Biomarkers: Finding Easier and Better Ways to Measure the Effects of Duchenne

Linda H. Cripe, M.D.
Professor of Pediatrics
Nationwide Children’s Hospital
The Ohio State University
Biomarkers for dummies smart people

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Objectives

• What are biomarkers?
• Why are biomarkers important to the patient with DMD?
“Our ability to study and treat disease and to develop effective health promoting interventions are hampered by a lack of unique, reliable, quantifiable, easily measured biomarkers that correlate well with disease progression”
What is a biomarker?

- Biomarker is a “biological indicator” used to measure onset or progression of a disease
  - How a disease is reacting to a treatment
  - How a drug is behaving in the body
- Common biomarkers include:
  - Body temperature
  - Blood pressure
  - Heart rate
  - Blood or protein in the urine
  - CT scan or MRI
- Patients with DMD require unique and specialized biomarkers
Biomarkers are “sick”!!

Google “biomarker”
- 5,860,000 hits

• Pub med
  - 566,670 articles pertaining to biomarkers

• Biomarkers are important in all diseases
  - Cancer, heart, lung, kidney, etc.

• Thousands of biomarkers have been identified to date
Biomarkers are not new

• 1845 Dr. Henry Bence Jones discovered an unusual substance in the urine of a patient with bone pain

• Substance would become known as “Bence Jones protein” and is a biomarker for multiple myeloma

• Felt to be the first cancer biomarker
Initiatives launched to address biomarkers

- Innovative Medicines Initiative Joint Undertaking: http://www.imi-europe.org/
- NIH RoadMap Initiative: http://nihroadmap.nih.gov/overview.asp
- NCI/FDA/AACR Cancer Biomarker Collaborative
- Critical Path (C-Path) Institute: http://www.c-path.org/
- Health and Human Services (HHS) Personalized Health Care Initiative: http://www.hhs.gov/myhealthcare/
- Standards for Reporting Diagnostic Accuracy (STARD)
- International Cancer Biomarker Consortium: http://www.fhcrc.org/science/international_biomarker/
- Secretary’s Advisory Committee on Genetics, Health and Society (SACGHS): http://www4.od.nih.gov/oba/sacghs.htm
- Personalized Medicine Coalition: http://www.personalizedmedicinecoalition.org/
- Advamed: http://www.advamed.org/MemberPortal/About/
- Coalition for the 21stCentury Medicine: http://www.twentyfirstcenturymedicine.org/
Biomarker types

- **Diagnostic** biomarkers
  - Identify, confirm or rule out a diagnosis
- **Prognostic** biomarkers
  - Determine disease progression in a patient
- **Predictive** biomarkers
  - A response to a proposed therapy
- **Pharmacodynamic** biomarkers
  - Tell us how a drug behaves in the body
  - Does a drug reach the targeted area?
  - Correlations between dose and response
  - Intended and unintended effects
An ideal biomarker is....

- **Specific**
  - Present when disease is present and not present when there is no disease

- **Sensitive**
  - Changes as the disease changes

- **Predictive**
  - Allows you to predict disease severity or course

- **Robust**
  - Rapid, simple, accurate, inexpensive and can be used in all individuals
    - Ideally should be easy to obtain the needed samples
    - More invasive and inconvenient the sampling procedure the less people are willing to participate
A Biomarker must be practically perfect in every way!
Biomarkers are important in clinical trials

Duchenne Muscular Dystrophy

- Prognosis
  - Treat or don’t treat?
  - Prediction of drug response
    - Which drug?
  - Pharmacodynamics
    - What dose?
Challenges presented by biomarkers

- Biomarker literature dominated by small studies with insufficient statistical power
  - Small patient cohorts
  - Lack of standardization
  - Very few biomarkers subjected to rigorous validation
  - Inadequate stringency in clinical phenotyping

- The ideal biomarker
  - Measured in a minimally invasive way,
  - Can be measured repeatedly over time
  - Identifies early stages of disease,
  - Is indicative of disease prognosis
  - Correlates well with progression and response to therapy.
Biomarkers in clinical trials

• Can be used to help determine patient selection and clinical trial eligibility
  – define the inclusion and exclusion criteria
  – help researchers ensure that randomized study groups within a trial are similar

• Reduce research costs by reducing the number of patients needed for the trial and the time for monitoring
Biomarkers in DMD and clinical trials

• Many trials are ongoing or about to begin in DMD
• The identification of informative biomarkers to assess the effect of these treatments would be invaluable
• Muscle biopsy has been the historical gold standard
• However…..
  – In a long trial
    • Monitoring by repetitive muscle biopsy is not ethical or feasible
  – In a short trial…..
    • Since disease progression is slow, monitoring changes of functional improvement is unrealistic
Biomarkers in DMD

- The lack of identification of informative biomarkers in DMD impacts clinical research
Muscle biopsy in DMD clinical trials

• Muscle biopsy allows you to determine if dystrophin protein has been restored to the muscle membrane

• Problems:
  – Invasive
    • Involves taking repetitive samples from individuals with decreased muscle mass
  – Susceptible to human error
    • Errors in interpretation
    • Errors in specimen processing
  – Variability of muscle involvement between muscles
    • All muscles in the body are not affected uniformly
  – Variability of involvement within a muscle
Muscle involvement in DMD is variable

Fig. 1. Representative T1-weighted fat-suppressed images of the lower leg of a boy with DMD that seems to have relatively little involvement (A) and of a boy in whom the disease is more progressed (B). tibialis anterior (TA), extensor digitorum longus (EDL), tibialis posterior (TP), peroneaus (Per), soleus (Sol), lateral gastrocnemius (LG), and medial gastrocnemius (MG).

Functional biomarkers in DMD

- Timed functional measures such as six minute walk are not perfect
  - Test results dependent on
  - Effort
  - Motivation and cooperation
  - Facility
  - Test administrator

- Other functional measures subject to similar problems
Biomarkers in DMD

• CPK commonly used blood biomarker
  – Increased levels reflect muscle damage or disease
  • Drawbacks
    – Levels fall when disease progresses
      » Due to loss of muscle tissue
    – Levels can reflect activity
    – CPK levels can be increased in normal individuals due to exercise, exertion or trauma

• CPK is not an ideal biomarker
• Better biomarkers in DMD are needed
Example of potential biomarker benefit in DMD

- Many boys are started on steroids
- Some boys that are “steroid responders” and some are steroid non-responders
- If we had a biomarker that would allow us to identify which boys are steroid responder or non-responder we could more effectively treat patients and potentially reduce morbidity
MRI as a biomarker

- MRI is a non-invasive imaging method that does not involve radiation
- There is current interest in using quantitative MRI imaging to monitor disease progression and efficacy of treatment
- Stay tuned!!
Progressive involvement of the extensor digitorum brevis (EDB) muscle on MRI grading (patients from left to right) Good correlation between the muscle MRI scoring of the EDB and tibialis anterior/posterior muscles.

Kinali M et al. Neurology 2011;76:346-353
MRI as a cardiac biomarker
Myocardial strain imaging as a potential cardiac biomarker
Conclusions

• Biomarkers are indicators of disease status or treatment effects
• If used as outcomes in clinical trials, biomarkers can shorten the length of a clinical trial
• Biomarkers should correlate with ultimate outcome: prolonged life
• We are in need of more and better biomarkers for DMD
We all want a Cure
Unfortunately, this is not......
Research is needed to find a cure
Informative biomarkers will play an important role in finding a cure.
THANK YOU