

***MGMT* Promoter Methylation Test is Prognostic and Predicts Drug Response in Glioblastoma**

The UNC Hospitals Molecular Genetics Laboratory tests for *MGMT* gene promoter methylation associated with sensitivity to alkylating agents in glioblastoma patients, and with prolonged survival following temozolamide therapy in oligodendroglioma patients.

Biology of the process: *MGMT* is a DNA repair enzyme that reverses alkylation of guanine by transferring the alkyl group to the active site of the enzyme. Diminished *MGMT* expression due to methylation of CpG sites in the 5' portion of the *MGMT* gene allows accumulation of alkylated DNA which, following incorrect base pairing of alkylguanine with thymine, causes DNA damage. *MGMT* methylation is associated with 1) improved prognosis and increased sensitivity of glioblastoma to alkylating agents such as temozolamide, BCNU (carmustine) or other nitrosureas, 2) improved prognosis in anaplastic glioma patients, and 3) prolonged progression-free survival in oligodendroglioma patients treated with temozolamide. Elderly glioblastoma patients with unmethylated *MGMT* are less likely to respond to temozolamide as sole treatment, and they may benefit from radiation therapy. The value of testing in *recurrent* glioblastomas is less clear. Evidence is accumulating on the role of testing in low grade glioma.

Clinical indications for *MGMT* promoter methylation testing: High grade glioma (anaplastic astrocytoma or glioblastoma) patient being considered for therapy with an alkylating agent, or oligodendroglioma patient being considered for temozolamide therapy.

Laboratory testing for *MGMT* promoter methylation: The preferred sample is five unstained paraffin sections, each 6µM thick on plain glass slides, plus an H&E-stained slide on which areas with >50% malignant cells are circled. Tumor is enriched by macrodissection, and DNA is subjected to bisulfite-treatment followed by pyrosequencing to determine methylation status of five CpG islands of the *O*⁶-*methylguanine methyltransferase (MGMT)* promoter using PyroMark reagents (Qiagen). Results are interpreted by a pathologist.

References:

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Questions? Consult a pathologist in the Molecular Genetics Lab at (919) 966-4408 or email Dr. Gully at margaret_gully@med.unc.edu
http://labs.unchealthcare.org/directory/molecular_pathology/index_html