Gene expression risk score and algorithm for clinically aggressive meningioma identification and therapy guidance

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TECHNOLOGY DESCRIPTION

Meningioma is the most common primary intracranial neoplasm, accounting for approximately 40% of newly diagnosed primary brain tumors and with approximately 42,000 new cases annually in the United States1. The estimated prevalence of persons living with meningioma in the United States is between 170,000 and 210,000, although this number may be much higher, up to 400,000 or more, based upon incidence and survival rates2. The World Health Organization (WHO) has historically graded meningiomas according to histological features such as mitotic count3. Although most WHO grade 1 meningiomas can be controlled with surgery or radiotherapy, many WHO grade 2 or grade 3 meningiomas recur and cause significant neurological morbidity and mortality4. Moreover, some WHO grade 1 meningiomas develop recurrences that cannot be predicted from histological features, and some WHO grade 2 or grade 3 meningiomas are unexpectedly well controlled with surgery and radiotherapy. The 10-year rate of local recurrence after meningioma resection is 20-30% for WHO grade 1 tumors5–7, 40-50% for WHO grade 2 tumors8–13, and in excess of 80% for WHO grade 3 tumors14,15. Meningioma recurrences and salvage surgery or repeat ionizing radiation are significant causes of neurologic morbidity and mortality6,16,17. Although adjuvant radiotherapy improves local control of meningioma18, there is no consensus on indications for meningioma radiation, and the benefit of radiation must be weighed against long-term toxicities, which can include neurocognitive deficits19,20, necrosis8,21, and secondary cancers19,22. To date, no clinically tractable biomarkers are available to guide patient selection for adjuvant radiation therapy, representing an unmet need.

Inspired by the success of targeted gene expression biomarkers in other solid tumor contexts such as breast and prostate cancers, we have developed a targeted gene expression biomarker which improves upon all contemporary classification systems and identifies meningioma patients benefiting from postoperative radiotherapy. As there are currently no other commercial technologies available to supplement pathologic review of meningioma samples, this invention will help address the need for more informed therapy decisions through improved risk stratification and recommendations for adjuvant radiotherapy to patients with

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OTHER INFORMATION

KEYWORDS

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CATEGORIZED AS

- Biotechnology
  - Health
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    - Diagnostics

RELATED CASES

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meningioma. we developed this biomarker using a discovery cohort of 173 meningiomas, and analytical and clinical performance in a cohort of 969 meningiomas, including investigator-blinded independent validation in 103 FFPE samples from a prospective clinical trial, RTOG 0539 (Figure 1). This work has recently been published in Nature Medicine (Chen et al, Nat Med, Online ahead of Print, 2023 Nov 9: https://pubmed.ncbi.nlm.nih.gov/37944590/), and will be presented in a plenary session at the 2023 Society for Neuro-Oncology conference in Vancouver, BC.

Clinical / Performance Summary

- The biomarker improved risk stratification compared to all other systems tested (N=9) in the clinical validation cohort for local recurrence (5-year area under the curve [AUC] 0.81) and overall survival (5-year AUC 0.80). The increase in AUC compared to the standard of care, World Health Organization 2021 grade, was 0.11 for local recurrence (95% confidence interval [CI] 0.07-0.17, P<0.001). Finally, the biomarker appeared to identify meningiomas benefiting from postoperative radiotherapy (hazard ratio 0.54, 95% CI 0.37-0.78, P=0.001) and our results suggested postoperative management could be refined for 29.8% of patients (**Figure 2**). Our rationally designed and inexpensive biomarker follows in the footsteps of similar biomarkers already in routine clinical use for prostate and breast cancer[23]. No similar biomarker currently exists for meningioma. Thus, our targeted gene expression assay leverages a well-established biomarker technology and has the potential to impact thousands of meningioma patients each year.

pasting

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SUGGESTED USES

Clinical utility and/or intended use

• Biomarker is to be performed on surgical specimens, using clinical FFPE samples. Surgery is the mainstay of treatment of meningioma, and the vast majority of patients undergo surgical resection. Tissue availability will not be a concern. Turnaround is rapid, as fast as standard RNA extraction followed by gene expression quantification is feasible. Computational burden is minimal.

• The resulting risk score and predicted recurrence risk group can be used to provide prognostic information for patients, as well as to predict patients likely to benefit from adjuvant radiation therapy

STAGE OF DEVELOPMENT

This biomarker has been externally validated in 866 meningiomas from 6 international centers, as well as in 103 meningiomas from a prospective clinical trial in an investigator-blinded fashion. The technology is ready for operationalization from a clinical and analytical standpoint. Further prospective validation is planned via an ongoing prospective registry, and utilizing samples from ongoing Phase 3 randomized trials expected to complete accrual in 2024: BN003 and ROAM-EORTC 1308.

Analytical validity, including reproducibility over time and across laboratories, paired frozen and FFPE meningioma samples, and different approaches for gene expression quantification was established using the multicenter analytical validation cohort (N=1219 meningiomas, 8 institutions). Test-retest conditions, different centers, and paired frozen/FFPE meningiomas generated concordant gene expression risk scores that were tractable and discriminatory for meningioma outcomes. The assay was reproducible when RNA sequencing or microarray approaches were used to assess the 34-gene signature indicating the underlying technology

could be implemented using a variety of gene expression quantification methods.

ADVANTAGES

• No other commercially available biomarker exists and outperforms current gold standard (pathology-based WHO grading system) across multiple measures

• Outperforms all contemporary molecular classification systems

• Cost and complexity are low (on the order of $40 per sample during development and validation phases, and turnaround time is rapid, as low as 2-3 days) compared to genome/exome and epigenetic profiling, and are anticipated to be lower than that of gene mutation panels used in routine clinical practice or DNA methylation profiling.

• Underlying technology can be repurposed to operate using different methods of gene expression quantification

• Reclassifies up to half of meningiomas, and refines post-operative management in ~30% of cases, potentially avoiding unnecessary radiation treatment and associated costs in one third of patient

DATA AVAILABILITY

Data available under CDA.

RELATED MATERIALS

▶ Can Gene Expression Predict if a Brain Tumor Is Likely to Grow Back? - 11/15/2023

▶ Targeted gene expression profiling predicts meningioma outcomes and radiotherapy responses - 11/09/2023

LOOKING FOR PARTNERS

To commercialize the technology for public benefit

PATENT STATUS

Patent Pending

OTHER INFORMATION

Link to Patent Application: WO2021189082A1

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