

**STRATEGIC ANALYSIS FOR A NOT-FOR-PROFIT  
BIOMEDICAL ORGANIZATION**

by

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# APPROVAL

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## **ABSTRACT**

A Vancouver-based not-for-profit biomedical organization is facing a challenging mandate: to create wealth and generate social benefits while becoming financially self-sustaining by the end of its current five-year government mandate. This analysis outlines the strategic alternatives available to the organization. The external environment is assessed for five of the organization's major programs. The analysis then summarizes the internal resources and capabilities of the organization, with a focus on their position within the value creation process. Current strategic intent and goals are reviewed, and the organization's strategic alternatives are outlined and evaluated. The external analysis, internal analysis and multi-goal assessment of the alternatives lead to proposal of a strategic plan for the organization. Together, this analysis defines a unique position for the organization, and will help it achieve the desired impact on patient and social health and well-being.

# **DEDICATION**

For Emilee, in loving memory.

## **ACKNOWLEDGEMENTS**

Thank you to the management team at the Prevention of Organ Failure Centre of Excellence, who sponsored this project. I look forward to continuing to learn from each of you. To Dr. Aidan Vining, my senior supervisor, and Dr. Rick Colborne, my second reader, I offer my sincerest gratitude. Your guidance and constructive criticism helped me learn and made this a much better project. Finally, to my family, this is the last one. I promise.

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## LIST OF ABBREVIATIONS

ASR	Analyte specific reagent
BD	Business development
BiT	Biomarkers in transplantation
CABG	Coronary artery bypass grafting
CECR	Centre of Excellence for Commercialization and Research
CKD	Chronic kidney disease
CLIA	Clinical Laboratory Improvement Amendments
COPD	Chronic obstructive pulmonary disease
CT	Computed Tomography
CVD	Cardiovascular disease
DHF	Diastolic heart failure
EMA	European Medicines Agency
ESRD	End-stage renal disease
FDA	Food and Drug Administration
HF	Chronic heart failure
IP	Intellectual property
IPO	Initial public offering
IVD	In vitro diagnostic
IVDMIA	In vitro diagnostic multivariate index assay
LDT	Laboratory developed test
MRI	Magnetic resonance imaging
MRM-MS	Multiple reaction monitoring mass spectrometry
MT	Molecular test
NCE	Networks of Centres of Excellence
NDA	New drug application
PCR	Polymerase chain reaction
PET	Positron emission tomography
PMA	Pre-market approval
PROOF	Prevention of Organ Failure Centre of Excellence
R&D	Research and Development
RUO	Research use only
SHF	Systolic heart failure
UBC	University of British Columbia
US	United States of America

# **1: OVERVIEW: THE PREVENTION OF ORGAN FAILURE CENTRE OF EXCELLENCE IN CONTEXT**

## **1.1 The Need for Biomarkers**

Biomarkers are cellular, biochemical or molecular indicators of a process, event, condition or response that can be measured in tissues, cells or body fluids (Pharma Matters, 2008). Physicians commonly use biomarkers as surrogate indicators for disease presence/progression; for example, blood cholesterol levels are a well-established biomarker of risk for developing coronary heart disease. Most currently utilized clinical biomarkers are single genes or proteins (single analyte) or are a small panel of proteins found circulating in the blood (multi-analyte).

The popular and scientific press heralded the publication of the human genome a decade ago as the advent of a new era of designing personalized therapeutics based on knowledge of an individual's genetics. It was thought that once scientists identified the particular genes, proteins or metabolites that were absent or dysfunctional in specific disease states, they could rationally design ways to correct this state. However, while diseases arising from single-gene deficiencies do exist (e.g. cystic fibrosis), most diseases are complex and involve multiple genetic factors and environmental influences (e.g. diabetes and cardiovascular disease). These diseases are therefore not easily "solved" by knowing an individual's genetic makeup or their risk profile.

Growing recognition of the complexity of disease has led to the use of new technologies to discover the molecular signatures associated with disease. The study of the full set of genes, proteins or metabolites associated with a particular disease is called genomics, proteomics, or metabolomics respectively. Such "discovery" studies are

completed using high performance technology platforms that generate a list of hundreds of analytes that are differentially regulated between normal and disease states. Scientists then validate, refine, and develop these genomic, proteomic, or metabolomic signatures to generate tests for improved diagnostic, predictive, or prognostic patient care.

The Oncotype Dx test, developed by Genomic Health, provides a useful example of the utility of “omics” technology in discovering and developing new disease biomarkers. Oncotype Dx analyzes a panel of genes within a breast tumour tissue sample to determine the likelihood of tumour recurrence (Paik et al., 2004). Of the 25,000 genes present in the human genome, Genomic Health identified 250 candidate genes linked with breast cancer recurrence. Of this panel, Genomic Health identified 16 genes that had expression levels that strongly correlated with breast tumour recurrence. These 16 genes, along with five stably-expressed control genes, were validated and developed into the Oncotype Dx test, which gives a readout of a patient’s risk of tumour reoccurrence. Clinicians use this biomarker information to determine the appropriate regimen and intensity of chemotherapy treatment for a particular breast cancer patient. Similar biomarker-based tests have been or are being developed not only in oncology, but also in other complex disease areas.

## **1.2 The Development Pathway for New Biomarkers**

Development of new, clinically useful biomarker-based tests (molecular tests) begins with a clearly defined clinical problem for which a set of biomarkers could improve patient management. The first phase in biomarker development is a biomarker discovery study. In this phase, clinical staff collects samples (tissue, blood, or urine) from a relatively small group of patients, and research staff performs biomarker

discovery. Scientists analyze and validate candidate biomarkers in a small population and then in a large, multi-centre clinical trial. Biomarker developers must also design clinical assays using platform technologies that are reliable, easy-to-use, rapid, and cost-effective, all within the desired targets for sensitivity and specificity. Commercialization and implementation of a new molecular test requires significant capital, acceptance by regulatory authorities and payers, and ultimately, adoption of the technology by physicians and clinical laboratories. Thus, the process of successfully bringing new biomarkers to the clinic is long, complex, and requires expertise in a broad range of areas.

### **1.3 History of the PROOF Centre of Excellence**

#### **1.3.1 The Networks of Centres of Excellence**

The Networks of Centres of Excellence (NCE) program was initiated by the Government of Canada in 1989 as a joint initiative shared amongst Industry Canada and the three major Canadian Granting Councils: the Natural Sciences and Engineering Research Council of Canada (NSERC), the Social Sciences and Humanities Research Council of Canada (SSHRC), and the Canadian Institutes of Health Research (CIHR). The government intended the NCE to facilitate knowledge exchange and multi-sectoral collaboration amongst Canadian researchers through virtual networks. The program goal was to nurture the scientific talent necessary to ensure global Canadian competitiveness and productivity. By 2004, the NCE had funded 21 networks, involving more than 7000 people at 1300 Canadian organizations and almost 350 international organizations (Networks of Centres of Excellence of Canada, 2004).

### **1.3.2 The Centres of Excellence in Commercialization and Research (CECR) Program**

In 2006, the Canadian government released a long-term economic strategy outlining plans to strengthen Canada's economy (Department of Finance, 2006). This plan acknowledged that despite Canada's strong research base, lagging innovation and productivity threatened Canada's economic competitiveness. To help promote innovation and increase productivity, the Canadian government committed more than \$350 million to create three new NCE-led programs: the CECR Program, the Business-Led NCE Program and an Industrial Research and Development Internship Program.

The goals of the CECR program are to increase private sector R&D investment, support the training of skilled researchers, and connect the resulting ideas and talent to Canadian businesses. To achieve this goal, the CECR Program funded centres focused on translation and commercialization of research. Centres focus on one of the four priority areas identified by the federal government as critical to Canadian competitiveness: environmental science/technology, natural resources and energy, life sciences, and information technology (Ekos Research Associates Inc., 2009). The NCE defined the anticipated benefits arising from the CECRs as increased Canadian economic activity and quality of life. Finally, the NCE mandated that CECR-funded centres become financially self-sustaining by the end of their funding period.

The NCE held the first CECR funding competition in 2008, and attracted 110 eligible letters of intent. Twenty-five applicants invited to submit full applications, and the NCE funded eleven of these. Another six Centres received CECR funding in the 2009 competition (Ekos Research Associates Inc., 2009).



### **1.3.3 The Increasing Socioeconomic Burden of Organ Failure**

Heart, lung, and kidney diseases are amongst are complex, poorly understood, and involve both genetic and environmental influences. Physical inactivity, tobacco use, and changing dietary habits have contributed to increasing obesity, hypertension, diabetes, and dyslipidemia that in turn are driving epidemic organ failure. Indeed, one in four Canadians is at risk for organ failure. This disease burden places significant pressure on already tight health care budgets.

Current approaches to predicting, diagnosing and monitoring organ failure do not allow for early intervention or prevention of irreversible organ damage. Clinicians typically use a “one-size fits all” approach, treating patients with the same regimen of medications and follow-ups. For example, chronic kidney disease (CKD) patients have multiple disease outcomes: stable, non-progressive disease; progressive disease that leads to fatal cardiovascular complications; or rapidly progressive disease requiring kidney replacement via dialysis or transplantation (Levin, Djurdjev, Beaulieu, & Er, 2008). In the absence of a way to identify which type of CKD an individual patient has, clinicians treat and monitor each individual identically. This means that patients with stable disease are likely over-medicated and over-monitored, at great cost both to the individual and to health care budgets. On the other hand, patients with rapidly progressing disease might benefit from more intensive treatment and follow-up than they would otherwise receive.

### **1.3.4 The Need for Biomarkers of Organ Failure**

Intervention in organ failure typically occurs only after significant and often irreversible damage has occurred. This greatly increases the costs associated with

managing disease, and results in poorer outcomes for patients. Moreover, current methods (e.g. tissue biopsy) are often invasive and uncomfortable for patients, and in some cases are themselves associated with adverse consequences (Evans et al., 2005). Thus, there is a clear need for biomarkers to help guide earlier, more effective interventions when disease processes are still modifiable. Prognostic biomarkers could guide tailored disease intervention efforts and prevent unnecessary and potentially harmful treatment. Finally, it is estimated that upwards of 50% of medicines dispensed to patients are ineffective or even harmful (Aspinall & Hamermesh, 2007). Biomarkers of response to treatment could reduce ineffective drug use by identifying patients unlikely to respond or likely to have an adverse reaction to a particular drug.

In addition to the use of biomarkers in patient care, pharmaceutical companies desperately need new biomarkers of organ function and fate for drug development. Despite the large patient populations affected by heart, lung, and kidney failure, relatively few effective treatments exist for these diseases. In this setting, biomarker panels could help identify drug-associated toxicities, which would allow drug companies to shelve ill-fated drug candidates earlier and redirect resources elsewhere. Drug companies could also use biomarkers to identify which patients are most likely to respond to treatment. This would reduce the size of clinical trials required to demonstrate drug safety and efficacy to regulatory authorities, and therefore decrease overall drug development costs. Firms could also use biomarkers as surrogate markers of disease state, providing an indicator by which the efficacy of new drug candidates could be judged. In all of these scenarios, biomarkers would hasten drug development efforts for organ failure.

#### **1.3.4.1 Organ Transplantation in Canada**

Each year in Canada, more than 1350 adults reach end-stage heart, kidney, or lung failure and undergo organ transplantation to replace this lost organ function. Many others die of disease complications or while awaiting a transplant (Canadian Institute for Health Information, 2010). In order to prevent the recipient's immune system from rejecting the transplanted organ, physicians treat transplant patients with a lifelong regimen of immunosuppressive drugs. However, these drugs are themselves toxic to the transplanted tissues, so ideally physicians prescribe the minimal effective dose for each patient. A second challenge associated with the management of transplant recipients is that it is difficult for physicians to know whether the transplanted organ is undergoing rejection. Surrogate clinical measurements of organ function (e.g. circulating creatinine levels for kidney transplant patients) are commonly used, but rarely differentiate between organ rejection and more general organ dysfunction. Thus, the most common means of diagnosing organ rejection is via tissue biopsy, in which a small tissue sample from the transplanted organ is analysed for signs of immune infiltration. However, organ rejection is often evident in biopsy samples only after irreversible organ damage has occurred, and biopsy analysis is subject to the interpretation of the pathologist viewing the sample. Moreover, tissue biopsies are costly (~\$4000 for heart transplant patients), can cause (rare) complications, and are painful and uncomfortable for the patients (Evans, Williams et al. 2005). There is therefore a significant need for more effective, minimally invasive ways of diagnosing organ rejection in transplant patients.

#### **1.3.4.2 The Biomarkers in Transplantation (BiT) Project**

The Biomarkers in Transplantation (BiT) project was designed to address the unmet need for better predictive and diagnostic tests for acute and chronic immune rejection in heart and kidney transplantation. In 2004, Drs. Bruce McManus, Paul Keown, and Rob McMaster assembled a team to collect blood and tissue biopsy samples, along with clinical data and transplant outcomes, from cohorts of heart or kidney transplant recipients. Biological samples were mined using genomic and proteomic tools in order to identify a blood-based biosignature of organ rejection. As one example, the team identified 24 circulating markers that are indicative of early rejection of transplanted kidneys (Gunther et al., 2009). The team intends to combine these markers into a single test that can be administered using a simple blood draw taken from patients.

The first phase of the BiT program, in which more than 700 transplant patients were recruited for biomarker discovery, was funded by Genome Canada, Novartis, IBM, and other partners. The next step was to refine the biomarker panels identified in Phase I of the study, and to test them in a larger, more diverse group of patients. However, in order to complete this second phase of development, the BiT team required significant additional funding.

#### **1.3.5 Launch of the PROOF Centre**

In 2008, Dr. Bruce McManus of the Providence Heart + Lung Institute at St. Paul's Hospital led a successful application for a new CECR called the PROOF Centre. The NCE contributed nearly \$15M of federal funding, and mandated that a minimum of \$10M in cash and/or in-kind funds must be sought from other partners. The PROOF

Centre solicited and successfully attracted these matching funds from multiple industrial, academic, and not-for-profit partners.

The PROOF Centre brought the BiT program into the organization as its lead program. In addition to BiT, PROOF currently has three other disease-focused biomarker programs (in chronic obstructive pulmonary disease, chronic heart failure, and chronic kidney disease) and an assay development program focusing on multiple reaction monitoring assays for measuring protein fragments.

### **1.3.6 PROOF Centre Organizational Structure**

The PROOF Centre is incorporated as a not-for-profit society in British Columbia and is governed by a Board of Directors. The PROOF Centre Core Management Team consists of the Director and Chief Development, Scientific, Information, and Operating Offices. The Director of the Centre, Dr. Bruce McManus, reports to the Board and provides leadership and direction for the organization. The Chief Development Officer (CDO) leads business development and commercialization activities. The Chief Scientific Officer (CSO) oversees technology development and scientific activities. The Chief Informatics Officer (CIO) directs information technology activities and leads the organization's computational team. The Chief Operating Officer (COO) develops, administers and operationalizes procedures and policies for the PROOF Centre, including financial and human resource management and project/program management.

In addition to this core team, PROOF management includes Medical Officers representing heart, lung, and kidney diseases, a Clinical Laboratory Applications Officer, a Statistical Officer, and several Scientific Liaisons. These individuals advise PROOF management on their respective areas of expertise. PROOF has also convened a

Translation Advisory Committee (TAC), which meets twice annually to review biomarker development programs. This group reports to and advises PROOF management and Directors on how to best position PROOF's programs for commercialization and implementation. In all, the organization is comprised of roughly thirty personnel, with many more clinical and academic affiliates.

### **1.3.7 The PROOF Centre Business Model**

The PROOF Centre model begins with identification of a clear clinical area in which a set of biomarkers could enhance patient care. In order to define these areas, PROOF consults partners in academia, healthcare, health policy, industry, and government. PROOF facilitates biomarker discovery and development activities using its own strategic resources (including access to patient populations, and computational, scientific, and clinical expertise), and in collaboration with its partners (which provide technology platforms, industry access, and expertise in intellectual property management, regulatory approval, commercialization, and implementation in health systems). PROOF's goal is to serve as a "one-stop-shop" for biomarker discovery, development, commercialization and implementation. The organization itself does not seek to market new molecular tests. Rather, it is pursuing a range of business development activities aimed at commercializing the intellectual property arising from each of its biomarker development programs. This may include out-licensing, technology co-development, companion diagnostics, biomarker trials, and/or forming spin-off companies.

## 1.4 Summary

As a not-for-profit entity operating with federal funds, PROOF bears a challenging mandate: to create wealth, provide social benefits, and become self-sustaining by the end of its funding period. It has garnered a total of \$10.8 million in cash and in-kind funding from a variety of sources, and continues to supplement its budget through grant funding mechanisms. There is a significant market for new medical tests; indeed, diagnostics drive 60-70% of clinical decision-making in hospitals (Batchelder & Miller, 2006). However, the average new molecular test requires 5 years and \$45 million for development and regulatory approval (Davis et al., 2009). PROOF's short timeline for results presents a significant obstacle to—and may be fundamentally incompatible with—its near-term commercialization mandate. While the NCE may extend the lifetime of (some of) the CECRs, this currently remains unknown.

As a result of these realities, PROOF is considering several strategies for bringing its intellectual property to market and becoming self-sustaining. These include joint development with one or more external industry partners, outlicensing or outright sale of intellectual property to industrial recipients, and/or in-house development through formation of a spin-out company. The organization has not systematically assessed which of these possible avenues for commercialization and implementation would be most advantageous for each of its programs.

PROOF has developed significant expertise in the computational analysis of biomarker discovery data in order to identify and validate the most promising biomarker candidates. The organization believes there is an external market for these services, which it perceives to be highly specialized and not widely available. PROOF is thus

considering offering computational services to other organizations on a contract, fee-for-service basis.

## **1.5 Aim and Scope of the Analysis**

The **aim** of this analysis is to define PROOF's current strategy and to evaluate the sustainability of this strategy given the competitive environment and PROOF's internal resources and capabilities. Chapter 2 analyzes the structure and features defining the industries in which PROOF's competes. Chapter 3 assesses the internal resources and capabilities of the organization, with a focus on the value creation process for new molecular tests. PROOF's current strategy, and the likely outcomes arising from this strategy, are then reviewed. Finally, the organization's strategic alternatives are outlined and analyzed. Together, this analysis defines a unique position for PROOF. It is anticipated that the analysis will help PROOF management better discern the organization's value proposition and the unique network of activities that support this position.

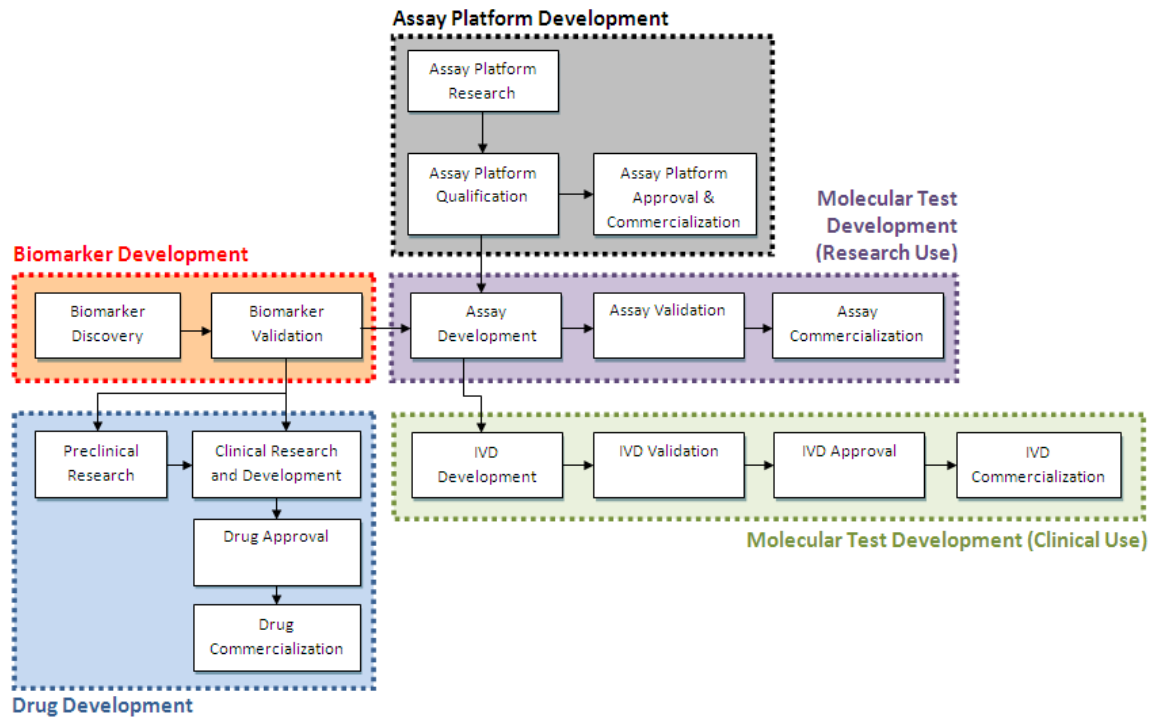


## **2: VALUE CREATION IN THE MOLECULAR TESTS META-INDUSTRY**

### **2.1 PROOF's Core Businesses—Biomarkers and Assay Technologies**

In order to understand PROOF's position within the marketplace, it is useful to assess the industries in which the organization operates. Broadly speaking, PROOF operates within the human health products sector—that is, the sector encompassing all regulated and unregulated products intended to promote, maintain, or restore human health. This is a very broad sector, including medical devices, pharmaceuticals, nutritional and natural health products, diagnostic tests and many other industries, some of which are not relevant to PROOF. PROOF is involved in several related but unique lines of business, so the organization actually operates in several interdependent industries. Figure 2-1 maps out the key activities in and connections between these industries, to which subsequent analysis will be limited.

**Figure 2-1: Key Activities in and Connections Between Relevant Industries within the Human Health Products Sector**



Source: by author

PROOF's core business is in the discovery and validation of panels of biomarkers of heart, lung and kidney health and disease (Figure 2-1; shown in orange). The organization has four major biomarker discovery and development programs, as well as several smaller programs. Because biomarker panels discovered through these programs have several potential uses, PROOF has multiple routes to commercialization. First, PROOF could develop its biomarker panels into molecular tests. Molecular tests quantify the relative levels of biomolecules (DNA, RNA, protein, and/or metabolites) in order to diagnose organ failure, predict organ disease risk, or predict response to therapy. PROOF could design its molecular tests for research (Figure 2-1; shown in purple) or for clinical use (Figure 2-1; green). Physicians would ultimately use these biomarker-based

tests to predict, diagnose, classify and monitor disease, and/or to predict and monitor response to therapy (see Figure 2-2 left panel).

**Figure 2-2: Potential Uses for Biomarkers in Clinical Care and in Drug Development**

<b>Biomarkers for Research/Clinical Use</b>	<b>Biomarkers for Drug Development</b>
<ul style="list-style-type: none"><li>• risk stratification</li><li>• prevention</li><li>• screening</li><li>• diagnosis</li><li>• disease classification</li><li>• prognosis</li><li>• prediction/treatment stratification</li><li>• therapy-related risk management</li><li>• therapy monitoring</li><li>• disease/complication surveillance</li></ul>	<ul style="list-style-type: none"><li>• target validation</li><li>• early screening for compound safety/efficacy</li><li>• pharmacokinetics: drug activity, dosing and scheduling studies</li><li>• patient inclusion/exclusion in clinical trials</li><li>• surrogate disease/drug efficacy endpoints</li></ul>

*Source: Adapted from Institute of Medicine, 2010*

Biomarkers are an essential input not only for the development of new diagnostics for clinical care, but also for drug development (Figure 2-1; shown in blue). Drug developers need biomarkers to develop new assays related to disease state, to repurpose existing drugs for another indication, and/or to identify new targets for drug development (see Figure 2-2; right panel). Pharmaceutical firms use drug development biomarkers as internal decision-making tools rather than in the clinic. The discovery and validation phases of development required for biomarkers for drug development and research are identical to those for clinical biomarkers. However, biomarkers intended for clinical usage require much more extensive and rigorous qualification and regulatory approval.

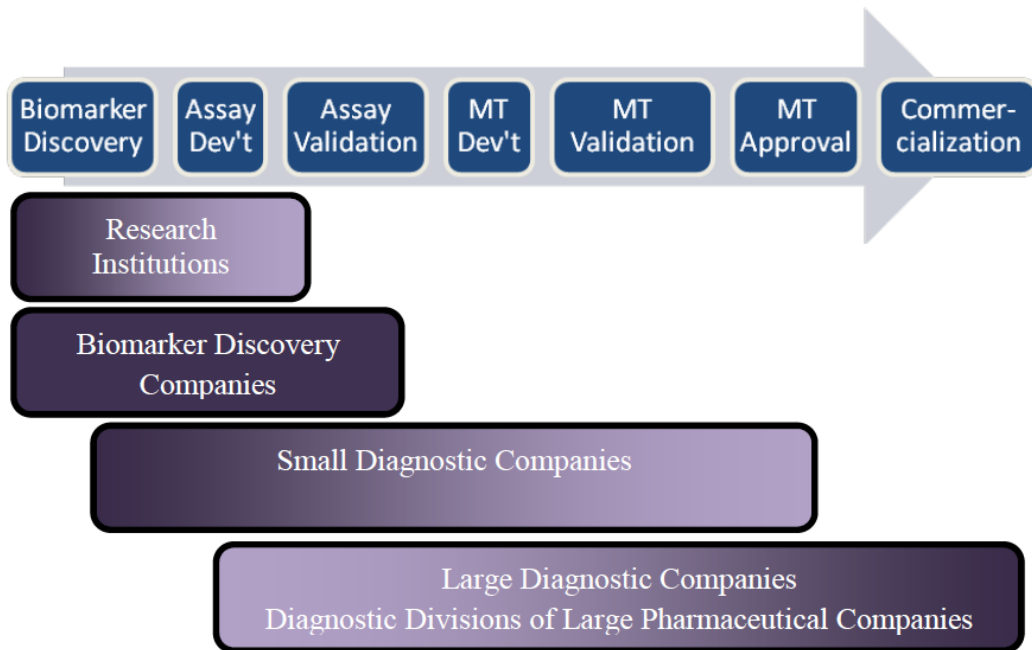
In addition to biomarker-based programs, PROOF has a program focused on developing novel assay technologies (Figure 2-1; shown in grey), which are a second

essential component of new molecular tests. Ultimately, the aim is to develop and validate these technologies as a platform for quantifying biomarkers in research and/or clinical settings.

## 2.2 Structure of the Molecular Tests Marketplace

PROOF anticipates that most of its programs will yield new molecular tests (MT). Thus, it is helpful to review the structure of the molecular tests meta-industry. Public and university research labs, biomarker discovery companies, diagnostic developers, and pharmaceutical companies may all seek to earn rents from at least one stage of the value chain linking biomarker discovery to molecular test commercialization (see Figure 2-3).

**Figure 2-3: Positioning of Organizations along the Value Chain for New Molecular Tests (MTs).** Darker colour indicates area of focus.



Source: by author

Research institutions, biomarker discovery firms, and smaller diagnostics companies are all involved in biomarker discovery. However, these firms and institutions typically lack end-to-end capacity for development and commercialization activities. On the other hand, large diagnostic companies have historical strength in the market for laboratory and research use only tests, but only recently have sought to expand into the market for clinical tests. Pharmaceutical companies have strengths in marketing, distribution, regulatory affairs, and reimbursement, but in general lack diagnostic-related capacity (Rosen, 2009). Thus, there is significant opportunity for acquisitions, collaborations, and strategic alliances in the molecular tests meta-industry. However, many pharmaceutical firms have begun to build capacity for diagnostics development in order to move backwards in and capture more value from new molecular tests (see Figure 2-3). As one example, Roche has indicated that a key priority for the firm is molecular tests (F. Hoffmann-La Roche Ltd, 2010).

Molecular testing platforms are essential complementary assets for molecular tests. However, first generation, multiplex-compatible platforms are large, expensive, and require specialized training to utilize. It is therefore unsurprising that in the U.S., perhaps only 10% of hospital-based clinical labs routinely run molecular tests, and that most molecular tests are run in reference labs or in large clinical centres only (Rosen, 2009). Most market leaders in molecular testing platforms—including Luminex, Roche Diagnostics, and Illumina—are therefore developing second-generation platform technologies that are more user-friendly, smaller, cheaper, and yet still have high-throughput multiplex capabilities.

## **2.3 Overview of External Analysis**

A useful way to summarize the current state and prospects of an industry in terms of long-term profit potential is by assessing the relative strength of five key competitive forces—*intra-firm rivalry, power of suppliers, power of buyers, threat of new entrants, and threat of product substitutes* (Porter, 1979). Industry analysis is imperative for not-for-profit organizations such as PROOF as a way of understanding the external influences impacting the organization.

PROOF is pursuing two lines of business: biomarker discovery and development, and novel assay technologies. As reviewed above (see Figure 2-1), biomarkers and assay technologies provide the building blocks for several related industries, including molecular tests for research, molecular tests for clinical use, assay platforms, and drug development. Each of PROOF's individual programs targets one or more of these industries, and each faces a distinct competitive environment. Thus, in order to understand the overall competitive position of the organization, subsequent sections will analyze five of PROOF's major programs individually in the context of their respective external industry environments.

## **2.4 Biomarkers of Heart and Kidney Transplantation**

### **2.4.1 Overview of PROOF's Biomarkers in Transplantation Program**

The objective of the BiT program is to discover, validate, and develop blood-based proteomic and genomic biomarkers to address the need for better diagnosis and prognosis of transplanted heart and kidney rejection. In Phase I, BiT investigators identified biomarker panels for the diagnosis of acute and chronic rejection. The goal of Phase II (BiT2) is to validate these biomarker panels in a larger group of transplant

patients, and to bring these biomarker panels to market in order to guide biopsy and treatment decisions. Phase II will include: prospective enrolment of and sample collection from transplant patients at multiple international clinical sites; biomarker panel refinement and panel selection via computational strategies; translation of biomarker panels from discovery platforms to clinically relevant platforms; regulatory review and approval; and commercialization and implementation.

PROOF's BiT program is operating in the molecular tests for heart and kidney transplant management industry. Transplantation is a last resort treatment option for patients with end-stage heart or kidney failure. It is relatively infrequent owing to lack of organ availability and the expense associated with organ transplantation and post-transplant management. Ultimately PROOF intends to develop up to four distinct tests each for heart and kidney transplant management (eight tests in total) to address unmet needs in organ transplant management. This includes tests to predict acute or chronic organ rejection, and tests to diagnose acute or chronic organ rejection.

This industry is new and remains in the embryonic stages. Regulatory processes guiding acceptance of new products remain unclear. With a limited market size, there are few industry participants. Most participants are in the research or very early commercialization phases; indeed, only one product has received marketing approval from the US FDA. Therefore, the industry as a whole has a high concentration ratio, and is characterized by negative cash flows and unprofitability resulting from resource-intensive new product development.

#### **2.4.2 Competition is Low in this Market**

While the prevalence of heart and kidney disease is growing rapidly worldwide, relatively few patients undergo organ transplantation for end-stage organ failure. In 2006, surgeons performed roughly 2,100 heart transplants and 17,000 kidney transplants in the United States (U.S. Department of Health and Human Services, 2008). Due to limited organ availability, organ transplantation rates will likely remain static in the future. Indeed transplantation may decrease as public policy and industry increasingly focus on preventing and delaying progression of organ disease. Thus, rivals that are developing new molecular tests will have to compete to gain market share amongst the physicians managing this limited number of patients.

On the other hand, the concentration ratio in this industry is relatively high—few firms are actively engaged in developing new molecular tests for organ transplant management, perhaps because of the small market size. This high concentration ratio tends to decrease inter-firm rivalry because few firms are competing for the same consumer base. Nevertheless, several firms are clear rivals to PROOF's BiT program.

XDx is a privately-held California-based company developing molecular tests for post-transplant patient management and for inflammatory diseases. It is the only competitor in this industry to have received market approval for a diagnostic test. The firm's AlloMap is a PCR-based in vitro diagnostic multivariate index assay (IVDMIA) testing service that measures expression levels of a set of 20 genes in the blood in order to diagnose the *absence* of acute rejection. The test was 510(k)-approved by the FDA in 2008 for use in patients at least 2 months post-transplant, and retails at approximately \$US 2950 (Evans et al., 2005). AlloMap is non-inferior to the cardiac biopsy, the current



standard for heart transplant monitoring, and reduces unnecessary biopsies by identifying patients not undergoing acute organ rejection (Pham et al., 2010). However, one certified central reference laboratory, managed by XDx, currently performs all AlloMap tests. This means that hospitals collect patient blood samples, ship them to the central lab, and must wait several days to receive results. The test diagnoses the absence of acute rejection, but has no utility in identifying patients undergoing acute organ rejection. Moreover, regulators have approved it for use only after the first two months after transplant, after most acute rejection occurs.

Despite these issues, XDx has enjoyed a first-mover advantage. Doctors have adopted AlloMap into clinical use at 65 clinical sites in the US (~30% market uptake) (Ray, 2010). XDx is also developing molecular tests for lung and kidney transplant management. The firm will be able to leverage its AlloMap experience and revenues to move these other programs forward. However, for now its focus is on full commercialization of AlloMap, and in this regard, it represents perhaps the most mature competitor for PROOF's BiT program.

While XDx is the only known competitor in the heart transplant management space, several other firms are developing biomarker panels for management of kidney transplant patients. Rules Based Medicine (RBM), a Texas-based firm, is developing a molecular test for early diagnosis of kidney rejection in kidney transplant patients in partnership with The Scripps Research Institute and Northwestern University. RBM already has a certified central laboratory, and the firm filed a registration of its intent to pursue a \$90M IPO with the US Securities and Exchange Commission in December 2009

(Rules Based Medicine Inc., 2010). Little information is publicly available about the development status for this potential competing test.

TcLand Expression, a privately held firm based in France, represents another competitor for PROOF's BiT program. TcLand is developing KRejX, a genomic panel intended to identify chronic rejection in kidney transplant recipients. KRejX is currently in the clinical validation phase of development, and TcLand plans to commercialize it as a laboratory-designed test in TcLand's central laboratory in 2011 (TcLand Expression, 2009). Thus, there are several firms developing tests that could compete with PROOF's BiT program. In addition, many academic and public research laboratories are investigating biomarkers of kidney graft rejection, though these studies tend to be preclinical in nature (Hartono, Muthukumar, & Suthanthiran, 2010).

Finally, molecular tests have high switching costs. For any new products, regulators must be convinced of product safety, payers must believe there are health economic benefits, and laboratories and physicians adopt the technology. Physicians who manage organ transplant patients are especially risk-averse owing to overwhelming desire to minimize potential harm to patients and precious transplanted organs. This may create a bias towards adherence to currently used protocols, even when doctors generally regard them as insufficient. The high switching costs in this industry tend to decrease rivalry because customers cannot and do not easily switch technologies once they have selected and are "locked into" a platform and a test. This is particularly true when a new diagnostic requires adoption of a new platform technology, which may not be available or utilized within a hospital or central lab.

In summary, the market for molecular tests for managing heart and/or kidney transplant patients is relatively small and slowly growing. The industry serving this market is highly concentrated, with only one test currently marketed and relatively few known competitors. Rivals in this industry face high switching costs for buyers (i.e. physicians) who have already committed to a competing molecular test and associated platform. Overall, this industry is thus characterized by a moderate degree of competition amongst rivals.

#### **2.4.3 Substitutes Exist for New Molecular Tests in this Industry**

Substitutes for new molecular tests in the heart and kidney transplantation arena take several forms, and collectively present a moderate to high threat. The cocktail of immunosuppressants used to prevent rejection of transplanted organs is itself toxic. This reality has driven the need for blood-based tests to predict rejection events such that physicians could decrease drug dosages and prevent organ toxicity if the risk of immune rejection were minimal. Many firms are attempting to develop new, less toxic anti-rejection drugs, which could obviate the need for such diagnostics. For example, the US FDA approved Novartis' everolimus, a newer version of a classical anti-rejection drug, in April 2010. This drug may preserve kidney function and permit lower dosing of adjunctive anti-rejection drugs (Novartis Pharmaceuticals Inc., 2010).

A second class of potential substitutes for new molecular tests for transplant patient management is other technologies for diagnosing/predicting organ rejection. The most widely deployed current method for diagnosing heart and kidney rejection is biopsy, in which a physician removes and examines a small tissue sample for signs of rejection. This has been the gold standard for diagnosing organ rejection for many years, although

it is subject to reader interpretation and often does not diagnose rejection until it has progressed beyond reversal. Despite these disadvantages, disrupting this generally accepted method will be difficult for firms developing new molecular tests. Physicians may also use echocardiography and right heart catheterization to monitor transplanted heart function.

Interestingly, an additional substitute that molecular tests may face is a vastly reduced number of biopsies in combination with increased clinical monitoring for reduced organ function. A recent publication reported that monitoring heart transplant recipients with XDX's AlloMap was no more effective than intensive clinical monitoring (Pham et al., 2010). Thus, new molecular tests for managing organ transplant patients may compete with the notion that simple, inexpensive clinical monitoring of organ function is sufficient for identifying organ rejection.

Perhaps the most threatening substitute for new molecular tests for transplanted organ management is the development of drugs and technologies that eliminate the need for organ transplants. Clinicians, health economists, and patient advocacy groups generally agree that human organ transplantation is hugely resource-intensive and would best be avoided altogether. Since the molecular tests industry essentially produces complementary assets for transplantation itself, any new drug/technology eliminating the need for transplantation would eliminate the need for associated molecular tests. Such substitutes could include new drugs that prevent progression of or reverse heart and kidney disease, and/or regenerative medicine techniques for replacing lost organ function (for example, via artificial organs or transplantation of cells derived from the patient's own stem cells).

In summary, the molecular tests for transplanted organ management industry faces a high threat of substitutes. Potential substitutes are diverse and include the current gold standard, biopsy and pathological assessment, as well as newer, less toxic immunosuppressants, and technologies eliminating the need for human organ transplantation altogether.

## **2.4.4 Buyers Hold Significant Power**

### **2.4.4.1 Payers**

The primary customers in the molecular tests market are the payers—largely public or private insurance companies. Obtaining reimbursement by third-party payers, who will evaluate the cost and the value added by a new molecular test, is an essential step for new molecular tests to be successful. The impetus is on the developer to begin to collect and analyze the data for these evaluations as early as possible in the development process. Molecular tests for organ transplant patient management face a highly concentrated payer environment. The U.S. Medicare and Medicaid systems together are the largest health care payer in the U.S., accounting for roughly 50% of American healthcare expenditures. If a drug, device or instrument achieves coverage by Medicare, it typically is eventually covered by the other private payers (Rosen, 2009), meaning that payers hold a very high degree of buyer power.

Molecular tests also face a more challenging payer environment than do pharmaceuticals. In the U.S., newly approved drugs are typically granted coverage by nearly all payers within a year of launch (Davis et al., 2009). Achieving coverage for new molecular tests typically takes much longer. For example, Oncotype Dx was approved in 2004, and yet is projected to achieve coverage by 100% of payers only in

2010 (Davis et al., 2009). Moreover, the activities of regulatory authorities and payers are minimally coordinated, meaning that granting of regulatory approval has little bearing on whether payers will reimburse a new molecular test.

In summary, health care expenditures are centralized and payers are highly price sensitive and slow to adopt. This is especially true where the technology is new and/or expensive. Payers demand clear demonstration of efficacy and cost-effectiveness in order to justify spending. They therefore exercise significant control over makers of new molecular tests since reimbursement coverage is essential to induce doctors to order tests on behalf of their patients.

#### **2.4.4.2 Laboratories, Physicians, and Patients**

Hospital laboratories and central reference labs also exert power as the facilities that actually run new tests. Laboratory technicians must be comfortable with the technology and have access to the platform necessary to implement it. Their willingness to implement new technology depends on the market demand, which is ultimately driven by physicians.

Physicians are the ultimate gatekeeper between molecular test developers and the patient. In the US, physicians receive disproportionate financial incentive for procedure-based services versus patient evaluation and management (Davis et al., 2009). There is thus an economic disincentive for physicians to order molecular tests that could discourage further treatment. For example, a test that indicates that a heart transplant patient is not likely to experience organ rejection eliminates the need for a diagnostic biopsy, for which a doctor would otherwise be reimbursed. While most physicians are motivated to provide good patient care, this misalignment of incentives is nevertheless a

concern. In addition, aside from a small community of early adopters, most physicians are conservative, and adopt new technologies only when the benefits are widely accepted by their peers. As the parties that make the decision about whether to order new molecular tests, physicians must therefore be convinced of the clinical value of tests.

While patients are the ultimate users of new molecular tests, they are not direct buyers. Nevertheless, the internet has allowed many patients and their families to become stronger advocates for their own care, to the degree that they may exert some degree of influence over prescribing physicians. Patient and public advocacy groups may also exert significant buyer power to push for lower-cost tests and wider access. For example, the Dialysis Patient Citizens group has launched a campaign advocating that US Medicare institute guaranteed lifetime coverage of immunosuppressive drugs for kidney transplant patients (Dialysis Patient Citizens, 2009). Moreover, 7 of the 23 patents held by Myriad Genetics on testing for the hereditary breast and ovarian cancer genes *BRCA1* and *BRCA2* were recently deemed invalid in a case led by the American Civil Liberties Union and the Public Patent Foundation, who argued that Myriad was restricting patient access to essential genetic tests. While Myriad has appealed this ruling, these examples highlight the susceptibility of firms operating in the molecular testing industry to patient pressure (Koppel, Wang, & Bray, 2010).

In summary, firms developing new molecular tests for managing organ transplant patients find themselves subject to a high degree of buyer power, not only because of the concentrated and challenging payer environment but also because physicians are conservative in changing clinical practices. However, buyer power is to some degree mitigated by patient advocacy and by the strong motivation for new solutions.

Physicians, hospital labs, and patients are all motivated to identify alternatives that could improve care of transplant patients, prolong organ function, and/or reduce downstream healthcare costs. Thus for a new molecular test that offers a truly novel and cost-effective solution to monitoring heart and kidney transplant rejection, buyer power may be reduced somewhat as patients and physicians demand access.

#### **2.4.5 Technology Suppliers Hold Significant Power**

The suppliers for new molecular tests are the manufacturers of the technology platform and components of the diagnostic tests. They hold significant power over firms developing molecular tests for organ transplant management. Many platform technology developers are realizing that they can capture more value if they sell the platform and molecular tests that utilize the platform. There is a very real threat of technology platform makers forward integrating. Luminex Corporation, a Texas-based developer of biological testing platforms, provides a useful example of this threat. Luminex's original revenue generation model combined: (1) direct sales of its diagnostic platforms to hospital/reference laboratories; (2) sales of reagents and services associated with its platforms; and (3) licensing and royalty revenues collected from test developers that outlicensed Luminex's xMAP Technology in order to develop and market multiplexed biological tests (Maloney, 2008). However, in recent years Luminex has moved downstream to capture more value. In 2007, Luminex acquired Tm Biosciences, a Toronto-based diagnostics firm developing tests for genetic disorders, drug metabolism, and infectious disease, in order to gain access to content for the Luminex platform (FinancialWire, 2007). Thus, the molecular tests industry faces the threat of technology platform suppliers becoming "one stop shops" for platforms and the tests themselves.



A second facet of the power held by suppliers to the molecular tests industry is the switching costs associated with selecting a technology platform. Firms typically develop diagnostic tests for a single platform, which itself requires regulatory approval for use in the clinic. Once a test developer has selected a platform, there are enormous costs associated with switching platforms. Developers would have to repeat test validation and regulatory approval processes on the new platform. For a firm developing diagnostics, these products are inextricably tied to the platforms provided by suppliers, increasing supplier bargaining power substantially.

The case of EraGen, a developer of multiplex assays for infectious disease, provides a useful illustrative example. EraGen originally selected Luminex as its technology platform partner, and obtained the rights to develop test kits in specific disease indications using the Luminex technology (Butkus, 2010). The firm was in the process of developing these tests when Luminex announced the Tm Biosciences acquisition. Given that Tm Biosciences had a strong focus on infectious disease diagnostics, the deal effectively made Luminex a direct competitor to EraGen. The two firms dissolved the licensing agreement, and EraGen had to seek out an alternative commercialization platform and redevelop its molecular tests. In 2009, EraGen forged a partnership with Illumina, giving EraGen rights to develop its tests using Illumina's BeadXpress platform (Butkus, 2010), but EraGen nevertheless lost significant time because its tests were "locked in" to the Luminex platform.

#### **2.4.6 Threat of New Entrants in the Biomarkers of Transplantation Sector**

There are significant disincentives for would-be entrants to this sector. The industry is characterized by a high degree of patenting, a tactic firms utilize to help

defend products and platforms from copycats. For example, XDX Inc. has been granted USPTO Patent #7691569, which encompasses “methods and compositions for diagnosing and monitoring transplant rejection” (Wohlgemuth, 2010). There may not be sufficient legal room for new entrants to develop products or technologies similar to existing patented ones. Even where there is, patent filing and defence are expensive and highly specialized activities, creating a barrier to entry.

Although molecular tests such as XDX’s AlloMap may be able to command a high price (\$3000 or more) and may have margins exceeding 70%, the capital-intensive nature of the industry also creates financial barriers for would-be entrants (Davis et al., 2009). This is especially true for molecular tests for organ transplant management, given the relatively small market size. McKinsey & Company recently modelled a prototypical firm developing a new molecular test. The average cost and time required for a new molecular test to achieve regulatory approval were \$45 million and 5 years respectively (Davis et al., 2009). Including the time to receiving payer coverage and widespread physician uptake increased these estimates to 6 and 8 years respectively. The analysis found that the average 10-year net present value associated with a new molecular test is roughly \$15M, but suggested that this estimate is highly sensitive to the time to achieve regulatory approval and payer coverage. The diagnostics industry has historically been unattractive for investors, since the potential returns for an investor are much higher in drug development (Batchelder & Miller, 2006). Although this is slowly changing, the capital required to fund discovery, validation, diagnostic test development, regulatory approval, and commercialization activities presents a significant barrier to new entrants to the industry.

The requirement for regulatory approval (discussed more fully in section 2.4.7) also presents barriers to entry. It requires significant capital and expertise to pursue regulatory approval. Moreover, incumbent firms benefit from economies of learning arising from having already navigated the regulatory pathway.

The need to access critical inputs for biomarker discovery and molecular test development also presents a barrier to entry for new firms in this industry. Access to patients, clinical data, and properly collected and banked biological samples requires deep relationships with clinicians. While patient/sample access is also an issue for incumbents, the hurdles facing the new entrant who must acquire these “from scratch” are considerable. Patient recruitment and clinical sample collection can add months or years, as well as considerable cost, to development timelines. Moreover, the pool of heart and kidney transplant centres from which to draw patients is relatively small.

Finally, incumbent firms that have previously brought a new molecular test through the development process may have economies of learning compared to new entrants, having been through the end-to-end process of test development and commercialization at least once. It may be difficult for new entrants, all else being equal, to compete against entrenched expertise. Thus overall, the threat of new entrants in the molecular tests industry is low.

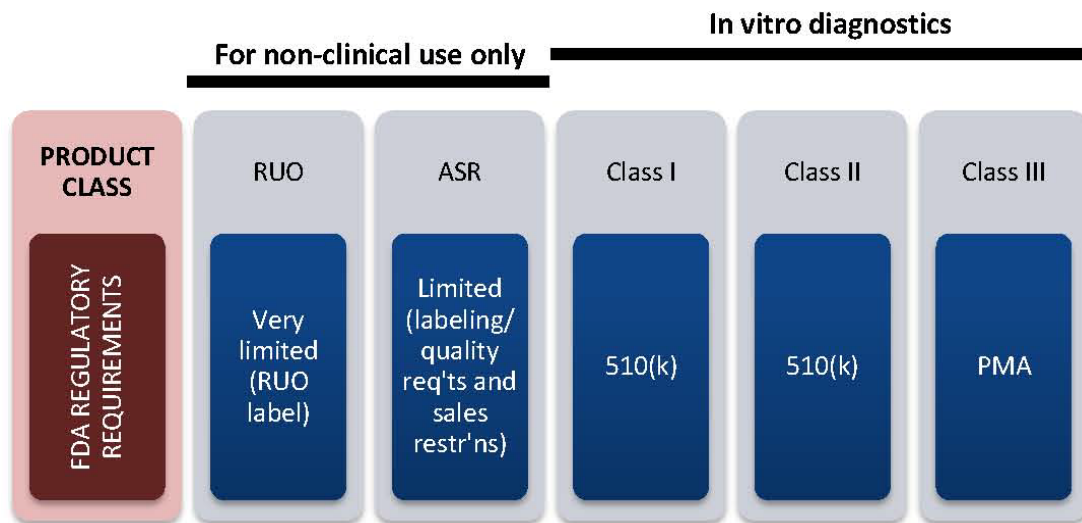
#### **2.4.7 Governments Hold a High Degree of Influence over Industry Participants**

Governments exert a high degree of influence over the molecular tests industry in the form of regulatory oversight. The Food and Drug Administration (FDA) regulates new drugs and diagnostics in the United States. New drug candidates must pass through

a defined, sequential series of regulatory phases prior to receiving marketing approval: an Investigational New Drug application; Phase I clinical trials, in which a drug's safety is tested; Phase II clinical trials, in which efficacy data is gathered; Phase III clinical trials, in which the drug is tested head-to-head with the current standard of care; and Phase IV post-market surveillance.

In comparison, the regulatory process is much less defined for new clinical tests. The FDA's Center for Devices and Radiologic Health (CDRH) regulates new molecular tests. In the general sense, firms must show that their tests detect what they claim to detect within specifications for accuracy, precision, sensitivity (ability to accurately

**Figure 2-4: Regulatory Pathways for Diagnostics in the United States**



Source: by author

identify true positives), and specificity (ability to accurately identify true negatives). However, the burden of proof required by FDA for regulatory approval depends on the intended purpose of the diagnostic (see Figure 2-4). The designation assigned to a new diagnostic will determine how a firm can market it. Firms can define and pursue approval for new diagnostics as in vitro diagnostics (IVDs), which are intended for

clinical use. The FDA subclassifies IVDs themselves on the basis of perceived risk (Class I, which is lowest risk, to Class III, which is highest risk); for Class I and Class II diagnostics, the FDA will accept a 510k application, while Class III diagnostics typically require pre-market approval (PMA). The PMA is a much more rigorous approval pathway requiring more time, money, and validatory clinical trials (Gibbs, 2008).

Alternatively, firms can build or utilize an existing laboratory that is compliant with the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and avoid regulatory oversight altogether to market their diagnostics as ‘homebrew’ kits. Firms can also develop diagnostics for research use only (RUO) or can sell components of a diagnostic kit individually as analyte-specific reagents (ASRs) that buyers can use to develop their own diagnostic kits. Both of these pathways preclude physicians from using the kits/reagents clinically, but have minimal premarket requirements imposed by the FDA. Thus compared to drug development, diagnostics face much more flexibility in selecting a regulatory strategy for new diagnostic development.

It appears, however, that the window of opportunity for bypassing the most rigorous regulatory processes by introducing new molecular tests as a lab service is closing. The FDA has begun to crack down on ASRs and laboratory-developed tests that are used for clinical diagnosis. It has also indicated that while the 510(k) route will likely be acceptable for prognostic tests, PMA approval is likely to be required for tests that directly guide therapeutic decision-making. It is widely believed that the FDA will soon require all IVDMIA—molecular tests in which the output provided to the ordering physician is a score or index that guides diagnosis/prognosis/treatment, created by an algorithm to which the physician is blinded—to be approved via the PMA route.

The PMA process in the US can take up to three years and cost millions of dollars (Gibbs, 2008). The European Medicines Evaluation Agency (EMA) equivalent of the PMA or 510(k) is the CE mark, which firms generally regard as more rule-bound, but more transparent than the FDA processes. While achieving CE certification is also costly and time-consuming, there is a perception that it may be easier to gain FDA approval if a product already holds CE certification. Many firms pursue CE certification first, allowing them to generate revenues, establish a commercial presence, and gain additional product data while pursuing FDA approval.

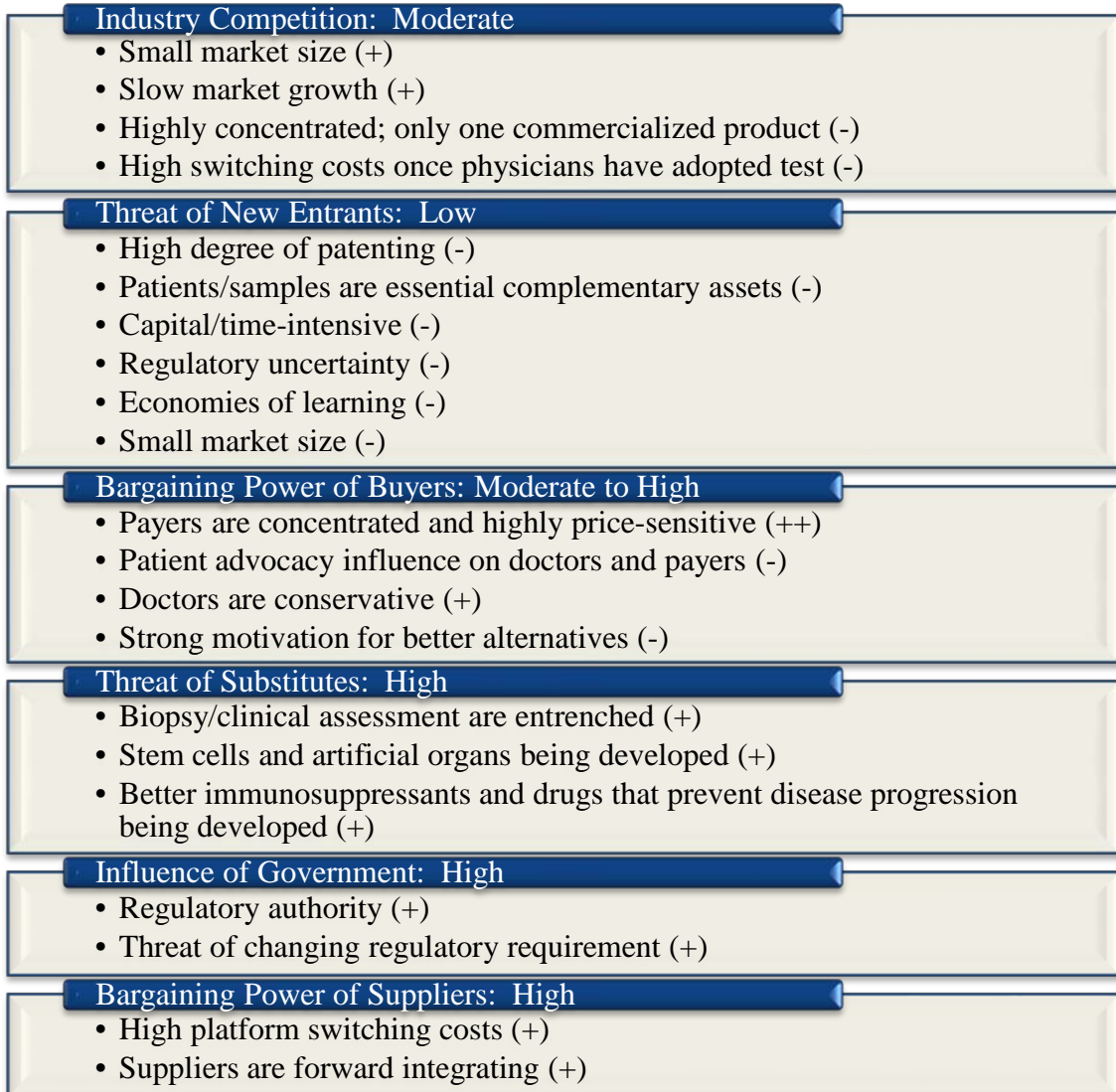
The time, cost, and burden of proving safety and efficacy to regulatory agencies is thus one of the biggest hurdles that developers of new molecular tests face in getting their products to market. Regulatory requirements for diagnostics are complex and widely expected to become more stringent in the United States under the FDA, which tends to influence requirements demanded by other regulatory authorities. A higher regulatory burden (and even the threat of stricter regulations) will have a significant impact on the attractiveness of the industry, since it will increase development times and costs, and thereby decrease profit potential for firms.

#### **2.4.8 Summary of External Analysis for Biomarkers of Transplantation**

The external influences impacting the molecular tests for organ transplantation management industry are summarized in Figure 2-5. Broadly speaking, the molecular tests industry for organ disease appears unattractive to the outside investor. Although the industry is relatively new, development efforts are costly and time-consuming relative to other investment alternatives. Buyers—payers, physicians, and patients—bear

considerable power, as do suppliers of platform technologies underlying new diagnostics. Moreover, significant barriers exist in the form of governmental regulatory authorities,

**Figure 2-5: Summary of Competitive Forces Impacting the Molecular Tests for Organ Transplant Patient Management Industry**



*Source: by author*

distribution channels, and clinical uptake. There is also a strong desire for alternatives to organ transplantation amongst all stakeholder groups, and such alternatives would obviate the need for transplant-associated tests, including those PROOF is developing. Nevertheless, transplant alternatives are still a significant way from clinical

implementation, and there is a strong desire to improve patient care and outcomes in the current organ transplant setting. Thus for the organization that believes its molecular tests to be more efficacious than alternatives, protected from infringement by competitors, and cost-effective from a health economics standpoint, this may be an attractive industry indeed.

## **2.5 Biomarkers of Chronic Kidney Disease**

### **2.5.1 Overview of PROOF's Biomarkers in Chronic Kidney Disease Program**

Chronic kidney disease (CKD) is characterized by progressive loss of kidney function, often arising as a complication of another disease. Diabetes is the most common cause of CKD, accounting for nearly half of new diagnoses (Evans et al., 2005). Physicians typically diagnose CKD using a blood test for creatinine, since gradual elevations in blood creatinine levels are indicative of decreased ability of the kidney to filter out waste products. However, patients with CKD can have drastically different disease outcomes: some patients have stable disease that never worsens; others will progress to end stage disease requiring dialysis or transplantation; some will develop secondary cardiovascular disease (CVD); and a fourth group will have very rapidly progressive disease leading to death (Rodriguez et al., 2010). While some clinical parameters (e.g. age, gender, ethnicity, and diabetes status) may predict disease outcome, clinicians currently have a limited ability to identify the likely disease trajectory of newly diagnosed CKD and implement a trajectory-appropriate disease management strategy.

PROOF's biomarkers in CKD program is operating in the kidney disease molecular tests industry. The goal of the program is to identify and validate genomic and proteomic biomarkers of CKD severity using blood samples collected from a cohort of



CKD patients having known disease outcomes. PROOF intends to develop biomarkers that will identify: (1) patients having rapidly progressing CKD, in order that they may be treated aggressively; (2) patients who are unlikely to progress to organ failure, in order to minimize unnecessary treatment; and (3) patients likely to progress to CVD, in order to increase the CVD monitoring and prevention component of their treatment plans.

The molecular tests for CKD industry is in its infancy. Regulatory processes guiding acceptance of new products remain unclear, and even with a large and growing market size, there are no known molecular tests currently approved for clinical use. Multiple firms, as well as many academic, clinical, and publicly-funded laboratories, are working to discover and develop biomarkers of CKD progression; however, most of these efforts are at the early stages. Thus, the industry as a whole has a moderate concentration ratio, and is characterized by negative cash flows and unprofitability arising from resource-intensive new product development.

### **2.5.2 Competition in Biomarkers of Chronic Kidney Disease**

The market for prognostic biomarker tests for CKD is large and rapidly increasing. Roughly 20 million patients have CKD in the United States, while in Canada CKD affects 1.9 to 2.3 million individuals (Levin et al., 2008). In most countries CKD prevalence is predicted to increase in coming years (Kronenberg, 2009), driven largely by increasing incidence of diabetes. Since there is room in a large and growing market for different firms to establish a market niche for their products, these factors tend to decrease competition.

Despite the large market size, this industry is moderately concentrated. There are no known biomarker-based molecular tests for CKD currently on the market, but many firms have established a presence in the CKD market with related products, and/or are developing prognostic tests for CKD. In addition, many academic and clinical laboratories and institutes have identified biomarkers of CKD progression (Kronenberg, 2009). This moderate degree of concentration means that many firms are competing to be the first to market. Moreover, many of these biomarker development programs are in the investigational stage, with evidence that is insufficient for translation into broad clinical use in the prediction of CKD progression.

Nevertheless, several firms deserve particular notice as potential competitors to PROOF's biomarkers of CKD program. Rules-Based Medicine launched a multiplexed predictive *biomarker test* for human kidney toxicity (Human Kidney MAP) in 2009 (Rules Based Medicine Inc., 2010). The panel is comprised of 16 biomarkers of *acute* kidney injury (i.e. not CKD) and is intended to reveal early signs of drug-induced kidney damage in order to wean out toxic drugs earlier in the development process and to guide drug dosing. Nevertheless, at least a portion of this panel could be transferrable to a panel of prognostic biomarkers for CKD if validated in this population.

SomaLogic, a Boulder, CO-based biotechnology firm, represents a second potential competitor for PROOF's CKD biomarker program. SomaLogic is using aptamer technology to identify novel biomarkers, and recently disclosed the discovery of 58 potential new biomarkers of CKD progression (Gold, L. Ayers, D. Bertino, J. et al., 2010). The firm is also developing a lung cancer diagnostic in partnership with Quest Diagnostics, one of the largest global laboratory test providers, which is to reach the

market in 2012 and could provide revenues for further development of the CKD panel (Petrone, 2010). Indeed, Quest holds an equity stake in SomaLogic, which could provide the latter with a direct path to market for the new molecular tests it is developing.

A final deterrent to rivalry in the molecular tests for CKD industry is the high switching costs associated with new tests. As has been noted, regulators must be convinced of product safety, payers must be assured of a health economic benefit, and laboratories and risk-averse physicians must learn to utilize the technology and adopt the product into standard clinical practice. These switching costs tend to decrease rivalry because customers cannot easily switch technologies once they have selected a platform and a test.

In summary, the market for molecular tests for predicting CKD outcomes is large and rapidly growing, particularly as diabetes incidence increases worldwide. The industry serving this market is fragmented, with no molecular tests currently marketed for CKD prognosis. Although several notable rivals are developing biomarker panels that may compete with PROOF's program, any players in this industry will face high buyer switching costs once physicians and laboratories have adopted a competing molecular test. Thus overall, this industry is characterized by a low degree of competition amongst rivals.

### **2.5.3 There is a Moderate Threat of Substitution**

There are multiple potential substitutes for molecular tests for the prognosis of CKD, and together they present a moderate threat. Perhaps the most significant threat is presented by better treatment of the conditions that commonly lead to CKD—particularly

diabetes. Worldwide prevalence of diabetes, especially Type 2 diabetes, is predicted to more than double between 2000 and 2030 (Srivastava et al., 2008), and prevalence of CKD secondary to diabetes will also increase. However, intensive diabetes management (i.e. maintaining blood glucose levels within a tight range through pharmaceutical, diet, and/or exercise interventions) has been estimated to reduce diabetes-associated CKD development by up to 50% (The Diabetes Control and Complications Trial Research Group, 1993). Therefore, a shift towards prevention and better treatment of diabetes could effectively shrink the population of CKD patients and reduce the need for diagnostics predicting CKD outcomes.

New drugs in the diabetes market have the potential to yield multi-billion dollar annual revenues (Srivastava et al., 2008). Given this immense market potential, virtually all major pharmaceutical companies are investing heavily in research and development of new diabetes drugs. For example, multiple firms are developing or marketing new diabetes therapies based on raising and/or stabilizing circulating levels of the hormone glucagon-like peptide-1, which improves glucose control and possibly long-term pancreas function in diabetes patients (Evans et al., 2005). These efforts could delay or prevent CKD development in this population. The same is true for the many cell replacement, stem cell, next generation insulin delivery, and artificial organ strategies under investigation. While many of these potential substitutes are still in the developmental stage, the strong motivation for new and better diabetes treatments—and ideally cures—is ultimately likely to reduce the burden of CKD in this population.

The cornerstone of current CKD management is treatment of the original disease where possible, and treatment with blood pressure regulating drugs and ACE inhibitors.

In some patients, these drugs themselves are themselves associated with progressive loss of kidney function. Thus, a major driver of demand for prognostic biomarkers for CKD is the toxicity of currently used treatments. Ideally, physicians would like to be able to identify patients with stable disease who do not need aggressive and potentially toxic treatment. The advent of newer drugs that treat CKD with less toxicity could obviate the need for prognostic biomarkers by reducing the fear of treatment-related toxicity. Newer, more effective drugs for CKD could also reduce the need for biomarker-based tests identifying disease prognosis. For example, Reata Pharmaceuticals is developing bardoxolone methyl, a first-in-class inflammatory modulator, which improved kidney function in diabetics with advanced CKD in Phase II trials. This study will be complete in mid-2010, and a second trial in CKD patients with diabetes will begin in late 2010. The firm recently raised an additional \$78M in funding that will see it through to NDA filing for bardoxolone (Carroll, 2010). Several other novel compounds, including olmesartan medoxomil, sulodexide, and avosentan, are also under development by other firms for CKD treatment. In addition, greater public knowledge about risk factors and prevention strategies for CKD (for example, dietary modification and smoking cessation) could reduce CKD incidence and therefore the need for prognostic tests.

While organ transplantation is a commonly used and relatively successful treatment for end stage CKD patients, there is a very limited supply of organs available for transplant, and this treatment is very costly. Kidney transplantation cannot realistically be widely implemented amongst CKD patients as a means of restoring kidney function. It is therefore not a viable substitute for molecular tests predicting CKD outcomes. However, several technologies may be useful in predicting CKD progression

and could serve as substitutes for new molecular diagnostics for CKD. Renal biopsy may have some utility, but as has been discussed, is expensive, uncomfortable for the patient, and subject to physician interpretation. Abdominal ultrasound and advanced nuclear medicine technologies including positron emission tomography (PET) and combined PET/CT imaging may be useful in determining CKD prognosis, although this requires further study. Thus, to summarize, new molecular tests for CKD prognosis face a moderate threat of substitution, with the most significant threat arising from CKD prevention efforts and improved treatments and possibly cures for diabetes.

#### **2.5.4 Buyers Hold a High Degree of Power**

Customers in the molecular tests for CKD industry hold similar power as has been described for new molecular tests for management of organ transplant patients. Payers are a key customer, and they are concentrated and highly price-sensitive, requiring detailed economic justification demonstrating the value of a new molecular test. Without reimbursement, it is very difficult for manufacturers of new molecular tests to induce adoption of the tests. Physicians, as the gatekeepers that ultimately decide whether to order a prognostic molecular test for a newly diagnosed CKD patient, are crucial customers as well. They do not hold direct influence over new product pricing. However, physicians are typically conservative, and must be convinced of the value that molecular tests for CKD will provide by allowing them to more accurately predict disease outcomes, and thus design more appropriate treatment plans, for their CKD patients. Without this conviction, physicians will choose not to utilize new tests. Physician demand for new molecular tests for CKD prognosis in turn drives uptake by the hospital and central laboratories that actually perform the tests. Where molecular

testing platforms are expensive and/or use new technology, industry participants face even more challenges in inducing uptake by physicians and laboratories. Finally, patient groups that advocate for better patient care and outcomes hold some influence over doctors and payers, and may indirectly reduce the power held by these customers.

Although payers, physicians, and laboratories all hold strong buying power in the market for new CKD prognostics, the strong motivation for better treatments and outcomes for CKD patients mitigates this power to some degree. Physicians are generally motivated to treat their patients as effectively as possible. Moreover, the cost of treating end-stage renal disease (ESRD) is overwhelming; indeed, ESRD programs are estimated to account for 6.7% of total Medicare spending in the US, and Medicare costs associated with ESRD increased by an alarming 57% between 1999 and 2004 (Foley & Collins, 2007). Thus, there is strong economic incentive for payers to seek out and approve reimbursement for new molecular tests that accurately predict CKD outcomes. Such tests would allow aggressive treatment of patients with rapidly progressing disease, delaying their progression to ESRD, and would reduce costly and unnecessary treatment of patients with stable CKD. The ethical and economic necessity for better prognostics for CKD therefore moderate the power held by payers and physicians in this industry.

### **2.5.5 Technology Suppliers Hold Significant Power**

As has been discussed for molecular tests for organ transplant patient management, the major suppliers for the new molecular tests for CKD industry are technology platform manufacturers. Technology platform developers include major pharmaceutical companies such as Roche, as well as specialized technology developers such as Luminex and Illumina. Platform developers in general are forward integrating,

hoping to capture more value by marketing not only their technology platforms, but also the molecular tests utilizing their platforms. In addition, developers of new molecular tests for CKD prognosis face very high platform switching costs—once firms have selected a technology platform supplier and have begun the development and regulatory processes necessary to bring their new tests to market, it is costly and time-consuming to switch platforms. Thus technology platform suppliers hold significant power over firms developing molecular tests for CKD management, permitting them to extract higher rents and more favourable deal structures than might otherwise be possible.

### **2.5.6 There is Little Threat of New Entrants**

Would-be entrants to the molecular tests for CKD management industry face very high barriers to entry. These have been discussed in detail previously (see section 2.4.6) and will be reviewed here only briefly. First, new entrants face high patent barriers erected by incumbent firms. Firms hoping to develop new molecular tests for CKD are also dependent on access to patients/samples, which are essential complementary assets. Given the huge patient population having CKD, this may be less of an issue than in the molecular tests for organ transplant patient management industry. The significant capital requirements, the long time horizon reasonably required for a return on investment, and the high degree of regulatory uncertainty in this industry all present formidable barriers to entry. Already established incumbent firms, who may be able to capitalize on knowledge gains from bringing previous related products to market, have a clear advantage.

Despite these realities, there has been significant interest in entering this market. In part, this is due to the large and growing market size, but new entrants have also been incentivized by funding agencies and governments. For example, in 2009 the US



National Institutes of Health (NIH) announced that it would award \$12.5 million in funding over the next five years to organizations to discover and validate biomarkers of CKD (GenomeWeb Daily News, 2009). Thus, the firm believing it has a scientifically sound biomarker panel for predicting CKD progression is likely to believe that it can be profitable in this industry despite the numerous disincentives to new entrants.

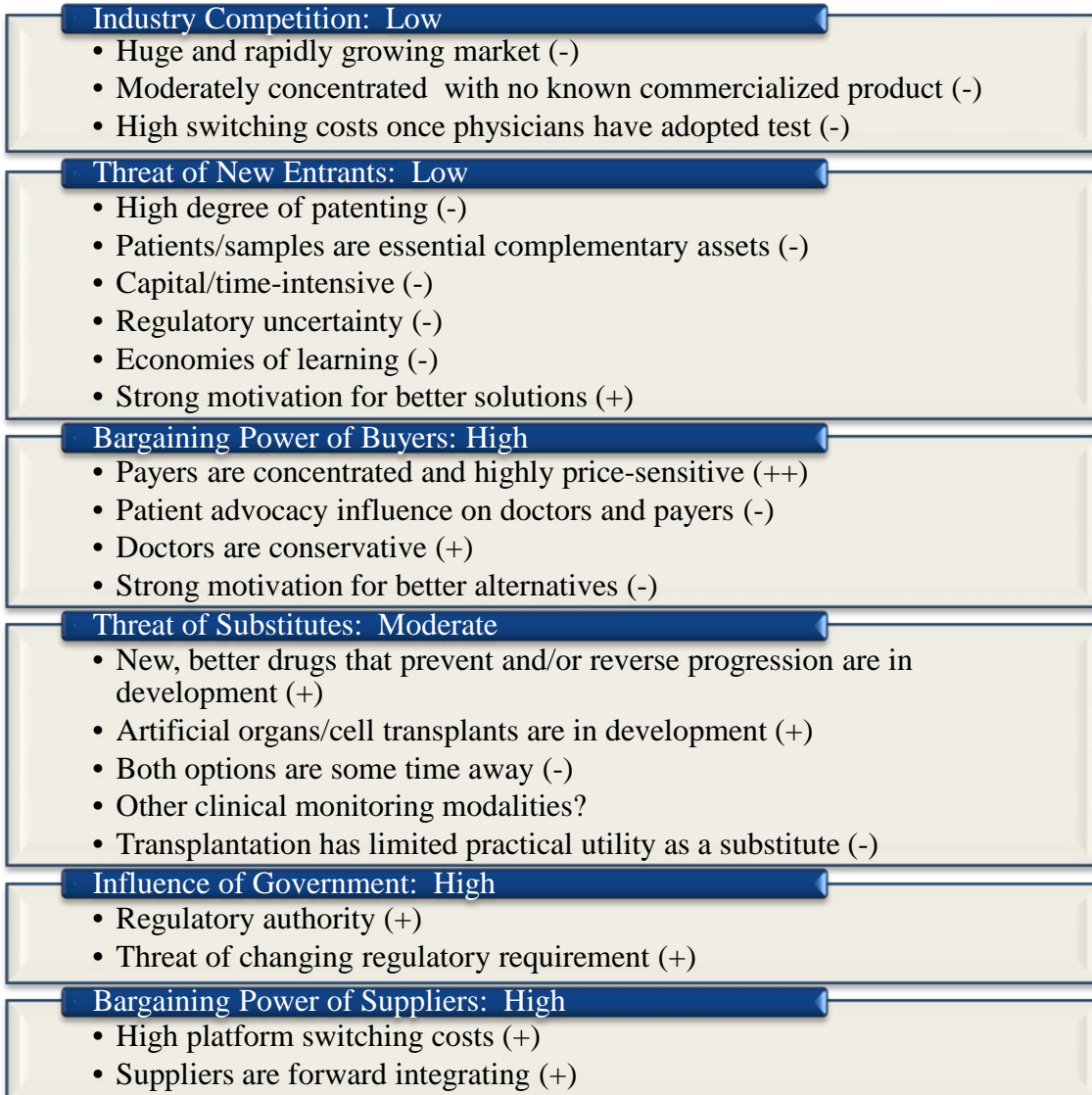
### **2.5.7 Government Regulators are Highly Influential**

As has been discussed, new molecular tests are highly regulated by governments in the interest of protecting public safety, and regulatory requirements for these tests are complex, require specialized knowledge, and are widely expected to become more burdensome in the US and elsewhere. The threat of stricter regulatory requirements negatively impacts the attractiveness of this industry since it will increase the cost and time required to develop new molecular tests. Thus, the requirement to prove safety and efficacy to government regulators presents one of the largest hurdles to developers of new molecular tests for CKD management face bringing their products to the market.

### **2.5.8 Summary of External Analysis for Biomarkers of Chronic Kidney Disease**

The external influences in the molecular tests for CKD management industry are summarized in Figure 2-6, and together, paint an unattractive picture of this industry. The

**Figure 2-6: Summary of Competitive Forces Impacting the Biomarkers of Chronic Kidney Disease Industry**



*Source: by author*

industry is still new and fragmented, with no known products approved for clinical use, although it has strong growth potential based on projected CKD prevalence.

Nevertheless, development efforts in this industry are costly and time-consuming relative to other investment alternatives, and multiple potential substitutes exist. The most notable

of these is better treatment and prevention of diabetes, which would reduce CKD prevalence if effectively implemented. Customers (particularly payers and physicians) and suppliers of platform technologies underlying new molecular tests both hold significant power. Moreover, significant barriers exist in the form of governmental regulatory authorities, distribution channels, and clinical uptake.

The negative features of the industry are somewhat countered by the growing recognition of the socioeconomic burden that CKD presents. As payers attempt to reduce long-term health care costs and physicians strive for better patient care, willingness to pay for truly effective diagnostics that will improve patient care is increasing. Thus for the organization that believes its prognostic tests for CKD to be more efficacious than potential substitutes, protected from infringement by competitors, and cost-effective from a payer perspective, this is an attractive industry despite the challenges it presents.

## **2.6 Biomarkers of Chronic Obstructive Pulmonary Disease**

### **2.6.1 Overview of PROOF's Chronic Obstructive Pulmonary Disease Program**

Chronic obstructive pulmonary disease (COPD) is characterized by progressive airway limitation and loss of lung function. In the US, it affects at least 12 million people, and is the fourth leading cause of death (National Heart Lung and Blood Institute, 2010). COPD is also the number one reason why people become sick enough to be hospitalized, and thus represents a large burden on the health care system. It is expected that global prevalence of COPD will continue rising, particularly in low- and middle-income countries. The biggest driver of this increase is cigarette smoking.

COPD is most commonly diagnosed when the forced expiratory volume in one second (FEV1) test shows a >20% reduction in the amount of air that can normally be expelled from the airways (Stockley, 2007). However, FEV1 is by definition an irreversible marker of disease progression, and thus is a poor surrogate marker by which to judge the efficacy of new COPD therapies. There is a desperate need for new therapies for COPD, given that existing drugs relieve symptoms of the disease but do not slow down or reverse declining lung function. However, many pharmaceutical companies have scaled back COPD drug development efforts until researchers identify more suitable surrogate markers of disease progression and reversal.

PROOF's COPD biomarker program operates in the biomarkers for COPD drug development and patient management industry; the program goal is to discover novel biomarkers of lung function that can enhance or replace FEV1. The first goal is to develop biomarkers into prognostic tests that differentiate between rapidly and slowly progressing disease, allowing physicians to match the degree of treatment and patient follow-up to a patient's individual risk. A second goal is to develop biomarkers for use as surrogate markers of drug efficacy in early clinical trials, to allow pharmaceutical companies to gain an earlier indication of whether a drug candidate is worth investing the resources necessary to pursue full clinical development.

The industry encompassing biomarkers for drug development and patient management in COPD is relatively new. The regulatory burden is significant and changing. Given the strong demand for drug development biomarkers and the large COPD patient population, many organizations are developing biomarkers of COPD. However, most of these efforts are in the developmental stages, and no multiplexed

COPD diagnostic/prognostic tests have reached the market thus far. Therefore, the industry as a whole is in the embryonic stages, and is experiencing negative cash flows and unprofitability arising from new product development.

### **2.6.2 Competition is Moderate in this Industry**

The market for biomarker-based tests and drug development biomarkers for COPD is largely determined by incidence of COPD. As has been discussed, COPD affects a large and rapidly growing number of people, so there is a robust end market for new molecular tests for COPD management. In such an environment, inter-firm rivalry tends to be decreased since the market can likely be divided into segments that are profitable for multiple competing firms.

However, many firms and laboratories have COPD biomarker discovery/development programs, meaning that the concentration ratio in this industry is low and driving up rivalry. For example, an NIH-funded team at Cornell University has identified a set of genetic biomarkers which may have utility in identifying those smokers most likely to develop COPD (iBridge Network, 2010). Most of these efforts are at the early developmental stage, so there is little information available with which to assess their commercial potential. Others—for example, the COPD biomarker discovery collaboration between American firms GenData and Batelle (Battelle Memorial Institute, 2004)—have been announced, but no results have been reported.

As has been discussed for other industries, a deterrent to rivalry in the biomarkers and molecular tests for COPD industry is the high switching costs associated with new tests. Regulators must be convinced of product safety, payers must believe there is a

health economic benefit, and laboratories and risk-averse physicians must learn to utilize the technology and adopt the product into standard clinical practice. These switching costs tend to decrease rivalry because customers cannot easily switch technologies once they have selected a test. This does not apply to pharmaceutical companies consuming COPD biomarkers to support drug development activities, however—in this case, switching costs are relatively low.

In summary, the COPD market is large and rapidly growing. Although no molecular tests are on the market for COPD management, multiple firms are developing them, as well as biomarkers for COPD drug development. All industry participants will face high buyer switching costs once physicians and laboratories have adopted a competing molecular test. Thus, biomarkers and molecular tests for COPD drug development and clinical management face a moderate degree of competition.

### **2.6.3 Substitutes Present a Moderate Threat**

There is consensus amongst clinicians that currently available substitutes for new molecular tests for COPD are insufficient. As noted above, FEV1 is widely utilized in the clinic, but physicians regard it poorly as a diagnostic. Unfortunately, there are few treatment alternatives with which to follow up diagnosis or prognosis of COPD. There is therefore a perception that physicians can do little to treat this disease even if they make an accurate diagnosis/prognosis. In other words, new molecular tests for diagnosing COPD effectively compete with the perception that no diagnosis is a viable and sensible “treatment” option. This will change as firms develop new drugs for COPD, although the pipeline for new COPD drugs is relatively lean. Only 34 new COPD drugs were under development in the US in 2009, compared to 235 for diabetes, despite comparable

affected patient populations (Pharmaceutical Manufacturers of America, 2010).

Nevertheless, there are several promising drugs in late-stage development. Perhaps the most notable is Nycomed's roflumilast, a novel anti-inflammatory treatment for COPD, which regulators approved for use in the EU in July 2010 (Nycomed Inc., 2010) and which the FDA is currently reviewing. More effective and/or less toxic COPD drugs may serve as substitutes for prognostic tests if they are effective in all COPD patients, regardless of disease severity/subtype.

New molecular tests for COPD diagnosis/prognosis also face substitutes in the form of diagnostic imaging (for example, chest x-ray and CT scanning), although these have not been widely adopted. Physiological measures of lung function may also have utility in diagnosing COPD and predicting outcomes. These include: blood oxygenation levels (measured via oximetry); six minute walking distance (a surrogate marker for exercise capacity); and the BODE score, which integrates four known risk parameters (body mass index, airflow obstruction, dyspnea, and exercise capacity) (Celli et al., 2004). This latter class of potential substitutes has the advantage of being easy to implement in community-based settings (i.e. family physician's offices) because they require minimal specialized equipment/training. However, the true diagnostic/prognostic value of such alternatives to FEV1 still requires further study.

Finally, more effective prevention strategies for COPD and curative therapies may also serve as indirect substitutes for molecular tests for COPD diagnosis/prognosis. Smoking is the leading cause of COPD, and effective public education and smoking cessation programs are likely to reduce incidence of COPD, albeit over a long timeframe (Yasothan & Kar, 2008). Several firms are working to develop cures for COPD. Osiris

Therapeutics, for example, is conducting a Phase II clinical trial investigating the ability of stem cells to repair lung tissue in COPD patients (Diamond, 2010). While regulatory agencies will impose a very high burden of safety data prior to accepting stem cell-based treatments, curative therapies would eliminate the need to diagnose or predict outcomes of COPD via molecular tests.

The second goal of PROOF's COPD program is to develop biomarkers for drug development. Drug developers need biomarkers to serve as surrogate disease endpoints, for pharmacokinetic analyses, and for target validation (see Figure 2-2). There is a low threat of substitution for this type of COPD biomarkers since no alternatives exist.

In summary, new molecular tests for COPD management face a moderate threat of substitution. FEV1 testing is the current standard, but is insufficient. Diagnostic imaging and physiological measurements may offer alternatives to new molecular tests, and so long as there are poor treatment options for COPD, choosing not to diagnose/prognose potential COPD remains an option. Finally, there are few if any alternatives to drug development biomarkers of COPD progression; COPD biomarkers for this purpose thus face a low threat of substitution.

#### **2.6.4 Buyers are Desperate for New Solutions in this Industry**

Participants in the biomarkers of COPD industry face low to moderate buyer power. As has been discussed, the major buyers for new molecular tests (in this case, for COPD management) are payers, physicians, and hospitals/laboratories, all of whom hold considerable power over test developers. However, several factors moderate this power. First, the price power exerted by payers on test developers is somewhat limited by the



motivation of health insurers to reduce downstream healthcare costs. COPD affects more than 6 percent of adults in the U.S., and accounts for \$32 billion in direct health care costs (Lindenauer et al., 2010). Payers therefore have strong incentive to reimburse new molecular tests that facilitate accurate diagnosis and prognosis of COPD, since these tests will allow earlier intervention, aggressive treatment of patients with severe disease, and prevention of costly COPD exacerbations.

Secondly, strong patient advocacy groups and physician motivation to diagnose and treat patients more effectively decreases the power exerted by hospitals and gatekeeper physicians. This is particularly true for COPD, given the poor prognostic options currently available. Finally, in the area of biomarkers for COPD drug development, pharmaceutical companies are the buyers. These firms have a strong need for better surrogate markers for disease endpoints in order to allow them to identify and terminate unpromising COPD drug candidates earlier, and to identify and direct resources towards the most promising drug candidates. As consumers of COPD biomarkers, they therefore exert minimal buying power over biomarker developers.

### **2.6.5 Suppliers Hold Significant Power**

The suppliers that support the industry in biomarkers for COPD are primarily technology platform manufacturers. As has been discussed, platform developers in general are forward integrating, hoping to capture more value by marketing not only their technology platforms, but also the molecular tests utilizing their platforms. In addition, once firms have selected a technology platform supplier and have begun the development and regulatory processes necessary to bring their new tests to market, it is costly and

time-consuming to switch platforms. Thus, technology platform suppliers hold a high degree of power over firms developing molecular tests for COPD management.

#### **2.6.6 New Entrants Present a Moderate Threat**

Many of the threats to would-be entrants to the industry in biomarkers for COPD have been previously reviewed (see section 2.4.6). New entrants face high barriers to entry in the form of existing patents, access to patients/samples (which are essential complementary assets), huge capital requirements, and long time horizons. The regulatory uncertainty surrounding the industry is a major disincentive for new entrants, though notably this is not an issue for drug development biomarkers, which carry a much lower regulatory burden of proof than biomarkers for use in clinical tests.

Despite these barriers to entry, there has been significant interest in entering this market for two key reasons: a large and growing market size, and strong demand from pharmaceutical companies for drug development markers to support internal portfolio management and decision-making. This strong demand to some degree counterbalances the barriers which would-be entrants face, and provides incentive for new firms to enter this industry. Overall, incumbent firms operating in the biomarkers for COPD industry therefore face a moderate threat of new entrants.

#### **2.6.7 Government Regulators Wield Significant Power**

As has been discussed, new molecular tests are highly regulated, meaning that government authorities hold significant influence over test developers. Regulations for molecular tests are widely expected to become more burdensome in the US. However, there is a markedly reduced regulatory burden placed on biomarkers intended for non-

clinical purposes such as drug development and pharmaceutical portfolio management. Thus in the biomarkers for COPD industry, where a major focus has been on producing biomarkers to support drug development, the influence of regulatory agencies is somewhat lower than in industries focused more exclusively on molecular tests. Nevertheless, demonstrating safety and efficacy to government regulators remains one of the largest hurdles for developers of molecular tests for COPD management.

### **2.6.8 Summary of External Analysis for Biomarkers of Chronic Obstructive Pulmonary Disease**

The external factors influencing the industry in biomarkers for COPD are summarized in Figure 2-7; on the whole, this industry appears unattractive to the outside investor, though less so when the subsector of the industry focused on developing COPD biomarkers to drug development is considered. The industry is relatively new and has strong growth potential, though development efforts are costly and time-consuming. Platform technology suppliers, as well as certain buyers—payers, physicians, and hospitals/laboratories—bear considerable power. However, pharmaceutical companies serving as buyers for biomarkers for COPD drug development hold minimal power, and this subsection of the industry faces a much lower governmental regulatory burden than that subsection developing molecular tests for COPD. Despite these realities, there is strong agreement that FEV1 is insufficient as a diagnostic, and that current COPD management leaves much to be desired. Thus, firms that believe they have discovered and validated a sound panel of biomarkers for use in COPD drug development and/or molecular test development may have strong incentive to enter this industry.

**Figure 2-7: Summary of External Forces In the Biomarkers of COPD Industry**

<b>Industry Competition: Moderate</b> <ul style="list-style-type: none"><li>• Large and growing end market (-)</li><li>• High switching costs once physicians have adopted test (-)</li><li>• Many firms and labs developing biomarkers—NIH trial etc. (+)</li></ul>
<b>Threat of New Entrants: Moderate</b> <ul style="list-style-type: none"><li>• High degree of patenting (-)</li><li>• Patients/samples are essential complementary assets (-)</li><li>• Capital/time-intensive (-)</li><li>• Regulatory uncertainty (-)</li><li>• Economies of learning (-)</li><li>• Huge demand from pharma (++)</li></ul>
<b>Bargaining Power of Buyers: Low to Moderate</b> <ul style="list-style-type: none"><li>• Pharma is a desperate for biomarkers for drug development (-)</li><li>• Payers are motivated to reduce downstream costs (-)</li><li>• Payers are price-sensitive and highly concentrated (++)</li><li>• Strong patient advocacy vs. doctors and payers (-)</li><li>• Physicians are motivated to adopt better alternatives (-)</li></ul>
<b>Threat of Substitutes: Moderate</b> <ul style="list-style-type: none"><li>• “Do nothing” is perceived to be an alternative (+)</li><li>• FEV1 is used but is regarded as very poor (+/-)</li><li>• Diagnostic imaging and physiological measures (+/-)</li><li>• Curative treatments and new drugs are under development (+/-)</li><li>• No good alternatives for biomarkers for drug development (-)</li></ul>
<b>Influence of Government: High</b> <ul style="list-style-type: none"><li>• Regulatory authority (+)</li><li>• Reduced regulatory influence for non-clinical biomarkers (-)</li><li>• Threat of changing regulatory requirement (+)</li></ul>
<b>Bargaining Power of Suppliers: High</b> <ul style="list-style-type: none"><li>• High platform switching costs (+)</li><li>• Suppliers are forward integrating (+)</li></ul>

*Source: by author*

## **2.7 Biomarkers of Chronic Heart Failure**

### **2.7.1 Overview of PROOF's Chronic Heart Failure Program**

Chronic heart failure (HF) is a progressive disease arising when the heart is unable to fill and/or pump blood sufficiently, often secondary to cardiovascular disease (e.g. coronary artery disease, hypertension). Common symptoms include shortness of breath and reduced exercise capacity. Symptomatic HF affects up to 2% of the general population, and up to 10% of the elderly population, and is responsible for more 6.5 million days spent in the hospital annually in the US (Kaye & Krum, 2007). Because HF impacts mostly elderly patients, prevalence of HF will rise significantly as the population ages and as more patients survive preceding cardiac events (Hunt et al., 2005). Given that the annual fully loaded cost associated with HF in the US is nearly \$30 billion, there is significant interest in treating the disease more cost-effectively (Hunt et al., 2005).

Current diagnostic approaches are imaging-based (echocardiography, MRI, CT) and require patients to travel to tertiary care centres for diagnosis. Once diagnosed, HF is treated with some combination of lifestyle modification (e.g. smoking cessation and exercise), pharmaceuticals (e.g. beta-blockers, angiotensin-converting enzyme inhibitors), and medical devices (e.g. implantable defibrillators) (Gerson, Abdallah, Muth, & Costea, 2010). Heart failure can be diastolic or systolic in nature, and while many therapies exist for systolic heart failure (SHF), these are ineffective in patients with diastolic heart failure (DHF). This means that many DHF patients gain no benefit from their drug regimens, and indeed are exposed to potentially harmful drugs unnecessarily. However, though the etiology of these different forms of the disease may differ, their

clinical presentation is often similar, making it difficult for physicians to determine which form of the disease patients have.

PROOF's biomarkers for HF program competes in the molecular tests for HF industry. The goal of the program is to develop blood-based genomic and proteomic tests to diagnose HF and distinguish between DHF and SHF. Development of a blood-based biomarker would allow general practitioners to diagnose HF in the primary care setting. This would allow earlier diagnosis and prevent patients from having to travel to tertiary care centres for diagnosis. PROOF may also develop additional prognostic biomarker tests to predict diastolic and systolic heart failure progression.

The molecular tests for HF industry are new and remain in the embryonic stages of the industry life cycle. As discussed, regulatory processes guiding acceptance of new products remain unclear, and despite a large and growing market, there are no known products currently marketed for clinical use. Many firms and academic laboratories are working to discover and develop biomarkers for HF diagnosis; however, most of these efforts are at the early stages. Therefore, the industry as a whole has a low concentration ratio, and is unprofitable because of resource-intensive new product development.

### **2.7.2 Competition is Low in this Industry**

Competition in the molecular tests for HF market is low overall. The market is large and is anticipated to undergo strong growth as the population ages and as more patients survive earlier cardiac events/CVD. There is room in such a large market for many different players to occupy profitable positions, particularly where differentiated products are developed. Moreover, with many different firms and institutions operating

in the industry, and no commercialized products in this area, no single firm holds significant market power. Finally, as has been discussed elsewhere, rivals in this industry face high switching high switching costs—for regulators, payers, laboratories, physicians, and patients. These switching costs tend to decrease rivalry because customers cannot easily switch technologies once they have adopted a particular test.

Although overall rivalry is low in this market, in the absence of any currently marketed multiplexed tests there is a rush to be the first to market, and several competitors deserve further mention. The Belgian firm Pronota has a proprietary platform for discovery of low-abundance plasma proteins which is it is leveraging for biomarker discovery and development for HF (Pronota NV, 2010). Furthermore, several large diagnostics and pharmaceutical companies have an established presence in the HF market in general, and physicians already use single biomarkers (e.g. NT-proBNP) for risk stratification of heart disease and HF patients in some places. Abbott Laboratories, for example, has developed a point-of-care platform for measuring blood biomarkers, and through a partnership with BG Medicine is developing galectin-3 as a potential biomarker for acute HF (Abbott Laboratories, 2009). While such firms may be lagging in the development of multiplexed panels of HF biomarkers, their availability of financial, regulatory, and marketing resources may allow them to expand their offerings in the HF space very rapidly and may thus represent formidable rivals.

### **2.7.3 There is a Moderate Threat of Substitution**

Substitutes for molecular tests for HF diagnosis present a moderate threat. Other modes of clinical assessment, including echocardiography and MRI are used, but are costly, can be invasive, and are generally unavailable in primary care settings. However,

if cheaper and less technologically complex version of these types of assessment tools are developed and adopted, these could present a significant threat to biomarker-based tests such as those PROOF is developing.

New drugs, cell/gene therapies, and/or devices (e.g. circulatory support systems and implantable defibrillators) that treat both SHF and DHF equally well would present a second substitute for molecular tests distinguishing SHF from DHF. However, the pace of drug discovery for HF has slowed in recent years, owing to several high-profile HF trial failures and to the astronomical cost of conducting large-scale HF trials (\$100-\$200 million) (Kaye & Krum, 2007). Although cell/gene therapy could conceivably cure HF and obviate the need for HF diagnostics, these treatments face many development and regulatory hurdles before they are widely adopted into clinical practice. Heart transplants may be helpful for end stage HF patients, but cannot be widely implemented because of lack of donor hearts and the cost of managing transplant patients. Finally, because of the lack of available treatments for DHF, molecular tests for distinguishing SHF from DHF may compete with the notion that no diagnosis is acceptable.

#### **2.7.4 Buyers Hold a Moderate Degree of Power over Industry Participants**

Firms operating in the molecular tests for HF industry face moderate buyer power for many of the reasons discussed previously. Payers, physicians, and hospitals/laboratories are the primary consumers, and hold considerable power over test developers. However, though payers are price sensitive and concentrated, they are motivated to reduce unnecessary expenditures associated with treating DHF patients with ineffective SHF drugs. Payers thus would rationally be open to reimbursing a diagnostic that distinguished DHF from SHF.



### **2.7.5 Suppliers of Platform Technologies are Powerful**

Participants in the molecular tests for HF industry face platform developers that are forward integrating, hoping to capture more value from the market by marketing not only their technology platforms, but also tests utilizing their platforms. In addition, once firms have selected a technology platform supplier and have begun the development and regulatory processes necessary to bring their new tests to market, it is costly and time-consuming to switch platforms. Thus, technology platform developers hold a high degree of power as suppliers to the firms developing molecular tests for HF management.

### **2.7.6 The Threat of New Entrants is Low**

The threat of new entrants in the industry in biomarkers for HF is low, as has been reviewed for other industries. New entrants face high patent barriers, require access to patients/samples, and face large capital requirements, long time horizons, and significant regulatory uncertainty. Despite these barriers to entry, the large and growing market size is an enticing incentive, and because of the burden of HF on individuals and on health care budgets, governments and funding agencies are actively encouraging new biomarker discovery and platform technology development in this area.

### **2.7.7 Government Regulators are Very Influential**

New molecular tests are highly regulated, and these regulations are widely expected to become more burdensome. Thus, governments hold a high degree of influence over firms operating in the molecular tests for HF industry.

### **2.7.8 Summary of External Analysis for Biomarkers of Chronic Heart Failure**

The external environment for the industry in new molecular tests for HF management is summarized in Figure 2-8 and generally renders the industry an unattractive one for potential investors. Despite strong and growing market potential, development efforts are costly and time-consuming, and payers, physicians, and platform technology suppliers hold considerable power. Nevertheless, because of the large socioeconomic burden presented by HF, firms believing their molecular tests to be more efficacious than alternatives, protected from infringement by competitors, and cost-effective from a health economics standpoint may still perceive this to be a very attractive industry.

**Figure 2-8: Summary of Competitive Forces Impacting the Biomarkers of Chronic Heart Failure Industry**

<p><b>Industry Competition: Low</b></p> <ul style="list-style-type: none"> <li>• Large, rapidly growing market (-)</li> <li>• Low concentration ratio low (+)</li> <li>• High switching costs once physicians have adopted test (-)</li> </ul>
<p><b>Threat of New Entrants: Low</b></p> <ul style="list-style-type: none"> <li>• High degree of patenting (-)</li> <li>• Patients/samples are essential complementary assets (-)</li> <li>• Capital/time-intensive (-)</li> <li>• Regulatory uncertainty (-)</li> <li>• Economies of learning (-)</li> </ul>
<p><b>Bargaining Power of Buyers: Moderate</b></p> <ul style="list-style-type: none"> <li>• Payers are concentrated and highly price-sensitive (++)</li> <li>• Buyers want to reduce unnecessary treatment of DHF patients with SHF drugs (-)</li> <li>• Strong patient advocacy vs. doctors and payers (-)</li> <li>• Doctors are conservative (+)</li> <li>• High motivation for better alternatives (-)</li> </ul>
<p><b>Threat of Substitutes: Moderate</b></p> <ul style="list-style-type: none"> <li>• Other modes of clinical assessment used but are expensive and unavailable in smaller centres eg. echo, MRI (+/-)</li> <li>• No biomarkers currently in the clinic (-)</li> <li>• New drugs that prevent disease progression to full-blown heart failure (+)</li> <li>• Transplants (+/available but not widely applicable(+/-)</li> <li>• No diagnosis perceived to be an option because of lack of treatments available for DHF (+)</li> </ul>
<p><b>Influence of Government: High</b></p> <ul style="list-style-type: none"> <li>• Regulatory authority (+)</li> <li>• Threat of changing regulatory requirement (+)</li> </ul>
<p><b>Bargaining Power of Suppliers: High</b></p> <ul style="list-style-type: none"> <li>• High platform switching costs (+)</li> <li>• Suppliers are forward integrating (+)</li> </ul>

*Source: by author*

## **2.8 Biomarker-Based Diagnosis of Early Cardiovascular Disease**

### **2.8.1 Overview of PROOF's Biomarker-Based Diagnosis of Early Cardiovascular Disease Program**

Cardiovascular disease (CVD) is the leading cause of death and serious illness in North America, where 1 in 3 people have some form of the disease. The full economic cost of CVD in the US in 2009, including health care services, medications, and lost productivity was nearly \$500 billion (American Heart Association, 2010). Many scholars have argued that earlier CVD diagnosis would permit earlier intervention and decrease downstream healthcare costs. Biomarkers (e.g. troponins and NT-proBNP) exist to diagnose CVD after an acute cardiac event such as a heart attack. However, while scientists have identified many proteins that might have potential as markers of early CVD, none of these markers have sufficient individual power to diagnose the very early stages or risk of developing CVD.

PROOF's program in biomarker-based diagnosis of early CVD operates in the industry focusing on CVD diagnostics. PROOF aims to use a quantitative, highly sensitive proteomics technique called multiple reaction monitoring mass spectrometry (MRM-MS) to develop an assay for determining the blood concentration of 95 published potential protein biomarkers for CVD. The goal is to commercialize the assay for early CVD detection. A second goal is to leverage the evidence and experience gained through this process to serve as proof-of-principle for using MRM-MS technology as a platform technology to develop assays for other disease indications.

There is a growing market for molecular tests for CVD diagnosis, and for new assay technologies that are amenable to clinical implementation. The molecular

diagnostics for CVD industry is new and has attracted significant funding and industrial and public attention. However, the industry has a low concentration ratio and remains unprofitable because most firms have few or no commercialized products.

### **2.8.2 Competition Presents a Low to Moderate Threat**

Firms operating in the molecular tests for early CVD diagnosis industry face low to moderate competition. The market is large and growing, leaving room for multiple firms with different products to identify a profitable niche. There is also very large demand for new, clinically relevant assay technologies as researchers, clinicians, and regulators seek to apply genomic and proteomic knowledge gains to improving human health. Again, this growing market tends to decrease competition as different buyer segments can be targeted by different firms. Firms operating in this industry face high switching costs once buyers have adopted a molecular test and platform technology. These costs tend to decrease inter-firm rivalry. However, it is worth noting that many organizations are developing biomarkers to serve this industry, and tests for some single biomarkers (e.g. troponins) are already being marketed. The low concentration and potential “head start” that these firms have tend to increase competition from an otherwise low level.

### **2.8.3 Many Potential Substitutes Exist**

New molecular tests for early CVD diagnosis face a high threat of substitution. Rigorous clinical assessment, including familial history, lipid profiling and diet/lifestyle assessment, is common and cost-effective, though it relies heavily on potentially inaccurate self-reporting. Angioplasty and coronary artery bypass grafting (CABG) are

commonly used to decrease risk of (further) cardiovascular events (Lloyd-Jones et al., 2010). While surgical interventions remain costly and invasive, as these procedures become more common, less costly, and more widely available they may present a viable substitute for early diagnosis. The development of new CVD drugs, cell/gene therapies, and/or devices that treat and reverse CVD could also reduce the demand for early CVD diagnostics. Finally, CVD prevention programs are increasingly being implemented, and present perhaps the biggest threat of substitution for new molecular tests for early diagnosis. Indeed, it has been argued that the most cost-effective strategy would be to shift public policy towards an intensive, broadly implemented CVD prevention strategy (Kraushaar & Kramer, 2009).

#### **2.8.4 Buyers Hold Considerable Power**

The ultimate buyers of technologies and assays facilitating early diagnosis of CVD include payers, hospital/central laboratories, and physicians which collectively hold considerable power over test developers, as has been discussed.

#### **2.8.5 Suppliers are Powerful and Forward-Integrating**

Participants in the molecular tests for CVD diagnosis industry face platform developers that are forward integrating. Suppliers of the technology for MRM-MS, which has historically been a research tool rather than a clinical one, are developing newer-generation technologies that may be appropriate for the clinical market. There is strong incentive for these firms to expand their customer base by entering the clinical markets. In addition, once firms have selected a technology platform supplier and have begun the development and regulatory processes necessary to bring their new tests to market, it is

costly and time-consuming to switch platforms. Thus, technology platform suppliers hold a high degree of power as suppliers to the firms developing molecular tests for early CVD diagnosis.

### **2.8.6 There is a Relatively Low Threat of New Entrants**

As in other industries discussed, the threat of new entrants in the industry in tests for CVD diagnosis is low. New entrants face high patent barriers, require access to patients/samples, and face large capital requirements, long time horizons, and significant regulatory uncertainty. However, the large and growing market size is an enticing incentive, and new firms are entering the industry despite these barriers to entry.

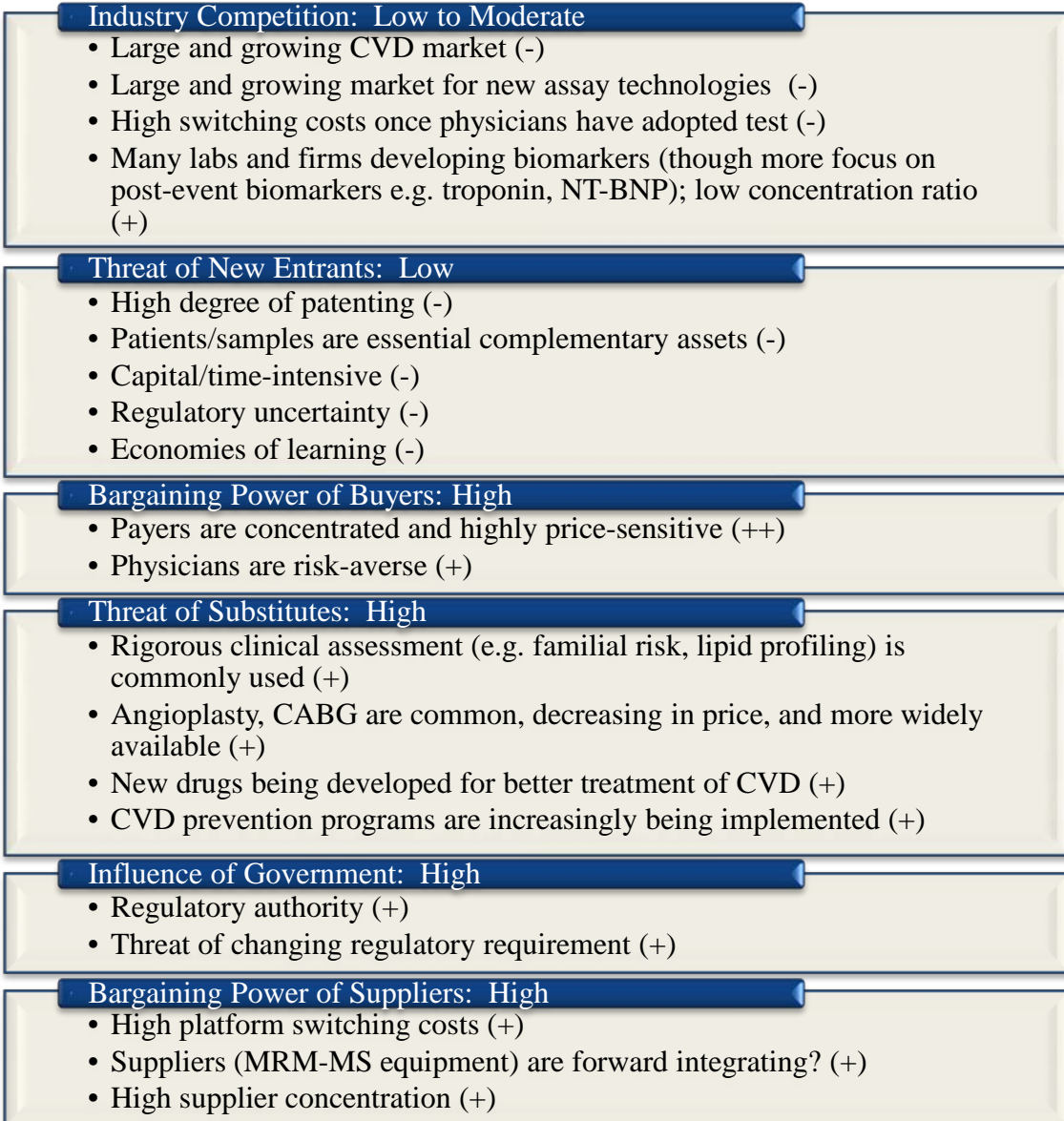
### **2.8.7 Government Regulators are Highly Influential**

New molecular tests are highly regulated, and these regulations are widely expected to become more burdensome. Thus, governments hold a high degree of influence over firms operating in the molecular tests for CVD diagnosis industry.

### **2.8.8 Summary of External Analysis for Biomarker-Based Diagnosis of Early Cardiovascular Disease**

The external influences impacting the industry in assays and technologies for early CVD detection is summarized in Figure 2-9. Although the industry is new, has strong growth potential, and is somewhat protected from new entrants, it also is costly and time-intensive, with buyers and suppliers both holding significant power.

**Figure 2-9: Summary of Competitive Forces Impacting the Biomarker-Based Diagnosis of Early Cardiovascular Disease Sector**



*Source: by author*

## **2.9 Summary—The Industries in which PROOF Operates**

This section utilized standard analytical tools for assessing the key external forces impacting an industry. From this analysis, we can draw several broad conclusions about the attractiveness of the industries in which PROOF operates. Firstly, all of the industries analyzed face a high degree of government and supplier influence, and this pressure is



likely to remain stable or intensify in the future. Perhaps the least attractive industry assessed is the industry in molecular tests for organ transplant patient management. This is because of the combination of small market potential, high inter-firm rivalry, and high threat of substitution. PROOF's programs in biomarkers for COPD, HF, and CKD operate in arguably more attractive industry environments. Buyer power in the market for drug development biomarkers and molecular tests for COPD is low compared to the other industries assessed, since pharmaceutical firms are desperate for this commodity and there are few substitutes. In the industry for new molecular tests for HF, physicians and payers have a strong desire to reduce unnecessary and potentially harmful treatment of DHF patients with SHF drugs, and have few substitutes. In the industry for new molecular tests for CKD, payers and doctors wish to reduce unnecessary treatment of stable patients, and increase monitoring and therapy for patients with rapidly progressing disease. Thus in all three industries buyer power is reduced to a moderate level.

### **3: PROOF'S INTERNAL SITUATION: ADEPT AND AGILE, BUT VULNERABLE**

The performance of a not-for-profit such as PROOF arises from the combination of the organization's external environment, its internal resources and capabilities, and the strategic choices it makes in response to both. Chapter 2 reviewed the structure and features of the industries in which PROOF's programs operate. Chapter 3 will assess the organization's internal activities within the context of value creation process for new molecular tests. PROOF's key resources and capabilities will be summarized, and subsequently analyzed in the context of the value creation process for new molecular tests. This final step of the internal analysis will demonstrate where PROOF's strengths and weaknesses lie in the value creation process.

#### **3.1 PROOF's Resources and Capabilities**

Internal resources and capabilities, if developed and deployed effectively, can help organizations define a unique and competitive strategic position. PROOF possesses several different types of resources, capabilities, and assets: financial (cash, capital, borrowing potential); physical assets (equipment); human resources (labour, managerial skills, loyalty); intangible assets (reputation, brand, values, culture); and technological assets (patents). The key strengths and weaknesses in PROOF's arsenal of resources and capabilities are outlined below.

##### **3.1.1 Financial**

PROOF has been exceptionally successful at building and leveraging relationships in order to attract investment. This has led to more than ten million dollars

in cash and in-kind investments from non-NCE partners, including academic, industrial, and government interests. Table 3.1 summarizes PROOF’s financial resources.

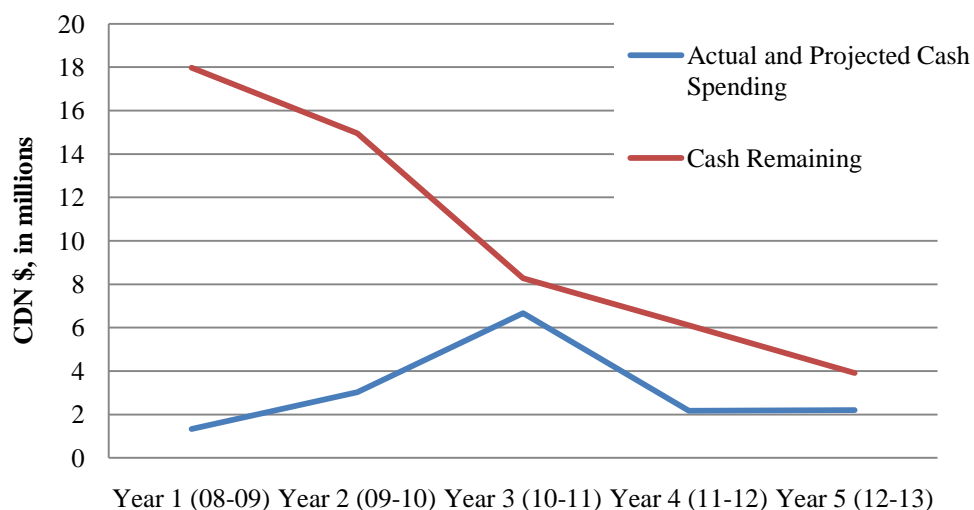
**Table 3-1: Cash and In-Kind Resources Committed to PROOF as of June 2010**

	Cash (\$)	In-Kind (\$)	Total (\$)
<b>NCE CECR Program</b>	15.0 million		15.0 million
<b>Other Partners</b>	4.4 million	6.4 million	10.7 million
<b>TOTAL FUNDING</b>	19.3 million	6.4 million	25.7 million

*Source: by author, adapted from PROOF Centre Annual Report 2009-2010*

Figure 3-1 shows PROOF’s actual (year 1 and 2) and projected (years 3-5) cash expenditures.

**Figure 3-1: PROOF’s Actual/Projected Cash Spending and Projected Cash Reserves**—Excludes cash gains from investment interest and potential revenues from licensing, product sales, and contract services.



*Source: by author, adapted from PROOF Centre Annual Report 2009-2010*

The projected cash reserve shown above assumes that PROOF fails to attract any additional cash investments, licensing revenues, product sales, or contract services

revenues. Even in this worst-case scenario, PROOF has more than sufficient resources to carry out its planned biomarker research and development activities, and should have flexibility to expand its programs if it can access additional investment or increase revenue generation.

It is worth noting that of projected cash expenditures, more than 75% (\$11.6 million of \$15.4 million total projected spending) is committed to biomarker programs (i.e. to research and development). This is exceptionally high; in comparison, between 1996 and 2005, ten of the largest global pharmaceutical companies spent \$288 billion on R&D, or 16.3% of \$1.77 trillion total spending (Lauzon L-P & Hasbani M, 2006). Genomic Health Inc., the early stage molecular diagnostics firm that markets *Oncotype Dx*, directed 30.4% of total spending to R&D in 2009, the first year it became cash-flow positive (Genomic Health Inc., 2009). PROOF has therefore been highly successful at directing most of its cash to directly productive spending. In part, this is the result of successfully attracting in-kind investment to pay for support functions (e.g. administrative staff, intellectual property management, and IT support).

Ironically, though it has excelled at fiscal management, perhaps PROOF's greatest long-term threat is also financial. PROOF's long-term financial security is unclear since its 5-year funding window from the NCE will end in 2013, and it remains unclear whether the NCE will hold a renewal funding competition. Although this is a reality of the external environment, PROOF's limited funding timeline seriously hinders PROOF's internal ability for long-term planning, and represents the single greatest weakness of the organization.

### **3.1.2 Physical**

PROOF has few physical resources, and instead operates largely by leveraging physical assets held by collaborators and partners. The organization is housed within St. Paul's Hospital via in-kind support. This could be viewed as a strength or a weakness. On one hand, it means that PROOF holds few capital assets that could be liquidated should the need arise; on the other hand, the organization has not had to sink precious financial resources into physical assets that depreciate over time.

### **3.1.3 Human Resources**

PROOF is fortunate to have a richly experienced and deeply committed team. The organization's management team includes clinical, laboratory medicine, business development, computational, and assay development expertise. The organization's Board of Directors and Translational Advisory Committee provide broad pharmaceutical, government, diagnostics, financial, and academic expertise. PROOF maintains a relatively small workforce and a flat organizational structure, which allows it to be nimble in introducing change and adjusting course. Its workforce is highly educated, loyal, and committed to helping PROOF bring new molecular tests to the patients that need them. PROOF is rich in individuals that possess T-shaped skills—that is, deep knowledge in a particular discipline paired with an understanding of how that discipline interfaces with a variety of related disciplines (Leonard-Barton, 1995).

However, PROOF may face several human resources-related weaknesses. While the small number of employees keeps payroll costs low, PROOF may be at risk of having insufficiently powered support for critical activities, particularly computation, program

management, regulatory affairs, and intellectual property management. This could create processing bottlenecks that delay biomarker development programs. In addition, PROOF relies on in-kind support from UBC for some contract management, intellectual property, and business development services. While this preserves cash resources, it may leave the organization at risk of hold-ups for these activities. Indeed, exceptionally lengthy contract negotiations have been a significant bottleneck for PROOF in the past two years. Finally, few PROOF personnel have direct experience in regulatory affairs, business development, and commercialization functions. The workforce has been eager to learn these skills and thus far has adopted a “learn-by-doing” approach with the support of key Board, TAC personnel and external consultants. However, as PROOF’s biomarker programs mature and move closer to commercialization and implementation, this approach may be insufficient, and the organization may need to hire in additional experienced personnel to support these critical areas.

#### **3.1.4 Intangible Assets**

PROOF’s greatest assets arguably fall into this category. The organization’s management team have leveraged deep clinical, academic, and industrial connections for the organization’s benefit. PROOF has built extensive reputational capital with physicians by building its biomarker research programs to address what clinicians report to be their greatest needs in patient care. Physicians and the public value the organization’s status as a not-for-profit because it signals lack of corporate bias and recognition of the social issues arising from new molecular test development. Industry, on the other hand, values PROOF’s deep connections with physicians. In this way,

PROOF has been able to build a very valuable brand as an entity that facilitates essential relationships between different sectors. This is one of the organization's greatest assets.

### **3.1.5 Technological Assets**

PROOF has significant technological assets in the form of patents and computational know-how. The firm holds patents related to biomarker panels for use in the diagnosis and prognosis of multiple disease states, and is taking an active approach to filing further disclosures. The organization has developed capabilities in computational strategies for biomarker discovery and validation, and in data management and processing.

### **3.1.6 Summary of PROOF's Resources, Capabilities, and Assets**

The above review of PROOF's internal environment reveals both reasons for optimism and areas that require attention from the organization's management. The biggest threat facing the organization is its limited ability for long-term financial and strategic planning owing to the 5-year timelines imposed by the NCE. The firm may require additional commercial expertise to support commercialization activities necessary to bring its products to market. However, PROOF benefits from a strong reputation as an organization that brings multiple sectors together in a collaborative fashion, and has core computational strengths.

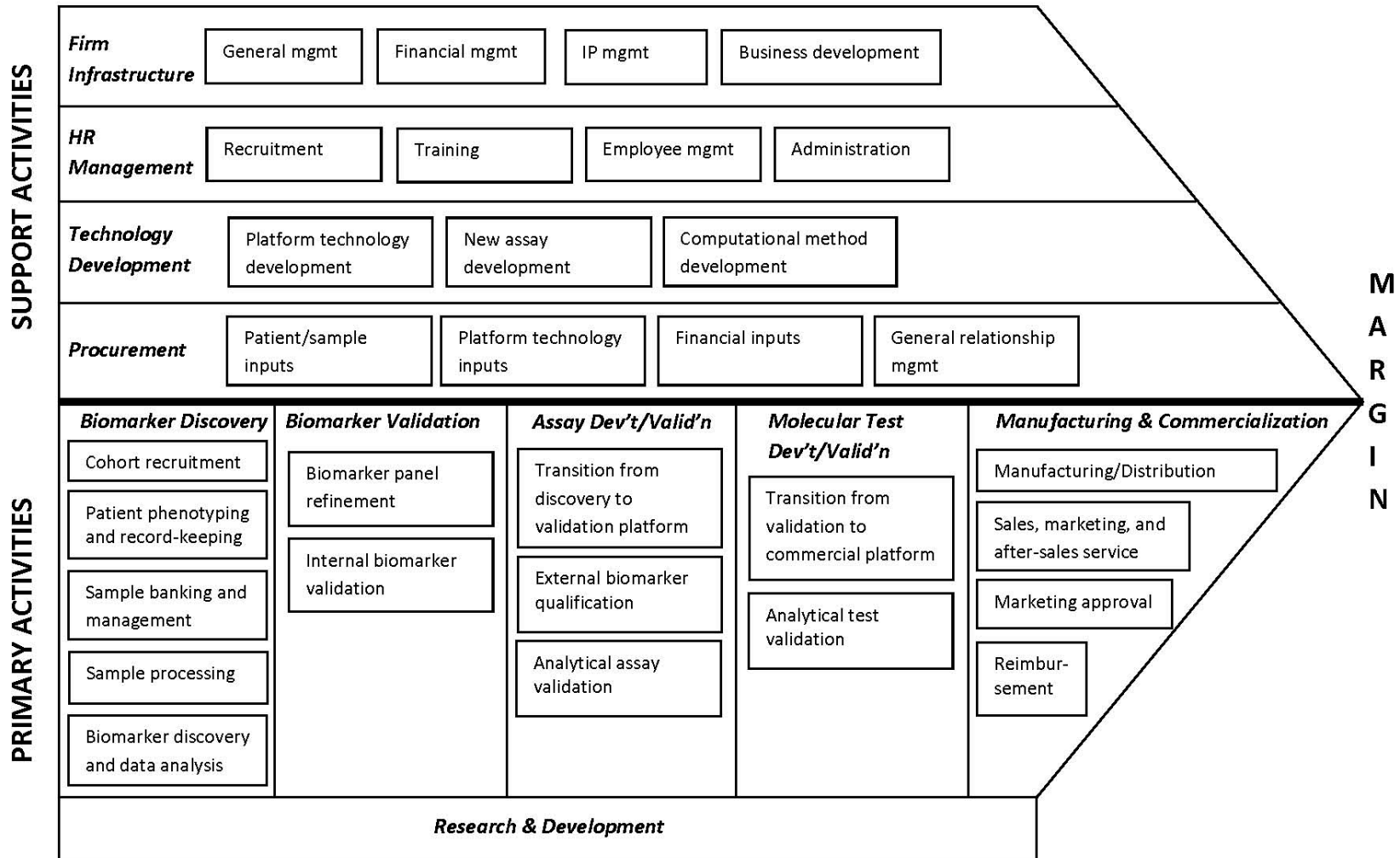
### **3.2 PROOF's Position in the Value Creation Process for New Molecular Tests**

Section 3.1 identified the key resources and capabilities held by PROOF. This section will assess the value creation process for new molecular tests. While this type of value chain analysis is most clearly applicable to firms that utilize a physical flow of activities to convert inputs to outputs, it is also useful in technology-based organizations such as PROOF to disaggregate the way in which a firm generates products or executes services (Porter, 1985). This analysis will identify and explain the activities that PROOF performs alone and via contracts/partnerships. Finally, PROOF's strengths and weaknesses will be mapped onto the value creation process for new molecular tests. This process will help identify where PROOF's potential competitive advantage lies in the context of the value creation process (Duncan, Ginter, & Swayne, 1998).

Figure 3-2 shows the value chain for an organization developing new molecular tests. Because PROOF is not in a manufacturing-based business, the prototypical value chain (Porter, 1985) has been adapted to reflect the set of value-adding activities required to bring new biomarker-based molecular tests to market. In this way, the primary activities shown represent incremental stages of increasing product value. The primary and support activities necessary for developing new molecular tests are outlined in the following sub-sections.



**Figure 3-2: Value Creation Process for Firms Creating New Molecular Tests**



Source: by author, adapted from Porter, 1985

### **3.2.1 Primary Activities in Creation of New Molecular Tests**

PROOF is primarily in the business of generating and processing new biomarker-related intellectual property. This includes panels of discriminative biomarkers and algorithms for the generation and application of these panels. In the adapted value chain shown above, five distinct sets of primary activities create value, while research and development is underlying all primary activities. At each stage of development, an organization such as PROOF has the option either to complete the subsequent stage in-house, or to out-source (some of) the activities associated with the subsequent stage by direct sale, out-licensing, or contracting activities to a partner. This decision will depend on internal resources and capabilities, availability of contract research organizations specializing in the activities in question, and the market for in-licensing deals at that particular stage.

#### **3.2.1.1 Biomarker Discovery**

In the biomarker discovery stage, potential biomarkers are identified from a small population of patients. This stage includes five different sets of activities. PROOF performs some of these activities internally and others through partnerships. Recruitment, phenotyping, sample collection, and sample banking typically occur at a single clinical site. For most programs, PROOF performs these activities itself.

The next steps are sample processing and biomarker discovery. PROOF performs sample processing itself. For genomic biomarker discovery, this entails extraction of RNA from whole blood; for proteomic biomarker discovery, this involves depletion of

the 14 most abundant proteins from banked plasma samples. PROOF contracts out biomarker discovery activities to partner organizations because of the cost and expertise required to set up and run high-performance biomarker discovery platforms internally.

The output of the biomarker discovery step is large, complex data files including tens of thousands of genes and proteins. Within these data sets, there are perhaps a handful of genes and proteins that are differentially expressed between the patient groups of interest. Identifying these genes and protein and combining them into a set of discriminative biomarker panels is the final and arguably the most value-adding step in biomarker discovery. This step requires deep expertise in statistics, data mining, bioinformatics, and combinatorial analysis. PROOF performs this activity in-house via its computational team.

#### **3.2.1.2 Biomarker Validation**

The output of biomarker discovery activities is a set of biomarker panels that each have the potential to distinguish amongst two or more types of patients. Once a set of biomarker panels is identified, PROOF must determine which panel is the most promising. This activity is called biomarker panel refinement. It involves testing different computational, statistical, and combinatorial methods to identify a robust discriminative biomarker panel. PROOF's computational team performs this step internally.

Once the biomarker panel has been refined, the next step is internal validation. The goal of internal validation is to test the performance of the biomarker panel in a different cohort of patients. This is primarily a computational activity involving rigorous

testing of the sensitivity, specificity, and diagnostic power of the test. PROOF typically performs this step via its computational team.

### **3.2.1.3 Assay Development and Validation**

The goal of assay development and validation is to transfer the internally validated biomarker panel to an assay platform. This is necessary because biomarker discovery platforms generally are not amenable to quantitative biomarker measurement. The first activity involved is developing a laboratory method for assaying the internally validated panel of biomarkers. Biomarker developers must then test the assay's performance in a prospective cohort of patients enrolled at multiple sites. PROOF is carrying out this process in collaboration with several industry partners.

The second step is external qualification. During this process, the firm tests the discriminative power of the biomarker panel in a larger, more diverse patient population. As in biomarker discovery, this requires patient recruitment, sample banking, and sample processing. However, external qualification requires hundreds of patients at multiple clinical sites, ideally internationally. PROOF has established relationships with enrolling sites through its professional networks to support this activity. For example, for the validation phase of PROOF's BiT program, patients are being recruited at thirteen Canadian and two international sites. PROOF contracts these sites to enrol, phenotype, collect, and bank samples from patients according to standard operating procedures that PROOF sets.

The third step is analytical assay validation, which tests the reproducibility and variability of the method used to measure biomarkers. PROOF has not reached this step

in the value chain for any of its programs. The organization plans to carry this activity out in collaboration with a partner having more experience in assay validation.

#### **3.2.1.4 Molecular Test Development and Analytical Validation**

The output from the previous phase of development is an externally validated assay that individual clinical laboratories could deploy as a laboratory-developed test (LDT). Currently, clinical labs can perform LDTs without requiring FDA approval. The fourth primary activity in the value creation process for new molecular test development involves converting an LDT into an FDA-approved molecular test. This involves transitioning the assay from a validation platform to a FDA-approved clinical platform, and re-validating the test on this platform. Again, PROOF has not reached this activity for any of its programs. The organization plans to pursue these activities within a strategic partnership, or to out-license prior to this stage.

#### **3.2.1.5 Manufacturing and Commercialization**

Manufacturing and commercialization is the end game of development of new molecular tests. PROOF does not have expertise in manufacturing, distribution, sales, marketing, or obtaining market approval and reimbursement. Therefore, it is seeking to out-license its products prior to this stage, or at least to heavily engage strategic partners to perform these functions. To build these capabilities internally would require many years and significant resources, neither of which the NCE's timelines permit. Therefore, these steps are given minimal attention here.

### **3.2.2 Support Activities in New Molecular Test Development**

Support activities do not directly create value but enable primary activities (Porter, 1985). A brief overview illustrates how each activity supports PROOF's primary activities discussed above.

#### **3.2.2.1 Technology Development**

Technology development functions support new molecular test development in three key areas: platform development, new assay development, and computational method development. Development of new technology platforms enables measurement of biomarker panels using clinically applicable platforms. This has thus far not been a major focus for PROOF, although it is at the early stages of developing MRM-MS technology for multiplex protein measurement in the clinical setting. New assay development is underway, heavily supported by industrial partners for the BiT program. Computational method development is a key internal strength for the organization, as has been discussed.

#### **3.2.2.2 Procurement**

Procurement refers to the ability of the organization to obtain the inputs critical to the value creation process. This includes patient samples, financial resources, platform technologies, and general relationship management. Patient samples are the critical input for high-quality biomarker discovery efforts. PROOF has been very successful at gaining access to patient cohorts by leveraging its clinical and industrial networks. As has been discussed, PROOF has also been highly successful at attracting financial and in-kind

inputs beyond the initial NCE investment. It has accessed the platform technologies necessary to enable biomarker discovery, qualification, and commercialization through partnerships with other non-profit organizations and for-profit firms. PROOF has accomplished this through highly successful management of relationships.

### **3.2.2.3 Firm Infrastructure**

PROOF's general management, financial management, intellectual property management, and business development capability underlie all of the organization's primary activities. General management encompasses many activities and includes quality control and regulatory affairs supporting early interactions with regulatory authorities. In most cases, PROOF has built general management capabilities on an as-needed basis. Overall, this has been successful approach. Financial management refers to the ability of the firm to obtain, manage, and sustain the resources necessary for new molecular test development. This will become increasingly important for PROOF as its programs mature into the costly assay and molecular test development and validation stages. Intellectual property management is an essential activity that can directly affect value in the later primary activities. If potential partners perceive the intellectual property around biomarker panels to be insufficient, the value of potential out-licensing deals decreases dramatically. Finally, PROOF needs access to key industry inputs to support all five primary activities, and therefore, business development activities are essential for PROOF's success. For example, the organization may need validated antibodies for assay and molecular test development. PROOF will have to develop relationships with potential industry partners to fulfil this need. Furthermore, business development activities are

essential for attracting potential out-licensing deals with pharmaceutical, biotechnology, and/or diagnostic firms.

#### **3.2.2.4 Human Resources Management**

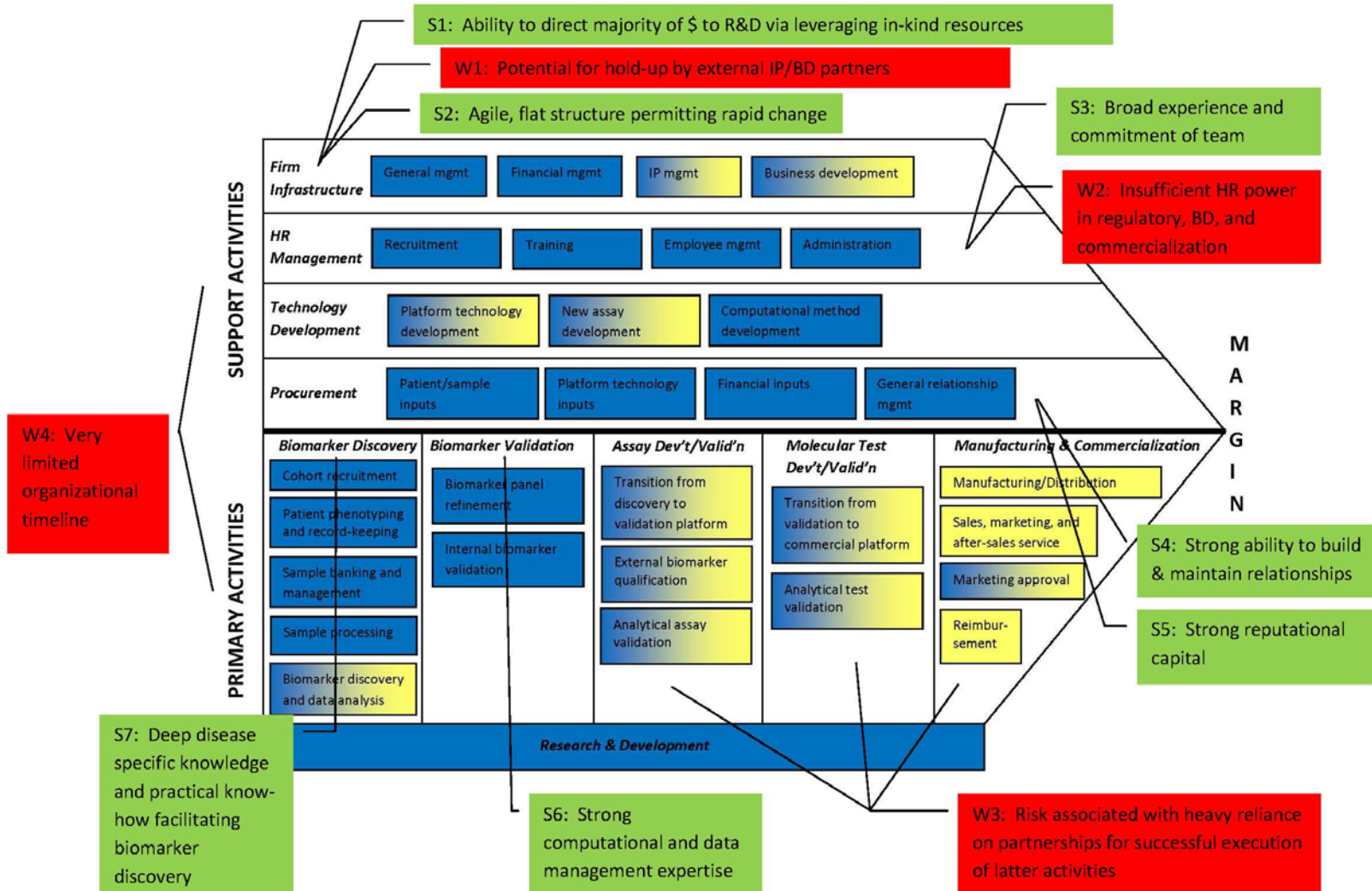
Human resources management includes all activities related to recruitment, development, and retention of the organizational workforce. This function is essential for the effective deployment of human resources to support PROOF's primary activities.

### **3.3 Where is PROOF's Competitive Advantage?**

Preceding sub-sections identified the strengths and weaknesses in PROOF's arsenal of resources and capabilities, and explained the primary and support activities in the value chain for new molecular test creation. In order to identify PROOF's competitive advantage, it is useful to map the organization's critical strengths and weaknesses onto a value chain indentifying the activities that PROOF does and does not perform itself (Duncan et al., 1998). Figure 3-3 summarizes this information using the value creation process outlined above in Figure 3-2. The activities that PROOF performs itself are shown in blue. The activities that PROOF performs (or intends to perform) in partnership or via contracting out are shown in mixed yellow/blue. Activities that are outsourced entirely are shown in yellow. Organizational strengths and weaknesses are depicted in green and red, respectively, and have been mapped to the primary and/or support activities that they impact most directly.



**Figure 3-3: PROOF's Strengths and Weaknesses in the Value Creation Process for New Molecular Tests**



Source: by author, adapted from Porter, 1985 and Duncan, 1998

Figure 3-3 reveals the focus of PROOF's activities within the value chain for new molecular tests. It also clarifies the positioning of PROOF's strengths and weaknesses within the value chain. Subsequent sections will elaborate on these issues separately.

### **3.3.1 PROOF's Position in the Value Creation Process for New Molecular Tests**

One can summarize PROOF's business model as follows. First, PROOF aims to offer best-in-class organ failure-related biomarker discovery and development services. This is the organization's unique value proposition. PROOF's goal is to own and develop intellectual property to the point that a pharmaceutical, biotechnology, or diagnostics firm is interested in in-licensing it. Thus, as is evident from Figure 3-3, PROOF's activities focus primarily on biomarker discovery, biomarker validation, and assay development and validation. An alternative strategy would be for PROOF to form a for-profit arm and sell molecular tests itself, which would require development of end-to-end capabilities across the entire spectrum of primary activities.

PROOF's model for revenue generation combines revenues from out-licensing deals (some combination of upfront payment, milestone payments, and/or royalties on sales of any commercialized products), contract services, and direct product sales should the organization opt to market its own products. Along the pathway of primary activities from biomarker discovery to new product manufacturing and commercialization, the original knowledge inputs become progressively more valuable. Therefore, the value PROOF could obtain from out-licensing is almost certainly greater the further developed the intellectual property is.

Figure 3-3 shows that PROOF's internal focus is on biomarker discovery and validation, general R&D, and certain support activities. This reflects the organization's strategy of out-licensing programs prior to full commercialization.

### **3.3.2 PROOF's Critical Strengths and Weaknesses**

The essential step in internal analysis is assessment of the relative contribution of a firm's strengths and weaknesses to competitive advantage based on their value, rarity, imitability, and sustainability (Duncan et al., 1998). Figure 3-3 maps out PROOF's key internal strengths and weaknesses in the context of the value creation process. This section will analyze these in turn.

First, PROOF has very successfully leveraged its relationships and its unique status as a university-affiliated non-profit to access in-kind resources. This has allowed it to direct most of its financial resources towards productive R&D. Secondly, a variety of academic, clinical, and industrial partners perceive PROOF as neutral because it is a non-profit. This perception, combined with PROOF's skill in relationship management, has given PROOF strong reputational and relationship-building capital. Third, the organization's agile structure, arising from cross-disciplinary team members and close affiliations with external organizations, allows it to adapt to changing priorities and environments. Finally, the organization has attracted and nurtured highly trained personnel holding deep domain-specific and cross-disciplinary knowledge in organ failure and in computational and data management strategies. Each of these strengths provides value to PROOF's clients, is rare amongst the organization's competitors, is difficult to imitate, and can be sustained.

From the perspective of rarity, imitability, and sustainability, two critical weaknesses stand out for PROOF. First, PROOF's NCE-imposed 5-year timeline seriously undermines the firm's ability to execute all of its other activities by limiting the organization's continued ability to build sustainable strengths. Few competing organizations face such limitations. Secondly, PROOF intends to rely on partnerships to support late-stage primary activities. PROOF likely lacks sufficient power and expertise to support maximally effective business development, regulatory affairs, and commercialization activities. It is therefore heavily reliant on the ability to form strategic partnerships and/or out-licensing deals with commercial partners. This is not surprising; indeed, few organizations hold end-to-end capabilities from biomarker discovery to molecular test manufacturing and commercialization. PROOF's timelines are likely too short to build these capabilities internally. Nevertheless, reliance on external partners makes PROOF subject to the changing fortunes of other organizations and industries. There is a significant risk that the organization may not be able to access the necessary expertise or forge the critical partnerships necessary to bring its products to market.

To summarize, PROOF is operating in rapidly changing, nascent industries. The organization must remain cognizant of the impact these internal weaknesses may have on its ability to compete successfully in these industries.

### **3.4 Summary: How PROOF's Internal Situation Drives Competitive Advantage**

This chapter assessed PROOF's resources and capabilities and reviewed the different primary and support activities required to bring a new molecular test to market. Analysis of the value creation process for new molecular tests showed that PROOF's

activities mainly focus on biomarker discovery, biomarker qualification, and early assay development and validation. Internal analysis identified several weaknesses of PROOF's, namely the organization's limited timelines and its related heavy reliance on partnerships. Both of these weaknesses increase the firm's vulnerability to competition in its chosen industries. However, the analysis also identified several key strengths: outstanding reputational and relationship-building capital, deep domain-specific knowledge, structural agility, and financial resource management. These strengths are at the heart of PROOF's competitive advantage. The remainder of the analysis will identify ways in which PROOF might nurture its strengths while managing its weaknesses in order to compete most effectively in its chosen industries.

## **4: PROOF'S CURRENT STRATEGY AND EXPECTED OUTCOMES**

This section will summarize PROOF's current strategy and assess the likely outcomes of this strategy. This part of the analysis will lay the framework for generation, evaluation and recommendation of strategic alternatives in the forthcoming chapter.

Strategy can be considered at four distinct levels: corporate, positioning, competitive, and functional strategy. At the corporate level, PROOF is in the business of discovery and development of biomarkers of organ health and disease. Positioning and competitive strategies summarize the customer segments that the organization targets, and how it competes in these segments. These business-unit levels of strategy will be the focus of this section. Functional strategy, which defines how various functional areas support higher-level strategy, will not receive significant attention here.

### **4.1 PROOF's Current Business Strategy: Develop and Outlicense Highly Differentiated Biomarker IP**

PROOF is developing high performance biomarker panels for the end user. The organization's goal is to add value to intellectual property to the point that an industry client decides to in-license it. Internal analysis (see Chapter 3) showed that PROOF is very development-oriented, with relatively less orientation towards production and marketing issues. The positioning and competitive stances outlined below therefore reflect the *intended* strategies at the commercialization stage of the value creation process and may change as PROOF's biomarker programs mature.

#### 4.1.1 PROOF has a Niche Positioning Strategy

PROOF's general positioning strategy for its products is niche-focused. PROOF aims to differentiate its products from existing alternatives (where they exist) in niche segments of the market for diagnostics/prognostics for organ health and disease. The organization's programs are positioned to yield validated biomarkers for clinical care or industry use, as summarized in Table 4-1.

**Table 4-1: Positioning Strategy for PROOF's Major Programs**

<b>Program</b>	<b>Positioning Strategy</b>
Biomarkers in Transplantation	Molecular tests for use in transplant centres, just before/after transplant
Chronic Kidney Disease	Molecular tests for nephrologists to predict disease outcomes in newly diagnosed CKD patients
Chronic Obstructive Pulmonary Disease	a. Molecular tests for pulmonary doctors to predict (severity of) COPD in new or at-risk patients b. Validated biomarkers used for internal drug company decision-making
Chronic Heart Failure	Molecular tests for family doctors to identify the subtype of CHF that a newly diagnosed patient
Early Diagnosis of Cardiovascular Disease	Molecular test for hospital-/lab-based diagnosis of CVD

*Source: by author*

#### 4.1.2 Competitive Strategy

At this point, PROOF intends to take a mixed approach to competitive strategy, combining differentiation and cost leadership. PROOF is pursuing this high degree of differentiation in its development programs through the following strategic choices:

- Carrying out discovery work in well-phenotyped patient cohorts with very high sample collection and sample management standards

- Designing biomarker discovery programs on the basis of detailed feedback from clinical thought leaders about where in the continuum of clinical care there is a need for new molecular tests
- Utilizing state-of-the-art computational and statistical methods for achieving the best possible biomarker panel performance
- Engaging industrial, government, clinical, patient, payer, academic and regulatory groups to “kick the tires” and refine biomarker development programs accordingly

Highly differentiated products tend to be more highly priced than alternatives. Indeed, most molecular tests that are marketed are priced at several thousand dollars, compared to traditional (less differentiated) diagnostics that cost less than \$100 (PriceWaterhouseCoopers, 2009b). However, PROOF management also has a strong desire to bring its molecular tests to the market at a reasonable cost. It will be difficult to achieve both a high degree of differentiation (e.g. a highly complex biomarker based test for use in the clinic) and a low or moderate cost. Trade-offs between these two goals will likely need to be made en route to commercialization. If biomarker programs are out-licensed to commercialization agents, PROOF will probably lose any influence over the ultimate cost of the products arising from its biomarker programs.

To summarize, internal analysis (Chapter 3) showed that PROOF’s current focus is primarily on the earlier stages of the value creation process for new molecular diagnostics. The organization does not have the internal capabilities or resources to bring new molecular tests to market alone. PROOF is therefore pursuing joint development,



out-licensing or sale of intellectual property to industrial recipients as the intended route to production and commercialization of its products.

#### **4.2 Successful Out-licensing is Likely, But Will it Happen Soon Enough?**

All of PROOF's programs are presently too immature for out-licensing. However, it is very likely that PROOF will be able to out-license at least one of its biomarker programs as they mature over the next 1-3 years. The market for molecular tests is predicted to grow at a 14% compound annual growth rate, reaching \$5 billion by 2012 (Aspinall & Hamermesh, 2007). Both pharmaceutical and diagnostics firms need access to biomarker content to support their activities and pipelines.

PROOF has very successfully nurtured relationships with large pharmaceutical companies. Indeed, PROOF has existing collaborations and/or has held exploratory partnering conversations with four of the ten largest global pharmaceutical companies. A major diagnostics firm holds an option to out-license intellectual property on one of PROOF's programs, and it is likely that PROOF's business development activities will yield other such deals. Thus, there is reason for optimism about PROOF's ability to attract potential licensors.

Despite this optimism, PROOF's biomarker programs still require significant maturation before they will attract external licensing interest. One corporate partner has indicated that clinical validation will be required in order for their firm to consider in-licensing. In other words, PROOF will have to fund development of its biomarker programs at least to the stage of a multi-site national or international clinical trial as it has done for the BiT program. PROOF's programs may not achieve the developmental

maturity necessary for out-licensing within the organization's time horizon. Moreover, licensing deals for biomarker IP typically involve some combination of up-front payments, development milestones, and royalties on any sales (PriceWaterhouseCoopers, 2009a). Licensors may not receive revenues from development milestones and sales royalties for some time, if at all. It is thus unclear whether PROOF will be able to harvest revenues arising from out-licensed programs in time to fulfil its sustainability mandate.

### **4.3 The Critical Issue: PROOF's 2013 Sustainability Horizon**

PROOF's current strategy is to focus on developing biomarker intellectual property, and to out-license biomarker programs to a commercialization agent for production, marketing, reimbursement, and sales activities. This approach is likely to be successful for at least some of the organization's biomarker programs. However, it remains unclear whether this plan will yield the financial returns necessary to achieve organizational sustainability within the 5-year timeline imposed by PROOF's sponsor.

The experience of the Canadian Genetic Diseases Network (CGDN), one of the first NCE-funded networks, reinforces the challenge facing PROOF. Despite its reputation as perhaps the most successful NCE network, it took the CGDN three funding terms—more than 10 years—to begin to achieve the commercialization goals that the NCE had set out in the first term (Atkinson-Grosjean, 2006). This reinforces the assertion that PROOF's biggest issue will be achieving sustainability by 2013. The next chapter will propose and evaluate several alternatives for PROOF going forward.

## **5: ANALYSIS OF PROOF'S STRATEGIC ALTERNATIVES**

Chapter 5 identified PROOF's critical challenge as meeting the NCE's requirement for sustainability by 2013. This chapter will describe and evaluate the strategic alternatives available to PROOF. Alternatives will be assessed using multi-goal analysis since PROOF is a not-for-profit institution with mandates and values that go beyond loss minimization (Boardman, Shapiro, & Vining, 2004).

### **5.1 PROOF's Strategic Alternatives for Near-Term Sustainability**

Based on the external and internal analyses performed in previous chapters, PROOF has several alternatives:

#### **5.1.1 Alternative 1: Maintain status quo**

PROOF's first alternative is to continue to seek out-licensing/joint development opportunities for biomarker programs. This would allow the organization to continue to focus on its internal strengths in early-stage, clinically driven biomarker R&D. This alternative would require PROOF to gain clinical validation for at least some of its biomarker programs through multi-site clinical trials. The organization would have to access additional resources—primarily in the form of non-dilutive grants and additional financial or in-kind donations—to fund this development. This should not present a major hurdle, given PROOF's historical success at identifying and capturing resources. However, under this scenario the organization would almost certainly lose control over the intellectual property, and therefore the ultimate pricing strategy, for its products.

### **5.1.2 Alternative 2: Spin out one or more programs into a biomarker R&D firm**

This alternative would require out-licensing one or more of its programs to a new spin-out company. Under this alternative, PROOF could maintain more of a relationship with the licensee and therefore potentially maintain more control over the ultimate fate of the IP arising from the out-licensed program(s). As with an out-licensing deal to an external entity, formation of a spin-out arm would yield revenues for PROOF. However, spin-out formation would depend on access to seed financing through angel investors, grant funding, and/or venture capital. It is difficult to assess the availability of funding for molecular test start-ups because deal terms are rarely disclosed in this industry (PriceWaterhouseCoopers, 2009a). However, there are many examples of creative ways to finance diagnostics spin-outs. For example, Arctic Diagnostics Inc. ([www.arcticdx.com](http://www.arcticdx.com)), spun out from a university research project, has thus far utilized 3F funding and non-dilutive grants to fund operations. The firm has maintained low overhead costs by headquartering within a technology incubator facility in Toronto. Both of these strategies could also be adopted by a PROOF spin-out.

### **5.1.3 Alternative 3: Expand contract computational services offerings**

A third alternative is for PROOF to offer contract computational and statistical services for biomarker development. PROOF has not conducted a thorough assessment of the market potential for contract services in biomarker data management and analysis. Presuming a stable or growing market for PROOF's contract computational and statistical services, this alternative would increase cash inflows for PROOF in the near term. However, the true value of this option would depend on the transaction costs

associated with managing the relationships with contractors. The cost of engaging PROOF's computational services in external projects could also be significant because it could delay development of PROOF's internal programs.

#### **5.1.4 Alternative 4: Spin out one or more programs and expand contract services**

A fourth alternative would be to combine spinning out one or more of PROOF's biomarker programs and expanding contract services.

## **5.2 PROOF's Goals**

PROOF's goals reflect the combination of NCE mandates and the vision of the organization's management team. The six key goals of PROOF are as follows. Goals are presented in neutral, non-directional language since alternatives may have either a positive or a negative impact on goals.

### ***(1) Impact on commercialization and clinical implementation of new molecular tests:***

Accelerating the commercialization and clinical implementation of new molecular tests is both an NCE mandate and a deeply held value of PROOF's management team. The organization believes that it is developing biomarker panels that have the potential to revolutionize patient care. There is a strong desire to get these products into the clinic, where they can help the patients that need them, as quickly as possible.

### ***(2) Impact on Canadian capacity for research, development and commercialization:***

The organization has a strong mandate to attract, retain and develop talent. The NCE requires a strong focus on facilitating the growth and success of Canadian companies.

**(3) Impact on short-term revenue generation:** Because of PROOF's 2013 funding horizon, a key consideration for the organization is how each alternative will impact short-term revenue generation.

**(4) Impact on ability to grow internal capabilities:** While PROOF has a funding horizon, management is cautiously optimistic that an additional funding cycle will be accessible through the NCE or another source. The organization therefore values alternatives that will help it development and strengthen capabilities within the value creation process for new molecular tests. These will position PROOF to apply these capabilities successfully to future projects.

**(5) Impact on international profile:** PROOF aims to be internationally recognized as a hub for ground-breaking, clinically applicable biomarker research and development activities. This aligns closely with the overall goals of the NCE CECR program.

**(6) Impact on pricing strategy:** PROOF management would ideally like to retain (some) influence over the market price of the molecular tests that arise from its products.

### **5.3 Multi-Goal Evaluation of PROOF's Strategic Alternatives**

The multi-goal evaluation matrix shown in Table 5-1 assesses the impact of each strategic alternative on the goals outlined above. In order to quantify the impact of each alternative, each of the goals is assigned a weight based on its relative importance to the organization (a percentage, summing to one hundred percent for all the goals). The impact of each goal on each proposed alternative is quantified using a weighted low to high impact scale (e.g. high =5, medium-high=4; medium=3; medium-low=2; low=1).

The product of the weighted goals and the impact values is then quantified and summed

for each alternative. The resulting weighted scores for each alternative quantify the degree to which each alternative fulfils the organization's goals.

The multi-goal analysis matrix reveals that PROOF's most favourable alternative is proceeding with plans to out-license its biomarker programs as they mature. This alternative had very positive impact on four of the six organizational goals considered. On the other hand, the alternative that would have the least impact on goal maximization is expanding contract services offerings, which had a strongly positive impact on only one goal.

**Table 5-1: Multi-Goal Analysis of PROOF’s Strategic Alternatives**

		Strategic Alternatives							
		Maintain Status Quo		Spin Out ≥1 Program		Expand Contract Services		Spin Out ≥1 Program & Expand Contract Services	
Goals	Weight	Impact	Value	Impact	Value	Impact	Value	Impact	Value
Accelerate commercialization and clinical implementation	30%	Medium-High (4)	1.2	Medium (3)	0.9	Low (1)	0.3	Medium-Low (2)	0.6
Develop Canadian capacity for research, development and commercialization	20%	Medium-High (4)	0.8	Medium (3)	0.6	Medium (3)	0.6	Medium (3)	0.6
Maximize short-term revenue generation	20%	Low (1)	0.2	Medium (3)	0.6	High (5)	1.0	Medium-High (4)	0.8
Develop internal capabilities to build long-term sustainability	15%	High (5)	0.75	Low (1)	0.15	Medium (3)	0.45	Medium-Low (2)	0.3
Increase international profile for excellence in biomarker R&D	10%	High (5)	0.5	Medium (3)	0.3	Medium-Low (2)	0.2	Medium-Low (2)	0.2
Maintain influence over pricing strategy	5%	Low (1)	0.05	Medium (3)	0.15	Low (1)	0.05	Medium (3)	0.15
<b>TOTAL</b>			<b>3.5</b>		<b>2.7</b>		<b>2.6</b>		<b>2.65</b>

Source: by author, adapted from framework outlined in Boardman, Shapiro, and Vining (2004).



## **5.4 Sensitivity of PROOF's Multi-Goal Analysis to Different Scenarios**

The multi-goal analysis shown above assumed the most likely scenario—that is, that the future external environment for new molecular tests and biomarkers will be similar to the present one. This scenario assumes that the development costs, regulatory costs, and overall timelines required to bring new molecular tests to market will remain relatively static. It also assumes that the market for new molecular tests will continue to grow, and therefore, that there will continue to be demand for in-licensing deals from pharmaceutical and diagnostic companies. More specifically to PROOF, the most likely scenario is that the organization will continue to be able to access additional resources, through NCE or other vehicles.

However, the analysis of PROOF's alternatives is undoubtedly sensitive to significant changes in the external environment. In the worst case scenario, regulatory requirements would be more burdensome and the market for molecular tests and in-licensing deals would contract, perhaps because of a high-profile failure of a market-approved test. It would be very difficult under this scenario to continue to access additional funds, and the NCE would fail to extend the CECR program beyond 2013. Under this scenario, short-term revenue generation would be much more important while development of Canadian capacity and internal capabilities would be relatively less important. Thus, the multi-goal analysis outcomes would favour different alternatives.

Under the best case scenario, regulatory approvals would become easier, driven by strong patient, payer, and government pressure for accelerating availability of new molecular tests. Seed capital and follow-on funding would be easy to access for small firms operating in the molecular tests space, and the NCE would grant PROOF additional

funding and extend the organization's mandate. Under this scenario, short-term revenue generation would be much less important than building internal capabilities and reputational capital in order to sustain long-term success. This scenario would also shift the relative attractiveness of the proposed alternatives in the multi-goal analysis above.

## **6: SUMMARY AND RECOMMENDATIONS FOR PROOF**

The external analysis, internal analysis, and multi-goal assessment of PROOF's strategic alternatives demonstrate that PROOF's best alternative at the current time is to maintain status quo. The organization should continue to seek out-licensing opportunities for its biomarker programs as they mature. Should PROOF choose to implement this strategy, it would build and capitalize on existing strengths in the early portions of the value creation process. Commercialization partners would retain control of production, marketing, and late-stage commercialization activities. Partnerships and out-licensing deals with industry would be a strong signal of the organization's quality and reputation, and would increase the international profile of PROOF and the Canadian biomarker community. If these deals could be negotiated with Canadian companies, this would give strong evidence for PROOF's capacity to build and support Canadian industry.

There are two major risks associated with this approach. The first is that market demand for in-licensing deals and/or strategic partnerships could be weak when PROOF's programs reach the stage of maturity appropriate for out-licensing. The second is that the NCE may fail to continue sponsoring PROOF beyond 2013, and/or that the organization may be unable to access the resources necessary to bring its programs to a marketable level of maturity.

The lowest ranked strategic alternative is expanding contract computational services offerings. Implementing this alternative would increase short-term revenue generation. However, it would also impose costs: diverting the focus of PROOF's computational team away from PROOF's own projects; and managing marketing, operations, and relationships with contractors to support these services.

PROOF should not consider the recommendation to maintain the status quo the organization's only option. Nor does this recommendation suggest that the organization should continue to do exactly what it is doing now, without changes. The analysis suggests that at the current time, under the current conditions, the most likely alternative to succeed is to continue according to the strategic plan laid out by PROOF. However, the analysis also suggests that the weight of the proposed alternatives is sensitive to changes in the external environment. It will therefore be important for PROOF to continue actively scanning its external environment for relevant changes, and to adjust course accordingly.

Finally, PROOF has an opportunity to influence a critical element in its external environment: the NCE. It is essential for PROOF to develop a political strategy for demonstrating the value of its activities to the NCE. This may help the organization circumvent the looming funding horizon. A political strategy could mobilize the public, industry leaders, and/or other NCEs as partners. Ideally, the strategy would target not only the NCE, but also Industry Canada, from which the NCE's funding flows. Successful political influence would help PROOF shift the most likely scenario to the best case scenario. Under such conditions, PROOF is much more likely to be able to achieve the impact on patient and social health and well-being that it desires.

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