February, 13th 2018

Data Sharing Consortiums and Large Datasets to Inform Cancer Diagnosis

Improving Cancer Diagnosis and Care: Patient Access to Oncologic Imaging and Pathology Expertise and Technologies: An NCPF Workshop

Amy P. Abernethy, MD, PhD
CMO, CSO & SVP Oncology
Flatiron Health

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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.

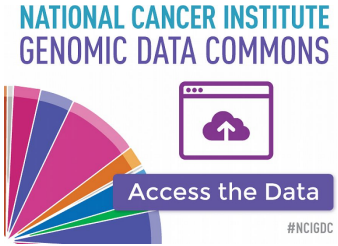
Data Sharing Consortiums

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

Flatiron Health as an example, but there are many others



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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

21st Century Cures

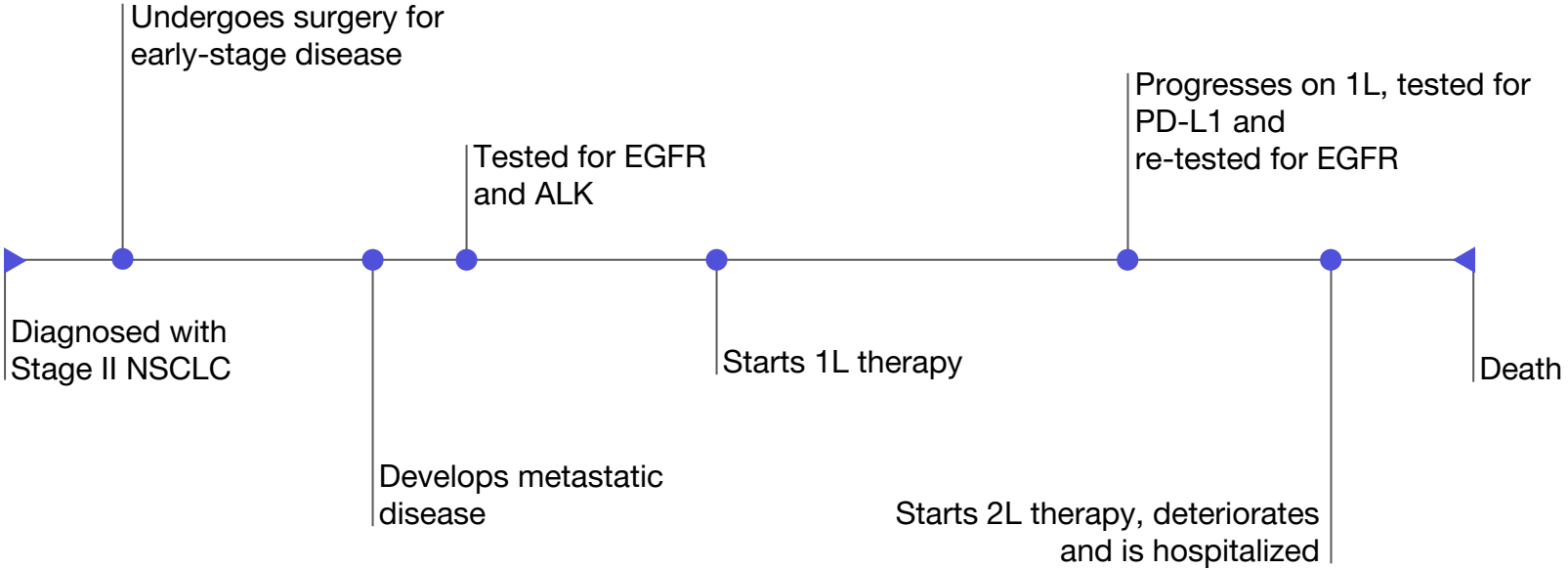
SEC. 505F. UTILIZING REAL WORLD EVIDENCE.

(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 postapproval study requirements.

Source: https://www.congress.gov/bill/114th-congress/house-bill/34/text#toc-HBC0DF02539024F65AEF0DD6A88063188



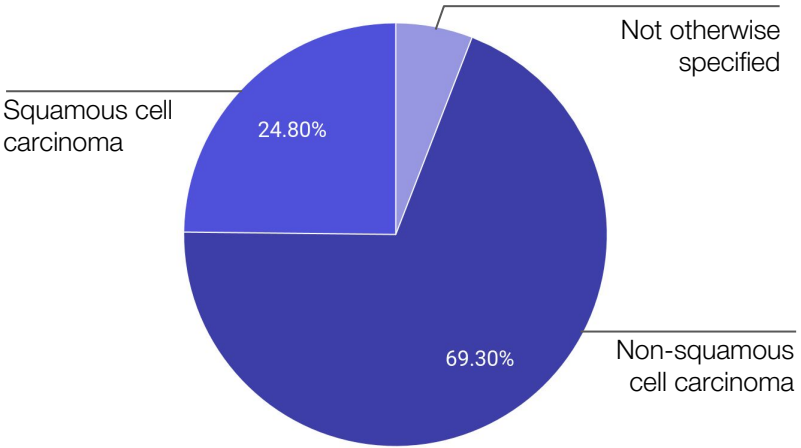
Large datasets can be used to inform cancer diagnosis and the interrelationship of diagnosis, treatment, and outcome, but it is important how they get curated

The Promise of Data Sharing at Scale

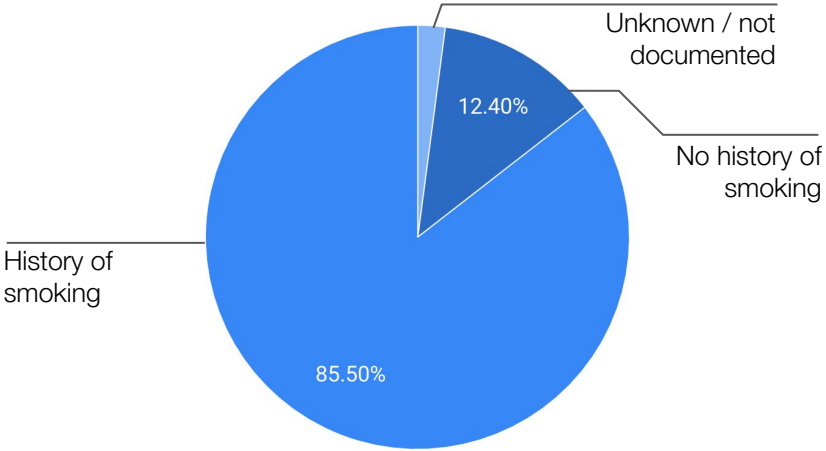
As of January 2018

Patients in cohort: 43,697 (Community: 39,915 | Academic: 3,782)

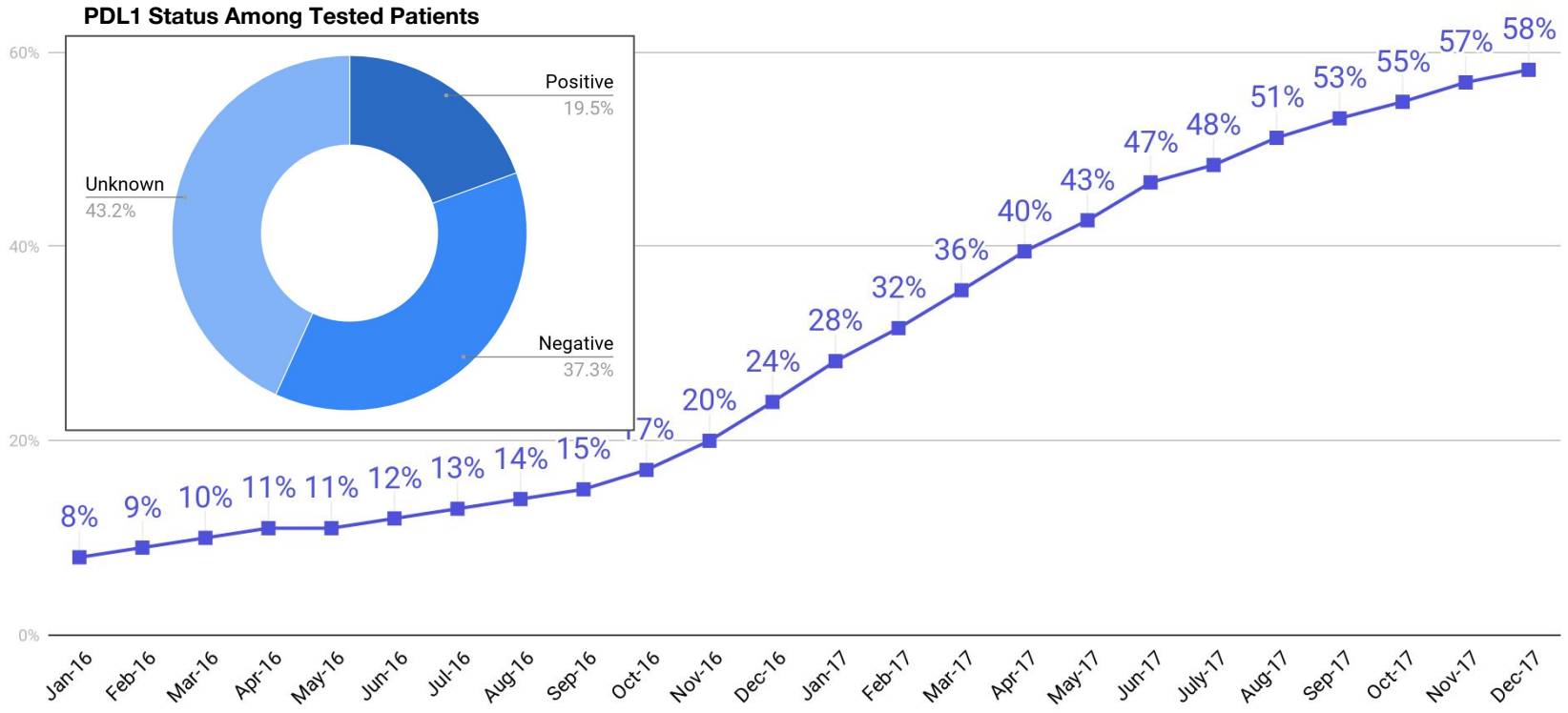
Histology



Smoking Status



PDL1 Biomarker Testing



PDL1 Testing Rate Among Actively Treated Patients

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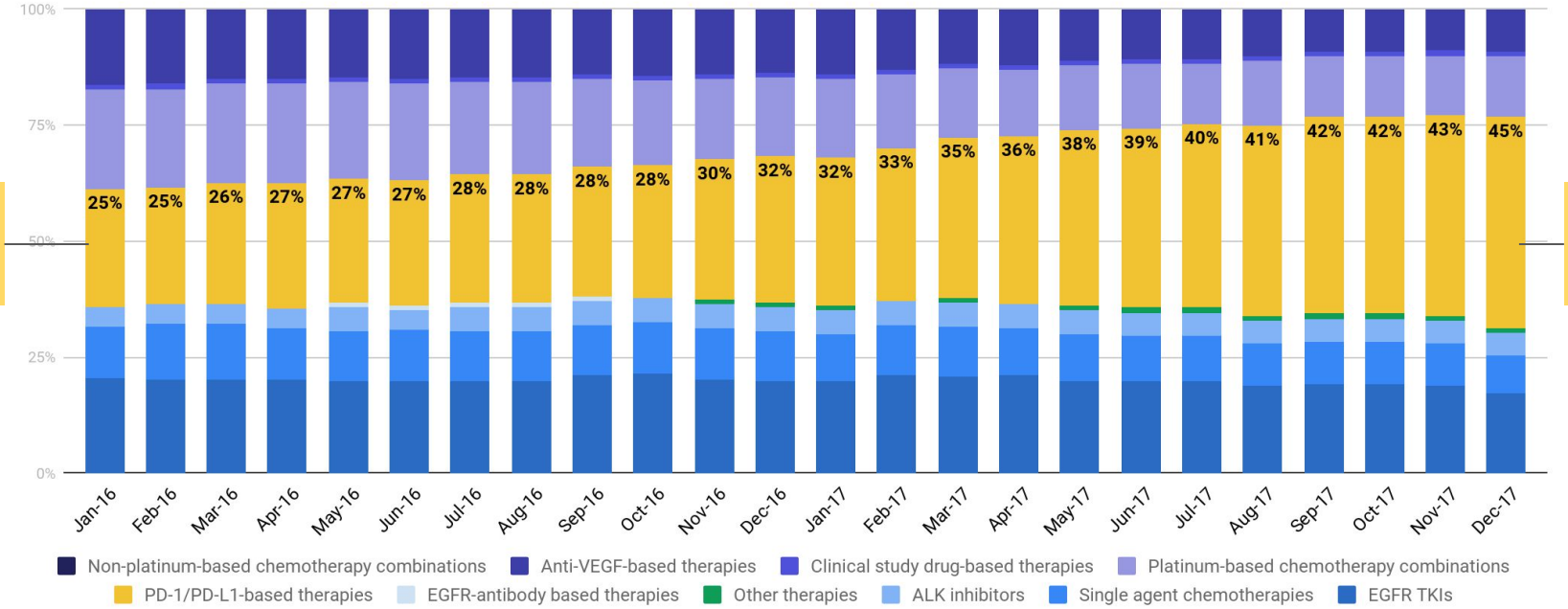
Patient Share by Therapy Class — PD1/PDL1

All Lines

25%
Jan 2016



45%
Dec 2017

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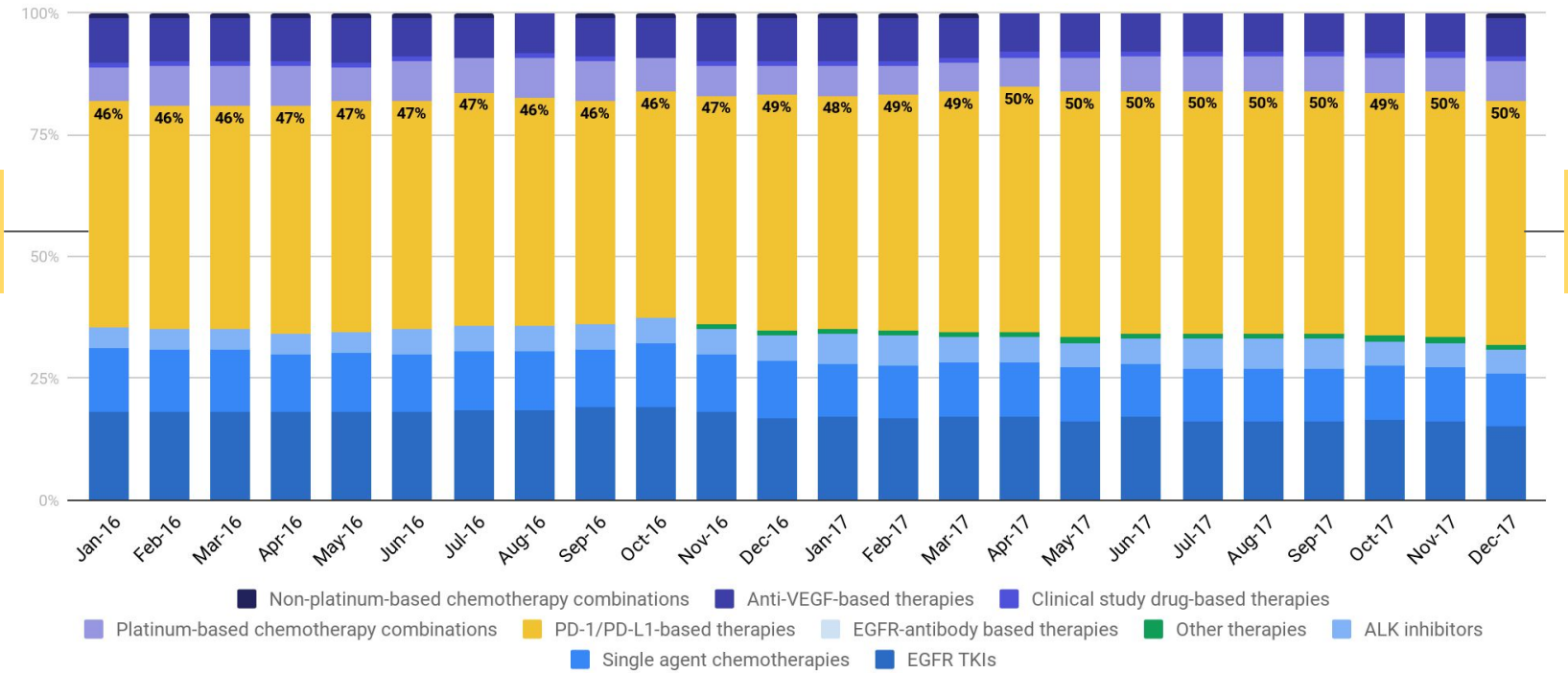
Patient Share by Therapy Class — PD1/PDL1

2nd or 3rd Line+

46%
Jan 2016



50%
Dec 2017

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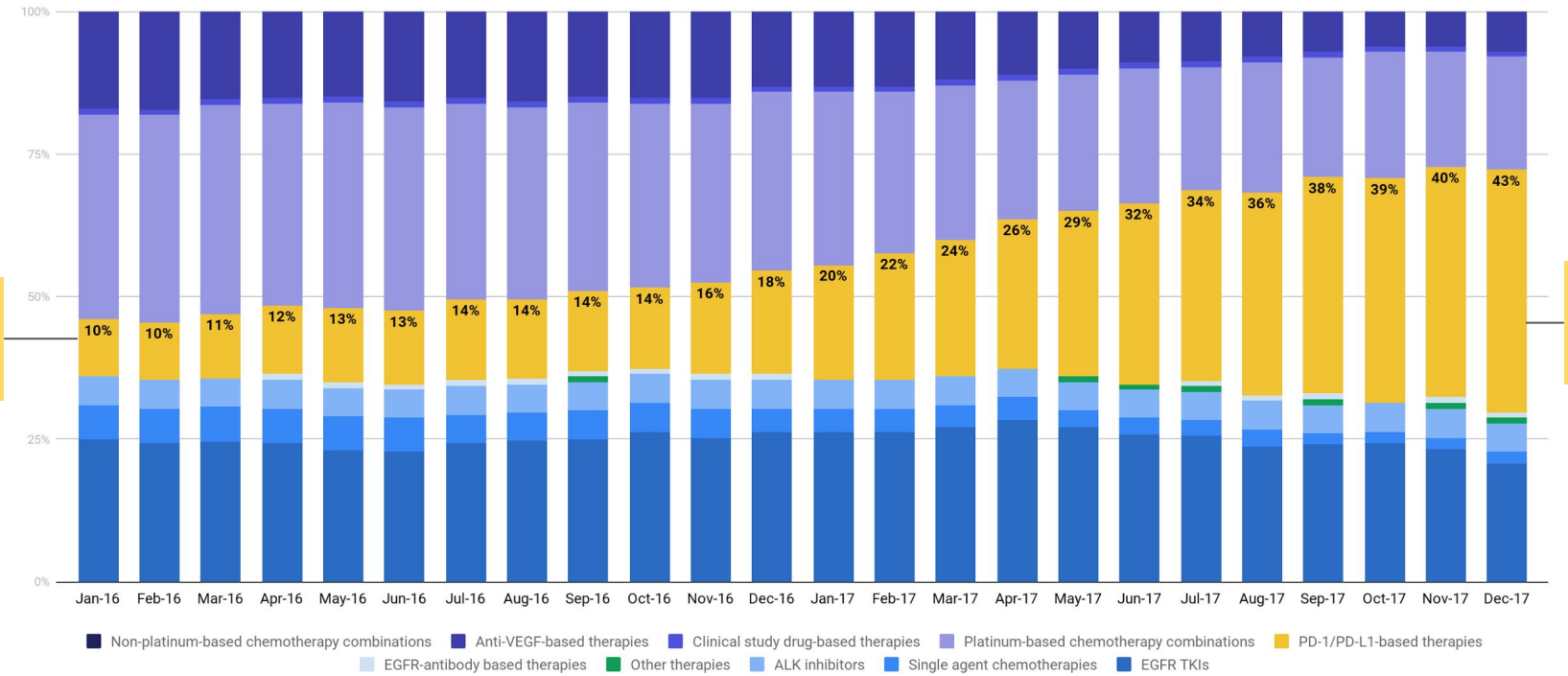
Patient Share by Therapy Class — PD1/PDL1

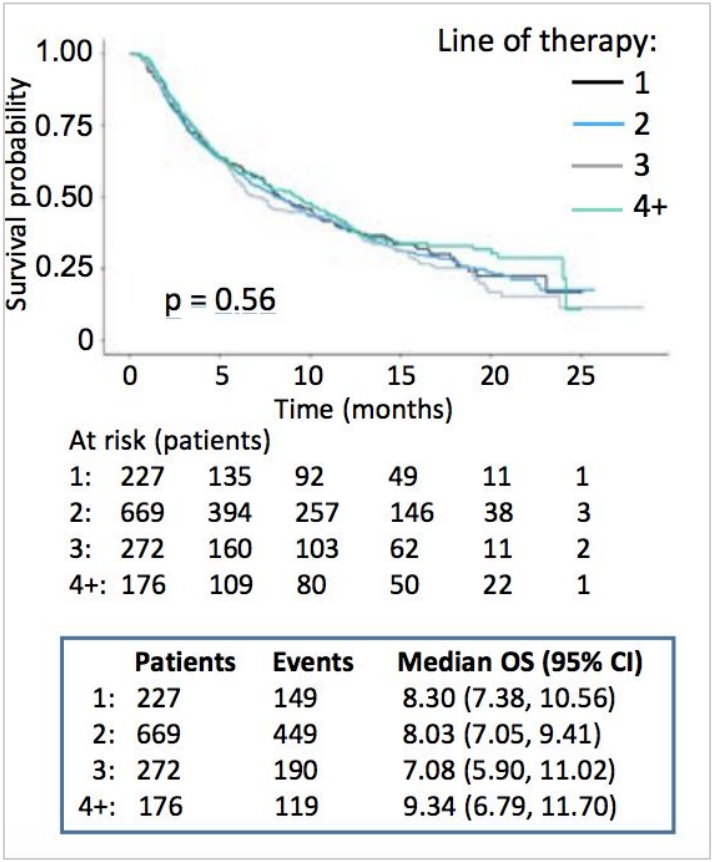
1st Line

10%
Jan 2016



43%
Dec 2017

Overall survival of PD-1 treated mNSCLC patients



At risk (patients)

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

	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)

Findings: Stratification by line of therapy in which patients received their first PD-1 inhibitor did not reveal significant differences in OS estimates

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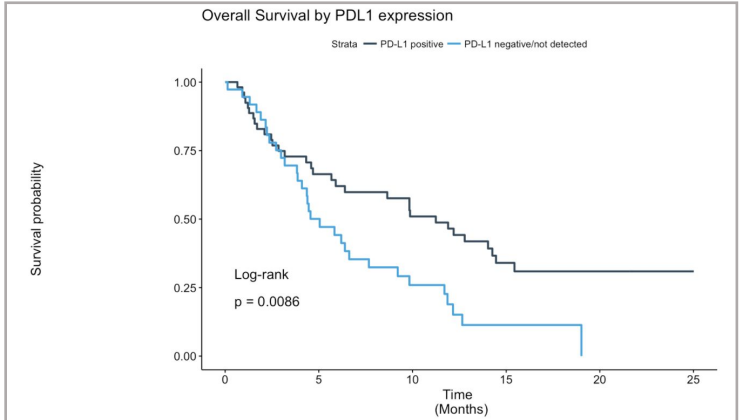
PDL1 expression predicts survival



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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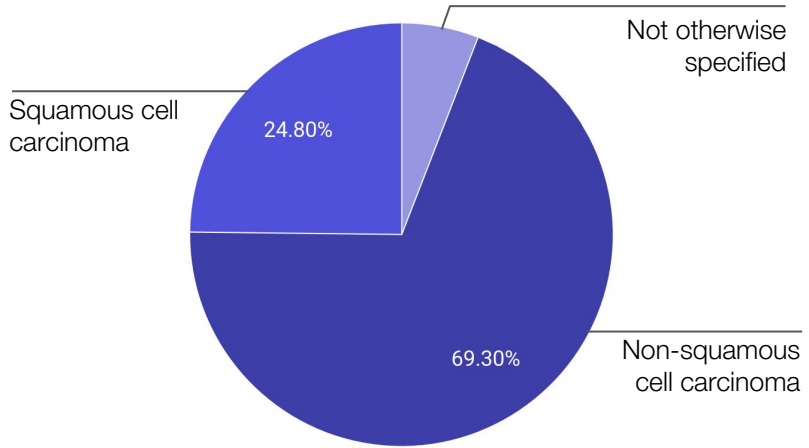
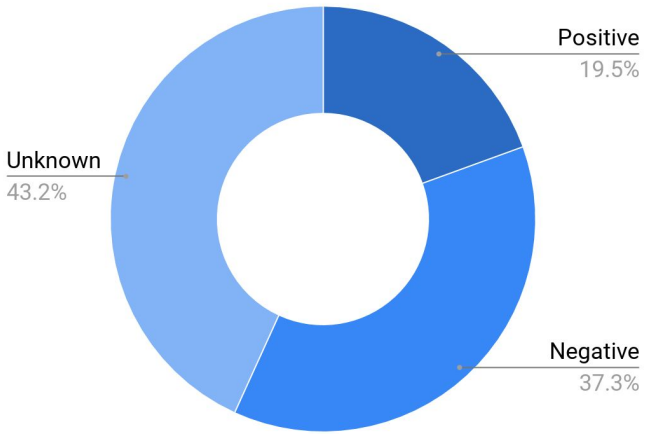
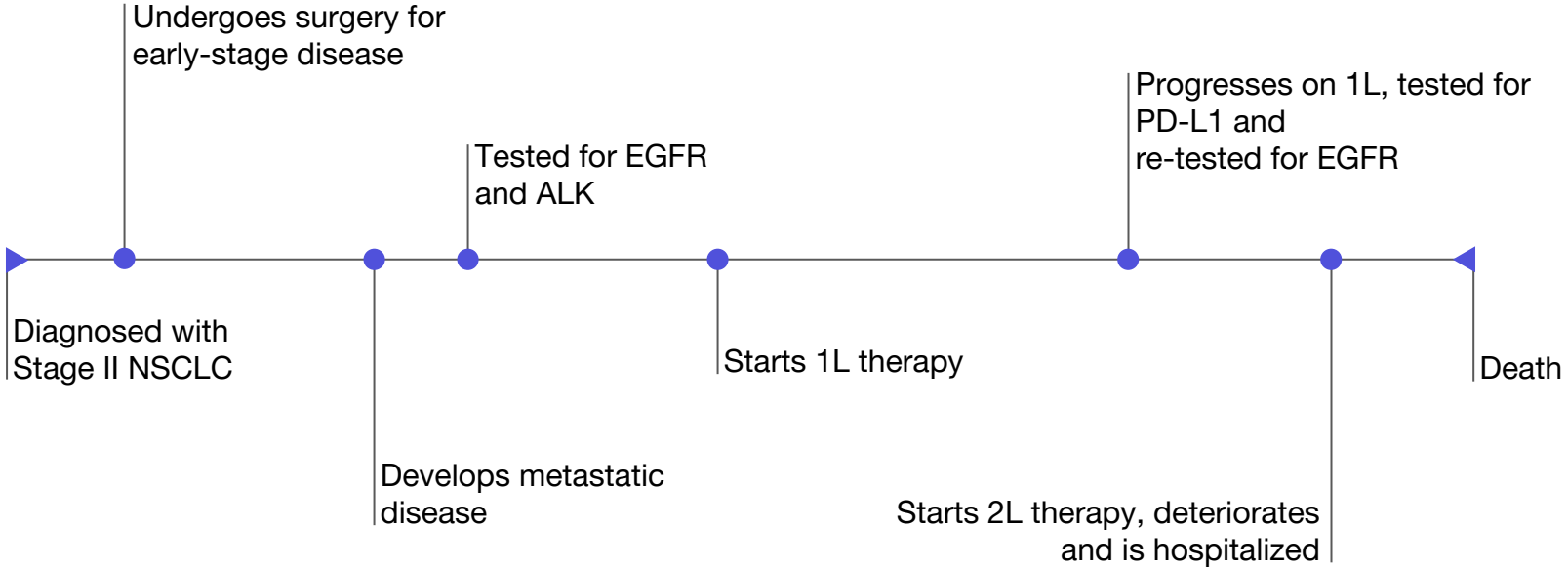
Hinges on Confident Diagnosis

Histology



PDL1 Status





Diagnostic events are a combination of clinical, pathological, radiological, & biomarker data - *in context*

Undergoes surgery for early-stage disease

Tested for EGFR and ALK

Progresses on 1L, tested for PD-L1 and re-tested for EGFR

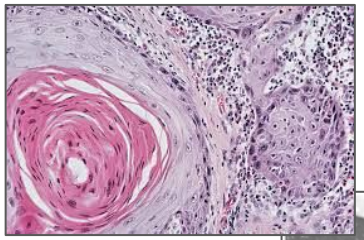
Diagnosed with Stage II NSCLC

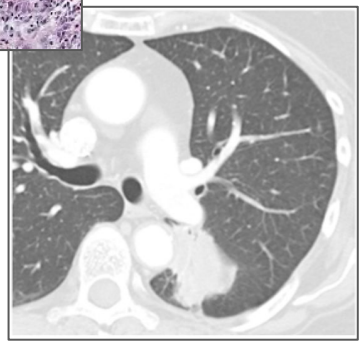
Starts 1L therapy

Death

Develops metastatic disease

Starts 2L therapy, deteriorates and is hospitalized





Gross Description
The specimen is received in formalin labeled with the patient's name. It consists of a 1 x 0.3 x 0.1 cm aggregate of pink-tan to red-pink soft tissue cores and fragments entirely submitted in one block.

Dictated by: GREGORY W SMITH PA
Entered: *02/06/12 - 1544 JAM*

Microscopic Description
The specimen consists of a well differentiated adenocarcinoma, favor lung primary. CK7 and TTF are positive. CK20 is negative. A colleague agrees with this malignant diagnosis.

Dictated by: THOMAS J GRIFONE MD
Entered: *02/07/12 - 1423 SML*

Diagnosis
SPECIMEN SUBMITTED AS TRUCUT BIOPSY LEFT LUNG NODULE:
- WELL-DIFFERENTIATED ADENOCARCINOMA, FAVOR LUNG PRIMARY.
- SEE ABOVE.

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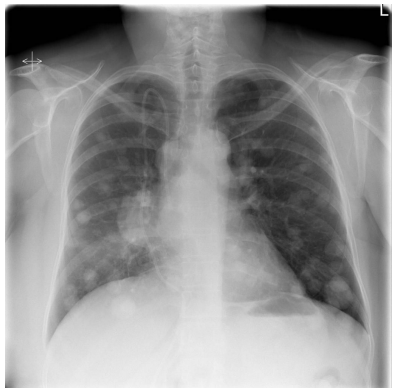

Path?

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Tested for EGFR and ALK

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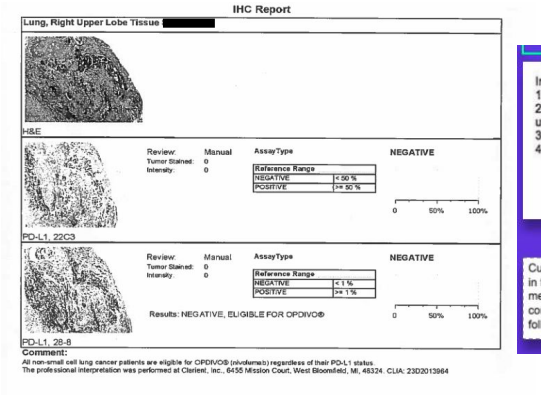
Death

Time to progression is dependent on when patient is evaluated


IHC Report

Lung, Right Upper Lobe Tissue [redacted]

H&E

PD-L1, 22C3

Review: Manual
Tumor Stained: 0
Intensity: 0

AssayType: NEGATIVE

Reference Range
NEGATIVE < 50 %
POSITIVE >= 50 %

0 50% 100%

PD-L1, 28-8

Review: Manual
Tumor Stained: 0
Intensity: 0

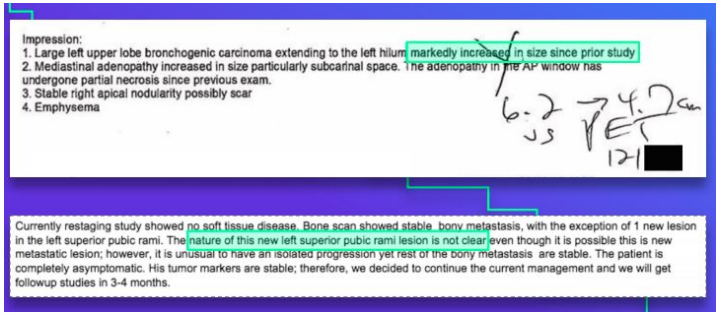
AssayType: NEGATIVE

Reference Range
NEGATIVE < 1 %
POSITIVE >= 1 %

Results: NEGATIVE, ELIGIBLE FOR OPDIVO®

0 50% 100%

Comment:
All non-small cell lung cancer patients are eligible for OPDIVO® (nivolumab) regardless of their PD-L1 status.
The professional interpretation was performed at Clarient, Inc., 6455 Mission Court, West Bloomfield, MI, 48324. CLIA: 23D2013964


Impression:
1. Large left upper lobe bronchogenic carcinoma extending to the left hilum markedly increased in size since prior study
2. Mediastinal adenopathy increased in size particularly subcarinal space. The adenopathy in the AP window has undergone partial necrosis since previous exam.
3. Stable right apical nodularity possibly scar
4. Emphysema

6.2 → 4.7cm
JS PET
121 [redacted]

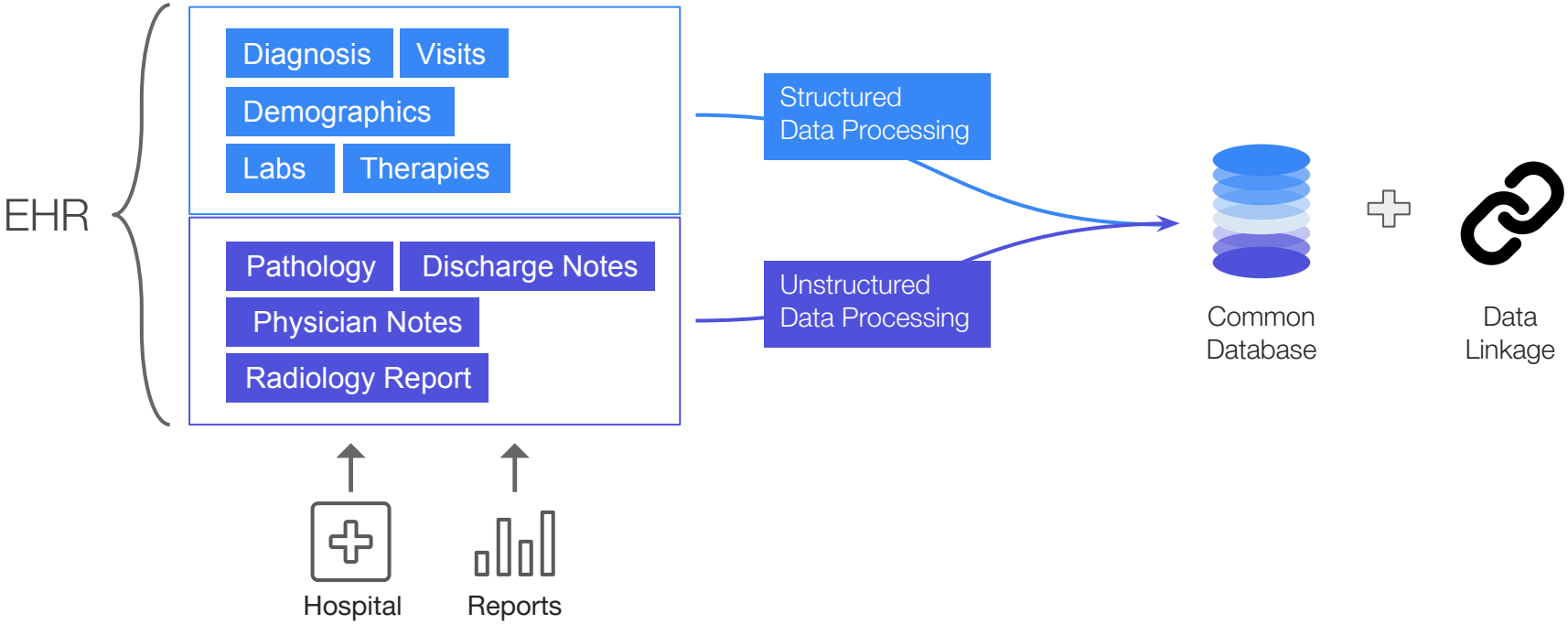
Currently restaging study showed no soft tissue disease. Bone scan showed stable bony metastasis, with the exception of 1 new lesion in the left superior pubic rami. The nature of this new left superior pubic rami lesion is not clear even though it is possible this is new metastatic lesion; however, it is unusual to have an isolated progression yet rest of the bony metastasis are stable. The patient is completely asymptomatic. His tumor markers are stable; therefore, we decided to continue the current management and we will get followup studies in 3-4 months.

Data Management Challenges

- Need for a common data model
- Scaled curation
- Access to identified source documents
- Differences in timing of assessments
- Data provenance
- Traceability
- Standard policies & procedures to synthesize complex clinical data
- Rigorous quality controls

Here's what that looks like at Flatiron...

Data source and curation



Curate in a reliable way (human, AI) and document data quality

and ALK

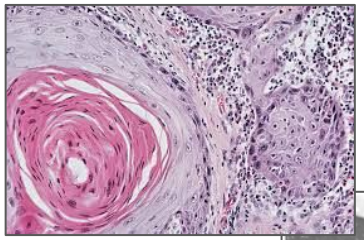
Diagnosed with Stage II NSCLC

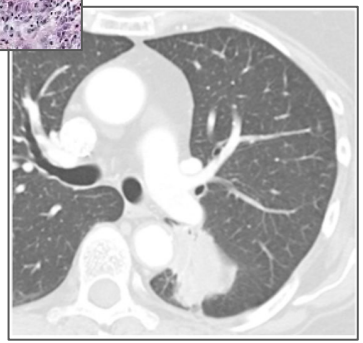
Develops metastatic disease

Starts 1L therapy

Starts 2L therapy, deteriorates and is hospitalized

Death





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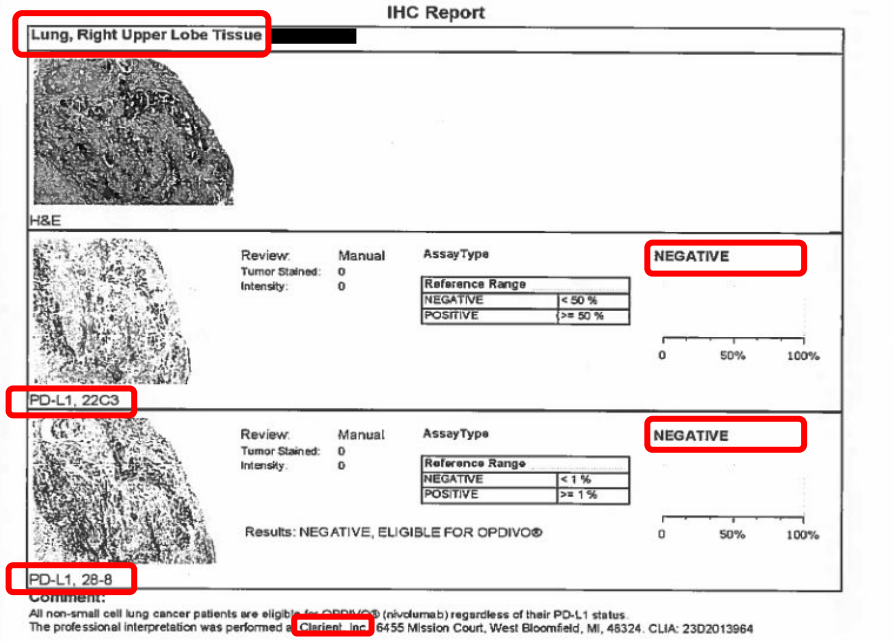
Consistent approach to curating unstructured data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The professional interpretation was performed at Clarient, Inc. 6455 Mission Court, West Bloomfield, MI, 48324. CLIA: 23D2013964

PD-L1 IHC Report Scanned into EHR Contains Rich Data:

- 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

… for every test the patient receives

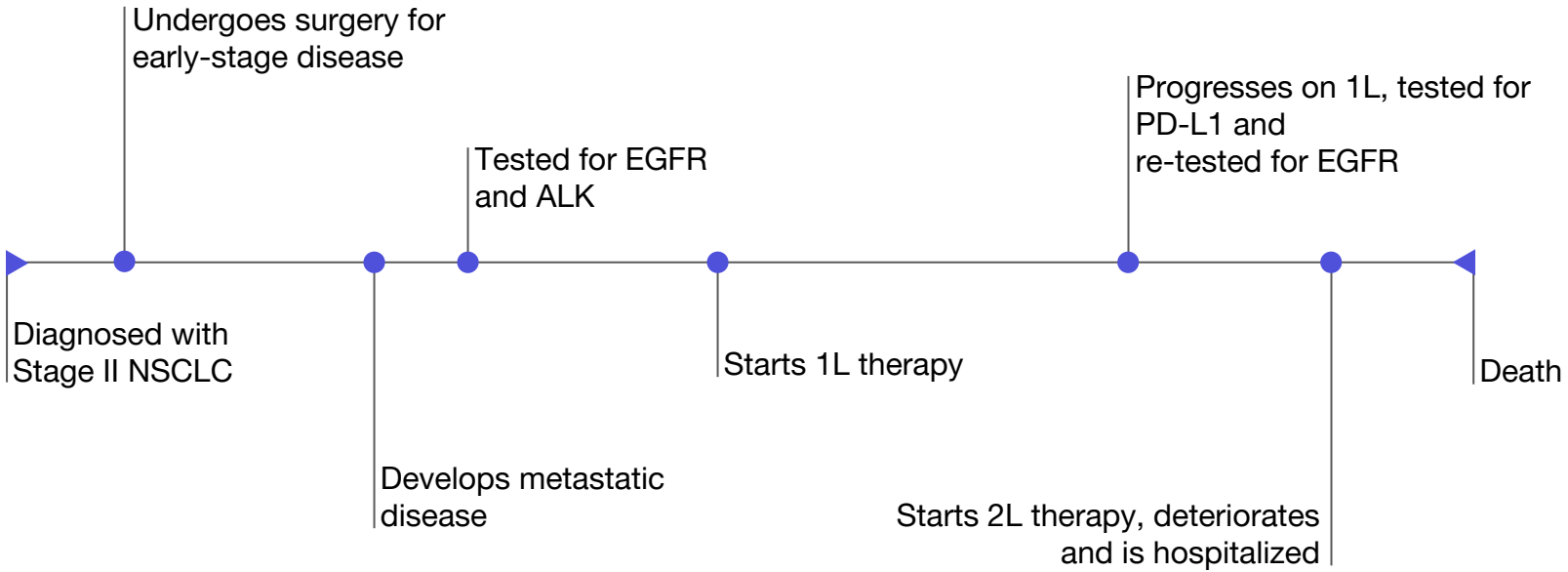
Technology Enabled Abstraction

Expert abstractors

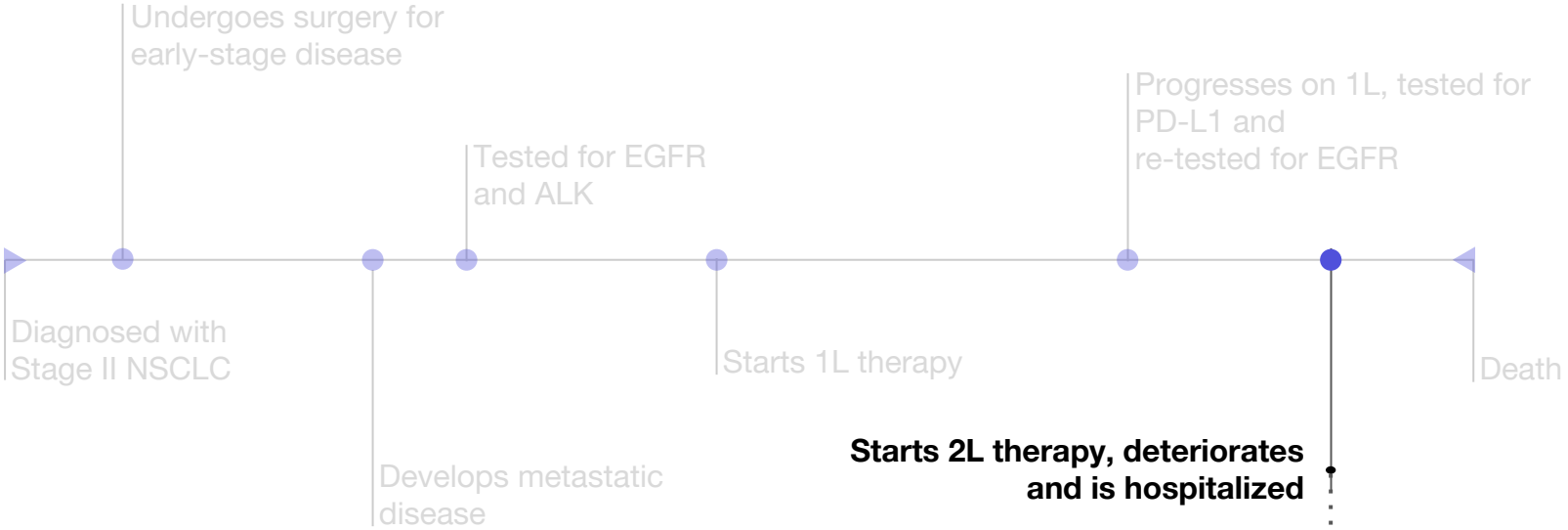
A network of abstractors comprised of oncology nurses, certified tumor registrars, and oncology clinical research professionals.

Flatiron Technology

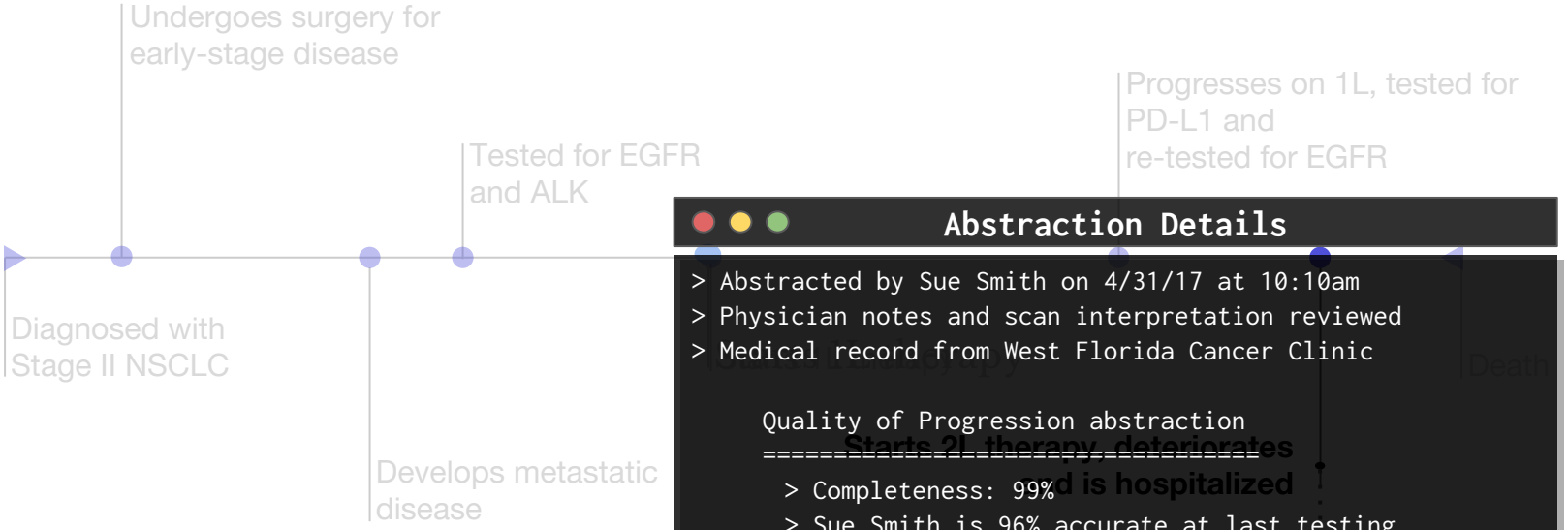
Software helps trained human abstractors efficiently organize and review unstructured documents to capture key data elements in predetermined forms.



Documentation of source, quality and provenance.



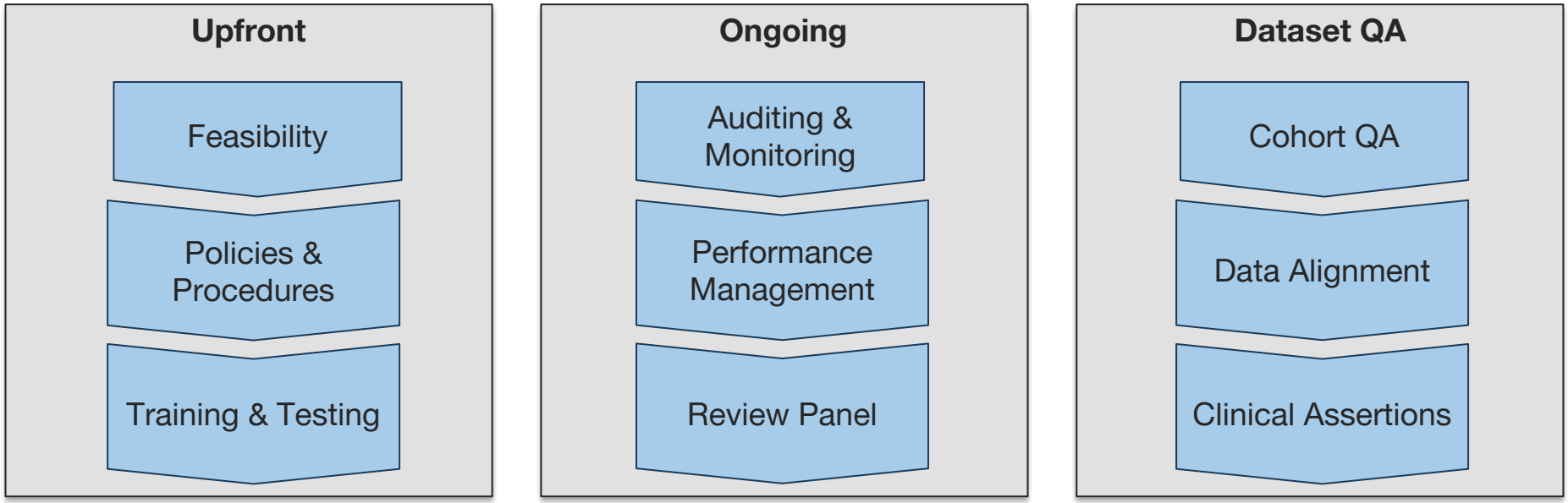
Patient	Stage at Dx	Biomarkers	2L Treatment	**Progression**	Date of Death
Jane Doe	II	EGFR-, ALK-, PD-L1-	nivolumab	2017-03-08	2017-04-12



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

Quality assurance & quality control

Centralized Controlled Environment



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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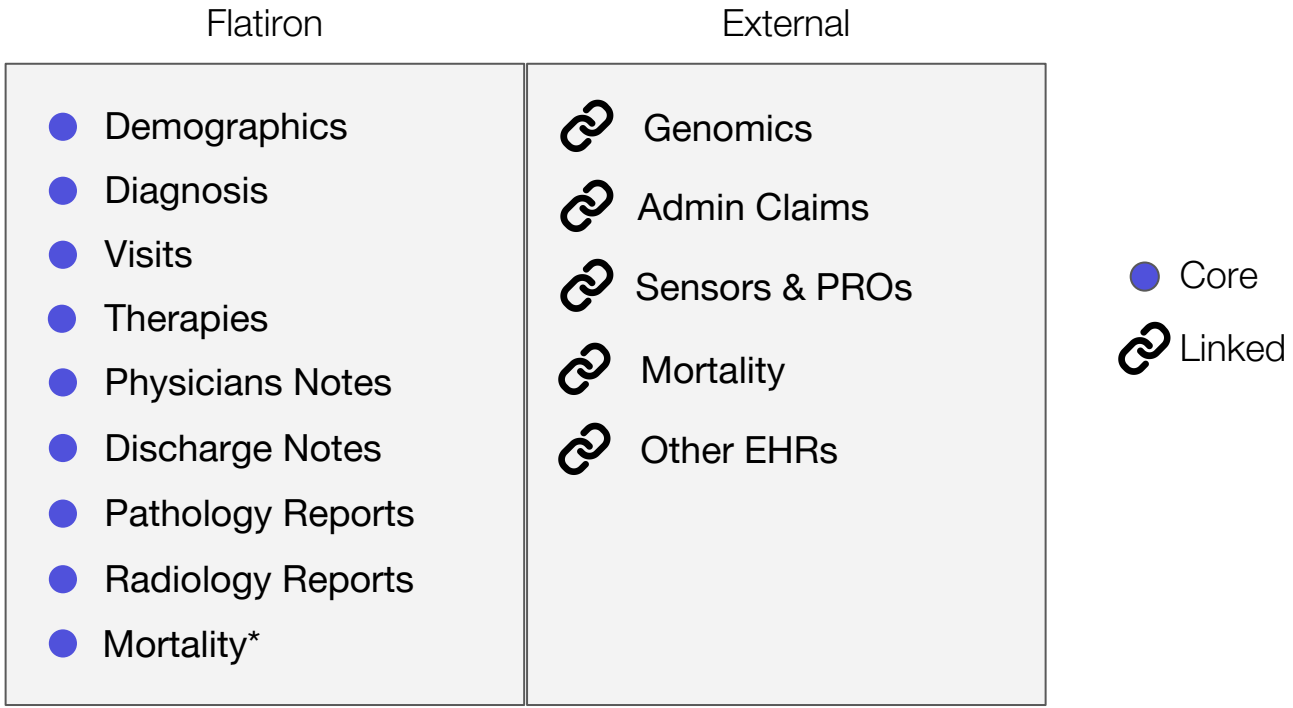
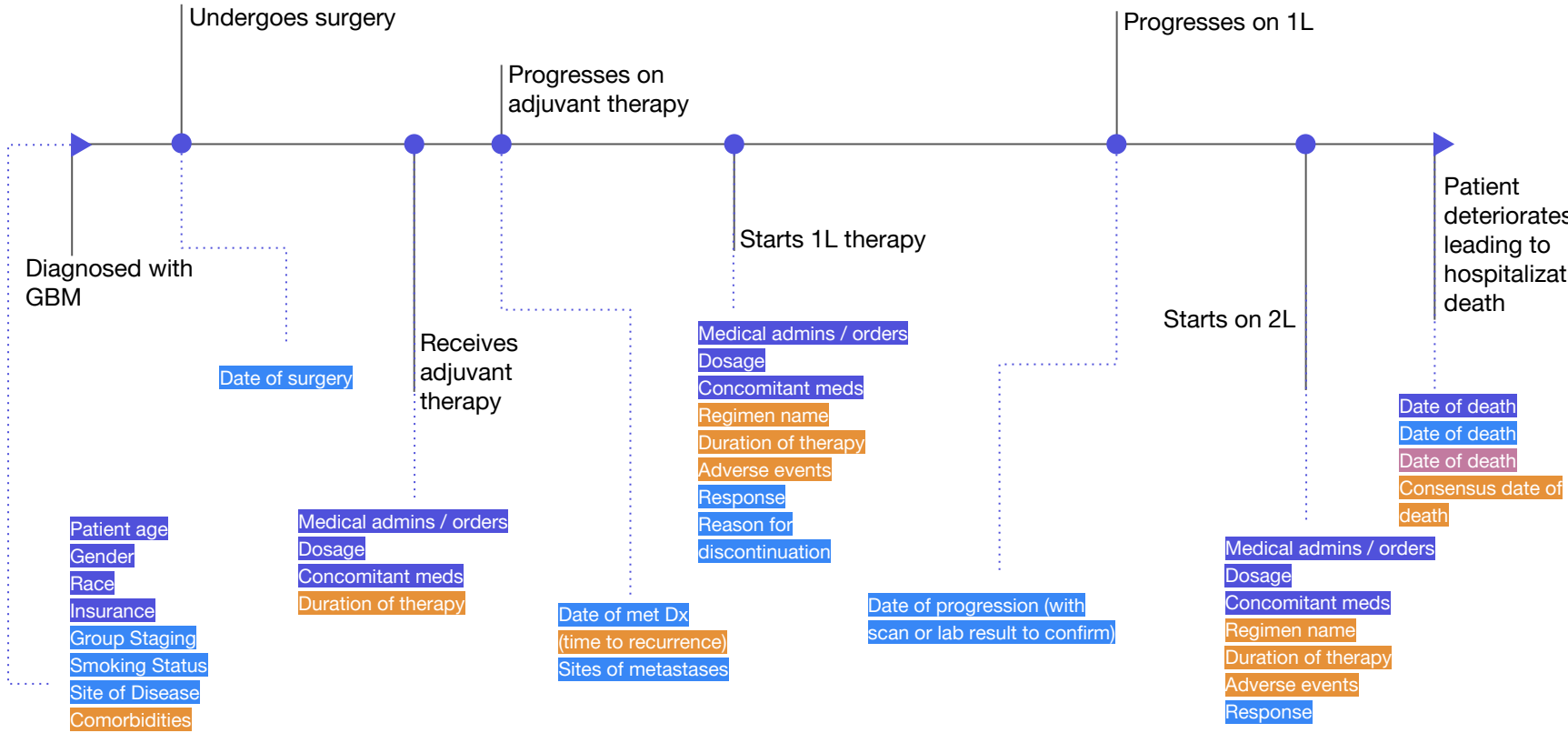
Link Datasets



A comprehensive view of the patient journey



*Relative timing not exact

Collaboration with the FDA

- Determine how and when Flatiron data can be used to document the effectiveness and safety of cancer drugs
- Define optimal ways to analyze Flatiron data
- Document endpoints (e.g., evidence of tumor burden or survival) that are clinically meaningful in the Flatiron data
- Best describe the reliability and quality of our data for end-users

elements.[2]

RWE QUALITY

RWE is generated from high-quality data that are 1)
from relevant RWD sources, 2) cleaned, harmonized,
ed 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).

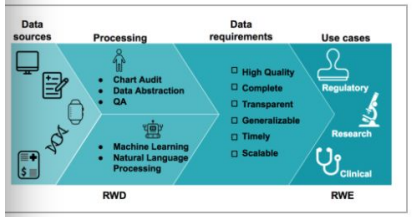


Figure 1. Open in figure viewer | Download Powerpoint slide

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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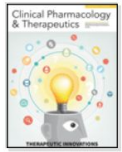
Citation tools

Early View



Browse Early View Articles

Online Version of Record published before inclusion in an issue

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 Concerns

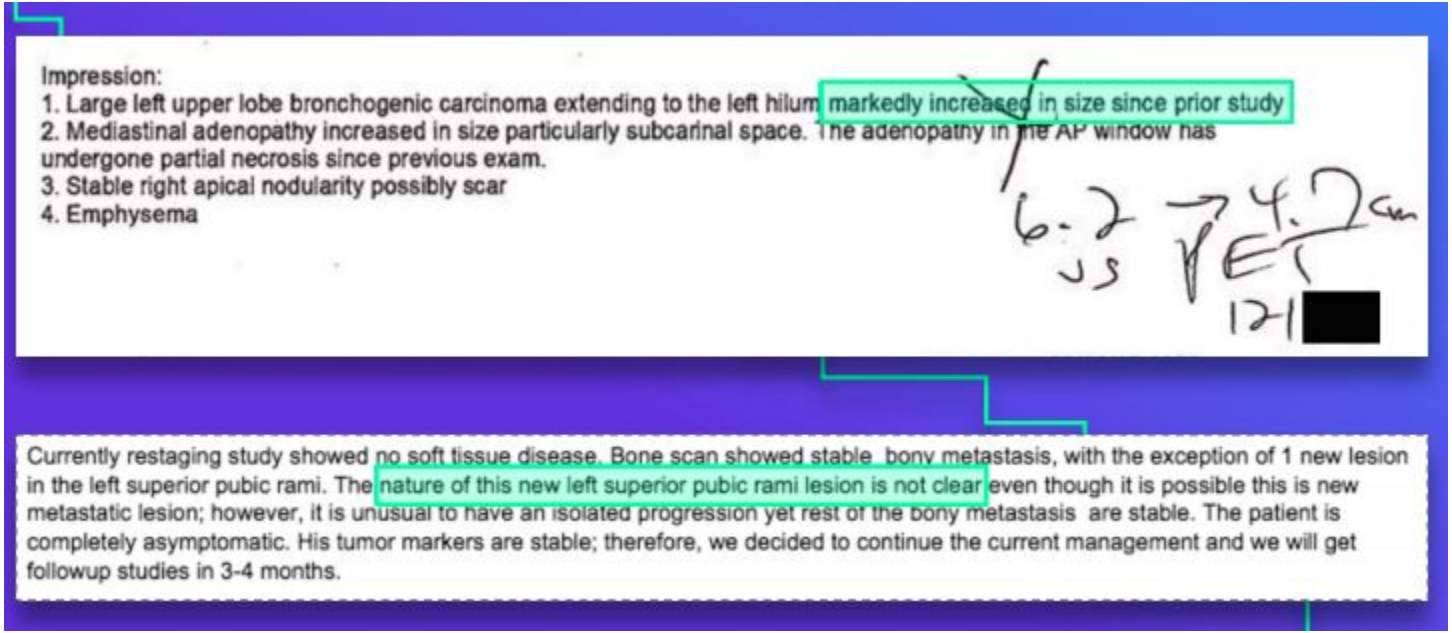
These will always be there, so, we need to figure out a way to address them

Challenges with Images

Images captured as part of routine care differ in meaningful ways from those captured within clinical trials:

- Raw images are not available for central review
- Imaging reports generated outside of clinical trials often lack info needed for RECIST
- RECIST requires comparison to prior charts. Radiologists interpreting imaging may not have access to prior images.

Accounting for Changing Interpretations Over Time



Impression:
1. Large left upper lobe bronchogenic carcinoma extending to the left hilum markedly increased in size since prior study
2. Mediastinal adenopathy increased in size particularly subcarinal space. The adenopathy in the AP window has undergone partial necrosis since previous exam.
3. Stable right apical nodularity possibly scar
4. Emphysema

6.2 → 4.7 cm
VS PET
121 [redacted]

Currently restaging study showed no soft tissue disease. Bone scan showed stable bony metastasis, with the exception of 1 new lesion in the left superior pubic rami. The nature of this new left superior pubic rami lesion is not clear even though it is possible this is new metastatic lesion; however, it is unusual to have an isolated progression yet rest of the bony metastasis are stable. The patient is completely asymptomatic. His tumor markers are stable; therefore, we decided to continue the current management and we will get followup studies in 3-4 months.

Need a consistent approach to documenting quality

Appendix B: Flatiron Health PD-L1: Inter-rater agreement and kappas on abstracted variable

Project: **FDA** **PD-1 inhibitors in aNSCLC**

Note: For questions where a high percentage of patients have a common answer (e.g., PD-L1 testing status), kappa may be significantly lower than inter-rater agreement. In these cases, it may be more accurate to use inter-rater agreement to measure reliability of the data.

Kappas scale	
Almost perfect	0.8 to 1.0
Substantial	0.6 to 0.8
Moderate	0.4 to 0.6
Fair	0.2 to 0.4
Slight	0 to 0.2

Table: Enhanced_AdvancedNSCLC

Summary of variable inter-rater agreement and kappas

Variable	Description of variable	Corresponding question(s) on abstraction form	Question type	Inter-rater agreement (exact day for dates)	Kappa (exact agreement)	Kappa (30-day window for dates)
DiagnosisDate	Date of initial diagnosis	Enter the date of initial diagnosis	date	0.795	0.794	0.902
AdvancedDiagnosisDate	Date of diagnosis of advanced disease: first recurrence or metastasis	Enter the date of the first diagnosis of metastatic or advanced NSCLC	date	0.695	0.695	0.796
MetastaticDiagnosisDate	Date of diagnosis of metastatic disease	Enter the date of initial diagnosis [for ~55% of patients in the cohort who are diagnosed metastatic]	date	0.795	0.794	0.902
		Enter the date of distant metastatic diagnosis [for ~45% of patients in the cohort who are diagnosed non-metastatic]	date	0.527	0.476	0.557
Histology	Histology	Select the histology	drop down	0.947	0.894	
GroupStage	Group stage at time of initial diagnosis	Select the group stage	drop down	0.848	0.768	
SmokingStatus	Documented history of smoking	Smoking status	drop down	0.934	0.695	
EgfrTested	Indicator of whether the tumor was tested for a EGFR mutation	Was the tumor tested for a EGFR mutation?	boolean	0.927	0.84	
AlkTested	Indicator of whether the tumor was tested for an ALK rearrangement	Was the tumor tested for an ALK rearrangement?	boolean	0.901	0.791	
PdL1Tested	Indicator of whether the tumor was tested for PD-L1 expression	Was the tumor tested for PD-L1 expression?	boolean	0.901	0.547	
KrasTested	Indicator of whether the tumor was tested for a KRAS mutation	Was the tumor tested for a KRAS mutation?	boolean	0.894	0.728	
Ros1Tested	Indicator of whether the tumor was tested for a ROS-1 rearrangement	Was the tumor tested for a ROS-1 rearrangement?	boolean	0.881	0.725	

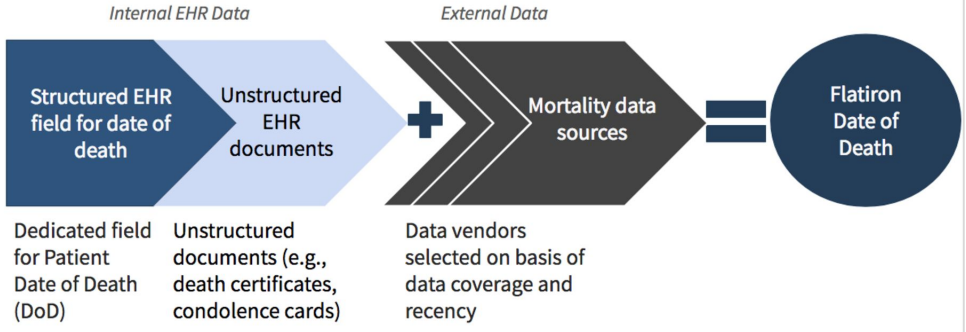
Validation of Endpoints

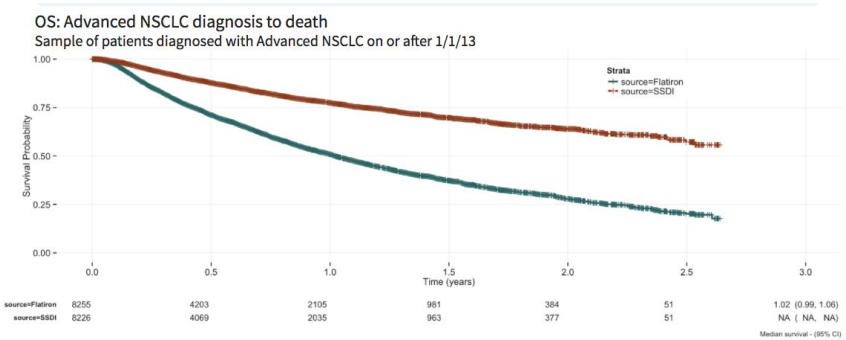
Data Quality & Validation Framework	
Face Validity	• Oncologist agreement with definition & approach
	• Regulator and other stakeholder agreement with definition & approach
Feasibility & Quality of Variables (structured & abstracted)	• Completeness of collected data
	• Inter-rater agreement on progression dates for duplicate abstracted patients
	• Qualitative feedback from abstractors reviewing the medical records
Validity of Outputs	• Likelihood of predicting a downstream event (e.g., overall survival)

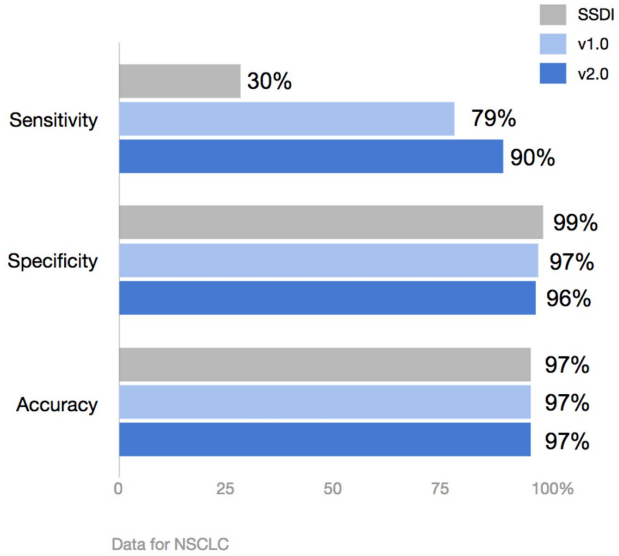
	• Association between OS and PFS/TTP
	  ○ Patient-level correlation
	  ○ Responsiveness of endpoint to treatment effects

Evaluate data against a reference standard

E.g., gold standard = National Death Index







flatiron

Data in context reinforces diagnostic accuracy

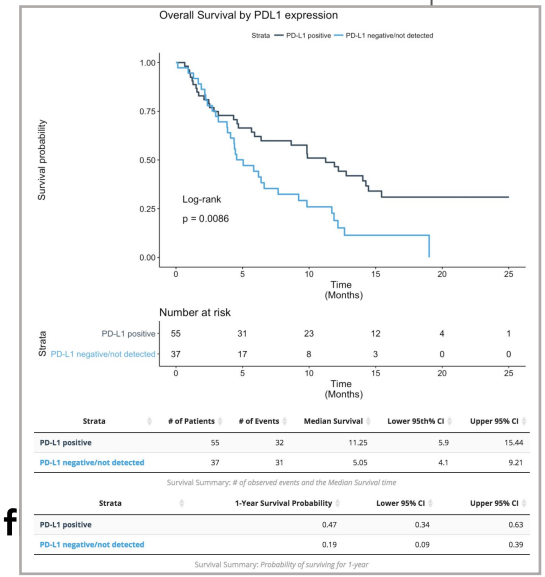
Progresses on 1L, tested for PD-L1 and re-tested for EGFR

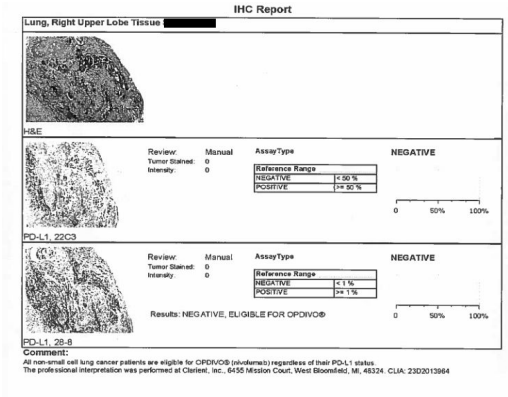
Diagnosed with Stage II NSCLC

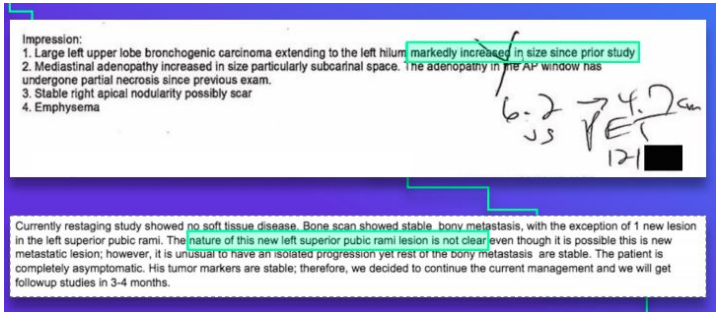
Starts 1L therapy

Starts 2L therapy, deteriorates and is hospitalized

Death



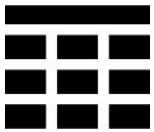




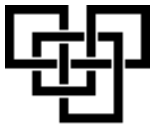
Labeled data helps with AI / machine learning

Increasing importance

Find **labeled data**



Extract good **features**



Train a **model**

> 500k patients processed

Clinically informed features

Duke Cancer Institute · imshealth · Genentech · Memorial Sloan Kettering Cancer Center · 23andMe · HUMEDICA An Optum Company · MERCK · Florida Cancer Specialists & Research Institute · Cleveland Clinic · McKESSON · Altos Solutions · ONYX Pharmaceuticals

Technical expertise

Google · Microsoft · IBM · a · Palantir · livingsocial · Spotify · Bloomberg

Problems to be Solved

- Ambiguous interpretation
- Differing issues in scan timing
- Data curation standards with appropriate labeling to support AI/ML
- Data linkage - privacy while maintaining adequate information for context
- Consistent approach to documenting data quality
- Consistent endpoint definitions
- Appropriate use of AI/ML

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
- Regulatory policy that drives standards
  - Consistent approach to documenting data quality
  - Consistent endpoint definitions
  - Incorporating machine learning and AI

Take Home Summary

- Data sharing consortiums 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
- With respect to diagnostic data quality, we must resolve issues related to ambiguous interpretation, differences in scan timing, data curation standards, evaluation of data in context, and the roles of machine learning and artificial intelligence