Welcome to the Sentinel Innovation and Methods Seminar Series

The webinar will begin momentarily

Please visit www.sentinelinitiative.org for recordings of past sessions and details on upcoming webinars.

Note: closed-captioning for today's webinar will be available on the recording posted at the link above.

Sentinel

March 30, 2021

Mortality in real world research

Development and Validation of a real world variable

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Senior Medical Director, Flatiron Health

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Agenda

Brief Overview of Flatiron Health

Development of a composite mortality variable

OUR MISSION

To improve lives by learning from the experience of every cancer patient.

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Over 2.5 million

patient records available for research.

Over 15 of the top

oncology-pharma companies are subscribers of Flatiron's products and services.

800 sites of care

use Flatiron's OncoCloud™ software.

7 academic centers

partner with Flatiron on outcomes research and quality improvement.

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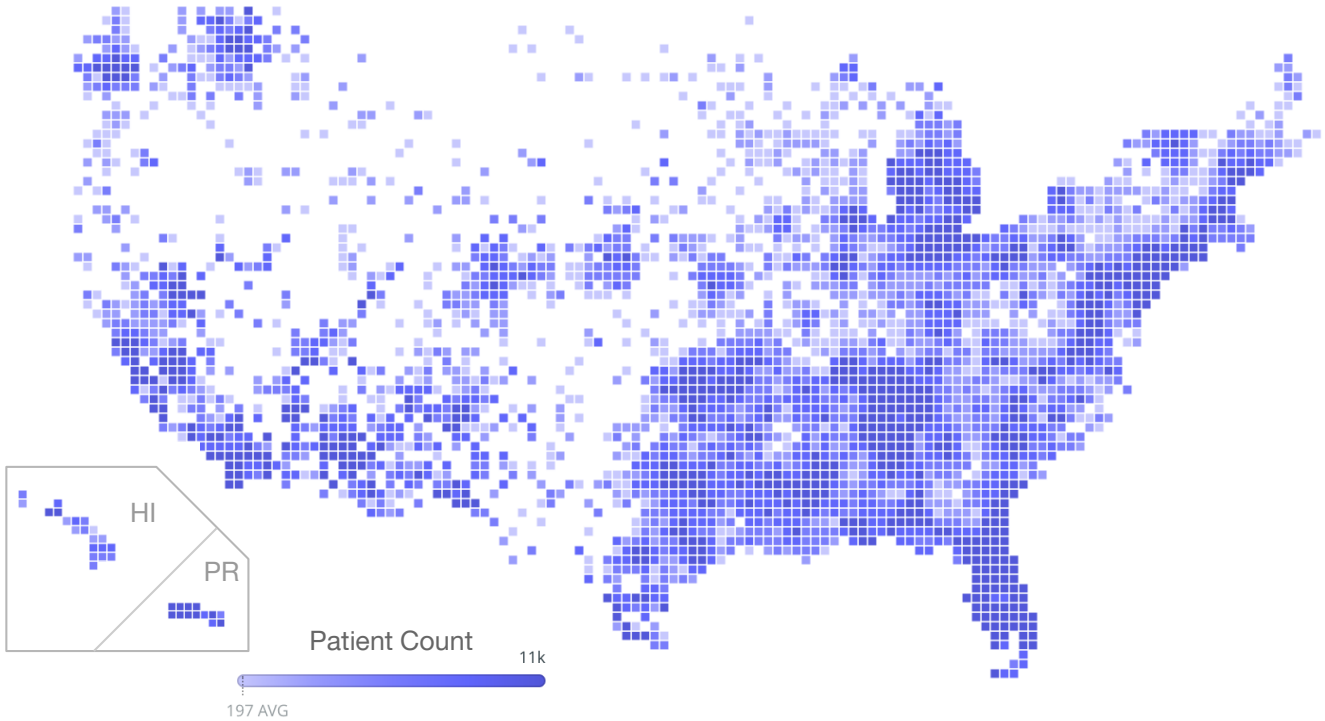
The Flatiron Network



2.5M+
Patients

2,600+
Clinicians

280
Cancer Clinics

7
Academic Medical Centers

800+
Unique Sites of Care

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Data is sourced through OncoEMR or Flatiron for Academics

ONCOEMR®

Cloud-based EHR with oncology-specific workflows used in the community setting

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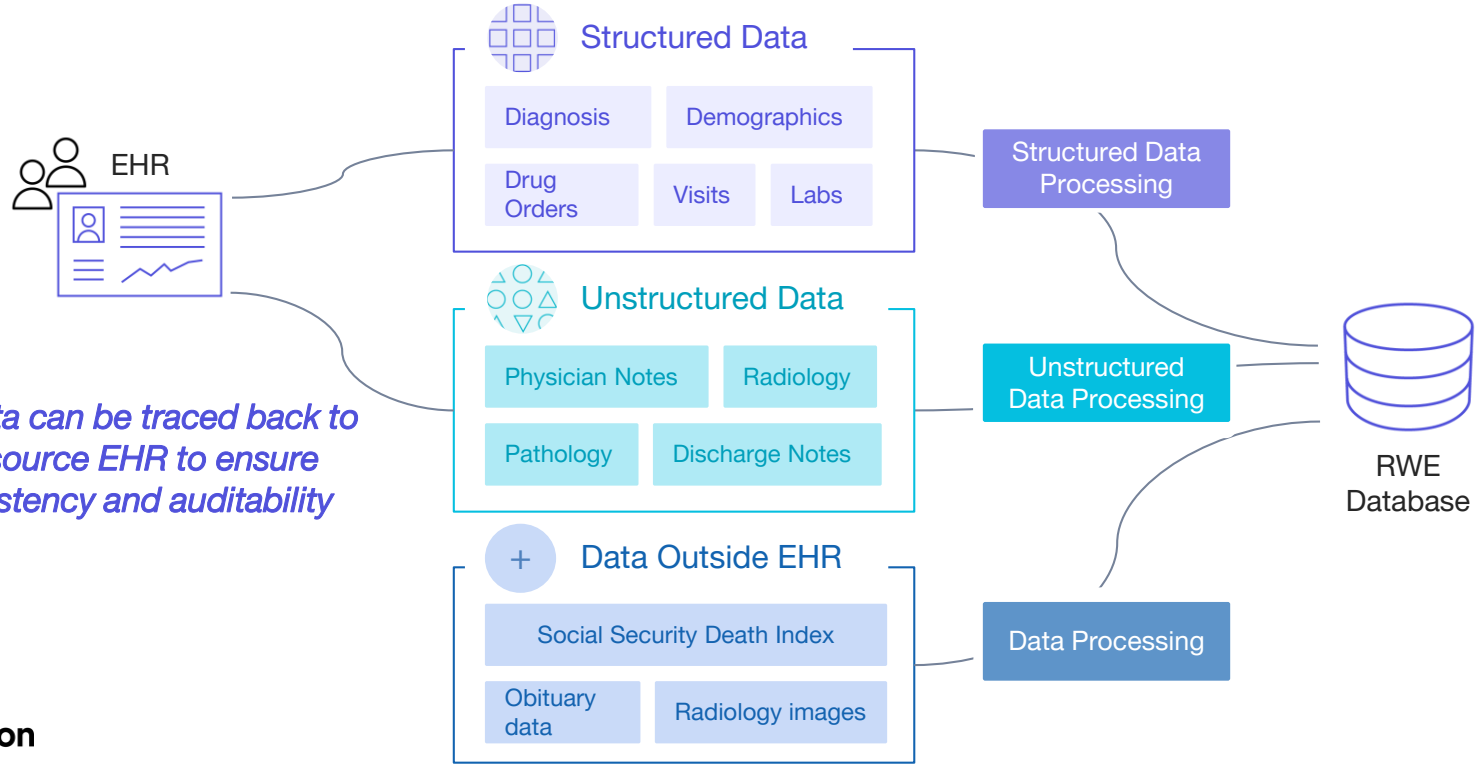
FOR ACADEMICS

Analytics platform that is integrated and ingests data from other EHR systems used in for academic institutions

Flatiron is fully integrated at the source for both OncoEMR and Flatiron for Academics and harmonize all data into uniform, standard data models

We combine structured and unstructured data in our real-world database to capture cancer patients' experience



Our data can be traced back to the source EHR to ensure consistency and auditability

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EDM

Our foundational data product reflects each cancer patient's longitudinal journey from diagnosis to real-world outcomes

Advanced NSCLC	Advanced G/E Cancer	Ovarian Cancer
Metastatic CRC	Metastatic Pancreatic Cancer	SCLC
Metastatic Breast Cancer	Early Breast Cancer	DLBCL
Metastatic Prostate Cancer	Advanced Urothelial Carcinoma	HCC
CLL	Metastatic RCC	Follicular Lymphoma
Multiple Myeloma	Advanced Head & Neck Cancer	Acute Myeloid Leukemia
Advanced Melanoma	Endometrial Cancer	Mantle Cell Lymphoma

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Why does a complete and timely mortality dataset matter?

- A key goal of cancer research is to show a survival benefit
- Death is the only objective outcome
- In clinical research, much effort is dedicated to collecting death data, yet in real-world datasets this data is inherently less complete

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A complete, timely, accessible source of real-world death data does not exist

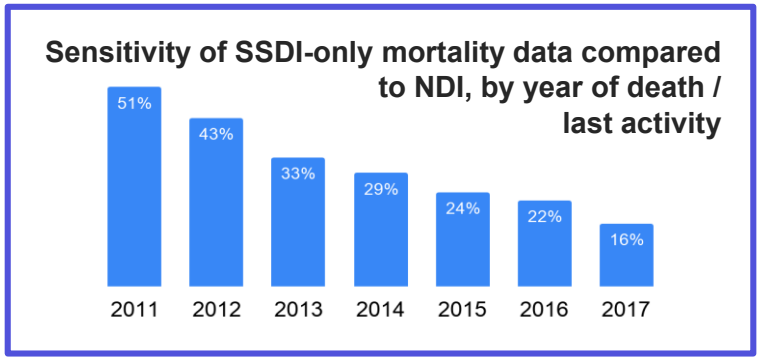
~~SSDI~~

- ✗ Complete
- ✓ Timely
- ✓ Accessible

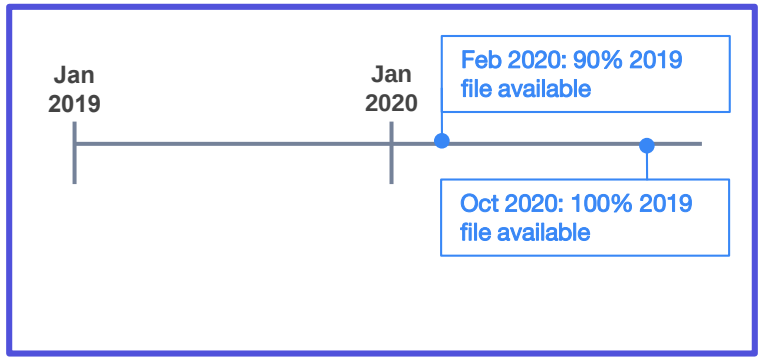
~~NDI~~

- ✓ Complete
- ✗ Timely
- ✗ Accessible

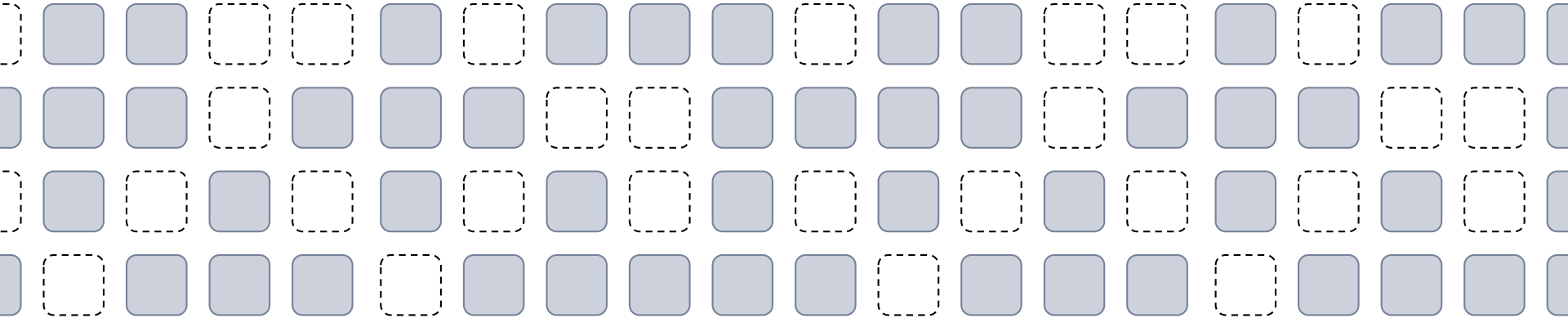
Precipitous decline in completeness since 2011



Records can be nearly 2 yrs delayed



In addition, approximately 35% of actual deaths are missing from structured EHR fields.



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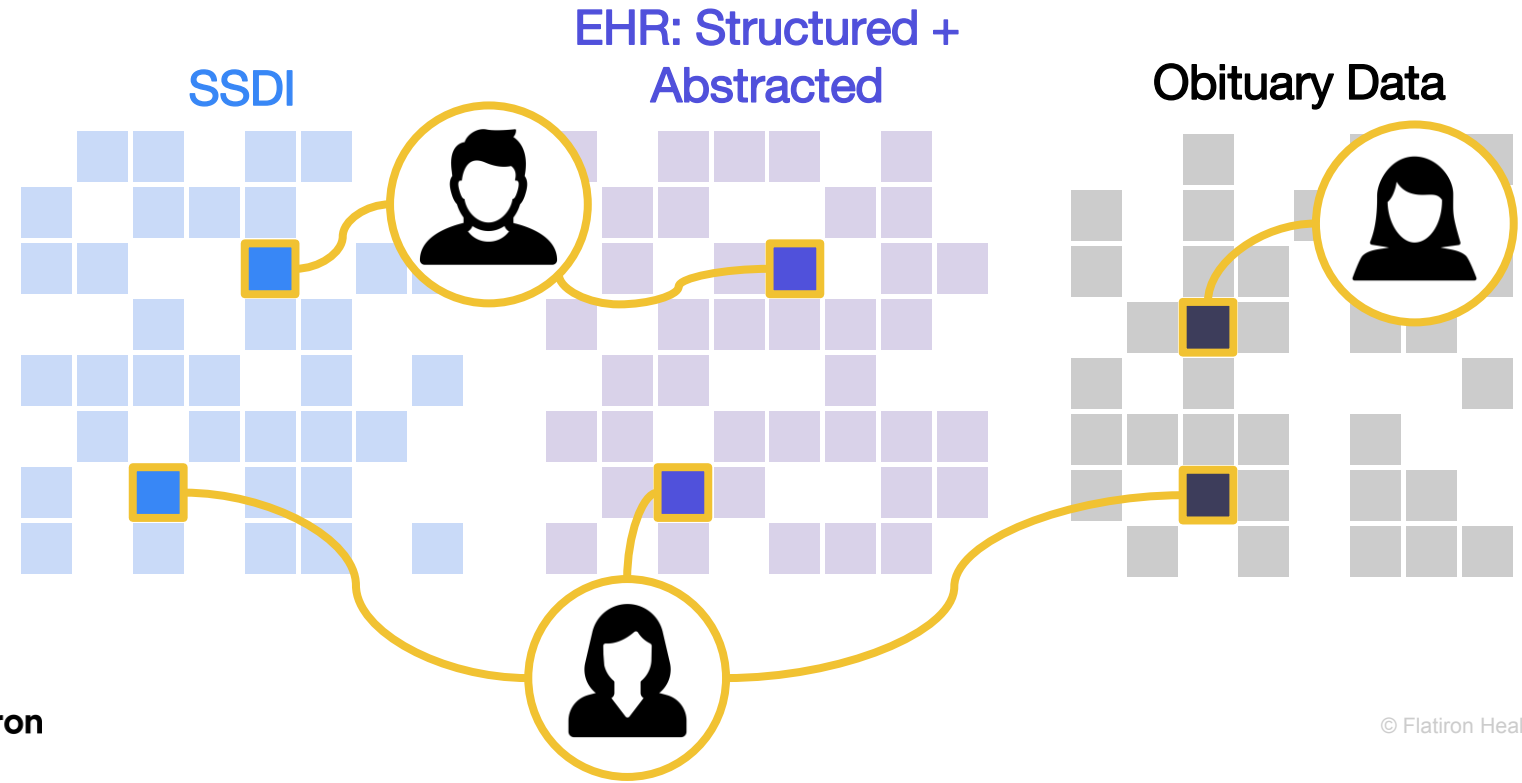
Our linking algorithm combines data across multiple data sets



Flatiron's approach: composite variable, maintaining versioning along the way

May 2018 *HSR* Publication*

v1.0

- Structured DoD
- Obituary data with 1.0 linking algorithm

v2.0

- Structured DoD
- Unstructured Documents
- Obituary data with next-generation linking algorithm
- SSDI

v2.1

- Structured DoD
- Unstructured Documents
- Further advances in obituary data linking
- SSDI

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*Curtis M et al. Development and Validation of a High Quality Composite Real-World Mortality Endpoint. *Health Services Research* 14 May 2018 doi:10.1111/1475-6773.12872

Flatiron's linkage is optimized based on comparative analyses with the gold-standard NDI

- We generate a consensus date of death across all 3 **structured** data sources, with the following hierarchy where there are multiple dates of death:

1. If all 3 dates are in agreement, FH selects the associated date
2. If any 2 dates are in agreement, FH selects the associated date
3. If none of the dates are in agreement, FH employs a ranking:
   1. SSDI
   2. Obituary data
   3. EHR

- We layer in the **abstracted date of death**, and use the abstracted date of death over the structured date of death when there is day-granularity available in the unstructured EHR

When benchmarking our composite mortality variable to the National Death Index across 18 cancer types, we observe:

- **high sensitivity** (≥ 87%)
- **high specificity** (≥ 94%)
- **high date accuracy** (≥ 96% with +/- 15 day window)

Date agreement

Table 1. Ranges of validity metrics for the composite mortality variable across the 18 cancer type-specific cohorts

		Composite mortality variable*	Structured EHR only	OD only	SSDI only
Sensitivity		83.9 - 91.5%	54.0 - 70.7%	53.8 - 67.2%	17.7 - 32.3%
Specificity		93.5 - 99.7%	95.7 - 99.9%	96.9 - 99.8%	98.5 - 99.9%
PPV		96.3 - 98.3%	97.3 - 98.7%	96.2 - 98.9%	96.1 - 99.2%
NPV		75.0 - 98.7%	46.4 - 96.4%	43.7 - 97.0%	28.9 - 94.1%
Date agreement	**Exact**	90.7 - 95.6%	86.8 - 91.4%	93.7 - 97.0%	93.8 - 98.3%
	+/- 15 days	95.6 - 97.6%	95.8 - 98.5%	96.2 - 98.4%	95.2 - 99.1%
	+/- 30 days	96.3 - 97.9%	96.8 - 98.6%	96.2 - 98.7%	95.7 - 99.1%

EHR=Electronic Health Record; OD=obituary data; NPV=negative predictive value; PPV=positive predictive value; SSDI=Social Security Death Index

*Components of the composite mortality variable: SSDI, OD, structured EHR data and unstructured EHR data

Update to Version 2.1 as of March 31, 2021

- The NDI benchmarking exercise offers the opportunity to ensure quality continuity and to identify additional opportunities for improvement.
- In the most recent exercise, Flatiron identified specific opportunities to improve our linking algorithms, resulting in increased sensitivity (~1% across datasets). We implemented these changes and updated the version labeling to “2.1” to reflect this improvement.
- No changes were made to:
    - The rules and hierarchy for combining data from the three mortality data sources
    - The delivered data schema (i.e. teams may continue to use existing functions, ingestion and study code without adjustments)

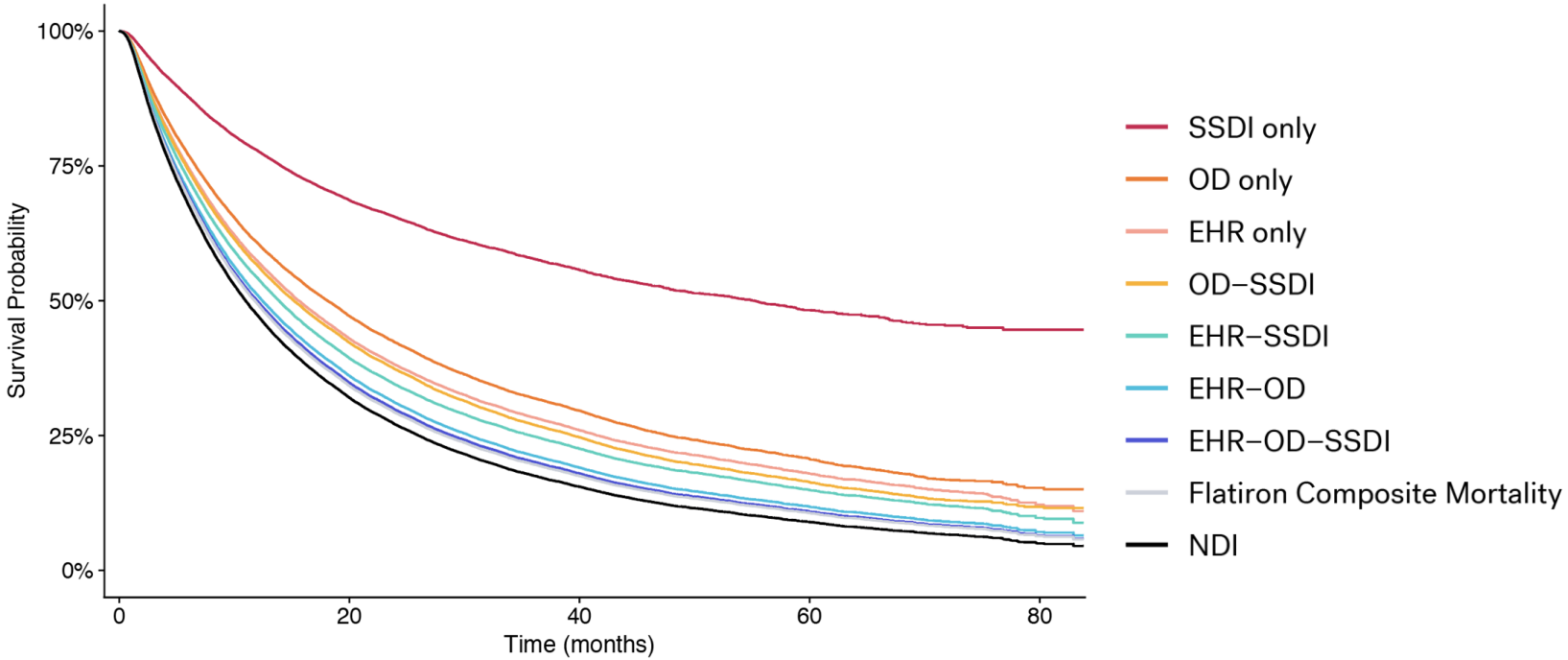
Comparison of Versions

	v1.0	v2.0	v2.1
Release Date	September 30, 2015	June 30, 2017	March 31, 2021
Structured EHR data	✓	✓	✓
Obituary data	✓	✓	✓
Abstracted EHR data		✓	✓
Social Security Death Index		✓	✓
Sensitivity *(varies by tumor type)*	74% - 79%	84% - 92%	87% - 92%
Specificity *(varies by tumor type)*	97% - 99%	94% - 99%	94% - 99%

In comparison to the gold standard NDI, sensitivity of the **composite mortality variable** is **higher** than **individual components**

Cancer Type	Flatiron's Composite Mortality Variable	Flatiron Structured EHR	Obituary data	SSDI
Breast (early)	87.1%	54.0%	67.7%	22.6%
Breast (metastatic)	89.1%	67.3%	63.7%	25.6%
Chronic Lymphocytic Leukemia	92.4%	70.7%	69.7%	32.3%
Colorectal (metastatic)	87.7%	64.8%	63.4%	23.5%
Diffuse Large B-Cell Lymphoma	90.1%	65.0%	67.0%	26.6%
Gastro-Esophageal (advanced)	89.4%	66.2%	64.4%	27.8%
Head and Neck (advanced)	90.4%	70.1%	63.5%	20.3%
Hepatocellular Carcinoma	86.6%	56.4%	59.6%	25.0%
Malignant Pleural Mesothelioma	92.4%	56.1%	72.5%	32.1%
Melanoma (advanced)	90.3%	65.0%	70.4%	25.4%
Multiple Myeloma	89.9%	62.7%	65.9%	28.0%
Non-Small Cell Lung Carcinoma (advanced)	91.3%	67.8%	67.0%	29.4%
Ovarian	87.4%	64.3%	66.1%	17.7%
Pancreatic (metastatic)	91.5%	67.0%	68.5%	23.2%
Prostate (metastatic)	90.2%	67.5%	66.6%	22.3%
Renal Cell Carcinoma (metastatic)	89.7%	66.7%	67.5%	27.0%
Small Cell Lung Carcinoma	91.3%	70.7%	68.7%	25.5%
Urothelial (advanced)	91.2%	68.2%	68.6%	24.6%

Using a less sensitive mortality variable may risk overestimating survival (aNSCLC example)



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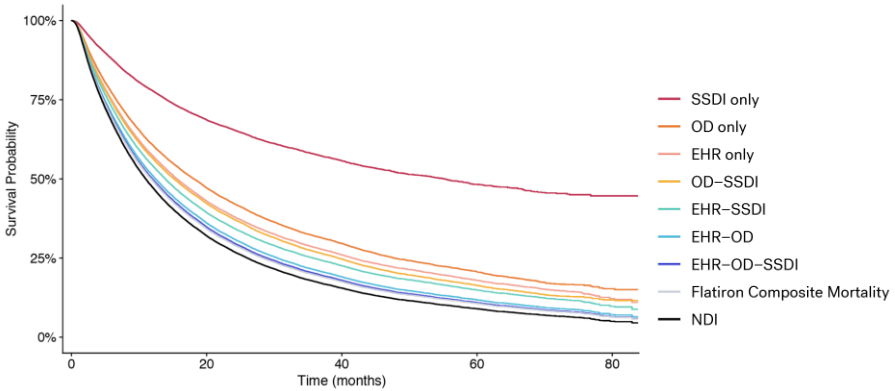
Using a less sensitive mortality variable may risk overestimating survival (aNSCLC example)

	Data Source	Median OS, mo (95% CI)
Single source	SSDI	55.2 (52.0 – 58.5)
	OD	16.7 (16.3 – 17.0)
	EHR	15.6 (15.3 – 15.9)
Combination	OD - SSDI	14.4 (14.1 – 14.7)
	EHR - SSDI	13.9 (13.6 – 14.1)
	EHR - OD	12.3 (12.1 – 12.5)
	EHR - OD - SSDI	11.9 (11.7 – 12.1)
Flatiron Composite Mortality		11.7 (11.5 – 11.9)
NDI		11.0 (10.8 – 11.2)



Sequential addition of OD, SSDI, and abstracted death dates onto structured EHR mortality data resulted in median OS estimates progressively closer to those using NDI

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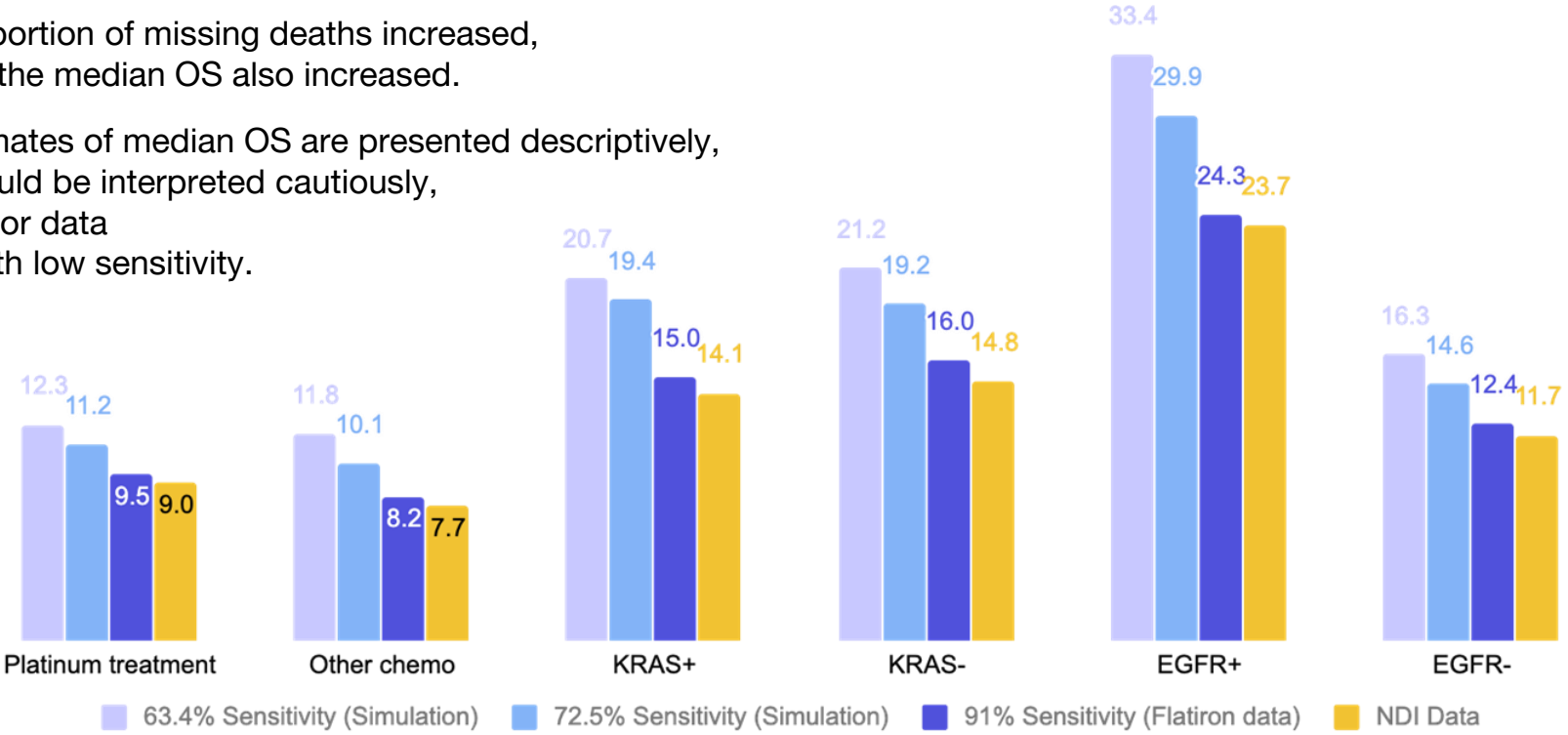
Bias in median OS increases with decreasing sensitivity of death data

- Using aNSCLC patients from the Flatiron database with data through 2015, data sets with lower sensitivity for mortality were generated through simulation: 20% and 30% of true positive patients (death in Flatiron and NDI data) were randomly selected and recategorized as false negatives (death in NDI but not Flatiron data).
- Median OS was calculated in each simulated data set, the true Flatiron data set, and the NDI data set (also with data through 2015). Percent bias in the median OS was calculated relative to the NDI.
- As the proportion of missing deaths increased, the bias in the median OS also increased.
- When estimates of median OS are presented descriptively, results should be interpreted cautiously, especially for data sources with low sensitivity.



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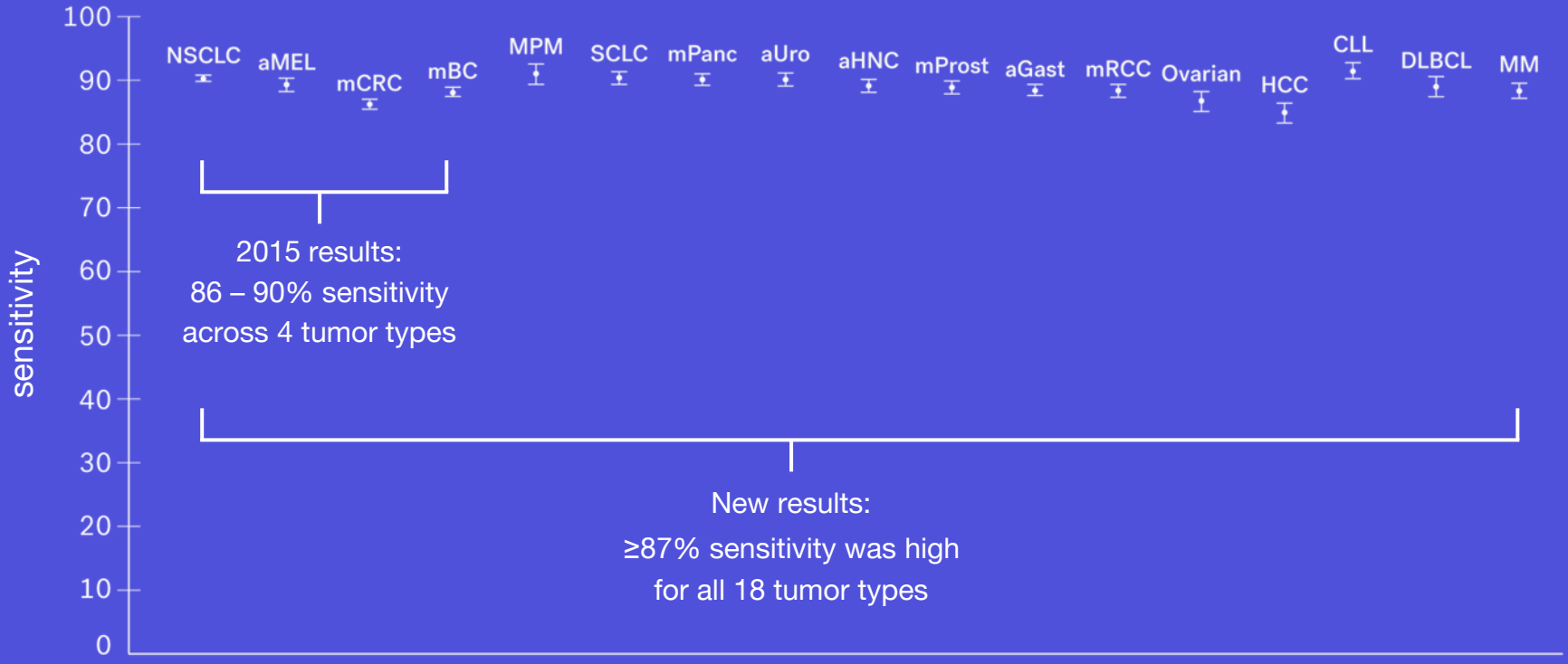
We have benchmarked our mortality variable to NDI



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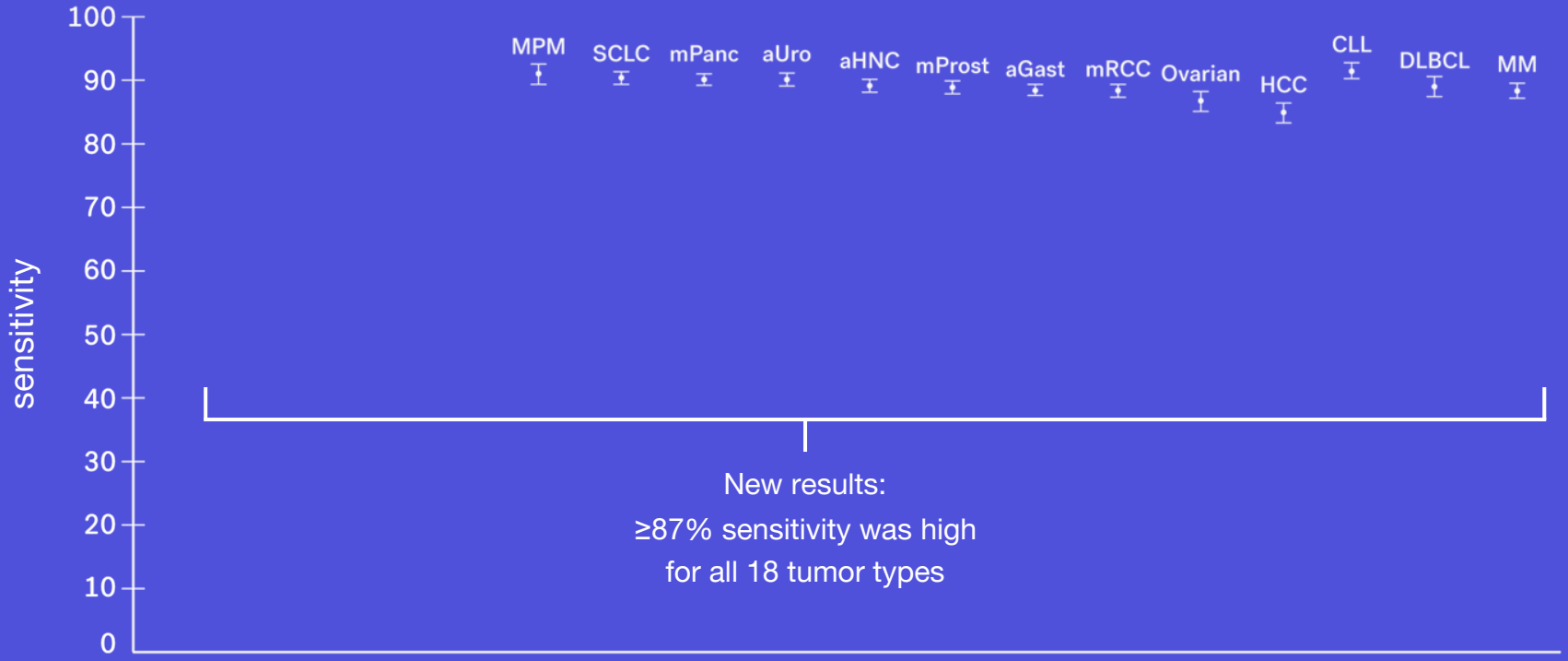

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Additional Analysis — Time Lag Analysis

We identified a subset of patients from the main analysis, who were included in various snapshots,
and calculated the validity metrics by snapshot (over time).

Jan 2018	0 months of post-2017 mortality data capture	allows for assessment of validity metrics using the earliest available Flatiron snapshot
July 2018	6 months of post-2017 mortality data capture	serves as a midpoint for an analysis of data maturity
Dec 2018	11 months of post-2017 mortality data capture	theoretically aligns with the amount of time the NDI takes to capture death records
May 2019	16 months of post-2017 mortality data capture	aligns with the amount of time to capture death records in the original analysis done in 2015, for apples to apples comparison (used in main analysis)

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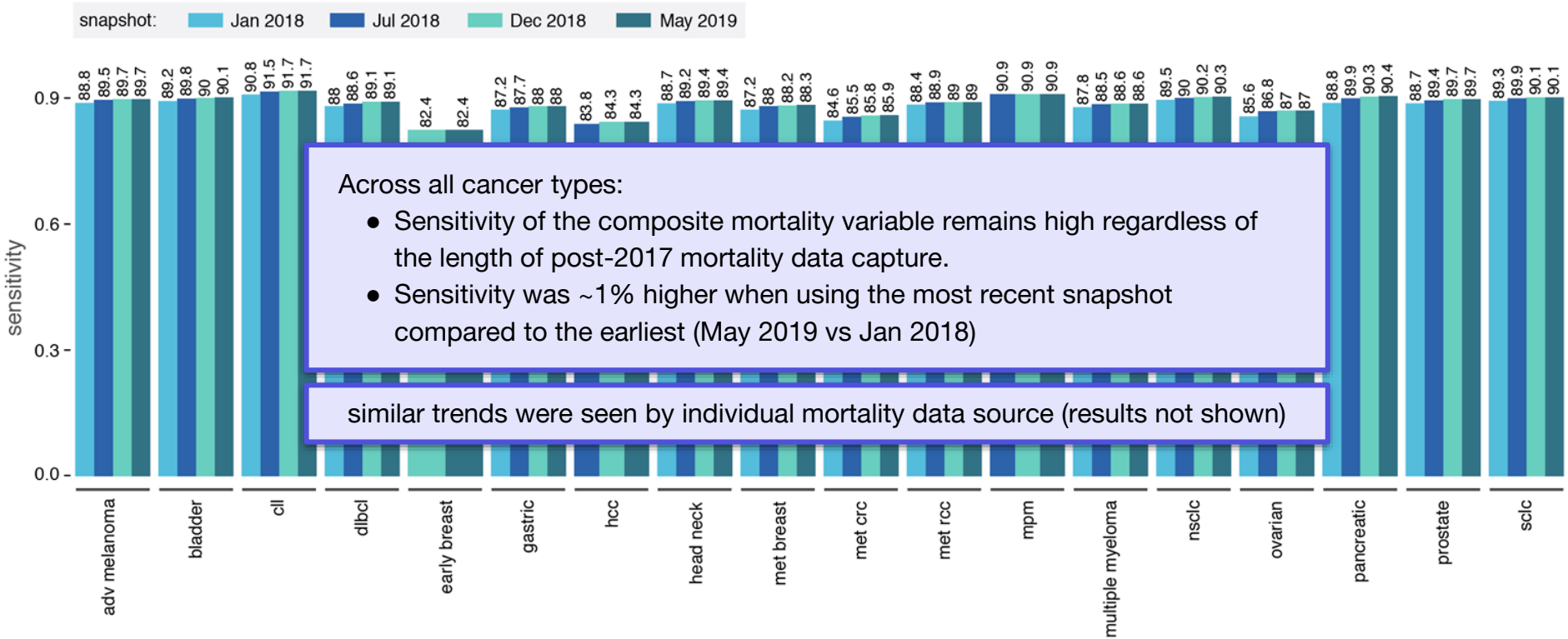
What does sensitivity look like for the same patients across different time snapshots?



Across all cancer types:

- Sensitivity of the composite mortality variable remains high regardless of the length of post-2017 mortality data capture.
- Sensitivity was ~1% higher when using the most recent snapshot compared to the earliest (May 2019 vs Jan 2018)

similar trends were seen by individual mortality data source (results not shown)

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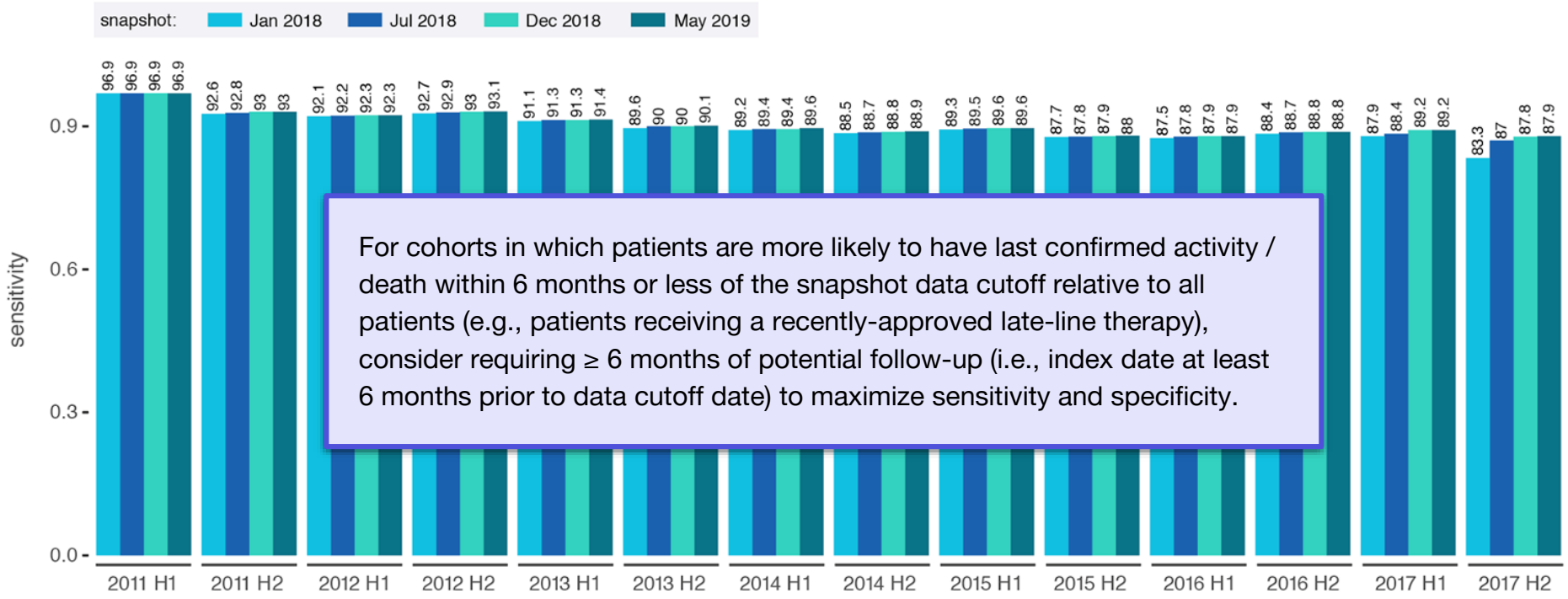
Once a death has occured, how long does it take for the death event to be reflected in Flatiron data?



For cohorts in which patients are more likely to have last confirmed activity / death within 6 months or less of the snapshot data cutoff relative to all patients (e.g., patients receiving a recently-approved late-line therapy), consider requiring ≥ 6 months of potential follow-up (i.e., index date at least 6 months prior to data cutoff date) to maximize sensitivity and specificity.

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Key Takeaways

Validation analysis of a composite real-world mortality endpoint

1. We observe **high sensitivity, specificity and date accuracy** of Flatiron's mortality variable across numerous cancer types

2. It is important to ensure the completeness and quality of a mortality variable in **broader populations** and **sub-cohorts** relevant to a given study.

3. Not all real-world mortality data sources have equal quality, and **understanding the sensitivity, specificity, and accuracy** of a given source is a critical step towards the generation of **reliable RWE**.

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Analytical Considerations for Overall Survival Analyses

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Differences by race/ethnicity and region:

> Patient records with certain characteristics may exhibit lower sensitivity than the overall disease cohorts

> Sensitivity analyses that exclude patients or stratify by these characteristics may be appropriate

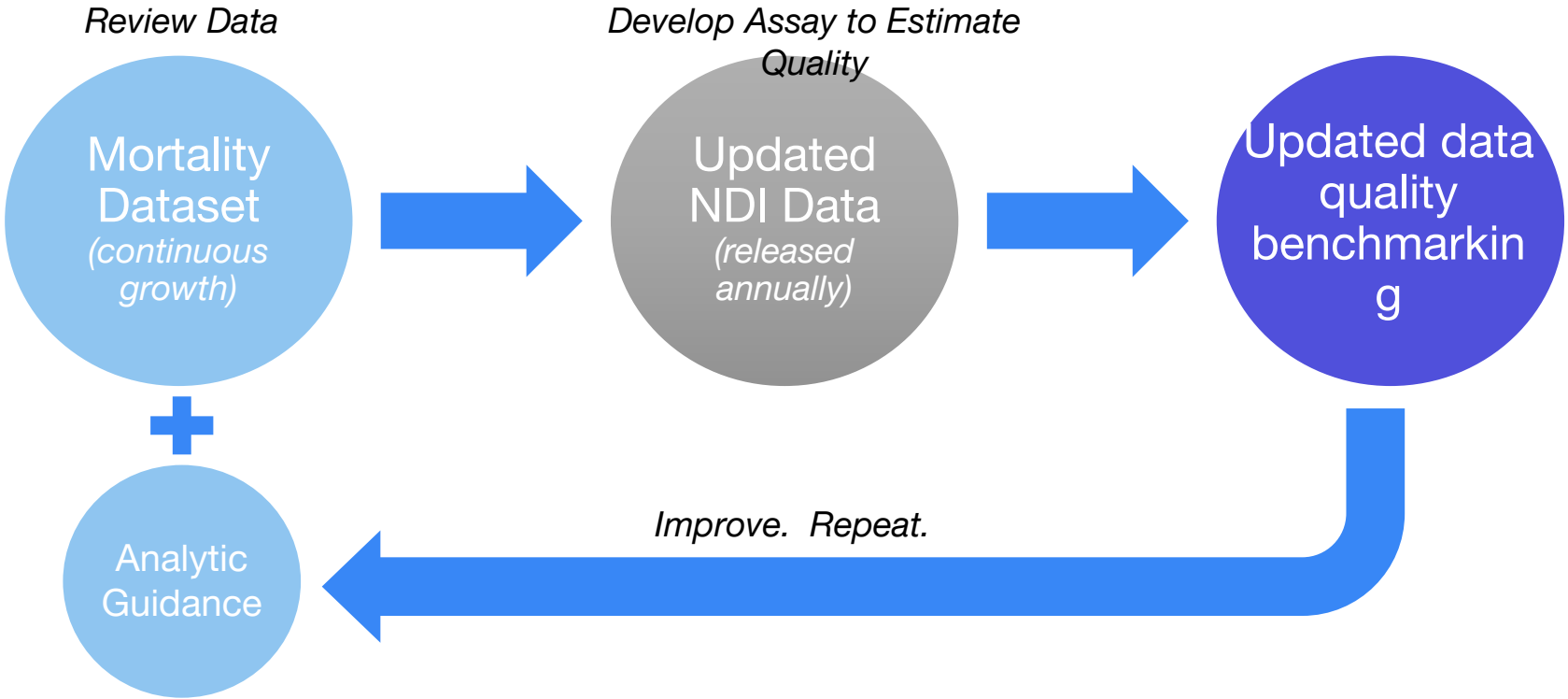
Follow-up time specifications:

> Consider requiring at least six months of potential follow-up to maximize sensitivity and specificity

EHR data considerations:

> A small number of patients records may include structured activity after the *DateofDeath* value. This is typically an issue with the structured activity, and not the date of death.

Continuous Data Quality Benchmarking



References for Related Publications

May 2018

Manuscript on Development of the Variable + Benchmarking of 4 Cancer Types

Curtis M et al. Development and Validation of a High Quality Composite Real-World Mortality Endpoint. *Health Services Research* 14 May 2018 doi:10.1111/1475-6773.12872

June 2020

AACR Poster and Abstract on Updated Benchmarking Across 18 Cancer Types

Zhang Q, Gossai A, Monroe S, Nussbaum NC, Parrinello CM. Validation analysis of a composite real-world mortality endpoint for US cancer patients. In: Proceedings of the 111th Annual Meeting of the American Association for Cancer Research; 2020 June 22-24. Philadelphia (PA): AACR; 2020. Abstract nr 5772 and poster presentation.

Thank you

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