Hereditary Cancer: When and How to Refer

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BC Cancer Agency
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www.screeningbc.ca
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

Lynch et al., 2006

BC Cancer Agency
www.screeningbc.ca
Sporadic, Familial & Hereditary Cancer

Sporadic

Familial

Hereditary
Goal is classification: who needs what?

Assessment

Risk Classification

Average/Sporadic
60-75%

Moderate/Familial
20-25%

High/Hereditary
5-10%

Intervention

Standard screening recommendations

Personalized screening recommendations

Referral for genetic evaluation with personalized screening recommendations
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

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Where to start...

Help your patients collect appropriate Family History Details:

• 3 generations if possible

• Maternal and paternal family history
  – Cancer status in 1st and 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

www.screeningbc.ca
Online tools to assess family history

- [https://familyhistory.hhs.gov/fhh-web/home.action](https://familyhistory.hhs.gov/fhh-web/home.action)
  - Pt enters family history to print, review with provider & share with family

- [http://www.yourdiseaserisk.wustl.edu/](http://www.yourdiseaserisk.wustl.edu/)
  - Interactive tool provides risk estimates & prevention advice for cancer & other common chronic diseases

- [http://premm.dfci.harvard.edu/](http://premm.dfci.harvard.edu/)
  - Enter cancer family history directly to calculate probability of a Lynch syndrome gene mutation

- [http://www.hughesriskapps.com/](http://www.hughesriskapps.com/)
  - Suite of software modules to download

  - 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

Modifier genes \[\rightarrow\] Response to DNA damage \[\rightarrow\] Carcinogens

Hormonal/reproductive factors

Not everyone with an altered gene develops cancer

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Caution

- Family histories are dynamic

*Family size is getting smaller

*Wider use of screening likely to prevent some cancers
Reporting Error

Verbally reported pedigree

- Stomach Ca
- Bone Ca d. 59
- Prostate Ca

Revised pedigree based on pathology reports

- Ovarian Ca dx 43, d. 49
- Breast Ca dx 45 d. 59
- BPH dx 54
Referring to the Hereditary Cancer Program
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

www.screeningbc.ca
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.
What is Hereditary Cancer?

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

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.

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.

http://www.screeningbc.ca/hereditary
HEREDITARY CANCER PROGRAM REFERRAL FORM

Patient's Name:

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

Hereditary Breast** and/or Ovarian*** Cancer

1. Breast cancer includes lobular carcinoma in situ (LCIS). Includes DCIS depending on age & grade – see website for details

2. **Breast Cancer** refers to invasive non-invasive epithelial breast cancer. Includes cancer of the breast tissue, primary sarcoma, and STIC (serous tubal intraluminal carcinoma). Excludes breast UADT cancer

   - Personal history of breast cancer diagnosed ≤ age 55
   - Personal history of non-hereditary 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 diagnosed, 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/or relatives with breast cancer and/or ovarian*** cancer
     - A close relative with personal history of breast cancer
     - A case of ovarian** cancer and a case of breast cancer in first-degree relatives
     - A case of male breast cancer and another family member with breast cancer or ovarian*** cancer
     - 2 or more cases of ovarian*** cancer in first-degree relatives
     - 2 cases of breast cancer in first-degree relatives, both diagnosed ≤ age 50
     - 2 or more cases of breast cancer in first-degree relatives, with at least 1 diagnosed ≤ age 50

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

1. Personal history of colorectal cancer diagnosed ≤ age 40

2. Personal history of colorectal cancer diagnosed ≤ age 40 AND no family history known due to adoption

3. Personal history of a Lynch syndrome** related cancer at any age with HNPCC features (HNPCC feature report required)

4. Personal history of 2 Lynch syndrome** related cancers, including at least 1 colorectal cancer and a cancer diagnosed ≤ age 50

5. Family history that includes:
   - A close relative with personal history of colorectal or ovarian cancer
   - 2 first-degree relatives with a Lynch syndrome** related cancer, both diagnosed ≤ age 50 and including at least 1 diagnosis of colorectal cancer
   - 3 or more Lynch syndrome** related cancers in first-degree relatives

6. Lynch syndrome feature report required

Other Hereditary Cancer Syndromes

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

www.screeningbc.ca/hereditary

http://www.screeningbc.ca/heritary

www.screeningbc.ca
Referrals

- Family Physicians
- Oncologists
- Surgeons
- Other Physicians
- Nurse Practitioners
- Patients/Family members
- Genetics Clinics

Patient Referred

Family History Form Sent to Pt

Review Family History

Patient Referred

Telephone Appointment

In Person / Video Conference

Genetic Counsellor or Nurse

Genetic Counsellor Appointment

Medical Geneticist Appointment
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: Borsekowsk et al., Genetics in Medicine, Dec 2013
Also: http://meetinglibrary.asco.org/content/136716-151

www.screeningbc.ca
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: www.screeningbc.ca/Hereditary/ForHealthProfessionals/ReferralProcess

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?

- Normal Gene: 65-75%
- Mutation: 10-15%
- Variant: 15-20%
<table>
<thead>
<tr>
<th>Gene</th>
<th>Syndrome</th>
<th>Associated Tumours</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRCA1, BRCA2</strong></td>
<td>HBOC</td>
<td>Breast, ovary, prostate, pancreas</td>
</tr>
<tr>
<td><strong>TP53</strong></td>
<td>Li Fraumeni</td>
<td>Breast (young), sarcoma, brain, adrenocortical, leukemia, others</td>
</tr>
<tr>
<td><strong>PTEN</strong></td>
<td>PTEN Hamartoma (includes Cowden)</td>
<td>Breast, thyroid, endometrial; benign lesions of breast, thyroid, GI tract, GU system</td>
</tr>
<tr>
<td><strong>CDH1</strong></td>
<td>Hereditary Diffuse Gastric Cancer</td>
<td>Diffuse gastric, (lobular) breast, colorectal</td>
</tr>
<tr>
<td><strong>STK11</strong></td>
<td>Peutz-Jegher</td>
<td>Breast, GI, gyne, nasal polyps</td>
</tr>
<tr>
<td><strong>MLH1, MSH2 MSH6, PMS2</strong></td>
<td>Lynch</td>
<td>Colorectal, endometrial, gastric, ovary, urinary tract, small bowel, hepatobiliary, pancreas, skin</td>
</tr>
<tr>
<td><strong>MUTYH</strong></td>
<td>MYH-assoc polyposis</td>
<td>Colorectal, GI polyposis</td>
</tr>
<tr>
<td><strong>APC</strong></td>
<td>FAP</td>
<td>Colorectal, small bowel, desmoids, other</td>
</tr>
<tr>
<td><strong>SMAD4, BMPR1A</strong></td>
<td>Juvenile polyposis</td>
<td>Colorectal, gastric, other GI (combined with hereditary hemorrhagic telangiectasia)</td>
</tr>
</tbody>
</table>
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 \( \leq \) age 40
- Colorectal cancer \( \leq \) 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 \( \leq \) 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 \( \leq \) age 50, 1 CRC
- 3 Lynch syndrome cancers: 1 dx \( \leq \) 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
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).

What causes Lynch Syndrome?

www.screeningbc.ca
Lynch syndrome genetic testing begins with tumour issue

**Immunohistochemistry (IHC):**
- MLH1
- MSH2
- MSH6
- PMS2

Stable (Normal)
Unstained

Stained Intact

Unstained
Deficient

**Microsatellite Analysis**

Stable (Normal)

Unstable (Abnormal)

CGL tests 7 markers:
- 3 dinucleotides
- 4 mononucleotides

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

www.screeningbc.ca
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?

- Lung Cancer dx.67 d.72
- Endometrial Cancer dx.60
- Gastric Cancer dx.54 d.56
- Michael
- No Info

- Ryan CRC dx.45 d.46
- Michael

- Jane

- d.85
- d.99
- d.75
- d.20s during childbirth
- d.65 MI
- d.65

- www.screeningbc.ca
<table>
<thead>
<tr>
<th>TYPE OF CANCER</th>
<th>GENERAL POPULATION RISK (Canada)</th>
<th>LYNCH SYNDROME RISK*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>MLH1/MSH2</td>
</tr>
<tr>
<td>Colorectal – men</td>
<td>7-8%</td>
<td>54-74%</td>
</tr>
<tr>
<td>Colorectal – women</td>
<td>6%</td>
<td>30-52%</td>
</tr>
<tr>
<td>Endometrial</td>
<td>2-3%</td>
<td>28-60%</td>
</tr>
<tr>
<td>Ovarian</td>
<td>1-2%</td>
<td>6-7%</td>
</tr>
<tr>
<td>Stomach</td>
<td>1%</td>
<td>6-9%</td>
</tr>
<tr>
<td>Hepatobiliary tract, urinary tract (renal pelvis), small bowel, pancreas, brain/CNS</td>
<td>&lt;1%</td>
<td>1-7%</td>
</tr>
</tbody>
</table>

*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 (www.genedx.com) - based in the U.S.; DNA samples sent to the U.S. for testing; no genetic counselling offered
  – Invitae (www.invitae.com) - based in the U.S; DNA samples sent to the U.S. for testing; genetic counselling is available with genetic testing
  – LifeLabs (www.lifelabsgenetics.com) – 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
Case Example

Erica

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

Genetic testing usually begins with an affected individual.

What is my risk for a second breast cancer?

Breast dx. 52
57 yr

Ovarian dx. 53
d. 57 yr

Breast dx. 48
d. 50 yr

Erica
38 yr

www.screeningbc.ca
Ovarian Cancer
dx. 55   d. 57
Breast Cancer
dx. 48    d. 50

Erica
38

Breast Cancer
dx. 52
57

There is nothing to worry about.
Should I have my breasts removed?

As a man, this does not impact me.

There is nothing to worry about.
<table>
<thead>
<tr>
<th>TYPE OF CANCER</th>
<th>RISK IN GENERAL POPULATION</th>
<th>BRCA1 CARRIER</th>
<th>BRCA2 CARRIER</th>
</tr>
</thead>
<tbody>
<tr>
<td>breast cancer - women</td>
<td>11%</td>
<td>47-66%</td>
<td>40-57%</td>
</tr>
<tr>
<td>ovarian cancer</td>
<td>1.2%</td>
<td>35-46%</td>
<td>13-23%</td>
</tr>
<tr>
<td>breast cancer - men</td>
<td>0.1%</td>
<td>up to 6%</td>
<td>6%</td>
</tr>
<tr>
<td>prostate cancer</td>
<td>12%</td>
<td>increased by approx 2-3 times</td>
<td></td>
</tr>
<tr>
<td>pancreatic cancer</td>
<td>1%</td>
<td>slight increase</td>
<td>slight increase</td>
</tr>
<tr>
<td>other cancers</td>
<td>varies</td>
<td>—</td>
<td>slight increase</td>
</tr>
</tbody>
</table>

*2nd primary breast cancer ~20-63% (avg up to 50%)
What is recommended if you are BRCA+ in BC?

Breast screening:

♀ 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.
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 ([www.screeningbc.ca/hereditary](www.screeningbc.ca/hereditary))
  – To order HCP materials, visit [www.screeningbc.ca/Hereditary/ForHealthProfessionals/Resources](www.screeningbc.ca/Hereditary/ForHealthProfessionals/Resources)
    • [Does Cancer Run in My Family?](#)
    • Family Tree tear-off pad
    • Referral Form
  – Information for patients

• Kaiser Permanente website

• Canadian Medical Association Journal website ([www.cmaj.ca](www.cmaj.ca))
  – Genetics Collection

• Gene Tests website ([www.genetests.org](www.genetests.org))
  – Gene Reviews ([www.genetests.org/resources/genereviews.php](www.genetests.org/resources/genereviews.php))

• Willow Breast & Hereditary Cancer Support website ([www.willow.org](www.willow.org))
  – New interactive resource for women which includes video clips and risk-reducing mastectomy decision guide ([www.willow.org/get-information/hereditary-breast-ovarian-cancer-hboc](www.willow.org/get-information/hereditary-breast-ovarian-cancer-hboc))

• American Society of Clinical Oncology website ([www.asco.org](www.asco.org))
Questions?

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Email: mmccullum@bccancer.bc.ca

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

www.screeningbc.ca