

Summary : Health Care and Health Policy Challenges in Genetic Laboratory Services

The genome plays a significant role in all individuals' health and response to health care. The influence of a genetic endowment on the health of populations is well recognized. Amongst the 6000 or so classical genetic diseases registered in Online Mendelian Inheritance in Man (OMIM), more than 1600 (the most frequent) have been pinpointed to specific gene mutations essentially through modern molecular genetics tools. Most gene mutations resulting in disease are rare, but taken together, they are estimated to affect up to 5% of the population, resulting, for example to 50% of all hospitalizations in pediatrics. Also, most of the major health problems contributing to the burden of disease according to Statistics Canada (e.g. cardiovascular disease, cancer, mental health, diabetes, obesity, osteoporosis, etc.) have significant genetic components (from 30% to 80%). However, in most cases, the major genes involved have not yet been identified or validated for clinical use, due to the very complex nature of gene-gene and gene-environment interactions in these "complex-traits".

Therefore, provision of health care services in genetics provides many challenges that dictate a structured research effort to address these services and policy issues in order to improve the health of the population. Genetic laboratory services play a significant role in the global offer of genetics services and also pose specific challenges in terms of service delivery and accessibility, cost-efficiency and cost-effectiveness, decision frameworks and knowledge transfer tools for health care providers and stakeholders at all levels.

RESEARCH PROPOSAL

Health Care and Health Policy Challenges in Genetic Laboratory Services

A) General objectives: CanGeneTest Consortium will aim to: 1) evaluate the effective-ness of genetic laboratory services in Canada by studying a) the dynamics between actors and institutions that impact on the ability to lead a rational development of genetics laboratories; b) the current status and use of genetic laboratory services; 2) study the validity and cost-effectiveness of various genetic diagnostic tools, using empirical data from the population; 3) develop tools and approaches to help decision makers to establish the relevance of introducing new genetic diagnostic technologies (with or without a solid evidence-base); 4) adapt health technology assessment approaches to genetic laboratory innovations; 5) lay the grounds for a systematic knowledge transfer strategy that will bridge producers, users, policy makers, service providers and consumers in genetic laboratory services; and 6) study the regulatory framework of the public offer of testing and of laboratory practices.

B) Background (underlined references are from this application's PIs)

The pace of genetic discovery. Since 1990, the rate of gene discovery has been exponential. These discoveries have set the foundation for the understanding and acceptance that genes are a significant determinant of health (1) and response to healthcare (2), and that virtually all disease has a genetic contribution to its causation. In the very next future, genetics will likely identify which individual genes, or group of genes, are associated to disease susceptibility or protection and which ones affect our response to therapy. For instance, knowledge of inborn errors of metabolism facilitates diagnosis, prevention and treatment. This experience sparked great interest in determining how genetic factors predispose to common disease. Since 1980, billions were invested in genetics and genomics research worldwide, to begin to answer this question. In the past decade, Canada alone invested an estimated \$600 million in human genetic research (3), and Canadians have made significant contributions to gene discovery. However, to date, there has been little research to determine how these discoveries can be translated into practice and therefore improve health. We do not yet know how best to capture the benefits of this new knowledge. This lack of knowledge is highlighted by the fact that the effectiveness of commonly used tests, such as the BRCA breast cancer gene test, is often not established. Indeed, all developed countries have failed to effectively deliver new medical knowledge to their populations, as outlined in a recent commentary by a leading health researcher (4).

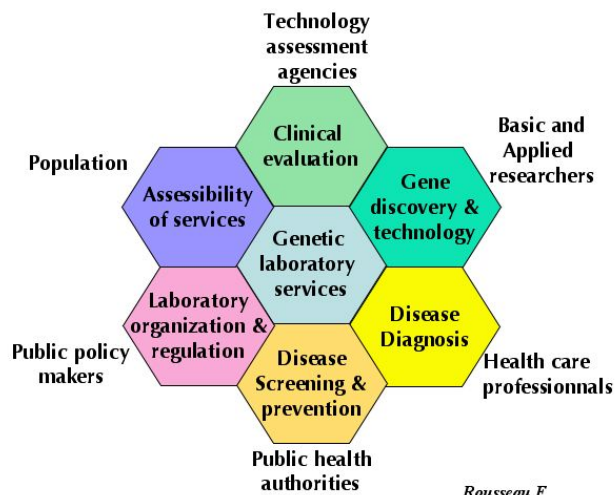


Figure 1

Capturing the health, social and economic benefits of genetic innovations is a significant opportunity for Canada, and a major objective of this research program. Genetic laboratory services are a corner stone of genetic services which rely on effective and timely diagnosis of a genetic condition or carrier status. Genetic testing is currently used to i)confirm a diagnosis where symptoms already exist (such as fragile-X syndrome), indicate whether someone with a family history of late-onset disease is likely to develop the disease (such as Huntington's disease), ii)test whether someone is a carrier of a recessive disorder (such as cystic fibrosis), or iii)screen before birth for genetic disorders (such as Down syndrome) or newborns for genetic disorders (such as phenylketonuria). Genetic laboratory services interface with all aspects of health services delivery and policy making. Indeed, as shown in figure 1, they are located at the interface with gene discovery and technology development in genetics, technology assessment and clinical evaluation, health care professionals (medical geneticists, genetic counselors, primary care and other physicians), public health, public policy and, not the least, the population through accessibility to laboratory services. Interactions between interfaces and stakeholders are principally realized through decision-making processes and tools, including evidence-based laboratory medicine, computer simulation, health economics, knowledge transfer tools and web-based education. Diagnostic tools emanating from gene discoveries need to be evaluated for their medical utility, cost-effectiveness and impact on quality of life. Government health agencies are currently ill prepared to provide a formal policy aimed at health professionals and decision makers in order to lead them to help the genetic field efficiently contribute to the general objectives of the health care system. Despite huge investments to discover and develop new technologies, Canada has minimal and dispersed capacity to evaluate not only the effectiveness of new tests and treatments, as mentioned in the Romanow and Kirby commissions and the 2003 Federal, provincial, territorial Health Care Renewal Accord (5, 6, 7), but also the dynamics that underlie the development of the field and their consequences on the continuous capacity of the health care system to meet its fundamental objectives. Recently, different projects, lead by members of this Consortium, were initiated to enhance technology transfer and knowledge translation downstream of genetic discovery. However, these initiatives are fragmented and do not individually encompass the full spectrum of expertise necessary to integrate cost-effective genetic innovations into health care in a timely manner. We propose to interface several such initiatives and build on them, thereby leveraging both the expertise and the resources.

Canada must efficiently integrate appropriate genetic innovations into health care. The impact of genetics on the provision of health care in the future might well be tremendous (8, 9). At an early stage, it is time to globally consider possible developments in order to ensure an efficient contribution to the main objectives of the Canadian health care system. Here is a unique opportunity to harness Canadian expertise and to increase significantly the efficiency of this process. Realization of this opportunity is in part made possible because of our nationally funded health system in which exchanges of expertise and resources are easier than in a privately funded system. The knowledge translation process from discovery to application requires a wide range of expertise, including technology development, technology and economic assessment, health services research, knowledge transfer, and professional and public education (10). All of these activities must take into account Canada's unique ethical, social and legal framework.

The promises of genetics for health care Genetic markers have the potential to improve or simply allow a clear diagnosis but few have been adopted by routine clinical laboratories. Classical monogenic disease genes have mutations severely affecting their function which are generally rare (< 1% of the population) and their prevalence is estimated from the occurrence of the trait using classical genetics mathematics. This does not account for possible modifier genes nor variable penetrance of a mutation. Thus, surprises are to be expected when mutation frequencies are estimated reliably by large population-

based studies (11, 12). These are often important because they provide critical information related to the true meaning of being a carrier of a mutation and help determining the counseling to be provided given a positive result (11, 13). The pathogenesis of most diseases involves genetic and environmental components in various proportions. Genes are involved in disease causation (14, 15, 16, 17, 18), disease susceptibility (19, 20), susceptibility to environmental agents (21), host response to disease (22, 23) as well as individual response to therapy – pharmacogenetics (24, 25, 26, 27, 28). Genetic effects may be strong, moderate or weak and strong effects are more easily detected but identification of gene variants involved in complex traits appears to be more complicated than anticipated (29). Genetic markers of risk could be integrated in disease-screening programs to refine the risk estimates or even to adjust the frequency of screening according of an individual's risk (30).

Introduction of genetic tools in medicine is not occurring efficiently. DNA-based markers are seen as the diagnostic markers of the future (2, 31, 32). Replication studies must confirm initial findings of an association between a gene and a trait (33, 34, 35, 36, 37, 38). The value of a given DNA test in the clinical setting in conjunction with existing diagnostic and therapeutic approaches needs to be evaluated to allow its evidence-based introduction (39,40). Analytical performance (detecting the mutation) and clinical performance (detecting the disease/condition) must be determined. Analytical performances are good for molecular tests (41) but are rarely systematically evaluated. Clinical performances suffer from the lack of reliable evaluation and this resulted in non-optimal introduction of molecular tests into clinical practice with some clear difficulties for clinicians in handling these novel tools (42). Physicians must know the meaning of a negative or positive test and its limits in terms of its capacity to detect the mutations they are looking for (40).

The rate of introduction of innovations (use of discoveries on markets) is slower for biomedical discoveries (innovations) than for discoveries in other industries for three major reasons: i) biomedical discoveries take a longer time to get approved by regulatory agencies than other types of discoveries that need only to be accepted by consumers; ii) decisions made by policy-makers and health services organizations require more time to be made than decisions made in the private sector; iii) the impact of introducing innovations on the overall cost of health care can be important, although some savings can also occur, and studies aimed at evaluating this point are costly and lengthy to conduct (43). However, because Canada invests 10.5% of its GDP in health services, results contributing to improve at the margin the effectiveness of introduction/implementation of useful discoveries have very significant impact in terms of cost savings and quality of services. One of our objectives is to study these processes in the field of diagnostic genetic innovations to improve the efficiency and timeliness of their evaluation and allow for an optimal implementation of relevant new diagnostic genetic services supported by a clear evidence-base.

Other factors have an impact on the uptake of genetic technologies by the health care system. Partly because of its rapid evolution and particular technologies and equipment used, molecular genetic diagnostic tools have been introduced in health care using a somewhat unusual mechanism. Indeed, several research laboratories have been involved in laboratory service delivery, and have offered testing for specific genetic diseases while the public hospital's clinical laboratories has limited resources to introduce new tests. This has affected accessibility to genetic testing and thus contravenes to the Canadian Law on Health (1984) which guarantees a one-tier system. Research laboratories and personnel are still involved in genetic testing for medical purposes, with all the associated problems such as quality assurance, liability insurance, unstandardized and incomplete reporting of results. Also health care professionals in general as well as the general public have difficulty making the difference between diagnostic, carrier, and predictive genetic testing. Moreover there is a lack of understanding of probability and risk communication (44). Other factors include funding issues, availability of expertise, and the fact that loose development of laboratory services in both the public and private arena results in

inequalities in access to services and undue pressure for public laboratories to use new tests without a solid evidence base for cost-effectiveness (5).

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