# Considerations for the use of biomarkers in the study of rare diseases

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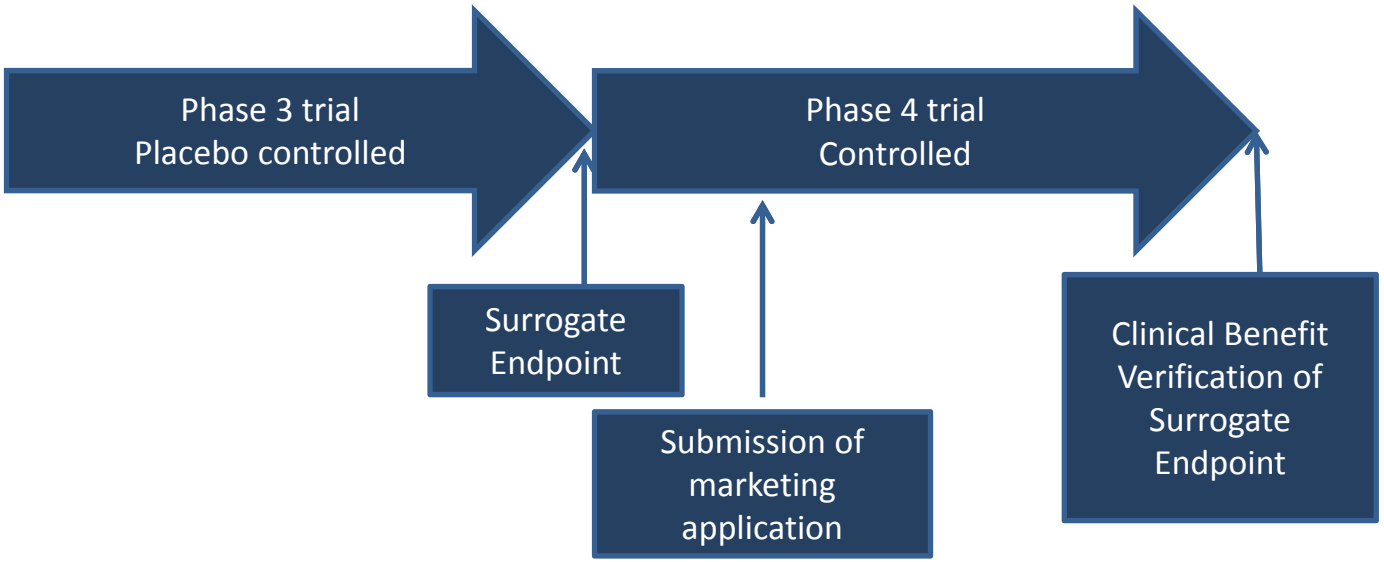
# Disclosure Statement

- No conflicts of interest
- Nothing to disclose
- This talk reflects the views of the author and should not be construed to represent FDA's views or policies
- In this talk "drug" refers to both drugs and biologics

# Biomarkers in Rare Disease Drug Development?

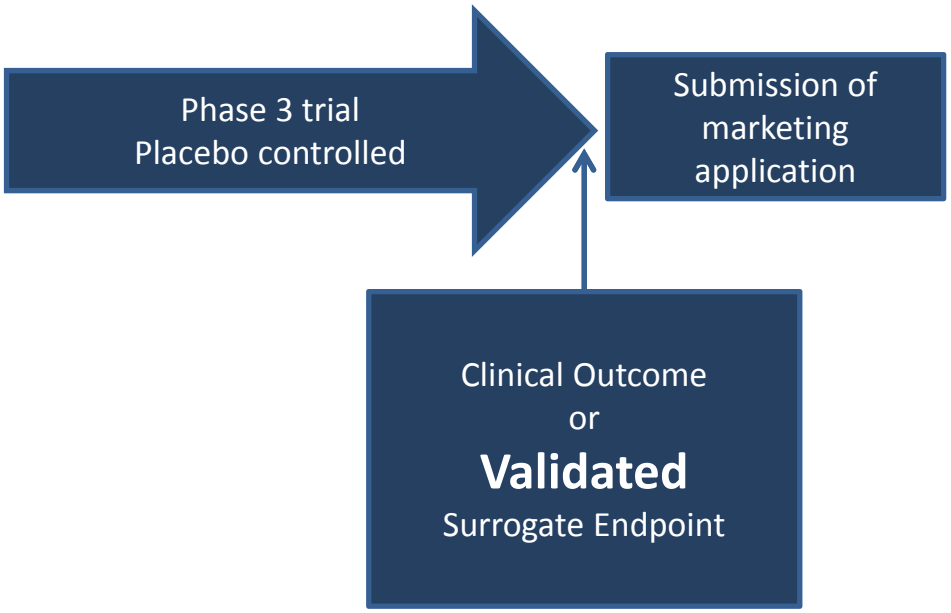

The upside down house in Bispingen, Germany

# Accelerated Drug Approval




FDA guidance – Expedited Programs
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf

# Traditional Drug Approval

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# Why surrogate endpoints fail

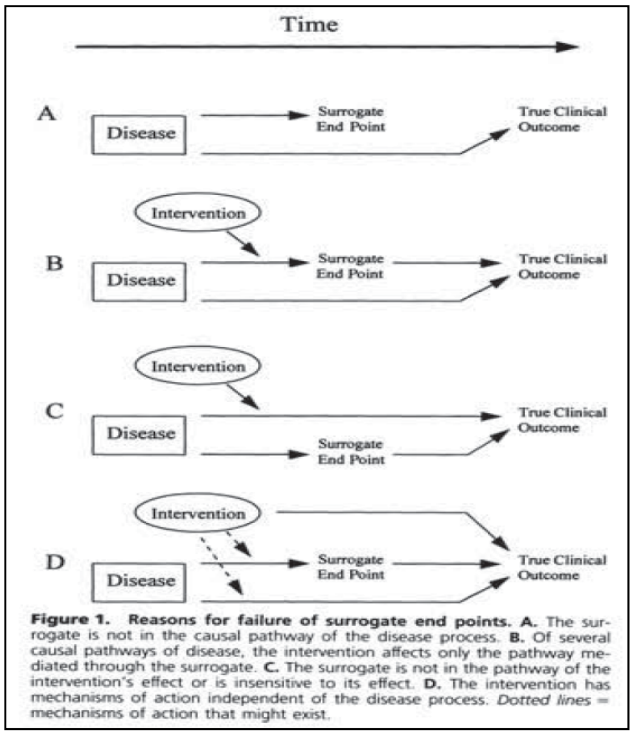



**Figure 1. Reasons for failure of surrogate end points. A.** The surrogate is not in the causal pathway of the disease process. **B.** Of several causal pathways of disease, the intervention affects only the pathway mediated through the surrogate. **C.** The surrogate is not in the pathway of the intervention's effect or is insensitive to its effect. **D.** The intervention has mechanisms of action independent of the disease process. *Dotted lines* = mechanisms of action that might exist.

**Fleming and DeMets; Ann Intern Med. 1996;125:605-613.**

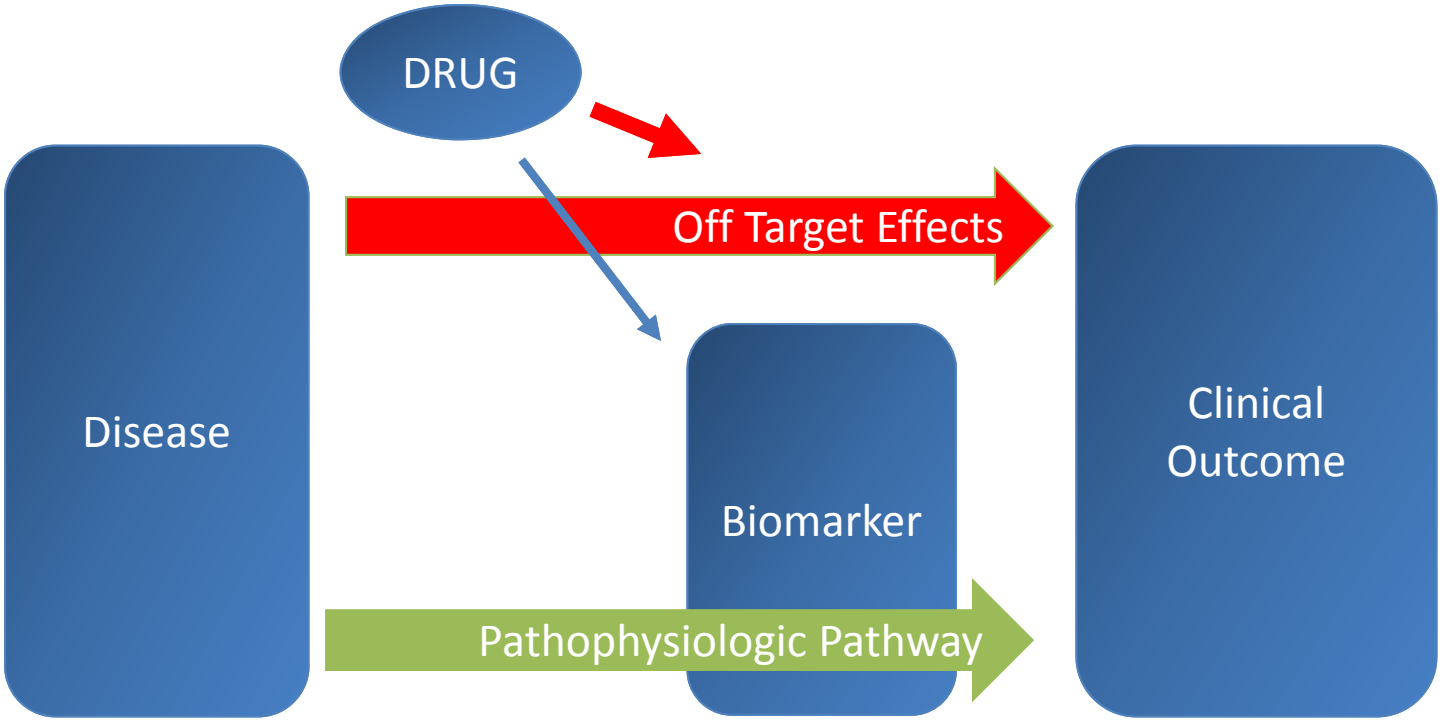
A. The selected surrogate is not in the causal pathway of the disease process

B. Multiple causal pathways exist for the disease, and the intervention affects the pathway mediated through the surrogate, but not others.

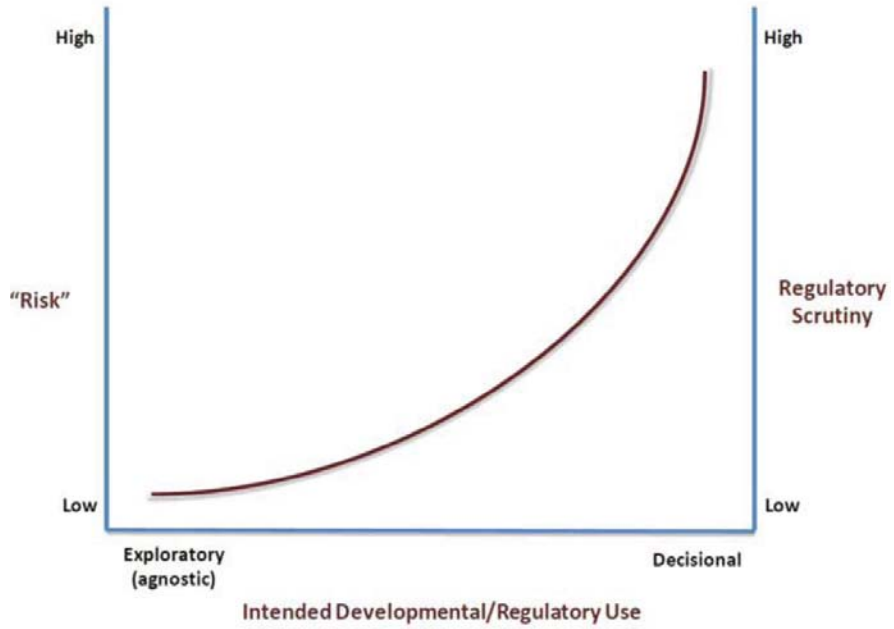
C. The surrogate is not in the pathway of the intervention's effect or is not sensitive to its effect.

D. The mechanisms of action of the intervention is independent of the disease process

# Why surrogate endpoints fail

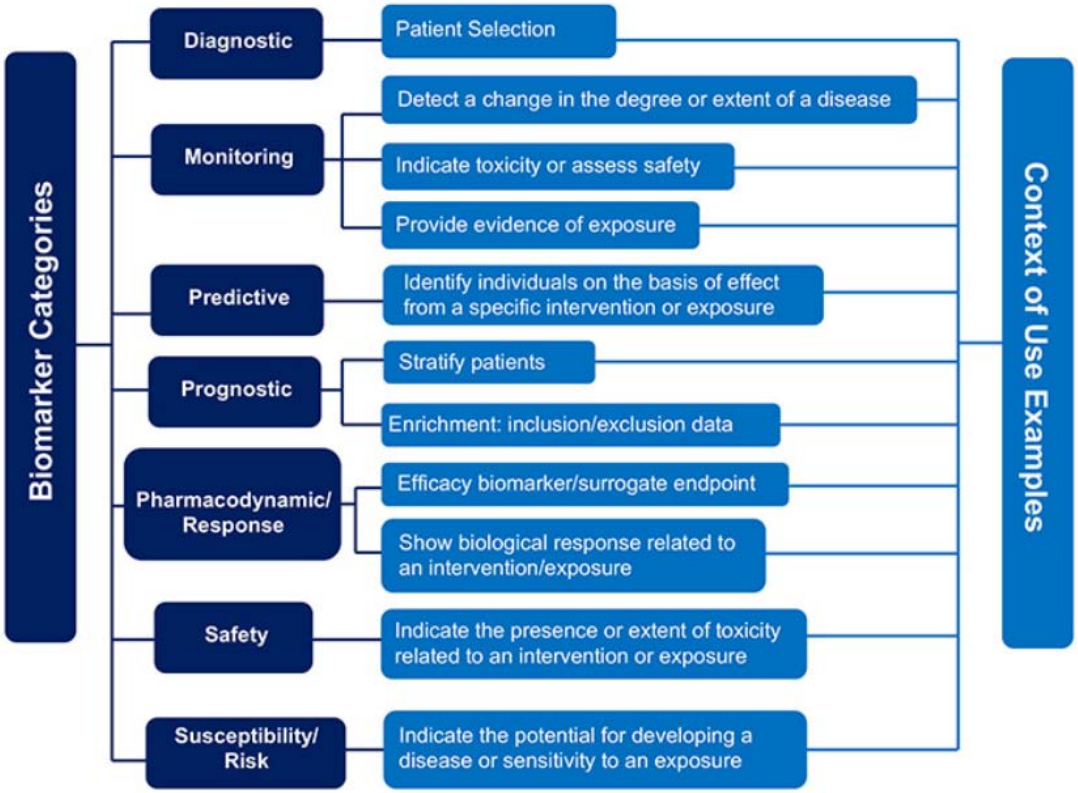


# more risk = more evidence




Woodcock, LaVange et al. Clinical Pharmacology & Therapeutics 2015

# Biomarkers have different jobs




https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/BiomarkerQualificationProgram/ucm535395.htm

# BEST:
# Biomarkers, EndpointS, and other Tools

- biomarkers and endpoints in basic biomedical research, medical product development, and clinical care
- the NIH-FDA Biomarker Working Group
- http://www.ncbi.nlm.nih.gov/books/NBK326791/

# Risk/susceptibility biomarker

*Definition*: A biomarker that indicates the potential for developing a disease or sensitivity to an exposure in an individual without clinically apparent disease.

*Example*: BReast CAncer genes 1 and 2 (BRCA1/2) mutations may be used as a susceptibility/risk biomarker to identify individuals with a predisposition to develop breast cancer.

**BEST -**http://www.ncbi.nlm.nih.gov/books/NBK326791/

# Diagnostic biomarker

*Definition*: A biomarker used to identify individuals with the disease or condition of interest or to define a subset of the disease.

*Example*: Blood sugar or hemoglobin A1c (HbA1c) may be used as a diagnostic biomarker when evaluating patients to identify diabetes mellitus.

**BEST -**http://www.ncbi.nlm.nih.gov/books/NBK326791/

# Prognostic biomarker

*Definition:* identifies likelihood of a clinical event, disease recurrence or progression

*Examples*: Total kidney volume to select patients with autosomal dominant polycystic kidney disease at high risk for progressive decline in renal function for inclusion in interventional clinical trials

BReast CAncer genes 1 and 2 (BRCA1/2) mutations to assess likelihood of a second breast cancer

**BEST -**http://www.ncbi.nlm.nih.gov/books/NBK326791/

# Predictive Biomarker

*Definition:* Identifies individuals who are likely to experience a favorable or unfavorable effect from a specific intervention or exposure

*Example:* Human leukocyte antigen allele (HLA)–B*5701 genotype identifies human immunodeficiency virus (HIV) patients at risk for severe skin reactions from abacavir treatment

**BEST -**http://www.ncbi.nlm.nih.gov/books/NBK326791/

# Pharmacodynamic response

*Definition:* A biomarker used to show that a biological response has occurred in an individual who has received an intervention or exposure

*Example*: Cholesterol may be used as a pharmacodynamic response biomarker when evaluating patients with hypercholesterolemia to assess response to a lipid-lowering agent or dietary changes

**BEST -**http://www.ncbi.nlm.nih.gov/books/NBK326791/

# Safety biomarker

*Definition:* A biomarker used to indicate the presence or extent of toxicity related to an intervention or exposure.

*Examples*: Corrected QT interval (QTc) may be used as a safety biomarker to assess the potential for drugs to induce Torsades de Pointes.

Serum creatinine may be used as a safety biomarker when evaluating patients on drugs that affect kidney function to monitor for nephrotoxicity.

**BEST -**http://www.ncbi.nlm.nih.gov/books/NBK326791/

# Monitoring biomarker

*Definition*: A biomarker measured serially and used to detect a change in the degree or extent of disease. Monitoring biomarkers may also be used to indicate toxicity or assess safety, or to provide evidence of exposure, including exposures to medical products.

*Example:* International normalized ratio (INR) or prothrombin time (PT) may be used as a monitoring biomarker for patients on warfarin.

**BEST -**http://www.ncbi.nlm.nih.gov/books/NBK326791/

# Surrogate endpoint

Definition: An endpoint that is used in clinical trials as a substitute for a direct measure of how a patient feels, functions, or survives. A surrogate endpoint does not measure the clinical benefit of primary interest in and of itself, but rather is expected to predict that clinical benefit or harm based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence.

A "validated surrogate endpoint" is one that is supported by a clear mechanistic rationale and clinical data providing strong evidence that an effect on the surrogate predicts a clinical benefit. Therefore, it can be used to support traditional approval without the need for additional efficacy information.

*Example*: HIV-RNA reduction is a validated surrogate endpoint for human immunodeficiency virus (HIV) clinical disease control and has been used for the basis for approval of drugs intended to treat HIV.

**BEST -**http://www.ncbi.nlm.nih.gov/books/NBK326791/

# Validation of biomarker tests

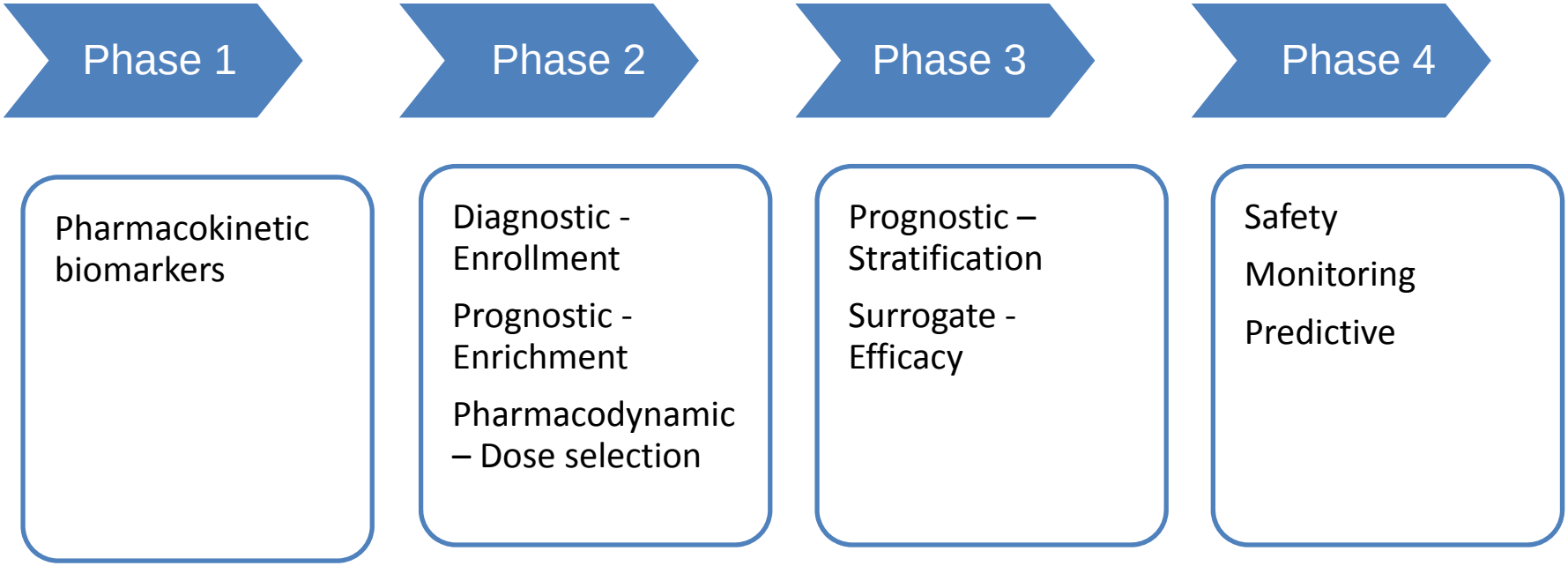
Validation – Establishing that the performance of a biomarker test, tool, or instrument is acceptable for its intended purpose

- *Analytical validation* –performance characteristics for sensitivity, specificity, accuracy, & precision, with a specified technical protocol for specimen collection, handling and storage

- *Clinical validation* – establishing that the biomarker acceptably identifies, measures, or predicts the concept of interest.

**BEST -**http://www.ncbi.nlm.nih.gov/books/NBK326791/

# Biomarkers in Drug Development

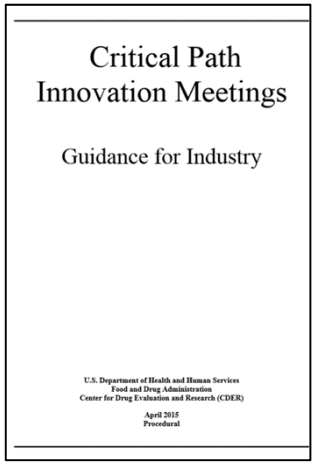


# Step 1


CPIMInquiries@fda.hhs.gov

# Critical Path Innovation Meeting

- Discussion of the science, medicine, and regulatory aspects of innovation in drug development
- Nonbinding meeting
- Not a meeting about a specific approval pathway
- Scope includes early biomarkers and clinical outcome assessments, natural history studies, technologies (not manufacturing), and clinical trial designs and methods


Critical Path
Innovation Meetings

Guidance for Industry

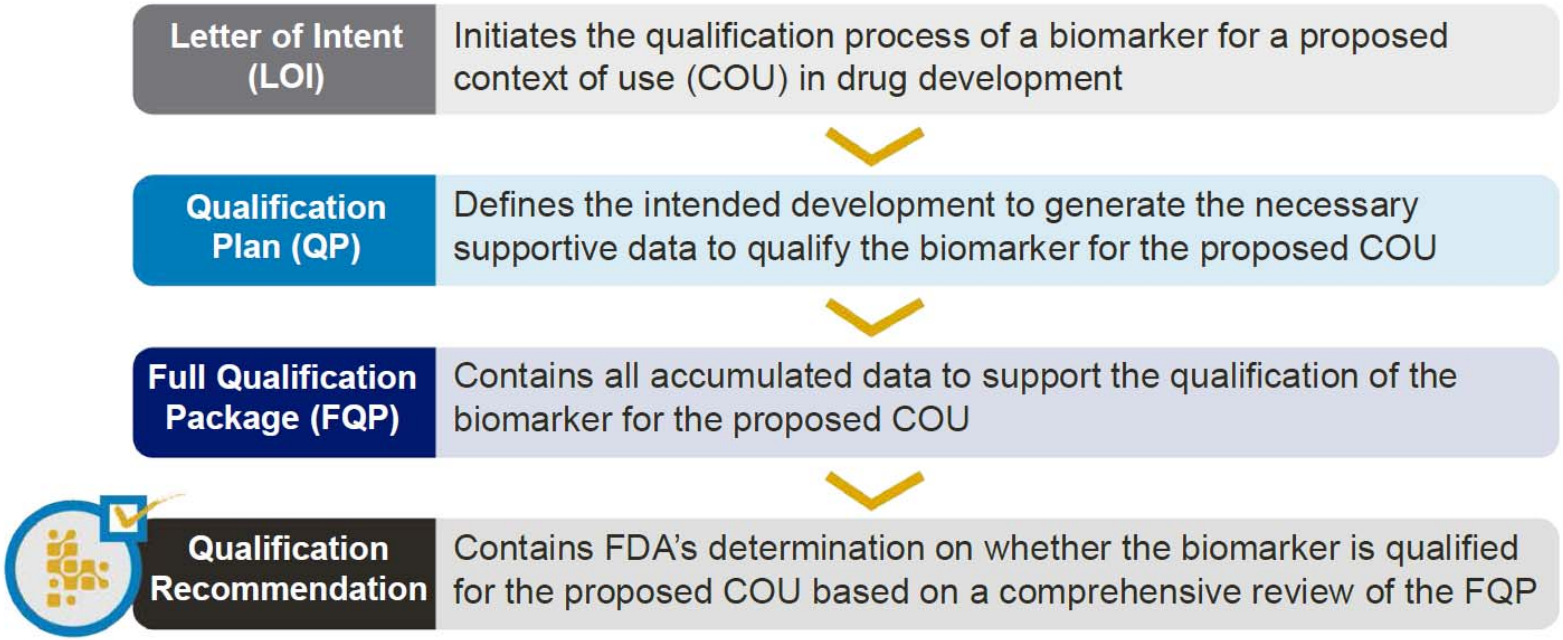
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

April 2015
Procedural

Office of Translational Sciences
Critical Path
Innovation Meeting

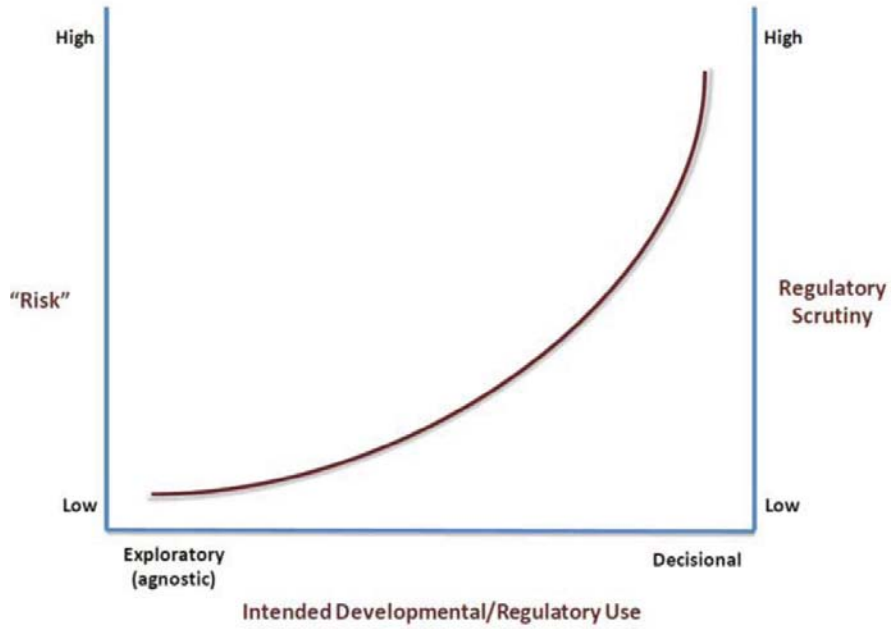
*https://www.fda.gov/drugs/developmentapprovalprocess/druginnovation/ucm395888.htm*

# Biomarker Qualification Process



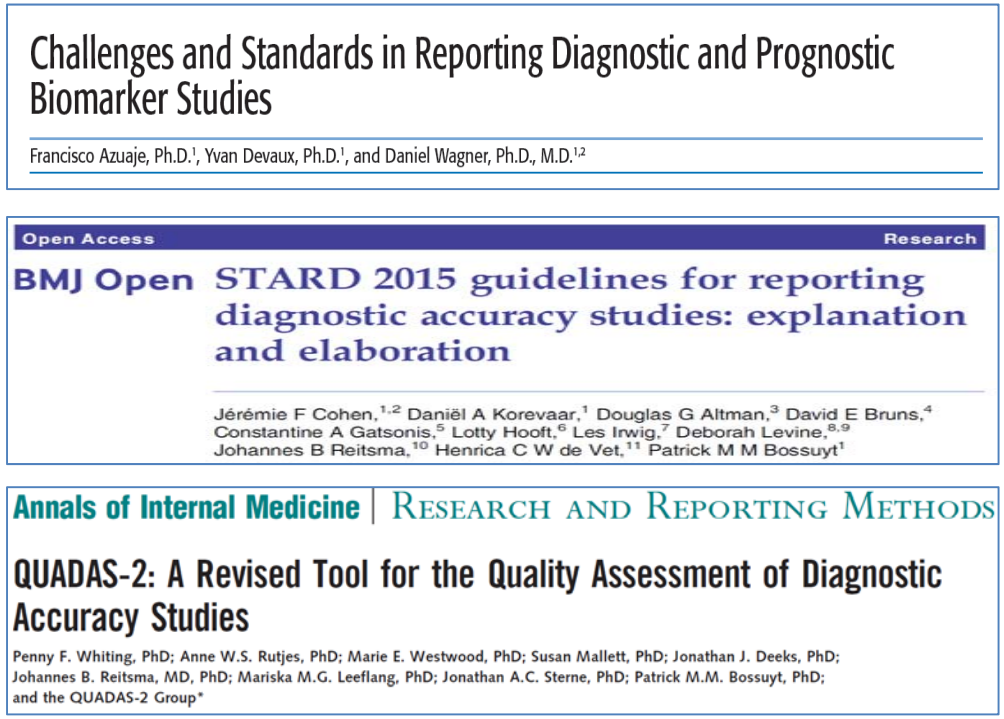

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/BiomarkerQualificationProgram/UCM576372.pdf

# more risk = more evidence




Woodcock, LaVange et al. Clinical Pharmacology & Therapeutics 2015

# Reporting Biomarker Studies



Challenges and Standards in Reporting Diagnostic and Prognostic Biomarker Studies

Francisco Azuaje, Ph.D.[1], Yvan Devaux, Ph.D.[1], and Daniel Wagner, Ph.D., M.D.[1,2]

Open Access Research

BMJ Open STARD 2015 guidelines for reporting diagnostic accuracy studies: explanation and elaboration

Jérémie F Cohen,[1,2] Daniël A Korevaar,[1] Douglas G Altman,[3] David E Bruns,[4] Constantine A Gatsonis,[5] Lotty Hooft,[6] Les Irwig,[7] Deborah Levine,[8,9] Johannes B Reitsma,[10] Henrica C W de Vet,[11] Patrick M M Bossuyt[1]

Annals of Internal Medicine | RESEARCH AND REPORTING METHODS

QUADAS-2: A Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies

Penny F. Whiting, PhD; Anne W.S. Rutjes, PhD; Marie E. Westwood, PhD; Susan Mallett, PhD; Jonathan J. Deeks, PhD; Johannes B. Reitsma, MD, PhD; Mariska M.G. Leeflang, PhD; Jonathan A.C. Sterne, PhD; Patrick M.M. Bossuyt, PhD; and the QUADAS-2 Group*

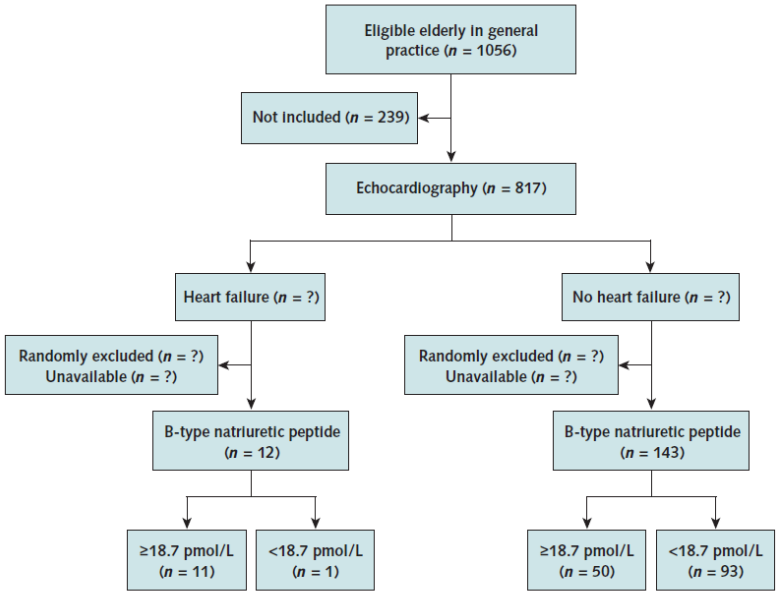
# QUADAS-2

*Table 1.* **Risk of Bias and Applicability Judgments in QUADAS-2**

| Domain | Patient Selection | Index Test | Reference Standard | Flow and Timing |
|---|---|---|---|---|
| Description | Describe methods of patient selection<br>Describe included patients (previous testing, presentation, intended use of index test, and setting) | Describe the index test and how it was conducted and interpreted | Describe the reference standard and how it was conducted and interpreted | Describe any patients who did not receive the index tests or reference standard or who were excluded from the 2 × 2 table (refer to flow diagram)<br>Describe the interval and any interventions between index tests and the reference standard |
| Signaling questions (yes, no, or unclear) | Was a consecutive or random sample of patients enrolled?<br>Was a case–control design avoided?<br>Did the study avoid inappropriate exclusions? | Were the index test results interpreted without knowledge of the results of the reference standard?<br>If a threshold was used, was it prespecified? | Is the reference standard likely to correctly classify the target condition?<br>Were the reference standard results interpreted without knowledge of the results of the index test? | Was there an appropriate interval between index tests and reference standard?<br>Did all patients receive a reference standard?<br>Did all patients receive the same reference standard?<br>Were all patients included in the analysis? |
| Risk of bias (high, low, or unclear) | Could the selection of patients have introduced bias? | Could the conduct or interpretation of the index test have introduced bias? | Could the reference standard, its conduct, or its interpretation have introduced bias? | Could the patient flow have introduced bias? |
| Concerns about applicability (high, low, or unclear) | Are there concerns that the included patients do not match the review question? | Are there concerns that the index test, its conduct, or its interpretation differ from the review question? | Are there concerns that the target condition as defined by the reference standard does not match the review question? | |

# QUADAS-2 Flow Diagram

*Figure 2.* Sample of a study flow diagram.




The diagram is based on a diagnostic cohort study on using B-type natriuretic peptide levels to diagnose heart failure. Based on data obtained from Smith H, Pickering RM, Struthers A, Simpson I, Mant D. Biochemical diagnosis of ventricular dysfunction in elderly patients in general practice: observational study. BMJ. 2000;320:906-8.

# Practical Guide to QUADAS

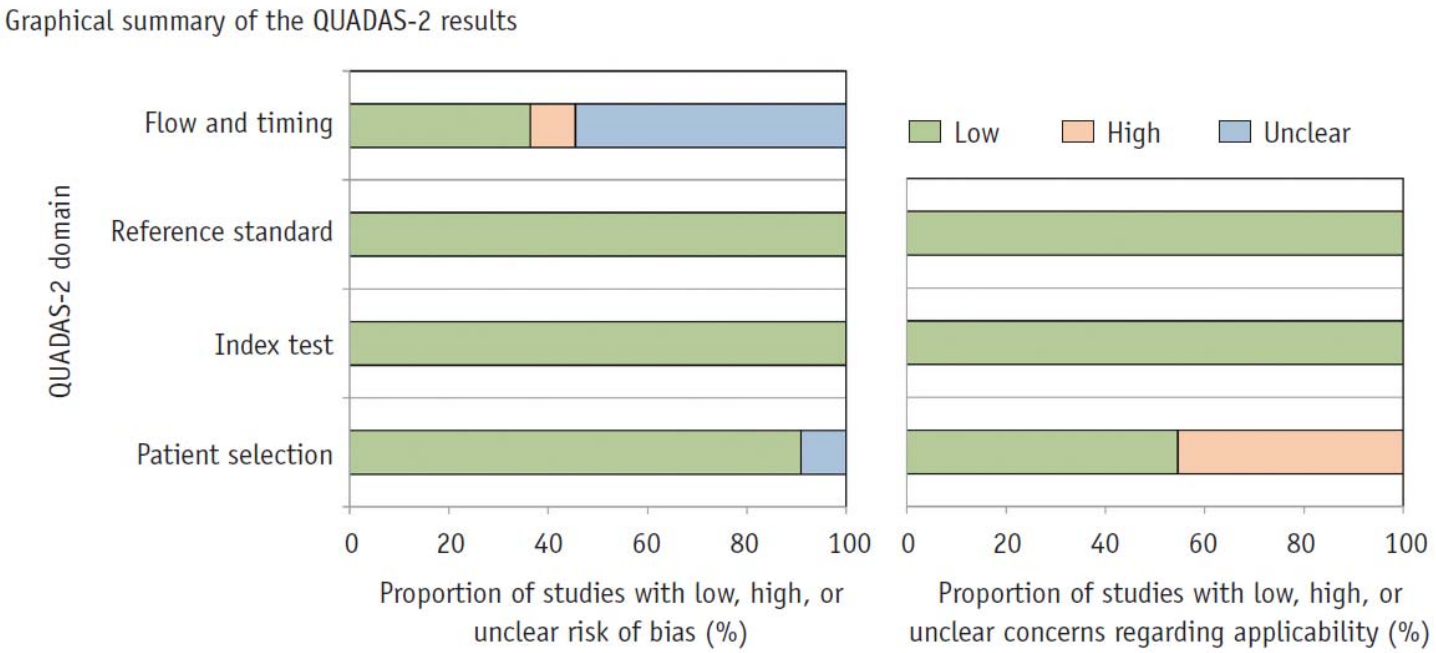
Tabular presentation of the QUADAS-2 assessments in each study

| Study | Risk of bias | | | | Applicability concerns | | |
|---|---|---|---|---|---|---|---|
| | Patient selection | Index test | Reference standard | Flow and timing | Patient selection | Index test | Reference standard |
| Study 1 | ☺ | ☺ | ☺ | ☹ | ☺ | ☺ | ☺ |
| Study 2 | ☺ | ☺ | ☺ | ? | ☺ | ☺ | ☺ |
| Study 3 | ☺ | ☺ | ☺ | ? | ☹ | ☺ | ☺ |
| Study 4 | ☺ | ☺ | ☺ | ☺ | ☹ | ☺ | ☺ |
| Study 5 | ☺ | ☺ | ☺ | ? | ☺ | ☺ | ☺ |
| Study 6 | ? | ☺ | ☺ | ? | ☹ | ☺ | ☺ |
| Study 7 | ☺ | ☺ | ☺ | ☺ | ☹ | ☺ | ☺ |
| Study 8 | ☺ | ☺ | ☺ | ? | ☺ | ☺ | ☺ |
| Study 9 | ☺ | ☺ | ☺ | ? | ☺ | ☺ | ☺ |
| Study 10 | ☺ | ☺ | ☺ | ☺ | ☹ | ☺ | ☺ |
| Study 11 | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ |

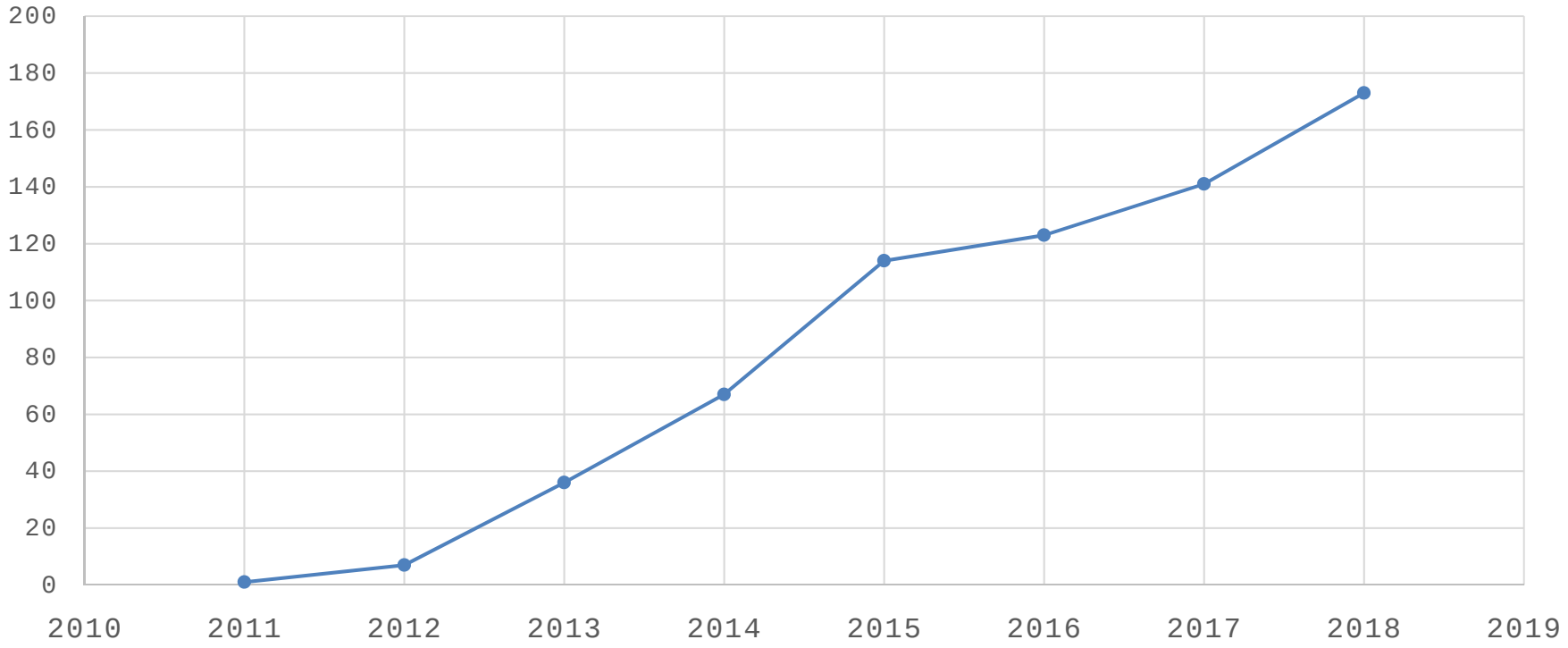
☺ Low risk ☹ High risk ? Unclear risk

Kim et al. – practical approach to evaluating diagnostic test accuracy
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4644738/

# Practical Guide to QUADAS



# QUADAS-2 Publications




FDA
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ADMINISTRATION

# Videos and Podcasts on FDA's Biomarker Qualification Program

https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/BiomarkerQualificationProgram/ucm558083