

IDH1 & IDH2 Mutation in Glioma and Chondrosarcoma

IDH1 and *IDH2* mutation tests are useful for detection of the most relevant mutations of *IDH1* (codon 132 in exon 4) and *IDH2* (codon 172 in exon 4) that are described in gliomas and hematologic malignancies.

(In blood or marrow, use the Myeloid Mutation Panel.)

Pathobiology: Mutation in an isocitrate dehydrogenase gene is highly associated with some glial neoplasms. The relevant mutations are *IDH1* (c.394-396 [R132H and variants]) or less commonly in *IDH2* (c.514-516 [R172K and variants]). Mutation can induce 2-hydroxyglutarate that outcompetes alpha ketoglutarate in energy metabolism, inhibiting prolyl hydroxylases that break down HIF and possibly contribute to angiogenesis. Other effects include reactive oxygen species that damage DNA, and gene promoter hypermethylation affecting gene expression.

Testing assists in differential diagnosis of brain lesions. Astrocytic and oligodendroglial neoplasms have the highest frequency of *IDH* mutation-- 95% in grade II but only rarely in grade III gliomas. Glioblastoma arising from low grade glioma frequently harbors a mutation, but primary glioblastoma (grade IV) does not. Tumors lacking *IDH* mutation include pilocytic astrocytoma, medulloblastoma, meningioma, schwannoma, ependymoma, and the vast majority of pleomorphic xanthoastrocytomas. Benign lesions lacking *IDH* mutation include inflammation, infection, ischemia/infarct, demyelination, and reactive gliosis which can mimic glioma. *IDH* mutation confers a better prognosis in low grade gliomas.

About 60% of chondrosarcomas harbor *IDH* mutation which helps distinguish it from chondroblastic osteosarcomas. Experimental targeted therapy thwarting *IDH* enzyme activity is available in clinical trials.

Clinical Indications: 1) To assess prognosis in glioma. 2) To assist in differential diagnosis of glioma and other neoplastic or reactive lesions in brain tissue. 3) To help differentiate chondrosarcoma from chondroblastic osteosarcoma.

Laboratory testing: The preferred specimen is paraffin-embedded brain tissue with a high proportion of atypical/tumor cells, provided as 10 unstained slides (plain glass) and an H&E stain marked by a pathologist to indicate the most atypical, tumor-rich region (e.g. >50% malignant cells). Fresh blood or marrow is preferred for hematopoietic neoplasia.

After macrodissection, segments of DNA containing *IDH1* exon 4 and *IDH2* exon 4 are amplified and sequenced by Sanger sequencing. Results are interpreted by a pathologist.

References:

1. Mur P, et al. Molecular classification defines 4 prognostically distinct glioma groups irrespective of diagnosis and grade. *J Neuropathol Exp Neurol*. 2015 Mar; 74(3):241-9. PMID: 25668564
2. Weller M et al. Molecular classification of diffuse cerebral WHO grade II/III gliomas using genome- and transcriptome-wide profiling improves stratification of prognostically distinct patient groups. *Acta Neuropathol*. 2015 May; 129(5):679-93.
3. Kerr DA, et al. Molecular Distinction of Chondrosarcoma from Chondroblastic Osteosarcoma through *IDH1/2* Mutations. *Am J Surg Pathol*. 37:787-95, 2013. PMID: 23598960.
4. Felsberg J et al. Rapid and sensitive assessment of the *IDH1* and *IDH2* mutation status in cerebral gliomas based on DNA pyrosequencing. *Acta Neuropathol*. 119:501-7, 2010.

5. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: acute myeloid leukemia, central nervous system cancers. www.nccn.org

To consult a pathologist about indications for testing or the significance of a result, call the Molecular Genetics Lab at (984) 974-1825 or Dr. Gulley at (919) 843-4595.
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