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December 12, 2016

The Use of Real-World Evidence in Drug Development

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Chief Medical Officer/Chief Scientific Officer
Flatiron Health

Agenda

- Role of real-world evidence in oncology drug development
- Key steps in preparing EHR data to contribute to real-world evidence
- Case study: Trastuzumab emtansine (Kadcyla)
- Policy recommendations

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Role of real-world evidence in oncology drug development

Real-world Evidence

Definition

- Information derived from healthcare delivered outside the traditional clinical trial setting
- Includes electronic health records (EHRs), claims/admin data, registries, and patient-generated health data
- Complements clinical trials ---> more generalizable knowledge
- Randomization may or may not be a feature of RWE studies

The NEW ENGLAND JOURNAL of MEDICINE

N ENGL J MED 375;23 NEJM.ORG DECEMBER 8, 2016

SOUNDING BOARD

Real-World Evidence — What Is It and What Can It Tell Us?

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21st Century Cures Act

PDUFA VI

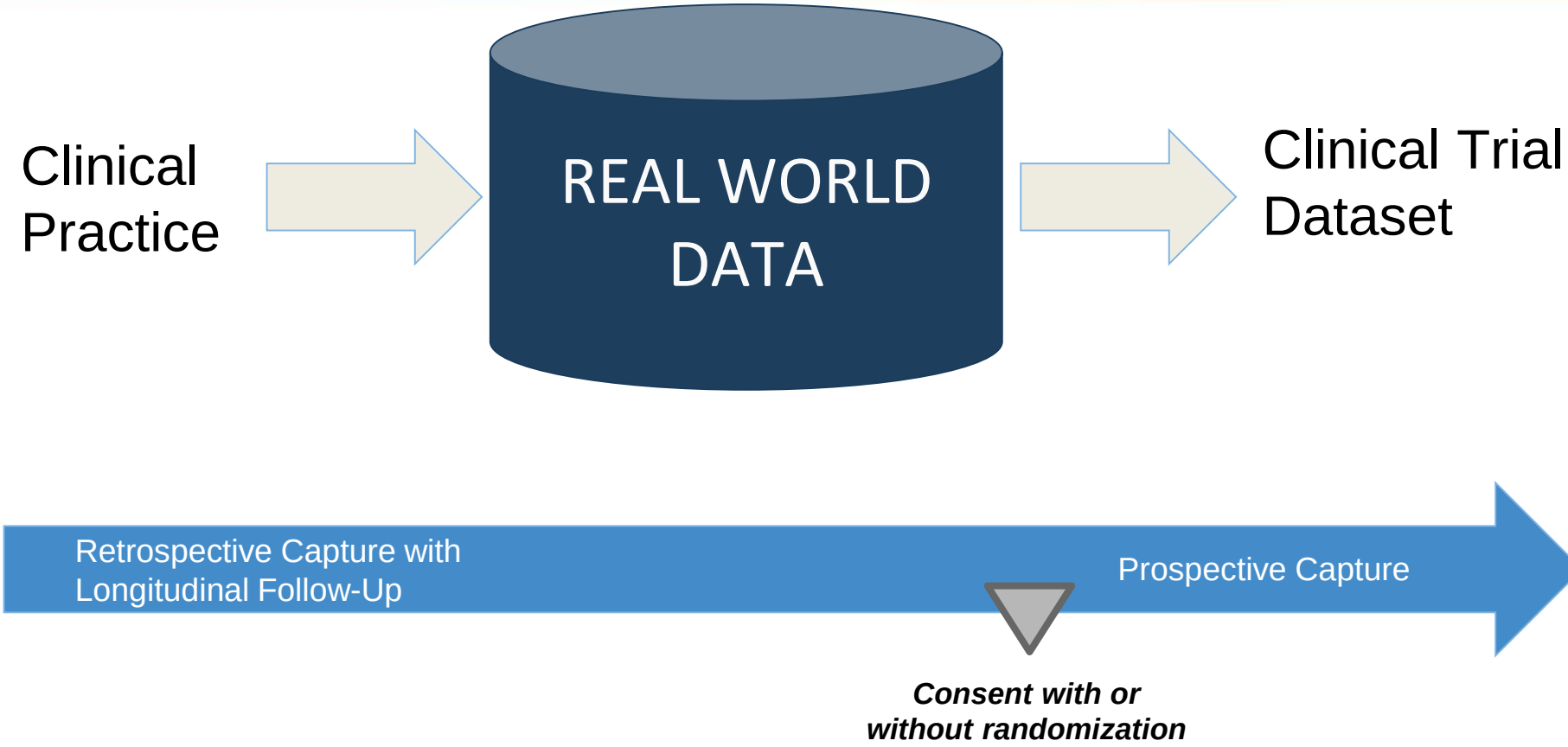
Real-world Data / Big Data / Real-world Evidence

Real-world data

- One dataset or many accumulated datasets can contribute to real-world data
- "Big data"
  - Amalgamation of data types to more clearly complete the picture of what is happening to patients in the real world
  - "Big" → velocity, volume, variety, veracity
- Real-world data analyzed in a consistent manner to generate clinically-meaningful generalizable evidence → RWE

- **Example applications of RWE in oncology:**
  - Confirming benefit for new indications → label expansion
  - Optimizing clinical use → label revisions
  - Post marketing requirements
  - Safety monitoring

RWE along the continuum



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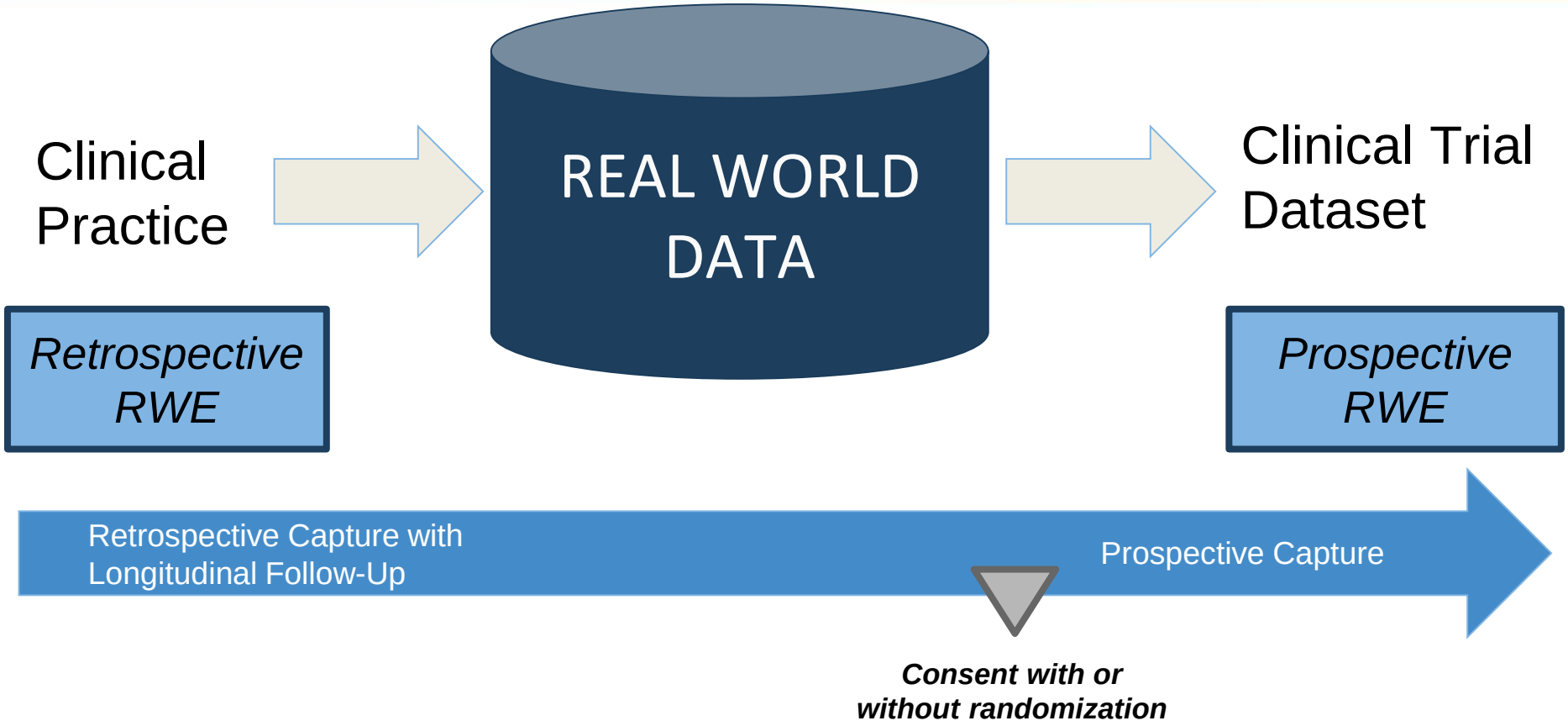
RWE along the continuum



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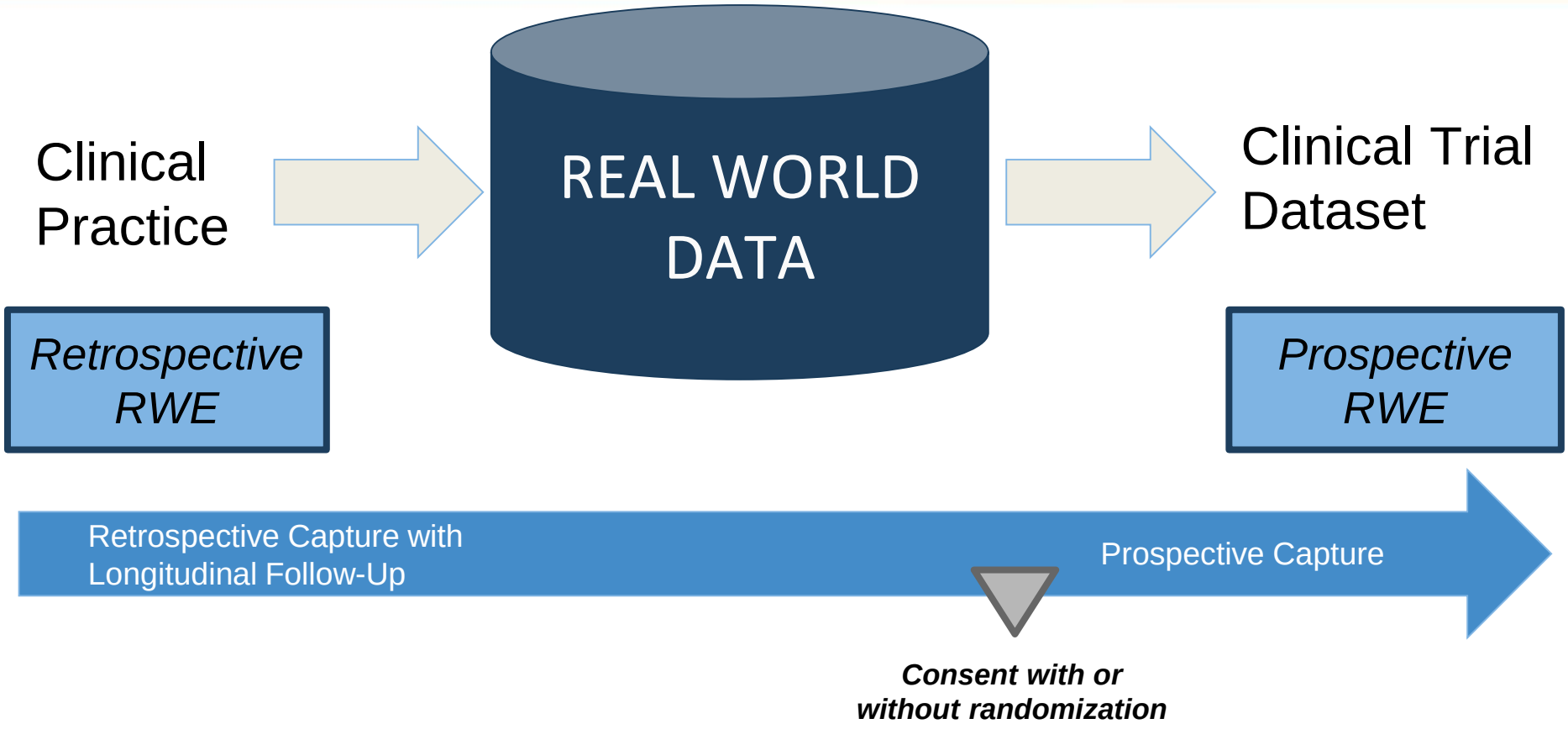
RWE along the continuum



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Data Requirements for Real-world Evidence

Data Requirements

- Drug development use cases (for the most part) require:
  - Aggregated, high quality, complete, longitudinal datasets
  - Reproducibility and provenance
  - Patient-level data linkage
  - Endpoints/outcomes
  - Study objectives and analysis plans
  - Careful cohort selection

EHRs as a way forward

- EHR data can act at the backbone and organizing framework
  - >90% of US oncologists use an EHR
  - Linkable
  - Quality can be documented and improved
  - Can use a registry analytic framework

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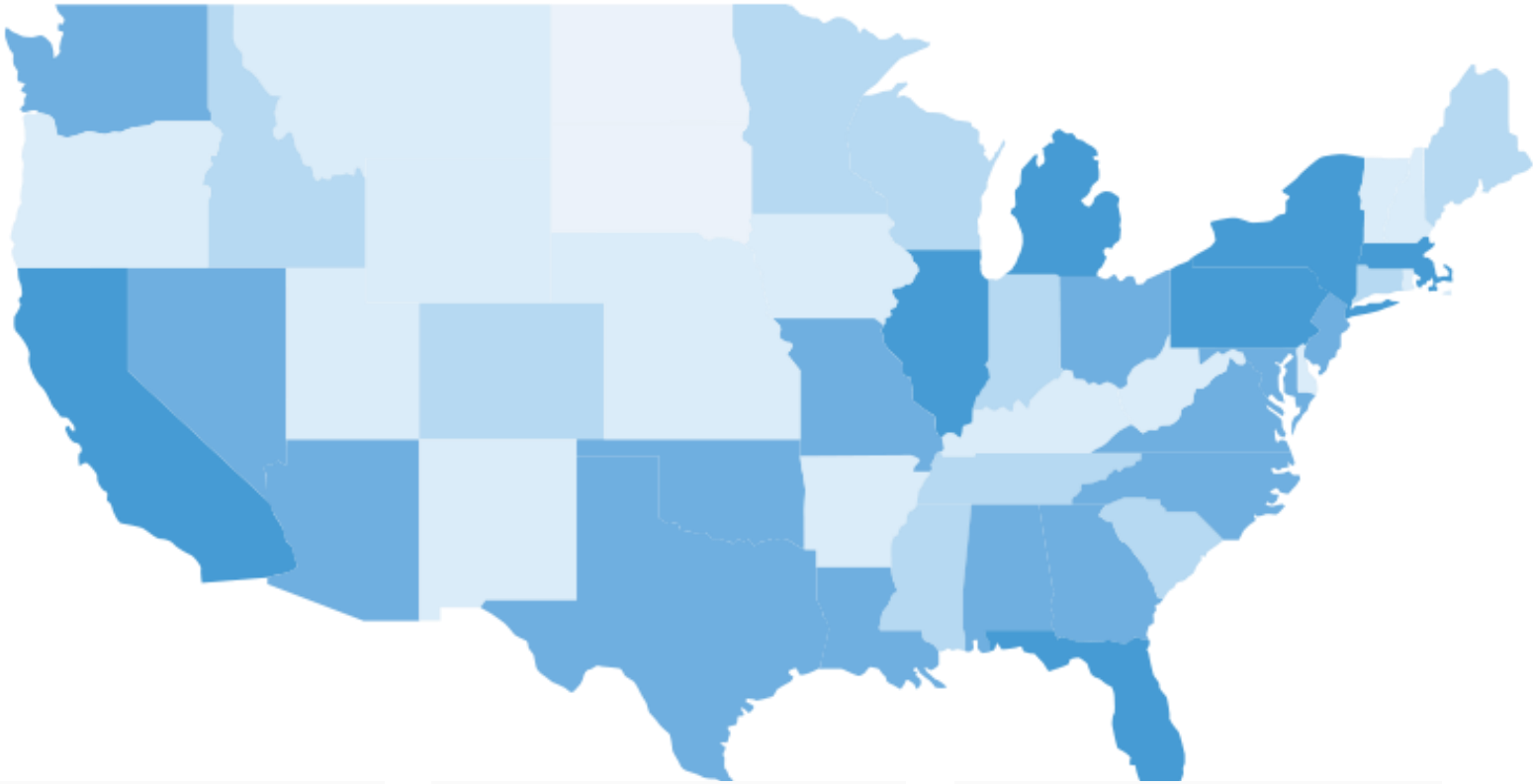
Key steps in preparing EHR data to contribute to real-world evidence

Aggregate EHR data into single common dataset



258

Cancer Clinics

2,400

Clinicians

1.5M

Active Cancer Patients in Network

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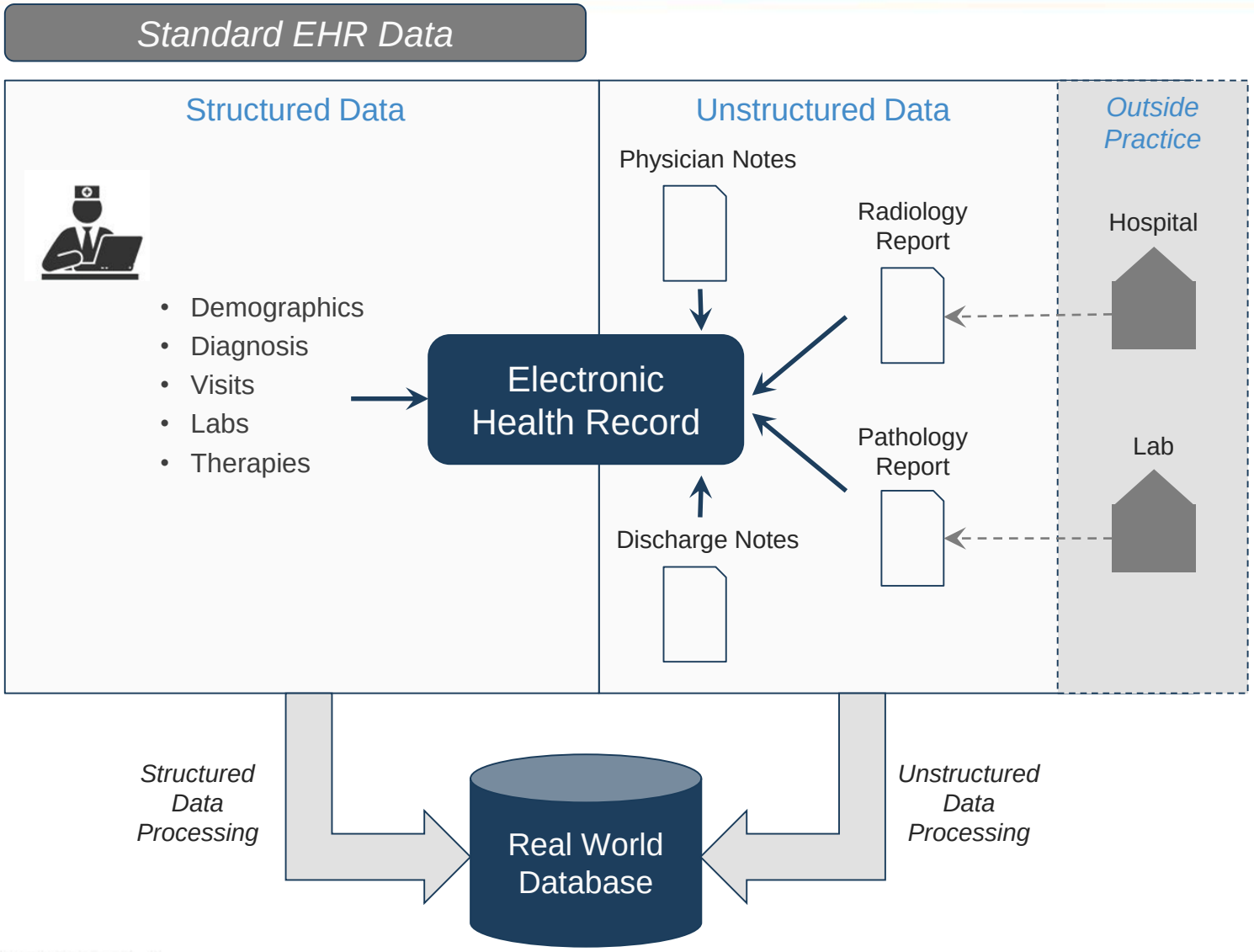
Standardize EHR data to a common data model



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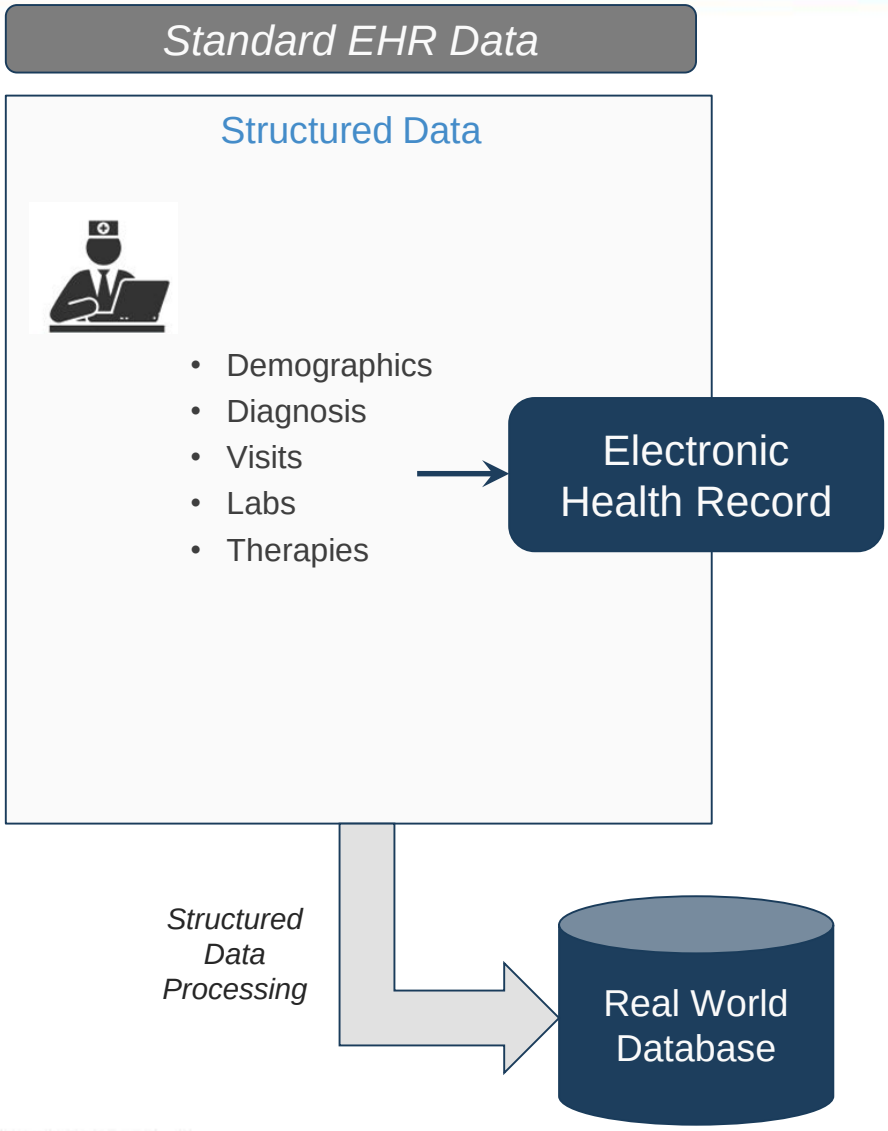

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Standardize EHR data to a common data model: Harmonization and normalization of structured data

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

- 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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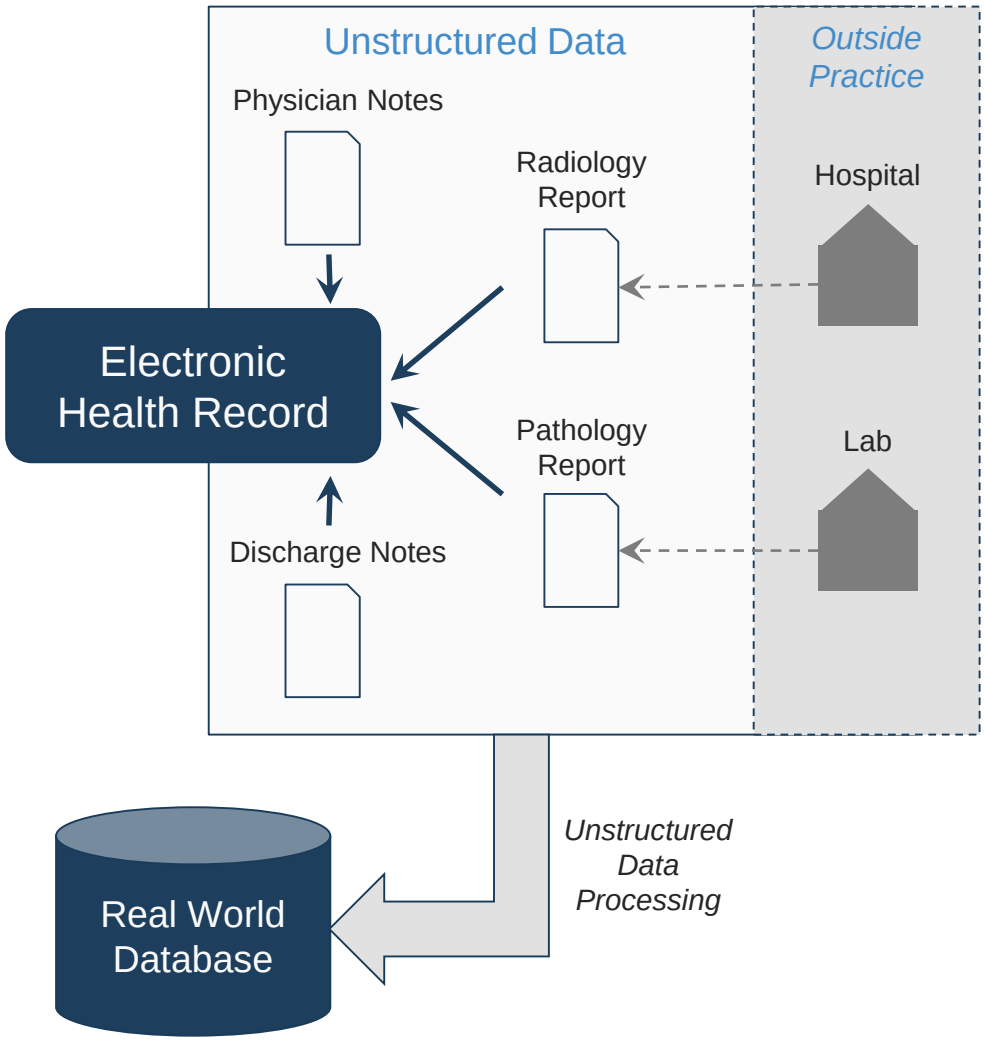
Standardize EHR data to a common data model



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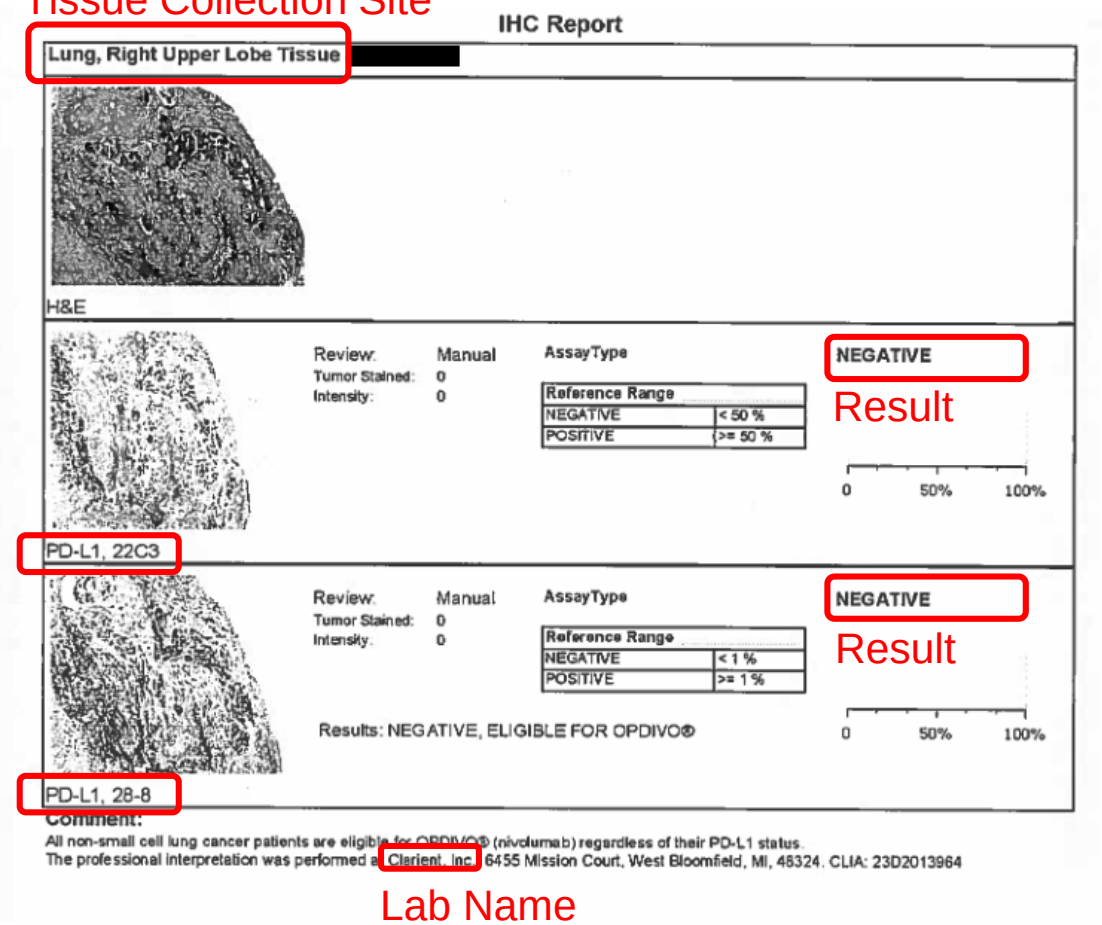
Standardize EHR data to a common data model: Curate unstructured data

Section of PD-L1 Report

Tissue Collection Site



Lab Name

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

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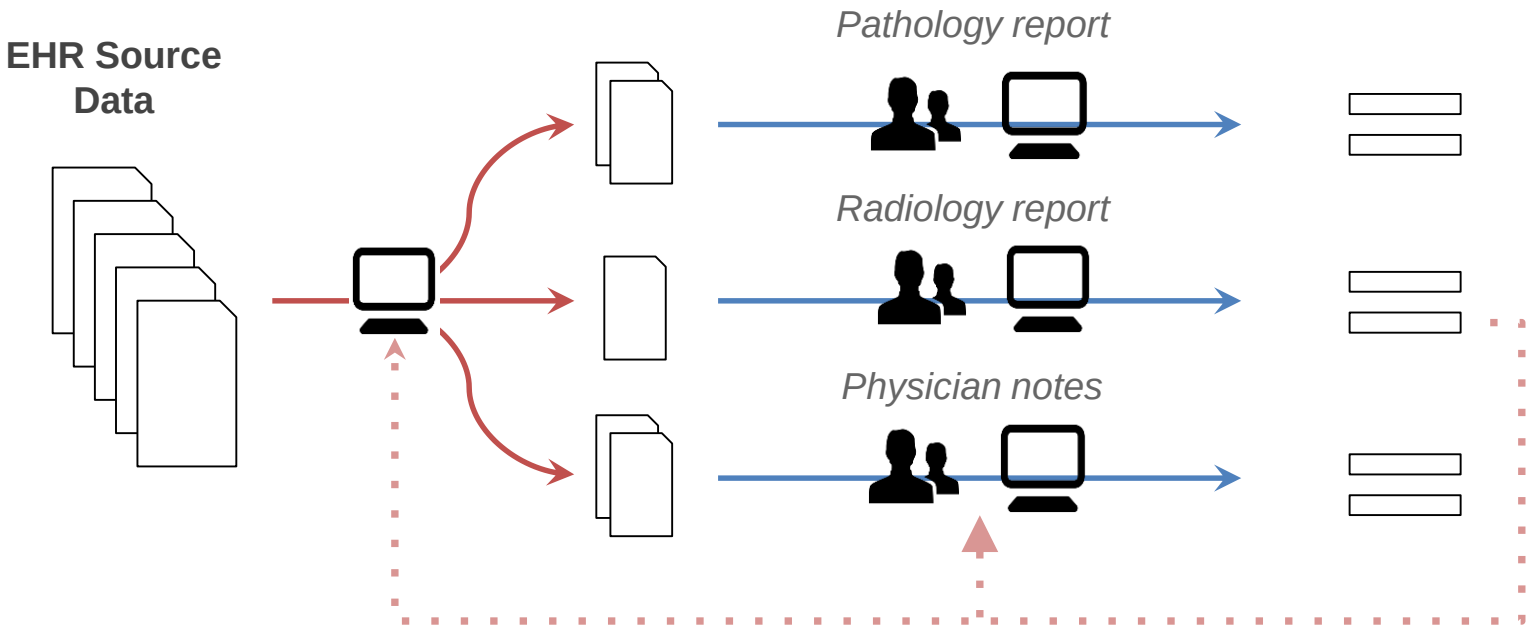
Standardize EHR data to a common data model: Curate unstructured data

Technology-Enabled Abstraction using Patient Manager®



- Abstraction of unstructured data through Patient Manager allows for comparability across patients as well as different oncology practices

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Standardize EHR data to a common data model: Centralized data processing and QA/QC

Operational Controls

- All abstracted data is collected through controlled forms
- All abstracted data is processed in accordance with approved procedures
- Structured clinical data is subject to medical informatics mapping
- Cross-functional oversight by oncology, statistical, technology, compliance teams
- Pre-specified protocol for IRB review and approval

Quality Controls

- Quantitative Scientists planning, oversight and final of data
  - Detailed analytic guide which pre-specified parameters
- Quality control and auditing of abstraction (unstructured data)
  - Edge cases escalated for review by oncologist for adjudication
- Agreement scores (e.g. kappas) and monitoring of abstracted data

System Controls

- Electronic Health Record (structured and unstructured data):
  - Full access to EHR data throughout the lifecycle of patient care
  - Updated in real time to allow for data recency
- Patient Manager Abstraction Software (unstructured data):
  - Audit trails, documentation and traceability of abstracted data
  - System does not allow for untrained staff to complete abstraction

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Characterize data quality

Completeness of technology-enabled abstraction

Example: Advanced NSCLC

Variable	Structured data only	Flatiron data completeness
Metastatic diagnosis	26%	100%
Smoking status	0%[1]	94%
Histology	37%	99%[2]
Stage	61%	95%
ALK results (of those tested)	9%	100%[3]
EGFR results (of those tested)	11%	99%[3]

1 58% are free text in dedicated field in EHR (requiring hand abstraction)
2 Including 8% of patients with results pending or unsuccessful test
3 Including 6% of patients with results pending or unsuccessful test

Accuracy of technology-enabled abstraction

Example: Sites of metastases

Site of met	Inter-abstractor agreement	Kappa
Bone	97%	0.93
Brain	96%	0.91
Liver	92%	0.83
Lung	94%	0.87

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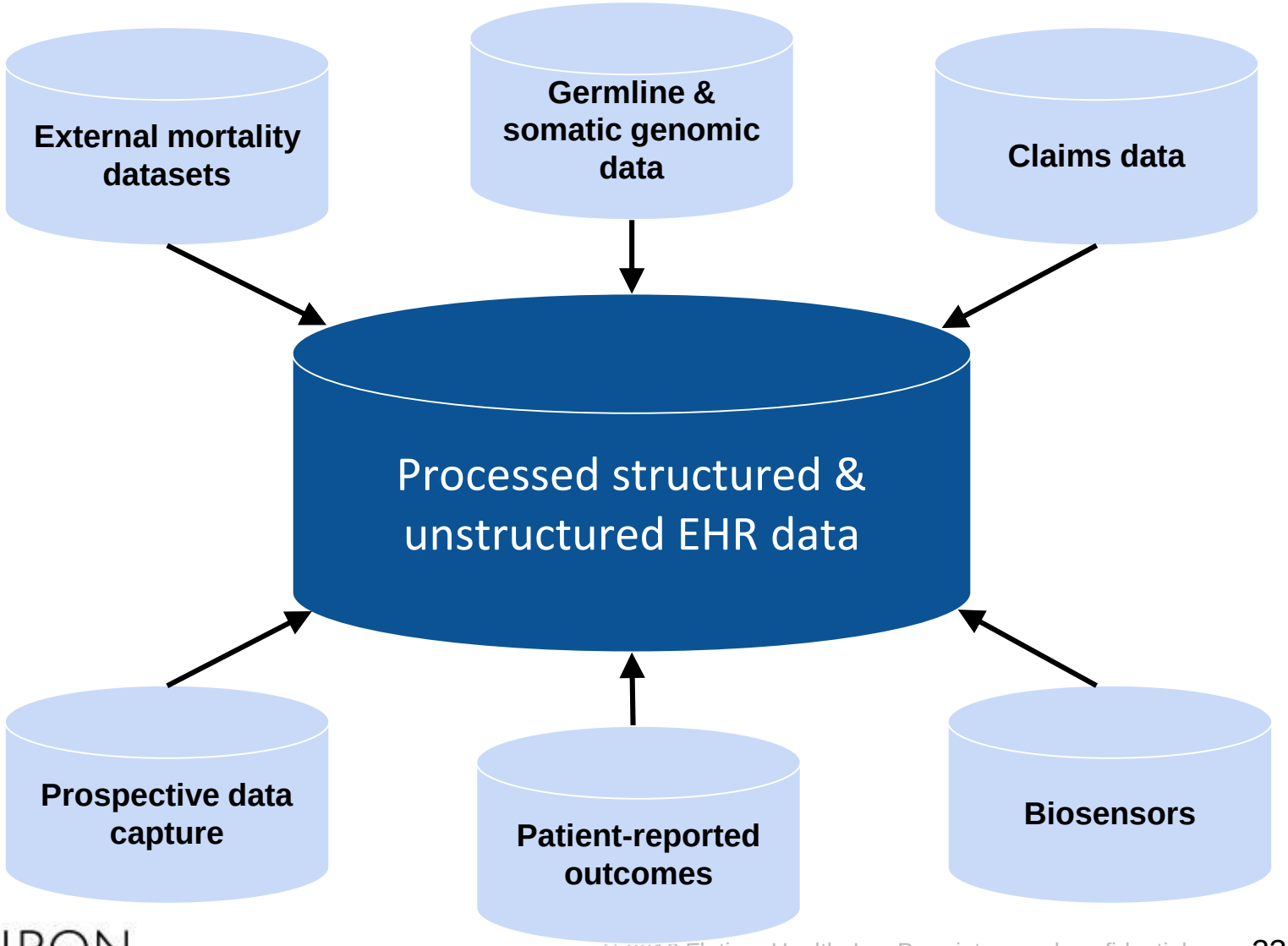
Link processed EHR data to other datasets



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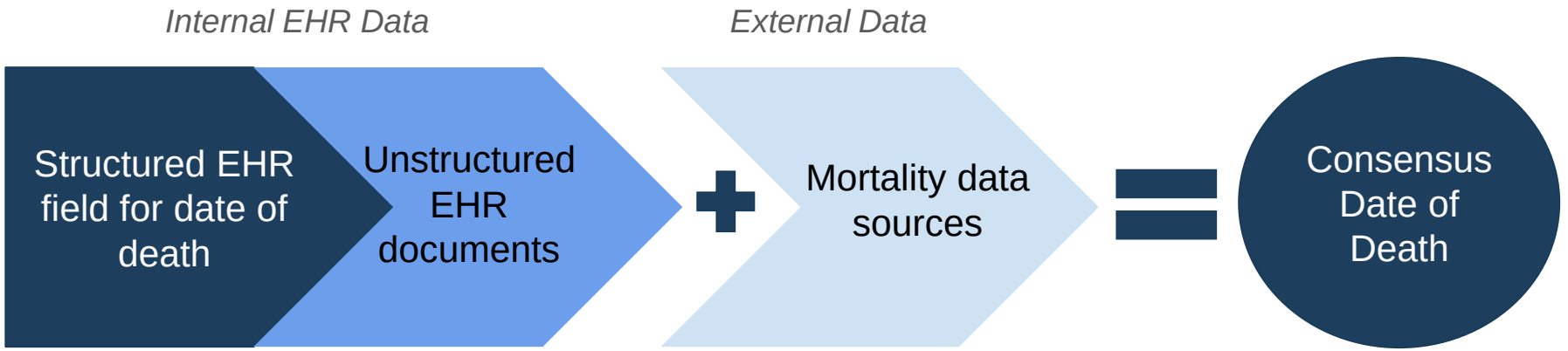
Incorporate endpoints / outcomes

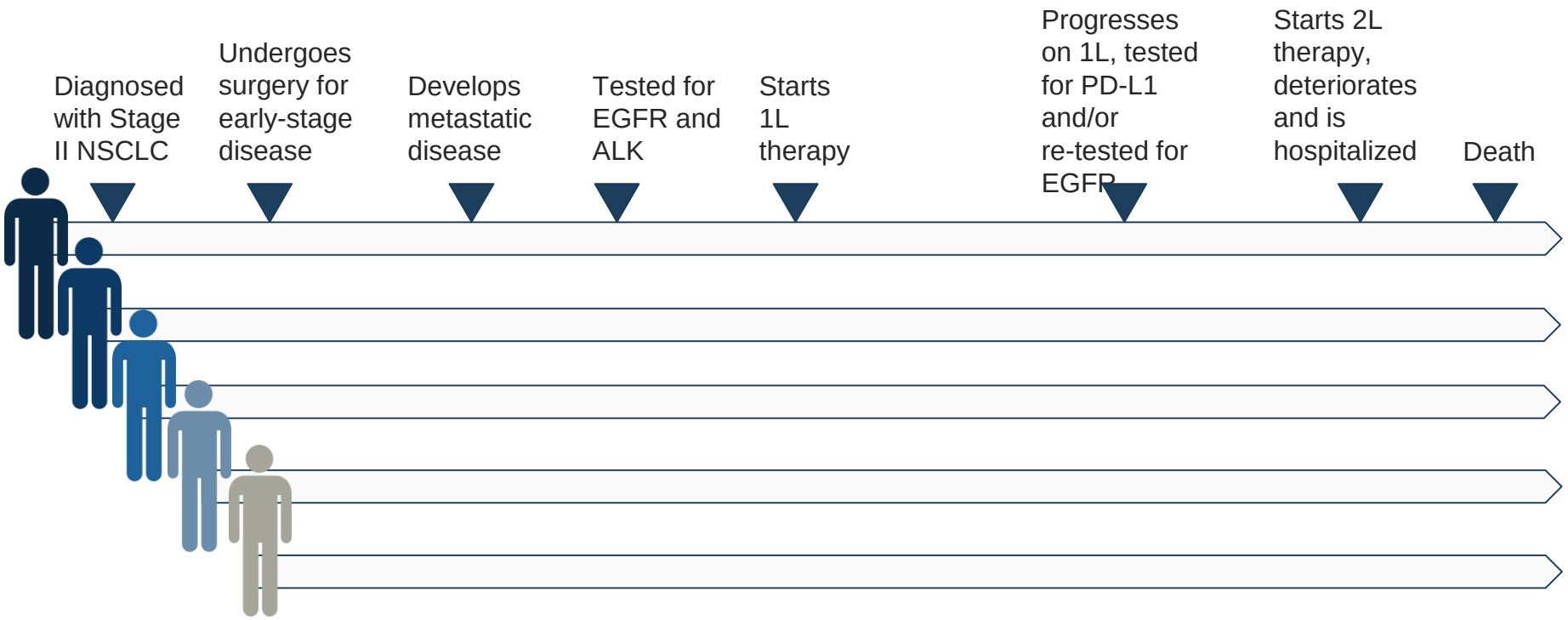
5 key types of outcomes

- Mortality
- Tumor response / treatment change
- Toxicity
- Patient-generated health data
- Health resource utilization



Combining data sources enables development of a high-quality consensus date of death for patients across the database

Organize datasets for analysis



Example: Non-small cell lung cancer

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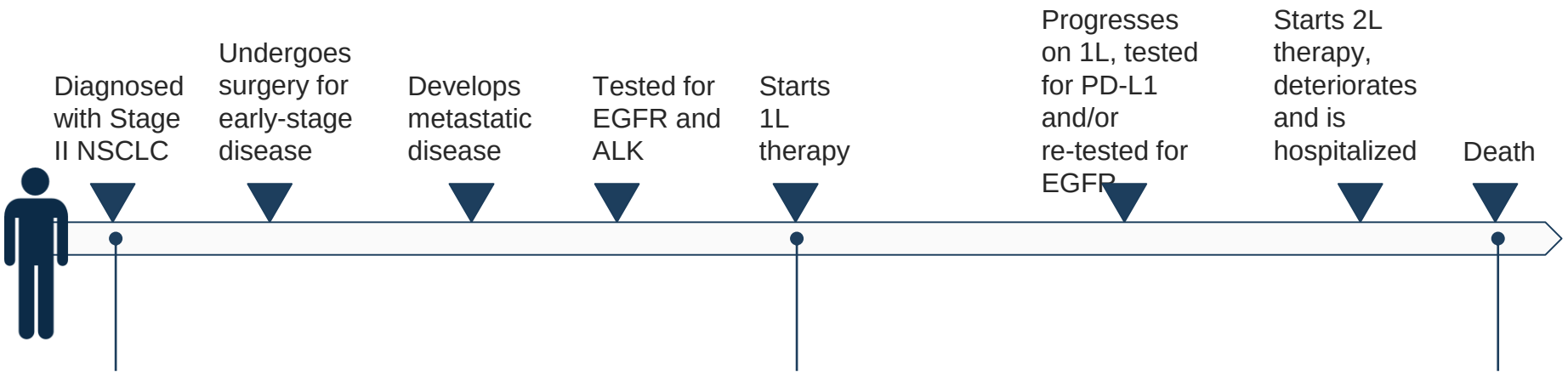
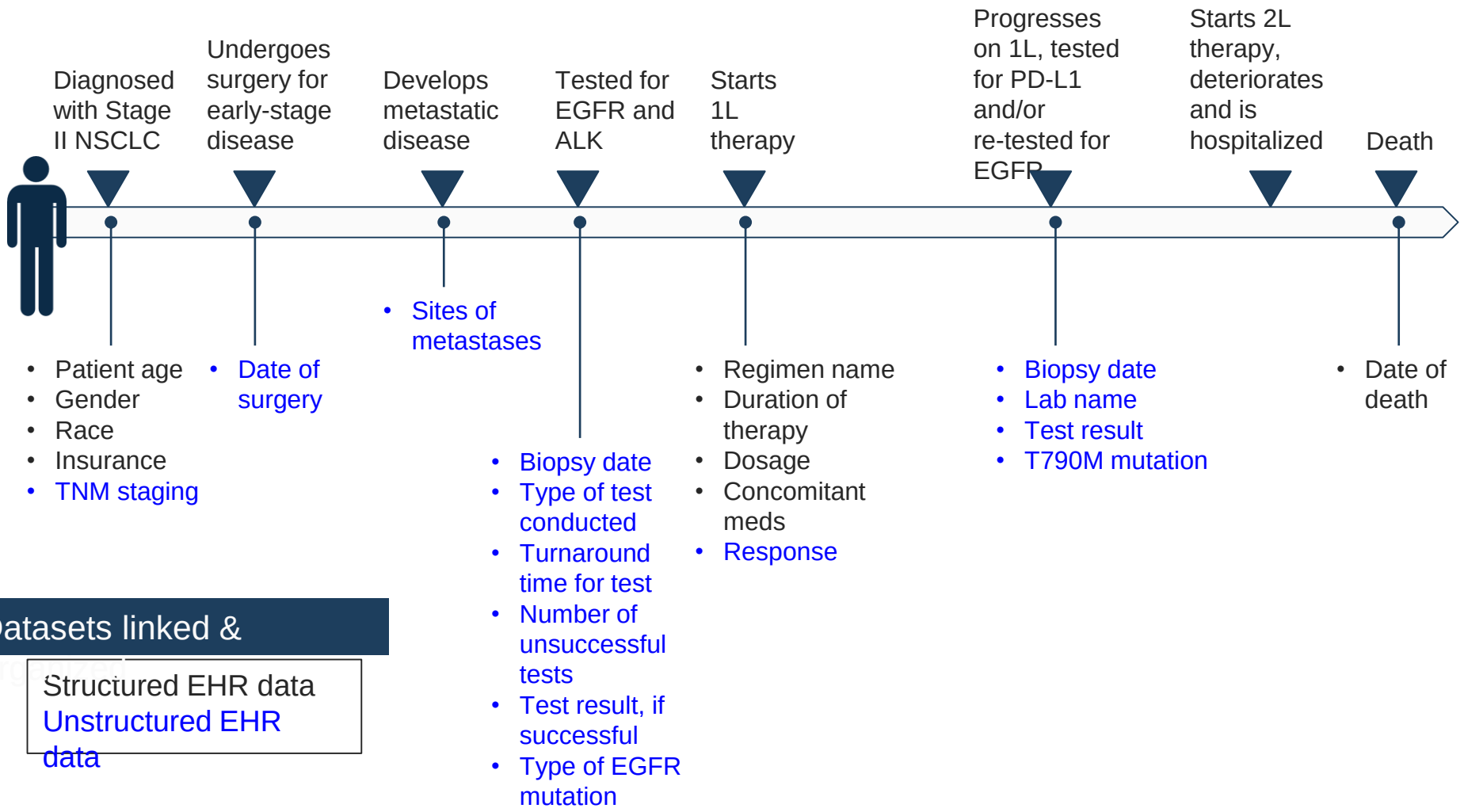


Datasets linked & organized

Structured EHR data

Organize datasets for analysis



Datasets linked & organized

Structured EHR data
Unstructured EHR data

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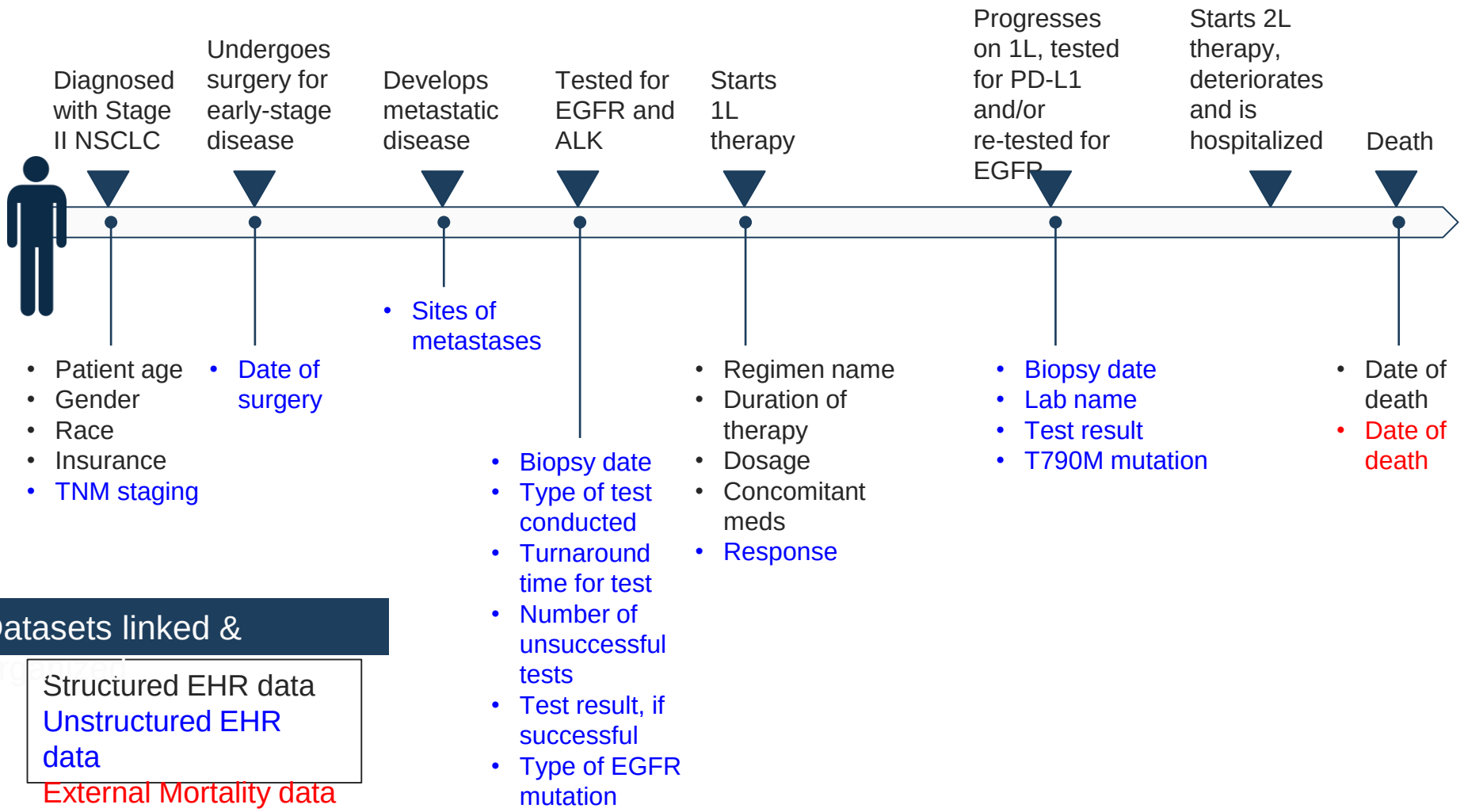
Organize datasets for analysis



Datasets linked & organized

Structured EHR data
Unstructured EHR data
External Mortality data

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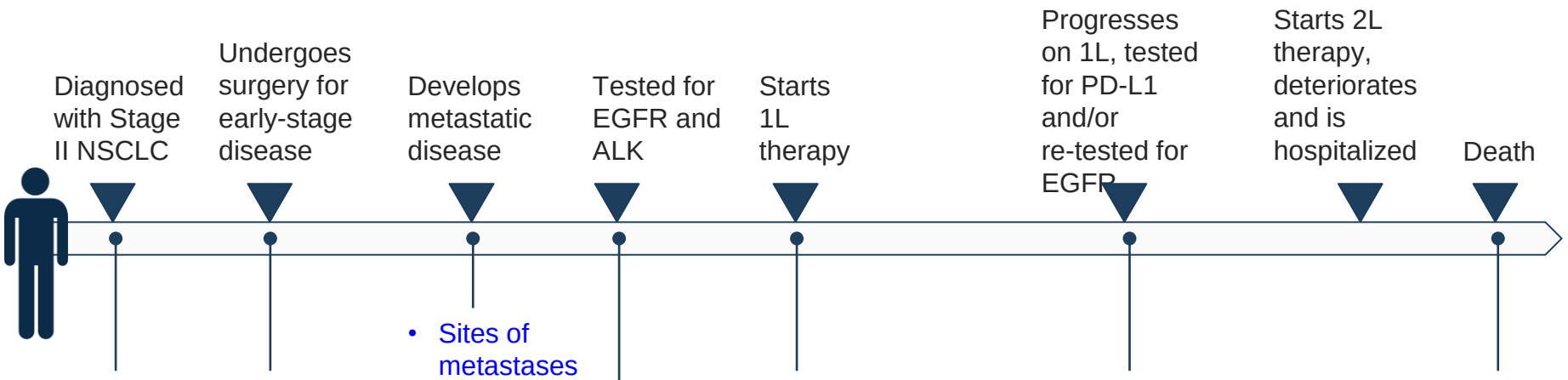
Organize datasets for analysis



- Patient age
- Gender
- Race
- Insurance
- TNM staging
- Comorbidities

- Date of surgery

- Sites of metastases
- Time to recurrence

- Biopsy date
- Type of test conducted
- Turnaround time for test
- Number of unsuccessful tests
- Test result, if successful
- Type of EGFR mutation

- Regimen name
- Duration of therapy
- Dosage
- Concomitant meds
- Response
- Reason for discontinuation

- Biopsy date
- Lab name
- Test result
- T790M mutation

- Date of death
- Date of death
- Consensus date of death

Datasets linked & organized

Structured EHR data
Unstructured EHR data
External Mortality data
Combined/Derived data

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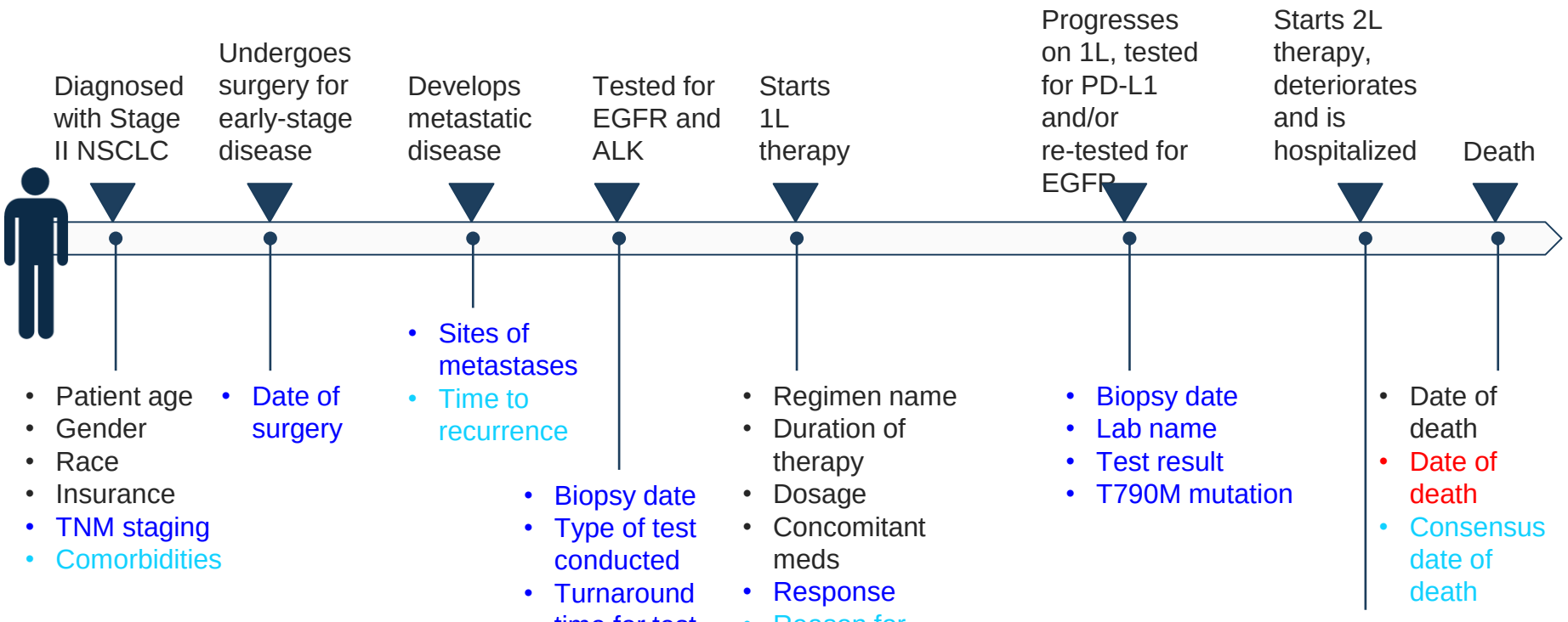
Organize datasets for analysis



Datasets linked & organized

Structured EHR data
Unstructured EHR data
External Mortality data
Combined/Derived data
Claims data

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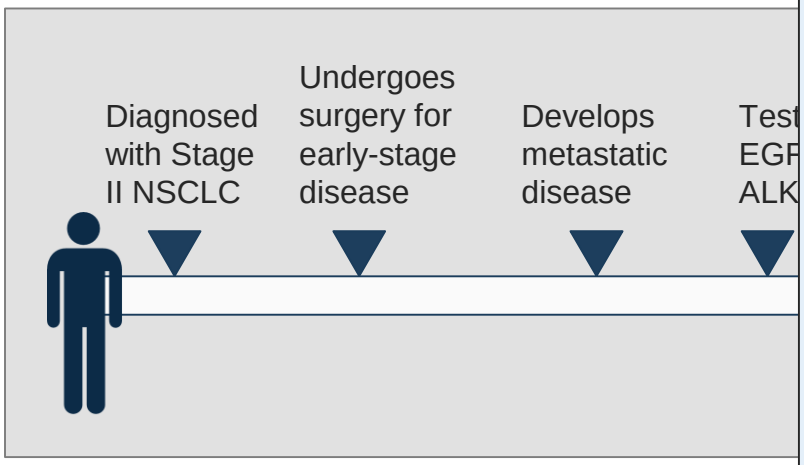
Document source, quality and provenance

Patient	Demographics	Stage	Diagnosis Date	Biomarkers	Treat-ment	Response	Hospital admissions	Mortality
A				EGFR				
B								
C								
D								

Document source, quality and provenance



- Abstracted by Sue Smith on 8/31/16 at 10:10am
- Biomarker documents were reviewed
- Medical record from West Florida Cancer Clinic
- Quality of EGFR abstraction
  - Completeness is 99%
  - Sue Smith is 96% accurate at last testing
  - Inter-abstractor agreement 97%
  - Kappa 0.93
- Audit trail for any changes
- Dataset freeze and storage

Patient	Demographics	Stage	Diagnosis Date	Biomarkers	Treat-ment	Response	Hospital admissions	Mortality
A				EGFR				
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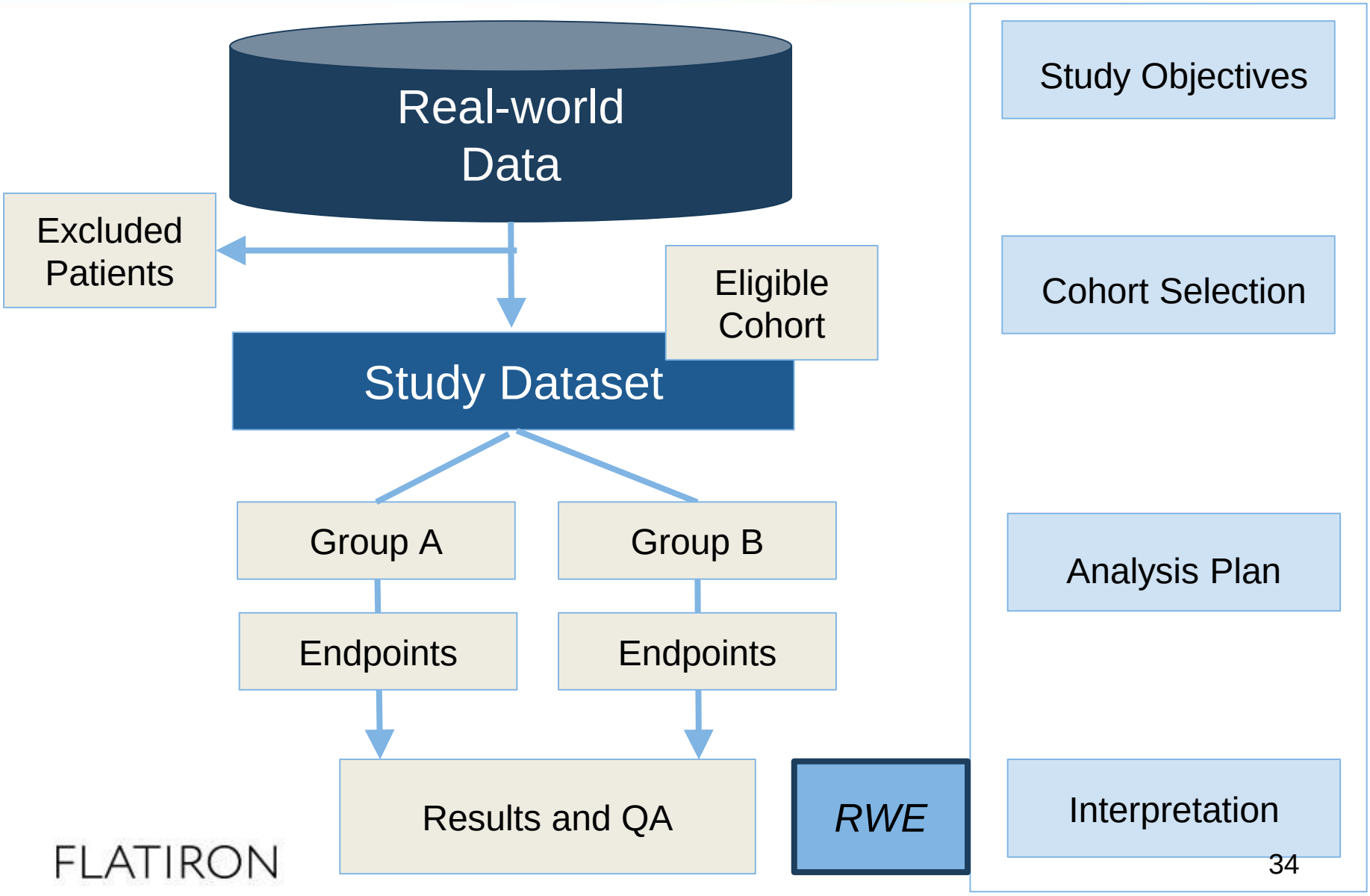
Explicit study objectives and analysis plan



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RWE data requirements can be met using EHR+

Reprise

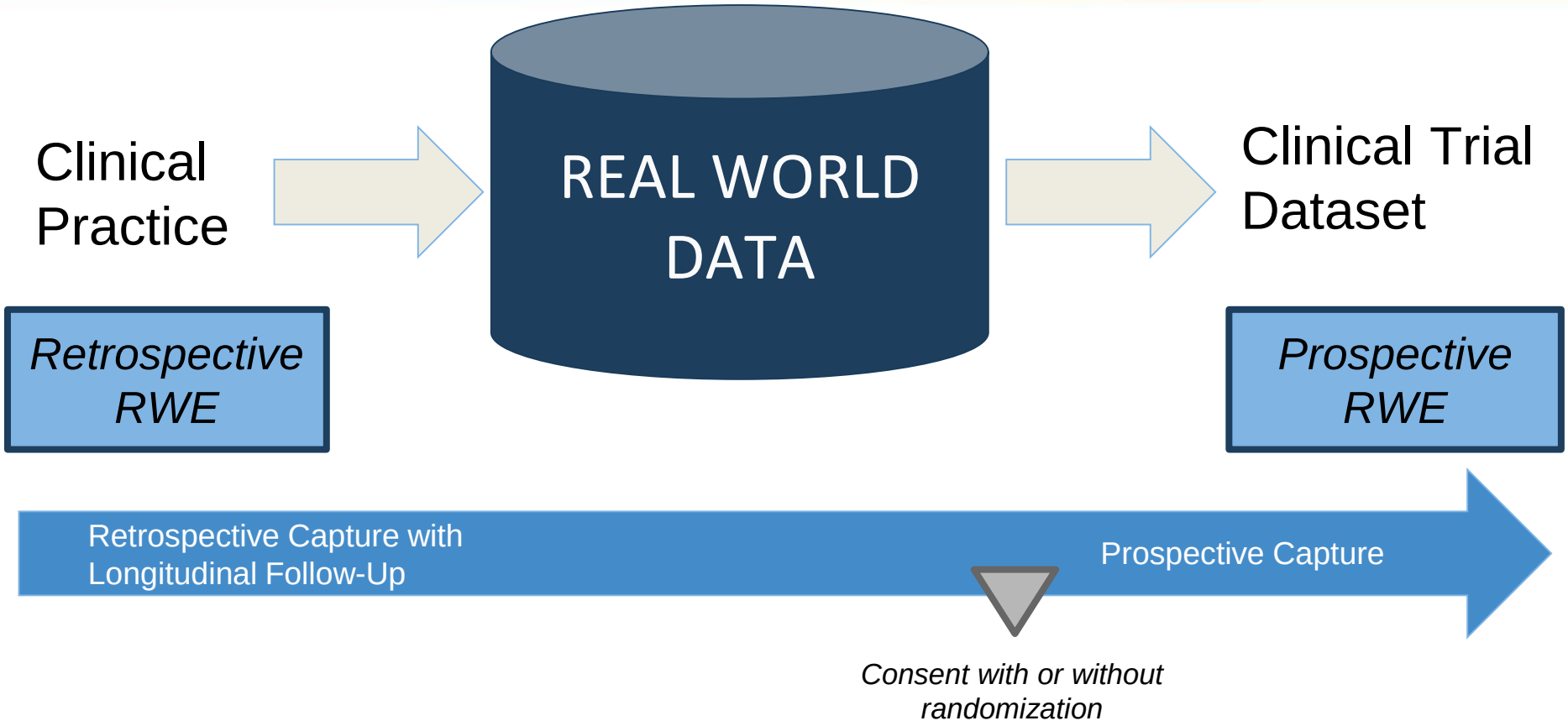
- Drug development use cases (for the most part) require:
  - Aggregated, high quality, complete, longitudinal datasets
  - Reproducibility and provenance
  - Patient-level data linkage
  - Endpoints/outcomes
  - Study objectives and analysis plans
  - Careful cohort selection
- Example applications of RWE in oncology:
  - Confirming benefit for new indications → label expansion
  - Optimizing clinical use → label revisions
  - Post marketing requirements
  - Safety monitoring

Example

- Case study: traztuzumab emtansine (Kadcyla)

Case study: Trastuzumab emtansine (Kadcyla)

RWE along the continuum



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RWE Case Study: Trastuzumab emtansine usage in low-LVEF patients

Context

- Anti-HER2 agents have known cardiotoxicity
- Major Kadcyla clinical studies excluded patients at risk for cardiotoxicity:
  - EF <50% or h/o CHF, serious cardiac arrhythmia requiring treatment, MI or unstable angina w/i 6 mo

The NEW ENGLAND JOURNAL of MEDICINE

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Trastuzumab Emtansine for HER2-Positive Advanced Breast Cancer

Sunil Verma, M.D., David Miles, M.D., Luca Gianni, M.D., Ian E. Krop, M.D., Ph.D., Manfred Welslau, M.D., José Baselga, M.D., Ph.D., Mark Pegram, M.D., Do-Youn Oh, M.D., Ph.D., Véronique Diéras, M.D., Ellie Guardino, M.D., Ph.D., Liang Fang, Ph.D., Michael W. Lu, Pharm.D., Steven Olsen, M.D., Ph.D., and Kim Blackwell, M.D., for the EMILIA Study Group

tients with measurable disease (according to modified RECIST) and those with nonmeasurable disease were included. Other eligibility criteria were a left ventricular ejection fraction of 50% or more (determined by echocardiography or multiple-gated acquisition [MUGA] scanning) and an Eastern Cooperative Oncology Group performance status of 0 (asymptomatic) or 1 (restricted in strenuous activity but ambulatory and able to do light work).

Major exclusion criteria were prior treatment with T-DM1, lapatinib, or capecitabine; peripheral neuropathy of grade 3 or higher (according to National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE], version 3.0)[14]; symptomatic central nervous system (CNS) metastases or treatment for these metastases within 2 months before randomization; a history of symptomatic congestive heart failure or serious cardiac arrhythmia requiring treatment; and a history of myocardial infarction or unstable angina within 6 months before randomization.

RWE Case Study: Trastuzumab emtansine usage in low-LVEF patients

Context

- Anti-HER2 agents have known cardiotoxicity
- Major Kadcyla clinical studies excluded patients at risk for cardiotoxicity
- 1 patient in the EMILIA study developed grade 3 cardiotoxicity on Kadcyla
- FDA issued a boxed warning

In the majority of patients, a left ventricular ejection fraction of 45% or more was maintained during the study treatment (in 97.1% of patients in the T-DM1 group and 93.0% of patients in the lapatinib–capecitabine group). Three patients in each group had a decrease from baseline to less than 40%. Of 481 patients in the T-DM1 group and 445 in the lapatinib–capecitabine group who could be evaluated, 8 patients (1.7%) and 7 patients (1.6%), respectively, had an ejection fraction that was less than 50% and at least 15 percentage points below the baseline value. To date, grade 3 left ventricular systolic dysfunction has developed in 1 patient in the T-DM1 group and in no patients in the lapatinib–capecitabine group.

- Kadcyla not well studied when EF≤50%
- If EF drops ≤40% (or 10% below pretreatment), repeat LVEF assessment and if persists d/c Rx

Left Ventricular Dysfunction (Boxed WARNING)

Patients treated with KADCYLA are at increased risk of developing left ventricular dysfunction (LVD). A decrease of left ventricular ejection fraction (LVEF) to <40% has been observed in patients treated with KADCYLA. In EMILIA, left ventricular dysfunction occurred in 1.8% of patients in the KADCYLA-treated group and 3.3% of patients in the comparator group.

Assess LVEF prior to initiation of KADCYLA and at regular intervals (eg, every 3 months) during treatment. Treatment with KADCYLA has not been studied in patients with LVEF <50% prior to treatment. If, at routine monitoring, LVEF is <40%, or is 40% to 45% with a 10% or greater absolute decrease below the pretreatment value, withhold KADCYLA and repeat LVEF assessment within approximately 3 weeks. Permanently discontinue KADCYLA if the LVEF has not improved or has declined further.

RWE Case Study: Trastuzumab emtansine usage in low-LVEF patients

Context

- Anti-HER2 agents have known cardiotoxicity
- Major Kadcyla clinical studies excluded patients at risk for cardiotoxicity
- 1 patient in the EMILIA study developed grade 3 cardiotoxicity on Kadcyla
- FDA issued a boxed warning

- Meanwhile, clinically, some patients with EF ≤50% still receive Kadcyla
  - Since patients with LVEF ≤50% do receive Kadcyla outside of the clinical trial setting, *real world evidence offers an opportunity to understand the experience of Kadcyla usage in these patients*

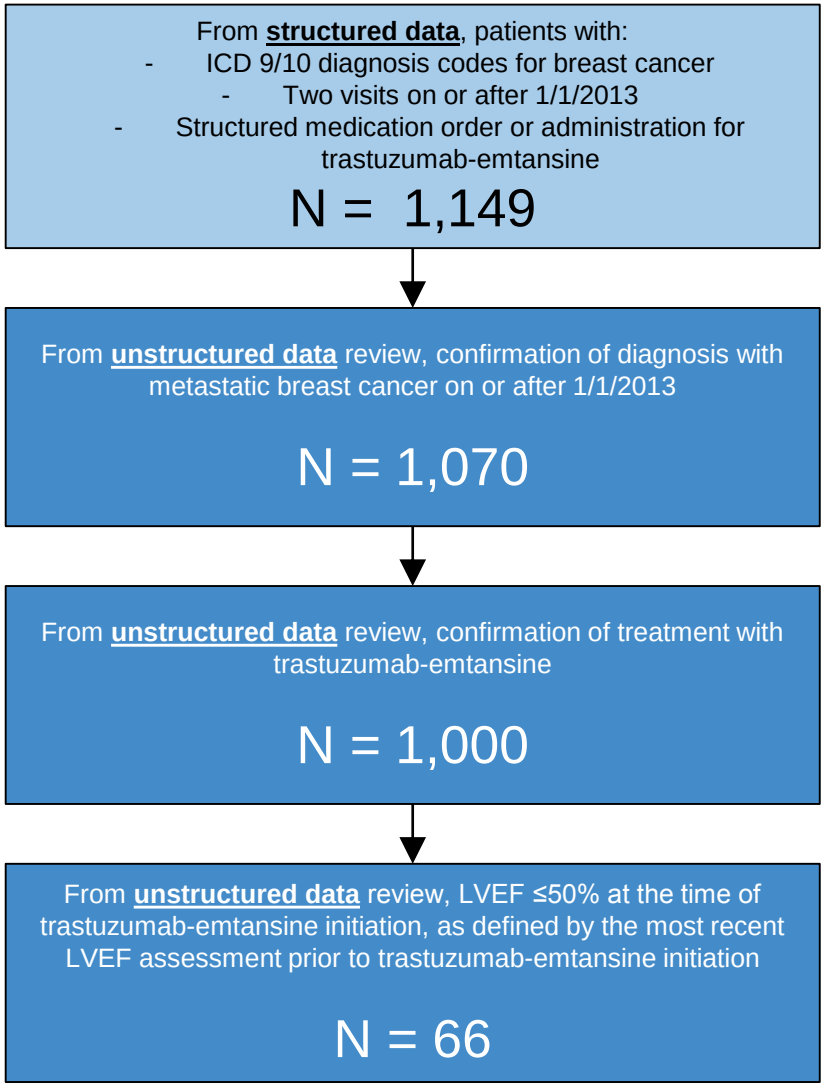
RWE Case Study: Trastuzumab emtansine usage in low-LVEF patients

Study Design

- Objectives:
  - To assess the rate and severity of cardiac events in patients with metastatic breast cancer treated with trastuzumab emtansine who have a LVEF ≤50% at treatment initiation
  - Characterize patient population
  - Other outcomes (OS, PFS, resource utilization)

- Eligibility criteria:
  - Diagnosis of breast cancer (ICD-9 174.x or ICD-10 C50.x)
  - At least two visits in the Flatiron Health database on or after 1/1/2013
  - Pathology consistent with breast cancer
  - Evidence of stage IV or recurrent metastatic breast cancer with a metastatic diagnosis date on or after 1/1/2013
  - Treatment with trastuzumab-emtansine (structured med admin data and confirmed via unstructured data review)
  - LVEF ≤50% at the time of initiation of treatment with trastuzumab-emtansine

RWE Case Study: Cohort selection



- Maintain a growing curated dataset in mBC
- At time of cohort selection >8,000 cases
- Allowed for the identification of >60 patients who had LVEF ≤50%

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RWE Case Study: Data quality control

INTERPRETATION SUMMARY
The global left ventricular systolic function is low normal.
LV EF is estimated at 50%
There is no evidence for regional wall motion abnormality.

Indication: Cardiomyopathy, assess LV function.

Left Ventricle Ejection Fraction: 46.9 %

Important task was to assess data quality of cardiac information

- Complex information in chart
- Duplicate abstraction
- Clinical adjudication
- Claims data comparison

Final Conclusions:

1. Sinus rhythm.
2. This was a technically adequate study.
3. This was a limited exam for LV function assessment.
4. The left ventricular size is normal.
5. Left ventricular wall thickness is normal.
6. Overall left ventricular systolic function is mildly impaired with, an EF between 45 - 50 %. Stable from 2014. Okay for Kadcyla
7. Compared to prior study of , no change.

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RWE Case Study: Baseline characteristics (N=66)

Age	Median = 62 years	Range 54-70
	65 or over = 39%	
Female	98.5%	
White race	58%	
Stage at diagnosis	I/II/III = 52%	
	IV = 27%	
	Not documented = 21%	
ER/PR	Positive = 65%	
Time from initial diagnosis to Kadcyla initiation	Median = 5.1 years	Range 2.7-11.5
Time from metastatic diagnosis to Kadcyla initiation	Median = 2.3 years	Range 1.2-4.1
Median follow up from index date	Median = 0.8 years	Range 0.5-1.5

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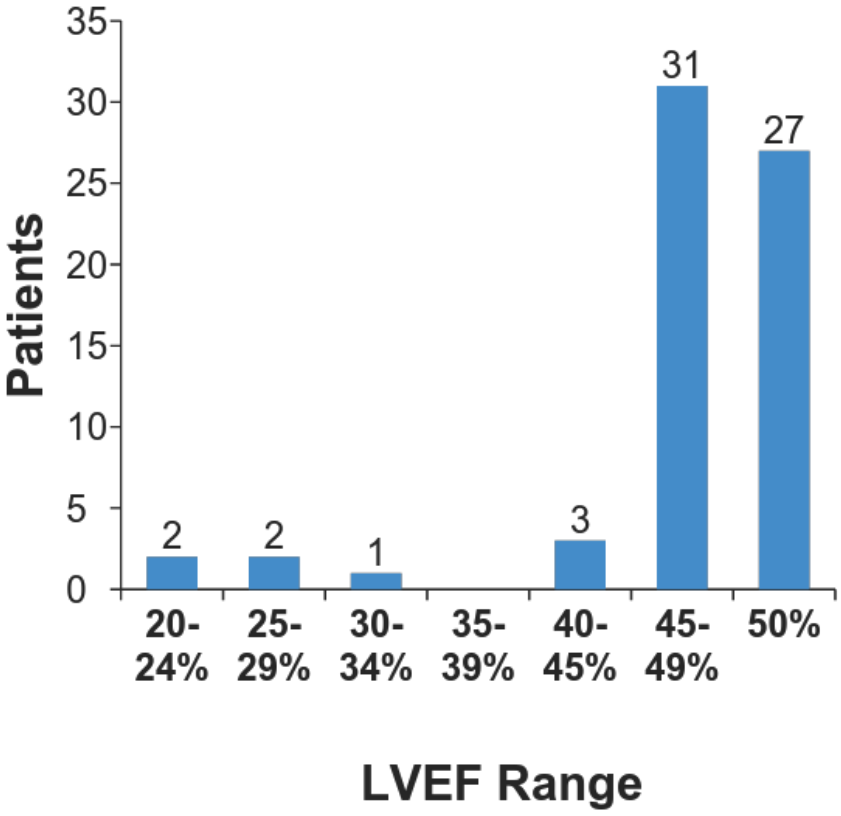
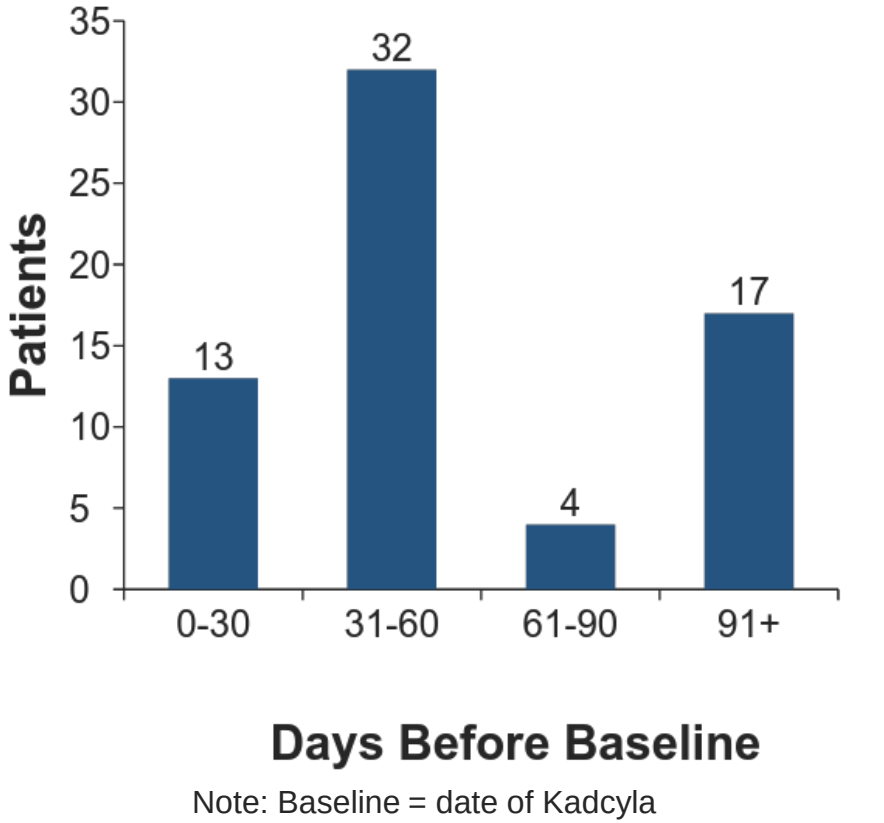
RWE Case Study: LVEF Data (N=66)

Breakdown By LVEF Value



Breakdown By Time Before Baseline



Note: Baseline = date of Kadcyla initiation

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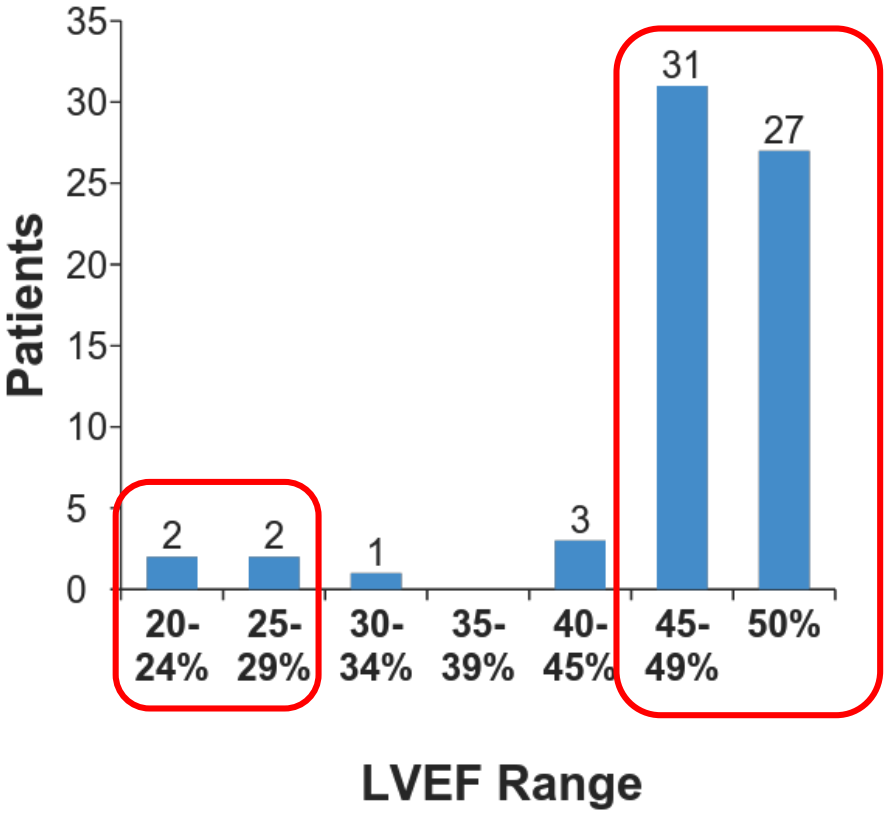
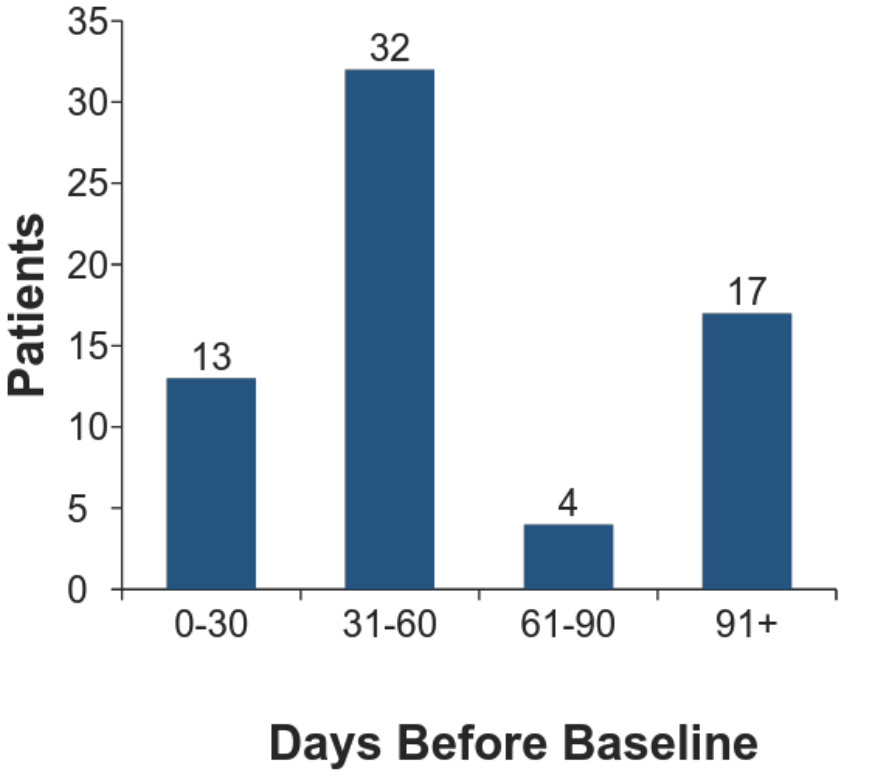


Breakdown By Time Before Baseline



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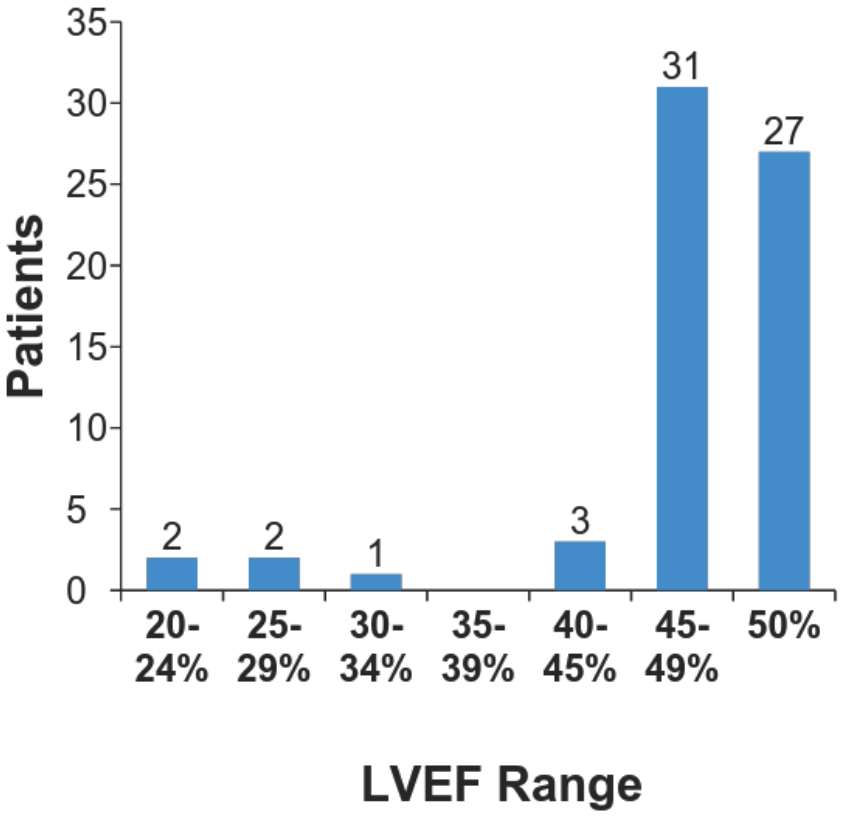

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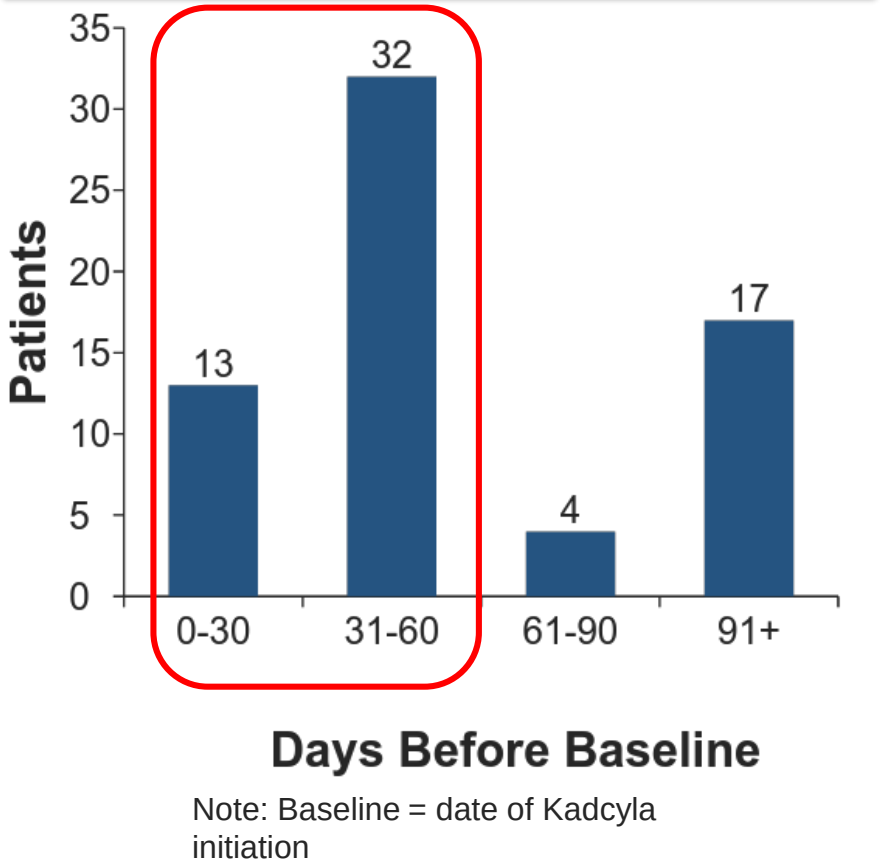

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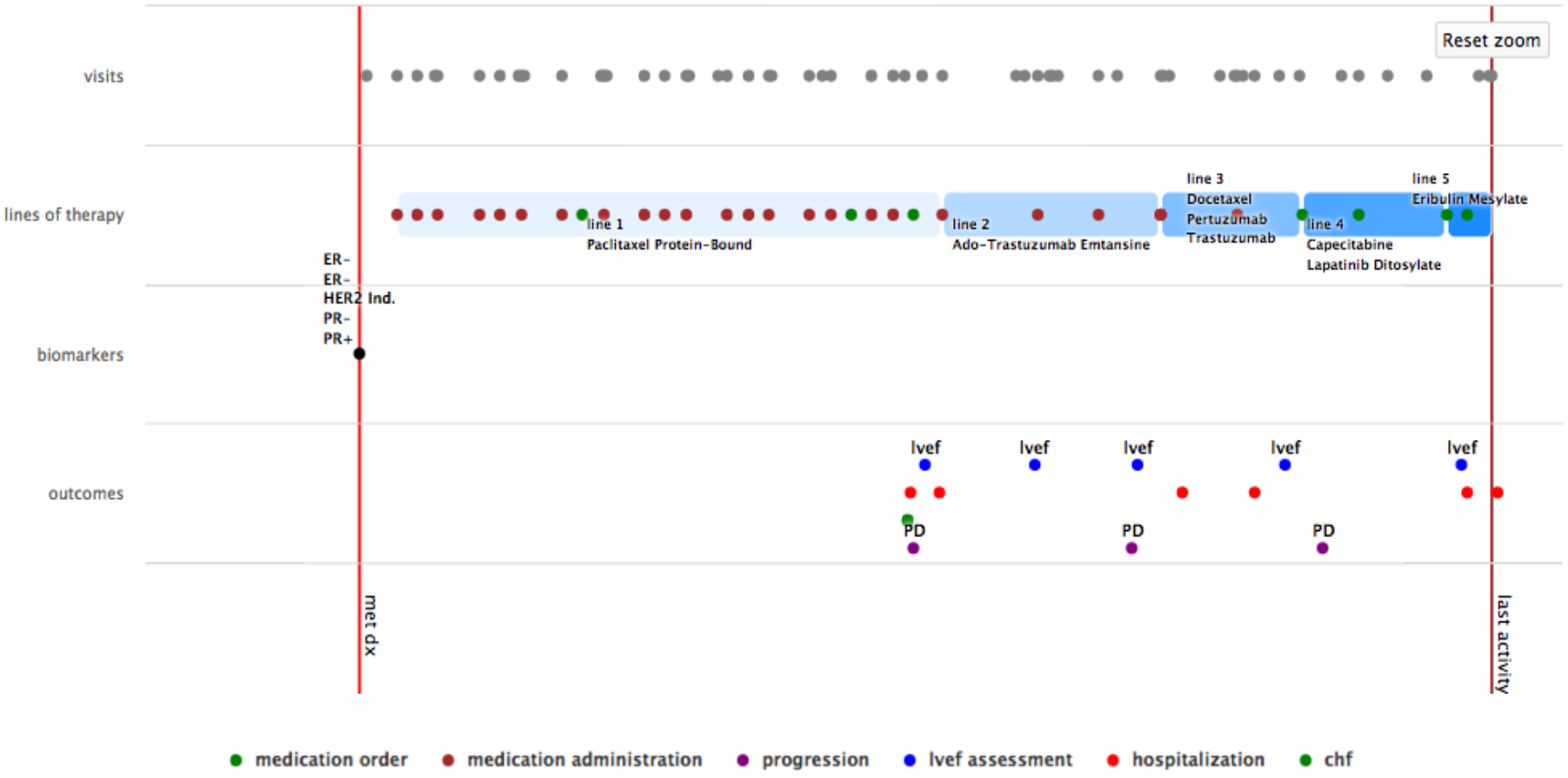
RWE Case Study: Patient Journey



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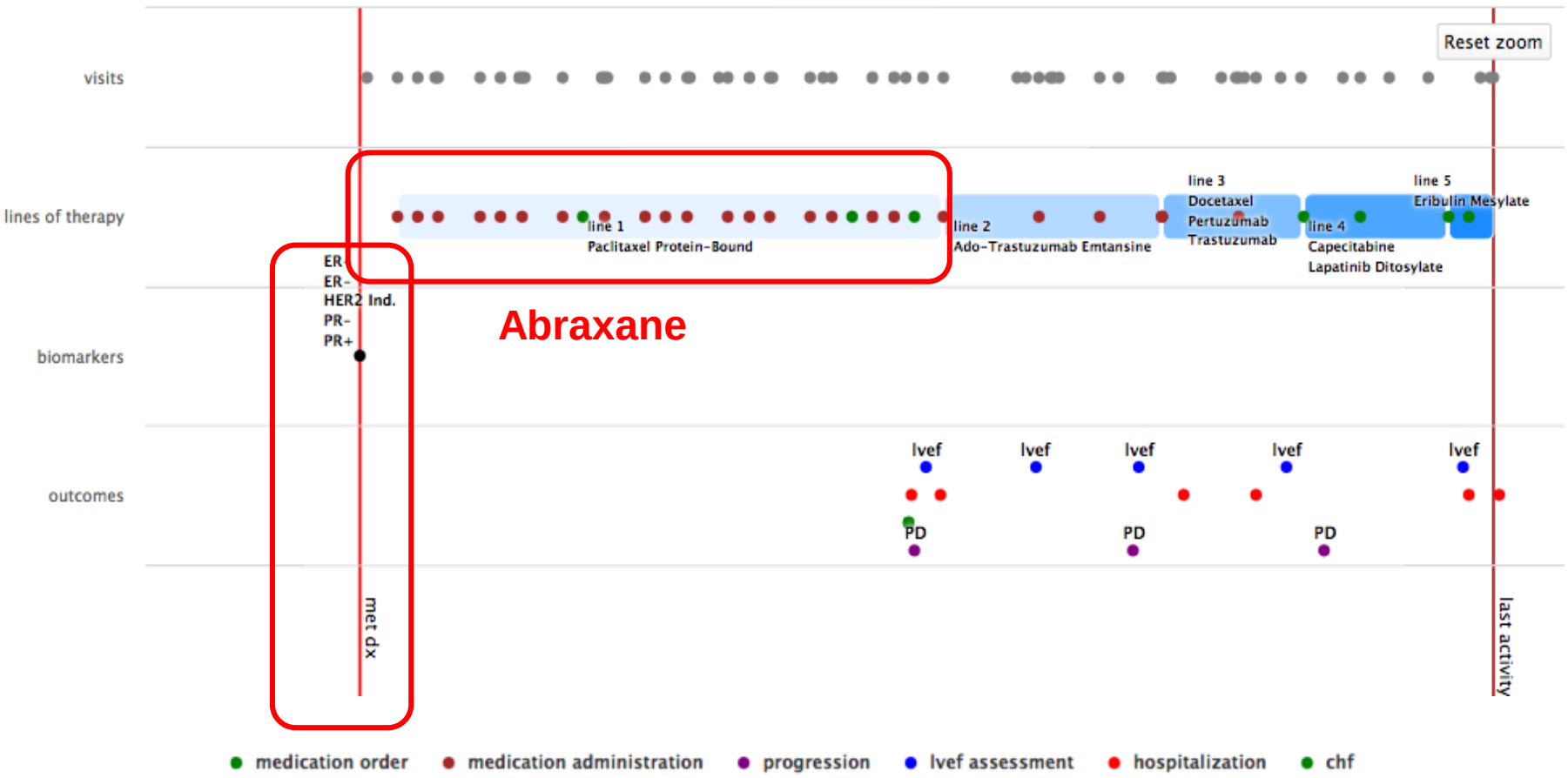
RWE Case Study: Patient Journey



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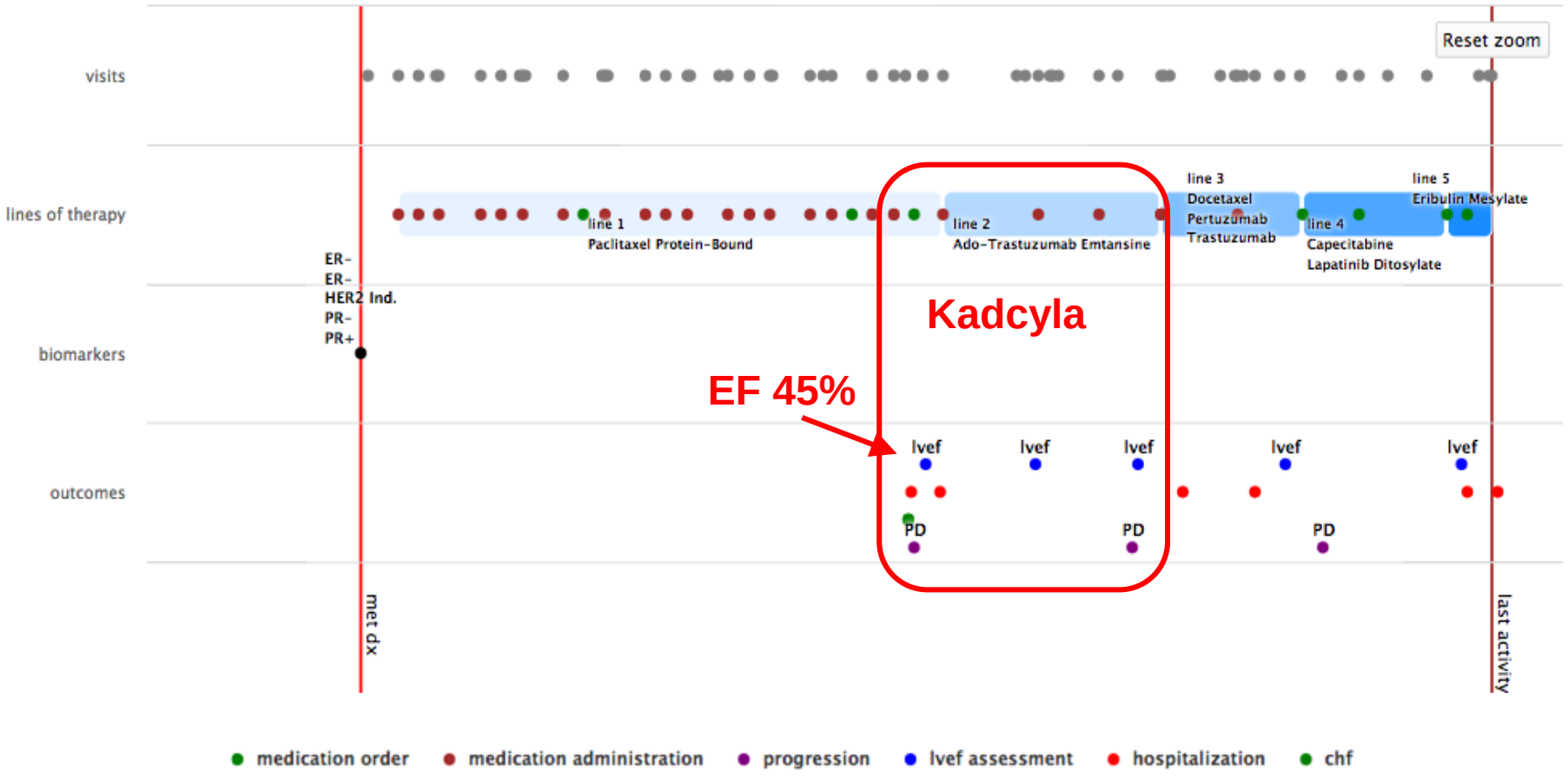
RWE Case Study: Patient Journey



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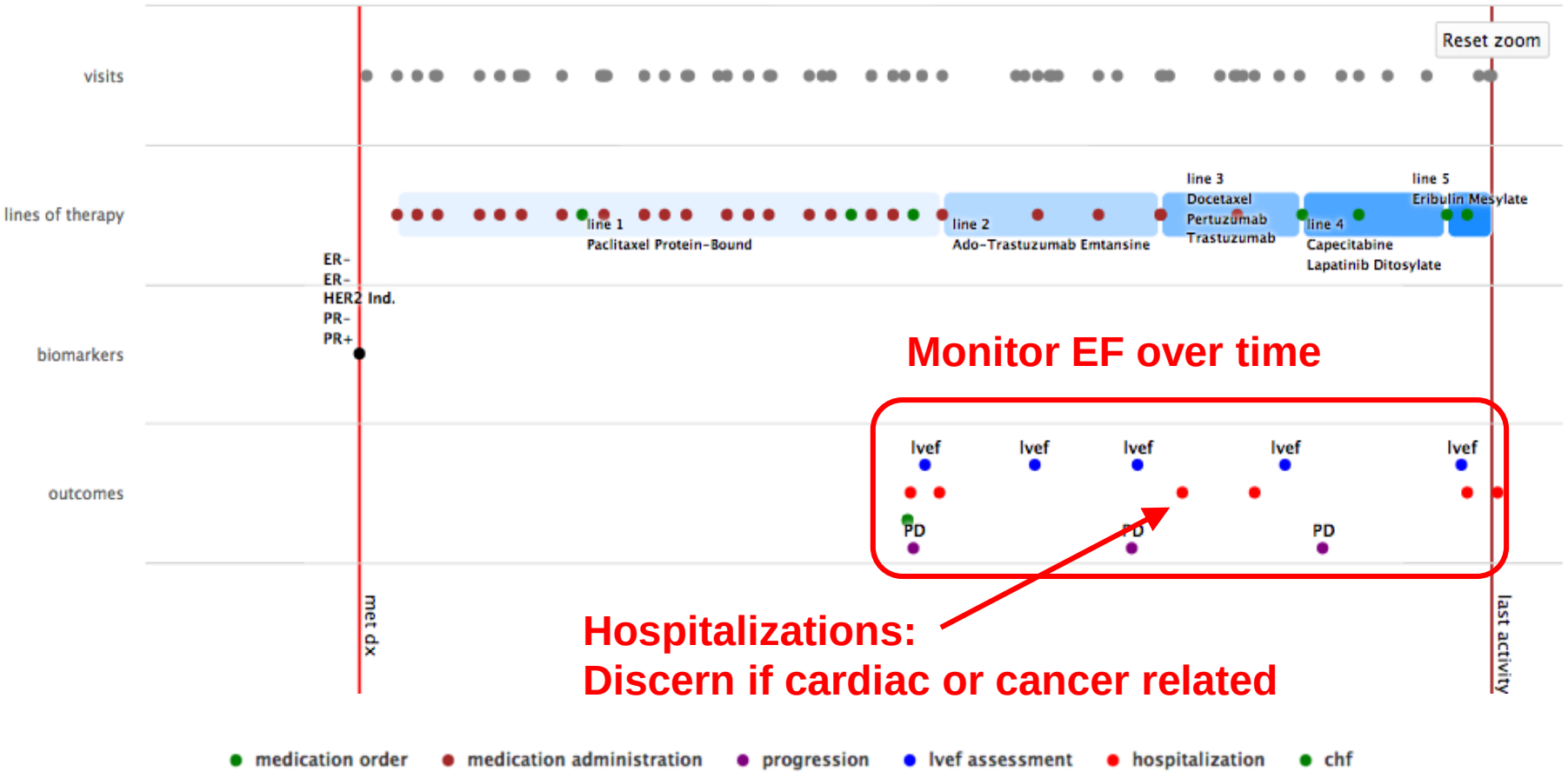

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Policy recommendations

Policy recommendations

- Clarify the role of RWE in oncology drug development
- FDA guidance on RWE
  - Drug development scenarios where most applicable
  - Data quality requirements
  - Data management and dataset production requirements
    - Retrospective
    - Prospective studies / pragmatic trials
  - Optimal analytic approaches
- Clarify how RWE will be represented in the label
- Develop an approach to real-world endpoints using a multi-stakeholder transparent process