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CSF-Seq: Whole-transcriptome Sequencing of Cerebrospinal Fluid Cell-free RNA for Molecular Profiling of Neurological Disease, Including Leptomeningeal Metastasis

Stanford scientists have developed CSF-Seq, a whole-transcriptome sequencing platform that reads cell-free RNA in cerebrospinal fluid to enable minimally invasive molecular profiling of neurological and neuro-oncologic disease, including leptomeningeal disease.

Many brain and central nervous system conditions are difficult to characterize at the molecular level because tissue is rarely accessible. This gap is especially acute in leptomeningeal disease, a rapidly fatal spread of cancer into the fluid surrounding the brain and spinal cord, where the current diagnostic standards of MRI and CSF cytology frequently miss disease and reveal little about its underlying biology. The result is delayed diagnosis, limited ability to predict which patients will progress quickly, and few tools to track disease over time.

CSF-Seq addresses this by capturing the entire transcriptome from the small amounts of fragmented, low-abundance RNA that circulate freely in cerebrospinal fluid, a sample type that had previously resisted broad molecular profiling. Using an optimized workflow for sample handling, RNA extraction, and deep sequencing, the platform produces reproducible molecular profiles from routinely collected CSF and reliably distinguishes leptomeningeal disease from other cancers and from non-cancer conditions. These profiles remain consistent regardless of how the fluid is collected or where it is processed, and the platform yields a prognostic signature that flags patients at highest risk of rapid progression, independent of standard

clinical measures. This gives clinicians a minimally invasive tool to support earlier diagnosis, risk stratification, and longitudinal monitoring across leptomeningeal disease and a broad range of other CNS conditions where CSF is accessible.

Stage of Development
Proof of Concept

Applications

- CSF-based transcriptomic test to support diagnosis and molecular characterization of leptomeningeal disease
- Prognostic risk score to stratify patients, guide treatment planning, and inform clinical trial enrollment
- Longitudinal monitoring of disease burden and treatment response through serial CSF sampling
- Research-use-only and, longer term, clinical assays for transcriptomic profiling of other CSF-accessible CNS conditions, including primary tumors, neuroinflammation, infection, and injury
- Biomarker discovery and companion diagnostic development support for CNS-active therapeutics
- Characterization of CNS disease biology to support target discovery and patient stratification approaches
- Pharmacodynamic biomarker platform for monitoring biological response to CNS-directed therapies in clinical trials

Advantages

- Enables whole-transcriptome profiling from cell-free RNA
- Overcomes technical barriers associated with low-input, fragmented cerebrospinal fluid cell-free RNA
- Robust across CSF collection modality and reproducible across independent processing sites
- Supports both disease classification and prognostic stratification in a single assay
- Captures signals from tumor, immune, and CNS-resident sources, offering richer biological insight than cell-free DNA alone

- Provides transcriptome-wide characterization of disease biology beyond conventional cytology, imaging, or DNA-based molecular assays
- Supports serial longitudinal sampling through routinely collected CSF, enabling dynamic assessment of disease evolution and treatment response
- Minimally invasive, using CSF obtained through routine clinical procedures

Innovators

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