Selections from current literature: issues in genetic testing for cancer

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The science of genetics has evolved from Watson and Crick to Wilmut and Dolly in less than 50 years. Ever since the discovery of the structure of DNA in 1953, genetic technology has been used to produce proteins and drugs for use in treating cancer and other diseases. However, no use of genetic technology has been more dramatic than the successful cloning of a mammal, specifically a sheep named Dolly, by Dr Wilmut. This development arrives in the midst of ongoing international efforts to map and sequence all the genes through the Human Genome Project.

Other uses of genetic technology include testing for susceptibility to potential diseases. Among the diseases for which genetic tests exist are haemophilia, phenylketonuria, Alzheimer’s disease and a variety of cancers. However, it must be understood that genetic testing is vastly different from genetic screening. Testing is possible for anyone. Screening implies conforming to several specific criteria. Genetic testing has the ability to provide great benefit to society but it also carries the risk of great harm if used indiscriminately.

Nevertheless, genetic testing may provide a new weapon in the war on cancer. This comes as added good news, since the expected cancer mortality is expected to decline for the first time in the USA this year. Every effort should be made to understand and fully exploit these new technological advances in genetic testing. This must be done even as we recognize the plethora of fundamental questions, ethical, legal, as well others, that pose myriad dilemmas which may take decades to resolve fully, and then perhaps only with the input from task forces created to come up with guidelines in these areas.

In this ‘Selections’, five recent papers and an editorial on genetic testing will be reviewed. Following this will be a discussion of the potential promise and problems of genetic testing. Finally, we will address the dilemma of what advice the practising family physician should give to a patient requesting genetic testing for cancer.

Colorectal and endometrial cancer


This study was conducted to evaluate the clinical use of APC gene testing performed by a commercial laboratory. Its specific aim was to identify areas for improvement in the delivery of cancer genetic services. The goals of the study were to: (i) assess indications for APC gene testing; (ii) ascertain whether the patient received formal counselling before gene testing; (iii) determine whether the person ordering the test obtained written informed consent; and (iv) determine whether the physicians would have correctly interpreted the results of the test when relaying them to their patients.

The final study sample consisted of 177 patients from 125 families undergoing APC gene testing by a commercial laboratory from 1 January to 31 December 1995. The authors considered two indicators for APC gene testing to be valid: (i) confirmation of the diagnosis of familial adenomatous polyposis in patients with typical colorectal adenomatous polyposis or multiple adenomas; and (ii) presymptomatic testing of first-degree relatives of affected persons. Data on the study group were obtained by conducting telephone interviews with the physicians ordering the test. These interviews were done at the time that the physicians ordered the test.

Of the patients tested, 83% had clinical features of familial adenomatous polyposis or were at risk for the disease. Prior to conducting the test, only 18.6% of the patients received formal genetic counselling. In addition, only 19 of the 108 physicians surveyed (17.6%) arranged the counselling service for their patients. Furthermore, only 16.9% of the study sample were requested to provide written informed consent and only 13 of the 108 physicians (12%) obtained such consent from their patients. In almost one-third of the cases (31.6%) the physician’s interpretation of the test results was incorrect and would have led to his misinforming the patients.

The authors conclude that patients who underwent genetic tests for familial adenomatous polyposis often received inadequate counselling and may have been given incorrectly interpreted results.
Comment
This study reveals several areas needing improvement in the delivery of cancer genetic services. It is widely accepted that a valid indication for genetic testing, formal genetic counselling, written informed consent and correct interpretation of test results are necessary when conducting genetic tests. Yet, almost 20% of the testing was not valid. Genetic counselling and the procurement of written informed consent was rarely carried out.

Perhaps of greatest significance, however, was the incorrect interpretation of the test results by the physician in nearly a third of the cases. This could have led to substantial psychological stress and unnecessary endoscopic testing for patients with false positive reports. Conversely, in the case of false negative reports, a failure to undergo appropriate endoscopic testing may have had the tragic consequence of the individual later developing an eminently preventable cancer.

One strong point of this study was the fact that even though it was based on the tests done at a single laboratory, physicians were represented from 32 states and nearly 70% of them had specialized knowledge of the disease as gastroenterologists, oncologists or genetics counsellors. Finally, topics not addressed by this study, requiring discussion, include the many medical, legal, ethical, social and psychological issues that are involved in the use of genetic testing.


This report comes from the members of a task force of the Cancer Genetics Studies Consortium (CGSC) provides recommendations for cancer surveillance, treatment options and follow-up for individuals carrying mutations associated with hereditary nonpolyposis colorectal cancer (HNPCC) and endometrial cancer. The CGSC conducts studies designed to assess the social and psychological effects of genetic testing for cancer. It is sponsored by the National Human Genome Research Institute and is funded by the National Cancer Institute, the National Institute of Mental Health, the National Institute of Nursing Research, the Office of Women’s Health and the American Cancer Society.

The task force developed their recommendations after 14 months of discussion of Medline studies evaluating cancer risk, surveillance and risk reduction in individuals genetically susceptible to colon cancer. While these recommendations are for individuals known to carry HNPCC-associated mutations, the authors note that they may also be appropriate for individuals whose mutation status is currently unknown, but who have a substantial likelihood of being carriers of the mutation. These recommendations can also be considered for individuals from families with an autosomal dominant predisposition to colon cancer, when molecular studies have not been done or have failed to identify a specific mutation.

There is an increased risk of colorectal, endometrial and ovarian cancer among carriers of mutations associated with HNPCC. Additionally, these cancers tend to develop at an earlier age than seen in random cases. By the age of 65, almost 70% of such carriers would have developed colorectal cancer. About 35% of female carriers would have developed endometrial cancer and this would have been 15 years before such cancers usually develop in the general population. The relative risk for the development of ovarian cancer in female carriers is 3.5, and these cancers usually develop about 20 years before they would normally be seen in the general population.

On the basis of observational studies, the authors recommended that colonoscopy be performed every one to three years, starting at the age of 25, for individuals known to have HNPCC-associated mutations. They also recommended annual screening for endometrial cancer beginning at the age of 25–35 years, but did not make a recommendation for or against prophylactic surgery because evidence of benefit is lacking in the literature. Since these recommendations are based on potential but unproven benefits, individuals at risk and their health care providers should share in the decisions about the timing and methods used to manage cancer risk, after review of the available evidence.

In addition to the recommendations for follow-up care, the authors also recommended that individuals having a predisposition to cancer receive thoughtful counselling regarding the options available to them for cancer surveillance and follow-up. They recommended that individuals considering testing be counselled regarding the uncertainties in risk estimates and efficacy of surveillance and that the counselling be repeated on a periodic basis for those individuals found to be mutation carriers.

The task force also endorsed counselling regarding the possible health benefits of low-fat, high-fibre diets, adequate intake of vegetables and fruit, regular exercise and cessation of smoking. At the same time, they recommended that sufficient explanation be provided concerning the uncertainties in cancer risk reduction from lifestyle modification to allow latitude for individual choice.

Comment
This task force did a good job of acknowledging the lack of controlled research trials of cancer surveillance conducted among genetically susceptible individuals. They were also thorough in noting the role of non-steroidal anti-inflammatory drugs in reducing the rate of adenoma development and colorectal cancer. Additionally, their frank discussion about the unknown
efficacy of prophylactic colectomy, hysterectomy and oophorectomy as measures for reducing cancer risk in individuals with mutations associated with HNPCC is clearly evidence based.

Due to a lack of research in these areas, the recommendations provided by the task force cannot be considered on a universal basis, but instead must be applied individually. Until researchers conduct randomized studies with long-term follow-up of large groups of carriers, more precise recommendations would be inappropriate. However, what they can provide, in addition to the recommendations for follow-up care, are guidelines that protect individuals who volunteer for testing.

The goal in predisposition testing should be to maximize the benefit and minimize the risks to the individuals being tested. Individuals undergoing testing should be counselled regarding the medical benefits of genetic testing and the weaknesses in the current state of the research. However, the individuals should also be counselled regarding psychological, social and economic risks. The authors note that one of the topics a counsellor should cover, prior to testing, is the risk of harming insurability.

Additional counselling topics not mentioned by the task force were the following: (i) risk of harming employability; (ii) risk of social stigmatization; (iii) disclosure of results to persons other than the patient; and (iv) the emotional and mental competence of the patient. These unanswered questions should spur the CGSC to convene another task force to specifically address such issues.

Ovarian and breast cancer


This article reports on women who were diagnosed with epithelial ovarian cancer before the age of 70. These incident and prevalent cases were treated at The Royal Marsden Hospital between July 1993 and September 1995. Prior to written consent being obtained, the possibility that the results might have suggested an increased risk of ovarian cancer and other cancers among family members was explained to the women. Of the 482 eligible women, only 80% (386) agreed to participate. Of the 386, DNA samples of 12 women could not be used, leaving 374 women in the study group. Only 75% (280) of the remaining women completed and returned questionnaires about the family history.

DNA sequence variations predicting a truncated BRCA1 protein, suggesting probable mutations, were identified in 12 out of 374 (3%) of the women (95% CI 2–6%). Among the 12 women with truncating mutations, nine reported a family history of breast and/or ovarian cancer. Six had affected first-degree relatives. In 12 out of 14 affected relatives, the diagnosis of either breast or ovarian cancer was made before the age of 55.

The mean age at diagnosis for both BRCA1 carriers and their first-degree relatives was 48 years, while the mean age was 52 for non-carriers and their relatives. The prevalence of BRCA1 mutations was six out of 119 cases of ovarian cancer cases diagnosed before the age of 50 (5%; 95% CI 2–11%). For those diagnosed at the age of 50 or older, the prevalence was 7 out of 255 (3%; 95% CI 1–6%).

This study did not specifically look at issues related to restricting genetic screening. It did, however, examine potential restrictions based on the results obtained. The study suggests that most of the BRCA1 mutations would be detected if screening were restricted to families with at least one case of breast cancer before the age of 60 or one case of ovarian cancer among first- or second-degree relatives in addition to the index case.

Twenty per cent or 55 women (or families) in this study meet such criteria for screening. Further selection on serous cystadenocarcinoma would have only reduced the screening from 55 to 47 women in this study. Restriction to families with three or more cases of either breast or ovarian cancer would not have been efficient in this study population, because 10 of 13 BRCA1 mutations would have been missed.

Comment

While this is a well-executed study, it does have several potential biases which could have altered its findings. One is the lack of participation by 20% of the initial study population and then ascertainment of a family history in only about 75% of the remaining women who chose to be in the study. Additionally, the inclusion of both incident and prevalent cases may have biased the study toward ovarian cases with better prognoses. This would have influenced the prevalence estimates of BRCA1 mutations, if the mutations are related to the prognosis, as most ovarian cancers in carriers of BRCA1 mutations are serious cystadenocarcinomas.

The lack of participation could have biased the results of this study, presumably because women who had a family history of cancer may be more likely to participate. Those with a positive family history of cancer may tend to be younger. A median age of 63 years was seen in the national Surveillance Epidemiology and End Results (SEER) data. This is much higher than the ages seen in this study for either the carriers and their families or the non-carriers and their families.

In order to address a potential age bias, the authors compared the age of 374 participants with the 108 non-participants. They found similar percentages of participants and non-participants below the age of 50. However, between the ages of 50 and 70, the participants
were more likely to be younger. If we assume that there is a bias such that women with a positive family history of cancer are more likely to participate, then the percentage of mutations found is likely to be an overestimate for the general population.

Such a bias would increase the incident rate when screening women with a positive family history of cancer. However, an extrapolation of BRCA1 screening to the general female population based on this study would be an overgeneralization of its findings.


The objectives of this paper were to identify predictors of utilization of genetic testing for breast-ovarian cancer and to evaluate outcomes of participation in a genetic screening programme. The study was a prospective cohort study of adult members of high-risk families with BRCA1-linked hereditary breast-ovarian cancer (HBOC). Subjects were recruited for a baseline 40-minute telephone interview, educational and counselling sessions and a one-month follow-up interview, and were offered test results.

Of an initial 279 family members, 192 completed the baseline interview; of those 76 declined the education and counselling session. One participant out of the 116 who sat through the educational session declined counselling and test results. Of those who obtained test results, 53 were mutation carriers and 62 were non-carriers. Of the 192 who completed the baseline interview, 140 completed the one-month follow-up telephone interview.

The education sessions, conducted by an oncologist/geneticist, covered the following topics: inheritance of breast-ovarian cancer susceptibility; cancer risks associated with BRCA1 mutations (breast, ovarian, prostate, colon); genetic linkage studies, gene identification and testing for mutation status; benefits of genetic testing (early detection); limitations of genetic testing (incomplete penetrance and aetiologic heterogeneity); risks of genetic testing (insurance or employment discrimination); options for prevention and surveillance; and assurance of confidentiality.

A variety of potential predictors of genetic screening use were examined, including: sociodemographic variables, clinical status, knowledge about inherited breast cancer and BRCA1 testing, and perceived importance of benefits, limitations and risks of BRCA1 testing. The outcomes examined included BRCA1 testing decisions, depression symptoms, functional health status and prophylactic decision-making.

The average age of the respondents was 43, all were white, 67% were female and 77% were married. Ninety-three per cent of respondents had health insurance and 90% had completed high school. Scores from the baseline knowledge measure suggested that on average subjects gave correct responses to about 55% of the items. Ninety-six per cent of respondents rated ‘to learn about my children’s risks’ as the most important benefit of BRCA1 testing. The most important perceived limitation or risk of testing was ‘test results might not be accurate’, by 40% of respondents. This was followed by 34% of participants ranking losing health insurance as an important limitation (ranked equally by those with and without insurance). The average scores for benefits of testing, 15.30, and limitations or risks of genetic testing, 8.47, were significantly different, with benefits outweighing the limitations or risks.

Forty-three per cent of family members who were offered the opportunity to receive their BRCA1 test results requested the results. Of those receiving their test results, 46% were mutation carriers. BRCA1 test use was associated with being female, having a high-school education, having health insurance, having two or more first-degree relatives with breast cancer, baseline knowledge and perceived importance of testing benefits. Marital status, employment, having two or more first-degree relatives with ovarian cancer and perceived importance of the limitations or risks of testing were not associated with test use.

In order to identify potential confounders, the authors examined baseline characteristics by mutation carriers, non-carriers, and those who declined the test. Carriers were more likely to be affected and to have more affected first-degree relatives. In addition, psychological and functional health status were examined by carrier/non-carrier/decliner groups. These groups had similar baseline levels of depression and sexual impairment, but differed with respect to role impairment.

The 1-month change in scores for depression, role impairment and sexual impairment were compared by carrier/non-carrier/decliner groups. After testing, a drop was seen for carriers and non-carriers in depression, role impairment and sexual impairment. An increase was seen for test decliners in all three psychological and functional health status variables. Some of these changes showed significant between-group differences.

Logistic regression models were generated to predict the three psychosocial outcomes of depression, role impairment and sexual impairment. Non-carriers exhibited a significant reduction in depression and role impairment compared with both carriers and decliners, controlling for baseline levels. For sexual impairment, non-carriers had significantly greater reduction than decliners. Carriers did not show an increase in depression, role impairment or sexual impairment.

Medical decision-making differed according to testing status, demonstrating a definite effect of testing. After receiving their BRCA1 test results, 17% of carriers intended to obtain prophylactic mastectomies, 33% of
carriers intended to obtain prophylactic oophorectomies and 17% remained undecided. None of the non-carriers intended to obtain prophylactic surgery.


This editorial on the previous article commends it as a good first step in learning about the psychological and behavioral impact of participation in genetic testing on self-image, family interactions and medical decision making. However, the lack of knowledge about genetics in this highly researched/educated group of participants was of concern. In the baseline interview, 26% of respondents thought that a woman without the BRCA1 gene could not get cancer and higher proportions of respondents gave incorrect answers to questions about tests limitations and risk-reduction strategies.

If physicians are going to counsel patients, they must also educate patients. This means learning more about genetic testing, deciding when to discuss testing and with whom. The offer of testing will require conducting several visits with patients before and after blood is drawn, counselling patients on various issues and educating the clinic staff on genetic testing. Due to these issues, physicians may want to refer interested patients to specialized centers. As genetic testing becomes more common, physicians need to prepare to help their patients face new and challenging opportunities.

Comment
The authors mention that the limitations and risks of BRCA1 testing were emphasized in all contacts with subjects. This may account for the selection into the educational intervention of those who wanted to obtain test results. Additionally, as this study included only whites and participants who had a high education level, its results may not be generalizable to other populations.

The lack of correct knowledge is of concern. While some the incorrect answers may be due to the inherent nature of true–false questions, 83% of respondents agreed that ‘the BRCA1 gene causes about one half of all breast cancers’. The authors, description of baseline knowledge emphasizes the need to educate better individuals before they consider genetic testing. Since these families had participated in prior genetic studies, other individuals or families from the general population are likely to be less knowledgeable about cancer risk in relation to genetic predispositions.

Given the current lack of evidence on the efficacy of prophylactic surgery and potential for psychological damage, high-risk women need to be better educated when receiving genetic counselling.


The objectives of this report were to provide provisional recommendations for cancer surveillance and risk reduction among individuals carrying mutations in the BRCA1 or BRCA2 genes. These recommendations were developed by a task force of the CGSC.

The risk of cancer among carriers of BRCA1 and BRCA2 mutations was based on families with early onset of cancer and/or multiple tumours, and meeting criteria for autosomal dominant inheritance. It is likely that this sample is biased towards an increased risk of cancer and may overestimate the cancer risk associated with BRCA1 and BRCA2 mutations. Women with the BRCA1 mutation have an estimated 85% risk of breast cancer by the age of 70. The estimated risk of ovarian cancer is 26% by the age of 70 for most carriers and 85% for a small subset of carriers.

Among women who have had breast cancer, there is an estimated risk of 64% for contralateral breast cancer by the age of 70 and a 44% cumulative risk of ovarian cancer by the age of 70. The risk of prostate cancer in male carriers is three times higher, or there is a cumulative risk of 8%, by the age of 70. The risk of colon cancer in both male and female carriers is estimated to be four times higher or have a cumulative risk of 6% by the age of 70. Women with the BRCA2 mutation have an estimated risk of breast cancer that is similar to BRCA1 carriers. The estimated risk of ovarian cancer is less than 10% by the age of 70 for carriers. There is insufficient information about BRCA2 and other cancers.

Provisional recommendations for breast cancer surveillance include a monthly breast self-examination beginning early in adult life. Beginning at the age of 25–35, an annual or semi-annual clinician breast examination is recommended along with annual mammography. However, individuals should be informed that the risks and benefits of mammography before the age of 50 are not established. Risk of mammography screening include false positive results, false negative results, and a potential increased risk of breast cancer.

Many experts believe that the benefit of early detection is likely to outweigh the risk for women with an inherited predisposition to breast cancer, even when mammography is initiated at an early age.

For ovarian cancer prevention, annual or semi-annual screening using transvaginal ultrasound and CA-125 levels is recommend to begin at the age of 25–35 for BRCA1 mutation carriers. For BRCA2 mutation carriers, ovarian cancer surveillance is also an option but would have less of a benefit due to the lower risk. For male carriers of BRCA1 mutations, there are insufficient data to make a recommendation either for
or against prostate cancer screening. BRCA1 mutation carriers should be informed of their possible increased risk of colorectal cancer and encouraged to follow screening recommendation for the general population, to include sigmoidoscopy and fecal occult blood tests beginning at the age of 50.

There is insufficient evidence to give provisional recommendations for or against prophylactic surgery to reduce either breast or ovarian cancer. There are insufficient data on oestrogen therapy to recommend use or avoidance by BRCA1 and BRCA2 mutation carriers. While there has been no demonstration among mutation carriers of reduction in cancer by chemoprevention, this area has many possibilities. The effect of lifestyle modification in carriers of mutations is not known. Regardless, the task force endorses counselling about the health benefits of high-fibre, low-fat diets, a balanced diet including vegetables and fruit, regular exercise and avoidance of cigarettes and other carcinogens.

In conclusion, these recommendations should be understood within the other uncertainties in genetic screening. Genetic counselling should include sufficient explanation about the uncertainty of risk estimates, efficacy and benefits in cancer risk reduction among genetically susceptible individuals. Psychological damage may occur from prophylactic surgery. Early and frequent mammography may increase the risk of breast cancer. Additionally, documentation of genetic risk may cause health insurance discrimination. Patients should share in the decision-making and consider issues related to quality of life.

Comment
In understanding the increased risk of cancer in BRCA1 and BRCA2 mutation carriers, individuals should be educated as to the risk in the general population. Based on SEER data, the lifetime risk of breast cancer for females is 13% and the lifetime risk of ovarian cancer is 2%.10 Clearly, BRCA1 and BRCA2 mutation carriers have a much greater risk of cancer. However, due to many uncertainties related to genetic testing, physicians should educate their patients and allow them to make the best decision for themselves.

Each patient may deal with the knowledge about genetic testing, its benefits and its limitations differently. Since the risks and limitations associated with breast cancer are not known, each woman will have to weigh up her own feelings and anxieties to decide whether or not watchful waiting, early and frequent mammograms, or prophylactic surgery are better for her current quality of life. These risks and her feelings about them may change over time and should be re-evaluated periodically.

Summary
Genetic testing has the power to transform radically the cancer-control programmes of the future by moving this basic science out of the laboratory and into the realm of public health practice.5,13 However, before this can occur, physicians will need to undergo additional training to be able to counsel their patients appropriately and to interpret correctly the results of such genetic testing, or refer such patients to specialized centres.14,15 There are several other issues that should be considered prior to using genetic testing in disease prevention.

These include: (i) the public health impact of the disease; (ii) the prevalence of the genotype; (iii) the standards of the laboratory carrying out the test; (iv) the magnitude of the association between the genotype and disease; (v) interaction with known modifiable risk factors for the disease; (vi) availability of intervention or prevention measures; (vii) the cost of testing and follow-up; and (viii) ethical, legal and social issues.5 Additionally, there should be some consideration of the potential physical, psychological and financial factors related to genetic testing.16 Informed consent should be written and obtained only after educating the patient about the complexities of genetic testing in a culturally sensitive and non-directive manner.14

Included among the risks of genetic testing are the possibility of misunderstanding the test results, misdiagnosis, stigmatization, labelling, loss of privacy for both the individual and their families, and discrimination.17 As a result of fears of discrimination, potential loss of health insurance and job loss, legislation has been proposed in the US Congress to ban genetic discrimination.18 Such steps are being taken to ensure that social policy keeps up with the science and because these legislators realize that genetic discrimination may become the civil rights issue of the next millennium.18

Cost–benefit analyses of genetic testing for asymptomatic predisposition for cancer will need to be done; however, such data are currently lacking. If genetic tests are to be cost-effective screens for cancer, the best way to identify appropriate cohorts for such testing may be by performing a detailed family history in order to identify those at greatest risk of developing cancer.19 Additionally, within the context of the family, genetic testing of minors requires extra effort to ensure that they understand why such testing is being done and what it may mean for them.20

Hopefully, by the time genetic testing becomes commonplace, there will be adequate guidelines for using such tests. Unfortunately, such guidelines are not now readily available and the practising family physician may be faced with the dilemma of having a patient ask for genetic testing for a particular cancer. In such situations, it would be prudent for the physician to explain to the patient that the inherited risk for common cancers is about 10%.21 Then, after taking a thorough family history to determine whether the patient is at an
increased risk for cancer, the physician should counsel the patient appropriately about the uncertainties of genetic testing. If the patient still wants to proceed after this discussion, written consent should then be obtained prior to performing any genetic testing. It is possible that the patient may choose not to undergo genetic testing once they fully realize the risks and benefits of undergoing genetic testing for cancer.

Finally, it is often easy for us as physicians to be so enthralled by technological advances that we fail to provide simple, low-tech, but highly beneficial, preventive medical care to our patients. More cancer can be prevented through counseling and screening than by genetic testing. It is important that we continue to encourage our patients to exercise regularly, to stop using tobacco and other carcinogens, and to eat a low fat, high-fiber diet, even as the promise of genetic testing for cancer begins to be fulfilled in the not-too-distant future.

References

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