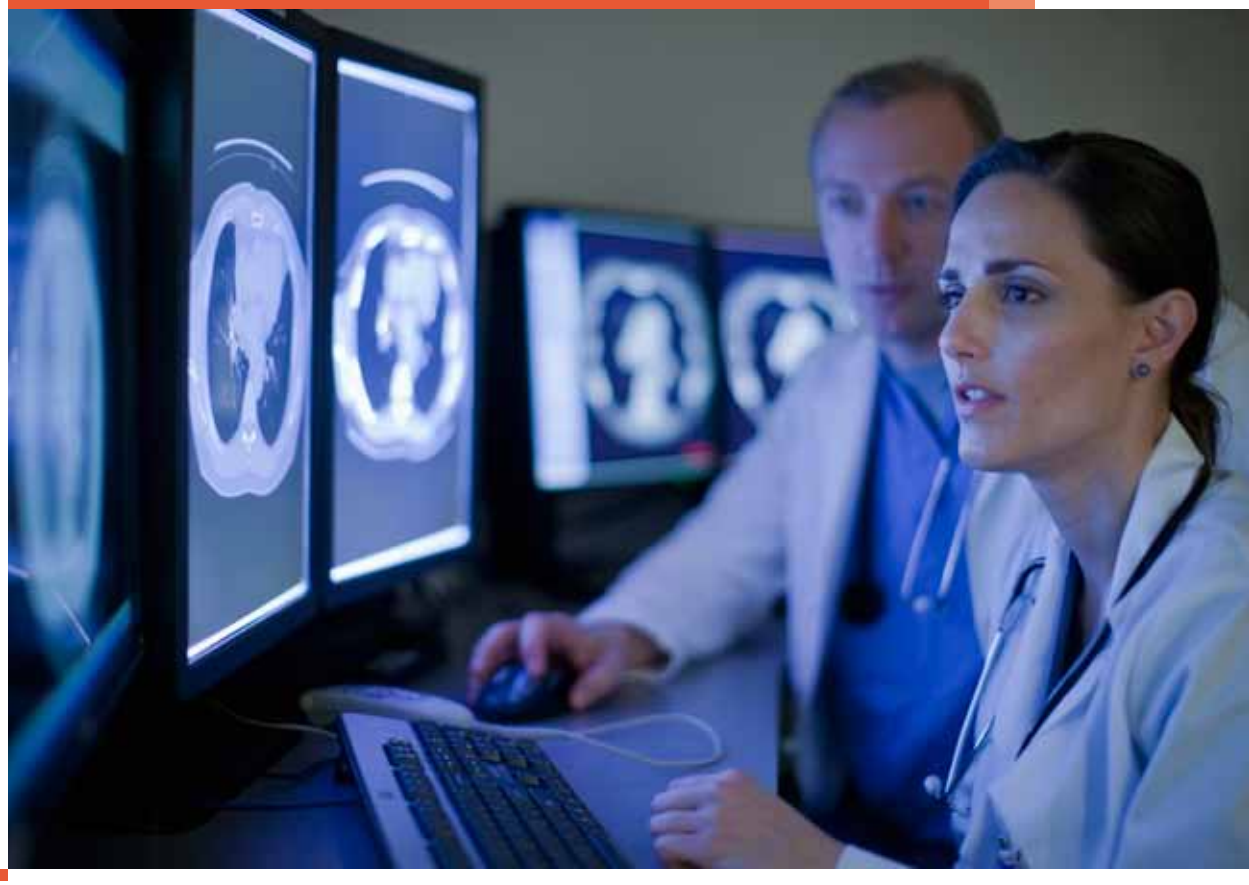
www.pwc.com/diagnostics2011

# *Diagnostics 2011:* M&A surges, companion diagnostics accelerate, and early detection offers new prospects



*Diagnostics 2011*
*Second edition*

*December 2011*

pwc

# Foreword

*"It is more important to know what sort of person has a disease than to know what sort of disease a person has."*

—Hippocrates, 460-370 B.C.
Quoted at a recent industry event by Iain Miller, Executive Director, Theranostics, bioMérieux

*Diagnostics 2011,* the second edition of our review of deal activity in the *in vitro* diagnostics[1] (IVD) sector, analyses M&A deal trends, diagnostics partnerships with the pharmaceuticals industry, and significant events for the development of personalised medicine since publication of our last report, *Diagnostics 2009.*

Personalised medicine, which is commonly defined as providing "the right treatment for the right person at the right time in the right dose," is central to the growing interest in the diagnostics sector.

This edition also explores important developments in the field of early-detection testing, which could play a significant role in improving prognosis.

*Diagnostics 2011* reveals a renewed momentum in deal making in the IVD sector, which marks significant interest in the growth prospects of certain market segments, including molecular and tissue diagnostics, as shown in Figure 1:

**Figure 1: IVD market sales by segment**

| Market Segments | 2009 ($bn) | 2014E ($bn) | CAGR 2009–2014E | Market Dynamics |
|---|---|---|---|---|
| Professional Diagnostics | 29 | 36 | 5% | Driven by testing efficiency and unmet medical needs. Serum work area is largest segment. |
| Diabetes Monitoring | 8 | 9.5 | 3% | Market growth declining due to pricing pressure. |
| Molecular Diagnostics | 3 | 6 | 11% | Fastest-growing market segment. HPV and other cancer and genetic testing are key growth drivers. |
| Tissue Diagnostics | 2 | 3 | 9% | Driven by continued lab automation and new cancer tests |
| **Total** | **42** | **53** | **5%** | |

Source: Presentation by Roche at the American Association for Clinical Chemistry meeting of July 2010

1 *In vitro* diagnostic (IVD) tests are medical devices to be used *in vitro* for the examination of specimens, including blood, urine, and tissue donations, derived from the human body to detect diseases, conditions, or infections. Some tests are used in laboratory or other health professional settings, and other tests are for consumers to use at home.

## M&A surges to exceptional values

M&A deal values increased strongly during 2010 and jumped to exceptional levels during 2011. The buyers were not only existing players in the IVD sector, but also financial investors, life sciences research groups, clinical laboratories, and medical technology players. New entrants also included a food company and a pharmaceutical company. The surge and diversity of bidders reflected a widespread belief in the growth prospects of selected IVD market segments as well as the potential for cross-industry synergies.

## Companion diagnostics partnerships gear up

The pharmaceuticals industry (pharma) would have little choice but to invest in companion diagnostics if regulators, payers, and markets were to signal the importance of doing so. Companion diagnostics complement targeted therapeutics to reduce side effects, improve efficacy, and help control healthcare costs.

The number of companion diagnostics partnerships with pharma more than tripled during 2010 compared with a trough in 2008. Strong deal activity continued during the first half of 2011.

Analysts are projecting billion-dollar revenues for some of the new drugs linked to a companion diagnostic. The mass-market blockbuster model may be disappearing, but the niche-buster model may still offer the prospect of creating significant shareholder value for pharma. One challenge to maintain a sustainable high level of innovation in the diagnostics industry is for partners to improve the industry's share of the drug-diagnostic combination value.

In this report, we look at the pharma (e.g., GlaxoSmithKline [GSK]) and diagnostics (e.g., Qiagen) players that have been most active at collaborating on companion diagnostics, thus showing their commitment to the on-going shift towards personalised healthcare.

## Early detection emerging as a new opportunity

Screening technology for early detection of major cancers has not been within reach of the IVD sector until now—with the exception of the prostate specific antigen (PSA) test for prostate cancer. However, for most cancers, early detection and treatment can provide significant improvement in survival prospects when compared with late detection and treatment. A noninvasive IVD-based test that would allow detection of a major cancer, with high accuracy and at an early stage, would be attractive, considering the many issues with current, mainly *in vivo*-based procedures.

A wave of new IVD-based tests has started to reach the market and could offer new hope for early detection of major cancers. In this report, we review a selection of 23 such tests and discuss the challenge of validating the IVD-based model within the next few years.

If this model were validated, drug-like blockbuster revenues could follow for some tests. The commercial payback for one such test could surpass the revenues of a companion diagnostic by a multiple of 10.

The IVD originators in this market segment will need large commercial partners to help them exploit the opportunity. Major IVD players or clinical laboratories would be the obvious candidates. By 2020, we expect several pharma players to have become involved as well, provided clinicians and payers have validated the most promising tests within the next few years.

## New FDA guidance contributes to development of personalised medicine

In this report, we review 10 events that are expected to influence significantly the continuing development of personalised healthcare, selecting from four categories:

- Government and legal (e.g., US government plans to develop a genetic testing registry)
- Regulatory (e.g., FDA's issuance of a black-box warning for a blockbuster drug, which could drive the development of companion diagnostics to guide the use of the drug)
- Science and technology (e.g., advances in genetic research related to obesity, which illustrate the emerging convergence between wellness and personalised medicine)
- Industry and society (e.g., the establishment of an association to promote the development of personalised medicine in Europe)

One long-awaited event that we include is the FDA's publication in July 2011 of draft guidance on companion diagnostics. The agency's document may be too concise for some but does provide a clear signal that pharma should continue its transition towards systematic integration of diagnostics into its development programs for targeted therapeutics.

The least-anticipated event may be Nestlé's acquisition of a gastrointestinal diagnostics company for an estimated $1.1 billion. The company wants to integrate science-based nutrition into the emerging therapeutic-diagnostic business model and promote the importance of nutrition as an obvious first step in any prevention and wellness policy.

## Two profiles show diversity of emerging IVD players

We profile MDxHealth and Genclis to illustrate the diversity of product types within the IVD sector. One company is developing companion diagnostics and prognostics to predict disease progression. The other is championing early detection of peanut allergy and breast cancer.

## Sustaining innovation will require strong action from stakeholders

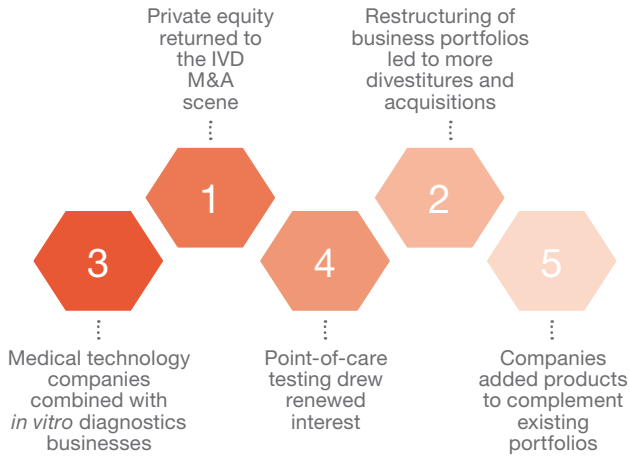
The momentum of strong deal activity and investment will continue as long as innovation and growth prospects remain strong. But rapid action will be needed from governments, regulators, payers, and industry to create a favourable environment for sustaining such innovation. Key areas to address include pricing, regulatory pathways, clinical trial design, reimbursement, and drug-diagnostic value sharing.

# Table of contents

Key findings

# I. M&A deal values rise sharply as IVD market leaders reshuffle

- Although the number of M&A deals in the IVD sector remained flat during 2009 and 2010, total deal value rose 57% to $4.7 billion during 2010.
- Five factors drove the top-10 deals for 2010:



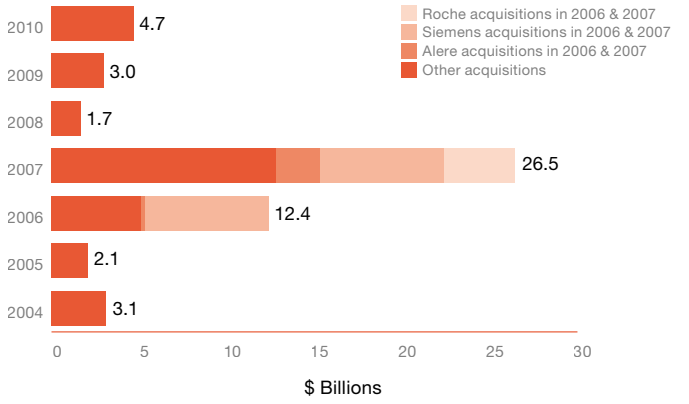

- The market shares of the top IVD players will reshuffle following two mega-deals announced in 2011 by Danaher and Thermo Fisher.
- In 2011, total M&A deal value is expected to more than triple following a number of multi-billion-dollar deals announced by July. This will make 2011 one of the strongest years in terms of the value of M&A since 2004.
- Within the next few years to 2015, we expect the following themes to shape some of the M&A activity in the IVD sector:

| | |
|---|---|
| 1 | New market entrants will continue to add IVD businesses to achieve critical mass. |
| 2 | The historical IVD majors will respond in kind or risk slipping down industry ranks. |
| 3 | Private equity will continue to look for strong players in niche market segments. |
| 4 | Major pharma players will be keen to acquire molecular or tissue diagnostics technology. IVD businesses have not been common M&A targets for pharma in recent years. But this is expected to change as drug-diagnostic co-development programs become more established and more pharma companies decide to change their business model to bring some companion diagnostics capability in house. |
| 5 | Early-detection businesses will attract interest from large diagnostics or pharma companies if the model of IVD-based early detection is validated within the next few years. |

## Deal value rises

Total M&A deal value in the IVD sector increased sharply to almost $5 billion during 2010, but the number of deals stayed almost flat at 45. The $4.7 billion 2010 deal value represented an increase of 57% over the $3 billion posted in 2009, based on the value of disclosed deals announced in each year. Figure 2

Figure 2: Value of disclosed M&A deals in the IVD sector 2004–2010




Source: PwC analysis using data from Thomson Financial, Windhover, Mergermarket, Zephyr and other publicly available sources

The rise in deal values during 2010 reflected the impact of a small number of higher-value deals and corresponded to an increase in industry-shaping events during the year, including:

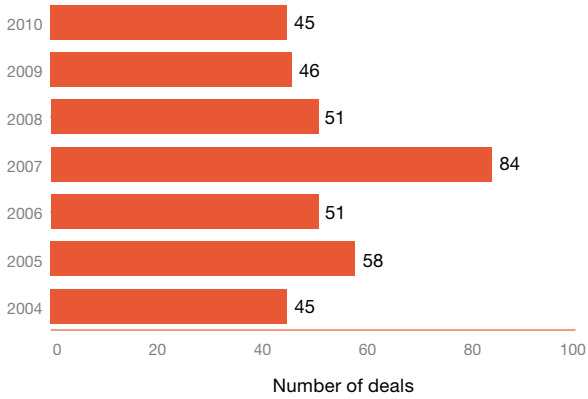
- Return of leveraged capital providers willing to fund larger transactions in the IVD sector. The $1.1 billion buyout of Sebia by Cinven, the largest deal of 2010, demonstrated this return, which was confirmed by the $2 billion offer for Immucor by Texas Pacific Group in July 2011.
- Decision by Genzyme Corporation to exit the IVD sector to refocus on therapeutics, following a takeover approach by sanofi-aventis. This led to the $925 million acquisition of Genzyme Genetics by LabCorp and the $265 million purchase of Genzyme Diagnostics by Sekisui Chemical.
- Strategic decision by GE Healthcare to develop its presence in the IVD space to complement its *in vivo*-focused diagnostics franchise. This drove GE Healthcare's $587 million acquisition of cancer diagnostics company Clarient.

In contrast to these high-value deals, the only transaction in 2009 worth more than $500 million was the $780 million acquisition of Olympus' diagnostics business by Beckman Coulter, which aimed to grow market share in existing business segments.

## Deal volume remains flat

During 2010, the number of M&A deals in the IVD sector showed virtually no change from the previous year, with 45 announced deals, compared with 46 in 2009. The number of deals by companies engaged in serial transactions also remained level with 2009 totals. Figure 3

Figure 3: Number of M&A deals announced in the IVD sector 2004–2010




Source: PwC analysis using data from Thomson Financial, Windhover, Mergermarket, Zephyr, and other publicly available sources

During 2010, seven deals were announced by companies making multiple M&A bids:

- Alere announced five bids totalling $665 million as the company continued to grow through acquisitions.
- EKF Diagnostics Holdings plc announced two deals amounting to $13 million. The company, chaired by former Axis-Shield executive David Evans, recently changed its name from International Brand Licensing plc following a reverse takeover by the German IVD company EKF-diagnostics GmbH. The renamed company, which is listed on the alternative investment market of the London Stock Exchange, is pursuing a strategy of seeking acquisition opportunities in the IVD sector, beginning with the announcement of two acquisitions in 2010:
  - The $9 million acquisition of Quotient Diagnostics, based in the United Kingdom.
  - The $4 million purchase of Argutus Medica, headquartered in the Republic of Ireland. The assets of Argutus Medica were formerly part of Biotrin, which was acquired by DiaSorin of Italy in 2008.

In comparison, during 2009, eight deals were announced by the four companies making multiple bids during the year. Each of the companies was involved in two deals:

- Alere announced two deals totalling $403 million: the $203 million offer for the UK drug- and alcohol-testing firm Concateno and the $200 million purchase of the "second-territory" rapid-diagnostics business of ACON Laboratories. ACON sold its assets related to its rapid-diagnostics business in another territory, known as the "first territory," in a previous transaction.
- Qiagen acquired DxS, based in the United Kingdom, for $130 million and SABiosciences, headquartered in the United States, for $90 million, continuing its push into the IVD space following its $1.6 billion acquisition of Digene, announced in 2007.
- Gen-Probe offered $130 million for Tepnel Life Sciences of the United Kingdom and $85 million for Prodesse in the United States.
- Lab21 acquired two other UK-based companies, Biotec Laboratories and Plasmatec Laboratory Products, for undisclosed amounts.

Looking back at the number of deals announced each year during 2004–2010, the year 2007 stood out as exceptional, with 84 announced deals, as discussed in the PwC report *Diagnostics 2009*. In all other years, deal count fluctuated between 45 and 58. The 45 deals announced in 2010 put the year at the bottom of the range, but deal values were higher in 2010 than in all other years except 2006 and 2007. During those two industry-changing years, nine deals exceeded $1 billion, including the three mega-acquisitions that catapulted Siemens to the top ranks of the industry: Bayer Diagnostics, Dade Behring, and Diagnostic Products Corporation.

# Five factors drive top-10 deals

The top-10 deals announced during 2010 ranged from $105 million to $1 billion, as shown in Figure 4.

### Five factors drove the top-10 deals of 2010:

#### 1. Return of the leveraged buyout

The largest deal of 2010 was a leveraged buyout (LBO). With the acquisition of Sebia at $1.1 billion, the London-based buyout firm Cinven added a second IVD business to its investment portfolio, which already contained the allergy diagnostics leader Phadia. Cinven said it would keep its two IVD investments as stand-alone businesses.

Sebia, based near Paris, France, occupies a strong position in the clinical electrophoresis field for the analysis of disease-associated proteins. Myeloma is an existing area of strength for Sebia, which hopes to extend its business to address diabetes and to expand geographically into Asia.

This deal provided an exit for another London-based private equity house, Montagu, which was the lead investor in Sebia following a 2006 buyout. Two minority investors that had stakes in Sebia following the 2006 transaction, Intermediate Capital and Astorg Partners, also will be bought out by Cinven.

#### 2. Domino effect of business portfolio restructuring

Genzyme Corporation decided to refocus its portfolio and divest noncore businesses. This decision triggered two of the top-10 deals of 2010. Also during 2010, Abbott had to divest a business it acquired earlier because of anti-trust issues. This led to an additional top-10 deal.

In May 2010, Genzyme Corporation, which had revenues of $4.5 billion in 2009, announced the potential sale of

**Figure 4: Top-10 M&A deals in the IVD sector during 2010**

| Rank | Value ($m) | Target | Country | Bidder | Country |
|---|---|---|---|---|---|
| 1 | 1,094 | Sebia | France | Cinven | UK |
| 2 | 925 | Genzyme Genetics | US | Labcorp | US |
| 3 | 587 | Clarient | US | GE Healthcare | UK |
| 4 | 265 | Genzyme Diagnostics | US | Sekisui Chemical | Japan |
| 5 | 255 | Epocal | Canada | Alere (Inverness) | US |
| 6 | 217 | Standard Diagnostics | S. Korea | Alere (Inverness) | US |
| 7 | 215 | Home Diagnostics | US | Nipro | Japan |
| 8 | 130 | Diagnostic Hybrids | US | Quidel | US |
| 9 | 112 | Innogenetics | Belgium | Fujirebio | Japan |
| 10 | 105 | Helixis | US | Illumina | US |

Source: PwC analysis using data from Thomson Financial, Windhover, Mergermarket, Zephyr and other publicly available sources

three noncore businesses—genetic testing, diagnostics, and pharmaceutical materials—as part of a wider plan to refocus and increase shareholder value following takeover interest by Big Pharma company sanofi-aventis.

**The two diagnostics-related deals were completed as follows:**

1. Genzyme Genetics: The $925 million sale of this division of Genzyme Corporation to LabCorp was announced in September 2010 and completed in December. With this acquisition, LabCorp will gain access to esoteric testing services, technology, intellectual property, and testing laboratories. The three business areas of Genzyme Genetics—oncology testing, reproductive testing and clinical trials, and test development—will either complement or strengthen LabCorp's existing testing business, which focuses on maternal serum screening, prenatal and postnatal diagnostics, carrier screening, hematopathology, and solid tumours.

2. Genzyme Diagnostics: The $265 million purchase of this division by Sekisui Chemical was announced in November 2010 and completed at the start of February 2011. The commercial infrastructure of Genzyme Diagnostics, which posted revenues of $167 million in 2009, should help Sekisui expand its business in the United States and Europe. The deal also should give the company access to rapid tests, infectious disease products, and HDL and LDL cholesterol tests.

   Genzyme retained its core business, the development of biological drugs for the treatment of rare inherited disorders (e.g., Gaucher's and Fabry's disease), kidney disease, cancer, and immune disease.

   On 16 February 2011, soon after completing the sale of the diagnostics business, Genzyme entered into a definitive agreement to be acquired by sanofi-aventis for an improved consideration of $20.1 billion, up from $18.5 billion, plus additional amounts contingent on achieving future milestones.

Portfolio restructuring led to another top-10 deal during 2010. Innogenetics, a Belgian business based near Ghent, was sold by Abbott Laboratories to Fujirebio for $112 million. Fujirebio, a Japanese diagnostics company, is part of the Miraca Holdings group, which also includes SRL, a leading clinical laboratory business in Japan.

Innogenetics had become a subsidiary of Solvay following a $256 million acquisition in 2008. But when Abbott completed its $6.2 billion acquisition of Solvay Pharmaceuticals in February 2010, approval by the EU Commission was subject to divesting at least part of Innogenetics. This condition was imposed to prevent a dominant position in certain diagnostics markets in Europe.

Innogenetics specialises in diagnostics in the fields of infectious diseases, genetic testing, transplantation, cancer, and degeneration of the nervous system. Fujirebio expects the addition of Innogenetics to boost sales and strengthen its marketing infrastructure in Europe, the United States, Brazil, Southeast Asia, and China.

### 3. Industry convergence

**Two of the top-10 deals of 2010 reflected the convergence of medical technology and IVD:**

1. In the third-largest deal, GE Healthcare announced the $587 million acquisition of Clarient in October 2010. The acquisition complemented GE's diagnostics business, which is mainly imaging-based. The deal highlighted the medical technology giant's continued strategic interest in entering the IVD sector. It followed GE's $8.1 billion bid for Abbott's IVD business, which was announced in January 2007 and subsequently aborted after the two companies were unable to reach an agreement. More recently, in May 2010, GE announced a $5 million investment in molecular diagnostics company CardioDx through its GE Healthymagination fund.

   Although Clarient started as a digital microscope and cellular imaging company, it has built a cancer-focused molecular diagnostics business, which had revenues of $92 million in 2009. This business transformation involved significant licensing and corporate activity, including the sale of imaging assets to Carl Zeiss in 2007 and the acquisition of Applied Genomics in 2009, which added the lung cancer immunohistochemistry panel Pulmotype. Clarient's portfolio also includes flow cytometry systems, polymerase chain reaction (PCR) and fluorescent *in situ* hybridization (FISH) tests, as well as companion diagnostics for oncology therapeutics.

2. A second medical technology-IVD deal, the $215 million acquisition by Nipro Corporation of Home Diagnostics, was announced in February 2010 and completed the following month. It represented another example of convergence between medical technology and IVD in specific disease areas—in this case, diabetes. US-based Home Diagnostics, which manufactures the TRUE brand of blood-glucose monitors, generated revenues of $124 million in 2008.

Following its acquisition by Nipro, Home Diagnostics merged with Nipro Diabetes Systems, which provides the Amigo brand

of insulin pumps, to form a diabetes business combination called Nipro Diagnostics. Nipro's other product areas include devices for dialysis, infusion, anaesthesia, and cardiopulmonary applications. By combining the commercial infrastructures of the two companies, Nipro expects to achieve synergies beyond the diabetes franchise.

### 4. Consolidation of point-of-care testing

A large number of deals during 2010 involved point-of-care (POC) testing. Two of the top-10 deals for POC businesses were completed by Alere, which already has a strong leadership position in POC. Alere develops near-patient diagnostics for infectious diseases, cardiology, oncology, drugs of abuse, and women's health.

**The two top-10 acquisitions announced by Alere in 2010 were:**

1. Epocal: This $255 million acquisition was announced in January 2010. This reported purchase price includes future milestone-related payments. Epocal's main product, the epoc (enterprise point of care) platform, is a POC analysis system that provides wireless bedside blood-gas and electrolyte-measurement testing for cardiology and emergency rooms. Alere sees the potential for epoc as an expandable platform that can incorporate additional testing parameters over time.

2. Standard Diagnostics: In January 2010, Alere (then Inverness) offered $217 million to acquire up to 75.79% of Standard Diagnostics, a company listed on KOSDAQ, the South Korean stock exchange. Standard Diagnostics specialises in rapid home healthcare tests for HIV, malaria, dengue, syphilis, and influenza. Its portfolio of products also includes tests for hepatitis, cancer, fertility, and drugs of abuse.

### 5. Addition of complementary products

**Two top-10 deals were completed by companies searching for products to complement existing portfolios:**

1. Diagnostic Hybrids: This $130 million acquisition by Quidel was announced in January 2010 and completed the following month. Diagnostics Hybrids develops cellular and molecular diagnostic kits for viral respiratory infections, herpes, chlamydia, and thyroid diseases. Quidel develops and manufactures rapid diagnostics for POC testing for pregnancy, infectious diseases, oncology, bone health, and autoimmune disorders. The acquisition will give Quidel a complementary portfolio of products for nonseasonal infectious and autoimmune diseases.

   Quidel views the IVD industry as consisting of three segments and focuses mainly on the first, assays for POC testing. Diagnostic Hybrids focuses primarily on the second segment, direct fluorescent antibody assays. Both companies have moved into the third segment, molecular diagnostic tests.

2. Helixis: This acquisition, announced in July 2010 and worth up to $105 million, will help Illumina fill a gap in its range of genetic analysis products. Helixis' PCR system, the Eco Real-Time PCR System, small enough to sit on a desktop, sells for about $13,000 in the United States. The system complements the larger DNA analysis machines offered by Illumina. The Eco Real-Time PCR should help physicians monitor disease progression—for example, by analysing the quantity of cancer-related genes before and after treatment.

As regards 2009, the top-10 deals announced during the year ranged from $107 million to $780 million. Figure 5

**Figure 5: Top-10 M&A deals in the IVD sector during 2009**

| Rank | Value ($m) | Target | Country | Bidder | Country |
|---|---|---|---|---|---|
| 1 | 780 | Olympus—Diagnostics | Japan | Beckman Coulter | US |
| 2 | 471 | Brahms | Germany | Thermo Fisher Scientific | US |
| 3 | 275 | HandyLab | US | Becton Dickinson | US |
| 4 | 203 | Concateno | UK | Alere (Inverness) | US |
| 5 | 200 | ACON-2nd Territory Rapid Dx | China | Alere (Inverness) | US |
| 6 | 130 | DxS | UK | Qiagen | NL |
| 7 | 130 | Tepnel Life Sciences | UK | Gen-Probe | US |
| 8 | 126 | Binding Site-Autoimmune Dx | UK | Werfen Life Group | Spain |
| 9 | 120 | Biotrove | US | Life Technologies | US |
| 10 | 107 | Monogram Biosciences | US | LabCorp | US |

Source: PwC analysis using data from Thomson Financial, Windhover, Mergermarket, Zephyr and other publicly available sources

**Five main factors drove the top-10 deals of 2009:**

1. Consolidation in existing market segments through geographical expansion and/or addition of new technology

- **Olympus:** Beckman Coulter gained a business expected to contribute $500 million of revenues during 2010 from products including automated chemistry analysers, blood transfusion tests, reagents, and lab automation systems. The deal was expected to strengthen Beckman's position in the clinical chemistry market.
- **Concateno:** The deal may help strengthen the position of Inverness Medical Innovation (renamed Alere during 2010) as a leading player in the European drugs-of-abuse testing sector, following the 2007 acquisitions of Cozart and Biosite, which were also active in this sector. In addition, Concateno provides point-of-care tests, which are another priority area for Inverness.
- **ACON Laboratories' second territory rapid diagnostics business:** This acquisition by Inverness is the sequel to a first deal announced three years earlier. In March 2006, Inverness announced the acquisition of ACON's lateral flow immunoassay business for a first territory and agreed to acquire the remaining part of this business provided certain financial and operating conditions were satisfied. The second territory, acquired in 2009, included China, Asia Pacific, Latin America, South America, the Middle East, Africa, India, Pakistan, Russia, and Eastern Europe. ACON will retain its other worldwide *in-vitro* diagnostics businesses including diabetes, clinical chemistry, and immunoassay products.
- **The Binding Site's autoimmune diagnostics business:** This deal continues Werfen Life Group's investment into the autoimmune disease diagnostics sector following its purchase of INOVA Diagnostics in 2008. Also, this acquisition should strengthen Werfen's position in the UK market. The business acquired from Birmingham-based The Binding Site develops assays to help diagnose and monitor the treatment of autoimmune diseases, including rheumatoid arthritis, antiphospholipid syndrome, vasculitis, and coeliac disease.

2. Continued penetration of the IVD market by major players in the life sciences research sector

- **Brahms:** Thermo Fisher's acquisition of Brahms continues the life sciences research group's drive to grow its clinical diagnostics business and develop its European presence. The main growth driver of Brahms is a procalcitonin assay for early detection and monitoring of sepsis. The company provides laboratory and point-of-care diagnostics for cancer, respiratory, cardiovascular, thyroid, and autoimmune diseases, and fertility and prenatal testing. Brahms was formed in 1994 as a buyout from Marion Merrell Dow's diagnostics division and was backed by VC firm HBM Bioventures.
- **DxS:** The DxS acquisition continues Qiagen's foray into the clinical diagnostics market following the Digene and other IVD business acquisitions. This deal is discussed further below.
- **Biotrove:** Life Technologies, the major life sciences research group, offered to buy Biotrove following a collaboration that started in 2007, which gave Applied Biosystems (now part of Life Technologies) responsibility for commercialisation of Biotrove's OpenArray business for genotyping applications. Another Biotrove product is the Standardised NanoArray PCR (SNAP) gene expression profiling system, which at the end of 2009 was being evaluated by the FDA for the rapid and specific detection of pathogens in the US blood supply.

3. Development of personalised medicine franchises

- **DxS:** Qiagen's DxS acquisition was presented as a significant move to develop Qiagen's personalised healthcare business. DxS signed several diagnostics partnerships with pharmaceutical companies during 2008–2009, and the new combined entity was reported to have more than 15 collaborations with pharma for the development and/or marketing of companion diagnostics for cancer. Qiagen planned to turn the Manchester headquarters of DxS into a "Center of Excellence in Pharma Partnering" for the group.
- **Monogram Biosciences:** LabCorp's stated ambition to develop its personalised medicine business was an important driver for this acquisition. Monogram's diagnostics aim to help physicians identify patients who will benefit most from specific drugs. For example, the Trofile assay was developed to identify patients eligible for Pfizer's HIV drug Selzentry (maraviroc). Other Monogram products include the HIV test PhenoSense and the VeraTag and HERmark cancer assays.

4. Entry into new market segments

- **Tepnel:** Gen-Probe offered to acquire Manchester-based Tepnel Life Sciences to enter the transplant typing market, grow its molecular diagnostics offering, and accelerate its European market expansion. Tepnel has a portfolio of human leukocyte antigen (HLA) tests to identify matching donor-recipient tissue types for organ transplantation and to aid in the on-going management of transplant recipients. Also, the UK-based company markets genetic tests—for Down's syndrome, cystic fibrosis, and familial hypercholesterolemia—and has a pharmaceutical services division providing microbiology analysis and SNP genotyping.

5. Development of molecular diagnostics offering

- **HandyLab:** With this acquisition, Becton Dickinson (BD) continues to develop its molecular diagnostics business. In particular, BD gains outright access to HandyLab's Jaguar system five months after a separate agreement gave the BD Diagnostics-TriPath division exclusive marketing rights to pathogen tests that use this system. Jaguar incorporates clinical sample preparation, nucleic acid extraction, and microfluidic real-time PCR amplification and detection. BD will continue to combine the Jaguar system with its GeneOhm assays that detect hospital-acquired pathogens, including MRSA, clostridium difficile, and vancomycin-resistant enterococcus. Other HandyLab products include the Lynx automated nucleic acid extraction system and Raider microfluidic real-time PCR system.

# Top-player ranks expected to reshuffle

The market share rankings of major IVD players are expected to reshuffle following two multi-billion-dollar M&A deals announced by Danaher and Thermo Fisher during the first half of 2011. Figure 6 shows how the top-nine IVD players ranked based on 2009 IVD revenues.

**Figure 6: Market leaders by share of 2009 IVD revenues**

| | Company | Market share |
|---|---|---|
| 1 | Roche | 20% |
| 2 | Abbott | 12% |
| 3 | Siemens | 11% |
| 4 | Johnson & Johnson | 9% |
| 5 | Beckman Coulter | 7% |
| 6 | bioMérieux | 3% |
| 7 | Bayer | 3% |
| 8 | Alere | 3% |
| 9 | Becton Dickinson | 3% |
| | | **71%** |
| | **Market size** | **$42bn** |

Source: Presentation by Roche at the American Association for Clinical Chemistry meeting of July 2010

Danaher and Thermo Fisher will appear near the top of IVD rankings provided some of the current majors do not announce mega-deals of their own.

## Danaher moving to fifth and challenging fourth position

Danaher will leapfrog many of the 2009 IVD majors with its acquisition of Beckman Coulter, which had clinical diagnostics revenues of $2.8 billion in 2009.

Danaher is a diversified instrumentation, technology, and tools group with total revenues of $13.2 billion in 2010 and a history of growth through acquisitions. The $6.8 billion offer for Beckman Coulter in February 2011 marks a major confirmation of Danaher's interest in the IVD sector. In December 2003, the group announced its first significant move into the sector, with a $730 million offer for Denmark-based Radiometer, which had annual revenues of approximately $300 million at the time, mainly from blood gas diagnostics used in hospitals.

A second acquisition partly connected with the IVD sector was announced in July 2005 with the $540 million offer for Germany-based Leica Microsystems. Leica produces precision optical systems for analysis of microstructures and operates in the microscopy, pathology diagnostics, surgical microscopes, and semiconductor equipment markets. The pathology diagnostics part of Leica's business is relevant to the IVD ranking.

With the Beckman acquisition, Danaher will jump to fifth at least in the IVD ranking and may overtake the fourth-largest player as it builds on the $500 million of 2010 revenues from Radiometer plus any clinical tissue diagnostics revenues from Leica.

The Beckman move follows three acquisitions announced during 2009–2010 in the life sciences and diagnostics sectors, worth a total of $1.2 billion:

1. $100 million for the acquisition of Genetix
2. $650 million for MDS Analytical Technologies
3. $450 million for the 50% of AB Sciex owned by Life Technologies

The Genetix acquisition added cell image analysis technology for the development of drugs and diagnostics, tissue quantification technology for digital pathology, and genetic testing products.

The MDS Analytical Technologies and AB Sciex businesses focus mainly on life sciences research rather than clinical diagnostics, but they offer expertise that may be relevant for the development of future IVD products, particularly in the molecular diagnostics segment of the market.

## Thermo Fisher moving to sixth and taking the leadership in allergy diagnostics

Thermo Fisher will add significant IVD revenues with the $3.5 billion acquisition of Sweden-based Phadia from Cinven, announced in May and completed in August 2011. The Phadia move follows the $471 million acquisition of Germany-based BRAHMS, announced in September 2009.

Thermo Fisher Scientific is a science-focused group with 2010 revenues of $10.6 billion from analytical technologies and laboratory products and services. The analytical technologies segment includes a specialty diagnostics division with 2010 revenues of $1.4 billion from anatomical pathology, microbiology, and specialty assays. Some of this specialty diagnostics revenue is from nonclinical applications, such as industrial microbiology. However, the existing clinical diagnostics business of Thermo Fisher is significant. With the additional business from the acquisition of Phadia, which had IVD revenues of $525 million in 2010, Thermo Fisher is expected to move up to sixth in the IVD market ranking. Also, the US company will become the global leader in the allergy diagnostics sector–one of Phadia's claims to fame.

## Other large players focused on smaller deals

By comparison with the above mega-deals, the top-four IVD players—those ranked above Beckman Coulter—announced only three acquisitions in the IVD sector during 2008–2010, all below $300 million:

1. $100 million offer for BioImagene by Roche
2. $215 million acquisition of Ibis BioScience by Abbott
3. $31 million purchase of Immunicon by Johnson & Johnson (J&J)

Figure 7 summarises the IVD M&A deals announced during 2008–2010 by the top-nine IVD players.

Alere, which changed its name from Inverness Medical Innovations in July 2010, was by far the most active buyer among the top-nine IVD players, driving half of the 14 M&A deals announced by the top nine during 2008–2010. Alere's high level of corporate activity is no surprise if we consider the 17 IVD acquisitions announced by the company during 2007.

**Figure 7: M&A deals in the IVD sector 2008–2010 by top-nine IVD players**

| Top-nine IVD Players | Value ($m) | Target | Country |
|---|---|---|---|
| Announced in 2010 | 765 | Number of deals: 7 | |
| Alere | 255 | Epocal | Canada |
| | 217 | Standard Diagnostics | S Korea |
| | 102 | Kroll Laboratory | US |
| | 83 | AdnaGen (78%) | Germany |
| | 8 | Quantum Diagnostics | UK |
| Roche | 100 | BioImagene | US |
| bioMérieux | na | Meikang Biotech | China |
| Announced in 2009 | 1,458 | Number of deals: 4 | |
| Alere | 203 | Concateno | UK |
| | 200 | ACON-Second Territory | China |
| Beckman Coulter | 780 | Olympus-Diagnostics | Japan |
| Becton Dickinson | 275 | HandyLab | US |
| Announced in 2008 | 306 | Number of deals: 3 | |
| Abbott | 215 | Ibis BioScience | US |
| bioMérieux | 60 | AviaraDx | US |
| Johnson & Johnson | 31 | Immunicon | US |
| Announced in 2008–2010 | 2,529 | Number of deals: 14 | |

Source: PwC analysis using data from Thomson Financial, Windhover, Mergermarket, Zephyr and other publicly available sources

Among the rest of the top nine, bioMérieux was the only player to announce more than one IVD M&A deal during 2008–2010; the company entered into one deal in the United States and another in China.

Future revenue growth generated from this deal activity will depend on the quality and relevance of the technologies and intellectual property acquired, as well as the commercial operations needed to support strong market access and sales.

It will be interesting to see how the majors react to the challenge raised by Danaher's and Thermo Fisher's recent investments.

## IVD an acquisition target for pharma?

Solvay Pharmaceuticals' acquisition of Innogenetics in 2008 was a rare case of a pharma company buying a diagnostics business in recent years. Will such a scenario become more common?

With pharma developing an increasing number of targeted therapeutics and the growing interdependence with companion diagnostics, the pharma industry is considering how to access diagnostics technology to complement its evolving product portfolio.

### Pharma has three main options to access diagnostics innovation

**Option 1—In-house cooperation:**
This option is available to healthcare products companies that have both a pharmaceutical and a diagnostics division. For example, Roche reported several in-house drug development projects for which the companion diagnostic was being developed in collaboration with Roche's Diagnostics division.

Pharma makes limited use of this option because only a handful of healthcare companies have both a pharmaceutical and a diagnostics division.

Also, discussions with pharma executives have highlighted a number of factors that may have mitigated in-house cooperation:

- The technology available in diagnostics divisions is not necessarily adaptable to companion diagnostics applications.
- The collaboration between people from different disciplines and divisional cultures can be challenging.
- The allocation of the overall value of the drug-diagnostic (Rx-Dx) combination between the two divisions can be an issue.

One way to address some of these factors is to develop a diagnostics business unit within the pharma division with diagnostics technology focused mainly on applications for its pharma business. Novartis provides the main illustration for this scenario. The Swiss group has two diagnostics businesses. First, a diagnostics division, focuses mainly on tests used by blood banks, following the acquisition of Chiron. Second, a molecular diagnostics business unit within the pharma division, focuses mainly on the diagnostics needs of the pharma business.

The greater use of in-house cooperation in the future will depend also on the extent of diagnostics business acquisitions during the next few years, as discussed below.

**Option 2—External partnerships:**
This is the main route used by pharma to access companion diagnostics technology and includes licensing-in and fee-for-service collaboration. Even those companies with both a pharma and a diagnostics division, such as Roche, pursue external companion diagnostics partnerships to access the technology best suited for their specific needs.

As with the previous option, one factor that has made some of the deal-making challenging has been the allocation of the overall value of the Rx-Dx combination. Diagnostics partners often feel they are not getting a fair share of the overall value considering the importance of the diagnostic in making treatment decisions. Diagnostics influence more than 60% of critical healthcare decisions but represent less than 2% of healthcare spend worldwide. Discussions to rebalance the value shares between the two industries are ongoing.

We discuss diagnostics partnerships with pharma in more detail in a separate section.

**Option 3—M&A:**
Cases of pharma buying diagnostics businesses have been rare in recent years. However, the year 2011 started with Novartis making a $330 million offer to buy Genoptix, a US-based diagnostics business, and we believe pharma could pursue this avenue with greater vigour in the future.

The M&A question is linked to pharma's thinking about business models, which we consider below.

## Business models for pharma to access diagnostics

Pharma companies have adopted at least four different business models as regards their in-house diagnostics capability, as shown in Figure 8 and discussed below.

### Model (1)—The company has a separate diagnostics division

Roche, Abbott, and Johnson & Johnson are the main examples for the model characterised by a stand-alone diagnostics division, separate from the pharmaceutical division. (Abbott is noted here in its 2011 guise, prior to separation of its proprietary pharma business, announced in October 2011 and set to complete by the end of 2012.) Among medium-sized companies, Italy-based Menarini is another example of a company with separate pharma and diagnostics divisions. Typically, the diagnostics business in these companies originated long before companion diagnostics became a market opportunity. Most of the revenues in such diagnostics divisions come from products that are not companion diagnostics.

The diagnostics divisions in many of these companies have technology that is relevant to supporting drug development programs, and they are actively involved in companion diagnostics partnerships with their in-house pharma divisions and other pharma companies as well.

The pharma divisions in Model (1) companies have the widest range of options among the four models to access companion diagnostic technology. They have the option of seeking companion diagnostics support in house or from external diagnostics partners.

**Figure 8: Diagnostics business models adopted by pharma companies**

| Model | Model (1): Dx Division | Model (2): Dx BU in Pharma Division | Model (3): Dx BD Group in Pharma Division | Model (4): Lx Division |
|---|---|---|---|---|
| Description of in-house Dx capability | • Stand-alone Dx business<br>• CDx are part of scope but non-CDx are main source of business | • Capability to develop own Dx<br>• CDx are the main (but not exclusive) focus of the Dx capability, and the CDx tests are mainly for own Rx products (although there is scope to license out noncore applications) | • Capability to license-in Dx technology<br>• Dx focus is exclusively on CDx to support own Rx products | • Stand-alone life sciences research products business<br>• Some of the technology could be adapted to Dx use in future |
| Company examples | • Roche<br>• Abbott<br>• J&J | • Novartis | • AZ<br>• Lilly<br>• GSK | • Merck KGaA (Millipore) |
| Options for growth of CDx activity | • Adapt Dx capability to CDx needs<br>• Pursue CDx partnerships in house as well as with external partners<br>• Acquire new technology | • Grow Dx development capability<br>• Grow Dx licensing-in capability<br>• Acquire new technology | • Add to licensing-in capability<br>• Grow biomarker discovery capability<br>• Shift to Model (2) by adding assay development capability | • Adapt technology from research use to clinical use with focus on CDx applications<br>• Acquire technology for clinical use |

Notes: BU = Business unit; Dx = Clinical diagnostics; CDx = Companion diagnostics; Lx = Life sciences research products (nonclinical)

Source: PwC analysis following discussion with industry contacts

### Model (2)—Diagnostics business unit within the pharma division

This model corresponds to the Novartis case, discussed under the in-house cooperation option above. As mentioned, one advantage of having a diagnostics business unit within the pharma division is that it removes some of the issues around sharing the overall value of the drug-diagnostic combination. These issues may be more acute when the collaboration is between separate divisions, even within the same company. A number of pharma companies are keeping an eye on developments at Novartis and may eventually follow its example when their practice of drug-diagnostic co-development has become more established.

Convergence towards Model (2) is more likely to come as a build-up from Model (3), through acquisition of a diagnostics business or following a period of organic development. However, we do not rule out such convergence to follow a refocusing of activities by a company with a Model (1) profile. In the latter scenario, a pharma company with a broadly based IVD business would have at least two options to refocus its portfolio to Model (2). A first option would be to divest most of its IVD business, with the exception of the technology areas most relevant to supporting its pharma business. The technology segments most relevant to companion diagnostics—molecular and tissue diagnostics—are also the fastest growing in the IVD spectrum. By keeping only those segments, the refocused IVD business could support the needs of its pharma division and target some noncompanion diagnostics applications; but those applications would focus on the fastest growing areas of the IVD sector.

To be sure, such a divestment would be an exceptional event. However, you could argue that Bayer made a related move when it sold most of its IVD business to Siemens in 2006 but kept its glucose-monitoring business, which fit well with its consumer healthcare franchise.

A second option for a Model (1) company to refocus its portfolio to Model (2) would be to divest its existing IVD business and then rebuild a new diagnostics business from scratch to support its pharma franchise with relevant CDx tools. This second option might be more relevant when the IVD division's key stakeholders consider a carve-out of the IVD technologies most relevant to CDx applications unfeasible or unacceptable.

### Model (3)—Diagnostics business development group within the pharma division

Among the illustrative company examples mentioned for Model (3), AstraZeneca (AZ) is the pharma company that was first at setting up a diagnostics business development group, followed by Eli Lilly and then GSK. Typically, these business development functions include sufficient diagnostics expertise to make decisions about which technology to invest in and on what terms. However, this diagnostics capability is not usually sufficient to conduct diagnostics development work in house.

Recently, AZ moved on from the basic version of this model by adding a biomarker discovery capability—a preliminary phase in the development of a diagnostic. This evolution underlines AZ's continued commitment to companion diagnostics.

### Model (4)—Life sciences research business in a separate division

Merck KGaA is the main illustrative example for this model. The company announced its $7.2 billion acquisition of Millipore in February 2010 and closed the deal in July 2010. Massachusetts-based Millipore generated $1.7 billion of sales during 2009 from technologies, tools, and services for bioscience research and biopharmaceutical manufacturing, in industry as well as academia. In particular, the acquisition provided Merck KGaA with significant diagnostics capability for research-use-only (RUO) applications.

In addition to pursuing external partnerships to access relevant companion diagnostics technology for its pharma business, companies with this model have the option of adapting some of their life sciences research technology to make it appropriate for clinical use. However, this approach would require investment into relevant clinical development work.

### IVD as a future acquisition target for pharma

Pharma has not acquired a high-value IVD business recently, with exception of the Innogenetics/Solvay Pharma (2008) and Genoptix/Novartis (2011) cases. With the strong acceleration of pharma's partnerships with the diagnostics industry, we believe this will change soon.

As discussed in a separate section, an increasing number of pharma players are combining their targeted therapeutics with a companion diagnostic. We believe that when the practice of drug-diagnostic co-development has become more established, pharma companies will consider buying diagnostics businesses to bring some of the required technology in house. In many cases, such acquisitions will correspond to companies wanting to shift their diagnostics business models from Model (3) to Model (2) in our discussion above.

The targets for such M&A activity by pharma are more likely to be niche IVD players than businesses with a presence across several segments of the IVD sector. If pharma's motivation is to acquire technology that is complementary to its therapeutics business, it will seek strong capabilities in molecular or tissue diagnostics—the most relevant for today's companion diagnostics programs.

# Outlook

## Highlights from the first half of 2011

The trend towards rising M&A deal values in the IVD sector has continued with an exceptional acceleration during 2011. The 57% increase in total deal value to $4.7 billion for 2010 will be followed by a total deal value increasing more than three times to more than $15 billion during 2011—provided the deals announced to date in 2011 become effective.

The year 2011 started strongly with two significant M&A deals announced during the first few weeks:

- The first was the $330 million offer for Genoptix by Novartis in January. This transaction represents the first major M&A deal driven by the Novartis molecular diagnostics business unit, created in 2008. Genoptix, a US-based clinical laboratory, which reported revenues of $184 million for 2009, specialises in diagnosis of cancers of the bone marrow, blood, and lymph nodes.
- The second was the $6.8 billion offer for Beckman Coulter by Danaher, announced 7 February 2011, which stole the headlines away from the comparatively smaller Novartis-Genoptix deal. Danaher's deal was significant not only because of its size, but also its impact on IVD market share as it acquired one of the top-nine IVD players.

The strong start to 2011 was followed by other significant M&A deals during the first half of the year, as reported in Figure 9.

Key themes in the M&A deals announced during 2011 include:

- **Continued appetite from bidders outside the IVD sector.** Two industries that have shown an interest in recent years include the clinical laboratory and life sciences research sectors, illustrated by acquisitions by Quest Diagnostics and Thermo Fisher Scientific respectively. Industries that are less common buyers of IVD companies include the pharmaceutical and food sectors, illustrated by acquisitions by Novartis and Nestlé respectively.

  The move by Novartis is not surprising if we consider the significant investment it has made into diagnostics since the creation of its molecular diagnostics business unit at the end of 2008. And Novartis may be showing the way for other pharma companies during the next five years.

  The move by Nestlé was less expected, but the size of the investment suggests a true statement of intent. The acquisition is consistent with the strategy announced in September 2010 of building a healthcare science nutrition business with a focus on personalised healthcare. The Nestlé case is discussed in more detail in the section reviewing 10 significant events for the development of personalised medicine.
- **Large deals to add significant overall market share.** The acquisitions of Beckman Coulter by Danaher and Phadia by Thermo Fisher Scientific will push the buyers up the ranks, possibly into top-six positions in the IVD sector.

**Figure 9: Selected M&A deals in the IVD sector during the first half of 2011**

| Value ($m) | Target | Country | Bidder | Country | Date |
|---|---|---|---|---|---|
| 330 | Genoptix | US | Novartis | CH | Jan-11 |
| 6,800 | Beckman Coulter | US | Danaher | US | Feb-11 |
| 344 | Celera | US | Quest Diagnostics | US | Mar-11 |
| 119 | PVT | Germany | Roche | CH | Mar-11 |
| 355 | Cellestis | Australia | Qiagen | NL | Apr-11 |
| 80 | Rules Based Medicine | US | Myriad Genetics | US | Apr-11 |
| 3,500 | Phadia | Sweden | Thermo Fisher Scientific | US | May-11 |
| 1,100 | Prometheus Labs | US | Nestlé | CH | May-11 |
| 32 | Stanbio Laboratory | US | EKF Diagnostics | UK | May-11 |
| 101 | Ipsogen | France | Qiagen | NL | Jun-11 |

Source: PwC research, using data from IVD Technology and company press releases

Note: Figure 9 includes selected CLIA labs (e.g., Genoptix), which, strictly speaking, are not IVD product businesses. However, we have chosen to include selected CLIA lab deals in the list of M&A deals in the IVD sector because CLIA labs are an important way of operating an *in vitro* diagnostics business in the United States through the laboratory-developed test route.

- **Smaller deals to acquire a specific technology or strengthen a specific market segment presence.** Illustrations for this include the acquisitions of PVT by Roche and Ipsogen by Qiagen.

During July 2011, the momentum of significant M&A deals continued with the $2 billion acquisition of Immucor by Texas Pacific Group, a US private equity firm, and the $266 million offer for mtm Laboratories by Roche.

One large rumoured deal that seems to have gone away is the potential takeover of Gen-Probe. At some stage during June 2011, the US-based company had a market capitalisation of approximately $4 billion amid press reports of an ongoing auction. During July, further press reports suggested that Novartis had withdrawn from the process, leaving no further known bidders.

The $15 billion minimum expected value of M&A for 2011 assumes that all announced deals are confirmed. It is based on the value of the selected deals in Figure 9 plus the two significant deals mentioned for July. Whatever happens during the remainder of 2011, the market dynamics in the IVD sector seem to have attracted a level of investor interest that is almost unprecedented. With five months left in the year at the time of writing this report, 2011 total deal value already ranks as one of the highest since 2004, second only to the $27 billion announced in 2007 and outpacing the $12 billion recorded during 2006.

## Outlook to 2015

Looking beyond 2011 to the next few years, we expect the following themes to shape some of the M&A activity in the IVD sector:

- **New entrants continuing to add IVD businesses:** For some of the newer entrants into the IVD sector, such as GE Healthcare, the recent deal activity may represent only a beginning. These companies may pursue additional acquisitions to maintain the momentum required to achieve critical mass quickly.
- **Historical majors responding in kind:** If the current industry leaders, shown in Figure 6, do not respond with significant acquisitions of their own, they may start losing market share in key segments. Doing the right deals will be challenging because we expect to see strong competition to buy those businesses developing compelling new technology.
- **Private equity houses searching for opportunities:** We expect more private-equity-backed deals to crystallise—provided capital markets do not slump. During the past few years, we have seen a number of significant deals of this type in the IVD sector, including the $1.6 billion buyout of Phadia by Cinven in 2006, the $1.3 billion deal to take Dako private by EQT in 2007, and the $1.1 billion acquisition of Sebia by Cinven in 2010. The $2 billion offer for Immucor by TPG in July 2011 confirms this trend.

  We expect even bigger private equity deals than these during the next few years. Some media reports indicated that a number of large private equity houses were leading the process to acquire Beckman Coulter before the $6.8 billion offer by Danaher was announced in February 2011.

  Smaller opportunities also will attract the interest of private equity investors, as highlighted by the $55 million acquisition of POC specialist International Technidyne. The deal, completed in November 2010, and backed by financial investor Warburg Pincus, rolled the business into Nexus Dx, another IVD player focused on POC testing.
- **Major pharmaceutical companies buying molecular or tissue diagnostics businesses:** We have not seen many examples of this scenario in recent years. However, an increasing number of major pharmaceutical companies are actively seeking companion diagnostics to complement their drug development programs. Those that are not part of a company with a significant IVD division have started building business development teams with diagnostics expertise to support better licensing decisions.

  We believe that some of these companies will consider buying a diagnostics business to deepen their expertise, increase technology options, and provide at least some direct commercial access. We do not expect such diagnostics acquisitions to target broad IVD players of a kind similar to Beckman Coulter or Dade Behring (acquisition by Siemens announced in 2007). Such additions are more likely to target focused molecular or tissue diagnostics businesses.
- **A significant player moving into early detection:** This last scenario may be the most speculative. As discussed later in this report, several companies are driving the development of a wave of new tests for early detection of major cancers. Only time will tell whether the market adopts the concept of using noninvasive *in vitro* diagnostics for early detection. If it does, a major diagnostics or pharmaceutical company could move to acquire one or several of the promising new ventures in this field.

# II. Companion partnerships with pharma increase

## Key findings

1 The number of IVD licensing deals with pharmaceutical companies increased significantly during 2009–2010. We identified 25 deals reported in 2010, compared with 19 deals in 2009 and seven in 2008.

2 Drivers: The strong appetite for companion deals was driven by increasing signals from regulators and payers, stressing the importance of biomarkers and diagnostics to improve drug performance and allow for more cost-effective allocation of tight healthcare budgets. Pharma is adapting by making more systematic use of companion diagnostic programs to increase drug response rates and reduce side effects. Diagnostic companies with strong molecular and tissue diagnostic capabilities have been active at developing tools to respond to pharma's specific needs.

Despite the increasing demand for companion diagnostics, the industry is concerned about the economics of diagnostics innovation, adversely affected by current pricing and reimbursement practices. In addition, many diagnostics partners feel they are not getting a fair share of Rx-Dx partnership values. These challenges are not expected to undermine deal activity in the near term but may have consequences on long-term diagnostics innovations if not addressed.

3 Pharma partners: While Big Pharma dominated, niche therapeutics specialists also showed an interest in diagnostics partnerships. Big Pharma remained dominant among the pharma partners for IVD deals, accounting for 34 of 44 deals during 2009–2010.

Given the complexity and expense involved in developing companion diagnostics, it was no surprise that larger pharma companies were more active in forming partnerships. However, the number of medium-sized or niche therapeutics players involved in IVD partnerships increased from one in 2008 to nine during the following two years, including OSI Pharmaceuticals (since acquired by Astellas), Merck KGaA, Aeterna Zentaris, Biogen Idec, Clovis Oncology, Daiichi Sankyo (one of two pharma partners in a collaboration with Accumetrics), Merz, Optherion, and Transgene.

This increased activity might encourage other smaller but well-funded specialist therapeutics players to pursue similar ventures.

4 Diagnostics partners: During 2009–2010, larger diagnostics companies became more active partners for the pharmaceuticals industry. After being the lone top-nine IVD player forming a partnership with pharma in 2008, Abbott was joined by two other top players during 2009–2010—Roche and bioMérieux. These IVD majors announced nine deals with pharma over the two-year period—a significant change from the single deal identified in 2008. Still, innovation and companion diagnostics partnerships with pharma continued to appear most relevant to niche IVD specialists, which were involved in 35 of the 44 deals during 2009–2010. Qiagen was the most active IVD partner among medium-sized and niche specialists as well as overall, with five deals reported during the two-year period.

5 Disease areas: Neurology and infectious diseases made an appearance alongside cancer during 2009–2010. Five of the 44 diagnostics partnerships with pharma focused on neurology and infectious diseases, while 34 collaborations focused on cancer. In particular, seven partnerships demonstrated a strong interest in lung cancer. While cancer remained the dominant focus, the marginal diversification into other disease areas during the last two years seemed noteworthy, given that all but one deal in 2008 focused on cancer.

6 Outlook: The appetite for companion deals will remain strong because the same drivers will continue and intensify in 2011 and beyond. In 2011, deal activity started in promising fashion, with 15 companion diagnostics partnerships with pharma identified by our preliminary review of the first half of 2011.

By 2020, if drug-diagnostic co-development becomes routine, most leading pharma companies are expected to change their business model to incorporate significant in-house diagnostics capabilities. The volume of external alliances is expected to remain high, but the trend may lose momentum.

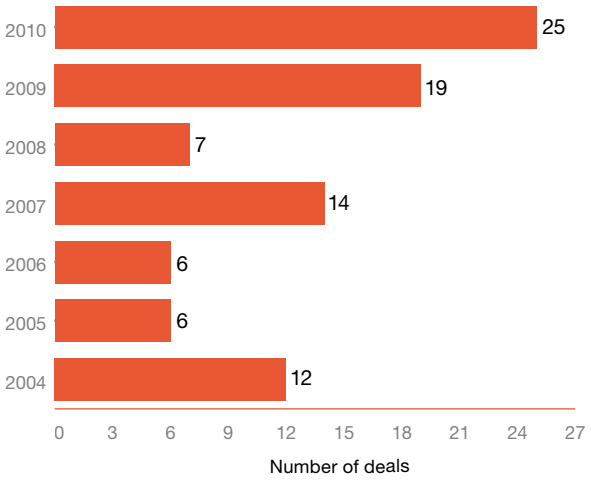
# Diagnostics partnerships with pharma increase sharply during 2009–2010

## The surge in companion diagnostics partnerships reflects a growing commitment by pharma

The rising numbers of IVD partnerships with pharma during 2009–2010 confirm that a larger number of pharmaceutical companies are taking more seriously the need for biomarker and diagnostic programs to accompany their drug development efforts. We know that more deals are completed than reported in the public domain. Some partners—typically, pharmaceutical companies—do not always wish to disclose their diagnostics partnerships. Other deals, although disclosed, are not widely discussed publicly. For the analysis in this report, we rely on deals that we have been able to identify through publicly available sources. Some announced deals might have been missed.

The number of IVD partnerships with pharma announced during 2004–2010, as shown in Figure 10, highlights a drop to seven deals in 2008, followed by a strong rise to 19 in 2009 and 25 in 2010.

**Figure 10: Number of companion diagnostics partnerships with pharma 2004–2010**




Source: PwC analysis, using data from Windhover, IVD Technology, and company press releases

The 44 companion diagnostics partnerships with pharma identified for 2010 and 2009 are shown in Figures 11a, 11b and 12 (pages 21-23).

# Regulators, payers, and pharma drive rising demand for companion diagnostics

The rising momentum in companion diagnostics partnership activity has been driven by the increasing role of diagnostics in the regulatory approval, reimbursement, and performance optimisation of new drugs.

## Regulators

Regulatory agencies have insisted on the need for validated diagnostics prior to considering marketing clearance for a number of drugs. The requirement for KRAS testing for the Vectibix (Amgen) and Erbitux (Merck Serono) cases has been well publicised. Another example is the April 2010 decision by the FDA to require a validated diagnostic prior to considering marketing clearance for Omapro, which is being developed by ChemGenex Pharmaceuticals for the treatment of adults with chronic myeloid leukaemia who have failed prior therapy with imatinib and have the Bcr-Abl T315I mutation.

The FDA released the long-awaited draft guidance on companion diagnostics in July 2011. This guidance can only enhance pharma's paradigm shift towards greater use of companion diagnostics.

## Payers

The availability of tests to identify patients that would not benefit from certain therapies has raised the bar for obtaining reimbursement for new drugs. Increasingly, payers see companion diagnostics as useful tools to allocate healthcare funds more effectively and control costs. Many insist on genetic testing prior to prescribing and reimbursing certain treatment regimens that are expensive and not efficacious in certain patient subpopulations.

In the United States, some pharmacy benefit managers are adapting their business models by forming partnerships with or acquiring specialist clinical laboratories. For example, during 2010, Medco Health Solutions acquired DNA Direct, a San Francisco-based laboratory that provides genetic testing services. Medco planned to introduce genetic testing as a requirement for prescribing tamoxifen, the breast cancer drug, and warfarin, the blood thinner.

Some payers have already stated their preference for drugs that come with a companion test, particularly when these drugs are expensive and may lead to severe side effects. This preference can only increase over time with the rising pressure on healthcare budgets and greater availability of appropriate diagnostic tools.

## Pharma industry

Pharma companies have started to seek improvements in drug response profiles through better patient targeting and have achieved some success. Drug response rates of up to 80% have been reported for targeted subpopulations for cancers that generally have a response rate of only 20%.

One example is Zelboraf (vemurafenib), the BRAF inhibitor previously referred to as RG7204/PLX 4032. The compound demonstrated tumour shrinkage in 81% of cases in a Phase I study with 32 metastatic melanoma patients, as reported in the *New England Journal of Medicine* in August 2010. This drug candidate, licensed by Roche from Plexxikon, completed Phase III trials as first-line monotherapy for metastatic melanoma cases with the V600E BRAF mutation and was co-developed with Roche's Cobas 4800 BRAF V600E mutation test. In May 2011, Roche announced it had filed marketing approval applications for vemurafenib in the United States and Europe. Roche is also seeking marketing clearance for the test in both territories. Daiichi Sankyo acquired Plexxikon during 2011 and plans to co-promote the drug in the United States. Zelboraf and its companion diagnostic were approved by the FDA in August 2011.

The prospect of repeating such technological wins is encouraging pharma to accept a number of changes that have appeared increasingly inevitable, including:

- The decline of the mass-market blockbuster drug model
- The emergence of smaller target markets
- The need for high-performance diagnostic tools to dominate well-defined smaller market segments

Seeking external partnerships has been pharma's main route to access companion diagnostic solutions. In-house development has not been pursued unless the pharma company had an existing diagnostics business affiliate. Even in such cases, sourcing has not been exclusively internal, as suggested by the external diagnostics partnerships reported by the pharma business of Roche, which also has the largest IVD business in the industry.

## Diagnostics industry

The factors discussed above concern the demand for companion diagnostics. On the supply side, the technological feasibility of companion diagnostic programs also is increasing. Advances in science and technology within the diagnostics industry are expanding the scope for effective companion programs: companies are continuing to develop relevant expertise in molecular and tissue diagnostics, which will enable the development of better tools to guide treatment decisions. Immuno-histochemistry products—developed by Ventana Medical Systems, acquired by Roche in 2007—illustrate tissue diagnostic technology. This technology is used in a number of companion diagnostic programs—for example, to support the pancreatic cancer drug program at Clovis Oncology.

# Challenges to the economics of diagnostics remain, despite strong demand

The diagnostics industry is providing new tools that could improve pharma's product offering to physicians and patients and create value for pharma's shareholders. Unfortunately, many industry players feel the economics of diagnostics innovation are undermined by the low pricing and reimbursement of diagnostics and the diagnostics partner's low share of Rx-Dx partnership values. In this context, government and its agencies have a key role to play to support the required changes.

**Industry players propose three main actions:**

1. Pricing should reflect the value of the test rather than its cost. The diagnostics industry wishes more tests were priced based on the value they create. The industry feels the price should reflect a reasonable proportion of the benefits the tests generate or costs they help to save. In the United States, the concept of value-based pricing is making gradual progress following the much publicised Oncotype DX breast cancer recurrence test from Genomic Health, priced at ca. $4,000. This and other US examples are provided by a March 2011 article authored by members of the European Personalised Medicine Association (EPEMED), which mentions eight personalised medicine tests priced on a value basis in the range $2,000 to $4,000 in 2008. These examples include prognostics (e.g., Oncotype DX and AlloMap) as well as companion tests (e.g., Trofile and HERmark).

   Europe has yet to see value-based pricing applied to a personalised medicine test. The diagnostics industry fears that unless pricing is adapted to the level of value creation, it will fail to achieve sufficient economic return to stimulate continued investment and innovation.

2. The process to gain reimbursement for diagnostics should be accelerated and harmonised across countries. In many countries, gaining reimbursement for a new test can take four to seven years following marketing clearance. Industry participants feel that health technology assessment (HTA) models need to be adapted to allow for faster decisions on reimbursement. One practical fix to address delays in reimbursement decisions has been for the pharmaceutical partner to subsidise the companion test. This situation is not ideal; but in cases where the test determines eligibility to the drug, the alternative would be to limit severely the availability of the companion drug. This would not be acceptable to pharma.

   As regards multicountry product launches, another issue is the diversity of HTA procedures across countries. This problem has been recognised by the European Commission, which has sponsored the European network for Health Technology Assessment (EUnetHTA) to start working on greater cooperation. The United States is also represented in this initiative through the Center for Medical Technology Policy (CMTP). The industry is waiting for improvements to come through in practice.

3. The share of value going to the diagnostic in Rx-Dx partnerships should be revisited. Diagnostics companies are concerned about not getting a fair share of the overall value of Rx-Dx combinations when negotiating deal terms with pharmaceutical partners. In this context, the diagnostic partner is suffering from a history of low recognition of the value of diagnostics. Traditionally, diagnostics have represented less than 2% of healthcare spend but influenced more than 60% of critical healthcare decisions. Diagnostics partners are now trying to rebalance their share of the Rx-Dx combination.

   One avenue diagnostics companies are pursuing is to get a form of royalty on sales of the companion pharmaceutical. Pharma is resisting such a move because they feel the Dx partner has not borne any of the risk or investment associated with developing the drug. However, diagnostics players insist that sooner or later this move will have to happen. The argument put forward by Dx partners is that in scenarios where Rx-Dx combinations are relevant, the companion drug would not be able to make it through clinical trials or be reimbursed and commercialised without the companion diagnostic. Thus, the value of the drug is critically dependent on the contribution of the companion diagnostic.

At best, the implications of not addressing these issues could be that diagnostics innovation is handed over too cheaply to pharma. At worst, these issues could eventually discourage continued investment into diagnostics ventures and delay patient access to important new health technology.

## Figure 11a: Companion diagnostics partnerships with pharma during first half of 2010

| Diagnostics Partner | Pharmaceutical Partner | Deal Subject | Disease Area | Deal Date |
|---|---|---|---|---|
| Dako (Denmark) | AstraZeneca (UK) | Develop new companion diagnostics for AZ's drug programs. Specific diagnostics and drug candidates were not specified. | Cancer—Undisclosed | Jan–10 |
| MDxHealth (Belgium) | Roche (CH) | Conduct testing to determine the MGMT gene promoter methylation status of patients enrolled in a Phase III clinical trial for the use of Avastin in newly diagnosed brain tumours. | Cancer—Glioblastoma | Jan–10 |
| CMIC (Japan) | Roche (CH) | Rights to use the Liver-Type Fatty Acid Binding Protein (L-FABP) to detect kidney injury and disease. This marker could help support new research into therapies for kidney disease. | Kidney disease | Jan–10 |
| Sequenom (US) | Optherion (US) | Develop tests to predict genetic predisposition to late-stage AMD using MassARRAY. This could lead to companion diagnostics for a protein therapeutic in Optherion's portfolio. | Ophthalmology—AMD | Feb–10 |
| Qiagen (DxS) (Netherlands) | Pfizer (US) | Develop a real-time PCR companion diagnostic kit for Pfizer's Phase II peptide vaccine for glioblastoma multiforme, which was licensed from Celldex Therapeutics. | Cancer—Glioblastoma | Feb–10 |
| Roche (Switzerland) | Merck & Co (US) | Use Roche's investigational PCR-based AmpliChip p53 microarray test in cancer drug development activities. | Cancer—Unspecified | Feb–10 |
| Prometheus (US) | Bayer Schering (Germany) | Nonexclusive rights to the ProOnc technology, which monitors microRNA expression, to identify target patients for cancer drug candidates and classify patients into specific treatment groups. | Cancer—Unspecified | Mar–10 |
| Abbott Laboratories (US) | GlaxoSmithKline (UK) | Develop an RT-PCR test as companion diagnostic for GSK's Phase III skin cancer therapeutic to run on Abbott's m2000 automated instrument. | Cancer—Skin | Mar–10 |
| AgaMatrix (US) | Sanofi-Aventis (France) | Develop new diabetes monitoring tests exclusively for sanofi incorporating AgaMatrix's WaveSense technology and sanofi's insulins and delivery systems. | Metabolic—Diabetes | Mar–10 |
| Almac Diagnostics (UK) | Merck KGaA (Germany) | Profile metastatic CRC samples from the COIN trial, conducted by the UK MRC, using PCR to assess biomarkers, apart from KRAS status, to define which patients benefit most from cetuximab. | Cancer—Colorectal | Apr–10 |
| Roche (Ventana) (Switzerland) | Clovis Oncology (US) | Develop an IHC assay for use with Clovis's lipid-conjugated form of gemcitabine, which is in Phase II trials for the treatment of pancreatic cancer. | Cancer—Pancreas | Apr–10 |
| Response Genetics (US) | GlaxoSmithKline (UK) | Nonexclusive rights to use PCR technology and related diagnostics expertise to analyse human tumour specimens with mutations in the BRAF gene. | Cancer—Unspecified | May–10 |
| bioMérieux (France) | GlaxoSmithKline (UK) | Develop an assay to detect BRAF gene mutations, beyond the V600E form, in Phase II and III metastatic melanoma patients to select those eligible for GSK's BRAF or MEK inhibitors. | Cancer—Skin | May–10 |
| Saladax Biomedical (US) | Bristol-Myers Squibb (US) | Develop and gain regulatory approval for companion diagnostics for use with undisclosed therapeutics in BMS's pipeline. | Cancer—Undisclosed | Jun–10 |
| Almac Diagnostics (UK) | Aeterna Zentaris (Canada) | Develop a companion diagnostic for AEZS-108, in Phase 2 for advanced LHRH receptor-positive ovarian and endometrial cancer. LHRH receptor expression is measured with IHC at present. | Cancer—Unspecified | Jun–10 |

Source: PwC research, using data from Windhover, IVD Technology, and company press releases

## Figure 11b: Companion diagnostics partnerships with pharma during second half of 2010

| Diagnostics Partner | Pharmaceutical Partner | Deal Subject | Disease Area | Deal Date |
|---|---|---|---|---|
| Pathwork Diagnostics (US) | Novartis (Switzerland) | Discover biomarker signatures that can serve as the basis for diagnostics across a range of tumor types. Both companies have the right to develop and sell diagnostics. | Cancer—Unspecified | Jul-10 |
| Accumetrics (US) | Eli Lilly & Daiichi Sankyo (US) | Inform professionals in the US how the VerifyNow System can be used to measure patient response to antiplatelet medication, including Effient (Lilly and Daiichi) and Plavix (sanofi-aventis). | Cardiovascular—Blood clotting | Jul-10 |
| LabCorp (US) | Merck & Co (US) | Nonexclusive rights to commercialise a genetic test to detect IL-28B polymorphism in hepatitis C patients and predict whether they will respond to peginterferon alpha therapy. | Infection—HCV | Jul-10 |
| MDxHealth (Belgium) | GlaxoSmithKline (UK) | Potential use of a DNA methylation-specific PCR biomarker in the development program of a GSK immunotherapy. The biomarker is designed for the analysis of noninvasive tissue samples. | Cancer—Unspecified | Sep-10 |
| Roche (Ventana) (Switzerland) | Transgene (France) | Develop an IHC assay to identify patients with MUC1-positive tumor cells as companion to Transgene's TG4010 immunotherapy, which is about to enter Phase IIb/III trials for advanced NSCLC. | Cancer—Lung | Sep-10 |
| Myriad Genetics (US) | Abbott Laboratories (US) | Conduct BRCA1 and BRCA2 mutation testing on patients to be enrolled in a Phase III multicenter, multinational clinical study of a drug candidate for the treatment of metastatic breast cancer. | Cancer—Breast | Oct-10 |
| Cepheid (US) | Novartis (Switzerland) | Exclusive rights to the Xpert BCR-ABL assay, which monitors the BCR-ABL gene transcript in blood samples from patients with Philadelphia chromosome-positive chronic myelogenous leukemia. | Cancer—Leukemia | Oct-10 |
| Roche (Switzerland) | Astellas (OSI) (Japan) | Develop a companion test for Tarceva to identify EGFR-activating mutations in NSCLC patients. It may help expand Tarceva's indication to advanced NSCLC with EGFR-activating mutations. | Cancer—Lung | Nov-10 |
| Prometheus (US) | Bayer Schering (Germany) | Conduct mutational analyses to improve patient stratification in clinical studies. This agreement broadens an existing oncology-focused molecular and pathway activation profiling collaboration. | Cancer—Unspecified | Dec-10 |
| DiaGenic (Norway) | Pfizer (US) | Discover biomarkers for various stages of cognitive impairment up to Alzheimer's disease using DiaGenic gene expression technology. Pfizer gets diagnostics rights to guide drug R&D. | Neurology—Alzheimer's | Dec-10 |

Source: PwC research, using data from Windhover, IVD Technology, and company press releases

## Figure 12: Companion diagnostics partnerships with pharma during 2009

| Diagnostics Partner | Pharmaceutical Partner | Deal Subject | Disease Area | Deal Date |
|---|---|---|---|---|
| Dako (Denmark) | OSI Pharmaceuticals (US) | Develop a test based on the pharmDx kit line to identify patients most likely to react positively to specific OSI (acquired by Astellas in 2010) cancer treatments. | Cancer—Unspecified | Jan-09 |
| XDx (US) | Bristol-Myers Squibb (US) | Identify biomarkers to help BMS develop its Phase III immunoglobin fusion protein abatacept in combination with prednisone for systemic lupus erythematosus. | Autoimmune—Lupus | Jan-09 |
| MDxHealth (Belgium) | Merck KGaA (Germany) | Conduct testing to determine the MGMT gene promoter methylation status of patients with newly diagnosed brain tumours to select dosage of cilengitide in the CORE Phase II trial. | Cancer—Glioblastoma | Mar-09 |
| Almac Diagnostics (UK) | Pfizer (US) | Use the Colorectal Cancer DSA research tool to conduct gene expression profiling of samples from the PETACC 3 trial, to identify molecular subtypes, biomarkers, and drug targets. | Cancer—Colorectal | May-09 |
| Qiagen (DxS) (Netherlands) | Boehringer Ingelheim (Germany) | Adapt the TheraScreen EGFR mutation kit to develop a companion diagnostic for the NSCLC compound Tovok (inhibitor of HER2 and EGFR tyrosine kinases), to undergo a multicenter Phase III trial. | Cancer—Lung | May-09 |
| DiaGenic (Norway) | Merz Pharmaceuticals (Germany) | Option for rights to mild cognitive impairment biomarkers to help identify patients likely to develop Alzheimer's and to segment patients into different groups for clinical trials of drugs. | Neurology—Alzheimer's | Jun-09 |
| Celera (US) | Bayer (Germany) | Bayer licensed rights to 5 cancer-related drug targets. Celera will be able to develop companion diagnostics for therapeutics developed by Bayer under the deal. | Cancer—Unspecified | Jun-09 |
| Asuragen (US) | Biogen Idec (US) | Identify a test to select patients likely to respond to a Biogen Idec therapeutic candidate in clinical development for the treatment of cancer. | Cancer—Unspecified | Jul-09 |
| Enigma Diagnostics (UK) | GlaxoSmithKline (UK) | Develop and sell worldwide the POC diagnostic Enigma ML for certain influenza strains with a European launch planned for early 2011. | Infectious—Influenza | Jul-09 |
| Abbott Laboratories (US) | GlaxoSmithKline (UK) | Use the m2000 system to develop an automated PCR test to detect tumor-specific MAGE-A3 antigen in NSCLC patients to determine eligibility to the ASCI immunotherapeutic in Phase III. | Cancer—Lung | Jul-09 |
| Qiagen (DxS) (Netherlands) | AstraZeneca (UK) | Use the TheraScreen EGFR29 mutation kit to test the mutation status of NSCLC patients and determine eligibility for treatment with Iressa (gefitinib). | Cancer—Lung | Jul-09 |
| Dako (Denmark) | Roche (Switzerland) | Collaborate on US regulatory submissions for HercepTest and HER2 FISH pharmDx as companion diagnostics for Herceptin in patients with advanced HER2-positive stomach (gastric) cancer. | Cancer—Stomach | Aug-09 |
| Abbott Laboratories (US) | Pfizer (US) | Develop a diagnostic to detect gene rearrangements to help identify NSCLC patients eligible for Pfizer's PF2341066—an oral ALK inhibitor—in Phase I trials. | Cancer—Lung | Aug-09 |
| Qiagen (Netherlands) | Merck & Co (US) | Provide free HPV vaccination (Gardasil) and HPV DNA testing in selected developing countries to address the cervical cancer burden in an integrated way. | Cancer—Cervical | Sep-09 |
| Almac Diagnostics (UK) | Eli Lilly (US) | Use the Disease Specific Array (DSA) to determine potential predictive markers to develop a companion test for Lilly's Alimta (pemetrexed), marketed since 2004 for NSCLC. | Cancer—Lung | Sep-09 |
| Qiagen (DxS) (Netherlands) | Bristol-Myers Squibb & Lilly (ImClone) (US) | Develop a TheraScreen companion diagnostic for ImClone's metastatic colorectal cancer product Erbitux (cetuximab). The test will identify patients with certain KRAS mutations. | Cancer—Colorectal | Sep-09 |
| Orion Genomics (US) | Novartis (Switzerland) | Use MethylScope and MethylScreen genome-wide technologies to discover and validate epigenetic biomarkers for multiple cancers. Both parties have rights to develop and sell diagnostics. | Cancer—Unspecified | Oct-09 |
| bioMérieux (France) | GlaxoSmithKline (UK) | Develop a test to help clinicians select the most appropriate treatment for different segments of breast cancer patients. This test will target both adjuvant and metastatic breast cancer cases. | Cancer—Breast | Nov-09 |
| Rules Based Medicine (Psynova Neurotech) (US) | Roche (Switzerland) | Develop a companion immunoassay for a Roche neurology drug candidate using Psynova schizophrenia biomarker panels and CNS pathology data and RBM profiling technology. | Neurology—Unspecified | Dec-09 |

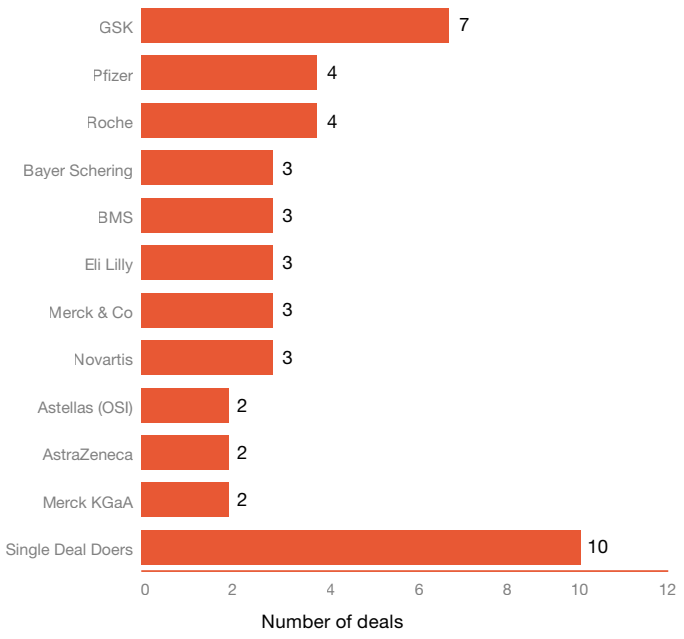
Source: PwC research, using data from Windhover, IVD Technology, and company press releases

# Pharma partners

## Large pharma multinationals lead IVD deal-making

GSK formed the most IVD partnerships of any pharmaceutical company during 2009–2010, with almost twice as many deals as the next most active pharma player, as shown in Figure 13.

Figure 13: Number of companion diagnostic deals by pharmaceutical partner 2009–2010




Source: PwC analysis, using data from Windhover, IVD Technology, and company press releases

Note: Two of the deals reported for 2009–2010 involved two rather than one pharma partner each—there was one such deal in 2009 and one in 2010. Consequently, the sum of the number of deals by each pharma partner (46) is equal to the total number of deals (44) plus two.

**GSK,** the most active pharmaceutical licensing partner for the IVD sector during 2009–2010, announced seven deals. This position represented a significant evolution for GSK, for which we identified no such collaboration during 2004–2008. Such a change was not unexpected, however, because the company had mentioned during 2009 that it was no longer advancing drug candidates into clinical trials without an associated biomarker or diagnostic development program. Of the seven diagnostics deals announced by GSK in the two-year period, six were for cancer; and the seventh focused on influenza.

**Pfizer** tied with Roche as the second most active pharma partner, with four reported deals during 2009–2010. The US company, already in a top-two position for 2004–2008 with six IVD partnerships, has increased its commitment to diagnostics partnerships by signing an average of two IVD collaborations per annum. The disease areas covered during 2009–2010 were cancer (lung, colorectal, and glioblastoma) and neurology (Alzheimer's).

**Roche Pharmaceuticals,** the other runner-up company during 2009–2010, announced four external IVD partnerships during the two-year period, covering stomach cancer, neurology, kidney disease, and brain cancer. This disease variety provides an illustration of the relevance of companion diagnostics beyond cancer.

Some might have expected a larger number of external diagnostics partnerships for Roche Pharmaceuticals during 2009-2010, consistent with the rising partnership momentum at Pfizer and GSK. During the five-year preceding period of 2004–2008, Roche Pharmaceuticals signed 10 external collaborations with the diagnostics sector (i.e., the same average of two collaborations per year as for 2009–2010), but dominated the partnership scene for 2004–2008. The runner up, Pfizer, reported only six deals during 2004–2008. With pharma's rising interest in companion diagnostics and Roche's well-publicised commitment to personalised medicine, some might have expected more activity from this company.

Far from representing a lack of enthusiasm or investment by Roche in combining its drug development programs with relevant diagnostics development initiatives, the status quo in external partnership activity may well point towards increased strength elsewhere within the Roche group.

CEO Severin Schwann recently confirmed that from 2007, Roche had implemented a system involving greater liaison between its pharma and diagnostics divisions. In particular, the company involves experts from Roche Diagnostics in key drug development meetings. Schwann said that such cross-disciplinary work aimed to explore how drug response could be improved—for example, by identifying certain mutations in a disease pathway that could be responsible for weakening a drug's efficacy in certain segments of a patient population.

Schwann mentioned that at least six new molecular entities were in late-stage development at Roche, where collaboration between the pharmaceutical and diagnostics business units had led to the development of a companion diagnostic that potentially would improve a drug candidate's response profile through better targeting of the drug's use. (Figure 14)

Roche's BRAF inhibitor development program aimed at treatment of metastatic melanoma is an example worth mentioning in this context. To complement the BRAF inhibitor work, the company's diagnostics business unit also is developing a diagnostic assay to help identify those patients most likely to benefit from the drug candidate.

By contrast, other pharmaceutical companies with BRAF inhibitor development programs have to turn to external partners if they want a related companion diagnostic program. For example, GSK is collaborating with bioMérieux in this field.

## Medium-sized and niche therapeutics players also take interest in companion diagnostics

In addition to Big Pharma, seven medium-sized or niche therapeutics players announced companion diagnostics partnerships for their drug development programs during 2009–2010: OSI Pharmaceuticals (since acquired by Astellas), Merck KGaA, Aeterna Zentaris, Biogen Idec, Clovis Oncology, Daiichi Sankyo (one of two pharma partners in collaboration with Accumetrics), Merz, Optherion and Transgene.

The most active dealmakers among these medium-sized and niche therapeutics players during 2009–2010 were OSI Pharmaceuticals and Merck KGaA:

- OSI Pharmaceuticals announced a lung cancer deal with Roche in 2010 and an unspecified cancer deal with Dako in 2009. OSI's interest in combining its drug candidates with a companion diagnostic is not new; in 2008, it announced a diagnostics partnership with Abbott for its lung cancer drug Tarceva, also marketed by Roche.
- Merck KGaA announced a colorectal cancer partnership with Almac Diagnostics in 2010 and a glioblastoma deal with MDxHealth in 2009. As the European marketer of Erbitux, one of the major targeted therapeutics that requires a companion diagnostic, it is natural for Merck KGaA to explore new opportunities to combine drugs and diagnostics.

# Diagnostics partners: Medium-sized or niche IVD players lead deals with pharma, but a few larger companies seal partnerships

Medium-sized or niche diagnostics players still drive the majority of IVD partnerships with pharma, but a small number of IVD majors have joined the ranks of the most active partners.

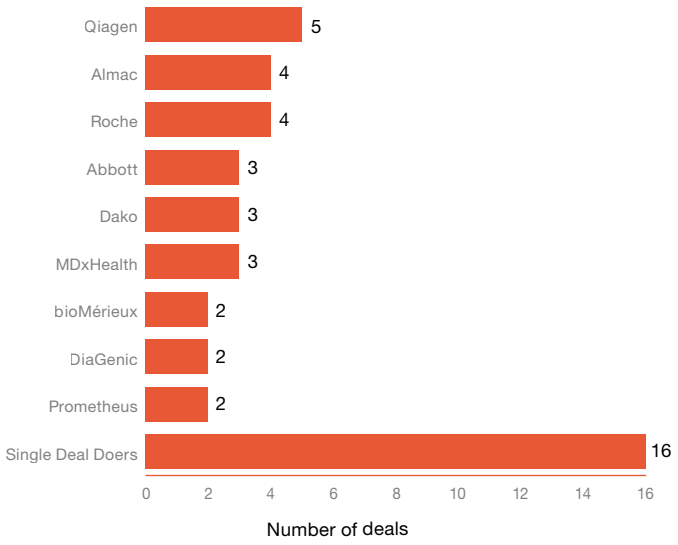
**Figure 14: Selected drug projects at Roche with an in-house companion diagnostic program**

| Drug Program (Phase II or III early 2011) | Indication | Diagnostic Marker |
|---|---|---|
| RG3638–MetMAb | Non-small-cell lung cancer | MET status |
| RG7204–BRAF Inhibitor | Metastatic melanoma | BRAF V600E mutation |
| RG3502–Trastuzumab-DM1 | Metastatic breast cancer | HER-2 expression level |
| RG1273–Pertuzumab | Metastatic breast cancer | HER-2/3 expression level |
| RG7128–Nucleoside Polymerase Inhibitor | Hepatitis C | HCV viral load, genotype |
| RG3637–Lebrikizumab/Anti-IL13 | Asthma | Periostin level |

Source: PwC analysis using publicly available information from Roche

During 2009–2010, the most active diagnostics companies involved in IVD partnerships with pharma were Qiagen, Almac, and Roche, with five, four, and four reported deals respectively. They were followed closely by a group of three companies announcing three partnerships each, including Abbott, Dako, and MDxHealth, as shown in Figure 15.

Figure 15: Number of companion diagnostics deals by diagnostics partner 2009–2010




Source: PwC analysis, using data from Windhover, IVD Technology, and company press releases

## The rise of IVD majors

For Roche and Abbott to appear on the list of top diagnostics partners for pharma represents a major change following the 2004–2008 period, when none of the top-nine IVD players were making multiple deals. In 2008, Abbott was the only IVD major announcing a companion diagnostics partnership with pharma.

Roche and Abbott were natural candidates to assume leadership positions in companion diagnostics deals because they have two of the largest molecular diagnostics businesses among the IVD majors as well as considerable expertise in tissue diagnostics. Both of these technologies are important components of current development work in companion diagnostics.

In this context, the acquisition of tissue diagnostics specialist Ventana Medical Systems provided Roche with critical competencies for some of the companion diagnostics deals it announced in 2010, including its partnerships with Transgene for lung cancer and Clovis for pancreatic cancer.

BioMérieux is another IVD major that has shown an interest in companion diagnostics through partnerships with pharma. The French company signed two collaborations with GSK during 2009–2010. In May 2010, it agreed to develop a test to guide treatment decisions in metastatic melanoma cases. This followed another deal with GSK, announced in November 2009, to develop a test to help characterise breast cancer cases into specific patient segments. BioMérieux is thus growing its cancer diagnostics franchise, which was boosted in 2008 following the $60 million acquisition of AviaraDx (since renamed bioTheranostics).

## Medium-sized and niche IVD players lead by numbers

The rise to prominence of some of the IVD majors does not mean they drive most of the companion diagnostics deal activity with pharma. Medium-sized and niche IVD players still are in the lead, involved in 35 out of 44 deals with pharma during 2009–2010, as shown in Figure 16. By contrast, the largest diagnostics companies announced only nine deals during that period. Smaller companies often prove more innovative and benefit from strong molecular diagnostics divisions.

The most active diagnostics partners among the niche IVD players were Qiagen, Almac, Dako, and MDxHealth. They drove 15 of the 35 deals announced by medium-sized and niche players during 2009–2010:

- **Qiagen:** This Netherlands-registered company has not broken into the ranks of the top IVD players yet but is growing fast. In 2010, it reported group revenues of $1.1 billion from its four business areas: life sciences, molecular diagnostics, applied testing, and pharmaceutical research and development. The company has been actively building a significant clinical diagnostics franchise, with personalised medicine as a core target. A key driver behind this specialisation was Qiagen's acquisition of DxS at the end of 2009.

  The five companion diagnostics partnerships mentioned for Qiagen for 2009–2010 include those driven by DxS before and after Qiagen acquired the company. These partnerships included a 2010 deal with Pfizer focused on glioblastoma, one of the cancers with the poorest survival prospects. In 2009, Qiagen announced three companion deals, focusing on major cancers, with AZ and Boehringer Ingelheim (lung cancer) and with BMS & Lilly (colorectal cancer).

- **Almac:** Since its founding in January 2002 by the late Sir Allen McClay, the Almac Group, based in Northern Ireland, has focused on providing services to the biotech and pharmaceuticals industry, including formulation development, clinical trial supplies, and commercial-scale manufacture.

**Figure 16: Number of companion diagnostics partnerships by type of IVD partner 2008–2010**

| IVD Players | 2008 | 2009 | 2010 | 2009–2010 |
|---|---|---|---|---|
| Top-nine | 1 | 3 | 6 | 9 |
| | **1** | **3** | **6** | **9** |
| Medium-sized & niche | | | | |
| DxS/Qiagen | 1 | 4 | 1 | 5 |
| Other | 5 | 12 | 18 | 30 |
| | **6** | **16** | **19** | **35** |
| **All segments** | **7** | **19** | **25** | **44** |

Source: PwC analysis, using data from Windhover, IVD Technology, and company press releases

In July 2009, the group opened a diagnostics division, Almac Diagnostics, to provide genomic-based solutions for the pharmaceuticals industry based on its proprietary Cancer DSA technology. During 2009–2010, Almac reported four IVD partnerships with pharma, including two colorectal cancer deals with Pfizer and Merck KGaA, one lung cancer deal with Lilly, and one partnership for ovarian and endometrial cancer with Aeterna Zentaris.

- **Dako:** This Danish private-equity-backed company is the only IVD player that reported multiple deals during 2004–2008. Dako emerged as one of the pioneers in the companion diagnostics field when it developed a test to help guide prescribing decisions for Herceptin, Roche's blockbuster breast cancer drug. Dako announced cancer-focused companion deals with OSI in 2009 and AZ in 2010. With revenues of approximately $340 million in 2009, Dako is not the smallest niche player.
- **MDxHealth:** This quoted Belgian molecular diagnostics company has been using its DNA methylation technology, licensed from Johns Hopkins University in Baltimore, to support a number of companion diagnostics programs at pharmaceutical companies. In particular, MDxHealth reported cancer diagnostics collaborations with Merck KGaA, Roche, and GSK during 2009–2010.

Eighteen medium-sized and niche IVD players completed an additional 20 deals. This diversity shows that innovation, which is pertinent to the development of companion diagnostics, is not limited to a select few. Pharma players will search beyond the most obvious players for potential diagnostic solutions.

Moreover, the relevance of molecular and tissue diagnostics to companion diagnostics may have favoured niche players. These target markets are still relatively small, when compared with some of the more established segments (e.g., clinical chemistry), and have relatively fewer barriers to entry. To date, these emerging market segments have been more attractive to small players than to large.

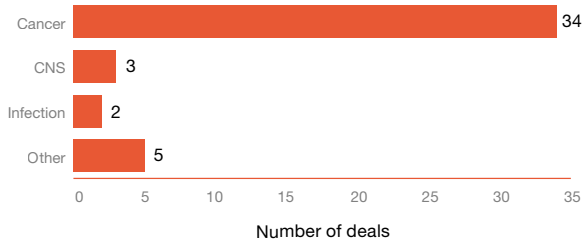
# Disease areas

## Cancer diagnostics drive deal activity, but other diseases emerge as targets

Cancer, the dominant 2009–2010 disease focus, was represented in 34 out of 44 companion diagnostics partnerships with pharma during 2009–2010, as shown in Figure 17.

Neurological, infectious, and other diseases made a small but noticeable appearance alongside cancer as the focus of IVD partnerships with pharma during this period, appearing in 10 out of 44 partnerships. The emergence of partnerships for these additional disease areas highlighted the need for better tools to target treatments for severe complex chronic diseases beyond cancer for which current therapies are not satisfactory in terms of efficacy or side effects.

Figure 17: Number of companion diagnostics partnerships by disease area 2009–2010




Source: PwC analysis, using data from Windhover, IVD Technology, and company press releases

The strong interest in cancer was driven by large patient populations, the large number of therapeutics targeting this disease area, and the high cost of certain cancer treatment regimens.

To compete and secure reimbursement in such an environment, it is essential to combine drugs with diagnostics. Faced with intense competition, many pharma players in the cancer market are signing deals with diagnostics partners to offer a more attractive therapeutic-diagnostic package that will help their drugs to compete more effectively.

Deals were signed for drugs already on the market as well as pharmaceuticals under development. Lung and other major cancers attracted significant interest, accounting for 12 out of 34 of the partnership deals focused on cancer during 2009–2010. The 22 remaining cancer deals were for unspecified forms of cancer or focused on cancers other than the four most common in the western world. In particular, brain cancer attracted three deals; and skin cancer, two.

### Cancer

- **Lung cancer:** Particular interest went to companion diagnostics partnerships for lung cancer, including five deals in 2009 and two in 2010. Lung cancer is the most common cancer worldwide, with 1.6 million new cases and 1.4 million deaths reported annually. The market for lung cancer therapeutics is large and competitive, involving several Big Pharma players as well as many smaller specialists. During 2009, the focus was on pharma majors, with companion diagnostics deals for lung cancer announced by Lilly, Pfizer, AZ, GSK and Boehringer Ingelheim. During 2010, deal-making shifted towards smaller specialists, with deals announced by OSI and Transgene:
  - **OSI:** This fast-growing emerging therapeutics player, based in the United States, had revenues of $428 million in 2009. The company shares the marketing rights for lung cancer drug Tarceva with Roche. OSI was acquired by Astellas in a $4 billion deal, completed in June 2010, a few months before the companion diagnostics partnership with Roche was announced in November 2010.
  - **Transgene:** This French company announced its companion diagnostics deal in September 2010, also with Roche. Transgene, listed on the Paris stock exchange, has strong financial backing from Institut Mérieux. In January 2011, the company added another diagnostics partnership for its lung cancer drug candidate TG4010, this time with IVD major Beckman Coulter. This deal provides an example of a therapeutics player collaborating with several diagnostics players to attempt to address several companion test needs of a single drug candidate.
- **Other major cancers:** Deals were announced for two other major cancers during 2009–2010: three deals for colorectal cancer and two for breast cancer.
- **Smaller cancers:** Interest in five less common cancers factored into nine deals announced during 2009–2010. Three deals were identified for brain cancer, two for skin cancer, and one deal each for four other cancers.
  - **Brain cancer:** Qiagen agreed to develop a real-time PCR companion diagnostic kit for a Phase II vaccine by Pfizer. MDxHealth reported collaborations with Merck KGaA in March 2009 and Roche in January 2010 around methylation-based markers to be tested during clinical trials of Erbitux and Avastin respectively.
  - **Skin cancer:** GSK announced two deals for companion diagnostics for skin cancer treatments under development—one with bioMérieux and the other with Abbott. The tests aim to detect mutations in the BRAF gene and support decisions regarding the eligibility of patients for GSK's BRAF or MEK inhibitors.
  - **Four other cancers:** One deal each was identified for leukaemia and cervical, gastric, and pancreatic cancers.
- **Unspecified cancers:** Thirteen additional deals were announced during 2009–2010 for unspecified cancers. This deal activity included collaborations focused on technology that could be relevant across several cancer types, as well as deals for specific but undisclosed cancers.

### Neurology

Three of the companion diagnostics partnerships with pharma announced during 2009–2010 focused on neurology, including two deals for Alzheimer's and one for an unspecified neurological condition.

- In December 2010, DiaGenic agreed to work with Pfizer to discover biomarkers for various stages of cognitive impairment leading up to Alzheimer's. DiaGenic technology will be used to assess longitudinal changes in gene expression patterns in patients. Pfizer will gain nonexclusive global rights to DiaGenic's diagnostics to guide therapeutic research and development.
- In December 2009, the UK company Psynova Neurotech agreed to help develop a companion immunoassay for one of Roche's neurology drug candidates. Psynova will use its schizophrenia biomarker panels and database of CNS pathology data. The US parent of Psynova, Rules-Based Medicine, will provide its multi-analyte profiling technology, DiscoveryMAP.

- In June 2009, DiaGenic granted Merz an option for rights to its mild cognitive impairment biomarkers. Merz will use these biomarkers to identify patients likely to develop Alzheimer's and segment them into groups for clinical trials of relevant drug programs.

Interest is growing in better diagnostic tools for Alzheimer's to support research into earlier detection and treatment of the disease as well as monitoring of its progression and patient responses to different therapies.

Because the prevalence of this disease is forecasted to expand during coming decades, we expect heightened interest in Alzheimer's and other neurological conditions to continue. A report issued in 2009 by the not-for-profit organisation Alzheimer's Disease International predicted the number of people with Alzheimer's and other dementias would exceed 35 million in 2010 and almost double every 20 years to 66 million in 2030 and 115 million in 2050.

### Infectious diseases

Two deals focused on infectious diseases during 2009–2010:

- In July 2009, Enigma Diagnostics agreed to work with GSK to develop a point-of-care diagnostic for certain influenza strains.
- In July 2010, LabCorp needed to access certain intellectual property rights from Merck & Co to commercialise a genetic test to detect certain polymorphisms in hepatitis C patients and predict their response to peg-interferon alpha therapy.

### Other disease areas

The remaining companion diagnostics partnerships with pharma during 2009–2010 involved one deal each for five other disease areas:

- **Autoimmune disorders:** One partnership, reported in January 2009, was for systemic lupus erythematosus (SLE or lupus).
- **Cardiovascular disease:** One deal, reported in July 2010, focused on the measurement of patient response to anti-platelet medication.
- **Metabolic disorders:** One partnership, announced in March 2010, focused on diabetes.
- **Ophthalmology:** One deal, reported in February 2010, focused on age-related macular degeneration (AMD).
- **Kidney disease:** One partnership, confirmed in January 2010, was for a test to detect kidney injury and disease.

# Outlook

## Success stories on the pharma horizon

Pharma's appetite for companion diagnostics will remain strong because the drivers discussed above—regulatory pressure for improved drug performance and payer pressure for more effective budget allocation—will continue and intensify over the next few years.

In addition, we expect the above "sticks" to be complemented by some "carrots" to provide further incentive for pharma to invest in companion diagnostics. A significant carrot may come in the form of economic success stories. Indeed, much has been said about the prospect of lower economic returns for the pharmaceuticals industry from the emergence of personalised medicine and its focus on smaller target markets. However, analysts are forecasting blockbuster-level revenues for certain therapeutics under co-development with a companion diagnostic.

One example is Pfizer's Xalkori (crizotinib), the oral ALK inhibitor previously referred to as PF 2341066 and that was developed for non-small-cell lung-cancer patients with the ALK mutation. Following recent clinical study findings reported at the American Society of Clinical Oncology in June 2011, analysts at Crédit Suisse have increased their forecasts of crizotinib sales from $600 million to $1 billion for 2015 and predict that sales will reach a peak of $1.5 billion by 2020. The target population for crizotinib of only about 4% to 5% of lung-cancer patients represents a global treatment-eligible population of approximately 54,000 patients. However, the strong expected prospects follow from a clinical study reporting target-lesion shrinkage in 83% of ALK-positive patients. Crizotinib and its companion diagnostic, developed by Abbott, were approved by the FDA in August 2011.

## From blockbusters to niche-busters:

Although pharma may have to give up on the mass-market model, which has produced so many blockbusters (exceeding $1 billion in sales), companion diagnostics may usher in an era of niche-busters. Analysts are forecasting sales topping the blockbuster mark for some of the new drugs paired with a diagnostic, despite their limited target populations.

## Preliminary 2011 highlights

The year 2011 started in promising fashion, with the 15 deals identified in Figure 18 from a preliminary review of companion diagnostics partnerships with pharma during the first half of the year. Key highlights from this deal activity included:

- **Big Pharma still accounts for a majority of deals but smaller specialists are closing the gap—**We note that smaller specialists are catching up with seven out of 15 deals coming from medium-sized or niche therapeutics players, including ARIAD, Astellas, BioMarin, Celgene, Clovis, Ipsen, and Transgene. Interestingly, among the Big Pharma partners, we see the presence of parties not frequently involved in companion diagnostics partnerships in the past, including Takeda and Johnson & Johnson.
- **Several newcomers to the companion diagnostics deal scene have emerged among niche IVD specialists—**Among the IVD majors, Roche is keeping a strong momentum, bioMérieux is present as in 2009–2010, but Beckman Coulter made a rare appearance. Among the niche IVD specialists, we note the emergence of several newcomers, including Biocartis, Cell Signaling Technology, Foundation Medicine, Invivoscribe, MolecularMD, Opko Health, and Zinfandel. This provides further illustration of the wide range of originators in the companion diagnostics field.
- **Neurology is confirmed as an important focus area alongside dominant cancer—**The majority of partnerships are for cancer; but the presence of several neurology deals, consistent with 2009–2010, could suggest this disease area is becoming another important application area for personalised medicine.

**Figure 18: Selected companion diagnostics partnerships with pharma during first half of 2011**

| Diagnostics Partner | Pharmaceutical Partner | Deal Subject | Disease Area | Deal Date |
|---|---|---|---|---|
| Foundation Medicine (US) | Novartis (Switzerland) | Develop, enhance and optimise a cancer genome panel test for Novartis' needs. If the pilot is successful, the parties will consider collaboration on the production and commercialisation of the test. | Cancer—Unspecified | Jan-11 |
| Beckman Coulter (US) | Transgene (France) | Develop a test to measure the level of activated Natural Killer (aNK) to select patients to be treated with TG4010, an MVA-MUC1-IL2 immunotherapy entering pivotal Phase IIb/III trials for NSCLC. | Cancer—Lung | Jan-11 |
| Zinfandel (US) | Takeda (Japan) | Study diabetes drug Actos as an Alzheimer's prevention treatment using Zinfandel's TOMM40 test to assess which older adults at high risk of disease onset to enroll in clinical trials. | Neurology—Alzheimer | Jan-11 |
| MDxHealth (Belgium) | Pfizer (US) | Identify and develop a biomarker predicting response to PF-01367338, a PARP-inhibitor for ovarian and breast cancer. Newcastle Univ. and Cancer Research Techn. are partners also. | Cancer—Ovarian and other | Jan-11 |
| Opko Health (US) | Bristol-Myers Squibb (US) | Investigate the utility of OPKO's blood-based technology to identify individuals with early-stage cognitive impairment that are likely to progress to Alzheimer's disease. | Neurology—Alzheimer | Jan-11 |
| Biocartis (Switzerland) | Johnson & Johnson (US) | Janssen Pharmaceutica to co-develop and commercialise assays on the Biocartis molecular diagnostics platform in the fields of neurological disease and certain viral infectious diseases. | Neurology—Unspecified | Jan-11 |
| Cell Signaling Technology (US) | Astellas (Japan) | Pool IP relating to the fusion kinase EML4-ALK to enable the development of diagnostics and therapeutics targeting this cancer enzyme. | Cancer—Unspecified | Feb-11 |
| bioMérieux (France) | Ipsen (France) | Identify programs for Rx-Dx co-development focused on hormone-dependent cancers, initially for prevention and treatment of prostate, breast, and neuro-endocrine and pituitary tumours. | Cancer—Prostate and other | Feb-11 |

## The impact of changing business models by 2020

By 2020, we anticipate that drug-diagnostic co-development will have become routine for drugs for which the use of biomarkers is relevant, and most leading pharmaceutical companies will have changed their business model to incorporate significant diagnostics capabilities in-house—through acquisition or otherwise.

If this scenario is confirmed, by 2020 we expect a slowdown in the growth of Rx-Dx deal activity because more pharmaceutical companies will seek companion diagnostics solutions in house. However, even in this scenario, pharma's volume of external diagnostics alliances is expected to remain high.

Government agencies involved in the pricing and reimbursement of diagnostics have an important role to play to improve the economics of innovation at emerging companies. Provided the current challenges to the economics of diagnostics are addressed, we expect innovation to continue in smaller companies, research institutes, and academia, thus attracting continued interest in partnerships from pharma.

**2020**
**Pharma's volume of external diagnostics alliances is expected to remain high**

**Figure 18: (continued)**

| Diagnostics Partner | Pharmaceutical Partner | Deal Subject | Disease Area | Deal Date |
|---|---|---|---|---|
| Invivoscribe (US) | Novartis (Switzerland) | Develop and commercialise a test to identify FLT3 positive acute myeloid leukemia patients for use with midostaurin (PKC412), in Phase III for newly diagnosed patients with FLT3 mutated AML. | Cancer—Leukemia | Feb-11 |
| MolecularMD (US) | ARIAD Pharmaceuticals (US) | Develop a test to identify the T315I mutation in CML patients and Philadelphia-positive ALL patients. ARIAD's pan-BCR-ABL inhibitor, ponatinib, is in trials for patients with resistant or intolerant CML and Ph+ ALL, or those with the T315I mutation. | Cancer—Leukemia | Mar-11 |
| Myriad Genetics (US) | BioMarin Pharma (US) | Conduct BRCA1 and BRCA2 mutation testing on patients to be enrolled in a Phase I/II study of the PARP-inhibitor BMN 673 for patients with advanced or recurrent tumours. | Cancer—Unspecified | Apr-11 |
| Agendia (Netherlands) | AstraZeneca (UK) | Assist AZ in defining sub-populations within CRC, to provide the basis for discovery of novel targeted medicines. The Netherlands cancer institute (NKI) is also a partner. | Cancer—Colorectal | May-11 |
| Foundation Medicine (US) | Celgene (US) | Develop a cancer genomics test to recruit patients suitable for Celgene drug candidate trials. The test will use next-generation sequencing to analyse more than 200 cancer-related genes. | Cancer—Unspecified | May-11 |
| Roche (Switzerland) | Merck & Co (US) | Develop assays for use with Merck & Co's investigational cancer therapy portfolio and expand use of the AmpliChip p53 assay to select and stratify patients for Merck's cancer clinical trials. | Cancer—Unspecified | Jun-11 |
| Roche (Switzerland) | Clovis Oncology (US) | Develop a PCR-based companion test for CO-1686, which is in preclinical development for advanced NSCLC, to identify activating EGFR mutations, including the EGFR T790M mutation. | Cancer—Lung | Jun-11 |

Source: PwC research, using data from Windhover, IVD Technology, and company press releases

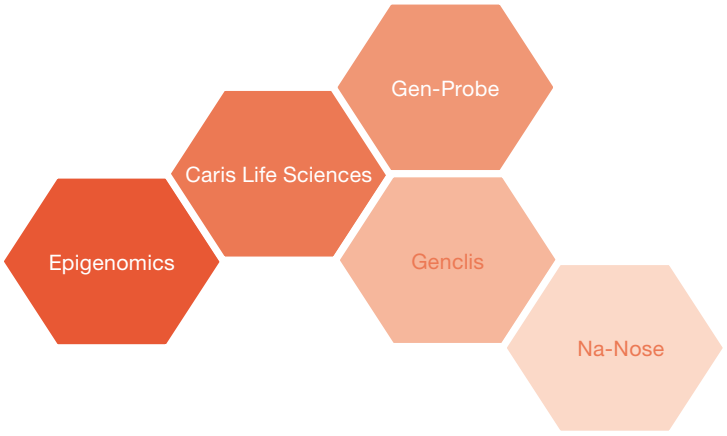
*"For me the biggest payoff in cancer research would be the discovery of biomarkers that can be measured in the blood that reflect the presence of early-stage cancer. For nearly all cancers, early detection means cure by standard treatments of surgery and radiation."*

—Dr. Leland H. Hartwell, March 2006
President, Fred Hutchinson Cancer Research Center
Nobel Prize in Medicine and Physiology, 2001

Key findings

# III. Early detection provides new prospects for improved outcomes

1. Innovation in *in vitro* diagnostics-based technology for early detection of cancer has produced a significant pipeline of new tests in recent years.
2. We focused on the four most common cancers in the Western world—lung, breast, colon, and prostate cancer—and found that for these cancers, several tests have come to market during the past two years, and others are nearing commercialisation.
3. We identified at least 23 such tests; and some of these may vie for a central role alongside the *in vivo* procedures, which currently dominate standard practice.
4. Players at the forefront of the emerging wave of innovation include:




Epigenomics: The first mover in the European colon cancer market

Caris Life Sciences: A challenger for prostate cancer with blood-based technology

Gen-Probe: A challenger for prostate cancer with urine-based technology

Genclis: A potential imminent market disrupter for breast cancer

Na-Nose: An emerging pioneer with technology for lung cancer based on exhaled breath

5. The next few years to 2015 could mark an important validation period for the concept of IVD-based early detection. Strong market adoption will be driven by the benefits of noninvasiveness and high sensitivity and specificity. These benefits will have to be complemented by favourable health economics to achieve favourable reimbursement terms.
6. Small, emerging diagnostics companies dominate the origination of IVD-based technology for early detection of cancer. However, larger companies have an important role to play for commercialisation because some of these tests could generate blockbuster revenues—provided preliminary data on performance is confirmed with robust prospective studies.
7. If a number of IVD-based early-detection tests achieve strong market adoption by 2015, we expect pharma players to take an increasing interest, with many choosing to become commercial partners for such products by 2020.

# Tests for early detection have not created many headlines in recent years. Could this change soon?

Diagnostics for screening (i.e., tests for early detection of disease) have attracted much less media attention than companion diagnostics in recent years, but research on the former has continued and is beginning to produce results. Several new *in vitro* diagnostics for early detection of cancer reached the market during the last two years, and several more are moving towards commercialisation.

Examples of recently developed tests for early detection of cancer:

- **DiaGenic's BCtect** test for **breast cancer** was cleared for European marketing in June 2009.
- **Epigenomics' Epi proColon** diagnostic for **colon cancer** was cleared for marketing in Europe in October 2009.
- **Oncimmune's EarlyCDT** test for **lung cancer** has been available in the United States since June 2010 under the Clinical Laboratory Improvement Amendments (CLIA) regime for laboratory-developed tests (LDTs).

The merits of these specific examples are unproven, but product candidates continue to multiply, which increases the likelihood of finding a breakthrough.

Key commercial success factors for these new tests will include their sensitivity and specificity, which need to be high, and their health economic profile, which needs to support favourable reimbursement decisions by leading health insurance systems.

In this section, we discuss the importance, challenges, and opportunities of early-detection testing for the four major cancers of the Western world. For this discussion, we use the concept of early detection rather than screening because it is broader, allowing for a narrower positioning of the test, as explained in the sidebar "Screening vs. early-detection testing."

## Sensitivity and specificity

The two key concepts to describe a test's performance are its sensitivity and specificity:

- **Sensitivity** measures the proportion of ill people that the test identifies correctly as having a given condition. For example, if a test has a sensitivity of 70%, it successfully detects 70% of those people who are indeed ill and fails to detect the disease in the other 30% of existing cases.
- **Specificity** measures the proportion of healthy people that the test correctly identifies as not having a given condition. For example, if a test has a specificity of 70%, then 70% of those who test positive actually have the condition, while the other 30% are false positives (i.e., they test positive but do not have the condition).

## Screening vs. early-detection testing

Screening and early-detection testing both refer to systematic testing of an asymptomatic target population with the goal of detecting a disease at an early stage of development when treatment opportunities are more favourable. However, in some countries (for example, France), health authorities draw a distinction between these two terms as follows:

- **Screening** involves testing of a target population that is as wide as possible.
- **Early-detection** testing involves testing of a target population that could be narrower.

Two factors could drive the rationale for choosing a narrower target population:

- **The performance of the test to be used:** The level of specificity could be too low, leading to the potential referral of too many healthy individuals—the false positive cases—to unnecessary invasive follow-up procedures.
- **The level of prevalence:** If the prevalence of a disease in the overall population is very low, for example 1/1,000, and the cost of the test too significant, then it may not appear economical to introduce systematic testing of this population.

The combined effect of these two factors could make the health economic case for screening too weak. However, there could be a case for systematic testing of a subpopulation where the level of prevalence of the disease is higher because this may compensate for the high cost and low specificity of the test.

If a certain subpopulation has common characteristics that significantly increase the likelihood of developing a condition—for example, age and a history of cancer among close relatives—it may be worth considering systematic early-detection testing of that higher-risk subpopulation.

## In principle, the case for early detection should be straightforward

Early detection of cancer is critical because it may improve prognoses. Typically, more treatment options are available when disease is found in the early stages; and for most cancers, the prospects for medium-term survival improve with early detection.

Figure 19 shows survival data for the four most common cancers in the United States. The five-year survival rate for each improves by at least four times when the cancer is detected early and still localised, compared with detection after the cancer has spread. The most dramatic improvement, for early detection of prostate cancer, increases the five-year survival rate by a multiple of 31, from 3% to 100%.

In principle, the case for early-detection testing should be clear-cut, if we consider the clear improvement in survival prospects that follows early detection. Nevertheless, actual detection is one thing; the quality and cost of the testing procedure to achieve early detection is quite another.

## In practice, issues with screening standards have created scepticism

A review of current standards of screening for the four most prevalent cancers in the Western world suggests there is significant room for improvement in addressing the challenges of early detection. The main issues with current screening tests are:

- **Low sensitivity:** Screening misses too many cases when sensitivity is low. For example, the sensitivity of mammography screening for breast cancer is age-dependent: the younger the patient, the more difficult it is to detect breast cancer with accuracy and objectivity using this screening tool.
- **Low specificity:** Too many false positives are produced when a test has low specificity, which leads to increased side-effect risks from unnecessary follow-up procedures. For example, people that test positive with the PSA test for prostate cancer screening are typically referred for biopsy. Those that are false positives represent a large proportion and thus will undergo unpleasant, invasive procedures although they do not actually have prostate cancer. Low specificity is an issue also with computed tomography (CT) scans for lung cancer detection.
- **Discomfort:** Invasiveness may create discomfort, as reported for colonoscopy, and this can lead to low compliance. People hesitate to come forward for the procedure although they qualify for it.
- **Radioactive exposure:** Increased side-effect risks can follow from recurrent use of screening procedures involving radioactive exposure. For example, many women are concerned about the risk of radiation-induced mutations, which may follow from regular use of mammography for breast cancer screening.

**Figure 19: Improvement in survival rates with early detection: the four most common cancers in the United States**

| Cancer | Incidence | | Mortality | | 5-Year Survival Rates by Stage | | Survival Improvement |
|---|---|---|---|---|---|---|---|
| | People | Rank | People | Rank | Localised | Distant | Localised/Distant |
| Lung | 215,021 | 1 | 161,841 | 1 | 53% | 4% | 15x |
| Prostate | 186,320 | 2 | 28,660 | 5 | 100% | 3% | 31x |
| Breast | 182,460 | 3 | 40,481 | 3 | 98% | 23% | 4x |
| Colorectal | 153,881 | 4 | 50,640 | 2 | 90% | 12% | 8x |
| | **737,682** | | **281,622** | | | | |
| **All cancers (1)** | **1,437,199** | | **565,644** | | | | |

Note: (1) The incidence and mortality figures for all cancers exclude nonmelanoma skin cancers.

Source: Analysis by PwC; survival rates from US National Cancer Institute; incidence and mortality data from GLOBOCAN 2008 (IARC), Section of Cancer Information (27/8/2010), IARC, 150 Cours Albert Thomas, 69372 Lyon CEDEX 08, France—Tel: +33 (0)4 72 73 84 85—Fax: +33 (0)4 72 73 85 75. © IARC 2010—All Rights Reserved—Email: www@iarc.fr

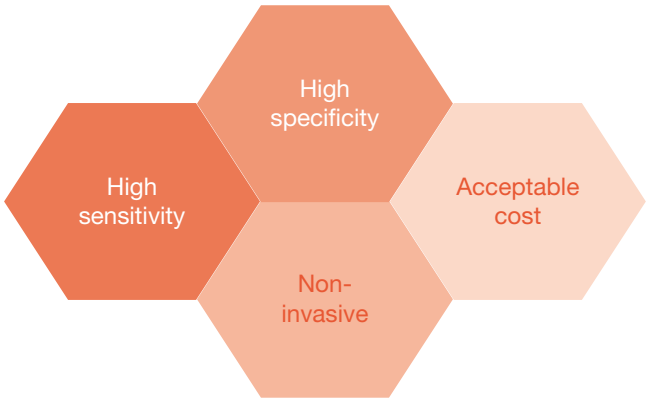
- **High cost:** Procedures that are too costly are inappropriate for frequent, systematic use among a wide asymptomatic target population. For example, colonoscopy to detect colorectal cancer and MRI scans to detect breast cancer have appropriate levels of accuracy. However, the high cost of these procedures means that cheaper alternative procedures are needed for more frequent screening. Unfortunately, these alternatives (the faecal occult blood test for colorectal cancer and mammography for breast cancer) may not have the same level of sensitivity or specificity.

The clinical community welcomes any new test for early detection of cancer with a degree of scepticism because it has experienced the significant issues associated with low-performance screening options. To be clear, tests that are not sufficiently sensitive and specific may be at odds with the principle of *primum non nocere*—first do no harm.

To achieve a breakthrough in clinical practice, a new test for early detection of cancer will need to have impeccable performance levels, backed up by robust clinical data. It will also need to be noninvasive, to minimise side effects and compliance issues, and be available at a reasonable cost. Figure 20 profiles an ideal test for early detection.

Defining acceptable absolute levels for these four attributes is beyond the scope of this discussion, but these criteria do provide a practical framework to assess the fitness of a test for early detection.

**Figure 20: Profile of an ideal test for early detection**




Source: PwC analysis following discussion with industry contacts

## The emergence of a wave of new IVD tests creates an opportunity to revisit early detection

IVD tests have not made significant inroads in replacing current standards of early detection for the four major cancers. With the main exception of the PSA test for prostate cancer, *in vivo* procedures dominate the space.

Could this dominance change soon? We identified at least 23 new IVD tests launched recently or in development for early detection of one of the four most common cancers in the Western world, as shown in Figure 21. And the preliminary performance data of some of these new IVD tests does raise the prospect of a new *in vitro* test becoming a systematic complement to some of the existing *in vivo* procedures.

**Players at the forefront of this new wave of emerging IVD tests for early detection of cancer include:**

1. The first mover in the European colon cancer market: Epigenomics—Epigenomics, which stands out as the first mover in the colon cancer market, also has brought a lung cancer test to market.

   The company is effectively playing a market-making role in Europe for the use of its blood-based IVD for early detection of colon cancer, its Epi proColon test launched in Europe in October 2009. The company also plans to submit a dossier in 2011 to seek FDA clearance to market the test in the United States. Other companies may soon challenge Epigenomics in the colon cancer early-detection field:

- Diagnoplex, which may submit a CE mark dossier by the end of 2011
- Signature Diagnostics, which expects to enter the German market in 2011
- Exact Sciences, which plans to submit a dossier with the FDA in 2012

## Figure 21: Selected tests for early detection of lung, breast, colon, and prostate cancer

| Originator | Test | Medium Type | Sensitivity | Specificity | Marketing Clearance |
|---|---|---|---|---|---|
| **Lung** | | | | | |
| 20/20 GeneSystems (US) | Lung: PAULA NSCLC test | Blood | 83% | 88% | 2011E (CLIA) |
| BioSystems International (France) | Lung: Blood-based test | Blood | 80% | 80% | 2011E (CE) |
| Celera (US) | Lung: Blood-based test | Blood | 92% | 93% | 2012E |
| Epigenomics (Germany) | Lung: Epi proLung | Bronchial lavage | 81% | 95% | Jul '10 (CE) |
| Genclis (France) | Lung: Blood-based immunoassay | Blood | 91% | 98% | 2011E (CE) |
| Na-Nose (Israel) | Lung: Lung cancer breath analyser | Exhaled Breath | 85%–89% | 87%–88% | 2014–2015E |
| Oncimmune (UK) | Lung: EarlyCDT-Lung | Blood | 40% | 90% | May '09 (CLIA)<br>2011E (CE) |
| SomaLogic (US) | Lung: Aptamer proteomic assay | Blood | 89% | 83% | NA |
| **Breast** | | | | | |
| BioCurex (US) | Breast: Serum-RECAF | Blood | 67%–90% | 85% | 2012E (FDA) |
| Diagenic (Norway) | Breast: BCtect | Blood | 72% | 73% | Jun '09 (CE) |
| Genclis (France) | Breast: Blood-based immunoassay | Blood | 95% | 97% | 2011E (CE) |
| Technion (Israel) | Breast: Breast cancer breath analyser | Exhaled Breath | 89% | 91% | 2014–2015E |
| **Colon** | | | | | |
| Diagnoplex (Switzerland) | Colon: COLOX | Blood | 70% | 93% | 2011E (CE) |
| Epigenomics (Germany) | Colon: Epi proColon | Blood | 70% | 90% | Oct '09 (CE)<br>2012E (FDA) |
| Exact Sciences (US) | Colon: Stool-based DNA test | Stool | 85% | 88% | 2013E (FDA) |
| GeneNews (Canada) | Colon: ColonSentry | Blood | 72% | 70% | 2008 (Canada)<br>2011E (US) |
| Signature Diagnostics (Germany) | Colon: Detector C | Blood | 90% | 88% | 2011E (LDT) |
| Technion (Israel) | Colon: Colon cancer breath analyser | Exhaled Breath | 79% | 83% | 2014–2015E |

Figure 21 continues on next page

| Originator | Test | Medium Type | Sensitivity | Specificity | Marketing Clearance |
|---|---|---|---|---|---|
| **Prostate** | | | | | |
| BioCurex (US) | Prostate: Serum-RECAF | Blood | 75% | 85% | 2012E (FDA) |
| Caris Life Sciences (US) | Prostate: Carisome Prostate cMV 1.0 | Blood | 85% | 86% | 2009 (CLIA) |
| Diagnocure (Canada) | Prostate: PROGENSA PCA3 assay | Urine | 58% | 72% | Nov '06 (CE) 2011E (FDA) |
| Epigenomics (Germany) | Prostate: Urine-based test | Urine | 74% | 96% | NA |
| ProteoSys (Germany) | Prostate: ANXA 3 test | Urine | 50% | 87% | 2012E (CE) |

Source: PwC research, using company press releases and discussion with industry contacts

Notes: ED = early detection; Dev = an estimated marketing clearance date was not available; 20YYE = estimated marketing clearance year; MMM YY = month and year that marketing clearance was obtained; CE = Certification Européenne (European marketing clearance); CLIA = US marketing clearance under CLIA regime for LDTs; FDA = US marketing approval or clearance under an FDA regime for IVD kits; LDT = laboratory-developed test.

The role of Epigenomics in the lung cancer market is less clear because the company's Epi proLung test for early detection of lung cancer involves bronchial lavage, making it more invasive than blood-based testing. However, the test does offer an important option because of its high level of specificity (95%). Epi proLung gained the CE mark in July 2010.

2. Two challengers in the prostate cancer arena: Caris and Gen-Probe—These companies lead the pack of challengers to complement the widely used PSA test for prostate cancer detection. Both companies have developed prostate cancer tests that have been cleared for marketing.

2a. Caris: This company has positioned its blood-based test, Carisome Prostate cMV 1.0, as a follow-up procedure for use when PSA test results are positive. The test has been marketed in the United States under the CLIA regime since 2010. Caris will pursue a CE mark to gain access to the European market.

2b. Gen-Probe: This company developed a urine-based test for prostate cancer, the PROGENSA PCA3 assay, which it licensed from Diagnocure. The technology originated at the University of Nijmegen Netherlands, but the university licensed relevant intellectual property rights to Diagnocure. Similar to the Caris test, this assay is positioned as a follow-up to positive PSA test results. Gen-Probe obtained marketing clearance for the test in Europe in 2006 and submitted an application for marketing clearance with the FDA in September 2010.

The dynamics of product adoption in the early-detection market for prostate cancer will be interesting to follow during the next few years for three reasons: First, the Caris and Gen-Probe tests are not directly comparable because one is a blood-based immunoassay, while the other is a urine-based test measuring DNA expression. Second, more competition could come from other companies, including one of the top-nine IVD players, bioMérieux, with its ANXA 3 test, originated by ProteoSys. Third, while the Caris, Diagnocure, and ProteoSys tests are positioned as complements to the PSA test, a fourth player, Epigenomics, has stated an ambition to replace the PSA test as the main first-line procedure. The feasibility of this ambition will depend on additional R&D to achieve the high levels of sensitivity and specificity required to dislodge such a strongly entrenched test.

3. A potential imminent market disrupter: Genclis—In 2007, Genclis reported its discovery of transcription infidelity (TI), a mechanism by which several distinct RNA molecules are produced from a single DNA sequence. The company discovered that these TI-induced variations in RNA are introduced nonrandomly, are present in healthy cells, but increase in cancer cells. TI thus may represent a major shift in our understanding of molecular biology because it implies that RNA transcription rules other than the canonical rules are at work with increased intensity in cancer. The mRNA resulting from TI will encode proteins different from those that would be expected from the starting DNA under canonical rules.

Based on its discovery, Genclis is developing blood-based tests for early detection of breast and lung cancer using TI proteins as biomarkers for the presence of cancer. Retrospective clinical proof-of-principle studies reported high sensitivity and specificity for the tests—95% and 97%, respectively, for the breast cancer test and 91% and 98%, respectively, for the lung cancer test. If ongoing prospective studies confirm these performance levels, Genclis could have a disruptive influence in the breast and lung cancer early-detection space. The company plans to submit dossiers for European marketing clearance for both cancers by the end of 2011.

4. An emerging pioneer: Na-Nose—Professor Hossam Haick of the Technion-Israel Institute of Technology in Haifa leads a program to develop a noninvasive nanoarray technology for detection of volatile organic compounds from exhaled breath as biomarkers of lung cancer. A separate company called Na-Nose was set up to continue the development of relevant intellectual property with Professor Haick as chief scientific officer. Breast and colon cancer programs are also under way, but these are still driven from within Technion.

   The technology is based on the premise that gene and/or protein changes associated with tumour growth may lead to per-oxidation of cell membrane species and emission of volatile organic compounds. The nanoarray technology was shown to be 85%–89% sensitive and 87%–88% specific in a retrospective study of approximately 180 lung cancer patients and approximately 200 controls.

   This novel procedure is still at an early stage of development. Professor Haick plans further research to improve the performance of the test and to provide further clinical validation. Marketing clearance is expected in 2014 or 2015.

## The performance of new IVD tests needs to be confirmed

In coming years, we expect to see additional data for most of the tests mentioned in Figure 21, including data from prospective clinical studies, new biomarkers, and larger-scale clinical studies:

- **Prospective clinical studies:** The performance data for many of the tests highlighted in Figure 21 are based on retrospective studies, which provide a clinical proof of principle. Most of the companies developing these tests will complement the data with prospective studies to provide stronger evidence of test performance.
- **New marker panels:** Some companies may change the combination of markers used for a given test to improve its performance profile. For example, in the colorectal cancer space, Exact Sciences plans to add DNA methylation markers, which it licensed from MDxHealth (formerly OncoMethylome Sciences), to the existing panel of markers used in its stool-based DNA test. The company plans additional clinical studies using the extended panel of markers.
- **Larger-scale studies:** For many tests, clinical studies will continue following marketing clearance. The objective will be to produce further evidence of test performance to support clinical adoption and seek reimbursement from payer organisations.

Strong performance, validated by robust data, will be critical to obtaining reimbursement and gaining a pivotal role alongside the current standard of care. Replacing current practice altogether may take some time. Certainly, it will take a special test in terms of performance, noninvasiveness, and cost. For such a special test, blockbuster revenues may well follow.

## IVD tests for early detection could generate blockbuster revenues

Some players have estimated that the products leading the new wave of early-detection tests could achieve revenues equivalent to those of pharmaceuticals industry blockbusters. For instance, in the colorectal cancer market, Epigenomics has estimated the addressable market for molecular diagnostics for early detection of colorectal cancer at $3.75 billion per year. This estimate encompasses the US, EU, and Japanese markets, and it assumes a targeted at-risk population of individuals in those markets who are at least 50 years old (assumed at 300 million people); a testing frequency of once every other year; a 50% compliance rate; and a $100 test price for the payer, with the revenue shared equally between laboratories and manufacturers.

Even if this market for early detection of colorectal cancer were shared among two to four significant tests, the potential exists for one or two $1 billion products to emerge.

In the lung and breast cancer markets, a similar scale of revenues can be expected because of the size of the target at-risk populations, provided the proposed tests deliver a high enough level of performance.

In the prostate cancer market, the PSA test already generates $1.25 billion in worldwide revenues annually despite the ongoing controversy over its level of specificity. This financial success illustrates that it is possible for an IVD test for early detection of a major cancer to achieve blockbuster status.

The first challenge for a new test to realise this revenue potential will be to gain strong support from the clinical community. Demonstrating a near-ideal profile in terms of sensitivity, specificity, noninvasiveness, and reasonable cost will provide a strong basis to achieve this. The next challenge will be to demonstrate strong health economics to gain favourable reimbursement terms.

## Health economics will be a key driver to achieve reimbursement and market adoption

The main costs and benefits driving the health economic case for systematic early-detection testing are summarised in the diagram on Figure 22 and include:

- The cost of the early-detection testing.
- The cost of any follow-up procedures to confirm the diagnosis. This will arise for people that test positive.
- The benefit of lower expected treatment costs following a shift in the distribution of the diagnosed patient population toward earlier stages of diseases. The time needed for such a shift to take place in a given country will depend on the scope and implementation of the program for early-detection testing.
- The benefit of increased wealth creation and fiscal income as more people resume economic activity following treatment.

How much of the economic benefits payers will take into account when making decisions about reimbursement terms remains to be seen. However, the clinical benefits seem clear enough for those tests that can demonstrate high sensitivity and specificity and are noninvasive. In this context, companies developing early-detection tests with strong profiles are hopeful of eventually obtaining favourable reimbursement terms.

## A narrow positioning of the test may accelerate market access

The strategy chosen by emerging companies for their initial market access will be a key factor for corporate survival because of the time it can take to get reimbursement for new diagnostics. In many Western countries, it can take four to seven years following marketing clearance to get reimbursement on the national health system.

One strategy that some companies are exploring is to narrow the initial target population to enable market entry with a small commercial infrastructure. Options for such a strategy include:

**Figure 22: Costs and benefits of introducing systematic testing for early detection of cancer**

| Costs | Benefits |
|---|---|
| Cost 1: Systematic early-detection testing of a defined target population:<br>**Test price x**<br>**Size of target population**<br>To get the annual equivalent cost, adjust for frequency of testing. For example, divide the above cost by two if testing is done once every two years. | Clinical Benefit: Shift of patient population toward earlier stages with better prognoses<br>Over time, the distribution of the diagnosed patient population is expected to shift toward earlier stages of the disease:<br>• Stage III => Stage II<br>• Stage II => Stage I |
| Cost 2: Diagnostic follow-up for people who tested positive with early-detection test:<br>**Price of follow-up procedure x**<br>**Number of people with a positive early-detection test**<br>The number of positive early-detection tests will include:<br>• True positives [% sensitivity of test x Absolute prevalence in target population]<br>• False positives [(100%–% specificity of test) x Size of target population] | Economic Benefit 1: Lower treatment costs<br>The larger percentage of patients at earlier stages of the disease may lead to lower overall treatment costs.<br>Economic Benefit 2: Greater economic activity<br>A larger number of people should be able to resume an economic activity following treatment. |

Source: PwC analysis following discussion with industry contacts

- **Targeting people covered by private insurance or those likely to make copayments:** The target segment for this strategy would be people with sufficient wealth to pay for testing out of pocket or who have complementary private insurance coverage for such testing. The expectation is that people in this segment would be more aware of certain health risks and more inclined to use new tests that could inform them early about certain conditions. For example, a high-income 47-year-old whose parent died from colon cancer might be inclined to spend $300 every two or three years on a blood-based test for early detection of the disease. A test with high sensitivity and specificity could provide this person an early signal to act quickly to gain a higher probability of long-term survival. The reimbursed but more invasive colonoscopy-based test could become a follow-up procedure for anyone testing positive with the blood-based assay.
- **Targeting people that are at higher risk:** If the product is positioned for testing of higher-risk people, a significantly smaller population could be targeted. This would help reduce the overall cost of early-detection testing (Cost 1 in the cost-benefit diagram). In addition, this smaller target population would have a prevalence rate that could be significantly higher than the wider population, leading to better allocation of the cost of follow-up procedures (Cost 2 in the cost-benefit diagram). A higher proportion of true positives should be present among the total number of people that test positive. Thus, targeting a small, higher-risk population should help improve the health economic case and could encourage a faster reimbursement decision.

  An illustrative example of such a strategy would be to target women with a suspected genetic risk of breast cancer rather than all women. If we consider women who are 30 or older in a country such as France, the target population could shrink from 21 million to 4 million by focusing on those who have a suspected genetic risk because of family history of breast cancer. This reduction in the size of the target population would result in an 81% reduction in the volume and cost of early-detection testing (Cost 1). Also, the breast cancer prevalence rate would increase from 6/1,000 to 30/1,000. A significant reduction of false positives sent to costly or risky follow-up procedures would result from the higher prevalence and smaller size of the target population. If the test performance is exceptional and current procedures are not satisfactory, such narrow targeting may even encourage a government to sponsor a study to collect the data required for its reimbursement decision.

As mentioned before, the chances of success of such strategies will depend heavily on the performance of the test and its noninvasiveness.

## IVD majors have not been involved in origination but have a key role to play in commercialisation

The revenue potential of emerging IVD tests for early detection of cancer represents a huge shift for diagnostics companies, which traditionally could expect a major product line to generate just one-tenth of the level of revenues of a blockbuster pharmaceutical product. But this begs the question: If early-detection tests have such tremendous revenue potential, where are the big players?

In terms of research into new early-detection tests, the involvement of major IVD players has been limited. Most of the current pipeline of products originated with small, emerging companies rather than large, established players. The largest player among the originators highlighted in Figure 21 is Celera, which had revenues of $167 million in 2009. None of the top-nine IVD players was an originator.

In terms of development and commercial partnerships, some of the major IVD players have started to show an interest:

- Abbott Laboratories is collaborating with Epigenomics for its colorectal cancer test and BioCurex for its breast and prostate cancer tests.
- BioMérieux signed up to collaborate with ProteoSys for prostate cancer testing.
- Johnson & Johnson, through its OrthoClinical Diagnostics unit, struck a partnership deal with 20/20 GeneSystems for its lung cancer test.

To be sure, larger partners will be needed to realise the revenue potential of early-detection diagnostics. To commercialise a blockbuster product requires significant sales and marketing resources. The budget to launch a test with wide appeal because of exceptional levels of performance could be a few hundred million dollars. Small originator companies do not have such resources and thus will not be able to realise the potential of their new diagnostics without involving a larger partner.

Few large IVD players have been involved in the development of new tests for early detection because this field represents unknown commercial territory. The game-changing potential of market disrupters, such as Genclis, could trigger renewed interest by large IVD players in new tests.

Historically, IVD tests have not been considered sufficiently noninvasive or accurate to become a standard of care for early-detection testing. The PSA test has been the exception in terms of market adoption, but even this test remains controversial due to its low level of specificity. Today, healthcare stakeholders expect higher levels of accuracy from new candidate tests for early detection of cancer. The consequence is a high perceived level of uncertainty about the reimbursement, clinical adoption, and general public appetite for the proposed early-detection tests.

Given the significant commercial budgets required to launch such new tests, many large IVD players might feel it is too soon to commit. Large players could wait for specific products and companies to be confirmed as the most likely winners before they decide where to invest. Some of the majors also might hope that a single underlying technology could be used to develop testing products for several cancers, which may increase the scope for synergies in product development and operations.

A small player that is able to stand alone for long enough during the initial marketing phase and build a strong case for reimbursement of its new test should be able to negotiate attractive terms when larger players finally decide to come to the table.

# Is early detection an opportunity for pharma?

At present, those who believe that early-detection testing could be an attractive commercial opportunity for pharma are a minority. However, we believe this prospect merits some thought.

And to help think about this, we propose to be optimistic and indulge for a moment in the following somewhat ideal scenario: A blood-based test has received marketing clearance for early-detection testing of a major cancer, has demonstrated sensitivity and specificity close to 100%, and is reimbursed at $300 per test by major payers in a large territory for testing of a large asymptomatic target population once every two years.

Could such a test be an attractive opportunity for a pharmaceutical company? We can think of several major reasons why a company could be interested:

- **The cash flow profile would be similar to that of a major drug:** The recurrent testing, every two years, of a sizeable at-risk population would produce cash flows similar to those of a drug to treat a major chronic condition.
- **Synergies with the commercial infrastructure of a pharmaceutical company could exist:** Those physicians typically visited by the target population would be major prescribers of the test. The test could thus be promoted by a pharmaceutical sales force targeting the same group of physicians. This would create a major cost and knowledge synergy with an existing commercial infrastructure at a pharmaceutical company.
- **In contrast with companion diagnostics partnerships, deal terms would be easier to negotiate for an early-detection test:** Because the test would be a stand-alone product not linked to a companion drug, partnership terms would be easier to negotiate than for a companion diagnostic. The prospective partners would not face a question of how to share the overall partnership value between the drug and diagnostic.
- **Early-detection tests can help put pharma on the path to improving health outcomes and economics:** Early-detection diagnostics can help pharma improve patient outcomes and boost its role in the healthcare industry's drive towards wellness and prevention. Although adding tests to a treatment plan increases healthcare costs in the short term, earlier detection has the potential to improve health economics in the long term by intervening before a disease grows to a stage where some of the more expensive forms of care are required.

Of course, obstacles to pharma taking up the commercialisation of such a test remain. Three main factors that may challenge pharma include:

- **The validation of the economic model:** Before considering a commercial partnership, pharma will need to feel confident that reimbursement will be forthcoming. The economic model for systematic IVD-based testing for early detection of cancer has yet to be validated. The case of the PSA test for prostate cancer screening does not provide a strong enough precedent. This validation will be an important prerequisite for any reimbursement decision.
- **The required change in business mind-set:** Today most pharmaceutical companies interested in diagnostics are still figuring out how to adapt their business models to deal with the increasing role of companion diagnostics in the development and marketing of pharmaceuticals. Going one step further and integrating a test for early detection—a stand-alone product not necessarily linked to a specific drug—would mean even greater adaptation. Some will find the change straightforward; others might struggle and need more time to adapt.
- **The technical feasibility of such high-performance, noninvasive IVD tests:** Another obstacle that could cause scepticism at this stage is the credibility of the scenario we assumed. Is it realistic to envisage in the near term the availability of a blood-based test with sensitivity and specificity above 95% and reimbursed at $300? Opinions will divide on this, but as the innovation momentum continues to build, with a growing wave of new products close to achieving marketing clearance, the technical feasibility of such a scenario could become more tangible.

The next few years will be critical to test the opportunity.

# Outlook

## 2011 to 2015 will be a critical test period for IVD-based early detection

The scenario to be tested is whether a noninvasive, high-performance IVD test can achieve widespread adoption for systematic early detection of one of the major cancers in the Western world.

The next few years to 2015 will be crucial to test this scenario because at least five new IVD tests for early detection were cleared for marketing in the United States or Europe during 2009–2010, and at least another 10 are expected to be cleared during 2011–2012, as shown in Figure 23.

Some of these 15 new diagnostics have a preliminary performance profile that suggests they could be strong enough to vie for a central role alongside established *in vitro* procedures.

Two key steps must follow to drive market adoption:

- **Confirm performance:** The preliminary sensitivity and specificity data, often based on retrospective studies, will need to be confirmed with robust prospective clinical studies.
- **Obtain reimbursement:** This is not a minor task and can take four to seven years in some of the major Western markets. By 2015, we should know whether the prime candidates in the current pipeline are passing the market adoption test.

In our view, the most important question is performance. That is, are we dealing with a test that can boast sensitivity and specificity of at least 95%? If such a test becomes available and is not reimbursed, despite major issues with current options, public pressure could mount.

Some tests that are not quite as impressive, with sensitivity and specificity below 95%, may still have a role to play as long as they target a sufficiently narrow and at-risk population. If the expected prevalence of the condition in the target population is sufficiently high, this may compensate for a slightly lower specificity. The issues associated with false positives (unnecessary follow-up procedures) would not become a major problem in terms of health risks and costs.

Sponsoring such tests is not a straightforward decision for payers because the tests could increase immediate healthcare spending. The cost could be controlled, however, by choosing a narrow target population for the reimbursed use of a test.

**Figure 23: Selected IVD tests for early detection cleared or expected to clear for marketing in the United States or European Union during 2009–2012**

| Cancer | New tests cleared or expected to clear for marketing in United States or Europe in 2009–2012 | | |
|---|---|---|---|
| | 2009–2010 | 2011E | 2012E |
| Lung | Epi proLung (Epigenomics)<br>EarlyCDT-Lung (Oncimmune) | PAULA NSCLC (20/20 GeneSystems)<br>A test by BioSystems Int'l<br>A test by Genclis | A test by Celera |
| Breast | BCtect (DiaGenic) | A test by Genclis | Serum-RECAF test (BioCurex) |
| Colon | Epi proColon (Epigenomics) | COLOX (Diagnoplex)<br>Detector C (Signature Diagnostics) | |
| Prostate | Carisome Prostate cMV 1.0 (Caris) | | Serum-RECAF test (BioCurex)<br>ANXA 3 test (ProteoSys) |

Source: PwC research, using company press releases and discussion with industry contacts

For example, reimburse a breast cancer test only for women aged 30 or more with a family history of breast cancer. Other women aged 30 or more might also access the test but without reimbursement—at least not until more data on the health economic benefits of wider testing become available.

## By 2020, pharma to adopt early detection in growing move towards earlier treatment

At present, many pharma players are sceptical about the concept of IVD-based early detection because it is not a tried and tested model. The PSA case is not seen as a credible precedent. Currently, any diagnostics thinking by the pharma industry focuses on companion diagnostics.

However, if several high-performance IVD-based early-detection tests achieve strong market adoption by 2015, we believe that several large pharma players will start considering the case for becoming commercial partners for such tests, particularly if some of these achieve blockbuster revenues. They will not view them as nonpharma products but simply as other profitable products they can sell through their existing commercial infrastructure. By 2020, provided early-detection innovation continues to produce strong product candidates, we believe that a majority of Big Pharma will have licensed at least one such test.

In addition, such a move by pharma will be consistent with the growing interest in preempting disease or its more severe later stages. Many large economies spend an increasing percentage of GDP on healthcare, and this trend will not be sustainable. Governments and payers are looking at what can be done differently and have started to encourage healthier lifestyles to mitigate some of the burden associated with severe chronic diseases. Early detection, for cancer or other diseases, will have an important role to play to supplement prevention and wellness efforts. The health economic objective of early detection and early treatment will be to avoid some of the more expensive forms of treatment associated with later stages of disease.

Key findings

# IV. Ten recent events impacting personalised medicine

4th on our list

One long-awaited event in our selection was the FDA's publication in July 2011 of draft guidance on companion diagnostics. The conciseness of this guidance may leave the diagnostics and pharmaceuticals industries wanting more detail on how to design and conduct clinical studies for the co-development of drugs and their companion diagnostics. However, the FDA's publication does provide a clear signal that the pharmaceuticals industry should continue its transition towards a more systematic role for diagnostics in its business model. The momentum behind the paradigm shift continues to increase.

10th on our list

The least-awaited event in our selection may be Nestlé's acquisition of Prometheus Laboratories for an estimated $1.1 billion, announced in May 2011. This deal represents a significant statement of intent by Nestlé following the creation of Nestlé Health Science in January 2011. Nestlé's vision is that disease prevention will have to play a much bigger role if our healthcare systems are to become sustainable. In this context, Nestlé believes personalised healthcare nutrition should be the first and most efficient step in an active prevention policy and for wellness and well-being. By acquiring Prometheus, Nestlé will add a nutritional dimension to an existing diagnostics-therapeutics business model.

# Event review

Looking at events that might be significant for the development of personalised medicine, we selected 10 reported between August 2009 and July 2011, as shown in Figure 24. Many of these events reflect a growing recognition that personalised medicine is becoming a reality that governments must address, whether through their own initiatives or in response to pressure from industry and consumers. The significant events include, by category:

- **Government and legal:** US government plans to develop a genetic testing registry
- **Regulatory:** The formation of a working group by a US trade association to tackle issues related to the development and regulation of companion diagnostics; FDA's issuance of a black box warning for a blockbuster drug, which could drive the development of companion diagnostics with significant revenue potential; and FDA's release of draft guidance on companion diagnostics
- **Science and technology:** Advances in genetic research related to obesity, which illustrate the emerging convergence between wellness and personalised medicine, and FDA approval of the first therapeutic cancer vaccine, an extreme form of personalised treatment
- **Industry and society:** The establishment of an association to promote the development of personalised medicine in Europe; acquisitions of genetic testing companies by Medco and CVS Caremark, highlighting the growing interest of insurers in personalised medicine tools to produce more cost-effective care; the push towards direct-to-consumer genetic testing; and the acquisition of diagnostics company Prometheus Laboratories by Nestlé to create the potential for a business model integrating nutrition as well as diagnostics and therapeutics

**We provide further background on each of the 10 events shown in** Figure 24.

1. National Institutes of Health announces creation of Genetic Testing Registry (March 2010)

The National Institutes of Health (NIH) announced that it is creating a public database of information on genetic tests. The Genetic Testing Registry (GTR) will be accessible to healthcare providers, researchers, consumers, and others, who will be able to search the database for information submitted voluntarily by providers of genetic tests.

Currently there is no comprehensive public source of information about the availability and validity of the more than 1,600

**Figure 24: Ten significant events for personalised medicine August 2009–July 2011**

| | Category | Date | Event |
|---|---|---|---|
| 1 | Government & Legal | Mar 10 | National Institutes of Health announces creation of Genetic Testing Registry. |
| 2 | Regulatory | Sep 09 | AMDM forms working group to tackle issues surrounding the development and regulation of companion diagnostics. |
| 3 | Regulatory | Mar 10 | FDA issues black box warning on Plavix, creating an opportunity for the development of companion diagnostics. |
| 4 | Regulatory | Jul 11 | FDA issues draft guidance and seeks comments on proposed policy for diagnostic tests used with targeted drug therapies. EMA preparing a white paper on personalised medicine. |
| 5 | Science & Technology | Mar 10 | Interleukin Genetics reports on its genetic test, which may predict how the obese will respond to diet plans. UK researchers link some cases of obesity to missing genes. |
| 6 | Science & Technology | Apr 10 | FDA approves the first therapeutic cancer vaccine, Dendreon's Provenge, boosting the prospect of more personalised treatment avenues through immunotherapy. |
| 7 | Industry & Society | Aug 09 | European personalised medicine association, EPEMED, is established to help promote the development of the personalised medicine field in Europe. |
| 8 | Industry & Society | Feb 10 | Genetic testing companies are acquired by Medco and CVS Caremark, two leading pharmacy benefit managers. |
| 9 | Industry & Society | May 10 | Walgreens announces partnership with Pathway Genomics to provide genetic test kits in its stores but backs out the next day after FDA questions the move. |
| 10 | Industry & Society | May 11 | Nestlé Health Science announces the acquisition of Prometheus Laboratories, a US gastrointestinal diagnostics company, to provide the basis for a personalised healthcare business model integrating diagnostics, therapeutics, and nutrition. |

Source: PwC research, using information from Windhover, IVD Technology, and company press releases

genetic tests on the market today. The GTR, which is expected to be available in 2011, will help to fill the information gap.

The primary goals of the GTR will be to promote research into the genetic basis of health and disease and to advance public health. The registry will attempt to make it easier to identity which laboratories perform specific tests. In addition, it will seek to facilitate the sharing of data to support further scientific research. The National Library of Medicine is developing and will administer the GTR, which will link electronically to other resources of the National Center for Biotechnology Information (NCBI).

### 2. AMDM forms working group to tackle issues surrounding the development and regulation of companion diagnostics (September 2009)

The Association of Medical Diagnostic Manufacturers (AMDM) has created a working group to address key issues related to the development and regulation of companion diagnostics. The Companion Diagnostics Working Group (CDx WG) was formed in response to requests from IVD industry players frustrated with the difficulty of submitting companion diagnostics to the FDA for approval and a request from the FDA Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD) for input to inform the development of new FDA guidelines.

Regulators are trying to develop a more effective framework for joint approval of drugs and diagnostics, which currently follow different regulatory pathways. The CDx WG is exploring this and other issues that must be resolved to create a workable regulatory framework, from coordination of review processes to incentive and reimbursement concerns. The group is recording these and other issues and making recommendations to the FDA.

The working group's membership includes large diagnostics companies, smaller IVD players, some biotech companies, and three FDA representatives. This diversity of stakeholders may help the group take into account challenges faced when developing companion diagnostics. Hopefully, the input from the CDx WG will help the FDA consider the diagnostics industry's diverse concerns when formulating new guidelines.

### 3. FDA issues black box warning on Plavix, creating an opportunity for the development of companion diagnostics (March 2010)

The FDA issued a black box warning on Plavix (clopidogrel), the blockbuster drug marketed by BMS in the United States and sanofi-aventis in Europe, which is widely prescribed to prevent blood clotting and reduce the risk of heart attacks and strokes in cardiovascular patients. It appears that the anti-clotting effect of Plavix is not activated until the drug is metabolised by a liver enzyme, CYP2C19. The FDA warning is based on research showing that 2%–14% of the general population have a mutation of the enzyme that makes them unable to metabolise Plavix well, rendering the drug less effective and leaving these patients at risk of a heart attack or stroke.

The FDA's action follows a less severe warning added to the Plavix label in May 2009. After reviewing more data, the FDA concluded that the more severe black box warning—the highest level issued by the agency—was warranted.

Plavix is the world's second-largest-selling drug (behind Lipitor), with $8.6 billion in sales in 2008. As a result, the black box warning could generate significant demand for diagnostics to identify mutations of the CYP2C19 enzyme and determine the appropriateness of treatment with the drug.

The FDA's decision may have given sanofi-aventis an incentive to find a companion diagnostic to maintain the value of the Plavix franchise. Sanofi's situation could follow a path similar to that of Amgen, whose cancer drug Vectibix was approved by the FDA but received approval in Europe only for use in patients with a KRAS gene mutation. This prompted Amgen to seek a companion diagnostic for Vectibix.

### 4. FDA issues draft guidance to facilitate the development and review of companion diagnostics (July 2011); EMA preparing a white paper on personalised medicine (December 2010)

The FDA's long-awaited draft guidance on companion diagnostics, issued 14 July 2011, invites the public to provide comments within 60 days.

With nine pages of content, the document is short. Accordingly, it focuses on a number of recommended principles rather than providing detailed guidance on how to design or conduct clinical studies to co-develop a targeted therapeutic and its companion diagnostic.

Those who were expecting more detail at this stage might be disappointed, but the nature of the document should come as no surprise if we consider a 10 June 2011 presentation by Elizabeth Mansfield, head of personalised medicine at the FDA's OIVD, at an event hosted by the AMDM. Talking about the preparation of personalised medicine guidance by the FDA, Mansfield made a distinction between guidance on *companion diagnostics,* for which a document was due for publication shortly, and guidance on *co-development,* for which work was under way but publication was not imminent.

Until the agency releases further guidance, the FDA's April 2005 draft *Drug-Diagnostic Co-Development Concept Paper* may still serve as main reference document on the practicalities of co-development. The FDA has not released a final version.

Regarding the July 2011 draft guidance on companion diagnostics, Jeffrey Shuren, director of the FDA's Center for Devices and Radiological Health, commented: "These proposed guidelines support the development of innovative new targeted medicines and their corresponding diagnostic tests and are intended to provide manufacturers with greater predictability." This statement confirms that personalised medicine is high on the agenda of the FDA even if industry may feel that further guidance from the FDA is needed on how to design and conduct co-development before "greater predictability" can be achieved.

In its 2011 draft guidance, the FDA defines an IVD companion diagnostic device as "an *in vitro* diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product."

This definition covers tests that do the following:

- Identify patients who are most likely to benefit from a particular therapeutic product
- Identify patients likely to be at increased risk for serious adverse reactions as a result of treatment with a particular therapeutic product
- Monitor response to treatment for the purpose of adjusting treatment (e.g., schedule, dose, discontinuation) to achieve improved safety or effectiveness

The word *essential* is important in the FDA's definition of an IVD companion diagnostic because it excludes tests that provide only useful information for physicians regarding the use of a therapeutic product. For example, well-understood common biochemical assays to monitor organ function would not be considered "a determining factor in the safe and effective use of the product."

The FDA recommends that the development and review of the therapeutic and its companion diagnostic be conducted simultaneously with the aim of approving or clearing both products at the same time. However, the agency also highlights cases where the process may deviate from this ideal scenario: "In cases where the therapy is intended to treat a serious or life-threatening disease or condition for which there is no available or satisfactory treatment and when the potential benefits outweigh the risks of not having a cleared or approved companion diagnostic, the therapy could be approved first while the companion diagnostic may be approved or cleared later through the appropriate device submission process."

Whilst the draft guidance does not provide details on a recommended study design for the co-development process, the agency recommends early exchanges between the FDA and sponsors of the therapeutic and diagnostic so that the agency's expectations can be included in development plans.

Regarding regulatory pathways for companion diagnostics, the agency expects most tests to be in the higher-risk category, Class III, requiring premarket approval (PMA). However, there may also be some Class II cases, which will require a 510(k) premarket notification or other form of submission. The draft guidance does not elaborate on LDTs, and industry is likely to seek further clarification on them.

Two implications we expect from the FDA's guidance are that (1) the diagnostics industry will be required to provide increased data as evidence that a companion diagnostic is fit for its purpose, and (2) the pharmaceuticals industry should continue its transition towards systematic incorporation of biomarkers and diagnostics in its drug development programs. Consequently, the success of the two industries is becoming increasingly interdependent. Pharma may have to find ways of helping fund some of the increased investments required of the diagnostics industry to achieve a win-win outcome.

In Europe, regulators are also busy with the challenges and opportunities arising from the growth of personalised medicine. In December 2010, the European Medicines Agency reported to PwC that it planned to release a reflection paper on personalised medicine during the second half of 2011.

### 5. Interleukin Genetics reports on its genetic test, which may predict how the obese will respond to diet plans (March 2010); UK researchers link some cases of obesity to missing genes (February 2010)

Interleukin Genetics, based in Massachusetts, reported that its Inherent Health test might help overweight people choose the optimal weight-loss diet based on their genetic profiles. The test searches for mutations of three genes linked to weight loss: FABP2, PPARG, and ADRB2. In a small study of about 140 women who were overweight or obese, researchers found that those who followed a dietary program that matched their genetic profiles, as measured by the Inherent Health test, lost more weight than those whose diets did not align with their genotypes. The optimal diet choice (low-fat, low-carbohydrate, or balanced) depended on which gene mutation was present.

In a related finding, scientists in the United Kingdom reported in Nature that, based on their research, a small proportion of obese people (roughly seven out of every 1,000) could be missing approximately 30 genes that are present in people who maintain a normal weight. The results suggest that in some cases, the tendency towards obesity could be inherited. The ability to identify the gene deletions causing obesity could lead to a new view of treatment options for those affected by the problem.

This research may promote more extensive use of personalised medicine tools in some wellness programs.

### 6. FDA approves the first therapeutic cancer vaccine, Dendreon's Provenge, boosting the prospect of more personalised treatment avenues through immunotherapy (April 2010)

In April 2010, the US FDA approved the first therapeutic cancer vaccine—a vaccine used to treat rather than prevent a disease. The new vaccine, Provenge (sipuleucel-T), was developed by the Seattle-based company Dendreon and approved to treat certain forms of metastatic prostate cancer. The FDA based its approval on a Phase III randomised controlled trial, which found a median increase in survival of 4.1 months among patients taking Provenge.

The treatment approach embodied by Provenge represents an ultimate form of personalised medicine because the active ingredient is produced using cells from each patient's own immune system. The patient's immune cells are collected and mixed with a protein designed to activate the cells and produce an immune response to prostate cancer. The activated immune cells are then infused into the patient. Each patient thus receives a uniquely personalised treatment.

Challenges remain for this approach, which is highly customised and costly—one course of treatment costs $93,000. In August 2011, the company reported slower-than-expected sales and referred to limited manufacturing capacity and lack of awareness by the medical community about the reimbursement process.

Dendreon is not the only company researching the opportunities for therapeutic cancer vaccines. For example, Copenhagen-based DanDrit Biotech is conducting clinical trials of immunotherapy for colorectal and non-small-cell lung cancer.

A significant future milestone would be for immunotherapy to be approved for earlier stages of cancer as well, including stages at which tumour cells have not yet spread.

### 7. European personalised medicine association, EPEMED, is established to help promote the development of the personalised medicine field in Europe (August 2009)

EPEMED was established in August 2009 as a not-for-profit organisation to help address some of the issues facing key stakeholders in the personalised medicine field in Europe, including industry, regulators, insurers, and government. Some of the challenges it plans to consider include how best to develop personalised treatments; regulatory guidance on the co-development of diagnostic tests and personalised drug therapy; improving market access for high-value, companion diagnostics; and value-based pricing and reimbursement of diagnostic tests.

EPEMED plans to offer a central clearinghouse for discussing such issues and promoting practical solutions. The association's board includes senior executives from small and large diagnostics companies with a particular interest in personalised medicine.

US and European companies could leverage EPEMED's work to gain wider access to the European market, where each country has a different pricing and reimbursement environment. In particular, smaller companies sometimes lack the experience to manage the complexities of the European market, and the association could provide valuable guidance to them.

### 8. Genetic testing companies acquired by leading pharmacy benefit managers Medco (February 2010) and CVS Caremark (December 2009)

In February 2010, Medco Health Solutions, one of the largest pharmacy benefit managers (PBMs) in the United States, announced its plan to acquire DNA Direct, a San Francisco-based laboratory that provides genetic testing services. Medco plans to use genetic testing to reduce healthcare costs by identifying patients who are not expected to benefit from certain expensive drug treatments because of genetic mutations.

Medco planned to focus initially on introducing genetic testing as a requirement for prescribing tamoxifen, the breast cancer drug, and warfarin, the widely used blood thinner. In the case of warfarin, Medco's expectation is that genetic testing could help in making dosage decisions. Determining the proper dosage of warfarin is tricky, and incorrect dosing can cause serious problems: with too small a dose, blood clots could form; with too high a dose, the patient could experience excessive bleeding.

The Medco announcement followed a similar investment in December 2009, when Caremark CVS, the largest PBM in the United States, increased its ownership stake in Generation Health, a New Jersey-based genetic testing company. One month earlier, Caremark CVS had formed a strategic partnership with Generation Health to develop pharmacogenomic clinical and testing services for its PBM clients.

The investments in genetic testing by CVS Caremark and Medco signal the importance assigned by payers to having better tools to personalise, or at least stratify, medical care for clinical as well as economic reasons.

### 9. Walgreens announces partnership with Pathway Genomics to provide genetic test kits in its stores but backs out the next day after FDA questions the move (May 2010)

On 11 May 2010, Walgreens, the leading US drugstore chain, announced that it would offer retail genetic test kits from Pathway Genomics, based in San Diego, California, in about 6,000 of the company's 7,500 stores. Consumers would purchase the kits and supply saliva samples to Pathway for analysis. They would pay separately for tests to identify genetic predisposition for a range of more than 70 conditions, including Alzheimer's, breast cancer, and diabetes.

The response from the US FDA was immediate. In a letter to Pathway, the agency noted that the company's saliva collection kit "appears to meet the definition of a device" under federal law. That makes it subject to FDA review, the agency argued. On 12 May 2010, Walgreens backed out of the distribution deal, announcing that it would delay selling the genetic test kits pending clarification from the FDA about the legality of selling the product in its retail stores.

The FDA's ongoing regulatory focus on direct-to-consumer (DTC) testing included a recent report by the Government Accountability Office (GAO) highlighting misleading DTC genetic test results and questionable marketing practices. In 2006, the GAO investigated DTC companies and found they made "medically unproven disease predictions." In response to ongoing concerns expressed by experts, the GAO investigated the current market and found that the picture had not improved.

This example illustrates the drive by industry and consumers to bring diagnostics closer to end users. Walgreens' foray into the DTC genetic test market may have been a case of too much too soon from a regulatory perspective. But the motivation remains, and industry is likely to continue pushing the limits of the system to bring personalised medicine tests closer to consumers. Questions about which DTC practices are appropriate and which might lack sufficient protection for end users will continue to challenge regulators.

### 10. Nestlé Health Science announces the acquisition of Prometheus Laboratories, a US gastrointestinal diagnostics company, to provide the basis for a personalised healthcare business model integrating diagnostics, therapeutics, and nutrition (May 2011)

The terms of this deal, announced in May and completed in July 2011, were not disclosed. But the press reported Nestlé might have offered $1.1 billion for the acquisition of San Diego-based Prometheus Laboratories. The size of Nestlé's investment highlights the importance of personalised healthcare for its health- and science-based nutrition business.

A separate company, Nestlé Health Science S.A. (NHS), was announced in September 2010 and became operational on 1 January 2011 with the stated mission of developing science-based nutritional solutions to deliver personalised healthcare for medical conditions. Nestlé felt that a new separate unit was needed to manage the different market dynamics of the NHS business—somewhere between food and pharma.

Nestlé believes there is a significant business opportunity in the personalised healthcare nutrition field following analysis of the macroeconomic environment that suggests our current healthcare system is not sustainable. Healthcare costs are expected to increase significantly as a percentage of GDP in developed and emerging countries. Consequently, Nestlé says, our current system, "which concentrates basically on treating sick people, is not sustainable and will have to be redesigned drastically. It is our strong conviction that disease prevention will have to play a much bigger role and, in this sense, personalised healthcare nutrition will become the first and most efficient step in an active prevention policy and for wellness and well-being."

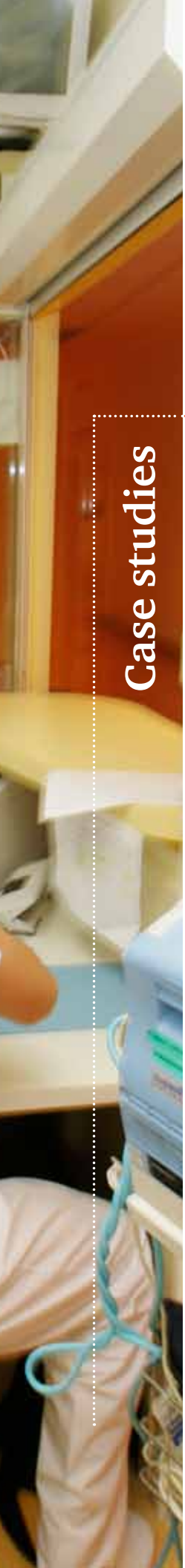
The CEO of NHS, Luis Cantarell, commented that the acquisition of Prometheus represented "a strategic move into gastrointestinal diagnostics" and provided leading-edge diagnostics technology and an outstanding sales force to help "develop an integrated approach to personalised healthcare" at Nestlé. "It will enable new personalised healthcare solutions based on diagnostics, pharma, and nutrition."

Joseph Limber, the CEO of Prometheus, confirmed this perspective and plans to "leverage Nestlé Health Science's nutritional product offerings and geographic presence to expand our successful Rx/Dx business model into a Dx/Nx/Rx model." The strategy of Prometheus includes the marketing and delivery of pharmaceutical products complemented by proprietary diagnostic testing services. By integrating therapeutics and diagnostics, Prometheus believes it can provide physicians with more targeted solutions to improve patient care. The company plans to add a nutritional dimension to its existing Rx-Dx business model.

The acquisition is expected to create new opportunities for developing personalised nutrition strategies that will help in the management and prevention of chronic health conditions. The research and development pipeline will encompass other areas of strategic interest for Nestlé Health Science, such as metabolic conditions, brain health, and oncology.

Other significant recent acquisitions announced by Nestlé to develop its health-science nutrition business included:

- **Vitaflo:** The Liverpool-based company with annual sales estimated at CHF 40 million, acquired in August 2010, targets the market for clinical nutrition products customised for people with inherited metabolic disorders. Vitaflo is developing products for phenylketonuria (PKU), maple syrup urine disease (MSUD), and homocystinuria (HCU).
- **CM&D Pharma:** The London-based company, acquired in February 2011, specialises in the development of products tailored for patients with kidney disease, inflammatory bowel disease, and colon cancer. CM&D was part of the portfolio of Inventages Group, an independent venture capital fund in which Nestlé invests. The company's leading product, Fostrap, is a medical food in the form of a chewing gum for kidney patients who have an elevated level of phosphate in the blood (hyperphosphataemia).
- **Vital Foods:** On 14 July 2011, Nestlé announced the acquisition of an 18-percent stake in this New Zealand maker of kiwi fruit-based products to prevent and treat constipation. Nestlé had helped fund the earlier development of Auckland-based Vital Foods through the Inventages venture capital fund. Created in 1991, the company has two products on the market in New Zealand, Kiwi Crush and Phloe, which have been clinically shown to be effective against constipation. The new capital provided by Nestlé is planned to take the products to the next stage, toward clinical trials and new markets. "We can invest more money in developing clinical trials to support evidence in IBS (irritable bowel syndrome) and, if these work, expand them," Luis Cantarell said.



Case studies

# V. Case studies

In this section we provide profiles for two *in vitro* diagnostics companies already mentioned in this report that provide an illustration of the diversity of product types within the IVD industry. MDxHealth is developing companion diagnostics as well as diagnostics for the prognosis of disease progression using DNA methylation markers. Genclis has developed a test for early detection of peanut allergy and is completing the development of a blood-based immunoassay for early detection of breast cancer.

## Case study 1—MDxHealth

MDxHealth is an oncology-focused molecular diagnostics company with global headquarters in Liège, Belgium, and US headquarters in Durham, North Carolina. The company, which was formerly known as OncoMethylome Sciences, was established in 2003.

Following a change of name and strategy in 2010, the company refocused on developing tests to assist physicians with the diagnosis of cancer, prognosis of recurrence risk, and prediction of response to a specific therapy.

MDxHealth is developing its tests using proprietary DNA methylation technology and proprietary biomarkers along three product lines:

- **ConfirmMDx** products are diagnostic aids to assess the presence or absence of cancer.
- **InformMDx** tests provide prognostic assessment to distinguish between aggressive and nonaggressive tumours.
- **PredictMDx** diagnostics will provide predictive information to indicate which drug or treatment regimen is likely to be most effective for an individual patient.

The company's most advanced test is PredictMDx Brain to predict the response of brain cancer patients to certain drugs. This test is commercially available as an LDT in North America through LabCorp and as an investigational-use-only (IUO) test in Europe through its own laboratory.

A current priority area for MDxHealth is to develop a franchise of prostate cancer tests, with a first product expected to be launched in 2012.

### Changing strategy in 2010

Until 2010, the company was investing significant resources in the discovery of screening tests for early detection of colon and other cancers. It was out-licensing these tests at early stages of development when significant validation work was still required for them to become market-ready.

In 2010, the company changed its management, name, and strategy. In particular, Jan Groen was appointed as the company's new CEO in April 2010.

As part of the new strategy, outlined in October 2010, MDxHealth plans to keep control of the development of its diagnostics and will move away from screening applications to favour prognostic and predictive assays. In the United States, MDxHealth will develop its own CLIA laboratory and commercial operation.

These initiatives aim to accelerate the creation of shareholder value from existing intellectual property. In particular, the company expects less challenging discussions with payers because the new product focus—diagnosis, prognosis, and prediction tests—will target patients that have already been screened or diagnosed with cancer.

In its former focus on screening applications, its products targeted large asymptomatic populations. Typically, the cost of such wide screening programs can be more significant for insurance funds; consequently, reimbursement decisions may require more stringent health economic validation studies.

### Technology

The main technology base for the company's products is DNA methylation. MDxHealth has exclusive

rights to significant methylation intellectual property from Johns Hopkins University in Baltimore. While research into methylation continues apace at many leading institutions, MDxHealth believes that no other place can claim as much accumulated knowledge in this field as the team of scientists at Johns Hopkins.

## Business model

MDxHealth intends to develop and market its proprietary assays in its own CLIA laboratory in the United States. Providing services in such a laboratory allows the company to accelerate reimbursement for its assays because they rely on routine laboratory steps and equipment for which reimbursement codes already exist. The CLIA approach can help build revenue streams faster.

The company has two main business units:

- In the **clinical diagnostics** business, assays are designed to aid in the assessment of the presence or absence of cancer (ConfirmMDx products) or provide indications of cancer recurrence or aggressiveness (InformMDx products).
- In the **companion diagnostics** business, tests are designed to provide predictive information to indicate which therapeutic is likely to be most effective for an individual patient (PredictMDx products).

## Business unit: Clinical diagnostics

Currently, MDxHealth is focusing on developing and launching five new clinical diagnostics products in the coming years: two for prostate cancer, two for lung cancer, and one for colorectal cancer. MDxHealth will initially concentrate most of its efforts on building a prostate cancer franchise with its ConfirmMDx and InformMDx products.

ConfirmMDx for prostate cancer is a molecular diagnostic test to assist physicians with the identification of cancer in men who have undergone a biopsy and have an elevated PSA level, abnormal digital rectal examination, or benign prostatic hyperplasia. The test should provide physicians with an important tool for assessing the presence or absence of cancer cells in biopsy tissue, ruling out healthy men from undergoing unnecessary repeat biopsies or excessive screening procedures.

In the United States, more than 900,000 men are biopsied for prostate cancer annually; but only 217,000 are diagnosed with the disease. It is reported that 25%–30% of histopathology procedures fail to detect cancer when it is present (the false-negative rate). MDxHealth has demonstrated that its ConfirmMDx test can be used to identify those patients with undetected occult cancer, while sparing otherwise healthy men unnecessary repeat biopsies.

InformMDx for prostate cancer provides physicians with a tool to help assess prognosis by determining the aggressiveness of the tumour. This additional quantitative information, in conjunction with Gleason scores of the biopsy, should help to distinguish high-risk patients who require more aggressive treatment from those who are at lower risk of disease progression and could be candidates for active surveillance under the care of an urologist.

Decisions on patient management after a diagnosis of prostate cancer are generally based on the positive diagnosis of biopsy tissue. However, evidence of aggressive cancer cells is frequently lacking in the biopsy tissue extracted for analysis and is most often detected only in surgical samples after prostatectomy (removal of the prostate). The failure to detect aggressive cancer cells in prostate biopsies thus often results in unnecessary, aggressive treatment in many men. A molecular test that provides an accurate diagnosis of cancer involvement and tumour aggressiveness in prostate biopsies might dramatically reduce such overtreatment.

## Business unit: Companion diagnostics

MDxHealth is rapidly expanding its capabilities in the development of companion diagnostics and expects to launch its first FDA-approved companion diagnostic product in 2013. The PredictMDx product pipeline currently focuses on two areas: brain and colon cancer. In addition, other biomarkers are ready for development.

PredictMDx for Brain, MDxHealth's most advanced targeted therapy product, is a test for predicting the response of patients with brain cancer to integrin inhibitors and to alkylation agents, the most commonly used class of chemotherapy drugs. The test, which uses tumour tissue, assesses the methylation status of the MGMT gene, a DNA repair gene that is correlated with response to drug therapy.

The MDxHealth brain test can be attractive for new developers of brain cancer drugs because they can more easily target their new drugs to the patients who usually do not respond to the traditional alkylation agent drug regime. A key partner of MDxHealth in developing the MGMT gene test is MerckSerono, with which it collaborates in clinical trials for cilengitide, MerckSerono's drug for glioblastoma multiform—a rare and devastating form of brain cancer.

PredictMDx for Colon Cancer is a molecular test that provides physicians with an assessment of recurrence risk following surgery in stage II colon cancer patients. This information, in conjunction with traditional risk factors, aims to provide

physicians with valuable insight into the likelihood that a patient will benefit from the use of oxaliplatin- or irinotecan-based chemotherapy cocktails.

## Partnerships

Recent partnerships announced by MDxHealth include:

- A partnership with Pfizer, Newcastle University, and Cancer Research Technology Limited (CRT) announced in January 2011. As part of this agreement, MDxHealth will collaborate on the identification and development of a biomarker predicting response to the drug candidate for PARP inhibition, PF-01367338. The partners believe identification of a successful predictive biomarker could potentially lead to the development of a companion diagnostic to guide treatment decisions in ovarian and breast cancers.
- A partnership with GSK announced in September 2010. This agreement with GSK Biologicals may lead to the potential use of one of MDxHealth's DNA methylation-specific PCR biomarkers in GSK's immunotherapy development program. The MDxHealth biomarker allows for the analysis of noninvasive tissue samples.
- A partnership with Roche announced in January 2010. Roche will conduct MGMT gene promoter methylation testing in a Phase III clinical trial for the use of Avastin in newly diagnosed glioblastoma brain tumours. This trial will compare the current standard-of-care therapy (chemo-radiation and adjuvant temozolomide) with the standard of care plus bevacizumab (Avastin, Roche). MDxHealth will receive payments for performing MGMT testing on patients enrolled in this trial.

## Financing

After two series of private funding rounds in 2004 and 2005, the company became publicly listed on the NYSE Euronext exchange in Brussels and Amsterdam following an IPO in June 2006.

The company's latest fund-raising came in the form of a placement of $11.7 million, which closed on 8 April 2011. Selected significant shareholders following the 8 April placement included ING Belgium NV (11.53%), Biovest NV (9.31%), Life Sciences Partners II BV (7.58%), IDInvest Partners SA (4.27%), APG Algemene Pensioen Groep NV (<3%), and BNP Paribas Fortis Investment Management (<3%).

Biovest, a major new shareholder, is the investment company of Rudi Mariën, the founder and former chairman of Innogenetics, the Belgium-based diagnostics business acquired by Solvay Pharmaceuticals in 2008 and sold on to Fujirebio in 2010 following Abbott's acquisition of Solvay Pharmaceuticals. Mariën was also founder and former managing director of the Barc Group, an international clinical laboratory dedicated to pharmaceutical studies. His investment is seen by MDxHealth as an endorsement for its strategy of setting up its own CLIA laboratory and marketing and sales infrastructure in the United States. "I feel privileged to become a major shareholder of MDxHealth. The company has accomplished an impressive turnaround over the past 12 months, and is now pursuing a strategy that can sustainably generate novel, high-value molecular cancer diagnostics," said Mariën.

Following its fund-raising, MDxHealth had $23.5 million in cash and cash equivalents at 8 April 2011.

## Methylation

MDxHealth's technology platform, called MSP (methylation-specific-PCR), is a proprietary, DNA-based technology that functions on standard commercial PCR equipment.

Individual genes (DNA biomarkers) in the human body can become modified in the presence of cancer. MDxHealth has the ability to identify these modifications at the genetic level, providing physicians with a tool to aid in the diagnosis of cancer, assess the risk of recurrence (metastasis) of the cancer, and predict an individual patient's likely response to cancer treatment.

DNA methylation may be a valuable tool for assessing cancer because methylated DNA biomarkers occur in most malignancies. The importance of DNA methylation in cancer was discovered in the 1990s. Gene methylation is a control mechanism that regulates gene expression in DNA and occurs when a methyl group is added to one of the four building blocks of DNA, a cytosine. In several diseases, however, the promoter regions that carry the instructions to produce an essential protein can be over- or hyper-methylated, effectively inhibiting protein production. Hypermethylation of genes, such as tumour-suppressor genes, is associated with the presence and development of most cancers. Although changes in DNA methylation were initially thought to be the result of cancerous transformations, it is increasingly believed that methylation plays an active, causative role.

The pattern of gene hypermethylation in tumour cells is often specific to the tissue of origin and can be used to improve cancer detection, assess risk of recurrence, and predict a tumour's response to therapy.

# *Case study 2—*Genclis

Genclis is a biotechnology company focusing on allergy and cancer. Its first product to receive marketing clearance was a blood-based test for early detection of peanut allergy. Genclis also develops blood-based tests for early detection of breast and lung cancer, for which the company expects European marketing clearance in the second half of 2011. The company formed in Nancy, France, in 2004 and currently employs approximately 40 people.

## Management

CEO and co-founder Bernard Bihain is a medical doctor turned scientist with a background in metabolism. At the end of the 1990s, Dr. Bihain discovered Famoxin, a drug to aid weight loss and the lead therapeutic protein of Genset SA, the largest French biotech company at the time. His work in allergy and cancer started at Genclis.

## Business model evolution

Consistent with the background of its CEO, cancer has not always been a focus area for Genclis. The company's business model and disease focus have passed through three main phases:

- **Focus on services (2004–2005):** Initially, the company adopted a service-based strategy to generate funds to finance subsequent proprietary product development work. Genclis was profitable during its first two years of operation, 2004 and 2005, thanks to the provision of molecular biology services to third parties in industry, academia, and clinical research.
- **Increase of proprietary R&D (2006–2007):** During 2006–2007, Genclis increased its focus on proprietary R&D with support from a Series A funding round in 2006. The financing provided some autonomy for the company to complete the development and CE marking of a blood-based test for early detection of peanut allergy in children. Also during this period, the company discovered the principle of transcription infidelity (TI), which provided new insights into the molecular biology of cancer and raised the prospect of developing new technology for early detection of several cancers.
- **Development of a cancer pipeline (2008–2010):** Following the discovery of TI during the previous phase, Genclis chose to focus most of its resources on developing new tests for early detection of cancer based on this principle. Accordingly, the company reduced its R&D service activities during this period.

## The allergy franchise

The company's close contacts with the community of food allergists in Nancy were a significant driver for its work in the allergy field. Discussions with local specialists provided insights into areas of severe unmet clinical need, which the company then targeted for product development initiatives.

The first product coming out of this work was a blood-based immunoassay for early detection of peanut allergy, which has been marketed in Europe since December 2007 by a leading player in the allergy diagnostics sector.

Availability of the test decreased the average age of diagnosis from 7 to 3 years and, by March 2010, led to the cure of more than 50 cases through early detection followed by controlled and progressive consumption of peanuts.

Today the company is exploring commercial partnerships in selected territories for a next-generation peanut allergy test.

## The cancer pipeline

In 2006, Genclis was approached by members of the French research community to investigate sequencing questions relating to cancer research. This dialogue triggered Genclis to start researching molecular mechanisms involved in cancer. The company did not have prior experience with cancer, and this may have been an advantage because it approached old questions from a fresh perspective. It used its functional genomics experience to make rapid progress with its cancer project; the outcome was the discovery of TI.

Following some promising early findings, the cancer research program at Genclis won a €1 million prize in a 2007 competition organised by the private foundation InNaBioSanté and involving more than 90 cancer projects.

The TI mechanism provided new insights on the molecular biology of cancer, which were used to develop blood-based immunoassays for early detection of cancer. Retrospective studies provided clinical proof of principle for the company's lung and breast cancer tests (performance data is shown in Figure 25).

Performance could improve further because these data were obtained before the company introduced standard operating procedures for blood sampling and improved analytical conditions.

Ongoing prospective clinical studies for both tests should provide data needed to complete CE mark dossiers. Submission of these dossiers will provide European marketing clearance, which is expected by the end of 2011.

The company will recommend a focused product positioning, where its tests are used mainly with higher-risk populations. For example, its breast cancer test will target women aged 30 or older with a family history of breast cancer or which have been referred to genetic testing following suspected genetic predisposition. The prevalence of breast cancer in such a target group is understood to be 30/1,000, significantly higher than the 6/1,000 prevalence expected among all women aged 30 or older. This focused approach is expected to improve the health economic case for systematic early-detection testing significantly when compared with a population-wide screening approach.

Genclis will consider commercial partnerships for its tests once they are market-ready.

## Fund-raising

Genclis raised €10.6 million of capital through an increase of share capital by its parent company Transmedi SA, as part of a Series B funding round, which comprised a first tranche in June 2010 and a second closing in March 2011. The share capital was provided by institutional and private investors. The institutions were led by Vizille Capital Innovation and included SudInnova, Banque Populaire Lorraine Champagne, and Institut Lorrain de Participation. The high sensitivity and specificity data and short expected time to market for the cancer detection tests provided the basis for significant participation from private investors.

In addition, Transmedi raised nondilutive capital for Genclis from the Lorraine region and from Oséo, the French agency promoting the development of small- and medium-sized enterprises.

**Figure 25: Preliminary performance data for Genclis lung and breast cancer tests**

| Test | Number of patients/controls | Number of markers | Sensitivity | Specificity |
|---|---|---|---|---|
| Lung cancer test | 224/277 | 6–24 | 91% | 98% |
| Breast cancer test | 287/227 | 24 | 95% | 97% |

Source: Genclis

## Outlook for Genclis

Major priorities for Genclis in 2011 include the CE marking of its first cancer-detection test, the publication of further findings about TI, and the development of new opportunities in allergy.

The company is planning to develop early-detection tests for several other cancers after it has obtained marketing clearance for its breast and lung cancer tests.

## Transcription infidelity

Genclis built its cancer program on the discovery in 2006 of transcription infidelity (TI), which may represent a paradigm shift in the scientific community's understanding of the molecular biology of cancer. The discovery that TI is nonrandom and increases in cancer cells was patented by Genclis and reported in the Proceedings of the National Academy of Sciences of the United States of America in 2007.

The markers used by Genclis for its early-detection tests are based on TI proteins, which are altered proteins resulting from the process of TI and predicted according to certain rules.

## Transcription

Transcription is the synthesis of RNA under the direction of DNA. In this process, DNA nucleotide sequence information is transferred to RNA to provide a coding for protein synthesis.

In normal cells, the transcription process (DNA => RNA) is expected to follow the canonical base-pairing rules:

Adenine (A) => Uracil (U)
Thymine (T) => Adenine (A)
Guanine (G) => Cytosine (C)
Cytosine (C) => Guanine (G)

The traditional belief is that fidelity with the canonical transcription rules is needed for normal cell function.

## Transcription infidelity mechanism

TI is a mechanism by which several distinct RNA molecules are produced from a single DNA sequence. TI can introduce single-base substitutions, insertions, or deletions at the mRNA level in the absence of a corresponding modification at the DNA level.

The mRNA resulting from TI will encode proteins that are different from those expected from the starting DNA under the canonical transcription rules because of differences in respective RNA nucleotide sequences. TI can thereby increase the range of proteins that can be synthesized from a single gene.

TI can also affect noncoding RNA sequences, thereby modulating their functions.

Experimental data show that TI is present in normal cells but is dramatically enhanced in cancer cells.

## TI proteins and antibodies

Other concepts used by Genclis include:

- TI proteins, which are altered proteins resulting from the process of transcription infidelity and predicted according to certain rules
- TI antibodies, which are antibodies directed against TI proteins

Both TI proteins and TI antibodies play a role in the early-detection technology developed by Genclis.

## Implication

The concept of TI may contribute to clarifying the dogma of molecular biology on the creation of protein diversity in eukaryotic cells.

# *Conclusion*

The IVD sector attracted exceptional levels of deal activity during 2010 and the first half of 2011, both in terms of M&A and companion diagnostics partnerships with pharma. This momentum will continue as long as innovation and growth prospects in key market segments, including molecular and tissue diagnostics, remain strong.

But to sustain high levels of innovation, a number of actions will be needed from governments, regulators, payers, and industry, including:

1. The pricing of diagnostics should be changed to reflect the value of the test rather than its cost.
2. The regulatory pathways to market should be clarified for each type of diagnostic—stand-alone and companion.
3. The regulatory requirements in terms of clinical trial design for drug-diagnostic co-development should be clarified.
4. The process to gain reimbursement for diagnostics should be accelerated and harmonised across countries.
5. The share of value going to the diagnostic in drug-diagnostic partnerships should be revisited.

Not taking action would damage the survival prospects of many emerging IVD players, specifically those that are most innovative. Diagnostics innovation could be handed over too cheaply to pharma, continued investment into diagnostics ventures could be discouraged, and patients' access to important new health technology could be delayed.

What will you do?

# *Acknowledgements*

**This report was developed by members of the Pharmaceuticals & Life Sciences and Healthcare practices at PwC:**

Author Loïc Kubitza

Research team Federica Amato, Sammy Lamali, Jean-Baptiste le Caron de Chocqueuse, Stéphane Soulard, Giulia Spalletti

Editorial team Steve Arlington, Janice Drennan, Anthony Farino, Simon Friend, Todd Hall, Attila Karacsony, Gerald McDougall, Erica Monfardini, Laurent Probst, Matthew Rosamond, Hindy Shaman

**Input was gratefully received from contacts in industry and related stakeholders:**

Mara Aspinall Chief Executive Officer On-Q-ity
Bernard Bihain Chief Executive Officer Genclis
Carl Borrebaeck Chief Scientific Officer Immunovia
Dan Calvo Chief Executive Officer Oncimmune
Erik Christensen Chief Executive Officer DiaGenic
Peter Collins Vice President of Diagnostics GlaxoSmithKline Biologicals
Noel Doheny Chief Executive Officer of US Subsidiary Epigenomics
Doug Dolginow Entrepreneur and Investor
Markus Ewert Global Head of Strategy Novartis Pharma
Guy Greiveldinger Business Development Director Novartis Pharma
Jan Groen Chief Executive Officer MDxHealth
Hossam Haick Chief Scientific Officer Na-Nose
William Hempel Director of Scientific Communications Biosystems International
Hans Herklots Corporate Communications Consultant Capricorn One
Andy Hu VP of Strategy & Business Development Predictive Biosciences
Alain Huriez Chairman EPEMED
David Jackson Senior Director of Companion Diagnostics Partnerships Qiagen
Gilles Karcher Head of Nuclear Medicine Unit University Hospital, Nancy-Brabois
Rainer Kramer Chief Business Officer Signature Diagnostics
Michael Leibowitz Director of R&D 20/20 GeneSystems
Helmut Matthies Chief Executive Officer ProteoSys
Mark Messenbaugh Director of Corporate Strategy SomaLogic
Iain Miller Executive Director, Theranostics bioMérieux
Lorenzo Monfardini Interventional Radiologist European Oncology Institute
Ricardo Moro-Vidal Chief Executive Officer BioCurex
Marisa Papaluca Section Head of Scientific Support and Projects EMA
Achim Plum SVP Corporate Development Epigenomics
Severin Schwan Chief Executive Officer Roche
Holger Schwarz Director Innovation Management, Chemicals Merck KGaA
Stavros Therianos Chief Executive Officer Diagnoplex
Cara Tucker Manager of Corporate Communications Exact Sciences
Werner Verbiest Head of Companion Diagnostics Virco, Johnson & Johnson
Michael Watts VP Investor Relations & Corporate Communications Gen-Probe

**For further information:**

## Principal contacts

Laurent Probst
Partner, Pharmaceuticals & Life Sciences
Industry Leader, PwC Luxembourg
laurent.probst@lu.pwc.com
+352 49 48 48 25 64

Loïc Kubitza
Director, Pharmaceuticals & Life Sciences,
Advisory Services, PwC Luxembourg
loic.x.kubitza@lu.pwc.com
+352 49 48 48 57 16

Gerald McDougall
Principal, Healthcare
Advisory Services, PwC US
gerald.j.mcdougall@us.pwc.com
+1 267 330 2468

Matthew Rosamond
Director, Healthcare
Advisory Services, PwC US
matthew.rosamond@us.pwc.com
+1 646 471 0953

## Pharmaceuticals & Life Sciences

### Leadership

Simon Friend
Partner, Global Pharmaceuticals & Life Sciences
Industry Leader, PwC UK
simon.d.friend@uk.pwc.com
+44 20 7213 48 75

Steve Arlington
Partner, Global Pharmaceuticals &
Life Sciences Advisory Services Leader, PwC UK
steve.arlington@uk.pwc.com
+44 20 7804 3997

Michael Swanick
Partner, Global Pharmaceuticals and
Life Sciences Tax Leader, PwC US
michael.f.swanick@us.pwc.com
+1 267 330 6060

### Marketing

Attila Karacsony
Director, Pharmaceuticals & Life Sciences, PwC US
attila.karacsony@us.pwc.com
+1 973 236 5640

Sara Solomon
Manager, Global Pharmaceuticals &
Life Sciences, PwC UK
sara.solomon@uk.pwc.com
+44 20 7804 1014

## Healthcare

### Leadership

David Levy, MD
Principal, Global Healthcare
Industry Leader, PwC US
david.l.levy@us.pwc.com
+1 646 471 1070

Fiona Nicholas
Partner, EMEA Healthcare
Industry Leader, PwC Arab Emirates
fiona.nicholas@ae.pwc.com
+971 4 304 3108

Guy Brandenbourger
Partner, Healthcare
Industry Leader, PwC Luxembourg
guy.brandenbourger@lu.pwc.com
+352 49 48 48 57 16

### Marketing

Todd Hall
Director, Global Healthcare
Marketing, PwC US
todd.w.hall@us.pwc.com
+1 617 530 4185

Cristina Santoro
Global Healthcare
Coordinator, PwC Italy
cristina.santoro@it.pwc.com
+39 06 570 83 24 17

***www.pwc.com***
***www.pwc.com/pharma***
***www.pwc.com/healthcare***
***www.pwc.com/medtech***

This publication has been prepared for general guidance on matters of interest only, and does not constitute professional advice. You should not act upon the information contained in this publication without obtaining specific professional advice. No representation or warranty (express or implied) is given as to the accuracy or completeness of the information contained in this publication, and, to the extent permitted by law, PricewaterhouseCoopers does not accept or assume any liability, responsibility or duty of care for any consequences of you or anyone else acting, or refraining to act, in reliance on the information contained in this publication or for any decision based on it.

© 2011 PwC. All rights reserved. Not for further distribution without the permission of PwC. "PwC" refers to the network of member firms of PricewaterhouseCoopers International Limited (PwCIL), or, as the context requires, individual member firms of the PwC network. Each member firm is a separate legal entity and does not act as agent of PwCIL or any other member firm. PwCIL does not provide any services to clients. PwCIL is not responsible or liable for the acts or omissions of any of its member firms nor can it control the exercise of their professional judgment or bind them in any way. No member firm is responsible or liable for the acts or omissions of any other member firm nor can it control the exercise of another member firm's professional judgment or bind another member firm or PwCIL in any way. NY-12-0250