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A New Era for Real-World Evidence

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A new era for real-world evidence

Thomas Jefferson University
Population Health Forum
June 12, 2019

Neal J. Meropol, MD
VP, Research Oncology
Flatiron Health
What is real-world evidence?

“...the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of real-world data...”

What are real-world data?

Real-world data are the data relating to patient health status and/or the delivery of healthcare routinely collected from a variety of sources:

- Electronic health records
- Claims & billing activities
- Product & disease registries
- Patient-generated data (e.g. in-home settings)
- Data gathered from other sources that can inform on health stats (e.g. mobile devices)
RWE isn’t new

“Course of the disease is predictable, and the effect of the drug is substantial” -- Corrigan-Curay, Sacks, Woodcock. JAMA 2018
We used to think there was only one situation when a randomized controlled clinical trial wasn’t appropriate.

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomized controlled trials

(BMJ 2003;327:1459-1461)
What has changed?

- Demand
- Supply
- Policy
The demand for evidence in oncology is at unprecedented levels

Exploding R&D Pipelines  
Combination therapies  
Value-based care  
Precision Medicine
Limitations of Prospective Randomized Clinical Trials

- Not representative
- Lengthy
- Costly
- Not feasible with rare clinical scenarios
- Randomization may be ethically-challenging
- Sponsors may not wish to compare 2 standard treatments

Real-world data can provide complementary evidence
The opportunity for RWE

Almost every cancer patient’s story lives in an electronic health record

But.....how do we overcome the limitations of these real-world data?
FDA recently drafted key documents on RWE to drive forward the 21st Century Cures mandate.

The Framework includes considerations of the following:

1. Whether the **RWD** are fit for use.

2. Whether the trial or study design used to generate RWE can provide **adequate scientific evidence** to answer or help answer the regulatory question.

3. Whether the study conduct meets **FDA regulatory requirements** (e.g., for study monitoring and data collection).

Series of draft guidances being released by the FDA.
RWE can be applied to various use cases to support regulatory submissions

**Regulatory Objective**

- New Filing
- Label Update or Expansion
- Post-Marketing Studies

**Use Cases for RWE Aligned to Objective**

- **To provide disease context**
  - To compare or provide context for a treatment arm in single arm trial

- **To characterize unmet need**
  - To modify indication (e.g., dose)

- **To evaluate safety and/or effectiveness**

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Demand

Supply

Policy
Getting from DATA to EVIDENCE

Structured and Unstructured Data in the EHR

- Diagnosis
- Visits
- Demographics
- Labs
- Therapies
- Discharge Notes
- Physician Notes
- Radiology
- Pathology

Hospital
Lab
### Example: Albumin

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>2220</td>
<td>Blood Serum Albumin</td>
<td>g/dL</td>
</tr>
<tr>
<td>QD25001600</td>
<td>ALBUMIN/GLOBULIN RATIO QD (calc)</td>
<td></td>
</tr>
<tr>
<td>QD25001400</td>
<td>ALBUMIN QD</td>
<td>g/dL</td>
</tr>
<tr>
<td>QD50058600</td>
<td>ALBUMIN</td>
<td>%</td>
</tr>
<tr>
<td>QD50055700</td>
<td>ALBUMIN</td>
<td>g/dL</td>
</tr>
<tr>
<td>CL3215104</td>
<td>Albumin % (EPR)</td>
<td>%</td>
</tr>
<tr>
<td>LC001081</td>
<td>ALBUMIN, SERUM (001081)</td>
<td>g/dL</td>
</tr>
<tr>
<td>LC003718</td>
<td>Albumin, U</td>
<td>%</td>
</tr>
<tr>
<td>LC001488</td>
<td>Albumin</td>
<td>g/dL</td>
</tr>
<tr>
<td>LC133751</td>
<td>Albumin, U</td>
<td>%</td>
</tr>
<tr>
<td>CL3215162</td>
<td>Albumin%, Urine</td>
<td>%</td>
</tr>
<tr>
<td>CL3215160</td>
<td>Albumin, Urine</td>
<td>mg/24hr</td>
</tr>
<tr>
<td>3234</td>
<td>ALBUMIN SS</td>
<td>g/dL</td>
</tr>
<tr>
<td>LC133686</td>
<td>Albumin, U</td>
<td>%</td>
</tr>
<tr>
<td>QD50060710</td>
<td>MICROALBUMIN</td>
<td>mg/dL</td>
</tr>
<tr>
<td>QD50061100</td>
<td>MICROALBUMIN/CREATININE RATIO, RANDOM URINE</td>
<td>mcg/mgcreat</td>
</tr>
<tr>
<td>QD85991610</td>
<td>ALBUMIN</td>
<td>relative %</td>
</tr>
<tr>
<td>50058600</td>
<td>ALBUMIN UPEP RAND</td>
<td>%</td>
</tr>
<tr>
<td>CL3210074</td>
<td>ALBUMIN LEVEL</td>
<td>g/dL</td>
</tr>
<tr>
<td>QD86008211</td>
<td>ALBUMIN/GLOBULIN RATIO (calc)</td>
<td></td>
</tr>
<tr>
<td>LC149520</td>
<td>Albumin</td>
<td>g/dL</td>
</tr>
<tr>
<td>QD45069600</td>
<td>PREALBUMIN</td>
<td>mg/dL</td>
</tr>
<tr>
<td>QD900415245</td>
<td>ALBUMIN, SERUM</td>
<td>mg/dL</td>
</tr>
</tbody>
</table>

Certain structured data elements may be coded and collected in multiple ways in the EHR across practices.
Unstructured documents contain essential information

Example: Unstructured Data Points
- EGFR testing status
- EGFR test result
- Specific mutation type (e.g., T790M)
- Date sample was collected
- Date sample was received in lab
- Date result was provided to physician
- Type of test (e.g., NGS)
- Type of sample (e.g., tissue)
- Sample collection site

... for every EGFR test the patient receives
ML will empower humans, not replace them

ML is great at:
- classification
- recommendation
- ranking
- pattern-recognition

Humans are great at:
- synthesizing information
- applying domain-specific knowledge
- adapting to novel information

Humans will always be necessary for:
- Generating training data
- Evaluating the performance of ML models

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The Process: Technology Enabled Abstraction

Expert abstractors
A network of abstractors comprised of oncology nurses, certified tumor registrars, and oncology clinical research professionals.

Flatiron Technology
Software helps trained human abstractors efficiently organize and review unstructured documents to capture key data elements in predetermined forms.
A Special Challenge for RWE in Cancer Research: Defining Endpoints

● The gold-standard = survival

● Surrogate endpoints for clinical benefit are commonly used in clinical trials
  ○ Tumor response and tumor progression - based on measurements on CT scans (RECIST Criteria)

● “Real-world Endpoints” are challenging
  ○ Survival dates often missing
  ○ CT scans not routinely available
  ○ Scan selection is variable
  ○ Scan timing is variable
  ○ Radiology report measurements are inconsistent and often qualitative
  ○ Direct comparisons to CT scans may introduce bias
Mortality is often missing from the EHR
This requires linking of EHR data with external sources
Sensitivity and specificity of mortality endpoint optimized by merging data sources

- Structured EHR Only: Sensitivity 65.97%, Specificity 97.06%
- + Commercial Dataset: Sensitivity 84.06%, Specificity 96.26%
- + SSDI Data: Sensitivity 88.83%, Specificity 96.06%
- + Abstracted EHR Data: Sensitivity 90.60%, Specificity 96.00%
Flatiron approach to rwResponse and rwProgression:

Based upon oncologist documentation in the context of supporting data

| Three-pronged framework for assessment of validity of real-world endpoints |
|---|---|
| **Develop an approach with face validity** | 1. Oncologist agreement with definition & approach |
|  | 2. Regulatory stakeholder alignment with definition & approach |
| **Ensure that the approach has internal validity** | 3. Completeness of collected data |
|  | 4. Inter-rater agreement on datapoint for duplicate abstracted patients |
| **Assess the external validity of the data point** | 5. Likelihood of predicting downstream events (e.g., treatment change, OS) |
|  | 6. Comparison to other endpoints (e.g., OS, RECIST) or external data sources (if available) |
To improve lives by learning from the experience of every cancer patient

OUR MISSION

DATABASE:
- Linked advanced genomics data

PATH. REPORT:
- EGFR-
- ALK-
- PDL1 staining

RADIOLOGY REPORT:
- Response

PROG. NOTE:
- New Diarrhea; treatment held

RADIOLOGY REPORT:
- Progression

AMALGAMATED ENDPOINT:
- Death

HOSPICE REFERRAL & CONDOLENCE CARD:
- Death

ICD:
- Lung cancer
- Metastatic

LAB REPORT:
- Normal

CHEMO ORDER:
- Start immuno-therapy

EHR:
- Death

structured data
unstructured data
linked data
Abstraction Details
> Variable: Response 8/3/2017
> Abstractor: Sue Smith
> Date/Time: 8/30/17 at 10:10am
> Source: Cancer Center Record
  8/3/2017 imaging report
  8/3/2017 note
> Result: Progression

Response Variable:
> completeness: 95%

Abstractor quality test 6/1/2017
> Sue Smith: 96% accurate

Variable quality test 6/1/17
> Inter-abstractor agreement: 97%
> Kappa: 0.93

<table>
<thead>
<tr>
<th>Patient</th>
<th>Joan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage at Dx</td>
<td>IV</td>
</tr>
<tr>
<td>Biomarkers</td>
<td>EGFR-, ALK-, PDL1+</td>
</tr>
<tr>
<td>1L Treatment</td>
<td>immunotherapy</td>
</tr>
<tr>
<td>Progression</td>
<td>2017-03-08</td>
</tr>
<tr>
<td>Date of Death</td>
<td>2017-04-12</td>
</tr>
</tbody>
</table>
Cohort Demographics
as of May 2019

Patients in cohort: 54,883 (Community: 50,132 | Academic: 4,751)

Histology

- Non-squamous cell carcinoma: 69.00%
- Squamous cell carcinoma: 25.50%
- Not otherwise specified

Smoking Status

- History of smoking: 86.60%
- No history of smoking: 12.10%
- Unknown / not documented

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PDL1 Biomarker Testing and FDA Approvals of Immune Checkpoint inhibitors in NSCLC

Opdivo for recurrent NSCLC [Oct 2015]

Keytruda for recurrent PDL1+ NSCLC [Oct 2015]

Opdivo for recurrent squamous cell [Mar 2015]

Keytruda for first line PDL1+ NSCLC [Oct 2016]

Keytruda for first line PDL1+ NSCLC [Oct 2016]

Keytruda plus chemo for first line NSCLC, regardless of PDL1 [May 2017]

Keytruda for any MSI-High tumor [May 2017]

PDL1 Testing Rate Among Actively Treated Patients

© Flatiron Health 2019
Patient Share by Therapy Class — PD1/PDL1

All Lines

Q3 2014: 0%
Q2 2019: 58%

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How is Flatiron RWD being used?

Commercial Applications
- Understanding Uptake of New Biomarkers and Treatments
- Discovery and Validation of New Predictive Biomarkers
- Comparative Effectiveness of Standard Treatments
- Quality Measurement / Impact of Healthcare Policy

Research and Clinical Applications
- Risk Modeling

Regulatory Applications
- Cost Effectiveness Modeling
- Submission of Real-World Outcomes for Regulatory Decisions
RWE Considerations

Data Quality

✓ Completeness
✓ Representativeness
✓ Clinical Depth
✓ Longitudinal Follow-Up
✓ Timeliness/Recency
✓ Clear Provenance
✓ Measurement Reliability/Validity

Analytic Rigor

✓ Pre-Specified Analysis Plan
✓ Confounders
✓ Bias
✓ Cohort Selection


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Case study: Does genomic testing improve survival for lung cancer patients?

Presley et al. JAMA 2018

Figure 2. Kaplan-Meier Estimates of Patients With Broad-Based Genomic Sequencing vs Routine Testing Propensity Score-Matched Sample (n = 1038)
TMB as Predictive Biomarker in NSCLC

Figure 2. Proportional uptake of anti-PD1 treatment among eligible patients according to age.

A. Melanoma

O'Connor JM, et al. JAMA Oncol, 2018
Evaluating real-world outcomes of NSCLC patients treated with PD-1 inhibitors

Real-world patients are different than trial patients

Table 1. Characteristics of a cohort of 1,344 metastatic NSCLC patients who received nivolumab or pembrolizumab in the metastatic setting in U.S. community practices

<table>
<thead>
<tr>
<th>Variable</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
</tr>
<tr>
<td>Age at PD-1 initiation, years, median (IQR)(^a)</td>
<td>69.0 (61.0–75.0)</td>
</tr>
<tr>
<td>Age categories at PD-1 initiation(^a)</td>
<td></td>
</tr>
<tr>
<td>&lt;49 years</td>
<td>45 (3.4)</td>
</tr>
<tr>
<td>50–64 years</td>
<td>435 (32.4)</td>
</tr>
<tr>
<td>65–74 years</td>
<td>500 (37.2)</td>
</tr>
<tr>
<td>75+ years</td>
<td>364 (27.1)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>597 (44.4)</td>
</tr>
<tr>
<td>Men</td>
<td>747 (55.6)</td>
</tr>
</tbody>
</table>

Median age in clinical trials = 62; <8% were 75 or over
Can RWE help provide context for clinical trials, and assist in their design?

- Assessing **generalizability**: did the patients in the clinical trial look like those treated in “the real world”?
- Assessing **relevance**: did the control arm actually reflect the current standard of care?
Standard of Care (SOC) Relevance and Generalizability

Eligible for trial

SOC Relevance score = C/A

Received treatment consistent with trial’s control arm

Generalizability score = C/B

Bennett et al. ASCO Annual Meeting 2019
Relevance and Generalizability of Randomized Clinical Trials

Median (range) of scores:
- Generalizability: 63% (35%-88%)
- SOC relevance: 37% (15%-74%)

Bennett et al. ASCO Annual Meeting 2019
Affordable Care Act Medicaid Expansion Impact on Racial Disparities in Timely Cancer Treatment

Adamson et al. ASCO 2019 Annual Meeting
Methods

Study sample: Adults 18-64 years, diagnosed with advanced cancer (N=30,386)

Outcome: **timely treatment** = systemic cancer treatment initiated w/in 30 days of diagnosis

Study design: Compares experience of black relative to white patients
  - Diagnosed in states **after Medicaid expansion** compared to pre-expansion or in states not expanding by 2019.

Adamson et al. ASCO 2019 Annual Meeting
Results: Demographics

Patient Population (N = 30,386)

<table>
<thead>
<tr>
<th></th>
<th>Not Expanded (n = 18,678)</th>
<th>Expanded (n = 11,708)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age, Years [IQR]</td>
<td>57.0 [51.0-61.0]</td>
<td>57.0 [52.0-61.0]</td>
</tr>
<tr>
<td>Male, %</td>
<td>47.1</td>
<td>48.4</td>
</tr>
<tr>
<td>Race: White, %</td>
<td>73.3</td>
<td>70.3</td>
</tr>
<tr>
<td>Race: Black, %</td>
<td>14.6</td>
<td>8.7</td>
</tr>
</tbody>
</table>

Adamson et al. ASCO 2019 Annual Meeting
Medicaid expansion associated with reduced racial disparities in timely treatment

**Adjusted Rate of Timely Treatment (%)**

- **White**: 48.3
- **Black**: 43.5

**NOT EXPANDED**
Overall Mean: 47.7%

-4.8% points
p < 0.001

Adamson et al. ASCO 2019 Annual Meeting
Medicaid expansion associated with reduced racial disparities in timely treatment

Adamson et al. ASCO 2019 Annual Meeting
Medicaid expansion associated with reduced racial disparities in timely treatment

- **White**: 48.3% (Adjusted Rate of Timely Treatment)
  - -4.8% points
  - p < 0.001

- **Black**: 43.5% (Adjusted Rate of Timely Treatment)

**Not Expanded**
- Overall Mean: 47.7%

**Expanded**
- Overall Mean: 49.8%

Difference-in-Differences
- Reduction in disparity: 4.0% points
  - p = 0.042
Impact of Oncology Care Model Reporting Requirements on Quality of Care

• The Oncology Care Model (OCM) is a voluntary Center for Medicare and Medicaid Innovation alternative payment model pilot program
  • Requires reporting of certain quality metrics, eg. frequency of biomarker testing in patients with lung cancer

• We conducted a natural experiment to assess the effect of an OCM reporting policy on quality of care for patients with advanced non-small cell lung cancer.
  • Quality metric: Rates of biomarker testing and of biomarker-directed therapy

Castellanos et al. ASCO Annual Meeting 2019
Result: Difference-in-Differences Model Showed no Changes in Downstream Care Associated to OCM

OR = 1.09 (95% CI: 0.88 - 1.34); $P = 0.45$
Quality Measurement: Trends in EOL Treatment in Urothelial Cancer

Figure 1. Initiation of new therapy in the last 60 days of life in patients with metastatic urothelial carcinoma, by treatment type. Abbreviations: q1, first quarter; q2, second quarter; q3, third quarter; q4, fourth quarter.

Real-World Data for Quality Improvement

- Real-time
- Site, clinical team, physician-level metrics

Kraut et al. J Oncol Practice, 2019
A look to the future - a new paradigm for RWE in drug development

The Continuum of RWE

Retrospective RWE

Prospective Evidence Generation

Consent
A look to the future - a new paradigm for RWE in drug development

The Continuum of RWE

- Use technology to bridge the gap between retrospective RWE and prospective evidence generation

- Apply to novel use cases including:
  - Biomarker validation
  - Post-marketing
  - Pharmacovigilance
  - Expanded indications
  - Real-world external controls
Thank you