

Diagnostics 2009

Moving towards personalised medicine*

What will you do?



*connectedthinking

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Overview

Diagnostics 2009 is the first edition of an annual review of deal activity in the in vitro diagnostics (IVD) sector and significant events for personalised medicine, a field which is fast rising to prominence in healthcare innovation.

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, as defined by the US National Cancer Institute – 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”.

The growth of molecular diagnostics

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. In this sense, significant improvements in personalised medicine should be expected in the next few years as molecular diagnostics represent one of the fastest growing segments in the \$37 billion IVD market – reported by Roche and Boston Biomedical Consultants at the annual meeting of the AACC in July 2008. The overall market is expected to grow by 5% per annum to \$50 billion between 2007 and 2012 with sales of molecular diagnostics expected to grow by 14% per annum from \$2.6 billion to \$5.0 billion. In the context of this market sizing, molecular diagnostics comprise only those tests that analyse the DNA or RNA of an organism – molecular diagnostics can also be more widely defined to include tests that analyse other types of molecules. The definition of the IVD market used in this report comprises all clinical in vitro diagnostics, including glucose monitoring for diabetes care but excluding diagnostics for research use.

Personalised medicine as a spectrum

As personalised medicine means different things to different people, other 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 also *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 – one way of defining a personalised medicine diagnostic – it would not have much sense.

Some testing concepts

Important concepts to understand the different shades of grey in the spectrum of personalised medicine diagnostics include:

- *Diagnostics*: products used to diagnose the presence or absence of a particular disease or condition;
- *Early diagnostics (ED)*: diagnostic products permitting the detection of a disease at very early stages of its development thus giving more treatment options (e.g. early lung cancer detection allowing surgery);
- *Prognostics (P)*: diagnostics that provide a prediction or estimate the risk of developing a particular condition based on:
 - *phenotypic* (e.g. transcriptomic, proteomic or metabolomic) parameters; or
 - *genomic* (e.g. hereditary or gene based) characteristics.
- *Companion diagnostics (CD)*: diagnostic products to evaluate an individual patient's (1) likelihood of benefiting from a particular therapeutic or (2) risk of suffering certain adverse events from a particular therapeutic. Companion diagnostics represent a greater integration between diagnostics and therapeutics;
- *Screening tests*: diagnostics performed on people prior to a clinical manifestation of disease – this contrasts with most other medical checks, which are performed when symptoms are already available. Screening typically involves testing a target population for a particular condition as part of a public health strategy;
- *Pharmacogenomic tests*: examine the influence of genetic variation on drug response in patients by correlating gene expression or single-nucleotide polymorphisms (SNPs) with a drug's efficacy or toxicity. The aim of pharmacogenomics is to take into account a patient's genotype to optimise drug therapy, i.e. to maximise efficacy whilst minimising adverse effects. Advances in pharmacogenomics are expected to support the development of personalised medicine as they should help better take into account an individual's specific nature;
- *Pharmacogenetic tests*: examine single gene interactions with drug response in patients whereas pharmacogenomic tests examine the whole genome's interactions.

Companion diagnostics represent the test type, which provides the most objective fit with the definition of personalised medicine. With early diagnostics and prognostics there is strong potential but the fit with personalised medicine is less conclusive; we would first have to consider how the information provided by such tests can be used to guide treatment decisions before we can judge on their fit. These test types are not necessarily exclusive – a given diagnostic may be simultaneously a CD an ED and a P. Furthermore, a companion diagnostic does not have to be pharmacogenomic (or pharmacogenetic) but many of those currently under development are.

Companion diagnostics and the future of pharma

In this report, we will use some of these concepts, which are defined in the sidebar *Some testing concepts*, to better monitor investments that may support the development of personalised medicine, when we review recent licensing deals by the industry.

The concept of companion diagnostic, and its role in the future of healthcare, is also mentioned in *Pharma 2020: Marketing the future*, a report published by PricewaterhouseCoopers in February 2009. This *Pharma 2020* 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. Many specialist therapies are very costly (e.g. 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 is still unsatisfactory, varying widely from "20% to 75% depending on the drug and the disease", as reported by Jürgen Schwiezer, CEO of Roche Diagnostics.

Specificity and sensitivity

Specificity and sensitivity are key measures, which are used to report on a diagnostic test's effectiveness in detecting a targeted condition in a tested population:

- *Sensitivity*: measures the percentage of actual targeted disease cases that are detected by the test. For example, a sensitivity of 90% would indicate that 10% of actual cases were not detected – false negatives represent 10%;
- *Specificity*: measures the percentage of the detected cases, which are true cases of the targeted disease. For example, a specificity of 90% would indicate that 10% of detected cases were not true cases of the actual targeted disease – false positives represent 10%.

To be sure, diagnostic tests, which have sensitivity and specificity both at 90% or higher, are very rare. This implies there is significant room for improvement for the effectiveness of future diagnostics.

Industry overview

The industry in the diagnostics sector is more concentrated than in the pharmaceutical sector with the ten largest IVD players representing approximately 75% of the market in 2007, compared with 45% for the top ten pharmaceutical companies. Roche is the largest IVD business with a 20% market share; Beckman Coulter, the largest pure play company with a 6% market share; and Inverness Medical Innovations, the most acquisitive player in recent years, with a 3% market share.

Related diagnostics industries include the medical imaging and electromedical equipment sectors, which both use in vivo (rather than in vitro) diagnostic procedures. We will not review these industry sectors here but note the recent entry into the IVD space of Siemens, a major diagnostic imaging player who now commands the second largest IVD market position behind Roche, following three major acquisitions in 2006-2007. Other in vivo players may well follow suit in the coming years as we have witnessed some appetite for horizontal industry consolidation in the emerging molecular medicine field – during 2007, GE Healthcare temporarily considered an acquisition of selected IVD assets from Abbott Laboratories prior to withdrawing.

Outline of *Diagnostics 2009*

The topics covered in *Diagnostics 2009* include M&A and licensing deal activity, regulatory developments on biomarker testing, partnerships with the pharmaceutical industry, significant events beyond deal activity, case studies and key drivers of future revenue growth for personalised medicine diagnostics.

M&A and licensing

Personalised medicine was a prominent topic in the sector's deal activity during the past year:

- At least three of the ten largest M&A deals made explicit reference to personalised medicine as a key motivation: the acquisition of Innogenetics by Solvay, the purchase of Proprius by Cypress, and the take over of AviraDx by bioMérieux.
- Four of the 18 licensing-in deals announced by the ten largest IVD companies were for companion diagnostics, including deals by Roche, Beckman Coulter and Becton Dickinson. Several other deals could also claim a potential personalised medicine ambition, as they were for prognostics or early diagnostics.

The largest M&A deal announced during 2008 was Hologic's acquisition of Third Wave Technologies for \$580 million. This contrasts with the much higher value of deals announced during 2006-2007, which included three acquisitions by Siemens valued between \$1.8 billion and \$7.1 billion, and another six deals in the range \$1.3 billion to \$6.5 billion. In early 2009, Beckman Coulter announced an \$800 million proposed acquisition of Olympus, so we can expect the overall value of deals in 2009 to exceed 2008 levels.

The licensing-in deals announced by the top ten IVD players in 2008, included a majority of deals for cancer and infectious diseases. Becton Dickinson was the most active major in 2008 with four in-licensing deals. Roche lead the way over 2004-2008 with 26 deals. The values of licensing deals were not analysed. Only a minority of about 10% of announced licensing deals in the IVD sector have disclosed deal terms – a much lower level of transparency than in the pharmaceutical sector.

Biomarkers and companion diagnostics

Given the importance of companion diagnostics for the development of cost-efficient personalised healthcare, we review the position of regulators on the need to accompany drug prescribing decisions with diagnostic testing of specific biomarkers. In particular, we present cases where the FDA (4 cases) and the EMEA (11 cases) insist on relevant biomarker testing to guide drug prescribing. Other cases where testing is "recommended" or "for information" rather than "required" are also discussed.

Partnerships with the pharmaceutical industry

We continue on the theme of companion diagnostics by exploring whether the importance of such tools has prompted growing licensing deal activity with pharmaceutical partners. The numbers indicate that whilst the clinical case for developing companion diagnostics is strong, we have yet to see significant deal-flow developing between the pharmaceutical and diagnostics industries. Only seven companion diagnostics deals with pharma were announced in 2008, with deal-count ranging from 6 to 14 over 2004-2007.

Significant events

Beyond the deal activity, we selected a number of other significant events for the development of personalised medicine that have taken place over the past year, including:

- Government funds being committed to research projects in personalised medicine in the US and Europe, including significant initiatives in The Netherlands and Luxembourg;
- Regulatory developments in the US and Europe with new legislation to protect individuals from discrimination based on their personal genetic information, and Genentech's citizen petition which has started a lively and crucial debate on the diversity of regulatory pathways available for diagnostics;
- Technology developments including a new DNA test to assess prostate cancer risk from deCode, and a large scale trial to study a gene guided dosing methodology for warfarin; and
- Clinical practice recommendations for Agendia's breast cancer test in The Netherlands.

Case studies

Case studies on three active players in the personalised medicine space in the US and Europe outline recent developments in diagnostic technologies from:

- The Translational Genomics Research Institute (US);
- Genomic Health (US); and
- DxS (UK).

Two further case studies – one discussing the health economics of warfarin and the other covering the renaissance of bio-banking – review new challenges linked to the development of personalised medicine.

Moving towards personalised medicine

We conclude with some thoughts on the likely drivers of future revenue growth for personalised medicine diagnostics.

M&A activity in the IVD sector

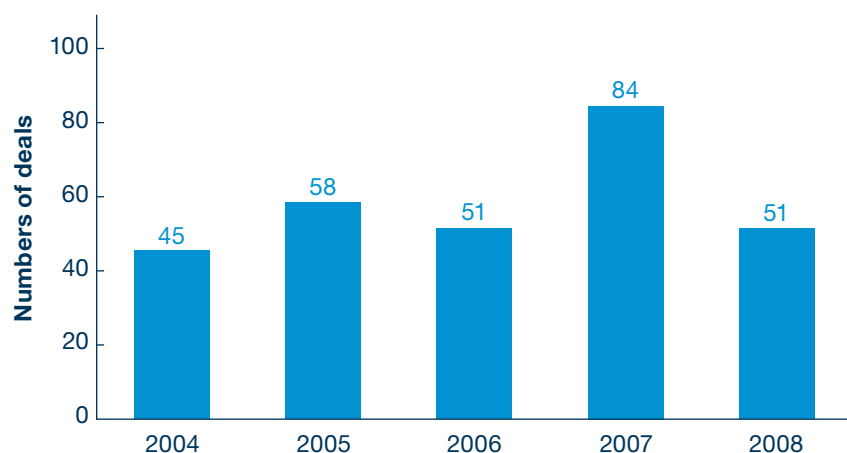
2008 deal numbers returned to 2006 levels following a spike in 2007

51 acquisitions or mergers were announced in the in vitro diagnostics (IVD) sector in 2008, representing a significant drop compared to the 84 deals announced in 2007. This is explained by the fact that many industry players were busy completing or integrating the significant deal volume announced during 2007. The trend of the past five years suggests that 2007 was indeed an exceptional year considering that deal numbers ranged from 45 to 58 during 2004-2006, a level which is comparable with 2008 but significantly less than in 2007.

Inverness and a group of multiple bidders drove most of the rise in 2007 and drop in 2008:

- Inverness Medical Innovations – we noted 17 acquisitions announced by Inverness in the in vitro diagnostics sector during 2007, compared with none in 2008. Inverness did announce a significant acquisition during 2008, with the \$900 million bid for Matria Healthcare in January. However, Matria is a disease management program and services business rather than an IVD company. Its activities include high-risk pregnancy and neonatal care management programs, oncology services, and women's health offerings. Inverness made the purchase to create a new "health management division" that combines Matria with two other businesses recently acquired by Inverness, Alere Medical and ParadigmHealth. This reflects a strategy by Inverness to develop service offerings beyond its diagnostic products businesses;
- Other multiple bidders – we also identified half a dozen companies, including China Medical Technologies (China), Concateno (UK) and IDS (UK), which announced multiple deals in 2007 but stayed away in 2008.

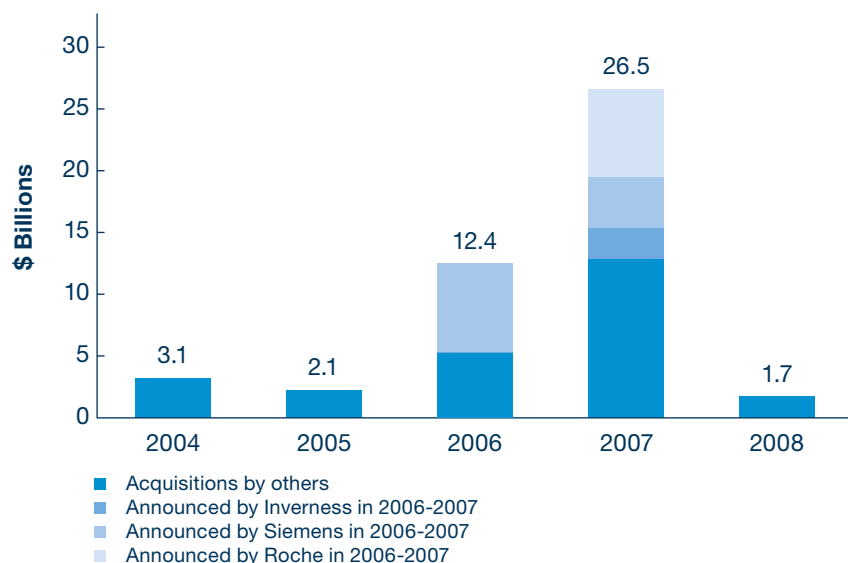
Number of All M&A Deals in the IVD Sector in 2004-2008



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

Acquisitions in 2008 focused on deals below \$1 billion

Value of Disclosed M&A Deals in the IVD Sector in 2004-2008



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

Significant change at the top following three mega-deals by Siemens

2006 and 2007 saw a major change at the top of the league table of the largest in vitro diagnostics companies by sales following the acquisition of three leading IVD businesses by Siemens, who did not have a significant presence in this sector prior to 2006:

- The \$5.3 billion acquisition of Bayer's in vitro diagnostics business, which excluding the diabetes care franchise, which stayed with Bayer, announced in 2006;
- The \$1.8 billion acquisition of Diagnostics Products Corporation, announced in 2006; and
- The \$7.1 billion take over of Dade Behring, announced in 2007.

The league table of the ten largest IVD suppliers by sales thus saw the appearance of Siemens near the top whilst Bayer moved down the ranks:

Ranking of the Largest Companies by IVD Sales* in 2004 and 2008

2004		2008	
1	Roche	1	Roche
2	Abbott	2	Siemens
3	Johnson & Johnson	3	Johnson & Johnson
4	Bayer	4	Abbott
5	Beckman Coulter	5	Beckman Coulter
6	Dade Behring	6	bioMérieux
7	bioMérieux	7	Bayer
8	Becton Dickinson	8	Inverness
9	Bio-Rad	9	Bio-Rad
10	Sysmex	10	Becton Dickinson

Source: PricewaterhouseCoopers analysis using company reports

* Ranking based on IVD sales as reported in published company accounts in the accounting periods ended in 2004 and 2008 respectively. Sales figures were converted into US dollars using the average exchange rate in each accounting period. IVD sales included glucose monitoring but excluded diagnostics for research use

The last time such a dramatic change took place at the top of the IVD league table was in 1997 when Roche announced it was buying Boehringer Mannheim (BM) through its acquisition of the Corange group. The combination of Roche's then niche diagnostics business with BM, one of the two world-leading IVD players, catapulted Roche to the top of the league.

Six other acquisitions over \$1 billion in 2006-2007

Nine deals over \$1 billion were announced during 2006-2007, the three mega deals by Siemens and the following six:

- Five deals announced in 2007:
 - Cytyc's \$6.5 billion merger with Hologic;
 - Ventana's \$3.4 billion sale to Roche;
 - Digene's \$1.6 billion purchase by Qiagen;
 - BioSite's \$1.6 billion acquisition by Inverness;
 - Dako's \$1.3 billion take private by the financial investor EQT.
- One deal announced in 2006:
 - Phadia's \$1.6 billion acquisition by the private equity house Cinven.

The ten largest deals of 2008 ranged from \$17m to \$580m

Supporting existing franchises with strategic technologies

In the top ten deals announced during 2008, we can see four major themes.

Four deals in the top ten reflected strong strategic links between the target and the bidder through existing partnerships or strong market synergies:

- Third Wave Technologies (TWT) was acquired by Hologic to grow its existing women's health and diagnostics business. The company was particularly interested in gaining access to TWT's test for Human Papilloma Virus (HPV), which can cause cervical cancer, and was being reviewed by the FDA for approval. This would bring Hologic into competition with Qiagen in the HPV testing market;
- BioArray's molecular diagnostics solutions for blood transfusion presented potential synergies with Immucor's blood transfusion business as well as an opportunity to expand into the transplantation market;
- Immunicon has had, since 2000, a partnership with Veridex, the Johnson & Johnson company, to develop cancer diagnostic platforms. Following Immunicon's bankruptcy filing, Veridex bid for Immunicon's assets including intellectual property (IP), product inventory, clinical data and technologies related to the CellSearch System. This system is reported as the first diagnostic test to automate the detection and enumeration of circulating tumour cells;
- OcuSense was already 50.1% owned by OccuLogix. The two ophthalmic devices companies agreed to bring the ownership to 100%. OcuSense brings a lab-on-a-card technology to help eye care practitioners test for biomarkers in tears at the point-of-care.

Pursuing the personalised medicine ambition

The personalised medicine theme was explicit in at least three deals in the top ten, 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's 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 (H/I 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 bioTheranostics, Inc.

Growing product portfolios

- Biotrin's portfolio of viral diagnostics was the main attraction for DiaSorin. In particular, Biotrin has a leading position with its test for Human Parvovirus B19, a virus that can cause miscarriage in pregnancy. Also, the company recently signed an exclusive licence agreement with the US National Institutes of Health to develop tests to monitor the efficacy of the new cervical cancer vaccines that have been licensed in Europe and the US. DiaSorin plans to adapt Biotrin's tests to its automated lab instruments;
- Ibis has a system for the rapid detection and characterisation of a broad array of pathogens for the management of infectious diseases in the clinical and hospital setting which attracted Abbott. According to Ibis, the Ibis T5000 Biosensor System interrogates common sequences among common classes of organisms and can identify "virtually all bacteria, viruses and fungi, and can provide information about drug resistance, virulence, and strain type of these pathogens within a few hours."

Venture funding for growth

- Chemclin raised \$16.5 million in a series B funding led by the China Healthcare Partnership with support from existing investors, WI Harper, Siemens Venture Capital, and SB China Venture Capital. Chemclin is reported to be the first company in China to launch a full panel of chemiluminescence immunoassays for blood-borne diseases, including AIDS, syphilis and hepatitis B and C. It also provides a panel of tumour diagnostics.

Top Ten 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	Biotrin	Ireland	DiaSorin	Italy
8	31	Immunicon	US	Johnson & Johnson	US
9	22	OcuSense (49.9%)	US	OccuLogix	Canada
10	17	Beijing Chemclin Biotech (Minority)	China	Investor Group	Germany

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

Outlook: expect further change at the top in 2009-2010

In 2009-2010 we can expect further change at the top of the industry. Indeed, we have noted the appetite of certain players for major scale changing deals in the past, as well as some early expressions of interest in 2009.

Two large deals that got away in the last couple of years:

- GE announced an \$8.1 billion bid in January 2007 to acquire two diagnostics business units from Abbott, excluding its glucose monitoring and molecular diagnostics businesses. The parties withdrew from the proposed deal in July 2007 due to differences on the proposed deal terms. GE has a leading presence in the diagnostic imaging space in terms of both imaging equipment and contrast media. However, to buy into the IVD space with a similar sized deal would be comparable with Siemens's move into the industry in 2006-2007;
- Beckman Coulter announced a \$1.6 billion bid for Biosite in March 2007. Biosite withdrew from the proposed deal in May 2007 and was eventually acquired by Inverness in that year.

Deals announced in early 2009 included a major addition of revenues by Beckman Coulter and further acquisitions by serial buyer Inverness, including its acquisition of selected business assets from ACON Laboratories:

- In February 2009, Beckman Coulter announced an agreement to acquire the diagnostic systems part of Olympus's life sciences business for about \$800 million to broaden its clinical chemistry offering, especially in the ultra-high throughput setting. This deal is expected to add revenues of about \$500 million in 2010 and could move Beckman up the league table. The transaction is expected to close in the third quarter of 2009;
- In March 2009, Inverness announced its \$200 million acquisition of selected rapid diagnostics business assets of ACON Laboratories, comprising lateral flow immunoassay products in China, Asia Pacific, Latin America, South America, the Middle East, Africa, India, Pakistan, and Russia. This followed Inverness's 2006 acquisition of ACON's business in the same product areas in a first selection of territories including the US, Canada, Europe (excluding Russia, the former Soviet Republics that are not part of the EU and Turkey), Australia, Israel, Japan and New Zealand. ACON will retain its other worldwide in vitro diagnostics businesses including diabetes, clinical chemistry and immunoassay products.

Selected M&A Deals in the IVD Sector in Early 2009

Value (\$m)	Target	Country	Bidder	Country
800	Olympus	Japan	Beckman Coulter	US
237	Concateno	UK	Inverness	US
200	ACON's lateral flow immunoassay business in selected territories	US	Inverness	US
132	Tepnel Life Sciences	UK	Gen-Probe	US
41	Exact Sciences	US	Sequenom	US

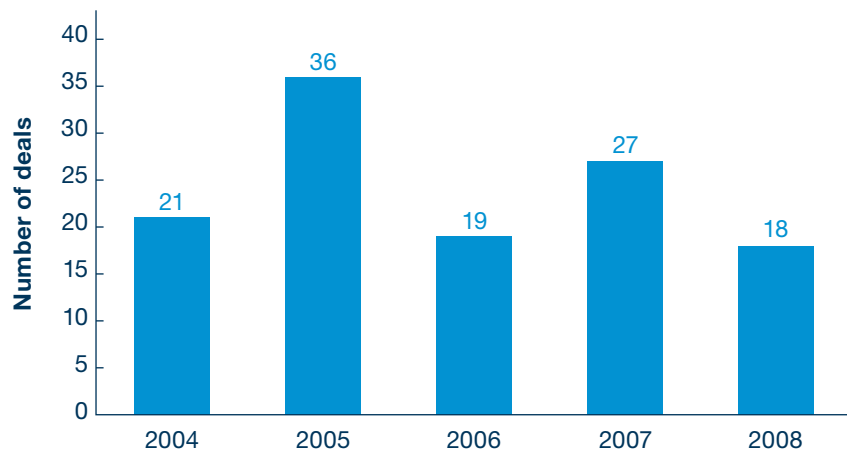
Source: PricewaterhouseCoopers analysis using Windhover, Clinica and other publicly available sources

Licensing by ten IVD majors

2009 could see a rise of in-licensing by the majors following the trough of 2008

Number of In-Licensing Deals Announced in 2004-2008 by Ten IVD Majors

Eighteen in-licensing deals were announced in 2008 by ten IVD majors – in this section we focus on the in-licensing activity in 2004-2008 of the ten largest in vitro diagnostics manufacturers by sales reported in accounting periods ended in 2008. This represented a 33% decrease over the 27 deals announced in 2007. In the past five years, those years with a relatively low number of deals were followed by years with significantly larger deal activity, as if some catching up was taking place. Deal count thus increased by 71% and 42% in 2005 and 2007, following the trough years of 2004 and 2006. If we average out these two troughs and the subsequent peaks we get an average of 2.6 deals per major per annum. On this basis, we could see a significant increase in deal numbers into the mid-twenties in 2009.



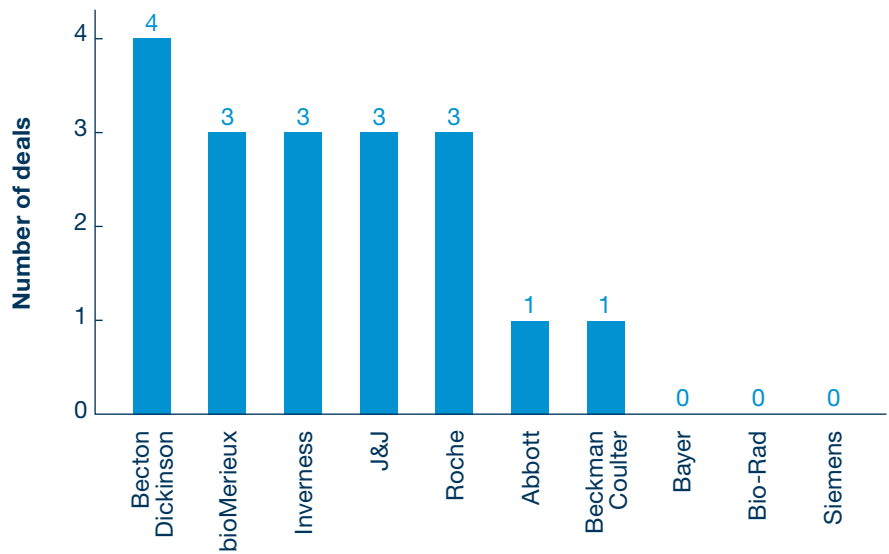
Source: PricewaterhouseCoopers analysis using Windhover data and other publicly available sources

Becton Dickinson was the most active licensee in 2008

Becton Dickinson was the most active in 2008 with 4 announced in-licensing deals, followed closely by bioMérieux, Inverness, Johnson & Johnson and Roche announcing 3 in-licensing deals each. These five players announced deal numbers above the average of 2.6 per annum for the group of majors over 2004-2007. However, for some of these parties the deal-flow was below the company's average for 2004-2007, e.g. Roche who announced an average of 5.8 deals per annum over this period.

One or no deal was announced by each remaining five IVD majors, including Abbott, Beckman Coulter, Bayer, Bio-Rad and Siemens. Some may be preparing to catch up soon, e.g. possibly Siemens who have already announced on-going licensing discussions with LabCorp. But others could continue with low numbers, e.g. Bayer who now have a much narrower IVD business focused on their diabetes care franchise.

Number of In-Licensing Deals Announced in 2008 by Ten IVD Majors

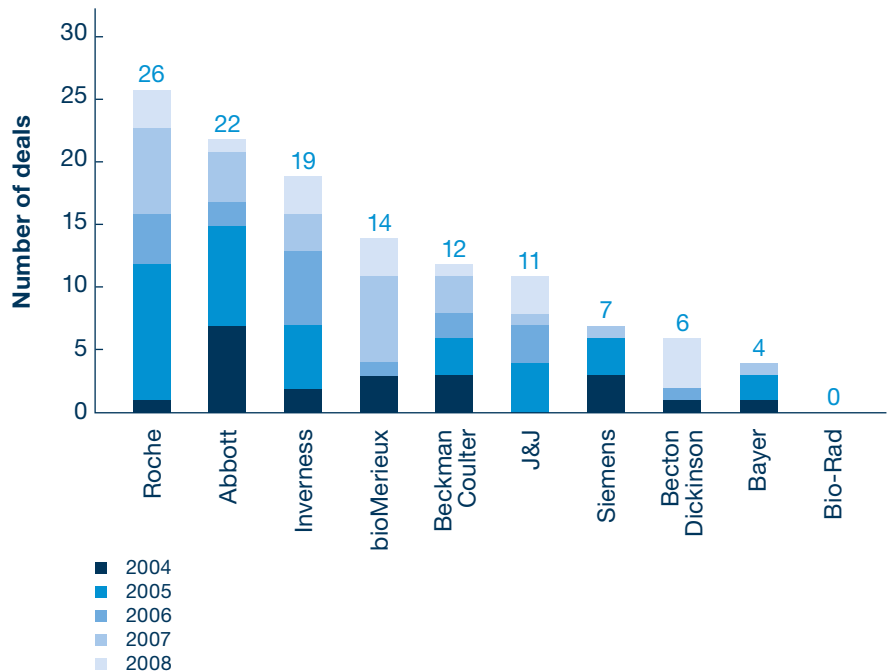


Source: PricewaterhouseCoopers analysis using Windhover data and other publicly available sources

Roche was the most active licensee over 2004-2008

Roche, Abbott and Inverness were the most active deal-makers over 2004-2008 with 26, 22 and 19 in-licensing deals respectively. For Roche, this represents an average of 5.2 deals per annum over 2004-2008. The other seven majors announced a significantly lower number of alliances, ranging from 0 to 14 deals over the same period.

Number of In-Licensing Deals Announced in 2004-2008 by Ten IVD Majors



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

Disease focus: cancer and infectious diseases attracted most interest in 2008

Eight in-licensing deals announced by the majors in 2008 focused on technologies for early detection of cancer. Five majors were involved in cancer deals:

- Roche gained rights from DxS to distribute its TheraScreen K-RAS Mutation Kit for metastatic colorectal cancer worldwide, and the TheraScreen EGFR29 for lung cancer worldwide (excluding North America and Hong Kong). Roche also gained co-exclusive rights for the use of the Universal ProbeLibrary PCR system of Exiqon;
- Becton Dickinson signed an agreement with Arbor Vita for the development of a cervical cancer biomarker. It has also announced development of new biomarker tests for certain cancers based on Luminex's xMAP technology;
- Johnson & Johnson acquired rights for early lung cancer detection, through licensing agreements with CeMines and GeneSystems;
- Inverness has acquired from BioCurex semi-exclusive worldwide rights for the RECAF cancer marker, to detect breast, prostate, colorectal, and lung cancers;
- bioMérieux licensed rights from ProteoSys to the Annexin 3 biomarker to develop a urine-based prostate cancer diagnostic.

A further six deals targeted better monitoring and cost effective management of infectious diseases. Four majors were involved in these deals:

- Beckman Coulter acquired intellectual property rights from Siemens to develop, manufacture and sell a quantitative viral load test for Hepatitis C for use with its own molecular diagnostic instrument in development;
- Becton Dickinson acquired an option to license exclusive rights to intellectual property from Accelr8, including its BACcel rapid pathogen diagnostics platform; and signed an agreement to develop a new infectious disease molecular diagnostic using US Genomics' DirectLinear Analysis technology;
- Abbott licensed rights from Luminex to sell its xTAG respiratory viral panel worldwide (except US) and obtained semi-exclusive US distribution rights;
- bioMérieux agreed to exclusively distribute Quidel's rapid point-of-care diagnostics for infectious diseases, QuickVue, worldwide except in the US, Japan, and Scandinavia. BioMérieux has also agreed to develop infectious disease diagnostics jointly with FIND, who specialise in diagnostics for poverty-related diseases.

Other disease areas targeted by the majors in 2008 included cardiovascular disease and diabetes.

Partner focus: smaller IVD businesses provided most of the licensed innovation

Personalised medicine focus: four tests licensed in 2008 could be classified as companion diagnostics

The majors sourced sixteen of the eighteen deals from small or medium sized IVD players in 2008, including for example: DxS (Manchester, UK), Arbor Vita (Sunnyvale, US) and BioCurex (Richmond, Canada) who signed deals with Roche, Becton Dickinson and Inverness, respectively. Other sources for in-licensing deals with the ten majors in 2008, included a research institute, Geneva-based FIND (Foundation for Innovative New Diagnostics), and another IVD major, Siemens.

At least four of the eighteen in-licensing deals announced by the ten majors in 2008 were for personalised medicine. There were indeed four deals for companion diagnostics - the test type, which provides the most objective fit with the definition of personalised medicine. In addition, most other deals had the potential of a good fit with personalised medicine too as they could often be classed as early diagnostics or prognostics, as discussed in the overview section.

In the next two sections we focus the analysis on companion diagnostics and the interface between the diagnostics and pharmaceutical industries.



In-Licensing Deals Announced in 2008 by Ten IVD Majors

Licensee/ Partner	Licensor/ Partner	Deal Headline	Disease Area	Test Type*
Roche	DxS	TheraScreen genetic mutation test	Cancer	CD, P
	Exiqon	Rights for the Universal ProbeLibrary PCR system	Cancer	D, ED, CD, P
	Response Biomedical	RAMP product line	Cardiovascular	D, ED, P
Johnson & Johnson	CeMines	IP rights for early lung cancer test	Cancer	D, ED, P
	DexCom	Right for DexCom 's Seven continuous glucose monitoring system	Diabetes	D, P
	GeneSystems	PAULA NSCLC test	Cancer	D, ED, P
Abbott	Luminex	xTAG test worldwide distribution	Infectious diseases	D, P
Beckman Coulter	Siemens	HCV testing rights	Infectious diseases	D, ED, CD, P
bioMerieux	F.I.N.D.	Infectious disease diagnostics	Infectious diseases	D, P
	ProteoSys	Annexin 3 prostate cancer biomarker	Cancer	D, ED, P
	Quidel	Point of care infectious diseases test line (QuickVue)	Infectious diseases	D, ED
Inverness	PrognostiX	Distribution of cardiovascular myeloperoxidase test (CardioMPO)	Cardiovascular	D, ED, P
	Compugen	Collaboration to develop a novel cardiovascular test	Cardiovascular	D, ED
	BioCurex	Rights to develop and market products employing the RECAF cancer marker	Cancer	D, ED, P
Becton Dickinson	Accelr8	BACcel diagnostic platform rights	Infectious diseases	D
	Arbor Vita	New diagnostic for cervical cancer	Cancer	D, CD
	Luminex	xMAP platform biomarkers screener	Cancer	D, P
	US Genomics	Molecular diagnostic with DLA technology	Infectious diseases	D, P

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

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

Biomarkers and companion diagnostics for drugs

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. This encouragement and guidance has taken several forms, including the FDA's Critical Path Initiative launched in March 2004 with the white paper *Innovation-Stagnation. Challenge and Opportunity on the Critical Path to New Medical Products*, the FDA's release in April 2005 of its *Drug-Diagnostic Co-Development Concept Paper* and the participation of regulators in a series of workshops with industry representatives on the topic of pharmacogenomics and regulatory decision making. More conclusively, both the FDA and EMEA now require that biomarker testing be performed prior to prescribing certain drugs.

The FDA's valid genomic biomarkers

The FDA recently started reporting a table of genomic biomarkers which it considers "valid" to guide the appropriate clinical use of approved drugs. These biomarkers can help differentiate patients into responder and non-responder groups, which can help estimate drug effectiveness, avoid toxicity, and adjust drug dosage. The agency has decided to provide its table as a reference point, to be updated quarterly, following the marked increase in the last decade of pharmacogenomic information contained in the labels of approved drugs. About ten percent of labels for drugs approved by the FDA now contain pharmacogenomic information.

Valid biomarker

The FDA provided the following definitions in its March 2005 paper, *Guidance for Industry: Pharmacogenomic Data Submissions*.

Biomarker

A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

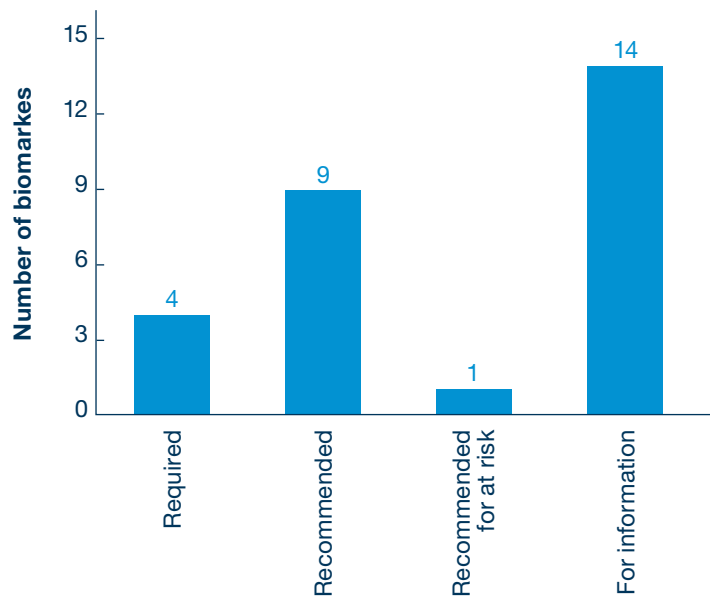
Valid biomarker

A valid biomarker is a biomarker that is measured in an analytical test system with well-established performance characteristics and for which there is an established scientific framework or body of evidence that elucidates the physiologic, toxicologic, pharmacologic, or clinical significance of the test results. The classification of biomarkers is context specific. Likewise, validation of a biomarker is context specific and the criteria for validation will vary with the intended use of the biomarker. The clinical utility (e.g. predict toxicity, effectiveness or dosing) and use of epidemiology/population data (e.g. strength of genotype-phenotype associations) are examples of approaches that can be used to determine the specific context and the necessary criteria for validation.

The FDA reported 28 valid genomic biomarkers on its website as at 20 March 2009, including some biomarkers that apply to several indications, as with EGFR expression, which is relevant to the prescribing of several drugs for several cancers (including colorectal and head and neck cancer) with different testing requirements. The disease area with most biomarkers is cancer, including 12 cases, followed by infectious diseases with 5. Neurological disorders and cardiovascular disease have 4 cases each, whilst three other disease areas have one biomarker each – rheumatic disease, anaemia and immuno-suppression. The larger number of biomarkers for cancer may reflect the relative importance of genetic causes in this disease as well as the relatively large number of research projects in this area.

The FDA has shown that it wants to encourage greater use of biomarkers and diagnostics to accompany drug development and prescribing. However, it is clear from the FDA’s table of valid genomic biomarkers that we are still at the start of the process. Of the 28 biomarkers, only four are “required” to be tested prior to deciding on the use of a companion drug. For the remaining 24 biomarkers, a test for the biomarker is only “recommended” or for “information only”.

Biomarker Testing Requirements by the FDA at Spring 2009



Source: PricewaterhouseCoopers analysis using data from the FDA’s website at 20 March 2009

The four biomarkers, for which testing is required prior to deciding on the use of the drug, are:

Biomarker	Representative Label	Indication	Drug	Drug Marketer
CCR5 - Chemokine C-C motif receptor	Selzentry, in combination with other antiretroviral agents, is indicated for treatment-experienced adult patients infected with only CCR5-tropic HIV-1 detectable, who have evidence of viral replication and HIV-1 strains resistant to multiple antiretrovira	Infectious Diseases (HIV)	Selzentry (maraviroc)	Pfizer
Epidermal growth factor receptor (EGFR) expression	Patients enrolled in the clinical studies were required to have immuno-histochemical evidence of positive EGFR expression using the DakoCytomation EGFR pharmDx™ test kit.	Cancer (Colorectal)	Erbix (cetuximab)	Bristol-Myers Squibb
Her2 / neu over-expression	Detection of HER2 protein overexpression is necessary for selection of patients appropriate for herceptin therapy. Herceptin should be used in patients whose tumors have been evaluated with an assay validated to predict HER2 protein overexpression.	Cancer (Breast)	Herceptin (trastuzumab)	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)	Sprycel (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

For each biomarker there may be several assays available from different companies to test for the biomarker. This highlights another aspect of the regulatory complexity associated with biomarkers as different assays available for the same clinical decision making purposes may have followed completely different regulatory avenues in being developed and made available for clinicians. The different pathways to market authorisation in the US include FDA clearance through a premarket approval (PMA) or premarketing notification (510(k)), depending on the risk classification of the diagnostic device; FDA clearance for IVD Multivariate Index Assays (IVDMIAs); or the CLIA laboratory certification process for laboratory developed tests (LDTs) (also known as *home-brew*).

There are pros and cons to having such a variety of regulatory paths but we expect lively debates in the coming months to seek a way forward following Genentech's citizen's petition submitted with the FDA on 5 December 2008. In this petition, Genentech is asking the FDA to require that "all in vitro diagnostic tests intended for use in drug or biologic therapeutic decision making be held to the same scientific and regulatory standards".

The EMEA's biomarker testing requirements for approved drugs

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, and it has a larger number of drugs for which biomarker testing is required.



Milestones in the US and European regulatory reviews of Vectibix

- September 2006 – The FDA granted accelerated approval of Vectibix for the treatment of EGFR-expressing metastatic colorectal carcinoma (mCRC);
- May 2007 – The EMEA's Committee for Medicinal Products for Human Use (CHMP) recommended against approval of Vectibix;
- Numerous retrospective studies suggested the mechanism of action for Vectibix may not work if K-Ras is mutated;
- Retrospective analysis of phase three trials showed “stark difference in response rates between colorectal patients with mutated and wild-type (WT) K-Ras”;
- November 2007 – The CHMP recommended approval based on the “ability to select patients with mCRC who are likely to benefit from Vectibix monotherapy treatment, allowing physicians to make an informed decision about the best treatment options for patients ...”;
- December 2007 – The EMEA approved Vectibix “... monotherapy for patients with EGFR-expressing mCRC with non-mutated (wild-type) K-Ras ...”;
- June 2008 – The CHMP recommend use of Erbitux in mCRC patients only if they have wild-type K-Ras;
- US physicians begin to use K-Ras gene tests regularly;
- December 2008 – The FDA Oncologic Drugs Advisory Committee convened a meeting to discuss conditions under which a retrospective analysis would be appropriate to support labeling, including:
 - An adequate, well-conducted and well-controlled trial;
 - A large sample size with ascertained K-Ras status in a large portion of the randomised subjects;
 - An assay with acceptable analytical performance;
 - An acceptable pre-specified analysis plan.
- The US label, as reported in May 2009, did not include K-Ras testing.

Source: Adapted from the presentation by Dr. Hans-Georg Eichler, EMEA, at the AAPS Workshop on Translational Biomarkers for Accelerating Drug Development: from Preclinical to Clinical, Baltimore, 6 – 7 May 2009

As with the FDA, the pool of drugs approved by the EMEA includes an increasing number of drug labels associated with genomic biomarkers – over 100 EMEA approved drugs were reported to have such labels. And the European agency has a similar practice of classifying approved drugs by diagnostic testing requirements. For illustration:

Drugs with tests ...	Example of drug	Guidance
... required	Abacavir	Contraindicated for patients known to carry the HLA-B*5701 allele
... recommended	Warfarin	CYP2C alleles are associated with increased risk of bleeding
... for information only	Lenalidomide	Drug indicated for patients with transfusion dependent anaemia associated with del(5q)

Source: Data extracted from the presentation by Dr. Hans-Georg Eichler, EMEA, at the AAPS Workshop on Translational Biomarkers for Accelerating Drug Development: from Preclinical to Clinical, Baltimore, 6 – 7 May 2009

Representatives from the EMEA reported at least 11 drugs requiring biomarker testing, as shown in the table below. This presentation of testing requirements by the EMEA is different from the FDA table as it starts with the drug for which there is a biomarker testing requirement rather than starting with the biomarker which needs to be tested for:

Drug	Drug Marketer	Test Requirement	Indication
Ziagen (abacavir)	GlaxoSmithKline	Screening for carriage of the HLA-B*5701 allele should be performed in any HIV-infected patient. Abacavir should not be used in patients known to carry the HLA-B*5701 allele, unless no other therapeutic option is available in these patients, based on the treatment history and resistance testing.	Infectious Diseases
Epitol / Tegretol (carbamazepine)	Novartis	Patients of Han Chinese and Thai origin should be screened for HLA-B*1502 as this allele strongly predicts the risk of severe carbamazepine-associated Stevens Johnson syndrome.	Neuropsychiatric Diseases
Herceptin (trastuzumab)	Genentech/ Roche	Susceptibility to the therapy is determined by the analysis for HER2/neu over-expression.	Cancer
Tasigna (nilotinib)	Novartis	Patients with imatinib-resistant Ph+ chronic myeloid leukemia.	Cancer

Drug	Drug Marketer	Test Requirement	Indication
Sprycel (dasatinib)	Bristol-Myers Squibb	Patients with imatinib-resistant Ph+ chronic myeloid leukemia.	Cancer
Trisenox (arsenic trioxide)	Cephalon	PML/RAR alpha gene+ [or t(15;17) translocation] acute promyelocyticleukemia.	Cancer
Erbitux (cetuximab)	Bristol-Myers Squibb, ImClone Systems, Merck	EGFR+ metastatic colorectal cancer after failure of irinotecan; KRAS wild-type metastatic colorectal cancer.	Cancer
Tarceva (erlotinib)	Genentech/ Roche	Advanced non-small cell lung carcinoma; no clinically relevant effects demonstrated for patients with EGFR- tumours.	Cancer
Vectibix (panitumumab)	Amgen	EGFR+, non-mutated KRAS, metastatic, previously treated colorectal cancer – Conditional Marketing Authorisation.	Cancer
Tykerb / Tyverb (lapatinib)	GlaxoSmithKline	In combination with capecitabinefor Her2+ breast cancer after failure of taxanes and trastuzumab – Conditional Marketing Authorisation.	Cancer
Iressa (gefitinib)	AstraZeneca, Teva	For the treatment of patients with locally advanced or metastatic non-small cell lung carcinoma with activating mutations of EGFR-TK.	Cancer

Source: Data extracted from the presentation by Dr. Marisa Papaluca Amati, Deputy Head, Sector Safety and Efficacy of Medicines, EMEA, at the SGPPH Spring Conference, London, 3 June 2009

International cooperation through the Critical Path Institute

In the spring of 2008, the FDA and EMEA jointly approved a new biomarker test for kidney damage – a key component of toxicology work in drug development.

The story behind that unique event gives insight into the ways in which the pharmaceutical industry is adapting to the new economic realities of the end of the era of blockbuster drugs and the new era of diagnostic driven personalised medicine.

The problem was that previous urine markers for kidney damage were only elevated when more than 70% of kidney function was lost.

The solution involved bringing together 16 leading pharmaceutical companies by an independent and neutral third party and sharing toxicity data from existing research studies with that party. 23 potential biomarkers were identified and cross-validated with all of the companies' internal databases. 7 of the markers had sufficient valid data to justify submission for regulatory approval.

In June 2007 the first ever joint submission to both the FDA and the EMEA was made for a cooperative decision. It was also the first submission under the FDA's Voluntary Submission Data process (VSDX) and the first trilateral face-to-face meeting of regulators (US-EU-Japan) with Japanese regulators observing the process.

The key ingredient was the Critical Path Institute (C-Path) as the independent third party. It occupied a unique position in neutral ground between the regulated and the regulator. C-Path was a trusted third party with whom pharmaceutical companies were willing to share confidential proprietary data and whom the FDA trusted to be independent of the commercial pressures of the pharmaceutical industry.

C-Path is an independent, non-profit organisation created in 2005 by the University of Arizona and the FDA. One of C-Path's goals is to develop the tools to facilitate personalised medicine, including by identifying biomarkers and related methods qualified by the FDA for use in the development of medical products, which will in turn support the creation of a more structured process for the tandem development of drugs and related diagnostics.

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

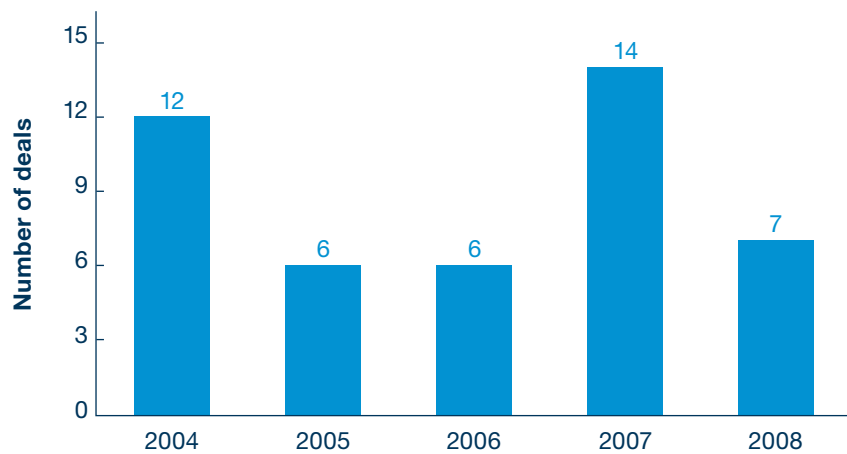
Companion diagnostics partnerships with the pharmaceutical industry



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 2004-2008, with annual deal numbers varying between 6 and 14 throughout. Companion diagnostics partnerships with pharma have yet to become an established industry practice.

Companion Diagnostics Partnerships with Pharma in 2004-2008



Source: PricewaterhouseCoopers analysis using Windhover data

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

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

- 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, six out of seven 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 also a co-partner in this collaboration by OSI with Abbott's diagnostics division to develop a pharmacogenomic test to identify patients most likely to respond to the 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 at the time of the deal and which became a full ownership during 2009;
- Niche specialists dominated as the 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 ten largest in vitro diagnostics companies.

Companion Diagnostics Partnerships Announced in 2008

Diagnostics Partner	Pharmaceutical Partner	Deal Subject	Disease Area
DxS	Amgen	Provide DxS's TheraScreen K-RAS 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 commercialise it with Abbott under an existing partnership between the two companies.	Undisclosed
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	OSI Pharmaceuticals, Genentech, Roche	Abbott's molecular diagnostics division is to develop a pharmacogenomic test to identify patients most likely to respond to the non-small cell lung cancer drug Tarceva (erlotinib). Abbott will use fluorescence in situ hybridisation (FISH) techniques to bind DNA probes to gene sequences encoding 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 morphometry, 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

Similar themes emerge when we analyse the pharmaceutical and diagnostics partners involved in companion diagnostics licensing deals over 2004-2008 in more detail.

Roche, Pfizer and Merck were the most active pharma partners over 2004-2008

Roche's pharmaceutical division, including Genentech, stands out as the most active third-party pharmaceutical licensing partner for the diagnostics sector over 2004-2008 with ten announced deals – an average of two deals per annum. Pfizer, Merck and AstraZeneca followed Roche with 6, 5 and 3 diagnostics partnerships respectively over the same period.

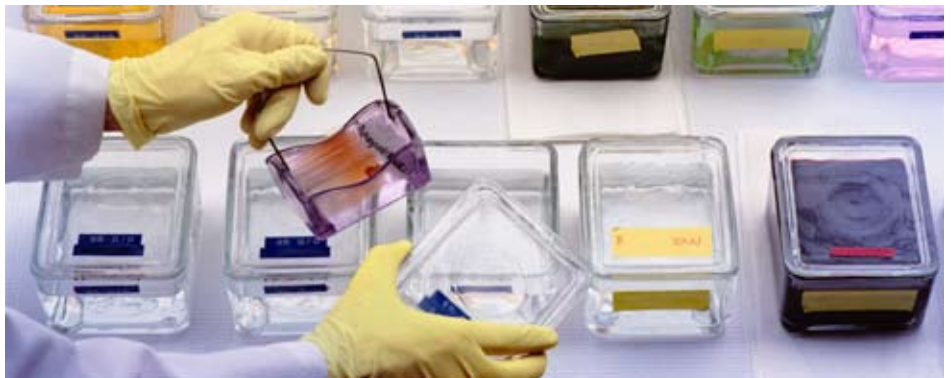
The position of Roche as the leading pharmaceutical partner for collaborations with diagnostics companies is remarkable if we consider that none of the other pharmaceutical companies with a major IVD affiliate – Abbott, Bayer and Johnson & Johnson – announced more than one partnership with a third-party diagnostics company over 2004-2008. 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 2004-2008 included:

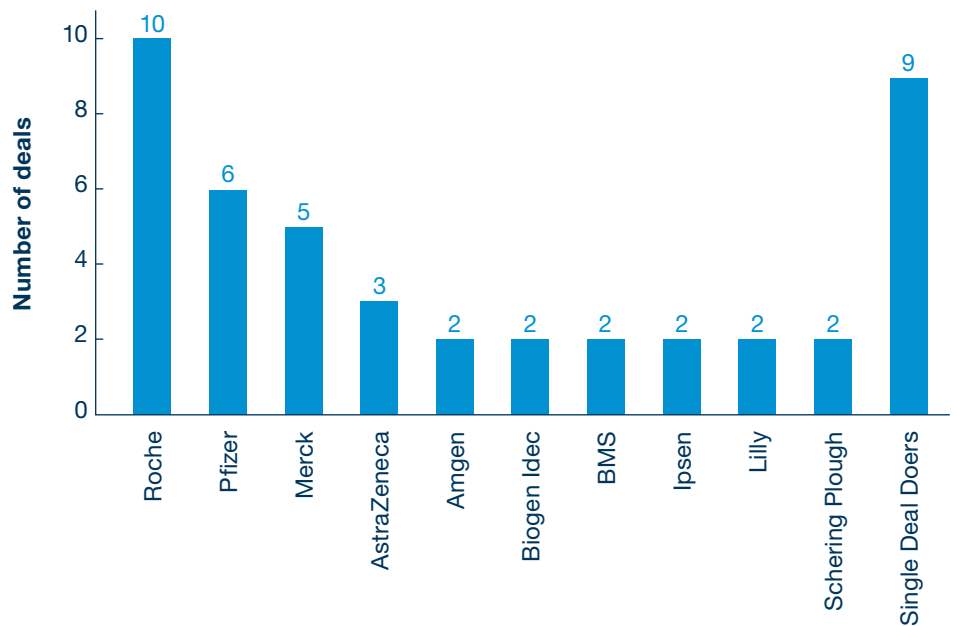
- Large pharma companies: Amgen, Bristol-Myers Squibb, Eli Lilly and Schering-Plough; and
- Medium-sized players: Biogen Idec and Ipsen.

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

- Large pharma companies: Abbott, Johnson & Johnson and Takeda;
- Medium-sized players: Eisai and Organon (prior 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 not counted here; instead, it was included under Roche's partnerships to avoid double counting this deal.



**Companion Diagnostics Deals
by Pharmaceutical Partner
in 2004-2008**



Source: PricewaterhouseCoopers analysis using Windhover data

**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 2004-2008.

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 2004-2008.

In Ipsen’s case, the company’s CEO, Jean-Luc Bélingard, had significant diagnostics industry experience, being a former senior executive of Roche Diagnostics and more recently 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 potential 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 agreed 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 antibodies 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 was to provide physicians with essential information to help guide their therapeutic approach.

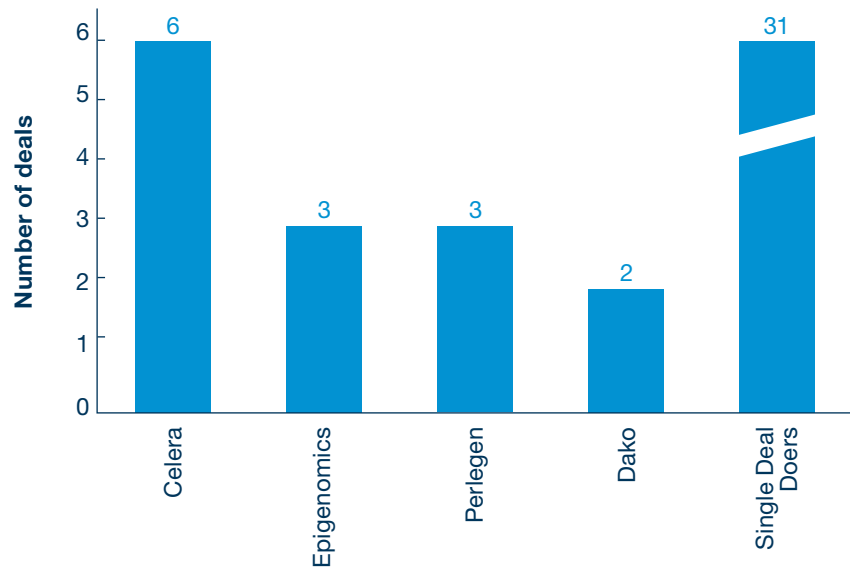
Serial deal making for companion diagnostics was limited amongst diagnostics companies. Only four diagnostics companies announced at least two partnerships with pharmaceutical companies over 2004-2008 and they were all niche diagnostic specialists: Celera, Dako, Epigenomics and Perlegen. Dako is the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

Three observations have followed 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;
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 to have a partnership or another form of public support from the targeted drug's marketer to underline the validity of the test as a companion diagnostic for the drug.

The most active diagnostics partners for deals with pharma were all niche players

**Companion Diagnostics Deals
by Diagnostics Partner
in 2004-2008**



Source: PricewaterhouseCoopers analysis using Windhover data

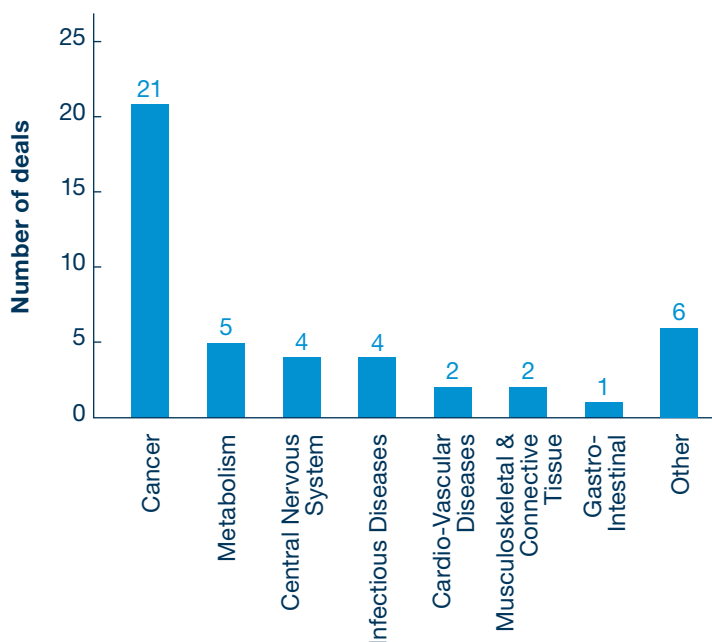


Cancer attracted half the companion diagnostics deal flow in 2004-2008

Companion Diagnostics Partnerships by Disease Area in 2004-2008

Nearly half the companion diagnostics partnerships announced in 2004-2008 – 21 of 45 deals – were for cancer diagnostics. Three key factors are driving the strong interest in cancer companion diagnostics:

1. The importance of genetic causes in the pathophysiology of the disease;
2. The extent of research done in this area; and
3. The high price of cancer therapies, which creates a strong demand by payers for a suitable companion tool to direct these costly treatments to those patients most likely to benefit.



Source: PricewaterhouseCoopers analysis using Windhover data

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.

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

Ten significant events for personalised medicine

The vision of developing a more personalised medicine is not new but has not quite moved from concept to reality yet, apart from a small number of much publicised cases e.g. Herceptin. Completion of the Human Genome Project, and the development of increasingly sophisticated molecular medicine tools, have given hope that personalised medicine might be just around the corner at the start of the millenium. But innovation in depth and shifts in clinical practice often take a littler longer than expected to come through. Beyond the time factor, a significant event or breakthrough is sometimes needed. Such an event is not necessarily science or technology related. The development of recombinant DNA technology may have been a prerequisite for the emergence of today's biopharmaceutical giants Amgen and Genentech, but some would say the key enabler was the Orphan Drug Act of 1983 which gave valuable market protection to the first product reaching the market for indications where the market was small. By analogy, the market for many biomarkers is also seen as relatively small and may have kept the largest diagnostics companies away from basic research in this area.



Looking at events that might be significant for the development of personalised medicine, we have selected ten that have been reported since the beginning of last year. The variety of areas involved suggests the steps we are making towards personalised medicine are indeed becoming more concrete. The significant events include:

- Government funding decisions in The Netherlands, in Luxembourg, at the EU level and in the US;
- Regulatory proposals in the US and Europe;
- Technology developments to be tested with consumers or through clinical trials; and
- Clinical practice recommendations for a new molecular diagnostic.

Ten Significant Events for Personalised Medicine since January 2008

	Category	Date	Event
1	Government	Apr 08	Dutch government commits €150 million to fund personalised medicine projects alongside industry and academia
2	Government	Jun 08	Luxembourg government commits €140 million to the development of a biobank, a lung cancer test and systems biology research
3	Government	Dec 08	EU funds project to develop a SMART-BIOMEMS DNA diagnostic device for the doctor's desktop
4	Government	Feb 09	US provides funding to compare the effectiveness of medical treatments for a given illness
5	Regulatory	May 08	US Genetic Information Nondiscrimination Act (GINA) signed. Council of Europe signs similar protocol
6	Regulatory	Dec 08	Genentech submits a Citizen Petition asking the FDA that all IVD tests for therapeutic decision making be held to the same standards
7	Regulatory	Dec 08	FDA considers collaboration with Centers for Medicare and Medicaid Services on diagnostics
8	Technology	Feb 08	deCode launches deCode PrCa, a DNA test to assess prostate cancer risk
9	Technology	Feb 09	Gene-guided warfarin dosing to be tested in a large scale trial
10	Clinical Practice	Feb 09	Agendia's breast cancer test MammaPrint standard of care at Netherlands Cancer Institute

Source: PricewaterhouseCoopers analysis using publicly available sources

Time will tell which events were more critical for the development of personalised medicine, but the outcome of the discussion triggered by Genentech about regulatory pathways for in vitro diagnostics in the US has the potential to be fundamental for the future of the industry and personalised medicine.

We provide further background on each of the ten events.

1 Dutch government commits €150 million to fund personalised medicine projects alongside industry and academia (7 April 2008)

The Centre for Translational Molecular Medicine (CTMM) of Eindhoven, The Netherlands, announced €300 million of funding for research projects in personalised medicine in the cardiovascular, cancer, neurodegenerative (mainly Alzheimer's) and infection and inflammatory disease areas. This public-private partnership is being funded by the Dutch government (50%), academia (25%), and industry (25%) and is now working on the realisation of an objective to improve the clinical and economic impact of selected diseases, and the decrease of future government spending needs in the healthcare sector. All funded projects must aim to accelerate disease diagnosis, to allow for less aggressive interventions, fewer side-effects, and more effective use of available medical resources. To achieve this, many of the CTMM projects will focus on the identification of biomarkers directly related to the early development of diseases. All CTMM projects were assessed by an independent advisory board and approved by a supervisory board based on their potential to translate research into clinical practice.

2 Luxembourg government commits €140 million to the development of a biobank, a lung cancer test and systems biology research (5 June 2008)

The government of the Grand Duchy of Luxembourg announced its commitment to invest up to €140 million over five years in three research projects in personalised medicine. One objective of the investment program, beyond its prime motivation for healthcare and research, is to trigger the development of a life sciences cluster in Luxembourg and help diversify the country's economy. The initiative will involve the participation of three US research institutions with expertise in personalised medicine: the Translational Genomics Research Institute (TGen) from Phoenix, the Partnership for Personalized Medicine (PPM) from Phoenix, and the Institute for Systems Biology (ISB) from Seattle. Three complementary projects are on the agenda:

- The creation of the Integrated Biobank of Luxembourg (IBBL): in partnership with TGen, to be founded by the three Public Research Centers, CRP Santé, CRP Henri Tudor and CRP Gabriel Lippmann, and the University of Luxembourg. The IBBL plans to collect and analyse biological samples (tissue, blood, etc.) to transform research findings into tools for prevention, diagnosis and treatment of diseases.
- The creation of the Centre for Systems Biology Luxembourg (CSBL): a partnership between the ISB and the University of Luxembourg, in collaboration with the three CRP research centres. The CSBL will focus first on genome sequencing, and then on molecular fingerprinting (using blood proteins) of the human body's main organs. The aim is to gain a better understanding of the molecular origin of diseases, and consequently allow a more "customised" approach to treatment protocols.
- The selection and validation of lung cancer biomarkers, for a more effective diagnosis and management of the disease: to be carried out through a research partnership between the PPM and the CRP-Santé.

3 EU funds project to develop a SMART-BIOMEMS DNA diagnostic device for the doctor's desktop (10 December 2008)

A new DNA diagnostic device for the physician's desktop is being prototyped, with commercialisation expected in 2012. The project to develop this device, called SMART-BIOMEMS, is being funded by the EU and has a particular focus on personalised medicine and direct clinical application. SMART-BIOMEMS consists of a portable diagnostic micro-system to be connected with a personal computer, which aims to allow a quick, precise, and cost effective detection of clinically relevant human gene mutations, to be used for the early diagnosis in a large spectrum of diseases. The prototype, scheduled to be ready for March 2009, has been specifically designed for cancer testing and diagnosis.

4 US Government provides funding to compare the effectiveness of medical treatments for a given illness (16 February 2009)

The \$787 billion economic stimulus bill approved by the US Congress includes \$1.1 billion to fund comparisons of the effectiveness of alternative treatments for illnesses. The coordination of research activities will be overseen by a panel of 15 federal employees, who will also advise the US President on how funds should be distributed. It is hoped that the research, which is expected to include reviews of the scientific literature as well as clinical trials designed to compare treatments, will provide evidence of the efficacy and value of many treatments. The US spends a total of \$2 trillion, or roughly 16% of its GDP, on health care annually, but does so with "little information about which treatments work best for which patients," said Representative Peter Stark, Chairman of the US House of Representatives' Ways and Means Subcommittee on Health. Supporters of the provision point to its potential to reduce costs by discouraging the use of ineffective treatments. As Congress has not specified how the findings should be used, critics fear the provision could interfere with the doctor-patient relationship and may result in the rationing of care. While the details of the program have still to be defined, the growing list of examples where diagnostics have been used to determine the most effective treatments for sub-populations within a given disease may suggest that diagnostics could play an important role in the program. The integration of diagnostics could allow for deeper insight into the molecular differences that separate responders from non-responders, such that researchers can more accurately assess which treatments work for which patients and perhaps also why they work.

**5 US Genetic Information Nondiscrimination Act (GINA) signed (21 May 2008)
Council of Europe signs similar protocol (7 May 2008)**

The Genetic Information Nondiscrimination Act (GINA), which was enacted in May 2008, is intended to protect individuals against discrimination they may face for health insurance and employment, based on genetic information contained in their dossiers. Similar laws were already in place in 34 US states but GINA is the first law of its kind enacted at the federal level in the US. GINA required 13 years of debate in Congress prior to its passage and should help individuals take advantage of new technologies for personalised medicine without fear of discrimination. The diagnostics industry is also expected to benefit as GINA should encourage increased enrolment in clinical trials and other research activities (including biospecimen donation), which are key to research, development and validation for new diagnostic tools. Increased patient education and understanding of the role of genetic disposition to disease is expected to lead to increased patient demand for testing for the diagnostics industry. While reimbursement for diagnostic tests, particularly newer tests that are based on genomic and proteomic technologies, is still rather limited

in the US, increased patient demand could lead to a need for reform. Diagnostics companies hope Congress adopts a favourable position on the reimbursement of molecular diagnostics supporting a more effective, personalised medicine. This would in turn encourage more research and development. On 7 May 2008, dispositions similar to those of GINA were adopted in Europe: the Committee of Ministers of the Council of Europe adopted a new Additional Protocol to the Convention on Human Rights and Biomedicine concerning Genetic Testing for Health Purposes. The rapid developments in biological and medical research prompted the Council of Europe to consider the ethical and legal aspects of applications of genetics, particularly genetic testing, and to draw up legal rules to protect fundamental human rights with regard to these applications.

6 Genentech submits a Citizen Petition asking the FDA that all IVD tests for therapeutic decision making be held to the same standards (5 December 2008)

Genentech has marketed several targeted therapeutics, including Herceptin, Avastin and Tarceva, for which a number of diagnostic tests are used to support prescribing decisions. Some of these tests have followed different clinical testing and regulatory procedures on their way to commercialisation. The petition Genentech submitted on 5 December 2008, requests from the FDA that all IVD tests “intended for use in drug or biologic therapeutic decision making be held to the same scientific and regulatory standards”. In particular, it is asking that the FDA should also regulate laboratory developed tests (LDTs), which at present fall under the CLIA laboratory certification process. These tests are not sold as kits separately from a clinical laboratory and are not currently regulated by the FDA. For kits, the agency is using the risk classification system for medical devices (I, II and III) to decide the level of “clearance” or “approval” required prior to commercialisation. Ten comments on the Genentech petition were filed with the FDA by 1 June 2009:

- Comments in support of the petition were received from the Johns Hopkins University Genetics and Public Policy Center (15 December 2008), Fujirebio Diagnostics (29 January 2009) and Agendia (28 May 2009).
- Comments opposing the petition were received from the Coalition for 21st Century Medicine in two instalments (30 December 2008 and 20 March 2009), the American Clinical Laboratory Association (ACLA) (18 February 2009), and the Association for Molecular Pathology (6 May 2009).
- Roche (6 March 2009), who signed a merger agreement with Genentech on 12 March 2009 to acquire the outstanding publicly held interest in Genentech, provided a comment stating that “currently, some of these tests are entering the market without any independent review of the evidence for claims made to support their use in patient care” and clarifying which principles it supported in this context.
- The Advanced Medical Technology Association (AdvaMed) (27 March 2009) filed a proposal for a new “Risk-Based Regulation of Diagnostics” – a risk-based tier triage model for regulating all diagnostic tests regardless of where they are produced.
- The California Healthcare Institute (15 April 2009) expressed support for the current procedures under CLIA and called on the FDA to review the current regulatory environment for diagnostics using greater consultation with all stakeholders.

7 FDA considers collaboration with Centers for Medicare and Medicaid Services on diagnostics (25 December 2008)

Representatives from the US FDA, which regulates the approval of in vitro diagnostic test kits, said the agency will "explore ways" to work with the Centers for Medicare and Medicaid Services (CMS), which regulates laboratory testing (except research) on humans in the US through the Clinical Laboratory Improvement Amendments (CLIA), to clarify their roles with respect to regulating genomics-based diagnostic products. The comment follows a September 2008 report by the President's Council of Advisors on Science and Technology (PCAST) on "Priorities for Personalised Medicine" which recommended "coordination of potentially redundant requirements between FDA and CMS". PCAST also encouraged the FDA to clarify its "regulatory approach to the co-development of diagnostics and therapeutics" and "criteria and procedures for adjusting therapeutic product labelling to incorporate use of diagnostics". Some experts point to the diversity in approval pathways as a significant obstacle to the development of new diagnostic tools. But there are several schools of thought on this subject, as suggested by the reactions to Genentech's Citizen Petition on 5 December 2008 (see the previous event), and we should expect a lively debate.

8 deCODE launches deCODE PrCa, a DNA test to assess prostate cancer risk (20 February 2008)

deCODE genetics announced the launch of deCODE PrCa, a test to identify genetic variations associated with increased risk of prostate cancer. The test, which is being marketed under the CLIA laboratory certification procedure, is designed to detect single nucleotide polymorphisms (SNPs), including six previously discovered SNPs that have been confirmed in many populations, as well as two SNPs on chromosomes X and 2 that are reported by deCODE scientists in a paper published in Nature Genetics. deCODE believes the test has significant clinical utility for improving and personalising prostate cancer screening and treatment protocols. Other tests available from deCODE target diseases including type 2 diabetes, atrial fibrillation and stroke, and heart attack.

9 Gene-guided warfarin dosing to be tested in a large scale trial (20 February 2009)

The optimal dose of warfarin, a drug which can prevent blood clots, can vary significantly from patient to patient. A clinical trial involving 2,700 patients and research teams from seven European countries will be conducted to test a method to determine the ideal dose of warfarin using patients' genetic profiles. The international research team has developed a mathematical formula based on genetic information, which appears to give a more accurate prediction of correct dosage than conventional clinical methods. The study is seen as a test case for using gene-guided dosing in medical practice.

10 **Agendia's breast cancer test MammaPrint standard of care at Netherlands Cancer Institute (4 February 2009)**

The molecular diagnostics company, Agendia, announced that its breast cancer tumour recurrence test, MammaPrint, has been included in the updated 2008 guidelines of The Dutch Institute for Healthcare Improvement (CBO). In February 2007, MammaPrint was reported to be the first in vitro diagnostic test to be cleared by the FDA under its new guidelines for in vitro diagnostic multivariate index assays (IVDMIA). The CBO now provides endorsement from the clinical community in The Netherlands for the prognostic value of MammaPrint, which aims to identify each individual patient's risk profile and guide subsequent treatment. MammaPrint is a DNA microarray-based test which measures the expression level of 70 genes in a sample of a woman's surgically-removed breast cancer tumour. A specific formula or algorithm is then applied to produce a score, which determines whether the patient is deemed at low or high risk for the cancer to spread to another site. The test's results aim to help doctors in planning treatment and appropriate follow-up for patients when used in combination with other clinical information and laboratory tests.



Case studies in personalised medicine

Case Study 1 - Translational Genomics Research Institute

The Translational Genomics Research Institute (TGen) is a non-profit organisation that works on developing predictive diagnostics and more accurate treatments. TGen was established in 2002 by Dr. Jeffrey Trent, the founding Scientific Director of the National Human Genome Research Institute, as a collaborative, public-private partnership among the State of Arizona, the City of Phoenix, the three Arizona universities, local hospitals, and other key constituents.

TGen researchers have contributed to the efficiency and effectiveness of the translational process – the process of moving research discoveries into concrete clinical development projects – by studying the genetic components of common and complex diseases, including oncology, neurology, and metabolic diseases, among others. Ultimately, TGen's goal is

an understanding of these genomic variations which can then be rapidly developed into the diagnosis and treatment of disease in a manner tailored to the individual patient – personalised medicine.

This focus has produced a number of developments since the start of 2008 related to diagnostics, genome technology, biomarker identification and commercial activity:

- In January 2008, TGen and a team of international collaborators announced the results of a study indicating that a blood test that targets five genetic variations can be used to identify men who are at greater risk of developing prostate cancer;
- In September 2008; TGen investigators announced they had developed a faster way to study the human genome that should be one-tenth the cost associated with other approaches. Using this new technique, which employs bar codes to index the genome, researchers can focus on those regions of the genome most likely

to show variation and more easily identify genes that might impact human health;

- Also in September 2008; an international, TGen-led team identified a link between a specific brain protein, known as KIBRA, and late-onset Alzheimer's disease. This finding sets the stage for the translation of this protein into a biomarker for diagnostic applications to identify patients at risk and a target for therapeutic applications to prevent and treat disease;
- In October 2008; TGen spun off its third company, MedTrust Online, which will enable cancer doctors to obtain information about the best-available treatment for their patients. Operating on an Internet-based platform, MedTrust Online provides physicians with clinically-relevant information and helps them communicate with each other about cancer treatment options to enable them to design customised treatments for individual patients.

TGen's partnership with the Grand Duchy of Luxembourg

In June 2008, TGen and the government of the Grand Duchy of Luxembourg announced a partnership between TGen and clinical and academic institutions in Luxembourg to create a biospecimen refinery and repository that will also house complete analytic capabilities.

The Integrated Biobank of Luxembourg (IBBL) – co-founded by the nation's three public research centres (CRP Santé, CRP Tudor and CRP Lippmann) and by the University of Luxembourg – plans to become the premier European hub for advanced biobanking, biotechnology and biomedical informatics. While most other European and US biobanks focus on collection and distribution of specimens, the IBBL aims to implement uniform standards for collection, storage and distribution of a full range of tissue samples, including blood, serum and tumour tissues. This next-generation biobank is expected to provide researchers with molecular-based characterisations of biospecimens linked to clinical studies. The project will leverage expertise in biology, pathology, informatics, IT infrastructure, laboratory operations, transportation, legal matters and ethics. The IBBL aims to provide a centralised resource for sharing and comparing research results through a robust, scalable and secure bioinformatics system that supports the collection, processing, storage, annotation and distribution of biospecimens and data. In this way, the biobank could play a critical role in supporting research aimed at the identification of biomarkers and their translation into diagnostic tests for personalised medicine.

Case Study 2 - Genomic Health

Genomic Health seeks to improve the specificity and efficacy of cancer treatments based on the development and commercialisation of genomic-based molecular diagnostics. The company was founded in August 2000 by current Executive Chairman Randy Scott and is based in Redwood City, California. Genomic Health aims to provide physicians with tools to offer more personalised cancer care based on the patient's genomic profile.

Genomic Health's research and development efforts focus on identifying the genes and gene expression patterns that uniquely characterise each subset of a given cancer. It is from these characterisations that Genomic Health seeks to develop diagnostic tests that help physicians understand whether a given cancer will respond to a certain course of therapy and whether the cancer will return once treated. Genomic Health has a network of clinical partners through which it validates these tests in a patient setting.

The company raised \$51 million in four rounds of funding prior to its initial public offering. Genomic Health went public in September 2005, raising more than \$60 million.

In January 2004, Genomic Health's clinical laboratory obtained

CLIA certification to perform the company's first test, Oncotype DX. The first commercial tumour sample analysis with Oncotype DX was performed in the same month. This test analyses expression levels of 21 genes in a breast tumour sample and is presented as the first diagnostic of its kind that has shown the capacity both to predict whether a patient's cancer will respond to chemotherapy and how likely the cancer is to return. Oncotype DX was approved for reimbursement in January 2006 by Medicare and in November 2006 by Aetna, one of the largest private insurers in the US. In total, Genomic Health has now secured reimbursement coverage for more than 90 percent of the US insured population through contracts, policies or agreements. Oncotype DX is recommended in the clinical guidelines and included in the standard of care for the majority of early-stage breast cancer patients of both the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN).

Since its release to the market in January 2004, numerous published studies have documented how Oncotype DX has helped physicians select the appropriate course of therapy for patients, as well as the cost-effectiveness of the care which it enables.

Genomic Health is also developing diagnostics for other cancers. In

June 2006, Genomic Health and the National Surgical Adjuvant Breast and Bowel Project (NSABP) presented results from a colon cancer study, which showed a correlation between gene expression and disease recurrence. In January 2009, Genomic Health announced that it initiated a clinical validation study for its Oncotype DX(R) colon cancer assay.

On the partnering front, in January 2008, Genomic Health announced an agreement with Pfizer to develop a diagnostic to estimate the risk of disease recurrence for non-metastatic renal cell carcinoma.

Distribution of Oncotype DX outside the US

In June 2007, Genomic Health announced that the company signed an exclusive agreement with Medical Solutions plc, a healthcare and diagnostics business specialising in diagnostic pathology and cytology services and products, to distribute the company's Oncotype DX breast cancer assay in the UK.

Oncotype DX is currently offered for sale in Israel under a testing and services agreement with Teva, and in Japan under an agreement with SRL. Patient tumour samples from these and other countries are analysed in Genomic Health's reference laboratory in Redwood City, California.

Case Study 3 - DxS

DxS is a personalised medicine company providing molecular diagnostics to aid doctors and drug companies select therapies for patients, in particular for the treatment of lung and colon cancer. The company uses its proprietary real-time polymerase chain reaction (PCR) technology, Scorpions, as the technological base for its products and services.

DxS is based in the technology quarter of Manchester in the UK and employs 60 people. It was founded in 2001 by Dr Stephen Little, CEO, and Dr David Whitcombe, CSO. The founders are former executives from AstraZeneca Diagnostics with significant experience in developing nucleic acid-based diagnostics and human genetic analysis services. The company is owned by its management and venture capital firms.

The products of DxS detect mutations in oncogenes associated with drug response and include a portfolio of CE-marked companion diagnostics as well as diagnostics for research use only:

- CE-marked diagnostics include the TheraScreen range of tumour mutation products, including kits to detect mutations in the EGFR and K-RAS genes to help doctors prescribe more effective treatments for lung and colon cancer patients. DxS plans to launch a range of diagnostic kits to help with the treatment of other cancers over the next two years;
- Research use only diagnostics include tumour mutation products for EGFR, RAS, RAF, BCR-ABL and other genes that

show a correlation between patient mutation status and drug response.

Partnerships with major industry players have helped DxS develop its commercial reach. Dr Stephen Little said: "The distribution deal signed with Roche in June 2008 means we now have a global presence with our TheraScreen: K-RAS Mutation Kit." DxS has signed numerous partnerships in addition to this distribution agreement including deals with:

- The pharmaceutical industry: in December 2008 DxS signed an agreement with Amgen to provide a K-RAS companion diagnostic for Vectibix (panitumumab); and
- The industrial diagnostics industry: in February 2009, DxS granted DuPont Qualicon a license to use its Scorpions diagnostic platform to develop tests for use by the food industry.

The company also offers genetic analysis services to support drug development through clinical genotyping, tumour mutation analysis and DNA extraction services. This business is supported by increasing demand from the pharmaceutical and contract research industries for the genetic analysis of clinical trial populations to help understand the individual variation in drug pharmacokinetics and pharmacodynamics.

DxS has chosen a business model where the diagnostics product development activities were originally supported by cash flows generated from the services business and are now starting to generate their own revenue stream. Dr Stephen Little said: "Our

business model has enabled DxS to grow its revenues faster and at a lower risk for our investors".

DxS plans to recruit a further 20 people as revenues are expected to grow from £3 million in the year ended 30 June 2008 to £10 million in the following year.

The TheraScreen: K-RAS Mutation Kit

Mutations in the K-RAS oncogene are frequently found in human cancers. They are common in colorectal cancer, pancreatic cancer, lung adenocarcinoma, gall bladder cancer, bile duct cancer and thyroid cancer. These mutations can indicate prognosis and are predictive of drug response. In particular, recent publications have shown that the successful treatment of metastatic Colorectal Cancer (mCRC), using monoclonal antibody therapies such as cetuximab (Erbix, Merck KgaA), or panitumumab (Vectibix, Amgen) is directly linked to the oncogenic activation of the K-RAS signalling pathway.

The TheraScreen: K-RAS Mutation Kit is the first molecular companion diagnostic to support targeted therapies in colorectal cancer. The kit detects seven mutations in codons 12 and 13 of the K-RAS oncogene. The TheraScreen: K-RAS Mutation Kit is not intended for use to screen for or diagnose cancer. Its use is intended as an adjunct to other prognostic factors currently used to identify colorectal cancer patients who may not benefit from anti-EGFR therapies, such as cetuximab and panitumumab, based on the patient's mutation status.

Case Study 4 - The health economics of genetic testing for warfarin dosage

The science

Warfarin, an anticoagulant commonly used to prevent and control blood clots, is complicated to use because the optimal dose varies greatly among patients. If the dose is too strong the risk of serious bleeding increases and if the dose is too weak, the risk of stroke increases.

Several studies suggest that variants in genes such as CYP2C9 and VKORC1 explain a large proportion of an individual's response to the drug. A relatively simple genetic test that currently costs less than \$500 would allow a physician to determine an accurate dose for about 30-40% of individuals. For those specific individuals the probability of an adverse bleeding or clotting event in the first 30-60 days would be greatly reduced.

The Critical Path Institute organised a consortium of major pharmaceutical companies and acted as trusted neutral third party to handle their proprietary data. The results were presented to the US Food and Drug Administration who changed warfarin's labelling in September 2007 to reflect such findings. Now, physicians in the United States are asked to consider genetic testing prior to treating an individual with warfarin. From a scientific standpoint this was a step forward in realising the clinical potential of personalised medicine.

The economics

In November 2006 the influential Brookings Institute in Washington published its estimates of the health benefits and savings in health care costs from using personalised warfarin dosing decisions based on appropriate genetic testing. Their conclusion was:

"We estimate that formally integrating genetic testing into routine warfarin therapy could allow American warfarin users to avoid 85,000 serious bleeding events and 17,000 strokes annually. We estimate the reduced health care spending from integrating genetic testing into warfarin therapy to be \$1.1 billion annually, with a range of about \$100 million to \$2 billion".

However, in April 2008 BlueCross-BlueShield, one of America's largest health insurers announced its conclusions that the genetic testing that "allegedly benefits patients" is to be considered investigational rather than standard of care.

Further studies have been published that confirm that the genetic tests for warfarin dosing will improve patient clinical outcomes, but that the cost of the improvement is too high. A study published in January 2009 in the *Annals of Internal Medicine* had calculations, based on the researchers' statistical models, showing that each quality-adjusted life year (QALY) gained by using the tests costs more than \$170,000. They further calculated that the tests would only be cost effective if selectively applied to those at high risk of haemorrhage thus preventing at least a third of all major bleeding

events and were available within 24 hours at a cost of less than \$200.

In May 2009, the US federal government health insurer for those over 65, Medicare, issued a proposed decision not to pay for the warfarin dosing genetic tests for the million patients a year that start warfarin therapy under Medicare insurance.

However, Medicare is proposing to pay for the genetic tests for patients who enrol in clinical trials that measure the clinical effectiveness and utility of the tests, thus keeping the door open for research to continue. The NIH's COAG large scale study running from April 2009 for 3 years will collect further evidence of the clinical and economic utility of genetic testing for warfarin dosing.

The bottom line

The adoption of new diagnostics into routine standards of clinical care will be determined by economic factors as well as by scientific discovery. Companies who have diagnostic tests as companions to targeted therapeutic treatments are likely to find the combination will meet health economics targets more easily than stand-alone diagnostic tests.

Case Study 5 - Current developments in biobanking

This case study was based on input from Dr. Robert Hewitt, designated executive director of the Integrated Biobank of Luxembourg and outgoing chairman of the International Society for Biological and Environmental Repositories (ISBER).

First some history

Since the beginning of medical research there has been the need to collect and analyse biospecimens such as blood, urine, saliva, healthy tissue samples and diseased tissue samples such as cancer tumours. Ideally, these biospecimens should have been treated and stored for future reference along with accurate data on the medical history of the donors in an ethically appropriate manner that preserves donor privacy.

Advances in medical science, particularly in our ability to conduct genomic and proteomic analyses and to create vast amounts of data on each sample, have elevated the importance of biobanking in the research process. There is a critical need, particularly in developing new diagnostic tests, to ensure the availability of high-quality, standardised biospecimens for research.

The field of biobanking is becoming progressively more organised in response to the growing need for research collaboration, sharing of samples and the adoption of common standards. Formation of the US Cooperative Human Tissue Network (CHTN) in 1987 was an important milestone in biobank

networking as was the formation of the International Society for Biological and Environmental Repositories (ISBER) in 1999. ISBER caters to the full spectrum of biobanks from clinical and population biobanks through to environmental and biodiversity collections. It has a strong presence in North America where it was formed by members of the US National Cancer Institute (NCI), Centers for Disease Control (CDC) and CHTN and it has held annual meetings in Europe (Perugia, 2004) and Asia (Singapore, 2007), and has recently established an Asian chapter.

The NCI Office of Biorepositories and Biospecimen Research (OBBR) was established in 2005 and is playing a key role in promoting the science of biospecimen research which underlies the development of evidence-based standards which are vital for biobank operations. Another key NCI initiative relevant here was the Cancer Bioinformatics Grid (CaBIG) launched in 2004 which aims to share data and knowledge in the cancer community.

Another organisation playing a leading role in biobank harmonisation is the Public Population Project in Genomics (P3G) formed in 2003, which focuses primarily on human population biobanks and genetic epidemiology. P3G is based in Canada, but is active internationally, especially in Europe where it is working closely with PHOEBE, an EU-funded initiative to encourage collaboration between population biobanks and longitudinal cohort

studies, and the pan-European biobanking initiative, BBMRI. This is supported by the parallel European bioinformatics infrastructure initiative, ELIXIR. BBMRI in turn is working closely with the International Agency for Research on Cancer (IARC).

To offer guidance to help coordinate these internationally active human biobanking organisations a small working group called the Forum for International Biobanking Organisations (FIBO) was formed in 2007. This includes representatives of each of the biobanking organisations mentioned above.

Let us also remember that there are a number of non human biobanks that also face the same biorepository and biorefinery issues:

- Frozen Ark has a mission to collect preserve and store DNA and viable cells from animals in danger of extinction;
- Svalbard Global Seed Vault, nicknamed the Doomsday Vault, aims to provide a safeguard for the world's crop diversity. The vault is in the permafrost 1000 km north of mainland Norway. The facility is owned and operated by the Norwegian government but the seeds themselves remain the property of the donating genebanks;
- GBIF is a global network of data providers that builds biodiversity information infrastructure and promotes the growth of biodiversity information content on the Internet by working with partner initiatives and coordinating activities worldwide.

Three new trends in biobanking

Three important trends in bio-banking include the need for organisation and collaboration, the need for harmonisation and the increased emphasis on quality. A number of drivers and roadblocks should be considered:

Trend	Organisation and collaboration	Harmonisation	Increased emphasis on quality
Drivers	<ul style="list-style-type: none"> • Need for large sample size for Genome Wide Association Studies; • Need to exchange samples for international collaboration. 	<ul style="list-style-type: none"> • Need for compatible standards to allow collaboration; • Need for international harmonisation to allow sharing of samples between countries; • Need for harmonisation between biobanks of human and non-human materials (Human and non-human diseases are not independent as recently demonstrated by Swine Flu, SARS and HIV). 	<ul style="list-style-type: none"> • Need to provide high quality samples for gene expression analysis; • Lack of high quality samples and clinical data (demonstrated by TCGA pilot studies); • Lack of development of collection databases (demonstrated by IWGSC survey).
Roadblocks		<ul style="list-style-type: none"> • Separation of US and European biobanking communities: <ul style="list-style-type: none"> - US emphasis on tumour based versus European emphasis on population based; - lack of information exchange. 	<ul style="list-style-type: none"> • Need for quality standards, which depend on biospecimen research; • Roadblocks for biospecimen research include funding, journals, status; • Need for good repository staff. The availability of enablers, including training courses and long-term job security will depend on long-term funding.

IBBL - The Integrated Biobank of Luxembourg

The distinguishing feature of the IBBL is that it integrates an in-house genomics facility for refining biospecimens with its biorepository and is underpinned by informatics. It will be able to provide molecular profiling information to researchers in addition to the samples themselves.

It will have state-of-the-art equipment and be well staffed and well funded to ensure the transfer of knowledge from its US partner, TGen. The integrated nature of the IBBL will allow it to be an active participant in research in biospecimen science.

The IBBL already has links with state-of-the-art facilities in Europe such as the Fraunhofer-Institut für Biomedizinische Technik (IBMT) in Germany and the new Centre for System Biology Luxembourg (CSBL) at Luxembourg University. Its network of collaborations and partnerships is planned to extend beyond Europe and the IBBL is already active in the major associations ISBER and BBMRI.

The value of biobanks is well recognised by pharmaceutical and diagnostic companies, many of whom have their own banks of samples collected during their clinical trials. Many have contracts with public sector banks as well as sourcing samples from commercial suppliers.

The IBBL aims to be a key enabler for the research and development of novel diagnostic biomarkers and thus help accelerate the development of personalised medicine.

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 even if past investments have not yet translated into significant revenues.

The future revenue growth prospects will be fuelled by seven drivers:

1 The growing Dx-Rx companionship

One driver will be the growing companionship between diagnostics and pharmaceuticals in guiding drug use. The foundation is already there with the FDA reporting 28 genomic biomarkers considered as valid to provide guidance on the prescription of FDA approved drugs. Only four of these biomarkers were actually “required” to be tested for by the FDA at the moment of writing this report. However, a dynamic has started which, together with efforts at other agencies – for example at the EMEA, which already requires biomarker testing for at least eleven drugs – should promote a growing use of biomarker testing as part of drug development and prescribing.

2 The rising hurdles in drug development

The current *entente cordiale* between the pharma and diagnostics industries could become an *entente nécessaire* should the FDA “insist on” rather than just “encourage” the use of a biomarkers and diagnostics to guide drug development. Some would argue that such necessity is de facto already in place as it is becoming always more challenging to promote the value of an expensive drug without having a companion diagnostic to ration or justify its use on a patient by patient basis.

3 The regulatory pathways debate

Another driver will be the outcome of the on-going discussions about the current diversity in regulatory pathways for the commercialisation of diagnostics, including the CLIA regime for laboratory developed tests and the FDA requirements for in vitro diagnostics sold as kits.

4 The access to high quality patient data

Access to patient samples will be a key ingredient for successful research. This is motivating some emerging diagnostics companies to keep commercialisation rights for selected territories when negotiating licensing deals with larger partners. An alternative approach is to access patient data through tissue banks like the one being developed in Luxembourg. In this context, a further driver of sustainable, long-term future growth is the quality and standards of sampling and storage of relevant specimens. Good science will not be sufficient to develop good assays without good materials. In this context, non discrimination legislation such as GINA will also help by encouraging people to donate specimens.

5 The clinical laboratory diversification

Developing a clinical laboratory activity alongside the product development business is an obvious diversification opportunity for IVD players as well as another avenue to access patient data.

6 The reallocation of venture funding

The current funding squeeze may benefit diagnostics companies as some funds will see the attraction of IVD businesses over the riskier ventures in therapeutics. Those businesses incorporating a service based revenue stream may even convince the more risk-averse principals to invest.

7 The reimbursement maze

The current procedures to obtain reimbursement status for an IVD product tend to be complex and vary significantly from one country to another. Greater harmonisation across countries would be a breath of fresh air. Products to enable more personalised medicine should be seen more favourably under current budgetary constraints. They can help avoid the use of expensive drugs for certain patient subpopulations where a diagnostic predicts they would cause significant side effects without any efficacy benefits.

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Research rewired

In the report *Research rewired*: Merging care and research information to improve knowledge discovery, we explore the challenges of being able to share electronic information across the entire continuum of medical research, from academic medical centers, through to the research labs of pharmaceutical and life-sciences companies and ultimately with regulatory agencies. The report investigates the benefits, barriers, and emerging approaches to creating an integrated information environment that will help to shape scientific diagnostic, drug, and device discovery in the future.



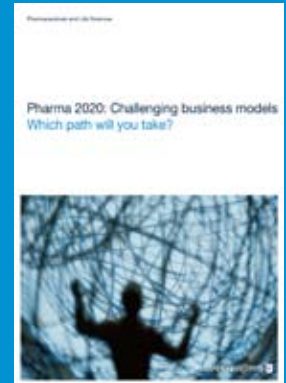
Pharma 2020: Marketing the future

Published in February 2009, this paper discusses the key forces reshaping the pharmaceutical marketplace, including the growing power of healthcare payers, providers and patients, and the changes required to create a marketing and sales model that is fit for the 21st century. These changes will enable the industry to market and sell its products more cost-effectively, to create new opportunities and to generate greater customer loyalty across the healthcare spectrum.



Behind the numbers

This report indicates that despite a slowdown in the economy, medical costs are expected to be tempered slightly, growing at 9% in 2010. However, these rates still significantly outpace real incomes and the rate of inflation. Reacting to higher medical costs as the economy recovers will require innovative approaches to deal with workers and healthcare stakeholders. This year's report addresses cost trends for the coming year, the impact the recession and promise for reform has had on the healthcare industry, and how businesses are reacting to higher medical costs.



Pharma 2020: Challenging business models

Fourth in the *Pharma 2020* series and published in April 2009, this report highlights how Pharma's fully integrated business models may not be the best option for the pharma industry in 2020; more creative collaboration models may be more attractive. This paper also evaluates the advantages and disadvantages of the alternative business models and how each stands up against the challenges facing the industry.

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