June 15, 2018

Research at scale—exploring what is possible with high-quality real-world data.

Examples from Flatiron Health

Amy Abernethy, MD, PhD
Chief Medical Officer/Chief Scientific Officer & SVP Oncology
Flatiron Health

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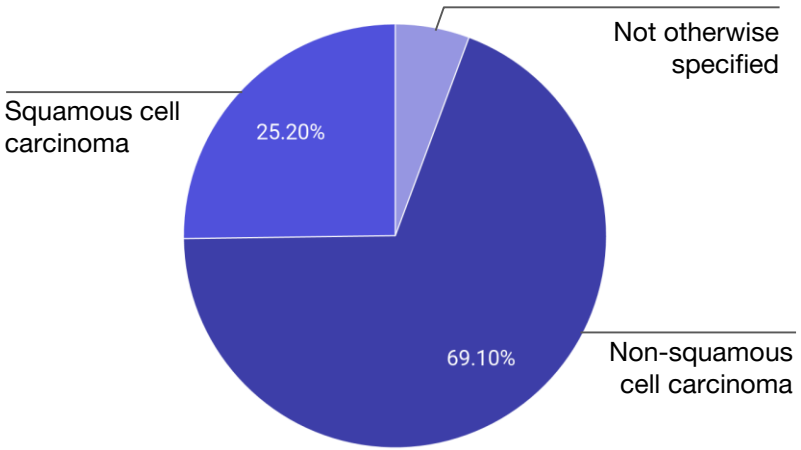
Cohort Demographics

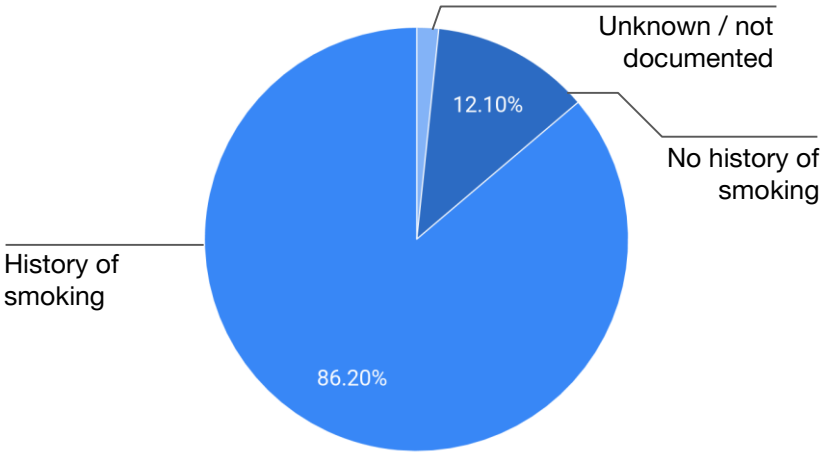
As of May 2018

Patients in cohort: 48,457 (Community: 44,422 | Academic: 4,035)

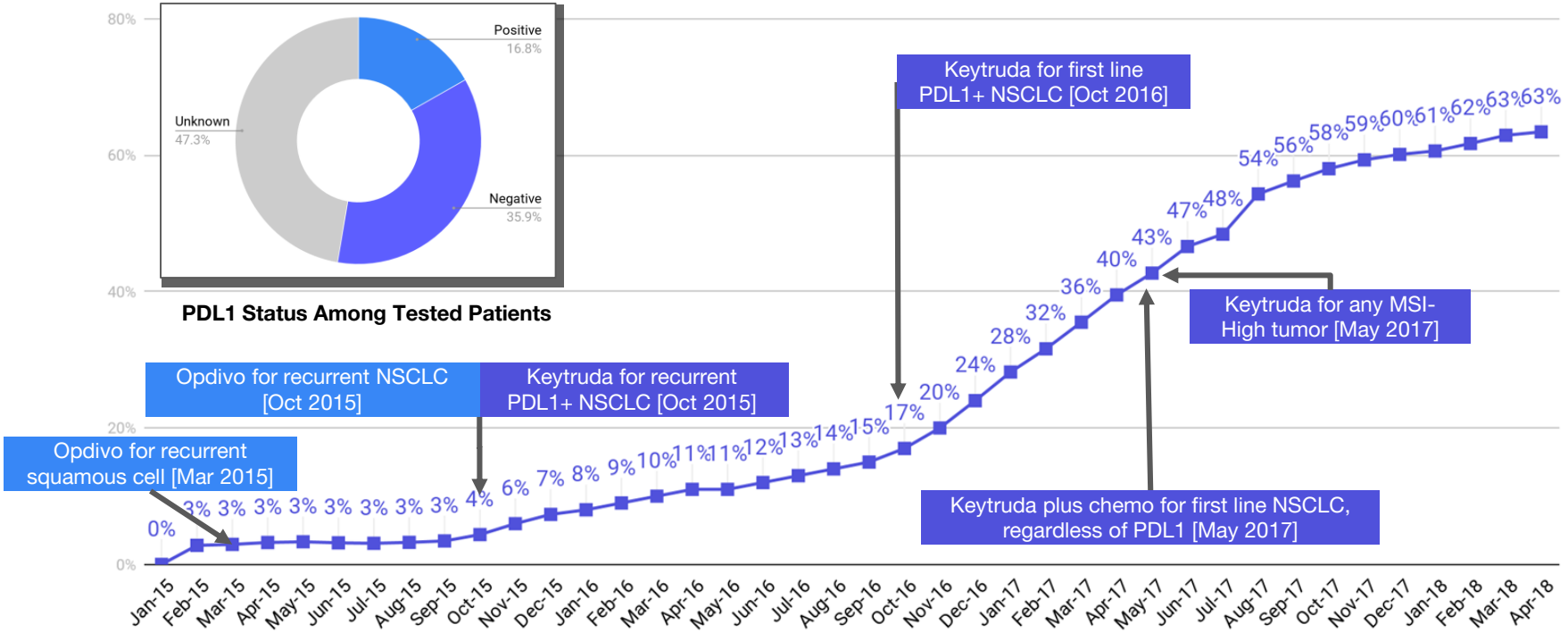
Histology



Smoking Status



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



PDL1 Testing Rate Among Actively Treated Patients

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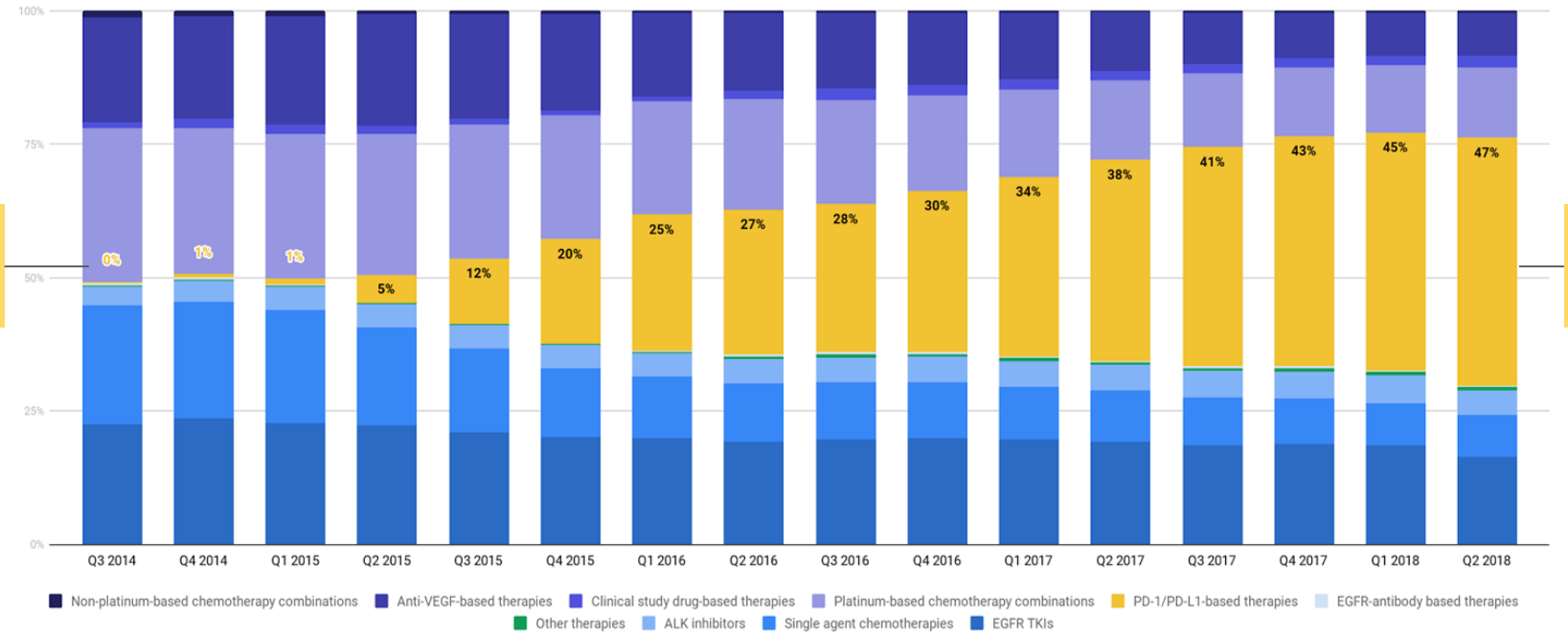
Patient Share by Therapy Class — PD1/PDL1

All Lines

0%
Q3 2014

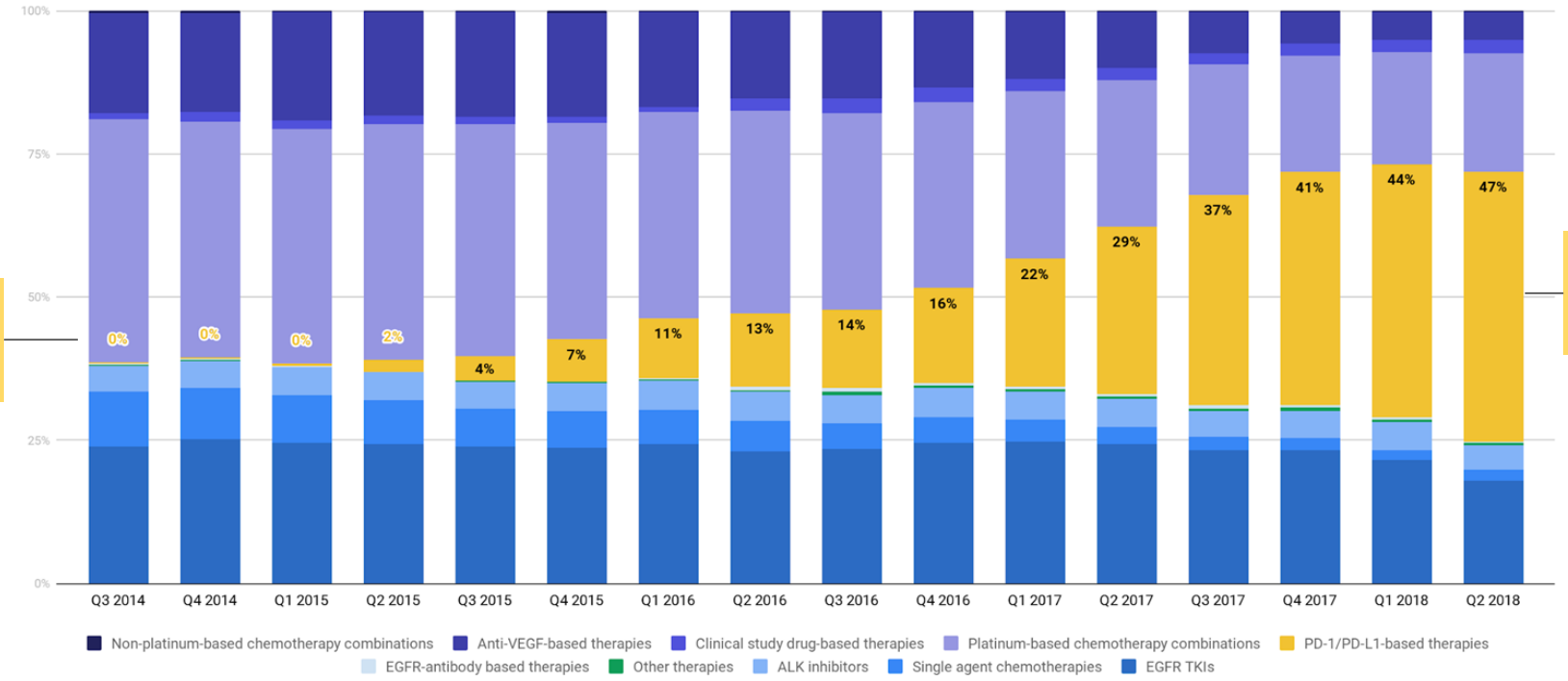


47%
Q2 2018

Patient Share by Therapy Class — PD1/PDL1

1st Line

0%
Q3 2014

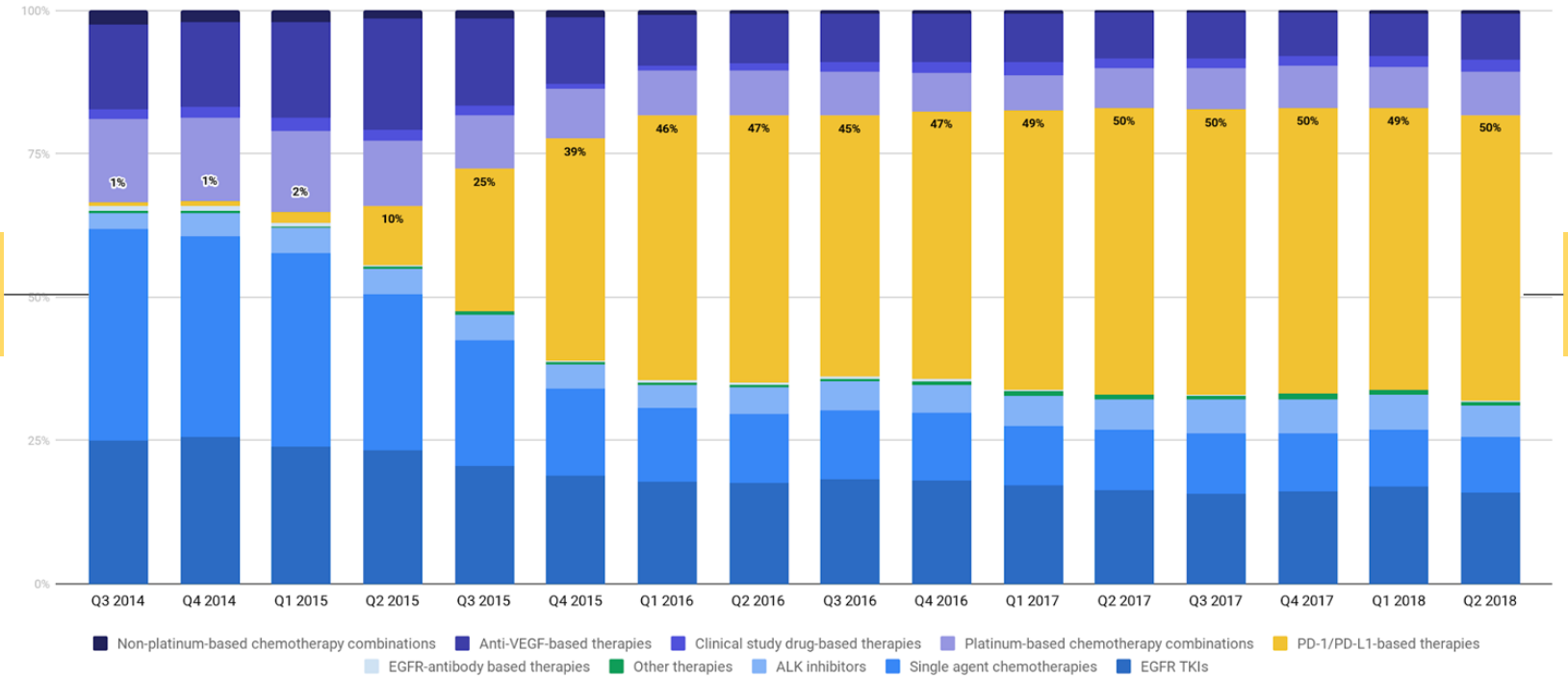


47%
Q2 2018

Patient Share by Therapy Class — PD1/PDL1

2nd or 3rd Line+

1%
Q3 2014



50%
Q2 2018

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NBC NEWS

Cancer Drug Keytruda Keeps Some Patients Alive For 3 Years

by MAGGIE FOX

HEALTH > CANCER

HEALTH

MAY 18 2016, 5:43 PM ET

91 years old!

▶ Cancer Drug Used by Pres. Carter Shows Signs of Being a Breakthrough 2:22

▶ Melanoma Drug Shows Promise 1:35

The drugs must be infused and they are pricey. Keytruda costs about $12,500 a month, or $150,000 a year.

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Published Ahead of Print on January 9, 2018 as 10.1634/theoncologist.2017-0353.

The Oncologist®

Lung Cancer

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

Sean Khozin,[a] Amy P. Abernethy,[b] Nathan C. Nussbaum,[b] Jizu Zhi,[a] Melissa D. Curtis,[b] Melisa Tucker,[b] Shannon E. Lee,[b] David E. Light,[b] Anala Gossai,[b] Rachael A. Sorg,[b] Aracelis Z. Torres,[b] Payal Patel,[b] Gideon Michael Blumenthal,[a] Richard Pazdur[a]

[a]U.S. Food and Drug Administration, Silver Spring, Maryland, USA; [b]Flatiron Health, New York, New York, USA

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Non-small cell lung cancer • Nivolumab • Pembrolizumab • Demography • Electronic health records

ePub
Jan 9, 2018

FDA

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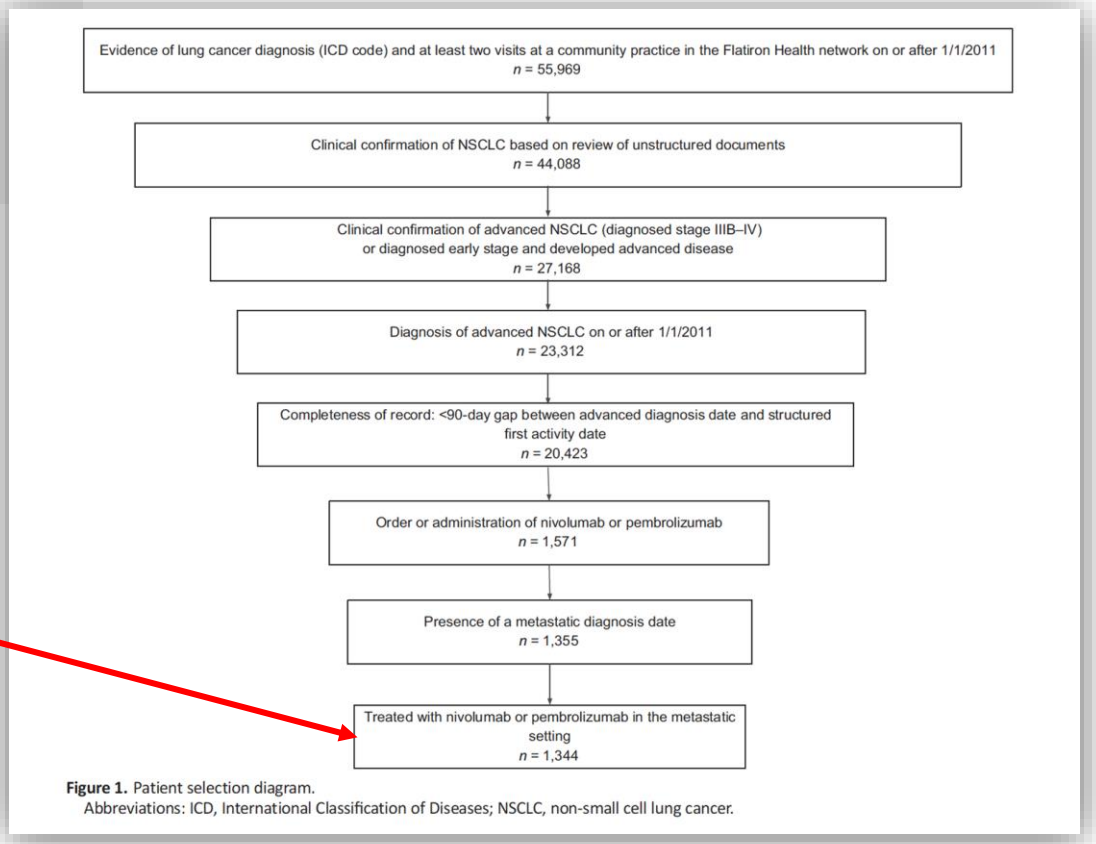

Figure 1. Patient selection diagram.
Abbreviations: ICD, International Classification of Diseases; NSCLC, non-small cell lung cancer.

1344 patients treated with PD1 inhibitors in the first year after approval

1 year follow up

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Table 1. Characteristics of a cohort of 1,344 metastatic NSCLC patients who received nivolumab or pembr
metastatic setting in U.S. community practices

Variable	*n* (%)
Demographics	
Age at PD-1 initiation, years, median (IQR)[a]	69.0 (61.0–75.0)
Age categories at PD-1 initiation[a]	
<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%

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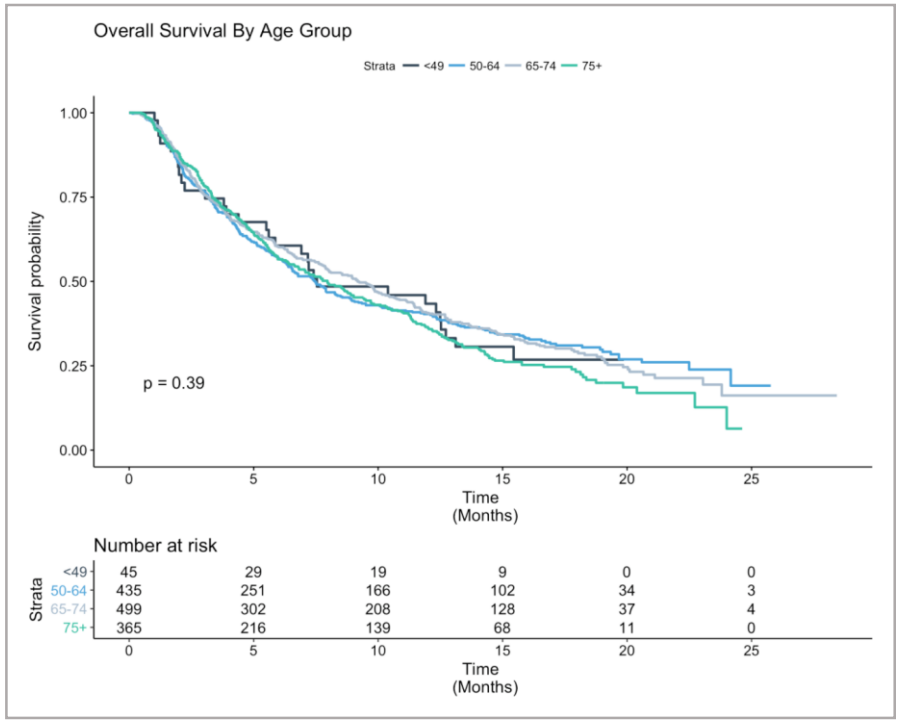
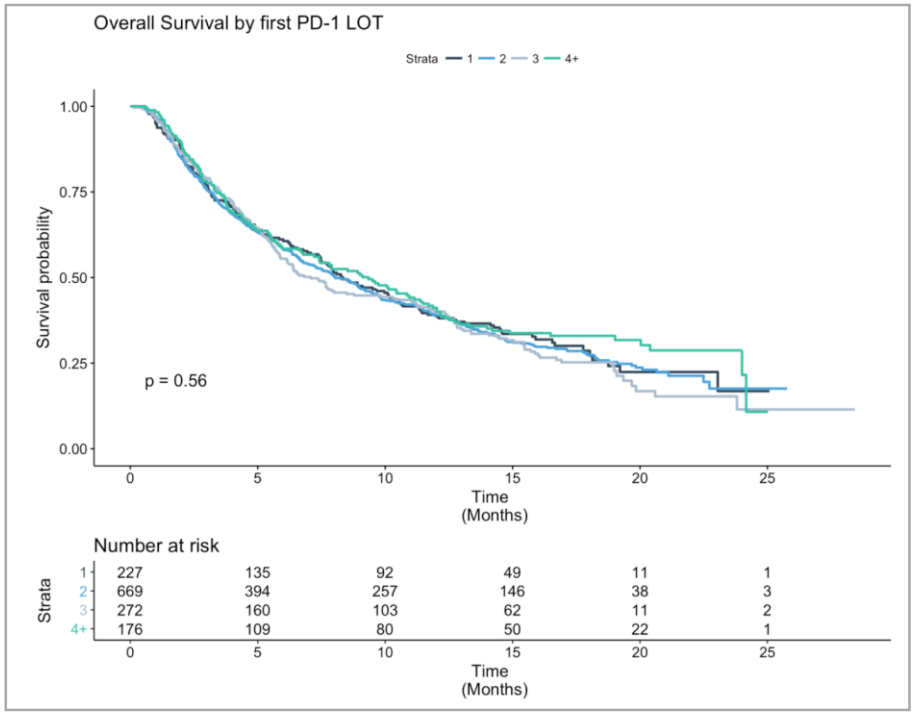
Median age in clinical trials = 62; <8% were 75 or over

No difference in overall survival by age group or line of therapy





Age

Line

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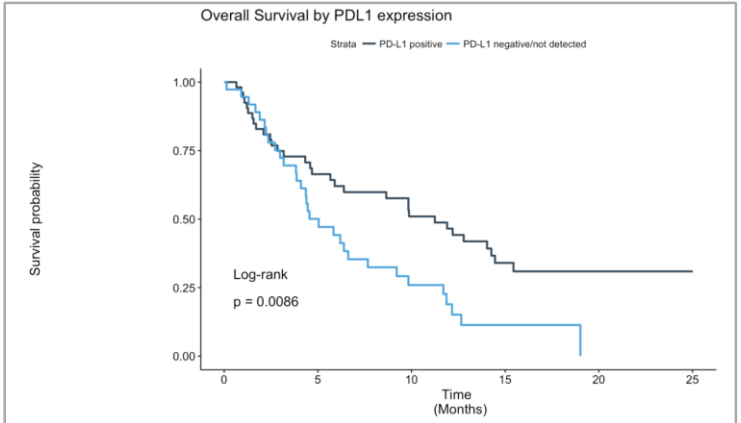
PDL1 expression predicts survival



Strata	# of Patients	# of Events	Median Survival	Lower 95th% CI	Upper 95% CI
PD-L1 positive	55	32	11.25	5.9	15.44
PD-L1 negative/not detected	37	31	5.05	4.1	9.21

Survival Summary: *# of observed events and the Median Survival time*

Strata	1-Year Survival Probability	Lower 95% CI	Upper 95% CI
PD-L1 positive	0.47	0.34	0.63
PD-L1 negative/not detected	0.19	0.09	0.39

Survival Summary: *Probability of surviving for 1-year*

Findings: Patients who were PD-1 positive had a significantly longer median survival time (by ~5 months) and higher 1-year survival probability than those who were PD-1 negative

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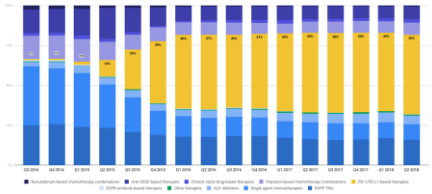
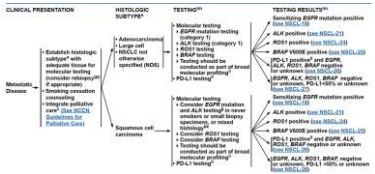
What does this story really tell us?

Speed, Biology, Evidence, Cost, Complexity, Impact

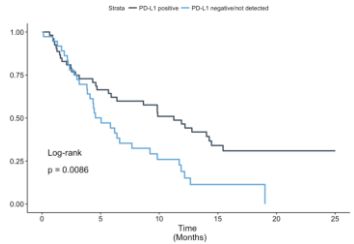
Exploding R&D Pipelines

Combination therapies





Segmenting patients & personalization



FDA

21st Century Cures

Rising cost & complexity of care

Value-based care
Better pricing models
Competition

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.”

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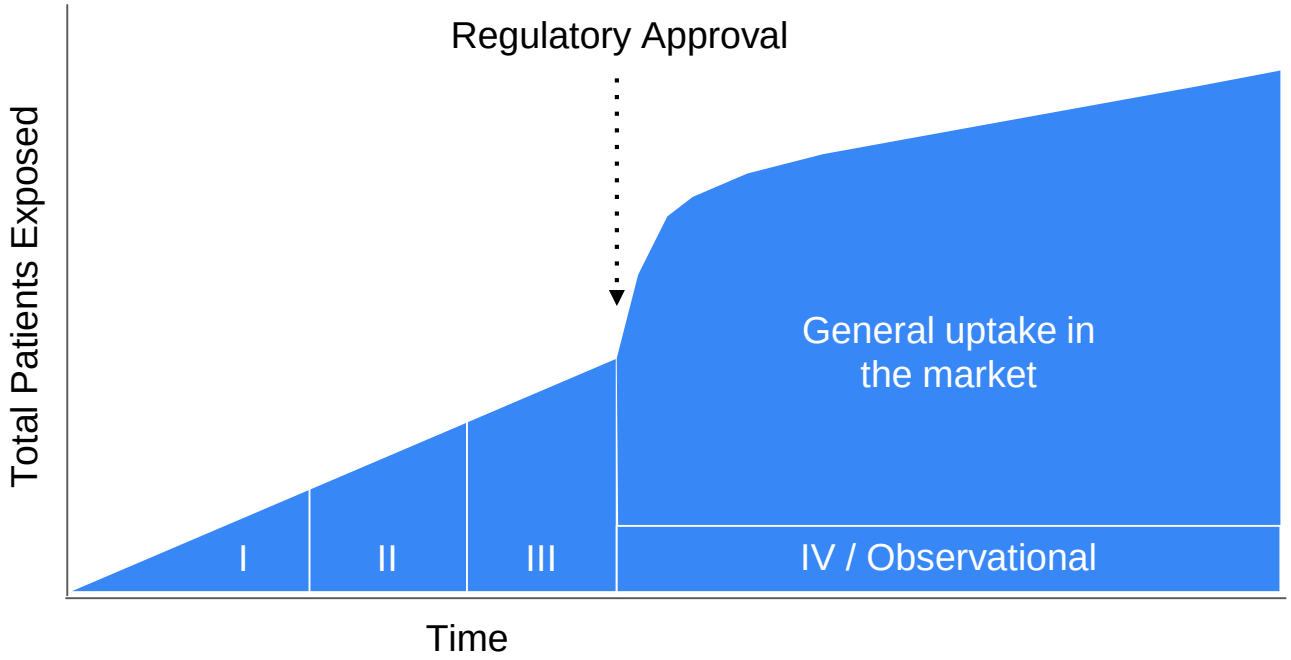
Current drug development paradigm



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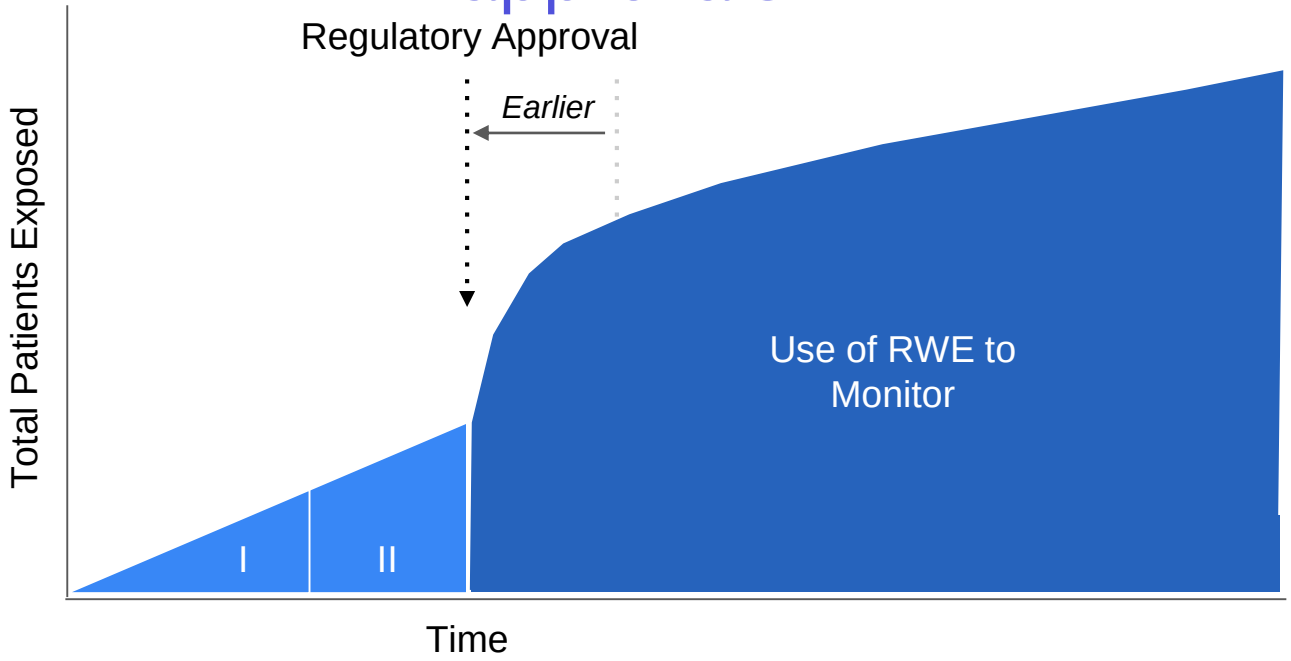
21st Century Cures - Shift towards earlier approvals



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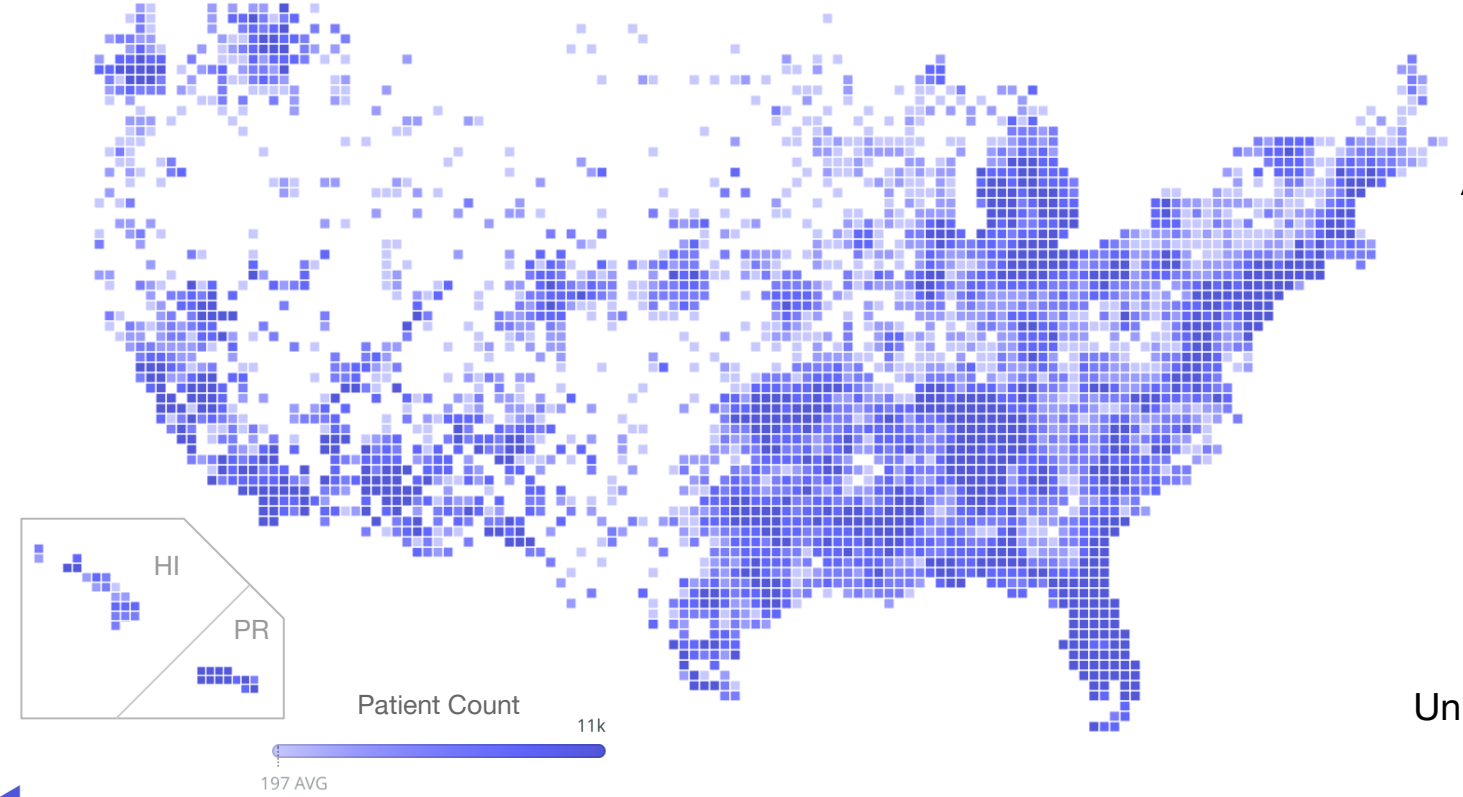
How are we addressing this evolving landscape at Flatiron?

The Flatiron Network



2M
Active Patients

2,500
Clinicians

265
Cancer Clinics

800
Unique Sites of Care

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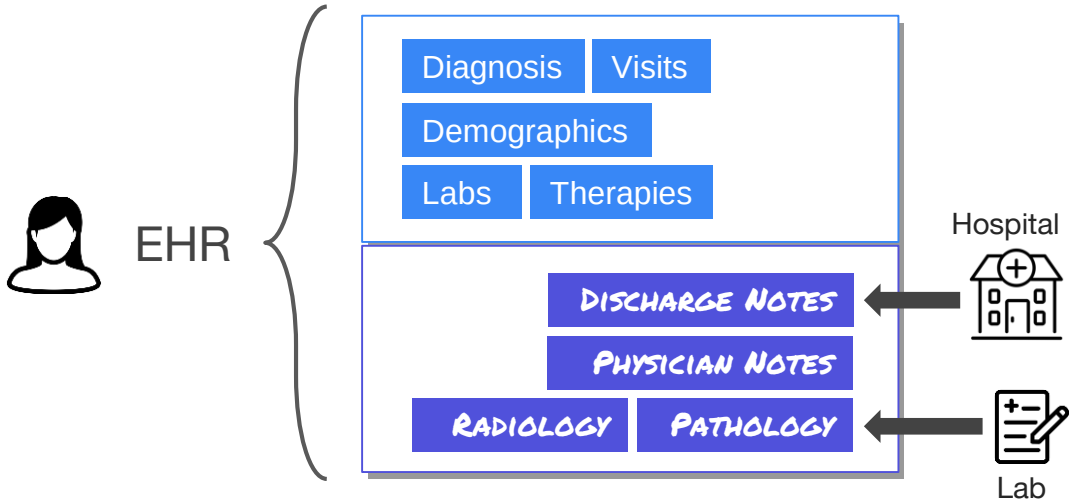
Millions of electronic health records in a single common dataset.



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

- 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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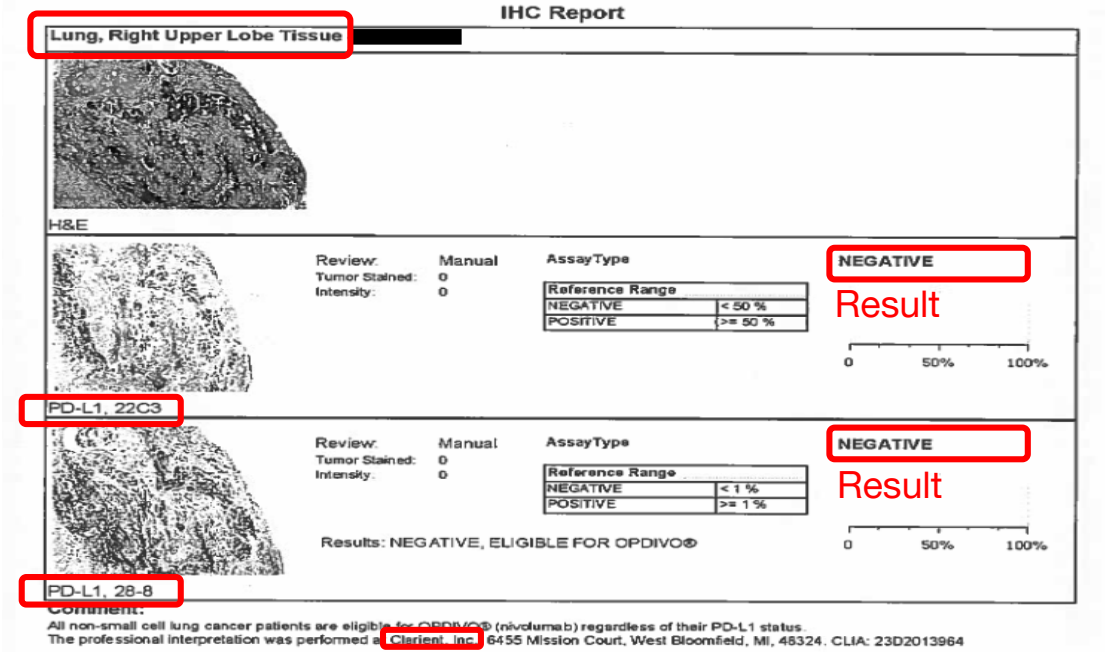
Standardize EHR Data to a Common Data Model

Curate unstructured data from the chart

Tissue Collection Site

Section of PD-L1 Report



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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Technology Enabled Abstraction

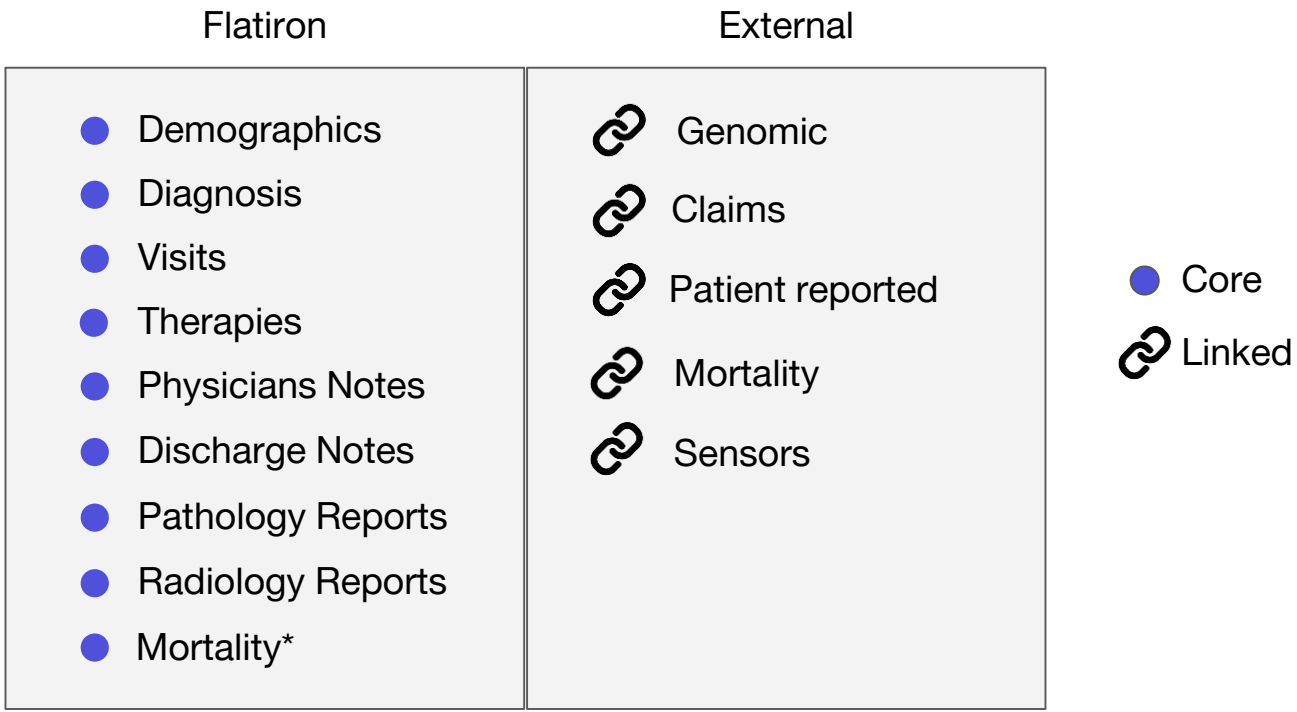
Expert abstractors

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

Flatiron Patient Manager

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

Expanded with linked datasets.



Resulting clinical data quality and completeness

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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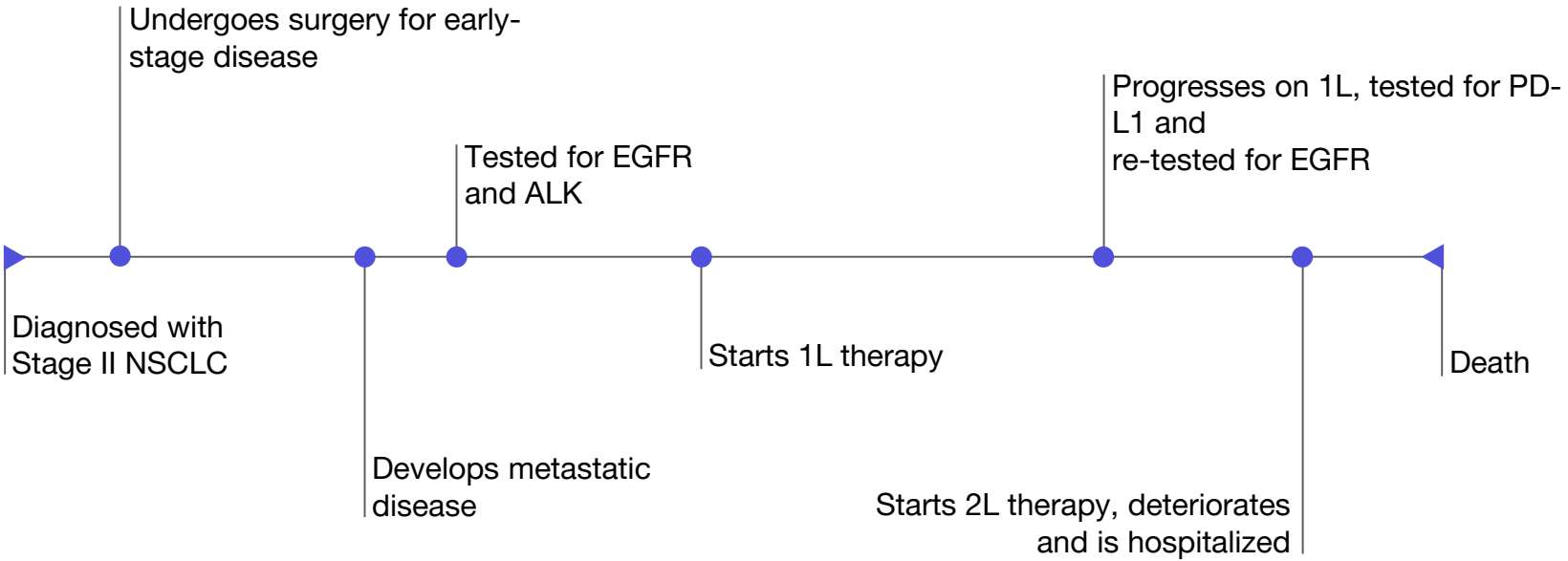
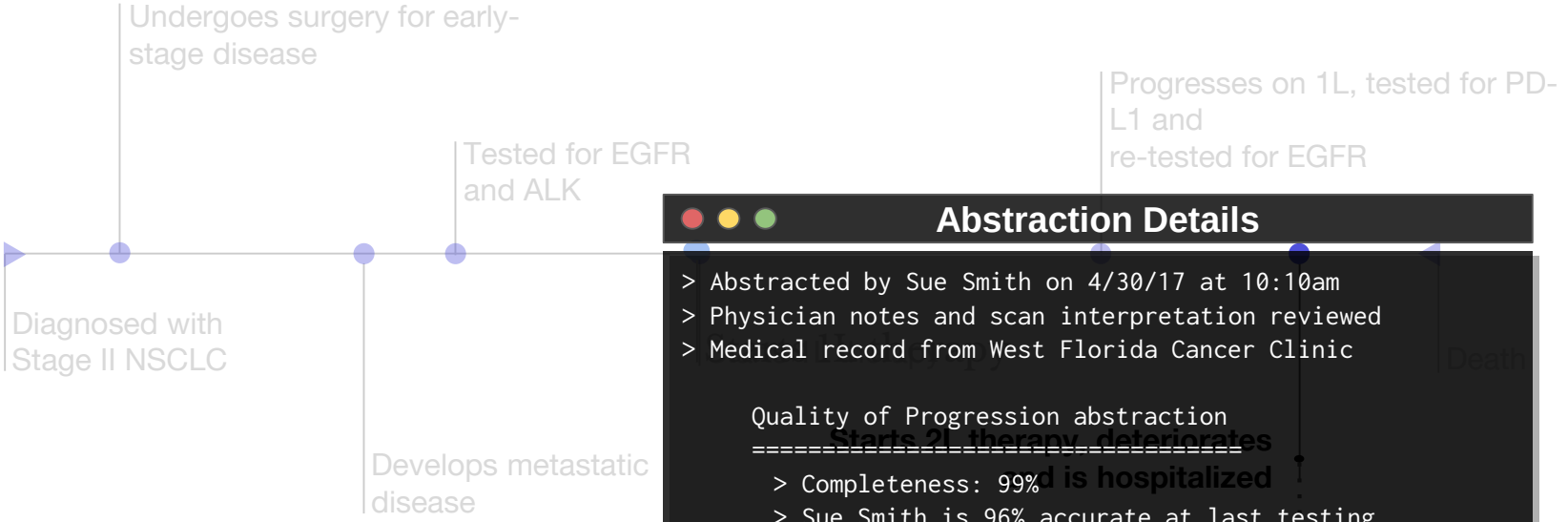


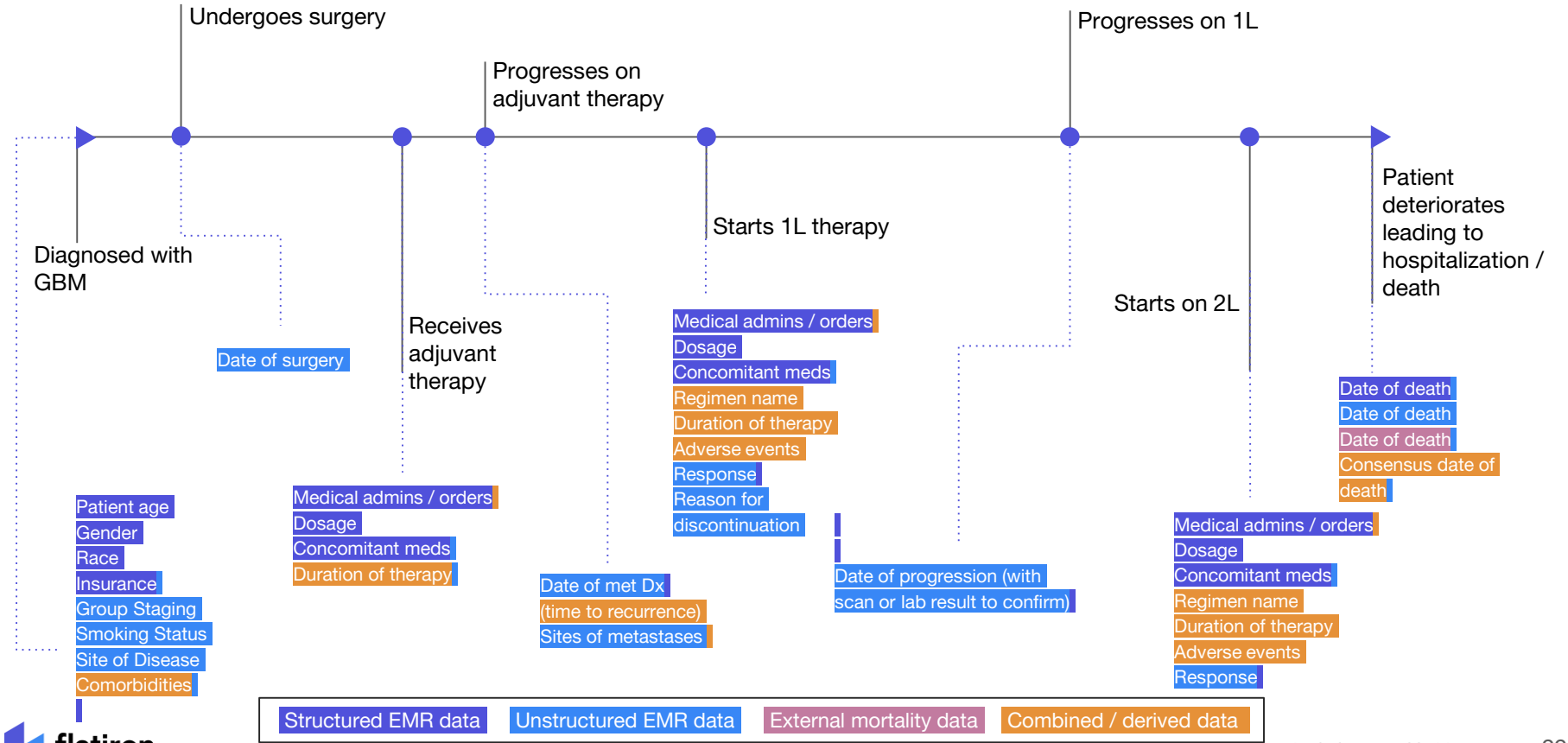
Documentation of source, quality and provenance.

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



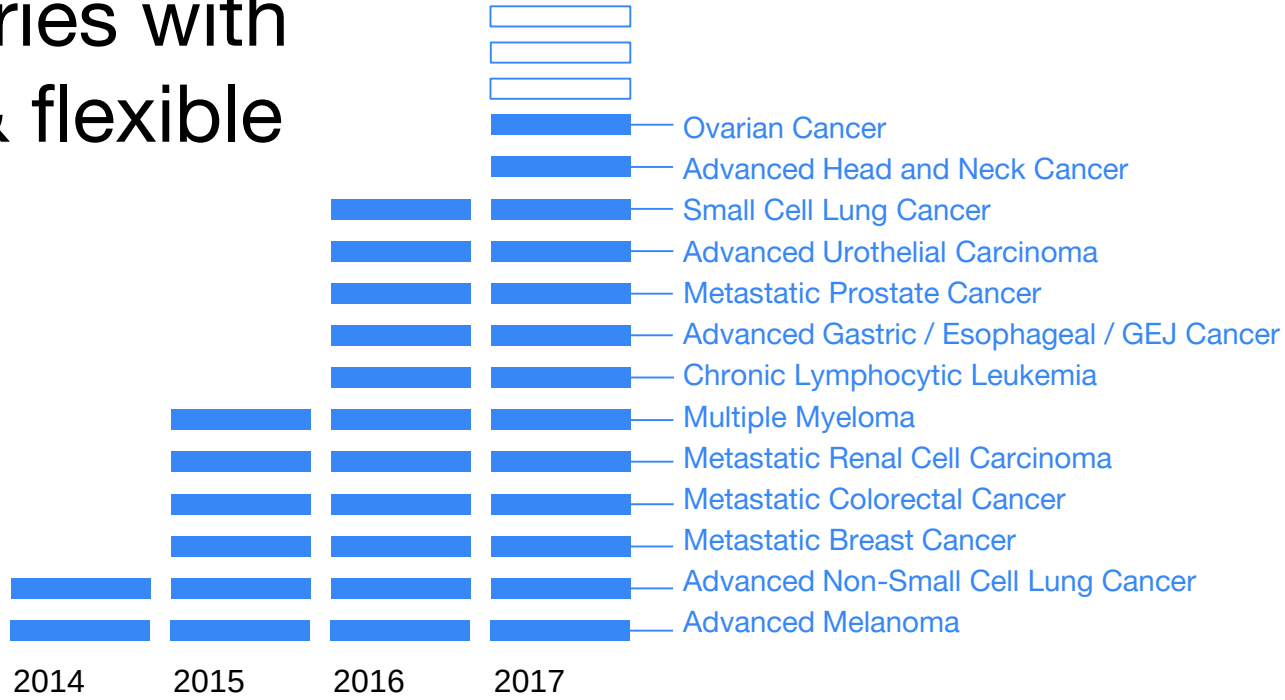
Patient	Stage at Dx	Biomarkers	2L Treatment	Progression	Date of Death
Jane Doe	II	EGFR-, ALK-, PD-L1-	nivolumab	2017-03-08	2017-04-12

A comprehensive view of the patient journey



*Relative timing not exact

Longitudinal cancer-specific registries with 30d recency & flexible data models



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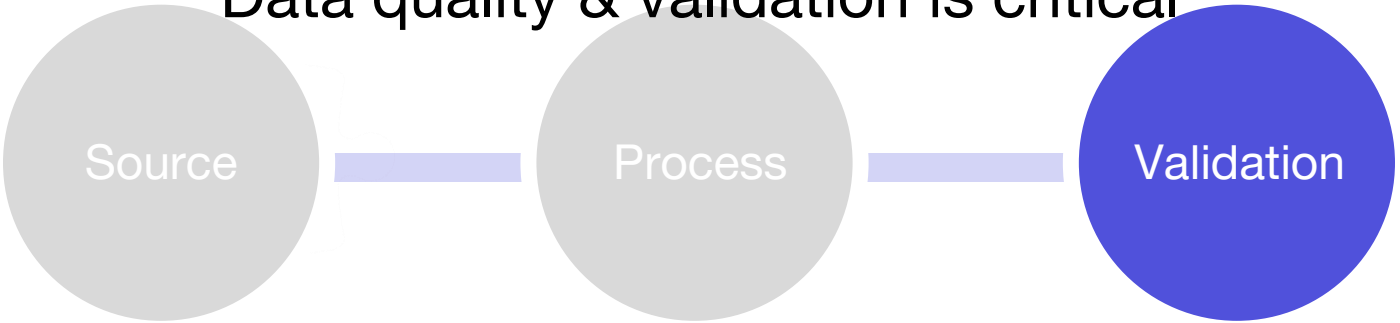
On the path to Regulatory Grade RWE

Data quality & validation is critical



FDA

FRIENDS of CANCER RESEARCH

NCCN

NIH

elements.[2]

RWE QUALITY

RWE is generated from high-quality data that are 1)
from relevant RWD sources, 2) cleaned, harmonized,
to fill in gaps, and 3) include endpoints. Quality
need to encompass the entire process to generate RWE,
a sources and processing to defining appropriate use
gure 1).

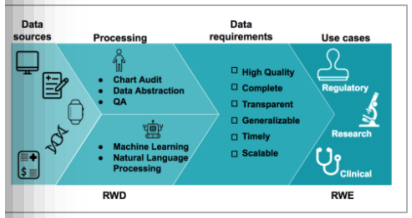


Figure 1. Open in figure viewer | Download Powerpoint slide

The journey from data to evidence. Real-world data (RWD) are data that are routinely collected in the form of electronic health records (EHRs), patient disease registries, wearables, genomic datasets, medical claims registries, and others. These data can be aggregated, linked, and processed to produce key conclusions in the form of real-world evidence (RWE). The proposed checklist can be used to assess if the quality of the RWD is regulatory-grade.

mal RWD source depends on the RWE hypothesis and
.[3] As the EHR is a contemporaneous (prospective or
ctive) account of the clinical narrative, it provides
al details and longitudinal follow-up for outcomes. The

Clinical Pharmacology & Therapeutics

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Development

Harnessing the Power of Real-World Evidence (RWE): A Checklist to Ensure Regulatory-Grade Data Quality

Rebecca A. Miksad, Amy P. Abernethy

First published: 6 December 2017 Full publication history

DOI: 10.1002/cpt.946 View/save citation

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Abstract

The role of real-world evidence (RWE) in regulatory, drug development, and healthcare decision-making is rapidly expanding. Recent advances have increased the complexity of cancer care and widened the gap between randomized clinical trial (RCT) results and the evidence needed for real-world clinical decisions.[1] Instead of remaining invisible, data from the >95% of cancer patients treated outside of clinical trials can help fill this void.

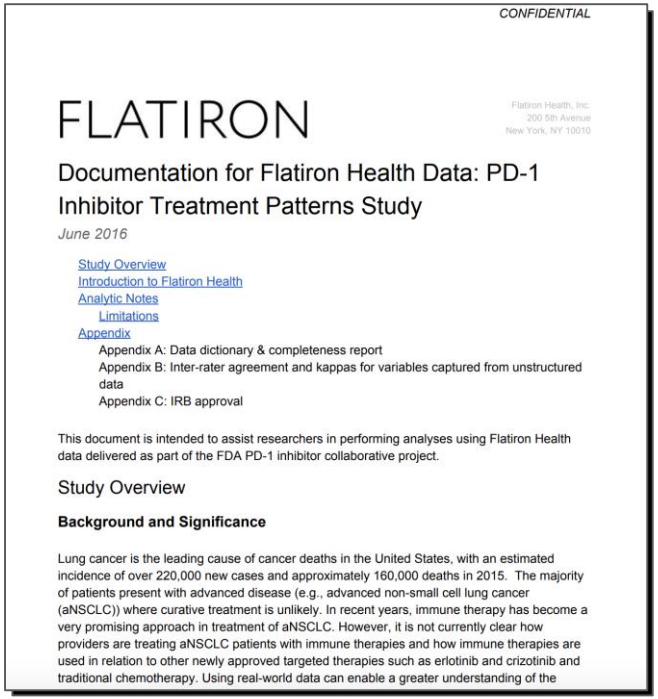
DEFINING RWE

Meta-characteristics of RWD and RWE

Regulatory grade RWE, a potential checklist

- ☐ **Clinical Depth**
  Data granularity to enable appropriate interpretation and contextualization of patient information.
- ☐ **Completeness**
  Inclusion of both structured and unstructured information supports a thorough understanding of patient clinical experience.
- ☐ **Longitudinal Follow-up**
  Ability to review treatment history and track patient journey going forward over time.
- ☐ **Quality Monitoring**
  Systematic processes implemented to ensure data accuracy and quality.
- ☐ **Timeliness / Recency**
  Timely monitoring of treatment patterns and trends in the market to derive relevant insights.
- ☐ **Scalability**
  Efficient processing of information with data model that evolves with standard of care.
- ☐ **Generalizability**
  Representativeness of the data cohorts to the broader patient population.
- ☐ **Complete Provenance**
  Robust traceability throughout the chain of evidence.

Data quality & analytic guidance provided with data deliverables



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FLATIRON

Flatiron Health, Inc.
200 5th Avenue
New York, NY 10010

Documentation for Flatiron Health Data: PD-1 Inhibitor Treatment Patterns Study

June 2016

This document is intended to assist researchers in performing analyses using Flatiron Health data delivered as part of the FDA PD-1 inhibitor collaborative project.

Study Overview

Background and Significance

Lung cancer is the leading cause of cancer deaths in the United States, with an estimated incidence of over 220,000 new cases and approximately 160,000 deaths in 2015. The majority of patients present with advanced disease (e.g., advanced non-small cell lung cancer (aNSCLC)) where curative treatment is unlikely. In recent years, immune therapy has become a very promising approach in treatment of aNSCLC. However, it is not currently clear how providers are treating aNSCLC patients with immune therapies and how immune therapies are used in relation to other newly approved targeted therapies such as erlotinib and crizotinib and traditional chemotherapy. Using real-world data can enable a greater understanding of the

- Deliver comprehensive analytic guide including:
  - Study Overview
  - Research Questions
  - Inclusion/Exclusion Criteria
  - Data Elements
  - Baseline Characteristics
  - Data Quality and Provenance
  - Data Freeze and Retention Process
  - Overview of Abstracted Variables Data Quality
  - Measure Inter-Rater Reliability
  - Interpreting Agreement
  - De-identification of Flatiron Data
  - Analytic Notes

Inbox
Search

GENERAL
Visit lists
Scheduler
Reports
New task

PATIENT CHART
Decision support
Demographics
Summary
Documents
Treatment plan
InHouse Rx
Orders
Visit notes
Referrals
Text note

LABS & VITALS
Collection record
Lab results
Vital signs

NURSE
MAR

Andrew Benjamin Morganstein SYC OCM RES

ROOM: Exam Room 1 SEX: Male MRN: #123456 MD: Bernadel-Huey, R.

MEMO: This patient has a copy of $40 and no known allergies documented.

Back to decision support

Non-small Cell Lung Cancer 1st line of therapy

View NCCN Guideline

NCCN Recommendation

- Molecular testing
  - Consider EGFR mutation and ALK testing in never smokers or small biopsy specimens, or mixed histology
  - Consider ROS1 testing
  - Testing should be conducted as part of broad molecular profiling
- PD-L1 testing

New orders

Testing

ALK Gene Rearrangement

○ Positive ◉ Negative ○ Not tested ○ Unknown Auto-filled from chart

EGFR Mutation Status

◉ Positive ○ Negative ○ Not tested ○ Unknown

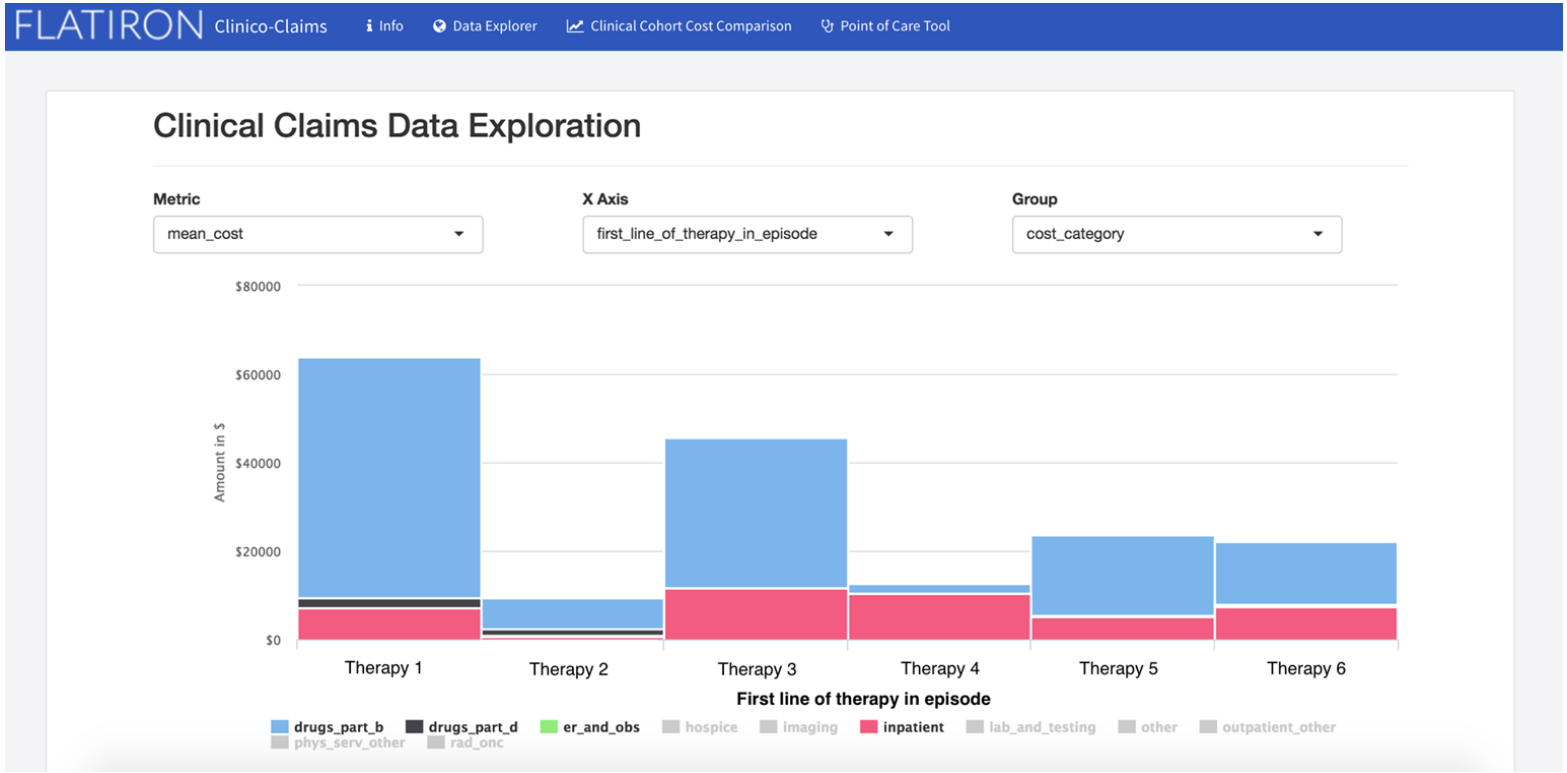
ROS1 Rearrangment

○ Positive ○ Negative ○ Not tested ○ Unknown

Summary

Clincal stage	IV (T1 N1 M1b)
Performance status	1
Extent of metastasis	Single site
Sites of metastasis	Brain
Systemic therapy recommended	Recommended

Effect of first line therapy on cost of care: NSCLC



What does this story really tell us?

- Data + technology infrastructure
- Tech + science + clinical + business
- Software enabled but still requires people
- Details matter
- Regulations matter
- Focus on your core customers & stakeholders

- Modernizing evidence development
- Democratization of care
- Better payment models

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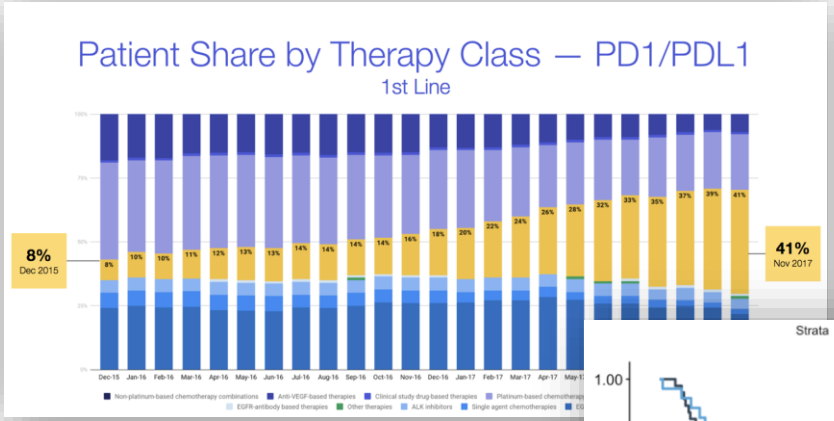
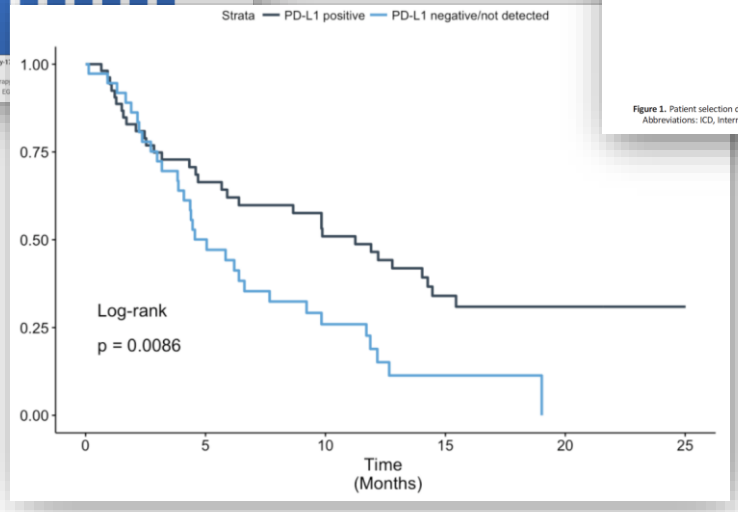
What is possible today?

What does this tell us about tomorrow?

Regulatory-Grade Real World Evidence





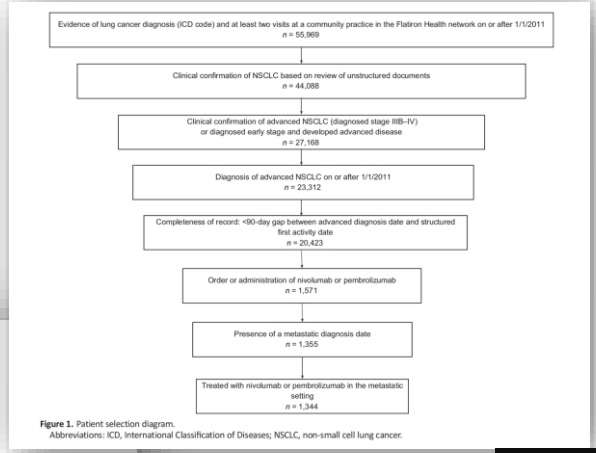


Figure 1. Patient selection diagram.
Abbreviations: ICD, International Classification of Diseases; NSCLC, non-small cell lung cancer.

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Use of real-world data to simulate clinical trial control arms:

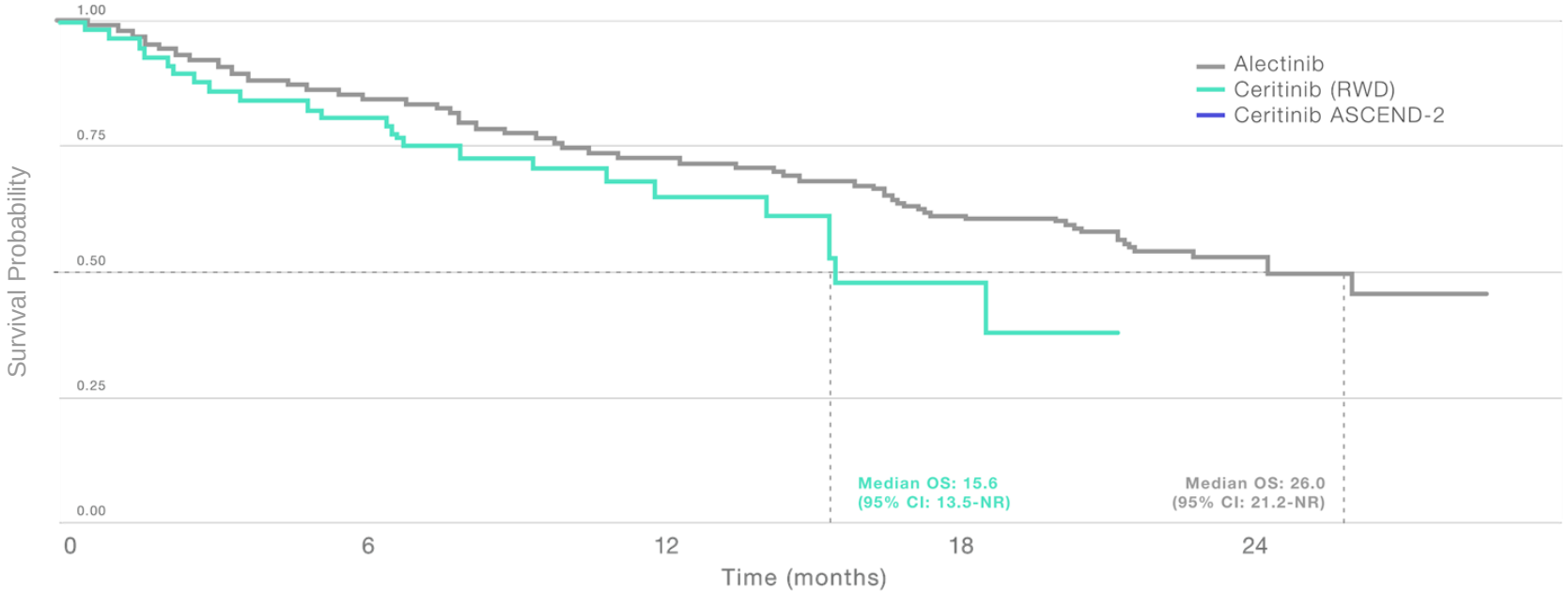
Moving from historical controls to contemporaneous rwCA

CASE STUDY 1

flatiron

Using RWE as a control arm

OS results: Alectinib Phase II data vs Flatiron RW control arm



Adapted from Davies J, Martinec M, Martina R, Delmar P, Coudert M, Bordogna W, Golding S, Crane G. Retrospective indirect comparison of alectinib phase II data vs ceritinib real-world data in ALK+ NSCLC after progression on crizotinib. European Lung Cancer Conference (ELCC). May 5-8, 2017; Geneva Switzerland

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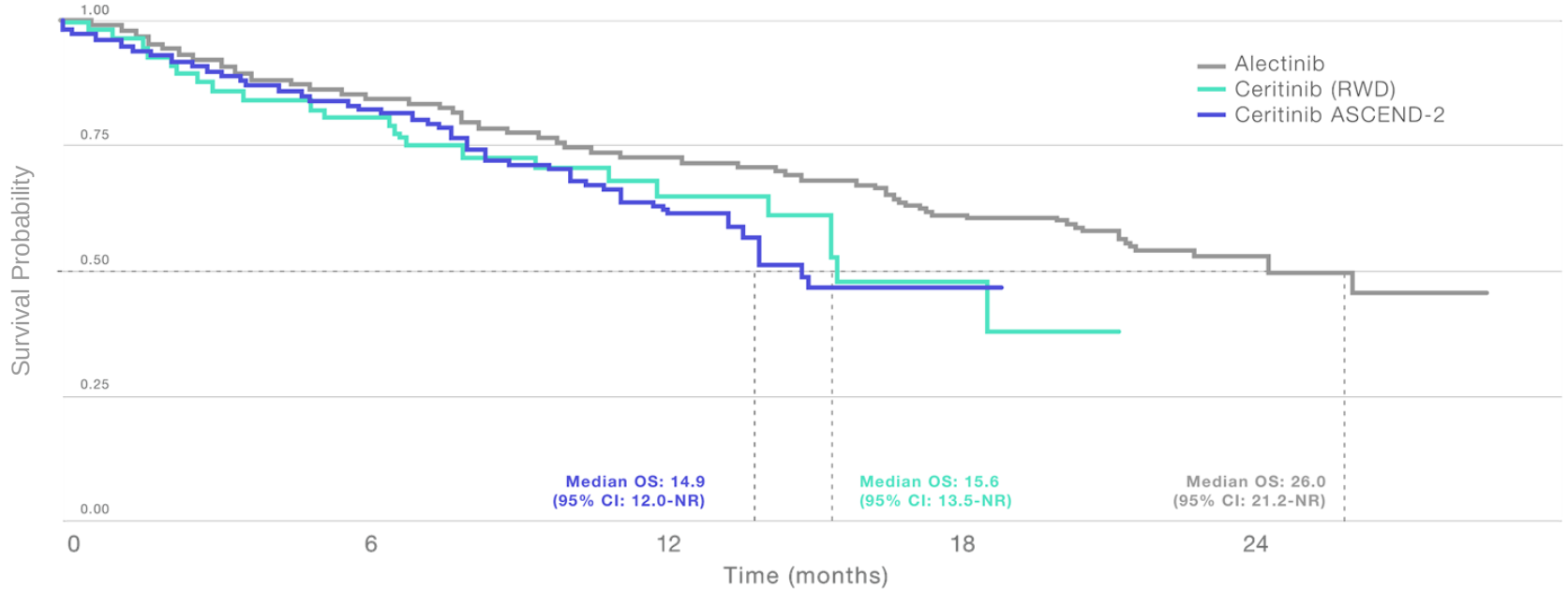
Using RWE as a control arm (OS)

OS results: Alectinib Phase II data vs Flatiron RW control arm



Adapted from Davies J, Martinec M, Martina R, Delmar P, Coudert M, Bordogna W, Golding S, Crane G. Retrospective indirect comparison of alectinib phase II data vs ceritinib real-world data in ALK+ NSCLC after progression on crizotinib. European Lung Cancer Conference (ELCC). May 5-8, 2017; Geneva Switzerland

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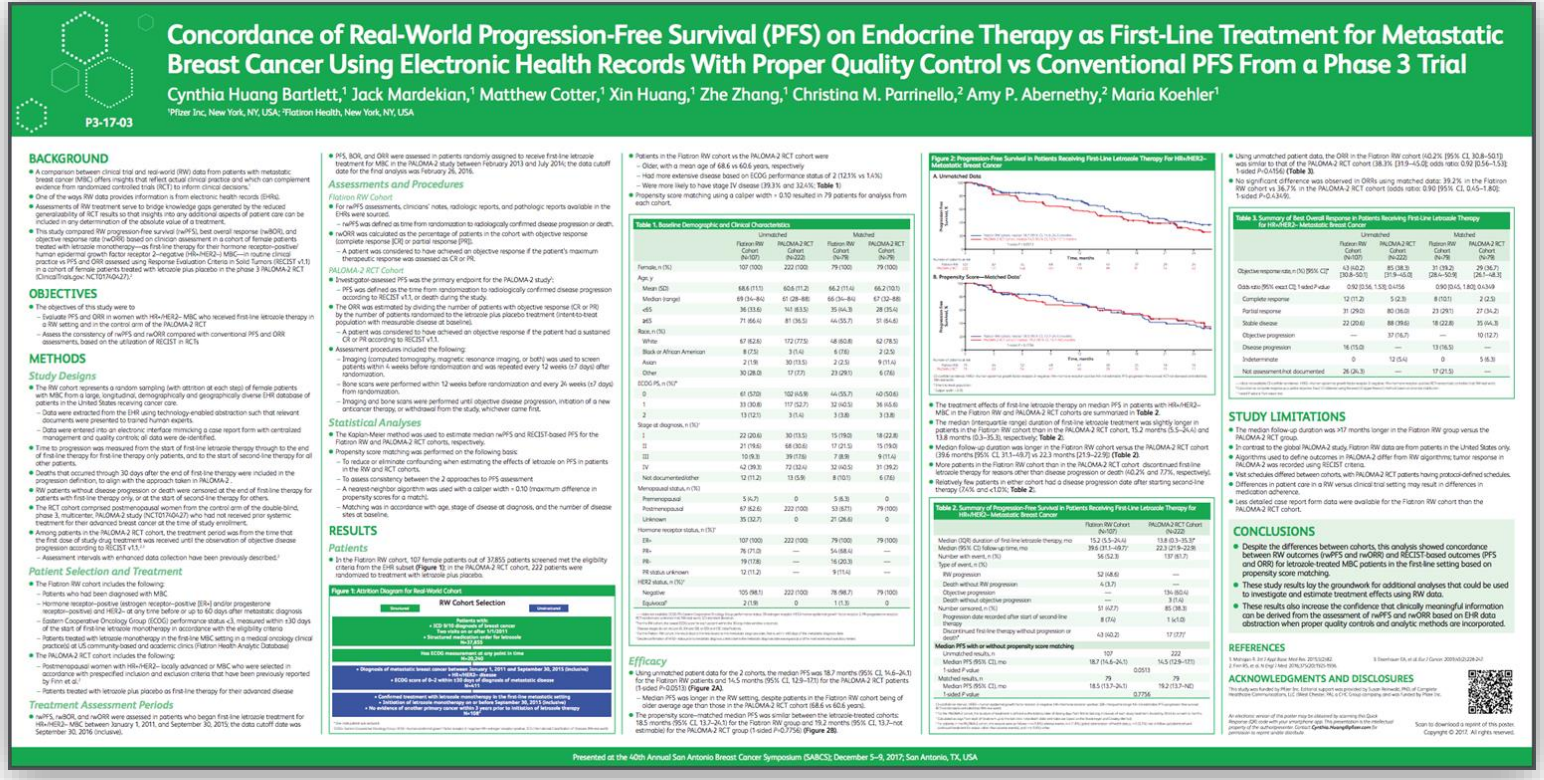
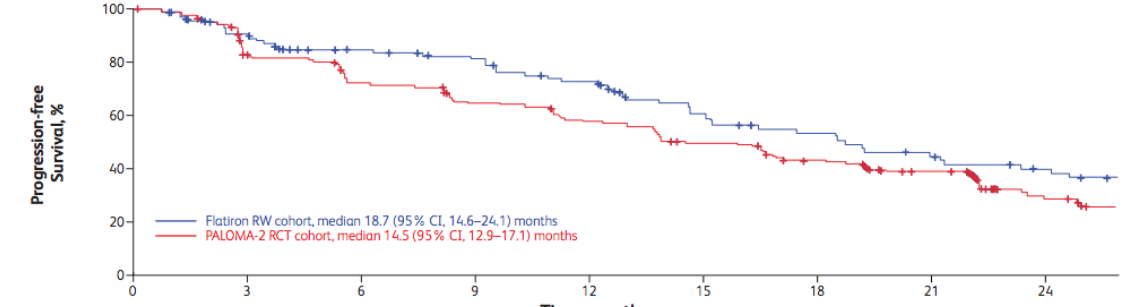
Using RWE as a control arm (RR/PFS)



Unmatched analysis		
	Flatiron (n = 107)	**PALOMA-2 (n = 222)**
PFS Median (95% CI)	18.7 months (14.6 - 24.1)	14.5 months (12.9 - 17.1)
ORR % (95% CI)	40.2% (30.8 - 50.1)	38.3% (31.9 - 45.0)
Matched analysis		
	Flatiron (n = 79)	**PALOMA-2 (n = 79)**
PFS Median (95% CI)	18.5 months (13.7 - 24.1)	19.2 months (13.7 - Not Estimable)
ORR % (95% CI)	39.2% (28.4 - 50.9)	36.7% (26.1 - 48.3)

Figure 2: Progression-Free Survival in Patients Receiving First-Line Letrozole Therapy For HR+/HER2– Metastatic Breast Cancer

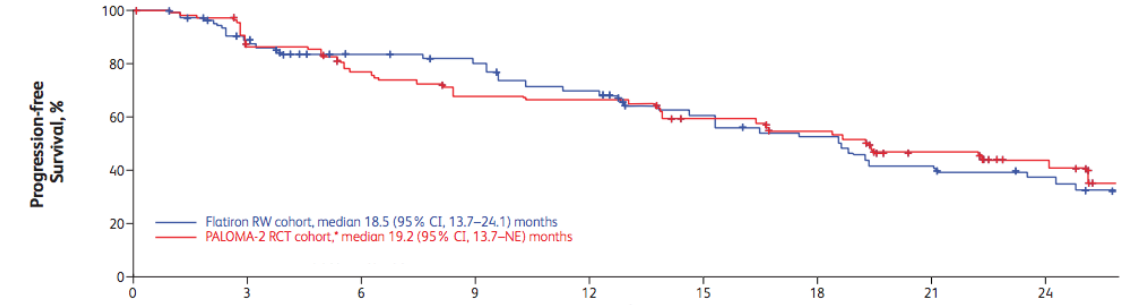
A. Unmatched Data



Number of patients at risk

Flatiron RW	107	87	74	68	59	43	37	29	24
PALOMA-2 RCT	222	171	148	131	116	98	81	54	22

B. Propensity Score—Matched Data†



Number of patients at risk

Flatiron RW	79	64	52	48	41	30	25	18	16
PALOMA-2 RCT	79	63	54	47	46	39	35	19	11

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.

Assessing safety in patients excluded from clinical trials:

Using real world evidence to fulfill a health authority request

CASE STUDY 2

flatiron

Trastuzumab emtansine usage in low LVEF patients

Data Need

- EMA Pharmacovigilance Risk Assessment Committee (PRAC) requested data on safety outcomes for patients at risk for cardiotoxicity. These patients were excluded from a clinical trial due to safety concerns
- Roche was only able to find 3 patients who met the profile of interest across multiple prospective registries

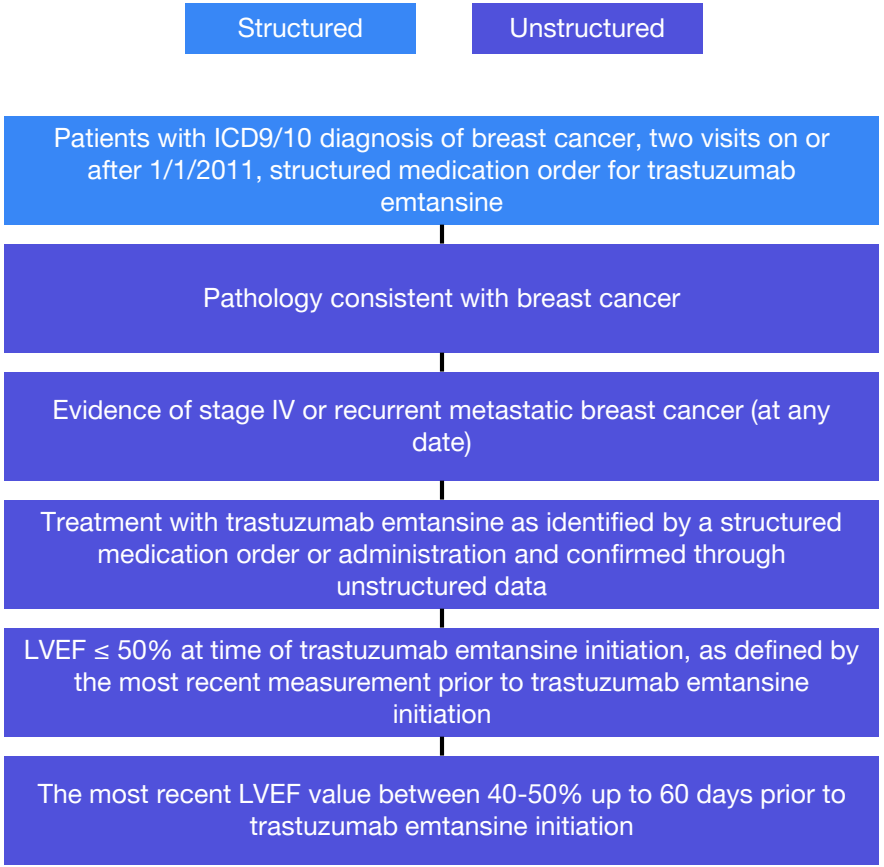
Methods / Analysis

- Flatiron and Roche developed a retrospective study of safety outcomes in metastatic breast cancer patients in the Flatiron network who received trastuzumab emtansine and who were in the subpopulation of interest (LVEF≤50% at treatment initiation)
- rwEndpoints: cardiac outcomes

Impact

- Flatiron was able to identify over 50 patients who received trastuzumab emtansine who also met the profile of interest, and delivered a dataset on those patients (with annual upcoming refreshes planned)
- Flatiron data submitted to PRAC to inform risk/benefit assessment in this patient population, and study design has been accepted to fulfill post-marketing commitment

Defining the cohort of interest



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Data quality control

Assessing data quality of cardiac information

- Complex information in chart
- Duplicate abstraction
- Clinical adjudication

Indication: Cardiomyopathy, assess LV function.

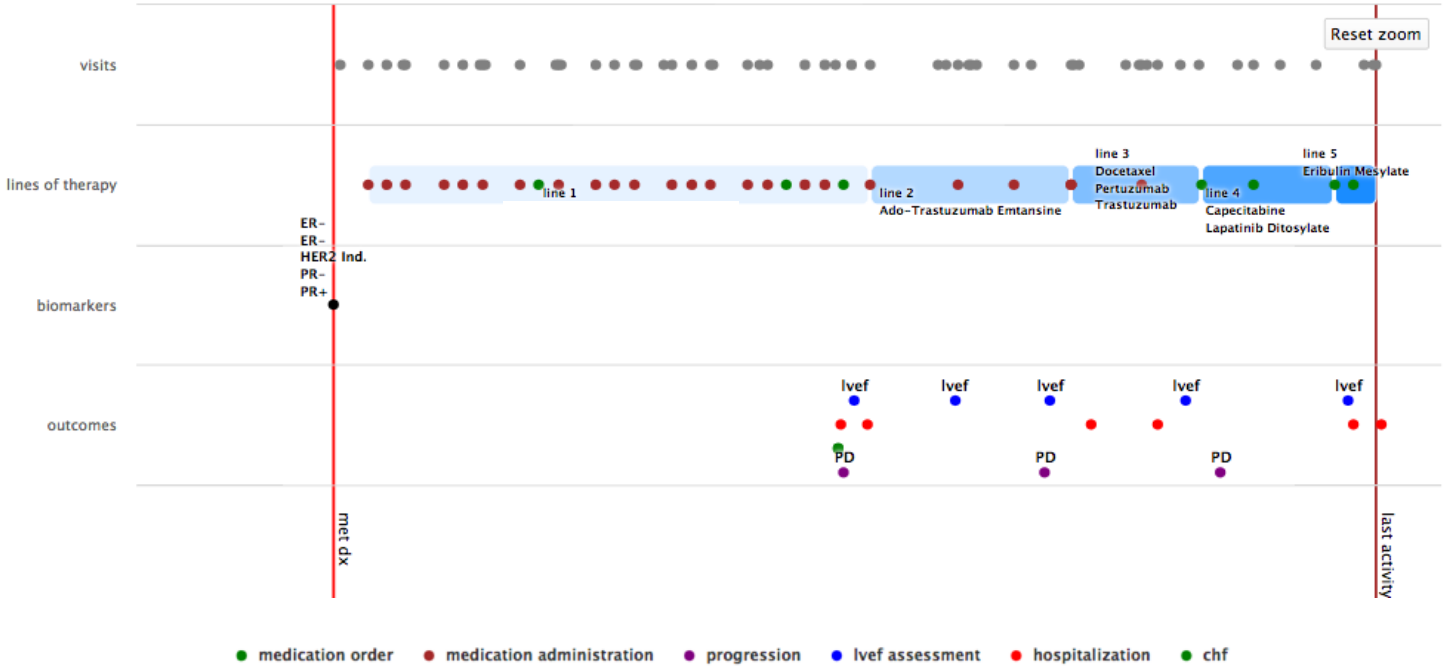
Left Ventricle Ejection Fraction: 46.9 %

Final Conclusions:

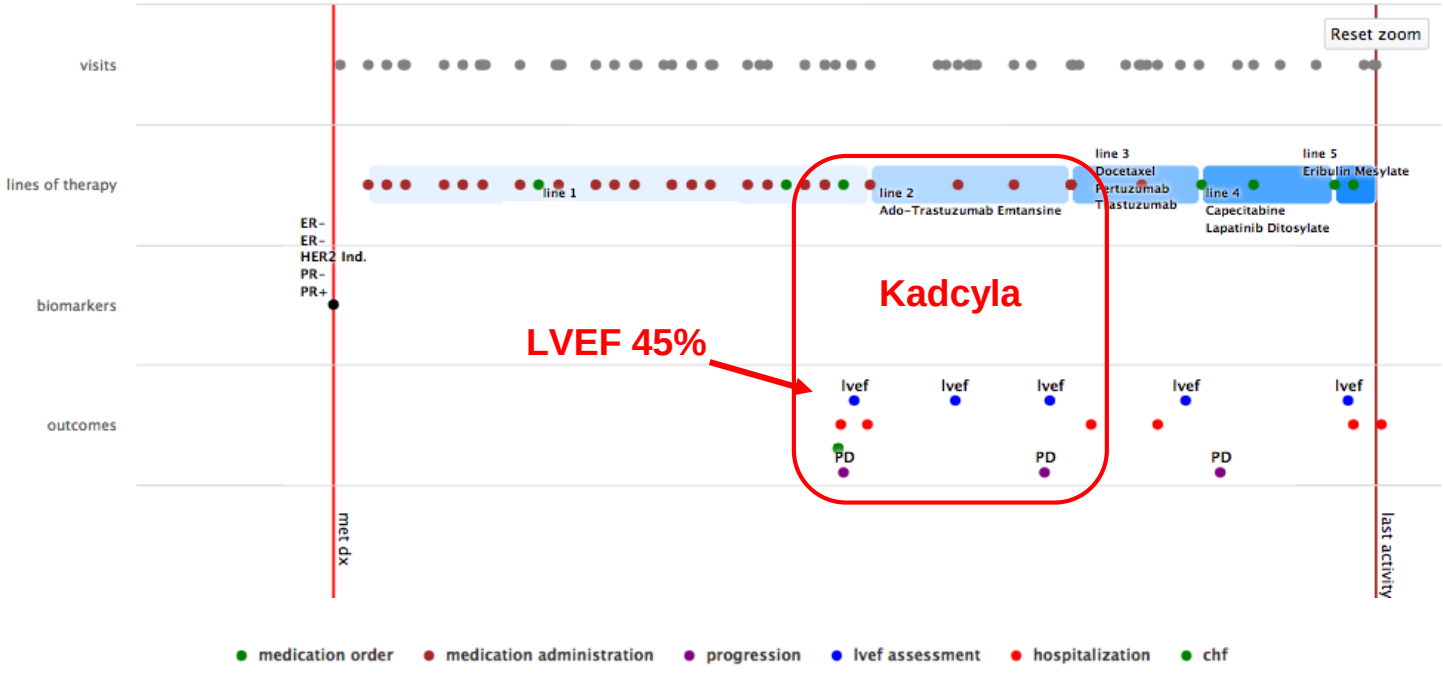
1. Sinus rhythm.
2. This was a technically adequate study.
3. This was a limited exam for LV function assessment.
4. The left ventricular size is normal.
5. Left ventricular wall thickness is normal.
6. Overall left ventricular systolic function is mildly impaired with, an EF between 45 - 50 %. Stable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

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.

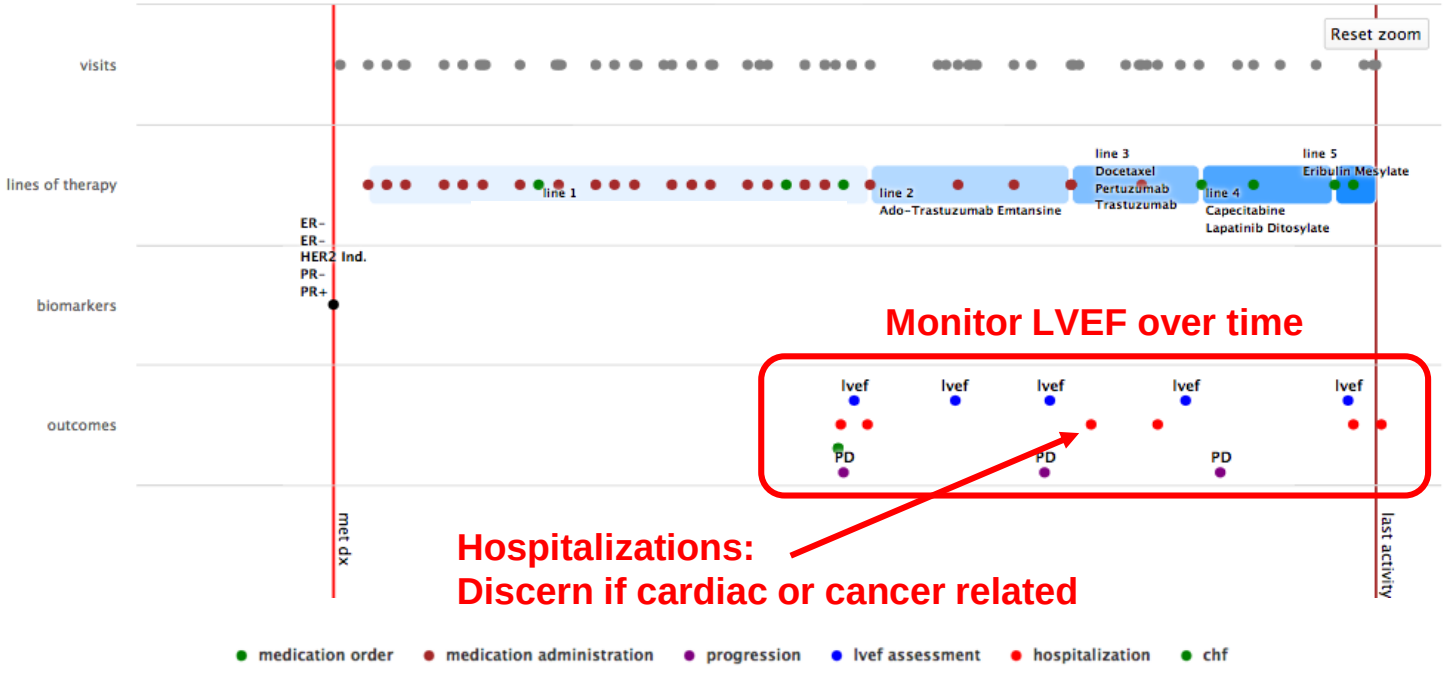
RWE Case Study: Patient Journey



RWE Case Study: Patient Journey



RWE Case Study: Patient Journey



Linking datasets in support of discovery:

Creating a continuously aggregating clinico-genomics database

CASE STUDY 3

flatiron

Linked Clincogenomic Data Support Discovery

Comparison to TCGA

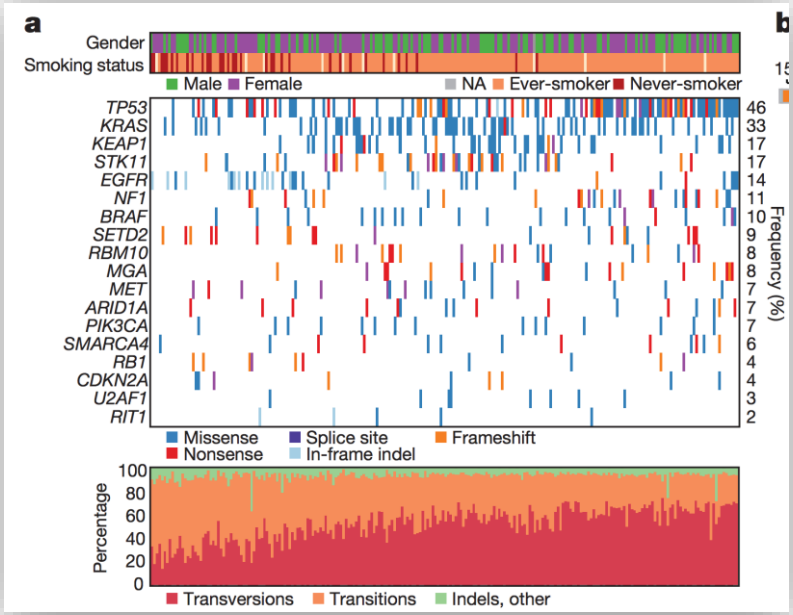
ARTICLE OPEN

doi:10.1038/nature13385

Comprehensive molecular profiling of lung adenocarcinoma

The Cancer Genome Atlas Research Network*

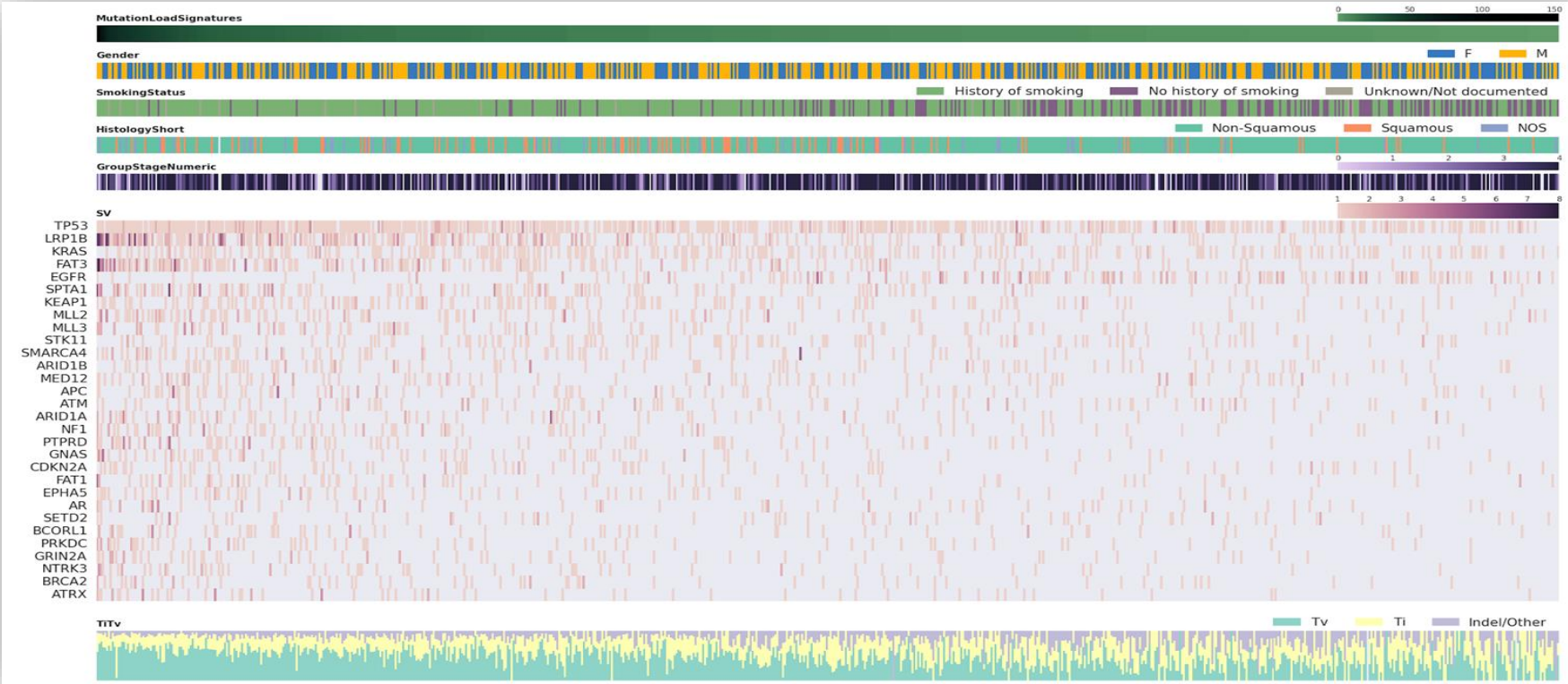
Figure 1 | Somatic mutations in lung adenocarcinoma. a, Co-mutation plot from whole exome sequencing of 230 lung adenocarcinomas. Data from TCGA samples were combined with previously published data[12] for statistical analysis. Co-mutation plot for all samples used in the statistical analysis ($n = 412$) can be found in Supplementary Fig. 2. Significant genes with a corrected P value less than 0.025 were identified using the MutSig2CV algorithm and are ranked in order of decreasing prevalence. **b, c,** The



DATA FROM FH-FMI NSCLC CG Database

Reproduces and extends findings of the The Cancer Genome Atlas project

***NOTE: Data shown below reflects initial Q1 2016 link (n=770). Dataset is now n=2139, nearly 10x that of TCGA**



Supporting clinical trials

CASE STUDY 4

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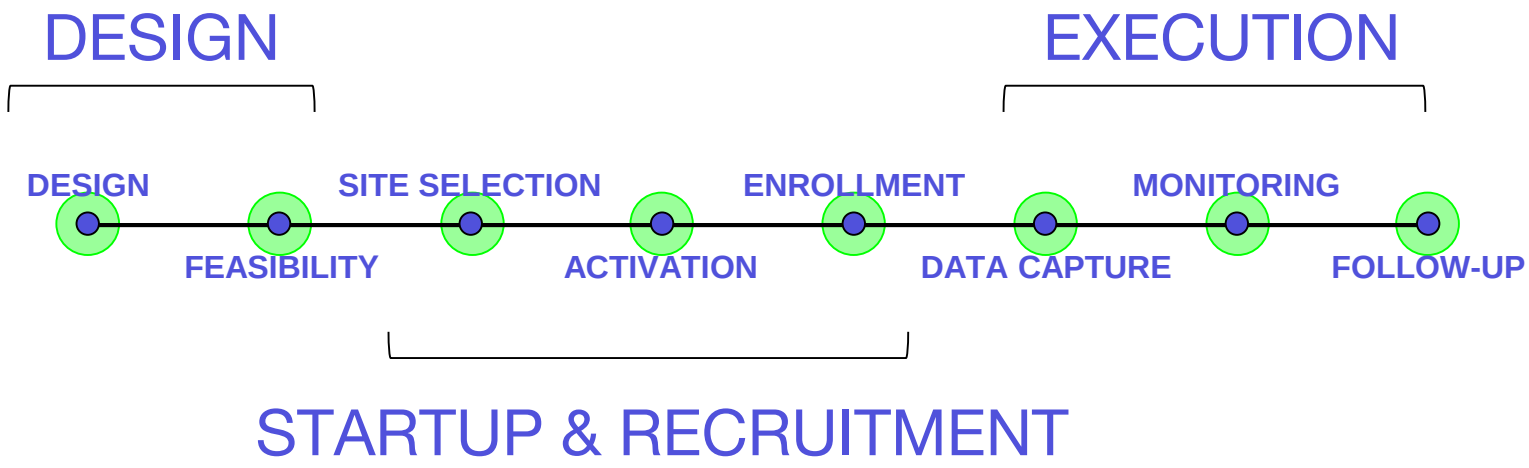
Reimagining the Clinical Trials Process



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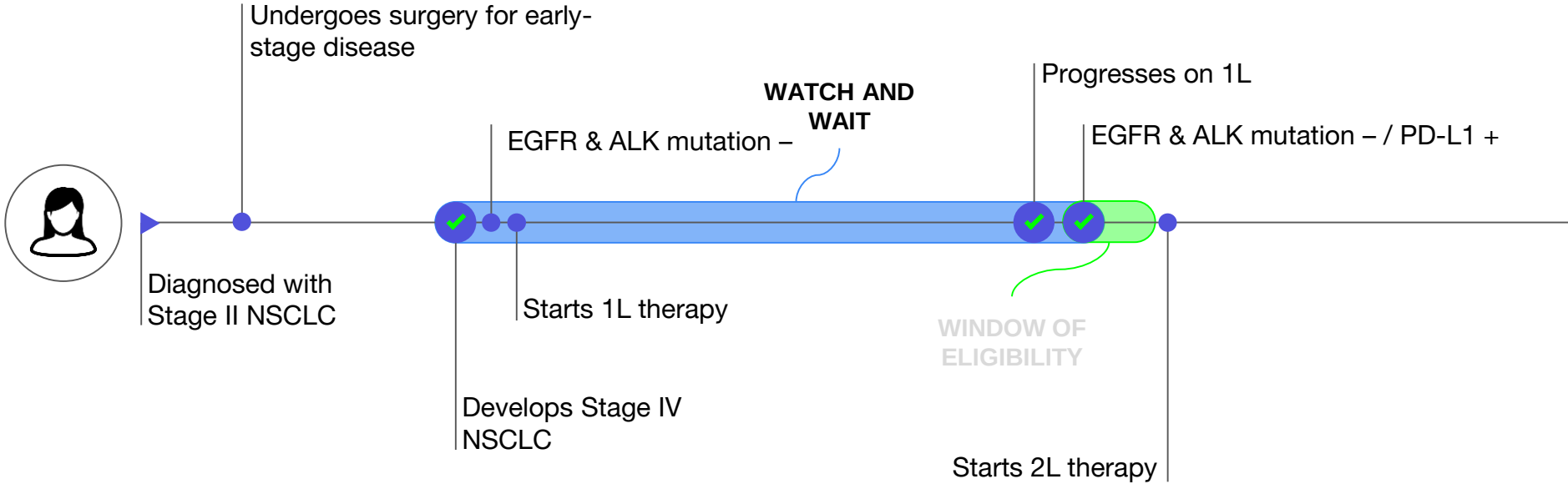
Review patient records on an ongoing basis, identifying potentially eligible patients at the right time.



Study data is captured from the EHR - any EHR

Clinical data entered into the EHR does not need to be re-entered into an EDC

Remaining study data is captured through trial-specific notes and documents in the EHR

Example: Domains in an oncology study with EHR data source

- Demographics (DM)
- Subject Visits (SV)
- Con Meds (CM)
- Exposure (EX)
- **Adverse Events (AE)**
- Disposition (DS)
- Med History (MH)
- Protocol Deviations (DV)
- I/E Criteria (IE)
- Lab Test Results (LB)
- Physical Exam (PE)
- Vital Signs (VS)
- Tumor ID (TU)
- Response (RS)
- Procedures (PR)
- Subject Elements (SE)
- Death (DD)
- Reproductive (RP)
- Healthcare Encounters (HO)

Example: Flatiron Note for Adverse Events

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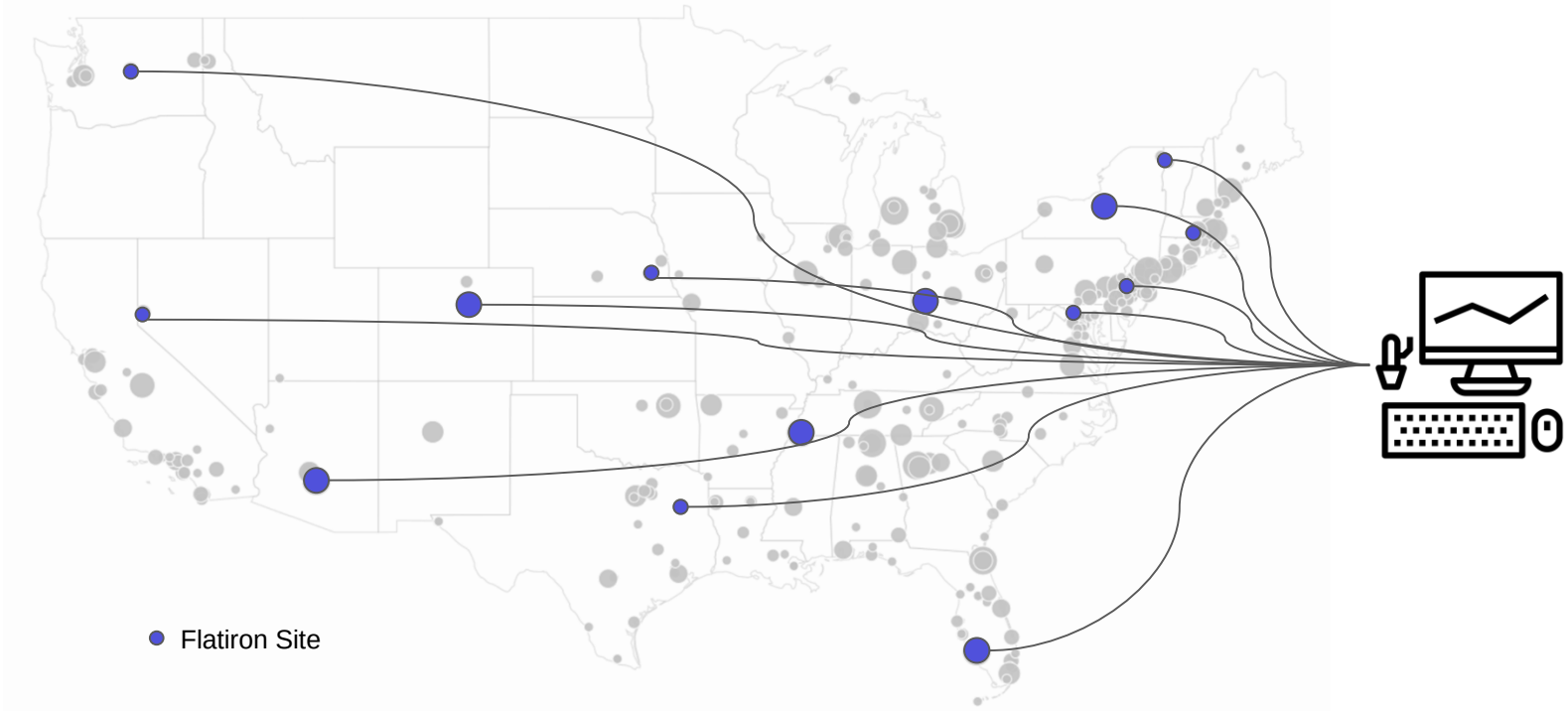
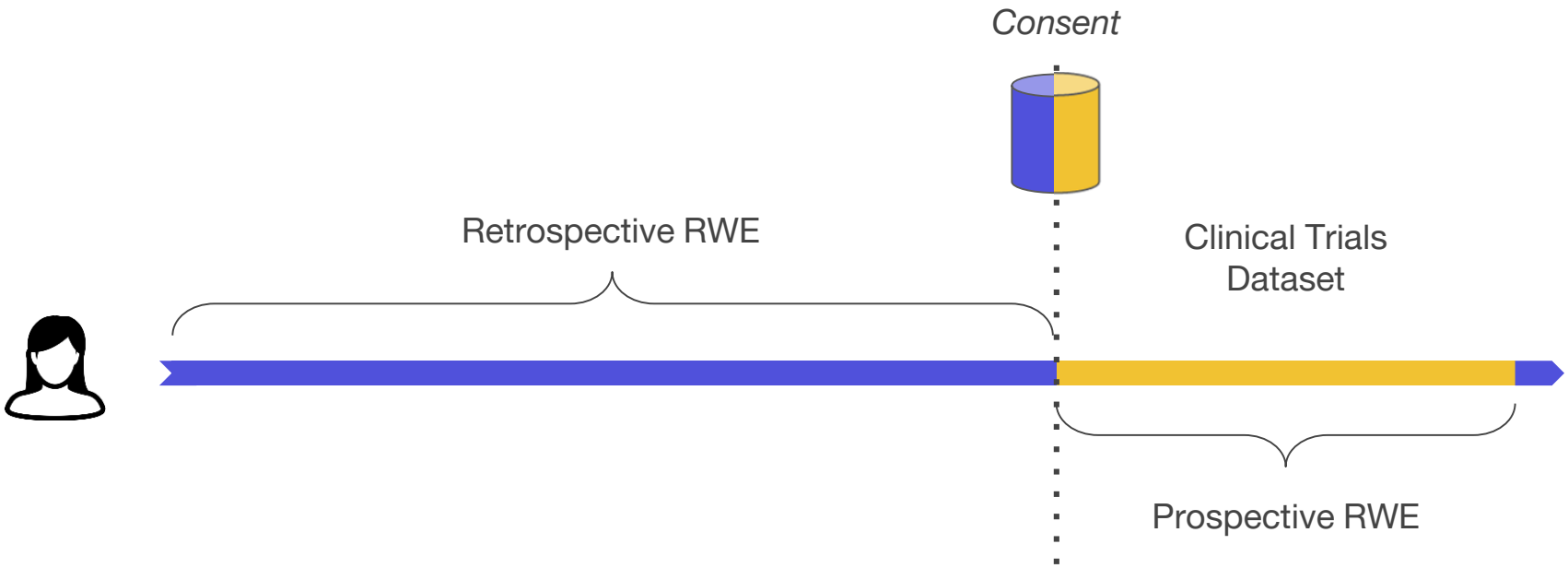
Monitor the trial centrally, using direct access to source data in the Electronic Health Record



Prospective real world evidence is on a continuum with traditional clinical trials.



What is possible today?

What does this tell us about tomorrow?

What does this tell us about tomorrow?

Evolving role of data & technology

Speed

Artificial intelligence accelerates

Rapidly changing standard of care

Blurring of retrospective & prospective research

Merging of care & research

Tools for clinicians & patients

Cost is just a variable in the model

Stakeholders are involved differently

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What does this tell us about tomorrow?

Learning Healthcare

Clinical Evidence Development

Personalized Medicine

Patient-centered Care

Value Based Care

Outcomes Based Pricing

Competition

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Thank you

amy@flatiron.com

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