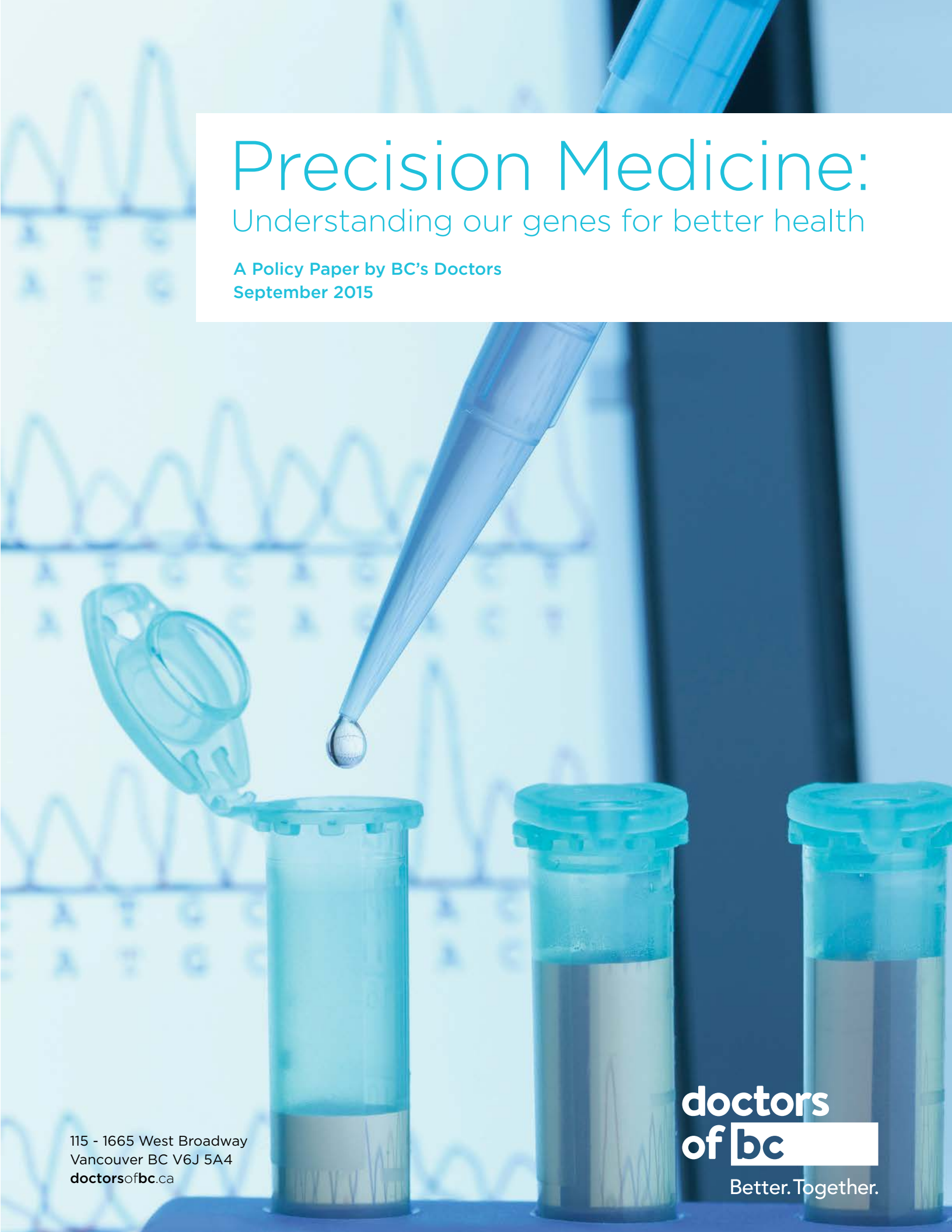

Precision Medicine:

Understanding our genes for better health

A Policy Paper by BC's Doctors
September 2015

115 - 1665 West Broadway
Vancouver BC V6J 5A4
doctorsof**bc**.ca

doctors of bc
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Doctors of BC's Council on Health Economics and Policy (CHEP) reviews and formulates policy through the use of project-oriented groups of practising physicians and professional staff.

Precision Medicine Project Group

Dr Andrew Attwell, Chair – Oncology, Victoria
Dr George Browman – Oncology, Victoria
Dr Martin Dawes – General Practice, Vancouver
Dr Gordon Hoag – Pathology, Victoria
Dr Gordon Hutchinson – General Practice, 108 Mile Ranch
Dr Kimberly Shaw – General Practice, Coquitlam

Doctors of BC Council on Health Economics and Policy (CHEP) Membership 2013–2015

Dr Alexander (Don) Milliken, Chair – Psychiatry, Victoria
Dr Andrew Attwell – Oncology, Victoria
Dr David Attwell – General Practice, Victoria
Dr Tommy Gerschman – Pediatrics, Vancouver
Dr Jaspinder Ghuman – General Practice, Surrey
Dr Brian Gregory – Dermatology, Vancouver
Dr Jeff Harries – General Practice, Penticton
Dr Dan Horvat – General Practice, Prince George
Dr Trina Larsen Soles – General Practice, Golden
Dr Tracy Monk – General Practice, Burnaby
Dr Lloyd Oppel – General Practice, Vancouver
Dr Jessica Otte – General Practice, Vancouver
Dr Alan Ruddiman – General Practice, Oliver
Dr Kimberly Shaw – General Practice, Coquitlam
Dr David Smith – Pediatrics, Vancouver
Dr Marianne Taylor – Oncology, Vancouver

Doctors of BC Staff Support

Mr Jim Aikman – Executive Director of Economics and Policy Analysis
Ms Deborah Viccars – Director of Policy
Ms Mary George – Policy Analyst
Ms Helen Thi – Policy Researcher
Ms Linda Grime – Executive Assistant
Ms Mallory Crew – Economics and Policy Analysis Assistant

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Executive Summary

In 1989, *Time* magazine described genome sequencing as the "key to the kingdom," depicting an imminent future where a simple saliva test could be used to diagnose and determine treatment for disease and illness.

Unprecedented scientific advances have since given us the ability to analyze an individual's genetic profile to help guide medical decisions in prevention, diagnosis, and treatment of disease. This innovative approach to tailoring health care based on an individual's genetic makeup is often referred to as "precision" or "personalized" medicine.

Precision medicine offers exciting opportunities to optimize care through more precise diagnoses and tailored treatment options. Examining our genetic makeup not only allows us to more precisely diagnose and treat diseases people develop, but also provides information that can guide lifestyle changes to prevent diseases from developing.

The age of precision medicine also brings with it new sets of challenges, such as issues of consent and privacy, the need for patient and provider education, concerns about medical liability and inadequate infrastructure for genetic testing, among others.

The combination of rapid innovation, dramatic increase in demand, and lack of patient and provider education has created an immediate need for the development of a responsive policy and regulatory framework to address issues as they emerge.

In this policy paper, Doctors of BC identifies challenges and opportunities in integrating precision medicine into the clinical care setting and proposes a "vision" of the effective integration of precision medicine into British Columbia's health care system. Doctors of BC aims to bring a physician perspective to the complex issues being considered by government, industry, and other stakeholders.

Doctors of BC has particular concerns regarding the potential impact of genetic tests marketed directly to consumers for health purposes. In order to address the unique issues presented by that aspect of genetic testing, Doctors of BC has, concurrent with publication of this policy paper, released a policy statement titled *Direct-to-Consumer Genetic Testing for Health Purposes*. The discussion on precision medicine in this policy paper pertains to clinically initiated genetic tests and related services and/or, in some instances, genetic tests undertaken in the context of medical research.

Terminology & Definitional Challenges

Illustrating the need for a coordinated policy approach, there is no single agreed-upon definition that captures the complexity of personalized, individualized, or precision medicine. Given the Obama administration's recent announcement of a $215 million Precision Medicine Initiative in the United States, it is likely that precision medicine will become the prominent term, at least in the short term.

Precision medicine refers to the use of an individual's genomic and epigenetic information, including individual patterns of disease, in order to provide targeted treatment that is tailored to the person's genetic profile, potentially leading to better individual treatment. For the purposes of this policy paper, the focus of discussion is on precision medicine generally and primarily on the use of genomic data as they help us understand individual patterns of disease. Other terms relevant to the discussion of precision medicine are highlighted below:

Epigenetics is the emerging study of heritable changes caused by the activation and deactivation of genes without any change in the underlying DNA sequence of the organism.[1]

Genes are the basic physical units of inheritance. Genes are passed from parents to offspring and contain the information needed to specify traits. Genes are arranged one after another on structures called chromosomes. A chromosome contains a single, long DNA molecule, only a portion of which corresponds to a single gene. Humans have approximately 20,000 genes arranged on their chromosomes.[2]

A **Genome** is an organism's complete set of DNA – basically a blueprint for an organism's structure and function.

Genomics is the science that aims to decipher and understand the entire genetic information of an organism encoded in DNA and corresponding complements such as RNA, proteins and metabolites.[3]

DNA is the chemical name for the molecule that carries genetic instructions in all living things. The DNA molecule consists of two strands that wind around one another to form a shape known as a double helix.[2]

[1] GeneEd Genetics, Education, Discovery. Epigenetics/Inheritance and the Environment; 2012. http://geneed.nlm.nih.gov/topic_subtopic.php?tid=35
[2] Genetics Home Reference. Glossary; 2015. http://ghr.nlm.nih.gov/glossary
[3] Genome BC. What is Genomics?; 2015. http://www.genomebc.ca/impacts/what-genomics/

Doctors of BC Policy

Doctors of BC recognizes the potential for precision medicine to improve health care delivery through more precise and timely diagnosis and treatment, and targeted prevention.

Doctors of BC also sees obstacles to effective integration of precision medicine into clinical practice. To ensure that precision medicine is driven by quality patient care and clinical needs, Doctors of BC calls for collaboration among stakeholders to:

- Develop patient-focused policy and legislation that supports integration of precision medicine into clinical care.
- Provide comprehensive up-to-date patient and physician education regarding medically significant genetic testing.
- Implement a robust province-wide clinical and economic evaluation of precision medicine interventions.

To support this policy position, Doctors of BC has identified the following commitments and recommendations.

Commitments

Doctors of BC commits to:

a. Collaborating with stakeholders to develop:

   i. A provincial strategy to integrate precision medicine into clinical care, balancing costs with improved quality of care.

   ii. Informed consent and privacy legislation applicable to genomic testing.

b. Supporting integration of precision medicine into clinical practice through promotion of physician participation in:

   i. Genomic research in clinical practice.

   ii. Economic and clinical evaluation of genomic tests.

   iii. Decision making regarding appropriate integration of genomic data into electronic health record systems.

c. Increasing physician and patient education in precision medicine by promoting the development of:

   i. Evidence-informed educational tools, including clinical practice guidelines.

   ii. Continuing education resources.

   iii. Materials and resources that translate complex clinical genomic information for patient audiences.

d. Advocating for the highest quality of genomic testing and clinical research in British Columbia.

Recommendations

Doctors of BC recommends that:

a. The provincial government create a provincial action plan for precision medicine that considers:

   i. Issues regarding integration into clinical practice, including lab accreditation and quality assurance processes.

   ii. Reviewing and updating, as necessary, applicable informed consent and privacy legislation.

   iii. How best to support clinical research across the province, including how to effectively and safely share data and prioritize clinical trials.

b. Industry develop technology in collaboration with practising physicians to ensure that innovation in precision medicine is supportive of and responsive to clinical practice and patients' needs.

c. Joint committees[1] and physician groups, including Divisions of Family Practice and Specialty Sections, support knowledge translation and sharing by:

   i. Developing and/or promoting accredited training opportunities in the use of precision medicine in clinical practice.

   ii. Funding pilot projects focusing on appropriate use of precision medicine in clinical practice, particularly in multidisciplinary and shared care settings.

   iii. Creating and/or maintaining multidisciplinary knowledge sharing networks for all physicians.

   iv. Developing decision-support tools for use by patients and providers.

[1] The Physician Master Agreement includes funding for joint committees of the Ministry of Health and Doctors of BC for the purpose of improving patient and provider experience in BC. The joint committees include the Joint Standing Committee on Rural Issues, the General Practice Services Committee, the Specialist Services Committee, and the Shared Care Committee. The joint committees represent the interests of rural care, family/general practice care, specialty care, and family practice/specialist collaborative care.

1. Introduction

Precision medicine has already demonstrated success in improving the speed and accuracy of diagnosis and the treatment of disease. However, complex ethical, legal, social, and clinical considerations have also emerged.

Issues of privacy and data storage, regulatory oversight, laboratory accreditation, and infrastructure development are just some of the issues that have been identified but are yet to be addressed. In order to harness precision medicine's promise to reduce costs and drive quality, a robust policy, legislative, economic, and scientific environment must be created.

In this policy paper, Doctors of BC identifies challenges and opportunities associated with integrating precision medicine across the clinical continuum of screening and diagnosis, prognosis, and therapeutics. This policy paper brings a physician perspective to the identification of issues that must be addressed to ensure that precision medicine can be used to benefit patients, their families, providers, and the health care system.

2. Policy Opportunity

We are in the midst of remarkable technological advancement in health care.

Certain specialties, such as oncology, have already seen considerable advances in clinical practice and patient outcomes. There is an opportunity for early successes to inform policy development. Policy development must encourage the continued appropriate integration of precision medicine into clinical practice and discourage those advances and practices that provide little benefit or have the potential for harm.

There is an opportunity to ensure that policy development in the area of precision medicine optimizes health system performance. It is important that policy support innovation that is aligned with the *Institute of Healthcare Improvement's* (IHI) Triple Aim[2] of improving health system performance by improving patient and provider experience, improving the health of populations, and reducing the per capita cost of health care through targeted spending.

British Columbia's health system has features that can support development and implementation of effective policy in this area. BC has well-supported research and

[2] The Triple Aim is a framework developed by the Institute for Healthcare Improvement and accepted by countries around the world. The British Columbia Ministry of Health, Health Authorities, and Doctors of BC support the principles of the Triple Aim as an approach to optimizing health system performance.

development in genomics, a single-payer health care system, existing collaborative infrastructure and networks between physicians and government, and a single integrated provincial medical school that provides training and continuing professional development through regional campuses.

Policy that supports the appropriate use of precision medicine can change clinical practice for the benefit of patients, their families, providers, and the broader health care system. However, it is important to ensure that clinical and population health needs shape the development of technology, and not the reverse.

Doctors of BC recognizes the opportunity to create a policy framework that will ensure that advances in precision medicine continue to contribute to improvements in health care delivery.

3. Background

A. The Human Genome Project

Only 60 years ago, James Watson and Francis Crick successfully described the DNA double helix, a discovery that opened the door to a better understanding of the genetic code. Five decades and $2.7 billion later, the Human Genome Project successfully mapped the entire human genome. James Watson's own genome was sequenced in 2007 for approximately $1 million, something that he could not have foreseen half a century earlier. Now there is promise on the horizon of a one-hour, $100, full genome sequence.

Scientists around the world, in both private and public sectors, have learned from the collaborative efforts of the Human Genome Project and shared their discoveries in the name of scientific advancement. While it remains to be seen when or if the $100 full genome sequence will be achieved, it is clear that the Human Genome Project ignited medical research. The attached Appendix A: Developments in Research and Technology highlights select research initiatives occurring in Canada and internationally.

B. Policy and Regulatory Development

The challenge for policy-makers and legislators is to create a robust long-term policy and legislative foundation to support patients and providers as innovation in precision medicine continues.

The immediate need for policy development and regulatory oversight is most apparent in connection with direct-to-consumer genetic testing. Direct marketing of genetic testing to consumers through television and the Internet introduces an unproven health-related decision tool outside the usual testing protocols. This raises unique challenges for patients, providers, and the health care system. In order to consider the unique challenges posed by direct-to-consumer genetic testing for health purposes, Doctors of BC has released a separate policy statement titled *Direct-to-Consumer Genetic Testing for Health Purposes*. The statement notes that Doctors of BC supports the continued integration of clinically initiated genetic testing into health care in BC, but raises concerns regarding direct-to-consumer genetic testing and calls for regulation and increased education to protect patients and support quality care.

While there is some overlap of policy and regulatory issues with genetic tests initiated by consumers and those initiated for a clinical purpose, Doctors of BC also sees opportunities that appropriately integrated precision medicine can offer, provided stakeholders work together to address the barriers to effective integration.

While efforts have been made provincially and federally to begin to create a regulatory and policy environment that will support advances in precision medicine, this process must be expedited in a thoughtful yet robust way.

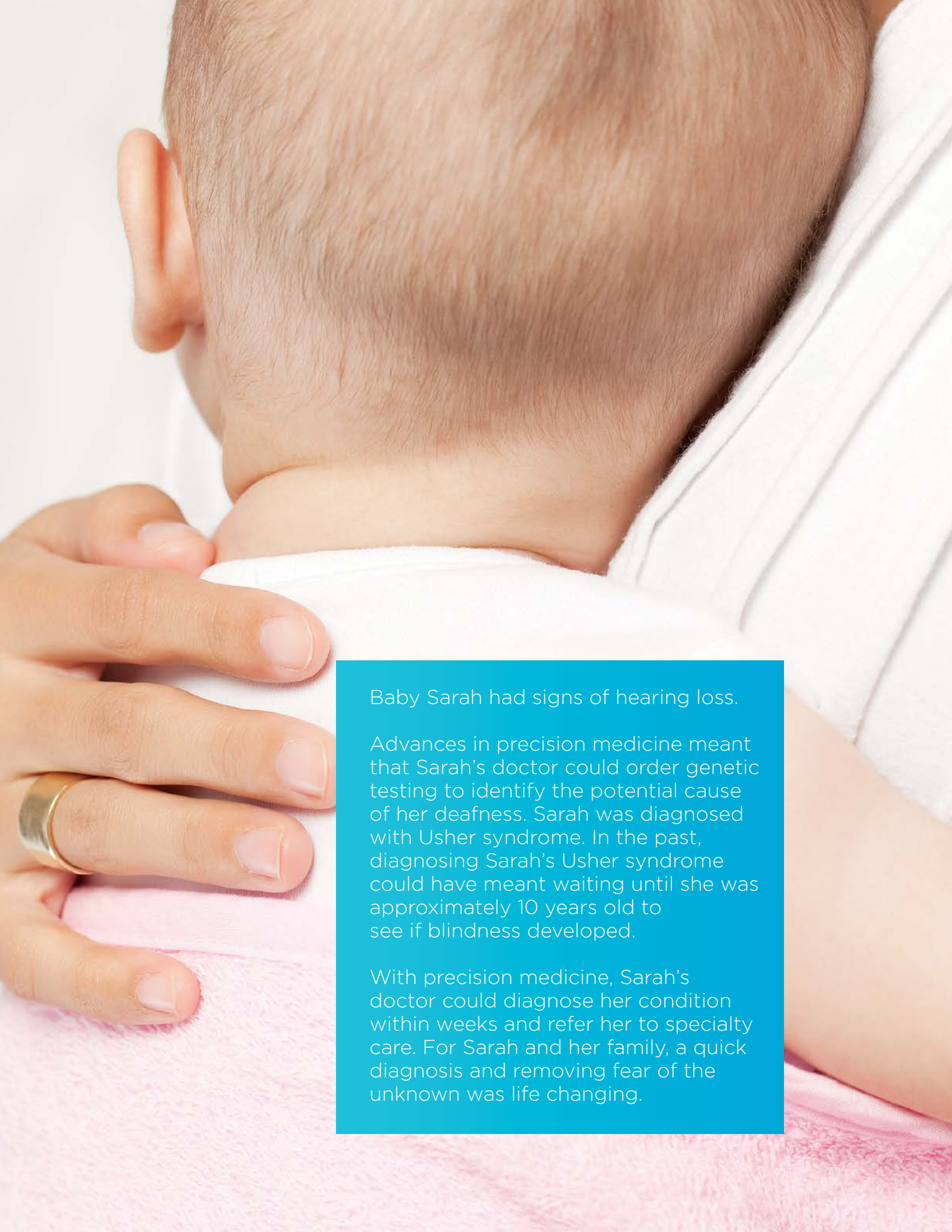
In June 2012, the BC provincial government, in collaboration with the McMaster Health Forum, held a stakeholder forum and produced a report titled *Coordinating the Use of Genetic Tests and Related Services in British Columbia*.[2] The process brought together stakeholders involved in the planning, funding, delivery, and evaluation of genetic tests and related services. The report outlines challenges in each of these areas and includes recommendations for addressing them. Doctors of BC applauds this effort and supports the continuation of this type of multisectoral collaboration.

The Canadian College of Medical Geneticists has produced numerous position statements and reports about genetic testing in Canada.[3] The Canadian Medical Association outlined the importance of a regulatory framework in its 2010 paper, *Regulatory Framework for Direct-to-Consumer Clinical Genetic Tests*.[4]

Despite some development of policy in the area of genomic medicine, more work is urgently needed. Comprehensive federal and provincial policy is required to consider how best to address issues of genetic discrimination, scope of practice, physician compensation models, data storage and security, medical liability, standards of care, and education, among others. The United States and Australia have led the way in policy development on genetic testing, and much can be learned from their efforts.[5, 6]

The United States is also ahead of Canada in terms of legislative development. Reflecting the uniquely sensitive nature of genetic information and the potential for discrimination, the *Genetic Information Non-discrimination Act* was passed by the US Congress in 2008. The act prohibits the use of genetic information for discriminatory purposes by employers and prohibits group health plans and health insurers from denying coverage or charging higher premiums based on genetic information.

In Canada, legislation has been tabled on a number of occasions, but to date has been voted down for various reasons, including limited examples of genetic discrimination in Canada and perceived sufficiency of the *Canadian Human Rights Act*. Canada remains the only G8 country that has not developed legislation to protect against genetic discrimination



Baby Sarah had signs of hearing loss.

Advances in precision medicine meant that Sarah's doctor could order genetic testing to identify the potential cause of her deafness. Sarah was diagnosed with Usher syndrome. In the past, diagnosing Sarah's Usher syndrome could have meant waiting until she was approximately 10 years old to see if blindness developed.

With precision medicine, Sarah's doctor could diagnose her condition within weeks and refer her to specialty care. For Sarah and her family, a quick diagnosis and removing fear of the unknown was life changing.

4. Discussion

The sections that follow outline the challenges and opportunities in integrating precision medicine into BC's health care system.

Discussion follows the clinical continuum of care from screening and diagnosis to prognosis and therapy. Each section provides a brief summary of the current state of precision medicine as it relates to that aspect of clinical care. Challenges and opportunities of continued integration are highlighted, and a vision of what effective integration of precision medicine into that aspect of care could look like is presented.

Some of the issues discussed are not limited to only one part of the continuum of clinical care. However, for the purposes of discussion, issues have been raised in connection with the most relevant aspect of care. For example, the need for patient and provider interests to drive innovation and integration of precision medicine is relevant to all aspects of clinical care, from screening and diagnosis, to prognosis, to therapeutics. Similarly, privacy and health information technology issues are also relevant across the continuum of care.

A. Screening and Diagnosis

i. Current State

Diagnosis has generally been a process of examination, testing, and (perhaps) elimination, but precision medicine provides an opportunity for more precise and rapid diagnosis of particular conditions. Over 4000 diseases are known to be caused by single gene disorders, including Huntington disease, cystic fibrosis, and some cancers. This knowledge has allowed more rapid diagnosis of these conditions.

Despite tremendous advances in diagnosis, there are still many genetic disorders for which tests have not yet been developed. For example, there are significant limitations to using genetic information to diagnose conditions related to multiple-gene interactions, changes in genetic expression, or gene-environment interactions.

Beyond diagnosis of symptomatic disorders, genetic testing can also provide predictive value by screening for genetic risk factors. For example, the alpha-1 antitrypsin deficiency is a genetic disorder that increases the probability of a person developing lung or liver disease later in life.

Identifying the presence of variations such as the alpha-1 antitrypsin deficiency can affect prevention strategies (prior to disease manifestation), treatment plans, and advanced care planning for patients and their families.

ii. Challenges and Opportunities

CHALLENGE:

Lack of a systematic approach to funding and eligibility for testing.

In BC, provincial funding for new genetic tests for diagnosis or screening is decided on an ad hoc basis, with no streamlined systematic approach. As a result, important advances are frequently not funded and therefore not readily accessible to patients and health care providers. Patients often have to go through a process of appeal for funding or pay for tests out of pocket. In oncology, a funding application process, similar to a drug funding application process, has recently been implemented. In other specialties, however, decisions to fund tests through the Medical Services Plan (MSP) are made on a case-by-case basis. With more and more tests becoming available, this approach to funding tests will no longer be sustainable.

In early 2008, the BC Ministry of Health began funding the Prenatal Genetic Screening Program through Perinatal Services BC. This funding allows for a centralized, coordinated system that oversees prenatal screening across the province, including measuring outcomes, evaluating evidence, and providing a central source of educational and informational resources for parents and providers. Tests include prenatal testing for Down syndrome, trisomy 18, and open neural tube defects. Funding has also been identified for the introduction of higher-quality prenatal screening tests that have improved detection rates and reduced false positive rates.

Eligibility for diagnostic genetic testing is based on individual risk of illness or disease. Risk factors can include symptoms, biophysical characteristics, or patient or family history. Publicly funded genetic tests currently include those for beta thalassemia, spina bifida, ankylosing spondylitis, Huntington disease, and some breast cancers. While patients may request a genetic test, they are responsible for the costs of testing if they do not meet the standard testing criteria.

OPPORTUNITY:

Develop a patient-centric systematic approach to funding and eligibility for genetic tests.

CHALLENGE:

Varied familiarity with available tests among health care providers.

While there is great potential for the use of genomics in primary care, testing is often limited by individual provider awareness of available tests. To date, there is no method of disseminating information to providers about which tests are available, which are funded by MSP, or the best use of genetic testing. Given the lengthy approval process, genetic tests may be privately available before being funded by MSP. Physicians need clear resources that outline which tests are supported by clinical evidence, as well as which are funded.

Family physicians, the preferred first point of care for patients, need support to determine the best use of genomics in clinical practice. Supporting family physicians in best use of genetic testing could result in more appropriate specialist referrals. Support for physicians could include training opportunities, such as continuing professional development modules on the use and interpretation of genetic testing and discussing these results with patients and families. Up-to-date information about currently available genetic tests as well as guidelines for further testing and consultation should be easily accessible.

OPPORTUNITY:

Increase physician awareness of, and access to, existing testing, diagnostic, and interpretation resources.

CHALLENGE:

Lack of clinical and economic evaluation.

In some circumstances, genetic testing will be a diagnostic tool that leads to cost avoidance. However, there is also the risk that it will increase resource utilization. Davis et al.[7] identify a number of barriers to reduced costs, including:

- An inability to predict or determine which tests could reduce costs.
- Lack of longitudinal accounting that follows individual patients and depicts a causal relationship between testing and cost avoidance.

Evidence-based decision-making tools should be developed to direct which genetic tests are more precise and cost-effective than traditional alternatives. In addition, economic and clinical evaluations could compare the use of separate panels, partial sequencing (also known as "SNPs"—pronounced "snip") and whole genome sequencing, particularly as time and cost of testing is continually being reduced. Cost avoidance, however, should not be prioritized over quality patient care and population health.

Single Nucleotide Polymorphism (SNP): A variation of a single base (A, T, C or G) within a sequence of DNA. For any single base variation to be called a SNP the minor allele must be found in more than 1% of the population. SNPs do not generally cause disease directly but some SNPs may indicate an individual's susceptibility to disease or the response to drugs and other treatments.[1]

Whole Genome Sequencing: Determines the order of all the nucleotides in an individual's DNA and can determine variations in any part of the genome.[2]

1 Genome BC. Glossary; 2015. http://www.genomebc.ca/education/glossary/

2 Genetics Home Reference. Genomic Research: Next in Studying the Human Genome; 2015. http://ghr.nlm.nih.gov/handbook/genomicresearch?show=all

OPPORTUNITY:

Identify clinically effective genetic tests and associated services through robust clinical and economic evaluation.

CHALLENGE:

Lack of resources for best practices for genetic testing.

With ever-growing public awareness of genomics and increased expectations of patients, fuelled by industry and the media, physicians will increasingly be expected to balance patient needs and requests for genetic testing against health care resources and optimal patient care. While precision medicine promises cost savings to the health care system by moving away from exploratory testing methods to enhanced precision in medicine, without adequate regulatory oversight there is a real risk for genetic testing to become a cost driver in the health care system.[7]

Without adequate resources and current information about best practices for genetic testing, providers are forced to resort to specialty referral. Unnecessary referral may drive costs and decrease access to specialty care. For example, the BC Cancer Agency has seen a 60% increase in referrals to its hereditary cancer program since May 2013, which they attribute to the "Angelina Jolie effect."[8]

> In 2013, film actress Angelina Jolie's decision to have genetic testing for the BRCA1 gene and subsequently undergo risk reducing mastectomy resulted in global news stories that appear to have increased demand for BRCA1/2 testing and inquires for risk reducing mastectomy.[1]
>
> 1 Evans DGR, Borwell J, Eccles DM, et al. The Angelina Jolie Effect: How High Celebrity Profile can Have Major Impact on Provision of Cancer Related Services. Breast Cancer Research 2014;16:442.

While some of these referrals may have been appropriate, support for physicians through guidelines (similar to Choosing Wisely Canada) could ensure efficient referral patterns by clarifying best practices.

OPPORTUNITY:

Support physicians with genetic testing referral guidelines in order to balance patient and health care system needs.

CHALLENGE:

Inadequate health resource planning.

Research indicates that receiving test results can be emotionally stressful for patients.[9] Genetic counselors are trained to meet specific and varied patient needs with respect to genetic testing. Unfortunately, the rapid integration of precision medicine into the health care system has not allowed adequate time to ensure that appropriate health human resource planning is in place.

Not only are there too few genetic counselors, but many family physicians and specialists do not have the support (including training, clinical resources, time, practice, and funding) to provide these necessary services. In addition to the specific training and clinical resources needed for these visits, physicians working with patients with results of genetic tests can also be faced with complex information that must be stored and managed.

OPPORTUNITY:

Improve patient and provider experience through physician support, including training, and health human resource planning.

CHALLENGE:

Informed consent laws do not adequately address issues related to incidental findings.

With decreased costs of genetic testing, more exploratory options are available to physicians who can now order "panel" tests to explore hundreds of genes at the same time or even a full genome sequence.

With increased genetic testing, the issue of "incidental findings" is of greater importance. Generally, before patients undergo a medical test, they provide their consent, which is informed by "clear appreciation and understanding of the facts, implications, and future consequences of an action."[9] Incidental findings are secondary findings that are flagged during testing because they may have medical significance but are unrelated to the initial reason that sequencing was ordered. In genetic testing, particularly when a panel or full sequence is run, the results may indicate that a patient is at risk of developing a significant health problem unrelated to the issue that initiated testing.

Research suggests that there is a net benefit to society if patients learn about other health problems.[10] Not all patients, however, want to know if they could potentially develop an illness. For instance, though not considered at the time of initiation of a genetic test, results may show at-risk markers for amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig's disease). ALS is a fatal neurodegenerative disease in which a person progressively loses muscular control. Given that so many view an ALS diagnosis as a "death sentence" (because of the severity of the symptoms and the fact that the outcome is terminal and nothing can currently be done to change the disease trajectory), many people choose not to know if they possess such a genetic mutation.

Regulators, providers, and patients need to consider ethical, legal, and medical concerns associated with testing. A qualitative study by Townsend et al.[11] identified the importance of patients' right to choose which findings they would like to receive or not receive. In this context, patients also must take responsibility for the associated consequences. While an approach to this issue is still being determined in the regulatory context, it is possible that undergoing testing can affect patients' lives in other ways, including having to disclose whether they have undergone testing when purchasing insurance or if seeking mortgage approval.

These ethical and legal considerations are made more complex by the fact that genetic testing may provide not a definitive diagnosis but information about probability. It can be argued that most medical tests provide information in shades of grey, indicating the strength of probability of developing a disease, but in practice may be interpreted, particularly by patients, as being much more definitive. Training about the interpretation of results requires education of health care professionals, patients, and other members of the care team.

In 2013, the American College of Medical Genetics and Genomics outlined a number of recommendations in its policy statement *ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing*[12] The statement suggests that laboratory clinical sequencing should include seeking and reporting of mutations for a number of genes. The response to their recommendation among the medical and medical ethics community has been mixed.

The issue of incidental findings is not unique to genomics and is frequently encountered in laboratory and imaging tests—for example, when something unexpected is discovered in an X-ray. Research in medical ethics suggests that a balance between informed consent and patient autonomy, as well as support for genetic counseling, are imperative both in research and clinical practice.[13] This may require reconsideration of current informed consent legislation in this context. Health care providers will need assistance in ensuring true informed consent and supporting patient and family decision making.

OPPORTUNITY:

Improve patient and provider experience by informing patients and health care providers about the risk of incidental findings, improving informed consent processes, and improving supports for patients and families when significant incidental findings are made.

iii. Vision: Genomics as an integrated screening and diagnostic tool

Doctors of BC envisions a provincial health care system that effectively integrates genomics as a screening and diagnostic tool and where:

- Physicians are aware of and have access to training opportunities and educational resources about current tests, the interpretation of results, and the use of genomics for screening and diagnosis.
- Resources to support physicians in balancing patient needs with health care system needs are readily available.
- Health care providers are assisted in their clinical decision making by current evidence, which includes economic analysis.
- Patient care is supported with a robust health human resource plan that includes family physicians, specialists, and other members of the multidisciplinary care team.
- Patients and health care providers fully understand and have access to resources regarding the risk of incidental findings.
- Informed consent legislation and processes reflect the risk of incidental findings arising out of genomic testing.
- Supports, including information, counseling, and specialist referral processes (where necessary) are in place and available for providers, patients, and families when significant incidental findings are made.

B. Prognosis

i. Current State

The use of precision medicine in prognosis, or predicting the progression of disease and the prospect for recovery, is still in its infancy. Much of the evidence produced to date has focused on cancers, including identifying biomarkers and cancer staging.[14]

At present, TNM Classification of Malignant Tumours (TNM) remains the most practical staging system for virtually all cancers, but there are drawbacks. The stage of disease often does not correlate with its aggressiveness. For instance, a breast cancer tumour may be very small at diagnosis, but that does not mean it is not aggressive. The molecular biology of a tumour, not just its size, determines a patient's prognosis.

Ludwig and Weinstein[14] identified three ways that precision medicine influences prognostication in cancer:

- Genome sequencing of molecular markers has meant that some cancers that were traditionally grouped together can be subdivided into groups that behave differently in response to treatment.
- Chemotherapy treatments are more effectively targeted than when the TNM staging system was developed.
- Oncologists can now determine whether treatment options will be effective based on how various markers are mutated or expressed.

For example, scientists from Cambridge and the BC Cancer Research Centre examined 2000 breast cancers and developed a new stratification system based on 10 distinctive prognostic subgroups.[15] As technology develops and sequencing costs decrease, clinicians have access to and can provide their patients with increasingly precise information.

At age 40, Sandra learned she had a breast cancer tumour.

Her oncologist explained that she would need surgery and possibly chemotherapy. Fortunately, there was hope in the form of a new genomic test that could look at the profile of her tumour to give clues as to how it would respond to treatment.

Individuals pictured are models and are used for illustrative purposes only.

ii. Challenges and Opportunities

CHALLENGE:

Lack of awareness of clinical trials and infrastructure for data sharing hinder opportunities for innovation.

The system of approval for new medical tests and treatments relies on randomized trials as the best source of evidence to support decision making. Government agencies rely heavily on clear evidence for efficacy and an analysis of their economic impact. When new technologies or treatments show initial promise, tests or treatments may be partially funded until results are more conclusive. This approach is appropriately designed to balance patient safety with evidence-based decision making.

Already lengthy research processes may be extended because of difficulty securing funding, slow pace of recruitment, and long research phases. It is a process that can frustrate patients and families hopeful for new technologies or treatments.

While maintaining research rigour and quality, information-sharing networks that increase physician and patient awareness of clinical trials could help accelerate recruitment. Recruitment could also be supported through the expansion of interprovincial collaboration. With increased use of electronic health records, there may be an opportunity to support clinical research through expanded information sharing.

Of course, information sharing and the increased rate of discovery raise many of the issues identified in this paper, such as privacy, data ownership, and effective integration of research into clinical practice. However, these challenges need to be addressed so they do not hinder continued innovation.

OPPORTUNITY:

Support clinical research and enhance the rate of discovery in BC.

CHALLENGE:

Physicians lack adequate training on the clinical application of precision medicine.

Given the rapid advancement of precision medicine, most physicians have never been trained in the clinical application of genomics. Some physicians are unaware of available opportunities or do not have the time to commit to informing themselves of the research and obtaining available training. Given the potential benefit to patients and providers, knowledge translation and sharing regarding precision medicine should be encouraged among physicians. This may include different levels of training, from introductory to more enhanced training. In addition, multidisciplinary information-sharing networks could assist in making expert knowledge available among physicians and further support dissemination of new developments in precision medicine.

OPPORTUNITY:

Improve provider experience through training opportunities and information sharing.

CHALLENGE:

Increasing awareness of precision medicine has the potential to overshadow emphasis on healthy lifestyle and behaviours as the primary predictor in determining health outcomes.

Despite encouraging initial results, genome sequencing and targeted treatments are not a panacea. In fact, in some instances where there is no meaningful therapy for an illness, it may be more beneficial for patients to avoid testing.

Healthy lifestyle and behaviours will continue to be a primary predictor in determining health outcomes. While modifying human behaviour can prove challenging,[16-18] physicians could have greater support in promoting healthy behaviour among patients. Patients and their families will continue to be interested in genomics and its benefits, and physicians have a role in empowering their patients through education about individual health risks. Physicians should be supported in educating their patients about the value (and limitations) of new technology in improving prognostic accuracy as well as the benefits of healthy behaviours, including diet and exercise.

OPPORTUNITY:

Improve patient experience and health outcomes through education about the value (and limitations) of precision medicine.

iii. Vision: Genomics as an integrated prognostic tool

Doctors of BC envisions a provincial health care system that supports the use of genomics in prognostics and where:

- Physicians have access to resources and are empowered to share information about the prognostic value of genomics in clinical practice.
- Clinical research is facilitated through patient and provider awareness of opportunities to participate in research.
- Physicians are positioned to educate their patients about the strengths and weaknesses of genomics as a predictor of health and health outcomes.

C. Therapeutics

i. Current State

Traditionally, "blockbuster drugs" have been developed for and used by many people who suffer from the same condition. The drugs are used by large populations and are cost-effective to produce, regulate, and monitor. Unfortunately, evidence indicates that many "blockbuster drugs" may lead to adverse drug events and potentially costly hospital admissions in certain patients.[19, 20]

Research suggests that one in nine emergency room visits are the result of adverse drug events.[21] For instance, Warfarin is frequently prescribed to patients with heart disease in order to reduce clotting, but individual response to the drug may vary as a result of genetic makeup.

Research in health genome sciences initially focused on which gene variations contribute to disease or illness. However, in the emerging sub-field of pharmacogenomics, research is focused on individual response to drugs (toxicities) and the extent to which these differences are attributable to genomics. Identifying variations in therapeutic response and adverse effects can significantly improve the patient experience and reduce costs to the system.

Building on the ability to identify variations in response, drug companies have focused on developing targeted treatments with accompanying genomic tests. Prescribing based on individual genetic makeup offers the potential for appropriately targeted, dose-adjusted, and significantly safer treatments.[22] At the time of writing of this paper, approximately 150 medications have particular genetic testing recommended as appropriate for quality patient care.

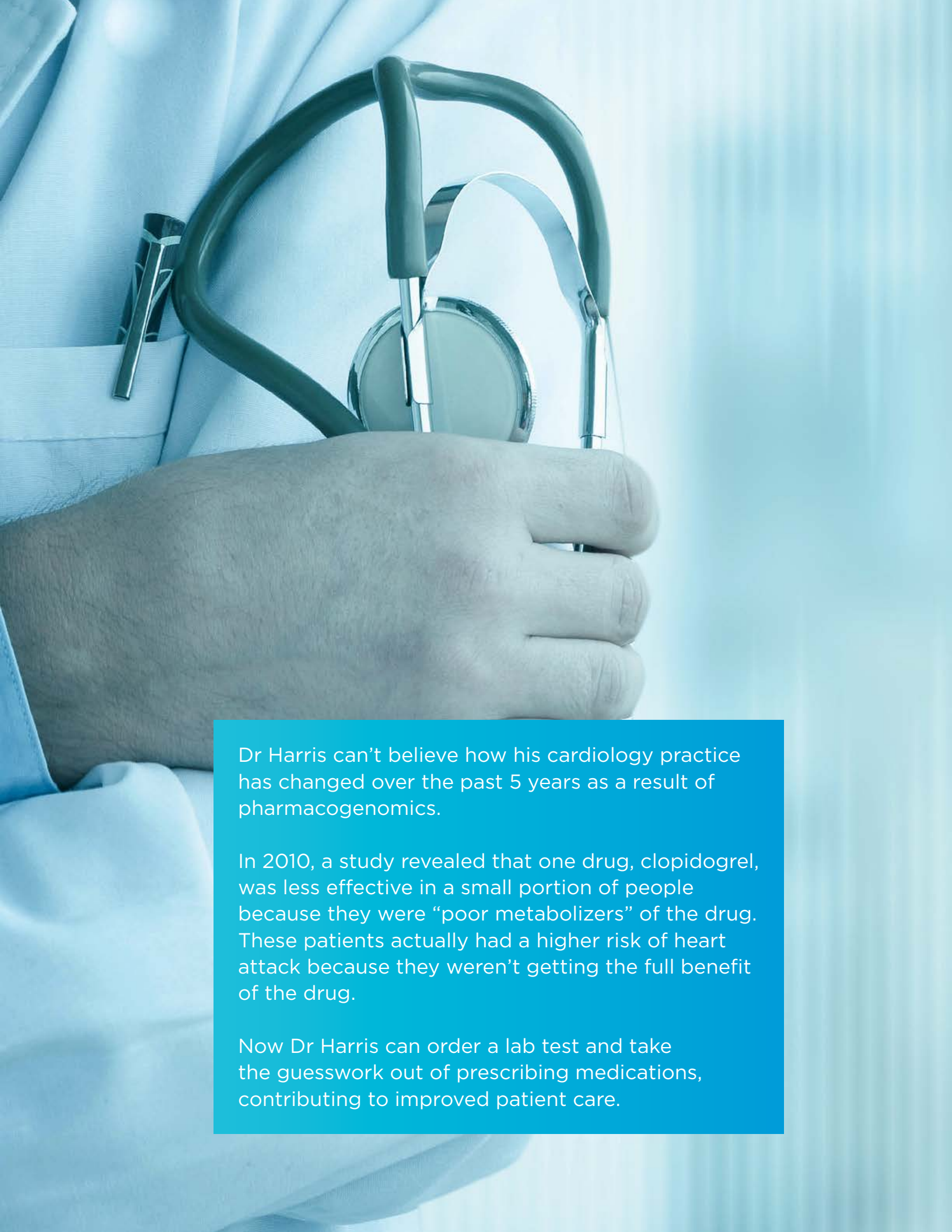
Unfortunately, these targeted drugs can be more difficult and costly to develop, particularly for rare conditions. Therefore, some proven therapies may be approved by Health Canada but may be too expensive to meet provincial

cost-effectiveness thresholds for coverage. In 2012, Health Canada developed an initial discussion document on orphan drugs for rare conditions,[23] but an official framework for orphan drugs has not yet been published or approved.

Now that more individualized treatment choices are available, pilot projects that may provide evidence for cost avoidance are being implemented. For instance, Kaiser Permanente, the US Food and Drug Administration (FDA), and other stakeholders are piloting a project to determine individual patient treatments based on their individual panel of genetic tests. The FDA will collect the data and publish the results as part of a larger data collection project aimed at creating a repository of data that can be mined for future research projects.

Research suggests that there is a sound business case for covering the costs of genetic testing in order to reduce the costs of adverse drug events.[24, 25] However, there is no definitive economic analysis that supports full genome sequencing, partial sequencing or SNPs, or individual gene testing to determine treatment choices for defined conditions or as part of an overall treatment strategy.

Each Canadian province has a respective agency overseeing the testing and approval of new technologies and drugs. The BC Laboratory Services Act (2014) [26] provides guidance for service provisions. A robust validation and evaluation process is still in development to ensure that regulatory processes for testing and approving new technologies are met.



Dr Harris can't believe how his cardiology practice has changed over the past 5 years as a result of pharmacogenomics.

In 2010, a study revealed that one drug, clopidogrel, was less effective in a small portion of people because they were "poor metabolizers" of the drug. These patients actually had a higher risk of heart attack because they weren't getting the full benefit of the drug.

Now Dr Harris can order a lab test and take the guesswork out of prescribing medications, contributing to improved patient care.

ii. Challenges and Opportunities

CHALLENGE:

Lack of a policy and regulatory framework to support integration of pharmacogenomics into BC's health care system.

Evidence related to reduction in drug interactions and hospital admission rates indicates that targeted therapies have clear benefits to patients, their families, providers, and the entire health care system.[19–21] The introduction of pharmacogenomics to maximize therapeutic benefit and minimize adverse events will require the resolution of many issues beyond the scientific challenges. Given that pharmacogenomics is still in its infancy, there has not been sufficient time to fully create policy frameworks or put regulations in place.

The paper *Coordinating the Use of Genetic Tests and Related Services in British Columbia*[2] outlines the need for a policy framework in pharmacogenomics that supports innovation and protects patients. An effective policy framework will require extensive collaboration between various stakeholders, including physicians, patients, scientists, other health providers, regulatory bodies, industry, and government. It will also require long-term commitment and funding from government, and should include meaningful input from practising physicians to ensure that innovation and integration of advances are driven by clinical need.

OPPORTUNITY:

Create a policy and regulatory framework, supported by robust economic analysis, that supports effective integration of pharmacogenomics into BC's health care system.

CHALLENGE:

Lack of decision-support tools related to the use of genomic data, including pharmacogenomics, in guiding therapeutic decisions in clinical practice.

A significant challenge to the advancement of the use of genomics to guide therapeutic decisions in BC is the lack of information and resources to support clinical decision making. As further discoveries are made, there is an opportunity to translate research into clinical practice and take findings from "bench-to-bedside."[27] Given the potential for more precision and reduced side effects, it is advisable to explore improved translation of scientific innovation in genomics into clinical practice.

Genomic data should not only be available but also be easily accessible by providers. The provincial health care system already has the advantage of being a single-payer system for the population. Successful implementation of pharmacogenomics as a clinical tool will require additional infrastructure that supports data collection, analysis, sharing, and effective use of the results. Linked health and research records would also allow for economic analysis. Physicians and government should collaborate with industry in the development of technology that can seamlessly integrate genetic information with clinical decision making.

OPPORTUNITY:

Support health care providers by developing decision-support tools that guide evidence-informed therapeutic decision making assisted by patients' genomic data.

iii. Vision: Genomics as an integrated tool in therapeutics

Doctors of BC envisions a provincial health care system that supports the use of genomics in therapeutics and where:

- There is a provincial policy and regulatory framework, supported by ongoing robust economic analysis, that supports effective integration of pharmacogenomics into BC's health care system.
- Pharmacogenomic information is readily available to physicians to support clinical decision making and they have access to current evidence-based decision-support tools.

5. Conclusion

While it remains to be seen whether precision medicine will have the transformational impact on health care that some suggest, it is already providing benefit to the BC health care system. Increased speed and accuracy of diagnosis, improved prognostic information, more effective treatment, and reduced adverse events mean that government, health care providers, and patients and their families all stand to benefit.

The associated challenges of incorporating precision medicine into the health care system cannot be understated. There will be demands on government, regulators, health care administration, and health care providers to re-evaluate the way services are provided.

These challenges are not insurmountable, and the promise that genome science brings to British Columbians is enormous. Patients hope for faster diagnoses and more effective treatments, physicians hope for better outcomes for their patients, and government hopes for improved population health and manageable expenditures. With collaboration among government, industry, physicians, and patients and their families to develop the necessary policy and regulatory foundation, it will be possible to realize the potential benefits of this emerging technology.

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Appendix A: Developments in Research and Technology

i. United States

The United States has invested in numerous initiatives, including private and public sector collaborations and projects seeking to integrate genome science into clinical practice. The US National Human Genome Research Institute, a division of the National Institutes of Health, supports the development of resources and technology for genome research. At the time of writing of this paper, over 90 clinical trials were recruiting study participants, including studies of attention deficit hyperactivity disorder, diabetes, and Parkinson disease.

Kaiser Permanente, an integrated medical consortium with approximately 8.9 million health plan members, has used its vast membership base to create one of the largest genome projects. The project began in 2011, in partnership with the National Institutes of Health and the University of California, San Francisco. The first phase included extracting and genotyping the DNA of 100 000 Kaiser Permanente members who agreed to be study participants. The project links individual genetic information with electronic health records, responses to health-related questionnaires, and environmental data.[28] The combination of data from a variety of sources, facilitated by collaboration among academic, for-profit, and government institutions, is intended to create an authoritative resource for researchers.

In addition to the above-noted government and private sector work, independent clinics in the United States are integrating genomics into research and clinical service. For example, the Cleveland and Marshfield Clinics are emphasizing the coordination of genomics research and clinical care across multiple disciplines, using electronic medical records to link their findings.

ii. Europe

The Stratified Medicine Programme in the United Kingdom is a public-private partnership of the government's Technology Strategy Board, AstraZeneca, and Pfizer. In phase 1 of the program, the National Health Service's cancer-focused pilot project is currently requesting donations of surplus tissue from selected surgical patients. By extracting and testing the DNA from these tissues, researchers are better able to understand the different genetic mutations of cancer cells. The intention is to use these data for individualized treatments that target particular cancer cells.

The UK10K project is also underway in the United Kingdom. The project aims to collect and study the genetic codes of 10 000 people. The study hopes to detect variations between people's individual genomes and link these differences to disease. The project will also provide data for future human genetic research.

In Iceland, researchers with deCode Genetics Inc. have taken advantage of the small and relatively homogeneous population by anonymously linking genetic sequencing with individual medical records. deCode Genetics Inc. successfully identified a gene variant that increases the risk of Type 2 diabetes and developed targeted treatment for a gene mutation linked to heart attacks. This project links individual-level data, including medical records, genome sequence, and environmental factors. Amgen Inc., a biotech company, has since purchased deCode Genetics Inc. with the intention of using its intellectual capital to validate existing targeted drug therapies and develop new associated tests.

iii. Canada

Federal

In March 2013, the federal government announced a $150 million investment into a genomics and precision medicine partnership between Genome Canada and the Canadian Institute of Health Research. This funding included a $16.5 million investment in three research projects in British Columbia related to:

- Predicting response to HIV therapies.
- Differentiating transient ischemic attacks ("mini-strokes") from other conditions, thereby avoiding expensive neuroimaging testing and better equipping doctors to direct patient care.
- Identifying patients at high risk for chronic obstructive pulmonary disease (COPD), aimed at assisting medical professionals to provide better treatment, reduce attacks, and reduce hospitalization and emergency visits.

British Columbia

An asset map highlighting BC's role in genome science depicts the BC genome sciences community, including 255 senior researchers, over 2000 research projects/awards, and the management of over $493 million by provincial institutions.[29] The bulk of this research is conducted through the University of British Columbia, its affiliated hospitals, and the BC Cancer Agency. Among the funded projects is a 2013 BC Cancer agency study of gene-specific treatments for lymphoid cancers, which has been awarded $10 million in research funding.[30]

UBC's Life Sciences Building also houses the Personalized Medicine Initiative (PMI), an umbrella organization designed to introduce technology for precision medicine into the BC health care system by bridging hundreds of scientists across private and public sector groups. PMI funds approximately $40 million in research each year.

Genome British Columbia is a non-profit research organization that coordinates funders and partner organizations (including pharmaceutical companies). The organization also coordinates research in genome science for forestry, fisheries, bioenergy, mining, agriculture, and the environment. Advancements in one area of genome sciences may provide insights for researchers in other areas. Major Genome BC investors include the governments of British Columbia and Canada through Genome Canada and Western Economic Diversification Canada.

Appendix B: American Medical Association Personalized Medicine Legislative Guiding Principles

Adopted by the AMA Board of Trustees on November 15, 2011.

I. Genetic-based personalized medicine (PM) including the use of genetic diagnostics and gene-based treatment modalities constitutes the practice of medicine.

II. PM laws, regulations, and policies must preserve and enable physician discretion to provide, utilize and/or direct the use of the most appropriate diagnostic and treatment options and recognize that physicians are essential to the PM team. (See Principle II, Framework on Laboratory Diagnostic Testing).

III. Physicians continue to play a central role in PM discovery, research (including clinical trials), and product and service development and delivery. Physicians drive scientific inquiry and innovation that promotes PM and patient access.

IV. Given the training of physicians and their direct relationship to patients, physicians have a central role to play in the development of laws, regulations, and policies that impact the clinical implementation of PM, which includes diagnostic testing, the interpretation of testing within the clinical context, and targeted therapies. Testing alone will not dictate patient treatment. A physician's diagnostic interpretation and interpretation of test results in the context of the patient's clinical situation and the treating physician's clinical expertise along with the patient's preference will guide treatment options.

V. It is essential to build stable clinical genetics infrastructure including workforce investments that are commensurate with development and the application of new genetic knowledge to the prevention and treatment of human disease.

VI. As personalized medicine matures, health information technology will play a key role in these advances. Investments in standards, bioinformatics, and health information technology infrastructure will be required to actualize the promise of PM in health information technology. PM coverage and reimbursement policies should not dictate which diagnostic or treatment options are available to physicians and should take into account the role of physicians in driving PM innovations, development, and application of improved products and services in this arena.

Notes

115 - 1665 West Broadway
Vancouver BC V6J 5A4
doctorsof**bc**.ca

@doctorsofbc

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