Familial Cancer (2006) 5:3–13
DOI 10.1007/s10689-005-2570-8

Partnering in oncogenetic research – The INHERIT BRCAs experience: Opportunities and challenges

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Key words: academic teams, clinical practice, collaboration, familial cancer, genetics, hereditary cancer, interdisciplinary, knowledge translation, research

Abstract

Today it is common to conduct research in collaboration with colleagues from different disciplines and institutions. The INterdisciplinary HEalth Research International Team on BReast CAncer susceptibility (INHERIT BRCAs), involves Canadian and international experts from diverse fields working with health service providers, patients and collaborators from the World Health Organization and other European networks. Evidence-based information and knowledge transfer drive our efforts to advance genomic research to understand the genetic basis of cancer susceptibility and treatment response. Several goals reveal the interdisciplinary team approach: (a) to estimate the prevalence and penetrance of *BRCA1* and *BRCA2* mutations and their deleterious impact upon different populations; (b) to pinpoint novel breast cancer susceptibility loci; (c) to assess the efficacy of clinical interventions; (d) to address changes in quality of life and health-related behaviour from the decision to undergo genetics testing and during follow-up; (e) to evaluate legal, social and ethical implications; and, finally; (f) to promote professional and public education by facilitating the transfer of research findings to clinical practice and informing policy makers. The lessons learned by the INHERIT research team and future challenges are presented.

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* The Interdisciplinary Health Research International Team on Breast Cancer Susceptibility (INHERIT BRCAs) is an international team of researchers with a major interest in inherited breast cancer. The team is funded by the Canadian Institutes of Health Research. Other members and collaborators of INHERIT BRCAs involved in this study are listed in Appendix A.

During the past 30 years, there has been great progress in understanding the molecular and genetic basis of complex diseases such as cancer. Since it is estimated that 6 in 10 people will develop a disease with a genetic component by age 60 [1, 2], human genetics will play a crucial role in medicine and public health by providing genetic information for disease prediction and prevention [2–4]. Still, within the next decade, cancer should replace heart disease as the leading cause of death in North America. It is already the leading killer of those under age of 75, and among those between 45 and 64, cancer is responsible for more deaths than the next three causes combined (heart disease, accidents and stroke). In this regard, the Standing Cancer Prevention Committee of the American Society of Oncology recognized that "until recently, practice in oncology has focused principally on intervening to slow or reverse cancer. Insights from molecular biology and molecular and population epidemiology justify interventions within a broadened definition of carcinogenesis that includes the continuum of events from initial genetic or epigenetic 'hit' to the terminal events" [5].

Research reveals that a positive family history is the major epidemiological risk factor for breast cancer [6]. All common cancers show familial clustering, with disease being more common in first-degree relatives of affected persons [7]. The identification of two genes, *BRCA1* and *BRCA2*, which, when altered, confer markedly increased susceptibility to breast and ovarian cancer, also helps to identify high-risk individuals [1, 8, 9].

Interdisciplinary research is the linchpin in major scientific progress [10]. In fact, it has become an important and necessary component in research given the increased complexities of investigative science and evidence-based research. Gradually researchers have been grasping the potential benefits of interdisciplinary research, which transcend traditional investigative methods, and provide opportunities to improve strategies for disease prevention, diagnosis and treatment. In a similar spirit, the International Symposium on 'Oncogenetics: Achievements and Challenges' held in Montreal, Canada, Oct. 7 and 8, 2004, provided a forum to discuss and encourage the marvels of interdisciplinary research, as well as to demonstrate the advantages and challenges of interdisciplinary cancer genetics research.

To highlight the interdisciplinary nature of the symposium, the articles in this special edition of *Familial Cancer* represent key findings from the meeting and are presented in distinct yet related sections. The first and second sections deal with the challenges of progress in genetic medicine and paediatric cancers. The third and fourth sections address cancer genetics management, counselling and methodological issues. The final section focuses on the ethical, legal and social challenges in cancer genetics. Together, the authors offer innovative approaches to cancer genetics research.

We introduce this special edition of *Familial Cancer* by presenting the INHERIT BRCAs experience as a model for interdisciplinary familial cancer research. In this article, we will gather multiple perspectives under a single heading by providing a brief description that will help to explain: the meaning of interdisciplinary research; why breast cancer is an appropriate prototype for familial cancer; and, finally, how researchers from different perspectives enhance the understanding of (i) the genetic basis of cancer susceptibility; (ii) the translation of genetic information into health applications; (iii) the psychosocial impacts, (iii) the social, legal and ethical implications; and (iv) the transfer of knowledge into appropriate health policies and services. We conclude with a summary of the lessons learned by the INHERIT BRCAs team and some future challenges.

What is an interdisciplinary approach?

'Interdisciplinary' is an imprecise concept that is difficult to define judging from current literature. There is no commonly agreed upon definition, which interchangeably uses the terms 'interdisciplinary', 'multidisciplinary', and 'transdisciplinary'. Since special consideration of this topic has been addressed elsewhere [11, 12], it is not our purpose to review the definitions or the management models of interdisciplinary research teams. In this discussion we will use the Qin et al.'s [13] explanation of interdisciplinary because the following characteristics they describe also apply to INHERIT BRCAs: (a) the research group represents different bodies of knowledge; (b) team members use different approaches to solve problems; (c) individuals play specific roles in finding solutions; (d) group members work on a common problem and share responsibility for the final product; (e) the group shares common facilities; and, finally, (f) the nature of the problem determines the composition of the team since all members come together to investigate, to understand and to improve health in the battle against genetic predisposition to breast and ovarian cancer.

Advantages of an interdisciplinary approach

Interdisciplinary research has emerged as the preferred method to achieve scientific progress and innovation [10, 14, 15] because it brings together unique, unrelated talents and resources to address and solve problems that individual investigators could not tackle alone. The synergistic combination promises to yield a more valid understanding of problems, and to provide richer potential findings [11]. In the case of genetic predisposition to breast cancer, for example, health-related questions often transcend traditional boundaries and draw upon such diverse disciplines as biology, medical genetics, molecular diagnostics, demography, psychology, sociology, law and public policy.

The experience of young women with early-onset breast cancer reveals how collaboration using an interdisciplinary model addresses the multiple phases of her

experience. Consider: she has breast cancer and requires immediate treatment (surgery, oncology, pathology), she is eventually discovered to have a strong family history of breast cancer (genetic counselling). She is recruited into the *BRCA1/2* research (ethics) and undergoes screening for potential deleterious mutations in her *BRCA1/2* genes (molecular diagnostics). She is found to have no mutation, which in her case increases her level of anxiety about her family history (psychosocial) because now there is no test to offer her sisters or daughters. She and other family members are recruited (genetic counselling, ethics) into a new research project to explore the possibilities of the presence of new susceptibility loci (*BRCAX*) and her family's DNA is studied by various gene-mapping approaches (molecular biology, molecular genetics, bioinformatics). Because she is from a region with unusual founder characteristics (molecular genetics, demography), a genetic demography study attempts to understand the role of such a founder effect. Evidence revealing a common haplotype emerges for her and her affected relatives on a specific chromosome. This needs to be further tested on comparison groups of other high-risk, non-*BRCA1/2* families enrolled in two Canadian cohorts, one with the unique genealogical characteristics of a founder population (Quebec), the other reflecting the general population in Canada (Alberta), and to compare them with linkage data from other several large families around the world. After this, a potential test can be developed and used for further studies (analytical validity, clinical validity and clinical utility) for which she would need to give further consent (ethics) before the start of any diagnostic testing (diagnostics). She eventually receives the result of her BRCAX-positive mutation status (genetic counselling, psychosocial) and is also eligible to participate in international studies for carriers of known mutations (genetic and clinical epidemiology).

In other words, this example resoundingly rejects the focus on isolated disciplines and places the spotlight on co-operation and collaboration of many different disciplines including basic science, medical genetics, molecular diagnostics, technology assessment, ethics and public policy. Teamwork is beneficial because it markedly reduces the time it takes to translate scientific discovery into clinically useful information or tests [16, 17]. It also provides a critical advantage when individuals, their families and their health-care providers make evidence-based decisions. Additionally, it will benefit government agencies, which are increasingly required to demonstrate the adequacy and accountability of their policies [18].

The INHERIT BRCAs research team

The INHERIT BRCAs (INterdisciplinary HEalth Research International Team on BReast CAncer susceptibility) program, funded in 2001 by the Canadian Institutes of Health Research, brings together Canadian and international experts from diverse fields to work in partnership with health-service providers and patients, as well as with collaborators from the International Agency for Research on Cancer (IARC, a WHO agency) and other European networks. The INHERIT BRCAs team calls for linking researchers, collaborators and their partners in a carefully chosen, overlapping web that plays a crucial role in the battle against familial cancer.

The phase I team includes 18 PIs and 23 collaborators from 10 universities in Canada, United Kingdom and France (World Health Organization-IARC). The team collaborates directly with another 40 more professionals, research assistants, nurses, computer scientists, psychologists, family doctors, medical geneticists, oncology specialists, gynaecologists, surgeons and haemato-oncologists, as well as more than 40 graduate students and post-doctoral fellows, all of whom work closely with experts in molecular genetics, genetic, clinical and psycho-social epidemiology, population health, ethics and law and were involved in the phase I program.

Familial diseases: breast cancer as a prototype

As stated earlier, all common cancers show familial clustering, with disease being 2- to 4-fold more common in first-degree relatives of affected persons [7]. Twin studies indicate that most of the familial aggregation not attributable to chance results from inherited susceptibility rather than life-style or environmental factors. In part, this may be explained by specific familial cancer syndromes in which variants of single genes confer a high risk of disease. During the past decade, the discovery of such gene variants has provided fundamental insights into various pathways of carcinogenesis [19]. The *BRCA1/2* genes account for about 20% of the heritability of breast cancer, while other rarer defects (*TP53*, *ATM* and *PTEN*) account for less than 5% [20]. The number and properties of the genetic variants in the remaining ~75% are unknown, but current data are most consistent with a polygenic model involving many genetic variants, each conferring a slight to moderate increase in risk [20, 21]. Based on this model, it has been estimated that 12% of women have a risk of breast cancer of at least 10% by age 70, and this subpopulation accounts for half of the total number of breast cancer cases diagnosed in the general population. By contrast, 50% of women are estimated to have a 3% or less risk of breast cancer by age 70 and this subpopulation accounts for only 12% of all breast cancer cases [20]. There is also evidence that environmental factors and other genes modify the risk of breast cancer in *BRCA1/2* mutation carriers [22, 23] suggesting that use of genetic-risk profiles, and consideration of gene–environment interaction, may provide substantial improvements in the efficacy of population-based cancer control [20]. The familial risks

for other common cancers are similar and therefore risk profiles based on genetic susceptibility would also be expected to improve the efficacy of measures to control these cancers.

How do researchers from different perspectives enhance our understanding of cancer genetics?

To demonstrate the advantages of interdisciplinary collaboration in cancer genetics research, we will highlight experiences from four years of work on the INHERIT BRCAs project (phase I) and provide examples of some of the challenges ahead in phase II.

Genetic basis of cancer susceptibility

Contribution and impact of BRCA1/2 on certain types of cancer

A decade ago, two main susceptibility genes for breast and ovarian cancers have been identified: *BRCA1* and *BRCA2*. Furthermore, those with a deleterious mutation in the *BRCA1* or *BRCA2* gene show a higher risk of developing certain types of cancer. Analysis of the Breast Cancer Linkage Consortium cohort, including families with at least four cases of breast cancer diagnosed before age 60, or of the ovary, suggests *BRCA1* gene mutations may be responsible for about 50% of families with a high incidence of breast cancer and 80% of families with cases of breast cancer and ovarian cancer [1, 8, 9]. As for the *BRCA2* genes, a deleterious *BRCA2* mutation is believed responsible for about a third of families with several cases of breast cancer, and this proportion doubles for those with at least six breast-cancer cases. *BRCA2* accounts for about 75% of high-risk families with at least one case of male breast cancer [1].

Despite advances in what we know about the *BRCA1* and *BRCA2* susceptibility genes, knowledge of their effect on the French-Canadian population is limited in several ways. Estimates of the relative contribution of the *BRCA1* and *BRCA2* susceptibility genes to the overall breast-cancer burden vary widely, but data based on other populations cannot easily be extrapolated to apply to the French-Canadian population because of the founder effect on the genetic profile of the population. Indeed, even though it has clearly been established from a clinical point of view that truncating mutations in *BRCA1* or *BRCA2* confer a substantial risk of developing breast and/or ovarian cancer, much debate has been generated over apparently diverging penetrance estimates obtained from different studies and in different populations. As risks will fluctuate according to the population tested, that is *BRCA1/2* carriers ascertained through multiple affected individuals within a family, versus subjects with no evidence of a family history, etc., there was a real interest for refining the penetrance in high-risk French-Canadian high risk families in order to provide more accurate genetic counselling to these women. Our recent findings indicated that the penetrance estimates of breast or ovarian cancer for French-Canadian *BRCA1/2* carriers are in line with those found in multiple-case families, but somewhat higher than those obtained from the meta-analysis of families of *BRCA1/2* carriers identified through population-based studies [24]. However, none of the estimates obtained in our study is significantly different from the meta-analysis estimates [25].

It should also be stated that these differences can be explained by modifier loci, which cluster in families and modify the cancer risks conferred by the major susceptibility locus. Indeed we expect that families with a greater number of affected individuals will have higher than average burden of deleterious modifiers clustering in them, therefore resulting in higher than average risks for carriers from high-risk families as compared to *BRCA1/2* carriers from population-based studies. Although there is evidence of variation in risk by mutation type, it is likely that the main source of variation is genotypes at other susceptibility loci; however, no such modifier loci have yet been identified definitively. In an attempt to identify genetic modifiers of breast cancer risk, large international cohorts of *BRCA1/2* carriers identified through studies coordinated and/or involving by INHERIT BRCAs members have been genotyped for select candidate genetic variants. These include genes involved in DNA repair, hormone regulation and metabolism and carcinogen metabolism [26].

Another major goal of our translational research program was to develop cost-effective, clinically useful guidelines for BRCA testing based on family history of breast, ovarian and other cancers, age at, and site of, diagnosis of the index case. Of particular importance, given the typically large structures of families in the French-Canadian population, is to devise the most relevant definition of 'family' to be used in the categorization of family history. The nature of our studies provide the unique opportunity to specifically examine the relative merits of pre-screening each sample for any given number of founder mutations in the Quebec French-Canadian population (e.g., BRCA1*R1443X, BRCA2*8765delAG), before embarking on more exhaustive (and expensive) mutation testing [27].

Making sense of missense

As genetic testing for common multifactorial diseases moves into clinical practice, the problems associated with the interpretation of sequence variants of unknown significance will result in psychological stress for patients and families and increased burden on health care providers. For example, these so-called unclassified variants (UCVs) account for about half of all unique variants in *BRCA1/2* reported in the Breast Cancer Information (BIC) database. An innovative

likelihood-ratio model has recently been developed by INHERIT BRCAs members, namely Goldgar, Easton, Tavtigian and other BIC collaborators, which is integrating direct epidemiological observations, including co-segregation with disease in families, and degree of family history of the disease and/or indirect measures on evolutionary-based comparative genomics and evidence from functional assays [28]. The availability of such an integrated approach should result in a more-reliable classification of UCVs, which in turn will improve the clinical utility of genetic tests not only for *BRCA1/2* genes, but also for other high-risk predisposition genes (e.g. *APC*, *MLH1*, *MSH2*, *PTEN*, and *TP53*). We will further refine algorithms of this model and to assess their predictive power using data from large cohorts, including those from Canadian high-risk families, in coordination with the BIC Consortium efforts. Modelling will also be performed for sequence variants conferring modest or moderate risk of disease, such as *CHEK2*.

Pinpoint novel breast cancer susceptibility loci

It is important to note that other as yet unknown susceptibility genes (*BRCAX*) may be responsible for 60% of families in which only four or five women contract breast cancer [1]. Indeed, *BRCA1/2* genes only account for about 20% of the familial risk and less than half of site-specific breast cancer families (≥4 cases), thus leaving 70–90% of individuals currently tested – depending upon eligibility criteria – with an inconclusive result. The number of families with four or five cases of early onset of breast cancer not due to *BRCA1* or *BRCA2* mutations is too large to be dismissed as chance clustering [29]. In our French-Canadian cohort of high-risk families, we have good evidence that such genes do exist, as ~75% of high risk families with undergoing *BRCA1/2* testing will receive an inconclusive result. Moreover, given that breast cancer is a genetically heterogeneous disease, it is likely that numerous genes remain to be identified among the non-*BRCA1/2* families. There is compelling evidence that inherited breast cancer is determined by a number of genes and current data suggest a polygenic model involving many genetic variants, each conferring a slight to moderate increase in risk, but some could still be due to high-penetrance mutations in unidentified genes [20, 21]. To maximize our chances of success, different approaches are considered in parallel. For example, we are performing a SNP-based/genome-wide scan in this *BRCAX* cohort, coupled to a genome-wide scan in a subset of these plus a large set of European *BRCA1/2*-negative families with microsatellite markers. The use of a SNP-based genome-wide scan would be particularly informative in this founder population, allowing reliable identification of shared haplotypes between families that may have arisen as a result of common founder mutations and also permitting identification of common moderate/low-penetrance genetic variants through case–control comparisons. In INHERIT phase II, in order to validate any associations found by genome-wide and/or candidate-gene approaches, we will analyze our findings using large national/international population/family-based cohorts, allowing a comprehensive characterization of novel cancer susceptibility alleles. Several approaches to improve their selection have been previously described thoroughly [21]. Sequence variants observed by high-throughput re-sequencing will be analyzed on a gene-by-gene basis to determine linkage disequilibrium structure and haplotypes. Both putative deleterious variants and tagging SNPs arising from such analyses will be compiled for use in downstream association studies. Our study design maximizes the power to detect pathogenic variants by using a panel of samples from high-risk, early-onset familial breast cancer cases from several countries. Indeed, the number of individuals to be genotyped can be markedly reduced by selecting cases enriched for genetic susceptibility [30, 31].

Demogenetic analyses, founder effect and identification of genetic risk factors

In the 17th century, about 5,000 immigrants, the majority from France, settled in Canada, and modern-day Quebecois are descends from 3,500 to 4,000 such pioneers [32]. Although the relative genetic contribution of each of these founders is highly variable, altogether they account for the major part of the contemporary French-Canadian gene pool. In order to get a better understanding of the origins of *BRCA1/2* mutations and of the role of the founder effect in the introduction and spread of these mutations in the French Canadian population, we used genealogical and haplotype data. We identified the founder couple with the highest probability of having introduced the *BRCA1* R1443X mutation in the population. Based on the descending genealogy of this couple, we detected the presence of spatial stratification in the diffusion pattern of the mutation throughout the province of Quebec [33]. This study demonstrates how molecular genetics and demogenetic analyses can complement each other to provide findings that could have an impact on public health. Indeed, establishing the origin of population-specific mutations in *BRCA1* and *BRCA2* is a critical step towards providing accurate counselling and developing inexpensive mutation detection in a specific founder population.

The heterogeneity of families displaying clustering of breast cancer represents a major factor of white noise in molecular analyses. We will build once again on the unique opportunities found in the Quebec population and the genealogical data will be used to study high-risk families with inconclusive results with the goal of defining subgroups displaying homogeneity in terms of demogenetic characteristics. These analyses and procedures will allow for the integration of detailed information on the population structure in research protocols with the goal of increasing the capacity to identify new genetic factors involved in breast cancer.

Translating genetic information into health applications

At present, the technology of genetic testing offers enormous potential to develop preventive and predictive medicine [34]. Yet there is much uncertainty about the clinical treatment of people carrying a gene that predisposes to breast and ovarian cancer. Moreover, relying on small samples or a retrospective approach makes it difficult to answer many questions including those that relate to prevention, testing, treatment responses, or the impact of the environment or reproductive factors that may alter risks conferred by *BRCA1/2* alterations. Several countries have initiated national and regional efforts [35–39], yet few can provide sample sizes large enough to ensure the precision and statistical power for the detection of risk modification. In response to this need, an International BRCA1/2 Cohort Study (IBCCS), a multi-centric epidemiological study was set up by the World Health Organization to study identified carriers of *BRCA1* and *BRCA2* mutations [40]. At present, over 3,000 subjects from 15 countries – including Canada through the INHERIT BRCAs program – carrying a *BRCA1/2* mutation have been recruited. The IBCCS study interacts with the European Network of Cancer Registries, the European Breast Cancer Linkage Consortium and the EPIC prospective study of nutrition and cancer, which will allow (where the populations overlap), the comparison of our results with age-specific cancer rates in a normal-risk population. We will now expand our collaboration with large international prospective studies of *BRCA* mutation carriers to identify risk factors that may be used in prevention strategies (if avoidable factors), and more individual-specific risk prediction (if not). Without the collaboration of our international colleagues, it would have been impossible to perform these rigorous genetic and epidemiology analyses, given the scale of the sampling required.

Psychosocial implications of BRCA1/2 genetic testing

Little is known about how genetic testing for cancer susceptibility influences an individual's long-term quality of life, compliance with screening recommendations or health-care utilization. Given the costly and psychologically challenging nature of such tests, we felt it was imperative to gain a better understanding of the impact of such tests on quality of life, health-related behaviours and family communication. In the context of INHERIT BRCAs, we initiated a prospective study to assess those issues at different times starting with the decision to undergo testing and ending up to three years after the disclosure of test results. Determinants of a participant's quality of life and risk-reduction behaviours were based on Baum's conceptual framework [41]. Until now, nearly 800 participants from more than 240 families have consented to take part in the study – a participation rate of approximately 85%. Although preliminary, we have reported short-term results on a wide range of psychosocial issues [42–45] and health behaviours [47, 48].

Because of the predictive nature of genetic testing for cancer, its effects are likely to span several years and to be enhanced by major life events including new cancer diagnoses or recurrences, death of family members from cancer, marital and pregnancy issues. The cohort we have assembled to date, one of the largest of its kind, puts us in a unique position to define more clearly the long-term implications of testing, and to identify factors that mediate the effects of testing.

In the second phase of INHERIT, we will extend our follow-up to 5 years post-disclosure. In addition, to allow for a description of the natural history of quality of life and health behaviours in the context of *BRCA1/2* testing, this long-term follow-up will provide opportunities for nested case–control studies that will aim to understand the impact of specific life events on psychosocial adjustment to test results. We will also further study the patterns of communication among family members and identify factors that facilitate or hinder optimal communication of genetic information [49]. Building upon the knowledge gained from our work with hereditary breast and ovarian cancer patients, we aim to develop a conceptual framework for the study and enhancement of family discussions about genetic predisposition to other late-onset disorders.

Social, legal and ethical implications

Breast cancer genetics has the potential to facilitate early detection, prevention and treatment. At the same time, such tests reveal genetic information about individuals and their families, which raise privacy-protection concerns and the potential that data could be misused [15, 50]. Although genetics affects almost every aspect of our lives, the public policy that protects these data often lags behind the science [51]. As a result, the social, ethical and legal issues posed by genetic research are not well addressed in terms of privacy and confidentiality. Our research presents an array of opportunities to examine ethical issues. We will mention only two in this paper. The potential loss of genetic privacy within the field of insurance is one area receiving critical review. The World Health Organization [52] states clearly that insurance companies must have the express consent of a patient before accessing medical and genetic information. However, a frequently raised question considers the potential for genetic discrimination if insurance companies have access to genetic information through medical records. To address this issue, we convened a task force of insurers, patient advocates, health-care providers and INHERIT BRCAs researchers to discuss how the life-insurance industry should use genetic tests. The group issued a joint 'Genetics and Life Insurance in Canada: Points to Consider' [53] and agreed on two

major issues: (1) genetic test results (excluding family history) must not be used for a set, moderate amount of insurance coverage for a limited five-year period; (2) an independent advisory board made up of consumers, government, clinicians, industry and researchers should review criteria concerning the reliability of genetic information for underwriting purposes. This body could also handle consumer complaints and queries.

Another implication of genetic testing concerns professional disclosure and the respect for the rights of individuals and families. Confidentiality, the hallmark of the physician–patient relationship, is being challenged by those who wonder if health professionals should disclose genetic information to individuals who may be affected by the knowledge. Since genetic testing can provide information about family members, results may show that related individuals should also be tested and monitored. Such information is relevant for preceding and succeeding generations and can affect reproductive, lifestyle and health-care decisions [54]. Usually it is the patient's responsibility to stay in contact with genetic-service providers, medical geneticists, counsellors and subspecialties or to notify at risk family members [55, 56]. However, the question now is whether genetic-services providers should share the responsibility. Our study indicates that these questions remain unresolved.

In phase II of our research program, we want to elucidate how health professionals can best deal with emerging and expanding physicians' duties, as well as consider the responsibilities of family members to inform, to warn and to recontact. We will also address three more questions: (1) How can we best address the psychological, social and legal impacts of labelling a person as high- or moderate-risk for a disease? (2) How can we preserve confidentiality and privacy to avoid potential discrimination and/or stigmatization? (3) How can we facilitate communication and understanding of risk in the context of family communication, beliefs, values and cultural factors?

Transfer knowledge into appropriate health policies and health services

INHERIT BRCAs also has a major interest in the development and dissemination of policies and medical applications that benefit clinicians, policy-makers and, ultimately, women and their family. It is a challenge to disseminate and encourage the use of research-based findings in clinical care, policy development or by the public. Although a great deal of money and time are spent on research studies and the publication of results, this is not enough. Often, a gap emerges between the publication of evidence and the application of those results [17, 57]. With the goal of reaching a broad audience, we developed tools to promote genetics education amongst health professionals. In order to assist them in the care of women with a family history of breast and ovarian cancer, we are currently completing recommendations addressing *Clinical Management/Risk Reduction of Hereditary Breast and Ovarian Cancer* for the Canadian context (D. Horsman, personal communication).

The development of our recommendations was influenced by consensus guidelines introduced by international advisory bodies on the clinical treatment of women with a predisposition to breast or ovarian cancer [58–59 and references therein]. Such recommendations were introduced to reduce clinical variations and to close the gap between what clinicians do and what the best scientific evidence supports. The goal was to help health professionals select the appropriate treatment and care for hereditary breast and ovarian cancer patients [60].

In a similar way and in order to develop recommendations for a Canadian context, the INHERIT BRCAs team, in collaboration with the Canadian Association Provincial Cancer Agencies [61] and Health Canada, established the National Hereditary Cancer Task Force. The consultation process involved extensive research into published recommendations from several countries [39, 58, 59, 62]. It brought together a multidisciplinary team of clinicians, experts and researchers, as well as representatives from the public and government, who conducted an extensive literature search, carried out a comparative review of existing guidelines, adopted evidence-based methodology, hosted an international meeting in Quebec City in 2002 and used peer review with relevant health care professionals, patient representatives to evaluate the information and develop recommendations that are expected to be completed by the summer of 2005. In addition, the National Hereditary Cancer Task Force will continue to oversee the dissemination strategy and implementation of the recommendations.

In addition to developing a National Hereditary Cancer Task Force with academic and oncogenetics researchers, INHERIT BRCAs is committed to integrating genetics education into the practices of clinicians across Quebec. The World Health Organization and others predict genetics will become essential in many aspects of medical practice so that genetic diagnosis and counselling will be integrated within medical services [63, 64]. Our challenge is to ensure clinicians are informed of the rapid advances in genetic research [2, 65–67]. In order to help attending physicians give their patients the best possible treatment upon receiving genetic tests results, doctors must have access to a network of researchers and clinicians acting as resource-people across Quebec. To empower health professionals in the genetics era, an Internet-based dissemination tool was developed that reaches out to approximately 900 specialists from all regions of Quebec, via the GEOQ, Groupe d'Etude Oncologie du Quebec [68].

The INHERIT BRCAs team also developed tools for policymakers, including a website and a database (HUMGEN) (http://www.humgen.umontreal.ca) for

professionals and policy makers seeking information on social, ethical and legal issues. The link to a cancer module 'CancerGen' on the Internet (http://www.inheritbrcas.info/) consists of resources on ethical, legal and social issues related to hereditary cancer, national and international policy statements (professional guidelines, ethical codes, recommendations and legislation), as well as selective literature about genetic testing and cancer dating to 2000.

To further the knowledge translation, we must create partnerships at the local, national and international levels. In order to form these partnerships, we will build on the existing infrastructure of the National Hereditary Cancer Task Force, expanding links and collaboration with policy makers and professional organizations, as well as with national voluntary organizations dedicated to promote the well-being of families. These partnerships will facilitate an integrated approach of relevant concerns to families and patients.

Future challenges and lessons learned by the INHERIT Team

In the immediate future, we do not expect to have a complete understanding of the role of all specific genetic factors and their interactions with environmental factors in health and disease. At least until that time, the most effective strategy will be to integrate robust genetic information with that on family history to improve personalized disease prevention and care.

The value of knowing 'your family history because it might save your life' [69] is now widely appreciated because it helps to identify people at increased risk for common complex diseases, such as cancer [6]. For instance, if a woman has a mutation in *BRCA1/2*, her risk of breast or ovarian cancer is higher if she has a positive family history [70]. In the situation where a patient has a hitherto unreported mutation in some identified susceptibility gene, family history may be valuable in determining the likelihood whether the mutation is pathogenic [71].

Indeed, family history may be especially important in identifying individuals in whom effective interventions might produce the greatest health benefit [4, 6]. Family history is important in assessing the clinical relevance of gene variants, thus enabling refinement of risk prediction. The expected volume of new information on specific genetic variants requires rigorous evidence of its validity in predicting health outcomes and its utility in improving health and preventing disease beyond approaches that do not use genetic information [4, 69]. To use family history information effectively and without causing harm, it is now essential to understand better the complex interplay between families, health and illness, and the peculiarity of genetic information for family relationships. We must address, for example: complex communication issues, the need for multiple members to be included in genetic studies, concerns about discrimination, privacy and new ways of defining 'illness' (to include, for example, presymptomatic phases of genetic testing), and possible emerging familial duties of communication.

Moreover it will be very important to integrate family history into innovative tools to improve the power and accuracy of methodological approaches in genetic epidemiology and population genetics. During the past decade, a real limitation in our understanding of familial breast cancer susceptibility was the absolute requirement for large cohorts to allow validation of initial findings by minimizing false alarms and to increase statistical power, to detect gene–gene/gene–environment interactions, especially for rare health outcomes. For example, compared with a standard case–control association study with cases unselected for family history, the sample size required to detect a common disease susceptibility allele will be markedly reduced if cases with family history are selected [31, 72]. The potential of such an approach to detect rare alleles conferring a relative risk less than 2.0 is well illustrated by the discovery of the rare breast cancer susceptibility allele *CHEK2* 1100delC [73]. The availability of several national/international cohorts is offering us a unique opportunity for testing our hypotheses through various kinds of robust epidemiological studies.

Conclusion

Important advances in understanding cancer susceptibility and future developments create opportunities for developing novel interdisciplinary approaches to cancer genetics that may lead to improvements in the use of genetic information to assess cancer risk and to improve interventions targeting cancer-risk reduction [5]. It is our belief that women could not receive outstanding clinical management, psychosocial support or access to cutting-edge research and diagnostics without the collaboration of an integrated team of investigators.

In 2003, the *Conseil Québecois de Lutte Contre le Cancer/Ministère de la Santé et des Services Sociaux du Québec* honoured our team for its leadership, inventiveness, humanism, 'client orientation' and for the significant gains we have made in the battle against cancer. For these reasons, the INHERIT BRCAs research team stands as a prototype for interdisciplinary research on genetic susceptibility for complex diseases. To reap the benefits of our efforts, however, it is imperative to maintain a dialogue about its demonstrated advantages of interdisciplinary cancer genetics research. To assist and encourage further dialogue, this special issue of *Familial Cancer* presents a collection of articles on the current debates in the rapidly developing area that is genetic predisposition to cancer. To reiterate the message, this article and special issue of *Familial Cancer* should reinforce the fact that each discipline or field has a contribution to provide a better understanding of

familial cancers. We hope this issue brings a new dimension to interdisciplinary dialogue and stimulates further discussion and exploration in familial cancer research.

Acknowledgements

We thank the Centre Jacques Cartier, the Canadian Institutes of Health Research – the Institute of Cancer Research, the Institute of Genetics, and the Institute of Gender Health, the Canadian Cancer Society, the National Cancer Institute of Canada, the Centre de Recherche en Droit Public of the University of Montreal for supporting the International Symposium 'Oncogenetics: Achievements and Challenges', and the preparatory work for this special edition. Moreover, this work was supported by the Fonds de la Recherche en Santé du Québec (FRSQ)/Réseau de Médecine Génétique Appliquée (RMGA), the Canadian Breast Cancer Research Alliance and the Canadian Institutes of Health Research (CIHR) for the INHERIT BRCAs research program. F.D. is a recipient of a Research Career Award in the Health Sciences by IRSC/Rx&D HRF, B.M.K is Chairholder of the Canada Research Chair in Law and Medicine and J.S. is Chairholder of the Canada Research Chair in Oncogenetics.

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