The Emerging Role of RWE in Oncology

The 7th Annual Big Data in Biomedicine Symposium
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Georgetown University

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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)
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)
"Course of the disease is predictable, and the effect of the drug is substantial" -- Corrigan-Curay, Sacks, Woodcock. JAMA 2018
What has changed?
We are experiencing a massive increase in oncology treatment complexity

Exploding R&D Pipelines
Combination therapies
Value-based care
Precision Medicine
The traditional approach to clinical trials is increasingly unsustainable

63% of cancer studies take 4+ years to accrue

Over 1,100 trials opened between 2015 and 2016

Year post initiation trial met enrollment goals

Cancer
12% 19% 63%

Other (MS, AD, Asthma)
17% 13% 29% 41%

1 year 2 years 3 years 4+ years

Number of cancer trials opened vs closed over time.

Source: ClinicalTrials.gov
Oncology post-market commitments are accumulating faster than they can be fulfilled

More approvals in early phase trials.

An accumulation of regulatory debt

Approvals via “Breakthrough” designation

Source: accessdata.fda.gov

New post marketing commitments (PMC) issued per year vs. currently unfulfilled PMCs as of that year.

Source: accessdata.fda.gov
Historical drug development paradigm

- **Regulatory Approval**
- **Total Patients Exposed**
- **Time**
- **I**
- **II**
- **III**
- **IV / Observational**
- General uptake in the market
21st Century Cures - Shift towards earlier approvals

Total Patients Exposed

Regulatory Approval

Use of RWE to Monitor

I

II

Earlier

Time
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
The Opportunity for Regulatory-Grade RWE

21st Century Cures Act

SEC. 505F. UTILIZING REAL WORLD EVIDENCE.

(a) In General.—The Secretary shall establish a program to evaluate the potential use of real world evidence—

(1) to help to support the approval of a new indication for a drug approved under section 505(c); and

(2) to help to support or satisfy post-approval study requirements.
What about the supply?
The opportunity for RWE

Fact: Very few patients take part in prospective clinical trials

But... how do we overcome the limitations of these real-world data?

Fact: Almost every cancer patient’s story lives in an electronic health record
The Source

2.1M
Active Patients

2,500
Clinicians

280
Cancer Clinics

800
Unique Sites of Care
Getting from DATA to EVIDENCE

Millions of electronic health records in a single common dataset.
The need to normalize and harmonize structured data

**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/mg creat</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.
For every PD-1/PD-L1 test a patient receives, Flatiron biomarker Data Model captures:

- Test status
- Test result
- Date biopsy collected
- Date biopsy received by laboratory
- Date result received by provider
- Lab name
- Sample type
- Tissue collection site
- Type of test (e.g., FISH)
- Assay / kit (e.g., Dako 22C3)
- Percent staining & staining intensity
ML will empower humans, not replace them

**ML is great at**
- classification,
- recommendation,
- ranking, and
- 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
Data curation is a part of the endeavor

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.
Oversight of abstraction quality assurance & quality control

Centralized Controlled Environment

**Upfront**
- Feasibility
- Policies & Procedures
- Training & Testing

**Ongoing**
- Auditing & Monitoring
- Performance Management
- Review Panel

**Dataset QA**
- Cohort QA
- Data Alignment
- Clinical Assertions
Diagnosed with GBM

Undergoes surgery

Receives adjuvant therapy

Progresses on adjuvant therapy

Starts 1L therapy

Starts on 2L

Progresses on 1L

Patient deteriorates leading to hospitalization / death

*Relative timing not exact
A comprehensive view of the patient journey

1. Diagnosed with GBM
2. Undergoes surgery
3. Receives adjuvant therapy
4. Progresses on adjuvant therapy
5. Progresses on 1L
6. Starts 1L therapy
7. Starts on 2L
8. Patient deteriorates leading to hospitalization / death

- Patient age
- Gender
- Race
- Insurance
- Group Staging
- Smoking Status
- Site of Disease
- Comorbidities

- Medical admins / orders
- Dosage
- Concomitant meds
- Regimen name
- Duration of therapy
- Adverse events
- Response
- Reason for discontinuation

- Date of surgery
- Date of met Dx (time to recurrence)
- Sites of metastases
- Date of progression (with scan or lab result to confirm)
- Date of death
- Consensus date of death

- Medical admins / orders
- Dosage
- Concomitant meds
- Regimen name
- Duration of therapy
- Adverse events
- Response

- Structured EMR data
- Unstructured EMR data
- External mortality data
- Combined / derived data

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Regulatory-Grade RWD/RWE

Clinical Depth
Longitudinal Follow-up
Completeness
Quality Monitoring

Timeliness / Recency
Scalability
Provenance
Generalizability

Miksad and Abernethy, Clin Pharmacol and Ther, 2017
A word about “Endpoints”

Deriving outcomes from EHR data requires the definition and validation of endpoints that go beyond what is used in clinical trials.

- Mortality
- Real-World Progression
- Real-World Tumor Response
- Adverse Events
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

Data shown for advNSCLC

Source

The Flatiron Provider Network

~2,500 clinics
280 Cancer Offices
800 Unique sites of care

Process

Technology-Enabled Abstraction

Expert abstractors

Flatiron technology

Application

Validation

Percent Surviving

Days Elapsed
Emergence of Precision Medicine

- Physicians need information to select treatments that are most likely to benefit individual patients
- Information that describes patient variability is increasingly complex
- Real world evidence can identify and validate the linkage between patient characteristics, specific treatments, and clinical outcomes

Credit: National Cancer Institute
Clinico-Genomic Database (CGDB)

**Patient Population**
- CG Registries
- ~35,000 patients

**Data Model**
- Enhanced Clinical RWD
- Clinical Outcomes
- Comprehensive Genomic Data
- Advanced Genomic Analysis

**Longitudinal, research quality clinical data**

**Outcomes data**

**Comprehensive molecular information**

**Advanced genomic analyses**
Applications of Real-World Evidence (RWE) In Oncology
How is Flatiron RWE being used?

**Commercial Applications**
- Understanding Uptake of New Biomarkers and Treatments

**Research Applications**
- Cost Effectiveness Modeling Based on Real-World Outcomes Data
- Discovery and Validation of New Predictive Biomarkers
- Comparative Effectiveness of Standard Treatments

**Regulatory Applications**
- Submission of Real-World Outcomes for Label Expansion, PMCs
Lung Cancer Cohort Demographics
As of August 2018

Patients in cohort: 50,220

Histology
- Squamous cell carcinoma: 69.00%
- Non-squamous cell carcinoma: 25.30%
- Not otherwise specified

Smoking Status
- No history of smoking: 86.40%
- History of smoking
- Unknown / not documented: 12.00%
PDL1 Biomarker Testing and FDA Approvals of Immune Checkpoint inhibitors in Lung Cancer

PDL1 Status Among Tested Patients

Keytruda for first line PDL1+ NSCLC [Oct 2016]
Keytruda for any MSI-High tumor [May 2017]
Keytruda plus chemo for first line NSCLC, regardless of PDL1 [May 2017]
Opdivo for recurrent NSCLC [Oct 2015]
Opdivo for recurrent squamous cell [Mar 2015]

PDL1 Testing Rate Among Actively Treated Patients
Patient Share by Therapy Class — PD1/PDL1

All Lines

Q3 2014

Q3 2014

Q4 2014

Q1 2015

Q2 2015

Q3 2015

Q4 2015

Q1 2016

Q2 2016

Q3 2016

Q4 2016

Q1 2017

Q2 2017

Q3 2017

Q4 2017

Q1 2018

Q2 2018

Q3 2018

Q3 2018

0%

51%

© Flatiron Health 2017
Real-world patients are different than trial patients

<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 initiationa</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><strong>65–74 years</strong></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

Case Study: Disparities Research

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

A. Melanoma

O’Connor JM, et al. JAMA Oncol, 2018
### Association between demographic or clinical characteristics and ALK testing

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
</tr>
<tr>
<td>55-64 v &lt; 55</td>
<td>0.86 0.76 to 0.98</td>
</tr>
<tr>
<td>65-74 v &lt; 55</td>
<td>0.77 0.68 to 0.86</td>
</tr>
<tr>
<td>75-84 v &lt; 55</td>
<td>0.66 0.58 to 0.75</td>
</tr>
<tr>
<td>85+ v &lt; 55</td>
<td>0.57 0.50 to 0.65</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Female v male</td>
<td>1.14 1.08 to 1.20</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
</tr>
<tr>
<td>Asian v white</td>
<td>1.08 0.91 to 1.27</td>
</tr>
<tr>
<td>Black or African American v white</td>
<td>0.99 0.90 to 1.09</td>
</tr>
<tr>
<td>Other race v white</td>
<td>0.71 0.66 to 0.76</td>
</tr>
<tr>
<td>Missing v white</td>
<td>1.04 0.95 to 1.13</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
</tr>
<tr>
<td>Hispanic v non-Hispanic</td>
<td>0.95 0.82 to 1.10</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td></td>
</tr>
<tr>
<td>NOS v non-squamous</td>
<td>0.35 0.32 to 0.39</td>
</tr>
<tr>
<td>Squamous v non-squamous</td>
<td>0.12 0.11 to 0.13</td>
</tr>
<tr>
<td><strong>Disease type</strong></td>
<td></td>
</tr>
<tr>
<td>Recurrent v de novo</td>
<td>0.82 0.77 to 0.87</td>
</tr>
<tr>
<td>Unknown v de novo</td>
<td>0.61 0.54 to 0.70</td>
</tr>
<tr>
<td><strong>Smoking status</strong></td>
<td></td>
</tr>
<tr>
<td>History of smoking v no history</td>
<td>0.72 0.66 to 0.78</td>
</tr>
<tr>
<td>Unknown history v no history</td>
<td>0.43 0.36 to 0.50</td>
</tr>
<tr>
<td><strong>Insurance</strong></td>
<td></td>
</tr>
<tr>
<td>Medicaid v commercial</td>
<td>0.60 0.49 to 0.72</td>
</tr>
<tr>
<td>Medicare v commercial</td>
<td>0.93 0.87 to 0.98</td>
</tr>
<tr>
<td>Other v commercial</td>
<td>0.93 0.88 to 0.99</td>
</tr>
<tr>
<td><strong>Region</strong></td>
<td></td>
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<tr>
<td>Midwest v West</td>
<td>0.72 0.66 to 0.78</td>
</tr>
<tr>
<td>Northeast v West</td>
<td>0.50 0.41 to 0.61</td>
</tr>
<tr>
<td>South v West</td>
<td>0.86 0.79 to 0.93</td>
</tr>
<tr>
<td>Missing v West</td>
<td>0.86 0.79 to 0.92</td>
</tr>
</tbody>
</table>

Illei et al. JCO Precis Oncol, 2018
Case study: Does genomic testing improve survival for lung cancer patients?

Presley et al. JAMA 2018
Case study: Can we predict who benefits from treatment?

Analyzing biomarkers of cancer immunotherapy (CIT) response using a real-world clinico-genomic database

**High TMB (>20 mutations/Mb) Predicts Duration of Treatment with Nivolumab**

Singal G et al. Analyzing biomarkers of cancer immunotherapy (CIT) response using a real-world clinico-genomic database. European Society of Medical Oncology; Sept 8 - 12, 2017; Madrid, Spain.
Real-world progression can reproduce findings from prospective clinical trials

**B. Propensity Score—Matched Data**

- **Flatiron RW cohort**, median 18.5 (95% CI, 13.7–24.1) months
- **PALOMA-2 RCT cohort**, median 19.2 (95% CI, 13.7–NE) months

**Number of patients at risk**

<table>
<thead>
<tr>
<th></th>
<th>Flatiron RW</th>
<th>PALOMA-2 RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>79</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>64</td>
<td>63</td>
</tr>
<tr>
<td>6</td>
<td>52</td>
<td>54</td>
</tr>
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<td>9</td>
<td>48</td>
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</tr>
<tr>
<td>12</td>
<td>41</td>
<td>46</td>
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<td>15</td>
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<td>21</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td>24</td>
<td>16</td>
<td>11</td>
</tr>
</tbody>
</table>

CI = confidence interval; HER2 = human epidermal growth factor receptor 2–negative; HR+ = hormone receptor–positive; NE = not estimable; PFS = progression-free survival; RCT = randomized controlled trial; RW = real-world.

* Intent-to-treat population.

Caliper width = 0.10.
Where are we going? A new paradigm for RWE in drug development

The Continuum of RWE

Retrospective RWE

Consent

Prospective Evidence Generation
How can we leverage RWE to support evidence generation in the context of clinical trials?
Where are we going? 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 it towards novel use cases including:
  - Biomarker validation
  - Post-marketing
  - Pharmacovigilance
  - Expanded indications
  - Real-world controls
Questions