Bridging the "Valley of Death" in stratified medicine: Commercializing molecular diagnostics in oncology

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Bridging the "Valley of Death" in stratified medicine: Commercializing molecular diagnostics in oncology

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Joshua Copp

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Abstract

Historically, the development of molecular companion diagnostics in oncology has underwhelmed the expectation of the medical field since the successful mapping of the human genome a decade ago. There have been several highly successful developments (Her2-neu, Genomic Health, etc.), but not the widespread revolution in clinical practice expected at the turn of the century. The primary goal of this document is to investigate the economics driving molecular diagnostics and its relationship with strategic decisions in developing a diagnostic technology.

The document begins with a broad analysis of the funding environment for molecular and esoteric diagnostics in oncology. Following a discussion of funding sources and current trends, the second section reviews the nature of the projects that funding supports. This is accomplished through a set of detailed case studies of Genomic Health and Immunicon to compare and contrast the strategic decisions that led to value creation events for both companies. Finally, the third section abstracts away from specific cases to develop a strategic analytic framework for evaluating the potential risk-adjusted NPV for a new diagnostic technology. Sensitivity analyses are conducted in addition to a discussion of current events that may change the structure of the underlying decision tree.

The conclusion revisits the topics discussed in the first three sections, connecting the implications of funding on different strategic decisions and chances of success. Areas for further investigation both for inputs to the current model proposed, as well as for more refined versions of the development model are discussed.

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1. Introduction

Stratified medicine, defined as using specific patient population characteristics to guide clinical decisions, has the potential to revolutionize the delivery of oncology therapeutics through enhanced response rates, superior risk stratification, and elimination of trial-and-error delivery of therapy[111]. However, for the past decade, development and adoption of clinically validated molecular diagnostics that enable patient stratification for oncology has been slow[19]. A lack of molecular pathway knowledge, delayed regulatory guidance, misaligned economics and an opaque reimbursement landscape have all contributed to the slow development of targeted therapies[113]. Recent increases in investment and partnership activity by pharmaceutical and diagnostic manufacturers suggest that clinical adoption of molecular diagnostics may accelerate in the future, but many diagnostic technologies are still multiple years away from regulatory approval and clinical adoption[95].

With such a promising technological progress, one must ask why there has not been significant disruption of clinical practice by molecular diagnostics, particularly in a space so scrutinized as oncology. The research sector has not been inactive, with nearly 270,000 articles related to biomarkers published in PubMed over the period 2000-2009[99]. Additionally, while 146 therapies are actively marketed as of 2011, only 30 have a pharmacogenomic biomarker in their label[26, 112]. It is clear that only a few diagnostic companies have managed to bridge the 'valley of death' – the period between company formation and commercial adoption. It is rare to see an industry so poised for significant innovation and yet not seeing significant venture and entrepreneurial activity rapidly pushing the boundaries of industry practice.

The uncertainty over reimbursement and the associated economic risk have been leading factors of this slow development of clinically validated molecular diagnostic technologies[19, 110]. Development of a diagnostic test will only occur if the potential economic gains are in-line with the clinical benefit and the risk inherent in the development of the new technology. For this thesis, I examine the economic dynamics of stratified medicine from the perspective of the diagnostic manufacturer, specifically in the context of 'high-value' molecular diagnostics. For the purpose of this discussion, 'high-value' indicates a list price that is on the order of several thousand dollars, and a technology often involving complex, multivariate algorithms to interpret molecular data.

Specifically, this thesis analyzes the following:

(1) **Funding environment for a 'high-value' diagnostic:** This section examines a fundamental question: for the new project, what resources are already available to bridge the gap from academic spin-out or newly issued patent to commercial viability? In this section I review the major sources of funding specific to oncology diagnostic development, activity in recent years, and the benefits and downsides of

using any one source of capital. Rather than restricting sources of capital to a traditional discussion of venture capital versus strategic partners, I examine alternative sources not often discussed and the potential advantages each source may provide.

(2) **Value drivers for an esoteric molecular diagnostic:** The second section examines the strategic decisions that ultimately determine whether or not a diagnostic manufacturer can achieve commercial adoption. Specific case examples for Genomic Health and Veridex/Immunicon are used to compare and contrast strategic differences in diagnostic development. Key decision variables in diagnostic development are identified, including factors such as development timeline, clinical validity, clinical trial requirements and commercial utility. Additional vignettes are discussed at the close of the chapter to highlight different strategic elements that can influence the development of a diagnostic.

(3) **Decision analytic model of strategic options:** Based on the discussion of where the money comes from (chapter 1) and the projects it has funded (chapter 2), I develop a decision analytic model to evaluate the sensitivity of key strategic decision points and diagnostic economic value to elements of diagnostic development. In the context of the model, I consider how value inflection points develop at different stages, and how this can impact value. Following an analysis of the sensitivities in the model, I provide a discussion of current trends to highlight where opportunities may be developing.

Note for the reader: For the purpose of the analysis contained in this thesis, the perspective largely pertains to the United States. Furthermore, the discussion is largely focused on commercialization of diagnostics within oncology. However, I would expect one would be able to translate some of the strategic factors highlighted by this analysis to environments outside the United States, and/or across different disease classes.

2. Funding for Oncology in Stratified Medicine

Always at the top of mind for the entrepreneur or new project manager is how to both gain access to, and efficiently use, funding. This is particularly relevant for new ventures in life sciences, where development costs to commercialization can be a significant investment. While technical development of a molecular diagnostic is significantly less than a therapeutic at $5-50 million and only takes about 3-5 years[20], funding a venture of this nature will still require resources beyond the means of many entrepreneurs. To evaluate the market for funding these types of ventures, I review major sources of funding and activity over recent years.

Each funding source carries its own advantages and disadvantage, and no one source of capital will likely be sufficient to bridge the gap to commercialization. For example, while venture capital is the most traditional source of capital, trends in funding indicate investors are more receptive to providing capital at later stages of development. Thus, funding from grants, strategic partners, or foundations will likely be necessary to get a new technology to commercialization. Furthermore, grant and foundation funding is typically non-dilutive, providing an extra incentive for securing capital from these sources. This section focuses on current trends and relative advantages of sources of capital, beginning with the most traditional funding before moving into less traditional avenues of funding.

2.1 Venture Capital

Venture capital is almost always a viable funding source in life sciences. Of $21.8 billion invested during 2010, biotechnology and medical devices received the second and fourth largest amount of investment, respectively (Appendix I) [83]. While some researchers have investigated the interest in and success of venture financing for life science firms[7], in this section of the analysis I focus on the activity specifically from the perspective of oncology diagnostics. My intent is to characterize the trends in venture capital investment for a new venture developing a new diagnostic technology.

Discussion of data and methods

Using Thomson VentureXpert, I initially screened for companies in the life sciences, based on the industry codes outlined in Appendix II. Additionally, the initial screen required that a company have received an investment during the period 01/01/1999 to 12/31/2010. This first screen yielded a list of 1,557 US-based companies. This list was further refined with key words, noted in Appendix II, to identify companies in the oncology diagnostics sector. Finally, a review of each company was conducted to ensure it met the category of interest. Filtering in this way yielded a final list of 131 companies involved in diagnostics for oncology. Where possible, data was supplemented from other sources, however it must be noted that not all deals are necessarily made public and even if announced, the details for any one deal may not be released.

Generally speaking, a diagnostic needs to have a platform on which to run, the kit or set of reagents for this test, and a lab in which to perform the test. In order to further characterize investment trends, the companies were divided into three separate groups:

- **Platforms:** Companies manufacturing platforms on which targeted diagnostics could be developed fall into this category. These can be in several technology applications, such as sequencers or high-throughput immunohistochemistry machines. Examples include Illumina, Falcon Genomics, and Celerus Diagnostics.
- **Services:** This category primarily comprises companies that provide tests and testing services through CLIA-certified laboratories. Even if it provides an innovative test, a company using their own CLIA lab as the commercialization channel is included in this category as it is not strictly a manufacturer of a test kit. Examples include Myriad Genetics, Genomic Health, and Clarient.
- **Kits:** These are companies focused on the manufacturing of testing kits with FDA approval, then purchased by clinical testing laboratories. They are differentiated from the Services category primarily in that they are not vertically integrated with the lab, instead serving as a primary supplier to the reference laboratory. Examples include Allegro Diagnostics, Saladax Biomedical, and Onconome.

Different business models have been evolving in the space, and this stratification is undertaken to give an indication of where venture investors have historically shown interest.

Results and conclusions on investment trends

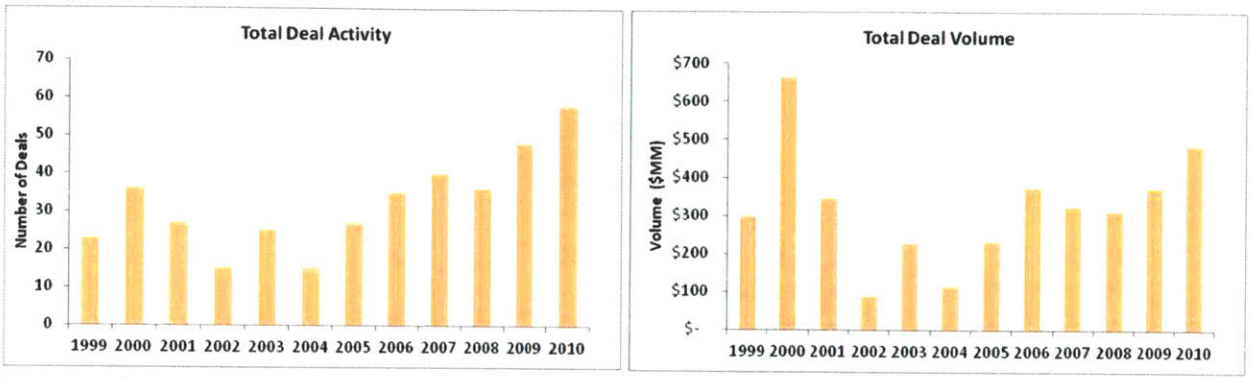
Based on the 131 oncology diagnostic companies identified for the analysis, a total of 385 investments were analyzed over the period 01/01/1999 to 12/31/2010 totaling approximately $3.8 billion dollars, adjusted for inflation and measured in 2010 dollars[a]. Figure 1 shows aggregate deal activity (number of deals) and deal volume (in dollars) from 1999 to 2010. Overall deal activity increased from an average of 24 deals per year for the period 1999 through 2004 to over 40 deals per year from 2004 through 2010, a 73% increase from the first period to the next. Additionally, it is interesting to note that while the technology boom and bust of the early 2000's affected both deal activity and volume quite dramatically, there was only a slight dip to both deal activity and volume in the most recent cycle from 2006-2008, with activity recovering above 2006-2007 levels by 2010.

Figures 2 and 3 capture the breakdown of deal activity by the three groups of companies described above. Overall, Platforms have received the largest aggregate amount of investment, as well as the highest number of investments. Services, however, have seen an increasing level

[a] The GDP deflator published by the BEA (www.bea.gov) was used to calculate the deal volumes in 2010 dollars.

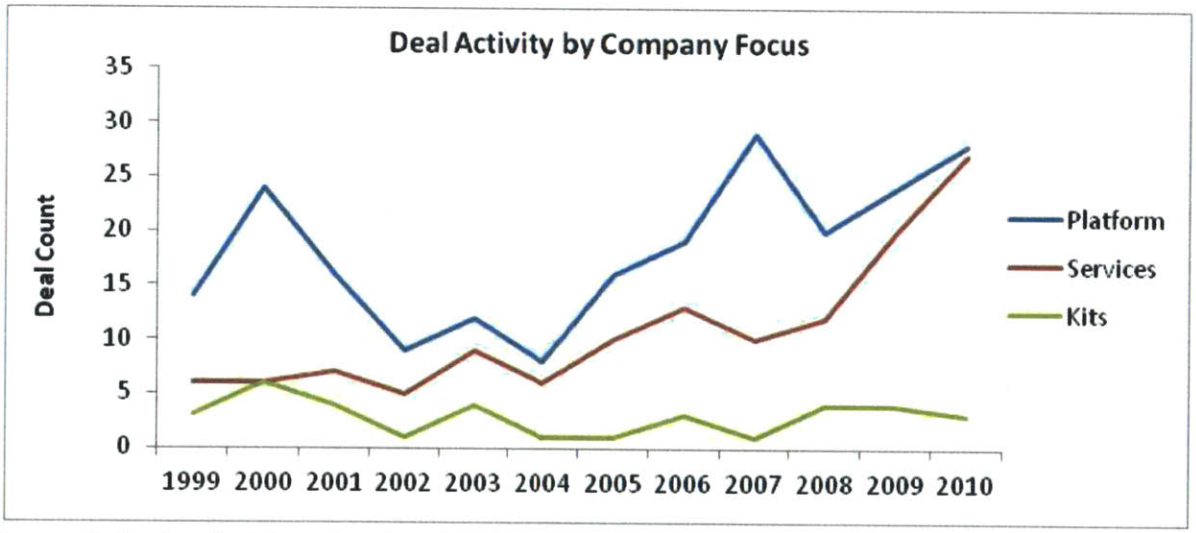
of investment activity, both in aggregate dollar amount invested and number of investments per year. Kits have attracted the least investment activity over the period.

Figure 1: Aggregate Deal Activity and Volume



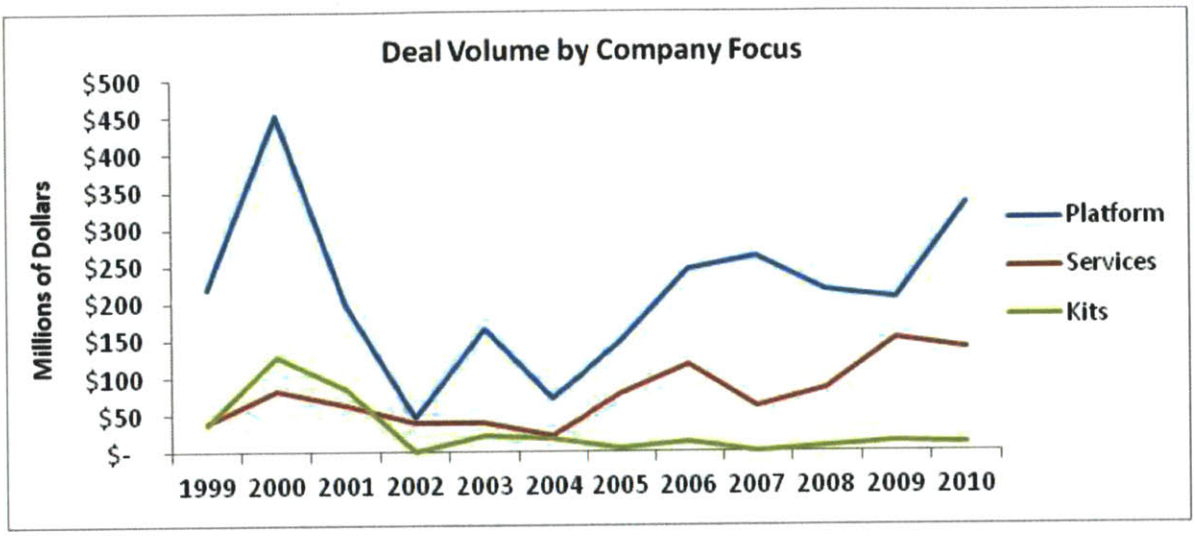
Source: Author's calculations, based on data from Thomson VentureXpert

Figure 2: Deal Activity by Company Business Model



Source: Author's calculations, based on data from Thomson VentureXpert

Figure 3: Deal Volume ($MM) by Company Business Model



Source: Author's calculations, based on data from Thomson VentureXpert

While it is useful to analyze the historical trend of any one of the three categories, care must be taken when drawing comparisons between the different categories shown in the graphs. This is due to the fact that each has a fundamentally distinct investment hypothesis and business model. For example, platforms deliver value to laboratories by providing a large menu of tests that can be run on their technology, representing a recurring set of revenues that pay back the investment in the platform. Furthermore, a large proportion of companies focused on platform technologies cater only to the Research Use Only market (academic labs and pharmaceutical research divisions), and have yet to pursue FDA approval or clinical adoption. Services, by contrast, typically focus on the clinical space, and must prove the clinical utility of their test(s) to both payers and physicians. Both the regulatory requirements for catering to the clinical space and a larger sales and marketing to 'detail' the end customers and promote test adoption constitute a different investment hypothesis when compared to platforms.

Returning to the historical trends for platforms, there are several hypotheses that could describe this investment pattern. For one, the successful mapping of the human genome at the turn of the century certainly helped spur investor interest in the frontier of diagnostic and therapy development platforms. Furthermore, continued scientific discoveries linking genetics to disease have kept genomics a hot topic in biotechnology. Finally, platforms are not restricted to any one indication. It is possible to run tests for oncology, infectious diseases, cardiology, etc. on one platform. For the purpose of this analysis, I have restricted the base set of platform companies to those with specific mention of or applications for oncology.

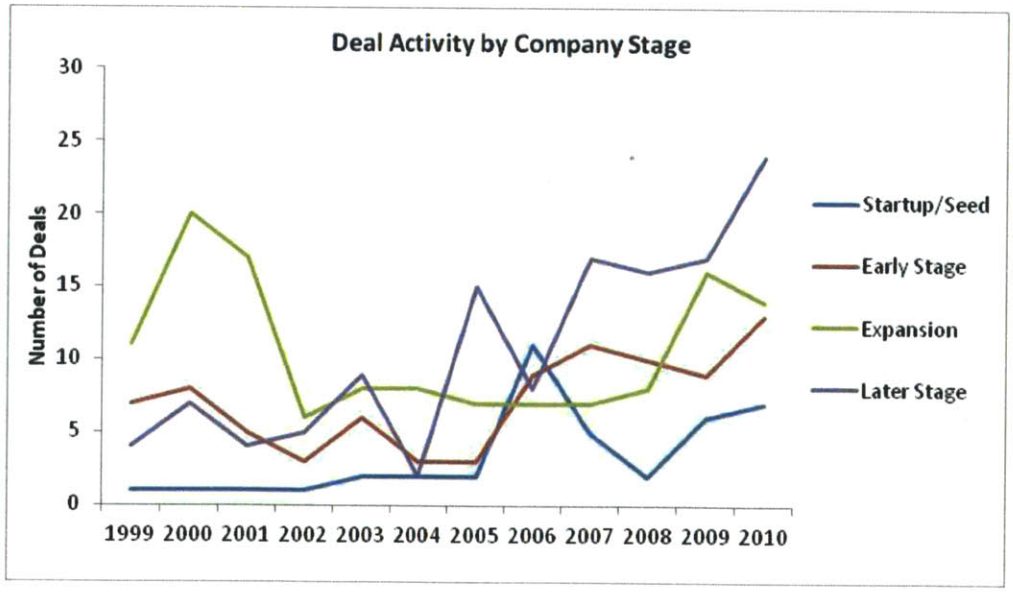
The growth in deal activity and annual investment in services is particularly striking. Both the number of deals and average aggregate amount invested has more than doubled, going from

an average of 7 to 15 deals per year and an average amount invested of $48 to $106 million, respectively. Venture investment has certainly increased as more assays have gained clinical adoption (e.g. Genomic Health's Onco *type* Dx), and the FDA has signaled they are open to the introduction of these tests (e.g. Agendia's *Mammaprint*).

In addition to the analysis by company type, I also stratified companies by the stage at which they receive investment. The goal of this analysis is to determine if there is any indication of investor preference for investment at a particular stage of company development. This is particularly relevant given the launch of the NCI Phase II Bridge grant program in 2009[58]. Intended to serve as a 'bridge' to outside investment, the program is designed to provide up to $3 million over 3 years to support the next stage for existing Phase II projects that aren't quite yet ready for outside investment[128]. This would provide a preliminary indication that investor appetite may be shifting towards those companies that are in a later stage of development.

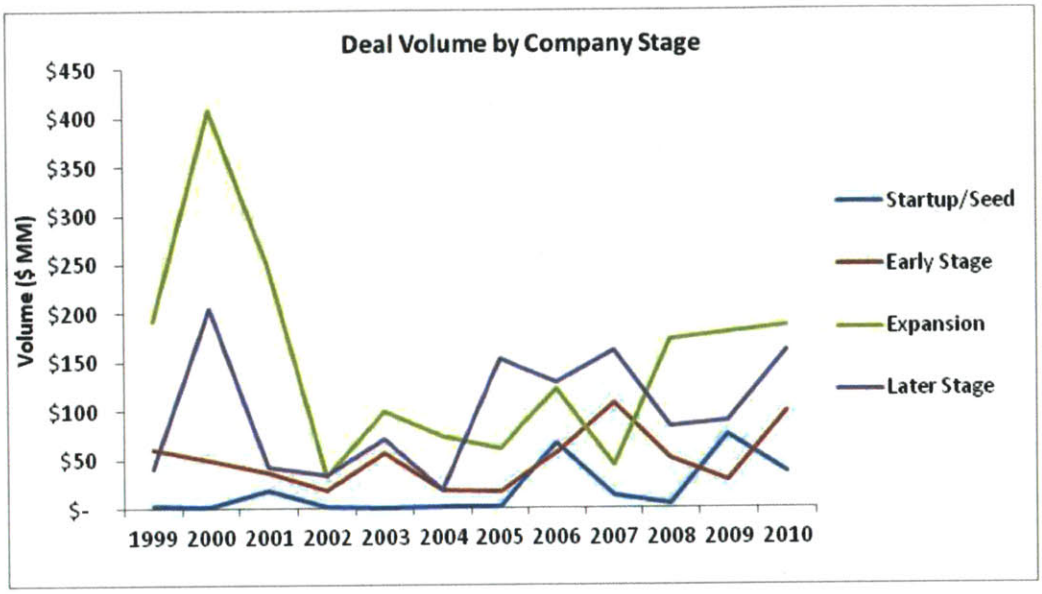
Figures 4 and 5 show deal activity and volume, similar to Figures 2 and 3, but broken down by investment stage. The stages are determined by definitions from Thomson VentureXpert. While early stage investment activity has remained relatively constant over the past 5 years at 10 average deals per year (2006-2010) later stage and expansion investment activity has significantly increased from seven expansion and eight later stage in 2006, to 14 expansion and 24 later stage in 2010. Multiple factors may have driven this increase, from a shift in investor appetite to the general maturing of companies in the space.

Figure 4: Deal Activity by Company Stage



Source: Author's calculations, based on data from Thomson VentureXpert

Figure 5: Deal Volume ($MM) by Company Stage



Source: Author's calculations, based on data from Thomson VentureXpert

Overall, the 73% increase in deal activity and 44% increase in funding volume from 1999-2004 to 2005-2010 represent a strong interest from investors in the sector. Venture capital may present a viable avenue for the entrepreneur attempting to commercialize a diagnostic targeting personalized cancer treatment, and will most likely be needed to fully bridge the gap from research laboratory to clinical adoption.

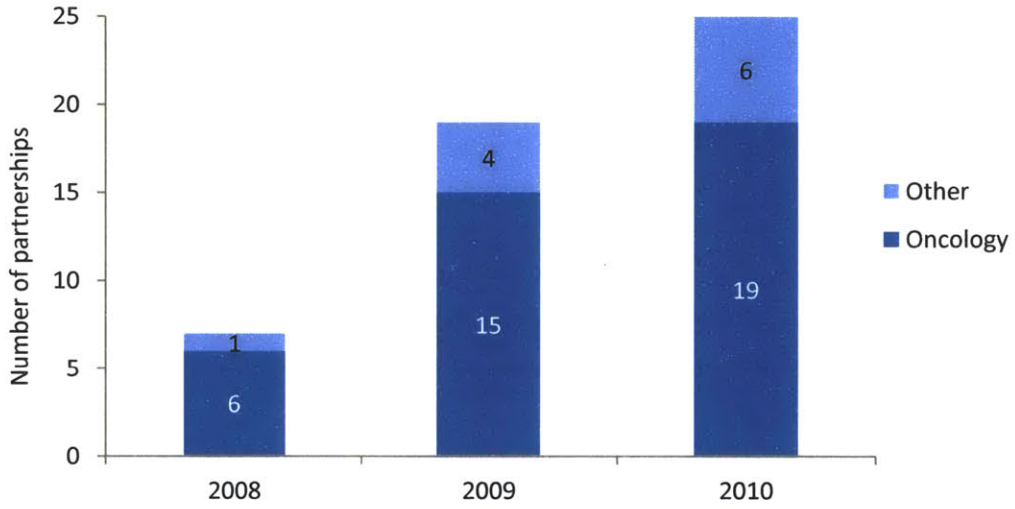
2.2 Strategic Partners: Pharmaceutical and Biotechnology Firms

A strategic partnership with a pharmaceutical or biotechnology firm is the most commonly discussed route to date for the commercialization of a diagnostic in stratified medicine. The landmark development of HercepTest™ by Dako in partnership with Genentech for the administration of trastuzumab (Herceptin) has served as an example of the initial development efforts for companion diagnostics. More recently, the approval of Zelboraf for the treatment of metastatic melanoma patients with active BRAF V600E mutations highlights the increasing partnership activity between therapeutics and manufacturers of molecular diagnostics[87, 95].

From the perspective of the diagnostic entrepreneur, how is it possible to compete with an established diagnostics manufacturer such as Roche or Dako for funding from a large pharmaceutical or biotechnology firm? The historical trend in activity, as described by PriceWaterhouseCoopers in their Diagnostics 2011 report, points to a strong case for specialized knowledge. As shown in Figure 6, there has been a significant increase in the partnership activity between therapeutic manufacturers and diagnostics companies for the development of companion diagnostics, with oncology maintaining the lion's share of these partnerships. Additionally, the partnerships being formed in recent years are not only with

dominant diagnostics manufactures, but also with medium sized firms or niche specialists such as Qiagen or MDxHealth[95].

Figure 6: Oncology partnerships 2008 - 2010



Source: PWC Diagnostics 2011

While the increased partnership activity with medium and smaller companies is a positive indicator for a new venture with unique topic expertise, this activity has been completely concentrated in the development of companion diagnostics. Companion diagnostics, strictly speaking, typically involve the co-development of a diagnostic and therapeutic for a newly discovered cohort of patients based on the biomarker. This means that there is an economic advantage of patent protection for the therapeutic, in addition to the novelty of the diagnostic test.

From the perspective of the entrepreneur, this may not present the most attractive path forward, as the value split between the drug and diagnostic is still heavily tilted in favor of the pharmaceutical company. The marginalization of value captured by the diagnostic test kit is a strong disincentive for development, and historically it seems diagnostic manufacturers have had a difficult time capturing the economic equivalent of the clinical value they deliver by dictating treatment decisions. For example, a Her2-neu test will be reimbursed for $400-800, constituting a market of approximately $250 million in testing every year, while Herceptin has now become a multi-billion dollar drug.

However, from the perspective of the pharmaceutical firm, this arrangement presents the potential for a 'niche-blockbuster' – i.e. a drug that, while restricted to a fraction of the cancer population, commands a significant price premium due to higher response rates and/or better treatment options. As noted by multiple authors to date[95, 111, 113], this presents a potential

attractive model for drug developers going forward, but the value equation between diagnostic and therapeutic will have to shift to encourage innovation on both sides of companion treatment.

2.3 National Cancer Institute: SBIR and STTR Grant Programs

In 1982, the Small Business Innovation Development Act established the Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) grant programs. This act stipulated that for federal agencies with research budgets greater than $100 million, 2.5% and 0.3% of their funding is to be set aside to fund SBIR and STTR grants, respectively[128]. The SBIR grant program is designed to provide funding for small business concerns with the explicit intent to create viable commercial entities from federal R&D dollars. The STTR program is similar to the SBIR program, but differs in that the principal investigator for the research project does not have to be primarily employed by the business concern, and the business concern must have a formal agreement for collaboration with the research partners at associated universities and/or non-profits[128].

As of 2010, the NCI SBIR and STTR programs had allocated budgets of $100 million, ranking them among the top five SBIR and STTR grant programs administered under the National Institutes of Health[128]. The funds are administered through the grant process in one of three phases, and are focused on bridging the gap between research lab and commercial viability. Specifically, they include:

Table 1: Funding Details for NCI SBIR and STTR Programs

	Objective	SBIR Funds	SBIR Time	STTR Funds	STTR Time
Phase I	Feasibility study	$150,000	6 months	$100,000	1 year
Phase II	R&D investment	$1,000,000	2 years	$750,000	2 years
Phase II Bridge	R&D gap funding	$1-3,000,000	1-3 years	n/a	n/a

Source: NCI SBIR website http://sbir.cancer.gov/about/structure/

The SBIR/STTR grant programs at the NCI are attractive first and foremost because they are non-dilutive. Unlike standard private venture financing, no equity stake is awarded for the funding provided. This is significant not only because it improves the entrepreneur's economics, but also because the funding can be used as leverage to secure additional venture financing from more standard sources. According to the NCI, on average funds provided through the STTR and SBIR programs have been leveraged for 2.3 times the amount of the grant in additional forms of financing[128].

However, the program is not without drawbacks. First, there are only select dates on which one can apply for the grant, and the review process can take several months. Second, the process is rather competitive, and if the grant does not score well with reviewers, this could

cost many more months in rewrite, wait and resubmission time. From initial grant submission, a year or two could easily pass before funding is awarded – and there is no guarantee that will be. For many in the field of stratified medicine, the industry is moving too fast to lose a year or two in the grant writing and approval process.

Third, the above phases are not independent: Phase II depends on successful completion of Phase I. Fourth, the grant writer and entrepreneur must realize that the NCI identifies areas of particular interest for investment, including companion diagnostics, and in 2010 committed 24% of grants to those programs[128]. This additional signal from the NCI can potentially reduce the utility of the program to potential applicants if they don't fit within the 24% and reduce the overall applicability of the grants to the field.

Finally, though the grants are generous, it is highly unlikely that a new venture can get to clinical adoption solely on NCI SBIR/STTR grant funding. It may provide enough funds to conduct a retrospective validation study for an assay or biomarker, but a prospective clinical trial will cost significantly more. For example, Genomic Health, which I will discuss in more detail below, spent $42 million in R&D before their IPO and commercial launch of their breast cancer assay. Additionally, there can be a lag between the award date, and the delivery of funds, either because of process delays or because the grant awarded is staged over multiple periods. As such, additional sources of funding will be needed to get an assay to commercial adoption.

2.4 Foundations and Non-Profits

To date, no significant investigation has been made as to the impact of foundation and non-profit funding for the promotion of new technologies in oncology, despite the increasing involvement of these institutions in funding research and venture development. Foundations are particularly relevant to several disease types (cancers, neurological disorders, etc.) as the major organizations often have significant resources at their disposal. For example, the Michael J. Fox Foundation supported $25.9 million in research for Parkinson's disease in 2008 in the US, and the Susan G. Komen Foundation offered $48.5 million in grants supporting breast cancer research in 2011[106].

Case examples demonstrate definitive interest from many foundations in targeted therapeutics, though diagnostics have yet to gain significant interest. For example, in 2011 the Susan G. Komen Foundation awarded two promise grants worth $6.5 million, their largest award. Both focused on personalized medicine and targeted therapies in breast cancer. Furthermore, many of Komen's smaller research grants awarded in 2011 are focused on biomarker discovery. It is likely that grant awards will be largely focused on the development of targeted therapies, more than the development of diagnostics for existing therapies.

2.5 Private payers and insurers

Over the past several decades the funding and development of healthcare innovation has lacked one participant with a large vested interest: the payer. Initially, insurers demonstrated an interest in managing the risk of their patients, as with the Health Insurance Plan (HIP) of Greater New York. In 1963, the HIP sponsored one of the first extensive investigations into the clinical benefit of breast cancer screening[82]. Since that time, however, payer activity in the space has declined significantly.

One hypothesis for this relative lack of interest is that health insurers moved from *managing* risk to *pricing* risk. They have essentially adopted an actuary's approach to controlling health costs: the inherent risk of an adverse event is exogenous to their control, and therefore they must pool a large enough number of patients whose premiums will offset the cost of adverse events. In reality, most individuals understand this is untrue, as health risk is affected by exercise level, diet, and a multitude of other factors. As the movement for better management of health by the individual takes root, one may see the reemergence of the payer as a funder for health innovations that reduce the health risk for patients through behavior and habit modifications.

Reimbursement and coverage decisions at private and public payers are increasingly driven by the ability of a new technology to reduce health risk and system cost. Specifically, the decision to reimburse or not for many payers is fundamentally driven by a pharmacoeconomic analysis of the benefit derived from a drug or device. In its simplest form, this entails an analysis demonstrating how the combination of downstream cost reduction and improvement in quality of life combine such that the price charged is less than (and more often significantly less than) the health-economic value delivered through the intervention. These negotiations can often be difficult in a system with privatized health insurance like the United States. Private payer populations will vary from one insurer to another, potentially presenting different health economic arguments based on the insured populations. This, along with other factors, can affect the extent to which a private payer can appropriate the benefits derived from the new technology, given their insured population.

Given the importance of pricing and the increasing uncertainty over reimbursement, a private insurer as an investor could present multiple advantages. For one, the insurer could provide expert knowledge of pharmacoeconomics and more accurate data on treatment costs and productivity losses for health economic arguments. In an era where diagnostics manufacturers are lobbying for a value-based rather than cost-based approach to reimbursement having an insider's perspective on how to prove and capture that value may greatly enhance the likelihood of securing favorable reimbursement rates. Second, there would be an implicit signal to the market that at least one payer considers the product valuable, and this signal would

come before the technology became available commercially. However, one must keep in mind that this value may only be useful in the later stages of development, and so a payer may not be the most advantageous partner at the earliest stages of development. Finally, one would have to address the perceived risk of freeloading by other private insurance providers. Free-riding describes the instance where one insurance provider is taking on development risk by providing funding for a new technology that will benefit all private insurers should it reach the market. While the exact calculation of this risk is beyond the scope of the thesis, I will note that at first pass, provided a widely adopted technology, this risk is likely offset by the investment gains the investor would have from investing. If value is captured effectively through pricing and market adoption is favorable, then the value of the investment made by the insurance provider should offset some of the risk from freeloading.

2.6 Conclusion and considerations for funding sources

In the sections above, I have identified multiple sources of funding for a new venture, each with its own advantages. However, it is unlikely that any one source of funding will be sufficient to take a new venture all the way to commercial adoption. More often, a mix of different sources will provide the necessary funds to launch a new molecular diagnostic.

From the perspective of the entrepreneur, this is important as it goes against the "standard" funding model. Historically, the assumption was that once one has the idea or preliminary laboratory data that indicates that a biomarker might work, one goes through several rounds of angel and venture capital funding as the product moves through different stages of clinical development. In reality, while a new venture's development path will likely include venture capitalists at some point, it is highly likely that other sources such as government grants, foundations or strategic partners will at some point be necessary sources.

This is particularly relevant given the trend toward later stage financings for venture capital investments. This means that initial development will have to be funded through grants and foundations, and to the extent those are secured, possibly venture capital money. In the absence of grant funding, venture capital funding early in a diagnostic's development is unlikely, if not impossible. Effectively, the power of grant funding is it may help 'de-risk' the company for the investor, leveraging the initial grants into venture investment at an earlier stage of product development. Further work will be needed in policy to effectively characterize the appropriate timing and magnitude of grant programs.

3. Value drivers for independent development of a diagnostic

Key to any entrepreneur's decisions is a comprehensive understanding of the factors that will unlock value for a new innovation. For this discussion, value will largely refer to the risk-adjusted NPV of future cash flows that a diagnostic could generate. Note that there are two fundamental ways value can be 'unlocked': reducing risk associated with the technology and generating cash flows. Ultimately, multiple factors affect these two value drivers clinical, from R&D expenses needed to develop an assay to successfully completing a clinical trial. In this section, I examine in depth the cases of Genomic Health and Veridex LLC, briefly discuss the activities of other companies emerging in the space of esoteric molecular diagnostics, and conclude with a generalized model for value drivers of an independent diagnostics manufacturer.

3.1 The case of Genomic Health

Brief History

Genomic Health was founded in August of 2000 by Randy Scott. Scott got the idea for the company while working at Incyte, a drug discovery and development company focused on oncology and inflammation. At the time, the academic community was pouring immense amounts of effort into genetic research, but with little yield for clinical applications. Furthermore, treatment decisions and risk stratification for cancer patients were informed by many subjective factors, as well as by a physician's experience. Scott decided to start Genomic Health with the goal of delivering high value molecular diagnostics that drive personalized treatment decisions based on a patient's genetic profile[30].

Following its founding, Genomic Health secured five rounds of venture financing before its IPO in September 2005. Table 2 shows a summary of its funding history. In total, Genomic Health raised just over $103 million - a significant sum for a diagnostic service provider - from the venture capital community from 2000 through 2004.

Table 2: Genomic Health Venture Funding History

Genomic Health Venture Investing Summary			
Year	Amount ($000's)	Stage	Series
2000	$ 7,935	Early Stage	A
2001	$ 29,000	Expansion	B
2001	$ 5,000	Later Stage	C
2002	$ 9,400	Later Stage	D
2004	$ 52,294	Later Stage	E
Total:	$ 103,629		

Source: Thomson SDC VentureXpert; Genomic Health S-1 filed September 2005
Note: The $103.6 million raised by Genomic Health is approximately $123.7 million in 2010 dollars.

The company filed for a public offering in July 2005, with the offering taking place in September 2005. Ultimately, its shares were priced at $12.00, with Genomic Health registering 5.02 million shares for net proceeds of $55.8 million. The company had 24.3 million shares of common stock outstanding after the offering, for a total market value of $292 million in September 2005.

Genomic Health's technology

The technology underlying Genomic Health's diagnostic is one of the first successful clinical applications of the Human Genome Project in oncology. Its first commercially developed test in breast cancer, Onco *type* DX™, relies on a technology known as reverse transcriptase-polymerase chain reaction (RT-PCR for short). RNA is formed when a specific enzyme, RNA polymerase, attaches to DNA and moves along the strand adding matching RNA nucleotides to complementary DNA bases. With RT-PCR, an analysis is done by Genomic Health on frozen paraffin-embedded solid tumor samples to extract and purify these RNA strands. Then, a rapid reverse transcription of the RNA to the complementary DNA takes place to effectively reverse engineer the original segments of DNA (genes) that created the RNA.

This technique is attractive for two reasons. First, the reverse transcription process is reproducible and allows for the synthesis of a large amount of DNA complements in a relatively short period of time. Second, the transcription of RNA described above is the first step in gene expression. Therefore, if one can reverse engineer the RNA to DNA, one is able to determine not only if a specific gene is in a person's genome, but also whether or not the gene is expressed. Using RT-PCR, Genomic Health then studied a set of 250 candidate genes to identify the 21 they now use in their diagnostic. Compared to a standard of care that relied on a physician's best judgment, Genomic Health's test offers a clinically validated, quantifiable assessment of a breast cancer patient's risk for recurrence and likelihood for chemotherapy response. To give some sense of the impact of this shift, consider a study comparing NCCN guidelines to Genomic Health's classification of patients by risk of 10-year distant recurrence - Genomic Health's Recurrence Score reclassified 6% of low-risk patients as high-risk, and 49% of high-risk patients as low-risk[37]. This represents a significant change as patients that are high-risk by NCCN would typically receive some form of chemotherapy to treat their breast cancer.

Genomic Health and competition

Genomic Health presents an interesting case because, from the time of the company's founding through IPO, the company did not have any significant direct competition. While research organizations had adopted RT-PCR technology, the clinic had yet to see any diagnostics gain traction. The standard of care they had to supplant was the oncologist's best judgment of risk based on risk factors such as age, tumor grade, and family history. Though changing provider decision-making is still a non-trivial hurdle, lack of competition can lead to more rapid adoption, given clinical validity and utility. For the new venture, Genomic Health provides one template that illustrates an opportunity to dominate a market (cancer prognosis) with a new technology

(gene sequencing), where the standard of care was constrained to an oncologist's best judgment based on non-quantitative factors.

Proving clinical utility

In the case of Genomic Health, a significant amount of resources was spent to prove clinical utility and provide justification for premium pricing for its Onco *type* DX test in breast cancer. From its founding through 2005 Genomic Health spent $47 million on R&D, consuming almost half of the funds it raised to finance the venture to its IPO. From 2006 through 2010, Genomic Health spent another $132 million developing its pipeline of products, with only one additional test for colon cancer launched in 2010. Additionally, in order to ensure adoption of Onco *type* DX in breast cancer, 13 independent studies have been conducted to prove both clinical validity and utility of the assay[31]. Table 3 presents a summary of Genomic Health's results for the past 10 years.

Table 3: Summary of Genomic Health Financial Results 2000-2010

Year	Product Revenues ($000's)	COGS ($000's)	R&D Spend ($000's)	Selling & Marketing ($000's)	G&A ($000's)	List Price ($/test)	Cumulative Tests Ordered	Annual Tests Ordered	Implied Reimburse-ment ($/test)
2000	-	-	169	-	566	-	-	-	-
2001	-	-	11,080	117	2,844	-	-	-	-
2002	-	-	7,053	754	3,753	-	-	-	-
2003	-	-	9,069	2,805	3,686	-	-	-	-
2004	227	1,828	10,040	9,856	3,869	3,460	500	500	454
2005	4,823	6,249	9,465	15,348	6,485	3,460	7,500	7,000	689
2006	27,006	9,908	12,841	24,625	12,765	3,460	21,500	14,000	1,929
2007	62,745	17,331	22,053	36,456	17,849	3,650	46,500	25,000	2,510
2008	108,658	27,185	28,624	46,668	25,617	3,820	85,000	38,500	2,822
2009	146,581	32,562	35,691	61,132	29,564	3,975	135,000	50,000	2,932
2010	174,870	34,634	33,225	71,405	34,913	4,075	190,000	55,000	3,179

Source: Genomic Health S-1, Annual 10-k filings, author's analysis (shaded columns)

What Genomic Health recognized early-on is that one of the biggest hurdles facing the introduction of 'high-value' diagnostics is proving clinical utility. Here I distinguish between clinical validity, defined as gaining regulatory approval to sell a test or drug, and clinical utility, defined as proving there is a health economic benefit to one's drug or test compared to standard practice in order to promote adoption by payers. For most diagnostics introduced over the past several decades, reimbursement and pricing captured so little value relative to drugs that payers paid little attention to the use of the diagnostic for clinical decision making. If a couple hundred dollars were spent on testing, how could that compare to several tens to hundreds of thousands spent on administering treatment to a patient? In this context, for most

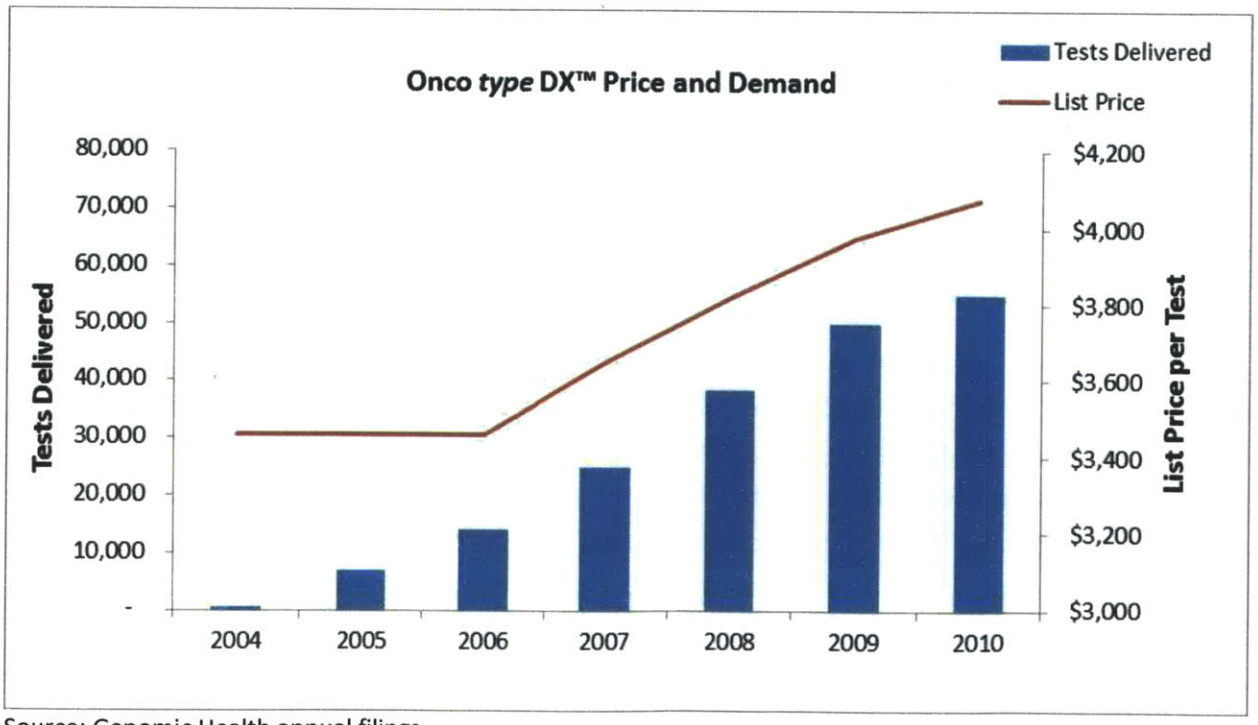
diagnostics proving clinical *validity* was equivalent to proving clinical *utility,* as scrutiny fell to the drug manufacturers to prove clinical utility of their treatments.

However, with the introduction of tests like Onco *type* Dx in the past five years, payers have refocused on diagnostics and are now requiring proof of clinical utility. This stems from the fact that for every five or ten people tested, only one will have a clinical decision changed based on the result of the test. Whether this is to avoid treatment that would be ineffective, or to identify the appropriate treatment, the incremental health economic benefit becomes harder to prove as the price of the test increases ten times. Appendix III presents a simple example to illustrate the health economic considerations for showing clinical utility.

Commercialization strategy and reimbursement

Clearing the clinical utility hurdle was important for Genomic Health because the company approached the clinical diagnostic field with the specific intent to develop 'high-value' diagnostics. Examining Genomic Health's pricing history for Onco *type* DX™ for breast cancer in Figure 7 one can observe that it was able to enter the market at a price an order of magnitude greater than traditional diagnostic pricing levels. When the test was introduced in 2004, the list price was $3,460 and has since been increased to $4,075 at year end 2010. Furthermore, given the significant investment the company made to prove clinical utility, clinical adoption has been rapid over the six years from 2004-2010, totaling approximately 55,000 tests ordered in 2010.

Figure 7: Onco *type* DX breast cancer test list price and unit sales



Source: Genomic Health annual filings

However, critical to Genomic Health's pricing decision was not just proving clinical utility, but also the ability to control pricing for its test. Typically when a new device or test enters the clinical market, there already exists some similar reimbursement code that can be used in place of developing a new code for the test. For example, if a new blood-based biomarker test were introduced, there are already several dozen tests on the market that use a code for blood-based biomarker detection, and set the price point for reimbursement.

In the case of Genomic Health, however, this technological precedent didn't exist. Molecular tests on the market were primarily single gene identification (e.g. Her2), not for multi-gene assays that relied on RT-PCR technology. At one point, the company faced the decision of whether to develop a kit that would be sold to reference laboratories across the nation, or whether to market its test through its own clinically approved (CLIA-certified) laboratory. Pursuing the first option, they would avoid the capital and operating investment needed for a laboratory, but likely would need FDA approval through either 510(k) or PMA approval in order for the test to reach the clinic. Pursuing the second option would allow the company to control how the test was marketed and reimbursed, but would require an additional investment in laboratory space. Genomic Health decided to commercialize the test through a CLIA-certified laboratory it owned and not to develop a commercial kit.

As soon as this decision was made, however, another challenge presented itself. One advantage of selling a commercial kit to reference laboratories is that as the manufacturer, one has mitigated some exposure to reimbursement risk and regulatory change. When a manufacturer commercializes through a CLIA-certified laboratory owned by the company, the company then bears the burden of ensuring that it is being paid for its tests. In the case of Genomic Health, this has been compounded by the fact that their asking price is 10x any other test in the market, and without strong precedent in the clinical market. As such, Genomic Health effectively had to go payer by payer to make the case for the clinical utility of its test, achieving reimbursement from plans covering 90% of covered lives in February 2009, five years after introducing the test[32].

A final point must be noted when considering strategic elements for diagnostic development. A test's list price will not be equivalent to the actual reimbursement paid. Three primary factors contribute to this. First, the largest payer for lab services in the US, Medicare, has federal policies in place that protect against high reimbursement. Currently, reimbursement rates for Medicare are typically 70-80% of the established list price for a testing service. Second, negotiated rates with private payers are undisclosed, allowing for multiple different contracted rates that could be equal to or lower than the list price disclosed by Genomic Health. Third, at times reimbursement must come through the provider (hospital) based on Medicare reimbursement regulations that bundle the total care provided to the patient into one

reimbursed value. Putting the hospital in between Genomic Health and the payer increases the possibility that Genomic Health will perform the test, send the results to a physician, and receive only nominal payment compared to their list price, because whatever is paid to Genomic Health comes out of the lump sum paid to the hospital, directly impacting the hospital's margin on the payment. Examining the list price compared to the implied average reimbursement in Table 3 (product revenues divided by number of tests ordered), I observe that Genomic health has averaged 75% reimbursement rates from 2008 to 2010, indicative of the disconnect between list price and the actual reimbursement obtained.

3.2 The case of Immunicon/Veridex LLC

Thus far I have examined in detail the case for Genomic Health and its RT-PCR assay developed for solid tumor samples. In addition to some of the strategic choices outlined above, a diagnostic developer also has to choose what kind of platform and corresponding tissue type will be best for its test. To date, solid tumor samples and associated tests have garnered the most attention, but there are other options for a developer. I now examine Immunicon/Veridex LLC, a division of Johnson & Johnson that has developed a system comprising a blood-based assay and platform that measures circulating tumor cells (CTCs). The Veridex case provides insight into some key strategic variables in diagnostic development, such as technology platform and sample type, advantages and disadvantages of partnerships, and channel choice for clinical adoption.

Brief History

The original manufacturer of the systems sold by Veridex LLC was founded under the name Immunicon in 1983. In 1999, its business model evolved to focus on the commercialization of circulating tumor cell technology for use in cancer diagnostic tests. Similar to Genomic Health, Immunicon viewed cancer as a field fraught with subjective and inefficient measures used for diagnosis and risk assessment. Central to the company's technology was the ability to predict survival in metastatic breast cancer, providing the potential for early detection, more accurate staging and monitoring of cancer and the ability to influence therapy selection[50]. In order to promote both diagnostic test development and CTC platform adoption, Immunicon entered into a commercial partnership with Veridex, a Johnson & Johnson company, in August of 2000. Under this agreement, Veridex would carry out the marketing and sales functions for the CTC technology in the field of cancer, in return providing Immunicon with a portion of its net sales of any reagents, test kits, or other consumables incorporating Immunicon's CTC technology.

Following Immunicon's shift to focus on CTCs in 1999, it went on to raise seven rounds of venture financing before its IPO in April of 2004 (Table 4). In total, Immunicon raise just over $86 million in venture financing before accessing the public markets, 97% of which was raised over the four years 1999 through 2003.

Table 4: Immunicon Venture Funding History

Immunicon Venture Investing Summary			
Year	Amount ($000's)	Stage	Series
1984	$ 1,500	Seed Stage	Founder
1988	$ 364	Seed Stage	A
1989	$ 300	Seed Stage	B
1990	$ 300	Seed Stage	C
1999	$ 10,597	Early Stage	D
2000	$ 21,612	Later Stage	E
2001	$ 27,142	Later Stage	F-1
2003	$ 24,800	Later Stage	F-2
Total:	$ 86,615		

Source: Thomson VentureXpert; Immunicon S-1 filed April 2004
Note: The $86.6 million raised by Immunicon is approximately $107.3 million in 2010 dollars.

The company filed for a public offering in December 2003, with the offering taking place in April 2004. Ultimately, its shares were priced at $8.00, with Immunicon registering six million shares for net proceeds of $42.9 million. The company had 21.9 million shares of common stock outstanding after the offering, for a total value of approximately $175 million in April 2004.

Following its public offering, the company experienced some success growing the sales of its CTC platform to laboratories. However, by 2007, growth was far short of expectations, and Immunicon executed their right to audit Veridex's effort promoting and selling the kits and products developed for Immunicon's CTC platform. This led to a costly legal battle between Veridex and Immunicon, ultimately pushing Immunicon to file for Chapter 11 protection a year later. Shortly after filing, Veridex acquired the assets of Immunicon for $31 million in cash, ensuring the technology would continue to be developed, but no longer under Immunicon's stewardship.

Immunicon's technology

As mentioned, Immunicon's technology is fundamentally different from that of Genomic Health. Circulating tumor cells are cells found in the bloodstream of patients with metastatic cancer, and are found on the order of 1-10 CTCs per mL of whole blood. By comparison, there would normally be a few million white blood cells, and a few billion red blood cells in a mL of whole blood. The breakthrough for Immunicon was its methodology for imaging the CTC's when so few are available in a sample. In order to measure CTCs, first a binding agent is introduced to a blood sample that will enrich the tumor cells immunomagnetically. Then a stain is introduced with fluorescent antibody conjugates to highlight specific markers when the

sample is scanned. This way, the technology is able to rapidly and accurately image the presence of CTC's for researchers and clinicians.

Circulating tumor cells are an attractive platform for diagnostic development for three key reasons. First, blood samples are much easier to obtain compared to solid tumor samples. Solid tumors can require invasive biopsies to acquire samples, though recent efforts to bank tissues may help reduce patient burden and sample acquisition. Drawing blood, by comparison, is a quick procedure that causes minimal discomfort for the patient. Second, solid tumor samples often suffer from poor sample preparation and heterogeneity in both sample preparation and tumor expression. Blood, on the other hand, has an established sampling and preparation process that reduces much of the variability in sampling found in solid tumors. Third, the test for CTCs provided potentially a much cheaper option to some of the imaging tests needed to detect metastasis of cancer from primary tissues.

Competition

Unlike the case of Genomic Health, competition in circulating tumor cells was already quite heated. Knowledge of CTCs had been around for almost a century, and the fundamental technology underlying the identification of circulating tumor cells, flow cytometry, was already widely adopted into clinical and research laboratories. Flow cytometry is, at its core, a technique for counting and examining microscopic particles and for oncology is most widely used in blood cancers. The difficulty with CTCs in solid tumors, as discussed above, is that there are so few in the blood. The unique aspect of Immunicon's technology was the application to solid tumors, with the intent to use the number of circulating tumor cells as an indicator of tumor aggressiveness and progression.

In this context, it means that Immunicon had to convince laboratories and clinicians of two things. First, that the technology was better than any existing techniques for analyzing blood cell counts, particularly in the context of circulating tumor cells. Second, that the tests Immunicon was going to provide on top of their platform would be better than anything the labs could develop themselves. Essentially, Immunicon faced competition with its own customer base. One can see how the CTC approach to the market faced more friction for clinical adoption relative to a technology like Genomic Health.

Partnership with Veridex and commercialization strategy

A significant decision point for many diagnostic manufacturers is whether or not to form a commercial partnership. These agreements can take many forms, ranging from companion diagnostic development where a diagnostic is explicitly tied to the label for a therapeutic, to commercial arrangements where the development, sales and marketing engines of a larger company promote the adoption of a fledgling start-up's product. In the case of Immunicon, it formed a development and sales license agreement with Veridex, a company backed by the

resources of Johnson & Johnson, that required Immunicon focus on the R&D backing new products, and Veridex handle the sales and marketing efforts for the CellTracks and CellSearch products. In this way, Veridex would not have to bear the large expenses with "detailing" doctors and laboratories, allowing for more effort and resources for R&D as they developed their CTC test and platform technology.

The license agreement is a model example of a commercial license agreement, where the contract is put in place to leverage the expertise of each party. Appendix IV contains the detailed discussion of the license agreement from Immunicon's S-1 filed December 2003. Immunicon, as the technical expert for the product, would manage all new product development and clinical trials associated with the cell analysis systems. For the cost of clinical trials, Immunicon would bear the first $5 million, Veridex the next $5 million, and any costs above $10 million would be negotiated in good faith. Veridex, on the other hand, would handle all sales and marketing related costs, as well as field service for the systems installed. Immunicon would be responsible for the manufacturing of all reagent and consumables, which would be reimbursed by Veridex. Upon the sale of a product, Veridex would pay 30% of net sales to Immunicon as a license fee, after deducting the bulk reagent costs. In this way, the agreement was structured such that Immunicon would gain the sales and marketing horsepower of Johnson & Johnson, and Johnson & Johnson would acquire a new product for which it didn't have to maintain the manufacturing or development expertise.

However, careful consideration of the arrangement highlights a couple of key risks for Immunicon that, in the context of events several years later, may have led to the unraveling of the partnership. First, the agreement was made in 2000, four years before Immunicon would gain clinical validity for its test. This means that, for four years, Immunicon would bear a large portion of the up-front costs associated with developing the product, with no control over the ultimate commercial success of its system. Second, from the details provided in the S-1, it is unclear how Immunicon can obtain any validation that the sales and marketing efforts of Veridex are being conducted to the best of their ability to drive sales volume. Clearly the volume of sales would be one indicator, but it is hard to determine ex-ante whether this would be due to the quality of the product, or the effort expended by Veridex. As such, it may have been more efficient to establish some measure of co-promotion, such that Immunicon could fairly gauge the effort expended by Veridex in the promotion and sale of the CTC systems. Third, while there was an explicit discussion of clinical trials, meant to establish clinical validity, there was no discussion about establishing clinical utility to ensure a laboratory offering the test would actually be paid for running a CellSearch test.

While a different monitoring approach for Immunicon may have helped, a more nuanced appreciation for Veridex's role would also have promoted a better relationship between the

two parties. For Veridex, there's a significant difference between selling platforms and selling tests. When approaching a commercial laboratory with a new platform, the lab wants to see how giving up the several square feet of desktop space for the new platform will benefit them economically. At times this can be determined by even the minutia of seconds saved in processing, but typically the platform's value is primarily driven by the expected volume of tests, and reimbursement per test. Effectively, the lab needs to see a strong ROI proposition in order to adopt the new platform.

However, when selling a new test, two dynamics need to happen. First, a commercial laboratory needs to have the test on hand, or at least want to buy the kit. There is an implicit assumption that a lab, somewhere, has purchased the platform required to run these tests. If true, then demand the lab will ultimately see is mostly driven by demand downstream from ordering physicians. Therefore, for a novel test, Veridex's effort will mainly be spent 'detailing' treating physicians to ensure a commercial laboratory sees enough order volume. The 'detailing' process can be expensive, because you have salespeople covering individual physicians, meeting with them to convince them of the clinical utility of the test.

In the context of these two selling dynamics, Veridex had a significant challenge ahead in promoting commercial adoption of both platform and test kits. On the one hand, the company had to try to sell a novel platform, for which there were only one or two clinically validated tests available. On the other, it was trying to promote adoption of the CellSearch® Circulating Tumor Cells Test on the Immunicon platform. This tension created a dynamic where the laboratory had to believe in the pipeline of tests, not actually validated and launched, to seriously consider the platform, and the physician had to believe there would be enough places from which to order the test. Analyzing the dynamics from this perspective, one can see how Veridex may have put forth the best effort it could, and still fell short of Immunicon's expectations.

Clinical validity versus clinical utility

At Genomic Health, a tremendous amount of effort went into proving clinical utility of the company's test, in addition to achieving clinical validity. In large part this was driven by a need for payer adoption of the test, as Genomic Health would be administering the test through its own CLIA-certified laboratory and depended upon reimbursement for the test. One advantage Genomic Health had was the RT-PCR technology platform had already been adopted into the research and testing space, providing a measure of market familiarity with the results. Manufacturers of these platforms, such as Roche's 454 or Qiagen's Taqman, had been actively building an installed base in laboratories across the US.

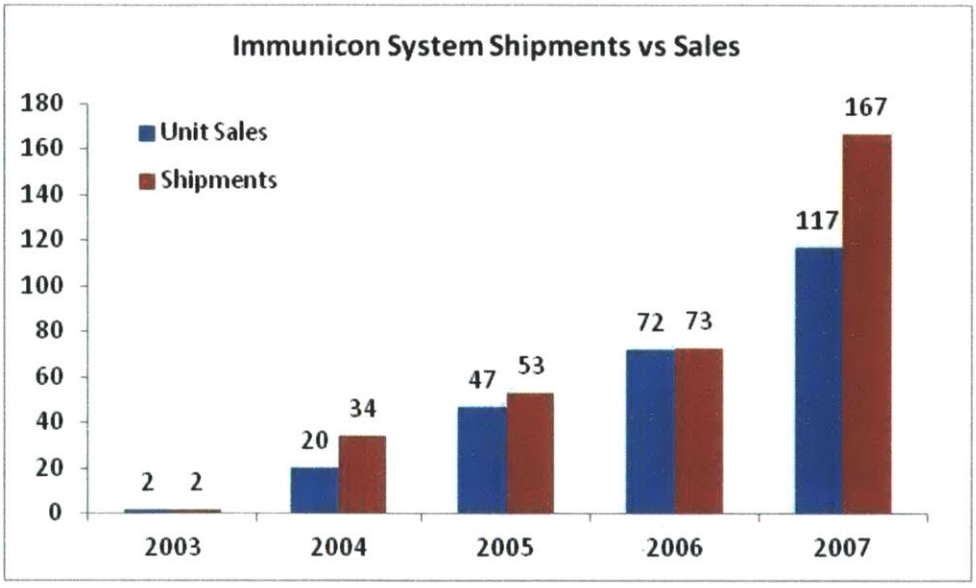
By comparison, circulating tumor cells were still a new technology at the time Immunicon and Veridex began pushing commercial adoption, creating two different hurdles in the marketplace.

First, adoption of the system by clinical reference laboratories would have to take place in order for a market for diagnostic test kits to even exist. Typically, provided clinical validity has been shown, labs will adopt a new testing platform as long as it's expected to generate a high enough volume of tests. Second, payer reimbursement would have to provide enough of a margin to laboratories such that the kits would be adopted and consumed in the testing market. However, for this second hurdle, Veridex-Immunicon had adopted a strategy that provided no direct incentive for proving clinical utility and ensuring test kits were adopted by clinicians. Specifically, proving clinical utility falls in between the responsibilities of Immunicon and Veridex in their partnership agreement. In one part clinical utility is derived from the technical R&D of the testing outcome, but on another it is dependent on understanding the cost constraints of payers and physicians. Additionally, Veridex was selling to the laboratory, and was therefore one step removed from the ultimate consumer of health economic data. In this way, Immunicon and Veridex had no incentive to prove clinical utility of their CTC-based test.

In January of 2004, the FDA cleared the CellSearch System through the 510(k) process as a diagnostic tool for identifying and counting CTCs in a blood sample as predictors of progression-free survival in metastatic breast cancer. Examining Immunicon's historical system shipment and sales data, one can see in Figure 8 that this prompted an initial wave of laboratory adoption of the system, increasing from 34 systems shipped in 2004 to 167 shipped in 2007. The difference between shipment and recognition of sale is driven by an evaluation period for the customer to ensure the necessary training and validation takes place. Note, the data displayed is for aggregate unit shipments, which includes both analyzers and autoprep systems manufactured by Immunicon.

However, while the unit sales were encouraging, the company was not selling them for a profit. For the four years 2004-2007, Immunicon generated $18.1 million in sales from instrument sales that cost the company $18.5 million to manufacture, meaning, on average, they were losing money on every system they sold. While it is impossible to know the exact cause without detailed internal company records, one can imagine factors that might have driven this dynamic. For one, the company could have adopted a penetration pricing strategy, where the first hundred or so units were sold near or slightly below cost to promote adoption, in the anticipation that they could generate positive margins in the future. Alternatively, the company could have viewed the systems as the equivalent of a printer to Hewlett-Packard or razors for Gillette. Selling the system at or slightly above cost would provide the platform for recurring profits from consumable test kits.

Figure 8: Historical Immunicon System Sales and Shipments



Source: Immunicon S-1 filed April 2004, Immunicon 10-k's filed 2005-2007.

Due to the fact that Veridex LLC is a private subsidiary of Johnson & Johnson, one cannot know the exact volumes of test kits ordered to determine whether or not clinical adoption of the test was lagging laboratory adoption of the system. However, from the legal action filed by Immunicon against Veridex in 2007, one can conclude that Immunicon was under the impression that Veridex had "squander(ed) the opportunity to promptly and aggressively launch Immunicon products in 2004," signaling that recurring product test sales were falling far short of expectations. With this knowledge, one can draw a comparison to the decisions Genomic Health made to promote the adoption of its new test. Specifically, investing the time and detailed analysis to prove clinical utility, over and above clinical validity, served as a key factor supporting clinical adoption and appropriate reimbursement.

3.3 Genomic Health and Immunicon: Success or Failure?

The detailed case examples above on Genomic Health and Immunicon highlight multiple dimensions of strategic decisions that affect product development and success of clinical diagnostics. Ultimately, however, the question remains as to whether these two case examples were a success, and if so, by what standards. In this section, I analyze the fundamental and market performance of the companies, and give consideration to the different stakeholders involved in the development of each company.

Genomic Health

A first glance the numbers for Genomic Health indicate the company did moderately well for investors and founders. The company required $103.6 million of nominal investment that funded development until IPO, at which point the company was valued at $292.0 million, for

approximately 2.82x cash-on-cash multiple, or a 182% return on the aggregate cash invested. However, this isn't entirely accurate, because portions of the $103.6 million were invested at different points in time, which affects the average annual return an investor would receive.

To illustrate the effect of timing, consider two extremes. First, if Genomic Health had received the $103.6 million right at founding, taken no additional funding, and successfully gone public at the end of 2005 for $292 million, then the internal rate of return (denoted IRR_5) for this investment would be the rate that solves:

$$-\$103.6 = \frac{\$292}{(1 + IRR_5)^5}$$

or, IRR_5 = 23%. At the other extreme assume Genomic Health, magically, took no investment until the year right before their IPO, at the end of 2004, and then went public for $292 million at year end 2005. In this case, the internal rate of return (denoted IRR_1) would be:

$$-\$103.6 = \frac{\$292}{(1 + IRR_1)^1}$$

or, IRR_1 = 182% (Note this is equivalent to the cash-on-cash multiple above). This methodology can be extrapolated for investments that occur at any point in time, but note that in theory, multiple IRR's may exist due to multiple roots existing in the polynomial.

Using data from Genomic Health's S-1, one can approximate the IRRs earned by the majority investors in the company. I have no knowledge of the exact term sheets arranged between Genomic Health and the company's investors, and have constructed this analysis based on data available from Genomic Health's S-1 filed September 2005. The IRRs shown are at best rough approximations, but do give an idea of the ex-post attractiveness of Genomic Health as an investment.

Figure 9 presents a summary of the data used and analysis output to estimate investor returns. Depending on the round of investment, at the time of IPO most investors made a decent return, averaging between 23-42% IRRs depending on the timing of investment. Note, the founders appear to have done quite well, maintaining a 5.5% stake in the company at the time of IPO with minimal up-front investment of their own. Investors' returns represent a significantly greater performance compared to the general market, where the S&P 500 returned 0.6% on average from year-end 2000 through year-end 2005, including dividends reinvested in the index.

Figure 9: Genomic Health Venture Return Analysis

Genomic Health Venture Investing Summary			
Date	Amount ($000's)	Stage	Round
2000	$ 4	Seed Stage	Founders
2000	$ 7,935	Early Stage	A
2001	$ 29,000	Expansion	B
2001	$ 5,000	Later Stage	C
2002	$ 9,400	Later Stage	D
2004	$ 52,294	Later Stage	E
Total:	$ 103,629		

Immunicon Venture Exit Analysis				
Equivalent Common	Stake	Value at IPO ($000's)	Multiple of Investment	IRR (%)
1,345	5.5%	$ 16,140	4,000	425%
2,645	10.9%	$ 31,740	4.0	32%
5,225	21.5%	$ 62,700	2.2	21%
751	3.1%	$ 9,008	1.8	16%
1,358	5.6%	$ 16,292	1.7	20%
6,890	28.3%	$ 82,684	1.6	58%
5,017	IPO Shares			
24,335	Total Common			
$ 292,025	**IPO Value**			

Source: Genomic Health S-1 filed September 2005; author's analysis

However, for a venture capitalist, this doesn't represent the typical desired magnitude of an exit (a 'home-run'). Typically, the methodology for a venture capital portfolio rests on the assumption that to break even, the investor needs to earn 5-10 times their investment. This is because they expect that ten percent of their investments will succeed, and thus to recoup the nine failed investments, they need ten times their money in one successful one. Considering an investment in Genomic Health generated multiples in the range of 1.5 times to 4.0 times investment, the company represents a positive, but mediocre outcome for the venture investor[b]. Additionally, these multiples were generated on an investment that would be impossible for any single fund. $100-120 million of total investment is a *significant* amount of money for many venture capitalists, and a business plan that is built expecting to raise that magnitude of funding initially will have a difficult time securing funding.

Ultimately, while Genomic Health's returns may not have met the strictest of requirements for a venture capitalist, the company earned significantly above market returns for their investors and founders. In addition, it built a strong pipeline of oncology assays and managed to deliver a wide-spread commercial clinical application of a technology that had largely remained in the research laboratory. In this context the company is a success, though future new ventures will likely have to find more capital-efficient ways to market and clinical adoption.

Immunicon/Veridex

The case of Immunicon presents a similar story at first glance. The company had raised the vast majority of its $86.6 million to develop and commercialize CTC technology, going public at a total enterprise value of $175.5 million. This yielded a 2.0x multiple of value to cash invested in nominal terms, and occurred over a time period similar to Genomic Health. While Immunicon

[b] Note, there are many different styles of investment for venture capitalists, and many different contractual arrangements that can affect the IRR and multiple for any one investor. The analysis here is conducted with data publicly available, and likely there was some variation investor to investor. Certainly a more nuanced analysis giving more insight into the specific investment terms would be intriguing.

doesn't provide enough data in their S-1 to estimate returns based on individual investors, one can still approximate the attractiveness of each series of investment.

Figure 10 presents a summary of the analysis. One can see that, in this case, the founders were effectively diluted out of the company once they decided to focus on circulating tumor cells in the late 1990's. Additionally, the timing of investment mattered in two ways. First, the closer to exit an investor put money into the company, the better its IRR. This makes sense as an IRR will move inverse to the time horizon of the investment, all else equal. Second, if an investor invested in 2000, during the peak year for venture investing, the return was almost equivalent to 'getting your money back' after 3-4 years. While not the worst outcome, it does present an interesting point for fundraising: if you're going to try to raise venture money, it can be advantageous to be fundraising during an up-cycle when it is a fundraiser's market.

Ultimately, Veridex represents a case where the outcome was certainly below expectation, and created relatively little value for investors. Multiple factors likely contributed to this lower than expected outcome, primary among them the decision to pursue platforms, the fact that the technology was not one of the 'new new things,' and the difficulty of raising money during a period of time that was just recovering from the boom and bust of 2000 to 2001. Considering each of these factors carefully, and how strategic decisions can be influenced by each, may have provided Immunicon with a much better outcome at IPO, and potentially in the longer term.

Figure 10: Immunicon Venture Return Analysis

Immunicon Venture Investing Summary			
Year	Amount ($000's)	Stage	Series
1984	$ 1,500	Seed Stage	Founder
1988	$ 364	Seed Stage	A
1989	$ 300	Seed Stage	B
1990	$ 300	Seed Stage	C
1999	$ 10,597	Early Stage	D
2000	$ 21,612	Later Stage	E
2001	$ 27,142	Later Stage	F-1
2003	$ 24,800	Later Stage	F-2
Total:	$ 86,615		

Immunicon Venture Exit Analysis				
Equivalent Common	Stake	Value ($000's)	Multiple of Investment	IRR (%)
10	0.0%	$ 80	0.05	-14%
669	3.1%	$ 5,355	14.71	18%
237	1.1%	$ 1,896	6.32	13%
296	1.3%	$ 2,368	7.89	16%
2,217	10.1%	$ 17,734	1.67	11%
3,059	13.9%	$ 24,472	1.13	3%
4,524*	20.6%	$ 36,191	1.33	10%
4,446*	20.3%	$ 35,567	1.43	43%

IPO Shares	6,000
Total Common	21,934
IPO Value	**$ 175,469**

Source: Immunicon S-1 filed April 2004, author's analysis

*Amount estimated based on pro-rated funding amounts from Thomson SDC VentureXpert

3.4 Additional activity in the high value molecular diagnostic space

In order to highlight several other factors that affect strategic decisions, I now provide a brief discussion of current activity of other companies in the molecular diagnostic space. This discussion is not meant to be comprehensive, but rather to highlight several major strategic

decision points, such as regulatory pathway, tissue selection, competition, market entry and clinical data, that did not come up in the previous case studies.

Agendia & Mammaprint

Agendia's commercial introduction of the Mammaprint test is interesting for this discussion for two specific reasons. First, the company chose to develop a test that relied of fresh tissue samples, not preserved paraffin-embedded tissue samples that can be kept at a lab. This decision is interesting as it may impact the clinical adoption of the test. Fresh tissue samples require more stringent packaging for shipment, and can be exposed to variability in sample preparation. While the company is developing a test that works for formalin-fixed, paraffin-embedded (FFPE) tissue, starting with fresh samples presents its own form of strategic decision point.

Second, the company proactively sought and was awarded FDA in-vitro diagnostics multivariate index assay (IVDMIA) clearance in February 2007. The FDA has ramped up its activity in the IVD space, particularly as it pertains to multiplexing and the use of multiple markers to determine a diagnostic outcome. Pursuing FDA approval from the start, while certainly more costly, may end up saving the company additional clinical development expenses it would have incurred if the FDA chooses to tighten regulation of IVDMIA testing.

bioTheranostics Breast Cancer Index™ (f.k.a. AviaraDX)

As a potential entrant to any market, one must consider the existing competitive dynamics and entry strategy, should entry be a viable option. bioTheranostics, previously known as AviaraDX, represents the third company to market with a breast cancer risk recurrence assay after Genomic Health (first in 2004) and Agendia (second in 2007). While data on whether or not the company has been successful is limited, its proposed launch of the test in 2009 highlights that it would be pricing almost identically with Genomic Health[109], with a list price of $3,000-4,000 dollars. This move - entering the market third with a technology almost identical to the first market entrant - significantly reduces the risk of market adoption for AviaraDX. However, though they benefitted from waiting and learning from Genomic Health, the company will not be able to capture as much upside, given that Genomic Health entered first and captured a network of prescribing oncologists.

MiraDX & PreOvar™

In July 2010 MiraDX commercially launched its PreOvar test for ovarian cancer. The primary use of PreOvar, at this stage, is to determine whether or not female relatives of ovarian cancer patients should be tested for a KRAS-variant as an indicator of risk of developing ovarian cancer. The test has been launched at a list price of $1,295, about one third lower than Genomic Health's Onco *type* DX ™ at the time of commercial launch. At present, the clinical application of the test is not as strong as that of Onco *type* DX. Genomic Health was able to

gain clinical validity for risk of recurrence and, ultimately, chemotherapy response, a powerful tool for an oncologist to use in the treatment of a patient. PreOvar, on the other hand, is still actively conducting clinical trials to define the patients who will derive the most benefit from testing[61]. As a result, they have had to offer a lower list price. This case provides a good example of the power of clinical data to effect the list price for a new diagnostic.

Myriad Genetics & BRCAnalysis™

A discussion involving value in diagnostic testing cannot overlook the success and impact that Myriad Genetics has had on the industry. Founded in 1991, Myriad has been a pioneer in oncology prognostics, and capturing value through a CLIA-certified laboratory. Their seminal test for breast cancer risk, BRCAnalysis, paved the way for a suite of hereditary risk tests for multiple cancers. Additionally, their exclusive licensing with the University of Utah and patenting of genes set an important precedent for intellectual property in the industry.

Once the BRCA1 gene was successfully sequenced in the academic setting, a couple of paths could have promoted commercial adoption. First there was a question of whether to patent or not. Second, if patented, the gene could be licensed broadly, to allow testing in any CLIA-certified laboratory, or it could be exclusively licensed to one party. Myriad chose to secure a patent for both BRCA1 and BRCA2, and to pursue an exclusive relationship with the University of Utah. These two factors, the relationship with academia and patentability of genes, provided a precedent that represented tremendous potential to capture commercial value of new genetic markers. However, one must be aware that the ultimate validity of patents is still not clear, given the recent judicial decisions for Myriad.

4. Decision analytic model to evaluate strategic options in oncology diagnostics

Life science development efforts present an interesting challenge compared to most industries. Consider the uncertainty in two cases: copper mining and a new consumer good. With copper mining, there is technical product risk: one knows that copper can be sold in the open market, but it is uncertain whether it is physically possible to extract the copper from the ground. By comparison, with consumer goods one faces market risk: it is likely a Procter & Gamble or Church & Dwight could develop a new consumer product, but it is uncertain whether that product will actually gain adoption in the market once launched. New enterprises in life sciences face both forms of uncertainty. First, there is no guarantee that a new molecular formulation or device will physically work if introduced to the human body. Second, even if one can design a workable drug or device, the anticipated market for the product may be drastically different thatn expected, or even non-existent. Multiple factors contribute to these two sources of uncertainty, from sheer technical difficulty to uncertainty around payer attitudes.

This two-sided uncertainty in healthcare makes new product development all the more challenging, and requires an approach that can capture the sensitivity of strategic decisions to different assumptions and inputs. In the sections above, I presented how one can fund a new venture and presented case studies to illustrate how one may reach clinical adoption of a new diagnostic. Drawing from these analyses, I now develop a more nuanced model to capture the impact of uncertainty on the strategic decisions facing a new venture in molecular oncology diagnostics. Traditional methods such as NPV and IRR are useful for evaluating projects, but are inherently rigid and can ignore many factors that influence project valuation and strategic decisions. Therefore, this analysis will rely on decision trees to understand a set of the conditions that promote development and clinical adoption of a new molecular diagnostic.

For this analysis, I use prostate cancer to illustrate the impact of different factors on strategic decisions. According to the ACS, in 2012 241,740 men will be diagnosed with prostate cancer, the leading type of cancer among men. Furthermore, 28,170 men will die from prostate cancer, making it the second leading cause of cancer death among men after lung cancer. However, beyond the sheer magnitude of the incidence among men, prostate cancer is also important to consider because its procedures come with severe side effects. Men undergoing procedures for prostate cancer, from biopsies to radical prostatectomy to hormone therapy, often experience severe side effects such as impotence and incontinence.

Despite the severity of side effects and risk associated with misdiagnosis, prostate cancer to date does not have a critical amount of 'high value' diagnostics. Myriad launched the Prolaris® test for prognostic assessment of men with prostate cancer for $3,400 in 2010, and Genomic Health is in the initial stages of developing a prognostic for prostate cancer similar to their Onco

type DX™ test for breast cancer. As such, there is tremendous opportunity for additional progress in the field to enhance prognosis, diagnosis, and treatment in prostate cancer.

For this analysis, I will be using the 2012 version of TreeAge Pro to construct and analyze the strategic decisions facing a new technology today. I will describe the model structure in detail, such that future adaptations can be made with the TreeAge software. For discounted cash flow analyses, Microsoft Excel™ 2007 was used to evaluate different scenarios of market adoption and NPV values for a new diagnostic technology. The thesis will primarily discuss the inputs used, assumptions, results and sensitivities of the model.

4.1 Decision tree model formulation and structure

Before developing any DCF models or partnership NPVs, I first characterize the decision tree structure to understand the primary inputs and data needed. For this analysis, there are several base assumptions I make to avoid continuous recursion between different branches of the decision tree. Specifically, I assume:

Assumption 1: Decision branches are mutually exclusive, and do not allow for switching between different options once a path has been committed. While in reality there are embedded real options in development that capture this flexibility, I will assume that once a project has committed to a particular path, that path will be pursued to its end. For example, if a company begins development independently, I assume that this choice precludes pursuit of partnership opportunities that may arise during further stages of development.

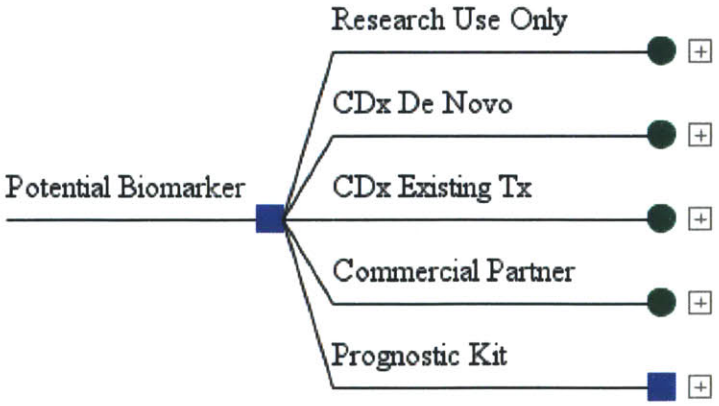
Assumption 2: For this analysis, I assume that there has been enough initial academic work and the project team has enough topic knowledge to begin technical optimization of the diagnostic technology. Said another way, no significant new invention will be needed for the technology to be able to enter initial development phases.

Assumption 3: One can argue that a new technology may be more valuable if owned and developed by an established company (e.g. Roche Diagnostics or Abbott Diagnostics) versus a start-up. This argument mainly stems from the fact that the larger players have established sales & marketing engines and general & administrative backbones that can take a new technology ready for commercial launch and push it to their existing clinical contacts. For this analysis, however, I assume that the incremental sales, marketing, general and administration expense facing an established player are roughly the same as those facing a start-up, as many mature diagnostic manufacturers have yet to achieve success with clinical adoption of genomic and sequencing technology.

Provided the assumptions above, a decision tree for a new technology entering prostate cancer has five fundamental branches:

1. A new technology could move through validation and utility studies with the goal to launch as an enhanced prognostic or recurrence-risk technology. This is the route initially traveled by Genomic Health, Myriad, and many of the tests launched over the past decade.
2. The project could focus on predicting chemotherapy benefit for a subset of patients for an *existing* therapy on the market. Companies have been pursuing this path for many years, but with little yet to show for regulatory or market adoption.
3. Development of a *de novo* companion diagnostic for a therapy in Phase II or III could be undertaken with a pharmaceutical partner. While this hasn't historically been the norm for complex molecular diagnostics, new partnerships indicate activity may increase in the future[24].
4. Similar to the path pursued by Immunicon, a commercial partnership could be established where development and manufacturing are done by the new venture/project, and commercial development is carried out by a more established player with those resources in place.
5. The new technology could stay in the research use only (RUO) segment and cater only to academic and pharmaceutical customers. As the ultimate focus for this thesis is to understand the path for clinical adoption, I view the RUO path as the well-traveled fallback decision against which clinical development pathways are benchmarked.

Graphically, the base branches for the tree are:

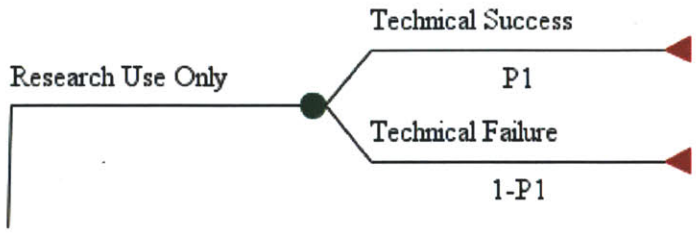


Note: The abbreviations above are CDx = companion diagnostic and Tx = therapeutic.

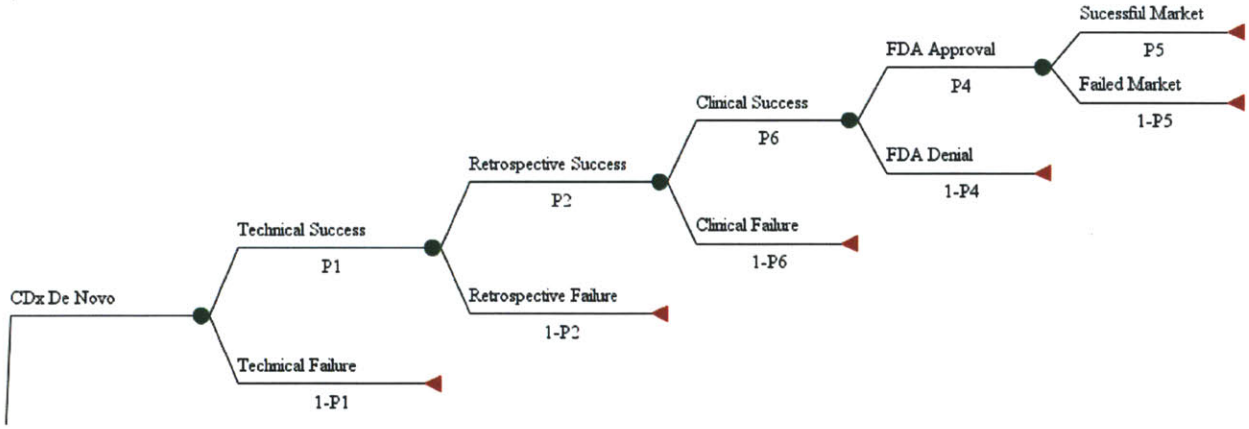
Each branch will carry its own nuances both in structure and data required. Common among all branches is the need for some measure of retrospective validation of the technology. Once

treatment decisions are being impacted, the technology will need to go through an FDA approval process before commercial launch. In the final two commercialization pathways, today there is still the option to go through CLIA certification to enter the market, or to pursue a full FDA approval process. The specifics of the tree structures are reproduced below to illustrate these different pathways. Note, some branches have identical structures, but will differ in their underlying fundamental data values.

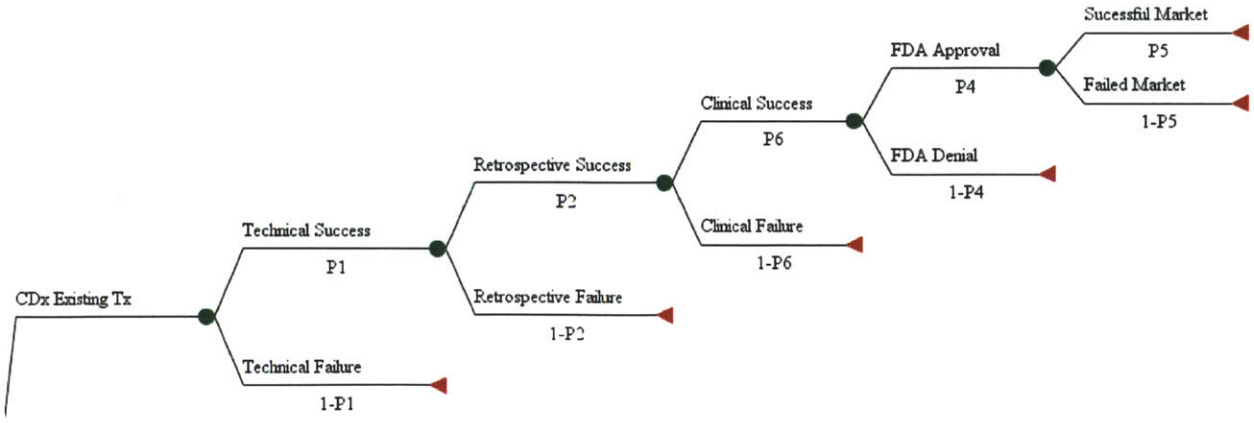
Research Use Only Branch



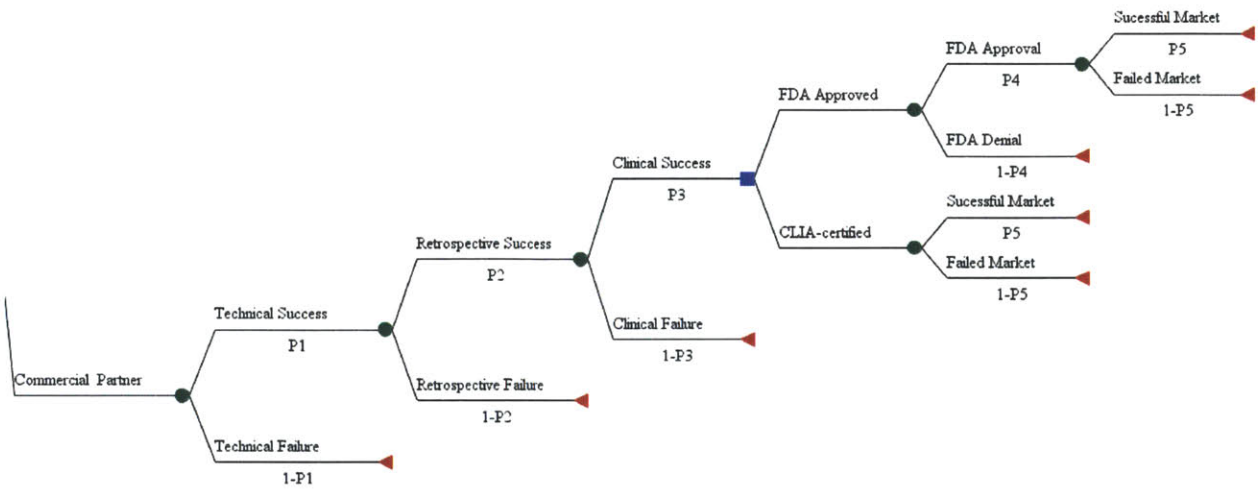
De Novo Therapy Companion Diagnostic (CDx) Branch



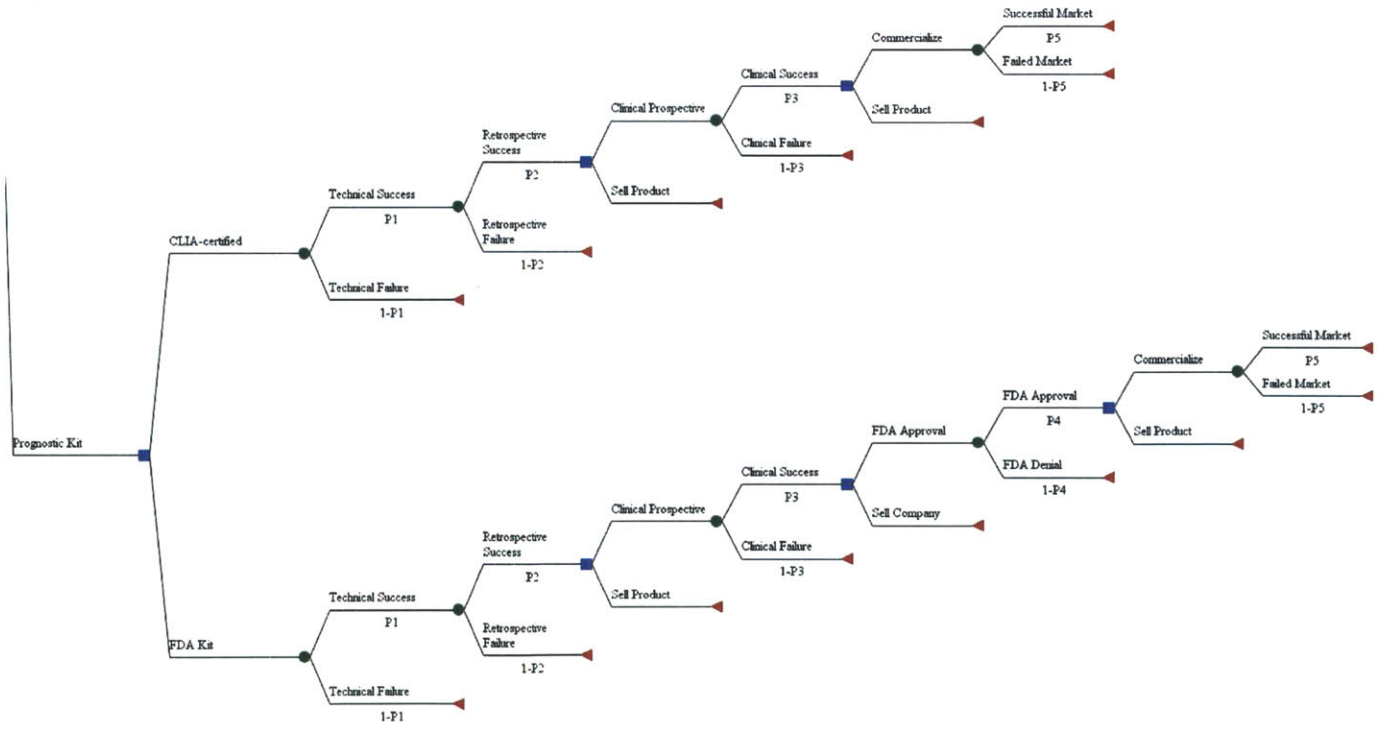
Existing Therapy Companion Diagnostic (CDx) Branch



Commercial Partnership for Prognostic Test



Independent Prognostic/Monitoring Test Branch



4.2 Model parameters and values

The goal for this section is to understand the sensitivity of the decision pathways to different inputs, and how those inputs may be changing given recent market developments. With the structure of the model as described above, I now describe the inputs that drive the base case for the tree and the associated ranges anticipated for those variables. The base case refers to the optimal decision pathway (i.e. most valuable for risk-adjusted NPV), assuming an initial set of conditions. To accomplish this, three major estimates drive the optimal strategic pathway: (i) the discounted cash flows (DCFs) associated with each path, (ii) the conditional probability of success for any one development pathway, and (iii) the discount rate.

The data for initial model parameters was compiled from public sources and comparable companies, where data was available. Note that while areas such as drugs have been studied in great detail (i.e. the Tufts Center for the Study of Drug Development) diagnostics have received little attention historically. As such, some data elements lack a statistically robust estimation, particularly when it concerns the probabilities for success in diagnostic development. The point of this thesis is not to develop a statistically robust catalogue of probabilities for success at different development milestones nor exact NPV's for different pathways. Specific data elements are discussed in the following sections, and Appendix VII presents the list of base case values defined for the decision tree.

i. Total commercial discounted cash flows

Pricing and reimbursement for complex diagnostics

Over the past decade, multiple companies have entered the market with complex diagnostics priced much higher than the traditional immunohistochemistry or blood-based cancer antigen tests. Figure 11 below shows a sample set of the companies and the associated tests they have launched over the past decade. Noted are the year of launch, target cancer or indication for the test, and the regulatory channel through which the company has commercialized the test.

FIGURE 11: Comparable diagnostic test pricing

Company	Test	List Price	Launched	Regulatory	Target Cancer / Indication
MiraDx	PreOvar	$ 1,295	2010	CLIA	Ovarian
Genomic Health	Oncotype DX	$ 4,175	2004	CLIA	Breast
Genomic Health	Oncotype DX	$ 3,280	2010	CLIA	Colon
Myriad Genetics	BRACAnalysis	$ 3,340	1996	CLIA	Breast
Myriad Genetics	Colaris	$ 3,150	2000	CLIA	Colon & Uterine
Myriad Genetics	Colaris AP	$ 2,050	2002	CLIA	Colon
Myriad Genetics	Melaris	$ 900	2001	CLIA	Melanoma
Myriad Genetics	Panexia	$ 3,025	2010	CLIA	Pancreas
Myriad Genetics	Prolaris	$ 3,400	2010	CLIA	Prostate
Myriad Genetics	Theraguide 5-FU	$ 1,175	2007	CLIA	5-FU toxicity
Myriad Genetics	OnDose	$ 300	2009	CLIA	5-FU exposure
Myriad Genetics	Prezeon	$ 500	2008	CLIA	Progression & Response
Intervention Insights	OncInsights	$ 3,950	2011	CLIA	All
Agendia	Mammaprint	$ 4,200	2007	FDA 510(k)	Breast
AviaraDX (bioTheranostics)	Breast Cancer Index	$ 3,500	2009	CLIA	Breast
Veridex	CellSights	$ 600	2004	FDA 510(k)	Breast
Monogram Biosciences	HERMark Breast Cancer Assay	$ 3,300	2008	CLIA	Breast
Vermillion	OVA1	$ 650	2010	CLIA	Ovarian

Note: List prices were compiled and recent as of December 2011. It is possible companies will update or change their pricing in future periods depending on market conditions. The prices were sources from SEC filings, investor presentations and company websites.

While one can observe the list prices for many companies, the rates they negotiate with individual payers can and will vary widely. As such, one must be careful to distinguish between pricing and effective reimbursement. As it pertains to prognostic test branch, I consider a range of effective reimbursement levels from $1,500 to $3,750 per test, in increments of $250 (10 possible scenarios for pricing).

In the case where a partnership is established, there are two different scenarios above that can significantly impact the potential value derived from the project. In the case of a *commercial partnership* similar to the Immunicon – J&J/Veridex agreement, the original technology developer will handle most all manufacturing and development costs, and the partner will incur all sales, marketing, and other commercialization expenses. Sales of the tests will be split based on a royalty percentage that is remitted back to the original technology developer, and likely there will be milestone payments made by the commercial partner to the technology development partner for meeting certain milestones. Figure 12 provides three examples of partnership agreements for commercial development.

Figure 12: Example commercial partnership structures in complex diagnostics

Company	Partner	Test	Structure
Immunicon	Veridex/J&J	CellSights	Veridex to pay Immunicon direct reagent costs plus 30% royalty on revenues after subtracting reimbursed costs
Vermillion	Quest Diagnostics	OVA1	Quest pays Vermillion a fixed $50 plus a 33% of gross margin royalty per test
Diagnocure	Signal Genetics	Previstage™ GCC Colorectal Cancer Staging Test	Up-front payment of $5.7M Annual installments of $5.1M R&D milestones of $2.5M

Source: Company annual filings and press releases.

A *companion diagnostic partnership* will have an arrangement that is slightly different in the economic layout compared to the commercial partnership. First, technology development will be handled by the diagnostic manufacturer to ensure they have a working platform and assay that finds the right gene(s). However, as soon as clinical validation studies begin, the partnership evolves in one of two ways. The diagnostic manufacturer could bear all costs of running the diagnostic side of the trial. Alternatively, the pharmaceutical partner may cover the entire cost of the clinical trial, including both diagnostic and drug evaluation. This is possible because the incremental cost of the diagnostic is small relative to the drug trial costs. Where the diagnostic might represent an incremental $5-10 million for the trial, the $100-200+ million in drug development costs overshadow this incremental expense. Once the drug and diagnostic have successfully navigated clinical trials, there is no standard approach to commercialization for companion diagnostics. In most cases to date, sales and marketing efforts are handled by the diagnostic manufacturer, such as the recently approved Abbott test for Pfizer's crizotinib in non-small cell lung cancer[3] and Dako's HercepTest launched for Genentech's Herceptin[14].

For the purpose of the base case analysis, I assume commercial partnerships will generate a 30% royalty on the gross margin of the test[3], and all development and manufacturing efforts will be performed by the diagnostic manufacturer. For a de novo companion diagnostic development partnership, I assume technology development costs are borne by the diagnostic manufacturer, but the clinical validation costs are predominantly covered by the therapeutic manufacturer. Post-approval, I assume that the diagnostic manufacturer will market the test as an FDA approved kit that is sold to commercial reference laboratories. I use Abbott's ALK test as a proxy for the amount of the reimbursement price the manufacturer keeps, assuming 20% of the reimbursement price is kept by the kit manufacturer.

Market entrance, adoption and patients tested

For this thesis, I am only considering diagnostics where tests are conducted once for patients during a patient's lifetime. Additionally, while testing may be conducted by physicians outside the indicated population, I only consider patients *diagnosed* with prostate cancer. In order to estimate the total number of tests administered in prostate cancer, I consider a bottom-up analysis starting with the number of biopsies. In the United States, the exact number of prostate biopsies is not tracked, but estimates indicate approximately one million biopsies are performed a year[81]. Based on the incidence of 241,740 from the ACS, this means that approximately 24.17% of biopsies result in diagnosed cancer, assuming all diagnosed cases result from biopsied tissue. This diagnosis rate of 24.17% is assumed to stay constant as a percentage of the total biopsies, which are grown at the expected population growth rate of 0.875% published by the US Census Bureau[114]. For this analysis, I consider a forecast horizon over 20 years (i.e. from 2012 to 2032), representing an increase in the total incidence of

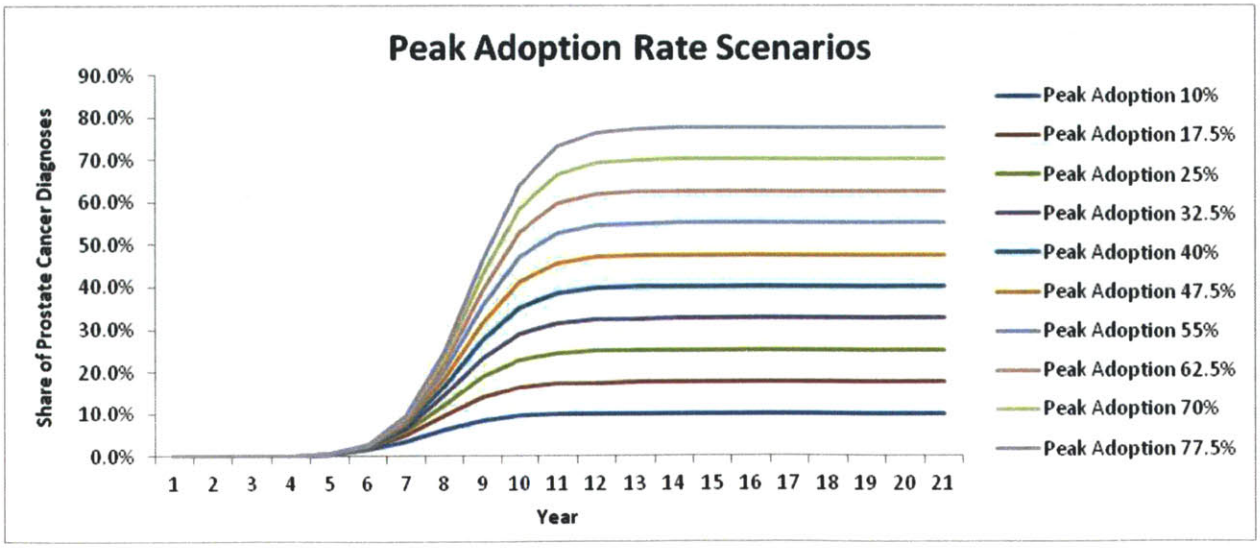
prostate cancer from 241,740 in 2012 to 287,430 cases in 2032. A more nuanced estimate based on age demographics of the US population may yield different results, but I use the above as a conservative estimate of the potential market for a prostate cancer diagnostic. I relax this assumption in the discussion of sensitivity of model output to certain key parameters.

In addition to estimating the total number of diagnosed cases for prostate cancer, I also model several different scenarios for peak market penetration. For the purpose of this analysis, I consider a diagnostic that takes four years to move through development to commercial launch, with another seven years to reach peak market penetration. In order to model peak market penetration, I adapt an S-shaped diffusion model to describe the percent penetration of diagnosed prostate cancer patients[27]. The alpha to achieve peak adoption by year seven is 0.75, with an initial seed market share of 0.1%. For this analysis, I only consider the case of four years until launch, and seven years to peak adoption (note, however, that the faster a product is introduced to the market and the faster it is adopted by the market, the greater the NPV as less time-value is being sacrificed, and vice-versa). A four year development time is based primarily on comparable company timelines, as shown in Figure 13 below.

FIGURE 13: Average development time and peak adoption rate

Company	Test	Development Start	Commercial Launch	Development Time (years)
Genomic Health	Onco *type* DX	2000	2004	4.0
Myriad Genetics	BRACAnalysis	1992	1997	5.0
MiraDx	PreOvar	2008	2010	2.0
Agendia	Mammaprint	2003	2007	4.0
AviaraDX (bioTheranostics)	Breast Cancer Index	2004	2009	5.0
Vermillion	OVA1	2003	2010	7.0
			Average	**4.5**

Source: Company annual filings and press releases.



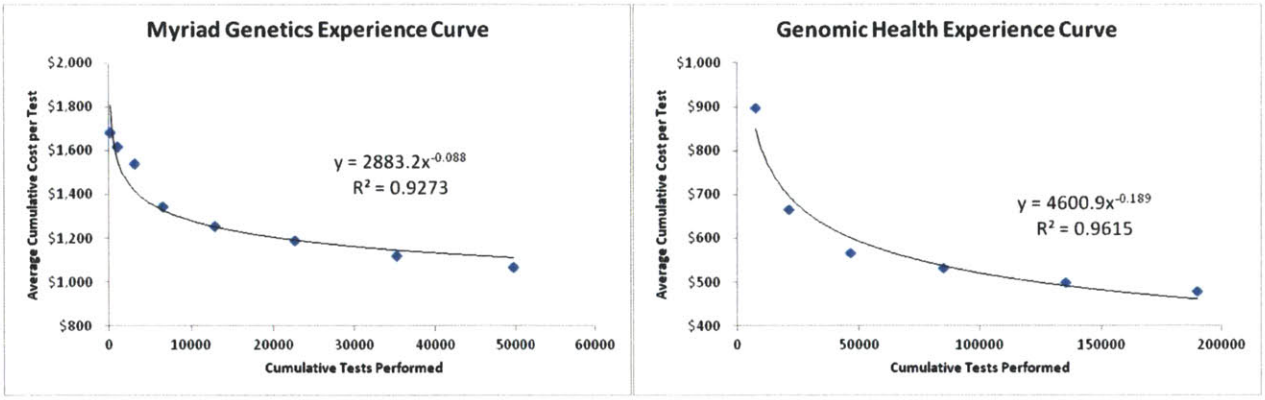
Most complex diagnostics have been launched only in the past couple years and have yet to reach peak market adoption. Additionally, many of the companies are still private, and unit sales are unavailable in public sources. I consider seven years as a decent estimate as it considerably slower than many peak drug adoption times, and the technology is relatively new for many of the treating physicians and therefore may face clinical adoption headwinds. Additionally, Genomic Health experienced a similar trend for their Onco *type* DX™ 21-gene assay. Indicated for early-stage invasive breast cancer that is node negative (N-) and estrogen receptor positive (ER+), the test was launched in January 2004. At year-end 2004, approximately 500 tests had been run representing approximately 0.5% of the indicated population. At 2011 year-end, 75,000 Onco *type* DX tests were run during the year, representing approximately 65% penetration rate of early-stage N- ER+ invasive breast cancers. Finally, I assume patents and intellectual property protections expire in 2033 such that competition significantly increases and market share drops to 10% of the diagnosed prostate cancer patients for 2033 onward.

Cost of testing

The cost of testing is driven by two primary components for complex diagnostics companies: the reagent costs consumed when processing tissue and licensing fees paid to the original platform manufacturer for use of their technology. The licensing fees are typically a simple flat percentage of sales generated from tests sold. Genomic Health is the only company where data was available regarding the split between licensing fees and tissue processing costs, and for this analysis I use their average 7% of sales as a licensing fee rate. Appendix IV presents a summary of relevant data from Genomic Health used for this analysis.

Tissue processing costs are modeled using an experience curve derived from Myriad Genetics' and Genomic Health's cumulative average cost to produce their BRACAnalysis and Onco *type* DX test in the first years of their launch, respectively. Displayed in Figure 14 are the analyses for Myriad Genetics and Genomic Health. The data correspond to the years 2005-2010 for Genomic Health, the first several years of full production for their Onco *type* DX test in breast cancer, and 1997-2004 for Myriad Genetics, the first set of years where Myriad was manufacturing only their BRACAnalysis test for breast cancer. One can see that there are varying levels of experience effects, with an average elasticity of cost of 13.85%, ranging from 8.8% to 18.9%. This analysis demonstrates the learning effects present in the processing of complex tests, capturing a more detailed view of the cost to perform testing services beyond assuming a strict percentage of sales. For the purpose of NPV modeling, I've assumed a conservative $4,000 initial testing cost, and 12.5% learning effect based on the Myriad and Genomic Health results.

FIGURE 14: Experience curves in complex molecular testing



Source: Company annual filings, author's analysis.

R&D costs for esoteric molecular diagnostics

Research and development is one of the most integral expenses, and for complex diagnostics one of the hardest to estimate. In their 2010 annual report Roche Diagnostics noted that "clinical validation is relatively new for the IVD industry...besides significant investment, it requires expertise in clinical development and increased interaction with non-traditional customers such as payers and healthcare professionals" (p. 74). In addition, for the NPV considerations in this thesis, there are two R&D costs that need to be captured: initial investments in diagnostic development and clinical research, as well as ongoing R&D expenses.

On-going R&D is the most-straight forward to address. This is composed of four elements: personnel costs, reagent and supply costs, collaboration expenses, and other R&D expenses. Personnel costs are estimated based on an average salary of $70,000 growing at 1.5% per year, and a ramp-up in R&D personnel during the first four years of development. Once the test has been launched commercially, personnel are assumed to grow at 10% for six years post launch, at which point personnel stays relatively constant through the patent life of the test. Note the initial ramp up in R&D personnel will be included in the investment stages, not in the NPV of the diagnostic following commercial launch. Reagents and lab supplies, other R&D expense, and collaboration expense are estimated based on Genomic Health data. Reagents and lab supplies and other expenses are kept at a percentage of sales, at 2% and 5% respectively. Collaboration expenses are a fixed amount every year, assumed to be $1.7 million per year following commercial launch.

Pre-launch R&D expenses are much more sensitive to the expertise of the team in place, the complexity of the biology involved in developing the test, and ultimately the development pathway selected for the diagnostic. For example, approaching test development with the goal of receiving FDA PMA/510(k) approval for a new test will incrementally add millions to the

development expense for the technology because of the more stringent requirements of the FDA and the expertise required to conduct the clinical trial itself across multiple sites.

FIGURE 15: R&D expenses pre-launch across all branches

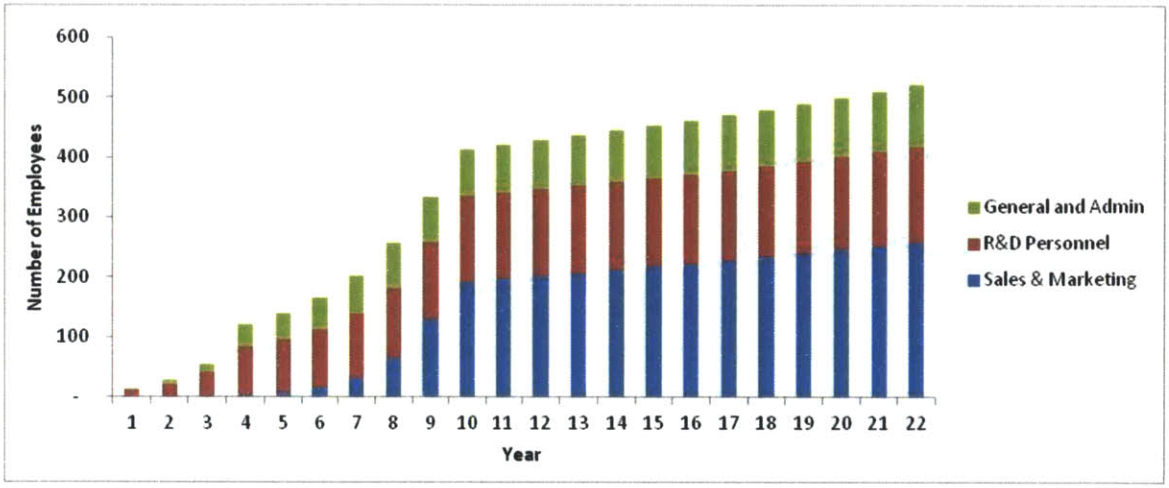
	Research & development expenses prior to launch ($000's)				
	Research Use Only	De Novo Tx CDx	Existing Tx CDx	Commercial Partner	Independent
(a) Technology Development	$ 15,000	$ 15,000	$ 15,000	$ 15,000	$ 15,000
(b) Retrospective Validation	–	$ 5,000	$ 5,000	$ 5,000	$ 5,000
(c) Clinical Validation (CLIA)	–	–	–	$ 7,500	$ 7,500
(d) Clinical Prospective (FDA)	–	$ 12,500	$ 25,000	$ 15,000	$ 15,000
(e) FDA Filing	–	$ 500	$ 500	$ 500	$ 500
CLIA-certified (=a+b+c)	$ 15,000	n/a	n/a	$ 27,500	$ 27,500
FDA PMA/510(k) (=a+b+d+e)	n/a	$ 33,000	$ 45,500	$ 35,500	$ 35,500

Operational expenses

In addition to direct manufacturing and R&D costs, building out a new product will require other operational expenses, specifically sales and marketing and general and administrative expenses. The largest expenses in these areas are personnel, which will be modeled similar to research and development. The modeled employee base is shown in Figure 16. General and administrative employees are initially limited, ramping up at commercial launch and growing through the first four years of commercial operations, after which growth is kept at a nominal 3% per year. Sales and marketing is aggressively built starting two years before launch and for four years post commercial launch, after which employees grow at a nominal 3% per year as well. Finally, sales and marketing personnel are paid an average of $200,000 per year (including incentives, commissions, etc.) and general and administrative employees are paid $225,000 per year, both growing at 1.5% per year. These numbers are derived from Genomic Health, as this is the only comparable company with sufficient detail to estimate each component.

Sales and marketing has an additional promotion and marketing expense that captures the costs of educating physicians, payers and other customers on the new technology. This is modeled as a percentage of sales, starting at 40% of sales at commercial launch and decaying to 7-8% of sales once steady state has been reached after seven years. Other sales and marketing expense is assumed to be 5% of sales, with an additional $10 million spent over the first two years prior to launch to generate initial awareness of the product.

FIGURE 16: Employee build up by function



General and administrative, beyond personnel expense, is driven primarily by billing and collections expenses and professional fees. Based on Genomic Health's data, billing and collection expenses are approximately 4% of sales on average, and capture the effort the company must expend in order to ensure they are being paid for their testing services in a timely manner. Professional fees capture accounting, legal, consulting and other advisory services consumed by an enterprise. These are assumed to peak at $9 million per year three years post commercial launch, and ramp up by $3 million per year from launch to peak.

In addition to the ongoing operational expenses detailed above, I also capture the operational expenses a project would bear in order to get to commercial launch. These expenses are again broken down by phase of the project, similar to R&D, and are captured below in Figure 17.

FIGURE 17: S&M and G&A expenses during development

	Sales & marketing expenses during development ($000's)				
	Research Use Only	De Novo Tx CDx	Existing Tx CDx	Commercial Partner	Independent
(a) Technology Development	$ 200	$ 500	$ 500	–	$ 500
(b) Retrospective Validation	–	–	$ 500	–	$ 500
(c) Clinical Validation (CLIA)	–	–	–	–	$ 1,000
(d) Clinical Prospective (FDA)	–	–	$ 1,000	–	$ 1,500
(e) FDA Filing	–	–	$ 2,000	–	$ 5,000
CLIA-certified (=a+b+c)	$ 200	n/a	n/a	$ -	$ 2,000
FDA PMA/510(k) (=a+b+d+e)	n/a	$ 500	$ 4,000	$ -	$ 7,500

	General & administration expenses during development ($000')				
	Research Use Only	De Novo Tx CDx	Existing Tx CDx	Commercial Partner	Independent
(a) Technology Development	$ 500	$ 500	$ 6,000	$ 6,000	$ 6,000
(b) Retrospective Validation	–	$ 500	$ 3,000	$ 3,000	$ 3,000
(c) Clinical Validation (CLIA)	–	$ 1,000	–	$ 4,000	$ 4,000
(d) Clinical Prospective (FDA)	–	$ 1,000	$ 5,500	$ 5,500	$ 5,500
(e) FDA Filing	–	–	–	–	–
CLIA-certified (=a+b+c)	$ 500	n/a	n/a	$ 13,000	$ 13,000
FDA PMA/510(k) (=a+b+d+e)	n/a	$ 3,000	$ 14,500	$ 14,500	$ 14,500

Total commercial DCFs: Base Case

Based on the factors described above around pricing, market adoption, and operational costs post launch, I assume two states for the market once the technology has been commercially launched: success and failure. A successful market environment is one that encompasses both high pricing and broad market adoption. A failed market environment is one in which the project still has a positive DCF value at the time of commercial launch, but will not recoup costs spent on R&D or initial company operations prior to launch.

For each of the branches noted above, the base case success and failure outcomes are noted below in Figure 18. Sensitivities to these values will be tested to determine where decisions will ultimately lead based on development costs.

Figure 18: Market success and failure DCFs for base case

	Market NPV ($MM)		
Decision Tree Branch	**Success**	**Failure**	**Description**
Commercial Prognostic - CLIA	$ 300.0	$ 30.0	Success is approximately 70% peak adoption with $3,500 effective reimbursement Failure is approximately 50% peak adoption with $2,500 effective reimbursement
Commercial Prognostic - FDA	$ 315.0	$ 30.0	Success gets ~5% greater than CLIA Failure is approximately the same as failed CLIA
Commercial Partner	$ 100.0	$ 10.0	Success is approximately 70% peak adoption with $3,500 effective reimbursement Failure is approximately 50% peak adoption with $3,000 effective reimbursement
CDx Existing Therapeutic	$ 300.0	$ 30.0	Success and failure comparable to commercial prognostic
CDx De Novo Development	$ 200.0	$ 40.0	Value approximately 50% of Existing therapeutic due to pharma partner
Research Use Only	$ 40.0	$ -	Based on 5% capture of $2.2B instruments market in 5 years

ii. Probabilities of success

Unlike drug development, diagnostics have not historically attracted much attention with respect to the probability of success for different research and development milestones. There are two primary reasons for this: (i) the FDA had not required many in vitro diagnostics to go through the approval process and (ii) typically the technology involved was not so advanced (e.g. immunohistochemistry) that anyone critically questioned the probability of success. With the advent of sequencing technology and molecular diagnostics adopted into the clinic, both of those previous assumptions are no longer valid.

The probability of technical success is just as important in evaluating strategic decisions as the ultimate NPV of a diagnostic once it gets to market. This is because the probabilities of success dictate the *risk-adjusted* NPV (rNPV) for a project today, effectively reducing the ultimate commercial NPV of a technology by the commensurate probability that the project does not make it to the market. To illustrate this, consider two technologies that, once they get to commercial launch, are expected to be worth $400 million, however one has a 10% chance of

making it successfully to commercial launch, while the other has a 50% probability. Of course, one would always prefer the technology with a 50% probability of reaching commercial launch.

As mentioned before, there is no great data source that assesses the probability of successful transition from one development phase to the next in molecular diagnostics. Therefore, for this analysis, I assume an initial set of rough estimate probabilities, for which a more detailed sensitivity analysis will examine the ranges in which decisions change from the base case. The probabilities described below represent the probability that a project entering that particular branch will exit at the successful end. In other words, these probabilities capture the single node or conditional probabilities, and not the total probability of technical success. The development point and associated probabilities are:

i. *Technical development*: For baseline, I assume a base case 85% chance that a new technology will be able to successfully be developed. This probability is meant to describe the ability to get a working platform selected, and says nothing about the ability of the diagnostic to accurately perform.
ii. *Retrospective validation:* For baseline, I assume a base case 75% chance of success that an assay can be validated retrospectively based on tissue samples. Two dimensions are captured in this probability. First, the chance that success can even be achieved, and second that it can be done within the development timeframe outlined above.
iii. *Prospective clinical (commercial partner and independent branches):* For baseline, I assume a base case 75% chance of success that an assay can succeed in a prospective clinical trial. This is one of the less robust initial assumptions, because there have been so few attempts and successful FDA approval processes for IVDMIAs.
iv. *Prospective clinical (companion diagnostic):* For the companion diagnostic option, the risk in development is a little more difficult. For this analysis, I assume that the diagnostic carries no value unless approved with the drug. Thus, the risk of diagnostic approval is completely tied to the success of the drug. Finally, I assume the drug candidate is in Phase III clinical trials. As mentioned before, the probability of success for drug candidates has been well studied[c], and a clinical phase III trial has a base case 65% chance of success for the clinical trial[11].
v. *FDA approval:* Provided a positive clinical trial, I assume there is a base case 90% chance for FDA approval. This is again an area where regulatory views are evolving, and a more conservative estimate may be more relevant depending on how regulatory attitudes evolve. For the baseline, I assume the comparable success probability for oncology drug candidates[12].

[c] Note there could be an argument that a companion diagnostic will increase the probability that a dug candidate will have a successful clinical trial. There isn't yet a robust data set for this, and so we use a conservative estimation based on the Tufts Center for Drug Development.

vi. *Successful market evolution:* For the purpose of this analysis, a successful market evolution describes a scenario where both pricing and adoption are favorable. As a baseline, I assume that a favorable market outcome has a base case 40% probability. This reflects the fact that achieving market success for a new diagnostic technology is often at least as difficult as technical validation, if not significantly more complicated as there are multiple parties that must be convinced of the value of the outcome in order for a favorable market evolution.

For this analysis, I have simplified some aspects of the decision tree structure and probabilistic outcomes, primarily as it relates to the decision nodes that occur later in time. For one, the terminal node "Sell project" is not a node that is 100% certain. In reality, there is a probability associated with a successful sale of a company. In addition, if an attractive offer doesn't materialize, then the "failure" branch would loop back into previous options such as continued development or partnership.

Additionally, it could be possible to differentiate different scenarios, or separate pricing from market adoption rates. This is particularly relevant for pricing, as proving cost-effectiveness in biotechnology in the United States is rapidly becoming the norm instead of the exception. Depending on the nature of a particularly technology, the analyst may need to ensure that the risks associated with price and market adoption are being treated appropriately. As it pertains to this thesis, I will not be differentiating these two risks, instead identifying what scenarios create an NPV aligned with a successful or failed market.

iii. Discount rate

The discount rate applied to the cash flows is one of the most debated topics in financial economics, and this is no different in life sciences. From a purely theoretical for an NPV-DCF analysis, the idiosyncratic risk of the business should be modeled explicitly in the cash flows and the discount rate adjusts for the systematic risk of the company (i.e. the risk relative to the market). However, many of the nice assumptions underlying traditional theories for discount rates don't exactly hold for new technology, project or company valuation (i.e. the assumption that there is minimal friction in the market to create a replicating portfolio of stocks). As such, many opinions exist in life sciences regarding the appropriate discount rate.

For some, particularly those in the professional asset management and investment industry, the appropriate discount rate is approximately the historical return on equities, or somewhere between 10-15%[9]. For those closer to the stage of company formulation, discount rates are typically much higher, ranging from 20% to 50%[9,12]. The potential risk of error with the discount rate is the relative weight for cash flows that occur in the future. This is particularly relevant to the life sciences, because it can often be years of negative research and development cash flows before positive earnings are finally generated from market activity.

Therefore, placing less weight on future cash flows through a higher discount rate is a conservative, but potentially skewed, valuation approach.

Depending on the modeling approach one uses, a number at one end of these ranges may be more appropriate than others. For this analysis, I will assume a base case 20% discount rate initially, and present the sensitivity of the NPV calculations to different discount rates when discussing sensitivities below. Choosing 20% is primarily motivated by the fact that this thesis focuses on a stage of development that is much earlier than traditional equity valuation, and thus many of the assumptions underlying a discount rate between 10-15% do not hold.

4.3 Base case summary

As discussed briefly above, multiple factors can drive the base case. The most fundamental elements driving the base case are summarized in Figure 19:

Figure 19: Base case primary model drivers

	Market NPV ($MM)		Description	Total Pre-Commercial
Decision Tree Branch	Success	Failure		Development Expenses
Commercial Prognostic - CLIA	$ 300.0	$ 30.0	Success is approximately 70% peak adoption with $3,500 effective reimbursement Failure is approximately 50% peak adoption with $2,500 effective reimbursement	$ 42.5
Commercial Prognostic - FDA	$ 315.0	$ 30.0	Success gets ~5% greater than CLIA Failure is approximately the same as failed CLIA	$ 57.5
Commercial Partner	$ 100.0	$ 10.0	Success is approximately 70% peak adoption with $3,500 effective reimbursement Failure is approximately 50% peak adoption with $3,000 effective reimbursement	$ 40.5
CDx Existing Therapeutic	$ 300.0	$ 30.0	Success and failure comparable to commercial prognostic	$ 64.0
CDx De Novo Development	$ 200.0	$ 40.0	Value approximately 50% of Existing therapeutic due to pharma partner	$ 36.5
Research Use Only	$ 40.0	$ -	Based on 5% capture of $2.2B instruments market in 5 years	$ 15.7

Conditional Probability of Success	
Prob. of Technical Development Success	85%
Prob. of Retrospective Validation Succes	75%
Prob. of Prospective Validation Success	75%
Prob. of FDA Approval	90%
Prob. of Successful Market State	40%

4.4 Sensitivity analysis of strategic outcomes

As discussed briefly above, the power of the decision tree is not to identify the risk-adjusted NPV of an optimal decision path today, but to understand the sensitivity of your decision to different parameters. This is particularly relevant to the probabilities of success for different development pathways, as there are wide error bars around the values. As such, it is imperative that one understands the thresholds above or below which a decision tips in favor of a different path from the baseline settings. Below I evaluate each of the major inputs discussed above, and their respective sensitivities.

Base case scenario

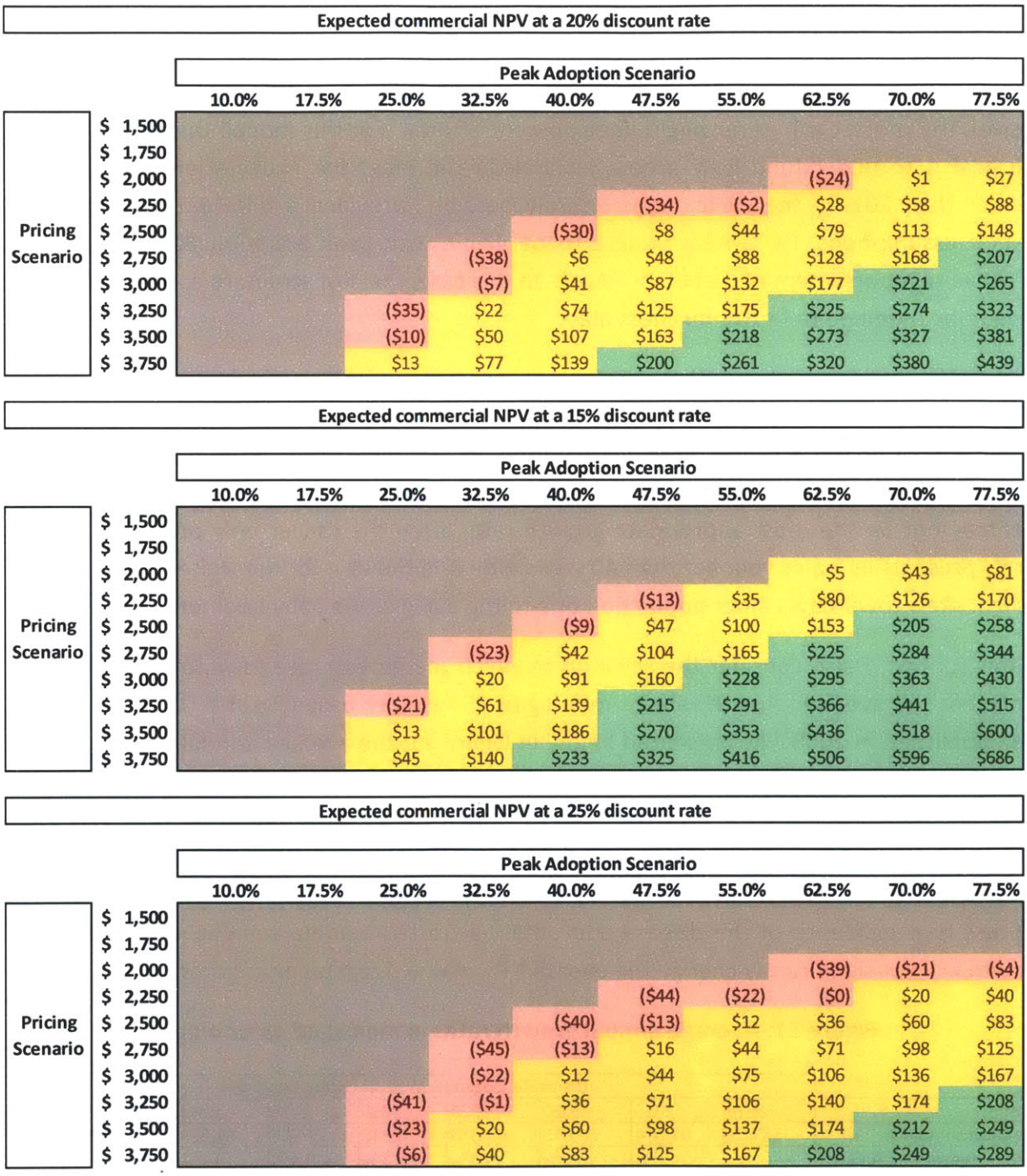
In the base case set-up described above and the values captured in Appendix IV, the optimal pathway is to pursue a CLIA-certified prognostic test, with a total risk-adjusted NPV of $23.2 million. Currently, pursuing an FDA-approved prognostic test, if not required, is a lower NPV project compared to the CLIA-pathway, with an NPV of $19.5 million. Pursuing a companion diagnostic for an existing therapy is only slightly NPV positive at $1.9 million, while both a commercial partnership and a de novo companion diagnostic partnership are negative NPV projects for the diagnostic manufacturer at -$17.9 and $8.5 million, respectively. Finally, the baseline RUO benchmark has risk-adjusted NPV of $18.3 million. This result for the NPV of the RUO only pathway is significant because it signals that, under the current set of assumptions, it is only marginally more attractive to pursue a CLIA-certified or FDA-approved prognostic test.

Commercial launch NPV sensitivity to market scenarios

Ultimately, the expected NPV of a project will dictate whether or not investment will happen. One key part is the risk adjustment associated with the probability of technical success, but just as important is the ultimate commercial NPV expected at the time of launch. Given the assumptions discussed in the previous section, I now present sensitivity of the commercial launch to three key inputs: effective average reimbursement, peak market adoption, and the discount rate.

Logically speaking, the lower the price and the lower the adoption rate, the lower the expected NPV. Similarly, the higher the discount rate, the lower the NPV, as the value of cash flows generated in future years will be diminished as the discount rate goes up. Given that the assumptions outlined below have cost inputs that are not directly variable with the level of sales, there exist market adoption rates and pricing scenarios for which a project will never generate positive cash flows. Under these cases, no matter how attractive the probabilities of technical success, the project will never be an attractive investment hypothesis. Presented below in Figure 20 is the expected NPV at commercial launch (i.e. not yet adjusted for the probability of success for different development milestones) for different effective average reimbursement, peak market adoption rate and discount rate, for the case where an independent prognostic is developed.

Figure 20: Commercial NPV scenarios



Expected commercial NPV at a 20% discount rate

Pricing Scenario	Peak Adoption Scenario: 10.0%	17.5%	25.0%	32.5%	40.0%	47.5%	55.0%	62.5%	70.0%	77.5%
$ 1,500										
$ 1,750										
$ 2,000								($24)	$1	$27
$ 2,250						($34)	($2)	$28	$58	$88
$ 2,500					($30)	$8	$44	$79	$113	$148
$ 2,750				($38)	$6	$48	$88	$128	$168	$207
$ 3,000				($7)	$41	$87	$132	$177	$221	$265
$ 3,250			($35)	$22	$74	$125	$175	$225	$274	$323
$ 3,500			($10)	$50	$107	$163	$218	$273	$327	$381
$ 3,750			$13	$77	$139	$200	$261	$320	$380	$439

Expected commercial NPV at a 15% discount rate

Pricing Scenario	Peak Adoption Scenario: 10.0%	17.5%	25.0%	32.5%	40.0%	47.5%	55.0%	62.5%	70.0%	77.5%
$ 1,500										
$ 1,750										
$ 2,000								$5	$43	$81
$ 2,250						($13)	$35	$80	$126	$170
$ 2,500					($9)	$47	$100	$153	$205	$258
$ 2,750				($23)	$42	$104	$165	$225	$284	$344
$ 3,000				$20	$91	$160	$228	$295	$363	$430
$ 3,250			($21)	$61	$139	$215	$291	$366	$441	$515
$ 3,500			$13	$101	$186	$270	$353	$436	$518	$600
$ 3,750			$45	$140	$233	$325	$416	$506	$596	$686

Expected commercial NPV at a 25% discount rate

Pricing Scenario	Peak Adoption Scenario: 10.0%	17.5%	25.0%	32.5%	40.0%	47.5%	55.0%	62.5%	70.0%	77.5%
$ 1,500										
$ 1,750										
$ 2,000								($39)	($21)	($4)
$ 2,250						($44)	($22)	($0)	$20	$40
$ 2,500					($40)	($13)	$12	$36	$60	$83
$ 2,750				($45)	($13)	$16	$44	$71	$98	$125
$ 3,000				($22)	$12	$44	$75	$106	$136	$167
$ 3,250			($41)	($1)	$36	$71	$106	$140	$174	$208
$ 3,500			($23)	$20	$60	$98	$137	$174	$212	$249
$ 3,750			($6)	$40	$83	$125	$167	$208	$249	$289

As one can see, **the higher the discount rate, the less likely that attractive NPV's can be realized** at the time of commercial launch. To illustrate successful, mediocre, and unreasonable outcomes, respectively, NPVs of $200 or greater are highlighted in green, between $0 and $200 are highlighted in yellow, and a project that eventually has positive cash flows but negative NPV is highlighted in red. Note that these represent the commercial DCF values once all R&D costs

have been incurred. Gray shaded boxes represent instances where cash flows never turn positive over the forecast horizon.

For the current set of assumptions, one can see that if peak adoption is less than 20% or effective average reimbursement is less than $2,000 (denoted with the gray shaded cells above), the project will never begin development efforts. For this model, this makes sense as the goal is to understand how a new technology can meet the expectation is for adoption greater than 20% in the clinic. It is entirely possible, provided a different technology and market assumptions, for a new project to be viable with peak adoption 20% or lower and effective reimbursement of $2,000 or lower. In this case, the cost structure assumptions would have to be modified to fit this business plan.

NPV sensitivity to market growth

In addition to the market scenarios outlined above, the current model assumes that the population of prostate cancer patients will grow at the average expected population growth rate of 0.875% as published by the US Census Bureau. However, in the case of prostate cancer, this may not be the most appropriate growth rate, given the cancer only occurs in men and rarely presents in males younger than 40 years old. Additionally, for the United States, there is a slight skew towards an older population due to the aging of the baby boomers.

In this context, I also consider the scenario in which the growth rate assumption is relaxed to represent the average growth rate of men aged 45 or older based on the US Census Bureau data published in 2008. As presented below in Figure 21, the average annual growth rates for every five year period are calculated for the population of men aged 45 or older. These growth rates are then incorporated into the market model for a newly launched prostate cancer diagnostic. On average, this adjustment to the growth rate resulted in a 6-8% increase in NPV at commercial launch. It is clear that the primary sensitivity of commercial NPV is the ability to capture new incidence of the disease and obtain attractive reimbursement, while population growth will not significantly change the overall NPV in one direction or another.

Figure 21: Average annual growth rates in men aged 45 or older

	US male population projections aged 45+								
Year	2010	2015	2020	2025	2030	2035	2040	2045	2050
Population (000's)	56,759	61,514	65,615	69,573	73,843	77,985	81,824	84,931	88,433
5-year average C.A.G.R.		1.6%	1.3%	1.2%	1.2%	1.1%	1.0%	0.7%	0.8%

Source: U.S. Census Bureau

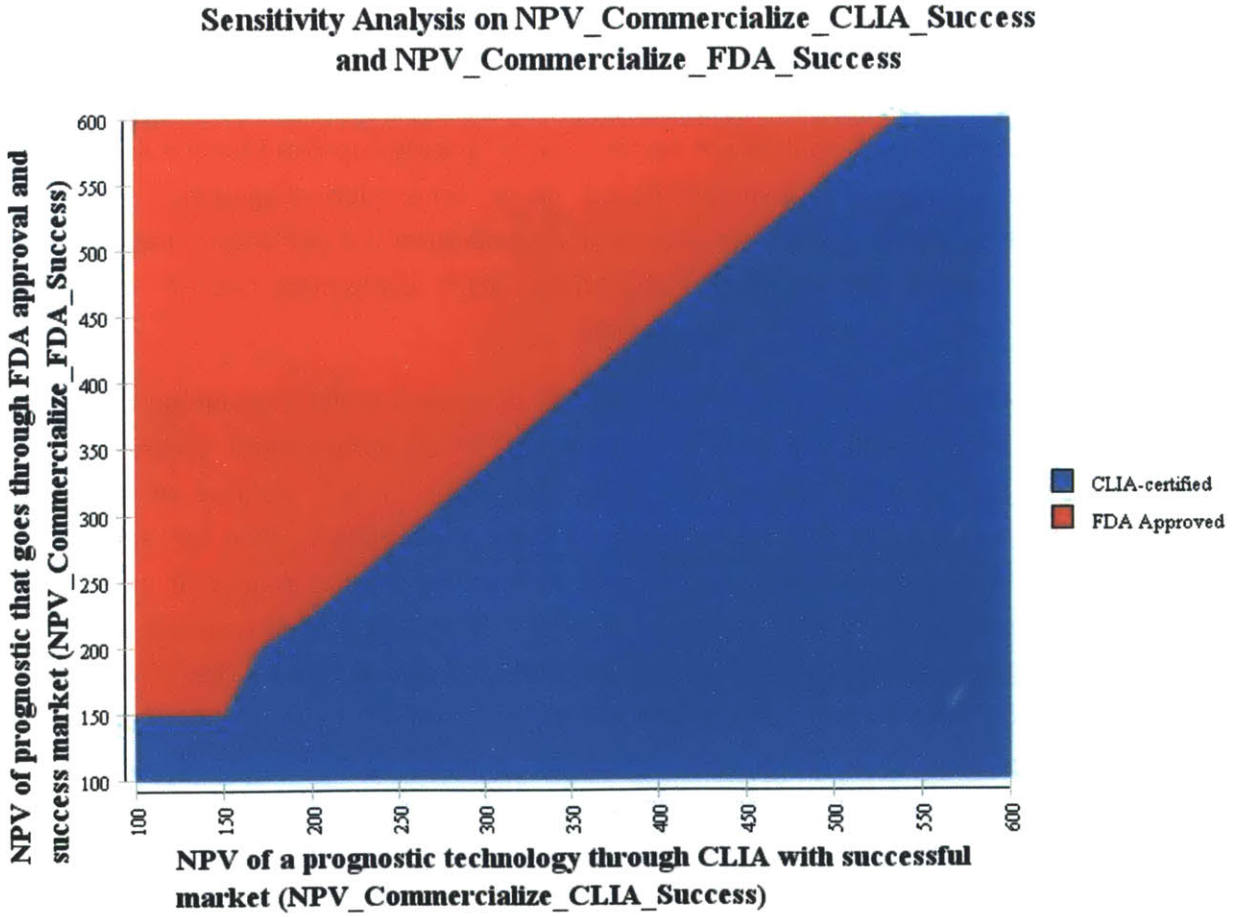
NPV of FDA approval vs. CLIA-certified

A big assumption in the current market success scenarios is that the NPV of a new technology at commercial launch is roughly the same whether it has been FDA approved or CLIA-certified There is a small benefit assumed for FDA approval with 5% more value as currently modeled in

base case. However, this is offset by the 90% FDA approval probability. So one may ask, what success state scenarios would change the decision to pursue FDA over CLIA certification? Or, alternatively, how much greater does the value derived from FDA approval have to be to offset this additional risk discount?

In Figure 22 below, all else equal, I present the two-way sensitivity analysis of the decision to pursue FDA vs CLIA commercialization channels based on the expected commercial NPV. One can see that, for the same commercial NPV, CLIA-certification will always be the dominant decision. This is in part due to a small incremental cost from FDA registration, but primarily driven by the additional risk incurred by seeking FDA approval. Additionally, because there is only a 90% chance for success of FDA approval, the value post-FDA approval has to be at least as great as the value prior to approval divided by the 90% chance of approval if FDA approval is to add value. That exactly describes the slope of the dividing line between the CLIA and FDA pathways.

Figure 22: Two-way sensitivity of CLIA vs FDA NPV's



Additionally, in the context of recent market events, there is another set of parameters that can create similar outcomes. This is the potential combination of a change in the expected success probability for CLIA-certified vs FDA-approved products. If the FDA should require that new diagnostics entering the market be FDA-approved in order to gain clinical adoption, then the likelihood of a successful market environment under CLIA-certification would be diminished. In this context, should the expected commercial NPV of a CLIA-certified product significantly diminish while the FDA-approved product stays relatively the same, then it becomes much more attractive to pursue the FDA approval path.

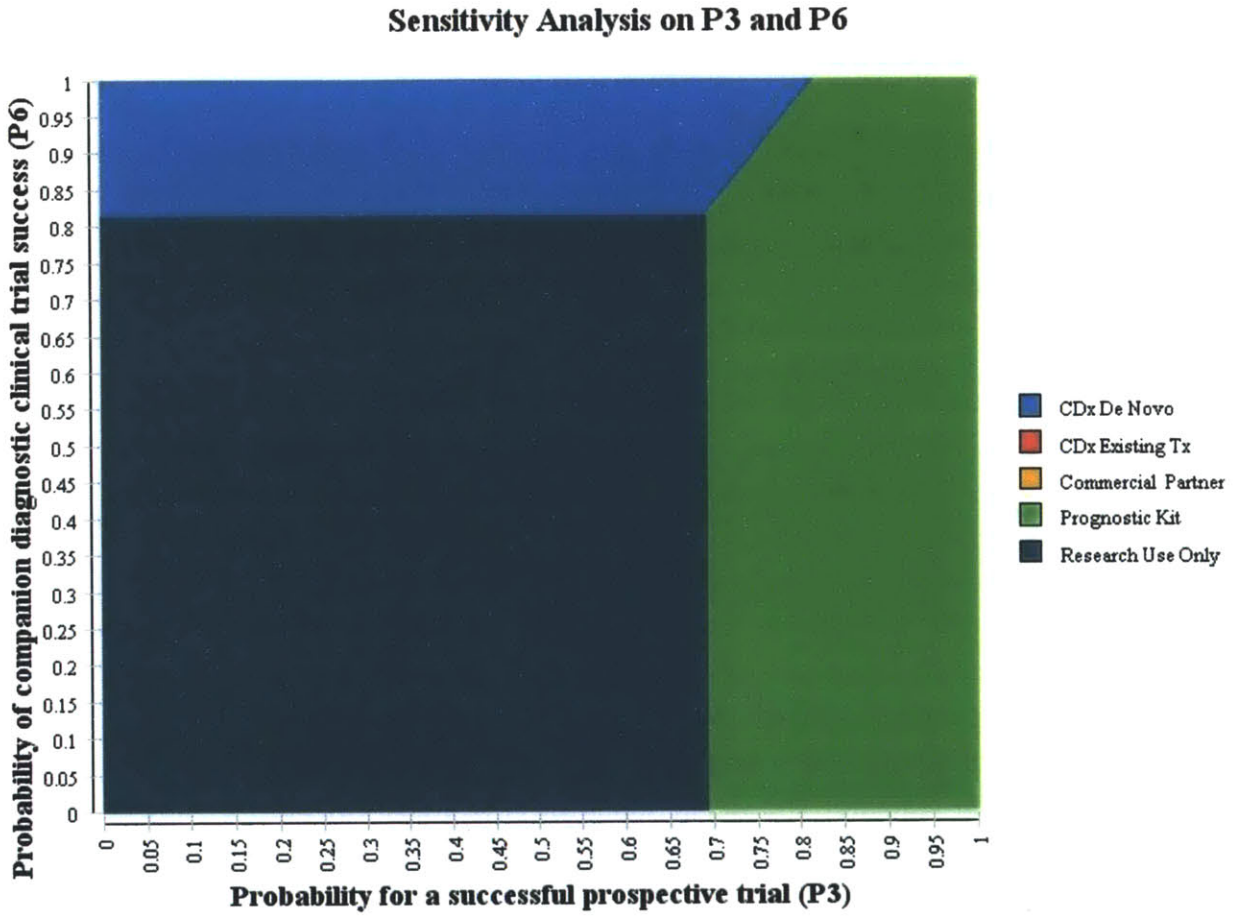
Finally, when comparing and contrasting FDA and CLIA, one must carefully consider the how the diagnostic will ultimately be used. In this analysis, I have restricted my perspective to the United States. However, if Europe is going to be an attractive market, CLIA is a difficult path because it is logistically impractical to ship biopsy tissue from France to the United States or vice-versa. Thus, if one is going to pursue a partnership with a pharmaceutical firm, pursuing FDA approval may be required as CLIA is not feasible assuming global distribution of the drug and associated diagnostic technology. In addition, if the drug label is going to include the diagnostic, then it is definitely required the FDA is involved in approving the diagnostic.

Probability of clinical trial success under CDx vs independent

In the recent publications surrounding companion diagnostics, there has been a lot of commentary about how the probability of success may be greatly improved for the drug when a patient selection algorithm is included based on a companion diagnostic. However, stereotypically the economic value for a diagnostic manufacturer has not been great relative to a drug. As such, while still seeking collaborations, many companies pushed ahead with independent prognostic or diagnostic development.

One may then ask by how much does the probability of success under companion diagnostics have to exceed the probability of clinical trial success for an independent prognostic for a manufacturer to rationally pursue the companion diagnostic route? Holding all else equal, Figure 23 below presents the two-way analysis of these probabilities. One can see that for probabilities greater than approximately 70% and *de novo* companion diagnostic probabilities less than 80%, the prognostic will always be a better path than the companion diagnostic. However, for a significant improvement in the probability of clinical trial success in companion diagnostics (i.e. >85%), companion diagnostics will be preferred if the probability of success for the prognostic is below 70%. Given that the current probability of success at phase III for oncology drugs in development is approximately 65%, it is possible success rates could improve to 80-85% based on the ability to differentiate patients with genetic markers indicative of treatment response, though this is still a dramatic improvement in the statistics for clinical trials.

Figure 23: Two-way sensitivity of CDx vs CLIA-certified prognostic



4.5 Market events and strategic pathway effects

There are a multitude of forces that can cause a market to either experience rapid growth or evaporate. In the context of complex molecular diagnostics, there are a couple of key recent events that could dictate the future of the complex diagnostic market, and whether or not the '-omics' revolution can gain wide clinical adoption. In the sections below, I present some of the most impactful events and how they could influence the structure of the strategic decisions outlined above.

Regulatory

Regulation in healthcare is one of the major forces that has gained significant weight over the past decade. In the complex diagnostics space, three draft guidance documents issued by the FDA have indicated what will likely be a more stringent approach to device approval. Two of the documents deal with companion diagnostics, which I address first, and one deals with in-vitro diagnostic multivariate index assays (IVDMIAs) which I address second.

The companion diagnostic documents present three key points that impact the development of in vitro companion diagnostics, and potentially the model structure above. First, if a therapy is going to depend on diagnostic results, the diagnostic will have to be approved by the FDA. This is in line with the FDA's stance that the higher the risk to the patient, the more involved the organization should be in allowing a device to enter the market. Second, the ideal scenario outlined by the FDA is for the device and the drug to go through clinical trials in tandem. The organization is open to in vitro diagnostics gaining approval for existing therapeutics, but still identifies the joint development as the ideal development pathway before seeking regulatory approval. Finally, labeling for companion diagnostics will identify the type of FDA approved test, not the specific manufacturer's test.

The regulatory approach described above has significant implications for the development of complex diagnostics. First, if the tests are going to impact treatment choices, they will have to go through the FDA. This directly impacts the cost of development by requiring fully-loaded prospective clinical trials to prove the device works. Additionally, as the technology underlying these tests becomes more complex, regulatory knowledge will have to expand in tandem to effectively interpret the methodology and results from the tests. Given the lag between the emergence of companion diagnostic technology in 1998 with Her2 testing and the issuance of an opinion on companion diagnostic development by the FDA in 2005, it is unlikely that regulatory knowledge will be able to keep pace with technological advancements. The increase in cost and the lag in regulator knowledge manifest in strategic decisions by decreasing the likelihood of regulatory approval, decreasing the risk-adjusted NPV of a project, all else equal.

Similar to the companion diagnostic guidance, the FDA has also issued a perspective on IVDMIAs. Per the FDA, IVDMIAs are "in vitro diagnostics that involve the interpretation of multiple variables for a single patient-specific result" and "provide a result whose derivation is non-transparent and cannot be independently derived or verified by the end user". The reason the FDA is addressing this category of testing directly is that nearly of the IVDMIAs introduced to date have used a CLIA-certified laboratory to reach the market, effectively avoiding the longer and more costly FDA PMA or 510(k) process. However, the opinion of the FDA is that IVDMIA use is typically high risk and the unique interpretation function embedded in many of the tests creates a scenario requiring FDA approval.

This guidance presents a significant shift in the structure of the decision tree outlined in Section 4.1 and the potential for success of a newly developed technology incorporating IVDMIA characteristics. For one, the CLIA-certified branch that avoids the cost of a fully-loaded prospective clinical trial effectively goes away. No longer can a test with a unique interpretation function (Genomic Health, AviaraDx, etc.) reach the market without a 510(k) or PMA approval. As with companion diagnostics, this increases the risk discount for the

development process, decreasing the risk-adjusted value of a new technology. Additionally, the decision to not include a manufacturer's specific test in the drug label means there is a much higher likelihood of 'me-too' competition with second and third entrants to the market for a specific test (e.g. Her2), representing a much more difficult market environment for a diagnostic.

Reimbursement and pricing

Reimbursement and pricing risk has increased over the past decade as more attention is directed towards to the total cost of healthcare in the United States. The risk of reimbursement is to some extent tied in with regulatory approval risk, in that depending on the regulatory pathway chosen for a new technology, different outcomes are more likely for reimbursement in both amount and classification. Though it is not guaranteed, if a technology goes through the FDA approval process, the technology is more likely to gain a category 1 CPT code. A category 1 code is significant, because it removes a significant barrier for gaining adoption among the payer community. When a category 1 code is assigned by the AMA, it "represents a procedure that is consistent with contemporary medical practice and is widely performed" and provides a standardized pathway for test reimbursement. Vermillion's OVA1 test for ovarian cancer is an example of a test benefitting from recently gaining a category 1 code classification.

In contrast, one could be assigned a category 3 code, representing investigational use and a procedure that does not yet have FDA approval. When in category 3, a company must go payer by payer to convince each that the test is worth paying for, representing a significant amount of effort to promote market adoption. Companies that have not pursued full FDA approval, such as Genomic Health, have had to convince individual payers that the benefit derived from their test is worth the price they're asking.

As it relates to the strategic decisions outlined above, uncertainty over pricing outcomes and reimbursement policies impacts both the potential success in the market, as well as the likelihood of commercial launch. If a test is going to remain in the laboratory-developed category, then the effort expended to promote market adoption must be justified by a similar premium in pricing or certainty around speed of market adoption. Alternatively, uncertainty over reimbursement decisions may increase the market adoption risk such that the relative attractiveness of a partnership increases to the point that it becomes the most attractive pathway.

Intellectual property protection

An implicit assumption in the analysis above is that a new project will have a strong enough IP position that the developer will be able to protect its test in the market. Historically, IP advantages have been derived from two sources: patented markers and proprietary algorithm development. While a company may be able to avoid filing patents for its algorithms and

maintain protection of their proprietary algorithms through careful human resource management and keeping testing in-house, recent events have created significant uncertainty around the 'patent-ability' of genes and biomarkers.

First, Myriad Genetics has been defending the validity of its patents for multiple years now, the primary question being whether or not the patents are claims on "laws of nature," which cannot be patented, or claims to specific applications of the laws of nature, which are patentable. This case appeared before the Supreme Court only to be sent back to the appeals court this month[d] for further deliberation and examination. At the same time, the US Supreme Court invalidated two patents held by Prometheus Laboratories, a subsidiary of Nestlé. Under the 'laws of nature' provision, the court found that the patents held by Prometheus Laboratories only presented a recitation of the laws of nature[39].

These rulings are significant for the companion diagnostic and IVDMIA industry because in the absence of patentability, or given increased risk that patents will be revoked, competition can significantly increase for a set of biological markers. This directly impacts the probability of a successful market outcome, making it less likely that successful market adoption levels can be achieved. Additionally, the temporary monopoly power gained through patent protection may jeopardize the ability of a new project to maintain pricing above marginal cost in future years, significantly eroding future value.

Roche's unsuccessful bid for Illumina

On a more positive note, Roche initiated a $44.50 per share hostile bid for all the shares of Illumina on January 25, 2012, representing a total consideration of $5.7 billion. In March this bid was revised upwards to $51.00 per share, representing a total value of $6.7 billion, in light of Illumina's rejection of Roche's initial bid. The revised bid represents an 83% premium over Illumina's $27.82 closing price on November 30, 2011, and approximately a 6x multiple on Illumina's annual sales. On April 18 2012, Roche decided to not extend their offer in the face of continued rejection by Illumina.

While the acquisition offer by Roche was ultimately unsuccessful, it sends a strong signal in the market as to the potential for sequencing technology, and potentially drug development. Already a market leader in companion diagnostics and sequencing technology, Roche's acquisition of Illumina was intended to accelerate the adoption of sequencing technology into companion diagnostics and clinical settings[22]. By rejecting the sweetened offer, Illumina has also sent a signal that their perspective for value creation over the next several years in the industry is likely greater than the offer made by Roche. Though ultimately not accepted,

[d] March 2012

Roche's offer is an encouraging event for companies at the forefront of sequencing and diagnostic technology, both as a signal for value creation events and potential exits.

4.6 Achieving commercial success with new ventures

It is clear from the decision tree analysis above that the there is a profitable and economically viable business model that can be built for a new molecular diagnostic technology. As discussed in the second section of this thesis, the most positive funding trend in venture financing has supported the CLIA-certified lab services segment. This is exactly in line with the outcome of the decision analytic model, providing an encouraging outlook for both the product manager and entrepreneur launching a new molecular diagnostic.

However, pursuing this pathway is ultimately dependent on several key assumptions about market structure. As the forces that shape the molecular diagnostic market continue to evolve, it is possible that different pathways may become the optimal pathway. If regulators decide that more stringent oversight of the sector is needed, it may be that a new diagnostic cannot reach the market without a prospective clinical trial intended for FDA approval. If the required investment in research and development for a working, validated technology continues to grow, it may become impossible for a new technology to survive independently, leaving only partnership arrangements for new ventures.

In addition, from the perspective of a new diagnostic technology that still has to achieve technical validation, a companion diagnostic is only a marginally positive NPV project. While many companies have indicated interest and actively pursued companion diagnostics, this has largely occurred only after the initial technical R&D efforts have been sunk with the goal of developing either a platform technology or prognostic test. If new technologies are ever going to be able to deliver a personalized medicine paradigm, then the value split between drug and diagnostic will have to shift. Currently, there is not a strong economic case from the perspective of the diagnostic manufacturer for a companion diagnostic, particularly for a completely novel technology.

As a final note on the modeling framework presented above, one must be cautious when adapting decision tree analyses to any negotiation or project evaluation. While the trees are powerful, it is an analysis that can be easily biased depending on the perspective of the analyst; an 'eye of the beholder' effect. For example, consider a new venture considering whether it should accept a partnership offer or go proceed to the next phase of commercial development based on a term sheet its investors have offered. In the scenario where a partnership is struck, there is a lump sum payment up-front with royalties based on expected sales of the product. In the continued development scenario, the company raises enough money from existing investors to fund their next clinical trial. How might the optimal decision change depending on your perspective?

Consider this potential scenario: in this hypothetical company's current capitalization table, the scientific founders own 25% of the company. If they take the funding, the scientific founders are diluted down to 10% ownership. The CEO, on the other hand, owns 8% now, and is stepped up to 10% after raising the additional funding. In this simple set-up, it's clear the scientific founders will prefer taking the partnership now, while the CEO will go for the internal investment (provided total NPV is roughly equivalent in both scenarios). In this way, stakeholder perspective can have a significant impact on the optimal decision pathway, without any change to the probabilities of success or total commercial NPV of the new project.

It is only through the positive combination of market economics, financing, and incentives that a new diagnostic technology will be able to bridge the gap to the clinic. There is currently an established pathway that provides an economically viable pathway for new technologies, though shifts in the market structure have to potential to accelerate or extinguish the evolution of 'high-value' molecular diagnostics. As these market shifts occur, using the framework developed in this thesis will provide a systematic way of understanding the ultimate impact on optimal development pathways and the best strategic decisions for a diagnostic technology.

5. Discussion and Conclusion

Common among most debates about genomic-based testing and personalized treatment paradigms is the perception that these new testing approaches, once available in the clinic, will improve patient outcomes and the quality of care. The hypothesis supporting this assumption is that with improved physician understanding of disease, the better able they will be to treat a patient. However, while general agreement exists that these technologies would be good for patients once in the clinic, bridging the gap from lab to clinic has proven more difficult than expected for molecular testing.

As discussed in the second chapter, improved efforts to provide funding for these ventures has brightened the outlook for these new technologies. Programs such as the NCI's new Phase II Bridge Award and increasing involvement from foundations point to an encouraging trend in bridging the gap between research and clinical use. Additionally, the positive trend in funding from the venture capital community for lab service companies further reinforces the perspective that these technologies have a viable path to market.

In the case examples of Genomic Health and Immunicon in the third chapter, one can see how that path can evolve for a new technology moving from the academic arena to clinical adoption. The strategic decisions faced by each company highlight the importance of technology platform, partnership specifications, clinical utility, tissue type, and regulatory pathway. While each managed to bridge the gap to the clinic, the degree to which they *successfully* managed to achieve clinical adoption was directly linked to the decisions made along their development pathway

Building off the case examples, chapter four develops a model to characterize and analyze the strategic decisions facing a new molecular diagnostic technology. Based on the base case parameters, it is clear that there currently exists an economically viable pathway to market for a new technology commercialized through a CLIA-certified laboratory. This pathway certainly represents a 'light at the end of the tunnel' for the entrepreneur or project manager, but one must note that it is quite sensitive to assumptions about market adoption, pricing, and the probability of success at each development point. If either the market expectations or probability of success for a prognostic fall below critical thresholds, a companion diagnostic technology may be the more attractive route. Ultimately, provided this economically viable basis for molecular oncology diagnostics, investment and development activity should continue to increase in the short term, ushering in improved outcomes for oncology patients.

Beyond this thesis, future work may also concentrate on specific elements of the decision tree to develop a more nuanced appreciation of certain development milestones. For example, different types of platforms and/or tissue types can be used in the initial stages of technical validation. It is entirely possible that choosing to use blood over solid tumor samples may

improve the chances of success for technical validation. Furthermore, developing a more robust statistical basis for the probability of success can provide a common basis to assess the viability of future projects. This focused examination of each phase of the project would enhance strategic decision making for molecular diagnostics, potentially attracting more activity beyond expectation.

In addition to evaluating the factors that ultimately drive the conditional probability of success for different nodes in the decision tree, a more nuanced evaluation of the ultimate commercial 'modes of success' would provide a more robust understanding of how to achieve commercial success. In the scenario analyzed above, this thesis has primarily focused on the scenario where commercial success assumes a single new test is widely adopted with a favorable reimbursement level. However, one can certainly imagine scenarios where a new technology only achieves moderate market adoption, but is a viable project because of different assumptions around cost structure or funding needs. Or, it is possible that the prospect of a portfolio of tests, instead of just one test, justifies initial investment in R&D. Finally, future work that develops a more robust understanding of the factors influencing exits for molecular diagnostics, whether an IPO or trade sale, will greatly enhance the ability of the new venture to evaluate strategic options.

This thesis lays out a base structure to evaluate strategic options for molecular oncology diagnostics, illustrating the underlying factors driving increasing investment in CLIA-certified laboratory services and identifying the conditions driving economic success in molecular diagnostics for oncology. Multiple factors will continue to influence both the structure and inputs that drive the strategic options facing a new project, from regulatory decisions to intellectual property rulings. However, even in the face of this uncertainty, investment and development activity in molecular diagnostics for oncology will likely increase with the goal of capturing the economic value derived from enhanced patient cost outcomes.

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Appendix I – 2010 Venture Capital Investment Summary

Industry	2010 Amount Invested (000's USD)				
	Qtr 1	Qtr 2	Qtr 3	Qtr 4	2010 Total
Biotechnology	744,869	1,353,077	902,638	684,934	3,685,517
Business Products and Services	158,482	139,298	73,389	76,838	448,007
Computers and Peripherals	130,246	146,116	91,348	148,904	516,614
Consumer Products and Services	112,681	169,844	112,274	134,195	528,994
Electronics/Instrumentation	92,747	126,224	79,026	77,240	375,237
Financial Services	220,133	146,124	89,950	71,722	527,929
Healthcare Services	24,934	49,849	139,440	58,700	272,923
Industrial/Energy	738,565	1,348,156	417,822	853,472	3,358,014
IT Services	317,800	434,951	480,927	434,742	1,668,420
Media and Entertainment	329,696	323,465	235,915	533,404	1,422,479
Medical Devices and Equipment	580,965	756,718	578,220	399,956	2,315,861
Networking and Equipment	127,996	284,877	118,430	134,537	665,840
Other	80	11,993	6,660	7,389	26,122
Retailing/Distribution	52,623	46,200	54,485	23,970	177,278
Semiconductors	329,168	261,280	235,810	125,459	951,717
Software	763,932	1,102,441	971,880	1,125,554	3,963,807
Telecommunications	236,331	199,589	356,714	125,989	918,622
Grand Total	4,961,248	6,900,202	4,944,927	5,017,003	21,823,380

Source: PriceWaterhouseCoopers/National Venture Capital Association MoneyTree™ Report
Data: Thomson Reuters
Retrieved from: http://www.nvca.org/

Appendix II – Thomson VentureXpert Industry Codes and Key Words

Code	Description
4100	Human Biotechnology
4110	Medical Diagnostic Biotechnology Products
4111	In Vitro Monoclonal Antibody Diagnostics
4112	In Vivo Monoclonal Antibody Diagnostics
4113	DNA/RNA Probes
4119	Other Medical Diagnostic Biotechnology
4120	Therapeutic Biotechnology Products
4121	Therapeutic Monoclonal Antibodies
4122	Immune Response Effectors (interferons, vaccinations)
4123	Other Therapeutic Proteins (incl. hormones)
4129	Other Therapeutic Biotechnology
4130	Genetic Engineering
4510	Biotech Related Analytical Instruments & Apparatus
4520	Biotech Related Production Equipment
4599	Other Biotech Research & Production Equipment
4600	Biotech Related Research & Other Services
4610	Pure & Contract Biotechnology Research
4699	Other Biotechnology Services
5110	Diagnostic Services
5130	Diagnostic Test Products & Equipment
5350	Medical Monitoring Equipment

Key Words
Cancer
Oncology
Diagnostic
Testing
Platforms
Biomarker
Services

Appendix III – Simplified example of clinical utility

Clinical utility is, by definition, the ability to deliver more clinical value given the cost of the intervention provided. This can manifest as providing the same results more cheaply, charging more but delivering superior patient outcomes, or a combination of the two. To illustrate this, I present a highly stylized example below for diagnostic testing.

Assume a test costs $3,500 and is used to decide whether a patient will respond to treatment or not. For this particular test, it identifies a patient subgroup based on their genetic profile to determine whether they will recover from the disease without receiving treatment. Also assume it's a perfect test that shows 20% of diagnosed patients should not receive treatment, which on average costs $20,000 per year. For this hypothetical disease, there are approximately 25,000 people per year who would receive the treatment in the absence of the diagnostic. Finally, if a patient receives the treatment, then they will experience a reduced quality of life, the equivalent of 0.6 quality adjusted life-years (QALYs[e]) for the year of receiving the treatment, after which they full recover back to normal life (equivalent of 1 QALY). If the patient did not receive the treatment, then they would only have a reduced quality of life from the disease, the equivalent of 0.8 QALYs, and recover back to normal life (equivalent of 1 QALY).

It should be clear that there are two sources of value for the test: reducing treatment costs and improving patient quality of life. Without the diagnostic, 25,000 people are treated per year, at a cost of $20,000 for $500 million in treatment costs per year. With the diagnostic, 20% of patients are now not indicated for the treatment, reducing treatment costs to $400 million per year and generating $100 million of treatment cost savings. In addition, that 20% that don't receive the treatment gain 0.2 QALYs per person, for a total of 1,000 QALYs gained through the use of the diagnostic.

Now we must introduce the question of testing costs. All 25,000 patients will have to receive the test in order to identify the 5,000 that won't get the treatment. So at a maximum, the diagnostic could perfectly offset the treatment cost savings of $100 million. This would represent a test price of $4,000, for a total testing cost of $100 million for the 25,000 indicated patients. More likely, however, the diagnostic manufacturer won't be able to capture 100% of the economic value delivered, and a price under $4,000 will be set to promote the cost effectiveness of the test.

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[e] QALYs are a measure of an individual's quality of life, rated on a scale from 0 to 1. 0 corresponds to death, and 1 corresponds to perfect health. For a more detailed discussion, see the NICE discussion here: http://www.nice.org.uk/newsroom/features/measuringeffectivenessandcosteffectivenessthegaly.jsp

Appendix IV – Genomic Health fundamental comparable data

	Values ($000's)					% of Sales					
	2006	2007	2008	2009	2010	2006	2007	2008	2009	2010	*Average*
Product Revenues	27,006	62,745	108,658	146,581	174,870	100%	100%	100%	100%	100%	
Cost of Products	9,741	16,956	26,694	32,198	34,292	36%	27%	25%	22%	20%	*26%*
Selling & Marketing	23,846	34,580	44,046	57,961	68,319	88%	55%	41%	40%	39%	*53%*
General & Admin	11,628	15,697	22,505	26,042	30,878	43%	25%	21%	18%	18%	*25%*
R&D	12,020	20,171	25,711	32,593	30,344	45%	32%	24%	22%	17%	*28%*
Cost of Product Revenues											
Tissue sample processing	7,568	12,071	18,893	22,103	23,802	28%	19%	17%	15%	14%	*19%*
Employee stock	167	375	491	364	342	1%	1%	0%	0%	0%	*0%*
License Fees	2,173	4,885	7,801	10,095	10,490	8%	8%	7%	7%	6%	*7%*
Total COGS	9,908	17,331	27,185	32,562	34,634	37%	28%	25%	22%	20%	*26%*
Selling & Marketing											
Personnel	11,371	17,225	21,208	29,589	35,288	42%	27%	20%	20%	20%	*26%*
Employee Stock Comp	779	1,876	2,622	3,171	3,086	3%	3%	2%	2%	2%	*2%*
Promotional & marketing	7,437	8,972	10,961	12,402	13,665	28%	14%	10%	8%	8%	*14%*
Travel, meetings, seminars	2,910	5,294	6,086	7,468	8,253	11%	8%	6%	5%	5%	*7%*
Infrastructure & other	2,128	3,089	5,791	8,502	11,113	8%	5%	5%	6%	6%	*6%*
Total S&M expense	24,625	36,456	46,668	61,132	71,405	91%	58%	43%	42%	41%	*55%*
R&D Expenses											
Personnel	6,211	11,487	16,534	18,413	16,650	23%	18%	15%	13%	10%	*16%*
Employee Stock Comp	821	1,822	2,913	3,098	2,881	3%	3%	3%	2%	2%	*2%*
Collaboration Exp	1,486	1,320	1,433	2,192	2,244	6%	2%	1%	1%	1%	*2%*
Reagents & lab Supplies	773	1,709	1,972	2,976	2,068	3%	3%	2%	2%	1%	*2%*
Infrastructure & Other	3,550	5,655	5,772	9,012	9,382	13%	9%	5%	6%	5%	*8%*
Total R&D	12,841	21,993	28,624	35,691	33,225	48%	35%	26%	24%	19%	*30%*
G&A Expenses											
Personnel	4,530	6,053	9,184	10,001	13,591	17%	10%	8%	7%	8%	*10%*
Employee Stock Comp	1,137	2,152	3,112	3,522	4,035	4%	3%	3%	2%	2%	*3%*
Billing & Collection Fees			3,922	5,611	6,524	--	--	4%	4%	4%	*4%*
Bad debt Expense			1,278	1,438	2,231	--	--	1%	1%	1%	*1%*
Professional Fees & Other	7,098	9,644	8,121	8,992	8,532	26%	15%	7%	6%	5%	*12%*
Total G&A Expense	12,765	17,849	25,617	29,564	34,913	47%	28%	24%	20%	20%	*28%*
Employees						*Payment per Employee*					
R&D			109	109	99	$ 67,683	$ 72,779	$ 71,887	**		$ 70,783
CLIA Lab Ops			72	84	87						
Info Tech			49	60	60						
S&M			117	152	169	$ 208,805	$ 194,664	$ 181,265			$ 194,911
G&A			40	48	57	$ 238,439	$ 208,354	$ 229,600			$ 225,464
Total	191	288	387	453	472	*** R&D includes CLIA Lab Ops and Info Technology*					
Test Volumes	14000	25000	38500	50000	55000						
Cumulative Volumes	21500	46500	85000	135000	190000						

Appendix V – Immunicon-Veridex License Agreement Summary

Source: Immunicon S-1 filed December 5, 2003

In August 2000, we entered into a development, license and supply agreement with Ortho-Clinical Diagnostics, or OCD, a Johnson & Johnson company, which subsequently assigned all rights and obligations under the agreement to Veridex, a Johnson & Johnson company. In November 2003, as a result of data from various clinical research and development trials and the overall status of our product development program, we and Veridex amended the agreement to redefine some of the development milestones that had not been completed as of the amendment date.

Under the terms of this agreement, we granted to Veridex a worldwide exclusive license in the field of cancer to commercialize cell analysis products incorporating our technologies.

With respect to the reagents for the products developed under the license to Veridex, we manufacture and provide bulk reagents to Veridex, and Veridex is responsible for the packaging and distribution of these products. Veridex is obligated to reimburse us at our cost for the bulk reagents, consumable products and disposable items we deliver to them. Upon the sale by Veridex of the products, Veridex is obligated to pay us approximately 30% of their net sales less the cost previously reimbursed for these products. We are obligated under the agreement to manufacture the CellSave Preservative Tube as well as certain other ancillary products and to sell these finished products to Veridex for resale in connection with the cancer-related cell analysis products.

We have also established a sales agency arrangement with Veridex with respect to our sample preparation and cell analysis systems, such as the CellSpotter Analyzer and CellTracks Analyzer. Under this arrangement, Veridex is our exclusive sales, invoicing and collecting agent and exclusive instrument and technical service provider for these systems in the field of cancer. Veridex is responsible for all expenses for marketing, sales and training, and we are responsible for all software development and validation as well as quality control and quality assurance. We are responsible for shipping systems pursuant to purchase orders received by Veridex. We pay Veridex a commission on each sale or lease of our instruments. Some customers may enter into a reagent rental agreement with Veridex, whereby the reagent price also carries an amortized cost of the instrument, based on an agreed test volume. In these cases, Veridex will pay us a percentage of the fully loaded cost of the instrument when it is placed in the account. We are responsible for the costs associated with the one year warranty period. Veridex has the option under the agreement to convert the sales agency relationship to a sole distributorship arrangement upon 12 months notice. Under this distributorship arrangement, we would be required to supply Veridex as forecasted and ordered.

We are responsible for developing these cell analysis products as well as our cell analysis systems under a development plan. We are also responsible for managing and administering all clinical trials under the development plan. This plan is subject to the approval of a joint steering committee comprised of members designated by us and Veridex. Veridex has the majority of votes on this committee, although the entire agreement is subject to arbitration provisions in the event of any disputes that may arise. We must pay the first $5 million in clinical trial costs for the first cell analysis product for general population screening for a major cancer, and Veridex is responsible for the next $5 million of such clinical trial costs. We have agreed to negotiate in good faith for the allocation of costs in excess of $10 million.

Beginning with commercialization of the first product under this agreement, we are obligated to invest in certain research and development activities an amount equal to at least 10% of Veridex's net sales from these products. However, beginning with the first calendar year after the amount of these net sales exceeds $250 million we are only required to invest an amount equal to at least 8.5% of these net sales. The agreement also provides that Veridex will make payments to us upon the completion by us of certain development and clinical trial milestones. To date, we have received $4 million of license and milestone payments. Veridex is responsible under the agreement for obtaining all regulatory approvals, in consultation with us, for these cell analysis products in the field of cancer.

The agreement has an initial term of 20 years and is automatically renewed for three-year terms unless earlier terminated. There are various conditions that allow either party to terminate the agreement, including a material breach by either party or by mutual agreement. Veridex may also terminate for additional reasons including upon a change of control of us, as defined in the agreement, at any time prior to commercialization of any cell analysis products under the agreement with or without reason upon 180 days' prior written notice, or at any time following commercialization of the first cell analysis product under the agreement with or without reason upon 24 months' prior written notice. In certain circumstances of termination, Veridex may, at its option, retain certain worldwide rights to sell our cell analysis products if it agrees to pay us any unpaid license and milestone payments and an ongoing net sales royalty.

Appendix VI – Reproduced press releases

Press Release 1: Plexxicon announcement of Zelboraf and BRAF V600E

http://www.plexxikon.com/view.cfm/95/Press-Releases

Plexxikon Announces FDA Approval of ZelborafTM (vemurafenib) and Companion Diagnostic for the Treatment of Patients with BRAF Mutation-Positive Metsatatic Melanoma

Zelboraf Improves Survivial in Patients with BRAFV600E Mutation-Positive Metastatic Melanoma, a Deadly Form of Skin Cancer

Berkeley, CA — August 17, 2011

Plexxikon Inc., a member of the Daiichi Sankyo Group, today announced that the U.S. Food and Drug Administration (FDA) has approved ZelborafTM (vemurafenib), for the treatment of patients with BRAFV600E mutation-positive inoperable or metastatic melanoma as detected by an FDA-approved test. Zelboraf is an oral drug that selectively targets this BRAF mutation that is present in about half of all cases of melanoma. Zelboraf was formerly known as PLX4032. The cobas 4800 BRAF V600 Mutation Test, a companion diagnostic which determines a patient's eligibility for Zelboraf treatment if the tumor tests positive for the BRAFV600E mutation, also was approved by the FDA.

Daiichi Sankyo, Inc. and Genentech, a member of the Roche Group, will co-promote Zelboraf in the United States. The companies expect Zelboraf to be available in the marketplace in August 2011.

"As the first personalized medicine approved for the treatment of patients with BRAFV600E mutation-positive melanoma, Zelboraf represents a significant new treatment option for these patients suffering from inoperable or metastatic melanoma. We are grateful for the clinical trial participants, clinical investigators, collaborators and dedicated employees, who have all contributed to this important advancement in cancer treatment," stated K. Peter Hirth, Ph.D., chief executive officer of Plexxikon. "Additionally, another benefit of a personalized medicine like Zelboraf has been the ability to accelerate development, enabling Plexxikon and its collaborators to bring this drug to market in less than six years from our discovery of the molecule in 2005. With that same focus and commitment, Plexxikon looks forward to advancing our pipeline of diverse product candidates and pursuing the discovery and development of other novel agents."

Zelboraf Efficacy in BRAFV600E Mutation-Positive Metastatic Melanoma

The FDA approval follows positive results of an interim analysis in January 2011 of BRIM3, a Phase 3 clinical study initiated in December 2009.

BRIM3 is a global, randomized, open-label, controlled, multicenter, Phase 3 study that compared Zelboraf to dacarbazine chemotherapy, in 675 patients with previously untreated BRAFV600E mutation-positive, unresectable (inoperable) or metastatic melanoma. The BRIM3 study met the pre-specified criteria for co-primary endpoints of overall survival (OS) and progression-free survival (PFS) in January 2011. Results were reported in June 2011 at the American Society of Clinical Oncology Annual Meeting and simultaneously published in the June 2011 issue of the New England Journal of Medicine. An updated analysis of the data as of March 31, 2011 showed:

• In BRIM3, the risk of death was reduced by 56 percent for patients who received Zelboraf compared to those who received chemotherapy (hazard ratio [HR]=0.44, $p<0.0001$).

• At the time of analysis, median overall survival of patients receiving Zelboraf had not been reached, and was 7.9 months for those receiving chemotherapy

• Patients who received Zelboraf also had a 74 percent reduced risk of the disease getting worse or dying (PFS) compared to those who received chemotherapy (HR=0.26, p<0.0001). Median PFS was 5.3 months for those who received Zelboraf compared to 1.6 months for those who received chemotherapy.

• The confirmed investigator-assessed response rate (those who experienced ≥30 percent tumor shrinkage) in patients who received Zelboraf was 48.4 percent (1 percent complete responses and 47.4 percent partial responses) compared to 5.5 percent (partial responses) for those who received chemotherapy (p<0.0001).

A Phase 2 study, BRIM2, initiated in September 2009, enrolled 132 previously treated patients with metastatic melanoma with the BRAF mutation. The primary endpoint was confirmed overall response rate as assessed by independent review. Results included:

• In BRIM2, Zelboraf shrank tumors thirty percent or greater in 52 percent of patients.

Important Safety Information for Zelboraf

This information does not take the place of the patient talking to their doctor about their medical condition or their treatment with Zelboraf.

Zelboraf is a prescription medicine used to treat a type of skin cancer called melanoma that has spread to other parts of the body or cannot be removed by surgery, and has a certain type of abnormal "BRAF" gene.

Zelboraf may cause a type of skin cancer called cutaneous squamous cell carcinoma (cuSCC), that usually does not spread to other parts of the body. Patients should check their skin and tell their doctor about skin changes including a new wart, a skin sore or reddish bump that bleeds or does not heal, or a mole that changes size or color.

While taking Zelboraf, patients should avoid going out in the sun. When patients go outside, they should wear clothes that protects their skin, including head, face, hands, arms and legs. They should use lip balm and a broad-spectrum sunscreen with SPF 30 or higher.

Possible serious side effects of Zelboraf include severe allergic reactions; severe skin reactions; changes in the electrical activity of the heart called QT prolongation, which can potentially be life-threatening; abnormal liver function tests; eye problems; or new melanoma lesions.

Common side effects of Zelboraf include joint pain, rash, hair loss, tiredness, sunburn or sun sensitivity, nausea, itching or warts.

These are not all of the possible side effects of Zelboraf. Patients must tell their doctor if they have any side effect that bothers them or does not go away. For more information about side effects, patients should ask their doctor or pharmacist.

Patients should call their doctor for medical advice about any side effects. Patients or their caregivers are encouraged to report negative side effects of prescription drugs to the FDA at 1-800-FDA-1088 or at www.fda.gov/medwatch. They may also report side effects to Genentech at 1-888-835-2555.

Patients should read the Zelboraf full Prescribing Information and Medication Guide for additional important safety information at www.zelboraf.com.

About Zelboraf (vemurafenib / PLX4032)

Zelboraf is an oral, small molecule, kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with BRAFV600E mutation as detected by an FDA-approved test. Zelboraf is not recommended for use in melanoma patients who lack the BRAFV600E mutation. Plexxikon utilized its structure-guided chemistry platform to discover Zelboraf, and initiated clinical development in 2006. Plexxikon and Roche

signed a license and collaboration agreement in 2006 to co-develop Zelboraf. Under a 2005 agreement, a DNA-based companion diagnostic to identify patients whose tumors carry the BRAFV600E mutation was co-developed by Roche Molecular Systems and Plexxikon in parallel with the therapeutic development of Zelboraf. In May 2011, Plexxikon also announced that a separate application for market approval of Zelboraf was submitted to the European Marketing Agency (EMA) in addition to the market approval application in the U.S.

Studies of Zelboraf in combination with other approved and investigational medicines as well as in other tumor types are being conducted by Roche, Plexxikon and Genentech. More information about ongoing Zelboraf studies is available at www.clinicaltrials.gov (in the U.S.) or www.clinicaltrialsregister.eu or on the Roche Clinical Trials Registry at www.roche-trials.com (in the EU). Genentech can also be contacted by calling the company's clinical trial call center at 888-662-6728 or emailing genentech@druginfo.com.

About Melanoma and BRAF mutation

Melanoma is the most serious type of skin cancer and is growing at a rate of about five to six percent annually. More than 70,000 people in the U.S. and 160,000 people worldwide are diagnosed with melanoma each year. It is one of the deadliest cancers, with a five-year survival rate of 15 percent for people with advanced (Stage IV) melanoma, according to the American Cancer Society. Risk factors for melanoma include a positive family history of melanoma, prior melanoma, multiple clinically atypical moles or dysplastic nevi, inherited genetic mutations, fair skin and sun exposure. However, melanoma can occur in any ethnic group and also in areas of the body without substantial exposure to the sun. The BRAF gene is a key component of a pathway involved in normal cell growth and survival. BRAF mutations may lead to uncontrolled cell growth, and are thought to occur in about half of all cases of melanoma and eight percent of all solid tumors.

About Plexxikon

Plexxikon, a member of the Daiichi Sankyo Group, is a leader in the structure-guided discovery and development of novel small molecule pharmaceuticals to treat human disease. The company's lead drug Zelboraf (vemurafenib/PLX4032) was approved by the FDA in August 2011, and will be co-promoted in the U.S. by Daiichi Sankyo, Inc. and Genentech. PLX3397, the company's next oncology candidate, has advanced to Phase 2 testing in 2011. The company is developing a portfolio of clinical and preclinical stage compounds to address significant unmet medical needs in oncology, as well as in several other therapeutic indications. Plexxikon's proprietary Scaffold-Based Drug Discovery™ platform integrates multiple state-of-the-art technologies, including structural screening as a key component that provides a significant competitive advantage over other drug discovery approaches.

Press Release 2: Immunicon – Veridex Legal Battles

http://www.cafepharma.com/boards/showthread.php?t=208311

Immunicon Seeks Termination of Exclusive Marketing Agreement and Damages from Veridex

Thursday May 31, 5:00 PM EDT

HUNTINGDON VALLEY, Pa., May 31, 2007 (BUSINESS WIRE) -- Immunicon Corporation (NASDAQ-GM:IMMC) announced today that it is seeking to end its exclusive arrangement with Veridex, LLC, a subsidiary of Johnson & Johnson. In an arbitration demand filed today with the American Arbitration Association, Immunicon seeks termination of the 20-year exclusive worldwide agreement to market, sell and distribute Immunicon's cancer diagnostic products, rescission of all licenses currently held by Veridex under that agreement, and compensatory and punitive damages based on "repudiation and fundamental breaches by Veridex of its contractual, agency and other fiduciary obligations to market, sell and distribute Immunicon's cancer diagnostic products."

Under the agreement, Veridex is appointed as exclusive sales agent, licensee and distributor responsible for selling cancer diagnostic products developed by Immunicon and remitting royalties on the sales of reagent kits to Immunicon. In its arbitration demand, Immunicon alleges, among other things, that Veridex breached its

"obligation to use its best efforts to market" those products by "squander(ing) the opportunity to promptly and aggressively launch the Immunicon Products in 2004" and thereafter "reneg(ing) on its express commitment to engage and deploy sales representatives to personally promote, or 'detail,' the Immunicon Products to doctors." According to the arbitration demand, "(w)hile seriously damaging to Immunicon and its shareholders, Veridex's actions are depriving cancer patients - who are in severe need of the best treatment and testing - and their doctors of Immunicon's FDA-approved cancer diagnostic tests."

The agreement provides that the arbitration will take place before a single arbitrator, and that an award must be rendered within six months of the selection of the arbitrator. Selection of the arbitrator is expected to occur within forty five days from today. Immunicon has retained Jonathan J. Lerner, Esq. of the law firm of Skadden, Arps, Slate, Meagher and Flom LLP to represent it in the arbitration.

Immunicon also announced it has discontinued its previously-disclosed contract audit following receipt of Veridex's response to the audit. The demand for arbitration alleges that "Veridex refused outright to permit a meaningful audit of its performance as exclusive sales agent and licensee for selling and marketing the Immunicon Products, and erected a series of other roadblocks to a meaningful audit."

On May 25, 2007, after Veridex was informed that Immunicon was discontinuing the audit and that Immunicon might file claims against it, Veridex sent Immunicon a notification asserting that Immunicon was in "material breach" of the agreement. Immunicon believes that Veridex's assertion is without merit.

Byron D. Hewett, Immunicon's President and CEO, stated, "We are mindful of the serious nature of the actions we are taking today, but we do not believe Veridex's conduct has left us any choice. We are at the mercy of our relationship with Veridex because Veridex represents our only sales and marketing outlet for the cellular analysis cancer diagnostic products covered by our agreement. Since the inception of this agreement in August 2000, we at Immunicon have successfully dedicated ourselves to our research and development obligations, as evidenced by the numerous FDA-cleared cancer diagnostic products we have developed. We have been frustrated by Veridex's unwillingness to devote sufficient efforts and resources to effectively promote those products. We have been rational, reasonable and patient with Veridex, but our management and board now believe that today's actions are in the best interests of our shareholders and are necessary to enable our products to reach the cancer patients who could benefit from the life-saving and life-enhancing capabilities of our diagnostic technology."

About Immunicon Corporation

Immunicon Corporation is developing and commercializing proprietary cell- and molecular-based human diagnostic and life science research products, and is providing certain analytical services to pharmaceutical and biotechnology companies to assist them in developing new therapeutic agents, with an initial focus on cancer disease management. Immunicon has developed platform technologies to identify, count and characterize a small number of rare cells in blood, such as circulating tumor cells and circulating endothelial cells that are important in many diseases and biological processes. Immunicon's products and underlying technology platforms also have application in cancer research and may have applications in other fields of medicine, such as cardiovascular and infectious diseases. For more information, please visit www.immunicon.com.

Forward-Looking Statements

This press release may contain "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. These forward-looking statements are often preceded by words such as "hope," "may," "believe," "anticipate," "plan," "expect," "intend," "assume," "will" and similar expressions. Immunicon cautions investors not to place undue reliance on these forward-looking statements, which speak only as of the date of this press release, are based on the current expectations and intent of the management of Immunicon and involve certain factors, such as risks and uncertainties that may cause actual results to be far different from those suggested by these statements. These statements are not guarantees of future performance and involve risks and uncertainties that are difficult to predict, including, but not limited to, risks and uncertainties associated with: Immunicon's dependence on Veridex, LLC, a Johnson & Johnson company, in the field of cancer cell analysis; the

ability to earn license and milestone payments under Immunicon's agreement with Veridex; Immunicon's capital and financing needs; research and development and clinical trial expenditures; commercialization of product candidates; Immunicon's ability to obtain licenses from third parties to commercialize products; Immunicon's ability to manage its growth; obtaining necessary regulatory approvals; reliance on third party manufacturers and suppliers; reimbursement by third party payors to Immunicon's customers; compliance with applicable manufacturing standards; retaining key personnel; delays in the development of new products or planned improvements to products; effectiveness of products compared to competitors' products; protection of Immunicon's intellectual property; conflicts with third party intellectual property; product liability lawsuits that may be brought against Immunicon; labor, contract or technical difficulties; and competitive pressures in Immunicon's industry. These factors are discussed in more detail in Immunicon's filings with the Securities and Exchange Commission. Except as required by law, Immunicon accepts no responsibility for updating the information contained in this press release beyond the published date, whether as a result of new information, future events or otherwise, or for modifications made to this document by Internet or wire services.

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SOURCE: Immunicon Corporation

Press Release 3: Veridex activity in CTC market

http://www.genomeweb.com/dxpgx/jj-building-portfolio-ctc-and-companion-diagnostics

J&J Building Portfolio for CTC and Companion Diagnostics

March 25, 2011

By Tony Fong

NEW YORK (GenomeWeb News) – With little fanfare, Johnson & Johnson is building out its capabilities in the molecular diagnostics space with a focus on circulating tumor cells and companion diagnostics development.

In recent interviews with GenomeWeb Daily News, officials from several J&J businesses outlined a strategy focused on continuing to build out the firm's CellSearch technology as well as the development of a next-generation CTC technology in collaboration with Massachusetts General Hospital.

Meanwhile, a new center of excellence focused on companion diagnostics is leveraging technology developed internally and by outside diagnostic firms to capitalize on growing interest in such tools among drug firms.

According to Werner Verbiest, head of the Companion Diagnostics Center of Excellence for the pharma group at J&J, "we really see molecular diagnostics as critical tools and critical enablers for personalized medicine," but clinicians need greater access to the technology.

"A lot of those technologies have been made at the hands of ... exotic and little labs, so we're looking at investments in companies and partnerships with companies to bring it closer to the clinic," said Verbiest, who is also the CEO of Virco, which J&J purchased in 2002. "We use different projects as drivers of those investments, so molecular diagnostics for us is fairly important."

J&J, he added, is evaluating how to approach the MDx market, and while some competitors have taken to making big-splash acquisitions, it may not be the best strategy for J&J in bringing companion diagnostics to the market.

"You go for targeted investments or targeted collaborations, and you don't need to own everything to make a difference," Verbiest said.

J&J is divided into three business segments — consumer sales, pharmaceutical, and medical devices and diagnostics. In 2010, the medical devices and diagnostics segment brought in sales of $24.6 billion, a 4 percent

increase from 2009, which included a 5 percent increase year over year in revenues for Ortho-Clinical Diagnostics to $2.1 billion.

In a research report last month, Goldman Sachs analyst Isaac Ro said that in a meeting with J&J management, an official was "bullish on the potential for molecular diagnostics as a high-growth category," and the firm's strategy focused on three areas: organic growth through investments in its Veridex business and Swiss molecular diagnostics firm Biocartis; licensing opportunities; and acquisitions.

J&J's interest in the molecular diagnostics space is evidenced by partnerships and investments that the New Brunswick, NJ-based firm has done in recent months. J&J Development Corp., the venture capital subsidiary of J&J, was part of an investor group that earlier this month participated in a $13 million round in protein biomarker company Astute Medical.

Last year, J&J was a participant in a Series B round by Biocartis that raised €30 million ($42.7 million).

In January, Janssen Pharmaceutica, part of J&J's Janssen Pharmaceutical division, announced it would develop assays on the Biocartis platform. In the same month, J&J participated in a $9 million Series C round by direct-to-consumer genomics firm 23andMe.

This year also started off with Veridex, a J&J business which develops in vitro oncology diagnostics, announcing a collaboration with Mass General aimed at technology for capturing, counting, and characterizing tumor cells from patient blood samples.

The five-year deal, the financial terms of which were not disclosed, is intended to create a next-generation platform for CTC detection and characterization.

Extending CTC to Personalized Medicine

In 2004, Veridex launched the first commercially available CTC test with the CellSearch platform. The test is now cleared by the US Food and Drug Administration for metastatic breast, prostate, and colorectal cancers. In addition, the firm is about to launch a test for melanoma based on the CellSearch technology, with a test for multiple myeloma to follow, said Bob McCormack, head of technology and strategy for Veridex.

The company is now in the midst of extending CellSearch's capabilities to, for example, image the cells and characterize them at the chromosomal, DNA, and protein levels. The platform now has the ability to characterize CTCs at the protein and chromosomal level, said McCormack.

Fluorescent in situ hybridization capabilities have also been developed for the technology "and we have that in the field now as a trial," he added, and RNA and DNA characterization can be achieved on CellSearch manually but not as an automated process.

That's where its deal with Mass General comes in. The partnership is focused on developing a benchtop platform for studies of the biology of rare cells at the protein, RNA, and DNA levels. The platform would be used by oncologists as a diagnostic tool for personalized care and by researchers "to accelerate and improve the process of drug discovery and development," Veridex and Mass General said in January.

Nicholas Dracopoli, vice president of biomarkers for Ortho Biotech Oncology Research & Development, told GWDN last week that a prototype device is in development. Early stage testing of the platform has begun and the testing of clinical samples are anticipated to take place during the next two years.

The platform is being designed around the functional analysis of CTCs "to extract actionable, clinical information from the cells," Dracopoli said. While the primary application of CellSearch has been for the enumeration of tumor cells of epithelial origin circulating in the patient's blood, the Veridex-Mass General system focuses on tumor cell characterization.

"So we want to set specifications around being able to isolate tumor cells with greater sensitivity, [and] to maximize the sensitivity in terms of the number of cells we can isolate from the blood," Dracopoli said.

"The critical point that we realized is that just creating another platform that isolates the cells is insufficient," Dracopoli said. What is needed, he said, is a system "that works within the context of a regulatory approved environment, that is able to deliver actionable, clinical information in real time, that will be able to inform oncologists as they treat patients, both to select therapy initially, and then to monitor that therapy for acquired resistance during treatment."

The goal ultimately is to develop a platform that will be used in house and by other companies developing companion diagnostics along with targeted therapies.

Dracopoli added that while the platform will be an immunoassay, the collaboration includes use of next-generation sequencing technology to sequence tumor cells "as a surrogate for an invasive biopsy of the tumor cells," in order to search for activating mutations in pathways.

By doing so, a better understanding can be gained of the critical cancer pathways that may be activated by genetic factors. Such mutations can then also be monitored for changes over time, Dracopoli noted, "and then you can adjust the targeted therapies to inhibit particular tyrosine kinases."

He emphasized, however, that the work between J&J and Mass General is not directed at inventing a new sequencing methodology. The plan is to partner with sequencing companies to develop integrated ways of progressing from cells captured by J&J and Mass General to DNA sequencing analysis, and then a computational biology read-out.

Traditional Sanger sequencing will be used for the same purpose, said Dracopoli, who did not rule out the possibility that a sequencing-based test could result from the collaboration.

"It would vary according to the individual biomarker," he said. "In some cases, it would be sequencing, in other cases, it would be a protein-based test. The difficulty we have when we think about companion diagnostics is there is no one test that is going to give us all the answers."

As a result, "many, many" assays may emerge from the collaboration that in addition to being DNA or protein-based, may be epigenetics- or RNA-based, Dracopoli said.

Diagnosing Drug Safety and Effectiveness

In addition to work being conducted at its individual businesses, J&J last year created its Companion Diagnostics Center of Excellence (COE) within its pharma group in order to centralize some of the development work, forge partnerships with outside parties, and explore commercialization opportunities.

"The vision of Johnson & Johnson in pharma is to have a patient-focused mindset and to move away from a one-size-fits-all [model] to more targeted and personalized therapy," Verbiest, the center's head, told GWDN. "You see now more and more therapeutic areas requiring ... a companion diagnostic. So from that perspective, we've brought together a team that supports all the therapeutic areas for companion diagnostics."

While companion diagnostics development is still in its early stages, it's a market that is anticipated to grow in the coming years. In a blog post in January, Prashant Dilwali, a senior analyst at life sciences consulting firm Scientia Advisors, wrote that companion diagnostics are appealing to pharma as a business and as partnership opportunities because they can provide potential revenue streams as well as "knowledge capital" to better match the most appropriate treatment with a patient.

"Better targeting can lead to more efficacious and safer therapies — potentially bringing back pipeline products previously thought to be ineffective," Dilwali said. "More important, diagnostics are viewed as viable businesses

because they offer opportunities for portfolio diversification, thus lessening pharma's risk without radically changing their core businesses."

J&J's rationale for creating the COE, Verbiest said, was "to build a cross-enterprise integrated capability and knowledge center to support the discovery, and the development, and the commercialization of companion diagnostics."

Eventually, the COE, which operates out of Raritan, NJ, and Beerse, Belgium, may partner with other drug manufacturers, but for now, collaborators include Quest Diagnostics and Laboratory Corporation of America, Verbiest said. Other partners include Abbott, Roche, and Quintiles. It also is working with molecular diagnostic firms, though Verbiest declined to identify them.

While the center is in the midst of several development projects, it has not yet brought any tests to market, and Verbiest said it may be two years before its first product is launched. The first test is being co-developed with a partner, which he declined to identify. He also declined to say what indication the test targets or to provide details about other tests in development

Though the center is a shared resource for all of J&J's businesses, each business may also conduct their own companion diagnostic development. Depending on the success of its development work and how the market evolves, "time will tell whether some of those companion diagnostics can be some interesting business opportunities in themselves," Verbiest said.

Press Release 4: College of American Pathologists on CTCs

http://www.cap.org/apps/cap.portal?_nfpb=true&cntvwrPtlt_actionOverride=%2Fportlets%2FcontentViewer%2Fshow&_windowLabel=cntvwrPtlt&cntvwrPtlt%7BactionForm.contentReference%7D=cap_today%2Ffeature_stories%2F0506CTC.html&_state=maximized&_pageLabel=cntvwr

Circulating tumor cell test shows clinical mettle

May 2006

Anne Paxton

If you think of magnetic nanoparticles zeroing in to capture and count, out of billions of cells in a 7.5-mL blood sample from a cancer patient, the exact number of circulating tumor cells—whether that number is zero or 700 or in between—you have an insight into why Arthur Clarke wrote that "any sufficiently advanced technology is indistinguishable from magic."

The assay that accomplishes this feat is the CellSearch Circulating Tumor Cell Kit, sold by Veridex, and it was no conjuring trick to develop it. Officials with manufacturer Immunicon Corp., Huntingdon Valley, Pa., say the process took 10 years and $120 million.

Because circulating tumor cells, or CTCs, in peripheral blood are few and difficult to isolate, Immunicon's technology was a major technical advance. But something that is just now coming into focus may constitute the real magic of the circulating tumor cell test. It is the way the assay's results might be used to lengthen the lives of patients with metastatic breast cancer.

Since the findings of a clinical trial on CTCs were published in the New England Journal of Medicine in 2004 (Cristofanilli M, et al. N Engl J Med. 2004;351:781–791), and the Food and Drug Administration granted Veridex pre-marketing approval for CellSearch the same year, the strong link between CTCs and breast cancer patients' overall survival rates is becoming more widely accepted. "CTCs are the strongest independent prognostic factor for survival of metastatic breast cancer patients ever found," asserts Immunicon president and CEO Byron Hewett.

The research to date has repeatedly confirmed that CTCs are a potent prognostic tool. Among the most dramatic examples: Overall survival for patients being treated for metastatic breast cancer is about 11 months if they have five or more CTCs and 23 months if they have fewer than five CTCs—so they essentially have an additional year of survival if they do not have CTCs, says Howard Robin, MD, medical director of laboratory services at Sharp Memorial Hospital, San Diego.

New analyses of the data and new clinical trials are indicating how oncologists can apply that information to prescribe the best treatments for breast cancer patients.

"There has been a growing interest in this test over the last two years," says Massimo Cristofanilli, MD, associate professor in the Department of Breast Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, which was the lead institution in the 2004 New England Journal clinical study.

Quest Diagnostics has been offering the test for more than a year and a half, and as of Dec. 31, 2005, Immunicon had shipped 47 CellTracks Analyzer II or CellSpotter Analyzers, and 42 CellTracks AutoPrep Systems. Immunicon has a strategic alliance with Johnson & Johnson, which through its subsidiary Veridex markets, sells, and distributes CellTracks technology as part of the Veridex CellSearch system.

Among clinical researchers, there isn't unanimity about using the CTC test to decide when to switch therapy for women with metastatic breast cancer. At least some have questioned this application, and many oncologists say they are not ready to abandon their traditional treatment approaches.

But increasing numbers of oncologists are requesting the test—and patients are too, Dr. Cristofanilli says. "When I talked about it in the past, not many people were aware of it, but now they're trying to find which will be the best use for it."

MD Anderson Cancer Center acquired the Veridex CellSearch system for the clinical laboratory and has since instituted the CTC test as a routine chargeable test procedure, says Herbert A. Fritsche, PhD, professor of laboratory medicine and chief of the clinical chemistry section at MD Anderson. "Our volume right now for clinical purposes is somewhere between 10 and 15 samples per week," he says.

"At this stage the data seem to be upholding the prognostic value of the test. But we've spent the last year running patient data, and it will take a couple more years of followup before you can really address whether patients are living longer."

Circulating tumor cells can be detected in several ways, explains Daniel F. Hayes, MD, clinical director of the Breast Oncology Program at the University of Michigan Comprehensive Cancer Center, another participant in the New England Journal clinical trial. Most of the methods are hospital-developed home-brew tests that do not cross state lines and do not require FDA approval, he notes.

"One way is by separating the CTCs from white cells based on their physical characteristics. They're bigger and heavier, so you can do density gradient separation or filtration. The second way is by performing RT-PCR for transcription factors that don't belong in the blood; in this case you're looking for epithelial tissue that shouldn't be there."

"The third way is to use immuno-magnetic separation, as the CellSearch does. The difference between CellSearch and all the others is that it is a highly automated, highly reproducible assay."

All of the CellSearch 510(k)s were cleared by the FDA in 2004, and the first commercial shipment of the system was in October 2004, Hewett says. More applications are pending; Veridex just received another 510(k) clearance from the FDA for use of the Linux operating system for the CellTracks Analyzer II. "We pursued that to use it as a sort of next-generation software platform to allow us to introduce a number of features that will enhance ease of use and give customers more flexibility."

But Hewett says one of the most important steps forward since the 2004 trial was the FDA's 510(k) clearance in October 2005 of additional data proposed for the CellSearch package insert.

"The claim we have is quite broad," he explains. "It says patients with five or more CTCs have shorter progression-free survival and shorter overall survival. But that information alone does not tell the physician how to use the test. We did further analysis of the data and noticed that patients with fewer than five CTCs at all points had much longer survival than those with persistent circulating tumor cells. And that's been added to the package insert."

Also in the insert is a "revealing" chart, he says, titled "A reduction in CTC count below 5 after the initiation of therapy predicts longer overall survival." It breaks the patients into four groups: green for those with fewer than five CTCs at all time points, blue for those with elevated counts at the start but lower counts later, red for those with elevated counts that persist, and amber for patients that start low and go to a higher cell count. (See chart, this page.)

"On the green line, we had a median survival of 22.6 months, while the red line had a median survival of only 4.1 months. This is a stark difference, but what's most significant is those patients that responded to therapy, the blue line, had a survival not statistically different from those that started with fewer than five CTCs: 19.9 months. Both the blue and green lines had almost a fivefold survival advantage over those with high CTC counts."

This tells the physician, Hewett says, that elevated cells, as a strong indicator of survival, "identify patients on treatments that may not be working and the physician should consider introducing other therapies."

"With CTCs, at the end of the first cycle you can see if a therapy is having the desired effect, while with imaging studies you have to wait considerably longer, possibly months, to evaluate what's going on. The other major difference between CTCs and imaging studies is that imaging reflects tumor burden, while CTCs are an indicator of how active and aggressive the disease is. That's information the physician never had before," he says.

"We found this to really resonate with oncologists. They can use this test to predict an outcome for the patient literally after each cycle of therapy."

Tumor burden is less informative, he says. "Many oncologists tell us they have some patients with a relatively large tumor mass who can live a long time, while others have a small mass but all of a sudden there are metastatic sites all over their body. People know the key is the metastatic process, not the tumor."

CTCs provide a "real-time" biopsy of a patient's cancer, Hewett says. "After removal of the primary tumor the only potential sources of tumor tissue are metastatic sites, and biopsying these areas involves significant risk. But CTCs give you a glimpse into what's going on with that specific patient's cancer today."

As it continues to explore applications of CTCs to cancer treatment, Immunicon is researching the development of tumor phenotyping and genotyping reagents for HER2/ neu, EGFR, Bcl-2, MUC 1, and others, Hewett says. "The idea is to look at the protein and gene expression on the CTCs. We are designing trials now to show that CTCs may be used to help select therapy for patients because they provide a real-time picture of what's going on with the disease." (Veridex last fall launched the HER2, EGFR, and MUC 1 CellSearch Tumor Phenotyping Reagents for research use only.)

Discussion about possible correlations between circulating tumor cell levels and survival time of metastatic breast cancer patients began in 1999, Dr. Cristofanilli says. "It was the first time we had the possibility with a blood test to be able to have a more rational discussion of treatment with the patient, and to develop some therapies that would be more effective" than the previous standard approaches.

And since the initial study released in 2004, "we've been expanding these observations and confirming the prognostic aspect of the test, which strikes me as a very significant factor in patients with metastatic disease."

Dr. Fritsche says circulating tumor cells are seen in about 50 percent to 60 percent of patients at the time they have documented development of metastatic progression. The CTC test is qualitative in nature, he stresses, and

has very good reliability. "We're not talking about using a test in a serial fashion where a 50 percent change in the marker might indicate a tumor is worse or better. You can't look at a change from five to 50 cells as having any significance. We are basically looking at whether there are more or less than five cells present," Dr. Fritsche says. With their test method, they're able to determine consistently with precision whether cells are absent or present defined by the five-cell cutoff value.

In Dr. Fritsche's experience, the test is also reliable in terms of biological variability. "Do patients with fewer than five cells come back with more than five cells? No, we do not see that." In the control subjects they have tested on multiple occasions, the results remain negative. "But in patients undergoing therapy, changes from negative to positive suggest progression of disease, and changes from positive to negative suggest a response to treatment." In those CTC-positive subjects who have greater than five cells, Dr. Fritsche says, biological variation may contribute to the variability in cell numbers observed in subsequent measurements.

The assay started as a "mom and pop" test, very hands-on, "with several cycles of manual washing required," Dr. Hayes says. "But it was improved over time and eventually changed into what it is now a 'black-box' assay that basically just requires sticking blood in the machine, and in a couple of hours you receive a readout."

Immunicon realized that circulating tumor cells are fragile and do not survive well outside the body. Therefore, the test developers combined a cell fixative with an anticoagulant in a vacuum draw tube called CellSave. The preservative keeps the cells intact for a minimum of 72 hours so the sample can be shipped around the world as needed. CellTracks' AutoPrep instrument takes the tube, reduces it to a 320-μL aliquot, and places it into a cartridge, which is inserted into the CellTracks Analyzer II.

Images are then presented on a computer monitor where they can be reviewed by a technologist or pathologist, producing a reproducible assay that is "really from A to Z pretty self-reliant," Dr. Hayes says.

The key study published in the New England Journal in August 2004 was unusual in being a prospectively written protocol, he notes. "It's one thing I am probably the most proud of. I've written several papers through the years regarding the design and evaluation of tumor markers, and I've made the point that most of the studies are 'studies of convenience'—they're put together without a lot of the controls and clinical trials that we perform for a new drug. But that wasn't the case with this test. It was a prospective, multi-institutional trial, funded by Immunicon."

The expense of such trials means they seldom materialize. But one of the reasons so few tumor markers have been widely accepted, he points out, is because the data are so unreliable. "There's a new tumor marker a week published in various journals, and they all end up with P-values of .03, but they are not directed toward understanding how to use them in the clinic. A lot of the things that get published never actually make it into routine clinical use because no one can figure out how to use them."

In the past, clinicians at MD Anderson would have used radiographs to determine if a particular therapy for metastatic breast cancer was working, Dr. Fritsche says. "But we would almost have to require completion of the treatment before there was radiographic evidence that the tumor was not responding. If you've given three or four courses of a toxic chemotherapy, the patients are likely not going to do as well as they could have if given the most appropriate therapy to begin with."

Since several active chemotherapy agents are available to treat patients with metastatic breast cancer, the challenge is picking the therapy most likely to work with the fewest side effects. "It's not always true that you have to wait," Dr. Hayes says. "For example, if the patient has horrible pain and then comes in pain-free, you did the right thing. Or if there's nothing palpable on the chest wall, then the patient has lumps and bumps," a change might be in order. "But those are the extremes. More commonly, using conventional radiographs, it takes two or three months to figure out if a therapy is working or not."

There are clinical and financial price tags attached to using the wrong therapy, he notes. First, it means something else that might work is not being used. Added to that are the toxicity and possible side effects of the therapy, and

finally the cost. "Chemotherapy is not cheap," he says, suggesting that the roughly $600 cost of a circulating tumor cell test may easily be justified if it saves a patient $5,000 in chemotherapy costs.

Many findings of the New England Journal study have generated provocative questions that researchers are now pursuing, Dr. Hayes says. For example, the full set of data on median time to progression of disease suggests that patients who still have five circulating tumor cells after three to five weeks of therapy have a 50 percent chance of showing classic signs of progression in the next month, although 10 or 15 percent of those patients did not progress rapidly.

"So these data suggest that most of the patients who continue to have elevated cells after a single cycle of chemotherapy are probably on inactive treatment. The question is whether these patients benefit from changing therapy right then, or whether they are patients for whom nothing works. And, of course, that small group of patients with elevated CTCs at this first followup time period who don't progress rapidly probably would not benefit from an early change in therapy."

Through the Southwest Oncology Group and the Breast Cancer Intergroup of North America, a cooperative of research institutions, Dr. Hayes and his colleague, Jeffrey Smerage, MD, PhD, are spearheading a trial funded by the National Cancer Institute and scheduled to start later this year that will address some of these issues. Unlike the New England Journal trial, which looked at a more heterogeneous group of patients with metastatic disease, the new study will look only at patients who will be starting a first-line chemotherapy for their metastatic breast cancer.

"They will be starting first-line chemotherapy and receiving whatever chemotherapy the doctor thinks is appropriate," he says. "CTCs will be analyzed at baseline and at first followup, and if they have elevated cells at first followup they will be randomly assigned to remaining on the first-line chemotherapy chosen by their oncologist—which is the standard of care without CTC data—or to changing to a different therapeutic regimen—again, left to their physician's discretion. The idea is to see if switching chemotherapy early makes sense."

When the necessary reviews are completed, Dr. Hayes says, "we hope we can actually start putting people on the study this summer." The study has generated excitement because it will test a new way to use a tumor marker. Markers like CA 15-3 and CEA, he says, have been considered inaccurate indicators at first followup, because 25 percent of patients treated with new chemotherapy will have the level of these "soluble" protein markers spike—become falsely elevated—before it goes down, probably because the therapy is killing cells that release the antigen. "We think that unlike circulating markers like CA 15-3, CTCs don't go through this spike. That's the basis of the next randomized trial."

Several other developments have taken place since the New England Journal study. The investigators in the initial Immunicon trial are now working on sub-analyses of that study to compare the accuracy of CTC levels versus assessment of classic clinical response to predict overall survival. Thomas Budd, MD, of the Cleveland Clinic is leading this analysis. Says Dr. Hayes: "With patients with non-measurable disease—one-third to one-half of metastatic breast cancer patients—it's notoriously difficult to decide if the patient is progressing or not. Many patients with metastatic breast cancer have it principally in their bones, and it's harder to a get a handle on the cancer." Lung metastases, for example, can be measured in two dimensions, but radiographic studies of bone often do not show the cancer. Rather, they show cancer-related epiphenomena happening around the cancer, like the appearance of lysis or sclerosis associated with osteoclastic and blastic activity.

An interesting finding so far is that CTCs were poor predictors for clinician-determined progression. "But they were actually better predictors for survival than was clinician-determined progression. In other words, clinicians' ability to determine progression is very bad when compared to the gold standard, whether the patient is alive or dead," Dr. Hayes says. CTCs, however, were more likely to predict survival accurately.

Most patients with metastatic breast cancer have subtle symptoms, he points out. "Ninety percent of them have their cancer internally, so there's nothing to feel or examine. And they're usually older women with arthritis or other conditions that can mimic cancer symptoms."

He is using the assay now to help decide if he should change therapy after several months of a therapy in patients for whom other parameters, such as history, physical exam, other markers, and radiographs, are uncertain. "I am, of course, very excited about our prospective randomized trial to determine if CTC levels at the very first followup time period after a patient starts chemotherapy will direct a change that improves a patient's outcome." He says he personally would not use CTC levels now at baseline to make decisions, though Dr. Cristofanilli is designing studies to determine whether the test might be used to direct "more or less 'aggressive' therapy right up front."

Other uses for the CTC test are taking shape. "We're talking right now about metastatic breast cancer," Dr. Fritsche says, "but there has been a shift to using this test in two other opportunities. One as an adjuvant treatment, after a primary treatment of either surgery alone or surgery with radiation, followed by an anti-hormonal treatment like tamoxifen or chemotherapy. In the adjuvant setting, you'd be treating patients with early-stage disease to postpone or reduce their chance for recurrence and metastasis."

Neoadjuvant use would be another. "That's chemotherapy before you have surgery, the primary treatment. The reason you do that is to shrink the tumor to make surgery more effective," Dr. Fritsche says. "So we have protocols in place where we're trying to identify who needs more than the current level of treatment at adjuvant and neo-adjuvant settings."

"We know in both breast and colon cancer that 20 percent to 30 percent of cases supposedly cured by surgery do develop metastatic disease. Most people believe that metastasis occurs through bloodborne CTCs, and that's why the CTC test is so important in early-stage cases."

Such adjuvant therapy might be particularly helpful in colon cancer, Dr. Fritsche notes. "Colon cancer most often metastasizes to the liver, so if you have evidence there is some disease you can maybe find earlier, you can do a hepatic resection."

In early prostate cancer there do not seem to be many patients who have CTCs. "With metastatic disease there does seem to be a large number with CTCs," he says. "However, successful chemotherapy for prostate cancer is really only at the early stages now, so we don't have the wide variety of treatment options that we have in metastatic breast cancer. So while there is interest, there's probably much less benefit."

The early data submitted to the FDA implied that CTCs have a valuable prognostic use in managing patients with late-stage disease. "Our current data is substantiating that," Dr. Fritsche says. In his view, now might be the time for oncologists to start getting their own level of confidence and experience with this test.

One problem with testing for CTCs in the past was the lack of a reliable, robust assay technology. Though there is a continuing need for better cancer markers, Dr. Fritsche says, "what we have now is a completely automated process for making the observation. So for the first time we have a way of generating results across the U.S. and providing a level of service that physicians could be comfortable in using. A lot of new technologies out there don't promise you that."

Dr. Cristofanilli hopes that other clinical trials will help clarify the appropriate uses of CTC testing in deciding on therapies. "Many times a patient will have a minimal response to a therapy and we don't know exactly what to do. But eventually the interpretations of CTC test results may lead us to make changes in treatment. One day we'll get more confident in this test to let it be really useful in moving us slowly away from expensive therapies."

Dr. Robin at Sharp Memorial Hospital recently received training on the CellSearch system and says one has been installed in his laboratory for research and clinical services. "Oncologists on the East Coast have been using the test for about a year and believe it has been very helpful in identifying when drugs are not working," he reports.

Potentially, the CTC test could supplant imaging studies that are used to gauge whether a therapy is working, he says. "Rather than measuring the size of tumor at baseline, then at one month, two months, and three months, which means significant exposure to x-rays as well as the costs of the studies, this is a simple blood test that may demonstrate effectiveness of therapy earlier than the imaging studies."

The CellSearch system enriches and stains CTCs and then presents the images to a pathologist, who then interprets them as being circulating tumor cells or mononuclear cells or unidentified cells," Dr. Robin says.

"It's a really intriguing process and different from any other test performed in our laboratory," he adds. "The iron-coated antibodies react with epithelial cells, the specimen is placed in a magnetic field that enriches for tumor cells now covered with antibodies, magnets hold the CTCs to the side of the container, and the pathologist enumerates the cellular images on the computer screen."

"The pathologist now plays an integral part in helping the oncologist choose the right therapy for his patient, and the right patient gets the right drug at the right time, which hopefully will reduce the use of expensive chemotherapeutic agents as well as reduce the significant risk they present."

But many other factors will decide whether the CTC test gains traction in the medical oncology community, Dr. Robin says. "Medical oncologists are concerned about what to do with the results if it appears the patient is not responding to therapy. Should they change the medication based on the laboratory test? They will have to get over their initial skepticism and determine if the CTC test helps them identify optimal therapy for their patients."

One oncologist he has spoken to said the test was helpful in a patient who developed an adverse reaction to a particular chemotherapeutic drug but didn't want to stop the drug if it was effective for his patient's tumor. When a followup CTC assay showed it was working, he kept her on the drug. On the flip side, if a woman had five or greater CTCs before therapy, and they did not decline after therapy, "Why subject her to chemotherapy? Why not change therapy or stop the drug?"

That will be a subject of ongoing debate as use of the test expands, Dr. Robin predicts.

Anne Paxton is a writer in Seattle.

Press Release 5: Myriad and Cephalon enter into companion diagnostic agreement

http://investor.myriad.com/releasedetail.cfm?ReleaseID=660165

Myriad and Cephalon Enter Into Companion Diagnostic Agreement

Myriad to Assess Germline BRCA Status in Phase I/II Study

SALT LAKE CITY, March 28, 2012 (GLOBE NEWSWIRE) -- Myriad Genetics, Inc. (Nasdaq:MYGN) announced today that it has signed an agreement with Cephalon Inc., a subsidiary of Teva Pharmaceutical Industries Ltd Company, to conduct BRCA1 and BRCA2 mutation testing on patients to be enrolled in a Phase I/II clinical study.

"We are extremely pleased to be working with Cephalon, one of the world's leading healthcare companies, on this exciting new clinical study," said Peter Meldrum, President and Chief Executive Officer of Myriad Genetics, Inc. "This collaboration is a further demonstration of Myriad's commitment to and leadership in the field of companion diagnostics."

Under the agreement, Myriad will assess the BRCA status in patients prior to being enrolled in the study. Myriad has entered into similar agreements with Abbott Pharmaceuticals, Astra Zeneca and BioMarin *Pharmaceuticals to* provide companion diagnostic testing with the BRACAnalysis® test for clinical trial enrollment.

Appendix VII – TreeAge base case model parameters

Listed below are the primary variables used for the TreeAge decision tree analysis. All dollar values are in millions and in NPV terms. Abbreviation notes:

SM or S&M = Sales & Marketing expenses
GA or G&A = General & Administrative expenses
CDx = Companion Diagnostic
MS = Milestone

Name	Description	Root Definition
NPV_Commercialize_CLIA_Success	NPV of a prognostic technology through CLIA with successful market	$ 300.00
NPV_Commercialize_FDA_Success	NPV of prognostic that goes through FDA approval and success market	$ 315.00
NPV_Partner_CLIA_Success	NPV of partnership with CLIA a successful market	$ 100.00
NPV_Partner_FDA_Success	NPV of a partnership with FDA Approval with a successful market	$ 100.00
NPV_CDx_ExistingTx_Success	NPV of companion diagnostic for existing TX in successful market	$ 300.00
NPV_Sale_PostRetro	NPV of a sale post retrospective	$ 10.00
NPV_Sale_PostClinical	NPV of a sale post clinical trial	$ 20.00
NPV_Sale_PostFDA	NPV of a sale post FDA approval	$ 30.00
NPV_CDx_DeNovo_Success	NPV of a de novo companion diagnostic in success state	$ 200.00
NPV_RUO	NPV of a research use only application	$ 40.00
NPV_CDx_DeNovo_Failed	NPV of a companion diagnostic in a failed market	$ 40.00
NPV_CDx_ExistingTx_Failed	NPV of companion diagnostic for existing TX in failed market	$ 30.00
NPV_Commercialize_CLIA_Failed	NPV of a prognostic technology through CLIA with failed market	$ 30.00
NPV_Partner_CLIA_Failed	NPV of a partnership with CLIA in failed market	$ 10.00
NPV_Partner_FDA_Failed	NPV of a partnership with FDA and failed market	$ 10.00
NPV_Commercialize_FDA_Failed	NPV of prognostic that goes through FDA approval and failed market	$ 30.00
Cost_TechnicalDevelopment	NPV of cost of technical development	$ 15.00
Cost_Retrospective	NPV cost of retrospective validation study	$ 5.00
Cost_Clinical_CLIA	NPV cost of clinical trial for CLIA lab	$ 7.50
Cost_FDA	NPV of cost of FDA registration	$ 0.50
Cost_Clinical_FDA_Prognostic	NPV cost of clinical trial for prognostic FDA	$ 15.00
Cost_Clinical_FDA_CDx	NPV cost of clinical trial for companion diagnostic FDA	$ 25.00
GA_Commercial_CLIA	Incremental G&A cost during clinical_CLIA	$ 5.50
GA_Commercial_Clinical	Incremental G&A cost during clinical_FDA	$ 4.00
GA_Commercial_Retro	Incremental G&A cost during retrospective	$ 3.00
GA_Commercial_Tech	Incremental G&A cost during tech development	$ 6.00
GA_DeNovo_Clinical	Incremental G&A cost during development	$ 1.00
GA_DeNovo_Retro	Incremental G&A cost during development	$ 1.00
GA_DeNovo_Tech	Incremental G&A cost during development	$ 1.00
GA_ExistingTx_Clinical	Incremental G&A cost during clinical	$ 5.50
GA_ExistingTx_Retro	Incremental G&A cost during retrospective	$ 3.00
GA_ExistingTx_Tech	Incremental G&A cost during tech development	$ 6.00
GA_Partner_CLIA	Incremental G&A cost during clinical_CLIA	$ 5.50
GA_Partner_Clinical	Incremental G&A cost during clinical_FDA	$ 4.00
GA_Partner_Retro	Incremental G&A cost during retrospective	$ 3.00
GA_Partner_Tech	Incremental G&A cost during tech development	$ 6.00
GA_RUO	Incremental G&A cost during development	$ 0.50

Name	Description	Root Definition
P1	Probability that technically successful	85%
P2	Probability for retrospective success	75%
P3	Probability for a successful prospective trial	75%
P4	Probability of FDA approval post clinical trial success	90%
P5	Probability that of success state for the market	40%
P6	Probability of companion diagnostic clinical trial success	65%
Partner_MS_Technical	Milestone for Technical developments	$ 2.50
Partner_MS_Retro	Milestone for retrospective	$ 1.50
Partner_MS_Clinical	Milestone for clinical validation	$ 4.00
Partner_MS_FDA	Milstone for FDA approval	$ 2.00
SM_Commercial_CLIA	Incremental S&M cost during clinical_CLIA	$ 5.00
SM_Commercial_Clinical	Incremental S&M cost during clinical_FDA	$ 1.00
SM_Commercial_FDA	Incremental S&M cost during FDA registration	$ 1.50
SM_Commercial_Retro	Incremental S&M cost during retrospective	$ 0.50
SM_Commercial_Tech	Incremental S&M cost during tech development	$ 0.50
SM_DeNovo	Incremental S&M cost during development	$ 0.50
SM_ExistingTx_Clinical	Incremental S&M cost during clinical	$ 1.00
SM_ExistingTx_FDA	Incremental S&M cost during FDA registration	$ 2.00
SM_ExistingTx_Retro	Incremental S&M cost during retrospective	$ 0.50
SM_ExistingTx_Tech	Incremental S&M cost during tech development	$ 0.50
SM_RUO	Incremental S&M cost during development	$ 0.20