BC Cancer Hereditary Cancer Program Eligibility Criteria

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Introduction

BC Cancer Hereditary Cancer Program (HCP) Eligibility Criteria outlines eligibility for publicly funded cancer genetic counselling and/or testing in BC and Yukon. This document is intended to be used by healthcare professionals as a guide for when to offer genetic testing directly to their patients (**mainstream genetic testing**) and/or when to **refer to HCP.**

These criteria are intended to capture the individuals and families most likely to have a germline pathogenic variant in a hereditary cancer gene. These guidelines may change over time as evidence and testing technology evolve.

Cancer genetic counselling and testing can help people understand why their cancer happened, or their risk of getting cancer based on their personal and family history. Test results and risk management recommendations can help with cancer prevention, early detection and treatment.

General Principles for Hereditary Cancer Genetic Testing and Referral

1. **If a germline hereditary cancer pathogenic variant** is identified, other relatives should be offered genetic testing for the pathogenic variant.

2. **If there is no known pathogenic variant in the family**, testing should start with an individual who has had a relevant cancer, tumour or polyp. This is called index testing. Index testing provides the most useful information for the family. Sometimes, DNA from a deceased relative (if available) may be used.

3. **If it is not possible to test a relative with a relevant cancer, tumour or polyp**, a person may still be offered testing if there is at least a 5-10% chance they carry a pathogenic variant. The Hereditary Cancer Program may use validated tools to assess the probability of a pathogenic variant, such as CanRisk or PREMM.

4. **If genetic test results are needed to guide immediate surgery or treatment, urgent testing may be available.** Urgent test requests should be made through referral to HCP.

5. Genetic testing is available at point-of-care for specific indications. This is called **mainstream genetic testing.** Read more about mainstream genetic testing here. If a person is eligible for mainstream testing, this is usually the fastest pathway for non-urgent genetic test results.

6. **If an individual has had previous genetic testing with outdated technology,** they may be offered updated testing using new methods. Availability of updated genetic testing will depend on the likelihood of a missed pathogenic variant. Validated tools such as CanRisk may be used to assess the probability.

7. For **referred individuals who do not meet eligibility criteria**, the Hereditary Cancer Program may still offer an appointment and/or testing based on clinical judgment following a case review with HCP team members.

8. **If tumour or research testing identifies a potential germline pathogenic variant,** germline genetic testing should be offered.

9. **If a pathogenic variant in a hereditary cancer gene is identified through a clinical laboratory outside of HCP for a BC or Yukon resident,** individuals can be referred for genetic counselling and for review of cancer risk management recommendations**.** For example, if individuals undergo private pay testing, or if they are known to carry a pathogenic variant and have since moved to BC/Yukon.

10. **Some inherited cancer conditions include other physical or health features.** In these

cases, a physical exam by a medical geneticist may help make a diagnosis.

11. **Genetic testing for adult-onset hereditary cancer conditions is typically offered from the age of majority (19y).** Testing may be considered at a younger age if desired by the young person and family following genetic counselling. For pediatric-onset hereditary cancer conditions, genetic testing should be offered at an appropriate age to guide management.

Definitions

Close relatives: usually refers to first or second-degree blood relatives on the **same side of the family**. This includes children, brothers, sisters, parents, aunts, uncles, grandchildren, and grandparents. This may also include third-degree relatives depending on the family structure.

Germline: Germline cells contain genetic information that is passed down from one generation to the next. Germline pathogenic variants can be inherited from parent to child. Also called constitutional.

Pathogenic variant: A genetic alteration that causes or increases an individual's susceptibility to a certain disease or disorder. Also called a mutation. In this document reference to pathogenic variants encompasses **likely** pathogenic variants. Likely pathogenic variants have a high probability of pathogenicity and are clinically managed the same as pathogenic variants.

Index testing: Genetic testing is offered to an individual in whom a hereditary cancer predisposition condition is suspected, with no known pathogenic variants in the family. The testing offered is typically a broad multi-gene panel.

Familial variant testing: Targeted genetic testing for a pathogenic variant previously identified in the family.

Mainstream genetic testing: the process whereby non-genetics providers initiate genetic testing and disclose results. Patients with positive genetic test results will have a **reflex referral** to HCP. People with psychosocial needs related to their testing can also be referred.

General/All Disease Sites

Mainstream Testing for:

1. Confirmation of germline status based on variants in tumour/biopsy specimen

Refer to HCP for:

1. Patient has a relative with a pathogenic/likely pathogenic variant
2. Patient has a pathogenic/likely pathogenic variant identified outside HCP (tested out of province, or private pay clinical testing)

Breast and Ovarian Cancer

For lobular breast cancer, see also Diffuse Gastric Cancer and Lobular Breast Cancer.

Mainstream Testing for:

1. HER2 negative breast cancer, eligible for Olaparib
2. Personal history of **breast cancer ≤ 35 years of age**
3. Personal history of **breast cancer 36 to 50 years of age and under active oncologic care**
4. A personal history of **≥2 primary breast cancers** at any age
5. A personal history of **male breast cancer** at any age
6. A personal history of **triple negative breast cancer**
7. A personal history of **invasive epithelial ovarian cancer[1], fallopian tube cancer[2], or peritoneal cancer** at any age
8. Ashkenazi Jewish ancestry **and** a family history of breast or ovarian cancer at any age

Refer to HCP for:

1. Personal history of **breast cancer at ≤50 years of age** AND:
    a. A close relative with breast cancer ≤50
    b. ≥2 close relatives with breast cancer at any age
    c. They were adopted
2. A personal history of **breast cancer** and **close relative with ovarian cancer.**
3. A personal history of **high-grade serous endometrial cancer** with any of these:
    a. Involvement of the fallopian tubes or ovaries.
    b. Family history that includes any of the criteria listed above.
    c. Ashkenazi Jewish ancestry.
4. **First-degree relative with ovarian cancer,** regardless of personal cancer history.

Individuals whose family history meets the listed criteria may be offered testing if there is at least a 10% chance they carry a pathogenic variant. The Hereditary Cancer Program may use validated tools to assess the probability of a pathogenic variant, such as CanRisk.

[1]Excludes ovarian cancers of borderline/low malignant potential
[2]Includes serous tubal intraepithelial carcinoma (STIC) and serous tubal intraepithelial

lesions (STIL)

Prostate Cancer

Mainstream Testing for:

1. A personal history of **metastatic prostate cancer** at any age
2. **Ashkenazi Jewish ancestry** and a personal or family history of prostate cancer

Refer to HCP for:

1. Prostate cancer with **intraductal or ductal histology** at any age
2. Prostate cancer diagnosed **≤50 years of age**
3. Prostate cancer at **any age AND a second primary cancer** including colon, stomach, upper urothelial, small bowel, brain, or male breast cancer
4. Prostate cancer at any age **AND family history** that meets Lynch syndrome or breast and ovarian cancer criteria
5. Prostate cancer (even if localized and not high grade) at any age and ancestry includes population with high prevalence of pathogenic variants including **Ashkenazi Jewish** or **Swedish/Nordic**
6. Prostate cancer at any age **AND ≥1 close relative with**:
    a. High-risk or metastatic prostate[3] cancer at any age
    b. Female breast cancer at ≤45 years of age
    c. Male breast cancer at any age
    d. Ovarian cancer at any age
    e. Pancreatic cancer at any age
7. Prostate cancer at any age **AND ≥2 close relatives** (or one close relative with ≥2 of these cancers) with any combination of: prostate, pancreas, ovarian, or breast cancer
8. **First-degree relative with metastatic prostate cancer**, regardless of personal history

Individuals whose family history meets the listed criteria may be offered testing if there is at least a 10% chance they carry a pathogenic variant. The Hereditary Cancer Program may use validated tools to assess the probability of a pathogenic variant, such as CanRisk.

[3]History of systemic chemotherapy, or death from disease can be sufficient evidence of high-risk or metastatic disease in a relative

Pancreatic Cancer

For PNET, see also Rare Genetic Syndromes.

Mainstream Testing for:

1. A personal history of **pancreatic ductal adenocarcinoma (PDAC)** at any age
2. A personal history of **pancreatic neuroendocrine tumour (PNET)** at any age
3. Ashkenazi Jewish ancestry **and** a family history of pancreatic ductal adenocarcinoma at any age

Refer to HCP for:

4. **First-degree relative with pancreatic ductal adenocarcinoma**, regardless of personal history
5. **First-degree relative with pancreatic neuroendocrine tumour**, regardless of personal history

Lynch Syndrome (Colon and Endometrial Cancer)

Several inherited conditions increase the risk of gastrointestinal (GI) cancers. The most common of these is Lynch syndrome. **Lynch syndrome** is associated with several cancers**, including** colorectal, endometrial, gastric, ovarian, pancreatic adenocarcinoma, urothelial (urinary tract, bladder, kidney), brain (usually glioblastoma), bile ducts, small intestine, sebaceous adenomas, sebaceous carcinomas, and keratocanthomas.

I**mmunohistochemistry (IHC)** for the mismatch repair proteins is often the first step for assessment and should be initiated on a Lynch-syndrome associated tumour if possible. In British Columbia, many hospitals initiate IHC automatically at time of diagnosis for colon or endometrial cancers.

Refer to HCP for:

1. A personal history of **IHC deficient (dMMR) colorectal or endometrial cancer** at any age

2. A personal history of **colorectal cancer ≤40 years of age**

3. A personal history of **colorectal cancer ≤50 years of age** AND:
    a. They were adopted
    b. A close relative with a Lynch syndrome related cancer at ≤50 years of age
    c. ≥2 close relatives with Lynch syndrome related cancers at any age

4. A personal history of **endometrial cancer at ≤50 years of age** AND:
    a. A close relative with Lynch syndrome related cancer at ≤50 years of age
    b. ≥2 close relatives with Lynch syndrome related cancers at any age

5. **First-degree relative with dMMR colon or endometrial cancer,** regardless of personal cancer history

Individuals whose family history meets the listed criteria may be offered testing if there is at least a 5% chance they carry a pathogenic variant. The Hereditary Cancer Program may use validated tools to assess the probability of a pathogenic variant, such as PREMM.

Gastrointestinal Polyposis Syndromes

Gastrointestinal polyposis syndromes are inherited conditions that cause multiple polyps to form in the digestive tract. See also Rare Genetic Syndromes.

Refer to HCP for :

1. Clinical diagnosis of Familial Adenomatous Polyposis (FAP)
2. ≥10 adenomas[4] at ≤60 years of age
3. ≥20 cumulative adenomas at any age
4. ≥2 hamartomatous polyps at any age
5. A personal history meeting WHO criteria for **Serrated Polyposis** Syndrome:
    a. ≥20 serrated polyps of any size distributed throughout the large bowel, with at least 5 polyps proximal to the rectum
    b. Five or more serrated polyps (including sessile serrated adenomas, traditional serrated adenomas, and hyperplastic polyps) proximal to the rectum, all ≥5 mm in size with at least two of them ≥ 1cm

Individuals with a personal history of polyposis that do not meet the listed criteria may be offered testing if there is at least a 5% chance they carry a pathogenic variant based on additional family history of cancer. The Hereditary Cancer Program may use validated tools to assess the probability of a pathogenic variant, such as PREMM.

[4]Adenomas include adenomatous polyps (tubular adenomas, villous adenomas, tubulovillous adenomas) and not sessile serrated lesions.

Diffuse Gastric Cancer and Lobular Breast Cancer

Refer to HCP for:

1. A personal history of **diffuse gastric cancer** at ≤50 years of age

2. A personal history of **diffuse gastric cancer** AND **lobular breast cancer**, both diagnosed ≤70 years of age

3. A personal history of **gastric cancer** at any age and ≥1 close relative with gastric cancer, with at least 1 confirmed diffuse gastric cancer

4. Bilateral **lobular breast cancer** at any age

5. A personal history of **lobular breast cancer** at ≤70 years of age and ≥1 close relative with **diffuse gastric cancer** at any age (or vice versa)

6. A personal history of **gastric in situ signet ring cells** or **pagetoid spread of signet ring cells** ≤50 years of age

7. **First-degree relative that meets the above criteria,** regardless of personal cancer history

Melanoma

Refer to HCP for:

1. Personal history of ≥3 melanomas at any age
2. Personal history of melanoma at ≤30 years of age
3. Personal history of ≥2 melanomas, at least one ≤40 years of age
4. Personal history of melanoma ≤40 years of age AND ≥1 close relative with melanoma
5. Personal history of melanoma at ≤60 years of age AND dermatology confirmed diagnosis of multiple moles (more than 50) and/or dysplastic nevi
6. Personal history of melanoma ≤60 years of age and Ashkenazi Jewish ancestry
7. Personal history of melanoma AND ≥2 close relatives with melanoma or pancreatic cancer[5] at any age
8. Personal history of melanoma at any age AND family history that meets breast and ovarian cancer criteria
9. Personal history of **uveal melanoma** at any age
10. Personal history of melanoma at any age AND personal history ≥1 of the following ***BAP1*-associated cancers**:
    a. Mesothelioma
    b. Renal cell carcinoma
    c. BAP1-inactivated melanocytic tumour
    d. High-grade rhabdoid meningioma
11. Personal history of melanoma at any age AND ≥1 of the following ***POT1*-associated cancers**: angiosarcoma, malignant glioma, chronic lymphocytic leukemia
12. First-degree relative with melanoma diagnosed at ≤30 years of age
13. Family history of **≥1 melanoma** in one or more relatives **AND** a ***MITF* p.E318K** pathogenic variant in the family

Close relatives without a personal history of cancer in families meeting the above criteria may also be accepted for assessment.

[5]Total 3 cases of melanoma, does not have to be 3 separate individuals

Renal Cancer

See also Rare Genetic Syndromes.

Mainstream Testing for:

1. Personal history of **renal cancer ≤47** years of age

Refer to HCP for:

1. **First-degree relative with renal cancer ≤47** years of age, regardless of personal history

Pheochromocytoma/Paraganglioma

See also Rare Genetic Syndromes.

Mainstream Testing for:

1. Personal history of **pheochromocytoma or paraganglioma** at any age

Refer to HCP for:

1. **Close relative with pheochromocytoma or paraganglioma**, regardless of personal history

Soft Tissue/Sarcoma/Li-Fraumeni Syndrome

Li-Fraumeni Syndrome (LFS) increases the risk of many different types of cancer at a young age. Families with LFS often have several members with cancers including sarcoma (excluding Ewing's sarcoma), breast cancer, brain tumors, or leukemia.

Refer to HCP for:

1. Personal history of LFS cancer[6] at ≤46 years of age, **AND:**
    a. 2nd primary LFS cancer **OR**
    b. ≥1 close relative with an LFS cancer[6] (except breast if proband has breast cancer) at 56 or younger, **OR**
    c. ≥1 close relative with multiple primary tumors at any age (if lung cancer, must be ≤ 56 years of age)

2. Personal history of sarcoma at ≤5 years of age

3. Personal history of osteosarcoma at ≤14 years of age

4. Personal history of rhabdomyosarcoma (embryonal anaplastic subtype) at any age

5. Low hypodiploid acute lymphoblastic leukemia at any age

6. Choroid plexus tumour at any age

7. Adrenocortical carcinoma at any age

[6]soft tissue sarcoma, osteosarcoma, pre-menopausal breast cancer, central nervous system tumor, adrenocortical carcinoma, leukemia or lung cancer

Biliary Tract Cancer

Including intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, and gallbladder carcinoma.

Refer to HCP for:

1. Personal history of biliary tract cancer ≤50 years of age

2. Personal history of biliary tract cancer at any age AND:
    a. Personal history of **multiple primary cancers** (excluding non-melanoma skin cancer [may include sebaceous carcinoma in consideration of LS])
    b. Ashkenazi Jewish ancestry

3. Close relative that meets criteria above

Thyroid Cancer

Mainstream Testing for:

1. Medullary thyroid cancer at any age

Refer to HCP for:

1. **First-degree relative with medullary thyroid cancer,** regardless of personal history

Lung Cancer

Refer to HCP for:

1. A personal history of **lung cancer** with an **EGFR T790M variant** found in the tumour *before* treatment with EGFR-tyrosine kinase inhibitor (TKI) therapy

2. A personal history of **lung cancer** at ≤50 years of age

3. A personal history of **pleural mesothelioma** AND
    a. personal history of a second **BAP1-associated cancer**[7] OR
    b. ≥1 close relative with a **BAP1-associated cancer**[7]

[7]*BAP1* associated cancers include renal cell carcinoma, *BAP1*-inactivated melanocytic tumour (BIMT), High-grade rhabdoid meningioma, melanoma, uveal melanoma

Multiple Primary Cancers

Refer to HCP for:

1. ≥ 3 primary cancers[8] **AND**
    a. All cancers were diagnosed **≤70 years of age**, or
    b. ≥1 diagnosed **before age 50**, or
    c. ≥2 **cancers are part of the same cancer syndrome**, such as Lynch syndrome or breast and ovarian cancer.

Individuals whose family history meets the above may be offered testing if there is at least a 5-10% chance they carry a pathogenic variant. The Hereditary Cancer Program may use validated tools to assess the probability of a pathogenic variant, such as CanRisk or PREMM.

[8]Not including common skin cancers (like basal or squamous cell) or cervical pre-cancer (CIN). However, vaginal or cervical **squamous cell carcinoma** *is* included.

Rare Genetic Syndromes

Referral to HCP is recommended for individuals with a confirmed or suspected clinical diagnosis of a rare genetic syndrome that increases the risk for cancer.

For example, please refer if any of the following conditions are suspected:

- Birt-Hogg-Dube
- Carney Complex
- Dyskeratosis Congenita
- Gorlin syndrome
- Hereditary Leiomyomatosis and Renal Cell Carcinoma
- Hyperparathyroidism/parathyroid adenomas
- Juvenile polyposis syndrome (JPS)
- Multiple Endocrine Neoplasia, Type 1 (MEN1)
- Multiple Endocrine Neoplasia, Type 2
- NF1(if personal history of breast cancer, otherwise consider referral to PMGP)
- NF2
- Peutz-Jeghers syndrome (PJS)
- PTEN
- Retinoblastoma
- Schwannomatosis
- Tuberous Sclerosis
- VHL

Refer to published criteria for more information:

- https://www.eviq.org.au/cancer-genetics/adult/genetic-testing-for-heritable-pathogenic-variants
- https://www.ncbi.nlm.nih.gov/books/NBK1116/

Appendix A: HCP Eligibility Quick Reference

The HCP Eligibility Quick Reference is intended to be a tool to quickly determine eligibility for mainstream genetic testing or referral to the HCP. Please refer to the full document for further details, explanatory notes, and references.

Category	HCP Eligibility Criteria – Quick Reference	
	Mainstreaming for:	**Refer to HCP for:**
General Criteria	Confirmation of germline status based on variants in tumour/biopsy specimen	1. Relative with P/LP variant 2. P/LP variant identified outside HCP (tested out of province, or private pay testing)
Breast & Ovarian Cancer	1. HER2-negative breast cancer, eligible for Olaparib 2. Breast cancer ≤ 35 years of age 3. Breast cancer 36 to 50 years of age and under active oncologic care 4. ≥2 primary breast cancers 5. Triple negative invasive breast cancer 6. Male breast cancer 7. Epithelial ovarian, fallopian tube or peritoneal cancer. 8. Ashkenazi Jewish ancestry and personal or family history of breast or ovarian cancer	1. Breast cancer at ≤ 50 AND: a. close relative with breast cancer ≤ 50 b. ≥2 close relatives with breast cancer at any age c. Adopted 2. Breast cancer and close relative with ovarian cancer 3. High-grade serous endometrial cancer AND: a. involvement of the fallopian tubes or ovaries b. family history meets breast and ovarian cancer criteria c. Ashkenazi Jewish ancestry 4. FDR with ovarian cancer
Prostate Cancer	1. Metastatic prostate cancer 2. Ashkenazi Jewish ancestry and a personal or family history of prostate cancer	1. Prostate cancer with intraductal or ductal histology at any age 2. Prostate cancer ≤ 50 3. Prostate cancer AND 2nd primary cancer: colon, stomach, upper urinary tract, small bowel, brain, or male breast cancer 4. Prostate cancer AND family history that meets Lynch or breast/ovarian criteria 5. Prostate cancer and Ashkenazi Jewish or Swedish/Nordic ancestry 6. Prostate cancer AND close relative with: a. High-risk or metastatic prostate cancer b. Female breast cancer ≤ 45 c. Male breast cancer d. Ovarian cancer e. Pancreatic cancer 7. Prostate cancer AND ≥2 close relatives (or one close relative with ≥2 of these

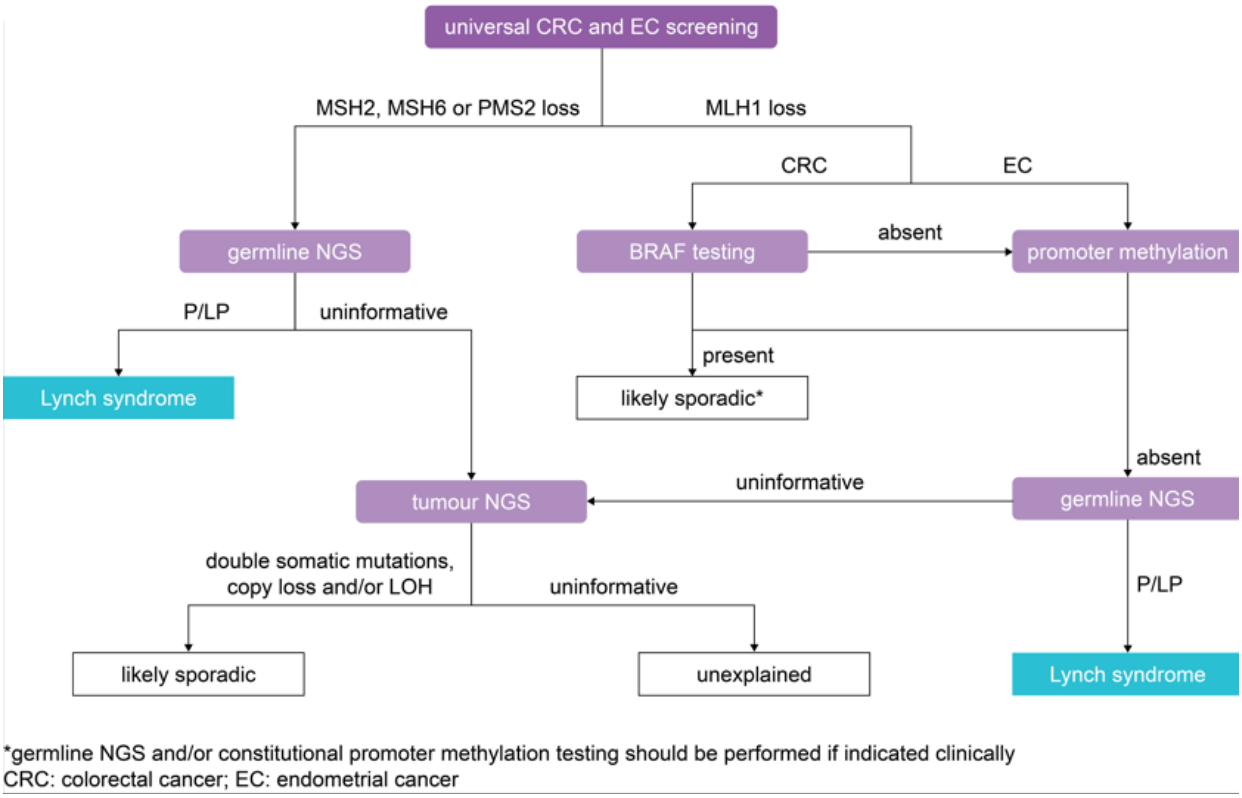
		cancers) with any combination of: prostate, pancreas, ovarian, or breast cancer 8. FDR with metastatic prostate cancer
Category	**Mainstreaming for:**	**Refer to HCP for:**
Pancreatic Cancer	1. Pancreatic ductal adenocarcinoma (PDAC) 2. Pancreatic neuroendocrine tumour (PNET) 3. Ashkenazi Jewish ancestry AND family history of PDAC	1. FDR with PDAC 2. FDR with PNET
Renal Cancer	Renal cancer ≤ 47	FDR with renal cancer ≤47 years of age
Pheo/PGL	Pheochromocytoma/paraganglioma, any age	Close relative with PCC/PGL
Thyroid Cancer	Medullary thyroid cancer	FDR with medullary thyroid cancer
Lynch syndrome		1. IHC deficient (dMMR) colorectal or endometrial cancer 2. Colorectal cancer ≤ 40 years of age. 3. Colorectal cancer ≤ 50 AND: a. Adopted b. Close relative with a Lynch syndrome related cancer ≤ 50 c. ≥2 close relatives with Lynch syndrome related cancers 4. Endometrial cancer at ≤ 50 AND: a. Close relative with Lynch syndrome related cancer at ≤ 50 b. ≥2 close relatives with Lynch syndrome related cancers 5. FDR with dMMR colon or endometrial cancer
Polyposis Adenomas include tubular adenomas, villous adenomas, tubulovillous		1. Clinical diagnosis of FAP 2. ≥10 adenomas at ≤ age 60 3. ≥ 20 cumulative adenomas any age 4. ≥ 2 hamartomatous polyps any age 5. Personal history meets WHO criteria for Serrated Polyposis Syndrome: a. ≥ 20 serrated polyps of any size distributed throughout the large

adenomas and **not** sessile serrated lesions.		bowel, with at least 5 polyps proximal to the rectum b. Five or more serrated polyps (including sessile serrated adenomas, traditional serrated adenomas, and hyperplastic polyps) proximal to the rectum, all ≥ 5 mm in size with at least two of them ≥ 1cm
Category	**Mainstreaming for:**	**Refer to HCP for:**
Diffuse Gastric Cancer and Lobular Breast Cancer		1. Diffuse gastric cancer ≤50 2. Diffuse gastric cancer AND lobular breast cancer, both ≤70 3. Gastric cancer AND ≥1 close relative with gastric cancer, ≥1 confirmed diffuse gastric cancer 4. Bilateral lobular breast cancer 5. Lobular breast cancer ≤70 and ≥1 close relative with diffuse gastric cancer at any age (or vice versa) 6. Gastric in situ signet ring cells or pagetoid spread of signet ring cells ≤ 50 7. FDR that meets the above criteria, regardless of personal cancer history
Melanoma		1. ≥3 melanomas any age 2. Melanoma ≤ age 30 3. ≥ 2 melanomas, at least one ≤ 40 4. Melanoma ≤40 AND ≥ 1 close relative with melanoma 5. Melanoma ≤60 AND dermatology confirmed diagnosis of ≥50 moles and/or dysplastic nevi 6. Melanoma ≤ 60 and Ashkenazi Jewish ancestry 7. Melanoma AND ≥2 close relatives with melanoma or pancreatic cancer 8. Melanoma AND family history that meets breast/ovarian criteria 9. Uveal melanoma at any age 10. Melanoma AND ≥1 of the following *BAP1*-associated cancers: • Mesothelioma • Renal cell carcinoma • BAP1-inactivated melanocytic tumour • High-grade rhabdoid meningioma 11. Melanoma AND ≥1of the following *POT1*-associated cancers: • Angiosarcoma • Malignant glioma

		• Chronic lymphocytic leukemia 12. FDR with melanoma diagnosed ≤ age 30 13. Family history of ≥ 1 melanoma in ≥ 1 relatives AND a *MITF* p.E318K pathogenic variant in the family
Category	**Mainstreaming for:**	**Refer to HCP for:**
Li Fraumeni syndrome LFS cancer = soft tissue sarcoma, osteosarcoma, pre-menopausal breast cancer, central nervous system tumor, adrenocortical carcinoma, leukemia or lung cancer		1. Personal history of LFS cancer at ≤46 years of age, **AND**: a. 2nd primary LFS cancer **OR** b. ≥1 close relative with an LFS cancer (except breast if proband has breast cancer) at 56 or younger, **OR** c. ≥1 close relative with multiple primary tumors at any age (if lung cancer, must be ≤ 56 years of age) 2. Sarcoma ≤5 years 3. Osteosarcoma ≤14 years 4. Rhabdomyosarcoma (embryonal anaplastic subtype) at any age 5. Low hypodiploid acute lymphoblastic leukemia 6. Choroid plexus tumour at any age 7. Adrenocortical carcinoma at any age
Biliary Tract Cancer		1. Biliary tract cancer ≤50 2. Biliary tract cancer **AND**: a. Multiple primary cancers **OR** b. Ashkenazi Jewish ancestry 3. Close relative with the above
Lung cancer		1. Lung cancer with EGFR T790M in the tumour *before* treatment with EGFR-tyrosine kinase inhibitor (TKI) therapy 2. Lung cancer ≤50 3. Pleural mesothelioma **AND** a. a second BAP1-associated cancer **OR** b. ≥1 close relative with a BAP1-associated cancer
Multiple Primary Cancers		3 primary cancers **AND** a. All cancers ≤70 **OR** b. ≥1 cancer ≤50, **OR** c. ≥2 cancers are part of the same cancer syndrome

Appendix B: MMR IHC Testing Algorithm Flowchart

This algorithm outlines the Lynch Syndrome (LS) testing process based on mismatch repair immunohistochemistry (MMR IHC) results.



*germline NGS and/or constitutional promoter methylation testing should be performed if indicated clinically
CRC: colorectal cancer; EC: endometrial cancer