

MEETING REPORT

Assessing biomarkers for brain diseases: progress and gaps

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Abstract

A report on the 2nd Wellcome Trust Scientific Conference on Biomarkers for Brain Disorders: Challenges and Opportunities, held at the Moller Centre, Cambridge, UK, February 3-5, 2013.

Current issues in biomarker development for brain disorders

Biomarker discovery for brain disorders is burgeoning with advances in technologies that permit molecular and functional disease measures taken from brain, cerebrospinal fluid (CSF), and plasma. The new advances pose the challenge of how specific markers or combinations of markers can be validated for their intended use in clinical research, drug development or clinical practice. There is a pressing need across neurological and psychiatric disorders for validated, fit-for-purpose biomarkers that can be used as quantitative indicators of disease risk, diagnosis or prognosis that will define homogeneous patient subgroups, predict responses, or monitor drug safety and treatment efficacy.

Patient responses to marketed and investigational drugs are heterogeneous, partly explaining recent failures of novel chemical therapeutics in psychiatric clinical trials, and reduced enthusiasm for drug discovery and development by the pharmaceutical industry. The keynote speaker Jeffrey Nye (Janssen Pharmaceuticals, USA) articulated the declining investment in neuroscience research and development by the pharmaceutical industry, which he juxtaposed with the unmet medical need for therapeutic interventions for brain disorders and the need to change the marketing model for central nervous system (CNS) therapeutics. Nye challenged conference attendees (from academia, advocacy, government

and industry backgrounds) to work collaboratively to validate the next generation of brain biomarkers, to define patient subgroups on the basis of disease etiology, and to measure the dynamic state of disease at the level of neurons, glia and synapses.

The meeting was organized into sessions focused on challenges in the development of biomarkers for a range of CNS disorders, including Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), autism spectrum disorder (ASD), multiple sclerosis (MS), Parkinson's disease and schizophrenia. Breakout groups focused on technical considerations for validating biomarkers. The meeting generated creative discussions and sharing of lessons learned about biomarker technology platforms, assay performance, and standardization of data collection to enable broad-based data sharing within and across CNS disease areas. Kalpana Merchant (Eli Lilly, USA) introduced the concept of starting with genetically identified subjects in order to define disease taxonomy on the basis of molecular biomarkers rather than clinical symptoms. Clifford Jack and colleagues' model of dynamic biomarkers as a framework for *in vivo* staging of AD, testing hypotheses of disease mechanisms, and refinement of the model was highlighted as an exemplar of biomarker collaboration. A lively discussion on the risks of 'over fitting' current biomarker data to promote a model rather than focusing on the gaps followed, setting the stage for the interpretation of subsequent presentations. Another theme was the need for a multimodal biomarker approach in longitudinal rather than cross-sectional studies to understand the sensitivity and specificity of various markers (for example, imaging, cognitive, CSF and blood-based markers). Algorithms were proposed for the early detection of disease in asymptomatic individuals at increased risk and for identifying factors that track disease progression in affected individuals. Here, I cover some of the meeting highlights, including recent progress and knowledge gaps in the application of fluid-based biomarkers, the development of imaging biomarkers, and efforts to advance the collaborative development of biomarkers in this field.

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Fluid-based proteomic biomarkers and considerations for translation from discovery to the clinic

Advances in proteomic technologies have led to their application as tools for early diagnosis and monitoring disease progression in brain disorders. In CSF samples, Kaj Blennow (University of Gothenburg, Sweden) reported the reliability and utility of a multiplexed panel of three markers - amyloid- β_{1-42} ($A\beta_{1-42}$), total tau, and phosphorylated tau assays - to diagnose AD with dementia and to identify prodromal AD in mild cognitive impairment (MCI) cases. He highlighted challenges in developing assays to detect synaptic proteins such as SNAP25, GAP43 and synaptotagmin in the CSF, citing sensitivity as a key issue. Addressing ALS, Martin Turner (Oxford University, UK) presented findings that indicate the potential utility of markers of neuronal loss (TDP-43, phosphorylated neurofilament heavy subunit) and glial activity (complement C3) in CSF samples for inclusion in a panel of diagnostic and prognostic biomarkers.

Reliable, plasma-based biomarkers continue to be a focus of several groups, even though efforts to identify such markers for AD have had little success so far. Plasma $A\beta_{1-42}$ assays have yielded variable results across studies and do not correlate with CSF $A\beta_{1-42}$ levels, perhaps due to epitope masking and analytical interference by plasma proteins. Several candidate blood biomarkers (BACE1 and clusterin) have failed to predict progression to AD (Harold Hampel, Goethe-University, Germany). Simon Lovestone (Kings College London, UK) proposed that plasma biomarkers in AD could be used as a high-throughput way to triage subjects for more costly, imaging-based marker studies. By contrast, plasma markers were reported to show promise in ALS (Turner) and in MS. Peter Schultz-Knappe (Protagen AG, Germany) described the use of a multiplex antibody array coupled with informatics to identify a panel of plasma markers that discriminated patients with MS from healthy controls with a higher level of precision than a single marker. Using a multiplex immunoassay panel, Sabine Bahn (University of Cambridge, UK) reported a molecular signature in plasma in first-episode schizophrenia. Aileen Healy (Seaside Therapeutics, USA) described a multi-faceted, mass-spectrometry strategy to identify a set of plasma biomarker candidates in fragile X syndrome. Although promising, independent replication studies are needed to confirm the validity and reproducibility of fluidic proteomics findings.

A breakout group co-chaired by Andrew Lockhart (GlaxoSmithKline, UK) and Andreas Jeromin (Nextgen Sciences Diagnostics, USA) was convened to identify and discuss technical obstacles and challenges in the validation of fluidic markers for molecular phenotyping and staging of brain disorders. Conflicting results from over a

decade of studies highlight the need to revisit basic principles. Defining the intended application of the biomarker (for example, will it be used for internal decision making, exploratory research, or as a diagnostic) will determine the rigor of method validation and assay documentation needed. Technical considerations for bioanalytical assays were discussed, including standardized sample collection, assays that are well-described and have good performance characteristics and accuracy, precision and reproducibility of the methods. An overarching issue was how to weigh the risk/benefit of investing in the time- and cost-intensive assay reagent and method development needed before the replication and verification of assay performance in well-controlled human studies. The group also discussed the need for an incentive structure to facilitate bioanalytical biomarker validation studies by investigators in the academic and biotechnology sectors.

Functional biomarkers: imaging and cognitive markers and considerations for validation

Functional imaging and cognitive biomarkers hold promise as sensitive indices for the early detection of abnormal circuit function in at-risk populations, for understanding disease mechanisms at the systems level, and for monitoring disease progression and response to treatment in brain disorders. Emilio Merlo-Pich (Hoffman La-Roche, Switzerland) described the use of task-based and resting-state functional magnetic resonance imaging (fMRI) as decision-making tools in the clinical development of novel drug candidates. He highlighted pharmacological MRI as a translational measure of a drug's pharmacodynamic action in the brain that can be used to guide dose selection in drug development. Mark Schmidt (Janssen Pharmaceuticals, Belgium) detailed the use of positron emission tomography (PET) imaging of glucose utilization and amyloid burden to monitor disease progression in AD, but cited sources of technical and biological variability (such as within-subject variability over time) that present challenges to the validation of PET imaging markers as treatment endpoints for clinical trials in AD and other disorders. Federica Agosta (San Raffaele Scientific Institute, Italy) reported the reliability of structural MRI and diffusion tensor imaging (DTI) to grade the extent of white and gray matter damage in MS and ALS, and the potential of resting-state fMRI to detect earlier changes in sensory motor function. Standardized assessments of cognition have the sensitivity for the early detection of functional abnormalities that precede the onset of disease. Keith Wesnes (Bracket, USA) described the use of computerized cognitive test batteries as a sensitive measure for the early detection of cognitive impairment in MCI. Jennifer Barnett (Cambridge Cognition, UK) described the use of cognitive tests as a

Table 1. Examples of consortia focused on enabling replication of brain biomarkers in multi-site studies

Consortia	Disorder	Protocols	Data analysis
BioMS-eu	MS	CSF collection, processing and biobanking	Standardized reporting
AddNeuroMed	AD, MCI	MRI acquisition MRI quality control	Automated analysis techniques
Parkinson's Progression Markers Initiative	PD	CSF and plasma collection and biobanking MRI, DTI acquisition	Standardized data collection and processing

AD, Alzheimer's disease; MCI, mild cognitive impairment; MS, multiple sclerosis; PD, Parkinson's disease. Charlotte Teunissen (VU Medical Center, Netherlands) reported on BioMS-eu, Simon Lovestone (Kings College London, UK) reported on AddNeuroMed, and Kenneth Marek (Institute for Neurodegenerative Disorders, USA) reported on the Parkinson's Progression Markers Initiative.

complement to imaging and fluidic markers of disease pathology. For ASD, a heterogeneous disorder for which there is a need of markers for early diagnosis, I described electrophysiological measures - resting-state activity and event-related potentials evoked by auditory and visual stimuli - that show promise as biomarkers in identifying infants at risk for ASD. Christine Ecker (Kings College London, UK) described an MRI-based pattern classification algorithm that, when combined with genetic risk factors, may be used to predict disease severity in individuals with ASD.

A breakout group co-chaired by Giovanni Frisoni (IRCCS Fatebenefratelli, Italy) and William Potter (National Institute of Mental Health, USA) focused on imaging technologies that are ready to be applied as biomarkers in multi-site studies of brain disorders. Relative to structural MRI quantification of hippocampal atrophy in AD, which has been qualified for use by the European Medicines Agency and the Food and Drug Administration as an enrichment and stratification marker in AD trials (Frisoni), amyloid PET imaging and advanced MRI technologies (such as resting-state connectivity fMRI and DTI) are at earlier stages of validation as biomarker tools. Collaborative efforts to standardize data acquisition, technical quality control and data analysis would speed the validation of these imaging modalities as fit-for-purpose biomarkers.

Collaborative efforts focused on standardization of biomarkers

Although many new biomarker findings were reported at the meeting, a critical roadblock to progress is marker

validation, determining whether biomarkers deliver on their intended use. Three examples of collaborative efforts to further standardization of protocols for sample collection, banking, data acquisition and biomarker development were highlighted (Table 1). Harkening back to a call by Lockhart for 'enterprise thinking' in biomarker discovery, the take-home message from this meeting is as follows. Integrated, collaborative efforts are needed to standardize a multi-modal set of biomarkers with dynamic range, optimize the methods, and conduct sufficiently powered, multi-site studies so that these tools progress rapidly to clinical qualification by regulatory agencies. Evolving technologies for fluid-based proteomics, cognitive batteries and functional imaging are enabling the identification of biomarkers as predictors of disease onset, and dynamic markers of disease severity and progression. It is now critical to set standards for validation in the field so that promising biomarkers can be applied in clinical trials and clinical practice.

Abbreviations

A β_{1-42} , amyloid- β_{1-42} ; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; ASD, autism spectrum disorder; CNS, central nervous system; CSF, cerebrospinal fluid; DTI, diffusion tensor imaging; fMRI, functional magnetic resonance imaging; MS, multiple sclerosis; PET, positron emission tomography.

Competing interests

The author declares that she has no competing interests.

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