AN INTRODUCTION TO REIMBURSEMENT SCIENCE

May 26, 2015
Sean R. Tunis, MD, MSc.
Research priorities from patients and clinicians
Studies with broad eligibility, relevant comparators, PROs
Expand practice-based infrastructure to conduct PCTs
Need for increased and sustained funding
Work on ethical / methodological challenges
TOPICS TO BE DISCUSSED

- The Evidence Problem
- Reimbursement Science
- Green Park Collaborative
- COMET Initiative
- EXCITE – Maryland
The Evidence Problem
<table>
<thead>
<tr>
<th>Brand &amp; Model</th>
<th>Ratings and Test results</th>
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Evidence Summary: Radiation Therapy for Clinically Localized Prostate Cancer

<table>
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<tr>
<th>Comparisons</th>
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Source: Tufts Evidence-based Practice Center: Draft AHRQ Technical Assessment, March 25, 2010
Scientific Evidence Underlying the ACC/AHA Clinical Practice Guidelines

Pierluigi Tricoci, MD, MHS, PhD
Joseph M. Allen, MA
Judith M. Kramer, MD, MS
Robert M. Califf, MD
Sidney C. Smith Jr, MD

**Context** The joint cardiovascular practice guidelines of the American College of Cardiology (ACC) and the American Heart Association (AHA) have become important documents for guiding cardiology practice and establishing benchmarks for quality of care.

**Objective** To describe the evolution of recommendations in ACC/AHA cardiovascular guidelines and the distribution of recommendations across classes of recommendations and levels of evidence.

**Data Sources and Study Selection** Data from all ACC/AHA practice guidelines issued from 1984 to September 2008 were abstracted by personnel in the ACC Science and Quality Division. Fifty-three guidelines on 22 topics, including a total of 7196 recommendations, were abstracted.
Level of Evidence A
Current Guidelines*

*Guidelines expressing Level of Evidence

AF: 11.7%
Heart failure: 26.4%
PAD: 15.3%
STEMI: 13.5%
Perioperative: 12.0%
Secondary prevention: 22.9%
Stable angina: 6.4%
SV arrhythmias: 6.1%
UA/NSTEMI: 23.6%
Valvular disease: 0.3%
VA/SCD: 9.7%
PCI: 11.0%
CABG: 19.0%
Pacemaker: 4.9%
Radionuclide imaging: 4.8%
Level of Evidence C
Current Guidelines*

- AF: 58.6%
- Heart failure: 54.3%
- PAD: 25.1%
- STEMI: 47.2%
- Perioperative: 32.0%
- Secondary prevention: 8.3%
- Stable angina: 54.5%
- SV arrhythmias: 56.5%
- UA/NSTEMI: 29.6%
- Valvular disease: 70.6%
- VA/SCD: 58.5%
- PCI: 47.8%
- CABG: 20.0%
- Pacemaker: 58.2%
- Radionuclide imaging: 26.3%

*Guidelines expressing Level of Evidence
THE PROBLEM – SIMPLY STATED

• “Because of the paucity of high quality evidence, the data available – though voluminous – may have little meaning or value for informing clinical practice”

THE EVIDENCE PARADOX

• 19,000+ RCTs published every year
• Tens of thousands of other clinical studies
• Systematic reviews intended to inform payers, guideline developers, patient education material routinely conclude that evidence is inadequate or poor quality
THE CER HYPOTHESIS

• Gaps in evidence will be reduced with increased involvement of payers, patients and clinicians

• A functional definition of CER would be research designed in light of meaningful engagement of these decision makers
DECISION-BASED EVIDENCE MAKING

- Lots of uncertainty about what type of evidence will impact payers, health systems, others
- Greater clarity and consistency may emerge from multi-stakeholder dialogue
- Insights from this should help guide design and implementation of more informative studies
REIMBURSEMENT SCIENCE
“Regulatory Science is the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of all FDA-regulated products.”

“FDA will advance regulatory science to speed innovation, improve regulatory decision-making, and get products to people in need...(and) to protect and promote the health of our nation and the global community.”
Several legitimate social objectives related to medical products:
  - Ensure that marketed products are safe and effective
  - Promote rapid patient access to promising new products
  - Promote life sciences innovation
  - Minimize burdens on product developers

These objectives create tension with respect to evidence standards.
Regulatory science provides an opportunity to develop a scientific framework that reflects multiple legitimate competing views.
Requires all stakeholders, transparency, iterative.
FDA provides the natural platform to support this process.
“Reimbursement Science is the science of developing new tools, standards, and approaches to assess the comparative effectiveness, value of products covered by public and private health plans.

CMTP will advance reimbursement science to (speed innovation), improve reimbursement decision-making, and get products to people in need…. (and) to improve population health outcomes and efficient use of resources.”
A multi-stakeholder forum to clarify the evidence expectations of public and private payers

- Informed by input from patients, clinicians, and regulators,
- Focus on comparative effectiveness and value

Other Key Stakeholders

- CMS, numerous private payers engaged
- FDA, NIH, PCORI, AHRQ, VA, etc.
- Ongoing involvement of life sciences

Output / Activities

- Develop “effectiveness guidance documents”
- Condition and technology specific workshops
# GPC – USA Advisory Committee

## Advisory Committee Structure

- **Chair:** Sean Tunis
- **Other Members:**
  - Amy Abernethy
  - Ethan Basch
  - Ellen Sigal
  - Janet Corrigan
  - Lisa Simpson/Erin Holve
  - Mark Skinner
  - Gary Palmer
  - Alexandra Clyde
  - James Murray
  - Alan Rosenberg
  - Murray Ross
  - Lew Sandy
  - Donna Cryer

## Ex Officio

<table>
<thead>
<tr>
<th></th>
<th>FDA</th>
<th>CMS</th>
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<tr>
<td>Bob Temple</td>
<td>Patrick Conway</td>
<td>Rachael Fleurence</td>
<td>Michael Lauer</td>
<td>Jean Slutsky</td>
<td>David Atkins</td>
<td>Tanisha Carino</td>
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<td>Murray Sheldon</td>
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<td>Jason Gerson</td>
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<td>Peter Marks</td>
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## Board Composition Key

- **Other**
- **Payers**
- **Life Sciences**
PAYERS INVOLVED IN GPC - USA

- America’s Health Insurance Plan
- BCBSA
- CMS central office
- MACs (Palmetto, Novitas, others)
- Humana
- Aetna
- United
- Kaiser
- Wellpoint
- Many regional payers (e.g. Johns Hopkins Health Plan)
Specific recommendations on design of clinical utility studies

- Multi-stakeholder process
- Aim to balance validity, feasibility, time, cost
- Targeted to researchers working in industry or academic settings
- Analogous to FDA guidance
# TECHNICAL WORKING GROUP MEMBERS

<table>
<thead>
<tr>
<th>TWG Member Name</th>
<th>Stakeholder Category</th>
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<tbody>
<tr>
<td>Linda Bradley</td>
<td>Geneticist/Lab Director</td>
<td>Women &amp; Children's Hospital of Rhode Island</td>
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<tr>
<td>Louis Jacques</td>
<td>Payer</td>
<td>Centers for Medicare &amp; Medicaid Services</td>
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<td>Gary Lyman</td>
<td>Clinician</td>
<td>Duke University</td>
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<tr>
<td>Howard McLeod</td>
<td>Researcher</td>
<td>UNC Institute PGx &amp; Individualized Therapy</td>
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<tr>
<td>David Nelson</td>
<td>Industry</td>
<td>Epic Sciences, Inc.</td>
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<td>Robert McCormack</td>
<td>Industry</td>
<td>Veridex LLC, a Johnson &amp; Johnson company</td>
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<td>David Parkinson</td>
<td>Venture Capital</td>
<td>New Enterprise Associates</td>
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<td>Margaret Piper</td>
<td>Payer</td>
<td>Kaiser Permanente (formerly BCBSA TEC)</td>
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<tr>
<td>Richard Simon</td>
<td>Methodologist</td>
<td>National Cancer Institute</td>
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<tr>
<td>Mary Lou Smith</td>
<td>Patients &amp; Consumers</td>
<td>Research Advocacy Network</td>
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MOLECULAR DIAGNOSTICS ADVISORY GROUP

Robert A. Beckman, MD
Executive Director, Clinical Development Oncology
Daiichi Sankyo Pharmaceutical Development

Donald A. Bergstrom, MD, PhD
Associate VP and Global Head, Translational and Experimental Medicine
Sanofi, Oncology

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Director, Worldwide Reimbursement & Reimbursement Policy
Becton, Dickinson and Company

Lorrie Carr, MBA
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Millennium: A Takeda Oncology Company

Nicholas Ferenc, MS, MBA
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Sanofi Oncology

Sheikh Usman Iqbal, MD, MPH, MBA
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MedImmune

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Rajiv Mallick, PhD
Director HEOR
Daiichi Sankyo Inc

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GlaxoSmithKline

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Cepheid

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Michele Schoonmaker, PhD
Vice President of Government Affairs
Cepheid

Art Small, MD
Director Oncology Outcomes Research US Medical Affairs
Genentech Inc.

William Trepicchio, PhD
Senior Director, Translational Medicine,
Millennium Pharmaceuticals: A Takeda Oncology Company

Richard J. Wenstrup, MD
Chief Medical Officer
Myriad Genetic Laboratories, Inc.
Measuring outcomes for CU studies

CU studies of MDx tests should include outcome measures that assess patient benefits and harms

• Should include patient-reported outcome measures appropriate and validated for the clinical context

• May also include endpoints such as survival and downstream health care resource utilization

• Process measures are insufficient

• Studies designed to report intended care plans following an MDx test are insufficient to demonstrate CU
Clinical Utility — RCTs

When assessing CU of an MDx biomarker with RCTs:

- RCT should evaluate the effectiveness of the clinical decision relative to control for both marker-positive and marker-negative patients
- Enrichment designs excluding patients with a particular marker status should be avoided
- Marker-based strategies randomizing patients to genomics-guided treatment vs. usual care are not optimal
In some circumstances, longitudinal observational study designs are acceptable options for assessing CU

- Must have compelling rationale for not doing RCT
- Steps to minimize confounding must be documented
- Good research practices followed
- Retrospective studies not adequate for CU of MDx tests
- Secondary databases may be one source for data collection, but prospective data collection is needed
RECOMMENDATIONS FOR LATE PHASE DRUG STUDIES IN TYPE 2 DIABETES
RECOMMENDATION 1: INCLUDE UNDER-REPRESENTED MINORITIES AND OLDER ADULTS

Racial and ethnic minorities and older adults are affected more by diabetes, but not enough is known about treatment effects in these groups.

Studies need to make every effort to include African-American and Hispanic patients, and patients age ≥65.
RECOMMENDATION 2: DON’T EXCLUDE PATIENTS WITH OTHER CONDITIONS

Diabetes patients with other medical conditions are often excluded from studies, which makes it difficult to know how treatments will affect these patients.

Patients should not be excluded just because they have cardiovascular disease, depression, a history of cancer, mild cognitive impairment, or diabetes complications.
RECOMMENDATION 4: REPORT QUALITY OF LIFE MEASURES

Quality of life is an important factor for patients evaluating treatments.

Studies should include quality of life measures, specifically the Audit of Diabetes-Dependent Quality of Life (ADDQoL-19) and the Diabetes Treatment Satisfaction Questionnaire before treatment and after 1 year of treatment.
RECOMMENDATION 5: MONITOR EFFECTS OF WEIGHT GAIN OR LOSS

Patients report they find treatment effects on weight extremely important.

Studies should report more information about treatment effects on weight, including how many patients lost or gained 5%, 5-10% and more than 10%.
Core Outcome Measures in Effectiveness Trials

www.comet-initiative.org
Core outcome set

• An agreed standardised set of outcomes that should be measured and reported, as a minimum, in all clinical trials in specific areas of health or health care
Commentary

OMERACT: An international initiative to improve outcome measurement in rheumatology

Peter Tugwell\(^1\), Maarten Boers\(^2\), Peter Brooks\(^3\), Lee Simon\(^4\), Vibeke Strand\(^5\) and Leanne Idzerda\(^6\)
Improvements over time (Kirkham et al, *Trials* 2013)

Studies reporting full RA COS (%)

Mean number of clinical outcomes

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WHO/ILAR RA COS guideline

EMA guideline

FDA guideline
The COMET Initiative

• An international network of trialists, systematic reviewers, health service users, practitioners, editors, funders, policy makers, regulators
  – To raise awareness of current problems with outcomes in clinical trials
  – To encourage COS development and uptake

• Increasing efforts to involve patients

• Limited focus to date on evidence for payers/HTA/market access
PCORI FUNDING FOR COS?

- Identify existing COS for conditions/topics that are current, future focus of PCORI work by
  - PPRN conditions, priority setting panels
- Evaluate quality of existing COS; determine for which topics additional work is needed
- Convene workshop to prioritize: critical, important, other
- PCORI provides funding for 6-12 COS on high priority topics
- Identify project lead, key experts and stakeholders
- Evaluate alternative methods for patient engagement during COS development process
EXCITE PROGRAM
ONTARIO → MARYLAND → USA?
MaRS Excellence in Clinical Innovation and Technology Evaluation program

MaRS is a member of

Ontario Network of Entrepreneurs
Concept

TIME

Pre-Market
- Systematic review
- Cost Effectiveness
  - Efficacy Safety
  - Value (CE)
  - Affordability
  - Ethical & societal
  - Post-market conditions

Regulation

Post-Market
- Systematic review
- Cost Effectiveness (CE)
  - Efficacy Safety
  - Value (CE)
  - Affordability
  - Ethical & societal
  - Post-market conditions

Reimbursement

Effectiveness
- Yes

Obsolescence

Diffusion

Unconditional No

Our Future Matters

March 2015
The EXCITE Collaboration Model

Management Board

MaRS EXCITE Secretariat

- Advice, oversight, direction
- Approve technologies, protocol, budget
- Senior reps: health, economic development, HTA, AHSCs, industry

Scientific Collaborative

- Advice on science, methodology
- Allocation of projects
- Heads of 5 methodology centres
  - Dr. Les Levin, CSO
- Review protocols for safety
  - Chair Tony Easty

OHTAC (Reimbursement)

- Advise prioritization of technologies
- Advice on clinical study design
- Support in conditions of adoption
- Comprised of implementation sub-committee of OHTAC

Safety Advisory Committee

Health Canada (Regulatory)

- Early advice on design of the evidence package and study

Methodology Centres

- Excellence in complex clinical trial design and execution in collaboration with 24 Research Hospitals
  - Contracted in by EXCITE
  - Design study with industry;
  - Execute and publish the study

AHRC
Applied Health Research CEI

theta Collaborative

PATH

The Ottawa Hospital

Healthcare Human Factors University
The EXCITE Process: 3 points of value-added

1. Prioritization
2. Study Design
3. Conditions Of Adoption
Evaluations range from 12-36 months

- Company obtains regulatory approval for trial
- MC contracts / activates participating sites

- MC prepares an evaluation report
- The report is then submitted to OHTAC

- EXCITE Secretariat conducts quarterly Check-In meetings with company and MC
- MC submits quarterly report on trial progress to EXCITE

The evaluation phase takes 12-36 months depending on the technology and study design
HIGH VALUE INNOVATION GRANTS

• Feb 2015 Press Release:
  – BioMaryland Center Awards $865,000 to Accelerate Life Sciences Commercialization

• For this year's awards, the BioMaryland Center launched a new partnership with Maryland's Department of Health and Mental Hygiene (DHMH) and the Center for Medical Technology Policy (CMTP) to incorporate improved health care quality and cost reduction criteria into the selection process.
ASSEMBLING EXCITE-MD

• Build on GPC, SAMA, CED, Collaboratory experience
• Working relationships with payers, employers, FDA, CMS, patient groups, professional societies
• BioMaryland DBED grants (with DHMH)
• BioHealthInnovation, ProductSavvy
• Maryland Medicare waiver links
  – Strong pressure to reduce costs, improve outcomes, pop health
  – HSCRC, DHMH, CareFirst, Maryland Hospital Association
• Relevant programs and people at JHU / UMD
• Initial funding through DBED/local foundations; later funding through companies (like MaRS)