Serial Assessments of Serum Biomarkers and When They Might Be Considered

Allan S. Jaffe, MD.*
Consultant - Cardiology & Laboratory Medicine
Chair, Core Clinical Laboratory Services
Professor of Medicine
Mayo Clinic and Medical School
Rochester, Minnesota

*Dr. Jaffe is or has been a consultant for and/or has received research support from most or all of the major diagnostic companies. He is also presently a consultant for Novartis.
Key Questions That Biomarkers May Help With

1. Is the risk intrinsic?
Impact of Biomarkers at Baseline in Cancer Patients

**NT-proBNP**
- Overall survival rate (%)
- Days
- No. at Risk: 545
- <125 pg/mL: 268, 257, 239, 185, 141, 62, 67%  
  >125 pg/mL: 277, 241, 205, 153, 112, 43, 49%
- P < 0.001

**MR-proADM**
- Overall survival rate (%)
- Days
- No. at Risk: 544
- <0.49 nmol/L: 192, 185, 170, 142, 109, 57, 71%  
  >0.49 nmol/L: 352, 312, 273, 196, 144, 49, 50%
- P < 0.001

**CT-proET-1**
- Overall survival rate (%)
- Days
- No. at Risk: 545
- <66.6 pmol/L: 395, 374, 340, 271, 204, 95, 65%  
  >66.6 pmol/L: 150, 124, 104, 67, 49, 11, 38%
- P < 0.001

**hsTnT**
- Overall survival rate (%)
- Days
- No. at Risk: 544
- <0.005 ng/mL: 271, 262, 243, 198, 150, 59, 69%  
  >0.005 ng/mL: 273, 236, 201, 140, 104, 47, 48%
- P < 0.001

Relationship of hscTnT to Cardiovascular Risk Factors

Survival – CHF/Death
Combined Troponin and NT-proBNP

Survival (%)

Top 20% both (159)
Top 20% BNP only (199)
Top 20% Trop only (206)
Others (1279)

Years

0 2 4 6 8 10 12

P<0.001

83.1 (22) 65.4 (45) 52.7 (61) 38.9 (78) 29.1 (90) 26.5 (92)
95.4 (9) 86.7 (26) 80.5 (38) 72.2 (54) 66.1 (65) 61.8 (69)
94.2 (11) 90.5 (18) 86.1 (26) 82.0 (33) 78.3 (39) 75.7 (41)
98.7 (16) 97.3 (32) 95.7 (50) 93.3 (76) 90.2 (108) 87.4 (125)
MACE in Patients With and Without BNP >50 ng/mL – STOP HF


No. at risk
Intervention 697 605 582 533 441 305 141 41
Control 677 587 558 501 418 296 118 27

All participants

Years since first study clinic visit

Proportion with major adverse cardiovascular events

Odds ratio 0.69
95% CI 0.49-0.98
P=0.04

Participants With BNP ≥50 pg/ml

Years since first study clinic visit

Proportion with major adverse cardiovascular events

Odds ratio 0.65
95% CI 0.40-1.05
P=0.08

Hospitalization or Mortality by Treatment Pontiac

Primary endpoint vs Months

Treatment (n=150) vs Controls (n=150)
P=0.035

Intensified Control

Key Questions That Biomarkers May Help With

1. Is the risk intrinsic?
2. Do we need serial values to unmask risk?
204 patients (661 cycles of high-dose CT)
39 males e 165 females (age 45±10 years).
Poor-prognosis cancer diseases:
  advanced or primary-resistant breast cancer
  refractory ovarian carcinoma
  Small-cell lung cancer
  high-grade non Hodgkin’s lymphoma
  refractory Hodgkin’s disease
High-dose chemotherapy
Results
Troponin I Positivity

n = 65 pts (32% )
TnI pos

n = 139 pts (68% )
TnI neg

Range = 0.5 - 2.0 ng/ ml
Mean = 1.0 ± 0.5 ng/ ml
**Change in LVEF**

- LVEF (%)
- Months

*P<0.001 vs baseline
§P<0.001 vs cTnl-group

J Am Coll Cardiol 36:517-22, 2000
Use of echo and hsTnI to predict cardiotoxicity following trastuzumab and anthracycline chemotherapy

- 19% of patients had concentrations of hsTnI >45pg/mL immediately after treatment.
- Of these, 54% had cardiotoxicity during follow-up.
- Troponin I measured 3, 6 and 9 months was not predictive of later cardiotoxicity.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Baseline HR (95% CI)</th>
<th>P</th>
<th>Visit 2 HR (95% CI)</th>
<th>P</th>
<th>Interval change HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>TnI</td>
<td>1.21 (0.92-1.61)</td>
<td>0.177</td>
<td>1.36 (1.07-1.73)</td>
<td>0.012</td>
<td>1.38 (1.05-1.81)</td>
<td>0.020</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>0.78 (0.48-1.25)</td>
<td>NS</td>
<td>0.89 (0.59-1.35)</td>
<td>NS</td>
<td>1.11 (0.80-1.54)</td>
<td>NS</td>
</tr>
<tr>
<td>CRP</td>
<td>1.18 (0.85-1.63)</td>
<td>NS</td>
<td>1.07 (0.72-1.60)</td>
<td>NS</td>
<td>0.95 (0.52-1.73)</td>
<td>NS</td>
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<tr>
<td>GDF-15</td>
<td>0.90 (0.59-1.37)</td>
<td>NS</td>
<td>1.26 (0.89-1.78)</td>
<td>0.189</td>
<td>1.33 (0.93-1.92)</td>
<td>0.118</td>
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<tr>
<td>MPO</td>
<td>0.66 (0.44-1.00)</td>
<td>0.052</td>
<td>1.23 (0.93-1.62)</td>
<td>0.149</td>
<td>1.34 (1.00-1.80)</td>
<td>0.048</td>
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<tr>
<td>PIGF</td>
<td>0.88 (0.55-1.40)</td>
<td>NS</td>
<td>1.17 (0.82-1.65)</td>
<td>NS</td>
<td>1.16 (1.73)</td>
<td>NS</td>
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<tr>
<td>sFlt-1</td>
<td>1.05 (0.70-1.56)</td>
<td>NS</td>
<td>0.76 (0.54-1.06)</td>
<td>0.109</td>
<td>0.75 (0.51-1.10)</td>
<td>0.139</td>
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<tr>
<td>Gal-3</td>
<td>0.70 (0.44-1.11)</td>
<td>0.128</td>
<td>0.94 (0.62-1.41)</td>
<td>NS</td>
<td>1.33 (0.86-2.05)</td>
<td>0.195</td>
</tr>
</tbody>
</table>

Ky et al: J Am Coll Cardiol 63:809-16, 2014
Modeling Prediction of Cardiotoxicity with cTnI and MPO

Ky et al: J Am Coll Cardiol 63:809, 2014
Key Questions That Biomarkers May Help With

1. Is the risk intrinsic?
2. Do we need serial values to unmask risk?
3. Can we treat biomarker defined risk?
443 pts
High-dose CT
TnI + = 114 pts (24%)

- Enalapril
  - n = 56 pts
  - started 1 month after HDC
  - continued for 1 year

- Controls
  - n = 58 pts

- physical examination, ECG, ECHO: b,1,3,6,12 months
**TnI Values in Both Groups**

**ACEI group**

**Control subjects**

<table>
<thead>
<tr>
<th>Time</th>
<th>No.</th>
<th>TnI (ng/mL)</th>
<th>No.</th>
<th>TnI (ng/mL)</th>
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</thead>
<tbody>
<tr>
<td>Early</td>
<td>56</td>
<td>0.18±0.38</td>
<td>58</td>
<td>0.23±0.44</td>
</tr>
<tr>
<td>M1</td>
<td>56</td>
<td>0.15±0.34</td>
<td>58</td>
<td>0.14±0.31</td>
</tr>
<tr>
<td>M2</td>
<td>56</td>
<td>0.02±0.02</td>
<td>58</td>
<td>0.10±0.17</td>
</tr>
<tr>
<td>M3</td>
<td>56</td>
<td>0.01±0.01</td>
<td>58</td>
<td>0.09±0.29</td>
</tr>
<tr>
<td>M6</td>
<td>56</td>
<td>0.01±0.01</td>
<td>57</td>
<td>0.03±0.06</td>
</tr>
<tr>
<td>M12</td>
<td>55</td>
<td>0.00±0.01</td>
<td>55</td>
<td>0.01±0.02</td>
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</tbody>
</table>

Circ 114:2474, 2006
# Blood Pressure and Biomarker Change for Responder and Non-Responder

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>OH</th>
<th>TA</th>
<th>OH/TA</th>
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<tbody>
<tr>
<td></td>
<td>0 mol/L</td>
<td>6 mol/L</td>
<td>P-value</td>
<td>0 mol/L</td>
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<tr>
<td><strong>Systolic BP, mmHg</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>All</td>
<td>135.2</td>
<td>122.5</td>
<td>&lt;0.001</td>
<td>135.0</td>
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<tr>
<td>Responder</td>
<td>140.5</td>
<td>117.4</td>
<td>&lt;0.001</td>
<td>139.3</td>
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<tr>
<td>Non-responder</td>
<td>128.5</td>
<td>128.8</td>
<td>NS</td>
<td>129.9</td>
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<tr>
<td><strong>Diastolic BP, mmHg</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>85.2</td>
<td>75.7</td>
<td>&lt;0.001</td>
<td>85.1</td>
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<tr>
<td>Responder</td>
<td>87.5</td>
<td>73.7</td>
<td>&lt;0.001</td>
<td>86.7</td>
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<tr>
<td>Non-responder</td>
<td>82.3</td>
<td>78.2</td>
<td>&lt;0.001</td>
<td>83.1</td>
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<tr>
<td><strong>Hs-cTnI, ng/L</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>All</td>
<td>4.6</td>
<td>4.2</td>
<td>&lt;0.001</td>
<td>4.7</td>
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<tr>
<td>Responder</td>
<td>4.7</td>
<td>4.0</td>
<td>&lt;0.001</td>
<td>4.7</td>
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<tr>
<td>Non-responder</td>
<td>4.6</td>
<td>4.4</td>
<td>&lt;0.001</td>
<td>4.7</td>
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<tr>
<td><strong>Hs-cTnT, ng/L</strong></td>
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<tr>
<td>All</td>
<td>2.1</td>
<td>2.1</td>
<td>NS</td>
<td>2.1</td>
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<tr>
<td>Responder</td>
<td>2.1</td>
<td>2.1</td>
<td>NS</td>
<td>2.1</td>
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<tr>
<td>Non-responder</td>
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<td>2.1</td>
<td>NS</td>
<td>2.1</td>
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<tr>
<td><strong>BNP, ng/L</strong></td>
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<tr>
<td>All</td>
<td>15.0</td>
<td>12.4</td>
<td>&lt;0.001</td>
<td>14.4</td>
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<tr>
<td>Responder</td>
<td>13.8</td>
<td>11.2</td>
<td>&lt;0.01</td>
<td>13.8</td>
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<td>Non-responder</td>
<td>17.0</td>
<td>13.7</td>
<td>&lt;0.05</td>
<td>15.7</td>
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<td><strong>NT-proBNP, ng/L</strong></td>
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<tr>
<td>All</td>
<td>64.8</td>
<td>53.3</td>
<td>&lt;0.001</td>
<td>62.5</td>
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<tr>
<td>Responder</td>
<td>62.2</td>
<td>48.0</td>
<td>&lt;0.001</td>
<td>60.6</td>
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<tr>
<td>Non-responder</td>
<td>70.4</td>
<td>60.7</td>
<td>NS</td>
<td>66.1</td>
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<tr>
<td><strong>eGFR, mL/min per 1.73 m²</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>All</td>
<td>92.9</td>
<td>90.4</td>
<td>&lt;0.001</td>
<td>91.7</td>
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<tr>
<td>Responder</td>
<td>93.7</td>
<td>91.3</td>
<td>&lt;0.001</td>
<td>92.1</td>
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<tr>
<td>Non-responder</td>
<td>91.2</td>
<td>89.1</td>
<td>0.0019</td>
<td>91.1</td>
</tr>
</tbody>
</table>

Jagodzinski et al: Clinical Chemistry 63:12, 2017
Key Questions That Biomarkers May Help With

1. Is the risk intrinsic?
2. Do we need serial values to unmask risk?
3. Can we treat biomarker defined risk?
4. Does such treatment improve outcomes?
**LVEF with and Without ACEI**

**Controls**

- No TnI increase
- TnI increase

**ACEI Group**

- No TnI increase
- TnI increase

**Circ 114:2474, 2006**
MACE in Patients With and Without BNP >50 ng/mL – STOP HF

All participants

- Odds ratio 0.69
- 95% CI 0.49-0.98
- P=0.04

No. at risk
- Intervention: 697, 605, 582, 533, 441, 305, 141, 41
- Control: 677, 587, 558, 501, 418, 296, 118, 27

Participants With BNP ≥50 pg/ml

- Odds ratio 0.65
- 95% CI 0.40-1.05
- P=0.08

No. at risk
- Intervention: 263, 251, 243, 223, 190, 133, 68, 18
- Control: 235, 225, 209, 189, 162, 125, 48, 7

Hospitalization or Mortality by Treatment Pontiac

Key Questions That Biomarkers May Help With

1. Is the risk intrinsic?
2. Do we need serial values to unmask risk?
3. Can we treat biomarker defined risk?
4. Does such treatment improve outcomes?
5. Does it provide insight into the mechanisms of the effects?
CTRCD by Arginine-NO Metabolite Levels at 2 Months

Arginine

Citrulline

Ornithine

ADMA

SDMA

MMA

Proportion Without CTRCD

Months

Finkelman et al: J Am Coll Cardiol 70:152, 2017
Changes in NTproBNP and hsTnT Over Time by Therapy Type*

*Courtesy BK - unpublished
We can use biomarkers at baseline to define a subgroup at risk. How are they optimally treated?

Can we use serial biomarkers to define risk and indicate who needs therapy?

Are there different treatments indicated by different patterns of biomarkers?

Can we follow the response to and predict its success with biomarkers?

IT IS TIME TO FIND OUT