June 22, 2019

Flatiron EHR-enabled Evidence Generation

A new paradigm in oncology

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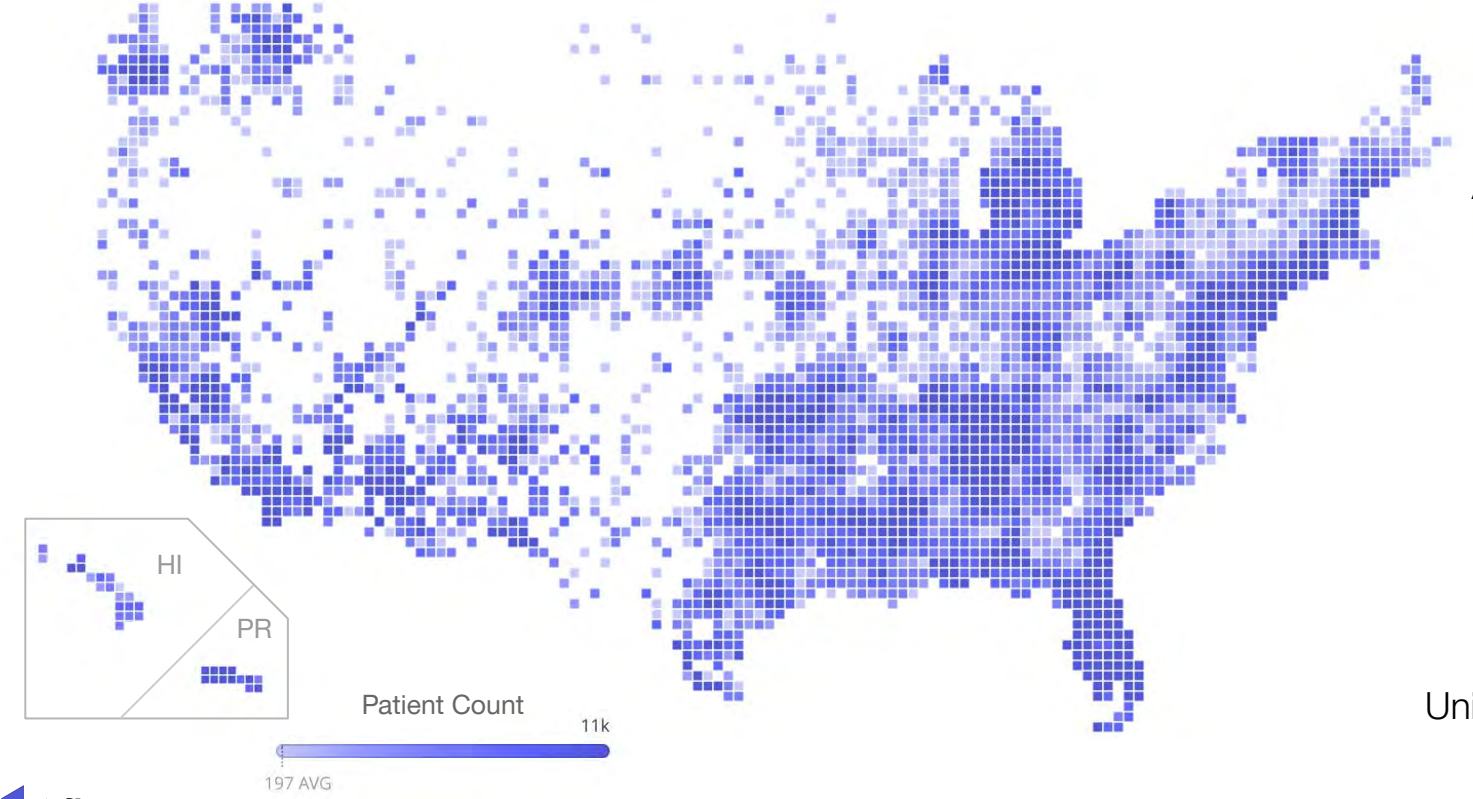
The Flatiron Network



2.2M
Active Patients

2,500
Clinicians

280
Cancer Clinics

800
Unique Sites of Care

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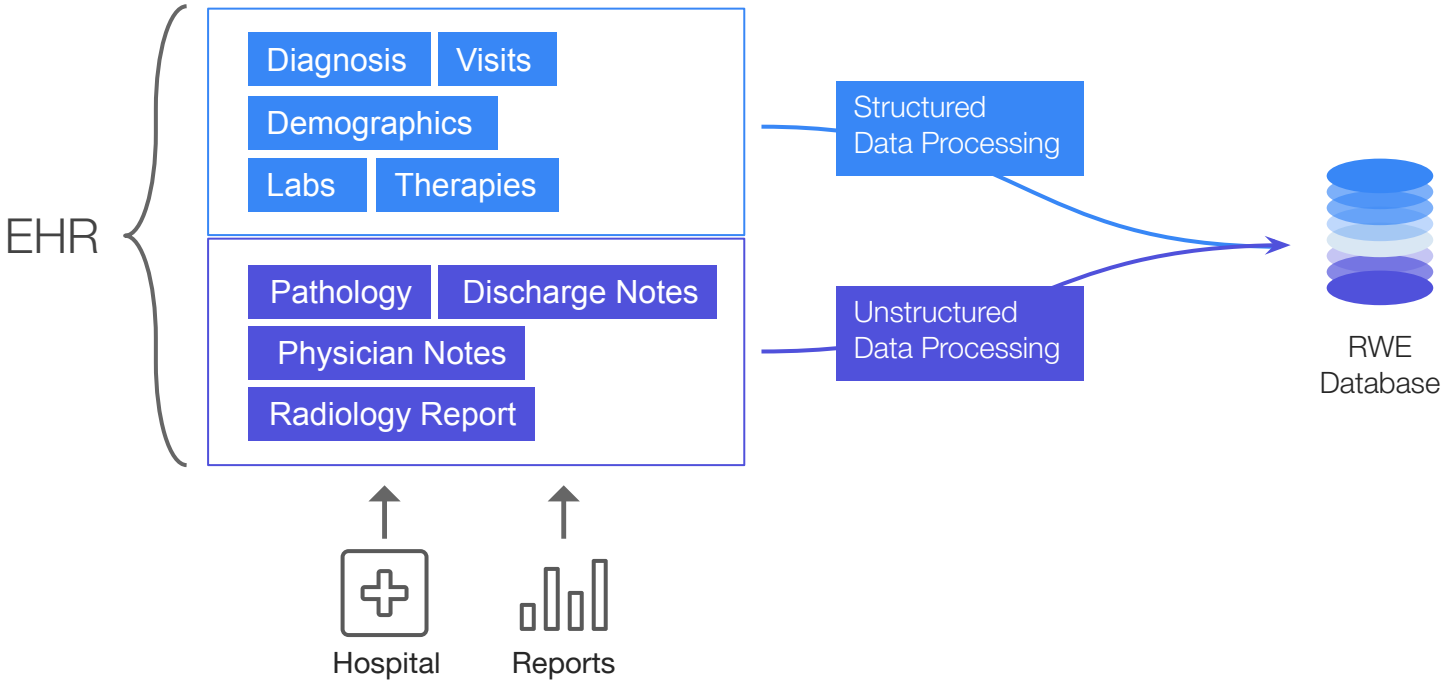
Standardize EHR data to a common data model



Standardize EHR data to a common data model

2220	Blood Serum Albumin	g/dL
QD25001600	ALBUMIN/GLOBULIN RATIO QD	(calc)
QD25001400	ALBUMIN QD	g/dL
QD50058600	ALBUMIN	%
QD50055700	ALBUMIN	g/dL
CL3215104	Albumin % (EPR)	%
LC001081	ALBUMIN, SERUM (001081)	g/dL
LC003718	Albumin, U	%
LC001488	Albumin	g/dL
LC133751	Albumin, U	%
CL3215162	Albumin%, Urine	%
CL3215160	Albumin, Urine	mg/24hr
3234	ALBUMIN SS	g/dL
LC133686	Albumin, U	%
QD50060710	MICROALBUMIN	mg/dL
QD50061100	MICROALBUMIN/CREATININE RATIO, RANDOM URINE	mcg/mg creat
QD85991610	ALBUMIN	relative %
50058600	ALBUMIN UPEP RAND	%
CL3210074	ALBUMIN LEVEL	g/dL
QD86008211	ALBUMIN/GLOBULIN RATIO	(calc)
LC149520	Albumin	g/dL
QD45069600	PREALBUMIN	mg/dL
QD900415245	ALBUMIN, SERUM	mg/dl
QD900429745	ALBUMIN	g/dL
CL3215124	Albumin Electrophoresis	g/dL
LC016931	Prealbumin	mg/dL
QD50060800	MICROALBUMIN, 24 HOUR UR	mg/24 h
QD50060900	MICROALBUMIN, 24 HOUR UR	mcg/min
QD85994821	ALBUMIN,SERUM	g/dL
CL3213320	PREALBUMIN	mg/dL
QD85995225	PROTEIN ELECTROPHORESIS ALBUMIN	g/dL

Harmonization and normalization of structured data

- Certain structured data elements may be coded and collected in multiple ways in the EHR across practices *(example: albumin)*
- Combine and map datasets across sites to a single dataset
- Map all data elements to a single set of definitions (data model)

1751-7	**Albumin [Mass/volume] in Serum or Plasma**	**g/dL**

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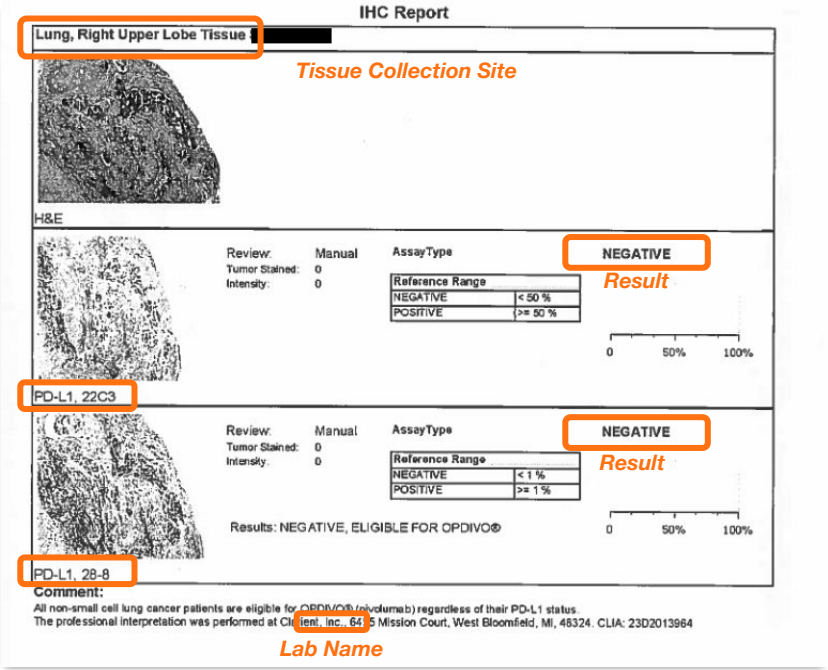
Key data elements in oncology are unstructured

Section of PD-L1 Report



For every PD-1/PD-L1 test a patient receives, Flatiron biomarker Data Model captures:

- 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., IHC)
- Assay / kit (e.g., Ventana 142)
- Percent staining & staining intensity

Technology Enabled Abstraction

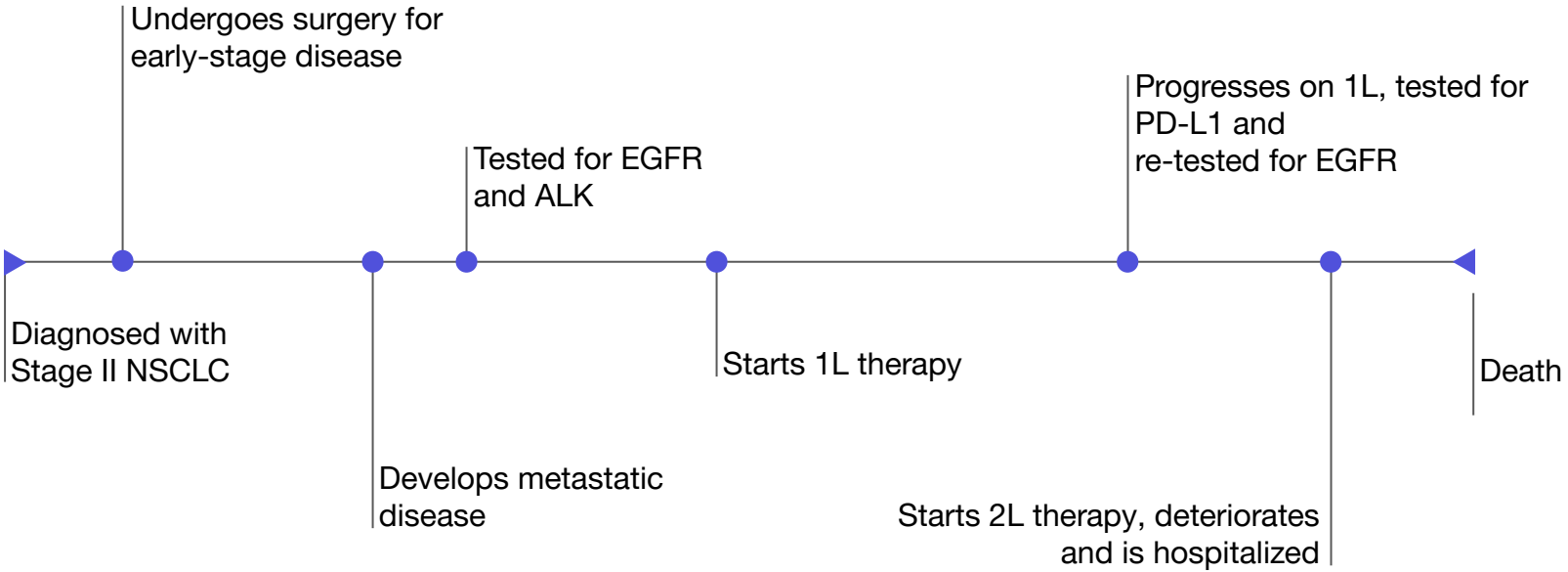
Expert Abstractors

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

Flatiron Technology

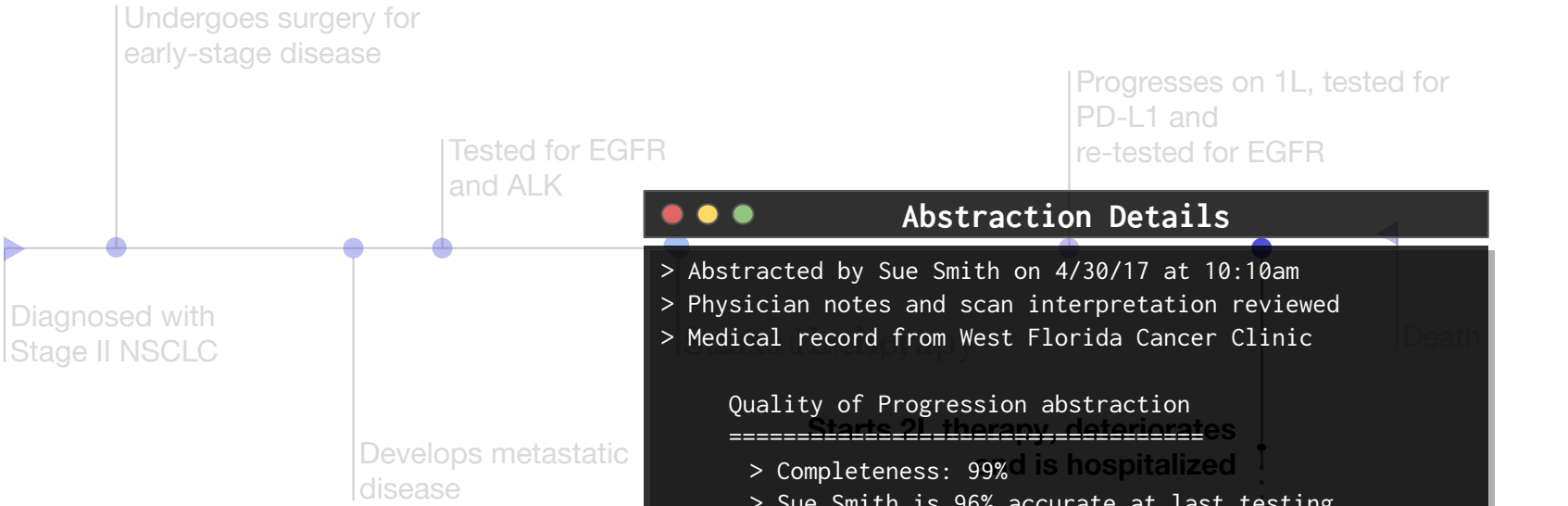
Software helps trained human abstractors efficiently organize and review unstructured documents to capture key data elements in predetermined forms.

Source Process Validation



Documentation of source, quality and provenance.

Source | Process | Validation



Patient	Stage at Dx	Biomarkers	2L Treatment	Progression	Date of Death
Jane Doe	II	EGFR-, ALK-, PD-L1-	nivolumab	2017-03-08	2017-04-12

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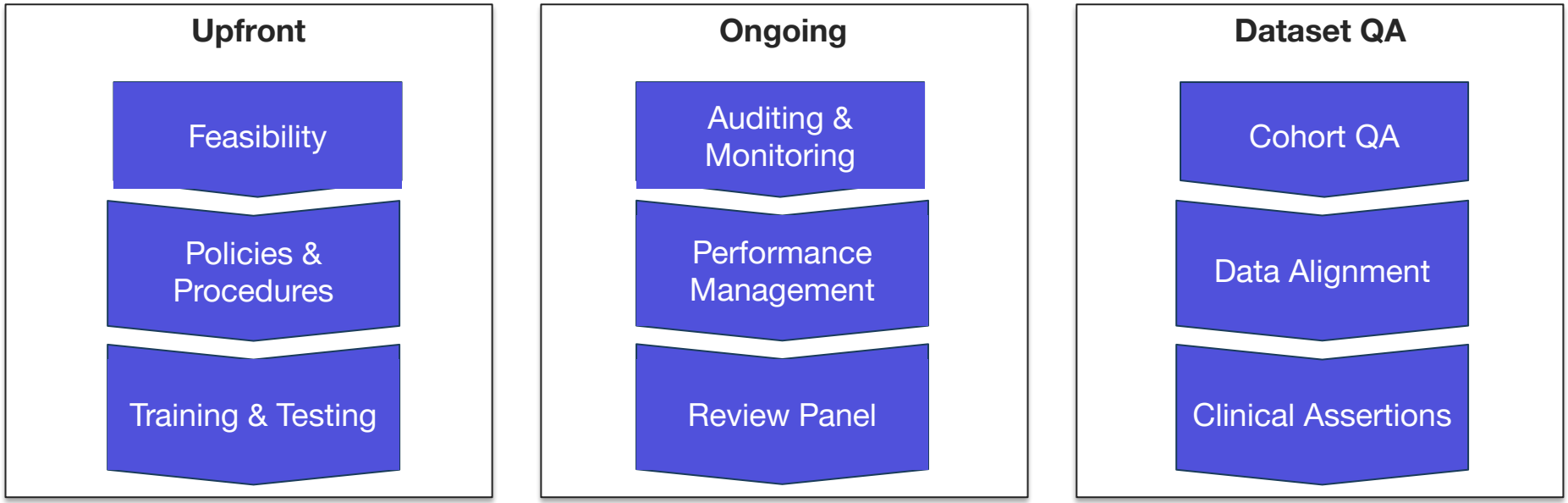
Flatiron abstraction quality assurance & quality control

Centralized Controlled Environment



Research Collaborations to Accelerate "Regulatory-Grade RWE"

Oncology Center of Excellence (OCE)

Dr. Sean Khozin, Associate Director

Cancer Therapy Evaluation Program

Dr. Elad Sharon, Medical Officer

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Objectives

1. Define specific types of regulatory decisions that can be informed by high quality real-world data/evidence
2. Define the quality (relevance and reliability) standards for each of these types of regulatory decisions
3. Develop and validate an approach to critical variables (endpoints) that meet the quality standard for each use case
4. Demonstrate the ability to use high quality RWE for specific, prioritized retrospective and prospective use cases through proof-of-concept projects

Our ongoing partnership with the FDA has resulted in peer-reviewed publications

Characteristics of Real-World Metastatic Non-Small Cell Lung Cancer Patients Treated with Nivolumab and Pembrolizumab During the Year Following Approval.

BACKGROUND:

Evidence from cancer clinical trials can be difficult to generalize to real-world patient populations, but can be complemented by real-world evidence to optimize personalization of care. Further, real-world usage patterns of programmed cell death protein 1 (PD-1) inhibitors following approval can inform future studies of subpopulations underrepresented in clinical trials.

MATERIALS AND METHODS:

We performed a multicenter analysis using electronic health record data collected during routine care of patients treated in community cancer care clinics in the Flatiron Health network. Real-world metastatic non-small cell lung cancer (NSCLC) patients who received nivolumab or pembrolizumab in the metastatic setting (n = 1,344) were selected from a starting random sample of 55,969 NSCLC patients with two or more documented visits from January 1, 2011, through March 31, 2016. The primary study outcome

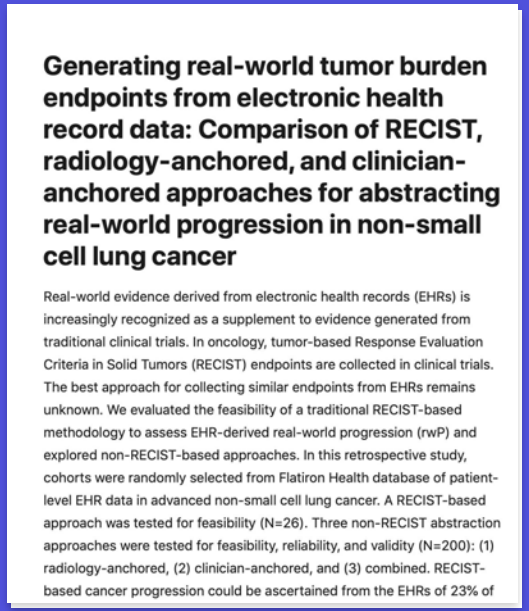
Real-World Outcomes of Patients with Metastatic Non-Small Cell Lung Cancer Treated with Programmed Cell Death Protein 1 Inhibitors in the Year Following U.S. Regulatory Approval.

BACKGROUND:

Evidence from cancer clinical trials has strong internal validity but can be difficult to generalize to real-world patient populations. Here we analyzed real-world outcomes of patients with metastatic non-small cell lung cancer (mNSCLC) treated with programmed cell death protein 1 (PD-1) inhibitors in the first year following U.S. regulatory approval.

MATERIALS AND METHODS:

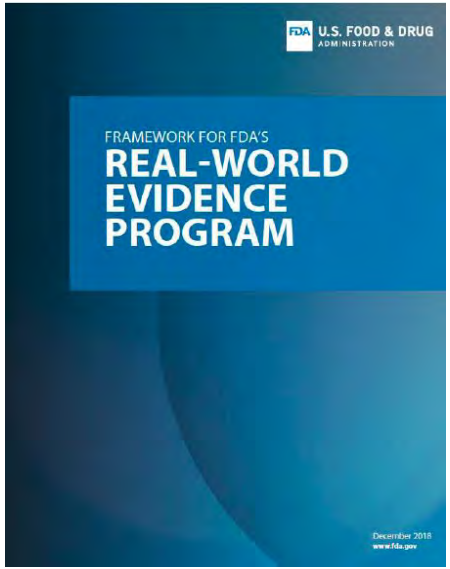
This retrospective study leveraged electronic health record (EHR) data collected during routine patient care in community cancer care clinics. The cohort included patients with mNSCLC who had received nivolumab or pembrolizumab for metastatic disease (n = 1,344) with >1 EHR-documented visit from January 1, 2011, to March 31, 2016. Patients with a > 90-day gap between advanced disease diagnosis and first EHR structured data entry were excluded.



Generating real-world tumor burden endpoints from electronic health record data: Comparison of RECIST, radiology-anchored, and clinician-anchored approaches for abstracting real-world progression in non-small cell lung cancer

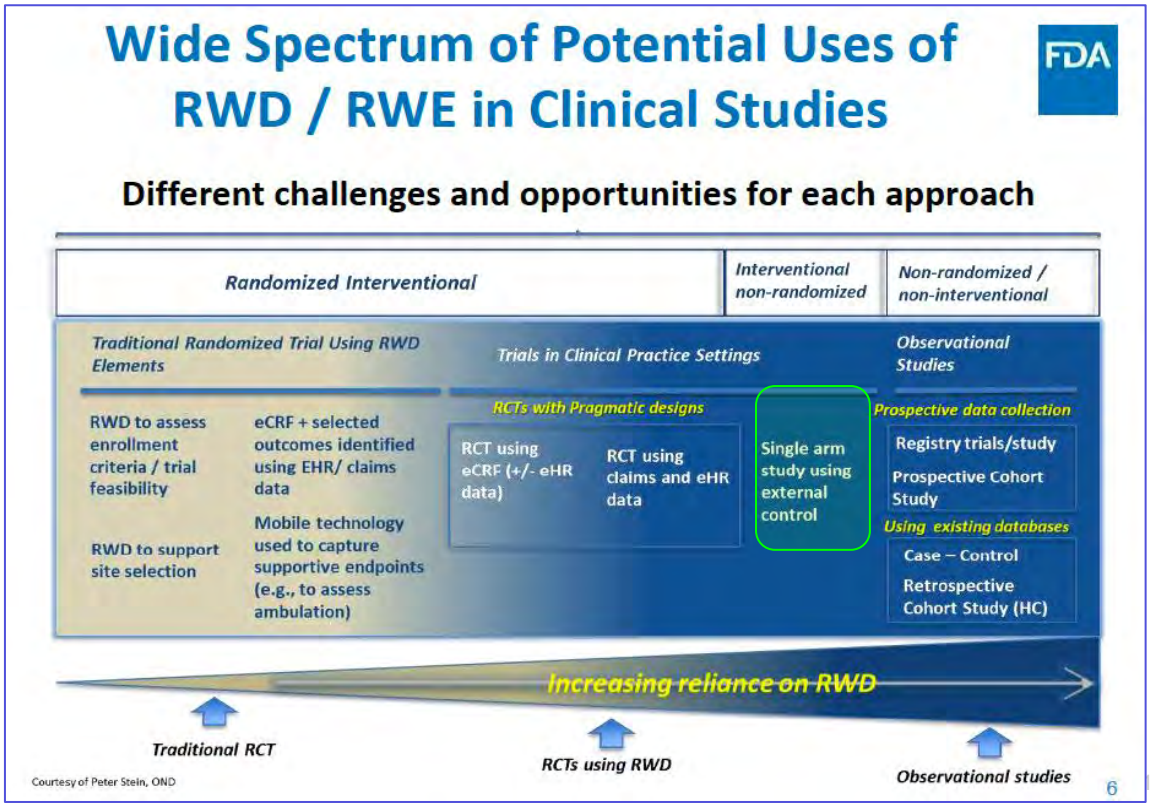
Real-world evidence derived from electronic health records (EHRs) is increasingly recognized as a supplement to evidence generated from traditional clinical trials. In oncology, tumor-based Response Evaluation Criteria in Solid Tumors (RECIST) endpoints are collected in clinical trials. The best approach for collecting similar endpoints from EHRs remains unknown. We evaluated the feasibility of a traditional RECIST-based methodology to assess EHR-derived real-world progression (rwP) and explored non-RECIST-based approaches. In this retrospective study, cohorts were randomly selected from Flatiron Health database of patient-level EHR data in advanced non-small cell lung cancer. A RECIST-based approach was tested for feasibility (N=26). Three non-RECIST abstraction approaches were tested for feasibility, reliability, and validity (N=200): (1) radiology-anchored, (2) clinician-anchored, and (3) combined. RECIST-based cancer progression could be ascertained from the EHRs of 23% of

FDA has legislative mandate to explore IF and WHEN RWE may support new indications (approved drugs)/post marketing requirements



Framework

https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RealWorldEvidence/UCM627769.pdf



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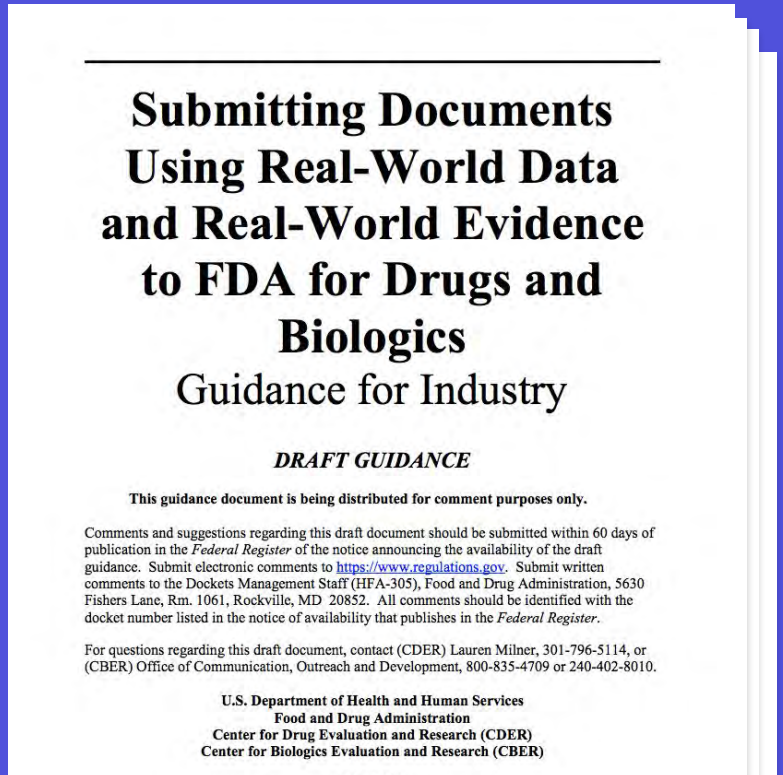
Source: Dr. Jacqueline Corrigan-Curay (Director Office of Medical Policy), FDA, "Framework for FDA's Real-World Evidence Program", webinar on March 15, 2019

We will continue to evolve our regulatory support as the FDA evolves its guidance for RWD/RWE



Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Lauren Milner, 301-796-5114, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

Draft guidance from May 2019:

FDA will start to track INDs, NDAs, and BLAs that contain RWD/RWE

To aid in this the FDA encourages sponsors to self identify if their submission contains RWD/RWE

April 2019:

Using RWE, FDA approved IBRANCE (palbociclib) for a label expansion

U.S. FDA Approves IBRANCE® (palbociclib) for the Treatment of Men with HR+, HER2- Metastatic Breast Cancer

Approval of expanded indication based predominately on real-world data

Thursday, April 4, 2019 - 2:57pm

Pfizer (NYSE:PFE) today announced that the U.S. Food and Drug Administration (FDA) approved a supplemental New Drug Application (sNDA) to expand the indications for IBRANCE® (palbociclib) in combination with an aromatase inhibitor or fulvestrant to include men with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced or metastatic breast cancer. The approval is based on data from electronic health records and postmarketing reports of the real-world use of IBRANCE in male patients sourced from three databases: IQVIA Insurance database, Flatiron Health Breast Cancer database and the Pfizer global safety database.

"With this approval, we are now able to offer IBRANCE to the underserved male breast cancer community and provide more patients with HR+, HER2- metastatic breast cancer the opportunity to access an innovative

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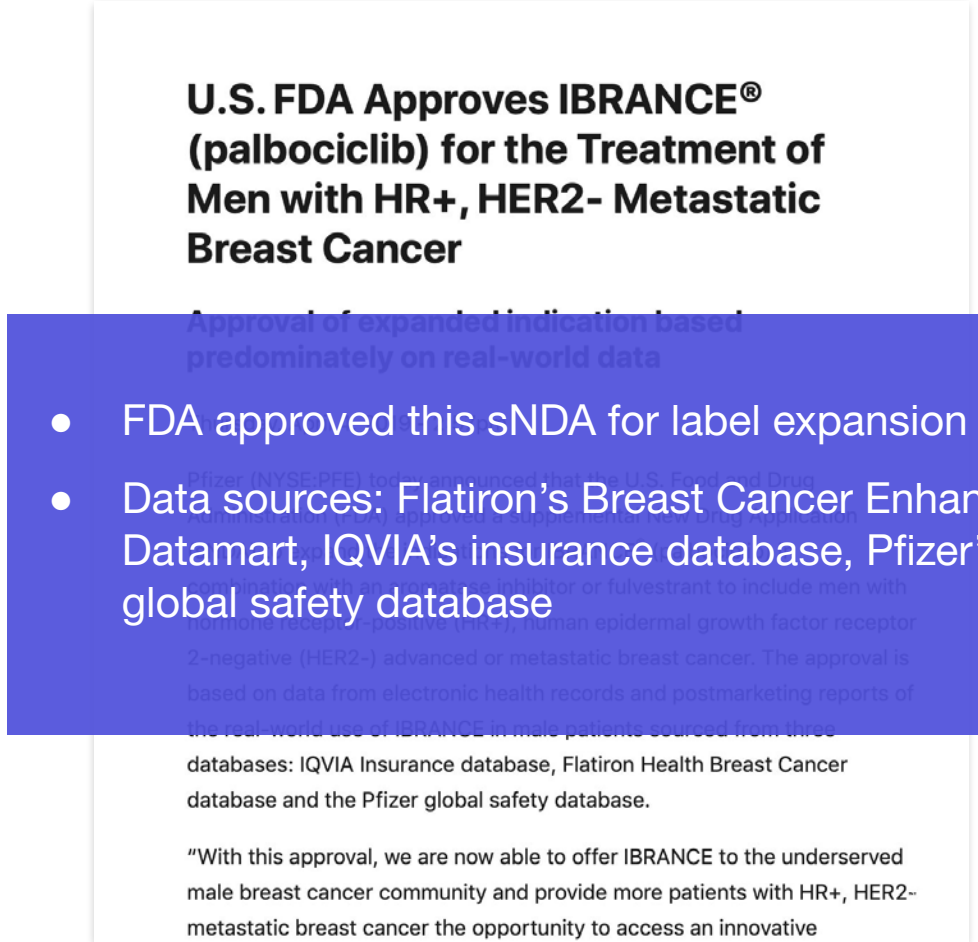

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- FDA approved this sNDA for label expansion
- Data sources: Flatiron's Breast Cancer Enhanced Datamart, IQVIA's insurance database, Pfizer's global safety database

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Thank you