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Target Audience: This activity is designed to meet the educational needs of oncologists, nurses, pharmacists, and other healthcare professionals who manage patients with cancer.

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Release date: April 10, 2020; Expiration date: April 10, 2021

Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic

Disclosure of Relevant Financial Relationships

The NCCN staff listed below discloses no relevant financial relationships:

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To view all of the conflicts of interest for the NCCN Guidelines panel, go to NCCN.org/disclosures/guidelinepanellisting.aspx.

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Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, Version 1.2020

Featured Updates to the NCCN Guidelines

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ABSTRACT

The NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic provide recommendations for genetic testing and counseling for hereditary cancer syndromes, and risk management recommendations for patients who are diagnosed with syndromes associated with an increased risk of these cancers. The NCCN panel meets at least annually to review comments, examine relevant new data, and reevaluate and update recommendations. These NCCN Guidelines Insights summarize the panel's discussion and most recent recommendations regarding criteria for high-penetrance genes associated with breast and ovarian cancer beyond *BRCA1/2*, pancreas screening and genes associated with pancreatic cancer, genetic testing for the purpose of systemic therapy decision-making, and testing for people with Ashkenazi Jewish ancestry.

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*Provided content development and/or authorship assistance.

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Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PLEASE NOTE

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. **The NCCN Guidelines Insights highlight important changes in the NCCN Guidelines recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further the understanding of these changes by summarizing salient portions of the panel's discussion, including the literature reviewed.**

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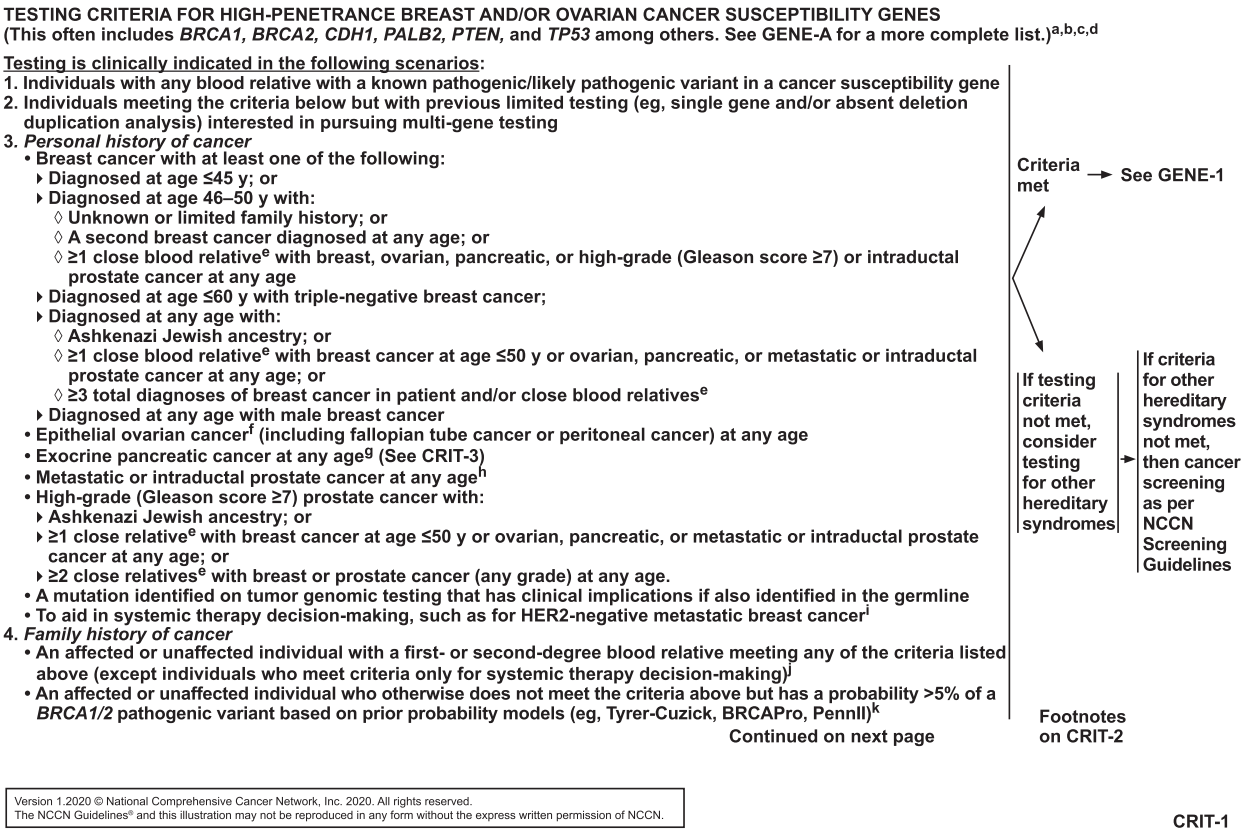


CRIT-1

Overview

Advances in cancer genetics, such as increased use of multigene panel testing, has transformed the clinical approach to testing at-risk patients and their families. Based on these rapid advances, the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Genetic/Familial High-Risk Assessment: Breast and Ovarian (now Breast, Ovarian, and Pancreatic) have undergone some major revisions for the 2020 update. These revisions include reorganization of the guidelines by disease and syndrome type; inclusion of criteria for high-penetrance genes associated with breast and ovarian cancer beyond *BRCA1/2*; the addition of pancreatic cancer to the title, with new information added about pancreas screening and genes associated with pancreatic cancer; clarification of testing indications for the purpose of systemic therapy decision-making; and new recommendations for testing of people with Ashkenazi Jewish ancestry.

Testing Criteria for High-Penetrance Breast and/or Ovarian Cancer Susceptibility Genes

Prior to the version 1.2020 update, these NCCN Guidelines focused largely on testing criteria for *BRCA1/2* and appropriate risk management for carriers of a *BRCA1* or *BRCA2* pathogenic or likely pathogenic variant. There is now strong evidence that genes beyond *BRCA1/2* confer markedly increased risk of breast and/or ovarian cancers, such as *CDH1*, *PALB2*, *PTEN*, and *TP53*. The "*BRCA1/2* Testing Criteria" page has been expanded to "Testing Criteria for High-Penetrance Breast and/or Ovarian Cancer Susceptibility Genes" (see CRIT-1 and CRIT-2, above and page 383, respectively). The criteria have been reorganized into 3 sections: (1) testing is clinically indicated, (2) testing may be considered, and (3) low probability of testing results having documented clinical utility. The testing criteria listed are for breast and/or ovarian cancer susceptibility genes with strong or moderate evidence of actionability (eg, *BRCA1/2*, *CDH1*, and *PALB2*; testing criteria for Li-Fraumeni syndrome and Cowden syndrome continue to be presented in their own dedicated sections). Included genes may change with emerging clinical data. Furthermore, the personal and/or family history criteria included may suggest the possibility of additional syndromes and would necessitate additional unlisted genes to be evaluated.

There are 2 additional revisions of note to the testing criteria for high-penetrance genes associated with breast

TESTING CRITERIA FOR HIGH-PENETRANCE BREAST AND/OR OVARIAN CANCER SUSCEPTIBILITY GENES (continued)
(This often includes *BRCA1, BRCA2, CDH1, PALB2, PTEN,* and *TP53* among others. See GENE-A for a more complete list.)[a,b,c,d]

Testing may be considered in the following scenarios (with appropriate pre-test education and access to post-test management):

1. **Bilateral breast cancer, first diagnosed between the ages of 50 and 65 y**
2. **An unaffected Ashkenazi Jewish individual[l]**
3. **An affected or unaffected individual who otherwise does not meet any of the above criteria but with a 2.5%–5% probability of *BRCA1/2* pathogenic variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, PennII)[b]**

There is a low probability (<2.5%) that testing will have findings of documented clinical utility in the following scenarios:

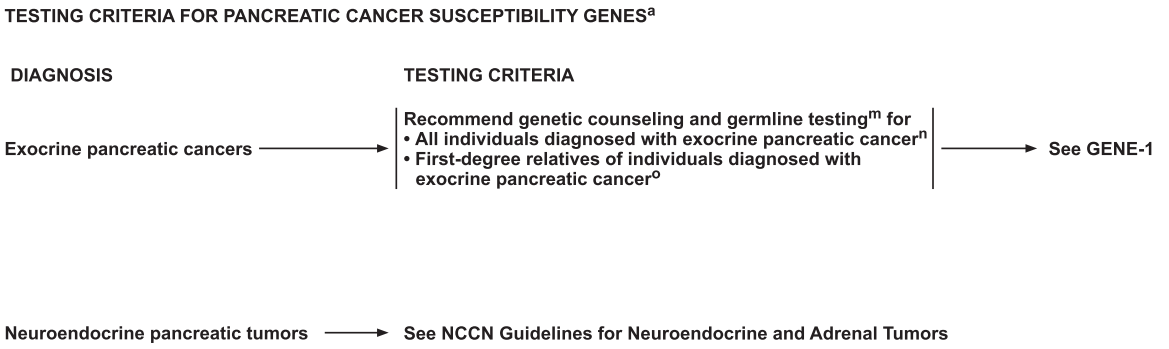
1. **Women diagnosed with breast cancer at age >65 y, with no close relative[e] with breast, ovarian, pancreatic, or prostate cancer**
2. **Men diagnosed with localized prostate cancer with Gleason Score <7 and no close relative[e] with breast, ovarian, pancreatic, or prostate cancer**

[a] For further details regarding the nuances of genetic counseling and testing, see EVAL-A.
[b] Testing for pathogenic variants in other genes should take into consideration factors such as patient preferences, turnaround time, and insurance restrictions to particular labs (and thus particular panels). The prevalence of VUS increases with testing of additional genes. Individuals should have pre-test education on the challenges in managing pathogenic variants in genes associated with specific syndromes (eg, *CDH1* and *TP53* given their expanding clinical phenotypes) in the absence of a family history typical of such syndromes (does not apply for de novo pathogenic variants). Patients should also have pre-test education regarding the uncertain clinical utility of identifying certain pathogenic variants (eg, monoallelic *MUTYH*).
[c] Meeting one or more of these criteria warrants further personalized risk assessment, genetic counseling, and often genetic testing and management.
[d] For the purposes of these guidelines, invasive and ductal carcinoma in situ breast cancers should be included.
[e] Close blood relatives include first-, second-, and third-degree relatives on the same side of the family. (See EVAL-B)
[f] *BRCA*-related ovarian cancers are associated with epithelial, non-mucinous histology. Lynch syndrome can be associated with both non-mucinous and mucinous epithelial tumors. Be attentive for clinical evidence of Lynch syndrome (see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal). Specific types of non-epithelial ovarian cancers and tumors can also be associated with other rare syndromes. Examples include an association between sex-cord tumors with annular tubules and PJS or Sertoli-Leydig tumors and DICER1-related disorders.
[g] Approximately 2%–5% of unselected cases of pancreatic adenocarcinoma will have a *BRCA1/2* pathogenic/likely pathogenic variant. However, the disease is highly aggressive and the option to test the affected relative may not be available in the future. Thus, there may be significant benefit to family members in testing these patients near the time of diagnosis. In addition, increasing evidence suggests that identification of a *BRCA1/2* pathogenic/likely pathogenic variant may direct use of targeted therapies for patients with pancreatic cancer (See NCCN Guidelines for Pancreatic Adenocarcinoma). (Holter S, Borgida A, Dodd A, et al. J Clin Oncol 2015;33:3124-3129. Shindo K, Yu J, Suenaga M, et al. J Clin Oncol 2017;35:3382-3390. Golan T, Hammel P, Reni M, et al. N Engl J Med 2019;381:317-327.)
[h] Metastatic prostate cancer is biopsy-proven and/or with radiographic evidence and includes distant metastasis and regional bed or nodes. It is not a biochemical recurrence only. Prostate cancer-specific mortality should be a surrogate for metastatic disease for family history purposes.
[i] Eg, PARP inhibitors for ovarian cancer, prostate cancer, pancreatic cancer, and metastatic HER2-negative breast cancer; platinum therapy for prostate cancer and pancreatic cancer. See the relevant NCCN treatment guidelines for further details.
[j] This may be extended to an affected third-degree relative if related through two male relatives (eg, paternal grandfather's mother or sister). If the affected first-degree relative underwent genetic testing and is negative for detectable mutations and there is no other family history of cancer, there is a low probability that any finding will have documented clinical utility. For probands with pancreatic cancer, only first-degree relatives should be offered testing unless indicated for other relatives based on additional family history.
[k] The approximate 5% threshold for probability of carrying *BRCA1/2* pathogenic variants is utilized because of availability of prior probability models; however, it is recognized that current model estimates vary substantially, and that different thresholds may be appropriate if other genes are included in the model utilized. If genes other than *BRCA1* and *BRCA2* are to be included in models evaluating the threshold for testing, the penetrance, clinical actionability, and phenotypic features of cancers associated with mutations in these genes should be considered. The panel encourages the development of validated models that include these parameters to determine eligibility and appropriateness for gene panel testing for inherited cancer risk. These models are only validated for *BRCA1/2*.
[l] Testing for three founder mutations of *BRCA1/2* may be offered to unaffected men and women as early as age 18–25 years, who have one grandparent identified as of Ashkenazi Jewish ancestry, irrespective of cancer history in the family, as part of longitudinal studies. For those without access to longitudinal research studies, testing may be provided if there is access to pre-test education along with post-test counseling, additional genetic testing if indicated, and high-risk management. Testing should not be offered outside of a medical framework or clinical trial.

CRIT-2

and/or ovarian cancer susceptibility. First, Ashkenazi Jewish ancestry without a personal cancer history is now included as a scenario for which genetic testing may be considered. The rate of the 3 founder pathogenic variants in this population is 2.2% to 2.5%,[1–3] which is equivalent to a level of risk for some other testing criteria, such as breast cancer diagnosed at age ≤45 years. In addition, studies have shown that genetic testing based on clinical guidelines emphasizing a family history of breast, ovarian, prostate, or other cancers missed approximately 38% to 56% of mutation carriers with Ashkenazi Jewish ancestry,[1,2,4,5] providing some evidence to support population-based genetic testing among the Ashkenazi Jewish population. However, the panel raised concerns about the demand on genetic counseling resources, the preparedness of healthcare professionals to provide cancer genetic counseling and management, and participants' fears and concerns about testing, including those regarding privacy, stigmatization, and the need for appropriate medical and/or surgical management in patients and family members found to have a founder mutation. Thus, although recognizing the rationale for widespread population screening, the panel recommends that universal testing for founder *BRCA1/2* mutations in individuals of Ashkenazi Jewish ancestry, regardless of personal or family history, be offered primarily in the setting of longitudinal research studies. If there is no access to longitudinal studies, then testing may be offered when pretest and posttest genetic counseling are available. There remains a vital need for longitudinal data from research studies exploring various methods of providing population-based genetic testing in the United States.

The second revision of note is regarding testing with the intent to aid in systemic therapy decision-making. Some NCCN treatment guidelines for *BRCA*-related cancers now recommend treatment with PARP inhibitors for patients with germline or somatic *BRCA1/2* mutations, because PARP inhibitors have been shown to be active in these patients. These agents include olaparib[6] and talazoparib[7] for HER2-negative metastatic breast cancer; niraparib,[8] olaparib,[9] and rucaparib[10] for chemotherapy-refractory ovarian cancer; and olaparib as a maintenance therapy option for metastatic pancreatic cancer.[11] Some studies investigating PARP inhibitors in patients who have germline *BRCA1/2* mutations with metastatic castration-resistant prostate cancer are promising.[12,13] Even though management of breast, ovarian, and/or pancreatic cancer risk in individuals with associated hereditary syndromes continues to be the focus of these



[a] For further details regarding the nuances of genetic counseling and testing, see EVAL-A.
[m] Genes that are typically tested for pancreatic cancer risk include *ATM*, *BRCA1*, *BRCA2*, *CDKN2A*, most Lynch syndrome genes (*MLH1*, *MSH2*, *MSH6*, *EPCAM*), *PALB2*, *STK11*, and *TP53*.
[n] Pancreatic cancer risk is higher in individuals of Ashkenazi Jewish descent. Genetic testing of Ashkenazi Jewish patients with pancreatic cancer may have higher yield of mutations than of non-Ashkenazi Jewish patients.
[o] Testing of first-degree relatives should only be done if it is impossible to test the individual who has pancreatic cancer. Some second-degree relatives may meet testing criteria based on additional family history.

CRIT-3

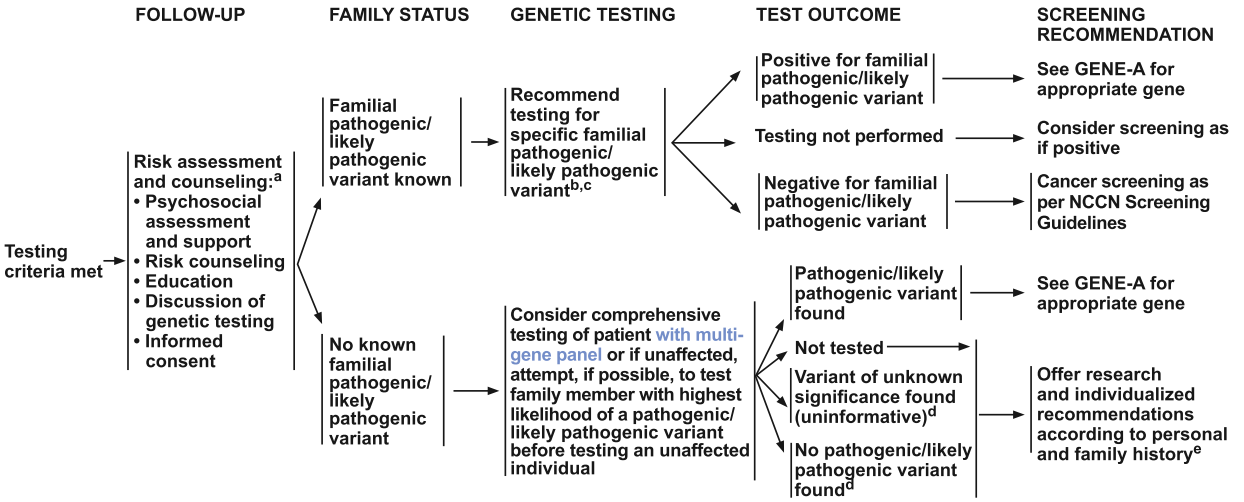
NCCN Guidelines, they now identify intent to aid in systemic therapy decision-making as a scenario in which germline testing is clinically indicated.

Genetic Counseling

Cancer genetic risk assessment and genetic counseling is a multistep process involving the identification and counseling of individuals at risk for familial or hereditary cancer. The purpose of cancer genetic counseling is to educate individuals about the genetic, biologic, and environmental factors related to a cancer diagnosis and/or risk for disease to help them derive personal meaning from cancer genetic information, and to empower them to make educated, informed decisions about genetic testing, cancer screening, and cancer prevention. A genetic counselor, medical geneticist, oncologist, surgeon, oncology nurse, or other health professional with expertise and experience in cancer genetics should be involved in every stage of the process.[14]

Testing should be considered in individuals for whom there is a personal or family history suggesting genetic cancer susceptibility and for whom results will aid in risk management and treatment. Selection of appropriate candidates for genetic testing is based on the personal and familial characteristics that determine the individual's prior probability of being a carrier of a pathogenic or likely pathogenic variant, and on their psychosocial degree of readiness to receive genetic test results. The genetic testing strategy is greatly facilitated when a pathogenic or likely pathogenic variant has already been identified in another family member. In that case, the genetic testing laboratory can limit the search for pathogenic or likely pathogenic variants in additional family members to the same location in the gene.

For most families in whom the presence of a pathogenic or likely pathogenic variant is unknown, it is best to consider testing an affected family member first, especially a family member with early-onset disease, bilateral disease, or multiple primaries, because that individual has the highest likelihood of a positive test result. Testing of an unaffected individual (or of unaffected family members) should only be considered when no affected family member is available for testing. In these cases, the unaffected individual or unaffected close relative with the highest likelihood of testing positive for the pathogenic or likely pathogenic variant should be tested. This may include the relative closest to the family member with the youngest age at diagnosis,



[a] For further details regarding the nuances of genetic counseling and testing, see EVAL-A.
[b] If of Ashkenazi Jewish descent, in addition to the specific familial pathogenic/likely pathogenic variant, test for all three founder pathogenic/likely pathogenic variants.
[c] Additional testing may be indicated if there is also a significant family history of cancer on the side of the family without the known pathogenic/likely pathogenic variant.
[d] If no pathogenic/likely pathogenic variant is found, consider testing another family member with next highest likelihood of having a pathogenic/likely pathogenic variant.
[e] Patients meeting Cowden syndrome clinical diagnostic criteria (see COWD-A 1 of 3) should be managed as pathogenic/likely pathogenic variant carriers.

GENE-1

bilateral disease, multiple primary tumors, or other cancers associated with a suspected hereditary syndrome. A negative test result in such cases, however, is considered indeterminate and does not provide the same level of information as when there is a known pathogenic or likely pathogenic variant in the family. Thus, one should be mindful that, when testing unaffected individuals (in the absence of having tested affected family members), significant limitations may exist in interpreting the test results, and testing multiple family members may be indicated, because absence of a mutation in one unaffected relative does not rule out a mutation in others.

Individuals who have received allogeneic hematopoietic stem cell transplantation (HSCT) should not have molecular genetic testing performed on blood samples, because the blood cells would represent donor-derived DNA. In such cases, DNA of the individual being tested should be extracted from a fibroblast culture, if available. If this is not possible, buccal cells may be considered as an alternative source for DNA[15]; however, one study reported that over time, buccal epithelial cells are replaced by donor-derived cells in allogeneic HSCT recipients.[16] Therefore, genetic testing using buccal swab samples may be limited given this known risk of donor DNA contamination. Fibroblasts are also indicated when testing individuals with active or recent hematologic malignancies.[17]

A counseling dilemma is posed by the finding of a variant of unknown significance (VUS), a genetic alteration that may actually represent a benign polymorphism unrelated to an increased cancer risk or may indicate an increased cancer risk. These patients should be considered for referral to research studies that aim to define the functional impact of the gene variant, such as variant reclassification programs through clinical laboratories or registries. Some examples of these programs and registries include ClinVar (the archival database at the National Center for Biotechnology Information), the NIH-funded Clinical Genome Resource (ClinGen), the Clinical Cancer Genomics Community Research Network of the United States, Mexico, and South America (CCGCRN), Prospective Registry of Multiplex Testing (PROMPT), the international Evidence-Based Network for the Interpretation of Germline Mutant Alleles (ENIGMA), and the International Society for Gastrointestinal Hereditary Tumours (InSiGHT). It is important to note that there may be inconsistencies in how programs and registries interpret the clinical actionability of some

VUS, which may lead to confusion regarding medical management.[18–20] Clinicians and scientists should work together to develop a VUS classification system as more information is discovered in research studies.[21]

Carriers of a pathogenic or likely pathogenic variant should be encouraged to participate in clinical trials or genetic registries. Carriers should be encouraged to recontact their genetics providers every few years for updates, because laboratories may issue amended reports as the knowledge base surrounding hereditary cancer risk expands.

Evaluating the Source of Genetic Testing Information

Reports regarding germline findings that may impact medical management should come from laboratories that are certified by the College of American Pathologists (CAP) and CLIA, with some US states (eg, New York) having additional reporting requirements. Recently, there has been an increase in genetic test results through direct-to-consumer (DTC) services or through tumor profiling. Testing typically used by companies providing ancestry information directly to consumers is microarray-based single-nucleotide polymorphism (SNP) testing that has not been validated for clinical use. These companies do not provide comprehensive genetic analysis that includes gross deletion or duplication analysis. Third-party services are available to assist patients with interpreting their raw data, but these services are not government-regulated. In addition to the errors inherent in working with raw uncurated data from DTC laboratories, other limitations of these services include inadequate informed consent processes, clinical validity and utility, and medical oversight.[22] An analysis of concordance between DTC and confirmatory test results for 49 patients showed a false-positive rate of 40%, as well as variant classification errors in 8 patients.[23] Given the limitations of the information obtained from DTC services, confirmatory germline testing by a certified laboratory is recommended, and changes to a patient's medical management based solely on DTC testing results are not recommended.[23]

Tumor profiling can be considered complementary to germline testing. However, the absence of a pathogenic or likely pathogenic variant for a given gene from tumor profiling does not rule out the possibility of a germline pathogenic or likely pathogenic variant in that gene. Tumor testing tends to be designed to address treatment actionability and prognosis.[24] Therefore, a variant interpreted as pathogenic or likely pathogenic in the germline may be interpreted as normal or as a VUS in the tumor, if that variant has no clear clinical implications. In addition, the sensitivity of most tumor testing is lower (particularly for intermediate-sized deletions and duplications) than that of most dedicated germline tests, sometimes due to filtering out of germline findings reported in tumor sequencing results. If a patient meets criteria for germline testing for a given gene, then confirmatory germline testing should be considered despite tumor profiling results.

Incidental germline findings discovered through other sources (eg, participation in a research study) should be reviewed by a genetics professional.[25] Confirmatory testing in these cases may be recommended, especially if the reporting laboratory is not appropriately certified.

Multigene Testing

Next-generation sequencing allows for the sequencing of multiple genes simultaneously, referred to as *multigene testing*. Multigene testing may detect pathogenic or likely pathogenic variants not found in single-gene testing.[26–28] Multigene testing may be most useful when more than one gene can explain an inherited cancer syndrome. In these cases, phenotype-directed testing based on personal and family history through a multigene panel test may be more efficient and/or cost-effective.[29–31] Multigene testing may also be considered for individuals who tested negative for one particular syndrome but whose personal and family history is suggestive of an inherited susceptibility.[29,32] Panel members indicated that it has become routine practice at their institutions to order phenotypically directed multigene panel tests to assess for pathogenic changes in multiple relevant genes simultaneously (see GENE-1, page 385).

There are several issues to consider regarding multigene testing. First, commercially available tests may differ significantly on a number of factors, such as number of genes analyzed, turnaround time, insurance coverage, laboratory expertise, and variant reclassification protocol. Therefore, the specific laboratory and multigene test should be chosen carefully.[29] In addition, pathogenic or likely pathogenic variants identified for more than one gene add complexity that may lead to difficulty in making risk management recommendations.[32] A management plan based on genetic test results should only be developed for identified pathogenic or likely pathogenic variants that are clinically actionable.

Major dilemmas regarding multigene testing are that there are limited data and a lack of clear guidelines regarding degree of cancer risk associated with some of the genes assessed and how to communicate and manage risk among carriers of these genes.[33–37] This issue is compounded by the low incidence rates of hereditary disease, leading to difficulty in conducting adequately powered studies.[33] Multigene tests often include low- to moderate-penetrance genes, for which there are few available data regarding degree of cancer risk and

guidelines for risk management.[29,34,38–40] Furthermore, it is possible that the risks associated with these genes may not entirely be due to that gene only, but may be influenced by gene/gene or gene/environment interactions. Also, certain variants in a gene may be associated with a different degree of risk than other variants in that gene.

Multigene tests also increase the likelihood of detecting a VUS.[27–29,34,40–42] However, as multigene testing is increasingly used, the frequency of a variant being interpreted as a VUS is expected to decrease. There is also an increase in the chance of finding genotypically distinct cell lines (ie, genetic mosaicism) with next-generation sequencing.[43] Clones of noncancerous cells (ie, aberrant clonal expansion) containing a pathogenic *TP53* variant have been found in healthy adults undergoing multigene testing. This phenomenon can often be attributed to clonal hematopoiesis, a condition in which a hematopoietic stem cell begins making blood cells with the same acquired mutation.[17] When there is no evidence of a hematologic malignancy, then it is referred to as *clonal hematopoiesis of indeterminate potential* (CHIP). Age-related CHIP is associated with increased risk of hematologic malignancies,[44,45] but may also lead to unnecessary clinical intervention. Ancillary testing of nonlymphoid noncancerous tissue can be used to help determine the true presence of a germline variant.[17]

Pretest and Posttest Counseling

For individuals potentially meeting established criteria for ≥1 hereditary cancer syndrome(s), genetic testing should be considered along with appropriate pretest and posttest counseling. Pretest counseling should include a discussion of why the test is being offered and how test results may impact medical management, cancer risks associated with the pathogenic or likely pathogenic variant in question, the significance of possible test results, the likelihood of a positive result, the technical aspects and accuracy of the test, cost considerations, risks of genetic discrimination, psychosocial aspects, confidentiality issues, the potential significance of the test results for family members, and other topics.[46] A discussion of confidentiality issues should include an explanation of the federal Genetic Information Nondiscrimination Act (GINA) enacted in 2008, which prohibits most health insurers and employers from discrimination based on genetic test results.[47] A detailed family history should be collected, which involves development of an expanded pedigree, beginning with the health of the individual diagnosed with cancer and proceeding outward to include first-, second-, and third-degree relatives on both the maternal and paternal sides. Factors that limit the informativeness of the pedigree are small family size, a small number of individuals of the susceptible sex for sex-limited cancers, reduced penetrance, early deaths in family members (which precludes the possibility that they will develop adult diseases), prophylactic surgeries that remove an organ from subsequent risk for cancer (eg, hysterectomy for uterine fibroids in which the ovaries are also removed), adoptions, and inaccurate or incomplete information on family members (eg, in the case of adoption or divorce).[48,49] It is also important to know the ancestry/ethnicity of the individual, because members of certain groups (eg, Ashkenazi Jewish) have increased risks of carrying pathogenic or likely pathogenic variants for specific diseases. Any family members who received genetic testing should also be noted, as well as test results. Finally, a detailed medical and surgical history from the proband should be collected, and a physical examination should be performed by a qualified clinician when appropriate.

Posttest counseling includes disclosure of results, a discussion of the associated medical risks, an assessment of the impact of the results on the individual's emotional state, a discussion of the impact of the results on the medical management of the individual, and determination of how and where the patient will be screened for cancer risk.[14] Counseling should include information on any available resources, such as disease-specific support groups, high-risk clinics, advocacy groups, and research studies.[50] Probands should be advised regarding possible inherited cancer risk to relatives and available options for risk assessment and management. Counselors should recommend genetic counseling and testing for at-risk relatives. Because some pathogenic or likely pathogenic variants are associated with rare autosomal recessive conditions (eg, Fanconi anemia or constitutional mismatch repair deficiency), testing the partner of a carrier of a pathogenic or likely pathogenic variant may be considered to inform reproductive decision-making.[51]

Pretest and posttest genetic counseling with involvement of an expert in cancer genetics is recognized as the gold standard. However, during the meeting for the 2020 update, the panel acknowledged that most genetic testing is conducted by providers with limited expertise in genetics, and often without pretest genetic counseling.[52–54] Shortages in genetics health providers,[55] expansion of testing indications, and increased accessibility of testing due to plummeting costs, inclusive of DTC models for testing, provided the impetus for the panel to identify scenarios in which referral to a genetics health provider should be considered. These scenarios include identification of a pathogenic or likely pathogenic variant; negative results despite family history suggestive of inherited disease; VUS result for which a provider considers altering clinical management; mosaic

or possibly mosaic result; discrepant interpretation of variants (eg, discordant results across laboratories); for interpretation of polygenic risk scores (ie, relative risk for disease, compared with the genomes of other individuals); and detection of pathogenic or likely pathogenic variants from DTC testing.

Hereditary Pancreatic Cancer

For the 2020 update, the panel expanded the guidelines to include a focus on pancreatic cancer, including the addition of a new section on pancreas screening and genes associated with pancreatic cancer. Pancreatic cancer is thought to have a familial or hereditary component in approximately 10% of cases.[56–60] Harboring a pathogenic or likely pathogenic variant has been found to be associated with a greater incidence of pancreatic cancer than family history alone (without the presence of an associated germline variant).[61] Germline mutations commonly found in pancreatic adenocarcinoma include *BRCA1*, *BRCA2*, *CDKN2A*, mismatch repair genes associated with Lynch syndrome (*MSH2*, *MLH1*, *MSH6*, *PMS2*, *EPCAM*), *ATM*, *PALB2*, *STK11*, and *TP53*.[57,58,61–71] *BRCA2* and *CDKN2A* are generally the most prevalent, with rates in moderate- to high-risk families ranging from 2% to 6% for *BRCA2* and 1.5% to 2.5% for *CDKN2A*.[58,59,72,73] In addition, hereditary pancreatitis, which is associated with a significantly increased risk for pancreatic cancer, is associated with the genes *PRSS1* and *SPINK1*.[57] Patients with pancreatic cancer and Ashkenazi Jewish ancestry may have a greater likelihood of testing positive for a *BRCA1/2* mutation, with prevalence of detected mutations in this group ranging from 5.5% to 19%, and mutations more common for *BRCA2*.[69,71,74,75]

Given the considerable rate of predisposing mutations in patients with pancreatic cancer, as well as the fact that typical clinical factors (eg, young age of onset, family history of cancer) are poorly predictive for identifying mutation carriers, universal genetic testing for these individuals is warranted (see CRIT-3, page 384). Given the elevated rates of pathogenic or likely pathogenic variants in pancreatic cancer and that pancreatic cancer risk increases when there is a family history,[76] testing of first-degree relatives of patients may be beneficial. However, testing the patient is preferred. Testing of second-degree relatives may be considered in select cases. Given that mortality rates for this cancer are high,[77,78] it may be beneficial to family members to test patients near the time of diagnosis, because the option to test the patient may not be available for very long. Detecting a germline mutation can potentially aid in treatment decision-making, particularly regarding systemic therapy options.

Pancreatic Cancer Screening

Evidence supporting pancreatic cancer screening comes from studies that include individuals harboring an associated germline mutation and/or those who have a particularly strong family history of pancreatic cancer (≥2 first-degree relatives on the same side of the family, or ≥3 first- or second-degree relatives on the same side of the family). An analysis of screening outcomes of 411 asymptomatic individuals from 3 European centers showed that pancreatic cancer was detected in 7% of *CDKN2A* mutation carriers and <1% of those with familial pancreatic cancer.[79] For the *CDKN2A* mutation carriers in whom a lesion was detected, 75% were resectable, with a 5-year overall survival rate of 24%. Another analysis of 354 asymptomatic high-risk individuals showed suspicious pancreas lesions in 19% who were screened.[80] Of the lesions detected through screening, 90% were resectable, and the 3-year overall survival rate was 85% in those with resectable lesions. The considerable rate of resectable asymptomatic lesions found through routine screening of high-risk individuals demonstrates the potential for downstaging (ie, identification of lesions at an earlier stage). There is also the potential for impact on mortality rates, although long-term studies are needed in this area. Lesions detected through routine screening may not always require resection (eg, sporadic branch duct intraductal papillary mucinous neoplasms). Therefore, larger long-term studies are needed to further determine the risks and benefits of routine pancreas screening in high-risk individuals, as well as the threshold for surgical intervention and biopsy.[80]

With the exception of *CDKN2A* and *STK11*, pancreas screening in individuals who have a pathogenic or likely pathogenic variant associated with increased risk of exocrine pancreatic cancer is not recommended unless there is additional family history of pancreatic cancer (at least 1 first- or second-degree relative).[81] If family history criteria are met, then pancreas screening may be considered at age 50 years, or 10 years younger than the earliest pancreatic cancer diagnosis in the family, whichever is earlier.[81] For carriers of a *CDKN2A* or *STK11* pathogenic or likely pathogenic variant, no additional family history is needed to warrant screening. For carriers of a *CDKN2A* pathogenic or likely pathogenic variant, screening may be considered at age 40 years, or 10 years younger than the earliest pancreatic cancer diagnosis in the family, whichever is earlier.[81] For carriers of a *STK11* pathogenic or likely pathogenic variant, screening may be considered beginning at age 30 to 35 years, or 10 years younger than the earliest pancreatic cancer diagnosis in the family, whichever is earlier.[81,82]

Hereditary pancreatitis is associated with increased lifetime risk of exocrine pancreatic cancer and is sometimes

caused by pathogenic or likely pathogenic variants such as *PRSS1* and *SPINK1*.[83–86] However, the clinical significance of these variants is unclear without a clinical history of pancreatitis. Therefore, germline testing for *PRSS1*, *SPINK1*, and other genes associated with pancreatitis is generally not recommended unless the individual's personal or family history is suggestive of hereditary pancreatitis.[85] Pancreas cancer screening is recommended in individuals harboring one of these variants only in the presence of a clinical phenotype consistent with hereditary pancreatitis. For individuals meeting these criteria, screening may begin at age 40 years, or 20 years after onset of pancreatitis, whichever is earlier.[81]

When screening is recommended, it may be performed with contrast-enhanced MRI/MRCP and/or endoscopic ultrasound.[80,81,87] MRI and endoscopic ultrasound have been shown to be superior in detecting subcentimeter pancreatic cysts compared with CT.[87] Screening at a high-volume center of expertise and in the context of a research study is preferred. For individuals in whom screening shows worrisome abnormalities, shorter screening intervals may be indicated.

Summary

These NCCN Guidelines Insights summarize some of the recent revisions made to the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. Updates include an expansion of genetic testing criteria to take into account other genes besides *BRCA1/2* that are associated with an increased risk of breast and/or ovarian cancer, streamlined organization of these testing criteria, revisions to testing criteria related to Ashkenazi Jewish ancestry, genetic testing for the purpose of systemic therapy decision-making, an increased focus on phenotypically directed multigene panel tests, and the addition of information regarding pancreas screening and genes with associated pancreatic cancer. Genetic testing should be considered in individuals for whom there is a personal or family history suggesting susceptibility to hereditary cancer and for whom results can potentially impact risk management and treatment.

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