Sequencing a Research Plan

Imaging as Biomarker for Prediction and Clinical Management: Need, Potential, and Issues for Multi-center Studies

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Financial Disclosures/COI

- None.
A Tale of Two Protocols

ACRIN 6677
ACRIN 6697
However, standardized techniques for acquiring and interpreting MRS spectra are lacking …,”
Jan. 29, 2004
ACRIN 6677
Staging with MR Perfusion Imaging and MR Spectroscopy

• “We have significant reservations about the cost implications of this trial to accomplish what would be simply a diagnostic sensitivity endpoint.”
• “By itself, an enhanced classification structure would not directly improve outcome unless it resulted in meaningful changes in therapy.”
ACRIN 6697
FDG-PET/CT in prediction of pathologic response of tumor in patients with localized esophageal cancer who undergo chemoradiation prior to surgical resection

• “It is critical however that a study design reflect an integration of the diagnostic study with standard therapeutic approaches so that the study has a good chance of being clinically relevant.”
Evaluation of Imaging Tests

Assumptions:
• Imaging provides information.
• Information affects physician thinking and behavior
• Physician thinking and behavior affects patient outcomes (mortality, morbidity, QOL, functioning, costs).

Questions:
• How accurate & reliable is the information?
• How valuable is the information?
“Value” Depends on Context

• Reimbursement?
• Regulatory?
• Liability?
• Personalized Medicine
“Value” Depends on Context

- Reimbursement?
- Regulatory?
- Liability?
- Personalized Medicine
“The medicine of the future is going to be driven by objective measurements of biomarkers.”

- Elias Zerhouni, March 6, 2007
Biomarker Basics

Broadest definition: Biomarkers are tools or traits that detect and/or measure biological conditions or events.
Biomarkers

NIH Workshop definition (1999): A characteristic that is objectively measured and evaluated as an indicator of normal biologic or pathogenic processes or pharmacological responses to a therapeutic intervention.
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Types of Biomarkers

- Screening
- Early Detection
- Diagnosis
- Prognostic
- Predictive
- Pharmacokinetic
- Pharmacodynamic
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Sequencing a Research Plan
Idealized Sequence

1. Discovery; Early development
2. Observations; Feasibility studies
3. Clinical Experiments
4. Application; Dissemination
Hierarchical Model of Efficacy

Level 1. Technical efficacy
• e.g., Physical Performance

Level 2. Diagnostic-accuracy efficacy
• e.g., Sens/Spec/AUC

Level 3. Diagnostic-thinking efficacy
• e.g., Effect on physician thinking

Level 4. Therapeutic efficacy
• e.g., Effect on clinical management

Level 5. Patient-outcome efficacy
• e.g., Patient benefit

Level 6. Societal efficacy
• e.g., Cost-effectiveness
• **Stage I: Discovery**
  - technical parameters and diagnostic criteria;

• **Stage II: Introductory**
  - early quantification of performance in clinical cohorts, usually single institution studies;

• **Stage III: Mature**
  - comparison to other modalities in large, prospective, multi-institutional clinical studies (“efficacy”)

• **Stage IV: Disseminated**
  - performance of the procedure as utilized in the community at large ("effectiveness")
Figure 1. TRWG Imaging Translational R&D Pathway

“I don’t reimburse. I validate. I listen and acknowledge how difficult it was for you to find a place to park.”
Validation: Definition

• In common usage, validation is the process of checking if something satisfies a certain criterion.

• Examples include
  • checking if a statement is true
  • if an appliance works as intended
  • if a computer system is secure
  • if computer data are compliant with an open standard.
PERSONAL VALIDATION

PROCESS

TOOLS FOR EMOTIONAL RELEASE
AND SELF-EMPPOWERMENT

PATRICK MARSOLEK
FDA Definition of Validation:

The FDA pharmacogenomics guidance defines a valid biomarker as “a biomarker that is measured in an analytical test system with well-established performance characteristics and for which there is an established scientific framework or body of evidence that elucidates the physiologic, toxicologic, pharmacologic, or clinical significance of the test results.”
FDA Definition of Validation:

The FDA pharmacogenomics guidance defines a valid biomarker as “a biomarker that is measured in an analytical test system with well-established performance characteristics and for which there is an established scientific framework or body of evidence that elucidates the physiologic, toxicologic, pharmacologic, or clinical significance of the test results.”
A test for which there is widespread agreement in the medical or scientific community about the physiologic, toxicologic, or clinical significance of the results.
NCI Investigational Drug Steering Committee
Definition of a “Validated Biomarker”

A test for which there is widespread agreement in the medical or scientific community about the physiologic, toxicologic, or clinical significance of the results.
Biomarker Validation

The validity of a biomarker is closely linked to what we think we can do with it.
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Imaging as an In Vivo Assay

Definition of Assay: An assay is an analysis done to determine the presence of a substance and the amount of that substance.

Webster’s Medical Dictionary
Assay “Validation”

- Accuracy
- Precision
- Limit of Detection
- Limit of Quantification
- Specificity
- Linearity
- Range
- Robustness
Reproducibility Of The FDG Signal In Untreated Tumors

50 lesions in 16 patients, 2 scans 2-3 weeks apart

Biomarker Validation Process

• Validation (or qualification) is not the same as the Performance Characteristics of a test.
• Validation is not an endpoint.
• “Validated” or “qualified” means the user is confident that the biomarker accurately represents the biologic or pathologic condition proposed.
Validation Process

Validation Process

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Validation Process

ACRIN 6678 - FDG-PET/CT as a Predictive Marker of Tumor Response and Patient Outcome: Prospective Validation in Non-small Cell Lung Cancer
Validation Process

• For drug development, no clear guidelines establish what data are needed for validation or qualification of imaging biomarkers.

• For clinical practice, there has been even less discussion or agreement.

• There is probably a lower threshold of evidence needed to accept imaging biomarkers as useful in clinical care than in drug development.
“Personalized medicine”
“Personalized Medicine”

Not to be taken literally.

Concept is to incorporate information from the individual's "molecular signature of disease" into therapeutic decision-making.
Example Types of Biomarkers

- Screening
- Early Detection
- Diagnosis
- Prognostic
- Predictive
- Pharmacokinetic
- Pharmacodynamic
Prognostic vs. Predictive Biomarkers

• Prognostic
  • Unrelated to a specific therapy (e.g., Staging; FDG-PET)
• Predictive
  • With regard to a specific therapy (e.g., FES-PET; MRS of 5-FU)
• “Most prognostic biomarkers are not therapeutically relevant.”
• “Oncology needs more predictive biomarkers, not prognostic.”
A Tale of Two Protocols

ACRIN 6677
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ACRIN 6677

• “We have significant reservations about the cost implications of this trial to accomplish what would be simply a diagnostic sensitivity endpoint.”
• “By itself, an enhanced classification structure would not directly improve outcome unless it resulted in meaningful changes in therapy.”
“...the proposal title indicates that the study will attempt to identify that MR perfusion or MRS will be 'predictive' markers. At best, this would be a 'prognostic marker', since predictive markers by definition identify an outcome following a specific intervention. Since therapy is not controlled in this study, it would be impossible to define a predictive marker, (unless the performance of the MRS or MR perfusion was the intervention, which is not the case).
ACRIN 6677

- Staging with MR Perfusion Imaging and MR Spectroscopy
- PI: G. Sorenson
- RTOG 0625, A randomized phase 2 trial of bevacizumab with irinotecan or bevacizumab with temozolomide in recurrent glioblastoma.
ACRIN 6697

• “Just assuming that the outcome of the trial will be independent of the treatment regimen, and other factors, requires rigorous proof.”
• “A pilot study to determine effect of chemoRT on early PET scan with a single regimen, and to assess association with outcome could be an important first step.”
ACRIN 6697

• “… 5 to 20 treatment groups”
• “In a 220 patient trial this will lead to subsets of 11-45 patients—how can the authors possibly compare outcome in so many subgroups?”
• “There will be only 1-8 pathologic complete responses per therapy subgroup.”
ACRIN 6697

• “It is critical however that a study design reflect an integration of the diagnostic study with standard therapeutic approaches so that the study has a good chance of being clinically relevant.”
“Cows have magnetic sense, Google Earth images indicate”

“Experts acknowledged that the research almost certainly has no practical applications.”

Los Angeles Times
August 26, 2008
Validation (Qualification)

- Biomarkers must be validated (qualified) for their intended use.
- This makes generalizability difficult.
- This is a major hurdle for imaging studies – which have to be validated in people rather than on in vitro samples.
  - Clinical trials of Imaging tests are expensive and difficult.
Possible Predictors:

- Imaging of drug localization
- Imaging of ligand localization
- Imaging of some physiological state, e.g., hypoxia, hemodynamic status, diffusivity
- Multi-parametric imaging
High Field (3T) Multi-parametric Approach - MRI/\(^1^H\) MRSI/DTI/

- **T2 MR Image**
- **<D> map**
- **DTI-EPI Parallel imaging sequence**
- **DCE - Uptake Curves**
  - 3D FSPGR w/ 3.4sec temporal resolution, 480 FOV, 5 mm thick slices, TR/TE/flip = 5ms / 2.1ms / 6º
  - Cancer PZ
  - Normal PZ
- **DCE - Peak Enhancement**
- **3-D \(^1^H\) MRSI**
  - 0.16 cc
  - Choline
  - Polyamine
  - Citrate

UCSF
Combining MRI/MRSI and Clinical Data
Prediction of Indolent Disease

- N = 220 pt; MR-RRP
- Indolent disease at surgery - localized disease, < 0.5 cc of cancer, no Gleason pattern 4 or 5.
- Clinical parameters without MRI/MRSI (AUC = 0.726)
  - PSA
  - Gleason
  - Clinical Stage
  - % Ca in specimen
  - % positive cores
  - Prostate volume

- Clinical parameters + MRI/MRSI
  - AUC = 0.854

Shukla-Dave, MSKCC BJU Int 2007
Pharmacodynamic Biomarkers for Assessment of Response or Progression
Tumor Response Biomarkers

- Linear measurements
  - RECIST (2000) – uni-dimensional
  - WHO (1979) – bi-dimensional
  - Macdonald (1990) – bi-dimensional

- Functional
  - FDG-PET change in SUV
  - Perfusion, permeability, diffusion MRI?
  - FLT-PET; F-MISO-PET?

- Multi-parametric
  - IWG (lymphoma - 2007): CT, FDG-PET, IHC, Flow Cytometry
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Sequencing Clinical Trials

- Overall Objective (Clinical Significance)
  - Specific Aim (Establish Performance Characteristics of Test $x$)
    - Observational Study 1
    - Observational Study $m$
  - Specific Aim (Correlate Test $x$ with Condition $y$)
    - Testable Hypothesis 1 (Designed Clinical Trial 1)
    - Testable Hypothesis 2 (Designed Clinical Trial 2)
    - Testable Hypothesis 3 (Designed Clinical Trial 3)
    - Testable Hypothesis $n$ (Designed Clinical Trial $n$)

- Cumulative data = High confidence level in clinical significance of results from Test $x$. 
Validation Toolkit

Get all the Data you Need Error-free

Professionally designed, from top to bottom. Magnificently navigable for the life of your site.
Thank you.