



# *Components of Presentation*

- Brief overview of context -- DRI development process and reliance on biomarkers
- Terminology: What are we talking about?
- What needs to be done to enhance the appropriate use of biomarkers in the field of nutrition and nutrition monitoring?

## Disclaimer

- IOM Report “*Dietary Reference Intakes for Calcium and Vitamin D*”
  - Nearing completion
  - Public release approx Nov 2010
  - Cannot be discussed until public release
- Remarks today **not** related to committee deliberations
- All remarks relate to non-committee publications, discussions and meetings

# What Are the DRIs?



# What Are the DRIs?

- Dietary reference values
  - Specify nutrient requirements and tolerable upper levels
- Used in the U.S. and Canada
- Purpose
  - Assure adequate nutrition
  - Backbone of nutrition policy
  - Standards for public health programs
- Science Based
  - Derived from experimental evidence

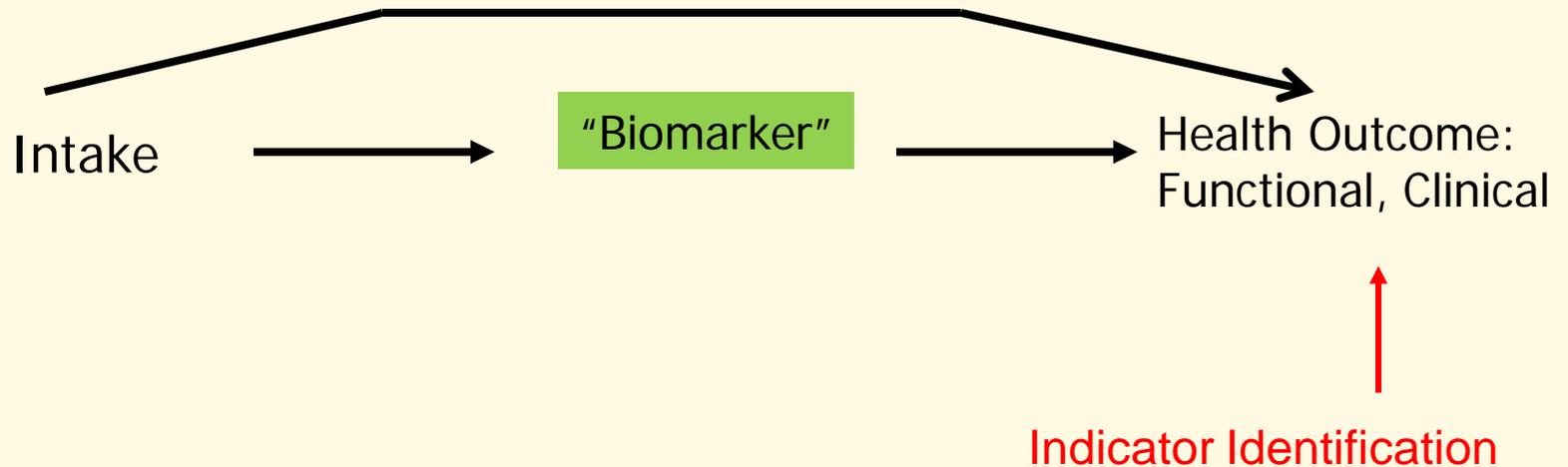
# The DRIs and Biomarkers

- Determine an average requirement (or upper level of intake) based on a health outcome
- What's a health outcome?
  - “Indicator” used for the DRI value
  - The “thing” which the intake affects  
How much of *this* affects *that*?
- Identifying the health outcome is the first step in DRI development

# Relevant Health Outcomes for DRIs

- Causal relationship  
Nutrient intake → Health Outcome
- Strength and quality of relationship
- Protective of public health
- May differ by life stage

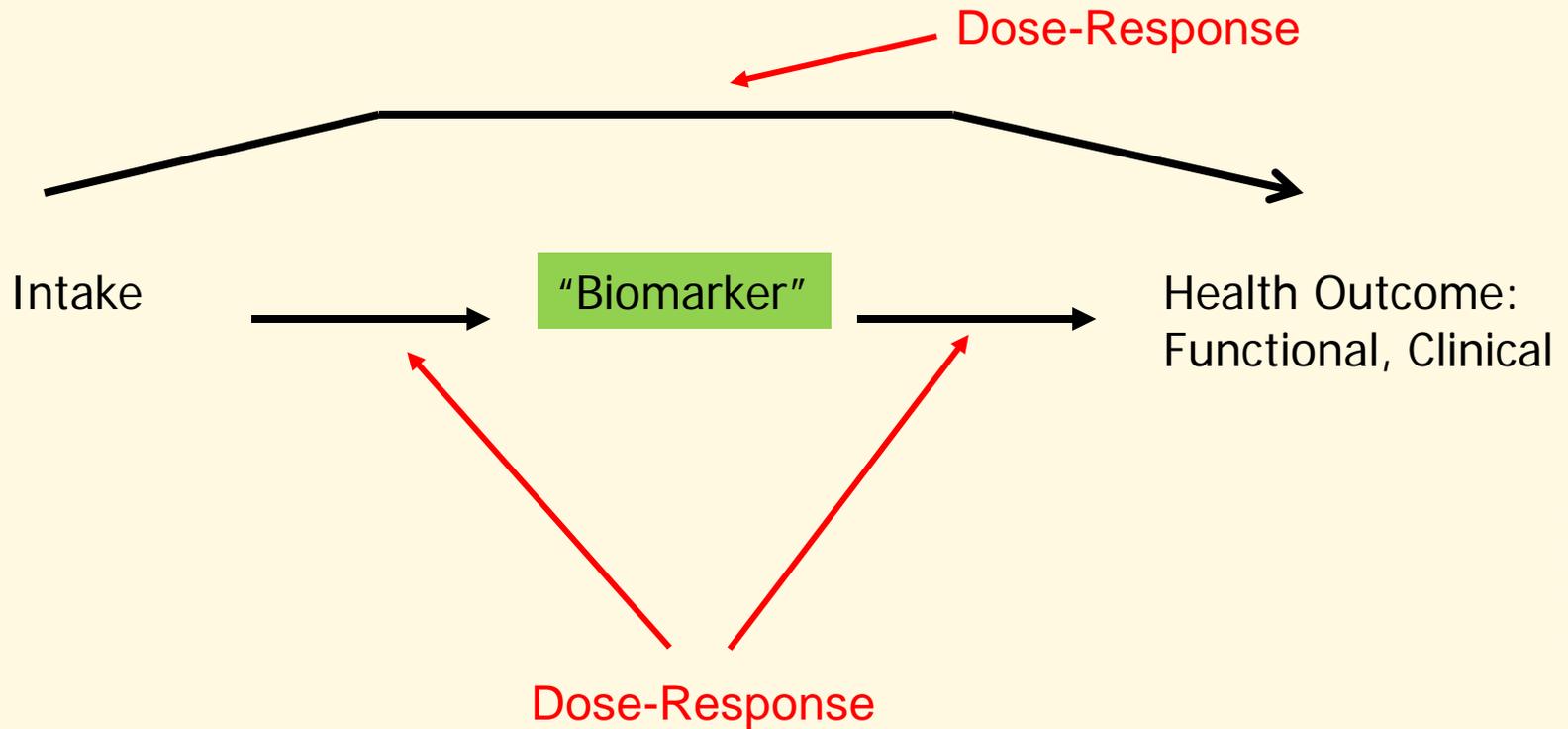
# First Step....Health Outcome (Indicator) Identification



# Why Biomarkers?

- Predictive (if causally associated)
  - Identify a situation early, before dysfunction or abnormalities may be present
  - Provide a signal
- Practical
  - Impractical to rely on measurable clinical outcomes in most research situations
    - Waiting for cancer to develop
    - Waiting for bones to break

# Later on... Specification of Dose-Response



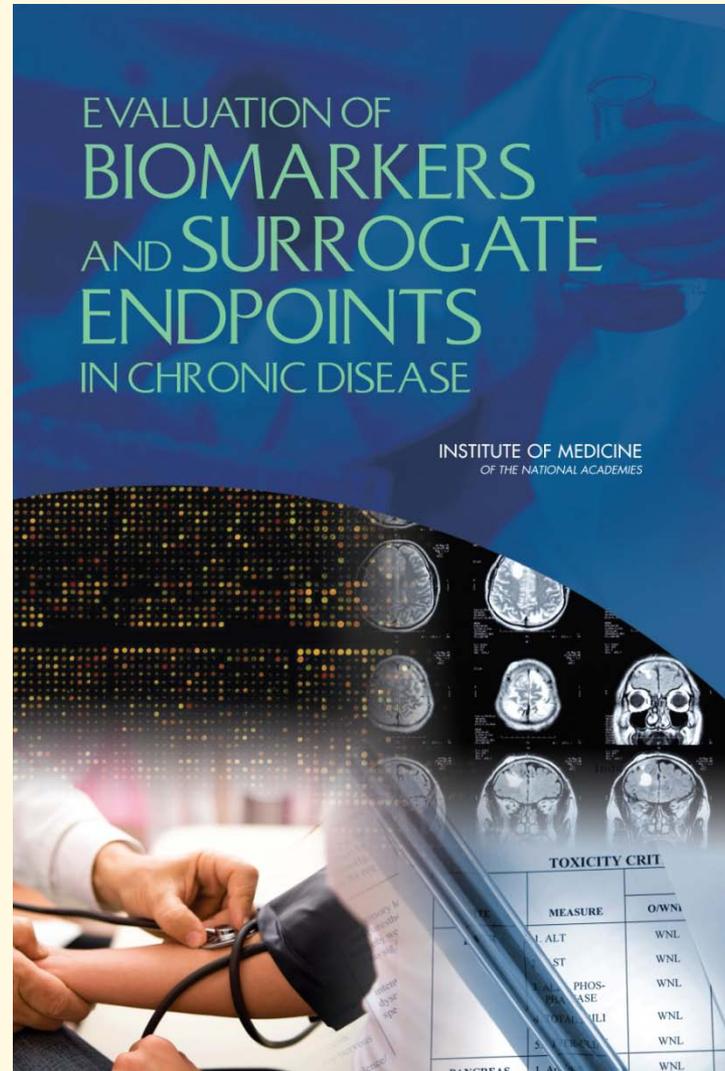
# Definitions and Terms

“There are several shades of meaning in the term *biomarker*, which are often used interchangeably to describe different attributes. This can lead to confusion and misunderstanding unless the term is strictly defined.”

*Prentice, AJCN, 2008:88(suppl):500S-6S*

# Recent IOM Report

- Report Released May 2010
- Discussion Forum with Stakeholders held June 21-22, 2010—Summary in development
- Contact IOM study director Christine Micheel, 202-334-1402, [cmicheel@nas.edu](mailto:cmicheel@nas.edu) for further information



# 2010 IOM Committee on Qualification of Biomarkers and Surrogate Endpoints in Chronic Disease

“Clinical Endpoint” [Health Outcome or DRI Indicator]

*A characteristic or variable that reflects how an individual feels, functions or survives (e.g., death).*

“Surrogate Endpoint” [Biomarker of Effect; Causal Biomarker]

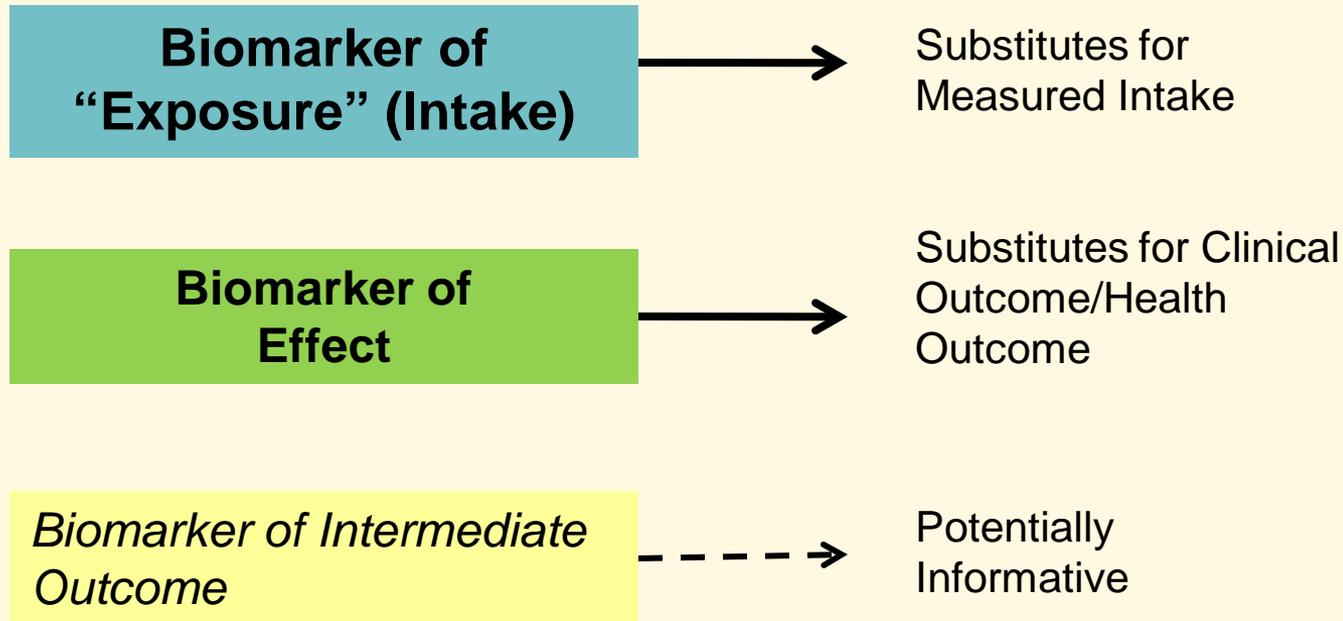
*A biomarker that is intended to substitute for a clinical endpoint; Predicts clinical endpoint.*

“Biomarker”

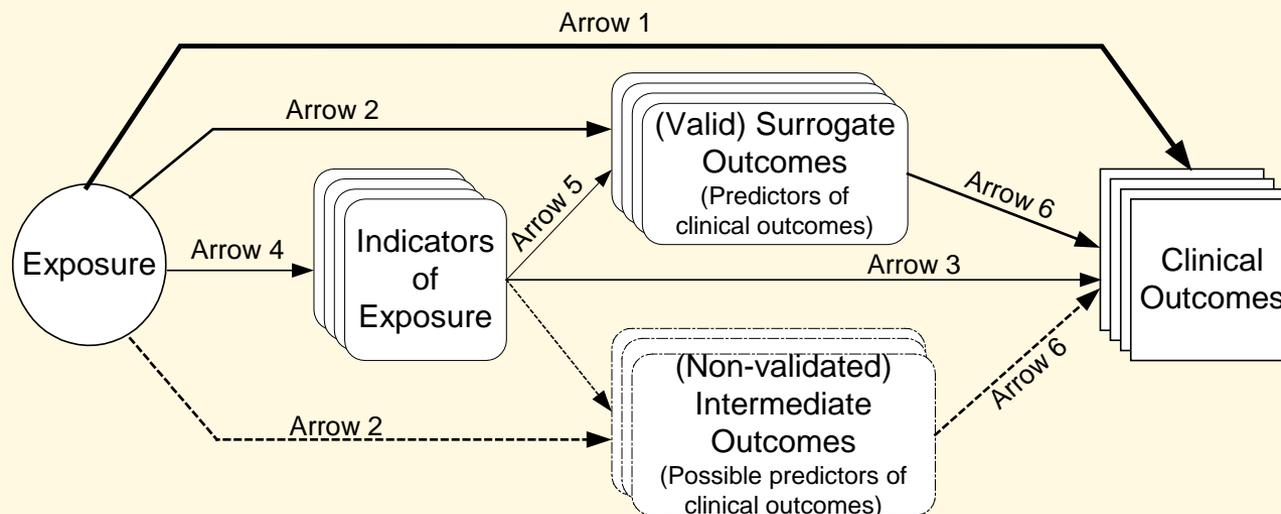
*A characteristic that is objectively measured and evaluated as an indicator of normal biological processes...*

# Biomarkers for DRIs

## 2 Main Types / 1 Adjunct Type



## Tufts Evidence-Based Practice Center: Generic analytic framework to assist formulation of key questions for the development of DRIs. (Chung et al., 2009)



Arrow 1: Association of exposure with clinical outcomes of interest.

Arrow 2: Association of exposure with surrogate or intermediate outcomes (with good or possible evidence for linkage with clinical outcomes).

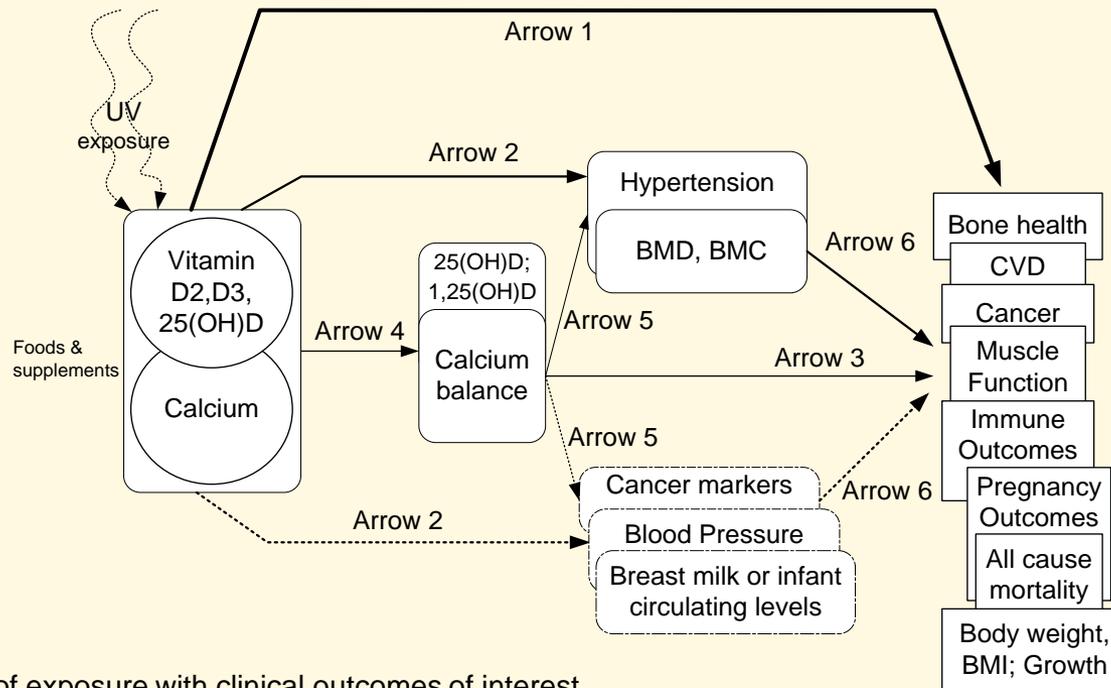
Arrow 3: Association of indicators of exposure to clinical outcomes.

Arrow 4: Association between exposure and indicators of exposure.

Arrow 5: Association of indicators of exposure to surrogate or intermediate outcomes (with good or possible evidence for linkage with clinical outcomes).

Arrow 6: Association between surrogate outcomes (with good or possible evidence for linkage) and clinical outcomes.

## Tufts Evidence-Based Practice Center: Analytic framework for vitamin D and/or calcium health outcomes (Chung et al., 2009)



Arrow 1: Association of exposure with clinical outcomes of interest.

Arrow 2: Association of exposure with surrogate or intermediate outcomes (that have good or possible evidence for linkage with clinical outcomes, respectively). (Surrogate outcomes are depicted in boxes with a solid outline, and intermediate outcomes are depicted in boxes with dashed outline.)

Arrow 3: Association of indicators of exposure to clinical outcomes.

Arrow 4: Association between exposure and indicators of exposure.

Arrow 5: Association of indicators of exposure to surrogate or intermediate outcomes.

Arrow 6: Association between surrogate or intermediate outcomes and clinical outcomes.

# Evidentiary Framework for Nutrient Biomarkers

IOM/Food and Nutrition Planning Meeting  
February 2008  
Washington, DC

(Supported by ODS/NIH)

# Evidentiary Framework for Nutrient Biomarkers

## Objective:

*What needs to be done to explore and clarify the general principles associated with identifying, validating and applying biomarkers of effect for health outcomes associated with nutrient adequacy and toxicity*

1. Stage-setting discussions
2. Exploration of issues: Terminology, methods of identification/validation, guidelines for application

# Evidentiary Framework for Nutrient Biomarkers

## Stage-Setting Discussions

- Types of biomarkers relevant to nutrients (“medical model” not always applicable)
- Specification of terminology
  - Clinical outcome, health outcome, indicator, endpoint, surrogate, risk factor, biomarker
- Enhanced use of animal models

# Evidentiary Framework for Nutrient Biomarkers

## Issues to be Explored Without Case Studies

- Grading of biomarkers
- Validating//qualifying, interpreting, documenting biomarkers
- Impact of multiple pathways

## Issues to be Explored With Case Studies

- Generalizability across clinical outcomes
- Primary versus secondary prevention
- Different (?) thresholds for validating biomarkers for adequacy versus those for excess
- Acceptable assumptions

# Dietary Reference Intakes for Calcium and Vitamin D

*For information:* [www.iom.edu/vitamind](http://www.iom.edu/vitamind)

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