**When is a Biomarker Ready for a Clinical Trial? 2024 Reference Sheet**

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**Definitions**

* Biomarker (per FDA BEST Resource)1 **– “**A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or intervention, including therapeutic interventions. Biomarkers may include molecular, histologic, radiographic, or physiologic characteristics. A biomarker is not a measure of how an individual feels, functions, or survives.”
* In Drug Development: Pharmacokinetic (PK) vs. Pharmacodynamic (PD)2
  + *Pharmacokinetics* – measurement of drug concentration over time (biomarkers can predict or indirectly assess PK when it cannot be measured directly)
  + *Pharmacodynamic* (PD) biomarkers are molecular indicators of drug effect on the target in an organism (*i.e*., based on the mechanism of action)
* In Clinical Trials: Integral vs. Integrated vs. Exploratory
  + NCI terms (for funding prioritization) recommended for randomized phase 2 or 3 trials (<https://www.cancer.gov/about-nci/organization/ccct/funding/biqsfp/biomarker-study-eval-guide.pdf>)
  + *Integral* biomarkers*:* biomarkers that are essential to the design of a specific trial and required for all patients; supports a trial hypothesis; ex: tests for eligibility, randomization, stratification, or treatment assignment
  + *Integrated* biomarkers: included for validation of potential future integral biomarkers; testing a hypothesis based on previously generated data using a preplanned statistical design; included as a secondary objective
  + *Exploratory* biomarkers: hypothesis-generating; may not be collected on all patients
* Association with patient outcomes: Prognostic vs. Predictive (vs. both?)
  + *Prognostic* biomarkers associate with clinical outcomes independently of treatment
  + *Predictive* biomarkers are linked to treatment responses, often directly related to the mechanism of action, and statistically requires a test of interaction using biomarker and outcome data from patients with and without treatment
  + Note: particularly for immunotherapy biomarkers, considerable *overlap* between predictive and prognostic signals may reduce the value of this distinction.3

* Biomarker Test Evaluation: Analytic Validity, Clinical Validity, and Clinical Utility1
  + *Analytic validity* –establishes performance characteristics of a test (*e.g.,* sensitivity, specificity, accuracy, and precision)
  + *Clinical validity* –establishes that the test identifies/measures/predicts the clinical/biological state of interest
  + *Clinical utility* – the determination that the test will lead to improvement in health outcomes or provide useful information about the diagnosis, treatment, management, or prevention of a disease

**Biomarker Applications and Initiatives**

* Biomarker Benefits
  + Robust biomarkers increase likelihood of a positive clinical trial by enriching for patients likely to respond to therapy (🡪 increased probability of regulatory approval and patient access to new/effective treatment options)
  + Clinical trials are a gatekeeper for translating biomarker targets into clinically available tests (via prospective validation in the context of a therapeutic application)
* Selection, Stratification, Monitoring, Endpoints
  + Patient Selection ex: the PD-L1 IHC saga4 (different assays, interpretation methods and thresholds leading to different clinical trial/regulatory outcomes)
  + Patient stratification ex:
  + Monitoring ex:
  + Endpoint ex: on-treatment biopsies for pharmacodynamics5,6 (e.g., most effective dose vs. maximum tolerated dose)

Relevant Initiatives:

* *(FDA) Project Pragmatica* seeks to improve the operational efficiency and patient centricity of clinical trials by enhancing the flexibility of trial design and aligning trials more closely with standards of routine clinical practice.

(<https://www.fda.gov/about-fda/oncology-center-excellence/project-pragmatica>)

* *(FDA) Project Optimus* focuses on modernizing practises for optimal dosing of novel therapies based on consideration of biological efficacy as well as safety and tolerability. (<https://www.fda.gov/about-fda/oncology-center-excellence/project-optimus>)
* (SITC) *Essential biomarkers for early phase immunotherapy clinical trials***7** – conensus-based recommendations for standardizing essential biomarker data collection and reporting across early phase immunotherapy clinical trials with plans for regular updates.

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