



# Germline Testing in Patients With Breast Cancer: ASCO– Society of Surgical Oncology Guideline

## Guideline 2024: sumário e principais mudanças

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






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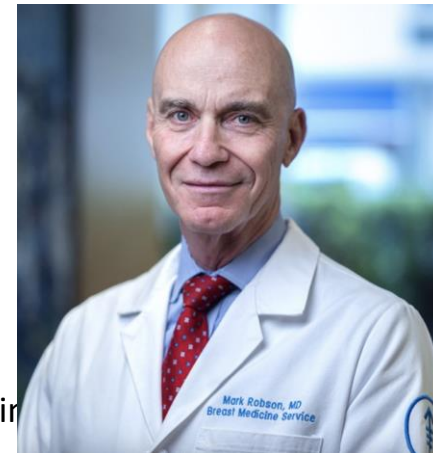
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ASCO Special Articles

## Germline Testing in Patients With Breast Cancer: ASCO–Society of Surgical Oncology Guideline

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# GUIDELINE QUESTIONS

Which patients with breast cancer should have germline genetic testing for pathogenic variants in cancer susceptibility genes?

This clinical practice guideline addresses five overarching clinical questions:

1. Should clinicians offer BRCA1/2 testing to all patients with newly diagnosed breast cancer?
2. Should all people with recurrent disease, local or metastatic, or with second breast primary, be offered BRCA1/2 testing?
3. Should people with a personal history of breast cancer (and no active disease) be offered BRCA1/2 testing?
4. What is the value of testing patients with a diagnosis of breast cancer for breast cancer predisposition genes other than BRCA1/2?
5. How should patients with breast cancer considering genetic testing be counseled?

# Methods

- An **Expert Panel was convened to develop clinical practice guideline recommendations** based on a systematic review of the medical literature and based, in part, on a formal consensus development process.
- A total of **47 articles** satisfied the inclusion criteria for the germline mutation testing–related recommendations (Recommendations 1.1 through 4.3) and these articles, **in combination with expert opinion, form the evidence base for the corresponding guideline recommendations.**

# Methods

- **Target Population**

- Patients with breast cancer and their families.

- **Target Audience Medical**

- Oncologists, radiation oncologists, surgical oncologists, medical geneticists, oncology nurses, patients, caregivers, oncology advanced practice providers, and genetic counselors.

# Recommendations

## Recommendation 1.1

- All patients newly diagnosed with breast cancer with **stage I-III or de novo stage IV/metastatic disease** who are **65 years or younger** at diagnosis should be offered BRCA1/2 testing (Type: Formal Consensus; Agreement: 87.50%).

original reports

### Evaluation of Germline Genetic Testing Criteria in a Hospital-Based Series of Women With Breast Cancer

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**MATERIALS AND METHODS** Women with breast cancer enrolled in a breast cancer registry at a tertiary cancer center between 2000 and 2016 were evaluated for germline pathogenic variants in 9 breast cancer predisposition genes (*ATM*, *BRCA1*, *BRCA2*, *CDH1*, *CHEK2*, *NF1*, *PALB2*, *PTEN*, and *TP53*). The performance of the National Comprehensive Cancer Network (NCCN) hereditary cancer testing criteria was evaluated relative to testing of all women as recommended by the American Society of Breast Surgeons.

**RESULTS** Of 3,907 women, 1,872 (47.9%) meeting NCCN criteria were more likely to carry a pathogenic variant in 9 predisposition genes compared with women not meeting criteria (9.0% v 3.5%;  $P < .001$ ). Of those not meeting criteria ( $n = 2,035$ ), 14 (0.7%) had pathogenic variants in *BRCA1* or *BRCA2*. The sensitivity of NCCN criteria was 70% for 9 predisposition genes and 87% for *BRCA1* and *BRCA2*, with a specificity of 53%. Expansion of the NCCN criteria to include all women diagnosed with breast cancer at  $\leq 65$  years of age achieved  $> 90\%$  sensitivity for the 9 predisposition genes and  $> 98\%$  sensitivity for *BRCA1* and *BRCA2*.

**CONCLUSION** A substantial proportion of women with breast cancer carrying germline pathogenic variants in predisposition genes do not qualify for testing by NCCN criteria. Expansion of NCCN criteria to include all women diagnosed at  $\leq 65$  years of age improves the sensitivity of the selection criteria without requiring testing of all women with breast cancer.

# Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic

Version 3.2024 — February 12, 2024

NCCN.org

# Recommendations

## Recommendation 1.2

- All patients newly diagnosed with **IV/metastatic disease**
  - they are **candidate** for early-stage or metastatic clinical trials
  - they have **triple-negative** breast cancer
  - their **personal or family history** meets criteria
  - they were assigned to a **clinical trial**
  - they are of **Ashkenazi Jewish ancestry** (increased prevalence of BRCA1/2 variants, 92.50%)

### TESTING CRITERIA FOR HIGH-PENETRANCE BREAST CANCER SUSCEPTIBILITY GENES (Specifically *BRCA1*, *BRCA2*, *CDH1*, *PALB2*, *PTEN*, *STK11*, and *TP53*. See [GENE-A](#))<sup>a,f,g,h,i</sup>

#### Testing is clinically indicated in the following scenarios:

- See General Testing Criteria on [CRIT-1](#).

- Personal history of breast cancer with specific features:

- ▶ ≤50 y

- ▶ Any age:

- ◊ Treatment indications

- To aid in systemic treatment decisions using PARP inhibitors for breast cancer in the metastatic setting<sup>j,k</sup> ([NCCN Guidelines for Breast Cancer](#))

- To aid in adjuvant treatment decisions with [olaparib for high-risk](#),<sup>l</sup> HER2-negative breast cancer<sup>l</sup>

- ◊ Pathology/histology

- Triple-negative breast cancer

- Multiple primary breast cancers (synchronous or metachronous)<sup>m</sup>

- Lobular breast cancer with personal or family history of diffuse gastric cancer [NCCN Guidelines for Gastric Cancer](#)

- ◊ Male breast cancer

- ◊ Ancestry: Ashkenazi Jewish ancestry

- ▶ Any age (continued):

- ◊ Family history<sup>n</sup>

- ≥1 close blood relative<sup>o</sup> with ANY:

- breast cancer at age ≤50

- male breast cancer

- ovarian cancer

- pancreatic cancer

- prostate cancer with metastatic,<sup>p</sup> or high- or very-high-risk group (Initial Risk Stratification and Staging Workup in [NCCN Guidelines for Prostate Cancer](#))

- ≥3 diagnoses of breast and/or prostate cancer (any grade) on the same side of the family including the patient with breast cancer

- Family history of cancer only

- ▶ Individuals affected with breast cancer (not meeting testing criteria listed above) or individual unaffected with breast cancer with a first- or second-degree blood relative meeting any of the criteria listed above (except unaffected individuals whose relatives meet criteria only for systemic therapy decision-making).<sup>q</sup>

- ▶ Individuals affected or unaffected with breast cancer who otherwise do not meet the criteria above but have a probability >5% of a *BRCA1/2* P/LP variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk)<sup>r</sup>



# Recommendations

## Recommendation 1.3



## NCCN Guidelines Version 3.2024 Breast, Ovarian, and/or Pancreatic Cancer Genetic Assessment

[NCCN Guidelines Index](#)  
[Table of Contents](#)  
[Discussion](#)

- Patients undergoing predisposition gene a provider experience should be made available (Agreement: 90%).

### PRINCIPLES OF CANCER RISK ASSESSMENT AND COUNSELING

- Risk assessment and discussion of genetic testing involves three related stages:
  - 1) Pre-test counseling done prior to ordering testing
  - 2) Consideration of the most appropriate tests to order
  - 3) Post-test counseling done when results are disclosed<sup>1-6</sup>
- It is recommended that a genetic counselor, clinical geneticist, oncologist, surgeon, oncology nurse, or other health professional with expertise and experience in cancer genetics be involved at each stage whenever possible.
- Testing should be considered in appropriate individuals where it is likely to impact the risk management and/or treatment of the tested individuals and/or their family members who also have increased risk.
- Pre-test counseling includes the following elements:
  - Evaluate patient's needs and concerns regarding:
    - › Knowledge of genetic testing for cancer risk, including benefits, risks, and limitations
    - › Variant-specific cancer risks
    - › Goals for cancer family risk assessment
  - Detailed family history including:
    - › Collection of a comprehensive family history
      - ◊ Assessment of family history; close blood relatives include first-, second-, and third-degree relatives on each side of the family, particularly around individuals with a diagnosis of cancer ([EVAL-B](#))
      - ◊ Types of cancer, bilaterality, age at diagnosis, subtype, and pathology report confirmation
      - ◊ Ethnicity (specifically Ashkenazi Jewish ancestry)
  - Detailed medical and surgical history including:
    - › Documentation of prior genetic testing results for patients and their family members
    - › Personal cancer history (eg, age, histology, laterality)
    - › Pathology reports of primary cancers and/or benign lesions (eg, breast biopsies)
    - › Carcinogen exposure (eg, history of RT)
    - › Reproductive history
    - › Hormone or oral contraceptive use
    - › History of risk-reducing surgeries
    - › Smoking, alcohol, or other exposures related to cancer risk
  - Focused physical exam (conducted by qualified clinician) when indicated:
    - › CS/PHTS specific: dermatologic,<sup>a</sup> including oral mucosa, head circumference, and thyroid (enlarged or nodular on palpation)
  - Generate a differential diagnosis and educate the patient on inheritance patterns, penetrance, variable expressivity, and the possibility of genetic heterogeneity

[Pre-test counseling continued](#)

# Recommendations: Genetic counseling

**TABLE 1. Critical Elements of Pre- and Post-test Counseling in Clinical Cancer Genetics**

Pretest Counseling	
Traditional Pretest Counseling for Susceptibility Testing (purpose of testing)	Pretest Counseling for Multigene Panel Testing (same general components as traditional counseling, with the following special considerations)
Information on specific genetic mutation(s) or genomic variant(s) being tested, including whether range of risk associated with variant will affect medical care	Discussions of specific genes may need to be batched, because it may not be feasible to review each gene individually; high-penetrance syndromes being evaluated should be described (eg, hereditary breast-ovary, Lynch, hereditary diffuse gastric, Li-Fraumeni); patients should be aware of possible detection of high-penetrance mutations not suggested by personal or family history; genes of uncertain clinical utility may need to be described more generally
Implications of positive (mutation confirmed to be deleterious), negative (no identified change in genetic sequence), or uncertain (genetic variant of unknown clinical significance) result	Particular attention should be paid to implications of positive results in less well-understood or lesser-penetrance genes and in findings of mutations in genes associated with syndromes not suggested by personal or family history
Possibility test will not be informative	Attention should be paid to current high rate of variants of uncertain significance
Risk that children and/or other family members may have inherited genetic condition	Highlight potential reproductive implications to family of mutations in genes linked to recessive disorders (eg, <i>ATM</i> , Fanconi's [eg, <i>BRCA2</i> , <i>PALB2</i> ], <i>NBN</i> , <i>BLM</i> )
Fees involved in testing and counseling; for DTC testing, whether counselor is employed by testing company	
Psychological implications of test results (benefits and risks)	
Risks and protections against genetic discrimination by employers or insurers	
Confidentiality issues, including DTC testing companies and policies related to privacy and data security	
Possible use of DNA samples for future research	
Options and limitations of medical surveillance and strategies for prevention after genetic or genomic testing	
Importance of sharing genetic and genomic test results with at-risk relatives so they may benefit from this information	
Plans for disclosing test results and providing follow-up	

# Recommendations: PARP INHIBITOR

## Recommendation 2.1

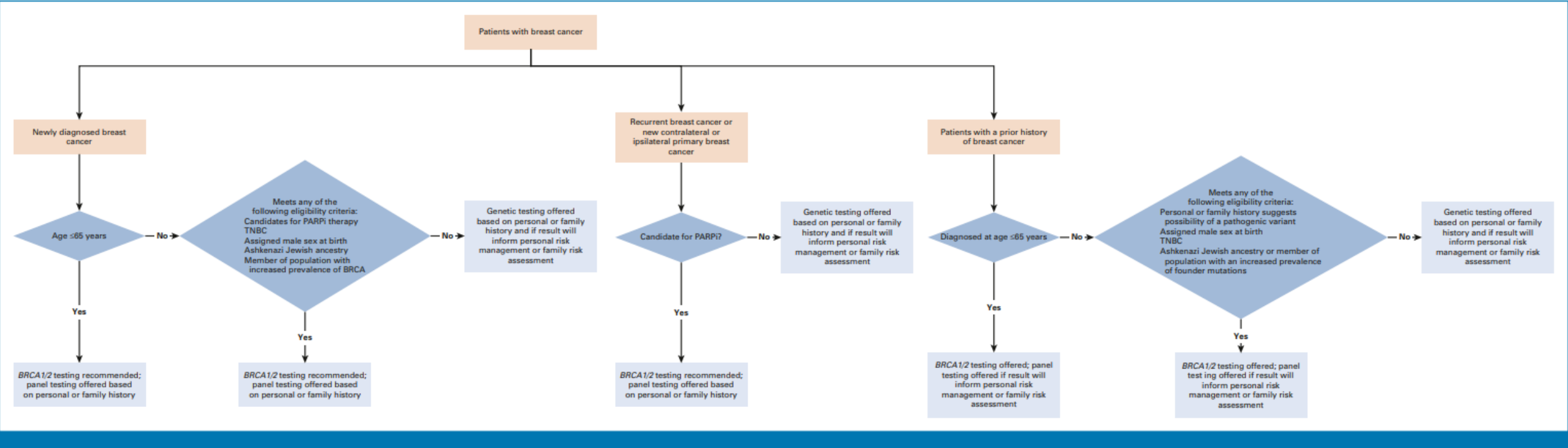


FIG 1. Algorithm for Germline Testing in Patients with Breast Cancer Abbreviations. PARPi, poly(ADP-ribose) polymerase inhibitors; TNBC, triple-negative breast cancer.

# Recommendations: SECOND PRIMARY BC

## **Recommendation 2.2**

- BRCA1/2 testing should be offered to patients with a second primary cancer either in the contralateral or ipsilateral breast (Type: Formal Consensus; Agreement: 89.74%).

# Recommendations: PREVIOUS DIAGNOSIS

## Recommendation 3.1

### DUTY TO RECONTACT

- All patients with a personal history of breast cancer diagnosed  $\leq 65$  years who are without active disease should be offered BRCA1/2 testing if the result will inform personal risk management or family risk assessment (Type: Formal Consensus; Agreement: 90%).

# Recommendations: PREVIOUS DIAGNOSIS

## Recommendation 3.2

### DUTY TO RECONTACT

- All patients with a personal history of breast cancer diagnosed over age 65 with no active disease, who meet one of the following criteria, should be offered BRCA1/2 testing if the result will inform personal risk management or family risk assessment:
  - their personal or family history suggests the possibility of a pathogenic variant
  - they were assigned male sex at birth,
  - they had triple-negative breast cancer,
  - they are of Ashkenazi Jewish ancestry or are members of a population with an increased prevalence of founder mutations (Type:Formal Consensus; Agreement: 94.87%)

# Recommendations: PANEL TESTING

## **Recommendation 4.1**

- Testing for high penetrance genes beyond BRCA1/2, including PALB2, TP53, PTEN, STK11, and CDH1, could inform medical therapy, influence surgical decision making, refine estimates of risks of second primary cancer, and inform family risk assessment, and thus should be offered to appropriate patients (Type: Formal Consensus; Agreement: 92.31%).

# Recommendations: PANEL TESTING

## **Recommendation 4.2**

- Testing for moderate penetrance breast cancer genes currently offers no benefits for treatment of the index breast cancer but may inform risks of second primary cancer or family risk assessment, and thus may be offered to appropriate patients who are undergoing BRCA1/2 testing (Type: Formal Consensus; Agreement: 87.50%).



# Recommendations: PANEL TESTING

## Recommendation 4.3

- If a multi-gene panel is ordered, the specific panel chosen should take into account the patient's personal and family history. **Consultation with a provider experienced in clinical cancer genetics** can be helpful in selecting a specific multi-gene panel or interpreting its results and should be made available to patients when possible (Type: Formal Consensus; Agreement: 91.43%).

# Recommendations: GENETIC COUNSELING

## Recommendation 5.1

- **Patients** undergoing genetic testing **should be given sufficient information before testing** to provide informed consent (Type: Formal Consensus; Agreement: 94.87%).

TABLE 1. Critical Elements of Pre- and Post-test Counseling in Clinical Cancer Genetics

Pretest Counseling

**PRE-TEST COUNSELING IN CLINICAL CANCER GENETICS SHOULD BE PROVIDED IN ALL CASES**

	or family history; genes of uncertain clinical utility may need to be described more generally
Implications of positive (mutation confirmed to be deleterious), negative (no identified change in genetic sequence), or uncertain (genetic variant of unknown clinical significance) result	Particular attention should be paid to implications of positive results in less well-understood or lesser-penetrance genes and in findings of mutations in genes associated with syndromes not suggested by personal or family history
Possibility test will not be informative	Attention should be paid to current high rate of variants of uncertain significance
Risk that children and/or other family members may have inherited genetic condition	Highlight potential reproductive implications to family of mutations in genes linked to recessive disorders (eg, <i>ATM</i> , Fanconi's [eg, <i>BRCA2</i> , <i>PALB2</i> ], <i>NBN</i> , <i>BLM</i> )

# Recommendations: GENETIC COUNSELING

## Recommendation 5.2

- Patients with pathogenic variants should be provided with **individualized post-test genetic counseling** and offered referral to a provider experienced in **clinical cancer genetics** (Type: Formal Consensus; Agreement: 95%).

TABLE 1. Critical Elements of Pre- and Post-test Counseling in Clinical Cancer Genetics

**POST-TEST COUNSELING IN CLINICAL CANCER GENETICS  
SHOULD BE PROVIDED IN ALL CASES**

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

NOTE. Adapted from Robson et al<sup>4</sup> and adapted with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic V.2.2024.<sup>73</sup> 2023 National Comprehensive Cancer Network, Inc All rights reserved. The NCCN Guidelines and illustrations herein may not be reproduced in any form for any purpose without the express written permission of NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to [NCCN.org](https://www.nccn.org). The NCCN Guidelines are a work in progress that may be refined as often as new significant data becomes available. NCCN makes no warranties of any kind whatsoever regarding their content, use, or application, and disclaims any responsibility for their application or use in any way.

# Recommendations: GENETIC COUNSELING

## Recommendation 5.3

- **Variants of uncertain significance should not alter management.** Patients should be made aware that **variants of uncertain significance may be reclassified as being pathogenic**, and they should understand that periodic follow up is necessary. **Consultation with a provider experienced in clinical cancer genetics** can be helpful and should be made available to patients when possible (Type: Formal Consensus; Agreement: 88.57%).

VUS COUNSELING IN CLINICAL CANCER GENETICS  
PROMPTS TO PERIODIC FOLLOW-UP

# Recommendations: GENETIC COUNSELING

## Recommendation 5.4

- **Patients without a pathogenic variant on genetic testing may still benefit from counseling, if there is a significant family history of cancer, and referral to a provider experienced in clinical cancer genetics is recommended** (Type: Formal Consensus; Agreement: 90%).

**A TEST WITHOUT A GERMLINE VARIANT DOES NOT  
MEAN THE FAMILY IS NEGATIVE!  
COUNSELING IN CLINICAL CANCER GENETICS SHOULD  
BE PROVIDED IN ALL VUS**

# 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**.
- **Racial and ethnic disparities in health care contribute significantly to this problem in the United States.** 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 care of poor quality than other Americans.
- Many other patients **lack access to care because of their geographic location and distance from appropriate treatment facilities.** Recent studies have also noted disparities in the collection of family history information necessary for determining testing eligibility.

# HEALTH DISPARITIES

- A **unique challenge** in germline genetic testing is the unequal distribution of **VUS**. These ambiguous results are more frequent among racial and ethnic groups who have received less testing of a particular gene or genes, and for whom the normal range of genetic variability is less well mapped.
- Essentially, a testing access disparity perpetuates a disparity in the clarity of genetic information. **Population-based studies have documented a widening racial and ethnic gap in VUS results**, which has been exacerbated by the trend toward sequencing many more genes.
- Efforts to expand genetic testing access among clinically indicated patients are crucial to reduce the unequal burden of uncertain results on non-White patients. Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and **health care providers should strive to deliver the highest level of cancer care to these vulnerable populations.**

# GUIDELINE QUESTIONS - CONCLUSIONS

Which patients with breast cancer should have germline genetic testing for pathogenic variants in cancer susceptibility genes?

This clinical practice guideline addresses five overarching clinical questions:

1. Should clinicians offer BRCA1/2 testing to all patients with newly diagnosed breast cancer?

**ALL BC AFTER AGE 65YO**

2. Should all people with recurrent disease, local or metastatic, or with second breast primary, be offered BRCA1/2 testing?

**YES**

3. Should people with a personal history of breast cancer (and no active disease) be offered BRCA1/2 testing?

**YES**

4. What is the value of testing patients with a diagnosis of breast cancer for breast cancer predisposition genes other than BRCA1/2?

**ALL PATIENTS SHOULD RECEIVE PANEL TESTING**

5. How should patients with breast cancer considering genetic testing be counseled?

**ALL PATIENTS SHOULD RECEIVE GENETIC COUNSELING**



O B R I G A D A !



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