# New Biomarkers – The Path to Scientific and Regulatory Approval

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Medifacts International

Medicine is a science of uncertainty and an art of probability.

Sir William Osler, 1849-1919

# Agenda

- Terms and Definitions
- Biomarkers & Surrogate End Points
- Examples of Cardiovascular Biomarkers
- Clinical Strategies for New BM Development
- Regulatory Acceptance of New Biomarkers
- Future Directions and New Initiatives

# Definition of Biomarker

**Biological Marker (Biomarker):**

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

**Biomarkers Definitions Working Group, Clin. Pharmacol. Ther 2001; 69, 89–95**

**Purpose:**

- Biomarkers are used in clinical practice to identify risk for disease, diagnose disease and its severity, guide intervention strategies, and monitor patient responses to therapy.
- When used in a clinical research setting, biomarkers may predict whether a drug or other intervention is safe and effective in a shorter time and at lower cost than clinical outcomes studies.

**CA Altar, Clin Pharmacol Ther 2008; 83: 361-364**

# Terms and Definitions

| | |
|---|---|
| Biological marker (biomarker) | A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention. |
| Surrogate end point | A biomarker that is intended to substitute for a clinical end point; a surrogate end point is expected to predict clinical benefit (or harm or lack of benefit or harm) on the basis of epidemiological, therapeutic, pathophysiological, or other scientific evidence. |
| Risk factor | A risk factor is associated with a disease because it is in the causal pathway leading to the disease. |
| Risk marker | A risk marker is associated with the disease (statistically) but need not be causally linked; it may be a measure of the disease process itself. |
| Clinical end point: | A characteristic or variable that reflects how a patient feels, functions, or survives. |
| Validation of a biomarker | A process for assessing performance characteristics (ie, sensitivity, specificity, and reproducibility) of a biomarker measurement or an assay technique. |
| Qualification of a biomarker | The evidentiary process linking a biomarker to disease biology or clinical outcome. |

**Vasan RS, Circulation. 2006;113:2335-2362**

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# Biomarkers Vs Surrogate End Points

- Surrogate endpoints are a subset of biomarkers.
- Only a few BMs will achieve surrogate endpoint status.
- The term surrogate endpoint applies primarily to endpoints in therapeutic intervention trials; however, it may sometimes apply in natural history or epidemiologic studies.
- The use of biomarkers as surrogate endpoints in a clinical trial requires the specification of the substituted clinical endpoints, class of therapeutic intervention and characteristics of population and disease state.
- The same biomarkers used as surrogate endpoints in clinical trials are often extended to clinical practice in which disease responses are measured.

# Use of Surrogate Endpoints In Regulatory Registration Trials

- The use of surrogate endpoint biomarkers to establish therapeutic efficacy in registration trials is an established concept that has been addressed in regulation that enables the US FDA to grant accelerated marketing approval for certain therapeutics.
- The regulation states the following:

*FDA may grant marketing approval for a new drug product on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity.*

**Food and Drug Modernization Act of 1997. Title 21 Code of Federal Regulations Part 314 Subpart H Section 314.500**

# Some Concerns with BMs/SEPs

- Use of SEP assume that the treatment effect is mediated by the pathway represented by the SEP. However, multiple pathways may exist.
- SEP may be influenced by physiological or pathological properties of the outcome, e.g., sensitivity to QT effects in women or patients with inherited QT abnormalities.
- SEP may reflect on one aspect (ie, clinical benefit) while ignoring other effects (ie, adverse reactions); eg, COX-2 inhibitors treat pain effectively but have major CV ADR.

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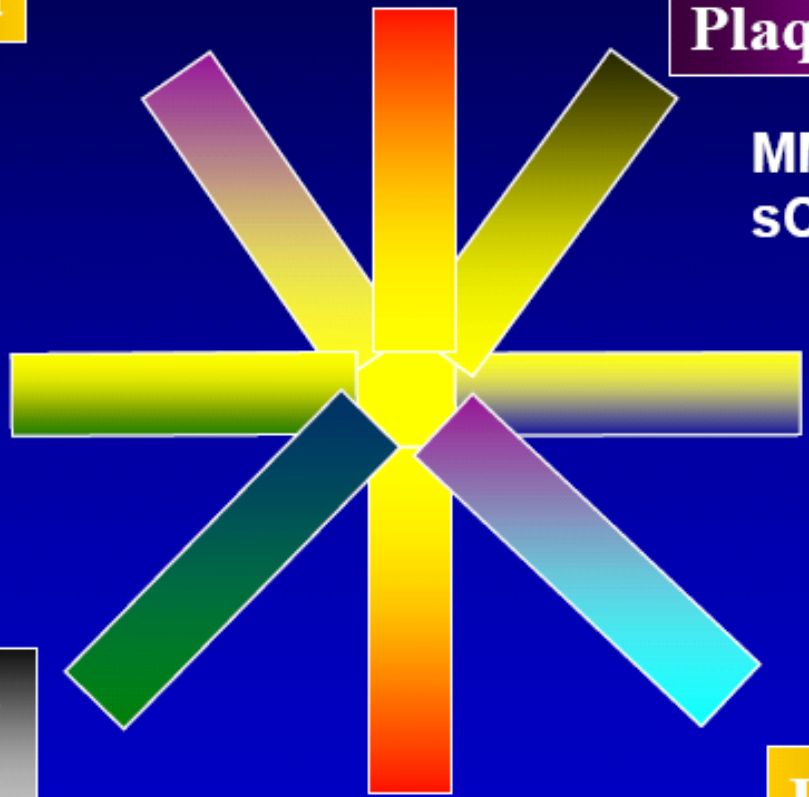
# Potential CV Biomarker Targets



**Necrosis**

cTnT, cTnI, Myo, CKMB, FABP

**Ischemia**

IMA, uFFA

**Plaque Rupture**

MMP's, PAPP
sCD40L, PIGF

**Arrhythmias**

**Thrombosis**

PAI-1, sCD40L
vWF, D dimer

**Neurohormone Activation**

BNP, NE

**Inflammation**

hs-CRP, Ox LDL
MCP-1, MPO, IL18

**Endothelial Activation**

sICAM, pSelectin

# Troponins - the Biomarker of Choice for Drug Induced Myocardial Injury

- TPNs are highly sensitive indicators of myocardial injury when measured in its critical diagnostic window of time
- Serum TPNs are detected as early, if not earlier, in the course of pathogenesis than are other biomarkers of myocardial injury
- The increases in serum TPNs , when measured in its diagnostic window, are proportionate to the extent of myocardial injury.
- The commercially available assays for cTnI and cTnT are simple, accurate, reproducible and inexpensive.
- Monitoring serum TPNs would be useful in investigating cases of concern for drug induced myocardial injury
- Monitoring serum TPNs can be useful when included in nonclinical studies to assess the potential for drug-induced myocardial injury.

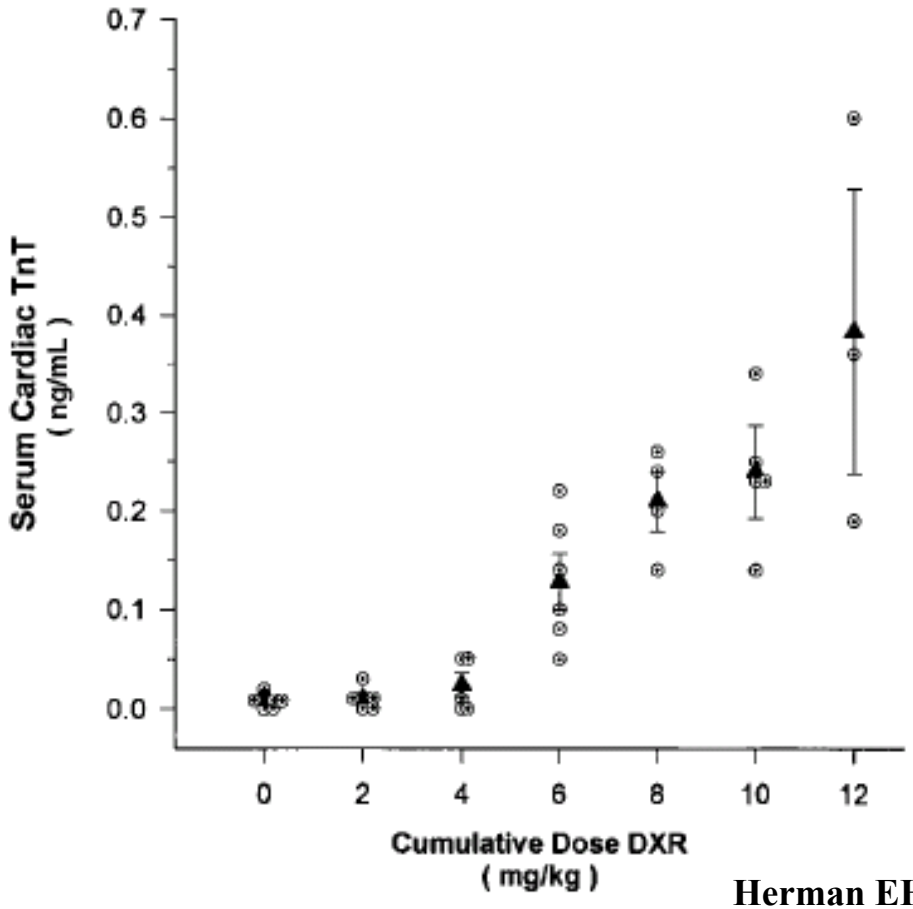
**FDA/NCSS Cardiotoxicity EWG, August, 2002**

# Troponins - the Biomarker of Choice for Drug Induced Myocardial Injury

**Troponins are the Serum Protein Biomarker of Choice For Monitoring Potential Drug Induced Myocardial Injury**

**FDA/NCSS Cardiotoxicity EWG, August, 2002**

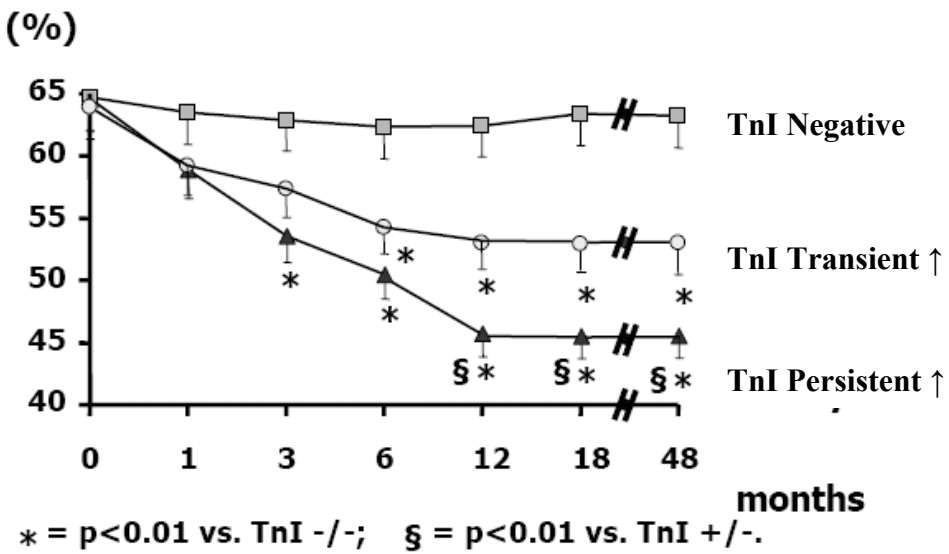
# Relationship Between the Cumulative Dose of DXR and Serum cTnT Levels in SHR




DXR = Doxorubicin
SHR = spontaneously hypertensive rats

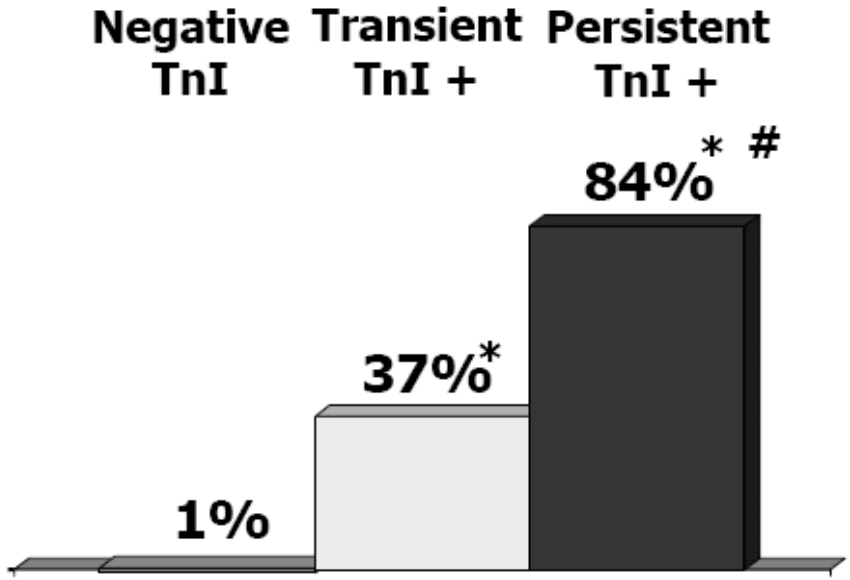
Herman EH, J Clin Oncol, 1999;17 (7): 2237-2243

# cTPN and LVEF Following HDC




# Cardiac Events Following HDC

## 3.5 year-follow-up

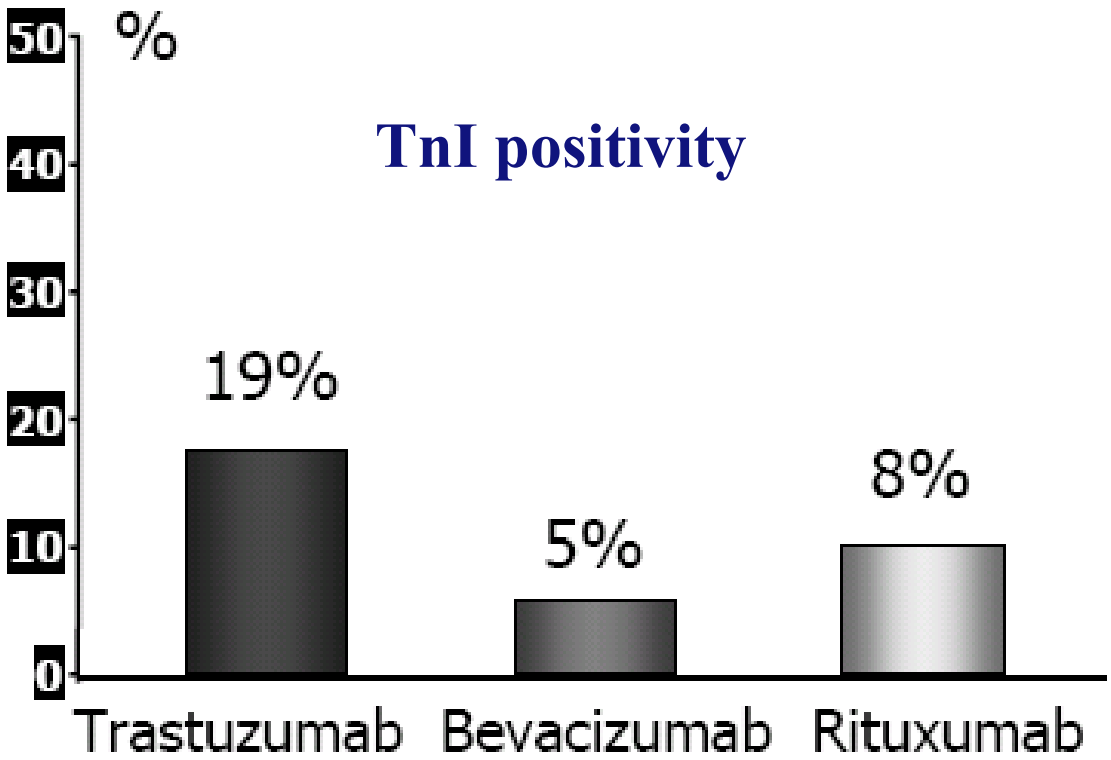



LVEF = Lt Ventricular Ejection Fraction
HDC = High Dose Chemotherapy

***CHF, Arrhythmia, PM, Death**

**Cardinale et al. Circulation 2004**

# Cardiotoxicity Associated with Monoclonal Antibodies Rx



# Some Examples of Potential and Established ECG BMs for Arrhythmia

- QT duration
  - Traditional Q-T (Ton-Toff)
  - TpTe (Tpeak –Tend)
  - J-T interval
- T-wave morphology
  - Amplitude
  - Area base
  - T loop
  - T slope (left & right)
  - T-amplitude/RR slope
  - T-wave symmetry (Tsym = |αL/αR|; no unit).
- T-wave morphology (cont.)
  - ERD (Early Repolarization Duration) 30% or 70%
  - LRD (Late Repolarization Duration) 30% or 70%
- QRS duration
  - QRS morpholgy
- QT/RR slope
- Rhythm
  - Heart rate variability
  - Heart rate Turbulation
  - Complex PVCs (CAST)

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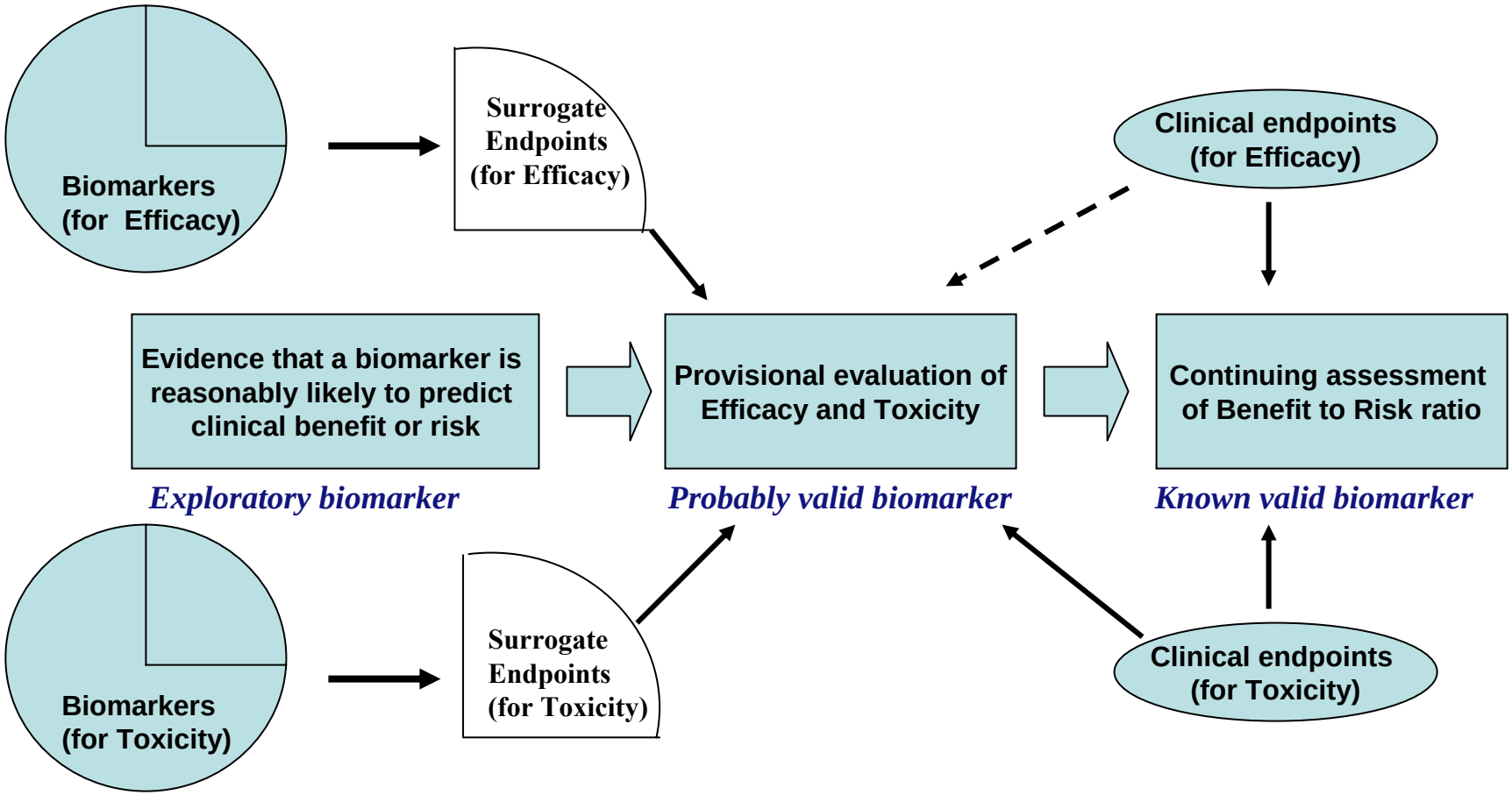
# A Conceptual Working Model for Biomarkers & Surrogate Endpoints Qualification




Biomarkers Definitions Working Group, Clin. Pharmacol. Ther 2001; 69, 89–95

# Strategy for Biomarker Development

| Phases: | Phase 1 Preclinical Exploratory | Phase 2 Clinical Characterization & Assay Validation | Phase 3 Clinical Association: Retrospective Repository studies | Phase 4 Clinical Association: Prospective Screening studies | Phase 5 Disease control |
|---|---|---|---|---|---|
| **Objective** | Target Biomarker Identification, Feasibility | Study assay in people with & without disease | Case-control studies using repository specimens | Longitudinal studies to predict disease | Clinical use |
| **Site** | Biomarker Development Lab | Biomarker Validation Lab | Clinical Epidemiologic Centers | Cohort Studies | Community |
| **Design** | Cross-sectional | Cross-sectional | Case-control | Prospective | RCT |
| **Sample Size** | Small | Small | Modest | Medium | Large |
| **Validity** | Content & construct validity | Criterion validity | Predictive validity | Efficacy of strategy | Effectiveness |
| **Result** | Assay precision reliability, sensitivity | Reference limits, intra-individual variation | Screening characteristics, true & false+ rates | ROC analyses | No.-needed-to screen/treat |

**Vasan RS, Circulation. 2006;113:2335-2362**

**Table 1 Prototype "evidence map"—categorical description of different types of scientific evidence potentially relevant to biomarker qualification; subcategorical graded weight of evidence from least to most**

| Evidence type | Grade D | Grade D+/C– | Grade C | Grade C+/B– | Grade B | Grade B+/A– | Grade A |
|---|---|---|---|---|---|---|---|
| Theory on biological plausibility | Observed association only | Theory, indirect evidence of relevance of the biomarker from animals | As for lower grade but evidence is direct | Theory, indirect evidence of relevance in humans | Theory, direct evidence in humans, non-causal pathway possible | As for lower grade, but biomarker on causal path | Human evidence based mathematical model of biology showing biomarker is on causal pathway |
| Interaction with pharmacologic | Biomarker identifies | | | Biomarker identifies target | Biomarker identifies target | | Biomarker identifies target in *in vivo* |

# A Prototypical Process for Creating Evidentiary Standards for Biomarkers and Diagnostics

CA Altar[1], D Amakye[2], D Bounos[3], J Bloom[4], G Clack[5], R Dean[4], V Devanarayan[6], D Fu[7], S Furlong[5], L Hinman[8], C Girman[9], C Lathia[10], L Lesko[11], S Madani[12], J Mayne[13], J Meyer[8], D Raunig[12], P Sager[5], SA Williams[14], P Wong[8] and K Zerba[15]

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 83 NUMBER 2 | FEBRUARY 2008

| | drug class | | disease effect | |
|---|---|---|---|---|
| Mathematics replication, confirmation | An algorithm is required to interpret the biomarker and was developed from this dataset | Algorithm was developed from a different dataset and applied here prospectively | | Algorithm developed from different dataset, replicated prospectively in other sets and applied prospectively here |
| Accuracy and precision (analytic validation) | | Sources of technical variation are unknown but steps are taken to ensure consistent test application | Major sources or variation known and controlled to be less than biological signal; standardization methods applied | All major sources of technical imprecision are known, and controlled test/assay accuracy is defined against standards |
| Relative performance | Does not meet performance of benchmark | Similar performance to benchmark | | Exceeds performance of benchmark or best alternative biomarker |

Not all types of evidence required all seven grades to be completed.

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# A Prototypical Process for Creating Evidentiary

**Table 1 Prototype "evidence map"—categorical description of different types of scientific evidence potentially relevant to biomarker qualification; subcategorical graded weight of evidence from least to most**

| Evidence type | Grade D | Grade D+/C– | Grade C | Grade C+/B– | Grade B | Grade B+/A– | Grade A |
|---|---|---|---|---|---|---|---|
| Pharmacologic mechanistic response | *In vitro* evidence that the drug affect the biomarker | *In vitro* evidence that multiple members of this drug class affects the biomarker | *In vivo* evidence that this drug affects biomarker in animals | As for lower grad but effect shown across drug class | Human evidenc that this drug affects the biomarker OR animal evidence of specificity | Human evidence across this mechanistic drug class | Human evidence that multiple members of this drug class affect the biomarker and the effect is specific to this class/mechanism |
| | | this dataset | | prospectively | | | sets and applied prospectively here |
| Accuracy and precision (analytic validation) | | | | Sources of technical variation are unknown but steps are taken to ensure consistent test application | Major sources or variation known and controlled to be less than biological signal; standardization methods applied | | All major sources of technical imprecision are known, and controlled test/assay accuracy is defined against standards |
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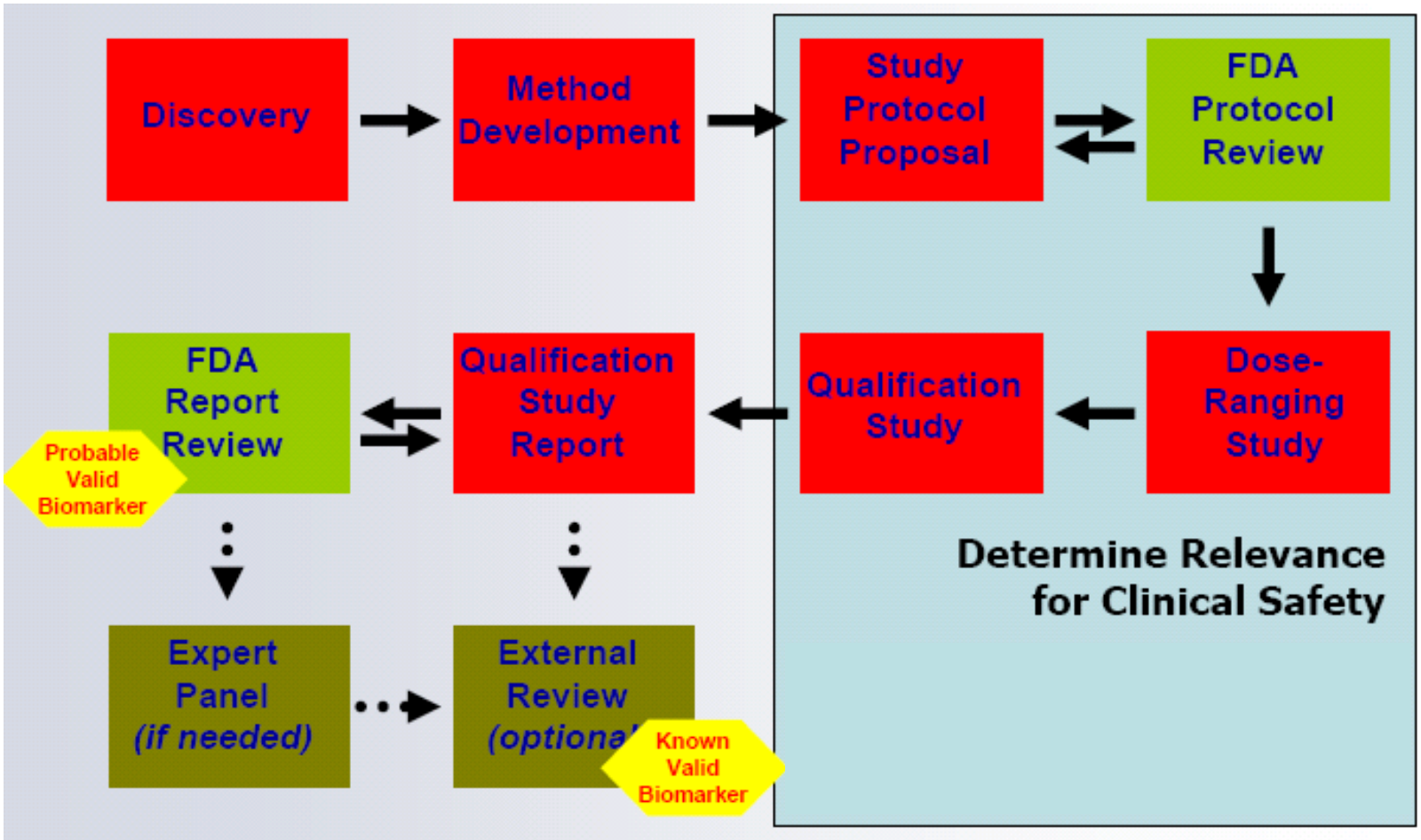
# Two Options for Qualifying a Biomarker:

- Wait long enough until we believe it, or
- Don’t wait, but have a good strategy

**Felix W. Frueh, PhD, OCP, CDER/FDA, 2007**

# Proposed Biomarker Validation Strategy in Preclinical Drug Safety Assessment




Felix W. Frueh, PhD, OCP, CDER/FDA, 2006

# Two Tiered Review Model

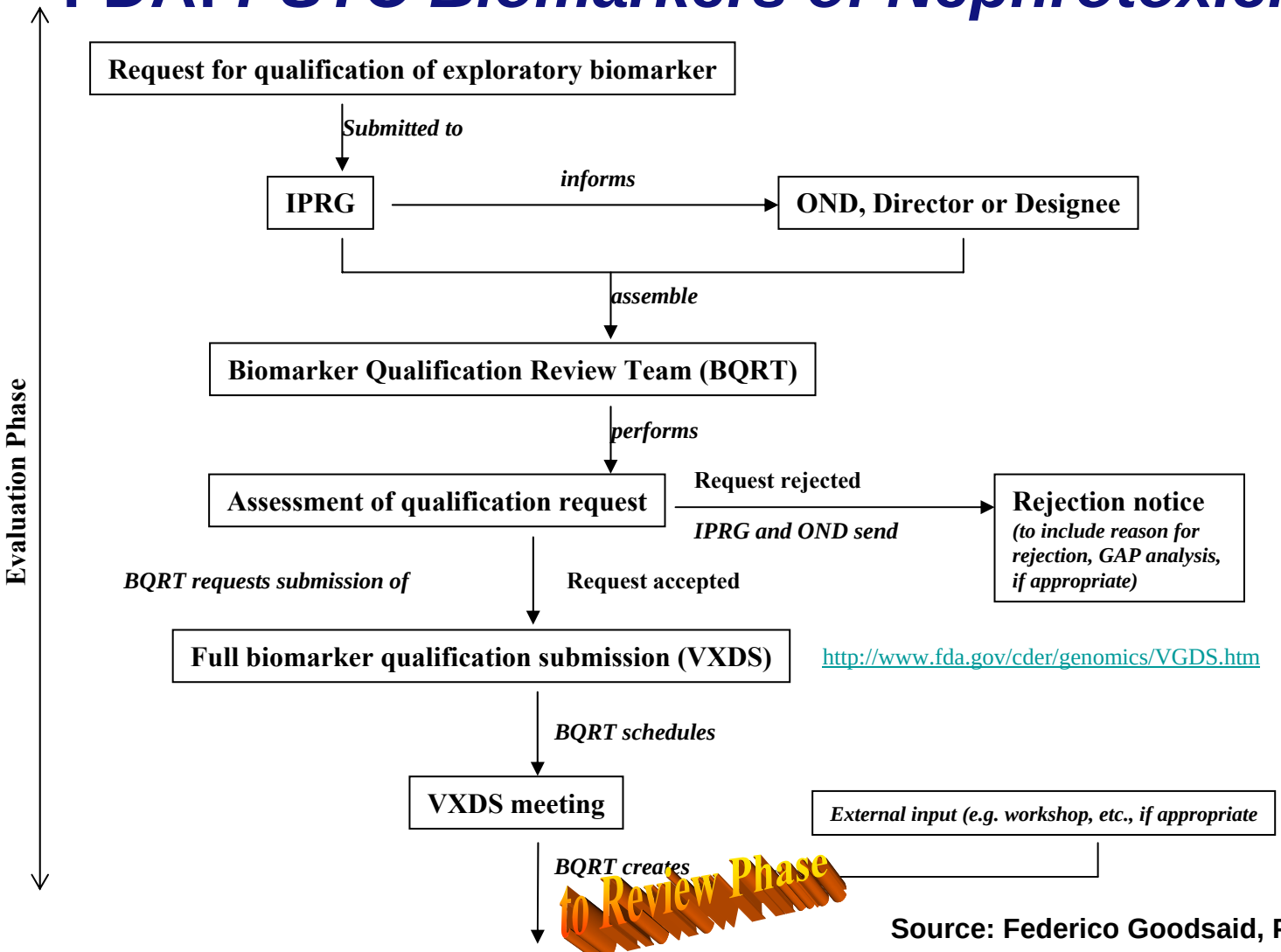
| FDA term | Interpretation |
|---|---|
| Probably valid biomarker | Conditional approval<br>– “approval as a process” |
| Known valid biomarker | Full approval<br>– “approval as an event” |

# A Two-track System Concept For Biomarker Based Drug Approval

- Track 1 – short-term evidence of benefit (based on biomarkers, short term outcomes, absence of sig. ADRs)
  - Results in conditional approval
  - Uncertainty reflected in labeling, promotion
  - Rapid patient access with prescribing/monitoring conditions
  - Obligation to continue development
- Track 2 – long-term evidence of the range of outcomes embracing studies of sub-populations, co-morbidities and comparator drugs
  - Allows qualification of new BMs and creation of diagnostics
  - Would lead to broader labeling

**Concept adopted from - Califf RM, Health Affairs, 2004; 23 (1):77-87**

# Biomarker Qualification Pilot Process at the FDA: *PSTC Biomarkers of Nephrotoxicity*




Source: Federico Goodsaid, Ph.D., CDER, FDA

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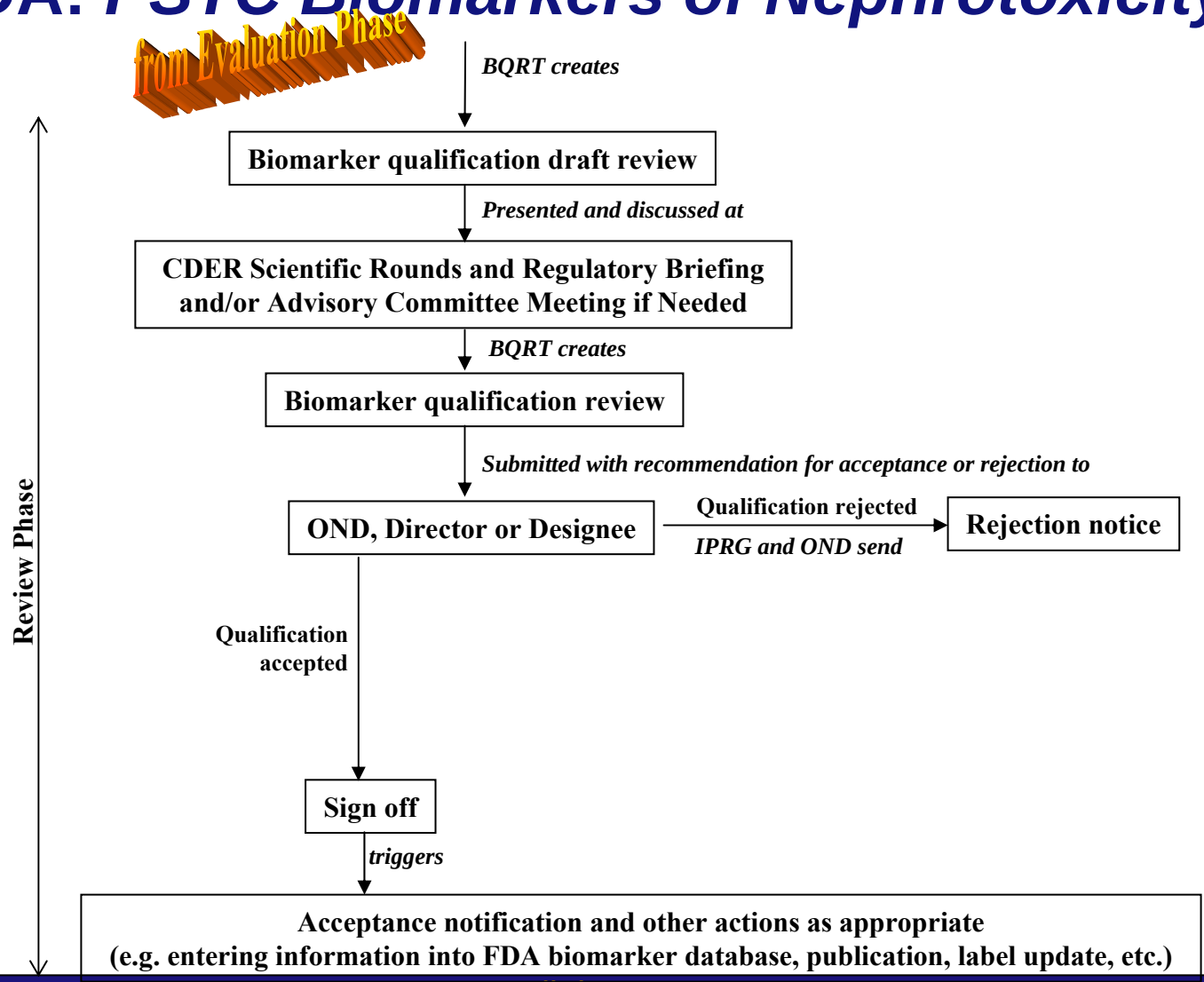

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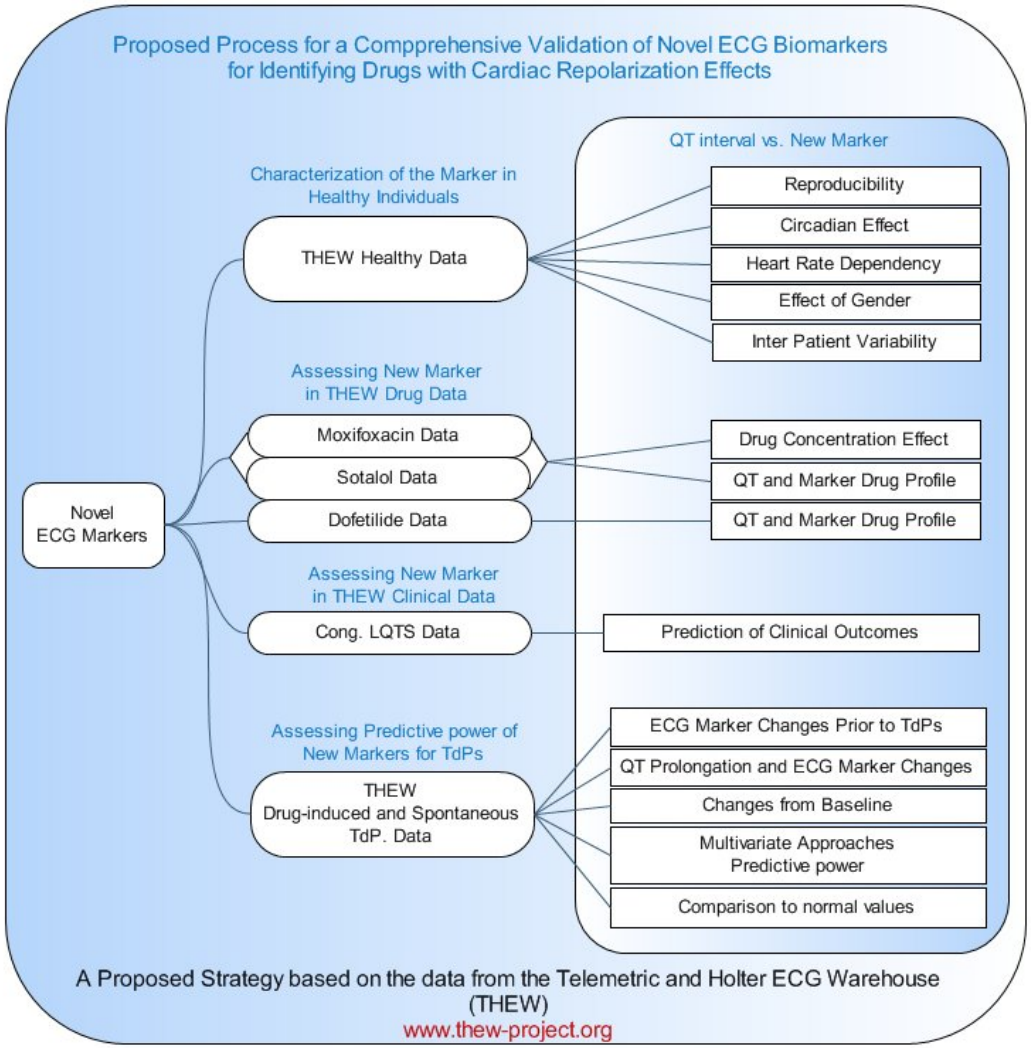
# Proposed Validation Strategy for ECG markers

## The Telemetric and Holter ECG Warehouse




**Source:**
**Jean-Philippe Couderc**
**University of Rochester**

# The Biomarkers Consortium: Goals

- Increase the number of qualified biomarkers
- Improve the standardization of methods to assess drug dosing, safety, and efficacy, and disease progression;
- Identify aggregates of accepted biomarkers to improve sensitivity and precision of assessments;
- Increase feedback about biomarker utility from a broader “grassroots” level of private clinical practice;
- Help create more highly predictive markers that have an impact during a patient’s illness or lifespan;
- Achieve a consensus between the scientific community and regulatory authorities on biomarker qualification.

**CA Altar, Clin Pharmacol Ther 2008; 83: 361-364**

# Conclusions

- There is an urgent need to formalize a work frame for biomarker validation and qualification
- This can only be achieved via collaboration between academia, industry and regulators
- Regulatory guidance to industry on best practices, qualification processes and regulatory acceptance criteria should be released in a timely manner, and
- For global implementation in drug development programs it is also mandatory to achieve international standardization and harmonization of biomarker and surrogate end point definition and approval criteria (ICH topic)

# Acknowledgements


- Federico Goodsaid, Ph.D., CDER, FDA
- Norman Stockbridge, MD, PhD, CDER, FDA
- Jean-Philippe Couderc, PhD, University of Rochester
- Borje Darpo, MD, PhD

# Thank You

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# Back up slides

# Characteristics of an Ideal Biomarker

**Clinical**

- Accurate
- Consistent
- Reproducible
- Standardized
- High sensitivity
- High specificity
- Easy to interpret
- Acceptable to patients
- Has an impact on clinical/risk management

Vasan RS, Circulation. 2006;113:2335-2362

**Regulatory**

- Specific
- Sensitive
- Favorable kinetics
- Robust detection assay
- Bridge non-clinical and clinical scenarios

FDA/NCSS Cardiotoxicity EWG, August, 2002

# Characteristics of Surrogate End Points

- **Outcome** - a surrogate end point can be used as an outcome in clinical trials to evaluate safety and effectiveness of therapies in lieu of measurement of the true outcome of interest.
- **Time relationship** - Alterations in surrogate end point should track closely with changes in the outcome of interest.
- **Time frame** - Surrogate end points may be gathered in a shorter time frame and with less expense than end points, e.g. morbidity and mortality, which require larger clinical trials for evaluation.
- **Related to exposure** - Surrogate end points are closer to the exposure/intervention of interest and may be easier to relate causally than distant events.

# Measures of Biomarker Test Performance

- **Sensitivity** is the ability of a test to detect disease when it is truly present, ie, it is the probability of a positive test result given that the patient has the disease.
- **Specificity** is the ability of a test to exclude the disease in patients who do not have disease, ie, it is the probability of a negative test result given that the patient does not have the disease.
- **Predictive value** is an indication of how good the test is at predicting the true positives or true negatives, ie, the probability that the test will give the correct diagnosis.
- **The positive predictive value** is the probability that a patient has the disease given that the test results are positive.
- **The negative predictive value** is the probability that a patient does not have the disease or condition given that the test results are indeed negative.
- **A ROC curve** is a plot of the sensitivity versus (1–specificity) of a diagnostic test, in which the different points on the curve correspond to different cut points used to determine whether the test results are positive.

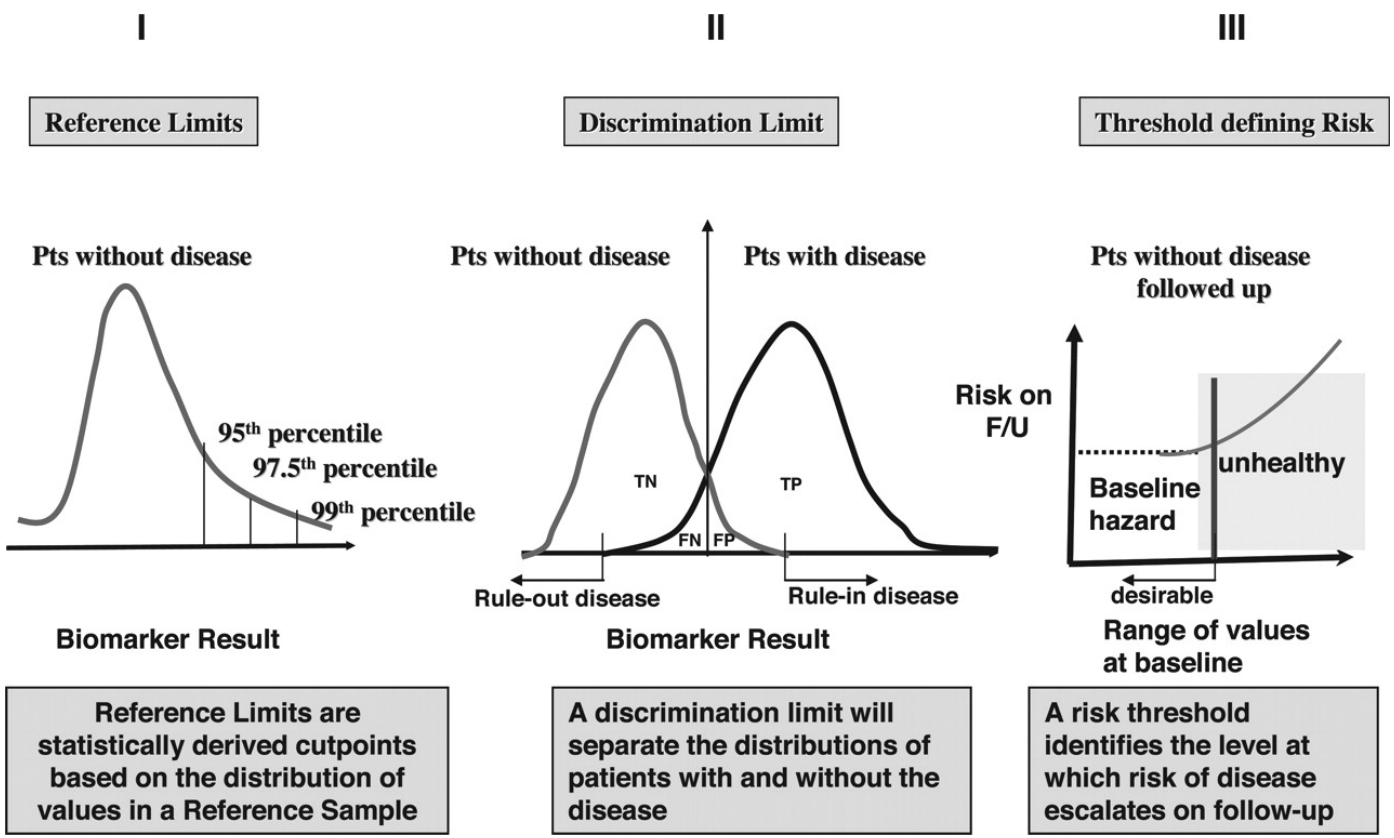
*Vasan RS, Circulation. 2006;113:2335-2362*

# Measures of Biomarker Test Performance - Cont.

- **Prevalence** is defined as the prior probability of the disease before the test is performed.
- **The likelihood ratio** is a simple measure of diagnostic accuracy, given by the ratio of the probability of the test result among patients who truly had the disease to the probability of the same test among patients who do not have the disease.
  - **Likelihood ratio** (test positive)=sensitivity/(1–specificity).
  - **Likelihood ratio** (test negative)=(1–sensitivity)/specificity.
- **Number needed to diagnose** is derived from 1/[sensitivity–(1–specificity)], number of tests that need to be performed to gain a positive response for the presence of disease.
- **Number needed to screen** is defined as the number of people that need to be screened for a given duration to prevent one death or adverse event.
- **Clinical trials of screening**: number needed to screen is calculated as number needed to screen equals 1 divided by absolute risk reduction.
- **Other trials**: number needed to screen is calculated by dividing the number needed to treat for treating risk factors by the prevalence of disease that was unrecognized or untreated.

*Vasan RS, Circulation. 2006;113:2335-2362*

# Approaches to defining "abnormal" biomarker values




*Vasan RS, Circulation. 2006;113:2335-2362*