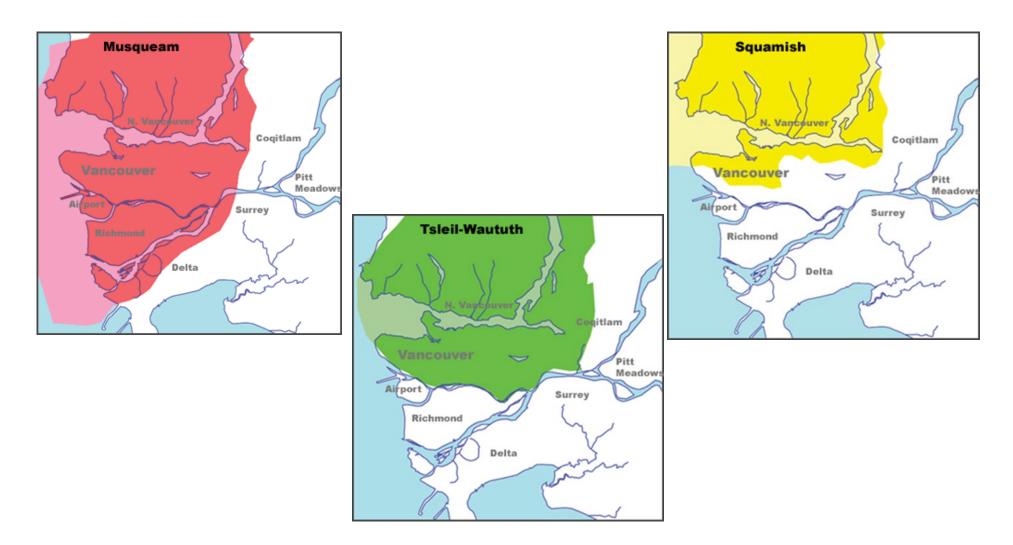
Cracking the Code on Cancer Predisposition Syndromes

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



Disclosure

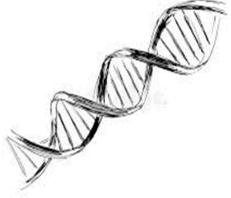
• A family member to Linlea Armstrong owes shares in a genomic testing company, Alamya

Mitigation

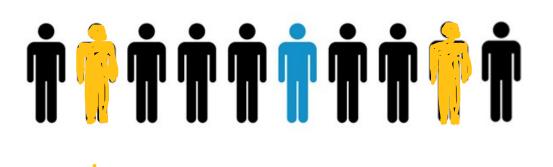
- No tests from that company will be discussed today
- This was disclosed in advance

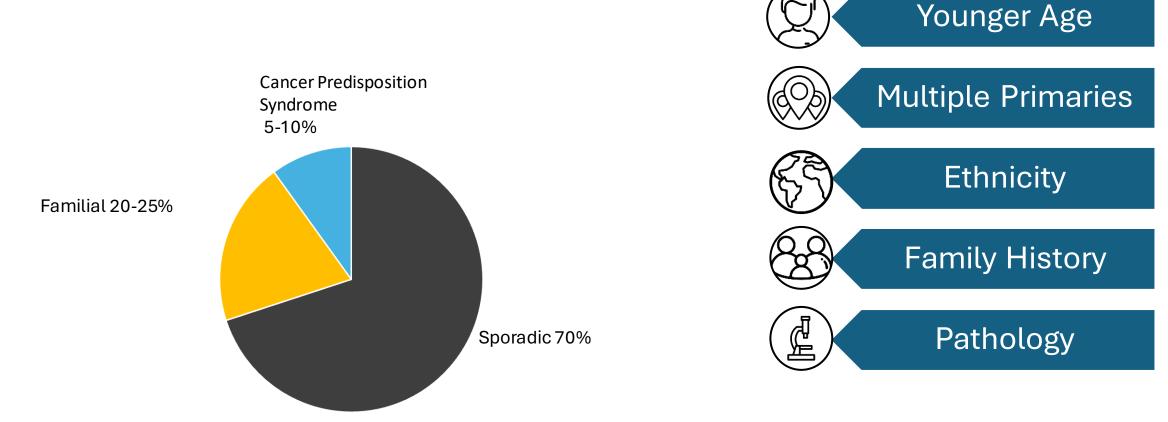
Objectives

- 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.

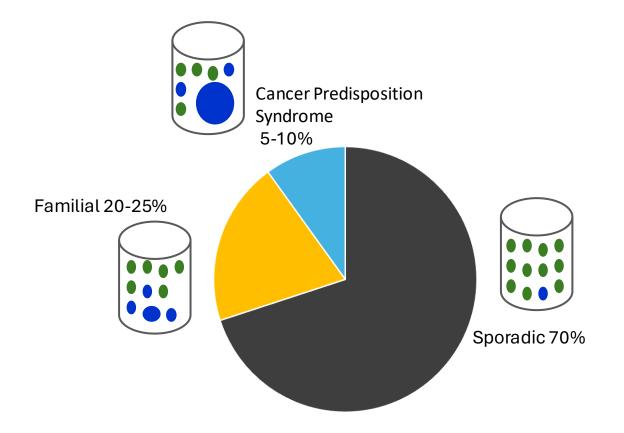


Cancer Predisposition Syndrome

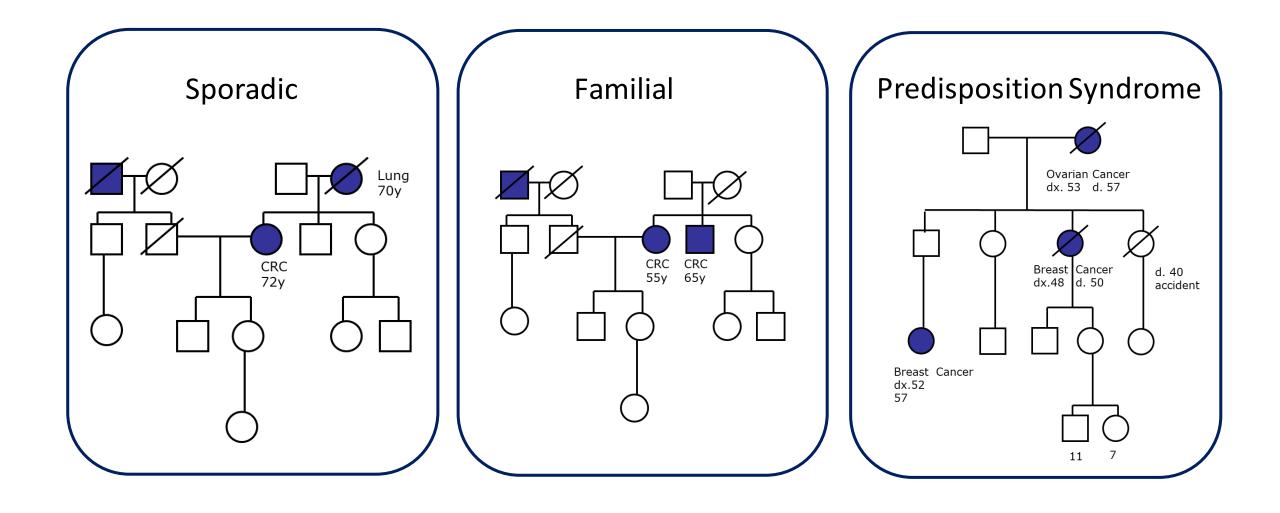




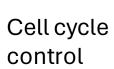
Model for Discussing Risk Factors



Genetic Factors Environmental Factors



Ascertainment

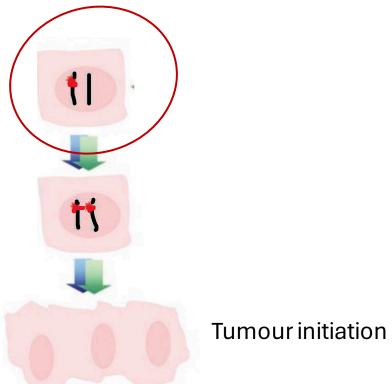


Germline cell

11



Germline cell



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

Tumour initiation

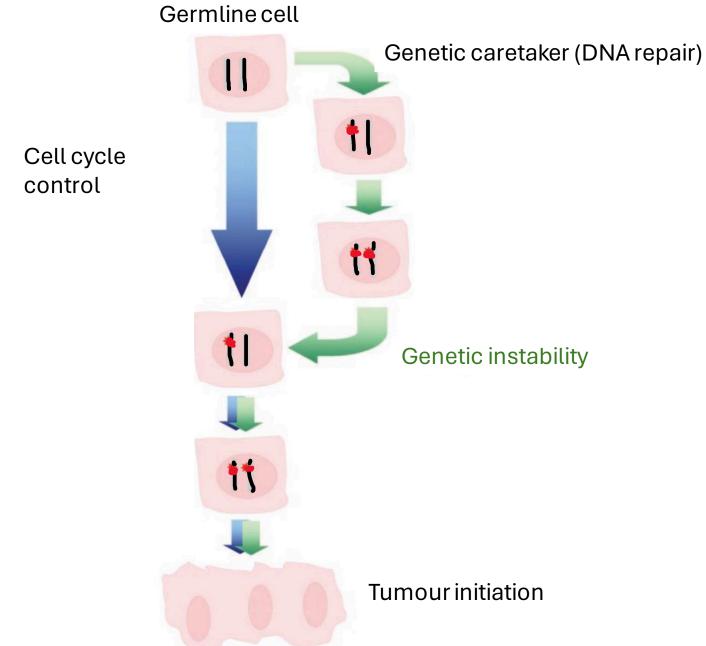
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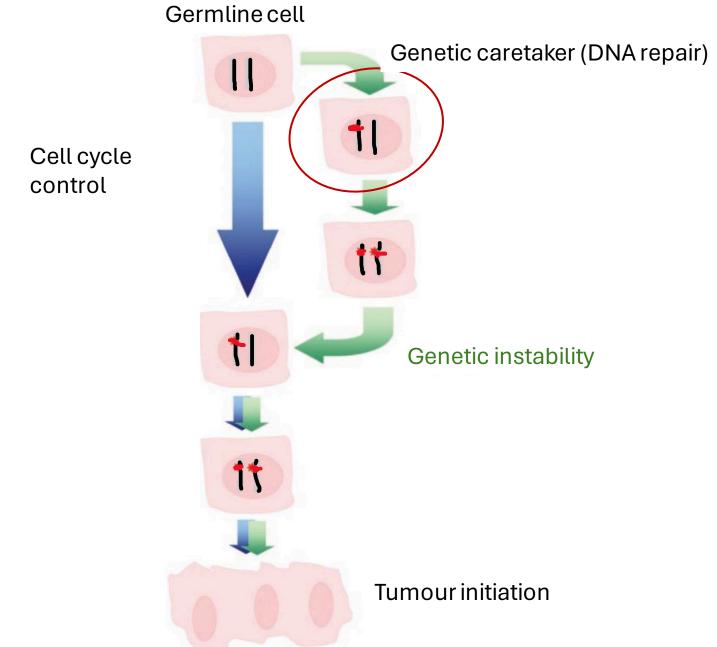


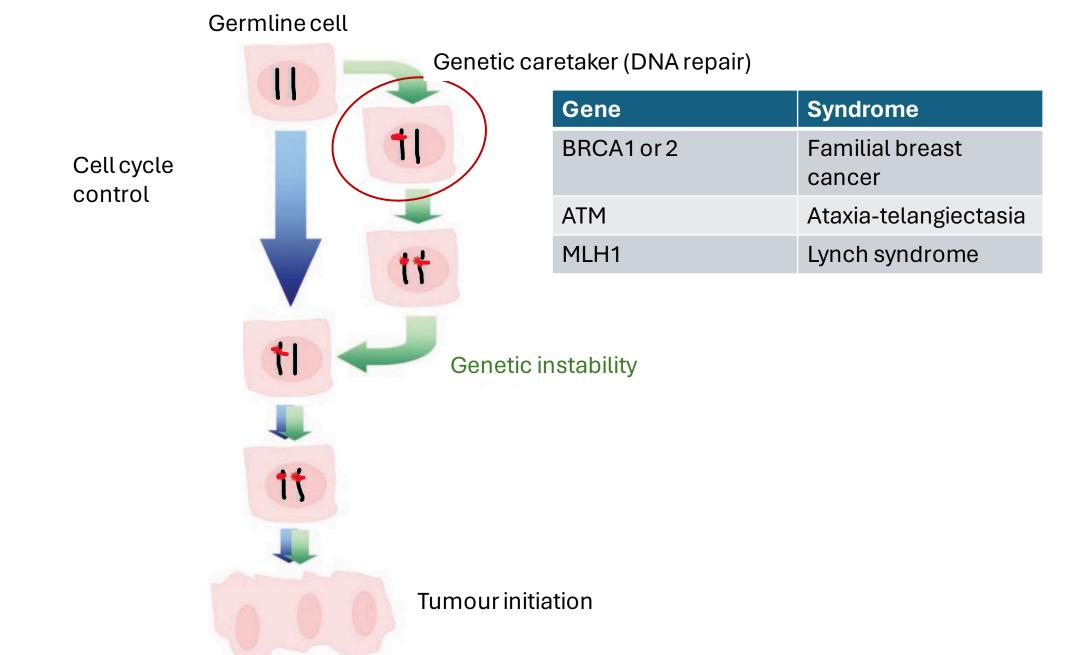
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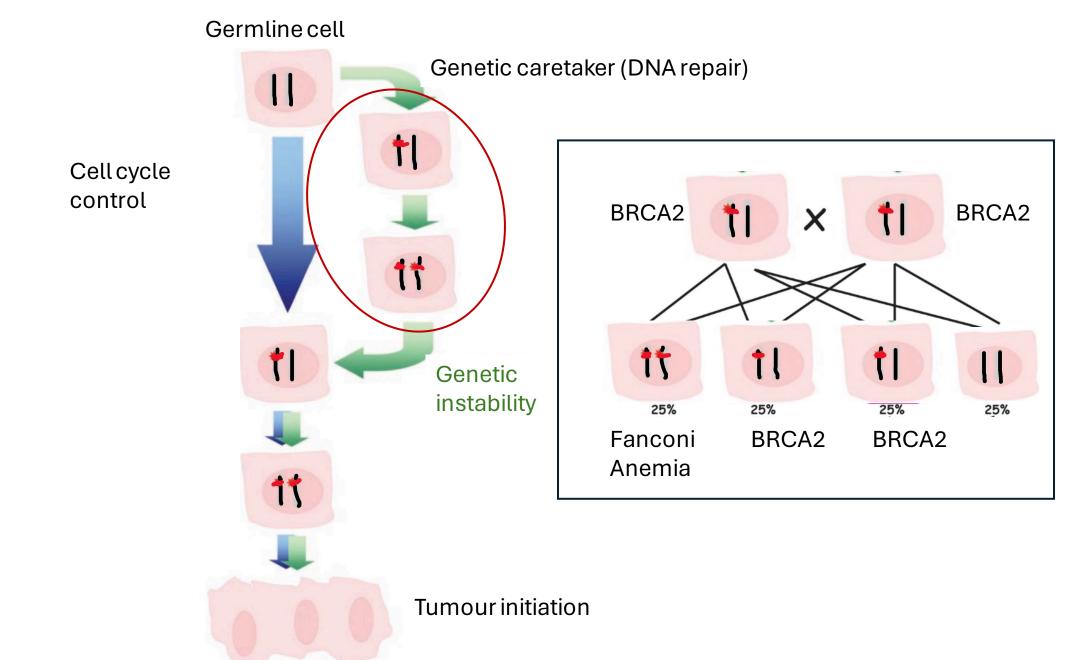
Tumour initiation

Modified from Fanale et al., 2021: https://link.springer.com/chapter/10.1007/978-3-030-56051-5_5 https://nf1andpninfo.com/









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

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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



Medical Genetics Child & Adult Assessment

The referral form must be completed by a referring healthcare provider.

The form, along with any other relevant medical records, can either be mailed to the address on the form or faxed to 604-875-2825

Medical Genetics General Triage Referral Form (PDF) (Fillable)

Follow us (
Our Services	Health Info	Our Research	About	Conta				
Menu = <u>Hered</u>	itary Cancer Program							

Hereditary Cancer Program

Please note, Screening Programs has launched a new website. To learn more about Hereditary Cancer Program, visit <u>http://www.screeningbc.ca/Hereditary/ForHealthProfessionals/Default</u>.

About the Hereditary Cancer Program

The Hereditary Cancer Program is part of the BC Cancer Agency. The program offer: families and individuals across British Columbia and Yukon. Services include genetic and information about cancer screening. People at risk of hereditary cancer may also

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

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
 - o 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)

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

Pancreatic

- personal history of:
 - o pancreatic ductal adenocarcinoma (see also urgent storage of a blood sample)
 - o intraductal papillary mucinous neoplasm or pancreatic intraepithelial neoplasia
 - o pancreatic neuroendocrine tumour
- family history of:
 - o 1 or more close relatives with pancreatic ductal adenocarcinoma

BC Cancer HCP staff live and work on the traditional, ancestral and unceded territories of the **Coast Salish peoples** from the x^wməθk^wəỷəm (Musqueam), Skwxwú7mesh Úxwumixw (Squamish), and səlilwəta? (Tsleil-Waututh) Nations, the Ləkwəŋən speaking people from the **Esquimalt and Songhees First Nations and** the Stó:lo people from the Matsqui and Sumas First Nations.





Outline

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



BC Cancer - Screening & Prevention

Staff on site:

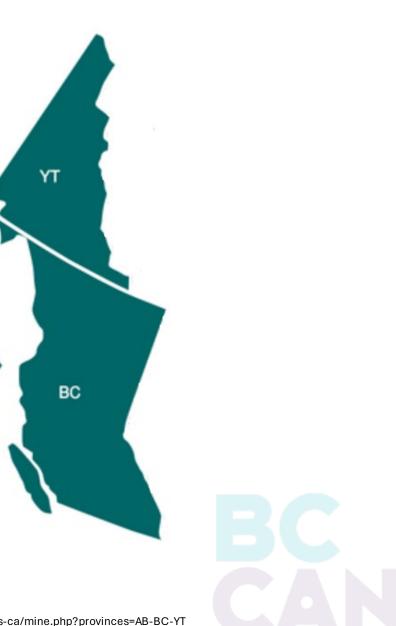
- \circ Vancouver
- \circ Abbotsford
- o Victoria

Services Provided:

- \circ Telephone
- Virtual Health
- Small # In-Person

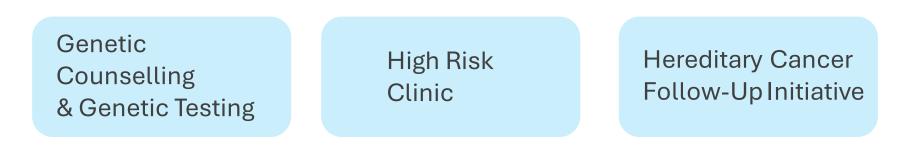
Team:

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



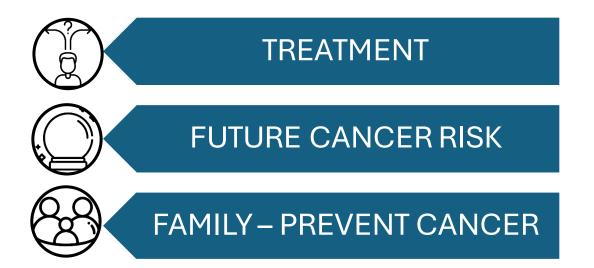
Reduce the morbidity and mortality from hereditary cancer syndromes

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





Why offer genetic testing?





How do you arrange genetic testing for your patients?

REFER TO HCP	
"MAINSTREAM"	
PATIENT PAY	

BC CAN

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



Refer

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Menu 🗮 Health	Professionals / Clinica	I Resources / <u>Hereditary (</u>	Cancer			<	

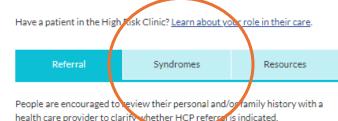


Hereditary Cancer

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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.







Refer

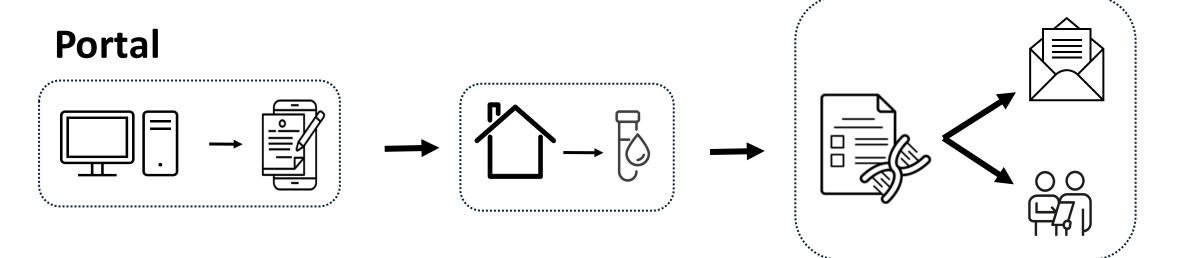
Hereditary Cancer Program Referral Form ##Exclusive Cancer Program Referral Form ##Fax page 1 (and completed Family History pages if required) to:		Name: PHN: DOB:		r Program Family	,	· ·			Name: PHN: DOB:	
(F) 604.851.4720 (F) 604.707.5351 RAL DATE: (T) 604.851.4710 local 645174 (T) 604.877.6000 local 672198	Provincial Health Services Authority	555.	Have you ever be	en diagnosed wit	h cancer? Type	of Cancer	4	Age at Diagno	sis City When	re Diagnosed
ing Clinician : Billing #: Phone: Fax: //Second Clinician: Billing #: Phone: Fax:	Family History *Complete these pages and give to your do		No	(es 🔲 If yes:						
Vysecond Clanical: Pairs: Promit: Promit:Pro	Please answer the following questions about your blood relatives (lin care. Your best guesses about ages and other details are fine. This in		List of any bloo	d relatives who h	nave had cancer.	Please inclu	ude children,	, brothers, si	sters, parents	, grandparents,
ast Name First and Middle Name Phone 1 Phone 2 Address City/Town Postal Code Email	I give consent for this information to be shared with family member Are you adopted? No Yes Were your parents adopted	ers referred to the HCP: Yes No d? No Yes, mother Yes, father	, ,	nd cousins. Your space. Please try	-			etails are fine	e. You may a	id another page
reter Required? Types, language:	Are you adopted? Were your parents adopted Are your parents related to each other? (e.g. first cousins)		Relative's full name		Age at Relation Death to yo		other's or ther's side	Type of cancer	Age when diagnosed	Location whe diagnosed
t Referral? (impact on immediate cancer management or patient is palliative):	Your Children How many daughters? How many sons? Your Brothers and Sisters How many sisters? How many brot	I have no biological children	e.g. Jane Doe	1941-Nov-08	cous		er's brother's loughter	breast	65	Victoria, BC
Timeline: <pre></pre>	None How many half-sisters? How many half	f- brothers? Same mother Same father								
nal History – attach pathology/other relevant report(s) if not available in CARS/Cerner/Care Connect CRI clagnoses: Al loss1 of the following Glagnoses: Al loss1 of the following Glagnoses at any age: autor of the clagnose of the following Clagnose of the relevant of the releva	Your Mother's Is your mother alive? No. Yes Wh Side How many sisters does your mother have? Are a	nat is her current age or age at death? any of them your mother's half-sisters? No Yes								
imary breast cancers, at least 1 ≤ ago 50 epithelial; includes STIC) le negative (ER- PR- HER2) breast cancer ≤ age 60 parrevait ductal adenocarrinoma	No info How many brothers does your mother have? Are a Is your grandmother alive? No Yes Wh	any of them your mother's half-brothers?				_				
ast cancer OR colorectal Cancer s age 50 AND no family ory known due to adoption rescal cancer s age 40 cores and an another the second or family history of breast, rescal cancer s age 40		hat is his current age or age at death?				_				
more colorectal adenomas 5 age 40 rectal or endometrial cancer r s age 50 AND > 5 adenomas > 10 conformetal adenomas (cumulative) > 10 conformetal adenomas (cumulative)	Side How many sisters does your father have? Are a	hat is his current age or age at death? any of them your father's half-sisters?NoYes				_				
nch syndhome related diagnoses, at least 1 ≤ age 50 sze gastric cancer ≤ age 50 *sdifesel HOC criteria es webste Lancer ≤ age 50 *sdifesel HOC criteria es webste Lancer ≤ age 4	No info How many brothers does your father have? Are a Is your grandmother alive? No Yes Wh	any of them your father's half-brothers? No Yes				_				
ary tract cancer ≤ age 50 *additional orderia on website par aganglioma or pheochromocytoma	Is your grandfather alive? No Yes Wh	hat is his current age or age at death?								
genc per variant read: - training and or training of the start of the	Your Family's Ethnic/Ancestral Background: please check all that apply	Jawish South and								
Definition with provide interpret and excern along and a second along a	Arica/ Carbbean Carbonia Europe/UK French (Canadan Metic, Inzt) Mother's mother	Andhanad Septradic Middle East America Other: Don't Know	Have you or any conditions?	one in your family	had any of the fo	llowing	No Yes	Don't Know		ne of your relationship to you
reast cancers in close female relatives, at least 1 s age 50 Advancess: Leider as usake strateging advancess, at least 1 s age 50 er more Lynch syndrome cancers, at least 1 s age 50 Belommain: Loders relatives: chiden, utiling, parent, aunts, under, grandhilten & wandarents. Cancer relatives at any ae	Mother's tather		Chronic pancreat	itis that started be	fore age 30		66	1		
ved by Hereditary Cancer Program r Testing - confirmed pathogenic variant in family; records required if testing done outside of BC/Yukon	Previous Cancer Genetics Appointment/Genetic Testing Has anyone in your family had genetic counselling or genetic testing for th	he family history of cancer?	Tumour or growt	h in the pituitary,	parathyroid or ad	renal gland				
Clinic/City where relative tested Relative Name Relative DOB How related to patient	If yes, full name of relative(s):	Date of Birth or current age (if known):		les/nevi (not freci	,					
sessment; describe reason for re referral Other Indication; describe or attach letter/medical records	Received Date:	page 1 of 2	More than 10 po	yps removed from	the colon or rect	um (bowel)				page 2
sceived at HCP: Version: October 2021	HELFED DILL.	P-0								

BC CAN

Page 1 = Provider

Page 2 & 3 = Patient

Hereditary Cancer Program (HCP) Referral Reviewed and Triaged



Traditional 1-1

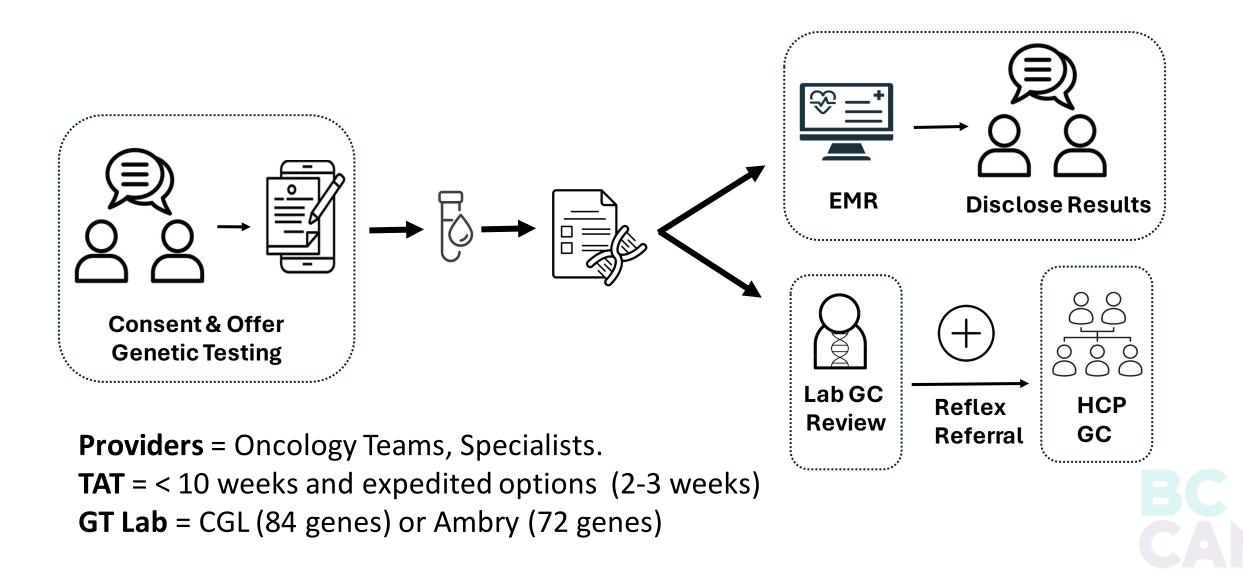




How do you arrange genetic testing for your patients?



BC CAN



Bringing genetic testing into the Mainstream

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

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

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





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Our Services Health Info			Our Research	About	Contact	Health Professionals	Donate	Careers	
	Menu 🗮 Health	Professionals / Clinica	I Resources / <u>Hereditary C</u>	<u>Cancer</u>			<	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.

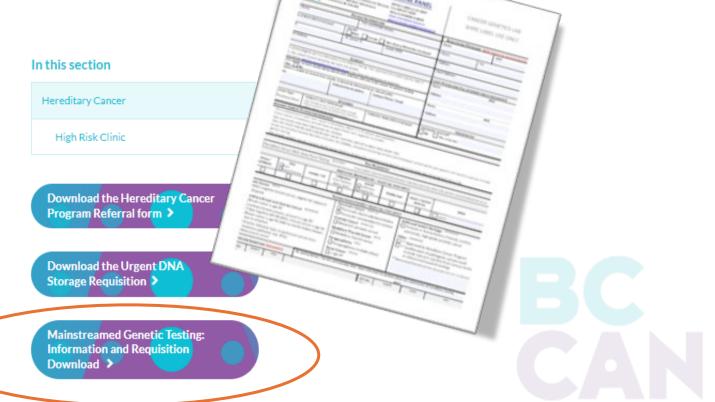
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Have a patient in the High Risk Clinic? Learn about your role in their care.

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.



CANCER	GENETICS AND	GENOM	ICS LABORATORY				
HEREDITARY CANCER MULTI-GENE PANEL					CANCER GENETICS LAB		
CAN CER	BC CANCER DEPT. OF PATHOLOGY AND LABORA ROOM 3307 - 600 WEST 10TH AV VANCOUVER BC V5Z-4E6	TORY MEDICINE FA	04-877-6000 ext 67-2094 ax: 604-877-6294 10n-Fri 8:30AM-4:30PM <u>ww.cancergeneticslab.ca</u> <u>enetic.counsellor@bccancer.bc.ca</u>	SHIRE LABEL USE ONLY			
	PATIENT IN	NFORMATION		REQUESTING PHYSICIAN NOTE: SIGNATURE REQUIRED (BELOW)			
Last Name	ast Name First and Middle Names			Name	MSC		
Date of Birth (dd/mmm/yyyy) Gender Male Female Non Binary/Other/Not Disclosed					Fax		
PHN	BC Cancer I	D	Cerner MRN	Address			
Email Address					Email Address		
Consent					COPY PHYSICIANS (ALL INFORMATION IS NECESSARY)		
	-		personal information (name, date of	Name	MSC		
birth, sex, cancer history) would be sent with the sample.							
Please contact <u>genetic.counsellor@bccancer.bc.ca</u> if you have any questions or concerns.							
Patient agrees to their results being shared with relatives referred to BC Cancer for genetic testing							
If patient is unable to receive their results, it should be disclosed to (or shared with):					MSC		
Name		p to patient	Contact Phone / Email	Name			
				Address			

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 / Asia Caribbean East Europe / South/Central	/ UK (First Nations, Metis, Inuit)	Jewish Ashkenazi Sephardic	Middle I	East	South / Ce Americ		Other		
						s s	pecify:		
TESTING INDICATION(S) – SELECT ALL THAT APPLY									
Breast Cancer (BRCA) HER2-negative breast cancer, eligible for a Olaparib Hereditary Breast and Ovarian Cancer (INHER) Breast cancer ≤ age 35 2 primary breast cancers, at least 1 ≤ age Triple negative (ER-PR-HER2-) breast cancer Breast cancer ≤ age 50 AND no family hist due to adoption Ovarian, fallopian tube or peritoneal cancer mucinous epithelial; incl. STIC) Male breast cancer	adjuvant □ Pano Prostate 2 50 Prostate 2 50 Medulla cer ≤ age 60 □ Med tory known cer (non- Paragar 2 Pano Paragar 2 Pano Paragar 2 Pano 2 Pa	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 PB EDTA Other ONLY			HCP USE ONLY	P	Progeny	Initials	Date		

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.

Mainstream – this year so far ...

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



High Risk Clinic

Team:

- \circ Physician
- Nurse Practitioners
- o Nurses

Referrals:

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



High Risk Clinic

Eligibility

- $\circ~$ 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.



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).

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



Jewish BRCA1/BRCA2 Testing Program

diamond

FOUNDATION

- 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:

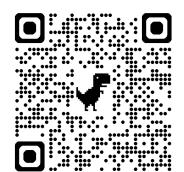
 Genetic testing (BRCA1/BRCA2 only) to any person of Jewish ancestry regardless of family history

o https://brcainbc.ca/



DNA Banking

BC CAN CER		Fo	9				
Our Services	Health Info	Our Research	About	Contact	Health Professionals	Donate	Careers
Menu 🗮 Health	Professionals / Clinica	Resources / Hereditary C	Cancer			<	



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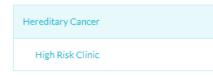
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In this section

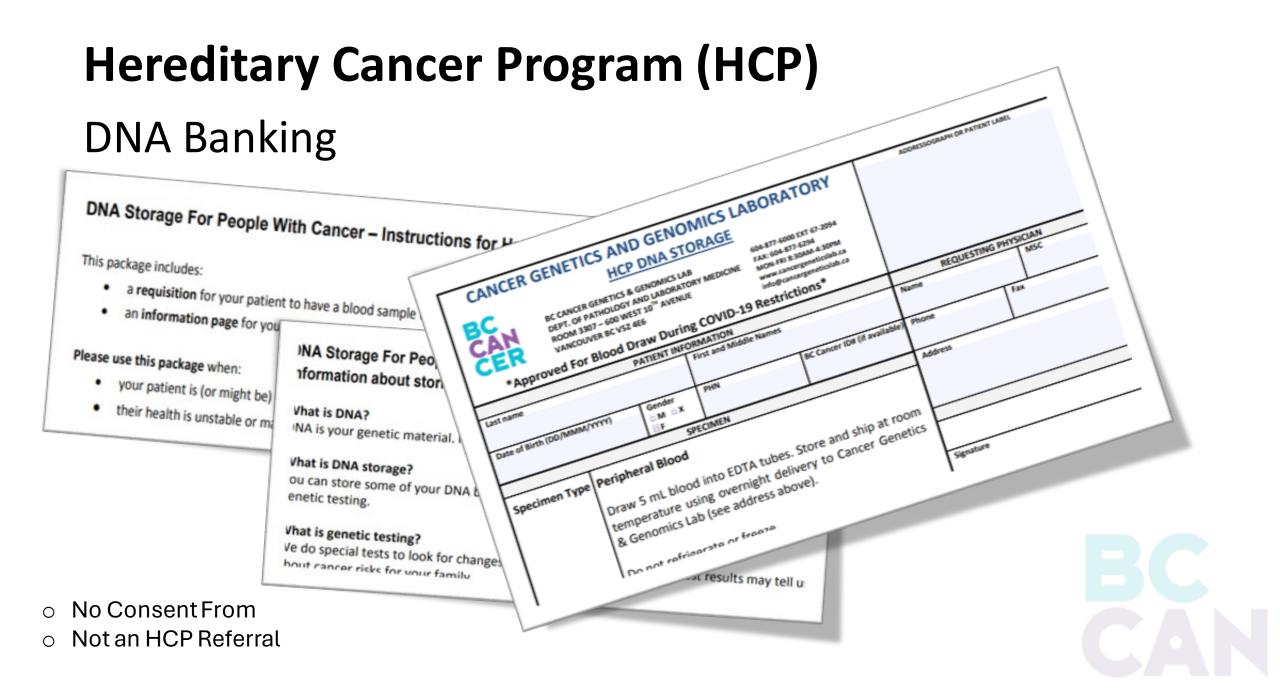


Download the Hereditary Cancer Program Referral form >

Download the Urgent DNA Storage Requisition >

Mainstreamed Genetic Lesting: Information and Requisition Download >







- 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



