DEVELOPING A COMPETITIVE STRATEGY FOR THE IN VITRO CANCER DIAGNOSTICS INDUSTRY

by

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ABSTRACT

This paper analyzes a firm which is developing a suite of new products for the early detection, localization and definitive diagnosis of lung cancer. The firm's products are in various stages of development with the first products ready for sale by the end of 2005. The paper focuses on the product line aimed at the early detection of lung cancer.

The analysis considers the firm in the context of the *in vitro* diagnostic development industry. It reveals issues relating to the company's focus and the difficulty of establishing a new testing paradigm in the face of physician scepticism. Furthermore, it faces the competitive threat of new technologies which will begin to appear in the next 3—4 years. It is recommended that the firm concentrate its resources around its core competencies and redirect its efforts to establishing its testing approach in common clinical practice while the opportunity exists.

DEDICATION

I dedicate this work to Jerrilin, whose support and perseverance have made it possible for me to do the EMBA program.

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1.1 The Company

Perceptronix Medical Inc. is a cancer diagnostics company founded in 1999 by researchers from the British Columbia Cancer Agency (BCCA). It is a transfer technology company created to bring technologies developed by the BCCA's Cancer Imaging Department to market. Perceptronix is developing products for the early detection, localization and definitive diagnosis of cancer—particularly lung cancer. The firm is privately owned and has grown from three staff to approximately 40 employees over the last five years.

Initially, Perceptronix is developing three product lines:

1. Assays for the early detection of lung cancer based on image analysis of cell nuclei of exfoliated epithelial cells;
2. Endoscopy products that allow for more precise localization of cancerous lesions of the lung;
3. Workstations to assist pathologists to make more reliable diagnoses of cytological preparations and sections from biopsy specimens.

The three product lines form a comprehensive approach to the detection and management of lung cancer. It is felt that they fit together like three pieces of a puzzle. The detection test stratifies patients into lower/higher risk categories for further follow-up. The higher risk patients are suitable for follow-up by *in vivo* localization using endoscopy. The result of an endoscopic examination is usually a series of biopsies and cytological preparations which can be better analyzed by pathologists through use of the

workstations, which are specialized computerized microscopes. Hence, the product lines are applied in sequence as part of a comprehensive approach for management of patients at risk for lung cancer.

Over the last five years each of the product lines have followed different development paths. The detection test has gone from a field study to a large scale clinical trial. The workstations have been developed and trained using the expertise of scientists and pathologists from the BCCA and abroad. The endoscope devices have been developed from concept to prototypes which are currently being evaluated at several clinical sites around the world. Perceptronix goal is to bring its detection test and workstation products to market by Q4-2005 and its endoscopy products one year later.

Of the three product lines, Perceptronix detection test is the product line that has the greatest long term promise. Lung cancer is difficult to detect reliably. The standard methods for detecting lung cancer in the past have been x-ray and sputum cytology. Both have poor sensitivity for early lung cancer. More recently, computed tomography (CT) examination, an imaging technology that uses x-rays from many angles to reveal internal structures in three dimensions, is being added to part of the routine workup for suspected lung cancer patients.

However CT has drawbacks. There have been problems with devising appropriate patient protocols for this technology, as it generates many false positive results. There are currently no widely used *in vitro* tests for lung cancer. Given the problems with CT and the lack of established competition from other *in vitro* test makers, Perceptronix would be a pioneer in an emerging space with its detection system.

Although the detection system has been developed for lung cancer, the underlying technology platform is applicable to other cancers as well. It is believed that assays can be created to detect bladder cancer from urine specimens, oral cancer from buccal scrapings and cervical cancer from pap smears. There is evidence that it is also possible to detect lung cancer and other cancers of the upper airways from buccal scrapings. If true, this would allow the detection of cancer in the upper airways based on a test that is simple to administer. Such a product would have enormous potential for Perceptronix.

The broad applicability of the cancer detection platform and the skills of the Perceptronix technical team to develop new assays suggest that the long term potential of the firm lies in its detection products. Therefore, this paper will examine Perceptronix in the context of the *in vitro* cancer diagnostics industry. It will discuss a market entry strategy for Perceptronix cancer detection assays and strategies that should be enacted to maintain competitive advantage over the long term. The other product lines will be discussed when appropriate, and since the first products under development target lung cancer, much of the analysis will focus on lung cancer specifically. A more complete overview of the Perceptronix comprehensive approach to lung cancer and its other products can be found in the SFU EMBA thesis of Lydia Taylor (Taylor, 2004).

1.2 The Product

The detection of cancer based on the observation of abnormal appearing cells using a light microscope has been understood for more than 100 years. The process is called cytology and is standard practice for screening programs for preventing cervical cancer. This approach of detecting cancer relies on obtaining good sampling of the entire epithelial region where a cancerous lesion may be located. The pathologist performing

the analysis of the specimen can only detect the disease if tumour cells are collected as part of the sampling procedure.

For the uterine cervix, which is accessible and has a relatively small surface area, this is not a problem. However, for the lung, which has a surface area the size of a tennis court, sampling is problematic. Standard practice for obtaining a good specimen is through a procedure called sputum induction. This procedure is done through the assistance of a respiratory technician and requires the inhalation of saline vapor. The salt water induces coughing and helps the patient produce a sputum specimen which contains exfoliated epithelial cells from the lining of the lungs.

Unfortunately, even with induction, it is still uncommon to find tumour cells in the sputum specimen for those patients who harbour an undiscovered lung cancer. Consequently, sputum cytology has a low sensitivity for detecting lung cancer. Large scale lung cancer screening trials which used sputum examination as part of their protocols were unsuccessful in detecting significant benefits in screening with sputum cytology. No major medical organization recommends lung cancer screening using *any* technology at present.

Perceptronix is developing assays for the early detection of lung cancer based on image cytometry. Image cytometry is a technology that combines computerized imaging with microscopy. Images of cells are collected and numerical measurements are made to describe cell properties in order to detect malignancy. This technology has been under development around the world since the 1950s. Perceptronix has developed a variant of this technology which involves the preparation of specimens using a staining procedure which makes properties of the DNA in the cell nucleus prominent. By measuring DNA

conformation, nuclear shape and texture, it is possible to predict whether a patient has lung cancer.

What is important about this technology is that it does not require the presence of diagnostic cells in order to detect the disease. Tumours produce chemical signals that alter the conformation of the nuclei of cells that surround them. The test detects these subtle changes and renders a positive result, even if no frankly abnormal cell is in the sputum specimen. This property differentiates the Perceptronix approach from conventional cytological (or cytometric) analysis and most molecular markers. These tests require sampling cells from the tumour itself, which is difficult in many tissues, especially the lung.

Perceptronix is conducting a clinical trial of two assays for early cancer detection. The trial accrual is complete and analysis is scheduled for August 2005. The first assay is based on analysis of induced sputum specimens and the second is based on analysis of scrapings of the buccal mucosa from the inside of the cheek. Preclinical data suggest that both detect lung cancer, but the induced sputum approach is the better test in terms of sensitivity to lung cancer and specificity for true-negative patients. Regardless, both will represent important new products in the lung cancer marketplace. One will have superior performance and the other will have far simpler administration, since the patients can collect the buccal scraping specimen themselves.

The product, as seen by the customer, will consist of a specimen collection kit and report that is returned a few days later. The report will contain the result of the analysis, which is essentially a score indicating the likelihood of the presence of lung cancer along with recommended follow-up. The report is meant to be used by physicians as part of

their management of patients at high risk for lung cancer. Consequently, the physician is an important actor in the process of delivering the test to the patient customer. Physicians recommend the test at the outset and they interpret results for their patients. Perceptronix must engage them in order to sell to the patients. The marketing plan must target pulmonologists, who normally deal with patients who have lung disease, especially lung cancer, and dentists, who are responsible for patient health as observed in the oral cavity.

1.3 The Market

There will be roughly 149,000 new cases of cancer and 69,500 cancer deaths in Canada in 2005 (Canadian Cancer Society, 2005). It is the second leading cause of death among Canadians, after heart disease, and the number one cause of premature death. In 2005, it has become the number one cause of death among Americans and is projected to become the same for Canadians by 2010. The costs to Canadians of the disease are significant as well. Direct costs, which measure goods and services for which payment was made to detect and treat the disease amounted to more than CAD $2.5 billion in 1998 (Health Canada, 2002). The indirect costs, due to lost economic output from disability or premature death amounted to an additional CAD $11.8 billion. For comparison purposes, Canada's Gross Domestic Product for 1998 was CAD $915 billion (Statistics Canada, 2005). Despite the fact that the costs of cancer are high, the market for diagnostic testing is largely undeveloped. It is expected that 10 million people will develop cancer in 2005, yet the worldwide market for cancer diagnostic products is less than USD $3 billion.

Lung cancer is the most deadly form of cancer, accounting for one third of all cancer deaths in both men and women. Lung cancer mortality exceeds that of the next four cancers—breast, colorectal, prostate and non-Hodgkin's lymphoma—combined.

Despite efforts to develop detection technologies and new treatments, little progress has been made in reducing lung cancer mortality over the last 30 years.

Overall, the five year survival rate for people who present with lung cancer is less than 15%. The problem is that people with lung cancer will typically be asymptomatic until the disease has progressed to stage where it is no longer treatable. When lung cancer is detected in Stage I (where the cancerous lesion is less than 3cm large and has not spread beyond the lung) it is >75% curable. Unfortunately only 20% of lung cancers are detected in Stage I.

This provides the rationale for early detection products such as those being developed by Perceptronix. If a test can be developed that is sensitive to early stage lung cancer, has adequate specificity for true-negative patients, is simple to deploy, it will address a great need in the marketplace. The goal of all detection approaches is to introduce a stage shift away from untreatable late stage cancers to Stage I cancer.

The customers who will purchase this product are smokers and ex-smokers over the age of 45. Lung cancer is mostly associated with having a history of smoking cigarettes (correlation is roughly 0.9) and provides the strongest indication for use for diagnostic products. Through aging and living with the damage caused by past smoking, these customers have a 10× or larger elevated risk for developing lung cancer over the general population.

The market for cancer diagnostics in the Western world is growing due to aging of the population. According to the American Geriatrics Society, the size of the over 65 population in the US will grow by 60% by 2020. The market is also growing due to

increasing sophistication among the target market as patients become aware of new technologies and demand better detection options.

1.4 Market Entry Strategy

The market entry approach that will be used by Perceptronix is to target the market segment for which the detection test will do the greatest good. The lung cancer detection test market can be segmented many ways, but one of the most important ways is based on patient cohort (which specifies the incidence rate). Table 1 shows the approximate incidence rates for different testing applications.

Table 1: Lung cancer market segmentation

Segment	Application	Incidence rate
General population	N/A	0.06-0.07%
Asymptomatic smokers, ex-smokers; >45 years old	Screening	.3%-1%
Patients with lung disease	Diagnosis	1-10% (depending on patient symptoms)
Post-surgical surveillance	Recurrence monitoring	>2% (strongly depends on stage of original cancer)

The incidence rates increase sharply as risk factors such as smoking history, age, other lung disease and previous cancers are added to consideration. The value of the test becomes correspondingly larger as the risk increases. Perceptronix feels that the market demand and acceptance of the test will match this risk. On the other hand, the size of the screening market is 10-20 times that of the diagnostic and recurrence monitoring market. The marketing problem is how to position the product given the tradeoff of market acceptance versus market size.

Perceptronix will take a two phased approach to entering the lung cancer detection market (Figure 1, below). Initially, Perceptronix will target the two highest risk

categories of patients for the test: patients symptomatic for lung disease and patients undergoing post surgical monitoring. For these two segments, the test performance parameters make it suitable for cancer detection (i.e. the number of cancers that will be found by the test will more than compensate for the burden of the false-positive outcomes for negative patients).

There is much that Perceptronix can learn from these patients that may lead to refinements of the test. Do certain other forms of lung disease give rise to a signal which may be falsely interpreted as cancer? Does inflammation interfere with the performance of the test? Are other forms of cancer accidentally detected when measuring the properties of sputum?

The current clinical trial will have limited power to address these questions. Longer term application of the test will give Perceptronix more data to address the questions and refine the test in two ways. Adding more cancers and high risk negative specimens to the training set will make it possible to develop more sophisticated rules for separating the two groups. Second, analyzing more patient co-morbidity data may lead to altering the inclusion criteria for the test.

Both efforts will lead to an improvement of the test's performance for the appropriate inclusion group. These improvements will help Perceptronix broaden the application of the test to the much larger lung cancer screening market as well. This will be the second phase of expansion within the Canadian market and other markets.

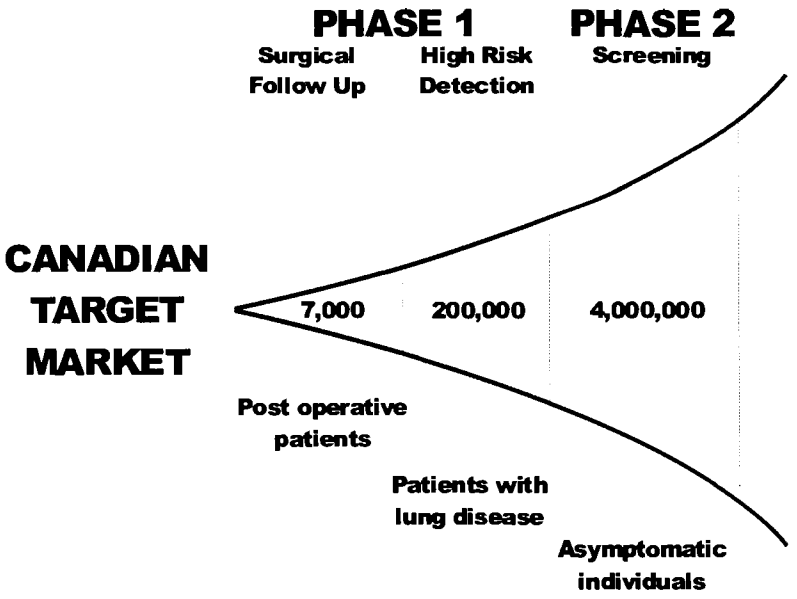

Figure 1: Canadian lung cancer detection market size by segment

Phase 1 - High risk detection

Each year in Canada 21,000 people are diagnosed with lung cancer. Among specialists who deal with high risk patients, the incidence rate of lung cancer is as high as 10%. This means that there are at least 200,000 people each year in Canada who are suspected of having lung cancer due to being symptomatic for lung disease. The specialists who track these patients are typically pulmonologists, which number approximately 420 in Canada.

This number is small enough that Perceptronix will be able to approach these specialists directly and through conferences in order to introduce them to the test. As well, these specialists have the ability to have sputum induction performed for their patients. This is important because the test is most sensitive for sputum collected in this

manner. This also ensures that test will initially perform in commercial application as well as it has performed in its clinical trial.

Phase 1 - Post-operative follow up

In Canada, roughly 7,000 of the 21,000 who develop cancer receive surgical resection of early stage lung cancers. Even if the surgery is successful, >50% of these patients will develop recurrent or second primary tumours within 5 years after surgery. There are around 225 thoracic surgeons in Canada responsible for lung resections. Perceptronix believes that these surgeons represent the group that will most quickly embrace the test for their patients. The detection test addresses three of the uncertainties that hamper the effective follow up of lung cancer surgery:

- Evaluating whether the original surgical treatment is effective
- Monitoring the recurrence of the original cancer
- Detecting the occurrence of a second primary lung tumour

Phase 2 - Screening

Asymptomatic smokers and ex-smokers over the age of 45 years have a tenfold increased risk of developing lung cancer versus the general public. In Canada roughly two million Canadians fit this risk profile. Among this group, 0.3-1% develop lung cancer each year and these cancers go undetected until the patient presents symptoms. There is currently no screening done on this population because any test applied to this group must be affordable, tolerable and have very high specificity (few false positive cases).

Reaching this group requires that GPs, of which there are more than 56,000 in Canada, be made aware of the test and Perceptronix have a distribution system in place so that they can order the test. The history of the Prostate Specific Antigen (PSA) test provides a relevant example of how such cancer *in vitro* testing can move from the specialist to the GP. The PSA test is a serum based assay that was developed in 1979 and first used by urologists to monitor the recurrence of prostate cancer. The test has marginal performance in terms of sensitivity and specificity and is only recommended for differential diagnosis and recurrence monitoring.

Despite this, the use of the test has jumped from the diagnostic segment, where it is considered to be effective, to the screening segment, where its usefulness is questionable. GPs routinely use it for screening purposes despite the fact that PSA tests done for screening purposes are not insurable in Canada. A survey (Statistics Canada, 2003) done by Statistics Canada in 2000-2001 showed that 69% of PSA tests in Canada were performed for screening purposes.

The PSA test shows how targeting specialists can lead to the adoption of the test by the GP segment. It also how a diagnostic test can become the dominant screening test, in spite of its performance, if substitutes are limited.

1.5 The Industry

There is a disconnect between what the customer wants and what the cancer detection industry provides. The customer wants to purchase health, or at least the promise of health and longevity. The question they want answered is "Do I have a malignancy, and if so what is the prognosis for me?" The detection industry can only

deliver a qualified answer to the first question and a more heavily qualified answer to the second.

For example, in lung cancer, CT detects non-calcified nodules may or may not be malignant. CT exams tend to find suspicious nodules that, after biopsy or several months of watchful waiting, usually turn out to be benign. These false positives are a cost to the patient in terms of increased anxiety and unnecessary follow-up.

Even when nodules are determined to be cancer, the question remains—what does this mean to the patient? CT lung cancer screening trials have led to a great increase in the number of early stage cancers with no significant decrease in the number of late stage cancers. This means that CT detects a lot of indolent cancers that would never have been discovered and never would have affected the patient during their lifetime. Similarly, lung cancer mortality has not declined measurably among the active screening groups in these trials, which means that active screening may only be detecting the disease earlier with no mortality improvement for the patient[1].

This problem exists for other cancers and other technologies as well, including that being developed by Perceptronix. It is uncertain what technology will give the best outcome for the patient in terms of reliable diagnosis and prognosis. A variety of competing technologies which share nothing in common all have the chance to ultimately prevail in the marketplace. It is necessary to consider the industry at multiple levels when naming the competition to Perceptronix lung cancer assays. In broad terms there

[1] Determining the effectiveness of a screening program is difficult. It is common to use an increase in the 5-year patient survival as the measure of effectiveness. When comparing patients undergoing screening versus those only receiving usual care, several biases affect the apparent survival. Because the test detects the disease before it becomes symptomatic, it gives the appearance of detecting the disease in an earlier, curable stage. Even if the patients dies at the same as they would have without screening, the appearance is that they survived longer with the disease, hence that the screening helped. This is referred to as lead-time bias.

are two major detection modes: imaging (x-ray, CT) or *in vitro* specimen analysis. Dividing the *in vitro* detection mode further there are:

1. approaches that require malignant cells to detect the cancer;
2. and those which measure some kind of systematic effect or product of the malignancy that is measurable without obtaining cells from the tumour.

Perceptronix direct competition will come from other companies that pursue this second approach. Some companies that are either in this category or that may soon be there are:

- Mensanna Research Inc. which has developed *BreathScanner 1.0*, a device that measures volatile organic compounds in the breath. Preliminary results reported in 2003 (Phillips, 2003) suggest that the device can detect lung cancer with 89.6% sensitivity and 82.9% specificity, albeit on a small sample size (187 patients). See Appendix A for a discussion of how to interpret diagnostic test performances.
- International Medical Innovations (IMI) which is developing a test called *LungAlert*, a test based on measuring a cancer-associated sugar that is present in sputum. It is just beginning clinical trials for the test and is likely several years behind Perceptronix.
- Cytyc Corp. which is a world leader in technologies related to conventional cytological specimen preparation and screening with almost USD $400 million in revenues in 2004. It has not yet announced initiatives into lung cancer, but has recently re-branded itself as a women's health company. Lung cancer has become the number one cancer killer of North American women and represents a logical target in line with its company vision.

- Tripath Imaging which is the world leader in automated cytometry hardware and $70 million in revenues in 2004. As with Cytyc, Tripath has not yet announced any initiatives into lung cancer detection, but it has the technical expertise and resources to enter this field quickly.

2 Industry Analysis

Perceptronix early lung cancer detection assays will compete in the lung cancer detection industry and more specifically against other *in vitro* based diagnostics. In this chapter, Perceptronix will be examined in the context of other makers of *in vitro* cancer detection products. This is an industry which is just beginning to form, so analysis will tend to be forward looking.

2.1 Analysis Using Porter's Five Competitive Factors

According to Porter, competition in an industry is governed by five competitive factors (Porter, 1979): rivalry among competitors, threat of entry, bargaining power of suppliers, bargaining power of customers and threat of substitutes. The strongest of these forces will determine the profitability of the industry, and hence its attractiveness. Figure 2 shows the summary of this analysis for Perceptronix in the *in vitro* cancer diagnostics industry.

Figure 2: Porter's Five Forces analysis of the *in vitro* cancer diagnostics industry.[2]

[2] Adapter from Porter, 1979.

Factor 1: Rivalry Among Competitors

The competitive environment in the cancer diagnostics industry is best categorized as **low to moderate** competition. There are many companies pursuing different approaches, which would suggest high rivalry. However, the potential size of the market is so large that there is plenty of room for growth for many companies if they have effective product offerings.

(+) Competitors are numerous and pursue different approaches

The mechanism and development of cancer in different organs is not well understood. There are many companies, some large some small pursuing a variety of ways of detecting the disease. Some are focusing on new ways to analyze cells: immunohistochemistry, cytogenetics, flow cytometry and image analysis (Perceptronix). Some are pursuing cancer markers in blood, some in DNA and some are seeking protein biomarkers.

With so many different approaches being taken, there is the potential that rival companies will develop very different solutions to the same problem. As a result the cancer diagnostics industry is an extremely competitive landscape.

(-) Potential market growth is high

The world cancer diagnostics market for 2005 is projected to be USD $2.6 billion with a growth rate of 15-17% per year (Theta Reports, 2003, pp 310—311). This number is very small when compared to the potential size of the industry. It is projected that if an effective marker for ovarian cancer (which constitutes 3% of cancer deaths among women) could be developed that it would lead to a USD $2.5 billion in the United States alone (Theta Reports, 2003, p. 337).

Since there are no existing screening programs for lung cancer, there is enormous potential for growth in this market. It is estimated that there are 1.1 billion smokers in the world and many of these people are at high risk of developing lung cancer. There is potential for many companies to grow into this market without competing directly against each other.

(-) High switching costs

Cancer diagnostic tests are extremely differentiated products. It takes time to convince physicians as to the value of the test in the management of their patients. As well they need to be educated so that they can interpret the results of tests to their patients. Depending on the nature of the *in vitro* test, it may require specialized equipment in the hands of physicians or special laboratory processes practiced by laboratory test distributors in order to process specimens.

These constraints impose significant switching costs on consumers of the test. Physicians will be skeptical about switching to a new diagnostic test until it is established. Laboratories will be hesitant to switch from one test to another if significant processing equipment is required.

Countering this trend is the complementary nature of many testing procedures. For example, in lung, CT is particularly effective at detection peripheral lesions and less effective at detecting lesions in the central bronchi. On the other hand, endoscopy and sputum examination are both suited to finding centrally located cancers. If one combines the detection approaches, it is more likely that undiscovered lung cancers will be found. The same trend may occur for *in vitro* diagnostic products once they are developed.

Since lung cancer is a multifarious disease it is likely that markers discovered for one form of lung cancer may complement markers discovered for another.

(+) Product quality is key

Countering the effect of high switching costs is the proposition that physicians want to use the best tests to manage their patients. Consequently, if a new diagnostic technology comes along that gives superior performance to the conventional approach, physicians will want to use it. As an example, consider CT versus x-ray (although they are not *in vitro* diagnostic modalities). It is well known that CT is superior to x-ray in detecting early lung cancer. CT can detect nodules as small as a few millimetres, which is 10× the resolution of x-ray.

In the US and Japan, where CT machines are common, it is usual to now send a suspected lung cancer patient straight to CT and bypass the standard x-ray diagnostic step. Both technologies give physicians information that they can understand in the same context (i.e. both report the appearance of masses in the lung, however CT does it in 3-dimensions and can locate small masses). Consequently, physicians will order a CT test over an x-ray if it is readily available.

If a firm develops a new diagnostic test with obvious performance advantages over existing tests and which can be readily incorporated by physicians into their practices, the firm will derive a significant competitive advantage.

(-) Firms enact defensive patents

Established firms enact as many patents as possible around their products and processes for defensive reasons. The scope of the patents may not be wide enough to prevent others from choosing narrowly different strategies. However, the patents allow

them to secure a space to operate and prevent large rivals from suing them. This practice reduces rivalry among established companies.

Factor 2: Threat of Entry

Many universities and medical institutes are engaged in developing systems to detect cancer. This introduces competitive pressures that counteract the barrier to entry that can be erected by firms engaging in expensive R&D and regulatory approval efforts. On the whole, the threat of entry in the *in vitro* cancer diagnostics market is **moderate to high**.

(+) Government support for cancer research

Effective detection and treatment of cancer is an important societal concern. There is significant government support for universities and medical institutions to perform R&D into cancer products. They act as de facto competitors in the *in vitro* diagnostic development space. Their discoveries will likely be spun off into competitive products—negating private R&D initiatives. This counteracts a private firm's ability to erect barriers through R&D spending.

(-) Regulatory barriers

There are several stages of regulatory barriers to becoming a medical product manufacturer. First, firms must implement and follow a quality management system for medical devices and be registered and certified by a recognized auditor. Canada and the EU recognize the same standard (ISO 13485) and most of the same third-party registrars. The US requires implementation of its Food and Drug Administration's (FDA) Quality System Regulations and, for the most part, conducts its own audits. The FDA does not generally recognize ISO standards.

Second, in Canada, the EU and the US, cancer detection related products are designated as Class III risk products and require clinical trials and governmental regulatory approval. The approval process for *in vitro* diagnostic devices (IVDDs) in Canada and the EU is driven by adherence to safety and effectiveness regulations.[3] The regulations for both jurisdictions are similar. The way to demonstrate a product's compliance to the regulations is to cite relevant standards (ISO, etc.) that were used in the development of the product. Both jurisdictions recognize the same standards, so it is possible to develop for both markets in parallel with little extra cost to developing for just one market.

Perceptronix is pursuing the approach of initially developing for Canada and the EU simultaneously for all its products. It is expected that the detection assays will be approved for sale by Health Canada approximately three months once development is completed. EU regulatory approvals are expected to follow three to six months later.

In the United States governmental approval is obtained through the FDA's Pre-Market Approval (PMA) process. The PMA process in the US can take 18 months to three years and cost millions of dollars. It is becoming common for companies investigating *in vitro* diagnostics to obtain approval in other jurisdictions before approaching the FDA. The belief is that establishing a successful commercial history with a test outside the US will aid the approval process within the US. A Perceptronix in-house survey was done for PMAs conducted in 2001 and 2003. It was found that 80% of the PMAs done in those years were for products that were already for sale in other

[3] In Canada, the device must follow Canadian Medical Device Conformity Assessment System (CMDCAS) regulations. In the EU, the device must follow the EU Council Directive for IVDs, 98/79/EC.

jurisdictions. The average length of time that those products were for sale outside the US prior to PMA was almost 60 months.

Different jurisdictions usually require additional local testing in order for the product to be approved in their market even though it may be approved in others. The regulatory application and review process delay diagnostics firms' expansions into new markets.

(-) Developing in vitro cancer diagnostics is capital intensive

Developing cancer diagnostics is expensive for technological and clinical reasons. First, firms must create these products through technological innovation, which tends to require significant R&D spending. Second, it is usually necessary to analyze many clinical specimens to create or validate a diagnostic test. Collecting these specimens through preclinical studies and clinical trials is expensive.

Furthermore it may take years for a firm to recoup all the costs that went into developing a diagnostic test. This limits the threat of entry to only those competitors that are well capitalized. Given the historical poor performance of medical diagnostic companies versus the rest of the market over the last ten years, it may be difficult for a firm to convince investors to stay in for the long haul, or it may make the cost of capital more expensive to them.

(-) Clinically relevant specimens are often difficult to obtain

Clinically relevant specimens consist of diagnostic material and extensive patient information. Even when adequate funding exists to obtain such specimens, clinics and physicians only see a limited number of patients per month suitable for enrollment into clinical studies. As a consequence studies and trials can take months or years and still

not reach their desired patient accrual. This can be mitigated by engaging many collection sites over a wider area, but establishing clinical relationships with suitable physicians takes time as well. This time delay lengthens the development process for new tests and reduces the competitive threat of entry.

(+) Patent protection exists for entrants

Cancer diagnostics form part of the intellectual property of the firms that develop them and are usually protected through patents. Although patents reduce rivalry among existing firms (since they grant each firm its own niche), they also make it possible for new firms to create a niche for themselves. This increases the threat of entry of a new firm which is able to develop a revolutionary new product. Competitors must negotiate licensing terms with them or innovate in response.

(-) Distributing *in vitro* diagnostic tests may be difficult

Depending on the nature of the specimen and the test, distributing a new in vitro cancer diagnostic test may be difficult. If the specimen is difficult to acquire or requires special processing immediately after acquisition, it may be difficult establish a viable test delivery process. The more novel the nature of the test (i.e. the more it deviates from normal laboratory practice) the more difficult it will be to distribute. These difficulties impose additional costs on test developers to develop test distribution infrastructure along with the test itself. This reduces the competitive threat of entry to incumbents.

Factor 3: Bargaining Power of Suppliers

The suppliers of the platform and components for cancer diagnostic testing tend to be large and may hold patents on relevant aspects of the diagnostic tests. This gives them significant leverage over firms creating diagnostic tests using their technology. Further,

since the regulatory approval process usually approves the platform as part of the delivery of the test, diagnostic creators are linked to their suppliers. Consequently, the bargaining power of suppliers is **high**.

(+) R&D requires specialized labour

Developing cancer diagnostics requires the talent of some of the brightest minds. It requires engineers, physicians, mathematicians and other highly trained professionals to develop such tests. These professionals are in high demand in today's marketplace and command significant salaries. This places financial pressure on *in vitro* diagnostic firms who wish to recruit and retain the best.

(+) Some test platforms may be patent protected

Promising avenues for *in vitro* diagnostic development may depend on the technology of other firms. An example is Affymetrix, which holds more than twenty patents on DNA chip technology and almost 100 others on related technology. The Theta Reports analysis suggests that gene chips may "transform the future of cancer diagnostics". Firms developing *in vitro* diagnostics built on the Affymetrix platform or other such platforms will have to negotiate terms with the platform developers.

(+) Suppliers of some technology components are large

Depending on the platform used by the *in vitro* diagnostic test, the suppliers may be large (as with Affymetrix and firms developing tests based on gene chips). In the case of Perceptronix, the underlying platform consists of high quality microscopes and other lab equipment. For each of the components used in Perceptronix detection test, there is only one supplier, or in some cases a few suppliers. This leaves Perceptronix with little strength to negotiate for lower prices for the components it uses in its system.

(+) Products have high switching costs

When a diagnostic test is approved, it is generally the entire testing platform that is approved. For example, Perceptronix is seeking approval for a lung cancer detection test built on a cytometry platform that uses an Olympus microscope. The exact model of microscope is named as part of the medical device. Changing the microscope to a Zeiss microscope would require extensive testing to satisfy regulatory authorities that the equipment change either improved or caused no significant effect to the efficacy of the diagnostic test. Furthermore, Perceptronix would be restricted as to which suppliers it could use based on International Standards Organization (ISO) quality requirements. Essential components can only be purchased from ISO-certified companies.

This situation is not unique to Perceptronix. Any firm creating *in vitro* diagnostic tests is in some way married to its suppliers. This imposes significant switching costs on the firm.

Factor 4: Bargaining Power of Customers

Whether a diagnostic test is reimbursable under public or private insurance programs determines who the customer is for *in vitro* diagnostic firms. If a test is accepted as standard practice and is reimbursed, firms must deal with governments and healthcare management organizations (HMOs). They act as large scale customers with significant power. If a test is not reimbursed then patients must pay out of their own pockets. In this case, it is usually their physician who would have to persuade the patient the test is in their best interests to purchase. So although the patient pays, it is their physician who is targeted for marketing. On the whole the bargaining power of customers is **moderate to high**.

(+) Health care spending is centrally managed

In many countries, patients rely on publicly funded health care to pay for diagnostic testing services. Governments and HMOs are slow to reimburse for new diagnostic tests. Achieving market approval does not mean that a test will be paid by the Medical Services Plan in British Columbia or by Medicare in the US, etc. A firm seeking reimbursement through the public medical system deals with a single large purchaser of test with enormous clout. This clout allows the purchaser the ability to negotiate contracts that give the diagnostic firm only normal profits for its innovation.

(+) Test distributors are concentrated

If the diagnostic test requires distribution through a testing service such as MDS Diagnostic Services, the firm creating the diagnostic test faces the additional pressure that diagnostic testing service providers are concentrated. According to a 2002 Polaris Institute corporate profile, MDS holds 30% of the Canadian laboratory testing market, and the top four lab firms hold >90% of the laboratory testing market.

(+) Physicians act as gatekeepers

Since physicians order diagnostic tests as part of their management of patients, they must be convinced of the value of the test, especially if the patient is expected to pay out of pocket. Firms must sell to the physicians in order to sell to the patients. This introduces an extra selling expense to the diagnostic firm to draw these "gatekeepers" into the test delivery process. The selling expense will consist of two components: advertising costs to engage and educate the physicians, and a fee to interpret the results of the test to the patients.

Countering the power of the physicians as gatekeepers is the fact that there are many of them. In principle, a patient who wants the test performed could go to a physician who believes in its value. In reality, it may be several years before patients become aware of the lung cancer test. During this time the power of the physician to determine its adoption rate is enhanced.

In the case of the Perceptronix buccal assay, which will likely be distributed through dentists, it is felt that there is motivation among the dentists to distribute the test. The dental industry is entrepreneurial in nature, and the decline of tooth decay in the North American population leaves dentists looking for alternate ways to bring revenue in to their practices. Furthermore, they are used to billing their patients directly for service, which addresses a major perceived obstacle for Perceptronix in deploying its test. Ultimately, the result of a positive buccal test is a referral to the pulmonologist, reinforcing the idea that they must be convinced of the value of the test.

(-) Size of customer base is increasing

For many cancers, the absolute market size is increasing. In Western countries, smoking as a proportion of the population has reached a plateau. But the population is aging and living longer. As a result, more lung cancers can be expected in the next 20 years. In Eastern Europe and Asia smoking is increasing as the population becomes more affluent. It is estimated that there are more than 350 million smokers in China alone. Most of these people will be at high risk for developing lung cancer and ten percent of them can be expected to develop the disease. This will be a large potential customer base for any company that develops an effective test.

Factor 5: Threat of Substitutes

The competitive threat of substitutes in the in vitro cancer diagnostic field is currently **moderate**. For many cancers there are limited diagnostic options available. With so many companies and universities pursuing cancer diagnostics, this may change in the future.

(+) Computed Tomography (CT) is advancing

CT is a rapidly advancing technology that creates 3D pictures of interior structures of the body using sophisticated x-ray equipment. The resolution of the technology is increasing so that now it can detect lesions as small as one or two millimeters. It has proven useful in detecting lung cancer, colon cancer and ovarian cancer, among others. It currently costs between $300 and $1000, depending on how one amortizes the expensive equipment. As well, it currently generates many false positive results, partly because adequate protocols have not yet been established. It represents a competitive threat that will grow with time. Companies like Siemens and GE are sponsoring research into effective protocols that will allow CT scanners to be used as part of routine patient management for a variety of cancers.

If CT is combined with a technology that can eliminate non-malignant nodes from consideration, the combination could prove to be a powerful tool for cancer localization and diagnosis. The other technology already exists and is an imaging process called Positron Emission Tomography (PET). It measures the metabolic activity of tissue and can be used to rule out benign growths and indolent cancers. It is not widely deployed yet since it requires administration of an expensive, hard to obtain radioactive tracer into

the patient. Nonetheless, it is a technology that will eventually become standard practice for increasing the specificity of cancer diagnostic procedures.

(+) "No diagnosis" is an option

If a cancer cannot be managed, there is no value in developing a diagnostic test for it. This has been the situation for lung cancer for many years. In the 1970s large scale clinical trials involving thousands of patients were conducted using sputum cytology (analyzing cells in sputum under a microscope by a pathologist) plus x-ray. The trials measured no reduction in lung cancer mortality for patients undergoing the more rigorous testing. It was felt that detecting the lung cancers was not useful since they could not be treated at the time. Part of the problem lay in the fact that these technologies could not detect lung cancer early enough. Regardless, it has been the position of every major medical association in the world for the last 30 years that *lung cancer screening is not recommended at the present time.*

New diagnostics must compete with the notion that "no diagnosis" is an option if there is a perception that nothing can be done about the disease anyway. This should decrease as treatment options advance.

2.2 Industry Attractiveness

Overall, the *in vitro* cancer diagnostics industry does not look attractive. Although the rivalry is low to moderate, the other four of Porter's competitiveness factors are all moderate or high. To an outsider, developing cancer diagnostics looks like a high risk proposition. The effort is extremely expensive. It takes a long time, which makes an investor question the opportunity cost. There is significant risk of being supplanted by a

newer, better technology. Even if a test reaches market, there are enormous difficulties in distributing it and having it adopted as part of standard practice.

On the other side of the balance is that cancer is bad. It is the number two cause of death behind cardiovascular disease and will continue to be an important issue throughout the 21st century. The world is becoming more affluent and people are living longer. People's concern about avoiding dying of cancer and willingness to purchase products to that end propels *in vitro* cancer diagnostic companies forward. The market looks attractive to the firm that believes it has that newer, better technology that supplants competitors, especially if has staked an effective ring of patent protection around its platform and products.

2.3 Key Success Factors

The key success factors for companies in the *in vitro* cancer diagnostic industry are: (1) developing early momentum behind a test paradigm, (2) developing effective marketing strategies to bring physicians into the test delivery system (3) maintaining R&D spending to keep improving the products, and (4) developing strong intellectual property (IP) protection around the technology.

1) Developing Momentum

As was discussed earlier, physicians are slow to adopt new testing techniques, especially if they are a radical departure from existing practices. Consequently, first mover advantage is significant in this industry. Having medical practice coalesce around a testing methodology assures the leading firm that it will be difficult to dislodge from its position. As well, once the medical community adopts a technology, government granting agencies are more inclined to give out grants to study the technology further.

These grants will pay for further validation of the technology and serve to entrench the leading firm's position. For example, now that CT has become a more regular part of cancer diagnostic practice, physicians apply for multimillion dollar grants to NIH, NCI and other granting agencies to study its use on their patients. This helps Siemens and GE, as producers of CT devices, entrench their testing paradigm at someone else's expense.

As mentioned in Section 1.4, the lung cancer screening market is 10-20 times the diagnostic market. The importance of establishing a diagnostic testing paradigm in the medical community is that it is extremely expensive to validate a technology as a *screening* test. A lung cancer diagnostic application can be validated with a limited study size, numbering from hundreds to a few thousand, depending on the test and how specific the inclusion criteria are. However, validating a lung cancer screening application can require ten thousand or more patients and up to ten years. The large number of patients is required because of the statistics of the screening group. Since around 0.3% of the group will develop lung cancer each year, one would only expect 30 cancers per year in the 10,000 person intervention arm of such a trial. This number is small from a statistical point of view. Because the screening population, by definition, is asymptomatic for cancer, it is necessary to demonstrate that any putative cancers found would have eventually led to the death of the patients. So mortality is the appropriate endpoint of such a trial. It takes 5-10 years to establish mortality reduction in the active screening arm of the trial versus the control arm (which receives only the current standard of care). These kinds of studies are expensive in both time and money, so firms will rely on government granting agencies to pay for them.

2) Marketing to Physicians

Once a test is approved, the physicians as gatekeepers still need to be convinced of its value and encouraged to use it for their patients. Developing a marketing strategy that achieves this goal represents a significant challenge and a significant milestone to be achieved by the *in vitro* cancer diagnostic firm. Achieving the technology establishment success factor (1) would certainly help convince physicians, but that acceptance can take many years to foster. The PSA test was developed in 1979 but grew slowly until the 1990s before PSA screening became common. CT was developed in the 1970s but CT lung cancer screening began only in the early 1990s. The marketing challenge for Perceptronix and other *in vitro* test makers is to hasten the acceptance process. Part of the solution will be to determine an effective way to engage the physicians.

3) Constant improvement

With so many technologies all pursuing the same detection goal, the market will keep demanding performance improvements, even from successful products. The firm must maintain a steady stream of clinical research efforts to keep improving the product and validating newer versions. Maintaining R&D spending provides two benefits. It makes it less likely that the firm will be blindsided by a newer technology that significantly outpaces the existing one. It also acts as a signal to competitors of the firm's commitment to compete in this area. Since it can take several years to develop a competing technology, competitors must plan to compete with a product that has undergone five years of improvements rather than the one they see today.

4) Developing strong intellectual property protection

The lung cancer detection market may look attractive to a firm with a breakthrough technology and a strong ring of patents around both the platform and the clinical application. The more novel the testing approach, the greater is the firm's ability to stake the IP landscape around the test. Although having strong IP protection is not a sufficient condition for success, it may be a necessary one for long term success.

3 Internal Analysis

While Chapter 2 looked at Porter's five forces model applied to the *in vitro* diagnostic creator industry, this chapter will focus on Perceptronix internals. First the firm's generic strategy will be presented, followed by the industry and firm-level value chain. The firm's organization and culture will be discussed. Finally, the Perceptronix product rollout plans and financial projections will be detailed.

3.1 Generic Strategy

Perceptronix generic strategy is **differentiation**. It is that of a creator of high value, high quality products based on the application of novel technologies to the problems of cancer detection, localization and definitive diagnosis. Figure 3 summarizes the nine variables that define the strategic fit model. Perceptronix score for each of the attributes is shown in the figure.

	Perceptronix Medical Inc. Generic Strategies Chart											
Variables	**Cost Based**											**Differentiation**
	Low Cost / Adequate Quality											*High Quality / Adequate Cost*
	Score:	1	2	3	4	5	6	7	8	9	10	
Product Strategy	Rapid Follower									☆		Innovative
R&D Expenses	Low R&D										☆	High R&D
Structure	Centralized							☆				Decentralized
Decision Making	Less Autonomy							☆	⇨			Autonomy
Manufacturing	Economies of Scale							☆				Economies of Scope / Flexible
Labour	Mass Production										☆	Highly Skilled / Flexible
Marketing	Comparative Push									☆		High Cost / Pioneering / Pull
Risk Profile	Low-Risk										☆	High-Risk
Capital Structure	Leveraged										☆	Conservative

Figure 3: Perceptronix generic strategy adapted from the Bukszar 2005 class notes.

Product Strategy: score=9

Perceptronix product strategy is that of an innovator of technological solutions to the detection and diagnosis of lung cancer. All the product lines are derived from new technology that has been originally developed at the BCCA and further developed by Perceptronix.

The sputum and buccal assays for lung cancer detection are automated tests based on nuclear image cytometry. The technology was originally developed at the BCCA for application to cervical cancer screening. It was adapted for lung cancer detection and automated to create completely automated detection systems for lung cancer. The tests use specialized, but commercially available microscope and camera equipment. Perceptronix innovation lies in the processes by which specimens are prepared for analysis and the software which drives the robotic microscope to analyze and score specimens. Certain aspects of the test are patentable, but others rely on superior know-how and expertise to accomplish. The know-how to operate the test and the large database of high quality clinical specimens present a significant value to the company and a challenge for competitors to replicate.

The endoscopy products consist of two variations of an attachment to make ordinary endoscopes more valuable to the physician performing bronchoscopy (examination of the lung through and flexible endoscope passed down the throat into the lung). The first is an *ease of use* offering that attaches to an endoscope to allow the simultaneous viewing of white light and fluorescent images. The second generation device, which is still in the research stage, will combine the ability of fluorescence to detect cancer with the use of spectral analysis to rule out lesions that are actually benign.

This device requires the analysis of thousands of biopsies and spectra in order to train the system. Perceptronix has one patent already and is pursuing several others for these products. The endoscope products are unique in both their hardware, which was designed and built by Perceptronix. The second generation device will have embedded software for sensitive and specific cancer detection that will make it the world leader for *in vivo* lung cancer detection and localization.

The workstation products consist of a device for interactive analysis of cytological specimens and another for interactive analysis of histological (biopsy) specimens. Both use commercially available hardware components combined with specialized software developed at Perceptronix. As with the detection test and the second generation endoscope attachment, the workstations have been embedded with algorithms to detect cancer based on Perceptronix analysis of thousands of clinical specimens.

In summary, the Perceptronix Product Strategy scores 9/10 for innovation. It does not score it 10 because many of the product offerings are based on commercial off the shelf (COTS) hardware. As well, most of the products are based on computerized image cytometry, a field which has existed for 50 years. Several companies already market cytometry related products, but not currently in Perceptronix space.

R&D Expenses: score=10

Perceptronix has been an R&D company throughout its existence. The company began with a medical doctor and a few scientists performing strictly R&D. As it has grown to more than 40 people over the five years, the payroll has grown to include other functions, but R&D has been the core effort of the company.

As the company matures, the percentage of company expenses devoted to R&D will decline, but they will remain high relative to others in the industry. Perceptronix believes that R&D will remain at least 20% of company expenses in the future. High R&D expenditure is a necessity for Perceptronix to keep its products viable at the forefront of technology. For example, performances of the detection assays are believed to be adequate to introduce them into the market. However, there is expected to be a limited lifespan for the tests in their current form as genetic and proteomic assays will eventually dominate the early detection market. Adding more clinical specimens to the database makes it possible to refine the decision systems used in the tests. This, plus engineering based refinements to the cytometry platform, will allow Perceptronix to improve the performance of the test—making it viable for a longer term. Consequently, Perceptronix must follow a continuous improvement model for the detection tests in order to "stay ahead of the other guys".

The same logic applies to the cytology workstation and to a lesser extent the endoscope devices. Both face threats from competitors pursuing different avenues of diagnosis and localization. Strong R&D efforts will continue to be part of Perceptronix differentiation strategy. For these reasons, the R&D Expense variable scores 10/10.

Structure: score=7

Perceptronix began its life as three separate companies Perceptronix Medical Inc. (1999), Spectra-Vu Medical Inc (SMI) (2001), and Cancer Prevention Centres (CPC) (1999). The companies were formed by different BCCA scientists to pursue the detection test, the endoscopes and the workstations, respectively. Different companies were incorporated for each product so that:

1. Each company could have a singular focus. Xillix (Richmond, BC) was founded by Dr. Branko Palcic in 1988 to develop fluorescent endoscopes and automated cytometers for cervical cancer screening. Xillix focused its efforts on endoscopy, leaving the cytometry product group under funded. Eventually Xillix stopped all cytometry R&D. Dr. Palcic founded Perceptronix with the single goal of developing a test for lung cancer based on automated cytometry.
2. Different investors could be brought in to back various product lines.

After three years it was felt that although the three product lines could stand on their own as businesses, the integrated approach to lung cancer detection and patient management represented a compelling vision. As well, there was crossover in the technology between the products. The detection test and the workstations are both based on image cytometry devices. The biopsy grading used to train the second generation endoscope can done better using the Pathology Workstation. For these reasons, the companies were merged into a single entity now called Perceptronix.

The history of the company and the disparateness of the product lines suggest a decentralized structure at Perceptronix. The comprehensive approach to lung cancer argues for some element of centralization. On the whole, the decentralized nature leads to Structure scoring 7/10. This is an appropriate value for a company that contains individual product groups linked under an overarching vision.

Decision Making: score=7 (increasing)

Just as Perceptronix structure is decentralized, so is its decision making. The three product groups are led by product directors and have significant autonomy with respect to development plans and marketing plans. The product directors draw their

human resources from four pools of personnel: engineering, clinical, scientific, and quality system staff. There is some element of centralized control in that business development is centralized and the marketing strategy is set at the level of the president. The product directors, the clinical affairs director, and the business development director all report to the president. Company priorities for resource allocation—both people and money—are set by the president based on factors such as:

1. the necessity of the company to generate revenues soon in order to attract further investment
2. the fit of particular products into the comprehensive lung cancer management approach
3. regulatory issues regarding the products

Currently, the company scores a 7/10 for the autonomy of its Decision Making and this variable will trend upward Perceptronix begins to generate revenues and the product groups pursue their differentiation strategies.

Manufacturing: score=7

Perceptronix detection test and workstation products are currently assembled using COTS wherever possible. Manufacture for these product lines consists of assembly microscopy components and computers, configuration of the specialized software and validation of the device performance. Both product lines use similar component inputs and technician skill sets to make the products ready for market. In both cases, Perceptronix keeps little inventory, relying on ordering components when needed.

The endoscope components are currently manufactured in-house for assembly, although this will change once the prototypes have been finalized. There no

commonality of component inputs and little cross over in the technical skill between the endoscopy manufacture and that of the other products.

Perceptronix plan for all product lines is eventual licensing or OEM manufacture once significant sales volumes are achieved. This will allow the company to maintain flexible manufacturing practices focused innovating new features or products. This is in line with Perceptronix differentiation strategy and the company scores 7/10 for Manufacturing attribute. The score would be higher except that the disparate nature of the hardware used in the cytometry-based and endoscope product lines prevent true economies of scope from being achieved.

Labour: score=10 (decreasing)

Perceptronix employee base consists of scientists, engineers, mathematicians and technicians with specialized skills. The technical staff is experienced in prototype development rather than manufacturing engineering. Through the reorganization of the staff into the pool structure, the plan is to develop technical staff with a more general skill set that can work across all the product lines. However, this process is just starting. The ISO quality management processes that are being put in place have imposed a common design paradigm across all the product lines. This common outlook will hasten the development of professional staff who can contribute to the development of multiple products. Perceptronix scores 10/10 for its highly skilled workforce on the Labour variable but the value will decrease in the future.

Marketing: score=9

Once approved, Perceptronix detection tests will be the only sputum and buccal based lung cancer assays on the market. This presents an obvious marketing opportunity and also a significant challenge. Pulmonary physicians, who are the specialists who see high risk patients, are not familiar with DNA cytometry, do not know that they could order such a test for a patient and do not know how to interpret the results. For these reasons, marketing the test will be expensive and require a great deal of education and evangelism. The detection tests stratify patients into low and high risk categories and require interpretation by a medical professional. Therefore marketing efforts should be aimed at the physicians rather than at consumers directly. Patients rely on their physicians' recommendations in this area. Physicians must be comfortable with their understanding of the tests and recognize their value before they will recommend them to their patients.

The workstation and endoscope products fall into existing product categories and can be marketed using more traditional marketing efforts. Both product lines will be marketed based on emphasizing their features and their superior performance to their competitors. This will require significant educational efforts, particularly in the case of the second generation endoscope device, whose use of spectroscopy as well as imaging is unique in the world of endoscopy. The competition will eventually bring out endoscopes with equivalent features to the first Perceptronix endoscope product, so some comparative marketing is likely to be done for that product line.

Consumers of the workstations will be pathologists, while pulmonologists will be the consumers of the endoscope products. Both consumer groups will need to be pulled

into the marketing channel in order to sell to them. Although marketing is only in the planning stage at the moment, the strategies that will be used will be high cost and educational in order to support Perceptronix differentiation strategy. Perceptronix scores 9/10 on the Marketing variable.

Risk Profile: score=10

Perceptronix is a biotech start up company that has not generated any revenues after five years of operation. The cancer detection test falls into the realm of in vitro diagnostics, an industry which is high risk and is currently underperforming the market[4]. Perceptronix attempt to turn this BCCA technology into a marketable product is the second attempt to do so after an earlier venture failed[5]. Even after the tests are brought to market Perceptronix must educate, evangelize and create distribution channels for the test. The other products do not have easier paths to market in front of them. There are significant clinical and regulatory hurdles, particularly for the endoscope products.

The biggest risk comes from Perceptronix financial position. Perceptronix is strictly financed by private equity. The company has enough money to operate until the end of 2005. By this point several of its products will have received regulatory approval and be ready for sales. Delays in the regulatory approval processes could sink the company. Perceptronix scores 10/10 for the Risk variable, which reflects the fact that biotech innovation is a risky endeavor.

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[4] In the BUS606 Financial Management course, the performance of different industries were analyzed by their Standard Industry Classification (SIC) codes. The industries with the worst EBITDA margins (by a significant amount) were "Biological diagnostics" and "In vitro, in vivo diagnostics".

[5] Xillix spun off its cytometry group into a separate company called Oncometrics which was acquired by Accumed of Chicago. Accumed and Oncometrics both failed.

Capital Structure: score=10

As mentioned earlier, Perceptronix is financed through private equity—no debt. Given its start up nature and the fact that there are no revenues, this has been entirely appropriate with the strategy of the company thus far. The high risk/high reward nature of the medical device industry tends to make more suitable for investors rather than lenders. Perceptronix intends to continue with equity financing in the near future with the idea of an eventual IPO. If the company survives and matures, it may eventually begin to use debt as well. Until then, the current Capital Structure scores 10/10, which fits Perceptronix differentiation strategy.

3.2 Conclusions Regarding Generic Strategy and Strategic Fit

Perceptronix Medical Inc. is a biotech innovator with high R&D expenses, decentralized structure and decision making and a highly skilled workforce capable of manufacturing specialized products in small amounts. It is engaged in a high risk industry and faces additional challenges of raising money in a market that is somewhat hostile to medical diagnostic companies. It must market its products through education, evangelism and personal selling (such as medical conferences and doctor visits)—all of which are high cost forms of marketing. All of these traits match Perceptronix profile of a company that is a differentiator.

The unified vision of comprehensive lung cancer detection and management bring some element of centralization into the Structure and Decision Making reduces the differentiation for these variables. That is entirely appropriate given the investor belief that the comprehensive lung cancer approach is larger than the individual pieces.

Strategic fit could be improved in the area of manufacturing. Perceptronix Manufacturing score does not match its differentiation strategy to the degree it should because there are not complete economies of scope in the manufacturing inputs. As mentioned earlier, this is because endoscopy and cytometry very different fields. This is a tension that works in opposition to the unified vision of the company, but it has not caused significant difficulties so far. The company has recently reorganized the engineering and analysis personnel to work across the three product groups rather than within individual product groups. It is hoped that this will lead to the development of cross-product expertise among the staff and the pollination of new ideas within the product groups.

3.3 Perceptronix Footprint in the Industry Value Chain

The cancer *in vitro* diagnostics value chain, shown in Table 2, consists of seven major areas: R&D, clinical trial activities, manufacture, marketing, distribution, selling/promotion and customer service. One could arguably divide it further, as distribution, selling and service may contain several subcomponents. One could also merge areas, since diagnostic test development is closely linked to the clinical trials that are used to validate the tests. The four areas in Table 2 are shaded to indicate the degree to which PMI has undertaken these activities during its five year existence.

Table 2: Industry value chain for the cancer in vitro diagnostics industry. Shaded regions show Perceptronix current footprint and the degree to which the activities are undertaken.

R&D	**Clinical Trials**	**Manufacture**	**Marketing**	Distribution	Selling, Promotion	Service

The development of new in vitro diagnostic tests tends to follow a similar pathway to that of new pharmaceutical development. Through research conducted in a private or public laboratory, a technology is discovered that may be useful in detecting cancer. Initial pilot studies involving a few or dozens of patients are conducted to measure the test's efficacy to justify further investigation. If initial indications are successful, a clinical trial is conducted—often involving hundreds to thousands[6] of patients. These clinical trials can cost millions of dollars. In a public setting they are typically funded through granting agencies.

In some cases, the initial data is compelling enough to form a company around the technology. This is how Perceptronix came into being. Initial lung cancer pilot data collected by the Cancer Imaging Department of the BC Cancer Agency suggested that it was possible to detect the cancer using automated microscope analysis of epithelial cells. The technology was spun off to create Perceptronix. Since then the company has conducted a follow-on pre-clinical study and a clinical trial of its lung cancer detection system.

Clinical trials of diagnostic tests are required for several reasons. First, blinded (and sometimes randomized) clinical testing is required to remove the researcher bias from the validation process. Second, independent application of the test in a variety of settings can reveal differences in patient populations that can affect the performance of the test. The third reason for conducting these clinical trials is that they constitute objective evidence required by regulatory authorities such as the Food and Drug Administration (FDA) in the US and Health Canada for approving a diagnostic test. As a

[6] If a test is being developed as a screening test (something applied to asymptomatic people) rather than a diagnostic test, many more participants are required.

consequence, the diagnostic test development phase is tightly bound to the clinical and regulatory phases. The distinction between the first two areas in Table 2 is not always clear cut.

The type of manufacturing conducted in that step of the value chain depends on whether the diagnostic system relies on specialized testing equipment or specialized reagents. In the case of Perceptronix, the manufacture consists of cytometer assembly. Specimen collection kits are put together using simple off the shelf components and a specialized lab procedure is applied to specimens before they are scanned using the cytometer. Because a single cytometer can scan thousands of specimens per year, it is believed that between one and twenty cytometers per year will need to be manufactured during the next five years. The assembly and commissioning of cytometers is expected to remain as an in-house activity until then.

The remaining areas of the value chain are all areas where Perceptronix has a small footprint or none at all. Perceptronix diagnostic tests are in the clinical trial phase with completion expected in Q3-2005. Also the company has successfully completed registration to the ISO 13485-2003 standard for manufacturers of medical devices in Q2-2005. Marketing efforts have commenced over the last 12 months and additional marketing staff has been hired. The firm currently engages in distribution of the test in a limited fashion through its interactions with the study clinicians. Perceptronix sends specimen collection processing materials to clinical sites through FedEx and receives (in most cases) prepared slides that are to be stained and scanned.

Since the test has not received approval, Perceptronix engages in no promotion of the test other than that which is necessary to attract physicians into the clinical trials. The

company does engage in some service activities through the feedback process that occurs through its clinical relationships. How should the test be sold once it is approved? This is a big question for Perceptronix. Two options come to mind: license the technology to *in vitro* testing experts such as MDS Diagnostic Services, or offer the test directly.

The decision affects who Perceptronix will sell to: labs and distributors or physicians and patients. Distribution does not represent a core competency of the company at present and outsourcing this area should be considered. Perceptronix does have a core competency in the clinical aspects of offering a diagnostic testing service but not the commercial aspects. Because of the difficulties involved in setting up a commercial lab, promoting the test service and selling the test, one would imagine that licensing the technology would be the clear choice.

In spite of the fact that Perceptronix has only a small footprint in the later part of the value chain, there are reasons why it makes sense to initially sell the test directly to customers:

1. The test system requires a specimen processing procedure which is not yet automated. This step is performed by a trained technician and can affect the performance of the testing system if not done with adequate precision. It is important to the firm that the system operates successfully at the outset. It is developing apparatus to automate the processing steps in the future.
2. Some of the intellectual property that is part of the test system is in the form of trade secrets and know-how. Perceptronix is starting to file patents to protect these aspects of the system, but it will take time to put adequate protective measures in place.

3. It is felt that initial adoption of the test by physicians will be done through pilot projects partly funded by the physicians' hospitals. These studies will yield reduced revenues for Perceptronix but provide additional clinical information in order to improve the performance of the test[7]. Furthermore, they will create champions for the product and additional scientific publications that will help promote the test.

3.4 Firm Level Value Chain

Figure 4 shows the firm level value chain model of Michael Porter applied to Perceptronix. The primary activities will be described in detail, followed by the support activities.

Primary Activities

As an *in vitro* cancer diagnostic manufacturer, Perceptronix will have two main lines of activities during the next few years:

1. Further development of its lung cancer detection platforms based on automated cell analysis, and broadening of the platform to other cancer areas. This will entail further software/hardware developments and additional clinical studies.
2. Operation of an in vitro diagnostic test laboratory to process specimens.

[7] The specificity and sensitivity of the test are limited by the size of the clinical data set from which it is developed. Obtaining additional clinical data will allow Perceptronix to optimize the test's performance and make it a more attractive offering to the market. In particular, the population for which a test is suitable is determined mostly by the *specificity* of the test. Perceptronix would like to position the test as a screening test, which would enlarge the potential patient market by a factor of 10. This requires that the test's false positive rate (1-specificity) be reduced—which requires additional clinical studies.

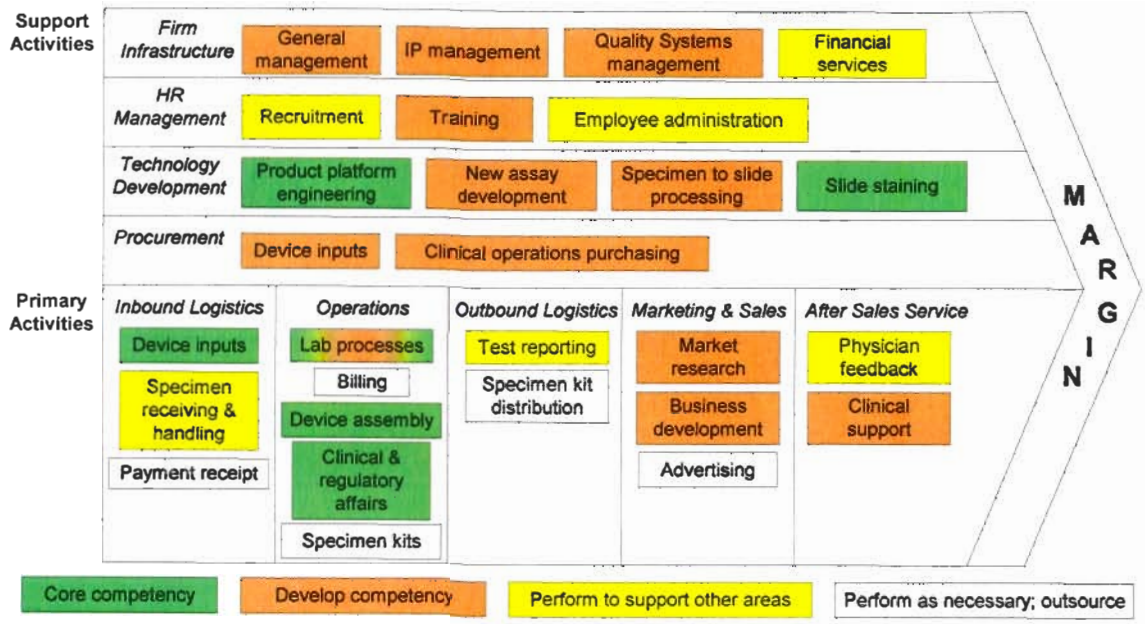


Figure 4: Firm level value chain for Perceptronix Medical Inc. and the *in vitro* assay product group in particular.[8]

These two areas are currently linked. The company requires more clinical specimens to help improve its systems and to automate steps of the test process that are still fragile. It also needs to generate revenues from the approved test. As mentioned earlier, the post market pilot projects will provide Perceptronix with data, revenue and create new customers among physicians who will order the test.

Inbound logistics:

The inbound logistics for Perceptronix currently consist of activities related to device development and assembly and clinical specimen receiving. Device development and assembly requires ordering, receiving and qualifying components for the medical devices. For both development and manufacture these processes are managed through a design control process under an ISO 13485 quality system.

[8] Adapted from Porter, 1985.

Clinical specimens are received in batches for each of half a dozen ongoing studies from various clinical sites around the world. Inbound and outbound shipping are done through standard shipping firms such as Federal Express. For clinical studies, the specimens also include patient information forms which detail patient-specific information (age, smoking history, relevant medical history, etc) and clinical assessment information. These forms are received after the diagnostic work-up has been completed, which can be several months after the patient cytological material is received. It is necessary to reconcile specimens with patient information that often comes in separately.

The inbound logistics for the testing laboratory will include the shipping and handling of specimen kits. Perceptronix will create specimen collection kits with prepaid shipping or some other collection arrangement. The specimens will be collected under the supervision of a physician who orders the test and returns the specimen kits to the Perceptronix laboratory to be processed. Initially, the test will be paid for by the patient. This will be done either through payment returned with the kit or through the physician. Logistically, Perceptronix must create a plan by which all these steps will occur, either through employee effort or outsourcing. Shipping and payment receipt represent the two steps that the company does not currently have systems in place. These steps of the process could be contracted out in the future.

The inbound logistical activities represent a point of repeated contact with clinical sites. Whereas the other aspects of a clinical study may only provide the opportunity for periodic feedback, logistical coordination (in both directions) occurs on a weekly or semi-weekly basis. They provide an opportunity for learning the practical aspects of clinical practices in other countries, such as patient management practices,

laboratory practices and turnaround time, and regulations regarding patient material transport. Perceptronix also learns directly from the sites how well its procedures are executed by their technicians.

The management of some of these activities could have been outsourced to a firm with greater experience in this area. This would be done by engaging an intermediary to handle the conduct of the clinical studies. Contract research organizations (CRO), for example, are commonly used in the pharmaceutical industry for these aspects of clinical development and validation studies. It would have the advantage of placing the concern for logistics in the hands of a firm that specializes in this area. It has the disadvantage of weakening Perceptronix tie to its clinicians and their technical personnel. If one looks at an in vitro assay as a testing system, which includes the delivery of the test and all its logistics, then there are significant learning opportunities from the testing logistics that can be used to improve the test. Consequently, Perceptronix will continue to perform the logistics for future clinical R&D projects internally, in spite of the fact that they are not core competencies[9] of the firm.

The patient information collected for R&D purposes is more extensive than that which would be collected by the commercial testing operation. The scale of the R&D operation is expected to be smaller than that of the commercial operation, so the logistics for reagents and other provisions may look different for a commercial laboratory than for the R&D lab.

[9] "Core competency - an activity that you would never outsource", source: Ed Bukszar, MBA607

Operations:

Perceptronix operations will consist of: commercial diagnostic test delivery, test platform development, clinical studies and kit assembly. When a specimen is received in the lab as part of the commercial operation, it will contain two logical components:

- diagnostic material that must be processed into a report for the patient and
- patient/billing information which must be processed to ensure that payment is received for work performed.

The processing of a specimen currently takes over a day. Specimen processing consists of four steps:

1. extracting cells from the liquid specimen and depositing them on a slide – The liquid specimen is shaken for several hours to separate cells and mucous. It is then deposited on a slide using standard lab equipment and procedures. This step of the procedure is not a competency unique to Perceptronix.
2. staining the slide – Perceptronix uses a proprietary variant of a standard DNA staining technique. The procedure takes four hours.
3. scanning the slides – The slide is batched and scanned using an automated image cytometer. The process of generating a score from a specimen once it has been transferred to slides is currently around 30 minutes
4. slide QC and reporting – Before the final results are transmitted for a specimen, a QC procedure is done to ensure the quality of the results.

Some aspects of the laboratory processes are competencies unique to Perceptronix, while others represent standard practices. Performing the processes in-house makes it possible

to determine which steps are critical to the success of the test and to learn how to improve these aspects of the testing system.

In the model where the patient pays directly, it would be necessary to link the payment to the report after the processing has occurred and before the report is sent out. Although the specimen processing is a core competency, billing is not. It is expected that the test will be paid for out-of-pocket for several years until its long term value in the management of lung cancer can be demonstrated through additional trials. At that time, it may be reimbursable through the Medical Services Plan in BC and through health insurers in other jurisdictions. Billing processes will begin in-house and eventually will be outsourced once the payment model supports that effort.

For manufacturing, devices are assembled for both R&D and commercial purposes. It is expected that the number of devices that need to be assembled for the commercial endeavor can be accommodated with addition of just a few technicians. This is the case because cytometers are assembled using COTS components. The Perceptronix value-add lies in the proprietary software components that drive the system. Configuring cytometers requires several weeks of optical performance measurements and scanning by technicians to turn raw devices into commissioned systems. The assembly and commissioning of devices is a core competency of the engineering team.

Further development of the existing platform and development of new tests for different cancers will require additional clinical studies. The company currently employs clinical affairs personnel who have significant experience in conducting studies and trials. These employees manage Perceptronix relationships with physicians and clinicians and represent the face of the company to the research collaborators. Enrolling physicians in

clinical studies can be challenging and requires their goodwill to participate. They participate on a voluntary basis, often with no compensation for their time, so it is necessary to have professional staff adept at maintaining good relations with them. The clinical affairs area represents a core competency for Perceptronix and one of its strongest assets. This function could be achieved by Perceptronix engaging a CRO. However, this would likely lead to studies becoming significantly more expensive to conduct and limit the firm's ability to generate new ideas from its collaborators.

Finally, it is necessary to assemble the specimen collection kits. The components of the kits are standard specimen collection and fixation supplies. This could change in the future if Perceptronix focuses efforts on developing better specimen preservation kits. Depending on the volume of the tests being delivered, this activity could be done in-house or outsourced. Initially, it will be done in-house for quality assurance reasons. Once the test is established it will likely be outsourced.

Outbound logistics:

Once a specimen has been processed, the test result is reported to the physician. This activity is currently done electronically for physicians participating in clinical studies and trials. This will be an important activity of the laboratory service as it provides Perceptronix with valuable physician feedback.

How to distribute the specimen collection kits remains one of the significant questions for Perceptronix. They are initially expected to provide no revenues to the firm—only costs, until the test becomes established in the marketplace. Distributing kits, even if done efficiently, occupies trade capital that could better be used elsewhere. Their distribution will need to be managed so that participating physicians will always have

enough on hand to serve their patients, but not so many that they constitute a cash drain to the company.

As an example, the company OralScan produces the OralCDX brush biopsy test marketed through dentists. They produce packages consisting of six test kits plus a video, which are sold to dentists for $10. Considering the constituents of the kits, they are likely selling the kits as a break-even endeavor to help them manage the distribution issue. Perceptronix may follow a model akin to this. As the market begins to accept the Perceptronix test, the kits can move from costing the firm money to at least being self supporting.

Marketing & Sales:

Marketing Perceptronix lung cancer detection test will pose a significant challenge to the firm. When managing a patient at risk of lung cancer, physicians do not routinely order *in vitro* assays for lung cancer, so the test will not merely displace an existing product. There is an aspect of market creation that will need to occur. Another consequence of the uniqueness of the lung cancer test is that, for sales purposes, there are no distributors of assays that have strong connections to pulmonary physicians. There is no existing distribution channel aimed at pulmonary physicians that Perceptronix can work with.

Perceptronix envisions that sales and marketing functions will be conducted in-house. The firm is developing sales and marketing personnel, but this area is not yet a core competency. It is recognized that in-house efforts will be necessary until the test becomes established and until the test system is mature enough that it can be licensed to others to deliver. Additionally, the firm plans to offer a portfolio of products aimed at

comprehensive lung cancer management. The marketing relationships created through the *in vitro* test offering may help Perceptronix sell its endoscopy products, which are also aimed at pulmonary physicians.

As mentioned earlier, Perceptronix engages in promotion aimed at recruiting physicians into clinical trials. Sales promotion is an area that is sensible to outsource.

Service:

Perceptronix currently engages in service related activities through the clinical affairs staff as part of its clinical studies and trials. Once the products are approved the service function will move to the sales and marketing department. Acquiring physicians and medical institutions as customers is going to be a long and expensive process. Retaining these customers will be therefore become a priority for the firm. This is area will be developed into a core competency of the sales and marketing team.

Support Activities

Firm Infrastructure

Most firm management functions are performed in-house at Perceptronix. IP management is an area where some patent searching and development functions are contracted out to patent lawyers. It is recognized that as the firm grows and knowledge creation accelerates, more IP expertise will be required in-house. Perceptronix is a knowledge generation firm and it needs to turn its knowledge protection efforts into a core competency.

Perceptronix has undergone a major culture change during the last year. It is transitioning from a high tech startup staffed by scientists and engineers into a professional, medical device manufacturer. Instantiating a functioning ISO 13485 quality

system has been an important but difficult endeavor. The quality systems management team is developing competencies in quality-related issues but they are not yet core competencies of the firm. The quality initiative will not end with the first certification—additional efforts will be needed both for further medical device development and for Perceptronix plan to create a commercial clinical lab.

HR Management

HR areas such as recruitment, training and employee administration functions are currently handled in-house. Given the current size and growth rate of the firm, these functions can be handled with the existing staff. Training is an aspect of particular importance because of its quality systems implications. Obtaining and maintaining ISO certification will require that managers pay close attention to employee training issues, such as currency of training, appropriateness of training, etc. The training at Perceptronix is specialized, so the firm needs to develop its training programs and staff to deliver the programs. The laboratory processes are a particular area of importance for two reasons. The accuracy of the *in vitro* test results depends on the skill and diligence of the laboratory staff that process the specimens. Second, the accreditation of a clinical lab requires that retraining and auditing of staff occur on a regular basis.

Technology Development

Technology development at Perceptronix occurs through:

- creating new hardware platforms for detecting cancer
- finding additional clinical applications for existing platforms
- developing ways to process specimens to make cancer more detectable

The engineering of new cytometry platforms is a core competency of the firm. The firm was created out of a technical development project and most of the technical staff has engineering or other development related backgrounds. Developing a cytometer platform is a three level process. At the low level, which is an optical engineering endeavor, cytometers are assembled from microscope and robotic hardware, and optically characterized for cytometry applications. At the middle level, the cytometer is programmed to scan cytological preparations, locate cells and capture collect precise cell images. These tasks require software programming skills and advanced image processing skills. At the high level, data sets of cell information from clinically relevant specimens are analyzed to develop decision systems to automatically distinguish cancer from non-cancer. This level requires skills in statistical pattern recognition and an understanding of the manifestations of lung cancer on the appearance of cells. The firm has personnel with at least 10, and in some cases, nearly 20 years of experience in each of the three levels of the cytometry development process.

The cytometry process, from specimen to score is shown in Figure 5 below. The figure shows the sequence of data collection and transformation as a stained slide is analyzed. The slide is scanned using an image cytometer, a robotic microscope that images between 500 and 5000 fields of view for each slide, depending on the size of the deposition. Each field of view contains typically 100 to 1000 objects, 90% of which are debris and 10% of which are interesting cell nuclei. Precisely focused images of the objects are collected and they are passed through a decision tree which sorts the cells from debris. The tree was created by a statistician with the assistance of cytotechnologist.

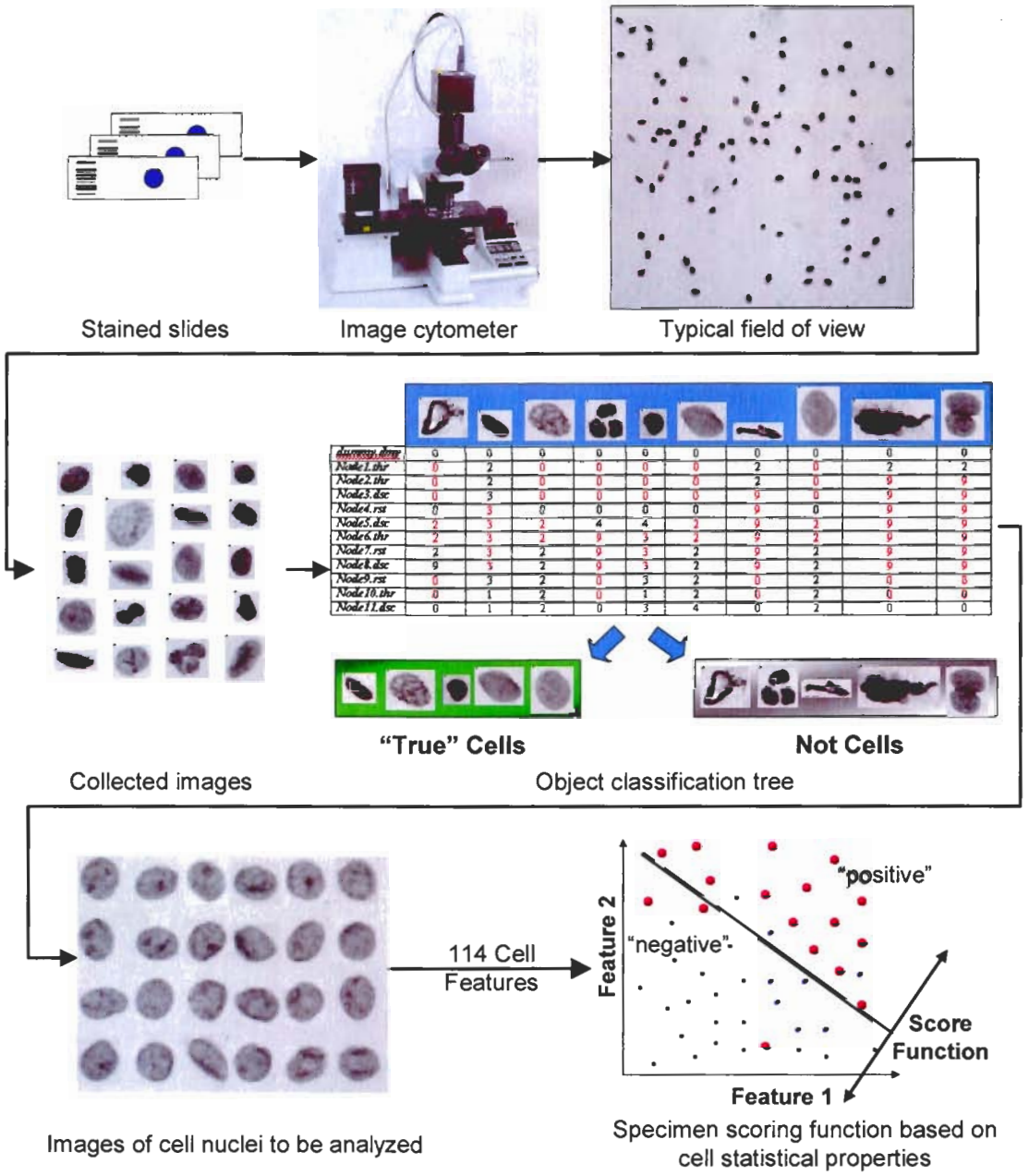


Figure 5: The image cytometry process, from slide to score, is depicted. Slides are scanned using an image cytometer, which collects objects from 500-5000 fields of view. Between 100,000 and 1 million objects may be collected, depending on the slide deposition. Objects are automatically classified and features are calculated for the cell nuclei. Finally, a scoring function combines the appropriate cell statistics to give a single score for the specimen.

Shape, darkness and texture features for the cells are calculated and the useful features are combined using a scoring function to give a single score for the specimen.

Scoring functions are created by analyzing clinical data sets of specimens from confirmed lung cancer patients and specimens from high risk negatives. The statistician looks for cell nuclear properties that correlate with a positive disease state. Reliable features are then incorporated into scoring functions, which separate (usually in an imperfect manner) the two patient groups.

The cytometry process shown in Figure 5 can also be viewed as a data reduction process that converts an overabundance of unprocessed data into a single useful result. This process is facilitated through the core competencies of the firm. The microscope slides at the start of the chain hold a great deal of information—too much to measure unless the context of their analysis is specified (i.e. imaging through absorbance microscopy). If one imagines all the ways that one could analyze such a slide, the size of the resulting dataset would have to be measured in terabytes.

The low level engineering efforts seek to develop cytometers with adequate precision necessary to preserve the fidelity of any signal that is present in the data, but not so high-precision as to be wasteful. The cytometer converts the raw slide into a series of fields of view with multiple focal planes whose electronic data is approximately 20-100GB (gigabytes) per slide.

At the middle level, image processing techniques are developed to efficiently detect possible cell objects and obtain precise images of them. These algorithms are embedded in software that drives the image cytometer. The scanning process consists of:

1. scanning the slide using Perceptronix developed cytometry software;
2. locating the best focal plane for each object;
3. segmenting the object from the background;

4. determining the numerical feature values for each object;
5. and writing the objects to a file

This process reduces the size of the specimen data to 2-10MB (megabytes)—a reduction of four orders of magnitude.

At the high level, knowledge of statistical pattern recognition and of the cytology of epithelia is used to create trees to discern epithelial cells from other cells and debris. This is shown in the centre of Figure 5. Processing the collected images through these trees reduces the data size by a factor of ten. Knowledge of cell-cycle processes and the effect of cancer on cells are used to create rules to aggregate individual cells into populations of particular cell types. This step reduces the data size by a further factor of 100, leaving roughly 1kB (kilobyte) of *information* per patient.

Finally, by working with clinical affairs staff to obtain specimens with confirmed diagnoses, the statistician creates a decision rule to convert that information into a single score for the patient. The three levels of cytometry competency work together to reduce terabytes of data into kilobytes of information and ultimately into a single result to aid patient management. For an individual specimen, the sequence from scan to score takes around 12 minutes.

Expanding the use of the platforms to new clinical applications (such as adapting a cytometer to detect, say, bladder cancer) requires engaging physicians and researchers in the relevant field. The clinical staff is experienced in developing protocols and conducting clinical trials, but there is limited experience in medical aspects of patient management for different cancers. Moving forward, creating new products from the

current technology platforms is one of the mandates for the product development staff. Enhancing the in-house expertise in this area will accelerate the development cycle.

The clinical processes for handling specimens are as important to detecting cancer as the hardware. The two important steps for detecting lung cancer from sputum are how the specimen is prepared to slide and how the slide is stained to make cancer-related changes in cells visible to the imaging hardware. The company has significant experience in the chemistry of the staining process and has recently filed a patent for a new staining protocol. This is not the end of the line for the staining research. The firm feels that there is a lot of unexplored territory that needs to be explored to make the staining process reliable enough to be able to license test. Perceptronix is developing competency in this area.

The issue of slide preparation is an area that is important for determining the reliability of the test. The more intact cells on the microscope slide, the more reliable is the test result. A sputum specimen may contain a million cells but it is difficult to reliably deposit a significant fraction of these cells on the slide each time. This is an area that Perceptronix may wish to look outside the firm for help. For example, in the area of cervical cancer screening, the Cytyc Corporation developed a liquid-based cytology preparation technology called ThinPrep, which replaces the conventional Pap smear. It solves the slide deposition problem, albeit in a different area. Sputum is harder to process, but this is the sort of technology which may be wise to acquire from companies with greater expertise.

Procurement

The main procurement areas for Perceptronix relate to acquiring device inputs and clinical laboratory supplies. The various aspects of procurement: purchasing, goods inward inspection, approved suppliers, etc. all fall under the Perceptronix quality system created to meet ISO 13485 requirements. The firm will need to further develop its skills in these areas so long as it intends to develop image cytometer platforms and to offer the *in vitro* diagnostic services.

3.5 Discussion of the Firm-level Value Chain

Perceptronix footprint in the *in vitro* cancer diagnostic industry is currently focused on R&D activities related to diagnostic test development. This reflects the young nature of the firm, which has grown over the last five years from a few scientists to more than 40 people. The firm level value chain (Figure 4) also shows that the firm's core competencies lie in the early parts of the *in vitro* test delivery process: building cytometers, processing specimens and engaging clinicians. These are the areas where the firm creates value.

The later parts of the test delivery process represent areas where Perceptronix is still developing its skills. Sales and marketing, for example, have been identified as the key areas for development. The corporate decision that comes under the greatest scrutiny is the plan to create a commercial clinical lab to offer the *in vitro* testing services. Other companies specialize in this area and should be more efficient in distributing the test and delivering test services. Nonetheless, the advantages of not licensing the test prematurely appear to outweigh the risks. Perceptronix has confidence that its *in vitro* tests will garner momentum in the marketplace. It is believed that through operating the

commercial lab, the firm will be in a stronger position to license the test technology a few years from now than it is today.

There are some synergies between the test development and test delivery processes that may also justify Perceptronix staying in the test delivery process in the near term. Table 3 provides another way to look at the primary activities of the firm level value chain shown in Figure 4. In this table, the activities that are common to both a test developer and test provider are shown. Activities that look significantly different between the two firms (such as billing) have been omitted.

Activity Type	Activity	Medical Device Developer	Testing Service Provider	Synergy	Comment
Inbound logistics	Specimen handling	Clinical studies for test development	Commercial logistics	Weak	If the scale of commercial operations is larger, the handling system and processes will differ
Operations	Lab Processes	New test development & improvement of existing test system	Commercial processing	**Strong**	The goal of device development is to make the test better, cheaper & more robust. These goals align perfectly with the commercial operation.
	Clinical & Regulatory Affairs	Physician networking & test approval	Physician engagement & lab testing accreditation	**Medium**	There are commonalities in the regulatory processes for both. As well, both require physician engagement to convince them of the merits of the testing procedure.
Outbound logistics	Test reporting	Clinical studies	Commercial	Weak	The physician/lab interaction is stronger during clinical development than during commercial operations
Marketing	Market research	Identifying potential new tests	Identifying potential new customers	Weak	Both marketing efforts seek to determine the demand for a test among physicians who would deliver it.
Service	Physician feedback	Part of new test development	Marketing function	Weak	The physician engagement has different goals between the development and commercial operations.

Table 3: Comparing the primary activities of an *in vitro* test development firm to a test provider for those activities which share commonalities.

The table shows that there are weak synergies between a firm that is purely an *in vitro* diagnostic developer and one that is a test provider for most primary firm activities.

This is due in part to the scale of the operations. The systems and procedures that are suitable for a small scale developer are inappropriate for a test provider. As well, a test development firm has greater engagement with stakeholders such as physicians and regulatory agencies like Health Canada. Both firms solicit the feedback of physicians for marketing purposes—one to further the development of assays, while the other to refine selling strategies.

However, the primary *Operations* activity of a test developer is strongly aligned with that of the test provider. The operational goal of the developer is to improve the test performance, make it cheaper, improve throughput and robustness, etc. These goals can be accomplished by studying and tweaking the laboratory processes that are done during test delivery.

The clinical and regulatory activities done by a test developer have moderate synergies of a test provider. Both firms engage clinicians, although with different goals. Both have interactions with regulatory bodies such as Health Canada. The approval processes for new tests entail significantly more regulatory efforts than obtaining the accreditation to provide those tests. However, both firms have the burden of demonstrating competency in testing system to the regulatory bodies.

3.6 Core Competencies

As discussed in the previous section, the core competencies of the *in vitro* assay product group lie in the development of devices and systems to measure the cancer signal in specimens, the chemistry of staining slides to make that signal visible, and the management of clinical studies to develop physician networks and procure relevant specimens for analysis. These competencies are shown in green in the firm level value

chain in Figure 4. These core competencies are concentrated in the *Technology Development* and *Operations* portions of the company. Although this paper focuses on the assay group, this concentration of competency is also seen in the other product groups. The workstation products are being developed by a team whose expertise lies in applying quantitation to cytology and histology (microscopy based analysis of the anatomy of tissue structure). The endoscopy products are being developed by a group whose expertise lies in lung autofluorescence endoscopy and tissue spectroscopy.

Perceptronix was created around its technologies and is developing competencies in the other areas of the firm level value chain. Most of the orange labeled activities in the value chain occur in support activities. Among the primary activities of the firm, it is in *Marketing & Sales* where the firm must develop its competency. Other areas are either performed to support learning and future development or they should be outsourced.

The core competencies of the firm lead to competitive advantages in the realm of *in vitro* assay development. Should the management of the firm decide to pursue a new cancer detection assay based on an analysis of the market potential, the team has the ability to:

- develop the appropriate protocol to address the clinical question;
- obtain regulatory approvals expeditiously;
- work with clinicians to obtain specimens;
- develop an absorbance microscopy based nuclear cytometry system to detect signal in the data;
- and create a decision system to detect that cancer.

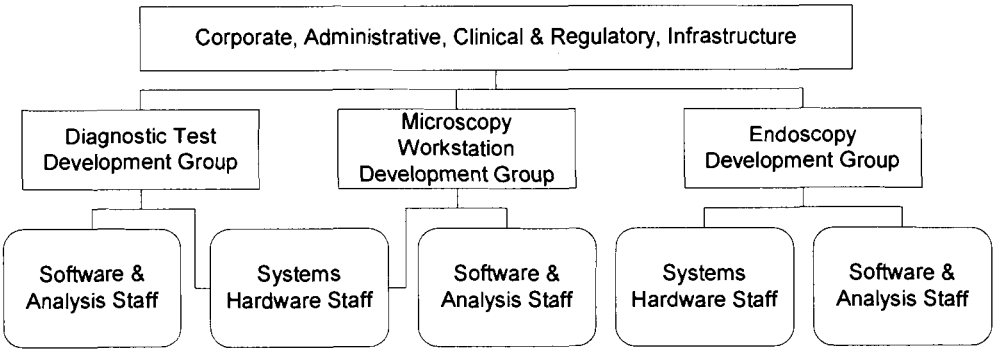
The firm's competitive advantage over rivals is that this sequence can be done more quickly and inexpensively at Perceptronix than almost anywhere in the world.

3.7 Firm Organizational Structure and Culture

The organizational structure at Perceptronix has adapted over time. The firm began as three separate corporate entities (an assay firm, a workstation firm and an endoscopy firm) with shared resources (administration, infrastructure, etc.) Amalgamations in 2003 and 2004 consolidated the entities into one firm with several product groups. Figure 6(a) shows the organizational structure that existed prior to Q4-2004. The firm had three product groups headed by product managers. The product groups had different development teams, with the exception that the diagnostic test group and workstation group shared systems hardware staff. Management, administration, clinical and business development functions were shared across the product groups.

A reorganization occurred in Q4-2004 where the company adopted a matrix style organizational structure. This is shown in Figure 6(b). Now the product groups consist of the product manager and one other person, and all resources exist in four departments across the company. This transition was done in part to facilitate the implementation of an ISO Quality System across the company. Under the old structure the groups followed their own development processes, which made it difficult to achieve a company-wide development philosophy and adherence to a quality standard. Under the new structure, it is easier for the quality management staff to ensure that the company remains in compliance with ISO standards for product design. It is also an attempt to implement a "best practices" professional design philosophy among personnel who are more accustomed to tinkering, rapid-prototyping and experimentation.

a) OLD PERCEPTRONIX ORGANIZATIONAL STRUCTURE



b) NEW PERCEPTRONIX ORGANIZATIONAL STRUCTURE

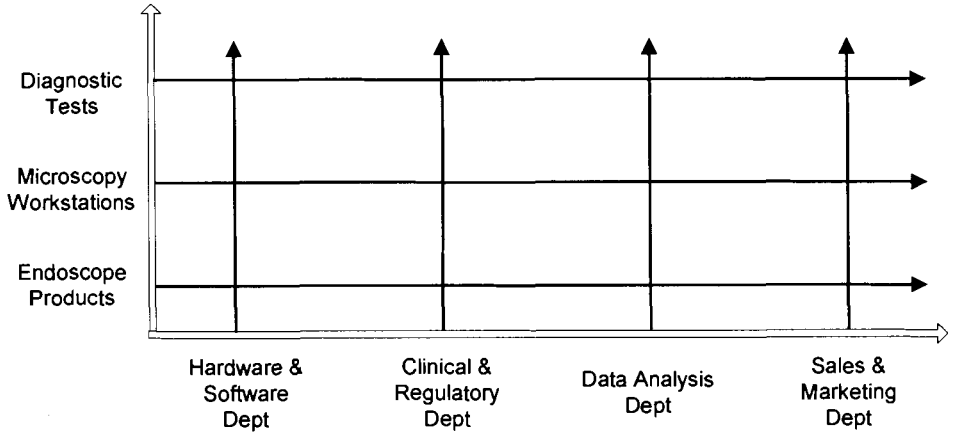


Figure 6: Perceptronix organizational structure (a) prior to Q4-2004; (b) after Q4-2004

Prior to the reorganization, the C&R and Marketing departments already functioned across the firm, so this was not a difficult transition. However, for the Hardware and Software and Data Analysis departments, the reorganization is still an ongoing process nine months later. In theory, it should be possible for product directors to request resources from these departments without specifying individuals. In practice, it is still necessary to recruit specific personnel from these departments for the various tasks—all that has changed is their oversight.

The culture of the firm is changing in parallel with that of the organizational structure. The firm used to have a more informal culture, with significant autonomy within the groups and freedom to experiment. The firm had a research minded orientation. As the technologies coalesced into products, and the number of staff grew, the need for more formal project management and reporting structures grew. The organization has become more bureaucratic, which at first glance appears to be out of synch with the differentiation strategy of the firm.

However, most of the products will be Class II and III medical devices and must undergo several rounds of regulatory scrutiny before they can be sold. Furthermore all product development must occur through methods specified by the newly implemented quality system. Perceptronix is attempting to be both a new product innovator and device manufacturer in an extremely regulatory environment. The cultural and organizational changes reflect an attempt to balance product development creativity with controlled design of medical device manufacture.

This change in the organization structure and culture has both positive and negative impact on the firm's ability to implement its strategy of being a developer of innovative cancer detection/diagnosis products. Before, a researcher was free to experiment with a new idea that may lead to a new product or improvement in the current design. Now, such experimentation should be preceded by a project proposal, engineering change request or software change request.

This formalism reduces the speed of development and makes the development process less adaptable. With respect to the generic strategy map from Chapter 3, it hampers innovation, centralizes corporate structure and reduces the autonomy of the

development groups. These effects pull the firm away from being a pure differentiator, misaligning the firm structure with its strategy.

On the positive side, these measures help enshrine knowledge within the company. As the firm grows it is inevitable that it must make the transition from a bunch of experts in different disciplines to a firm which holds their competence among its staff and its procedures. This is an important consideration for the long term since the company currently depends on two or three technical experts within each of the product groups for development. Should any key individuals leave, the company's interests would be hurt in those areas. Having the groups follow a formal design control process adds additional documentation burdens to development, but it ensures that their expertise is gradually transferred into the company. This serves Perceptronix long term interests.

3.8 Business Plan

Perceptronix has the goal of bringing a portfolio of products for early detection, localization and diagnosis of lung cancer to market. All of the products are still in development, although some are just a few months away from being ready for sale. The three product lines can be subdivided into a total eight products which are in various states of development. The eight products are shown in Table 4 along with the date of their expected availability for sale.

Table 4: Perceptronix product list and schedule of when they will be ready for sale

Product Line	Product	Expected Completion Date
In Vitro Diagnostics	Sputum test for lung cancer	Q4 2005
	Buccal test for lung cancer	Q4 2005
Endoscopy	Autofluorescence/white light system	Q4 2006
	AF/WL + spectroscopy system	2007
Workstations	Cytology workstation	Q4 2005
	Pathology workstation	Q1 2006
	Staining kit	Q4 2005
	Automated stainer	2007

The development of these products has occurred entirely through equity investments into Perceptronix. These investments total $32.7 million and have occurred through several finance rounds between 2000 and 2005. Table 5 shows the rounds of investment into Perceptronix made by various investors. The $31.7 million invested in the first four rounds has come primarily from angel investors and one institutional investor—the BC Investment Management Corporation, a large pension fund. The latest investment came from the owners of Motic Incorporated, a Chinese based microscope manufacturer.

Table 5: Funds received by Perceptronix

Funding Round	Date Closed	Amount Raised (CDN$)
Round A	Dec 2000	$ 8,989,000
Round B	Oct 2002	$ 5,466,000
Rights Issue	Apr 2003	$ 9,745,000
Rights Issue	May 2004	$7,500,000
Motic (China) investment	Apr 2005	$1,040,000
Total Raised		**$ 32,740,000**

Perceptronix current business plan calls for sales of products to Canada and the EU to begin by the end of 2005. The workstations and detection tests will provide initial revenues to the company. The workstations, particularly the cytology workstation, will compete in an existing market of laboratory products aimed at pathologists. There are laboratory equipment trade shows and distributors to facilitate sales and distribution of these products. It is believed that they will form the bulk of the Perceptronix revenues for the first two years of company revenues.

Although the assays represent exciting new technologies for cancer detection, Perceptronix does not expect them to be overnight successes. As was mentioned in Section 1.5, Perceptronix is selling a detection result, a score, which correlates with the presence of cancer. It is not selling a confirmed prognosis or a cure. The usefulness of the test is dependant on whether the lung cancers it detects are curable. Hence, it will take time for physicians to recognize that this test will help them manage their patients.

It will take additional time to gather the data regarding the large scale application of the test to determine the optimal application of the technology in practice. The data will also help Perceptronix perform the cost benefit analyses of the assays in diagnostic and screening settings. These results of these analyses will be required to convince the authorities who control health care spending that the assays are worthy of reimboursement.

This process of convincing specialists, then GPs and administrators will require several years. In the mean time, Perceptronix should expect to operate the next 3—5 years through direct sales and partial payment pilot studies. The task before the company

is to develop a strategy to propel the assay product line through those years with the goal of eventual reimboursement.

Perceptronix will provide the cancer detection assays as a service from its existing laboratory for the first two years of operation. This period will allow the firm to:

1. ensure the operational diagnostic performance of the test at the outset;
2. conduct pilot projects with physicians in various jurisdictions to build demand for the test;
3. establish how the test should be incorporated into clinical practice in different jurisdictions (since patient management varies significantly between countries);
4. further engineer the test to make it robust enough to operated by others;
5. improve the performance of the system by adjusting it using additional clinical specimens received from pilot projects;
6. and solidify the firm's IP protections around the technology.

As a consequence the revenues from the assays are projected to be modest during the first two years. Perceptronix goal is to license the assays as soon as conditions are favorable. It is anticipated that by late 2007, the assays will be licensed to reference laboratories in Canada (such as MDS Diagnostic Services) and the EU to operate. This will directly address the distribution problems that Perceptronix faces when offering the test itself. At this time the revenues from the test are expected to increase substantially.

Figure 7 shows the projected revenues from each of Perceptronix product lines for the next five years. Although the assays are among the first products that will be approved for sale, their sales growth is expected to be modest compared to the other

products. The workstations are expected to carry the company until 2008, when the revenue potential of the assays should be realized.

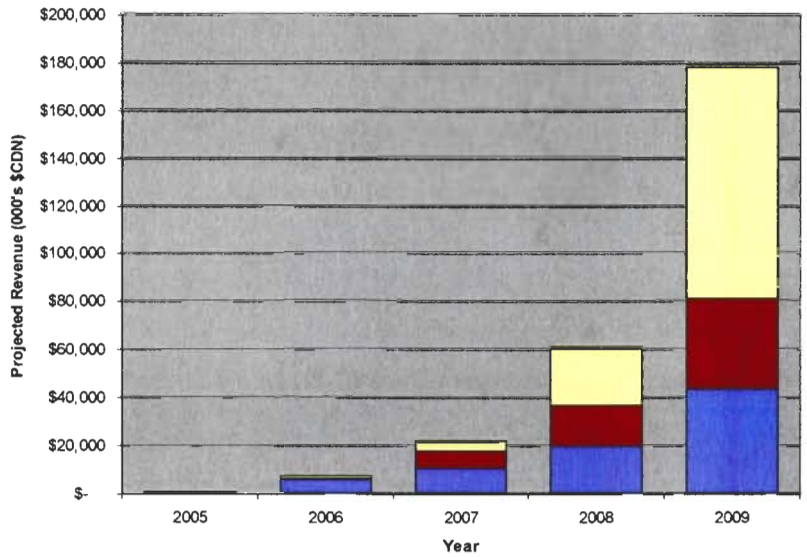


Figure 7: Projected total revenue per year by product group (yellow—lung cancer assays, maroon—endoscopy products, and blue—workstation products).

As was discussed in the Industry Analysis in Section 2.1, the regulatory barriers of getting a cancer diagnostic product approved in the US are significant. The assays are considered Class III medical devices, so Perceptronix can expect to spend 18 months and millions of dollars on the FDA's PMA process to get them approved for sale in the US. To ease the PMA process, Perceptronix will approach the FDA after the tests have demonstrated their performance in Canada and the EU. Assay revenues from the US are not expected until late-2008.

The successful licensing of the assays will help propel Perceptronix into profitability. Figure 8 shows the projected earnings and cash flows until the end of 2009. The magenta cash flow curve shows that the company will require additional investment by the start of 2006. Cash flows will become more negative until mid-2007, where they

bottom out and begin to improve. By that point the company will require additional investment totaling $13.3 million to execute its plans.

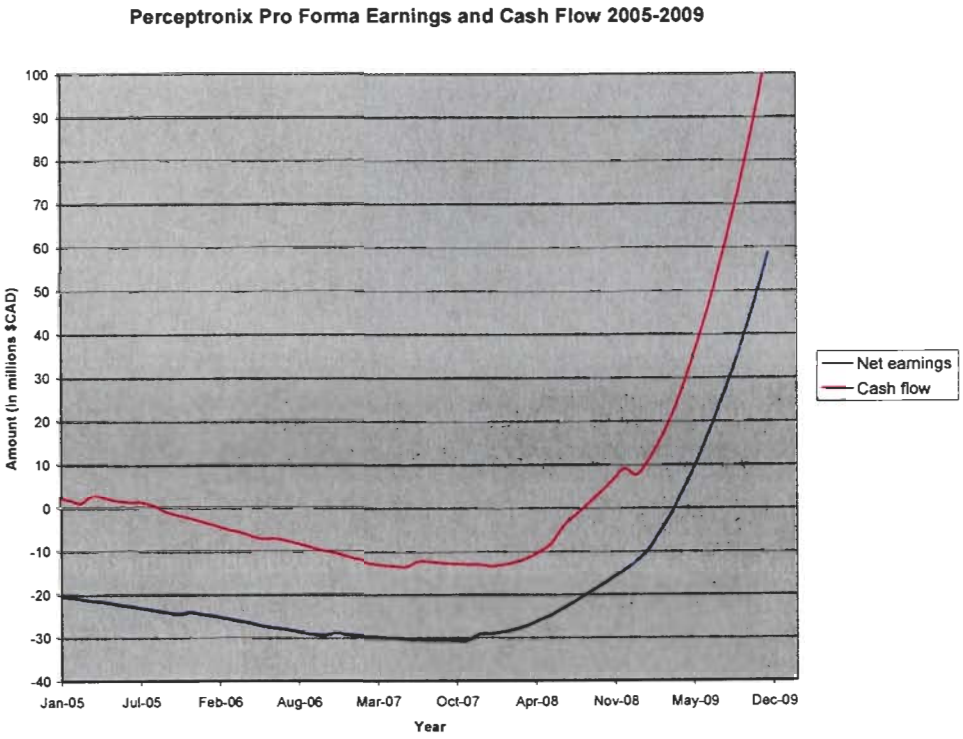


Figure 8: Projected net earnings and net cash flow over the next five years.

The net earnings curve in Figure 8 remains negative until September 2008. At that time Perceptronix will become profitable and start providing returns to its shareholders. As with most business plans, the sky's the limit in year five of the Perceptronix plan.

4 Issues

This chapter identifies the major issues facing Perceptronix, particularly those that relate to its *in vitro* cancer diagnostics, based on the examination presented in the previous chapters.

4.1 Too many products or too little money?

Perceptronix is pursuing an ambitious plan of an integrated suite of products for the management of the lung cancer diagnosis process. The rationale for the suite is that lung cancer is typically not detected until it becomes symptomatic. At that point it is normally too late to perform any curative treatment. It has become recognized by physicians around the world that the key to reducing worldwide lung cancer mortality is prevention (through programs such as smoking cessation) and early diagnosis.

The diagnosis problem is largely one of developing an effective patient management paradigm that detects early lung cancer and is cost effective. Perceptronix has pursued several technologies that target different parts of the patient management problem: a detection test that may become a screening tool, a better localization tool for finding early cancers, and workstations to help pathologists, who rarely see biopsies from early lesions.

The rationale for pursuing them simultaneously is that the management feels that there is currently a void in the management of patients with early disease. When describing the products to physicians, several rejoinders are brought up. "What's the point of your early detection test if it doesn't tell me where the lesion is?" "If I use your

bronchoscope to find more lesions, what will I do with the biopsies that I will take? My pathologist never sees early cancer and wouldn't be able to give me a clear recommendation of what to do with the patient."

Although the rationale for a company to pursue the three product lines simultaneously is sound, it is a fair question to ask whether Perceptronix was the right company to do so. Simultaneously developing three disparate technologies to intervene at several points in the patient management process is a grand vision. Grand visions usually require a lot of money to bring into being. Looking back at the financing that Perceptronix has obtained from its investors (Table 5), management has had to go back to its investors three times since the initial investment of $9 million in December 2000. It is a testament to the patience and vision of the investors that they have contributed to successive financing rounds even though the company was years away from its first dollar of revenue.

The decision to tackle eight individual products at once has undoubtedly delayed the process of bringing the assays and other products to market. Some aspects of the assay development, such as regulatory processes and clinical trial accrual cannot be hastened with more resources. However, other aspects of the development could have been done more quickly with additional resources. With so few staff, many parallelizable tasks have been done in a serial fashion.

Looking forward, Perceptronix requires another $13.3 million of investment to carry out the existing business plan. The assays and the cytology workstation are a just few months from approval. The others are between one and two years away from market. Company resources are allocated approximately equally among the three product

groups. Arguably, the assays consume closer to 40% of company specific resources. Should Perceptronix maintain its current product development schedule? Or should the company put its money on fewer horses rather than betting the field?

4.2 Threat of imitation

The technology of the lung cancer assays is based on computerized cytometry of images collected using absorbance microscopy. The images are of cell preparations stained using the Feulgen reaction. Robert Feulgen developed the quantitative nuclear staining technique in 1924. It has been a standard approach for quantitating nuclear DNA for many years. Computerized cytometry is a field which has been developing since the 1950s. Semi-automated image cytometers were developed in the 1960s. Automated image cytometers can now be purchased from many vendors.

The message here is that there is significant prior art on both the automated microscopy side and on the cell preparation side of the technology used by Perceptronix. It will be difficult to establish effective platform patents that would bar others from using a similar approach to detect cancer. It is possible patent the assays, but the scope of the patents will be narrow, meaning that it will be possible to work around them and not infringe on their claims.

Even strong patents on various aspects of the test would not necessarily protect Perceptronix against imitators. The assays measure changes in nuclear conformation and DNA amount and correlate these changes to the presence of lung cancer. The Feulgen reaction is used because it quantitatively stains DNA—the amount of darkness that you measure is proportional to how much DNA is present. It is conceivable that one could use another staining technique, such as Pap staining or fluorescent staining, and measure

some of the same nuclear changes. It may be more difficult to measure the cancer signal this way, but it would effectively circumvent any Perceptronix staining-related patents.

If Perceptronix is successful with its assays it will draw the interest of its competitors. Cytyc and Tripath, discussed in Section 1.5, represent two of the larger examples of firms with experience in cytology automation. They have the technical skill, clinical expertise and resources to develop cytometry based assays.

4.3 Threat of new approaches

The Perceptronix lung cancer assays measure the effect that a lung cancer lesion has on distant cells. The theory of their operation is that malignant cells multiply and give off various growth factor proteins. These proteins diffuse out and cause adjacent cells to undergo modified transcriptional activity that can be seen under absorbance microscopy. For the buccal assay to work, this signal would have to diffuse a significant distance. It is known that growth factors associated with cancer can be measured in the blood stream of patients. Saliva, which is a filtrate of the blood, also carries this signal. This may explain how the cells of the oral mucosa can change in response to a distant cancer.

The importance of this is that Perceptronix measures the presence of a cancer indirectly, by measuring its effects on other cells. If a set of proteins exist that are a hallmark of early lung cancer, and if they can be identified, one could develop a blood or saliva based test to detect the disease. Because it measures the signal of malignancy directly, it would be more sensitive than looking for the effects of those proteins on other cells.

Some of the most exciting research in lung cancer detection is in the area of proteomics, which seeks to identify the protein or combination of proteins that are given off by malignant cells. This technology is becoming more affordable and it will soon be practical to conduct large clinical scale studies with this analysis approach. The future of lung cancer detection likely lies in proteomics.

The question is: how long will it take before a rival technology is used for lung cancer detection assay? Perceptronix probably has a three or four year window to establish the widespread clinical use of its cytometry based assays if the assays are to succeed at all.

5 Recommendations

5.1 Too many products or too little money?

As Perceptronix is currently seeking the funding required to carry out the business plan, this is an appropriate time for the firm to reassess whether the plan still makes sense. The detection assays and the underlying platform are regarded as the product line with the greatest long term potential. The projected revenue chart for the lung cancer assays (Figure 7) confirms this thinking, but the payoff occurs only after the assays are ready to be licensed to others. It is expected to take another two years to complete this process, which is outlined in the six steps outlined in Section 3.8.

The reassessment should occur at two levels: the product group level and the management/business development level. At the product group level, all activities during the next two years need to be identified and planned for. All activities which can occur in parallel should be identified. The planning should assume that additional resources exist to perform these tasks. The goal of this analysis is to establish a new shorter critical path to the state where the detection product line can be delivered by outside parties.

Looking at the six item list, items #1 and #4 can be attacked from an engineering standpoint. It will be easier to ensure that the assay is being delivered successfully if additional work is done in the QC process. Work done to hasten the transition to the next generation of more robust cytometer will help this as well. The laboratory processes would also benefit from further analysis of the sensitivity of system to the specimen handling and preparation steps.

Items #2, #3 and #5 all require developing protocols for studies and recruiting physicians, as well as joining on to existing lung cancer studies to acquire specimens, gain adherents to its technology and learn how the assays interact with other diagnostic technologies (such as CT). With additional resources the company could be more aggressive about performing these studies and acquiring more specimens to improve the system. Addressing these items would require the combined efforts of the product staff, the C&R staff and the marketing staff.

The outcome of the product level analysis is a new time estimate for the critical path. At the business development level, the reassessment should analyze a question along the lines of "Would diverting resources to the assays give a greater return on investment, if it sped up the commercialization process by, say, eight months?" This will be a hard decision for the firm since it has spent years and millions of dollars pursuing the other products. The money spent so far must be ignored and treated as sunk costs. The reanalysis need not assume that those projects would simply stop. Some of the technologies could be licensed and any financial analysis should consider this.

One of the assumptions of the Perceptronix plan is that the void in the management of early stage lung cancer will exist two years from now when the all its products are complete. It does not admit the existence of viable substitutes for localization and diagnostic confirmation.

In the area of localization, this is changing. Other firms sell fluorescence endoscopes and their products will improve over the next two years. Previous chapters have discussed CT as a potential technology for detection and localization. It is becoming better and cheaper. The devices incorporate computer aided detection software

that is becoming more precise at characterizing the size and growth of lesions. It is funded by some of the biggest medical equipment manufacturers in the world. It would be foolish to disregard its impact on diagnostic management.

Consequently, the management level analysis must imagine the playing field as it will exist in two years. The medical diagnostic field is changing rapidly. Perceptronix should not make its plans based on what the field looks like today.

5.2 Threat of imitation

Perceptronix must go forward under the assumption that others will find non-infringing was to apply cytometry to lung cancer detection. It is inevitable that others will begin to take the same approach of detecting systematic changes in epithelial cells (essentially, an enhanced risk profile for the patient) to manage patients. The key for Perceptronix is to find ways to stay ahead of the competition.

To do so, Perceptronix must reexamine its core competencies. It is a leader in nuclear cytometry and analysis techniques that lead to the development of new assays. It has expertise in quantitative staining and clinical relationship management. It creates value compared to any other firm when performing these tasks.

Perceptronix must (1) leverage its core competencies and (2) develop its competency in other relevant areas to stay ahead of its competitors. The solution to (1) is straightforward. Perceptronix will be first to market with a cytometry based assay. It is built on a clinical database of approximately 3000 specimens with patient information, acquired through various studies. This is a relatively large number given the resources available to the firm. Collecting specimens takes time. It requires recruiting physicians interested in research and patient volunteers. If Perceptronix refocuses its efforts on

further clinical development as was mentioned in Section 5.1, it may able to stay ahead of the competition. This could be done by expanding the network of pulmonologists who participate in Perceptronix studies. It would have the benefit of evangelizing the technology to these physicians as well.

From an engineering perspective, the cytometry platform can be improved. Most of the expertise for building a better cytometer already exists in-house. However, the engineering staff is all engaged in getting version 1 of the product out the door. With more resources and a company vision of continual product improvement, it would be possible to redirect those talents to where they give the greatest value to the firm.

The second activity, developing core competencies, is equally important. The firm level value chain (Figure 4) showed areas where Perceptronix is attempting to develop its competencies. There is also a diagnostic assay specific competency Perceptronix should develop that relates to how it can stay ahead of its competitors. It relates to the firm's approach to product development. The Perceptronix approach to developing its products can be outlined with five steps:

1. collect relevant specimens from patients (i.e. specimens from patients positive for the disease and from negative patients with the appropriate inclusion conditions);
2. obtain a clinical diagnosis (or prognosis) for each patient
3. apply image cytometry, histometry or spectrum analysis to specimens and generate statistics;
4. use statistical pattern recognition to create classification systems from these statistics;
5. and test the system in a clinical trial to validate it.

This is a phenomenological approach to creating detection or classification products for lung cancer. It is not critical to know why a certain cytometry pattern or endoscope reflectance spectrum arises due to the cancer. What matters is does it work for prediction. It does not specifically address the underlying biological processes that give rise to the disease.

This approach is not unique to Perceptronix. The breath test being developed by Mensanna (Section 1.5), which looks for an abnormal volatile organic compound signature, follows the same paradigm. This approach is a good approach for version 1 of either firm's product, but it has limitations. As the measurement platform matures and the size of the clinical database increases, both firms will be able to make only diminishing improvements based on their phenomenological approach. Both will have to address the underlying biology that gives rise to the signal.

Perceptronix will have to look beyond its current approach to characterizing specimens. Can the nuclear cytometry be optimized further? Should specimens be counterstained to look for other expression patterns in combination with the current assays? Can studying the development of other diseases and their effects on cell nuclear cytometry help Perceptronix improve the specificity of its system?

Perceptronix does not have the expertise it needs to answer these all these questions adequately. It gain competency in these areas by either sponsoring research with partners such as the BC Cancer Agency or by hiring the right people to fill these knowledge gaps in the company. This will provide a source of continued improvement of the assay product line and make it more viable for the long term.

5.3 Threat of new approaches

The threat of new approaches poses many of the same risks the threat of imitators. Perceptronix success with its measurement approach will attract the attention of others. The demonstration that distant cells are altered by a cancer signal will encourage others to explore new approaches to measuring the signal.

Some of the steps necessary to deal with this threat are the same as coping with imitators. It should leverage its clinical and cytometry competencies to keep the lung cancer assays moving forward. It should expand its competencies beyond the phenomenological approach to the cytometry of lung cancer.

There are also differences in the way that Perceptronix should cope with new approaches versus imitators. One of the key success factors (Section 2.7) for Perceptronix was to develop momentum for the assays. Physicians are slow to adopt new testing techniques. Perceptronix must push forward with measures to entrench the cytometric assay paradigm in clinical practice.

The first way to do this is through larger scale validation trials. As was mentioned in Section 2.7, once the validity of the technology is accepted, it should be possible to obtain government granting agency funding to conduct larger scale trials. Perceptronix has clinical partners interested in conducting such studies. It will benefit from them because the clinical data collected will allow refinement of the assays and laboratory practices. More importantly, participating physicians pulled into the marketing channel and converted to the Perceptronix testing approach.

The second way to entrench cytometric assays in clinical practice is to adapt the platform to other cancers, such as breast, bladder or oral cancer. One of the biggest

hurdles that Perceptronix faces is the perception that Feulgen cytometry is old technology. When the assays are described to clinicians, the response is usually "Oh, you measure *ploidy*."

It is true that one of the first uses of Feulgen cytometry was simply to measure the amount of DNA present (called "DNA ploidy"). Tumour cells can usually be identified by their abnormal ploidy, but it is difficult to obtain these cells in specimens from early cancers. By measuring DNA conformation of neighboring cells, Perceptronix goes far beyond measuring just ploidy. However, but it is difficult to break the clinicians' conception that nuclear staining is an old technology that just tells you how much DNA is present. Measuring nuclear conformation is an important tool for patient management. Perceptronix must make this known in the medical community.

By adapting the platform to detect other cancers, Perceptronix can develop a suite of assays for various cancer types. This will help efforts to establish the indirect approach of cancer signal measurement through adjacent and distant cells as a valid technique for patient management. It will evangelize the assays to the specialists directly, and have the benefit of reaching the GPs indirectly. For various cancers with the knowledge the specialists will know how to interpret the results to provide further follow up for the patient. This approach makes sense from a resource allocation standpoint as well. In Canada, the numbers of specialists for various cancers are in the hundreds and therefore more targetable than approaching GPs.

Combining these two measures, larger trials and new assays, will also help Perceptronix answer one of the lingering questions about its assays. If a patient scores positive by the buccal assay, do they have lung cancer, laryngeal cancer, oral cancer or

something else? Can the buccal assay be used to measure the presence of multiple cancers? The answer to these questions may help transform Perceptronix from a lung cancer diagnostic firm to a comprehensive cancer diagnostic firm.

6 Appendix: Understanding Clinical Tests

6.1 Screening and diagnostic testing

Screening and diagnostic testing are similar in that both are done to detect the presence of a condition in test subjects. Both involve analyzing specimens and obtaining quantitative results that can used to decide the appropriate follow up for the individuals. The testing technologies or assays may be identical for both applications.

The difference between the testing modes lies in how the tests are applied. Diagnostic testing is the application of the test to patients who are suspected of having the disease for the purpose of ruling it out. Screening, on the other hand, is defined as the application of a test to asymptomatic individuals. If no inclusion criteria are specified, then it is referred to as mass-screening. If inclusion criteria such as age or smoking history (in the case of lung cancer) are added then it is referred to as high-risk screening.

The purpose of lung cancer screening is to identify ostensibly healthy individuals who in fact harbour the disease in its early, preclinical phase. It is a worthwhile activity only if the disease is more easily treated in this phase, if the screening procedure is easily tolerated and if the program is affordable (Gotway & Webb, 2002). Evidence suggests that lung cancer is curable if caught early. The Perceptronix sputum assay is easily tolerated. Whether a screening program based on this assay, or any other current testing technology, is affordable depends on the performance of the test on a screening population—something that is not yet known.

6.2 Test performance: specificity & sensitivity

The performance of a test is described using two terms:

1. sensitivity – proportion called "positive" among those who have the disease. The complement of sensitivity is the false negative (FN) rate (i.e. FN=1-sensitivity).
2. specificity – proportion called "negative" among those who are truly negative for the disease. The complement of sensitivity is the false positive (FP) rate (i.e. FP=1-specificity).

A test may produce a dichotomous result (i.e. disease is present or absent) or a continuous measure of abnormality. An example of a dichotomous test is conventional cytology of sputum. If the cytopathologist sees malignant cells the specimen is deemed positive, otherwise it is deemed negative[10].

The Perceptronix sputum test is an example of a test that produces a continuous measure. Figure 9 shows the distribution of scores assigned to the specimens used to create the sputum assay. A total of 1138 specimens from high risk negative patients and 326 specimens from patients with confirmed lung cancer where used to develop the automated testing system. The figure shows that the test, which is based on a linear discriminant function of sputum cell properties, returns a score that ranges roughly from -5 to +7. There is significant overlap between the two groups, which shows the imperfect nature of the test.

[10] This simplifies the cytology process somewhat. BCCA cytopathologists classify sputum specimens as either: normal, benign, mild atypia, moderate atypia, severe atypia, carcinoma, or unsatisfactory for review. However a result of mild atypia or less is not acted upon, while moderate atypia or higher warrants follow-up.

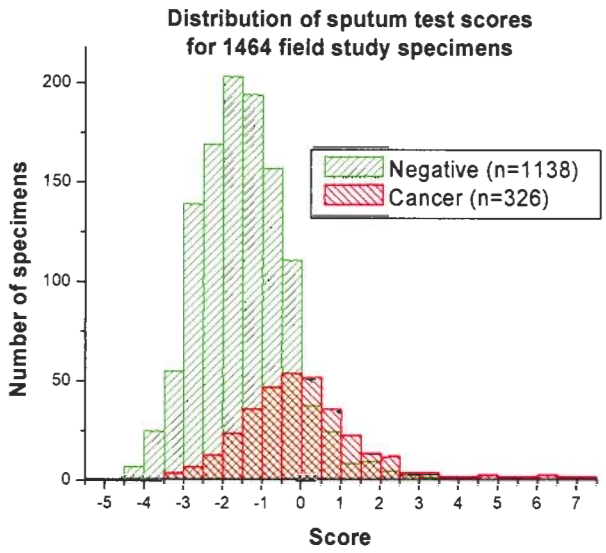


Figure 9: Distribution of scores assigned to preclinical data from high-risk negatives and patients with lung cancer

Interpreting the test scores in conjunction with an operating threshold determines the sensitivity and specificity of the test. For example, consider choosing a threshold of zero and designating any case with a score<0 as "negative" and those with score>=0 as "suspicious for lung cancer". Roughly half of the 326 cancers have a score of zero or larger (half of the red distribution lies to the right of zero). Hence the sensitivity at this operating point is ~50%. Roughly 90% of the 1138 negative cases have a score below zero (90% of the green distribution lies to the left of zero). Hence the specificity is ~90%.

This process can be repeated for each possible operating threshold, generating a list of possible specificities and sensitivities. Plotting these points gives rise to a Receiver Operator Characteristic (ROC) curve, which is a standard tool used when assessing diagnostic tests. Figure 10 shows the ROC curve for the Perceptronix sputum test described in Figure 9. It is a plot of the sensitivity of the test versus its specificity for all possible operating thresholds. The diagonal line in Figure 10 is the chance line or

null-test line. If one ignores the data and calls every specimen "negative", that test would correspond to the point (100%,0%) on the line. Calling every specimen "suspicious" corresponds to the point (0%,100%) on the line. Finally, flipping a coin with heads=negative and tails=suspicious corresponds to the point (50%,50%) on the line. All non-trivial tests are can be represented by either points or curves that lie above the chance line. A good diagnostic test will have a point or curve that comes as close as possible to the top-right corner of the graph.

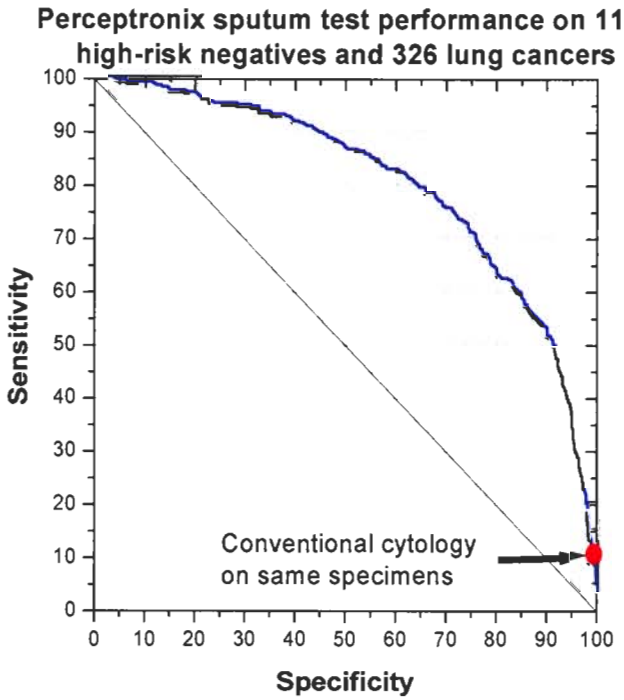


Figure 10: ROC curve of the preclinical data used to create the Perceptronix sputum assay. The performance of conventional cytological analysis on smears prepared from the additional material from the specimens is shown by the point (99%,11%).

With reference to Figure 9, an ideal test is one that completely separates the green and red populations. It would then be possible to choose a threshold that provides 100% specificity and 100% sensitivity for that test. The ROC curve for that test would hug the top and right axes of Figure 10. In the realm of early cancer detection, such tests do not

exist. Perceptronix goal for the sputum test is to continue improving the performance of the test, particularly in the high specificity region. This is a prerequisite transitioning the test to a screening application.

As mentioned before, conventional cytology is an example of a dichotomous test. Conventional cytology is very specific—when the cytopathologist sees abnormality, it is usually cancer. Unfortunately, locating cancer is difficult. Figure 10 also shows the performance of conventional cytology on material from the field study same specimens prepared as smears. It is an operating point (because of the binary nature of their decisions) at around 99% specificity and 11% sensitivity. This performance estimate excludes unsatisfactory specimens from the analysis. For roughly one quarter of the specimens, they return a result of "unsatisfactory for review" because the slide does not contain cells indicative of a deep cough. As a result, they were only able to detect lung cancer in roughly 8% of the specimens which came from patients with the disease.

The ROC curve for the sputum test in Figure 10 lies very close to the cytology operating point. Setting the threshold at around +2 for Figure 9 produces a test whose overall performance is equivalent to conventional cytology. This shows how the sputum test is more than just automated cytology. If one is willing to accept more false positive outcomes, it is possible to detect far more cancers than can be accomplished with conventional cytology.

6.3 Effect of inclusion criteria on apparent test performance

The purpose of an *in vitro* diagnostic test for lung cancer is to aid physicians in their management patients suspected of having lung cancer. The test should be designed based on the properties of specimens from this patient cohort. The operating point of the

test must also be selected to be appropriate for this discrimination task. Including specimens from patients who do not have the appropriate inclusion criteria is at best irrelevant and at worst deleterious to designing an effective test.

Consider Figure 11, which shows the distribution of test scores for three patient groups by a hypothetical diagnostic test. For this test, there is a clear separation between the typical scores assigned to healthy patients (population 1) versus those with the disease (population 3). On the other hand there is significant overlap between scores assigned to a group at high risk of developing the disease (population 2). The discrimination task described is to determine if a patient is a "2" or a "3". This population-specific behavior can be seen in the PSA test, which measures the level of prostate-specific antigen in blood. PSA levels increase with age. So the level that is typical for a man under 40 (2ng/mL or less) is significantly less than a man over 70 (6.5ng/mL or less).

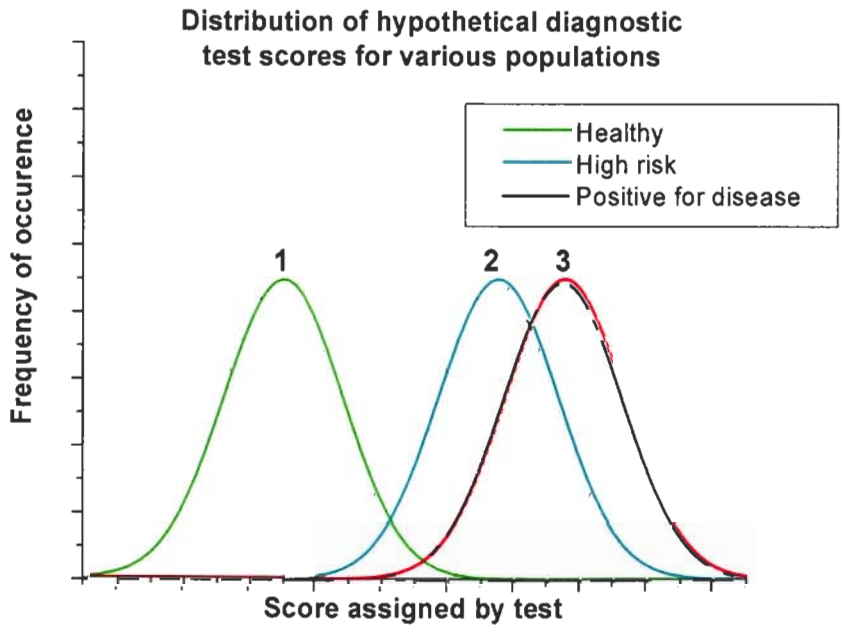


Figure 11: Distribution of test scores for a hypothetical diagnostic test applied to three testing populations. It is common for tests that measure some sort of physiological abnormality to have distribution ranges for different patient groups.

Selecting a PSA threshold by comparing the levels in 40 year old men versus those with prostate cancer selects a level which may be inappropriately low for older men—leading to too many false positives. Similarly, including data from population 1 in Figure 11 to set a threshold selects a low threshold that does not help separate a "2" from a "3". The message here is that including data from inappropriate subjects when creating a diagnostic test leads to poorer tests.

Having the correct inclusion criteria is just as important for measuring the performance of a test as for its design. Figure 12 below shows the ROC curves for two tests designed to separate the healthy versus positive populations (1 versus 3) and the high-risk versus positive populations (2 versus 3) in Figure 11. Because there is almost no overlap between populations 1 and 3, the ROC curve hugs the top and right axes, and it is possible to select a threshold that provides nearly 100% specificity and sensitivity. On the other hand, the significant overlap between populations 2 and 3 lead to an ROC with more modest performance.

Imagine a study that seeks to measure the performance of the hypothetical measure shown in Figure 11. For a diagnostic application, if the inclusion criteria are set properly, then the lower ROC curve should result. If the researcher is not careful about the inclusion criteria, and healthier negatives are admitted into the study, the apparent performance of the test will improve. At the extreme, if the negative controls are dominated by healthy subjects, the test appears to provide the discrimination of the upper ROC curve.

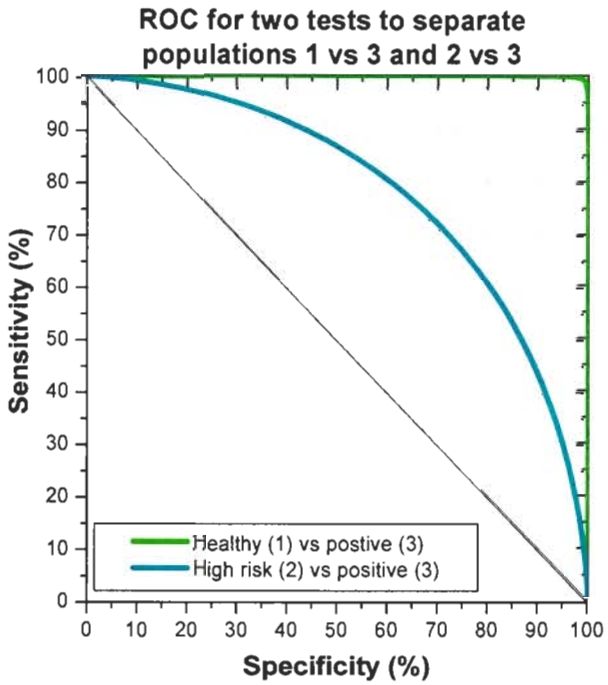


Figure 12: ROC performances of tests designed to separate the two negative groups in Figure 11 from the positive group. The higher the curve, the better is the separation of the two populations.

The take-away message is that the nature of the negative controls is a paramount concern when assessing the performance of a diagnostic testing technology. You can obtain *any* ROC performance curve you like for a test if you use enough healthy controls in your negative population. This provides a healthy sense of skepticism when reading the accounts of small scale studies of new diagnostic technologies. If the inclusion criteria for the negative cases are not adequately documented, one should regard the results with caution. Similarly, the performance of a test on a few hundred cases may not bear itself out over the next few thousand. This is why new diagnostic technologies undergo multiple trials of increasing magnitude.

A second outcome of this discussion is that a diagnostic test will have a different ROC curve when applied in a screening context. The hypothetical measure in Figure 11

can be used for mass screening, and its correct ROC curve *is* close to the upper one in Figure 12. It would require a large scale trial involving thousands of subjects to confirm the curve. But in principle, it could be done. It is important that one should not confuse the screening ROC with the diagnostic ROC.

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