

The growth of personalised medicine will drive alliances between diagnostic and pharmaceutical industries

With the growing encouragement of global drug approval agencies and pressure from healthcare payers, this article argues that personalised medicine will have a significant theme in the M&A and licensing activities of pharmaceutical and diagnostic companies, accelerating the development of new diagnostics for personalised medicine in the future.

Personalised healthcare is rising up the agenda of pharmaceutical and diagnostics companies. Plus, the growth of personalised medicine, which aims to better target treatments to patients, is expected to increase the number of alliances between diagnostic and pharmaceutical businesses. This trend is evidenced by GlaxoSmithKline's July 2009 deal with Enigma, a British diagnostics company, to develop a new test which can diagnose specific strains of influenza, including swine flu, in just an hour.

The future of pharma is inextricably linked with smart diagnostics

The molecular level of personalised medicine

Personalised medicine – or the use of information about a person's genes, proteins and environment to prevent, diagnose and treat disease – has been much talked about in recent years. And some observers are wondering what the excitement is all about. In the words of Roche's CEO Severin Schwann: "Personalised healthcare is nothing new. Doctors have always tried to fit the therapy to the patient if possible. But what's happened more

recently is that we've begun to go a level deeper. We're now exploring the biology of disease and treatment at the molecular level."

Molecular medicine does not *per se* define personalised medicine, but molecular tools are important as they should enable greater relevance in the information provided by diagnostic tests.

Personalised medicine as a spectrum

As personalised medicine means different things to different people, additional complementary ways of characterising diagnostics may further help distinguish different shades of grey in the personalised medicine spectrum.

In the strictest sense, personalised medicine diagnostics may consist exclusively of companion diagnostics, which are by definition geared towards supporting a therapy decision for a particular drug, patient by patient. At the more permissive end of the spectrum, personalised medicine tests may include early diagnostics, prognostics and possibly all other types of diagnostics. You may indeed argue that if a diagnostic were not designed to inform treatment decisions for individual patients

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Figure 1: Top 10 M&A deals in the IVD sector in 2008

Rank	Value (\$m)	Target	Country	Bidder	Country
1	580	Third Wave Technologies	US	Hologic	US
2	256	Innogenetics (93.2%)	Belgium	Solvay	Belgium
3	215	Ibis Biosciences	US	Abbott	US
4	117	BioArray	US	Immucor	US
5	75	Proprius	US	Cypress	US
6	60	AviraDx	US	bioMérieux	France
7	39	Biotin	Ireland	DaSerni	Italy
8	31	Immuricon	US	Johnson & Johnson	US
9	22	OcuSense (49.9%)	US	OcuLogix	Canada
10	17	Beijing Chemin Biotech (Minority)	China	Investor Group	Germany

Source: Thomson Financial, Windhover, Mergermarket, Zephyr and other publicly available sources

– one way of defining a personalised medicine diagnostic – it would not have much sense.

Companion diagnostics and the future of pharma

The concept of companion diagnostics (CD) and its role in the future of healthcare was also mentioned in *Pharma 2020: Marketing the Future*, a report published by PricewaterhouseCoopers (PwC) in February 2009. This report discusses the key forces reshaping the pharmaceutical marketplace and the changes required to create a sales and marketing model that is better adapted to the stakeholder priorities expected for 2020. Of particular relevance to the diagnostics industry is the move from mass market therapies to specialist therapies, which is highlighted in this Pharma 2020 report. Many specialist therapies are very costly (eg almost \$300,000 annually for Fabry's or Gaucher's disease) and are used to treat smaller target patient populations with specific disease subtypes. In this context, there is thus a growing imperative, both clinical and budgetary, to accompany therapies with diagnostic tools of increasing sensitivity and specificity to better enable the identification of those patients in the relevant disease subtype and most likely to benefit from the therapy. The marketing model foreseen for most specialist therapies in 2020 will include a companion diagnostic as a key component.

Highlighting a movement towards personalised medicine is not straightforward with a concept that is so widely open to interpretation. It is, however, important that we try as the response rates on drugs are still unsatisfactory, varying widely from "20% to 75% depending on the drug and the disease", as reported by Jürgen Schwiezer, CEO of Roche Diagnostics.

The prominence of personalised medicine in IVD deal activity

In a July 2009 report entitled *Diagnostics 2009: Moving Towards Personalised Medicine*, PwC highlights the prominence of personalised medicine in current mergers and acquisitions (M&A) and licensing deal activity in the *in vitro* diagnostics (IVD) sector.

In 2008, personalised medicine motivated three of the 10 largest M&A deals in the IVD sector and four of the 18 licensing deals by the 10 largest IVD companies.

The top 10 M&A deals in the IVD sector

The 10 largest IVD M&A deals announced during 2008 ranged from \$17 million to \$580 million and followed four major themes:

1. Supporting existing franchises with strategic technologies;
2. Pursuing the personalised medicine ambition;
3. Growing product portfolios; and
4. Venture funding for growth.

Here we focus on the personalised medicine theme (Figure 1).

Pursuing the personalised medicine ambition through M&A

The personalised medicine theme was explicit in at least three of the top 10 M&A deals announced in 2008, including two deals involving pharma buyers and one deal to pursue a cancer theranostics vision:

- Innogenetics went to Solvay following a rival bid by Gen-Probe. Solvay wants to follow a dual strategy of expanding Innogenetics' diagnostics business and leveraging the R&D competencies of both companies to develop Solvay's therapeutic pipeline. The company stated its belief that the future of drug development lies in the development of personalised treatments and targets the development of biomarkers, diagnostics and eventually companion diagnostics. Innogenetics' therapeutics division GENimmune was non-core to Solvay's plans and was closed prior to completion of the acquisition by Solvay.
- Proprius has a portfolio of proprietary diagnostic, prognostic and predictive technologies to provide physicians with information for the treatment of rheumatoid arthritis patients. Cypress, whose lead pharmaceutical candidate is being developed for fibromyalgia, plans to use its pharma sales force to promote both therapeutics and

personalised medicine laboratory services to rheumatologists and other pain specialists.

● AviraDx was acquired by bioMérieux as an investment to promote its vision of personalised, predictive medicine for the treatment of cancer. AviraDx has two proprietary diagnostic tests provided to US based physicians through its CLIA certified service lab: Avira CancerTYPE ID provides improved cancer classification, especially for metastatic cancer where the origin is uncertain; Avira Breast Cancer IndexSM offers a combined assessment of two Avira markers (HI and MGI) for risk prognosis and treatment response prediction for chemo and hormonal therapy. bioMérieux plans to keep AviraDx as an independent legal entity called bioTheragnostics, Inc.

Licensing by the 10 largest IVD companies

Personalised medicine was a key theme in the licensing-in deals announced by the top 10 IVD majors during 2008. In particular, four of the 18 licensing deals announced by these majors in 2008 were for companion diagnostics (Figure 2).

Other deals (out of the 18) also had a personalised medicine potential but were not specifically for companion diagnostics.

Companion diagnostics partnerships with the pharmaceutical industry

We have seen some licensing-in of CD tests by the 10 largest IVD companies; but what about the pharma industry? If diagnostics are so important to improving the value of therapeutics to patients, we should expect the pharmaceutical industry to be entering significant CD partnerships with the IVD industry. Is it the case today?

Diagnostics collaborations with pharma have yet to become an established practice

Seven partnerships were announced in 2008 between pharmaceutical and diagnostic companies to develop a companion diagnostic. This represents a significant drop from the 14 collaborations announced in 2007, but there is no clear up or downward trend over the period 2004-08, with annual deal numbers varying between 6 and 14 throughout. Companion diagnostics partnerships with pharma have yet to become an established industry practice (Figure 3).

Most 2008 deals focused on cancer and involved a big pharma partner

Three key themes were reflected in the partnerships announced in 2008:

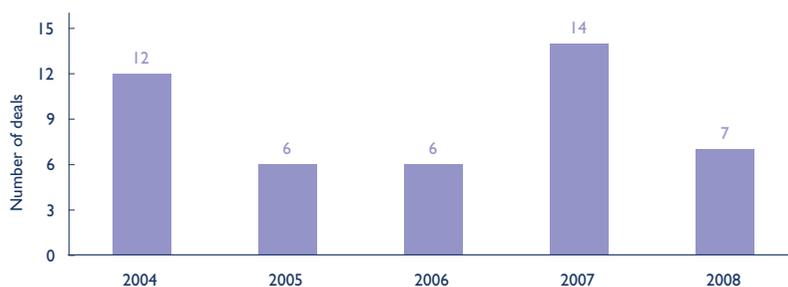
Figure 2: In-licensing deals for companion diagnostics by 10 IVD majors announced in 2008

Licensor/ Partner	Licensor/ Partner	Deal Headline	Disease Area	Test Type*
Roche	DxS	TheraScreen genetic mutation test	Cancer	CD, P
	Exigon	Rights for the Universal ProbeLibrary PCR system	Cancer	D, ED, CD, P
Bedman Coulter	Siemens	HCV testing rights	Infectious diseases	D, ED, CD, P
Becton Dickinson	Arbor Vita	New diagnostic for cervical cancer	Cancer	D, CD

*Test types: D - diagnostics, ED - early diagnostics, P - prognostics, CD - companion diagnostics.

Source: PricewaterhouseCoopers analysis using Windhover data and other publicly available sources

Figure 3: Companion diagnostics partnerships with Pharma in 2004-08



Source: PricewaterhouseCoopers analysis using Windhover data

● Cancer attracted strong interest as the disease area of choice for the development of companion diagnostics. In 2008, all deals focused on diagnostics for cancer.

● Big pharma was dominant as pharmaceutical partner for collaborations with the diagnostics industry. In 2008, all pharmaceutical partners were top 20 companies by sales of prescription pharmaceuticals (2008 ranking from IMS Health). OSI Pharmaceuticals was the only exception but big pharma company Roche was a co-partner in OSI's collaboration with Abbott's diagnostics division to develop a pharmacogenomic test to identify patients most likely to respond to cancer drug Tarceva (erlotinib) for non-small cell lung cancer. In this study, we counted any deals involving Genentech as a big pharma deal due to Roche's majority ownership in Genentech

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Figure 4: Companion diagnostics partnerships with Pharma announced in 2008

Diagnostic Partner	Pharmaceutical Partner	Deal Subject	Disease Area
DxS	Amgen	Provide DxS's Therascreen KRAS mutation kit as a companion diagnostic to Amgen's colorectal cancer therapeutic Vectibix (panitumumab) in the US, where the drug was awaiting approval.	Cancer
Dako	Genentech	Develop a new cancer diagnostic to be used as a companion product to an investigational drug candidate being developed by Genentech.	Cancer
Dako	Bristol Myers Squibb	Use Dako's pharmDx assays to design companion pharmacogenomics tests for BMS's cancer drug candidates.	Cancer
Celera	Abbott	Celera will help Abbott identify genetic markers for one of its candidates in development. Celera also has the option to develop a companion diagnostic that comes out of the collaboration and commercialize it with Abbott under an existing partnership between the two companies.	Unclassified
Celera	Merck & Co	Using its proteomics platform Celera identified cancer targets that are over expressed on certain tumour cells. Merck will study up to ten of them for potential development as RNA-interference-based drugs. Celera retains rights to develop and sell companion diagnostics specific to Merck's resulting compounds.	Cancer
Abbott	CDI Pharmaceuticals, Genentech, Roche	Abbott's molecular diagnostics division is to develop a pharmacogenomics test to identify patients most likely to respond to the non-small cell lung cancer drug Tarceva (erlotinib). Abbott will use fluorescence in situ hybridization (FISH) techniques to find CDK4 protein to gene sequences involving epidermal growth factor receptor (EGFR). The test will determine if multiple copies of the EGFR gene are present.	Cancer
Aureon Laboratories	Pfizer	Aureon will apply its integrated systems pathology methods to Pfizer's prostate cancer studies to develop a test to predict how individuals respond to hormone therapies. Aureon's technology integrates information about tissue morphology, cell-type specific biomarkers, and in situ RNA expression with clinical data from patients to determine therapeutic effectiveness.	Cancer

Source: PricewaterhouseCoopers analysis using Windhover data

at the time of the deal and which became a full ownership during 2009.

● Niche specialists dominated as *in vitro* diagnostics partner for collaborations with the pharmaceutical industry. In 2008, Abbott was the only IVD major involved in collaborations with third-party pharmaceutical companies for companion diagnostics. None of the other diagnostics partners announcing deals in 2008 – Aureon, Celera, Dako and DxS – were ranked among the 10 largest *in vitro* diagnostics companies.

Similar themes emerge when we analyse the pharmaceutical and diagnostics partners involved in companion diagnostics licensing deals over 2004-08 in more detail (Figure 4).

The pharma partners

Roche, Pfizer and Merck were the most active pharma partners over 2004-08. Roche's pharma-

ceutical division, including Genentech, stands out as the most active third-party pharmaceutical licensing partner for the diagnostics sector over 2004-08 with 10 announced deals – an average of two deals per annum. Pfizer, Merck and AstraZeneca followed Roche with six, five and three diagnostics partnerships respectively over the same period (Figure 5).

The position of Roche as the leading pharmaceutical partner for collaborations with diagnostics companies is remarkable if we consider that none of the other pharmaceutical companies with a major IVD affiliate – Abbott, Bayer and J&J – announced more than one partnership with a third party diagnostics company over 2004-08. However, the full picture about these diagnostics majors is not available as there is little visibility about any intra-group diagnostics collaborations with their respective pharmaceutical divisions.

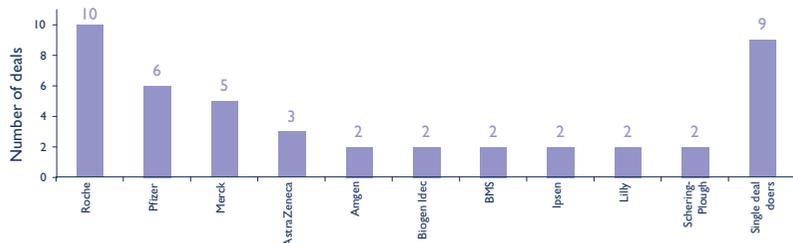
Pharmaceutical companies announcing two partnerships for companion diagnostics over 2004-08 included:

- Large pharma companies: Amgen, Bristol-Myers Squibb, Eli Lilly and Schering-Plough; and
- Medium-sized players: Biogen Idec and Ipsen.

Nine other pharmaceutical companies announced just one licensing deal for a companion diagnostics, including:

- Large pharma companies: Abbot, Johnson & Johnson and Takeda;
- Medium sized players: Eisai and Organon (prior

Figure 5: Companion diagnostics partnerships by Pharma partner in 2004-08



Source: PricewaterhouseCoopers analysis using Windhover data

to its 2007 acquisition by Schering-Plough from Akzo Nobel); and

- Emerging companies: Aphton, ARCA, Isis and Keryx. OSI Pharmaceuticals's 2008 deal with Abbott was included under Roche's partnerships to avoid double counting this deal.

Medium pharma pioneers

Biogen Idec and Ipsen were the most active partners from medium pharma. Serial diagnostics deal making by pharmaceutical partners was mainly in the hands of big pharma. Only two pharmaceutical companies beyond the top 20 announced at least two deals over 2004-08.

Biogen Idec of the US and Ipsen of France, respectively 44th and 69th by sales of prescription drugs (2008 ranking from IMS Health), stood out with two diagnostics licensing deals each announced over 2004-08.

In Ipsen's case, the company's CEO, Jean-Luc Bélingard, has significant diagnostics industry experience, being a former senior executive of Roche Diagnostics and currently a board member of a number of diagnostics companies. Compared to other medium-sized pharmaceutical companies, Ipsen may thus be more aware of when and how best to exploit the potential value from companion diagnostics. In Biogen Idec's case, the antibody-based technology used by the company is typically conducive to strong synergies with *in vitro* diagnostics applications.

Ipsen announced its two diagnostics collaborations in 2007, with bioMérieux and Celera:

- BioMérieux agreed to develop a test using its NucliSENS EasyQ molecular diagnostic platform to help doctors determine which patients could respond best to Ipsen's drug candidate BN83495, which at the time was in Phase I clinical trials for post-menopausal breast cancer patients.

- Celera was due to help develop pharmacogenomic tests for Ipsen's hormone replacement therapies for short stature. Celera would first identify and characterise genetic markers associated with growth failure and then develop diagnostic predictors that Ipsen could use in clinical trials. The objective being to develop a companion diagnostic for Ipsen's therapeutics.

Biogen Idec announced its two diagnostics partnerships in 2004, with Dyax and Epigenomics:

- Dyax agreed to provide Biogen Idec access to its fully human antibody libraries to identify and characterise therapeutic and diagnostic antibod-

ies for up to 30 of Biogen Idec's protein targets per annum.

- Epigenomics announced it would use its DNA methylation technology to help Biogen Idec identify potential cancer biomarkers and examine selected candidate biomarkers as predictors of patient response to drug therapy. The objective is to provide physicians with essential information to help guide their therapeutic approach.

The diagnostics partners

The most active diagnostics partners for deals with pharma were all niche players. Serial deal making for companion diagnostics was limited among diagnostics companies. Only four diagnostics companies announced at least two partnerships with pharmaceutical companies over 2004-08 and they were all niche diagnostic specialists: Celera, Dako, Epigenomics and Perlegen. Dako is the largest among these diagnostic companies with \$322 million of net sales reported in 2008.

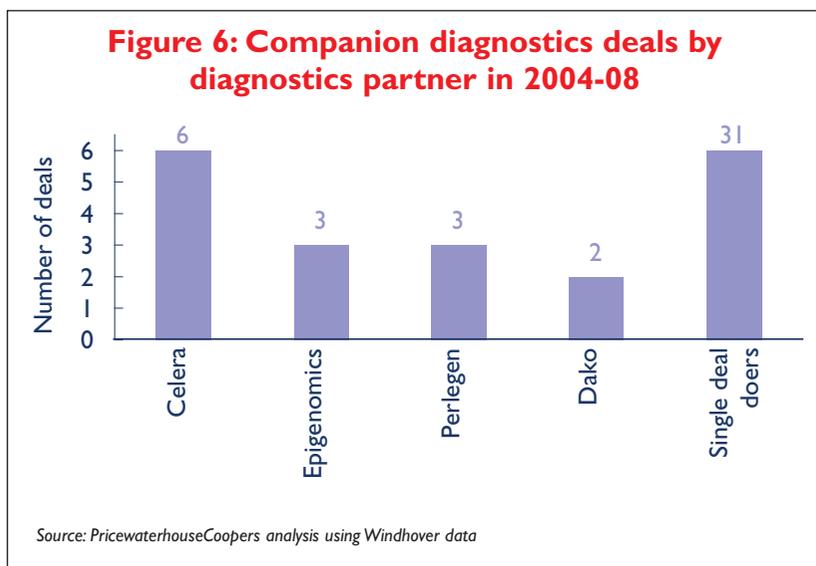
Three observations follow from this analysis and our discussions with selected industry players:

1. The pharmaceutical industry is not currently a priority market for large diagnostics companies. The development risk and time to market associated with drug candidates make the development of a companion diagnostic significantly less attractive to major diagnostics manufacturers than the revenues currently available from its more traditional target market of clinical laboratories.

2. The limited deal flow by company suggests that even for niche diagnostic companies, the prospective economics of developing a companion diagnostic may not always be attractive. Key factors that impact the net present value expected from companion diagnostics projects include the strength of the intellectual property, the pricing and reimbursement coverage and the extent of testing required by regulators to obtain key marketing authorisations. Achieving a positive net present value from a companion diagnostics development project will be a challenge unless some of these factors become more favourable.

3. For those diagnostic companies that do target the pharmaceutical industry, some are developing companion diagnostics without entering a partnership with a pharmaceutical company. When diagnostics companies have the required funding and access to sufficient, high-quality biological samples to conduct such development work without partnering with pharma, this approach can help keep more of the value in-house. In due course, however, it can be helpful

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to have some form of public support from the targeted drug's marketer to underline the validity of the test as a companion diagnostic for the drug (Figure 6).

Outlook

Dako announced the first companion diagnostics partnership with pharma of 2009. As part of the deal, Dako will use its pharmDx line of kits to develop a new cancer test to be used alongside an OSI Pharmaceuticals drug.

Another CD deal announced during the year was Pfizer's August 2009 collaboration with Abbott's diagnostics division to develop a molecular diagnostic test intended to screen non-small cell lung cancer (NSCLC) tumours for the pres-

ence of gene rearrangements. Pfizer has developed a novel investigational agent that selectively targets cancer-causing genes implicated in the progress of many cancers. To be eligible to receive Pfizer's oral therapy, a particular genetic translocation (rearrangement) known to be found in NSCLC tumours and a wide variety of other cancers, but not in normal cells, must be present. The test will aim to determine a patient's genetic status and will be used in patient selection for future clinical trials of PF-02341066.

We expect the annual number of diagnostics partnerships between pharmaceutical and diagnostic companies to increase over the next five years. A key factor will be increased pressure on pharmaceutical companies from regulators and payers to provide a diagnostic alongside pharmaceuticals to guide their use.

Biomarker testing requirements

Drug approval agencies, including the FDA and EMEA, are encouraging greater use of biomarkers and diagnostics in drug development and prescribing decisions, thus promoting the concept of companion diagnostics for drugs.

The FDA recently started reporting a list of genomic biomarkers that it considers valid to guide the appropriate clinical use of approved drugs. The list is being updated on a quarterly basis and counted 32 valid genomic biomarkers in mid September 2009.

Most drug labels in the list provide pharmacogenomic information with no immediate recommendation for genetic testing. However, testing is 'recommended' or 'required' in a few cases. At March 20, 2009, four biomarkers were 'required' to be

Figure 7: The four biomarkers requiring testing prior to deciding on the drug use

Biomarker	Representative Label	Indication	Drug	Drug Marketer
CCR5 - chemokine C-C motif receptor	Genentry, in combination with other antiretroviral agents, is indicated for treatment-experienced adult patients infected with only CCR5-tropic HIV-1 isolates, who have evidence of viral replication and HIV-1 strains resistant to multiple antiretrovirals.	Infectious Diseases (HIV)	Genentry (maraviroc)	Pfizer
Epidermal growth factor receptor (EGFR) expression	Patients enrolled in the clinical studies were required to have immunohistochemical evidence of positive EGFR expression using the DakoCytomation EGFR pharmDx™ test kit.	Cancer (Colorectal)	Erlotinib (tarceva)	Bristol-Myers Squibb
Her2 / neu over-expression	Detection of HER2 protein overexpression is necessary for selection of patients appropriate for trastuzumab therapy. Trastuzumab should be used in patients whose tumors have been evaluated with an assay validated to predict HER2 protein overexpression.	Cancer (Breast)	Trastuzumab (herceptin)	Genentech
Philadelphia chromosome-positive responders	Dasatinib is effective for the treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy.	Cancer (Leukemia)	Dasatinib (dasatinib)	Bristol-Myers Squibb

Note: We show only one drug per biomarker, using the drug presented as prototype by the FDA. For each of the biomarkers reported above, there may be other drugs for which prescribing is affected in the same way as the representative drug shown above.
Source: PricewaterhouseCoopers analysis using data from the FDA's website at 20 March 2009

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tested for – three for cancer and one for infectious disease indications (Figure 7).

We are still at the start of the process if we consider that only four biomarkers are ‘required’ to be tested for. However, the FDA was prompted to publish its list following a marked increase over the last decade of approved drugs labels containing pharmacogenomic information. The FDA estimates that 10% of approved drug labels now contain pharmacogenomic information and this is expected to continue increasing.

The EMEA’s communication on the requirement for biomarker testing is less transparent than the FDA’s but its initiatives should not be overlooked. For example, the European agency played a key role in requiring biomarker testing for Amgen’s Vectibix, following the FDA’s accelerated approval without specific testing requirements. The EMEA also has a larger number of drugs for which biomarker testing is required – in mid-2009, we counted at least 11 drugs with the requirement.

We expect greater harmonisation between different regulatory agencies to develop over time through greater consultation but also following pressure from clinician communities as stakeholders in one country push to implement practices already included in drug labels in other countries.

Moving towards personalised medicine

Personalised medicine was a significant theme in IVD deal-making in the past year; it was prominent in both M&A and licensing. We expect continued interest in personalised medicine in future deals driven by the growing encouragement of drug approval agencies but also by anti-discrimination legislation, market access changes and the increasing need for complementary clinical validation:

- Legislation to encourage more people to undergo genetic testing or participate in innovative research. For example, legislation was introduced in May 2008 in the US (Genetic Information Nondiscrimination Act) and Europe (Additional Protocol to the Convention on Human Rights and Biomedicine Concerning Genetic Testing for Health Purposes) to protect individuals against discrimination resulting from the use of genetic information.
- Changing market access routes for diagnostics. Genentech submitted a Citizen Petition in December 2008 asking the FDA that all IVD tests for therapeutic decision making be held to the same standards. Genentech is marketing several targeted therapeutics for which a number of diagnostic tests are used to support prescribing deci-

sions. Some of these tests have followed different clinical testing and regulatory procedures on their way to commercialisation. Thus, the Petition has created a new momentum around the discussion of the diversity of regulatory paths to market for *in vitro* diagnostics.

- Clinical validation of new technologies. The formal adoption of new diagnostic technologies in the guidelines of important clinical communities should accelerate their market adoption. Agendia’s MammaPrint (a DNA-based test for evaluating an individual’s risk of breast cancer spreading to other sites) is an example of a new diagnostic tool to help personalise treatment, which was recently validated by an influential national clinical group – the Dutch Institute for Healthcare Improvement (CBO).

Increasingly, pharmaceutical companies will not move a drug candidate to the clinical development stage without a clear biomarker development programme. These companies understand the contribution of biomarkers and diagnostics in improving the design and probability of success of clinical trials. In addition, pressure from healthcare payers is putting more emphasis on the availability of a companion biomarker test when deciding on a drug’s reimbursement. These factors will combine to accelerate the development of new diagnostics for personalised medicine. Together we anticipate that alliances and collaboration will be inevitable as the market need expands.

Notes to the editor

- Early diagnostics: diagnostic products permitting the detection of a disease at very early stages of its development thus giving more treatment options (eg early lung cancer detection allowing surgery).
- Prognostics: diagnostics that provide a prediction or estimate the risk of developing a particular condition based on phenotypic (eg transcriptomic, proteomic or metabolomic) parameters; or genomic (eg hereditary or gene based) characteristics. **DDW**

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