Dietary Reference Intake Framework: Biomarkers

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National Conference on Health Statistics
August 2010
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 $\rightarrow$ Health Outcome
- Strength and quality of relationship
- Protective of public health
- May differ by life stage
First Step….Health Outcome (Indicator) Identification

Intake → “Biomarker” → Health Outcome: Functional, Clinical

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 measureable clinical outcomes in most research situations
    - Waiting for cancer to develop
    - Waiting for bones to break
Later on… Specification of Dose-Response

Intake → “Biomarker” → Health Outcome: Functional, Clinical

Dose-Response
“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 for further information
“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

- **Biomarker of “Exposure” (Intake)**
  - Substitutes for Measured Intake

- **Biomarker of Effect**
  - Substitutes for Clinical Outcome/Health Outcome

- **Biomarker of Intermediate Outcome**
  - Potentially Informative
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

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