Ontario Health

2021 Hereditary Cancer Testing Eligibility Criteria

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Introduction

On April 1, 2021, Ontario Health – Cancer Care Ontario (OH-CCO) implemented Provincial Hereditary Cancer Testing (HCT) for adults. This work was the result of a collaborative effort of laboratories and genetics clinics over 18 months to develop an evidence-based provincial list of targeted genes to meet the current needs of patients, and to position the system to meet their future needs. In the fall of 2020, OH-CCO formed a working group of members from Ontario Genetics Clinics to establish eligibility criteria that aligns with the new laboratory testing menu. Through this initiative, patients will have access to hereditary cancer testing that is standardized, evidence based and coordinated across the province.

This document serves as a companion tool to Ontario's standardized Hereditary Cancer Testing Gene List (see Appendix A) and should be used to determine hereditary cancer testing eligibility. For a condensed, quick reference guide to the HCT eligibility criteria covered in this document, please see Appendix B.

Background

Cancer genetic counselling and assessment is a process that utilizes clinical assessment and genetic testing, when indicated, to provide cancer risk management recommendations to individuals with a personal and/or family history of cancer. Increasingly, cancer genetic testing is also recognized as an integral component of surgical, radiation and systemic treatment planning in oncology patients. Advances in technology, including next generation sequencing, have facilitated rapid high-throughput analysis of cancer multi-gene panels in both somatic and germline samples making genetic testing faster, less expensive and more accessible to a greater number of individuals.

In Ontario, eligibility criteria for hereditary cancer testing has been limited to Breast and Ovarian Cancer (2002) and Lynch Syndrome and Polyposis (2005) despite remarkable expansion and evolution of knowledge in the area of hereditary cancer predisposition syndromes. Implementation of the Provincial Hereditary Cancer Testing Program and associated eligibility criteria will increase clinically appropriate access to cancer genetic testing; and includes a mechanism to review and respond to emerging evidence through feedback, review and evaluation.

Eligibility for cancer genetic testing has traditionally been offered to individuals who have a 10% or greater likelihood of having a germline pathogenic/likely pathogenic variant[1] in common cancer susceptibility genes such as *BRCA1* and *BRCA2.* Given limited resources, it is important to focus efforts on the individuals and families that are most likely to benefit. However, with the advent of cancer gene panel testing, it is now recognized that a significant proportion of individuals with actionable germline variants in cancer susceptibility genes do not meet established criteria for genetic testing. Further, there is a growing list of targeted therapies (mostly notably PARP inhibitors) proven through clinical trials to benefit individuals with hereditary forms of cancer. Finally, the increased utilization of genomic analysis of tumour and/or biopsy specimens has resulted in the identification of tumour incidental findings that raise the possibility of underlying germline pathogenic/likely pathogenic variants. Eligibility criteria for cancer genetic testing needs to consider all established and emerging factors and indications for testing.

[1] The American College of Medical Genetics and Genomics and the Association for Molecular Pathology guidelines recommend using the term 'variant' with classifiers (1) pathogenic, (2) likely pathogenic, (3) uncertain significance, (4) likely benign, or (5) benign, to replace the term 'mutation'. The term variant is used throughout this document. PMID: 25741868

It is important to emphasize that criteria were selected using best available evidence and expert consensus. Clinical relevance and appropriateness to guide patient care were prioritized over existing resource limitations. Cancer risk management recommendations, including early detection, prevention and/or treatment options, should be personalized for each individual based on age, medical history, family history and genetic test results if applicable. Recommendations related to provincial clinical cancer genetics services are provided in the OH-CCO report *Enhancing Clinical Cancer Genetic Service Delivery in Ontario Recommendations for a New Model of Care*.[2] Sustainability of an expanded cancer genetic testing program in Ontario requires a robust workforce in laboratory and clinical genetics, however, there is a current shortage of health and human resources available to provide this expert clinical care.

General Principles

This document is intended to be used primarily by genetics professionals providing genetic counselling, risk assessment and risk management to individuals with, and at risk for, hereditary cancer syndromes. In order to address the goal of providing standardized and equitable care across the province of Ontario for this patient population, a set of guiding principles was developed to assist in the implementation of these criteria.

1. Hereditary cancer testing should be offered to individuals meeting eligibility criteria following a formal cancer genetic risk assessment in a genetics clinic and consent for testing. Genetic counselling should be provided by a qualified geneticist, genetic counsellor and/or physician with specialized training in genetics.

   Oncology initiated testing or 'mainstreaming' is an emerging area of practice and refers to testing initiated by a referring specialist in patient populations that meet eligibility for testing based on their own personal cancer history, regardless of family history. This pathway should be established in collaboration with institutional and/or regional cancer genetics services and the ordering provider should subsequently follow the locally established protocols and processes for result disclosure and risk assessment.

2. In the absence of a known familial pathogenic/likely pathogenic variant, hereditary cancer testing should be initiated when possible on a source of germline DNA from an affected/informative individual. This may include testing stored DNA of a deceased relative if it is the most informative DNA source[3].

[2] https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/67891

[3] When considering a non-neoplastic (normal/non-tumour) archival tissue sample for hereditary cancer testing, the lab performing the testing must be validated on the specimen type in question.

3. If a hereditary cancer syndrome has been confirmed in a family, predictive genetic testing should be offered for the known familial pathogenic/likely pathogenic variant(s). Expanded testing can be considered if there is a significant cancer history on the other side of the family, increased risk related to founder variants, and/or for unaffected children of individuals with adult-onset recessive cancer predisposition syndromes (e.g. *MUTYH*-related polyposis).

4. Hereditary cancer syndromes are often associated with features such as young age of onset, and increased likelihood of multiple primary cancers. Most hereditary cancer syndromes follow an autosomal dominant pattern of inheritance which results in a striking family history of cancer over multiple generations. However, due to reduced penetrance and variable expression, limitations in knowledge of family history and the possibility of other inheritance patterns, the lack of contributory family history should not prevent consideration of genetic testing in individuals with other risk factors.

5. Some hereditary cancer syndromes may be associated with dysmorphic features and/or syndromic presentations with associated, non-tumour features. At-risk individuals may require a physical exam by a clinical geneticist or physician with specialized training in genetics in order to establish a correct diagnosis in conjunction with cancer genetic testing.

6. Expedited testing is indicated for eligible individuals for whom the results of germline genetic testing could impact surgical and/or oncologic treatment planning that is scheduled within the next 4-8 weeks.

7. Clinical judgement is an essential component of genetic assessment, to be used in conjunction with established genetic testing criteria.
    a. In families that are suspicious for hereditary risk, genetics clinicians may use clinical judgement to support genetic testing in individuals that do not fit established criteria and/or expanded genetic testing after traditional genetic testing strategies have not identified the underlying cause of disease.
    b. Conversely, in a family that appears low risk following genetic risk assessment, supporting evidence such as review of family medical records and/or formal calculation of the probability of carrying a pathogenic/likely pathogenic variant, should be documented to support the decision to offer genetic testing. Lower risk families may include large families with relatively few affected relatives or families with older ages of disease onset.
    c. Decisions regarding genetic testing that rely on clinical judgment, as opposed to strict application of criteria, should be made following consensus of the clinical cancer genetics team and/or discussion with genetics experts.

2021 Hereditary Cancer Testing Eligibility Criteria

General Criteria: All Disease Sites

Criteria in this section may be appropriate to apply in consideration of any hereditary cancer syndrome and/or cancer genetic test as they are not specifically linked to a tumour type/location.

1. Published empirical evidence or established risk models should be used to determine eligibility for genetic testing of unaffected individuals when an affected proband is not available for testing. Germline genetic testing may be considered for individuals with ≥ **5%** likelihood of carrying a pathogenic/likely pathogenic variant.

2. Genetic testing should be offered after genetic counselling to an individual with a blood relative with a known pathogenic or likely pathogenic variant in a cancer susceptibility gene on the approved gene list.

3. When there is an approved targeted therapy that may benefit a patient based on their germline variant status, cancer genetic testing can be initiated by a treating oncologist to aid in systemic therapy planning. Individuals may be eligible regardless of their age and/or family history (see General Principle 1).

4. Genetic testing may be offered to individuals who meet eligibility criteria and previously tested negative with prior testing methods or protocols (i.e., single gene, no del/dup). The decision to update genetic testing should be made in collaboration with local laboratory genetic services and should be associated with a reasonable likelihood of clinical benefit to the patient/family.

5. Some pathogenic/likely pathogenic variants are associated with autosomal recessive conditions (e.g., Ataxia telangiectasia, Fanconi anemia, Constitutional Mismatch Repair Deficiency, *MUTYH*-associated polyposis). Carrier testing for partners of pathogenic/likely pathogenic variant carriers may have implications for risk to family members and/or reproductive decision-making. Factors associated with determining eligibility for partner testing include consanguinity, founder variants, population carrier frequency and/or disease penetrance.

6. Clinical Judgement: In families that are suspicious for hereditary risk, genetics clinicians may use clinical judgement to support genetic testing in individuals that do not fit established criteria and/or expanded genetic testing after traditional genetic testing strategies have not identified the underlying cause of disease.

7. Identification of potential germline results from tumour/biopsy genetic testing for variants in genes on the Hereditary Cancer Testing Gene List[4]:
    a. Confirmatory germline genetic testing should be considered if clinical implications are present for the variant in the germline state.
        - Tumour/biopsy genetic testing can reveal germline and somatic (non-germline) variants. Without a matched germline sample, variant(s) found from tumour/biopsy genetic testing cannot be reliably classified as germline or somatic. The variant should be interpreted in the germline context from a laboratory with experience in germline annotation.
    b. Germline genetic testing should be initiated by, or in consultation with, a clinician on a genetics team.
        - Guidelines and/or recommendations[5] should be used in combination with clinical judgement to determine when germline genetic testing should be offered following tumour/biopsy results.

8. Tumour immunohistochemistry (IHC) of the mismatch repair (MMR) proteins is a cost-effective tool in identifying patients with Lynch Syndrome (see Hereditary Gastrointestinal (GI) Cancers Testing Criteria for MMR IHC deficiencies). IHC of other proteins may also be used as a screening tool for several additional rare and under-recognized hereditary cancer predisposition syndromes. Using clinical judgment, individuals identified as having IHC deficient tumours may benefit from germline genetic testing.[6]

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[4] Negative tumour/biopsy results without a matched germline sample: Due to differences in technology, gene coverage, and rapidly advancing literature, a negative tumour/biopsy test does not necessarily preclude genetic counselling and possible germline genetic testing.

[5] Guidelines/recommendations for which tumour/biopsy results require germline confirmation may include, but are not limited to:

i. Mandelker, D., Donoghue, M., Talukdar, S., Bandlamudi, C., Srinivasan, P., Vivek, M., Jezdic, S., Hanson, H., Snape, K., Kulkarni, A., Hawkes, L., Douillard, J. Y., Wallace, S. E., Rial-Sebbag, E., Meric-Bersntam, F., George, A., Chubb, D., Loveday, C., Ladanyi, M., Berger, M. F., … Turnbull, C. (2019). Germline-focussed analysis of tumour-only sequencing: recommendations from the ESMO Precision Medicine Working Group. *Annals of oncology: official journal of the European Society for Medical Oncology, 30(8),* 1221–1231. https://doi.org/10.1093/annonc/mdz136

ii. Klek, S., Heald, B., Milinovich, A., Ni, Y., Abraham, J., Mahdi, H., Estfan, B., Khorana, A. A., Bolwell, B. J., Grivas, P., Sohal, D., & Funchain, P. (2020). Genetic Counseling and Germline Testing in the Era of Tumor Sequencing: A Cohort Study. *JNCI cancer spectrum, 4(3),* pkaa018. https://doi.org/10.1093/jncics/pkaa018

iii. Clark, D. F., Maxwell, K. N., Powers, J., Lieberman, D. B., Ebrahimzadeh, J., Long, J. M., McKenna, D., Shah, P., Bradbury, A., Morrissette, J., Nathanson, K. L., & Domchek, S. M. (2019). Identification and Confirmation of Potentially Actionable Germline Mutations in Tumor-Only Genomic Sequencing. *JCO precision oncology*, *3*, PO.19.00076. https://doi.org/10.1200/PO.19.00076

iv. DeLeonardis, K., Hogan, L., Cannistra, S. A., Rangachari, D., & Tung, N. (2019). When should tumor genomic profiling prompt consideration of germline testing? American Society of Clinical Oncology, 15(9), 465-473. https://doi.org/10.1200/JOP.19.00201.

[6] J. Andrici, A. Gill, J. Hornick. Next generation immunohistochemistry: Emerging substitutes to genetic testing? *Seminars in Diagnostic Pathology 35,* 161-169 (2018)

Hereditary Breast and Ovarian Cancer

A personal and/or family history of breast and/or ovarian cancer is a common indication for referral to a cancer genetics clinic. In recent years, there have been increasing calls to extend genetic testing criteria to include all women with epithelial ovarian cancer and breast cancer. The criteria below represent current evidence and expert consensus, and will be amended as needed as evidence evolves over time.

Note: HBOC criteria #7 can be satisfied by a wide variety of family history presentations but should prompt referral for genetic counselling and consideration of genetic testing. Clinical judgement should be used in determining eligibility for testing (see General Principle 7).

1. Personal history of breast cancer ≤45 years of age.

2. Personal history of breast cancer ≤50 years of age with limited family structure (e.g., adoption, few close relatives assigned female at birth)

3. Personal history of breast cancer ≤50 years of age with a second primary breast cancer.

4. Personal history of triple negative breast cancer ≤60 years of age.

5. Personal history of male breast cancer at any age.

6. Personal history of epithelial ovarian cancer[7], including fallopian tube cancer and peritoneal cancer at any age

7. Personal history of breast or ovarian cancer any age with ≥1 close relative(s)[8] with:
    a. Breast cancer or ovarian cancer (in families with 2 breast cancers, one must be diagnosed ≤50 years of age)
    b. Triple negative breast cancer ≤60 years of age
    c. Male breast cancer any age
    d. Pancreatic adenocarcinoma any age
    e. High risk prostate[9] cancer any age
    f. Two or more close relatives[8] with breast cancer or prostate cancer at any age

[7] Excludes borderline, pure clear cell, mucinous and low malignant potential tumours.
[8] Close relatives typically refers to first and second degree blood relatives on the same side of the family, but may include third degree relatives based on the family structure.
[9] High risk prostate cancer can be confirmed with evidence of one or more of the following features:
T3 (or higher) staging, Grade Group 4 or 5, lymph node involvement, PSA ≥20.

Hereditary Prostate Cancer

Prostate cancer is a common malignancy that is frequently associated with hereditary cancer syndromes, particularly when individuals present with advanced and/or metastatic disease. Evidence of high risk, invasive disease may be found in pathology reports, operative reports, urology notes and/or oncology notes. A history of systemic chemotherapy, distant metastasis and/or death due to disease can be considered sufficient evidence to confirm metastatic prostate cancer in a patient or family member. Hereditary cancer testing can be considered for individuals with a:

1. Personal history of metastatic prostate cancer.
2. Documented personal history of high risk, locally advanced, prostate cancer.
    - High risk prostate cancer can be confirmed with evidence of one or more of the following features:
        - T3 (or higher) staging[10], Grade Group 4 or 5 (Gleason Score 8 to 10)[11], lymph node involvement, PSA ≥20.
3. Personal history of prostate cancer with ≥1 close relatives with prostate cancer.
    - One relative must have evidence of high risk or metastatic disease.
4. Personal history of prostate cancer with ≥2 close relatives[12] with prostate, pancreas and/or breast cancer regardless of age or stage.

Note: There is currently conflicting evidence for prostate tumours with intraductal/ductal pathology and this feature is not considered to be independently sufficient to confirm eligibility for genetic testing at this time. The evidence will be reviewed periodically and this criteria will be amended if needed.

[10] Resources for Staging Prostate Cancer: https://www.cancer.ca/en/cancer-information/cancer-type/prostate/staging/?region=on

[11] Resources for Grading Prostate Cancer: https://www.cancer.ca/en/cancer-information/cancer-type/prostate/grading/?region=on

[12] Close relatives typically refers to first and second degree blood relatives on the same side of the family, but may include third degree relatives based on the family structure.

Hereditary Gastrointestinal (GI) Cancers (Lynch Syndrome, Gastric, Pancreas, Polyposis)

Hereditary cancer syndromes that are associated with increased risks for GI cancers include a number of different conditions. The most common hereditary GI cancer syndrome is Lynch syndrome. Lynch syndrome (LS) associated cancers include colorectal (CRC), endometrial (EC), gastric, gastroesophageal junction (GEJ), small bowel, pancreas, hepatobiliary, ovarian, renal pelvis, ureter, glioblastoma, sebaceous neoplasm (including keratoacanthoma). Less commonly associated cancers such as bladder, adrenal cortical, sarcoma, breast and prostate cancer are typically not suggestive of LS in isolation, but may be considered in conjunction with personal or family history of hallmark LS cancers.

For evaluation of Lynch syndrome (LS), immunohistochemistry (IHC) for the mismatch repair proteins should be initiated on a LS-associated tumour as a first step when possible. In some cases, when tumour is not accessible for high-risk individuals or in individuals with metastatic disease, panel testing may be prioritized or ordered concurrently with IHC. As of December 17, 2018, reflex MMR IHC to screen for LS should be performed on tumours of newly diagnosed patient with invasive colorectal and endometrial adenocarcinoma under 70 years of age. *BRAF* testing and *MLH1* methylation testing should also be performed as applicable. This testing should be coordinated by the diagnosing laboratory.

1. **Immunohistochemistry (IHC) for MMR proteins in individuals with a:**
    a. Personal history of LS cancer ≤50 years of age
    b. Personal history of 2 primary LS cancers, with the first diagnosed ≤60 years of age
    c. Personal history of a LS cancer with ≥2 close relatives[13] with LS cancer

    For additional details, see Appendix C: MMR IHC Results Flowchart.

2. **Lynch Syndrome Panel in individuals with a:**
    a. Personal history of a IHC deficient tumour (exception of sebaceous neoplasm), as suggested by algorithm (Appendix C) or NCCN table: Tumor Testing Results and Additional Testing Strategies[14]
    b. Personal history of a IHC deficient sebaceous neoplasm plus ≥1 of the following: diagnosed ≤60 years of age, multiple primary sebaceous neoplasms, personal and/or close relative(s)[13] diagnosed with LS cancer

[13] Close relatives typically refers to first and second degree relatives on the same side of the family, but may include third degree relatives based on the family structure.
[14] National Comprehensive Cancer Network. (2020). *Genetic/Familial High-Risk Assessment: Colorectal (version 1.2020).* Retrieved from: https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf

3. Polyposis Panel (CRC/polyps only) or Hereditary GI Panel:

a. Affected and unaffected first degree relatives (FDR) from Amsterdam I/II[15] families. Lynch syndrome should be ruled out when possible (see Lynch Syndrome Panel).

b. Personal history of polyposis as described in Table 1: Polyposis Table

c. Personal history of any of the following suspicious extracolonic tumours:

i. Cribiform-morular variant of papillary thyroid cancer

ii. Hepatoblastoma

iii. Desmoid <40 years of age

iv. Retinal pigment epithelium (RPE) hamartomas* associated with FAP (RPEH-FAP)

* RPE hamartomas are defined by (1) bilateralism, (2) occurrence in multiple quadrants, (3) pisiform shape, and (4) irregular borders

Note: The term "CHRPE or bear tracks" are not specific to FAP and alone would not qualify for genetic assessment

Table 1: Polyposis Table

Number of polyps	Additional Risk Factors Required
≥20 colorectal adenomas	None
10-19 colorectal adenomas	≤60 years of age
5-9 colorectal adenomas	Personal history of 5-9 colorectal adenomas diagnosed at: • <40 years of age and extracolonic manifestation[16] commonly associated with FAP or MAP • <50 years of age and ≥1 of the following: CRC ≤50 years of age, EC ≤60 years of age, glioblastoma, astrocytoma, or ≥10 additional polyps (i.e., serrated adenoma, hyperplastic and especially unbiopsied polyps that could represent additional adenomas) Personal history of 5-9 colorectal adenomas with: • one FDR with of CRC <50, EC <60 or GBM or astrocytoma, OR • ≥2 FDR or SDR with CRC or EC at any age
Fundic gland polyposis (FPG)	• 100 or more FGP (may be described as carpeting) • Description of clustering, multiple FGP in absence of proton pump inhibitor (PPI) use and sparing the antrum and lesser curvature of the stomach • >30 FGP (in absence of PPI) sparing antrum and curvature + FDR who has path confirmed gastric cancer <50 or path confirmed FG polyposis
≥2 hamartomatous polyps	Clinical assessment for hamartomatous polyposis syndromes

[15] Vasen, H. F., Watson, P., Mecklin, J. P., & Lynch, H. T. (1999). New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. Gastroenterology, 116(6), 1453–1456. https://doi.org/10.1016/s0016-5085(99)70510-x

[16] Vasen, H. F., Möslein, G., Alonso, A., Aretz, S., Bernstein, I., Bertario, L., Blanco, I., Bülow, S., Burn, J., Capella, G., Colas, C., Engel, C., Frayling, I., Friedl, W., Hes, F. J., Hodgson, S., Järvinen, H., Mecklin, J. P., Møller, P., Myrhøi, T., … Wijnen, J. (2008). Guidelines for the clinical management of familial adenomatous polyposis (FAP). Gut, 57(5), 704–713. https://doi.org/10.1136/gut.2007.136127

4. Serrated Polyposis (*RNF43*)

a. Personal history of serrated polyposis (WHO/NCCN criteria)

   i. Personal history of >20 serrated polyps in colon/rectum, with at least 5 being proximal to rectum

   ii. Personal history of ≥ 5 serrated polyps/lesions proximal to rectum, all polyps measuring ≥ 5 mm and at least 2 polyps measuring ≥10 mm

Note: If individual meets criteria for both polyposis and serrated polyposis, add *RNF43* to larger panel.

5. Gastric Panel[17]

a. Personal history of gastric or gastroesophageal junction adenocarcinoma at ≤50 years of age

b. Personal history of diffuse gastric cancer (DGC) at any age in individuals of Maori ethnicity

c. Personal history of DGC at any age in individual with personal or family history of cleft lip/palate

d. Personal history of DGC and lobular breast cancer, both diagnosed <70 years of age

e. Personal history of bilateral lobular breast cancer, diagnosed <70 years of age

f. Personal history of gastric in situ signet ring cells or pagetoid spread of signet ring cells <50 years of age

g. An affected individual in a family meeting any of the following criteria:

   i. ≥2 close relatives[18] with gastric cancer any age, with at least one confirmed as DGC

   ii. ≥1 close relative with DGC at any age, and ≥1 close relative with lobular breast cancer at age <70 in different family members on the same side of the family

   iii. ≥2 close relatives with lobular breast cancer at <50 years of age

   iv. ≥3 close relatives with gastric cancer (any type) in close relatives

h. Indirect testing of unaffected family members may be considered if the family history meets criteria 'g' and it is not possible to first test an affected/informative individual (see General Principle 2)

[17] Gastric panel criteria are based on the International Gastric Cancer Linkage Consortium (IGCLC) 2020 guidelines, with additional criteria to incorporate other hereditary gastric and gastroesophageal junction cancers:
Blair, V. R., McLeod, M., Carneiro, F., Coit, D. G., D'Addario, J. L., van Dieren, J. M., Harris, K. L., Hoogerbrugge, N., Oliveira, C., van der Post, R. S., Arnold, J., Benusiglio, P. R., Bisseling, T. M., Boussioutas, A., Cats, A., Charlton, A., Schreiber, K., Davis, J. L., Pietro, M. D., Fitzgerald, R. C., … Guilford, P. (2020). Hereditary diffuse gastric cancer: updated clinical practice guidelines. The Lancet. Oncology, 21(8), e386–e397. https://doi.org/10.1016/S1470-2045(20)30219-9

[18] Close relatives typically refers to first and second degree blood relatives on the same side of the family, but may include third degree relatives based on the family structure.

Hereditary Pancreatic Cancer

1. Personal history of pancreatic adenocarcinoma regardless of age or family history.

Gastrointestinal Stromal Tumours (GISTs)

1. Personal history of multiple primary GISTs.
2. Personal history of GIST with syndromic manifestations.
3. Personal history of SDH-deficient GISTs, or GISTs with NF1/SDH variants.[19]
4. Personal history of GIST at any age and ≥1 close relative(s)[20] with a GIST at any age.

Familial Melanoma

1. Personal history of ≥3 primary malignant melanomas
2. Personal history of malignant melanoma with ≥2 FDR/SDR relatives with melanoma and/or pancreatic cancer.
3. Personal history of malignant melanoma under 40 years of age with at least 1 FDR/SDR with melanoma or pancreatic cancer.
4. Personal history of uveal melanoma.

   Note: In melanoma families with in situ melanoma (lentigo maligna melanoma), or other cancer history such as breast/prostate cancer, genetic testing may be indicated based on clinical assessment[21]

[19] Refer to General Criteria for all Disease Sites #3

[20] Close relatives typically refers to first and second degree blood relatives, but may include third degree relatives based on the family structure.

[21] Leachman, S. A., Lucero, O. M., Sampson, J. E., Cassidy, P., Bruno, W., Queirolo, P., & Ghiorzo, P. (2017). Identification, genetic testing, and management of hereditary melanoma. Cancer metastasis reviews, 36(1), 77–90. https://doi.org/10.1007/s10555-017-9661-5

Hereditary Renal Tumour Syndromes

1. Personal history of a renal tumour with ≥1 of the following:
    a. Bilateral/multifocal disease[22].
    b. Diagnosis ≤45 years of age.
    c. Family history of a close relative[23] with a renal tumour.
    d. Non-clear cell pathology (papillary, chromophobe, oncocytic, hybrid tumours).
    e. Evidence of syndromic presentation (e.g., seizures, pneumothorax).
    f. Personal/family history of associated tumours (e.g., hemangioblastoma, leiomyomas, angiomyolipomas).

Pheochromocytoma/Paraganglioma

1. Personal history of a pheochromocytoma/paraganglioma.

Soft Tissue/Sarcoma

1. Personal history of sarcoma <45 and family history of young onset malignancy in close relative(s) and/or evidence of syndromic presentation. Single gene testing may be prioritized based on genetics assessment (e.g., NF1).

[22] Synchronous, unilateral tumours should be considered a single site of disease
[23] Close relatives typically refers to first and second degree blood relatives, but may include third degree relatives based on the family structure.

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Appendix A: Hereditary Cancer Testing – Summary of Genes and Syndromes

Provincial Hereditary Cancer Testing Gene List				
AIP	*APC*	*ATM*	*AXIN2*	*BAP1*
BARD1	*BMPR1A*	*BRCA1*	*BRCA2*	*BRIP1*
CDC73	*CDH1*	*CDK4*	*CDKN1B*	*CDKN2A*
CHEK2	*CTNNA1*	*DICER1*	*EGFR*	*EGLN1*
EPCAM	*EXT1*	*EXT2*	*FH*	*FLCN*
GALNT12	*GREM1*	*HOXB13*	*KIT*	*LZTR1*
MAX	*MEN1*	*MET*	*MITF*	*MLH1*
MLH3	*MSH2*	*MSH3*	*MSH6*	*MUTYH*
NBN	*NF1*	*NF2*	*NTHL1*	*PALB2*
PDGFRA	*PMS2*	*POLD1*	*POLE*	*POT1*
PRKAR1A	*PTCH1*	*PTEN*	*RAD51C*	*RAD51D*
RB1	*RECQL*	*RET*	*RNF43*	*RPS20*
SDHA	*SDHAF2*	*SDHB*	*SDHC*	*SDHD*
SMAD4	*SMARCA4*	*SMARCB1*	*SMARCE1*	*STK11*
SUFU	*TMEM127*	*TP53*	*TSC1*	*TSC2*
VHL				

Hereditary Cancer Testing Common Gene Panels and Single Gene Disorders

Hereditary Cancer Testing Common Gene Panels	
Syndrome / Disease Site	**Associated Genes**
Hereditary Breast/ Ovarian/ Prostate	*ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, HOXB13, MLH1, MSH2, MSH6, PALB2, PMS2, PTEN, RAD51C, RAD51D, STK11, TP53*
Hereditary Endometrial	*BRCA1, BRCA2, EPCAM, MLH1, MSH2, MSH6, PMS2, POLD1, POLE, PTEN*
Hereditary GI (Lynch Syndrome, Gastric, Pancreas, Polyposis)	*APC, ATM, BMPR1A, BRCA1, BRCA2, CDH1, CDKN2A, CHEK2, CTNNA1, EPCAM, GREM1, MLH1, MLH3, MSH2, MSH3, MSH6, MUTYH, NTHL1, PALB2, PMS2, POLD1, POLE, PTEN, SDHB, SDHD, SMAD4, STK11, TP53*
Lynch Syndrome	*EPCAM, MLH1, MSH2, MSH6, PMS2*
Gastric	*APC, ATM, BRCA1, BRCA2, CDH1, CTNNA1, EPCAM, MLH1, MSH2, MSH6, PALB2, PMS2, SDHB, SDHD, SMAD4, STK11, TP53*
Pancreas (Adenocarcinoma)	*ATM, BRCA1, BRCA2, CDKN2A, EPCAM, MLH1, MSH2, MSH6, PALB2, PMS2, STK11, TP53*
Polyposis	*APC, BMPR1A, EPCAM, GREM1, MLH1, MLH3, MSH2, MSH3, MSH6, MUTYH, NTHL1, PMS2, POLD1, POLE, PTEN, SMAD4, STK11, TP53*
Familial Gastrointestinal Stromal	*KIT, PDGFRA, SDHA, SDHAF2, SDHB, SDHC, SDHD*
Familial Melanoma	*BAP1, BRCA2, CDK4, CDKN2A, MITF, POT1, PTEN*
Familial Renal	*BAP1, FH, FLCN, MET, MITF, PTEN, SDHA, SDHAF2, SDHB, SDHC, SDHD, TP53, TSC1, TSC2, VHL*
Hereditary Pheochromocytoma and Paraganglioma	*FH, MAX, MEN1, NF1, RET, SDHA, SDHAF2, SDHB, SDHC, SDHD, TMEM127, VHL*
CNS	*APC, EPCAM, LZTR1, MLH1, MSH2, MSH6, NF1, NF2, PMS2, POLE, POT1, PTCH1, PTEN, SMARCB1, SMARCE1, SUFU, TP53, TSC1, TSC2, VHL*
Soft Tissue	*APC, ATM, BRCA1, BRCA2, CHEK2, EPCAM, MLH1, MSH2, MSH6, NF1, PMS2, TP53*

Single Gene Syndromes or Small Panels	
Syndrome	**Associated Genes**
AXIN2-related Attenuated Familial Adenomatous Polyposis	*AXIN2*
BAP1 Tumour Predisposition Syndrome	*BAP1*
Birt-Hogg-Dube Syndrome	*FLCN*
Carney Complex	*PRKAR1A*
Familial Adenomatous Polyposis (name changed from: CHRPE, CMV Thyroid, Desmoid)	*APC, (+/-MUTYH)*
DICER-associated Syndrome	*DICER1*
Dysplastic Nevus Syndrome	*CDK4, CDKN2A*
Familial Isolated Pituitary Adenoma	*AIP*
Hereditary Hyperparathyroidism	*CDC73, MEN1*
Hereditary Leiomyomatosis and Renal Cell Cancer	*FH*
Hereditary Lung Cancer	*EGFR* (T790M; V834I; V769M)
Li-Fraumeni Syndrome	*TP53*
MEN1 Syndrome	*MEN1, CDKN1B*
Multiple Endocrine Neoplasia Type 2	*RET*
Neurofibromatosis, type 1	*NF1*
Nevoid Basal Cell Carcinoma Syndrome/ Gorlin Syndrome	*PTCH1, SUFU*
Nijmegen Breakage Syndrome	*NBN*
Peutz-Jeghers Syndrome	*STK11*
PTEN Hamartoma Tumour Syndrome	*PTEN*
Rare Polyposis Genes	*GALNT12, RPS20*
Retinoblastoma	*RB1*

Single Gene Syndromes or Small Panels	
Syndrome	**Associated Genes**
Rhabdoid Predisposition Syndrome	*SMARCA4, SMARCB1*
Schwannomatosis	*NF2, LZTR1, SMARCB1*
Sessile Serrated Polyposis Cancer Syndrome	*RNF43*
Small Cell Carcinoma of the Ovary, Hypercalcemic Type (SCCOHT)	*SMARCA4*
Tuberous Sclerosis	*TSC1, TSC2*
Von Hippel-Lindau Syndrome	*VHL*

Appendix B: HCT Eligibility Quick Reference

The HCT Eligibility Quick Reference may be helpful to quickly determine eligibility. Please refer to full document for further details, explanatory notes, and references.

General Criteria All Disease Sites	1. ≥5% likelihood of P/LP variant in affected/unaffected individual 2. Relative with P/LP variant 3. Systemic therapy planning 4. Updated testing 5. Partner testing/ reproductive risk 6. Confirmation of germline status based on variants in tumour/biopsy specimen 7. Confirmation of germline status based on non-MMR IHC deficiency 8. Clinical judgement
Hereditary Breast Ovarian Cancer	1. Breast ≤45 2. Breast ≤50 with limited family structure 3. Breast ≤50 with second primary breast cancer 4. Triple negative breast cancer ≤60 5. Male breast cancer 6. Epithelial ovarian cancer (excludes clear cell, mucinous, low grade/borderline) 7. Breast or ovarian cancer + ≥1 family history breast cancer ≤50, triple negative breast cancer ≤60, ovarian cancer, male breast cancer, high risk prostate cancer, pancreatic cancer, ≥2 additional breast/prostate cancer cases
Prostate Cancer	1. Metastatic prostate cancer 2. High risk, locally advanced, prostate cancer 3. Prostate cancer + ≥1 close relatives with high risk prostate cancer 4. Prostate cancer + ≥2 close relatives with breast/prostate cancer
Melanoma	1. ≥3 primary malignant melanomas 2. Malignant melanoma + ≥2 close relatives with melanoma and/or pancreatic cancer 3. Malignant melanoma ≤40 with ≥1 close relatives with melanoma and/or pancreatic cancer 4. Uveal melanoma
Hereditary Renal Tumour Syndromes	1. Renal tumour + ≥1 of the following: a) bilateral/multifocal disease b) diagnosis ≤45 years of age c) F/H of a close relative with a renal tumour d) non-clear cell pathology e) syndromic presentation f) personal/family history of associated tumours (e.g., hemangioblastoma)
Pheo/PGL	1. Pheochromocytoma/paraganglioma, any age
Soft Tissue/ Sarcoma	1. Sarcoma ≤45 years a) F/H close relative with early onset malignancy b) Syndromic presentation (*single gene testing may be prioritized based on genetics assessment

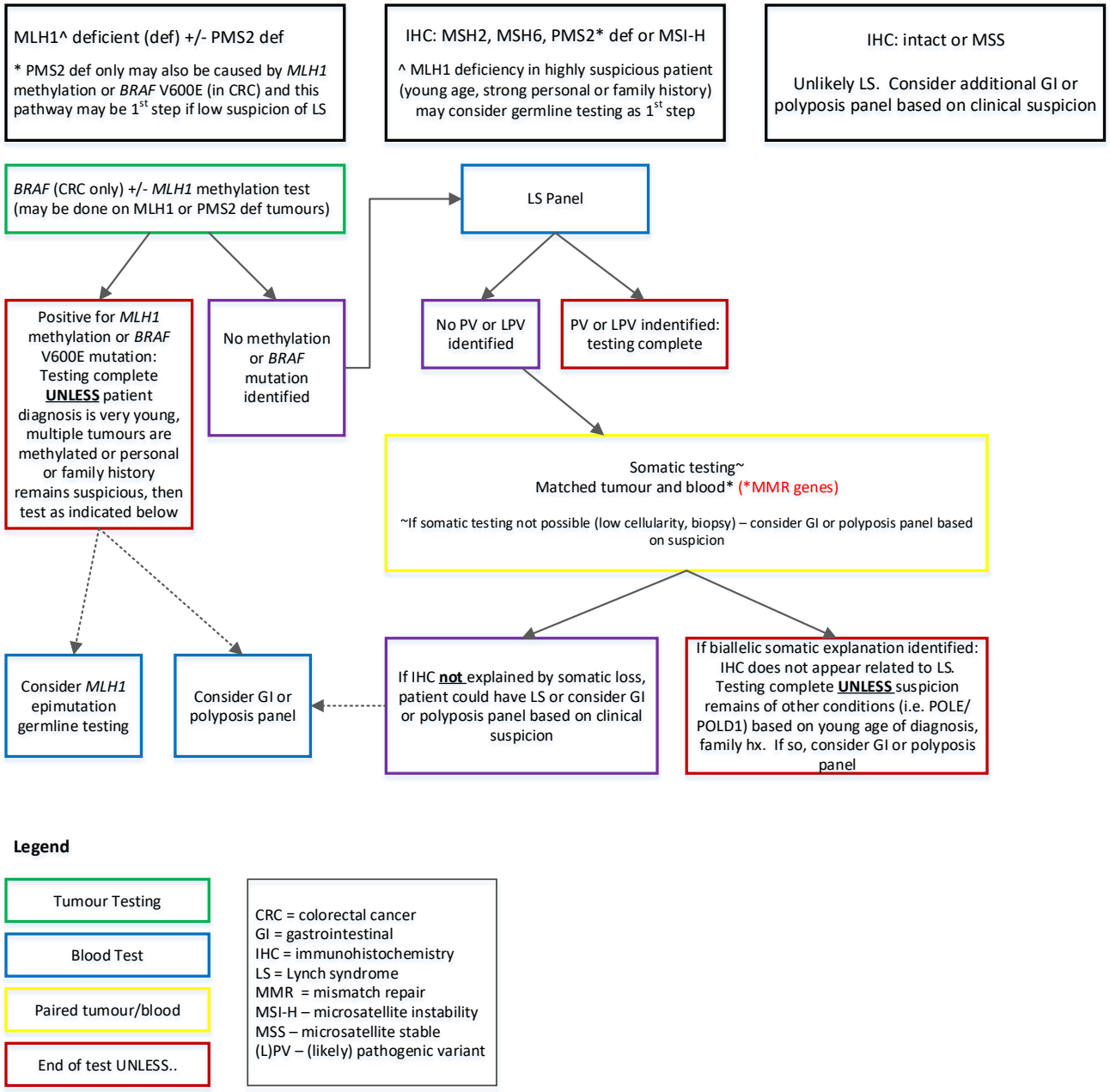
Lynch Syndrome	Criteria	Test
	1. a) LS cancer ≤50 b) LS cancer + second primary LS cancer <60 c) LS cancer + ≥2 close relatives with LS cancers	IHC
	2. a) IHC deficient tumour (exception sebaceous neoplasm) b) IHC deficient sebaceous neoplasm + <60 OR multiple OR F/H ≥1 close relative LS cancer	LS panel
Polyposis or GI panel	3. a) Affected and unaffected FDR's from Amsterdam I/II[24] families.	
	b) Personal hx of polyposis that meets one of the following: 1. ≥20 colorectal adenomas, any age 2. 10-19 colorectal adenomas ≤ 60 years 3. 5-9 colorectal adenomas diagnosed <40 years of age and extracolonic manifestation[25] commonly associated with FAP or MAP 4. 5-9 adenomas <50 years of age and ≥1 of the following: CRC ≤50 years of age, EC ≤60 years of age, glioblastoma, astrocytoma, or ≥10 additional polyps (i.e., serrated adenoma, hyperplastic and especially unbiopsied polyps that could represent additional adenomas) 5. 5-9 adenomas + FDR with of CRC <50, EC <60 or GBM or astrocytoma 6. 5-9 adenomas + ≥2 FDR or SDR with CRC or EC at any age	
	7. Fundic Gland Polyposis a. 100 or more FGP (may be described as carpeting) b. Description of clustering, multiple FGP in absence of proton pump inhibitor (PPI) use and sparing the antrum and lesser curvature of the stomach c. >30 FGP (in absence of PPI) sparing antrum and curvature + FDR who has path confirmed gastric cancer <50 or path confirmed FG polyposis	
	8. Hamartomatous Polyposis	
	c) Personal hx of any of the following suspicious extracolonic tumours: 1. Cribiform-morular variant of papillary thyroid cancer 2. hepatoblastoma 3. desmoid <40 4. RPE hamartomas	
Serrated polyposis (*RNF43*)	4. a) Personal history of >20 serrated polyps in colon/rectum, with at least 5 being proximal to rectum b) Personal history of ≥5 serrated polyps/lesions proximal to the rectum, all polyps measuring ≥5mm and at least 2 polyps measuring ≥10 mm Note: Add *RNF43* to larger panel both polyposis and serrated polyposis criteria are met.	

[25] Vasen, H. F., Möslein, G., Alonso, A., Aretz, S., Bernstein, I., Bertario, L., Blanco, I., Bülow, S., Burn, J., Capella, G., Colas, C., Engel, C., Frayling, I., Friedl, W., Hes, F. J., Hodgson, S., Järvinen, H., Mecklin, J. P., Møller, P., Myrhøi, T., … Wijnen, J. (2008). Guidelines for the clinical management of familial adenomatous polyposis (FAP). Gut, 57(5), 704–713. https://doi.org/10.1136/gut.2007.136127

Gastric Cancer	5. a) Gastric/GE cancer ≤50 years b) Diffuse gastric cancer (DGC) + Maori ethnicity c) DGC any age with personal/family history cleft lip/palate d) DGC and lobular breast cancer (LBC), both ≤70 e) Bilateral LBC, diagnosed ≤70 f) Gastric in situ/pagetoid spread of signet ring cells ≤50 g) Informative/affected individual in a family meeting any of the following: i) ≥ 2 close relatives with gastric cancer, one confirmed DGC ii) ≥1 DGC AND ≥1 LBC <70 in different family members, on same side of the family iii) ≥2 LBC ≤50 iv) ≥3 gastric cancer (any type) in close relatives h) Unaffected relative if family history meets criteria 'g'
Pancreatic cancer	1. Personal history of pancreatic adenocarcinoma, any age
GISTs	1. Multiple primary GISTs 2. GIST with syndrome manifestations 3. SDH-deficient GISTS or GISTs with NF1/SDH variants 4. Personal history of GIST, any age, and ≥1 closer relative with a GIST

Appendix C: 2021 MMR IHC Results Flowchart

MMR IHC Results Flowchart



Legend

- Tumour Testing
- Blood Test
- Paired tumour/blood
- End of test UNLESS..

CRC = colorectal cancer
GI = gastrointestinal
IHC = immunohistochemistry
LS = Lynch syndrome
MMR = mismatch repair
MSI-H – microsatellite instability
MSS – microsatellite stable
(L)PV – (likely) pathogenic variant