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 does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

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 dequencing	81216
BRCA1/2 185delAG, 5385insC, 617delT variants	81212
BRCA1/2 deletion/duplication analysis	81164
BRCA1/2 known familial variants	81215

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Procedures addressed by this guideline	Procedure codes
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
Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer, hereditary pancreatic cancer, hereditary prostate cancer), genomic sequence analysis panel, 5 or more genes, interrogation for sequence variants and copy number variants	81432
Hereditary cancer syndrome gene tests	81400 81401 81402 81403 81404 81405 81406 81407 81408 81479

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Procedures addressed by this guideline	Procedure codes
Hereditary colon cancer-related disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); genomic sequence analysis panel, 5 or more genes, interrogation for sequence variants and copy number variants	81435
Hereditary neuroendocrine tumor-related disorders (e.g., medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma); genomic sequence analysis panel, 5 or more genes, interrogation for sequence variants and copy number variants	81437
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

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Procedures addressed by this guideline	Procedure codes
PTEN deletion/duplication analysis	81323
PTEN known familial variants	81322
PTEN sequencing	81321

What is germline hereditary cancer testing following somatic tumor testing?

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

- In oncology, next generation sequencing (NGS) technology makes it feasible to catalog the DNA sequence mutations 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 mutations can also serve as biomarkers of an individual's prognosis and aid in diagnosis.[3,4]
- Germline mutations 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 mutations 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 mutations that are genetic "drivers" of the individual's malignancy.[4,5,8]
- Laboratories may also use bioinformatics to subtract the inherited mutations from the somatic tumor profiling findings. Germline mutations may be missed during this process without performing further analysis.[8-11]

Guidelines and evidence

American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics (ACMG, 2020) stated the following regarding germline mutations 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)."

American Society of Clinical Oncology

The American Society of Clinical Oncology (ASCO, 2024) published the following recommendations regarding genes for which mutations identified with somatic testing should prompt consideration of germline genetic testing:

- All patients with tumor pathogenic variants in the following genes should be offered germline testing:[13]
  - BRCA1, BRCA2, BRIP1, MLH1, MSH2, MSH6, MUTYH, PALB2, PMS2, RAD51C, RAD51D, RET, SDHAF2, SDHB, SDHC, SDHD, TMEM127, TSC2, VHL. Test only if patient <30 years of age: APC, PTEN, RB1, TP53.
    - For MUTYH: "germline follow-up testing should only be performed when two (biallelic) pathogenic variants are detected in the tumor."
    - For VHL: "renal cell carcinoma may be excluded from testing."
    - For TP53: "brain tumors may be excluded from testing."
- Any patient with tumor pathogenic variants in these genes may also be offered germline testing:
  - ATM, BAP1, BARD1, CHEK2, DICER1, FH, FLCN, NF1, POLD1, POLE, SDHA. Test only if patient <30 years of age: CDKN2A, SMARCA4
    - For CHEK2: "CHEK2 variants c.1283C>T (S428F) and c.470T>C (I157T) are low-penetrant variants with relative risk of 1.5 for cancer and do not affect screening recommendations the same way other CHEK2 variants do."
- However, if a conservative testing approach is preferred, testing for these genes may be limited to patients who have a mutation in a relevant tumor (ie, only test if a mutation is found in certain cancers):
  - ATM (breast, gastric, epithelia ovarian, pancreatic, or prostate cancers), BAP1 (melanoma, renal cell carcinoma, or malignant mesothelioma), BARD1 (breast cancer), CDKN2A (melanoma or pancreatic adenocarcinoma), CHEK2 ((breast, colon, prostate, or thyroid cancers. CHEK2 c.1100del testing should occur regardless of tumor type), DICER1 (pleuropulmonary blastoma, cystic nephroma, embryonal rhabdomyosarcoma, ovarian Sertoli-Leydig cell tumors, ovarian sarcoma, neuroblastoma, or thyroid cancer), FH (paraganglioma, pheochromocytoma, or renal cell carcinoma), FLCN (renal cell carcinoma), NF1 (breast cancer, GIST, paraganglioma, or pheochromocytoma), POLD1 (colorectal

cancer), POLE (colorectal cancer), SDHA (GIST, paraganglioma, or renal cell carcinoma), SMARCA4 (small cell carcinoma of the ovary, hypercalcemic type or malignant rhabdoid tumors).
    - "Do not test if a conservative testing approach is preferred: PTCH1, SMAD3, SMARCB1, SUFU"
        - Regarding SMAD3: "Germline SMAD3 causes Loeys-Dietz syndrome 3 and nonsyndromic thoracic aortic aneurysms and dissections. It is highly actionable although it is not associated with cancer risk."
- "If there is uncertainty around whether a variant identified through tumor genetic testing is pathogenic, oncologists may want to confer with genetics experts. The germline variant database ClinVar is another useful resource to help with this determination."
- "Variant allele frequency (VAF) is not sufficient in and of itself to confirm or exclude a germline origin. While a VAF <30% for a variant identified from tumor genomic profiling is unlikely to be germline, other factors (eg, tumor purity) must be considered and some laboratories do not report VAF. VAF identified from circulating tumor DNA testing is not informative with respect to germline origin."
- "Founder mutations are almost always germline and confirmatory germline testing is indicated, regardless of the patient's ancestry or tumor type."
- ""Patients who meet criteria for germline genetic testing should be offered germline testing regardless of results from tumor testing."

European Society of Medical Oncology

The European Society for Medical Oncology (ESMO, 2019) published recommendations for germline analysis of tumor-only sequencing data.[14,15] Factors considered include the gene, tumor type, the age of the affected individual, and VAF to determine if germline testing is recommended. These guidelines were recently updated (ESMO, 2023) and stated:[16]

- "We analysed an expanded dataset including 49 264 paired tumour-normal samples. We applied filters to tumour-detected variants based on variant allele frequency, predicted pathogenicity and population variant frequency. For 58 cancer-susceptibility genes, we then examined the proportion of filtered tumour-detected variants of true germline origin [germline conversion rate (GCR)]. We conducted subanalyses based on the age of cancer diagnosis, specific tumour types and 'on-tumour' status (established tumour-gene association)."
- Forty genes were identified for potential germline follow-up testing.
- Four different approaches were provided for germline follow-up of tumor-only sequencing results:
    - "Permissive: germline follow-up for all 40 genes in all tumour types
    - Intermediate-permissive: germline follow-up for all 23 MA-CSGs/HA-CSGs [most-actionability cancer-susceptibility gene/high-actionability cancer-susceptibility

gene] in all tumour types but germline follow-up only in 'associated' tumour types for 17 SA-CSGs [standard-actionability cancer-susceptibility gene].
    - Intermediate-conservative: germline follow-up in all tumour types for the 7 MA-CSGs but germline follow-up only in 'associated' tumour types for the other 33 HA-CSGs/SA-CSGs.
    - Conservative: germline follow-up only in 'associated' tumour types for all 40 genes"
- "Strategic filtering improves the GCR with minimal loss of true germline variants present in the tumour."
- "GCR of filtered tumour-detected variants is very high (>80%) for genes such as BRCA1, BRCA2 and PALB2."
- "GCR of filtered tumour-detected variants is very low (<2%) for genes such as APC, TP53 and STK11."
- "Germline follow-up should involve multidisciplinary expertise and follow expert guidance regarding tumour context."

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN, 2024) stated the following regarding germline testing following somatic tumor testing:[17]

- "Tumor profiling can be considered complementary to germline testing. However, the absence of a P/LP [pathogenic/likely pathogenic] variant for a given gene from tumor profiling does not rule out the possibility of a germline P/LP variant in that gene. … Therefore, a variant interpreted as P/LP 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 for most dedicated germline tests, sometimes due to filtering out of germline findings reported in tumor sequencing results."
- “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."
- "Somatic P/LP variants seen in tumor specimens are common in some genes with germline implications (eg, TP53, STK11, PTEN) and may not indicate the need for germline testing unless the clinical/family history is consistent with a P/LP variant in the germline."
- "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, 2024) stated the following regarding interpreting information obtained from tumor-only profiling:[18]

- "Because tumor genomic testing is designed to address treatment actionability, not germline status, a variant that may be considered as P/ LP in the germline may not be reported at all, or reported as normal in the tumor if it lacks clinical implications."

- "The filtering of raw sequencing data may differ between tumor and germline testing labs so that variants reported out with one analysis may not be reported with the other."
- "Somatic P/LP variants seen in tumor specimens are common in some genes with germline implications (eg, TP53, STK11, PTEN, APC) and may not indicate the need for germline testing unless the clinical/family history is consistent with a P/LP variant in the germline."
- "Tumor-only sequencing may not detect about 10% of clinically actionable P/LP germline variants (eg, deletion, duplication, and splicing variants)"
- "The fraction of PVs in cancer susceptibility genes identified through tumor-only testing, and also present in the germline, is highly variable between genes."
- "Regardless of findings in the tumor, when germline testing is clinically indicated, it should be performed in a CLIA-approved lab with established experience in germline testing…"

National Society of Genetic Counselors

The National Society of Genetic Counselors (NSGC, 2022) provided a "Somatic Research Task Force Incidental Findings Worksheet" which gave guidance for making decisions regarding the indications for germline testing after somatic testing. This stated the following:[19]

- First, determine if the gene with the mutation has an associated germline risk. If not, no further testing is indicated based on the somatic results. If so, then determine if the testing performed on the tumor was tumor paired with a normal sample such as blood or saliva. If it was paired testing, then determine if the mutation is a founder mutation or if the mutation is present in a relative to determine if confirmatory germline testing is necessary. Additionally, following-up with the testing laboratory to determine their germline confirmation policy may be necessary.
- If the testing was on tumor only, the following was stated:
  - If the following apply, then the mutation is likely somatic and no further testing may be indicated based on the somatic results:
    - The variant allele frequency is less 30%
    - The gene mutation(s) is/are associated with the tumor type
    - There is a lacking phenotype consistent with the gene mutation
    - The individual's age of diagnosis is not consistent with the gene mutation
  - If any of the following apply and the mutation is classified as pathogenic/likely pathogenic when present in the germline, then confirmatory genetic testing is appropriate:
    - The variant allele frequency is 30% or greater
    - The phenotype matches the gene mutation
    - The individual's age at diagnosis is consistent with the gene mutation

        - Of note, if a mutation is not found in databases to confirm pathogenicity, confirmatory testing may still be indicated.
    - If the gene change is classified as a variant of uncertain significance when present in the germline, confirmatory germline testing is generally not indicated however could be considered if:
        - Germline testing may be of benefit to the individual/family in the future
        - The individual/family are eligible for family or follow-up studies
        - There is clinical suspicion about the gene change
    - If the gene change is classified as benign/likely benign when present in the germline, no further testing in indicated based on the somatic results.

Additionally points noted were:

- "Consider multigene panel testing rather than targeted variant testing based on personal/family history of cancer AND/OR other NCCN criteria met for germline testing."
- "Germline testing may be necessary despite paired tumor-normal report. Some somatic testing labs are not validated for germline analysis."

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.[2,3,20,21]
    - 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.[14,15,20,22]
    - 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.[2,3,10,11,20]
    - 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.[2,3,23]
- 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.[2,3,23]
- 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.[2,3,23] 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.[24]
- 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.[10,18,20] 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 30%.[19,25-27]
  - One of the identified variants on tumor testing is a highly-recurrent or founder mutation (i.e., BRCA1 c185delAG, the recurrent inversion of MSH2 seen in some families with Lynch syndrome, the p.R337H TP53 mutation).[3,28]
  - The tumor profile shows thousands of somatic variants, suggesting a germline mutation in a DNA mismatch repair gene or in the POLE proofreading domain.[3,29]
  - 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.[17]

Note: This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for hereditary (germline) testing after tumor (somatic) testing will ensure that testing will be available to those members most likely to benefit from the information provided by the assays. For those not meeting criteria, it ensures alternate diagnostic/management strategies are considered. However, it is possible that

some members who would benefit from the testing, but do not meet clinical criteria, will not receive an immediate approval for testing.

Criteria

Introduction

Requests for germline hereditary cancer testing following somatic tumor testing are reviewed using the following 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, the p.R337H TP53 mutation), 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 30%.

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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