Biomarkers, alcohol and health: recognizing the switch from moderation to abuse

Pamela Bean, Ph.D., M.B.A.
Millennium Strategies, Madison, WI
Rogers Memorial Hospital, Oconomowoc, WI
Outline

- The value of biomarkers
- Types of biomarkers
- Past – Present – Future
- Clinical Utility – Benefits
- Lessons learned – combinations
- Challenges today
What is a biomarker?

A biomarker is a biological indicator which varies with the amount of alcohol consumed.
Conventional methods to evaluate alcohol abuse are anecdotal and crude

- Smells like alcohol
- Fails duck walk (age effects)

- Mother looks into eyes or smells breath
  (very accurate, but inefficient and costly because mother not always available)
Self-Report Measures

**Strengths**
- Flexible
- Cost-effective
- Well-validated

**Weakness**
- Dependent on recall and honesty
VALUE OF BIOLOGICAL CORRELATES OF ALCOHOL ABUSE

- More objective than interviews
- More reliable than interviews
- Not influenced by patient or family denial
- Measure the effects of alcohol in the body
Chronology of biomarkers

- Classical:
  - Blood Alcohol Concentration (BAC)
  - Gamma glutamyltransferase (GGT)

- Contemporary:
  - Carbohydrate Deficient Transferrin (CDT)
  - Early Detection of Alcohol Consumption (EDAC)

- Future:
  - Hemoglobin Associated Acetaldehyde (HAA)
  - Fatty Acid Ethyl Esters (FAEE)
MOST DESIRABLE FEATURES FOR ANY BIOMARKER

- Simple
- Inexpensive
- Accurate
  - sensitivity plus specificity

Market Research - Millennium Strategies - 2001
Diagnostic Performance
Blood Alcohol Level (BAL, BAC)

Blood alcohol concentration (BAC) after the rapid consumption of different amounts of alcohol by eight adult fasting male subjects.* (Adapted from Wilkinson et al., Journal of Pharmacokinetics and Biopharmaceutics 5(3):207–224, 1977.)

100 mg% is the legal level of intoxication in most States. 50 mg% is the level at which deterioration of driving skills begins. (JAMA 255:522–527, 1986.)

*If the same number of drinks are consumed over a longer period of time, BAC’s will be lower.
GGT

- Elevated in serum due to liver damage
- Elevated levels observed at >40 g ethanol/day
- Half-life is 14 to 26 days
- Many false-positives:
  - non-alcoholic liver disease, hyperthyroidism, obesity, anticonvulsants, and anticoagulants

- **Trend**: Useful when used with other tests
Contemporary biomarkers

- CDT
- EDAC

- Technical background
- Diagnostic performance
- Clinical utility
Carbohydrate Deficient Transferrin

N-Acetylg glucosamine
Mannose
Galactose
Sialic acid

N1 - ND1 - ND2 - ND3 - CD1 - CD2 - CD3 - C1
Fe³⁺
The CDT assay

- CDT tests have 2 steps:
  - Separation of CDT
  - Quantification of CDT

- TAT = 2hrs, same day results, automation

- Distributors in the U.S. – Bio-Rad and Equal

- CPT code: 82373 (reimbursement = $25)
CDT performance parameters

- **Specificity:** 95%
- **Sensitivity:** 65-70%
Diagnostic performance of CDT

- **Specificity**: best asset
- **Sensitivity**, varies with:
  - date of last drink
  - grams of alcohol ingested
  - extent drinking behavior
- **False-positives**:
  - Chronic HCV
  - Severe liver disease
- **False-negatives**:
  - young, one-time heavy drinkers
Effects of alcohol in the body

- Sleep disorders
- Anxiety
- Hypertension
- Palpitations
- Gastritis
- Liver diseases
- Nicotine stains
- Hand tremor
- Muscular weakness
Routine blood chemistries

- Cl, K, Na
- AST, GGT
- Bilirubin Ratio
- HDL-Cholesterol
- MCV, WBC, Monocytes, Platelets

EDAC Threshold Levels

- **Men**
  - Average 4 Drinks Per Day For 2 Weeks Prior To Testing

- **Women**
  - Average 3 Drinks Per Day For 2 Weeks Prior To Testing
How does the EDAC work?

- **EDAC** is calculated from routine test results.
- Statistical analysis uses a pattern recognition program to form a fingerprint for each subject.
- This fingerprint is matched to previous fingerprints derived from known heavy and light drinkers (Database 1500+ individuals).
Three Part EDAC Results

- Prediction of heavy drinking:
  - Positive versus Negative

- Probabilities
  - $P_1 = \text{Probability of Heavy Drinking}$
  - $P_2 = \text{Probability of Non-heavy Drinking}$

- Risk Level
  - High – Average - Low
The EDAC test

- The EDAC test has 3 steps:
  - Ordering the routine panel
  - Performing the statistical analysis
  - Making a prediction

- Data analysis is fast and straightforward
- TAT = same day results
- Available through Alcohol Detection Services
EDAC performance

- Specificity
  - 89%

- Sensitivity
  - 70-75%
When to use them: Clinical utility

- Screening in general population?
- Confirm a suspicion?
- Routine health examination?
- Monitor relapses?
Case Study 1: Screening

- *Kaiser Permanente* wants to screen all applicants for alcohol abuse,

Can we use CDT to screen for heavy drinking in the general population?
POSITIVE PREDICTIVE VALUE

- **PPV is key in the clinic:**
  - If my patient has an abnormal biomarker, how likely is he to be a heavy drinker?
  - Sensitivity is key in the lab:
    - If my patient is a heavy drinker, how likely is he to have an abnormal biomarker?
Prevalence = 7%
Sensitivity = 65%
Specificity = 95%
N = 1000

<table>
<thead>
<tr>
<th>Alcohol abuser</th>
<th>+</th>
<th>-</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marker (+)</td>
<td>46</td>
<td>47</td>
<td>93</td>
</tr>
<tr>
<td>Marker (-)</td>
<td>24</td>
<td>883</td>
<td>907</td>
</tr>
<tr>
<td>Total</td>
<td>70</td>
<td>930</td>
<td>1000</td>
</tr>
</tbody>
</table>

PPV = 0.50 (46/93)
Improving PPV

Two ways to improve PPV:

- Improve test’s performance
- Increase disease prevalence
Prevalence = 7%
Sensitivity = 80%
Specificity = 98%
N = 1000

<table>
<thead>
<tr>
<th></th>
<th>Alcohol abuser</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Marker (+)</td>
<td>56</td>
</tr>
<tr>
<td>Marker (-)</td>
<td>14</td>
</tr>
<tr>
<td>Total</td>
<td>70</td>
</tr>
</tbody>
</table>

PPV = 0.76 (56/74)
### Alcohol abuser

<table>
<thead>
<tr>
<th>Marker (+)</th>
<th>163</th>
<th>37</th>
<th>200</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marker (-)</td>
<td>87</td>
<td>713</td>
<td>800</td>
</tr>
<tr>
<td>Total</td>
<td>250</td>
<td>750</td>
<td>1000</td>
</tr>
</tbody>
</table>

**Prevalence = 25%**

**Sensitivity = 65%**

**Specificity = 95%**

**N = 1000**

**PPV = 0.82 (163/200)**
Combining biomarkers

- When test performance and disease prevalence improves, PPV improves

- Both can be accomplished by....
Size of the U.S. market for CDT

- Clinical testing: 25%
- Life Insurance: 75%

300K CDT tests done in the U.S. annually
Case Study 2: Confirm suspicion

- Jim Beam is a heavy smoker and his record shows one reckless driving offense
- He admits having a couple of drinks/night but denies heavy drinking
- Routine lab panel shows elevated Liver enzymes
- Underwriter requests CDT

Liver enzymes
Elevated

CDT–
Non-abuser

CDT+
Abuser
On the Risk, 2002; vol 18: 72 - 76.
Reflex Criteria

- ALT ≥ 90 U/L
- AST ≥ 100 U/L
- GGT ≥ 100 U/L
- CDT ≥ 6%
## EDAC combined with CDT

<table>
<thead>
<tr>
<th></th>
<th>Conventional</th>
<th>EDAC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Subjects</strong></td>
<td>535</td>
<td>535</td>
</tr>
<tr>
<td><strong>Positive Markers</strong></td>
<td>28</td>
<td>33</td>
</tr>
<tr>
<td><strong>% of Total Subjects Tested</strong></td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td><strong>Confirmed Subjects CDT</strong></td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td><strong>% Subjects Confirmed</strong></td>
<td>18%</td>
<td>39%</td>
</tr>
</tbody>
</table>
Case study 3: Health Assessment

- 45 year exec. drinks every day:
  - 1 beer at lunch (15 grams)
  - 1 margarita (15 grams) during happy hour
  - 2 glasses of wine (30 grams) - with dinner

- He doubles this amount during the weekends
- He goes to work everyday, feels well
- Normal liver enzymes and elevated HDL
- Is he drinking too much?
## Alcohol Marker Positive Rates

<table>
<thead>
<tr>
<th>HDL-C</th>
<th>% CDT+</th>
</tr>
</thead>
<tbody>
<tr>
<td>60-64</td>
<td>6.1%</td>
</tr>
<tr>
<td>65-69</td>
<td>9.3</td>
</tr>
<tr>
<td>70-74</td>
<td>12.0</td>
</tr>
<tr>
<td>75-79</td>
<td>15.6</td>
</tr>
<tr>
<td>80-84</td>
<td>19.4</td>
</tr>
<tr>
<td>85-90</td>
<td>24.7</td>
</tr>
<tr>
<td>&gt;90</td>
<td>36.6</td>
</tr>
</tbody>
</table>

HDL and CDT = good combination to detect harmful drinking

On the Risk 1997: vol 13; 67-72
CDT as a health risk marker
Case Study 4: Monitoring drinking

- Mrs. Beam starts outpatient treatment
- Clinician monitors abstinence and relapses using CDT and GGT
- CDT: a useful monitoring tool
DUI Offender

Monitoring 5th offense: Male - Age 39

<table>
<thead>
<tr>
<th>Date</th>
<th>EDAC</th>
<th>P1</th>
<th>P2</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/09/01</td>
<td>Positive</td>
<td>.58</td>
<td>.42</td>
<td>Average</td>
</tr>
<tr>
<td>2/23/01</td>
<td>Negative</td>
<td>.37</td>
<td>.63</td>
<td>Average</td>
</tr>
<tr>
<td>3/24/01</td>
<td>Positive</td>
<td>.67</td>
<td>.33</td>
<td>High</td>
</tr>
<tr>
<td>4/16/01</td>
<td>Negative</td>
<td>.00</td>
<td>1.00</td>
<td>Low</td>
</tr>
</tbody>
</table>
Take-home messages

- **Case Study 1**: Screen with conditions
- **Case Study 2**: Good to evaluate suspicion
- **Case Study 3**: Are we drinking too much?
- **Case Study 4**: Good to monitor relapses
Biomarkers more objective than interviews

Combinations of biomarkers is the trend

Clinical utility includes several benefits:
- Confirm a suspicion of abuse
- Health risk assessment
- Monitoring relapses
Challenges Today

- **Lab challenges:**
  - Standardization of tests
  - Proficiency testing
  - Codes and re-imbursement

- **Clinicians challenges:**
  - To test or not to test?
  - Need for patients’ consent
Contact information:

PamBean@charter.net

608-829-1973
Alcohol-related liver disease

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>Mild</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDT</td>
<td>++++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>GGT</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
</tbody>
</table>

CDT more sensitive than GGT in early stage LD
Non-alcohol-related LD

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>Mild</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CDT</strong></td>
<td>-</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td><strong>GGT</strong></td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
</tbody>
</table>

CDT more specific than GGT in non-alcoholic LD
**CDT and GGT combined**

<table>
<thead>
<tr>
<th>Females (n=613)</th>
<th>%Sensitivity (&gt;40 g/day)</th>
<th>%Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CDT</strong></td>
<td>29</td>
<td>92</td>
</tr>
<tr>
<td><strong>GGT</strong></td>
<td>44</td>
<td>90</td>
</tr>
<tr>
<td><strong>GGT+CDT</strong></td>
<td>61</td>
<td>81</td>
</tr>
</tbody>
</table>

The WHO/ISBRA Collaborative study
ICD-9 CM codes for CDT

- 303.00 (acute alcoholic intoxication)
- 303.90 (alcohol dependence)
- 357.5 (alcoholic polyneuropathy)
- 571.0 (chronic liver disease/cirrhosis)
- 573.0 (disorders of the liver)