

IDH1 and IDH2 Genetic Testing for Conditions Other Than Myeloid Neoplasms or Leukemia

Effective: April 1, 2024

Next Review: January 2025

Last Review: February 2024

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Isocitrate dehydrogenase genes, *IDH1* and *IDH2*, are involved in cellular metabolism and epigenetic regulation. These genes are defining features in classifying primary brain tumors and are proposed as diagnostic and prognostic indicators for a number of other cancers.

MEDICAL POLICY CRITERIA

Notes:

- This policy does *not* address *IDH1* and *IDH2* testing for myeloid neoplasms or leukemia which is addressed in a separate policy.
 - Please refer to the Cross References section below for genetic testing not addressed in this policy.
- I. Genetic testing for *IDH1* and *IDH2* variants may be considered **medically necessary** for patients with gliomas of any grade (Note: gliomas include, but are not limited to astrocytoma, ependymoma, and oligodendroglioma).
 - II. Genetic testing for *IDH1* variants may be considered **medically necessary** for patients with cholangiocarcinoma who are considering treatment with ivosidenib (Tibsovo®).

- III. Genetic testing for *IDH1* and *IDH2* variants is considered **investigational** for all other circumstances, including but not limited to chondrosarcoma and colorectal cancer.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

GLIOMAS

Gliomas are the most common types of brain tumors, and are named for their origin (i.e., the tumor begins in cells called glial cells, which surround nerve cells). The three major types of glioma include:

- Astrocytoma,
- Ependymomas, and
- Oligodendrogliomas.

Initial workup will include radiologic evaluation, wherein a tumor may be initially stratified as a high- or low-grade glioma. Further workup, including genetic molecular studies will further classify the tumor.

GENETIC TESTING

Strategies for testing may include testing for individual genes or in combination, such as in a panel.

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION:

The information below **must** be submitted for review to determine whether policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome:

1. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
3. The exact gene(s) and/or mutation(s) being tested
4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing
6. Medical records related to this genetic test:
 - o History and physical exam including any relevant diagnoses related to the genetic testing
 - o Conventional testing and outcomes
 - o Conservative treatments, if any
 - o Sample collection date

CROSS REFERENCES

1. [Genetic and Molecular Diagnostic Testing](#), Genetic Testing, Policy No. 20
2. [Genetic Testing for Myeloid Neoplasms and Leukemia](#), Genetic Testing Policy No. 59
3. [Medication Policy Manual](#), Do a find (Ctrl+F) and enter drug name in the find bar to locate the appropriate policy.

BACKGROUND

ISOCITRATE DEHYDROGENASE

Isocitrate dehydrogenase (IDH) genes encode IDH proteins which are homodimeric enzymes involved in numerous cellular processes, including adaptation to hypoxia, histone demethylation and DNA modification. In humans, IDH exists in three isoforms. IDH3 is a catalyst in the citric acid cycle, converting NAD⁺ to NADH in mitochondria. IDH1 and IDH2 catalyze the same reaction outside the citric acid cycle and are associated with the formation of (D)-2-hydroxyglutarate. High concentrations of (D)-2-hydroxyglutarate inhibits the function of other enzymes, causing differentiated gene expression which ultimately may lead to activated oncogenes and inactivated tumor-suppressor genes. This cascade effect may ultimately develop into cancer.

TUMORS OF THE CENTRAL NERVOUS SYSTEM

The 2016 World Health Organization Classification of Tumors of the Central Nervous System presented a major restructuring of CNS tumor categorization.^[1] Specifically, diffuse gliomas, medulloblastomas and other embryonal tumors were better defined by a combination of histologic and molecular features. As of this update, diagnostic criteria heavily rely on IDH gene status. The combined genotypic and phenotypic approach improves the diagnostic process compared to previous versions by inclusion of the objective utilization of genotyping. Potential for discordance is increased with this approach, e.g., tumors that histologically appear astrocytic are proven to have an IDH mutation, however, according to the criteria, genotype trumps phenotype in these situations. Tumors of the CNS are hence designated by their histological name followed by a comma, and the genetic features as adjectives, as in: *Diffuse astrocytoma, IDH-wildtype*.

REGULATORY STATUS

More than a dozen commercial laboratories currently offer a wide variety of diagnostic procedures for genetic testing related to *IDH1* and *IDH2*. These tests are available as laboratory developed procedures under the U.S. Food and Drug Administration (FDA) enforcement discretion policy for laboratory developed tests (LDTs). Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; LDTs must meet the general regulatory standards of Clinical Laboratory Improvement Act (CLIA) and laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, FDA does not require regulatory review of LDTs.

For *IDH1* and *IDH2* testing related to treatment with Tibsovo[®] (ivosidenib) and Idhifa[®] (enasidenib) for hematologic disorders, please refer to Genetic Testing for Myeloid Neoplasms and Leukemia in the Cross References section, above.

EVIDENCE SUMMARY

GENETICS NOMENCLATURE UPDATE

Human Genome Variation Society (HGVS) nomenclature is used to describe variants found in DNA and serves as an international standard.^[2] It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term “variant” is used to describe a change in a DNA or protein sequence, replacing previously-used

terms, such as “mutation.” Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

SCOPE OF THIS REVIEW

The clinical utility of testing for variants in the *IDH1* and *IDH2* genes to inform the combined process of phenotypic and genotypic classification for the diagnosis of glioma brain tumors has been unequivocally demonstrated. These molecular markers also inform prognosis and treatment selection for the management of gliomas. Therefore, the scientific evidence for the clinical utility of *IDH1* and *IDH2* related to gliomas will not be included, as testing may be considered medically necessary.

Validation of the clinical use of any genetic test focuses on three main principles: 1) The analytic validity of the test, which refers to the technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent; 2) The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and 3) The clinical utility of the test, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

The focus of this review is on evidence related to the ability of test results to:

- Guide decisions in the clinical setting related to either treatment, management, or prevention, and
- Improve health outcomes as a result of those decisions.

SYSTEMATIC REVIEWS

No systematic reviews regarding IDH genes within the scope of this review were identified.

RANDOMIZED CONTROLLED TRIALS

No randomized controlled trials regarding IDH genes within the scope of this review were identified.

NONRANDOMIZED STUDIES

Associations between *IDH1* and *IDH2* variants are being investigated for potential diagnostic and prognostic significance in several other cancers, including but not limited to: chondrosarcoma^[3-8], and colorectal cancer^[9]. Although *IDH1* and *IDH2* variants may be present in approximately half of chondrosarcoma cases, the evidence for clinical utility regarding these markers for the many conditions is uncertain. Reported associations are typically in small case series or cohorts, demonstrating potential targets for additional investigation in larger, well-designed studies.

PRACTICE GUIDELINE SUMMARY

National Comprehensive Cancer Network

National Comprehensive Cancer Network (NCCN) guidelines for central nervous system cancers (v.1.2023) are consistent with World Health Organization diagnostic criteria, and

recommend ivosidenib for certain gliomas with an *IDH1* variant.^[10]

NCCN guidelines for bone cancers (v.1.2024) list ivosidenib as a treatment option for *IDH1*-mutated chondrosarcoma,^[11] however this medication is only FDA approved for acute myeloid leukemia and cholangiocarcinoma. Other guidelines based on research regarding *IDH1* and *IDH2* genetic testing were not identified.

SUMMARY

There is enough research to show that genetic testing for *IDH1* and *IDH2* contributes to diagnoses and risk stratification in people with gliomas, which contributes to improved overall health outcomes. Therefore, genetic testing for *IDH1* and *IDH2* variants may be considered medically necessary for gliomas of any grade (including but not limited to astrocytoma and glioblastoma).

There is enough research to show that genetic testing for *IDH1* can be used to identify patients with cholangiocarcinoma that may be eligible for treatment with ivosidenib, has been FDA-approved for the treatment of this disease. Therefore, genetic testing for *IDH1* variants may be considered medically necessary for patients with cholangiocarcinoma considering this treatment.

There is not enough research to show that genetic testing for *IDH1* and *IDH2* variants improves overall health outcomes in any other condition. Therefore, genetic testing for *IDH1* and *IDH2* variants is considered investigational for all other circumstances, including but not limited evaluation for chondrosarcoma and colorectal cancers.

REFERENCES

1. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta neuropathologica*. 2016;131(6):803-20. PMID: 27157931
2. den Dunnen JT, Dalgleish R, Maglott DR, et al. HGVS Recommendations for the Description of Sequence Variants: 2016 Update. *Human mutation*. 2016;37(6):564-9. PMID: 26931183
3. Chen S, Fritchie K, Wei S, et al. Diagnostic utility of *IDH1/2* mutations to distinguish dedifferentiated chondrosarcoma from undifferentiated pleomorphic sarcoma of bone. *Human pathology*. 2017;65:239-46. PMID: 28552826
4. Kitamura Y, Sasaki H, Yoshida K. Genetic aberrations and molecular biology of skull base chordoma and chondrosarcoma. *Brain tumor pathology*. 2017;34(2):78-90. PMID: 28432450
5. Jour G, Liu Y, Ricciotti R, et al. Glandular differentiation in dedifferentiated chondrosarcoma: molecular evidence of a rare phenomenon. *Human pathology*. 2015;46(9):1398-404. PMID: 26198745
6. Jin Y, Elalaf H, Watanabe M, et al. Mutant *IDH1* Dysregulates the Differentiation of Mesenchymal Stem Cells in Association with Gene-Specific Histone Modifications to Cartilage- and Bone-Related Genes. *PloS one*. 2015;10(7):e0131998. PMID: 26161668

7. Suijker J, Oosting J, Koornneef A, et al. Inhibition of mutant IDH1 decreases D-2-HG levels without affecting tumorigenic properties of chondrosarcoma cell lines. *Oncotarget*. 2015;6(14):12505-19. PMID: 25895133
8. Cleven AH, Zwartkruis E, Hogendoorn PC, et al. Periosteal chondrosarcoma: a histopathological and molecular analysis of a rare chondrosarcoma subtype. *Histopathology*. 2015;67(4):483-90. PMID: 25648524
9. Li WL, Xiao MS, Zhang DF, et al. Mutation and expression analysis of the IDH1, IDH2, DNMT3A, and MYD88 genes in colorectal cancer. *Gene*. 2014;546(2):263-70. PMID: 24887488
10. National Comprehensive Cancer Network (NCCN) Guidelines. Central Nervous System Cancers. [cited 1/30/2024]. 'Available from:' https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf.
11. National Comprehensive Cancer Network (NCCN) Guidelines. Bone Cancer. [cited 1/30/2024]. 'Available from:' https://www.nccn.org/professionals/physician_gls/pdf/bone_blocks.pdf.

CODES

Codes	Number	Description
CPT	81120	IDH1 (isocitrate dehydrogenase 1 [NADP+], soluble) (eg, glioma), common variants (eg, R132H, R132C)
	81121	IDH2 (isocitrate dehydrogenase 2 [NADP+], mitochondrial) (eg, glioma), common variants (eg, R140W, R172M)
HCPCS	None	

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