Roadmap for Bringing Personalized Medicine to British Columbians

“Preventing, Diagnosing and Treating Disease Are Soon to Change Forever”
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Executive Summary

Healthcare systems worldwide are currently in a state of creative disruption and stress. On one hand, there is a revolution occurring due to extremely rapid technological advances that enable detailed molecular profiling of individuals to achieve more precise diagnoses of disease and to more accurately match therapies to the individual. This is known as personalized medicine, precision medicine, or molecular medicine. On the other hand, the healthcare system is under increasing strain as health-related spending reaches unsustainable levels due in large part to an aging population. It is imperative to align the innovative potential of personalized medicine with healthcare needs to generate benefits for patients, the healthcare system, and the economy. Efforts to achieve such alignment are gaining momentum worldwide. Health economies internationally are investing heavily in ways to implement personalized medicine because there is a clear opportunity to develop healthcare delivery systems that result in improved patient outcomes and that are more efficient and cost-effective.

British Columbia (BC) is well positioned to become an international leader in the practice of personalized medicine. BC has remarkable resources to build on, including a first-rate medical system, globally competitive expertise in molecular medicine technologies, and internationally recognized efforts in the implementation of personalized medicine approaches. Particular strengths include the treatment of: cancer, infectious disease, heart disease, lung disease, and neurological disorders. BC also has significant advantages arising from its single-payer system, including the potential availability of extensive population-wide longitudinal healthcare data that, when analyzed, would be of major value for advancing individualized medicine.

Efforts to introduce personalized medicine in BC have so far been made through the separate efforts of a small number of clinical centres, not-for-profit organizations, private companies, and BC’s universities, partially assisted by uncoordinated support from various government agencies. This needs to change. Further advancement now requires large-scale whole system action from the province in order to make BC a leader in patient-centric, molecularly-based personalized medicine. We need to mobilize together – public sector, private sector, academic centres and not-for-profit agencies – to secure the resources and commitments necessary to accomplish shared goals using a coordinated approach. The time to act is now. We need to act collectively to ensure that BC is at the forefront of molecular medicine, that we deliver the best possible healthcare to our citizens, and that BC becomes a personalized medicine innovation hub with resulting economic benefits.

In order to catalyze the movement towards personalized medicine in BC, the Personalized Medicine Initiative (PMI), together with partners Genome BC (GBC), Life Sciences BC (LSBC), the Centre for Prevention of Organ Failure (PROOF), the Centre for Drug Research and Development (CDRD), and the Life Sciences Institute (LSI) at UBC have organized a Personalized Medicine Summit that was held at UBC in June 2015. This document has been produced in partnership with PricewaterhouseCoopers (PwC), and is a “Green Paper” intended to stimulate discussion regarding ways to introduce personalized, molecularly-based medicine in BC.
Figure 1 - What Will Personalized Medicine Achieve?

Full population-wide implementation of personalized medicine in BC is an enormous task that will take ten years or more. It is important to start laying the groundwork now. Critical objectives that could be achieved over the next three years in order to drive coordinated whole system implementation of personalized medicine in BC are:

1. The government (Ministries of Health, Finance, Innovation, and Advanced Education) should make a political commitment to implement personalized medicine.
2. BC should establish a coalition of stakeholders to coordinate whole system change to enable personalized medicine by addressing: policy, regulation, privacy, education, and economic issues and barriers.
3. BC should capitalize on near-term opportunities to incorporate and integrate molecular medicine technologies into healthcare treatment.
4. BC should establish a longitudinal database of molecular medicine and healthcare data for 5,000 British Columbians to drive patient-centric healthcare, translational research, and innovation.

BC needs to rapidly and collectively implement personalized medicine to provide the best healthcare in the world to our citizens, potentially reduce the cost of healthcare delivery, and benefit economically from the resulting new industries. This discussion document provides background regarding personalized medicine, indicates current strengths that we can build upon, and suggests a pathway towards making personalized medicine a population-wide reality in BC.
Why is Personalized Medicine Important to British Columbians?

Personalized medicine (also referred to as precision medicine or molecular medicine) is on the brink of transforming the practice of medicine by making it more tailored to, and effective for, the individual. A remarkable convergence of events is leading to this transformation. A major driver is the rapid advancement of technologies that are capable of providing definitive molecular-level, person-specific data while increasingly becoming more accurate, comprehensive, and inexpensive. Examples are genomic analyses to characterize the DNA in our cells, proteomic and metabolomic analyses of molecules in our blood and other biosamples, and microbiomic analyses of the microbes coexisting with our bodies.

Advanced computing can now be used to correlate these molecular profiles with states of health and disease (phenotypes). This correlation leads to increasingly accurate diagnostic “biomarkers” for risk of disease, for actual disease and better matching of treatment to the individual. Dramatic improvements in the understanding of human biology are leading to more effective ways of treating disease and wearable devices are enabling new ways of monitoring health. Taken together, these advances are revolutionizing healthcare worldwide by providing more effective and efficient patient-centred personalized care.

The potential of personalized medicine is recognized globally. The CEO of Britain’s National Health Service has said that England must become a world leader in personalized medicine. Barack Obama has indicated that precision medicine must be a priority for the US. Enormous investments are being made to develop clinical applications particularly in the cancer arena. Massive commercial commitments are being made to exploit the economic and clinical potential of personalized medicine. Other provinces in Canada, particularly Ontario and Quebec, have made substantial investments. An environmental scan of other genomic/personalized medicine initiatives around the world is given in Appendix iii.

A public commitment is required in BC to prioritize and resource this crucially important area of medical and scientific discovery. This commitment is necessary for BC to remain at the forefront of molecular medicine innovation, to gain from potential efficiencies in healthcare delivery, to participate in the new industries that will result, and to provide optimal healthcare to British Columbians.

Box 1: Trish Keating and Personalized Genomics for Cancer Therapy

The Personalized Onco-Genomics (POGs) Program at the BC Cancer Agency, led by Dr. Marco Marra and Dr. Janessa Laskin, uses genomic sequencing technology to guide treatment for cancer patients. The goal is to decode the cancer genome to identify genes giving rise to proteins that cause tumour growth and then inhibit these proteins to kill the cancer. Trish Keating was diagnosed with colorectal cancer and underwent five years of treatments including chemotherapy, surgery, and radiation therapy. Her disease was then classified as incurable and terminal. She was then enrolled in the POGs program and her tumour was sequenced, revealing a gene that over-expressed a protein that was potentially causing cancer growth. Importantly, a drug – normally used to treat high blood pressure – was available that inhibits the protein in question. Within weeks of treatment with the blood pressure drug, Ms. Keating’s tumour was rendered nearly undetectable.
Personalized Medicine Is Enabled by Genomic and Other Individual Molecular Profiles

The human genome provides a unique blueprint for each individual. The genome consists of two long strings of DNA molecules known as “bases” that are interwoven in the familiar double helix structure. Each DNA string consists of over three billion bases that code for the proteins that make up your body and approximately three million (0.1%) of these bases differ from person to person. These differences are largely responsible for the differences between people, such as physical appearance, propensity for certain diseases, and reaction to drugs.

Significant progress has been made in sequencing genomes. The cost of sequencing a human genome has decreased from greater than $1 billion in 2000 to as little as $1,000 today¹ (see Figure 2). This has been accomplished while dramatically increasing accuracy and speed. The lower costs are driving an exponential growth in gene sequencing². In 2014, over 200,000 human genomes were sequenced and it is estimated that 1.6 million genomes will have been sequenced by 2017³. The increasing availability of population-wide genomic data is informing and improving clinical practice in a host of areas, including cancer treatments (see Box 1), identifying and treating infectious diseases, prevention of...

Figure 2 - Rapidly Falling Costs Drive Growth in Human Genome Sequencing

Moore’s Law is the observation that over the history of computing hardware, the number of transistors in an integrated circuit has doubled approximately every two years.

A $1,000 genome is regarded as the catalyst for exponential growth in human genome sequencing.

¹ (National Human Genome Research Institute, 2014)
² (Church, 2005)
³ (Regalado, 2014)
adverse drug reactions, cardiac care, and identification and treatment of rare diseases.

Genetic analyses are vital for diagnosis and treatment of many, but not all, diseases. The genome does not change over time, whereas other molecular profiles such as an individual’s transcriptome, epigenome, proteome, metabolome, and microbiome (refer to Glossary in Appendix i for definitions) change constantly in response to lifestyle, diet, and state of health and disease. Profiles that include these additional molecular analyses can provide real-time diagnostics for the presence of disease, response to therapy, and can indicate whether preventive medicine approaches or lifestyle changes are effective.

Profiles of molecules in the blood are providing a particularly useful window on health. Blood bathes every organ in the body. Many of the molecules in the blood are derived from these organs as well as disease sites such as tumours. Thus blood contains an enormous amount of diagnostic information to potentially detect early stage disease as well as to identify and monitor response to therapy. Inexpensive technologies are increasingly coming online to simultaneously measure hundreds, if not thousands, of blood molecules to identify signatures (biomarkers) associated with disease and health.

Human health is also affected by environmental factors such as the enormous number of bacteria and other microbes that live in and on each of us. Again, inexpensive technologies are increasingly available to simultaneously measure 1,000 or more of the bacteria in the colon or other locations; this provides insights into causes of immune disorders and other diseases.

The sum total of all these molecular profiles provides definitive molecular-level information about each individual. Thus the nascent field of creating personal “data-clouds” consisting of genomic, proteomic, metabolomic, and other “Omic” profiles to characterize each individual has major potential for early stage detection of disease and monitoring response to therapy. Sequential profiling of blood molecules over time has been used for early stage detection of type 2 diabetes and its rapid rectification4 and has been used to measure bacteria in the colon leading to diagnosis of inflammatory bowel disease5,6. Other examples include biomarker diagnostics for early detection of diseases such as cancer7 and Alzheimer’s8,9. There is a crucial need for such diagnostics even when there is no effective therapy, such as is the case for Alzheimer’s. Without an accurate diagnostic it is often difficult to ascertain whether a particular therapeutic regime is working which inhibits the development of new, more effective therapies.

The Landscape of Personalized Medicine

There is a worldwide movement towards personalized medicine practices. The use of genomic analyses to personalize the treatment of cancer as noted in Box 1 is a lead example. Cancer is increasingly being treated according to the genetic profile of the cancer itself rather than the tissue it originates from (e.g. breast, colon, prostate, etc.). BC has considerable strengths in this area as demonstrated by the BC Cancer Agency (see Box 1).

Other genetic tests for cancer are coming on line to limit patient exposure to potentially harmful side effects of cancer treatments. BC researchers are leaders in efforts to determine whether certain cancer drugs will elicit unacceptable side effects in pediatric cancer patients. In the US, the FDA has approved the Oncotype DX Breast Assay to determine whether a patient will benefit from radiation or chemotherapy after breast cancer surgery.

The pharmaceutical industry is increasingly developing genetic biomarkers as “companion diagnostics” to determine whether a drug is safe and effective for an individual. Approximately one-third of drugs in late clinical development, and two-thirds that are in pre-clinical development, use biomarkers9 to guide prescription. These biomarker tests target therapeutics to the appropriate patients by identifying who will derive benefit and who will not

4 (Cohen, 2012)
5 (Fehlbaum-Beurdeley, 2012)
6 (Humpel, 2011)
7 (Ludwig, 2005)
8 (Sutherland, Janitz, & Kril, 2011)
9 (Personalized Medicine Coalition, 2014)
and this targeting process can reduce costs in addition to helping the patient.

Genetic tests are also becoming available to avoid adverse drug reactions to commonly prescribed drugs. Currently many common drugs have FDA-approved genetic biomarkers to guide drug prescription to avoid adverse reactions10. These biomarkers are usually ignored as doctors do not know the genetic profile of their patients leading to dangerous “trial and error” prescription practices.

Genetic analyses are also improving diagnosis and management of rare diseases. Patients with these obscure conditions often undergo a “diagnostic odyssey” to determine the reason for their symptoms. This exacerbates patient suffering and places expensive demands on the healthcare system. Whole genome sequencing is proving effective for more timely and specific diagnosing of rare and inherited genetic disorders and, in some cases, is providing a treatment strategy.

A final point is that the introduction of molecular medicine will also address inequities in healthcare arising from differences in gender, ethnicity or age. Medicine based on individual molecular-level profiles will take such differences into account in a natural manner.

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10 (U.S. Food and Drug Administration, 2015)
**Barriers to Implementation of Personalized Medicine in BC**

While personalized medicine is clearly the future of medicine, there are barriers to be overcome. A central issue is that to achieve data-driven, patient-centric individualized medicine, the clinician must have complete, timely, and seamless access to all clinical and healthcare data records through a patient’s electronic medical record (EMR). Currently, healthcare data resides in silos that do not necessarily communicate with one another. Rectifying this situation will require new government policies around data security and privacy as well as improved platforms for integrated electronic health records.

Interpretation of patient-specific molecular-level data requires far more expertise than any one person can have. The development of computerized clinical decision support systems (CDSS) that enable clinician interpretation of individual data-clouds is therefore vital. These CDSS will use advanced algorithms to decipher a patient’s combined genetic and clinical data and suggest optimized therapies. Such computerized approaches will have considerable diagnostic and prescriptive power11.

When applied to patient-specific molecular data, the CDSS will detect particular molecular profiles (biomarkers) that indicate states of disease as based on laboratory-developed diagnostics. Regulatory guidance is needed for use of these laboratory tests (as well as use of companion diagnostics to guide drug prescription) as these tests will guide treatment decisions. The US FDA has produced draft guidance documents in these areas12,13 and we need to do the same. In addition to improving patient outcomes, these diagnostics enable comparative effectiveness research14,15,16,17 to discover cost-effective ways of improving healthcare.

Systematic studies relevant to the BC healthcare system are critically required to evaluate the cost/benefit equation associated with the introduction of molecular diagnostics. There are immediate opportunities to evaluate genetic tests in three areas: namely, the use of pharmacogenomics to reduce adverse drug reactions, the use of genetic analyses to guide the choice of chemotherapeutics to treat cancer, and the use of genomic analyses to guide treatment of infectious diseases such as HIV and hepatitis C (HCV). Such analyses require understanding costs beyond those of the molecular test such as the cost implications of the choice of drug and the number of hospitalizations avoided.

BC should also generate healthcare data to enable implementation of more precise medical practices in complex, high-cost disease states, many of which are associated with old age. Molecular-level profiles of many patients will be required to ascertain biomarkers associated with disease, disease progression, and identification of those who will benefit from standard therapy and those who will not. Interpretation of this data will require advanced data analytics capabilities. Access to the rich datasets available in the BC healthcare system would contribute to such clinical effectiveness studies.

Informed consent of patients is critical for their participation in studies where benefits only accrue from analyses of data arising from large numbers of patients. BC needs a clear governance framework that enables harmonized consent both for initial analysis and for re-contact, to ensure that samples and data can be leveraged to capitalize on technological and scientific advances.

Education and training programs are also necessary. A wide range of healthcare professionals (physicians, genetic counsellors, pharmacists, and nurses) will be involved in the gathering, communicating, and interpreting of molecular information. These professionals must be trained, resourced, and incentivized. Clinical practice guidelines and educational materials must be updated to include guidance regarding molecular analyses. Resourcing personalized medicine will require re-balancing of existing resources as well as training or recruitment of key specialists and the creation of new specialities.

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11 (Bisognano & Schummers, 2014)
12 (U.S. Food and Drug Administration, 2014)
13 (U.S. Food and Drug Administration, 2014)
14 (Naik & Petersen, 2009)
15 (Lantos & Spertus, 2014)
16 (Mushlin & Ghomrawi, 2010)
17 (VanLare, Conway, & Sox, 2010)
How Can We Implement Personalized Medicine in BC?

Current progress to implement personalized medicine in BC results from uncoordinated, grassroots efforts. We now require a system-wide, collective commitment of resources and effort. The objective will be to place BC at the forefront of the personalized medicine revolution. The results will be: the best healthcare possible for our citizens, a more efficient and effective healthcare system, and considerable economic benefits stemming from the creation of new knowledge-based industries.

BC is well-placed to be a global leader in the practice of personalized medicine, however the window of opportunity will be lost if we do not act quickly. Our advantages include an advanced, comprehensive medical system, many world-leading intellectual and clinical resources (see Appendix ii), and a single-payer universal healthcare system that leads to an inherent interest in preventing disease and improving efficiencies in healthcare delivery.

This Green Paper, which is intended to stimulate discussion, makes four recommendations that provide a pathway towards implementing personalized medicine in BC. These are that: (1) BC should make a political commitment to implement personalized medicine; (2) we make the whole system changes required to do this; (3) we capitalize on near-term opportunities; and (4) we initiate the programs that will lead to population-wide implementation of personalized medicine practices. These recommendations are summarized in Figure 4 and expanded upon in the sections that follow.

Figure 4 – Implementation Recommendations

1. Making a Whole System Commitment
   The government (Ministries of Health, Finance, Innovation, and Advanced Education) should make a political commitment to implement personalized medicine.

2. Engaging Stakeholders
   BC should establish a coalition of stakeholders to coordinate whole system change to enable personalized medicine by addressing: policy, regulation, privacy, education, and economic issues and barriers.

3. Taking Advantage of Near-Term Opportunities
   BC should capitalize on near-term opportunities to incorporate and integrate molecular medicine technologies into healthcare treatment.

4. Constructing a Patient-Centred Clinical Database for BC
   BC should establish a longitudinal database of molecular medicine and healthcare data for 5,000 British Columbians to drive patient-centric healthcare, translational research, and innovation.
1. Make a Whole System Commitment

Making a Political Commitment to Personalized Medicine

In order for BC to develop a leadership position in molecularly-based, personalized medicine, it must become a priority at all levels of government. We need strong and coordinated leadership that will work across the healthcare, finance, innovation, and education sectors to provide resources and to set priorities in order to maximize benefits to patient health and to the economy. This would be facilitated by the appointment of high-level Ministry champions for personalized medicine.

Benefits for the Population

The benefits of personalized molecularly-based medicine to the population (i.e., the patient and healthcare consumer in BC) will be extraordinary. Individualized treatments for cancer patients will lead to better outcomes. Improved matching of drugs to the individual will reduce adverse reactions and enhanced diagnostics will result in better matching of therapy to disease. New biomarkers will allow for earlier disease detection and more effective preventive medicine. Definitive information as to whether diet or lifestyle changes are of benefit will have significant impact on treatment options for patients.

Particular benefits will arise from sex- and gender-specific therapy to decrease inequities and permit tailored diagnosis and treatment. Current therapies are not sensitive to ethnic or gender differences in disease presentations or response to treatments.

Personalized medicine will also improve the treatment of common, expensive chronic diseases that are not well managed by “one-size-fits-all” therapies. An example is type 2 diabetes, where molecular technologies are revealing multiple subtypes\(^\text{18}\) - patients with kidney diseases, patients with cardiovascular and immune disorders, and patients with abnormal cholesterol levels\(^\text{19}\). This is enabling the development of personalized treatments for them.

Benefits for the Healthcare System

The Canadian healthcare system urgently needs to identify ways that healthcare can be delivered more efficiently and effectively. Forces leading to increased healthcare spending include the fact that Canada’s population is aging rapidly. Currently 44\% of the healthcare budget\(^\text{20}\) ($215 billion) is spent on people over the age of 65, whom constitute 16\% of the population\(^\text{21}\). The proportion of Canadians over the age of 65 is projected to be 21\%\(^\text{22}\) by 2040. The cost of treating seniors will consume more than 50\% of healthcare dollars by 2028 if current trends continue.

The situation is even more critical in BC. We are aging faster than most of Canada\(^\text{23}\) and BC seniors will comprise 25\%\(^\text{24}\) of the BC population by 2040 and will consume more than 50\% of healthcare costs by 2022 (see Figure 5).

Personalized medicine represents one way in which medical costs can potentially be controlled. For example, 50\% of prescribed drugs do not help the person they are prescribed for\(^\text{25,26}\) partly due to genetic differences between patients. This is estimated to cost BC $1.5 billion annually. Further, adverse drug reactions to prescribed drugs cost BC

\(^{18}\) (American Diabetes Association, 2014)
\(^{19}\) (Krol, 2014)
\(^{20}\) (Canadian Institute for Health Information (CIHI), 2014)
\(^{21}\) (Statistics Canada, 2014)
\(^{22}\) (Statistics Canada, 2014)
\(^{23}\) (Statistics Canada, 2011)
\(^{24}\) (BC Stats, 2014)
\(^{25}\) (Evans & Relling, 1999)
\(^{26}\) (Spear, 2001)
approximately $0.5 billion annually in hospital care. Lack of adherence often arises from unpleasant side effects of the drug regimen, which again is usually due to genetic factors.

As a concrete example of the potential benefits of molecularly-based medicine to the healthcare system, an independent analysis of the Pharmacogenomics in Primary Care project led by Martin Dawes (UBC Family Practice) for six classes of drugs indicates cost savings of $2.1-2.3 billion per year in Canada (see Box 2) while improving or maintaining the standard of care. On a population basis this would suggest cost savings in the range of $200 million per year in BC.

There is a vast potential for preventive medicine to significantly contain the costs required to maintain wellness. Personalized medicine empowers individuals to take care of their own health. Evidence suggests that quantitative individualized data can be a powerful driver of lifestyle changes27.

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27 (Swan, 2009)
**Benefits to the Economy**

Personalized medicine is an enormous driver of innovation and economic growth. The opportunities range from: commercial development of biomarkers to diagnose disease, to biomarkers that match drugs to individuals (right drug at right dose to right person at the right time), to applications (apps) that use molecular-level information to guide individual behavior. It is also possible that entirely new classes of drugs will be developed to prevent trending towards disease, as opposed to treating overt disease.

The availability of detailed molecular-level profiles of individuals in combination with their healthcare data is also accelerating the discovery of drug targets and the development of targeted therapeutics. The clinical trials process can be expedited by correlating drug efficacy with molecular makeup. The use of molecular information is also enabling new clinical indications for established drugs (see Box 1).

**Box 3: Xenon Pharmaceuticals**

Genomic technologies are accelerating drug discovery. A BC company, Xenon Pharmaceuticals Inc., used genomic approaches to investigate individuals with a syndrome called Congenital Indifference to Pain (CIP). This led to the discovery that the sodium channel Nav1.7 was deficient in these individuals, which led to the development a small molecule inhibitor (TV-45070) of Nav1.7 and other related sodium channels. Xenon and Teva Pharmaceutical Industries Ltd. are now in clinical testing to test the safety and efficacy of TV-45070 in patients suffering from uncontrollable pain such as Postherpetic Neuralgia (PHN).

Personalized medicine will dramatically accelerate new drug discovery and development, and the formation of new knowledge-based companies that will benefit the BC economy. BC is already home to established companies such as Xenon Pharmaceuticals that have developed novel classes of drugs discovered through molecular analyses of large patient cohorts (see Box 3). The remarkable potential of the personalized medicine revolution to create new companies and new jobs is illustrated by the fact that at least five new biotechnology companies have started up in BC in this area in the last two years alone (see Box 4).

Personalized medicine will drive major commercialization opportunities in the device and apps areas. For example, there will be increased demand for apps that inform patients regarding their risks of an adverse reaction to prescribed drugs. Other apps that inform consumers as to whether their lifestyle change, diet, or drug regimen are having beneficial effects as reflected by molecular measurements will be popular, as will apps that allow early detection of disease. Apple’s iPhone feature called “ResearchKit” allows researchers to design and market apps for gathering of data (e.g., patient-reported data such as physiological readings from remote sensors) for research. Five such apps are already available to study asthma, breast cancer, cardiovascular health, diabetes, and Parkinson’s disease.

**Box 4: Personalized Medicine Drives Formation of Knowledge-Based Companies in BC**

Contextual Genomics (established 2013) was set up to sequence the tumours of cancer patients to determine which drugs will work most effectively to treat their cancers. GenXys HealthCare Systems (established 2014) is introducing a genetic test to guide drug prescriptions to avoid adverse drug reactions. Microbiome Insights (established 2015) is providing analyses of 1,000 or more bacteria and other microbes in the colon that could affect the immune system. Cyon Therapeutics (established 2014) is developing a personalized medicine approach to the treatment of septic shock. The Molecular You Corporation (established 2014) is developing a standardized series of molecular analyses to enable effective preventive medicine for participants.

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28 (Milne, 2014)
29 (Artenstein & Opal, 2011)
30 (Teva Pharmaceutical Industries, 2015)
31 (Shen, 2015)
2. Engage Stakeholders

Establishing a Coalition of Stakeholders to Drive Whole System Change

We recommend that BC establish a not-for-profit Umbrella Organization representing a coalition of stakeholders in personalized medicine to manage the introduction of personalized medicine in BC. The mandate of the organization would be to drive the implementation of personalized medicine into the frontlines of healthcare, to lead the associated system change required, and to ensure the realization of economic benefits. Further, this organization would be expected to play a lead role in establishing a national presence and enabling Canada to become an international leader in the field.

In order to achieve the vital objective of whole system change, it is suggested that the Umbrella Organization set up a task force with appropriate representation from stakeholders (e.g. patient organizations, Ministry of Health, Health Authorities, and Doctors of BC) to drive the necessary system change in government, healthcare delivery, and society to effectively implement patient-centred molecular medicine. These changes are needed in:

- Policy and regulation, such as providing guidelines to monitor safety and effectiveness of molecular medicine tests;
- Laws to ensure privacy protection and proper use of personal information;
- Data acquisition, management, and analysis to ensure all medical data is gathered, linked, and accessible regardless of locale;
- Preventive medicine initiatives to encourage and empower the patient to use molecular medicine technology to maintain health;
- Integration of the healthcare and basic life science communities to develop new diagnostics and therapeutics; and
- Funding priorities such that studies to introduce and monitor the effectiveness of personalized medicine practices are promoted.

Further, amplified efforts should be made to capitalize on commercialization opportunities arising from implementation of personalized medicine. This is to establish BC as a major driver of innovation and wealth creation in the application of personalized medicine and to benefit from the creation of high-quality employment opportunities in this knowledge-based industry.
3. Take Advantage of Near-Term Opportunities

Building on Our Strengths

In order to implement personalized medicine in BC we must build on our strengths. BC has already had major global successes in personalized medicine. Here we provide five examples of ongoing personalized efforts in BC that must receive prioritized support. These examples are not exhaustive and there are many other ongoing initiatives in BC. Genome BC has played a lead role in funding many of these examples and thus has played a vital role in building these strengths.

A comprehensive program of treatment optimization coupled with outreach and supported by personalized medicine has allowed Julio Montaner and colleagues at the BC Centre of Excellence in HIV/AIDS to virtually control the HIV/AIDS epidemic. This work and other initiatives stemming from it (see Example 1) have been identified as a priority for support.

Example 1: Personalized Medicine for treatment of HIV/AIDS and Hepatitis C

By using the genetic information of both the patient and their HIV and/or Hepatitis C strains, clinicians are able to determine the most effective drug cocktail to use and minimize side effects that may lead to the patient discontinuing treatment. This project is helping to save time and money while also significantly decreasing the number of new HIV/AIDS cases. This has already led to reductions in morbidity and mortality of more than 90% in BC.

Example 2: Tailoring Chemotherapy to the Patient’s Cancer Genome to Enhance Anti-Cancer Potency

Approximately 75% of the drugs used for cancer chemotherapy do not work on the patient they are prescribed for\(^{32}\). Dr. David Huntsman and his team are developing a genetic analysis that tests for 90 mutations in the tumour genome that can be targeted by currently available drugs. This “National Access Project”, with 10 clinical sites across the country, will initially test 2,000 cancer patients with the goal of providing personalized and optimized treatment.

Example 3: Tailoring Cancer Therapy to Avoid Adverse Drug Reactions

Dr. Carleton and Dr. Hayden are identifying genetic factors that lead to severe adverse drug reactions (ADRs) in children undergoing chemotherapy for cancer. For example, approximately 40% of children being treated for solid tumours become stone-deaf as a result of treatment. Approximately 20% of children treated for blood cancers will suffer from heart failure, sometimes necessitating a heart transplant. The study has identified genetic profiles that can predict, with up to 90% accuracy, who will

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BC also has strengths in the development of genetic tests to avoid adverse drug reactions to commonly prescribed drugs used in family practice situations. ADRs are currently the fourth leading cause of death in North America (>100,000 deaths per year). Predictive tests to determine who is at risk of an adverse reaction to a prescribed drug will be of considerable benefit to patients and could lower healthcare costs substantially (see Box 2).

Dr. Martin Dawes (UBC Family Practice) is developing a genetic test (see Example 4) to guide prescription practices in the family practice setting, where 85% of drugs are prescribed. Remarkably, this represents the first time in the world that genetic data is being used to guide drug prescription in family practice. This work is complemented by Dr. Cory Nislow’s (UBC Pharmaceutical Sciences) efforts to enable community pharmacists to flag potential issues with prescribed drugs that could lead to ADRs.

### Example 4: Pharmacogenomics (PGx) in Primary Care and Community Pharmacies

The PGx in primary care initiative will develop and implement a clinical decision support system (CDSS) that incorporates genetic and clinical information to guide prescriptions for 150 commonly prescribed drugs. It is anticipated that implementation of this CDSS by family doctors will result in improved patient outcomes (i.e., fewer adverse drug reactions) and reduced costs (i.e., fewer hospital admissions). The PGx in community pharmacies project will use the patient’s genetic information to alert pharmacists across BC and Canada about potential ADRs and avoid inappropriate dosing decisions.

Organ failures such as heart failure, lung failure, kidney failure, and brain failure result in enormous morbidity and mortality in the aging population. Accurate biomarkers in blood or other bodily fluids indicating the imminence of failure and the effectiveness of therapy will have significant impact.

Example 5: Biomarkers for Organ Failure

The PROOF centre develops molecular assays for organ failure. For example, the “Biomarkers in Transplantation” (BiT) program is developing a biomarker test for detecting acute immune rejection in heart transplant patients. The objective is to avoid the need for most heart biopsies in the first 12 months post-transplant, thus reducing costs and decreasing harmful impacts on patients.

A final example concerns the microbiome which consists of the bacteria and other microbes that live in us and on us. Dr. Deborah Money at the Children’s and Women’s Hospital in Vancouver is leading a Canada-wide personalized medicine program to reduce prematurity births and subsequently reduce neonatal care admissions and prevent the long-term poor health outcomes for these children (see Example 6).

Example 6: Personalized Medicine for Women’s Health

High-throughput sequencing technologies can be used to profile the vaginal microbiome in health and disease. Dr. Money and colleagues are studying the microbiome of the female genital tract with the objectives of predicting unexpected preterm births and preventing the adverse outcomes for women, infants, and their families related to prematurity.

In summary, BC has major strengths on which to build a globally competitive and internationally recognized personalized medicine program. Focused resources must be applied to these endeavours to gain near-term wins that demonstrate the value of personalized molecular medicine and to accelerate adoption into the broader community.

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33 (Giacomini et al., 2007)
4. Construct a Patient-Centred Clinical Database for BC

Implementing the Medicine of the Future

The medicine of the future will be data-driven and will be focused on the individual patient. All patient-related data will be accessible via electronic medical records (EMRs), and population-wide patient data will be deposited into large, secure databases that can be collectively analyzed. This analysis will be used, in conjunction with standard clinical data, to establish correlations between individual molecular profiles and states of health and disease. In order to gradually transition to this new form of medicine, a staged implementation process is needed that can eventually be expanded population-wide.

As a first step, we recommend that BC gather standardized, longitudinal (over 3 years), personal molecular data clouds for 5,000 volunteers representing a cross-section of the patient communities that incur the highest costs, both in terms of mortality/morbidity as well as monetary costs to the healthcare system. These volunteers will be drawn from cohorts representing most major disease states and will involve all socioeconomic, age, gender, and ethnic states. The molecular analyses will begin with a whole genome analysis followed by proteomic, metabolomic, microbiomic, and possibly other molecular analyses in four-month intervals. Participants will wear an electronic monitoring device to report on vital signs and they will meet with a healthcare professional every four months to interpret the data. All volunteers will be required to provide written consent that their data can be used for research purposes. The project will require establishing a province-wide database that will contain not only the molecular and vital sign data from participants, but also be linked to their personal health data and records.

The areas of disease focus will include: cancer, autism, and chronic diseases of the aged such as dementia, Alzheimer’s, Parkinson’s, diabetes, heart failure, and COPD, among others. The generation of molecular data clouds around individuals suffering from these disorders will provide an engine of discovery to: identify biomarkers associated with progression to disease, respond to therapy and maintenance of health, and potentially give insight into ways of enhancing clinical outcomes and reducing health expenditures.

The database will allow clinicians to stratify patients (based on their molecular profiles) in any given disease cohort into those who respond to current therapy and those who do not. This will allow the development of more appropriate therapies for non-responders and will begin to address the fact that more than 50% of prescribed drugs do not work on the patients for whom they are prescribed.34,35,36

The clinical database will catalyze considerable basic research, translational research, innovation, and commercialization. It will enable BC’s research community to use human data to inform basic research aimed at understanding the causes of disease and methods to treat disease. Further, establishing and utilizing the database will provide a driving force to make the necessary system changes in order to enable personalized medicine to be effectively practiced in BC.

34 (Evans & Relling, 1999)
35 (Spear et al., 2001)
36 (Schork, 2015)
### Conclusion

This Green Paper summarizes the need for introduction of personalized medicine practices, the advantages this will bring, the strengths that BC can build on, and the ways that personalized medicine can be introduced. We hope that the strategy and priorities suggested here will stimulate the stakeholder discussions necessary to introduce personalized care in BC. It is important that the benefits of the personalized medicine revolution be made available to our population and that BC becomes a leading force in the movement towards individualized care. A potential implementation roadmap is summarized in Figure 7.

**Figure 7 - Implementation Roadmap for Personalized Medicine in BC**
Appendix

i. Glossary

**Adverse drug reactions** (ADRs): Detrimental effects of a medication that was correctly administered at the right dose for therapeutic or prevent use.

**Big data**: Large and complex sets of data that cannot be manipulated or analyzed using standard data processing applications and tools. In biology, it refers to the rapidly growing amount of digital data such sequence data, other molecular information (e.g., proteome), connectomics (the comprehensive mapping of every neuron in the brain with its neighbour), and other biological information. Advanced computing infrastructure and predictive analytics (i.e., modelling, machine learning, and data mining) are used to process and unlock the value contain within big data sets.

**Biobank**: A large collection of human biosamples for research purposes.

**Biomarker**: A molecular signature (e.g., DNA, RNA, protein, metabolite, microflora, or a combination of thereof) indicative of some biological state or condition (usually in reference to a particular diseased state).

**Biosamples**: Samples containing biological materials such as blood, urine, saliva, stool, tissue, etc.

**Companion diagnostic**: A medical device or laboratory test that provides information to guide for the safe and effective use of a corresponding treatment (i.e., drug or biological product such as an antibody therapy). The test helps determine whether a particular therapeutic product’s benefits are greater than any potential side effects or risks to the patient.

**Comparative Effectiveness Research** (CER): Research that directly compares existing health care interventions to determine which work best for which patients and which pose the greatest benefits and harms.

**Data cloud**: A “virtual” environment (i.e., remote computing infrastructure) where information of all types can be stored and accessed in real-time. When used in relationship to health, the data cloud encompasses the individual’s identification, medical history (i.e., electronic medical records), clinical information (e.g., blood work), molecular information (e.g., genome, proteome, metabolome, microbiome), and information measured by wearable technology.

**DNA** (deoxyribonucleic acid): Self-replicating polymer (sequence) of nucleic acids that is present in nearly all living organisms. It is the carrier of genetic information that encodes the instructions for the development and functioning of all known living organisms.

**Electronic medical records** (EMRs; or electronic health records [EHRs]): An electronic record of an individual’s health information that is theoretically capable of being shared across different healthcare settings.

**Epigenomics**: The study of the chemical compounds and the processes that modify (i.e., epigenetic marks) the genome and its associated proteins to regulate the expression of genes in a cell.
**Gene**: A sequence of DNA that codes for a particular protein with a specific function in a cell.

**Genome**: The complete set of genes or genetic material encoded in the DNA in a cell or organism.

**Genomics**: The study of the structure, function, evolution, and mapping of the genetic material (i.e., DNA, RNA) present in a cell or organism.

**Metabolites**: Small molecule intermediaries and products of metabolism (usually less than 1500 Daltons).

**Metabonomics**: The study of the complete set of metabolites within an organism, cell, or tissue and the chemical processes involved in their production and breakdown.

**Microbiome**: The study of the complete set of indigenous microbial organisms in a biological specimen or those associated with another organism, such as a human.

**Omics**: Refers to fields of biology that at aims at the collective characterization and quantification of pools of biological molecules (or measurements) that translate into the structure, function, and dynamics of an organism(s). These biological measurements include, but not limited to, DNA (genome), RNA (transcriptome), proteins (proteome), metabolites (metabolome), microflora (microbiome), and neural connections in the brain (connectome).

**Personalized Medicine (precision medicine or stratified medicine)**: The use of molecular-based individual information to guide medical decisions, practices, and/or therapies.

**Pharmacogenomics**: The study of the individual’s genetic information and how it affects drug response.

**Phenotype**: An organism’s observable characteristics or traits (e.g., physical appearance, biochemical or physiological properties, behaviour).

**Preventive healthcare** (preventive medicine): Healthcare that focuses on proactive strategies to avoid disease development as opposed to disease treatment. Molecular understanding such as genetic sequencing of an individual can inform of disease risk, thus allowing the individual to take pre-emptive measures such lifestyle changes or preventive surgery (i.e., in the case of certain breast/ovarian cancers, the ‘Jolie effect’) to avoid development of disease.

**Proteomics**: The study of the complete set of proteins that is or can be expressed by a cell, tissue or organism.

**RNA** (ribonucleic acid): Like DNA, it is a polymer of nucleic acid present in all living cells and organisms, that act as a messenger carrying instructions from DNA for controlling the synthesis of proteins.

**Sequencing** (DNA sequencing, genetic sequencing, whole genome sequencing): The process of determining the order of nucleotides within a genetic sequence.

**Transcriptomics**: The study of all the messenger RNA molecules expressed from the genome of an organism.

**Wearable technology** (wearable devices): Wearable electronic devices that contain wireless sensors to remotely measure the body’s physiological parameters (e.g., blood pressure, beats per minute, blood oxygenation, brain activity) as well as physical activity (e.g., steps taken, flights of stairs climbed).
### ii. Personalized Medicine Resources in BC

#### Academic Research Institutes
- University of British Columbia
- Simon Fraser University
- University of Victoria

#### Spinal Cord Injury and Neurology
- NeuroDevNetNCE
- iCORD
- Djavad Mowafaghian Centre for Brain Health

#### Cancer
- BC Cancer Agency
- Michael Smith Genomic Sciences Centre
- The Vancouver Prostate Centre

#### Infectious Diseases
- BC Centre for Disease Control
- BC Centre for Excellence in HIV / AIDS

#### Cardiovascular Lung and Health
- PROOF Centre
- Centre for Heart Lung Innovation
- Canadian Arrhythmia Network (CANet) NCE
- Institute for Heart + Lung Health

#### Drug Development
- Centre for Drug Research & Development (CDRD)
- CDRD Ventures Inc.

#### Pediatrics
- Child & Family Research Institute
- Centre for Molecular Medicine and Therapeutics
### iii. Details on Other Genomic Initiatives

<table>
<thead>
<tr>
<th>Name of Initiative (Organization)</th>
<th>Public/ Private</th>
<th>Main Objective</th>
<th>Cohort Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision Medicine Initiative</td>
<td>Public</td>
<td>Establish a molecular (genomics) database of 1 million voluntary Americans to conduct research to improve diagnostics and treatments for disease, starting first with cancer.</td>
<td>1 million</td>
</tr>
<tr>
<td>(United States Government)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>100,000 Genomes Project</td>
<td>Public</td>
<td>Establish a database of 100,000 genomes to enable new scientific discoveries and insight to bring benefits to patients with rare diseases or cancer.</td>
<td>100,000</td>
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<tr>
<td>(Genomics England; NHS)</td>
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<tr>
<td>Million Veterans Project</td>
<td>Public</td>
<td>Establish a database of genomic and medical data to understand how genes affect health and disease, such as diabetes, cancer, and post-traumatic stress, in order to improve healthcare for veterans.</td>
<td>1 million (&gt;345,000 volunteers registered)</td>
</tr>
<tr>
<td>(US Department of Veterans Affairs)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Personal Genome Project</td>
<td>Public</td>
<td>Establish an open-access database of non-anonymized whole genome and longitudinal clinical data to better understand human traits and health.</td>
<td>100,000</td>
</tr>
<tr>
<td>(Harvard Medical School)</td>
<td></td>
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<tr>
<td>Million Omics Database Project</td>
<td>Private</td>
<td>Establish a molecular medicine database for 1 million people that include: genomic, transcriptomics, epigenomics, metabolomic, and microbiomics data for health and commercial benefits.</td>
<td>1 million</td>
</tr>
<tr>
<td>(Beijing Genome Institute)</td>
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<tr>
<td>23andMe</td>
<td>Private</td>
<td>Provide whole genome sequencing services to consumers and establish a database of genomic information for use in health research and development of new drugs.</td>
<td>&gt;1,000,000 clients</td>
</tr>
<tr>
<td>The Baseline Study</td>
<td>Private</td>
<td>Collect genetic and molecular data to analyze and uncover biomarkers for disease.</td>
<td>&gt;100,000</td>
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<tr>
<td>(Google X Life Sciences)</td>
<td></td>
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<tr>
<td>Human Longevity Inc.</td>
<td>Private</td>
<td>Compile the most comprehensive database on human genotypes and phenotypes using the latest genomics, proteomics, microbiomics, informatics, computing, and cell therapy</td>
<td>100,000 per year</td>
</tr>
<tr>
<td>Initiative</td>
<td>Ownership</td>
<td>Description</td>
<td>Participants</td>
</tr>
<tr>
<td>------------</td>
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<tr>
<td>Human Genetics Initiative (Regeneron Pharmaceuticals Inc.)</td>
<td>Private</td>
<td>Collect and analyze the genetic information of 100,000 individuals to develop new drug targets and pharmacogenomics markers.</td>
<td>&gt;100,000</td>
</tr>
<tr>
<td>100K Wellness Project (Institute for Systems Biology)</td>
<td>Private</td>
<td>“P4 Medicine” using the latest molecular profiling and wearable technologies to amass a database for understanding health at the molecular level and enabling preventive medicine.</td>
<td>100,000</td>
</tr>
</tbody>
</table>
iv. References


Statistics Canada. (2014, September 17). *Selected age structure indicators, observed (1923 to 2013) and projected (2023 to 2063) according to the low-growth (L), medium-growth (M1) and high-growth (H) scenarios, Canada*. Retrieved from http://www.statcan.gc.ca/pub/91-520-x/2014001/tbl/tbl2.4-eng.htm


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