

Overview

Useful For

Identifying mutations and rearrangements that may support a diagnosis or help determine prognosis for patients with central nervous system tumors

Identifying specific mutations and rearrangements within genes known to be associated with response or resistance to specific cancer therapies

This test is **not intended** for use for hematological malignancies.

Genetics Test Information

This test uses next-generation sequencing to evaluate for microsatellite instability (MSI) status, somatic mutations, and rearrangements (fusions and abnormal transcript variants) involving 160 genes associated with tumors of the central nervous system. This panel includes a DNA subpanel for the detection of sequence alterations in 89 genes and an RNA subpanel for the detection of rearrangements in 81 genes, including 104 known gene fusions and 29 known abnormal transcript variants. See [Targeted DNA Gene Regions Interrogated by Neuro-Oncology Panel](#) and [RNA Targeted Gene Fusions and Abnormal Transcript Variants](#) for details regarding the targeted gene regions identified by this test.

Of note, this test is performed to evaluate for somatic (ie, tumor-specific) mutations within the genes listed. Although germline (ie, inherited) alterations may be detected, this test cannot distinguish between germline alterations and somatic mutations with absolute certainty. Follow-up germline testing using non-neoplastic (normal) tissue can be performed for confirmation of suspected clinically relevant germline alterations. Germline testing should be performed along with genetic counseling.

Additional Tests

Test Id	Reporting Name	Available Separately	Always Performed
SLIRV	Slide Review in MG	No, (Bill Only)	Yes

Testing Algorithm

When this test is ordered, slide review will always be performed at an additional charge.

Special Instructions

- [Targeted DNA Gene Regions Interrogated by Neuro-Oncology Panel](#)
- [RNA Targeted Gene Fusions and Abnormal Transcript Variants](#)
- [Tissue Requirements for Solid Tumor Next-Generation Sequencing](#)

Highlights

This next-generation sequencing tumor profiling assay interrogates targeted gene regions and rearrangements across 160 genes associated with central nervous system tumors to assess for the presence of somatic mutations and rearrangements, such as mutations in *IDH1/2*, *TERT* promoter, *ATRX*, *TP53*, *H3-3A* (previously *H3F3A*), *H3C2/H3C3*

(previously *HIST1H3B/C*), *BRAF*, *FGFR1*, *NF1*, and *SMARCB1*, and gene fusions including *KIAA1549::BRAF*, *ZFTA::RELA* (previously *C11orf95::RELA*), and *EGFR* transcript variants (eg, *EGFR* vIII).

Microsatellite instability (MSI) status is also determined (MSS, MSI-H) as part of this test and is often clinically actionable for determining the efficacy of immunotherapy in solid tumors.

Method Name

Sequence Capture and Targeted Polymerase Chain Reaction (PCR)-Based Next-Generation Sequencing (NGS)

NY State Available

Yes

Specimen**Specimen Type**

Varies

Ordering Guidance

Multiple oncology (cancer) gene panels are available. For more information see [Hematology, Oncology, and Hereditary Test Selection Guide](#).

Necessary Information

A pathology report (final or preliminary), at minimum containing the following information, **must accompany specimen for testing to be performed**:

1. Patient name
2. Block number-must be on all blocks, slides, and paperwork (can be handwritten on the paperwork)
3. Tissue collection date
4. Source of the tissue

Specimen Required

This assay requires at least 20% tumor nuclei.

- Preferred amount of tumor area with sufficient percent tumor nuclei: tissue 360 mm(2)
- Minimum amount of tumor area: tissue 72 mm(2)
- If ordered in conjunction with CMAPT / Chromosomal Microarray, Tumor, Formalin-Fixed Paraffin-Embedded, the preferred amount of tissue is 430 mm(2), the minimum amount is 180 mm(2).
- These amounts are cumulative over up to 15 unstained slides and must have adequate percent tumor nuclei.
- Tissue fixation: 10% neutral buffered formalin, not decalcified
- For specimen preparation guidance, see [Tissue Requirements for Solid Tumor Next-Generation Sequencing](#). In this document, the sizes are given as 6 mm x 6 mm x 10 slides as preferred: approximate/equivalent to 360 mm(2) and the minimum as 4 mm x 4 mm x 10 slides: approximate/equivalent to 144 mm(2).

Preferred: Submit 2, if available, of the following specimens.

Acceptable: Submit at least one of the following specimens.

Specimen Type: Tissue block

Collection Instructions: Submit a formalin-fixed, paraffin-embedded tissue block with acceptable amount of tumor tissue.

Specimen Type: Tissue slide

Slides: 1 Hematoxylin and eosin-stained and 15 unstained

Collection Instructions:

Submit the following slides:

1 Slide stained with hematoxylin and eosin

AND

10 Unstained, nonbaked slides with 5-micron thick sections of the tumor tissue.

Note: The total amount of required tumor nuclei can be obtained by scraping up to 15 slides from the same block.

Additional Information: Unused unstained slides will not be returned.

Forms

If not ordering electronically, complete, print, and send an [Oncology Test Request](#) (T729) with the specimen.

Specimen Minimum Volume

See Specimen Required

Reject Due To

All specimens will be evaluated at Mayo Clinic Laboratories for test suitability.

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Ambient (preferred)		
	Refrigerated		

Clinical & Interpretive

Clinical Information

Molecular biomarkers, including clinically relevant gene mutations (ie, sequence variants) and fusions, have been incorporated in the World Health Organization classification of central nervous system (CNS) tumors. This test evaluates targeted regions across 160 genes associated with a variety of adult and pediatric-type CNS tumors for the presence of somatic mutations and rearrangements (fusions and abnormal transcript variants) including, but not limited to, mutations in *IDH1/2*, *TERT* promoter, *ATRX*, *TP53*, *H3-3A* (previously *H3F3A*), *H3C2/H3C3* (previously *HIST1H3B/C*), *BRAF*, *FGFR1*, *NF1* and *SMARCB1*, and *KIAA1549::BRAF* and *ZFTA::RELA* (previously *C11orf95::RELA*) fusions, and *EGFR* transcript variants (eg, *EGFR* vIII).

See [Targeted DNA Gene Regions Interrogated by Neuro-Oncology Panel](#) and [RNA Targeted Gene Fusions and Abnormal](#)

[Transcript Variants](#) for details regarding the targeted gene regions identified by this test.

Reference Values

An interpretive report will be provided.

Interpretation

The interpretation of molecular biomarker analysis includes an overview of the results and the associated diagnostic, prognostic, and therapeutic implications.

Cautions

This test cannot differentiate between somatic mutations and germline alterations. Additional testing may be necessary to clarify the significance of results if there is a potential hereditary risk.

Variants of uncertain significance may be identified.

A negative result does not rule out the presence of a variant or fusion that may be present below the limits of detection of this assay. The analytical sensitivity of this assay for sequence reportable alterations is 5% mutant allele frequency with a minimum coverage of 500X in a sample with 20% or more tumor content. The analytical sensitivity for fusions is a minimum coverage of 10 targeted fusion reads with 5 unique fusion molecules in a sample with 10% or greater tumor content.

Point mutations and small insertion/deletion mutations will be detected in 89 genes. This test may detect single exon deletions but does not detect multi-exon deletions, duplications, or genomic copy number variants in any of the genes tested. Deletions-insertions (delins) of 1000 base pairs or less are detectable with at least 50 supporting reads.

This test cannot reliably determine if a variant identified in *PMS2* exons 11-15 originated from *PMS2* or the highly homologous pseudogene *PMS2CL*. In the instance that a reportable variant is detected in *PMS2* exons 11-15, additional testing will be recommended in the patient report.

RNA is particularly labile and degrades quickly. Rapid preservation of the tumor sample after collection reduces the likelihood of degradation, but there are sometimes biological factors, such as tumor necrosis that interfere with obtaining a high-quality RNA specimen despite rapid preservation.

This panel can detect in-frame and out-of-frame fusions. There may be lower sensitivity in detecting out-of-frame fusions, such as exon-intron, intron-intron, or big insertions. This assay will only detect fusions involving at least one gene in the defined gene fusion target list of interest.

The presence or absence of a variant may not be predictive of response to therapy in all patients.

Rare alterations (ie, polymorphisms) may be present that could lead to false-negative or false-positive results.

Test results should be interpreted in the context of clinical, tumor sampling, histopathological, and other laboratory data. If results obtained do not match other clinical or laboratory findings, contact the laboratory for discussion. Misinterpretation of results may occur if the information provided is inaccurate or incomplete.

Reliable results are dependent on adequate specimen collection and processing. This test has been validated on formalin-fixed, paraffin-embedded tissues; other fixatives are discouraged. Improper treatment of tissues, such as decalcification, may cause polymerase chain reaction failure.

Genes may be added or removed based on updated clinical relevance. Refer to the [Targeted DNA Gene Regions Interrogated by Neuro-Oncology Panel](#) for the most up to date list of genes included in this test.

Supportive Data

Performance Characteristics

The limit of detection for calling a somatic variant (single nucleotide variants [SNV] and deletions-insertions [delins]) is 5% variant allele frequency (VAF) and having at least 500x deduplicated coverage.

Verification studies demonstrated concordance between this test and the reference method for detection of SNV and delins is 99.7% (699/701) and 96.6% (226/234) of variants, respectively. Concordance for the detection of delins was 98.9% (186/188) in variants 1 to 10 base pairs (bp) in size, 95.8% (23/24) in variants 11 to 50 bp in size, and 88.9% (8/9) in variants 51 to 200 bp in size.

Microsatellite instability (MSI) evaluation is accurate at a tumor purity of at least 10% for colorectal tumors and 20% for other tumor types. During verification studies, 98% (200/204) concordance for MSI status was observed between this test and the reference method.

Detection of fusion transcripts (RNA): The RNA fusion portion of the test exhibited 94.2% sensitivity (49/52) in detecting fusion transcripts (confirmed detection by reverse transcriptase polymerase chain reaction or chromosomal microarray). No fusion transcripts were detected in 25 unique samples (100% specificity compared to chromosomal microarray), resulting in an overall concordance of 96.1%.

To ensure accuracy, this test will be performed on cases estimated by a pathologist to have at least 20% tumor cells.

Clinical Reference

1. Schwartzenbuber J, Korshunov A, Liu XY, et al. Driver mutations in histone H3.3 and chromatin remodelling genes in paediatric glioblastoma. *Nature*. 2012;482(7384):226-231
2. Zhang J, Wu G, Miller CP, et al. Whole-genome sequencing identifies genetic alterations in pediatric low-grade gliomas. *Nat Genet*. 2013;45(6):602-612
3. Jones DT, Hutter B, Jager N, et al. Recurrent somatic alterations of FGFR1 and NTRK2 in pilocytic astrocytoma. *Nat Genet*. 2013;45(8):927-932
4. Brennan CW, Verhaak RG, McKenna A, et al. The somatic genomic landscape of glioblastoma. *Cell*. 2013;155(2):462-477
5. Brastianos PK, Horowitz PM, Santagata S, et al. Genomic sequencing of meningiomas identifies oncogenic SMO and AKT1 mutations. *Nat Genet*. 2013;45(3):285-289
6. Clark VE, Erson-Omay EZ, Serin A, et al. Genomic analysis of non-NF2 meningiomas reveals mutations in TRAF7, KLF4, AKT1, and SMO. *Science*. 2013;339(6123):1077-1080
7. Wu G, Diaz AK, Paugh BS, et al. The genomic landscape of diffuse intrinsic pontine glioma and pediatric non-brainstem high-grade glioma. *Nat Genet*. 2014;46(5):444-450
8. Cancer Genome Atlas Research Network, Brat DJ, Verhaak RG, et al. Comprehensive, integrative genomic analysis of

diffuse lower-grade gliomas. *N Engl J Med.* 2015;372(26):2481-2498

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10. Ceccarelli M, Barthel FP, Malta TM, et al. Molecular profiling reveals biologically discrete subsets and pathways of progression in diffuse glioma. *Cell.* 2016;164(3):550-563

11. Pajtler KW, Mack SC, Ramaswamy V, et al. The current consensus on the clinical management of intracranial ependymoma and its distinct molecular variants. *Acta Neuropathol.* 2017;133(1):5-12

12. Northcott PA, Buchhalter I, Morrissey AS, et al. The whole-genome landscape of medulloblastoma subtypes. *Nature.* 2017;547(7663):311-317

13. WHO Classification of Tumours Editorial Board: Central Nervous System Tumours. 5th ed. World Health Organization; 2021. WHO Classification of Tumours. Vol 6.

14. Nabors LB, Portnow J, Ammirati M, et al. Central nervous system cancers, version 1.2015. *J Natl Compr Canc Netw.* 2015;13(10):1191-1202

Performance

Method Description

Hybridization and capture-based next-generation sequencing (NGS) are performed to determine microsatellite instability (MSI) status and evaluate the presence of a mutation in targeted regions of 89 genes. Polymerase chain reaction amplification-based NGS is also performed to test for the presence of rearrangements in 81 genes, including 104 known gene fusions and 29 known abnormal gene transcript variants.

See [Targeted DNA Gene Regions Interrogated by Neuro-Oncology Panel](#) and [RNA Targeted Gene Fusions and Abnormal Transcript Variants](#) for details regarding the targeted gene regions identified by this test.(Unpublished Mayo method)

A pathology review and macro dissection to enrich for tumor cells is performed prior to slide scraping.

PDF Report

No

Day(s) Performed

Monday through Friday

Report Available

12 to 20 days

Specimen Retention Time

Tissue blocks: Unused portions of blocks will be returned; Tissue slides: Unused slides are stored for at least 5 years; Extracted DNA/RNA: 3 months

Performing Laboratory Location

Mayo Clinic Laboratories - Rochester Main Campus

Fees & Codes

Fees

- Authorized users can sign in to [Test Prices](#) for detailed fee information.
- Clients without access to Test Prices can contact [Customer Service](#) 24 hours a day, seven days a week.
- Prospective clients should contact their account representative. For assistance, contact [Customer Service](#).

Test Classification

This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. It has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information

81455

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
NONCP	Neuro-Onc Expanded Panel	73977-1

Result ID	Test Result Name	Result LOINC® Value
603048	Result Summary	50397-9
603049	Result	82939-0
603050	Interpretation	69047-9
603051	Additional Information	48767-8
603052	Specimen	31208-2
603053	Source	31208-2
603054	Tissue ID	80398-1
603055	Released By	18771-6