Ontario Health
Cancer Care Ontario

Hereditary Cancer Testing Eligibility Criteria: Version 3

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Summary of Changes

Updates in Version 3 of Ontario's Hereditary Cancer Testing Eligibility Criteria from Version 2 include:

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Introduction

On April 1, 2021, Ontario Health – Cancer Care Ontario (OH-CCO) implemented Provincial Hereditary Cancer Testing (HCT). 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. The Version 3 update is the product of an annual review process to ensure patients have access to HCT that is standardized, evidence based and coordinated across the province. For a full list of updates, please see Summary of Changes on page 3.

This document is intended to be used primarily by genetics professionals and serves as a companion tool to Ontario's standardized Hereditary Cancer Testing Gene List (see Appendix A). Oncologists, surgeons, specialist teams, and primary care providers may also use this document when working in conjunction with the clinical genetics team to facilitate cancer genetic services for their patients. This document 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 have 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

[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

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.

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 the Provincial HCT program in Ontario requires a robust workforce in laboratory and clinical genetics, and an effort should be made to overcome the current shortage of resources available to provide this expert clinical care.

General Principles

In order to address the goal of providing standardized care and equitable access to hereditary cancer services across Ontario, 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].

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 a family history of adult-onset recessive cancer predisposition syndromes (e.g. *MUTYH*-related polyposis).

[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.

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.

8. Diagnostic genetic testing in children and adolescents (under the age of 18), may be offered in order to confirm a hereditary cancer syndrome in a child who fits diagnostic criteria for a hereditary cancer predisposition syndrome. Genetic testing in children for a known familial pathogenic/likely pathogenic variant(s) may be offered if it will inform early detection, screening and/or prevention recommendations in childhood. However, HCT is not indicated in individuals <18 years if results will not guide medical management until adulthood or if the results will be used solely to inform future reproductive risks. A family centred approach to genetic counselling, including a full discussion of risks, benefits and limitations is recommended. Pre and post-test genetic counselling should involve the child and/or adolescent in an age-appropriate manner along with appropriate consent from parent or substitute decision makers when needed based on developmental capacity. (For more information, see: Genetic testing and screening in children | Canadian Paediatric Society (www.cps.ca)).

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, hereditary cancer testing (HCT) can be initiated by a treating oncologist to aid in systemic therapy planning if all other criteria for the therapy/treatment are met. Individuals may be eligible for HCT based on their eligibility status for the treatment alone, regardless of other hereditary cancer syndrome risk factors (see General Principle 1 for implementation considerations).

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]

   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. Confirmatory germline genetic testing should be considered if clinical implications are present for the variant in the germline state.

   - The variant should be interpreted in the germline context from a laboratory with experience in germline annotation.
   - 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]

[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 invasive breast cancer ≤60 years of age.

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

6. Personal history of invasive epithelial ovarian cancer (any grade)[7], epithelial fallopian tube[8] or peritoneal cancer at any age.

7. Personal history of breast or ovarian cancer any age with ≥1 close relative(s)[9] 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[10] cancer any age
    f. Two or more close relatives[9] with breast cancer or prostate cancer at any age

[7] Includes serous, endometrioid, mixed, clear cell, mucinous and poorly differentiated. Borderline (formerly low malignant potential) tumours of the ovary are excluded.
[8] Includes serous tubal intraepithelial carcinoma (STIC). Testing for patients with serous tubal intraepithelial lesions (STIL) may also be considered, particularly in the presence of additional risk factors/family history.
[9] 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.
[10] 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[11], Grade Group 4 or 5 (Gleason Score 8 to 10)[12], 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[13] with prostate, pancreas, ovarian 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.

Hereditary Endometrial Cancer

The Hereditary Cancer Testing Criteria Working Group recommends that either the Hereditary GI panel or Hereditary Breast/Ovarian/Prostate panel should be used preferentially over the Hereditary Endometrial panel. This decision should be guided by the patient's clinical and family history.

Follow *Lynch Syndrome and Gastrointestinal Polyposis Syndromes* eligibility criteria.

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

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

[13] 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.

Lynch Syndrome and Gastrointestinal Polyposis Syndromes

Includes Lynch Syndrome, Hereditary Gastrointestinal (GI), and Polyposis panels

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 (see criterion 3a below). In Ontario, there is a provincial program for reflex mismatch repair immunohistochemistry (MMR IHC) testing at the time of diagnosis. This document recommends hereditary cancer testing that might be indicated based on these MMR IHC results, as well as when to initiate MMR IHC (if not yet performed) and/or hereditary cancer testing that might be indicated based on personal and/or family history.

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[14] 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[15]
    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)[14] diagnosed with LS cancer

[14] 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.
[15] 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[16] 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[17] (RPEH-FAP)

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

d. MMR intact/MSS cases or IHC deficient cases with biallelic somatic mutations are unlikely to be LS. Consider panel testing based on clinical assessment/judgement (e.g., LS cancer ≤35 years of age). See General Principle #7a.

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[18] 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

[16] 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

[17] The term "CHRPE or bear tracks" are not specific to FAP and alone would not qualify for genetic assessment

[18] 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: Single gene testing of *RNF43* is appropriate for individuals with a personal history of serrated polyposis as outlined above. Consider offering the polyposis or GI panel to these individuals if any adenomas/suspicious polyps are also identified, or cannot be ruled out.

Hereditary Gastric Cancer

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[19]

1. Personal history of gastric or gastroesophageal junction adenocarcinoma at ≤50 years of age
2. Personal history of diffuse gastric cancer (DGC) at any age in individuals of Maori ethnicity
3. Personal history of DGC at any age in individual with personal or family history of cleft lip/palate
4. Personal history of DGC and lobular breast cancer, both diagnosed <70 years of age
5. Personal history of bilateral lobular breast cancer, diagnosed <70 years of age
6. Personal history of gastric in situ signet ring cells or pagetoid spread of signet ring cells <50 years of age
7. An affected individual in a family meeting any of the following criteria:
    a. ≥2 close relatives[20] with gastric cancer any age, with at least one confirmed as DGC
    b. ≥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
    c. ≥2 close relatives with lobular breast cancer at <50 years of age
    d. ≥3 close relatives with gastric cancer (any type) in close relatives
8. Indirect testing of unaffected family members may be considered if the family history meets criteria '7' and it is not possible to first test an affected/informative individual (see General Principle 2)

[19] 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

[20] 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.[21]
4. Personal history of GIST at any age and ≥1 close relative(s)[22] 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[23]

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

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

[23] 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[24].
    b. Diagnosis ≤45 years of age.
    c. Family history of a close relative[25] 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).

Hereditary Pheochromocytoma/Paraganglioma

1. Personal history of a pheochromocytoma/paraganglioma.

Central Nervous System (CNS)

1. Personal history of a brain tumor with any of the following:
    a. Multiple tumors and/or cancers in one person (e.g. brain, soft tissue, LS cancers)
    b. ≥2 close relatives with brain tumours and/or associated cancers (Lynch syndrome cancer, Li-Fraumeni syndrome tumours, soft tissue, etc.) on the same side of the family

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).

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

Ashkenazi Jewish

When applying Ashkenazi Jewish (AJ) criteria for testing, family history criteria should be reflective of the side/relative that is of AJ descent. Note: NCCN suggests AJ ancestry criteria can be considered for individuals with at least one grandparent of AJ descent on the side of the family with a cancer history.

Individuals of Ashkenazi Jewish descent **who do not otherwise meet cancer gene panel criteria** may be offered the Ashkenazi Jewish Panel if one of the following criteria are met:

1. Personal history of breast cancer, prostate cancer[26], colorectal cancer and/or GI polyposis at any age.
2. Indirect testing of unaffected family members may be considered if it is not possible to test an affected/informative individual (see General Principle 2), in families that include ≥1 first- or second-degree relative with breast cancer, epithelial ovarian cancer, pancreatic cancer, metastatic prostate cancer, or GI polyposis any age, or CRC diagnosed <60 years of age.

For individuals of Ashkenazi Jewish descent who meet criteria for a full cancer gene panel based on personal and/or family history, consider offering a more comprehensive panel that also includes the following genes: *APC, BRCA1, BRCA2, CHEK2, GREM1, MSH2* and *MSH6*.

[26] Carter, H. B., et al (2019). Germline Mutations in ATM and BRCA1/2 Are Associated with Grade Reclassification in Men on Active Surveillance for Prostate Cancer. *European urology*, *75*(5), 743–749. https://doi.org/10.1016/j.eururo.2018.09.021

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

Provincial Hereditary Cancer Testing Gene List (76 genes)

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

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[27]	*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, GALNT12, GREM1, MLH1, MLH3, MSH2, MSH3, MSH6, MUTYH, NTHL1, PALB2, PMS2, POLD1, POLE, PTEN, RNF43, RPS20, 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, GALNT12, GREM1, MLH1, MLH3, MSH2, MSH3, MSH6, MUTYH, NTHL1, PMS2, POLD1, POLE, PTEN, RNF43, RPS20, 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*

[27] The Hereditary Cancer Testing Criteria Working Group recommends that either the Hereditary GI panel or Hereditary Breast/ Ovarian/ Prostate panel should be used preferentially over the Hereditary Endometrial panel. This decision should be guided by the patient's clinical and family history.

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*

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*

Ashkenazi Jewish Panel

#	Human Genome Variation Society Nomenclature	Alternate Name
1	NM_000038.6(APC):c.3920T>A (p.Ile1307Lys)	APC I1307K
2	NM_007294.4(BRCA1):c.68_69del (p.Glu23fs)	BRCA1 (185delAG or 187delAG)
3	NM_007294.3(BRCA1):c.5266dupC (p.Gln1756Profs)	BRCA1 (5382insC or 5385insC)
4	NM_000059.4(BRCA2):c.5946del (p.Ser1982fs)	BRCA2 (617delT)
5	NM_007194.4(CHEK2):c.1283C>T (p.Ser428Phe)	CHEK2 1283C>T
6	GREM1 40 kb dup	*N/A*
7	NM_000251.2(MSH2):c.1906G>C (p.Ala636Pro)	MSH2 A636P
8	NM_000179.2 (MSH6):c.3984_3987dupGTCA (p.Leu1330Valfs)	MSH6 c.3984_3987dupGTCA
9	NM_000179.2(MSH6):c.3959_3962delCAAG (p.Ala1320Glufs)	MSH6 c.3959_3962delCAAG

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.

Category	HCT Eligibility Criteria – Quick Reference
General Criteria All Disease Sites	1. ≥5% likelihood of P/LP variant (General Principle 2) 2. Relative with P/LP variant 3. Systemic therapy planning 4. Updated testing 5. Partner testing/ reproductive risk 6. Clinical judgement 7. Confirmation of germline status based on variants in tumour/biopsy specimen 8. Confirmation of germline status based on non-MMR IHC deficiency
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 invasive breast cancer ≤60 5. Male breast cancer 6. Invasive epithelial ovarian cancer (excludes borderline/low malignant potential), and/or epithelial fallopian tube (including STIC and STIL) or peritoneal cancers. 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 pancreas/ovarian/breast/prostate cancer
Hereditary Endometrial	The Working Groups recommends that the Hereditary GI panel or Hereditary Breast/Ovarian/Prostate panel should be used preferentially over the Hereditary Endometrial panel. This decision should be guided by the patient's clinical and family history. *Follow Lynch syndrome eligibility criteria.*
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

Category	HCT Eligibility Criteria – Quick Reference
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	IHC 1. a) LS cancer ≤50 b) LS cancer + second primary LS cancer <60 c) LS cancer + ≥2 close relatives with LS cancers LS Panel 2. a) IHC deficient tumour (exception sebaceous neoplasm) b) IHC deficient sebaceous neoplasm + <60 OR multiple OR F/H ≥1 close relative LS cancer
Polyposis or GI panel	3. a) Affected and unaffected FDR's from Amsterdam I/II[28] 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[29] 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 d) MMR intact/MSS cases or IHC deficient cases with biallelic somatic mutations are unlikely to be LS. Consider panel testing based on clinical assessment/judgement (eg. LS cancer ≤35 years of age).

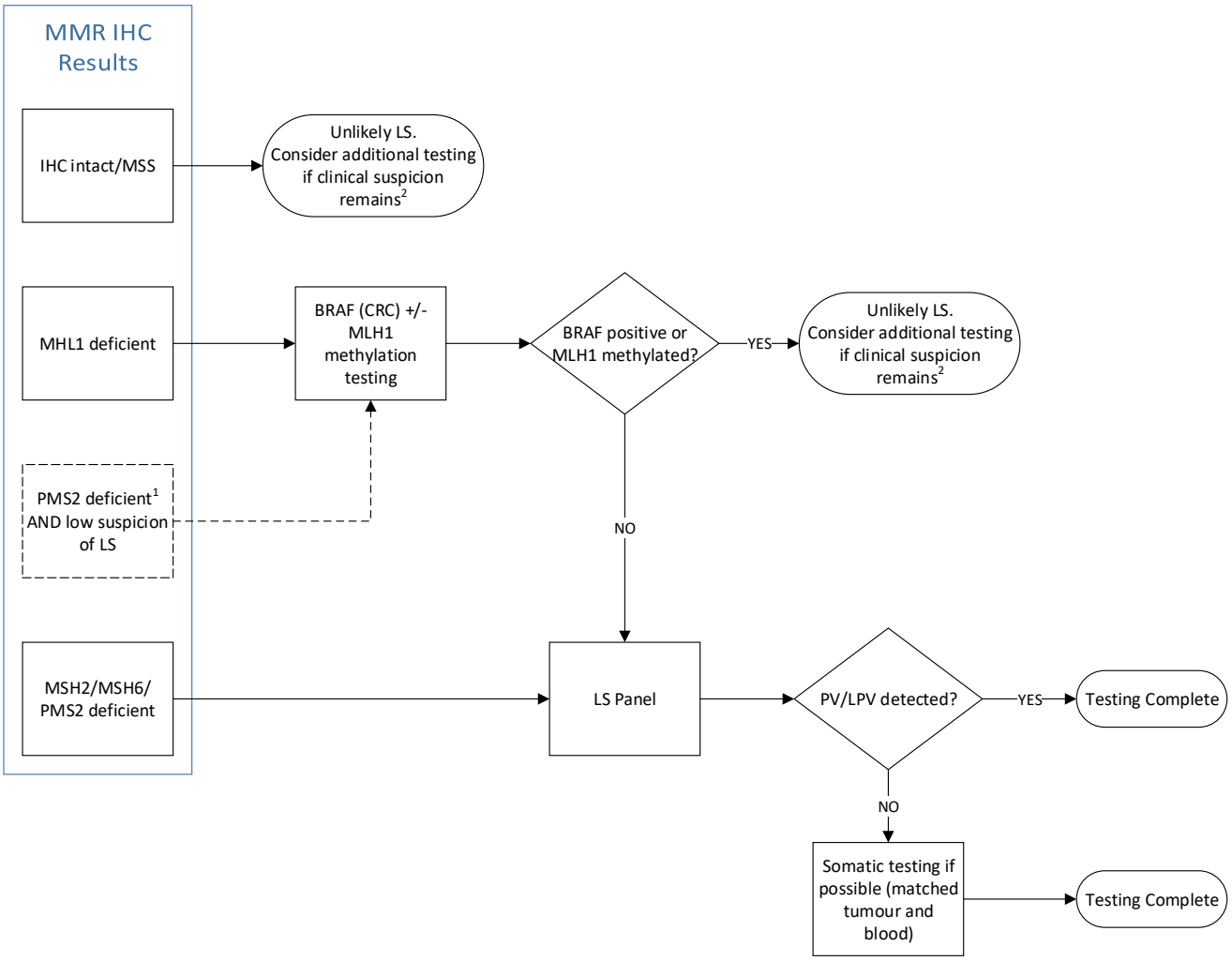
[29] Vasen, H. F., et al. Wijnen, J. (2008). Guidelines for the clinical management of familial adenomatous polyposis (FAP). Gut, 57(5), 704–713. https://doi.org/10.1136/gut.2007.136127

Category	HCT Eligibility Criteria – Quick Reference
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: Single gene testing of *RNF43* is appropriate for individuals with a personal history of serrated polyposis as outlined above. Consider offering the polyposis or GI panel to these individuals if any adenomas/suspicious polyps are also identified, or cannot be ruled out.
Gastric Cancer	1. Gastric/GE cancer ≤50 years 2. Diffuse gastric cancer (DGC) + Maori ethnicity 3. DGC any age with personal/family history cleft lip/palate 4. DGC and lobular breast cancer (LBC), both ≤70 5. Bilateral LBC, diagnosed ≤70 6. Gastric in situ/pagetoid spread of signet ring cells ≤50 7. Informative/affected individual in a family meeting any of the following: a. ≥ 2 close relatives with gastric cancer, one confirmed DGC b. ≥1 DGC AND ≥1 LBC <70 in different family members, on same side of the family c. ≥2 LBC ≤50 d. ≥3 gastric cancer (any type) in close relatives 8. Unaffected relative if family history meets criteria '7'
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
CNS	1. Brain tumour + ≥1 of the following: a. Multiple tumors and/or cancers in one person b. ≥2 close relatives with brain tumours and/or associated cancers, on the same side of the family
Ashkenazi Jewish	AJ panel may be offered to individuals of AJ descent that otherwise do not meet the cancer gene panel criteria, as long as one of the following is met: 1. Personal hx of breast cancer, prostate cancer, CRC and/or GI polyposis at any age. 2. Indirect testing of unaffected family members may be considered if it is not possible to test an affected/informative individual (see General Principle 2), in families that include ≥1 FDR or SDR with breast cancer, epithelial ovarian cancer, pancreatic cancer, metastatic prostate cancer, or GI polyposis any age, or CRC diagnosed <60 years of age. Note: AJ + cancer gene panel criteria met, consider offering a panel that includes: *APC, BRCA1, BRCA2, CHEK2, GREM1, MSH2* and *MSH6*.

Appendix C: 2021 MMR IHC Results Flowchart

This algorithm outlines the Lynch Syndrome testing process based on MMR IHC results.

If patient and/or family history are highly suspicious based on age at diagnosis/family history, or additional tumour testing not possible, expanded germline panel testing may be offered and/or prioritized in the testing pathway



——— Typical pathway

- - - - Optional pathway

[1] PMS2 deficient only may also be caused by *MLH1* methylation or *BRAF* V600E (in CRC) and this pathway may be 1st step if low suspicion of LS

[2] For example, patient is diagnosed at a young age (e.g., ≤35 years), suspicion remains of other conditions or based on family history

Appendix D: Single/Small Gene Panel Clinical Criteria Reference List

Selection of single/small gene panels should be made based on clinical judgement combined with clinical criteria found in literature. Below is a reference list to assist in this process.

Syndrome	Associated Genes	Reference
AXIN2-related Attenuated Familial Adenomatous Polyposis	*AXIN2*	https://www.ncbi.nlm.nih.gov/medgen/324868 Rivera, B., Perea, J., Sánchez, E., Villapún, M., Sánchez-Tomé, E., Mercadillo, F., Robledo, M., Benítez, J., & Urioste, M. (2014). A novel AXIN2 germline variant associated with attenuated FAP without signs of oligondontia or ectodermal dysplasia. European journal of human genetics : EJHG, 22(3), 423–426. https://doi.org/10.1038/ejhg.2013.146
BAP1 Tumour Predisposition Syndrome	*BAP1*	Pilarski R, Carlo M, Cebulla C, et al. BAP1 Tumor Predisposition Syndrome. 2016 Oct 13 [Updated 2020 Sep 17]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK390611/
Birt-Hogg-Dube Syndrome	*FLCN*	Sattler EC, Steinlein OK. Birt-Hogg-Dubé Syndrome. 2006 Feb 27 [Updated 2020 Jan 30]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1522/
Carney Complex	*PRKAR1A*	Stratakis CA, Raygada M. Carney Complex. 2003 Feb 5 [Updated 2018 Aug 16]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1286/
DICER-associated Syndrome	*DICER1*	Schultz KAP, Stewart DR, Kamihara J, et al. DICER1 Tumor Predisposition. 2014 Apr 24 [Updated 2020 Apr 30]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK196157/
Dysplastic Nevus Syndrome	*CDK4, CDKN2A*	Eckerle Mize D, Bishop M, Resse E, et al. Familial Atypical Multiple Mole Melanoma Syndrome. In: Riegert-Johnson DL, Boardman LA, Hefferon T, et al., editors. Cancer Syndromes [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2009-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK7030/
Familial Isolated Pituitary Adenoma	*AIP*	Korbonits M, Kumar AV. AIP Familial Isolated Pituitary Adenomas. 2012 Jun 21 [Updated 2020 Apr 16]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK97965/

Syndrome	Associated Genes	Reference
Hereditary Hyperparathyroidism	*CDC73, MEN1*	Hyde SM, Rich TA, Waguespack SG, et al. CDC73-Related Disorders. 2008 Dec 31 [Updated 2018 Apr 26]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK3789/
Hereditary Leiomyomatosis and Renal Cell Cancer	*FH*	Kamihara J, Schultz KA, Rana HQ. FH Tumor Predisposition Syndrome. 2006 Jul 31 [Updated 2020 Aug 13]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1252/
Hereditary Lung Cancer	*EGFR (T790M; V834I; V769M)*	Lebrett, M. B., Crosbie, E. J., Smith, M. J., Woodward, E. R., Evans, D. G., & Crosbie, P. (2021). Targeting lung cancer screening to individuals at greatest risk: the role of genetic factors. *Journal of medical genetics*, *58*(4), 217–226. https://doi.org/10.1136/jmedgenet-2020-107399 Benusiglio, P. R., Fallet, V., Sanchis-Borja, M., Coulet, F., & Cadranel, J. (2021). Lung cancer is also a hereditary disease. *European respiratory review : an official journal of the European Respiratory Society*, *30*(162), 210045. https://doi.org/10.1183/16000617.0045-2021
Li-Fraumeni Syndrome	*TP53*	Schneider K, Zelley K, Nichols KE, et al. Li-Fraumeni Syndrome. 1999 Jan 19 [Updated 2019 Nov 21]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1311/
MEN1 Syndrome	*MEN1, CDKN1B*	Giusti F, Marini F, Brandi ML. Multiple Endocrine Neoplasia Type 1. 2005 Aug 31 [Updated 2017 Dec 14]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1538/
Multiple Endocrine Neoplasia Type 2	*RET*	Eng C. Multiple Endocrine Neoplasia Type 2. 1999 Sep 27 [Updated 2019 Aug 15]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1257/
Neurofibromatosis, type 1	*NF1*	Friedman JM. Neurofibromatosis 1. 1998 Oct 2 [Updated 2019 Jun 6]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1109/

Syndrome	Associated Genes	Reference
Nevoid Basal Cell Carcinoma Sydrome/ Gorlin Syndrome	*PTCH1, SUFU*	Evans DG, Farndon PA. Nevoid Basal Cell Carcinoma Syndrome. 2002 Jun 20 [Updated 2018 Mar 29]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1151/
Nijmegen Breakage Syndrome	*NBN*	Varon R, Demuth I, Chrzanowska KH. Nijmegen Breakage Syndrome. 1999 May 17 [Updated 2017 Feb 2]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1176/
Peutz-Jeghers Syndrome	*STK11*	McGarrity TJ, Amos CI, Baker MJ. Peutz-Jeghers Syndrome. 2001 Feb 23 [Updated 2016 Jul 14]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1266/
PTEN Hamartoma Tumour Syndrome	*PTEN*	Yehia L, Eng C. PTEN Hamartoma Tumor Syndrome. 2001 Nov 29 [Updated 2021 Feb 11]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1488/
Retinoblastoma	*RB1*	Lohmann DR, Gallie BL. Retinoblastoma. 2000 Jul 18 [Updated 2018 Nov 21]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1452/
Rhabdoid Predisposition Syndrome	*SMARCA4, SMARCB1*	Nemes K, Bens S, Bourdeaut F, et al. Rhabdoid Tumor Predisposition Syndrome. 2017 Dec 7. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK469816/
Schwannomatosis	*NF2, LZTR1, SMARCB1*	Dhamija R, Plotkin S, Asthagiri A, et al. Schwannomatosis. 2018 Mar 8. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK487394/
Sessile Serrated Polyposis Cancer Syndrome	*RNF43*	Rosty N, Brosens LAA, Nagtegaal ID. Genetic tumour syndromes of the digestive system. In Arends MJ, Carneiro F, Lax SF eds. WHO Classification of Tumours Editorial Board, vol. 1, 5th edn. Lyon: IARC Publications, 2019.
Small Cell Carcinoma of the Ovary, Hypercalcemic Type (SCCOHT)	*SMARCA4*	Hampel, H., Bennett, R., Buchanan, A. et al. A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: referral indications for cancer predisposition assessment. Genet Med 17, 70–87 (2015). https://doi.org/10.1038/gim.2014.147

Syndrome	Associated Genes	Reference
Tuberous Sclerosis	*TSC1, TSC2*	Northrup H, Koenig MK, Pearson DA, et al. Tuberous Sclerosis Complex. 1999 Jul 13 [Updated 2020 Apr 16]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1220/
Von Hippel-Lindau Syndrome	*VHL*	van Leeuwaarde RS, Ahmad S, Links TP, et al. Von Hippel-Lindau Syndrome. 2000 May 17 [Updated 2018 Sep 6]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1463/