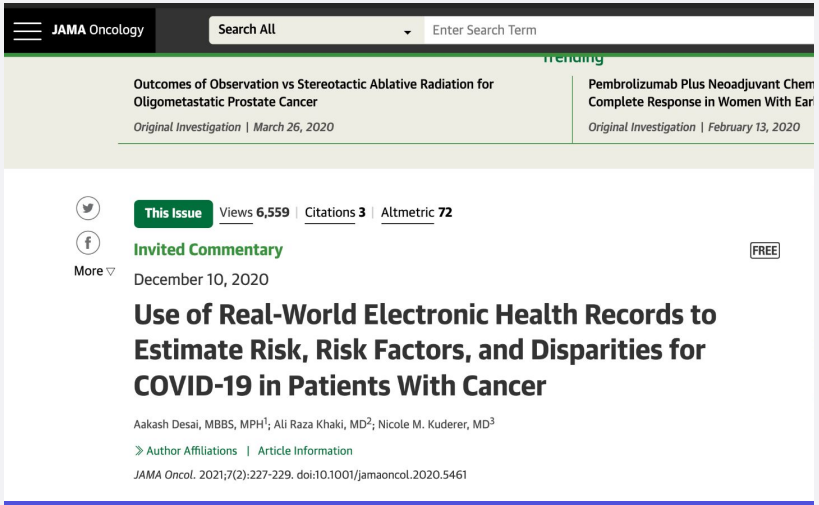
WE WILL BE STARTING AT 1PM ET

A decade of health records: 2010 – 2021

"Real-world data" circa 2010



EHR-based Study, JAMA 2021

U.S. FOOD & DRUG ADMINISTRATION

21st Century Cures Act

December 2016

LABEL EXPANSION

Men with breast cancer have an approved therapy option.

REAL WORLD EVIDENCE

HOW FDA, PFIZER, AND FLATIRON HEALTH DID IT

APPROVAL OF IBRANCE FOR MEN AFFORDS A GLANCE AT USE OF REAL WORLD DATA

By Paul Goldberg

Real world data played a role in FDA's recent decision to expand the indications for Pfizer's drug Ibrance (palbociclib) to include men.

U.S. FOOD & DRUG ADMINISTRATION

21st Century Cures Act

December 2016

DOSING

Patients with EGFR+ mCRC or SCCHN have an alternative dosing regimen available.

Flatiron Health Real-World Data Support FDA Approval of New Dosing Regimen for ERBITUX® (cetuximab)

Approval of additional dosing regimen allows cancer patients to significantly reduce frequency of treatment visits

NEW YORK, NY, July 20, 2021

Flatiron Health real-world data (RWD) supported the U.S. Food and Drug Administration (FDA)'s recent approval of a new dosing regimen for

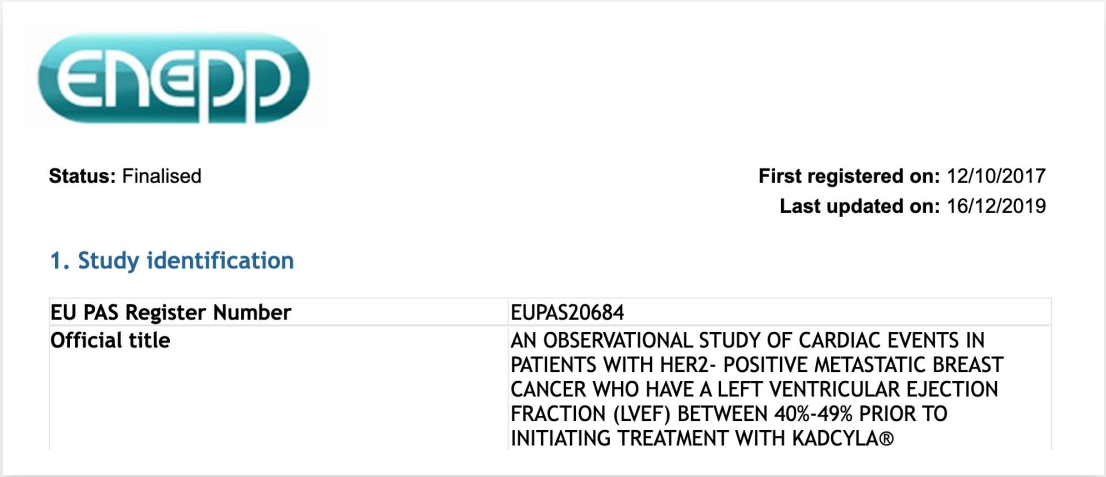
U.S. FOOD & DRUG ADMINISTRATION

SAFETY

Women with low LVEF have access to a HER2 targeted therapy option.

21st Century Cures Act

December 2016



Status: Finalised

First registered on: 12/10/2017
Last updated on: 16/12/2019

1. Study identification

EU PAS Register Number	EUPAS20684
Official title	AN OBSERVATIONAL STUDY OF CARDIAC EVENTS IN PATIENTS WITH HER2- POSITIVE METASTATIC BREAST CANCER WHO HAVE A LEFT VENTRICULAR EJECTION FRACTION (LVEF) BETWEEN 40%-49% PRIOR TO INITIATING TREATMENT WITH KADCYLA®

Despite advances in the past decade, significant challenges remain

- Spiraling costs
- Patient access
- “The right” technologies
- Complexity of trials
- Complexity of and variability of guidelines
- Trial governance and oversight
- Hiring and training

In the next 10 years, the human body is becoming a data platform…

- Electronic health records
- Genetics & Genomics
- Resistance detection diagnostics
- Radiomics
- Transcriptomics
- Proteomics
- Early detection diagnostics
- Remote monitoring
- Digital therapeutics
- Patient Reported Outcomes
- Medical grade wearables
- Digital pills

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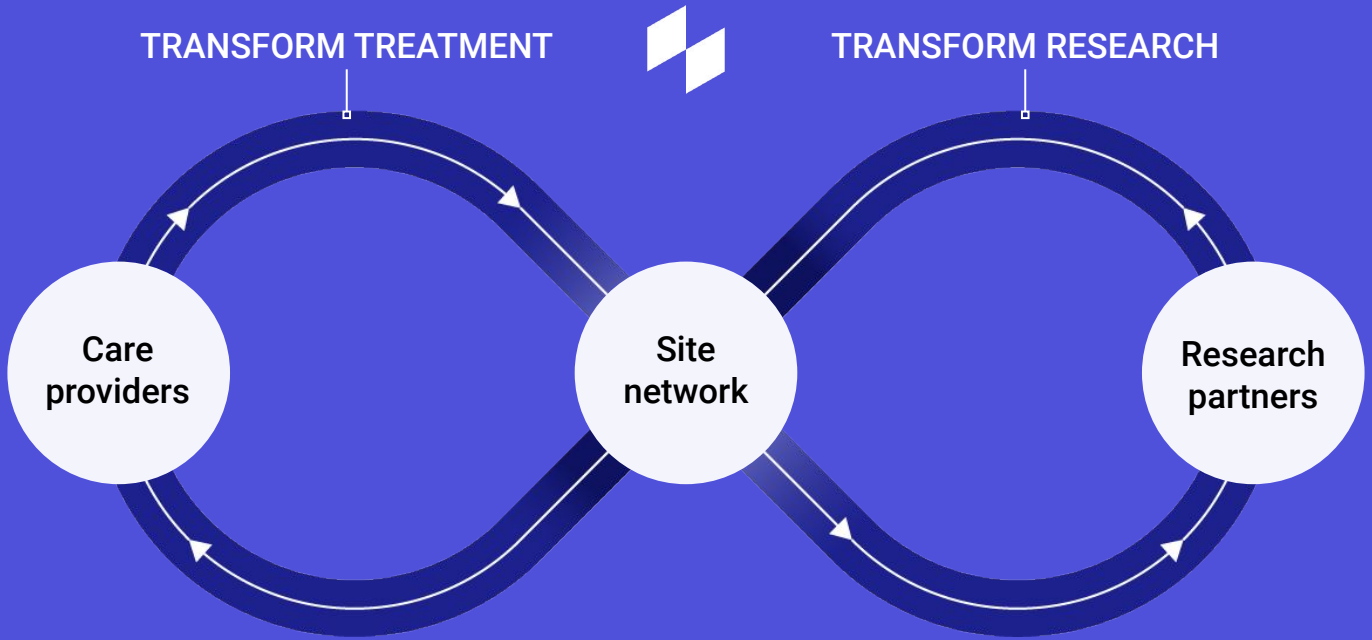
The intersection of care and research



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

Beyond real-world data, how integrated evidence will power smarter care for every patient.

Beyond real-world data, how integrated evidence will power smarter care for every patient.

Beyond real-world data, how integrated evidence will power smarter care for every patient.

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Integrated evidence can

Accelerate R&D and access

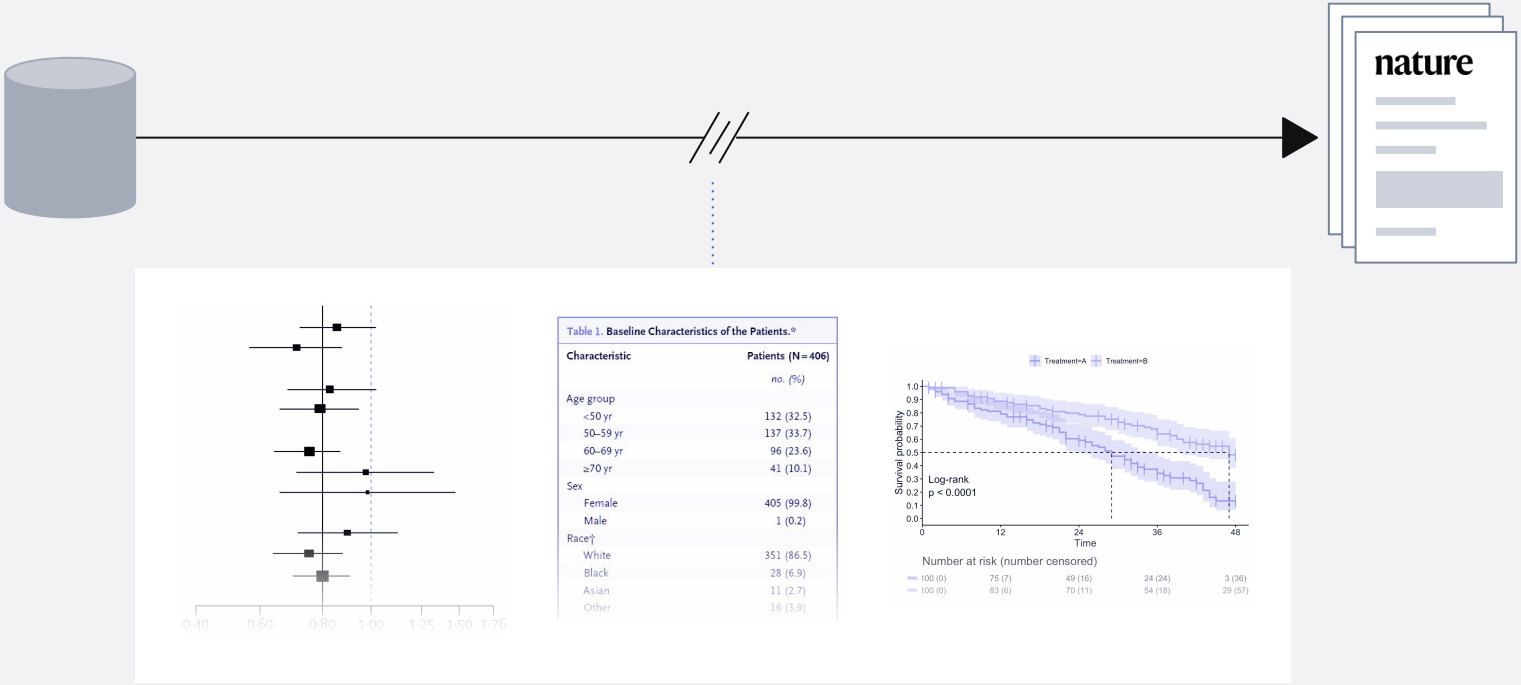
Make research more inclusive

Make healthcare more sustainable

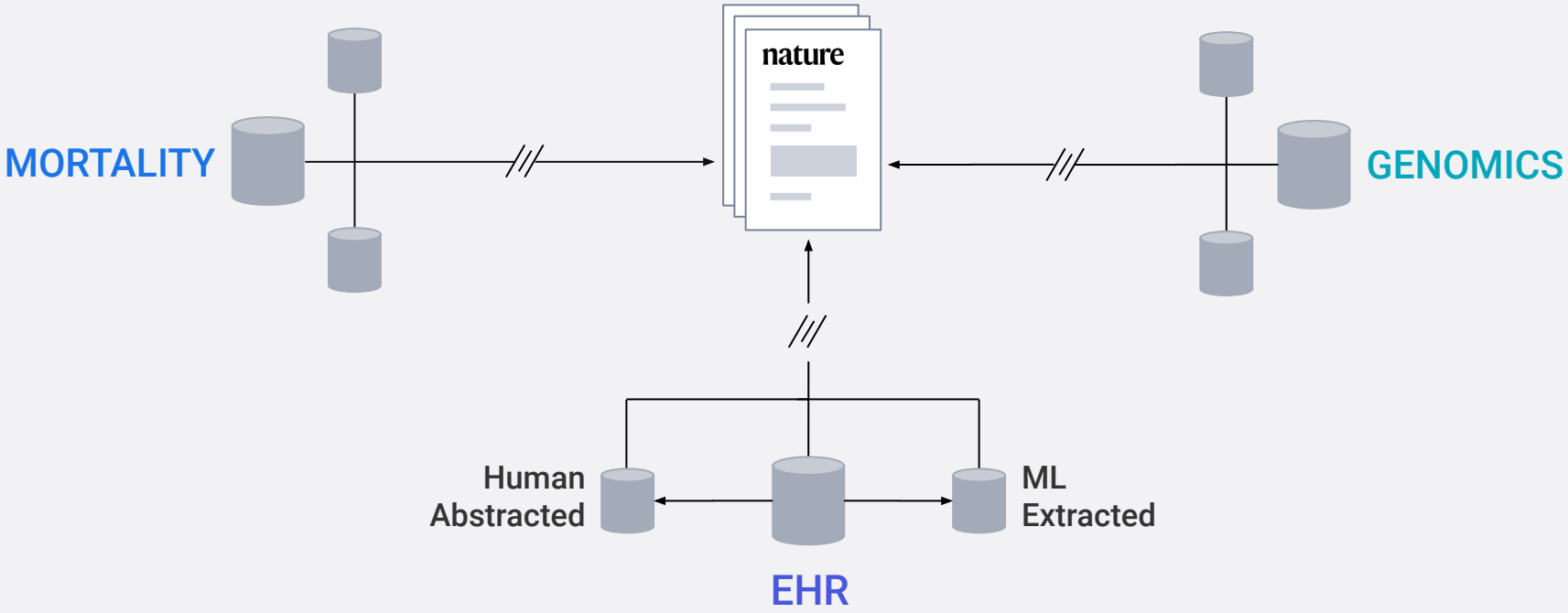
Integrated evidence:

Evidence that is more robust as a result of bringing together multiple sources of data.

Single-Source Evidence



Integrated Evidence: Multiple Data Sources



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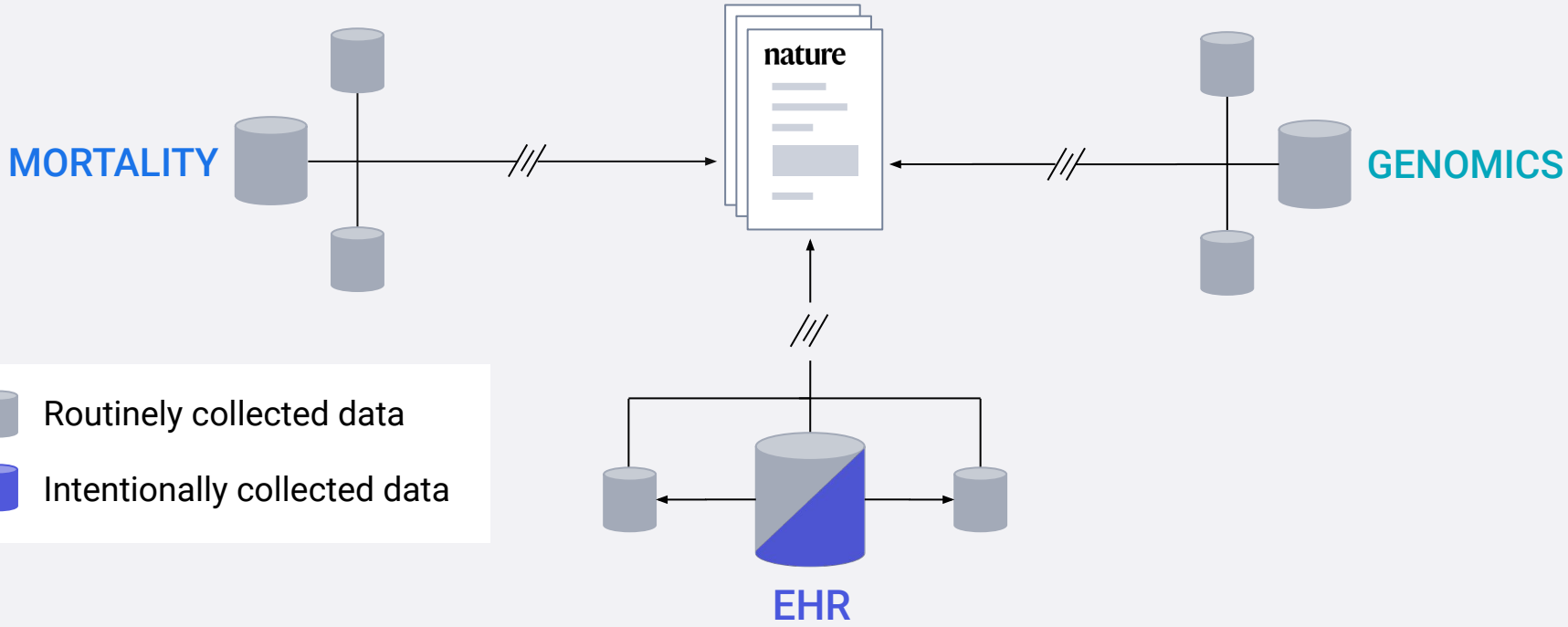
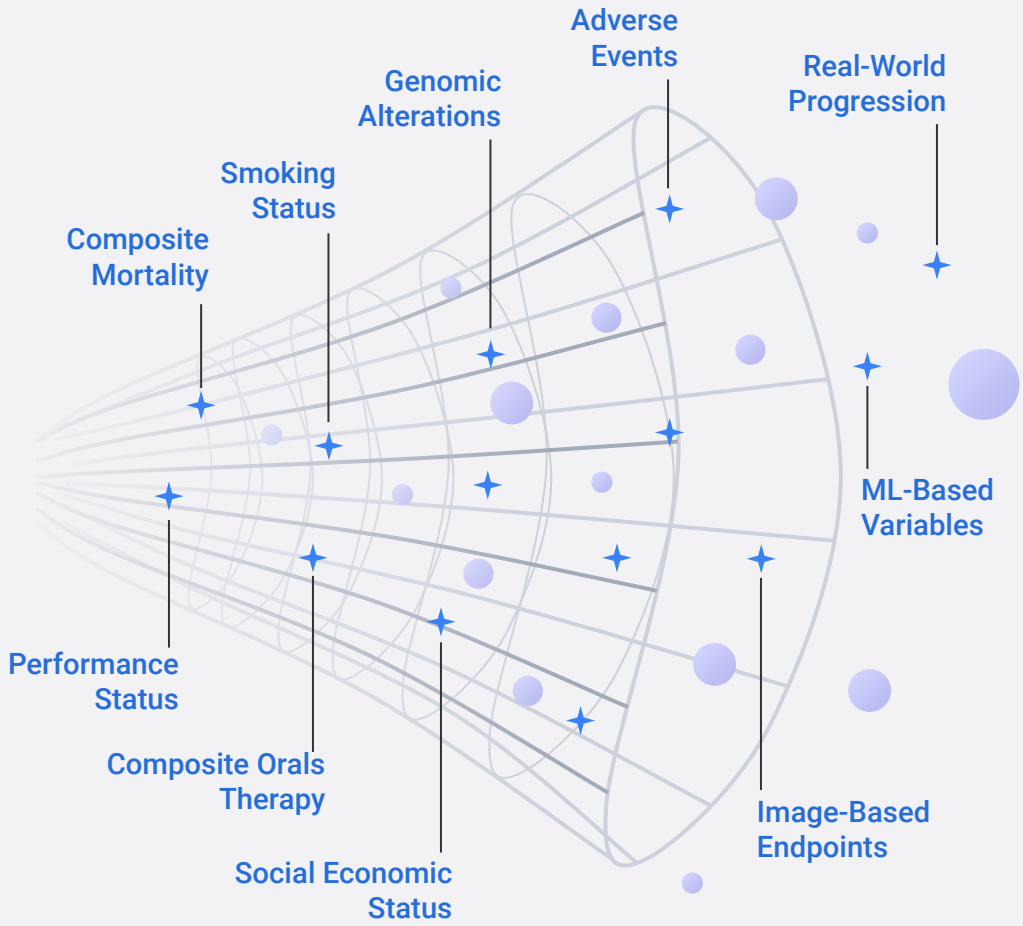
Integrated Evidence: Multiple Approaches to Data Generation



Widening the aperture for **integrated evidence.**

As we expand our view of the patient, we can address more opportunities to advance research.



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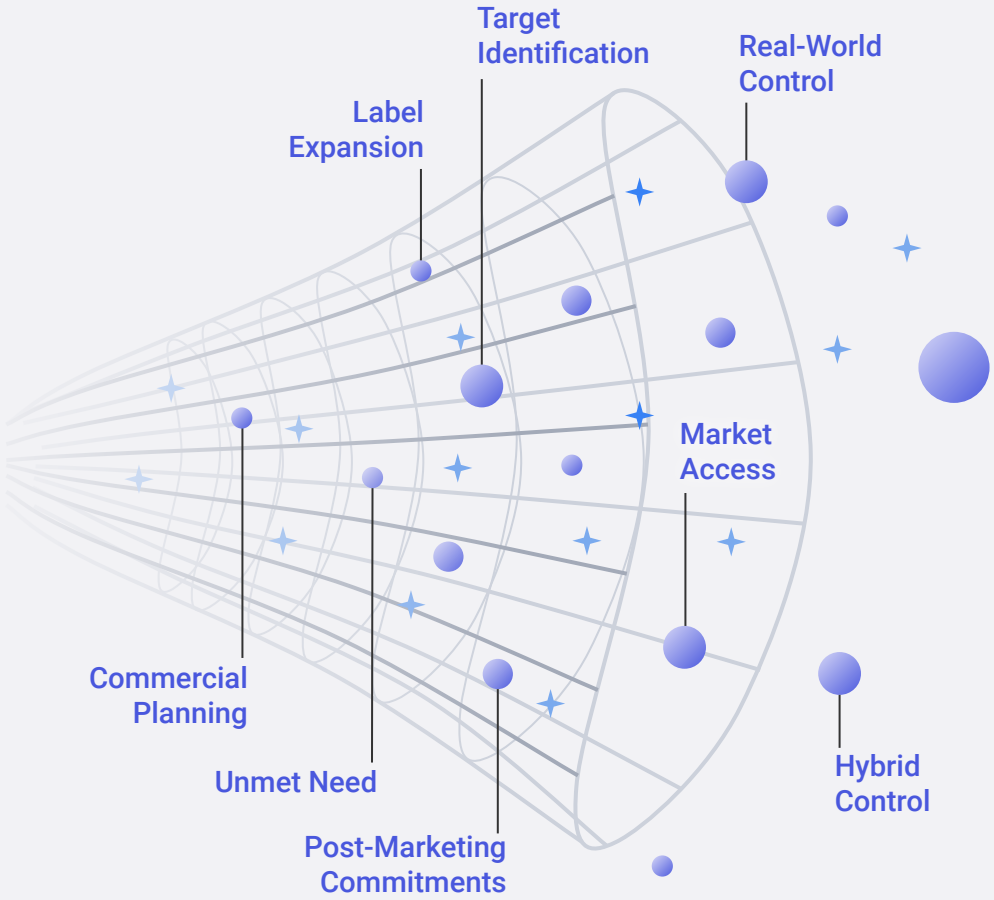

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Integrated Evidence

GENERATE

New approaches to generating, curating and sourcing data.

COMBINE

Bringing together different data modalities: e.g., claims, genomics, and imaging.

ANALYZE

Interpreting and contextualizing a broader totality of evidence.

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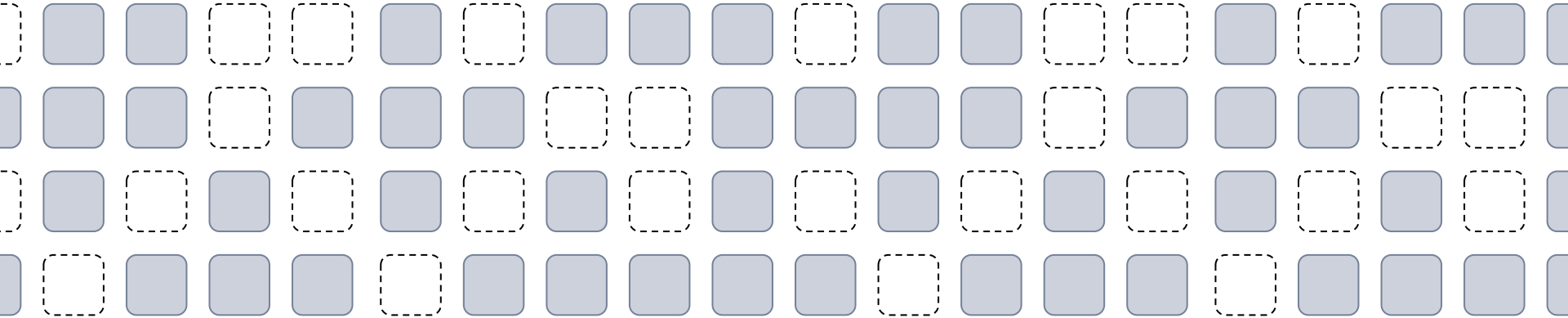
Flatiron’s Composite Mortality Variable

Approximately 35% of actual deaths are missing from structured EHR fields.



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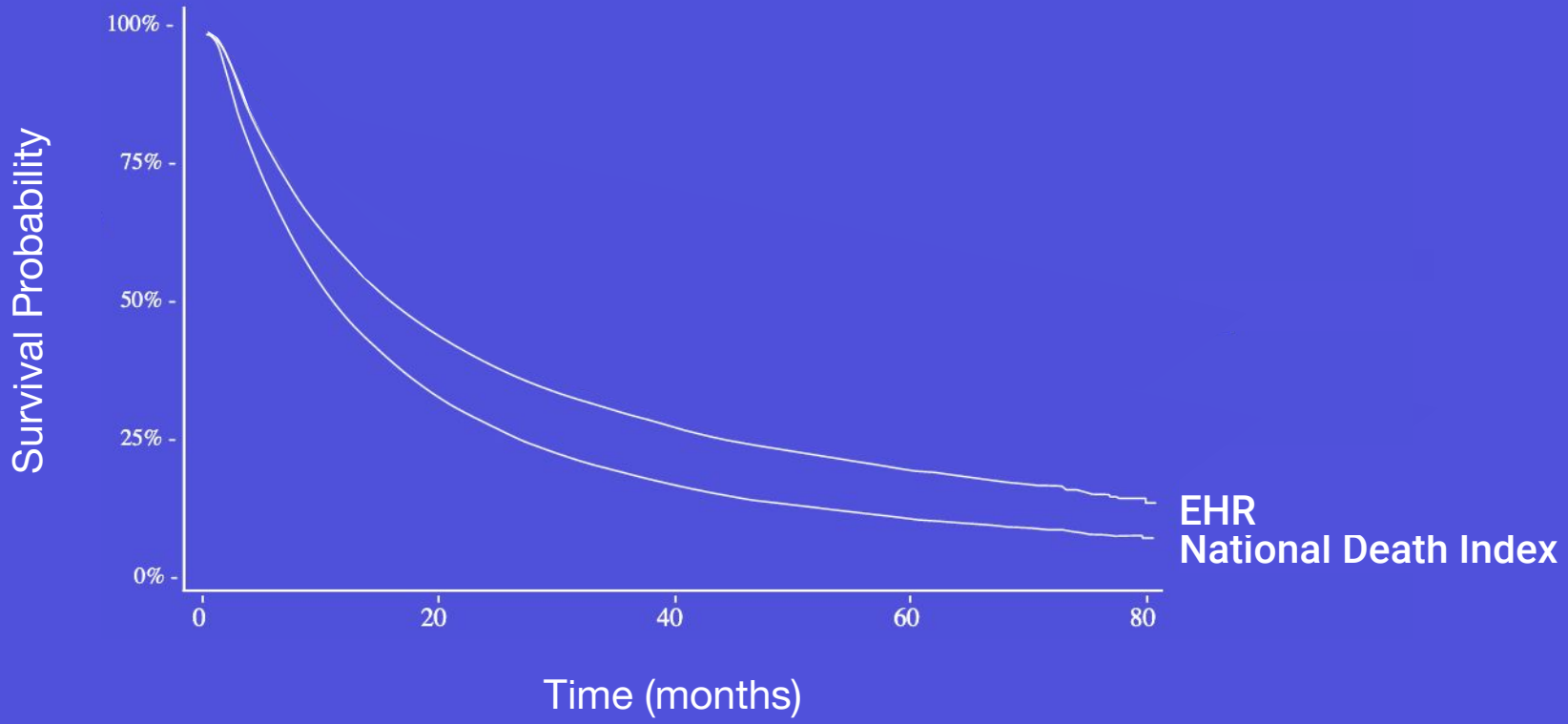
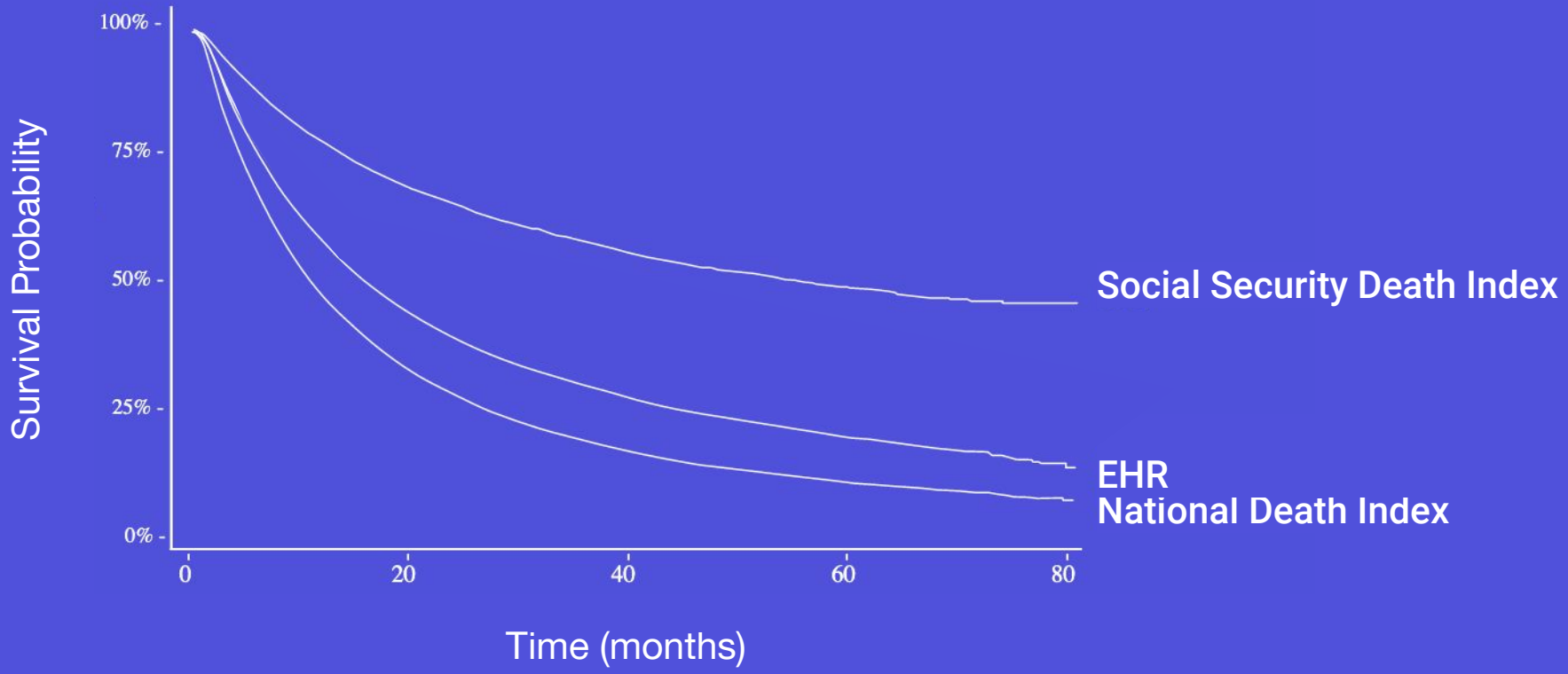


Adapted from Zhang Q et. al. Validation analysis of a composite real-world mortality endpoint for US cancer patients. AACR Annual Meeting. May, 2020; San Diego, CA.



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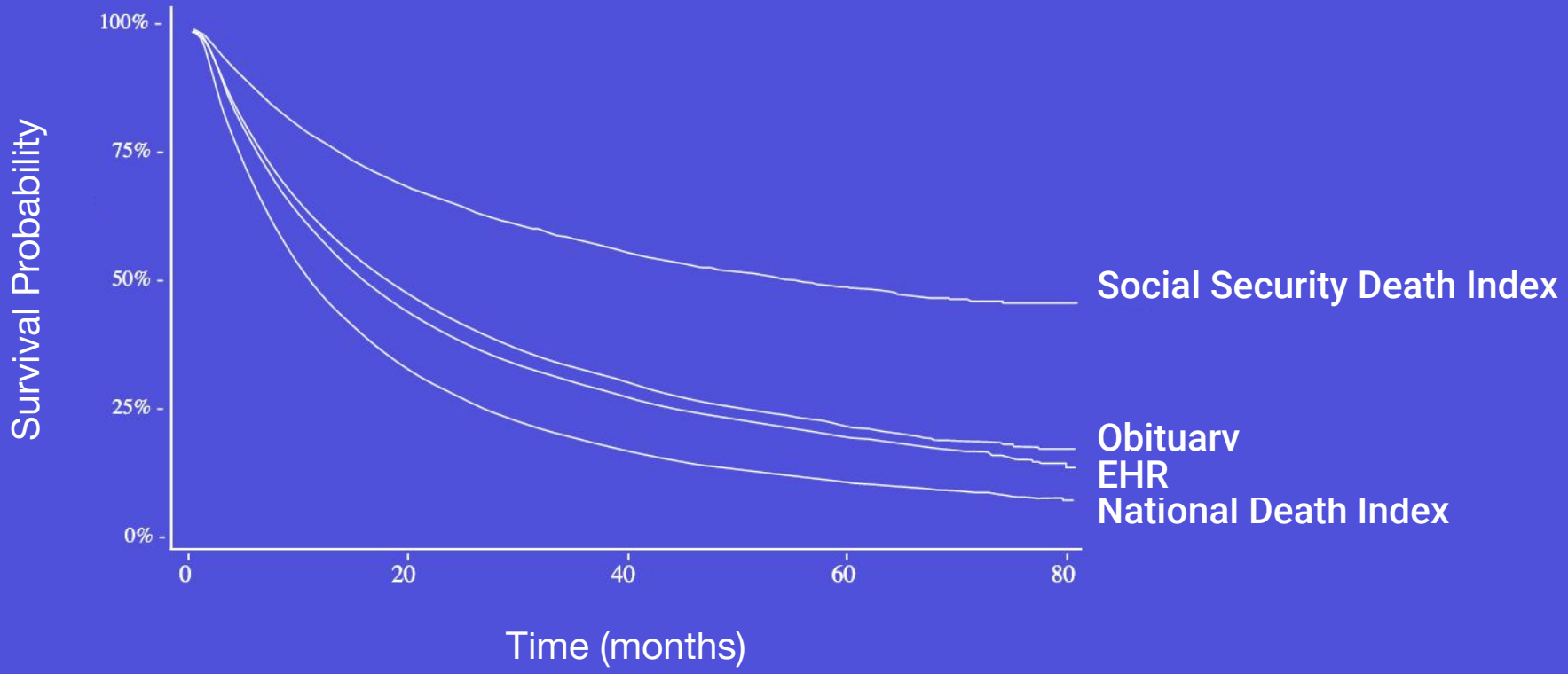
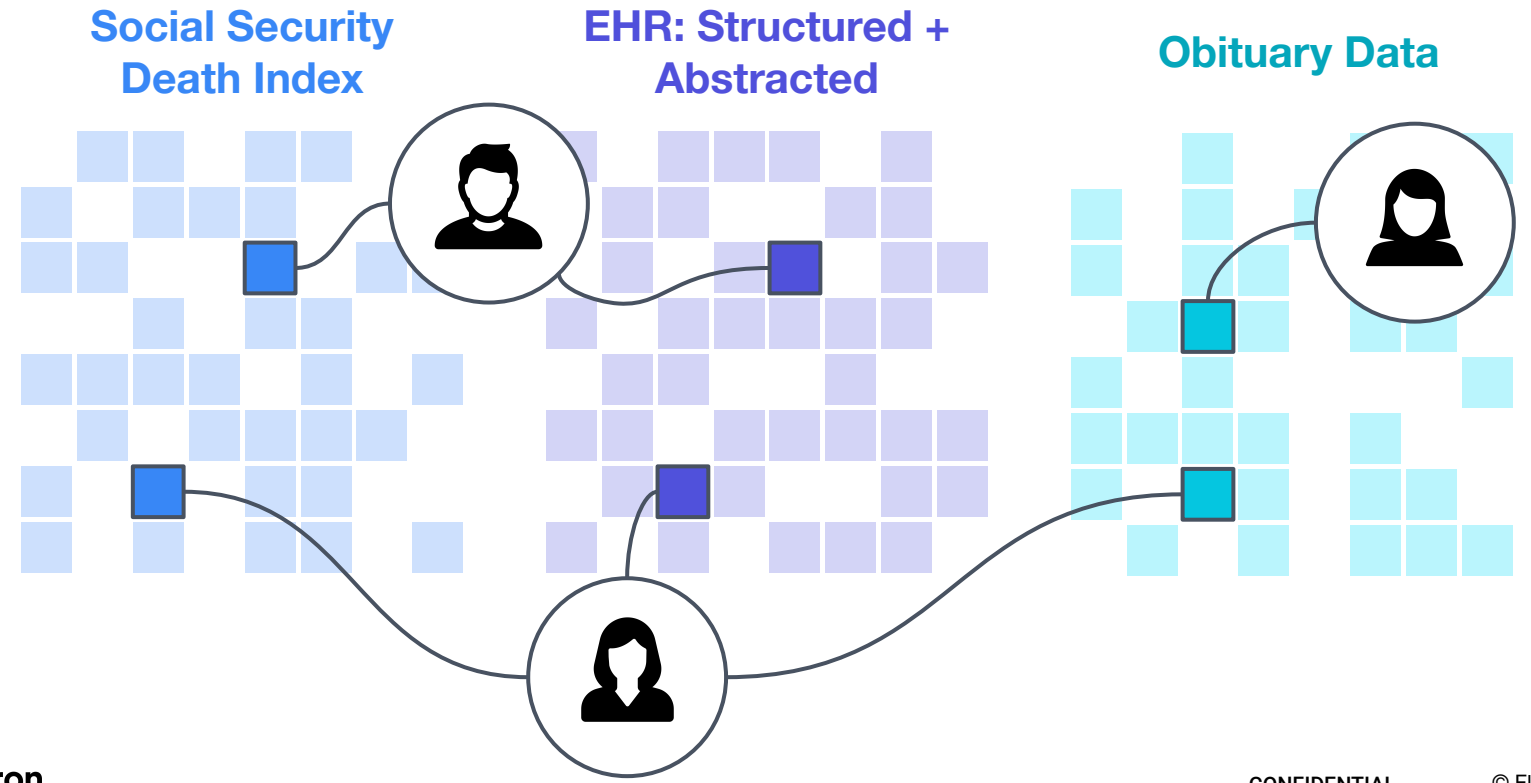
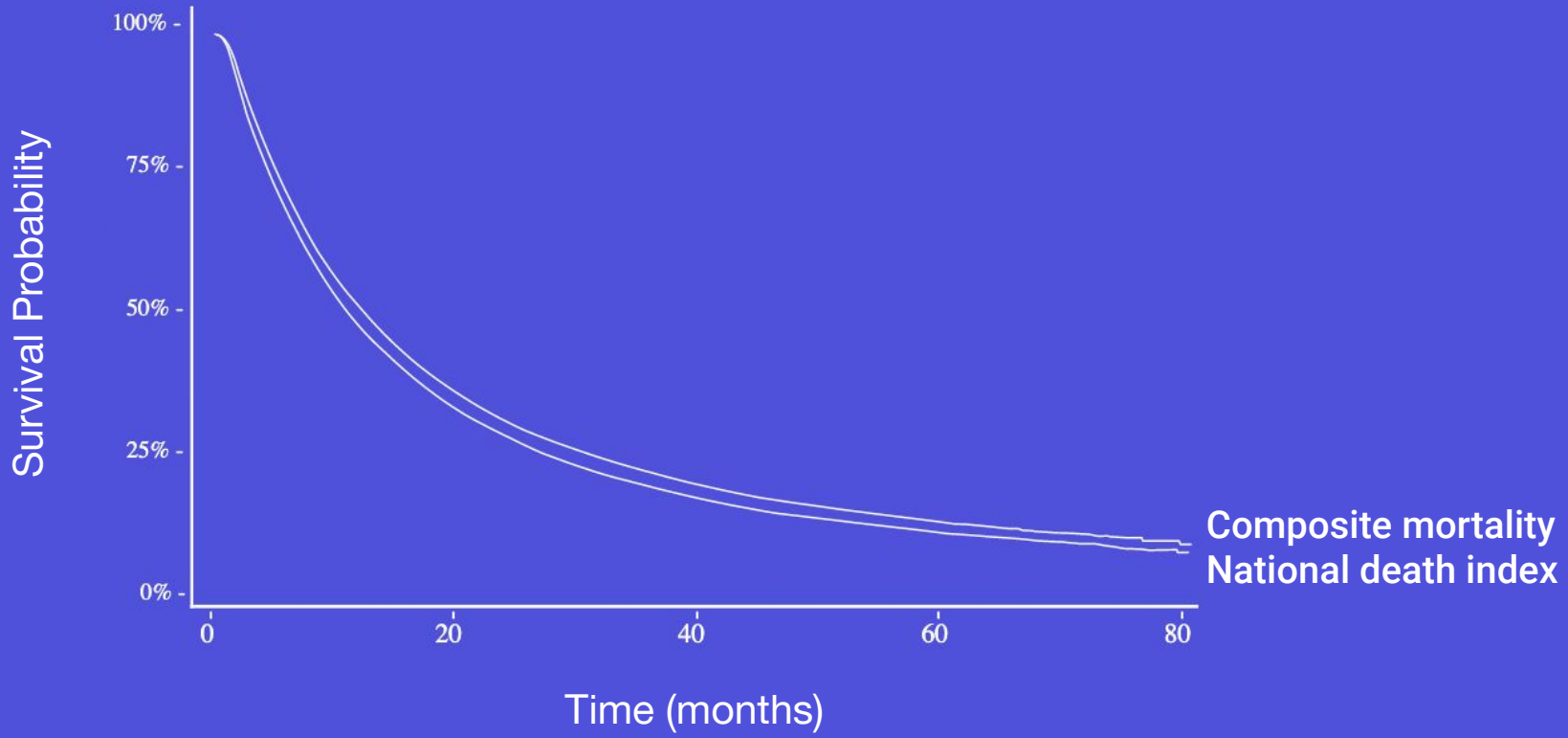


Adapted from Zhang Q et. al. Validation analysis of a composite real-world mortality endpoint for US cancer patients. AACR Annual Meeting. May, 2020; San Diego, CA.

Our linking algorithm combines data across multiple data sets





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Adapted from Zhang Q et. al. Validation analysis of a composite real-world mortality endpoint for US cancer patients. AACR Annual Meeting. May, 2020; San Diego, CA.

Flatiron's composite mortality variable supports long-term survival estimates

HSR Health Services Research

Development and Validation of a High-Quality Composite Real-World Mortality Endpoint

Melissa D. Curtis, Sandra D. Griffith, Melisa Tucker, Michael D. Taylor, William B. Capra, Gillis Carrigan, Ben Holzman, Aracelis Z. Torres, Paul You, Brandon Arnieri, and Amy P. Abernethy

Objective. To create a high-quality electronic health record (EHR)–derived mortality dataset for retrospective and prospective real-world evidence generation.

Data Sources/Study Setting. Oncology EHR data, supplemented with external commercial and US Social Security Death Index data, benchmarked to the National Death Index (NDI).

Study Design. We developed a recent, linkable, high-quality mortality variable amalgamated from multiple data sources to supplement EHR data, benchmarked against the highest completeness U.S. mortality data, the NDI. Data quality of the mortality variable version 2.0 is reported here.

Principal Findings. For advanced non-small-cell lung cancer, sensitivity of mortality information improved from 66 percent in EHR structured data to 91 percent in the composite dataset, with high date agreement compared to the NDI. For advanced melanoma, metastatic colorectal cancer, and metastatic breast cancer, sensitivity of the final variable was 85 to 88 percent. Kaplan–Meier survival analyses showed that improving mortality data completeness minimized overestimation of survival relative to NDI-based estimates.

Conclusions. For EHR-derived data to yield reliable real-world evidence, it needs to be of known and sufficiently high quality. Considering the impact of mortality data completeness on survival endpoints, we highlight the importance of data quality assessment and advocate benchmarking to the NDI.

Key Words. Mortality data, electronic health records, data quality, external validation, oncology

Received: 2 August 2018 | Revised: 17 January 2019 | Accepted: 24 January 2019
DOI: 10.1002/pds.4758

ORIGINAL REPORT WILEY

An evaluation of the impact of missing deaths on overall survival analyses of advanced non–small cell lung cancer patients conducted in an electronic health records database

Gillis Carrigan[1] | Samuel Whipple[1] | Michael D. Taylor[1] | Aracelis Z. Torres[2] | Anala Gossai[2] | Brandon Arnieri[1] | Melisa Tucker[2] | Philip P. Hofmeister[2] | Peter Lambert[1] | Sandra D. Griffith[2] | William B. Capra[1]

[1]Genentech, Inc, South San Francisco, CA, USA
[2]Flatiron Health, New York, NY, USA

Correspondence
G. Carrigan, Genentech, Inc, 1 DNA Way, South San Francisco, CA, USA.
Email: carrigan.gj@gene.com

Funding information
F. Hoffmann La Roche

Abstract

Purpose: The aim of this study was to assess the impact of missing death data on survival analyses conducted in an oncology EHR-derived database.

Methods: The study was conducted using the Flatiron Health oncology database and the National Death Index (NDI) as a gold standard. Three analytic frameworks were evaluated in advanced non-small cell lung cancer (aNSCLC) patients: median overall survival (mOS), relative risk estimates conducted within the EHR-derived database, and "external control arm" analyses comparing an experimental group augmented with mortality data from the gold standard to a control group from the EHR-derived database only. The hazard ratios (HRs) obtained within the EHR-derived database (91% sensitivity) and the external control arm analyses, were compared with results when both groups were augmented with mortality data from the gold standard. The above analyses were repeated using simulated lower mortality sensitivities to understand the impact of more extreme levels of missing deaths.

Results: Bias in mOS ranged from modest (0.6–0.9 mos.) in the EHR-derived cohort with (91% sensitivity) to substantial when lower sensitivities were generated through simulation (3.3–9.7 mos.). Overall, small differences were observed in the HRs for the EHR-derived cohort across comparative analyses when compared with HRs obtained using the gold standard data source. When only one treatment arm was subject to estimation bias, the bias was slightly more pronounced, but increased substantially when lower sensitivities were simulated.

Conclusions: The impact on survival analysis is minimal with high mortality sensitivity with only modest impact associated within external control arm applications.

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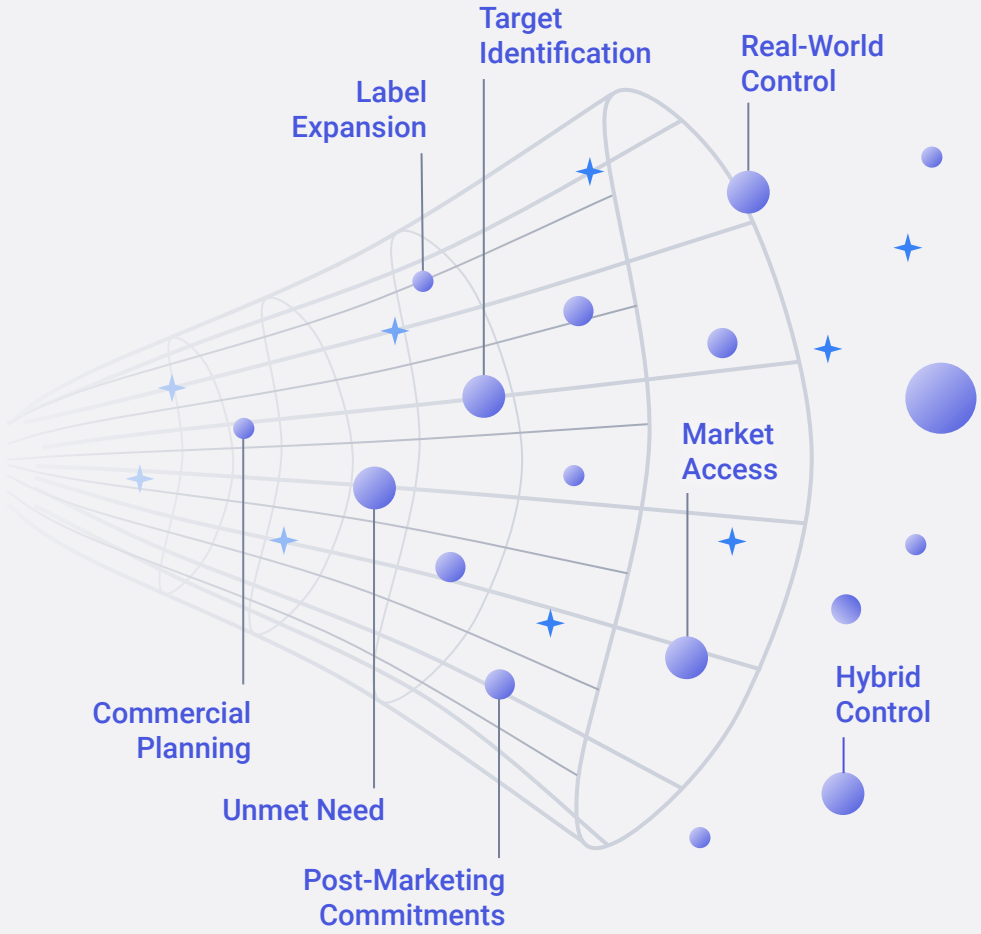
Widening the aperture for **integrated evidence.**

As we expand our view of the patient, we can address more opportunities to advance research.



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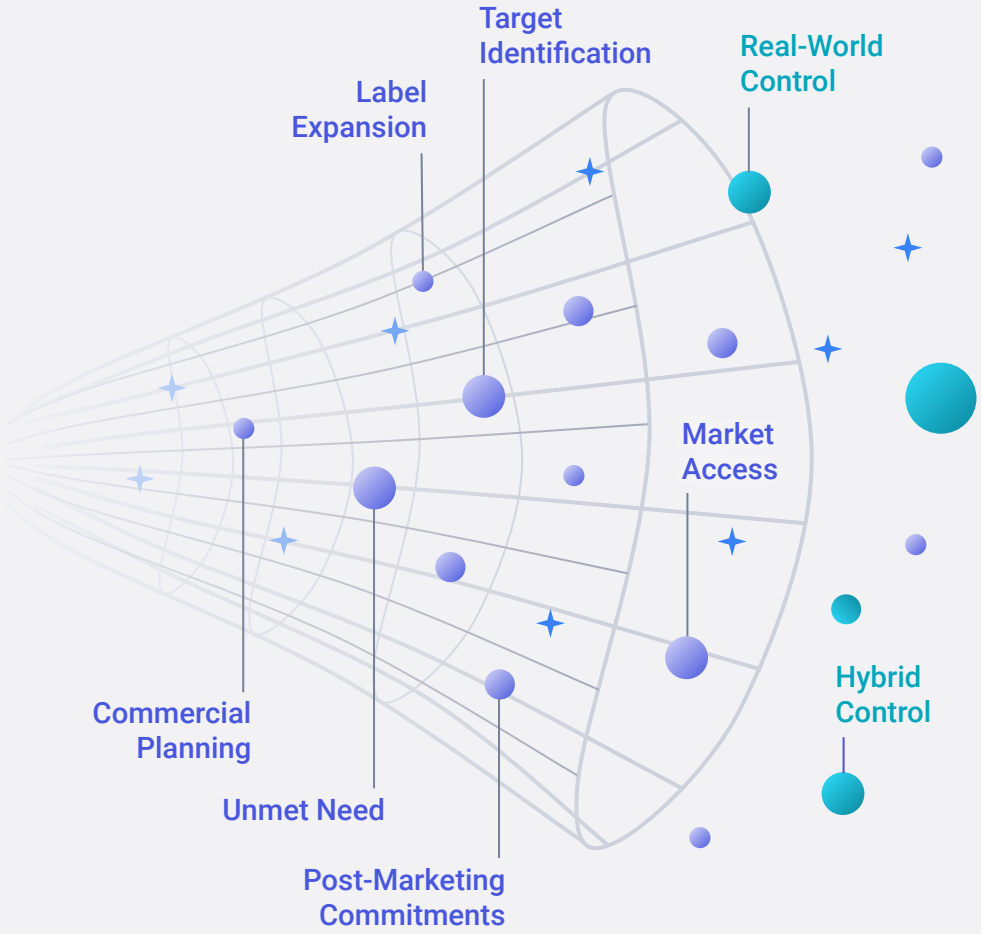
Widening the aperture for **integrated evidence.**

- Observational studies
  PROSPECTIVE OR RETROSPECTIVE
- Interventional trials
  PROSPECTIVE



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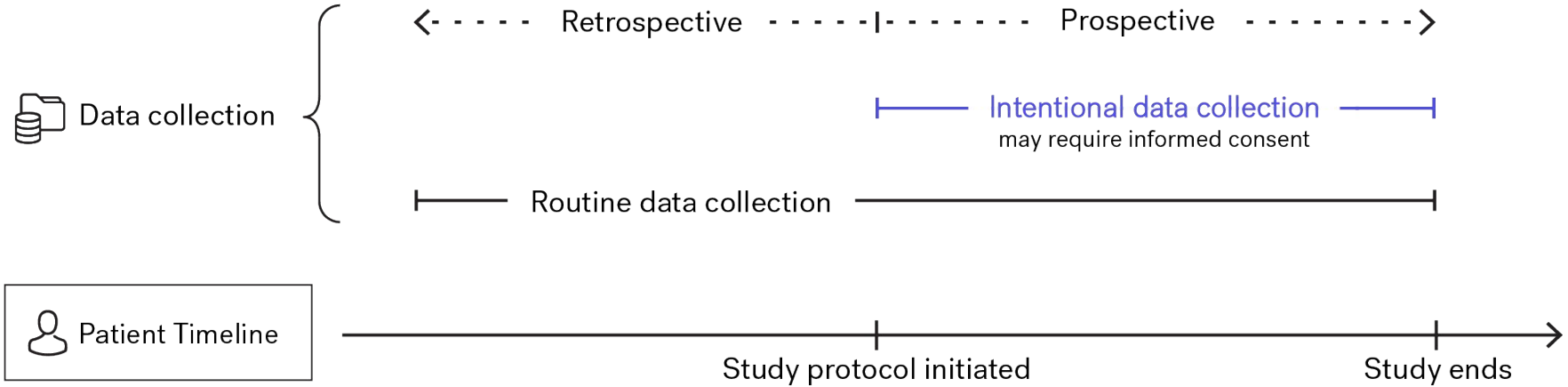
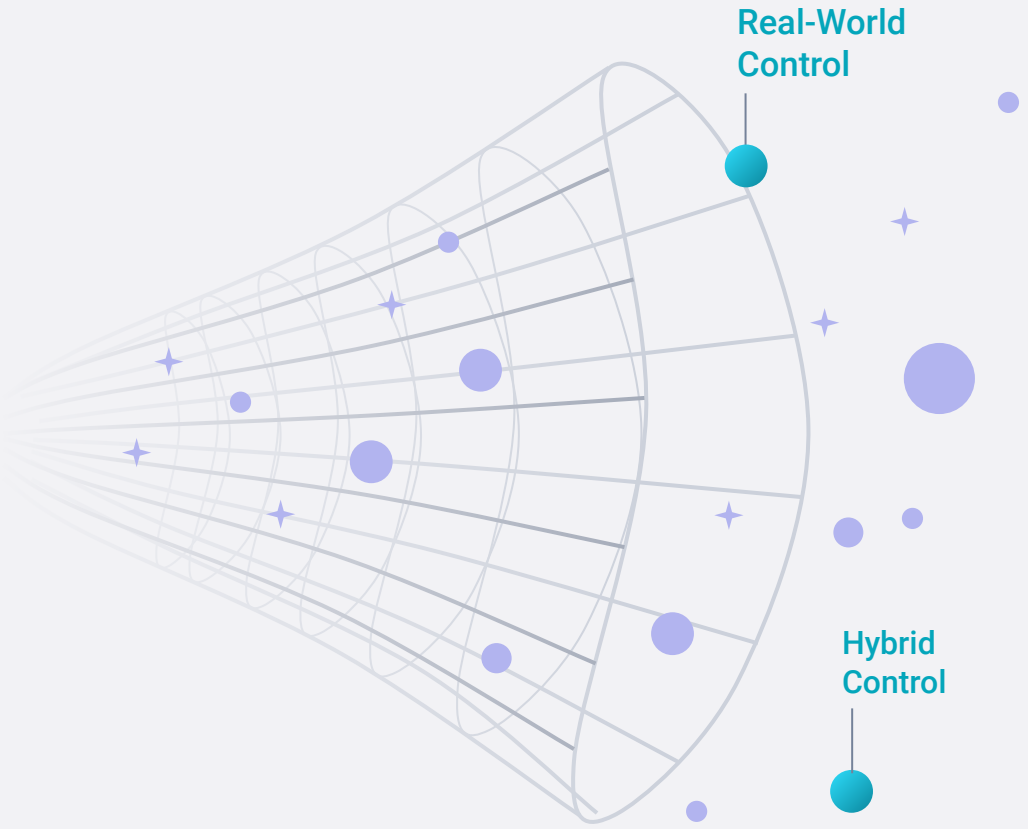
A platform for integrating clinical research into routine clinical care



Bourla and Meropol, Digital Health, 2021

CASE STUDIES

Novel Interventional Study Designs



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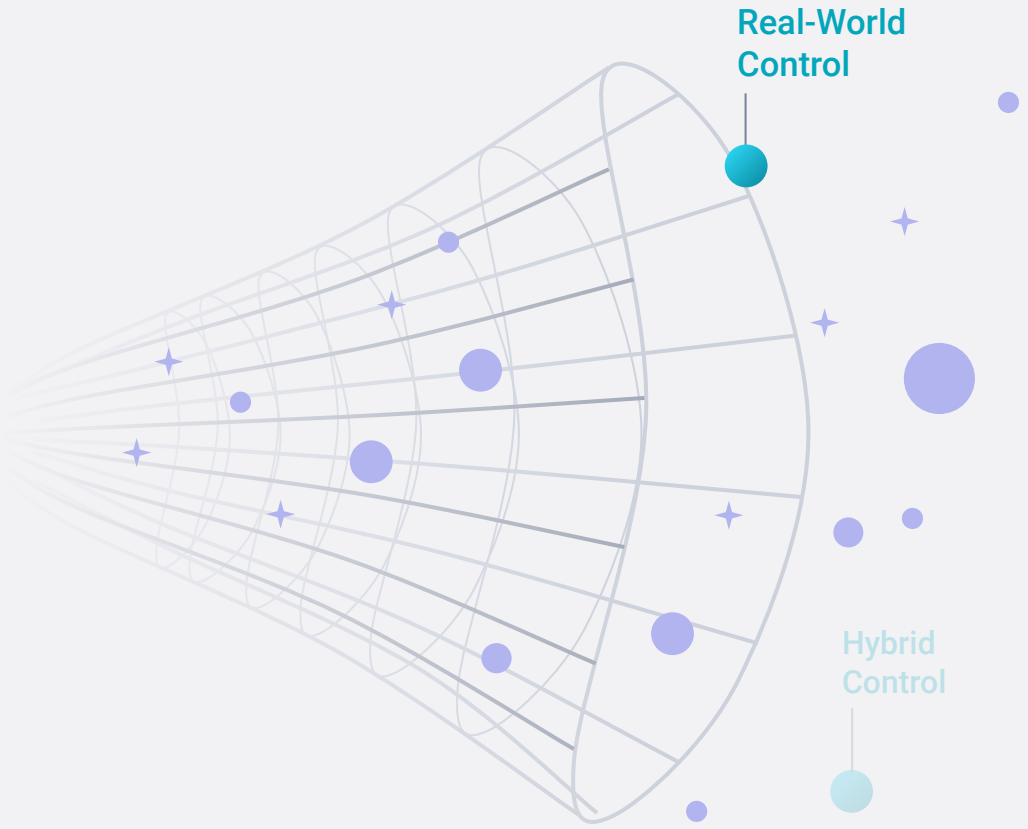
CASE STUDIES

Novel Interventional Study Designs



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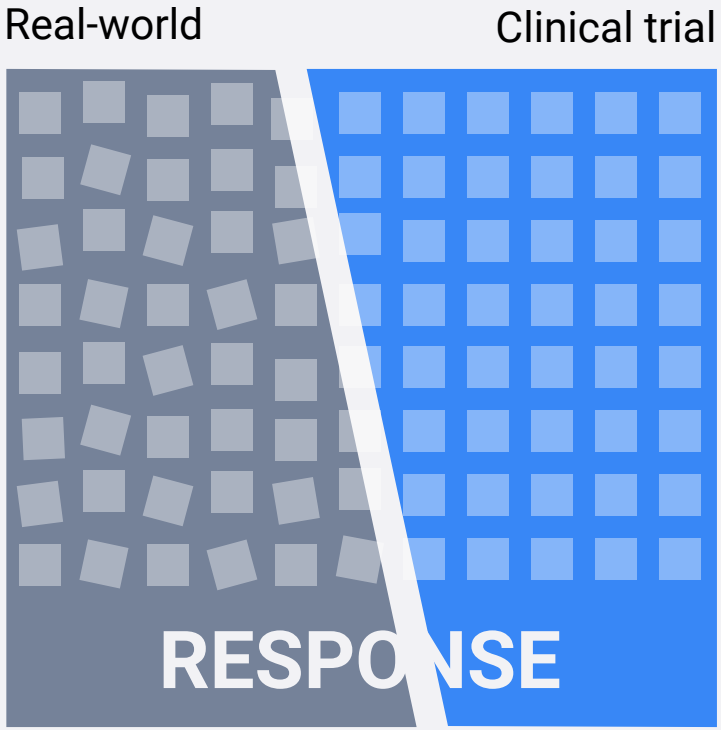
REAL-WORLD CONTROL

Applying an integrated evidence based approach

→ Real-World Endpoints

Comparability of endpoints:



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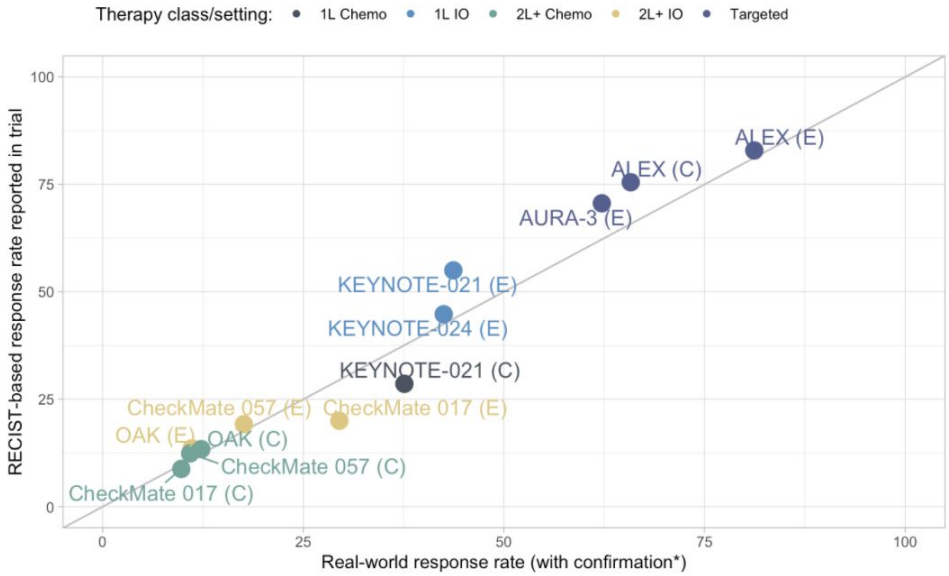
REAL-WORLD CONTROL

Applying an integrated evidence based approach

→ Real-World Endpoints

Study level association of real world response and imaging based response from clinical trials in aNSCLC



Chemo=chemotherapy; IO=immunotherapy; C=control arm; E=experimental arm.
* Except ALEX and AURA-3, which did not require confirmation in the trial

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REAL-WORLD CONTROL

Concordance rate and reasons for disagreement

71% agreement rate between real world response and imaging-based response

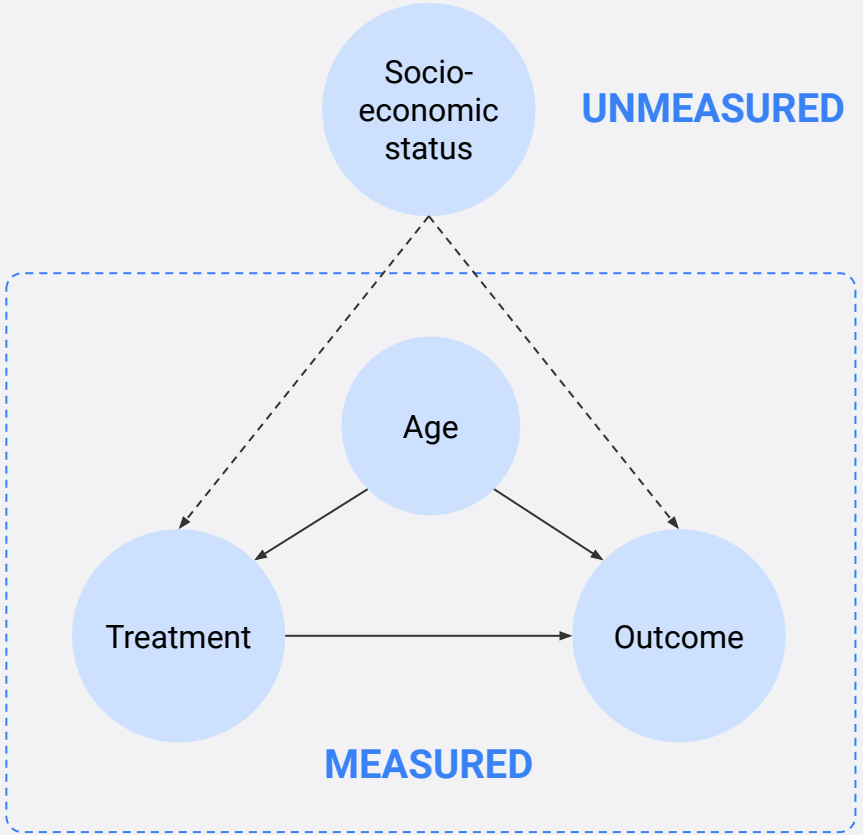
		Real-World Response	
		Non-responder	Responder
Imaging-based response	Non-responder	51 (51.0%)	20 (20.0%)
	Responder	9 (9.0%)	20 (20.0%)

Reasons for discordance included not meeting the strict thresholds, scans with disease outside baseline windows, missing follow-up scans, abstractor error, missing EHR documentation

REAL-WORLD CONTROL

Applying an integrated evidence based approach

→ Unmeasured confounding and bias



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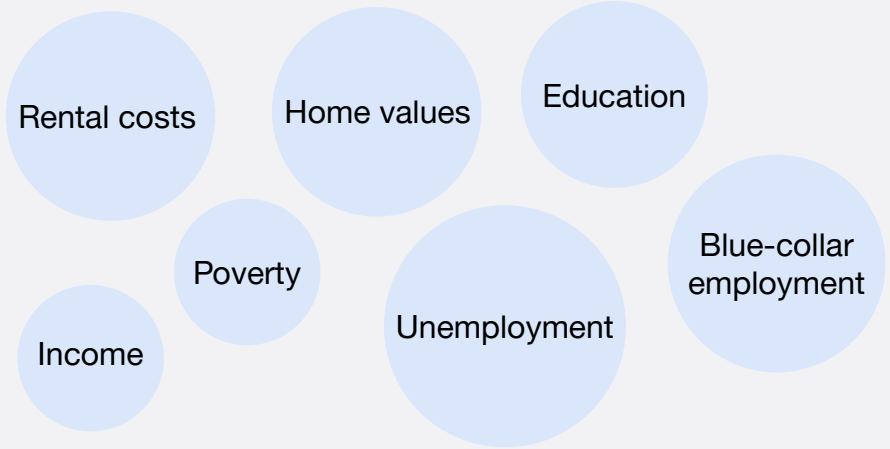
REAL-WORLD CONTROL

Applying an integrated evidence based approach

→ Unmeasured confounding and bias

Integrating Evidence on Socio-economic Status

To what extent do socio-economic disparities in outcomes remain unaccounted for in oncology RWE studies?



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REAL-WORLD CONTROL

Applying an integrated evidence based approach

→ Unmeasured confounding and bias

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Smoking Status

PD-(L)1 Status

ECOG

STK11 Status

Adv NSCLC Dx Date

KRAS Status

Hemoglobin

Met Dx

ALK Status

Lactate Dehydrogenase

Histology

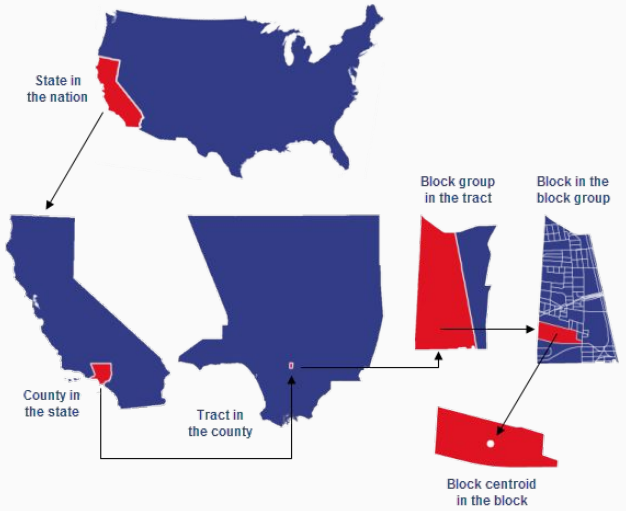
REAL-WORLD CONTROL

Applying an integrated evidence based approach

→ Unmeasured confounding and bias

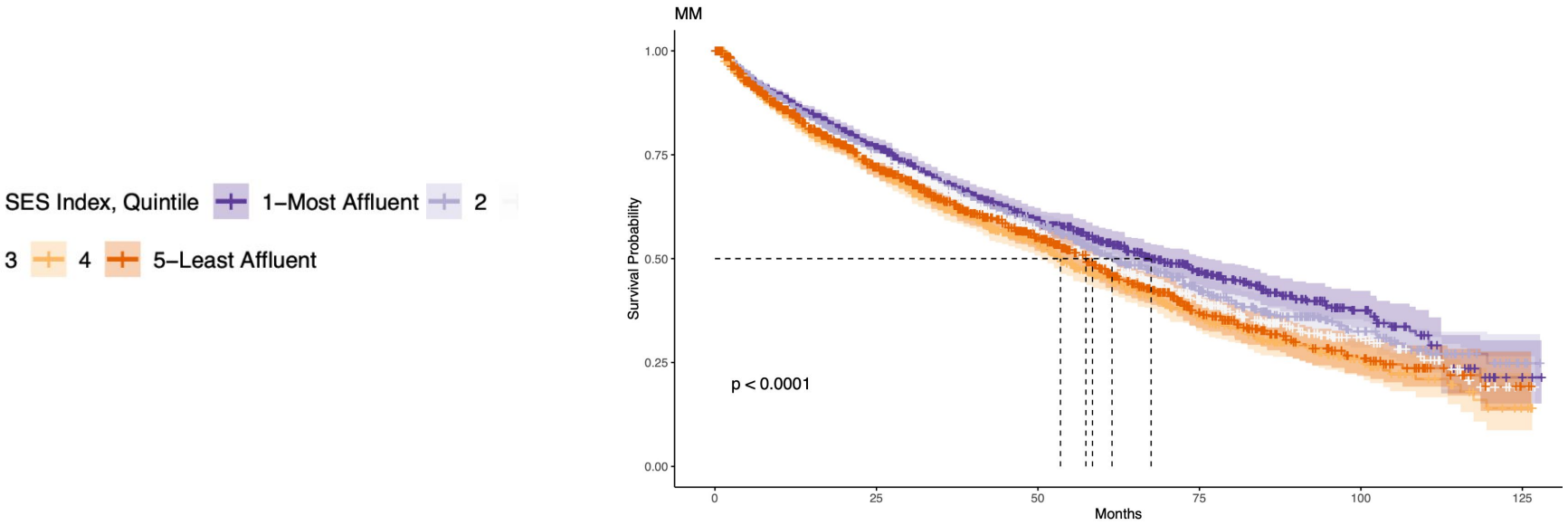
Integrating Evidence on Socio-economic Status

The Flatiron-Yost SES Index incorporates information on seven area-level indicators at the block group

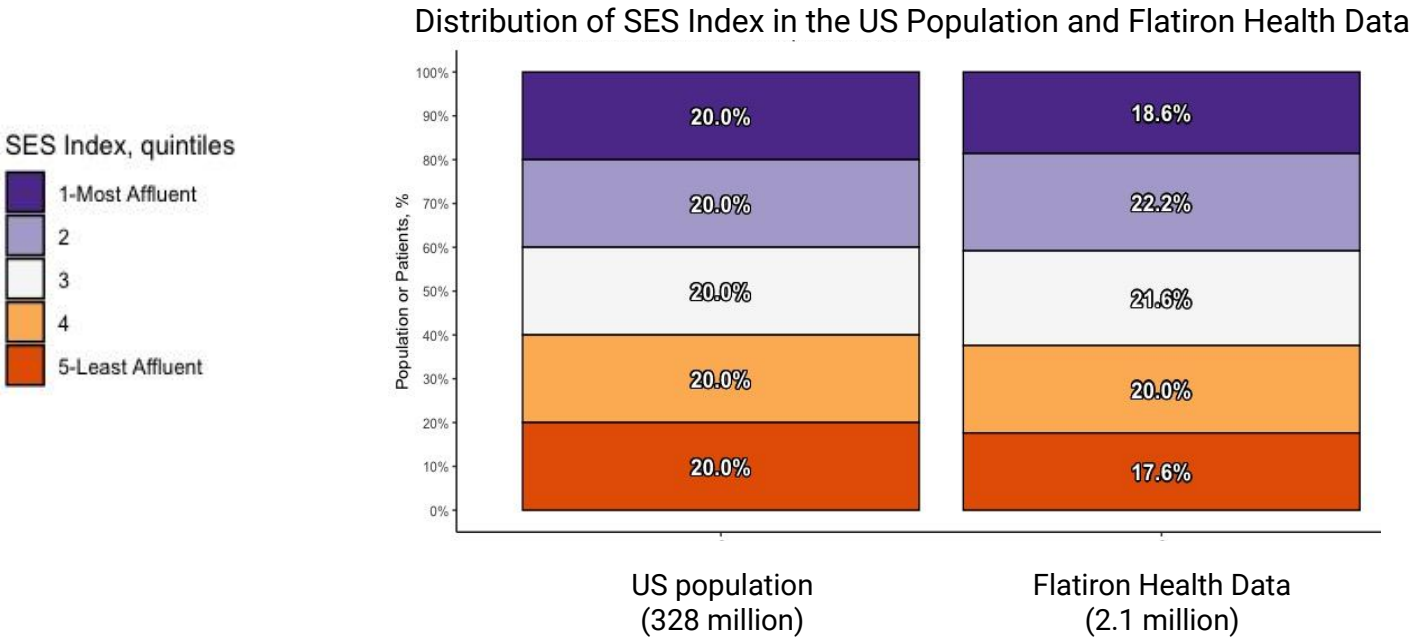


Source: Yu et al. (2014) Five-year cause-specific survival rates by Yost's SES quintile, race, and stage, 2000–2002, SEER 17 combined

Integrating Evidence on Socio-economic Status: Outcomes by Socio-economic Status



Integrating Evidence on Socio-economic Status: Representativeness of Flatiron Data



REAL-WORLD CONTROL

Understanding representativeness of Flatiron data in observational studies

→ Comparison with SEER and NPCR

Comparable to SEER and NPCR across sex and geography.

There are observable differences by region.

→ Comparison with US SES status

Comparable by quintiles

→ Global expansion of Flatiron's healthcare network

Bringing needed local data to support observational research

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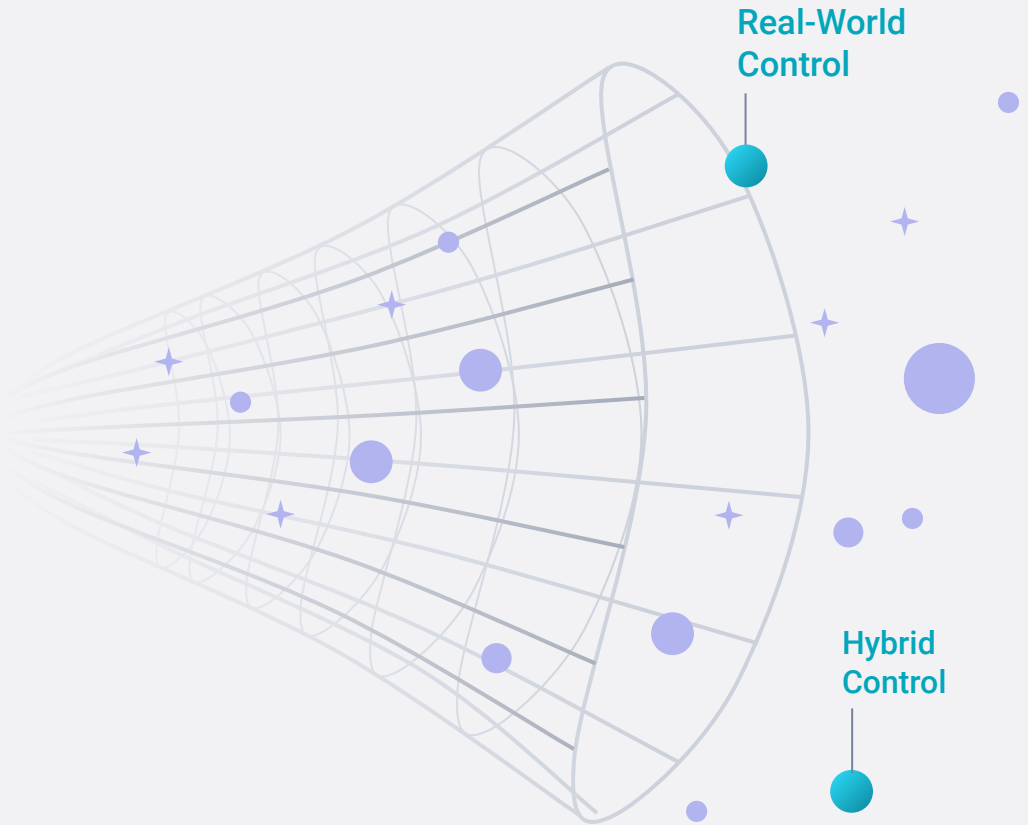
CASE STUDIES

Novel Interventional Study Designs



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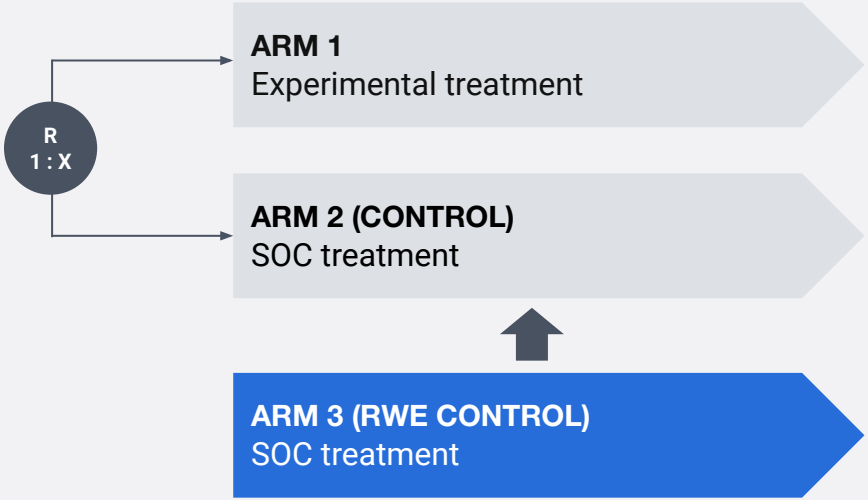
HYBRID CONTROL

→ **Hybrid Controlled Trials** are RCTs where the control arm is augmented with data from external sources, including EHR data when appropriate.

Study design uses internal statistical benchmark to combine data



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HYBRID CONTROL

What we have learned from our simulation studies:

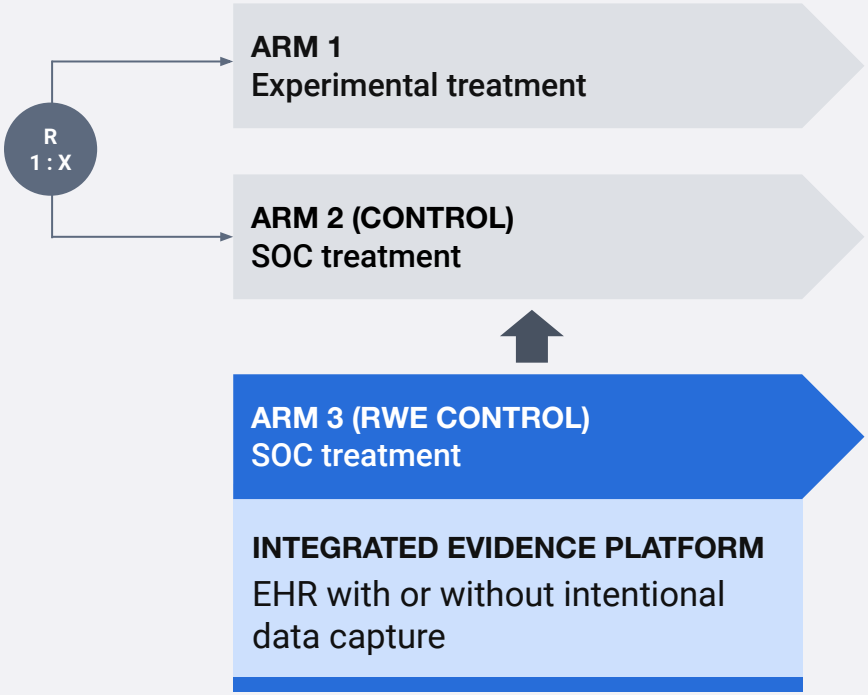
- As differences in patient characteristics between cohorts or bias in the outcomes increases, information borrowed from the RW-control arm decreases
- Statistical power for detecting differences between treatment groups increases as we borrow more data, however, Type I error (probability of falsely declaring a treatment effective) can be inflated under some scenarios, but is bounded
  - Some methods can be tuned for different amounts of borrowing to optimize power/Type I error tradeoff in the specific context
- Need to pay attention to timing of interim assessment as well as cohort size

Augmenting control arms with Real-World Data for cancer trials: Hybrid control arm methods and considerations W. Katherine Tan (1), Brian D. Segal (1 and 7), Melissa D. Curtis (1 and 8), Shrujal S. Baxi (1), William B. Capra (2), Elizabeth Garrett-Mayer (3), Brian P. Hobbs (4), David S. Hong (5), Rebecca A. Hubbard (6), Jiawen Zhu (2), Somnath Sarkar (1), Meghna Samant (1) ((1) Flatiron Health, Inc., (2) Genentech, (3) American Society of Clinical Oncology Center for Research and Analytics, (4) Dell Medical School, University of Texas, Austin, (5) University of Texas, M.D. Anderson Cancer Center, (6) University of Pennsylvania School of Medicine, (7) Indigo AG, (8) EQRx)

HYBRID TRIAL DESIGN

HYBRID CONTROL

Borrowing of real-world data could leverage the **Integrated Evidence Platform** if intentional data capture is needed in the real-world cohort.



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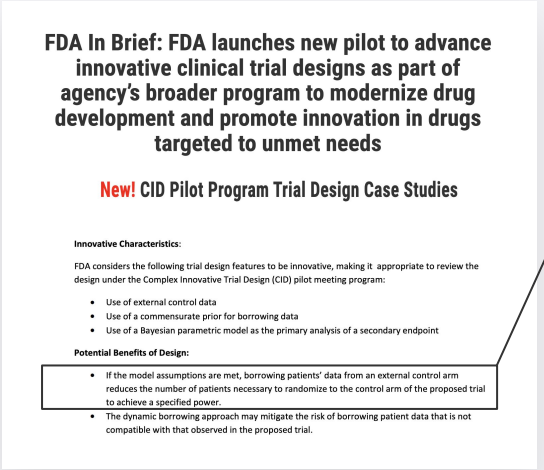
HYBRID CONTROL

Integrated Evidence Based Approach has the ability to transform clinical research



FDA In Brief: FDA launches new pilot to advance innovative clinical trial designs as part of agency's broader program to modernize drug development and promote innovation in drugs targeted to unmet needs

New! CID Pilot Program Trial Design Case Studies

Innovative Characteristics:

FDA considers the following trial design features to be innovative, making it appropriate to review the design under the Complex Innovative Trial Design (CID) pilot meeting program:

- Use of external control data
- Use of a commensurate prior for borrowing data
- Use of a Bayesian parametric model as the primary analysis of a secondary endpoint

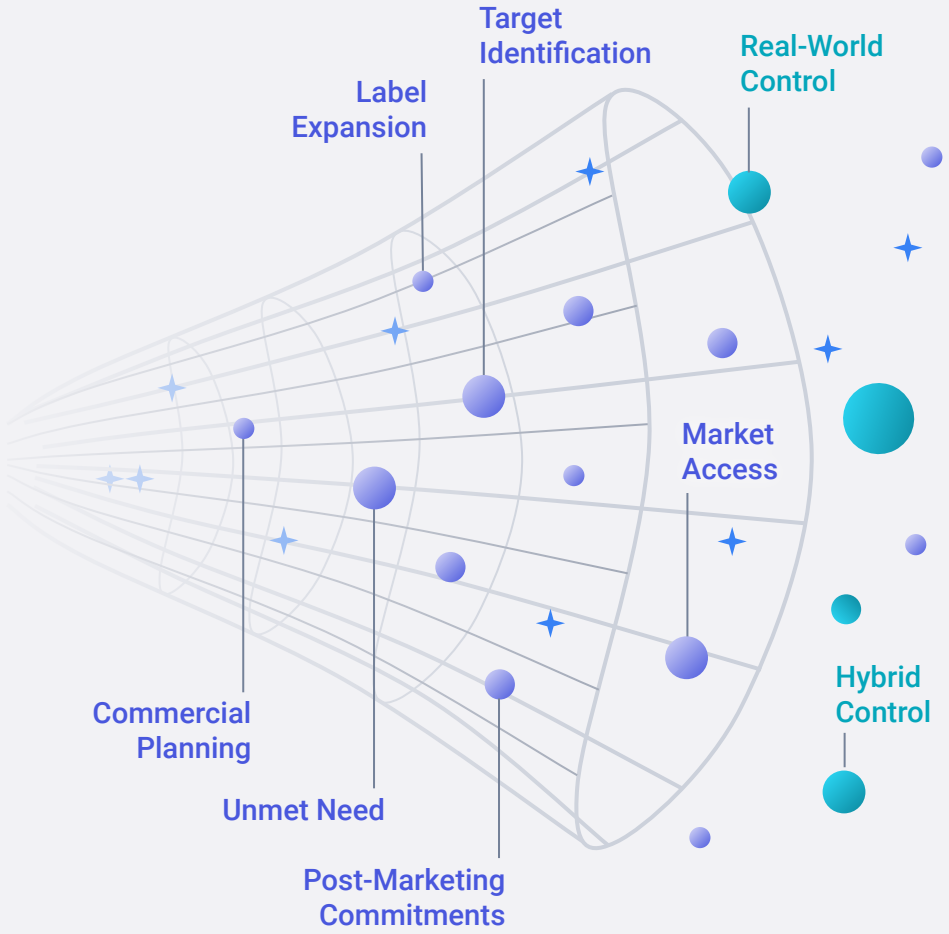
Potential Benefits of Design:

- If the model assumptions are met, borrowing patients' data from an external control arm reduces the number of patients necessary to randomize to the control arm of the proposed trial to achieve a specified power.
- The dynamic borrowing approach may mitigate the risk of borrowing patient data that is not compatible with that observed in the proposed trial.

If the model assumptions are met, **borrowing patients' data from an external control arm** reduces the number of patients necessary to randomize to the control arm of the proposed trial to achieve a specified power.

FDA

Widening the aperture for
integrated evidence



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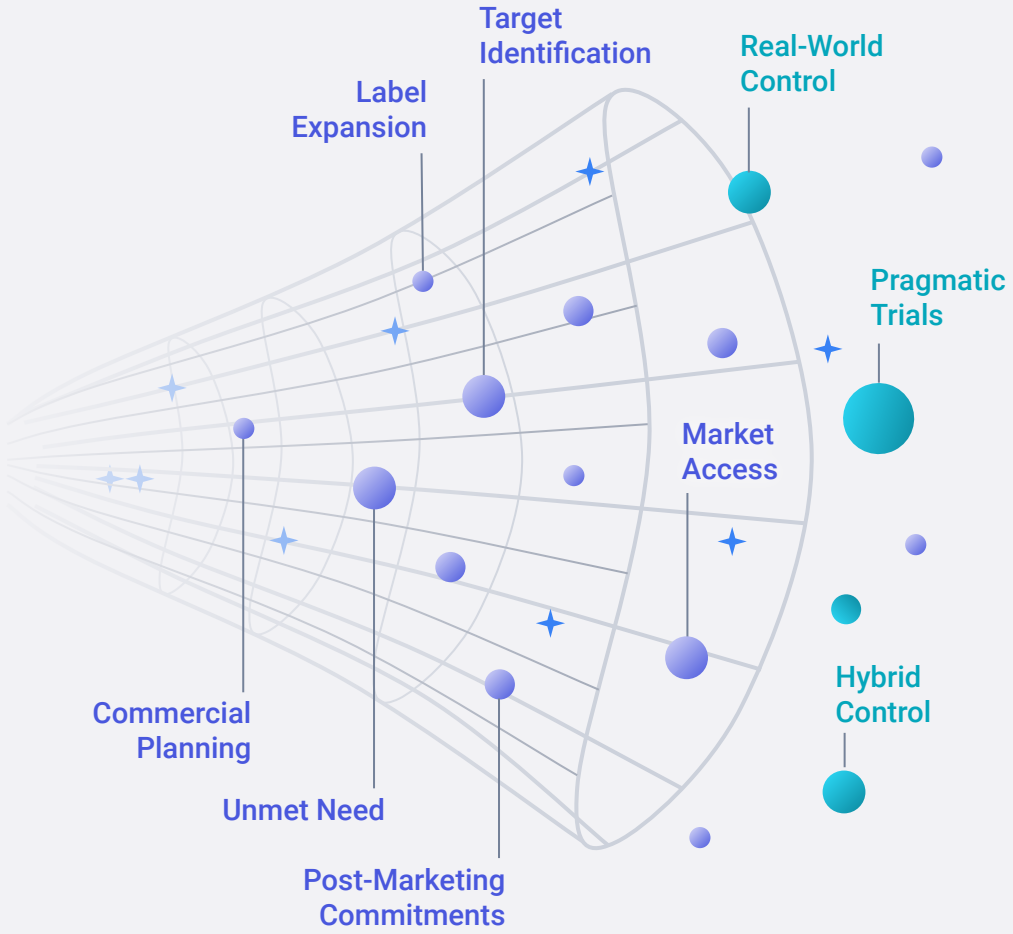
Generating integrated evidence requires developing new best practices and advanced methods across various fields.



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Integrated evidence can

Accelerate R&D and access

Make research more inclusive

Make healthcare more sustainable

We’re in this together.

Q&A

Please submit questions through the Q&A feature at the bottom of your screen.

Shane Woods, PhD
Chief Commercial Officer
Flatiron Health

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