Use of EHR data in drug development and patient access

- Applications and key considerations

PHUSE Conference
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Outline

- Introduction to Electronic Health Record (EHR) data, data at Flatiron
- Example use cases of real-world data (RWD) in drug development and patient access
- Key analytical considerations in gathering insight from RWD

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The Flatiron Network

ONCOEMR®
Cloud-based oncology-specific electronic health record.

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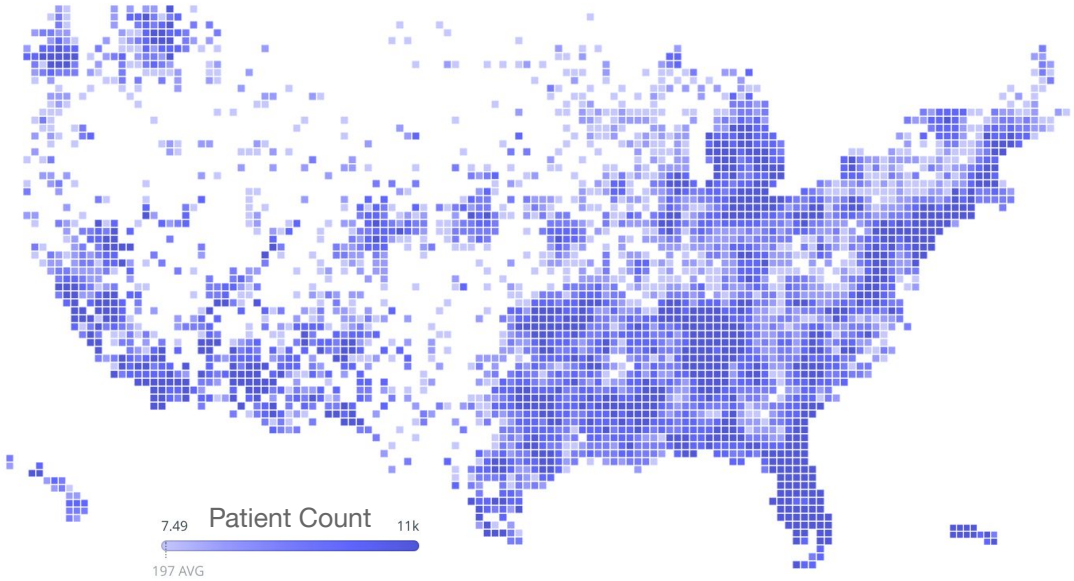
FOR ACADEMICS
An analytics platform for Academic Institutions



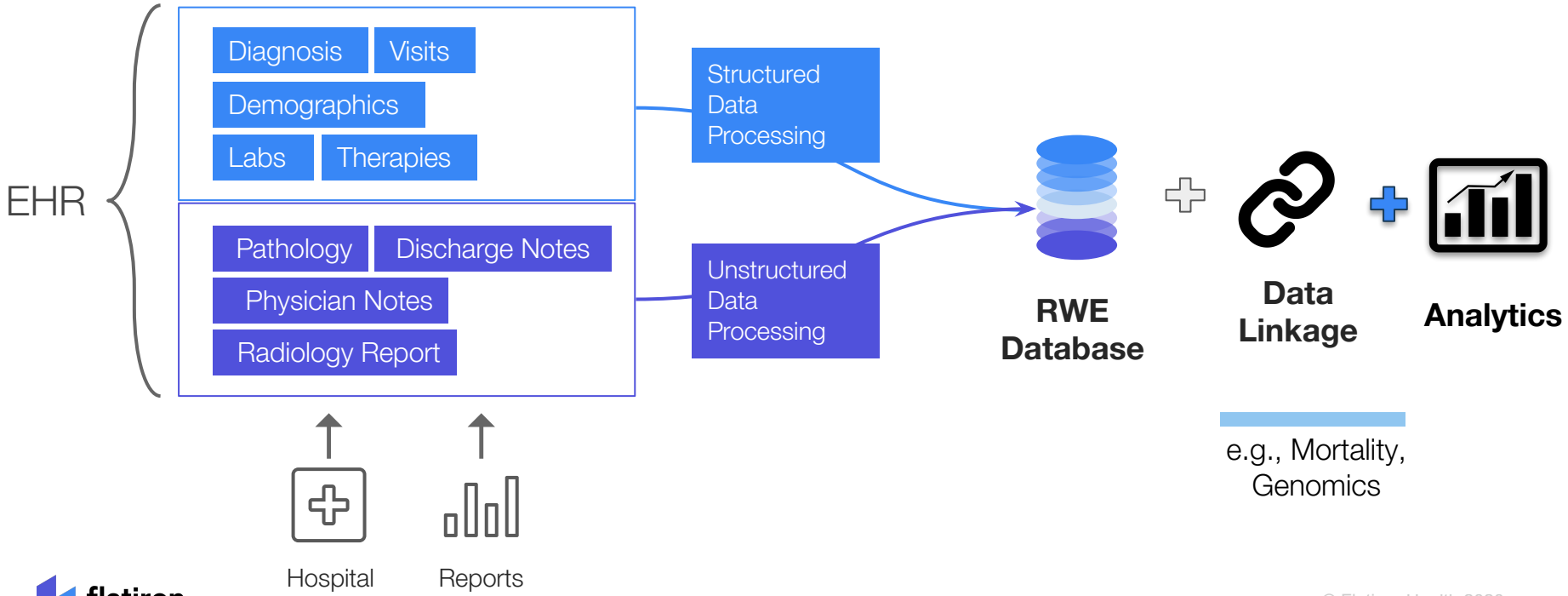
2.2M
Active Patients

2,600
Clinicians

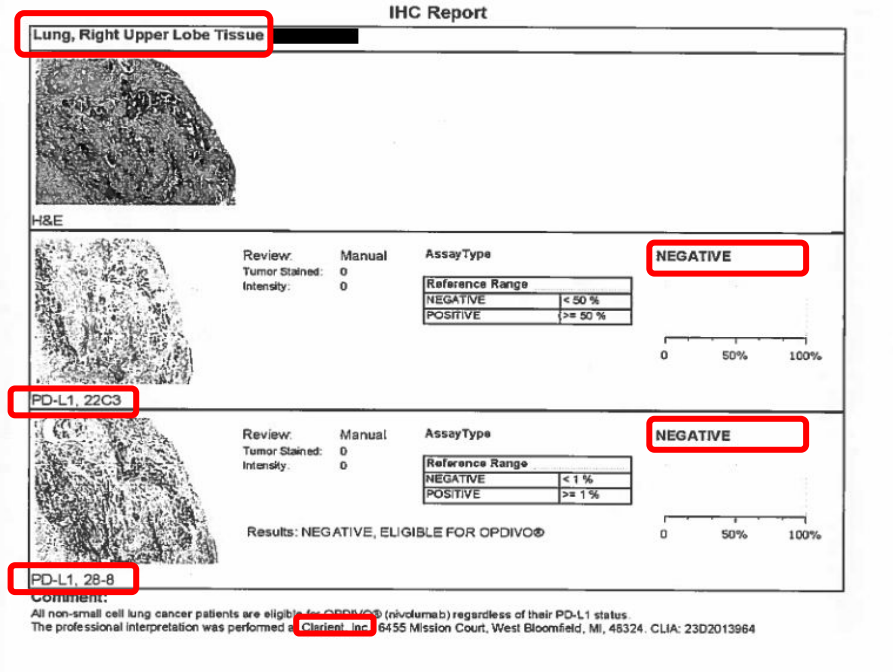
280
Cancer Clinics

800
Unique Sites of Care

Getting from data to evidence



Key data elements in oncology are unstructured


IHC Report

Lung, Right Upper Lobe Tissue

H&E

Review: Manual
Tumor Stained: 0
Intensity: 0

AssayType

Reference Range	
NEGATIVE	< 50 %
POSITIVE	>= 50 %

NEGATIVE

0 50% 100%

PD-L1, 22C3

Review: Manual
Tumor Stained: 0
Intensity: 0

AssayType

Reference Range	
NEGATIVE	< 1 %
POSITIVE	>= 1 %

NEGATIVE

Results: NEGATIVE, ELIGIBLE FOR OPDIVO®

0 50% 100%

PD-L1, 28-8

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

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 Human “Abstraction” (unstructured data cleaning)

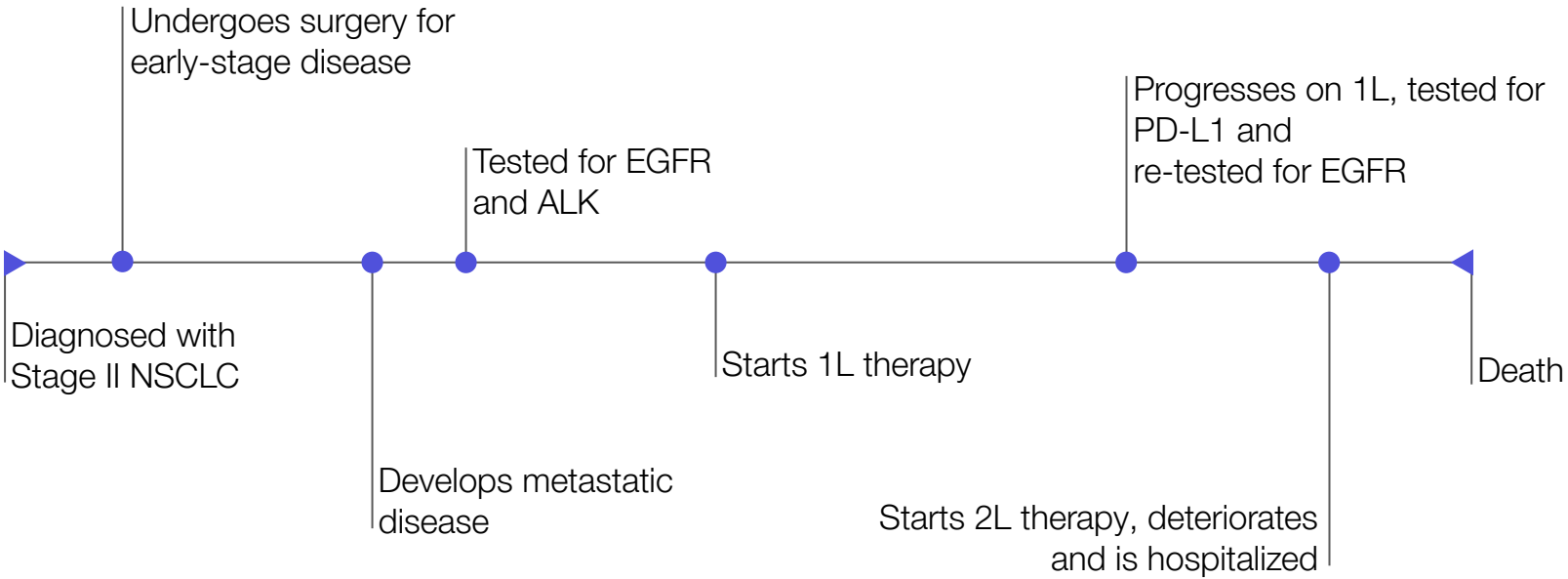
Expert Abstractors

1000+ trained data “abstractors” (oncology nurses and cancer registry professionals) use Flatiron Health instructions to review unstructured documents and enter data in a structured format

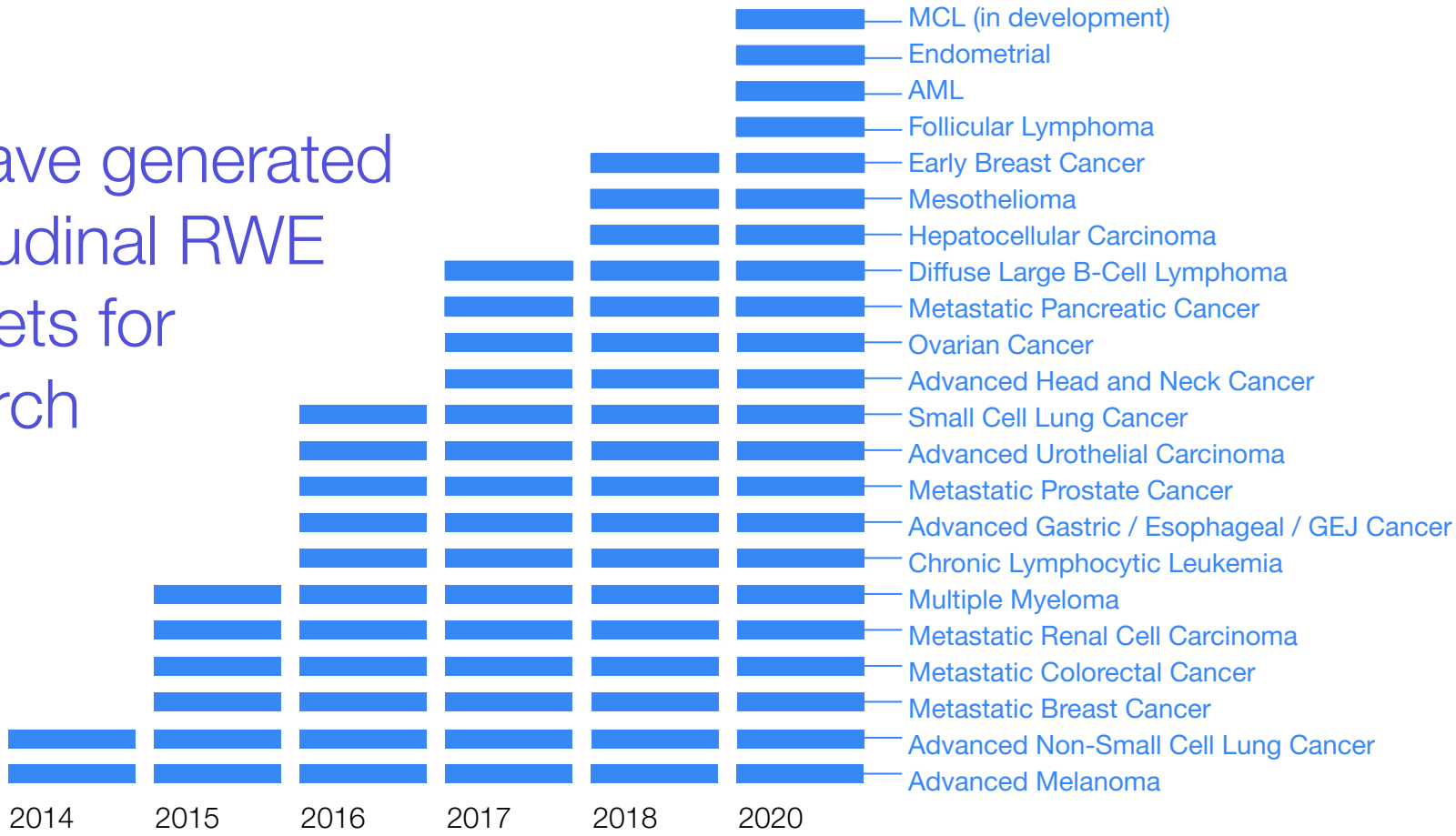
Flatiron Technology

Flatiron Health software organizes EHR documents from all sites, provides forms for entering data, and controls access/ quality, increasing quality and efficiency of unstructured data processing

Clinically-relevant data points for each patient are captured



We have generated longitudinal RWE datasets for research



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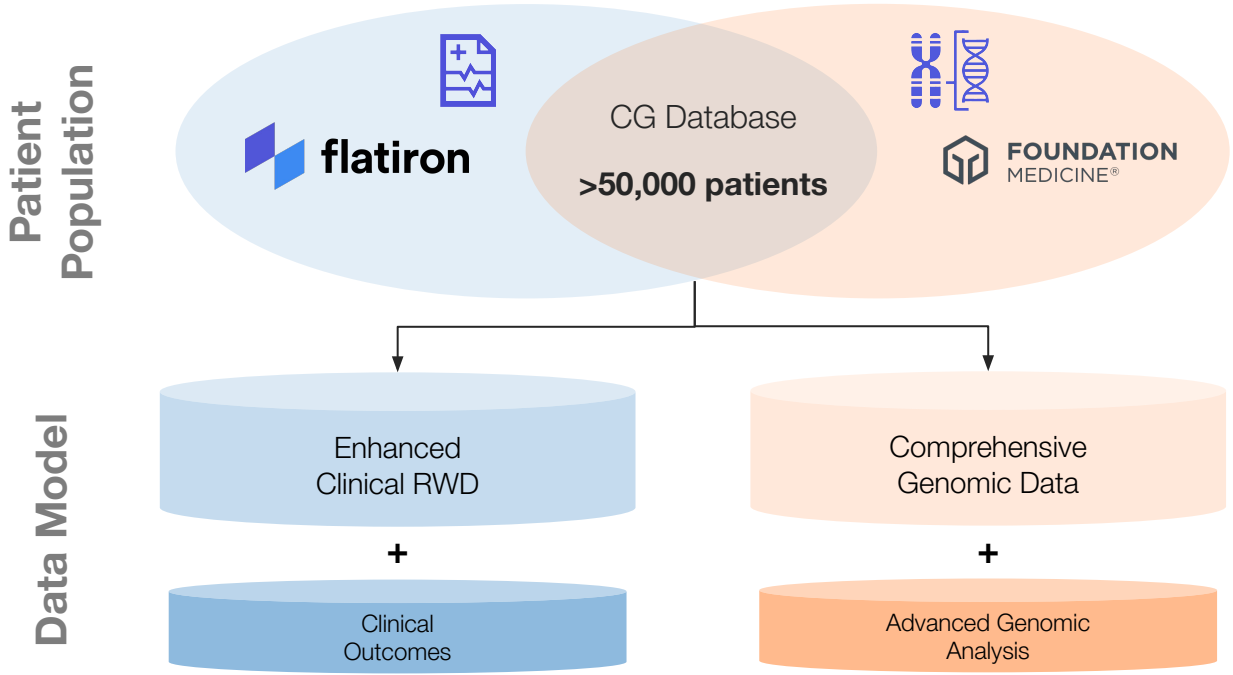
Pan-Tumor Linked Clinico-Genomics Database



- Combines rich clinical data with comprehensive genomic profiling for each patient
- Ability to segment patients by histology, biomarker, or abstracted disease, via:
  - 19 disease models
  - A pan-tumor "universal" data model

EHR data is being used in a variety of ways across BioPharma

Trial Design	• External control, Hybrid control, Pragmatic trials, CER studies • Control arm assumptions • Treatment patterns and choice of control regimen
Internal decision making	• Benchmark for regimen selection • Molecule selection • Dose selection
Regulatory submissions	• Rare populations or those not studied in clinical trials • Label expansions and post-marketing commitments • Characterize natural history, unmet need
HTA and access	• Support reimbursement and pricing discussions for patient access in Europe
Scientific publications	• Characteristics and outcomes of patient populations • Real world endpoints • Methods research, e.g. trial replications

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PFIZER

Securing FDA Approval using RWE

Palbociclib - Breast Cancer Treatment for Males

ROCHE
Case Study

Utilizing an external control to secure reimbursement

PROBLEM

Following compelling results from a single-arm study, Roche submitted for EMA approval for alectinib for ALK+ Lung Cancer in advance of their pivotal study

To secure reimbursement in Europe, Roche needed to demonstrate superiority of alectinib vs. ceritinib (standard of care)

CONTEXT

- Using Flatiron RWD, Roche generated an external control arm of patients receiving ceritinib, enabling a comparison to alectinib trial data
- Used IPTW (inverse probability of treatment weights) from a propensity score model to adjust for differences in baseline characteristics
- Presented at 2017 European Lung Cancer Conference
- Results helped to expand access in 20+ countries over a year earlier than anticipated
- External control arm from Flatiron RWD was then compared with the ceritinib arm of the contemporary ASCEND-2 trial for validation

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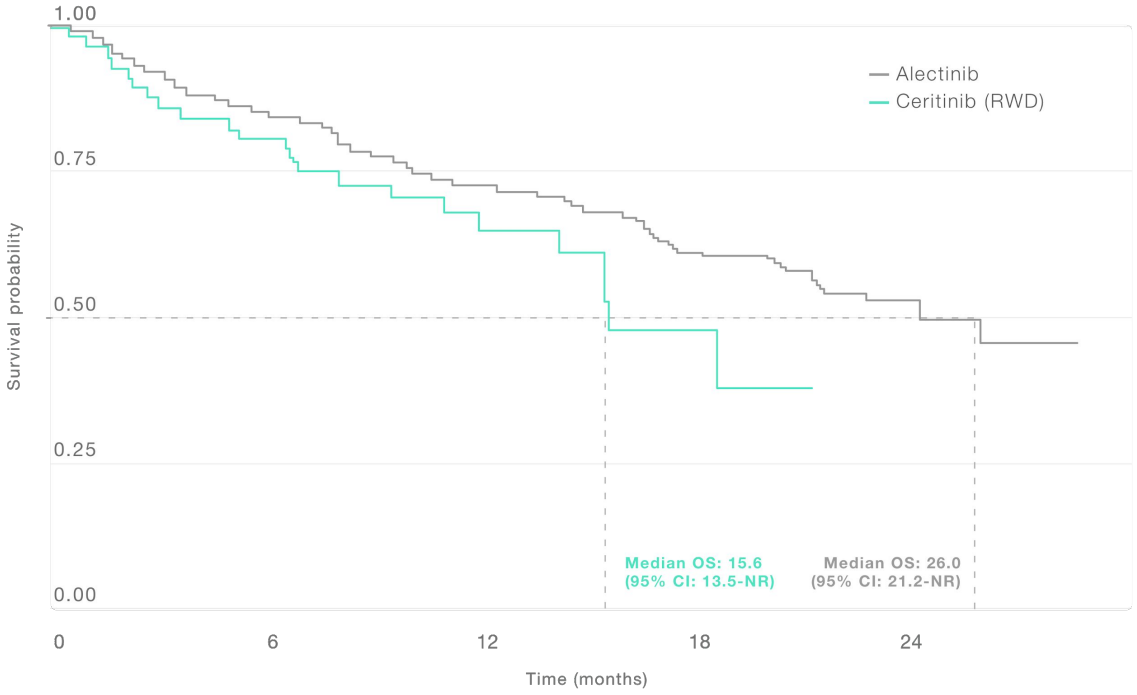
ROCHE
Case Study

Utilizing an external control to secure reimbursement



Adapted from Davies J, Martines M, Martina R, Delmar P, Coudert M, Bordogna W, Golding S, Crane G. Retrospective indirect comparison of alectinib phase II data vs ceritinib real-world data in ALK+ NSCLC after progression on crizotinib. European Lung Cancer Conference (ELCC). May 5-8, 2017; Geneva Switzerland

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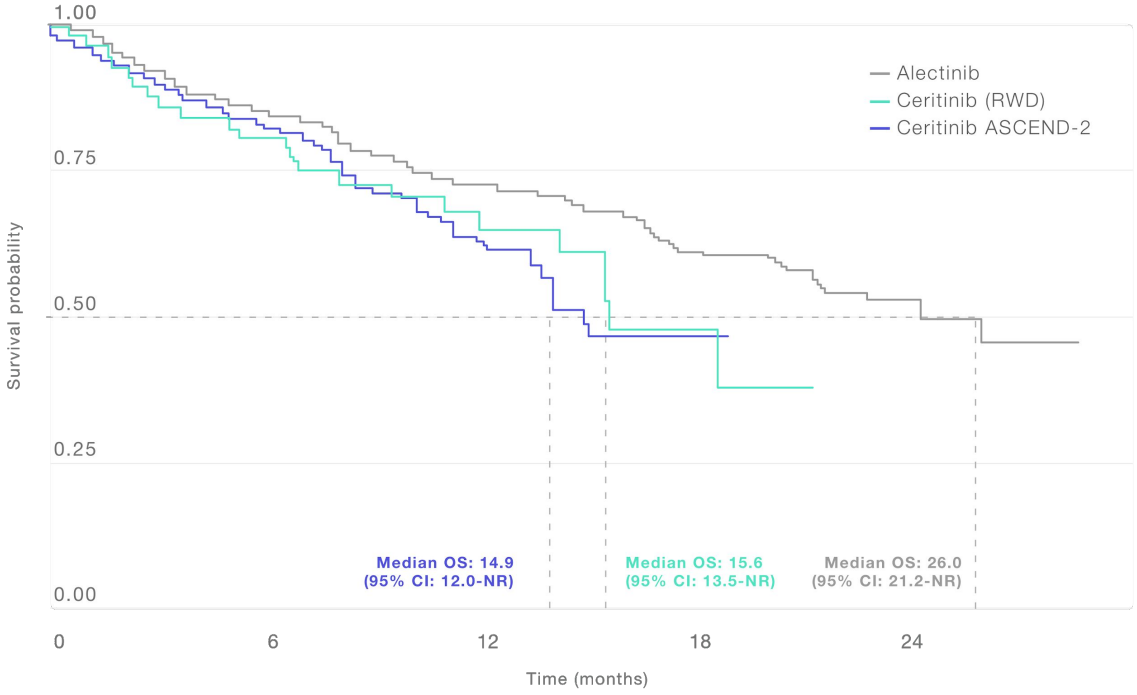
ROCHE
Case Study

Utilizing an external control to secure reimbursement



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Practical Case Study: Improving the evidence-base for evaluating effectiveness of a new therapy

Your company has developed a drug to treat patients with cancer X who show alterations in biomarker Y, which is identified using next generation sequencing (NGS).

- A single-armed clinical trial was conducted in patients with biomarker Y
- You want to understand the unmet need in the biomarker population and benchmark your trial results
- Historical trial data are not available or outdated, and you turn to RWD sources, e.g. EHR data

How do you evaluate RWD to address the questions of interest?

5 key considerations for gaining insight from RWD

- **Prespecification of study and analytical plans**
- **Assurance of relevancy and data quality**
- **Appropriate cohort selection**
- **Suitability of real-world endpoints**
- **Fit-for-purpose analytical methods**

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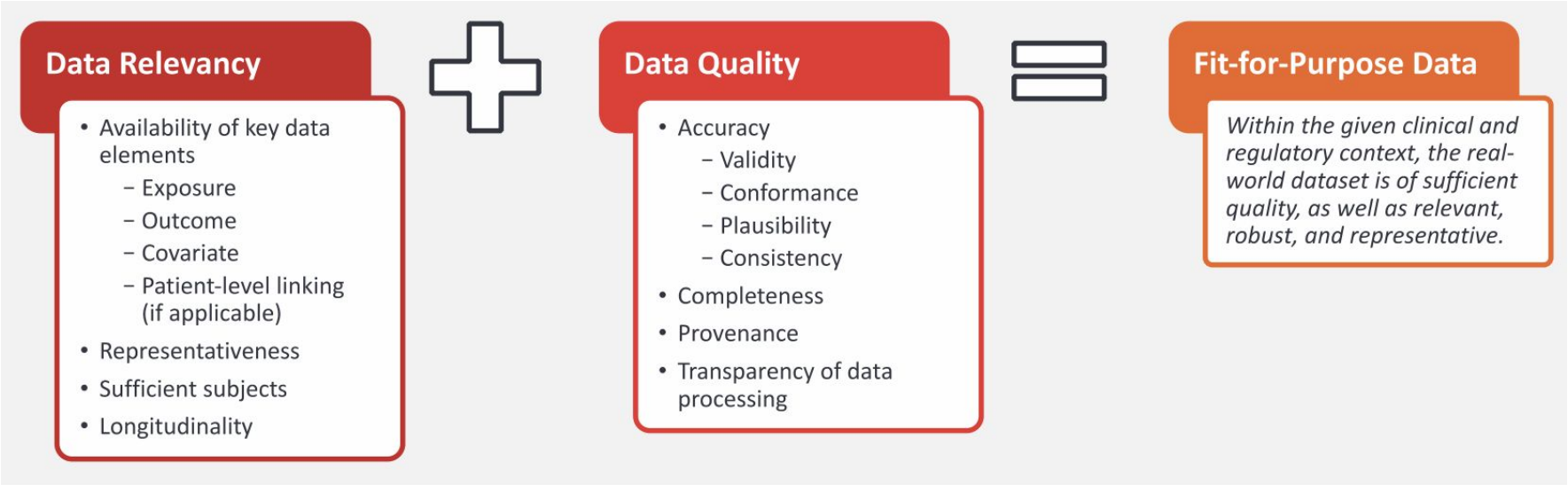
Using relevance and quality to assessing "Fitness" of RWD (Duke-Margolis Framework)



Source: Duke-Margolis Center for Health Policy. Characterizing RWD Quality and Relevancy for Regulatory Purposes. 1 October 2018. Available at: https://healthpolicy.duke.edu/sites/default/files/atoms/files/characterizing_rwd.pdf

Example: Completeness

- EHR may have lower completeness than prospectively collected data, such as clinical trial data, for a variety of reasons:
  - Some elements may not be present at all in EHR data
  - Data may be available in documents, but not structured data
  - Variability in type and presence of clinician documentation across providers/sites
- Impact of completeness can be estimated by:
  - Measurement of missingness
  - Assessment of variable criticality
    - If a critical variable does not meet a pre-defined quality metric requirement, conclusions based on RWD may not be robust or meaningful
    - ***Key values may include: Cohort Inclusion/Exclusion Criteria (e.g. ECOG), Exposure Definition, Outcome/Endpoints***

Features of appropriate cohort selection

- Relies on identification and capture of **clinically meaningful variables**
  - Alignment on eligibility criteria can lead to significant attrition in cohort sizes, changes in patient composition
- **Prespecification** of selection criteria and methodologies to address missing data and potential biases
- **Transparent** and **traceable selection process** via documentation (e.g., detailed cohort diagram)

Additional considerations in cohort selection

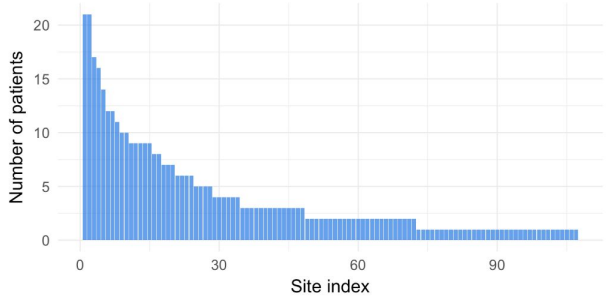
Representativeness

- Selection bias can lead to increased risks of false-positive findings

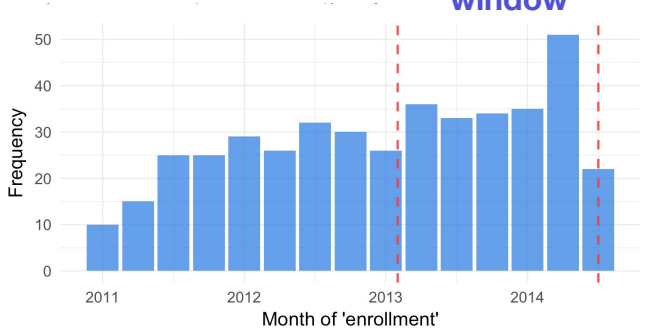
Concurrency

- Drift in outcomes over time can introduce bias and increased type I error

Representativeness
(Distribution of sites)



Trial recruitment window



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Additional considerations when selecting a biomarker-defined population

Testing Modality	Clinico-genomic data may include a variety of assays and specimen collection methods. **Do I need to limit the cohort by type of sample (e.g., tissue vs. blood, identical assay used in trial recruitment)?**
Biomarker Definition	Clear definitions for biomarker positive and wild type (if applicable) cohorts are essential. **What genomic details are crucial to this definition (e.g., known protein effects, splice sites, gene fusion partners)?**
Test Timing	Patients may receive results from a biomarker test at various points during their care. **Should I limit to biomarker tests prior to an index date (e.g., start of first LOT)?**

Characterizing the quality and performance of real-world endpoints is essential:

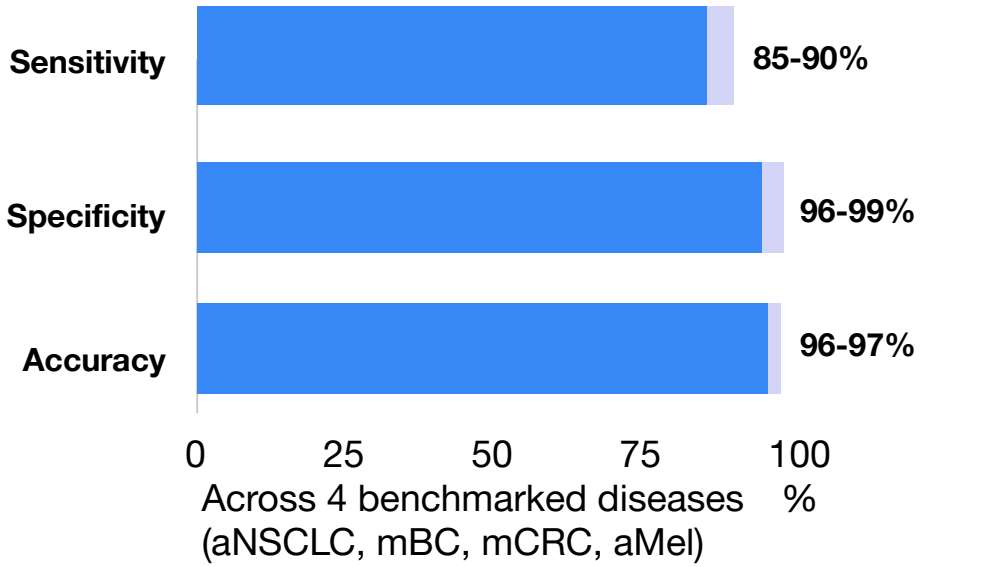
- Are the measurements reliable?
- Can the measurements be benchmarked to a reference or gold standard?
- Is what is being measured clinically meaningful?
- In the context of a real-world control arm, how does the index date and endpoint compare to the respective clinical trial?

Flatiron has developed a composite mortality endpoint that amalgamates data across four sources

May 2018 *HSR* Publication*

- Structured DoD
- Unstructured Documents
- Commercial death dataset with next-generation linking algorithm
- SSDI

Results



*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

How Real-World Response differs from RECIST in clinical trials

	RECIST	Real-World Response
Context	Tightly defined visit and scan schedule Patient being treated in standardized way in context of clinical trial protocol	Cadence of assessment varies based on clinician/patient factors
Imaging	Baseline imaging always available Scan modality and anatomic coverage are predefined and consistent over time	Availability of baseline imaging varies Scan modality and anatomic coverage may potentially vary
Assessment	Lesions identified/measured at baseline Same lesions measured at follow-up time points Response categories assigned according to rules (thresholds of % change in sum lesion diameter relative to baseline/nadir)	Radiology reports in routine care not based on standardized rules Clinicians may incorporate other factors (ex: other treatment options) into their assessment of scans Response categories assigned through abstraction of clinician documentation

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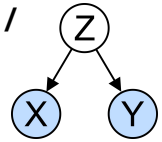
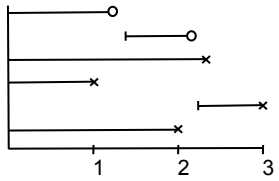
Goals in developing fit-for-purpose analytic methods:

- Directly answer scientific questions which are supportable by available data
- Tailor study design to address biases inherent in RWD that might affect internal and external validity

Some crucial analytical considerations in a real-world biomarker-defined study

Consideration	Description	Potential analytical approaches
Small sample size 	Small cohorts can arise in precision medicine use cases, particularly when applying strict eligibility criteria	Approaches to quantify uncertainty, qualitative approaches (narratives) to describe cohorts
Selection bias / confounding 	Patients with access to NGS / advanced biomarker tests may not be representative of the overall cancer patient population	Descriptive analyses of differences, Covariate adjustment / weighting / matching
Left truncation 	Patients need to survive long enough to have record of cancer treatment and receive NGS / biomarker test to enter the study cohort; can results in biases survival times and dependence of outcome on entry time	Risk set adjustment methods, limiting analyses to patients with a biomarker result prior to an index date (e.g. start of line of therapy)

Not accounting for left truncation in biomarker-defined analyses can result in upwardly-biased OS estimates

- BLUE = Non-small cell lung cancer (NSCLC) patients with NGS who had 1L therapy, regardless of when sequenced and NOT ADJUSTED for left truncation
- RED = NSCLC patients with NGS limited to those sequenced on or prior to start of 1L therapy
- GREEN = NSCLC patients with NGS who had 1L therapy, regardless of when they were sequenced and ADJUSTED for left truncation

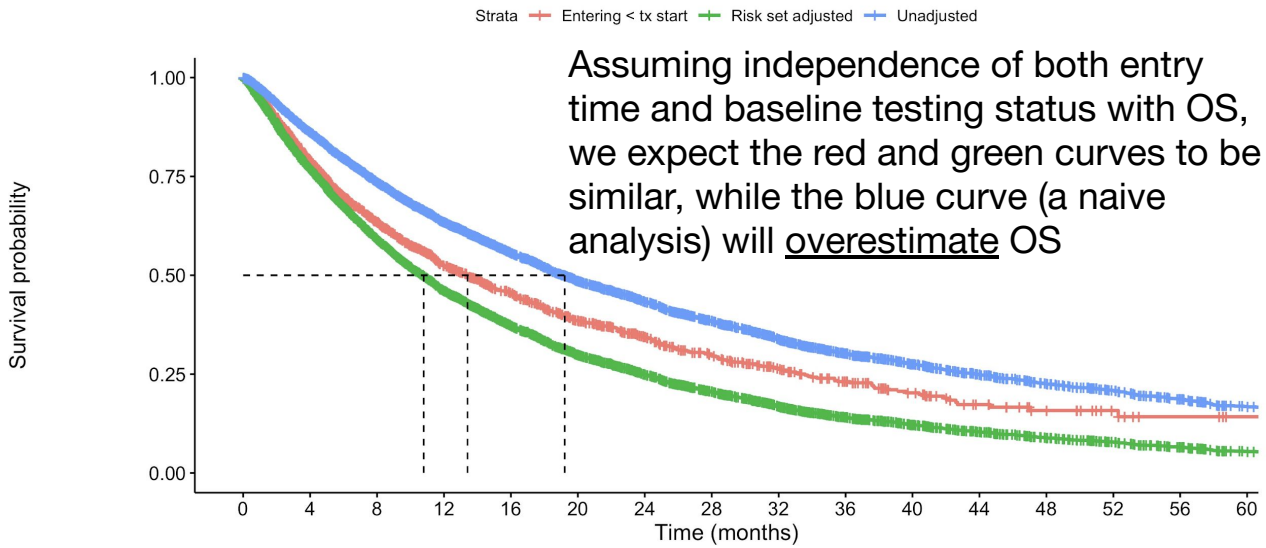


Figure. Overall survival (OS) from start of first line of therapy for patients with non-small cell lung cancer in the Flatiron/FMI Clinico-genomic Database

Conclusions

- Oncology drug development paradigm continues to evolve
  - Rapidly changing standard of care
  - Blurring of retrospective/prospective and observational/interventional research
- EHR data have the potential to provide research/regulatory-grade evidence and supplement/complement evidence from clinical trials
  - Care must be taken in the design, implementation and communication of studies, particularly those using complex (e.g. clinico-genomic) data
  - Important to evaluate and incorporate data fitness and analytical considerations