SPECIALTY PHARMACEUTICALS:
HOW OUTCOMES AND COMPARATIVE DATA CAN INFLUENCE EVIDENCE-BASED MEDICINE

PRESENTERS:
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AND


FOR PRESENTATION AT THE 12TH ANNUAL EFFECTIVELY MANAGING SPECIALTY THERAPIES STRATEGIES FOR BALANCING COST, ACCESS, AND QUALITY A FORUM FOR PAYERS
JANUARY 29-30, 2015 – LAS VEGAS, NV
GOAL:
Understanding the cost effectiveness of specialty therapies is extremely valuable in order to achieve success. This session will strengthen knowledge on the types of cost comparative effectiveness analyses and data that is most critical to the use of specialty therapies.

LEARNING OBJECTIVES:
• How can economic analysis be conducted on specialty therapies?
• What value is provided by clinical trial data like quality-of-life, pharmacoeconomics, surrogate outcomes, and comparative data?
• Describe how outcomes and comparative data can influence evidence-based medicine?
• What cost-effectiveness and comparative effectiveness evidence is available on specialty drugs?
Mirta Millares works for Kaiser Permanente and has no potential conflicts of interest to disclose.

C. Douglas Monroe works for Kaiser Permanente and has no potential conflicts of interest to disclose.
ALL DRUGS: NEW DRUG APPROVALS

Innovation is UP. Approvals are UP. Indications are UP. Prices are UP. Evidence is DOWN.

FDA Approvals by Year

NME or NBE = new molecular or biologic entity
**Specialty Drugs:** Over 50% of New Drug Approvals in the Last 4 Years

New Specialty Drug Approvals are UP.

<table>
<thead>
<tr>
<th>Year</th>
<th>Specialty - New Drugs</th>
<th>Non-Spec - New Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>2012</td>
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<td>30</td>
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<tr>
<td>2013</td>
<td>35</td>
<td>25</td>
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<tr>
<td>2014</td>
<td>50</td>
<td>40</td>
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1/26/2015 Specialty Drug Evidence - [Millares & Monroe - KPDIS]
**Specialty Drugs: Add New Indications to New Drugs in the Last 4 Years**

New Specialty Drug + New Indication Approvals are UP.

- **Specialty - New Indications**
- **Specialty - New Drugs**
- **Non-Spec - New Indications**
- **Non-Spec - New Drugs**

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1/26/2015 Specialty Drug Evidence - [Millares & Monroe - KPDIS]
Top Expense Categories: Cancer, HIV, Immunomodulatory (RA, Psoriasis, Crohn’s, etc.), Hepatitis C, Multiple Sclerosis.

2000: Most Specialty Drugs were Biotech Drugs.

2014: Specialty Drugs have passed 50% of new drug approvals and passed one-third of drug expense.

2020: Specialty Drugs will pass 50 to 60%, not counting Gene Therapies, Cell Therapies, et al.

Biotech Drugs, ~10%

Bio-&-Specialty-Drugs, >35%

Bio-&-Specialty-Drugs, >60%
**ALL DRUGS: FDA APPROVAL TRENDS/CHALLENGES**

**Trends:**
- FDA meets or exceeds User Fee Goals (PDUFA)
- More accelerated approvals and breakthrough designations → drug approvals earlier in clinical trial path [ref: PDUFA V]

**Leading to:**
- Safety Concerns
  - Fewer patients/exposures
  - Significant-but-low -frequency events may not be captured with small populations
  - REMS-with-ETUSA - High risk drugs with significant safety concerns
  - Post-marketing study requirements, some leading to approval withdrawal

**Evidence is DOWN.**

**FASTER APPROVALS + FEWER PATIENTS = MORE UNANSWERED QUESTIONS**

1/26/2015 Specialty Drug Evidence - [Millares & Monroe - KPDIS]
FDA Trajectory for New Drug Approvals

**FDA Action**
- More and faster approvals
- Expedited programs
- Orphan drugs
- REMS
- Additional indications

**Less Evidence**
- Effectiveness
- Safety
- Comparative data
- Meaningful outcomes

**Cost**
- Per treatment regimen
- Per patient
- Organizational
- Societal
- “Because we can” drug pricing
- Hurdles for biosimilar approvals

**Societal Forces**
- Effective Pharma influence
- Regulatory (national and state)
- FDA approval is “enough”
- Every drug that “might” help
- Pharmacoeconomic assessments not fully accepted
- Fear of “rationing”

Approvals are UP. Evidence is DOWN. Pricing is UP. Challenges to affordability are UP.
CHALLENGES IN ECONOMIC ANALYSIS

- **Perspective**
  - Societal (generally accounting for productivity changes)
  - Health delivery system
  - Payer
  - Patient and caregiver

- **What price?**
  - AWP, rebates, discounts
  - Co-insurance, tiers

- **Method**
  - Budget impact model (budget silos)
  - Cost benefit analysis
  - Cost effectiveness
**Real-world, post-marketing CER**

- Integrated health care system and EHR* provide opportunity to gather real world outcomes data in populations.
- Opportunity to compare multiple therapeutic alternatives vs standard of care.
- In addition to comparative efficacy, CER* can provide institution-specific data on
  - Medication adherence and persistence
  - Adverse events
  - Subpopulations
  - Resource utilization
  - Total health care cost

* EHR = Electronic Health Record; CER = Comparative Effectiveness Research

[Drug cost
Hospitalization
Clinic visits
Labs (e.g. genotyping)
Monitoring
ER visits
Adjuvant therapy]
REAL-WORLD, POST-MARKETING CER

- CER data can be used to
  - Support, repeal, or modify formulary status
  - Inform contracting
  - Identify subpopulations
  - Identify safety issues
  - Inform prescribing
  - Support risk-sharing, value-based contracting
Specialty Drugs are Defined by Cost & Complexity

**Definition:** “Specialty Pharmaceuticals” or “Specialty Drugs” at Kaiser Permanente are defined as those drug products which at minimum meet at least one of the following criteria…:

- **High cost per patient**
- **Unusual steps** in procurement, dispensing, etc.
- **Safety issues or REMS**
- **Manufacturer requirements** for limited/restricted dispensing.
- **Opportunities to optimize efficacy, safety, adherence, cost-efficiency**…

Specialty drugs may include drugs used in any treatment venue – outpatient, inpatient, medical office, infusion center, clinic, or other.

*REMS = Risk Evaluation and Mitigation Strategy (required by FDA)*
**Specialty Drugs: Defined by Cost & Complexity**

...but mostly, it’s about cost...

<table>
<thead>
<tr>
<th>Category (a few examples)</th>
<th>Drugs (a few examples)</th>
<th>Cost-per-patient-per-year&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid Arthritis, Psoriasis, Crohn’s Dis.</td>
<td>Enbrel&lt;sup&gt;2&lt;/sup&gt;, Humira&lt;sup&gt;2&lt;/sup&gt;, Remicade&lt;sup&gt;3&lt;/sup&gt;, Orencia&lt;sup&gt;2,3&lt;/sup&gt;</td>
<td>~$20,000 to $40,000</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>Copaxone&lt;sup&gt;2&lt;/sup&gt;, Avonex&lt;sup&gt;2&lt;/sup&gt;, Tysabri&lt;sup&gt;3&lt;/sup&gt;, Tecfidera&lt;sup&gt;4&lt;/sup&gt;</td>
<td>~$45,000 to $65,000</td>
</tr>
<tr>
<td>Cancer</td>
<td>Many new agents&lt;sup&gt;2,4&lt;/sup&gt; in combination or sequence</td>
<td>&gt;$80,000 to &gt;$120,000</td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>Kalydeco&lt;sup&gt;4&lt;/sup&gt; for a subset, expanding</td>
<td>$300,000 to increase</td>
</tr>
<tr>
<td>Morquio A Syndrome</td>
<td>Vimizim&lt;sup&gt;3&lt;/sup&gt;</td>
<td>$600,000 to ~$1.5 million</td>
</tr>
</tbody>
</table>

1. Note that $600/month is “only” $7,200/year.
**SPECIALTY DRUGS:**

**ACCELERATED INFLATION IS CUMULATIVE**

Prices are UP.
Utilization is UP.

\[
\text{COST IMPACT} = \text{PRICE} \times \text{USAGE}
\]

- **Price**
  - Cost/Pt-Yr-of-Tx \( \Delta \)

- **Usage**
  - Pt-Yrs-of-Tx \( \Delta \)

1/26/2015
Specialty Drug Evidence - [Millares & Monroe - KPDIS]
**Why is Outcomes Evidence Important?**

The FDA does not evaluate comparative efficacy...

Multiple Sclerosis (MS) Drugs have all been approved based on clinical trial comparisons to PLACEBO....
And baselines for patients have changed over the years....

Evidence is DOWN.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Annualized Relapse Rate (ARR) Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betaseron / Extavia</td>
<td>ARR Active Drug: 0.8, Placebo: 1.2</td>
</tr>
<tr>
<td>Copaxone</td>
<td>ARR Active Drug: 0.7, Placebo: 1.1</td>
</tr>
<tr>
<td>Avonex</td>
<td>ARR Active Drug: 0.9, Placebo: 1.3</td>
</tr>
<tr>
<td>Rebif</td>
<td>ARR Active Drug: 2.5, Placebo: 2.0</td>
</tr>
<tr>
<td>Tysabri</td>
<td>ARR Active Drug: 0.5, Placebo: 0.7</td>
</tr>
<tr>
<td>Aubagio</td>
<td>ARR Active Drug: 0.4, Placebo: 0.6</td>
</tr>
<tr>
<td>Gilenya</td>
<td>ARR Active Drug: 0.3, Placebo: 0.5</td>
</tr>
<tr>
<td>Tecfidera</td>
<td>ARR Active Drug: 0.2, Placebo: 0.3</td>
</tr>
<tr>
<td>Copaxone TIW</td>
<td>ARR Active Drug: 0.1, Placebo: 0.2</td>
</tr>
</tbody>
</table>

So... How do we know which drugs are most effective?

1990's Trials & Post-2000 Trials
A sample search for treatment of chronic plaque psoriasis:

- Authors leverage published aggregate data by “adjusting average patient characteristics in trials with IPD to match those reported for trials without IPD.” “Treatment outcomes, including continuous, categorical and censored time-to-event outcomes, can then be compared across balanced trial populations.”

- Identified DB PC RCTs, PASI-75 @ 12-weeks. The “weighted average for each reported regimen was calculated to determine the efficacy…”
- “Various biologic agents... were effective at 12 weeks in placebo-controlled trials. Available data cannot fully account for situations in clinical practice...”

- Identified pivotal, DB PC RCT using ITT analysis. “...using the method of Bucher adjusted with the ITC calculator, etanercept being the reference..” Indirect comparison reveals that ustekinumab, adalimumab and infliximab were statistically superior to etanercept ... However, in all situations, the 95% confidence interval does not achieve clinical relevance...
The Search for Comparative Effectiveness Data

So... where do we go to find comparative effectiveness data?

Places we cannot rely on for comparative effectiveness data:
- Qualifying clinical trials
- Specialty Drug sponsors
- Published independent studies

Comparative Evidence Analysis:
- AHRQ (Agency for Health Research & Quality)
- Cochrane collaborative
- CADTH (Canadian Agency for Drugs and Technologies in Health)

Internal data sources:
- Targeted studies within a plan population (not claims)
- Focused Specialty Drug patient registries
- Internally-reported outcomes metrics and safety data
**Specialty Drugs: Treatment Outcomes Evidence**

A new generation of drugs needs a new way of thinking about patient care, evaluation, and resources.

**Specialty Pharmaceuticals Focused Registry**

1. **Assign Specialty Drug to Focused Registry**
   - E.g., at time of new approval

2. **Determine Metrics and Add Drug to the Registry Structure**
   - [Outcomes Metrics, Safety Metrics, etc.]

3. **Refine Metrics & Registry During Formulary Review**
   - [Pharmacy, Specialty Physicians, P&T]

4. **Monitor and Report Individual and Collective Metrics**
   - [Pharmacy, Specialty Physicians, P&T]

**Registry May Include...**

- Outcomes Metrics
- Process Metrics
- Safety Data (AEs)
- Patient Selection
- Demographics PRO (Pt-Reported)
- Quality Data
- Cost Data

1/26/2015 Specialty Drug Evidence [Millares & Monroe - KPDIS]
THE SEARCH FOR COMPARATIVE EFFECTIVENESS DATA

Example: Multiple Sclerosis focused registry

- **MS type & duration** - standardized (relapsing remitting, progressive)
- **EDSS** (or valid equivalent) [Extended Disability Status Score]
- **Functional testing** (e.g., 9-hole peg test)
- **Exacerbations and type** (standardized definitions)
- **Sustained disability post-relapse**
- **MRI results** (with standardized MRI procedures & definitions)
- **Medication history** (with switch-history & adherence levels)
- **Cost data – drug therapy and overall cost-of-care**

**Individualized Reports:**
Used by Neurologist to track tx & guide tx decisions

**Collective Reports:**
Allowing Neurology MS Group to evaluate therapies and value
KP CER Example #1: Boceprevir and Telaprevir

- Approved mid-2011
- RCTs vs best available therapy; no boceprevir-vs-telaprevir CER
- Contracting potential
- KP IR Hepatitis Workgroup
  - guideline development
  - PORG* CER Study
- Formulary status with implementation date pending future recommendations
- Drug Use Management

* PORG = Pharmacy Outcomes Research Group
KP CER Example #1: Study Purpose

• To evaluate the relative effectiveness of boceprevir and telaprevir in genotype 1 hepatitis C infection in KP California
  – Part 1: early indicators of comparative effectiveness and safety
  – Part 2: SVR and development of a predictive model based on patient characteristics and treatment selection
KP CER Example #1: Study Design and Setting

• Concurrent data collection
• Retrospective cohort analysis
• Population
  – all patients initiated on boceprevir or telaprevir
• Data sources
  – KPNC and KPSC
  – Legacy data and HealthConnect
KP CER Example #1: Measurable Outcomes

• Patient groups:
  – Treatment naïve vs. previously treated
• Proportion of patients with early virologic response (EVR) and sustained virologic response (SVR)
• Proportion of patients who had early discontinuation due to futility rule
• Proportion of patients who had early discontinuation due to apparent intolerance
• Proportion of patients with anemia and proportion prescribed EPO
• Cost effectiveness analysis
• Compliance to recommended algorithm for dosing and monitoring
• Estimate preventable and non-preventable wastage
KP CER Example #1: Outcome Measures for Early Interim Analysis

• Primary
  – Proportion of patients who reached early undetectable viral load (<615 IU/mL for KPNC and <43 IU/mL for KPSC)

• Secondary
  – Proportion of patients with an initial 2 log drop in viral load
  – Proportion who discontinued treatment
  – Proportion who initiated treatment with erythropoietin
KP CER Example #1: Early Interim Analysis

- Proportion of patients reaching early undetectable viral load not significantly different
  - TEL earlier with BOC catch-up with treatment completion
  - Difference between regions was also evaluated
- Proportion of patients with an initial 2 log drop in viral load
  - Trend for TEL, NS
- Proportion who discontinued treatment
  - NS
- Proportion who initiated treatment with erythropoietin
  - Significantly higher for BOC
- Consequences:
  - Evaluation of care management differences (best practices)
  - Guideline endorsement
  - Coordinated care management
KP CER Example #2:
Comparative Effectiveness of Chemotherapies in Non-Small Cell Lung Cancer (IIIB and IV)

- A variety of chemotherapy regimens were being used based on published data or ASCO abstracts
- Computerized oncology electronic medical record (Beacon)
- KP statewide cancer registry
KP CER Example #2:
Comparative Effectiveness of Chemotherapies in Non-Small Cell Lung Cancer (IIIB and IV)

• Outcomes of interest
  – Overall survival
    • All-cause mortality
    • Number of months from initial chemotherapy dose until death
  – One year survival
  – Overall survival by age over and under 65 years

• Chemotherapy regimens grouped by primary agent
# A Declaration of Specialty Drug Usage Management Principles

## Principle #1:
High-Cost Specialty Drugs → demand → NEW WAYS OF PLANNING for care, clinical evaluation, & resource mgt.

## Principle #2:
With LESS clinical trial evidence, healthcare providers need METHODS & TOOLS to track efficacy & safety post-approval.

## Principle #3:
Use of a Specialty Drug requires COLLABORATIVE MONITORING in a focused registry with outcomes metrics.
Payers will be looking for evidence of value

Value assessment is needed

- Evidence-based clinical evaluation with additional “value” assessments
  - Relevant and meaningful outcomes including patient-centered outcomes
  - Pharmacoeconomic assessments
    - Cost to achieve desired outcome(s)
    - Indirect Costs
  - Comparative net health benefits
Providers will be looking for evidence of value

ASCO Value Task Force

Desired State
- Enhanced clinical benefit
- Tolerable toxicity
- Affordable cost

Not Desired
- Modest clinical benefit
- High toxicity
- High cost

\[ V = \frac{Q + S}{\$} \]

V = Value; Q = Quality; S = Service; $ = Cost
COMPARATIVE OUTCOMES DATA SUPPORTS EVIDENCE-BASED DECISIONS

Patients
• Participate in joint decision-making
• Ability to provide Informed consent
• Meaningful outcomes
• Patient-centered outcomes (QOL, functionality, long term outcomes, affordability)
• Options/alternatives

Providers
• Informed patients participate in joint decision-making
• Transparency
• Level of certainty
• Risk vs benefit
• Low value vs high value interventions
• Options/alternatives
COMPARATIVE EFFECTIVENESS DATA SUPPORTS EVIDENCE-BASED DECISIONS

Payers

• Low value vs high value interventions (health system value)
• Budget impact
• Resource impact
• Cost to achieve desired outcome(s)
• Indirect Costs
• Comparative net health benefits
• Affordability
Why is Outcomes Evidence Important?

Other reasons why it will be important to measure outcomes and to compare products with real-life evidence:

• **INNOVATION**: Continued innovation in Specialty Drugs (e.g., new drugs coming for Duchenne Muscular Dystrophy, TTR-FAP/C, Sickle Cell, focal segmental glomerulosclerosis, etc....).

• **PRICING**: Continued new high-water-marks for Specialty Drugs

• **BIOSIMILARS**: How will providers/plans reassure patients and prescribers in the use of biosimilars? Got Evidence?

• **GENE THERAPIES**:
  • Talimogene laherparepvec: Filed with FDA for malignant melanoma
  • Alipogene tiparvovec (Glybera): Approved in Europe for pts genetically deficient in lipoprotein lipase (LPL).

• **CELL THERAPIES**: >5 already approved

• **COMPETITION**: Who can show the benefit to overall care and cost?
WHY IS OUTCOMES EVIDENCE IMPORTANT?

Two major reasons....

STEWARDSHIP OF HEALTH CARE RESOURCES:
• There is no limit to potential targets for Specialty Drugs.
• There appears to be no limit to the cost for Specialty Drugs.
• Dollars spent unnecessarily on Specialty Drugs limit the dollars available to treat patients effectively.

FRAMEWORK FOR THE FUTURE: Specialty is just the beginning. Many future high-cost therapies will require strategies similar to those used to manage Specialty Drugs – i.e., patient selection, effective disease management models, outcomes evidence
• Gene Therapies
• Cell Therapies
• Pharmacogenomic Applications

etc., etc., etc., into the Future....
Discussion