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Key Discussion Points

• Challenges in our Current HealthCare System:
  • Cost, Quality and Coordination
  • Gaps in evidence impacting decision making

• Observational research designs utilized to address gaps in evidence

• Evaluation of biosimilars in the current and future healthplan environment

• Overview of Biologics and Biosimilars Collective Intelligence Consortium (BBCIC)
Key Challenges in U.S. Health Care System

**Unsustainable Cost**
- **20%** of GDP by 2021
- **$700B** waste across U.S. system
- **2x** cost per capita versus OECD nations

**Variation in Quality**
- **$210B** unnecessary services
- **45%** care inconsistent with recommended guidelines
- **3x** variation in hospital days in last 6 months of life

**Lack of Coordination**
- **19.6%** Medicare hospital readmissions
- **$45B** annual costs for avoidable complications
- **$91B** redundant administrative practices
Explosion in New Medical Evidence
Last 50 Years

Additions to MEDLINE by Year of Publication

Currently houses more than 20 million citations
5,640 journals referenced in PubMed (as of July, 2013)
Represents 20-25% of the Journals in circulation

Source – National Library of Medicine
In the age of too much information...

- Diagnostic imaging: functional and anatomical
- Proteomics and other effector molecules
- Functional genetics: gene expression profiles
- Structural genetics: eg, SNPS, haplotypes
- Decisions by clinical symptoms

**Source:** *JCO 2010*
Evaluation of Our Evidence Base
Example in Cardiovascular Disease

- A review of the level of evidence informing cardiovascular practice guidelines

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.

Data Extraction: The number of recommendations and the distribution of classes of recommendation (I, II, and III) and levels of evidence (A, B, and C) were determined. The subset of guidelines that were current as of September 2008 was evaluated to describe changes in recommendations between the first and current versions.

JAMA. 2009;301(8):831-841

16
Current guidelines report levels of evidence

2,711
Total guideline recommendations

11%
Evidence classified as “A”
89% based upon a single trial or simply expert opinion
Origins in the Gap in Evidence
Real-world utilization quickly outpaces available clinical evidence

Real world evidence development initiatives are focused on expanding evidence *effectively, rapidly and cost effectively* (e.g., FDA EvGen, PCORI, NIH Collaboratory)

6-7 years & $0.8B-$1.2B on a few thousand patients

**CONSEQUENCE**
- Great variation between study cohorts and real-world population
- Resistance from payers to reimburse for new therapies
- Hesitation of physician to prescribe therapy
- Undetermined real-world effectiveness of treatments

<table>
<thead>
<tr>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Phase 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-100 healthy volunteers</td>
<td>100-500 patients with target condition</td>
<td>1000-5000 patients with target condition</td>
<td>Post-marketing research and monitoring</td>
</tr>
</tbody>
</table>
Precision Medicine
Knowing in whom treatments work is critical for population health

Traditional clinical trials can help determine if a product is relatively safe and effective for regulatory approval

- Rarely can RCTs provide detailed answers that address payer concerns and emerging population health metrics that require more targeted interventions
Observational Research Designs to Fill Evidence Gaps

A focus on Pragmatic Clinical Trials
Common Types of Observational Research

- Retrospective Database Analysis
- Large Simple Trials
- Registries
- Prospective Observational Study
- Pragmatic Trials
Value of a Retrospective Claims Database Analysis

Data sources with complete claims capture on the individual provides:

• A very good overview of the patient’s exposure to the healthcare system
• Good proxy(ies) for medical conditions and procedures performed
• Reasonable measure of clinical outcomes, though PPV is highly variable
• A good history of drug exposure and utilization
• Very good source for assessing healthcare costs, overall and segment
Pragmatic Clinical Trials are designed to inform clinical and health policy decisions by evaluating the risks and benefits of health interventions in real-world, clinical practice settings.
Pragmatic Trials to Fill Evidence Gaps

When do you need a PCT?

• To create evidence of the value of a new therapy or intervention
• To provide evidence regarding the placement of a new therapy or intervention in the treatment paradigm
• To provide evidence of effectiveness of a therapy or intervention in real-world practice

What can be learned from a PCT?

• How are treatments used in clinical practice
• How effective a treatment is in a non-RCT population
• Supplementing the evidence from the RCT studies
## Pragmatic Trials vs Randomized Controlled Trials

<table>
<thead>
<tr>
<th></th>
<th>Randomized Controlled Trial</th>
<th>vs</th>
<th>Pragmatic Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tests if the Intervention Works Under</strong></td>
<td>Ideal Circumstances</td>
<td>vs</td>
<td>Real-World Circumstances</td>
</tr>
<tr>
<td><strong>Conducted in</strong></td>
<td>Controlled Setting</td>
<td>vs</td>
<td>Usual Clinical Practice</td>
</tr>
<tr>
<td><strong>Comparator</strong></td>
<td>Placebo</td>
<td>vs</td>
<td>Standard Care</td>
</tr>
<tr>
<td><strong>Inclusion Criteria/ Patient Population</strong></td>
<td>Extremely Restrictive</td>
<td>vs</td>
<td>Minimally Restrictive</td>
</tr>
<tr>
<td><strong>Treatment Regimen</strong></td>
<td>Fixed and Protocol Driven</td>
<td>vs</td>
<td>Flexible and Patient-Oriented</td>
</tr>
<tr>
<td><strong>Goal</strong></td>
<td>Regulatory Approval</td>
<td>vs</td>
<td>Reimbursement Approval and Success in the Marketplace</td>
</tr>
</tbody>
</table>
Evaluating Biosimilars

A Commercial HealthPlan Perspective
Outcomes-Based Formulary Management

<table>
<thead>
<tr>
<th>General Approach</th>
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</thead>
<tbody>
<tr>
<td><strong>Consider the complete burden of disease</strong></td>
</tr>
<tr>
<td>Clinical Burden</td>
</tr>
<tr>
<td>Epidemiology</td>
</tr>
<tr>
<td>Natural History of Disease</td>
</tr>
<tr>
<td>Total Cost of Care</td>
</tr>
<tr>
<td>Productivity Impact</td>
</tr>
<tr>
<td>Quality of Life Impact</td>
</tr>
</tbody>
</table>

Leverage the formulary process to improve patient outcomes:

- **Improve Quality of Care**
  (clinical status, quality of life)
- **Reduce Total Cost**
  (pharmacy, medical, ancillary, home health, nursing home, etc.)
- **Optimize Value of Care**
  (cost effectiveness)
- **Improve Productivity**
P & T Process and Committee Overview

Clinical Review Committee (CRC)

Pharmacy and Therapeutics (P&T) Committee

Value Assessment Committee (VAC)

Integrated Pharmacy and Medical Analysis

Critical review of the literature, Assigns a clinical designation based on the evidence. Recommendations sent to the VAC

OUTCOMES ADVISORY COMMITTEE
Outcomes / Pharmacoeconomic Review

Reviews the clinical, outcome, and financial data and makes final tier placement decisions

Clinical Appropriateness

FIRST

Financial Considerations

SECOND
**Clinical Review Committee Designations**

- **Favorable**: The drug provides a **better overall treatment profile** for the majority of individuals taking the product as compared to other available products.

- **Comparable**: The drug provides a **comparable treatment profile** for the majority of individuals taking the product as compared to other available products.

- **Insufficient Evidence**: The drug has an **unclear treatment profile** for the majority of individuals taking the product as compared to other available products.

- **Unfavorable**: The drug provides an **unfavorable treatment profile** for the majority of individuals taking the product as compared to other available products.
Clinical Review Committee – Clinical Comments

Substantive clinical comments about the products under review or issues pertaining to the therapy of a disease the drug(s) is/are used to treat.

**Clinical Comments:**

- May highlight important safety, efficacy, or clinical attribute concerns
- May be used to provide further detail supporting a *Clinical Designation*
- May be used to further differentiate important clinical points between products given the same *Clinical Designation*
- Emphasize key clinical concerns in the treatment of a disease state pertaining to the choice of drug therapy
Pharmacoeconomic and Outcomes Data

• How well does the drug perform in the real world (effectiveness vs. efficacy)?

• Are we achieving the outcomes we expect based on clinical trial data?

• Is the drug being used properly (right patient, dose, duration, etc.)?

• Are there quality of life or productivity benefits?
### Efficacy vs. Effectiveness

<table>
<thead>
<tr>
<th></th>
<th><strong>Efficacy</strong> (Clinical Trial Data)</th>
<th><strong>Effectiveness</strong> (Real-World Data)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective</strong></td>
<td>Does it work under <strong>ideal</strong> circumstances</td>
<td>Does it work under <strong>usual</strong> circumstances</td>
</tr>
<tr>
<td><strong>Setting / Design</strong></td>
<td>Controlled clinical trial</td>
<td>Real-world clinical practice</td>
</tr>
<tr>
<td><strong>Purpose</strong></td>
<td>Regulatory approval (FDA)</td>
<td>Drug performance in real-world</td>
</tr>
<tr>
<td><strong>Intervention or treatment</strong></td>
<td>Fixed regimen</td>
<td>Flexible regimen</td>
</tr>
<tr>
<td><strong>Comparator</strong></td>
<td>Placebo</td>
<td>Active comparator/usual care</td>
</tr>
<tr>
<td><strong>Subjects</strong></td>
<td>Homogenous/highly selective (stringent inclusion/exclusion criteria)</td>
<td>Heterogeneous / any subjects</td>
</tr>
<tr>
<td><strong>Compliance</strong></td>
<td>High</td>
<td>Low to High</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Clinical endpoints (e.g. BP, HbA1c, LDL)</td>
<td>Example: Cardiovascular events, hospitalizations; moving to clinical endpoints</td>
</tr>
<tr>
<td><strong>Internal Validity</strong></td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td><strong>External Validity (generalize to other populations)</strong></td>
<td>Low to medium</td>
<td>Medium to high</td>
</tr>
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Biologics and Biosimilars
Collective Intelligence Consortium (BBCIC)
With the advent of the new science of biosimilars in the U.S., physicians, patients and other stakeholders will have questions about the safety and effectiveness of these products, similar to what was experienced with the introduction of generics more than a generation ago.

As biosimilars come to market, the BBCIC will actively monitor biosimilars and their innovator products, using anonymous data from more than 100 million patients.

- The BBCIC will use well tested data and analytic methods (which FDA has spent $150M developing) to help ensure the safe passage of biosimilars. This improves the efficiency and cost-effectiveness of post-marketed observational studies.

- BBCIC’s multi-stakeholder model allows for a larger voice with more credibility. A consortium of MCOs, IDNs, PBMs, medical societies, researchers & biopharma is less easily ignored.

www.bbcic.org
Scientific Partners Bring Expertise

Lead – HPHC Institute

Data and scientific partners

Scientific partners

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BBCIC Progress to Date

- Consortium officially kicked off in June 2015
- Governance approved October 2015. The BBCIC uses a transparent organized process to characterize patient populations and generate evidence for biologics
- 16 founding participants including Managed Care Organizations, Integrated Delivery Networks, PBMs & Harvard-Pilgrim Health Care Institute

AbbVie • Aetna • Amgen • Anthem-Healthcore • ApoPharma • Boehringer Ingelheim • Express Scripts • Group Health Cooperative • Harvard Pilgrim Health Plan • HealthPartners • Hematology Oncology Pharmacy Association (HOPA) • Henry Ford Health Systems • Merck • Momenta • Optum • Pfizer Inc. • Sandoz

- Public representatives on Planning Board: ASCO (Miller), American College of Rheumatology (Curtis), National Health Council (Peretto)
- Research plan started February 2016
- 3 Research Protocols approved by Science Committee Jun-Aug 2016; Results are expected in the next 4-6 months

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