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RWD/E for Drug Development

Jacqueline Law, Ph.D., VP, Corporate Development
Flatiron Health

Drug Development Ecosystem Summit, July 30, 2024

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Flatiron RWD/E solutions* power every phase of the biopharma lifecycle

RESEARCH

Discovery & Translation
- Target discovery and identification
- Identifying predictive / prognostic gene signatures to guide biomarker research
- Uncovering and understanding resistance mechanism

DEVELOPMENT

Product Strategy
- Indication prioritization
- Defining target product profile
- Clinical development planning

Clinical Trial Design
- Protocol design; e.g. I/E criteria, control arm assumptions
- Diversity planning
- External / hybrid control arms

Clinical Trial Execution
- Site identification
- Patient matching and recruitment
- Clinical trial data collection

APPROVAL & ACCESS

Regulatory Submission
- Characterizing natural history, unmet medical need, therapeutic context
- Contextualizing trial results e.g. control arm

Value & Market Access
- Characterizing disease burden
- Cost and clinical effectiveness
- Healthcare resource utilization

Medical Affairs
- Peri-/post- launch evidence generation
- Developing scientific literature

LAUNCH & IN MARKET

PMC / PMR
- Regulatory requirements on safety, efficacy in special populations
- Long-term / real-world safety and effectiveness

Commercial Strategy
- Launch planning
- Pricing and forecasting
- Market tracking, commercial activities

Label Expansion
- Identifying unmet needs
- Optimizing dosing

Portfolio Strategy
- Asset and indication prioritization
- Due-diligence on external innovation

NON EXHAUSTIVE

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* based on RWD from the US, Japan, UK and Germany

PMC / PMR: Post-Marketing Commitments / Post-Marketing Requirements; RWD/E: Real-World Data/Evidence

Flatiron RWD/E have directly contributed to expanded treatment options and quality of life for patients

LABEL EXPANSION:

IBRANCE® palbociclib

Men with breast cancer have an approved treatment option, rather than guessing with off-label options

U.S. FDA Approves IBRANCE® (palbociclib) for the Treatment of Men with HR+, HER2- Metastatic Breast Cancer

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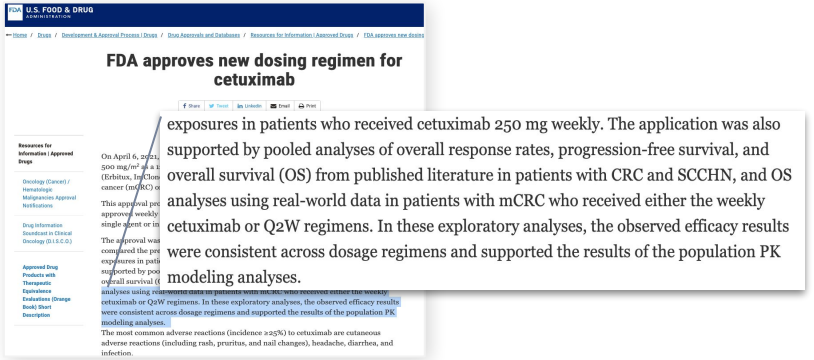
"With this approval, we are now able to offer IBRANCE to the underserved male breast cancer community and provide more patients with HR+, HER2- metastatic breast cancer the opportunity to access an innovative

DOSING:

ERBITUX® CETUXIMAB

mCRC and SCCHN patients can move from weekly to bi-weekly dosing regimen, giving them valuable time back



U.S. FOOD & DRUG ADMINISTRATION

FDA approves new dosing regimen for cetuximab

exposures in patients who received cetuximab 250 mg weekly. The application was also supported by pooled analyses of overall response rates, progression-free survival, and overall survival (OS) from published literature in patients with CRC and SCCHN, and OS analyses using real-world data in patients with mCRC who received either the weekly cetuximab or Q2W regimens. In these exploratory analyses, the observed efficacy results were consistent across dosage regimens and supported the results of the population PK modeling analyses.

The most common adverse reactions (incidence ≥25%) to cetuximab are cutaneous adverse reactions (including rash, pruritus, and nail changes), headache, diarrhea, and infection.

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RWD/E: Real-World Data/Evidence

Flatiron enables pragmatic evidence generation through point-of-care technology, data and services in our research network

OPERATIONALIZING TRIALS IN 100+ COMMUNITY ONCOLOGY SITES AND AMCs

Site network with diverse patient population

- In 2 year timeframe, **>1,300 clinical trials** were open across 64 practices[1]
- **81% of practices** were running 10+ studies[1]

Tech-enabled support of trials

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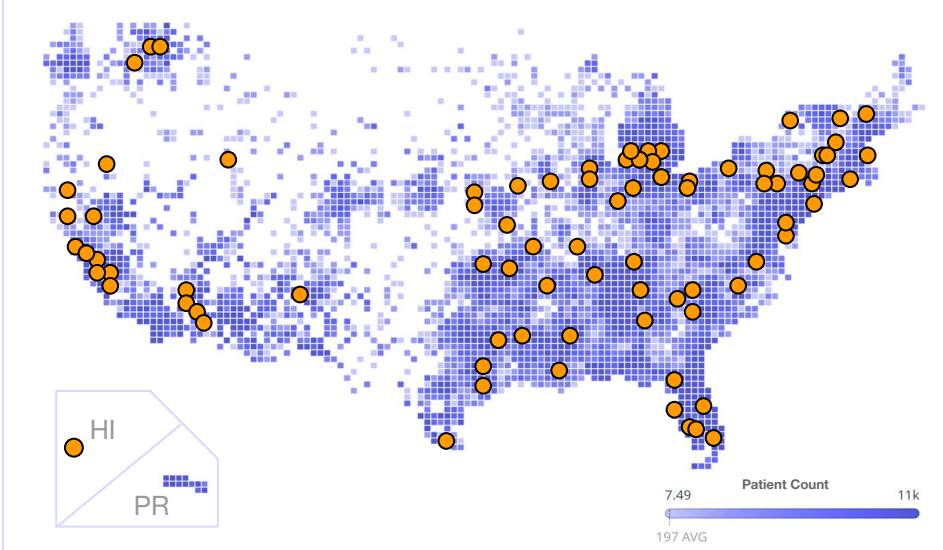

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AMC: Academic Medical Centers; EDC: Electronic Data Capture; EHR: Electronic Health Records; RWD: Real-World Data

Outline

- Flatiron Health Quick Overview
- RWD/E Use Cases & Impact for Drug Development
- Flatiron RWD/E Solutions ‘the How’
- Future Direction: Pragmatic Evidence Generation

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Who we are

OUR MISSION

To improve and extend lives by learning from the experience of every person with cancer.

OUR VISION

To build a world where technology and science close the gap between research and care.

Quick facts

3M
patient records
available for research, 80% from community practices

4
countries
Offices in New York, San Francisco, Tokyo, Berlin and London

8
academic centers
partner with Flatiron Health on outcomes research and quality improvement

>200
community cancer centers
including 2,000 doctors partner with Flatiron Health

800
sites of care
use Flatiron's OncoEMR software

2,500 employees
including software engineers, data scientists, biostatisticians, epidemiologists, health professionals and other experts

Partnerships
U.S. Food & Drug Administration, the National Comprehensive Cancer Network and Friends of Cancer Research and others

>100 sites
Using clinical research technology at the point of care

There is a critical need to accelerate and streamline clinical research

Core challenges

Cancer innovation & investment is growing

- **193 new cancer drugs** approved since 2014
- Oncology **R&D spend of $120B** in 2023
- **>2,000 drugs** in development today

R&D remains slow, costly and isn't representative

- It still takes **>10 years and $1-2B** to bring a new therapy to market
- 80% of trials **fail to meet enrollment** target and timeline
- Only **3-8% of patients** participate in trials

Clinical trials are burdensome and inefficient

- 75% of research sites say **staffing** is their top challenge
- 25-40% of trial costs are in **data management and monitoring**, even though up to 70% of trial data already exist in the EHR

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EHR: Electronic Health Records

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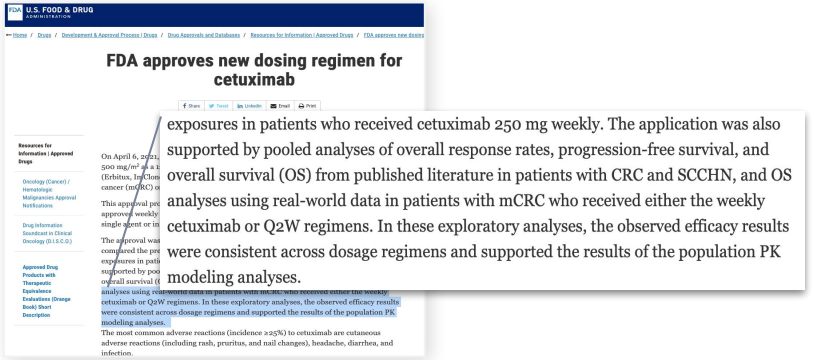

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RWD/E: Real-World Data/Evidence

Since 2019, Flatiron has supported sponsors in Japan using RWE in pharmaceutical regulatory applications for PMDA

Flatiron Services to support PMDA regulatory applications:

Supported:
2 RWD protocols
1 CSR development
1 PMDA meeting prep

Responded to:
2 PMDA requests for information

Participated in:
1 PMDA meeting

Flatiron RWD included in:
1 submission to PMDA
1 application to PMDA

Regulatory Use of Flatiron RWE to-date in Japan:

- Flatiron RWD was used in non-interventional studies to support label expansion for 2 pharmaceutical products.
- Flatiron RWD was used to characterize outcomes in patients receiving standard of care versus patients receiving the treatment of interest in the clinical trial.
- Both label expansion applications received PMDA approval.

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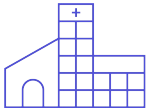
CSR: Clinical Study Report; RWD / E: Real-World Data / Evidence

We partner with a vast set of leading oncology providers and research institutions across the globe

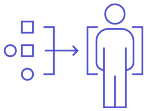


Independent Cancer Clinics

The leading national network of community oncologists across **200+** cancer practices in the US

Academic Medical Centers (AMCs)

Deep research collaborations with **8** leading research universities and health systems in the US



Clinical Trial Sites

Data and technology integration with **100+** current U.S. research sites

International Partners

Established and growing international partners, initially focused on **UK**, **Japan** and **Germany**

We have deep in-house expertise and close partnership with regulators and thought leaders

DEEP IN-HOUSE EXPERTISE

Oncology Clinicians, many of whom are practicing, provide expertise to curation and research projects.

Quantitative Scientists, including biostatisticians, epidemiologists, and health economics outcomes researchers, provide expertise in study design and statistical analysis.

ML / Data Software Engineers, experts in Flatiron's data and infrastructure, provide expertise in machine learning, processing and visualization.

CLOSE PARTNERSHIP WITH STAKEHOLDERS

5+ years direct collaboration with **FDA** utilizing RWE insights

3+ years direct collaboration with **NICE** and other HTA bodies

6+ years direct collaboration with **NCI** on clinical trial designs

90+ **co-authored publications** with Life Science partners

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HTA: Health Technology Assessment; ML: Machine Learning

Our best-in-class data processing approaches, including machine learning and abstraction, optimize data generation

EXPERT ABSTRACTION

Tech-enabled human abstraction that drives efficiency and quality from a network of expert clinical abstractors

HYBRID

Utilizing both ML-extraction and human abstractions to optimize for accuracy and scalability

MACHINE LEARNING

Trained ML models extract data points directly from EHR to deliver RWD faster and at scale

Large-scale, gold-standard, labeled training dataset
compiled over 10+ years of expertly-validated, human abstraction

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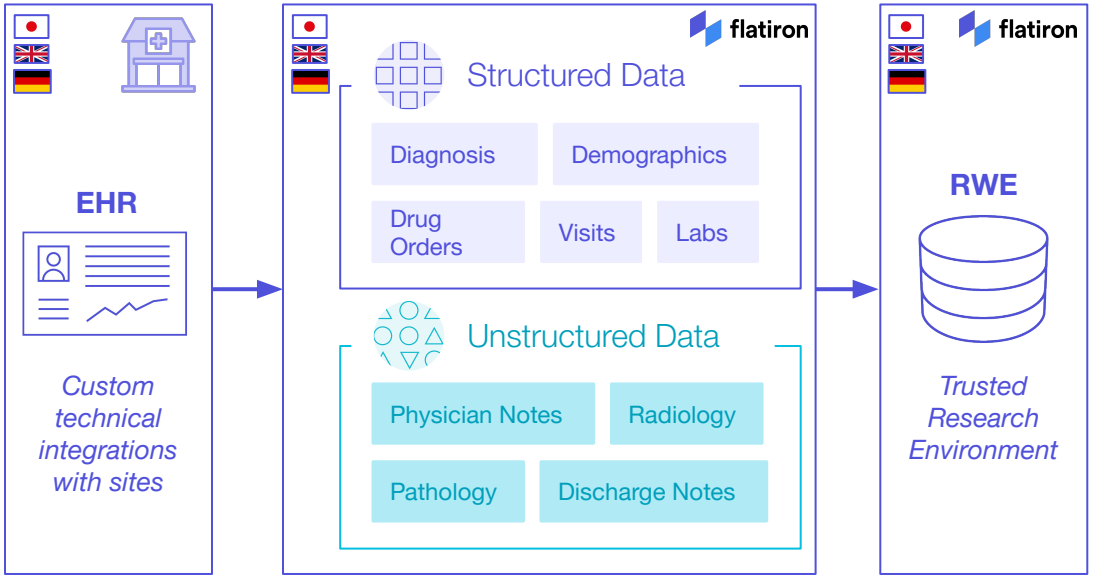
EHR: Electronic Health Records; ML: Machine Learning; RWD: Real-World Data

For international markets, Flatiron processes data into RWE through local teams and technical infrastructure



- **In-country technical infrastructure** enables access to and processing of raw data from site EHRs
- Flatiron has in-country **teams of 70+** professionals, processing data into **cancer-specific RWE datasets**
- Data processing and sharing are fully compliant with **local laws and regulatory requirements** (incl. GDPR and APPI) and secondary health data use norms

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Note: Flags indicate location of data hosting

EHR: Electronic Health Records; RWE: Real-World Evidence

Our data models and oncology-specific variables are led by science and validated with outside peer review

Flatiron data model overview

Fully abstracted and processed, pan-tumor and tumor-specific *Derived Variables (in italics)*

Patient Geography

- United States
- Germany
- Japan
- United Kingdom

Patient Characteristics

- Demographics
- Insurance
- Practice
- *Socioeconomic status*
- *Smoking status*

Disease-Specific Clinical Characteristics

- Diagnosis / Stage
- Histology
- Comorbidities
- *Sites of Metastases*

Testing

- SoC biomarkers
- Cytogenetic
- Immunophenotype

Treatments

- Medication / surgery
- *Line of therapy*
- *Drug episodes*
- *Reasons for discontinuation*

Real-World Endpoints

- Overall survival
- Progression
- Response
- Adverse events

Additional modalities

Genomics

- WES, WTS, Digital Pathology via Caris
- NGS via FMI

Claims

via tokenization

- Open and closed
- Payer, Pharmacy

Images

- Radiology scans

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NGS: Next Generation Sequencing; SoC: Standard of Care; WES: Whole Exome Sequencing; WTS: Whole Transcriptome Sequencing

Our local teams work closely with in-market stakeholders to drive acceptance of RWE solutions

Regulators & HTA bodies

HAS HAUTE AUTORITÉ DE SANTÉ

Zorginstituut Nederland

cadth acmts Canada's Drug and Health Technology Agency

EUROPEAN MEDICINES AGENCY SCIENCE · MEDICINES · HEALTH

IQWiG

NICE National Institute for Health and Care Excellence

pmda

Research groups & patients

国立がん研究センター 東病院 National Cancer Center Hospital East

CANCER RESEARCH UK

GETREAL INSTITUTE

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HTA: Health Technology Assessment

There is a steady drumbeat from the FDA for more pragmatic evidence generation, particularly in the post approval space

				
	Nov 2022	*Nov 2023*	*May 2024*	*May 2024*
DEPARTMENT	Oncology Center of Excellence (OCE)	Reagan-Udall Foundation	Oncology Center of Excellence (OCE)	Center for Drug Evaluation & Research (CDER)
PRIMARY AIM	Explore the appropriate use of *pragmatic design elements* in trials for *approved oncology medical products*	Inform the development of a framework to facilitate *post-market* medical product *research integrated into clinical care*	Identify 5 clinically relevant questions that can be answered through use of *pragmatic clinical trials*, using *FDA-approved oncology therapies*, over the next 5 years	Test, implement, and *scale innovation* in clinical trials, initially focused on: Bayesian Supplemental Analysis, *Selective Safety Data Collection*, and *Streamlined Trials Embedded into clinical Practice*

PRAGMATIC EVIDENCE GENERATION: *Refers to conducting prospective clinical (preferably randomized) studies of medical products already on the market for at least one indication (post-market)*
(Proposed definition by Reagan-Udall)

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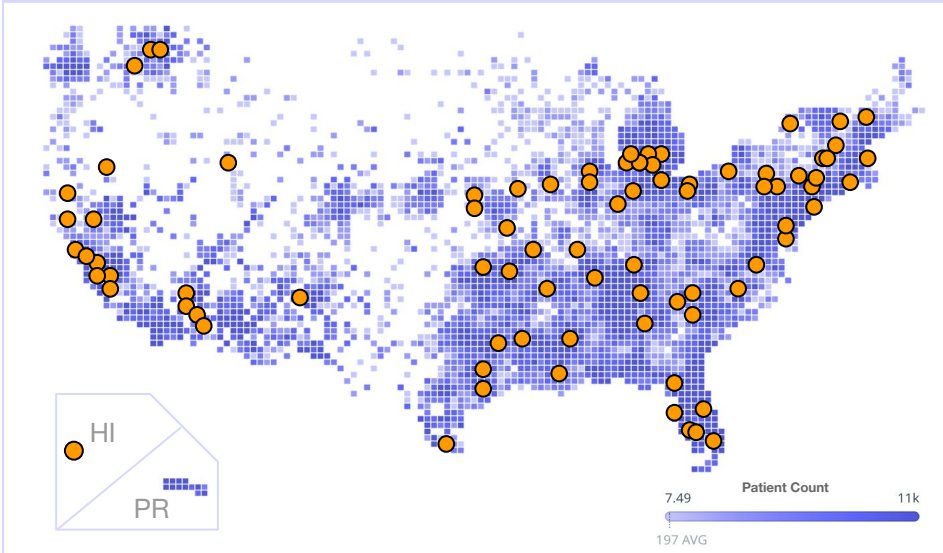

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PROSPECTIVE REAL-WORLD STUDY CASE STUDY

Post-Marketing Requirement in Multiple Myeloma

large pharma company

Sponsor faced limited site interest and slow recruitment via a traditional CRO-led approach.

Sponsor and Flatiron designed and launched a more pragmatic prospective study leveraging Flatiron's clinical research solutions and site network.

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GOALS

- ✓ Assess the risk of severe safety events, including associations between incidence, severity and potential risk factors
- ✓ Demonstrate study data capture directly in EHR and transfer to EDC with appropriate quality controls & minimal site burden
- ✓ Enrich for enrollment of underrepresented participants using RWD for site identification and EHR-based Patient ID
- ✓ Demonstrate utility of Flatiron platform for prospective evidence generation, particularly in the post-approval space

APPROACH

Co-development and execution of a prospective study optimized to run in the **community setting** with a focus on **enriching diversity** and generating evidence to satisfy the PMR more efficiently

Intentionally collect critical study data related to safety and risk factors often missing from routinely collected EHR data to increased FDA confidence in study design

CRO: Contract Research Organization; EDC: Electronic Data Capture; EHR: Electronic Health Records; PMR: Post-Marketing Requirement; RWD: Real-World Data

PROSPECTIVE REAL-WORLD STUDY CASE STUDY

Operational metrics highlight our ability to accelerate timelines, increase probability of success, and lower costs

OUTCOMES

- Enrollment exceeding forecast **with ~16 day average from activation of site to first-patient-in (FPI)**
- **>20%** of target enrollment reached **within first 3 months**
- **55%** of participants from **underrepresented race/ethnicity** groups
- **Sponsor feedback:** study is 20-30% cheaper and enrolling ~2x faster than traditional PMR studies

Site Activation	
Multiple community sites rapidly activated using Flatiron's pre-existing contracting infrastructure	• Initial site outreach to sponsor approval: **~33 days** (avg) • IRB Submission to IRB Approval: **2 days** • Site contract execution: **~32 days** (avg)

Clinical Data			
# of EHR data fields transferable to EDC through Flatiron Clinical Pipe	**Avg. Days from Visit Date to data In EDC**	**# of Protocol Deviations**	**Avg. Days from Query Entered to Query Closed**
>1.4k	~4.5	0	~2

EDC: Electronic Data Capture; EHR: Electronic Health Records; IRB: Institutional Review Board; PMR: Post-Marketing Requirement; RWD: Real-World Data