Circular No.(2025 / 68) تعميـم رقم

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To: All
Healthcare Facilities
All Healthcare Professionals

إلى:
جميع
المنشآت الصحية
المهنيين الصحيين

Subject: Germline Genetic testing for Cancer Patients Abu Dhabi

الموضوع: الاختبار الجيني "Germline" لمرضى السرطان في إمارة أبوظبي

We extend our greetings and best wishes for your continued success>

بدايةً، يسرُّنا أن نتقدم لكم بخالص التحية والتقدير متمنين لكم دوام التوفيق والسداد.

Further to DoH Circulars No. (04/19), No. (49/2021), No. (58/2021), No. (243/2022), and No. (297/2022), and in line with DoH's commitment to advancing precision medicine practices, through the inclusion of genetic testing, DoH has published the "Guidelines on Germline Testing in Oncology" including various types of cancer such pancreatic, colorectal, and prostate cancers.

إلحاقاً بتعاميم دائرة الصحة رقم (2019/04)، ورقم (2021/49)، ورقم (2021/58)، ورقم (2022/243)، ورقم (2022/297)، وفي إطار سعي دائرة الصحة للارتقاء بممارسات الطب الدقيق، وذلك من خلال إدراج الاختبارات الجينية، قامت دائرة الصحة بنشر "الدليل الإرشادي لاختبار الخلايا الجينية الإنتاشية في علم الأورام" ويشمل أنواع مختلفة من السرطان ومنها سرطان البنكرياس، القولون والمستقيم، والبروستات.

This germline genetic testing is essential for identifying hereditary cancer syndromes, aiding in enhancing cancer diagnosis & surveillance, as well as informed preventive and treatment strategies.

ويُعدُّ اختبار الخلايا الجينية الإنتاشية ضرورياً لتحديد حالات السرطان الوراثية، والمساهمة في تعزيز التشخيص والرصد، بالإضافة إلى وضع استراتيجيات علاجية ووقائية مستندة إلى البيانات.

Accordingly, and effective as of the date of this circular, healthcare facilities are required to adhere to the guidelines,

including germline testing for individuals who meet the criteria.

Contact Details:
For any inquiries regarding ordering germline oncology tests, please contact M42 via email address: clinical.genomics@m42.ae

We hope that all will adhere to the above, for the best interest of the health sector in the Emirate.

Thank you for your cooperation,

"This circular is designed for regulatory procedures and should not be used as media publication".

وعليه، واعتبارًا من تاريخ هذا التعميم، نود التنويه على ضرورة اتباع الدليل الإرشادي والذي يشمل الاختبارات الجينية الإنتاشية للأفراد الذين تنطبق عليهم المعايير.

بيانات التواصل:
لأي استفسارات تتعلق بطلب اختبارات الخلايا الجينية الإنتاشية للأورام، يُرجى التواصل مع مجموعة M42 عبر البريد الإلكتروني: clinical.genomics@m42.ae

آملين من الجميع الالتزام بما ورد أعلاه، لما فيه مصلحة القطاع الصحي في الإمارة.

شاكرين لكم حسن تعاونكم معنا،،،

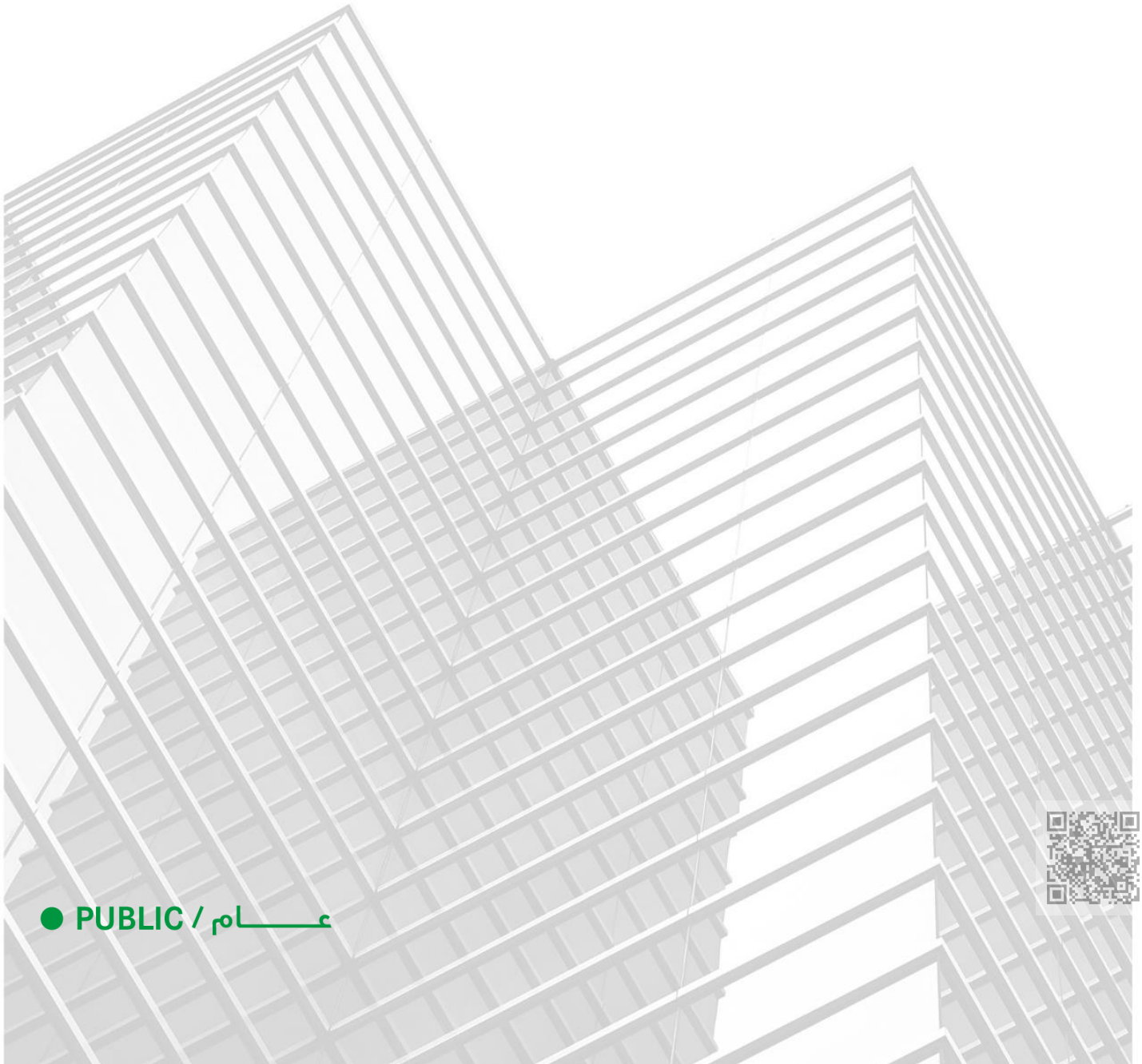
"هذا التعميم للإجراءات التنظيمية وغير مخصص كمحتوى للنشر الإعلامي".

د. نورة خميس الغيثي

وكيل دائرة الصحة

دائـــــرة الـصـــحـــة
DEPARTMENT OF HEALTH

GUIDELINES ON GERMLINE TESTING IN ONCOLOGY



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1.Guideline Purpose and Brief

The goal of this guideline is to help oncologists and healthcare providers (HCPs) who treat cancer patients identify inherited causes of cancer and ensure that patients and their families receive proper germline testing. Germline genetic testing is typically done for patients suspected of having hereditary cancer syndromes to enhance cancer surveillance and plan preventive strategies. However, it is also important for treatment decisions. As precision medicine and genetic data continue to evolve, the Department of Health (DoH) in Abu Dhabi developed germline genetic testing guidelines relevant to the United Arab Emirates.

Recently, germline testing has become more common to help guide treatment choices and clinical trial participation, thanks to the discovery of more cancer-related genes and advancements in sequencing technology. It is recommended for patients with various cancers, such as breast, ovarian, pancreatic, colorectal, and prostate cancer, as it can aid in treatment decisions and improve survival rates. Additionally, it can benefit relatives by informing them about cancer screenings and preventive measures.

The main aims of the guideline include identifying family history factors relevant to germline testing, outlining the conditions for testing, and recommending multi-gene panels that are specific to certain cancers and relevant to personal and family cancer histories.

The goal is to help health care providers (HCPs) when germline testing is needed, which methods to use, and how to handle genetic mutations. Subject matter experts (SMEs) were convened to provide guidance on genomic sequencing and to inform therapeutic selection and prognosis. The expert's consensus was conveyed through meetings and emails. The experts contributed to the development of the guideline, provided critical review and finalized the recommendations, which are adapted from international standards. All references are provided at the end of the document.

The guidelines are designed to offer recommendations and guidance for healthcare professionals in their practice areas. These guidelines should not be interpreted as comprehensive or exclusive of other valid approaches or methods. They do not guarantee specific outcomes, nor do they establish a standard of care. Treatment decisions for individual patients must be made based on the independent judgment of healthcare providers, considering each patient's unique circumstances.

The Department of Health (DoH) makes no warranties, express or implied, regarding these guidelines and specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. The DoH shall not be liable for any direct, indirect, special, incidental, or consequential damages arising from the use of the information contained herein.

2. Definitions and Abbreviations

No.	Term / Abbreviation	Definition
2.1	Actionable Mutation	Genetic alterations that can be targeted with specific therapies to potentially improve clinical outcomes. In lung cancers, mutations in the EGFR gene can be treated with drugs like erlotinib or gefitinib. This mutation is called "actionable" because there's a specific treatment available for it.
2.2	Biomarker	A biologic marker that can be detected and measured by a validated test to diagnose or treat disease.
2.3	Cancer-specific panel	Panel that tests for more than one gene associated with a specific type of cancer
2.4	Cascade Testing	The process of testing family members for a known germline mutation identified in a relative. It helps in early detection and prevention of hereditary cancers.
2.5	Genetic Counseling	A process that involves evaluating family history, providing education, and discussing the potential outcomes and implications of genetic testing with individuals or families.

2.6	Genomic alteration	Alteration of a gene from its original wild-type (normal) status through mutation, CNV, or rearrangement.
2.7	Genomic instability	A high frequency of mutations with the tumor's genome, which may be caused by loss of expression or function of proteins that direct DNA repair and/or are involved in mitotic checkpoints.
2.8	Germline Mutation	Heritable genetic alteration is present in the egg or sperm, which can be passed to offspring. These mutations exist in all cells of the body from birth and may predispose individuals to certain hereditary cancers.
2.9	Germline testing	Germline testing refers to testing that identifies genetic mutations inherited from a person's parents, which can be passed on to their children. These mutations are present in all cells of the body from birth and can increase the risk of certain types of cancers, such as breast, ovarian, or colorectal cancer.
2.10	HCS-Hereditary Cancer Syndrome	Individuals inherit a higher risk of developing certain types of cancer due to germline mutations in specific genes.
2.11	HRD - Homologous recombination deficiency	Cells that cannot efficiently repair damaged DNA via homologous recombination.
2.12	HRR - Homologous Recombination Repair	A DNA repair pathway that is frequently altered in cancer, making it a target for therapies like PARP (poly adenosine diphosphate-ribose polymerase, a type of enzyme that helps repair DNA damage in cells) inhibitors.
2.13	IHC- Immunohistochemistry	A test that uses an antibody to detect the expression, or loss of expression, of a specific protein or mutated protein form.
2.14	Immunotherapy	A type of therapy that activates the body's immune system to target cancer cells.
2.15	Liquid Biopsy	A laboratory test was done on a sample of blood, urine, or other body fluids to look for cancer cells from a tumor or small pieces of DNA, RNA, or other molecules released by tumor cells into a person's body fluids.
2.16	LS-Lynch Syndrome	A hereditary condition caused by mutations in mismatch repair (MMR) genes (e.g., MLH1, MSH2, MSH6, PMS2) that increases the risk of colorectal, endometrial, ovarian, and other cancers.
2.17	MMR - Mismatch Repair	A system for recognizing and correcting errors in DNA replication. Defects in MMR can lead to microsatellite instability (MSI) and cancer.
2.18	MSI - Microsatellite Instability	A condition of genetic hypermutability that results from impaired MMR and can be a target for immunotherapy.
2.19	Multigene panel	Laboratory test that includes testing for PVs (pathogenic variants) of more than one gene
2.20	NGS - Next-Generation Sequencing	Next-Generation Sequencing, a high-throughput method that allows for the rapid sequencing of large stretches of DNA, including multi-gene panels.
2.21	Orthogonal test	Orthogonal validation uses additional methods that provide very different selectivity to the primary method to confirm or refute a finding.
2.22	PARP Inhibitors - Poly (ADP-ribose) polymerase	A class of drugs used to target cancers with deficiencies in HRR, particularly those with BRCA1/2 mutations. PARP inhibitors work by preventing cancer cells from being repaired, allowing them to die.

2.23	Somatic Testing	The analysis of non-germline (acquired) genetic mutations within tumor cells to identify actionable targets for therapy.
2.24	SDM- Shared Decision Making	Shared decision making (SDM) is a method of care on the basis of conversations conducted to arrive at a cocreated plan of care that addresses the problematic situation of each patient.
2.25	Syndrome-specific panel	Panel that only tests for one syndrome (eg, LS, adenomatous polyposis)
2.26	Targeted Therapy	Cancer treatment that uses drugs to target specific genetic changes in cancer cells that drive their growth and survival.
2.27	VAF - Variant allele frequency	The fraction of alleles sequenced within a single tumor sample that contains the genomic alteration of interest.
2.28	VUS	A change in a gene's DNA sequence that has an unknown effect on a person's health cannot be used for clinical purposes either to identify individuals at risk or to drive treatment.

3. Guideline Content

This guideline must be read in conjunction with:

- *DoH Guidelines on Somatic Testing for Cancers*
- *DoH Guidelines on Liquid Biopsy for Cancers*
- *DoH Guideline for Breast Cancer Germline Testing*
- *DoH Standard for Laboratory Accreditation for Genomic-Related Services and Products*

3.1. Germline Genetic testing

Germline genetic testing is done to identify inherited pathogenic variants in a cancer patient and unlike somatic testing that identifies genetic variants in a tumor, which can either be acquired (somatic) or inherited (germline), germline genetic testing is done to establish inherited germline variants. Germline testing is increasingly recommended in recent years for cancer patients to identify an inherited etiology. Family history of the patient and personal cancer history determines the appropriate germline testing. Timely testing for pathogenic germline variants is essential as results of the genetic test can play a crucial role in selection of therapy and surgery.

3.2. General recommendations for germline testing

Germline genetic testing for identification of pathogenic variants is increasingly recommended for a growing number of patients with cancer to identify an inherited etiology.

3.2.1. Testing Criteria and Sample Collection

3.2.1.1. Recommendations for germline genetic testing should be based on specific details of a patient's diagnosis (eg. Cancer type, patient age) and/or family history of cancer

3.2.1.2. Germline analysis should be conducted (Figure 1) in an appropriate germline sample such as lymphocytes, saliva/buccal swab.

3.2.1.3. Germline testing should be conducted in a DoH/CAP/ISO- 15189 accredited laboratory that performs hereditary testing.

3.2.1.4. Adequate information should be provided to the patient regarding the implications of germline testing, along with documentation of their informed consent before proceeding for germline analysis.

3.2.2. Personnel

Personnel requirements for all HCPs involved in Germline testing for cancers:

3.2.2.1. All HCPs must be qualified to perform their duties with appropriate education, training, experience and skill. Evidence of these qualifications must be provided.

3.2.2.2. All HCPs personnel must be licensed by DoH and perform their activities in compliance with DOH Clinical Laboratory standards, DoH standard for Clinical Privileging Framework, DoH Healthcare Professionals Manual and Unified Healthcare Professional Qualification requirements (PQR).

3.2.3. Laboratory and Workflow Requirements

3.2.3.1. Germline-focused tumor analysis can be delivered via an automated pipeline so as not to add substantial additional manual work, cost or delay to tumor analysis.

3.2.3.2. Samples known or suspected to be hypermutated should be included for germline-focused tumor analysis.

3.2.3.3. Flag variants are likely to cause protein truncation in loss-of-function genes and those classified as Pathogenic/Likely Pathogenic in resources like ClinVar.

3.2.3.4. Limit analysis to variants with VAF >30% (single-nucleotide variants -SNVs) or >20% (insertions/deletions), with local validation for PCR-based methods.

3.2.3.5. Focus on 'High Actionability- Cancer Suspecting Genes (CSGs') for off-tumor contexts and restrict 'standard actionability'-CSGs to on-tumor settings.

3.2.3.6. Before germline test reporting, formal variant review and classification should be undertaken by an experienced molecular geneticist/pathologist.

3.2.3.7. Genetic Counseling: Genetic counselling (pre-and post-test genetic counselling) is highly recommended. Cancer genetic counselling should be offered by dedicated genetic counsellors or by healthcare professionals trained in genetic counselling.

3.2.4. Reporting and follow up

3.2.4.1. Have experienced clinical scientists (as per Unified Healthcare Professional qualification requirements issued by DoH) formally review and classify variants before patient re-contact and germline testing.

3.2.4.2. Report recessively acting 'High Actionability- Cancer Suspecting Genes (CSGs') (e.g., MUTYH) only if two pathogenic variants are detected.

3.2.4.3. A patient in whom a germline pathogenic variant is detected should be referred to a certified genetic counselor and hereditary high risk cancer service for long term follow-up and management of the family.

3.2.5. Quality and Review Standards

3.2.5.1. Re-evaluate the testing workflow, analyses, and recommendations every two years to incorporate updated data on variant pathogenicity, gene penetrance, germline conversion rates, and VAF cutoffs

3.2.6. Legal and Regulatory Compliance

3.2.6.1. Federal Law No. 2 of 2019

Germline testing in the UAE must adhere to Federal Law No. 2 of 2019, which governs the use, transfer, and processing of genetic data. Compliance with this law ensures that genetic data is handled ethically and securely.

3.2.6.2. ADHIC (Abu Dhabi Health Information Center)

Testing facilities and research activities should align with ADHIC standards and guidelines, which regulate the storage and usage of patient health information, ensuring data privacy and security in line with Abu Dhabi regulations.

3.2.6.3. Federal Data Privacy Mandates

All germline testing processes must comply with UAE's federal data privacy mandates to ensure the confidentiality of patient information, particularly when transferring or storing data outside the country. Specific approvals may be required for sample export to ensure compliance.

3.3. Umbrella criteria for germline genetic testing

Patients should be referred for germline testing only when the following criteria is/are met:

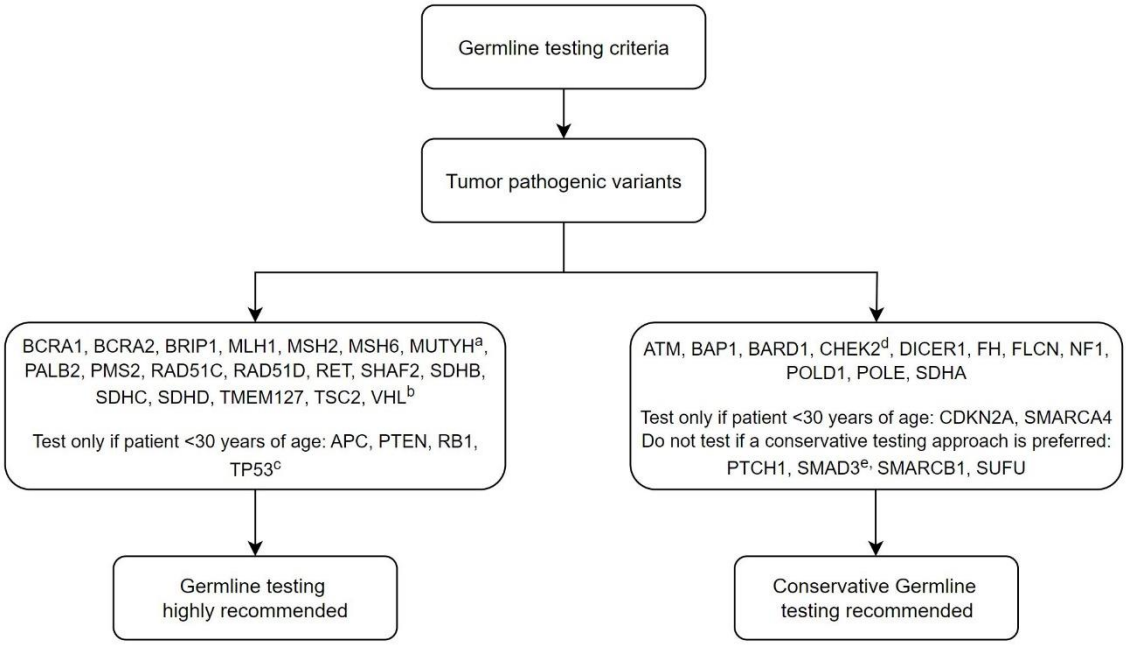
3.3.1. Germline testing for genetic alterations linked to approved therapies in patients with cancers

3.3.2. Germline-focused tumor analysis can be restricted to variants of variant allele frequency (VAF) >30% (SNVs) or >20% (small insertions/deletions).

3.3.3. Germline testing should be recommended when tumor pathogenic variants are identified as per figure 1.

3.3.4. Individuals with first or second degree relative with a known P/LP variant in a cancer susceptibility gene

3.3.5. Individuals with metastatic or recurrent cancer.



[a] Germline follow-up testing should only be performed when two (biallelic) pathogenic variants are detected in the tumor.

[b] Renal cell carcinoma may be excluded from testing.

[c] Brain tumors may be excluded from testing.

[d] CHEK2 variants c. 1283C>T (S428F) and c.470T>C (I157T) are low-penetrant variants with relative risk of 1.5 for cancer and do not affect screening recommendations the same way other CHEK2 variants do.

[e] Germline SMAD3 causes Loeys-Dietz syndrome 3 and nonsyndromic thoracic aortic aneurysms and dissections. It is highly actionable although it is not associated with cancer risk.

Figure 1 Genes for which pathogenic variants identified via tumor testing should prompt Germline genetic testing

3.4. Germline testing workflow

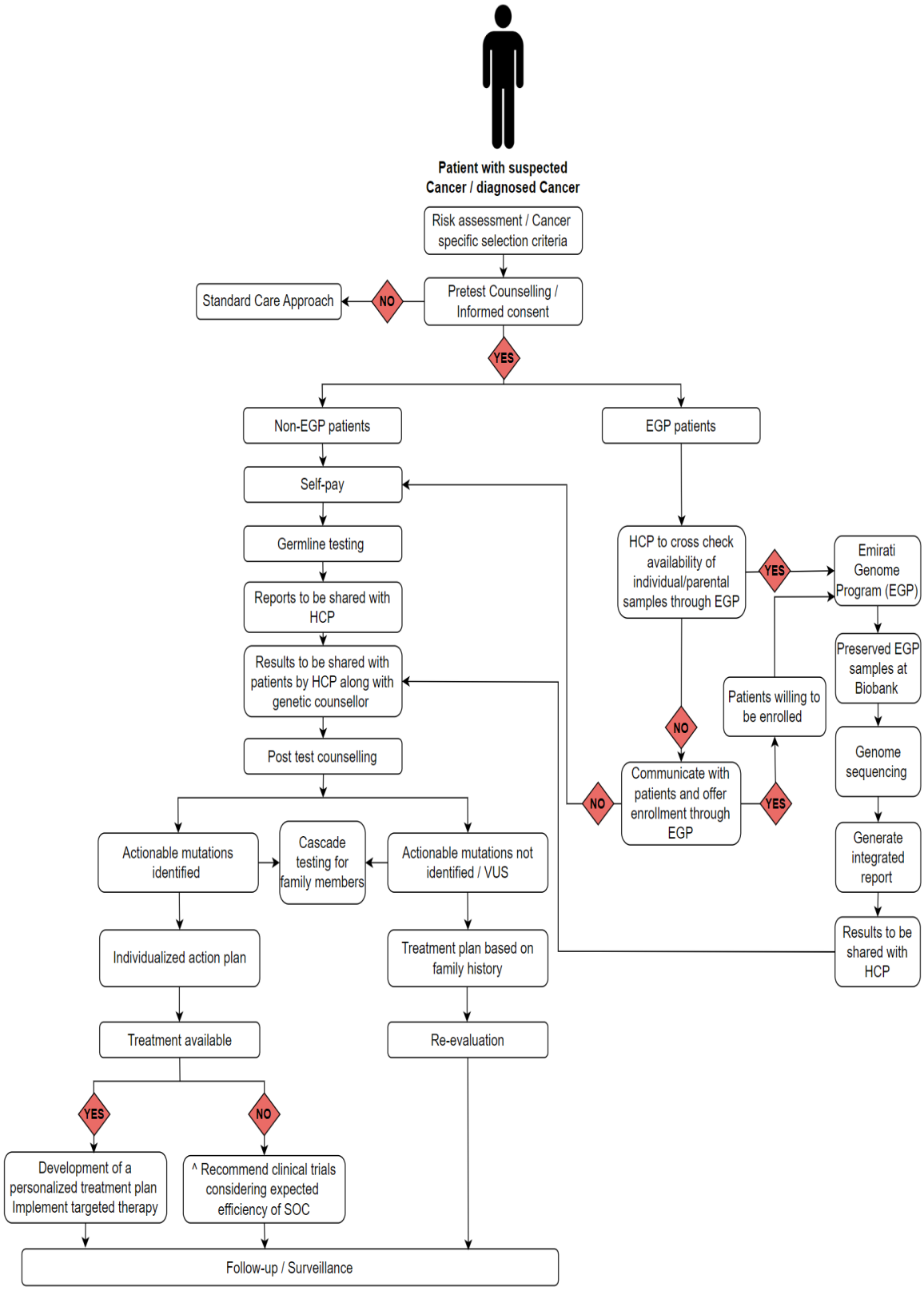


Figure 2. Germline Testing Workflow

^ When there is no clinical evidence of meaningful efficacy or when a clinical trial is available, off-label and off-study use of genomic biomarker-linked therapies approved in other diseases are not recommended

3.5. Risk assessment for germline testing

Risk assessment for germline testing includes three main stages (i) pre-test assessment including family history, pre-test counselling and comprehensive history, etc. (ii) choice of testing considering the most appropriate test to order and choice of multigene testing (iii) post-test assessment including discussion of the results and post-test counselling.

3.5.1. Pre-test counselling focuses on assessing patients' needs and concerns, preparing for possible outcomes and possible inherited cancer risk to family members and planning for results disclosure. It includes:

3.5.1.1. Preparing the patient for possible outcomes of testing including positive (pathogenic, likely pathogenic [P/LP]), negative, uncertain, or mosaic results and unexpected findings such as a pathogenic variant (PV) in a gene that does not currently explain the patient's personal or family history of cancer

3.5.1.2. Discussing possible management options if a P/LP variant is identified (ie, enhanced surveillance, risk-reducing chemo preventive agents, risk-reducing surgery)

3.5.1.3. Obtaining informed consent and documenting in the patient's medical record

3.5.1.4. Discussing plan for results disclosure, including patient consent for possibility of releasing results to the patient's relative or other designated individual if necessary

3.5.1.5. Discussing the financial costs of genetic counseling and testing

3.5.2. Testing should be considered in individuals who fulfill the testing criteria where it is likely to impact on the management and treatment of the tested individuals or their family members who also have increased risk.

3.5.3. Genetic testing is not recommended for children <18 y when results would not impact medical management.

3.5.4. Patients who have received an allogeneic bone marrow transplant should not have molecular genetic testing via blood or saliva samples due to unreliable test results from contamination by donor DNA. In such cases, DNA of the individual being tested should be extracted from a fibroblast culture from a skin punch biopsy. If this is not possible, buccal cells may be considered as an alternative source of DNA, subject to the risk of donor DNA contamination or malignant cells from the hematologic malignancy. However, it has been reported that over time buccal epithelial cells can be replaced by donor-derived cells. Fibroblast culture is also indicated when testing individuals with active or recent hematologic malignancies.

3.5.5. LP variants are usually clinically managed similarly to PVs, while patients with variants of uncertain significance (VUS) and likely benign variants should be cared for based on the type of cancer present in the family. Post-test counseling is done when results are disclosed and it is recommended that the results are discussed with a panel of experts which include genetic counselor, clinical geneticist, oncologist, surgeon, oncology nurse, or other health professional with expertise and experience in cancer genetics be involved at each stage whenever possible.

3.5.6. Post-test counselling includes:

3.5.6.1. Discussion of results and associated medical risks

3.5.6.2. Interpretation of results in context of personal and family history of cancer

3.5.6.3. Discussion of recommended medical management options including discussion of therapeutic implications by a qualified health care provider if positive

3.5.6.4. Discussion of the importance of notifying family members and offering materials/resources for informing and testing family members who also have increased risk

3.5.6.5. Discussion of available resources such as high-risk clinics, disease-specific support groups, and research studies

3.6. Family history collection

3.6.1. Family history is central to the value of germline testing and is crucial not only to document the reasons for testing and inform the selection of genes for analysis but also for the interpretation of the genetic test results and for the assessment of future cancer risk. It also can be equally important to the members of the patient's family, who may benefit from appropriate screening and prevention interventions.

3.6.2. Patients should be asked to provide the following information as part of their family history. Patients may

not have complete information, but that should not be considered an impediment to asking these questions. Only information about biologic relatives is pertinent

3.6.2.1. Does the patient know of any cancers in any first-degree biological relatives: siblings, parents, children?

3.6.2.2. Does the patient know of any cancer in any second-degree biological relatives (on both maternal and paternal sides): grandparents, aunts, uncles, grandchildren, nieces, nephews, half siblings?

3.6.2.3. For each cancer in the family, ask for the following details: Type of primary cancer(s); age at cancer diagnosis for each primary cancer; were multiple cancers of one type involved (eg, bilateral breast cancer or multiple colon cancer primaries)?

3.6.2.4. Does the patient know of any relative who has had germline genetic testing for cancer predisposition, and if so, what were the results?

3.6.2.5. What is the patient's ethnicity?

3.6.2.6. Where it is possible and time permits, information on third-degree relatives (eg, cousins), consanguinity, and personal and family history of colon polyps can help inform genetic testing and counseling, especially with interpretation of results.

3.7. Cascade testing

A systematic process to identify individuals within a family at risk of developing a hereditary condition. Cascade testing begins with finding a pathogenic variant through testing (such as multigene panel testing) in 1 family member, usually affected by the condition. Then, testing just for the specific family variant is extended to blood relatives. This process is repeated as more affected individuals or pathogenic variant carriers are identified.

3.7.1. Points to consider in testing within family members:

3.7.1.1. The probability of familial P/LP variant detection will vary based on family structure including family size, number of male female relatives, age of the family members, early death, adoption, and the number of unaffected relatives

3.7.1.2. If more than one family member is affected by cancers highly associated with the gene in question consider initial testing of a family member with youngest age at diagnosis, bilateral disease (in case of breast cancer), multiple primary cancers, or other cancers associated with the gene, or most closely related to the patient.

3.7.1.3. If there are no available family members with cancer consider testing first- or second-degree family members affected by other cancers related to the gene in question (e.g., prostate or pancreas with BRCA1/2).

3.7.1.4. Testing of an unaffected individual (or of unaffected family members) should only be considered when no affected family member is available for testing. Significant limitations of interpreting test results should be discussed, because absence of a mutation in one unaffected relative does not rule out a mutation in others.

3.7.1.5. Individuals with unknown or limited family history/structure, such as fewer than 2 first- or second-degree relatives having lived beyond age 45 in either lineage, may underestimate the probability of familial P/LP variant detection.

3.7.1.6. The estimated likelihood of P/LP variant detection may be low in families with a large number of unaffected relatives.

3.8. Multi-gene panel testing

3.8.1. Points to consider in multigene testing:

3.8.1.1. The minimal panel should include at least the more strongly recommended genes for that patient based on the patient's personal and family history of cancer (Refer Appendix- Table 2)

3.8.1.2. A broader panel may be ordered when the potential benefits of such a panel can be clearly identified.

3.8.1.3. When ordering a panel (especially a broader panel), the clinician should ensure that potential harm is mitigated.

3.8.1.4. A smaller panel of genes may be tested initially when results are needed quickly for treatment decision making with subsequent expansion to a larger panel of genes.

3.8.2. Multigene panel testing is recommended in individuals meeting the criteria below:

3.8.2.1. Individuals who tested negative with previous limited testing (e.g., single gene and/or absent deletion duplication analysis)

3.8.2.2. A P/LP variant identified on tumor genomic testing that has clinical implications if also identified in the germline

3.8.2.3. To aid in systemic therapy and surgical decision-making

3.8.2.4. Individual who meets Li-Fraumeni syndrome (LFS) testing criteria (CRIT-7) or Cowden syndrome (CS)/PTEN hamartoma tumor syndrome (PHTS) testing criteria (CRIT-8) or Lynch syndrome (LS)

3.8.2.5. Individuals with metastatic or recurrent cancer

3.8.2.6. Patients with personal or family histories suggest an inherited predisposition, even when no germline alterations are identified during tumor genomic sequencing using various sequencing panels.

3.8.2.7. Metastatic or recurrent cancer

3.9. Laboratory Recommendations for Germline testing

3.9.1. Genetic testing findings used for clinical management, should be obtained only from genetic laboratories with accreditations from relevant bodies including but not restricted to the College of American Pathologists (CAP).

3.9.2. Laboratories performing germline testing should follow DoH standard for Laboratory Accreditation for Genomic-Related services and products.

3.9.3. Special considerations for laboratories offering multigene NGS panel testing:

3.9.3.1. Clinical laboratories offering germline testing using NGS should establish a written policy regarding orthogonal confirmation of NGS results.

3.9.3.2. Laboratories' orthogonal confirmation policy should be overseen and approved by a qualified and appropriately certified medical professional with training (As per the Professional Qualification Requirement (PQR) DoH Document) and experience in NGS.

3.9.3.3. Laboratories' confirmatory methods should be orthogonal. Discrepant results between NGS and confirmatory assay should be investigated and resolved.

3.9.3.4. Laboratories should perform confirmatory testing for reported germline variants with significant clinical implications, except for variant calls meeting technical criteria rigorously demonstrated to ensure high positive predictive value from NGS alone.

3.9.3.5. Laboratories should clearly articulate their specific policies, criteria, and methods regarding orthogonal confirmation in written materials readily available on request.

3.9.3.6. Laboratories' clinical test reports should summarize orthogonal confirmation policy in every report, and when exceptions to the policy are made, these should be clearly indicated.

3.9.3.7. Special considerations apply to certain NGS-based test types and findings regarding conformation policies on sample identity conformation, Indel resolution, location resolution, mosaic variants and haplotyping etc.

3.10. Clinical utility of Germline testing

Germline analysis following tumor sequencing often produces findings that may impact patient care:

3.10.1. Identifies actionable mutations that enable personalized treatment strategies, optimizing therapy effectiveness and making surgical decisions.

3.10.2. Provides crucial prognostic information, aiding in clinical decision-making and risk assessment.

3.10.3. Enables integrating genetic information into treatment planning leading to minimizing side effects, better patient outcomes and survival rates.

3.10.4. Informs eligibility for clinical trials exploring novel therapies targeting specific genetic alterations.

3.10.5. Identifies hereditary cancer risk, which may extend the benefits of high-risk screening programs and counselling to family members.

3.11. Informed consent for germline testing

3.11.1. Informed consent should be unambiguous, ensuring individuals fully understand the purpose, process, risks, and benefits of genetic testing, particularly in germline testing. It guarantees that the decision to participate is freely given and voluntary.

3.11.2. Informed consent is strongly recommended for germline genetic testing and HCPs and patients engage in the process of obtaining consent as a part of pre-test counselling

3.11.3. The process must be handled ethically, ensuring full comprehension and voluntary agreement before proceeding with any clinical or diagnostic testing.

3.11.4. Consent must be documented and securely stored in a manner that allows it to be easily retrieved in case of regulatory or legal requests. The record should include details of when and where the consent was provided. Furthermore, a clear and efficient mechanism should be in place to allow individuals to withdraw their consent at any time, ensuring it is promptly removed from the system in accordance with their request.

3.11.5. For detailed description of informed consent Refer to the "DOH Patient consent standard"

3.12. Cancer specific Germline testing criteria

3.12.1. Breast cancer

Please refer to DoH Guideline for Breast Cancer Germline Testing

3.12.2. Ovarian cancer

Please refer to DoH Guideline for Breast Cancer Germline Testing

3.12.3. Pancreatic cancer

3.12.3.1. Patient Selection Criteria

3.12.3.1.1. All individuals diagnosed with exocrine pancreatic cancer

3.12.3.1.2. First-degree relatives of individuals diagnosed with exocrine pancreatic cancer (Testing of first-degree relatives should only be done if it is impossible to test the individual who has pancreatic cancer)

3.12.3.1.3. A known P/LP germline variant in a pancreatic cancer susceptibility gene (ATM, BRCA1, BRCA2, CDKN2A, MLH1, MSH2, MSH6, EPCAM, PALB2, STK11, and TP53; see GENE-A) and a family history of pancreatic cancer (first-degree or second-degree relative) from the same side of the family as the germline P/LP variant

3.12.3.1.4. A family history of exocrine pancreatic cancer in ≥1 first-degree and ≥1 second-degree relatives from the same side of the family, even in the absence of a known P/LP germline variant

3.12.3.2. Multigene panel recommendation

The minimum gene panel for Pancreatic cancer should include ATM, BRCA1, BRCA2, CDK4, CDKN2A, Lynch syndrome genes [MLH1, MSH2, MSH6, EPCAM], PALB2, STK11, and TP53, APC

3.12.3.3. Assessment, Risk Management and Surveillance

Gene Test	**Risk Management/ Surveillance (**Management: Screen P/LP variant carriers with a family history of pancreatic cancer as described below)
Individuals with P/LP germline variants in one of the other pancreatic cancer susceptibility genes (ATM, BRCA1, BRCA2, MLH1, MSH2, MSH6, EPCAM, PALB2, TP53	Consider pancreatic cancer screening beginning at age 50 years (or 10 years younger than the earliest exocrine pancreatic cancer diagnosis in the family, whichever is earlier) for individuals with exocrine pancreatic cancer in ≥1 first- or second-degree relatives from the same side of (or presumed to be from the same side of) the family as the identified P/LP germline variant. Pancreatic cancer screening is currently not recommended for carriers of P/LP variants in genes other than STK11 and CDKN2A in the absence of a

	close family history of exocrine pancreatic cancer.
All individuals with P/LP germline variants in STK11	Consider pancreatic cancer screening beginning at age 30–35 years (or 10 years younger than the earliest exocrine pancreatic cancer diagnosis in the family, whichever is earlier).
All individuals with P/LP germline variants in CDKN2A	Consider pancreatic cancer screening beginning at age 40 years (or 10 years younger than the earliest exocrine pancreatic cancer diagnosis in the family, whichever is earlier).
Hereditary Pancreatitis Genes	For individuals with P/LP variants in PRSS1 or other hereditary pancreatitis genes AND a clinical phenotype consistent with hereditary pancreatitis Consider pancreatic cancer screening 20 years after onset of pancreatitis, or at age 40 years, whichever is earlier.

3.12.3.4. Summary Recommendations

3.12.3.4.1. Recommendation for pancreatic cancer screening should take place after an in-depth discussion about the potential limitations to screening, including cost, the high incidence of benign or indeterminate pancreatic abnormalities, and uncertainties about the potential benefits of pancreatic cancer screening.

3.12.3.4.2. Consider screening using annual contrast-enhanced MRI/magnetic resonance cholangiopancreatography (MRCP) and/or endoscopic ultrasound (EUS), with consideration of shorter screening intervals, based on clinical judgment, for individuals found to have potentially concerning abnormalities on screening.

3.12.3.4.3. Consider screening with contrast-enhanced MRCP and/or EUS in individuals at increased risk for pancreatic cancer. The panel emphasizes that most small cystic lesions found on screening will not warrant biopsy, surgical resection, or any other intervention.

3.123.4.4. Clinical judgment is advised for recommendation of pancreas surveillance for P/LP variant carriers in the absence of family history.

3.12.4. Prostate cancer

3.12.4.1. Patient Selection Criteria

3.12.4.1.1. Germline testing should be considered in respect to family and personal history of cancer and known germline variants at time of initial diagnosis

3.12.4.1.2. Cancer specific criteria for patients with prostate cancer are:

3.12.4.1.2.1. Personal history of prostate cancer with specific features:

By tumor characteristics (any age)- if the tumor is metastatic or if it falls under high or very high-risk stratification group based on clinical/pathological features

3.12.4.1.2.2. A personal history of other specific cancer.

Patients with a personal history of prostate cancer and intermediate-risk prostate cancer and intraductal/cribriform histology or a personal history of exocrine pancreatic cancer, breast cancer, colorectal, gastric, melanoma, pancreatic cancer, upper tract urothelial cancer, glioblastoma, biliary tract cancer, and small intestinal cancer.

3.12.4.1.2.3. A positive family history and ancestry, defined as having one or more blood relatives (first-, second- or third-degree relatives on the same side of the

family) with any of the following:

3.12.4.1.2.3.1. breast cancer at age ≤50 y

3.12.4.1.2.3.2. triple-negative breast cancer at any age

3.12.4.1.2.3.3. male breast cancer at any age

3.12.4.1.2.3. 4. ovarian cancer at any age

3.12.4.1.2.3. 5. pancreatic cancer at any age

3.12.4.1.2.3.6. metastatic, high-, or very-high-risk group based on clinical/pathological features based on NCCN guidelines at any age

3.12.4.1.2.3.7. ≥3 close blood relatives with prostate cancer (any grade) and/or breast cancer on the same side of the family including the patient with prostate cancer

3.12.4.1.3. Testing may be considered in the following scenario:

Personal history of prostate cancer with intermediate-risk prostate cancer with (intraductal/cribriform histology)

3.12.4.2. Multigene panel recommendation

BRCA1, BRCA2, ATM, PALB2, CHEK2, HOXB13, EPCAM, MLH1, MSH2, MSH6, and PMS2 are recommended.

3.12.4.3. Assessment, Risk Management and Surveillance

Gene Test	Risk Management/ Surveillance
BRCA2	Prostate cancer early detection is recommended at age 40 for BRCA2 carriers.
BRCA1, BRCA2, ATM, PALB2, CHEK2, HOXB13, EPCAM, MLH1, MSH2, MSH6, and PMS2	Consider prostate cancer screening starting at age 40 years

3.12.4.4. Summary Recommendation

3.12.4.4.1. There is no sufficient data to definitively inform the best strategy for prostate cancer early detection in these populations, but the following is recommended:

3.12.4.4.2. It is recommended for individuals with other germline mutations to consider beginning shared decision-making about PSA screening at age 40 years and to consider screening at annual intervals rather than every other year.

3.12.4.4.3. Individuals with a suspicious family cancer history should begin shared decision-making about PSA screening at age 40 years.

3.12.5. Colorectal Cancer (CRC)

3.12.5.1. Patient Selection Criteria (Colorectal Cancer)

3.12.5.1.1. Personal History of CRC:

3.12.5.1.1.1. Diagnosed <50yr

3.12.5.1.1.2. Personal history of a P/LP variant identified on tumor genomic testing that has clinical implications if also identified in the germline

3.12.5.1.1.3. A synchronous or metachronous LS-related cancer* at any age

3.12.5.1.1.4. First or second degree relative with LS-related cancer diagnosed <50yr

3.12.5.1.1.5. Two or more 1st or 2nd degree relatives with LS-related cancers at

any age

3.12.5.1.1.6. Personal history of a tumor with MMR deficiency determined by polymerase chain reaction (PCR), next-generation sequencing (NGS), or IHC diagnosed at any age

3.12.5.1.1.7. An individual who meets adenomatous polyposis testing criteria (POLYP-1)

3.12.5.1.1.8. Individual who meets clinical criteria for: JPS (JPS-1), PJS (PJS-1)

3.12.5.1.2. Family History of CRC:

Family history of any of the following:

3.12.5.1.2.1. One or more 1st degree relatives with uterine or colorectal cancer diagnosed <50yr

3.12.5.1.2.2. One or more 1st degree relatives with uterine or colorectal cancer and a synchronous or metachronous LS-related cancer at any age.

3.12.5.1.2.3. Two or more 1st or 2nd degree relatives with LS–related cancers (with ≥1 diagnosed <50yr).

3.12.5.1.2.4. Three or more 1st or 2nd degree relatives with LS–related cancers at any age if testing is not possible for an affected relative, multi-gene cancer panel may be offered.

3.12.3.2. Multigene panel recommendation

APC, EPCAM, MLH1, MSH2, MSH6, MUTYH, NTHL1, PMS2, POLD1, POLE, BMPR1A, SMAD4, STK11, TP53, AXIN2, CHEK2, MBD4, GREM1, MSH3, PTEN, RNF43

3.12.3.3. Colorectal Cancer Surveillance

Cancer Type	Gene Test	Surveillance
Colorectal Cancer Surveillance	(MLH1) and (MSH2 and EPCAM) Lynch Syndrome:	High-quality colonoscopy at age 20–25 y or 2–5 y prior to the earliest CRC if it is diagnosed before age 25 y and repeat every 1–2 y.
	(MSH6) and (PMS2) LYNCH SYNDROME:	High-quality colonoscopy at age 30–35 y or 2–5 y prior to the earliest CRC if it is diagnosed before age 30 y and repeat every 1–3 y
	Familial Adenomatous Polyposis	If a patient had colectomy with ileorectal anastomosis (IRA), then endoscopic evaluation of the rectum every 6–12 months depends on polyp burden. If a patient had TPC with ileal pouch-anal anastomosis (IPAA), then endoscopic evaluations of the ileal pouch and rectal cuff annually depending on polyp burden. Surveillance frequency should be shortened to every 6 months for large, flat polyps with villous histology and/or high-grade dysplasia identified. If a patient had an ileostomy, consider careful visualization and stoma inspection by ileoscopy to evaluate for polyps or malignancy annually; evidence to support this recommendation is limited. Chemoprevention may be considered to facilitate management of the remaining rectum or pouch post-surgery in select patients with progressive polyp burden (e.g., based on size, number, and

		pathology).

3.12.3.4. Summary Recommendation

3.12.3.4.1. All individuals with LS who have a risk for future CRC (i.e., excluding those with prior total proctocolectomy [TPC]) should consider using daily aspirin to reduce their future risk of CRC. The decision to use aspirin for reduction of CRC risk in LS and the dose chosen should be made on an individual basis, including discussion of individual risks, benefits, adverse effects, and childbearing plans.

3.12.3.4.2. Clinical expertise is recommended in determining whether an individual with LS should take aspirin and in deciding on the appropriate dosing taking into account increased age, prior allergy, concurrent use of antiplatelets/anticoagulants, untreated H. pylori or unconfirmed H. pylori eradication—as well as patient-specific factors that indicate a comparably low future cumulative risk of CRC (ie, increased age, PMS2-associated LS, history of prior colectomy) and who may thus be less likely to experience significant benefit.

3.12.6. Endometrial Cancer

3.12.6.1. Patient Selection Criteria

3.12.6.1.1. Personal History of the EC:

3.12.6.1.1.1. Diagnosed <50yr

3.12.6.1.1.2. Personal history of a P/LP variant identified on tumor genomic testing that has clinical implications if also identified in the germline

3.12.6.1.1.3. A synchronous or metachronous LS-related cancer* at any age

3.12.6.1.1.4. First or second degree relative with LS-related cancer diagnosed <50yr

3.12.6.1.1.5. Two or more 1st or 2nd degree relatives with LS-related cancers at any age

3.12.6.1.1.6. Tumour with MMR deficiency determined by IHC analysis and/or MSI-high features

3.12.6.1.2. Family History of EC:

Family history of any of the following:

3.12.6.1.2.1. One or more 1st degree relatives with uterine or colorectal cancer diagnosed <50yr

3.12.6.1.2.2. One or more 1st degree relatives with uterine or colorectal cancer and a synchronous or metachronous LS-related cancer at any age.

3.12.6.1.2.3. Two or more 1st or 2nd degree relatives with LS–related cancers (with ≥1 diagnosed <50yr).

3.12.6.1.2.4. Three or more 1st or 2nd degree relatives with LS–related cancers at any age if testing is not possible for an affected relative, multi-gene cancer panel may be offered.

3.12.6.2. Multigene panel recommendation

EPCAM, MLH1, MSH2, MSH6, PMS2, PTEN, STK11

3.12.6.3. Endometrial Cancer Surveillance

Cancer Type	Gene Test	Surveillance
Endometrial Cancer	Lynch Syndrome (MLH1) and (MSH2 and EPCAM), MSH6 and PMS2:	Because EC can often be detected early based on symptoms, patients should be educated regarding the importance of prompt reporting and evaluation of any abnormal uterine bleeding or postmenopausal bleeding. The evaluation of these symptoms should include endometrial biopsy. Total hysterectomy has not been shown to reduce EC mortality, but can reduce the incidence of EC. Therefore, hysterectomy is a risk-reducing option that can be considered. The timing of total hysterectomy can be individualized based on whether childbearing is complete, comorbidities, family history, and LS gene, as risks for EC vary by LS gene. For patients requiring colorectal surgery such as for CRC resection, coordination with hysterectomy should be considered. Given the higher risks of early EC in MLH1, MSH2, EPCAM and MSH6, hysterectomy with bilateral salpingectomy may be considered starting at age 40y with delayed bilateral oophorectomy starting at age 50y. Given the higher risks of EC in PMS2, hysterectomy with BSO may be considered starting at age 50 y Screening via endometrial biopsy every 1–2 y starting at age 30–35 y can be considered. PMS2 carriers appear to be at only modestly increased risk of EC in contrast to MLH1, MSH2, and MSH6.

3.12.7. Gastric Cancer

3.12.7.1. Patient Selection Criteria

3.12.7.1.1. Individual with a known CDH1 PV in the family

3.12.7.1.2. An individual with diffuse gastric cancer (DGC) at any age

3.12.7.1.3. Family history of ≥2 first-degree or second-degree relatives with gastric cancer with at least one diagnosed at age ≤50 y or at least one confirmed to be DGC at any age

3.12.7.2. Multigene panel recommendation

The Panel recommends that germline testing includes CDH1, as well as the following genes: APC, BMPR1a, BRCA1, BRCA2, CTNNA1, EPCAM, MLH1, MSH2, MSH6, PMS2, PTEN, SMAD4, STK11, and TP53

3.12.7.3. Assessment, Risk Management and Surveillance

Gene	Risk Management/Surveillance
CDH1	**Management Options** Management options for CDH1 PV carriers include gastrectomy versus endoscopic surveillance. **Gastrectomy is recommended for CDH1 PV carriers to meet any of the following criteria:** • Established stage pT1b or higher SRCC • Persistent signs and symptoms that may be associated with more advanced-stage SRCC that are unexplained by other medical

	conditions, including weight loss, early satiety, anemia, abdominal pain Individuals without any of the above features should have the opportunity to engage in shared decision-making, offering the option of risk-reducing gastrectomy versus endoscopic surveillance taking into account pros and cons of surveillance and patient preference. Shared decision-making should include a multidisciplinary team of clinicians with expertise in genetics, endoscopic surveillance, and surgical oncology. Age for prophylactic gastrectomy and/or initiation of surveillance, including among children aged <18 y should be based on a multidisciplinary discussion taking into account personal and family history and patient preference. **Gastrectomy** May be preferred by patients who put a higher value on maximizing prevention of developing advanced gastric cancer and gastric cancer death, and a lower value on the risks of gastrectomy and lifestyle changes associated with gastrectomy. Decision to undergo gastrectomy may be influenced by experiences with gastric cancer in a patient's family. **Endoscopic surveillance** May be preferred by patients who put a higher value on avoiding risks and lifestyle changes associated with gastrectomy and uncertain likelihood of developing and dying from gastric cancer, and a lower value on the uncertain data regarding whether a program of upper endoscopy surveillance can prevent development of advanced gastric cancer and gastric cancer mortality.
MLH1, MSH2, EPCAM, MSH6, PMS2	Upper gastrointestinal (GI) surveillance with high-quality EGD starting at age 30–40 y and repeat every 2–4 y, preferably performed in conjunction with colonoscopy Age of initiation prior to 30 y and/or surveillance interval <2 y may be considered based on family history of upper GI cancers or high-risk endoscopic findings (such as incomplete or extensive gastric intestinal metaplasia [GIM], gastric or duodenal adenomas, or Barrett esophagus with dysplasia). Random biopsy of the proximal and distal stomach should at minimum be performed on the initial procedure to assess H. pylori (with treatment indicated if H. pylori is detected), autoimmune gastritis, and intestinal metaplasia. Push enteroscopy can be considered in place of EGD to enhance small bowel visualization, although its incremental yield for detection of neoplasia over EGD remains uncertain. Individuals not undergoing upper endoscopic surveillance should have one-time noninvasive testing for H. pylori at the time of LS diagnosis, with treatment indicated if H. pylori is detected. The value of eradication for the prevention of gastric cancer in LS is unknown. There is limited available data on upper GI cancer risk in PMS2 LS, and new evidence is likely to inform changes to these recommendations in the future.

3.12.8. Cowden syndrome (CS) also PTEN hamartoma tumor syndrome (PHTS)

3.12.8.1. Patient Selection Criteria

3.12.8.1.1. An individual from a family with a known PTEN P/LP variant

3.12.8.1.2. Individual with a personal history of Bannayan-Riley-Ruvalcaba syndrome (BRRS)

3.12.8.1.3. Individual meeting clinical diagnostic criteria for CS/PHTS,

3.12.8.1.4. Individuals not meeting clinical diagnostic criteria for CS/PHTS and with a personal history of:

3.12.8.1.4.1. Adult Lhermitte-Duclos disease (cerebellar tumors); or

3.12.8.1.4.2. Autism spectrum disorder and macrocephaly; or

3.12.8.1.4.3. Two or more biopsy-proven trichilemmomas; or

3.12.8.1.4.4. Two or more major criteria (one must be macrocephaly); or

3.12.8.1.4.5. Three major criteria, without macrocephaly; or

3.12.8.1.4.6. One major and ≥3 minor criteria; or

3.12.8.1.4.7. minor criteria

3.12.8.1.5. Individual with a relative with a clinical diagnosis of CS/PHTS or BRRS for whom testing has not been performed

3.12.8.1.6. Individuals must have the following:

3.12.8.1.6.1. Any one major criterion or

3.12.8.1.6.2. Two minor criteria for Cowden Syndrome/PTEN Hamartoma Tumor Syndrome

3.12.8.1.7. PTEN P/LP variant detected by tumor genomic testing on any tumor type in the absence of germline analysis

3.12.8.1.8. Patients with a known or likely familial variant, only testing for those relevant genes is recommended.

3.12.8.1.9. Patients with no known familial variant, multigene panel testing for other hereditary syndrome `is recommended

3.12.8.2. Gene recommendation

PTEN

3.12.9. Renal Cell Carcinoma (RCC)

3.12.9.1. Patient Selection Criteria

3.12.9.1.1. An individual with a close blood relative with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene

3.12.9.1.2. An individual with RCC with any of the following criteria:

3.12.9.1.2.1. Diagnosed at age ≤46 y

3.12.9.1.2.2. Bilateral or multifocal tumors

3.12.9.1.2.3. One first- or second-degree relative with RCC

3.12.9.1.3. An individual whose tumors have the following histological characteristics:

3.12.9.1.3.1. Multifocal papillary histology

3.12.9.1.3.2. HLRCC-associated RCC, RCC with fumarate hydratase (FH) deficiency or other histological features associated with HLRCC

3.12.9.1.3.3. Birt-Hogg-Dubé syndrome (BHDS)-related histology (multiple chromophobe, oncocytoma, or oncocytic hybrid)

3.12.9.1.3.4. Angiomyolipomas of the kidney and one additional tuberous sclerosis complex (TSC) criterion in the same person

3.12.9.1.3.5. Succinate dehydrogenase (SDH)-deficient RCC histology

3.12.9.1.4. An unaffected individual, with any of the following criteria:

3.12.9.1.4.1. Two first- or second-degree relatives with RCC (on the same side of the family)

3.12.9.1.4.2. Any first-degree relative who meets the criteria in boxes 2 or 3 who is unable or unwilling to genetically test

3.12.9.2. Multigene panel recommendation

BAP1, FH, FLCN, MET, SDHA, SDHB, SDHC, SDHD, TSC1, TSC2, VHL

3.12.9.3. Assessment, Risk Management and Surveillance

Gene	Screening Recommendations
BAP1-TPDS	Abdominal MRI (preferred) or CT, both exams obtained with and without IV contrast, every 2-y starting at age 30 y
BHDS	Abdominal MRI (preferred) or CT, both exams obtained with and without IV contrast, every 3-y starting at age 20 y
HLRCC	Abdominal MRI (preferred) or CT, both exams obtained with and without IV contrast, annually starting at age 8–10 y
HPRC	Abdominal MRI (preferred) or CT, both exams obtained with and without IV contrast, every 1–2 y starting at age 30 y
PGL/PCC	Abdominal MRI (preferred) or CT, both exams obtained with and without IV contrast, every 2 years concurrently with PGL/ PCC screening recommendations starting at age 12 y
TSC	Abdominal MRI (preferred) or CT, both exams obtained with and without IV contrast, every 1–3 y starting at age 12 y
VHL	Abdominal MRI (preferred) or CT, both exams obtained with and without IV contrast, to assess kidneys, pancreas, and adrenals every 2-y starting at age 15 y

3.12.10. Non-Small Cell Lung Cancer (NSCLC)

3.12.10.1. Patient Selection Criteria

Patients with lung cancer and somatic EGFR p.T790M variant with no previous EGFR TKI therapy.

3.12.10.2. Gene recommendation

Germline EGFR p.T790M

3.12.11. Osteosarcoma

3.12.11.1. Patient Selection Criteria

3.12.11.1.1. Patient with osteosarcoma before 46 years of age AND at least one first- or second-degree relative with a TP53 core tumour (breast cancer, soft-tissue sarcoma, osteosarcoma, central nervous system tumour, adrenocortical carcinoma) before 56 years of age.

3.12.11.1.2. Patients with osteosarcoma and another TP53 core tumour, the first of which occurred before 46 years of age, irrespective of family history.

3.12.11.2. Gene Recommendation:

TP53

3.12.11.3. Summary Recommendation

Identification of germline disease-causing TP53 variants can impact disease management and follow-up. In carriers, radiotherapy, contributing to the possible development of subsequent primary tumours (incidence >40%) should be, if possible, avoided.

3.12.12. Soft-Tissue Sarcoma (STS)

3.12.12.1. Patient Selection Criteria

3.12.12.1.1. Germline TP53 testing should be carried out, if possible, before treatment initiation inpatients <46 years of age with STS and at least one first- or second-degree relative <56 years of age with a TP53 core tumour (breast cancer, STS, bone sarcoma, central nervous system tumour, adrenocortical carcinoma), or

3.12.12.1.2. Patients with STS (especially in RT fields) and with another TP53 core tumour <46 years of age.

3.12.12.2. Multigene panel recommendation

TP53, NF1, RB1, FAP

3.12.12.3. Summary Recommendation

3.12.12.3.1. In TP53 carriers, RT should be avoided if possible after multidisciplinary discussion, while an annual whole-body MRI is recommended.

3.12.12.3.2. TP53 testing should be carried out in selected patients with STS under the age of 46 years.

3.12.13. Medullary Thyroid Carcinoma (MTC)

3.12.13.1. Patient Selection Criteria

Germline testing for RET PV is recommended for all patients with newly diagnosed MTC or clinically suspected sporadic MTC.

3.12.13.2. Multigene panel recommendation

MEN2/RET

3.12.14. Melanoma

3.12.14.1. Patient Selection Criteria

3.12.14.1.1. Patients with 3 or more cutaneous melanomas, or a mix of invasive melanoma, pancreatic cancer, and/or renal, and/or breast cancer, and/or uveal melanoma, and/or mesothelioma and/or astrocytoma diagnoses in an individual or family member or

3.12.14.1.2. Patients with invasive cutaneous melanoma who have a first-degree relative are diagnosed with pancreatic cancer.

3.12.14.2. Multigene panel recommendation

P16/CDKN2A In some cases: CDK4, MC1R, BAP1 (especially for uveal melanoma), TERT, MITF, PTEN

3.12.15. Adrenocortical Tumors

3.12.15.1. Patient Selection Criteria

Patients diagnosed with adrenocortical carcinoma

3.12.15.2. Multigene panel recommendation

MEN1, MLH1, EPCAM, MSH2, MSH6, PMS2, APC, TP53

3.12.16. Gastrointestinal Stromal Tumors (GISTs)

3.12.16.1. Patient Selection Criteria

Patients with GISTs that are SDH-deficient and those with GIST that have NF1 or SDH somatic mutations.

3.12.16.2. Multigene panel recommendation

Implied testing for SDH and NF1

3.12.17. Urothelial Cancer

3.12.17.1. Patient Selection Criteria:

Younger age at presentation and/ or personal or family history of Lynch syndrome-related cancer

3.12.17.2. Multigene panel recommendation

Lynch syndrome (LS) panel

3.12.18. Acute Lymphocytic Leukemia

3.12.18.1. Patient Selection Criteria

3.12.18.1.1. Patients with ALL

3.12.18.1.2. Family history of leukemia, other hematologic cancers or the associated conditions including Familial platelet disorder with propensity to myeloid malignancies, Thrombocytopenia, PAX5-associated leukemia predisposition, IKZF1-associated leukemia predisposition, Li-Fraumeni syndrome

3.12.18.2. Multigene panel recommendation

RUNX1, ETV6, PAX5, IKZF1, TP53

3.12.19. Acute Myeloid Leukemia

3.12.19.1. Patient Selection Criteria

3.12.19.1.1. Allogeneic related donor HCT candidate of patients with suspected HMMPS

3.12.19.1.2. All patients with MDS and adults <50 y with AML

3.12.19.1.3. Clinically suspected genetic predisposition syndrome at any age

3.12.19.1.4. Hypocellular MDS

3.12.19.1.5. Newly diagnosed aplastic anemia

3.12.19.1.6. Personal history of MDS or AML (including therapy-related) and ≥1 additional cancer(s)

3.12.19.2. Multigene Panel Recommendation

RUNX1, ANKRD26, CEBPA, DDX41, ETV6, GATA2, MBD4, MECOM/EVI1 complex, SAMD9/SAMD9L, TERC/TERT, ATG2B/GSKIP

3.12.20. Myelodysplastic Syndrome (MDS)

3.12.20.1. Patient Selection Criteria

3.12.20.1.1. Allogeneic related donor HCT candidate of patients with suspected HMMPS

3.12.20.1.2. All patients with MDS and adults <50 y with AML

3.12.20.1.3. Clinically suspected genetic predisposition syndrome at any age

3.12.20.1.4. Hypocellular MDS

3.12.20.1.5. Newly diagnosed aplastic anemia

3.12.20.1.6. Personal history of MDS or AML (including therapy-related) and ≥1 additional cancer(s)

3.12.20.2. Multigene panel recommendation

CEBPA, DDX41, ATG2B/GSKIP, XP C/XPC, ERCC6L2, ANKRD26, ETV6, GATA2, RUNX1, LIG-4, SAMD9/SAMD9L, SRP72, Diamond-Blackfan anemia, FA, Shwachman-Diamond syndrome, short telomere syndromes, congenital neutropenia, myeloid neoplasms associated with Down syndrome, constitutional mismatch repair deficiency (CMMRD), BRCA1/BRCA2, LFS/TP53, RASopathies, another rare DNA repair syndromes/BLM, MBD4, XPC

3.13. Guideline Implementation

The DoH guidelines are developed for implementation across all health care settings in Abu Dhabi. The guidelines will be posted in DoH website. The guideline should be reviewed and updated at regular intervals to accommodate newer findings and therapeutic changes.

4.Relevant References Documents

No.	Reference Date	Reference Name	Relation Explanation / Coding / Publication Links
1.	2024	NCCN Guidelines	NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic https://www.nccn.org/professionals/physician_gls/pdf/genetics_bopp.pdf
2.	2024	ASCO Guidelines	Selection of Germline Genetic Testing Panels in Patients with Cancer: ASCO Guideline | Journal of Clinical Oncology (ascopubs.org) https://ascopubs.org/doi/10.1200/JCO.24.00662
3.	2024	ESMO Guidelines	Recommendations for the use of next-generation sequencing (NGS) for patients with advanced cancer in 2024: a report from the ESMO Precision Medicine Working Group https://www.annalsofoncology.org/article/S0923-7534(24)00111-X/fulltext
4.	2024	NCCN Guidelines	NCCN Guidelines Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric https://www.nccn.org/guidelines/guidelines-detail?category=2&id=1544
5	2024	Society of Surgical Oncology Breast Disease Site Work Group	Updated Guidelines on When to Consider Germline Testing for Patients with Breast Cancer - PubMed (nih.gov) https://pubmed.ncbi.nlm.nih.gov/38969855/
6	2024	NCCN Guidelines	NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Myelodysplastic Syndromes https://www.nccn.org/professionals/physician_gls/pdf/mds.pdf
7	2024	NCCN Guidelines	NCCN Guidelines Version 2.2024 Acute Lymphoblastic Leukemia https://www.nccn.org/professionals/physician_gls/pdf/all.pdf

8	2024	NCCN Guidelines	NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Prostate Cancer Early Detection https://www.nccn.org/professionals/physician_gls/pdf/prostate_detection.pdf
9	2024	NCCN Guidelines	NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Kidney Cancer https://www.nccn.org/login?ReturnURL=https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf
10	2023	DoH	DoH standard for Laboratory Accreditation for Genomic-Related services and products https://www.bing.com/ck/a?!&&p=a051872d2167daabe03aa36d22002ed6e721fc0e44fc6633d3b4c313b73a8cfbJmltdHM9MTczNTg2MjQwMA&ptn=3&ver=2&hsh=4&fclid=1fabaf9b-1af9-6abb-13f7-bb9a1b226b1d&psq=DOh+DOH+standard+for+Laboratory+Accreditation+for+Genomic-Related+services+and+products&u=a1aHR0cHM6Ly93d3cuZG9oLmdvdi5hZS8tL21lZGlhL0ZlYXR1cmUvUmVzb3VyY2VzL1N0YW5kYXJkcy9zdGFuZGFyZC1mb3ItbGFib3JhdG9yeS1hY2NyZWRpdGF0aW9uLWZvci1nZW5vbWljLXJlbGF0ZWQtc2VydmljZXMtYW5kLXByb2R1Y3RzLmFzaHg&ntb=1
11	2023	DoH	Guideline for Breast Cancer Germline Testing https://www.bing.com/ck/a?!&&p=ebcc5781cf7147df3b7388866b1960f52cd5e540ee8bd04529946181cd95031bJmltdHM9MTczNTg2MjQwMA&ptn=3&ver=2&hsh=4&fclid=1fabaf9b-1af9-6abb-13f7-bb9a1b226b1d&psq=Breast+cancer+DOH+guideliens&u=a1aHR0cHM6Ly93d3cuZG9oLmdvdi5hZS8tL21lZGlhL0MzMjBGOEFENjZDRDRGNEU5MzQ2RkM5NTJFM0NGNDNBLmFzaHg&ntb=1
12	2025	DoH	DOH Patient consent standard https://www.bing.com/ck/a?!&&p=379d58955f822b3651aeea8dc9fc7bb43720deb1dae8b97d836a9fcca80f9a22JmltdHM9MTczNjEyMTYwMA&ptn=3&ver=2&hsh=4&fclid=1fabaf9b-1af9-6abb-13f7-bb9a1b226b1d&psq=DoH+patient+consent+standard&u=a1aHR0cHM6Ly93d3cuZG9oLmdvdi5hZS8tL21lZGlhLzIwMzRFMUUzQz
13	2022	DOH	Unified Healthcare Professional Qualification Requirements https://www.doh.gov.ae/en/pqr
14	2023	DoH	Standard for clinical privileging of healthcare workforce and clinical services https://www.doh.gov.ae/-/media/87DBE2A3226940E8A5712D3577064672.ashx

6.Appendices

Table 1. Tumours Relevant to Each Gene If a Conservative Testing Approach Is Preferred

Gene	Relevant Tumors (ie, only test if a pathogenic or likely pathogenic variant is found in these cancers)
ATM	Breast cancer, gastric cancer, epithelial ovarian cancer, pancreatic adenocarcinoma, or prostate cancer
BAP1	Melanoma, renal cell carcinoma, malignant mesothelioma
BARD1	Breast cancer
CDKN2A	Melanoma or pancreatic adenocarcinoma
CHEK2	Breast cancer, colon cancer, prostate cancer, thyroid cancer CHEK2 c.1100del testing should occur regardless of tumor type
DICER1	Pleuropulmonary blastoma, cystic nephroma, embryonal rhabdomyosarcoma, ovarian Sertoli-Leydig cell tumors, ovarian sarcoma, neuroblastoma, thyroid cancer
FH	Paraganglioma, pheochromocytoma, or renal cell carcinoma
FLCN	Renal cell carcinoma
NF1	Breast cancer, GIST, paraganglioma, pheochromocytoma
POLD1	Colorectal cancer
POLE	Colorectal cancer
SDHA	GIST, PPGL, renal cell carcinoma
SMARCA4	SCCOHT and malignant rhabdoid tumors (malignant rhabdoid tumors

Table 2: Genes Recommended for Testing and Inclusion in Multigene Panels for Selected Cancers

Cancer Type and Specific Population	More Strongly Recommended (higher relative risk of cancer or highly actionable)	Less Strongly Recommended (moderate relative risk of cancer or potential impact for therapy/change in medical management)
*Breast cancer	BRCA1, BRCA2, PALB2 CDH1, PTEN, STK11, TP53	ATM, BARD1, CHEK2, RAD51C, RAD51D NF1
Colorectal cancer	APC, EPCAM, MLH1, MSH2, MSH6, MUTYH, NTHL1, PMS2, POLD1, POLE BMPR1A, SMAD4, STK11, TP53	AXIN2, CHEK2, MBD4 GREM1, MSH3, PTEN, RNF43
Endometrial cancer	EPCAM, MLH1, MSH2, MSH6, PMS2 PTEN, STK11	NA
Gastric cancer	APC, CTNNA1, EPCAM, MLH1, MSH2, MSH6, PMS2 BMPR1A, CDH1, SMAD4, STK11	NA
Gastrointestinal stromal tumors	KIT, PDGFRA If SDH-deficient or SDH-mutant tumor: SDHA, SDHAF2, SDHB, SDHC, SDHD If NF1-mutated tumor: NF1	If tumor is not SDH-deficient, SDH-mutated, or NF1-mutated: NF1, SDHA, SDHAF2, SDHB, SDHC, SDHD
Medullary thyroid carcinoma	MEN2/RET	NA
Non–small cell lung cancer—if EGFR tumor pathogenic variant (such as p.T790M) found with no previous EGFR-TKI therapy	EGFR STK11	TP53
Adrenocortical tumors	APC, EPCAM, MEN1, MLH1, MSH2, MSH6, PMS2, TP53	NA
Melanoma, cutaneous	CDKN2A, CDK4	BAP1, MC1R, MITF, POT1, TERT PTEN
Melanoma, uveal	BAP1	NA
*Ovarian cancer (epithelial)	BRCA1, BRCA2, BRIP1, EPCAM, MLH1, MSH2, MSH6, PALB2, PMS2, RAD51C, RAD51D	ATM
Pancreatic adenocarcinoma	ATM, BRCA1, BRCA2, CDK4, CDKN2A, EPCAM, MLH1, MSH2, MSH6, PALB2, PMS2 STK11, TP53	APC

Phaeochromocytomas and paragangliomas	FH, MAX, RET, SDHA, SDHB, SDHC, SDHD, TMEM127 NF1, VHL	EGLN1, EPAS1, KIF1B, MET, SDHAF2
Prostate cancer	BRCA1, BRCA2, EPCAM, HOXB13, MLH1, MSH2, MSH6, PMS2	ATM, CHEK2, PALB2
Renal cell carcinoma	BAP1, FH, FLCN, MET, SDHA, SDHAF2, SDHB, SDHC, SDHD PTEN, VHL	TSC1, TSC2
Sarcoma (soft tissue or osteosarcoma)	TP53	NF1, RB1
Wilms Tumor (Nephroblastoma)	Denys-Drash syndrome (WT1), WAGR/WAGRO syndrome (WT1), Perlman syndrome (DIS2L2), Beckwith-Wiedemann syndrome (CDKNIC), Frasier syndrome (WT1), Bohring-Opitz syndrome (ASXL1), MULIBREY syndrome (TRIM37), LFS (TP53), trisomy 18 syndrome	NA
Urothelial Cancer	Lynch Syndrome (LS)	NA
Pediatric Acute Lymphoblastic Leukemia	LFS/TP53 association with low hypodiploid ALL	NA
Myelodysplastic Syndrome	CEBPA, DDX41, ATG2B/GSKIP, XP C/XPC, ERCC6L2, ANKRD26, ETV6, GATA2, RUNX1, LIG-4, SAMD9/SAMD9L, SRP72, Diamond-Blackfan anemia, FA, Shwachman-Diamond syndrome, short telomere syndromes, congenital neutropenia, myeloid neoplasms associated with Down syndrome, constitutional mismatch repair deficiency (CMMRD), BRCA1/BRCA2, LFS/TP53, RASopathies, other rare DNA repair syndromes/BLM, MBD4, XPC	NA
Acute Lymphocytic Leukemia	RUNX1, ETV6, PAX5, IKZF1, TP53	NA
Acute Myeloid Leukemia	RUNX1, ANKRD26, CEBPA, DDX41, ETV6, GATA2, MBD4, MECOM/EVI1 complex, SAMD9/SAMD9L, TERC/TERT, ATG2B/GSKIP	NA

* Please refer to DoH Guideline for Breast Cancer Germline Testing