Clinical Use Guidelines

Hereditary (Germline) Testing After Tumor (Somatic) Testing

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Introduction

Germline hereditary cancer testing following somatic tumor testing is addressed by this guideline.

Procedures Addressed

The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

Procedures addressed by this guideline	Procedure codes
APC Deletion/Duplication Analysis	81203
APC Known Familial Variants	81202
APC Sequencing	81201
ATM Sequencing	81408
BRCA1 Deletion/Duplication Analysis	81166
BRCA1 Sequencing	81165
BRCA2 Deletion/Duplication Analysis	81167
BRCA2 Sequencing	81216
BRCA1/2 185delAG, 5385insC, 617delT variants	81212
BRCA1/2 Deletion/Duplication Analysis	81164
BRCA1/2 Known Familial Variants	81215
BRCA1/2 Sequencing	81163
Chromosomal Microarray [BAC], Constitutional	81228
Chromosomal Microarray [SNP], Constitutional	81229
Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and loss-of-heterozygosity variants, low-pass sequencing analysis	81349

Procedures addressed by this guideline	Procedure codes
Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); duplication/deletion analysis panel, must include analyses for BRCA1, BRCA2, MLH1, MSH2, and STK11	81433
Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel, must include sequencing of at least 10 genes, including BRCA1, BRCA2, CDH1, MLH1, MSH2, MSH6, PALB2, PTEN, STK11, and TP53	81432
Hereditary cancer syndrome gene tests	81400 81401 81402 81403 81404 81405 81406 81407 81408 81479
Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); duplication/deletion analysis panel, must include analysis of at least 5 genes, including MLH1, MSH2, EPCAM, SMAD4, and STK11	81436
Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); genomic sequence analysis panel, must include sequencing of at least 10 genes, including APC, BMPR1A, CDH1, MLH1, MSH2, MSH6, MUTYH, PTEN, SMAD4, and STK11	81435
Hereditary neuroendocrine tumor disorders (e.g., medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma); duplication/deletion analysis panel, must include analyses for SDHB, SDHC, SDHD, and VHL	81438
Hereditary neuroendocrine tumor disorders (e.g., medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma); genomic sequence analysis panel, must include sequencing of at least 6 genes, including MAX, SDHB, SDHC, SDHD, TMEM127, and VHL	81437

Procedures addressed by this guideline	Procedure codes
MLH1 Deletion/Duplication Analysis	81294
MLH1 Known Familial Variants	81293
MLH1 Sequencing	81292
MSH2 Deletion/Duplication Analysis	81297
MSH2 Sequencing	81295
MSH2 Known Familial Variants	81296
MSH6 Deletion/Duplication Analysis	81300
MSH6 Known Familial Variants	81299
MSH6 Sequencing	81298
PMS2 Deletion/Duplication Analysis	81319
PMS2 Known Familial Variants	81318
PMS2 Sequencing	81317
PTEN Deletion/Duplication Analysis	81323
PTEN Known Familial Variants	81322
PTEN Sequencing	81321

What Is Germline Hereditary Cancer Testing Following Somatic Tumor Testing?

Definition

Most cancer is sporadic and due to the acquisition of somatic variants. About 5-10% of cancer has a hereditary etiology due to constitutional germline variants.[1]

- In oncology, next generation sequencing (NGS) technology makes it feasible to catalog the DNA sequence variations within a person's cancer (i.e., somatic mutation profiling). This helps define therapeutic targets which might improve outcomes through the use of specific medications directed at those mutations.[2] These genomic variations can also serve as biomarkers of an individual's prognosis and aid in diagnosis.[3,4]
- Germline variants can also be identified as an ancillary finding during primary tumor profiling to identify somatic mutations. "In the course of analyzing tumor DNA (without matched normal DNA), sequencing can identify potential constitutional (germline) DNA variations that are associated with disease or susceptibility to disease as well as carrier states for Mendelian disorders.[4] Centers may use matched tumor-normal sequencing to facilitate more accurate calling of somatic mutations by using the normal DNA to exclude germline variants from the tumor cells." [3,4]

- In a study by Schrader et al, "Targeted tumor sequencing with a panel of 341 genes and matched normal DNA in 1566 individuals with advanced malignant neoplasms revealed presumed pathogenic germline variants (PPGVs) in about 16% of individuals. Most PPGVs (80.5%, 95% CI, 75.1%-85.0%) were in genes related to cancer susceptibility. The PPGVs in genes previously designated as clinically actionable cancer targets were seen in 5.0% (95% CI, 4.1%-6.2%) of individuals. Most cancer-susceptibility PPGVs were retained in the tumor (91.9%; 95% CI, 87.3%-95.0%).[5] This study is in line with other published studies investigating the prevalence of incidental findings with somatic tumor profiling." [5-7]

- The debate continues regarding whether there is an obligation to test for and report these germline findings, which are secondary to the original purpose of somatic tumor profiling. In making this determination, pre-test informed consent is of utmost importance. "Honoring patient preferences requires oncology providers to communicate the potential for incidental and secondary germline information specific to the test being offered, the relevance and potential benefits of this information for patients and their relatives, and the limitations and risks of receiving incidental and secondary germline information" [2]

Test Information

Introduction

Mutations detected on somatic testing may be indicative of a hereditary cancer syndrome due to a germline mutation. Thus, germline hereditary cancer testing following somatic tumor testing may be indicated in certain situations.

- Testing to investigate somatic and germline DNA variants has become more common as sequencing technology has evolved from the more labor intensive Sanger sequencing to next generation sequencing (NGS). "NGS is a powerful technology that permits the characterization of large amounts of DNA sequence much quicker and at lower cost than traditional Sanger sequencing." [2]
- Laboratories performing somatic mutation profiling may include paired germline testing, not in an effort to identify hereditary etiologies, but to report pure somatic alterations, clarify interpretation, and identify variants that are genetic "drivers" of the individual's malignancy.[4,5,8]
- Laboratories may also use bioinformatics to subtract the inherited variants from the somatic tumor profiling findings. Germline variants may be missed during this process without performing further analysis.[8-11]

Guidelines and Evidence

Introduction

This section includes relevant guidelines and evidence pertaining to germline hereditary cancer testing following somatic tumor testing.

American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics (ACMG, 2020) stated the following regarding germline variations in individuals undergoing somatic tumor testing:[12]

- "Individuals undergoing tumor testing should undergo informed consent of the possibility that a PGPV [presumed germline pathogenic variant] might be discovered. However, if there is clinical indicator for germline cancer predisposition, then dedicated germline testing should be ordered."
- "Patient choice and autonomy (opt-out of PGPV result return) should be respected."
- "When automated methods are used for pre- and post-testing education and counseling, clinicians with experience in cancer genetics should be available to answer specific questions."
- "Patients should be informed that discovery of a PGPV would prompt referral for genetic consultation and the possibility of confirmatory germline testing."
- "Confirmatory germline testing should be performed in a clinical laboratory that has adequate resources and expertise in conducting germline testing and interpreting and reporting the test results."
- "Positive germline test results should be returned by qualified and experienced clinicians (e.g., oncologists with genetics expertise, geneticists, and genetic counselors)."

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN, 2022) stated the following regarding germline testing following somatic tumor testing:[13]

- "If a mutation is detected through tumor profiling that has clinical implications if identified in the germline, then germline testing for this variant is indicated."
- "If a patient meets testing criteria for germline testing for a given gene, then confirmatory germline testing should be considered through a CLIA-approved lab despite tumor profiling results."

The National Comprehensive Cancer Network (NCCN, 2021) stated the following regarding interpreting information obtained from tumor-only profiling:[14]

- "Pathogenic/likely pathogenic variants reported by laboratories providing tumor-only profiling may be of somatic or germline origin. Although germline origin can sometimes be inferred with a high degree of confidence, confirmatory germline testing is indicated for pathogenic/likely pathogenic variants with a reasonable clinical suspicion of being of germline origin (based on patient/family history or clinical characteristics [and in some cases pathogenic/likely pathogenic variant frequency])."

- "Somatic pathogenic/likely pathogenic variants in several genes with germline implications are common (e.g., TP53, STK11, PTEN), and will rarely be indicative of a need for germline testing unless clinical/family history features suggest the possibility of a germline pathogenic/likely pathogenic variant."
- "It should be noted that the absence of reported pathogenic/likely pathogenic variants in a particular gene does not rule out the possibility of a germline pathogenic/likely pathogenic variant in that gene. Clinically indicated germline testing is still appropriate for patients meeting testing guidelines regardless of tumor profiling."

Selected Relevant Publications

There have been various peer-reviewed publications that reviewed pre- and post-test considerations for germline testing following somatic tumor testing.

- Pre-test considerations:
  - Somatic tumor-only NGS testing is used to guide treatment for an affected person. The testing is not designed to elucidate a hereditary etiology. A germline variant may not be detected (due to differences in coverage in the testing, cellularity of the sample, allelic loss of the germline mutation) or may not be reported by the somatic testing laboratory.[2,3,15]
  - Directed germline genetic testing can be ordered to identify a potential hereditary etiology for the person's tumor. Referrals to oncology genetic counselors or other specialized healthcare providers should occur if the individual's personal and/or family history meets established criteria to warrant a more detailed discussion.[13,15,16]
  - Ancillary findings from somatic or germline testing may include variants in genes that cause a hereditary cancer syndrome, a non-oncologic hereditary syndrome, or identify carrier status for Mendelian disease. Specific findings are dependent on specific testing performed by the laboratory.[2,3,10,11,15]
  - Many individuals undergoing somatic tumor profiling have advanced stage disease. Centers performing somatic tumor profiling should consider obtaining a surrogate individual to receive results in the event that the proband has passed away or is otherwise unable to receive the results.[2,3,15]
- Post-test considerations:
  - Clinicians must determine the technical specifications of the laboratory used for somatic tumor profiling and determine if this includes paired germline testing. Some laboratories may not report germline variants, include certain known germline variants on a panel, or be able to detect certain types of variants (such as copy number variants) depending on the assay methodology used.[2,3,17]
  - Somatic variant interpretation differs from the variant interpretation and classification process for germline variants. For example, a laboratory profiling a somatic tumor may classify a certain variant as pathogenic

whereas a laboratory testing a germline mutation may classify that same variant as a variant of uncertain significance (VUS), or vice versa.[2,3,17] Resources, such as ClinVar, should be used by the provider to determine if a pathogenic variant classification provided by germline testing laboratories is consistent with independent assessments of that variant.[18]

- Referrals to oncology genetic counselors or other specialized healthcare providers should occur if the individual's personal and/or family history meets established criteria to warrant a more detailed discussion, regardless of somatic tumor profiling results.[10,14,15] In individuals meeting criteria for germline DNA testing, analysis of the entire gene, as opposed to single site testing for the identified somatic variant, is recommended.[6]
- Germline testing may also be considered in individuals when any of the following apply:
  - The individual does not meet published criteria for germline testing, but variant(s) within genes known to play a role in tumor biology and to cause an inherited cancer syndrome (including but not limited to TP53, APC, CDH1) are identified and the variant allele frequency in the tumor is at least 33%.[19-21]
  - One of the identified variants on tumor testing is a highly-recurrent or founder mutation (i.e., BRCA1 c185delAG or the recurrent inversion of MSH2 seen in some families with Lynch syndrome).[3]
  - The tumor profile shows thousands of somatic variants, suggesting a germline mutation in a DNA mismatch repair gene or in the POLE proofreading domain.[3,22]
  - Two separate primary tumors are sequenced and both harbor the same genetic variant.[9]
  - The individual's tumor harbors a mutation in BRCA1 or BRCA2.[13]

Criteria

Introduction

Requests for germline hereditary cancer testing following somatic tumor testing are reviewed using these criteria.

- Requests for single-site or full-gene sequence germline testing following somatic tumor analysis will be considered medically necessary when at least one of the following criteria is met:
  - The individual's personal or family history is suggestive of a germline mutation, a specific germline variation is identified by somatic tumor testing, and the individual meets the published test-specific criteria to test for that variant, OR

- One of the identified variants is a highly-recurrent or founder mutation (i.e., BRCA1 c185delAG or the recurrent inversion of MSH2 seen in some families with Lynch syndrome), OR
- The tumor profile shows thousands of somatic variants, suggesting a germline mutation in a DNA mismatch repair gene or in the POLE proofreading domain, OR
- Two separate primary tumors are sequenced and both harbor the same genetic variant, OR
- The individual's tumor harbors a mutation in BRCA1/2, OR
- The individual does not meet published criteria for germline testing, but variant(s) within genes known to play a role in tumor biology and to cause an inherited cancer syndrome (including but not limited to TP53, APC, CDH1) are identified and the variant allele frequency in the tumor is at least 33%.

Exclusions and Other Considerations

- Germline testing of somatic variants of uncertain significance (VUS) is not considered medically necessary.
- Germline testing for asymptomatic individuals based solely on a family member's somatic testing result is not considered medically necessary.
- In individuals meeting criteria for germline DNA testing, analysis of the entire gene, as opposed to single site testing for the identified somatic variant, is recommended.
- Clinically indicated germline testing is still appropriate for individuals meeting testing guidelines regardless of tumor profiling results.
- Resources, such as ClinVar, should be used by the provider to determine if a pathogenic variant classification provided by germline testing laboratories is consistent with independent assessments of that variant.

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