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Systematic Review of the Social, Ethical, and Legal Dimensions of Genetic Cancer Risk Assessment Technologies

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TABLE OF CONTENTS

Tables:

INTRODUCTION

With the mapping of the human genome, linkages between genes and health conditions are expected to increase exponentially [1]. Insight into the development of many cancers has been fostered by advances in cancer genetics. Some genes, found to be frequently altered in malignant neoplasms, have been shown to be heritable in mutated forms associated with increased susceptibility to particular cancers [2]. Inherited from germline tissues, these altered genes are present in all nucleated cells of the body. Analysis of a blood sample, for example, can provide information about an individual's risk of developing a specific cancer [2]. For example, the first genetic marker for cancer susceptibility, the *RB* (retinoblastoma) gene, was identified in the mid-1980's [3]. The more widely known breast cancer gene *BRCA1* was cloned in September, 1994 [4], ending a four year search that began with the localization of the gene to the long arm of chromosome 17 [5]. The breast cancer gene *BRCA2* was identified in 1995 [6].

The identification of susceptibility genes and advances in other areas of basic and applied research (e.g., gene therapy, the development of genetic testing kits, etc.) offers the hope of new approaches to cancer prevention, diagnosis and treatment. However, these scientific advances have also generated concerns about the social, legal and ethical implications of these relatively new predictive technologies, yet there is no mechanism currently in place to fully inform stakeholders about these issues.

In this systematic review, we have critically reviewed the literature addressing the social, legal and ethical issues related to genetic testing for cancer susceptibility, synthesized current information and identified existing gaps in knowledge. We believe the review will prove valuable to policy- and decision-makers faced with integrating these technologies into the health care system.

Please note that we had originally proposed to review the literature regarding "genomic" and "proteomic" technologies used to assess heritable cancer risks. However, to the best of our knowledge, at the time of this review, substantive literature regarding these technologies had not been published. Accordingly, this review was limited to the issues pertaining to existing tests that facilitate assessment of an individual's genetic susceptibility to cancer. It focuses specifically on the social, ethical and legal implications of these tests, rather than the scientific aspects of the tests themselves (e.g., methods of mutation detection, test sensitivity, etc). Interested readers are referred to the "GeneTests" website sponsored by the National Institutes of Health, the Health Resources and Services Administration and the U.S. Department of Energy (www.genetests.org). The website provides excellent summary information on heritable cancers, their clinical presentations, available molecular genetic tests and listings of international laboratories where testing is currently being offered in both research and clinical settings.

METHODS

Literature Search Strategy

Our search strategy, designed by a multi-disciplinary team to ensure that a broad range of issues and literature were considered, included the following elements:

- electronic database searches;
- searches of key government and organization web sites;
- Internet searches using two search engines and identified search terms; and
- examination of the bibliographies in primary research articles

Search results were limited to documents published in English, French or German from January, 1990 to May, 2003. Twenty-eight electronic databases were searched, including Medline, Embase, EconLit, LegalTrac, PsycINFO and Social Sciences Abstracts. A complete list of the databases searched and the search terms used is provided in Appendix A.

The web sites of 108 government agencies and research organizations were searched to identify relevant published and "grey" literature documents (see Appendix B). Finally, using the articles ultimately selected for inclusion in the review, citation searches were run in the Web of Science to identify additional applicable documents. The bibliographic software program Reference Manager was used to organize the search results.

It was decided *a priori* to limit the review to literature addressing the social, legal and/or ethical issues associated with technologies that assist in the evaluation of an individual's genetic predisposition to developing cancer. Examples include tests for germline mutations in the adenomatous polyposis coli (*APC*) gene (implicated in the dominant inheritance of familial adenomatous polyposis and subsequent colorectal cancer) and in the breast cancer associated genes *BRCA1* and *BRCA2* (associated with hereditary breast and ovarian cancers). Tests for markers useful in the early detection of existing cancers (e.g., prostate-specific antigen (PSA) for prostate cancer, cancer antigen 125 (CA-125) for ovarian cancer, etc.) were not considered.

Literature search results

Our search of the published literature yielded 5,474 original records for initial review. Two reviewers independently screened the titles and abstracts (if available) of these records and applied initial exclusion criteria. The reviewers were in agreement for 5,403/5,474 (98.7%) records. Discrepancies were resolved through discussion. Following this initial screen, irrelevant documents (n=4,649), documents consisting only of abstracts (n=87) and review articles (n=43) were excluded. If relevance could not be determined from the title and an abstract was unavailable, the document was selected for further review.

A total of 695 documents were selected for retrieval. Of these, 11 could not be attained as the citations were invalid or the documents were not held by North American libraries, six cited ongoing projects with no published data yet available and 306 were excluded after further review (three abstracts only, 30 review articles, seven duplicate publications and 266 papers not relevant to the topic). Of the remaining 372 documents, 158 were narrative, non-research reports (e.g., editorials, commentaries, position statements, etc.), 193 were reports of primary quantitative research and 21 were reports of primary qualitative research.

The grey literature search, the review of the bibliographies of the primary research reports and the citation search via the Web of Science identified an additional 30 quantitative research papers (one of which also contained qualitative data), two qualitative research papers and 30 narrative documents. In total, 223 quantitative research papers, 24 qualitative research papers and 188 narrative documents were reviewed. All of the documents were reviewed by a single reviewer. The primary research papers were subject to quality assessment (discussed below) and common themes in the narrative documents were identified and summarized.

Quality assessment: primary research papers

To assess the quality of the primary research reports, we had originally proposed to use the checklist developed by the British Sociological Association Medical Sociology Group [7]. However, it was designed specifically for use with qualitative studies and did not lend itself to the evaluation of quantitative research. Further, our review differs from a number of published systematic reviews in that a single research question was not defined *a priori*. Rather, it was designed to identify multiple important issues associated with cancer risk assessment technologies. The studies selected for review thus covered a range of research topics and employed a number of designs.

While acknowledged as important, appraising the quality of evidence is a difficult task complicated by the consideration of a disparate collection of evidence. Quality checklists for assessing randomized controlled trials abound [8, 9], yet it is acknowledged that even within this single study design the reliability, validity, feasibility and utility of the various tools are either unmeasured or quite variable [8]. To the best of our knowledge, standard criteria for simultaneously assessing the quality of diverse study designs do not currently exist. Individual checklists have been adapted for use with other study designs (such as Cho et al..'s instrument for assessing the quality of observational and experimental but not randomized drug studies [10]) or alternate forms of research communications (such as Timmer et al..'s quality scoring tool for abstracts [11]). Other more general tools are available, but have limited operational utility as the quality assessment criteria are largely focused on the quality of reporting, or specify items to use when abstracting data in a standard fashion from research reports (for example, see [12, 13]).

The Cochrane Collaboration Non-Randomised Studies Methods Group is currently developing guidelines for the review of non-randomized studies, but the draft chapter on quality assessment is pending [14].

Given the lack of a standard, empirically grounded quality assessment tool suitable for use with a variety of study designs, we developed and implemented a tool (QualSyst) that consists of two scoring systems to evaluate the quality of the studies potentially eligible for inclusion in our review; one for quantitative research and one for qualitative research. The scoring systems and the process used to establish inter-rater reliability are published in a peer reviewed Health Technology Initiative Report by the Alberta Heritage Foundation for Medical Research: *Standard quality assessment criteria for evaluating primary research papers from a variety of fields"* (AHFMR: www.ahfmr.ab.ca).

Our scoring systems draw upon existing published tools, relying particularly upon the instruments developed by Cho et al.. [10] and Timmer et al.. [11] for quantitative studies and the guidelines suggested by Mays and Pope [15] and Popay et al.. [16] for qualitative studies. "Quality" was defined in terms of the internal validity of the studies, or the extent to which the design, conduct and analyses minimized errors and biases [17]. Rather than developing explicit definitions for the two types of research, our distinction between the two was practical. Studies employing quantitative methods were appraised using the system for quantitative studies while studies identified by the researchers as qualitative or employing qualitative methods (e.g., focus groups, semi-structured interviews, etc. [18]) were appraised using the system for qualitative studies. The quality scores were used to define a minimum threshold (i.e., 75%) for inclusion of studies in the systematic review. This threshold was chosen following a discussion by the authors of the balance between efficiency and inclusiveness.

While useful in the course of our work, our scoring tool has limitations. First, the use of summary scores to identify high quality studies can, in itself, introduce bias into a systematic review. Our checklists are admittedly subjective and reflect our perceptions of the key components of study quality. Given the absence of standard operational definitions of internal validity in the literature and the absence of a "gold standard" to compare our tool with, we cannot be certain that it accurately measure what it is supposed to measure. However, our system may foster discussion of this issue, and ultimately, the development of superior instruments. Second, our assessment of inter-rater reliability was limited. Practical time and resource constraints on this project prevented us from reviewing a larger number of studies and estimating standard statistical measures of agreement (e.g., Kappa coefficients and related confidence intervals). Further, assessment of inter-rater agreement by a range of reviewers from both the quantitative and qualitative research arenas who were not involved in the development of the tool would increase our confidence in reliability. Funding is currently being sought to pursue this work.

RESULTS

Of the 247 primary research papers reviewed, 77 received scores of 75% or more: 66/223 (29%) of the quantitative papers and 11/24 (46%) of the qualitative papers. Studies meeting this minimum threshold criterion were included in the review and data were extracted from each in a systematic fashion by a single reviewer. Detailed study information and abstractions are available upon request from the authors.

The primary research papers encompassed a range of designs, including case studies and series, descriptive and analytic surveys, retrospective and prospective cohort studies, randomized controlled trials, decision analyses and qualitative studies employing focus groups and/or semi-structured interviews. All of the studies were related to genetic testing for cancer susceptibility genes. Studies of truly genomic and proteomic approaches to assessing inherited susceptibility to (as opposed to early detection of) cancer have not, to the best of our knowledge, been published.

Primary research reports: major content areas

Awareness of cancer susceptibility genes/genetic testing for cancer susceptibility

Awareness of cancer susceptibility genes and genetic testing for cancer susceptibility has been studied in the general population and in clinical populations of women at low risk for hereditary cancer (Table 1). In the general population, about 82% of respondents were at least somewhat aware of hereditary cancer or cancer genes [19, 20] and 26%-55% were at least somewhat aware of genetic testing for cancer susceptibility [21-23]. Among women with at least one relative affected by breast cancer, 81% were aware of hereditary disease [24] and 71% were aware of genetic testing for breast cancer risk [25]. Finally, 83% of women with breast cancer (unselected for family history) were at least somewhat aware of breast cancer genes [20].

Two studies found that awareness of hereditary cancer and genetic susceptibility testing was higher among Caucasian respondents than African American respondents [21, 24]. A higher level of education (at least college versus less) was also associated with greater awareness of genetic susceptibility testing [21].

Table 1: Summary of results from studies assessing awareness of cancer susceptibility genes/genetic testing for cancer susceptibility

Study Reference Number	Year	Study Population	Cancer Type	% Aware of Cancer Susceptibility Genes/Genetic Testing for Cancer Susceptibility
Andrykowski et al.. [19] 1997	1995	General population Random sample of adult Kentucky residents without a personal history of cancer (n = 654)	Cancer in general	**Aware of the topic of hereditary cancer risk:** 18% not at all 40% a little 42% a lot
Armstrong et al.. [21] 2002	1997-1998	General population Random sample of female primary care patients in Pennsylvania (n = 400)	Breast cancer	**Aware of *BRCA* testing:** 53% yes
Bosompra et al.. [22] 2000	1996	General population Random sample of the adult population in Glenn Falls and surrounding New York area (n = 622)	Cancer in general	**Before today, ever heard about genetic testing for cancer risks?** 55% yes
Bunn et al.. [23] 2002	1997-1998	General population Random sample of the adult general population in New Hampshire, Maine and Vermont (n = 1,836)	Cancer in general Breast cancer Colon cancer Prostate cancer	**Heard about genetic tests for:** cancer risk - 43% breast cancer risk - 36% colon cancer risk - 26% prostate cancer risk - 26%
Bottorff et al.. 20 2002	Not stated	General population Random sample of 20-79 year-old women in British Columbia without a personal history of breast cancer (n = 761)	Breast cancer	**Awareness of breast cancer genes:** 18% almost nothing 47% a little bit 35% a fair amount/a lot

Table 1: Summary of results from studies assessing awareness of cancer susceptibility genes/genetic testing for cancer susceptibility (cont'd)

Study Reference Number	Year	Study Population	Cancer Type	% Aware of Cancer Susceptibility Genes/Genetic Testing for Cancer Susceptibility
Bowen et al.. [25] 2002	Not stated	Volunteer sample of unaffected women at low risk for hereditary breast cancer, with one relative (any degree) affected by breast cancer (n = 357) Awareness of/interest in genetic testing assessed before and after counseling	Breast cancer	**Amount read or heard about genetic testing for breast cancer risk (at baseline):** 29% almost nothing 44% relatively little 24% a fair amount 3% a lot
Hughes et al.. [24] 1997	Not stated	Unaffected women with at least one first degree relative affected by breast and/or ovarian cancer (n = 407)	Inherited disease (including cancer)	**Amount read or heard about inherited disease:** 19% almost nothing 47% a little 25% a fair amount 9% a lot
Bottorff et al.. [20] 2002	1994-1998	Population-based sample of women with breast cancer, unselected for family history (n = 260)	Breast cancer	**Awareness of breast cancer genes:** 17% almost nothing 47% a little bit 36% a fair amount/a lot

Interest in genetic testing for cancer susceptibility

Interest in genetic testing for cancer susceptibility has been examined in the general population, among health care providers and in clinical populations at varying levels of hereditary cancer risk (Table 2). General population surveys have shown that interest in testing ranges from 20% to 87% for cancer in general [19, 22, 26], from 29% to 93% for breast cancer [20, 21, 26, 27] and from 19% to 81% for colon cancer [23, 28]. A single survey of female gynecologists in northern France found that 88% of respondents were interested in *BRCA* testing [29].

The large degree of variability in the general population estimates of interest in testing likely reflects methodological differences across the surveys. First, questions were worded differently across surveys. For example, two studies asked respondents if they would like to be told of their increased risk status if they had in fact inherited something making them more likely to develop cancer than most people [19, 26]. The relatively high estimates of interest in testing obtained from these studies are perhaps not surprising given that respondents were essentially required to contemplate a possibly threatening situation. Others studies asking more general questions about the likelihood of seeking testing if it were available obtained lower estimates of interest in testing [22, 23]. Second, response options varied from simple yes/no dichotomous choices to multiple choice options reflecting degree of interest (e.g., not at all, somewhat, very, etc.), making direct comparisons of interest levels across studies difficult. Finally, there was evidence that "qualifying" the survey questions influenced responses. For example, when asked if they would have a test for colon cancer risk in the next 6 months if it was available, 32% of respondents reported that they probably or definitely would. However, when asked if they would have the same test in the next month, only 19% reported that they probably or definitely would [23]. Similarly, 40% of respondents were very interested in a genetic colon cancer susceptibility test which would indicate (if positive) an 80% lifetime risk of developing colon cancer. However, given a test that was only 90% accurate, only 33% were very interested in testing, and when informed that the general population risk of inheriting a mutation is less than 1%, only 19% were very interested in testing [28].

Surveys of unaffected individuals with varying family histories of cancer have revealed similar levels of interest in testing across a number of scenarios. Eighty-seven percent of African-American men recruited from a family study of prostate cancer and from a prostate cancer education and screening study reported interest in a hypothetical test for genetic susceptibility to prostate cancer [30]. Interest in *BRCA* testing ranged from 30% to 69% among unaffected women with at least one relative affected by breast cancer [31, 32], 35% to 45% among individuals from a large African-American kindred with a known *BRCA* mutation [33] and was 40% among women with at least one Jewish parent [34]. Similarly, 46% of first degree relatives (FDRs) of patients with confirmed or suspected hereditary nonpolyposis colorectal cancer (HNPCC) were

interested in genetic susceptibility testing [35]. There was some indication that interest in testing was greater among individuals personally affected by cancer. Between 31% and 72% of women with breast cancer expressed interest in *BRCA* testing [20, 27].

Eleven cross-sectional studies examined variables associated with interest in genetic testing for cancer susceptibility [19-23, 26-28, 31, 33,34]. Summarizing the findings, however, was difficult for a number of reasons. First, the outcome of interest was assessed in various ways across studies (as discussed above), precluding a direct comparison of results. Second, the predictors of interest considered in the analyses varied widely across studies, and control for confounding was either variable or impossible to assess as variables included in multivariate analyses were often not specified. Third, the measures of association employed differed across studies. Some studies treated Likert-type categorical scale responses as continuous measures and calculated correlational coefficients, yielding results which were difficult to compare with studies which reported odds ratios. Fourth, some analyses were poorly described (e.g., binary logistic regression coefficients were reported for outcome variables with more than two categories, yet a description of the data grouping was not provided). Finally, some analyses were inappropriate and yielded results with limited interpretability (e.g., logistic regression models were used to generate odds ratios which, given very common outcomes, were inappropriately interpreted as measures of relative risk [36, 37]). Given these limitations, synthesizing the findings into a meaningful summary format was not possible. Interested readers can contact the authors for individual study details.

Table 2: Summary of results from studies assessing interest in genetic testing for cancer susceptibility

Study Reference Number	Year	Study Population	Cancer Type	% Interested in Genetic Testing for Cancer Susceptibility
Andrykowski et al.. [26] 1996	1994	Random sample of adult Kentucky residents (n = 649)	Cancer in general Breast cancer (women only)	**In being informed of risk:** 87% "yes" 10% "no" 3% "not sure/refused" 93% "yes" 5 % "no" 2% "unsure/refused"
Andrykowski et al.. [19] 1997	1995	Random sample of adult Kentucky residents without a personal history of cancer (n = 654	Cancer in general	**In being informed of risk:** 87% "yes" 8% "no" 5% "not sure/refused" **In having an inexpensive, easy to perform test done:** 82% "yes" 12% "no" 6% "unsure/refused"
Armstrong et al.. [21] 2002	1997-1998	Random sample of female primary care patients in Pennsylvania (n = 400)	Breast/ovarian cancer	**Would have a convenient, affordable *BRCA* test**: 58% "yes"

Table 2: Summary of results from studies assessing interest in genetic testing for cancer susceptibility (cont'd)

Study Reference Number	Year	Study Population	Cancer Type	% Interested in Genetic Testing for Cancer Susceptibility
Bosompra et al.. [22] 2000	1996	Random sample of the adult population in Glenn Falls and surrounding New York area (n = 622)	Cancer in general	**Would be tested in next 6 months if a test were available:** 20% "probably/definitely" **Would be tested if physician recommended it:** 62% "probably/definitely"
Graham et al.. [28] 1998	Not stated	Random sample of the adult population of Ontario (n = 501)	Colon cancer	**If a positive test indicated an 80% (vs. 5%) lifetime risk of developing colon cancer:** 40% were "very interested" in testing 41% were "somewhat interested" 18% were "not interested" **Asked to consider a test that was only 90% accurate:** 33% were "very interested" in testing 44% were "somewhat interested" 22% were "not interested" **When told the general population risk of inheriting a mutation is < 1%:** 19% were "very interested" in testing 48% were "somewhat interested" 32% were "not interested"

Table 2: Summary of results from studies assessing interest in genetic testing for cancer susceptibility (cont'd)

Study Reference Number	Year	Study Population	Cancer Type	% Interested in Genetic Testing for Cancer Susceptibility
Bottorff et al.. [20] 2002	Not stated	Random sample of 20-79 year-old women in British Columbia without a personal history of breast cancer (n = 761)	Breast cancer	**Considering/probably will/will/have had *BRCA* testing:** < 50 years of age: 31% 50+ years of age: 23%
Cappelli et al.. [27] 1999	Not stated	Women (18-50) recruited from an orthopedic outpatient clinic/ by word of mouth in Ottawa (n = 50)	Breast cancer	**Intend to be tested for *BRCA1/2* mutations:** 46% "yes"
Bunn et al.. [23] 2002	1997-1998	Random sample of the adult general population in New Hampshire, Maine and Vermont (n = 1,836)	Colon cancer	**Would have a test for colon cancer risk in the next 6 months if it was available:** 32% "probably/definitely" 49% "probably/definitely not" **Would have a test for colon cancer risk in the next month if it was available:** 19% "probably/definitely" 69% "probably/definitely not'
Weinrich et al.. [30] 2002	Not stated	Survey of African-American men recruited from a family study of prostate cancer and from a prostate cancer education and screening study (South Carolina and Texas) (n = 320)	Prostate cancer (hypothetical testing for a prostate cancer susceptibility gene)	**Would be interested in the test if it became available:** 87% "yes" 5% "no" 8% "don't know"
Bottorff et al.. [20] 2002	1994-1999	Population-based sample of women with breast cancer, unselected for family history (n = 260)	Breast cancer	**Considering/probably will/will/have had *BRCA* testing:** < 50 years of age: 60% 50+ years of age: 24%

Table 2: Summary of results from studies assessing interest in genetic testing for cancer susceptibility (cont'd)

Study Reference Number	Year	Study Population	Cancer Type	% Interested in Genetic Testing for Cancer Susceptibility
Cappelli et al.. [27] 1999	Not stated	Women with early onset breast cancer, identified from the Ottawa Regional Cancer Registry (n = 60)	Breast cancer	**Intend to be tested for *BRCA1/2* mutations:** 72% "yes"
Green et al.. [32] 2001	1998	Women, recruited via newspaper advertisements, with at least one FDR affected by breast cancer (Washington DC) (n = 72)	Breast cancer	**Would "definitely/most likely" be tested:** 69%
Jacobsen et al.. [31] 1997	Not stated	Adults women with at least one FDR affected by breast cancer, recruited from mammography screening clinics (New York City) (n = 74)	Breast cancer	**Would seek testing, if it were available:** with the next week - 46% within the next 6 months - 30% in more distant future - 5% no, might change mind - 16% no - 2%
Kinney et al.. [33] 2001	1998-1999	Survey of a six-generation African-American kindred with a known *BRCA* mutation (n = 95)	Breast/ovarian cancer	**Would seek *BRCA* testing:** within next month - 45% within next 6 months - 35% in more distant future - 2% would not be tested - 18% ** estimates may be biased upward; 44% of respondents had participated in a previous study to isolate *BRCA1*

Table 2: Summary of results from studies assessing interest in genetic testing for cancer susceptibility (cont'd)

Study Reference Number	Year	Study Population	Cancer Type	% Interested in Genetic Testing for Cancer Susceptibility
Lehmann et al.. [34] 2002	1998	Survey of women in Boston with at least one parent of Jewish descent (n = 200)	Breast/ovarian cancer	**Interest in *BRCA* testing:** 40% "yes" 40% "no" 20% "uncertain"

Uptake of genetic testing for cancer susceptibility

Five prospective observational cohort studies and one descriptive survey assessed the uptake of genetic testing for cancer susceptibility (Table 3).

Two familial cancer studies assessed the uptake of genetic testing among at-risk relatives of patients with known or suspected HNPCC. In the first [35], 46% of at-risk relatives enrolled in a familial cancer registry by an affected proband were interested in testing, 45% of those interested underwent genetic counseling and 74% of those counseled underwent genetic testing. Overall, 15% of the at-risk relatives were tested. In the second [38], 67% of those invited to participate in the research study agreed to a baseline interview and 60% of those interviewed went on to receive genetic test results. Overall test uptake among at-risk relatives was about 40%. In a similar study of relatives at risk for *BRCA* mutations [39], 69% agreed to a baseline interview and 60% of those interviewed went on to receive genetic test results. Overall test uptake among at-risk relatives was about 40%.

The estimates of testing uptake obtained in these three research studies may have been biased upwards for a number of reasons. First, at-risk individuals were identified through familial cancer registries. It is unclear what percentage of individuals with cancer who were tested (i.e., probands) agreed to enroll their family members in the registries. Those who chose to do so may have had family members with more favorable attitudes towards research and genetic testing. Indeed, in the two studies yielding the highest overall uptake estimates [38, 39], some participants had been involved in prior genetic studies. Further, the study conditions (e.g., counselling and testing was provided free of charge and no medical record was generated after testing [35]) may have favorably influenced individuals' decisions to undergo testing.

A single study examined the spontaneous diffusion of *BRCA1* testing among families in France with confirmed mutations [40]. Geneticists at breast/ovarian family cancer clinics were asked to review family histories and medical records to determine the uptake of testing among first and second degree relatives of affected probands. A minimum of 8 months had elapsed since the proband had received his/her test results (range 8-48 months). Relatives were not contacted with offers of counseling or testing. Overall, 32% of at-risk relatives attended a clinic and 84% of those underwent *BRCA* testing. Overall uptake of *BRCA* testing was 27%.

Finally, two studies examined *BRCA* testing uptake among women who self-referred to testing centers. In one, 82% of women with breast cancer who were at high risk for carrying *BRCA* mutations underwent testing [41]. In the other, 50% of women who attended a clinic offering testing to anyone who completed genetic counseling decided to undergo testing [42].

Table 3: Summary of results from studies assessing interest in the uptake of genetic testing for cancer susceptibility

Study Reference Number	Year	Study Population	Cancer Type	Uptake of Genetic Testing for Cancer Susceptibility
Codori et al.. [35] 1999	1995-1998	FDRs of HNPCC patients or patients with family histories suggestive of HNPCC (n = 505) Relatives were enrolled in a familial cancer registry by the affected proband	Colorectal cancer (HNPCC testing)	46% of those contacted were interested in the study 45% of them underwent counseling 74% of those who underwent counseling actually had blood drawn Overall testing uptake was 15%
Lerman et al.. [38] 1999	Not stated	At-risk relatives of probands in 4 HNPCC families (U.S.) (n = 208)	Colorectal cancer (HNPCC testing)	67% agreed to a baseline interview Of those, 60% went on to receive test results Overall, about 40% of those at-risk underwent HNPCC testing **Note:** This study may have overestimated testing uptake rates among at-risk relatives, as some participants had been involved in earlier genetic studies.
Lerman et al.. [39] 1996	1994-1995	At-risk relatives of probands in 13 extended HBOC families (U.S.) (n = 279)	Breast/ovarian cancer (*BRCA* testing)	69% agreed to a baseline interview Of those, 60% went on to receive test results Overall, 40% of those at-risk underwent *BRCA* testing **Note:** This study may have overestimated testing uptake rates among at-risk relatives, as some participants had been involved in earlier genetic studies.

Table 3: Summary of results from studies assessing interest in the uptake of genetic testing for cancer susceptibility (cont'd)

Study Reference Number	Year	Study Population	Cancer Type	Uptake of Genetic Testing for Cancer Susceptibility
Schwartz et al.. [41] 2000	Not stated	290 women with breast cancer at high risk of carrying *BRCA* mutations who self-referred to a cancer risk assessment and evaluation program in Washington (n = 290)	Breast/ovarian cancer (*BRCA* testing)	82% of those who attended the program received *BRCA* test results
Julian-Reynier et al.. [40] 2000	1999	Survey of geneticists at familial breast/ovarian cancer clinics in France Asked about uptake of genetic testing among FDRs and SDRs of probands with confirmed *BRCA1* mutations (n = 506 at-risk relatives)	Breast/ovarian cancer (*BRCA1* testing)	Overall, 32% of the at-risk FDR/SDRs attended a clinic Among those who attended the clinic, *BRCA* test uptake was 84% Overall, 27% of those at-risk underwent *BRCA* testing
Armstrong et al.. [42] 2000	1998	Women who had attended a breast and ovarian cancer risk evaluation program in Pennsylvania where clinical *BRCA1/2* testing was available (n = 251) Testing was offered to anyone who had completed genetic counseling	Breast/ovarian cancer (*BRCA1/2* testing)	50% tested 34% declined 16% undecided

In summary, the interpretation of estimates of the uptake of genetic testing requires consideration of the denominators used in the calculations (e.g., those identified as being "at risk", those who attended counseling, etc.). Uptake of genetic testing is generally high among those who have chosen to attend hereditary cancer clinics and have undergone preliminary counseling or interviews. Overall uptake among the entire pool of at-risk individuals is considerably lower. This likely reflects the fact that only a percentage of those at-risk actually decide to attend such clinics in the first place, and this fraction is likely overestimated in settings where research participants are actively sought.

Variables associated with the uptake of genetic testing for cancer susceptibility

Variables associated with the uptake of genetic testing (in multivariate analyses) have been examined in the context of testing for *BRCA* and HNPCC-associated mutations. In the research setting, acceptors of HNPCC testing were more likely than decliners to have participated in previous genetic studies [38], to have had one or more colonoscopies in the past (vs. none) [35], to be at least 90% certain (vs. less) about their ability to cope with a positive result [35], and to have lower (vs. higher) depression scores [38]. Among those who perceived moderate increases (up to 70%) in their risk of developing colorectal cancer, those who frequently or sometimes thought about cancer were more likely to be tested than those who rarely or never thought about cancer [35]. However, among those whose perceived risk exceeded 75%, testing uptake declined irrespective of the frequency of cancer thoughts [35]. Age [38], gender [35, 38], race [35], income [38], marital status [35, 38] and personal [38] and family histories of cancer [35] were not associated with the likelihood of undergoing testing. Results were contradictory for education. One study found that a higher level of education was associated with testing uptake [38] while another did not [35].

Uptake of *BRCA* testing in a research setting was associated with having (vs. not having) health insurance, higher (vs. lower) breast cancer genetic knowledge scores, a higher (vs. lower) perception of testing benefits and having an increasing number of FDRs affected by breast cancer [39]. Gender, age, education, employment status, marital status, personal cancer history and the number of FDRs affected by ovarian cancer were not associated with testing uptake [39].

Among women who self-referred to *BRCA* testing centers, opting for testing (vs. declining) was associated with having (vs. not having) a known familial *BRCA* mutation, being of Ashkenazi Jewish (vs. other) descent and considering it "very important" (vs. less important) to obtain risk information for family members [42]. Fear of insurance discrimination was associated with deciding against testing [42]. Among those with a low perceived risk of developing breast cancer, those with "very strong" levels of spiritual faith (vs. all others) were less likely to be tested [41]. Among those with a high perceived risk of developing breast cancer, however, spirituality did not influence testing decisions [41]. Age [41, 42], race [41], marital status [41], education [41], religious affiliation [41], personal history of breast cancer [42], the number of relatives affected by

breast/ovarian cancer [41], fears of job discrimination [42] and the perceived importance of obtaining information to use when deciding about prophylactic surgery [42] were not associated with testing uptake.

The results from these studies warrant cautious interpretation. The predictor variables considered, the means of assessment, and the level of control for confounding varied across the studies, making a direct comparison of the findings difficult. Additionally, all of the studies calculated odds ratios as measures of association (available upon request from the authors), which can be misleading when used to approximate relative risks in studies with common outcomes [36, 37]. For example, referring to an odds ratio of 0.2, Schwartz et al. report that women with high levels of spirituality were "80% less likely to receive test results than less spiritual women". Their univariate data, however, showed only an 11% difference in the likelihood of receiving results. Seventy-six percent of those with "very strong" spirituality received results, compared with 87% of all others [41]. Similarly, referring to an odds ratio of 4.3, Lerman et al. report that individuals who had participated in previous genetic research were "about four times more likely to receive test results" [38]. Their univariate data, however, revealed a far less than two-fold difference in the likelihood of receiving results (71% vs. 52% of previous participators vs. non-participators). Finally, the samples in these studies were largely heterogeneous (e.g., primarily Caucasian and well-educated) and the power to detect associations of interest may have been limited.

Knowledge of breast/ovarian cancer genetics

Knowledge of breast/ovarian cancer genetics was assessed in 8 studies [20, 24, 32-34, 39, 43, 44]. The results from four studies [20, 24, 33, 39] which provided information on the proportion of respondents answering specific true/false items correctly are shown in Table 4. The other studies provided summary data only [32, 34, 43, 44].

In general, knowledge of breast/ovarian cancer genetics was limited among individuals at varying levels of increased risk for *BRCA* mutations. Knowledge of hereditary mechanisms, the penetrance and prevalence of *BRCA* gene mutations and the efficacy of prophylactic surgeries in preventing the development of cancer (particularly the efficacy of prophylactic oophorectomy) was notably limited. African-American individuals had larger knowledge deficits when compared with Caucasian individuals [24, 33]. Of note, one study found that knowledge of breast cancer genetics did not differ between breast cancer patients (unselected for family history) and the general population [20].

Table 4: Summary of results from studies assessing knowledge of breast/ovarian cancer genetics

Study	Study population	% Answering Correctly
Knowledge Item (TrueFalse)		
A father can pass down a breast/ovarian cancer gene		
Bottroff et al.. [20] 2002	Breast cancer patients unselected for family history of cancer	37-75
Hughes et al.. [24] 1997	Women with at least one FDR affected by breast and/or ovarian cancer	
Kinney et al.. [33] 2001	Members of a large African-American kindred with a known *BRCA1* mutation	
Lerman et al.. [39] 1996	At-risk relatives of probands with confirmed *BRCA* mutations	
Alterations in breast/ovarian cancer genes cause about 50% of all breast cancers		
Bottroff et al.. [20] 2002	Breast cancer patients unselected for family history of cancer	17-34
Hughes et al.. [24] 1997	Women with at least one FDR affected by breast and/or ovarian cancer	
Kinney et al.. [33] 2001	Members of a large African-American kindred with a known *BRCA1* mutation	
Lerman et al.. [39] 1996	At-risk relatives of probands with confirmed *BRCA* mutations	
A woman without a breast/ovarian cancer gene mutation can get breast/ovarian cancer		
Bottroff et al.. [20] 2002	Breast cancer patients unselected for family history of cancer	57-92
Hughes et al.. [24] 1997	Women with at least one FDR affected by breast and/or ovarian cancer	
Kinney et al.. [33] 2001	Members of a large African-American kindred with a known *BRCA1* mutation	
Lerman et al.. [39] 1996	At-risk relatives of probands with confirmed *BRCA* mutations	
About 1 in 10 women carries an altered breast/ovarian cancer gene		
Bottroff et al.. [20] 2002	Breast cancer patients unselected for family history of cancer	5-19
Hughes et al.. [24] 1997	Women with at least one FDR affected by breast and/or ovarian cancer	
Kinney et al.. [33] 2001	Members of a large African-American kindred with a known *BRCA1* mutation	
Lerman et al.. [39] 1996	At-risk relatives of probands with confirmed *BRCA* mutations	

Table 4: Summary of results from studies assessing knowledge of breast/ovarian cancer genetics (cont'd)

Study	Study population	% Answering Correctly
Knowledge Item (TrueFalse)		
A woman with an altered *BRCA1* gene has a 50% risk of passing it to her children		
Kinney et al.. [33], 2001	Members of a large African-American kindred with a known *BRCA1* mutation	51
A woman with a sister who has a mutated breast/ovarian cancer gene has a 50% chance of carrying the mutation herself		
Bottroff et al.. [20] 2002	Breast cancer patients unselected for family history of cancer	59-84
Hughes et al.. [24] 1997	Women with at least one FDR affected by breast and/or ovarian cancer	
Lerman et al.. [39] 1996	At-risk relatives of probands with confirmed *BRCA* mutations	
There are tests currently available to detect alterations in breast cancer genes		
Bottroff et al.. [20] 2002	Breast cancer patients unselected for family history of cancer	79
A woman with an altered *BRCA* gene has an increased risk of ovarian cancer		
Hughes et al.. [24] 1997	Women with at least one FDR affected by breast and/or ovarian cancer	71-77
Lerman et al.. [39] 1996	At-risk relatives of probands with confirmed *BRCA* mutations	
A woman who has her breasts removed can still get breast cancer		
Hughes et al.. [24] 1997	Women with at least one FDR affected by breast and/or ovarian cancer	65
A woman who has her ovaries removed can still get ovarian cancer		
Hughes et al.. [24] 1997	Women with at least one FDR affected by breast and/or ovarian cancer	24-31
Kinney et al.. [33] 2001	Members of a large African-American kindred with a known *BRCA1* mutation	
Lerman et al.. [39] 1996	At-risk relatives of probands with confirmed *BRCA* mutations	

Perceptions of the risks and benefits of genetic testing

In both the general population and various clinical populations, the majority of respondents believed that genetic testing would yield valuable information about cancer risk (both personal and to relatives) [22, 23, 31, 33, 39, 42], could guide cancer surveillance and prevention activities [22, 23, 31, 33, 39, 42] and would provide reassurance given a negative test result [31, 33, 39, 42]. Similarly, they often perceived that a positive test result would likely increase their anxiety levels [31, 33, 42].

Fewer respondents reported concern about some potential risks and limitations of testing. Concern about the potential for discrimination or the potential negative impact of testing on interpersonal relationships was low to moderate [22, 23, 31, 33, 39, 42]. Additionally, and perhaps a reflection of the perceived informational value of testing, awareness of the possibility of receiving an inconclusive test result was very limited [31, 33]. The tendency to perceive more benefits than risks of testing was not surprising, given that in the clinical studies, participants were asked about their perceptions *before* attending counselling and information sessions, and in the general population, up to 57% of survey respondents had not previously heard of genetic testing for cancer susceptibility [22, 23].

Psychological implications of the genetic counseling/testing process

Numerous studies have examined the psychological distress experienced by individuals at various stages of the *BRCA* genetic counseling and testing process. Two studies examined pre-test levels of event-related (i.e., genetic testing-related) [45, 46] distress using the Impact of Events Scale (IES). Anchored to a specific stressful event, this scale measures intrusion (e.g., the frequency of intrusively experienced thoughts; scores range from 0-35) and avoidance (i.e., the frequency of consciously avoiding such thoughts; scores range from 0-40) associated with the event. Mean intrusion and avoidance scores were fairly low in both studies (4.9-6.3 and 4.4-6.9, respectively). In another study, mean pre-test anxiety, measured using the state anxiety subscale of the State-Trait Anxiety Inventory (STAI), was relatively low (mean = 34.6, with possible summary scores ranging from 20-80) [47]. Pre-test levels of cancer worry were also found to be relatively low in another study, but significantly higher among women less than 35 years of age compared with older women (means of 11.8 and 10.2 respectively, with possible scores ranging from 6 to 24) [46]. The same study found that the pre-test prevalence of psychiatric morbidity, indicated by scores greater than 9 on a general health questionnaire (the GHQ-28), was 10% among women and 7% among men [46]. A comparison of these estimates with those in the general population was not reported.

A single study assessing intrusive thoughts and avoidance of them during the 6-8 week period between having blood drawn and receiving *BRCA* test results [48] reported slightly higher intrusion and avoidance scores (measured using the IES) when compared with the above studies examining pre-test distress. The mean intrusion score was 7 (range 0-13) and the

mean avoidance score was 8 (range 0-29). Mean anxiety and depression scores, assessed using the Hospital Anxiety and Depression Scale (HAD), were similar to those observed in the general female population (mean anxiety score = 5.5 and mean depression score = 2.4, with possible scores ranging from 0-21 for each subscale). Follow-up of the same study population found that anxiety, depression and intrusion/avoidance scores following disclosure of results decreased among non-carriers of *BRCA* mutations and increased slightly among carriers [49]. A similar pattern was observed in another study where mean anxiety scores, measured using the state anxiety subscale of the STAI, decreased (from 37.3 to 28.4) from pre-to post-disclosure of results among non-carriers of *BRCA* mutations, but remained essentially unchanged among carriers (39.2 pre-disclosure vs. 40.9 post-disclosure) [47].

Two studies have examined the psychological distress associated with genetic testing for colorectal cancer susceptibility. Among individuals undergoing familial adenomatous polyposis (FAP) susceptibility testing, mean pre-test levels of intrusion and avoidance (measured using the IES) were relatively low (4.0 and 4.4, respectively) [45]. A survey of colorectal cancer patients awaiting results of HNPCC susceptibility testing [50] found that "high distress" patients (characterized by higher depression and anxiety scores, lower social support and lower quality of life scores) were more likely than "low distress" patients to worry about carrying an altered gene and were less likely to feel able to cope with their results. However, distress levels were not associated with intent to be informed of test results.

The importance of considering measures of psychological distress in context was illustrated in a study [51] which measured the stress (on a scale from 1 to 5) experienced by women at high risk of carrying *BRCA* mutations associated with being in a high risk family, being offered genetic testing, anticipating a positive test result and anticipating a negative test result. Among women without cancer, being a member of a high risk family (mean stress score = 3.5) was slightly less distressing than anticipating a positive test result (mean = 3.7) and was considerably less distressing than being offered genetic testing (mean = 1.9). Among women with cancer, being a member of a high risk family (mean = 3.8) was slightly more distressing than anticipating a positive test result (mean = 3.5) and considerably more distressing than being offered testing (mean = 1.8). These women also reported that receiving their diagnosis was considerably more distressing (mean = 4.5) than anticipating a positive test result (mean = 3.5). Further, none of the cancer-specific distress scores reported by the women were associated with generalized distress or maladjustment (measured using the Hopkins Symptom Checklist and the Medical Outcomes Study Short-Form-36). The authors noted that "distress" reported by those undergoing genetic testing may not be attributable to the testing process itself, and that researchers should take care to interpret their measures in the context of the greater, pre-existing stress associated with being aware of one's high risk status. These findings were supported by a qualitative study describing the genetic testing experiences of women with

breast and/or ovarian cancer [52]. For these women, the genetic testing process was largely perceived as a "non-event" when compared with the experience of dealing with cancer. Most women viewed genetic testing as an opportunity to gain valuable information about their family members' risks.

In addition to the above studies which reported quantitative data on distress levels, a number of case studies and case series reported on specific stressors experienced by individuals undergoing *BRCA* testing. The testing process has been reported to evoke a range of emotional reactions, including grief reactivation, resentment, fear, guilt, denial, and regret over past surgical decisions as well as intense fear of developing cancer again (among cancer patients) [52-57]. A single qualitative study of women who sought but were refused *BRCA* testing based on their low risk status (a largely unstudied group) revealed that being denied testing evoked similar emotional reactions [58].

Individuals have reported agreeing to genetic testing out of a sense of family duty, raising concerns among researchers about coercion infringing upon autonomous decision-making [55]. One study found that men were generally reluctant to discuss their personal risks, were more concerned with the risks faced by their children or potential children, and felt they had "no right to complain" given the illness and death experienced by female family members [59].

The psychological impact of genetic testing may be disease specific. A qualitative study of families with known HNPCC-associated mutations found that the notification of genetic susceptibility was not particularly surprising, often confirmed previous suspicions about familial patterns of cancer, and was not viewed as a medical crisis or a matter requiring urgent attention [60]. Similarly, another qualitative investigation found that the anxiety experienced by individuals with and without cancer who were awaiting test results for genetic susceptibility to HNPCC may indeed be functional, permitting individuals to work through the implications of an unfavorable test result [61].

Interventional studies in the genetic counseling/testing setting

Four studies compared the impact of various interventions on knowledge of breast cancer genetics, perceived risk of developing breast cancer and breast cancer-related anxiety. One study randomized women with a family history of breast cancer to standard genetic counseling or to an interactive computer program plus standard genetic counseling [32]. At follow-up, knowledge of breast cancer genetics had increased similarly in both groups. The participants, who were generally highly educated and very computer literate, reported favorable attitudes towards using the computer program to obtain information, but the majority preferred interacting with a genetic counselor [62].

Another study compared the impact of a multidisciplinary counseling service with that of standard care (i.e., assessment by a surgeon) among women with a family history of breast cancer and found that over a nine month follow-up period, breast cancer worry and perceived risk of developing breast cancer decreased slightly and similarly in both groups while knowledge of breast cancer genetics increased slightly and similarly in both groups [43].

In a similar study, unaffected women with a family history of breast cancer were randomized to one of three groups: education only, education plus genetic counseling or control [63]. Both interventions were associated with significant, similar increases in knowledge of breast cancer genetics (relative to control). From baseline to follow-up, the education-only group but not the education plus counseling group showed a significant reduction in the perceived likelihood of carrying a *BRCA* mutation (which was generally over-estimated at baseline). Testing intent (hypothetical only) did not differ by study group at follow-up and remained stable over time.

These findings contrast with those of study which randomized women judged *not* to be appropriate candidates for *BRCA* testing based on their family cancer histories to genetic counseling, group psychosocial counseling or control [25]. At the six month follow-up point, all participants (regardless of the intervention arm they were assigned to) had reduced interest in risk testing and were less likely to regard themselves as appropriate test candidates.

Economic studies

The costs and cost-effectiveness of providing genetic screening for susceptibility to FAP, hereditary retinoblastoma and hereditary breast and ovarian cancer (HBOC) has been examined in a number of decision analyses. Analyzed from the perspective of a third-party payer, two studies found that screening approaches employing genetic testing for *APC* mutations in FAP could result in substantial direct cost savings when compared with conventional clinical screening (i.e., regular sigmoidoscopy examinations from late childhood to the age of 50 years) [64, 65]. In the first study, the genetic screening approach involved testing an affected family member (i.e., the proband) and subsequent testing of all FDRs if a mutation was found. Given the identification of a mutation in the proband, mutation-negative FDRs would be released from conventional clinical screening. Mutation-positive FDRs, FDRs of probands without confirmed mutations and untested FDRs would follow conventional clinical screening [64]. The cost of screening a prototype family using the genetics approach was estimated at $4,975 (vs. $8,031 using the conventional approach). However, cost savings were not realized if the frequency of conventional screening was increased among confirmed mutation carriers. The second study, using a similar approach, estimated the total screening costs per person to be $2,625 for a genetic strategy beginning with an affected proband, $2,674 for a genetic strategy beginning with an at-risk FDR and $3,208 for a conventional clinical screening strategy [65]. The cost savings realized using the genetics approach increased as the size of the family increased.

Also considered from a third-party payer perspective, a genetic screening approach incorporating *RB1* mutation searching in hereditary retinoblastoma was found to be less expensive than conventional screening [66]. For the genetic screening strategy the total cost for a prototype family was $8,764, compared with $31,430 for the conventional screening strategy.

A single study examined the cost-effectiveness of *BRCA* testing (among women at varying levels of hereditary risk) followed by the prophylactic measure offering the greatest number of quality-adjusted life years (QALYs) as estimated by expert physicians [67]. The cost-effectiveness of testing women in the general population (where the probability of carrying a *BRCA1* or *BRCA2* mutation is about 0.0006 and 0.0002, respectively) exceeded $1.6 million per quality-adjusted life year (QALY) gained. For women with slight to moderate hereditary risk increases (i.e., with estimated probabilities of carrying mutations between 0.05 and 0.1), the cost-effectiveness ranged from $15,000 to $34,000 per QALY gained. For women with high hereditary risks (i.e., with estimated probabilities of carrying mutations between 0.25 and 0.50), the cost-effectiveness ranged from $3,500 to $4,900 per QALY gained. The authors concluded that *BRCA* testing in the general population is not sufficiently cost-effective to warrant adoption but is likely to be relatively cost-effective for women with elevated levels of hereditary risk.

Another study compared the costs of providing genetic counselor-based *BRCA* counseling/testing in a research setting with an alternate, hypothetical program providing brief, physician-based counseling/testing [68]. The average costs per mutation detected in the counselor-based program ranged from $8,034 in a high risk population where the minimum prior probability of carrying a mutation was 10%, to $79,104 in breast cancer patients unselected for family history, to $1.5 million in the general population. Overall, the cost of genetic counseling accounted for only 16% of the total costs. The authors concluded that *BRCA* testing in the general population is unlikely to prove cost-effective, as it is unlikely that sufficient benefit will be produced to justify the high cost per mutation detected. Further, the authors suggested that offering abbreviated, physician-based counseling rather than comprehensive counselor-based counseling is unlikely to achieve appreciable cost savings.

Finally, an analysis comparing the costs of direct sequencing of the entire *BRCA* gene (the technique for which Myriad Genetics, Inc. hold the patent) with the costs of other mutation-detecting technologies currently available in France found that two alternate, less expensive approaches can reach the same level of accuracy as direct screening [69]. The authors noted that gene patents may prevent health care systems from identifying and adopting the most cost-effective genetic testing strategies.

Issues surrounding prophylactic interventions

Five studies assessed the intention to obtain a prophylactic mastectomy or oophorectomy among women being tested for *BRCA* mutations. Before receiving results, the proportion of women planning to undergo a prophylactic mastectomy if they were found to be mutation-positive ranged from 19% to 43% [48,70]. The proportion planning to undergo an oophorectomy ranged from 23% to 50% [48,71]. About one third of women were undecided [71, 72]. Elevated cancer-specific distress scores, measured using the Impact of Events Scale (IES), predicted intention to seek both prophylactic measures [71, 72]. However, given the cross-sectional nature of the data collection, the direction of the associations was not clear. It is conceivable that thinking about undertaking the surgeries caused cancer-specific stress scores to increase.

Among women known to carry *BRCA* mutations, 17% intended to undergo prophylactic mastectomy and 33% intended to undergo prophylactic oophorectomy [39]. Compared with those who had not yet received results (above), the proportion of those who were undecided was lower (i.e., 17% for both procedures) [39].

A single survey of female gynecologists in northern France found that 30% would accept a prophylactic mastectomy and 52% would accept a prophylactic oophorectomy [29].

Four decision analyses evaluated the gains in life expectancy and quality-adjusted life expectancy (QALE) associated with prophylactic surgery following *BRCA* testing. Among proven mutation carriers of various ages, prophylactic mastectomy resulted in greater average gains in life expectancy than prophylactic oophorectomy (when compared with life expectancy given no surgery) [73]. The gain in life expectancy from both procedures exceeded the sum of the gains realized from each procedure alone [73, 74]. Surgery produced little benefit for older women (e.g., 60 year-old women gained less than one year of life expectancy from either surgery) [73]. When QALE was considered, oophorectomy tended to be a better option than mastectomy [67, 74].

The importance of considering the population at risk when determining the impact of prophylactic surgery on quality of life was illustrated in a study which showed that healthy, average risk women perceived the negative impact of prophylactic oophorectomy and/or mastectomy to be relatively high, when compared with healthy, high risk women and women with breast cancer [75]. Case studies have also revealed that decisions about prophylactic surgery are extremely difficult for women, and that carriers may face opposition from relatives and medical professionals despite making “personal best” decisions [53, 56].

One study evaluating *BRCA* testing in various populations found that the majority of women will not benefit from genetic testing, as their pre-test risks are low and surgical prophylaxis is

undesirable [76]. Women with family histories of breast and/or ovarian cancer may gain up to two QALYs by allowing genetic testing to guide their medical management decisions [76]. The "ideal testing candidate" (i.e., the candidate who would benefit most from genetic testing) was found to be a woman at moderate to high risk of carrying a mutation, with no more than moderate concerns about the quality-of-life implications of prophylactic surgery [76].

A decision analysis comparing life expectancy and QALE associated with various colorectal cancer prevention strategies among carriers of HNPCC-associated mutations found that compared with no surveillance, all of the colectomy strategies resulted in substantial gains in both outcomes [77]. However, when compared with standard clinical surveillance, immediate proctocolectomy or subtotal colectomy in a 25 year-old carrier resulted in smaller life expectancy gains and losses in QALE [77]. The authors concluded that assuming reasonable effectiveness, standard surveillance provides a reasonable alternative to prophylactic colectomy for those at risk of HNPCC. However, prophylactic surgery was thought to be a better alternative for those unwilling to undergo surveillance.

Finally, the impact of genetic testing on screening behavior was assessed in a single study of individuals confirmed *not* to be carriers of *APC* mutations associated with FAP [78]. In the U.K., 67% of individuals who received care from a non-geneticist and 33% who received care from a geneticist still planned to participate in future, unnecessary bowel screening. None of the Australian respondents, all of whom received care from a geneticist and who were more likely to report feeling that their DNA results were certain, planned to do so. The authors noted that the delivery of genetic test results to patients may influence their subsequent surveillance decisions.

Informed consent

Given the complexity of the information prospective recipients of genetic testing must assimilate, some researchers have directed their attention to informed consent issues. Evaluations of informed consent documents currently in use at U.S. centers providing *BRCA* testing have revealed considerable variation in content and organization [79], the omission of important information [79] and language that largely exceeds the average reading levels in the general population [79, 80]. Policies guiding the generation of these documents also appear to be inadequate. A survey of directors of the human protocols offices at National Cancer Institute designated cancer centers found that more than half of the respondents did not feel adequately informed of the issues, legislation and professional policy statements related to genetic testing and research [81]. Further, 75% of the centers did not require Institutional Review Board (IRB) approval for genetic testing protocols at their centers, 64% did not have formal genetic testing policies and 43% did not have formal genetic research policies in place to guide the IRB review process.

Surveys of general practitioners have shown that while they are generally supportive of genetic testing for cancer susceptibility and perceive a major role for themselves in identifying patients at risk, providing counseling, delivering test results and providing follow-up care, their knowledge of hereditary cancer genetics and testing is generally quite limited [82-85]. This relative lack of relevant expertise has obvious implications for patients, who have themselves been shown to have limited knowledge of genetics and limited awareness of the risks and benefits of genetic testing (discussed above).

Finally, it has been suggested that the traditional, nondirective approach to genetic counseling may not meet the needs and expectations of all patients considering genetic testing for cancer susceptibility. A survey of women who had undergone *BRCA* testing found that when deciding whether or not to be tested, 49% had wanted the opinion of their personal physician and 77% had wanted the opinion of a cancer center specialist [86]. The appropriateness of providing directive counseling, however, has not been evaluated and would likely be contentious.

Testing of vulnerable populations

The testing of vulnerable populations (e.g., children, those with limited intellectual capacity, etc.) is a controversial issue that has received little attention from researchers. A single survey of adults from a large kindred who had themselves undergone genetic testing for a known familial *BRCA1* mutation found that 25% believed genetic testing should be available to children, yet only 17% of those with children would permit testing of their own children [87]. A positive (vs. negative) overall attitude towards the genetic testing process, non-carrier (vs. carrier) status, male (vs. female) gender, and a positive (vs. negative) maternal history of breast cancer were positively associated with endorsing testing for minors. Qualitative studies have suggested that the differing concerns of parents and children (i.e., parents tend to focus on the implications of the test results while children tend to focus on short-term risks such as the discomfort associated with specimen collection) and differing opinions on the extent to which children should be involved in the decision-making process may impact the informed consent process [88, 89].

A single case study documented the difficulties experienced by genetic counsellors when deciding whether or not to offer testing to a woman with limited intellectual capacity seeking *BRCA* testing after a physician recommended a prophylactic oophorectomy given her family cancer history [90]. The counsellors ultimately decided that while her understanding of the possible implications of testing was limited, she could explain the “good” and “bad” news in rudimentary terms and should not be denied testing.

Potential discrimination

The availability of genetic testing for cancer susceptibility has raised concerns about the potential for genetically-based discrimination. However, little research has been devoted to the issue.

In a population-based survey of women with at least one parent of Jewish descent, 71% of respondents believed that there was a scientific reason to offer genetic testing to Jewish women and 82% were *not* concerned that such testing would increase anti-Semitism [34]. However, men asked about their attitudes toward hypothetical testing for genetic susceptibility to prostate cancer were concerned that testing would negatively affect their ability to obtain health and life insurance [91].

The potential for insurance discrimination following genetic testing appears to exist, but the prevalence of such discrimination has not yet been well studied. A 1998 survey of private insurers operating in Norway [92] found that a family cancer history strongly suggestive of a *BRCA* mutation would not influence either the offer or the cost of life or disability insurance. Given a family cancer history strongly suggestive of HNPCC, however, 11% of insurers would offer both products at raised premiums. The authors noted that individuals fearing genetically-based insurance discrimination cannot avoid it simply by avoiding genetic testing; discrimination may occur based on family history alone.

Insurance demand and adverse selection

More research has been devoted to the impact of genetic testing on insurance demand and insurance industry concerns regarding adverse selection (i.e., the situation whereby people at high risk of premature death/illness, using information not available to insurers, purchase more insurance at rates which are not actuarially fair).

To date, the impact of genetic testing on the demand for insurance appears to be minimal. A survey comparing known *BRCA* mutation carriers with the general U.S. population found that on average, the number of life insurance policies held and the total amount of insurance coverage were similar in both groups [93]. A similar survey comparing women who had undergone *BRCA* testing with women in the general U.S. population found that while industry fears of adverse selection may be partly justified, they may be somewhat misplaced [94]. Overall, the purchase of cancer-specific insurance was quite rare. However, 10.4% of mutation carriers, 8.9% of non-carriers and 3.8% of respondents in the general population had purchased such policies, suggesting that genetic testing itself, rather than genetic test results, may stimulate consumer demand [94].

A decision analysis estimating adverse selection costs in a life insurance market potentially influenced by *BRCA* testing found that the average adverse selection cost in a portfolio is likely to be well below 10%. Adverse selection costs exceeding 10% will likely result from the purchase of larger amounts of insurance, rather than from the purchase of a greater number of policies. The authors suggested that the problem of adverse selection could be avoided if insurers were allowed to use genetic test results for underwriting policies with very large payouts in exchange for a ban on the use of test results for policies with reasonable payouts [95]. This is the current practice of the Association of British Insurers [95].

The prevalence of insurance coverage for genetic testing itself has not been reported. However, a population-based survey revealed that only 9%, 3% and 3% of respondents would "probably" or "definitely" be willing to pay $500, $1000 and $1,500, respectively, to have a genetic test for cancer risk [96]. Interest in the topic of insurance coverage for genetic testing for cancer susceptibility may grow if it becomes more widespread.

Currently, insurance coverage for prophylactic surgeries which might be considered following a positive genetic test result is variable. A 1999 survey of U.S. insurance providers found that between 41% and 64% of private and governmental health insurance carriers had no coverage policies for prophylactic mastectomy or oophorectomy while 11% to 56% did not cover the procedures [92].

Narrative documents: major content areas

Gene patents

Gene patenting has proven to be a highly divisive issue. While genes in their natural form are not patentable, isolated and pure forms of genes that have been the object of considerable human intervention (i.e., cloning, amplifying and sequencing) can be the subjects of a patent claim [97]. Proponents of gene patenting argue that patents ensure high quality tests [97], encourage scientific innovation and investment in research [97-99] and facilitate information sharing (as patent applications require full disclosure) [97]. They also assert that biotechnology companies have a right to recoup research and development costs [97, 98, 100].

Critics of gene patenting attest that the human genome is fundamentally different from traditional patent matter (e.g., consumer goods) and is an inappropriate subject of property rights [97, 101]. This view is endorsed by the International Bioethics Committee of the United Nations Educational, Scientific and Cultural Organization (UNESCO) and the Human Genome Organization (HUGO) [97]. Critics also maintain that patents may impede cancer research and stifle innovation [97, 99], and that monopoly pricing will limit public access to testing and could result in the collapse of publicly funded health care [97, 101]. Indeed, the granting of several international patents on the *BRCA1* and *BRCA2* genes to Myriad Genetics, Inc. generated

considerable backlash from both the research community and governmental health care systems [97, 98, 101-107].

In Canada, an isolated gene sequence shown to be novel and have a useful function is patentable under the federal *Patent Act* [97]. The Supreme Court of Canada has strongly stated that patent rights are broad in scope, and without legislative or regulatory reform the courts will likely enforce broad subject matter patentability and a broad scope of exclusive rights to patent holders [97]. The law, however, does not address the ethical and financial consequences of broad patent protection and no policy framework currently exists at the federal level to deal with these issues [97].

Other legal issues

The narrative documents frequently cited evidence that while biological and medical research is rapidly developing, the evolution of the legal framework addressing relevant, non-scientific issues is lagging behind. Directives guiding the application of new predictive technologies are clearly required [1, 108-113].

A range of issues requiring regulatory consideration were mentioned, including liability for laboratory errors [114-116], family law issues (e.g., disclosure of non-paternity, the rights of children placed for adoption, the screening of embryos for "medical" indications, etc.) [113, 116, 117], physician liability (e.g., for failing to recognize a familial cancer syndrome or warn at-risk relatives, for "wrongful birth" or "wrongful life" when testing was available but not suggested, for inaccurate interpretation of accurate test results, etc.) [114-116, 118-121], the legal definitions of "illness" and "disability" in the context of cancer susceptibility genes [113, 114, 122, 123], DNA control and property rights [114], and the confidentiality of medical records, DNA databanks and public health registries and data bases [124, 125].

The protection of patient confidentiality, a principle of the Hippocratic Oath and the historic basis for trust in the physician-patient relationship, will likely pose an increasing number of challenges (both legal and ethical) for physicians [126]. Conflicting physician responsibilities (i.e., the duty to protect patient confidentially vs. the duty to warn others at risk) have received considerable legal attention. In the U.S., little direct statutory guidance exists on this issue. Courts and official organizations are divided on the issue; but where statutes exist they tend to permit rather than mandate giving priority to the disclosure of genetic information [113, 114, 116, 120, 127-130].

Regulation addressing the "quality control" of available screening tests is also scarce [1, 110, 113, 131-133]. The U.S. Health Care and Financing Administration, the body responsible for the certification of laboratories, does not have a process in place to oversee genetic testing. It requires analytic validity but does not require that tests have clinical validity or utility [1, 108]. Further, while the U.S. Food and Drug Administration (FDA) regulates the production of test kits

manufactured for use by others in laboratories, manufacturers and private laboratories can circumvent the FDA review process by using their own reagents in-house and offering testing *services* through primary physicians [1, 134]. A similar situation exists in Canada, where a comprehensive framework for dealing with the integration of genetic testing services into the health care system is lacking [135].

Concerns have also been raised about the lack of comprehensive regulations governing the use of genetic testing information by employers and insurers, a deficit which may well influence an individual's decision to pursue genetic testing [2, 113, 114, 116, 124, 136-138]. In the U.S., the federal Health Insurance Portability and Accountability Act of 1996 prohibits group health insurance plans from treating most genetic characteristics as "pre-existing conditions" and from using genetic information to determine insurance eligibility [114, 127, 139]. It does not, however, restrict the ability of insurers to increase rates or impose coverage limitations [114], nor does it protect those who must purchase individual policies [127]. At the state level, over half of the states prohibit health insurers from requiring genetic tests as a condition of coverage or from using genetic test results to deny coverage [114]. When compared with health insurance, life and disability insurance are less regulated at both the federal and state levels [114]. Several European countries have no legislation or guidelines governing insurers, some have imposed indefinite moratoriums on the use of genetic testing information and others have developed explicit regulations [138]. Canada has no specific, relevant legislation [138].

Ethical issues

The ethical issues related to genetic testing for cancer susceptibility are many, and often overlap many of the legal issues discussed above.

Issues related to the principles of beneficence/nonmaleficence

Two themes dominated the discussions related to these two principles: the ethics of providing information about potential cancer risks in the absence of established options for reducing risk [2, 103, 112, 124, 132, 133, 136, 140-160] and the ethics of providing genetic susceptibility testing when many of the psychological and social consequences of testing and the long-term risks and benefits of available medical management strategies remain unknown [111, 112, 124, 133, 136, 140, 142, 144, 147, 152, 161-171].

Concerns have also been raised about providing testing when an uninformative, inconclusive test result is possible [172]. Specifically, a negative test result on genetic testing for hereditary cancer can only be informative if the mutation responsible for increased cancer risks in a family has previously been identified in another family member. The circumstances under which genetic testing provides information which proves to be more beneficial than burdensome are far from clear [126, 166, 167, 173, 174]. The commercialization of genetic testing has led to the concern

that predictive tests will become the equivalent of "biological Tarot cards", subject to misinterpretation and over-reliance [1]. The potential for harmful, unexpected information to be revealed as a result of genetic testing (e.g., the disclosure of non-paternity) has also been discussed [144, 172, 175-177].

Genetic testing for susceptibility to cancer also raises issues surrounding prenatal testing, preimplantation testing (i.e., testing *in vitro*-conceived embryos for genetic alterations before implantation) and reproductive decision-making [116, 124, 178-183]. Concerns have been raised that testing for the possible development of late-onset disorders will result in a "slippery slope" leading to genetic perfectionism or eugenic social policies [2, 111, 119, 120, 136, 151, 166, 177, 179, 184]. Complicating this issue, the ethics of prenatal and preimplantation testing are expected to differ depending upon the type of condition being tested for (e.g., testing for genes that confer an increased risk of childhood vs. adult-onset cancer) [167, 179, 182, 185], the degree of gene penetrance [179], the severity of the disease and the availability of treatment (which may differ substantially at the time of disease onset from that which is available at the time testing) [179, 182, 183].

Finally, it is unclear if genetic testing will cause healthy individuals to perceive themselves as "sick" [166] or will stigmatize those found to carry mutated genes [111, 112, 144, 145, 152, 156, 178, 186].

Issues related to the principle of justice

Questions regarding equal access to genetic testing for cancer susceptibility abound in the literature. For example, given the limited resources allocated to health care, can the costs of genetic susceptibility testing be justified? [163, 169, 187] If so, who has the right to be tested? Should genetic testing be made available to all who seek it or should it be restricted to those who fall into high-risk categories? [2, 116, 161, 165, 169, 177, 186] If testing should be made available to all, can the expense be justified if the only reason testing is being sought is to reduce uncertainty? [2, 161] Who should pay for testing and subsequent screening or preventive measures? [2, 161, 188] Is regulation of access to testing appropriate, or should the free market determine what tests are available and to whom and at what price? [186] Could socioeconomic, geographic or "ineligibility" barriers to both counseling and testing services impede equal access [111, 145, 150, 166, 177, 185], resulting in the creation of a "genetic underclass"? [124] Consensus is lacking on these issues, and primary research informing the debates is limited.

Concerns that predisposition testing may lead to insurance, employment and/or ethnic discrimination are plentiful [2, 108, 111, 112, 115, 116, 119, 120, 124, 129, 132, 133, 137, 140, 141, 144, 145, 147, 149-153, 156, 158, 161, 163, 167-169, 171, 174, 177, 178, 185, 189-208]. Specific discrimination against communities in which a high prevalence of susceptibility mutations has been identified (e.g., the Ashkenazi Jewish community) is of particular concern [209]. Fear of discrimination could impede equal access to genetic testing. On the other hand, industry fears of adverse selection (discussed above) [199, 206, 210, 211] have led to speculation that insurers might be forced to increase premiums globally, rising

prices could in turn cause markets to shrink and insurance policies could eventually become unaffordable [199]. One report noted that insurers are in a difficult position, as sound actuarial principles cannot be applied to the prediction of illness and mortality risks associated with genetic mutations until sufficient longitudinal data has been collected, yet strong public support to restrict access to genetic test results may render the collection of such data impossible [212].

Issues related to the principles of autonomy

Numerous concerns have been raised about the possible impact of genetic testing on various aspects of personal autonomy, including the right to privacy and self-determination in the absence of coercion. First, ensuring that consent is truly informed is difficult given the emotionally charged context of genetic testing and the complexities involved in appreciating both the probabilistic nature of the test results and the potential risks and benefits of testing [111, 112, 129, 149, 151, 166, 167, 169, 177, 183, 196, 213, 214]. Ensuring that people are fully aware of what they are consenting to is also problematic, given that DNA samples are often banked and possible future uses of the samples and/or their derivatives may be unspecified at the time of initial testing [2, 146, 147, 149, 150, 166, 171, 177, 215].

The potential for violations of autonomy (in the context of making informed choices) may increase as testing moves from the relatively tightly regulated research arena to the commercial arena. For example, in contrast to most existing research protocols, Myriad Genetics Laboratories, Inc. (a commercial provider) recommends but does not require that individuals receive genetic counseling prior to testing. Whether or not the informed consent process and/or the disclosure of test results can and will be handled appropriately under these circumstances is questionable [116, 151, 153, 169, 196, 216-218]. Further difficulties are envisioned if the demand for testing surpasses the existing, limited capacity for genetic counseling services [2, 192].

Genetic testing also brings up a number of privacy-related issues which highlight potential conflicts between autonomy, beneficence and maleficence. The familial nature of testing makes it difficult to ensure that testing decisions are free from direct or subtle coercion, which may be very difficult to distinguish from largely unavoidable family influence and altruistic intentions [2, 124, 142, 185]. Keeping individual results confidential is also challenging [121, 124, 129, 147, 162, 203]. Whether or not individuals have a moral obligation to inform their at-risk relatives about their results is a matter of great debate, and it is unclear where the moral limits to medical confidentiality should be set in the “right to privacy vs. the duty to warn” debate [2, 121, 124, 126, 127, 136, 145, 149, 161, 162, 164, 171, 177, 183, 200, 203, 219-222]. Balancing the “right to know” against the “right not to know” is a similarly complex issue [2, 124, 132, 145, 149, 150, 156, 162-164, 171, 177, 183, 197, 203, 204, 215]. Conflict may arise when some family members wish to receive genetic information while others do not or were not asked if they wanted to [124, 132, 149, 162-164, 171, 215], or when testing identifies obligate mutation carriers (e.g., individuals sandwiched between an older and a younger generation of proven carriers) who do

not wish to know their genetic status [2, 132, 203]. This issue is also bringing about a paradoxical shift in the physician-patient relationship, where the therapeutic privilege of a physician to withhold certain information from patients is being transformed into a right of patients not to know [197].

Privacy concerns also arise in the context of the storage of specimens, the disposition of information about stored samples and the security of sensitive information. The prevention of both inadvertent and deliberate disclosure of test results to third-parties is difficult to ensure and raises serious issues [2, 108, 126, 129, 136, 146, 147, 166, 190, 203]. For example, health management organization (HMO) salesmen and government employees in Maryland were charged in 1995 with bribery and selling thousands of confidential patient records to competing HMOs [136].

Testing of vulnerable populations

The testing of vulnerable populations (e.g., children, individuals with limited intellectual capacity, pregnant women, etc.) has generated a number of ethical questions [2, 4, 120, 121, 124, 145, 149, 151, 156, 162, 171, 177, 178, 183, 185, 192, 205, 223-229]. For example, at what age do children become competent to make their decisions? [121, 223] When is assent required and when is dissent binding? [2, 162] When should testing be made available to children? [121, 185, 224-226]

Regarding the timing of the testing of children, the "rule of earliest onset" has been proposed. It purports that genetic testing should be permitted at an age no earlier than the age at first possible onset of cancer [227]. This rule is thought to maximize benefit while minimizing risk as it does not deny standard medical benefit to any child. However, it is recognized that strict application of the rule in a research setting may prevent children from realizing benefits available only through research participation (e.g., knowledge of the genetic basis of cancer is rapidly evolving and the continuum from research to practice should accommodate some level of ambiguity regarding potential benefit to pediatric research subjects) [227].

Additional questions that have been raised include: Is testing in childhood for genes which predispose to late-onset disorders justifiable when effective preventive strategies do not exist [178, 192] or do not have to be undertaken until adulthood? [178, 223]. Can parents refuse to have children tested when genetic information will facilitate early detection and successful treatment of a potentially life-threatening disease (e.g., hereditary retinoblastoma) [192], or would they be liable under child protection laws for denying indicated care? [120] Among any vulnerable population, do the risks of psychological harm (poorly elucidated at this point in time) outweigh the potential benefits of testing? [192, 226, 228, 229]. Again, consensus is lacking on these issues, and primary research informing the debates is limited.

Social issues

Genetic susceptibility testing will inevitably impact the organization of primary care services and the structuring of physician-patient relationships. For example, a report from the Cancer Research Campaign and the Imperial Cancer Research Fund in England revealed that physicians were unnecessarily referring large numbers of low-risk women for *BRCA* testing [230]. Whether they were simply erring on the side of caution or were unaware of appropriate referral criteria was unclear. However, it is clear that primary care physicians will face increasing pressure to remain well informed about genetic testing [165, 167, 169, 193, 196]. Genetic counseling, a required prerequisite to testing in research settings and a required or recommended prerequisite in other settings, is viewed as key to ensuring informed consent. However, geneticists, physicians with sufficient knowledge about genetic testing, and genetic counselors are in short supply [1, 116, 151, 158, 183] and concerns have been raised that this intellectual and personnel void will grow as genetic testing becomes more widespread [111, 112, 132, 167, 196, 201, 231]. To whom the responsibility for developing and disseminating educational materials should fall is unclear [134, 144, 147, 205].

Genetic testing may also blur the boundaries in traditional patient-provider relationships. Will the primary care provider be the general practitioner? the geneticist? the laboratory?[165, 171]. Could the nature of the relationships change from therapeutic to commercial? [165] In the context of recruiting patients for genetic susceptibility research, potential conflicts of interest arising from the moral differences between the physician-patient relationship and the investigator-subject relationship will require deliberation [143, 149]. For example, should a physician disclose test results with unknown clinical value and accuracy that were obtained in a research setting to a patient? [143] Will physicians seeking participants for their own research studies engage in inappropriate, aggressive recruiting? [149]

The appropriate setting for genetic susceptibility testing (i.e., research vs. clinical vs. commercial) is also a matter of debate. For example, when *BRCA1* testing was first developed, leading scientists and commercial testing laboratories agreed informally *not* to offer testing to the general public, given concerns that the risks associated with mutations and the efficacy of strategies to mitigate risk were largely unknown [171]. Accordingly, controversy erupted when OncorMed, Inc., the Genetics and I.V.F. Institute in Virginia and Myriad Genetic Laboratories, Inc. began offering commercial testing in 1996 [1, 232].

Supporters of commercial testing argued that women had a right to know if they carried a mutation, that it was indefensible and patronizing to tell them to wait for testing while research continued, and that extending *BRCA* testing beyond the research setting would save lives via intense surveillance and prophylactic measures. Critics countered that the risks of disease

associated with mutations were not well known and the benefit of surveillance and prophylactic measures had not been proven [151, 158, 173, 174, 232-237]. Official positions on this issue vary. For example, the American Society of Clinical Oncology finds clinical testing acceptable, while other organizations, including the National Advisory Council for Human Genome Research and the National Breast Cancer Coalition endorse confining testing to the research setting [238].

Opponents of commercial testing also argue that direct-to-consumer marketing of genetic testing by for-profit industry can be manipulative, misleading (e.g., overstating the utility of the information provided while omitting information on possible risks of testing) and misguiding (e.g., suggesting women contact companies directly rather than contacting their health care providers) and is targeted inappropriately at the general public rather than high risk individuals [239, 240]. Some believe that marketing tactics exploit the ignorance of consumers [151] and stop just short of "out-and-out deception" [240].

Population-based genetic susceptibility testing has also received attention in the literature. A number of documents have examined whether or not existing criteria for assessing whether or not to adopt population-based screening programs (e.g., the framework outlined by Wilson and Jungner [241]) are applicable to susceptibility testing [120, 131, 186, 207, 242, 243]. Given that a goal of screening is the early detection of disease, the importance of distinguishing between existing cancer screening programs, which identify actual cases of cancer, and genetic screening programs, which identify individuals who *may* be likely to develop cancer, has been pointed out [218, 244]. Further, the extent to which genetic and/or environmental modifiers of the risks associated with susceptibility mutations exist is largely unknown, in both high-risk and population-based samples [245]. Lastly, as the predictive values of the tests depend on test sensitivity, test specificity and the prevalence of the mutations being screened for, the low frequency of cancer susceptibility genes in the general population may seriously limit the information value of susceptibility tests [245-247]. For effective use in the general population, screening tests will often require specificities far higher than 99% [247]. More information is required on the relationship between the criteria used to refer individuals for genetic counseling/testing and the potential demand for service that will be created if those criteria are applied on a population basis [248].

Policy-makers will also need to weigh the benefits of population-based cancer susceptibility testing against the benefits associated with other public health care initiatives [152, 155, 156, 168, 218, 249]. Consideration must be given to the cost-effectiveness of susceptibility testing [144, 171, 217, 250, 251] and the possibility that population-based testing may increase the need for other cancer screening programs [2, 218].

It has been noted that genetic testing for cancer susceptibility may undermine cancer surveillance and prevention strategies by contributing to "genetic myopia" in society, or the tendency to view everything from the perspective of genetics. Such a reductionist viewpoint may lead to the dismissal of other modifiable factors (such as environmental toxicants and lifestyle characteristics) that contribute to cancer risk [124, 249]. Concerns have also been raised that the multitude of privacy concerns associated with genetic testing and DNA banking may threaten the legitimacy and viability of cancer registries, thus hindering traditional surveillance activities of benefit to the public and to medical research [197].

DISCUSSION

The Canadian Institutes of Health Research Institutes of Genetics has identified five areas of interest associated with social, ethical and legal dimensions of genetic testing (see: http://www.cihr-irsc.gc.ca/e/services/19529.shtml). This review synthesized the available literature (subject to constraints as noted) relevant to these topics.

Definitions of "normal" and "abnormal", "disease" and "health", etc.

Where an identified genetic susceptibility to cancer development lies on the continuum from health to illness is unclear. For most cancers for which genetic predisposition testing is currently available, test results provide probabilistic as opposed to "certain" information about disease risk. Accordingly, the limited predictive power of many of these tests complicates the interpretation of their results. The risk of developing cancer may be greatly increased among carriers of a specific genetic alteration (compared with the general population), but the risk among non-carriers is not zero.

The probabilistic nature of this information is blurring the distinctions between "normal" and "abnormal", "healthy" and "ill", and "able-bodied" and "disabled". The need to establish legal definitions of these terms in the context of susceptibility testing has been identified, and the social and ethical implications of such definitions (particularly in the areas of reproductive and prenatal medicine) may be profound. Concerns have been raised that testing for the *possible* development of late-onset disorders will result in a "slippery slope" leading to genetic perfectionism or eugenic social policies.

Concerns have also been raised that knowledge of personal susceptibility may cause healthy individuals to perceive themselves as ill or may result in the stigmatization of individuals as somehow "abnormal", yet little research has been done in this area. The genetic counseling and testing process certainly conveys "patient" status onto individuals. Further, being identified as a susceptibility mutation carrier may lead individuals to pursue prophylactic interventions (e.g., total mastectomy) more disfiguring than many actual cancer treatments.

Genetic contribution to multifactorial diseases

It has been suggested in the literature that genetic testing for cancer susceptibility may lead individuals to ignore other modifiable factors (such as environmental toxicants and lifestyle characteristics) which contribute to cancer risk. Little prospective research has addressed this issue. However, survey data suggests that the majority of individuals seeking genetic testing believe that it will provide them with important information that could guide cancer surveillance and prevention activities. Whether or not individuals who test "negative" would abandon such activities (based on population-based recommendations) is unknown.

Central to this issue is the information value of a genetic test and the communication of information to tested individuals. In most settings where susceptibility testing is currently offered, testing must begin with a family member affected by a cancer of suspected heritable origin (i.e., the proband). Test results for the proband are only definitive if a mutation is found. A negative test result is considered uninformative, as the individual could carry an as yet unidentified susceptibility mutation or a mutation not identified by the particular test used. Accordingly, a negative test result for an at-risk relative of the proband is informative only if a familial mutation has previously been identified. Research has shown that while interest in genetic testing is quite high, knowledge of cancer genetics and awareness of the possible risks of testing (including an uninformative result) is comparatively low. Although unlikely at the present time, the adoption of population-based genetic testing for cancer-susceptibility will create the need for extensive education of both the public and health care providers.

Ownership and control of genetic material

While little research has been done in this area, genetic susceptibility testing raises numerous issues surrounding the ownership and control of genetic material. These range from informed consent issues related to the storage of personal data and specimens to issues related to gene patents and their potential impact on the delivery of cost-effective health care. While these issues are discussed frequently in narrative discourses, they have received little attention in the primary research literature.

Selection of populations for genetic testing

Concerns about possible discrimination (racial, ethnic, employment and insurance) against individuals and groups resulting from genetic testing abound in the narrative literature. The need for an examination of how moral positions on genetic testing and its implications vary in different cultural and theological environments has also been identified [148, 252-254].

Little primary research has been done in this area. Most has focused on insurance discrimination and has shown that potential for discrimination, while minimal, is real. Additionally, given the limited response rates in many studies, it is possible that this potential is even larger than reported.

The current debate about the appropriate setting for genetic testing research (i.e., research vs. clinical vs. commercial) will grow as testing becomes more widely available. A variety of practice guidelines, policy recommendations and professional position statements addressing this issue (and others) have been published [183, 255-274], yet it is clear that agreement has not been reached. The level of disagreement will likely grow should population-based testing ever be considered.

Selecting the appropriate population for testing requires consideration of a number of issues, including test sensitivity and specificity (which vary according to the number and type of mutations being looked for) [140, 149, 155, 169, 189], the nature of the inheritance mechanism (e.g., autosomal dominant, autosomal recessive, etc.) and the extent of the connection between a genetic alteration and disease [275-285], what is known about the availability and efficacy of prophylactic interventions, *particularly* among mutation carriers [98, 111, 112, 140, 194, 207, 286-288], and absolute risk (vs. relative risk, which can be misleading). For example, *BRCA1* and *BRCA2* are very large genes and hundreds of mutations have been identified to date. Yet even with full sequencing, a sizable proportion of mutations may be missed (e.g., large deletions, "regulatory mutations" not actually within the genes' coding regions that affect gene expression, etc.) [108, 289]. Early *BRCA* studies suggested that mutation carriers had an 85% chance of developing breast cancer and a 60% chance of developing ovarian cancer by age 70, yet more recent work suggests the risk are 56% and 16% for breast and ovarian cancer, respectively [108, 216]. Finally, the 15-fold increase in the relative risk of breast cancer among male carriers of *BRCA2* mutations relative to the general population translates into a very low absolute risk given that only about 4,000 men are diagnosed with the disease in the U.S. each year [140].

Informed consent

A host of potential issues surrounding the informed consent process have been identified. While interest in genetic testing is generally quite high, relevant knowledge is relatively low. The potential benefit of genetic testing is often overestimated, and individuals appear to have difficulty comprehending both the potentially limited information value of the tests. Studies aimed at determining which intervention strategies will best address knowledge deficits, help individuals come to an accurate perception of their personal cancer risks (which tend to be largely overestimated) and facilitate fully informed decision-making have, to date, been inconclusive. More questions than answers have been proposed and will likely be the subject of ongoing debate.

SUMMARY AND RECOMMENDATIONS

Despite the high level of concern about the social, ethical and legal implications of genetic testing for cancer susceptibility, rigorous research in this area is far from definitive. As described above, many questions remain unanswered and will require further attention. Future research could improve on many deficits identified in the current literature. There is a clear need for studies with samples of sufficient size and heterogeneity to adequately address associations of interest. Greater use of validated, reproducible measures and appropriate analytic methods would greatly improve study quality, as would careful consideration of clinically meaningful differences as opposed to statistically significant differences. Attention to the description of study contexts would better facilitate assessments of the extent to which research findings are generalized beyond the study samples.

In some cases, published papers were of very low quality. This is perhaps not unusual in any field, but we found it surprising that, for example, it was impossible to determine the study question from some papers, even after reading the entire text. These low-quality papers were excluded from further review by our quality scoring system. We recommend use of such systems for the purpose of systematic reviews, but also to facilitate publication of clear, informative papers in a consistent fashion by authors and journals.

Researchers would also do well to consider both the appropriateness of their study populations and the information value of their results. For example, the utility of assessing interest in and knowledge of genetic testing for cancer susceptibility in the general population is unclear, considering that well over 99% of respondents would not be candidates for most existing tests and would have no reason to possess knowledge specific to the topic.

Further consideration should be given to “understudied” populations. For example, numerous studies have evaluated the psychological implications of genetic testing among those who ultimately underwent genetic testing. Among these individuals, the distress associated with testing appears to be minimal. However, a large proportion of individuals refuse initial involvement in studies offering genetic testing, and the psychological impact of simply being informed of one’s high risk status and being offered unwanted testing is largely unknown. Similarly, qualitative work has suggested that those denied testing because they fail to meet eligibility requirements experience considerable distress, but this group has remained largely unstudied. Admittedly difficult but not impossible to study, such populations deserve greater attention by researchers seeking to fully understand the psychological and social implications of genetic susceptibility testing.

Genetic testing for cancer susceptibility is currently available, and may indeed become more widespread despite important social, ethical, and legal concerns. The development of a policy framework for integrating these tests into a publicly funded health care system is lagging behind the science. This is a problem that is not limited to genetic testing issues, but this field may be more subject to the "research-policy-practice gap" than others. A number of working papers and technology assessments have been published in recent years [275-285], but there appear to be substantial gaps between this information, guidelines, and practice. Careful policy analysis, as in some of the economic analyses reviewed here, is an important step in bridging these gaps.

This review has taken a "broad brush" to important social, ethical, and legal issues that affect policy makers and stakeholders worldwide. We hope that it provides a useful summary of the state of research, and a useful guide for funding of primary research in the future.

APPENDICES

APPENDIX A: LITERATURE SEARCH: ELECTRONIC DATABASES

Limits: Human studies
Languages: English, French, German
Dates: 1990 to 2003

- **Medline/PubMed** (1990 to May 8, 2003)
- **CancerLit** (OVID 1990 to October 2002)
- **Cochrane Controlled Trials Register** (OVID 2nd Quarter 2003**)**
- **Health Technology Assessment Database** (University of York CRD1990 to May 2003)

Search One

neoplasms[Mesh Major Heading] OR cancer* OR neoplasm* OR tumor* OR tumour*[Keywords/Text Words]

AND

genetics OR genetic predisposition to disease OR genome, human OR heredity OR genetic privacy OR proteome OR genetic markers[Mesh Major Headings] OR genetic* OR genome* OR genomic* OR heredit* OR inherit* OR proteome* OR proteomic*[Keywords/Text Words]

AND

socioeconomic factors[Medline Mesh Heading] OR attitude OR confidentiality OR disclosure OR economics OR ethics OR genetic privacy OR human rights OR informed consent OR insurance OR jurisprudence OR legislation OR mandatory programs OR OR patient compliance OR patient rights OR prejudice OR privacy OR public opinion OR religion OR self disclosure OR social problems OR sociology, medical[Mesh Major Headings] OR attitude OR attitudes OR bioethic* OR confidential OR confidentiality OR cost* OR coverage OR disclosure OR economic* OR ethical OR ethics OR human rights OR insurance OR insure* OR insuring OR law OR legal OR legislation OR legislative OR patient rights OR prejudice OR prejudicial OR privacy OR public opinion* OR religion OR religious OR social OR society OR societal OR socioeconomic* OR socio-economic*[Keywords/Text Words]

Search Two

neoplasms/genetics[Mesh Major Heading]

AND

socioeconomic factors[Medline Mesh Heading] OR attitude OR confidentiality OR disclosure OR economics OR ethics OR genetic privacy OR human rights OR informed consent OR insurance OR jurisprudence OR legislation OR mandatory programs OR OR patient compliance OR patient rights OR prejudice OR privacy OR public opinion OR religion OR self disclosure OR social problems OR sociology, medical[Mesh Major Headings] OR attitude OR attitudes OR bioethic* OR confidential OR confidentiality OR cost* OR coverage OR disclosure OR economic* OR ethical OR ethics OR human rights OR insurance OR insure* OR insuring OR law OR legal OR legislation OR legislative OR patient rights OR prejudice OR prejudicial OR privacy OR public opinion* OR religion OR religious OR social OR society OR societal OR socioeconomic* OR socio-economic*[Text Words]

Database	Platform	Edition	Search Terms/Textwords
Embase	OVID	1990 to Week 19 2003 * all subject headings exploded	malignant neoplastic disease OR neoplasm[Major Subject Headings] OR cancer* OR neoplasm* OR tumor* OR tumour*[Text Words] AND cancer genetics OR cancer screening OR genetic analysis OR genetic marker OR genetic screening OR genetics OR genomics OR heredity OR proteomics OR proteome[Major Subject Headings] OR genetic* OR genome* OR genomic* OR heredit* OR inherit* OR proteome* OR proteomic*[Text Words] AND socioeconomics[Subject Heading] OR attitude OR confidentiality OR cost OR economic aspect OR economics OR ethics OR health care cost OR health economics OR human rights OR informed consent OR insurance OR law OR legal aspect OR patient attitude OR patient compliance OR patient right OR privacy OR public opinion OR religion OR self disclosure OR social aspect OR social problem OR social psychology OR sociology [Major Subject Headings] OR attitude OR attitudes OR bioethic* OR confidential OR confidentiality OR cost* OR coverage OR disclosure OR economic* OR ethical OR ethics OR human rights OR insurance OR insure* OR insuring OR law OR legal OR legislation OR legislative OR patient rights OR prejudice OR prejudicial OR privacy OR public opinion* OR religion OR religious OR social OR society OR societal OR socioeconomic* OR socio-economic*[Text Words]
PsycINFO	OVID	1990 to May Week 1 2003	Neoplasm[Major Subject Heading] OR cancer* OR neoplasm* OR tumor* OR tumour*[Text Words] AND cancer screening OR genes OR genetics OR genetic disorders OR heredity[Major Subject Headings] OR genetic* OR genome* OR genomic* OR heredit* OR inherit* OR proteome* OR proteomic*[Text Words] AND attitudes OR client rights OR costs and cost analysis OR economics OR ethics OR family socioeconomic level OR health behavior OR health care costs OR human rights OR informed consent OR insurance OR laws OR legal decisions OR morality OR prejudice OR privacy OR privileged communication OR professional liability OR public opinion OR religion OR self disclosure OR social influences OR social issues OR social problem OR socioeconomic class attitudes OR socioeconomic status

Database	Platform	Edition	Search Terms/Textwords
PsycINFO (cont'd)	OVID	1990 to May Week 1 2003	OR sociocultural factors OR sociology[Major Subject Headings] OR attitude OR attitudes OR bioethic* OR confidential OR confidentiality OR cost* OR coverage OR disclosure OR economic* OR ethical OR ethics OR human rights OR insurance OR insure* OR insuring OR law OR legal OR legislation OR legislative OR patient rights OR prejudice OR prejudicial OR privacy OR public opinion* OR religion OR religious OR social OR society OR societal OR socioeconomic* OR socio-economic*[Text Words]
CINAHL	OVID	1990 to May Week 1 2003	neoplasm[Major Subject Heading] OR cancer* OR neoplasm* OR tumor* OR tumour*[Text Words] AND cancer screening OR heredity OR health screening OR genetics OR genetic* OR genome* OR genomic* OR heredit* OR inherit* OR proteome* OR proteomic*[Text Words] AND socioeconomic factors[Subject Heading] OR attitude OR consent OR data security OR decision making OR economics OR ethics OR human rights OR insurance OR jurisprudence OR legislation OR patient compliance OR patient rights OR prejudice OR privacy and confidentiality OR public opinion OR religion and religions OR self disclosure OR social problems OR truth disclosure[Major Subject Headings] OR attitude OR attitudes OR bioethic* OR confidential OR confidentiality OR cost* OR coverage OR disclosure OR economic* OR ethical OR ethics OR human rights OR insurance OR insure* OR insuring OR law OR legal OR legislation OR legislative OR patient rights OR prejudice OR prejudicial OR privacy OR public opinion* OR religion OR religious OR social OR society OR societal OR socioeconomic* OR socio-economic*[Text Words]
ABI Inform	Proquest	1990 to May 2003	cancer OR breast cancer OR prostate cancer OR lung cancer OR leukemia[Subject Terms] OR tumor* OR tumour* cancer* OR neoplasm*[All Basic Search Fields] AND genetics[Subject Term] OR gene OR genes OR genetic* OR genom* OR heredit* OR inherit* OR proteom*[All Basic Search Fields] AND privacy OR legislation OR social control OR social costs OR social impact OR socioeconomic factors OR sociology OR prejudice OR ethics OR medical ethics OR public opinion OR consent OR disclosure OR human rights OR patient rights OR confidentiality OR economic impact OR economic policy OR economics OR cost analysis OR cost control OR costing OR costs OR

Database	Platform	Edition	Search Terms/Textwords
ABI Inform (cont'd)	Proquest	1990 to May 2003	attitudes OR insurance OR health insurance OR religion[Subject Terms] OR attitude OR attitudes OR bioethic* OR confidential OR confidentiality OR cost* OR coverage OR disclosure OR economic* OR ethical OR ethics OR human rights OR insurance OR insure* OR insuring OR law OR legal OR legislation OR legislative OR patient rights OR prejudice OR prejudicial OR privacy OR public opinion* OR religion OR religious OR social OR society OR societal OR socioeconomic* OR socio-economic*[All Basic Search Fields
Academic Search Premiere	EBSCO	1990 to May 2003	cancer OR tumors[Subject Terms] Or cancer OR neoplasm* OR tumor* Or tumour[All Basic Fields] AND genetic screening OR genetic markers OR genetic disorders OR genetics OR human genetics[Subject Terms] OR gene OR genes OR genetic* OR heredit* OR inherit* OR proteom* OR genom*[All Basic Fields] AND attitude OR attitudes OR bioethic* OR confidential OR confidentiality OR cost* OR coverage OR disclosure OR economic* OR ethical OR ethics OR human rights OR insurance OR insure* OR insuring OR law OR legal OR legislation OR legislative OR patient rights OR prejudice OR prejudicial OR privacy OR public opinion* OR religion OR religious OR social OR society OR societal OR socioeconomic* OR socio-economic*[All Basic Fields]
Applied Science Index **Humanities Abstracts**	WilsonWeb	1990 to May 2003	cancer* OR neoplasm* OR tumor* OR tumour*[All Basic Fields] AND genetic* OR genome* OR genomic* OR heredit* OR inherit* OR proteome* OR proteomic*[All Basic Fields] AND attitude OR attitudes OR bioethic* OR confidential OR confidentiality OR cost* OR coverage OR disclosure OR economic* OR ethical OR ethics OR human rights OR insurance OR insure* OR insuring OR law OR legal OR legislation OR legislative OR patient rights OR prejudice OR prejudicial OR privacy OR public opinion* OR religion OR religious OR social OR society OR societal OR socioeconomic* OR socio-economic*[All Basic Fields]

Database	Platform	Edition	Search Terms/Textwords
LegalTrac **Social Sciences Abstracts**	Gale WebSpirs	1990 to March 2003	cancer* OR neoplasm* OR tumor* OR tumour*[All Basic Fields/Text Words] AND genetic* OR genome* OR genomic* OR heredit* OR inherit* OR proteome* OR proteomic*[All Basic Fields/Text Words]
Sociological Abstracts	WebSpirs	1990 to 2003	cancer[Descriptor] OR cancer* OR neoplasm* OR tumor* OR tumour*[Text Words] AND genetic engineering OR genetic testing OR genetics[Descriptors] OR genetic* OR genome* OR genomic* OR heredit* OR inherit* OR proteome* OR proteomic*[Text Words]
NSHEED Economic Evaluation Database	University of York CRD	1990 to May 2003	neoplasms[Mesh Major Heading] OR cancer* OR neoplasm* OR tumor* OR tumour*[Text Words] AND genetics OR genetic predisposition to disease OR genome, human OR heredity OR genetic privacy OR proteome OR genetic markers[Mesh Major Headings] OR genetic* OR genome* OR genomic* OR heredit* OR inherit* OR proteome* OR proteomic*[Text Words]
CABOT Database	Canadian Health Economics Research Association	1990 to May 2003	genetic* OR genome* OR genomic* OR heredit* OR inherit* OR proteome* OR proteomic*[Text Words]
Biological Abstracts	WebSpirs	1990 to April 2003	oncology[Subject] OR cancer* OR neoplasm* OR tumor* OR tumour*[Text Words] AND genetic disease OR genetics OR medical genetics OR molecular genetics OR population genetics[Subjects] OR genetic* OR genome* OR genomic* OR heredit* OR inherit* OR proteome* OR proteomic*[Text Words] AND economics OR government and law OR philosophy and ethics OR sociology[Subjects] OR attitude OR attitudes OR bioethic* OR confidential OR confidentiality OR cost* OR coverage OR disclosure OR economic* OR ethical OR ethics OR human rights OR insurance OR insure* OR insuring OR law OR legal OR legislation OR legislative OR patient rights OR prejudice OR prejudicial OR privacy OR public opinion* OR religion OR religious OR social OR society OR societal OR socioeconomic* OR socio-economic*[Text Words]

Database	Platform	Edition	Search Terms/Textwords
Index to Canadian Legal Literature	WebSpirs	1990 to March 2003	cancer*[Descriptor] OR cancer* OR neoplasm* OR tumor* OR tumour*[Text Words] AND cancer-genetic aspects OR gene OR genetic* OR genetics[Descriptors] OR genetic* OR genome* OR genomic* OR heredit* OR inherit* OR proteome* OR proteomic*[Text Words]
Philosophers Index	WebSpirs	1990 to March 2003	cancer[Descriptor] OR cancer* OR neoplasm* OR tumor* OR tumour*[Text Words] AND genetic* OR genetic screening OR genetic testing OR genetics*[Descriptors] OR genetic* OR genome* OR genomic* OR heredit* OR inherit* OR proteome* OR proteomic*[Text Words
Canadian Research Index **Cochrane Database of Systematic Reviews**	WebSpirs Microlog OVID	1990 to 2003 2nd Quarter 2003	cancer[Descriptor] OR cancer* OR neoplasm* OR tumor* OR tumour*[Keywords/Text Words] AND genetic OR genetic disorders OR genetic engineering OR genetics OR genetics research OR genetics testing[Descriptors] OR genetic* OR genome* OR genomic* OR heredit* OR inherit* OR proteome* OR proteomic*[Keywords/Text Words] AND attitude* OR cost* OR cost effective OR economic OR ethics* OR discrimination OR health insurance* OR insurance* OR human rights* OR law* OR legal* OR legislation* OR prejudice OR privacy* OR public opinion* OR religion OR social* OR society OR socioeconomic[Descriptors] OR attitude OR attitudes OR bioethic* OR confidential OR confidentiality OR cost* OR coverage OR disclosure OR economic* OR ethical OR ethics OR human rights OR insurance OR insure* OR insuring OR law OR legal OR legislation OR legislative OR patient rights OR prejudice OR prejudicial OR privacy OR public opinion* OR religion OR religious OR social OR society OR societal OR socioeconomic* OR socio-economic*[Keywords/Text Words]

Database	Platform	Edition	Search Terms/Textwords
Digital Dissertations **NTIS National Technical Information Service** **WorldCat** **PapersFirst** **Proceedings First**	Proquest OCLC OCLC OCLC	1990 to May 20 2003 1990 to 2003 1990 to 2003 1990 to 2003 1990 to 2003	cancer OR neoplasm[Keywords] OR cancer* OR neoplasm* OR tumor* OR tumour*[Text Words] AND genetic* OR genes OR genom* OR proteom*[Keywords] OR genetic* OR genome* OR genomic* OR heredit* OR inherit* OR proteome* OR proteomic*[Text Words] AND attitude OR attitudes OR bioethic* OR confidential OR confidentiality OR cost* OR coverage OR disclosure OR economic* OR ethical OR ethics OR human rights OR insurance OR insure* OR insuring OR law OR legal OR legislation OR legislative OR patient rights OR prejudice OR prejudicial OR privacy OR public opinion* OR religion OR religious OR social OR society OR societal OR socioeconomic* OR socio-economic*[Keywords]
EconLit	Ebsco	1990 to May 2003	cancer* OR neoplasm* OR tumor* OR tumour*[Default Fields] AND genetic* OR genome* OR genomic* OR heredit* OR inherit* OR proteome* OR proteomic*[Default Fields]
PAIS Public Affairs Information Service	WebSpirs	1990 to April 2003	breast cancer OR cancer OR cervical cancer OR colon cancer OR lung cancer OR prostate cancer[Descriptors] OR cancer* OR neoplasm* OR tumor* OR tumour*[Text Words] AND genetic research OR genetics OR medical genetics[Descriptors] OR genetic* OR genome* OR genomic* OR heredit* OR inherit* OR proteome* OR proteomic*[Text Words]

APPENDIX B: GREY LITERATURE: INTERNET SEARCH

Note: The Internet search identified a number of documents or links to documents captured earlier by the search of the published literature. It also identified a number of documents which were retrieved but were found not to be relevant to this review. This appendix lists only relevant documents not previously identified.

Canadian Web Sites

- Alberta Provincial Health Ethics Network
  http://www.phen.ab.ca/
  Searched May 6, 2003
- Li, F. P. et al.. Recommendations on predictive testing for germ line *p53* mutations among cancer-prone individuals. *J Natl Cancer Inst* 1992;84:1156-60 [273]
- Agence d'Evaluation des Technologies et des Modes d'Intervention en Sante AETMS (French)
  http://www.aetmis.gouv.qc.ca/
  Searched May 6, 2003: no relevant publications
- Alberta Heritage Foundation for Medical Research
  http://www.ahfmr.ab.ca/
  Searched May 6, 2003: no relevant publications
- Biomedical Ethics Unit, McGill University
  http://www.mcgill.ca/biomedicalethicsunit/
  Searched May 6, 2003:
- American College of Medical Genetics. Policy Statement on Population Screening for *BRCA-1* Mutation in Ashkenazi Jewish Women, 1996 [271]
- Genetic susceptibility to breast and ovarian cancer: Assessment, counseling and testing guidelines. American Council of Medical Genetics Foundation, 1999 [272]
- British Columbia Office of Health Technology Assessment
  http://www.chspr.ubc.ca/bcohta/index.html
  Searched May 6, 2003: no relevant publications
- C.D. Howe Institute
  http://www.cdhowe.org/
  Searched May 6, 2003: no relevant publications
- Canadian Bioethics Society
  http://www.bioethics.ca/
  Searched May 21, 2003: no relevant publications

- Canadian Coordinating Office for Health Technology Assessment
  http://www.ccohta.ca/
  Searched February 6, 2004:
- Predictive genetic testing for breast and prostate cancer. Technology Report [275]
- Molecular diagnosis for hereditary cancer predisposing syndromes: Genetic testing and clinical impact. Technology Report [283]
- Canadian Health Services Research Foundation
  http://www.chsrf.ca/
  Searched May 6, 2003: no relevant publications
- Canadian Institute for Advanced Research
  http://www.ciar.ca/
  Searched May 6, 2003: no relevant publications
- Canadian Institute for Health Information
  http://secure.cihi.ca/cihiweb/dispPage.jsp?cw_page=home_e
  Searched May 6, 2003: no relevant publications
- Canadian Institutes of Health Research
  http://www.cihr-irsc.gc.ca/
  Searched May 6, 2003: no relevant publications
- Canadian Policy Research Networks
  http://www.cprn.org/
  Searched May 6, 2003: no relevant publications
- Centre for Applied Ethics, University of British Columbia
  http://www.ethics.ubc.ca/
  Searched May 6, 2003: no relevant publications
- Centre for Health Economics and Policy Analysis
  http://www.chepa.org/
  Searched May 6, 2003:
- Miller, F. et al.. Predictive Genetic Tests and Health Care Costs: A Policy Framework and Illustrative Estimates. Research Working Paper 02-03 [278]
- Centre for Health Services & Policy Research, Queens University
  http://chspr.queensu.ca/
  Searched May 6, 2003: no relevant publications
- Centre for Health Services & Policy Research, UBC
  http://www.chspr.ubc.ca/
  Searched May 21, 2003: no relevant publications

- The Centre for Rural and Northern Health Research, Laurentian University
  http://cranhr.laurentian.ca/
  Searched May 21, 2003: no relevant publications
- The Centre for Rural and Northern Health Research, Lakehead University
  http://flash.lakeheadu.ca/~cranhr/home.html
  Searched May 21, 2003: no relevant publications
- Clinical Trials Research Group, McGill University
  http://www.mcgill.ca/ctrg/
  Searched May 21, 2003: no relevant publications
- Fraser Institute
  http://www.fraserinstitute.ca/
  Searched May 21, 2003: no relevant publications
- Health Services Utilization and Research Commission
  http://www.hsurc.sk.ca/
  Searched May 21, 2003: no relevant publications
- HumGen, Universite de Montreal Law Faculty
  http://www.humgen.umontreal.ca/
  Searched May 21, 2003:
- Statement of the National Breast Cancer Coalition. Presymptomatic Genetic Testing for Heritable Breast Cancer Risk. Washington, September 1995. Available from: http://www.cancer.gov/cancer_information/doc.aspx?viewid=3C5EFFC8-7047-464E-9A44-CE02E92D0DE3#address [274]
- Institute for Clinical and Evaluative Sciences
  http://www.ices.on.ca/
  Searched May 21, 2003: no relevant publications
- Institute of Health Economics
  http://www.ihe.ab.ca/
  Searched May 21, 2003: no relevant publications
- John Dossiter Health Ethics Centre, University of Alberta
  http://www.ualberta.ca/BIOETHICS/index.html
  Searched May 21, 2003: no relevant publications
- Joint Centre for Bioethics, University of Toronto
  http://www.utoronto.ca/jcb/
  Searched May 21, 2003:

- Lemmens, T. et al.. Genetic services in Ontario: Mapping the future. Report of the Provincial Advisory Committee on New Predictive Genetic Technologies. 2001. Queen's Printer for Ontario [279]
- Manitoba Centre for Health Policy
  http://www.umanitoba.ca/centres/mchp/1mchpe.htm
  Searched May 27, 2003: no relevant publications
- Newfoundland and Labrador Centre for Applied Health Research
  http://www.nlcahr.mun.ca/
  Searched May 27, 2003:
- Genetic Testing for Late Onset Diseases: Current Research Practices and Analysis of Policy Development. Health Canada, September 2001 [280]
- Genetic Testing for Late Onset Diseases: In-depth Thematic Analysis of Policy and Jurisdictional Issues [282]
- Programmes de bioethique, Universite de Montreal (French)
  http://www.fes.umontreal.ca/bioethique/cadres.htm
  Searched May 27, 2003: no relevant publications
- University of Laval E-Watch Bulletin & database on Knowledge Utilization
  http://kuuc.chair.ulaval.ca/english/index.php
  Searched May 27, 2003: no relevant publications

Canadian Federal/Provincial and Territorial Governments and Departments of Health

- Health Canada
  http://www.hc-sc.gc.ca/english/index.html
  Searched May 27, 2003:
- Selected legal issues in genetic testing: Guidance from human rights. Health Policy Working Paper 01-04, October 2001 [281]
- Alberta Health and Wellness
  http://www.health.gov.ab.ca/
  Searched May 27, 2003: no relevant publications
- Government of Alberta
  http://www.gov.ab.ca/home/
  Searched May 27, 2003: no relevant publications
- British Columbia Health Planning
  http://www.gov.bc.ca/healthplanning/
  Searched May 27, 2003: no relevant publications

- British Columbia Health Services
  http://www.gov.bc.ca/healthservices/
  Searched May 27, 2003: no relevant publications
- Government of British Columbia
  http://www.gov.bc.ca
  Searched May 27, 2003: no relevant publications
- Manitoba Health
  http://www.gov.mb.ca/health/index.html
  Searched May 27, 2003: no relevant publications
- Government of Manitoba
  http://www.gov.mb.ca/index.shtml
  Searched May 27, 2003: no relevant publications
- New Brunswick Health & Wellness
  http://www.gnb.ca/0051/index-e.asp
  Searched May 27, 2003: no relevant publications
- Government of New Brunswick
  http://www.gnb.ca/
  Searched May 27, 2003: no relevant publications
- Newfoundland & Labrador Health & Community Services
  http://www.gov.nf.ca/health/
  Searched May 27, 2003: no relevant publications
- Government of Newfoundland & Labrador
  http://www.gov.nf.ca/
  Searched May 27, 2003: no relevant publications
- Northwest Territories Health & Social Services
  http://www.hlthss.gov.nt.ca/
  Searched May 27, 2003: no relevant publications
- Government of Northwest Territories
  http://www.gov.nt.ca/
  Searched May 27, 2003: no relevant publications
- Nova Scotia Health
  http://www.gov.ns.ca/heal/default.htm
  Searched May 27, 2003: no relevant publications
- Nova Scotia Government
  http://www.gov.ns.ca/
  Searched May 27, 2003: no relevant publications

- Nunavut Health Centre
  http://www.nunavut.com/health/english/index.html
  Searched May 27, 2003: no relevant publications
- Government of Nunavut
  http://www.gov.nu.ca/gnmain.htm
  Searched May 27, 2003: no relevant publications
- Ontario Health
  http://www.health.gov.on.ca
  Searched May 27, 2003: no relevant publications
- Government of Ontario
  http://www.gov.on.ca
  Searched May 27, 2003: no relevant publications
- Prince Edward Island Health
  http://www.gov.pe.ca/hss/index.php3
  Searched May 27, 2003: no relevant publications
- Government of Prince Edward Island
  http://www.gov.pe.ca/
  Searched May 27, 2003: no relevant publications
- Quebec Health
  http://www.msss.gouv.qc.ca/
  Searched May 27, 2003: no relevant publications
- Government of Quebec
  http://www.gouv.qc.ca/
  Searched May 27, 2003: no relevant publications
- Saskatchewan Health
  http://www.health.gov.sk.ca/
  Searched May 27, 2003: no relevant publications
- Government of Saskatchewan
  http://www.gov.sk.ca/
  Searched May 27, 2003: no relevant publications
- Yukon Health
  http://www.hss.gov.yk.ca/
  Searched May 27, 2003: no relevant publications

- Government of Yukon
  http://www.gov.yk.ca/
  Searched May 27, 2003: no relevant publications

International Web Sites

- American Society for Bioethics and Humanities
  http://www.asbh.org/
  Searched May 27, 2003: no relevant publications
- Bioethics Institute, Johns Hopkins
  http://www.hopkinsmedicine.org/bioethics/
  Searched May 27, 2003: no relevant publications
- Blue Cross/Blue Shield Association Technology Evaluation Centre (U.S.)
  http://www.bluecares.com/healthprofessionals/tec.html
  Genetic Testing for Inherited Susceptibility to Colorectal Cancer: Part I - Adenomatous Polyposis Coli Gene Mutations [284]
- Genetic Testing for Inherited Susceptibility to Colorectal Cancer: Part II - Hereditary Nonpolyposis Colorectal Cancer [285]
- Center for Bioethics, University of Pennsylvania
  http://www.med.upenn.edu/bioethic/
  Searched May 27, 2003: no relevant publications
- Center for the Study of Bioethics, Medical College of Wisconsin
  http://www.mcw.edu/bioethics/
  Searched May 27, 2003: no relevant publications
- Centre for Human Bioethics, Monash University (AU)
  http://www.arts.monash.edu.au/bioethics/
  Searched May 27, 2003: no relevant publications
- Centre for Health Economics, University of York (UK)
  http://www.york.ac.uk/inst/che/
  Searched May 27, 2003: no relevant publications
- Centre for Health Economics Research and Evaluation (AU)
  http://www.chere.usyd.edu.au/
  Searched May 27, 2003: no relevant publications
- Centre for Health Program Evaluation (AU)
  http://chpe.buseco.monash.edu.au/
  Searched May 27, 2003: no relevant publications

- Centre for Reviews and Dissemination, University of York (UK)
  http://www.york.ac.uk/inst/crd/dissem.htm
  Searched May 27, 2003: no relevant publications
- ELSI Human Genome Project
  http://www.kumc.edu/gec/prof/geneelsi.html
  Searched June 3, 2003:
- Harrison Poll #26, June 5, 2002: If Genetic Tests Were Available for Diseases Which Could be Treated or Prevented, Many People Would Pay to Have Them [290]
- ETHICA - Ethics and Health: An International and Comparative Arena
  http://www.hf.uib.no/i/Filosofisk/ethica/
  Searched June 3, 2003: no relevant publications
- Hastings Center (U.S.)
  http://www.thehastingscenter.org/
  Searched June 3, 2003: no relevant publications
- Health Economics Research Unit – HERU (UK)
  http://www.abdn.ac.uk/heru/
  Searched June 3, 2003: no relevant publications
- HSTAT: Health Services/Technology Assessment Texts (U.S. National Library of Medicine)
  http://hstat.nlm.nih.gov/hq/Hquest/screen/HquestHome/s/39932
  Searched June 16, 2003:
- Genetic Testing for Susceptibility to Breast Cancer. Health Technology Advisory Committee -- Minnesota [277]
- International Bioethics Committee, UNESCO
  http://www.unesco.org/ibc/
  Searched June 3, 2003: no relevant publications
- International Network of Agencies for Health Technology Assessment
  http://www.inahta.org/
  Searched June 3, 2003
- Predictive Genetic Testing for Hereditary Breast and Colorectal Cancer. ITA Report [276]
- Kennedy Institute of Ethics, Georgetown University (U.S.)
  http://www.georgetown.edu/research/kie/
  Searched June 3, 2003: no relevant publications
- National Reference Centre for Bioethics Literature
  http://www.georgetown.edu/research/nrcbl/nrc/
  Searched June 3, 2003:

- Helmes, A.W. et al.. Patient preferences of decision-making in the context of genetic testing for breast cancer risk. *Genetics in Medicine* 2002; 4(3): 150-7 [291]
- Cameron, L.D. et al. . Responses to information about psychological consequences of genetic testing for breast cancer susceptibility: Influences of cancer worry and risk perceptions.
  Journal of Health Psychology 2001; 6(1): 47-59 [292]
- Bottorff, J. L. et al.. Falling through the cracks -- Women's experiences of ineligibility for genetic testing for risk of breast cancer. *Canadian Family Physician* 2000 July; 46: 1449-56 [58]
- France, L. et al.. Genetic testing considerations in breast cancer patients. *Journal of Genetic Counseling* 1999: 8(5): 289-99 [55]
- Evans, D. et al.. Uptake of genetic testing for cancer predisposition. *Journal of Medical Genetics* 1997; 34: 746-8 [293]
- Hopper, J.L. Some Public Health Issues in the Current State of Genetic Testing for Breast Cancer in Australia. *Aust N Z J Pub Health* 1996; 5: 467-72 [159]
- Leonard Davis Institute of Health Economics (U.S.)
  http://www.upenn.edu/ldi/
  Searched June 11, 2003: no relevant publications
- Monash Institute of Health Services Research (AU)
  http://www.med.monash.edu.au/publichealth/cce/
  Searched June 11, 2003: no relevant publications
- National Bureau of Economic Research
  http://papers.nber.org/
  Searched June 11, 2003: no relevant publications
- National Coordinating Centre for Health Technology Assessment (UK)
  http://www.hta.nhsweb.nhs.uk/main.htm
  Searched June 11, 2003: no relevant publications
- New York Academy of Medicine Grey Literature Report
  http://www.nyam.org/library/greylit/glrindex.shtml
  Searched June 11, 2003: no relevant publications
- New Zealand Health Technology Assessment Clearinghouse for Health Outcomes and Health Technology Assessment (NZTA)
  http://nzhta.chmeds.ac.nz/default.htm
  Searched June 11, 2003: no relevant publications

- Nuffield Council on Bioethics (UK)
  http://www.nuffieldbioethics.org/home/
  Searched June 11, 2003: no relevant publications
- President's Council on Bioethics (U.S.)
  http://www.bioethics.gov/
  Searched June 11, 2003: no relevant publications
- RAND Organization
  http://www.rand.org/
  Searched June 11, 2003: no relevant publications
- U.S. Agency for Healthcare Research and Quality
  http://www.ahcpr.gov/
  Searched June 11, 2003: no relevant publications
- U.S. General Accounting Office – GAO
  http://www.gao.gov/
  Searched June 16, 2003: no relevant publications
- UK National Institute for Clinical Excellence (NICE)
  http://www.nice.org.uk/
  Searched June 16, 2003: no relevant publications
- UK National Research Register
  http://www.update-software.com/national/
  Searched June 16, 2003: no relevant publications
- U.S. Congress Office of Technology Assessment
  http://www.wws.princeton.edu/~ota/
  Searched June 16, 2003: no relevant publications
- World Bank
  http://www.worldbank.org/
  Searched June 16, 2003: no relevant publications
- World Health Organization
  http://www.who.int/
  Searched June 16, 2003: no relevant publications

International Departments of Health (Developed Countries with English, French & German websites)

- Australia Department of Health and Aging
  http://www.health.gov.au/g8/
  Searched June 16, 2003: no relevant publications

- Austria. Federal Ministry for Health and Women's Issues
  http://www.bmgf.gv.at/
  Searched June 16, 2003: no relevant publications
- France State Secretariat of Health and the Handicapped
  http://www.sante.gouv.fr/index.htm
  Searched June 16, 2003: no relevant publications
- Germany Ministry of Health
  http://www.bmgs.bund.de/eng/gra/index.cfm
  Searched June 16, 2003: no relevant publications
- Ireland Department of Health and Children
  http://www.doh.ie/
  Searched June 16, 2003: no relevant publications
- Malaysia Ministry of Health
  http://www.moh.gov.my/
  Searched June 16, 2003: no relevant publications
- Netherlands Ministry of Health Welfare and Sport
  http://www.minvws.nl/english/index.html?folder=470
  Searched June 16, 2003: no relevant publications
- New Zealand Ministry of Health
  http://www.moh.govt.nz/moh.nsf
  Searched June 16, 2003: no relevant publications
- Northern Ireland Department of Health Social Services and Public Safety
  http://www.dhsspsni.gov.uk/
  Searched June 16, 2003: no relevant publications
- Norway Ministry of Health
  http://odin.dep.no/hd/engelsk/index-b-n-a.html
  Searched June 16, 2003: no relevant publications
- Singapore Ministry of Health
  http://app.internet.gov.sg/scripts/moh/newmoh/asp/index.asp
  Searched June 16, 2003: no relevant publications
- Sweden Ministry of Health and Social Affairs
  http://www.social.regeringen.se/inenglish/index.htm
  Searched June 16, 2003: no relevant publications

- U.S. Health and Human Services
  http://www.hhs.gov/
  Searched June 16, 2003: no relevant publications
- UK Department of Health
  http://www.doh.gov.uk/
  Searched June 16, 2003: no relevant publications

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1. Malinowski MJ, Blatt RJR. Commercialization of genetic testing services: the FDA, market forces, and biological tarot cards. *Tulane Law Review* 1997;71:1211-1312.
2. Garber JE Patenaude AF. Ethical, social and counselling issues in hereditary cancer susceptibility. *Cancer Surv* 1995;25:381-97.
3. Dryja TP, Friend S, Weinberg RA. Genetic sequences that predispose to retinoblastoma and osteosarcoma. *Symp Fundam Cancer Res* 1986;39:115-19.
4. Miki Y et al.. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. *Science* 21994;66:66-71.
5. Hall JM et al.. Linkage of early-onset familial breast cancer to chromosome 17q21. *Science* 21990;50:1684-89.
6. Wooster R, et al.. Identification of the breast cancer susceptibility gene BRCA2. *Nature* 1995;378:789-92.
7. Blaxter M. Criteria for evaluation of qualitative research. *Medical Sociology News* 1996;22:68-71.
8. Lohr KN Carey TS. Assessing "best evidence": issues in grading the quality of studies for systematic reviews. *Jt Comm J Qual Improv* 1999;25:470-79.
9. Moher D, et al.. Assessing the quality of randomized controlled trials: an annotated bibliography of scales and checklists. *Control Clin Trials* 1995;16:62-73.
10. Cho MK, Bero LA. Instruments for assessing the quality of drug studies published in the medical literature. *JAMA* 1994;272:101-04.
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