Real World Data in Oncology: When and how is it valid to use?

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• Collaboration on RWD with:
  • AACR GENIE
  • FDA
  • Cancer-LINQ
  • Flatiron
  • NCI-SEER
Outline:
Real World Data and Evidence in Oncology

- Reasons for intense interest in RWD/RWE
- Use cases for RWD/RWE
- Challenges in using RWD/RWE
- Expanding capacity for RWD/RWE use
21st Century Cures Act in USA Requires Investment in RWD

- Act passed by US Congress in 2016
- Intensive lobbying by patients and industry
- Focuses on improving access to medicines and accelerating research
- The Cures Act requires FDA to establish a program to evaluate RWE to:
  - Support the approval of a new indications for a drug approved under section 505(c) of the Federal Food, Drug, and Cosmetic Act
  - Support or satisfy post-approval study requirements
  - FDA released draft framework with guidance for industry in December 2018
Definitions of Real World Data (RWD) and Real World Evidence (RWE) from the FDA Draft Guidance

• RWD is defined as: data relating to any aspect of patient health status that are collected in the context of routine health care delivery

• RWD come from a variety of sources including:
  • Billing claims and encounter records
  • Population-level registries
  • Disease and device registries
  • Electronic health records
  • Patient-reported data
  • Electronic surveillance data (activity trackers, implants, wearables)
  • Large pragmatic trials—eg cluster RCTs

• RWD is defined by what it is not----data from prospective RCTs

• RWD’s purpose is to generate Real World Evidence
Challenges in Development of Effective Cancer Medicines

Drug Development is lengthy and Failure Rates are High

Length of Drug Approval

It is estimated that it takes an average of 10-12 years for a drug to be approved.

10-12 YEARS

https://www.drugs.com/cda-approval-process.html

Percentage of Phase Transition Success in Clinical Trials

Phase I: 70%
Phase II: 33%
Phase III to Approval: 20-30%
What is the motivation for RWD/RWE focus?

Public demand for accelerated progress

Problems with the traditional paradigm

Too few participants means that RCT results:

- Have high internal validity
- Often lack external validity
- Do not generalize to typical patients

**Average # of people joining a clinical trial**

1 in 33

adult cancer patients participate in clinical trials.

Leveraging RWD to Accelerate Discovery Requires Data Integration

- <5% of patients are treated on a clinical trial
- To learn from the other 95%, we need to focus on strengthening the RWD ecosystem
Challenges for Traditional Phase III Clinical Trials

- Take a long time
- Require many patients
- Fail to detect small subsets that derive benefit

Randomized trial of 1137 patients with metastatic colorectal cancer

Venook et al. JAMA 2017
Tumor Biology Reveals Heterogeneity but Treatment is “One Size Fits All”
Scientists now find that patients’ tumors are often driven by unique combinations of DNA mutations. Collectively, these changes are called a tumor’s mutation profile. When it comes to treating cancer, knowing which mutations are in a tumor’s profile may be more important than where the tumor is found.

For example, the same brain tumor in three children might have a different mutation profile in each child.

Meanwhile, tumors in three different children might have the same mutation profile, even though the tumors are found in different places in the body.
Factors Enabling Use of RWD/RWE

- Growth and dissemination of Electronic Health Records
- International data standards that facilitate meaningful data sharing
- Growth in computational power
  - Fast computers
  - Declining costs for data storage
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Two Main Categories of Use for RWD in Drug Life Cycle

- To support drug development, testing and regulatory approval

  - Relatively new
  - Controversial

- After a drug receives regulatory approval from FDA/EMA or other regulatory authority

  - Quite standard
  - Use cases are expanding
Use Cases for RWD in Oncology Drug Development

- RWD in the Post Drug Approval Space
  - Meet post-marketing commitments
  - Pharmacovigilance
  - Identify exceptional subgroups
  - Monitor dissemination
  - Measure efficacy-effectiveness gap and public health impact
  - Expand drug label to new indications
## RWD for Phase IV Trials and Postmarketing Commitments

<table>
<thead>
<tr>
<th>Traditional Approach</th>
<th>RWD Approach</th>
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<tbody>
<tr>
<td>Commitments often not met</td>
<td>Use standardized EHRs to:</td>
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<tr>
<td>Expensive for industry</td>
<td>Evaluate treatment experience for all drug recipients</td>
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<tr>
<td>Often have low scientific yield</td>
<td>Capture outcomes that can be extracted from the EHR</td>
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<tr>
<td>Often in select populations</td>
<td>- Dosing, dose modifications</td>
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<td>Capture pre-specified outcomes on case report forms</td>
<td>- Major or lab toxicities</td>
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<td>- Health system use-ER/Hospitalizations</td>
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<td>- Measure time to treatment discontinuation</td>
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<td>- Measure overall survival</td>
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<td>- Challenging to measure response, DFS</td>
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<tr>
<td>TRADITIONAL APPROACH</td>
<td>RWD APPROACH</td>
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<tr>
<td>------------------------------------------------------------------------------------</td>
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<tr>
<td>• Rely on voluntary reports from users—difficult to sift through and inconsistently submitted</td>
<td>• Use standardized EHRs to</td>
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<tr>
<td></td>
<td>• Interrogate lab data for all users</td>
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<tr>
<td></td>
<td>• Measure standardized outcomes including hospitalizations, dose delays, dose reductions</td>
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<td></td>
<td>• Use Patient Reported Outcomes</td>
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<td></td>
<td>• Measure toxicity from patient perspective</td>
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<td></td>
<td>• Understand the patient experience</td>
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<tr>
<td>• Rely on firms to meet post-marketing commitments in timely fashion</td>
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<tr>
<td>• Minimal patient reported data</td>
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## RWD for Identification of Distinctive Subgroups

### Traditional Approach

- Extensive analysis of RCT patient data subsequent to drug approval to identify “exceptional responders” or “exceptional resistance” as well as severe and/or mild toxicity
- Focus on select subgroups in Phase IV trials at select study sites

### RWD Approach

- Use standardized EHRs combined with routinely performed molecular profiles to identify very small molecular subsets
- Measure outcomes in all patients with available EHR data
- Creative and strategic data partnerships
  - Foundation Medicine-genomic data
  - Flatiron Health-EHR data curation
RWD for Label Expansion

TRADITIONAL APPROACH

- New drug labeling indication requires new clinical trial demonstrating benefit
- Many trials in niche populations never performed
- Clinicians left to extrapolate and make decisions to the extent permissible by regulatory authorities
- Decisions get made but knowledge not captured for use in future cases

  - Appendix cancer?
  - Duodenal cancer?
  - Her2+ colorectal cancer?

RWD APPROACH

- Capture “off label” use and measure outcomes in consistent fashion from EHR data
- Use data to expand/contract the label
- Label then used to dictate coverage and/or reimbursement levels
RWD for Label Expansion

- FDA expanded palbociclib label to include men with HER2+/ER- breast cancer in 2019

- ~2700 cases of male breast cancer per year in US
- RCTs would be challenging
- PALOMA2 and PALOMA3 excluded men

- Multiple data sources
  - Data from company registry (Pfizer)
  - EHR data from Flatiron
  - Insurance claims data from IQVIA
Use Cases for RWD in Oncology Drug Development

- **RWD in the Pre-Approval Space**
  - Identifying clinical need
  - Selecting optimal sites to conduct study
  - Informing study design
    - Inclusion/exclusion criteria
    - Realistic timeline for accrual
    - Realistic target endpoints and appropriate sample size
  - Clinical trial execution
    - Simplifying case report forms
    - Decreasing burden and expense of data collection
    - Facilitate interoperability across studies
  - Support applications for accelerated approval based on uncontrolled studies
  - Avoid the need for randomization by using “synthetic control” arm from RWD
Label Expansion

- Blinatumomab received approval for Philadelphia chromosome-negative relapsed and refractory B-cell precursor acute lymphoblastic leukemia based on a single phase II trial.

- The results were compared with historical data from 694 comparable patients extracted from 2,000 patient records in the U.S. and E.U.
RWD to Support Initial Drug Approval

- Avelumab was approved by the FDA in 2017 for treatment of metastatic Merkel Cell Carcinoma (~1600 cases per year in the USA)
- Phase II data demonstrated significant and durable response
- RWD describing outcomes in historical cohorts of patients were included in the application
- Ideal use case for RWD:
  - Very rare cancer
  - No previous effective treatment
  - Very clear strong signal from phase II
  - Very homogeneous treatment in RWD
  - Clear reproducible endpoint (Overall Survival)
Use of RWD to Avoid Need for Randomization: Only in Rare Cases

- Extremely challenging to use “synthetic controls” for common cancers
- Validity traps abound
- Unlikely to be acceptable to regulators absent very strong signal
- Observational data cannot control for confounding by unmeasured factors
- Trials with endpoints other than survival are especially challenging
- RCTs will remain the backbone of progress
- Strategies to improve execution and conduct of RCTs must be prioritized
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Challenges in Use of RWD/RWE

- Data privacy and security concerns
- Many obstacles to data sharing
- Poor interoperability across and within systems
- Lack of international standards for measuring the most salient outcomes
  - RECIST is a standard for measuring PFS in RCTs
  - RECIST isn’t workable in real world contexts
  - No standards for measuring DFS, PFS, response from unstructured EHR data
Challenges with use of RWD

- Observational data from study of MSI vs MSS patients treated with or without chemotherapy
- Appears that MSI patients obtain greater benefit from chemotherapy
- Misleading because MSI patients are younger and healthier
- Very difficult to remove selection bias

Figure 5: Kaplan-Meier survival curves for patients with and without MSI

Elsaleh Lancet 2000
Oncology Has Had Complete Transition to EHRs

THEN: Paper Records

NOW: 100% EHRs
EHRs Have Made Data Accessible but not Interpretable

- Same old problem:
  - Uninterpretable by computers;
  - Unusable for research
Unstructured Data

Immense information to be gleaned from unstructured data but it requires intelligence to analyze and interpret.
Structured Data are Amenable to Rapid Analysis and Interpretation: Unstructured Data Are Not
Missed Opportunities to Transform Big Data to Actionable Knowledge

Today, EHRs are a black box
Most of the information they contain is not structured and therefore not interpretable

Even in the best EHRs, only a small % of “big data” is structured

WE NEED TO UNLOCK THE BLACK BOX
PRISSMM is a **standard taxonomy** for classification and communication of structured information about cancer status and treatment outcomes following the assignment of TNM stage for patients with solid tumors.

Each letter in PRISSMM corresponds to a dimension of cancer status or treatment response.
PRISSMM: A Taxonomy for Defining Cancer Outcomes

- Pathologic evidence of locoregional or distant evidence of tumor
- Radiographic evidence of locoregional recurrent or persistent tumor
- Imaging evidence of distant/disseminated tumor beyond the primary site
- Symptoms of tumor on physical exam or symptoms that can be attributed to tumor
- Signs of cancer on physical exam or symptoms that can be attributed to tumor
- Tumor Marker evidence of persistent or recurrent tumor
- Oncology Medical Provider assessment

Each curation effort may focus on some or all of the PRISSMM components.

- Signs may be relevant for melanoma outcomes
- Markers may not be relevant for lung outcomes
What Problems Does PRISSMM Aim to Solve?

- Expedites structuring unstructured data (gold standard)
- Enables interoperability and data sharing across sites
- Streamline EHR abstraction by research staff/registrar
- Facilitates “computer assisted” abstraction
- Breaks abstraction/annotation into discrete tasks for machines
- Creates a “lingua franca” that is understood by the clinical and research community
- Allows customized definitions of PFS/DFS from “real world” data
- Data standard works for all solid tumors
PRISSMM: Curation of Individual Patient Trajectory
Colon Cancer Stage IV, First Treatment [R1]

PATHOLOGY (P)
- Evidence of Invasive Cancer
- No Evidence of Invasive Cancer

IMAGING (R, I)
- Tumor Decrease
- Increase
- No Change

SIGNS (S)
- Signs of Cancer Present
- Not Present

SYMPTOMS (S)
- Symptoms Improving
- Symptoms Worsening
- Not stated/Indeterminate

MEDICAL ASSESSMENT (M)
- Improving/Responding/Decreasing
- Progressing/Worsening/Enlarging
- Not stated/Indeterminate

Cancer Dx:
- 06/15/2015 Colon Cancer (C18.0), Clin Stage IVA

Treatments:
- Bevacizumab; Fluorouracil; Leucovorin Calcium; Oxaliplatin

Pathology (P):
- LR
- D

Imaging - LR (R):
- Decrease
- Increase
- No Change

Imaging - Distant (I):
- Decrease
- Increase
- No Change

Signs (S):
- Decrease
- Increase
- No Change

Symptoms (S):
- Decrease
- Increase
- No Change

Medical Assessment (M):
- Decrease
- Increase
- No Change

Tumor Markers (M):
- CEA Lab Results ng/ml
PRISSMM: Curation of Individual Patient Trajectory
Real World Progression-Free Survival [Anchored from Diagnosis: Dx]

Cancer Dx
06/15/2015
Colon Cancer (C18.0), Clin Stage IVA
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Pathology (P)
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Symptoms (S)
- Symptoms Improving
- Symptoms Worsening
- Not stated/Indeterminate

Medical Assessment (M)
- Improvement/Responding/Decreasing
- Worsening/Enlarging
- Indeterminate

Tumor Markers (M)
CEA Lab Results ng/ml

PFS_l: Dx-13
PFS_md: Dx-16
PFS_l or MD: Dx-13
PRISSMM: Curating Patient Outcomes
Real World Progression-Free Survival: Anchored from Treatment

06/15/2015
Colon Cancer (C18.0), Clin Stage IVA
Bevacizumab; Fluorouracil; Leucovorin Calcium; Oxaliplatin

PFS\textsubscript{MD}: R\textsubscript{k-15}

PFS\textsubscript{MD}: R\textsubscript{k-15}

PFS\textsubscript{MD}: R\textsubscript{k-12}

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PATHOLOGY (P)
- Evidence of Invasive Cancer
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- Improving/Responding/Decreasing
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- Not stated/Indeterminate

Tumor Markers (M)
CEA Lab Results ng/ml
PRISSMM Curation

Cancer Dx
06/15/2015
Colon Cancer (C18.0), Clin Stage IVA

Treatments
- Bevacizumab
- Fluorouracil
- Leucovorin Calcium
- Oxaliplatin

Pathology (P)
- LR
- D

Imaging - LR (I)
- ↓

Imaging - Distant (I)
- ↘

Signs (S)
- ↑

Symptoms (S)
- ↑

Medical Assessment (M)
- ↓

Tumor Markers (M)
- CEA Lab Results ng/ml

Years: 2015-2018
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Combination of RWD and Genomic Sequencing is Changing the Nature of Clinical Trials in Oncology

Novel designs mandate strategic use of RWD

Impossible to execute these trials without a robust data ecosystem that efficiently permits access to RWD

Novel precision medicine trial designs

**Umbrella trial**
- 1 type of cancer
- Different genetic mutations

Test drug 1
- Test drug 2
- Test drug 3

**Basket trial**
- Multiple types of cancer
- 1 common genetic mutation

Test drug

West H, JAMA Oncology 2017
Basket Trial:
A Master Protocol Where Each Sub-Trial Enrolls Multiple Tumor Types
Just because vemurafenib has efficacy for BRAF+ melanoma doesn’t mean it will have efficacy for BRAF+ colorectal cancer.
A Landmark in 2018:
Larotrectinib for TRK Fusion + Cancers
1st FDA approval based on basket trial (N=55)

A Maximum Change in Tumor Size, According to Tumor Type

Drillion et al. NEJM 2018
Effective Use of RWD to Accelerate Drug Development Requires Integration Across Data Streams

Knowledge Integration to Accelerate Discovery

Important Strategies:
- Engaging patients directly: PROs
- Artificial intelligence and Machine Learning
RCT and RWD Data are Synergistic

- RCTs will:
  - Become more varied in design
  - Innovative designs depend on nimble data ecosystem
  - Will rely on RWD to become more strategic across the life cycle

- RWD will:
  - Grow and expand rapidly
  - Depend on ability to overcome non-technical barriers
  - Never completely replace RCTs
Thank you for your attention!

Questions?