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Medical Policy Manual

Topic: DecisionDX-GBM and UM Gene Expression Assays

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Section: Genetic Testing

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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

Glioblastoma Multiforme

Glioblastoma multiforme (GBM), also known as grade IV astrocytoma, is an aggressive type of primary brain tumor. This tumor type may in fact be a progression of other, less invasive tumor types (e.g., anaplastic astrocytoma).[1] Age of onset of GBM is somewhat later in life compared with other tumor types, typically in the beginning of the 6th decade of life. Nevertheless, due to lack of effective treatment for this disease, prognosis following diagnosis with GBM is around 15 months, the lowest survival rate of all patients with primary brain tumors.[2] Citing the aggressive nature and poor prognosis of this disease, genetic testing, in particular, gene expression assays, has been proposed for use in risk stratification of patients with GBM.

The DecisionDx-GBM test (Castle Biosciences, Inc.) is one such example of a gene expression assay[3] that predicts risk stratification in GBM patients. Using a proprietary gene expression assay of 9 active and 3 control genes, this assay is proposed for risk assessment and subsequent treatment planning. Following the analysis of the 9 genes, the total sum of their expression provides the DecisionDx-GBM Score. Based on this score, a patient falls into one of five categories (quintiles) which correspond to a percentage likelihood of 2 year survival and a median survival in months.

According to Castle Biosciences Inc., the DecisionDx-GBM test results are used for determining the following:

- Frequency of monitoring
- Alternative treatment regimens
- Quality of life management
- Life-planning

Uveal Melanoma

Uveal melanoma (UM), also referred to as ocular or choroidal melanoma, is the most common, but rare, primary ocular malignancy in adults and shows a strong tendency for metastases to the liver. Even with successful treatment of the primary tumor, up to 50% of individuals subsequently develop systemic metastases, with liver involvement in up to 90% of these individuals. Even with aggressive systemic treatments, metastatic liver disease remains the most common cause of tumor-related mortality in choroidal malignant melanoma, with a median survival rate of two to seven months and a one-year survival rate of less than 10%. The primary clinical issue in the management of uveal melanoma is accurately predicting risk of metastasis.

Gene expression profiling assays are being investigated as a tool to assist in the risk stratification and clinical management of individuals with uveal (ocular) melanoma. The DecisionDx-UM test (Castle Biosciences Inc.) is a commercially marketed gene expression profiling test intended for use in assessing metastatic risk in individuals with this condition. It consists of a 15-gene polymerase chain reaction (PCR)-based assay that stratifies individuals with uveal melanoma into two classes based on the molecular signature of tumor tissue. Uveal melanomas cluster into two molecular groups based on their gene expression profile. Tumors with the class 1 signature rarely metastasize, whereas those with the class 2 signature have a very high rate of metastasis.

According to Castle Biosciences Inc., the DecisionDx-UM test results are used for the following:

- To initiate referral to a medical oncologist for treatment planning which may include adjuvant treatment.
- To develop specific monitoring or surveillance plans:
    - More frequent monitoring with advanced imaging procedures may be recommended for those individuals identified as having a high risk of developing metastasis.
    - For individuals at a low risk of developing metastasis, a less intensive surveillance plan may balance the risks of radiation exposure associated with less frequent imaging.
- To improve life-planning.

Regulatory Status

The DecisionDx-GBM and DecisionDx-UM tests are performed in a Clinical Laboratory Improvement Amendment (CLIA)-certified laboratory and do not require U.S. Food and Drug Administration (FDA) clearance.

MEDICAL POLICY CRITERIA

I. Gene expression assays, including but not limited to DecisionDx-GBM, are considered **investigational** for guiding diagnosis, treatment, and surveillance decisions in patients with glioblastoma multiforme.

II. Gene expression assays, including DecisionDx-UM, are considered **investigational** for guiding diagnosis, treatment, and surveillance decisions in patients with uveal melanoma.

POLICY GUIDELINES

Currently, prognostic screening for metastatic disease in GBM and UM is achieved through administration of standard clinical and histopathological risk assessment measures (including location, size, and thickness of tumor). Within this context, assessment of the proposed use of a gene expression assays for risk of metastatic death following GBM or UM must fulfill 3 parameters:

- Establish technical feasibility of the new test, including a focus on test reproducibility and establishment of the test protocol.
- Demonstrate the diagnostic performance (sensitivity, specificity, positive and negative predictive values) of the new test compared with a gold standard test (and/or long-term patient follow-up measuring actual risk of disease).
- Evaluate clinical outcomes based on the performance of the new test versus the standard of care (i.e., establish clinical utility). Following risk stratification with a new test, prospective comparative trials which demonstrate subsequent changes in clinical management are needed to demonstrate the impact of the test on net health outcomes.

Clinical utility is best demonstrated by randomly allocating new versus current prognostic testing to an appropriate patient spectrum, determining treatment based on test results, and allowing for long-term follow-up of health outcomes.

SCIENTIFIC EVIDENCE

Review of the literature focused on identifying evidence related to clinical utility, specifically, whether the tests can be used to improve treatment planning compared with the standard of care and whether their use results in improved health outcomes.

Literature Appraisal

<u>DecisionDx-GBM</u>
There are no published trials addressing the clinical utility of the DecisionDx gene expression profile for risk assessment in patients with GBM. There were no studies that addressed the specificity, sensitivity, or positive- and negative-predictive values, and no studies compared patient health outcomes of clinical management with vs. without this testing.

- One article was identified which detailed the identification process for the set of genes used in the DecisionDx-GBM test.[4] The gene expression data was derived from expression microarray studies on frozen tumor specimens from a total of 110 patients from 4 institutions. 38 genes were identified whose expression was significantly associated with survival. The 9-gene assay was validated on a final set of 101 formalin-fixed, paraffin-embedded (FFPE) GBM tumor

specimens. However, this publication does not address the diagnostic accuracy or clinical utility of this protocol.

- A 2010 summary of the DecisionDx test found no published clinical utility trials and in general, determined that the evidence was limited and inconclusive due to small numbers of specimens and a lack of transparency in the proprietary risk assessment algorithm.[5]

DecisionDx-UM

Studies for gene expression in UM are mainly tissue studies with the aim of establishing associations between various genes and clinical outcomes. There are no published studies that address the specificity, sensitivity, or positive- and negative-predictive values of DecisionDx-UM, and no studies that compare patient health outcomes as a result of patient management with vs. without this testing.[6]

- In the initial study of DecisionDx-UM, Onken and colleagues reported on the selection process of a 26-gene expression profile from a set of 25 patient samples (obtained from enucleation) constructed to correctly classify low-grade (class 1; associated with lower risk of metastatic death) vs. high-grade (class 2; associated with higher risk of metastatic death) tumor class.[7] The primary intent of the study was to evaluate whether presence of this genetic signature was associated with correct identification of 50 patients with uveal melanoma (the 25 specimens used to create the diagnostic protocol, plus another 25 patients). Although this article adds to the body of evidence on gene expression assays for prediction of risk in uveal melanoma, the gene expression profile described in this study consisted of 26 genes, while that of the DecisionDx-UM test consists of 15 genes. Therefore, findings from this study may not be generalized to the use of the DecisionDx-UM test.[8]
- An early study by Worley and colleagues reported the sensitivity and specificity for a molecular classifier using two microarray gene expression profiling platforms (84.6% and 92.9%, respectively) was superior when compared to monosomy 3 detected by an array comparative genomic hybridization (aCGH) (58.3% and 85.7%, respectively) and fluorescence in situ hybridization (FISH) (50.0% and 72.7%, respectively).[8] The investigators concluded that, "molecular classification based on gene expression profiling of the primary tumor was superior to monosomy 3 and clinicopathologic prognostic factors for predicting metastasis in uveal melanoma." This study, however, was limited by inconsistencies in the reported data.
- In 2010, Onken and colleagues conducted a larger prospective technical validation study (n=609) that describes the derivation of the DecisionDx-UM test utilizing the PCR-based 15-gene assay comprising 12 discriminating genes and three endogenous control genes from previously published data sets[9] collected from the same group . Technical performance of the assay was assessed in tumor samples, including 553 fine needle aspiration biopsy and 56 enucleation specimens from the authors' laboratory (n=188) and 11 collaborating sites (n=421). According to the study protocol, sample failure rate due to incorrect specimen handling was low, occurring in 32 of 609 (5.3%) of samples ($p<0.0001$). Preliminary data suggested the potential for increased sensitivity of gene expression profiling compared with cytologic diagnosis, as the assay failed in only 1 of 51, or 2% of samples with insufficient material for cytological diagnosis; however, point estimates of overall test accuracy (e.g., sensitivity, specificity, or both) were not provided. In a subset of 172 individuals with uveal melanoma, the relationship between tumor class and metastasis was studied with available clinical data and a median follow-up time of 16 months. Within this group, the assay was reported to correctly identify individuals who went on to develop metastatic disease. Kaplan-Meier analysis showed approximately 24% class 2 individuals with uveal melanoma surviving at 48 months and close to 100% survival in the class 1 group, although more specific data was not provided. This study evaluated primarily fine

needle aspiration biopsy specimens (553 of 609, or 90.8%) rather than enucleation specimens; however, the data reported on the relationship between tumor class and metastasis are limited, and median follow-up time was reported as a relatively short duration (16 months).

- In a prospective, multicenter study, the prognostic performance of a 15 gene expression profiling (GEP) assay that assigns primary posterior uveal melanomas to prognostic subgroups: class 1 (low metastatic risk) and class 2 (high metastatic risk) was evaluated in 459 patients with posterior uveal melanoma from 12 independent centers.[10] Tumors were classified by GEP as class 1 or class 2. The first 260 samples were also analyzed for chromosome 3 status using a single nucleotide polymorphism assay. Net reclassification improvement analysis was performed to compare the prognostic accuracy of GEP with the 7th edition clinical Tumor-Node-Metastasis (TNM) classification and chromosome 3 status. Patients were managed for their primary tumor and monitored for metastasis. The GEP assay successfully classified 446 of 459 cases (97.2%). Metastasis was detected in 3 class 1 cases (1.1%) and 44 class 2 cases (25.9%) (log-rank test, P<10(-14)). At 3 years follow-up, the net reclassification improvement of GEP over TNM classification was 0.43 (P = 0.001) and 0.38 (P = 0.004) over chromosome 3 status. The GEP provided a highly significant improvement in prognostic accuracy over clinical TNM classification and chromosome 3 status. The impact of the test results on health outcomes were not identified in the study.

Guidelines

There are no evidence-based clinical practice guidelines which specifically recommend the use of gene expression assays, specifically DecisionDx-GBM or DecisionDx-UM, to guide the clinical management of patients with GBM or UM.

Summary

There is insufficient evidence to determine how gene expression profiling may be used to guide clinical decisions related to the diagnosis and treatment of glioblastoma multiforme and uveal melanoma. Specifically, it is not known how or whether decisions concerning treatment and surveillance are improved over the current standard of care, and it is unknown whether health outcomes are improved as a result of those decisions. Therefore, the use of gene expression assays, including DecisionDx-UM and DecisionDx-GBM, are considered investigational in patients with uveal melanoma and glioblastoma multiforme.

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CROSS REFERENCES

Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20

CODES	NUMBER	DESCRIPTION
CPT	81479	Unlisted molecular pathology procedure
	81599	Unlisted multianalyte assay with algorithmic analysis
	84999	Unlisted chemistry procedure
	88299	Unlisted cytogenetic study
HCPCS	None	