Selection of Germline Genetic Testing Panels in Patients with Cancer

ASCO Guideline

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1 Background & Methodology

Introduction

- Genetic testing for an inherited pathogenic variant (germline genetic testing)[1] is increasingly recommended for a growing number of patients with cancer to identify an inherited etiology.
- 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 multi-gene panels;
    3. identifying the most relevant cancer susceptibility genes to include in a germline multigene panel based on a patient's personal and family history of cancer;
    4. understanding when germline genetic testing is indicated for patients who have had tumor genomic profiling.
- The objective of this framework is to provide direct & comprehensible guidance to oncologists and other health practitioners who may have limited familiarity with, or access to, genetics expertise, to better ensure 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 can use as a basis for cancer-specific recommendations.

ASCO Guideline Development Methodology

- The ASCO Evidence Based Medicine Committee (EBMC) guideline process includes:
  - a systematic literature review by ASCO guidelines staff
  - an expert panel provides critical review and evidence interpretation to inform guideline recommendations
  - final guideline approval by ASCO EBMC

- The full ASCO Guideline methodology manual can be found at: www.asco.org/guideline-methodology

Quality of Evidence Rating Definitions

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.
Insufficient	Evidence is insufficient to discern the true magnitude and direction of the net effect. Further research may better inform the topic. Reliance on consensus opinion of experts may be reasonable to provide guidance on the topic until better evidence is available.

Strength of Recommendation Rating Definitions

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/ Conditional	• 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.

Clinical Questions

This clinical practice guideline addresses four overarching clinical questions:

1. What is the importance of family history collection in the setting of germline multi-gene panel testing and what elements of family history are most important?
2. When and how should multi-gene 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 (i.e. tumor genomic profiling)?

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

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.

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2 Summary of Recommendations

Summary of Recommendations

Clinical Question 1

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

Recommendation 1.1

- All patients should have a family history taken and recorded.

Evidence Quality	Strength of Recommendation
Not Rated	Strong

Summary of Recommendations

Recommendation 1.2

Evidence Quality	Strength of Recommendation
Not Rated	Strong

- 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 (e.g., 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?

Summary of Recommendations

Qualifying Statements for Recommendation 1.2.

- 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 (e.g., cousins), consanguinity, and personal and family history of colon polyps can help inform genetic testing and counseling, especially with interpretation of results.

Summary of Recommendations

Clinical Question 2

- When and how should multi-gene panel germline testing be used when germline genetic testing is indicated?

Recommendation 2.1

- When germline genetic testing is indicated for a patient with cancer, multi-gene panel testing should be offered if more than one gene is relevant. (See Table 2 in the guideline for details.)

Evidence Quality	Strength of Recommendation
Not Rated	Strong

Summary of Recommendations

Recommendation 2.2

Evidence Quality	Strength of Recommendation
Not Rated	Not Rated see Clinical Interpretation in the guideline

- When considering what to order for multi-gene panel testing, clinicians should apply the following principles:
    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 from Table 2 of this guideline and may include the less strongly recommended genes.
    2. A broader panel may be ordered when the potential benefits of such a panel can be clearly identified.
    3. When ordering a panel (especially a broader panel), the clinician should ensure that potential harms are mitigated. See Clinical Interpretation (in the guideline) 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.
- 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.

Summary of Recommendations

Clinical Question 3

- Which genes are generally recommended for germline genetic testing for patients with selected cancers?

Recommendation 3

Evidence Quality	Strength of Recommendation
Not Rated	Strong

- If germline multi-gene panel testing is offered, testing for pathogenic variants in the genes in Table 2 (in the guideline) 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 in the guideline for criteria for the column assignments.

Summary of Recommendations

Clinical Question 4

- Which patients should be offered germline genetic testing who will have or have had somatic genetic tumor testing (i.e. tumor genomic profiling)?

Recommendation 4.1

- Patients who meet criteria for germline genetic testing should be offered that testing regardless of results from tumor testing (i.e., genomic profiling from tumor biopsy or circulating tumor DNA testing).

Evidence Quality	Strength of Recommendation
Low	Strong

Summary of Recommendations

Recommendation 4.2

Evidence Quality	Strength of Recommendation
Moderate	Strong

- Regardless of germline genetic testing criteria, when a pathogenic variant is identified with tumor testing in a gene listed in Table 3 (in the guideline) germline genetic testing should be offered according to the criteria in Table 3 and Table 4 in the guideline.

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3 Discussion

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.[2]
- 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.[3]

Health Disparities

- Many of the inequities seen broadly in oncology care are amplified in cancer genetics.
- The evidence upon which testing recommendations are based is often biased towards White non-Hispanic populations.[4,5]
- Fewer Asian, Black, and Hispanic individuals receive germline genetic testing.[6] Because of this undertesting, interpretation of identified variants in these populations leads to a higher frequency of VUS results.[7]
- Undertesting contributes to greater disparities in care.[8]
- 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 co-insurance.[9]
- 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 may only have coverage for a single episode of germline genetic testing, and therefore have difficulty 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.

Additional Resources

- More information, including a supplement and clinical tools and resources, is available at www.asco.org/molecular-testing-and-biomarkers-guidelines

- Patient information is available at www.cancer.net

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Abbreviations

- ASCO, American Society of Clinical Oncology
- DNA, deoxyribonucleic acid
- EBMC, Evidence Based Medicine Committee
- VUS, variants of uncertain significance

References

1. Martin NA, Tepper JE, Giri VN, et al: Adopting Consensus Terms for Testing in Precision Medicine. JCO Precis Oncol 5, 2021
2. Ladd MK, Peshkin BN, Isaacs C, et al: Predictors of genetic testing uptake in newly diagnosed breast cancer patients. J Surg Oncol 122:134-143, 2020
3. Gilligan T, Coyle N, Frankel RM, et al: Patient-Clinician Communication: American Society of Clinical Oncology Consensus Guideline. J Clin Oncol 35:3618-3632, 2017
4. Paiella S, Azzolina D, Gregori D, et al: A systematic review and meta-analysis of germline BRCA mutations in pancreatic cancer patients identifies global and racial disparities in access to genetic testing. ESMO Open 8:100881, 2023
5. Weise N, Shaya J, Javier-Desloges J, et al: Disparities in germline testing among racial minorities with prostate cancer. Prostate Cancer Prostatic Dis 25:403-410, 2022
6. Kurian AW, Abrahamse P, Furgal A, et al: Germline Genetic Testing After Cancer Diagnosis. Jama 330:43-51, 2023
7. Chapman-Davis E, Zhou ZN, Fields JC, et al: Racial and Ethnic Disparities in Genetic Testing at a Hereditary Breast and Ovarian Cancer Center. J Gen Intern Med 36:35-42, 2021
8. Liu YL, Maio A, Kemel Y, et al: Disparities in cancer genetics care by race/ethnicity among pan-cancer patients with pathogenic germline variants. Cancer 128:3870-3879, 2022
9. Schnipper LE, Davidson NE, Wollins DS, et al: American Society of Clinical Oncology Statement: A Conceptual Framework to Assess the Value of Cancer Treatment Options. J Clin Oncol 33:2563-77, 2015

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