

Hereditary Cancer: When and How to Refer



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Conflict of Interest Disclosure

• Nothing to disclose



Objectives

- 1. To be familiar with the Hereditary Cancer Program referral process and eligibility criteria
- 2. To be aware of new approaches to hereditary cancer genetic testing
- 3. To identify hereditary cancer resources for practice



Sporadic, Familial & Hereditary Cancer



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Sporadic, Familial & Hereditary Cancer





Goal is classification: who needs what?





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When to consider hereditary cancer?

Family history may include:

- Same cancer, 2 or more close relatives (same side of family)
- Multiple generations affected
- Earlier than "usual" age at diagnosis
- Multiple primary tumours
- Rare cancers
- Constellation of tumours consistent with specific cancer syndrome (e.g. colorectal and endometrial; breast and ovarian)

Personal history

• See specific syndromes





Where to start...

Help your patients collect appropriate Family History Details:

- 3 generations if possible
- Maternal and paternal family history
 - Cancer status in 1st <u>and</u> 2nd degree relatives
- Ethnic background
- Medical history details:
 - Age at cancer dx
 - Primary versus metastatic cancer
 - Precursor lesions, benign tumours
 - Other causes of death and age



BC Cancer Agency

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Cy | Hereditary Cancer Program

Sample Family Tree

Date completed (DD/MM/YY):_

- Use this form or copy it on your own paper
- Add, delete, or change boxes as needed. Include other relatives with cancer (cousins, children, etc.)

• Fill in the boxes to the best of your knowledge

- Type of cancer and age it was diagnosed are important
- If you see a pattern of cancer on either side of your family, bring your family tree to your doctor





Online tools to assess family history

- https://familyhistory.hhs.gov/fhh-web/home.action
 - Pt enters family history to print, review with provider & share with family
- <u>http://www.yourdiseaserisk.wustl.edu/</u>
 - Interactive tool provides risk estimates & prevention advice for cancer & other common chronic diseases
- <u>http://premm.dfci.harvard.edu/</u>
 - Enter cancer family history directly to calculate probability of a Lynch syndrome gene mutation
- <u>http://www.hughesriskapps.com/</u>
 - Suite of software modules to download
- <u>http://www.ems-trials.org/riskevaluator/</u>
 - Download IBIS Breast Cancer Risk Evaluation Tool (UK)



Autosomal Dominant



- penetrance is often incomplete
- may appear to "skip" generations
- individuals inherit cancer susceptibility gene mutation, not cancer diagnosis
 - * De novo mutations; recessive inheritance



Factors affecting penetrance



Not everyone with an altered gene develops cancer



Caution

• Family histories are dynamic



*Family size is getting smaller

*Wider use of screening likely to prevent some cancers



Reporting Error

Verbally reported pedigree



Revised pedigree based on pathology reports





Referring to the Hereditary Cancer Program





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Hereditary Cancer Program BC Cancer Agency Provincial Clinical Service

Permanent Clinics

- Vancouver
- Abbotsford

Outreach Clinics

- Vancouver Island
- Surrey
- Kelowna
- Prince George

Videoconference/Telehealth

• most BC/Yukon communities



Hereditary Cancer Program (HCP)

Medical Director: Dr. Gillian Mitchell

Interdisciplinary Team

- Nurse Educator
- Genetic Counsellors
- Medical Geneticists

Provide:

- Genetic counselling
- Genetic testing
- Clinical management
- Evaluation & research
- Education

Genetic Counsellor

Specialized training & experience in the areas of medical genetics and counselling (MSc).

Providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to support informed medical and personal decisions.





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About Cancer Screening	Breast	Cervix	Colon	Hereditary

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Get a Referral Facts & Myths Next Steps

Steps For Health Professionals



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What is Hereditary Cancer?

Research has identified genes linked to some specific patterns of cancers. Those patterns are called hereditary cancer syndromes.

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About 7 cancers in 10 occur in people aged 60 years or older. Less than 1 cancer in 10 is hereditary.

How are Referrals Made?

For a referral to the Hereditary Cancer Program, talk to your health care provider and find out if you are eligible. Referrals to the program are accepted for people from anywhere in BC and the Yukon.

Want More Information?

If you have specific questions about your personal or family history of cancer, contact Mary McCullum, Nurse Educator, at 604-877-6000 ext. 2325 or mmccullum@bccancer.bc.ca.

http://www.screeningbc.ca/hereditary

Does Cancer Run In Your Family?

Most people have a history of cancer in their family, but only 5-10% of all cancers in BC are caused by an inherited gene mutation. While cancer is common, hereditary cancer is not.





About Cancer Screening

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	Get a Referral	Facts & Myths	Next Steps	For Health Professionals	
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Breast

Cervix

Colon

Hereditary



Statistics & ResearchGuidelines & FormsResources• Hereditary Colorectal
Cancer• HCP Referral Form
• HCP Materials Order Form• Recommended Links for
BRCA1/2

http://www.screeningbc.ca/hereditary/ForHealthProfessionals/Default.htm

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Quick Links

What's New

- Lynch Syndrome Criteria
- HBOC Criteria
- Hereditary Cancer Rounds

Most Viewed Pages

- Eligibility
- How Do I Re-connect with the Hereditary Cancer Program?



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BC Cancer Agency CARE & RESEARCH A segment of the Provincial Health Services Authority	AGENCY CHART NO. SURNAME GIVEN NAME(S)
HEREDITARY CANCER PROGRAM REFER	
	BIRTHDATE (D/M/Y) HEALTH CARE PLAN No.
Date of Referral: (dd/mm/yy)	MAILING ADDRESS
Relearning Physician Dining w	CITY / POSTAL CODE
Phone: ()Fax: ()	
	HOME PHONE WORK / CELL PHONE
Expedited/Urgent Referral?: No Yes-ap	prox. timeframe:
Indicate preferred location for HCP appt:	FAX completed Referral Form to office noted below: Please do not zend paper copy of Referral Form.
Abbotsford Centre	• Fax 604-851-4720

Indicate preferred location for HCP appt:		FAX completed Referral Form to office noted below: Please do not send paper copy of Referral Form.		
	Abbotsford Centre Surrey – Fraser Valley Centre	:	Fax Phone	604-851-4720 604-851-4710 local 645236
	Kelowna - Centre for Southern Interior Prince George – Centre for the North Vancouver Centre Victoria – Vancouver Island Centre Videoconference appt to((or closest available)	:	Fax Phone	604-707-5931 604-877-6000 local 672198

Is an interpreter required?

No Yes If yes, which language?

Reason for Referral - Please complete section A, B or C.

Note: Family history will be assessed by HCP staff and triaged to the most appropriate follow-up.

	Name of Relative	Report Attached
B.	Assess for specific hereditary cancer syndrome Hereditary Breast/Ovarian Cancer (<i>BRCA1, BRCA2</i>) Lynch Syndrome (Hereditary Nonpolyposis Colorectal Cancer/HNPCC) Other (specify):	*Page 2 must also be completed*
C.	Other personal / family history suggesting inherited pattern of ca	ancer – please describe:

BC Cancer Agency - Hereditary Cancer Program Referral

12 November 2015

BC Cancer Agency ARE & RESEARCH



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Patient's Name: _

Please complete the appropriate section below if this referral is for a specific syndrome.

Note: Family history refers to close relatives on one side of the family and includes the "index" case.

Hereditary Breast* and/or Ovarian** Cancer

- * breast cancer excludes lobular carcinoma in situ (LCIS). Includes DCIS depending on age & grade see website for details. ** ovarian cancer refers to invasive non-mucinous epithelial ovarian cancer; includes cancer of the fallopian tubes, primary peritoneal. cancer, and STIC (serous tubal intraepithelial carcinoma); excludes borderline/LMP ovarian tumours
- □ personal history of breast* cancer diagnosed ≤ age 35
- □ personal history of non-grade 1 breast cancer diagnosed ≤ age 50 AND no family history known due to adoption
- □ personal history of "triple negative" breast cancer diagnosed ≤ age 60
- □ personal history of more than 1 primary breast* cancer diagnosis, at least 1 of which was diagnosed ≤ age 50
- personal history of ovarian** cancer at any age (pathology report required)
- personal history of both breast* and ovarian** cancer
- family history that includes 1 or more of the following:
 - Ashkenazi Jewish heritage and 1 or more relatives with breast" cancer and/or ovarian" cancer
 - a close relative with personal history as above
 - 1 case of ovarian** cancer and 1 case of breast* cancer in close female relatives
 - 1 case of male breast cancer and another family member with breast* cancer or ovarian** cancer
 - 2 or more cases of ovarian** cancer in close relatives
 - 2 cases of breast* cancer in close female relatives, both diagnosed ≤ age 50
 - ☐ 3 or more cases of breast* cancer in close female relatives, with at least 1 diagnosed ≤ age 50

Lynch Syndrome (also known as Hereditary Nonpolyposis Colorectal Cancer/HNPCC)

- personal history of colorectal cancer diagnosed ≤ age 40
- □ personal history of colorectal cancer diagnosed ≤ age 50 AND no family history known due to adoption
- personal history of a Lynch syndrome' related cancer at any age with IHC-deficient/MSI-H result (report required)
- personal history of 2 Lynch syndrome¹ related cancer diagnoses, including at least 1 colorectal cancer and a cancer diagnosed \leq age 50
- family history that includes:
 - a close relative with personal history as above, OR

2 first degree relatives with a Lynch syndrome¹ related cancer, both diagnosed ≤ age 50 and including at least 1 diagnosis of colorectal cancer, OR

3 or more Lynch syndrome¹ related cancers, involving more than 1 generation, at least 1 case of colorectal cancer, and at least 1 case diagnosed ≤ age 50

Lynch syndrome related cancers include: colorectal, endometrial, ovarian, gastric, small bowel, hepatobiliary, pancreatic, kidney, ureter, brain fumours, sebaceous gland adenomas, or pathologically-confirmed colorectal adenomas < age 40.

Other Hereditary Cancer Syndromes

Please identify the specific syndrome(s) and provide all relevant clinical information on which this referral is based. Attach copies of pathology reports or other pertinent investigations as appropriate.

www.screeningbc.ca/hereditary

BC Cancer Agency - Horoditary Cancer Program Referral November 2015

http://www.screeningbc.ca/hereditary



Referrals



Current referral patterns

- ~ 3500 new referrals/year
 - ~ 2200/year before May 2013
- Majority of referrals are for Hereditary Breast/Ovarian Cancer
- Lynch syndrome is # 2 indication



The "Angelina Jolie Effect"



See: Borsekowski et al., Genetics in Medicine, Dec 2013 Also: <u>http://meetinglibrary.asco.org/content/136716-151</u>



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Timeline for HCP appointments

Current waiting list

- Up to 12-18 months for regular 1st GC appt
- Approx 3 months for appt to discuss carrier testing

When is Urgent HCP assessment indicated?

- Genetic test results will impact (immediate) clinical management
 - New breast cancer dx and surgical decisions
 - New: CAP access to olaparib for recurrent ovarian cancer
- Poor health status (potential index case)
 - Storage of blood sample +/- urgent GC appt
 - Print paperwork from: <u>www.screeningbc.ca/Hereditary/ForHealthProfessionals/ReferralProcess</u>

Integration of genetic testing into oncology clinics

- Specific process & criteria for oncologist to offer genetic testing
- GC provided at the time of genetic test results



Cancer Genetic Counselling Session

- Personal medical history
- Review of family history
- Education
 - ✓ Review of genes, chromosomes & inheritance
 - Discussion of sporadic, familial, hereditary cancer
- Empiric risk and likelihood of specific cancer syndrome
 - ✓ Associated cancer probabilities
 - ✓ Strategies for cancer screening & risk reduction
- Genetic testing
 - ✓ Eligibility, potential harms & benefits, limitations
- Psychosocial issues, resources
- Communication with family members
- Documentation to referring provider and patient



What are the possible results?



HCP – Current 14 Gene Panel

Gene	Syndrome	Associated Tumours
BRCA1, BRCA2	HBOC	Breast, ovary, prostate, pancreas
TP53	Li Fraumeni	Breast (young), sarcoma, brain, adrenocortical, leukemia, others
PTEN	PTEN Hamartoma (includes Cowden)	Breast, thyroid, endometrial; benign lesions of breast, thyroid, GI tract, GU system
CDH1	Hereditary Diffuse Gastric Cancer	Diffuse gastric, (lobular) breast, colorectal
STK11	Peutz-Jegher	Breast, GI, gyne, nasal polyps
MLH1, MSH2 MSH6, PMS2	Lynch	Colorectal, endometrial, gastric, ovary, urinary tract, small bowel, hepatobiliary, pancreas, skin
MUTYH	MYH-assoc polyposis	Colorectal, GI polyposis
APC	FAP	Colorectal, small bowel, desmoids, other
SMAD4, BMPR1A	Juvenile polyposis	Colorectal, gastric, other GI (combined with hereditary hemorrhagic telangiectasia)

Case Example

Michael

Tells a physician that his father died of colorectal cancer and his aunt was recently diagnosed with endometrial cancer.

She told him that he needs to start having a colonoscopy every year.







Lynch Syndrome (formerly known as HNPCC)

Personal history:

- Colorectal cancer < age 40
- Colorectal cancer < age 50 and adopted (with no family history available)
- Lynch syndrome cancer that is IHC-deficient/MSI-H (any age)
- 2 Lynch syndrome cancers: 1st dx < age 50, 1 CRC

Family history:

- Confirmed *MLH1, MSH2, MSH6, PMS2* mutation
- Close relative with personal history as above
- 2 FDR with a Lynch syndrome cancer: both dx < age 50 , 1 CRC
- 3 Lynch syndrome cancers: 1 dx < age 50, 1 CRC, more than 1 generation

Lynch syndrome cancers: colorectal, endometrial, ovarian, gastric, small bowel, hepatobiliary, pancreatic kidney, ureter, brain; also sebaceous adenomas or colorectal adenomas \leq age 40



What causes Lynch Syndrome?



DNA mismatch repair (MMR) genes

MMR complex functions as "spell-check" system to repair errors occurring in DNA replication during cell division

Loss of MMR leads to errors in short, repetitive sequences (microsatellites) leading to instability (MSI)



Lynch syndrome genetic testing begins with tumour issue

Immunohistochemistry (IHC):



10-15% sporadic colorectal tumours are MSI + Up to 95% of Lynch CRC have MSI

Microsatellite Analysis



CGL tests 7 markers:

- 3 dinucleotides
- 4 mononucleotides



Ryan's Tumour Results

Immunohistochemistry

- MLH1 Intact
- MSH2 Intact
- MSH6 Deficient
- PMS2 Intact

Microsatellite Analysis

- 4 / 7 markers were unstable
- All mononucleotides were unstable.

These results are suggestive of a *MSH6* gene mutation.



To whom do we offer germline genetic testing?





TYPE OF CANCER	GENERAL	LYNCH SYNDROME RISK*		
	POPULATION RISK (Canada)		MSH6	
Colorectal – men	7-8%	54-74%	22-42%	
Colorectal – women	6%	30-52%	20-42%	
Endometrial	2-3%	28-60%	20-40%	
Ovarian	1-2%	6-7%	6-7%	
Stomach	1%	6-9%	6-9%	
Hepatobiliary tract, urinary tract (renal pelvis), small bowel, pancreas, brain/CNS	<1%	1-7%	1-7%	

*Note: Cancer risks for PMS2 gene mutation carriers may be much lower than the other mismatch repair genes; however, the PMS2 research is limited at this time.



Lynch Syndrome Screening Colorectal Cancer*

Colonoscopy beginning at 25, or 5-10 years before the youngest age of colorectal cancer diagnosis in the family

- every 1-2 years until age 40
- every year after age 40

- * Average age at diagnosis younger than in general population
- * Tend to be right-sided (proximal) colon tumours
- * Rapid progression from polyp to CRC
- * Risk of second primary CRC up to 40%



Lynch Syndrome Screening Endometrial Cancer*

• For most women, abnormal vaginal bleeding is the first sign of endometrial cancer

• Prompt investigation of any abnormal bleeding

•Annual endometrial biopsy & transvaginal ultrasound starting at age 25-35 is controversial

Women with Lynch syndrome may consider risk-reducing hysterectomy and bilateral salpingo-oophorectomy.



Case Example

Judy

Asks for information about the "breast cancer gene test".

She feels that with her family history, breast cancer is inevitable.

She has no other risk factors for breast cancer.







Assessment

- Judy is in "Moderate/Familial" risk category
- Can begin screening mammography at age 40
- Counselling issues:
 - Low risk for *BRCA1* or *BRCA2* mutation
 - Screening and preventive strategies
 - Psychosocial perceived risk, fears
 - Support resources
 - Referral for genetic counselling NOT indicated
- Judy may ask about options to pursue private pay genetic testing



Private Pay Genetic Testing

- Assessment as ineligible for publicly funded hereditary cancer genetic testing may be reassuring news for some people
- For those who still feel a genetic test would provide important information, many commercial labs now provide hereditary cancer genetic testing with MD referral
- Some examples:
 - GeneDx (<u>www.genedx.com</u>) based in the U.S.; DNA samples sent to the U.S. for testing; no genetic counselling offered
 - Invitae (<u>www.invitae.com</u>)- based in the U.S; DNA samples sent to the U.S. for testing; genetic counselling is available with genetic testing
 - LifeLabs (<u>www.lifelabsgenetics.com</u>) based in Canada; DNA samples sent to Europe for testing; no genetic counselling offered
- HCP cannot endorse any specific lab; pt and provider need to investigate the options
- HCP will provide appointments about the clinical implications of the result for the tested person and their family members
- Relatives are eligible for publicly-funded genetic counselling and genetic testing when a gene mutation is confirmed in a family



Considerations

• Different technologies and test options

- GUIDELINES-BASED PANELS
- CROSS-CANCER PANELS
- BREAST AND GYNECOLOGIC CANCER PANELS
- GASTROINTESTINAL CANCER PANELS
- GENITOURINARY CANCER PANELS
- ENDOCRINE CANCER PANELS
- HEMATOLOGIC MALIGNANCY PANELS
- INDIVIDUAL HEREDITARY CANCER CONDITIONS
- Informed consent prior to testing
 - Possible insurance implications
 - Likely results & implications (pt and family)
- Be prepared for possible results
 - Mutation found in "expected" gene
 - Mutation found in "unexpected" gene
 - No mutation found
 - Variant (s) of uncertain significance



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Case Example

Erica

Asks her physician about her risk to develop breast cancer based on her family history.



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Hereditary Breast*/Ovarian** Cancer

Personal history:

- Breast cancer < age 35
- Breast cancer < age 50 and adopted (with no family history available)
- "Triple negative" breast cancer < age 60
- 2 or more primary breast cancers: 1st dx < age 50
- Ovarian cancer at any age (pathology required) +/- breast cancer

Family history:

- Confirmed BRCA1, BRCA2 mutation
- Close relative with personal history as above
- Ashkenazi Jewish heritage and at least 1 breast or ovarian cancer dx
- 1 breast cancer + 1 ovarian cancer dx in close relatives
- 1 male breast cancer + 1 close relative with breast or ovarian cancer
- 2 close relatives with breast cancer: both dx < age 50
- 3 close relatives with breast cancer: 1 dx < age 50
- * breast cancer includes DCIS, depending on age & grade; excludes LCIS
- ** ovarian cancer (high-grade serous) includes fallopian tube, primary peritoneal, "STIC"; excludes borderline/LMP tumours



Who is offered genetic testing?









TYPE OF CANCER	RISK IN GENERAL POPULATION	BRCA1 CARRIER	<i>BRCA2</i> CARRIER
breast cancer - women	11%	47-66%	40-57%
ovarian cancer	1-2%	35-46%	13-23%
breast cancer - men	0.1%	up to 6%	6%
prostate cancer	12%	increased by approx 2-3 times	
pancreatic cancer	1%	slight increase	slight increase
other cancers	varies	_	slight increase

*2nd primary breast cancer ~20-63% (avg up to 50%)



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What is recommended if you are BRCA+ in BC?

Breast screening:

P BSE – personal choice CBE q6 months in conjunction with imaging Mammography q12 months age ≥30 MRI q12 months age 25-65 Ultrasound as advised by radiologist

CBE q12 months Prostate screening from age 40

No effective way to screen for ovarian cancer

Referral to Hereditary Cancer Program High-Risk Clinic (Vancouver) typically made by genetic counsellor after results disclosure

Canadian Hereditary Cancer Task Force, JOGC 2007



Risk-Reducing Surgery

- mastectomy (with reconstruction) personal choice
 - reduces breast cancer risk by 90-95%
 - no routine imaging of reconstructed breasts; GP follow-up for routine chest wall & regional node exam
- bilateral salpingo-oophorectomy
 - recommended to all *BRCA1/2*+ women by age 40
 - reduces ovarian cancer risk by 85-95% AND reduces breast cancer risk ~50% if done prior to menopause
 - attention to effects of surgical menopause
 - short term use of HRT does not negate protective effect of BSO on breast cancer risk

Canadian Hereditary Cancer Task Force, JOGC 2007



Other Hereditary Cancer Syndromes

Susan

Susan brings a letter from a relative to her doctor, and asks how to get a test for the *SDHB* gene mutation.



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Other syndromes (genes)

- Familial adenomatous polyposis (APC)
- Other polyposis syndromes
- Hereditary diffuse gastric cancer (*CDH1*)
- Li Fraumeni (*p53*)
- Hereditary paraganglioma/pheochromocytoma (*SDHB*, *SDHC*, *SDHD* and others)
- von Hippel Lindau
- Multiple endocrine neoplasias
- And others ...



Key Points to Remember

- Hereditary cancer is rare (<10%).
- Most hereditary cancer syndromes are inherited in an autosomal dominant manner, but not all.
- Not everyone with hereditary risk will develop cancer.
- Options for risk reduction and/or early detection are available.
- Hereditary risk can come from either the maternal or paternal side.
- Genetic testing usually starts with an affected family member when to consider storing a blood sample.



If your patient's personal or family history is suspicious, refer and we will assess!



Hereditary Cancer Resources

- Hereditary Cancer Program website (<u>www.screeningbc.ca/hereditary</u>)
 - To order HCP materials, visit <u>www.screeningbc.ca/Hereditary/ForHealthProfessionals/Resources</u>
 - Does Cancer Run in My Family?
 - Family Tree tear-off pad
 - Referral Form
 - Information for patients
- Kaiser Permanente website
 - HBOC video series (<u>http://mydoctor.kpnvly.org/cancer-care/home/breast-and-ovarian-cancer/</u>)
- Canadian Medical Association Journal website (<u>www.cmaj.ca</u>)
 - Genetics Collection
- Gene Tests website (<u>www.genetests.org</u>)
 - Gene Reviews (<u>www.genetests.org/resources/genereviews.php</u>)
- Willow Breast & Hereditary Cancer Support website (<u>www.willow.org</u>)
 - New interactive resource for women which includes video clips and risk-reducing mastectomy decision guide (<u>www.willow.org/get-information/hereditary-breast-ovarian-cancer-hboc</u>)
- American Society of Clinical Oncology website (<u>www.asco.org</u>)
 - Updated ASCO Policy Statement on Genetic & Genomic Testing for Cancer Susceptibility, April 2015 (www.asco.org/press-center/asco-releases-updated-policy-statement-genetic-and-genomic-testing-cancer)



Questions?

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For more information on cancer screening... Visit the BC Cancer Agency Screening Programs website: <u>www.screeningbc.ca</u> or email <u>screening@bccancer.bc.ca</u>



