Markers as Substitutes of Clinical Endpoints

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IOM Definition: Biomarkers

• Characteristics that are:
  – objectively measured and evaluated
  – indicator of normal biological processes ... or responses to a[n] ... intervention

• Describe:
  – risk, exposures, intermediate effects of intervention, and biologic mechanisms

• Examples:
  – Cholesterol, blood sugar, enzyme levels, tumor size

Source: IOM, Evaluation of Biomarkers and Surrogate Endpoints, 2010
IOM Definition: Clinical Endpoint

• A characteristic or variable that reflects how:
  – consumer feels, functions, or survives
• May include biomarker(s) ± clinical event
• Range:
  – Less to more closely related to consumer experience
• Example: death, MI with full recovery, LDL-C

IOM Definition: Surrogate endpoint

• A biomarker that is:
  • intended to substitute for a clinical endpoint
  • expected to predict clinical benefit or (harm)

• Example:
  – blood pressure

Source: IOM, Evaluation of Biomarkers and Surrogate Endpoints, 2010
Terminology

• Diet:
  – dietary patterns
  – one or more specific nutrients

• Surrogate marker = surrogate endpoint

• Biomarker validation = biomarker qualification

• Intervention = treatment
Selected Histories: Successes

• ↓Blood pressure ➔ ↓CVD risk and events

• Evidence:
  – Consistency across populations
  – Consistency across measurement parameters
  – Consistency across >75 drugs from 9 therapeutic classes
  – Mechanism is BP lowering

• Generalizability: Diet effectively ↓ BP
Selected Histories: Drug Failures

• Failures > Successes
  – Trials often reject common medical practice

• Arrhythmia suppression:
  – Ho: suppression of arrhythmia $\rightarrow \downarrow$ death after myocardial infarction
  – Trial: arrhythmia suppression $\rightarrow \uparrow$ death
Selected Histories: Drug Failures

• Exercise tolerance
  – Ho: Improved exercise tolerance $\rightarrow$ ↓ mortality with congestive heart failure
  – Trial: ↑ exercise tolerance $\rightarrow$ ↑ mortality

• Hormone replacement therapy (HRT)
  – Ho: HRT $\rightarrow$ ↓ LDL-C and ↑ HDL-C $\rightarrow$ ↓ CVD
  – Trial: HRT $\rightarrow$ ↑ risk CVD deaths
Selected Histories: Drug Trials

• HDL-Cholesterol and CVD
  – Ho: ↑ HDL-C → ↓ cardiovascular disease
  – Trial: Drug → ↑ HDL-C → ↑ death
Selected Histories: Diet Failures

• Failures > Successes
  – Evidence from observational studies not supported in clinical trials

• β-carotene in smokers:
  – Ho: ↑ serum β-carotene → ↓ risk of lung cancer in smokers
  – Trial: β-carotene supplements → ↑ cancer incidence
Selected Histories: Diet Failures

- B vitamins, homocysteine, cardiovascular disease risk
  - Ho: ↓ serum Hcy with B vitamins ⇒ ↓ risk CVD
  - Trials: B vitamins ⇒ ↓ Hcy but had no effect on CVD risk
History of LDL-C and ↓ CHD

• Significant uncertainties – warrants caution

• Evidence:
  – Statins $\rightarrow$ ↓ LDL-C $\rightarrow$ ↓ CHD risk
    • Inconsistencies between amount of LDL-C lowering and degree of benefit
    • ↓ LDL-C does not always correlate with improved patient outcome
    • Requires significant ↓ LDL-C (25-40%) to see benefit
  – Some interventions do not mediate their effects by ↓ LDL-C
History of LDL-C and ↓ CHD (cont.)

• To validate true clinical effect, importance of:
  – long duration of intervention
  – profound lowering to validate true clinical effect

• Generalizability of statin trial results to diet and nutrition studies?
  –Magnitude of effect much smaller with diet studies
  –Usefulness of small, short-term studies?
  –Warrants further consideration and review
IOM Case Study of LDL-C and CVD

• Strength of LDL-C as a surrogate endpoint is not absolute due to the heterogeneity of:
  – CVD processes
  – LDL-lowering effects of drugs and foods
  – LDL-particles themselves

• LDL-C, although not perfect, is one of the best biomarkers for CVD

Source: IOM, Evaluation of Biomarkers and Surrogate Endpoints, 2010
Why Problems?
Setting with Greatest Potential For the Surrogate Marker to be Valid

- Surrogate on causal pathway
- Intervention’s entire effect on outcome
- Intervention effect via surrogate
- Rarely occurs
Reasons for Failure:
Surrogate is not on the Causal Pathway

Surrogate
Marker

Intervention → True Clinical Outcome

- If measure only I and SM → wrong conclusions
- SM is not a substitute for outcome
- Ex: B vitamins (I), Hcy (SM), and CVD
Example: Surrogate Marker Not on the Causal Pathway

Observational Studies
Elevated Hcy predicts CVD risk

Hypothesis
\[ \uparrow \text{B vitamins} \rightarrow \downarrow \text{Hcy} \rightarrow \downarrow \text{CVD} \]

Trial Results
\[ \uparrow \text{B vitamins} \rightarrow \downarrow \text{Hcy} \rightarrow \text{CVD} \]

Possible Mechanism
\[ \text{CVD} \rightarrow \uparrow \text{Hcy} \]
Reasons for Failure: Multiple Pathways

Intervention → Surrogate Marker → True Clinical Outcome

Measuring only I and SM will result in misleading conclusions
Generalizability of a “Validated” Surrogate Marker to Different Interventions

“\text{A}” \rightarrow \text{Surrogate Marker} \rightarrow \text{True Clinical Outcome} \rightarrow “\text{B}”

- SM valid for both interventions:
  - If entire effect of each is via SM
- Validate SM with “\text{A}”
- Generalize SM to “\text{B}”
- Example: different BP-lowering agents
Generalizability of a “Validated” Surrogate Marker to Different Interventions

- SM on causal pathway of “A” and “B”
- “A” effect primarily via Surrogate Marker
- “B” effect primarily via Alternate Pathway
Generalizability of a “Validated” Surrogate Marker to Different Interventions

- If measure only “B” and SM → misled
- Validity of SM is context specific
- To generalize from “A” to “B”, need to understand mechanisms of action
IOM Recommended Biomarker Evaluation Process

1. Analytical Validation:
   – analytical performance of an assay

2. Qualification:
   – systematic review of evidence

3. Utilization:
   – contextual analysis based on proposed use

Context of Use

• Surrogate marker must be fit-for-purpose:
  • Populations
  • Intervention characteristics
  • Mechanisms of action
  • Potential benefits and harms

• Qualification of surrogate marker required for each intervention

• Evaluation requires scientific judgment

IOM Biomarker Evaluation Process

• Generic
  – foods, drugs, medical devices and biologics
• Same scientific standard
  – for all applications

Summary and Conclusions: Surrogate Markers

• History: Failures > Successes
  – Drugs and Diets/Nutrients

• Caution replacing enthusiasm

• Need strong evidence for surrogate markers:
  – Associations surrogate marker and outcome (observational data)
  – Causality established with clinical trials

Summary and Conclusions: Surrogate Markers

• Causality:
  – Surrogate on causal pathway between intervention and outcome
  – Surrogate reflects full effect of intervention on outcomes

• Surrogate is fit-for-purpose
  – Qualification is context specific
  – Needs scientific judgment
Complexities

• Outcomes with multifactorial causes
• Interventions with multiple effects
• Modifiers:
  – Population characteristics
  – Intervention characteristics
  – Disease characteristics
  – Timing
How to Move Forward?

• Public/private collaboration is needed

• Analytical validation of
  – Biomarker assays (nutritional and surrogate)

• Preliminary human trials
  – Smaller sample size
  – Meaningful study duration
  – Measure multiple biomarkers & pathway effects
  – Results to inform design of large clinical trials
How to Move Forward?

• Preliminary studies:
  – Create enthusiasm for government and foundation funding of large clinical trials
  – Information to help in designing the clinical trial:
    • Best form and dosage of the intervention
    • Most sensitive population targets
    • Likely magnitude of the effect
    • Likely biological mechanisms of action

• Large clinical trials – design based on results from preliminary studies