BUSINESS CASE FOR ESTABLISHING A PHARMACOGENOMICS TESTING PROGRAM FOR CARBAMAZEPINE SENSITIVITY AT CHILDREN'S AND WOMEN'S HEALTH CARE CENTRE IN VANCOUVER BRITISH COLUMBIA CANADA

by

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ABSTRACT

This report was prepared for the molecular diagnostic laboratory at Children's and Women's Hospital in Vancouver B.C. and makes a business case for the introduction of a new genetic diagnostic test designed to detect patients that are susceptible to adverse reactions to the drug carbamazepine. This is a relatively small market requiring a maximum of 2,600 tests a year which could easily be integrated into the laboratory's current operations. It is proposed that provision of the service be free to the patients of British Columbia at maximum added cost of $20,000 per year, which could be more than recovered by offering the test to the rest of Canada at a recommended $99 per test. At this time, this program is an ideal starting point for the laboratory to expand the scope of its services into safety pharmacogenetics and establish itself as a leader in this emerging field.

Keywords: Business Case, molecular diagnostics industry, market analysis pharmacogenomics

EXECUTIVE SUMMARY

The emerging field of pharmacogenomics, which allows healthcare providers to tailor medication to an individual's genetic profile in order to improve safety and efficacy, is now ready for the clinic; however, the healthcare system has not kept up. While there are at least 27 drugs on the market with recommendations for pre-therapy pharmacogenetic testing, less than a handful are routinely applied in the clinic. This oversight exposes patients to suboptimal therapy and/or unacceptable risk and exposes the system to unnecessary costs associated with hospitalization when therapies fail or result in severe adverse reactions. The molecular diagnostic laboratory at Children's and Women's hospital proposes to address this situation by initiating a pharmacogenomics program for British Columbia with the introduction of testing for hypersensitivity to the drug carbamazepine.

Because of its simplicity and potential to save lives, carbamazepine sensitivity testing is an ideal candidate for initiating these services. While effective for epilepsy, bipolar disorder and neuropathic pain, carbamazepine is known to cause rare but deadly skin reactions called Steven's Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). Fortunately, recent research has uncovered a genetic marker that will predict the risk of these reactions in patients of Han Chinese descent – a population where it has been reported that 1 in 400 patients suffer from carbamazepine induced SJS/TEN. Both Health Canada and the Food and Drug Administration in the United States recommend pre-therapy genetic testing for hypersensitivity in this population. The costs of initiating

such a program in British Columbia is examined here as well as the potential for providing this service to the rest of the Canada for a fee.

According to estimates, approximately 900 patients of Han-Chinese descent are at risk of carbamazepine – induced SJS each year in British Columbia and therefore eligible for testing. It is anticipated that the laboratory has the capacity to take on this work with its current resources and therefore the only new money required will be to cover the variable costs associated with testing. This is estimated to be a maximum of approximately $20,000 if all eligible patients access the program and about half that based on projected uptake by the medical community. As the average costs of treating a case of SJS/TEN is approximately $20,000, averting just one of these reactions per year will pay for the program.

Establishing a carbamazepine sensitivity program in BC presents an opportunity for the laboratory to become the reference laboratory for this test in the rest of Canada where it is estimated that 1,700 Han-Chinese patients per year are exposed to this risk. Most provinces do not have the patient population to warrant their own programs and therefore physicians in those jurisdictions will be looking externally for this service. With strategic pricing (*ca.* $99 per test) and marketing plan, it is anticipate that the laboratory could garner all this work and realize an annual gross profit of $25,000 per year based on projected uptake and up to $95,000 with full uptake (i.e. 1,700 test per year).

It is the conclusion of this report that initiation of this program is a relatively low risk venture with a very positive upside. Not only does it offer the best care for the patients of British Columbia but it has the potential to save the system money and generate a source of funds to support laboratory overhead costs. Importantly, the

program is expected to generate other opportunities as the laboratory expands its horizons and becomes a transitional leader in bringing pharmacogenomic research to the clinic.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

GLOSSARY

Abacavir	Anti viral drug indicated for HIV infection
Adverse Drug Reaction (ADR)	An unintended response to a medication that worsens a patient's health or wellbeing.
Azathioprine	Immunosuppressant indicated for organ transplant and autoimmune diseases.
Carbamazepine	Anticonvulsant and mood stabilizer indicated for epilepsy, trigeminal neuralgia and bipolar disorder
Genotyping	Characterizing an organism according to its genetic code.
Human Leukocyte Antigen (HLA)	Describes the genes that encode the proteins presented on the surface of white blood cells which identify the cells as being endogenous to the organism.
Incidence	Epidemiological term used to describe the number of new cases of a disease or conditions diagnosed in a year.
Irinotecan	Anticancer drug indicated for metastatic carcinoma of the colon or rectum
Lamotrigine	Anticonvulsant and mood stabilizer indicated for the treatment of epilepsy and bipolar disorder.
Neuropathic Pain	Pain derived from injury to the nerves rather than injury to a body part
Pharmacogenetics	The study of genetic factors that affect the response to a drug. Generally used interchangeably with pharmacogenomics.
Pharmacogenomics	The clinical management of disease with the use of genetic information. Generally used interchangeably with pharmacogenetics.
Phenytoin	Anticonvulsant indicated for epilepsy

Phlebotomy	The practice of drawing blood from a vein
Polymorphism	Describes any variation in the genetic code that is prevalent in greater than 1% of the population
Rasbuicase	Medication indicated for hyperuricemia (build up in the blood of uric acid)
Valproic Acid	Anticonvulsant drug indicated for Epilepsy
Warfarin	Anticoagulant drug indicated for treatment and prophylaxis of atrial fibrillation, thrombolytic embolism and stroke.

1: INTRODUCTION

The purpose of this report is to develop a business case for the creation of a clinical pharmacogenomic testing program in the province of British Columbia for averting adverse drug reactions (ADRs). Briefly, this is the practice of pre-testing patients for known genetic markers of ADRs allowing physicians to better assess the risks and benefits associated with certain drugs. When provided with a result suggesting a patient might be susceptible to an ADR, doctors might choose to prescribe alternative medication or simply monitor the patient more closely. This is in contrast to the current practice of prescribing a drug and counselling the patient to watch out for the early symptoms of ADRs and to discontinue therapy if they appear.

This report was prepared on behalf of the Molecular Diagnostic Testing Laboratory at Children's and Women's Hospital in Vancouver British Columbia with the intention of presenting the case to the Provincial Health Service Authority (PHSA). The PHSA is responsible for the funding and administration of all healthcare programs with a province-wide scope including all genetic testing services. Currently the only such testing offered provincially is limited to genetic disease (e.g. cystic fibrosis, Huntington's disease etc.) and a case is made here to extend the laboratory's mandate to include pharmacogenetic safety testing.

While there are a number of drugs on the market where pharmacogenomic testing is warranted, this report focuses on the development of a testing program for the drug carbamazepine, to serve as a demonstration project for a larger more extensive program.

The primary purpose of this program is to provide the patients of British Columbia with state-of-the-art health care service; however, the report also examines the potential of providing this test to physicians in the rest of Canada as a means of recovering some of the costs.

Thus this document develops the business case for HLA-B genotyping for carbamazepine sensitivity and is organized to facilitate a well developed understanding of the potential of this opportunity. As such the report progressively provides the following:

- An analysis of the clinical laboratory testing industry.
- A description of the potential for pharmacogenomics in healthcare with a specific focus on the current opportunity (i.e. carbamazepine sensitivity testing).
- A description of the resources and capabilities of the laboratory and team leaders to highlight the reasons why the molecular diagnostics laboratory and Children's and Women's Hospital is the ideal setting for this program.
- An analysis of the market as it pertains to carbamazepine sensitivity testing.
- An examination of the resources that will be required to provide this service for the patients of British Columbia.
- An analysis of the potential for the laboratory to serve as a reference laboratory to the rest of Canada providing the test for a fee. This analysis includes a recommended pricing strategy designed to minimize risk while encourage demand and discourage potential competition.

- A high level plan for the program role out and commercialization including a communication plan and financial requirements.
- An examination of the risks and opportunities associated with the introduction of the program.

It is believed that these analyses provide an accurate and comprehensive portrait of the opportunity. In addition to a thorough review of the medical, scientific and biotech business literature, these analyses drew upon the databases of Brogan Inc, a research firm that compiles drug reimbursement data from selected private research firms across the country. Costs analysis included the opinions of molecular diagnostics laboratorians and representatives from a number of prominent suppliers within the industry (e.g. Applied Biosystems, Qiagen, Illumina, Luminex). Furthermore, the opinions and experience of a number of relevant healthcare professionals have been integrated into the analysis including neurologists, psychiatrists, pharmacy doctorates working within the BC Healthcare/Research system, and a retired senior healthcare executive currently working within the healthcare evaluation and intelligence industry. After completion of this analysis, it is the opinion of the author that genotype testing for carbamazepine sensitivity represents a good investment of healthcare dollars allowing the province to lead the way to a future of safer, more manageable healthcare for Canadians and British Columbians alike.

2: THE INDUSTRY

Clinical laboratory diagnostic testing is an essential component of healthcare delivery providing hundreds of conventional tests (American Association for Clinical Chemistry, 2008) that inform over 80% of medical decision making (Boone, 2004). In British Columbia these service account for approximately 5% of all healthcare expenditures (British Columbia Provincial Laboratory Coordinating Office, 2005). While currently representing only a small percentage of the market, the relatively new field of molecular diagnostics is having a disruptive effect on the industry attracting hundreds of new players to the market. Molecular diagnostic testing is a term that has been used to describe tests specifically characterizing the nucleic acid make up of DNA and/or RNA. Because these molecules encode the entire complexity of human form and function, we are only just beginning to scratch the surface of our understanding of their effect on human health – new knowledge is emerging daily. At the same time, technological advances have made it practical to rapidly and economically apply this new knowledge to patient care once it becomes clinically indicated. Under these circumstances, the market for these services has become highly fragmented with a minimum of 408 North American and 189 foreign clinical laboratories currently providing these services internationally, as listed on the National Institutes of Health's GeneTest website (National Institutes of Health, 2008). In fact, fragmentation is most probably greater than these numbers imply as this count likely represents only the most reputable laboratories in the world and is probably a considerable underestimate of the competition worldwide.

In 2005, molecular diagnostic testing represented approximately 3% of the $36.5 billion in vitro diagnostic industry; however this sector is undergoing tremendous growth. Annual worldwide sales of these tests have grown from approximately 1.1 billion in 2005 (Doig, 2007) to an estimated 2.5 billion last year; although that growth has been driven primarily by infectious disease (Figure 1). In these cases, genetic tests are characterizing the genetic profile of the invading pathogen and not the human host. Such tests have proven to be very useful in diagnosing infection or predicting treatment response and in many cases have been rapidly embraced by the medical community. In contrast, the more human application of molecular diagnostics is still early in the technological lifecycle and has tremendous potential for growth. In fact, the cancer, personalized medicine and traditional genetics sectors of in Figure 1are projected to experience annual growth rates of 20%, 20% and 15% respectively in a five year period (Sannes, 2008). With proper planning and execution, it should be possible to prosper from this growth.

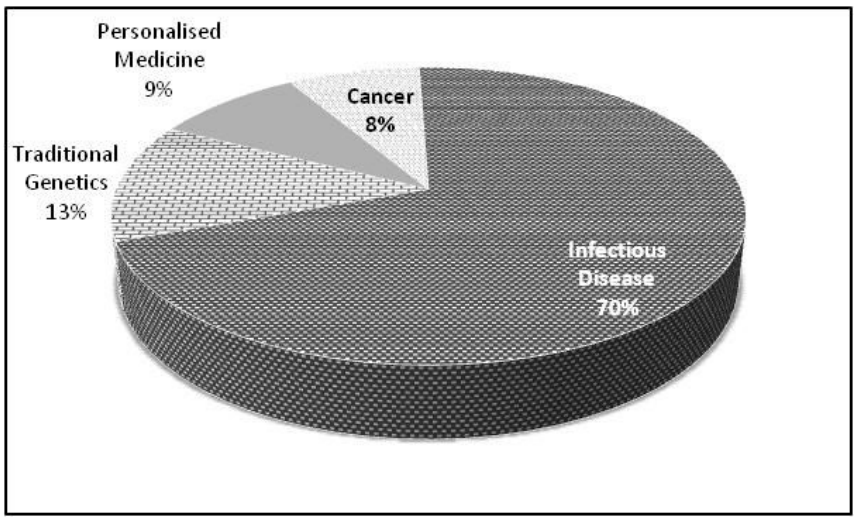

Figure 1: Breakdown of Laboratory services provided by the Molecular Diagnostic Market. Derived from data provided in (Sannes, 2008).

In spite of the seemingly competitive molecular diagnostic market, margins on many of these tests are relatively high making this an attractive business. The reasons for this are two –fold. First, many tests are relatively esoteric and for many laboratories, the low demand does not warrant the resources that would be required to supply the service. Therefore, only larger laboratories generally take on this work; but only at a premium. In addition, current market prices often reflect older methodologies and have not kept pace with falling operating costs. There is little incentive to lower price in a supply challenged market. These conditions have created an environment that is lucrative enough that the two biggest players, LabCorp and Quest diagnostics, are increasing their esoteric operations (Laboratory Corporation of America Holdings Inc, 2007; Quest Diagnostics, 2007). With in excess of 1500 tests from which to choose (National Institutes of Health, 2008), this should still leave enough room in the market for smaller players to find a niche.

Of course the molecular diagnostics industry is defined by more than just the laboratories providing these services. It encompasses the entire value chain from the multitude of suppliers to an even greater number of consumers within the healthcare community. In addition there are a number of peripheral players that can influence the course of events. Figure 2, shows the familiar five forces originally outlined by Porter (Porter, 1980) plus two other important forces that diagnostic laboratories need to contend with; regulators and complements. Each of these forces represents threats and/or opportunities to molecular diagnostic laboratories and it important to develop an understanding the pressures they exert.

Figure 2: Forces influencing the molecular diagnostics reference laboratory. Arrows represent the direction and relative magnitude of force exerted by each party on the other.

Suppliers: While there are easily over 50 companies supplying machinery, reagents, consumables, and/or test kits for molecular diagnostic testing, the transaction costs associated with dealing with more than a few can be overwhelming. These companies offer a myriad of technological platforms for the characterization of DNA; however, given the time and money involved in adopting these technologies, most laboratories restrict themselves to just a few. Thus, the original choice(s) can lock a laboratory into a

proprietary technology for years potentially limiting its bargaining position with respect to ongoing purchases associated with that technology. For smaller operations, negotiating favourable prices for consumables can be challenging. Fortunately, this is becoming somewhat less of an issue as the degree of standardization and the availability of generic supplies has increased. Nevertheless, most technologies require an ongoing relationship with the original vendor for at least some supplies and service contracts and these are usually priced at a premium. There is a limitation to opportunism on the part of vendors, however, as the lifecycle of most technological platforms in this field have become so abbreviated that it is counterproductive to exploit their customers – they must provide value. Most major vendors recognize this and they differentiate themselves with quality, ease of use and superior customer service which in most cases are at least as important as ongoing costs of supplies. In this respect, power is shifting in favour of the clinical laboratory.

Substitutes: Being relatively new, molecular diagnostic testing is considered by most to be the substitute for the current standard of care. Whether that involves an alternative test, clinical monitoring, or doing nothing at all, the major question from the perspective of the diagnostics laboratory is: does a new test offer value beyond the current clinical practice. In the case of adverse drug reactions, the standard of care often involves simply counselling the patient to monitor themselves for early signs of adverse events and discontinuing the drug if they appear. If caregivers feel that that is enough, new tests may be a difficult sell – if not, the tests are likely to be welcomed. In general, the relative strength of a substitute test in the market will be case dependant.

Complements: Clinical application of molecular diagnostic testing is primarily for the prognosis and/or diagnosis of heritable disease and response to drugs. In the case of the latter, understanding drugs as a complement to testing is relatively straightforward – without the drug, the test would serve no purpose. This might suggest that pharmaceutical companies would be natural allies of the pharmacogenetic testing laboratories; however, drugs with dangerous side-effects have been marketed for years without complementary safety tests and therefore the interest of pharmaceutical companies in this technology is less straightforward. If a new drug is not being adopted by healthcare professionals or is at risk of being pulled from the market because of ADRs, pharmaceutical companies would be far more likely to support a test that could improve their competitive position. On the other hand, they are far less likely to be interested in diagnostic tests for older, off-patent drugs that have become generic, especially if healthcare providers have become accustomed to managing the side effects. Thus, the relative influence of laboratories offering pharmacogenetic tests over the pharmaceutical companies supplying the complementary drugs will be case dependant.

Customers: Like most healthcare services, the customer configuration for diagnostic services in complex. The patients are the main beneficiaries while physicians are the purchase decision makers and in Canada, provincial health ministries and agencies thereof make the decisions about payment on behalf of the taxpayer. While all these stakeholders are important, the general power brokers are physicians. Individually they decide whether a diagnostic test is appropriate for use on a case-by-case base basis and collectively, they determine whether a test qualifies as the standard of care. The latter is crucial for convincing health authorities (whether provincially, regionally or

locally) that diagnostic tests should receive public funding. Generally speaking, it can be costly to convince the medical profession to adopt new technologies because it requires strong scientific and clinical evidence.

Laboratories have little leverage in their relationship with physicians. Like any other product, new diagnostic tests must win over physicians by proving their clinical worth and the onus is on the laboratories offering these tests to educate physicians about the test and make the test as compatible as possible with clinical practice. Even when a diagnostic test becomes mainstream, industry standards with respect to the cost, speed and quality of service give physicians the upper hand. In spite of the relative newness of the technology and associated lack of standards, molecular diagnostic tests will not change this dynamic – at least in the long run. Checks and balances (and communication) within the medical profession are pervasive, so that opportunistic laboratories will not survive for very long. In the final analysis, the balance of power is with the customer.

Regulators: All diagnostic service laboratories are subject to regulatory oversight to assure good laboratory practice (GLP). In British Columbia, oversight is provided by the Diagnostic Accreditation Program of the BC College of Physicians and Surgeons (DAP) while in the US it is the Clinical Laboratory Improvement Amendment (CLIA). Without accreditation by these and other regional organizations, laboratories cannot provide diagnostic services in the associated jurisdictions. While diagnostic laboratories have little leverage in these relationships, the regulators provide a stabilizing influence by clearly laying out the rules; however the situation is a little less clear with respect to molecular diagnostics.

Regulation of molecular diagnostic testing is in a state of flux. Because of the complexity of the science, many of the rules associated with conventional diagnostic testing cannot be applied to molecular diagnostic testing. As such, many regulatory agencies do not have fully developed codes for molecular diagnostic operations. This raises the risk of future unforeseen costs for molecular diagnostic laboratories as new regulatory requirements emerge. Once the regulations are developed, laboratories operating in this space will have no option but to comply. In the developed world, regulations are supreme.

Potential Entrants: University hospitals are often the birthplace of much of new knowledge associating genetic variations with clinical outcomes and the researchers involved are generally ahead of the curve with regard to techniques and understanding of the science. Under these circumstances, research results can be rapidly commercialized with the principle investigators being the natural candidates to spearhead these efforts. Thus, university research laboratories are the foremost new entrants to the molecular diagnostic testing industry. Regulations provide a modest barrier to entry as research laboratories do not routinely follow GLP; however, with a modest investment these laboratories can adapt their operations within a few months. Still incumbent laboratories likely have the advantage over these players as they possess the infrastructure and expertise to quickly provide service on a broad scale and thus can pick and choose the most commercially attractive prospects. Strong intellectual property (IP) offers the greatest advantage for entrants; however, without the tacit operational, marketing and distribution capabilities of the incumbent players, they are likely to be limited in their reach.

Summary: Rapid progress in genomic research is having a disruptive impact on the diagnostic industry. The new genetic tests that are emerging from this work represent tremendous growth potential for the entire industry which is attracting new players. At the same time regulators and healthcare providers are struggling to keep up even though it is the needs of these players that will drive the future of this technology. Healthy competition among suppliers has equipped clinical laboratories with high quality affordable technologies that have now made it possible to meet some of these needs (i.e. quality, speed and cost); however the appropriate clinical application of this technology is not always clear and uptake by the medical profession can be unpredictable. The current selection of clinically utilized molecular diagnostic tests is primarily focused on infectious disease, cancer and inherited diseases, with pharmacogenomic applications being relatively rare. The relatively slow induction of pharmacogenomics into the clinic likely reflects inertia within the industry as drugs have been introduced into the market without the benefit of tests to predict how patients are likely to react for centuries. Pharmaceutical companies, regulators and physicians alike have come to accept the risks associated with differential drug response; however, the concept of personalized medicine has been discussed in the literature for many years and is now gaining acceptance in these quarters. As such, pharmacogenomic testing is positioned to displace the current standards of care in many cases. As the knowledge base grows, pharmacogenetic applications have the potential to become the next great growth area of molecular diagnostic. The present dearth of services in this field presents an exciting opportunity for forward looking laboratories to lead the way.

3: THE OPPORTUNITY

The opportunities in molecular diagnostics are extensive. With approximately three billion base pairs encoding the 20 to 25 thousand genes in the human genome (Human Genome Program, 2008), the possibilities seem endless. In fact the field is even greater, as these methods extend beyond human DNA to the multitude of pathogens that plague humanity. As previously mentioned, it has been the treaters of infectious disease that have led the way with this technology. Human applications are emerging more slowly.

With respect to the human genome, there are two general clinical applications; diagnosis or prognosis of genetic disease and prediction of response to drug therapy. It is the former that has received the most attention in the research and medical communities with over 1500 tests now available to serve that need. In contrast, there have only been a few molecular diagnostic tests applied in the clinic to pre-assess patients' likely response to drug therapy. Thus the clinical potential of pharmacogenomics has yet to be realized. It is this untapped market that the molecular diagnostic laboratory and Children's and Women's Hospital proposes to enter.

3.1 Pharmacogenomics/Pharmacogenetics

Pharmacogenomics and pharmacogenetics are two interchangeable terms used to describe the study of the genetic differences that explain why individuals respond differently to different medications. While differential drug responses are well known, it

is only recently that science has advanced to the point where we are beginning to understand the fundamental reasons for many these differences with at least part of the answer being found in the DNA. Furthermore, it is possible to rapidly and to cheaply test an individual's genetic profile to predetermine how, or even if certain drugs should be used for that patient. Diagnostic pharmacogenomic testing as such is one of the pillars of the so-called "personalized medicine" paradigm (Wie H-G, 2005) which is the holds out the promise of improved patient outcomes and reduced healthcare costs.

The objective of clinical pharmacogenomic testing is to maximize the efficacy of the drug treatment while minimizing the potential for adverse drug reactions (ADR). It is the prevention of the latter, which will be the initial focus of the proposed program. Curtailing ADRs is of particular importance in healthcare management from both ethical and an economic perspective. They are not only responsible for over 100,000 unnecessary deaths in the United States each year, but they are also estimated to account for six to seven percent of all hospital admissions and/or extended hospital stays with associated costs likely exceeding $100 US billion (Eichelbamum M, 2006; White JT, 1999). Although similar statistics are not available for Canada the impact of ADR is expected to be proportional to the population, and pharmacogenomic testing holds the promise of mitigating both the personal and economic costs of these reactions.

In spite of its tremendous potential, there are currently little more than a handful of medications where the science supports the practical application of clinical pharmacogenomic testing. In fact, there only six drugs on the market with FDA recommendations for pre-therapy testing to assess the risk of ADRs. They are: Azathioprine (leukemia), Warfarin (anticoagulant), Irinotecan (colon cancer), Valproic

Acid (anticonvulsant), Rasbuicase (plasma uric acid management), and Carbamazepine (anticonvulsant, mood stabilizer) (US Food and Drug Administration, 2008). As far as the Author is aware, there are currently no public laboratories within Canada offering routine clinical pharmacogenomic testing for these medications[1]. This is an oversight that places both the health of patients and the integrity of the provincial healthcare system at risk. This proposal is the first step in addressing this issue.

An analysis of all the appropriate candidates for pharmacogenomic testing is beyond the scope of this report. Therefore the analysis will focus on only one drug, carbamazepine, for which there is significant medical evidence to support the introduction of pharmacogenomic testing at this time (see section 3.2). However, the long term goal of the molecular genetics laboratory at Children's and Women's hospital is to expand this program to include all suitable drug candidates when it becomes appropriate. Therefore, the analysis and recommendations within this report should be considered as part of a more expansive vision, even though specific guidelines focus specifically on pharmacogenomic testing for carbamazepine.

3.2 Carbamazepine

Carbamazepine is a potent suppressant of central nervous system (CNS) activity which is approved for the treatment of epilepsy (partial and grand mal seizures), bipolar disorder (acute mania and prophylaxis), and trigeminal neuralgia (severe sensitivity in the facial nerves) (Canadian Pharmacists Association, 2004) and is also used off label for

[1] Based on personal communication with Drs Casey and Carleton.

other neuropathic pain[2]. The drug has been in use for over 30 years and is currently sold in Canada under the Tegretol® brand (Novartis Pharmaceuticals) as well as under 12 different generic monikers (Health Canada, 2008) (e.g.Apo-Carbamazepine, Gen-Carbamazepine, Novo-Carbamaz, etc). In spite of its benefits, use of carbamazepine can give rise to a number of side effects associated with central nervous system such as drowsiness, headaches, dizziness etc. While uncomfortable, these effects are not generally serious and are usually short-lived. Of much greater concern are the rare yet potentially deadly allergic skin reactions of Steven Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) which have been link to carbamazepine use (Mockenhaupt M, 2000; Tennis P, 1997) and usually occur within the first 60 days of therapy. Both SJS and TEN are gruesome afflictions that are characterized by detachment of the skin and also affect the mucous membranes of the mouth, genitalia and the eyes. Approximately 10% and 45% of cases respectively result in death (Warnock & Morris, 2003). Generally TEN is simply a more extensive form of SJS affecting a larger surface area of the body (i.e. less than 15% for SJS, 15-30% for SJS/TEN and greater than 30% for TEN). While the risk is remote, the consequences of SJS and TEN are devastating (see Figure 1) and there is a human imperative to further reduce or eliminate the risk entirely. Fortunately, a pharmacogenomic solution is available – at least to some patients.

Recently, researchers in Taiwan published the results of a study on 44 patients suffering from carbamazepine-induced SJS and/or TEN, and found that all of them exhibited a unique genetic feature in a gene encoding immune functionality called

[2] Based on interviews with five neurologists

Human Lymphocyte Antigen B (HLA-B) (Chung, Hung, Hong, Hsih, & Yang, 2004; Hung, Chung, & Chen, 2005). Based on a comparison to patients that were tolerant

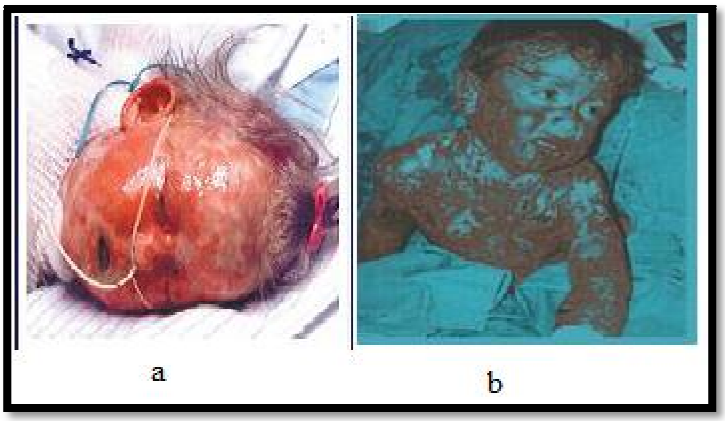

Figure 3: Examples of: a) Steven's - Johnson Syndrome b) Toxic Epidermal Necrolysis

of carbamazepine (i.e. no SJS or TEN), the researchers concluded that the presence of this unique HLA-B feature, which was prevalent in up to 8.6% of the Han-Chinese population, increased the risk of carbamazepine induced SJS/TEN by 10-fold in this population. Subsequent studies revealed that this genetic association was in fact specific to Han Chinese patients and could not be demonstrated in Caucasian patients (Lonjou C, 2006; Alfirevic A, 2006). Based on these and subsequent result (Man CBL, 2007), both the FDA and Health Canada are recommending pre-therapy testing for the unique HLA-B genotype for all high risk patients being considered for carbamazepine therapy (US Food and Drug Administration, 2007; Health Canada, 2008). The FDA recommendations extend to all patients of Asian descent who come from areas where the HLA-B feature is highly prevalent and includes China, Thailand, Malaysia, Indonesia, Philippines, Taiwan, and South Asia including India.

Currently, there is no system in place to provide at-risk British Columbians with HLA-B genotyping prior to carbamazepine therapy. In fact, there is a general gap in provincial healthcare services with respect to pharmacogenomic testing primarily due to the absence of mandate. That is, while there are a number of organizations dedicated to researching pharmacogenetics, there is no centre dedicated to introducing the technology into the clinic. The one exception is the BC Centre for Excellence in HIV/AIDS at St. Paul's Hospital which is currently routinely providing HLA genotyping for all patients being considered for the HIV drug abacavir, which can also cause a fatal allergic response in some patients. However, that organization is dedicated to the treatment of HIV and is therefore limited in its focus. On the other hand, the molecular diagnostic laboratory at Children's and Women's Hospital is a more generalized laboratory operation and would be an ideal locale for establishing a provincial program for clinical pharmacogenomic testing.

3.3 Cost/Benefit Analysis

While the humanitarian reasons for pharmacogenomic testing for the risk of SJS/TEN is unquestionable, it is nevertheless important to determine how the introduction of such testing will affect the healthcare costs. Funding for healthcare is always challenging and often, tradeoffs between competing interests must be considered. It becomes important to assess the economic impact caused by the introduction of pharmacogenomic testing for all high risk patients starting carbamazepine therapy.

Ideally, the carbamazepine sensitivity genotyping program would pay for itself by averting hospitalization costs due to SJS and/or TEN; however, both these reactions are exceedingly rare. While there are approximately 100 drugs known to cause these

reactions (Mittmann N, 2004), the combined population incidence is estimated to be only 2 to 4 cases per million people per year (Ghislain P-D, 2008). This translates to between 62 and 124 cases annually in all of Canada with only 8 to 16 cases occurring in BC; however, carbamazepine use likely contributes significantly to those numbers. In the Han-Chinese population, the incidence of carbamazepine induced SJS/TEN is estimated to be as high as 0.25% (Hung, Chung, & Chen, 2005) among new users of the drug which translates to approximately 2 cases per year in BC. Of note, it is likely that all these estimates err on the low side as studies suggest that cases of SJS and TEN are significantly underreported (Mittmann N, 2004). Thus the incidence may be higher than suggested here.

The cost of a case of SJS or TEN is not insignificant as these adverse drug reactions are treated in the same way as severe burns. Based on data from three burn care units in the US, it was determined the average cost of treating a case of TEN to be approximately $28,000 while the cost of SJS was $14,538 (Kagan RJ, 2007). While there are no comparable domestic studies, these costs are consistent with a recent report on the average Canadian cost of burn care treatment which was stated to be an average of $23,000 per patient (Canadian Institute of Health Information, 2008). Based on this figure, if the carbamazepine sensitivity genotyping program averted just one case of SJS/TEN in BC each year, this would cover all new costs associated with testing (see section 6.3.2). Furthermore, the saving are likely to be much greater than suggested as these calculations only account for the immediate costs of care and ignore downstream costs necessitated by the severe damage SJS/TEN inflicts on it victims.

While it is certainly important to control costs, there are many other compelling arguments in favour of implementation of such a program including:

1. Humanitarian – carbamazepine- induced skin reactions are devastating to the victims and usually afflict the most vulnerable in our society (children, elderly, mentally ill).
2. Legal Liability – failure to comply with Health Canada recommendations expose the province to legal action.
3. Goodwill – this is a modest program with a small amount of testing anticipated. With a relatively modest investment, the province can be seen to be providing patients of British Columbia with the best that healthcare has to offer.
4. Strategic Objectives – Program fits with the strategic objectives of the Canadian Pharmacogenomics Network for Drug Safety (see section 4.1).
5. Commercial Opportunity – if the program is established quickly, there may be an opportunity to offer this testing to other provinces for a fee. This model was successfully implemented by the BC Centre for Excellence in HIV/AIDS with its drug resistance testing program which is still generating revenue for the Centre after more than eight years. The out of province sales could generate enough revenues to cover all direct costs associated with the BC program, and may generate profits.

4: RESOURCES AND CAPABILITIES

Successful translation of the latest pharmacogenomics research into viable clinical services will be by no means trivial. Not only will it be necessary to possess the considerable resources and organizational capabilities required to process patient specimens into diagnostic results in a manner that is compliant with regulatory oversight, it will also be crucial to effectively meld the relatively complicated science with the clinical and systemic needs to produce something that is understandable and useful. That is, this is an extremely knowledge intensive field and there is a significant knowledge gap within the healthcare community which developers will have to fill. Successful navigation of this arena will require a cross-disciplinary perspective of multiple fields including but not limited to: molecular biology, biology and genetics, medicine (multiple specialties), pharmacology, epidemiology, pharmacoeconomics, marketing and public and social policy. Organizations that are best able to interpret this complex web of knowledge will be most likely to prosper.

4.1 The Laboratory

The Molecular Diagnostics Laboratory at Children's and Women's Hospital in Vancouver, is the primary provider of genotyping services to healthcare professionals throughout British Columba. It is an accredited (Diagnostic Accreditation Program of the British Columbia College of Physicians and Surgeons), full equipped facility that performs more than 5000 genotype tests per year for 42 distinct genetic diseases and conditions (e.g. haemophilia, muscular dystrophy, cystic fibrosis). As such, it houses the

infrastructure, technology and expertise necessary to deliver analogous pharmacogenomic services to the province.

In addition, Children's and Women's Hospital has been chosen as the hub of a nation-wide research initiative called the Canadian Pharmacogenomics Network for Drug Safety (CPNDS) which will be committed to accelerating the translation of pharmacogenomics research of ADRs (Genome British Columbia, 2008) to the clinic. The mandate of this organization ranges from the discovery and validation of genetic markers of ADRs, to the commercialization of the technology and includes all associated activities such as the education of stakeholders and formulation of guidelines and policy. The CPNDS is an extension of a previously developed clinical surveillance program designed to identify and recruit patients suffering from ADRs across the country. As such the program will leverage a well developed network of top scientists and medical professionals offering access to some of the most important opinion leaders in the country. In addition, the CPNDS initiative will also have access to the resources of its partners in government (including regulators) and the pharmaceutical industry. The diagnostic laboratory at Children's and Women's Hospital plays a key role in this program as the pilot site for the commercialization of all new advancements emerging from this initiative. As such it will be operating at the leading edge of knowledge, technology and medical policy, placing it in the best position for the timely provision of pharmacogenomic genotyping services.

4.2 The Team

Dr. Brett Casey

Director, Molecular Diagnostic Laboratory, Children's & Women's Health Centre of British Columbia

Dr. Casey is a pioneer in clinical pathology, being one of the first physicians on the continent to combine his pathology training with clinical molecular diagnostics. Since finishing his residency in the latter, he has been a leader in bringing molecular diagnostics to the mainstream through his research and clinical activities. He currently wears a number of hats including: Assistant Professor at the University of British Columbia where he carries on an active research program focus on genetic birth defects, Director of Molecular Diagnostics at Women & Children's Hospital in Vancouver and a member of the Scientific Advisory Committee for the CPNDS. Dr. Casey will responsible for all medical activities associated with the clinical pharmacokinetics program.

Dr. Bruce Carleton

Director of Pharmaceutical Innovations Program, Children's and Women's Health Centre of British Columbia

Dr Carleton is a full Professor in the Faculty of Pharmaceutical Science at the University of British Columbia where he leads an active pharmacogenomics research program focused on managing adverse drug reaction in paediatric patients. He also serves as the Director of Pharmaceutical Innovations Program at Children's at Women's Hospital in Vancouver that functions to address the multiple needs of governments attempting to manage drug budgets, clinicians attempting to improve patient care, and the public who demand safe, effective and cost efficient drug programs. In this capacity Dr

Carleton is an opinion leader at both the level of the clinical and public policy. Dr. Carleton is also a project leader for Genome Canada's Genotype-specific Approaches to Therapy in Childhood (GATC) program and co-leader of the CPNDS.

4.3 Summary

With two of the most preeminent experts in the country leading the way and a fully equipped laboratory with a proven track record of providing this type of service, the molecular diagnostic laboratory at Children's and Women's Hospital is the ideal location for British Columbia's pharmacogenetics program. There is no doubt that this Centre harbours all the scientific, medical and operational resources and expertise necessary to meet the needs of such a program, and, in its association with the CPNDS, the laboratory has access to leading medical and scientific institutions and opinion leaders nation-wide which will allow it to stay ahead of curve well into the future. With the right strategic plan the laboratory should be able to establish itself as a translational leader, assuring that the most appropriate breakthrough in pharmacogenetics are delivered to the patients of British Columbia and Canada in a timely and cost efficient manner.

5: MARKET RESEARCH AND ANALYSIS

5.1 Overview

The market for any diagnostic medical services or products is highly complex and variable with multiple stakeholders. While the ultimate beneficiaries are the patients, it is physicians who are the gate keepers, and in Canada, it is the agencies of provincial governments that pay for these services. The nature of patient cohorts and care providers can vary significantly depending on the indication for the diagnostic service as can the disposition of the payer to pay. For example, the decision making process for a neurologist treating an epilepsy patient in private practice is likely to be different from that of a salaried psychiatrist treating bipolar disorder in a hospital ward. In addition to the different clinical considerations, reimbursement concerns will vary as payment for services are likely to come from a provincial health insurance plan in the first case and from a global hospital budget in the latter. Payment decision makers will likely have different priorities in these two cases. The picture becomes even more convoluted as each provincial jurisdiction will have its own set of players with different interests. Furthermore, in the case of pharmacogenomics, the regulatory agencies and pharmaceutical companies may also play a role depending on the associated risks and benefits. Given this complex web of players, considerable finesse is required to successfully launch a new diagnostic service. The market for HLA-B genotyping to inform carbamazepine therapy will be no exception.

As previously discussed, carbamazepine is indicated for epilepsy, neuropathic pain and mood disorders; however interviews with physicians suggested that it is primarily prescribed to treat the first two and only rarely for the latter. Epilepsy and neuropathic pain are normally managed by neurologists and there are reportedly 733 of these in the country (Canadian Medical Association, 2008) with approximately 60 specializing in treatment of epilepsy (Theodore, et al., 2006). The corresponding counts in British Columbia are 109 and 10. Although epilepsy is generally diagnosed before the age of 18 (i.e. approximately 80% of the 15,500 annual new cases in Canada), carbamazepine is generally reserved for adults (see Table 1 below). The incidence of neuropathic pain on the other hand generally increases with age with the vast majority of cases occurring in patients over 45 (Hall, Carroll, Parry, & McQuay, 2006). Thus, the most typical scenario which would lead to utilization of carbamazepine sensitivity testing would involve a neurologist, in an office setting, prescribing carbamazepine for the first time to an adult patients suffering from epilepsy or neuropathic pain.

While care providers for the mentally ill are a much smaller consumer group, they may turn out to be enthusiastic users of an HLA-B genotyping service because of the vulnerability of their patient population. Carbamazepine is normally used as a second line therapy for hard-to-treat cases of bipolar disorder or in rare cases, for the treatment of manic episodes in a hospital setting (Goodwin, 2003; Sach, Printz, Kahn, Carpenter, & Docherty, 2000). Under these circumstances, the prescribing physician is most likely to be one of 4200 psychiatrists in the country; or in BC, one of 650 (Canadian Medical Association, 2008). Thus, the typical scenario for accessing the test in this context would involve a psychiatrist prescribing the carbamazepine for the first time to an adult patient

in order to manage ongoing therapy or to control a manic episode in either a hospital or private practice setting. Of importance, there is a significant overlap between mental illness and epilepsy which creates a channel between the different types of practitioners.

While the total number of practicing neurologists and psychiatrist in the country is sizable, marketing efforts need only concentrate of a few major Centres as over 80% of the appropriate ethnic populations live in one of six cities. Listed in order of decreasing population density they are: Toronto, Vancouver, Montreal, Calgary, Edmonton and Ottawa (Statistics Canada, 2008). Toronto and Vancouver alone are home to over 65% of this cohort and therefore initial marketing efforts should concentrate on appropriate practitioners in these two cities.

5.2 Total Market Size

The total market size for HLA-B genotyping program is defined by the number of patients of Han Chinese heritage that are prescribed carbamazepine for the first time (i.e. carbamazepine naive) for any reason in any given year. These are the only patients for whom the HLA-B genotyping test would be of value. To estimate this, the databases of the private healthcare research organization, Brogan Inc. were consulted for all new (incident) carbamazepine prescriptions and the proportion of patients that were in high-risk group was estimated using Canadian census data (Satisitcs Canada, 2008). The final results of these calculations are provided in Table 1and Table 2 for British Columbia and the rest of Canada respectively. The strengths, limitations and implications of these estimates are discussed below.

Table 1: Estimated annual number of carbamazepine naive patients of Han Chinese descent initiating carbamazepine therapy in British Columbia.

	2003	2004	2005	2006	2007	Average
Under 19	49	32	37	34	39	38
19 and up	970	766	811	821	959	865
Total	1,019	798	848	854	998	**904**

Derived from Brogan Data (**Appendix A**) and 2006 Canadian census data (Statistics Canada, 2008).

Table 2: Estimated annual number of carbamazepine naive patients of Han Chinese descent initiating carbamazepine therapy in the rest of Canada.

	2003	2004	2005	2006	2007	Average
Alberta	459	394	396	429	404	416
Saskatchewan	23	25	25	22	22	23
Manitoba	80	67	75	74	73	74
Ontario	1,167	1,230	1,141	1,027	998	1,113
Quebec	67	63	60	58	60	62
Maritimes	20	21	18	21	17	19
Rest of Canada	1,,816	1,800	1,715	1,631	1,574	**1,707**

Derived from Brogan Data (**Appendix A**) and 2006 Canadian census data (Statistics Canada, 2008).

Brogan Inc is a private research company specializing in healthcare intelligence services which compiles data provided by a selection of private health insurance companies across the country. For the purpose of this report, Brogan was contracted to query its database for patients newly prescribed carbamazepine therapy (carbamazepine naive) each year between 2003 and 2007 stratified by region, age (younger than 19 vs. 19 and older) and gender (Appendix A). Patients were assumed to be carbamazepine naive if they had not received the drug in the year preceding their first claim. Final total carbamazepine utilization estimates were obtained by adjusting for the estimated capture

rate defined as the percentage of the population represented by the data for each region (Appendix A).

Based on the Brogan data, the estimated average total number of patients newly prescribed carbamazepine therapy on an annual basis was approximately 6,700 and 30,800 for BC and the rest of Canada respectively. This means that 16 out of every 10,000 people in BC take their first dose of carbamazepine each year while the corresponding rate in the rest of Canada is 10 out of 10,000. Please note, these rates seem high when compared to those reported in other countries. For example researchers in each of Germany (Mockenhaupt M, 2000), the Netherlands (Tsiropoulos B, 2006) and Demark (Knoester PD, 2004) reported incident carbamazepine use to be 9, 2.5 and 4 per 10,000 per year respectively. On the other hand, drug utilization can vary significantly between jurisdictions, and over time and therefore it is difficult to draw conclusions from these differences. In the absence of more direct evidence, the estimates derived from the Brogan database were used without modification.

The annual number of at-risk carbamazepine naive patients was estimated by adjusting the total naive carbamazepine utilization estimates by the proportion of the population represented by at-risk groups using the 2006 Canadian census data (Appendix B). At-risk groups were defined as nationalities identified in the US FDA warning of December 2007 with the exception of East Indians. The latter were excluded because Health Canada does not refer to these or any other nationalities in its warnings (Health Canada, 2008) but rather only to "patients of Asian– particularly of Han Chinese ancestry." Furthermore, the literature to date has only identified individuals of Han Chinese descent harbouring the HLA-B polymorphisms as being at-risk and therefore,

only regions where a significant proportion of the population meets this description are included in this analysis. It should be noted that the final decision of which patients to include in the program is a policy decision that should be driven by the medical community and not by the Author.

Thus the number of patients eligible for HLA-B genotyping to manage carbamazepine therapy is approximately 900 and 1700 for BC and the rest of Canada respectively. This translates to a maximum weekly demand of 49 tests nation - wide; 17 for British Columbia and 32 for the rest of the country. Clearly the potential Canadian market for HLA-B genotyping to inform carbamazepine therapy is relatively modest. Based on current pricing standards for a similar test for abacavir therapy (John Hopkins, 2008; Veenstra, 2004; United States Department of Veterans Affairs, 2008), the price of the proposed test would likely be limited to approximately $100 leaving the size of the entire Canadian market at $260,000. Because the intent is to provide this service for free for patients in British Columbia, the total annual revenue potential for the rest of Canada is $170,000.

5.3 Determinants of Demand

The total size of a market is generally not a good indication of demand - especially for newer technologies. During the early stages of its lifecycle, the uptake of a new product or service is usually slow and without a concerted marketing effort can stay that way. Good marketers understand this and begin planning their marketing strategies during the conceptual stage of design and continue their efforts throughout the product lifecycle.

Probably the most important determinant of demand is the consumers need (or desire for the product/service offering. If it is difficult to convey the benefit, it will be difficult to sell. Even when the offering is beneficial, it takes time for consumers to become aware and develop enough of an interest to pursue information about the benefits before becoming convinced that it is worth adopting and buying in. Different consumers advance through the process at different rates depending upon their level of involvement and it is important when bringing a new product of service to the market to understand these factors. It is therefore instructive to examine who the consumers are, their motivation and their decision making processes. In turn, this exercise will assist in the development of a marketing plan by identifying market segments with the most motivation to adopt a new technology and therefore the most amenable to marketing efforts. Finally it is important to understand the competitive landscape to plan for differentiation of the offering in order to maximize market share. These issues and how they relate to the proposed program of HLA-B genotype testing for carbamazepine sensitivity are discussed in this section.

Buyer Behaviour

As previously discussed, there are a number of players in the market with an interest in HLA-B genotyping; however, physicians are probably the most important with respect to marketing efforts. Not only are they the decision makers in the purchasing process but they are also essential to lobby provincial health authorities to pay for new medical services. As a whole, physicians are an extremely demanding when considering new technologies for the clinic and the burden of proof is high; however, this can be tempered by the perception of need.

Modern medicine is evidence-based with statistically significant prospective clinical trials being the highest standard of evidence, followed by retrospective studies and finally anecdotal evidence. Generally speaking, the profession will follow medical protocols that have been established in prospective clinical trials first and will experiment with new ideas and procedures only when those fail, do not exist, or as part of well controlled clinical trials. However, when a new treatment option comes with little risk (i.e. it does no harm) and there is at least retrospective evidence of its value, there is more freedom to experiment with new treatment options – or not, depending on the judgement of the treating physician. Thus the decision to adopt a new medical option comes down to a risk/benefit analysis based on the strength of the medical evidence and the clinical imperative. If the profession as a whole has not passed judgment, then the decision is left to the discretion of the treating physician.

In the case of carbamazepine, the new treatment option is to adopt, or not to adopt a harmless new test in order to avoid a very rare, but very serious adverse reaction to a drug that has been used for decades. Under these circumstances, both the perception of need and the burden of proof will be somewhat subjective. Other issues such as the convenience of the service and the impact on the course of patient care will weigh heavily on the decision. Each of these issues is discussed below with respect to the factors influencing physician perceptions of HLA-B genotype testing for carbamazepine sensitivity.

The perceived need of the HLA-B genotyping test

Carbamazepine has been used in clinical practice in Canada for over thirty years without the benefit of an HLA-B genotyping tests and it is likely that most physicians

have not experienced an advanced case of SJS and/or TEN in that time. Indeed, two physicians interviewed for this analysis each reported experiencing only one possible case of SJS/TEN in their careers (30 years in one case) and in both cases, the severity of the reaction was mitigated by immediately discontinuing therapy (although both patients were hospitalized). The current standard of care involves advising patients new to carbamazepine to monitor themselves for skin reactions for the first 60 days of therapy and to discontinue the drug if a rash is detected. If experienced physicians have successfully managed care by this method for years, it might be difficult convincing them that the test is needed. Indeed one neurologist in BC interviewed for this study expressed the opinion that the test would be a "waste of money."

On the other hand there are clinical scenarios where physicians may perceive the need. Inexperience with carbamazepine, previous bad experience with SJS/TEN, a high proportion of Han-Chinese patients in their clinical practice or lower functioning patients (i.e. unable to monitor themselves for skin rash) may be enough to induce physicians to utilize the test. Given that the SJS/TEN can be fatal, it is expected that some physicians would 'just rather not take the chance.' In fact at least two neurologists and two psychiatrists practicing in the province suggested they would likely use the test if and when it became available.

Of interest, the advisories issued by Health Canada and the FDA coupled with the inclusion of this information on the product monographs may have created a need as these announcements have created a potential for legal action if the test is not utilized. Regardless of the legal merit of the argument, it is an eventuality that many physicians

would usually prefer to avoid. Therefore, some might choose to access the test for legal rather than clinical peace of mind.

Perceptions of "the proof" for HLA-B genotyping

To date the evidence for the test is based on retrospective studies, which is less than ideal. A randomized clinical trial that demonstrated that patient outcomes were better when the test was utilized in managing therapy versus when it was not would be more convincing; however, such a trial is unlikely to be undertaken in any meaningful way because the number of Han-Chinese carbamazepine patients is low and SJS/TEN is so rare. Such a trial would require an enormous sample size and would be extremely challenging; at least in this part of the world. However, the retrospective data is quite compelling and there is a general consensus in the scientific and healthcare communities that the association between these skin reactions and the HLA-B polymorphism in Han-Chinese patients is very real (Health Canada, 2008; US Food and Drug Administration, 2007; Ingelman-Sundberg, 2008; Depondt, 2008). Given the benign nature of the test, it is unlikely that it will be rejected because it hasn't met the burden of proof.

The perceived convenience of HLA-B genotyping.

Like most professionals, physicians have limited time and generally do not readily tolerate new technologies if they cannot be easily integrated into their practices. If a new test requires extra time, money and/or effort on the part of the physician, then the need and/or the burden of proof for the test will be higher. Although accessing and interpreting tests for carbamazepine sensitivity will be simple, the test will necessitate an extra visit by the patient to the doctor's office, thus increasing the physician's workload. This might be a good thing if the doctor works on a fee for service basis; however, it

would be a burden if he/she is salaried. In reality this is not likely to be a significant issue in the minds of most neurologists. With over 40 working in the Greater Vancouver area, the average physician would have to accommodate an extra 22 extra patient visits a year (assuming all 900 eligible patients in the province are referred for testing) which translates to approximately six extra minutes per week or a 0.2% increase in the median 48.4 patient care hours worked per week (Freeman, 2003).

The perceived clinical value of HLA-B genotyping

Diagnostic and prognostic tests are used as part of the clinical decision making process and it is important from a physicians perspective to know if and how clinical action will be altered by the new information. Many medical conditions detectable by molecular diagnostic tests are not treatable and may only serve to answer questions or inform clinical monitoring decisions. Generally speaking, pharmacogenetic results offer more clinical options as physicians can choose to alter the dose (or dose frequency), select alternative drugs or simply monitor response more closely. It is important to know how HLA-B testing for carbamazepine-induced SJS/TEN will alter clinical options.

Current data (Hung, Chung, & Chen, 2005) suggest that, within the Han-Chinese population, 8% of individuals testing positive for the carbamazepine sensitive genotype will develop SJS and/or TEN if given carbamazepine whereas those testing negative have no chance of this adverse reaction. Given a positive result, physicians can choose to avoid carbamazepine altogether and choose one of many other available drugs (at least 12 for epilepsy, six for bipolar disorder and four for trigeminal neuralgia) or monitor the patients more closely for skin reactions. If the patient test negative, physicians can

manage the therapy as normal. Thus, the proposed test appears to have some merit providing actionable information in some cases and peace of mind for others.

Summary

For physicians, the decision to bring a new diagnostic test to clinical practice can be very involved. They are obligated to provide the best care for their patients; however they need proof that changes are going to help. Generally they tend to look to opinion leaders/experts to gather the necessary supportive evidence and come to a consensus on how the technology should be introduced into care. For truly superior advances, positive recommendations represent a leap across the market 'chasm' and generally the technology will be rapidly taken up by the early and late majority alike. When the impact of a new technology is more modest, recommendations can be more equivocal and vendors must work this market like any other seeking out champions in strategic sectors and work those sectors until they can gain a foothold. Peer to peer recommendations are probably more important under these circumstances.

The potential for consensus on testing for carbamazepine sensitivity is uncertain. Based on interviews with three neurologists and two psychiatrists there has been very little debate occurring within the medical community since the original recommendations were issue by the FDA last December. This is likely because without an available test, the discussion would be purely academic. It is likely that the introduction of the test will initiate some debate based on opinions expressed by physicians interviewed which ranged from:

"the test is a waste of money"

to

"I think it is an issue that is generally being ignored by the Neurology community, and is particularly relevant in a place like Vancouver with a higher Chinese population. They don't view a rash as a big deal, but I have seen horrendous cases of S-J Syndrome and Toxic Epidermal Necrolysis. I think the data for testing in the Chinese community is compelling and with so many other drug options for epilepsy or neuropathic pain, it should be done."

Of note, only one out of seven of the medical professionals interviewed was opposed to the idea of carbamazepine sensitivity testing; although only a few had given the issue much consideration. The opposing voice was that of a neurologist who was a specialist in epilepsy with over thirty years experience who might have had some status as an opinion leader among local practitioners. In any case, there are strong arguments on both sides of the issue (Table 3) and until the there is a consensus, HLA-B genotyping for carbamazepine will not become a standard of care and will remain up to the discretion of the individual physician.

5.1 Segmentation and Targeting

Consumers of healthcare products and services can be segmented by a several criteria. In Canada the market is first segmented geographically by province and territories which means dealing with at least 11 separate jurisdictions. Within each province the market can be further broken down by health authorities, disease, medical specialities, organizational structure (hospital vs. private practice), and finally physician

Table 3: Incentives and Disincentives for HLA-B genotype testing to manage carbamazepine therapy

For	Against
• SJS/TEN can be fatal (30 to 40% of cases result in death) • Risk of SJS/TEN 10-fold higher in Han-Chinese patients (1 in 400)	• Carbamazepine – induced cases in SJS/TEN are very rare. (2 to 4 in 10,000)
• Genotype association with SJS/TEN very strong in retrospective studies.	• Value of test has not been demonstrated in prospective clinical trial
• Many physicians inexperienced with carbamazepine • Low functioning patient may not be able to reliably monitor themselves for rash.	• Carbamazepine has been used for decades without such a test. • SJS/TEN can be avoided by monitoring for rash – easy for high functioning patients.
• Absolute negative predictive value – provides some peace of mind	• Marginal positive predictive value of the test (7.7%).
• Test will be easy to access (free to BC).	• Rest of Canada: cost of test is not covered.
• Health Canada and FDA all recommend pre-therapy HLA-B testing. • Ignoring recommendations raise potential for malpractice suit.	• Regulatory agencies have no authority over physicians • Merit of malpractice cases would be questionable

and patient demographics. Figure 4 illustrates the higher level segments of the market for an HLA-B carbamazepine sensitivity test.

Outside of British Columbia, neurologists in Ontario represent the biggest potential user group for the test. This is the province with the largest Han-Chinese population and neurologists are the care providers that are most likely to be the first to

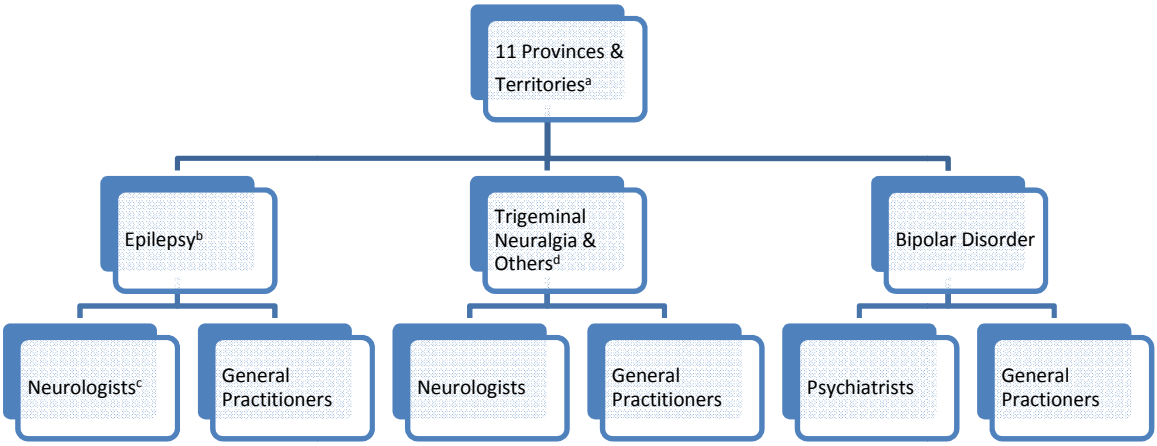

Figure 4: Hierarchy of the market segments that are potential users of HLA-B genotyping test for carbamazepine sensitivity: a) largest market is Ontario; b) primary indication; c) primary prescribers; d) Carbamazepine is used off-label for other neuropathic pain.

prescribe carbamazepine for either epilepsy or neuropathic pain (e.g. trigeminal neuralgia). While it will be necessary to make the availability of the test universally known throughout the medical profession, most efforts should concentrate on targeting these physicians.

In addition to Han-Chinese heritage, the patient characteristic that is most conducive to utilization of HLA-B genotyping for carbamazepine sensitivity would be competency. As discussed previously, highly functioning patients can normally prevent severe skin reactions by discontinuing therapy at the first sign of a rash; however, it may be asking too much for lower functioning patients to do this. This might include children, the mentally handicapped and the mentally ill. With respect to the former, approximately 5% of incident carbamazepine users are under the age of 19 (Appendix A). The balance of incident use of the drug is expected to be mostly for adult epilepsy and neuropathic pain with a small contingent of patients being treated for bipolar disorder.

Patient of diminished capacity are over represented in at least two of three patients groups indicated for carbamazepine. For example, an estimated 23% of epileptics suffer from varying degrees of mental retardation and up to 18% of newly diagnosed patients suffer from dementia associated with stroke (Shorvon, Fish, Perucca, & Dodson, 2004). Furthermore approximately 6% of epileptics suffer from severe psychiatric disorders (Shorvon, Fish, Perucca, & Dodson, 2004) with up to 50% suffer from mood disorders (Kanner, 2007). In patients with bipolar disorder, carbamazepine is used as a mood stabilizer and for manic episodes. While treatment can restore functionality, these patients are by definition operating at diminished capacity at treatment initiation. In contrast, neuropathic pain can affect all age groups (Hall, Carroll, Parry, & McQuay, 2006) and there is no reason to believe that prevalence of reduced capacity is any greater or any less in this group than the population at large - approximately 5% (e.g. 1% schizophrenia, 1% organic brain disorder, 1.6 % substance abuse, 5.8% mood disorder etc. (Arboleda-Florez, 2005)). Thus among these patient cohorts, there is reason to believe that genotyping for carbamazepine sensitivity would be of benefit at least 25% of Han-Chinese patients initiating therapy with the drug, based on the anticipated mental health of the patients involved.

5.2 Competition

Although there are currently no laboratories in British Columbia or Canada providing HLA-B genotyping services for carbamazepine therapy, the number of molecular diagnostic laboratories and/or research laboratories is considerable, raising the threat of competition. Any laboratory with genotyping capabilities could establish an assay for this purpose within a few months. While the logistical challenges of providing

such a service present a barrier, there are at least 11 Canadian molecular diagnostic laboratories with the operational capabilities to rapidly enter the market (National Institutes of Health, 2008). In addition, some of the more generalized diagnostic laboratories have the capabilities to provide HLA-B genotyping with equal efficiency including industry giants Quest Diagnostics and LabCorp. It will be necessary to be both fleet and lean in order to gain advantage in this environment.

At this time, the major barriers delaying the introduction of HLA-B genotyping for carbamazepine therapy are indecision and market size. The Canadian recommendations for carbamazepine sensitivity testing were issued in March of this year and the organizations with the capabilities to do this work need to weigh the costs, benefits and risks associated with such and initiative. Also, because the pharmacogenomics market has not completely emerged, it is likely that uncertainty exists in the minds of the decision makers about investing in such an effort. Furthermore, only BC and Ontario have a sufficient incident of carbamazepine use among Han-Chinese populations large enough to justify such a program (Table 1 and Table 2) and even then, the test would be considered to be relatively esoteric on a provincial level.

Ideally, a single reference laboratory would provide this service for the entire country allowing for the operation to capitalize on the economies of scale. The vision of this proposal is to position the molecular diagnostic laboratory at Children's and Women's Hospital as the national reference laboratory for carbamazepine sensitivity testing. It is anticipated that if the laboratory can be the first in the country to offer a high quality, cost efficient HLA-B genotyping service to inform carbamazepine therapy, it will capture the entire market. The BC Centre for Excellence in HIV/AIDS was successful in

employing this strategy 10 years ago when it became the sole provider of HIV resistance testing in Canada. In order for the strategy to work, it will be important to control costs and strategically price the service to discourage entry.

5.3 Estimated demand for HLA-B genotyping service carbamazepine sensitivity

Definitively forecasting the demand for HLA-B genotyping for eligible carbamazepine patients is challenging. Much will depend on the communications efforts put forth by the leaders at Children's and Women's Hospital and the Pharmacogenomics Network for Drug Safety. While reports from other parts of the world indicate that clinical adoption of pharmacogenomic testing has been slow (Martin, Lewis, Smart, & Webster, 2006), research has shown that uptake is greatest when the service is associated with a strong research program (Corkindale, Ward, & McKinnon, 2007).

To date, market uptake of other pharmacogenomic testing options has been erratic. For example tests for genetic markers to predict potentially fatal mylosupression due to azathiopurine therapy for leukemia have been generally ignored by the medical community whereas genotyping for hypersensitivity to the HIV drug abacavir has been rapidly adopted (Alfirevic & Pirmohamed, 2008); but, only after prospective randomized clinical trials demonstrated a reduction in adverse reactions when genotyping was employed. Being a relatively new testing procedure with no supporting prospective clinical evidence, it is expected that the initial uptake of HLA-B genotyping for carbamazepine sensitivity will be slow. Decisions are likely to be made on a case by case basis driven by the perceived vulnerability of the patients involved, with children, the mentally challenged and the mentally ill being the primary users of the service. These

combined cohorts are estimated to account for at least 25% of incident carbamazepine use among epileptics as previously discussed (see page 40). Early adopters and physicians with high Chinese patient populations are expected to be secondary drivers. Full uptake is not expected take place until consensus is reached among the medical community.

Based on strength of the scientific evidence, the ease of access and interpretation of the test, the recommendations by the regulatory agencies, the potential to avert tragedy (and the accompanying lawsuits) and interviews with neurologists and psychiatrists, it conservatively predicted the HLA-B genotyping for carbamazepine sensitivity will eventually be adopted to manage the carbamazepine therapy of 50% of eligible patients - 20% in the first year after launch, 35% in year two and 50% thereafter. Because of logistical issues and the associated costs, uptake in the rest of Canada is expected to be slower with 10% accessing the test in the first year, 20% by year two and 30% thereafter. Assuming no other laboratories begin offering this test in that time, all this work will come to the molecular diagnostics laboratory at Children's and Women's Hospital in Vancouver. Based on these assumptions, the projected workload for the program is given in Table 4.

5.4 Summary

Estimates of the total number of British Columbian and Canadian patients that are newly prescribed carbamazepine each year combined with estimates of how many of those would be Han-Chinese indicates that approximately 900 and 1700 patients respectively would be eligible for HLA-B genotyping to predict sensitivity to the drugs (see Table 1 and Table 2). Of course uptake of the test would not be 100% as at least

Table 4: Projected Provincial and National demand for HLA-B genotyping for carbamazepine therapy in the first three years after launch

Year	Demand Annual (weekly)	
	British Columbia	Rest of Canada
1	180 (3 -4)	170 (*ca.* 3)
2	315 (*ca.* 5)	340 (6 – 7)
3	450 (*ca.* 8)	510 (*ca.* 10)
4	450 (*ca.* 8)	510 (*ca.* 10)

some physicians would be resistant to adopting a new test to manage a drug that they have been using for decades. Until there is a professional consensus on the best application of the test, utilization will be discretionary; however, at least four out of seven prescribers of this drug suggested they would access the test if it became available with two others being noncommittal and the last being firmly against adoption. Based on these informal results and an assessment of the pros and cons of the test, it is estimated that the test will eventually be adopted by at least 50% of prescribers in BC and 30% in the rest of Canada or 450 and 510 tests per year respectively. These estimates are judgement based and it is recommended that a survey of neurologists be conducted in order to get a better idea of who would access the test and under what conditions.

6: ECONOMICS OF THE TESTING PROGRAM

6.1 Overview of the Process

The molecular diagnostics laboratory at Children's and Women's hospital is currently well established in British Columbia as the primary provider of medical genetic tests for physicians across the province. As such, systems and protocols for delivering these services in BC are fully developed (Figure 5). Briefly, when a physician orders a test, a form (designed and provided by the laboratory) is given to the patient who reports to the nearest hospital or commercial blood collection facility where five to ten millilitres of blood are collected. The blood sample is then transported to the testing laboratory where it is received, labelled (i.e. numbered) and logged into the laboratory information system (LIS) which is designed to track the sample throughout the remaining processes. The blood sample is then stored until ready for DNA extraction and genotype analysis both of which are usually performed in batches. Results from the test are reviewed by the laboratory staff and, if acceptable, will be entered into a form report (usually automatically). The report is then reviewed and signed off by the laboratory medical director before it is packaged and mailed to the ordering physician by clerical staff. Each step in the process has its associated costs; however, in this analysis only the major costs associated with the new carbamazepine genotyping program is examined.

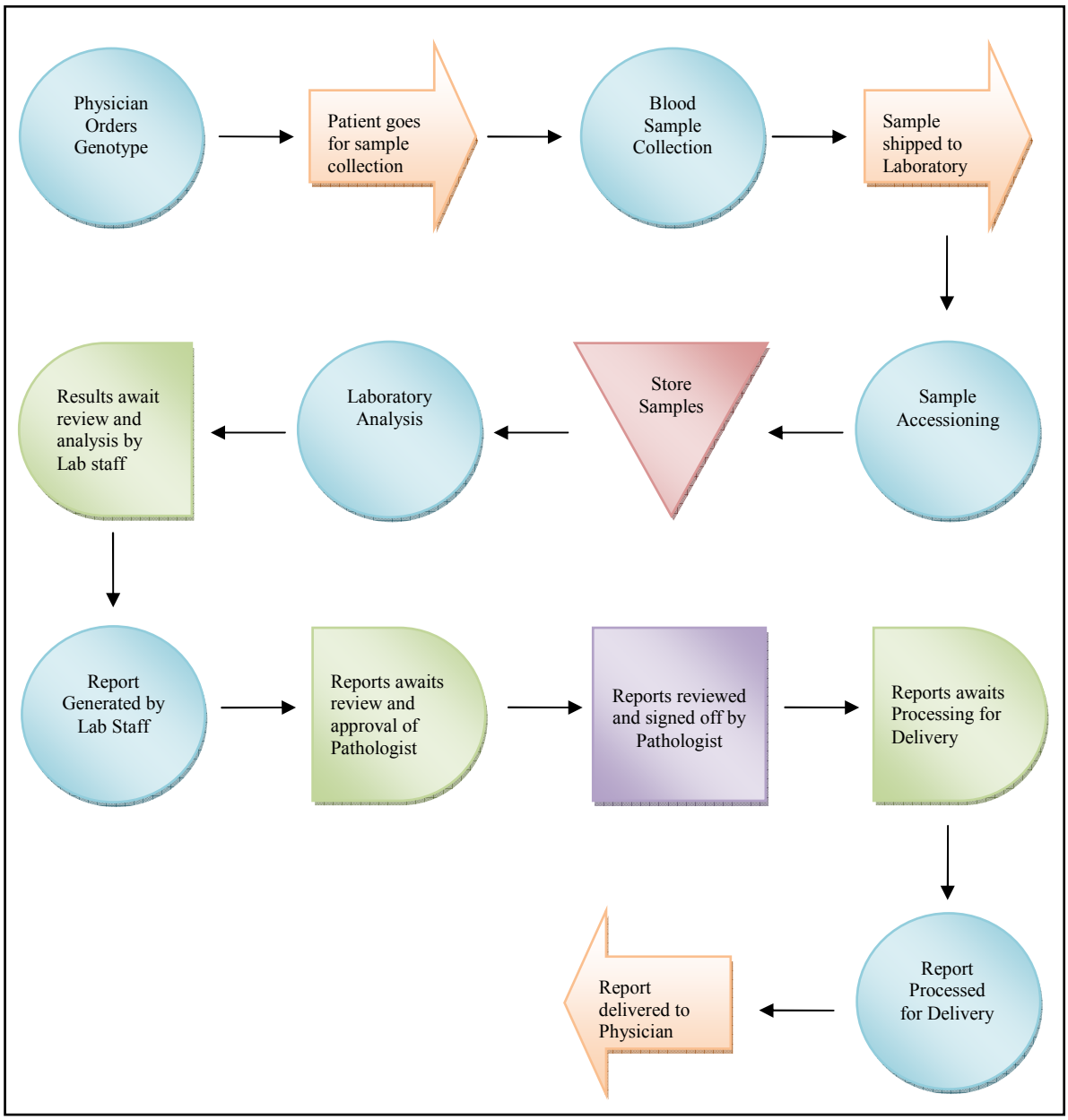

Figure 5: Process Scheme currently employed in the provision of clinical genotyping service in BC

6.2 Cost Breakdown

As illustrated in Figure 5, diagnostic testing of blood samples requires handling by at least three different cost centres; blood collection, shipping and the laboratory. The per sample expense of each process can vary significantly depending on the volumes involved, however, based on expected demand (Table 4), the average cost per sample is

expected to be approximately $61 in year one (Figure 6) dropping to $49 by year three. The breakdown of cost is as follows.

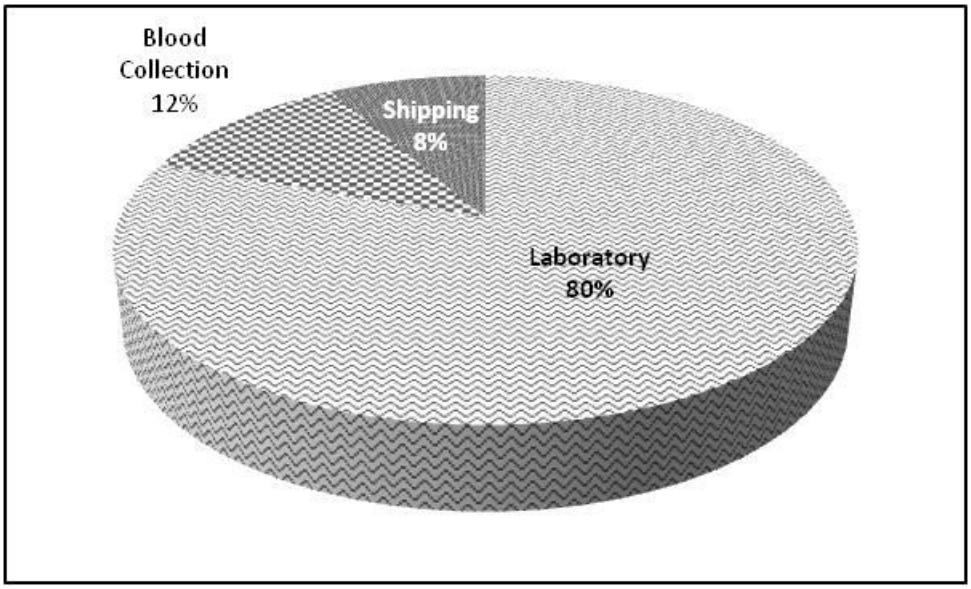

Figure 6: Functional breakdown of the average per-sample cost of providing eight genotype tests per week to patients in British Columbia.

6.2.1 Blood Collection

Introduction of carbamazepine genotyping program in most cases will necessitate a dedicated blood sample. It is estimated that each blood draw costs the system approximately $3.50 in consumables (blood tube, needle and holder, gloves, alcohol swab, cotton) and approximately $3.50 in labour (approximately 10 minutes of clerical and phlebotomy).

6.2.2 Shipping

Shipping can be one of the most expensive components of diagnostic services involving blood tubes. In order to ensure timeliness of service and integrity of the samples, blood sample tubes must be shipped to the molecular diagnostics laboratory

within 24 hours of collections. Within Vancouver there are cost efficient procedures in place for inter-hospital transport; however, it is likely that many patient samples will need to be shipped by courier from locations outside the hospital network. Further, because it is a 'biological', there are rigorous packing requirements for specimens travelling extended distances (Harvard University, 2002).

Thus shipping costs can range from no cost for a sample collected within the hospital network in downtown Vancouver to approximately $15 per sample for specimens transported within the greater Vancouver area and up to $35 for a sample collected in other parts of the province. However, given that the majority of the Han Chinese population lives in the lower mainland of British Columbia, it is estimated that the majority of patient blood samples will be coming from this region and shipping costs will be minimized to a great extent by batch shipments. Thus the average specimen shipping cost for BC is expected to be relatively low and is estimated to be a maximum of $5 per sample[3].

6.2.3 Laboratory: Analytical Costs

Processing in the laboratory is extensive and sophisticated; however the current technologies can be very cost efficient. Progress in automation now enables a single technician to process from hundreds to thousands of patient samples a day for less than $10 per sample; however, the economies of scale are important in achieving this efficiency. Molecular diagnostic laboratories rarely work on this scale and rigorous

[3] Based on personal conversation with the manager of the accessioning laboratory at Children's and Women's Hospital and private discussion with Corporate Couriers of Vancouver and list prices provided on FedEx.ca.

quality requirements imposed on diagnostic laboratories limit their ability minimize costs.

Because of the stakes involved (human health and life), quality assurance in diagnostic laboratory is paramount and as such it is necessary to reference each diagnostic test result to a series of quality control samples that test the limits of the assay as well as all the possible results that might be observed (College of American Pathologists, 2007). A valid HLA-B assay for carbamazepine would likely require a minimum of five control samples for each batch. The cost of analysing each quality control sample would be at least as much as a patient sample and these must be included in each batch regardless of whether the batch involves one patient sample or one-hundred. Approximately $8 in reagents and consumables are involved in the analysis of each batch unit (including controls) which means the associated per patient costs for a batch size of one would be $48 dollars; that is, $8 for the patient sample plus $40 for the controls. In contrast, it would cost only $8.40 per sample for a batch size of 100 patient samples because the associated cost of controls is $1/100^{th}$ of the previous example. Clearly it is desirable to maximize batch size as much as possible.

Limiting the HLA-B genotyping program to British Columbia will make maximizing batch size challenging. Based on the projected demand (Table 4) the laboratory should receive three to four samples per week from British Columbians in the first year growing to eight per week in the third. In order to make the program workable to physicians these samples will all have to be analyzed within 5 business days. The corresponding per sample costs range from $36 to $23 (including labour) for three patient and eight patient batches respectively. Expanding the program to the rest of Canada is

predicted to raise demand to 18 tests per week (Table 4) at a cost of approximately $19 per sample.

6.2.4 Laboratory: Post Analytical Costs

The last major cost associated with HLA-B genotyping is associated of with the medical interpretation of the results. This requires high value time of the laboratory pathologist to review, troubleshoot (if necessary) and sign off on the results and is estimated to cost approximately $25 per sample under ideal conditions. At higher throughputs, this constitutes over half the costs of all laboratory processes. Automating the process as much as possible would be an effective use of resources.

All laboratory processes and the estimated associate cost are summarized in Table 5. By summing these estimates the total direct laboratory costs associated with a single test would be approximately $49 by year three based on the weekly throughput projected in Table 4 (i.e. 8 to 9 patients). These do not take into account overhead cost associated with general laboratory operations.

Table 5: Estimated per sample cost value associated with the laboratory processes involved in the delivery of an HLA-B genotyping report for carbamazepine sensitivity (assuming a weekly batch size of eight).[1]

	Reagents	Consumables	Labour
Sample Accessioning[2]			$2.00[3]
DNA Extraction	$2.00[4]		$1.50[5]
Laboratory Analysis	$5.50[6]	$7.50[7]	$3.00[8]
Verification and Report Entry			$1.00[9]
Pathologists Review			$25.00[10]
Delivery of Report		$0.50	$0.50[11]
Total	$7.50	$8.00	$33.00

Notes for Table 5

1. All estimates have been rounded to the nearest $0.50.

2. Refers to receipt and cataloguing of sample.

3. Assumes clerical effort of 5 minutes at a cost of $25 per hr (wage and benefits).

4. Cost was based on that estimated for a robotic system reported in the literature (Ivanova, DeWaard, & Herber, 2006).

5. Assumes 60 minute effort on 24 samples by a medical technologist at cost of $30 per hr.

6. Per reaction reagent costs were estimated as the average of three estimates provided by three different vendors (Applied Biosystems, Qiagen and Luminex) with technological platforms suitable for HLA-B genotyping (average = $3.51). Per sample cost were based on a batch size of eight patient samples and five internal controls.

7. Per reaction consumable costs were estimated by summing all the vials, test tubes, pipette tips etc. for a typical analytical procedure and applying the list prices given in the Fisher or VWR Canlab catalogues (*ca.* $4.50 total). Per sample cost were based on a batch size of eight patient samples and five internal controls.

8. Assumes 40 minutes effort on seven samples by a medical technologist at a cost of $30 per hour.

9. Assumes 15 minutes effort on the results of eight samples by a medical technologist at a cost of $30 per hour.

10. Assumes 6 minutes effort per report by the pathologist at a cost of $250 per hour.

11. Assumes 1 minute clerical effort per report at a cost of $25 per hour.

6.3 New money for HLA-B genotyping program for British Columbia.

6.3.1 Start-up

Diagnostic laboratories are heavily regulated and they cannot introduce a test into the market until they can demonstrate it works the same way every time. When a diagnostic test is not commercially available, laboratories must not only invent their own in-house assay; but also challenge that assay in every conceivable way in order to identify the conditions under which it does and does not work. This means that in addition to the obvious chemical reaction conditions (e.g. reagents, concentrations, temperature etc), it is necessary to establish acceptable pre-laboratory conditions including sample collection, storage, and shipping conditions. In addition, it is necessary to identify as much as possible, interfering substance that could alter the results of the test. Only after all this work is complete is the assay considered validated and ready for the market.

Because of the experimental nature of the work, the time and cost associated with validating a molecular diagnostic test is uncertain. However, the laboratory at Women's and Children's Hospital has been performing this type of work for over 10 years and it is anticipated that it will be able to validate a HLA-B assay for carbamazepine therapy in the minimum possible time at the minimum possible costs. It is estimated that validating a new assay and creating the laboratory systems (database, forms etc) necessary to handle the new work will require a minimum of $3000 excluding labour.

6.3.2 Operations

With the current infrastructure in place, the molecular diagnostic laboratory at Children's and Women's hospital could easily integrate the anticipated demand into its

current operations for BC (or all of Canada). No new personnel or equipment would be required. Thus the only relevant costs would be variable costs, which range from approximately $3,000 to $20,000 based on the worst to the best case scenario. These monies include all costs associated with blood collection shipping and laboratory operations. Based on projected demand (Table 4), the program will need approximately $10,500 in new money for operations by year 3.

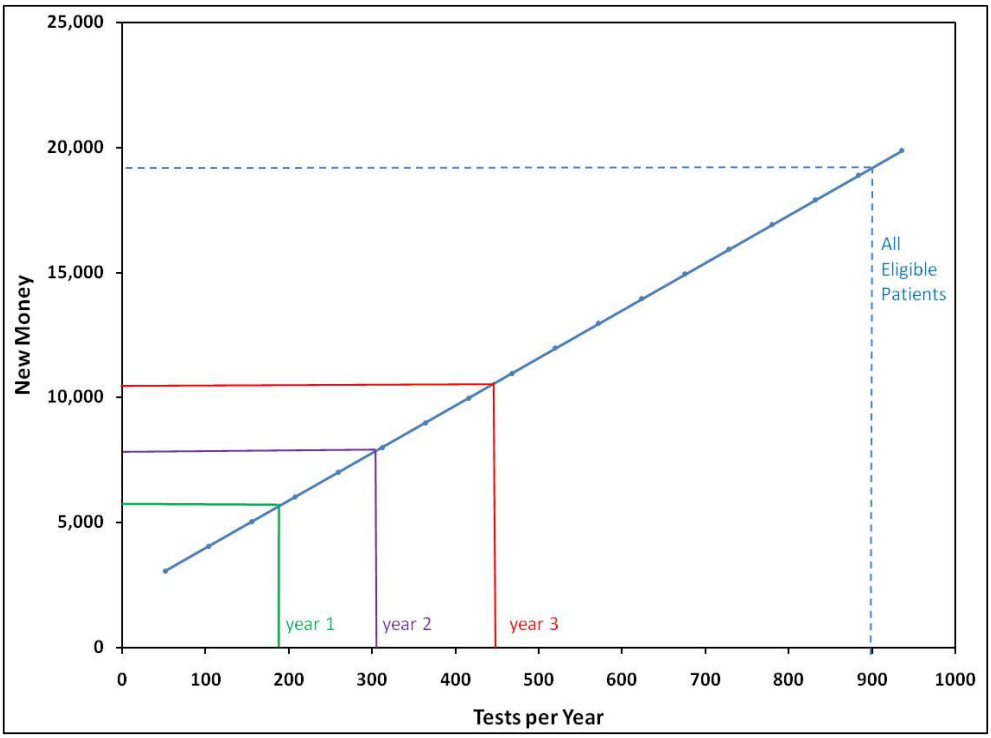

Figure 7: New Operation Money required for BC HLA-B genotyping based on projected demand.

7: HLA-B GENOTYPING FOR THE REST OF CANADA

7.1 Cost Analysis

Given the investment involved in developing a validated assay and the relative ease and practicality of integration of the work into the BC program, it makes sense to extend the HLA-B genotyping service to the rest of Canada. The objective would be to offer the service at a marginal profit in order to augment the British Columbian program. With the exception of Ontario, no other province has sufficient numbers of patients (Table 2) to justify development of its own program and therefore all are likely to be open to externally sourcing of this service. With respect to Ontario, there is precedent for outsourcing genotyping service as HIV resistance testing for that province has been performed at St Paul's hospital in Vancouver for over eight years. Thus, conditions may be favourable for the molecular testing laboratory at Children's and Women's hospital to become the national reference laboratory for HLA-B genotyping for carbamazepine sensitivity.

As phlebotomy and shipping cost would be borne by the originating province, it is only the laboratory expenses which are relevant to the consideration of the cost of providing HLA-B genotyping for the rest of Canada. As previously mentioned, costs are based on batch size, and therefore there are a number of scenarios that must be considered. In theory, the laboratory could be required to test as few as one non-BC sample per week or as many 32 for all the at - risk patients that are projected to newly initiate carbamazepine somewhere in the rest of Canada (Table 2). Thus the per sample

cost of providing HLA-B genotype testing for the rest of the country could conceivable fall between approximately $44 and $103 (Figure 8).

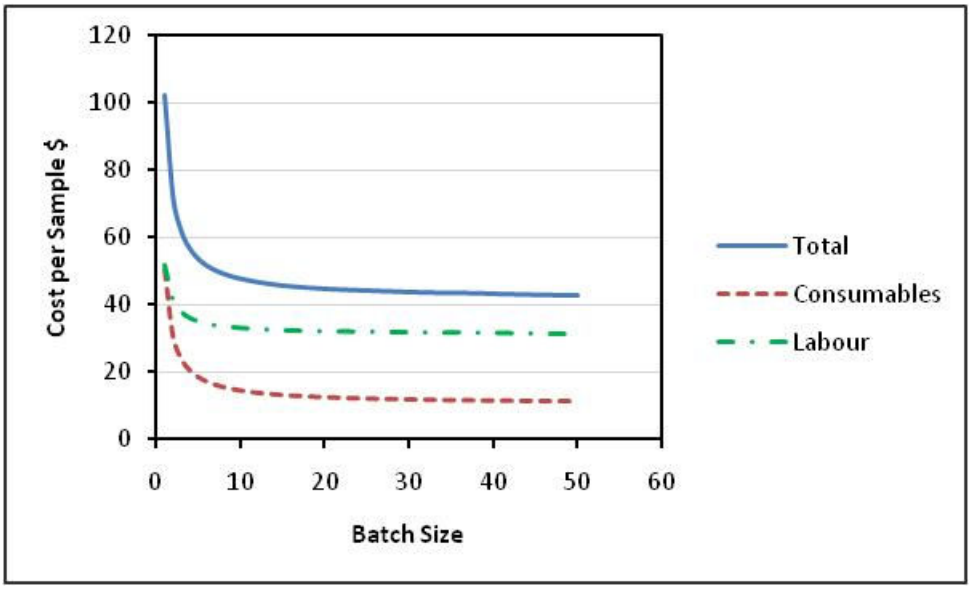

Figure 8: Changes in direct per-sample laboratory costs associated with HLA-B genotyping with increasing batch size.

7.2 Pricing

Cost analysis provides a reference point when considering pricing strategies for a new product or service; however, other factors also play an important role in the final decision. It is also necessary to consider the market and the price that it will accept, the competition and how they are likely to respond, the risk and the organizations tolerance of risk, and finally the organizational strategy and how the new offerings fit into that strategy. Each of these issues is discussed with respect to HLA-B genotyping for carbamazepine sensitivity.

To eliminate risk, the discussion of pricing for the genotyping service should begin at around $100 per test as this is the potential cost of a single test in the worst case scenario (i.e. one test per week). The ability to raise the price above this limit to generate

profit is then dependent upon what consumers are willing to accept. While the price of genetic tests can reach thousands of dollars, the most relevant comparable is probably HLA-B testing for abacavir sensitivity which is almost identical to the HLA-B test proposed here. In the United States, list prices for this test range from $70 to $150 (John Hopkins, 2008; United States Department of Veterans Affairs, 2008) which roughly translates to $80 to $175 in Canada. Thus, setting the price point above $100 is not inconsistent with market expectations. Indeed, relatively simple genetic tests for heritable disease list for approximately $250 per test in Canada (Childrens Hosptial of Eastern Ontario, 2007).

In a business such as this with low volumes and high fixed costs there is a strong inclination to maximize margins; however, there are good reasons to exercise restraint in setting the price for this test. First, the price should not be so high that it becomes prohibitive in the minds of physicians or health authorities in other parts of the country. Ambivalence about the value of the test and specimen shipping costs (*ca.* $40 from Toronto Ontario) may prove to be discouraging issues for other parts of the country and it may take lower pricing to compensate. Furthermore, a lower price will likely discourage other Canadian laboratories from developing the same service as there would be no profit in splitting the market. Also, prices should not deviate too far from those in the United States as the border between the two countries provides a negligible barrier to having the analysis done there. Thus keeping the price reasonably low maximizes the chances of achieving and maintaining a monopoly for this service in Canada which in theory will increase volumes and subsequently margins and profit. The risk in this strategy is if the expected volumes never materialize.

Maximizing price also has merit. In the event that demand does not meet expectations due to market indifference or unexpected competition, the laboratory could maximize profit. On the other hand, this strategy might create a self fulfilling scenario depending on the price elasticity of supply and demand. If higher prices encourage competition in the market and/or induce physicians to reserve the test only for their neediest patients, the laboratory would never be able to realize the economies of scale. In light of these concerns, two price points will be examined: $99 and $149.

Table 6 and Figure 9 show the potential gross profits that could be realized by the out-of-province genotype program under the two different pricing strategies. Three sales volume scenarios are examined. All things being equal, the higher price point yields more profit; however, because it has the potential to increase competition and decrease demand, there is the possibility that these increased profits will not be realized. It can be seen from Figure 9 that the profit advantage of the $149 price point would be lost if the demand dropped to half that of the lower priced model. Such a dramatic drop would more likely be associated with competitive entry into the market rather than a significant drop in subscription to the test because the price elasticity of demand among early adopters (i.e. those with vulnerable patients) is not expected to be great.

Based on the examination presented here, it is recommended that the price of the test be set at $99 per patient. This is not only consistent with comparable tests, but it would also allow the laboratory to achieve reasonable profits by encouraging demand, discouraging competition and increasing margins by leveraging the economies of scale. Importantly, profit under the medium term projected demand (10 tests per week) will be more than enough to subsidize the BC program. While aggressive, the lower price would

Table 6: Annual Gross profits based of sales volume and price.

	$99 per test			$149 per test		
	Worst Case[a]	Projected Case[b]	Best Case[c]	Worst Case[a]	Projected Case[b]	Best Case[c]
Annual Revenues	5,148	50,490	164,736	7,748	75,990	247,936
COGS[d]	5,330	24,774	72,431	5,330	24,774	72,431
Gross Profit	-182	25,716	92,305	2,418	51,216	175,505

a) One test per week b) 10 tests per week c) 32 tests per week d) Cost of Goods Sold

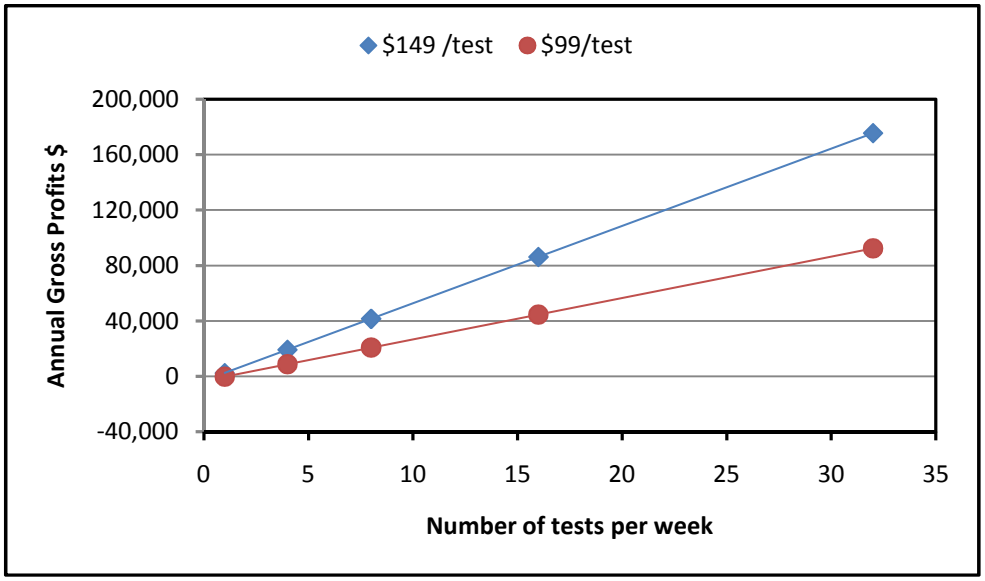

Figure 9: Annual gross profits by price point and sales volume

generate enough to cover all direct costs associated with providing this service under the worst case scenario (one test per week). Even under these circumstances the out-of-province program would still be subsidizing the BC program as the weekly costs of batch controls will be applied to the external patient sample.

Thus, even under the 'next to worst' circumstances (no external sales would be worse), the out-of-province genotyping program has a good potential to help pay for the

BC program while at the same time establishing the molecular genetics laboratory at Children's and Women's Hospital as a leader in the field of safety pharmacogenetics. If the lower pricing strategy is successful in cornering the Canadian market for this service, the laboratory will have succeeded in extending its reach and creating a place for itself in the consciousness of medical professionals across the country. This should make the introduction of future pharmacogenetic tests easier. This position would be lost if the laboratory were to lose some or all this work to other laboratories and it is the opinion of the author that the lower price strategy provides the best potential for meeting all of the laboratory's goals and objectives.

8: COMMERCIALIZATION PLAN

The public healthcare markets in Canada are similar to most other markets with the exception of the distance between vendors with new technologies and the ultimate payers. In this country, provincial health authorities hold the purse strings and they are well insulated from those with new products or services to sell. Funding decisions are usually based on a groundswell of support from the end users and therefore the key to successful commercialization of a new offering depends on convincing a critical mass of physicians of the value. In practice, this generally means convincing the majority of opinion leaders and ideally, achieving recommendation in treatment guidelines. As previously discussed, physicians need to be satisfied that the new technology provides a solution to a need that is as good as, or better than the alternatives and doesn't create more problems than it is worth.

The only sure way to gain acceptance for a new medical technology is to complete a prospective randomized clinical trial that demonstrates a significant improvement in outcomes when the technology is used to manage therapy versus when it is not. Unfortunately in the case of HLA-B genotyping for carbamazepine sensitivity, this cannot be accomplished in North America because there are simply not enough patients of Han Chinese descent to power such a study. At this time, professional acceptance of this test will have to depend on the results of the retrospective studies; however, there are those in the medical community who are intrinsically mistrustful of these types of studies because there is no assurance that the medical records (or the

interpretation thereof) used for these analyses are consistent or correct as the data was usually not collected with the study in mind.

Because of this potential controversy, and because it is a respected part of the medical community, the molecular diagnostic laboratory at Women's and Children's hospital will be restricted in its promotional efforts. It must be very cautious about appearing to be too profit motivated (in the rest of Canada) by pushing a test that the medical community is undecided about. Promotion will necessarily be limited to informing patients and physicians of the availability of the tests and making it as easy as possible to access; however, it would be in the best interest of the program if the laboratory were to align itself with an academic champion(s) of such testing and support any research efforts in which that/those individuals may be engaged.

8.1 Launching in BC

A potential timetable for launching the HLA-B genotyping program for carbamazepine sensitivity is given in Figure 10. It is recommended that the test be launched in British Columbia approximately three months prior to launch in the rest of the country. This will provide time to work out any operational issues and a chance to better understand the market for the test in an environment where there is no issue around payment. It will give a better idea of who is accessing the test and from where allowing for refinement of the communication plan when the test is launched in the rest of Canada. Also, it may serve to identify visionaries and champions outside the province as word of the availability of the test is almost certain to diffuse to other provinces during that time.

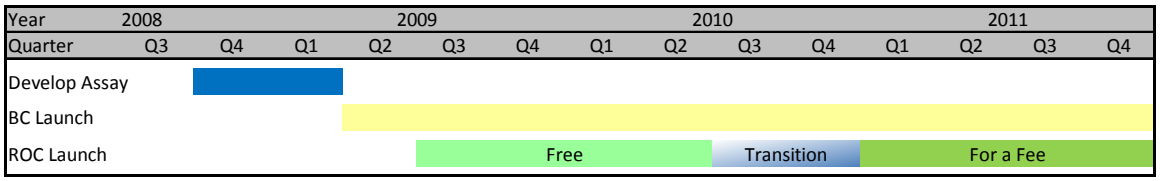

Figure 10: Proposed timetable for the role out of HLA-B genotyping testing in BC and the rest of Canada

It is estimated that the assay will take four months to develop assuming adequate commitment of resources and depending upon the availability of controls and standards. During the development period the laboratory can begin its marketing efforts by recruiting those in the neurological community who support the testing (if possible). Pre-announcing release of the test via channels selectively targeting neurologist (e.g. Neurology BC) may be enough to initiate debate and determine who is positioned on each side of the argument. Approximately one month prior to launch, a more general announcement should be made by exploiting the following channels (listed according to priority).

- **General mailing:** Informational packages including test description, order forms and specimen collection instruction should be delivered to all appropriate physicians (neurologists, GPs and psychiatrists) in the provinces as well as the Directors and Heads of Hospital Medical and Pharmacy Departments across the province.

- **Professional Societies:** Information packages should be distributed to all appropriate professional associations and societies in the province (BCMA, College of Physicians and Surgeons, Neurology BC, BC College of Family Physicians, College of Registered Nurses of BC, BC Pharmacy Society etc.).

If possible, the laboratory should get this information in newsletters distributed by these organizations.

- **Patient Advocacy Groups:** Multilingual Information packages should be distributed to the appropriate patient advocacy groups in the province (BC Epilepsy Society, Mood Disorders Association of BC, etc).

Once the program is up and running, the following communications channels should be utilized to maintain awareness and advance the debate. In order of decreasing priority:

- **Scientific/Medical Presentations and Publications:** Ideally this program should be launched in association with a research program (e.g. prevalence of the HLA-B*1502 genotype, genetic determinants of SJS/TEN within the drug class, physician response to test results etc.) spearheaded by a credible member of the academic medical/scientific community who is willing to champion the test. Publication/presentation of the results of these studies will serve to maintain positive public exposure for the laboratory and the program. Leverage within the medical and scientific communities is dependent on research programs and without some sort of ongoing exposure in these channels, the laboratory will fail to establish itself leader in safety pharmacogenetics.

- **Continuing Medical Education (CME):** If possible, champions of the test should attempt to influence associated CME events and publications such that the regulatory recommendations for the tests continue to be presented around the discussion of carbamazepine.

- **Media:** If possible, the laboratory should employ the local media to reinforce the message (BC CTV, Vancouver Sun, Fairchild TV). Although this is not the first program of its kind in Canada, pharmacogenetics is a relatively new field and the local media generally repeat these stories about once a year. This channel is not necessarily useful to reach physicians but will assure that the contributions of the laboratory are reinforced in the minds of the government and health authorities.

8.2 Launching in the rest of Canada

When the test is released to the rest of Canada, there will be no public money to pay for the test and it can be a very long road to getting a new technology on the reimbursement schedules of the provincial health insurance plans. It almost always begins with the recruitment of a few visionaries who champion the offerings first to the profession, and then the authorities. During this process, vendors often must supply goods and service for free in order to support the efforts of their champions. For drugs and commercial diagnostic products, the process begins during clinical trials – well before they make it to market. Even if approved by Health Canada, provincial authorities often insist on additional studies to determine how new technologies best fit into existing healthcare services. In order to expedite the process, the laboratory will likely have to provide free HLA-B genotyping for carbamazepine sensitivity for a period of 12 to 18 months.

The initial release of the test in the rest of Canada should be a more muted process than BC. Introduction should focus on both Provincial and National professional societies (Canadian Medical Association, The Association of Ontario Neurologists, etc)

and patient advocacy groups (Epilepsy Canada, Epilepsy Ontario etc) with more direct efforts concentrated on centres with large Asian populations. Initial mailings should be targeted towards neurologist and GPs practicing in large Asian catchment areas of Toronto and neurologists in Montreal, Edmonton, Calgary and Ottawa.

Extra attention should be focused on Toronto. Prior to launch, the laboratory should work with public and private blood collection facilities in the city and/or the province to establish systems to expedite delivery of specimens to the laboratory in Vancouver. This has already been done for HIV resistance testing and the laboratory may be able to model the approach taken there. In addition, accelerating the delivery of results by setting up electronic reporting systems would likely increase satisfaction with the test. By concentrating on the Toronto area, the laboratory will be assuring familiarity with the test among practitioners serving the largest Asian community in the country. Awareness of the test is sure to diffuse out from there as communications channels in the medical community are extraordinarily efficient and ideal for viral marketing. Word of the test should spread readily and early adopters outside the Toronto area will be able to access the laboratory and the test via colleagues, the internet or by directly contacting the laboratory.

Importantly, the initial announcements should clearly indicate that the testing service will be provided for free for a limited time. Free testing is a fundamental part of the business development plan; however, the laboratory must press the issue of reimbursement at no later than eight months after launch. To do this, it should provide four months notice of termination of the free service but be prepared to continue providing free access for as much of as eight months. This will force physician that have

come to rely on the test to lobby their provincial or regional health authorities for funding; although these efforts are likely to take more than four months.

The transition from free to for fee provision of HLA-B genotyping will require some finesse because every province must allocate and approve funding. Most marketing efforts will be focussed on Toronto but it is assumed that practitioners in other jurisdictions will be seeking out and utilize the test during the free trial period; however, they likely to be behind in the process of securing funding. Provincial approval of funding is likely to be staggered and it will be difficult to sustain a situation where one province is receiving the service for free while others are paying. Once the first province signs on there should be a six month limit to the withdrawal of free services for the rest of the country.

Finally, the program should be launched in association with a champion in the research community and/or as part of a research initiative if possible. Having a credible advocate increases the chances that the test will gain wide scale adoption ultimately receive public funding in other provinces.

8.3 Financial requirements

The strategy for launch of HLA-B genotyping for carbamazepine therapy will require significant funds for business development. For example, approximately $17,000 will be required over a period of 18 months to provide free access to the service in other provinces while physicians in those jurisdictions secure funding. In addition, approximately $23,000 more will be needed for activities such as preparing guidelines for clinical application of the test and for direct mailings for physicians across the country.

These figures also include $10,000 over a two year period to cover travel expenses to various parts of the country for purposes such as educating physicians, coordinating shipping logistics, presenting research results or alternatively hosting associated researchers. With these and the other expenses previously discussed (start-up and operations of the BC program), the program is not expected to see a profit until the second quarter of 2011. The annual financial outlook based on the timetable presented in Figure 10 is provided in Table 7.

Table 7: Four year projected financial outlook for HLA-B genotyping program for carbamazepine sensitivity

Year	2009	2010	2011	2012
Sales[a]			29,452	50,488
COGS	2,275	10,728	17,541	22,896
Gross Profit	-2,275	-10,728	11,911	27,592
Operations				
Assay & Systems Development[b]	-5,000			
BC Program[c]	-2,970	-4,444	-5,631	-5,852
Business Development				
Preparation of guidelines[d]	-2,500			
Direct Mailings[e]	-8,000			
Travel[f]	-5,000	-5,000		
Balance	-25,745	-20,172	6,152	21,740

Notes for Table 7

a) Based on projected demand in the rest of Canada (Table 4) and proposed timetable in Figure 10.

b) *ca.* estimated costs of acquiring controls, standards and developing the assay and databases for data tracking and report generation.

c) Based on projected demand for BC (Table 4) and proposed timetable in Figure 10.

d) For the preparations of guidelines for utilization of the test – based on an estimated 10 hours work for a neurologist(s) at $250 per hour.

e) Estimated direct mailing costs to 5,000 general practitioners and 650 psychiatrist in BC and 770 neurologists nationwide.

f) Contingency funds for travel for the purposes of business development (presentation of program or research results, logistical arrangements etc.).

9: RISK AND OPPPORTUNITIES

9.1 Risk

While the analysis presented here predicts a moderate revenue stream from an HLA-B genotyping program for carbamazepine therapy, it has included numerous estimates and assumptions based on the best available information at this time. Variables such as demand or competitive responses to the introduction of this test cannot be guaranteed and can change due to unforeseen circumstances. Therefore all such analyses contain inherent risks that must be taken into account. Such risks associated with the initiation of a provincial and nation-wide program of HLA-B genotyping for carbamazepine sensitivity are detailed and qualitatively assessed with respect to probability and impact in Table 8.

Table 8: Risks associated with the initiation of HLA-B genotyping for carbamazepine sensitivity

Risk	Comments	Estimated Probability[a]	Estimated Impact[a]
No Demand in BC	- Investment of $14,000 for a test nobody wants.	low	low
Underestimate of the Demand in BC	- The rate and extent of utilization of the test could be greater than projected - maximum operating requirements of *ca.* $20,000 starting in the first year	moderate	low
No Demand from ROC	- Investment of $5,000 - No subsidy for BC Program	moderate	low
Less demand in ROC or competition	- Reduces or eliminates extra-provincial work and subsidy for BC program - At least 9 laboratory is the country have the capabilities to offer these services - lowers laboratories profile in Canada	moderate	low

a) Judgement based estimates.

9.2 Opportunities

In addition to the risk, involvement in a safety pharmacogenetics program such as this presents some potential opportunities. Table 9 list some of the opportunities. In many cases the probability and/or impact of these opportunities cannot be judged with confidence because not enough is known about these potentials; however the ideas presented in this table should serve as a starting point for further research.

Table 9: Opportunities associated with the initiation of HLA-B genotyping for carbamazepine sensitivity

Opportunities	Comments	Estimated Probability[a]	Estimated Impact[a]
Demand from the United State	- Over 4.5 million people of Asian descent living on the Pacific Coast of the US (US Census Bureau, 2006) which suggest a greater market than all of Canada - would require CLIA and CAP certification to serve this region	moderate	unknown
Demand for Other Drugs	- The same HLA-B polymorphism has been implicated in SJS/TEN cases associated with phenytoin and lamotrigine use (Man CBL, 2007) - requires confirmation	unknown	unknown
Cost reduction for ROC by switching to buccal swabs or blood spots	- Technology is available for automated isolation of DNA from these types of specimens - may require a change in clinical protocols for neurologists.	moderate	low
Future Collaborations	- superior service and research presentation have the potential to attract collaborators on future genotyping testing studies	moderate	moderate

a) Judgement based estimates

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9.3 Conclusion

Although there are clear financial risks associated with initiating a genotyping program for carbamazepine sensitivity, these are relatively minor and the potential benefit is much greater. In addition to making life safer for patients in British Columbia, the laboratory has the opportunity to help patients in the rest of the country as well while realizing a modest profit at the same time. The intangible benefits of this are invaluable. Such a program would provide the laboratory with an opportunity to extend its reach and develop networks in the medical community which do not currently exist. This would almost certainly lead to other commercial and research opportunities as the laboratory gained a reputation in these circles.

Importantly, realizing the benefits of the program will require a certain degree of commitment on the part of the leaders. Marketing considerations should be at least as important as the science/research; although, the two are inextricably linked. While associating the service with the strong research program of the Canadian Pharmacogenomics Network for Drug Safety is probably the strongest marketing strategy of all, the laboratory must remain attentive to its message and continuously exploit all available channels to keep the story alive. In addition, the laboratory should strive to pursue all future opportunities in pharmacogenetic services. HLA-B testing for carbamazepine sensitivity is meant to be only the beginning and the laboratory must be vigilant in searching for the next big opportunity if it wants to establish and maintain a position as a major leader in safety pharmacogenetics.

10: APPENDICES

Appendix A

Objective

The objective was to identify patients newly administered the chemical Carbamazepine.

This was done separately according to region, age and gender.

Study Period

January 1st, 2003 through December 31st, 2007

Data Source

The data is extracted from the Brogan Inc. Private Drug Plan Database.

Methodology

New to chemical patients were those who did not show a claim for Carbamazepine in the year prior to their first claim in the study period.

Patients are unique according to age, gender and province.

New to Chemical Carbamazepine Patients

Year	Province	Age	Gender	Chemical	Claimants
2003	AB	<19	F	Carbamazepine	96
2003	AB	<19	M	Carbamazepine	93
2003	AB	19+	F	Carbamazepine	1,448

Year	Province	Age	Gender	Chemical	Claimants
2003	AB	19+	M	Carbamazepine	1,109
2003	BC	<19	F	Carbamazepine	61
2003	BC	<19	M	Carbamazepine	66
2003	BC	19+	F	Carbamazepine	1,455
2003	BC	19+	M	Carbamazepine	1,064
2003	East	<19	F	Carbamazepine	47
2003	East	<19	M	Carbamazepine	48
2003	East	19+	F	Carbamazepine	1,541
2003	East	19+	M	Carbamazepine	1,048
2003	MB	<19	F	Carbamazepine	11
2003	MB	<19	M	Carbamazepine	10
2003	MB	19+	F	Carbamazepine	241
2003	MB	19+	M	Carbamazepine	228
2003	ON	<19	F	Carbamazepine	361
2003	ON	<19	M	Carbamazepine	408
2003	ON	19+	F	Carbamazepine	6,783
2003	ON	19+	M	Carbamazepine	5,058
2003	QC	<19	F	Carbamazepine	81
2003	QC	<19	M	Carbamazepine	83
2003	QC	19+	F	Carbamazepine	1,383
2003	QC	19+	M	Carbamazepine	1,331
2003	SK	<19	F	Carbamazepine	10
2003	SK	<19	M	Carbamazepine	18
2003	SK	19+	F	Carbamazepine	390
2003	SK	19+	M	Carbamazepine	288
2004	AB	<19	F	Carbamazepine	62
2004	AB	<19	M	Carbamazepine	84
2004	AB	19+	F	Carbamazepine	1,156
2004	AB	19+	M	Carbamazepine	1,050
2004	BC	<19	F	Carbamazepine	39
2004	BC	<19	M	Carbamazepine	43
2004	BC	19+	F	Carbamazepine	1,113
2004	BC	19+	M	Carbamazepine	877
2004	East	<19	F	Carbamazepine	50
2004	East	<19	M	Carbamazepine	44
2004	East	19+	F	Carbamazepine	1,558
2004	East	19+	M	Carbamazepine	1,108
2004	MB	<19	F	Carbamazepine	11
2004	MB	<19	M	Carbamazepine	16
2004	MB	19+	F	Carbamazepine	209
2004	MB	19+	M	Carbamazepine	174

Year	Province	Age	Gender	Chemical	Claimants
2004	ON	<19	F	Carbamazepine	353
2004	ON	<19	M	Carbamazepine	410
2004	ON	19+	F	Carbamazepine	7,233
2004	ON	19+	M	Carbamazepine	5,290
2004	QC	<19	F	Carbamazepine	57
2004	QC	<19	M	Carbamazepine	103
2004	QC	19+	F	Carbamazepine	1,341
2004	QC	19+	M	Carbamazepine	1,187
2004	SK	<19	F	Carbamazepine	15
2004	SK	<19	M	Carbamazepine	17
2004	SK	19+	F	Carbamazepine	407
2004	SK	19+	M	Carbamazepine	323
2005	AB	<19	F	Carbamazepine	59
2005	AB	<19	M	Carbamazepine	82
2005	AB	19+	F	Carbamazepine	1,259
2005	AB	19+	M	Carbamazepine	966
2005	BC	<19	F	Carbamazepine	51
2005	BC	<19	M	Carbamazepine	46
2005	BC	19+	F	Carbamazepine	1,175
2005	BC	19+	M	Carbamazepine	930
2005	East	<19	F	Carbamazepine	34
2005	East	<19	M	Carbamazepine	41
2005	East	19+	F	Carbamazepine	1,334
2005	East	19+	M	Carbamazepine	985
2005	MB	<19	F	Carbamazepine	9
2005	MB	<19	M	Carbamazepine	19
2005	MB	19+	F	Carbamazepine	261
2005	MB	19+	M	Carbamazepine	173
2005	ON	<19	F	Carbamazepine	343
2005	ON	<19	M	Carbamazepine	379
2005	ON	19+	F	Carbamazepine	6,663
2005	ON	19+	M	Carbamazepine	4,941
2005	QC	<19	F	Carbamazepine	60
2005	QC	<19	M	Carbamazepine	68
2005	QC	19+	F	Carbamazepine	1,202
2005	QC	19+	M	Carbamazepine	1,234
2005	SK	<19	F	Carbamazepine	11
2005	SK	<19	M	Carbamazepine	17
2005	SK	19+	F	Carbamazepine	437
2005	SK	19+	M	Carbamazepine	307
2006	AB	<19	F	Carbamazepine	65

Year	Province	Age	Gender	Chemical	Claimants
2006	AB	<19	M	Carbamazepine	82
2006	AB	19+	F	Carbamazepine	1,237
2006	AB	19+	M	Carbamazepine	1,178
2006	BC	<19	F	Carbamazepine	47
2006	BC	<19	M	Carbamazepine	40
2006	BC	19+	F	Carbamazepine	1,193
2006	BC	19+	M	Carbamazepine	938
2006	East	<19	F	Carbamazepine	49
2006	East	<19	M	Carbamazepine	38
2006	East	19+	F	Carbamazepine	1,581
2006	East	19+	M	Carbamazepine	1,080
2006	MB	<19	F	Carbamazepine	28
2006	MB	<19	M	Carbamazepine	15
2006	MB	19+	F	Carbamazepine	246
2006	MB	19+	M	Carbamazepine	167
2006	ON	<19	F	Carbamazepine	303
2006	ON	<19	M	Carbamazepine	347
2006	ON	19+	F	Carbamazepine	6,021
2006	ON	19+	M	Carbamazepine	4,429
2006	QC	<19	F	Carbamazepine	59
2006	QC	<19	M	Carbamazepine	69
2006	QC	19+	F	Carbamazepine	1,181
2006	QC	19+	M	Carbamazepine	1,159
2006	SK	<19	F	Carbamazepine	16
2006	SK	<19	M	Carbamazepine	16
2006	SK	19+	F	Carbamazepine	362
2006	SK	19+	M	Carbamazepine	282
2007	AB	<19	F	Carbamazepine	75
2007	AB	<19	M	Carbamazepine	78
2007	AB	19+	F	Carbamazepine	1,267
2007	AB	19+	M	Carbamazepine	992
2007	BC	<19	F	Carbamazepine	52
2007	BC	<19	M	Carbamazepine	50
2007	BC	19+	F	Carbamazepine	1,438
2007	BC	19+	M	Carbamazepine	1,052
2007	East	<19	F	Carbamazepine	27
2007	East	<19	M	Carbamazepine	38
2007	East	19+	F	Carbamazepine	1,251
2007	East	19+	M	Carbamazepine	916
2007	MB	<19	F	Carbamazepine	10
2007	MB	<19	M	Carbamazepine	12

Year	Province	Age	Gender	Chemical	Claimants
2007	MB	19+	F	Carbamazepine	250
2007	MB	19+	M	Carbamazepine	180
2007	ON	<19	F	Carbamazepine	322
2007	ON	<19	M	Carbamazepine	337
2007	ON	19+	F	Carbamazepine	5,804
2007	ON	19+	M	Carbamazepine	4,321
2007	QC	<19	F	Carbamazepine	82
2007	QC	<19	M	Carbamazepine	83
2007	QC	19+	F	Carbamazepine	1,246
2007	QC	19+	M	Carbamazepine	1,139
2007	SK	<19	F	Carbamazepine	13
2007	SK	<19	M	Carbamazepine	15
2007	SK	19+	F	Carbamazepine	375
2007	SK	19+	M	Carbamazepine	261

Overall rates of capture for the Brogan Inc. private drug plan data by province are shown below. Data presented in this report has not been extrapolated based on the reported capture rates.

Province	Capture Rate
British Columbia	33%
Alberta	37%
Saskatchewan	52%
Manitoba	32%
Ontario	84%
Quebec	73%
Nova Scotia	83%
Newfoundland	69%
New Brunswick	77%
Prince Edward Island	64%

Appendix B

Ethnic Population Breakdown by Province (Satisitcs Canada, 2008)**.**

	BC	Alb	Sask	Man	Ont	Quebec	NS	NB	NF	PEI	Canada
Total Population	4,074,385	3,256,355	953,850	1,133,510	12,028,895	7,435,905	903,090	719,650	500,610	134,205	31,241,030
Chinese	432,435	137,600	11,100	17,930	644,465	91,900	5,140	2,895	1,650	300	1,346,510
Filipino	94,250	54,305	4,160	39,205	215,750	25,680	7,709	620	340	25	436,190
Indonesian	4,640	1,980	180	355	6,325	645	130	45	0	15	14,320
Malaysian	3,860	1,740	120	255	5,525	525	60	35	20	0	12,165
Thai	2,410	1,130	255	285	4,075	1,680	45	85	25	0	10,015
Singaporean	550	145	0	10	650	40	0	0	0	0	1,390
Asian‡	130	75	20	10	210	65	35	10	0	0	555
West Asian‡	1,525	865	100	205	7,440	1,715	160	45	25	0	12,080
East or Southeast Asian‡	1,430	930	50	220	5,045	1,245	25	15	10	10	8,990
South Asian‡	7,915	2,830	175	420	45,675	3,520	140	140	50	0	60,895

REFERENCES

Alfirevic A, J. A. (2006). HLA-B Locus in Caucasian Patients with Carbamazepine Hypersensitivity. *Pharmacogenomics , 7* (6), 813-8818.

Alfirevic, A., & Pirmohamed, M. (2008). Adverse Drug Reactions and Pharmacogenetics: Recent Advances. *Personalized Medicine , 5* (1), 11-23.

Alfirevic, A., Jorgensen, A. L., Williamson, P. R., Chadwick, D. W., Park, B. K., & Pirmohamed M, M. (2006). HLA-B Locus in Caucasian Patients with Carbamazepine Hypersensitivity. *Pharmacogenomics , 7* (6), 813-8818.

American Association for Clinical Chemistry. (2008). Retrieved August 30, 2008, from Lab Tests Online.

Arboleda-Florez, J. (2005). *The epidemiology of Mental Illness in Canada.* Retrieved August 23, 2008, from Canadian Public Policy - Analyses de Politiques: http://economics.ca/cgi/jab?journal=cpp&view=v31s1/CPPv31s1p013.pdf

Bass, F. M. (1969). A New Product Growth Model for Consumer Durables. *Management Science , 15* (5), 215-227.

Boone, D. J. (2004). Is it safe to have a laboratory test? *Accreditation and Quality Assurance , 10* (1-2), 5-9.

British Columbia Provincial Laboratory Coordinating Office. (2005). *B.C.'s Current Laboratory System*. Retrieved August 30, 2008, from British Columbia Provincial Laboratory Coordinating Office: http://www.plco.ca/services2.html

Bussey HI, W. A. (2008). Genetic Testing for Warfarin Dosing? Not Yet Ready for Prime Time. *Pharmacotherapy , 28* (2), 141-143.

Canadian Institute of Health Information. (2008). *The Cost of Acute Care Hospital Stays by Medical Condition in Canada, 2003 – 2005 Appendix C.* Ottawa: CIHI.

Canadian Medical Association. (2008, January). *Statistical information on Canadian physicians* . Retrieved August 10, 2008, from Number of Physicians by Province/Territory and Specialty, Canada, 2008: http://www.cma.ca/multimedia/CMA/Content_Images/Inside_cma/Statistics/01SpecProv.pdf

Canadian Pharmacists Association. (2004). *Canadian Pharmacists Association Compendium of Pharmaceuticals and Specialties.*

Centers for Disease Control and Prevention. (1995, March). *Guidelines for the Shipment of Dried Blood Spot Specimens*. Retrieved July 31, 2008, from http://www.cdc.gov/od/ohs/biosfty/driblood.htm

Children's Hospital of Eastern Ontario. (2007). *Programs & Services: Genetics*. Retrieved July 31, 2008, from Laboratory Services: Molecular Genetics Diagnostic Laboratory: http://www.cheo.on.ca/english/8000_genetics_molec.shtml

Childrens Hosptial of Eastern Ontario. (2007, April 7). *Programs & Services – Genetics*. Retrieved August 16, 2008, from Childrens Hosptial of Eastern Ontario: http://www.cheo.on.ca/english/8000_genetics_molec.shtml

Chung, W.-H., Hung, S.-I., Hong, H.-S., Hsih, M.-S., & Yang, L.-C. (2004). A marker for Stevens-Johnson Syndrome. *428*, 486.

College of American Pathologists. (2007). *Commission on Laboratory Accreditation: Molecular Pathology Checklist.* College of American Pathologists.

Corkindale, D., Ward, H., & McKinnon, R. (2007). Low adoption of pharmacogenetic testing: an exploration and explanation of reasons in Australia. *Personalized Medicine , 4* (2), 191-199.

Depondt, C. (2008). Pharmacogenetics in Epilepsy Treatment: Sense or Nonsense? *Personalized Medicine , 5* (2), 123-131.

Doig, A. R. (2007, February 1). *Molecular Diagnostics Market Assessment.* Retrieved August 08, 2008, from Genetic Engineering & Biotechnology News: http://www.genengnews.com/articles/chitem.aspx?aid=2006&chid=4

Eichelbamum M, I.-S. M. (2006). Pharmacogenomics and individualized drug therapy. *Annu Rev Med , 57*, 119-127.

Epilepsy Canada. (2008). *Epilepsy Facts*. Retrieved July 23, 2008, from http://www.epilepsy.ca/eng/mainSet.html

Epilepsy Canada. (2005). *Types of Seizures*. Retrieved July 23, 2008, from http://www.epilepsy.ca/eng/mainSet.html

Epilepsy.com. (2004, Feb 27). *Mental Handicap & Cerebral Palsy*. Retrieved Aug 16, 2008, from http://www.epilepsy.com/info/family_kids_cpalsey

Freeman, B. (2003). *The Ultimate Guide to Choosing a Medical Specialty* . New York: Lange Medical Books/McGraw-Hill.

Genome British Columbia. (2008). *Research Projects*. Retrieved September 1, 2008, from Genome British Columbia: http://www.genomebc.ca/genomics_programs/research_projects/tpah/drug_safety.htm

Ghislain P-D, R. J.-C. (2008). Treatment of severe drug reactions: Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis and Hypersensitivity syndrome. *Dermatology Online Journal , 8* (1).

Goodwin, G. M. (2003). Evidence-based guidelines for treating bipolar disorder: recommendations from the British Association for Psychopharmacology. *Journal of Psychopharmacology , 17* (2), 149 - 173.

Haga SB, B. W. (2008). Pharmacogenetic testing: not as simple as it seems. *Genet Med , 10* (6), 391-395.

Hall, G. C., Carroll, D., Parry, D., & McQuay, H. J. (2006). Epidemiology and treatment of neuropathic pain: The UK primary care perspective. *Pain , 122*, 156-162.

Harvard University. (2002). *Shipping Biological Material*. Retrieved Aug 1, 2008, from http://research.dfci.harvard.edu/ehs/Biosafety/2002-ship.pdf

Health Canada. (2008, March 20). *Patients of Asian Ancestry using Epilepsy Drug Carbamazepine may be at Increased Risk of Serious Skin Reactions.* Retrieved July 23, 2008, from http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2008/2008_48-eng.php

Healthcommunities.com. (2008, April 14). *mentalhealthchannel*. Retrieved Aug 10, 2008, from Biopolar Disorder (Manic Depression): http://www.mentalhealthchannel.net/bipolar/index.shtml

Hopkins, M. M., Ibarreta, D., Gaisser, S., Enzing, C. M., Ryan, J., Martin, P. A., et al. (2006). Putting pharmacogenetics into practice. *Nature Biotechnology , 24* (4), 403 410.

Human Genome Program. (2008, July 24). *Human Genome Project Information*. Retrieved August 10, 2008, from Home Page: http://www.ornl.gov/sci/techresources/Human_Genome/home.shtml

Human Genome Project. (2008, August 27). *How Many Genes Are in the Human Genome?* . Retrieved August 30, 2008, from Human Genome Project Information: http://www.ornl.gov/sci/techresources/Human_Genome/faq/genenumber.shtml

Hung, S.-I., Chung, W.-H., & Chen, Y.-T. (2005). HLA-B Genotyping to detect carbamazepine induced Steven's Johnson Syndrome: implications for personalizing medicine. *Personalized Medicine , 2* (3), 225-237.

Ingelman-Sundberg, M. (2008). Pharmacogenetic Biomarkers for Prediction of Severe Adverse Drug Reactions. *New England Journal of Medicine , 358* (6), 637-639.

Ivanova, N. V., DeWaard, J. R., & Herber, P. D. (2006). An inexpensive, automation-friendly protocol for recovering high-quality DNA. *Molecular Ecology Notes , 6* (4), 998-1001.

John Hopkins. (2008, Jul 23). *HIV Guide*. Retrieved Aug 10, 2008, from Abacavir: http://www.hopkins-hivguide.org/drug/antiretrovirals/nucleoside_analog/abacavir__abc_.html

Kagan RJ, E. L. (2007). DRG 272: Does it Provide Adequate Burn Centre Reimbursement for the Car of Patients with Stevens – Johnson Syndrome and Toxic Epidermal Necrolysis? *J. of Burn Care & Research , 28* (5), 669 - 674.

Kane MD, S. J. (2008). Drug safety assurance through clinical genotyping: near-term considerations for a system-wide implimentation of personalized medicine. *Personalized Medicine , 5* (4), 387-397.

Kanner, A. M. (2007). Epilepsy and mood disorders. *Epilepsia , 48* (s9), 20-22.

Katusic S, B. C. (1990). Incidence and clinical features of trigeminal neuralgia, Rochester, Minnesota, 1945–1984. *Ann Neurol , 27*, 89–95.

Katusic, S., Beard, C. M., Bergstralh, E., & Kurland, L. T. (1990). Incidence and Clinical Features of Trigeminal Neuralgia, Rochester, Minnesota, 1945-1984. *Annals of Neurology , 27* (1), 89-95.

Kennedy N, M. R. (2005). Do we know the clinical course and epidemiology? In S. K. McDonald C, *Bipolar Disorder: The Upswing in Research and Treatment.* New York: Tohen M. Taylor & Francis.

Knoester PD, B. S. (2004). Diffusion of the new antiepileptic drug lamotrigine. *60*, 751-758.

Laboratory Corporation of America Holdings Inc. (2007). *2007 Annual Report.* Burlington NC.

Laboratory Corporation of America® Holdings and Lexi-Comp Inc. (2007). *HLA B*1502 Carbamazepine Sensitivity*. Retrieved July 31, 2008, from http://www.labcorp.com/datasets/labcorp/html/chapter/mono/nf10015120.htm

Lazarou J, P. B. (1998). Incidence of Adverse Drug Reactions in Hospitalized Patients: A Meta-analysis of Prospective Studies. *JAMA , 279*, 1200 - 1205.

Lonjou C, T. L. (2006). Lonjou C, Thomas L, Borot N, Ledger N, de Toma C, LeLouet H, Graf E, Schumacher M, Hovnanian A, MockenhA Market for Stenens-Johnson Syndrome ... Ethnicity Matters. *Pharmacogenomics , 6*, 265-268.

Lonjou, C., Thomas, L., Borot, N., Ledger, N., de Toma, C., LeLouet, H., et al. (2006). Marker for Steven's-Johnson Syndrome ... Ethnicity Matters. *Pharmacogenomics , 6*, 265-268.

Man CBL, K. P. (2007). Association between HLA-B*1502 Allele and Antiepileptic Drug-Induced Cutaneous Reactions in Han Chinese. *Epilepsia , 48* (5), 1015-1018.

Martin, P. A., Lewis, G., Smart, A., & Webster, A. (2006). *False Positive? Prospects for the Clinical and Commercial Development of Pharmacogenetics.* University of Nottingham/University of York.

Mittmann N, K. S. (2004). Evaluation of the Extent of Under-Reporting of Serious Adverse Drug Reactions: The Case of Toxic Epidermal Necrolysis. *27* (7), 477-487.

Mockenhaupt M, M. J. (2000). Mockenhaupt MRisk of Steven-Johnsom Symdrome and Toxic Epidermal Necrolysis in New users of Antiepileptics. (64), pp. 1134-1138.

Moore, G. A. (2006). *Crossing the Chasm: Marketing and Selling Disruptive Products to Mainstream Customers Revised Edition.* New York: HarperCollins Publishers.

National Institutes of Health. (2008). *International Clinic Directory Search*. Retrieved August 15, 2008, from GeneTest: http://www.geneclinics.org/servlet/access?id=8888891&country_id=201&submit=+++Search+++&submit=Clinic&prg=j&db=genetests&fcn=clinicsearch_intl_details&key=EkjeYeDaE89Rp

Porter, M. E. (1980). *Competitive Strategy: Techniques for Analyzing Industry and Competitors.* New York: Free Press.

Quest Diagnostics. (2007). *2007 Annual Report.* Madison NJ.

Sach, G. S., Printz, D. J., Kahn, D. A., Carpenter, D., & Docherty, J. P. (2000, April). *The Expert Consensus Guideline Series: Medication Treatment of Bipolar Disorder.*

Retrieved June 21, 2008, from Expert Consensus Guidelines/Expert Knowledge Systems: http://www.psychguides.com/Bipolar_2000.pdf

Sannes, L. J. (2008, January 15). *Biomarket Trends: Molecular Diagnostics on the Move.* Retrieved August 8, 2008, from Genetic Engineering & Biotechnology News: http://www.genengnews.com/articles/chitem.aspx?aid=2330&chid=0

Satisitcs Canada. (2008, Feb 04). *Ethnic origins, 2006 counts, for Canada, provinces and territories - 20% sample data.* Retrieved July 23, 2008, from Ethocultural Portrait of Canada: http://www12.statcan.ca/english/census06/data/highlights/ethnic/pages/Page.cfm?Lang=E&Geo=PR&Code=59&Table=2&Data=Count&StartRec=1&Sort=3&Display=All

SchafferA, C. J. (2006). Community Survey of Bipolar Disorder in Canada: Lifetime Prevalence and Illness Characteristics. *Can J Psychiatry , 51* (1), 9-16.

Sharovon, S. D. (2000). *Handbook of Epilepsy Treatment.* Boston: Blackwell Publishing.

Shorvon, S. D., Fish, D., Perucca, E., & Dodson, W. E. (2004). *The treatment of epilepsy* (2nd Edition ed.). Boston: Blackwelll Publishing.

Statistics Canada. (2008, Mar 2). *2006 Census Data*. Retrieved Aug 10, 2008, from Ethnocultural Portrait of Canada: http://www12.statcan.ca/english/census06/data/highlights/ethnic/pages/Page.cfm?Lang=E&Geo=CMA&Code=01&Table=1&Data=Count&StartRec=1&Sort=9&Display=Page&CSDFilter=5000

Steingberg, K., Beck, J., Nickerson, D., Garcia-Closas, M., Gallagher, M., Caggana, M., et al. (2002). DNA Banking for Epidemiological Studies: A review of current practices. *Epidemiology , 13* (3), 246-254.

Tennis P, S. R. (1997). Risk of serious cutaneous disorders after initiation of use of phenytoin, carbamazepine, or sodium valproate: A record linkage study. *49*, pp. 542-546.

Theodore, W. H., Spencer, S. S., Wiebe, S., Langfitt, J. T., Ali, A., Shafer, P. O., et al. (2006). Epilepsy in North America: A Report Prepared under the Auspices of the Global Campaign against Epilepsy, the International Bureau for Epilepsy, the International League Against Epilepsy, and the World Health Organization. *Epilepsia , 27* (10), 1700-1722.

Tsiropoulos B, G. A. (2006). Trends in utilization of antiepileptic drugs in Denmark. *Acta Neurol Scand , 113*, 405-411.

United States Department of Veterans Affairs. (2008, July 25). *National HIV/AIDS Program*. Retrieved August 13, 2008, from HLA-B*5701 Testing in Abacavir Patients: http://www.hiv.va.gov/vahiv?page=al-2008-07-abac

University of Pennsylvania. (2005, August). *Environmental Health and Radiations Safety*. Retrieved July 31, 2008, from Shipping Infectious Substances, Biological Substances, Biological Products,Substances, Biological Products,: http://www.ehrs.upenn.edu/resources/docs/biosafety/ShippingManual.pdf

US Census Bureau. (2006). *Percent of the Total Population Who Are Asian Alone: 2006* . Retrieved August 27, 2008, from

http://factfinder.census.gov/servlet/ThematicMapFramesetServlet?_bm=y&-PANEL_ID=tm_result&-_MapEvent=displayBy&-tm_name=ACS_2006_EST_G00_M00630&-ds_name=ACS_2006_EST_G00_&-tm_config=|b=50|l=en|t=306|zf=0.0|ms=thm_def|dw=1.9557697048764706E7|dh=1.445568912

US Food and Drug Administration. (2007, 12 12). *Information for Healthcare Professionals: Carbamazepine(marketed as Carbatrol, Equetro, Tegretos and generics)*. Retrieved July 23, 2008, from http://www.fda.gov/cder/drug/InfoSheets/HCP/carbamazepineHCP.htm

US Food and Drug Administration. (2008, April 07). *Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels*. Retrieved June 21, 2008, from http://www.fda.gov/cder/genomics/genomic_biomarkers_table.htm

Veenstra, D. L. (2004). Bringing genomics to the bedside: a cost-effective pharmacogenomic test? *Pharmacogenetics , 14*, 333–334.

Warnock, J. K., & Morris, D. W. (2003). Adverse Cutaneous Reactions to Mood Stabilizers. *American Journal of Clinical Dermatology , 4* (1), 21-30.

West Midlands Regional Genetics Laboratory. (2008). *Genetic tests*. Retrieved July 31, 2008, from Private Tests Guide Price List: http://www.bwhct.nhs.uk/regionalgenetics/downloads/PP%20Prices%202008%20Short%20Summary.pdf

White JT, A. A. (1999). Counting the Costs of Drug-Related Adverse Events. *Pharmacoeconomics , 15* (5), 445-458.

Wie H-G, F. F. (2005). Pharmacogenomics steps towards personalized medicine. *2* (4), 325-337.