What Are Biomarkers and Why Should We Develop Them?

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Disclosures

Positron Emission Tomography Imaging Biomarker Tracers: Development and Uses

National Institutes of Health
Alzheimer’s Disease Drug Discovery Foundation
ALS Association
Department of Defense
Objectives

• To define what a biomarker is and their importance in relation to pre-clinical and clinical studies relative to disease

• To inform on biomarker types, sampling variables and some key criteria

• To convey some examples of diagnostic, pharmacodynamic, prognostic and predictive biomarker driven clinical studies as related to Alzheimer’s disease
General Resources

Books


Papers

- Other disease specific biomarker review papers: NCBI PubMed
A biomarker (biological marker) is a biological observed quantitative measure that substitutes for and ideally predicts a clinically relevant endpoint or intermediate outcome that is more difficult to observe. Biomarker use should be for both pre-clinical and clinical studies.
Why Biomarkers?
The use of clinical biomarkers is easier and less expensive than direct measurement of the final clinical endpoint, and biomarkers are usually measured over a shorter time span.
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What does it measure and how does it quantify disease and changes?
Novel biomarker development requires a significant resource commitment to translate candidate markers into clinical assays. Consequently, it is imperative high quality candidates are selected early in a biomarker development program.

Califf (2018)
Biomarker Goals: Types

- **Diagnostic**: detects - confirms the presence of disease/condition, or identifies individual disease subtypes
- **Monitoring Pharmacodynamic/Response**: serially assessing disease status for evidence of an effect of a therapy
- **Predictive**: predicts individual or cohort favorable unfavorable response to therapy (responder/non-responder)
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- **Predictive**: predicts individual or cohort favorable unfavorable response to therapy (responder/non-responder)
- **Prognostic**: identifies the likelihood of a clinical event, disease recurrence or progression (differential disease outcomes)
- **Susceptibility/Risk**: Individuals for developing a disease not currently apparent with the disease
- **Safety**: measures likelihood of adverse effects from therapy
Biomarker Criteria & Disease Surrogate

The single most common and serious error in the evaluation of biomarkers is the assumption that a correlation between the measured level of a biomarker and a clinical outcome means that the biomarker constitutes a valid surrogate. In fact, for a biomarker to qualify as a surrogate, the biomarker must not only be correlated with the outcome, but the change in the biomarker must “explain” the change in the clinical outcome [statistical inference…], which can only be made with confidence if the observation is made in multiple therapies that all change the biomarker.

Califf (2018)
Some Biomarker Sampling

- Genomic – Proteomic: profiling
- Protein & nucleic acid, biochemical-
  Pharmacological: as target or surrogate
  - *in vivo*, minimally invasive tissue &
    blood – *imaging* scans, recordings
  - *in vitro assays*
    - fluids: blood, cerebral spinal fluid
      (CSF), saliva, mucous
    - cells: endoscopic, surgery
- Digital - sensor and personal device data
  (digital phenotypes) vs. traditional outcomes
Biomarker Functions

Disease Models
- Initial judicious selection
- animal, post-mortem tissue, cellular
- Direct or surrogate MOA
- Multiple biomarkers

Therapy Development
- Proof-of-concept
- Target engagement, theranostic
- Pharmacodynamic changes
- Dose-response, toxicology, pharmacokinetics, Adverse drug effects
- FDA Animal Rule
- IND & IRB package submissions
Biomarker Functions

**Pre-clinical**

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**Clinical**

**Disease**
- Correlated: symptoms vs. Other biomarkers
- Screening
- Diagnosis & definition
- Progression
- Trial cohorts (Inc./Exc. criteria)
- Adaptive biomarked trials

**Therapy Use**
- Prognostic indications
- Pharmacodynamic studies
- Dose-response studies
- Adverse drug reactions
- Precision medicine interventions
Biomarker Considerations

- Multiple quantitative biomarkers – greater measurement resolution vs. disease pathology heterogeneity
- Temporal disease changes – some markers good early, (initial onset, acute phase) others better later (latent phase or end stage), pathology changes
Biomarker Considerations

- Initially selected & validated pre-clinical biomarkers may not translate into clinical biomarkers – iterate if needed
- Bio-banking fluids and post-mortem tissues, animal models & patients – useful for biomarker discovery, more rapid validation, retrospective analyses – aids discovery
Example

Alzheimer’s Disease Biomarkers
Alzheimer’s Disease Biomarkers

• One of the best comprehensive examples of biomarker development for a disease
• Decades of efforts from the clinical and pre-clinical sides
• Biomarker Goal Types: diagnostic, PD monitoring, predictive, prognostic, susceptibility /risk, safety
• Allowing deeper disease understanding & new hypotheses tested
Alzheimer’s Disease Biomarkers

- Genomic profiling
- In vivo tissue evaluations vs. post-mortem data:
  - Imaging:
    - positron emission tomography (PET)
    - magnetic resonance (MR)
- In vitro: blood, CSF
- Digital: cognitive, physical activity, diet
Alzheimer’s Disease Biomarkers

• Imaging (ADNI & related consortia)
  • PET
    • Fluorodeoxyglucose (FDG)
    • A-beta
    • Tau
    • TSPO (neuroinflammation)
    • Synaptic vesicle glycoprotein 2A (SV2A, synaptic density)
    • Others
  • MR
    • Structural (volume changes)
    • Functional (connectivity)
    • Arterial Spin Labeling (metabolism)
    • Diffusion Tensor (DTI, white matter tracts)
    • Combinations & Others
Alzheimer’s Disease Biomarkers

• Blood & CSF Markers

  A-beta forms
  tau forms
  Neurodegeneration
  Inflammation
  Immune modulators
  Neurovascular
  Metabolism
  Oxidative stress
  Others
Some AD Biomarker Resources

• **General**

• **PET & MR Imaging**

• **CSF & Blood**
Diagnostic AD Biomarkers: Utilization


Targets of anti-A-beta drugs. MOAs of the main anti-amyloid drugs currently in Phase III trials.

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What existing or new biomarkers are needed for an early, prodromal (clinical asymptomatic) strategy?
AD Biomarkers: Utilization

Clinical Approach:
• Tripartite synapse integrity changes

PET Imaging
• Synaptic density, SV2A
• Circuits: NE, 5HT, DA, etc.
• Neuroinflammation, microglia TSPO and related
• Astrocyte targets

What existing or new biomarkers are needed for an early, prodromal (clinical asymptomatic) strategy?
Astrocyte Glutamate Transporter: PET Biomarker Target for Early Assessments

Bennaroch 2010

ADDf &
RIO PHARMACEUTICALS

EAAT2 PET Imaging Target
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