

CYTOGENETIC ANALYSIS OF GLIOMA

CHROMOSOMAL MICROARRAY, TUMOR, FORMALIN-FIXED PARAFFIN-EMBEDDED

TEST ID: CMAPT

This microarray utilizes an Affymetrix Oncoscan platform containing 220,000 unique SNPs, targeting genes of relevance in cancer with a resolution of approximately 50 kb for copy number variants (CNV) in targeted genes and approximately 500 kb for genome-wide CNVs. In addition, the chromosomal microarray will detect loss of heterozygosity (LOH) at approximately 5 Mb. CMAPT is appropriate for many tumor types, and is particularly beneficial in the characterization of gliomas.

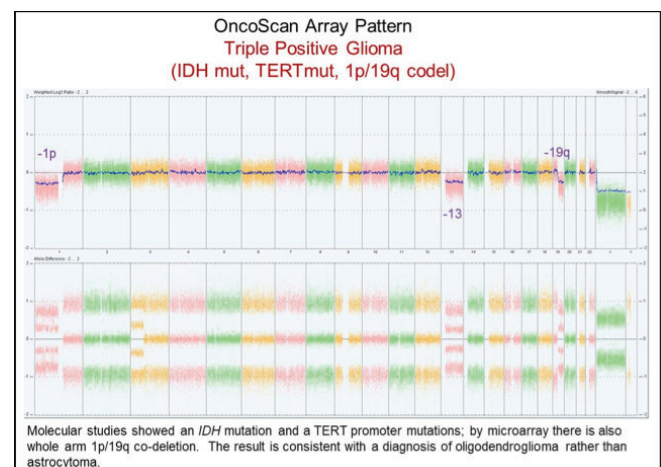
Q What are the indications for ordering a chromosomal microarray on FFPE tumors?

A The importance of identifying chromosome abnormalities in malignant neoplasms is well established and often provides important diagnostic, prognostic, and therapeutic information critical to proper patient management. Although conventional chromosome analysis can detect many chromosomal abnormalities, many others are below its level of resolution and conventional chromosome analysis does not detect copy-neutral loss of heterozygosity. Thus chromosomal microarray improves the diagnostic yield through the utilization of single nucleotide polymorphism probes to detect small copy number changes and regions of copy-neutral loss of heterozygosity.

Q What is the diagnostic benefit of chromosomal microarray on gliomas?

A The chromosomal microarray facilitates further molecular sub-classification of adult gliomas through the detection of distinctive patterns of copy number alterations. Associations between these molecular sub-classifications may further predict prognosis and response to chemotherapy and radiation treatment.

For example, what appears to be an oligodendroglioma by histological evaluation and a positive molecular study for an IDH mutation, chromosomal microarray could determine the true diagnosis as a low-grade astrocytoma through the finding of associated chromosome anomalies. Another example is classic histology showing a low grade glioma, but chromosomal microarray detects a pattern of abnormalities consistent with a glioblastoma.



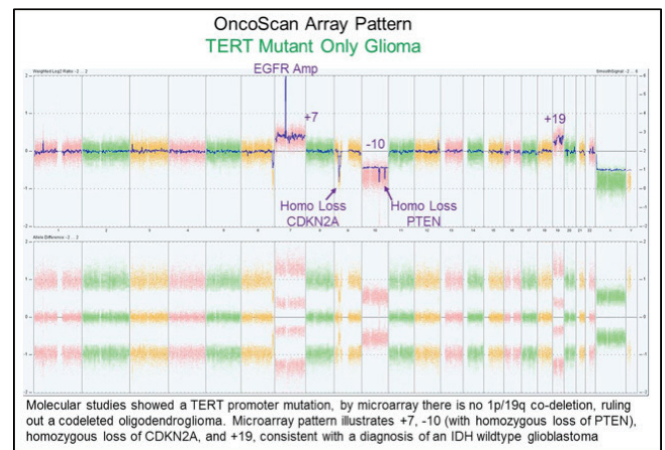
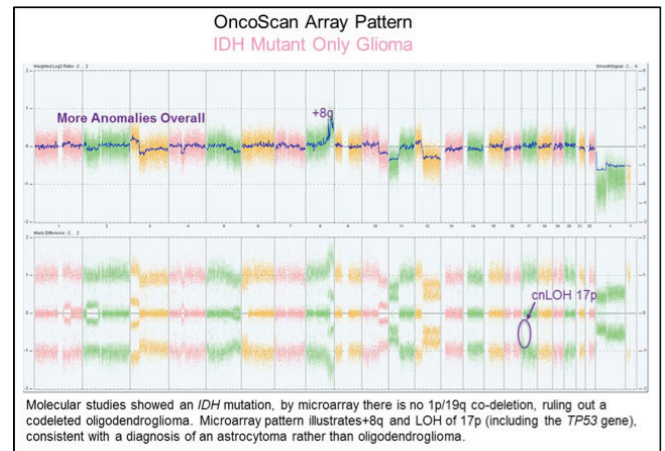
Q & A continued >

Q How does chromosomal microarray for tumor (CMAPT) compare to FISH analysis of gliomas?

A Whole arm co-deletion of 1p and 19q predicts gliomas of oligodendroglial lineage, which have been shown to have a better prognosis and response to chemotherapy and radiation therapy. For many years FISH was the standard method to detect these 1p/19q co-deletions.

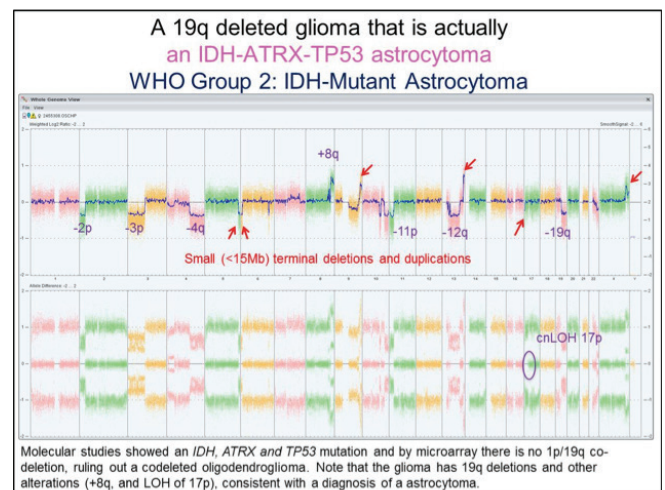
Microarray analysis of FFPE material is a more sensitive method of detecting whole arm 1p/19q co-deletion. Some gliomas have small deletions of 1p/19q, but we now know that gliomas with small 1p and or 19q deletions belong to different subtypes of glioma. The subtypes with small 1p and 19q deletions have very different prognoses and responses to chemo- and radiation therapy. FISH should not be used to detect whole arm 1p/19q deletions as it does not differentiate between these different types of deletions. Microarray analysis, with its high-resolution method for detecting copy number changes across the entire genome in a single assay, easily differentiates between whole arm co-deletions versus smaller deletions of 1p and 19q, and thus is a better test for determining prognosis and response to treatment.

In addition, the array test facilitates further molecular sub-classification of adult gliomas through the detection of distinctive patterns of copy number alterations beyond the 1p and 19q co-deletion.



Q What will be reported on the chromosomal microarray on FFPE tumor?

A All technically valid, known and suspected clinically-relevant findings that are technically valid will be reported. In addition, all deletions greater than 1Mb and duplications greater than 2Mb will be reported, regardless of known clinical relevance. Regions of LOH of 5 Mb or greater will also be reported. Suspected constitutional findings that are known to be pathogenic will be reported.



Q & A continued >

Q What are the limitations of this test?

A The chromosomal microarray cannot detect balanced rearrangements, point mutations, small deletions or insertions below the resolution of this assay, or other types of mutations such as epigenetic changes. This test does not perform genotyping for cancer-relevant point mutations. In contrast to karyotype and FISH, this test does not analyze single cells, and therefore independent clones may not be appreciated. Chromosomal microarray may not be capable of detecting low-level clone mosaicism; as such it may not be the most appropriate test for diagnostic specimens where the tumor percentage is less than 20% of the sample.

Q Are there any cautions to be aware of when offering this test to patients?

A When counseling patients regarding the chromosomal microarray on FFPE tumor, it is appropriate to discuss the potential for unknown or incidental findings, or findings which may not be related to the patient's clinical presentation, such as constitutional genetic findings. Additional follow-up studies on a different specimen source may be recommended for some results.

If you have questions about ordering this test or interpretation of results on a patient, please call the genetic counselor on-call number at 507-284-1668. Genetic counselors are available Monday – Friday from 8 am – 5 pm CST.

1. Buckner J, Giannini C, Eckel-Passow J, et al. Management of diffuse low-grade gliomas in adults - use of molecular diagnostics. *Nat Rev Neurol*. 2017 May 12. doi: 10.1038/nrneuro.2017.54. [Epub ahead of print]
2. Eckel-Passow JE, Lachance DH, Molinaro AM, et al. Glioma Groups Based on 1p/19q, IDH, and TERT Promoter Mutations in Tumors. *N Engl J Med*. 2015 Jun 25;372(26):2499-508.
3. Cimino PJ, Zager M, McFerrin L, et al. Multidimensional scaling of diffuse gliomas: application to the 2016 World Health Organization classification system with prognostically relevant molecular subtype discovery. *Acta Neuropathol Commun*. 2017 May 22;5(1):39.