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## Technological Forecasting &amp; Social Change



## The future of drug discovery and development: Shifting emphasis towards personalized medicine

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### ABSTRACT

The drug discovery sector is being revolutionized by the current rate of advances in the public and private human genome projects and by the development of new technologies for biomarker testing. In effect, as the genetic roots of disease, disease progression and treatment effectiveness are uncovered, the demand for sophisticated prognostic, diagnostic and monitoring tests will be increasing. Already this has led to the development of innovative diagnostics products meeting the criteria of improved efficacy and safety as well as better cost-benefits. In order to achieve the ultimate goal of a more predictive and personalized medicine requires the drug discovery industry to implement more synergies between the two worlds of clinical research and diagnostics. The therapeutics that are enabled by that strategy are often called “theranostics” – highly specific tests that allow for the diagnosis of the disease, but to administer the most appropriate treatment regimen, and to monitor a patient’s response to therapy. Biomarkers will constitute a critical component of the health care delivery system in order to detect, diagnose and monitor diseases and other medical conditions as well as to evaluate treatment options and effectiveness. While diagnostic breakthroughs typically precede therapeutic advances, the presence of new therapies can stimulate the demand for testing. The main question that remains to be answered is how will the biomarker paradigm alters these companies’ innovation and commercialization strategies. Whereas developing drug targets may offer greater long-term value, initial commercial opportunities often arise in diagnostics.

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### 1. Introduction

The blockbuster strategy (drugs with sales exceeding USD 1 billion) has allowed drug discovery companies to secure adequate resources to offset the cost of expensive research and development (R&D) programs. This paradigm is no longer a viable alternative for the drug discovery companies because of a growing criticism of the blockbuster model in terms of its therapeutic effectiveness. In effect, studies have shown that many drugs may be efficacious in only a slim majority of the prescribed population. Moreover, the blockbuster model does not provide the necessary level of predictability in developing innovative, safe and effective treatments for patients with specific disease subtypes. In addition, lack of optimal treatment consistent with best practice protocols, adverse drug events, and inaccurate or incomplete diagnoses are still widely encountered. Thus, the hope of providing optimal treatment resulting in improved outcomes and reductions in costs continues to be a major industry goal. Unfortunately, many of the initiatives for realizing these goals have proven to be too costly, complex, long or ineffective.

Furthermore, the demand for evidence-based therapeutics by the regulatory authorities are becoming more pressing for the industry in order to adopt a novel and more appropriate paradigm for drug discovery and development. This paradigm change in

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medicine is closely associated with an increased interest in the discovery of biomarkers. A biomarker is, according to the National Institute of Health (NIH), “A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention”. An individual’s genetic profile will increasingly play an important role in clinical decision making as it relates to the selection of appropriate treatment for each patient.

Biomarkers can play a crucial role in understanding patient differences and help the business model of the drug discovery industry to move away from mass-marketed products towards targeted treatments. The knowledge provided by biomarkers should contribute to a better understanding of the biological properties of cells and organisms. Such dynamics will lead to a range of commercial opportunities arising from genetic variability with direct benefits for the drug development such as target identification and validation, development of diagnostics, clinical trial development, outcomes data, product launch and marketing support, and market label and expansion (Fig. 1).

In effect, a biomarker based approach uses information based medicine which combines both clinical and biomedical data (including genomic, transcriptomic, proteomic and imaging), to ultimately help the drug discovery industry address its innovation deficit, cost structure and R&D productivity problems. Biomarkers will ultimately enable the convergence of chemistry, biology and informatics towards the concept of theranostics (*Therapeutics + Diagnostics*).

The dual combination of diagnostics and therapeutics suggests that it offers attractive business opportunities in the near and long-term because of increasing demand for laboratory services. Such business opportunities will play an increasingly important role in the strategies of biomarker focused companies in expanding their capability and expertise within the drug discovery value chain. However, despite the huge potential of biomarker applications, no dominant development model for early-stage biotechnology companies has emerged in exploiting the new possibilities brought by technology to create and capture valuable services. Consequently, actors must experience with a variety of strategic approaches and constantly reposition themselves in order to find the most favourable competitive position in the industry.

This paper attempts to provide a better understanding of the reality of the biomarker landscape and its business implications.

## 2. Introduction to biomarkers

Recent technological advancements along with the information generated by the human genome project offer great promise for making personalized medicine a reality in the near future. The concept of personalized medicine is closely associated with an increased interest in the discovery of biomarkers. The biomarker field is disparate and rapidly evolving. A biomarker was traditionally considered to be any physical trait used to measure or indicate the effects or progress of a disease or condition. However, genomics and proteomics based technologies have further refined the concept to molecular indicators of specific biological properties. Throughout the process of drug discovery and development, biologically validated biomarkers can be used as one of the approaches to gauge a patient’s response to a specific treatment and with respect to both efficacy and toxicity [1].

The research community has utilized large arrays for mRNA and SNP profiling, along with epigenetic DNA methylation, as genome-wide biomarker discovery technologies. Gene expression profiles can be detected in tissues and aid clinicians to diagnose early-stage disease and stratify similar pathologies. Also, they can help distinguish those diseases which respond to current therapy from those that do not. However, it is unlikely that human tissue will be routinely analyzed in large populations for the presence of such predictive gene expression profiles. Therefore, there is a pressing need to develop alternative approaches that allow for routine and reliable identification and validation of biomarkers in readily accessible patient samples, such as blood or urine.

As such, the qualitative and quantitative protein composition of the serum can provide information about the state of organs and the whole organism. The task for a successful proteomics based blood biomarker strategy therefore involves the analysis of the disease perturbed cellular networks, the identification of cellular proteins that indicate the state of the perturbed networks [2].

Again, as with pharmacogenetic testing, the diagnostic challenge for protein based biomarkers is an economical, accurate, and rapid testing solution. Advances in studies of protein–protein interactions, protein expression profiling, annotated proteomics databases, and sophisticated protein function methodologies will no doubt provide an increasing spectrum of biomarker and therapeutic candidates.

1. **A better understanding of the molecular mechanisms of diseases and drug response**
2. **A safer, faster and more efficient drug development process**
3. **A safer utilization of therapeutic drugs**
4. **Increased efficiency**
5. **Better post marketing surveillance**
6. **Methods for differentiating competitors**
7. **New indications for new and existing therapeutic drugs**

**Fig. 1.** Biomarker related benefits. With the help of novel technologies such as biomarkers it will be possible to stratify patient populations into particular subpopulations. This will result in a change of the mass-market paradigm into a tailor market paradigm that will, ultimately, reshape dramatically market segments, change the speed, the cost and the outcome of clinical trials, create opportunities for novel pricing strategy and produce cost-effective drugs.

According to Heath et al. [3], the sequence of individual human genomes will permit us to determine with ever increasing accuracy the probable future health of an individual. Inexpensive measurements of blood proteins will permit us to assess, regularly and comprehensively, how that individual's health is evolving.

**3. Drug discovery industry: Benefits from biomarker utilization**

Drug discovery companies are increasingly using biomarker based strategies and data to improve the drug discovery process (Fig. 2).

*3.1. Disease understanding*

Disease is typically a multistep cascade. If a biomarker is directly involved in the pathophysiology of a disease, it may occur early or late in the cascade. Biomarkers that occur early in the pathophysiologic cascade are known as upstream biomarkers. Upstream biomarkers provide information on physical or biological interactions with the molecular target of the drug. Biomarkers that occur late in the pathophysiologic cascade are known as downstream biomarkers. Qualified downstream biomarkers are capable of predicting clinical benefit.

A biomarker based approach can impact the quality of drug development pipelines by providing more specific information as to the mechanisms of drug pathologies and providing it earlier in the discovery-development process. Second, it can improve the efficiency of the process because biomarker information complements genomic target identification and characterization methods used in discovery and leads to reduce attrition during drug development for unfavourable compounds.

*3.2. Project prioritization through early attrition*

Pharmaceutical profiling has resulted in a strong need for appropriate biomarkers both at the discovery as well as at the clinical end of drug development process for patient population profiling. Biomarkers can help screen and identify drug candidates for variable response in efficacy against the most common variants of a particular target. This approach helps identifying drug candidates that risk being rejected at a later stage in the drug development value chain. In effect, profiling data assists the diagnosis of compound performance at various barriers, assists prioritization and optimization, and highlights factors that affect development attrition. The application of this approach to compounds at different stages of preclinical testing would allow the elimination of unfavourable compounds early in development, and increase the quality level of lead selection. Any reduction in risk during the early phases of the process will have a multiplier effect on added value.

Thus, employing biomarker technologies that improve the early identification of drugs that are likely to suffer failure in clinical trials is an essential strategy for addressing high failure rates in the development stages. The result is a radical change in the lead compound selection process with better use being made of information for revealing pharmacological and genetic toxicity [4-7]. For example, the identification of expression 'signatures' to define cancer phenotypes is a particularly good example of the impact of RNA profiling on detailed disease characterization [8]. Gene expression profiles provide the possibility of identifying biological

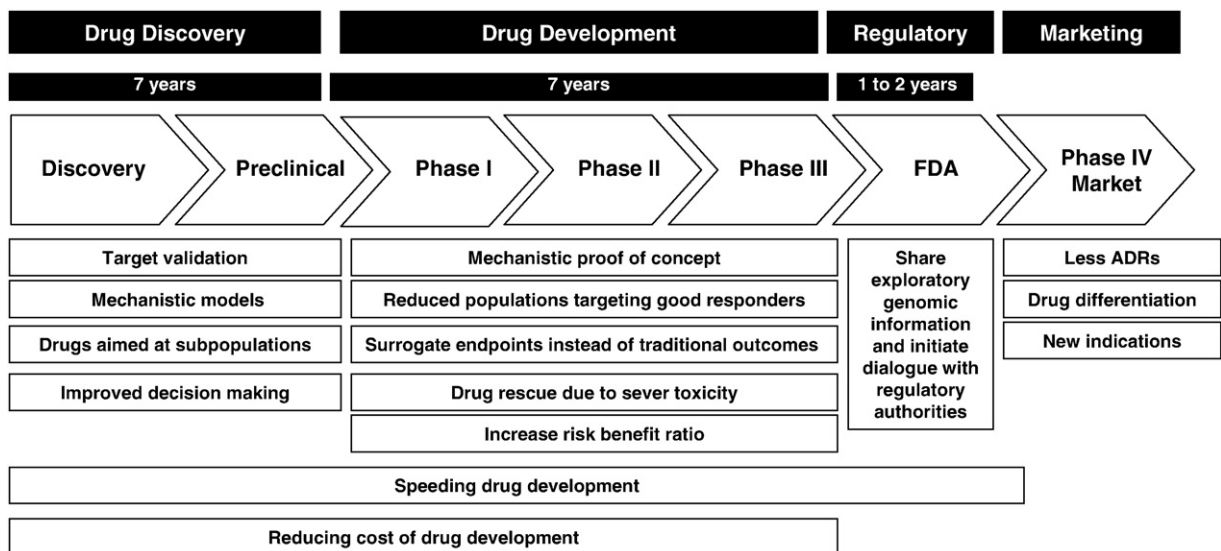


Fig. 2. Drug discovery companies are increasingly using biomarker based strategies and data to improve the drug discovery process. Biomarkers will constitute a critical component of the healthcare delivery system in order to detect, diagnose and monitor diseases and other medical conditions as well as to evaluate treatment options and effectiveness.

mechanisms and pathways initiated further to the exposure of pharmaceutical compounds. This approach is particularly relevant to drug discovery because of its combination of genomics/proteomics and bioinformatics can lead to the identification and characterization of novel targets and the mechanism of action of new drugs.

Furthermore, pharmacodynamic markers are being sought to help demonstrate that a drug candidate is reaching the target in the desired body compartment ('target engagement') and to help determine the optimal dose(s). The identification of such markers is initiated before Phase I clinical trials, and this strategy fits with the guidelines put forth by regulatory agencies aiming at the early evaluation of the pharmacokinetic and pharmacodynamic properties of candidate drugs in man [9].

### 3.3. Streamlining clinical trials

Failure of compounds in late preclinical development, in the clinic and even worse while being marketed, represents a very important economic burden for the pharmaceutical industry. According to a recent study by Czerepak and Ryser [10] of the 103 new drug applications (NDAs) approved by the FDA, 67 (65%) originated from the biotech industry. Furthermore, for each FDA approval, there was, on average, one Phase III failure, and 95% of these failures were products originating from biotech companies [10]. This has had a negative impact on the confidence level and risk assessment of investors in the biotech industry. When considering only novel drugs, the failure rate was even higher, with 1.6 Phase III failures for every approval. Novel drugs and drugs with new chemical structures developed by biotech companies fared worse, on average, with 4.7 failures for every approval. (9 approvals, 42 failures) [10].

By incorporating biomarkers in preclinical and clinical trials, drug discovery companies can create knowledge feedback loops into their development strategy. These steps increase operational efficiency and give a company a competitive advantage. Patient stratification based on biomarker tests can allow scientists to develop a trial design comprised of a genetically differentiated patient pool, using genomic biomarkers to predict response of a group of individuals to a therapeutic. In undifferentiated patient pools, the number of non-responders could jeopardize a trial's endpoint, thereby possibly preventing advancement of a therapeutic to a genetically responsive subpopulation.

For example, in a Phase III clinical trial designed to evaluate Chronic Myelogenous Leukaemia (CML) patient response to Gleevec, biomarker testing was able to identify a 31-gene biomarker within the patient population that predicted clinical response with 94% accuracy [11]. Also, in a Phase II clinical trial designed to evaluate Myeloma patient response to Velcade, biomarker testing identified a 30-gene biomarker that predicted responders with 71% accuracy and non-responders with 84% accuracy [12].

In addition to patient stratification based on biomarker tests, the ability to measure biological signals in patient samples may accurately assess or even better, predict drug-induced toxicity [1]. Thus, the identification and validation of sensitive and specific toxicity biomarkers not only may define mechanisms involved in toxicity, but also improve risk assessment, a fundamental process in drug development.

### 3.4. Reducing cost of drug development

Drug discovery is an increasingly costly and time-consuming process. In 2003 it costs for major drug discovery companies from USD 500 to 800million to develop a new pharmaceutical product and of that 75% represents risk in the form of products that fail [13,14]. However, the main cause of this inefficiency is due to the fact that almost half of drug candidates fail during the development phase.

Bains [15] has reported that these costs are shared fairly evenly between the discovery and preclinical studies (39.7%) and clinical development (43.9%) and the remaining 6.4% being devoted to the registration/approval phase of drug development. More specifically, major pharmaceutical companies spend on average between 40 and 60million dollars annually per compound being investigated for their R&D efforts for each until that potential drug candidate reaches the market. It becomes fairly obvious that through the utilization of biomarkers early in preclinical development can have considerable impact on a company's R&D cost structure.

### 3.5. Speeding drug development

The total development time for a successful drug candidate is around 12.5 years [15]. However, for drug discovery companies the race to shorten the time to market has created a dangerous and a highly uncertain environment. In effect, drug development requires numerous clinical trials that need to be completed for an average drug before approval is granted. As a consequence, the chances for limited studies (both in duration and in group size) to miss particular side effect or potential risk are much higher than studies conducted on large test groups over an extended period of time. The potential of biomarkers to increase the speed of bringing a product to market presents enormous opportunities. Undertaking extensive safety tests in large and heterogeneous populations prior to market approval would significantly increase the time and cost of clinical evaluation and create a significant barrier to drug development. In effect, biomarkers can help address misconceptions about accelerated drug development without compromising in the completeness of development and diminished quality. Through the identification of "good responders" and toxicity risk factors companies can optimize their clinical trials which can ultimately increase the chance of a drug reaching the market.

Other than the costs and uncertainty of drug development, the length of time that it takes for a drug candidate to successfully reach the market is also of major concern to the drug discovery industry. The utilization of both target (upstream) and disease

(downstream) related biomarkers in the early clinical development of Sitagliptin [16] provided an opportunity to proceed directly to Phase IIb dose range-finding studies following completion of the Phase I program, bypassing a traditional Phase IIa study. The average time taken for a new molecule to progress from first dose in humans to Phase III is approximately 3.5 years [17,18]. In the case of the Sitagliptin clinical development the biomarker strategy effectively employed in early development enabled the time between first dose in humans and Phase III to be as little as 2.1 years. The reduced time to filing was supported by strategic biomarker use in alignment with a simple pharmacokinetic/pharmacodynamic modeling and increased drug development efficiency [18].

### 3.6. Improved decision making

Scientific advances in biomarker identification have set the stage for fundamentally improving healthcare delivery. Furthermore, laboratory practices and the clinic have set the stage for the use of biomarkers to create tests to determine which individuals will experience optimal benefit from specific therapies. Optimization of therapy for individuals will in turn result in more desirable clinical outcomes while at the same time possibly leading to reductions in the total cost of care. A number of companies are developing strategies to create new drugs aiming through population profiling in identifying the individuals most likely to benefit from therapy, so called “good responders”. In principle, this might increase the chance of an effective drug being approved.

By reducing the time it takes to bring an effective drug to the market, a company can benefit greatly from an unchallenged market position and extend the period of patent-protected sales. Furthermore, any shortening of this time frame will also help maximise profits by extending a product's life cycle through an increase of the commercialisation period. Thus, by reducing the time that it takes to bring an effective drug to market, a company can benefit greatly from an unchallenged market position and extend the period of patent-protected sales.

With the use of tests, specific therapies may no longer be appropriate for use across an unselected population. Specific therapies may be useful only in populations defined by the presence or absence of a biomarker and therefore, the use of market share drivers to reduce costs may no longer be viable in these cases.

### 3.7. Avoiding adverse drug reactions (ADR)

The premature approval and marketing of dangerous drugs which are ultimately found to pose far greater risks than any benefit they may have had. As highlighted by the Vioxx case, addressing Adverse Drug Reactions (ADR) is a major problem from a public health perspective as well as for the development of new medicines. Lazarou et al. [19] have demonstrated that ADR is between the fourth and sixth cause of death in the United States, accounting for more than 100,000 deaths in 1994. Furthermore, Lasser et al. [20] concluded that one in five new drugs has unrecognized ADRs that do not show up until after the drug has been approved. The study analyzed 548 drugs approved from 1975 through 1999 and discovered that 56 of them were later given a serious side effect warning or even taken off the market completely. The study specifically focused on “black box” warnings, which highlight the most serious side effects that were added to the drug's label after its release. Biomarkers can help identify life-threatening side effects prior to release, thus avoiding major problems and a serious hazard for the general public once the drug is on the market.

Toxic effects are a main reason for compound failure and there is a significant need for their detection as early as possible in development. In effect, Hepatic, cardiac and neurological toxicity have caused 66% of the terminations during clinical testing [21]. The application of toxicity biomarkers in the early-stages of the drug discovery process will help extrapolating the relevance of the preclinical data to human. For example, gene expression changes from short-term studies can serve as more sensitive markers of a toxicity that manifests pathologically in vivo only with longer duration treatment when evaluated against the context of a large reference database [22]. When preclinical studies have accurately predicted human toxicity, 94% were detected in studies 30 days or less. Such studies generally support Phase I clinical trials [21].

### 3.8. Rationalizing dosing regimen

The use of preclinical and early clinical biomarker exposure response information helps to guide the design of future dose-response, pharmacokinetic pharmacodynamic (PK-PD) and clinical efficacy studies. Historically, drugs have been marketed at excessive doses with some patients experiencing adverse events. The recent success of several targeted drugs has changed the rationale for drug discovery and development. Biomarker information obtained in early clinical development about dose-response relationship in the target population for a drug's desirable and undesirable effects lays the foundation for future dose-response studies in drug discovery and development. Drugs such as Gleevec, Iressa, Herceptin, and Velcade some of which have genetic markers for identifying the most suitable patients aim for maximum biological efficacy which differs from traditional treatment that was based on maximum tolerated doses.

Although some therapies might have the effective dose determined by the traditional maximum tolerated (MTD) dose concept in a conventional Phase I to Phase II sequence, there might be therapies for which the intended maximum biological activity of a drug is missed by overdosing to MTD. For example, the epidermal growth factor receptor blocker Iressa, has shown a tendency towards lower treatment efficacy (and more side effects) at higher doses compared with lower doses [23].

In contrast to the parallel increase of therapeutic and toxic effects for traditional, non-specific anticancer drugs, an alternative dose–response relationship could exist. For targeted therapeutics like Iressa, the paradigm of “more is better” does not have inherent validity. As a result of their specific mechanism of action, targeted therapeutics might have therapeutic activity that is far below toxic doses.

Defining maximal biological efficacy, however, requires extensive preclinical evaluations to validate the drug target, establish optimal target inhibition and incorporate validated analytical assays into early phase I trials as demonstrated for Sitagliptin. In effect, preclinical experiment studies demonstrated that 80% inhibition of DPP-4 activity is associated with maximal lowering of glucose levels by Sitagliptin [24]. Moreover early in clinical development, a Phase Ib placebo-controlled study in patients with type 2 diabetes revealed that single oral doses of Sitagliptin dose-dependently inhibited the target engagement biomarker DPP-4 activity and decreased the disease-related biomarker of glucose excursion after a glucose load [25]. Because a single dose of 100 mg provided maximally effective DPP-4 inhibition (>80%) for 24 h, these studies suggested that a once-daily dosing regimen was appropriate, and a dose of 100 mg per day would be optimal. This dose was later confirmed in a dose-ranging Phase II study in patients with type 2 diabetes [26].

### 3.9. Drug repositioning

A key focus on drug repositioning is on rescuing drugs that have failed and identifying or creating alternative development routes for those drugs. Biomarker related efforts can offer repositioning approaches that can be employed for existing drugs to identify a route to market. The identification through biomarkers of a subset of patients for whom the drug is safe and develop a companion diagnostic which could “rescue” or “reposition” the failed drug.

For example, over expression of epidermal growth factor receptor (EGFR) occurs in many types of cancer and has become a target for cancer therapy. The EGFR tyrosine kinase inhibitor (TKI) Iressa targets the tumor protein to treat non-small cell lung cancer (NSCLC). Specific mutations on EGFR gene correlate with clinical response and screening for these mutations has become increasingly integrated into clinical practice to identify those individuals who will most benefit from treatment. In effect, researchers have highlighted that Iressa (Gefitinib) has a profound impact in a small population of patients (10 to 20% of the patients). This small number of patients in the trial was most probably diluted out by the lack of response from the other patients [27].

## 4. Factors influencing development strategies to embrace biomarkers

Biomarkers will constitute a critical component of the healthcare delivery system in order to detect, diagnose and monitor diseases and other medical conditions as well as to evaluate treatment options and effectiveness. Facing such revolution and its formidable scientific and economic potential, the strategies of the various factors involved in the healthcare delivery arena have changed considerably. As a consequence numerous pharmaceutical, laboratory service, diagnostics, biomedical instrumentation and early-stage biotechnology companies have undertaken enormous efforts in the field of biomarkers (mainly genomics and proteomics) hoping to secure a competitive position by increasing the safety and effectiveness of new medical entities as well as reducing the timeframe necessary for their commercialization. However, despite a rapidly growing interest among regulators scientific and commercial hurdles remain (Fig. 3).

### 4.1. Favourable regulatory context

The FDA recognizes biomarkers as a critical element in evidence-based medicine. The 2004 FDA white paper “Innovation or stagnation” has explicitly stated that: today’s revolution in biomedical science has raised new hope for the prevention, treatment and cure of serious illnesses. However, there is a growing concern that many of the new basic discoveries may not quickly yield more effective and more affordable and safe medical products for patients [28]. In response, the FDA is advocating much greater emphasis on translational and critical path research focused on the clinical assessment of novel products. In effect, the sequencing of the human genome has not only considerably simplified the search for genes that predispose people to develop certain diseases

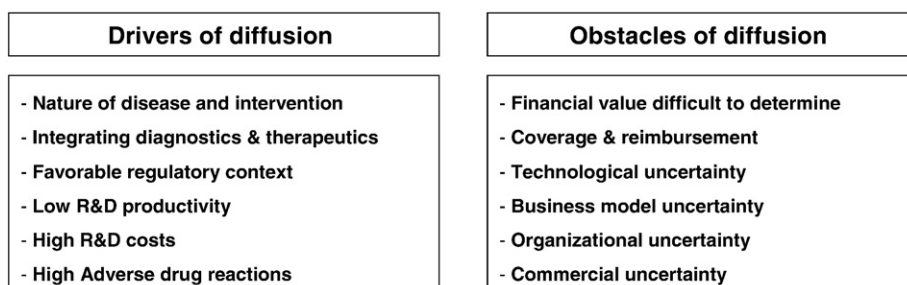


Fig. 3. Drivers and obstacles of diffusion for biomarkers.

but has also provided the drug discovery industry with a wide spectrum of new opportunities for the discovery of innovative drugs and improved treatments [29–31]. As a consequence, biomarker discovery tools being applied today will provide the opportunity to find the underlying genetic factors in complex polygenetic diseases.

Notably, FDA's Pharmacogenomic Data Submissions, introduces a classification for genomic biomarkers; clarifies what type of genomic data needs to be submitted to the FDA and when; introduces a new data submission pathway to share information with the FDA on a voluntary basis and encourages the voluntary submission of exploratory genomic data. The document also introduces a new agency-wide review group and clarifies how the FDA will review genomic data submissions. Also, toxicogenomics and pharmacogenomics have led to several valid genetic tests that provide clinical dosing recommendations by the FDA [32].

Noteworthy, the FDA's critical path initiative has put pressure on companies to find valid biomarkers in their drug discovery and development efforts. This has resulted in the identification of novel putative biomarkers from intense genomic and proteomic research. These biomarkers have been utilized in clinical settings for exploratory, demonstrative or characterization purposes as part of the process of developing mechanism-specific biomarkers toward the ultimate goal of identifying surrogate endpoints.

#### 4.2. Success in clinical laboratory

Technical advancements in the platforms used for discovery of novel biomarkers have been enormous, allowing for the study of expression profile of thousands of genes, gene products and small molecules. The gradual evolution of emphasis from therapeutics to screening assays has created a new dynamics of interaction comprising drug discovery and clinical laboratory companies. In effect, there are significant opportunities for many new assays, including tests that will predict predisposition or monitor disease progress, look at disease severity, and predict response to therapy.

Clinical laboratory testing has been, and will continue to be, dramatically impacted by the introduction of sophisticated new technologies such as biomarkers that enable more precise and timely diagnosis and prognosis. While diagnostic breakthroughs typically precede therapeutic advances, the presence of new therapies can stimulate the demand for testing. Therapeutic advances that create new and improved treatments for diseases such as cancer, infectious diseases will drive demand for testing. In the short-term opportunity for diagnostics companies will be the development of tests that are linked to currently marketed therapies. Currently marketed drugs that could benefit from a test to identify optimal responders are near-term target markets for diagnostics companies.

In the near future biomarker testing can contribute in rendering more efficient comprehensive disease management programs by helping monitoring a patient's disease progression and pinpointing treatment choices through improved clinical assessments.

In the medium/long-term drugs will be developed in concert with simple and reliable tests for molecular markers, which demonstrate continuing efficacy. Given these observations, the impact of newly discovered biomarkers on clinical diagnostics is likely to evolve toward an interdependent dynamic between novel drugs and novel diagnostics.

Furthermore, the vast amounts of data generated through the study of biomarkers, once validated, processed and integrated are capable of reflecting a network of inter-related events within the organism. Ultimately this will allow for a disease state to be viewed as a consequence of something perturbing the network's normal programmed patterns of information [3]. Such patterns of information can in the long run be programmed into computer models. However, this will require measurements of expression profiles of RNA and protein levels in order to comprehensively capture the dynamics of the system's transition from health to disease [3].

##### 4.2.1. Cancer

The cancer market is moving away from general chemotherapy toward targeted therapy or “predictive oncology”. A greater percentage of treatment decisions are now being made based on data that is unique to a particular patient as opposed to using population-based averages. As cancer treatment and therapies have become more sophisticated, specialized diagnostic and prognostic tests have assumed increased importance.

The recent success of several targeted drugs has changed the rationale for drug discovery and development. Drugs such as Gleevec for CML, Iressa for advanced or metastatic non-small cell lung, Herceptin for breast cancer, and Velcade for multiple myeloma which have genetic markers for identifying the most suitable patients aim for maximum biological efficacy which differs from traditional treatment that was based on maximum tolerated doses.

Such novel rationalized drugs for cancer, with their relatively low levels of toxicity contrast dramatically with conventional cytotoxic chemotherapy. These therapeutics for cancer treatments have resulted from the application of rational drug-design strategies to the development of molecularly targeted therapeutics that have been shown to be involved in the key steps of carcinogenesis. Such targeted therapeutics act as specific cancer cell signals to halt growth of cancer cells, unlike conventional cytotoxic chemotherapy that kills all dividing cells leading to a wide range of side effects afflicting cancer patients such as: nausea, hair loss and skin afflictions.

##### 4.2.2. Infectious diseases

The demand for complex infectious disease testing is expected to grow at a rapid pace mainly driven by the development of new tests as well as the availability of new therapies to treat AIDS and hepatitis C [33]. AIDS and hepatitis C are viral infections diseases that can be incurable and lethal. Patients with these diseases can undergo prolonged courses of treatment, which necessitates ongoing laboratory testing. The current treatments for these diseases are inadequate due to limited efficacy, poor compliance, or the emergence of viral resistance.

The demand for resistance testing is being driven by an increase in the number of patients being treated and by treatment limitations. These limitations include: high rates of viral breakthrough (HIV can rapidly mutate and develop resistance to specific therapies), increasing frequency of primary transmission of resistant viral strains, and the complexity of current treatment protocols. Since particular strains of HIV are resistant to particular drugs and since patients may develop new, drug resistant strains of the virus during the course of treatment, patients must be tested to determine whether specific drug combinations will be effective. Today, genotyping is the most common technology employed for resistance testing for HIV. Genotyping is a technology for detecting genetic mutations that may trigger resistance to certain therapies.

#### 4.2.3. Pharmacogenomics

Essential to fulfilling the promise of individualized therapeutic intervention is the identification of drug activity biomarkers that stratify individuals based on likely response to a particular therapeutic, both positive response, efficacy, and negative response, development of side effect or toxicity [34,35]. Proprietary approaches have been utilized to organize multiple single nucleotide polymorphisms (SNPs) into HAP markers (Haplotypes), and correlate this information with clinical outcomes. HAP markers represent the distinct patterns of genomic variability that have accumulated over time in the human population. In many cases, this variation can explain why some people experience a better response to medication than others do. Conversely, it can also help explain why certain people develop side effects when others do not.

Initiatives such as the open source model (HapMap) provide a valuable framework for collective knowledge production and dissemination. Such initiative is enabling companies to access knowledge-based resources critical to drug development. In effect, the International HapMap Project has produced a genome-wide database of human genetic variation for use in genetic association studies of common diseases. The initial output of these studies has been overwhelming with over 150 risk loci identified in studies of more than 60 common diseases and traits [36]. These associations have suggested previously unsuspected etiologic pathways for common diseases that will be of use in identifying new therapeutic targets and developing targeted interventions based on genetically defined risk. The greatest initial utility of publicly available HAP mapping initiatives is in the clues that it can provide for disease etiology, therapeutic targets and gene function [36].

The occurrence of the variations among individuals in the drug response may involve many different causes, such as, genetic variations, expression levels in the drug response, drug metabolizing components, enzymes and drug transporters. The development and widespread application of biomarkers is an involved process and for most disease states it is just at the early-stages of the transition towards individualized therapy and improved clinical outcome.

For example, Warfarin is an anticoagulant medication prescribed worldwide to prevent stroke and venous thromboembolism. Warfarin therapy is complex due to a narrow therapeutic window, notably because of the wide interindividual variability in patient response. It is now clear that genetic polymorphisms in genes influencing metabolism (CYP2C9) and pharmacodynamic response (VKORC1) are strongly associated with Warfarin responsiveness. Therefore, a strong basic science argument is emerging for prospective genotyping of Warfarin patients.

The value of such diagnostic tests is increasingly appreciated and explored by the pharmaceutical industry, bearing in mind that these diagnostic tests are the first step to personalized, tailored treatment options. In effect, Clinical data has developed a test capable of detecting genetic variants in the above mentioned genes that are associated with metabolism of Warfarin and with sensitivity to Warfarin's effect.

A randomized trial using both the CYP2C9 and VKORC1 genotypes to guide therapy in the treatment arm versus the control arm receiving standard therapy has been reported by Stevens et al. [37,38]. For these groups of subjects, the pharmacogenetic algorithm quite accurately predicted the stable dose, whereas large adjustments to the empirical algorithm were required [37,38].

The immediate value of the discovery may lie in improved understanding of a disease process and may open up the identification of drug discovery process targets in the future. The value of the gene itself would then rise from its disease indicator role. In this instance, gene-based products may be developed for a prediction, diagnosis and disease management.

#### 4.3. Technological challenges remain

In order to produce substantial impact on mainstream medicine biomarker research must address prevalent complex disorders, where a number of genes and environmental factors influence disease progression or drug response [39]. New genomic and proteomic technologies provide powerful tools for the selection of patients likely to benefit from a therapeutic without unacceptable adverse events. However, in spite of the large literature on developing predictive biomarkers, there is considerable uncertainty about the validation of biomarker based diagnostics for treatment selection. This is in part due to the difficulty of translating a tissue difference into a test that can be performed on blood samples. Moreover, these same technologies despite their value-added have mainly contributed in increasing the complexity of drug discovery. In effect, the escalating amount of information and data arising from the human genome project has created a situation where handling the existing information and making use of it, while at the same time absorbing the constant flow of new information from a wide range of different disciplines has become an extremely daunting task.

Such various genomic programs were undertaken with the ultimate goal to characterize and determine highly specific tests that allow for the diagnosis of the disease, but to administer the most appropriate treatment regimen, and to monitor a patient's response to therapy. However, roughly eight years after the sequencing of the human genome in June 2000, it has become fairly obvious that efforts undertaken in the field of biomarker discovery represent only one step within the drug discovery process. Hopkins et al., [40] have established the timeframes suggested in many early accounts of pharmacogenomics testing were

unrealistic. In effect, there are many potential molecular markers known in the scientific literature that could be valuable diagnostic tools, and the human genome project has generated thousands more. Thus, discovering a new marker for a disease is now almost a trivial exercise, as the technology of genomics, proteomics and other techniques of high-throughput biology allow the differences between individuals, or between normal and pathological tissue in one individual, to be characterized rapidly and effectively. This, however, has not produced a corresponding number of commercially valuable clinical markers.

#### 4.4. Complexity

Prior to the widespread clinical application of biomarkers multiple scientific studies must be completed to identify the genetic variants and delineate their functional significance in the pathophysiology of a carefully defined phenotype. Thus, integrating data through information technology is necessary in order to provide the requisite tool in decision making to include all these new variables. However, the overall data mining dilemma is characterized by a situation where different formats and applications have so far been utilized creating an environment where the identification, validation and the processing of relevant data by different applications with incompatible formats and platforms is not only effective but extremely time-consuming and expensive. The applicability of the biomarker in the human population must then be verified through both retrospective studies utilizing stored or clinical trial samples, and through clinical trials prospectively stratifying patients based on the biomarker. The risk conferred by the polymorphism and the applicability in the general population must be clearly understood.

Torcetrapib's recent failure in clinical trials highlights that correlation between a certain biomarker and the health outcome does not necessarily mean causation. Torcetrapib acts by inhibiting cholesteryl ester transfer protein, driving higher HDL and lower LDL cholesterol levels. Historical data demonstrates an unambiguous correlation between high HDL/low LDL and a slower progression of atherosclerosis. However, the drug failed to demonstrate any benefit on carotid artery thickness, a measurement that reflects accumulation of atherosclerotic plaque [41].

Moreover, a recent study [42] has focused on the added value of several cardiovascular biomarkers for determining heart disease risk compared with standard risk factors in the general population. Wang [42] reported in a study published in the *Journal of the American Medical Association* on a group of more than 5000 Swedes without cardiovascular disease for about 12 years, looking at standard risk factors – such as smoking, diabetes, and high blood pressure as well as six biomarkers: C-reactive protein, cystatin C, lipoprotein-associated phospholipase 2, midregional proadrenomedullin, midregional proatrial natriuretic peptide, and N-terminal pro-B-type natriuretic peptide. The authors found that several biomarkers could predict cardiovascular and coronary events on their own. But overall, the biomarkers only slightly improved their ability to predict such events when integrated into models including standard risk factors.

The researchers reported that integrating information on one or several biomarkers only slightly improved risk prediction compared to standard risk factors alone. Adding in biomarker information reclassified just 8% of participants with respect to cardiovascular risk and 5% with respect to coronary risk. And many of these individuals moved from the intermediate- to the low-risk group based on biomarker information.

Based on these results, the authors further highlight that there's not much evidence supporting the use of biomarkers for screening the general population. The authors further added that studies focusing on high-risk populations often yield favourable estimates of biomarker performance but the greatest need for new risk markers exists in low-to-intermediate-risk populations, for whom the data are most conflicting. It is highly unlikely that a biomarker will be found that fully predicts the clinical outcome of novel classes of medications [42]. To understand the significance of each biomarker and its hierarchy in disease development requires enormous amounts of biological information.

Solving these problems and making biomarkers truly relevant to drug discovery and patient management requires multi-disciplinary comprising such technologies as genomics/proteomics and nanotechnology as well as disciplines such as, pathology, statistics, and epidemiology. Thus, an efficient management of information, knowledge, and organizational learning appears as the principal source of competitiveness. In order to secure competitive sustainability a biomarker based company needs to source and evaluate information; organize and harmonize information, integrate data and process information in order to generate knowledge [43]. As such, Genomic Health Inc. spent up to \$30 million in order to develop, optimize, clinically test, and validate the assay for the Oncotype Dx test that could predict which women with node-negative, estrogen receptor-positive breast cancer would have recurrence if they were treated only with tamoxifen [44].

#### 4.5. The quest for value remains to be determined

Technologies such as genomics, proteomics and other techniques of high-throughput biology allow the differences between individuals, or between normal and pathological tissue in one individual, to be characterized rapidly and effectively. Linking a diagnostic to a therapeutic decision is often extremely challenging. The time needed to develop, launch and gain market acceptance for a new diagnostic product should not be underestimated.

In effect, biomarker based molecular diagnostics involved in assay development have encountered some difficulty in getting accepted their assays by the medical community. For example, it has taken about three years for Genomic Health Inc.'s breast cancer assay Oncotype Dx, which was offered as a service in 2004, to be included in the American Society of Clinical Oncology's (ASCO) clinical practice guidelines, where it is recommended for use in the selection of breast cancer therapies. As of September 2007, the assay had been approved by Medicare and an increasing number of insurance companies.

In the course of 2008 the company delivered more than 39,600 Oncotype Dx test results, a 62% increase over 2007 (Company Annual Report). This growth reflected rapid adoption of the test and was supported by its inclusion as the only multi-gene expression assay in the clinical practice guidelines of the national Comprehensive Cancer Network and the American Society of Clinical Oncology.

Diagnostics have historically been perceived as being of less value than drugs and thus there is more reluctance to pay high prices for diagnostics. The rising cost of healthcare has forced governments and healthcare providers in implementing cost containment measures. Reimbursement can be considered the ultimate incentive for industry to bring diagnostic products to the market. It is believed that inadequate reimbursement constitutes a key reason for not developing diagnostic products. The concern among insurers is that using expensive tests for large populations will wipe out any potential savings from targeting drugs.

Furthermore, the low margins of the diagnostics business has made it extremely difficult for these companies to generate enthusiasm within the healthcare arena! In effect, a new test competes with very many others for the attention of a small number of major corporations. The law of supply and demand therefore dictates that a new marker, no matter how scientifically fascinating, will have a high value. This is even more so when the diagnostics company can use its diagnostics to support pharmaceutical sales and vice versa. Once launched as a product, single marker-based tests can gain substantial market share, but their establishment in the market-place is not certain unless they are directly linked to a therapeutic approach. A consequence of this is that the market value of a new test can only be established when it is brought to market, not (as in therapeutics development) in stages during its development.

Unfortunately, many of the initiatives undertaken to reduce costs such as disease management and drug formularies, have had only modest impacts on medical cost trends. Rising costs and inappropriate utilization of healthcare services have all led to the need for significant reforms in the current system and new approaches to cost containment. For molecular biomarker testing to outweigh its inherent costs, the testing procedures should be integrated into the total disease assessment value chain in order for it to realize its true financial impact.

Increasingly, FDA is encouraging pharmaceutical companies to utilize biomarkers as surrogate endpoints to predict clinical benefit/harm based on epidemiologic, therapeutic, pathophysiological, or other scientific evidence.

As a result of the new high-throughput, low cost testing has the potential to contribute to decreasing the cost of healthcare and making it widely accessible. Again, as with pharmacogenetic testing, the diagnostic challenge for biomarkers is an economical, accurate, and rapid testing solution. The advent of proteomics will no doubt provide an increasing spectrum of biomarker candidates. The move to multiplexing will allow multiple biomarkers to be analyzed in one sample. When this develops into a fully automated technology, multiple markers will be screened in thousands of patients.

As a consequence the combination of cost and performance will lay the foundation for studying and treating disease and allowing predictive and personalized medicine to become a reality. In the short-term because of the difficulty of establishing clinical utility of the test results, there is a need for governmental regulation and public education before any Direct-to-Consumer (DTC) commercialization. Otherwise, tests being marketed can be seen as uninformative and cost inefficient. Also, they may contribute negatively to the well being of consumers.

In summary, the strategic application of biomarkers to the earliest stages of a drug discovery program offers a valuable opportunity to identify potential safety hurdles early, and ultimately reduce the time required to uncover the optimal drug candidate. Doing so will reduce the inefficiency in the current paradigm, which is still heavily weighted on lengthy *in vivo* studies and will assist in solving the current pharmaceutical pipeline productivity dilemma of long cycle times and high attrition during drug discovery and development.

As new drug candidates advance through the phases of clinical development, newly discovered biomarkers will demonstrate their value as sensitive indicators of both efficacy and safety. However, in late-phase development only the most valuable biomarkers can become surrogate endpoints in clinical trials. The challenge faced by drug developers is to identify “high value” biomarkers for specific disease indications and incorporate them into early phase protocols.

#### 4.6. No dominant development model has yet emerged

The term business model has been used to describe how various types of firms execute their business activities. In general, a business model can be defined as a firm's core competencies and strategic orientations in order to create and capture value within a value chain network [45]. Thus, choosing the right entry mode for an emerging and uncertain market is a critical decision and affects the long-term success of a firm. Such early choices are made on the basis of particular company trajectories and strategic orientation. The relationship between strategic orientations taken by individual firms and the emergence and establishment of new technological paradigms is often complex. Thus, the challenge for a biomarker specialized company is to implement a business model capable of bridging the gap of its intellectual property value and the reality of the business environment (Fig. 4).

The recent progress in our understanding of biomarkers and its contribution to human therapeutics has been accompanied by the formation of many early-stage research intensive companies. We have identified a universe of 31 publicly listed companies with a significant interest in developing the technology (Table 1), and a further 40 private companies with interest in this area. The great majority of the firms being US based. Companies report revenues in three segments: Diagnostic and prognostic services; biopharmaceutical/genomics services and information services.

- **Healthcare companies manufacturing tests and analyzers**
- **Diagnostics/Pharmaceutical companies**
- **Molecular services businesses**
- **Companies developing drug discovery technologies**
- **Companies developing molecular diagnostics and genetics tests**
- **Drug discovery companies**
- **Laboratory Services**
- **Contract Research Organizations**

**Fig. 4.** Competitive environment. In effect, strategic uncertainties are a common situation in emerging industries whose essential characteristic from the viewpoint of formulating strategies is that there are no established rules of the game. A wide of range of companies ranging from drug discovery, genomics to reagent and tool kit companies *via* diagnostics, research and providers of service have entered the field of biomarkers. Early strategic choices made by these companies about the development of biomarker based products and the marketing of such products have had major consequences for the way in which the technology has subsequently been shaped.

Early strategic choices made by these companies about the development of biomarker based products and the marketing of such products have had major consequences for the way in which the technology has subsequently been shaped. For the great majority of the companies such strategic choices comprise one of the following:

1. To provide state-of-the-art technologies and medical expertise for diagnostic and prognostic assessment to enable clinicians to make better treatment decisions.
2. To improve access to patients, physicians, technologies and information throughout the therapeutic and diagnostic development process.
3. To establish relationships that facilitate faster, cost-effective, targeted drug development

Similar to other emerging industries, biomarkers are characterized by a continuously changing and complex environment, which creates important uncertainties at the levels of technology, demand and strategy. In effect, early genomics companies with

**Table 1**

Publicly listed companies with commercial interest in biomarkers (September 5, 2008 and June 29, 2009).

Source: Google Finance & Yahoo Finance.

Company	Activity	Location	Market capitalization	2007 sales	Market capitalization	2008 sales	Other
			(Sep 5, 2008)		(June 29, 2009)		
Avalon	Technology platform	USA	USD 10.7 M	USD 0.81 M	NA	NA	Acquired Oct 08
Bio Imaging Technologies	Medical imaging CRO	USA	USD 111.2 M	USD 47.9 M	USD 53.84 M	USD 69.12 M	
Celera <sup>1</sup>	Products and services	USA	USD 1.14B	USD 43.4 M	USD 617.72 M	USD 138.67 M	
Clinical data <sup>2</sup>	Pharmacogenomics	USA	USD 338 M	USD 3.83 M	USD 269.26 M	USD 5.1 M	
Combimatrix	Technology platform	USA	USD 91 M	USD 6.03 M	USD 53.74 M	USD 6.26 M	
Curidium	Companion diagnostics	UK	UK£ 35.4 M	No revenue	NA	No revenue	Acquired March 09
Diagnocure <sup>3</sup>	Diagnostics and lab services	Canada	CAN\$ 122 M	CAN\$ 2.27 M	CAN\$ 40.7 M	CAN\$ 0.79 M	
Epigenomics	DNA methylation biomarkers	Germany	€ 66.8 M	€ 2.6 M	€ 67.34 M	€ 3.7 M	
Exact Sciences	DNA testing	USA	USD 29.4 M	USD 1.8 M	USD 83.09 M	USD – 0.87 M	
Genelink	SNP testing	USA	USD 29.4 M	USD 0.1 M	USD 15.9 M	USD 6.38 M	
Gene News Ltd	Molecular diagnostics	Canada	CAN\$ 44.7 M	CAN\$ 2.17 M	CANE 15.1 M	CAN\$ 1.42 M	
Genomic Health	Molecular diagnostics	USA	USD 623.6 M	USD 64 M	USD 492.44 M	USD 110.58 M	
Genetic Technologies <sup>1</sup>	Genetic testing and services	Australia	USD 21 M	AUD 14.26 M	USD 16.23 M	AUD 14.74 M	
Helicos Biosciences	Genetic testing	USA	USD 82.8 M	USD 0.58 M	USD 27.28 M	USD 0.81 M	
IVAX Diagnostics	Diagnostics	USA	USD 19.3 M	USD 20 M	USD 16.4 M	USD 20.8 M	
Imaging diagnostics sys <sup>1</sup>	Molecular imaging	USA	USD 9.58 M	USD 0.07 M	USD 3.51 M	USD 0.04 M	
Interleukin Genetics	Genetic tests	USA	USD 35 M	USD 9.7 M	USD 16.01 M	USD 9.9 M	
Monogram Biosciences	Lab services and diagnostics	USA	USD 99.4 M	USD 43.2 M	USD 104.4 M	USD 62.19 M	Acquired June 09
Nanogen	Technology platform	USA	USD 26 M	USD 38.2 M	USD 3.79 M	USD 46.92 M	
Nanosphere	Technology platform	USA	USD 178.7 M	USD 1.2 M	USD 115.81 M	USD 1.4 M	
NeoGenomics	Oncology focused testing	USA	USD 30.8 M	USD 11.4 M	USD 41.66 M	USD 20.02 M	
Orchid cellmark	DNA testing	USA	USD 97.4 M	USD 60 M	USD 50.94 M	USD 57.59 M	
Ore Pharmaceuticals	Drug repositioning	USA	USD 6.6 M	USD 1.6 M	USD 3.22 M	USD 1.95 M	
Oncomethylome	Cancer detection tests	Belgium	€ 91.5 M	€ 2.6 M	€ 84.4 M	€ 3.02 M	
Pacific biometrics <sup>1</sup>	Lab service for clinical research	USA	USD 8.8 M	USD 8.5 M	USD 12.41 M	USD 8.3 M	
PreMD	Predictive testing	Canada	CAN \$ 1 M	CAN \$0.09 M	NA	CAN \$ 0.08 M*	Delisted Apr 09
Radnet	Diagnostics imaging	USD	USD 199 M	USD 425 M	USD 84.7 M	USD 502.12 M	
Rosetta Genomics	MicroRNA diagnostics	Israel	USD 44.3 M	No revenue	USD 39.07 M	1.51 M	
Transgenomic	Genetic testing	USA	USD 32.96 M	USD 23 M	USD 16.72 M	USD 24 M	
Vermillion	Diagnostics	USA	USD 8.23 M	USD 0.04 M	NA	NA	Bankruptcy Apr 09

<sup>1</sup>12 months ending June 30th; <sup>2</sup>12 months ending March 31st; <sup>3</sup>12 months ending October 31st; \*End of September 2008.

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capabilities in pharmacogenomics such as Genset, Genaissance and Variagenics do not provide a satisfactory benchmark in gauging biomarker business models since they were acquired by Serono, Clinical data and Hyseq respectively.

Moreover, few companies with biomarker interest are successful by the criterion of stock price performance (Table 1). In effect, the stock market valuation of a great majority of biomarker based companies demonstrates the enormous difficulty that early-stage companies experience in implementing adequate business models in order to capture the value of their knowledge assets and convey the realism of their business strategy to industrial partners, existing shareholders and potential institutional investors. In effect, value is determined not only by the perception of competitive advantage, but also by the prospect for it to be sustainable.

As early-stage companies take advantage of new commercial opportunities they will face multiple challenges and greater competition from larger companies that are already well established. In effect, in the face of an increasingly competitive market, laboratory services, instrumentation and reagents and pharmaceutical companies are in the process of implementing strategies such as mergers and acquisitions, spin-off, research alliances and in-licensing in order to help improve their biomarker R&D capabilities. Such external deals for major players are attractive growth options because they offer rapid access to both intellectual property and capability (Table 2).

For example, the business plans of suppliers of reagents and instruments are evolving to keep up with their increasingly sophisticated customers. In effect, in June 2007 Qiagen NV, the world's premier supplier of solutions for pre-analytical sample preparation, announced the acquisition of publicly listed molecular diagnostics firm Digene for approximately \$1.6 billion. Digene holds a leading position in HPV (human papillomavirus) targeted molecular diagnostic testing. This transaction allowed Qiagen to gain instantaneous market and technology leadership in molecular diagnostics and strategically position the company for future growth. Similarly, in October 2006, Qiagen NV acquired Genaco Biomedical Products, Inc. (Genaco), an early-stage company applying a proprietary PCR-based multiplexing technology, TEM-PCR, to develop Templex™ molecular diagnostic tests. Multiplex assays are typically applied in situations in which one or more of several pathogens or disease markers could be present in one sample. Depending on the number of markers present in a sample, the Templex™ products provide a qualitative and a semi-quantitative answer. Multiplexing is typically used in cases where patients present symptoms which could be caused by one or more out of a significant number of different pathogens or other causes.

Also, Affymetrix, Inc. a major player in the field of gene chip technology spun-off in October 2000 a new genomics subsidiary called Perlegen Sciences, Inc. in order to utilize Affymetrix's latest DNA scanning technology to identify the millions of genetic variations between individuals and find patterns in those variations. Perlegen's business objective being to secure alliances with major pharmaceutical partners in order to associate the patterns with health factors and drug responses.

Technology oriented mergers will play an increasingly important role in the strategies of clinical research organizations, clinical laboratory companies (e.g. Laboratory Corporation of America or Quest Diagnostics), tools and equipment companies and biotechnology companies in expanding their biomarker capability and expertise within the drug discovery and development value chain.

## 5. The impact of the financial crisis

The biotechnology industry is feeling more and more strongly the effects of the financial crisis. Moreover, from the investor perspective, there is an overwhelming feeling that financial metrics no longer provide enough indication of a company's long-term

**Table 2**

Acquisitions have multiplied over the last years mainly fuelled by such requirements as managing product portfolios, accessing critical capabilities, entering new markets, building critical mass, accelerating R&D, reducing costs and the financial crisis.

Activity	Acquiring company	Target company	Date	
Biomarker dedicated, genetic tests, molecular services and diagnostics providers	Clinical Data	Genaissance	October 05	
		Icoria	December 05	
		Genome Express	March 06	
		Epidaurus Biotech	August 07	
	Celera	Avalon	October 08	
		Berkely hearthlab	October 07	
		Atria Genetics	October 07	
		Sequenom	Michigan CLIA	September 08
		Quest diagnostics	Labone	August 05
			Focus Diagnostics	May 06
Laboratory services	Lab. Corp. of America	Monogram Biosc.	June 09	
		Qiagen	June 07	
	Siemens	Genaco	October 06	
		Bayer Diagnostics	June 06	
		Diagnostics Products	April 06	
		GenOhm Sciences	January 2006	
	Becton Dickson	Fisher Scientific	Athena Diagnostics	March 06
		Affymetrix	Pranomics	November 08
		Avacta Group	Curridium	March 09
	Pharmaceutical company	Roche	Ventana	June 07

potential. Furthermore, investors' lack of knowledge of the nuances of these complicated industries is keeping many of them from investing.

The question that remains to be answered is why with a clear need for new diagnostics is there such an apparent lack of enthusiasm from investors for technology based biomarkers diagnostics companies? Despite the challenges and complexities of investing the biomarker sector the investment community has immense difficulty in understanding on how value can be generated from different business models in a context where value is perceived in therapeutics and less in diagnostics.

Under the impact of the current crisis and extremely competitive markets for strategic alliances biomarker companies find themselves in the obligation to embark on a perilous journey in order to secure a firm's long-term survivability and capitalize on a firm's intangible assets and reach profitability.

Considering the sector's low R&D productivity, increasing complexity, technological uncertainty, long product development time lines and increasing R&D costs it has become extremely challenging for biomarker based companies to implement a business model capable of bridging the gap of the uncertain outcome of its intellectual property and the reality of the current business environment. Furthermore, they live with the constant need to raise cash either through partnerships with large companies or through the capital markets. Moreover, the capital markets short-term focus is not particularly adapted for publicly listed biomarker companies with long product development time frames and highly uncertain outcomes. Even with greater efficiency in biomarker identification and optimization, improvements will also need to be made in clinical development and the overall speed to market.

The overall consequence of the stock market environment characterized by highly volatile share prices has resulted in a major shift in market perception and attitudes towards early-stage biomarker companies (Table 1). In addition, institutional investors are increasingly demanding that companies build up critical mass in order to reach large market capitalizations. As a result, small biotechnology companies have embarked on organizational changes mainly through M&A and geared towards product based drug discovery with measures comprising cuts in staff, eliminating early discovery programs, and refocusing on advancing their most promising products. As such, a focus on commercialization, and a maximum degree of financial independence have become prerequisites for success in the sector.

Moreover, since publicly listed companies evolve in an environment which is constantly being monitored by the investment community for short-term performance are in desperate need for close-to-market products capable of generating revenues in the short-term and not early-stage technologies that will eventually deliver products only in a distant future. Companies with broader-based product portfolios have so far been able to ride out uncertain markets since they are perceived by investors as less risky. It will not be surprising to observe in the near and mid-term a growing trend of companies securing in-licensing opportunities for late-stage products or embarking on M&A activity in order to access innovative products and enjoy the necessary financial resources in order to advance biomarkers without jeopardizing their survival.

## 6. Concluding remarks

Advances in chemistry, information technology, robotics and bioinformatics, for instance mean that the technological bases of many industries are changing rapidly and unpredictably. In a dynamic environment, formulating a successful strategy depends to a significant degree on learning with new directions and on recognizing opportunities that materialize during that process. It is crucial to understand the nature of change in the industry and to exploit this knowledge by identifying areas where resources should be committed. Companies can only be successful if they have the ability to “constantly re-evaluate resource allocation and strategic direction”.

As the genetic roots of disease, disease progression and treatment effectiveness are uncovered, the demand for sophisticated prognostic, diagnostic and monitoring tests will be increasing. Moreover, the role of laboratory testing will be expanding beyond diagnosis into virtually every facet of health care delivery, including detection of genetically based health risk factors, evaluation of treatment options and effectiveness, and monitoring of patient health status. The gradual evolution of emphasis from therapeutics to diagnostics has created new dynamics of interaction comprising major pharmaceutical companies, clinical laboratory companies and biotechnology companies.

While new molecular diagnostic assays are already proving their worth in screening patients for their susceptibility to commonly prescribed drugs such as Warfarin dosing and Rituxan response others are helping select the appropriate patients for clinical trials of experimental therapies. This approach has been especially important to the development of the new AIDS drugs Selzentry and Isentress, both of which aim at new targets.

However, because of the low test quality and validation issues only several biomarkers have been validated and required by the FDA in guiding prescribing (drug/indications: Erbitux/Colon cancer, Selzentry/HIV and Herceptin/Breast cancer). Even if such a linkage between diagnostic and therapeutic can be achieved in principle, the time taken from discovery of the marker to achieving sales of a diagnostic product can be substantial. Moreover, such issues and the scarcity of early successes in biomarkers have made it very difficult to interest major drug discovery companies that the biomarker strategy was feasible.

Those companies within an expertise in biomarkers that can demonstrate their ability to increase drug discovery productivity will be the partners of choice of pharmaceutical and larger clinical laboratory companies. Stock market valuation of biomarker based companies demonstrates the enormous difficulty that such companies experience in implementing adequate business models in order to capture the value of their knowledge assets and convey the realism of their business strategy. The situation is rendered further challenging that their product offering is essentially cost-driven and not value-driven.

However, the main challenge facing biomarker focused companies is that drug discovery, clinical laboratory and tools and equipment companies have the possibility of choosing among a vast array of technologies and approaches in order to gain biomarker capabilities. In each case, a major partner's ability to implement a biomarker strategy wisely will have a large impact on the performance of its R&D organization in terms of time to market, productivity and product quality. Therefore, the need for a new way of looking and assessing the value created at each level, determining what capabilities are available in order to build an organization capable of coordinating across boundaries will become increasingly important. To that end biomarker based companies have to re-tool their R&D operations to help increase the success rate for new products and services.

Biomarkers impact on the health care delivery system will continue to grow as major players involved in drug discovery and clinical testing will fully integrate this technology into the core of their discovery efforts and commercial offerings. Thus, it is imperative that biomarker development is accelerated along with the development of new therapies. The ideal biomarker would be highly predictive of clinical response. A biomarker that could predict clinical response early would be extremely valuable by allowing to avoid efficacy studies that take numerous years and a large number of patients. Without new markers, advances in targeted therapy will be limited and treatment will remain largely empirical.

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