July 17, 2018

An Overview of How Real World Evidence, Data Sharing, and Precompetitive Collaboration May Influence the Development of PD-1/PDL-1 Combination Therapies

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Flatiron Health

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Overview

- Case examples
- Some practical issues
- Data sharing mechanics
- Precompetitive collaboration?
- Policy implications

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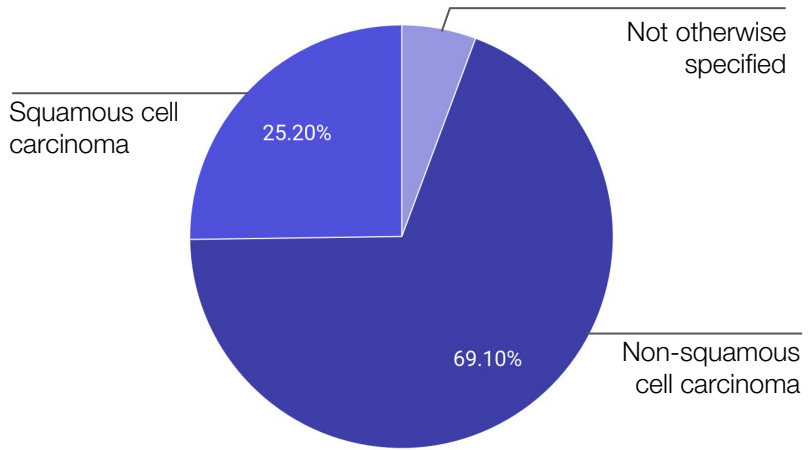
Real-world data enables a different kind of discovery

Cohort Demographics

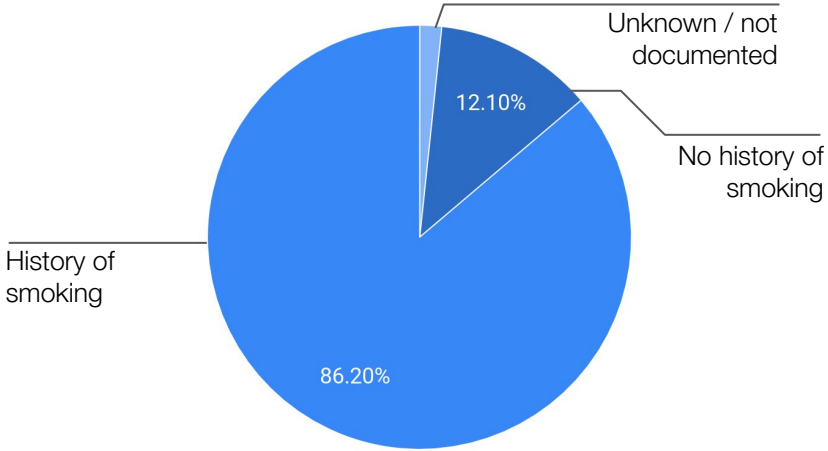
As of June 2018

Patients in cohort: 48,856 (Community: 44,770 | Academic: 4,086)

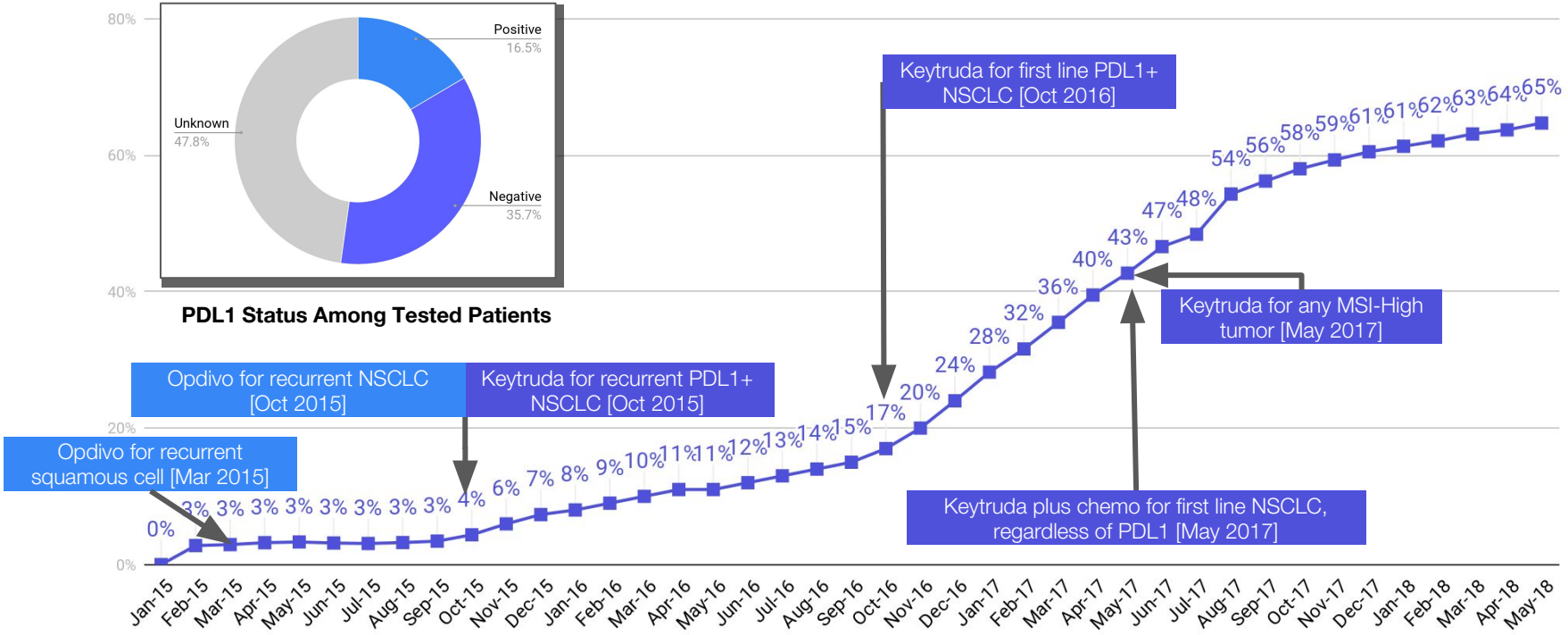
Histology



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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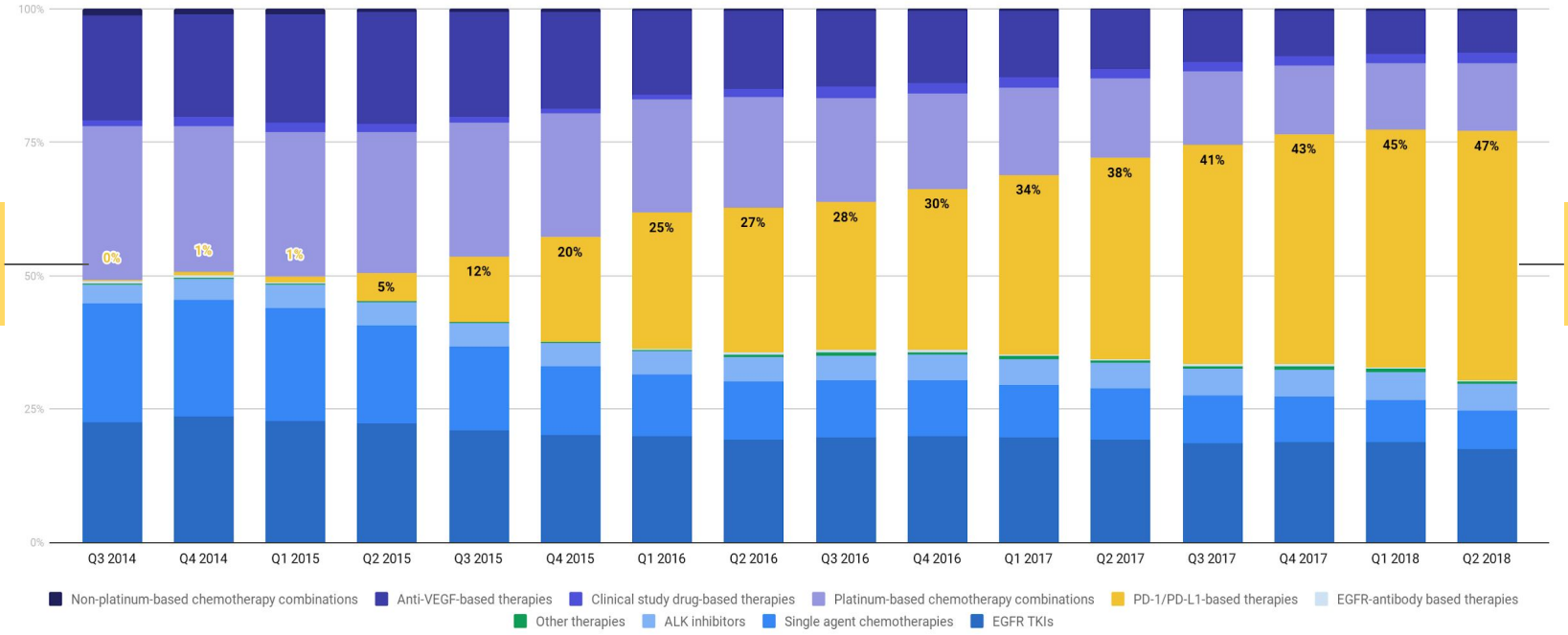
Patient Share by Therapy Class — PD1/PDL1

All Lines

0%
Q3 2014

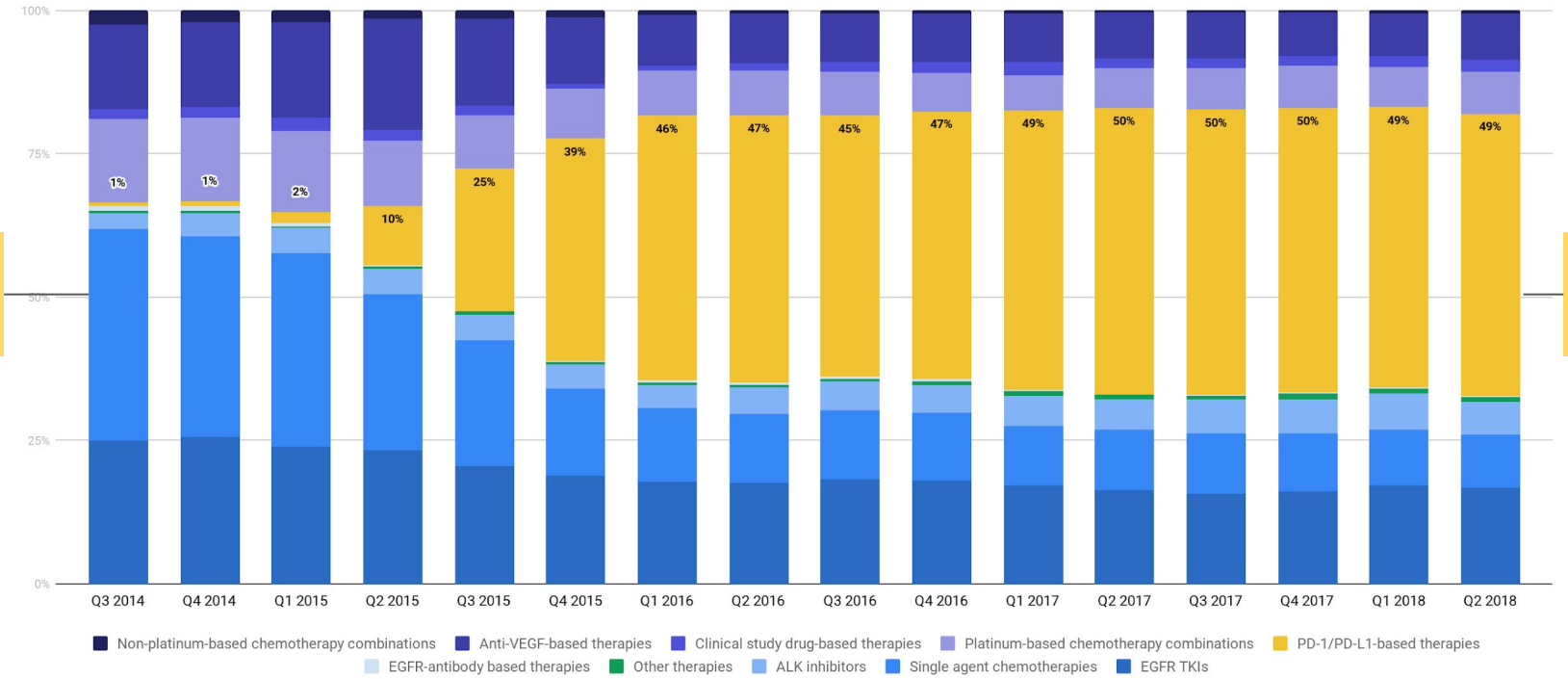


47%
Q2 2018

Patient Share by Therapy Class — PD1/PDL1

2nd or 3rd Line+

1%
Q3 2014

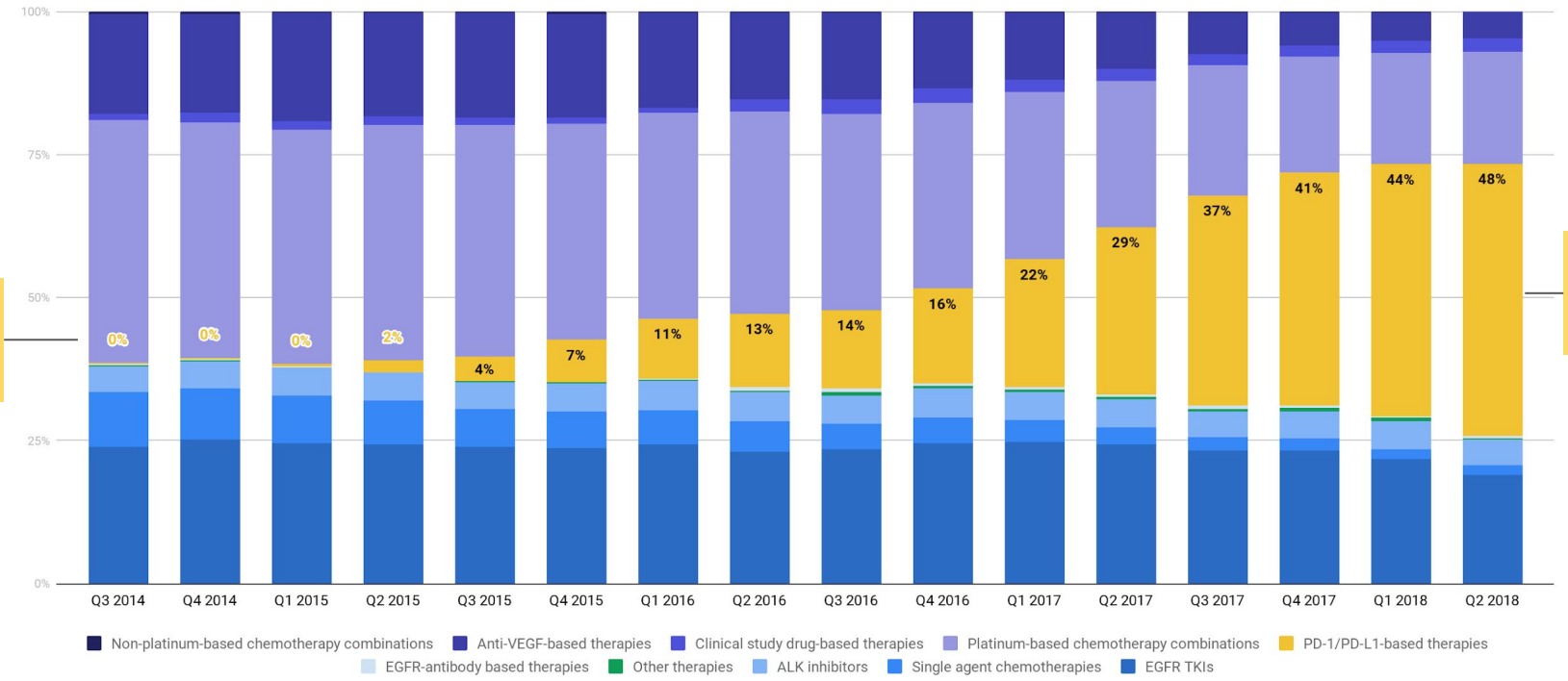


49%
Q2 2018

Patient Share by Therapy Class — PD1/PDL1

1st Line

0%
Q3 2014



48%
Q2 2018

NBC NEWS

Cancer Drug Keytruda Keeps Some Patients Alive For 3 Years

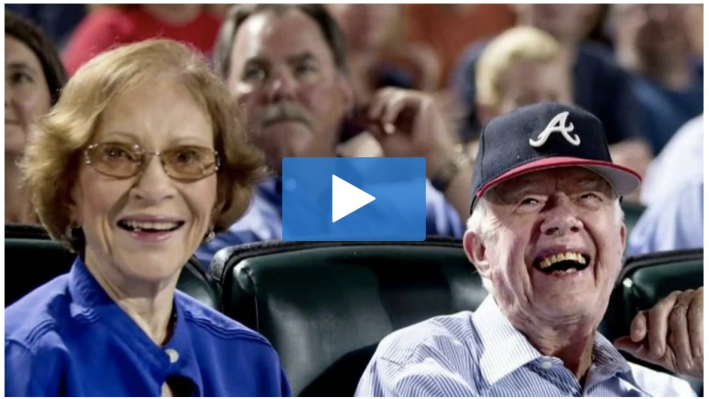
by MAGGIE FOX

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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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]

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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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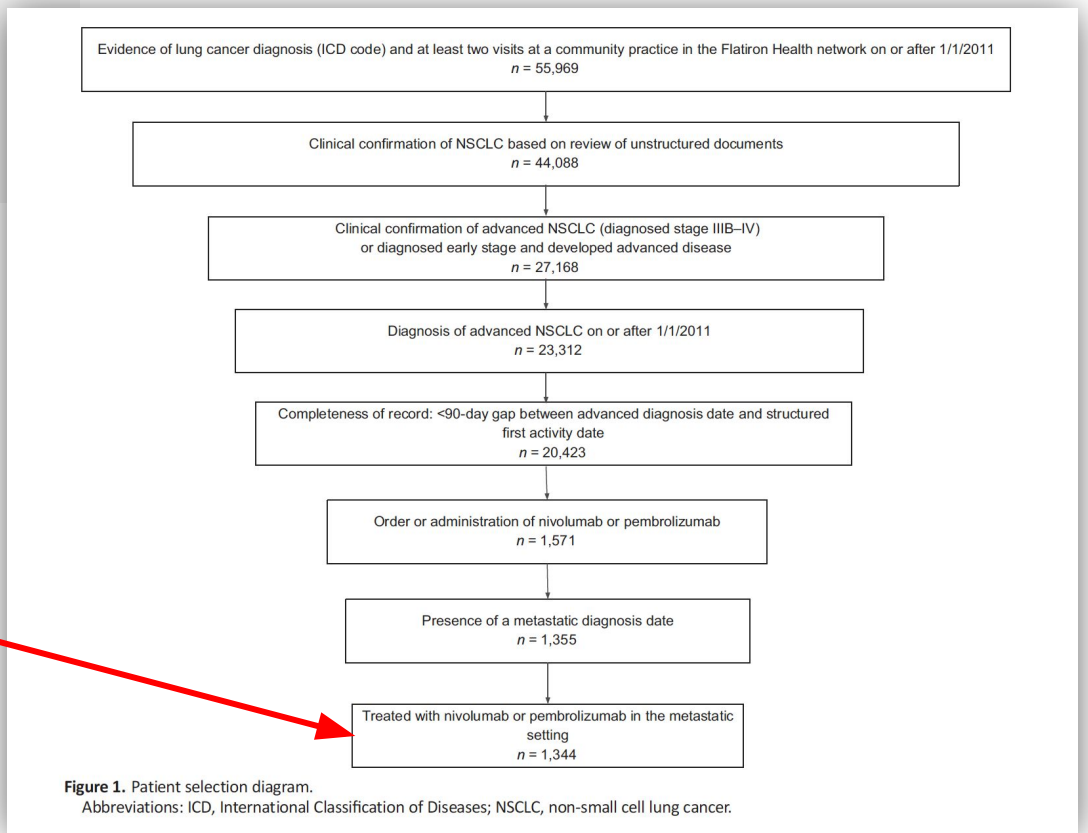

Figure 1. Patient selection diagram.
Abbreviations: ICD, International Classification of Diseases; NSCLC, non-small cell lung cancer.

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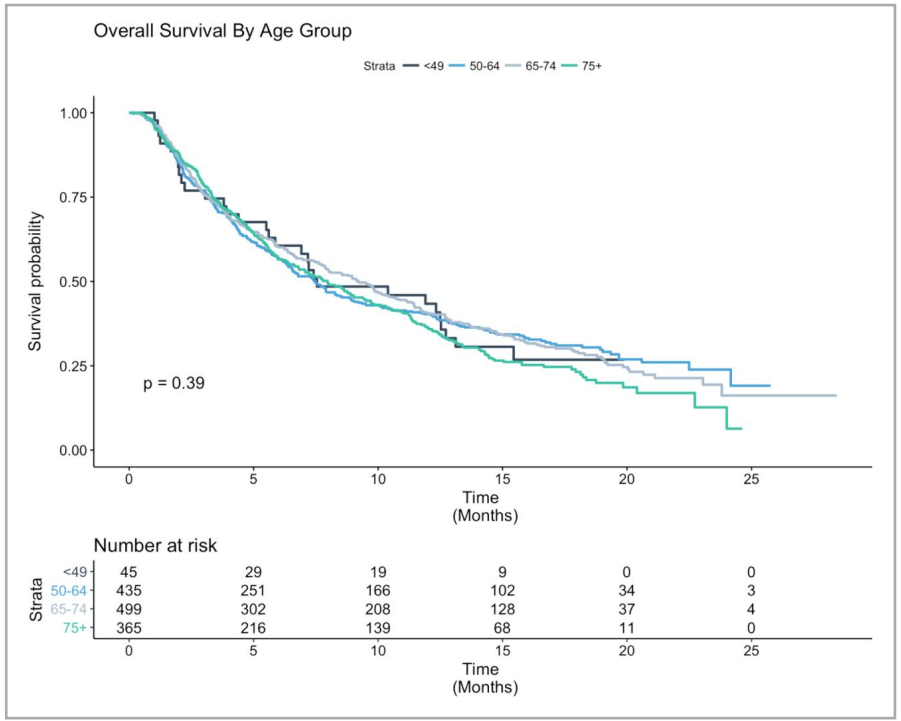
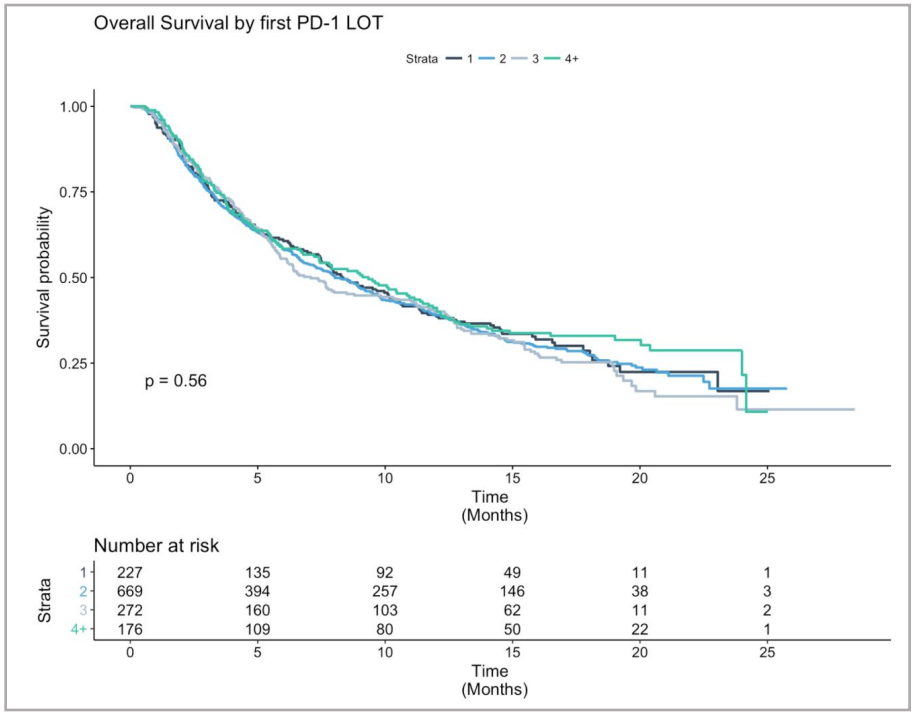
Median age in clinical trials = 62; <8% were 75 or over

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





Age

Line

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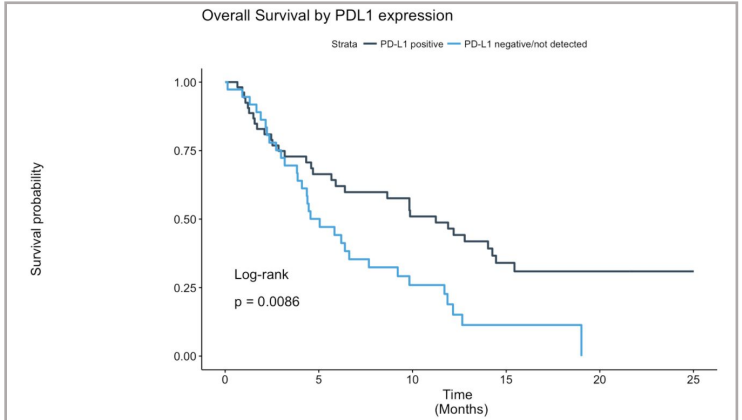
PDL1 expression predicts survival



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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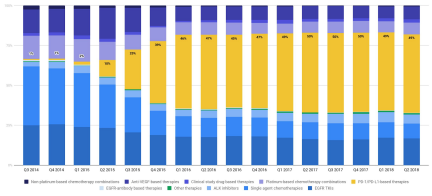
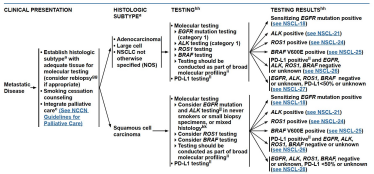
What does this story really tell us?

Speed, Biology, Evidence, Cost, Complexity, Impact

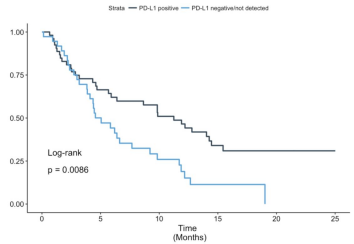
Exploding R&D Pipelines

Combination therapies

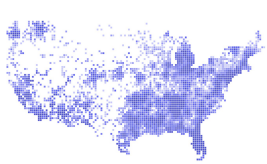




Segmenting patients & personalization



Rising cost & complexity of care



FDA

21st Century Cures

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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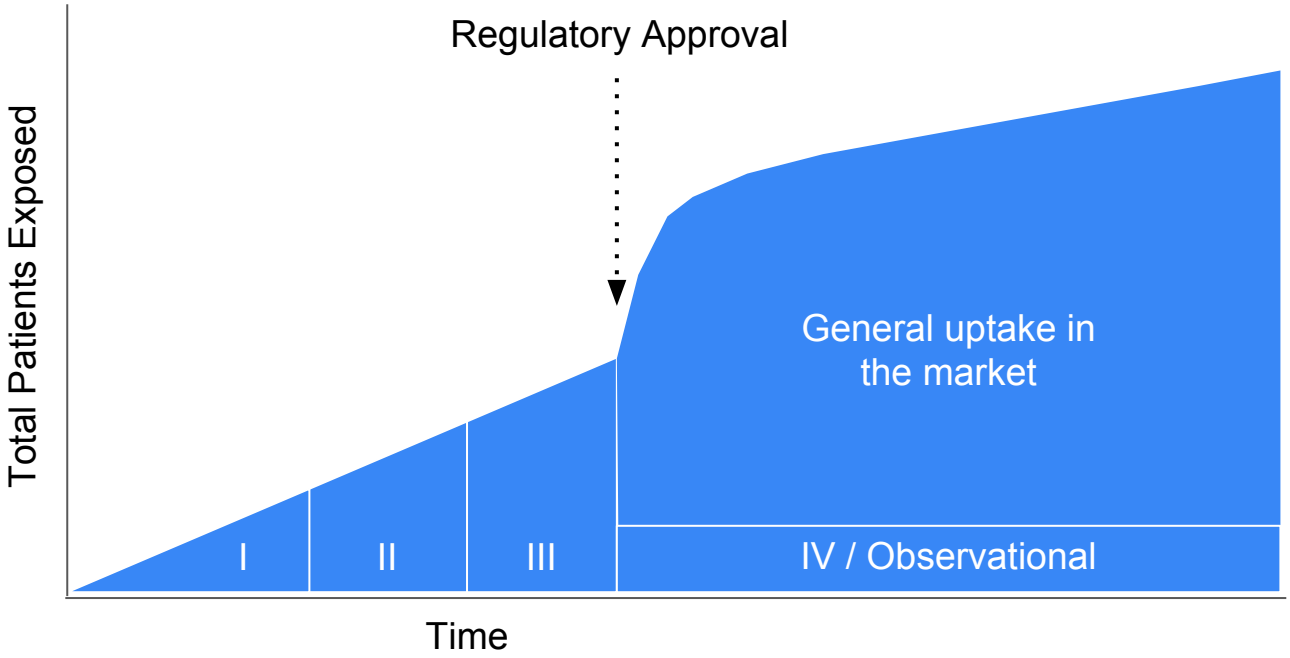
Current drug development paradigm



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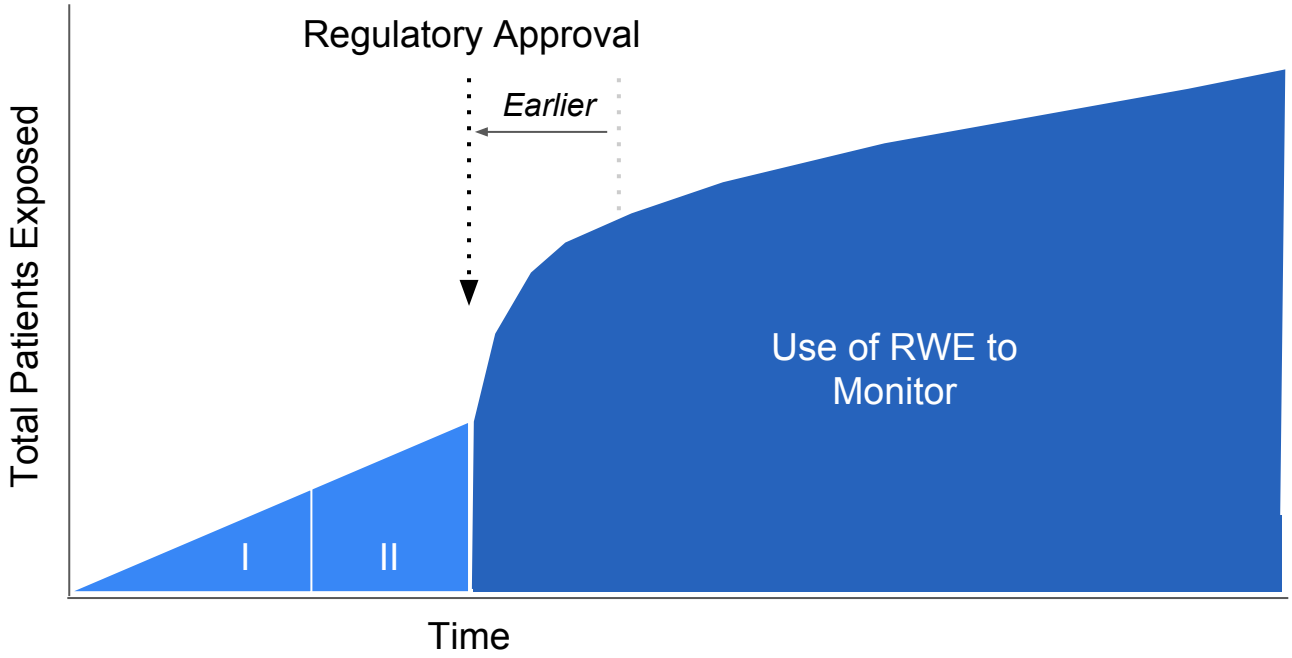
21st Century Cures - Shift towards earlier approvals



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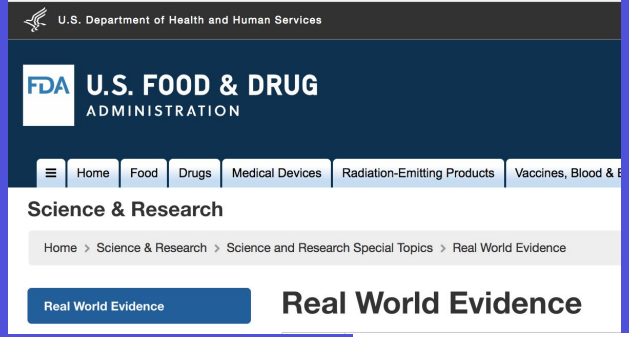
What are real-world data?



What are RWD and where do they come from?

Real world ***data*** are the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources. RWD can come from a number of sources, for example:

- Electronic health records (EHRs)
- Claims and billing activities
- Product and disease registries
- Patient-generated data including in home-use settings
- Data gathered from other sources that can inform on health status, such as mobile devices

What is RWE?

Real world ***evidence*** is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD.

This Website was designed to capture up-to-date information about the status of FDA activities around the development and use of RWD and RWE.

Contemporary features

Aggregated at scale

Cleaned and curated

Common data model

Linkable

Readily analyzable

Quality assessment

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

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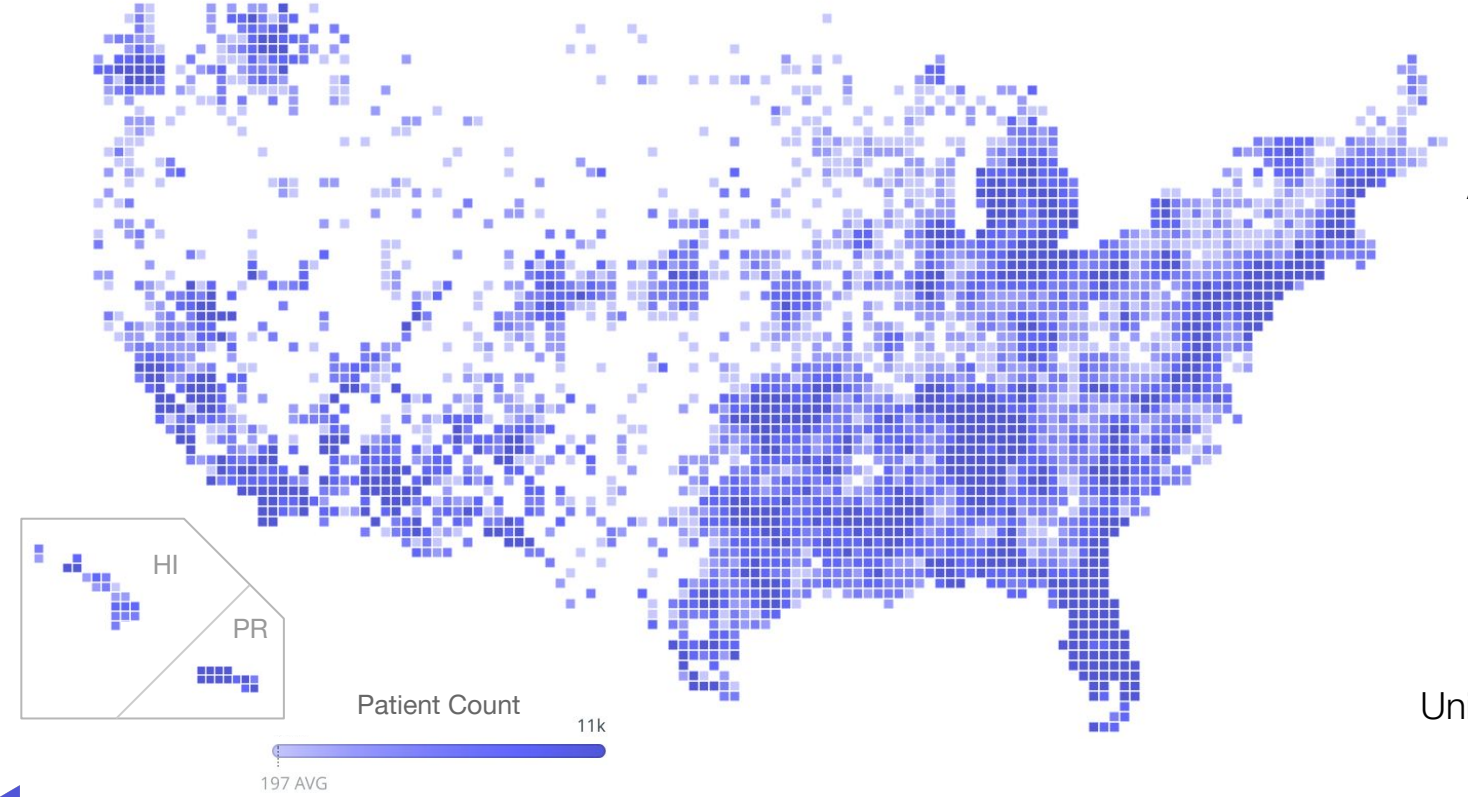
Meta-characteristics of RWD and RWE

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.

Aggregate across silos



2M
Active Patients

2,500
Clinicians

265
Cancer Clinics

800
Unique Sites of Care

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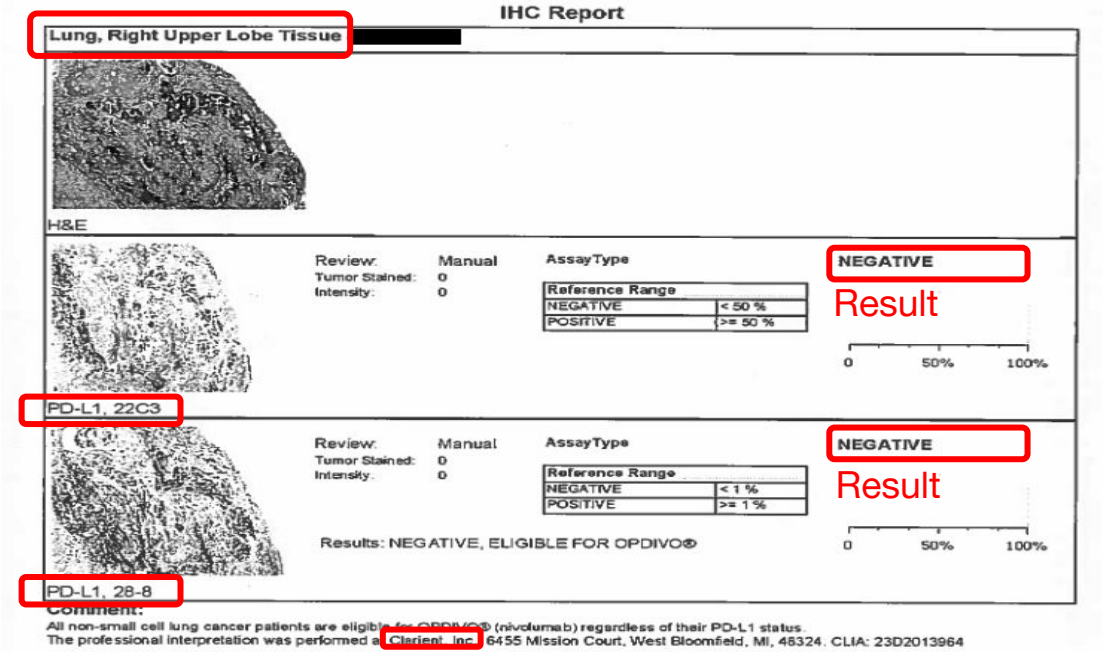
Standardize EHR Data to a Common Data Model

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

Data curation is a part of the endeavor

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.

Document 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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Emerging use cases

ROCHE

Development of an External Control Arm as a Comparator for a Single Arm Trial

Alectinib

Assessing outcomes and safety of patients excluded from a clinical trial

Kadcyla, Post-Marketing Commitment

NCI + FLATIRON

Patients excluded from a clinical trial

Evaluating patients with renal and hepatic dysfunction

FLATIRON

Answering questions quickly

With IO in lung cancer, should we treat past progression?

Multiple organizations are working on this

Friends of Cancer Research Pilot Project

pcornet®

IQVIA™

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COTA®

OPTUM

Correlation of real-world endpoints to overall survival among immune checkpoint inhibitor-treated aNSCLC patients

- 6 datasets
- 6 months project timeline with 2 months of analysis time
- Prespecified and agreed upon cohort selection and analysis plan
- Variables currently available
- N=269 to 6924

Friends of Cancer Research Pilot Project

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OPTUM

Correlation of real-world endpoints to overall survival among immune checkpoint inhibitor-treated aNSCLC patients

- **Lots of activities and vendors out there**--6 came together willingly to share their data + run analyses in < 2 months
- **Similarity** in demographic and clinical characteristics **despite differences in data source**
- Again, challenge is that **we don't have data standards** for many things (e.g., PDL1 testing) so we have to invent it
- **Harmonization** can be achieved through translation tables between datasets, instead of predefining the same common data model up front

What if you combined (all of) the datasets?

Friends of Cancer Research Pilot Project

Correlation of real-world endpoints to overall survival among immune checkpoint inhibitor-treated aNSCLC patients

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

Strengthening Research through Data Sharing

Elizabeth Warren, J.D.

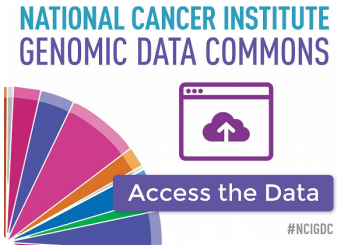
DATA SHARING HAS INCREDIBLE POTENTIAL TO STRENGTHEN ACADEMIC research, the practice of medicine, and the integrity of the clinical trial system. Some benefits are obvious: when researchers have access to complete data, they can answer new questions, explore different lines of analysis, and more efficiently conduct large-scale analyses across trials. Other advantages, such as providing a guardrail against conflicts of interest in a clinical trial system in which external sponsorship of research is common and necessary, are less visible yet just as critical.

Data Sharing Consortiums

Historical definition: “the practice of making data used for scholarly research available to other investigators” (Wikipedia & NIH)

Aggregation of datasets (different variables, to generate critical mass)

Increasing focus on real-world data collected as a routine byproduct of care



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AACR American Association for Cancer Research FINDING CURES TOGETHER

PROJECTGENIE Genomics Evidence Neoplasia Information Exchange

ORIEN ONCOLOGY RESEARCH INFORMATION EXCHANGE NETWORK

pcornet® The National Patient-Centered Clinical Research Network

ASCO CANCER·LINQ™ Learning Intelligence Network for Quality

NIH Collaboratory Health Care Systems Research Collaboratory

A few comments about data sharing

- It isn't free…
- Precompetitive collaboration? Precompetitive for which parties and when?
- Need common standards (e.g., PDL1, endpoints)
- ...

Policy Context for Data Sharing

- Enabling policy (21st Century Cures, PDUFA VI)
- Privacy, security and governance
  - Need approaches to maintain privacy while ensuring adequate contextual information
- Incentives for data sharing
- Mortality data!
- Regulatory policy that drives standards
  - Consistent approach to documenting data quality
  - Consistent endpoint definitions
  - Incorporating machine learning and AI

Take Home Summary

- Real world data offer the opportunity to observe the interrelationship between diagnosis, treatment, and outcomes at scale
- To achieve this we must solve the challenges of data aggregation, curation, and confident assessment of data quality - this can be achieved
- Interesting challenges such as mortality data
- Data sharing isn’t free