored. IVDs are most often performed in clinical laboratories and usually test for a single parameter. Contemporary advances in genomics, proteomics, nanotechnology, fluidics and microarray technology provide a practical means to quantify thousands of parameters simultaneously from a single sample.

As a result panel tests are becoming more available and can increasingly be performed near the patient or at the point-of-care (POC). The diagnostic benefit of panel tests is likely to surpass that of single parameter products in the future. PM will grow and evolve as both diagnostic and pharmaceutical companies engage these technologies.

IVDs can be defined by their potential applications:

- Diagnostic – biomarkers for early detection, efficacy/response
- Prognostic – biomarkers for efficacy/response/recurrence
- Predictive – biomarkers for baseline risk and targeted therapy
- Pharmacodynamic – biomarkers for optimal dose and compliance
- Pharmacokinetic – biomarkers for uptake, optimal dose and compliance

**Molecular Diagnostics**

The biggest impact on the use of diagnostics in drug development today is the drastic improvement in genetic sequencing and analysis. There is now great optimism that large-scale genome sequencing efforts will lead to many new targeted therapies. Knome, Illumina and Complete Genomics currently sequence, analyse and store the complete genome for around $5,000 compared with around $350,000 in 2008. Several companies – such as Otogenetics, DecodeMe, 23andme and Navigenics – offer genotyping services for $1,000 or less to analyse the genetic risk of around 47 diseases and traits ranging from heart attack and diabetes to alcohol flush reaction and male pattern baldness by mapping SNPs on the exome (1).

Life Technologies and Illumina claim that they will have the capability to sequence the complete genome in less than a day and for less than $1,000 before the end of 2012. BioNanomatrix and Complete Genomics make claim to the probability of a $100 genome in eight hours with an instrument they are co-developing. Pacific Biosciences reported its technology may complete a genome sequence in 15 minutes some time in the near future (2).

It is expected that, once costs drop to under $1,000 per sequence, many individuals will have their genome sequenced. Once these sequences are correlated with demographic and medical information, researchers will gain a much better understanding of the relationship between genetics, diseases and drug metabolism (2).

Today, we understand that if novel agents can be developed against disease-driving events and targeted to the right patients using diagnostic tests, then remarkable responses can be seen – for example, the
PLX-4032 B-Raf inhibitor in B-Raf mutant melanomas – and even tailored, or ‘personalised’ to match, for example, the unique cancer genetics of a patient.

Current Medical Practice and the Ideal of Personalised Medicine

Two statistics highlight the inevitability of the role of IVDs in PM:

- IVDs direct over 60 per cent of clinical decision-making but accounts for only two per cent of global healthcare spend (3)
- 90 per cent of drugs currently on the market work in only around 40 per cent of individuals – translating annually into $350 billion worth of ineffective prescriptions (4)

Disease states are developed over a person’s lifetime and evolve through complex contributions from multiple sources, including a person’s genome, epigenetic changes, protein and metabolite modifications, and the effects of xenobiotics. Generally, a disease is diagnosed late in its progression when multiple parts of a biological system are dysfunctional producing much complexity to the understanding of cause and effect; it isn’t surprising that most molecularly targeted therapies available today have a limited influence on the course of a disease.

A new paradigm is emerging to develop high-value niche-busting drugs that target particular patient groups with the use of IVDs and will enable:

- Earlier detection of disease states, making it easier and cheaper to treat effectively
- Selection of optimal therapy reducing trial-and-error prescribing
- Reduction of adverse drug reactions
- Increased patient compliance
- Better selection of targets for drug discovery
- Reduction in time, cost and failure rate of clinical trials
- Use of drugs that failed clinical trials or were withdrawn
- Reduction in withdrawals of marketed drugs
- A shift in medicine from reaction to prevention
- Reduction in the costs of healthcare

The result of all this diagnostic capability is personalised healthcare leading eventually to a lifestyle health management plan (5).

PM can, in part, be achieved by pharmaceutical companies realising the value, to their products, of approved diagnostics, and diagnostics providers recognising that their products can positively impact the development and promotion of medicines (6,7). External pressures are also guiding change in that healthcare providers are demanding more cost-effective therapies, regulators are demanding treatments that have demonstrable efficacy, and users are gaining greater awareness of disease pathogenesis and treatment options. The next generation of therapeutics will be safer and more efficacious, and less expensive to develop and implement. That is, drugs will be intelligently targeted or ‘personalised’.

Personalised Medicine in Practice in 2011

There are at least 72 examples of drugs, treatments or diagnostics currently used in PM, revealing a growth in the use of IVDs and genetic testing (8). Furthermore, there are increasing requirements for the use of ‘companion diagnostics’ – that is, a diagnostic test is defined in the drug label (usually submitted during registration) such that the drug must not be prescribed without the use of the diagnostic. Co-development of a companion IVD and new drug is even more challenging, since the risk/benefit of the drug and the IVD are evaluated in parallel with little or no prior knowledge of the benefit.

In July 2011, the FDA released its companion diagnostics draft guidance (9). Immediately afterwards, two new linked companion diagnostic and drug targeted oncology therapies were approved: Roche/Genentech’s Zelboraf linked to BRAFV600E and Pfizer’s Xalkori, linked to structural variants of anaplastic lymphoma kinase (ALK). These are the first linked oncology companion diagnostics since Herceptin/Her2 was approved in 1998; furthermore, there are around 40 personalised medicine products, mainly in oncology, currently in late stage registration trials that could enter the market in the near future (4).

Point of Care and Adoption of IVDs

To provide the biggest benefit to PM, many diagnostic tests will need to be provided at the point of care (POC). There are many POC diagnostic devices being developed – both nucleic acid- and immunoassay-based – and these are coming close to commercialisation. There is a technology lag in the development of integrated POC diagnostic devices as they need to fulfil requirements such as simple operation, robust use and clear results. Increasingly, simple and robust microfluidics approaches can provide unequivocal results to clinicians comparable with central laboratory results.

Stakeholder Influence

Many payers of healthcare treatments recognise that IVDs can contribute to better treatments and reduce costs in several circumstances. Some payers are becoming increasingly proactive in sponsoring trials and performing analyses of their patient and prescribing data to identify areas where early, targeted interventions would reduce disease burden and cost.
Payers are also communicating their willingness to reimburse for targeted therapies in these areas. As regulators and payers see the benefits offered by a PM approach, so those involved in the development of companion diagnostics will require additional guidance and support. The marketing approval of diagnostics in the EU will become more regulated, requiring evidence of efficacy in clinical trials akin to the approval of medicines by the EU Mutual Recognition Procedure, rather than a ‘simple’ self-certification to achieve CE marking. In addition, some drugs have been refused approval because they did not have a companion diagnostic, one example being Chemgenex’s Omapro (11).

Conclusion
The use of IVDs for PM is beginning to transform the practice of medicine. It is allowing healthcare providers to:

- Shift the emphasis in medicine from reaction to prevention
- Predict susceptibility to disease, improve disease detection and pre-empt disease progression
- Customise disease prevention strategies
- Prescribe more effective drugs and avoid prescribing drugs with undesirable side effects
- Reduce the time, cost and failure rate of clinical trials
- Eliminate trial-and-error inefficiencies that inflate healthcare costs and undermine patient care

A plethora of activity has occurred over the last two years between pharmaceutical and diagnostic companies, including an increase in M&A activity (10). Many healthcare and technology businesses are overlapping in sectors such as medical devices and diagnostics for targeted therapies. This convergence of life sciences and technology will create more opportunities for companies to develop new solutions to old problems – improving efficiency and compliance, and ultimately driving down healthcare costs.

Currently PM is seen with a diagnostic focus; however, over time the industry will broaden this view and apply other patient stratification tools and approaches such as patient monitoring, medical/surgical devices, data management solutions and clinical decision support systems.

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