# Biomarker Development for TBI

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# Overview

- Biomarkers
  - Objectively measured characteristics indicating normal biological or pathogenic processes, or pharmacologic responses to a therapeutic intervention
- Clinical endpoints
  - Variables that reflect or characterize how a study subject in a clinical trial “feels, functions, or survives”
- Surrogate endpoints
  - Biomarkers that can be trusted to serve as stand-ins for clinical endpoints
  - Require solid scientific evidence (e.g., epidemiological, therapeutic, pathophysiological) that a biomarker consistently and accurately predicts a clinical outcome

Biomarkers Definition Working Group Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Therapeutics. 2001;69:89–95.

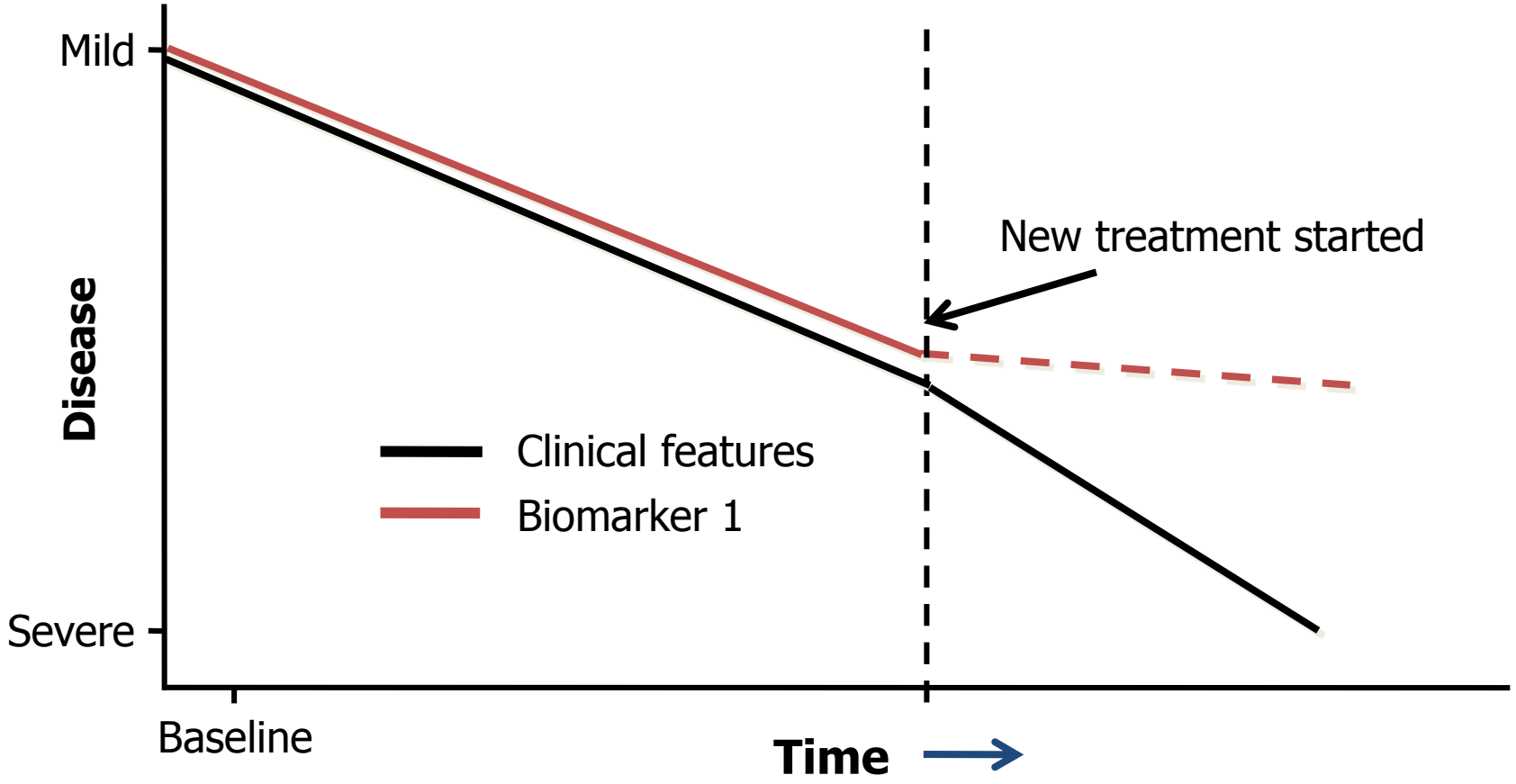
# Benefits of Biomarkers as Surrogate Endpoints

- Increase diagnostic accuracy/homogeneity of subjects in clinical trials for stratification and enrichment
- More accurate dosing and monitoring of treatments
- Provide researchers interim/early evidence about safety/efficacy of treatments
  - Reduce risk of harm to subjects
  - Allow researchers the opportunity to stop potentially ineffective or harmful interventions
  - Circumvent primary clinical endpoints, which may occur infrequently making their use in clinical trials impractical, or even unethical
- Shorten time to approval of new treatments, allowing effective treatments to reach target patient populations sooner

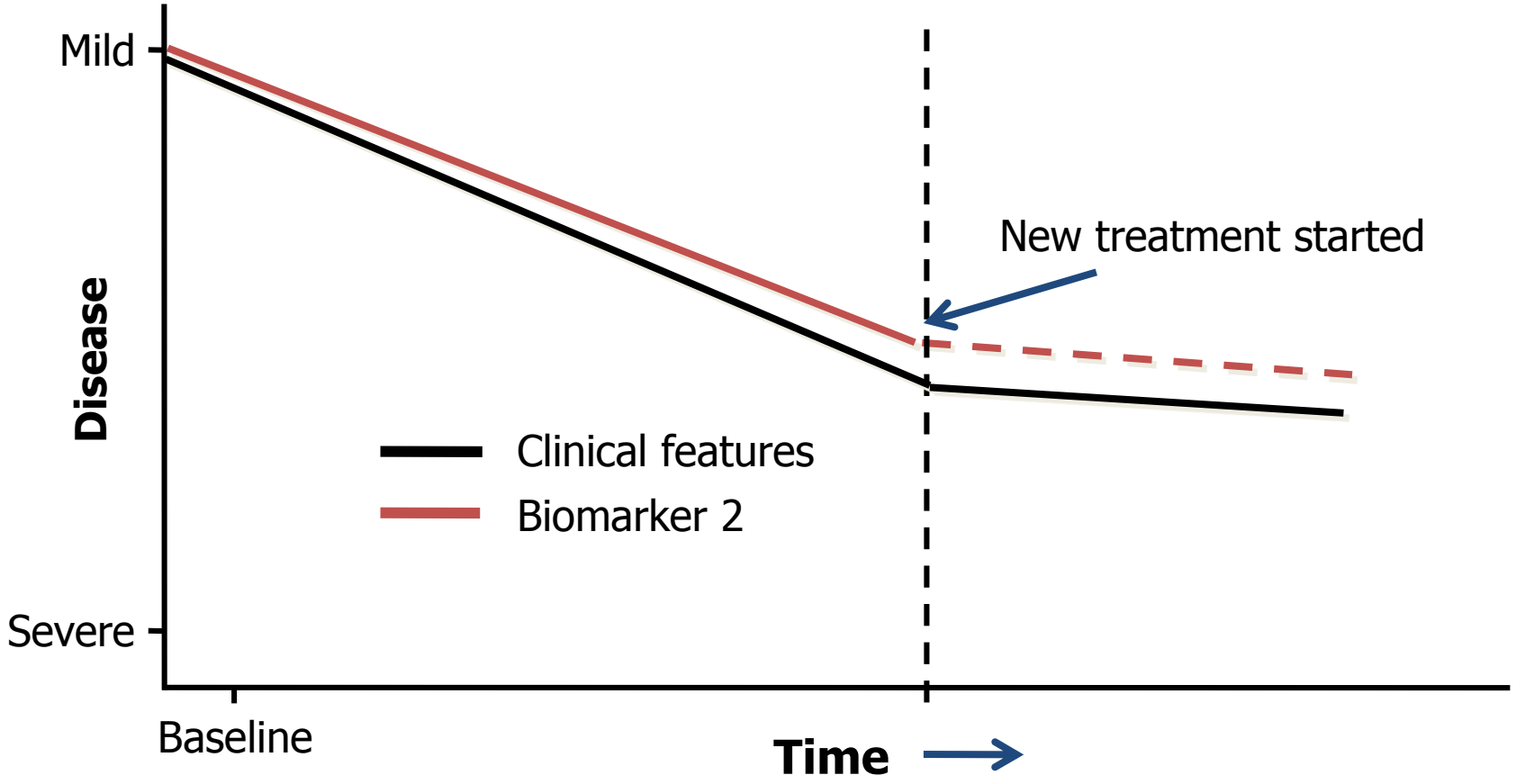
# Challenges to TBI Biomarker Development

- Variability in type, timing, and duration of injury
  - Acute vs. chronic, civilian vs. military
- Pathophysiological complexity of short-term and long-term injury
  - Multiple interrelated disease pathways may be involved
  - Biomarkers might be indirect signs of pathways that are not fundamental to the key disease processes
  - Variable blood brain barrier injury and the complex contribution of efflux via the glymphatic system represent special challenges to successful development of serum biomarkers of brain injury
- Even biomarkers statistically validated as surrogates for a given clinical endpoint may not actually be part of the pathophysiological pathway that results in that endpoint
- Need for proactive involvement and guidance from stakeholders, including FDA, federal funding agencies, and TBI biotechnology and scientific communities

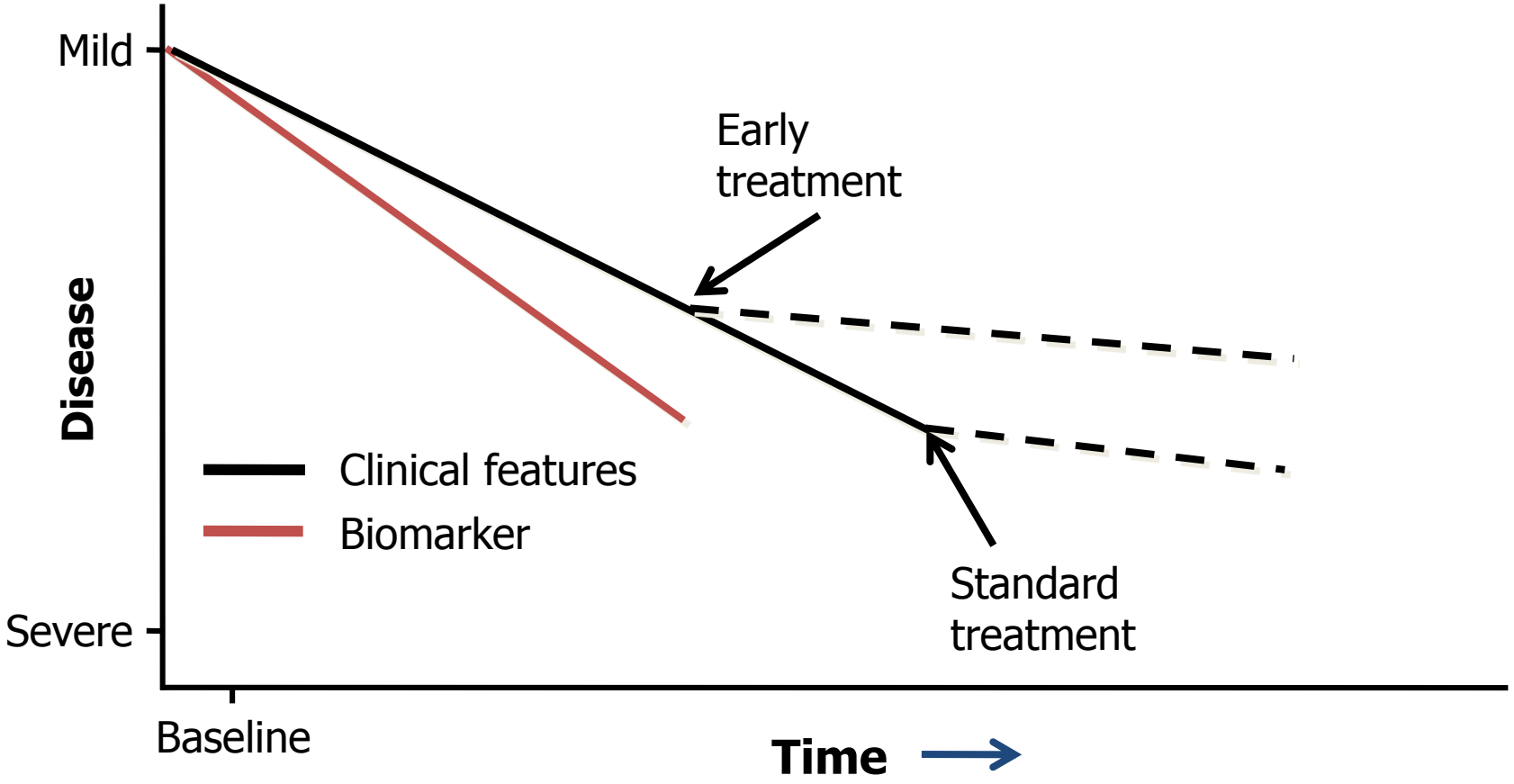
# Biomarker & Clinical Endpoint Example 1



# Biomarker & Clinical Endpoint Example 2



# Biomarker May Signal Need for Early Treatment that Improves Outcome



# Why Treatment/Biomarker Development Fails

- Overemphasis on singular disease mechanisms
  - e.g., amyloid in Alzheimer's drug development
- Treatment trials too late or too early in disease progression
- Individuals/research groups championing only their target(s) of interest
- Over-reliance on "consensus science"
  - Science requires only one investigator who produces verifiable and reproducible results
  - "…it is the consensus in the field" – used as a justification for shutting down ideas not associated with beliefs
- Lack of clarity/education on translational pathways from bench to bedside to curbside
- Inefficient "interfacing" between academia and industry

Barrio JR. Consensus science and the peer review. Molecular Imaging and Biology. 2009;11:294.

# How Biomarkers Might Facilitate TBI Therapy Development

- Objectively quantify injury severity
- Predict patient outcome/risk for later neurodegeneration
- Identify injury mechanisms/therapeutic targets
- Assess time course of pathobiological responses to TBI and therapeutic windows
- Aid in assessment of therapeutic efficacy
- Monitor recovery of function or decline rate
- Aid in assessment of CNS drug toxicity

# Examples of Potential Resources

- Operation Brain Trauma Therapy (OBTT)
  - Multicenter preclinical drug-screening consortium that screens TBI therapies
- TBI Endpoints Development (TED)
  - Establish multicenter team to ID/validate assessments/outcomes/biomarkers
- Post-hoc Analyses of Data from Ongoing/Previous Research
  - Biomarkers of Injury and Outcome in ProTECT III (BIO-ProTECT III): collected during failed progesterone trial
  - ALERT-TBI (Banyan Biomarkers, Inc): multicenter pivotal trial seeking to validate clinical utility of UCH-L1 and GFAP for acute TBI diagnosis
  - TRACK-TBI Multicenter Initiative – test/refine biomarkers in TBI
  - ADNI DoD – examines connections between TBI and PTSD
- Biomarkers Developed for Other Disease Processes
  - Alzheimer's, inflammation (multiple sclerosis), Parkinson's

# Future Pathways

- Create and ensure funding for large multi-site/inter-disciplinary teams (e.g., ADNI [Alzheimer's Disease Neuroimaging Initiative])
- Diversify research pathways and target portfolios
- Determine priority disease states/stages for treatment/biomarker development
- Expand available funding for individual projects (e.g., R01s) to foster new ideas/strategies
- Base funding and strategic planning on broad and dispassionate interpretation of the evidence rather than belief systems and research areas of personal interest
- Foster team-work among diverse disciplines
- Initiate trials using biomarkers developed in related areas (e.g., Alzheimer's/stroke)
- Engage relevant stakeholders and provide incentives for collaboration

# Immediate Action Items

- Identify champion(s) vested with the authority and resources to create an effective partnership with the FDA, which would name specific participants within the FDA and their roles and responsibilities
- The mission of this partnership would be to articulate FDA sanctioned pathways to use biomarkers to accelerate TBI drug development, clinical trial design and assessment of neurotoxicity
- FDA guidance would include defining different regulatory steps for different biomarker applications (e.g., diagnostic vs. surrogate markers)
- Once a framework for these pathways has been established, a broader discussion with stakeholders can take place, including the identification of needed resources and timelines