OA Biomarkers: What is required for validation and qualification? Part I. Evaluation Frameworks

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Key concepts

BIOMARKER (BioM)

A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to an intervention*
OA examples: serum MMP-3; JSW

- Exploding number of technology-driven physiologic, pathologic, anatomic, **imaging**, molecular, genetic, 'omic measurements
- "Disease-related BioM": occurs at a point in pathophysiology such that it is plausibly linked to clinical outcomes, and may predict a clinical benefit of Tx (Wagner, 2008)
  - Vs. more distal BioM e.g. target engagement, bioanalysis
- The utility of disease-related BioMs a function of how well they link disease biology and pathogenic processes with clinical outcomes

*Biomarkers Definitions Working Group, 2001

Key concepts

Clinical outcome / endpoint: A characteristic or variable that reflects how a patient feels, functions, or survives.*

OA example: joint pain, mobility

Efficacy of Intervention (BIPEDS): A biomarker whose **Δ** is indicative or predictive of Tx effects on an outcome.

Surrogate endpoint (SEP): A biomarker that can substitute for a clinical endpoint. It is expected to predict clinical benefit or harm, or lack of clinical benefit or harm.*

OA example: None;

BP is an accepted SEP for certain classes of antihypertensive drugs.

- More efficient endpoints: Greater sensitivity to Tx effects → smaller, shorter trials and expedited decision-making

*Biomarkers Definitions Working Group, 2001

Evolution of Biomarker Evaluation

- Historically: BioM "acceptance" in clinical research and practice a gradual development of consensus in the scientific community based on largely unstructured and qualitative processes
- Move to more uniform, structured, evidence-based process with defined criteria and consensus standards: "Qualification"
  - Keyed to the proposed use of BioM - "fit for purpose"
  - Goals: acceleration, transparency and better decisions
- Initiatives to realize BioM potential to improve Tx development
  - FDA Critical Path: BioM a 'Key Area of Opportunity', 2006
  - C-Path Institute (2005)
  - Biomarkers Consortium, 2006
  - OARSI-FDA Initiative on OA Tx Development (2009)
  - FDA Guidance: Qualification Process for Drug Development Tools (2010)
  - Institute of Medicine: Evaluation of BioM and SEPs in Chronic Disease (2010)

Application of OMERACT Filter Criteria to Evaluation of OA BioMs

BIPEDS	Purpose	Discrimination	Validity (Truth)
Burden of disease	Indicate extent, severity	Reliability	Concurrent criterion
Prognostic	BL value predicts onset or progression	Reliability	Concurrent criterion Predictive criterion
Efficacy of intervention	Δ Indicates or predicts efficacy of Tx	Reliability Responsiveness	Concurrent criterion Predictive criterion

Reliability: getting the same results over time, varying conditions (e.g. inter-rater)

Responsiveness/ sensitivity: change in the BioM relative to its variability; ability to distinguish response from non-response; *SRM, Min Det Change*

Concurrent criterion: cross-sectional assoc with relevant pathological, disease and/or clinical states; *correlation, classification analysis (AUC)*

Predictive criterion: assoc of BioM (ΔBioM) with future pathological, disease and/or clinical outcomes; *relative risk, classification analysis (AUC)*

OARSI – FDA Initiative: Performance of Imaging BioMs of OA Structural Progression

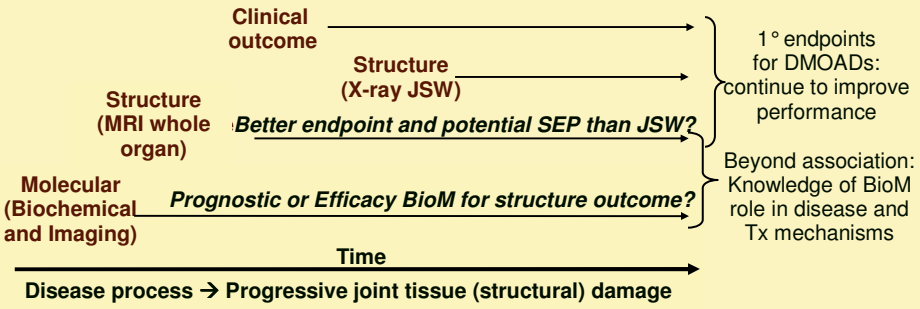
- Pooled analysis, literature synthesis addressing OMERACT Filter criteria

Imaging BioM for structural progression	Reliability (pooled ICC)	Responsive-ness (pooled SRM)	Criterion Validity		
			Concurrent structural	Concurrent clinical	Predictive clinical
Medial minimum JSW	Intra: **0.93;** Inter; **0.97;** No diff by x-ray method	**0.33** (0.26, 0.41); diff by F-Up time, x-ray method	mod assoc: arthroscopy/ MRI cart & meniscus	"weak assoc with Symptoms"	few data; mod assoc with TKR
Medial Fem quantitative cartilage morphology	Intra: **0.92**; Inter: **0.90**	**0.51** (0.28, 0.74); similar for other plates	mod assoc: histology/ arthroscopy/ JSN	"weak assoc with Symptoms"	few data; mod assoc with TKR

- Reliability, responsiveness, concurrent structural validity support use of both Imaging BioM as structural endpoints in OA Tx trials
- Similar (weak, inconsistent) associations with pain, function
- Insufficient data on ability to predict clinical outcome

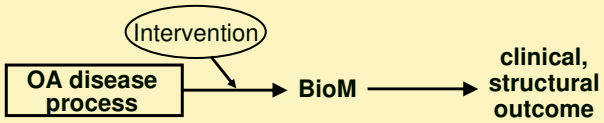
OA BioM Evaluation: Where next?

- OMERACT Filter useful summary of state of the evidence
  - critical knowledge gaps (e.g. prediction of clinical outcomes)
- Quant cartilage morphology performs at least as well as JSW
  - acceptable endpoint in trials; may facilitate trials in earlier OA
- Weak associations/knowledge gaps for structural BioM and clinical outcomes: *no change in requirement that DMOADS show both structural and clinical benefits (pain, function) in definitive trials*



Efficacy of Intervention BioMs

- Criteria for "efficacy of intervention" OA BioM
  - BioM on causal pathway that
    a) links disease biology with clinical or structural outcome, and
    b) is on a pathway targeted by a Tx

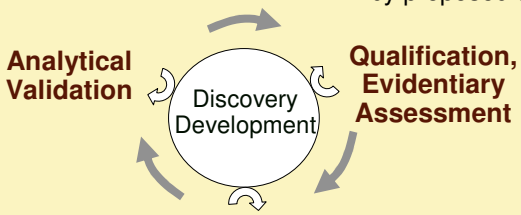


  - responsive to intervention
  - effect of Tx on BioM predicts outcome
- Surrogate endpoint (SEP): BioM reliably predicts the net effect of Tx on clinical outcomes
- Efficacy of Intervention BioMs are useful even if not formally qualified as SEPs for definitive trials
  - Early Tx development, dose setting, POC, etc.

Biomarker Evaluation Framework
Institute of Medicine, 2010*

Evaluation of evidence on measurement performance; how well an image assessment or assay quantitates a target BioM (method validation)

Evaluation of evidence linking a BioM with biology/disease pathways, response to Tx, and clinical outcomes, as required by proposed use of BioM.



Given contextual factors, does the analytical validation and qualification conducted provide support for the proposed use?

*Micheel and Ball, eds, Nat Acad Press, 2010

Analytical Validation (IOM)

- How well does an image assessment or assay quantitate a BioM?

Evidence:
- Accuracy (sensitivity/specificity) for target (preclinical, human)
- Limits of detection and quantitation, reference ranges, cutoffs
- Precision (reproducibility, repeatability)
- Sources of variability: biological, acquisition, data collection, analytical
  - **Biochemical**: variability across samples, assay kits, labs
  - **Imaging**: variability across platforms, techniques, readers, core labs

Focus of evaluation and conclusions:
- What are the conditions under which measurements and data collection processes give accurate, reliable, standardized and generalizable data?
- Can we trust the data when the BioM is used in diverse real-world settings? Different drug development programs? Tx trials in varied populations?

Qualification (IOM)

- Evidentiary and statistical process linking a BioM with disease processes, response to interventions and clinical outcomes

Evidence

- Discrimination between disease states and response/nonresponse
- Responsiveness to Δ in disease state and interventions
- Association of BioM at one point in time (and Δ) to concurrent clinical status (and Δ)
- Association of BioM (and Δ) to future clinical status
- Role in causal pathway of disease that impacts clinical outcome
- Interventions targeting the BioM impact clinical outcomes

Focus of evaluation and conclusions

- Type and level of evidence needed for proposed use
- Is the BioM on a clinically important causal pathway?
- Strength, consistency, specificity, temporality of disease → BioM → outcome associations?
- Does the evidence support use of the BioM as a surrogate endpoint

Utilization (IOM)

- Contextual evaluation of analytical validation and qualification with regard to 'fitness' for proposed use

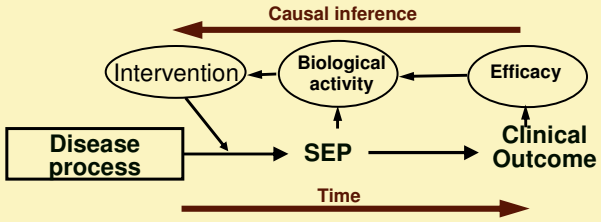
Some contextual factors

- **Intended use as a SEP for clinical outcome (#1 "Critical factor")**
- Drug development: POC? Use in confirmatory trial?
- Tolerance for uncertainty and risk
- Prevalence and impact of the disease (morbidity, mortality)
- Benefits and risks of Tx in defined population
- Available Tx options
- Advantages of using the BioM vs other endpoint

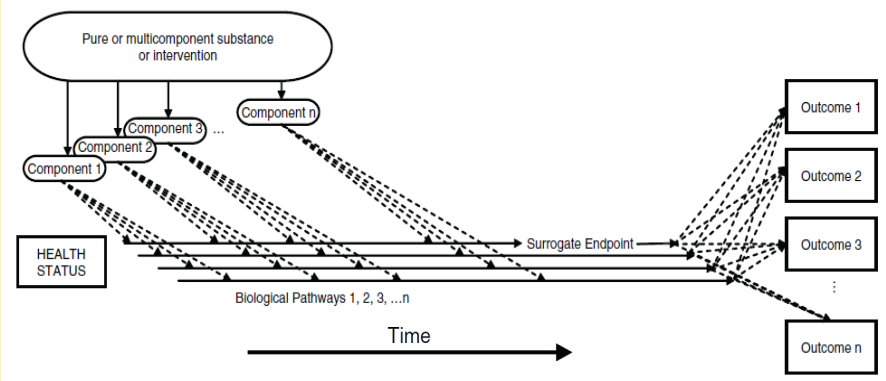
- Potential for 'surrogacy' a key factor in qualification framework

Best potential for Surrogacy

- Change in BioM reliably predicts clinically important effects on a clinically meaningful endpoint:
  - BioM is on the only or main causal path of disease process → clinical outcome
  - Txs entire effect on outcome is mediated by effect on SEP



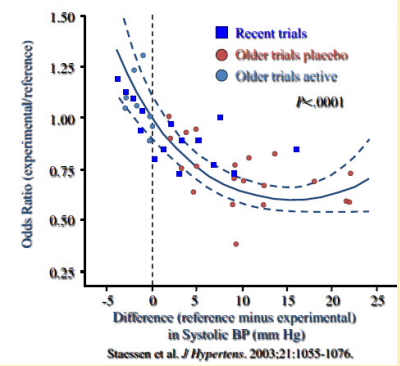
Reasons for SEP failure



- In reality, causal pathways affecting clinical outcome in chronic disease are multiple and complex; comprehensive knowledge unlikely
  - BioM not on a primary pathway affecting outcome
  - Tx has effects (good or bad) on clinically important non-target outcomes
  - Off-target effects of Tx on various outcomes or AEs

Clinical trial data for SEP qualification

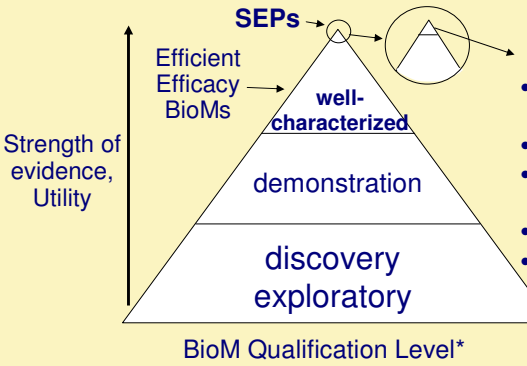
- The most reliable evidence for surrogacy comes from meta-analyses of clinical trials that allow reliable predictions of net effects of Tx on both BioM and outcome
- Possible when BioM has been assessed in multiple Tx trials with measured effects on clinical endpoints e.g. BP, HDL cholesterol, BMD



- RCTs of antihypertensive agents, with BP as SEP and major CVD events as endpoint
- BP confirmed as accepted SEP for specific drug classes

Potential for surrogacy: a filter for BioM utility

- The cost of failure is high, so hurdles for SEPs are high
  - Patients have been harmed by failed SEPs



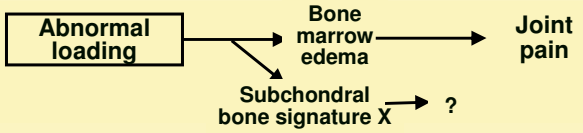
"Accepted" SEPS for definitive trials
- BP for some classes of antihypertensives for CVD endpoints
- LDL-C for CVD endpoints
- HIV-1 RNA for progression to AIDs or death
- HgA1c for diabetes complications?
- OA: none

* Wagner, et al. Biomarkers and SEPs for Fit for Purpose Development and Regulatory Evaluation of New Drugs. TransMed, 2007; 81:104.

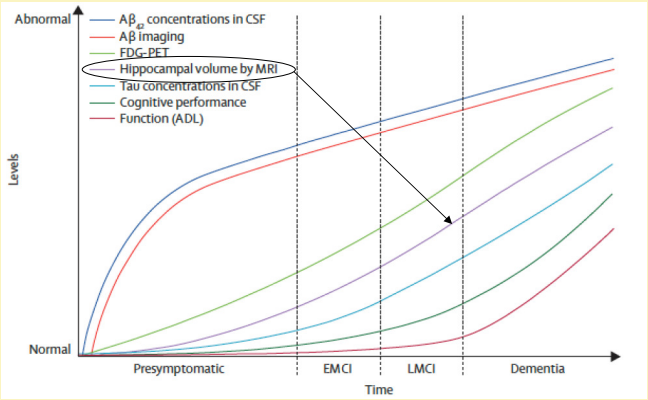
Is potential for surrogacy a productive filter for OA BioMs?

- Progress in OA Tx development may depend on more efficient "Efficacy" endpoints
- Well-characterized "Efficacy BioM" that are not formally qualified SEPs for definitive trials have valuable uses in Tx development
- Include promising BioMs in OA Tx trials for future analysis of potential for surrogacy

- What about BioM that are prognostic for OA outcomes?
  - Strong association with clinical outcome, but needn't be on a direct causal pathway



Baseline Hippocampal Vol (MRI) "Qualified" as prognostic BioM for progression to Alz-dementia



- Use: selection of pts with prodromal Alz likely to evolve to dementia
- Structural BioM for neurodegeneration
- Links early pathology to later dementia
- Prognostic value of Δ suggests SEP potential

[European Medicines Agency (2011); Applicant: CAMD/C-Path Institute]

- Understanding a prognostic BioM's role in pathogenesis, progression and clinical outcome
  - Focus qualification efforts on prognostic BioM with greatest potential utility
  - if BioM Δ*s* with progression, it enters the pipeline of potential SEPs
  - Provide insight into potential Tx targets

Proposition

- An OA BioM evaluation framework that includes potential for surrogacy as a major emphasis requires an understanding of BioM roles in modifiable disease pathways affecting patient outcomes.
- This will necessitate intensive and challenging, but worthwhile, efforts to identify and advance the BioM with the greatest promise.

Thank you