Cracking the Code on Cancer Predisposition Syndromes

Mary-Jill (MJ) Asrat, Genetic Counsellor, Hereditary Cancer Program, BCC

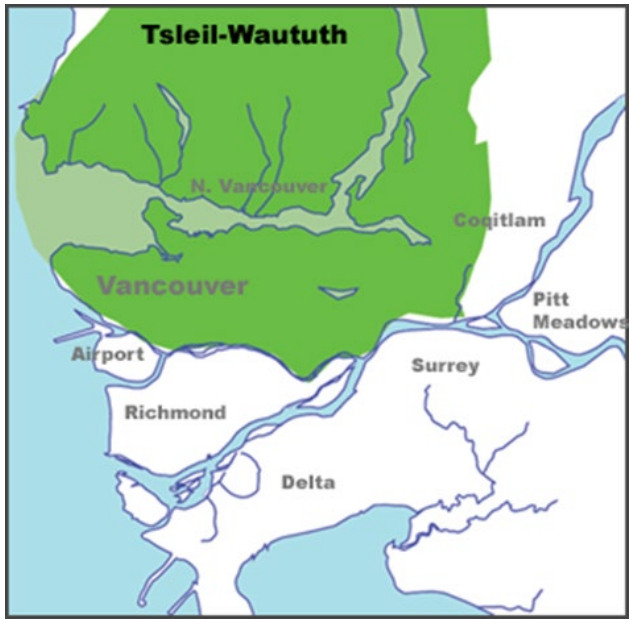
Linlea Armstrong, Medical Geneticist, Provincial Medical Genetics Program

29 May 2024

VCH Family Medicine Rounds
Thank you for the invitation

We would like to acknowledge that we are gathered today on the traditional territories of the Musqueam, Squamish and Tsleil-Waututh peoples.

Source: www.johomaps.net/na/canada/bc/vancouver/firstnations/firstnations.html



Disclosure

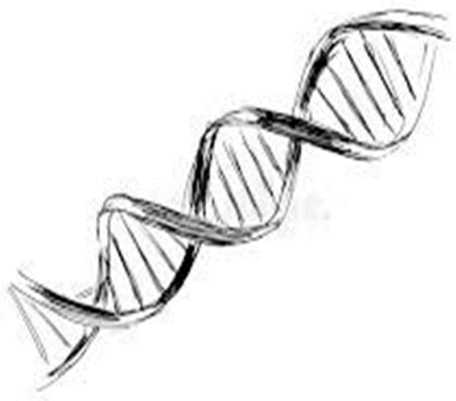
- A family member to Linlea Armstrong owes shares in a genomic testing company, Alamya

Mitigation

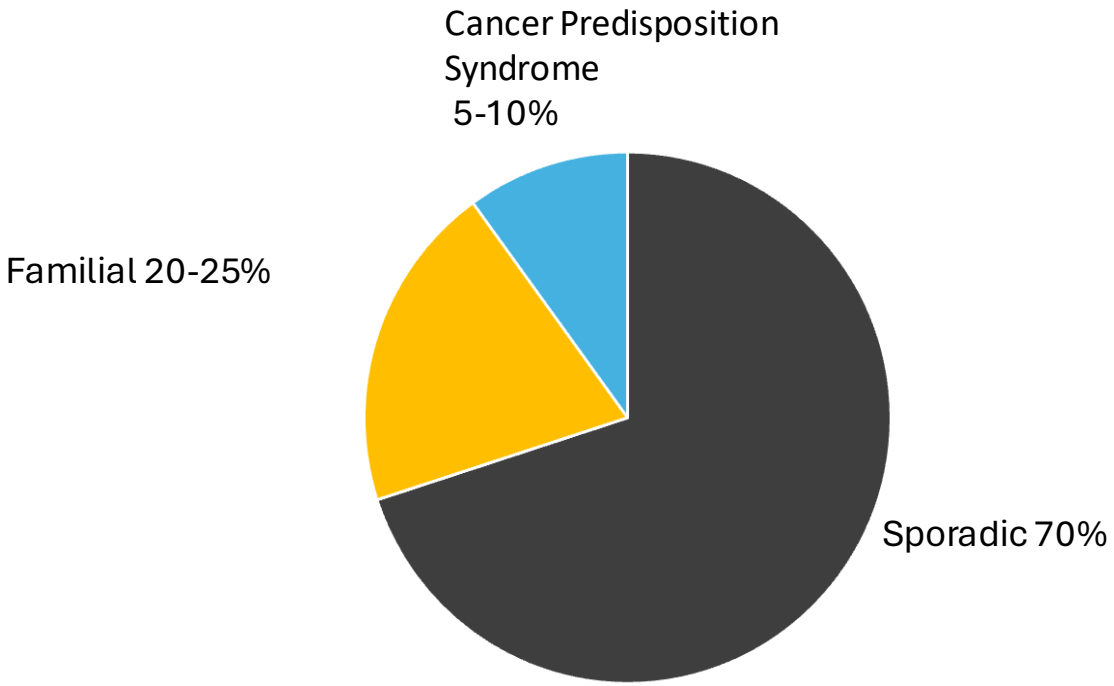
- No tests from that company will be discussed today
- This was disclosed in advance

Objectives

- Define what is meant by “genetic cancer predisposition” and describe common clinical features.
- Outline the contribution of germline genetics to cancer.
- Describe the pathway of care for individuals and families, with attention to the emerging concept of mainstreaming for equitable, sensitive, and efficient ascertainment.
- Discuss the roles of primary care providers in risk management of affected individuals.

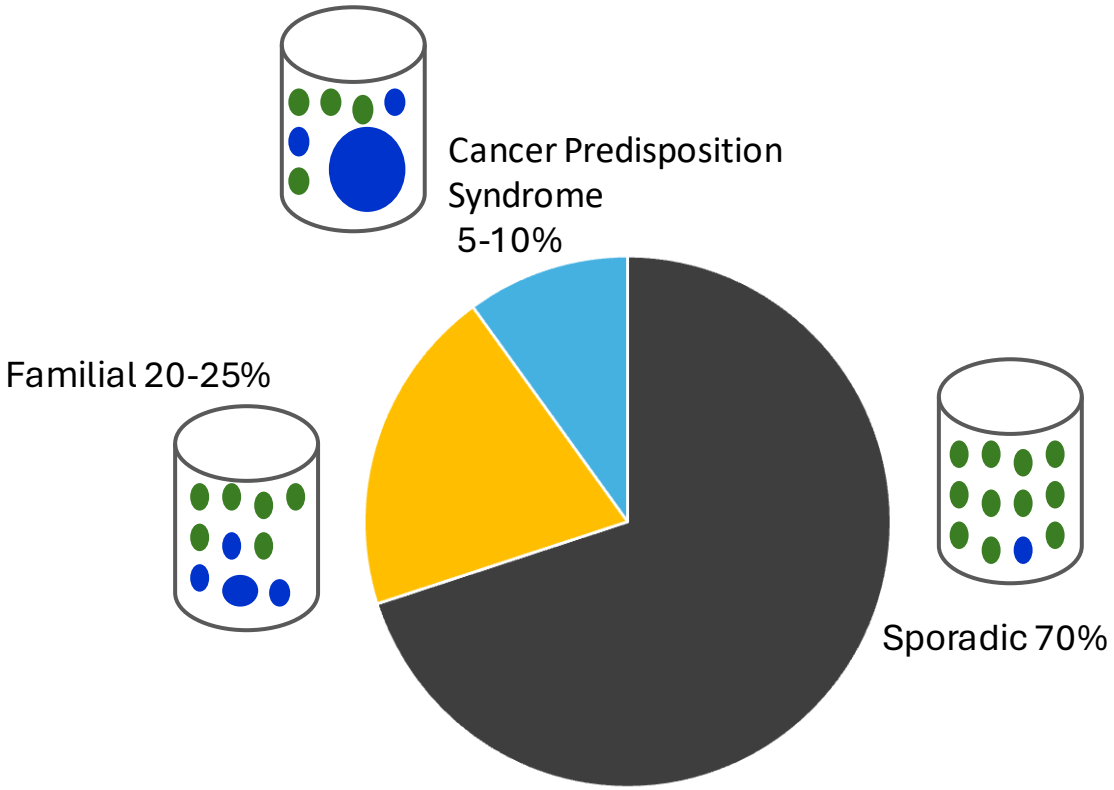


Cancer Predisposition Syndrome



- Younger Age
- Multiple Primaries
- Ethnicity
- Family History
- Pathology

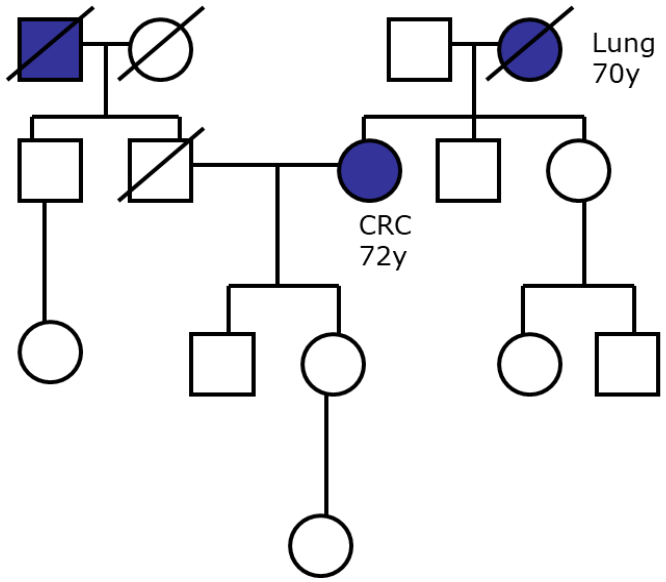
Model for Discussing Risk Factors



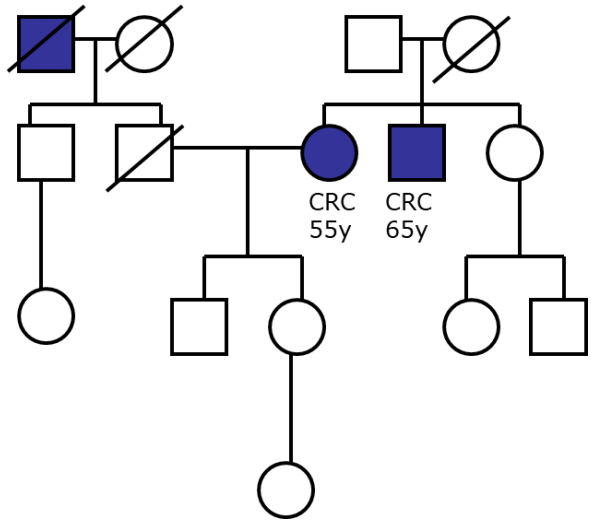
Genetic Factors

Environmental Factors

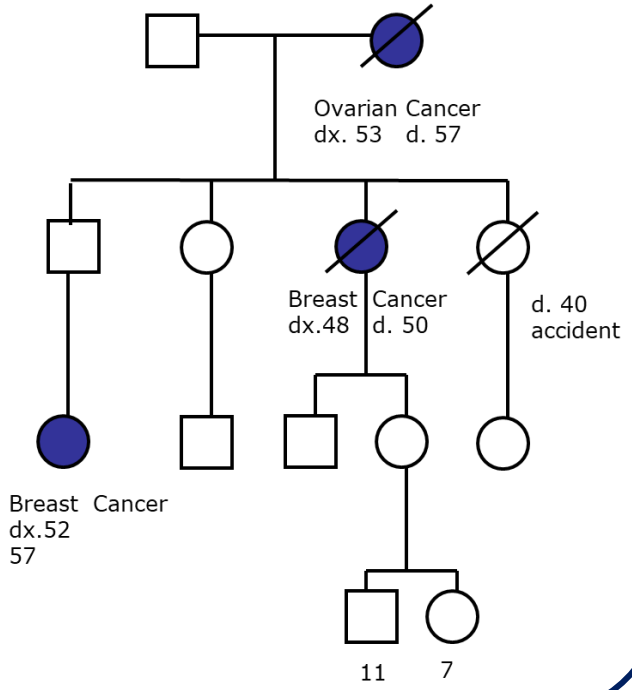
Sporadic



Familial

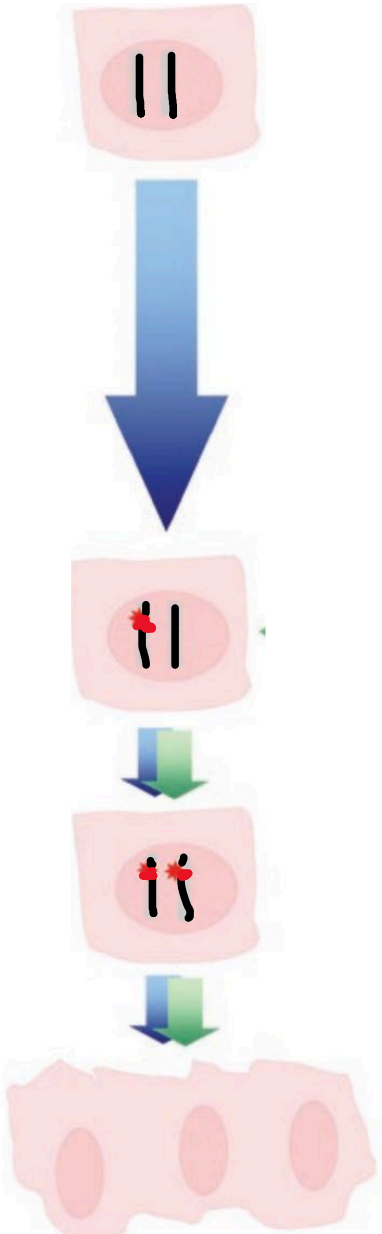


Predisposition Syndrome



Germline cell

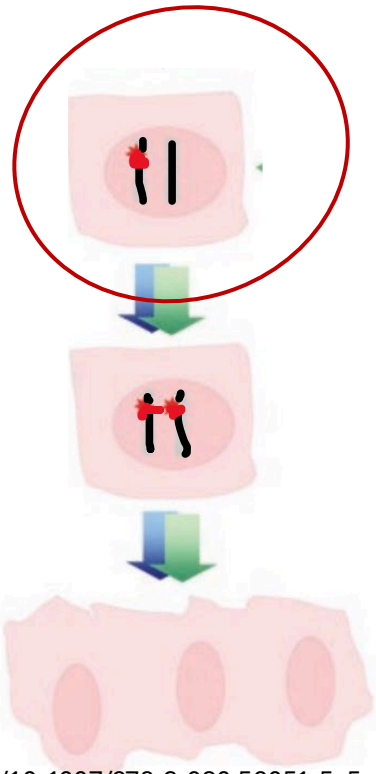
Cell cycle control



Tumour initiation

Modified from Fanale et al., 2021: https://link.springer.com/chapter/10.1007/978-3-030-56051-5_5

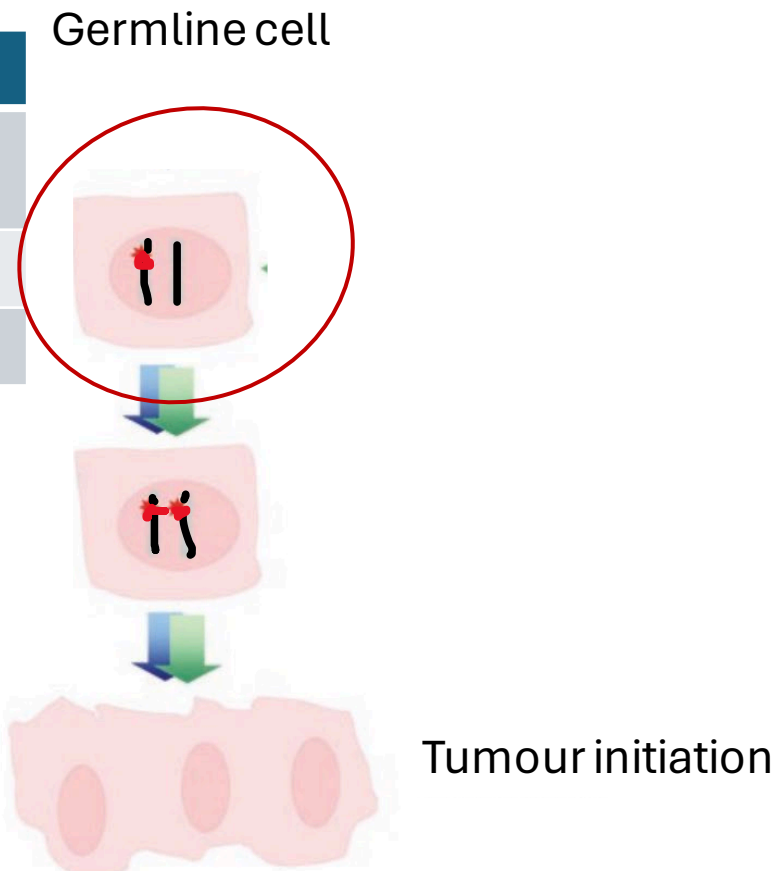
Germline cell



Tumour initiation

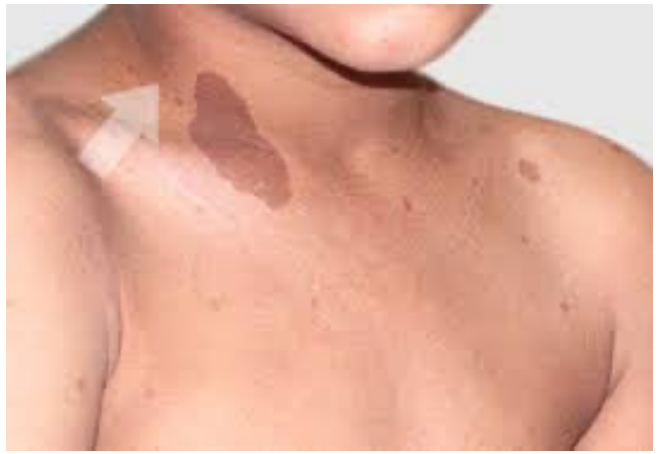
Modified from Fanale et al., 2021: https://link.springer.com/chapter/10.1007/978-3-030-56051-5_5

Gene	Syndrome
APC	Familial adenomatous polyposis
NF1	Neurofibromatosis type 1
TP53	Li-Fraumeni syndrome

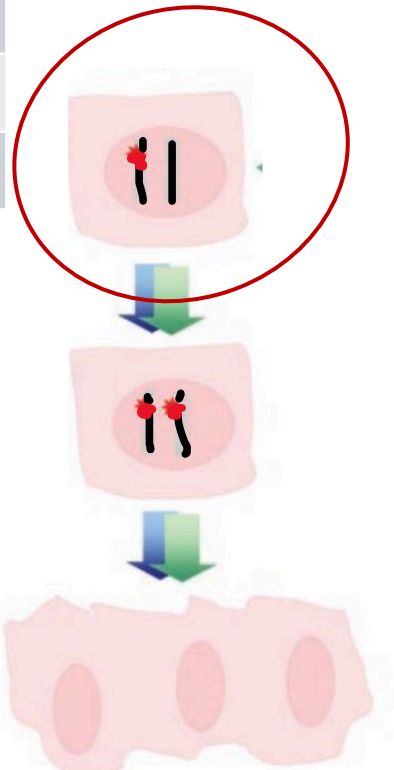


Modified from Fanale et al., 2021: https://link.springer.com/chapter/10.1007/978-3-030-56051-5_5

Gene	Syndrome
APC	Familial adenomatous polyposis
NF1	Neurofibromatosis type 1
TP53	Li-Fraumeni syndrome



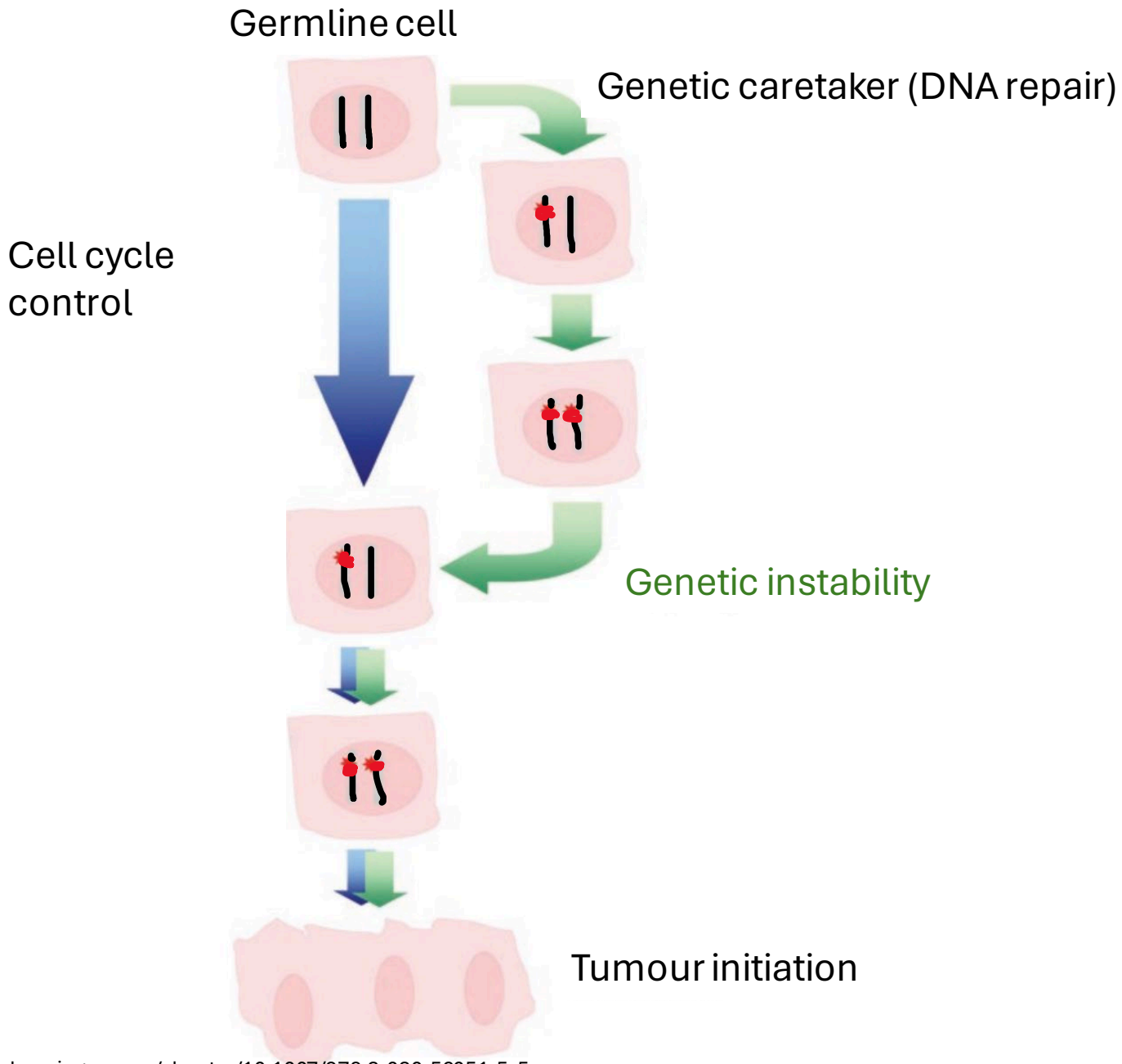
Germline cell



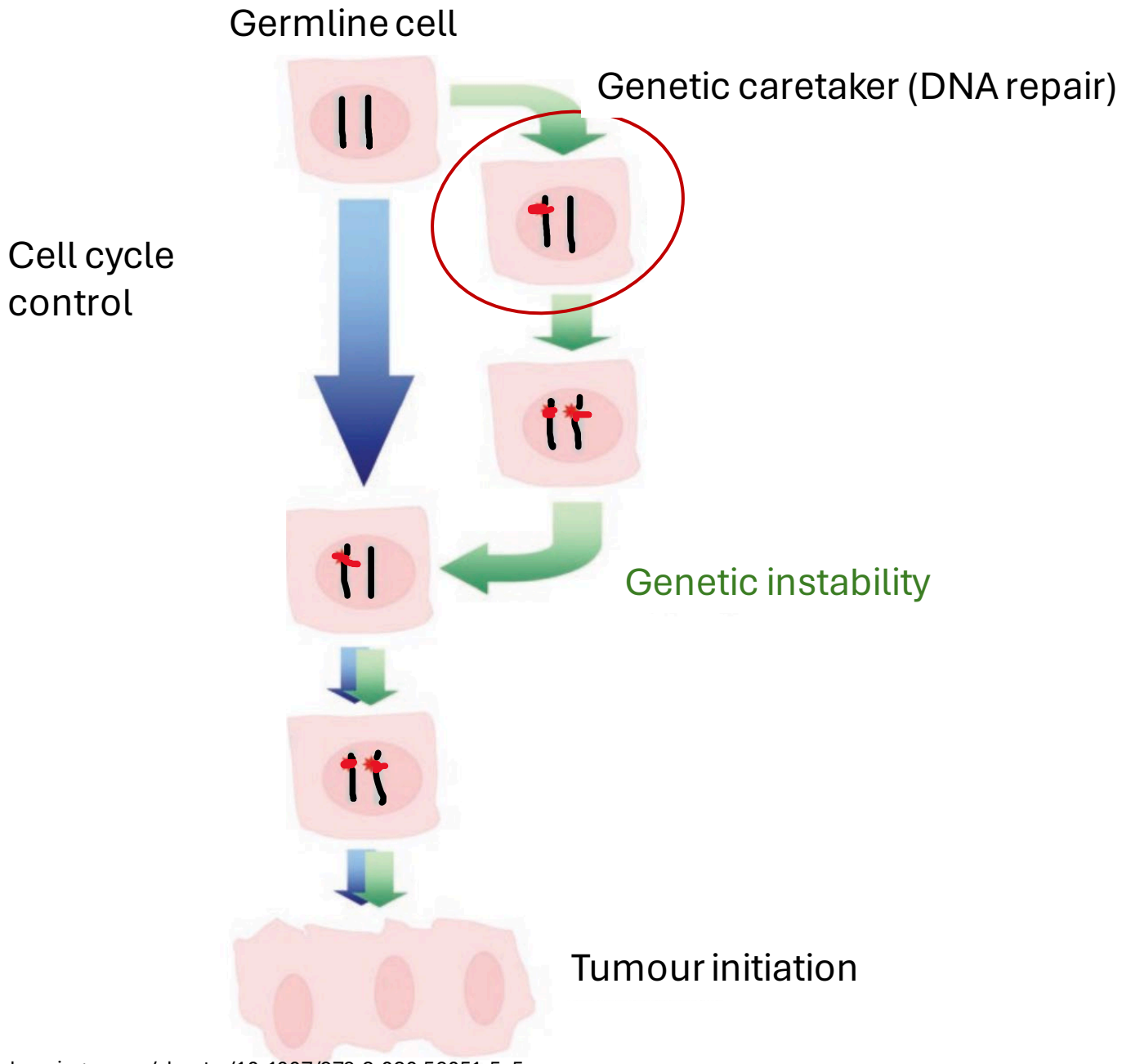
Tumour initiation

Modified from Fanale et al., 2021: https://link.springer.com/chapter/10.1007/978-3-030-56051-5_5

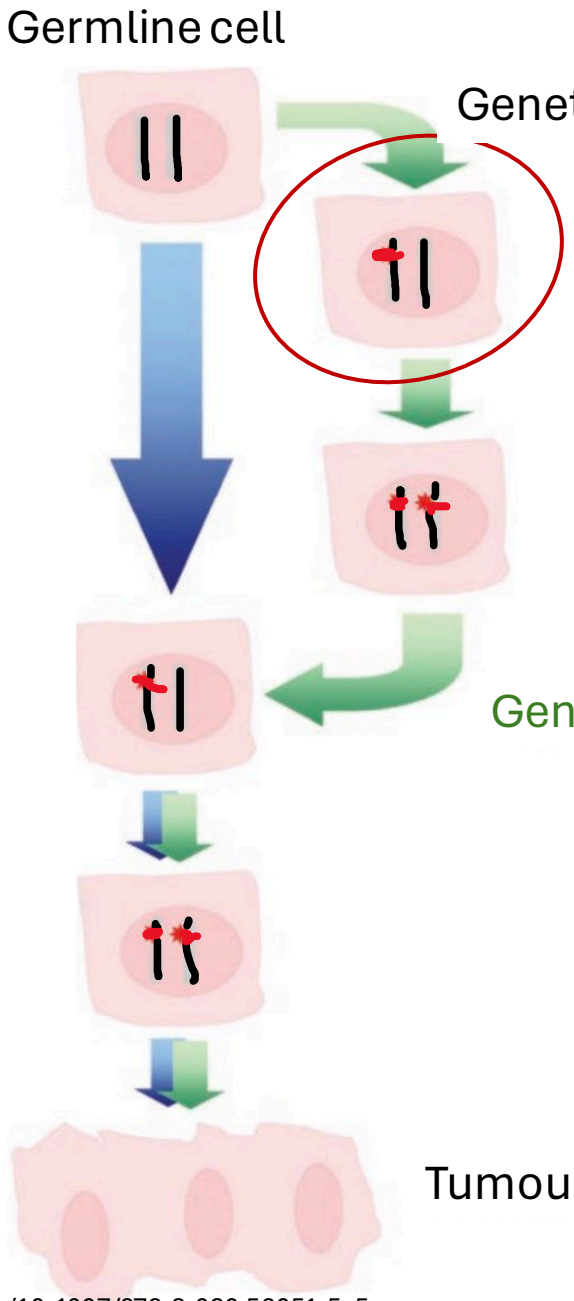
https://nf1andpninfo.com/



Modified from Fanale et al., 2021: https://link.springer.com/chapter/10.1007/978-3-030-56051-5_5



Modified from Fanale et al., 2021: https://link.springer.com/chapter/10.1007/978-3-030-56051-5_5



Gene	Syndrome
BRCA1 or 2	Familial breast cancer
ATM	Ataxia-telangiectasia
MLH1	Lynch syndrome

Modified from Fanale et al., 2021: https://link.springer.com/chapter/10.1007/978-3-030-56051-5_5

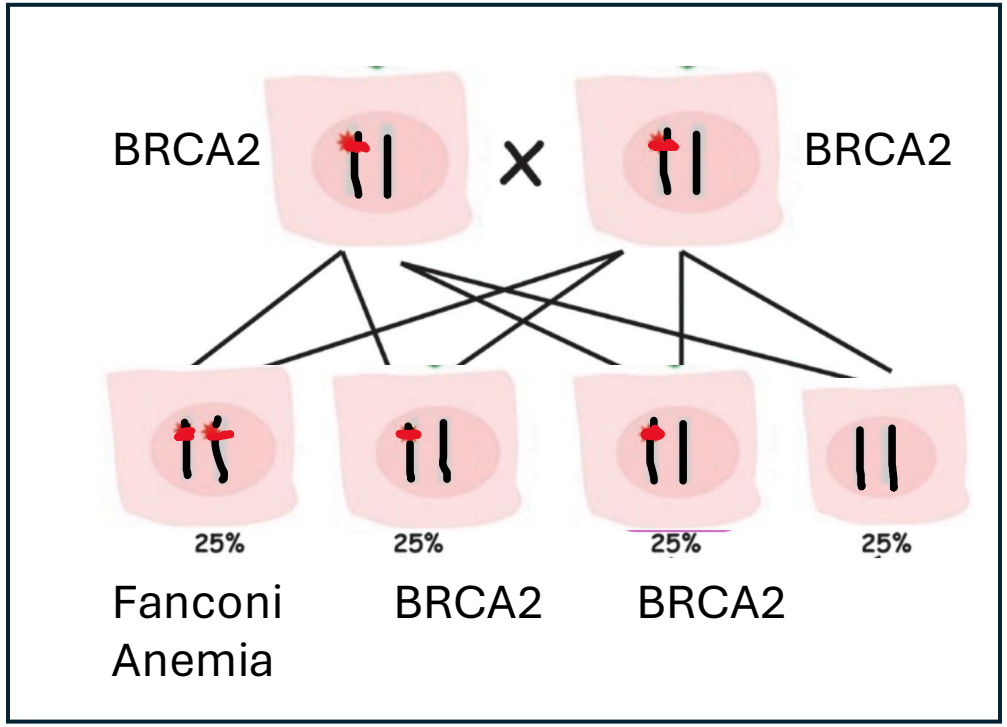
Germline cell

Genetic caretaker (DNA repair)

Cell cycle control

Genetic instability

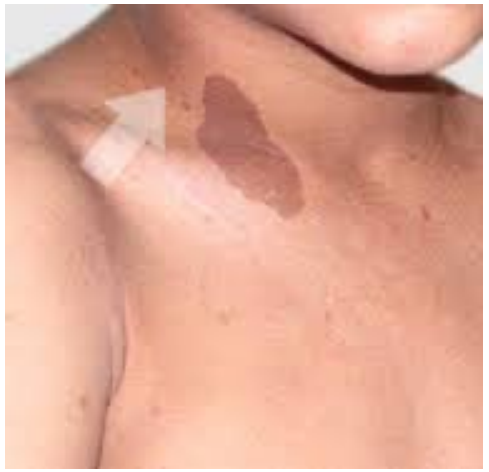
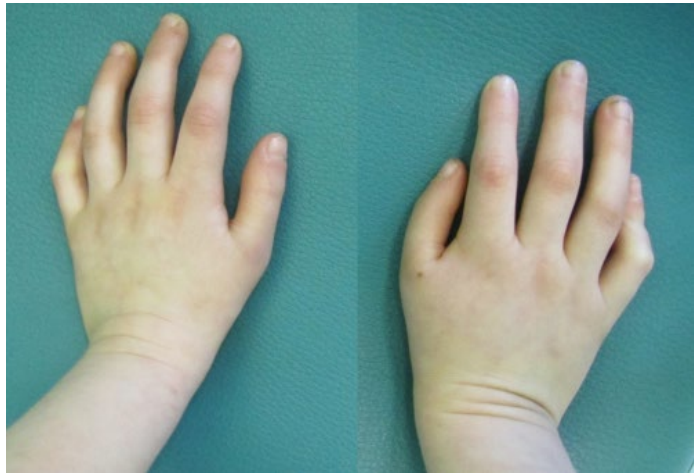
Tumour initiation



Modified from Fanale et al., 2021: https://link.springer.com/chapter/10.1007/978-3-030-56051-5_5

Think Predisposition when:

1. Personal or family history of a predisposition diagnosis
2. Features of a syndrome

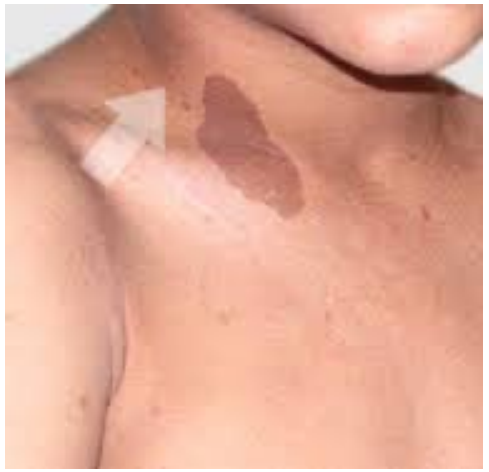
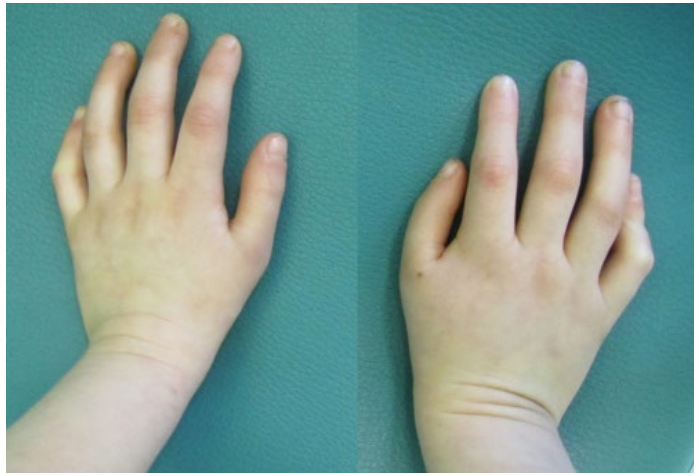




3. Suggestive personal or family cancer history

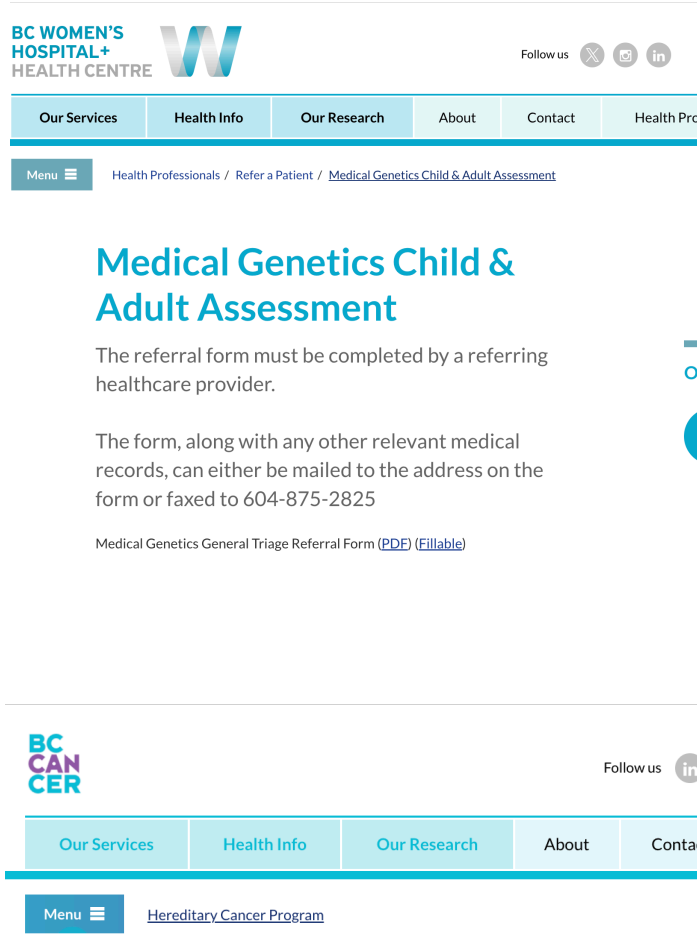
https://www.customink.com/fundraising/bwsawareness
https://nf1andpninfo.com/
https://moleculartcytogenetics.biomedcentral.com/articles/10.1186/s13039-020-00503-4

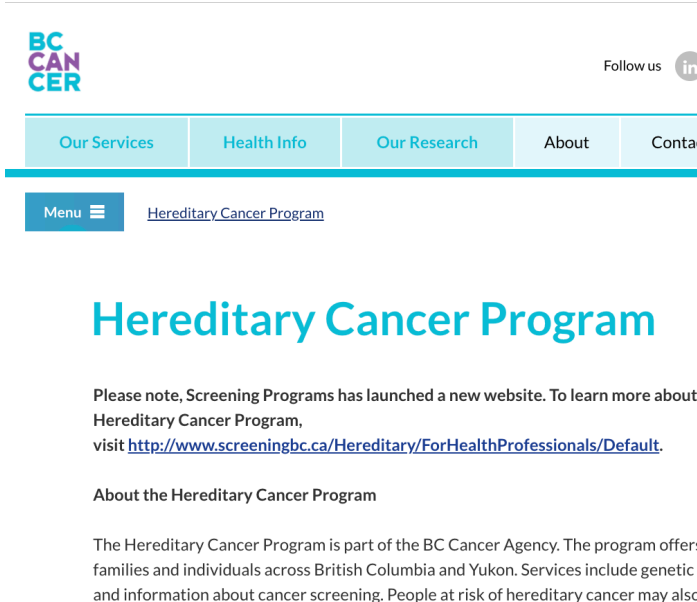
Think Predisposition when:

1. Personal or family history of a predisposition diagnosis
2. Features of a syndrome

3. Suggestive personal or family cancer history





https://www.customink.com/fundraising/bwsawareness
https://nf1andpninfo.com/
https://moleculARcytogenetics.biomedcentral.com/articles/10.1186/s13039-020-00503-4
http://www.bcwomens.ca/health-professionals/refer-a-patient/medical-genetics-child-adult-assessment
http://www.bccancer.bc.ca/health-professionals/clinical-resources/hereditary-cancer#Referral

Breast & Ovary

Your patient's personal history (refer to notes above) – at least 1 of:

- breast cancer diagnosed at age 35 or younger
- "triple negative" (ER, PR, HER2 receptors) breast cancer diagnosed at age 60 or younger
- breast cancer diagnosed at age 50 or younger AND no family history known due to adoption
- male breast cancer
- 2 primary breast cancers with at least 1 diagnosed at age 50 or younger
- ovarian cancer at any age
- breast or ovarian cancer and Ashkenazi Jewish heritage

Your patient's family history (includes your patient; refer to notes above) – at least 1 of:

- family member with confirmed *BRCA1*, *BRCA2*, or other gene mutation – refer for carrier testing
- a close relative with personal history as above
- 1 breast cancer and 1 ovarian cancer in close relatives
- 2 close relatives with breast cancer diagnosed at age 50 or younger
- 2 close relatives with ovarian cancer
- 3 breast cancers in close relatives, with 1 diagnosed at age 50 or younger
- breast or ovarian cancer and Ashkenazi Jewish heritage

http://www.bccancer.bc.ca/coping-and-support-site/Documents/Hereditary%20Cancer%20Program/

Polyposis

- personal history of:
  - 10 or more adenomatous polyps, OR
  - 2 or more hamartomatous polyps, OR
  - 5 or more serrated polyps proximal to the sigmoid colon (serrated polyps include: hyperplastic polyps, sessile serrated adenomas/polyps, traditional serrated adenomas) OR
  - multiple polyps of different types (adenomatous, hamartomatous, serrated, hyperplastic)
- family history of:
  - a confirmed mutation in a polyposis gene – refer for carrier testing
  - 1 or more close relatives with polyposis (as defined above)

http://www.bccancer.bc.ca/coping-and-support-site/Documents/Hereditary%20Cancer%20Program/

Lynch syndrome (Previous Name HNPCC)

Your patient's personal history (refer to notes above) – at least 1 of:

- any LS cancer with abnormal MSI/IHC screening test result (MMR deficient)
- colorectal cancer at age 40 or younger
- colorectal cancer at age 50 or younger AND no family history known due to adoption
- colorectal cancer and another LS cancer, at least 1 diagnosed at age 50 or younger

Your patient's family history (includes your patient; refer to notes above) – at least 1 of:

- family member with a confirmed *MLH1, MSH2, MSH6, PMS2,* or *EPCAM* gene mutation – refer for carrier testing
- a close relative with personal history as above
- 2 close relatives with a LS cancer, both diagnosed at age 50 or younger
- 3 or more close relatives with a LS cancer, at least 1 diagnosed at age 50 or younger

http://www.bccancer.bc.ca/coping-and-support-site/Documents/Hereditary%20Cancer%20Program/

Pancreatic

- personal history of:
  - pancreatic ductal adenocarcinoma (see also urgent storage of a blood sample)
  - intraductal papillary mucinous neoplasm or pancreatic intraepithelial neoplasia
  - pancreatic neuroendocrine tumour

- family history of:
  - 1 or more close relatives with pancreatic ductal adenocarcinoma

http://www.bccancer.bc.ca/coping-and-support-site/Documents/Hereditary%20Cancer%20Program/

Hereditary Cancer Program (HCP)

BC Cancer HCP staff live and work on the traditional, ancestral and unceded territories of the **Coast Salish peoples** from the xʷməθkʷəy̓əm (Musqueam), Sḵwx̱wú7mesh Úxwumixw (Squamish), and sə̓lilw̓ətaʔɬ (Tsleil-Waututh) Nations, **the Lək̓ʷəŋən speaking people** from the Esquimalt and Songhees First Nations and the **Stó:lō people** from the Matsqui and Sumas First Nations.

Hereditary Cancer Program (HCP)

Outline

- HCP
- Referral
- Portal
- Mainstream
- High Risk Clinic
- DNA banking

Hereditary Cancer Program (HCP)

BC Cancer - Screening & Prevention

Staff on site:

- Vancouver
- Abbotsford
- Victoria

Services Provided:

- Telephone
- Virtual Health
- Small # In-Person

Team:

- Medical Geneticists
- Genetic Counsellors
- Genetic Counselling Assistants
- Physicians
- Nurse Navigators
- Nurse Practitioners
- Clerical Staff
- Research Staff

https://m.maploco.com/visited-provinces-ca/mine.php?provinces=AB-BC-YT

Hereditary Cancer Program (HCP)

Reduce the morbidity and mortality from hereditary cancer syndromes

- Identify people with hereditary cancer syndromes
- Cancer risk assessment
- Provide screening and prevention recommendations
- Information to guide cancer treatment decisions
- Identify resources and supports

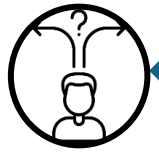
Genetic Counselling & Genetic Testing

High Risk Clinic

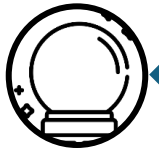
Hereditary Cancer Follow-Up Initiative

Hereditary Cancer Program (HCP)

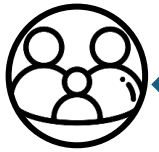
Why offer genetic testing?



TREATMENT



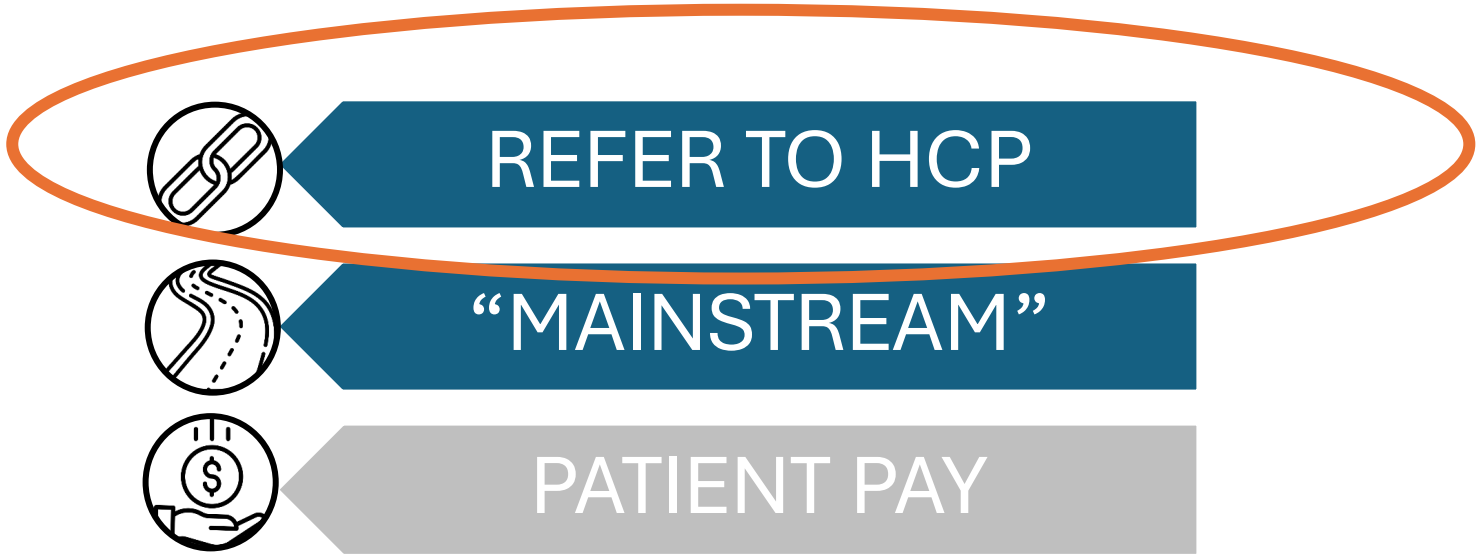
FUTURE CANCER RISK



FAMILY – PREVENT CANCER

Hereditary Cancer Program (HCP)

How do you arrange genetic testing for your patients?



Hereditary Cancer Program (HCP)

Refer to HCP

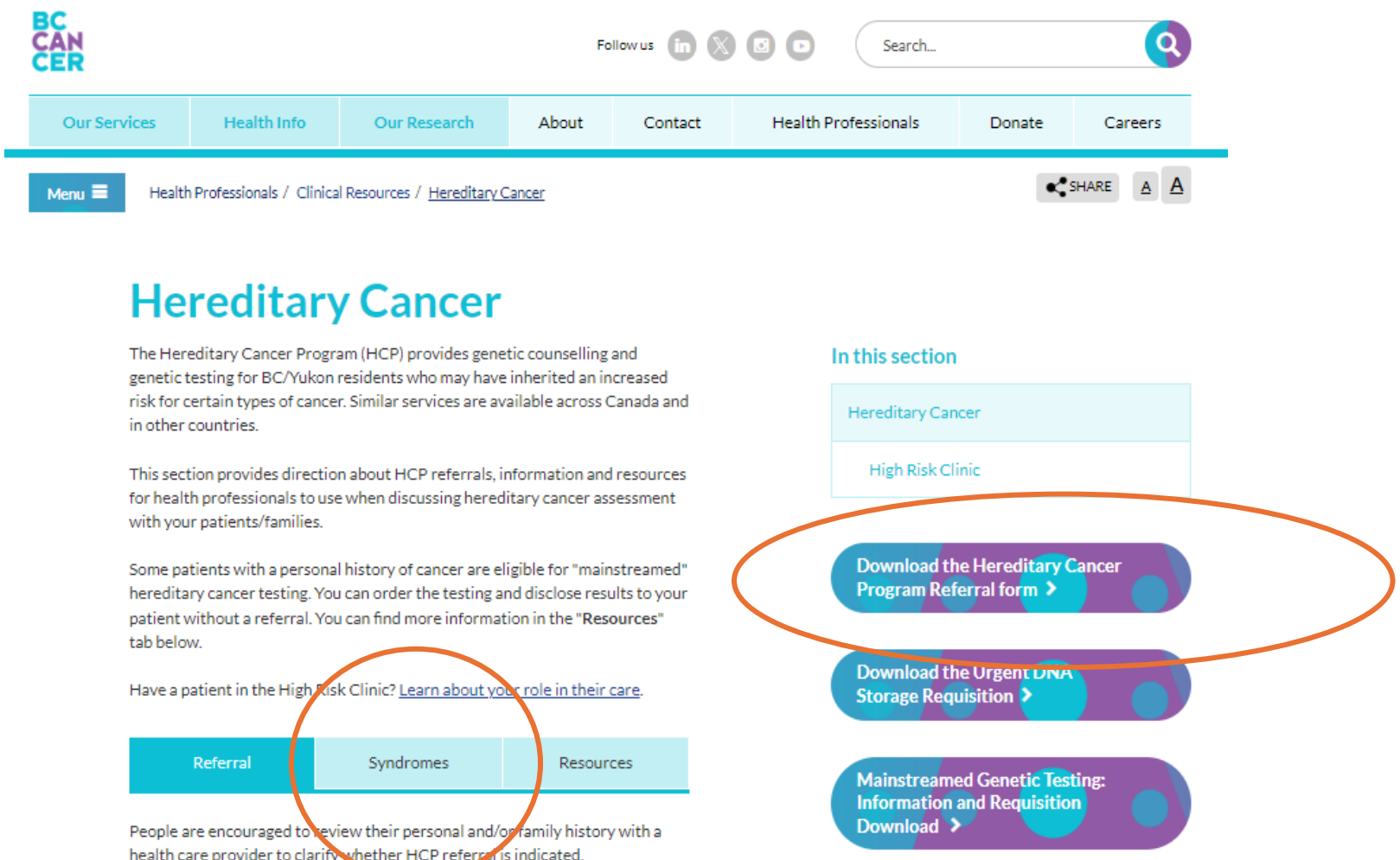
Criteria

- Criteria on website
- Patient outside criteria – OK to refer
- Any health care provider or patient can refer
- It is OK if people do not know their full family history
- Family history form not required if patient meets criteria on their own

High demand for services – working to reduce waitlist

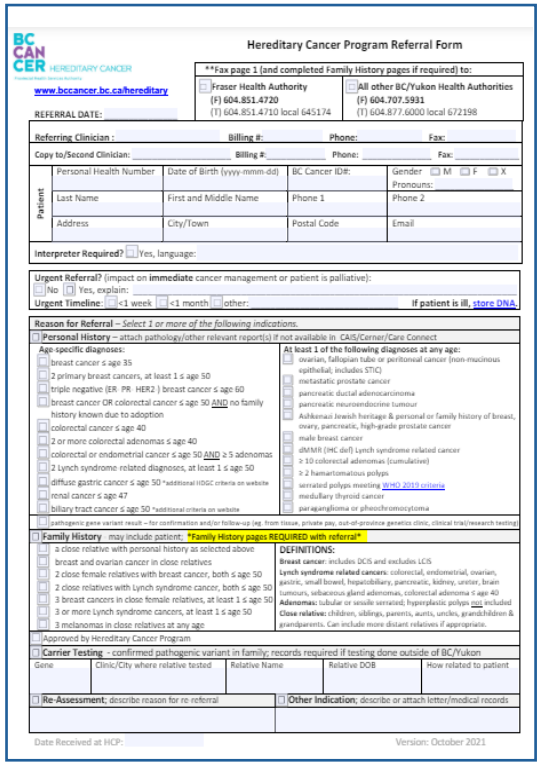
Hereditary Cancer Program (HCP)

Refer



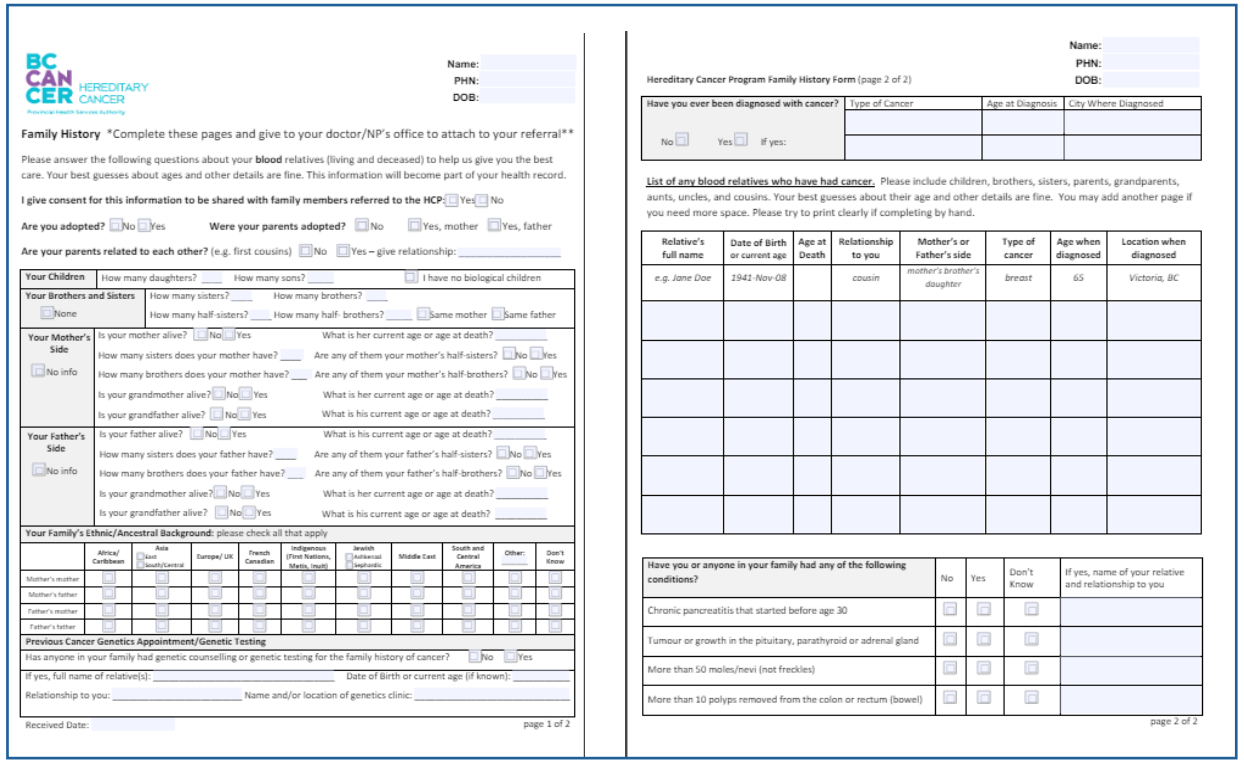
Hereditary Cancer Program (HCP)

Refer



Hereditary Cancer Program Referral Form

Page 1 = Provider



Family History *Complete these pages and give to your doctor/NP's office to attach to your referral**

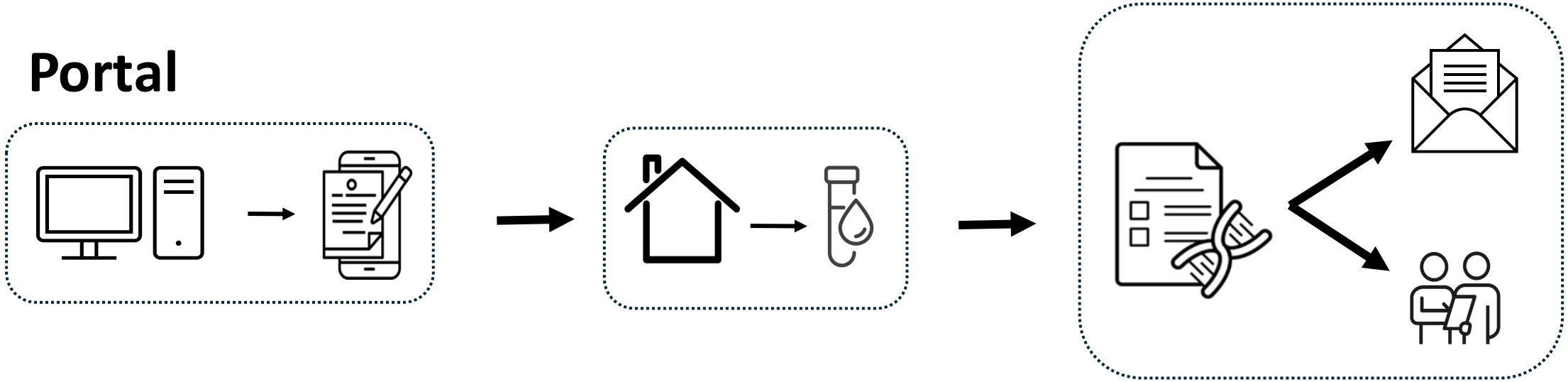
Hereditary Cancer Program Family History Form (page 2 of 2)

Page 2 & 3 = Patient

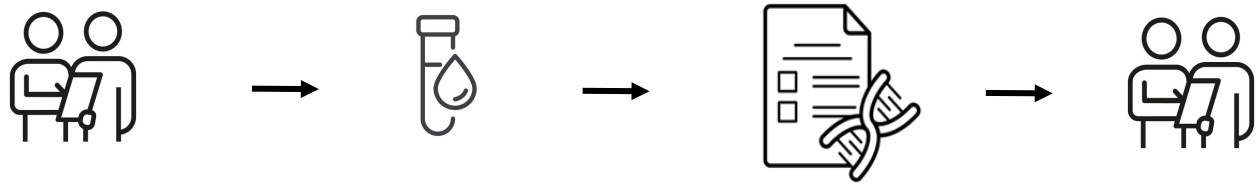
Hereditary Cancer Program (HCP)

Referral Reviewed and Triaged

Portal

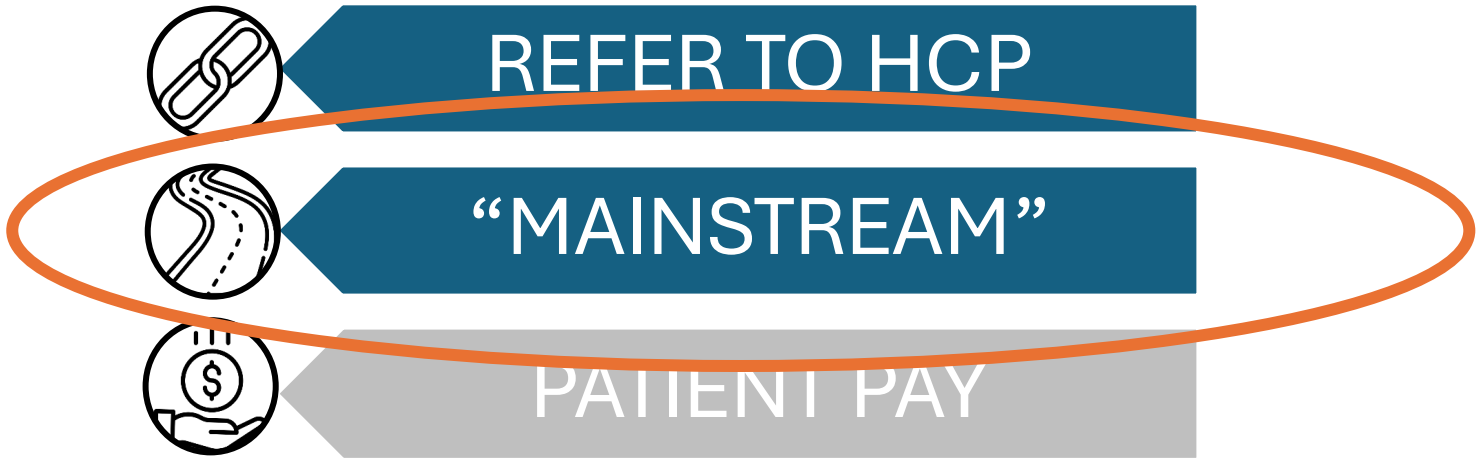


Traditional 1-1

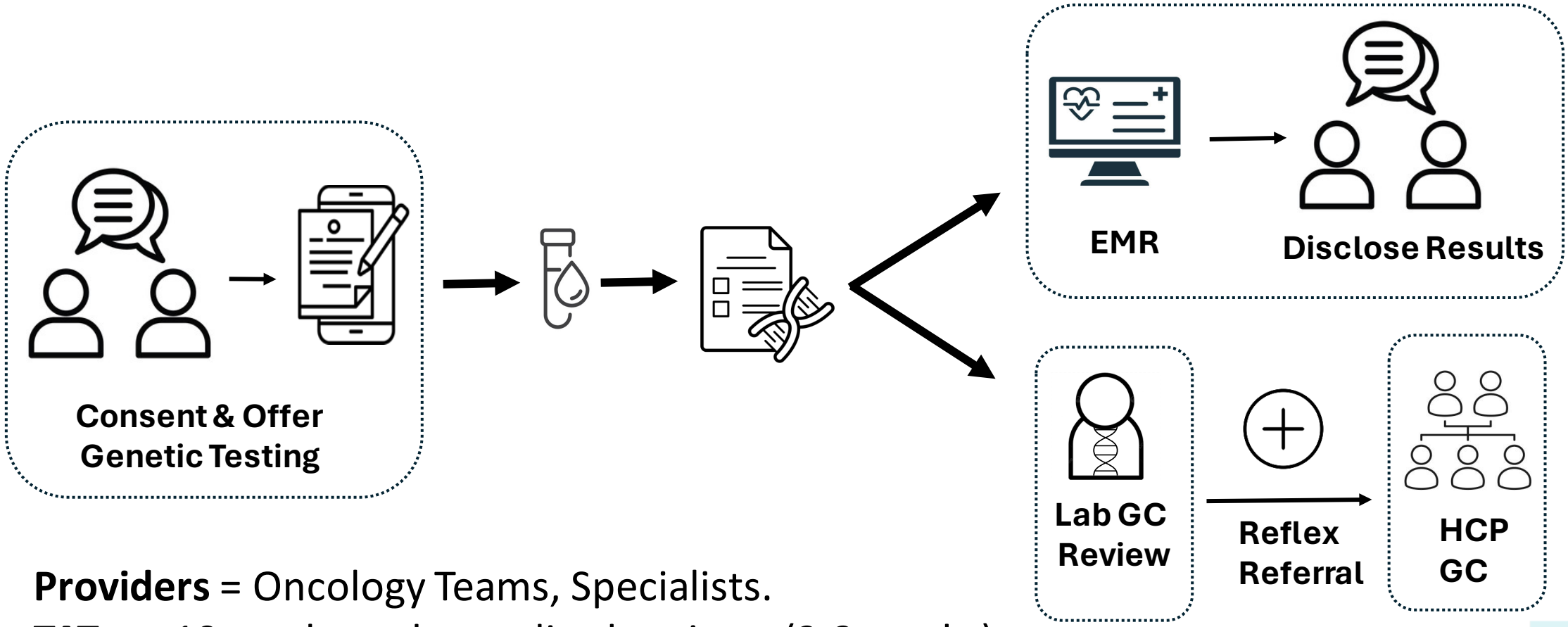


Hereditary Cancer Program (HCP)

How do you arrange genetic testing for your patients?



Hereditary Cancer Program (HCP)



Providers = Oncology Teams, Specialists.
TAT = < 10 weeks and expedited options (2-3 weeks)
GT Lab = CGL (84 genes) or Ambry (72 genes)

Hereditary Cancer Program (HCP)

Bringing genetic testing into the **Mainstream**

Oncology Clinic-Based Hereditary Cancer Genetic Testing in a Population-Based Health Care System

by Matthew Richardson [1], Hae Jung Min [2], Quan Hong [2], Katie Compton [2], Sze Wing Mung [2], Zoe Lohn [2], Jennifer Nuk [2], Mary McCullum [2], Cheryl Portigal-Todd [2], Aly Karsan [3], Dean Regier [4,5], Lori A. Brotto [6], Sophie Sun [2,7,8,*] and Kasmintan A. Schrader [2,9,10,*]

Cancers **2020**, *12*(2), 338; **https://doi.org/10.3390/cancers12020338**

- **Time to Results**
- **Acceptable Patients**
- **Acceptable Providers**

Hereditary Cancer Program (HCP)

BC CANCER

Follow us

Search...

Our Services | Health Info | Our Research | About | Contact | Health Professionals | Donate | Careers

Menu

Health Professionals / Clinical Resources / Hereditary Cancer

SHARE A A

Hereditary Cancer

The Hereditary Cancer Program (HCP) provides genetic counselling and genetic testing for BC/Yukon residents who may have inherited an increased risk for certain types of cancer. Similar services are available across Canada and in other countries.

This section provides direction about HCP referrals, information and resources for health professionals to use when discussing hereditary cancer assessment with your patients/families.

Some patients with a personal history of cancer are eligible for "mainstreamed" hereditary cancer testing. You can order the testing and disclose results to your patient without a referral. You can find more information in the "**Resources**" tab below.

Have a patient in the High Risk Clinic? Learn about your role in their care.

Referral | Syndromes | Resources

People are encouraged to review their personal and/or family history with a health care provider to clarify whether HCP referral is indicated.

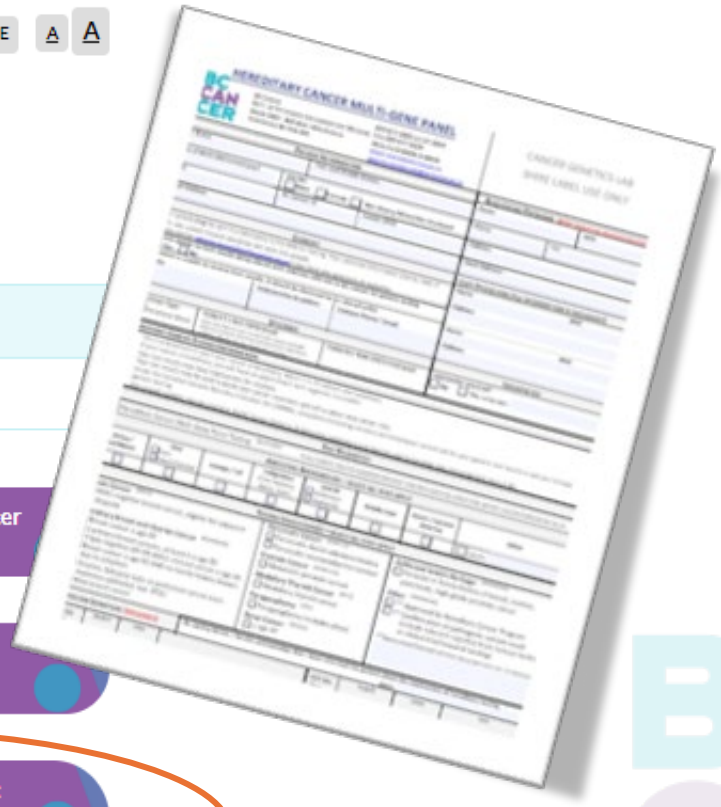
In this section

- Hereditary Cancer
- High Risk Clinic

Download the Hereditary Cancer Program Referral form ›

Download the Urgent DNA Storage Requisition ›

Mainstreamed Genetic Testing: Information and Requisition Download ›



Hereditary Cancer Program (HCP)

CANCER GENETICS AND GENOMICS LABORATORY
HEREDITARY CANCER MULTI-GENE PANEL

BC CANCER
DEPT. OF PATHOLOGY AND LABORATORY MEDICINE
ROOM 3307 - 600 WEST 10TH AVENUE
VANCOUVER BC V5Z-4E6

604-877-6000 EXT 67-2094
FAX: 604-877-6294
MON-FRI 8:30AM-4:30PM
WWW.CANCERGENETICSLAB.CA
GENETIC.COUNSELLOR@BCCANCER.BC.CA

CANCER GENETICS LAB

SHIRE LABEL USE ONLY

PATIENT INFORMATION

Last Name | First and Middle Names

Date of Birth (dd/mmm/yyyy) | Gender ☐ Male ☐ Female ☐ Non Binary/Other/Not Disclosed

PHN | BC Cancer ID | Cerner MRN

Email Address

REQUESTING PHYSICIAN NOTE: SIGNATURE REQUIRED (BELOW)

Name | MSC

Phone | Fax

Address

Email Address

CONSENT

Your sample **may** be sent to a laboratory in the USA for testing. Your personal information (name, date of birth, sex, cancer history) would be sent with the sample.
Please contact genetic.counsellor@bccancer.bc.ca if you have any questions or concerns.

Patient agrees to their results being shared with relatives referred to BC Cancer for genetic testing
☐ Yes ☐ No

If patient is unable to receive their results, it should be disclosed to (or shared with):

Name | Relationship to patient | Contact Phone / Email

COPY PHYSICIANS (ALL INFORMATION IS NECESSARY)

Name | MSC

Address

Name | MSC

Address

Hereditary Cancer Program (HCP)

Who is eligible for mainstream genetic testing?

TEST REQUESTED

☒ Hereditary Cancer Multi-Gene Panel Testing SQ HCAGPB — If your patient requires expedited testing for treatment planning, please email genetic.counsellor@bccancer.bc.ca

ANCESTRAL BACKGROUND – SELECT ALL THAT APPLY

Africa / Caribbean	Asia ☐ East ☐ South/Central	Europe / UK	Indigenous (First Nations, Metis, Inuit)	Jewish ☐ Ashkenazi ☐ Sephardic	Middle East	South / Central America	Other
☐	☐	☐	☐	☐	☐	☐	☐ Specify:

TESTING INDICATION(S) – SELECT ALL THAT APPLY

Breast Cancer (BRCA)
- ☐ HER2-negative breast cancer, eligible for adjuvant Olaparib

Hereditary Breast and Ovarian Cancer (INHERCAN)
- ☐ Breast cancer ≤ age 35
- ☐ 2 primary breast cancers, at least 1 ≤ age 50
- ☐ Triple negative (ER-PR-HER2-) breast cancer ≤ age 60
- ☐ Breast cancer ≤ age 50 AND no family history known due to adoption
- ☐ Ovarian, fallopian tube or peritoneal cancer (non-mucinous epithelial; incl. STIC)
- ☐ Male breast cancer

Pancreatic Cancer (PANC CA)
- ☐ Pancreatic ductal adenocarcinoma
- ☐ Pancreatic neuroendocrine tumour

Prostate Cancer (INHERCAN)
- ☐ Metastatic prostate cancer

Medullary Thyroid Cancer (MTC)
- ☐ Medullary thyroid cancer

Paraganglioma (PGL)
- ☐ Paraganglioma (includes pheo)

Renal Cancer (RENAL)
- ☐ ≤ age 47

Ashkenazi Jewish Heritage (INHERCAN)
- ☐ Personal or family history of breast, ovarian, pancreatic, high-grade prostate cancer

Other (INHERCAN)
- ☐ ** Approved by Hereditary Cancer Program
- ☐ ** Confirmation of pathogenic variant result (include relevant report(s) from tumour testing or clinical trial/research testing)

**INDICATION/VARIANT DETAILS (REQUIRED FOR TEST TO PROCEED):

PHYSICIAN SIGNATURE (REQUIRED) — By signing below, I hereby acknowledge that I have informed the patient about the implications of hereditary testing. DATE

LAB USE ONLY	PB EDTA	Other		HCP USE ONLY	Progeny	Initials	Date

The personal information collected on this form is collected under the authority of the Personal Information Protection Act. The personal information is used to provide medical services requested on this requisition. The information collected is used for quality assurance, management and disclosed to healthcare practitioners involved in providing care or when

Hereditary Cancer Program (HCP)

Considerations:

Understanding a factor in my personal / family history of cancer.

Learn of other cancer risks, screening and prevention.

Information may be used for my current care.

Help my family – give options.

Increased worry.

Strained family relationships.

Hereditary Cancer Program (HCP)

Mainstream – this year so far …

- ~ 200 samples / month
- > 500 Genetic Test Results Reported
- ~12% Positive Rate
- Indication: Metastatic Prostate >> Breast > Pancreatic > Ovarian

Hereditary Cancer Program (HCP)

High Risk Clinic

Team:

- Physician
- Nurse Practitioners
- Nurses

Referrals:

- Genetic Counsellor disclosing (+) result
- GP if Pt discharged from oncology care and has breast tissue
- Pt new to GP practice with variant identified outside of BC – refer to HCP

Hereditary Cancer Program (HCP)

High Risk Clinic

Eligibility

- Not under the care of an oncologist
- People with breasts and a mutation in a gene associated with > 25% lifetime risk for breast cancer (ie, BRCA1/2, ATM, CHEK2, CDH1, PALB2).
- People with Li Fraumeni syndrome (*TP53*), a syndrome associated with an increased risk of many different cancers.
- People with breasts between ages 30 to 50 with Neurofibromatosis 1 because of increased breast cancer risk.

Hereditary Cancer Program (HCP)

High Risk Clinic

- Physical Exam
- Screening management for breast cancer: MRI & Mammograms
- Medication for cancer risk reduction
- Prophylactic surgery referral
- Yearly follow-up appointments

Primary care provider for new problems in between visits (like a breast lump or pain or discharge).

Hereditary Cancer Program (HCP)

Caring for Patients with Pathogenic Variants

- Genetic Counsellor / Medical Geneticist Letter
  - Recommendations for the patient
  - In some cases, recommendations for family members
- Breast related pathogenic variants – High Risk Clinic

- Hereditary Cancer Follow Up Initiative
  - Annual survey check-in

Hereditary Cancer Program (HCP)

Jewish BRCA1/BRCA2 Testing Program

- 1/40 (2.5%) people with Ashkenazi Jewish ancestry have a *BRCA1/BRCA2* pathogenic variant
- Chance increases with family history of breast, ovarian, pancreatic or prostate cancer

Pilot:

- Genetic testing (BRCA1/BRCA2 only) to any person of Jewish ancestry regardless of family history
- https://brcainbc.ca/

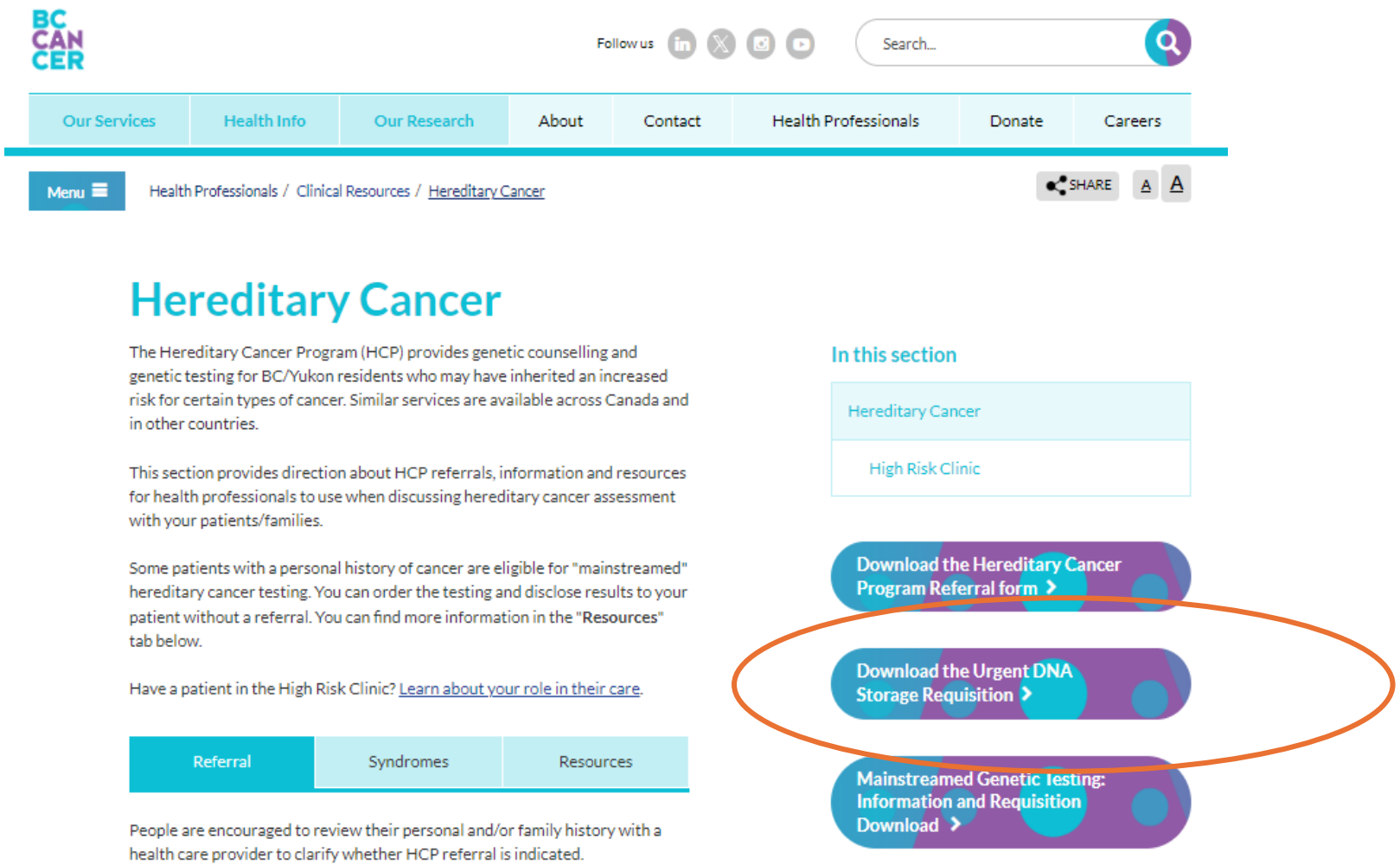
BC CANCER FOUNDATION

diamond FOUNDATION

BC CAN

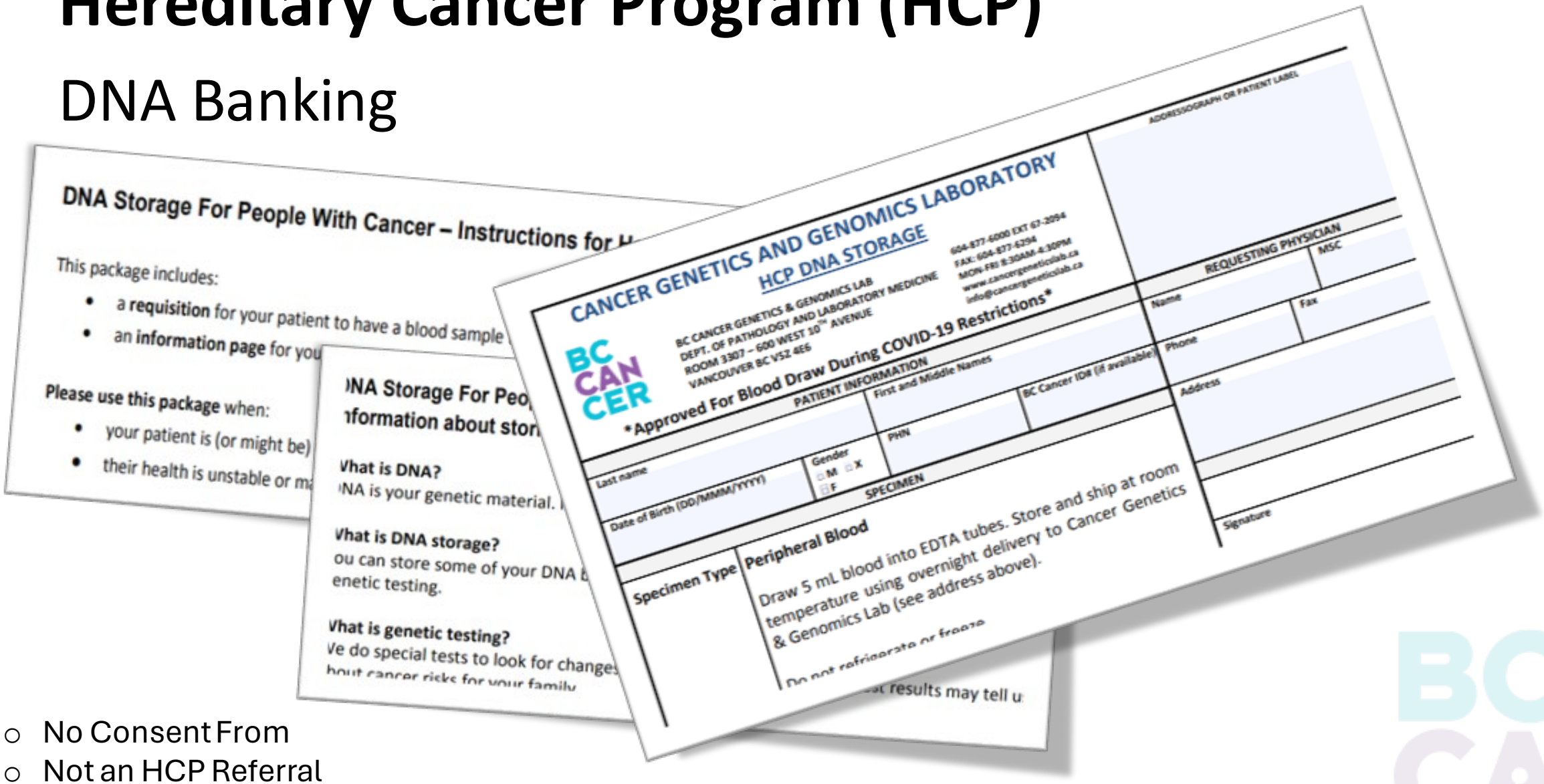
Hereditary Cancer Program (HCP)

DNA Banking



Hereditary Cancer Program (HCP)

DNA Banking



- No Consent From
- Not an HCP Referral

Hereditary Cancer Program (HCP)

General: HereditaryCancer@bccancer.bc.ca

Mainstream: Genetic.Counsellor@bccancer.bc.ca

High Risk Clinic: HCPHRC@bccancer.bc.ca

1.800.663.3333 local 672198

www.bccancer.bc.ca/hereditary

Mary-Jill Asrat, MSc CCGC
Genetic Counsellor & HCP Clinical Coordinator
mjasrat@bccancer.bc.ca