Hereditary Cancers

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Background: Genetic Counselling and Genetic Testing in the Maritimes

Hereditary cancer syndromes are responsible for only a small percentage of cancer cases in our population—between 5 and 10 per cent. For individuals affected by such syndromes, however, it can be an issue of life and death: These people have a significantly increased lifetime risk of developing cancer. The level of risk depends on the specific cancer they have.

This issue of In Practice provides an overview of the role of genetic counselling and testing for hereditary cancer syndromes and the Maritime Hereditary Cancer Service (MHCS) based within the Maritime Medical Genetics Service at the IWK Health Centre.

We hope it will help you determine when a referral for genetic consultation may be appropriate for your patient; familiarize you with the counselling and testing services available; and describe some of the complex issues involved. This is not meant to be a comprehensive introduction or review of the medical aspects of hereditary cancer syndromes, but rather of the services available.

Where and When to Refer

Maritime Hereditary Cancer Service

As a family physician, you can refer patients with suspected hereditary cancer risk to the Maritime Hereditary Cancer Service. A multi-disciplinary clinic, the MHCS offers assessment, education, counselling, genetic testing, interpretation of test results, and screening recommendations for individuals and families. It is the only publicly funded service of its type in the Maritimes.

The MHCS team includes genetic counsellors, medical geneticists, and social workers, as well as a gynecologic oncologist. Team members work closely with other oncologists and health care professionals.

At the MHCS, we use an approach called a non-directive genetic counselling model. This means we do not advocate for or against genetic testing. We provide individuals with relevant information, and support the decision that they make.

The MHCS team:

- Identifies individuals and families at risk for hereditary cancers through family history and pathology assessment;
- Increases the effectiveness of genetic testing by focusing on those individuals and families for whom it is most likely to be helpful;
- Targets surveillance to those individuals at highest risk versus those in the general population; and
- Ensures these services are accessible to all individuals and families in the Maritimes.

The MHCS provides the following services:

Education of the public, primary health care physicians and other health care providers is provided to help ensure accurate information and effective genetic services.

Genetic assessment of family history is based on information provided by the family as well as on clinical and laboratory (pathology) data, when available. A genetic counsellor and a medical geneticist complete the assessment, which seeks to identify families for whom genetic testing may be indicated as well as which individual in a family would be the most appropriate to test.

Genetic counselling is necessary to provide individuals with the information they need to understand their potential inherited cancer risks and make informed choices about whether to undergo genetic testing.

Genetic testing for hereditary cancer predisposition, when appropriate and possible, is overseen and coordinated by the clinic.

Please note: Although genetic counselling is provided to all referred patients, genetic testing may not be appropriate for everyone and would, therefore, not be offered to all patients. Genetic testing is offered to those with a significant likelihood of having a detectable mutation. In keeping with national and international standards, genetic testing is offered only in conjunction with appropriate pre- and post-test genetic counselling.
Sporadic, Familial, and Hereditary Categories of Cancer

When genetic testing is contemplated, one factor to consider is whether the cancer falls into the sporadic, familial or hereditary category. Most cancers are not hereditary.

### Sporadic Cancer
- Vast majority of cancer cases (85 per cent)
- Typically, onset later in life
- Single, unilateral tumours
- Genetic consultation is generally not indicated

Exceptions may include an individual with certain specific tumour types (e.g., medullary thyroid cancer or pheochromocytoma)

### Familial Cancer
- Approximately 10 percent of cancer cases
- Cluster of related cancer cases within a family
- Two or more first or second degree relatives with cancer
- Unilateral disease
- Pattern unclear (possibility of chance alone, common environment, or genetic factors)
- Genetic consultation may or may not be indicated

### Hereditary Cancer
- Approximately 5 per cent of cancer cases; could be as high as 10 per cent
- Inherited cancer predisposition
- Family history includes individuals with early onset of cancer
- Bilateral and multifocal disease more likely
- More than one type of cancer in the same individual
- Tumour in sex not usually affected (e.g., male breast cancer)
- Specific types or combination of cancers types in the same family
- Affected individuals over several generations
- Referral indicated
- Genetic testing may be possible

The general features of each category of cancer are detailed in the next two columns. However, exceptions are plentiful, and the MHCS team welcomes any questions you may have regarding the appropriateness of a referral. (See “If You Are Uncertain” at the end of this article.)

In the following diagrams, □ = male and ○ = female.

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**Distribution of Sporadic, Familial, and Hereditary Cancer**

- Sporadic - 85%
- Familial - 10%
- Hereditary - 5%

**Sporadic Cancer**

- Breast Cancer dx 70
- Colon Cancer dx 62

**Familial Cancer**

- Breast Cancer dx 85
- Breast Cancer dx 60
- Ovarian Cancer dx 54
- Breast Cancer dx 49

**Hereditary Cancer**

- Breast Cancer dx 37
- Breast Cancer dx 49
- Ovarian Cancer dx 54

All hereditary cancers are familial, but not all familial cancers are hereditary. A familial cancer may be due to chance alone, or it may be related to factors that are shared in families, such as diet or environment. On the other hand, hereditary cancer syndromes are linked to mutations in specific genes. As research continues, additional genes associated with hereditary cancer syndromes will be identified.
Types of Cancer

Cancer is common, and it is not unusual to see many individuals within the same family affected with the disease. Table 1 (to the right) outlines some examples of the cancer types that may be seen together in a hereditary cancer syndrome.

Hereditary Breast/Ovarian Cancer Syndrome (HBOC)

The greatest numbers of referrals received at the MHCS are for hereditary breast/ovarian cancer syndrome. Currently, there are two genes known to be associated with this cancer syndrome: BRCA1 and BRCA2. One in every 300 to 500 people is estimated to carry a BRCA mutation.

These mutations are more common in people of Eastern European Jewish and Icelandic descent. It is estimated that one in every 40 people of Eastern European Jewish descent (2.5% of this population) carries a BRCA mutation. Various factors—such as the number of people with cancer in the family, their relationship to each other, age of onset of cancer, and types of cancer—affect the likelihood of a BRCA mutation within a family.

Although it is called hereditary breast/ovarian cancer syndrome, families with a gene mutation may present with only breast cancer or only ovarian cancer. As well, a combination of breast, ovarian or other associated cancers may be seen, as noted in table 1. The penetration of BRCA1 and BRCA2 mutations appears variable, even within families with the same mutation.

The pathology for most BRCA1/BRCA2 breast tumours is invasive ductal carcinomas. BRCA1-related tumours are more likely to be estrogen and progesterone receptor-negative than sporadic tumours. Information regarding BRCA2-related tumours is more limited, but they are just as likely to be hormone receptor-positive as control tumours.

An excess of serous adenocarcinomas of the ovary has been observed in women with BRCA1 and BRCA2 mutations when compared to controls. Over 90 per cent of tumours in women with BRCA1 mutations are serous compared with approximately 50 per cent in women without a BRCA1 mutation. Serous adenocarcinomas are generally of higher grade and are more frequently bilateral than mucinous cancers. Tumours of the fallopian tube and primary peritoneal cancer are also part of the spectrum of hereditary breast / ovarian cancer syndrome.

The sensitivity of BRCA testing is limited. About one-third of high-risk families (families with four or more members affected with breast or ovarian cancer in sequential generations in a pattern indicating inherited risk) do not have an identifiable BRCA1 or BRCA2 mutation to explain the inherited risk.

The detection rate for those of Eastern European Jewish ancestry is about 90 per cent with testing for three founder mutations. Individuals identified as...
carrying BRCA1/2 mutations are candidates for more intensive cancer surveillance as well as risk-reducing interventions such as prophylactic mastectomy and/or oophorectomy.

There are other conditions that can predispose to an increased risk of breast cancer including: Li-Fraumeni syndrome, associated with soft-tissue sarcoma, breast cancer, leukemia, osteosarcoma, melanoma, and cancer of the colon, pancreas, adrenal cortex, and brain; Cowden syndrome, a multiple hamartoma syndrome with a high risk of benign and malignant tumours of the thyroid, endometrium, and breast; Hereditary Diffuse Gastric Cancer syndrome (discussed later); and Ataxia-telangiectasia as well as other syndromes with increased sensitivity to ionizing radiation.

Testing for BRCA1/BRCA2 is mentioned frequently in the medical and lay press. Because of this, many patients may ask about the availability of gene testing for breast cancer. Most women with a positive family history of breast cancer have only modestly increased risk and can follow the same screening program recommended for women with average breast cancer risk. Evaluation of family history information helps to identify the rare high-risk families that may have an inherited predisposition.

Many often over-estimate their risk of breast cancer. They may view themselves as candidates for genetic testing when their likelihood of a positive test is very low. In one survey, women between 40 and 50 over-estimated their short-term risk of dying from breast cancer by 22-fold and their lifetime risk by 12-fold.

Some common misconceptions that patients may have prior to genetic counselling for hereditary breast/ovarian cancer are that:

• Any patient with a strong family history of breast/ovarian cancer is a good candidate for genetic testing. Currently, for appropriate families, genetic testing starts with a living affected family member to provide informative results.

• Only the maternal history is relevant for assessment. Breast cancer risk can be inherited from either side of the family. In evaluating family history, it is important to consider affected relatives on the father’s side.

• All family history of cancer increases the risk of breast/ovarian cancer. The assessment must consider the maternal and paternal sides of the family history separately. These histories are not cumulative unless they are biologically related.

• It is better to just have the genetic test to rule out an increased risk. For most women, the pre-test risk would not be changed by a “normal” test result because they are not expected to have a cancer-predisposing mutation. Actually, a normal test result could lead to a mistaken belief that the result indicates lowered risk. Genetic testing is not appropriate for most women.

• When genetic testing is appropriate, the test results provide a yes or no answer. Genetic testing is a complex process and results may not provide clear information for all families.

• They don’t see the need to complete a family history questionnaire or release medical information forms they receive as part of their referral. Family history is the most useful way to identify women who may have an inherited predisposition to breast cancer. Medical records are often sought for any family member with a history of cancer to confirm the specific type of cancer and, if possible, the age at diagnosis.

Colon Cancer
Hereditary colon cancer is divided into two main types: Familial Adenomatous Polyposis (FAP) and Lynch syndrome, also called Hereditary Non Polyposis Colon Cancer (HNPPC).

Individuals with FAP will develop hundreds to thousands of pre-cancerous colon polyps. These polyps can present in the early teen years, so screening of children should begin by age 10. This is one of the few hereditary cancer syndromes where genetic testing may be appropriate for children as it can affect screening and medical-management decisions. Without colectomy, colon cancer invariably develops; the average age of diagnosis is 39. Associated features beyond the polyposis may include polyps of the gastric fundus and duodenum, osteomas, dental anomalies, congenital hypertrophy of the retinal pigment epithelium (CHRPE), soft tissue tumours and desmoid tumours.

The mutation detection rate for FAP is very good: approximately 95 per cent of mutations in individuals affected with classical FAP are detected. The gene involved is the APC gene, which is also associated with attenuated FAP (fewer polyps and later age of onset), Gardner syndrome (polyposis, osteomas and soft tissue tumours) and Turcot syndrome (polyposis and CNS tumours, typically medulloblastomas). These syndromes are all inherited in an autosomal dominant manner.

Lynch Syndrome is caused by a mutation in one of at least six genes involved in DNA mismatch repair (MMR). The two most common genes are called MLH1 and MSH2. Approximately 60-70 per cent of families with cancer suggestive of Lynch syndrome (or HNPPC) have a mutation in one of these two genes. In HNPPC, the lifetime risk for colon cancer is increased to about 80 per cent. Females who carry a gene mutation have an increased risk of developing endometrial cancer (20-60 per cent) and ovarian cancer (12 per cent). Carriers also have an increased risk for cancers of the stomach, small intestine, hepatobiliary tract, renal pelvis or ureter, and central nervous system (usually glioblastoma). HNPPC is inherited in an autosomal dominant manner.
Testing strategies for HNPCC vary depending on the individual’s personal and family history. In some cases, the MMR genes are directly analyzed in an affected individual. In other cases, tissue is tested using immunohistochemistry for the expression of the proteins produced by the MMR genes. If the protein is missing, this increases the suspicion that the gene for that protein has a mutation. If the protein is present, then the gene is more likely working correctly.

The genetic assessment may also suggest that genetic testing for an autosomal recessive form of colon polyposis/colon cancer (MYH-associated polyposis) or other rare polyposis syndrome (e.g., Peutz-Jeghers syndrome) is most appropriate.

**Gastric Cancer**

About 5-10 per cent of all gastric cancers are hereditary. In about 1-3 per cent of individuals with gastric cancer, who have a family history of the disease, the condition may be the result of a mutation in the CDH1 gene, which encodes the protein E-cadherin. These mutations increase the likelihood of developing a form of gastric cancer called hereditary diffuse gastric cancer (HDGC). The typical pathology finding is a poorly differentiated adenocarcinoma that infiltrates into the stomach wall causing thickening of the wall without forming a distinct mass. Sending pathology reports with the referral is extremely helpful in these cases.

In individuals with CHD1 mutations, the lifetime risk of developing gastric cancer is 67 per cent in men and 83 per cent in women. The risk of developing lobular breast cancer is about 39 per cent for a woman carrying a CDH1 mutation. As with other cancers, it is important to note that in people who are known to have a mutation in the CDH1 gene there can be variation in the types of cancer and age at which these occur.

It is strongly recommended that all first-degree relatives of an affected person have clinical management (including gastrectomy or frequent surveillance) until they are proven not to be at risk by genetic testing. As with other cancers, it is important for at-risk individuals to report any changes in breast tissue, bowel habits, abdominal pain, or discomfort to their family doctor or treating physician.

**Multiple Endocrine Neoplasia, Type 2**

There are three subtypes of multiple endocrine neoplasia, type 2 (MEN2): MEN2A, MEN2B and FMTC (familial medullary thyroid carcinoma). The diagnosis of the subtype depends on the exact change in the causative gene and the different symptoms. All three subtypes have a high risk for development of medullary thyroid carcinoma (MTC). This cancer originates in calcitonin-producing cells of the thyroid gland, and MTC and c-cell hyperplasia are suspected in the presence of an elevated plasma calcitonin concentration, a specific and sensitive marker.

In FMTC, the only feature is the presence of MTC, which is typically diagnosed in middle age. In MEN2A and 2B, MTC is typically diagnosed at an earlier age and both types also have an increased risk for pheochromocytomas. In MEN2A, MTC development is typically the first manifestation in early adulthood. There is also an increased risk of parathyroid adenoma or hyperplasia. In MEN2B, MTC can present in early childhood. Other features that can be present in MEN2B are mucosal neuromas of the lips and tongue, ganglioneuromatosis of the gastrointestinal tract, and a “Marfanoid” body habitus.

The RET proto-oncogene is the only gene associated with MEN2 and mutations result in a gain-of-function (over-activation) for the gene. Genetic testing identifies an RET gene mutation in 95 per cent of individuals with MEN2A and MEN2B and in about 88 per cent of families with FMTC. Such testing is available clinically and used primarily for presymptomatic identification of at-risk individuals to reduce morbidity and mortality through early intervention. All MEN2 subtypes are inherited in an autosomal dominant manner.

**Von Hippel-Lindau**

Von Hippel-Lindau syndrome (VHL syndrome) is characterized by hemangioblastomas of the brain, spinal cord, and retina; pheochromocytoma; endolymphatic sac tumours; and renal cysts and clear cell renal cell carcinoma. Renal cell carcinoma occurs in about 40 per cent of individuals with VHL and is the leading cause of mortality. The VHL gene is the only gene that has been identified in this condition. Genetic testing is excellent, and mutations are detected in about 99 per cent of cases.

Most cases (~80%) are inherited, with the other 20 per cent being de novo. VHL is inherited in an autosomal dominant manner. All children of an individual with VHL syndrome have a 50 per cent risk of inheriting the gene mutation.
Special Issues

Genetic assessment and testing involve a number of issues that need to be considered within the counselling framework. Below is one patient’s story, illustrating the complexity of the decisions involved:

Meet Susan and her sister Marilyn
Susan was her sister Marilyn’s biggest support when Marilyn underwent breast cancer surgery at age 40. The bond between the two has always been strong, especially since their teens when they lost their mother to that same disease. She was only 49 at the time of her death.

Today, the sisters’ relationship is strained. Susan wants genetic testing for hereditary breast/ovarian cancer—for herself and, if her results are positive, for her two young daughters. As the family member who has had cancer, Marilyn would have to give the first blood sample for testing. But Marilyn says no. She has agreed to go with Susan to the genetic counselling session, but that is all. Susan hopes the counsellor will urge Marilyn to do “what is right.” She can’t believe her sister would put her own needs before the rest of the family’s, including both their children.

Case Example

What should be done?
There is no right or wrong answer. The bottom line is that the genetics team must respect Marilyn’s right to refuse testing. Due to the complex implications of the testing, any decision to proceed must be completely voluntary. Marilyn’s reasons may include concerns about discrimination in insurance or employment. And she may be afraid of a result that indicates a genetic mutation, an outcome that may not change her follow-up care but would heighten her anxiety. She may not want to know that she carries a genetic change that she could have passed on to her children.

The counselling session will cover the implications of genetic testing, and also its limitations. For example, Susan may not know that one common outcome of a genetic test is “no mutation found,” and if this is the case with Marilyn, no further testing would be available for other family members. Also, in discussion with the counsellor, Susan may reveal that if she was tested, and a mutation was found, she would not take any action at this time. She is already getting appropriate screening based on her family history, may not be ready to go further (i.e., a preventative mastectomy); and neither her daughters nor Marilyn’s children are old enough to be tested or even screened.

By the end of the session, Susan may realize that genetic testing is complex and there are many dynamics that come under consideration.

Genetic Test Results May Not Provide a Definitive Answer
A genetic test result does not provide a diagnosis of disease. Not everyone who carries a mutation in a cancer susceptibility gene will develop cancer. Genetic testing for cancer risk is new and the interpretation of test results is not always straightforward. A positive test result (presence of an inherited mutation in a cancer susceptibility gene) cannot predict when cancer will develop, what type of cancer it will be, or that it will happen at all. At the same time, those individuals with no mutation found can still develop cancer, and can still be at a higher-than-average risk of developing cancer because of their family history.

Genetic testing may also detect a genetic change but the medical significance of that specific change may be unclear. These changes are called variants of unknown significance and usually indicate that the genetic change has not been reported in the medical literature before and may only subtly, if at all, alter encoded protein. It may not be known if the change affects the function of the genes or proteins involved, and as a result, it may not be clear if it is causative for the disease in question or a benign polymorphism not associated with the disease in that family.

Psychological Reactions
Psychological reactions to genetic counselling and testing are not well understood. It is difficult to predict who may be at an increased risk for emotional or family distress. Possible responses to receiving genetic test results include relief, empowerment, anxiety, guilt, and uncertainty.

Questions of Privacy
Many concerns are expressed about who should have access to an individual’s genetic test results. Although the implications of genetic testing extend beyond the individual to the family, a health
care practitioner cannot share a patient's results with other family members without consent.

**Family Communication**
Some patients may be reluctant to contact an affected family member to initiate the process, or to discuss test results. However, test results may help individuals and family members plan appropriate preventative care.

**Potential for Discrimination**
The potential for discrimination in insurance and/or employment is discussed in a genetic counselling appointment. Some people may choose to delay or decline genetic testing because of such concerns.

**Genetic Testing of Children**
For most hereditary cancers, genetic testing in children is NOT appropriate. There are a few exceptions where testing may alter the screening and management of a child's care, for example Familial Adenomatous Polyposis (FAP).

**Pros and Cons of Genetic Testing**

**Pros**
Results may:
- Help people to make medical and lifestyle decisions;
- Help some individuals make decisions about prophylactic surgery;
- Provide helpful information for family members;
- Help to explain why people in the family have had cancer;
- Have a positive impact on family relationships and communication; and
- Provide an opportunity to contribute to research.

**Cons**
Results may:
- Show a mutation is present and may increase anxiety for some people;
- Indicate no mutation was found and may provide a false sense of security;
- Cause stress and difficulty in family relationships; and
- Prompt employers and insurance companies to treat individuals differently if they learn they carry a genetic mutation.

**Proceeding with a Referral**

**Referral and Triage Process**
Referrals are received and assessed by the genetic counsellor on cancer triage at the MHCS. Each case is assigned a triage category—urgent, semi-urgent, or routine—based on such factors as cancer type, information available at referral, and patient health status. For example, if advised a patient is terminally ill, they would be triaged as urgent, and the patient would be contacted as soon as possible, typically within days of the referral.

A semi-urgent referral would include situations where a gene mutation has been identified and confirmed in a family indicating other family members would have an increased risk of developing cancer (up to 50 per cent).

To ensure that a referral is triaged quickly and accurately please:
- Send complete contact information for your patient;
- Send pathology information regarding your patient's diagnosis, when applicable;
- Ensure the referring physician's name and contact information is legible; and
- Provide information regarding your patient's current health status.

Referral froms are available by calling 902-470-8754 or faxing your request to 902-470-8709.

Please note: Turnaround time for most cancer genetic testing is currently in the order of 8-10 months; therefore, testing is unlikely to have short-term management implications.

**Preparing Your Patient for their Appointment**
You can inform your patient that:
- Their appointment will be either in person, via Telehealth or by telephone;
- Appointments typically last one hour;
- Testing may or may not be offered to the family;
- In some cases, testing is offered to a family member other than the referred patient;
- Genetic test results can take up to 8-12 months; and
- All results are reviewed in person or via Telehealth (not by telephone).

**Preparing Your Patient for Genetic Counselling**
Please let your patient know that genetic counselling helps individuals whose history of cancer is suggestive of a hereditary syndrome. It helps them to learn more about hereditary forms of cancer and to better understand their own risk factors. Genetic counselling includes:
- A review of genes and how they are passed down from parents to children;
- A review of current information about genes and cancer;
- A detailed review of the patient’s family tree, with special attention to anyone who has had cancer;
- A discussion of differences between sporadic, familial, and hereditary cancers;
- An interpretation of the patterns of cancer that appear in the patient’s family history and their significance to an individual in the family. Some patients may learn that their cancer risk is lower than they thought; others may learn that it is higher.
- Discussion of whether genetic testing will be available to the family or individual;
- Discussion about the risks, benefits and limitations of genetic testing including the possible impact on family relationships;
Cancer Care Nova Scotia is a program of the Department of Health. Its mandate is to evaluate, coordinate and strengthen the cancer system in Nova Scotia. Cancer Care Nova Scotia works with and supports professionals and stakeholders in the health care system to bring about patient-centred change. Its ultimate goal is to reduce the burden of cancer on individuals, families, communities and the health care system.

In Practice is a supplement to Cancer Care Nova Scotia’s newsletter. It is written specifically for primary care practitioners with information that we hope will make a difference in your cancer practice.

Please contact Christine Smith, Communications Coordinator, Cancer Care Nova Scotia, by phone at 902-473-2932 or by email at christine.smith@ccns.nshealth.ca with comments or suggestions for future topics.

- Support with informing other family members about genetic information;
- Current recommendations for cancer screening options related to early detection and/or prevention of cancers for which the individual may be at increased risk;
- Testing, if indicated and desired, will be arranged by the MHCS. This may involve specific paperwork for each laboratory used and may involve the testing of blood or of archived tumour tissue samples.
- Genetic counsellors at the MHCS use a non-directive approach. This allows patients who are offered genetic testing to make an independent decision about whether to proceed with testing in a supportive environment.

Guidelines for Referral
Guidelines for Referral, developed by the MHCS, are included as an insert in this publication to help doctors identify individuals and families who will be most likely to benefit from genetic consultation. These criteria are reviewed and updated regularly.

If you are uncertain whether a patient is appropriate for genetic counselling or testing, please contact the Maritime Hereditary Cancer Service. A genetic counsellor on cancer triage is available from 8:30 a.m. to 4:30 p.m., Monday through Friday, to answer your questions about possible referrals. You can reach us at (902) 470-8754 or send a fax to (902) 470-8709.

A Public Lecture
“Hereditary Cancers: Genetic Testing – what it means for you and your family,” will be presented on Tuesday, May 20, 2008 in Halifax as part of Cancer Care Nova Scotia’s Cancer Answers lecture series. The lecture will be held in the Royal Bank Lecture Theatre of the Halifax Infirmary. It will be available by video conference in district health authorities throughout the province.

For more information about the Cancer Answers lecture series, call 1-866-599-2267 or visit the CCNS website at www.cancercare.ns.ca

*Cancer Care Nova Scotia supports the work of the Maritime Hereditary Cancer Service, through education and service development to ensure high quality, evidence-based care.