BIOVOX

WHITE PAPER
MAY 2016

Sharing Life Sciences Innovations

In Vitro Diagnostics

In this issue:

1

BIOVOX WHITE PAPER: IN VITRO DIAGNOSTICS

Table of contents

INTRODUCTION

This white paper discusses the challenges and opportunities of in vitro diagnostics (IVD) in Europe and the US. For example, why do VCs shy away from IVD investments? Maybe a diagnostics company doesn't need big money? We review successful business models – turns out that there are different roads to success, though partnerships are definitely a key factor – and discuss why American IVD companies are having trouble implementing their (successful) US-business models in the European market.

We compare home-brew tests with strict FDA-regulated tests and the technology transfer process with easy-to-use off-the-shelf kits, and we examine closed systems that control every step of the diagnostic process. Technology changes quickly in the IVD market, but the regulatory and reimbursement aspects are lagging behind. IVD companies face many challenges, not the least of which is the fact that they make up a mere 2% of the healthcare budget even though 70% of healthcare decisions are influenced by the outcome of diagnostic tests. It seems diagnostics are severely undervalued by healthcare stakeholders. But at the same time they are on Google's radar … So what's happening here?

We also take a closer look at successful Belgian IVD companies: Belgium turns out to be an important hotspot of IVD technology and R&D, monitored closely by big IVD players. The Belgian companies lack the support of a collaborative ecosystem and a stronger focus on commercialization might just be the potion for success!

Ann Van Gysel – CEO Turnstone Communications

Turnstone and BioVox invited six experts from the Belgian Diagnostics industry to discuss these topics:

- Paul Appermont, CBO and Chairman of ADx NeuroSciences
- Geert Maertens, CSO at Biocartis
- Werner Verbiest, Global Head of Janssen Diagnostics
- Luc Segers, Vice President of Marketing & Sales at Multiplicom N.V.
- Emil Pot and Thea van der Wijk, European patent attorneys with biotech expertise at NLO

Moderated by:
Ann Van Gysel and Jef Van der Borght, Turnstone Communications and BioVox

EDITORIAL – BELGIUM: AN IVD TECHNOLOGY PROVIDER WITH POTENTIAL

What better place to dive into the state of the art of Belgium's IVD sector than Ghent's Technology Park, one of the country's most prominent life sciences hotspots? At NLO's brand-new Belgian offices, we're joined by Paul Appermont (CBO and Chairman of ADx NeuroSciences), Luc Segers (Vice President of Marketing & Sales at Multiplicom), Werner Verbiest (Global Head of Janssen Diagnostics), Geert Maertens (CSO at Biocartis) and Emil Pot and Thea van der Wijk (European patent attorneys with biotech expertise at NLO). For a few hours, we were able to pick their brains and find out how they view the sector's challenges and opportunities.

The different faces of IVD

Home-brewed vs FDA-approved tests

The US Food and Drug Administration (FDA) views IVD as the reagents, instruments and systems used in the diagnosis of disease. In the field, the subject isn't always that strictly delimited. A large percentage of the assays performed by laboratories are developed in-house. In contrast to commercial products, these aren't FDA approved or registered. They are merely subject to the accreditation processes of the labs, which aren't as strict as the rules imposed by the FDA. While they are used in clinical practice, these home-brew tests can't be considered true IVD tests, due to the lack of validation and guaranteed quality. Consider the amount of effort IVD companies dedicate to the development and validation of new assays: at Biocartis, for example, six people spent three years optimizing the KRAS mutation test for Idylla™. No laboratory can assign this kind of effort to the development of an assay that will only be used internally. The FDA is aware of this problem and is seeking the authority to oversee these laboratory-developed tests.

In addition to a regulatory context, the term "in vitro diagnostics" is also highly important in a contractual environment, where it specifies for which types of assays a biomarker can be used. Here, IVD use is distinguished from, for example, research-only use.

Clinical practice

In clinical practice, the boundaries of IVD are well defined in pathology, where there is a patient waiting for a clinical decision. In the standard procedure, the laboratories receive patient samples from physicians and report the results back to them. The borders are less clear in genetic testing, as leaps in sequencing technology are blurring the line between diagnostics and research. As the cost of sequencing goes down each year, more genes can be covered within the same reimbursement cycle. For example, in breast cancer, the *BRCA1* and *BRCA2* biomarkers are well known. The latest panels tend to characterize a lot more genes. In Belgium, reimbursement is arranged for 4 or 5 genes, but laboratories typically include 25 genes, as the impact on cost is negligible. These additional genes are used for research purposes. The data is pooled and coupled with relevant patient information.

Some companies have built a business model around this, hoping to capitalize on the giant amounts of information collected. However, in recent years there has been a countermovement in which public initiatives collect data from laboratories and physicians, who have treated the patient and seen the effect of mutations and drugs firsthand. Multiplicom, which has recently added data analysis to its services, has made it part of its policy to make its results open to these public initiatives to help further diagnostic and clinical research.

Luc Segers – Vice President of Marketing & Sales at Multiplicom N.V.

Our results are available for public research initiatives

European reimbursement policies present a serious challenge for companies like Multiplicom. Tailoring products to the market in a fast-evolving field isn't easy. We currently include 25 genes in our *BRCA* hereditary cancer panel. Some countries consider that too many, while others point out that additional genes could be included. We created a consensus, and our products are successful in different markets.

The approval of these panels is very much locally driven, but overall we notice a cycle, influenced by technological innovation and medical added value. I expect that the panels will become more focused within 2 to 3 years. For example, in Germany, where 34 genes are currently included, reforms are underway that will limit the reimbursement to 5 genes, and the remaining 29 will be strictly for research purposes.

More on Multiplicom on page 27

Building a business: many roads to success

Europe has a distinct ecosystem for diagnostic companies. Its customers are typically clinical laboratories that provide services to physicians. In the United States, a centralized system that offers service testing to end users directly is more common. This distinction makes it difficult for US companies to find initial success in the European market.

A centralized system is hampered in Europe by a number of constraints. First, European labs don't send out samples. Historically, our logistics services weren't as well developed as in the US, resulting in higher shipping costs. Furthermore, protectionist legislation prevented the introduction of this model. For example, in Switzerland, a test is only reimbursed when the analysis is performed in a Swiss lab. US companies were obliged to transfer knowledge and technology to the European labs in order to bring their tests to the market. The enormous upfront cost, however, limits the number of labs that can be reached.

Multiplicom successfully overcame these issues by creating easy-to-use kits, compatible with standard equipment that allowed laboratories to perform the tests themselves at a low cost. As a result, they no longer needed to sends samples to specialized labs, here or abroad.

> *Laboratories acquiring NGS instruments needed to have reliable, ready-to-use panels to run diagnostics. Multiplicom was the first to offer such a solution.*
>
> *LUC SEGERS – Vice President Marketing & Sales at Multiplicom N.V.*

In Europe, this is the model that works best. Multiplicom's strategy consists of making established and validated gene panels available in a better, easier way. These panels are more affordable, more sensitive and more accurate, creating great added value for the customer. In addition to these kits, the company's services were recently expanded to include data analysis. Service testing is also available to their customers, so they can offer the new tests immediately, while they are still setting up the analysis internally. Multiplicom will not offer service testing to physicians directly, as it would lead to a direct competition with Multiplicom's main customers, the genetic labs.

ADx NeuroSciences' approach to valorizing its assets is entirely different. Instead of enabling access to well-known biomarkers, the company focuses on the identification of new markers for neurodegenerative diseases. This includes the early detection and clinical monitoring of Alzheimer's and Parkinson's disease, brain injury, ALS and some other indications. The essence of the company's R&D strategy is discovering new antibodies or identifying promising candidates on the market for licensing. As a supplier of unique antibodies, ADx has the know-how to help IVD companies develop an assay on its own system or platform. The ADx antibodies are used in kits that are created and marketed by a commercial partner, such as Euroimmun.

Paul Appermont – CBO and Chairman of ADx NeuroSciences

We've chosen a niche and strive to be the very best. Our R&D approach and business model are unique worldwide. We are the only supplier of novel antibodies and know-how for companies developing tests for neurodegenerative diseases. In addition to other IVD companies, we also focus on pharmaceutical companies. Their success depends on which route they have chosen to develop anti-Alzheimer therapeutics. Most efforts currently fail, mostly because they are not able to focus on the correct patient groups. About 80% of the current R&D efforts in therapeutics are in amyloid-β. We can offer a range of additional biomarkers such as neurogranin, synuclein or even ApoE. These new markers allow researchers to pick up the right signals early on in the disease, and help them select the right patient populations. Our technology can be used as an initial inclusion criterion for clinical trials, and in the future as a companion diagnostic to stratify patients once a treatment is available.

More on ADx NeuroSciences on page 18

In addition to pathology laboratories, new biomarkers provide the pharmaceutical industry with the tools to stratify patients, and they can be used as an inclusion criterion for clinical trials of new therapeutics. Unfortunately, convincing "big pharma" of the added value of innovative biomarkers can be a slow and frustrating process, despite the consensus on the importance of patient stratification and early diagnosis.

Although Janssen Diagnostics is part of a major pharmaceutical company, its business model is primarily externally oriented. Instead of trying to control the entire diagnostic process from sample preparation to result, they look for optimal partners and platforms to ensure their assays and biomarkers are as widely available as possible. In contrast with the smaller diagnostic companies, the value doesn't only come from selling kits or assays, but also involves bringing solutions to the entire company. For example, companion diagnostics have a direct link with Janssen's therapeutics. In addition to complementary diagnostics aimed at improving a patient's entire regimen, new biomarkers are being developed to facilitate earlier detection. This is an essential part of Janssen's disease interception strategy, where diseases will be treated before the first symptoms arise. Naturally, the developed solutions are also used internally to stratify patients in the company's own clinical trials. Service testing for these trials is only performed in a central lab in Beerse.

In the near future, key drugs will be approved for subsets of patients, and the borders between pharma, diagnostics and device companies will fade. In personalized and precision medicine, bringing the right medication to the right patients is crucial. The different technologies and the branches of the healthcare industry will further converge. More and more attention will go to early interception and prevention, too.

WERNER VERBIEST – Global Head of Janssen Diagnostics

Biocartis' business model takes a more challenging route, bringing existing biomarkers to genetic labs in a more user-friendly way. The company developed a new hardware molecular diagnostics platform — a kind of minilab called Idylla™ — that works in combination with assays for oncology and infectious diseases. In this hermetically sealed system, the entire diagnostic process is fully automated and controlled, from sample preparation to result. All steps of the process are engineered in depth and fully validated, which represents a significant investment of time, money and effort. This holistic approach is worth it, however, as Idylla™ allows a fast and highly accurate in-depth diagnostic analysis.

Geert Maertens – CSO at Biocartis

Flexibility is key in a fast-changing sector

The inherent risk of our strategy is the lack of flexibility to adapt to changes in the IVD sector. When embarking on an endeavor like this, you need a strong vision of what will be relevant in 5 years. And the potential to invest upfront. Our Idylla™ platform development cost has been close to €500 million, an effort that is out of scope even for major IVD companies including Abbott or Roche Diagnostics. We strive to make a big impact on healthcare worldwide and today, we see that we are on track, delivering the intended intermediate results year after year. This helps consolidate the trust of our investors and grow the company.

More on Biocartis on page 21

Biocartis also wants to enter the US market. While the optimal route for commercialization is still being investigated, a solid product strategy is already in place. The first goal is getting FDA approval for the Idylla™ IFV-RSV Panel test (flu and RSV) developed together with Janssen Diagnostics, followed by FDA approval requests for a number of oncology assays. In terms of the number of specialized molecular labs that will use Idylla™, Biocartis sees no fundamental difference between the European market and the centralized-testing-focused US market. However, its ambition is to eventually break out of these molecular labs and make the Idylla™ "minilab" available to clinicians

directly. Key opinion leaders in IVD agree that accessibility to testing is a big problem, as high-precision diagnostics are needed to enable high-precision treatments. This is what drives Biocartis' collaborations with companies who develop these high-precision treatments, such as Merck and Amgen.

> *There is a great dichotomy, even within some EU countries, in the availability of diagnostic facilities to perform high-quality diagnostic tests. With our platform, patients will be helped faster, better and closer to their homes.*
>
> *GEERT MAERTENS – CSO at Biocartis*

Belgium has more than one trick up its sleeve

A great diversity of companies is present in the Belgian IVD scene, ranging from small, early-stage spin-offs to divisions of the biggest international firms. At its heart, Belgium is an R&D country.

Belgium doesn't have a representative among the biggest IVD companies, but it has a number of unique assets and smaller companies that create technical expertise, ensuring a strong overall position. In turn, strong academic groups and clinicians performing groundbreaking clinical research are a continuous source of input for the Belgian companies. Fundamental research is used to develop prototype testing, which is immediately evaluated in the lab or even in a clinical setting. This leads to new products and publications, so both parties benefit from the close collaboration.

> *Looking at diagnostics suppliers worldwide, there is no Belgian company in the top 10 players. However, they do use our technology.*
>
> *PAUL APPERMONT – CBO and Chairman of ADx NeuroSciences*

Belgium is one of the key players worldwide in clinical research. A high concentration of top-level labs in different disease areas is present, as evidenced by their publications. Furthermore, many clinical trials in any disease area from phase I to phase III are conducted here. This is driven by the universities and hospitals and supported by a swift and accommodating regulatory process, as well as by well-organized governmental ethical committees.

It is a well known fact among pharmaceutical companies that Belgium is the ideal country to set up new clinical trials fast.

EMIL POT – European patent attorney at NLO

Based in a small country, the Belgian market is too limited for companies to thrive. This drawback, however, works to the industry's advantage, as it forces the companies to keep a wide view on the world and become multicultural and polyglottal in nature. Belgian companies have learned to travel the world, listen to clients and find a consensus. Their ability to tailor solutions to the customer is well honed. This is a relevant skill that is often underestimated by US-based companies that move into the European market and suddenly face different cultures, regulatory processes and languages.

Another strength is the capital available to support young companies. Government institutes such as VLAIO (formerly IWT) provide non-dilutive funding of up to 70% of the research budget to evaluate whether new products or services have potential, to help them overcome initial hurdles or even to perform larger industry research projects. This kind of support creates the opportunity to build a company in smaller incremental steps, thereby limiting the overall risk. Belgium offers a great mix of funding sources that are willing to invest in great ideas and act as vessels to bring research to the market, including venture capitalists, family offices and holdings, commercial parties and universities.

In Belgium, a unique type of private investor is present who believes in technology and has a long-term vision. This stands in stark contrast to other countries, where often mostly traditional VCs are present, expecting a quick return of investment.

GEERT MAERTENS – CSO at Biocartis

Belgian family offices are very knowledgeable in the field and understand the inherent risk of their investment. This makes the route more accessible. Thanks to these measures, Belgium has surpassed even bigger countries like The Netherlands in terms of the number of start-ups. The challenge is being able to grow these companies past a certain threshold in a small country. Biocartis has set the standard in IVD, taking a broader view and aiming for stock markets such as Euronext for additional capital.

It's not only investors who provide financial incentives. The Belgian government instituted a very favorable tax break system, one that, despite criticism, has proven its value in stimulating employment. While founded in Switzerland, Biocartis transferred its patents to its Belgian branch in return for a more favorable tax regime. Biocartis has grown from 30 to 300 people in a couple of years' time.

> *Despite the war on talent caused by international companies moving to Belgium, we still succeeded in finding the right people quite easily.*
>
> *LUC SEGERS – Vice President Marketing & Sales at Multiplicom*

Another advantage that draws IVD companies to Belgium is the availability of highly skilled, specialized personnel. Not only do the universities ensure a steady stream of new talent, but Belgium also has a longstanding tradition in the field. A second generation of healthcare companies is already being built. The senior employees in these companies have been through the motions, both in terms of research and business. Being able to hire people that bring immediate value to your company is priceless.

Time to make money! Protect your assets

For the IVD sector to thrive further, young R&D companies new to this field should be more aware of the importance of intellectual property. They have a tendency to focus on publications, possibly undermining patentability (and potential future value).

> *R&D countries such as Belgium have one main asset to sell: Intellectual Property Rights*
>
> *EMIL POT – European patent attorney at NLO*

Belgium may be great at innovation, but it is way behind in protecting IP compared to neighboring countries and technologically advanced countries of a similar size such as Sweden or Switzerland. Belgium files significantly fewer patent applications, indicating that changes are needed in the country's IP culture.

IP turns out to be especially challenging for early IVD companies, as it is very difficult to patent diagnostic methods (see page 40). This has created a negative atmosphere, leading investors to snub diagnostics, as it seems more difficult to make money with this type of technology. The costs of patenting are also extremely high, which makes them hard to bear, especially for young companies, who often need a commercial partner or investor to cover the expense. However, patenting is a must, as a strong IP position provides important leverage in negotiations with investors and pharmaceutical companies.

Emil Pot – European patent attorney at NLO

IP professionals and scientists should start working together early on

IP attorneys should take a proactive role in the research environment and create more 'IP awareness' among scientists. In this respect, the IP attorney can play a valuable role while interacting with the scientist in an early stage, contributing to the ongoing research with suggested additional experiments, which at the same time can result in a better support of the patent claims. These results are more often than not also very interesting for a scientific publication. Early phase interactions allow you to review results together, find out what others are working on and design a strategy that leads to more competitive research and better IP.

Thea van der Wijk – European patent attorney at NLO

Patents will help you serve the patient and market your invention

Researchers often don't have an incentive to valorize their results. The mindset is 'we do our research with public funds, so our results should go to the community.' Very true, but this doesn't help the patient! Awareness should be created that when you make your data public, no company is going to invest in it to bring it to the market, because there is no way to earn back the enormous investment needed. This is also a problem in politics, where policymakers challenge the price of drugs whose inception was funded with public money. They don't take into account the additional investment costs made by the private sector to commercialize early stage research. This is the change in mindset that is needed: If you have a valuable invention, make sure you patent it, so someone will be willing to help you create a finished product.

Even for Janssen Diagnostics, which is part of a big pharmaceutical company and can rely on internal venture capital, a strong patent portfolio is essential to ensure the widest possible market for its the products and maintain an optimal strategic position.

A shift in value toward diagnostics is also needed in the entire healthcare sector. Not only academia, but also investors, payers, government and big pharma historically attribute more value to new therapeutics. While the validation of new biomarkers takes longer and the return on investment is further away, diagnostics will be an essential element in medical treatment, providing early insight into diseases and allowing an earlier and more targeted therapeutic intervention.

Diagnostics provide value, delivering information about how to better treat the patient. This should be valued more than just the revenue obtained from selling kits and reagents. However, this requires a mind shift in all stakeholders involved in healthcare.

"In the early days of HIV care, payers were prepared to spend $ 20,000 per patient each year for a treatment that was uncertain to be successful. At the same moment, the reimbursement of a $ 500 Dx test that provided valuable diagnostic information on the efficacy of these regimens was approved after several years of generating a ton of data. There is a change happening now and a shift to evaluate outcomes."

WERNER VERBIEST – Global Head of Janssen Diagnostics

Tackling future challenges

How to survive the first years?

Diagnostics companies face very specific challenges. Start-ups are often in a position that forces them to get a product on the market as soon as possible. Generating income from sales early on is a huge challenge, successfully conquered by the Belgian companies ADx NeuroSciences and Multiplicom. Often companies spend years developing a test without focusing on how to bring these products to the market. You will need a significant cash reserve to survive. The new and fast-evolving diagnostic market presents a continuous challenge for an IVD business development team, and the process is often further impeded by strict clinical guidelines and complex reimbursement schemes.

> *We were fortunate to connect with a supportive commercial partner – Euroimmun – early on. We could focus on what we do best – R&D and building a prototype – and they took care of the rest. Having a product on the market in our first year turned out to be very important.*
>
> *PAUL APPERMONT – CBO and Chairman of ADx NeuroSciences*

Convincing investors and partnering with big pharma is an essential step in growing your diagnostics company. A deal with a pharmaceutical company for the use of certain biomarkers is often seen as a validation that you're doing good work.

Controlling variability of test results

In addition to the large investments needed to gain a strong IP position, other costs can hamper the evolution of a diagnostics company. In the European model, where each clinical laboratory is preferably capable of performing the tests themselves, validation is essential. Both molecular and non-molecular diagnostic tests are faced with a certain level of variability, leading to different results in different labs.

Companies have to find solutions to overcome variability and ensure their products are used properly. There is a trend to evolve toward an integrated system that controls all steps from sample to result. This requires huge technological investments or strategic partnerships with hardware developers. A more short-term solution is investing in a technical team to ensure customer education and support. However, such a technical team, in addition to a sales team, would double the costs, making them difficult to support for small start-ups.

Creating a collaborative ecosystem

Compared to the US or Asia – where you can find a more open and collaborative ecosystem – the dynamic in Europe is completely different. Europeans seem to lack the attitude to strive for an ecosystem where everyone can gain value. Creating more collaboration, communications and transparency will be an important driver for increased business and innovation. It will also create leverage when it comes to tackling common challenges involving regulations and reimbursement. More and more European companies understand that now. Only labs that are open to collaboration will continue to thrive; it's called natural selection.

Ann Van Gysel – CEO Turnstone Communications

Collaboration is key to success

In a country as small as Belgium, the communication and collaboration between the regions Flanders and Wallonia can be improved. Both regions have world-renowned research centers, clinical expertise and many spin-offs, but we hardly know what's going on across the border. Within Flanders, VIB is centralizing top-notch biotechnology research, but diagnostics is not a main focus. The sector calls for a dedicated national diagnostics platform that stimulates collaboration and brings the sector to a higher level. Pooling clinical research and expertise would mean a giant leap forward. Also, on an international scale, more collaboration is always the key to success. Look at how AIDS was tackled: By joining forces in well-funded consortia and sharing data and best practices, researchers managed to turn AIDS from a very deadly disease into a chronic but treatable condition.

> *There is a steep hill to climb, but technologies like the IMEC chips or nanoparticles such as Google's nanobots will disrupt diagnostics. However, they are complementary, and 'classical' IVD companies will still be able to leverage expertise such as biomarker development, sample preparation or automatization.*
>
> *GEERT MAERTENS – CSO at Biocartis*

Non-healthcare companies are gaining interest

A new challenge is the introduction of outside players in the healthcare sector, which is driving consumerization. Consumer electronics companies, the automobile industry and IT giants such as Google are entering the field and leveraging their expertise in collecting and analyzing data. Also, new disruptive scientific breakthroughs such as nanotechnology will impact the field and make current platforms obsolete. IVD companies should be extremely vigilant, monitoring the latest trends to stay relevant, adapting their technology and setting up partnerships that will allow them to stay on top of their game. To ensure a successful future, they must adopt a multidisciplinary approach and collaborate with external parties.

Werner Verbiest – Global Head of Janssen Diagnostics

These new types of companies entering the market will boost the diagnostic industry. They will help make the value of data more clear to investors. Companies have to make sure they don't get stuck in the old ways and always be open for new collaborations. At Janssen Diagnostics, we have joined forces with Philips to create a point of care test for neuropsychiatric disorders. We are constantly scouting for new opportunities worldwide through the Janssen Innovation Centers.

More on Janssen Diagnostics on page 24

Regulatory hurdles

A final challenge to innovation in the IVD sector is the pre-market approval system that Europe is preparing to implement in addition to the current CE marking. This will require companies to perform a health economic study of their new products. Innovation will be drastically set back, as for many of the smaller companies in diagnostics, it will be a challenge to fund these studies. This will result in a proliferation of research-only assays. Such hyper regulation is converging with the FDA strategy, which resulted in an ecosystem where 80% of assays in practice are homebrew and not monitored at all.

BELGIAN IVD COMPANIES IN THE PICTURE

ADx NeuroSciences

ADx NeuroSciences might be described best as the Intel of biomarker assays for neurodegenerative disease. They don't create complete kits, but their top-notch biomaterials are included in the assays detecting disorders from Alzheimer's disease to ALS to traumatic brain injury. Over the years, ADx has created an extensive network of partners and by combining knowledge and expertise, these collaborations are leading to innovative markers and valuable new insights in neurodegenerative diseases.

"The pharmaceutical industry is in need of objective and efficient methods to diagnose neurodegenerative diseases, more specifically in early stages," explains **Koen Dewaele, CEO at ADx NeuroSciences.** "In clinical trials, being able to select the right patients and stratify them into groups is of crucial importance. This way, the right conclusions can be drawn from the data that these trials provide. Determining whether or not a therapy is effective can largely be dependent on the patient selection process."

With more than 25 years of experience in diagnostics, Dewaele knows what he is talking about. Together with three colleagues, he led Innogenetics' Alzheimer's division, and when the company dissolved in 2011, the four companions decided to start their own company revolving around Alzheimer's diagnosis: ADx NeuroSciences.

Knowing your place

Although diagnostics for neurodegenerative diseases is ADx's focus, the company is not a classic IVD company; instead, it occupies a unique place in the market. ADx offers services to both IVD and pharmaceutical companies.

"At ADx, we supply IVD companies with the biomaterials they need to incorporate in their test kits. We use our expertise to develop top-notch antibodies that IVD companies can then implement in their products, assays and diagnostic platforms. I often compare it with the example of Intel: They don't produce their own computers, but they deliver the microchips present in the computers of all of their partners. We don't sell our own diagnostic kits, as we are a truly R&D-focused company, but the tests of our partners all have the ADx technology inside."
– Koen Dewaele, CEO, ADx NeuroSciences

"For pharmaceutical companies, we take a custom approach. We look at the goal of a certain clinical trial and deliver custom products and support in collaboration with our IVD partners. We help labs to select the right tests and perform them in a validated manner for clinical trials. Sometimes our pharmaceutical clients have very specific needs. In those cases, we help our IVD partner in adding modifications to their products. Through this three-way alliance between ADx, pharma and IVD partners, we bring fit-for-purpose solutions to pharmaceutical companies."

Since partnering is central to ADx's strategy, their network is impressive. Next to IVD and pharma, collaborations with academic institutes form the third pillar of ADx's business model.

"Universities and other academic institutions provide access to new antibodies and human samples for testing and validating our assays. Their research leads to innovative biomarkers or new insights into disease states, which is invaluable for a company that wishes to bring these innovations to the clinic. Our academic partners are also important promoters of our company. Co-authorship on important publications emphasizes ADx's search for novelty, and principle investigators that are approached by pharmaceutical companies for clinical trials can facilitate collaborations that includes ADx. They can decide to implement our tests in trial protocols."

"The materials we use are a mix of licensed molecules from universities and materials developed in house. We're not suffering from the so-called not-invented-here syndrome, where all external input is avoided or distrusted. We simply use the best materials. Sometimes we find them with an external partner, and sometimes our own materials outperform the rest. Our neurogranin and phospho-tau antibodies, for instance, were fully developed in-house."

The FDA delay

Despite the fact that some classic markers for neurodegeneration, such as amyloid-β and tau, have been around for years, the market of neurodegenerative biomarkers is still in its infancy. Dewaele is confident that this will rapidly change once therapies and medicines become available that rely on biomarkers for correct application. However, one essential hurdle still needs to be overcome: "We can see that acceptance of the use of these markers in clinical trials is growing rather slowly, as they're not officially approved by the authorities. FDA approval is crucial to demonstrate the robustness of a test and that it is manufactured according to certain standards. The fact that none of the neurological markers are FDA-approved at present causes pharmaceutical companies to remain skeptical. Many companies like ours are looking into the possible trajectory to get approval because it would be a hugely important milestone for the entire industry. Everyone in the business feels that these markers are full of potential and are making beautiful progress. Once the first marker is approved, others will swiftly follow. FDA approval is really necessary to break through to the routine market."

Getting biomarker tests to be routinely used in clinical trials is a second important factor that would significantly expand the market. Neurodegenerative markers can act as companion diagnostics, guiding researchers and caregivers in the decision-making process. Once therapies that benefit from biomarker information are commercialized, reimbursement of these assays can be considered. Dewaele elaborates: "The aging population and related increase in neurodegenerative disease prevalence will greatly increase the need for biomarker assays. Whether these assays will be reimbursed will entirely depend on the benefits they provide: If these tests give crucial information regarding medicine dosage or patient profiling, insurance companies will most definitely cover the costs. Treatments themselves are always much more expensive than the accompanying assay, and if the assay can cut back on unnecessary treatments, insurances will find the test worthwhile, no matter how expensive the test may be. Currently, there is no reason to reimburse the test, because there is simply no validated treatment available for many neurological diseases. Because of that, we can't act on the information biomarkers can provide."

More markers in more diseases

While awaiting the first FDA-approved biomarker, research isn't standing still. As more and more is uncovered about the pathological processes of Alzheimer's and other neurodegenerative diseases, the role and importance of biological markers become more pronounced, especially in an early stage of the disease.

"While amyloid-β and tau are the most established markers within Alzheimer's disease, we are starting to notice how these are not revealing everything. Amyloid-β accumulation can start very early, up to 20 years before the first symptoms of Alzheimer's disease appear. This gives us the opportunity to detect the disease early on, but also means that amyloid is not very suitable for assessing disease symptoms. The neurodegenerative field is focusing more and more on synaptic markers, as the synapses are good indicators of the overall health of neurons. When the synapses start to degenerate, we know that disease symptoms won't be far away. Although amyloid can indicate Alzheimer's pathology, as long as the synapses remain intact, patients won't become sick.

"Each biomarker gives away a specific piece of information, gradually revealing a patient's condition."

"While amyloid can be used as a diagnostic marker, synaptic markers such as neurogranin confer information about the patient's prognosis. For example, this innovative marker can indicate whether a patient will progress to symptomatic disease within one or five years. Again, this is very valuable information for pharmaceutical companies. If these groups can't be distinguished, it's very hard to determine the effectiveness of a therapy or treatment method.

While we initially focused on Alzheimer's disease, we noticed that many of the markers relevant in Alzheimer's are also popping up in other neurological disorders. Alzheimer's disease was pioneering in the research for neurodegenerative biomarkers, but the field is now expanding to Parkinson's disease, MS, ALS and brain trauma. A good example is tau, a marker for neuron damage in Alzheimer's disease. We know that tau is also released into the bloodstream after a concussion, so the protein can also serve as a marker for traumatic brain injury."

Century of the brain

Although the market is still in an early stage, there is no doubt that biomarkers will play an important role in patient diagnosis, prognosis, monitoring and treatment for neurological diseases. Knowledge about the field is growing rapidly, and ADx is ready to bring this knowledge to the physicians and patients. Their unique antibodies for detecting neurological markers rank among the world's best.

"The quality of our biomaterials is the best on the market. You can easily find antibodies online, but they can't be bought in large quantities, are terribly expensive and often not in conditions or of sufficient quality to use in assay design. We produce state-of-the-art antibodies, ideally suited for biomarker detection and implementation on various technology platforms."

The 21st century in medicine will definitely be the century of the brain. Vast uncharted territories are being explored in neurology, new methods and models are becoming available and early diagnostics are giving a new impulse to treatment research. With ADx, we are gradually building a neurodiagnostic company that contributes significantly to the wellbeing of patients suffering from a broad range of neurodegenerative diseases."

ADx NeuroSciences NV
+32 9 261 69 80
Koen Dewaele, CEO
Koen.Dewaele@adxneurosciences.com
Paul Appermont, CBO
Paul.Appermont@adxneurosciences.com
www.adxneurosciences.com

BELGIAN IVD COMPANIES IN THE PICTURE
Biocartis

While there are many innovative biotech companies in Belgium, few are in a position as enviable as that of Biocartis. Over the past few years Biocartis has made a name for itself with the release of its revolutionary diagnostic platform Idylla™ and a more than successful IPO on Euronext Brussels. Since the launch of Idylla™, back in September 2014, the company has been able to fully focus on expanding its menu of available assays. With more and more tests being released, Biocartis rapidly increases its reach and with each available Idylla™ cartridge, it comes closer to becoming an absolute reference within the biotech and diagnostics industry. **Geert Maertens, CSO** at Biocartis explanins.

In 2007, serial biotech entrepreneur Rudi Pauwels founded Biocartis in Lausanne, Switzerland. When looking for suitable regions to accommodate its expansion, Biocartis soon looked to Belgium, and in 2011 the company decided to establish its R&D center and first production unit in Mechelen. Biocartis has been a well-known and respected member of the Belgian biotech community ever since.

Tools of the trade

The Idylla™ molecular diagnostics platform is the foundation upon which Biocartis is built. Idylla™ is the first diagnostic instrument that integrates all steps from sample preparation to analysis, resulting in a fully automated workflow from sample to result. This shortens the necessary hands-on time to less than two minutes. In total, the tests can be completed in a timeframe between 35 and 150 minutes; comparable analyses with previously existing methods can take days or even weeks.

The assays are developed in cartridge form, which can then be run on the Idylla™ platform. Biocartis consciously chose to focus its assay development on the largest and fastest-growing market segments of IVD: infectious diseases and oncology, respectively. As of now, the repertoire of assays includes mutational panels for melanoma, colorectal and lung cancer and an assay that can detect influenza and respiratory syncytial viruses. In the coming years, however, Biocartis will expand its "diagnostic app store" with both solid and liquid biopsy cancer tests when it comes to its oncology test menu, and Ebola and MERS assays, a respiratory pathogen panel and a meningitis panel in terms of its infectious disease test menu.

Broadening the scope

"In the fields of oncology and infectious diseases, we can leverage an important asset of Idylla™: its tremendous potential for multiplexing," says **Geert Maertens, Chief Scientific Officer at Biocartis.** "We can detect a large range of mutations related to a specific cancer. Our KRAS test for colorectal cancer, for instance, analyses 21 relevant mutations in one assay. While today clinicians only need to know whether or not a mutant is present, many drugs are in development that target specific KRAS mutants. By reporting 21 mutations in detail, we have developed a product that can be routinely used for diagnosis, e.g., in hospital settings, and for drug development in clinical trials. We know that in the near future, this additional, detailed info can possibly be very valuable for patient-specific or 'personalized' medicine. This is already the case for BRAF mutations in melanoma, where patient treatment depends on which kind of BRAF mutation is present in the tumor."

"In the market segment of infectious diseases, there is a large demand for syndromic panels. Patients often show general symptoms such as fever, diarrhea or respiratory problems. In these cases, it could be relevant to scan a broad spectrum of possible pathogens in one sample, as quickly as possible. Idylla™ is excellently suited for such use, and here, the speed and multiplex capacity of the system can truly make a difference. An important trend, not only in infectious diseases but in the diagnostics market as a whole, is the move towards a more comprehensive approach. Idylla™ fits perfectly with that notion."
– Geert Maertens, CSO Biocartis

Getting rid of the time factor

With infectious diseases, it is easy to see why time is an important element: infections such as meningitis can have serious consequences in the short term. For cancer, however, this is less obvious, as the disease is generally more chronic in nature. Regardless, the speed of Idylla™ has heralded a true transformation for the diagnostic process in cancer. Maertens elaborates: "Two years ago, people told us that time wasn't important in oncology. It takes a few days before patients can be scanned, the medical board needs to convene to decide on further action, molecular testing takes another two or three weeks. Now that we are able to drastically decrease the time for molecular testing to a couple of hours, the whole process could be sped up."

"We see that Idylla™ has become an enabler: Based on the turnaround time of our tests, certain hospitals try to carry out everything from scans to molecular testing to diagnosis and treatment selection in one single day."

"As such, Idylla™ becomes an essential part of the fast decision-making process. As with many revolutionary technologies, users get accustomed to the fact that it works so tremendously fast. Once they are used to a certain advantage, it's taken for granted, and users start fitting it into their workspaces or daily lives. Idylla™ simply offers the possibility of rapid and highly accurate analysis, which impacts the entire workflow."

Beyond the test

There are still a lot of possibilities for Biocartis in infectious diseases and oncology, and the coming years will see the release of many more cartridges in those fields. In the longer term, however, the company wants to expand the applicability of its technology and use it to design next-generation sequencing preparatory panels. A strange transition? Not according to Maertens: "The Idylla™ tests scan samples for mutations that are most frequently related with a certain type of cancer. For most cancer patients, these assays offer a clear answer to what mutation is causing their cancer and what

types of targeted therapy might be suitable. Regrettably, a small fraction of patients have tumors in which the most prevalent markers are absent. In these cases, the next logical step is sequencing the entire tumor DNA. With our NGS prep panels, we want to form the bridge between regular testing and full sequencing, which requires complex infrastructure and long preparation time. The idea is to incorporate our NGS prep panels in our regular assays. In that way, if our tests would not provide a conclusive answer, running them will already create the NGS library and make it available for sequencing. This again reduces the time of the entire process from several days to a couple of hours with only one minute of actual work."

Risk assessment and synergy-searching

Now that Idylla™ is starting to establish itself as a valuable diagnostic system, it's highly important to expand the existing menu of tests as fast as possible. Luckily for Biocartis, many parties are interested in partnering up for the development of tests relevant to them. For example, pharmaceutical companies could develop specific cancer treatments that fit a certain mutation or cancer. As such, some programs can be accelerated through partnerships.

"The platform offers so many possibilities, sometimes we don't know what to do first. Of course you can't do everything by yourself, so partnerships are an important aspect of our strategy. Because of all the possible roads we can take with Idylla™, we really need to carefully select the projects to invest our time in. Some pharmaceutical companies propose to co-develop totally new tests, linked to a specific treatment offered by the partner in question. If the developed test is very specific, narrow and only useful in conjunction with the therapy, we take a huge risk: should the therapy fail in clinical trials, the tests have no further purpose. Making that risk assessment is utterly important. Ideally, we choose to set up partnerships for the development of tests that are already in our pipeline. Recently, we announced our commercial and development partnerships with Amgen and Merck, two industry greats. Together, they possess 60% to 70% of the colon cancer market, and both require RAS mutation tests on a routine basis. Thanks to the collaborations with these companies, we can drastically accelerate these programs that were already in our pipeline. Synergies such as these are really what we are looking for in partnerships and collaborations. In general, accessibility to sophisticated molecular testing is a very important need for pharma companies. This is where Idylla™ can create that market access.

The choice of whether to develop a product internally or to start a partnership is also highly dependent on the technology behind the assay. If we have already released a similar product, we will opt to develop the new product ourselves instead of going through an entire tech transfer to an external party. If the test is relatively simple and the expertise is with the potential partner, setting up a collaboration is a logical step. In those cases, we can support in the sample prep part of cartridge development and help with general platform support."

An even better future

Biocartis just keeps gaining momentum. The number of installed Idylla™ instruments is increasing rapidly, the R&D engine is running at full capacity with 17 ongoing projects and cartridge production is scheduled to receive a significant boost with a second, larger manufacturing line operational by 2017. Idylla™ is also preparing for its FDA evaluation at the end of the year, hopefully opening the door toward the US market. With a bright future ahead, Biocartis has many things to look forward to.

Biocartis
www.biocartis.com

Renate Degrave
Manager Corporate Communications & Investor Relations
rdegrave@biocartis.com
+32 15 63 17 29

BELGIAN IVD COMPANIES IN THE PICTURE

Janssen Diagnostics

The diagnostic experts within the Janssen Pharmaceuticals group refer to themselves as the engineers of precision medicine solutions, or Janssen Dx for short. **Werner Verbiest, Global Head of Janssen Dx**, explains: "We are evolving the traditional pharmaceutical mode in line with the current healthcare reality and trends. We are focusing on improved healthcare outcomes for patients by bringing better and personalized solutions to the market. Diagnostics are all about predicting better outcomes, better efficacy, lower toxicity and improved compliance."

A jack-of-all-trades

Janssen Dx aims to bring precision medicine to the market in several fields, including infectious diseases, cardiovascular diseases, metabolism, oncology, immunology and neuroscience. Verbiest says: "In each disease field, the research teams are developing biomarkers of which some will evolve in true companion diagnostics, where there is a direct link between the drug and the diagnostic, to target the population that will benefit from the drug. In addition, some of these may evolve to complementary diagnostics, which may be beneficial to the disease state and the drug, but not directly linked to the drug."

Infectious diseases

Historically, in infectious diseases, precision in personalized medicine has always played a key role. Determination of the specific organism that causes the infection is of major importance. "When you have a fever, you go to the doctor and are often treated empirically. But what is causing the disease? Is it a bacteria or a virus? And what type of virus? RSV (Respiratory Syncytial Virus), a coronavirus or the flu? We want to determine this exactly and treat the patient with the right therapeutic," explains Verbiest. Janssen Dx develops diagnostics and Real World Dx information with their internal Johnson and Johnson's Global Public Health teams for emerging markets, as for example for multi-drug resistant bacteria, and for latent tuberculosis. They also develop novel diagnostic strategies for *Onchocerca volvulus,* a soil-transmitted worm that causes river blindness. With hepatitis, they are exploring novel approaches and diagnostics to follow-up on the progression of the liver via non-invasive diagnostics.

At Virco, which Janssen acquired in 2002, HIV was the area where the first steps in personalized medicine were made. "We had access to a database containing over 650,000 samples from different HIV patients, characterized geno- and phenotypically for viral resistance. Based on this information, we were able to develop a new generation of drugs that were still active against resistant viruses and could give personalized guidance to physicians. We are now applying what we learned in HIV to other disease fields."

Oncology

Oncology is an area that is growing incredibly fast, where all kinds of molecules – small, large, monoclonal and many others – are in development. Janssen Dx has a strong pipeline for the assessment and management of hematological and prostate cancer. "We are developing platforms with multiple partners to improve the diagnosis of different cancer types, for FDA-regulated in vitro diagnostics as well as for laboratory developed tests," adds Verbiest. Ultimately, these diagnostic tests will ensure the appropriate use of our therapeutic approaches and increase the beneficial outcomes of many patients.

Neurology

It is estimated that one in three people in the world will get Alzheimer's disease. "Like other pharmaceutical companies active in Alzheimer's, together with the Janssen R&D teams we are actively looking for diagnostics, including non-invasive diagnostics, that can detect Alzheimer's pathology even before patients get symptoms." Furthermore, Janssen Dx is active in the field of treatment-resistant depression and the importance of genetic factors. They are developing diagnostics alongside the development of the drug.

Collaboration is key

"We are convinced that innovation is mainly happening outside, in different corners of the world, in academia, in small companies. Innovation is all about accessing new insights and approaches."

Some of Janssen Dx's products are developed in-house, but in general, they reach out to the diagnostics ecosystem and a network of partners for cutting-edge innovations. Verbiest explains: "We evaluate the diagnostic need for a program, and then we try to find partners that can offer platforms that suit our demand. As we are active in so many fields, it is impossible and ineffective to develop each platform on our own. You really have to work with external parties to bring precision medicine to reality." In parallel to this model, Janssen Dx has CLIA-CAP ISO certified labs on both sides of the ocean, where they can validate candidate biomarkers to more rapidly advance diagnostic developments. "Our model is to complement internal capabilities with a large network of external partners," explains Verbiest.

Janssen Dx's partners are very broad and range from academic centers that perform early-stage research to startup biotech companies and even direct competitors. Some examples of how Janssen Dx capitalizes on new external platforms are its collaborations with Biocartis and Philips.

"We invested in Biocartis, but are also co-developing assays with them," says Verbiest. "For example, assays to diagnose infectious diseases such as Ebola, and multi-parameter tests for respiratory infections, allowing us to detect different types. These assays are developed to be used on Biocartis' Idylla™ platform."

Another example, in neuroscience, is a project with Philips. Philips developed a hand-held device that can be used for point-of-care diagnostic testing. "We created an assay using Philips' device to assess drug levels of patients on certain schizophrenia medication in order to provide the physician with real-time information to better understand a patient's response to the drug and whether lack of adherence could be an issue. The diagnostic information allows the physician to better engage with the patient and the family in a conversation to further improve the regimen and also to explore alternative treatment options," continues Verbiest.

"Medicine is split in many different disciplines, but the model I described is a holistic model. In order to move to a new model, you have to connect the dots, link the different components and measure the outcome. One of the key hurdles is that we are not yet fully digitalized and are not yet capturing data in a longitudinal way. This kind of information is invaluable. It is why Facebook and Google are among the biggest and most successful companies in the world. They have access to the data of 1.5 billion people on the globe, opening a tremendous amount of opportunities. Imagine what this could do if this would be the same in healthcare. Despite some privacy and ICT issues that we – meaning patients, physicians, academia and industry – have to overcome, we are making a lot of progress in that direction. Precision medicine for everyone is not that far away. I am positive that it will become the overall standard in the near future."
- Werner Verbiest, Global Head of Janssen Diagnostics

Even with competitors

Janssen Dx is in a rather unique position, as they aren't a traditional diagnostic player, but more of an integrated organization. "Some pharma companies are our main competitors, but at the same time, we have to collaborate closely with them to advance science and patient care. We create complementary products such as diagnostics, devices and mobile apps alongside new drugs to support a better quality of life and improved outcomes. We move toward early screening and stratification of patients, and interception of diseases before symptoms arise. Janssen Dx heavily invests in that area."

"Creating a diagnostic is not an objective by itself; it is a means to an end. It is a vehicle for finding a deeper understanding of a disease and for bringing a solution. I think Janssen, and our Dx teams, puts more emphasis, more brains and more resources into this than many of our competitors."

Janssen Diagnostics
a division of Janssen Pharmaceutica

www.janssen.com

Frederik Wittock, Global Communications Director
Janssen Research & Development
fwittock@its.jnj.com

BELGIAN IVD COMPANIES IN THE PICTURE

Multiplicom N.V.

Multiplicom offers molecular diagnostics products, focused on human genetics, oncology and prenatal testing. The company was built on a technology that came from the University of Antwerp and VIB, allowing multiplexing on a very high level. They combined this technology with Next Generation Sequencing (NGS), resulting in convenient and reliable products, enabling a simplified workflow for all laboratories who want to implement molecular diagnostic tests within these fields.

A strong focus on DNA analysis

Multiplicom is constantly expanding its product range. Human genetics was implemented in 2011, oncology tissue testing in 2013, and prenatal testing was brought to the market last year.

Multiplicom

Enabling personalized medicine

Human genetics

Multiplicom offers genetic tests for predisposition for cancer and specific monogenic diseases such as cystic fibrosis. They create library preparations targeted to specific genes that are indicative for certain diseases. **Luc Segers, Vice President of Marketing and Sales at Multiplicom**, comments: "In the beginning, we only provided the library preparation, but now we are also involved in the analysis of the data. Companies can upload their sequencing data (the FAST-Q file) on our server, which does the analysis for them. Based on these results, laboratories can make a diagnosis. The complete process from sample to result takes 2.5 days on average." These diagnostic tests work with an Illumina as well as with a Life Tech apparatus.

Oncology

The company also creates diagnostic tests to analyze tumors. Based on the mutation results, a certain treatment decision can be made. Tissue as well as liquid biopsies from tumors can be examined. "The biggest challenge for liquid biopsies is the sensitivity," mentions Segers. "The cell-free tumor DNA in the blood is less than 1%, which is very low for detection. However, we have set up a program to optimize the whole library preparation, which makes it technically possible to detect these low levels." The test consists of a panel of 3 to 5 genes, present in tumors causing the 5 major druggable cancers, i.e., prostate, breast, lung and colorectal cancer. "We also have a product that targets 26 'hotspot' genes in tumors. With these panels, we can do 90% of what a pathology lab can."

Prenatal

In October 2015, Multiplicom launched a CE-marked non-invasive prenatal test (NIPT). This test only requires a blood sample from the mother, which always contains a small amount of baby DNA, for the detection of trisomy 21 (Down syndrome), trisomy 13 and trisomy 18. Segers says: "The reaction to the test was overwhelming. The interest is very high, the test is well received by gynecologists and laboratories. The adoption of NIPT in the clinical practice is happening now."

For the development of its assays, Multiplicom cooperates with different universities and research groups, such as the Department of Medical Genetics at the University of Antwerp (Prof. Dr. C. Vrints, Dr. J. Saenen, Prof. Dr. B. Loeys and Prof. Dr. Lut Van Laer) and universities in France, Germany and Switzerland. Multiplicom also cooperated with AstraZeneca for the validation of the BRCA panel for the treatment of ovarian cancer with their PARP inhibitor.

Reimbursement of NIPT for low-risk pregnancies makes the difference

Multiplicom has about 25 products on the market for genetic and pathology labs. "Since the startup of the company in 2011, we immediately started selling products, so we had a revenue model from the beginning. Over 90% of our customers are in Europe. Last year, we sold over 8 million euros, and this year we are aiming for 14 million euros. The market adoptions for our tests depend on the reimbursement of tests such as NIPT," explains Segers.

Because the KCE put in a good word with the ministry concerning NIPT, it is likely that it will be implemented in the general clinical guidelines and that the reimbursement will be not only for high-risk pregnancies, but also for low-risk pregnancies. In Belgium alone, this means an increase from 10,000 to 100,000 tests per year.

Belgium was one of the European markets where NIPT became available in an early stage. Many other countries are now starting to perform studies to evaluate the benefit of NIPT, and laboratories are preparing to implement NIPT.

Multiplicom's position in the market

Laboratories have a couple of options to set up NIPT. They can either use Multiplicom's kit format, set up the technology themselves by licensing it in from another company or use a home-brew method, as initially developed by the KU Leuven. A fourth option is to use a centralized service for testing, which requires that the samples be sent outside Belgium.

One of the advantages of Multiplicom's assay is its targeted sequencing approach, which requires much less sequencing capacity compared to whole-genome sequencing methods: Multiplicom's assay can process 5 to 10 times more samples compared to the latter.

"Other benefits of Multiplicom's format are its capacity to run on existing machines from Illumina and Life Tech and its low startup cost. On the contrary, technology transfer requires a high investment, and home-brew methods are not suited to do NIPT in a high amount," assures Segers.

"Home-brew technology is our most significant competition. Illumina and Life Tech, for example, have their own library preparations for certain applications, as does Agilent," continues Segers. "We position ourselves as the first company in the field of NGS that offers products for in vitro diagnostics use. Illumnia, Life Tech and Agilent are strong players in the research field, but diagnostic labs have a different set of needs than research labs. Therefore, we tailor our products to the needs of diagnostic labs. One of these necessities is a reliable assay. You need strong performance data in order to prove the reliability of your assay. Several of our assays have been brought to a CE-IVD level, allowing the laboratory to implement and validate the diagnostic test rapidly and at low cost. All our assays have the same workflow, and they all conform to the requirements of diagnostic labs. Furthermore, we have our highly developed customer service team. This team goes out into the field, gives trainings and demonstrations to customers and helps to solve issues. It is crucial for diagnostic labs to feel supported."

"**NGS** is a young and promising technology. However, the market is still learning how to valorize it in a clinical setting. This technology allows sequencing of the whole genome. In so doing, a patient might be provided with all the genetic information that he needs for his entire lifetime by performing just one single test. The challenges of sequencing a whole genome are the high costs, and the necessity of profound data analysis. This goal is so ambitious that the market is not ready for it. The clinical market is still focused to targeted sequencing, i.e., only investing money on the genes that matter. Nevertheless, the gene panels of interest are constantly changing. We work on solutions to stay flexible and to make cost-effective analysis for sequencing, because the market is evolving quickly."
– Luc Segers, vice president of marketing & sales, Multiplicom N.V.

What's more next to NIPT?

Multiplicom is currently working on a new pipeline of products concerning organ transplantation. For example, they are making products to monitor the free-floating DNA of the donor organ in the blood of a patient, which is a measure for the acceptance of the donor organ. "The more free-floating DNA of the donor organ that can be found in the blood, the more likely that the organ will be rejected, and this can be seen in a very early stage," explains Segers.

"We are broadening our solution to the customer by making more data analysis solutions. Moreover, Multiplicom is expanding geographically. Last year we initiated activities in the US, and from this year on, we will have the first customer running our products in a routine way over there."

"An IPO? That is not incorporated in our plans yet," continues Segers. "We are still growing thanks to the funding from our current investors. This, in combination with the revenues from our product sales, allows us to sustain this path. We are definitely open to cooperating with more partners in the future. We are exploring that strategy. Correspondingly with our current extra focus on data analysis, we aim to cover the entire process from sample to end result in the future."

Multiplicom N.V.

www.multiplicom.com

Luc Segers, Vice President of Marketing and Sales
customerservice@multiplicom.com
+32 3 289 14 00

BELGIAN IVD COMPANIES IN THE PICTURE

Coris BioConcept

With almost 20 years of experience, Coris BioConcept knows the world of infectious disease diagnostics inside and out. Their straightforward chromatography-based assays for pathogen detection, which are used in more than 80 countries, provide results within 10 to 15 minutes. Since 2015, however, Coris has upped its game. The company is tackling the problem of antibiotic resistance by developing two diagnostic tools: the RESIST assays, similar to the pathogen detection assays but focused on resistance markers, and the diagnostic platform TRAPIST$_{v6}$, a fully automated system for multiplex detection of pathogens and resistance markers. These innovative tools aid researchers and clinicians in the rapid assessment of various infectious diseases and their susceptibility to antibiotics.

Ever since antibiotics entered the therapeutic scene, they have been widely used to counter bacterial pathogens. Their overwhelming success, however, turned out to be a double-edged sword: while many lives were saved and diseases cured with antibiotics, their subsequent overuse led to a rapid spread of resistance. Today, antibiotic resistance has become arguably the most pressing problem of modern healthcare, with multidrug resistant bacteria (or "superbugs") becoming more and more prevalent.

The identification of the pathogens involved in infectious disease accounts for the largest part of the diagnostics market. Molecular techniques are gradually replacing the laborious and time-consuming bacterial culturing methods, and the advantages of these molecular diagnostic tools are already leaving their mark. Rapid pathogen identification not only improves patient care, but is also crucial in avoiding broad-spectrum or inappropriate antibiotics use.

Coris BioConcept: pathogen detective since 1996

Diagnostics for infectious disease is Coris BioConcept's main business, and the company has a considerable history in the market. Since 1996, Coris has developed and produced immunochromatography strips and cassettes for the detection of more than 25 different viruses and bacteria, ranging from enteric to respiratory to gastric pathogens. With these simple and easy-to-use assays, the presence of a specific pathogen can be tested in 10 to 15 minutes. Currently, the Coris BioConcept tests are distributed in more than 80 countries worldwide.

Although Coris has been up and running for almost 20 years now, the company still strives to innovate. With its gravity-driven test (GDT) or V-TesT for liquid samples, Coris has completely removed the need for a dilution buffer. The V-TesT is particularly suited for testing urine for infections. While their GDTs are based on pathogen-specific antigen recognition, their proprietary oligochromatogra-

phy (OC) technology allows for the fast detection of amplified DNA/RNA fragments. These genotypic assays are implemented in Coris' OligoC-TesT and its new proprietary diagnostics platform TRAPIST$_{v6}$.

Thwarting the resistance

When considering innovative and useful diagnostics in the field of infectious disease, antibiotic resistance soon springs to mind. The problem has also caught the attention of Coris BioConcept, and since 2015 the company has been zealously developing not one but two solutions for the detection of antibiotic resistance markers. The RESIST range of products comprises a series of assays that detect various carbapenemase variants. The carbapenemase enzyme confers resistance to carbapenem-type antibiotics, which are considered a last-resort drug for many resilient infections. On a total of five planned RESIST tests, two are already commercially available and CE-marked: the KPC and OXA-48 carbapenemase assays. A third test aimed at the detection of the NDM-type carbapenemase is now entering clinical validation trials worldwide.

Coris' second solution might be its greatest accomplishment yet. With TRAPIST$_{v6}$, The Rapid Advanced PCR & Immunoassay SysTem, the company proudly presents its fully automated diagnostic platform. Thanks to the combined effort of biologists and engineers, Coris was able to develop a multiplex diagnostic platform based on microfluidic technology. TRAPIST$_{v6}$ offers rapid genetic assays that detect pathogen presence and antibiotic resistance markers simultaneously. TRAPIST$_{v6}$ is scheduled for release by the end of 2016.

With this platform comes consumable "lab-on-a-chip" tests. Coris has designed two panels, one for Gram-negative bacteria and a second for Gram-positive bacteria, each of which can detect up to 10 different bacterial pathogens and up to 11 common antibiotic resistance markers in a single assay. With only two pipetting steps, the microfluidic chips, in conjunction with TRAPIST$_{v6,}$ allow for the rapid screening of samples with improved diagnostic efficiency.

With RESIST and TRAPIST$_{v6}$, Coris BioConcept offers two ranges of products to aid researchers and clinicians with the rapid and parallel detection of common pathogens and their antibiotic resistances. These products will prove to be valuable tools in a business where time and multiplex testing are becoming increasingly important.

Coris BioConcept
www.corisbio.com

Christel Boudry, Business Developer
christel.boudry@corisbio.com
+32 81 71 99 13
+32 495 49 93 43

BELGIAN IVD COMPANIES IN THE PICTURE

MyCartis

MyCartis is an early-stage company that was founded in September 2014 when Pronota (Ghent, Belgium) and the Biocartis Evalution Business unit (Lausanne, Switzerland) joined forces. This was an ideal match, as Pronota was developing biomarker panels for a range of diseases and Biocartis was producing a multiplex platform to evaluate such biomarkers. MyCartis further develops this next-generation multiplex biomarker analysis platform as Evalution™, previously known as DMAT. It is designed for the detection of a broad range of biomolecules such as antibodies, antigens, nucleic acid probes, carbohydrates and metabolites, etc., and it has many clinical and pharmaceutical applications.

Next to making the technology available to the research and clinical community, this young company develops a portfolio of biomarker assays in-house or together with selected partners from industry or academia. It aims to provide the diagnostic market with tools to easily assess syndromic biomarker panels in diseases like heart failure, preeclampsia, renal dysfunction, allergy, autoimmune

Barcoded particles reveal every secret of your sample

Evalution™ is a multipurpose multiplex platform, allowing for the analysis of 1 to 16 samples at once. These samples can be all kinds of liquefied matrices such as blood, cerebrospinal fluid, stool and tissue. The platform makes use of barcoded microparticles to determine which different types of capture molecules can be attached. Different microparticle populations have different barcodes, which are formed by the presence or absence of holes: one code, one assay. When such codes or assays are combined into one microfluidic channel, a multiplex assay environment is formed. Each channel can contain a multiplex assay environment for up to 150 analytes. This instrument can read the code of each particle at any time and link it to a fluorescent signal that builds up as target analytes bind to it.

As microparticle code reading and fluorescent signal build-up are determined and quantified in real time, end-point as well as kinetic measurements are possible. Furthermore, all the steps of a typical assay protocol, such as incubation, washing and readout, happen in the platform under extremely well-controlled conditions, allowing fast, simple and robust workflows.

A unique combination of technological features

With this technology, MyCartis positions itself against other next-generation multiplex technology providers such as Luminex and Simoa, but also big clinical analyzers. **Wouter Laroy, VP Scientific Marketing at MyCartis**, adds: "The combination of technological features brought together in Evalution™ is unique and is brought by no other competitor. It is that combination that facilitates the high-end analytical assay specifications of the platform, such as speed, sensitivity, dynamic range and reproducibility."

Within its go-to-market strategy, MyCartis is seeking two types of partners. First, these are partners that could benefit from the features provided by the technology and that would build and commercialize their content on top of it. Other partners would bring their biomarker content or clinical question to MyCartis who then develops and commercializes the application. The two types of partners bring different types of revenues, respectively through indirect sales (royalties) and direct sales.

"We will make the technology commercially available in the first half of 2016 and are actively building a partner network to develop innovative biomarker applications on top of the Evalution™ technology," concludes Laroy.

Researchers as well as clinical users can use the Evalution™ platform. For researchers, the open MyCartis technology provides the opportunity to progress their research beyond biomarker discovery, the step where most programs end. For clinicians and patients, the technology provides new solutions with yet unseen features to measure the individual's biomarker profiles and support fast and accurate treatment decisions.

MyCartis

www.mycartis.net

Wouter Laroy, VP Scientific Marketing
wlaroy@mycartis.net
+32 9 241 11 43

IVD EXPERTS IN THE PICTURE
Panaxea

Developing a diagnostic test is one thing. Bringing it to the market while taking into account the product's value for different stakeholders is a very different task. While clinicians might estimate the value of a test by its impact on the patient, many more factors influence the success of a diagnostic product. All stakeholders, from caregivers to patients to manufacturers to payers and policy makers, expect different benefits from a product, and only if the diagnostic tool meets the criteria of all these groups will it thrive in the market.

Although industry insiders will be able to value the merits of a certain diagnostic test, this is often unclear for external parties judging the product. By performing a **health economic analysis**, a product's clinical and economical value can be clearly presented, allowing companies to inform and convince stakeholders of the benefits of a diagnostic tool. Convincing doctors, patients and payers of these benefits is usually harder for a diagnostic product than for a therapeutic product.

"Diagnostics are notoriously undervalued," says **Isabelle Lepage-Nefkens, CEO of Panaxea**. "They take up a mere 2% of the healthcare budget while 70% of healthcare decisions are influenced by the outcome of diagnostic tests! On top of that, insurance companies and governments who pay the healthcare bills fear that more diagnostic tools will lead to higher use of therapeutics. This is an important misconception, since diagnostics allow a more efficient use of the healthcare budget. Tests that succeed in identifying the right therapy for the right patient or in detecting diseases early on likely improve patient outcomes and may drastically reduce costs. Diagnostics aim to remove the trial and error workflow or 'casino approach' of treatment options."

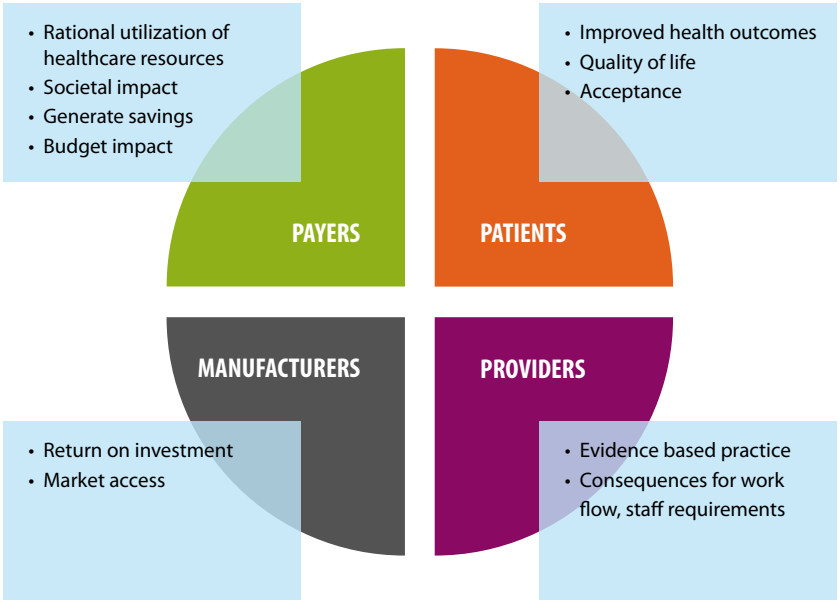
Panaxea is a consultancy firm for health care innovators such as pharmaceutical and biotech companies, and it specializes in health economic analyses. Many companies lack market access insight, and Panaxea helps these enterprises to define the true value of their products. Panaxea aids companies in making well-informed decisions and advises them on how to bring products to the market in a quick and efficient way. Their health economic models can reveal the clinical and societal impact of innovations and the specific needs of the market, allowing them to guide the R&D process to deliver a product suited to those needs.

"It often occurs that stakeholders aren't convinced of a diagnostic product. Our analyses articulate the added value, both in clinical and economical, long and short terms. This supports acceptance and adoption of the products by the caregivers, policymakers and the market. While these health economic analyses are already mandatory for therapeutics, no clear regulations are in place for diagnostic products. This will most likely change soon, since the value of these assessments is gradually being recognized by all involved parties. Budget cuts in healthcare raise the need for more informed and rational decisions to ensure that only innovations with a significant impact on the healthcare system are allowed. A health economics study is essential to guide these decisions. Also, manufacturers can benefit from an assessment. If we do these studies in an early stage of development, it can also offer recommendations for adjusted research activities, to tailor a product to the needs of all stakeholders."

These needs and the value of innovations most surely differ between stakeholders. Caregivers and doctors require an innovation to simplify the workflow, and need scientific evidence of higher accuracy or other advantages the test may offer. Payers and policy makers are more concerned with the pricing and budget impact of these innovations and the associated societal impact they can have, since this group of stakeholders is responsible for the rational use of healthcare resources.

Also, patients are gaining in importance, and their view on value is critical. A patient's opinion can determine whether a test is accepted. He or she might not be willing to endure a painful process to get a diagnosis of a severe disease due to anxiety. In this context, patient outcomes, quality of life and comfort are additional factors that need to be considered. Lastly, the product manufacturer needs its product to find market access and ensure a return on investment.

This all demonstrates how multiple criteria, exceeding clinical relevance, need to be fulfilled by a diagnostic assay. Panaxea is dedicated to mapping these possible challenges and presenting possible solutions to optimize a diagnostic product for all stakeholders. Additionally, point-of-care (POC) testing, telemonitoring and ICT-linked diagnostics are causing a revolution in healthcare and diagnostics. In this context, Panaxea is well situated to anticipate these innovations and has already built expertise in the conceptualization, evaluation and implementation of these entirely new models of care delivery.



The evaluation of the clinical and economic value of a diagnostic can be quite complex because it requires detailed knowledge of existing and emerging steps in the care pathway, starting from diagnosis all the way to therapy. Although a single stakeholder might experience short-term negative effects (for example, budget impact on medical lab or payers), the final health outcomes and societal benefits typically occur in the longer term. The different timings of these outcomes means that stakeholders do not experience the same benefits or burdens, and as such they have different decision drivers and evidence needs.

Panaxea

Isabelle Lepage-Nefkens, CEO
isabelle.nefkens@panaxea.eu
+32 472 31 66 98

www.panaxea.eu

BELGIAN IVD COMPANIES IN THE PICTURE

Protea Biopharma

Protea Biopharma started with one biomarker license for a relatively unknown disease. Now, eight years later, Protea has an impressive portfolio of unique diagnostic and therapeutic products for an equally impressive scope of diseases. From diagnostics for viral and inflammatory diseases to a one-of-a-kind screening platform for mitochondrial disorders, Protea Biopharma has several technological tricks up its sleeve.

Protea Biopharma was founded in 2008, based on an acquired license from Temple University (Philadelphia, Pennsylvania, USA). The license gave Protea the exclusive rights to the commercialization of a new marker for chronic fatigue syndrome (CFS), the enzyme RNase L. This mRNA digesting enzyme is an essential part of the innate immune response and is produced in response to viral infection.

The RNase L link with immunity caused Protea's research area to expand from CFS to viral infections. Further research and development on the subject led to Protea Biopharma's unique and extensive experience in the field of innate immunity and antiviral responses. With its development of rapid and broad-spectrum diagnostics, Protea is tackling the challenges associated with emerging viruses and resistance against anti-viral compounds. The quick identification and avoidance of treatments that might lead to drug resistance is crucial to efficiently treating viral infections.

Chronic conditions, such as inflammatory diseases and auto-immunity, have also become part of Protea's expertise. These disorders affect millions of people worldwide and are often difficult to treat or diagnose. Because an inflammatory or immune-activated state can be detected by leukocytes in the body, Protea developed its Urine Balance Test (UBT). The assay measures the balance of T_{h1} and T_{h2} cells to determine a patient's susceptibility to infections, allergies, auto-immunity and cancer. By monitoring the T_{h1}/T_{h2} balance during therapy, the patient's response and progress can be evaluated in an easy and non-invasive way.

The key to mitochondria

Many chronic diseases are linked to mitochondria, the organelles crucial for a cell's metabolism and energy homeostasis. Mitochondrial dysfunction can hint at conditions as diverse as Alzheimer's disease, diabetes and cancer. Neurodegenerative, auto-immune, cardiovascular and metabolic diseases all have a mitochondrial factor that significantly influences pathology. Even the natural aging process is believed to be caused in part by a loss of control over mitochondrial activities. With the same broad-spectrum approach as in the viral field, Protea is developing a hand-held diagnostic tool. This test, based on microfluidics and luminescence technology, allows for the measurement of mitochondrial activity in blood and tissue samples. Not only can this device detect a myriad of diseases associated with mitochondria, the assay can also be used as a follow-up test to monitor therapy efficacy during treatment periods.

Protea initially started as a biomarker discovery company, but it has gradually incorporated drug discovery and development activities. Its unique screening platform is used to detect various opportunities for treatment and disease detection in a broad range of medical conditions. Today, the company specializes in both therapeutic and diagnostic solutions relating to chronic viral infections, mitochondrial diseases and inflammatory and auto-immune disorders.

Protea Biopharma N.V.

www.proteabiopharma.com

info@proteabiopharma.com
+32 2 266 87 44

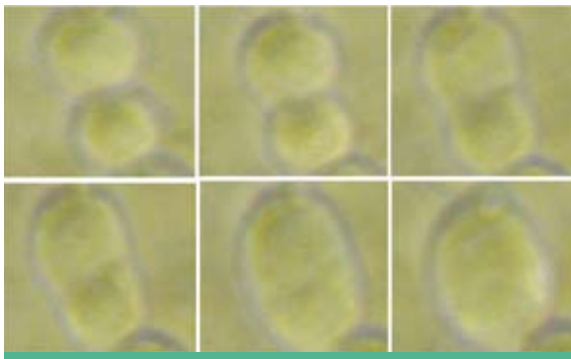
C. Roelant, Ph.D. , Managing Director
croelant@proteabiopharma.com
E. Buts, Ind. Pharm., Operations Manager
ebuts@proteabiopharma.com

BELGIAN IVD COMPANIES IN THE PICTURE
SynAbs

SynAbs is a young UCL spin-off company, founded in September 2015 with the support of Walloon life science incubator WBC, UCL's tech transfer office LTTO and the French investment group Biotech Investissement. As a producer of monoclonal antibodies (mAbs), SynAbs is dedicated to bringing innovative concepts to the R&D and IVD markets. Next to conventional mouse and rat antibodies, the company also develops antibodies of guinea pig origin. The unique characteristics of these first-in-class antibodies significantly expand upon the applications of their mouse counterparts.

Antibodies are one of the most widely used biomaterials in IVD due to their selective binding to a broad range of biomolecules. Their ability to specifically detect proteins or small molecules in complex mixtures has made them an invaluable tool in molecular diagnostics.

An estimated 70% of all commercially available R&D and IVD antibodies are produced in mice. However, the repertoire of immunogenic antigens in mice has its limits. Phylogenetically, mice are relatively close to humans, and the high degree of homology between mouse and human proteins frequently results in low immune responses to human proteins. Also, many small molecules fail to elicit a strong immune reaction in mice. This makes the development of antibodies against hormones, antibiotics, toxins and lipids, etc., problematic with mice.



Cell fusion for the creation of the Syn2.2 hybridoma

In search for alternatives

SynAbs' rat antibodies can solve many of the challenges faced by the mouse versions. Rats respond to a broad spectrum of antigens, enabling them to produce antibodies that mice cannot. Additionally, the rat-rat hybridomas are stable and productive, two key characteristics of a successful hybridoma. Other advantages include high affinity and specificity. Despite these benefits, the homology with human proteins remains a problem for rat antibody production.

Another alternative to murine-based antibodies is their rabbit equivalents. Rabbit monoclonals have known significant success, claiming more than 10% of the R&D & IVD antibody market in a decade. Rabbit hybridomas, however, are rather expensive and poor antibody producers. Sheep are also used for antibody production, but they face the same problems as rabbits do. Both animals are also more expensive to use as experimental animals compared to mice and rats.

From lab rats to guinea pigs

SynAbs has now developed a concept that combines the best of both worlds: guinea pig monoclonal antibodies. From stable hybridomas to a broad, non-murine antigen repertoire, guinea pigs offer various advantages in the field of antibody production:

1. In evolutionary terms, guinea pigs are more distant from humans than mice.

Many human proteins and their rodent counterparts have identical amino acid sequences. This homology is much weaker in guinea pigs, as they are phylogenetically more distant from rodents and humans. The amino acid sequence of glucagon, for instance, is identical in humans, mice, rats, rabbits and sheep. In contrast, the guinea pig sequence differs in 5 out of 29 amino acids. The same can be said for insulin, of which the human version has 94% homology with mice and rats and is identical with that of rabbits and sheep but has only 72% homology with guinea pigs. This difference is important when considering antigen immunogenicity; it enables guinea pigs to develop antibodies against many human antigens where mice, rats or rabbits would fail.

2. Guinea pigs are excellent antibody producers

The humoral response of guinea pigs has been observed to be twice as high as that of mice or rats. This extraordinary immune activity also translates into lower amounts of antigen necessary to elicit a sufficient immune response. On top of this, approximately 10^7 lymphocytes can be isolated from a guinea pig spleen, which is about twice as much as from a mouse spleen.

3. Guinea pigs are suitable for lab environments

Guinea pigs are docile and easy to manipulate. Their small size makes them easy and cheap to accommodate, an asset they share with mice and rats but definitely not with rabbits and sheep. Easy access to the lymph nodes is an additional advantage of their size.

After a year of research, SynAbs has developed a successful fusion cell line, Syn2.2. Syn2.2 efficiently fuses with guinea pig B lymphocytes to obtain stable hybridomas: The fusion rate with guinea pig lymphocytes is comparable to that obtained with SP2O for mice or IR983 for rats, i.e., approximately 12 hybridomas per million fused lymphocytes. More than 1,000 hybridomas can be obtained from a single guinea pig spleen. While guinea pig hybridomas divide slightly more slowly than mouse or rat hybridomas, their production rates are comparable, and combined with the previously mentioned advantages, guinea pig mAbs are most certainly a competitive alternative to mouse, rat and rabbit mAbs.

For these reasons, Guinea pig monoclonals have a very promising future. SynAbs is currently focusing its research on antigens for which it is difficult to obtain murine antibodies and improving immunization methods for guinea pigs. Other R&D areas include infectious diseases and blood sugar hormones, for which SynAbs is open to partnership proposals.

SynAbs, Monoclonal Antibody Manufacturing Center

www.synabs.be

+32 2 764 95 21

Didier Argentin, CEO
argentind@synabs.be

Yannick Nizet, CSO
nizety@synabs.be

DIAGNOSTICS, PATENTABLE OR NOT?
NLO

Patents are well appreciated as tools to stimulate innovation in technology and science. In exchange for making the invention available for the public, the patent holder can use the patent to get a return on investment by excluding others from practicing the patented invention, obtaining damages for infringement and/or granting licenses. This is particularly crucial in the medical field, where the costs involved in drug development and market authorization are enormous. However, within this field, it is this monopolistic character of a patent that is often considered to be in conflict with the interest of human health. In almost all jurisdictions around the world, patent claims on medical inventions are restricted. This is also true for claims on diagnostic methods. **Emil Pot and Thea van der Wijk, Patent Attorneys from NLO** explain.

In Europe and in many other jurisdictions, legislation prohibits diagnostic methods performed on the human or animal body from being patented, in order to make sure that medical doctors can do their jobs without worrying about patents. Core to this prohibition is that the claimed diagnostic method comprises a step that involves a specific interaction with the human or animal body (e.g., for collection of a sample) within a multistep process that leads to the final diagnosis, irrespective of the invasiveness of this interaction (Decision of the EBoA G1/04).

NLO
EUROPEAN PATENT AND TRADEMARK ATTORNEYS

There is an easy way out. Keeping this step of interaction with the human or animal body out of the claims renders the claim on a diagnostic method patentable. In other words, IVD methods are patentable in Europe and many other jurisdictions.

In the United States, this goal of making sure that medical doctors can never be accused for infringing a claim on a medical method when performing their profession is reached differently. The United States is one of the few countries that in principle considers medical methods to be patentable subject matter, i.e., by exempting licensed medical professionals (e.g., doctors) and related health care entities (e.g., hospitals) from liability for infringement of medical method patents (35 U.S.C §287c).

Nevertheless, there is a different factor that seriously impedes diagnostic methods from being patented in the US: the banning of almost all claims on inventions that have a natural character (rejection under 35 U.S.C §101). In two recent higher court rulings on the 101 rejection, the Supreme Court's decision of Mayo Collaborative Services v. Prometheus Laboratories, Inc. in 2012 and the Federal Circuit decision of Ariosa v. Sequenom in 2015, a diagnostic method was at stake, and in both cases the patent was held ineligible.

In both these decisions, the diagnostic methods were held patent ineligible, basically because they were alleged to be directed to a law of nature only comprising subsequent steps that were routine practice. In general, diagnostic methods typically relate to a natural phenomenon, i.e., the relation between a biomarker and a particular disease or condition. Usually, these methods involve multiple steps, each of which are routine, as otherwise such individual steps would have been patented instead. It is therefore clear that after these court decisions it will be hard for such claims to be ever held patent eligible in the US.

However, there may be ways around this. For instance, inserting meaningful limitations into the claim (specific sample material, drugs and/or administration methods) may shift the balance to patent eligibility, as the criterion for eligibility is that the claim should recite significantly more than the excepted natural law or product. Another possible way might be to draft the claim as a method of treatment (see Classen v. Biogen IDEC). For instance, "A method of diagnosing A by detecting B" could be drafted as "A method of treating A by administering C to subjects diagnosed A by detecting B." As such a claim is no longer directed to an alleged law of nature, but can at most be regarded as involving such a judicial exception, such claim should not trigger a rejection under 101.

It should be noted that enforceability of such multi-step method claims was made easier after the Federal Court decision of Limelight Networks, Inc. v. Akamai Technologies, Inc. and the later decision of Eli Lilly & Co. v. Teva Parenteral Meds., Inc., rendered it more likely that the party that exploits a drug, indicating on the label that it should be administered to subjects diagnosed according to the patented method, can be held liable for induced infringement, even if the administrator and the one performing the diagnostic method are different persons.

Taken together, the case for the patentability of diagnostic methods is relatively clear-cut in Europe, where IVD methods are held to be patentable. In the US, claims on diagnostic methods will more frequently run into rejections, in particular natural law type rejections under 35 U.S.C §101, but there may be ways around this.

NLO

www.nlo.eu

+32 9 240 98 88

Emil Pot, European Patent Attorney
pot@nlo.eu

Thea van der Wijk, European Patent Attorney
vanderwijk@nlo.eu

THE DIAGNOSTIC INDUSTRY IN BELGIUM: A BRIEF OVERVIEW

Despite having no typically Belgian companies among the sector's greats, Belgium has a thriving ecosystem of IVD companies that excel in their own fields. They range in size from one-man consultancy firms to local divisions of industry giants that employ hundreds of skilled workers. Most large international companies such as **Abbott**, **bioMérieux** or **Roche Diagnostics** have Belgian divisions or Belgian-based European HQ. They typically offer integrated solutions consisting of reagents, instruments, software and services.

Locally founded companies from different scientific backgrounds position themselves as technology or service providers. They leverage clinical and academic expertise to find new biomarkers or create new assays and reagents. Examples include kits for the turbidimetric measurement of serum proteins in plasma or urine developed by **APTEC** or the use of nanoparticle technology for the quantification of specific proteins such as ferritin or cystatin C by **DiAgam**. **HistoGeneX** has created over 1,000 tissue-based biomarker assays bridging histology and molecular biology techniques. Others look at gene expression, like **Probiox**, who creates DNA chips to measure those involved in oxidative stress and inflammation.

Alternative business models support diagnostics companies in the development of new assays and instruments. Laboratories such as **Anacura** have a broad expertise in clinical diagnostic parameters, clinical chemistry, immuno-assays and bacteriology. These areas of knowledge can be applied in the creation of new laboratory or point-of-care tests. For custom hardware, **WOW Technology** specializes in prototyping and building robotic gantries for the development of detection kits of biomolecules.

Belgium also harbors a number of bio-informatics companies that offer essential data-analysis services. A successful example is **Cartagenia**, recently acquired by **Agilent**. They have created a clinical-grade SaaS solution that can be used to interpret genomic variants. **DNAlytics** uses its expertise in data-mining and mathematical modeling to assist IVD companies.

Many companies are focused on a specific disease area. The most represented are cancer and infectious diseases. In cancer research, **OncoDNA** is working toward a personalized treatment for solid tumors by combining DNA sequencing and pathology with data analysis and bio-informatics solutions for sharing data. **Belgian Volition** leverages its nucleosome technology to detect the presence of cancer and differentiate between different types from a blood sample. Finally, **MDx Health** develops and commercializes tests based on its proprietary gene methylation technology for prostate, colon and lung cancer.

In infectious diseases, **BioMARIC** develops ELISA assays for lab and blood bank screening of various diseases such as HIV, HCV or HTLV. While the assays are developed in-house, they are produced in other countries by selected partners. The company's services range from a full technology transfer to the production of selected biomaterials or complete OEM kits. **Diagenode** uses its expertise in multiplex and monoplex real-time PCR (qPCR) for viral, bacterial and parasite detection.

While those are the most active disease areas, Belgian experts can be found tackling other diseases as well. For the detection of auto-immune diseases, **Icometrix** offers quantitative biomarkers for the prognosis and follow-up of MS patients, using MRI images to generate clinically relevant reports for physicians. **DIAsource ImmunoAssays** creates clinical products in the field of endocrinology as well as infectious diseases. **LaCar** provides instruments and kits for the SNP analysis of genetic thrombosis, sickle cell and hemochromatosis. **Artialis** has some proprietary markers for joint and musculoskeletal disorders, for which they create ELISA kits. Finally, **Diploid** focuses on rare disease diagnosis through genome interpretation services, combining manual and automated bio-informatics approaches by scanning literature and annotation sources to associate genetic variants with phenotypic data.

This list of these examples is in no way exhaustive; it merely shows the diversity of companies present in Belgium. The landscape is constantly changing as new spin-offs are created, building on the excellent clinical expertise present in a wide range of disease areas. Belgium's IVD ecosystem offers a number of stimulation conditions that are conducive to successful start-ups. This will help fortify our position as an R&D country and international technology provider, with the expertise to valorize the obtained results.

The Belgian life sciences cluster

"The in vitro diagnostics companies in our life sciences cluster form a critical component of a very active trend towards precision medicine. We are convinced Belgium can play a leading role in this domain of health management. Combining the IVD expertise in our region with expertise in stratified therapeutics and in smart data management, advanced micro-electronics and 3D printing puts Belgium in a unique position in this field" explains **Henk Joos, Managing Director of FlandersBio**.

FlandersBio
FlandersBio is the cluster organization and the engine for the life sciences-driven network economy in Flanders (Belgium), with more than 320 current members. FlandersBio supports and facilitates the cluster's development and its members through a series of networking activities, allowing you to find your partner within the network of cluster actors and beyond. FlandersBio also offers a number of focused advocacy activities and directed services and training to the cluster.

FlandersBio is a proud member of the Flanders Welcome Team - Life Sciences (www.flanderslifescienceshotspot.be), together with VIB, FIT and Flanders Innovation & Entrepreneurship.

More info on www.flandersbio.be

IVD RESEARCH IN BELGIAN ACADEMIA – FINANCING BY PHILANTHROPIC INVESTORS

Each diagnostic tool that eventually benefits patients is the fruit of many years of intensive research and validation. Although "diagnostics" isn't regarded as a research field in itself, it is most certainly embedded in medical research. Biomarkers form the basis on which modern molecular diagnostics are built. Unlike research into new therapies, discoveries of novel biomarkers can be developed into applications for the clinic relatively quickly. In this way, research into biomarkers can have a profound effect on patient care in a short time span. Philanthropic investors, such as the Fournier-Majoie Foundation, are specifically funding cancer biomarker projects and guiding them towards commercialization, so that patients can benefit from these scientific innovations as fast as possible.

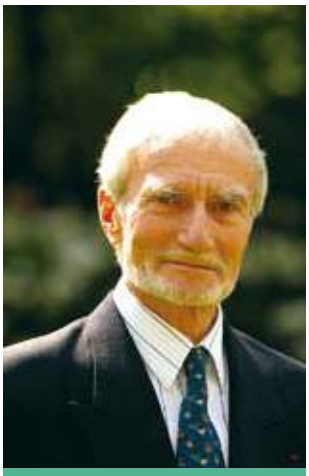
Belgium is internationally renowned for its top-notch clinical research. It is in part due to the strength of the academic medical research groups that Belgium has become a true biotechnology hotspot. Although diagnostics might not be a research field as such, the subject finds significant interest within the context of various disease categories. Within the framework of cancer, infectious disease, neurology, immunology, etc., research into biomarkers is central to improving patient welfare and represents a line of investigations that can quickly be applied in clinical practice.

Biomarkers have become a particularly hot topic in cancer, where they provide a wealth of information. In the first place, biomarkers are a useful way of identifying cancer or confirming an oncologist's suspicions. Biomarkers such as genetic aberrations or unusual concentrations of specific proteins can be diagnostic for certain types of cancer. Secondly, biomarkers can give important prognostic indications; tumor aggressiveness, disease progression and survival prediction can all be estimated with established biomarkers. Finally, biomarkers can be used in a therapeutic context. Patients can be stratified in groups based on the presence of certain biomarkers to predict which therapy will be most suitable for a certain group. Monitoring biomarkers can also be an efficient and easy way to monitor treatment efficacy. All in all, biomarkers give invaluable insight into cancer behavior and grant a window of opportunity to act on this information.

Many Belgian research groups are looking into cancer biomarkers. With a focus ranging from miRNA signatures to protein glycosylation to lipid metabolism and novel imaging techniques, biomarker research in Belgium is diverse and covers a broad spectrum of cancer types.

Many Belgian research groups are looking into cancer biomarkers. With a focus ranging from miRNA signatures to protein glycosylation to lipid metabolism and novel imaging techniques, biomarker research in Belgium is diverse and covers a broad spectrum of cancer types.

A philanthropic investor with a mission



The **Fournier-Majoie Foundation** is a philanthropic organization founded by **Bernard Majoie**. It provides funding and guidance to cancer research projects that are trying to develop their discoveries into practical applications. The foundation selects projects with well-defined goals that can have a true impact on the patient in the short term. This mainly consists of biomarker research, since these discoveries can be commercialized relatively quickly, certainly when compared to therapeutics, and can drastically improve patient diagnosis, prognosis and therapy selection.

The Fournier-Majoie Foundation encourages scientists to take the leap toward industry and tries to spread the entrepreneurial spirit in scientific circles. This enables innovative science to be translated into applications that benefit the patient.

Patient-centered research

The research unit led by Prof. Jo Vandesompele and Prof. Frank Speleman is one of the groups supported by the Fournier-Majoie Foundation. Located at the Center for Medical Genetics Ghent (CMGG, UGent), this group specializes in neuroblastoma, a particularly aggressive type of brain tumor present in young children. The group uses cancer-specific mRNA and miRNA signatures as well as DNA methylation patterns to stratify patients in risk groups, defining which patients benefit from different therapies. These mRNA, miRNA and methylation signatures can be detected in primary tumor tissue samples or blood serum. Not all neuroblastoma patients require a biopsy, and a simple, non-invasive blood test can prevent unnecessary biopsy sampling.

Also, the group of Prof. Bernard Gallez at the UCL is guided by the foundation. Prof. Gallez' research deals with improved imaging methods for brain, head and neck tumors. The new MRI method developed within this research group, MOBILE, is able to visualize the oxygen supply in tissues. This is a very valuable tool, since hypoxia can trigger tumor metastases or the regeneration of blood vessels, which makes the tumor less susceptible to radiotherapy.

At the KU Leuven, the unit of Prof. Johan Swinnen is focused on renal cell carcinoma (RCC), the most common form of kidney cancer. During the development of RCC, changes in the phospholipid profile of exosomes can be observed. Prof. Swinnen's group is now developing a platform for lipidomic and transcriptomic analysis on exosomes extracted from patient blood serum and urine.

Fournier-Majoie Foundation

www.fournier-majoie.org

Barbara Wecks, Executive Assistant
Barbara.Wecks@fournier-majoie.org
+32 2 370 47 25

Prof. Massimiliano Mazzone and Prof. Sabine Tejpar both lead a separate research group on colorectal cancer at the KU Leuven. While Prof. Mazzone's group is working on a diagnostic test based on monocyte gene-expression profiles, Prof. Tejpar's unit is constructing the world's most comprehensive molecular map of colorectal cancer.

With the aid of the Fournier-Majoie Foundation, all of these projects have been drastically accelerated. Thanks to the foundation, each group has been able to publish numerous high-impact articles, continue its groundbreaking research activities and, perhaps most importantly, secure IP that can serve as a basis for the industrialization of innovative discoveries.

IVD WHITE PAPER PARTNERS

ADx NeuroSciences

ADx NeuroSciences develops state-of-the-art biomarker assays that can diagnose a wide variety of neurodegenerative diseases and conditions and provides access to unique antibodies for the early detection of Alzheimer's disease, Parkinson's disease and traumatic brain injury.

Biocartis

Biocartis (Euronext Brussels: BCART) is an innovative molecular diagnostics (MDx) company providing innovative, rapid and highly accurate diagnostic solutions addressing key unmet clinical needs in oncology and infectious diseases.

Janssen Diagnostics

Janssen Diagnostics strives to achieve the promise of precision medicine and its potential to improve patient outcomes. We embrace an open approach to develop the best technologies, either in-house or by partnering with those who own them, to ultimately improve patients' health in collaboration with our customers.

Multiplicom N.V.

Multiplicom creates and markets molecular diagnostic kits that are essential to providing everyone with access to effective, affordable and personalized medicine.

This IVD White paper was developed with support of Coris BioConcept, MyCartis, Panaxea, Protea BioPharma and SynAbs.

BIOVOX STRATEGIC PARTNERS

BioCentury

BioCentury is the leading provider of value-added information, analysis and data for biotechnology and pharmaceutical companies, investors, academia and government on the strategic issues essential to the formation, development and sustainability of life science ventures.

Biowin

BioWin is the Health Cluster of Wallonia and the reference player for all the stakeholders involved in innovative R&D projects and/or skill development in the field of health biotechnology.

Bridge 2 Health

Bridge 2 Health (B2H) provides a personal and integrated access to a wide range of tools and know-how developed at the University of Liège (ULg) and its University Hospital (CHU), complemented with a broad network of pharmaceutical, biotech and medical device spin-offs.

Essenscia/bio.be

Essenscia/bio.be is the federation of Belgian companies active in the biosciences, representing the interests of its members regarding legislation and standards at various policy levels (Belgium, EU, OECD).

FlandersBio

FlandersBio is the cluster organization and the engine for the life sciences-driven network economy in Flanders, with more than 320 members.

Janssen Pharmaceutical Companies of Johnson & Johnson

At Janssen, we are dedicated to addressing some of the most important unmet medical needs in oncology, immunology, neuroscience, infectious diseases and vaccines, and cardiovascular and metabolic diseases. Driven by our commitment to patients, we develop innovative products, services and healthcare solutions to help people throughout the world.

NLO

NLO European patent and trademark attorneys:
As one of Europe's largest full service firms in the field of Intellectual Property, NLO can protect and strengthen your innovations, ideas, designs and trademarks.

VIB

VIB (Flanders Institute for Biotechnology) performs groundbreaking research on the origins of life, health and disease. The results of the scientific research are applied in medicine, agriculture and industry.

BIOVOX

TURNSTONE COMMUNICATIONS

BioVox.be showcases life sciences breakthroughs for and from Belgian innovators. Register for the free BioVox newsletter at **BioVox.be**!

Through our partnership with BioCentury we share relevant worldwide news while our local editors focus on regional highlights in healthcare, agriculture and the bio-based economy. Do you have news to share? Contact us via **news@biovox.be**.

BioVox provides tailor-made solutions to reach out to selected life sciences audiences in Europe and US. Discover our services at **www.biovox.be/services**.

BioVox is a service brought to you by **Turnstone Communications**. Turnstone is an established life sciences communications and marketing agency servicing companies and research organizations operating in healthcare, bio-economy and life sciences markets. Our long-term relationships are a great testament of how we contribute to our clients' businesses in US and Europe - biotech startups and large companies alike.

An agile team of scientist entrepreneurs and communication & marketing experts makes for efficient collaboration and quick results. We transform your innovations into compelling stories for investors, media, partners and clients.

More at **www.turnstone.be**.