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WE WILL BE STARTING AT 1PM ET

EP 02

Integrated evidence: Using multi-modal data to create new insights

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Agenda

Integrating clinical + genomics

Lev Demirdjian, PhD
Senior Data Scientist, *Janssen R&D*

Building blocks of integrated evidence

Prashni Paliwal, PhD
Director, Quantitative Sciences, *Flatiron Health*

Learnings from integrated evidence

Tamara Snow
Senior Product Manager, *Flatiron Health*

Which of these data sources is your organization using today?

A. Clinical
B. Genomic
C. Imaging
D. Claims
E. Patient Reported Outcomes (PROs)
F. None of the above

Building blocks of integrated evidence

Prashni Paliwal, PhD

Director, Quantitative Sciences, Flatiron Health

03.16.2022

Integrated Evidence

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

GENERATE

COMBINE

ANALYZE

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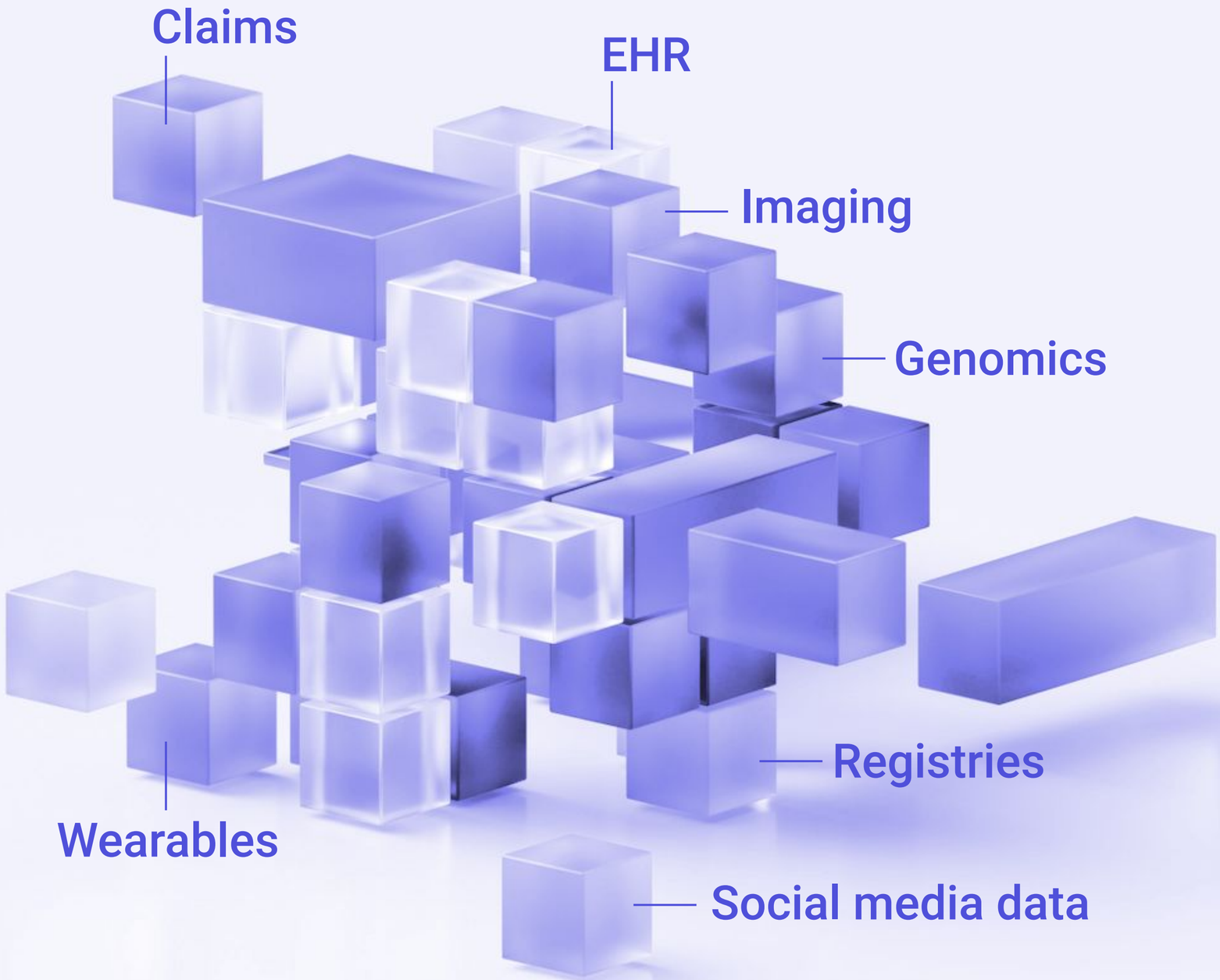
Data sources are the building blocks of integrated evidence.

Each have their own strengths and limitations.



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Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry

DRAFT GUIDANCE

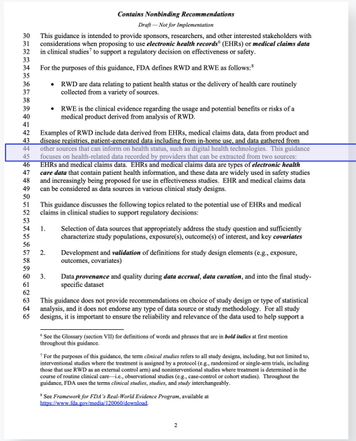
This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document or the RealWorld Evidence Program, please email CDERMedicalPolicy-RealWorldEvidence@fda.hhs.gov

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

September 2021
Real World Data/Real World Evidence (RWD/RWE)



Contains Nonbinding Recommendations

Draft — Not for Implementation

This guidance is intended to provide sponsors, researchers, and other interested stakeholders with considerations when proposing to use ***electronic health records***[4] (EHRs) or ***medical claims data*** in clinical studies[5] to support a regulatory decision on effectiveness or safety.

For the purposes of this guidance, FDA defines RWD and RWE as follows:[6]

- RWD are data relating to patient health status or the delivery of health care routinely collected from a variety of sources.
- RWE is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD.

Examples of RWD include data derived from EHRs, medical claims data, data from product and disease registries, patient-generated data including from in-home use, and data gathered from other sources that can inform on health status, such as digital health technologies. This guidance focuses on health-related data recorded by providers that can be extracted from two sources: EHRs and medical claims data. EHRs and medical claims data are types of ***electronic health care data*** that contain patient health information, and these data are widely used in safety studies and increasingly being proposed for use in effectiveness studies. EHR and medical claims data can be considered as data sources in various clinical study designs.

This guidance discusses the following topics related to the potential use of EHRs and medical claims in clinical studies to support regulatory decisions:

1. Selection of data sources that appropriately address the study question and sufficiently characterize study populations, exposure(s), outcome(s) of interest, and key ***covariates***
2. Development and ***validation*** of definitions for study design elements (e.g., exposure, outcomes, covariates)
3. Data ***provenance*** and quality during ***data accrual***, ***data curation***, and into the final study-specific dataset

This guidance does not provide recommendations on choice of study design or type of statistical analysis, and it does not endorse any type of data source or study methodology. For all study designs, it is important to ensure the reliability and relevance of the data used to help support a

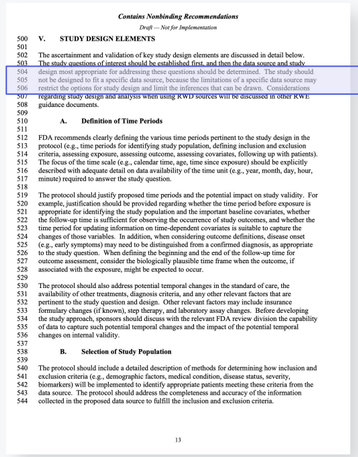
[4] See the Glossary (section VII) for definitions of words and phrases that are in ***bold italics*** at first mention throughout this guidance.

[5] For the purposes of this guidance, the term *clinical studies* refers to all study designs, including, but not limited to, interventional studies where the treatment is assigned by a protocol (e.g., randomized or single-arm trials, including those that use RWD as an external control arm) and noninterventional studies where treatment is determined in the course of routine clinical care—i.e., observational studies (e.g., case-control or cohort studies). Throughout the guidance, FDA uses the terms *clinical studies*, *studies*, and *study* interchangeably.

[6] See *Framework for FDA's Real-World Evidence Program*, available at https://www.fda.gov/media/120060/download.

2

Selection of data sources that **appropriately address the study question and sufficiently characterize** study populations, exposure(s), outcome(s) of interest, and key covariates



Contains Nonbinding Recommendations

Draft — Not for Implementation

V. STUDY DESIGN ELEMENTS

The ascertainment and validation of key study design elements are discussed in detail below. The study questions of interest should be established first, and then the data source and study design most appropriate for addressing these questions should be determined. The study should not be designed to fit a specific data source, because the limitations of a specific data source may restrict the options for study design and limit the inferences that can be drawn. Considerations regarding study design and analysis when using RWD sources will be discussed in other RWE guidance documents.

A. Definition of Time Periods

FDA recommends clearly defining the various time periods pertinent to the study design in the protocol (e.g., time periods for identifying study population, defining inclusion and exclusion criteria, assessing exposure, assessing outcome, assessing covariates, following up with patients). The focus of the time scale (e.g., calendar time, age, time since exposure) should be explicitly described with adequate detail on data availability of the time unit (e.g., year, month, day, hour, minute) required to answer the study question.

The protocol should justify proposed time periods and the potential impact on study validity. For example, justification should be provided regarding whether the time period before exposure is appropriate for identifying the study population and the important baseline covariates, whether the follow-up time is sufficient for observing the occurrence of study outcomes, and whether the time period for updating information on time-dependent covariates is suitable to capture the changes of those variables. In addition, when considering outcome definitions, disease onset (e.g., early symptoms) may need to be distinguished from a confirmed diagnosis, as appropriate to the study question. When defining the beginning and the end of the follow-up time for outcome assessment, consider the biologically plausible time frame when the outcome, if associated with the exposure, might be expected to occur.

The protocol should also address potential temporal changes in the standard of care, the availability of other treatments, diagnosis criteria, and any other relevant factors that are pertinent to the study question and design. Other relevant factors may include insurance formulary changes (if known), step therapy, and laboratory assay changes. Before developing the study approach, sponsors should discuss with the relevant FDA review division the capability of data to capture such potential temporal changes and the impact of the potential temporal changes on internal validity.

B. Selection of Study Population

The protocol should include a detailed description of methods for determining how inclusion and exclusion criteria (e.g., demographic factors, medical condition, disease status, severity, biomarkers) will be implemented to identify appropriate patients meeting these criteria from the data source. The protocol should address the completeness and accuracy of the information collected in the proposed data source to fulfill the inclusion and exclusion criteria.

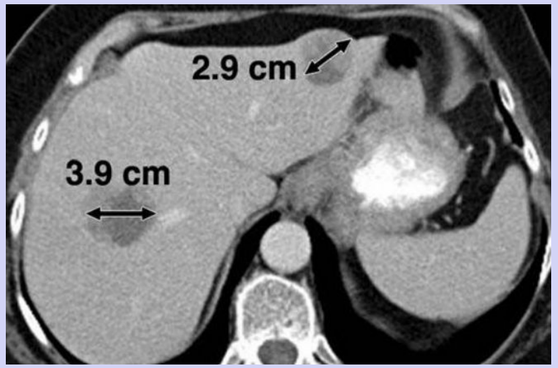
13

The study **should not be designed to fit a specific data source**, because the limitations of a specific data source may restrict the options for study design and limit the inferences that can be drawn.

RUBIES: Using imaging data to characterize abstracted response variable from EHR

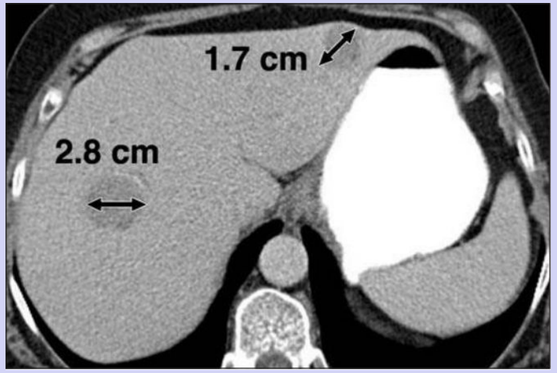
Example RECIST assessment

Baseline scan



Sum Lesion Diameter = 6.8cm

Follow-up scan #1



Sum Lesion Diameter = 4.5cm

% change from baseline = **-34% = PR**

Example rwR assessment

Radiology report for follow-up scan #1

IMPRESSION:
1. Primary lesion in the left lower lobe is significantly decreased in size. Tiny 5 mm nodule in the right upper lobe is decreased in size, and previou sly identified subpleural nodule in the left upper lobe is no longer seen.
2. Mediastinal lymphadenopathy has completely resolved.
3. No new foci of metastatic disease. No evidence of metastatic disease in the abdomen or pelvis.

Clinical assessment of follow-up scan #1

Patient Name: [redacted] Date: [redacted]
Patient Number: [redacted] Date Of Birth: [redacted]

FOLLOW UP VISIT

Reason for Visit:
Follow-up regarding lung carcinoma [redacted]

Impression

CT CAP in [redacted] showed interval response. = PR

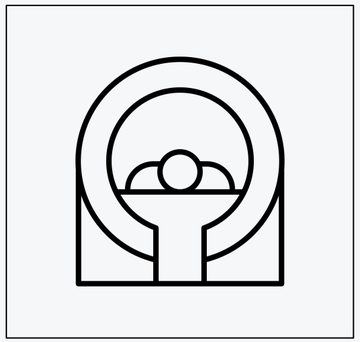
STARTED OSIMERTINIB [redacted] CAP [redacted] after 3m with stable disease.

New palpable left cervical lymph node first noticed [redacted] which is resolved clinically after about 2 months of treatment with osimertinib.

Insomnia, occasional use of Ambien

CT CAP in [redacted] showed interval response. Brain MRI negative

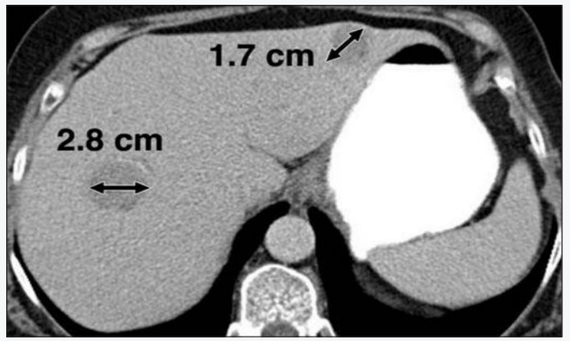
In order to complete the RUBIES study, we needed to acquire imaging on real world patients



Scans

PACS database

Flatiron database



CRO modified RECIST reads

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

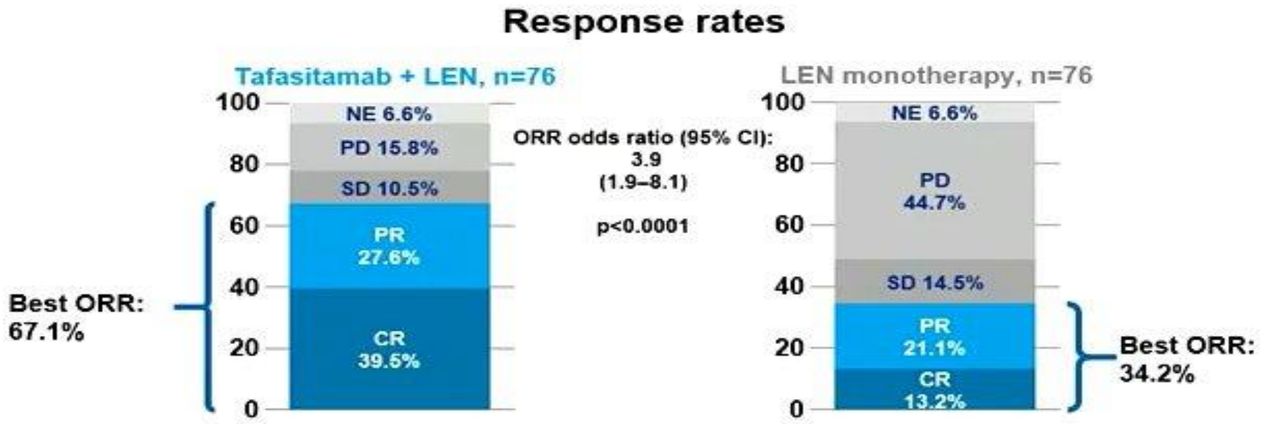
RE-MIND Study: Validation of Response Variable

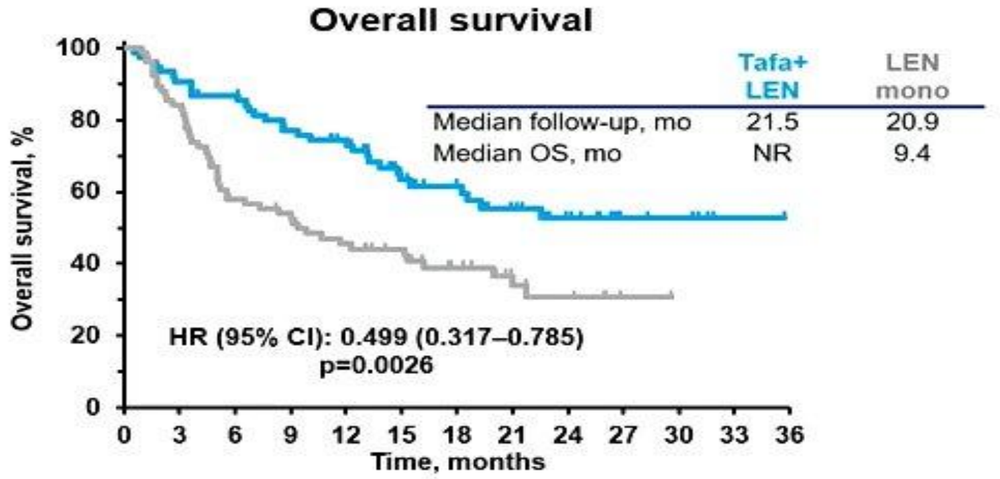
EUROPEAN HEMATOLOGY ASSOCIATION

EHA25 VIRTUAL

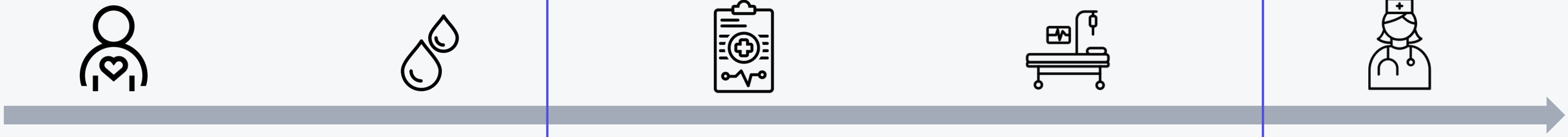
RE-MIND study: comparison of tafasitamab + lenalidomide (L-MIND) vs lenalidomide monotherapy (real-world data) in transplant-ineligible patients with relapsed/refractory diffuse large B-cell lymphoma

- Tafasitamab + LEN provides significant and clinically meaningful improvements in ORR, CR rate, DoR, and OS compared with LEN monotherapy
- Effect sizes in all time-to-event endpoints and all sensitivity analyses support the primary endpoint results
- The study provides an important example of the utilization of real-world data to support drug development





Zinzani PL, et al. EHA 2020 (Abstract S238)



Patient visit to PCP

Patient has blood in urine

Captured within Flatiron EHR:

Detailed clinical oncology care data

Patient visits is diagnosed with RCC

Patient undergoes tests, lines of therapy

Patient is referred elsewhere

Captured in healthcare claims:

Administrative/billable services data

Patient goes to ED for stitches after accident

Patient hospitalized for treatment-related event

Looking forward

Studies to assess completeness of other key variables

GENERATE

COMBINE

ANALYZE

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Lev Demirdjian, PhD

Senior Data Scientist, Janssen

03.16.2022

Using multimodal data to support clinical development programs within Janssen R&D

Lev Demirdjian, PhD
Senior Data Scientist, Janssen R&D Data Science Analytics and Insights
March 16, 2022

Presentation Roadmap

1. **Introduction**
2. **Supporting JRD Clinical Development Programs using the Flatiron Health - Foundation Medicine CGDB: Use Cases**
3. **Summary and Conclusions**

Introduction – Leveraging Clinico-Genomic Data to Support JRD Clinical Development Programs

JRD Data Sciences has utilized the Flatiron Health - Foundation Medicine Clinico-Genomic Database (CGDB) in a variety of capacities to support our clinical development programs

Understanding the real-world therapeutic landscape

- Understanding standards of care (SOC) in the real-world setting
- Understanding real-world patient treatment journeys
- Identifying subpopulations with unmet medical needs or disparities in care

Predictive and prognostic modeling

- Identify biomarkers that can be targets for therapy
- Understand and predict
  - ➢ Recurrence in patients who receive curative treatment
  - ➢ Duration of progression free survival and other endpoints in patients with metastatic disease

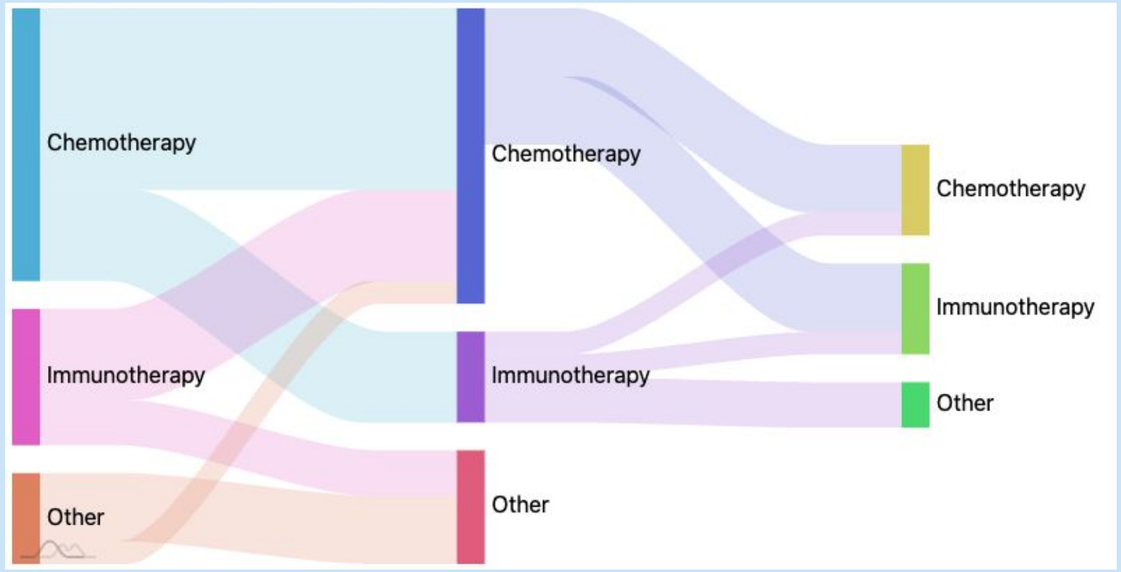
Real-world external comparators

- Comparative effectiveness to support Janssen RCTs
- Contextualizing safety events using real-world data (RWD)

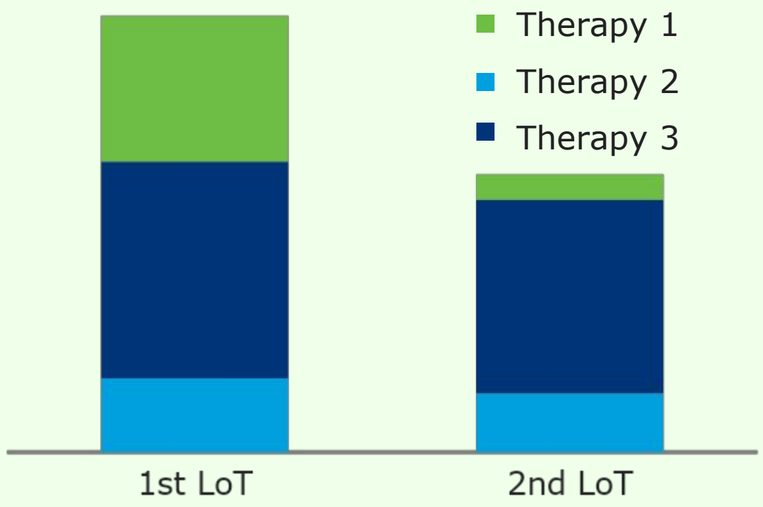
Use Case 1: Understanding the therapeutic landscape in the real-world setting

The Flatiron/FMI CGDB offers insight into patient treatment journeys that can identify unmet medical needs as well as disparities in care.

What do patient treatment journeys look like in the real-world?



What does the therapeutic landscape look like in the real-world?

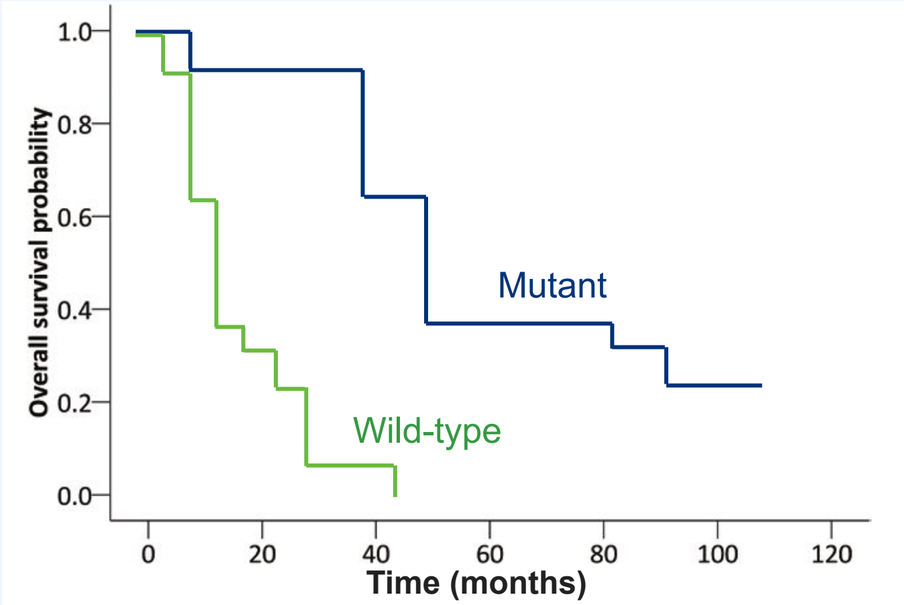


Use Case 1: Understanding the therapeutic landscape in the real-world setting

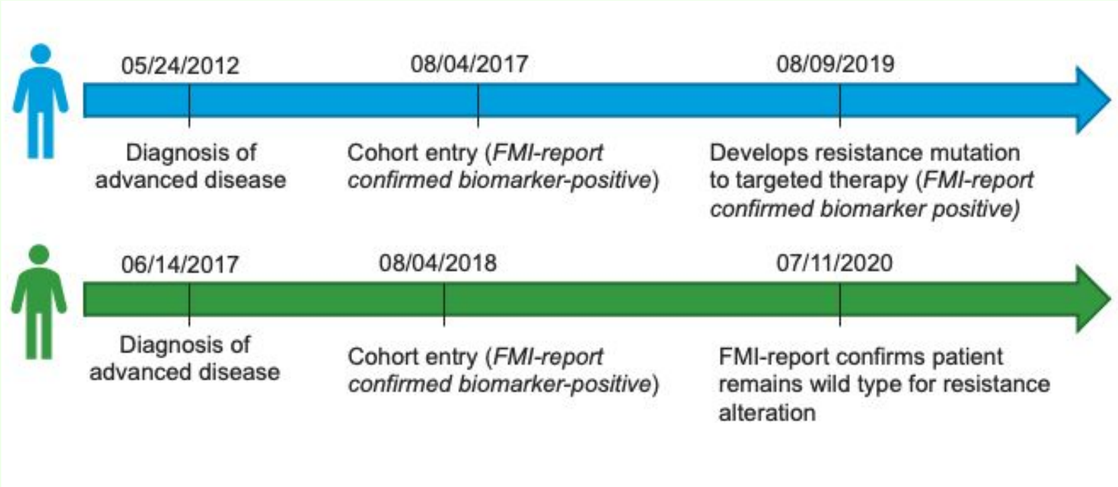
Identification of differential outcomes between biomarker-defined subgroups

- Longitudinal genetic testing data allow the identification of resistance mutations to targeted therapies and their prognostic / predictive effects.

Are there differences in survival between biomarker-defined subgroups?



Are there differences in survival for patients who develop resistance mutations to target therapies?



Use Case 2: Predictive and prognostic modeling

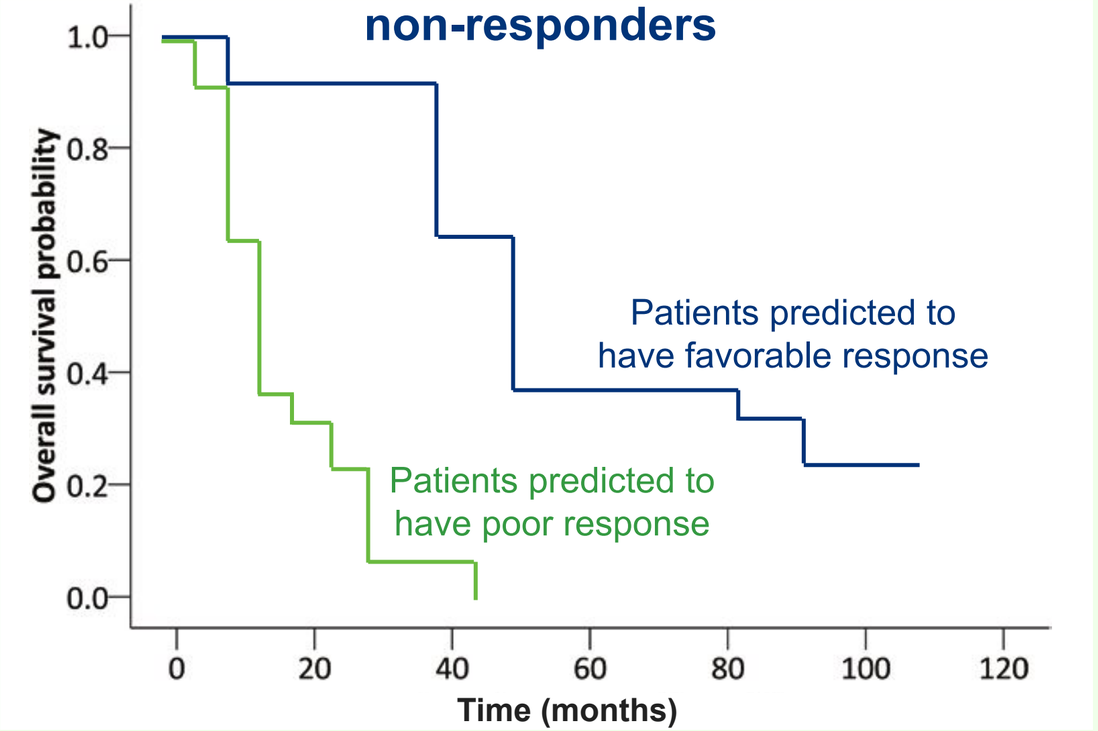
Prognostic factor: Associated with outcomes and is *treatment agnostic*

Predictive factor: Associated with outcomes and is *treatment dependent*

Using the CGDB, we have developed statistical and machine learning models to:

- *Identify patients who are more likely to respond to certain therapies*
- *Identify patients who are likely to have poor outcomes regardless of therapy received*
- *Identify the factors underlying differential response*

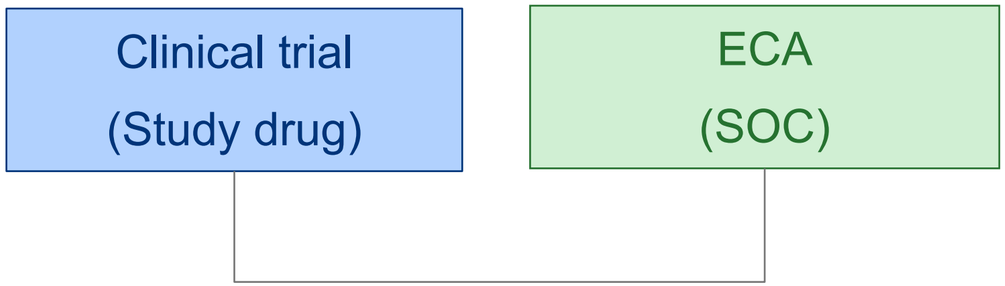
Example: Observed survival among predicted subgroups of responders vs. non-responders



Insights from such models have informed clinical trial design / recruitment strategies.

Use Case 3: Comparative effectiveness and safety using real-world external comparators

- An *externally controlled trial* compares patients receiving a study treatment to comparable patients outside of the trial, e.g. in a real-world setting receiving standard of care.
- External control arms (ECAs) address several limitations of clinical trials including those around cost, ethical considerations, etc.



Goal: Assess the treatment benefit of a trial drug by comparing endpoints of patients under standard of care to trial patients treated with the study drug

Use Case 3: Comparative effectiveness and safety using real-world external comparators

Leveraging ECAs to support regulatory approvals

FDA has highlighted key aspects of well-designed ECAs

Key aspects of well-designed ECAs	How JRDDS has addressed these considerations using the Flatiron Health - Foundation Medicine CGDB
Similarity of the ECA to the trial cohort	• Mapping trial criteria to their real-world analogues using clinical guidance and subject matter expertise • Biomarker-defined inclusion criteria, determined by FMI testing • Abstraction of custom data elements via Flatiron Spotlight projects • Statistical / epidemiological techniques
Minimal bias, including selection and confounding bias	• Appropriate statistical adjustments (e.g. propensity score models, negative control outcomes) • E-values for assessing unmeasured confounding
Well-defined & reliable outcome assessments	• Using validated real-world endpoints like Flatiron's mortality metrics

FDA Draft Guidance (2019): Rare Diseases: Natural History Studies for Drug Development Guidance for Industry

Use Case 3: Comparative effectiveness and safety using real-world external comparators

Amivantamab compared with real-world therapies in patients with NSCLC with EGFR Exon 20 insertion mutations who have progressed after platinum doublet chemotherapy

- Amivantamab is an epidermal growth factor receptor (EGFR)-MET bispecific antibody with immune cell-directing activity.
- A protocol-driven treatment comparison was conducted of amivantamab vs real-world therapies in pts with Exon20ins aNSCLC who progressed after platinum chemotherapy using data from Flatiron Health and two other data sources.

**The ECA used clinico-genomic data from a Flatiron Spotlight dataset*

Endpoint	Values
Median Overall Survival	22.8 mo (Ami) vs 13.1 mo (ECA) HR = 0.53 [95% CI, 0.33, 0.86]
Progression Free Survival	8.3 mo (Ami) vs 2.9 mo (ECA) HR = 0.46 [95% CI, 0.33, 0.63]
Time to Next Treatment	14.8 mo (Ami) vs 4.8 mo (ECA) HR = 0.42 [95% CI, 0.29, 0.6]

Amivantamab compared with real-world therapies in patients with NSCLC with EGFR Exon 20 insertion mutations who have progressed after platinum doublet chemotherapy. Minchom et al, Journal of Clinical Oncology 2021 39:15_suppl, 9052-9052

Summary and Conclusions

JRD Data Sciences has leveraged Flatiron Health - Foundation Medicine's CGDB in a variety of capacities to support our clinical development programs

The insights derived from the CGDB have allowed

- Deeper understanding of the real-world therapeutic landscape
- Deeper understanding of the prognostic/predictive value of select biomarkers
- Construction of ECAs to support regulatory decision-making

Contact information

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janssen
PHARMACEUTICAL COMPANIES OF
Johnson & Johnson

Learnings from integrating evidence

Tamara Snow

Senior Product Manager, *Flatiron Health*

03.16.2022

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It’s not just the ingredients…

it’s how you bring them together.


CORN
FLAKES
MILK

Considerations when integrating evidence

Generate

- Data curation

Combine

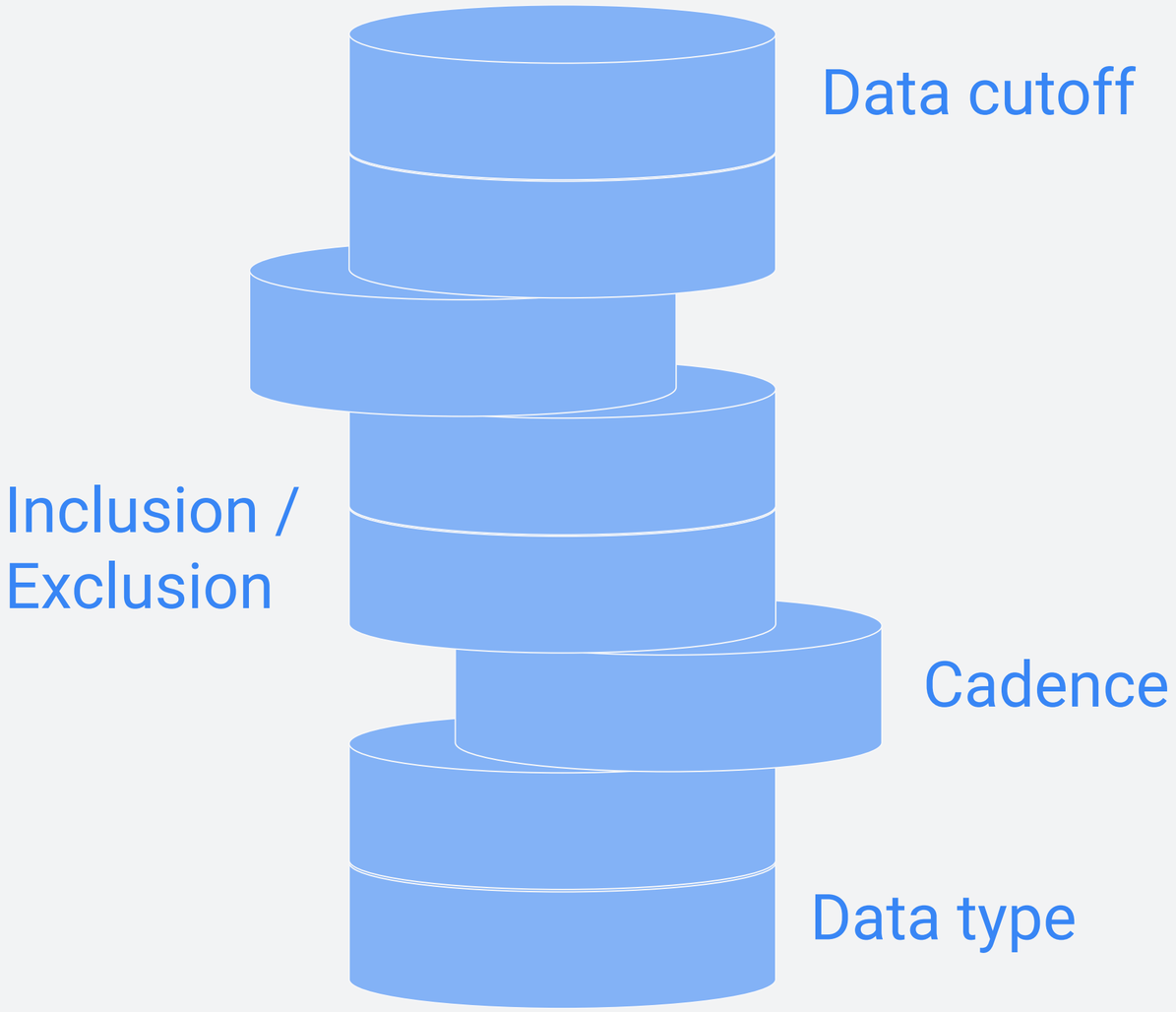
- Provenance
- Matching patients
- Privacy implications

Analyze

- Sample size
- Longitudinality
- Representativeness

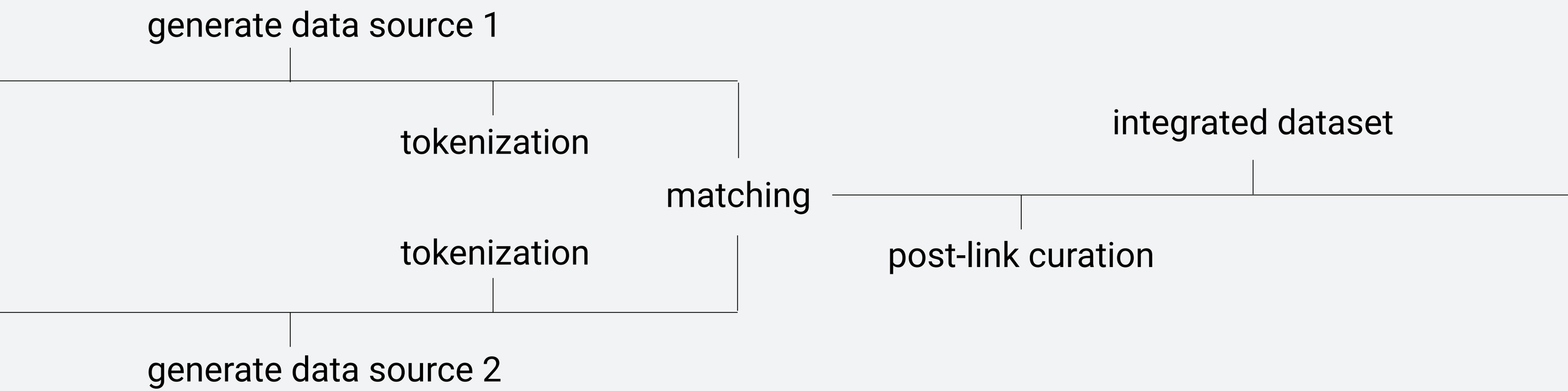
Data curation

Understanding how each data source is built to ensure compatibility of the integrated dataset



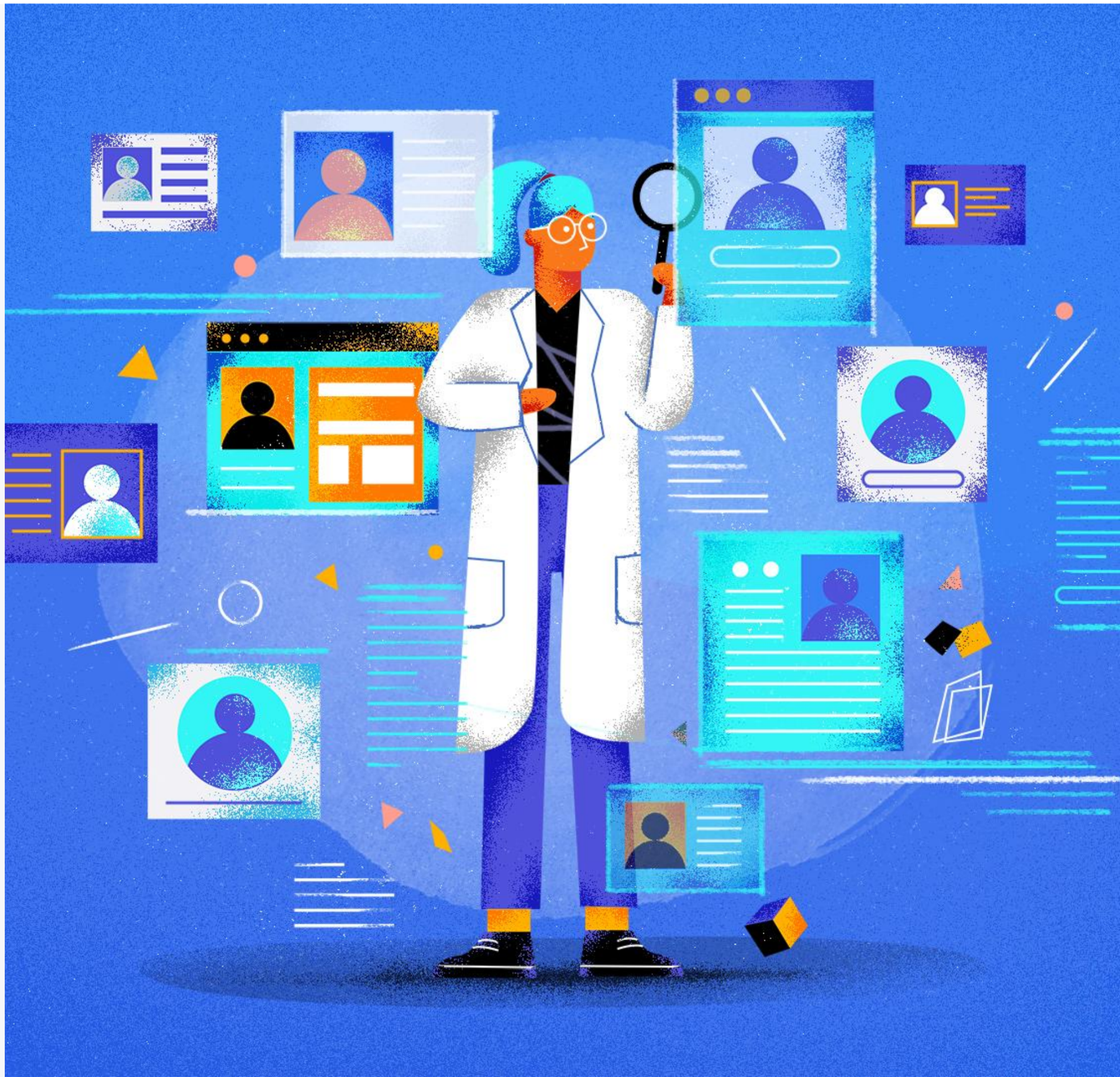
Provenance

Ensuring transparency into all decisions made to create and link all datasets



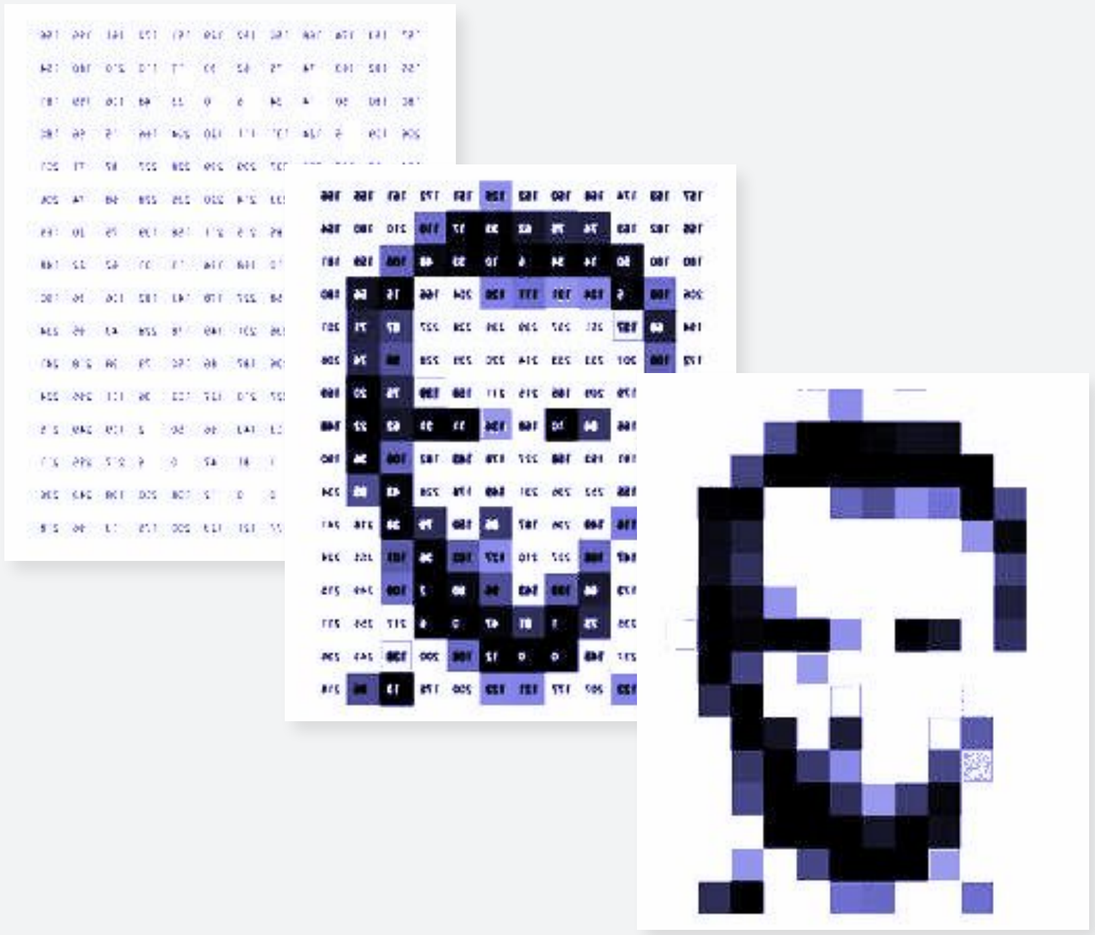
Matching patients

Identifying the same patient across multiple data sources to maximize accuracy and matches



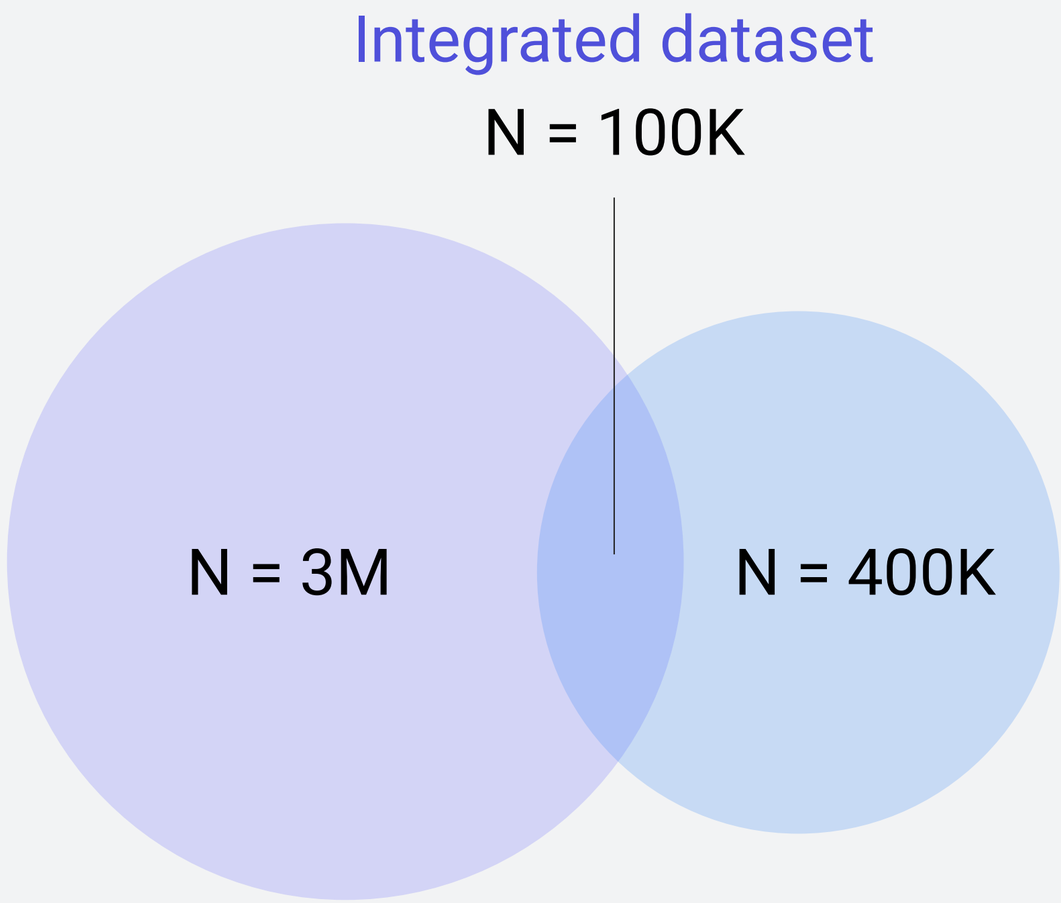
Privacy implications

Creating a linking process and an integrated dataset that upholds privacy principles



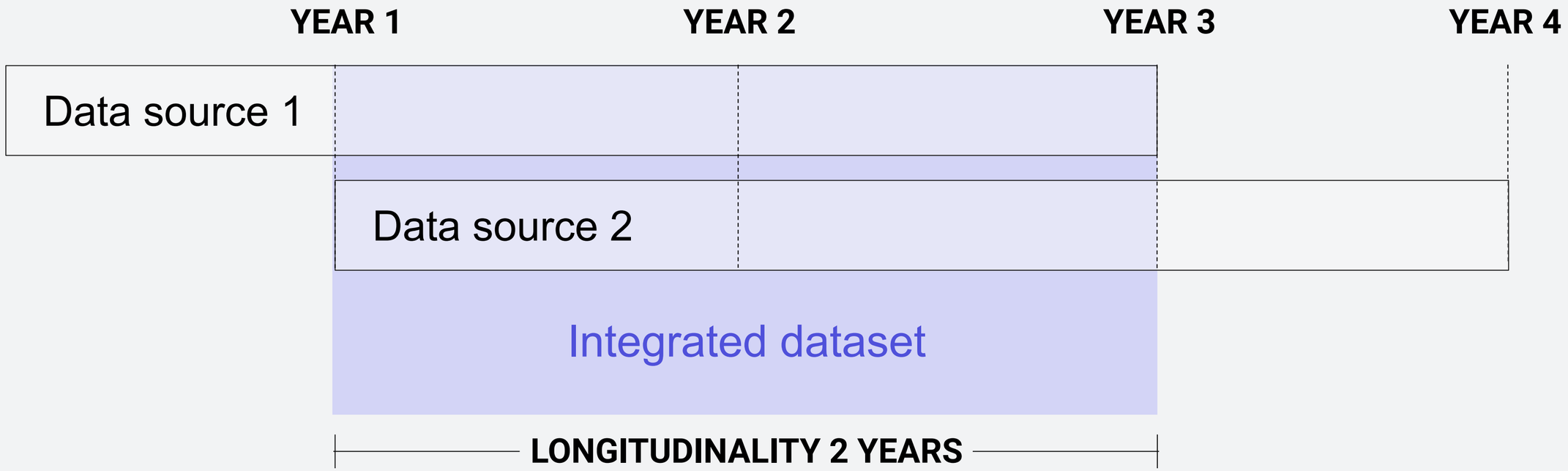
Sample size

Understanding trade-offs between the sample size and depth of the integrated data model



Longitudinality

Knowing how timing can impact the strength of analyses using the integrated dataset



Representativeness

Combining patients
from different data sources
impacts the representativeness
of the integrated dataset to the
broader patient population

We can start to see a more complete picture of the patient experience

Genetics & genomics

Resistance detection diagnostics

Electronic health records

Medical grade wearables

Early detection diagnostics

Digital therapeutics

Transcriptomics

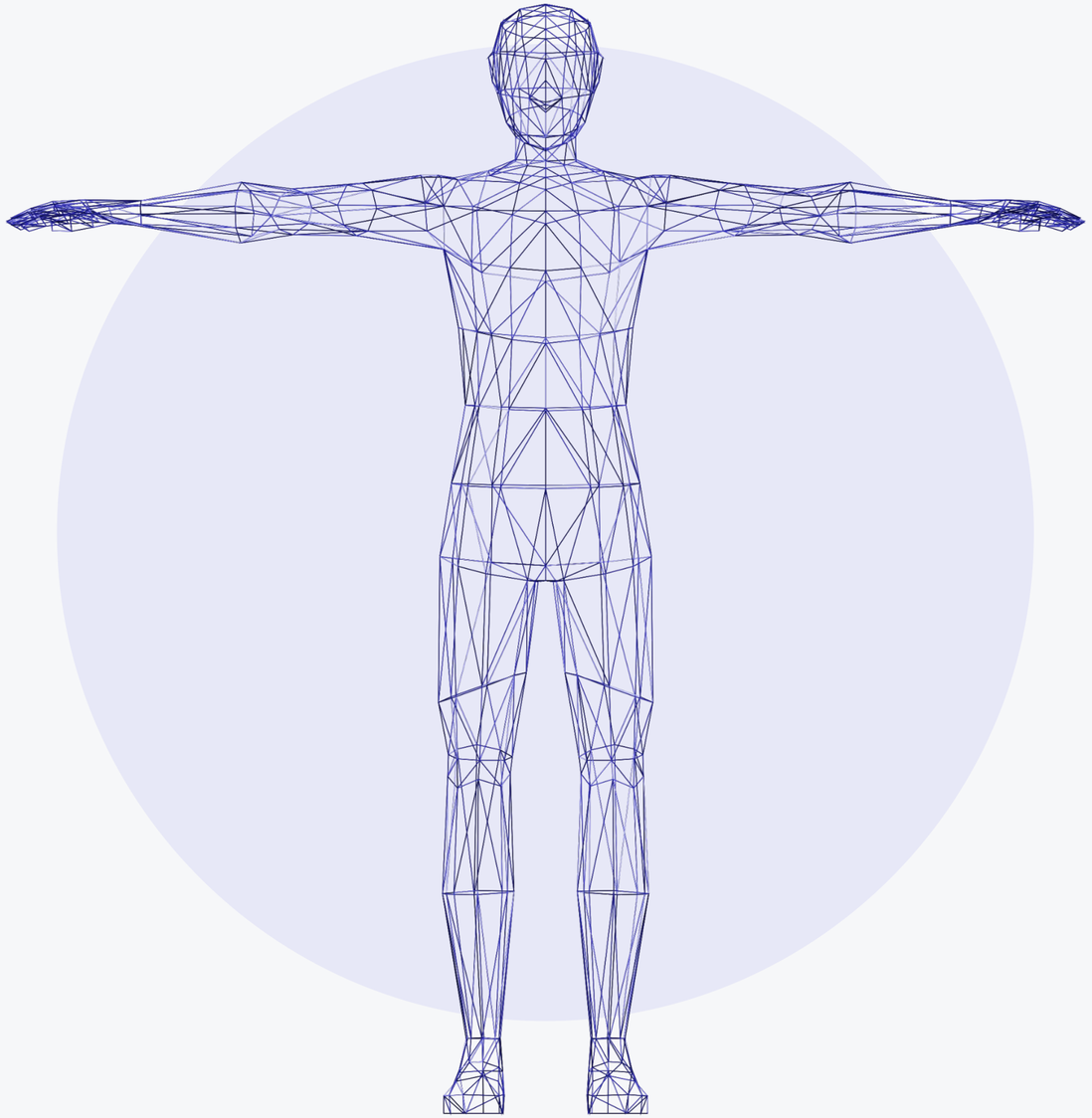
Patient reported outcomes

Proteomics

Digital pills

Radiomics

Remote monitoring



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Q&A

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

Lev Demirdjian, PhD,
Senior Data Scientist,
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Prashni Paliwal, PhD,
Director, Quantitative Sciences,
Flatiron Health

Tamara Snow,
Senior Product Manager,
Flatiron Health

Cheryl Cho-Phan, MD,
Moderator
Medical Director,
Flatiron Health

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EP 03 | March 30
Bridging the divide: Opportunities to integrate clinical research into everyday care

EP 04 | April 13
How novel methodologies and analytics are powering integrated evidence

EP 05 | April 27
Life sciences case studies: Using RWE to support decision-making

EP 06 | May 11
Centering the patient’s voice: A discussion

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