CLINICAL TRIALS AND REGULATORY AFFAIRS

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WHAT IS A BIOMARKER?

NIH Biomarkers Definition Working Group:

> "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention."

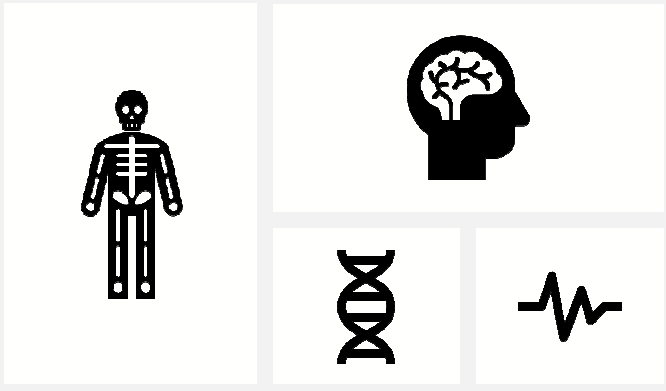
International Programme on Chemical Safety:

> "any substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease"

Can be an image-based feature, using MRI or PET-CT;

Can be a molecular feature, like a SNP or CNV in the genome or a protein expression;

Can be a physical measurement, like heart rate or an EEG.

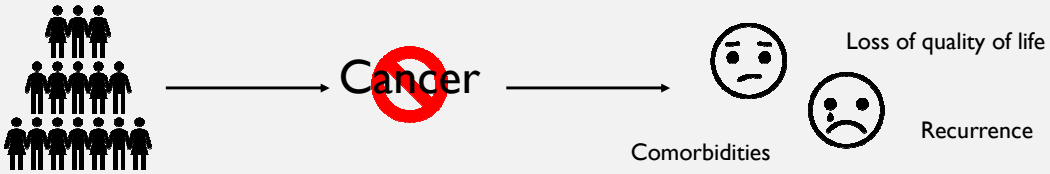


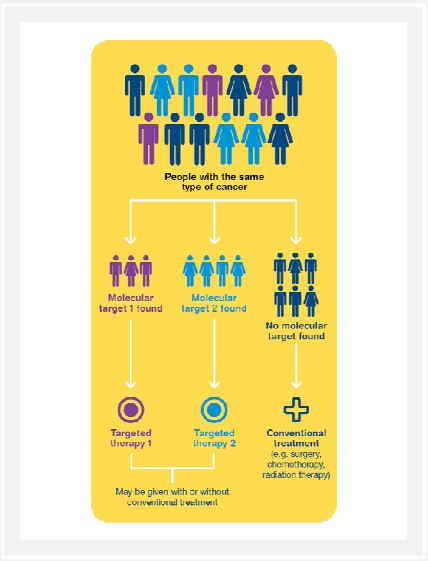
BIOMARKERS VS. SYMPTOMS

- Biomarkers need to be completely objective measurements that are reliably and reproducibly detected
- Symptoms, by contrast, are self-reported by the patient and are subjective – a symptom cannot be a biomarker
- Sometimes, a biomarker will cause no outward symptoms, or will not affect the patient's overall perception of well-being
- However; symptoms are often phenotypic representations of an observable biomarker – sometimes the symptom can lead you to the marker!

WHY ARE BIOMARKERS NEEDED?

- Classical drug trials relied on an "all comers" approach, enrolling anyone who had a particular diagnosis to join a trial – largely because drugs weren't so targeted
  - Cisplatin, etoposide, vincristine – all early chemotherapeutic drugs with broad, cytotoxic effects
  - In theory, anyone who had cancer, and thereby uncontrolled cell growth, would "respond" to these cytotoxic agents – but at what cost?





https://www.cancercouncil.com.au/cancer-information/cancer-treatment/targeted-therapy/who-can-get-targeted-therapy/

WHY ARE BIOMARKERS NEEDED?

Chemotherapy has continued to advance and become highly targeted – attacks the tumor and spares the patient, in ideal circumstances

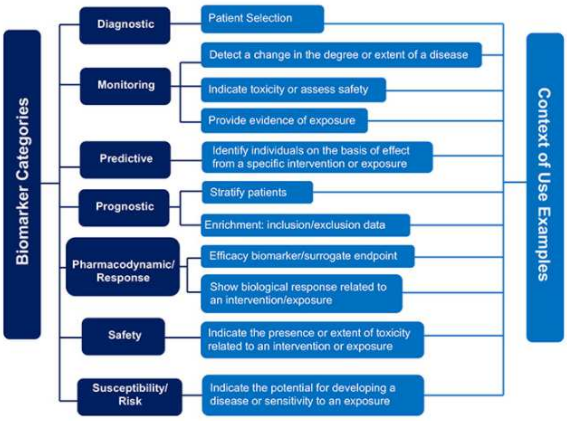
- Preferentially acts on mutant proteins only present in the cancer, or targets proteins that are differentially expressed in tumor vs. normal tissue

But now you need to know if you possess the mutation or differentially expressed target in your specific tumor – the biomarker assessment

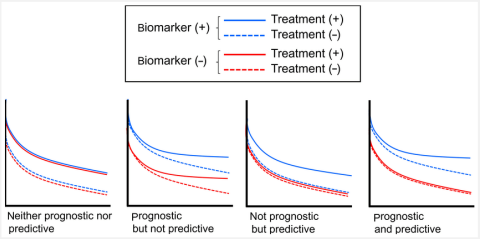
This is the route to PERSONALIZED MEDICINE

TYPES OF BIOMARKERS

BEST Biomarker Category and Examples of Corresponding Drug Development Uses



https://www.fda.gov/drugs/biomarker-qualification-program/context-use



Diagnostic biomarkers = identify the pathology

- Example; fasting blood glucose >100 mg/dl is diagnostic for diabetes mellitus

Prognostic biomarkers = identify outcome **independent** of therapy

- Example; Gleason scoring of a prostate cancer, or BRCA germline mutation

Predictive biomarkers = identify the most beneficial treatment

- Example; ALK alterations in NSCLC indicate response to crizotinib

Mukohara, Toru. (2015). PI3K mutations in breast cancer: Prognostic and therapeutic implications. Breast cancer (Dove Medical Press). 7. 111-23. 10.2147/BCTT.S60696.

BIOMARKER DETECTION AND USE IN DRUG DEVELOPMENT

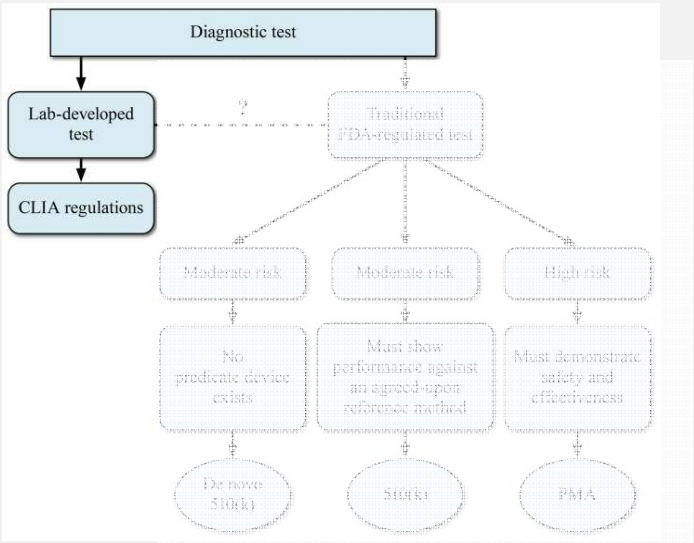
Genomic and suggested biomarker evaluation parameters.

Analytical validity	Reproducibility; is the test accurate?
Clinical validity	Are the results medically meaningful; can a biomarker distinguish one group from another in a meaningful manner?
Clinical utility	Does a test improve health care; will the results of a test change outcomes?
Other (cost-effectiveness, psychological implications, ethical implications)	Is there value added or cost saved by knowing the results? Do we have a treatment or risk reduction strategy to implement based on results?

Adapted from Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Initiative[30] with modifications.

- **Reliable** – if a test is being used for trial enrollment, it should perform the same way in all trial participants
- **Reproducible** – the test should be able to be repeated if needed, and should have reproducible performance on individual samples
- **Accessible** – the test should be as fast as possible, use an easy to obtain sample input, and should be affordable
- **Sensitive and Specific** – the test should reliably detect the analyte if it is present, and render a negative if the analyte is not present

REGULATORY APPROVAL

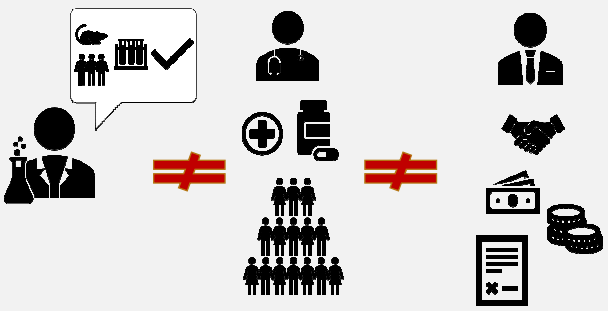


Pant, Saumya et al. *Frontiers in oncology* vol. 4 78. 17 Apr. 2014, doi:10.3389/fonc.2014.00078

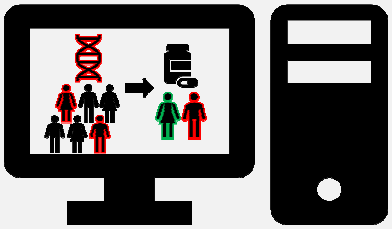
CLIA-CERTIFIED LABORATORY TESTING

BEFORE WE DECIDE TO DEVELOP/LAUNCH AN LDT: THREE MAIN QUESTIONS

1. What is the clinical incidence of the biomarker/patient population size?
2. Will the use of the biomarker change/improve treatment or outcomes for patients?
3. Will payors cover the testing?



(OPTIONAL) INITIAL CLINICAL VALIDATION - IN SILICO



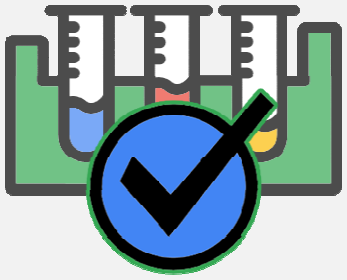
Diagnostic biomarker detected and identified

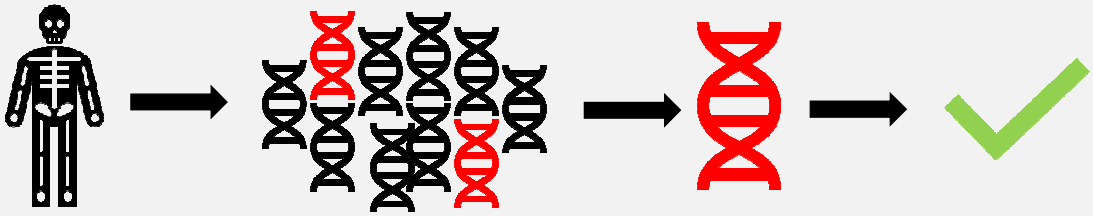
Biomarker-directed treatment initiated

Patient outcomes improved?

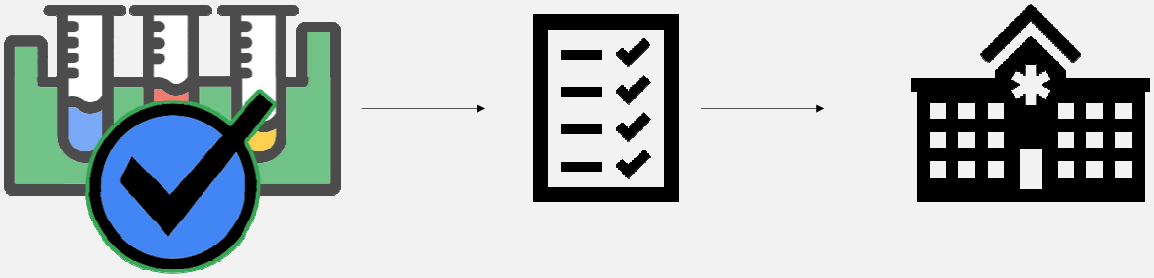
ANALYTICAL VALIDATION

- Sensitivity
- Specificity
- Positive predictive value (PPV)
- Negative predictive value (NPV)
- False-positive rate
- False-negative rate
- Limit-of-Detection (LoD)





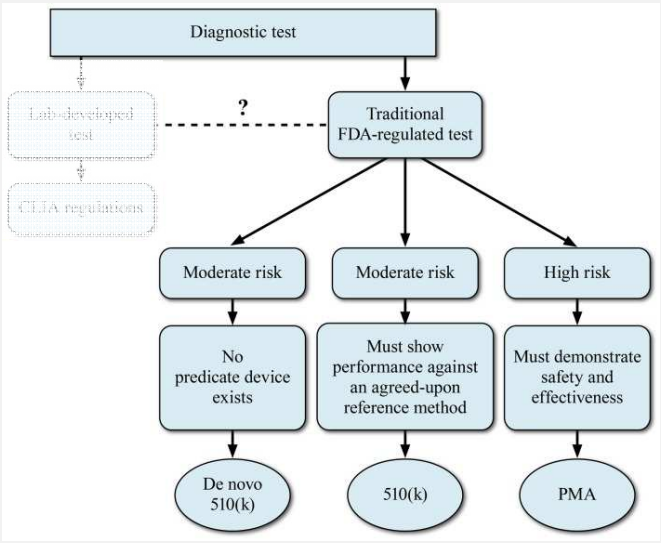
LDT LAUNCH



Analytical validity? | Signed validation report | Test launched in clinic

Clinical validity? OPTIONAL!
But of great interest to PAYORS

REGULATORY APPROVAL



Pant, Saumya et al. *Frontiers in oncology* vol. 4 78. 17 Apr. 2014, doi:10.3389/fonc.2014.00078

APPROVAL PATHWAYS

Intended for low- to moderate-risk devices (class I and II) that do not have a substantially equivalent predicate device.

Two ways to do this:

1) Submit a 510(k), receive "not substantially equivalent" determination from FDA, then request De Novo
2) Determine there is no predicate device and request De Novo without first submitting 510(k)

CLINICAL INVESTIGATION REQUIREMENTS

- Laboratory must be certified – at least CLIA, plus GCLP, CAP, ISO, NYS
- Personnel must be competent
  - Doctoral level staff must have appropriate licensures and credentials
  - Technologists must have documented training and competencies on file
- Assay must be proficiency tested
- Standard Operating Procedures must be up-to-date and electronically stored
- All trial documentation should be readily accessible and up-to-date

CLINICAL ENDPOINTS

- Biomarkers are often **surrogate endpoints** that indirectly indicate the likelihood or incidence of a **clinical endpoint:**

Examples of surrogate endpoints and clinical endpoints.

Disease	Surrogate Endpoints	Clinical Endpoints
Hypertension	Blood pressure	Stroke
Dyslipidemia	Cholesterol, LDL	Coronary artery disease
Diabetes	Glycosylated hemoglobin (HbA1c)	Retinopathy, nephropathy, neuropathy, heart disease
Glaucoma	Intraocular pressure	Loss of vision
Cancer	Biomarkers Tumor shrinkage, Response rate	Progression-Free Survival Overall Survival

Clin Cancer Res. 2008 Oct 1; 14(19): 5967–5976. doi: 10.1158/1078-0432.CCR-07-4535

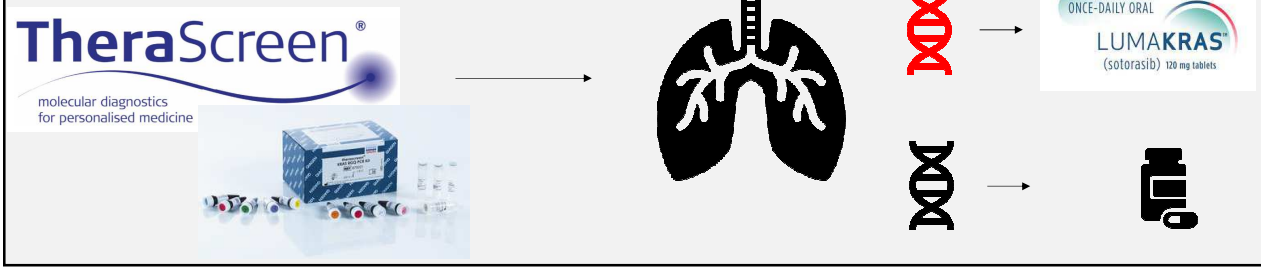
WHAT MAKES A GOOD CLINICAL ENDPOINT?

- Clinical endpoints have historically been black-and-white
  - Overall survival
  - Progression-free survival
  - Tumor size reduction
- But what about **Real-World Evidence**?
  - Mine medical records and other databases for additional information – side effects, co-morbidities, quality of life measures (mental health, physical health, disabilities, etc.)
  - Allows collection of endpoints OUTSIDE of the trial scope – can assess additional variables that cannot possibly be accounted for systematically in the trial

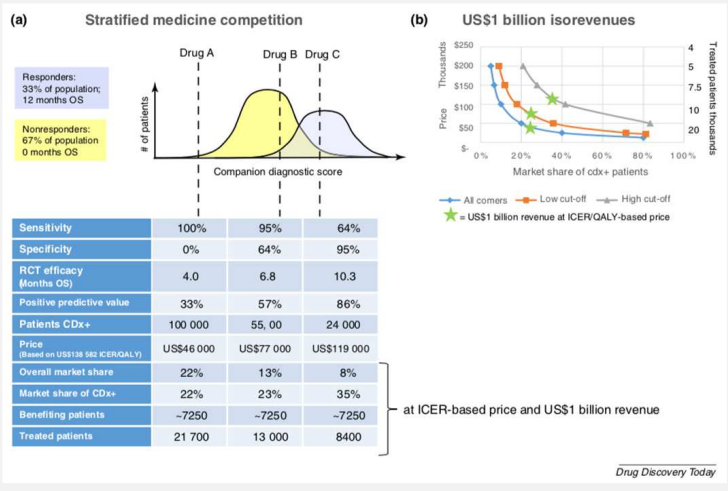
Figure 1. Disparate real world data sets must be fully integrated together to generate effective real world evidence.

WHAT ABOUT COMPANION DIAGNOSTICS?

- Allows for the simultaneous evaluation of a diagnostic test with a drug or treatment – the diagnostic test is used to enroll patients into the trial's treatment arms
- If approved, the device becomes the on-label diagnostic test to indicate whether a patient is eligible for treatment with that therapy

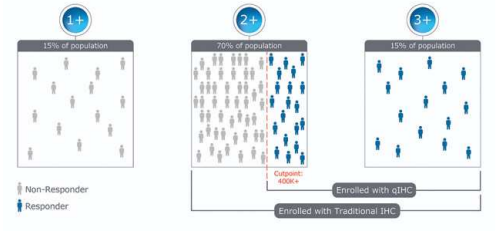


BENEFITS OF CDX TRIALS



Sensitivity	100%	95%	64%
Specificity	0%	64%	95%
RCT efficacy (Months OS)	4.0	6.8	10.3
Positive predictive value	33%	57%	86%
Patients CDx+	100 000	55, 00	24 000
Price (Based on US$138 582 ICER/QALY)	US$46 000	US$77 000	US$119 000
Overall market share	22%	13%	8%
Market share of CDx+	22%	23%	35%
Benefiting patients	~7250	~7250	~7250
Treated patients	21 700	13 000	8400

at ICER-based price and US$1 billion revenue



Trusheim and Berndt Drug Discovery Today 2015 20;12

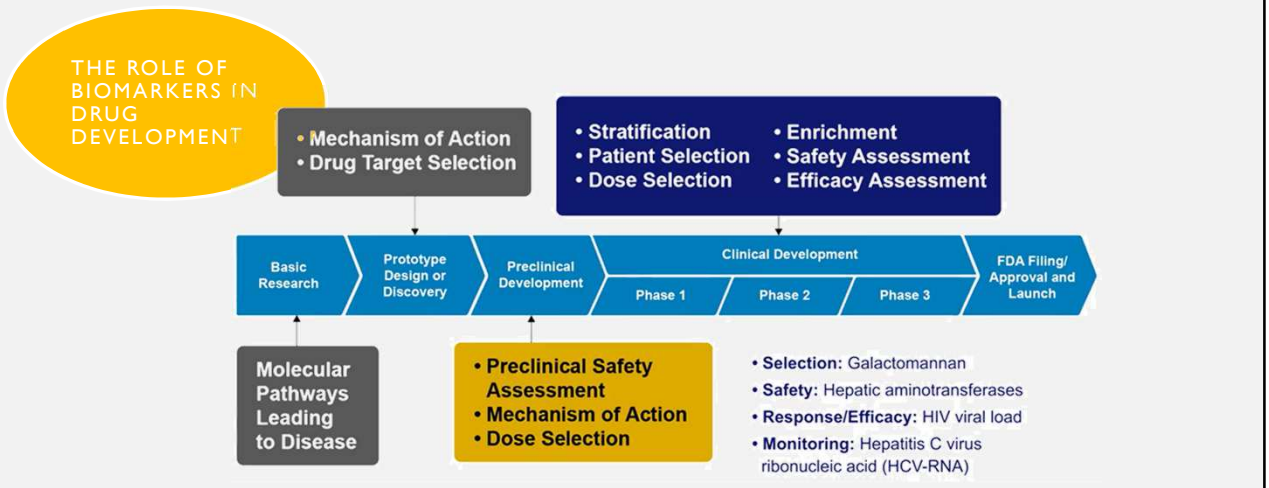
BIOMARKER COMPANION DIAGNOSTICS

By its very definition, for a companion diagnostic to be an **essential** part of safe and effective drug use it needs to be accessible

i. The nature of the marker:
- its concentration
- the sample type
- its stability

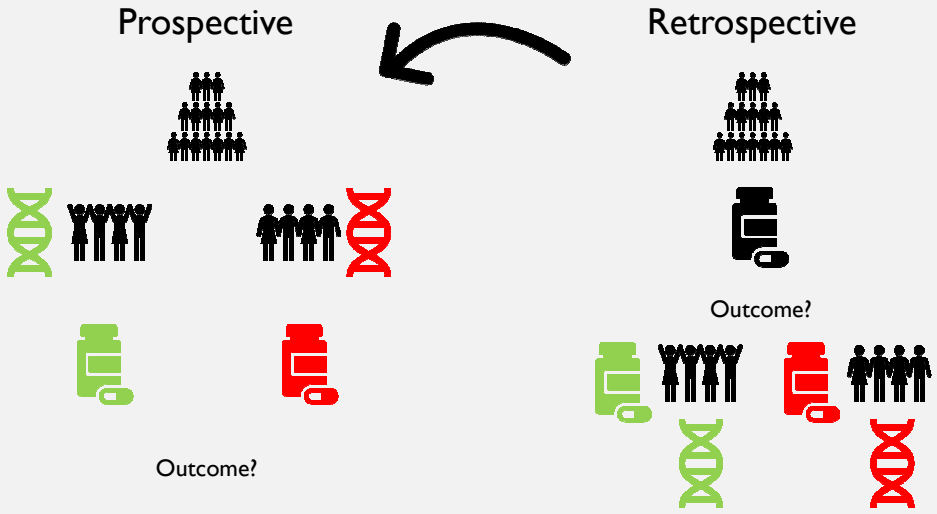
ii. What is the required turnaround time of the result:
- minutes?
- same day?
- one to two weeks?

iii. What is the coverage of this testing from a financial perspective?
- niche testing?
- are there existing ways to measure this that are covered?
- is the technology very expensive to deploy?



https://www.fda.gov/drugs/biomarker-qualification-program/about-biomarkers-and-qualification

PROSPECTIVE VS. RETROSPECTIVE CDX/BIOMARKER-DRIVEN TRIALS



HOW TO DESIGN CDX/BIOMARKER-DRIVEN TRIALS

Criteria for choice of design for initial marker validation trials.

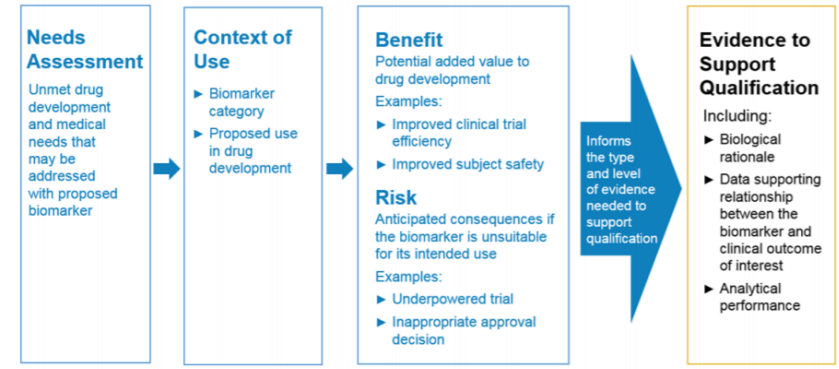
Criteria	Design		
	Enrichment	Allcomers	Adaptive
Preliminary evidence			
Strongly suggest benefit in marker-defined subgroups.	Optimal	Not recommended	Appropriate (assess multiple treatments/biomarker subgroups)
Uncertain about benefit in overall population versus marker-defined subgroups	Not recommended	Appropriate	Appropriate (learn and adapt as the trial proceeds)
Assay reproducibility and validity			
Excellent (high concordance between local and central testing; commercially available kits, and so forth)	Required	Not recommended	Required
Questionable	Not recommended	Appropriate	Not applicable
Turnaround times			
Rapid (2–3 days; without causing delay in the start of therapy)	Optimal	Optimal	Optimal
Slow to modest (1 week or more)	Not recommended	Appropriate (retrospective marker subgroup assessment)	Appropriate in some cases
Marker prevalence			
Low (<20%)	Optimal	Not recommended	Appropriate
Moderate (20–50%)	Appropriate	Appropriate (stratified by marker status)	Appropriate
High (>50%)	Appropriate	Appropriate	Appropriate

Clin Investig (Lond). 2011 Dec; 1(12): 1629–1636. doi: 10.4155/CLI.11.152

"Table 1 lists some of the key considerations when deciding between enrichment versus allcomers versus adaptive designs in a Phase II setting. The four main components include the marker prevalence, strength of the preliminary evidence, the assay reliability and validity and turnaround times for marker assessment."

FINAL QUALIFICATION OF A BIOMARKER

Figure 1: Evidentiary Framework



Key difference between IVD and LDT: **CLINICAL VALIDITY AND UTILITY!!**

https://www.fda.gov/media/119271/download