Marker Initiative in Nutrition Research

An ILSI Europe initiative looking at markers in nutrition research

Mike Gibney
Agnes Meheust
23rd January 2012
1. ILSI Europe and MARKERS, a long history...

2. The Marker Initiative
The FUFOSE project

FUFOSE: From evidence based on markers for functional foods to types of claims relevant to them

FUFOSE used the following concepts:
- Functional Foods
- Evidence based nutrition
- Rational for intelligent and strategic use of markers following specific criteria
- Factors and indicators
- Interest of using intermediates or surrogate markers

But it did not consider:
- Data derived from animal or other models
- Confounders associated with the evidence (age, growth, epigenetic effects…)

Consumption of functional food component

Markers of exposure to food component

Markers of target function / biological response

Markers of intermediate endpoint

Enhanced target function

Reduced risk of disease

TYPE A CLAIMS (enhanced function)

TYPE B CLAIMS (reduced risk of disease)
PASSCLAIM

Generic guidance tool to assess the scientific support for health claims on foods:

- Direct evidence of benefits to humans
- Usefulness of markers of intermediate effects
- Effects evaluated by the markers should be statistically and biologically meaningful.

Novelties regarding markers:
- Ideal need for dose-related change in the values observed

7 reviews as the basis for the development of the criteria
- CVD, bone health, physical performance, body weight and diabetes, diet-related cancer, mental state... and Gut and Immunity
ILSI Europe publications

2005 2006 2007 2008 2009 2010 2011 2012

2nd International ILSI Symposium

Concise Monograph

Int. activities

Polyphenols

Human Intervention Studies

PROCLAIM

Proceedings + Report

Workshop

Report

ILSI Europe Initiative on markers

EC

Regulation

EFSA

Guidance report on applications

Conference on Claims

Principles Substantiation Claims + Stakeholder Consultation
1. ILSI Europe and MARKERS, a long history...

2. The Marker Initiative
Timeframe & workflow

- 3-year project
- 3 steps
- 9 TFs involved
To identify…

• … consensus criteria for evaluation and adequate selection of markers in nutrition research

• … examples of consensus markers in different fields of nutrition research
Objectives

To identify...

• ... consensus criteria for evaluation and adequate selection of markers in nutrition research

• ... examples of consensus markers in different fields of nutrition research

Defining criteria will help to provide guidance for the development of future markers in nutrition research
2 combined approaches

**STEP 1 - 2011**

**Approach A**
Review of existing validation criteria
Done by a selected EG through a literature search covering all fields of nutrition research

**Approach B**
Identification of validation criteria for markers based on broadly used markers in the various fields of nutrition research

- Dietary Carbohydrates
- Nutrient Requirements
- Eating behaviour and Energy Balance
- Functional Foods
- Metabolic Imprinting
- Nutrition and Immunity
- Nutrition and Mental Performance
- Addition of Nutrients to Food
Approach A

Review of criteria existing in the scientific literature

Done by a selected EG through a literature search covering all fields of nutrition research
One member of the expert group reviewed the titles and abstracts of every record retrieved along the following lines:

- The aim of the paper
- Any discussion on criteria to validate markers
- Papers were discarded when the abstract did not indicate that proper criteria for a possible validation process were addressed.
A cross check on this process was performed by 2 other additional members of the expert group on a 10% sample of the search results.

This process resulted into **4 additional papers** to be included in the list of relevant publications.

<table>
<thead>
<tr>
<th>Search</th>
<th>Time-line</th>
<th>Key search term</th>
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**Multiple support search terms**
Appendix A
Table of Papers About Biomarker Qualification
Methodology

<table>
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<th>Search</th>
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<tr>
<td>2</td>
<td>2010-2011</td>
<td>Marker validation</td>
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</table>

Initial database of 1168 potential papers

Final database of 164 papers
**Biomarkers of Nutritional Exposure and Nutritional Status**

**Biologic and Methodologic Issues for Nutritional Biomarkers**

Nancy Potischman²,³

*National Cancer Institute, Bethesda, MD 20892*

**ABSTRACT**

Nutritional biomarkers are used for a variety of purposes in large-scale population surveys and epidemiologic studies as well as smaller clinical studies. The main reasons for using nutritional biomarkers are to provide measures of nutritional status that have less error than dietary data, nutrient status for nutrients with...
ORIGINAL ARTICLE

What is a biomarker? Research investments and lack of clinical integration necessitate a review of biomarker terminology and validation schema

ADAM S. PTOLEMY & NADER RIFAI

Department of Laboratory Medicine, Children’s Hospital Boston, Boston, MA, USA

Abstract

Abstract text follows...
Chapter 3

Biomarkers

Helen R. Griffiths a, Lennart Møller b, Grzegorz Bartosz c, Aalt Bast d, Carlo Bertoni-Freddari e, Andrew Collins f, Marcus Cooke i, Stefan Coolen g, Guido Haenen d, Anne-Mette Hoberg m, Steffen Loft h, Joe Lunec i, Ryszard Olinski j, James Parry k, Alfonso Pompei l, Henrik Poulsen m, Hans Verhagen g, Siân B. Astley n

a Pharmaceutical Sciences, Aston University, Birmingham, UK  
b Karolinska Institute, CNT Novum, Stockholm, Sweden  
c Department of Molecular Biophysics, University of Łódź and Department of Cell Biochemistry and Biology,
Evaluation of Biomarkers and Surrogate Endpoints in Chronic Disease
## Structure of the database

<table>
<thead>
<tr>
<th>Field</th>
<th>Description</th>
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<tbody>
<tr>
<td>Source</td>
<td>Original publication</td>
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<tr>
<td>Definitions</td>
<td>All relevant definitions</td>
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<td>Validation</td>
<td>Criteria used</td>
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<td>Rationale</td>
<td>The “why” behind the criteria</td>
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<tr>
<td>Methodology</td>
<td>How was validation achieved</td>
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<tr>
<td>Context</td>
<td>The area of research addressed</td>
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### Annex I

<table>
<thead>
<tr>
<th>Author</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Schatzkin</td>
<td>Cancer Epidemiol Biomarkers Prev 1998;7:947-53</td>
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<tr>
<td>De Gruttola</td>
<td>J Infect Diseases 1997;175:237-46</td>
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<tr>
<td>Begg</td>
<td>J R Statist Soc A 2000;163:15-28</td>
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<td>Li</td>
<td>Stat Med 2001;20:3171-88</td>
</tr>
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<td>Molenberghs</td>
<td>Controlled Clin Trials 2002;23:607-25</td>
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<td>Taylor</td>
<td>Controlled Clin Trials 2002;23:628-34</td>
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<td>Wang</td>
<td>Biometrics 2002;58:803-12</td>
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<td>Alonso</td>
<td>Biometrics 2004;60:724-6</td>
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<td>Alonso</td>
<td>Biometrics 2007;63:180-6</td>
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<tr>
<td>Lasserson</td>
<td>J Rheumatol 2007;34:607-15</td>
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<tr>
<td>Schold</td>
<td>Am J Transplant 2010;10:1162-6</td>
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<tr>
<td>Temple</td>
<td>JAMA 1999;282:270-6</td>
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<tr>
<td>Bucher</td>
<td>JAMA 1999;282:771-8</td>
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<tr>
<td>Fleming</td>
<td>Am J Pub Health 2000;90:139-43</td>
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<td></td>
<td>JAMA 2000;283:2325-30</td>
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</table>

### Definitions retrieved from and/or used in publications

A surrogate for a true endpoint is a response variable for which a test of 1) the null hypothesis of no relationship to the treatment groups under comparison is also a valid test of 2) the corresponding null hypothesis based on the true endpoint.

An intermediate endpoint is a response variable which is correlated with the clinical endpoint.

Biomarkers of intermediate end points, then, can be defined as measurable markers of cellular or molecular events associated with specific stages of the multistep evolution and progression of carcinogenesis.

A surrogate may be defined as a clinical measurement, known to be statistically associated with and believed to be pathophysiologically related to a clinical outcome.

A laboratory measurement or a physical sign used as a substitute for a clinically meaningful end point that measures directly how a patient feels, functions or survives.
### Definitions

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<td>Biomarker</td>
<td>A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.²</td>
</tr>
<tr>
<td>Prognostic biomarker</td>
<td>Biomarker that forecasts the likely course of disease irrespective of treatment.</td>
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<tr>
<td>Predictive biomarker</td>
<td>Biomarker that forecasts the likely response to a specific treatment.</td>
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<tr>
<td>Clinical end point</td>
<td>Measurement providing systematic information on how a patient feels, functions or survives.³</td>
</tr>
<tr>
<td>Surrogate end point</td>
<td>Measurement providing early and accurate prediction of both a clinical end point, and the effects of treatment on this end point.</td>
</tr>
<tr>
<td>Validation</td>
<td>Confirmation by robust statistical methods that a candidate prognostic biomarker, predictive biomarkers or surrogate end point fulfills a set of conditions that are necessary and sufficient for its use in the clinic</td>
</tr>
</tbody>
</table>

Ref: Buyse et al, Nat Rev Clin Oncol 2010. doi:10.1038/nrclino.2010.43
Table 1. Draft validation criteria for a soluble biomarker to be regarded as a valid biomarker reflecting structural damage in RA/SpA generated prior to consensus voting by Delphi technique.

A. Truth
1. A preclinical body of evidence that the soluble biomarker reflects tissue remodeling in established animal models of disease (e.g., collagen arthritis).
2. Evidence that the biomarker reflects tissue remodeling in human ex vivo models of tissue remodeling (e.g., cartilage, bone, synovial explant).
3. The biomarker has been immunohistochemically localized to joint tissues.
4. The molecular target and/or proteolytic cleavage site has been well characterized.
5. The biomarker demonstrates sensitivity and specificity for target of joint tissue origin.
6. Relation of biomarker to synthesis, degradation, turnover of joint tissue components has been characterized.
7. Levels of the biomarker correlate with scores for other biomarkers that have been established as possessing predictive validity for structural damage (e.g., MRI for erosive RA).

B. Discrimination
1. The assay for measurement of the biomarker is reproducible (coefficient of variation: intra assay ≤ 10%, inter assay ≤ 15%).
2. The effects of the following sources of variability on levels of the biomarker in normal individuals are known (rate each item independently): age, sex, menopause, circadian rhythms, body mass index, ethnicity, physical activity, meals, seasonal variation (9 criteria).
3. The effects of the following sources of variability on levels of the biomarker in patients are known: NSAID, renal and hepatic disease, the contribution of different affected joints (3 criteria).
4. The metabolism, clearance, and half-life of the biomarker have been characterized in (A) normal individuals and (B) patients with arthritis (2 criteria).
5. The biomarker demonstrates high sensitivity and specificity in comparisons of the disease population with age and sex matched healthy controls.
6. The biomarker demonstrates independent association with the structural damage endpoint (van der Heijde modification of Sharp Score for RA, mSASSS for AS) at the level of both absolute and relative change in (A) a clinically well defined prospective cohort, (B) a randomized controlled trial, and (C) a clinically well defined prospective cohort of patients with preradiographic disease. These should be of adequate sample size, and followup should be of sufficient duration to detect change (3 criteria).
7. The biomarker demonstrates increased responsiveness (i.e., magnitude of change) compared to the structural damage endpoint (e.g., erosion score) in patients receiving disease-modifying therapies.

C. Feasibility
1. The assay for measurement of the biomarker has been well characterized and is internationally standardized (availability of reference standards).
2. The assay for measurement of the biomarker is (A) methodologically simple and (B) commercially available (2 criteria).
3. The biomarker assay should demonstrate adequate analytical dilution recovery, sensitivity, and quantification limit.
4. Stability of the biomarker at room temperature and in frozen specimen has been documented.
5. Analytical performance of the biomarker assay has been documented in several body fluids (serum, synovial fluid, urine).
Draft validation criteria for a soluble biomarker to be regarded as a valid biomarker for RA generated prior to consensus voting by Delphi technique

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Box 1  Strength-of-evidence criteria for evaluating biomarkers

In line with previous work carried out elsewhere\textsuperscript{10,24}, the PSTC considered several criteria in initial selection of renal biomarkers for investigation. These criteria are outlined below.

- Availability of a sufficiently validated analytical assay
- Biological plausibility of the association of the biomarkers with injury to the organ of interest
- Understanding of the molecular mechanism of the biomarker response
- Strong association of changes in biomarker levels to pathological outcomes and superior performance relative to currently accepted biomarkers
- Consistent response across mechanistically diverse toxicants, sexes, strains and species
- Both dose-response and temporal relationships relating the magnitude of biomarker alterations to the severity of injury, and the onset of and recovery from injury
- Adequate specificity to ensure that the biomarker does not respond to injury of other organs or to benign activation of physiological processes in the organ of interest

Ref: Sistare, Nat Biotech 2010, 28; 5
Methodology workshop:

• Compare criteria from both approaches
• Analyse similarities and differences
• Identify consensus criteria applicable to all fields in nutrition research
• Identify specific criteria for specific fields, if relevant
• Can we create a grading system (e.g. GRADE)?
Methodology of application:

- Create list of recognised markers
  - Based upon markers of Approach B
  - Supplemented by relevant others from approach A and workshop
- Apply the consensus criteria on the markers
- Discuss the correspondences and discrepancies
Potential outcomes:

• List of consensus criteria
• List of commonly used markers that comply with consensus criteria
• List of infrequently used markers that comply with consensus criteria
• List of commonly used markers that do not comply with consensus criteria
• Clear overview of gaps in ‘validation’ of markers for nutrition research
• List of specific criteria for specific fields

Publications

• From the workshop a supplement with chapters on:
  o The proceedings of the workshop with the consensus list of criteria
  o The report on the Approach A
  o The report on the Approach B reporting forms

• Interim articles provided by several expert groups with a review on the markers in their field of expertise
Current state?

Step 1 – 2011:
• Approach A
  o Extracting the criteria from the relevant literature
  o Pointing out gaps & discrepancies
• Approach B
  o Reporting forms sent out
  o Concluding on the chosen markers the upcoming month
  o Deadline handing in forms 20 December

• External initiatives: contact with
  NutriTech, Food Industry Consortium, ILSI Branches,

Who else should be involved?

Step 2 – 2012
• Workshop 27-29 June 2012
You want to know more?

About ILSI Europe  [ILSI.EU]

About the Marker Initiative in Nutrition Research
[http://www.ilsi.org/Europe/Pages/MarkerInitiative.aspx]

ameheust@ilsieurope.be
jgarst@ilsieurope.be

About the Functional Foods Task Force
[http://www.ilsi.org/Europe/Pages/TF_FunctionalFoods.aspx]

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