Role of biomarkers in drug development

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Disclaimers

- Views expressed in this presentation are those of the speaker and do not necessarily represent an official FDA position

Overview

- Types of biomarkers
- Biomarker development process
- Surrogate endpoints – value and limitations

BEST Resource: Biomarkers, EndpointS, and Other Tools

- A glossary of terminology and uses of biomarkers and endpoints in basic biomedical research, medical product development, and clinical care
- Created by the NIH-FDA Biomarker Working Group
- Publicly available at http://www.ncbi.nlm.nih.gov/books/NBK326791/
- BEST harmonizes terms and definitions and addresses nuances of usage and interpretation among various stakeholders, including:

- Biomedical scientists
- Translational and clinical researchers
- Medical product developers
- Patient/disease advocacy groups
- Government officials
- Clinicians

Biomarker: definition

"A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. *Molecular, histologic, radiographic, or physiologic characteristics* are types of biomarkers."

BEST (Biomarkers, EndpointS, and other Tools) Classification: Range of Biomarker Types

- **Susceptibility / risk biomarker**
- **Diagnostic biomarker**
- **Prognostic biomarker**
- **Monitoring biomarker**

Measures of disease presence and status

- **Predictive biomarker**
- **Pharmacodynamic/Response biomarker – including surrogate endpoints**
- **Safety biomarker**

Measure aspects of response to treatment

CONSIDERATIONS FOR BIOMARKER UTILITY

Context of Use (COU): 1) BEST biomarker category and 2) how the biomarker impacts the clinical trial or drug development program

What question is the biomarker intended to address. Examples include:

- Inclusion/exclusion criteria for prognostic or predictive enrichment?
- Alter treatment allocation based on biomarker status?
- Result in cessation of a patient's participation in a clinical trial because of safety concern?
- Result in adaptation of the clinical trial design?
- Establish proof of concept for patient population of interest?
- Support clinical dose selection for first in human or Phase 3 studies?
- Evaluate treatment response (e.g. pharmacodynamic effect)?
- **Support regulatory acceptability of a surrogate endpoint for accelerated or traditional approval?**

"Total Kidney Volume, measured at baseline, is a prognostic enrichment biomarker to select patients with ADPKD at high risk for a *progressive decline* in renal function (defined as a confirmed 30% decline in the patient's estimated glomerular filtration rate (eGFR)) for inclusion in interventional clinical trials. This biomarker may be used in combination with the patient's age and baseline eGFR as an enrichment factor in these trials."[1]

[1] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM458483.pdf

ANALYTICAL ASSAY AND CLINICAL VALIDATION CONSIDERATIONS IN BIOMARKER QUALIFICATION

FDA

The Specific Context of Use for a Biomarker Drives the Extent of Evidence Needed for Qualification

Analytical Validation

(establish performance and acceptance characteristics of the biomarker assay)

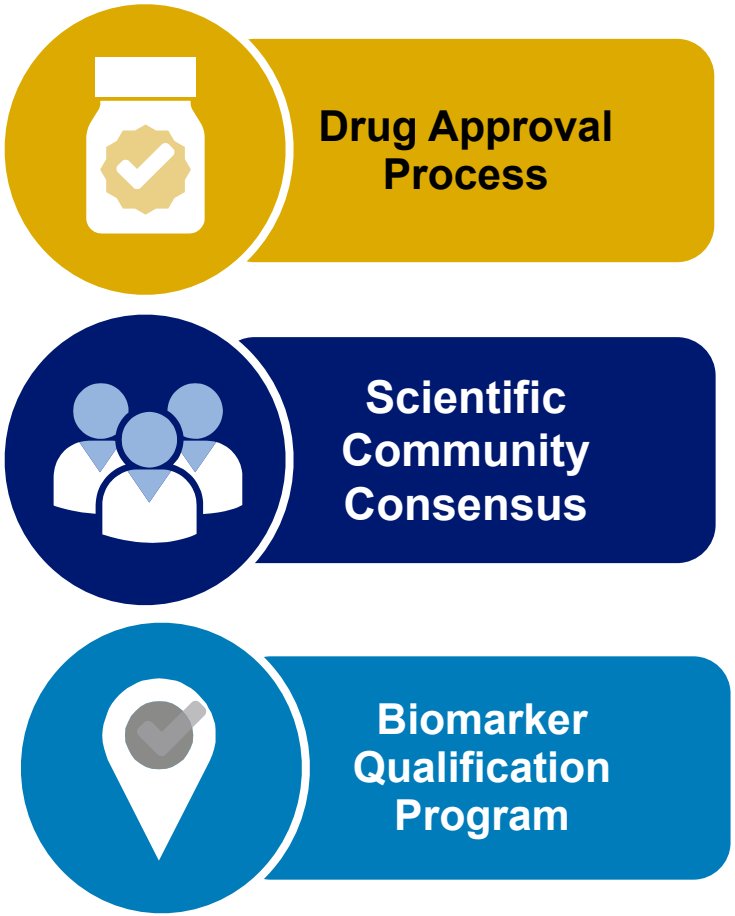
- Reference Ranges/ Decision Points
- Pre-Analytical and Assay Performance Characteristics
- Analytical Rigor/ Reproducibility
- Sample Handling/ Stability

Clinical Validation

(establish that the biomarker acceptably identifies, measures, or predicts the concept of interest)

- Study Design Acceptability
- Clinical Meaningfulness/ Decision Points
- Benefit/Risk Assessment

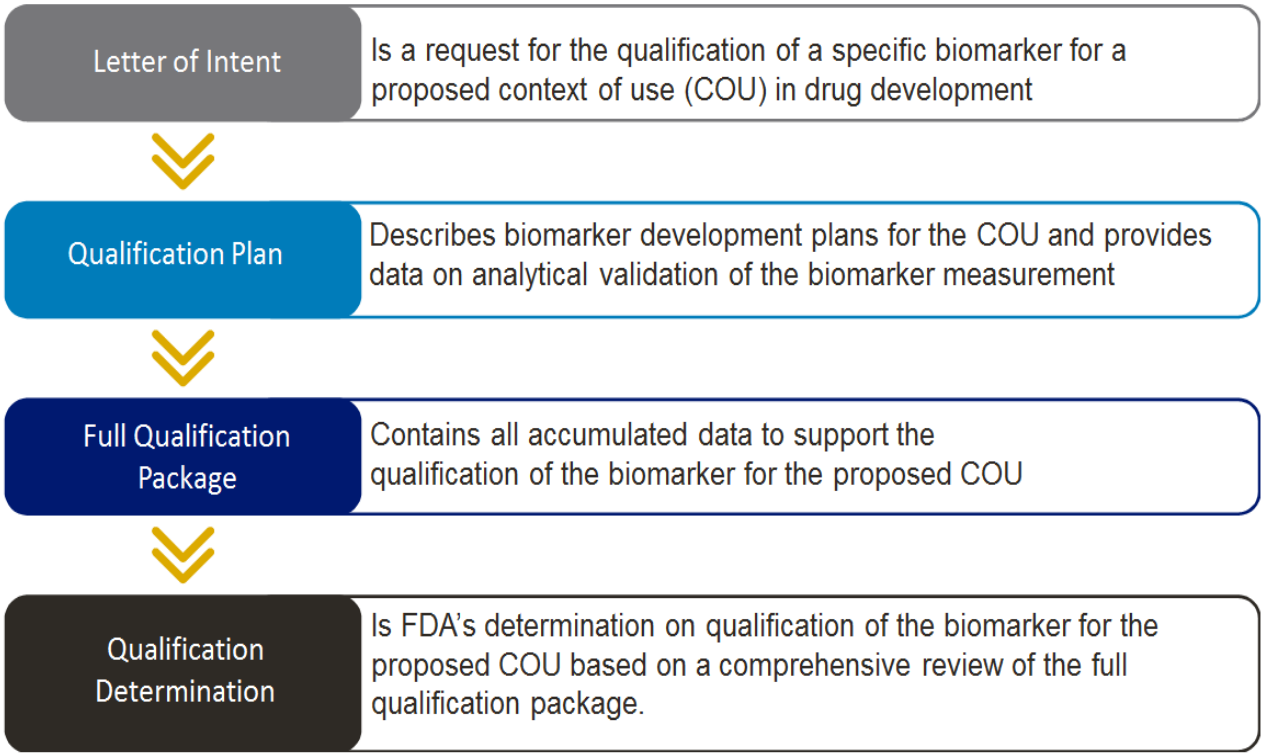
BIOMARKER INTEGRATION INTO DRUG DEVELOPMENT



Note: These pathways do not exist in isolation and many times parallel efforts are underway within or between pathways. All share common core concepts, are data-driven, and involve regulatory assessment and outcomes based on the available data.

Facilitating Biomarker Development: Strategies for Scientific Communication, Pathway Prioritization, Data-Sharing, and Stakeholder Collaboration; Published June 2016, Duke-Margolis Center for Health Policy

Biomarker Qualification Process



BEST (Biomarkers, EndpointS, and other Tools)
Classification: *Pharmacodynamic / Response BMs*

To support approval, FDA expects substantial evidence of effectiveness – that shows that a drug improves meaningful clinical outcomes: how a patient ***feels, functions, or survives***

- A **validated surrogate endpoint**: accepted by FDA that the effect on the biomarker *predicts* a specific clinical outcome. Validated endpoints have strong and diverse evidence supporting the relationship of the BM and the outcome

- A **"reasonably likely" surrogate endpoint**: an endpoint supported by strong mechanistic and/or epidemiologic rationale such that an effect on the surrogate endpoint is *expected* to be correlated with a clinical benefit, but not yet reaching the standard for validation.

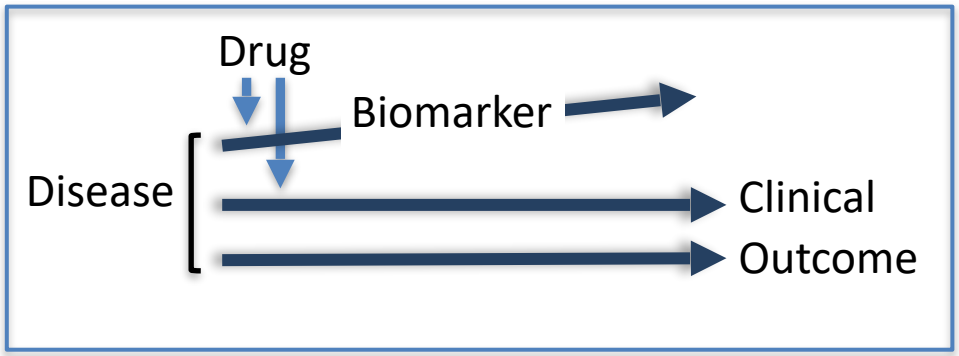
The limitations of surrogate endpoints

- Not a direct measure of how a patient *feels, functions or survives*
- Intended to reflect and predict clinical benefit not measure the outcome
- With a surrogate endpoint, the benefit / risk assessment therefore must be based upon *assumptions / predictions of benefit*
  - Translating the extent of clinical benefit from an *indirect* measure, and also using a *limited* dataset on risk to assess harms
  - Challenging when a drug shows clear effects on a *surrogate endpoint* – but also has safety issues
- And biomarkers may *fail* to predict clinical benefit

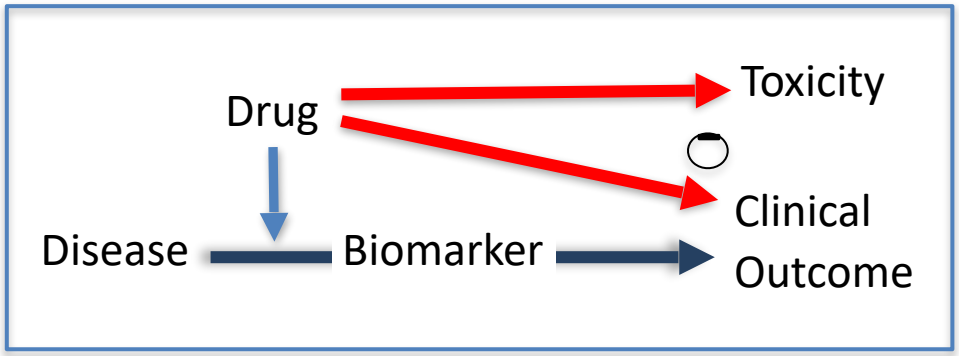
The limitations of surrogate endpoints

Surrogate on **causal pathway** modulated by drug

Surrogate ***not*** **on causal pathway** by which drug leads to benefit, or **multiple pathways of leading to clinical outcome,** BM *may or may* not reflect key pathways

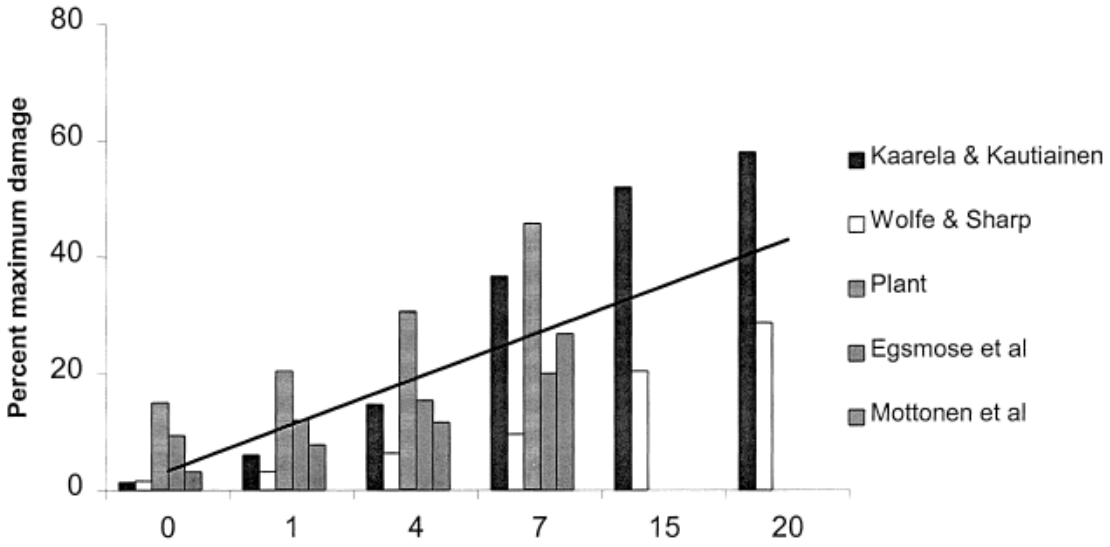


Drug may induce **adverse effects on desired clinical outcome** through a pathway *not reflected* by BM, or may lead to other toxicities = BM does not reflect benefit (or risk)

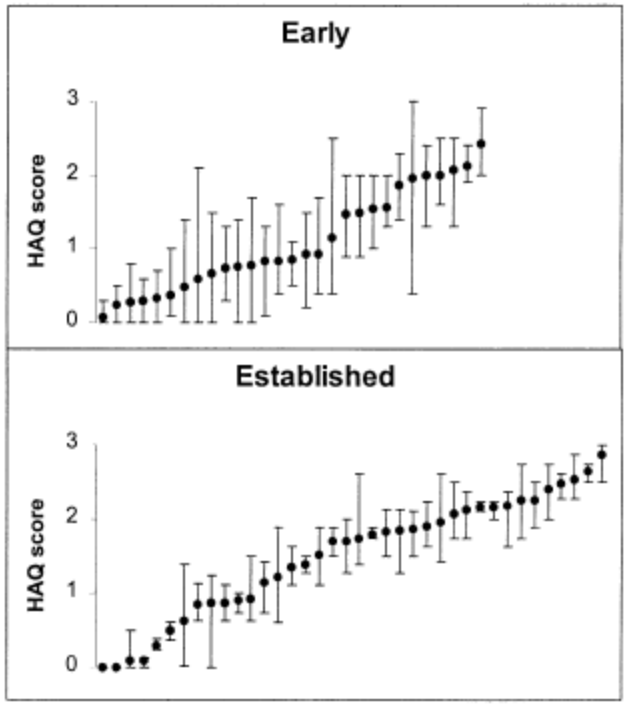


After Fleming Statistics in Medicine 2012

Challenges in biomarker clinical validation: Radiographic Progression in RA



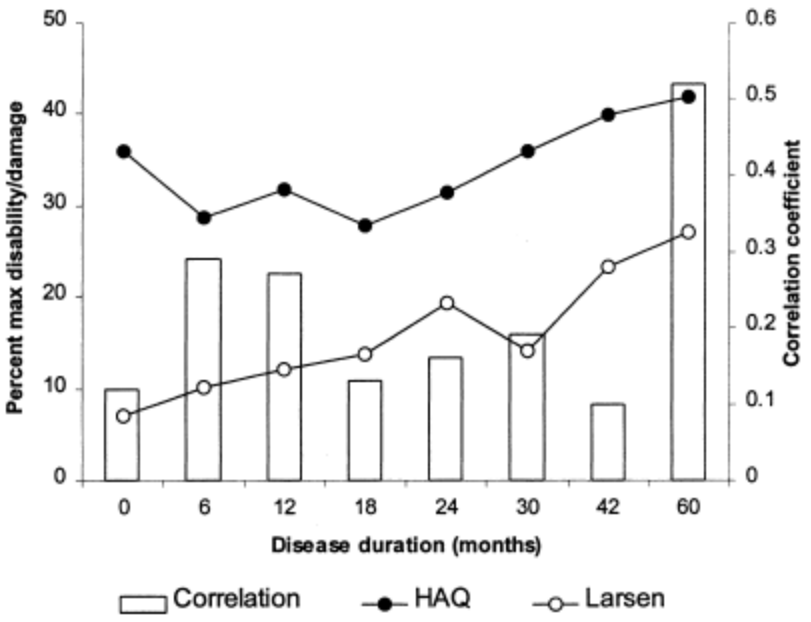
Radiographic progression



Disability

DL Scott et al. Rheumatology 2000;39:122–132

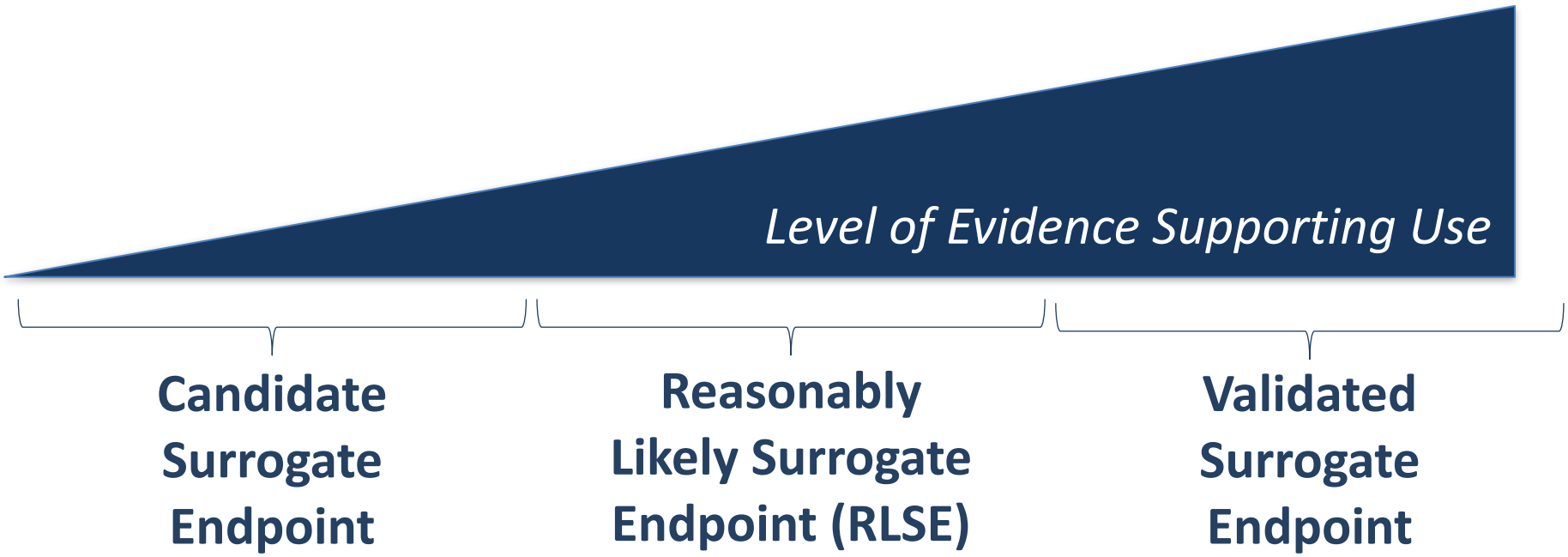
Correlation between physical function & X-ray



- Disability in Truro cohort initially variable
- Later progressive
- Radiographs progressed throughout
- Correlation marked only after 5 yrs
- Other studies support strong correlation (r = 0.31-0.68) only in "late" RA

DL Scott et al. Rheumatology 2000;39:122–132

Type of Surrogate Endpoints



Type of Surrogate Endpoints

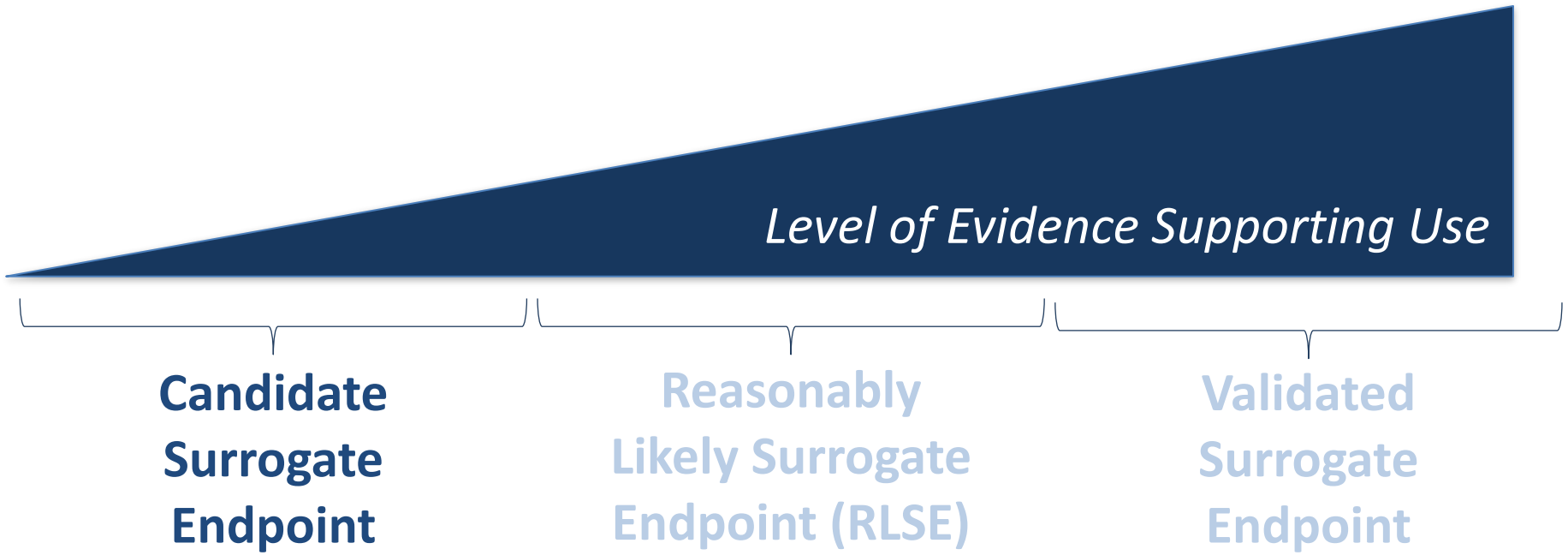
Candidate Surrogate Endpoint

Reasonably Likely Surrogate Endpoint (RLSE)

Validated Surrogate Endpoint

Traditional Approval
Ex: sUA for gout

Type of Surrogate Endpoints



Not appropriate for regulatory decision making

Type of Surrogate Endpoints

Candidate Surrogate Endpoint

Reasonably Likely Surrogate Endpoint (RLSE)

Validated Surrogate Endpoint

Accelerated Approval

FDA's Benefit-Risk Assessment

When efficacy is established via the effect on a surrogate endpoint with unquantifiable clinical benefit, the risk/ benefit assessment must balance an unmeasured clinical benefit against measured risks

Hypothetical Therapy

Benefit

Risks

Accelerated Approval

- For serious and/or life-threatening conditions
- Endpoint is often a RLSE
- Requires postmarketing studies to confirm clinical benefit
- Pros and Cons of Accelerated Approval:
  - Pros: Faster access to promising treatments
  - Cons: Patients may be exposed to the risks of a drug that does not show benefit; potential for less safety information; confirmatory trial may not be completed in a timely manner

Considerations for potential surrogates in OA

- What is the clinical benefit expected?
- How strong is the scientific evidence tying the biomarker to clinical outcomes?
- How much change in the biomarker would indicate a clinically meaningful benefit to patients?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