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## A New Era for Real-World Evidence

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*Flatiron Health*

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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...”

Corrigan-Curay, Sacks, Woodcock. Real-World Evidence and Real-World Data for Evaluating Drug Safety and Effectiveness. *JAMA* 2018

# What are real-world data?

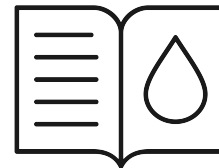
*Real-world data are the data relating to patient health status and/or the delivery of healthcare routinely collected from a variety of sources*



Electronic health records



Claims & billing activities



Product & disease registries

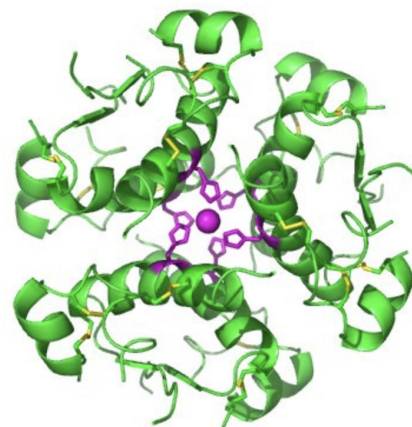
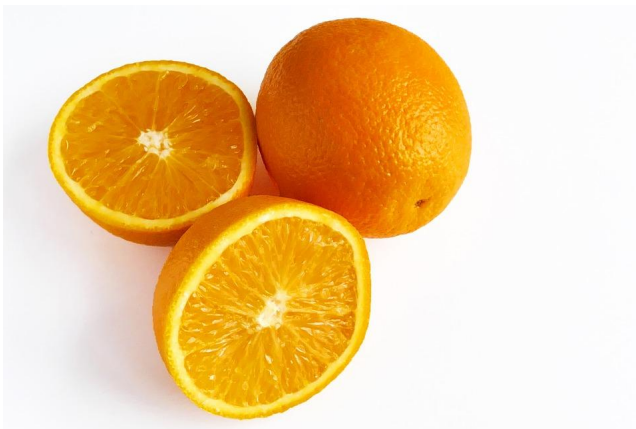


Patient-generated data  
(e.g. in-home settings)



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)



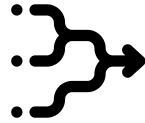
# What has changed?

- 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

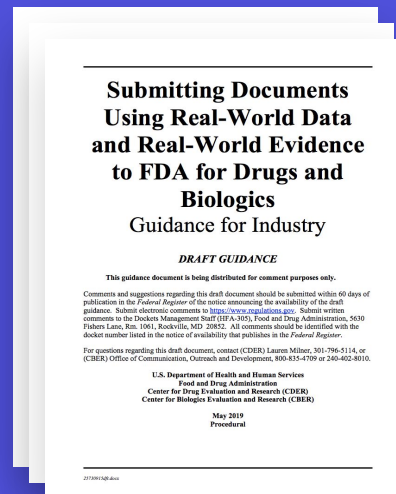


*But.....how do we overcome the limitations of these real-world data?*

# FDA recently drafted key documents on RWE to drive forward the 21st Century Cures mandate



Series of draft guidances being released by the FDA



## 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)

# 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 characterize  
unmet need*

*To evaluate safety and/or  
effectiveness*

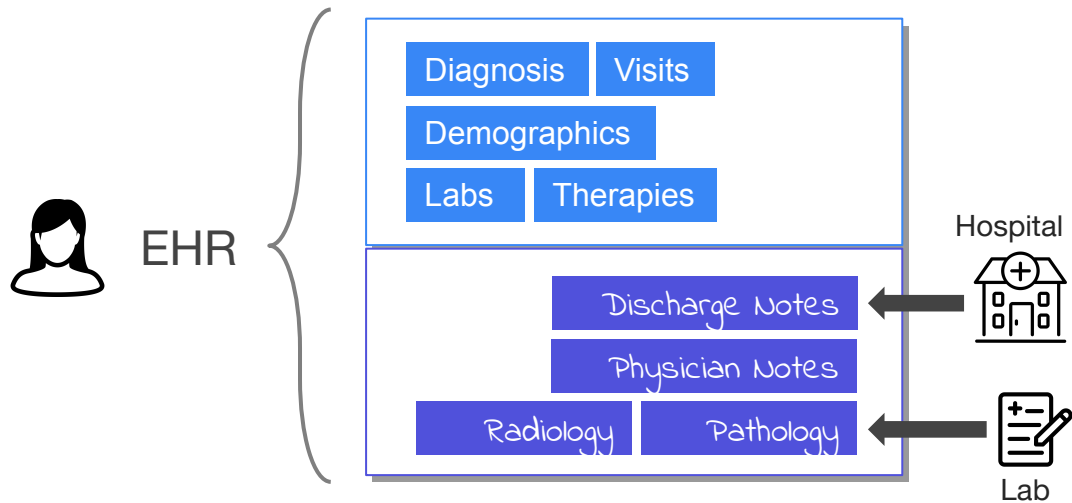
*To compare or provide  
context for a treatment arm  
in single arm trial*

*To modify indication  
(e.g., dose)*



# Getting from *DATA* to *EVIDENCE*

## Structured and Unstructured Data in the EHR



# Structured data requires normalization and harmonization

## Example: Albumin

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

Certain structured data elements may be coded and collected in multiple ways in the EHR across practices



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

# Unstructured documents contain essential information

**trovogene** **EGFR**  
Test Report | PCM™ EGFR Mutation Detection in ctDNA

Phone: 888.581.7552 Fax: 856.982.7665 Email: service@trovogene.com

**PATIENT INFORMATION**

Name [REDACTED] SSN [REDACTED]  
MID/Lab ID # [REDACTED] DOB [REDACTED] Gender [REDACTED]

**PHYSICIAN INFORMATION**

[REDACTED] Phone [REDACTED]  
[REDACTED] Fax [REDACTED]  
[REDACTED] Trovogene Access # [REDACTED]

**TEST INFORMATION**

Order # [REDACTED] Date Collected [REDACTED]  
Sample # [REDACTED] Date Received [REDACTED]  
Laboratory Sample ID # [REDACTED] Date Reported [REDACTED]  
Sample Type [REDACTED]  
Request Comments [REDACTED]  
Assay Comments [REDACTED]

**PATIENT RESULTS**

EGFR MUTATIONS: EXON 19 DELETION, EXON 21 L858R AND EXON 20 T790M ARE TESTED USING THIS ASSAY

MUTATIONS	EX19DEL	L858R	T790M
RESULT	Not Detected	Not Detected	Detected
GENOME EQUIVS TESTED (eqs)	10,100	10,100	10,100
COPIES/100,000 seq			13
95% CONFIDENCE INTERVAL			10 - 20

REFERENCE RANGE: MUTATIONS NOT DETECTED

**METHODOLOGY**

EGFR was isolated from the tumor or plasma, quantified and amplified by real-time polymerase chain reaction using primers specific for PCR Exons 18, 19 and 21. Mutations were detected using Real-Time PCR sequencing.

**REVIEW & APPROVAL**

Results were reviewed and approved by: John C. Sphar, M.D., Laboratory Director



## 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

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## **Humans will always be necessary for**

- Generating training data
- Evaluating the performance of ML models

# 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

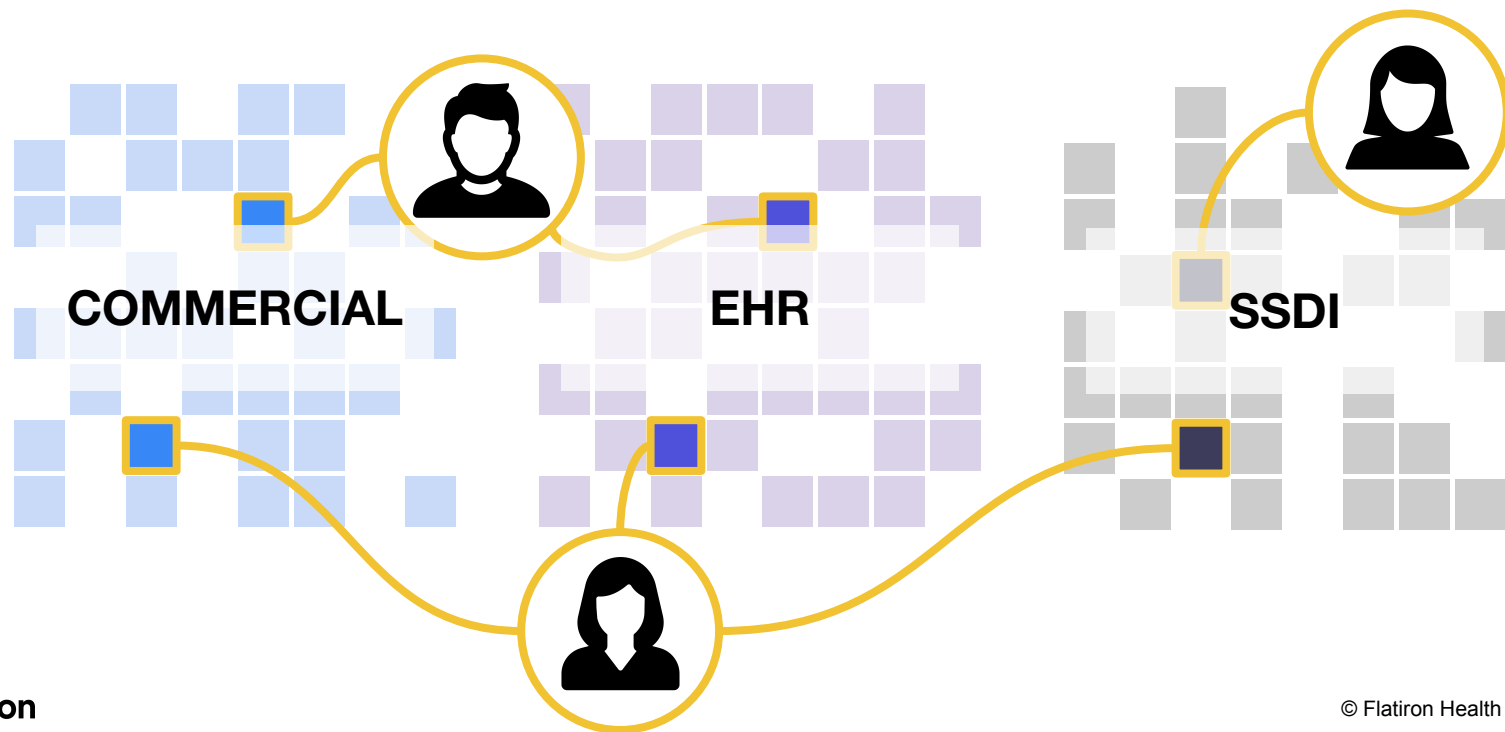
Software helps trained human abstractors efficiently organize and review unstructured documents to capture key data elements in predetermined forms.

# A Special Challenge for RWE in Cancer Research: Defining Endpoints

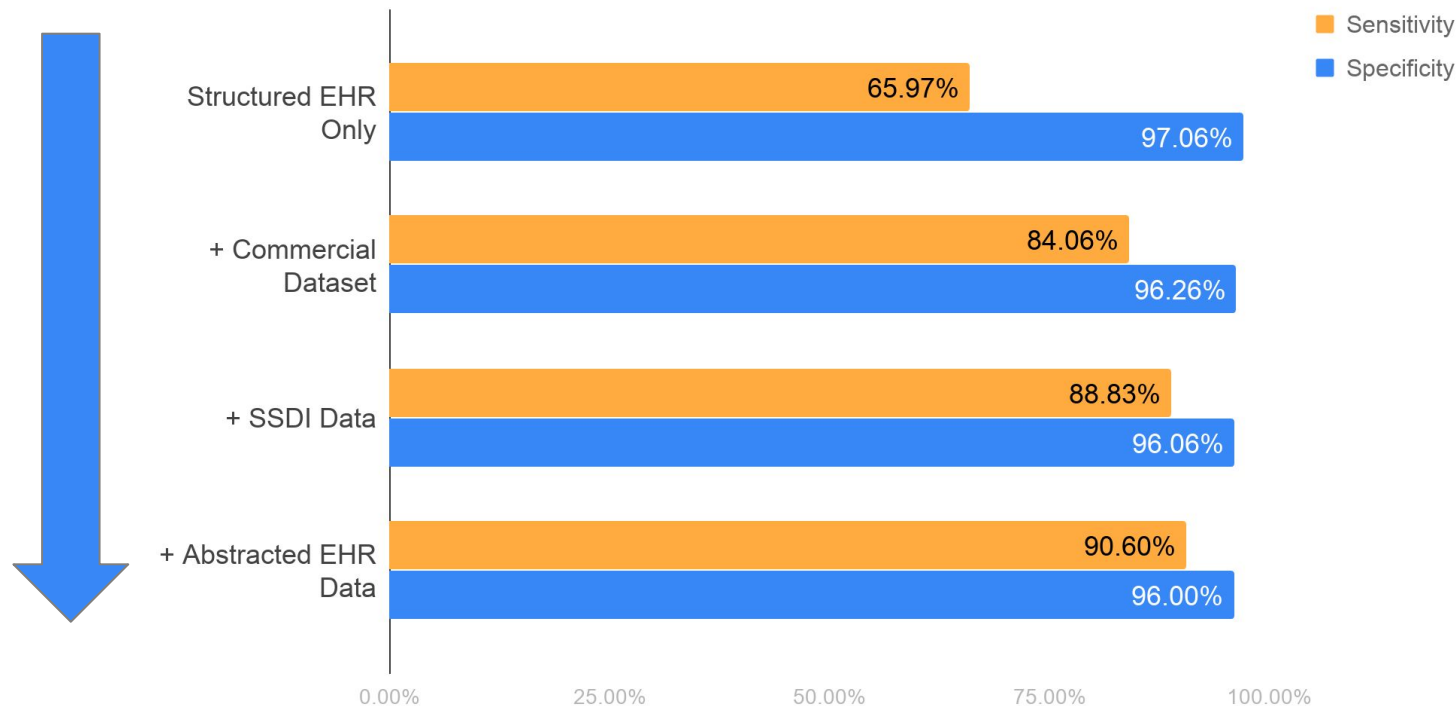
- The gold-standard = survival
- Surrogate endpoints for clinical benefit are commonly used in clinical trials
  - Tumor response and tumor progression - based on measurements on CT scans (RECIST Criteria)
- “Real-world Endpoints” are challenging
  - Survival dates often missing
  - CT scans not routinely 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



Data shown for advNSCLC

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**

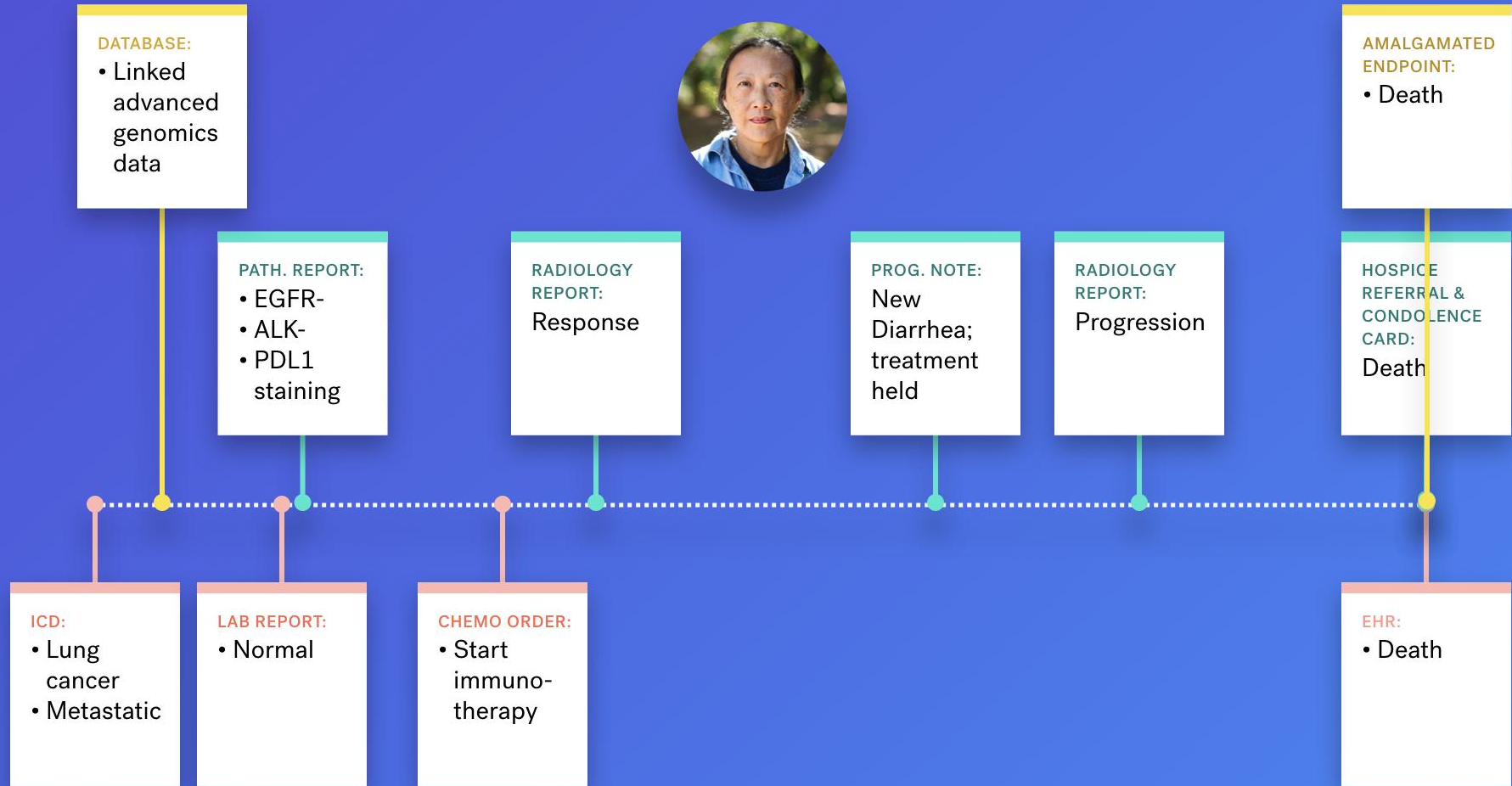
1. Oncologist agreement with definition & approach
2. Regulatory stakeholder alignment with definition & approach

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)





#### 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
```

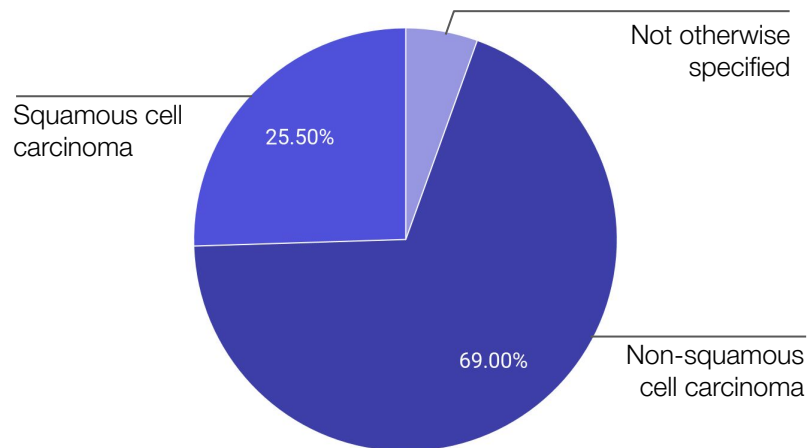
Patient	Joan
Stage at Dx	IV
Biomarkers	EGFR-, ALK-, PDL1+
1L Treatment	immunotherapy
Progression	2017-03-08
Date of Death	2017-04-12

# Cohort Demographics

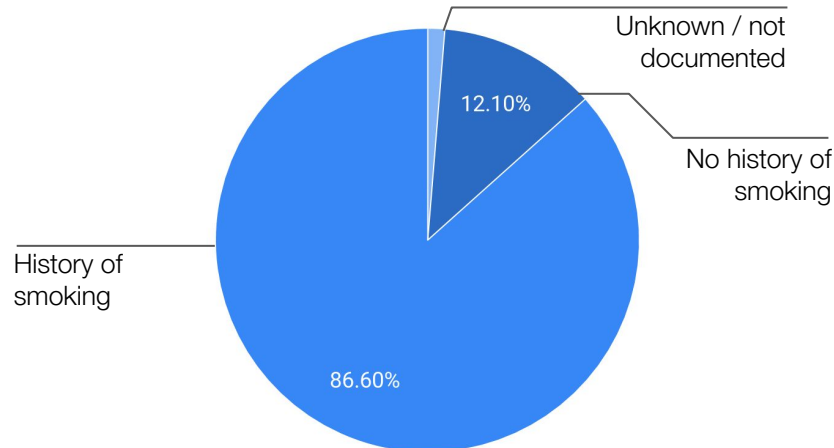
## as of May 2019

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

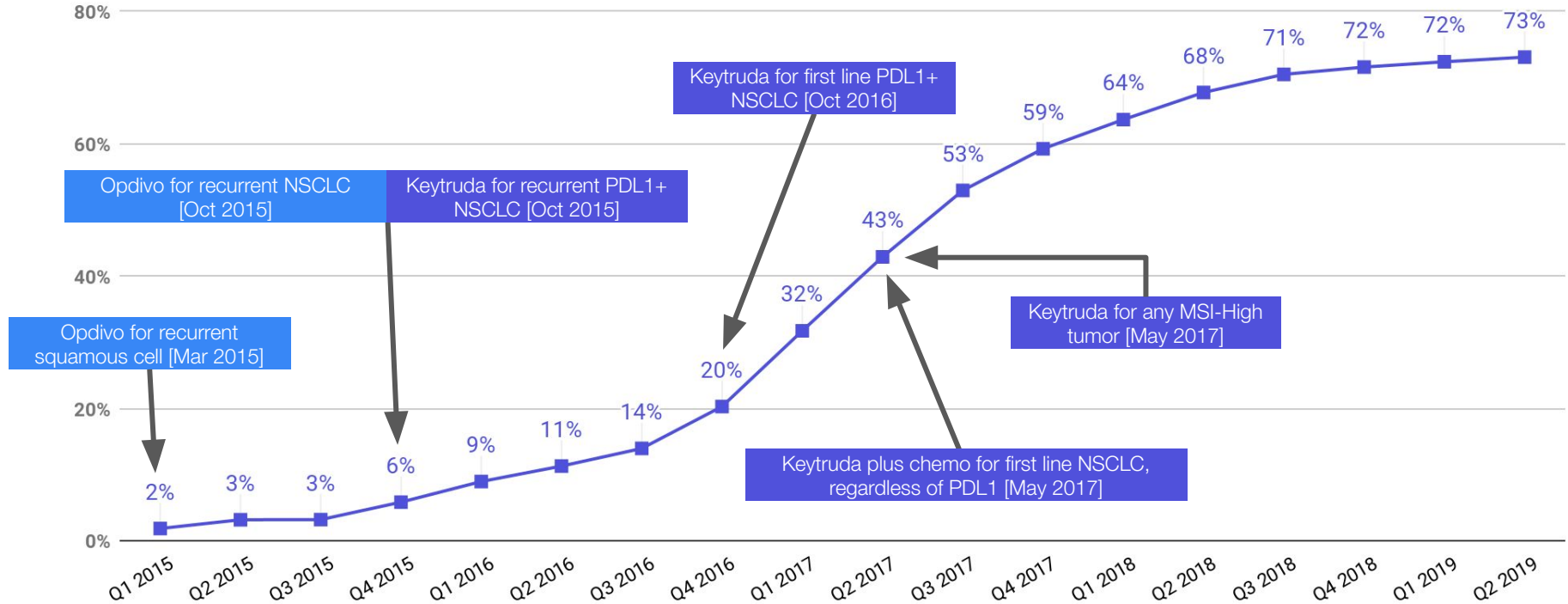
### Histology



### Smoking Status

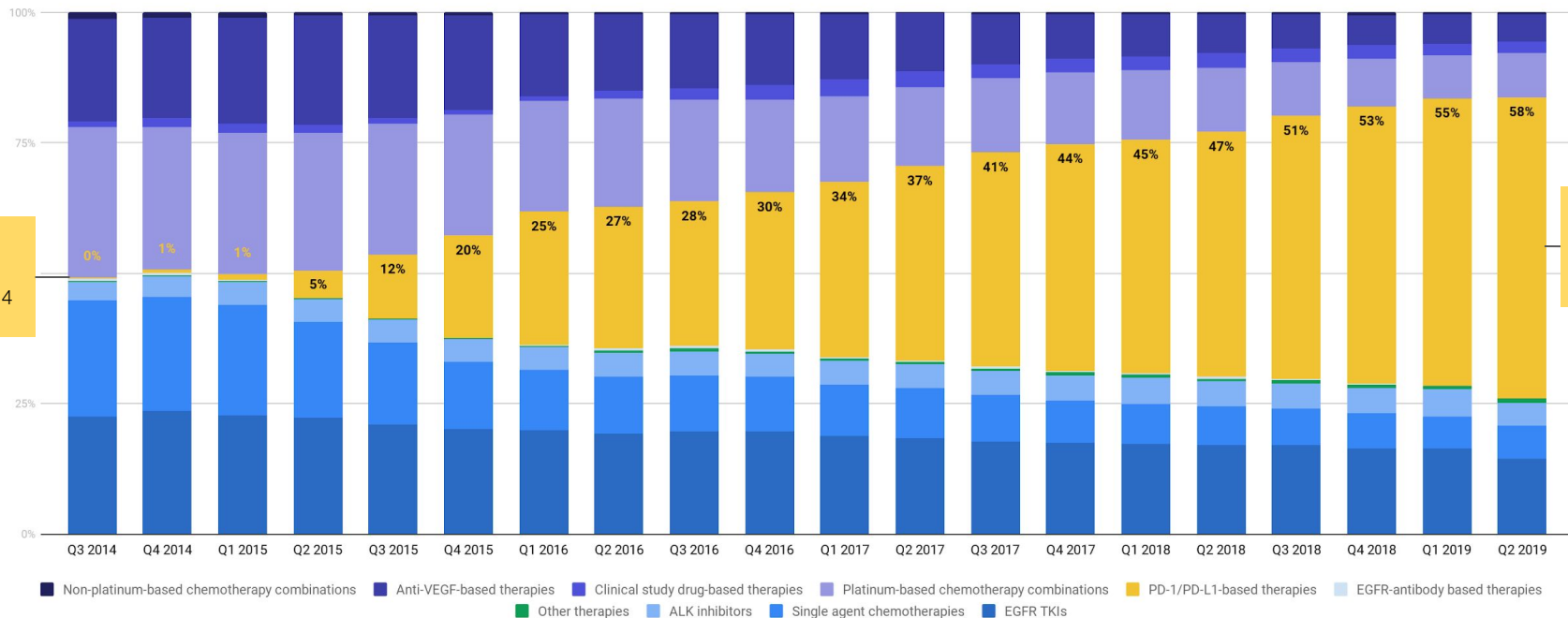


# PDL1 Biomarker Testing and FDA Approvals of Immune Checkpoint inhibitors in NSCLC



# Patient Share by Therapy Class — PD1/PDL1

## All Lines



# How is Flatiron RWD being used?

Commercial  
Applications

Research and Clinical  
Applications

Regulatory  
Applications

**Understanding Uptake of New Biomarkers and Treatments**

**Discovery and Validation of New Predictive Biomarkers**

**Comparative Effectiveness of Standard Treatments**

**Risk Modeling**

**Quality Measurement / Impact of Healthcare Policy**

**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

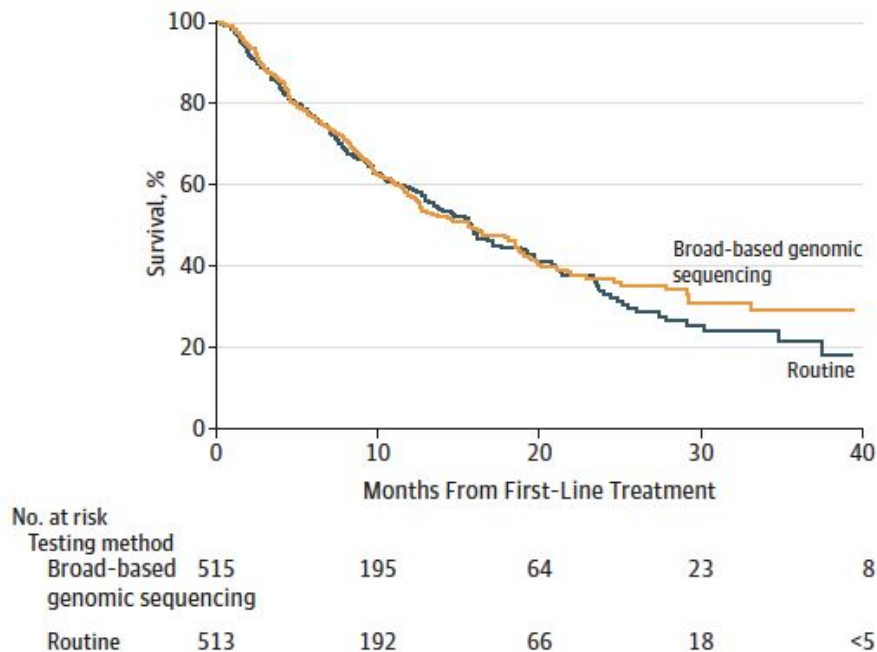
## Analytic Rigor

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

Adapted from: Berger et al. on behalf of ISPOR-ISPE Special Task Force on Real-World Evidence in Health Care Decision Making. Value in Health, 2017; Miksad and Abernethy, Clin Pharmacol Ther, 2018.

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

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

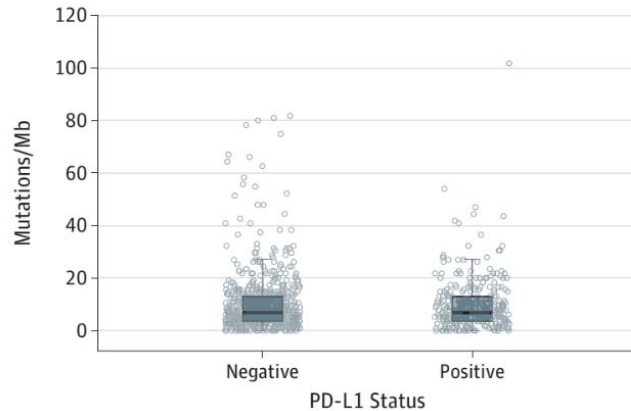


Presley et al. *JAMA* 2018

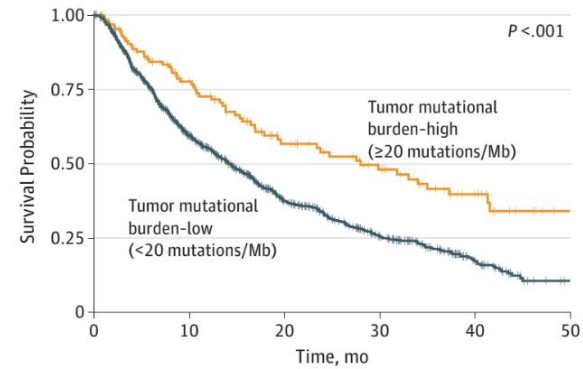
# TMB as Predictive Biomarker in NSCLC

**Figure 4. Immunotherapy and Tumor Mutational Burden**

**A** Tumor mutational burden between PD-L1-negative and -positive tumors



**B** Tumor mutational burden status



No. at risk

Tumor mutational burden-low (<20 mutations/Mb)

768    461    230    123    41    5

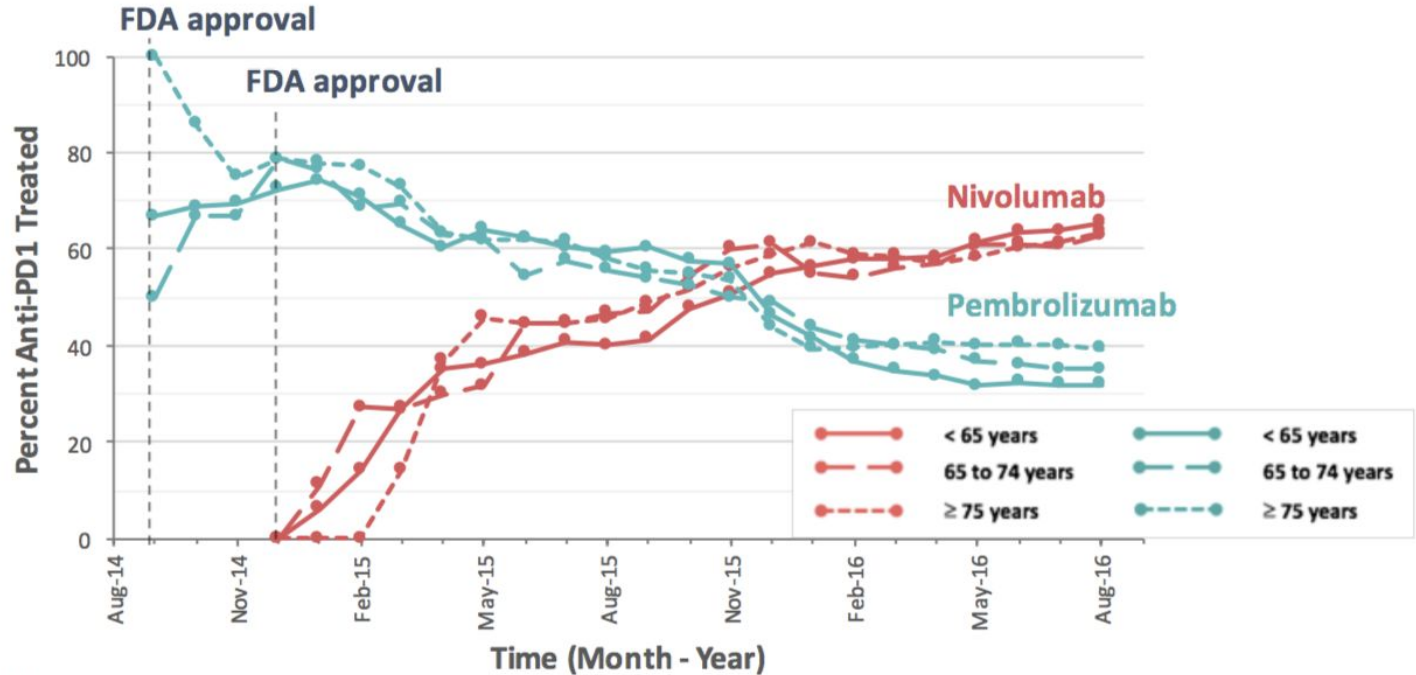
Tumor mutational burden-high (≥20 mutations/Mb)

122    79    40    31    17    4

# Case Study: Disparities Research

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

A. Melanoma

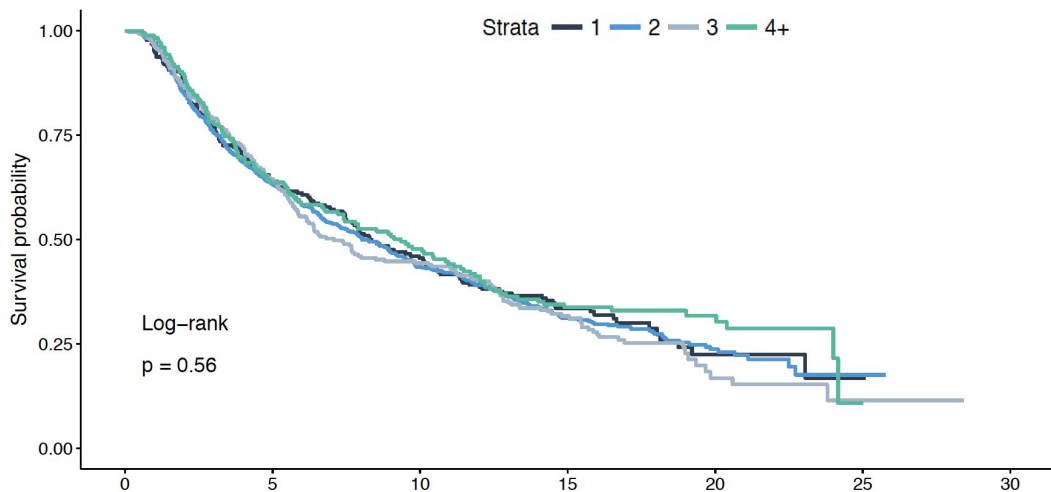


## FDA + FLATIRON

# Evaluating real-world outcomes of NSCLC patients treated with PD-1 inhibitors

Khozin et al. *The  
Oncologist*, 2019.

## Overall survival of PD-1 inhibitor treated patients based on lines of therapy



At risk (patients)					
1:	227	135	92	49	11
2:	669	394	257	146	38
3:	272	160	103	62	11
4+:	176	109	80	50	22

	Patients	Events	Median OS (95% CI)
1:	227	149	8.30 (7.38, 10.56)
2:	669	449	8.03 (7.05, 9.41)
3:	272	190	7.08 (5.90, 11.02)
4+:	176	119	9.34 (6.79, 11.70)

# 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 a metastatic setting in U.S. community practices

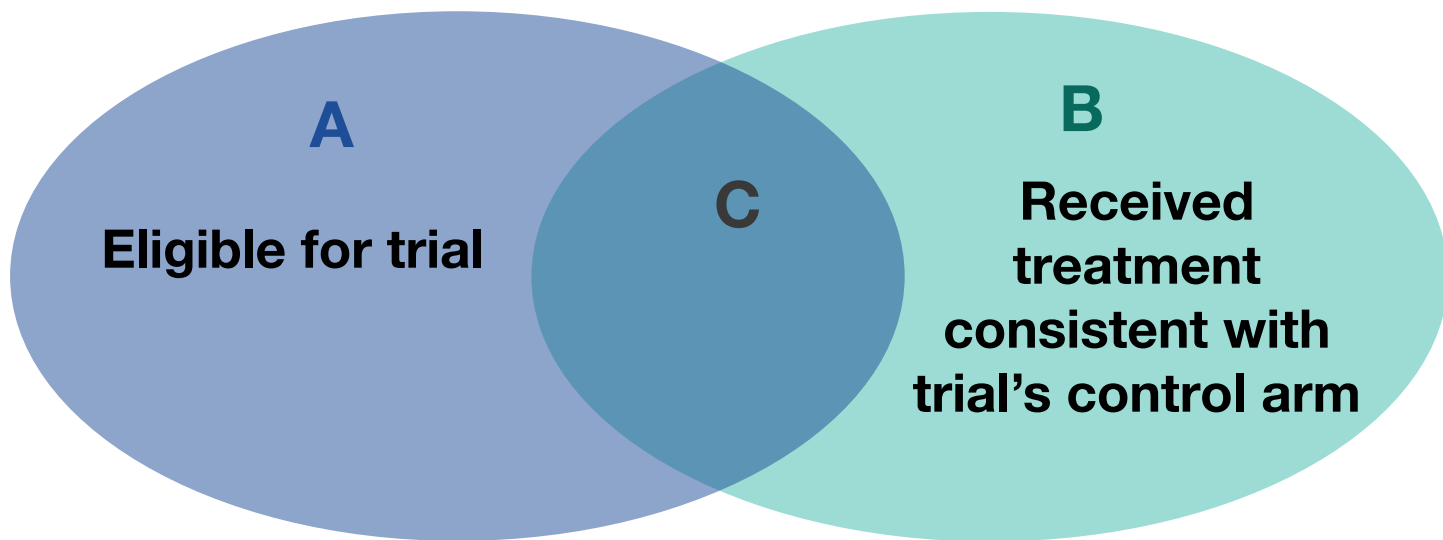
Variable	n (%)
Demographics	
Age at PD-1 initiation, years, median (IQR) <sup>a</sup>	69.0 (61.0–75.0)
Age categories at PD-1 initiation <sup>a</sup>	
<49 years	45 (3.4)
50–64 years	435 (32.4)
65–74 years	500 (37.2)
75+ years	364 (27.1)
Sex	
Women	597 (44.4)
Men	747 (55.6)

64%

# 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?

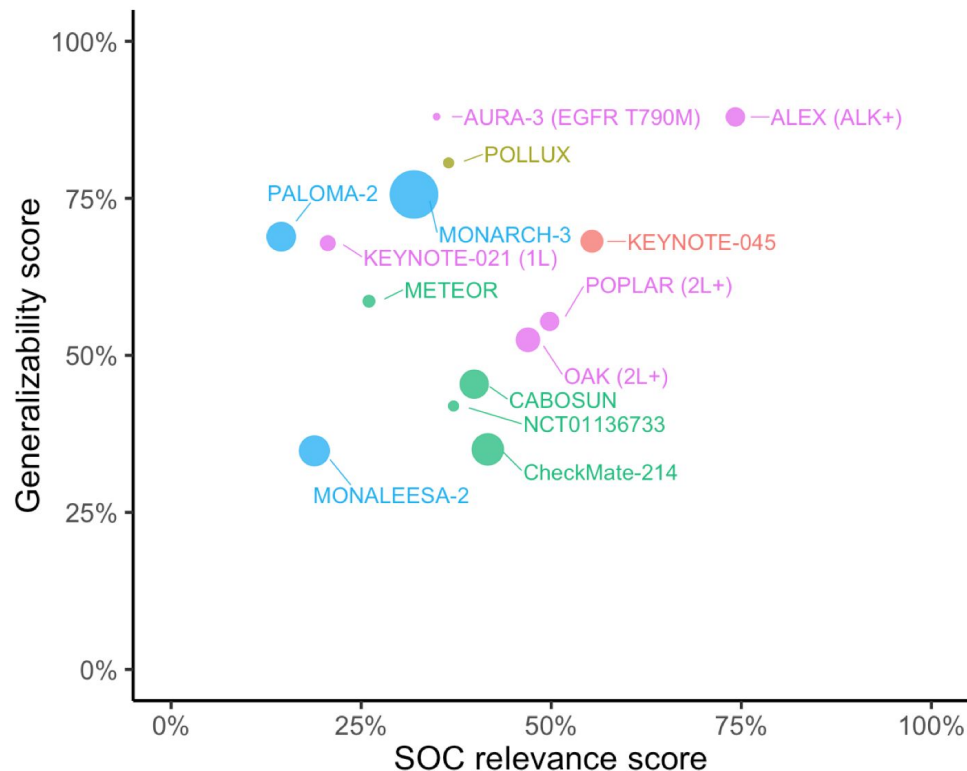
# Standard of Care (SOC) Relevance and Generalizability



**SOC Relevance  
score =  $C/A$**

**Generalizability  
score =  $C/B$**

# Relevance and Generalizability of Randomized Clinical Trials



- Urothelial
- Multiple myeloma
- Renal cell carcinoma
- Non-small cell lung cancer
- Breast cancer

Median (range) of scores:

- Generalizability: 63% (35%-88%)
- SOC relevance: 37% (15%-74%)

# Affordable Care Act Medicaid Expansion Impact on Racial Disparities in Timely Cancer Treatment

Adamson et al. ASCO 2019 Annual Meeting

# Methods

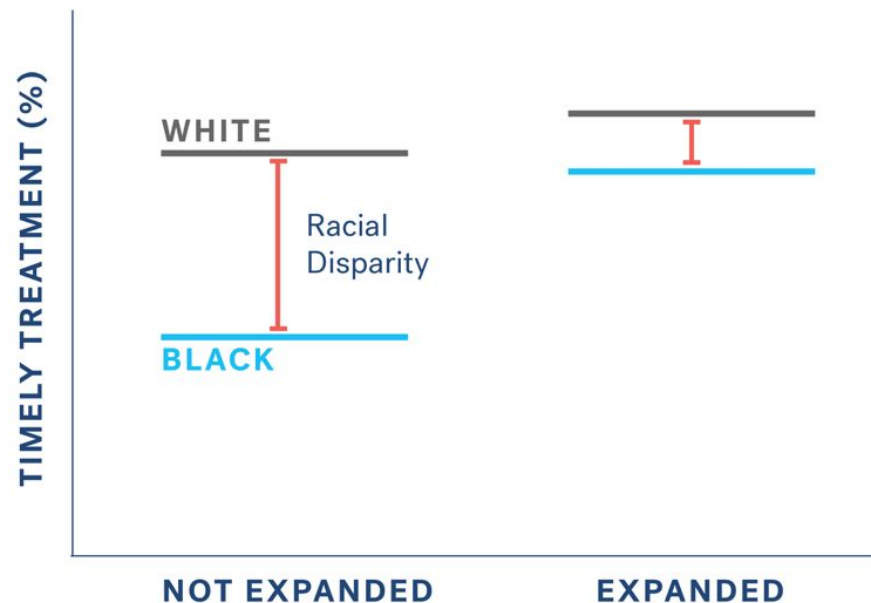
Study sample: Adults 18-64 years, diagnosed with advanced cancer (N=30,386)

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

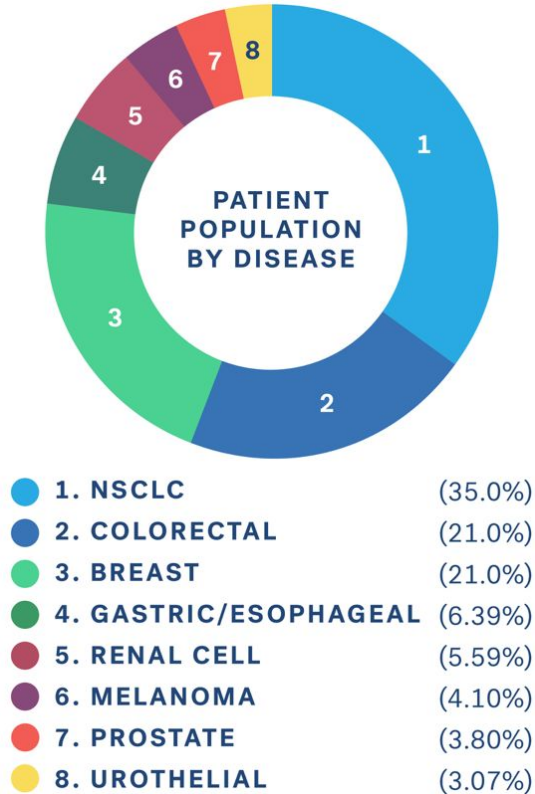
Study design: Compares experience of **black relative to white patients**

- Diagnosed in states **after Medicaid expansion compared to pre-expansion or in states not expanding by 2019.**

## Difference-in-Differences



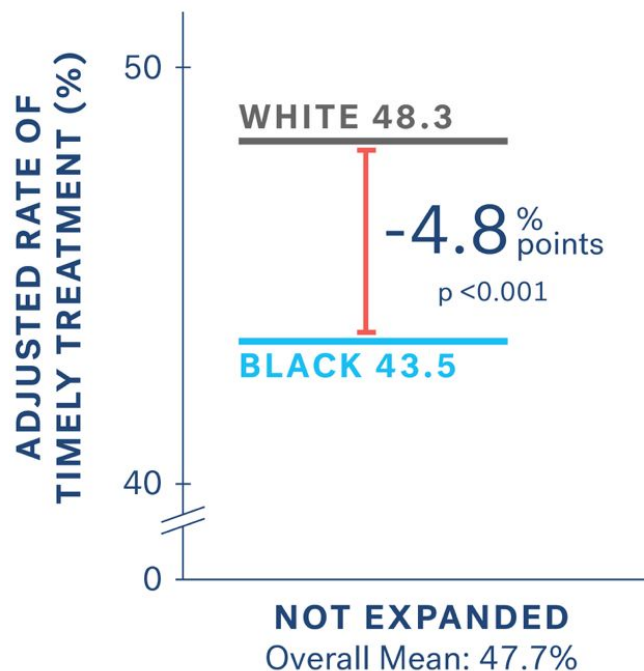
# Results: Demographics



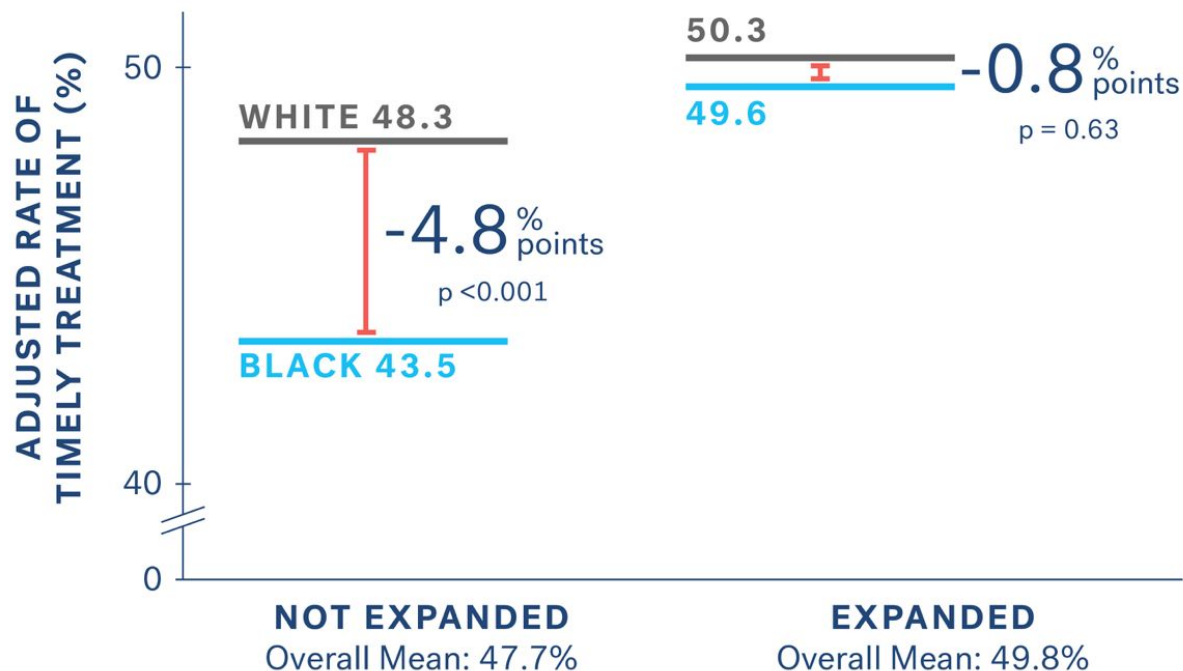
## Patient Population (N = 30,386)

	Not Expanded (n = 18,678)	Expanded (n = 11,708)
Median Age, Years [IQR]	57.0 [51.0-61.0]	57.0 [52.0-61.0]
Male, %	47.1	48.4
Race: White, %	73.3	70.3
Race: Black, %	14.6	8.7

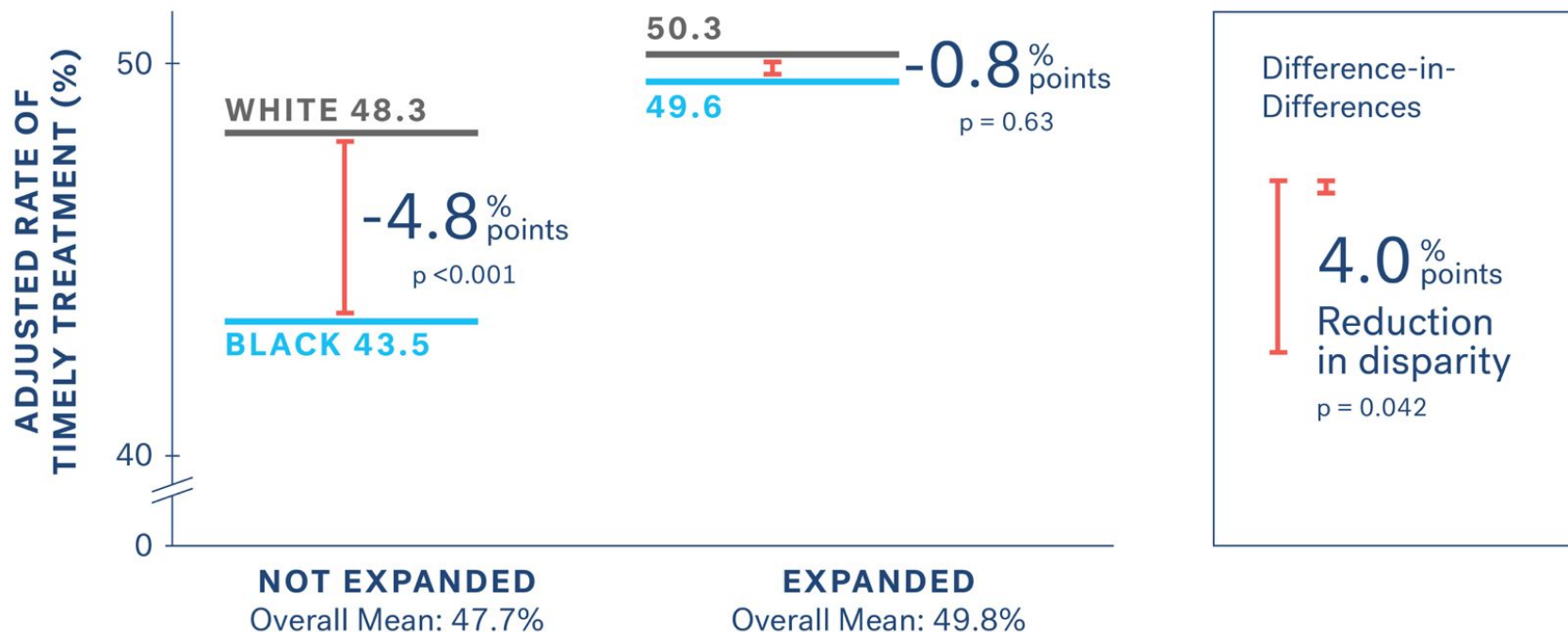
# Medicaid expansion associated with reduced racial disparities in timely treatment



# Medicaid expansion associated with reduced racial disparities in timely treatment



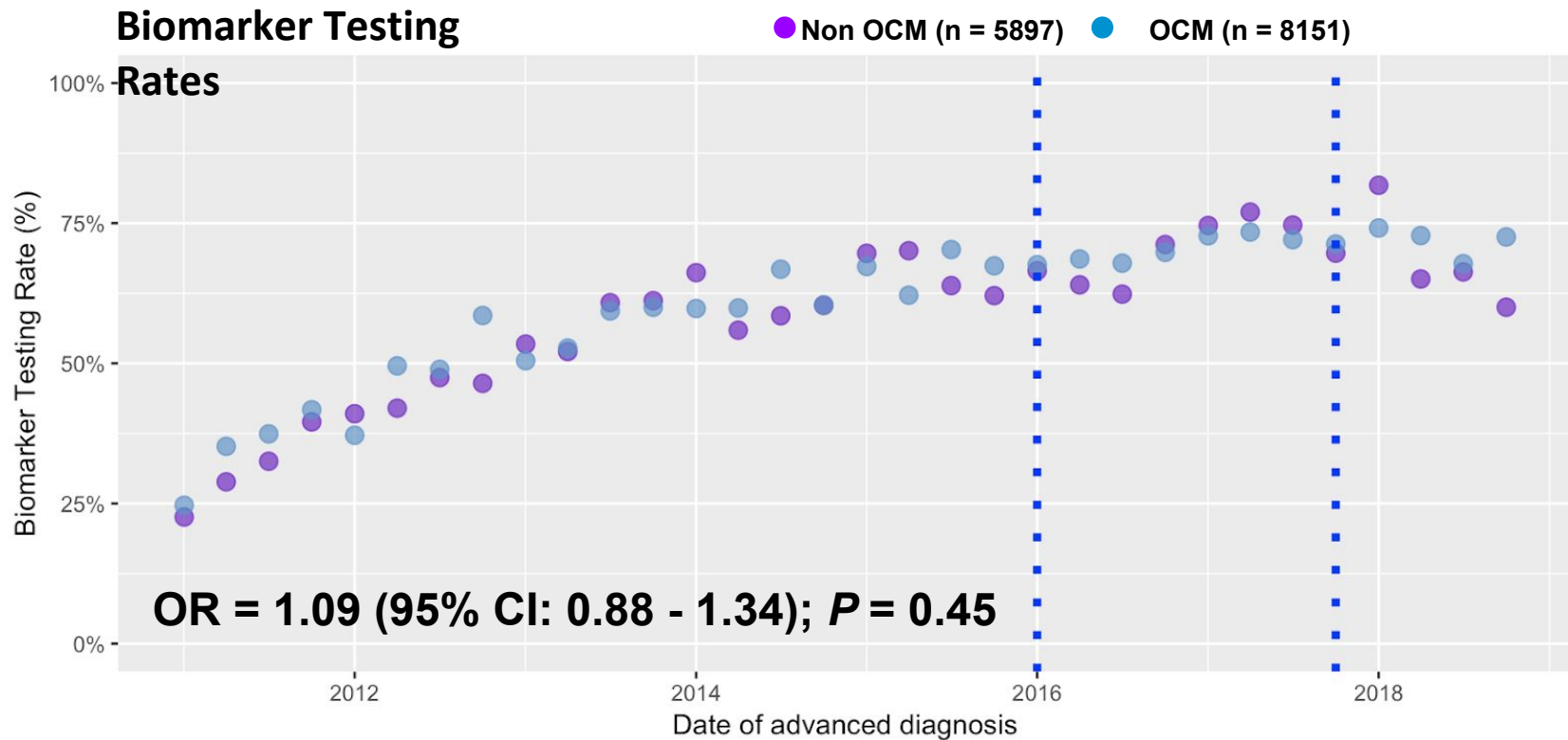
# Medicaid expansion associated with reduced racial disparities in timely treatment



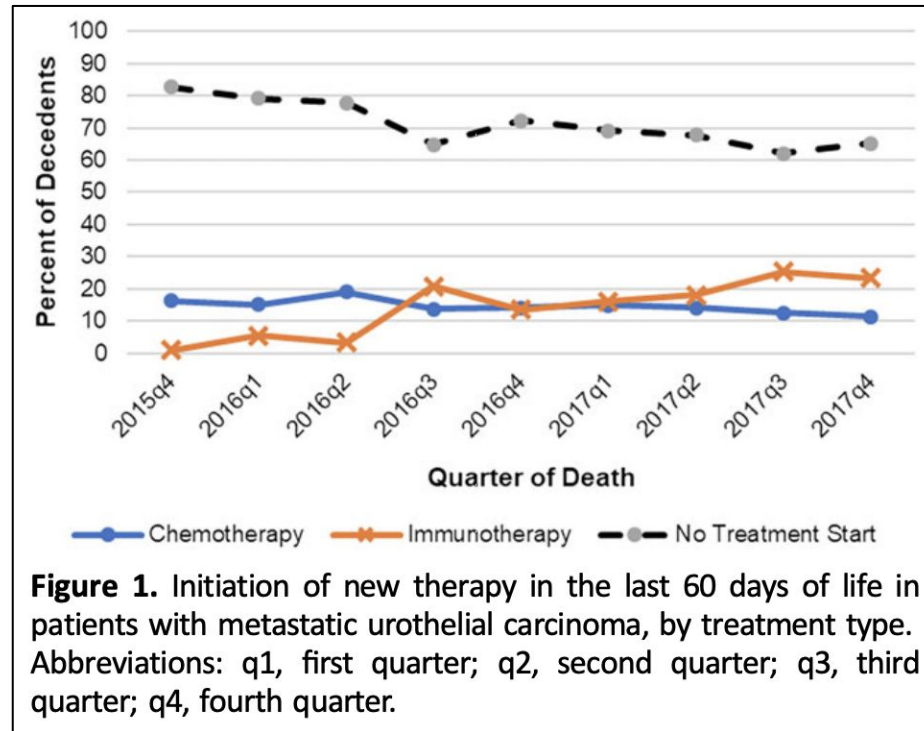
# Impact of Oncology Care Model Reporting Requirements on Quality of Care

- 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
  -

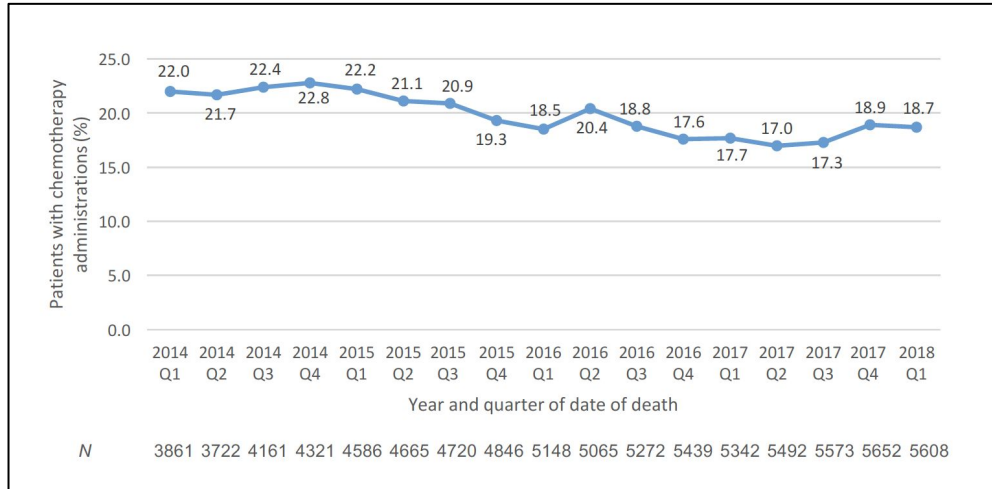
# Result: Difference-in-Differences Model Showed no Changes in Downstream Care Associated to OCM



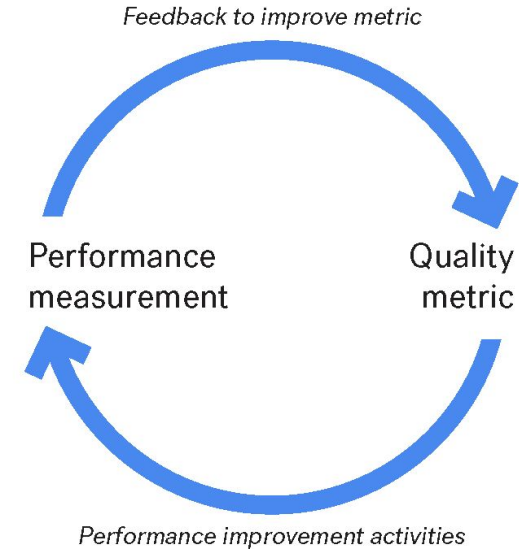
# Quality Measurement: Trends in EOL Treatment in Urothelial Cancer



# Real-World Data for Quality Improvement

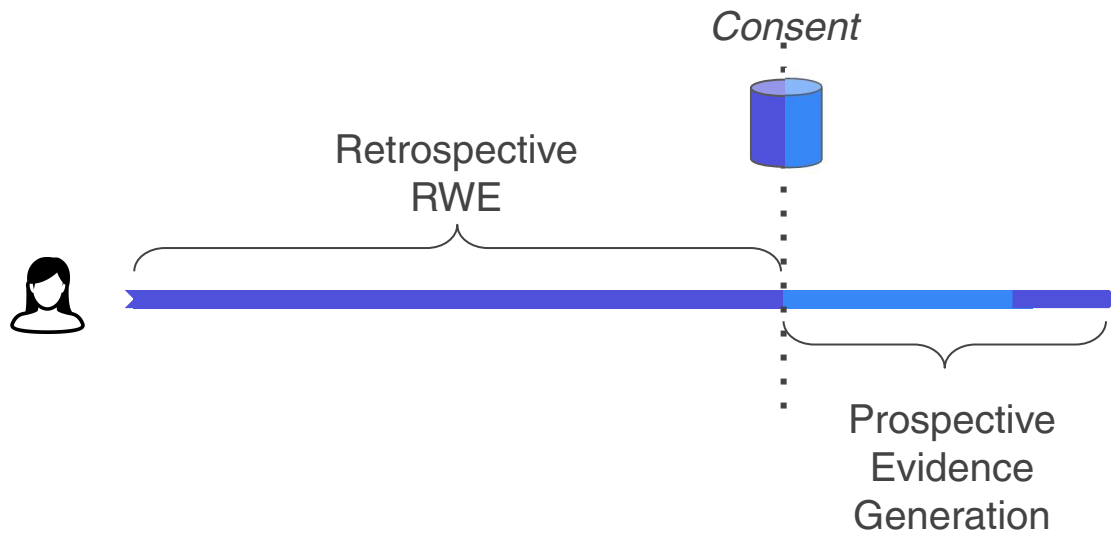


- Real-time
- Site, clinical team, physician-level metrics



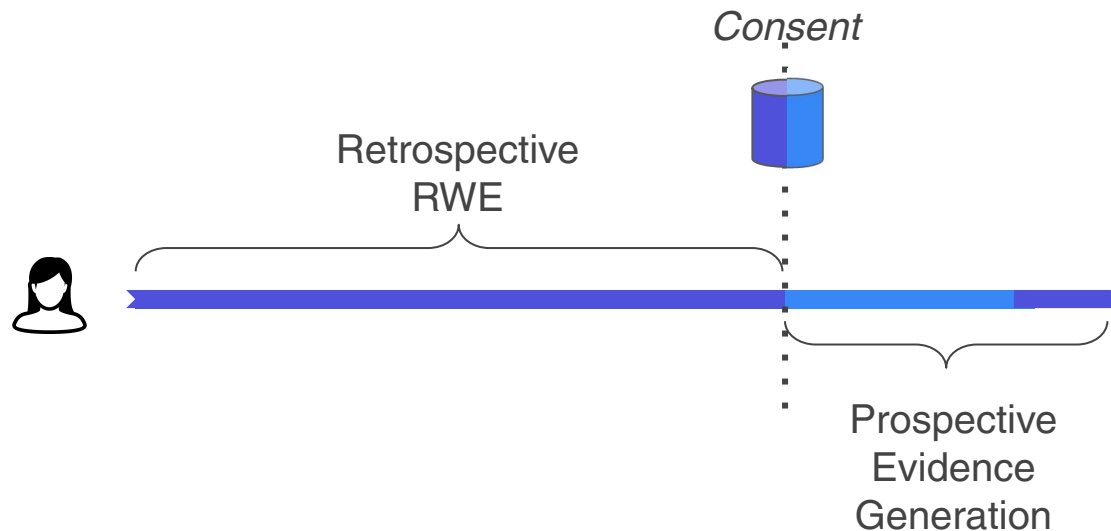
# A look to the future - a new paradigm for RWE in drug development

## The Continuum of RWE



# 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