

Molecular diagnostics and personalized medicine: value-assessed opportunities for multiple stakeholders

Acceptance and operation of a personalized medicine strategy within modern healthcare requires that all key stakeholders are able to understand and assess the benefits offered by the approach. In addition to the technological aspects of molecular diagnostics, as enablers of personalized medicine, stakeholders must also be apprised of the value-adding effects of the strategy in terms of improved treatment efficacy and health economics. This review attempts to cover these broad stakeholder interests by articulating the scientific feasibility, the beneficial medical outcomes and the commercial attractiveness offered by the integration of molecular diagnostics and personalized medicine into healthcare systems, principally by demonstrating how technology integration and value addition can be robustly assessed and represented.

KEYWORDS: biologicals ■ companion diagnostics ■ drugs ■ pharmaceuticals ■ pharmacogenetics ■ prediction ■ prevention ■ value assessment

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Personalized medicine has for some time been expected to provide a solution for the problems in healthcare associated with the indiscriminate prescribing of partially efficacious, potentially unsafe [1] and ever more expensive medicines. In one thoroughly 'disruptive' leap [2], the use of objective testing to aid a physician in selecting the best treatments for an individual patient offers, in theory, a thoroughly desirable outcome for all stakeholders. However, in practice, adoption is perhaps more likely to be incremental based on the growing experience described in this review. Companion test-guided medicine will be both more effective and safer for the specific patient and, although the price may be higher, the value realized in terms of health economics will reduce the expense in many cases [3]. In this review, value is taken to illustrate, in context, a beneficial outcome that may have more than a simple economic value, for example, a better practice of diagnosis and treatment that benefits society.

Given this move to practice, why did a respected study suggest in 2005 that the era of personalized medicine is 15 or more years away [101]? Part of the answer lies in the gaps that exist in the understanding, appreciation and indeed basic knowledge of personalized medicine amongst all stakeholders. Thus, much of the early 'false dawn' of personalized medicine was associated with trying to patch over these gaps in order to gain a consensus view on the true benefits of the personalized medicine paradigm. In addition, while not the only event to facilitate personalized medicine,

the completion of one or more human genome sequences, and the annotation thereof, has given scientists a fundamental roadmap to human health and disease [102]. Therefore, after several years, many initiatives, conferences, meetings, networking events and white papers, the time is approaching when widespread application of the personalized medicine ethos has arrived; the talking can end and the real activities have begun [103]. Now scientific capability is able, in theory, to provide the right medicine to the right person, and at the right dosage and time. However, the long gestation period involved in the technology adoption can lead to some frustration with this now maturing approach to healthcare [104].

Behind this scientific capability is the development of new diagnostic (Dx) technologies, particularly in molecular (nucleic acid-based detection) Dx (MDx), to target treatments based on their likely response in terms of safety and effectiveness. MDx are often viewed as detecting and/or profiling nucleic acids (RNA or DNA), but we prefer a broader view that includes protein-based detection and/or profiling using so-called 'omics' technologies. In addition, new business models, where the clinical benefit is translated to enhanced value for all constituents of the healthcare system, have been developed. This review covers such ground to provide a short reference for all stakeholders in the hope that the gaps may be filled rather than patched over. It begins by examining how the provision of more personalized treatments was first perceived.

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Road to personalized medicine

In this section, we examine how the opportunity to integrate personalized medicines in most, if not all, pharmaceutical (Rx) therapy areas came about. We do this by first considering the history behind testing for guiding infectious disease and cancer therapies, the therapy areas where this 'test-and-treat' approach was most readily embraced, and then address areas where unmet need currently exists.

■ Historical perspective: HIV & oncology

Molecular biologists will be aware of the use of antibiotics, such as ampicillin and chloramphenicol, to select for the transduction of a plasmid conferring antibiotic resistance. In a similar way, antibiotic resistance is transferred in hospitals or in the community, to give rise to methicillin-resistant *Staphylococcus aureus* and other so-called 'superbugs'. The acquisition and transmission of resistance by human pathogens was further highlighted by acyclovir-resistant herpes simplex and, towards the end of the late 1980s, less than 10 years from its discovery as the etiological agent of AIDS, the emergence of zidovudine-resistant HIV. HIV drug resistance represents a complex form of resistance, with point mutations at multiple sites within viral genes resulting in both single and broad resistance to all major drug classes,

particularly reverse transcriptase and protease inhibitors. As more information was acquired and resistance patterns matched to drug selection, it became possible to predict the effects of single and multiple changes in the viral genome to the relative sensitivity of viral 'pseudotypes' to a variety of antiviral agents. The true value of such genotyping was demonstrated in studies such as VIRADAPT [4], where treatment based on genotyping profiles gave a more substantial response than treatment based on best prevailing practice (FIGURE 1). A test-and-treat approach is now employed, particularly in the developed world, and indeed features in the International AIDS Guidelines [105,106]; as a result, prospects of long-term survival for those infected by HIV are extremely good. More recently, a companion test for a new type of HIV therapy has been developed which relies not on the genetic profile of the virus but on the functionality of its envelope proteins; the Trofile™ test from Monogram (CA, USA) which was co-developed with Pfizer's (NY, USA) maraviroc (Selzentry®) determines whether the predominant virus subtype uses the CCR5 receptors, as opposed to CXCR4, to gain entry to T cells. If it does, then maraviroc is a potent inhibitor of viral replication and, thus, is an effective therapy. Technically, the test is not a MDx, that is, it is not based on the detection of nucleic acid sequences, but nonetheless, it fits with the long-held approach to personalization of HIV therapies. Furthermore, early indications in the management of hepatitis C virus liver disease, where viral genotyping robustly guides the duration of interferon therapy required, suggest that a test-and-treat strategy will be required for other classes of therapy, particularly as viral resistance becomes of greater clinical significance [107].

The other therapy area in the vanguard of personalized medicine is oncology, where the molecular definition of the disease has facilitated the development of targeted therapies. Such therapies act through well-defined molecular pathways, therefore the key to effectiveness of such chemical or biological entities is the presence of the functional target components of the pathway. The first example of using a companion Dx (CDx) to guide a targeted therapy was the use of EGF receptor (EGFR) tissue stains to determine if Roche's (Basel, Switzerland) therapy, trastuzumab (Herceptin®), would be effective, because only tumors expressing high levels of EGFR (subjectively scored 2+ and 3+) would respond to this therapy. True MDx have also been used for long periods of time to select patients who would benefit best from imatinib

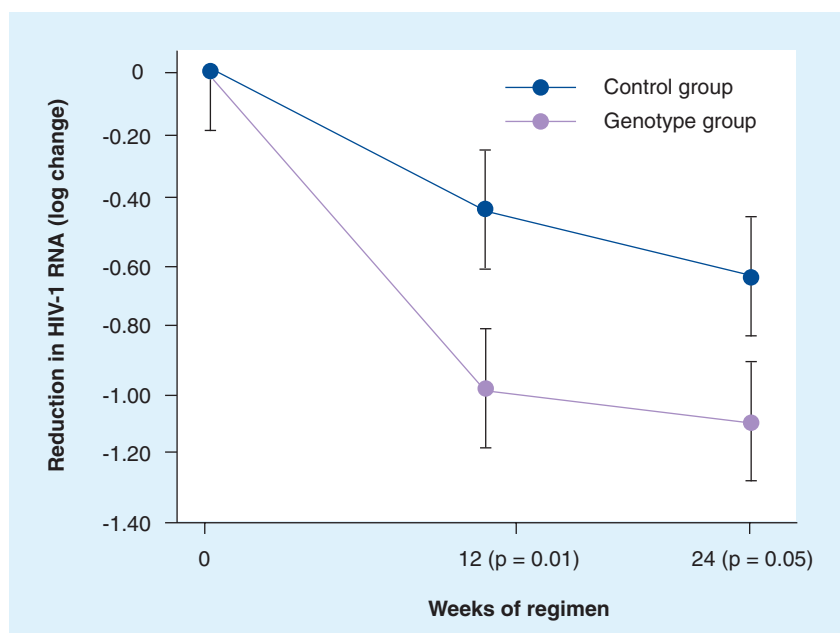


Figure 1. Effects of prior genotyping on reduction of HIV load.

The control group is patients receiving therapies without prior testing; the genotype group is those tested for mutations affecting resistance before treatment. Reprinted from the *Lancet*, 353, Durant J, Clevenbergh P, Halfon P *et al.*: Drug resistance genotyping in HIV-1 therapy: the VIRADAPT randomised controlled trial [4]. Copyright (1999), with permission from Elsevier.

mesylate (Gleevec®), developed by Novartis (Basel, Switzerland). In acute myeloid leukemia, the Philadelphia chromosomal translocation was fine mapped to a gene recombination resulting in the production of a BCR–ABL fusion protein; the presence of the gene fusion is key to the effectiveness of imatinib and the test is essential for guiding drug use. With advances in technology, particularly the ability to detect key mutations in small amounts of tumor tissue and/or in a high background of ‘normal’ genetic material, molecular tests continue to be key in guiding a number of new cancer therapies, such as panitumumab (Vectibix®; Amgen, CA, USA) and cetuximab (Erbix®; Eli Lilly, IN, USA; Merck Serono, Geneva, Switzerland) (see ‘MDx as CDx: value-driven adoption’ section).

■ Other applications: met & unmet therapy areas

Molecular diagnostics should also play a key role in determining the safe use of medicines, irrespective of predicted effectiveness, and indeed genetic tests that guide the metabolic potential of individuals are used to guide dosing of a number of widely-used drugs, such as warfarin (Coumadin®; Bristol-Myers Squibb, NY, USA), atomoxetine (Strattera®; Eli Lilly) and fluoxetine (Prozac®; Dista Products Co., IN, USA). Such tests are based on SNPs in the genes that encode key metabolic enzymes, such as the P450 cytochrome variants, CYP3A4, CYP2D6 and CYP2C19, and can guide whether an individual is likely to be a slow or a fast metabolizer. As well as tests that guide effectiveness of HIV therapies, the safety test for the key HIV antiviral abacavir (Ziagen®, GlaxoSmithKline [GSK], London, UK) has been responsible for the resurgence of this drug in the market, concurrent with a reduction in life-threatening inflammatory side effects. Genetic mapping has demonstrated that a change in the human MHC complex, HLA-B, is strongly associated with drug hypersensitivity manifested by a rash on the torso and elsewhere of sensitive individuals (see ‘MDx as CDx: value-driven adoption’ section). As with tests of effectiveness, these safety tests can be the absolute key to the successful deployment of effective medicines on a personalized basis.

Given the rise in chronic disease associated with longer and more opulent lifestyles, it is likely that additional therapy areas will provide the next wave of medicines that are enhanced by CDx. Neurodegenerative disease conditions, such as Alzheimer’s and Parkinson’s, are predicted to the major cause of morbidities and poor

quality of life in the late 21st Century [5], and as more therapies are developed, the key to their safe and effective use is likely to be the better definition of the patients illness and/or metabolic profile, akin to early 21st Century cancer medicines. Other therapy areas – obesity, diabetes, rheumatoid arthritis and cardiovascular disease – are all likely to have substantial need for companion tests as more individualized treatments are developed, but factors such as economic attractiveness and scientific feasibility of developing companion tests may impact on prioritization [3].

Of course, with an aging population and the increase in chronic diseases, healthcare systems are faced with inexorable increase in healthcare expenditures (forecast to be US\$3 trillion, 16% of gross domestic product in the USA alone by 2015) [2,108]. These soaring healthcare costs are forcing a complete re-evaluation of medical care delivery. Prioritizing diseases and common therapies which would benefit from the application of genomic-based MDx could provide potential support.

MDx technologies

In this section, we briefly consider two technology platforms that demonstrate continuing promise as part of the personalized medicines toolkit [6]: expression profiling of RNA or proteins, and DNA sequence profiling to look at point mutations and epigenetics. The strengths, weaknesses and applications of the two platforms are assessed (TABLE 1) and their link with amplification methods (TABLE 2), particularly by quantitative PCR, is articulated.

■ Expression profiling RNA & pharmacogenomics

This particular platform has grown from a relatively low-density, manual spotting activity to one that is highly commercialized and offering large numbers of gene probes on high-density chips and arrays. Thus, in a single experiment it is possible to monitor ‘global’ expression patterns from small quantities of well-defined primary tissues or from culture-derived cells. Such biological material may be treated by defined chemical entities such that the perturbation of selected pathways, in terms of gene expression, can be monitored. The technology relies heavily on nucleic amplification technologies to accurately boost the level of target RNA species to be probed by the complimentary capture sequences on arrays (TABLE 2). Care over sample preparation and the use of robust internal controls and calibrators

Table 1. Molecular platforms for companion diagnostics.

Technology	Strengths	Weaknesses	Applications
Pharmacogenomics (including gene-expression analyses and qPCR)	Directly targets patient subpopulations with specific molecular characteristics Limits toxicity and untoward side effects Cost-effective and well-established technical methodology	Limited knowledge regarding global gene-network interactions Limited pharmaceutical alternatives for individuals with polymorphic variants leading to adverse reactions Sample heterogeneity	Targeted therapeutics Disease subclassification RNA expression for diagnosis/response classification
Pharmacoproteomics (protein-expression profiling)	Direct functional interactions with drugs and molecular targets	Difficulty in large-scale target identification Inaccurate and inefficient expression quantification Sample heterogeneity Limited access to high-quality preserved samples	Testing and patient stratification for drug sensitivity
Pharmacogenetics (SNP testing and differential qPCR, haplotyping)	Cost-effective large-scale genetic variation screening in patients Low error rate Well-established analysis tools	Limited biological implications Difficult to find direct gene targets Unable to detect target functions	Many disease applications Prediction of therapeutic response Metabolic potential High-risk variations
High-throughput gene sequencing	Comprehensive sequence information Emerging insight into epigenetics Cost-effective 'deep' sequencing	Expensive experiment per sample Overwhelming quantity of data with high-analysis challenges No direct detection of target functions	Tumor classification Epigenetic assessments

qPCR: Quantitative PCR.
Adapted with permission from Overvest et al. [6].

is key to ensuring that output data is accurate and that the correct interpretation can be made. Examples of expression profiling used to guide the value of treatment are the 21-gene OncoType Dx[®] test from Genomic Health (CA, USA) and the MammaPrint[®] 70-gene array from Agendia (Amsterdam, The Netherlands). An abundance of other similar multigene tests exist but many remain unvalidated and/or in early development.

Proteins & pharmacoproteomics

This platform has benefited through development as a means of spatially resolving disease with tissue biopsies using immunohistochemistry (IHC) as a principle detection methodology. While nucleic acid-based detection on tissue has also proven robust, the introduction of multiplexed IHC, for example, using quantum dot-based detection, has allowed mapping of disease progression and also the effects of treatment regimens. Systems from Ventana (AZ, USA), Monogram (CA, USA) and Dako (Glostrup, Denmark) all offer the substantial benefits of protein-based detection on structurally intact specimens. Pharmacoproteomics has proven somewhat less robust with vendors of promising systems often failing to build robust businesses. New variants, such as Biosignatures (Newcastle upon Tyne, UK), Pronota (Gent Area, Belgium) and Metanomics (Berlin, Germany), may

benefit from the technological advances in this area over the last few years, but the jury largely remains out on proteomics and its cousins, metabolomics and glycomics.

■ DNA sequence profiling Pharmacogenetic & SNP analysis

The development of long-run DNA sequencing methods and the further exploitation of differential hybridization has facilitated the ongoing identification of SNPs, particularly those associated with drug responses. Some effects may be broad, such as polymorphisms in drug metabolizing genes, for example, cytochrome P450 2D6 or 2C19, or some effects may be highly specific, such as changes in key gene-response pathways (*KRAS*, *MEKK* or *EGFR*). Furthermore, the linkage of certain SNPs in haplotyping studies allows a more detailed and complex understanding of how mutations can affect individual responses to medicines. The development of amplification-based tests that have gained regulatory approval demonstrates that SNP profiling can be both rapid and robust, while offering a plausible tool for personalizing medicines. Treatments such as cetuximab (Erbix) and panitumumab (Vectibix) have benefited from KRAS CDx based on the DxS (Manchester, UK) Scorpions platform technology (see 'MDx as CDx: value-driven adoption' section).

Table 2. Selected methods of nucleic acid amplification.

Technology	Vendor	Enzymes				Isothermal	Speed	Sensitivity	Specificity	PoC potentials
		DNA polymerase	RNA polymerase	DNA ligase	Rnase H					
Target nonamplified										
Direct hybridization	QIAGEN (Hilden, Germany) and Gen-Probe (CA, USA)	-	-	-	-	+	*****	*****	*****	*****
Signal amplified										
bDNA	Chiron (CA, USA)	-	-	-	-	+	*	*****	****	**
SMART	British Biocell International (Cardiff, Wales)	+	+	-	-	+	*****	*****	*****	*****
Target amplified										
PCR	Roche (Basel, Switzerland)	+	-	-	-	-	***	****	****	****
LCR	Abbott (IL, USA)	+/-	-	+	-	-	***	****	*****	*****
NASBA	Organon (Oss, The Netherlands)	-	+	-	+	+	****	****	***	****
TMA	Gen-Probe	-	+	-	-	+	*****	*****	*****	*****
LAMP	None	+	-	-	-	+	*****	*****	*****	*****
HDA	QIAGEN	+	-	-	-	+	*****	****	*****	*****

The number of asterisks shows the level of validation (i.e., * is equivalent to poorly validated; ***** is equivalent to very well validated).
 +: Applicable; -: Not applicable; bDNA: Branched DNA; HDA: Helicase-dependent amplification; LAMP: Loop-mediated amplification; LCR: Ligase chain reaction; NASBA: Nucleic acid sequence-based amplification; PoC: Point of care; SMART: Signal-mediated amplification of RNA technology; TMA: Transcription-mediated amplification.
 Adapted with permission from [27].

High-throughput sequencing

The automation and increased throughput of chain termination-based sequencing has offered both a rich toolkit for personalized medicine as well as a bioinformatics headache. Terabytes worth of data are being generated in relatively short periods of time, which then require annotation for the full meaning to be extracted. The fall in costs of sequencing (US\$1000 per genome read) and the coordinated efforts to sequence large numbers of representative diploid human genomes (the 1000 Genome Project) means that benchmark sequence profiles are available for the assessing the significance of SNPs potentially associated with illness or treatment response. Variations in high-throughput sequencing allows mapping of DNA methylation sites which consequently allow the assessment of epigenetic influences on illness and treatment response too. Solexa/Illumina (CA, USA) and 454/Roche are organizations in the vanguard of high-throughput and 'deep' DNA sequencing.

■ Role of amplification technologies

All of the nucleic acid-based platforms have benefited from and indeed may require prior sequence amplification by one of a variety of isothermal or thermal cycling-based methods (TABLE 2). While many technologies have been developed with a key purpose of overcoming the dominant intellectual property held on quantitative PCR – the base PCR licenses expired in March 2005 [7] – it is PCR that remains the most widely used and most robust method of target amplification. Without PCR, the platforms described above and in TABLE 1 would not reach the analytical sensitivity and specificity required. For example, differential PCR is able to provide the selectivity to find a mutation represented by less than one copy in 100 sequences.

Although not intended as exhaustive, this short section aims to identify key MDx technologies that underpin the development of personalized approaches to medicine. A discussion of associated bioinformatics needs has been omitted, but the reader is referred to the European Bioinformatics Institute [109] for a series of informative monographs on scientific and political developments in this field. However, in addition to technology and scientific developments, the adoption of a personalized medicine approach requires the coordinated involvement of several stakeholder groups, which are considered next.

Stakeholder values, needs & expectations

Healthcare, irrespective of its geographical location and sociopolitical environment, can be viewed as comprising three stakeholder groups (providers, supporting industry and governance) sharing the common aim of providing the best service to a fourth stakeholder group – the patients, as consumers, or beneficiaries, of this service (FIGURE 2). Each of these stakeholders will have shared and differing, indeed often competing, values, needs, expectations and challenges, which will ultimately form the growth drivers – or resistors – to the enablement of a common practice of personalized medicine. In this section, we consider these values, needs, expectations and challenges from the perspective of each of the stakeholders involved. As there are many factors coming into play in the landscape of personalized medicine affecting each stakeholder, either selectively or generically (see FIGURE 3), we have selected three – effectiveness and safety, demonstration of value and the rise in chronic disease – as being the key generic factors that will affect the interests of all stakeholders. Here, we sample three representative stakeholders, while alluding to the impact on other members of the same stakeholder grouping where appropriate.

■ Rx companies

Effectiveness & safety

A strong driver for personalized medicine advancement is patient stratification and sub-population targeting as part of clinical studies, given increasingly stringent regulatory requirements for drug efficacy and control of adverse events. Other approaches are being suggested by different stakeholders, for example, adaptive clinical studies and stepwise drug approval, or regulatory guidelines for algorithm based-clinical decision support systems (see 'MDx as CDx: value-driven adoption' section).

There is a considerable enthusiasm for the inclusion of biomarkers information and ultimately patient stratification considerations in the drug lifecycle management, with molecular assays supporting late Phase I/early Phase II studies and beyond, ultimately to post-market Phase IV studies of new and repositioned drugs. Indeed, the need for biomarker-enabling studies is now more widely supported than it was 5 years ago. Being able to design trials and better select patient populations seems to be a clear benefit of biomarker data generation. Indeed, there is some evidence to suggest that a good biomarker/CDx

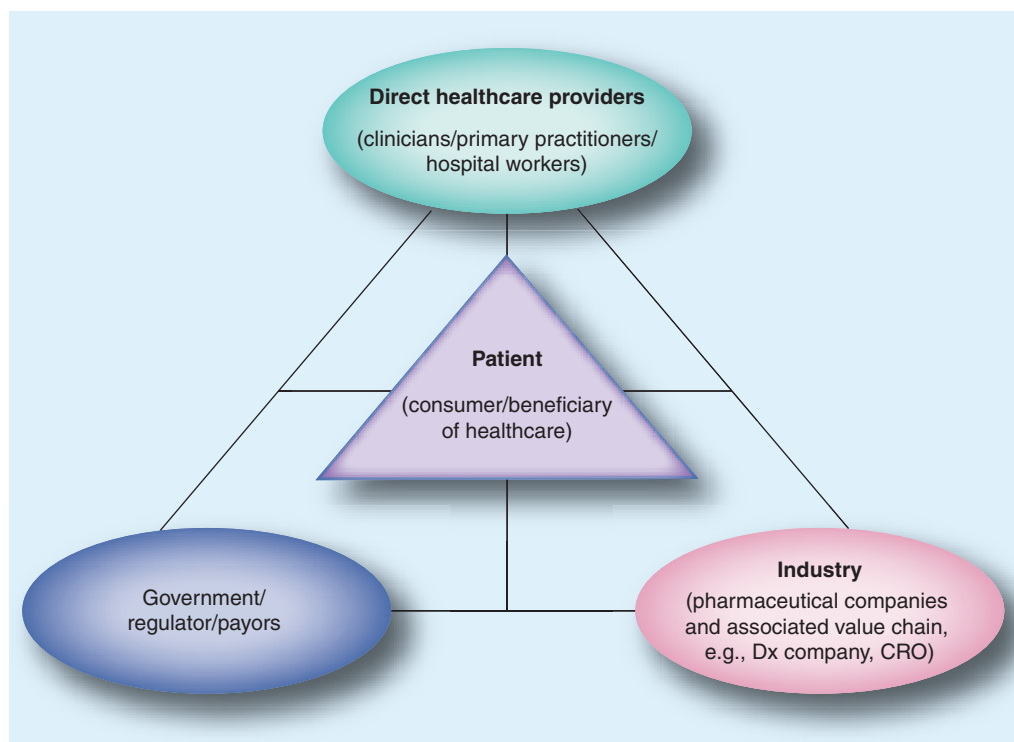


Figure 2. A healthcare 'value-net'.

CRO: Contract research organization; Dx: Diagnostics. Adapted with permission from Little and Blair [120].

strategy can favorably alter attrition rates of targeted medicines over conventional medicines [8]. Rx company project teams now include additional expertise in product decision and strategy processes to factor information regarding, for example, drug, device and Dx regulatory agencies or payer groups, as early as possible in the development process. Thus, internal stakeholder engagement is a key aspect of gaining industry support for the personalization of medicines.

Demonstration of value

Over the last decade, many articles and reviews have described the Rx 'innovation gap', where continually increasing capital investment has not provided the expected return on that investment in terms of the number of new molecular entities gaining regulatory approval [110]. Considering such large investment, particularly in the clinical trial phases of drug development, and the high (>90%) failure rate in reaching Phase III from Phase I [9], as well as the large opportunity costs in failing to identify winners, there is a definite need for new and potentially more successful approaches. The Rx industry is at a critical point where it needs to reinvent its R&D processes to eventually return to an attractive return on investment [111] for its investors and become a more sustainable industry sector again. There is evidence that

a biomarker/CDx strategy can substantially boost the net present value of new medicines by approximately US\$2 billion [3,10], thus providing considerable economic incentives for Rx companies.

To address the need for drug-development process re-engineering, various mechanisms are currently being considered [110]:

- Large merger and acquisitions announcements over the last year, for example, Pfizer and Wyeth (NJ, USA), Roche and Genentech (CA, USA), Merck (NJ, USA) and Schering Plough (NJ, USA);
- Increased investment in biological drug R&D and consequent pipelines;
- Further increases in outsourcing across all drug discovery and development steps;
- New forms of partnering relationships where the Rx companies devolve all clinical research activities to the future business partner, for example, Merck selling clinical study sites to Pharmaceutical Product Development, Inc. (NC, USA) and Covance (NJ, USA), Covance acquiring Eli Lilly facilities;
- Rx company experimentation with different strategic business relationships, such as the GSK–Pfizer combined activities in the HIV therapeutic area;

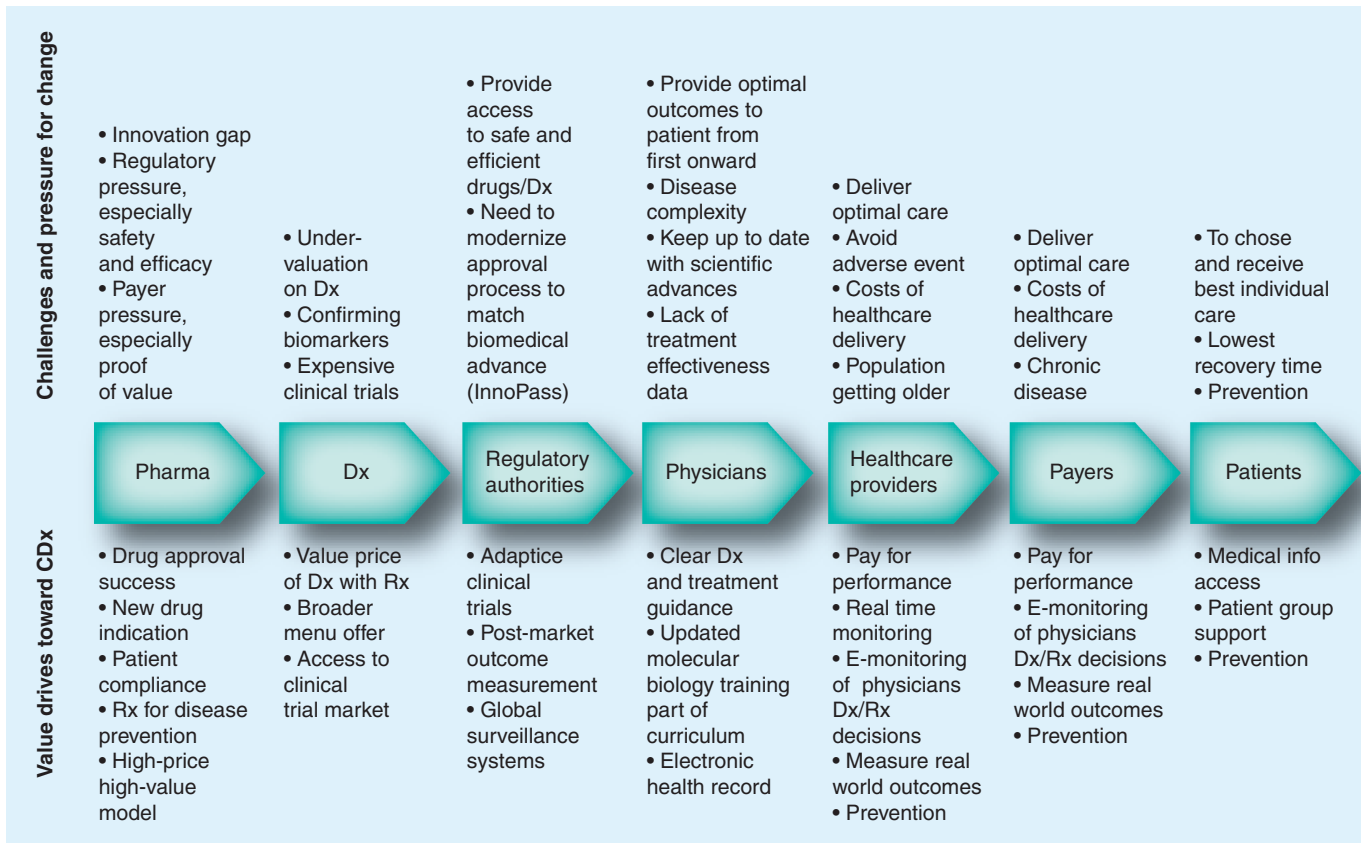


Figure 3: Value drivers and pressures for change driving companion diagnostics and personalization of medicines.

CDx: Companion diagnostics; Dx: Diagnostics; Rx: Pharmaceutical.

[BLAIR ED & MARCHAND M-C, UNPUBLISHED DATA].

- Precompetitive research consortia such as the Innovative Medicines Initiative [11], part funded by industry and EU governments, supporting, for example, large-scale clinical studies and data access for personalized medicine benefit;
- Biotechnology ‘venture’ funds operated by Merck, Eli Lilly, Pfizer, GSK and Novartis;
- Trend-bucking internalization of CDx activities, for example, Roche Personalized Healthcare and Novartis Molecular Diagnostics.

The impact of many drugs coming off-patent in the next 5 years [12], as well as the intense competition Rx companies will increasingly face in bringing new drugs to market, should not be neglected. We have seen moves toward targeted therapeutic areas which will require Rx companies to experiment with the new economic models of targeted therapies compared with the traditional medicines blockbuster model [13]. These more targeted therapies are often more expensive and *in vitro* Dx (IVD) and CDx tests are expected to be required to support demonstration of value

for these next-generation drugs. That said, there is evidence that personalized medicines will be a substantial market opportunity for CDx in the range of US\$42 billion [112] to US\$67 billion [10].

Rise in chronic disease

Pharmaceutical companies have to interact on a worldwide basis with a multitude of regulatory agencies for which both the therapeutics and Dx need to meet different approval criteria. Managing the complexity for Rx–Dx submission, approval and launch is currently extremely challenging, given that a final guidance on regulatory requirements is still being developed. If medicines are likely to be used on a long-term basis to treat chronic disease, then not only will it be more expensive to conduct long-term preapproval clinical trials, it is also likely that greater post-approval monitoring of therapies will be required. In the context of post-approval monitoring, it is likely that bespoke and objective MDx can reduce costs while offering protection against generics that lack the bespoke companion tests [113], as noted previously.

■ Regulatory authorities

Effectiveness & safety

One element impacting Rx organizations and that provides positive push toward personalized medicine is the heightening regulatory scrutiny worldwide for increased drug safety and improved efficacy over current treatment options [14]. As noted previously, Rx companies now need to demonstrate value for their products and provide greater certainty about the treatment outcomes to regulatory agencies [15], as well as payors, private and public. There is an increased demand from these stakeholders for larger comparative studies for pre- and post-market approval, rather than placebo-controlled studies [4].

Over the last 5 years we have seen different tentative activities to help define further the regulatory landscape which would support advance in personalized medicine. A few examples are listed below:

- 2004: US FDA's Critical Path White Paper, which was a call for applications of new technologies for later phases of medical product development;
- 2005: FDA's Final Pharmacogenomic Data Submission Guidance;
- 2005: Royal Society London policy report entitled "Personalized Medicine Hopes and Realities", which provided an overview of the entry barriers and challenges ahead for widespread clinical practice;
- 2006: FDA published a draft guidance on "IVD Multivariate Index Assays" (IVDMIA) and held a public meeting on the subject;
- 2007: FDA clearance of different IVD tests based on genomic information: Mamma-print, warfarin label on dosing variability related to cytochrome P2C9, and tropisms test for HIV drug, maraviroc, from Pfizer, warning added to abacavir label for HLA-B 5701 prior to therapy initiation and so on;
- 2008: Predictive Safety Testing Consortium, project of the C-Path institute (AZ, USA) on pooled data and assays on biomarkers for drug organ injury. Renal package accepted by both FDA and EMA;
- 2009: Voluntary Exploratory Data Submissions became a novel way to share information with the FDA;
- 2009: KRAS testing became mandatory for certain EGFR kinase-targeted therapies.

Demonstration of value

However, even with all the above steps, modernization of the regulatory process remains an imperative requirement before personalized medicine can become part of standard clinical practice. The industry is still expecting further clarity on IVD regulation, for example, the FDA IVDMIA guidance and laboratory-developed test performance standards, as well as finalization of drug-Dx co-development review processes. Another aspect of regulation will be the inclusion of health economic benefits as both proof of value and as a guide to reimbursement for innovative medicines, particularly through health technology assessments (see the sections that follow).

Rise in chronic disease

As noted above, this is likely to see the introduction of post-approval monitoring and supply of evidence to regulators by the company developing the medicine in question.

■ Healthcare systems, payers & reimbursement practice

Effectiveness & safety

One new initiative for the US private healthcare system is the recent bill proposal from President Obama, where the prime goal is to enable physicians and healthcare providers to compare the effectiveness of different medical treatments for the same illness. As part of the US\$787 billion economic stimulus bill approved by Congress in 2009, substantial amounts of money (US\$1.1 billion) will be invested for the federal government to compare the effectiveness of different treatments for the same illness. The program is set to build solid evidence of the value of many treatments with the end goal of improving the quality of care and making it more efficient.

However, in the USA, not everyone sees the push for comparative effectiveness as a good thing. There is fear amongst different stakeholders that study findings could lead to situations where insurance coverage might be denied. It is not yet clear what the future impact of these finding on the Centers for Medicare and Medicaid Services agency (MD, USA) will be, as this agency does not yet have legal authority to take costs into account when deciding whether to cover a particular treatment.

Advocates of comparative effectiveness policies say their focus is on the patient first and believe that decisions should not be driven by

cost but by clinical merit. Therefore, it remains to be seen what impact this new initiative will have on the progress of personalized medicine.

Demonstration of value

Confounded by the challenging global economic environment, many governmental authorities are reviewing healthcare spending and considering innovative ways to support healthcare delivery to patients while not compromising on benefits and access. There is an increased pressure for the different healthcare system stakeholders to provide evidence for the valuation of the benefits of a drug and Dx test in the real-world system. In the future, these potentially combined evidences could be developed as part of clinical trials to secure reimbursement coverage for both the drug and the CDx test. Expanded data on value generation could be compiled from post-market surveillance and included in future medical practice.

Britain, France and other countries already have organizations that assess health technologies and compare the effectiveness, and sometimes the cost, of different treatments. The UK's National Health Service (NHS) works with a comparative effectiveness board, the National Institute for Health and Clinical Excellence (NICE; London, UK), which links cost-effectiveness with evidence-based clinical effectiveness. The bottom line is improving healthcare outcomes by producing reliable data to improve clinical decision making. Such value-based reimbursement suggests that the Rx industry will benefit from personalized medicine if it can demonstrate proof-of-value and develop pricing strategies linked to medical outcomes. One type of proof-of-value example is the risk-sharing agreement for Velcade® (bortezomib; Millenium Pharmaceuticals, Inc., MA, USA) [16]:

“Johnson and Johnson’s (J&J; NJ, USA) Velcade for multiple myeloma for which the UK’s NICE reached a deal with J&J, to make the drug ‘cost-effective’ for prescription by the NHS in England...is now recommended for use in UK and the NHS picks up the bill for patients who respond well and continue their treatment. However, those demonstrating minimal or no response are taken off treatment, and the drug’s costs (~GBP£18,000/year) are refunded by J&J. This scheme was the first of its kind in the UK, and could help pave the way for a value-based medical approach.”

However, there are already precedents in the USA [17], despite the absence of a federal health technology agency.

It seems increasingly likely that other new medicines and other regulators/payors in the EU, USA and Japan will be reimburse Rx companies on the basis of a proof-of-value, based on objective evidence-based assessment [18]. In addition, the ‘Innovation Pass’ strategy being considered by the UK Department of Health aims to make selected innovative medicines available on the NHS for a limited time period prior to a NICE appraisal, thus giving patients with the greatest need earlier access to innovative drugs while also facilitating the collection of further information to support subsequent NICE appraisal [114].

Rise in chronic disease

Healthcare systems supporting reimbursement and payment schemes will need to take a wide assessment to encompass how long-term treatment can have health economic benefits through maintaining a better quality of life and reduce the need for expensive in-patient care and surgery. In addition, prevention or effective treatment of one disease may affect quality of life and morbidities associated with subsequent or consequent disease [5].

■ Physicians

In addition to the three generic factors alluded to above (performance, value and chronic disease), the front-line utilization of personalized medicines relies very much on the training of physicians and other direct-care providers; therefore, we focus on this training aspect for this particular stakeholder group. So far, the limited numbers of genomic tests which have reached the market are performed in a laboratory environment and have required limited current practice changes for their adoption. However, as the field of personalized medicine progresses further into clinical practice, one key element will be to focus on the evolution of medical education for physicians. To date, personalized medicine Dx tests are being released in speciality areas, such as oncology and HIV treatment, but as we gain further insights into the understanding and mechanisms of other diseases, the clinical decisions that physicians are required to make will become more complex. Enhanced communication methodologies and decision-support systems will be required as well as electronic medical records to effectively support data generated by genomics-based personal information to facilitate clinical work. Physicians will also need to be properly trained on the interpretation and use of genomics-based MDx tests.

Recent recommendations from the UK House of Lords Science and Technology Committee urged the NHS to revamp its provisions for genetic testing. They specifically called on legislators in the UK to prepare a White Paper on 'genomic medicine' in order to "address the challenges ahead". The last time the British government published a White Paper on genetics was in 2003. However, the UK Modernizing Scientific Careers program began in October 2009, with a strong focus on enhancing physician's knowledge of genetics and genomic medicine [115]. The expectation is that even short consultations with general practitioners/primary care physicians will involve informative objective testing to augment the physicians assessment of suitability for treatment; therefore, the education of these stakeholders remains key to the successful adoption of more personalized medicines. However, there is concern that health services are not "ready to capitalize on the gene medicine revolution" [116].

Of course, the net effect of these changing stakeholder perspectives is that the Rx industry is no longer selling treatments, but rather it is selling successful outcomes, that is, safe and efficacious interventions, which are assessed on value rather than pricing. The delivery of value into healthcare is driving a new set of intra-industry relationships that offer pre-eminence to providers of MDx who, through partnerships with Rx companies, are able to offer value-enhancing CDx. These relationships are considered in the next section.

MDx as CDx: value-driven adoption

One of the key issues in the adoption of any new technological or scientific solution is the assessment of the real impact on existing practices. Here, we describe how the demonstration of value in both fiscal and behavioral terms can be used to influence the acceptance of CDx as a stepping stone to the widespread adoption of the personalized medicine paradigm.

■ Behavioral impact

Within the Rx industry, there has long been acceptance that the 'blockbuster' model of one-size-fits-all medicines is not tenable in 21st Century healthcare, and Trusheim *et al.* coined the term 'nichebuster' for a strategy that is heavily dependent on the use of predictive tests to identify the patients most likely to respond effectively and safely to a higher priced, niche medicine [13]. A third category, lying between these two extremes is the 'segment-buster' strategy that utilizes CDx to identify patients with the condition to which the medicine is targeted within a particular disease

area [19]. This group of medicines will not be as low priced as 'blockbuster' medicines nor as high priced as low-volume niche medicines, but will nonetheless command a premium price, which includes CDx cost, such that sales of US\$1 billion are achievable (FIGURE 4). The key behavioral change is for healthcare providers, and their supporting stakeholders, to embrace the test-and-treat strategy described for HIV/infectious disease and for targeted cancer therapies (see 'MDx technologies' section). The economic concerns of large Rx companies remain satiated, in that sales remain at the 'blockbuster' level, but not through a blockbuster strategy. At the core of the behavioral change in healthcare provision is the convergence of the Dx and Rx industries to provide the integrated tools to support testing and treatment; this can be driven by many factors but economics is perhaps the most tangible facilitator.

■ Economic impact (value-based vs cost-plus pricing)

Development of CDx involves the close working between two unequal partners – the Rx industry and the Dx industry. The inequalities are often portrayed on the basis of annual sales, where the Rx industry earned US\$773 billion [117] in 2008 and Dx earned US\$40 billion [118], of which MDx was US\$3 billion [119], but other basic differences are striking. Rx have long, high-risk and expensive development paths and are sold at some 80% profit margin on the production cost to reflect this path, whereas Dx tend to be less costly to produce and of limited risk, reflected in a profit margin of only 20% above the production cost. In addition, the actual unit pricing of goods is often substantially lower for Dx (\leq US\$100) relative to Rx (\geq US\$1000), although generic drugs come in at substantially lower prices. However, a new breed of Dx tests – the prognostic test – has been developed by a number of companies for cancer (Genomic Health, Agendia) and diabetes (Tethys, CA, USA). A prognostic test illustrates the risk or likelihood of developing a particular form of disease, whereas a predictive test determines how likely it is that an individual will respond to a treatment intervention. It is possible for a predictive test to also have prognostic value and vice versa, and so it is often the primary application of the test that determines its real value and positioning. These prognostics command high (\geq US\$1000) but fully reimbursed prices because their value is not determined by cost plus 20% pricing, but rather is based on a health economics justification. Similarly, the

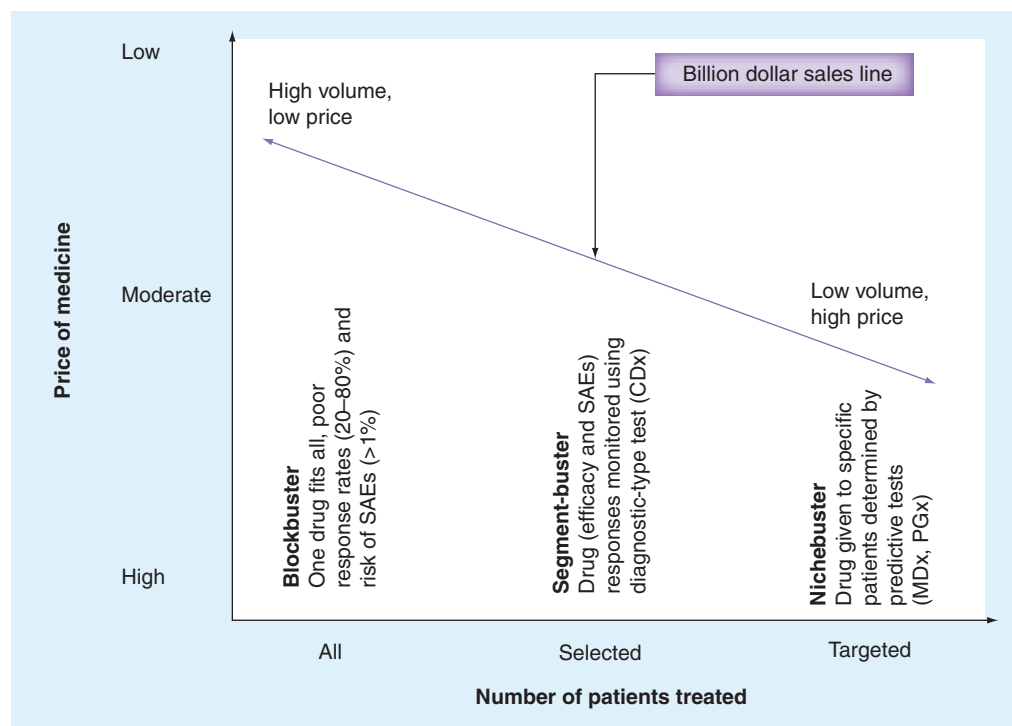


Figure 4. Companion diagnostics in the segment-buster strategy. Both the segment-buster and nichebuster approaches involve objective testing to enhance treatment decisions. CDx: Companion diagnostics; MDx: Molecular diagnostics; PGx: Pharmacogenomics; SAE: Serious adverse event. Reproduced with permission from [19].

true value of CDx, as part of a relationship with Rx, is perhaps better assessed by considering the outcome of their use in terms of appropriate sale and reimbursement of effective medicines. By considering the value of CDx based on Rx sales, it has been concluded that the CDx market is US\$40–90 billion [10,112]. This market is driven by four primary forms of Rx–Dx partnership – integrated, turnaround, use-to-order and make-to-order (FIGURE 5) – that are determined by how the Dx companies sees revenue and how urgent the CDx is to the Rx companies. Both these aspects then influence how the relative value added is apportioned between the partners. For example, a Dx company receives 1–10% of value; Rx company receives 90–99% of value (FIGURE 5). Another aspect of these relationships is when decisions to partner are made and the relative framework of these relationships, for example, exclusivity, royalty sharing, duration, penalty clauses, risk sharing, relative contributions, number of entities involved (service laboratories), research only, commercialization and so on. Although these relationship forms were developed theoretically [120], there are now examples of all four that validate this framework; these are described in the following case studies.

■ Case studies

The following case studies are offered as indicators of how the proposed relationship models might operate; however, each case study also has broader significance in that they further enhanced the case for personalized medicine by exemplifying the use of Dx-type testing in guiding more favorable therapeutic outcomes.

Turnaround: abacavir hypersensitivity safety prediction

As noted in the 'Road to personalized medicine' section, the nucleoside-based reverse transcriptase inhibitor, abacavir (Ziagen), became an important component of multidrug HIV therapies following clinical development in the mid-to-late 1990s. However, its role in 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 MHC locus, that is, 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 SNP locus, called *HLA-B*5701*, with

hypersensitivity and established a clinical utility for the test [20]. The test, offered by a number of clinical laboratory organizations, now appears in the label of all abacavir-containing drug formulations, and since its introduction there have been no reported serious adverse events associated with abacavir hypersensitivity. In essence, this predictive test has rescued a whole disease-management strategy for HIV/AIDS and not just a single drug.

Integrated development: maraviroc & Trofile test

Early in the development of a new type of HIV antiviral called maraviroc, Pfizer scientists recognized that because their inhibitor only worked on a particular phenotype of HIV, that which used the CCR5 receptor rather than the CXCR4 receptor, they would need to identify the so-called tropism of the virus circulating in the target patient as a prerequisite to appropriate and effective treatment. Thus, they engaged Monogram Biosciences to develop a CDx that would identify CCR5-tropic viruses throughout patient recruitment during maraviroc clinical development. Successful utilization of this new but unapproved test was key to compiling the approvable packages submitted by

Pfizer to regulatory agencies, containing data supporting clear drug efficacy against CCR5-tropic viruses as expected. During regulatory assessment of maraviroc, Monogram were able to secure marketing approval of the Trofile test; therefore, when maraviroc reached the marketplace, the companion test was waiting. It is known that Monogram are receiving the revenues of the Dx test directly but they may also be receiving some revenues from Pfizer to reflect drug sales.

Use-to-order: inflammatory bowel disease Serology 7 test & enteric-coated budesonide

Poor sales of Entecort® EC (enteric-coated budesonide) for inflammatory bowel disease (IBD) lead AstraZeneca (AZ; London, UK) to out-license the drug formulation to Prometheus (CA, USA), who also had developed an IBD Dx called Serology 7. This test differentiated major forms of the disease and, thus, could guide more efficacious prescribing of the drug. By using the test to select the most appropriate patients and thus demonstrate effectiveness, Prometheus raised sales by a volume of fivefold and price by twofold over a period of 5 years, such that the drug now makes US\$125 million per year

Diagnostics partner revenues and advantage	Indirect and scope economy	<p>Make-to-order Outcome: market penetration \$1.9 billion (98% R, 2% D)</p>	<p>Integrated Outcome: co-developed test and medicine \$1.8 billion (97% R, 3% D)</p>
	Direct and scale economy	<p>Use-to-order Outcome: market expansion \$1.3 billion (99% R, 1% D)</p>	<p>Turnaround Outcome: Product rescue \$1.8 billion (90% R, 10% D)</p>
		Low	High
Diagnostics partner power (equates to pharmaceutical partner urgency)			

Figure 5. Scenarios for the development of companion diagnostics. Cash figure is net present value increase from base of US\$0.9 billion, except turnaround where base is net present value of -US\$0.9 billion; figures in brackets are percentage of net present value gained by R or D partner. D: Diagnostic; R: Pharmaceutical.

Adapted with permission from Little and Blair [120].

in the USA, representing a 59% growth for the period [113]. Conversely, AZ retained rights in the EU and did not commit to a CDx; annual growth has been 7% for the same period to US\$12 million. All Prometheus have done differently is to make use of a pre-existing test, albeit their own, to more effectively target patients for effective treatment. Another AZ drug, Iressa® (gefitinib), has been approved for advanced/metastatic lung cancer where activating *EGFR* mutations are present and so the use of pre-existing tests to identify the 10–15% of these activating mutation cases is a prerequisite to prescription.

Make-to-order: K-ras tests & panitumumab (Amgen)/cetuximab (MerckSerono)

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 new EFGR-modulating products, such as panitumumab (Vectibix) and cetuximab (Erbix), reached the marketplace, it was demonstrated that individuals with activating mutations in RAS respond less well. Individuals expressing a normal *KRAS* molecule, on the basis of *KRAS* genotyping, demonstrate substantial benefit, in terms of improved survival (overall and 'progression free') whilst those with 'activating' mutations in the *KRAS* gene demonstrate no benefit from cetuximab treatment. *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 in the UK by NICE [121], owing to the beneficial predictive value of these molecular diagnostic tests.

While these case studies illustrate the basic models described in FIGURE 5, the financial details of the relationship have not been revealed, and so it is not yet possible to validate the perceived value in each case derived from cash-flow modeling. Also, we note that related models may exist, such as those articulated by colleagues at DxS Ltd [LITTLE S, PERS. COMM., 2009], a UK company based on a SNP detection technology that offers the pre-eminent *KRAS* and *EGFR* tests. Most business models will broadly fall into the four categories described above, and indeed the Personalized Medicine Coalition (Washington, DC, USA) has asked that the FDA include all such models in its revisions to the 2005 Concept Paper on Drug–Diagnostic Co-Development [122].

Growth vectors for MDx

The global IVD market in 2008 stands at US\$42 billion, of which MDx accounts for US\$3.1 billion of annual sales, following on from an average annual growth rate of 15% since 2002 [21, 119]. Projections suggest that MDx will continue to grow faster than any other IVD sector (12% vs average sector growth of 5%) to 2013, driven by a number of widely accepted factors [21, 119]. It is these growth-driving factors that will briefly be considered in this section.

■ Instrumentation

The large central testing laboratories, such as those operated by the Laboratory Corporation of America (NC, USA) and Quest Diagnostics (NJ, USA), have long benefited from fully automated high-throughput Dx testing, including instruments that undertake robust molecular testing. However, advances in miniaturization and complex assay performance are behind a 'de-centralization' drive away from such central laboratories to more disperse locations, such as hospital laboratories and physicians offices. While traditional molecular testing, such as quantitative real-time PCR, is now to be found in a variety of near-patient instruments, the increasing use of tissue-based testing on fully automated nearer-patient locations is seen as a huge driver in the development of more spatially accurate diagnosis of complex, but localized disease, such as cancer. Of course, in many situations it may hold that centralized- and/or laboratory-based testing remains the most appropriate route for supporting patient management, but the attempts of the FDA to regulate laboratory-developed tests through the IVDMA guidelines may also lead to de-centralization in the context of personalized medicine.

■ Assay menu

In addition to the miniaturization of MDx instrumentation, another driver is the ability of automation to offer a range of ways to run tests as an alternative to traditional high-throughput batch methods. With the rise of multiplexing technologies and, indeed, multiparameter instrumentation, it has become possible to run several defined test types measuring a variety of specific molecules in a flexible and time- and cost-efficient way. Furthermore, with enhanced connectivity to laboratory information management systems and electronic patient records, it is increasingly possible to integrate both remote- and near-patient testing, together with supporting

information, thus enabling prompt actionable outcomes irrespective of testing location, that is, laboratory based or near patient.

■ Value-based pricing

As noted in the 'MDx as CDx: value-driven adoption' section, a change in how Dx are priced and reimbursed will serve as driver in enhancing the overall value of the Dx sector. Indeed, one prominent business expert has suggested that CDx will supersede reimburseable pricing of medicines [2]. This disruption of the traditional relative valuation of the Rx and Dx industries suggests that MDx will play an increasingly important role in extracting value from the health economics of healthcare systems. The switch to value-based pricing, as in the case of Oncotype Dx and Mammaprint tests, is based on robust assessment of health econometric impact of testing at an appropriate time and performance level rather than pricing against manufacturing costs to produce a 20% profit.

■ Rx line extension driven by CDx

It is reasonable to expect that robust objective testing to monitor and demonstrate response to treatments is likely to increase compliance amongst patients to provide better outcomes. However, another aspect of molecular testing to assess response may be the development of alternate interventions if the expected benefit does not arise. The use of pathway-based (systems biology-based) testing and treatment could lead to either off-label use of therapies or, where regulated, to new applications for existing medicines. Such product line extensions, or drug repositioning, can be attractive to Rx companies as many development costs and risks are avoided. More broadly, there is the additional possibility that the use of the same tests for different indications could lead to the recognition of new uses for existing medicines. Precompetitive sharing of clinical data, including experience with CDx testing, could be a driver of such line extension benefits and opportunities. For the CDx vendor, the case may be that exclusive partnerships may be avoided so that a test is more widely used.

These drivers are seen as those activities most likely to drive a near-term growth in CDx. A longer view into the future is offered in the next section.

Future perspective

Having established the current trends that impact on the development of MDx as CDx for personalizing medicines, we take a peak at

the future of healthcare and offer four major trends that form part of the late 21st Century healthcare vision.

■ Rx–Dx for disease prevention

There is quite a reasonable perception that treatment of late-stage chronic disease, whether in oncology, cardiovascular or any other therapy area, is likely to be poorly effective and little more than symptom relieving. Generally, as disease severity increases, the effectiveness of a treatment diminishes (FIGURE 6). Therefore, earlier intervention is likely to provide greater effectiveness and offer true disease modification. While widespread prophylaxis, with or without requisite lifestyle management, can be attractive if the medicines on offer are known to be almost risk free, for example, statins for reducing hypercholesterolemia and atherosclerosis, long-term use of medicines is not widely supported. Alternative approaches to disease prevention through use of prophylactic vaccines for viral disease (e.g., influenza or even HIV) or for virus-initiated tumors (e.g., human papillomavirus and cervical cancer) have proven successful and are being extended to other disease areas, including nonviral cancers and Alzheimer's disease. However, it is through the use of predictive tests that the real benefits of proactive preventative medicine may be realized. Thus, the use of predictive tests to assess the relative risk of a treatment preventing disease worsening with acceptable side effects is a hugely valuable toolkit to future healthcare management. Combined with prognostic tests to illustrate the relative risk of disease development, without intervention or lifestyle management, the predictive test is a key component of extracting full value from high-price but safe and effective medicines. As these tests also support interventions that alter the advance of disease and the timeframes for which an individual might require secondary and/or tertiary care, their true value is best assessed through broad health economics analysis.

The Genomics Health Oncotype Dx test commands a substantial and fully reimburseable price of approximately US\$3500 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 that an individual will experience a particular outcome, that is, recurrence-free survival, and thus guide on an earlier, less expensive and more effective intervention. The reimbursement of such tests was agreed by

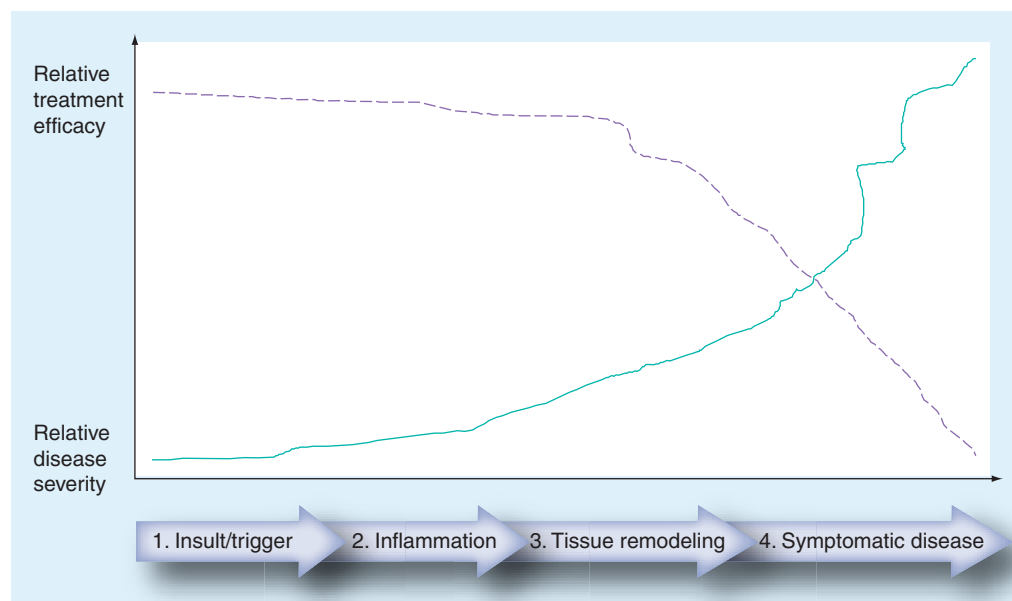


Figure 6. Inverse relationship of treatment efficacy and disease severity. As disease severity increases (solid line) through a series of generic stages (1–4), the effectiveness of treatment diminishes (dotted line). The benefit of predictive medicine is earlier intervention and thus greater effectiveness. [BLAIR ED, UNPUBLISHED DATA].

judicious health economics analyses [22]. A similar case has been made for prognostic tests from Agendia (Mammaprint for cancer) and Tethys (PreDX™ for Type 2 diabetes), each of which command large but reimburseable price tags (US\$4200 [23] and US\$465 [24], respectively).

The various predictive tests that indicate the likelihood of an individual responding to trastuzumab (Herceptin) or to imatinib (Gleevec) are able to guide, with great 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 yet command a high reimburseable price, despite offering high-value information. This is often because (as discussed in the ‘MDx as CDx: value-driven adoption’ section) the full economic value of the test has not been assessed through health economic analysis. There have been suggestions that such tests, when their full value is recognized, will become the expensive component of a Rx–Dx bundling [25]. The further application of such tests may be in guiding who will respond most appropriately to particular forms of both prophylactic and therapeutic vaccines, as noted previously.

■ CDx/personalized medicine in emerging markets

Much of the preceding discussion has focused on the developed world view of healthcare, but as globalization of healthcare continues to

impact all countries, the need arises to consider the role of companion testing in geographically, ethnically or socioeconomically determined disease subtypes. Benevolent funds, such as Bill & Melinda Gates (WA, USA) or the UK Wellcome Trust (London, UK), currently target developing world diseases through technologically simpler lower costs, and thus low-price solutions. However, the time may well come where approaches that have become standard in the West become standard in the developing world, owing to both technology developments and scale economies. Presently, many Rx companies supply medicines at a low cost to the developing world on the basis of one-size-fits-all, but low-cost Dx testing could soon make it possible to offer objective pretreatment testing in nontraditional markets. It is likely that Brazil, Russia, India and China (BRIC) countries, already viewed as emerging markets for various industries, including healthcare, will become early adopters of the personalized medicine paradigm [26]. In addition, the rise in distance-based telemedicine and patient monitoring may allow physicians to introduce Dx/Rx effectiveness to patients outside the hospital setting.

■ Computational biology involving CDx/personalized medicine

As noted above, oncology is a therapy area that has demonstrated immense benefits from a molecular pathway-based approach to disease

characterization and treatment. Furthermore, as whole-genome scanning, linkage analysis and haplotyping become less expensive and more routine, the ability to introduce computational biology to personalized medicine will become ever more likely. Indeed, much of the content of both future MDx and future medicines may be determined from the same computational analyses, ensuring that Rx and Dx are truly linked.

Conclusion

The provision of healthcare in the developed world is clearly changing. The rise in evidence-based medicine and the demands of payment decision makers, such as the UK NICE, that benefit should be demonstrated before reimbursement is sanctioned, can only lead to a greater reliance on objective testing to identify patients most likely to benefit from an intervention in a cost-effective manner. Similarly, objective testing to monitor responses as a surrogate for long-term clinical outcomes will also become significantly more prevalent. While the technologies currently employed are likely to be superseded by MDx, additional factors such as decentralized and near-to-patient testing are predicated on the ability of the end users to willingly employ and

interpret the tests. Thus, the ongoing development of personalized healthcare is dependent on many factors outside of just the Rx industry and its immediate supply chain. Furthermore, for Rx companies their long-term role will migrate from selling medicines to selling medical outcomes; placing a true value on such a healthcare offering again requires the vision and input of the wider stakeholder group. The aspects of future healthcare that have been described draw on the requisite stakeholder vision.

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Executive summary

- This core of this review is the assessment of the value of molecular diagnostics (MDx) in the development of personalized medicines, as viewed from a number of stakeholder perspectives. This is considered after the foundations of MDx in guiding HIV and cancer therapies are articulated through the lens of recent history.

Technology

- The key basic MDx platforms offering accurate and reproducible diagnosis, in the context of prescribing effective and/or safe medicines as an outcome of testing, are briefly reviewed. Those technologies assessed are pharmacogenomic-lead expression profiling, using RNA patterns (transcriptomics) and protein patterns (proteomics) to guide the use of medicines, plus methods for assessing inherited features that influence response to medicines, namely SNP/haplotyping and high-throughput sequencing.

Stakeholder acceptance: key factors amongst many

- The pharmaceutical industry alone cannot drive widespread adoption of personalized medicine, but rather must be integrated in a multistakeholder value proposition that demonstrates the overall healthcare benefits of introducing the right medicine at the right time, and at the right price. Out of many factors coming into play in the landscape of personalized medicine, three are selected as being key to acceptance to all stakeholders - effectiveness and safety, demonstration of value and the rise in chronic disease.

Development of valued relationships within the pharmaceutical & diagnostics industries

- A key focus on better industry integration is the move from the relative sales-based valuation of the pharmaceutical and diagnostic industries towards a more value-added proposition realized through close-working relationships. Four basic relationship forms are considered with case studies of each cited.

MDx as a growth driver for personalized medicine

- Long recognized as the fastest growing sector of the *in vitro* diagnostics market, the trends driving further growth of the MDx sector are considered in the wider context of companion diagnostics (CDx) and the consequent enablement of the widespread use of personalized medicine. Assessment of the continuing trends of decentralization, simplified automation and greater connectivity are augmented by consideration of CDx-specific trends in co-development, co-regulation and co-marketing.

Role of personalized medicine in disease prediction & prevention

- MDx, CDx and personalized medicine sit on a trajectory that takes healthcare from a reactive position of treating disease, to a proactive position of predicting disease risk and seeking to prevent the onset of severe disease. These impacts are considered through examination of a number of future perspectives that include the role of computational (synthetic) biology and developing world markets.

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