Integrating Biological Markers into Clinical Research Study Design: A Biomarker is a Biomarker is a Biomarker

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  – i-STAT
  – Abbot POC
  – Roche
  – BRAHMS
  – Dianippon
  – Inovise
  – Biosite
  – GILEAD

• Provisional patent for a Sepsis Biomarker Risk Model
Outline

- What a biomarker is

Context

Content

- Extracting information
- Diagnostic research
- Risk stratification and prognosis
- Use in clinical trials
What is a biomarker?

• An objective measure of physiological state
  – Biological process
  – Disease state
  – Pharmacologic response
It starts like this...
...and ends like this
What is a biomarker?

Information

context
content
users
The importance of context: 
The case of elevated troponin

Appearance of troponin in blood after AMI (upper line) and microinfarction (lower line)

Adapted from Wu WHB et al. Clinical Chemistry 45: 1104–1121 (1999)
The problem: 

*troponitis agitans paralytica*¹

¹Evert Lamfers, Canisius-Wilhelmina Hospital in Nijmegen, the Netherlands
The problem:

troponitis agitans paralytica

Small rise in troponin noted on work up
The problem:

*troponitis agitans paralytica*

The cardiologist is called and there are agitated demands for extensive work up (catheterization, CT Angiography)
The problem:

troponitis agitans paralytica

The referring physician is instructed in no uncertain terms to do nothing
“...a misdiagnosis of acute MI, which is only based on the elevated troponin level, might lead to inappropriate and sometimes harmful management such as considering antithrombotic therapy in the presence of bleeding or coronary angiogram in the presence of renal failure.”

The flip side:

Missed heart attacks lead to extensive medical malpractice payouts

Median $941,000 (Range $81,000 to $9,000,000)\textsuperscript{1}

\textsuperscript{1}Jury Verdict Research, 1990-2000
When designing a study to evaluate a biomarker for detection of disease (diagnostic), the context of decision making will inform the utility of the results:

- Severity of disease
- Timeline of disease
- Consequences of true/false decision
Context ↔ Content

How the biomarker is used should depend on the context and information content
Information Content

Massive heart attack

Minor infarct

Adapted from Wu WHB et al. Clinical Chemistry 45: 1104–1121 (1999)
Outcomes associated with small changes in normal-range cardiac markers

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
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<tr>
<td>Decreasing troponin Versus stable</td>
<td>1.03</td>
<td>0.30-3.51</td>
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<tr>
<td>Increasing troponin troponin</td>
<td>3.59</td>
<td>1.40-9.21</td>
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<tr>
<td>Decreasing troponin Versus stable</td>
<td>1.19</td>
<td>0.33-4.23</td>
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<td>4.81</td>
<td>1.60-14.46</td>
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<td>ACI-TIPI</td>
<td>1.03</td>
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<tr>
<td>Decreasing CK-MB Versus stable</td>
<td>1.06</td>
<td>0.59-1.92</td>
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<tr>
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<td>1.87</td>
<td>0.83-4.20</td>
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<tr>
<td>Decreasing CK-MB Versus stable</td>
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<td>0.59-2.18</td>
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<tr>
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<td>0.49-3.85</td>
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<td>ACI-TIPI</td>
<td>1.03</td>
<td>1.02-1.05</td>
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Unadjusted models and models adjusted for probability of ischemia defined by ACI-TIPI are shown. OR indicates odds ratio.

Outcomes associated with small changes in normal-range cardiac markers

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Unadjusted models and models adjusted for probability of ischemia defined by ACI-TIPI are shown. OR indicates odds ratio.

Timing of Release of Various Biomarkers After Acute Myocardial Infarction

Information content is not always straightforward

Outcomes associated with discordant cardiac biomarkers

| CKMB(+) / CK(-) | 5.70  | (4.38–7.40)  |
| CKMB(+) / CK(+) | 4.36  | (3.64–5.23)  |
| CKMB(-) / cTn(+) | 4.79  | (3.40–6.76)  |
| CKMB(+) / cTn(-) | 2.17  | (1.72–2.75)  |
| CKMB(+) / cTn(+) | 26.58 | (18.00–39.30) |

*For the group with cardiac troponin, the reference category had negative troponin and negative CKMB results. For the group with creatine kinase, the reference category had a negative CKMB but either positive or negative creatine kinase result.

Information content: The case of HbA1c
Hemoglobin A1c is a time integrated measure of glucose exposure, and therefore:

- Diagnostic
- Prognostic
- Theragnostic
MPG versus HbA1c: $n = 1,439; r = 0.82; \text{PG (mmol/l)} = (1.98 \cdot \text{HbA1c}) - 4.29.$

Rohlfing C L et al. Dia Care 2002;25:275-278
MPG versus HbA1c: n = 1,439; r = 0.82; PG (mmol/l) = (1.98 \cdot 1 \text{HbA1c}) - 4.29.
Is the discordance real or is it measurement error?

If it is real, what does it mean?

What could cause a high HbA1c despite normal mean plasma glucose, and vice versa?

When information isn’t neatly aligned with our thinking, it becomes controversial…

…but it should stimulate research and practice
Enter Fructosamine

- Glycated serum protein
- Time-integrated measure of glucose exposure
- Independent of red cell physiology
- Also shows discordance with HbA1c – a “Gap”
The ‘Gap’ is...

- Heritable, independent of hemoglobin A1c
- Associated with outcomes, additive to mean plasma glucose

Cohen et al. Diabetes Care 2006; 1739-1743

It is probably real, but the physiology is still a mystery
Serum glucose

Transport across the red cell membrane

Glycation of hemoglobin

Hemoglobin A1c is a time integrated measure of glucose exposure
Serum glucose

Transport across the red cell membrane

Glycation of hemoglobin

HbA1c is a time integrated measure of glucose exposure
Serum glucose

Transport across the red cell membrane

Glycation of hemoglobin

HbA1c is a time-integrated measure of glucose exposure

Cohen et al. Blood 2008; 112: 4284-4291
Some persons with diabetes and well controlled HbA1c have poor outcomes, while some persons with diabetes and poorly controlled HbA1c have good outcomes, but why?

Perhaps the answer lies in the information content of biomarkers.
Clinical and translational research designed to understand the information content of a biomarker can answer fundamental clinical questions by exposing physiological mechanisms.
What is a biomarker?

• An objective measure of physiological state
  – Biological process
  – Disease state
  – Pharmacologic response

• Information
  – Content
  – Context
When a physician reduces decision-making to complete reliance on a biomarker, especially if relying on cut-points, does the researcher become the medical decision maker?

"OK, all those in favour of delegating decision-making, shrug your shoulders"
Biomarkers in diagnostic test research

If a researcher promulgates information loss by recommending arbitrary decisions on cut points, or fails to consider the information content of a biomarker, is he or she committing malpractice?
We have a duty to

- Design rigorous, unbiased studies of biomarkers appropriate to the state of knowledge
- Analyze and present data in a way that minimizes the chances of misinterpretation and maximizes appropriate medical decision making
• The biomarker
• The criterion standard
• The condition of interest
• Diagnostic accuracy
- The biomarker
- The criterion standard
- The condition of interest
- Diagnostic accuracy

The measure under investigation
• The biomarker
• The criterion standard
• The condition of interest
• Diagnostic accuracy

The assumed truth against which the biomarker is judged
• The biomarker
• The criterion standard
• The condition of interest
• Diagnostic accuracy

The condition or physiological state which the participants are suspected of having
• The biomarker
• The criterion standard
• The condition of interest
• Diagnostic accuracy

Measure of performance
The biomarker

Information intended to contribute to decision making about a patient’s health status

Etc…
Study design

The choice of study design should be guided by the state of knowledge.

Do biomarker levels differ between those with the condition of interest and those without the condition of interest?

Test for differences

≠

Are patients with ‘positive’ biomarker results more likely to have the condition of interest than patients with ‘negative’ biomarker results?

Predictive accuracy
The criterion standard

The best available method for establishing the truth about the presence or absence of the condition of interest

- Testing
- Follow up
- Chart / case review
- Combination of methods
The condition of interest

An identifiable condition, the presence or absence of which prompts clinical action, such as further diagnostic testing or modification or initiation of treatment.

Cincinnati Center for Clinical and Translational Science and Training
Accelerating and Improving Clinical and Translational Research
Diagnostic accuracy

The amount of agreement between the biomarker and the criterion standard

- Sensitivity and specificity
- Likelihood ratios
- ROC Curves
- Reclassification information
Diagnostic accuracy describes the behavior of the biomarker under the circumstances in which it was evaluated.
If subjects are not selected for study in the same way they would be selected for clinical evaluation, bias is introduced

- If patients with a condition not of interest but known to affect the biomarker are excluded, the accuracy will likely be inflated

- If patients with mild/questionable disease state are excluded, the accuracy will likely be inflated
If the biomarker is being evaluated as a confirmatory test, it may not perform with the same accuracy when it is used as a screening test.

The spectrum of the condition of interest can vary from practice setting to practice setting.

Wherever possible, diagnostic biomarkers should be studied in their natural setting.
Perhaps the greatest challenge to studies of diagnostic accuracy is ensuring fidelity of the criterion standard.
A study is flawed when the criterion standard inadvertently includes the biomarker

- If the clinician has the biomarker data and the criterion standard includes information about clinician action

- If two biomarkers are being compared and one of those biomarkers is accepted clinical practice

  - Is it possible to improve upon troponin as a biomarker for evaluating NSTEMI?
  - How can the biomarker under study ever be better than the assumed truth?
The answer lies in the information content of biomarkers
Timing of Release of Various Biomarkers After Acute Myocardial Infarction

Time

The most important context of all?
Diagnosis → Theragnosis

Onset  Progression  Tx  Outcome

Prognosis
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