

**Life Sciences: Molecular Diagnostics**  
New Tools for Evidence-Based Medicine



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# Table of Contents

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## **Introduction / 1**

Definitions / 1

Current and Future Growth Potential / 1

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## **Drivers for MDx Growth / 2**

Health-Care Environment / 2

Pharmaceutical- and Biotechnology-Industry Environment / 3

Scientific and Technological Advancements / 3

---

## **Challenges / 3**

Science and Technology / 5

Intellectual Property / 5

Regulatory Environment / 7

Adoption / 9

Reimbursement / 10

VC Investments / 11

---

## **Clinical Applications / 11**

Personalized Medicine / 11

Targeted Therapies / 15

---

## **Showcase / 18**

Biomedical Photometrics Inc. (BPI) / 18

Geneplex / 20

ArticDx / 22

Fio / 24

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## **References / 27**

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## Introduction

The medical diagnostic (Dx) sector is playing a central role in the shifting health-care and drug discovery landscape. Energized by the demand for changes in the health-care environment and driven by a wave of molecular advances, the Dx sector is responding with innovative new tools and technologies. In this report, we highlight some of the developments fueling this resurgence, focusing not only on key areas of accomplishment and promise, but also on the challenges facing the sector. We place an emphasis on the molecular diagnostics market (MDx), which has the greatest potential to enable the practice of personalized medicine.

Ontario is at the forefront of the diagnostics space, with a cluster of vibrant molecular diagnostics and imaging companies, underpinned by an exceptional and collaborative research base possessing strengths in biomarker discovery, optics, materials science and cancer research.

### Definitions

Diagnostics can be classified as *in vitro* or *in vivo*. *In vitro* diagnostics (IVD) comprise the multitude of reagents, instruments and systems used to test specimens taken from the body, while *in vivo* diagnostics encompass techniques that image or assess health status directly in the patient.

The *in vivo* sector includes imaging equipment and imaging reagents. *In vitro* diagnostics can be categorized as routine or esoteric. Routine IVD tests are standard-of-care tests that generally measure a function of the body's organs, such as glucose monitoring, cholesterol testing or urine analysis. Esoteric (or specialized) tests are those that require more sophisticated technology, supplies and equipment, as well as highly skilled professionals (Datamonitor, 2008).

A key segment of *in vitro* diagnostics is molecular diagnostics, which applies molecular technologies to elucidate, diagnose and monitor human diseases. Methodologically, it can be defined as a subdivision of the esoteric IVD market using immunochemistry, as well as genomic, proteomic and metabolomic techniques (Datamonitor, 2008).

### Applications of MDx include

- infectious disease molecular testing
- molecular oncology
- blood screening
- genetic testing
- DNA fingerprinting (e.g., paternity testing, forensic testing)
- histocompatibility testing/HLA typing (e.g., tissue-type matching for transplants)

The linkage of drugs and diagnostics is expected to become the prevailing model. It presents advantages for both the prescription drug (Rx) and Dx sectors, from the benefits of employing biomarkers during the course of drug development to linking drugs to companion diagnostics developed separately or deriving synergies from developing the drug-diagnostic pair together. For the Dx sector, the existence of a companion drug is a powerful driver of sales, especially when the test is a requirement for prescribing the drug. This is also a crucial factor for achieving a higher price point for the Dx product. Pressure from FDA and payers also may encourage the co-development and co-marketing of drugs and diagnostic tests.

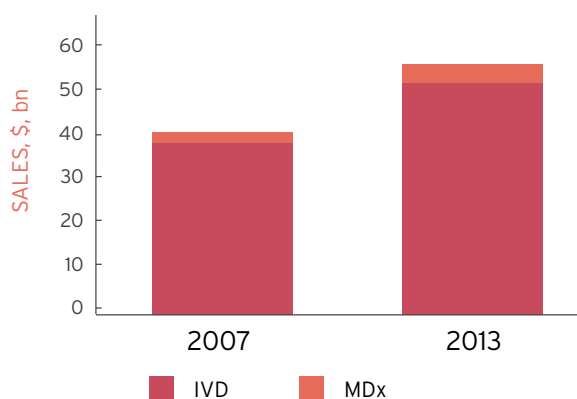
### Current and Future Growth Potential

The worldwide IVD market was estimated at \$39 billion in 2007, with MDx estimated at less than 7% of this, or \$2.66 billion. The total IVD market grew at a compound annual growth rate (CAGR) of 9.4% from 2001-2007, but is expected to slow to 5% over the 2007-2013 forecast period. In contrast, the MDx market grew by 16.9% from 2001-2007 and is projected to grow by 14% in the 2007-2013 period. Based on this forecast, the total global market in 2013 will have grown to over \$52 billion of which over 10% will be the MDx component. From 2007-2013, the MDx market is expected to account for almost a quarter of the total IVD forecast market growth (Refer to Figure 1).

The global IVD market (including the MDx) is dominated by three key players: Siemens, Roche Diagnostics, and Abbott Diagnostics. These three companies accounted for two-thirds of total IVD market sales in 2007. Beckman Coulter, Johnson & Johnson, Becton Dickinson, and bioMérieux also held significant market share of the IVD market. Several hundred smaller players compete for the remaining market share. Roche is the dominant player in the MDx field, with a 20% market share. Siemens has aggressively penetrated the IVD market through several large acquisitions in recent years. In 2007 it was the

market leader, with an estimated IVD market share of 36%. Its objective is to bring together technologies in diagnostic imaging, health care, information technology, molecular biology and biochemistry for the advancement of personalized health care. The company is the first to bring

**Figure 1 Market Size data IVC/MDx segments, US\$ million**



Source: Datamonitor, 2008

IVDs, in vivo diagnostics and health-care IT under one roof. Leading IVD companies Roche and Abbott illustrate the synergies between diagnostics and pharmaceuticals. Both have development projects for new biomarkers in the fields of oncology and infectious diseases (Datamonitor, 2008).

While the majority of the larger companies participate in most of the market segments, smaller companies tend to focus on specific areas, such as home tests or cancer diagnostics. Some have established their market presence through differentiated technology that targets niche markets. Small innovative companies provide new technologies, which feed the development of products by leading players and represent potential acquisition targets.

Few pharmaceutical companies have the capability to develop and market companion diagnostics linked to their targeted therapies. The service model for biomarker discovery and development as a contract service to

big pharmaceutical and biotechnology companies has quickly gained momentum. A common practice is for pharmaceutical companies to engage a diagnostic company once it has determined that the drug is a viable candidate in humans before embarking on Phase III studies. For pharmaceutical companies without the expertise or infrastructure to handle the regulatory, marketing and distribution aspects of the diagnostic component, selecting a diagnostic partner after Phase II clinical studies with the drug is viewed as an attractive option to building up in-house capabilities (Marchant, 2009).

Of 28 drug-diagnostic collaborations identified for the 2005-2009 period, 60% were in the oncology field. The other applications were heart failure, autoimmune diseases, schizophrenia and growth failure (Marchant, 2009).

## Drivers of MDx Growth

Several key drivers are behind the rise of the MDx sector, notably pressing needs in the health-care and pharmaceutical industries and a wave of scientific and technological advances.

### Health-Care Environment

Health-care systems are already straining under the burden of rising demand and soaring costs and this trend is projected to worsen. The current challenges tend to be chronic age-related conditions such as cardiovascular disease, cancer and neurological disease, and these will grow more prevalent as population demographics shift upwards. The increase in health-care costs related to these conditions creates a need for improved tools for clinical decision-making—ones that are more specific, faster, more accurate, more informative, more affordable and less invasive than those in current practice. These tools hold promise to help shift the emphasis in medicine from reaction to prevention.

### Technology Adoption

New technologies also create new demand. Patients increasingly take responsibility for decisions relating to their own health care. Broad access to information on new technologies, largely via the Internet, has empowered consumers who are taking a prominent role in driving

## Definitions

# BioMarkers

**Biological marker (biomarker):** A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention (NIH Biomarkers Definitions Working Group, 2001).

Biomarkers can be any kind of physical trait or physiological index, such as blood pressure, heart rate, blood glucose or PSA level. The term has now come to be associated with molecular biomarkers, including the multivariate profile data of 'omics analysis. They can take many forms and measure single parameters or a specific combination of parameters, such as a genetic variant associated with a particular disease outcome or defined profiles in a panel of RNA transcripts, proteins or metabolites. The key is that the presence of a measurable trait indicates the presence of a particular biological event.

Biomarkers can be used clinically to screen for, diagnose or monitor the activity of diseases and to guide molecularly targeted therapy or assess therapeutic response. In the biopharmaceutical industry, biomarkers define molecular taxonomies of patients and diseases and serve as surrogate endpoints in early-phase drug trials. Biomarkers can be categorized into different functions along the continuum of care.

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demand. Baby boomers are drawn to new information about scientific advances and their enthusiasm for learning about their health will fuel this market.

### Health-Care Inefficiencies

The traditional "one size fits all" model for drugs is now recognized as overly simplistic. Drug choice and dosing remain largely empirical processes, even though most drugs only work in half of patients, on average.<sup>1</sup> Some patients develop drug resistance. Prescription by trial and error leads to ineffective treatment, wasted time and extra expense. It also increases the likelihood of adverse drug reaction (ADR), a leading cause of hospitalization and death. The economic burden associated with drug-related morbidity and mortality is considerable, with annual costs estimated earlier this decade at more than \$177 billion (SACGHS PGx, 2008). Incorporating personalized medicine into the fabric of health-care systems can help resolve many entrenched inefficiencies, hospitalization due to ADR, poor compliance, reactive treatment and late diagnoses. Although potentially associated with increased initial costs, MDx, through personalized medicine, could dramatically increase the effective targeting of new as well as existing therapies.

### Pharmaceutical- and Biotechnology- Industry Environment

The growth of the global pharmaceutical market is projected to slow, particularly from 2011 onwards as many blockbuster drugs lose patent protection. As a result, mass brand sales erosion is expected (Datamonitor, 2007). Adding to the problem, new products are not making it through pipelines and reaching the market at a sufficient rate to compensate for these losses, despite major scientific achievements and investment that might have predicted otherwise.

In order to fulfill unmet medical needs, drug discovery is increasingly focused on more complex and chronic diseases. Meanwhile, the established methods of drug development are struggling to deliver safe and effective new products. The investment required to launch a new drug has risen by 55% since 1995 (BI Biomarkers, 2008). The proportion of drugs entering Phase I trials that are eventually approved by the US Food and Drug Administration (FDA) has declined from approximately 14% to 8% in the last two decades. The attrition rate is highest for oncology drugs, with over 95% of compounds failing

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to successfully complete clinical development. It has been estimated that the identification of potential problems before a drug enters clinical trials could save as much as \$100 million in drug development costs (Marchant, 2009).

Solutions are required to address the falling productivity and rising costs associated with developing therapeutics. Some solutions are being sought from the Dx sector as biomarkers are increasingly being used in drug discovery and development programs. The aims are to reduce failures in clinical trials through safety assessment in the preclinical stage, to accelerate proof-of-concept trials, and to define clinical safety and efficacy biomarkers early in the process.

### Scientific and Technological Advancements

Recent years have seen a surge in the pace at which scientific discovery has elucidated intricate biological processes as well as the molecular foundations of cancer and other chronic diseases. These discoveries have been combined in a powerful way with information from the human genome project, facilitated by advanced analytical technologies.

For the MDx sector, these advances have provided a rich source of biomarker information, which provides content to combine with the platforms.

## Challenges

As with many emerging health-care technologies, the new MDx hold great promise but also face hurdles. New 'omics technologies (proteomics, genomics, metabolomics) are yielding many potential biomarkers and profiles. Companies are developing new platforms and offering biomarker discovery and screening services; others are working on diagnostics to guide prescribing, some are developing Rx/Dx pairs. The list of companion diagnostics is growing and the field is broadening beyond cancer and HIV. Iconic successes such as Herceptin and Gleevec serve as reminders of the power and potential of pharmacogenomics. The biomarkers used as companions to those drugs, however, were identified through conventional means. So far, only a few biomarkers discovered in the post-genomic era have been integrated into clinical practice, and only a handful of pharmacogenetic

## Definitions cont'd

### 'Omics

'Omics focuses on large scale and holistic data to understand biological processes in encapsulated omes (in many distinct biolayers). In 'omics, the main focus is on mapping information objects such as genes and proteins, finding interaction relationships among the objects, and engineering the networks and objects to understand and manipulate the regulatory mechanisms. A relatively new discipline, systems biology, aims at integrating the enormous amount of existing 'omics data in order to better understand their functional relationships at a whole systems level (BI Biomarkers, 2008).

The sequencing of the genome together with advances in multiplexing high-throughput technologies have opened the way to vast new levels of discovery and analysis. 'Omics analysis tools are particularly useful in the discovery of biomarkers.

### Pharmacogenomics / Pharmacogenetics (PGx)

*Pharmacogenetics* is generally recognized as the study of how individual genetic differences cause variation in the efficacy, uptake, distribution and toxicity of a drug, known together as the drug response. In contrast, the study of *pharmacogenomics* encompasses the role of the whole genome in pharmacology and drug design. These two terms often are used inconsistently and interchangeably (SACGHS PGX, 2008). Identification of the genetic differences that cause people to respond differently to the same drugs is paving the way to tailor-made treatments for individuals, which will maximize efficacy and minimize side effects.

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<sup>1</sup> The percentage of the patient population for which a particular drug in a class is ineffective, on average: anti-depressants (SSRIs)—38%; asthma drugs—40%; diabetes drugs—43%; arthritis drugs—50%; Alzheimer's—drugs 70%; cancer drugs—75% (Spear et al, 2001).

and diagnostic tests have been formally approved by regulatory agencies (Allison, 2008; SACGHSPGx, 2008). Several key challenges contribute to this result.

## Science and Technology

Biomarkers are becoming an integral tool in the development of personalized health care, but the identification of clinically useful biomarkers can be as challenging as drug discovery. From several thousand exploratory biomarkers, only one may have clinical use, and the process can take up to seven years (Marchant, 2009).

Before bringing a new biomarker to the market, three successive developmental phases have to be completed:

1. Biomarker discovery– in which ‘omics technologies may be applied
2. Validation– in which the diagnostic performance of candidate biomarkers has to be assessed in defined sample collectives of sufficient size
3. Product development, with the transfer of the biomarker to a robust test platform (BI Biomarkers, 2008)

The ‘omics technologies have been prolific discovery engines, extremely successful in the first phase. By 2006, the scientific literature contained some 150,000 reports of disease-associated molecular markers (Nature Biotechnology- 24, 869 (2006)). The gap is downstream at the validation stage, with failures at all stages of the evaluation, including analytical validity, clinical validity and clinical utility. Overall, the data generated by ‘omics technologies have not yet been reproducible or robust enough for clinical use. Multiple technical challenges contribute to the situation, and these challenges grow as the ‘omics platform moves “downstream” from nucleic acids to proteins and metabolites. In addition, an abundance of clinical samples is crucial for evaluating test performance. There are inherent limitations to obtaining these samples, especially in the case of solid tumours. Another major challenge specific to cancer diagnostics is the high level of variability of biomarker levels across the human population, and the considerable molecular heterogeneity of individual cancers, even from a single tissue. These failures are also due to the lack of a coherent pipeline connecting marker discovery with well-established methods for validation (Phillips et al, 2006).

It should be noted that while the number of biomarkers introduced into widespread clinical use has been very low, there has been no shortage of biomarkers marketed as diagnostic tests—well over 1000 are available. In the US, it is possible to bypass the rigorous validation and clinical qualification processes and market the biomarkers through a different route (see “Regulatory environment”, below). However this lack of validation directly impedes their widespread adoption and integration into patient management paradigms.

## Intellectual Property

Intellectual property (IP) is not only a powerful driver of research and innovation but also vital to the success of the pharmaceutical and biotech industries. It is central to the current diagnostics revitalization given the close link to the discovery and development of new content for diagnostic tests. As such, concerns regarding IP have substantial impact.

The most common types of patents in MDx are “gene patents,” which can include several types of sequences. Patent claims can be specific to the identified nucleotide sequence or broad enough to cover all possible variants that code for a polypeptide sequence. As tests become more complex, incorporating multiple genes and parameters with the anticipated eventual development of whole-genome sequencing for clinical use, so does the challenge with respect to IP. The cost of obtaining patents for multiple components of a test can be prohibitive. Furthermore, the more patents covering test components that are already held by others, the greater the complexity of navigating the so-called “patent thicket” and the greater the likelihood of impediment. Already some 20% of the human genome is included in patent claims (Jensen & Murray, 2005). The royalty costs required to assemble the rights to multiple components could cut prohibitively into profits. This phenomenon of “royalty stacking” could particularly affect the MDx sector, with its characteristically lower profit margins (Barton, 2006; Datamonitor, 2008).

### A Shifting IP Landscape?

Several recent developments have the potential to dramatically shift the IP landscape.

With a growing backlog of applications and multiple issues

waiting to be addressed in a system not overhauled since 1952, the US Congress has made successive attempts at patent reform (2005 and 2007), with a current attempt still underway.<sup>2</sup> These bills have been highly controversial, pitting the high-tech industry against the fervent opposition of biotech/pharma. The prospects for passage improved in 2009, with the removal of some of the more contentious sections of the bill. Opinions vary as to whether this patent reform will succeed, but what is not in dispute is its potential (Ledford, 2009; Coombs, 2007).

### Products of Nature

The concept that “products of nature” such as genes and correlations between genetic variants and biological states can be patented has long been contentious and divisive. Beyond the core principle, arguments centre on the resulting effects on cost, quality and accessibility to genetic tests, and on the balance between the incentives for innovation that patents provide and purported barriers to innovation and product development (Cook-Deegan et al, 2009; Lei et al, 2009; Holman 2008).

The “products of nature” issue is particularly critical to the MDx sector, whose value and current growth surge are tied to the IP generated by the ongoing spate of genetic discovery. In the US, the following developments are underway, any of which could fundamentally change the patent landscape.

In March 2009, the US NIH Secretary’s Advisory Committee on Genetics, Health, and Society (SACGHS PGX, 2008), issued a public consultation draft report on gene patents and licensing practices and their impact on patient access to genetic tests. In addition to the panel’s preliminary findings and identification of concerns regarding the key issues, the report offers a range of options for change. These include:

- limiting or prohibiting the patenting of nucleic acid sequences and the patenting of diagnostic tests that rely on an association of a particular genotype with a disease or disorder
- withholding the right of injunctive relief from patent holders or their licensees who are impeding patient access to a genetic diagnostic test
- creating exemptions from patent infringement liability for medical practitioners and researchers

The final report containing the specific policy recommendations is to be presented in October 2009. In direct response to public concern, two bills were introduced in the US Congress in recent years specifically addressing gene patenting: The Genomic Research and Diagnostic Accessibility Act of 2002 and The Genomic Research and Accessibility Act of 2007 (Holman, 2008a). The latter sought to “prohibit patents from being obtained for a nucleotide sequence, or its functions or correlations, or the naturally occurring products it specifies.”<sup>3</sup> Neither bill was acted on, but this avenue for change remains.

In a case that could have profound impact on the diagnostics sector, the US Federal Circuit Court of Appeals issued a decision in October 2008 (*In re Bilski*) that addresses the question of what can be patented under US law. An invention must fit into one of the categories of: process, machine, manufacture, or composition of matter to be eligible; abstract ideas, laws of nature or natural phenomena are not. In its decision, the court modified its previous eligibility standard for a process. It recognized that a process involving a specific application of an abstract idea or natural law is patent-eligible, even though abstract ideas or natural laws themselves are not. The court then elaborated that a process is limited to a specific *application* of an abstract idea or natural law (and thus patentable) if (1) it is tied to a particular machine or apparatus, or (2) it transforms a particular article into a different state or thing. Although this was a business methods case, the decision applies to any technology. It would apply to patents on diagnostic processes based on the biological relationship between a gene and a disease. Such patents, which are critical to the MDx sector, could now become harder to obtain and existing ones more susceptible to challenge. Much remains to be clarified, however, and the Supreme Court has agreed to review the decision (SACGHS PGx 2008; Zhang, 2009; Kraus & Oberst, 2009).

Restrictions to gene patenting have come from the US Patent and Trademark Office (USPTO) itself. For example, in 2008 the USPTO Board of Patent Appeals and Interferences made a precedent-setting decision (*Ex parte Kubin*) that makes it harder to obtain claims to a polynucleotide encoding a protein when that encoded protein is already known, even if the protein has not been purified. This case, which will also impact issued patents, changes a long-standing obviousness standard for gene patenting (Yamanaka, 2008; Zhang, 2009).

<sup>2</sup> Patent Reform Act of 2009: S.610: <http://www.govtrack.us/congress/billtext.xpd?bill=s111-610>, HR.1260: <http://www.govtrack.us/congress/bill.xpd?bill=h111-1260>

<sup>3</sup> Genomic Research and Accessibility Act of 2007 <http://www.govtrack.us/congress/bill.xpd?tab=summary&bill=h110-977>

In May 2009, the principle of gene patenting went under direct challenge in US federal court in what could be a landmark case. A lawsuit was filed seeking to invalidate the BRCA1 and BRCA2 gene patents, naming 12 defendants, including Myriad Genetics and the USPTO. It is led by the American Civil Liberties Union (ACLU) and the Public Patent Foundation on behalf of breast cancer and women's health groups, individual women, the Association for Molecular Pathology (AMP), and other scientific associations representing over 150,000 researchers and pathologists. The main argument is that as products of nature the patents should never have been granted. The complaint goes further, charging that in violation of the First Amendment, gene patents interfere with the free flow of information and knowledge and that Myriad violated freedom of speech by using its monopoly to impede rival research, restrict clinical practice and deny people access to medical information (Marshall, 2009).

## Regulatory Environment

The regulatory environment is a critical modulating factor for the pharmaceutical and biotech industry. Here, the Dx sector has benefits over the Rx sector, with regulatory requirements that are generally less onerous in terms of time and resources. There are also more options for regulatory approval (F&S CMD, 2008).

Nevertheless, depending on the route, it can take over seven years to bring a new IVD product to market. New molecular technologies are more likely to be classified as high-risk products, increasing the required time and cost; biomarkers can take up to ten years to identify and validate. Development of a companion diagnostic has special regulatory complications stemming from the need to coordinate parallel Dx and Rx regimes (Marchant, 2006; F&S CMD, 2008).

Additionally, the same technological advances that revolutionize the industry also create restraints. Regulatory bodies have been struggling to adapt to these technologies and keep up with the rapid rate of change. The resulting flux in the regulatory environment—including lack of clarity, changing rules and uncertain timelines—increases market uncertainty and hampers growth and innovation (F&S CMD, 2008; Marchant, 2009). This has been particularly significant in the US market. Because it is generally considered the most stringent in its regulatory requirements and also critical to capture, the

US regulatory regime is deemed the benchmark and will be the focus of this discussion.

### Uncertainty in the US Regulatory Environment

In the USA, diagnostics are regulated under different regimes, depending on the nature of the product. IVDs are considered medical devices, as are imaging systems. Imaging systems may also be regulated as radiation-emitting electronic products, and imaging reagents administered to patients are regulated as pharmaceuticals. With the introduction of new technologies and the increasing convergence of in vitro and in vivo diagnostics and therapeutics, unforeseen regulatory hurdles may be encountered. A key issue for the FDA in regulation of medical devices, for example, is “intended use” and a new indication for even a well-established diagnostic device may require full FDA scrutiny (Brock, 2006).

The potential regulatory pathways are complex, and currently the regulatory environment faces significant flux and controversy. This is particularly true for IVDs.

### Four Potential Pathways for IVDs

1. Obtain pre-market regulatory clearance from the Food and Drug Administration (FDA) to sell a diagnostic *kit* (a packaged product)
2. Develop an LDT (laboratory-developed test) and sell the performance of the test in-house as a *service*. These so-called “home brews” are regulated via the clinical laboratory improvement amendments of 1988 (CLIA)
3. Sell one or more of the components of diagnostic tests as ASRs (analyte-specific reagents). ASRs, individually, are exempt from pre-market notification, thus enabling early-market penetration and enhancing early adoption of the technology
4. Position the product for research use only (RUO), a tactic sometimes used for diagnostics that have not established clinical utility

### FDA Route

IVDs sold as kits (reagents, instruments, and systems) are regulated by the FDA as medical devices and are subject to pre-market and post-market controls. Products are classified as Class I, II or III according to the level of control required to assure safety and effectiveness. In this context, this refers to the impact on patients of the *results* generated by the device, particularly false negative or false positive results (Marchant, 2006).

Classification determines the pre-market process, and thus the complexity, level of scrutiny and corresponding time and expense required. Some well-established, low-risk assays are exempt from the need for FDA pre-market authorization. Class I IVDs that are substantially equivalent to an existing approved product (a predicate IVD) may submit a pre-market notification–510(k)– 90 days before marketing. Class II involves special controls in addition to the general controls of Class I. Class III devices—which includes all “first-in-class” kits—are subject to pre-market approval (PMA), the most stringent type of application, which entails a scientific review of all available evidence of the safety and effectiveness of a device for its intended use. IVD applications for new types of assays will almost always need supporting clinical data. The regulatory framework for these studies, however, is different than pharmaceuticals.

#### **CLIA Route**

Laboratory-developed tests (LDTs) are tests that are developed for use in a single laboratory. A company can elect to create an LDT in-house (“home brew”) and must sell the performance of that test as a service rather than a kit. The FDA does not typically review these tests but they are subject to the test performance standards of CLIA. Under CLIA provisions, certification requires laboratories to adhere to standards of quality control, personnel qualifications, and documentation, but it does not address the underlying validity of the test. The level of scrutiny of CLIA inspections and certification requirements will depend on the complexity of the tests performed.<sup>4</sup>

#### **Choosing a Regulatory Pathway**

The FDA route has not been the path usually taken for IVDs. It is inherently the costliest and most time-consuming option. In one estimate, the FDA route requires a market opportunity of \$10–50 million<sup>5</sup> to generate a positive return on investment (Batchelder & Miller, 2006; Datamonitor, 2008). More than 1000 biomarkers are currently marketed as diagnostic tests. They are almost all offered as home-brew tests in central laboratories. For example, in the US cancer molecular diagnostics market in 2007, the revenue distribution between CLIA and FDA-approved products was 98% CLIA, 2% FDA (F&S CMD, 2008).

A strategy of bringing a product to market via the CLIA route in parallel with an FDA approval process can be beneficial. A company can approach the FDA early to identify the pertinent issues and how to address them, as well as the extent and nature of required patient data, the type of trial to be designed, and a rough timeline for the process. This can be done in parallel with a CLIA strategy for bringing a product to market. This would provide the fast market entry, revenue generation, and market and physician awareness of the CLIA route, with an eye toward the long-term attainment of the credibility, acceptance and reimbursement potential provided by FDA approval. It would also allow for growth, with initial sales for the performance of the test in the CLIA-approved lab, and the potential for the global market reach afforded by selling test kits (F&S CMD, 2008).

#### **A Shifting Regulatory Landscape**

The surge in new technologies in the past few years has raised multiple issues for the regulatory system to address. While much uncertainty remains, the FDA has made progress in clarifying some of these issues.<sup>6</sup> This includes the establishment of a US regulatory pathway for pharmacogenomic data submissions with the publication of final guidance for new drugs developed in conjunction with biomarkers. The FDA has also set up a new Office of Combination Products to handle the review of products that require both a diagnostic kit and a drug. Further guidance on drug-diagnostic co-development is still needed to provide clear requirements and standards in regulatory procedures.

#### **CLIA vs FDA: IVDMIAs**

An area of continuing uncertainty and controversy exists in the regulation of “in vitro diagnostic multivariate index assays” (IVDMIAs) and it has the potential for considerable impact on the MDx landscape.

The strong tendency for tests to be offered as LDTs in order to bypass FDA scrutiny has become a focus of strong concern for the FDA. With the proliferation of MDx tests that employ complex biomarker panels and other esoteric technologies, the increasing number, variety, and potential clinical impact of non-reviewed tests raises “significant issues of safety and effectiveness.”<sup>7</sup> In 2006 and 2007, the

4 <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVDRegulatoryAssistance/vem124105.htm>

5 The bar is set even higher for turning a promising molecular biomarker into an in vivo imaging reagent. Because these are regulated as pharmaceuticals, the process is more costly, bringing the required market opportunity to an estimated \$100 million. This is difficult to attain for a niche reagent, making regulation a significant barrier for their development (Frangioni, 2006).

6 <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm079148.htm>

7 Ibid

FDA issued draft guidance defining laboratory-developed IVDMIAs as a discrete category of device<sup>8</sup> and asserted its authority to regulate them. IVDMIAs measure multiple parameters and analyze data with algorithms that are often proprietary, using correlations with clinical outcomes that have not necessarily been validated, making it difficult to interpret results.

Most IVDMIAs will require some level of FDA review, and some will require full regulatory approval. Beyond IVDMIAs, the FDA has not developed an overarching position regarding oversight of home-brew assays as a class.

The FDA's position has sparked much controversy among health-care interest groups and industry stakeholders. Proponents cite multiple causes for concern under the current system, contending that IVDMIAs have a novelty and risk profile distinct from other home brew devices and that the existing regulatory framework is not adequate to assure safety and effectiveness. Opposition to the proposed changes has been fierce, contending that IVDMIAs are not sufficiently well-defined and could include well-established tests and that there will be difficulty dovetailing with existing CLIA guidelines, which would still apply. Some voice concerns as to whether the FDA even has the legal authority to regulate this realm—cost burdens and delays will become a disincentive to innovation and development, and will prevent some products from reaching the market at all, since a larger market size would be required to offset the added development costs. (Losing out will be indications that have smaller patient populations, and conditions divided into subpopulations.) Those tests that do reach the market will also be more costly, thus limiting patient access to new technology, particularly for indications with a relatively small market size.

### **Upshot for the Dx Industry**

The number of tests that would be defined as IVDMIAs is likely to continue to increase. These tests which would previously have been marketed as home brew tests and sold as services, will most likely be regulated by FDA. Some may continue to be sold under the same in-house model, while others may be marketed as test kits.

FDA regulation is likely to impose an increased burden in cost and time. Sectors that increasingly utilize IVDMIA-type tests (e.g., cancer MDx: 98% CLIA in 2007) will experience a greater impact. This sector also has high costs associated with carrying out due diligence, which can cost \$5-30 million (F&S CMD, 2008).

The pharmaceutical industry will also be significantly affected by the regulatory changes to IVDMIA technology. According to recent pharmaceutical drug trend reports, during the next five to 10 years, about 10% to 20% of drugs in development will likely be associated with genetic tests. In addition, in the next three years, as many as seven products could be introduced with genetic or other biomarker information included in product labeling. Thus, regulatory changes to these home-brew tests may delay drug development and approvals, affect drug labeling, and ultimately affect treatment and advertising or promotional claims.

The FDA's draft guidance is not legally enforceable but it is taken seriously and is likely, in some final form, to become so. Some companies have chosen to seek voluntary clearance. In addition, the industry has been put on notice that the policy of enforcement discretion by the FDA is changing and could apply in other areas as well. Meanwhile, the intense debate over IVDMIAs continues and the US regulatory pathway remains unclear for IVDMIAs, pending final FDA guidance. At present, the FDA is expected to publish another set of guidelines, leading to discussions that will eventually culminate in a drafting of the rules (F&S CMD, 2008).

## **Adoption**

### **Awareness and Acceptance**

Opting for a strategic pathway that bypasses rigorous regulatory scrutiny may lower that particular hurdle, but it can dramatically raise the next one. One of the biggest barriers to the success of a new test is adoption. Meeting the high standards of a regulator like the FDA goes a long way toward convincing a clinician of a test's validity, while a market flooded with unapproved tests leads to skepticism. Beyond validation lies the issue of whether the results will make a real difference to quality of care and clinical outcomes relative to standard practice, and whether it will provide new information for an important decision that has to be made. Also of importance are the pressing need for education and awareness among clinicians and patients, and the sheer dominance of the established, entrenched way of doing things in many medical settings. Even under very similar conditions, the uptake of a new test can vary significantly between sites. Additionally, underlying societal concerns remain about the ethics and confidentiality posed by genetic testing.

Unlike therapeutics, which go to market relatively quickly

<sup>8</sup> Provides a result whose derivation is non-transparent and cannot be independently derived or verified by the end-user.

once approved, diagnostics are adopted more slowly. Even with approval, diagnostics tend to need several years to gradually win community acceptance, penetrating the market through peer-reviewed journals, thought leaders and, sometimes, direct-to-consumer advertising.

### Large-scale Implementation

The adoption hurdle involves a chicken-and-egg predicament not unlike the jostling that takes place in retail for positioning on store shelves. To become widely adopted, a test must be offered by the big clinical testing labs. These labs are not likely to offer it unless enough clinicians request it, especially if the test requires a large upfront capital investment. Previously, the route to secure uptake by the clinical testing labs required the support of one of the large entrenched firms dominating the Dx sector. That has been changing with the increased use of the CLIA route to bring tests to market. However, the CLIA route does not provide a successful strategy to achieve large-scale distribution, even though the samples can be physically shipped to CLIA labs. In this respect, distributing a test as an IVD kit rather than as a service can realize better market penetration (F&S CMD, 2008).

Another issue is the requirement for standardization and repeatability of tests. A widely used test must be extremely robust in terms of accuracy, specificity and sensitivity, and be consistent at multiple sites in the hands of multiple technicians. This proves challenging when so many new tests involve highly complex platforms and procedures, advanced equipment and sophisticated skill sets to perform. Thus switching the format of a test from performing it in an established CLIA lab to shipping it out as an IVD kit can be very difficult.

Of course, intertwined with adoption is reimbursement, in another chicken-and-egg scenario. This situation is considered different, however, in the US compared with Europe and other international markets. Whereas in the US Dx sector, adoption is thought to drive reimbursement, in Europe reimbursement is a prerequisite for generating sales. Endorsement of a test by professional bodies favours coverage, although drug labeling that includes recommendation for testing is of paramount importance (Marchant, 2009).

Widespread adoption of pharmacogenomic diagnostics in clinical practice is thus a long process. For diseases such as cancer, the application of genomics-based diagnostic

tests to guide treatment decisions will present fewer obstacles than for genomic tests that assess risk factors for common conditions. The high cost of cancer care and the serious nature of the disease justify the cost of a test. For less serious diseases that can be treated with relatively inexpensive drugs, or in which trying different treatment options is not too onerous, convincing data will be needed to support clinical and economic arguments for drug-diagnostic test combinations. Gene-disease correlations discovered for conditions that are affected by multiple genes will require significant investment to demonstrate clinical benefit (Marchant, 2009).

### Reimbursement

Reimbursement is another critical success factor for health-care products. The Dx sector has had longstanding reimbursement challenges.

Diagnostics have historically had commodity status, perceived as being of lesser value than drugs. Low reimbursement rates have contributed to the sector's characteristically low margins. Spending for Dx is only at ~2% of total health-care expenditure (Billings, 2006). The prospect of low reimbursement is a disincentive for investment that further reinforces the sector's low valuation. Thus low reimbursement has been a key barrier to development of diagnostic products (Phillips et al, 2006).

The expectation is that the new generation diagnostics will break this cycle, either by linking the products with companion therapies or by demonstrating value such as cost reduction through targeted therapies and reduction in adverse effects. It will be necessary to demonstrate value, because these products, especially those requiring the development of clinically useful biomarkers, tend to require substantial investment yet are targeted to niche markets. For companion diagnostics, the trials needed to evaluate a test used with a drug can be as expensive, if not more so, than traditional drug trials (Allison, 2008).

The approach of determining reimbursement for diagnostics has been described as "textbook-like," providing little leeway for arguments in favour of prices that reflect the true value of the product in the context of both clinical value and overall economic benefit. An ongoing challenge for diagnostic companies is to achieve a reimbursement price that covers the costs involved,

<sup>9</sup> The bar is set even higher for turning a promising molecular biomarker into an in vivo imaging reagent. Because these are regulated as pharmaceuticals, the process is more costly, bringing the required market opportunity to an estimated \$100 million. This is difficult to attain for a niche reagent, making regulation a significant barrier for their development (Frangioni, 2006).

particularly if the test panel involves several markers (Marchant, 2009). (In the US, some improvement to this situation will result from the US Medicare Improvement for Patients and Providers Act (MIPPA) 2008, which increased reimbursement levels for some Dx products as of January 2009).

Economic evaluation approaches will play a role and facilitate the development of new criteria for reimbursement that adequately values novel diagnostics. There is plenty of movement on this critical issue and multiple options are available for cooperation between industry, government and payers (Phillips et al, 2006).

### VC Investments

Due to their perceived commodity status, reimbursement challenges, and IP uncertainties, Dx companies tend to get lower valuation than their Rx counterparts. While the average valuation for an early-stage biotech start-up for the past three years was \$20.53 million, the valuation of Dx companies in US was only \$10.32 million, and their average valuation has decreased with 24% over this period.

The situation worsened with the recessionary environment in the US in 2008, with investment levels dropping to less than 20% of 2007 levels. It is expected that investment capital will continue to be hard to find over the next few years (Refer to Figure 2).

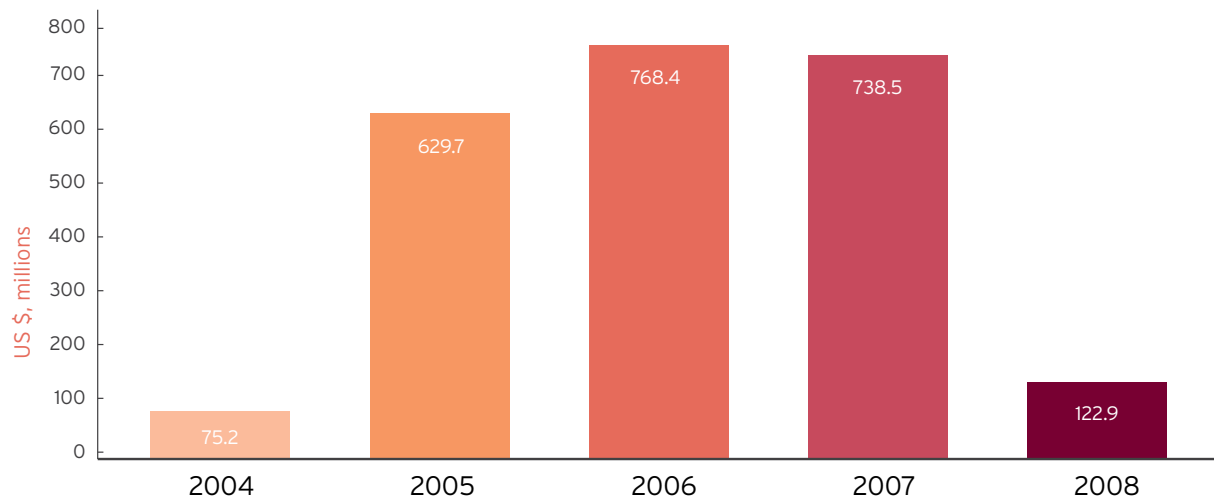
## Clinical Applications

New scientific discoveries are leading to increasingly detailed molecular characterization of both patient and disease and have paved the way to a new paradigm of evidence-based medicine. In this paradigm, treatment strategies are based on this molecular information, as are

### Personalized Medicine

A major component of this paradigm shift is the movement away from "one-size-fits-all" medicine to tailoring care to the individual patient, in order to provide the right therapy to the right person. Pharmacogenomics (PGx) refers to how individual genetic differences affect drug response. Personalized medicine is about obtaining

Figure 2 Dx Investment Trends in North America, US\$ million



Source: VentureXpert, 2009, VC Reporter, 2009

specific information about the individual patient and then using that information to optimize care. This depends on the existence of known traits, or biomarkers, that can distinguish that patient and predict a specific outcome. The arsenal of biomarkers available to medicine has been limited, however, to a relatively small number of single traits related to a relatively small number of diseases. This is not sufficient to reflect the complexity of health and disease. There is a growing consensus that biomarker profiles obtained through genomics and other 'omics technologies should provide much richer information to better reflect complex biological processes and disease states.

The application of biomarkers, whether as single traits or profiles, is expected to provide benefits at all stages across the continuum of care. Some examples are provided below and in Figure 3.

#### Risk Assessment

Sometimes predisposition to disease can have a strong association with a single trait and there are examples of such biomarkers in use. The BRCA1/2 tumour suppressor genes are well-known examples. It is estimated that 5% to 10% of all breast and ovarian cancer cases arise due to inheritance and the breast cancer susceptibility genes BRCA1 and BRCA2 have been identified as being

## Figure 3 MDx: New Tools for Evidence-Based Medicine Applications in Personalized Medicine and Targeted Therapies



**Screening** of infectious agent to predict disease severity

**Assess risk** of contracting disease:  
 • BRCA 1 and 2 for breast cancer  
 • MC1R for skin cancer

**Diagnosis** of degenerative brain diseases through detection of aggregated misfolded proteins

**Prognosis** for AMD: biomarkers associated with prognosis of blindness

**Assessment:** Identify HPV virus subtypes likely to cause cervical cancer

**Disease Staging:** molecular staging for cancer patients - e.g. colorectal cancer

**Therapy Selection:** Test tumour tissue for biomarkers to determine whether to undergo chemotherapy

**Dosage Selection:** Determine the dosage for warfarin based on the presence/absence of VKORC1 variant genes

**Resistance Development:** Antiretroviral resistance screening for HIV patients

**Monitoring** for rejection heart transplant: blood tests instead of biopsy

**Follow-up:** Identify HLA variants developing resistance to treatment regimen

responsible for 21% to 40% of these cases. Women who carry a specific germline (inherited) mutation in BRCA1, for example, have a cumulative lifetime risk of 50% to 85% of developing breast cancer and 12% to 60% of developing ovarian cancer (Couch et al, 1997; Berry et al, 1997). The corresponding screening tests are owned and marketed by *Myriad Genetics*.

Another example is Genescreen™—a screening tool developed by Genesis Genomics ([www.genesisgenomics.com](http://www.genesisgenomics.com)). Genescreen™ is designed to identify variants in the pigmentation gene (melanocortin 1 receptor gene [MC1R]) which is a factor in both hair colour and skin type. Research has demonstrated that variants in the gene are associated with increased risk for melanoma and non-melanoma skin cancer in Caucasians. The results of the test can help people make decisions on their sun protection and sun lifestyle habits.

### Diagnosis

The diagnosis of a variety of diseases has been facilitated with the use of biomarkers and many are in standard use. Many other diseases do not have associated biomarkers and diagnosis is a challenge.

One of the most promising areas still uncharted is that of neurodegenerative conditions, such as multiple sclerosis, Alzheimer's disease (AD), Parkinson's disease (PD) and variant Creutzfeldt-Jakob disease. Currently, the only definitive diagnostic for these diseases is post-mortem examination of brain tissue. Over five million people in North America have AD, and an equal number have dementia—they too may be suffering from AD, but it is impossible to diagnose this due to a lack of a blood test. Worldwide there are 460 million people over the age of 65 who should be tested annually for AD (and potentially for PD) now that effective therapies are available.

Two examples of companies trying to take advantage of opportunities in this territory are Amorfix Life Science and Axela Biosensors.

### Prognosis

Once diagnosed, the natural course of a disease varies depending on multiple factors, many of which stem from the patient's own makeup. Biomarkers associated with a particular prognosis could predict the likelihood of a particular outcome, and aid in the determination, for example, of who to treat, and how. ArcticDx ([www.](http://www.arcticdx.com)

[arcticdx.com](http://www.arcticdx.com)); see Showcase section in this report) has compiled a biomarker panel associated with age-related macular degeneration (AMD). A diagnosis of AMD means a 20% chance of losing vision with age. Macula Risk® is a prognostic test to determine if AMD patients are in the 20% likely to go blind and consequently whether that patient should undergo a specific preventive regimen.

### Therapy Selection

Pharmacogenomics (PGx) can help predict whether a drug is likely to work, cause an adverse drug reaction (ADR) or be ineffective. This allows stratification of a patient population so that only the appropriate patients will be treated.

One of the most anticipated potential benefits of PGx is the reduction of ADRs. Few prescribed medications are effective for all who use them and most ADRs are caused by an exaggerated effect of a drug. Drug response can be influenced by genetically mediated variations that affect its metabolism, transport, distribution, absorption, and excretion. In vitro diagnostic tests may be useful in identifying individuals who are more likely to experience ADRs from particular medications because of genetic variations in drug targets in the body or in the enzymes that metabolize drugs. The cytochrome P450 (CYP450) enzyme metabolizes approximately 25% of all prescription medications. A variant of the CYP2D6 gene, which affects expression of the CYP450 enzyme, is associated with slower metabolism of these drugs and is prevalent at differing rates among various population groups. Roche's AmpliChip CYP450 detects the most common variants of the CYP450 oxidase, the CYP2D6 and CYP2C19 genes. Genotyping CYP450 has the potential to improve the efficacy of 10% to 20% of all drug therapy, reduce adverse reactions by 10% to 15% and reduce unnecessary costs in inappropriate treatment. Also, by identifying patients who are more likely to suffer side effects from a particular medication, the safety profile of that drug in clinical practice will be enhanced, potentially obviating the need to remove certain medications from the market because of high risk factors. A few drugs now contain labeling information related to pharmacogenomic data regarding drug-metabolizing enzymes (SACGHS PGx, 2008; Marchant, 2006).

Another test predicts patient response to thiopurine 6-mercaptopurine, a mainstay drug used to treat acute lymphoblastic leukemia (ALL) in children. The drug is

metabolized by the enzyme thiopurinomethyltransferase (TPMT); however, individuals who have a germline variation resulting in low TPMT activity are at increased risk for life-threatening myelosuppression (inhibition of bone marrow function) when treated with the drug. Due to decreased levels of enzyme production, the concentration of this drug in the bloodstream of these individuals can reach toxic levels. Before scientists learned of this variation and its effect, a child treated for ALL with thiopurine 6-mercaptopurine was at risk for an adverse event leading to destruction of bone marrow and death. Numerous studies have shown a correlation between the TPMT genotype and frequency of myelosuppression. PGx testing now allows identification of TPMT variants to help guide treatment (SACGHS PGx, 2008).

### Dosing

The application of pharmacogenomics in helping to predict the appropriate dose of a particular drug is in its infancy, but has potential to radically improve treatment.

Roche's AmpliChip CYP450 can be used not only to identify patients at risk for ADRs to certain medications, but also to help determine optimal dosages (F&S CMD, 2008).

Warfarin, a drug commonly prescribed for those at risk for harmful blood clots, is affected by complex factors that affect proper dosing. If an individual is homozygous for the \*3 variant of the CYP2C9 gene, clearance of the drug is greatly reduced. The action of warfarin is also affected by the VKORC1 gene. The optimal maintenance doses of warfarin can vary depending on whether an individual has two copies of the low-dose VKORC1 variant or two copies of the high-dose variant. VKORC1 variants are reported to be responsible for about 30% of the variation in the final warfarin dose, and CYP2C9 is thought to be responsible for about 10%. Tests to provide greater accuracy in warfarin anticoagulation therapy are available that assess the presence of CYP2C9 and VKORC1 gene variants that correlate with warfarin metabolism (F&S CMD, 2008; SACGHS PGx, 2008).

### Monitoring

The AlloMap® Molecular Expression Test by XDx is a 20-gene MDx quantitative blood test used in conjunction with standard clinical assessment to help identify heart transplant recipients with a stable allograft function who have a low probability of moderate/severe acute cellular rejection. Heart transplant patients remain at continual

## Amorfix Life Sciences Ltd.

Amorfix Life Sciences Ltd. ([www.amorfix.com](http://www.amorfix.com)) is a theranostics company developing therapeutic products and diagnostic devices that target degenerative brain diseases including ALS, Alzheimer's disease, Parkinson's disease and variant Creutzfeldt-Jakob disease (vCJD). Amorfix's proprietary Epitope Protection™ (EP) technology enables it to specifically identify very low levels of aggregated misfolded proteins (AMP) in a sample of normal protein. Aggregated misfolded proteins are a common element of many brain-wasting diseases and the ability to identify AMPs and understand their structure and mechanism of folding are the first steps to developing new treatments for these devastating diseases. Amorfix's lead programs are a diagnostic blood-screening test for vCJD and a therapy for ALS.

## Axela Biosensors

Axela Biosensors ([www.axelabiosensors.com](http://www.axelabiosensors.com)) commercializes products that accelerate the validation of protein biomarkers from discovery to routine clinical diagnostic use. The company's proprietary Diffractive Optics Technology (dot) is a patented combination of two technologies: grating-based light diffraction and immobilized capture surfaces. According to the company, this unique combination produces a simple, highly sensitive, cost-effective platform for measuring protein levels and characterizing their interactions in real time without labels. It allows researchers to rapidly move biomarker discoveries through the reagent qualification and assay the development process into routine use. Recently, Proteome Sciences entered into a license agreement with Axela Inc. for the development of assays to measure its proprietary brain damage biomarkers on Axela's multiplex biomarker assay dotLab™ System. Working in collaboration with the Biomedical Proteomics Research Group (BPRG) at the University of Geneva, Proteome Sciences has established a strong portfolio of patent-protected blood biomarkers of brain damage-related disorders. The range of diseases covered by Proteome's patents include stroke, subarachnoid hemorrhage, traumatic brain injury, and neurodegenerative conditions such as Parkinson's disease, amyotrophic lateral sclerosis (ALS) and Alzheimer's disease.

risk for the development of acute cellular rejection (ACR). The incidence of ACR is highest in the immediate post-transplant period and declines thereafter, but it remains a clinical concern even many years after transplantation. Diagnosis of ACR requires biopsy and pathological evaluation, and is performed either as part of scheduled surveillance monitoring or when clinically indicated at any time. Some of the AlloMap Molecular Expression Technology developed and implemented by XDX with heart transplant patient management may be applicable to other diseases that involve transplant rejection and the immune system. XDX's non-invasive technology offers the potential to decrease health-care costs and significantly improve the quality of life for patients who have a variety of life-threatening or life-altering immune-mediated diseases. In 2008, FDA clearance was obtained as an in vitro diagnostic multivariate index assay (IVDMIA).

### Targeted Therapies

In addition to enabling personalized medicine, MDx can facilitate the tailoring of care to the individual disease. Molecular characterization of a disease can lead to the development of more targeted, effective treatments. That information can also become the basis of an MDx test. As with personalized medicine, MDx tests can be applied throughout the continuum of care to provide a more detailed and informative diagnosis and better-targeted treatment. Infectious diseases currently represent approximately 75% of this market. Oncology is the other main application and others are emerging.

### Infectious Disease

There are clear advantages to applying MDx technologies to the diagnosis of infectious disease. Classical culturing methods can require long periods for growth. Some pathogens cannot be cultured at all and may require an unacceptably long incubation period in the patient before a sample can be taken. The sensitivity of antibody-based tests is often inadequate. MDx tests can quickly identify the cause of an infection without the need for culturing organism-specific tests. The three weeks required to test for mycobacteria with previous methodologies, for example, can be reduced to same day results. Sensitive and rapid tests have been developed to detect the avian influenza virus H5N1 and the SARS coronavirus. These tests will contribute to early identification of these emerging diseases, enabling rapid preventive measures and treatment. Furthermore, tissue samples from a biopsy

that are fixed in formalin cannot be cultured because the organism will have been killed, whereas DNA is not destroyed by fixation. These tests also lend themselves to automated high throughput configurations to further improve efficiency (Marchant, 2006).

In addition to detecting the pathogen, MDx tests can provide clinically useful information about the infection. For example, human papilloma virus (HPV) is the most common sexually transmitted virus and the primary cause of cervical cancer. The recognition that only certain subtypes of HPV are likely to cause cervical cancer has led to the development of screening tests that distinguish patients with ubiquitous and benign infections from high-risk cases. For HIV infection, drug resistance tests are vital in guiding treatment. Up to 50% of individuals being treated for HIV in the US may carry drug-resistant forms of HIV. Combinations of mutations in the protease and reverse transcriptase regions of the AIDS virus develop over time within an individual patient. To tailor the most effective anti-HIV treatment for someone, antiretroviral resistance screenings are conducted before a patient begins or changes drug therapy.

Pfizer's Selzentry (maraviroc) is the first in a new class of antiretroviral drugs designed to prevent the CCR5-tropic HIV (R5 virus) from entering uninfected CD4+ cells by blocking the CCR5 co-receptor. Not all HIV patients have the R5 form of the HIV virus, and thus Selzentry therapy should be restricted to patients with R5 HIV infections. Monogram Biosciences' Trofile was developed as a companion diagnostic for Selzentry. Trofile is a molecular assay that identifies the tropism of a patient's HIV with respect to the co-receptors CCR5 and CXCR4 (BI Biomarkers, 2008).

Differential diagnosis of infectious diseases, especially respiratory disease, is a common clinical challenge. Since clinical syndromes are seldom specific for single pathogens, there is a need for assays that allow multiple agents to be considered simultaneously. Luminex's xTAG® Respiratory Viral Panel (RVP) is a comprehensive assay for the detection of multiple viral strains and subtypes. It tests for the major respiratory viruses commonly tested for in surveillance and patient management, which combined are responsible for 85% of respiratory viral infections, including respiratory syncytial virus (RSV), influenza, parainfluenza, rhinovirus, and adenovirus ([www.luminexcorp.com](http://www.luminexcorp.com)).

Sepsis is an infection-induced syndrome involving systemic inflammation which can lead to acute organ dysfunction and death. Sepsis and septic shock conditions affect more than 10% of the patients treated in intensive care units in US hospitals. It is also estimated that as many as one in 4,000 blood transfusions lead to a severe septic reaction. Delayed diagnosis is associated with increased mortality but results from culture alone can take up to 48 hours. Until recently, there has not been a well-accepted diagnostic biomarker for sepsis. Spectral Diagnostics' EAA™ Endotoxin Activity Assay is the only FDA-approved rapid whole blood assay for detection of human endotoxemia ([www.spectraldx.com](http://www.spectraldx.com)). Endotoxin is the most important microbial trigger for sepsis.

There are many future challenges including the need to improve the diagnostic tools for certain infections such as gonorrhea, sepsis in neonates, and hospital-acquired infections (e.g., methicillin-resistant *Staphylococcus aureus* [MRSA] infection). New pathogens continue to emerge (Dong et al, 2008). Accurate, early detection of causative agents will be vital in the event of a pandemic.

The largest segments in the MDx market at present are HIV, hepatitis C virus (HCV), *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoea* (NG). However, the growth rates in these segments have been stagnant, even declining. The markets are saturated and the competition is intense. In contrast, two emerging molecular diagnostics markets, HPV and MRSA, are enjoying rapid growth and have the potential to surpass the market size of the more established infectious disease tests. In 2007, the HPV and MRSA MDx markets generated \$192.8 million and \$80.7 million respectively in revenues in the US. The CT/NG, the HIV, and the HCV markets generated approximately \$260 million, \$200 million, and \$140 million, respectively. The latter four are centered on diagnosis and disease monitoring, but the emerging HPV and MRSA markets are based on widespread screening practices for all potential patients, creating a much larger test volume and market. The HPV testing and MRSA screening markets are poised for continued rapid growth, and each has the potential to reach more than \$1.0 billion in the US (F&S InfDis, 2008).

## Cancer

The application of biomarkers to cancer has enormous potential due to the unique association of genomic

changes in cancer cells with disease pathophysiology and outcome. The ability to identify and specifically target these changes offers the prospect of improved treatment outcomes and reduced toxicities compared to conventional broad-spectrum chemotherapy drugs. The effectiveness of this targeted therapy strategy can be bolstered by the use of *companion diagnostics* to determine which patients will or will not benefit.

Traditionally, the diagnosis and staging of cancer, as well as the evaluation of response to therapy, have been primarily based on morphology. This is due, in part, to the relatively small number of reliable cancer biomarkers. Conventional biomarker studies have focused on single genes or discrete pathways. This approach can be successful as illustrated in the examples described below. The examples also include tests based on multiple genes, which are expected to become more prevalent. Because the changes in cancer cells are typically complex and heterogeneous, the analysis of cancer cells in terms of biomarker profiles rather than single markers is expected to yield a wealth of new information. These will inform future targeted therapies and companion diagnostics. Molecular alterations can potentially be identified in tumours not only at the level of DNA mutation but also in DNA modifications such as methylation, transcription to mRNA, transcription to microRNA, translation of proteins, post-translational modifications of proteins, and synthesis of metabolites. All of these are becoming increasingly amenable to molecular analysis.

Treatment decisions in breast cancer are guided by a test for over-expression of the HER2/neu oncogene. In 25% to 30% of women with metastatic breast cancer, an aberrant expression of HER2/neu and subsequent over-expression of the HER2 protein, a growth factor receptor, are associated with genetic alterations in specific cell types. Immunohistochemistry tests can identify women whose tumours over-express the HER2 protein, and fluorescent *in situ* hybridization (FISH) tests can identify women who have the HER2/neu alteration. Women who test positive for either assay respond better to Genentech's Herceptin® (trastuzumab), allowing targeted drug therapy. In 2003, the testing became a prerequisite for choosing Herceptin® (SACGHS PGX, 2008; F&S CMD, 2008).

The Oncotype DX breast cancer test introduced by Genomic Health ([www.genomichealth.com](http://www.genomichealth.com)) is based on the detection of 21 genes that together indicate the likely

response to chemotherapy of patients who have node-negative, estrogen receptor-positive breast cancer, as well as the likelihood of recurrence.

Oncotype DX (Genomic Health) and MammaPrint (Agendia) use panels of markers to estimate the probability of breast cancer recurrence after its surgical removal to help the medical team decide which patients should receive chemotherapy (F&S CMD, 2008).

Predictive tests that monitor patients for the development of drug resistance are a significant adjunct to targeted therapies. Genzyme's BCR-ABL Mutation Analysis test, for example, monitors the development of drug resistance to Novartis' molecular targeted therapy for chronic myeloid leukemia (CML). Approximately 4% to 5% of CML patients that are initially treated successfully with Gleevec (imatinib) will develop resistance during therapy. The BCR-ABL mutation that is the specific target for Gleevec is found in 95% of patients with CML. In relapse patients, the majority of secondary mutations in the ABL portion of the gene correlate with treatment failure. Genzyme's test detects all secondary BCR-ABL mutations, predicting resistance to Gleevec and helping oncologists to personalize treatment of leukemia patients (F&S CMD, 2008).

ColonSentry is a blood test from GeneNews ([www.genenews.com/](http://www.genenews.com/)) that measures the expression of a panel of seven biomarkers. The test can stratify patients into defined risk groups (low, intermediate, high) for colon cancer, providing clinical data that can be used by patients and physicians when making decisions about further colorectal screening. By using this risk stratification tool as part of a regular screening program, individuals who have an increased risk can progress to further diagnostic testing where colorectal cancer can be identified in the early, treatable stages of the disease. This helps ensure better patient compliance and allocation of scarce colonoscopy resources.

The Pathwork® Tissue of Origin test is designed to aid in the diagnosis of tumours whose origin cannot be definitively determined. This can occur if the cancer is found in an unexpected location, if the tumour cells are poorly differentiated or undifferentiated, or if cancer is found in multiple locations indicating metastatic disease without a clear primary site. The test measures the expression patterns of a panel of more than 1,500 genes

in the tumour sample and compares these with the gene expression patterns of a panel of 15 known tissue types—representing 58 morphologies and covering 90% of solid tumours. An objective similarity score for each of 15 potential tissue types is generated and an interpretation of the results can rule in or rule out specific tumour types. The test was found to provide patterns that confirm existing tissue of origin of the 15 common tumour types using standard clinical and pathological information. This accuracy of this test is similar to that achieved by expert pathologists using current standards of practice. The test has been cleared by the FDA as an in vitro diagnostic multivariate index assay (IVDMIA).

The total US cancer MDx market for 2007 was estimated at \$271 million, with a predicted compound annual growth rate (CAGR) of 31.5% through 2014, to a predicted value of \$1.834 billion. The segments for 2007 were as follows:

- breast cancer, \$174 million (CAGR 24.1%)
- colorectal cancer, \$41 million (CAGR 33.2%)
- prostate cancer, \$2.5 million (CAGR 62.9%)
- other cancers, \$53.5 million (CAGR 44.1%)

In 2007, the breast cancer MDx market was by far the largest segment of the total market (64.2% of total revenues). However, rapid growth of the colorectal, lung, ovarian and especially prostate markets (CAGR 62.9%) was predicted (F&S CMD, 2008).

Molecular diagnostics and in vitro diagnostics generally offer plenty of commercial opportunities that are enabled by the scientific and technology advancements in recent years and by the need for better diagnostic tools for the health-care and pharma/biotech sectors. However, the current economic environment and shifting regulatory environment pose significant challenges that any investor or entrepreneur involved in the diagnostics industry should keep in mind.

Given this context, learning from people in the trenches how to use these opportunities while mitigating the risk factors is important. The following pages provide some examples of such people and companies from the Ontario cluster of diagnostics companies.

Driven by increasing demand for quantitative molecular diagnostic assays, anatomic pathology is entering a new technological era. Biomedical Photometrics Inc. (BPI) may offer some of the best available tools.

Radiology and other medical disciplines have adopted digital technologies over the past decade, however, most pathologists continue to examine glass slides manually under a microscope even though the scanning and digitizing of pathology slides offers clear advantages. It is no longer necessary to store, retrieve and ship slides or deal with loss, breakage or fading of signals. Images can be readily accessed, shared and examined, and computer algorithms add an additional layer of analysis. Data can then be integrated with health information systems. The reasons for the lag in adoption have been both technical and cultural. Recent advances, however, are changing this landscape.

Digital pathology not only improves efficiencies but also provides direct benefits for patients. One of the drivers of the fast-growing molecular diagnostics segment is the demand for quantitative pathology based on fluorescence *in situ* hybridization (FISH), immunohistochemistry (IHC) and special staining of tissues and body fluids. These DNA, RNA or protein-based assays are used to guide diagnosis, prognosis and treatment selection in a range of human diseases. MDx are critical "companion diagnostics" for personalized medicine in oncology.

The demand for accurate MDx assays is transforming the role of the pathologist. Traditionally, the anatomic pathologist used a standard microscope to examine a biopsy or surgical specimen that had been placed onto a glass slide and stained for visual examination. Based on visual analysis of the morphology of the cells in the specimen, the pathologist provided routine clinical diagnosis of cancer and other diseases. Today, this level of characterization is

insufficient and profiling at a molecular level is required. The key drivers to the rapidly growing \$4.5 billion MDx market are the increasing number of MDx assays and the demand for increased automation in sample preparation, digital slide scanning and automated quantitative analysis.

An important clinical application is the assessment of HER2 expression in breast cancer biopsies in order to determine candidacy for treatment with Herceptin. In this area, FISH is considered to be the gold standard. "There have been some disasters recently in HER-2 imaging, one of them in Newfoundland, where some 20% of breast cancer patients had been incorrectly diagnosed. What we're seeing is that FISH is not an easy test to do manually," says Ted Dixon, PhD, CEO and co-founder of Biomedical Photometrics (BPI). Diana Pliura, PhD, a consultant to the company, adds, "The way it is done now, the tissues are processed, the glass slide is made and the technologists sit in a dark room with a fluorescence microscope and count dots. They routinely analyze ~1% to 2% of the entire specimen that is on the slide. With the current manual technology, it is completely impractical to interrogate the entire specimen. BPI now have a tool that will be able to automate, digitize and record information on the full specimen, which is critical."

The applications are not limited to HER2 testing. "Currently," says Pliura, "the FDA has approved about 13 FISH kits for different applications, some for HER-2, also EGF-R, urinary tract infection, cytogenetics assays, and for assessment of a fetus for Downs Syndrome. Virtually every important cancer has either a validated FISH assay in use as a prognostic, diagnostic or guided therapy, or there is something in development for that cancer right now. It's not just an important tool in oncology. You see it increasingly in other disease states as well."

The technology that led to the founding of BPI emerged from the physics department at the University of Waterloo. BPI was co-founded by Dixon together with colleagues Brian Wilson, PhD, and Melanie Campbell, PhD. "The new technology was developed in my laboratory in physics and patented, and we knew it had considerable advantages over microscopy and were really passionate about bringing that technology forward", said Dixon.

BPI has replaced the traditional scanning-laser microscope optical train with a proprietary MACROscope® confocal, submicron laser scanning technology. "Briefly," says Dixon, "the instrument is like a scanning laser microscope except instead of using a microscope objective, we use a laser scan lens which is specially designed for this application. And of course that changes the intermediate optics as well, but the important part of it all is the laser scan lens gives us ten times the field of view of a microscope in a single scan." This enables very rapid, high-resolution imaging across a full range of specimen sizes.

BPI's present instrument, the TISSUEScope™ 4000, is equipped with a large viewing stage and permits panoramic images of whole mount specimens of up to 5x7 inches, such as whole breast lumpectomy specimens or whole prostates, at high resolution. Both bright field and multi-fluor fluorescence microscopy can be performed in the same instrument. "In fact," says Dixon, "we are delivering an instrument today to the US Army Medical Research Institute for Chemical Defense."

The new instrument—the TISSUEScopeMDx—will be ready in 2010. "We are designing a new high resolution lens. It will have two-fold greater resolution than the 4000 and will image even faster in fluorescence and bright field. It was developed specifically for the pathology clinic whereas the 4000 was developed for research. It will provide digital high resolution, multi-coloured fluorescent or bright field images of clinical specimens in a matter of minutes. Analytic software will be offered to facilitate quantitative analysis. We hope to deliver the first instrument in the October/November time frame."

There are several other digital pathology companies offering instruments for FISH and other quantitative pathology assays, but BPI's TISSUEScopeMDx offers several key advantages. "We can do a very high speed preview scan, which I don't think any of our competitors can do. We can do both fluorescence and bright field in the same instrument. Some of the competition does fluorescence in one instrument and bright field in a different one. The field of view is much larger and this is one of the reasons why the idea of imaging the whole specimen is such a natural in our instrument. In a 40x microscope objective, the field

of view is usually 250 um by 250 um. The field of view of our instrument at 40x is a scan 5 mm wide by the length of the microscope slide. That's an amazing difference in the size of the field that you can look at. Nobody else can do the broad field that we can. The other people do it by taking a whole series of tiny images and then stitching them together. In addition, our instrument is confocal; most of our competitors are not. The confocal technology not only allows us to do three-dimensional scanning of thick tissue, but also considerably reduces background signal in fluorescence."

Other key factors are image size, which has long been a technical issue in digital pathology, and time. "The technology affords the capability to rapidly acquire large images; they tend to be a few gigabytes to a few hundred, sometimes up to half a terabyte per image. In the fluorescence mode we have the capability to capture the four different fluorophores in the same pass simultaneously. Our competitors need to scan separately for each fluorophore and then overlay all the images. They have to stitch and overlay. In some of the traditional microscope tiling systems, that can take hours whereas we can reduce that to minutes, and with greater fidelity."

Like other instruments on the market, the TISSUEScopeMDx is fully automated. "It does automated focus, it automatically finds the tissue, it automatically does the imaging, it automatically puts the final image together and saves it as a TIFF file, and so on. So all of those things are similar to our competitors but we do it very well."

There are a few steps remaining to complete the instrument. "One of the things we need to do is develop analysis software to do reliable counting of the markers. We hope to do that in partnership with others. We would like to work with people who are developing fluorescent biomarkers for cancer." Investment and partnership are also being sought for productization of the new MDx and Tissuescope 4000 to get both instruments manufactured offsite by a commercial manufacturer and to expand sales and marketing activities. "We have a validated instrument, we have the IP, and the market is there. We have a superior product. We now need to get this commercialized."

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**Biomedical Photometrics Inc. (BPI)**

[www.confocal.com](http://www.confocal.com)

Interview with: A.E. (Ted) Dixon, PhD, CEO and Chairman  
Professor Emeritus of Physics, University of Waterloo

## GenEplex is a highly versatile, ultra-sensitive, cost-effective electronic molecular diagnostic platform for point-of-care use.

GenEplex is the tentative name for a new company emerging from the lab of University of Toronto professor Shana Kelley, PhD. The GenEplex system is a molecular diagnostics platform co-developed by Kelley and Ted Sargent, PhD, University of Toronto Professor of Electrical and Computer Engineering. The platform has been under development in Kelley's lab.

The vision for GenEplex is to bring a set of devices to market that will make molecular diagnostics amenable for use at the point of care.

Molecular approaches bring clear benefits to diagnostics and there has been increasing demand for better speed and convenience in the provision of test results. "We have developed a low-cost, high-sensitivity approach to molecular diagnostic instrumentation that we think will finally take molecular diagnosis out of research labs and even out of hospital labs—and bring it to point of care so that it can be used in hospitals, even at the patient's bedside, where the information can be provided in real time to make clinical diagnosis much more effective."

Kelley has worked on the development of new molecular diagnostics technologies for over a decade and has experience with their commercialization. She was a co-founder of GeneOhm Sciences, which was based on a molecular diagnostics platform. The company developed a test for infectious pathogens and was eventually acquired by Becton Dickinson. "Through that experience I know what the opportunities are in the industry and where there are still unmet needs. This has motivated me to develop something in my own lab that would solve the problems that existing technologies were never going to meet. One of the key features that will be integrated into the GenEplex platform is the ability to do direct sample analysis: to take a sample from the patient and process it

directly in a hand-held unit that could be operated by any kind of person in the health-care environment."

The GenEplex platform consists of a nanomaterial-based chip that reports molecular binding events as electronic signals. This makes it possible to use smaller, cheaper and simpler instrumentation compared to platforms in which the readout is based on optical signals or spectroscopy. The chips can be built to detect DNA, RNA and protein levels as well as protein activity. The platform can perform assays in multiplex format, with a very high sensitivity, large dynamic range, and speed. It can also be readily modified to detect different markers for different disease states, making it highly adaptable for multiple applications.

This combination of versatility, sensitivity and practicality makes the GenEplex platform especially well suited for point-of-care applications. It is portable, easy to use, inexpensive, and can accommodate a range of biological samples, including whole blood. Results can be produced in minutes, compared to hours or days for conventional tests.

Several possible applications for the GenEplex platform are being explored. It has now been validated in threemain areas:

1. Infection control, mainly within the hospital environment
2. Oncological management, including early diagnosis, treatment and follow-up monitoring
3. Pharmacogenetic testing to stratify patients for therapy selection

The pharmacogenetic testing could be applied either in the clinic or during clinical trials. One of these applications listed will be targeted for further development and carried through to clinical validation and regulatory approval.

The company is still at a very early stage and is currently carrying out pre-commercialization work in partnership with a variety of provincial and federal agencies. Last April, Kelley and Sargent received an award from the Ontario Institute for Cancer Research.

"They've been very generous with giving us funding for the next stage of technology development and to

prepare a technology that is working well in a research lab to go into a company. Within the next six months we want to take the next step and transfer the technology out of the university. At the moment we are looking for new partnerships in the form of financial backing. We envision going to market with a venture-backed company, but are also enthusiastic about partnering with a larger diagnostics company and doing it that way."

"We'll have a prototype in hand within six months. We have a number of engineers on our team that are making a handheld instrument. This will be the precursor to what we go to market with. We also have several sets of proof-of-principle data that we have collected with clinical samples showing validation of the platform. We are optimistic that having these assets in hand will attract financing to the company."

"In the longer term, there are many applications for this type of technology. The number of tests that we could eventually weave into our menu is very high because of the versatility of the platform and its performance with a variety of analytes."

## ArcticDx is a molecular diagnostics company being built purely on content.

ArcticDx Inc. is a private Canadian company that is developing two molecular tests: Colo Risk® for colorectal cancer and Macula Risk® for age-related macular degeneration.

ArcticDx was founded by medical oncologist and geneticist, Brent Zanke, MD, PhD, Chairman and Chief Medical Officer. In 2004 Dr. Zanke and Dr. Tom Hudson (Ontario Institute for Cancer Research) initiated the ARCTIC project—Assessment of Risk for Colon Tumours in Canada—with a \$10 million grant from Genome Canada. The Genome Wide Association Project which studied genetic associations in colorectal cancer grew into an international program including nine studies in five countries. The intellectual property that was generated was ultimately assigned to Cancer Care Ontario (CCO) with other related discoveries going to Cancer Research UK. Zanke created ArcticDx in September 2005 and negotiated with CCO an exclusive worldwide license to the genetic markers from the ARCTIC project. He then approached Greg Hines (who was leaving the molecular diagnostic company, Tm Bioscience, following its sale in March 2007) to help commercialize the markers. Hines partnered with Zanke. They then invited other Tm Bioscience executives James Pelot (CFO) and Alan Coley (VP Operations/Regulatory Affairs) to join ArcticDx.

Hines and Zanke moved early to bolster the colorectal cancer IP portfolio with licenses from Cancer Research UK. “We put the pieces together,” he said, “and developed a colorectal cancer test that is now in the last phase of product development.”

“While we were doing that we were looking for a second product because you can’t build and finance a company on one horse,” he continued. “Zanke had noted that some very strong genetic outcomes around age-related macular degeneration (AMD), one of the leading causes of blindness in the elderly, were appearing in the scientific

literature. The genetics of that disease are extremely strong—about 80% of the disease is caused by genetics.” Hines moved to collect and secure the rights to the genetic markers that had been identified.

“The vision for the company was to become a catalyst for the development of molecular diagnostic tests. In my last business at Tm Bioscience, we were a platform company and the platform consisted of an instrument and some unique chemistry. We’d have to go out and license the intellectual property, the genetic content to put on it, to build a test. Unique proprietary content was difficult to attract. It was the real value in any test. In the ArcticDx business model, the vision was to just focus on acquiring high value content.”

With the colorectal cancer and AMD intellectual property as assets, they built the company using a variable cost business model. “All of the technologies that need to be bolted on to that content to make it a genetic test can become a variable cost.” All possible steps in the development and marketing of the test would be outsourced. They found a company to handle sample collection and a lab to design the genetic probes, and another lab to develop the assay and the patient report and to provide the testing service for physicians. In exchange for developing the assay, the lab received exclusive rights to provide the testing service in Canada.

ArcticDx also ensured that every step was performed according to FDA specifications to position the test for approval and to submit all of the validation data that were generated. The plan was to build a lab-developed test under CLIA regulations that could also be sold as an FDA-approved kit. The test was to be marketed initially only in Canada. They found a Canadian distribution partner. In addition, because costs were kept down, financing was not done through venture capital. However, there has been significant investment activity from strategic partners and potential customers, including members of the ophthalmology community who recognize the value of the AMD test.

The goal was to develop the tests to the point where ArcticDx could demonstrate three things to a worldwide

strategic partner: a strong intellectual property portfolio, reduced regulatory risk by taking the product straight to the FDA, and a demonstrated commercial viability by putting the product into the market in small areas. "If we could do those three things, then we could go talk to the likes of Abbott, Johnson and Johnson, or Roche and negotiate a value against risk."

According to Hines, a diagnosis of AMD means a 20% chance of losing vision as you age. "Macula Risk® is a prognostic test to identify if AMD patients are in the 20% that are going to go blind or the 80% that won't. If you're in the 20%, then you need to see your optometrist or ophthalmologist routinely, maybe as often as every four to six months to monitor disease progression. There are different treatments to either prevent or arrest the disease."

"It's a huge disease. AMD is as common as diabetes. About one in ten people over the age of 60 have it. Macula Risk® is the only licensed test available and the market for this test is enormous. There are two million people per year in the US that are diagnosed with early disease, and about 34 million people who already have early or intermediate AMD. Macula Risk® is being reimbursed in the US by Medicare and from some private insurers at the present time. On the incident AMD population alone, this is a billion dollar a year market."

With regard to companion diagnostics, "There are up to 12 drugs in development and many of them work on the genetic pathways we now own the rights to."

Another large intended use lies in the cataract surgery and, possibly, the contact lens businesses. According to Hines, in cataract surgery, lenses are replaced in 15 million people every year worldwide, with up to three million in the US. Of the three main types of replacement lens, there is a clear monofocal lens with the right focal length for average vision, a multifocal lens, and various lenses with ultra-violet filters. The multifocal lens may be contraindicated in anybody with AMD whereas the filtering lens prevents damage to the retina and may help prevent the development of AMD. The filtering lenses are more expensive and are associated with some colour distortion

and tend not to be chosen unless necessary. Similarly, contact lenses can come with UV filters and are associated with the same cost and performance issues. The ArcticDx AMD test is already being adopted by cataract surgeons to help guide lens selection.

"I have no idea what the product is worth, but some very large sales and marketing companies are doing due diligence with us right now."

"But," he adds, "we don't want to sell the company just yet. We think there's too much value to be created by generating some revenue, especially now that Macula Risk® has some insurance coverage. By the end of this year we want to have a US strategic partnership for sales and marketing."

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**ArcticDx Inc.**

[www.arcticdx.com](http://www.arcticdx.com)

Interview with: Greg Hines, President and CEO

Fio (“fee - oh”): It’s short for “fiovanana,” which means “treating strangers like family” in Malagasy, the language of Madagascar. Fio was created to address the problem of infectious diseases in the developing world.

The first business venture for Michael Greenberg, MD followed a fairly classic trajectory of develop a technology then build the business. Prior to getting involved in Fio or another technology company, he arrived in Toronto to do a residency in neurosurgery. “I took 6 months off near the end of my residency to help a little startup build some technology, and within 12 months I found myself as the president of the company.” That company was later rebranded Cedara Software, a medical imaging software company. “We became the largest supplier of image-processing software to diagnostic imaging companies and we pioneered the first image-guided surgery system approved by the FDA. Our software was the core image processing software for diagnostic imaging equipment manufacturers, surgical system companies, and healthcare IT companies: Philips, GE, Toshiba, Hitachi, Siemens, Carl Zeiss, Cerner, to name some. I left the company in 2002, and about 18 months later it was bought by a US company in a deal worth over \$475 million.”

Among the many rich experiences from Cedara, Greenberg had gained a strong sense of relationship-building and of focus on a company’s mission. In that sense, Fio began almost as soon as he left Cedara and began contemplating his next step. It was Jay Godsall, who was to become one of Fio’s co-founders, who taught him the word “fiovanana.” Godsall’s commitment to the developing world had brought him to Africa dozens of times. One time he came back deathly ill with what turned out to be a misdiagnosed case of malaria. His life was saved by Dr. Kevin Kain, Professor of Infectious Diseases at UHN. Godsall introduced Kain to Greenberg, who was drawn into the global problem of

infectious diseases. This became the seed for Fio.

Millions die each year from malaria, acute respiratory infections, enteric infections, tuberculosis, AIDS, and parasitic infections. Together with the added burden of morbidity, this human tragedy poses an enormous barrier to economic development in the developing world. Most of these diseases are treatable, and access to drugs has improved markedly. A major stumbling block, however, is the need for better diagnosis.

“We began looking for a solution. However, this time I did not want to begin with a technology, I wanted to have a business model first, and work backwards towards a technology. We designed a business model and it turned out we could patent it.” Fio has several key values: the business model leads everything else, the product has to work in both the developed and developing world, and business development should not wait for the technology to be in place. “Our team had enough contacts and track record to build business relationships in parallel with building the technology. We incorporated in 2006, and co-applied with UHN and U of T for a Genome Canada competitive research award. It was unusual in that Fio was not only the commercialization partner but also the co-applicant. In the application, Kevin [Kain] and I were co-PIs, representing the McLaughlin-Rotman Center (MRC) for Global Health and Fio. Joe Rotman, the sponsor behind the MRC, and I developed a wonderful relationship, and Fio continues close collaboration with the MRC and its management, Drs Peter Singer and Abdallah Daar.”

Fio explored several technologies until they found one that would meet their requirements and began the process of development. The target device is a handheld, simple to use, multiplex (i.e., capable of analyzing multiple molecular targets simultaneously) point-of-care diagnostic that is able to simultaneously look at pathogen and host targets.

The platform consists of a convergence of nanotechnology, biotechnology, and information technology. The nanotechnology (“quantum dots”) includes fluorophores with unique optical properties. Because of their brightness, they can be excited by inexpensive light emitting diodes and detected inexpensively. Quantum dots are bright enough to be macroscopically detectable with

inexpensive instrumentation and small enough to bind to individual molecules, allowing macroscopic signaling of molecular events.

So far, the versatile point-of-care technology performs competitively when compared with specialized, laboratory-based gold standard diagnostics. The next phase is engineering design, and Fio is working with several engineering companies to create a prototype.

The first application will be malaria. The biomarker panel will determine if a patient has malaria and what type it is. If it is not malaria, the instrument will determine the nature of the infection. The first target customers will be travel clinics in Canada and in the developing world. Discussions have begun with a variety of groups, clinics and institutional buyers who have employees at risk in malaria zones. These include the malaria program at WHO, senior health officials in the developing world, and distributors.

The business is scalable. The reader is universal and the panel can be set up for a variety of infectious diseases. Fio is not developing new biomarkers, but employing existing or emerging ones and future applications are in development. A public offering is planned after the first panel is released.

“The product is moving to the engineering phase now, we’re also moving into our second round of financing. We were successful, oversubscribed, with the first financing three years ago. This is a very different financial market now. Yet our commitment is huge and things seem to work out. In my previous company, my first presentation to potential investors at the Toronto Stock Exchange happened to be Tuesday, October 20th, 1987, the day after Black Monday when the market crashed. I am confident we will be successful raising money and will find the right partners to help us fulfill our mission”.

We asked Greenberg to talk about Fio’s future and his reply, “Once we raise the money, the company will race to get the product out and demonstrate what we have envisioned. After we get the financing behind us, the facts will do our talking.”

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**Fio Corporation**  
www.fio.com

Interview with:  
Michael Greenberg, MD, Co-Founder and CEO

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