What is a biomarker and what can it be used for?
DSBS meeting February 21, 2011
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Outline

- Biomarker definition
- Classical examples of biomarkers
- Purposes of biomarkers (more examples)
- Clinical trial programs
- (Regulatory aspects)
- Gene expression biomarkers

Biomarker definition

- A characteristic that is objectively measured and evaluated as an indicator of healthy biological processes, pathological processes, or pharmacological responses to therapeutic intervention
- Note: ”an indicator of” means ”reflecting”
- ”evaluated as” means ”with the purpose of”, not ”proven to be”

Properties of a biomarker?

- Constant (vs. Time-dependent)?: Yes (like genes), but constant biomarkers cannot be outcomes
- Binary? Yes, but outcome biomarkers are more useful if they are continuous, I think
- Multivariate? Yes (but often this is used to derive a univariate summary)

Examples that are not biomarkers

- Rating scales (MADRS)
- PRO (patient reported outcomes)
- Tolerability
- Pain
- Imaging interpretation (picture alone is a biomarker)

Surrogate endpoint definition

- A biomarker that is intended to substitute for a clinical endpoint. A surrogate endpoint is expected to predict clinical benefit (or harm or lack of benefit or harm) based on epidemiological, therapeutic, pathophysiological, or other scientific evidence

Weight

- Most classical example
- Doctors office: Light clothes, no shoes
- Home: very light clothes, morning
- Daily variation in the kg-range
- Does weight reflect health? Age-dependence; height adjustment; composition: fat versus muscles: apple-shape (abdominal fat)
- Does weight-change reflect health?
- Is weight-reducing treatments helpful? Water-reducing; metabolism-increasing

Related variables

- BMI (weight/height^2)
- LBM (lean body mass) formula
- LBM concept
- BSA (body surface area) formula
- Waist circumference
- Waist hip ratio

FDA (weight)

- Primary endpoint: %weight loss (mean difference to placebo stat. sign. and ≥5%) + response criteria
- Inclusion: BMI≥30 or BMI≥27+comorbidity
- Reasonable sample size: 4500 for 1y
- DEXA scanning on some
- Safety important: Recently a drug was taken off the market due to increased cardiovascular risk

Temperature

- Circadian variation
- Core temperature versus surface temperature
- Measurements: rectal, mouth, ear
- Monthly variation (females)
- Fever (increased temperature) present with many infections

Blood pressure

- Systolic and diastolic
- Supine or sitting
- White coat hypertension
- High measurement error
- Office versus 24h measurements
- EMA guideline (2010): 3 baseline visits; systolic primary; diastolic secondary; sufficient number of patients for mortality (1y); no suspicion of adverse target organ effect

Cardiovascular markers

- Cholesterol (high-density versus low-density)
- Free fatty acids
- Triglycerides

Diabetes biomarker primer

- Blood glucose sensitive to meals. Strategies:
- 1. Unrestricted (high upper normal limit)
- 2. Fasting (overnight)
- 3. Fasting supplemented with specific challenge (glucose tolerance test)
- 4. HbA1c (reflecting average blood glucose over 6 weeks)

Diabetes biomarkers

Biomarker	Type 1	Type 2
Urine glucose (UT)	↑	↑
Blood glucose (UT)	↑	↑
Hba1c (target)	↑	↑
Insulin (UT)	↓	↔
C-peptide	↓	↔
Antibodies (sel.)	↑	Normal
Insulin resistence	Normal	↑
Age	Flat incidence	Old
BMI	Normal	↑
pH/HCO3 (UT)	↓ (severe)	

Conclusion on classical biomarkers

- Many classical biomarkers are widely used and accepted, both to define diseases and for treatment decisions
- However, it is also well known that they are far from perfect

Types of biomarkers

- Diagnostic
- Early detection
- Monitoring
- Prognostic
- Predictive/Safety/dose

Examples-diagnostic

- Disease vs. healthy or disease vs. other diseases?
- Temperature
- Bacterial tests (streptococcal)
- Origin of cancer tissue

Examples – early detection

- Gene test for monogenic diseases (like cystic fibrosis)
- PSA (still controversial)
- Breast cancer screening

Examples – Monitoring

- HbA1c (diabetes)
- Immune markers (after transplantation)
- Temperature (during infection)
- Titre (after vaccination)
- Tumour size (cancer)
- Blood oxygen (heart and lung diseases)
- QT_c (specific safety study)

Prognostic

- Mammaprint: 70 gene expression to split breast cancer patients into high vs. low risk of metastases

Predictive (which treatment; which dose)

- "Companion diagnostic", "personalized medicine": Measurable before/without treatment
- Body weight
- P450 enzymes (normal or poor metabolizers)
- Herceptin (Her2 positive breast cancer)

Biological understanding

- Useful
- But regulatory pathway does not require this
- Recommended to follow up on this in parallel to other activities

Practical issues

- Timing: A diagnostic needs fast turn-around time
- Other: Inconvenience to patient; risk to patient; circadian variation (incl. meals); sex, age, weigth dependence; storage; stability; transportation; central lab.

Validation and qualification

- Validation:
- The measurement is correct in the technical sense: Including sources of random error
- Qualification (clinical validation):
- The measurement is related to the clinical state of the patient

Clinical trials to qualify a biomarker for monitoring

- Example: For HbA1c, DCCT (1993) was the turning point
- 1441 patients; stratified by retinopathy; followed for up to 9 years; price-tag 1 bill. $
- Intensified insulin treatment lead to both reduced HbA1c and reduced risk of complications (vs. conventional therapy)
- Relation between post-treatment HbA1c and complications in intensive group

Clinical trials to qualify a biomarker as diagnostic

- Trial in relevant population (meaning similar to the one where it will be applied)
- If multivariate diagnostic, formula derivation should be pre-specified
- Evaluate sensitivity/specificity compared to gold standard. Evaluate AUC for ROC curve

Evaluation as diagnostic (in targeted population!)

Subject count	Diseased	Healthy
Biomarker+	A	B
Biomarker-	C	D

Diseased/healthy according to reference standard

Sensitivity: A/(A+C); Specificity: D/(B+D)

PPV: A/(A+B); NPV: D/(C+D)

Odds ratio: A D / (B C)

Agreement: (A+D)/(A+B+C+D) not relevant!

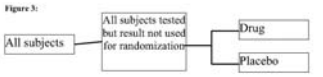
AUC - ROC

- Vary the threshold between Biomarker + and – subgroups
- Combined values of sensitivity and specificity gives ROC curve
- Evaluate performance by the AUC (more robust evaluation than selecting a single threshold)

Clinical trials to qualify a biomarker as predictive

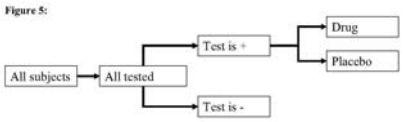
- If multivariate biomarker, formula derivation should be pre-specified
- Positive subgroup effect checked according to standard practice (two adequate and well-controlled studies)
- Confirmed in later independent studies
- Negative subgroup effect checked, but potentially not as rigorous (interaction expected) depending on biological understanding

Potential trial designs I (FDA guideline)



Alternatively, in Figure 4, randomization within differing strata by diagnostic test result (e.g., positive or negative subgroup) may be favored, particularly in circumstances where the test results are readily available at all clinical sites. Randomization ensures a balance in patient allocation between the treatment and the control for both the diagnostic test positive and test negative subsets.

Potential trial designs II (FDA guideline)



Genes or proteins?

- Genes (DNA): Constant, discrete, massively parallel
- Gene expresssions (mRNA): time-varying, continuous, microarray (massively parallel), qPCR (parallel)
- Proteins: time-varying, continuous, difficult sample handling (freezing), separate measurements

Gene expression biomarkers

- Measure RNA for treatment choice
- Multivariate so a selection step is necessary
- Define subgroup to be treated:
- Show effect in subgroup
- Show/argue for no effect in complementary subgroup

Regulatory issues

- FDA: a biomarker is a device (handled by CDRH, center for devices and radiological health)
- Derivation of a gene-based biomarker (selection based on many genes) require pre-specified gene selection method
- Endpoint for diagnostic biomarkers is AUC-ROC
- Only few have passed the regularity hurdle

Lundbeck biomarker examples

- Gene expressions in depression
- Imaging (such as PET)
- EEG
- Various measurements known to reflect occupancy on specific receptors

Summary

- Classical well-known biomarkers are far from perfect
- Many new biomarkers are suggested
- Diagnostic; Prognostic; Predictive; Surrogate endpoints
- Only few have passed the regularity hurdle
- Biological understanding is key
- Biomarkers are the future