**IDH1 & IDH2 Mutation in Glioma and Chondrosarcoma**

IDH1 and IDH2 mutation tests are useful for diagnosis and prognosis of gliomas and for classifying subtypes of sarcoma. (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 oligodendrogial 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 IDH1 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. >20% malignant cells). After macrodissection, segments of DNA containing IDH1 exon 2 and IDH2 exon 4 are amplified and pyrosequenced. Results are interpreted by a pathologist.

**References:**

**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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