Melanoma Mutation Panel

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Molecular testing for melanoma may be useful in patients with metastatic disease and in patients being considered for clinical trial participation.[1] This test uses targeted massively parallel sequencing (MPS; next generation sequencing [NGS]) to identify hotspot variants in genes critical for the diagnostic, prognostic, and therapeutic assessment of melanoma and can help guide decision-making for targeted therapy.[1]

Featured ARUP Testing

Melanoma Mutation Panel 3017233

Method: Massively Parallel Sequencing

Recommended test to detect mutations in *BRAF*, *KIT*, *KRAS*, and *NRAS* genes in melanoma to determine patient eligibility for targeted therapy.

Disease Overview

Melanoma is a malignancy of melanocytes and one of the leading causes of skin cancer morbidity and mortality.[2] Histology is the mainstay of diagnosis, and other laboratory testing is not generally used for melanoma diagnosis or staging. However, molecular testing may be useful in cases of metastasis or equivocal histologic results, in the selection of patients for targeted gene therapy, and in genetic risk assessment for select patients. Laboratory testing may also be useful for prognosis and monitoring.[1] For more information about the recommended testing strategy for Melanoma, refer to the ARUP Consult Melanoma topic.

Genetics

Genes Tested

Clinically significant single nucleotide variants (SNVs), multiple nucleotide variants (MNVs), and small insertions and deletions (1-25 base pairs [bp]) and variants of uncertain significance within the preferred transcripts of the genes below are reported.

Gene	Transcript (NM)	Covered Exon(s)[a]	Covered Regions
BRAF	NM_004333.4	15[a]	chr7:140453100-140453172
KIT	NM_000222.2	9, 11, 13, 14, 17, 18	chr4:55592013-55592226, chr4:55593572-55593718, chr4:55594167-55594297, chr4:55595491-55595661, chr4:55599226-55599368, chr4:55602654-55602785
KRAS	NM_004985.4	2[a], 3[a], 4[a]	chr12:25398230-25398318, chr12:25380261-25380349, chr12:25378541-25378683
NRAS[b]	NM_002524.4	2[a], 3[a], 4[a]	chr1:115258706-115258781, chr1:115256488-115256578, chr1:115252188-115252330

[a]Indicated exons are partially covered for hotspots only and not reported in full.

[b]Only SNVs are reported for the indicated gene.

Test Interpretation

Limitations

- This test does not detect variants in areas outside the targeted genomic regions or below the limit of detection. Additional evaluation should be considered for complete genetic analysis, including detection of variants outside of the hotspot regions covered by this test, translocations, or gene rearrangements, if clinically indicated.
- Copy number alterations (losses or amplifications), translocations, microsatellite instability, tumor mutational burden, deep intronic variants, insertions/deletions larger than 25bp, and RNA variants are not detected.
  This test evaluates for variants in tumor tissue only and cannot distinguish between somatic and germline variants. If a hereditary/familial cancer is of clinical concern, additional clinical evaluation and genetic counseling should be considered before additional testing.
- In some cases, variants may not be identified due to technical limitations related to the presence of known pseudogenes, GC-rich regions, repetitive or homologous regions, low mappability regions, and/or variants located in regions overlapping amplicon primers.
- Tissue samples yielding between 1 ng and 5 ng total DNA input may yield suboptimal results and will be accepted for testing with a client-approved disclaimer.
- Benign or likely benign variants in the preferred transcript are not reported.
- Variant allele frequency (VAF) is not reported.
- Results of this test must always be interpreted within the context of clinical findings and other relevant data and should not be used alone for a diagnosis of malignancy, determination of prognosis, or recommendation of therapy.
- This test is not intended to detect minimal residual disease (MRD).

Limit of Detection (LOD)

10% VAF for all variant classes detected by the assay. For variants near the assay LOD, positive percent agreement (PPA) was found to be greater than 90%for all variant classes.

Analytic Accuracy/Sensitivity (PPA)

The PPA estimates for the respective variant classes (with 95% credibility region) are listed below.

Variant Class	Analytic Sensitivity (PPA)[a] Estimate (%)	Analytic Sensitivity (PPA)[a] 95% Credibility Region (%)
SNVs	98.4	95.1-99.7
Deletions (1-25bp)	96.8	90.2-99.3
Insertions/duplications (1-25bp)	96.8	90.2-99.3
MNVs	98.2	91.8-99.8

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.

References

1. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Cutaneous melanoma. Version 2.2021. Last update Feb 2021; accessed Apr 2021.

2. Swetter SM, Tsao H, Bichakjian CK, et al. Guidelines of care for the management of primary cutaneous melanoma. *J Am Acad Dermatol.* 2019;80(1):208-250.