Selection of Germline Genetic Testing Panels in Patients With Cancer: ASCO Guideline

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ABSTRACT

ASCO Guidelines provide recommendations with comprehensive review and analyses of the relevant literature for each recommendation, following the guideline development process as outlined in the ASCO Guidelines Methodology Manual. ASCO Guidelines follow the ASCO Conflict of Interest Policy for Clinical Practice Guidelines.

Clinical Practice Guidelines and other guidance ("Guidance") provided by ASCO is not a comprehensive or definitive guide to treatment options. It is intended for voluntary use by providers and should be used in conjunction with independent professional judgment. Guidance may not be applicable to all patients, interventions, diseases, or stages of diseases. Guidance is based on review and analysis of relevant literature and is not intended as a statement of the standard of care. ASCO does not endorse third-party drugs, devices, services, or therapies and assumes no responsibility for any harm arising from or related to the use of this information. See complete disclaimer in Appendix 1 and Appendix 2 (online only) for more.

PURPOSE To guide use of multigene panels for germline genetic testing for patients with cancer.

METHODS An ASCO Expert Panel convened to develop recommendations on the basis of a systematic review of guidelines, consensus statements, and studies of germline and somatic genetic testing.

RESULTS Fifty-two guidelines and consensus statements met eligibility criteria for the primary search; 14 studies were identified for Clinical Question 4.

RECOMMENDATIONS Patients should have a family history taken and recorded that includes details of cancers in first- and second-degree relatives and the patient's ethnicity. When more than one gene is relevant based on personal and/or family history, multigene panel testing should be offered. When considering what genes to include in the panel, the minimal panel should include the more strongly recommended genes from Table 1 and may include those less strongly recommended. A broader panel may be ordered when the potential benefits are clearly identified, and the potential harms from uncertain results should be mitigated. Patients who meet criteria for germline genetic testing should be offered germline testing regardless of results from tumor testing. Patients who would not normally be offered germline genetic testing based on personal and/or family history criteria but who have a pathogenic or likely pathogenic variant identified by tumor testing in a gene listed in Table 2 under the outlined circumstances should be offered germline testing.

Additional information is available at www.asco.org/molecular-testing-and-biomarkers-guidelines.

ACCOMPANYING CONTENT

Appendix

Data Supplement

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TARGET POPULATION AND AUDIENCE

Target Population
Adult patients with cancer, excluding hematologic malignancies.

Target Audience
Clinicians and others providing care for patients with cancer, patients and their family members, payers, and other institutional stakeholders in germline genetics care.

INTRODUCTION

Genetic testing for an inherited pathogenic variant (herein referred to as germline genetic testing)[1] is increasingly recommended for a growing number of patients with cancer to identify an inherited etiology. *BRCA1/2* testing is advised for those with epithelial ovarian cancer, pancreatic adenocarcinoma, metastatic prostate cancer, or metastatic human epidermal growth factor receptor 2–negative breast cancer, for whom poly (ADP-ribose) polymerase (PARP) inhibitor use is appropriate.[2] This testing can reveal future cancer risks for patients and potentially their relatives. Moreover, the awareness that germline pathogenic variants may affect the use of targeted cancer therapies, such as PARP inhibitors for *BRCA* pathogenic variant carriers or immune therapy for tumors with microsatellite instability or mismatch repair deficiency, has heightened oncologists' recognition of the significance of genetic testing. Germline genetic testing should be distinguished from biomarker testing (herein referred to as tumor genomic profiling) that identifies genetic variants in a tumor, which can be acquired (somatic) or inherited (germline). To establish whether gene variants identified in a tumor are germline, germline genetic testing must be performed.

With advancements in next-generation sequencing technology, genetic panels now encompass an expanding list of available genes. These multigene panels include genes in which pathogenic or likely pathogenic variants confer a high relative risk of cancer (*BRCA1/2* and Lynch syndrome genes [*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*]) and genes associated with a more moderately increased risk of cancer (<5× risk; eg, *ATM*, *CHEK2*). The inconsistency in data regarding the risk of cancer associated with pathogenic variants in some cancer susceptibility genes (ie, clinical validity) is partly due to differences in populations studied and methodologies used among studies.

Given the uneven distribution of genetic counselors and the need for timely genetic results for therapeutic decision making, many oncologists are increasingly involved in initiating germline testing. While genetic expertise is so valuable in all steps of testing, increasingly genetic experts are often involved only with complicated cases or with interpreting positive or uncertain genetic results. Simultaneous testing of multiple genes is more efficient, especially for patients with cancer and a medical or family history suggestive of a potential pathogenic variant in more than one gene. The challenge of recalling multiple cancer syndromes, coupled with the recognition that family history knowledge is often imperfect, has made multigene panels attractive to many oncologists. For numerous clinicians, the identification of pathogenic variants in high-penetrance genes without a predictive personal or family history has reinforced the decision to use these panels.[3]

Other clinicians prefer more focused panels that include genes informed by the patient's personal and family history of cancer or limit testing to genes with higher penetrance for which recommendations are well established. Smaller panels avoid including genes with uncertain clinical validity and limit the number of identified variants of uncertain significance (VUS), which may lead to misinterpretation and overtreatment.[4,5]

Appropriate germline genetic testing depends on an accurate family history of cancer. While testing for some patients is indicated regardless of family history, for others, family history can determine testing eligibility. In addition, family history informs which genes should be included in a genetic panel beyond those indicated by a patient's personal history. Family history is also crucial for the proper interpretation of genetic test results (both positive and negative) to guide personalized screening and prevention recommendations for patients and their family members. Previous studies have shown poor performance in the collection of cancer family history by oncologists.[6]

The purpose of this guideline is to aid oncologists in (1) identifying the components of family history most relevant to germline testing, (2) understanding the potential benefits and harms of ordering multigene panels, (3) identifying the most relevant cancer susceptibility genes to include in a germline multigene panel on the basis of a patient's personal and family history of cancer, and (4) understanding when germline genetic testing is indicated for patients who have had tumor genomic profiling. Given the concerns with germline testing outlined above, the ASCO Evidence-Based Medicine Committee (EBMC) authorized the development of a guideline on germline genetic testing that covered all cancers. The objective of this framework is to provide direct and comprehensible guidance to oncologists and other health practitioners who might have limited familiarity with, or access to, genetics expertise, to better ensure that patients and their family members receive appropriate and beneficial testing. This guideline has added value in providing an overall framework that current and future ASCO guidelines such as the recently published "Germline Testing in Patients with Breast Cancer: ASCO–Society of Surgical Oncology Guideline"[7] can use as a basis for cancer-specific recommendations.

GUIDELINE QUESTIONS

This clinical practice guideline addresses four overarching clinical questions:

1. What is the importance of family history collection in the setting of germline multigene panel testing and what elements of family history are most important?
2. When and how should multigene panel germline testing be used when germline genetic testing is indicated?
3. Which genes are generally recommended for germline genetic testing for patients with selected cancers?
4. Which patients should be offered germline genetic testing who will have or have had somatic genetic tumor testing (ie, tumor genomic profiling)?

The population addressed by all questions is adult patients with selected cancers, excluding hematologic malignancies.

This guideline's scope does not include making recommendations on the criteria for which patients should receive germline genetic testing. These criteria vary widely across cancers depending on many factors, and a systematic inclusion of those criteria is best handled in cancer- or syndrome-specific guidelines. For guideline questions 2, 3, and 4, the assumption is that appropriate criteria have been referenced for the patient's context and the decision to either offer or not offer germline testing has been made. The criteria applied to determine if germline genetic testing is indicated can be straightforward for some cancers (ie, all patients with epithelial ovarian cancer and exocrine pancreatic cancer) or more complex, requiring additional personal or family history characteristics, such as age at diagnosis and/or multiple family members with the same or associated cancers or metastatic or advanced disease status. Historically, these criteria have adapted over time as our understanding of the contribution of germline variants to disease etiology and treatment decision making has advanced. The National Comprehensive Cancer Center Network (NCCN) provides at least annual updates to genetic testing criteria, mostly informed by *BRCA1*- and *BRCA2*- associated[2] and Lynch syndrome–associated cancer[8] risk and presentation. Notably, several cancer-specific treatment guidelines by NCCN also contain guidance related to germline genetic testing,[9,10] as do multiple professional organizations and consensus groups.[11-14] ASCO has also published guidelines on ovarian cancer,[15] pancreatic cancer,[16] and very recently on breast cancer.[7,15,16] The tables in Data Supplement 1 (online only) present a number of these resources that may be of value. Not all patients with cancer and/or with a family history of cancer will fit easily into established genetic testing criteria, so recognition of the hallmarks of inherited cancer predisposition is key as well as the utilization of genetics providers as a resource in the identification of appropriate candidates for germline genetic testing.

METHODS

Guideline Development Process

This systematic review-based guideline was developed by a multidisciplinary Expert Panel, which included a patient representative and an ASCO guidelines staff member with health research methodology expertise (Appendix Table A1, online only).

The recommendations were developed by using a combination of methods. Across all the questions, a PubMed search was conducted on May 17, 2022, for guidelines (called identified documents in this guideline) that provide recommendations on germline genetic testing. Websites of other guideline developers (National Institute for Health and Care Excellence, NCCN, Scottish Intercollegiate Guidelines Network, European Society for Medical Oncology [ESMO], College of American Pathologists, Association for Molecular Pathology) and the Guidelines International Network library were scanned during April and May 2022 for additional guidelines, and that scan was updated in June 2023. Only guidelines published since January 2014 were included; this date was chosen to only include guidelines published around or after the publication of the large and comprehensive guideline by Hampel et al in 2015.[17] The recommendations from each guideline pertinent to each question were summarized by the ASCO guideline specialist and can be found in Data Supplement 1 (Table S1). The recommendations and evidence base from these guidelines were used to inform the recommendations drafted by ASCO's panel. Both clinical practice guidelines and consensus statements were included, per this definition:

1. A clinical practice guideline is defined minimally as any document that (1) comes from a stated group of expert authors (eg, Country X Society of Specialty Y), (2) clearly identifies a set of specific recommendations (either as statements or in the form of an algorithm), (3) provides at least some description of the methods used to develop the recommendations, and (4) makes reference to at least some form of systematic review of available evidence
2. A consensus statement is defined minimally as any document that meets tests (1) through (3) but not (4).

Documents that do not meet at least the definition of a consensus statement were excluded. As many relevant clinical practice guidelines and consensus statements were expected and they were likely to vary widely in quality, no formal assessment of guideline quality was performed. The Expert Panel believed that it was better to consider guidance, especially in rarer cancers, even if high-quality formal guideline development methods were not used.

In the protocol for the guideline, the option was available to conduct a targeted systematic review for specific questions or subtopics within a question. As development continued, only one additional systematic review of PubMed was

conducted to identify studies relevant to Clinical Question 4 using the following criteria:

1. Population: Adult patients with cancer, excluding hematologic malignancies.
2. Intervention and comparison: Patients received both a somatic and a germline test.
3. Data sought: Prevalence of relevant germline markers cross-indexed to somatic findings.
4. Study criteria: Comparative study where both somatic testing and germline genetic testing were conducted on the same patient, with more than 300 patients included.
5. Publication date from: On or after January 1, 2016. This date was chosen as the time frame after which broad somatic tumor panel testing was available and to focus on only the more recent, relevant studies.
6. Exclusions: Meeting abstracts not subsequently published in peer-reviewed journals, editorials, commentaries, letters, news articles, case reports, and narrative reviews, published in a non-English language.

In response to feedback received at open comment, the genes initially selected for inclusion in Table 1 for Recommendation 3.2 were cross-checked against the ClinGen online database.[20] The evidence assessment of the ClinGen expert panels informed the final selection of genes and the strength of the recommendation for each.

Five full panel meetings were held as well as several subpanel meetings, and members were asked to provide ongoing input on the guideline development protocol, quality and assessment of the evidence, generation of recommendations, and draft content and review and approve drafts during the entire development of the guideline. ASCO staff met routinely with the Expert Panel cochairs and corresponded with the Expert Panel via e-mail to coordinate the process to completion. Ratings for type and strength of the recommendation and evidence quality are provided with each recommendation, defined in Appendix Table A2. The quality of the evidence for each outcome was assessed using elements of the GRADE quality assessment and recommendations development process.[21,22] GRADE quality assessment labels (ie, high, moderate, low, very low) were assigned for each outcome by the project methodologist in collaboration with the Expert Panel cochairs and reviewed by the full Expert Panel. All funding for the administration of the project was provided by ASCO.

Guideline Review and Approval

Draft recommendations were released to the public for open comment from October 18, 2023, through November 1, 2023. Response categories of "Agree as written," "Agree with suggested modifications" and "Disagree. See comments" were captured for every proposed recommendation with a large volume of written comments received on each recommendation. A total of 55 respondents completed the open comment survey. The level of disagreement was low (<8%) except for Recommendation 2.2 (17.31%) and Recommendation 3.1 (11.11%). The cochairs reviewed comments from all sources and determined whether to maintain original draft recommendations, revise with minor language changes, or consider major recommendation revisions. All changes were incorporated before EBMC review and approval.

Several comments warrant discussion. One respondent recommended that the evidence for each gene included in Table 1 should be cross-checked with the information available in the ClinGen online database.[20] This was completed and is described as a postprotocol alteration to the methods in the Methods section. Regarding Recommendation 2.2, most of the disagreement centered around point 4 in the recommendation regarding smaller panels followed by larger, where respondents questioned whether this was of value. No changes were made to the recommendation. Disagreement related to Recommendation 3.1 was split between those who believed that wider panel testing should be recommended and those who thought the recommendation was too broad. No changes were made in response to those comments.

The draft was submitted to three external reviewers with content expertise and the ASCO Multisite Guideline Advisory Group. Reviewers generally believed that the guideline was thorough, and the recommendations were adequately justified. In response to external reviewer comments, several important changes were made by the cochairs before EBMC review. Recommendation 2.1 and Tables 2 and 3 were reworded and restructured to improve readability. Consanguinity was added to the qualifying statement of Recommendation 1.2.

All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO EBMC before submission to the *Journal of Clinical Oncology* for editorial review and consideration for publication.

Guideline Updating

The ASCO Expert Panel and guidelines staff will work with cochairs to keep abreast of any substantive updates to the guideline. On the basis of formal review of the emerging literature, ASCO will determine the need to update. The ASCO Guidelines Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the guideline update process. This is the most recent information as of the publication date.

RESULTS

A total of 52 documents[2,3,8-16,23-63] were included after the systematic review for guidelines. These documents came from multiple organizations and addressed a wide spectrum of diseases. Their relevant recommendations are broken down by clinical question in Data Supplement 1 (Table S1). A total of 19 articles[3,64-82] that met the inclusion criteria for the

TABLE 1. 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*,[a] *PTEN*,[a] *STK11*,[a] *TP53*[a,c]	*ATM*, *BARD1*, *CHEK2*, *RAD51C*, *RAD51D* *NF1*[a,b]
Colorectal cancer	*APC*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *MUTYH*,[d] *NTHL1*,[d] *PMS2*, *POLD1*, *POLE* *BMPR1A*,[a] *SMAD4*,[a] *STK11*,[a] *TP53*[a,c]	*AXIN2*, *CHEK2*, *MBD4* *GREM1*,[a] *MSH3*,[a] *PTEN*,[a] *RNF43*[a]
Endometrial cancer	*EPCAM*, *MLH1*, *MSH2*, *MSH6*, *PMS2* *PTEN*,[a] *STK11*[a]	NA
Gastric cancer	*APC*, *CTNNA1*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *PMS2* *BMPR1A*,[a] *CDH1*,[a] *SMAD4*,[a] *STK11*[a]	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	*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*[a]	*TP53*[a,c]
Adrenocortical tumors	*APC*, *EPCAM*, *MEN1*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *TP53*	NA
Melanoma, cutaneous	*CDKN2A*, *CDK4*	*BAP1*, *MC1R*, *MITF*, *POT1*, *TERT* *PTEN*[a]
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*,[a] *TP53*[a,c]	*APC*
Phaeochromocytomas and paragangliomas	*FH*, *MAX*, *RET*, *SDHA*, *SDHB*, *SDHC*, *SDHD*, *TMEM127* *NF1*[a], *VHL*[a]	*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*[a], *VHL*[a]	*TSC1*[a], *TSC2*[a]
Sarcoma (soft tissue or osteosarcoma)	*TP53*[a,c]	*NF1*[a], *RB1*[a]

NOTE. Given the importance and prevalence of *BRCA1*, *BRCA2*, and the Lynch syndrome genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*), it is reasonable to include these genes in multigene panels for any patient with cancer undergoing germline genetic testing. NOTE 1: This table is intended to guide the choice of genes for panel testing on the basis of specific selected cancers that a patient has and the cancers in that patient's family. This table is not intended to specify which patients should receive genetic testing, but rather to provide information on genes to include in multigene panel testing assuming that the decision to test has been made. Genes that are related to specific syndromes are incorporated into the list for relevant cancer types. A table of this nature can never capture the nuance and specificity of necessary testing and should be considered a summary of the most relevant genes to be tested and included in a panel. This table is not exhaustive for all cancers. It must also be acknowledged that the list of genes in Table 1 will evolve over time as more research clarifies both the relationship between certain genes and the associated risk of cancers as well as the efficacy of various targeted therapies for patients with germline pathogenic variants in various genes. NOTE 2: Germline pathogenic variants in several genes both listed and not listed here are eligibility criteria for one or more therapies (eg, poly (ADP-ribose) polymerase inhibitors in prostate cancer). They may not be themselves associated with increased relative risk of that specific cancer. The location of a gene in either column should not preclude testing for a gene to determine eligibility for therapy. See the text for more information.

Abbreviations: NA, not applicable; PPGLs, paragangliomas; SDH, succinate dehydrogenase; TKI, tyrosine kinase inhibitor.

[a]These genes with a higher relative risk of cancer are usually associated with specific syndromes. Because of the rarity of pathogenic variants in these genes, some providers/patients may or may not choose to include syndrome-related genes if personal history and family history do not support the syndrome phenotype. Specific Clinical Phenotypes (syndromes) are listed here; autosomal dominant unless otherwise indicated: *BMPR1A*: Juvenile polyposis syndrome; *CDH1* hereditary diffuse gastric cancer (HDGC), and lobular breast cancer; *GREM1*: Hereditary Mixed Polyposis syndrome (HMPS); *NF1*: Neurofibromatosis 1; *MSH3* (autosomal recessive): colon polyposis syndrome; *PTEN*: PTEN hamartoma tumor syndrome (Cowden's syndrome); *RB1*: hereditary retinoblastoma; *RN43*: Serrated polyposis syndrome; *SMAD4*: Juvenile polyposis syndrome; *STK11*: Peutz-Jeghers syndrome (PJS); *TP53*: Li-Fraumeni syndrome; *TSC1, TSC2*: Tuberous sclerosis complex; VHL: Von Hippel-Lindau syndrome.

[b]Patients with clinical neurofibromatosis have a significantly increased risk of breast cancer before age 50 years. The risk of breast cancer for patients without clinical neurofibromatosis who are heterozygous for an *NF1* pathogenic variant is less clear.[18,19]

[c]*TP53* pathogenic variants are rare in patients with breast cancer diagnosed over age 45 years, unless there is also a personal or family history of a Li-Fraumeni–associated cancer (eg, breast cancer before age 46 years, soft tissue sarcoma, osteosarcoma, CNS tumor, adrenocortical carcinoma). Testing for *TP53* in older patients without suspicious family history needs to balance the risks of identifying *TP53* as a variant of clonal hematopoiesis of indeterminate potential (CHIP) that is not inherited.

[d]For these genes, the increased risk is associated with the biallelic state (meaning that both copies of the gene must have a pathogenic variant).

TABLE 2. Genes for Which Pathogenic Variants Identified via Tumor Testing Should Prompt Germline Genetic Testing

Population	Genes to Be Tested
All patients with tumor pathogenic variants in these genes should be offered germline testing	*BRCA1*, *BRCA2*, *BRIP1*, *MLH1*, *MSH2*, *MSH6*, *MUTYH*,[a] *PALB2*, *PMS2*, *RAD51C*, *RAD51D*, *RET*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, *TMEM127*, *TSC2*, *VHL*[b] Test only if patient <30 years of age: *APC*, *PTEN*, *RB1*, *TP53*[c]
Any patient with tumor pathogenic variants in these genes may also be offered germline testing However, if a conservative testing approach is preferred, testing for these genes may be limited to patients who meet the criteria in Table 3	*ATM*, *BAP1*, *BARD1*, *CHEK2*,[d] *DICER1*, *FH*, *FLCN*, *NF1*, *POLD1*, *POLE*, *SDHA* Test only if patient <30 years of age: *CDKN2A*, *SMARCA4* Do not test if a conservative testing approach is preferred: *PTCH1*, *SMAD3*,[e] *SMARCB1*, *SUFU*

NOTE. Tumor testing reports may use other terms instead of pathogenic variants. Clinicians will need to understand the terminology used by their laboratories. Adapted with permission from Elsevier and European Society for Medical Oncology.[3]
Abbreviation: ESMO, European Society for Medical Oncology.
[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.

Clinical Question 4–related systematic review were identified. These articles reported analyses of 14 data sets. Their full details, including the target population, means of testing used, and the reported prevalence data, are fully provided in Data Supplement 1 (Table S2). See the search strategies in Data Supplement 2 and the PRISMA diagram for Clinical Question 4 in Data Supplement 3 for full details of how both searches were conducted.

TABLE 3. Tumors 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)

NOTE. Adapted with permission from Elsevier and European Society for Medical Oncology.[3]
Abbreviations: GIST, gastrointestinal stromal tumor; NA, not applicable; PPGL, paraganglioma; SCCOHT, small cell carcinoma of ovary, hypercalcemic type.

RECOMMENDATIONS

All recommendations are available in Table 4.

In this guideline, the phrase "multi-gene panel testing" is used to describe any testing where several genes are tested simultaneously, except in a few cases where the simultaneous testing is for a single syndrome caused by several different genes (eg, Lynch syndrome). The Expert Panel recognizes that in practice, this phrase is frequently applied to large panels of genes whose composition is prespecified by the laboratory or manufacturer.

Also, in this guideline, the word "pathogenic variant" is used throughout to refer to both *pathogenic and likely pathogenic* variants (ie, cancer predisposing mutations) in a specific gene being discussed.

CLINICAL QUESTION 1

What is the importance of family history collection in the setting of germline multigene panel testing and what elements of family history are most important?

Development of Recommendations

In developing the recommendations for Clinical Question 1, the Expert Panel took as the starting point the "American Society of Clinical Oncology Expert Statement: Collection and Use of a Cancer Family History for Oncology Providers" by Lu et al,[34] published in 2014. This statement already provided a strong justification for the need for family history collection and a set of minimal details to be collected.

Starting from this foundation, one reviewer (H.M.) scanned the identified documents detailed in Data Supplement 1

TABLE 4. Summary of all Recommendations

Clinical Question	Recommendation	Evidence Quality	Strength of Recommendation
Q1—Family history collection	1.1. All patients should have a family history taken and recorded	Not rated	Strong
	1.2. Patients should be asked to provide the following information as part of this 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 Does the patient know of any cancers in any first-degree biological relatives: siblings, parents, children? Does the patient know of any cancers in any second-degree biological relatives (on both maternal and paternal sides): grandparents, aunts, uncles, grandchildren, nieces, nephews, half siblings? 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)? Does the patient know of any relative who has had germline genetic testing for cancer predisposition, and if so, what were the results? What is the patient's ethnicity? *Qualifying Statements:* The gender assigned at birth of biological relatives is important to the family history 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	Not rated	Strong
Q2—Germline multigene panel testing	2.1. When germline genetic testing is indicated for a patient with cancer, multigene panel testing should be offered if more than one gene is relevant (Table 1 for details)	Not rated	Strong
	2.2. When considering what to order for multigene panel testing, clinicians should apply the following principles: 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 from Table 1 of this guideline and may include the less strongly recommended genes A broader panel may be ordered when the potential benefits of such a panel can be clearly identified When ordering a panel (especially a broader panel), the clinician should ensure that potential harms are mitigated. See Clinical Interpretation for further clarification 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	Not rated	Not rated—See Clinical Interpretation
Q3—Genes to be included in multigene panels	3. If germline multigene panel testing is offered, testing for pathogenic variants in the genes in Table 1 is recommended for the indicated populations of patients with cancer. Testing the genes in the left-hand column is more strongly recommended based on the higher relative risk for that cancer and/or higher actionability than those on the right but testing all genes relevant to the patient personal and family cancer history is reasonable. See text for criteria for the column assignments	Not rated	Strong
Q4—Germline testing in association with somatic genetic tumor testing	4.1. Patients who meet criteria for germline genetic testing should be offered that testing regardless of results from tumor testing (ie, genomic profiling from tumor biopsy or circulating tumor DNA testing)	Low	Strong
	4.2. Regardless of germline genetic testing criteria, when a pathogenic variant is identified with tumor testing in a gene listed in Table 2 germline genetic testing should be offered according to the criteria in Tables 2 and 3.	Moderate	Strong

(Table S1) for potential new elements to be included, changes to existing elements, or elements that might no longer be necessary. The identified documents were also consulted for additional current issues and context that should be provided to clinicians around family history collection. A subpanel considered the elements from Lu et al and the recommendations of other guidelines and developed an initial draft set of recommendations for this guideline. These recommendations were refined by the full panel during their deliberations.

Clinical Interpretation

The Expert Panel strongly believes that collection of family history is central to the value of germline testing. Family history information 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. Table 1 is a guide for inclusion of relevant genes based on a patient's personal and family history of cancer. While germline genetic testing is recommended regardless of family history for some individuals with specific cancer diagnoses and clinical features or to inform therapeutic options, family history is still valuable in building a differential for the patient and family which can include genes beyond those indicated by the patient's diagnosis. Given that not all genetic components of risk are known and/or can be measured at this time, family history is integral to provide a risk assessment to the patient and family. Some patients have increased risk despite negative genetic test results, and family history collection is necessary to identify and appropriately guide these individuals. Family history may also inform screening and prevention recommendations for individuals found to have pathogenic variants (eg, the need for pancreatic screening in a patient with an *ATM* or *BRCA* pathogenic variant when there is also a family history of pancreatic cancer; the need for breast magnetic resonance imaging screening in a woman with a pathogenic variant in *CHEK2*). Family history may be collected at various points in the process but should be considered in the context of the genetic test results disclosure and risk assessment. If time permits, family history should be updated annually since a patient may not have indications for genetic testing at first but may over time if their family history of cancer changes.

The Expert Panel made several alterations to the criteria as initially presented by Lu et al.[34] First, the criteria were phrased more clearly as questions to render them more actionable for clinicians. Second, the word biological has been added given the importance of relationship to genetic testing. Third, an element has been added to ask the patient about multiple cancers of a single type in their family members, to better evaluate the potential for syndromes that are related to bilateral or multiple cancers.

The Expert Panel recognizes that the patient's knowledge may be incomplete with respect to the questions in Recommendation 1.2. Patients may not know what cancers, if any, are present in their second-degree relatives. They may not have been informed by their parents that they were adopted or conceived with the aid of fertility technology. However, the Expert Panel believes that both the information itself, despite its potential incompleteness and inaccuracy, and the process of asking the patient for the information, is valuable. Many individuals seek more information about the cancers in their family only after initiating the genetic testing process and being asked about family history. Raising general questions about gender at birth and methods of assisted reproduction can initiate conversations within families that may provide important information to gauge the relevancy of cancers in the family history.

Detailed guidance on how collection of these minimal elements of family history should be operationalized in clinical practice is beyond the scope of this guideline. Factors such as the population being served, the cancers being seen in the practice, access or lack thereof to technology (eg, electronic medical record systems), all make a difference in how these recommendations might be implemented. There is no universally accepted set of tools that will work in all situations. The panel has provided a listing of potentially useful resources in Data Supplement 5 that practices may review to help in implementation.

CLINICAL QUESTION 2

When and how should germline multigene panel testing be used?

Development of Recommendations

The full listing of the identified documents relevant to Clinical Question 2 is provided in Data Supplement 1 (Table S1). The guidance in the identified documents was diverse and frequently highly specific to the cancer type addressed by the document. One reviewer (H.M.) summarized the recommendations in the guidelines, and a subpanel reviewed this material and developed a set of principles they believed should be recommended to help clinicians make judgments around multigene panel testing. These initial recommendations were refined by the Expert Panel during further discussions.

Clinical Interpretation

The Expert Panel believed that any consideration of multigene panel testing must begin with acknowledging that there are potential advantages and disadvantages of ordering multigene panel testing that includes genes with limited and/or uncertain connections to the patient's personal and family history. Potential benefits to broader multigene panels (ie, beyond the recommended genes in Table 1) include recognition that patients may be unaware of family history to inform selection of appropriate genes. In addition, unexpected pathogenic variants in clinically significant high—or moderate—penetrance genes can be identified by using broader panels that include genes beyond what would be indicated by the patient's personal or family history (eg, Lynch-related genes in a breast cancer–only family). The Expert Panel also recognizes that the interpretation of variants and the clinical significance of pathogenic variants may change over time, and the information from testing additional genes may confer benefits in the future.

The Expert Panel also felt that given the prevalence and high actionability of pathogenic variants in *BRCA1/2* or Lynch syndrome genes (*MLH1, MSH2, MSH6, PMS2, EPCAM*), including these genes when germline multigene panel testing is ordered for patients with any cancer is reasonable.

There is increasing use of very large panels, especially among nongenetics-trained healthcare providers. However, there are potential harms of ordering a large multigene panel that includes genes not suggested by personal or family history. First, there is the possibility of increased patient anxiety due to findings without clear clinical significance.[83,84] In addition, there can be misinterpretation of results, especially with respect to VUS and findings in genes with uncertain clinical validity. This misinterpretation can result in unnecessary surveillance and risk reduction measures, including prophylactic surgeries.[4,5] Increasing use of larger panels creates potential for such harm when providers ordering or interpreting the tests have limited genetics understanding. Also, the estimates of cancer risk typically associated with pathogenic variants in specific genes are derived from patients with the characteristic personal or family cancer phenotype; risk estimates for patients without the representative history are less established. Therefore, the application of established risk estimates in these individuals may lead to an overestimation of risk. Finally, testing for a larger number of genes increases the possibility of identifying variants that represent clonal hematopoiesis rather than germline variants, especially in older patients.[85] Proper interpretation of complicated results is essential, and timely access to genetic experts is important. The Expert Panel balanced these potential benefits and harms in drafting the recommendation.

Given this balance, the Expert Panel sought to make conservative recommendations while recognizing the important potential benefits that may be accrued from larger multigene panel testing. Collection of data from a larger list of genes may have research value and can contribute to our understanding of the clinical significance of variants and genes. The purpose of this guideline is to provide guidance for testing for pathogenic variants in genes that currently have established or potential value based on a patient's personal or family history of cancer and serves as a minimum list of genes for clinical use. Benefits of ordering panels that include genes beyond those listed in Table 1 must be weighed against the potential harms discussed previously.

It is important that providers recognize that limitations to genetic testing technology exist and may vary across commercial laboratories. A patient may have a clinical syndrome based on a personal and/or family phenotype even though a germline pathogenic variant is not detected. Similarly, patients may have an increased risk of cancer based on family history, regardless of a negative genetic test result, emphasizing the importance of family history in the interpretation of results and risk assessment. Providers should be aware of and inform their patients of these limitations and when appropriate consult with or refer to a genetics expert in such cases.

Instead of making specific recommendations regarding the use of larger multigene panels, the Expert Panel crafted a set of recommended principles that clinicians will be able to apply consistently to make reasonable decisions about what to offer their patients. Of course, patients' preferences need to be sought and respected in making these decisions; each patient's balance of tolerance of potential uncertainty versus desire for more information is different. Consideration of the patient's insurance coverage may lead to the use of specific panels. Given the complexity of these principles, the Expert Panel decided that a formal strength of recommendation rating was not appropriate.

As VUS are re-evaluated by commercial laboratories over time, reclassification of the pathogenicity of a variant can change. Ninety percent of VUS results will be reclassified as benign, and a small proportion will be reclassified as pathogenic, impacting clinical management.[86-93] Anyone who orders genetic testing should understand that there is a commitment to notify patients if the VUS classification is changed to one that is clinically significant (ie, pathogenic or likely pathogenic) to ensure they receive proper information, genetic counseling, follow-up care, and guidance regarding cascade testing. Because the use of broader panels potentially increases the likelihood of a VUS finding, clinicians should be attuned to this need and have a plan for notifying patients of these changes in classification.

In some cases, a clinician may find themselves caring for a patient who has only had testing for pathogenic variants in a single gene or a very limited set of genes that did not include all the genes recommended in Table 1. A clinician will need to evaluate the likelihood that further testing will be of benefit on a case-by-case basis; multigene panel testing for the full list from Table 1 may be valuable.

Clinicians caring for patients with breast cancer should refer to the recent Germline Testing in Patients with Breast Cancer: ASCO-SSO Guideline[7] for detailed guidance.

CLINICAL QUESTION 3

Which genes are generally recommended for germline genetic testing and for which patients?

Development of Recommendations

The full listing of the identified documents relevant to Clinical Question 3 is provided in Data Supplement 1 (Table S1). Only documents that made explicit recommendations for testing for pathogenic variants in specific genes were summarized. To make sense of these diverse recommendations, the Expert Panel first considered a listing of genes recommended for pathogenic variant testing with them broken down by cancer type, with syndrome-related genes

listed in any relevant cancer, and by the raw number of documents that recommended testing for pathogenic variants in that gene. This was taken as a rough estimate of the level of widespread support for testing for pathogenic variants in that gene. Based on this initial summary, a subpanel was formed to go through the genes in detail and, based on the justifications provided in the identified documents, evidence known to the subpanel and the expertise of the members, an initial listing of genes was formulated, and a draft recommendation was developed. In creating the list, the subpanel and panel considered genes that were associated with at least a moderate lifetime risk of cancer OR genes that had clear potential action that could or should be taken in response to a germline pathogenic variant found in that gene. After open comment, the classification of all genes in the ClinGen online database[20] was checked and this information was used in the final determination. All the genes in Table 1 are associated with an increased risk of that cancer. The specific justification for inclusion of each gene for each cancer is provided in Data Supplement 1 (Table S3).

Among those genes, the Expert Panel determined which should be more or less strongly recommended. More strongly recommended genes are those the Expert Panel believed to have a higher relative risk (≥4-fold increased risk) for that specific cancer or genes with a lower relative risk that are highly actionable (eg, recommendation for prophylactic surgery). These genes should be tested in all patients with that cancer or with a family history of that cancer. Genes with a higher relative risk of cancer that are known to be associated with specific syndromes or subpopulations of patients with a particular cancer are noted in the table. Due to the rarity of these genes, some providers and/or patients may or may not choose to include these genes if personal and family history do not support the syndrome phenotype.

Less strongly recommended genes are those that have a moderate relative risk (<4-fold increased risk) for that cancer or are less actionable. For this reason, these genes are included in the less strongly recommended column for testing. Some patients and providers will decide not to include such genes in the testing, while other providers will include genes from both columns. Genes with a moderate relative risk of cancer that are only associated with specific syndromes or subpopulations of patients are noted in the table with a superscript 1.

While the wording "more strongly" and "less strongly" is used in the recommendations and in Table 1, testing of all genes in Table 1 is rated as strongly recommended per ASCO's strength of recommendations definitions (Appendix Table A2).

This initial listing was refined and finalized during discussions of the full panel. The Expert Panel took into consideration the volume and certainty of the evidence regarding potential risk and actionability of each gene.

Clinical Interpretation

The Expert Panel carefully considered the potential benefits and harms that could be caused by germline genetic testing with a multigene panel, testing all relevant genes in Table 1 initially rather than a sequential approach. Testing genes simultaneously can result in efficient clinical testing and more rapid availability of complete results. The Expert Panel also recognizes that some patients may have insurance that only covers a single instance of germline testing; in those cases, multigene panel testing may be more efficient and cost-effective. Potential harms of multigene germline genetic testing, especially for larger panels that include genes beyond those listed in Table 1 for a specific cancer, were discussed in Clinical Question 2. The Expert Panel recognizes that any summary such as is presented in Table 1 will leave out important context and nuance, especially with respect to complicated cancer-related syndromes.

However, the Expert Panel believed that providing this summary listing would be useful to clinicians and cause relatively little harm compared to the potential benefits. Many clinicians find themselves in a context where they must decide whether to order a multigene panel and must confirm that the panel includes the most relevant genes for their patients, but do not have access to colleagues or other resources with deep expertise in the germline genetics of cancer. For these clinicians, a relatively simple listing of the most relevant genes can help ensure that more patients receive needed testing.

In Table 1 the Expert Panel chose cancers that were relatively common and that had more clear hereditary components and where the Expert Panel felt the most useful recommendations could be made. Germline testing may still be valuable in patients with cancers that are not listed in Table 1. Clinicians should seek out relevant expertise in potentially hereditable risks for those cancers.

The Expert Panel recognizes that there are commercially available panels that test for pathogenic variants in more genes than those listed in Table 1 in any one cancer. The use of such panels is addressed in Recommendations 2.1 and 2.2 of this guideline.

Recent regulatory approval of PARP inhibitor therapy has included as eligibility criteria germline pathogenic variants in several genes, for example, *BARD1*, *BRIP1*, *FANCA*, *FANCL*, *MRE11A*, *RAD51B*, *RAD51C*, *RAD51D*. There are also several other situations where approved indications may include germline pathogenic variants (eg, selpercatinib for RET-associated medullary thyroid cancer); Stadler et al[77] provide a useful summary of these situations. However, the evidence for this association is often based on a very small number of patients from the underlying trial for that particular therapy. The Expert Panel decided not to formally recommend testing for pathogenic variants in these genes solely based on this factor. Clinicians should keep these potential therapeutic options in

mind when considering what testing to offer, however testing for germline pathogenic variants may not be easily available for all these genes.

CLINICAL QUESTION 4

Which patients should be offered germline genetic testing who will have or have had somatic genetic tumor testing?

Development of Recommendations

The full listing of the identified documents relevant to Clinical Question 4 is provided in Data Supplement 1 (Table S1), and data from the 14 identified studies is presented in Data Supplement 1 (Table S2).[3,64-82] The guidance in the identified documents was diverse and frequently specific to the cancer type addressed by the document. One reviewer (H.M.) summarized the recommendations in the guidelines, which were considered by the full panel, who then directed the further systematic review of primary studies noted in the Methods. This review identified studies that reported on the prevalence of germline genetic findings in relation to tumor testing findings.

During development, the Expert Panel became aware that the ESMO Precision Medicine Working Group (PMWG) had updated its recommendations for germline testing in response to tumor testing findings.[3] These recommendations are based on a detailed analysis of data from the MSK-IMPACT registry of test results from 2014 to 2021, including 49,264 tumors and paired germline test results. Given the volume of data available to the ESMO PMWG and the transparent and reasonable methods they used, the Expert Panel decided to use the approaches outlined by that group as a framework to develop recommendations. The ESMO PMWG divided up the genes into three actionability classes: most actionable, highly actionable, and standard actionability. Using these actionability classes, they presented four potential approaches based on their analysis, with "actionability" here used as defined in their guideline:

1. Approach A (permissive) was germline testing if pathogenic variants in any of the genes in Table 2 of this guideline are identified in any tumor, with age restrictions as listed.
2. Approach B (intermediate-permissive) was germline testing if a pathogenic variant in a most or highly actionable class gene was identified in any tumor, and if pathogenic variants in the standard actionability class were found in tumors relevant to that gene.
3. Approach C (intermediate–conservative) was germline testing if a pathogenic variant in the most actionable class g gene is identified in any tumor or if a pathogenic variant in a high or standard actionability class gene is identified in a tumor relevant to that gene.
4. Approach D (conservative)—germline testing only when the identified gene was relevant to the tumor type.

The ESMO PMWG recommended Approach C in their guideline but noted that in other contexts (eg, North America) other approaches may be more suitable. The Expert Panel considered these approaches and rejected Approach D as not representing current best practice.

The Expert Panel weighed the increased likelihood of identifying germline pathogenic variants in the more permissive approaches with the increased burden of performing germline genetic testing for a larger percentage of patients. Based on the ESMO PMWG's analysis, a higher proportion of patients would be referred for genomic analysis (11.3% with A; 7.6% with B; and 6.7% with C) and a lower percentage of the referred patients would be found to have a germline pathogenic variant (A: 51.7%; B: 59.6%; C: 60.3%) for Approach A versus B versus C. The Expert Panel also weighed the value of simple recommendations that might cloud important nuance and context versus more complicated recommendations that would be difficult for community oncologists to follow and implement.

The Expert Panel achieved a consensus on a hybrid of ESMO PMWG's Approaches A and B. As with Approach A, germline testing was broadly recommended if a tumor pathogenic variant was found in any of the genes listed in Table 2, assuming age criteria are met. As with Approach B, additional criteria and the relevant tumors are presented for the oncologists who may want to be more conservative in testing. The goal of these recommendations was to ensure that oncologists knew the core list of genes that should receive germline testing in nearly all cases where pathogenic variants are identified in a tumor (the left-hand column of Table 2) but also to allow for practice variation for a more conservative approach in germline testing of genes listed in the right-hand column (Table 2).

If there is uncertainty around whether a variant identified through tumor genetic testing is pathogenic, oncologists may want to confer with genetics experts. The germline variant database ClinVar[94] is another useful resource to help with this determination.

Variant allele frequency (VAF) is not sufficient in and of itself to confirm or exclude a germline origin. While a VAF <30% for a variant identified from tumor genomic profiling is unlikely to be germline, other factors (eg, tumor purity) must be considered and some laboratories do not report VAF. VAF identified from circulating tumor DNA testing is not informative with respect to germline origin.

Founder mutations are almost always germline and confirmatory germline testing is indicated, regardless of the patient's ancestry or tumor type. An example is the three common *BRCA1/2* pathogenic variants originally identified in patients with Ashkenazi Jewish ancestry or the common c.1100del pathogenic variant in *CHEK2*.

Summary of the Identified Primary Study Literature

Why is germline testing necessary if no suggestive results are found in tumor testing? A meaningful proportion of germline pathogenic variants can be missed in tumor genomic profiling. In Terraf et al,[80] 10.5% of germline pathogenic variants were missed with tumor testing using the MSK-IMPACT test across a range of cancer types. In Lincoln et al[71] 8.1% of germline pathogenic variants were missed with tumor testing. There are several potential reasons that this may occur. First, germline pathogenic variants are sometimes filtered out because of computational algorithms to focus on tumor pathogenic variants relevant to treatment. Second, germline copy number variants, intronic variants, large structural variants, and repetitive element insertions may not be included in tumor profiling assays. In addition, acquired changes in the tumor (eg, chromosomal loss) can result in a deletion of the germline pathogenic variant. Some laboratories may analyze only select (disease relevant) exons or have different levels of depth of sequencing than laboratories performing germline testing. Finally, not all genes associated with known hereditary cancer syndromes are included in tumor genomic testing panels.

Why would patients who do not otherwise meet testing criteria need germline testing based on somatic findings? Significant proportions of patients may not meet germline testing criteria but still have relevant germline pathogenic variants identified by tumor genomic profiling. In Mandelker 2017,[74] 19.7% (205/1,040) of patients with advanced cancer had a germline pathogenic variant (76 genes tested) found with somatic testing. Of these patients, 49.2% (101/205) did not meet guideline-based criteria for germline testing. In Mandelker-Bernstam 2016,[75] 4.3% (43/1,040) of patients with advanced cancer had a germline pathogenic variant in one or more of 18 genes tested found initially with somatic testing and 34.9% of those patients (15/43) did not meet guideline-based criteria for germline testing. However, it is important to note that some genes relevant to germline testing (eg, *TP53*) are frequently mutated in tumor tissue and are not germline. In some cases, the age of the patient and the tumor type can help assess the likelihood that a pathogenic variant found by tumor genomic profiling is germline. A family history of an associated cancer (eg, relative with sarcoma when a *TP53* pathogenic variant is identified) may be helpful as well.

Clinical Interpretation

Given the available evidence, there are two separate clinical scenarios, each of which is addressed by a recommendation. In the first scenario, for patients where germline testing would normally be offered, as is the case in Recommendations 2.1, 2.2, and three of this guideline, patients should receive germline testing per those recommendations regardless of any results of tumor testing. The evidence demonstrates that approximately 8%-10% of germline pathogenic variants are missed on tumor testing. This recommendation is consonant with, but more strongly asserted, than the similar guidance found in the 2022 *Somatic Genomic Testing in Patients with Metastatic or Advanced Cancer: ASCO Provisional Clinical Opinion*[26] PCO 1.5 and its qualifying statement.

In the second scenario, while tumor testing cannot be relied upon for germline testing, it nevertheless may reveal potentially important germline pathogenic variants in a clinically relevant proportion of patients, including many who may not otherwise meet germline genetic testing criteria based on personal and family history. Therefore, those patients should be offered germline testing despite not meeting typical criteria.

DISCUSSION

The use of germline multigene panel testing for patients with cancer is likely to increase as genetic testing guidelines expand. Similarly, the use of genomic analysis of cancer is rapidly increasing to identify therapeutic targets and is identifying pathogenic variants in tumor tissue in cancer susceptibility genes, which may prompt germline testing. However, there is ample evidence that germline genetic testing remains underutilized even for patient populations for whom testing has been strongly recommended for many years.[95-99] Many barriers contribute to the underutilization of germline testing in appropriate patients with cancer.[100-103] Given that timely germline testing is especially important for patients with cancer as results can affect therapy and surgery, an increasing number of oncologists are becoming more directly involved in the initiation of germline genetic testing, with post-test genetic counseling after results are received.[104-106]

This guideline aims to help oncologists identify the relevant cancer susceptibility genes for patients with the most common cancers to guide germline genetic testing. In addition, it addresses the potential advantages and disadvantages of ordering large multigene panels that include genes not suggested by a patient's personal or family history. It reviews the importance of obtaining family history and the important components of that history, even when broad germline multigene testing is performed. Family history not only serves to inform the proper selection of genes for germline testing but is also essential for interpreting the result and estimating a patient's risk of other cancers, especially if germline testing is negative or uninformative. Finally, this guideline outlines which pathogenic variants identified through tumor genomic testing should prompt germline testing.

The recommendations in this guideline support a wide need for access to genetic counseling services. The interpretation of genetic test results requires genetic expertise, especially as the number of genes tested increases. In addition, the support and facilitation of cascade testing in families with pathogenic variants may be difficult as part of routine oncologic care.

It is increasingly the norm that germline genetic testing occurs with large panels of genes. The Expert Panel underscores the need to balance the benefits of such an approach with potential harms. While larger panels may reveal unexpected clinically important pathogenic variants, it may lead to difficulty with proper interpretation of genetic results, which is essential to avoid misinterpretation of results that can lead to anxiety and unnecessary screening or prevention practices.

PATIENT AND CLINICIAN COMMUNICATION

One of the predictors of patient uptake of genetic testing is a referral for and/or discussion about genetic testing with a patient's physician.[107] Therefore, it is crucial that clinicians provide their patients with clear and understandable explanations of the need for germline testing and the results of this testing. The Clinical Interpretation for Recommendations 2.1 and 2.2 describes a number of issues that a clinician will need to navigate when ordering large panels. For recommendations and strategies to optimize patient-clinician communication, see "Patient-Clinician Communication: American Society of Clinical Oncology Consensus Guideline."[108]

HEALTH DISPARITIES

Although ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care or receive fragmented care. Factors such as race and ethnicity, age, socioeconomic status, sexual orientation and gender identity, geographic location, and insurance access are known to affect cancer care outcomes.[109] Patients with cancer who are members of racial and/or ethnic minorities suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving fragmented care or poor-quality care than other Americans.[110,111] Many other patients lack access to care because of their geographic location and distance from appropriate treatment facilities.

Many of the inequities seen broadly in oncology care are amplified in cancer genetics. The evidence on which testing recommendations are based is often biased toward White non-Hispanic populations.[112,113] Fewer Asian, Black, and Hispanic individuals receive germline genetic testing.[95] Because of this undertesting, interpretation of identified variants in these populations leads to a higher frequency of VUS results.[114] As appropriate care for patients and their family members is contingent on accurate and appropriate testing, undertesting of these populations contributes to greater disparities in care.[115] Finally, access to genetics expertise is not equally distributed and may be limited in rural settings or in community-based practices with disproportionately large populations of underserved patients.

Given these disparities in testing and care, researchers should work to ensure that studies of germline testing include diverse populations and undertake studies of undertested populations. Clinicians and institutions should implement policies and practices that ensure all patients receive relevant testing, accounting for the underlying biases in the available evidence.

COST IMPLICATIONS

Increasingly, individuals with cancer are required to pay a larger proportion of their treatment costs through deductibles and coinsurance.[116] Higher patient out-of-pocket costs have been shown to be a barrier to initiating and adhering to recommended cancer treatments.[117,118] Discussion of cost can be an important part of shared decision making.[119]

These concerns are magnified in the context of germline genetic testing for patients with cancer. Not all patients will have insurance coverage for testing. Patients might only have coverage for a single episode of germline genetic testing and therefore have difficulty in paying for later testing if initial testing was incomplete. Family member testing will be addressed by that family member's coverage, which may or may not be sufficient. Institutions, payers, and relevant government agencies should implement policies to ensure that the ability to pay for relevant testing for the patient and their family members is not an impediment to needed and valuable germline genetic testing and related genetic counseling services.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Each ASCO guideline includes a member from ASCO's Practice Guideline Implementation Network (PGIN) on the Expert Panel. The additional role of this PGIN representative on the guideline panel is to assess the suitability of the recommendations to implementation in the community setting but also to identify any other barrier to implementation a reader should be aware of. Barriers to implementation include the need to increase awareness of the guideline recommendations among frontline practitioners and survivors of cancer and caregivers and to provide adequate services in the face of limited resources. The guideline recommendations table and accompanying tools (available at www.asco.org/molecular-testing-and-biomarkers-guidelineswww.asco) were designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO PGIN. ASCO guidelines are posted on the ASCO website and most often published in the *Journal of Clinical Oncology*.

ADDITIONAL RESOURCES

For current information, including selected updates, supplements, slide sets, and clinical tools and resources, visit www.asco.org/molecular-testing-and-biomarkers-guidelines. The Data Supplement for this guideline includes additional evidence tables, the search strategy, PRISMA diagram, and results of the implementability review. Guideline recommendations and algorithms are also available in the free ASCO Guidelines app (available for download in the Apple App Store and Google Play Store). Listen to key recommendations and insights from panel members on the ASCO Guidelines podcast. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.net.

ASCO welcomes your comments on this guideline, including implementation challenges, new evidence, and how this guideline impacts you. To provide feedback, contact us at guidelines@asco.org. Comments may be incorporated into a future guideline update. To submit new evidence or suggest a topic for guideline development, complete the form available at www.asco.org/guidelines.

GENDER-INCLUSIVE LANGUAGE

ASCO is committed to promoting the health and well-being of individuals regardless of sexual orientation or gender identity.[120] Transgender and nonbinary people, in particular, may face multiple barriers to oncology care including stigmatization, invisibility, and exclusiveness. One way exclusiveness or lack of accessibility may be communicated is through gendered language that makes presumptive links between gender and anatomy.[121-124] With the acknowledgment that ASCO guidelines may impact the language used in clinical and research settings, ASCO is committed to creating gender-inclusive guidelines. For this reason, guideline authors use gender-inclusive language whenever possible throughout the guidelines. In instances in which the guideline draws upon data based on gendered research (eg, studies regarding women with ovarian cancer), the guideline authors describe the characteristics and results of the research as reported.

RELATED ASCO GUIDELINES

- Patient-Clinician Communication[108] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)
- Somatic Genomic Testing in Patients With Metastatic or Advanced Cancer[26] (https://ascopubs.org/doi/10.1200/JCO.21.02767)
- Evaluating Susceptibility to Pancreatic Cancer[16] (https://ascopubs.org/doi/10.1200/JCO.18.01489)
- Germline Testing in Patients with Breast Cancer[7] (https://ascopubs.org/doi/10.1200/JCO.23.02225)

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EDITOR'S NOTE

This ASCO Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a supplement with additional evidence tables, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/molecular-testing-and-biomarkers-guidelines.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Selection of Germline Genetic Testing Panels in Patients With Cancer: ASCO Guideline

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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APPENDIX 1. GUIDELINE DISCLAIMER

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APPENDIX 2. GUIDELINE AND CONFLICTS OF INTEREST

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at http://www.asco.org/guideline-methodology). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

TABLE A1. Germline Genetic Testing Expert Panel Membership

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Yanin Chavarri-Guerra, MD, MSc	Instituto Nacional de Ciencias Médicas y Nutrición, Salvador Zubirán, Mexico City, Mexico	Medical Oncology
Stephanie A. Cohen, MS, LCGC	Ascension St. Vincent, Indianapolis, IN	Genetic Counseling
Deborah Cragun, PhD, CGC	University of South Florida, Tampa, FL	Genetic Counseling
Katherine D. Crew, MD, MS	Columbia University, New York, NY	Medical Oncology
Susan Domchek, MD, FASCO	University of Pennsylvania, Philadelphia, PA	Medical Oncology
Judith Balmaña, MD, PhD	Vall d'Hebron University Hospital, Barcelona, Spain	Medical Oncology
Michael J. Hall, MD, MS	Fox Chase Cancer Center, Philadelphia, PA	Medical Oncology
Gregory Idos, MD, MS	City of Hope Comprehensive Cancer Center, Duarte, CA	Medical Oncology
Ghecemy Lopez, DSW(C), MAED	USC Norris Comprehensive Cancer Center, Los Angeles, CA	Patient Advocate
Tuya Pal, MD	Vanderbilt-Ingram Cancer Center, Nashville, TN	Clinical Genetics
Sara Pirzadeh-Miller, MS, CGC	Simmons Cancer Center, University of Texas Southwestern Medical Center, Dallas, TX	Genetic Counseling
Colin C. Pritchard, MD, PhD	University of Washington, Seattle, WA	Molecular Pathology
Huma Q. Rana, MD, MPH	Dana-Farber Cancer Institute, Boston, MA	Clinical Genetics and Genomics
Elena Martinez Stoffel, MD, MPH	University of Michigan Rogel Cancer Center, Ann Arbor, MI	Gastroenterology and Cancer Genetics
Hans Messersmith, MPH	ASCO, Alexandria, VA	ASCO Practice Guideline Staff (Health Research Methods)
Umang Swami, MD	Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT	Medical Oncology
Gregory A. Vidal, MD, PhD	The West Cancer Center and Research Institute and The University of Tennessee Health Sciences Center, Germantown, TN	Medical Oncology

TABLE A2. Recommendation Rating Definitions

Term	Definition
Quality of evidence	
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
Strength of recommendation	
Strong	In recommendations for an intervention, the desirable effects of an intervention outweigh its undesirable effects In recommendations against an intervention, the undesirable effects of an intervention outweigh its desirable effects All or almost all informed people would make the recommended choice for or against an intervention
Weak	In recommendations for an intervention, the desirable effects probably outweigh the undesirable effects, but appreciable uncertainty exists In recommendations against an intervention, the undesirable effects probably outweigh the desirable effects, but appreciable uncertainty exists Most informed people would choose the recommended course of action, but a substantial number would not