New Biomarkers

- **Advances in technology and in biology lead to new markers**
  - Circulating proteins, lipids, metabalome, etc.
  - Genetic markers – 9p21.3, PCSK9, etc.
  - Imaging – CT, MRI, PET, etc.

- **Uses?**
  - Understand pathophysiology
  - New treatment “targets”
  - Clinical application
Clinical Use of Markers

- **Diagnosis**
- **Risk assessment**
  - Development of disease
  - Prognosis of established disease
- **Treatment selection**
- **New markers often heavily promoted**
- **How do we evaluate them?**
AHA Committee sought to develop standards for how to “keep score” about novel markers.

Focus was on the criteria for reporting studies in journals.

- Examples – CONSORT statement for RCTs, STROBE statement for epidemiologic studies.

Ultimate goal is to improve the design and conduct of research on novel risk markers.
Novel Risk Marker Evaluation

- **Statistical criteria**
  - Univariate association
  - Independent of standard markers (multivariate)

- **Decisional criteria**
  - Risk reclassification
  - Treatment change

- **Outcome criteria**
  - Better management, better outcomes

- **Cost-effectiveness criteria**

Circulation 2009;119:2408-2416
Key points of concern were:

- Full and transparent reporting of performance
- How much new marker adds to simpler, cheaper standard clinical evaluation
- No single statistic provides a complete picture of performance, so several should be reported
Assessing Added Predictive Ability

- If goal is to improve predictions using new information, one can look at whether
  - Predicted risk increased in patients who had events/disease
  - Predicted risk decreased in patients who did not have events/disease

- Idea is to see whether patients move “in the right direction”
New Measures

Two new measures assess whether predicted risk moves in the right direction

- By enough to cross into the next risk category (net reclassification improvement = NRI)
- By any amount (integrated discrimination improvement = IDI)

Stat Med 2008:27;157-172
HDL as a “New Marker”

- Framingham Offspring Data, 10 year f/u
- HDL adjusted hazard ratio 0.65 (CL 0.53-0.80, p<0.0001)
- But c-index increased only from 0.76 to 0.77, p=0.09
- IDI increased by 0.009 (p=0.008)
- NRI increase of 0.121 (p<0.001)

Stat Med 2008:27;157-172
Reclassification Table

<table>
<thead>
<tr>
<th>Model without HDL</th>
<th>Model with HDL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;6 per cent</td>
</tr>
<tr>
<td>Frequency (Row per cent)</td>
<td></td>
</tr>
<tr>
<td>Participants who experience a CHD Event</td>
<td></td>
</tr>
<tr>
<td>&lt;6 per cent</td>
<td>39 (72.22)</td>
</tr>
<tr>
<td>6–20 per cent</td>
<td>4 (3.81)</td>
</tr>
<tr>
<td>&gt;20 per cent</td>
<td>0 (0.00)</td>
</tr>
<tr>
<td>Total</td>
<td>43</td>
</tr>
</tbody>
</table>

Participants who do not experience a CHD Event

|                   | Model without HDL | Model with HDL |
|-------------------|                   |                |
| Frequency (Row per cent) |         |               |
| <6 per cent       | 1959 (93.24)     | 142 (6.76)     | 0 (0.00)      | 2101 |
| 6–20 per cent     | 148 (16.78)      | 703 (79.71)    | 31 (3.51)     | 882  |
| >20 per cent      | 1 (1.02)         | 25 (25.51)     | 72 (73.47)    | 98   |
| Total             | 2108            | 870            | 103           | 3081 |

- **Events:** 29 patients reclassified “upward” vs. 7 patients “downward”
- **Non-Events:** 173 patients reclassified “upwards” vs. 174 “downwards”
Genetic Score for CHD

- Cohort of 30,725 people in Finland, Sweden free of CHD
- 13 SNPs associated with CHD in GWAS
- Risk score = \( \sum \text{(alleles 0,1,2)} \times \text{HR for CAD} \)
- Score predicted CHD (p<0.0001)
  - Q5 OR = 1.63

Lancet 2010;376:1393-1400
Reclassification Analysis

- **Four risk categories (<5, 5-10, 10-20, >20)**
- **Change in 10 year risk categories**

<table>
<thead>
<tr>
<th></th>
<th>Up</th>
<th>Down</th>
<th>Net</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>37</td>
<td>28</td>
<td>+ 9</td>
</tr>
<tr>
<td>Non-Cases</td>
<td>301</td>
<td>353</td>
<td>+52</td>
</tr>
</tbody>
</table>

- **NRI = 0.022 (p=0.18)**
- **IDI = 0.004 (p=0.0006)**

*Lancet* 2010;376:1393-1400
Phase of Evaluation of a Novel Risk Marker

- **Proof of concept**
- **Prospective Validation**
  - predict development of future outcomes
- **Incremental value**
  - add predictive information to established, standard risk markers
- **Clinical Utility**
  - change recommended therapy
- **Clinical Outcomes**
  - randomized clinical trial
Conclusions

- **Novel risk markers**
  - *Aim to improve prediction*
  - *Driven by new technology*
- **Critical assessment is important before wide-spread adoption**
  - *Incremental information essential*
  - *Effect on clinical decision-making*
  - *Impact on outcomes*