

Biomarkers – Challenges and Opportunities

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Biomarkers

- Prostatic acid phosphatase – 1936
- Biomarkers --360,000 peer reviewed reports
- Genomic tests –18,000
- Proteomic tests - 264
- Several hundred FDA approvals or clearances including perhaps several dozen genomic or genetic

Biomarkers

- Only a handful in mainstream common clinical use
- Most remain single proteins (troponin, BNP, PSA)
- Most common genetic markers – Factor II and V Leiden, Cystic Fibrosis
- Most common for selecting drug use – ER/PR, Her 2, long QT?

Promise of Biomarkers

- Completion of genomic map – April 2003
- New diagnostic technologies – NAT, microarrays, bioinformatics
- Objective to use personalized medicine to improve patient outcomes and drug business outcomes

Right Questions

- Simplest marker – troponin
- Most complex – an expression microarray or complex pattern of proteins integrated by complex artificial intelligence
- Questions the same

Scientific Questions -- Fryback and Thornbury (1991)

- Technical efficacy (correct analytical signal)
- Diagnostic accuracy efficacy (correct clinical signal)
- Diagnostic thinking efficacy (impact on decision making)

Scientific Questions -- Fryback and Thornbury (1991)

- Therapeutic efficacy (impact on therapy)
- Patient outcome efficacy (impact on outcome)
- Societal efficacy (public health good)

Administrative Questions

- Who will pay for development
- How will test be used
- Who will pay for test
- What business models, issues (IP) must be addressed
- How will tests be regulated
- How will users be educated
- What outcomes will be expected

Root Cause of Failure

- Both
- Not an agnostic on this one
- It's the science stupid
- SARS model

Clear Road Maps

- Literature
- FDA guidances
- CLSI standards
- FDA templates (www.fda.gov/cdrh/oivd)

Analytical Performance

- Accuracy
- Precision
- Specificity
- Sensitivity*

Feasibility Studies

- Set hypothesis
- Determine patients for study
- Determine test sites
- Establish cut-offs for testing (opera isn't over until the testing set sings)
- Determine criteria for success so can power study correctly

Clinical Studies

- Clinical sensitivity
- Clinical specificity
- Predictive values of a positive or negative
- Likelihood ratios

Methodological Challenges

- Preanalytical vagaries
- Selection bias
- Spectrum bias
- Verification bias
- Discrepancy resolution
- Lack of gold standards

Not the Most Esteemed Track Record

- Troponin
- Poorly standardized analytically
- Cut-off problem
- Practice outcomes emerging

Biomarker Initiatives

- Good news
- Common and friendly scientific principles
- Need for robust test (however designed and decided)
- Need for information on clinical test use
- Need to separate testing from training

Biomarker Initiatives

- Bad news
- Different dances to the same music
- Lack of agreement on basic terms – validation, verification, qualification
- Lack of agreement on methodologies
- Little specimen and data sharing
- Rife with financial uncertainties

Life Cycle of Test

- Analytical performance
- Feasibility studies
- Clinical performance -- effectiveness
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- Clinical use
- Real world use

Forces of Nature

- Health care costs – 16% of GNP
- Multiple expensive new competing technologies
- Stakeholders interested in IOM report and safety in medicine
- Evolution of Evidence Based Medicine – AHRQ and CDC
- Trump regulation

Good Science

- FDA has dual mission
- Promote public health
- Protect public health

Not One Path to Truth

- Different tolerance for uncertainty
- Different designs
- Differences in the math
- Tension between what works for the individual and what works for the greater good

...let us be true

To one another! for the world, which seems
To lie before us like a land of dreams,
So various, so beautiful, so new,
Hath really neither joy, nor love, nor light,
Nor certitude, nor peace, nor help for pain;
And we are here as on a darkling plain
Swept with confused alarms of struggle and
flight,
Where ignorant armies clash by night.