U.S. FOOD & DRUG ADMINISTRATION

American Association for Cancer Research

FINDING CURES TOGETHER™

FDA-AACR
Real-world Evidence Workshop

July 19, 2019 | Bethesda, MD

@FDAOncology

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U.S. FOOD & DRUG ADMINISTRATION

American Association for Cancer Research

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Workshop Cochairs:

Pallavi Mishra-Kalyani, PhD

Deborah Schrag, MD, MPH

Sean Khozin, MD, MPH

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SESSION I:

Intro to Real-world Evidence

Speakers:

Jacqueline Corrigan-Curay, JD, MD

Elad Sharon, MD, MPH

Framework for FDA's Real-World Evidence Program

Jacqueline Corrigan-Curay, J.D., M.D.
Director, Office of Medical Policy
Center for Drug Evaluation and Research
Food and Drug Administration
July 19, 2019

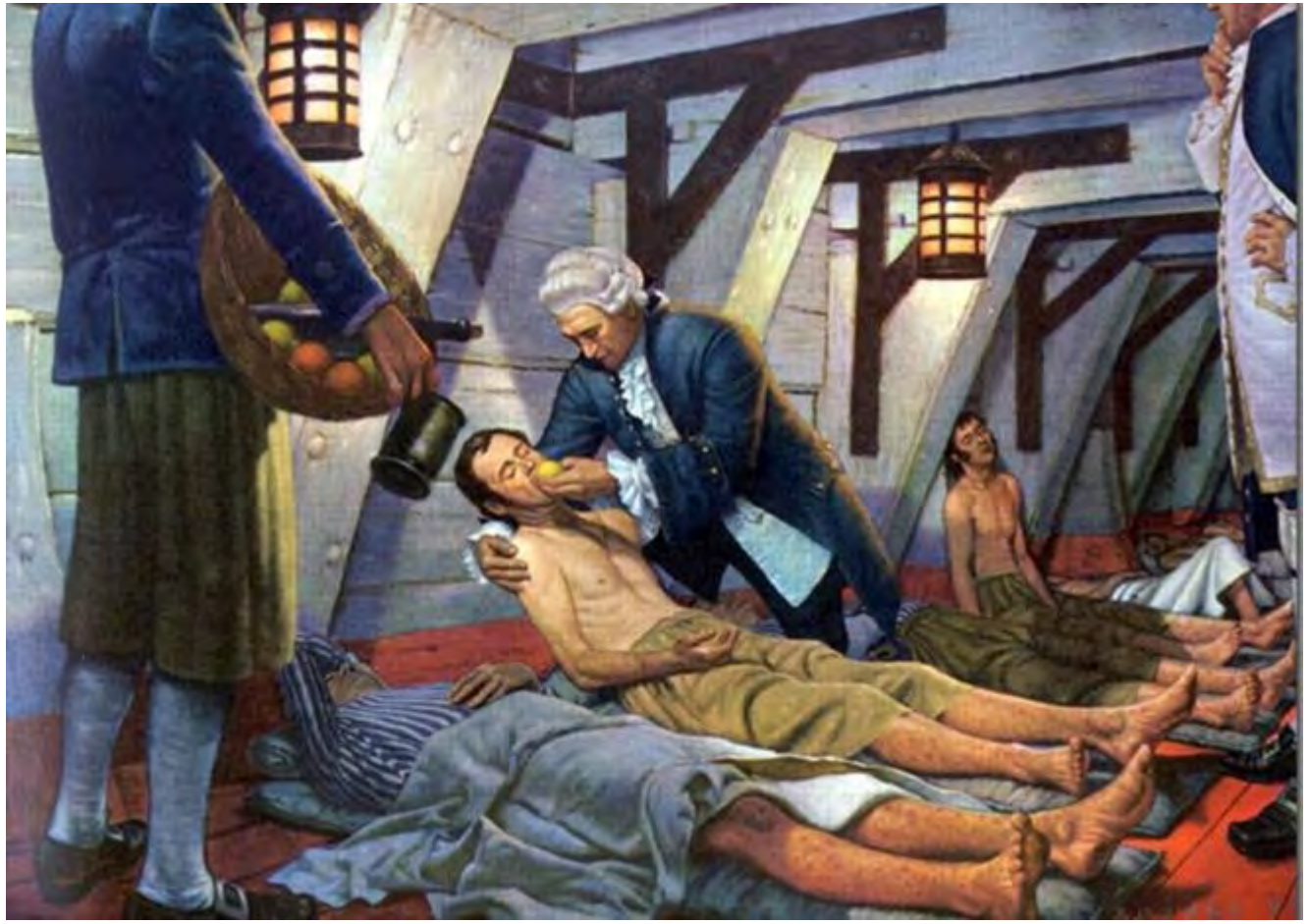
Disclaimer

- **The views and opinions expressed in the following slides are those of the individual presenter and should not be attributed to the FDA.**
- **No relevant financial relationship exists**

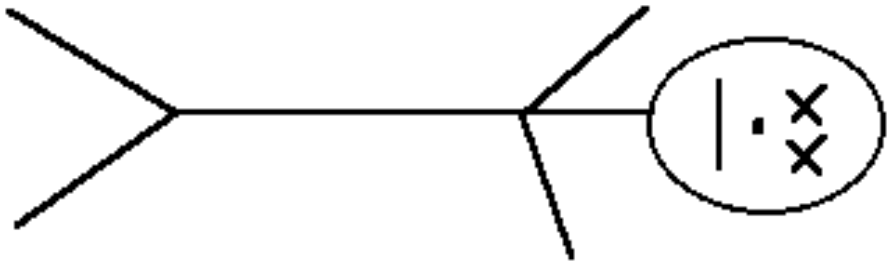
Overview

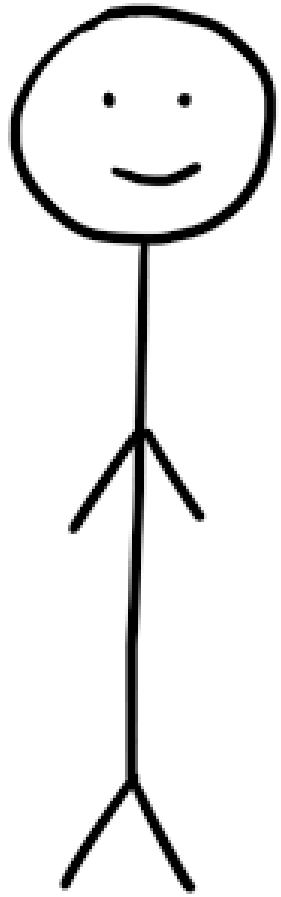
- Why real-world evidence?
- Mandate and goals
- Program areas
- Demonstration projects

RWE is Not New



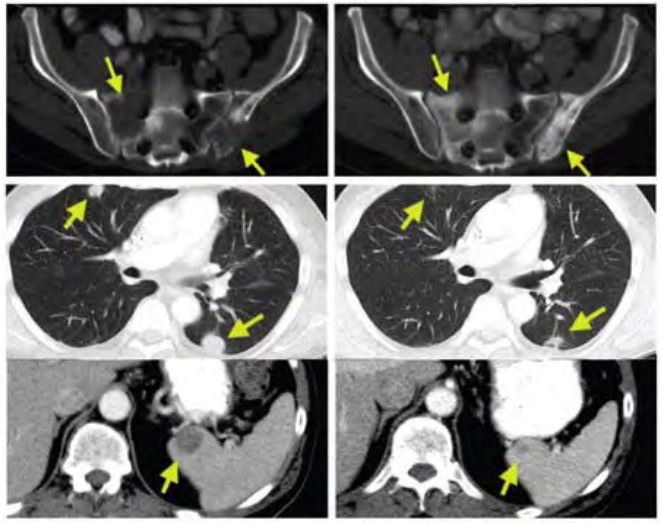
Observations Can Be Compelling





Observations Can Be Compelling

A



Pretreatment 2 months posttreatment

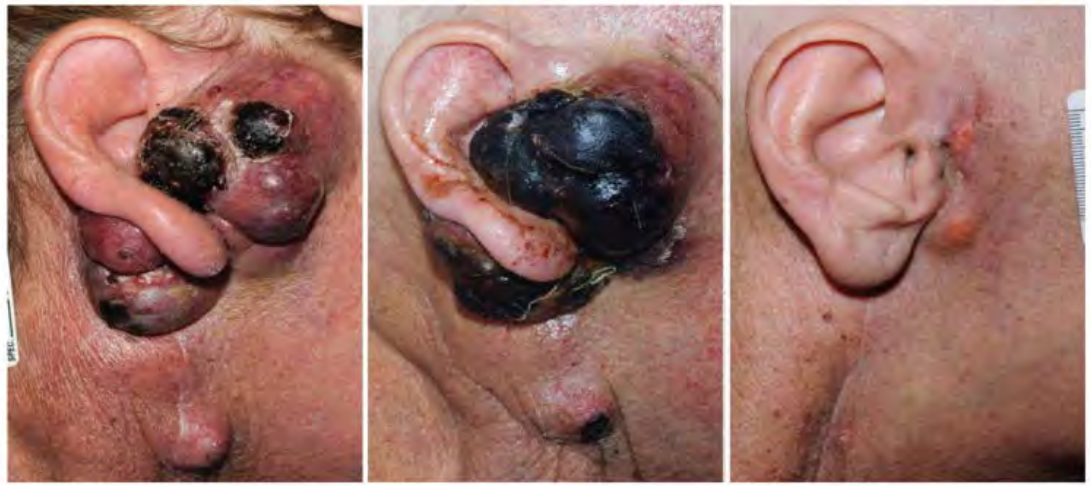
Cancer Therapy: Clinical

CD8+ Enriched "Young" Tumor Infiltrating Lymphocytes Can Mediate Regression of Metastatic Melanoma

Mark E. Dudley, Colin A. Gross, Michelle M. Langhan, Marcos R. Garcia, Richard M. Sherry, James C. Yang, Giao Q. Phan, Udai S. Kammula, Marybeth S. Hughes, Deborah E. Citrin, Nicholas P. Restifo, John R. Wunderlich, Peter A. Prieto, Jenny J. Hong, Russell C. Langan, Daniel A. Zlott, Kathleen E. Morton, Donald E. White, Carolyn M. Laurencot, and Steven A. Rosenberg

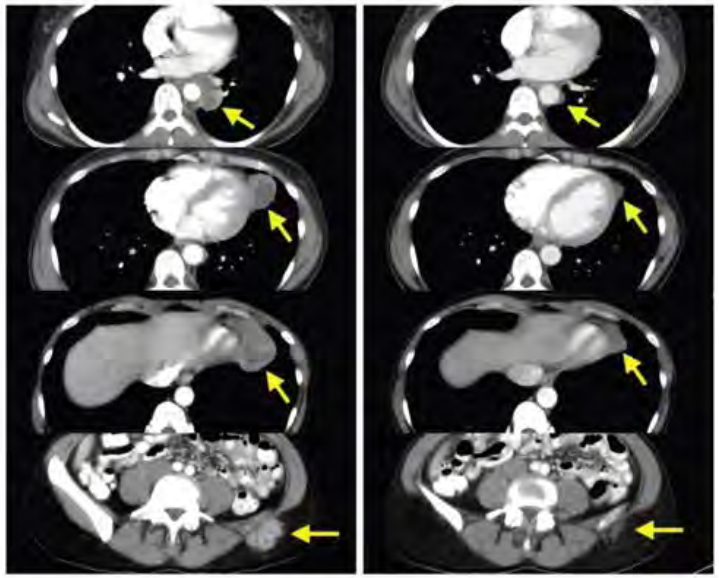
DOI: 10.1158/1078-0432.CCR-10-1297 Published December 2010

B



Day –9 Day +11 Day +76

C



Pretreatment 1 month posttreatment

Limits to Observational Studies and Even RCTs Conducted in Practice

Why Did the Randomized Clinical Trial Become the Primary Focus of My Career?

*David L. Sackett, OC, MD, FRSC, FRCP (Canada, England, and Scotland)**

Department of Clinical Epidemiology & Biostatistics, McMaster University, Hamilton, ON, Canada

- **Clinicians might preferentially give new treatments to patient with better prognosis**
- **Compliant patients might have better prognosis, regardless of their treatment**
- **Patients who liked their Rx might report better outcomes unrelated to the true efficacy of their treatments**
- **Clinicians who like their Rx might report spuriously better outcomes among patients who receive them**

RWE Plays an Important Role for FDA

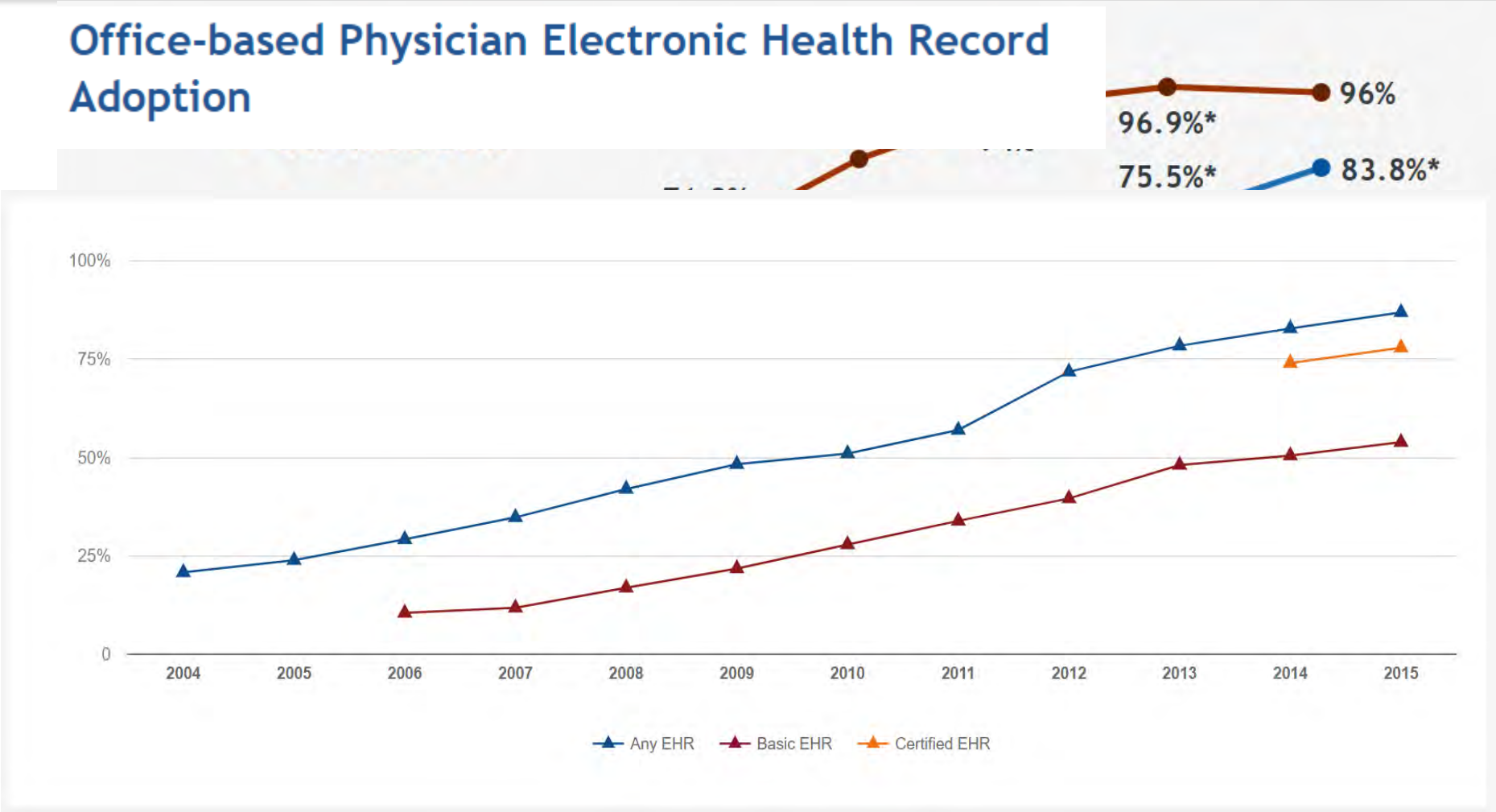
RWE Informs Effectiveness when Fit-for-Use

DRUG	INDICATION	STATUS	DATA
Lutathera *(lutetium 177 dotate)*	GEP-NET Gastropanc. Neuroendo tumors	Approved 2017	▪ Open label clinical trial ▪ **Analysis of 360 patients in an investigator sponsored, open-label**, single-arm, single institution study of 1214 patients*
Voraxaze *(glucarpidase)*	Treatment of MTX toxicity	Approved 2012	▪ Approval based on open-label, **NIH compassionate Use Protocol**
Uridine Triacetate	Treatment of 5 FU overdose	Approved 2015	▪ Two single-arm, open label expanded access trial of **135 patients compared to case history control**
Defitelio *(defibrotide sodium)*	Severe hepatic veno-occlusive disorder	Approved 2016	▪ Two prospective clinical trials enrolling 179 patients and **an expanded access study with 351 patients**
Blincynto *(Blinatumomab)*	Treatment of Acute Lymphoblastic Leukemia	Approved 2014	▪ Single arm trial ▪ Reference group weighted analysis of patient level **data on chart review of 694 patients at EU and US study sites***
Carbaglu carglumic acid	Treatment of NAGS deficiency	Approved 2010	▪ Retrospective, non-random, un-blinded **case series of 23 patients** compared to **historical control group**
Myozyme (alglucosidase alfa)	Treatment of Pompe disease	Approved 2004	▪ Open-label, non-randomized study of 18 patients compared to **historical control group of 62 untreated patients**
Refludan®	Anti-coagulation in heparin-induced thrombocytopenia	Approved 1998	▪ Two non-randomized, open-label multicenter trials using **historical control comparator group from HIT Registry**

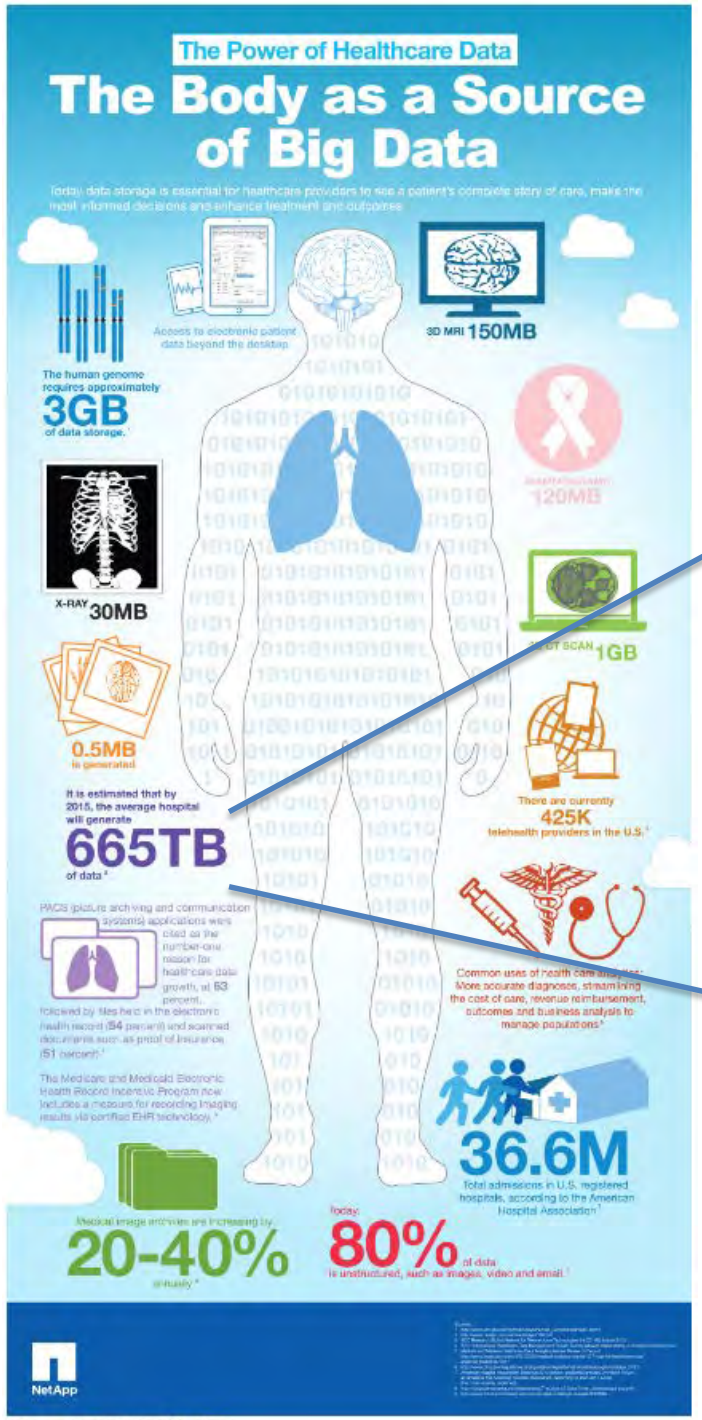
Bold = RWE NOT EXHAUSTIVE

*https://www.nature.com/bcj/journal/v6/n9/full/bcj201684a.html

Why RWE Now?


Office-based Physician Electronic Health Record Adoption
96%
96.9%*
75.5%*
83.8%*
100%
75%
50%
25%
0
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
Any EHR
Basic EHR
Certified EHR

Data are Available



Infographic courtesy of NetApp

It is estimated that by 2015, the average hospital will generate

665TB

of data [1]

Endpoints in FDA Registrational Trials 2007–2015

Type of Endpoint	% of NDA	Examples of Endpoints Measured
Chemistry data	11	HBA1c, pregnancy test, GFR
Hematology	6	Severe neutropenia Apheresis yield > 5 million CD34+ cells/kg
Pathology	2	Increase/decrease of parabasal cells; biopsy proven acute rejection, clearing of anterior chamber cells
Microbiology	6	Sustained virological response, plasma viral load, conversion to negative sputum
Imaging +/- (survival, clinical signs)	17	Bone mineral density; vertebral fractures, spleen volume, progression free survival
Physiological/ functional measurement	9	6 minute walk, normal sinus rhythm, FEV1, sleep studies
Clinical event /clinical sign	19	Death, hospitalization, MACE, MS relapse, Lice free head
CRO/PRO	30	Toronto western spasmodic torticollis rating scale, Hamilton depression rating scale, Rheumatology scale ankylosing spondylitis scale, psoriasis severity index, seizures, sleep, prostate symptom score

Why Expand Use of RWD/RWE?

- **Improve the efficiency of clinical research by capitalizing on data that is being captured every day**
  - **Digitization of health care provide new opportunities to close the divide between research and clinical care**
    - **Additional settings, access to more diverse populations**
- **Big data – potential for detection of infrequent events, long-term but infrequent outcomes**
- **Lower resource intensity – more questions answered**

Scope of RWE Program

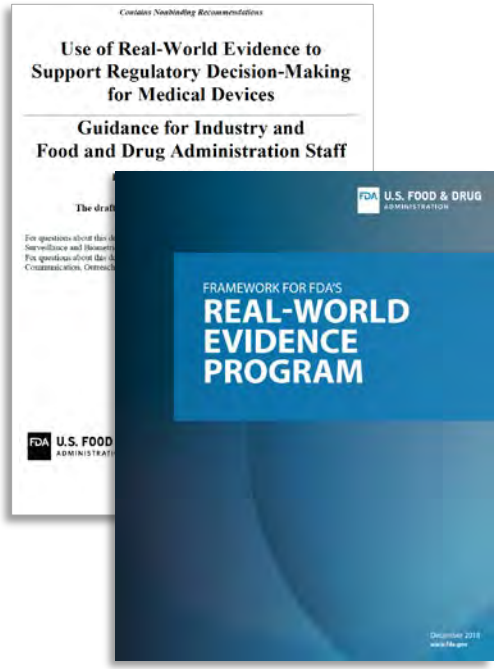
Scope of RWE Program Under 21st Century Cures Act

Under the Cures Act, FDA's RWE Program must evaluate the potential use of RWD to generate RWE of product effectiveness to help support approval of new indications for drugs approved under FD&C Act Section 505(c) or to help to support or satisfy postapproval study requirements. FDA's RWE Program will also apply to biological products licensed under section 351 of the Public Health Service Act.

https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RealWorldEvidence/UCM627769.pdf

Definitions

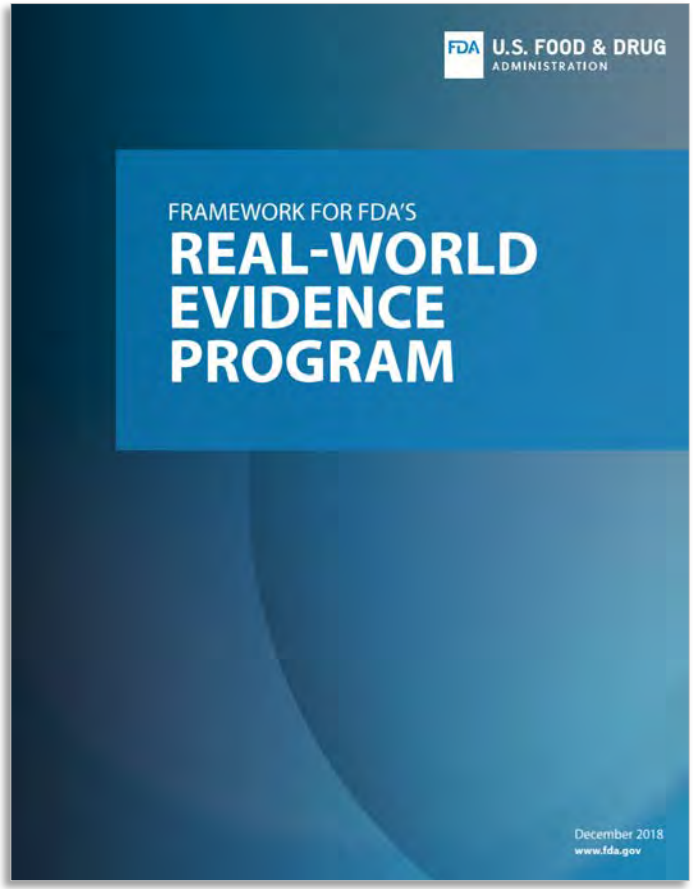
Real world evidence means data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than *traditional clinical trials*



Real-World Data (RWD) are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.

Real-World Evidence (RWE) is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD.

FDA Real-World Evidence Program



- **Outlines FDA's plan to implement the RWE program**
- **Focus on adding or modifying an indication, comparative effectiveness, and comparative safety**
- **Multifaceted program**
  - **Internal processes**
  - **Guidance development**
  - **Stakeholder engagement**
  - **Demonstration projects**

https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RealWorldEvidence/UCM627769.pdf

Benchmark

- **Substantial evidence standard unchanged**
  - **Goal is to distinguish the effect of the drug from other influences such as spontaneous change in disease course, placebo effect, or bias**
  - **Common practices:**
    - **Probabilistic control of confounding through randomization**
    - **Blinding**
    - **Controlled/standardized outcome assessment**
    - **Adjudication criteria**
    - **Audits**

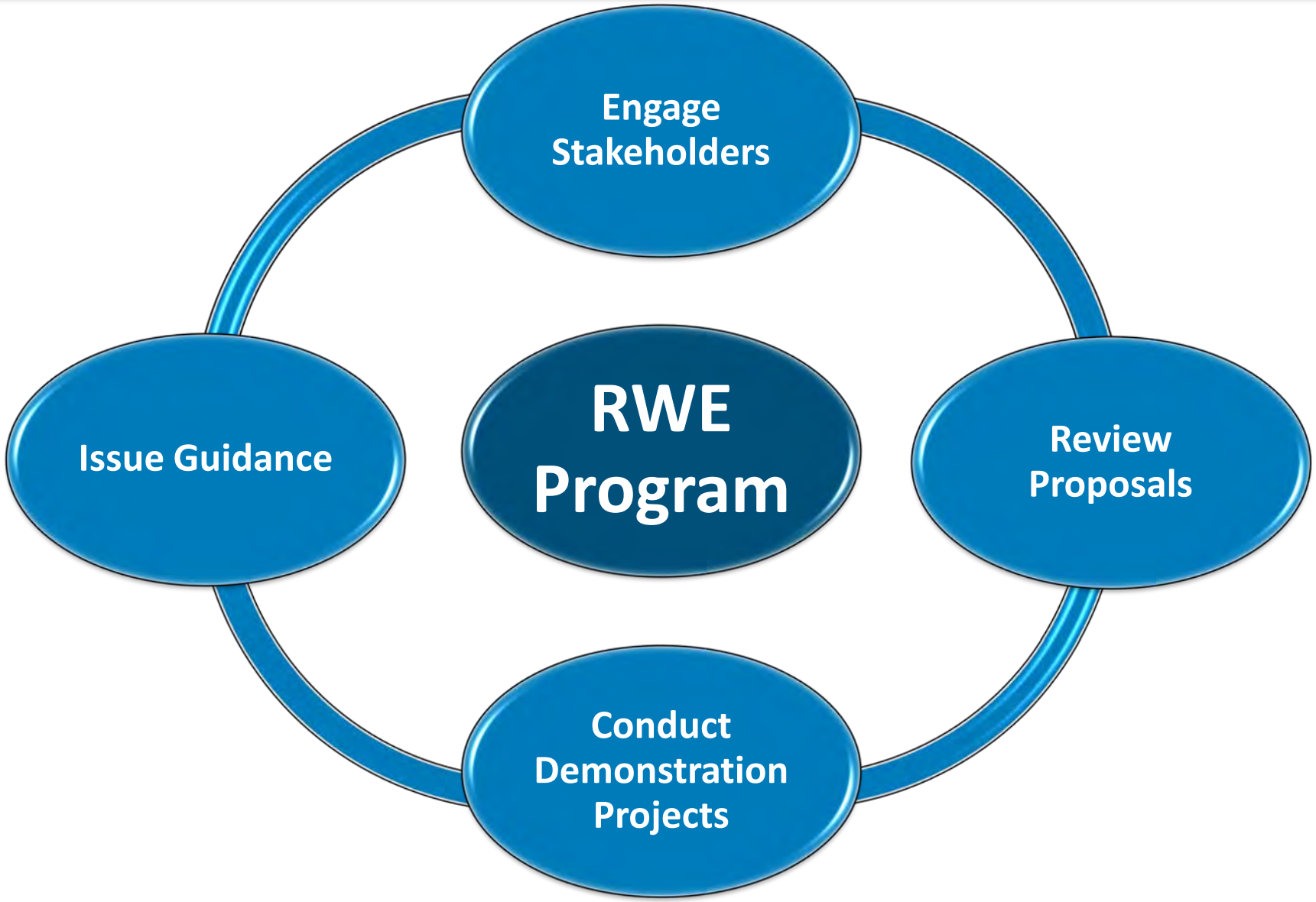
Framework for Evaluating RWD/RWE for Use in Regulatory Decisions

Consider:

Clinical

- Whether the RWD are fit for use
- trial or study design
- rate RWE can provide
- entific evidence to
- lp answer the
- uestion
- study conduct meets
- requirements

RWE Program


Engage Stakeholders
Issue Guidance
RWE Program
Review Proposals
Conduct Demonstration Projects

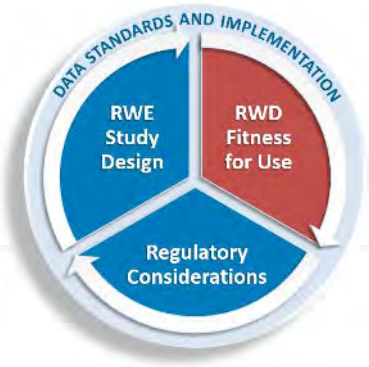
Demonstration Projects

- Relevancy
- Quality
- Linkage

- Common data models
- Mobile technologies

- Randomized trials
- Assessment of observational studies

RWD FIT FOR USE



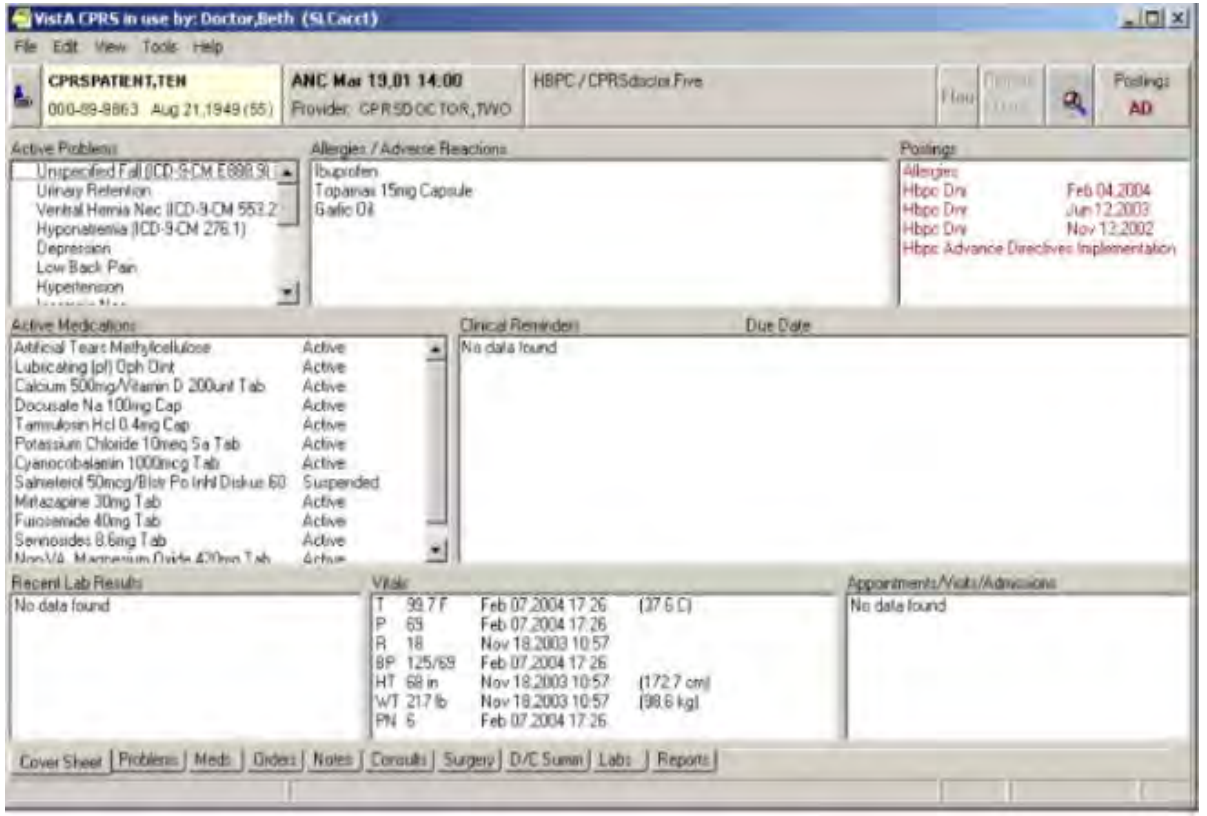
RWD Fitness for Use

- **Data reliability (data accrual and data quality control) and relevance**
  - **Data must be collected and maintained in a way that provides an appropriate level of reliability**
  - **Data must be suitable to address specific regulatory question of interest - relevance**
- **FDA does not endorse any one type of RWD**
- **<u>Challenge</u>: A single source of RWD may not capture all data elements, and multiple data sources may be needed**

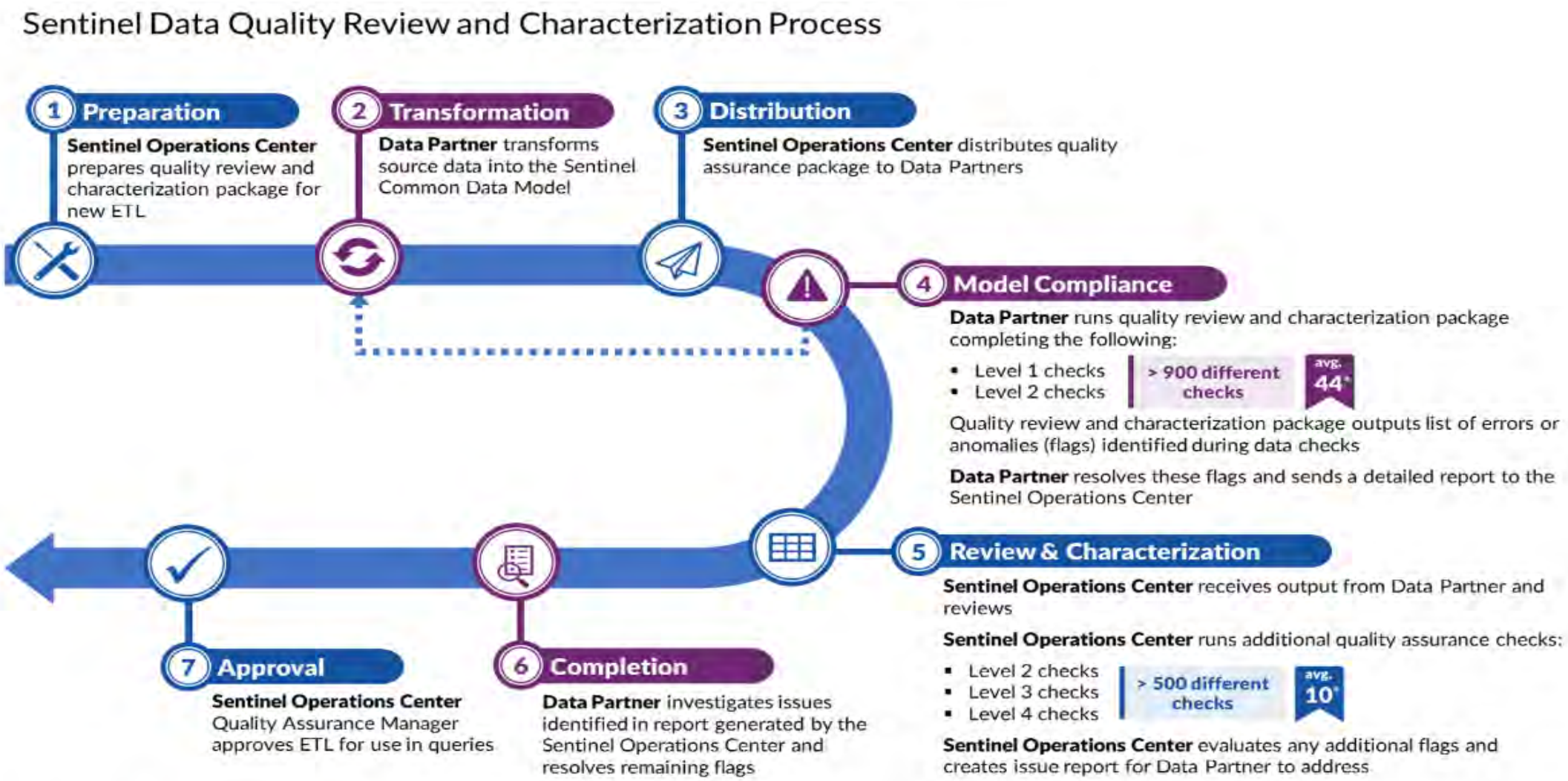
EHRs: Potential and Challenge

Potential for a more complete and granular clinical picture; challenges include:

- Data in pathology/ radiology and clinical notes are often unstructured (80%) and images might be necessary
- Structured data ≠ Standardized data
- Typing ≠ consistency/complete documentation
- Interoperability
- Clinical outcome measures for drug approvals may not be used or consistently recorded in practice



Sample Sentinel Process for Data Quality Assurance



* On average, there are 44 flags identified by the program and 10 additional flags identified by the Sentinel Operations Center per ETL

Patient-Generated Health Data (Digital Health Tools)

Alignment of Demonstration Projects with the Framework

Understanding EHRs in the Context of Clinical Trials

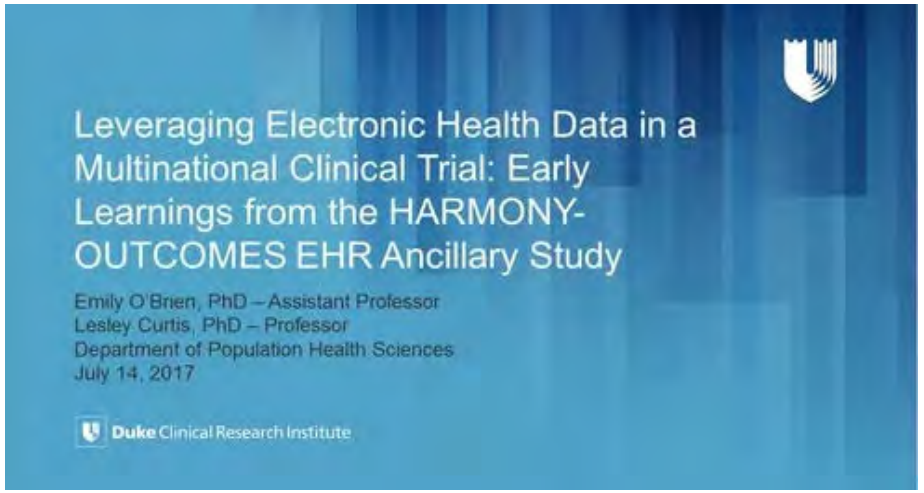
- Harmony- Outcomes Ancillary Study
- One Source - ISpy

Use of Mobile Technologies to Enhance RWD

- Trial in Juvenile Idiopathic Arthritis
- Inflammatory Bowel Disease Registry
- Mobile devices and novel endpoints

HARMONY-Outcomes Ancillary Study

- **Collaboration with Duke Clinical Research Institute and Glaxo SmithKline**
- **Supported by FDA**
- **Assessed EHR ability to:**
  - **Facilitate recruitment**
  - **Populate baseline characteristics**
  - **Identify clinical endpoints**



July 14, 2017: Leveraging Electronic Health Data in a Multinational Clinical Trial: Early Learnings from the HARMONY-Outcomes EHR Ancillary Study

http://www.rethinkingclinicaltrials.org/grand-rounds-7-14-17/

Effect of Albiglutide, When Added to Standard Blood Glucose Lowering Therapies, on Major Cardiovascular Events in Subjects With Type 2 Diabetes Mellitus – NCT02465515

Creating Quality Clinical/Research Records – Design for Multiuse

- OneSource: "enter the right clinical data once, use many times"
- FDA collaboration with Dr. Laura Esserman (UCSF)
- Integration of standards based tools into the EHR to bring together health care and research
- Demonstration in breast cancer clinical trials

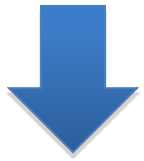
Courtesy of Dr. Laura Esserman and Susan Dubman

Common EHR Data Structure

mCODE™

Minimal Clinical Oncology Data Elements

Data standards to improve the quality and usability of EHR data

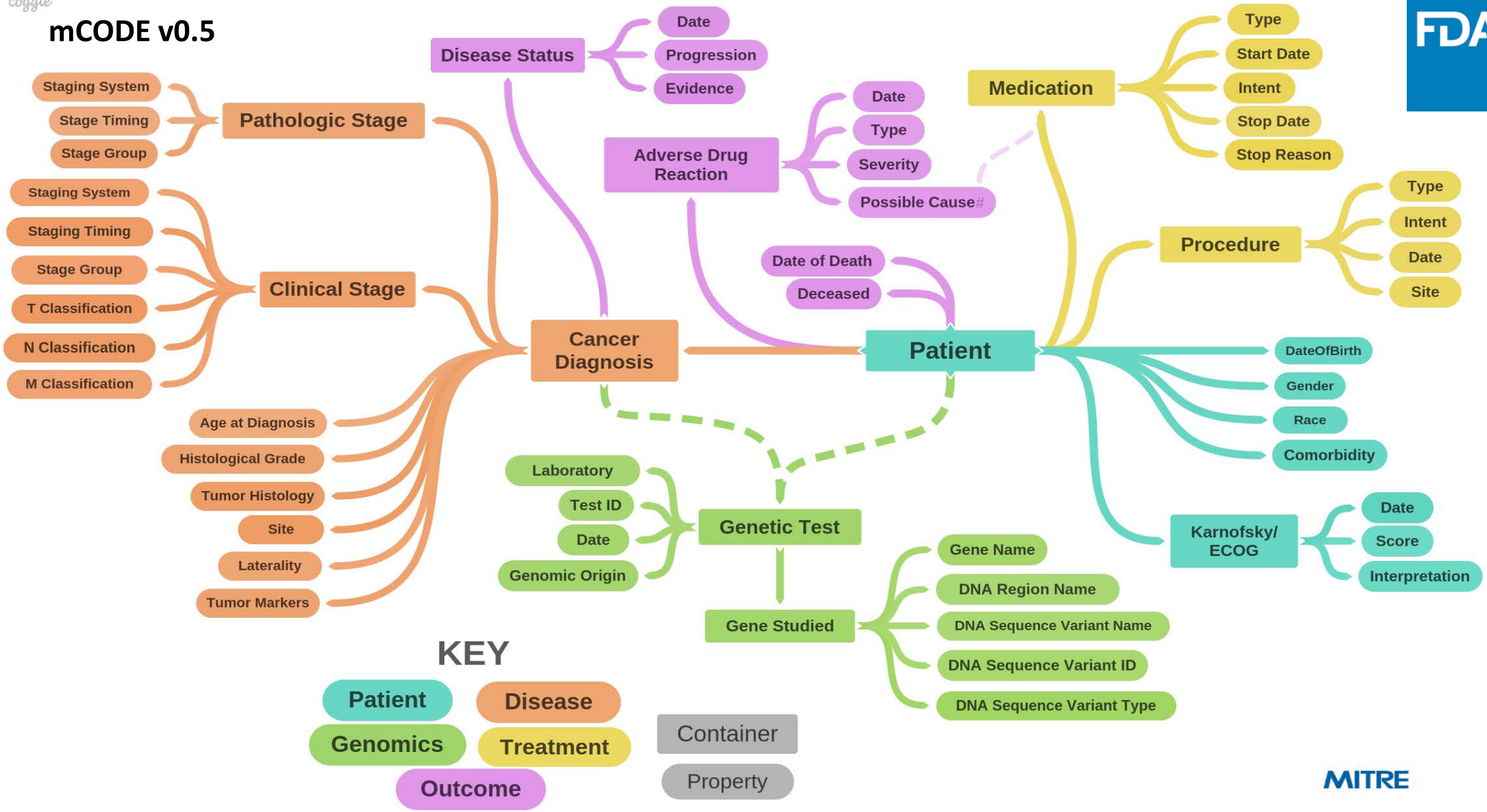


Collection of clinical trials data using the EHR

Courtesy of ASCO/MITRE

coggle

mCODE v0.5



FDA MyStudies

- **Mobile App**
  - Standard frameworks - ResearchKit (iOS), ResearchStack (Android)

- **Web-based Configuration Portal (WCP)**
  - Enables support of multiple types of medical product effectiveness and safety studies with minimal software development

- **Secure Storage Environment**
  - Generates secure tokens
  - Separates registration information and responses
  - Partitioned for multisite, decentralized, or distributed models

Demonstration Project

LimitJIA

pcori

FDA

Table 1: Primary Inclusion and Exclusion Criteria	
Inclusion Criteria: • Clinical diagnosis JIA by a pediatric rheumatologist within the past 6 months • Arthritis affecting ≤4 joints between disease onset and enrollment • Clinically active arthritis of at least 1 joint at the time of enrollment • Age ≥ 2 years old and < 17 years old • Prior or concurrent enrollment in the CARRA Registry	**Exclusion Criteria:** • Systemic JIA as defined by 2004 ILAR criteria[1] • Sacroiliitis (clinical or radiographic) • Inflammatory bowel disease • Psoriasis • History of uveitis or currently active uveitis • Prior treatment with systemic DMARD(s) or biologics • Current treatment with systemic glucocorticoids (past 30 days)

- **Use the MyStudies app to support:**
  - **Collection of primary outcome (uveitis) from ophthalmology appointments (also reminders for appointments)**
  - **Potential support for the Childhood Arthritis & Rheumatology Research Alliance (CARRA) Registry**

CARRA
Childhood Arthritis and Rheumatology Research Alliance

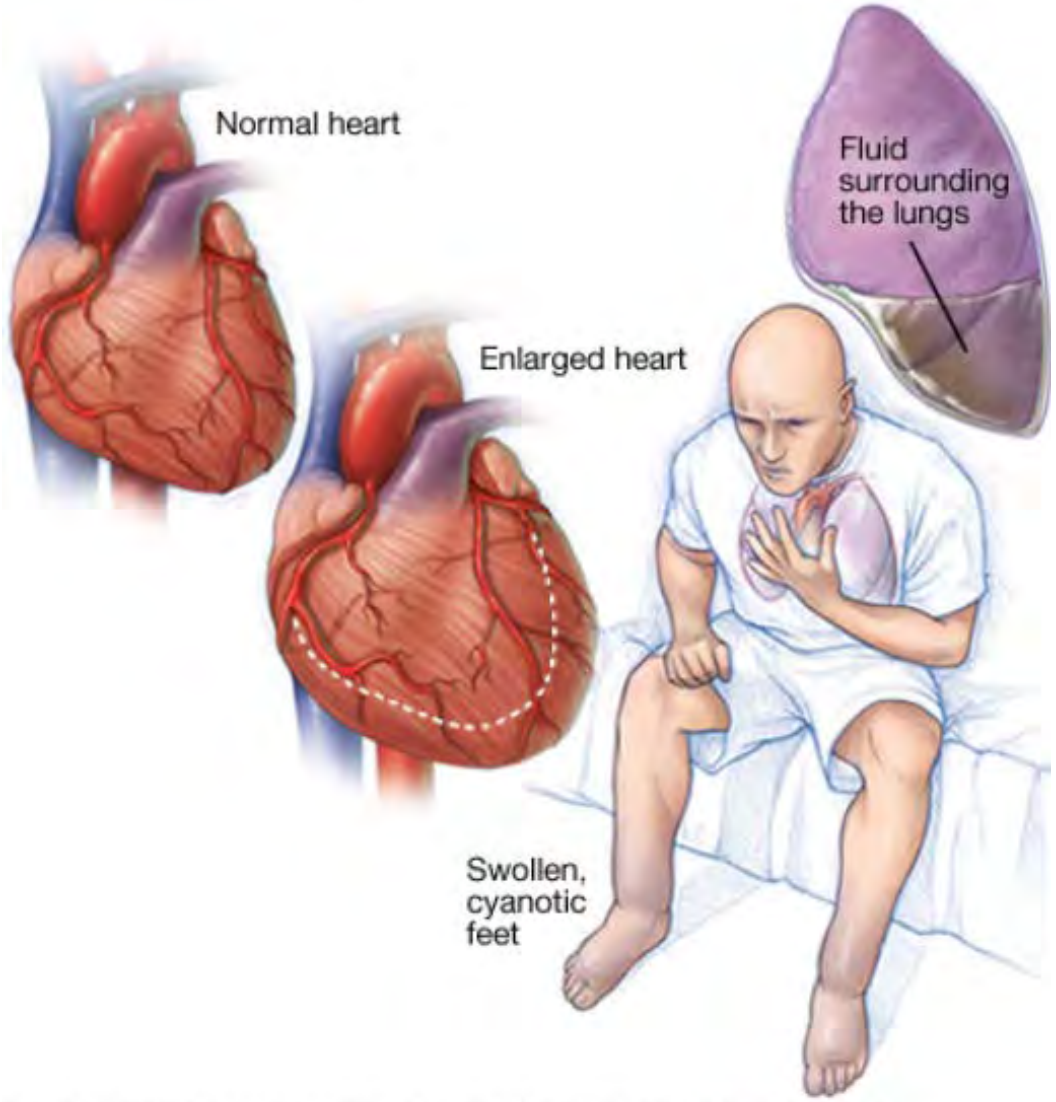
Demonstration Project

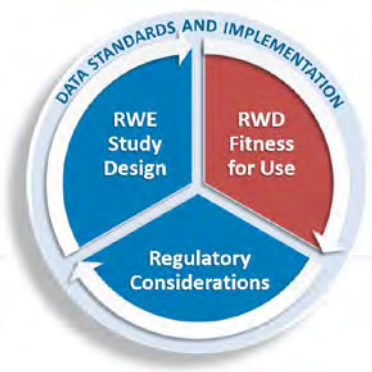
- **SPARC Inflammatory Bowel Disease cohort within the IBD Plexus research exchange platform**
  - **Provider based recruitment of individuals >18 years of age with a confirmed IBD diagnosis from academic and community sites**

- **FDA-Catalyst will align with the registry by providing support from the My Studies App**

Exploring Wearable Sensors for Patients with Heart Failure

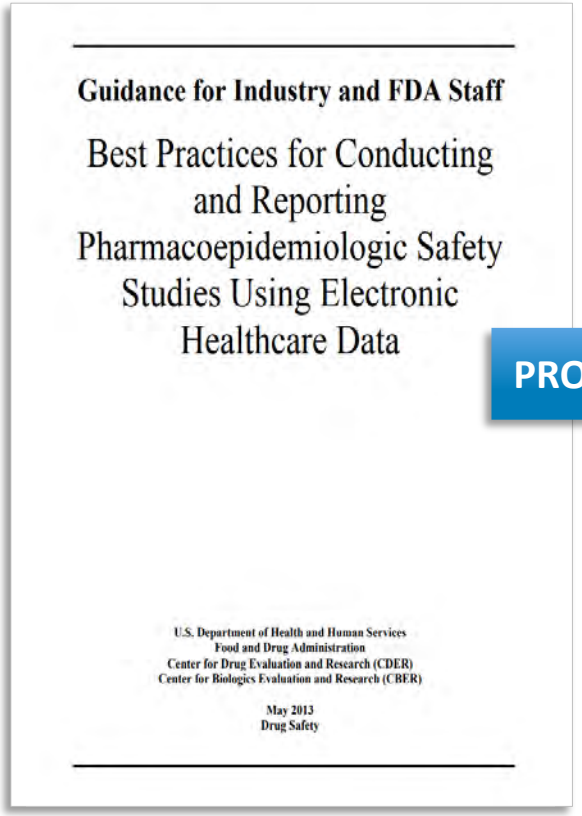
- To evaluate the feasibility and performance of two novel wearable and smartphone-based mobile health platforms for real-world surveillance of surrogate endpoints for heart failure drug approvals in 150 patients
- Novel health platforms will measure ECG data, heart rate, respiratory rate, accelerometer data, steps, activity, and sleep





RWD Fitness for Use

Leveraging the principles from the 2013 guidance on electronic health care data and our demonstration projects:



Guidance for Industry and FDA Staff

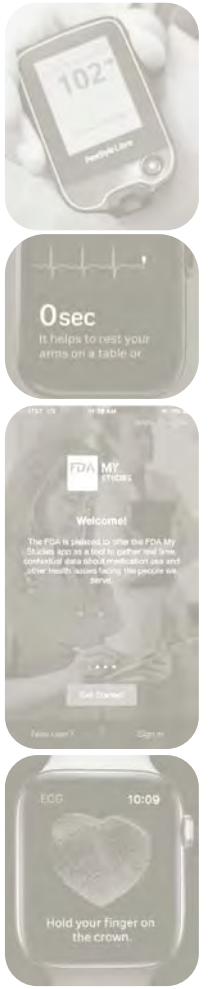
Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data

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)

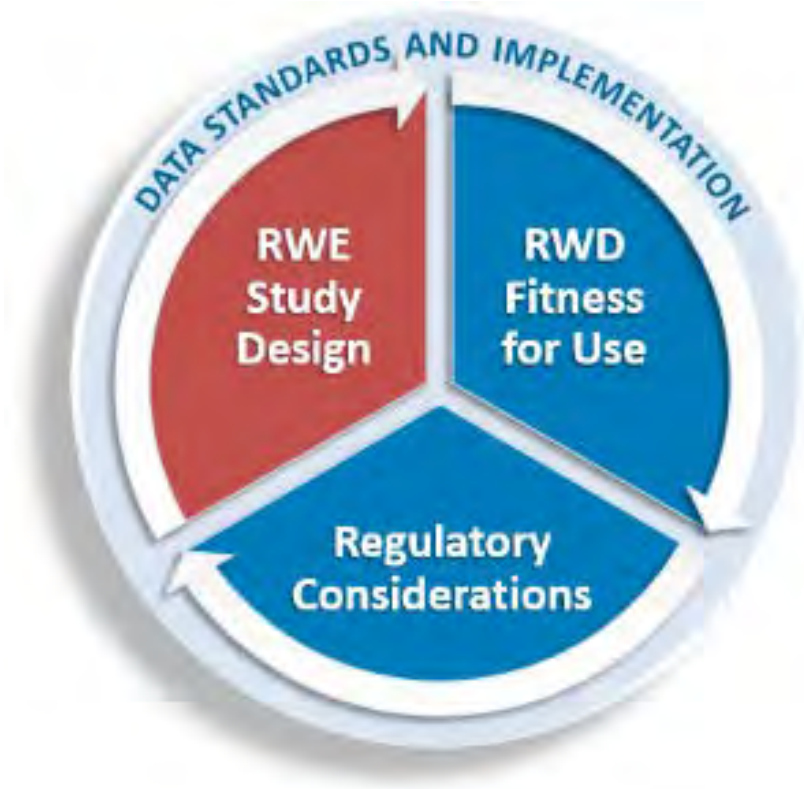
May 2013
Drug Safety

PROGRAM ITEMS:

- **How to assess RWD from medical claims and EHRs and registry data to generate RWE regarding drug product effectiveness**
- **The use of mobile technologies, electronic PROs, and wearables to potentially fill gaps**

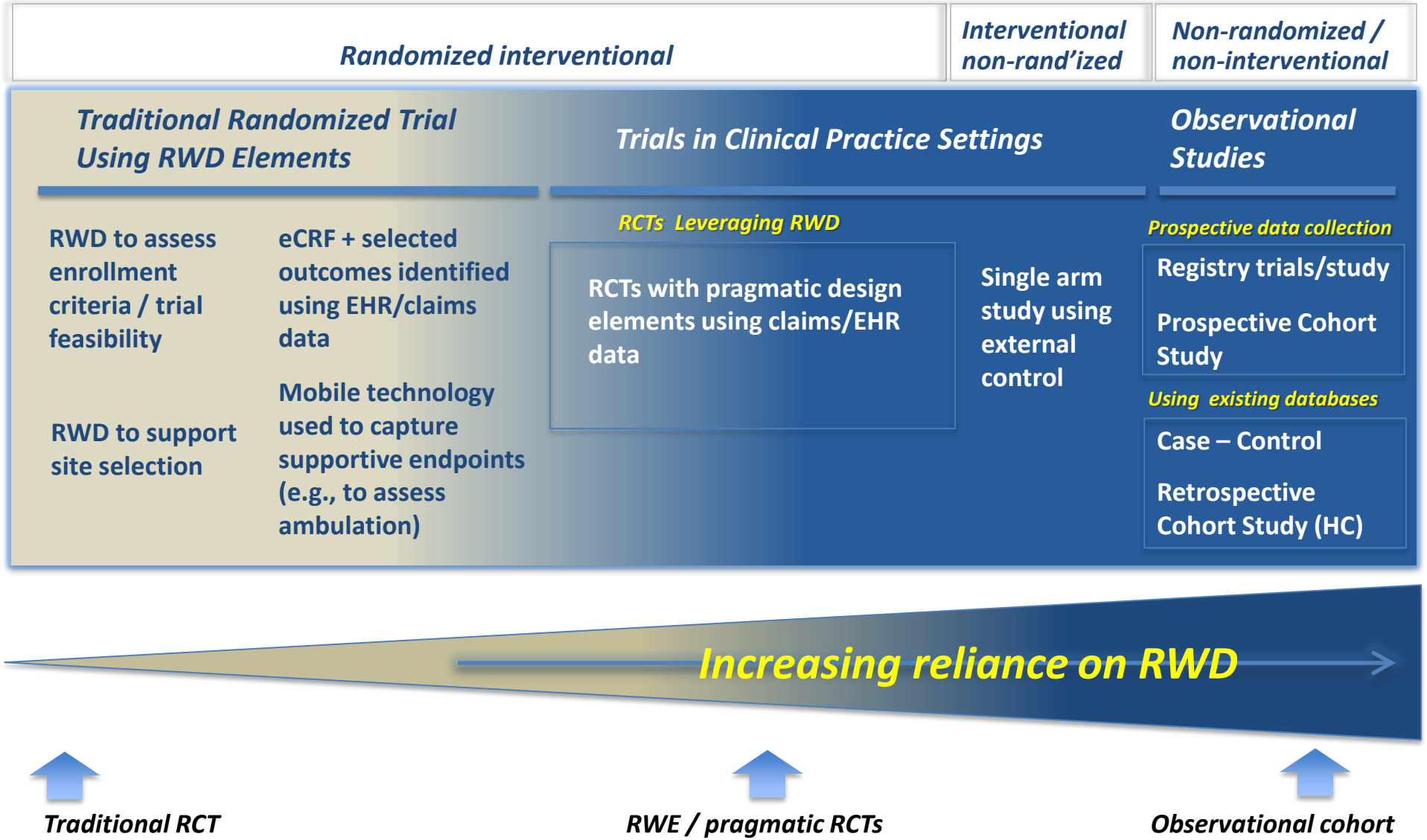


Sentinel

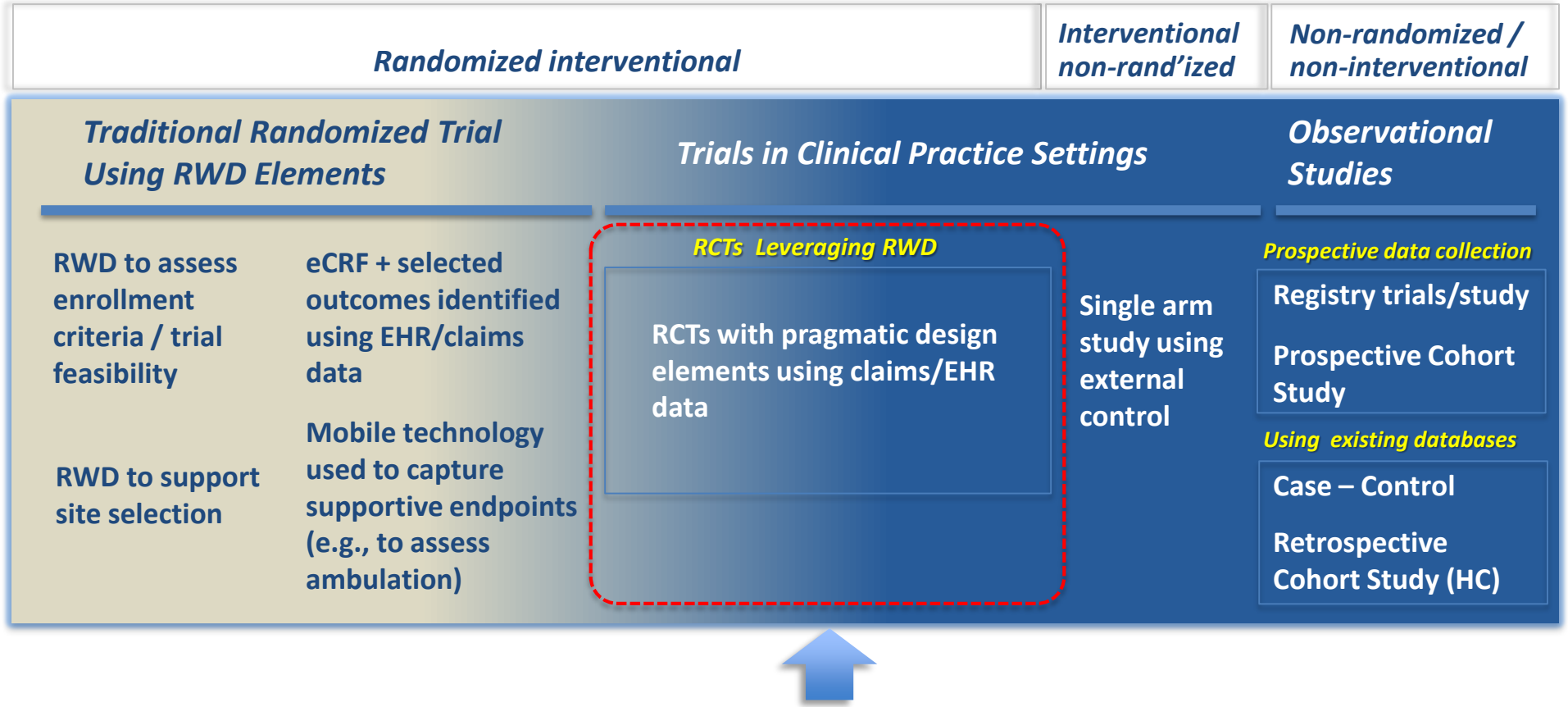


RWE STUDY DESIGN

Wide Spectrum of Potential Uses of RWD / RWE in Clinical Studies



Wide Spectrum of Potential Uses of RWD / RWE in Clinical Studies



- Limitations of claims databases may be addressed by linking to EHR for richer covariates, more options for trial endpoints

https://healthpolicy.duke.edu/events/leveraging-randomized-clinical-trials-generate-real-world-evidence-regulatory-purposes

Potential for Study Designs Using RWD to Support Effectiveness

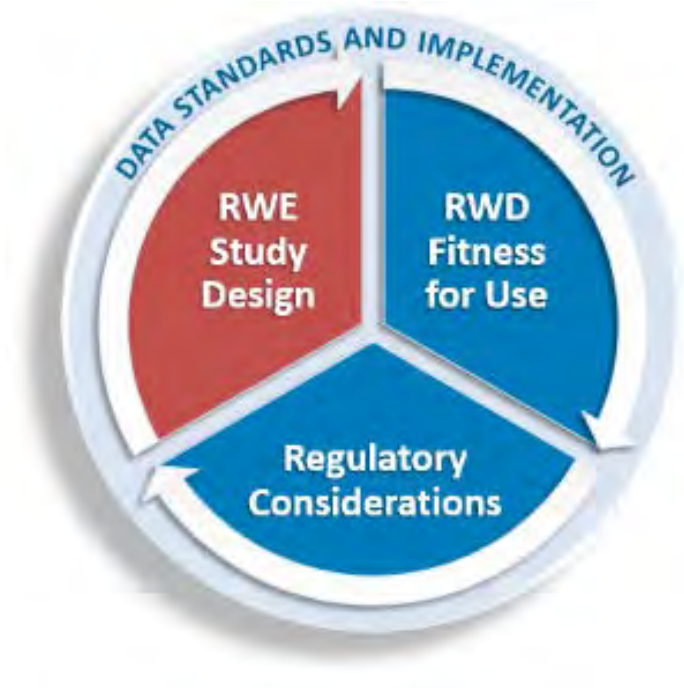
FDA

Factors when considering embedding a randomized trial in clinical settings in order to access RWD

- What is the question we are trying to answer and is this the best setting?
- How will RWD be captured in these settings?
  - What is the impact on lags in data capture
- Is blinding necessary?
- Bridging between regulatory endpoints and clinical practice
- Site inspections and monitoring

PROGRAM ITEM: Guidance on considerations for using RWD in randomized clinical trials for regulatory purposes, including use of pragmatic design elements

Alignment of Demonstration Projects with the Framework



IMPACT-AFIB – FDA Catalyst

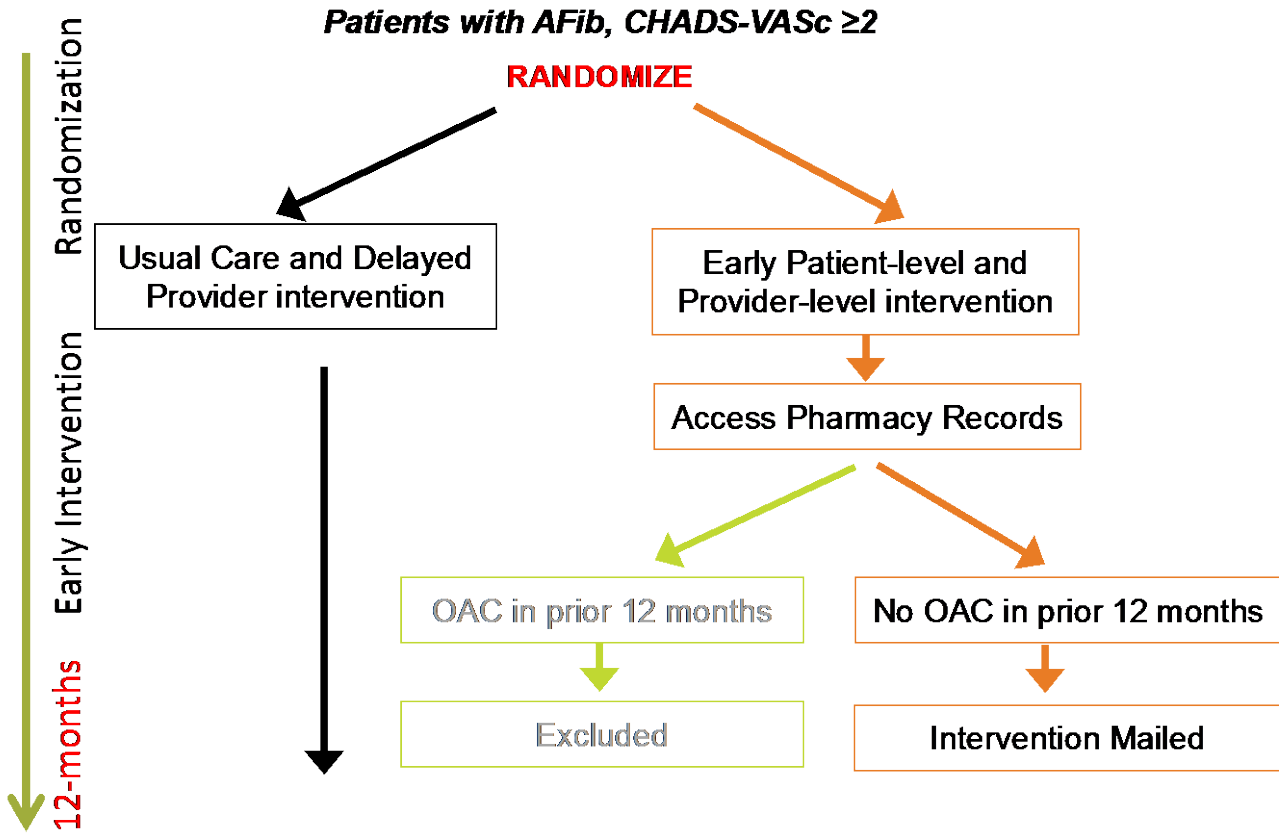
RELIANCE Trial – PCORI – FDA Catalyst

IMPACT Afib Trial

IMplementation of a randomized controlled trial to imProve treatment with oral AntiCoagulanTs in patients with Atrial Fibrillation

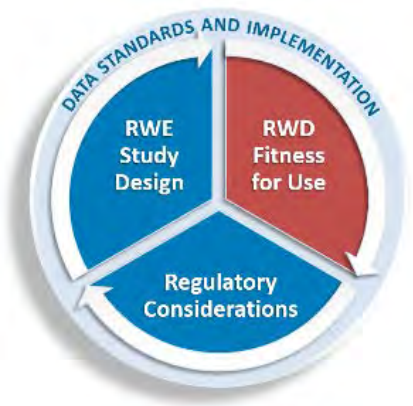
- **Test the ability of an education intervention to increase the appropriate use of oral anticoagulants in a patient population with atrial fibrillation (afib) at high risk of stroke**

- **Enrollment of approximately 80,000 individuals in the early and late intervention arms**

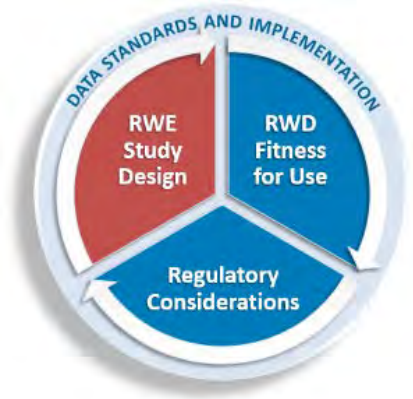


https://www.sentinelinitiative.org/FDA-catalyst/projects/implementation-randomized-controlled-trial-improve-treatment-oral-anticoagulants-patients

RELIANCE Trial

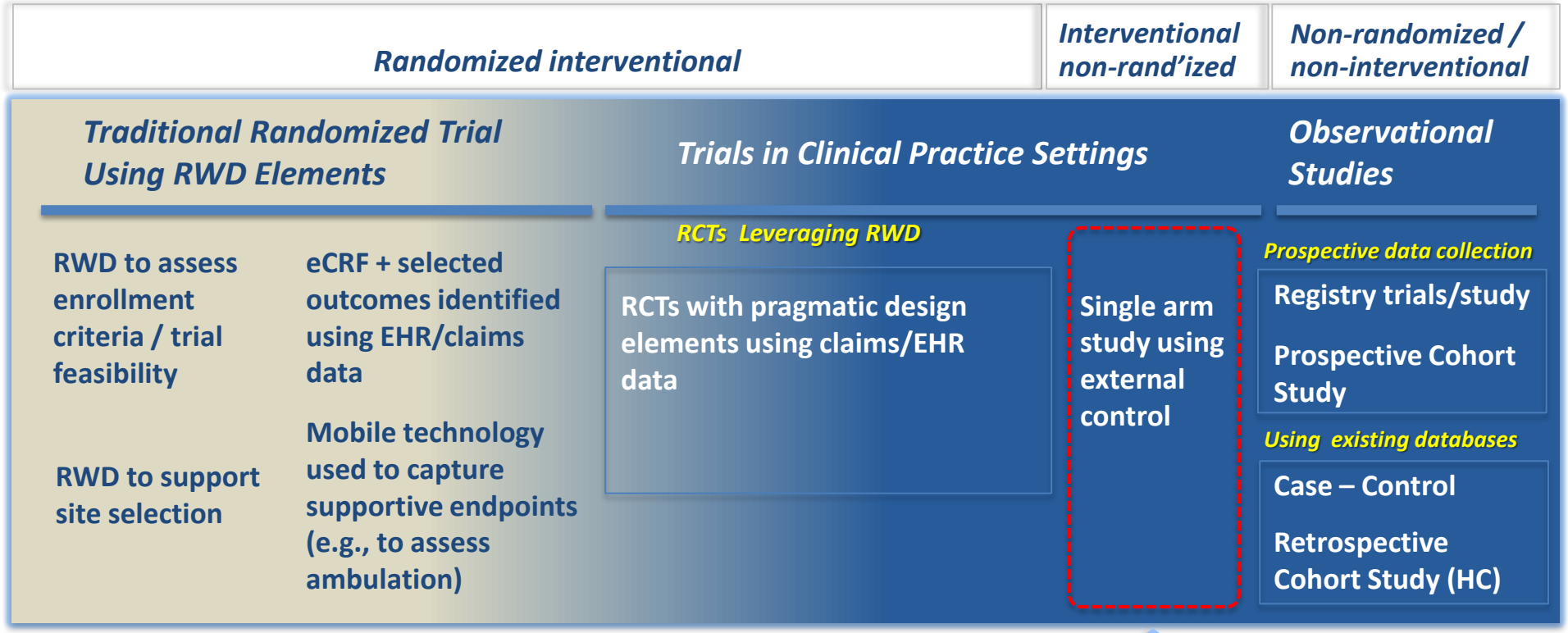


- **RofLumilast or Azithromycin to prevent COPD Exacerbations**
  - Randomized “real world” trial; 1,600 adults in each arm
  - Azithromycin - macrolide with anti-inflammatory properties
  - Roflumilast - noncorticosteroid anti-inflammatory; phosphodiesterase type 4 inhibitor



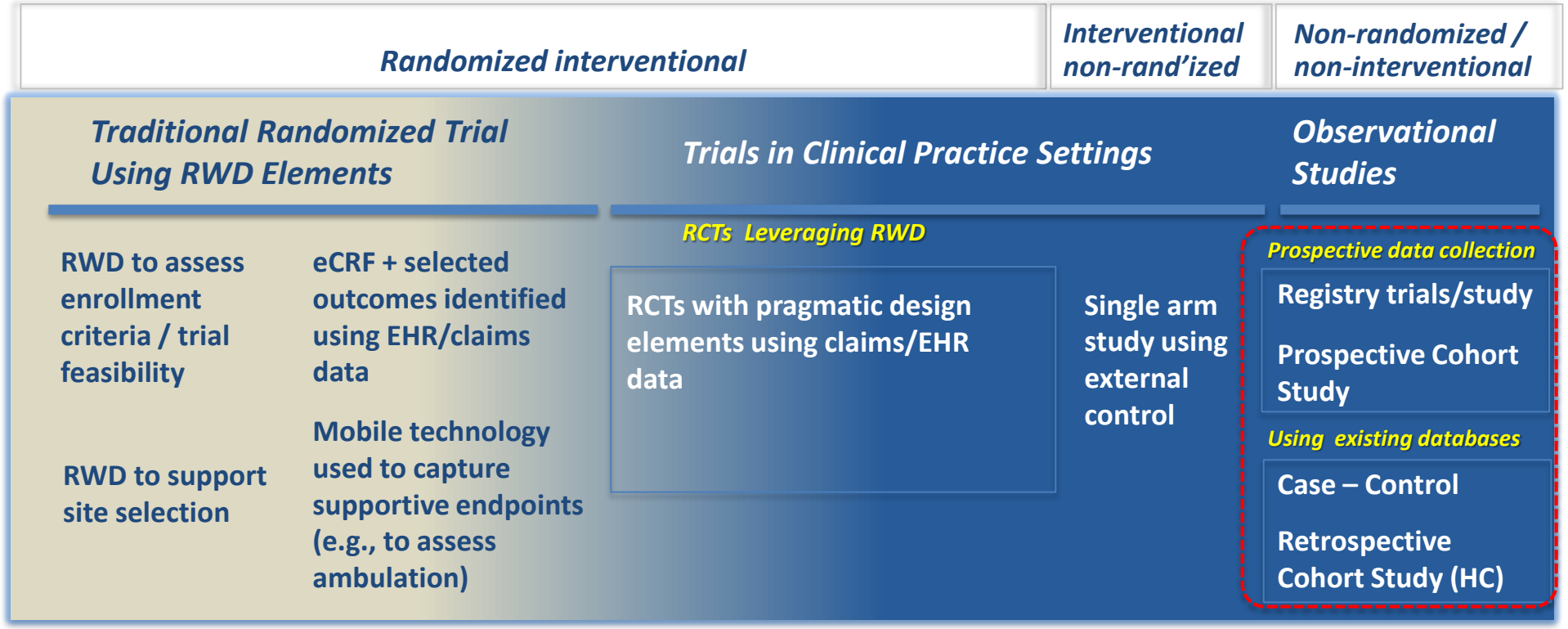
- **Primary outcomes**
  - All cause hospitalization
  - All cause mortality
- **Follow-up**
  - 6-36 months, no visits, call center, Patient Portal, Site EMR
  - CMS linkage through FDA-Catalyst for outcomes and exposures

Wide Spectrum of Potential Uses of RWD / RWE in Clinical Studies



- Commonly applied to rare diseases, oncology
- Requires well-defined natural history, covariate rich external control dataset
- Objective endpoints, substantial drug effect

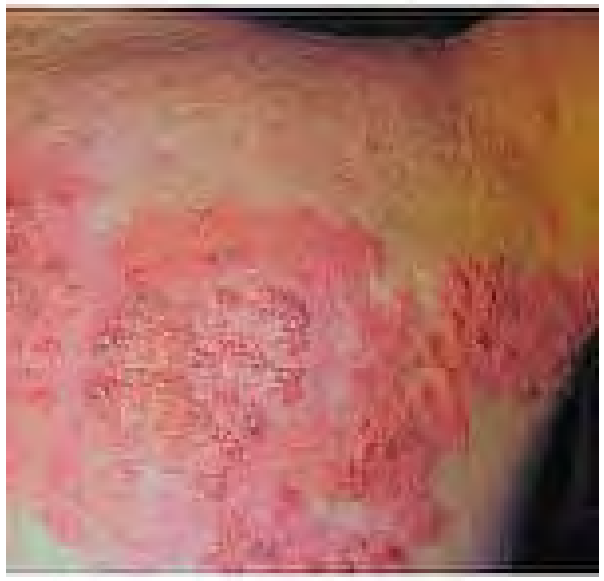
Wide Spectrum of Potential Uses of RWD / RWE in Clinical Studies



MERCK Zostavax for Herpes Zoster (HZ)

Pre-approval efficacy trials:

- **Shingle Prevention Study (SPS)**
  - **Double-blind, placebo-controlled (DBPC) RCT 38,000 individuals > 60**
  - **Median follow-up 3.1 years - reduction in HZ incidence 51%**



- **ZOSTAVAX Efficacy and Safety Trial (ZEST)**
  - **DBPC RCT of 22,200 individuals 50-59 years of age**
  - **Median follow-up 1.3 years - reduction in HZ incidence 70%**

MERCK Zostavax for Herpes Zoster (HZ) *(cont.)*

Post Marketing Commitment to study long-term efficacy in ages 50-59

- Prospective observational study run by Kaiser Permanente Northern California
- Data on 1.3 million members, with over 350,000 individuals who received Zostavax and 100,000 individuals with more than 5 years follow up post vaccination
- Study is ongoing and will continue through 2023

Clinical studies section of labeling updated:

- In assessing effectiveness adjustments made for calendar time, age, sex, race/ethnicity, healthcare resource utilization, comorbid conditions, and immunocompromise status
- Vaccine effectiveness (VE) against HZ for 50-59 over first 3 years following vaccination was 60%
- For individuals 60-69, 70-79 and 80 or older average VE against 49%, 46% and 44% respectively.

Observational Studies and Treatment Effects?

RANDOMIZED, CONTROLLED TRIALS, OBSERVATIONAL STUDIES, AND THE HIERARCHY OF RESEARCH DESIGNS

JOHN CONCATO, M.D., M.P.H., NIRAV SHAH, M.D., M.P.H., AND RALPH I. HORWITZ, M.D.

N Engl J Med 2000;342:1887-92

TABLE 2. TOTAL NUMBER OF SUBJECTS AND SUMMARY ESTIMATES FOR THE EFFECT OF FIVE INTERVENTIONS ACCORDING TO THE TYPE OF RESEARCH DESIGN.

CLINICAL TOPIC	TYPE OF STUDY	META-ANALYSIS*	TOTAL NO. OF SUBJECTS	SUMMARY ESTIMATE (95% CI)†
Bacille Calmette–Guérin vaccine and tuberculosis	13 Randomized, controlled	Colditz et al.[14]	359,922	0.49 (0.34–0.70)
	10 Case–control	Colditz et al.[14]	6,511	0.50 (0.39–0.65)
Mammography and mortality from breast cancer	8 Randomized, controlled	Kerlikowske et al.[15]	429,043	0.79 (0.71–0.88)
	4 Case–control	Kerlikowske et al.[15]	132,456	0.61 (0.49–0.77)
Cholesterol levels and death due to trauma	6 Randomized, controlled	Cummings and Psaty[16]	36,910	1.42 (0.94–2.15)
	14 Cohort	Jacobs et al.[17]	9,377	1.40 (1.14–1.66)
Treatment of hypertension and stroke	14 Randomized, controlled	Collins et al.[18]	36,894	0.58 (0.50–0.67)
	7 Cohort	MacMahon et al.[12]	405,511	0.62 (0.60–0.65)
Treatment of hypertension and coronary heart disease	14 Randomized, controlled	Collins et al.[18]	36,894	0.86 (0.78–0.96)
	9 Cohort	MacMahon et al.[13]	418,343	0.77 (0.75–0.80)

*Meta-analyses that included either randomized, controlled trials or observational studies are cited.

†CI denotes confidence interval.

The results of well-designed observational studies (with either a cohort or a case–control design) do not systematically overestimate the magnitude of the effects of treatment as compared with those in randomized, controlled trials on the same topic.

misleading.

Sacks, L. Letter to Editor, NEJM Volume 343 Number 16 · **1195**

Cochrane Library

Cochrane Database of Systematic Reviews

Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials (Review)

Anglemyer A, Horvath HT, Bero L

2014

ıational studies are misleading (just as
ıg), but that no one has devised a
re useful from those that are

Methods Matter

JAMA The Journal of the American Medical Association

Exposure to Oral Bisphosphonates and Risk of Esophageal Cancer

Cardwell et al.
JAMA, August 11, 2010—Vol 304, No. 6

Among patients in the UK General Practice Research Database, the use of oral bisphosphonates was not significantly associated with incident esophageal or gastric cancer.

BMJ

Oral bisphosphonates and risk of cancer of oesophagus, stomach, and colorectum: case-control analysis within a UK primary care cohort

Jane Green, clinical epidemiologist,[1] Gabriela Czanner, statistician,[1] Gillian Reeves, statistical epidemiologist,[1] Joanna Watson, epidemiologist,[1] Lesley Wise, manager, Pharmacoepidemiology Research and Intelligence Unit,[2] Valerie Beral, professor of cancer epidemiology[1]

BMJ 2010;341:c4444

The risk of oesophageal cancer increased with 10 or more prescriptions for oral bisphosphonates and with prescriptions over about a five year period. In Europe and North America, the incidence of oesophageal cancer at age 60–79 is typically 1 per 1000 population over five years, and this is estimated to increase to about 2 per 1000 with five years' use of oral bisphosphonates.

Efforts to Enhance Transparency

Transparency about study design and analysis <u>before</u> execution is critical for ensuring confidence in the result

Good Practices for Real-World Data Studies of Treatment and/or Comparative Effectiveness: Recommendations from the Joint ISPOR-ISPE Special Task Force on Real-World Evidence in Health Care Decision Making

Marc L. Berger[1,*], Harold Sox[2], Richard J. Willke[3], Diana L. Brixner[4], Hans-Georg Eichler[5], Wim Goettsch[6], David Madigan[7], Amr Makady[6], Sebastian Schneeweiss[8], Rosanna Tarricone[9], Shirley V. Wang[8], John Watkins[10], C. Daniel Mullins[11]

1. *A priori*, determine and declare that a study is a Hypothesis Evaluation Treatment Effectiveness (HETE) study or an Exploratory study based on conditions outlined below
2. Post a HETE study protocol and analysis plan on a public study registration site prior to conducting the study analysis.
3. Publish HETE study results with attestation to conformance and/or deviation from the study protocol and original analysis plan. Possible publication sites include a medical journal, or a publicly available web-site.
4. Enable opportunities to replicate HETE studies (i.e., for other researchers to be able to reproduce the same findings using the same data set and analytic approach). The ISPE companion paper lists information that should be reported in order to make the operational and design decisions behind a RWD study transparent enough for other researchers to reproduce the conduct of the study.
5. Perform HETE studies on a different data source and population than the one used to generate the hypotheses to be tested unless it is not feasible (e.g., another data set is not available)
6. Authors of the original study should work to publicly address methodological criticisms of their study once it is published.
7. Include key stakeholders (patients, caregivers, clinicians, clinical administrators, HTA/payers, regulators, manufacturers) in designing, conducting, and disseminating HETE studies.

JAMA Internal Medicine | Original Investigation

Use of Health Care Databases to Support Supplemental Indications of Approved Medications

Michael Fralick, MD; Aaron S. Kesselheim, MD, JD, MPH; Jerry Avorn, MD; Sebastian Schneeweiss, MD, ScD

- **Comparison of Ramipril to Telmisartan that was previously studies in RCT - ONTARGET**
- **Methods**
  - **New user, active comparator**
  - **Propensity score matching after adjusting for 73 patient characteristics**
  - **Sensitivity assay using angioedema outcome comparison**
- **Results: "As seen in ONTARGET, the composite risk of MI, stroke, hospitalization heart failure was similar for the 2 medications"**
- **…But does not include death, which can include out of hospital MI**

Invited Commentary

Comparison of Observational Data and the ONTARGET Results for Telmisartan Treatment of Hypertension

Bull's-eye or Painting the Target Around the Arrow?

Robert M. Califf, MD

The study by Fralick et al is valuable and technically excellent; however, it examines only 1 drug indication pair of many. Thus, it is open to the criticism that generalizing from positive finding to a vast field of potential treatment comparisons with observational data is analogous to painting the target around the arrow, especially considering the high probability that the telmisartan-ramipril comparison would work.

RCT Duplication Demonstration Projects

- **Substantial assessment of the comparability of randomized and non-randomized designs necessary to gain confidence that non-interventional designs could provide credible evidence of drug effect**
  - **Comparable results with similar clinical questions?**
  - **Reasons for differences?**
- **Retrospective replication: 40 trials -> approximately 30**
- **Goal: approximately 30 retrospective trial replications completed by March 2020**

https://www.rctduplicate.org/

Demonstration Project: Assessment of Non-Interventional Designs (2)

FDA Expands Real-World Evidence Partnership with Brigham and Women's Hospital and Aetion

RCT DUPLICATE adds new studies to inform FDA - the first to use real-world evidence to predict treatment safety and efficacy

Using the same methods, duplicate the results of 7 additional studies in advance of the RCT results

https://www.rctduplicate.org/

Implementation Process

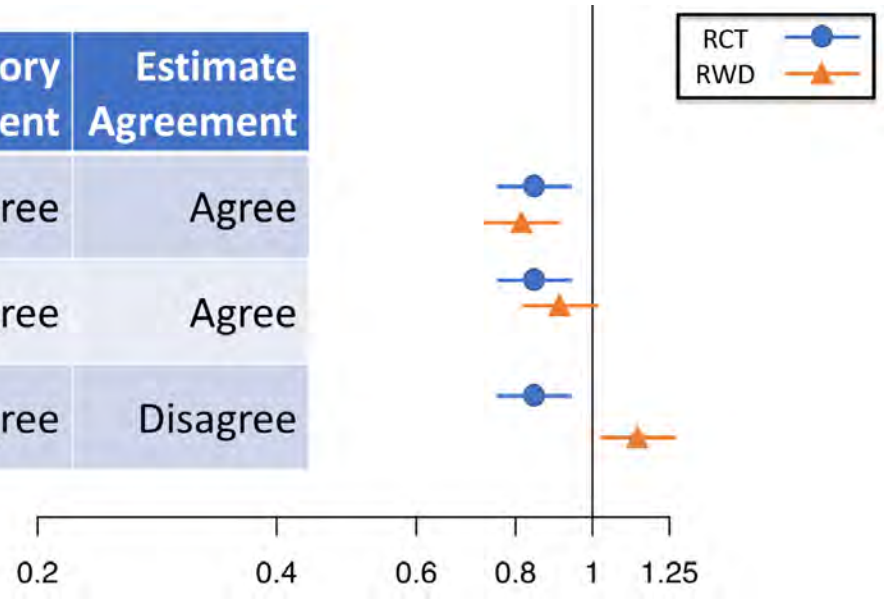
1. Prospective engagement with FDA during protocol development and initial feasibility and power calculations
2. FDA review of final definitions of cohort identification, exposure, outcome, and covariates
3. While blind to differential outcome, final power analyses and covariate balance checks are completed – joint go/no go decision
4. Study protocol registered on ClinicalTrials.gov
5. Analyze outcome data and calculate effect measures
6. Document findings
7. Apply prespecified measures of agreement
8. Audit trail visible to FDA throughout the process – FDA sub-team may at its option engage in additional post-hoc sensitivity analyses for training purposes

Real World Data Sources

- Early logistical decision that replication of large amount of trials with a short timeline would benefit from the highly structured nature of claims
- FDA does not endorse a specific type of Real World Data
- Retrospective
  - Optum© Clinformatics® Data Mart from 2004 through September 2017
  - Truven MarketScan from 2006 through December 2017
  - Medicare Parts A, B, and D across varying time ranges for select therapeutic areas with continuing data accrual
  - No Laboratory Values
- Prospective
  - will include Laboratory values if needed for endpoint

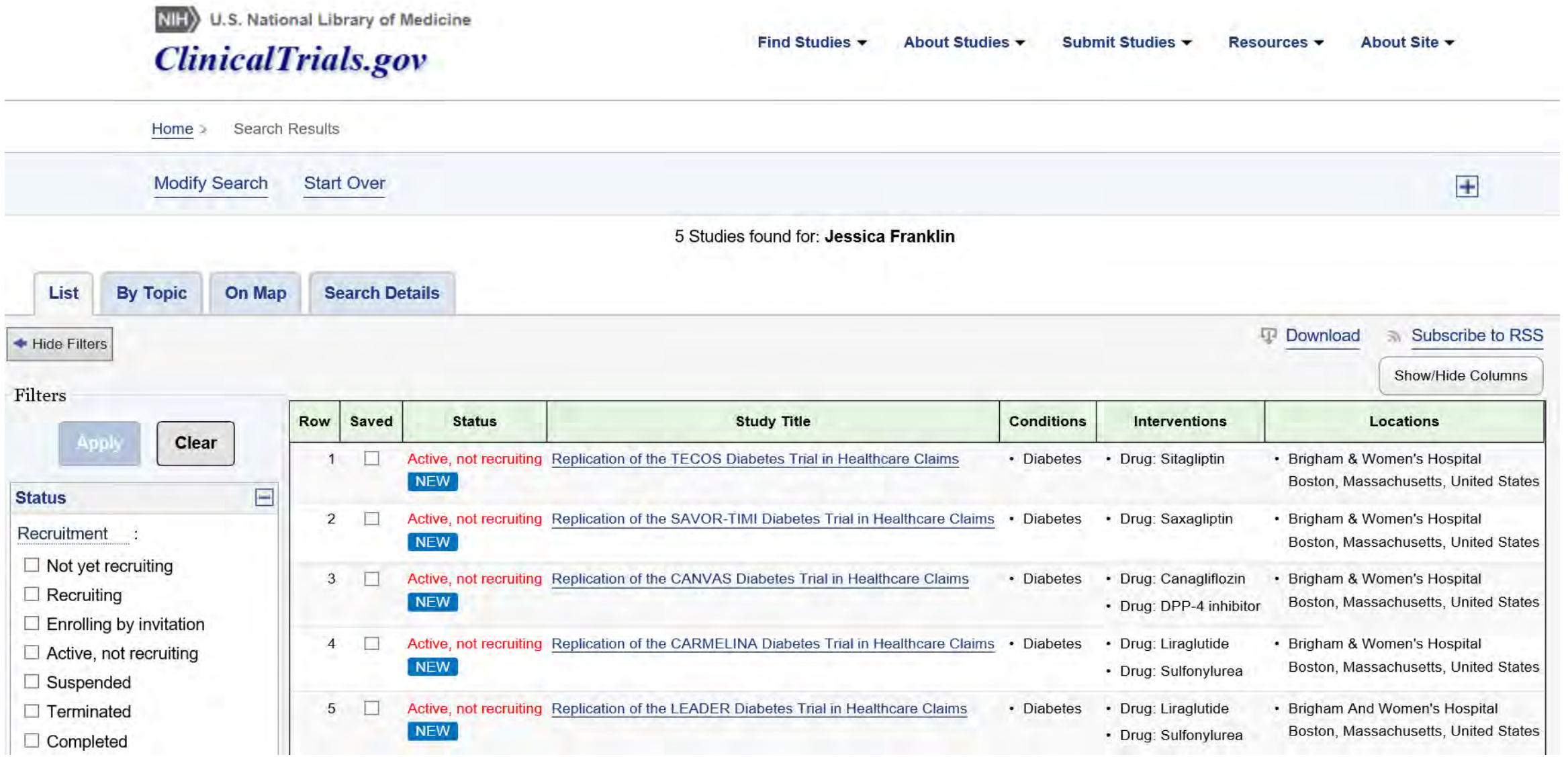
Evaluating Agreement

Regulatory Agreement	Estimate Agreement
Agree	Agree
Disagree	Agree
Disagree	Disagree



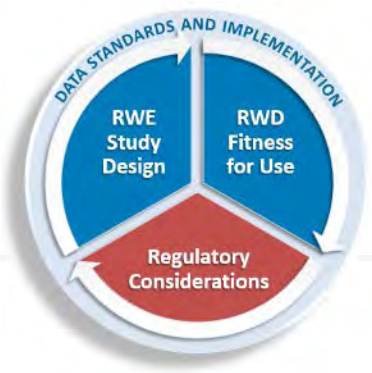
- **"Regulatory Decision" Agreement (RA): RWD study would have come to the same conclusion as RCT based on statistical significance of effect estimate**
  - **Same significance finding (reject / do not reject H_0)**
  - **Same non-inferiority margin required when applicable**
- **Estimate Agreement (EA): RWD effect estimate lies within the 95% CI from the RCT**

Duplications Underway

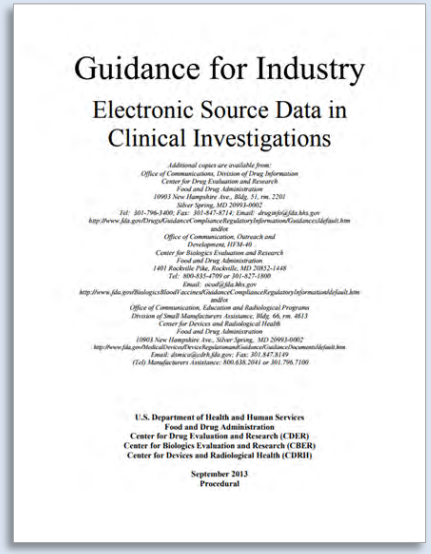


Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	☐	Active, not recruiting NEW	Replication of the TECOS Diabetes Trial in Healthcare Claims	• Diabetes	• Drug: Sitagliptin	• Brigham & Women's Hospital Boston, Massachusetts, United States
2	☐	Active, not recruiting NEW	Replication of the SAVOR-TIMI Diabetes Trial in Healthcare Claims	• Diabetes	• Drug: Saxagliptin	• Brigham & Women's Hospital Boston, Massachusetts, United States
3	☐	Active, not recruiting NEW	Replication of the CANVAS Diabetes Trial in Healthcare Claims	• Diabetes	• Drug: Canagliflozin • Drug: DPP-4 inhibitor	• Brigham & Women's Hospital Boston, Massachusetts, United States
4	☐	Active, not recruiting NEW	Replication of the CARMELINA Diabetes Trial in Healthcare Claims	• Diabetes	• Drug: Liraglutide • Drug: Sulfonylurea	• Brigham & Women's Hospital Boston, Massachusetts, United States
5	☐	Active, not recruiting NEW	Replication of the LEADER Diabetes Trial in Healthcare Claims	• Diabetes	• Drug: Liraglutide • Drug: Sulfonylurea	• Brigham And Women's Hospital Boston, Massachusetts, United States

REGULATORY CONSIDERATIONS



Regulatory Considerations

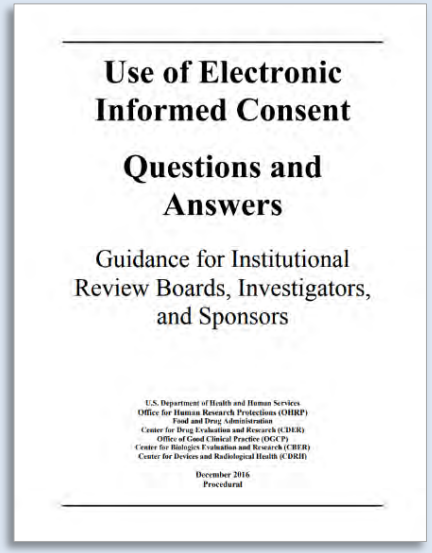


Guidance for Industry

Electronic Source Data in Clinical Investigations

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)
Center for Devices and Radiological Health (CDRH)

September 2013
Procedural

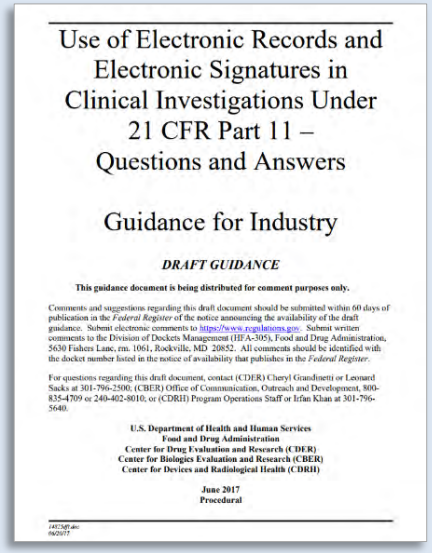


Use of Electronic Informed Consent Questions and Answers

Guidance for Institutional Review Boards, Investigators, and Sponsors

U.S. Department of Health and Human Services
Office for Human Research Protections (OHRP)
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Office of Good Clinical Practice (OGCP)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

December 2016
Procedural



Use of Electronic Records and Electronic Signatures in Clinical Investigations Under 21 CFR Part 11 – Questions and Answers

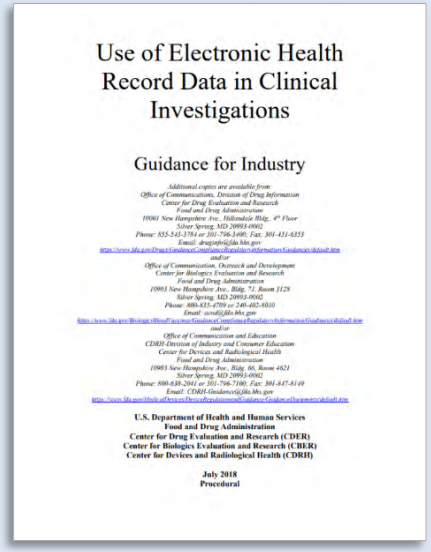
Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

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)
Center for Devices and Radiological Health (CDRH)

June 2017
Procedural



Use of Electronic Health Record Data in Clinical Investigations

Guidance for Industry

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)
Center for Devices and Radiological Health (CDRH)

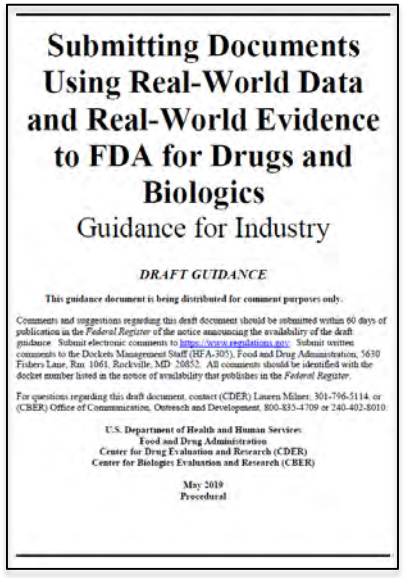
July 2018
Procedural

PROGRAM ITEMS:

Develop guidance as needed regarding the applicability of regulatory requirements to use of RWD in RCTs and observational studies, including informed consent and oversight

Assess whether current guidance documents on the use of electronic source data are sufficient

Identifying Submissions Using RWD and RWE



Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics

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, contact (CDER) Lauren Milner, 301-796-5114, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

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)

May 2019
Procedural

- **Published May 2019**
- **Comment period closes July 8, 2019**

- **Identify RWE being used as part of a regulatory submission in cover letter or table**
- **Provide information on the use of RWE in a simple, uniform format**
- **Internal tracking only**

Purpose(s) of Using RWE as Part of the Submission (Select all that apply)
☐ Provide evidence in support of efficacy or safety for a new product approval
☐ Support labeling changes for an approved drug
☐ Add or modify an indication
☐ Change in dose, dose regimen, or route of administration
☐ Use in a new population
☐ Add comparative effectiveness information
☐ Add safety information
☐ Other labeling change. Specify:
☐ Use as part of a postmarketing requirement to support a regulatory decision
Study Design(s) Using RWE (Select all that apply)
☐ Randomized clinical trial
☐ Single arm trial
☐ Observational study
☐ Other study design. Specify:
RWD Source(s) Used to Generate RWE (Select all that apply)
☐ Data derived from electronic health records
☐ Medical claims and/or billing data
☐ Product and/or disease registry data
☐ Other data source that can inform health status. Specify:

LINK to Guidance: https://www.fda.gov/media/124795/download

DATA STANDARDS AND IMPLEMENTATION

Data Standards and Implementation

FDA

Identify **gaps** between RWD/ RWE data standards and existing systems

Identify and assess data standards and implementation strategies **required** to use RWD/ RWE

Collaborating with Stakeholders to adopt or develop standards and implementations strategies

RWD Submission Standard


Internal educational program to promote shared learning
Continue to host public meetings for stakeholder engagement
Consider mechanisms and standards to assess RWD quality
Identify additional topics where guidance development may be needed
Evaluate situations in which observational studies can be used
Collect and Analyze Use-Cases
U.S. FOOD & DRUG
FRAMEWORK FOR FDA'S
REAL-WORLD EVIDENCE PROGRAM

U.S. FOOD & DRUG ADMINISTRATION

CDERMedicalPolicy-RealWorldEvidence@fda.hhs.gov


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Real-world evidence: Utility and clinical decision support

Elad Sharon, MD, MPH
Senior Investigator/Medical Officer
Cancer Therapy Evaluation Program
Division of Cancer Therapy & Diagnosis
National Cancer Institute

NIH NATIONAL CANCER INSTITUTE

National Cancer Institute

Disclosures

- Nothing to Disclose

National Cancer Institute

RWD: What is it?

RWD is data on health care that is derived from multiple sources outside typical clinical research settings, including electronic health records (EHRs), claims and billing data, product and disease registries, and data gathered through personal devices and health applications

National Cancer Institute

Types of Evidence: Efficacy, Effectiveness…

- Clinical Efficacy:
  - Performance of an intervention under ideal and controlled circumstances
- Clinical Effectiveness:
  - Performance under real-world conditions
- Efficacy and Effectiveness can be thought of as a continuum rather than a dichotomy

Singal AG, Higgins PD, Waljee AK. *Clin Transl Gastroenterol.* 2014

National Cancer Institute

… & Efficiency

- Efficiency is an economic concept which relates efficacy and effectiveness to resource use
- Assessment of efficiency is concerned with whether acceptable efficacy and effectiveness are achieved with the most prudent or optimal mix or resources

Mackenzie R, Dixon AK. *Clin Radiol.* 1995

National Cancer Institute

Why do we need RWD/RWE?

- Rapidly find patients with characteristics required to answer a potential clinical question and or the specific effectiveness for patients with a specific:
  - Treatment History
  - Past Medical History
  - Range of demographics
  - Range of geographies (e.g. rural/urban)
- Rapidly identify potential sites/investigators for clinical trials
- Saving time and money for manufacturers, clinical trial sponsors, healthcare providers, researchers, & patients
- Potential to identify additional “off-label” uses for approved drugs

FDA News Release

FDA approves first cancer treatment for any solid tumor with a specific genetic feature

For Immediate Release May 23, 2017

Release

The U.S. Food and Drug Administration today granted accelerated approval to a treatment for patients whose cancers have a specific genetic feature (biomarker). This is the first time the agency has approved a cancer treatment based on a common biomarker rather than the location in the body where the tumor originated.

Keytruda (pembrolizumab) is indicated for the treatment of adult and pediatric

Inquiries

Media

Angela Stark
301-796-0397

Consumers

888-INFO-FDA

Related Information

- FDA: Office of Hematology and Oncology Products
- FDA: Approved Drugs: Questions and Answers

National Cancer Institute

One FDA approval, A Giant Set of Questions for the Clinician

- Which MSI test is best?
- Does the efficacy shown in trials predict real-world effectiveness?
- Various tumors included in trials with a tissue-agnostic approval
  - Is clinical effectiveness the same in each tumor type?
  - Do divergent populations respond similarly? (i.e. comorbidities, geography, socioeconomic status)

National Cancer Institute

Possible Areas Questions to ask RWD

- What is the appropriate duration of PD1/PDL1 therapy?
  - Most trials have given therapy for up to two years – could this be decreased?
- Which comorbidities would preclude potential treatment? Which comorbidities are safe?
  - Should ESRD and patients with liver dysfunction expect the same results?
  - How do these conditions affect the duration of therapy for these patients?
  - Should trials be expanded to broaden inclusion criteria for these widely used therapies?
    - Should those patients be informed of their specific risks?
- Are there rare sub-populations we can study?

National Cancer Institute

Sequencing Trials and Dosing Issues

- For diseases like BRAF-mutant melanoma, could real world data provide suggestions as to the appropriate sequencing of therapy? (BRAF/MEK inhibitors vs. PD1/CTLA4 inhibitors)?
  - NCI-sponsored clinical trial EA6134 to answer that question
- What doses are actually being used in the real world
  - Do clinicians use FDA-approved doses, or does expert opinion, other trial data, use in other settings come to play?

National Cancer Institute

Real World Data Can Enhance Drug Development

- Retrospective analysis of real world data (duration of therapy and its relation to OS) could help guide trials in other cancers and other settings
- Are novel combinations are being missed? Can real world data point us toward or away from certain strategies?

National Cancer Institute

Limitations of RWD

- Thousands of real-world data systems (EHRs, claims data, etc.)
- Have to optimize one-by-one
- Rare cancers (or sub-populations) still difficult to curate
- Unmeasured bias impossible to deconvolute
  - Does sequencing of therapy reflect bias among investigators?

National Cancer Institute

In an ideal world (of real world data)

- Thousands of real world data systems would be accessible to researchers
- Secure
- Privacy protected / data de-identified
- Sources would retain ownership and control of raw data
- Crosses demographics, geography, rural/urban, etc.
- Mechanisms to get rapid answers to research questions from pools of millions of patients
- Population-based data

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Limited groups of connected RWD systems

- Different networks use various sources of healthcare and research data.
- Creation of different mini-networks for research
- Allows researcher to query (ask question) and simultaneously, receive results from many different sources.

BUT: Each network communicates with different agreed upon methods: "Common Data Model"

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Two Possible Strategies for Use of RWD

- Going Deep
- Going Broad

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Two Possible Strategies for Use of RWD

- Going Deep
- Going Broad

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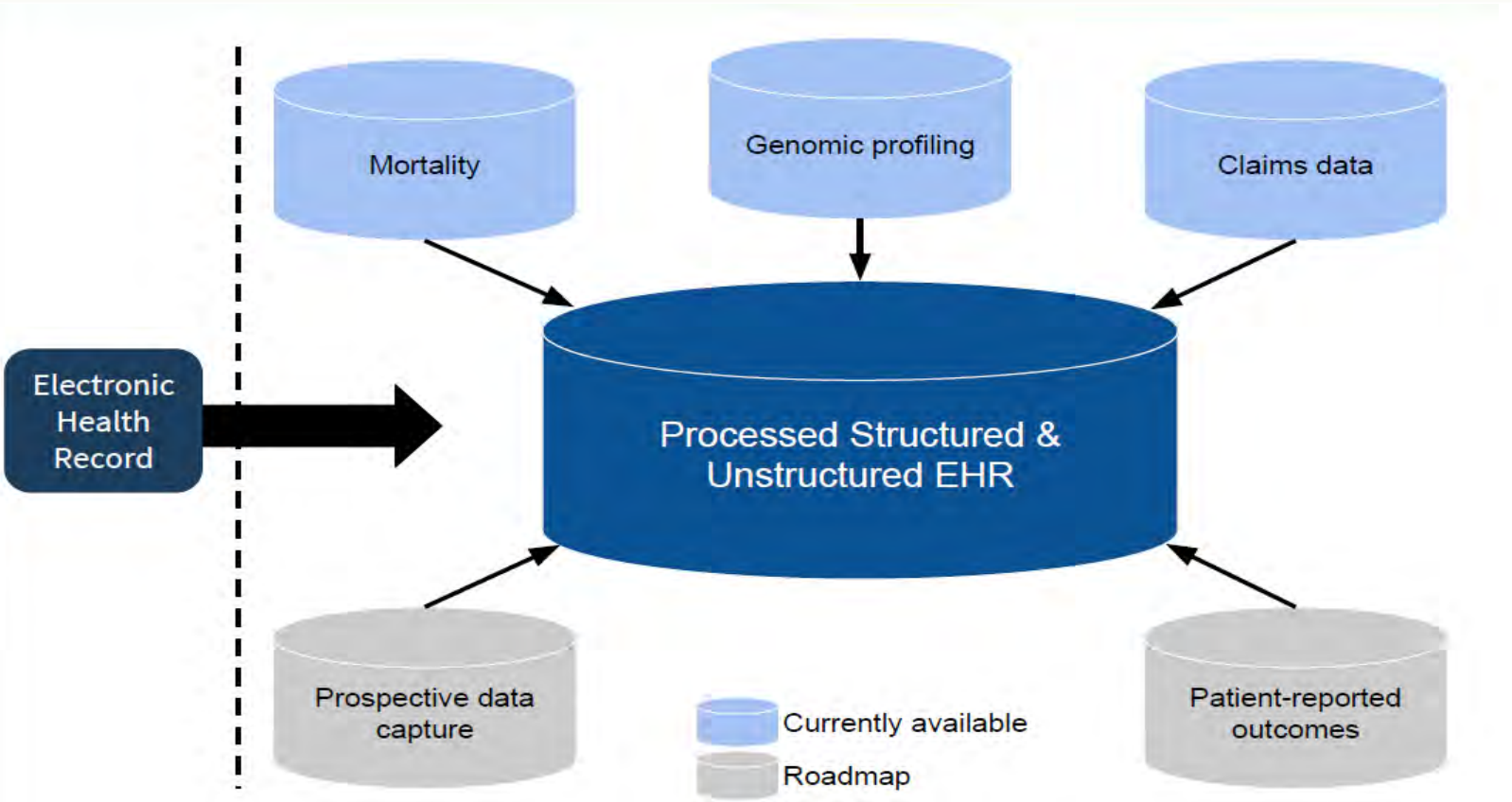
Links Across Data Sources



Source: National Cancer Policy Forum: The Drug Development Paradigm in Oncology: A Workshop, December 2016

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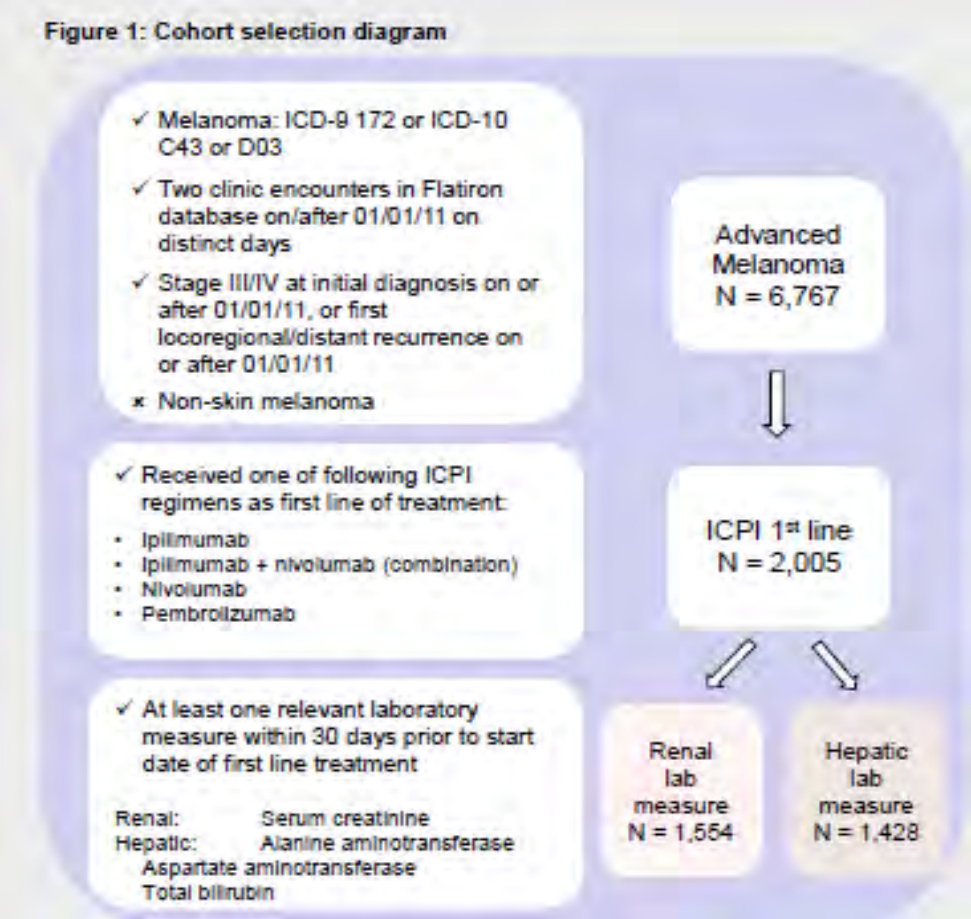
How do I treat the patient in front of me?



Spillane, S. ASCO 2018

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Renal Dysfunction in aMEL

Figure 2a: Overall survival by baseline renal function

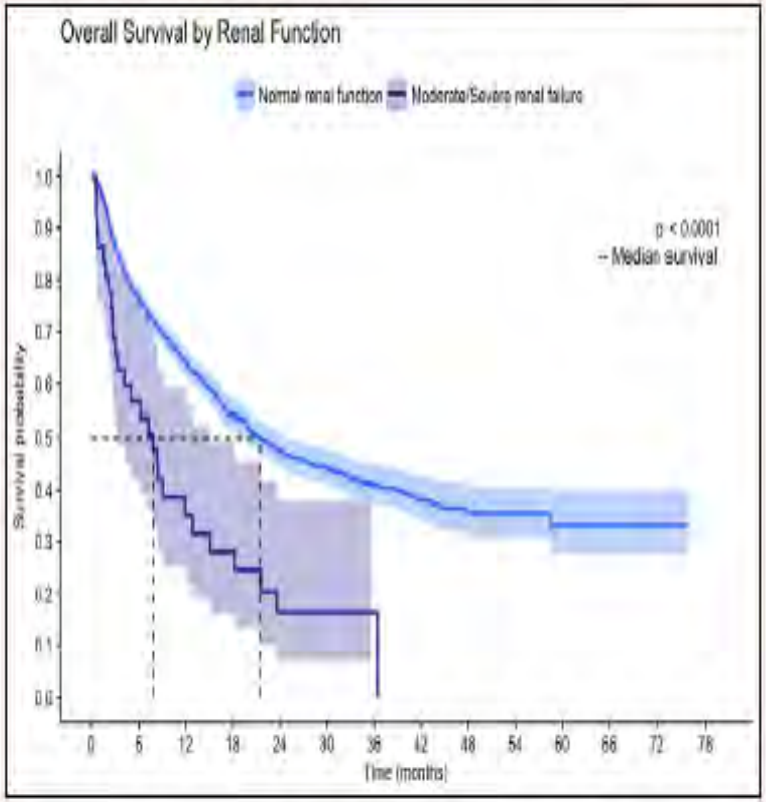
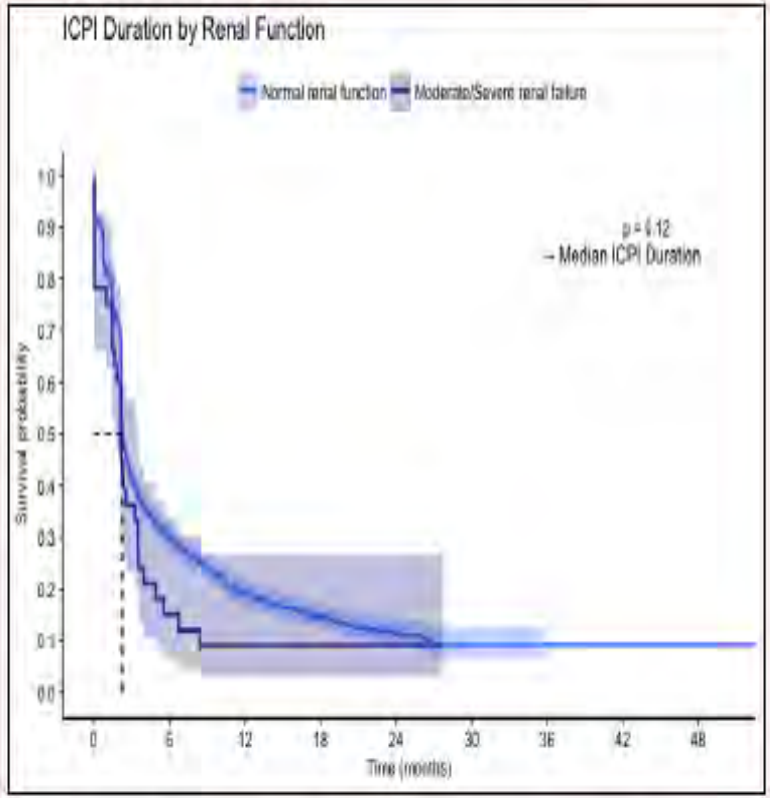


Figure 2b: ICPI duration by baseline renal function



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Hepatic Dysfunction in aMEL

Figure 3a: Overall survival by baseline hepatic function

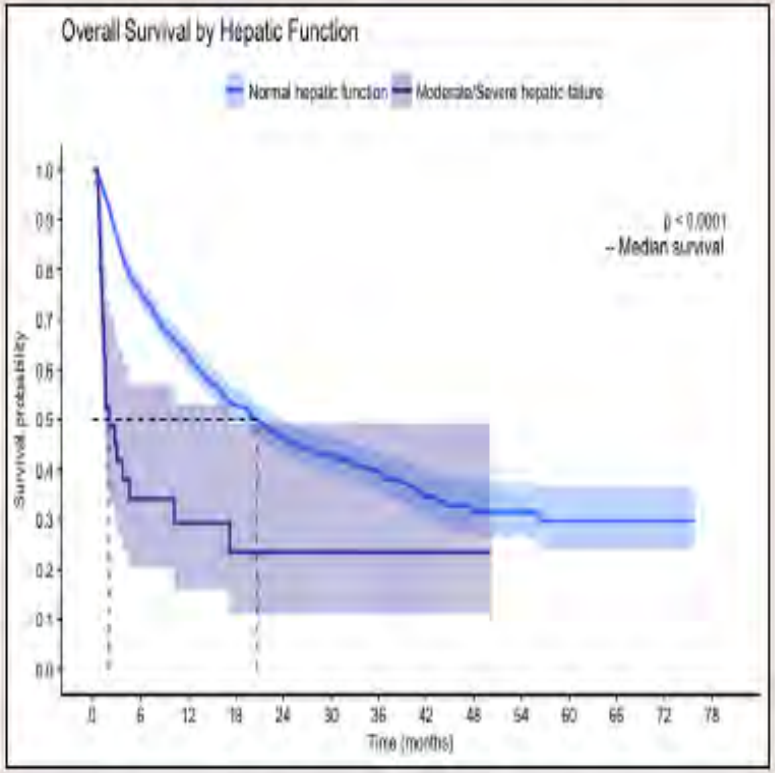
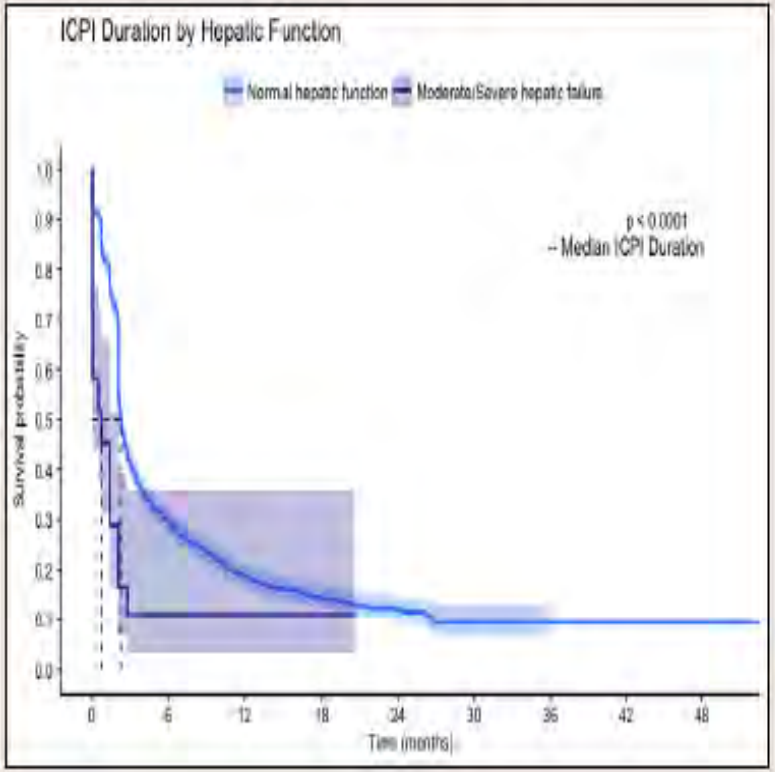


Figure 3b: ICPI duration by baseline hepatic function



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Going Deep is Iterative and Scalable

Table 2a. Renal Function Analysis: Unadjusted Median Estimates for Disease Outcomes, months (95% CI)

	aGastric		aH&N		aMelanoma		aNSCLC		mRCC		All Tumors	
	OS	rwTTD	OS	rwTTD	OS	rwTTD	OS	rwTTD	OS	rwTTD	OS	rwTTD
Normal	4.6 (3.7, 6.0)	2.1 (2.1, 2.8)	8.7 (7.9, 9.7)	3.2 (2.8, 3.5)	15.9 (14.0, 19.2)	2.3 (2.2, 2.6)	9.6 (9.2, 10.1)	3.7 (3.5, 3.9)	15.3 (13.4, 19.9)	4.1 (3.7, 4.8)	10.2 (9.8, 10.6)	3.4 (3.2, 3.5)
Mild	4.6 (3.0, NR)	1.6 (1.3, NR)	7.6 (5.7, 12.4)	3.0 (2.3, 4.5)	15.0 (9.0, 24.6)	2.4 (2.1, 3.5)	10.3 (9.1, 11.1)	3.7 (3.2, 4.1)	18.3 (15.0, 23.0)	4.6 (4.0, 6.0)	11.4 (10.8, 12.5)	3.6 (3.2, 4.1)
Moderate	2.3 (0.2, NR)	0.0 (0.0, NR)	11.4 (5.4, NR)	5.6 (3.2, 9.8)	5.8 (2.0, 12.9)	2.1 (1.4, 3.5)	9.6 (7.0, 13.2)	3.4 (3.2, 4.6)	11.6 (8.2, 19.2)	4.1 (2.7, 5.0)	9.8 (8.0, 11.8)	3.4 (3.1, 4.1)
Severe	NR (NR, NR)	NR (NR, NR)	4.0 (3.6, NR)	3.0 (1.6, NR)	NR (8.1, NR)	NR (1.4, NR)	8.2 (2.6, 17.0)	1.4 (0.9, 9.6)	10.6 (7.5, NR)	3.7 (2.8, NR)	8.2 (7.4, 15.5)	3.4 (2.1, 7.3)

NR = Not reached

Table 2b. Hepatic Function Analysis: Unadjusted Median Estimates for Disease Outcomes, months (95% CI)

	aGastric		aH&N		aMelanoma		aNSCLC		mRCC		All Tumors	
	OS	rwTTD	OS	rwTTD	OS	rwTTD	OS	rwTTD	OS	rwTTD	OS	rwTTD
Normal	6.0 (5.0, 6.8)	2.8 (2.1, 3.3)	8.9 (8.1, 10.1)	3.4 (3.0, 3.7)	17.7 (15.0, 20.7)	2.6 (2.3, 2.8)	10.3 (9.8, 10.7)	3.9 (3.7, 4.1)	16.0 (13.9, 19.3)	4.4 (4.0, 5.0)	11.0 (10.6, 11.3)	3.7 (3.4, 3.7)
Mild	2.3 (1.7, 3.2)	0.9 (0.7, 1.9)	6.3 (4.1, 9.0)	2.1 (1.4, 4.8)	7.7 (4.8, 11.7)	2.0 (1.4, 2.1)	6.8 (5.7, 7.6)	2.8 (2.4, 3.0)	16.9 (10.5, 21.7)	3.5 (2.8, 4.8)	6.9 (6.1, 7.7)	2.3 (2.3, 2.8)
Moderate	1.2 (1.1, NR)	0.7 (0.0, NR)	2.8 (1.3, NR)	1.4 (0.9, NR)	2.7 (1.4, 20.2)	1.4 (0.7, 2.9)	2.5 (1.5, 4.9)	1.4 (0.5, 2.9)	8.5 (6.9, NR)	3.2 (0.7, 6.9)	3.1 (2.0, 5.7)	1.4 (0.9, 2.3)
Severe	0.6 (0.2, NR)	0.0 (0.0, NR)	2.5 (1.2, NR)	1.4 (0.9, NR)	4.3 (2.5, NR)	1.4 (0.7, NR)	1.4 (0.5, 5.4)	0.2 (0.0, 1.4)	6.7 (1.7, NR)	2.7 (0.0, NR)	2.1 (1.3, 4.3)	0.7 (0.5, 1.4)

NR = Not reached

ICI therapy represents any PD-1/PD-L1 agent (monotherapy) except for the following:

- *Ipilimumab + anti-PD(L)1 therapy: aGastric <1%, aH&N <1%, aMelanoma 24%, aNSCLC <1%, mRCC 17%*
- *ICI + non-ICI therapy: aGastric 9%, aH&N 5%, aMelanoma 2%, aNSCLC 20%, mRCC 6%*
- *Single agent ipilimumab: aGastric 0%, aH&N 0%, aMelanoma 28%, aNSCLC <1%, mRCC <1%*

Liu, Q. ASCO 2019

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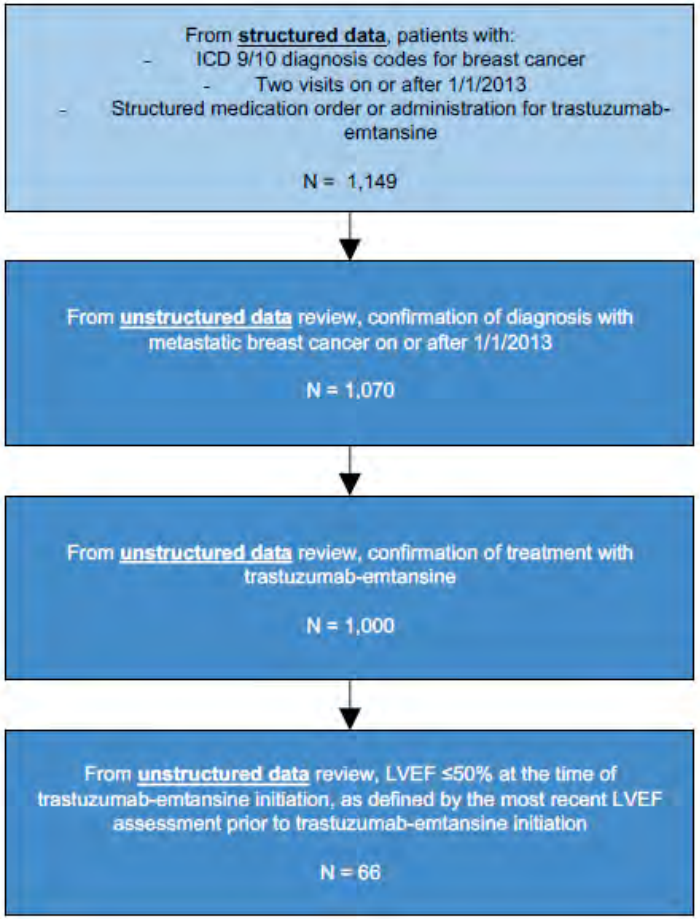
Flatiron low LVEF Use Case



- Maintain a growing curated dataset in mBC
- At time of cohort selection >8,000 cases
- Allowed for the identification of >60 patients who had LVEF ≤50%

Source: National Cancer Policy Forum
The Drug Development Paradigm in Oncology: A Workshop
December 2016

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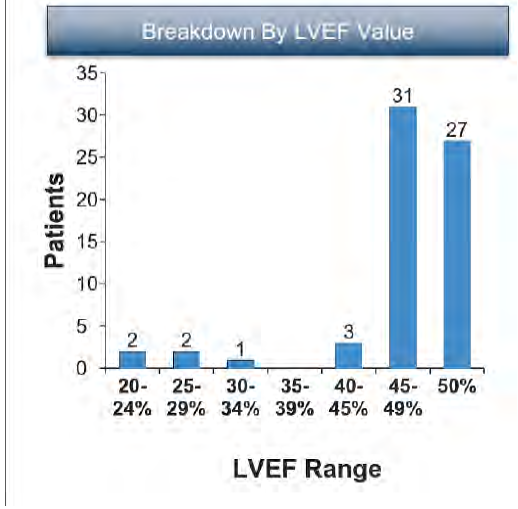
Baseline characteristics

RWE Case Study: Baseline characteristics (N=66)

Age	Median = 62 years	Range 54-70
	65 or over = 39%	
Female	98.5%	
White race	58%	
Stage at diagnosis	I/II/III = 52%	
	IV = 27%	
	Not documented = 21%	
ER/PR	Positive = 65%	
Time from initial diagnosis to Kadcyla initiation	Median = 5.1 years	Range 2.7-11.5
Time from metastatic diagnosis to Kadcyla initiation	Median = 2.3 years	Range 1.2-4.1
Median follow up from index date	Median = 0.8 years	Range 0.5-1.5



Source: National Cancer Policy Forum
The Drug Development Paradigm in Oncology: A Workshop
December 2016

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Going Deep Can Also Inform Policy

REAL WORLD EVIDENCE

HOW A FLATIRON HACKATHON TEAM LINKED MEDICAID EXPANSION WITH REDUCTION IN RACIAL DISPARITIES IN TIME TO CANCER TREATMENT

By Matthew Bin Han Ong

Last December, Flatiron Health convened a "hackathon," an event where programmers, developers, and scientists pitch novel ideas and aggressively crunch data in a competitive sprint.

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Two Possible Strategies for Use of RWD

- Going Deep
- Going Broad

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FOCR Pilot Project 2.0 on RWE

Establishing the Utility of Real-World Endpoints Project Overview

Workflow	Step 1: Standardize Analysis of Real-World Endpoints	Step 2: Data Analyses	Step 3: Public Meeting
Goals	Define real-world endpoints Describe analysis methods for measuring real-world endpoints	Work with partners to develop datasets to assess real-world endpoints definition and methodology Assess quality metrics and propose refinements to real-world endpoint definitions and methodology	Present findings Establish recommendations for real-world endpoint analysis Evaluate whether real-world endpoints are indicators of clinical benefit
Timeframe	February 2019	Spring 2019	September 18, 2019

10 Healthcare research organizations and additional stakeholders participating in this pilot project include:
Aetion, ASCO CancerLinQ, Cancer Research Network, COTA, FDA, Flatiron Health, IQVIA™, Mayo Clinic, McKesson, NCI SEER-Medicare Linked Database, OptumLabs®, Syapse, Tempus

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Possible Limitations of RWE

- Can Efficacy Be Firmly Established in the Absence of a Clinical Trial
- Rare Cancers (or even rare subpopulations with more common cancers) still difficult to study
- Population-based studies lacking
  - (NCI SEER, HDRP Patterns of Care Studies)
- Studying by drug challenging
  - e.g. all patients exposed to pembrolizumab

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Summary

- Big Data and Real World Data has an unrealized potential in optimizing drug development, clinical trials planning, and evaluation of special populations
- NCI and partners at FDA, industry, and academia are searching for ways to optimize this tool to improve outcomes for patients
- Real World Data has challenges as well, with significant limitations in interpreting results

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American Association for Cancer Research

FINDING CURES TOGETHER℠

SESSION II:

Premarket Use Cases

Session Moderator: Pallavi Mishra-Kalyani, PhD

Speakers:

Michael Kelsh, PhD, MPH

William Capra, PhD

Weili He, PhD

USE OF REAL-WORLD EVIDENCE TO ASSESS THE BENEFITS OF NEW THERAPIES IN REGULATORY DECISION-MAKING: A CASE STUDY OF RELAPSED/REFRACTORY ACUTE LEUKEMIA (R/R ALL)

MICHAEL A KELSH, PHD, MPH
EXECUTIVE DIRECTOR, AMGEN
CENTER FOR OBSERVATIONAL RESEARCH (CFOR)

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Presentation Overview

- Considerations for use of RWE in oncology
- Relapsed/Refractory Acute Lymphoblastic Leukemia (R/R ALL) – Blinatumomab Case Study
- Challenges in use of historical controls
- FDA Framework for use of RWE – application in this case study

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The Role of Nonrandomized Trials in the Evaluation of Oncology Drugs

R Simon[1], GM Blumenthal[2], ML Rothenberg[3], J Sommer[4], SA Roberts[5], DK Armstrong[6], LM LaVange[2] and R Pazdur[3]

Although randomized trials provide the most reliable evidence of a drug's safety and efficacy, there are situations where randomized trials are not possible or ethical. In this article we discuss when and how single-arm trials can be used to support full approval of oncology drugs. These include situations in which an unprecedented effect on tumor response is observed in a setting of high unmet medical need, clinical trial patients have been well characterized, enabling a target population to be clearly defined, experience exists in a sufficient number of patients to allow adequate assessment of the risk: benefit relationship, and a proper historical context can be provided for analysis. We also discuss how response rates might be considered predictive of long-term outcomes or clinically meaningful in and of themselves in certain contexts.

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R/R ALL – Blinotumomab: Use of RWE to inform regulatory assessment

Objective - to provide context for the single-arm clinical trial for the approval of blinatumomab in the USA and Europe

Considerations	Low	Likelihood of FDA accepting RWE	High
Medical need	Adequate therapeutic options	...	No adequate therapeutic options
Disease urgency	Non-serious disease	Serious not typically life threatening disease	Serious and life threatening disease
Patient population size	Large population / public health concern	Medium population	Small / rare disease or patient sub-populations
Drug effect size	Small effect	Medium effect	Large, easily measured effect

In development programs with some or all of these characteristics, traditional approaches may not always be appropriate or may be excessively difficult, making RWE more attractive

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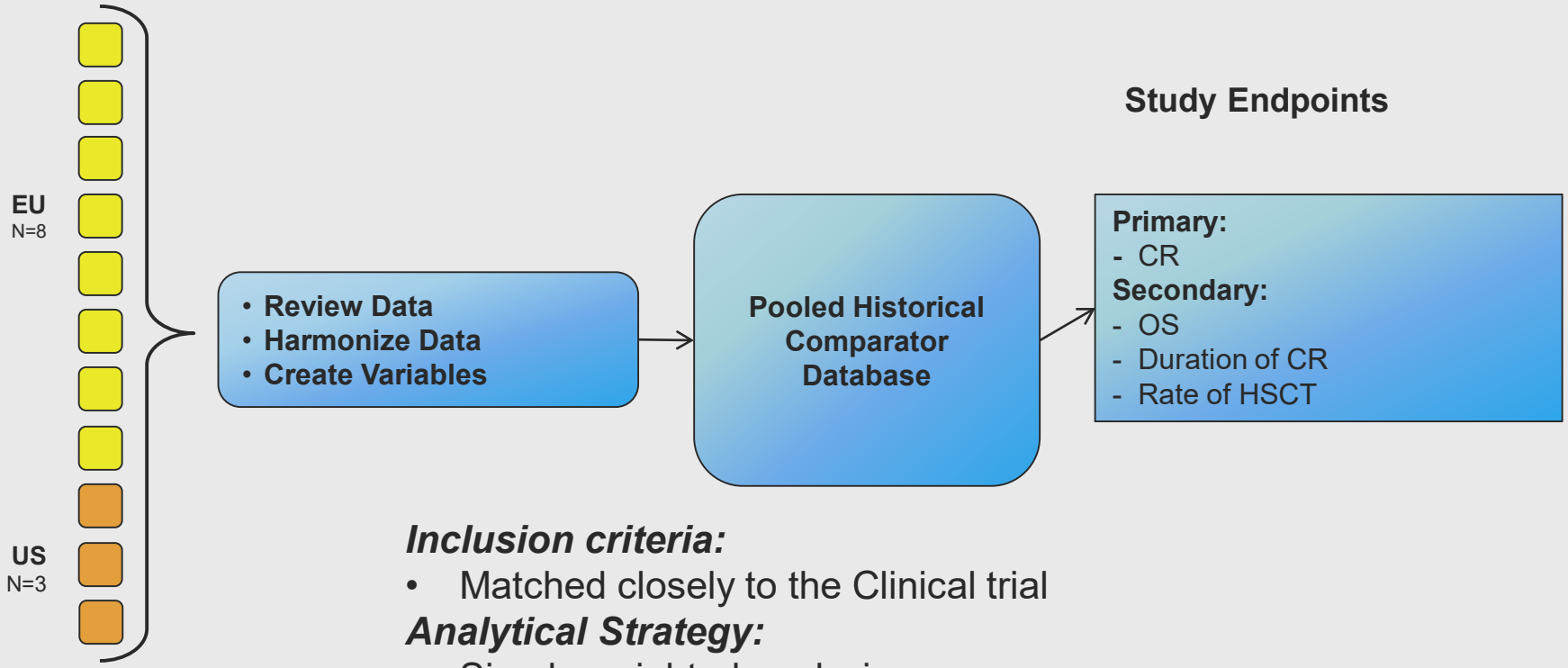
Blinatumomab Case Study - Adult R/R ALL Historical Comparator Study



Inclusion criteria:

- Matched closely to the Clinical trial

Analytical Strategy:

- Simple weighted analysis
- Propensity Score weighted analysis
- Sensitivity analyses

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Many challenges in use of external historical controls – Characteristics/Approaches adopted

- Access to external control data
  - Approach: collaboration with academic centers
- Data definitions – outcomes, exposure, covariates
  - Characteristics: Similar outcome definition (response) used and reported across clinical centers
  - Did not assess safety data
- Study biases
  - Selection – Similar inclusion criteria to clinical trial
  - Confounding – Stratification, Weighting, PS analysis
  - Immortal Time – Exclusion
- Treatment differences: across time, geographic regions
  - Sensitivity Analysis – by calendar time periods, region

Simple Weighted Analysis: Complete Remission (CRsg) among adult ALL Patients from RWD and the Single Arm Blinotumomab Clinical Trial

Stratum	Age at Treatment	Prior lines of Treatment	n/N	Stratum % Observed	Stratum % Observed in Trial	CRsg Proportion (95% CI)
1	<35	alloHSCT	14/48	6.9%	21.2%	0.29 (0.17, 0.44)
2	<35	In 1st salvage	52/119	17.2%	5.3%	0.44 (0.35, 0.53)
3	<35	In 2nd+ salvage	27/150	21.6%	21.2%	0.18 (0.12, 0.25)
4	>=35	alloHSCT	11/41	5.9%	12.7%	0.27 (0.14, 0.43)
5	>=35	In 1st salvage	57/187	27.0%	10.1%	0.30 (0.24, 0.38)
6	>=35	In 2nd+ salvage	25/149	21.5%	29.6%	0.17 (0.11, 0.24)
Weighted estimate for historical data						**0.24 (0.20, 0.27)**
Clinical trial data*						**0.43 (0.36, 0.50)[1]**

n = number of patients achieving CRsg, N = number of patients evaluated for CRsg

- Topp et al. Lancet Oncology 2015;16:57-66.
- 1. CR/CRh* 2. CR

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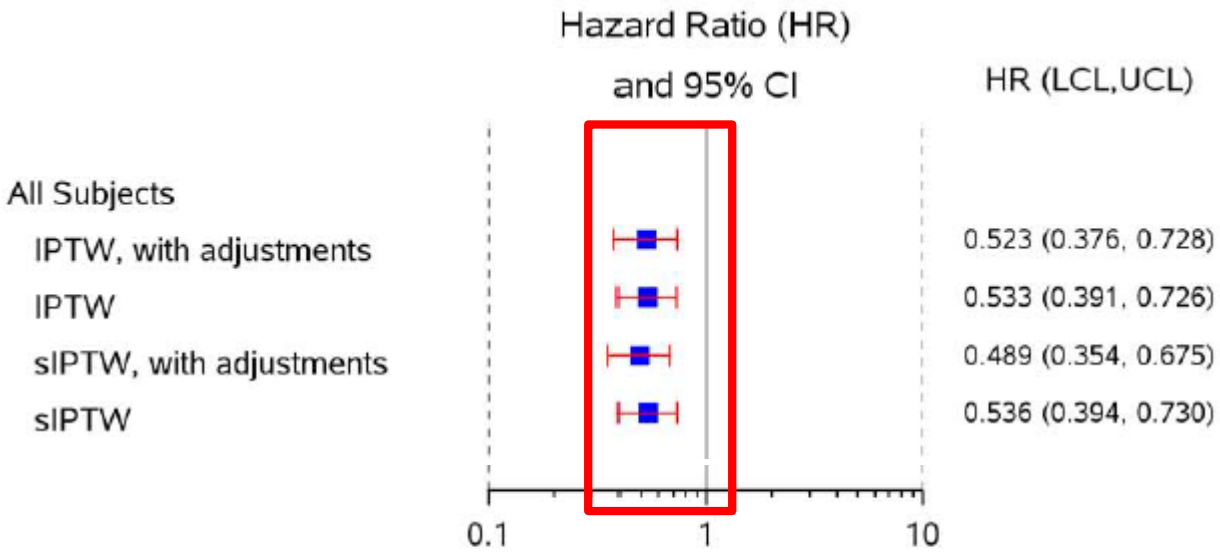
Propensity Score Analysis: Hazard Ratios show evidence of survival benefit among Blinatumomab patients



IPTW=Inverse probability of treatment weighting. sIPTW=Stabilized inverse probability of treatment weighting.

Historical Control Data - Publications in 2016

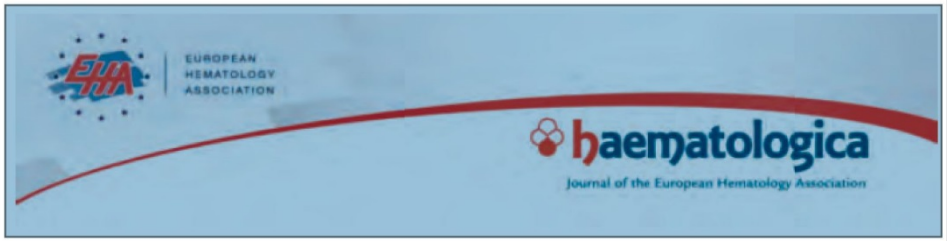
ORIGINAL ARTICLE

Blinatumomab vs historical standard therapy of adult relapsed/refractory acute lymphoblastic leukemia

N Gökbuget[1], M Kelsh[2], V Chia[2], A Advani[3], R Bassan[4], H Dombret[5], M Doubek[6], AK Fielding[7], S Giebel[8], V Haddad[9], D Hoelzer[1], C Holland[10], N Ifrah[11], A Katz[2], T Maniar[12], G Martinelli[13], M Morgades[14], S O'Brien[15], J-M Ribera[14], JM Rowe[16], A Stein[17], M Topp[18], M Wadleigh[19] and H Kantarjian[15]

We compared outcomes from a single-arm study of blinatumomab in adult patients with B-precursor Ph-negative relapsed/refractory acute lymphoblastic leukemia (R/R ALL) with a historical data set from Europe and the United States. Estimates of complete remission (CR) and overall survival (OS) were weighted by the frequency distribution of prognostic factors in the blinatumomab trial. Outcomes were also compared between the trial and historical data using propensity score methods. The historical cohort included 694 patients with CR data and 1112 patients with OS data compared with 189 patients with CR and survival data in the blinatumomab trial. The weighted analysis revealed a CR rate of 24% (95% CI: 20–27%) and a median OS of 3.3 months (95% CI: 2.8–3.6) in the historical cohort compared with a CR/CRh rate of 43% (95% CI: 36–50%) and a median OS of 6.1 months (95% CI: 4.2–7.5) in the blinatumomab trial. Propensity score analysis estimated increased odds of CR/CRh (OR = 2.68, 95% CI: 1.67–4.31) and improved OS (HR = 0.536, 95% CI: 0.394–0.730) with blinatumomab. The analysis demonstrates the application of different study designs and statistical methods to compare novel therapies for R/R ALL with historical data.

Blood Cancer Journal (2016) **6,** e473; doi:10.1038/bcj.2016.84; published online 23 September 2016



International reference analysis of outcomes in adults with B-precursor Ph-negative relapsed/refractory acute lymphoblastic leukemia

by Nicola Gökbuget, Hervè Dombret, Jose-Maria Ribera, Adele K. Fielding, Anjali Advani, Renato Bassan, Victoria Chia, Michael Doubek, Sebastian Giebel, Dieter Hoelzer, Norbert Ifrah, Aaron Katz, Michael Kelsh, Giovanni Martinelli, Mireia Morgades, Susan O'Brien, Jacob M. Rowe, Julia Stieglmaier, Martha Wadleigh, and Hagop Kantarjian

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Nearly Two Years Later the Phase 3 Study is Published

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia

Hagop Kantarjian, M.D., Anthony Stein, M.D., Nicola Gökbuget, M.D., Adele K. Fielding, M.B., B.S., Ph.D., Andre C. Schuh, M.D., Josep-Maria Ribera, M.D., Ph.D., Andrew Wei, M.B., B.S., Ph.D., Hervé Dombret, M.D., Robin Foà, M.D., Renato Bassan, M.D., Önder Arslan, M.D., Miguel A. Sanz, M.D., Ph.D., Julie Bergeron, M.D., Fatih Demirkan, M.D., Ewa Lech-Maranda, M.D., Ph.D., Alessandro Rambaldi, M.D., Xavier Thomas, M.D., Ph.D., Heinz-August Horst, M.D., Ph.D., Monika Brüggemann, M.D., Wolfram Klapper, M.D., Ph.D., Brent L. Wood, M.D., Ph.D., Alex Fleishman, M.S., Dirk Nagorsen, M.D., Ph.D., Christopher Holland, M.S., Zachary Zimmerman, M.D., Ph.D., and Max S. Topp, M.D.

ABSTRACT

BACKGROUND

Blinatumomab, a bispecific monoclonal antibody construct that enables CD3-positive T cells to recognize and eliminate CD19-positive acute lymphoblastic leukemia (ALL) blasts, was approved for use in patients with relapsed or refractory B-cell precursor ALL on the basis of single-group trials that showed efficacy and manageable toxic effects.

METHODS

In this multi-institutional phase 3 trial, we randomly assigned adults with heavily pretreated B-cell precursor ALL, in a 2:1 ratio, to receive either blinatumomab or standard-of-care chemotherapy. The primary end point was overall survival.

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Kantarjian at the Department of Leukemia, University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, or at hkantarjian@mdanderson.org.

N Engl J Med 2017;376:836-47.
DOI: 10.1056/NEJMoa1609783

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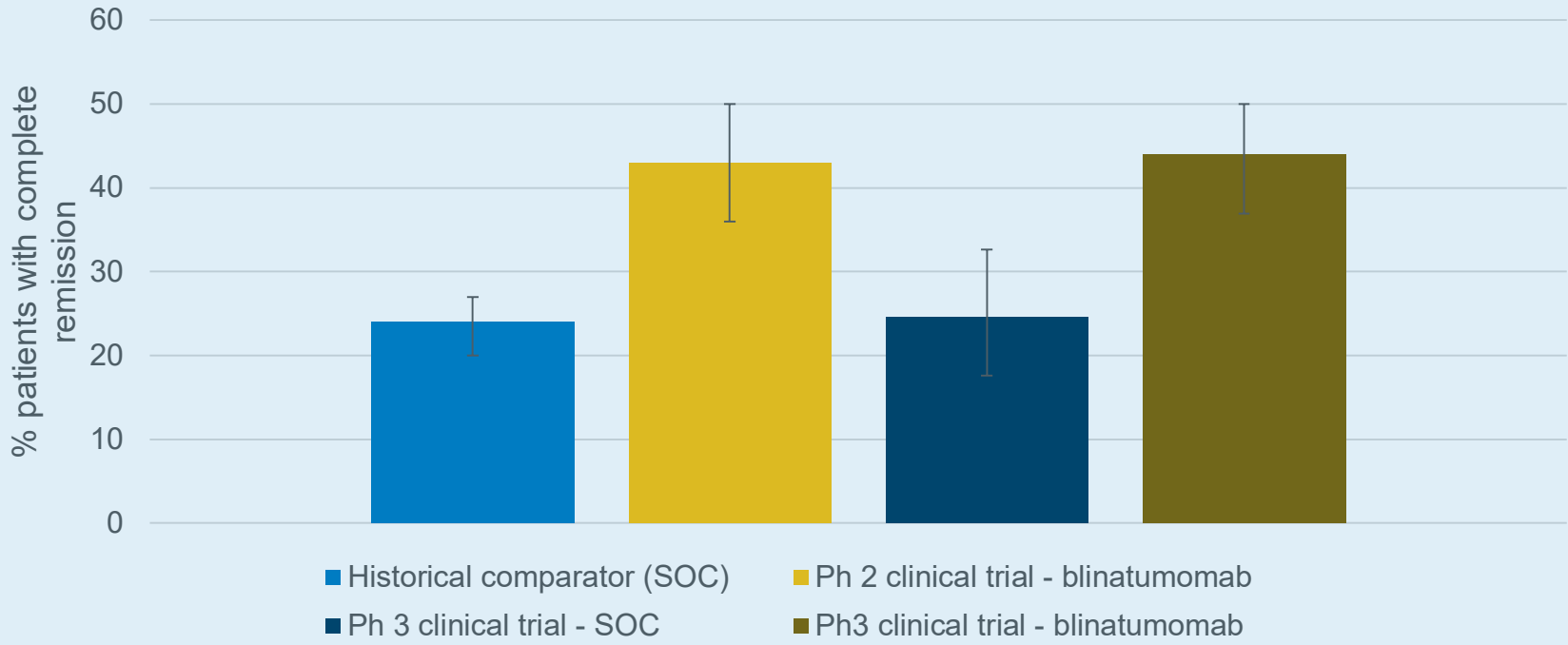
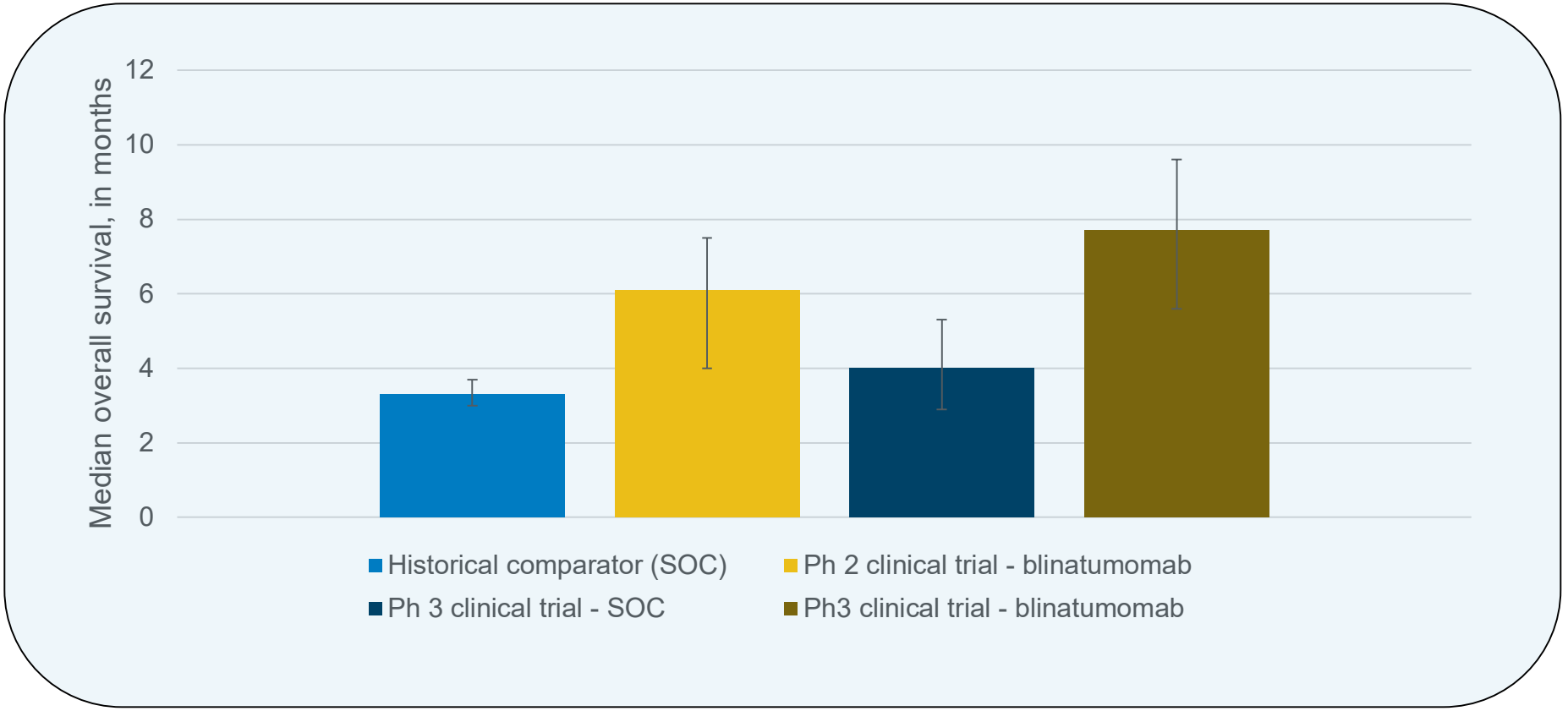
Complete remission in the historical comparator group - confirmed by the Phase 3 clinical trial



Median overall survival in the historical comparator group was confirmed by the Phase 3 clinical trial SOC arm



Blinatumomab Case Study in context of Recent FDA Framework for use of RWE

- Shared learning on use of historical control:
  - Comparable populations
  - Standardized diagnostic criteria, definitions
  - Follow-up
- RWD comes in many forms – in this case clinical "registry-type" data from numerous sites
- RWD fit for purpose, reliable and relevant
- Transparency in data sources, analytical approach:
  - Provided protocol for FDA review
  - Pre-specified analysis plan
  - Sensitivity Analyses
  - Publication intent
- Implications for Phase 3 Studies

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Study Collaborators

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  - Hôpital Saint-Louis, Paris, France
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- **Sebastian Giebel**
  - Maria Sklodowska Curie Memorial Cancer Center and Institute of Oncology, Gliwice, Poland

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  - Dana Farber Cancer Institute, Boston, Massachusetts
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  - H. Germans Trias I Pujol, Barcelona, Spain
- **Jacob M Rowe**
  - Rambam Medical Center, Haifa, Israel
- **Victoria Chia, Aaron Katz, Michael Kelsh, Julia Steiglmaier**
  - Amgen

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Premarket Use Cases for Real World Evidence

Using a comparative effectiveness study in support of regulatory and payer submissions – an example from 1L TNBC

Bill Capra, Senior Director RWD Oncology, Genentech

FDA-AACR RWE Workshop, July 17, 2019

Acknowledgement

This regulatory use case example is based upon original research conducted by Tricia Luhn, Stephen Chui, Angela Hsieh, Jingbo Yi, Almut Mecke, Preeti, Bajaj, Waseem Hasnain, Adeline Falgas, Thanh GN Ton, Allison Kurian and presented at EMSO 2018.

Many accepted areas where RWE already used in drug development

Pre-Phase I:

- Understand natural history of disease / frequency of biomarker alteration by tumor type
- Characterize the standard of care used in specific populations
- Understanding disease burden (use of steroids, rate of hospitalizations, etc.)
- Quantify outcomes / establish unmet medical need

Phase I

- Give context to specific AEs in relation to rates of medical claims in a specific population
- Real world outcomes used as benchmark for phase advancement decisions

End of Phase 2:

- Quantify event rate of control arm for sample size calculations
- Calculate expected event timing for operational support for interim / final analysesReg

Submisson:

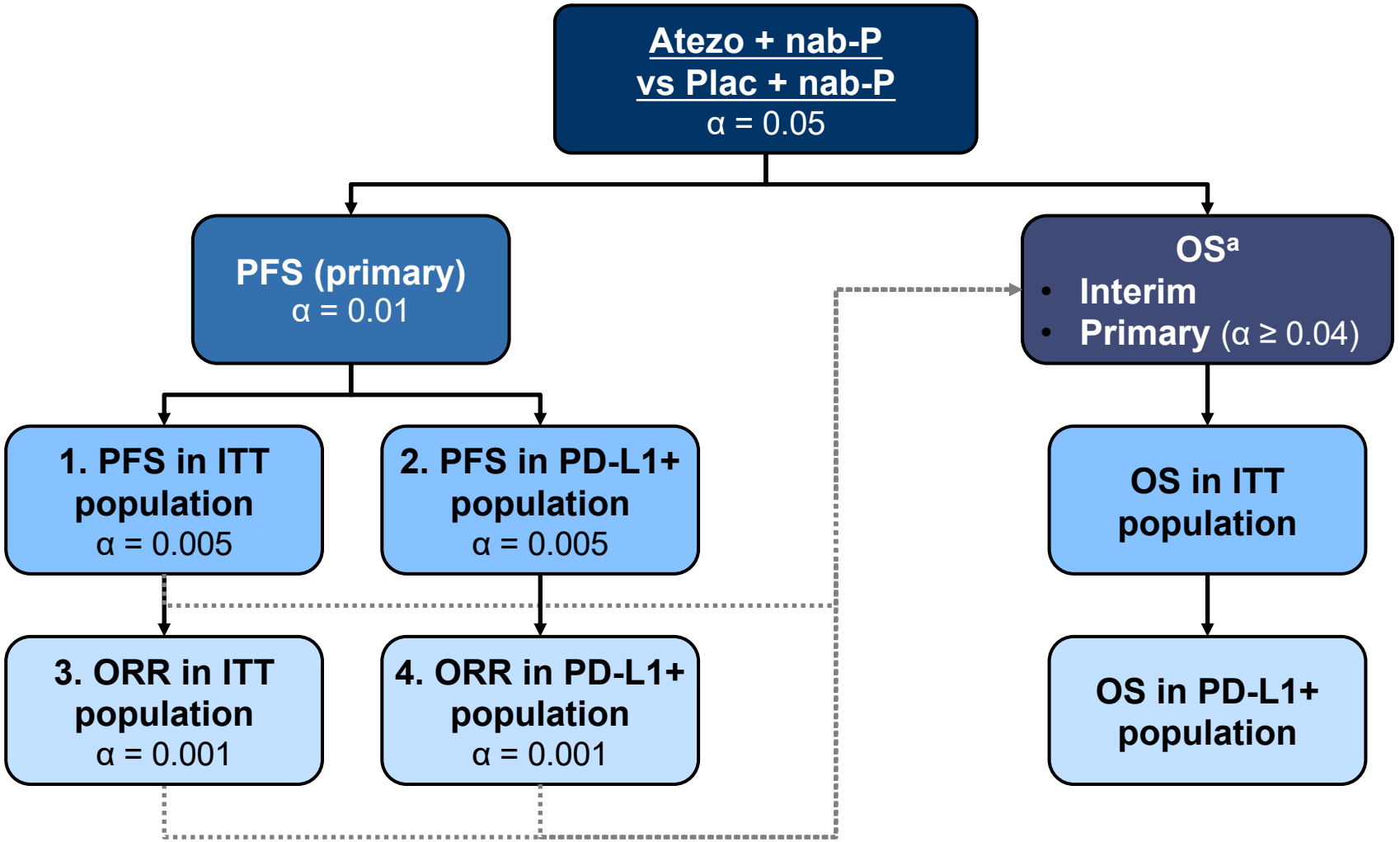
- Real world outcomes used as a reference benchmark in rare tumor types

Case study: RWE to support regulatory and payer submissions

Background

- Patients with advanced or metastatic Triple Negative Breast Cancer (TNBC) experience poor outcomes with a median OS of ≈ 18 months or less
  - No targeted therapies have improved OS to date
- Standard of care first-line treatment typically includes choice of single-agent taxane or anthracycline chemotherapy
  - Nab-paclitaxel not commonly used in 1L setting in EU
- Checkpoint inhibition in combination with chemotherapy may be a useful approach in the treatment of TNBC
  - RCT (IMpassion130) of atezolizumab+nab-paclitaxel vs placebo+nab-paclitaxel unblinded by independent DMC at prespecified analysis based on positive efficacy.

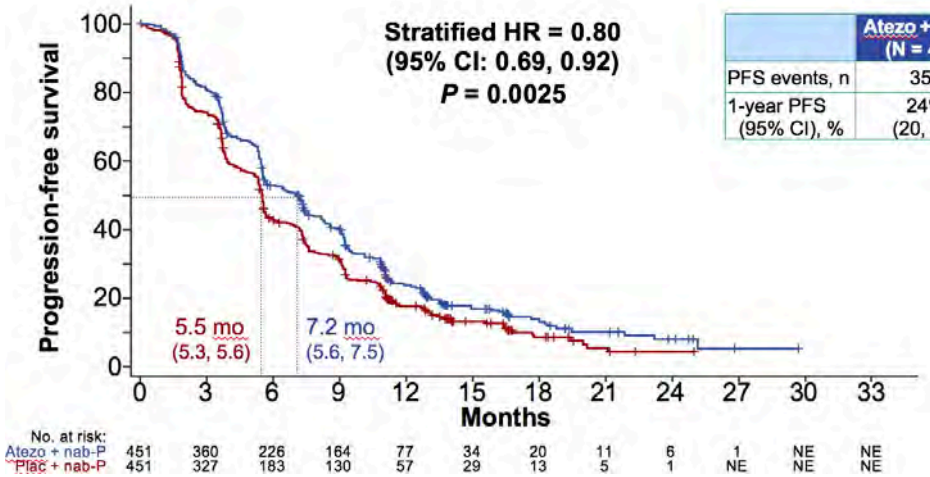
IMpassion130 RCT
Statistical testing on co-primary endpoints in ITT and targeted populations



- Primary PFS analysis (PFS tested in ITT and PD-L1+ populations)
- First interim OS analysis (OS tested in ITT population, then, if significant, in PD-L1+ population)

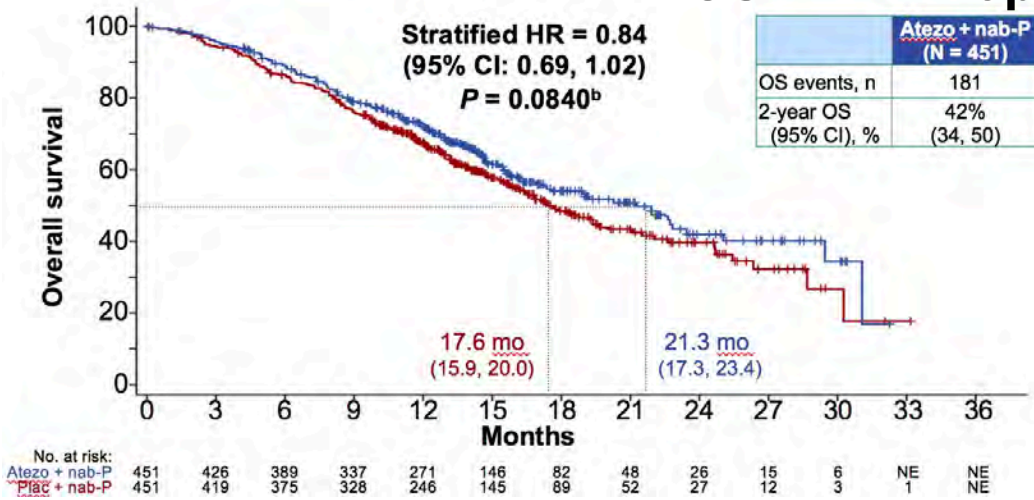
IMpassion130 Interim Analysis results on co-primary endpoints

PFS in ITT Population



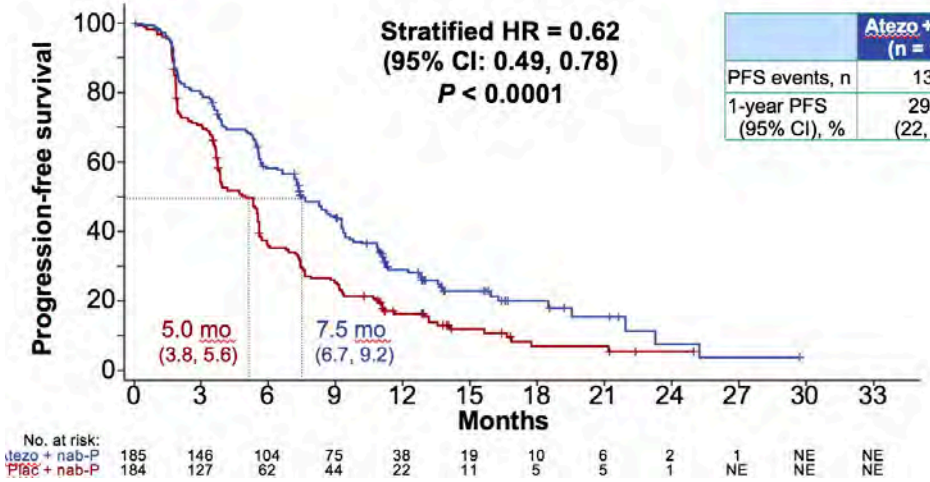
	Atezo + nab-P (N = 451)	Plac + nab-P (N = 451)
PFS events, n	358	378
1-year PFS (95% CI), %	24% (20, 28)	18% (14, 21)

OS in ITT Population



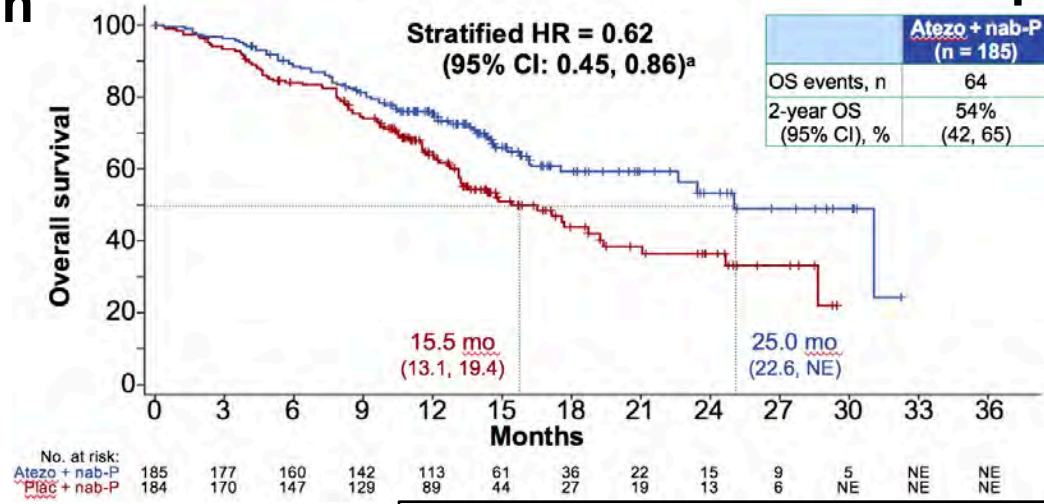
	Atezo + nab-P (N = 451)	Plac + nab-P (N = 451)
OS events, n	181	208
2-year OS (95% CI), %	42% (34, 50)	40% (33, 46)

PFS in PDL1+ Population



	Atezo + nab-P (n = 185)	Plac + nab-P (n = 184)
PFS events, n	138	157
1-year PFS (95% CI), %	29% (22, 36)	16% (11, 22)

OS in PDL1+ Population



	Atezo + nab-P (n = 185)	Plac + nab-P (n = 184)
OS events, n	64	88
2-year OS (95% CI), %	54% (42, 65)	37% (26, 47)

Schmid P., et al. N Engl J Med 2018;379:2108-21.
DOI: 10.1056/NEJMoa1809615

Context for RWE case study

- Atezolizumab in combination with nab-paclitaxel received US accelerated approval in metastatic TNBC based on Impassion 130.

However

- The prescribing information for nab-paclitaxel does not include 1L mTNBC at the dose chosen for the IMpassion130 trial (100mg/m2).
- The acceptability of nab-paclitaxel as a comparator in Phase III studies in 1L mTNBC has been questioned by ex-US Health Authorities (HAs) and payers
- EU HAs have commented that nab-paclitaxel, and specifically the dose (100mg/m2) is not approved for 1L mTNBC and is considered a weak comparator.

Real world evidence may demonstrate comparable effectiveness of nab-paclitaxel and paclitaxel in 1L mTNBC to support EU regulatory filing and payer submissions.

RWE study objectives and design

Objectives:

- Primary: Evaluate the overall survival (OS) of patients with mTNBC treated with nab-paclitaxel monotherapy compared with the OS of patients treated with paclitaxel monotherapy in 1L therapy.
- Exploratory: Evaluate the impact of the dose and schedule of nab-paclitaxel treatment on outcomes.

Study population:

- Adult mTNBC patients who received nab-paclitaxel or paclitaxel monotherapy in 1L treatment between 01Jan2011 and 31Oct2016 in the Flatiron network. Patients were followed through 30June2017 (min of 8 months of follow up)
  - Final study population: N=200
    - Nab-paclitaxel: n=105 / Paclitaxel: n=95

Analytic methods:

- Survival estimated by Cox regression models and Kaplan Meier
  - Unadjusted and adjusted models used to account for potential differences in key prognostic factors
- A number of sensitivity analyses were performed to determine robustness of estimate
  - Overall population, Patients receiving 100mg/m2 nab-paclitaxel or 80mg/m2 paclitaxel (ordered and received), Remove fast relapsers (TFI≤12 mo)

Demographic characteristics

	nab-Paclitaxel N=105	Paclitaxel N=95	P-value
Age at 1L initiation			
Median, (IQR)	66 (53, 73)	65 (58, 75)	0.22
Metastatic diagnosis year, n (%)			
2011-2013	46 (44)	36 (38)	0.43
2014-2016	59 (56)	59 (62)	
Race/Ethnicity, n (%)			
White	67 (64)	57 (60)	0.81
African American	15 (14)	18 (18)	
Other	13 (12)	10 (11)	
Missing	10 (10)	10 (11)	
Insurance status, n (%)			
Commercial	52 (50)	36 (38)	0.43
Medicare	13 (12)	14 (15)	
Other	10 (10)	11 (12)	
Missing	30 (29)	34 (36)	

Clinical characteristics (1)

	nab-Paclitaxel N=105	Paclitaxel N=95	P-value
Stage at diagnosis, n (%)			
I	9 (8)	13 (14)	
II	28 (27)	18 (19)	
III	31 (29)	10 (11)	**0.001**
IV	28 (27)	48 (50)	
Unknown	9 (9)	6 (7)	
Recurrent vs De novo, n (%)			
Recurrent	77 (73)	46 (48)	
TFI ≤12 mo	32 (42)*	11 (24)*	**<0.001****
TFI >12 mo	43 (56)*	33 (72)*	
De novo	28 (27)	49 (52)	
ECOG prior to 1L, n (%)			
0	26 (25)	19 (21)	
1	20 (19)	20 (21)	0.46
2+	6 (6)	<4 (<4)	
Missing	53 (50)	>50 (>53)	

*Percentages are out of recurrent patients only; **p-value is for both de novo vs. recurrent as well as TFI distribution

Clinical characteristics (2)

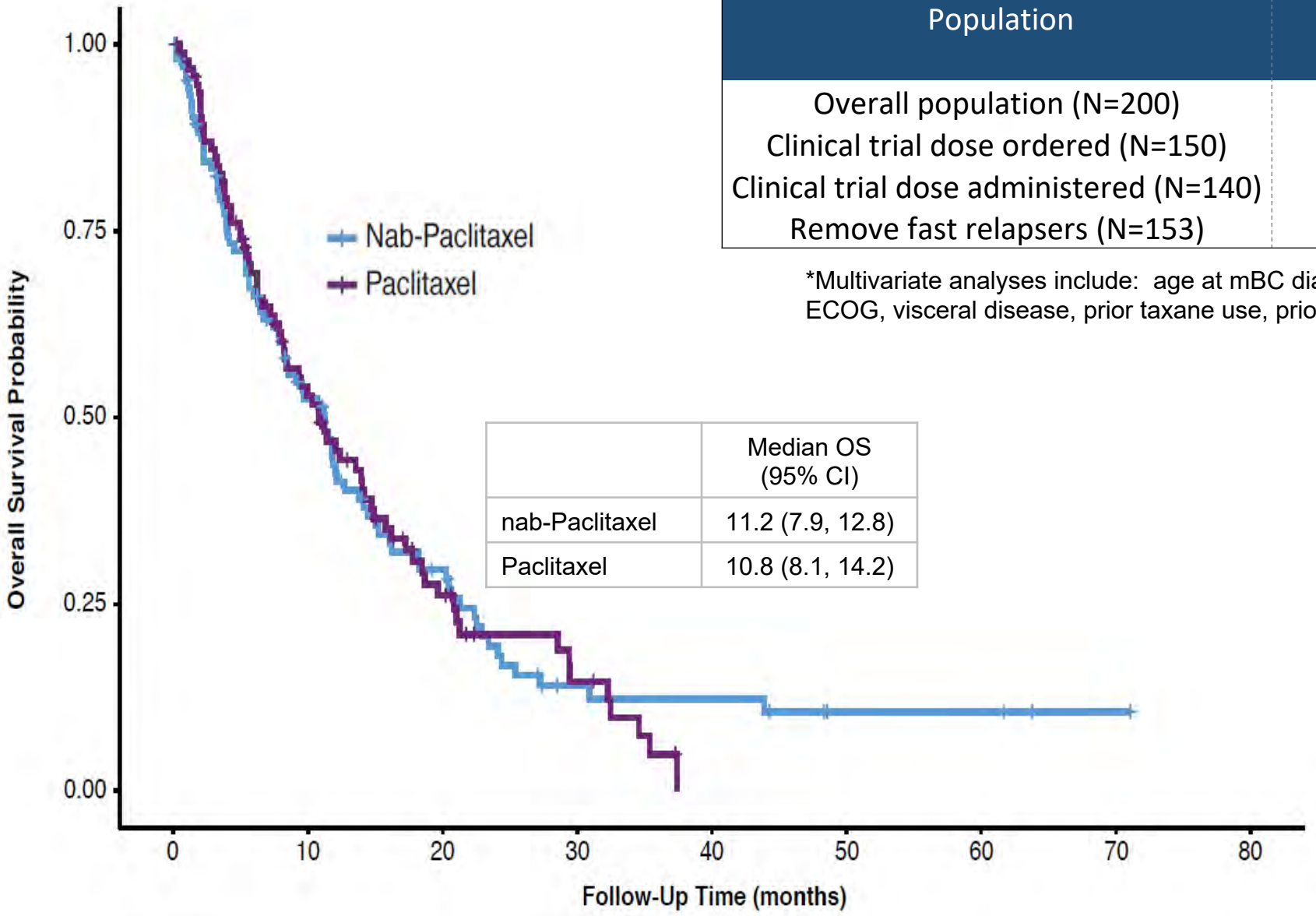
	nab-Paclitaxel N=105	Paclitaxel N=95	P-value
Site of metastases, n (%)			
Bone	49 (47)	54 (57)	0.15
Liver	25 (24)	22 (23)	0.91
Lung	61 (58)	54 (57)	0.86
Brain/CNS	7 (7)	14 (15)	0.06
Distant Lymph Node(s)	42 (40)	31 (33)	0.28
Other	13 (12)	15 (16)	0.49
Number of metastatic sites, n (%)			
1	44 (42)	37 (39)	
2	36 (34)	34 (36)	0.91
3+	25 (24)	24 (25)	
Visceral disease, n (%)			
Yes	78 (74)	67 (71)	0.55
No	27 (26)	28 (29)	
Prior (Neo)Adjuvant taxane use, n (%) *			
Yes	57 (74)	18 (39)	
No	20 (26)	28 (61)	**<.0001**
Prior neuropathy, n (%)			
Yes	28 (27)	12 (13)	**0.01**
No/Unknown	77 (73)	83 (87)	

*Percentage out of recurrent patients only

Results: No observed treatment difference in overall survival

Population	nab-Paclitaxel vs. Paclitaxel Multivariate* HR (95% CI)
Overall population (N=200)	0.98 (0.67, 1.44)
Clinical trial dose ordered (N=150)	1.12 (0.71, 1.75)
Clinical trial dose administered (N=140)	0.99 (0.61, 1.59)
Remove fast relapsers (N=153)	0.88 (0.56, 1.37)

*Multivariate analyses include: age at mBC diagnosis, stage at initial diagnosis, race, TFI, ECOG, visceral disease, prior taxane use, prior neuropathy, comorbidity index



	Median OS (95% CI)
nab-Paclitaxel	11.2 (7.9, 12.8)
Paclitaxel	10.8 (8.1, 14.2)

Results: Dose and schedule of taxane treatments

Predominate dose of nab-paclitaxel used was 100mg/m2 consistent with the RCT

	nab-Paclitaxel N=104*	Paclitaxel N=91*
Weekly (qw)		
Dose reductions	7 (7)	9 (9)
80mg/m2	0 (0)	67 (76)
90mg/m2	0 (0)	5 (6)
100mg/m2	81 (78)	0 (0)
125mg/m2 or 150mg/m2	8 (8)	0 (0)
Every three weeks (q3w)		
175mg/m2	0 (0)	8 (9)
260mg/m2	8 (8)	0 (0)

*Not all patients have information to determine dose and/or schedule and thus are removed for this analysis

Conclusions and actions

- Most demographic and clinical characteristics were similar between patients treated with nab-paclitaxel and paclitaxel monotherapy in 1L mTNBC
  - Patients with de novo disease were more likely to receive paclitaxel
- Dose of nab-Paclitaxel used in RCT consistent with routine clinical practice.
- Overall survival estimates (~11 months) is in line with expectations for 1L mTNBC.
- Overall survival is similar for patients who received nab-paclitaxel compared with those who received paclitaxel in 1L mTNBC.
- **This study was referenced in regulatory and payer submissions in regions where nab-paclitaxel is not commonly used in TNBC, including EMA.**
- **Atezolizumab in mTNBC recently received positive CHMP opinion.**

Additional thoughts

- Identifying RWE solutions requires an understanding of the medical, regulatory, and reimbursement context.
  - There is value for data scientists integrated within molecule teams.
- This is an example of how real world evidence can add to the totality of data. This observational study brought greater context to ex-US stakeholders when assessing the RCT.
  - RWD complementing, not replacing, clinical trial data.

Thank you

Use of Real-World Evidence to Inform Clinical Development

Weili He, PhD, David Van Brunt, PhD, Hongwei Wang, PhD, Ivan Chan, PhD, and Chris Pashos, PhD

AbbVie Inc.

July 19, 2019

FDA-AACR Regulatory Science and Policy Workshop

Disclaimer

- The comments provided here are solely those of the presenters and are not necessarily reflective of the positions, policies or practices of presenters' employers.

- The support of this presentation was provided by AbbVie Inc. AbbVie participated in the review and approval of the content.

- All contributors of this presentation are employees of AbbVie Inc.

Introduction

- RWD/RWE research is evolving rapidly and is playing an increasingly important role in clinical development and life-cycle management.
- Many RWE use cases exist at AbbVie to assist and improve efficiencies in clinical development and execution.
- Challenges remain and sharing of use cases and best practices will help move the field forward!

1. **A few RWE use cases at AbbVie**
2. Key challenges
3. Applying quantitative approaches in RW research
4. Concluding remarks

RWE Use Cases at AbbVie – **Population Identification**

Issue	RWE Support
Finding Investigators	• What providers care for these patients? • How do typical care maps vary by severity or by country?
Geo-strategy	• How does disease prevalence or severity vary across countries or regions? • How does medical practice vary across countries or regions?
Disease Prevalence	• How common is this disease in sub-population defined by phenotype and genotype?
Patient journey	• What is the diagnostic journey and how long does it take? What physician specialties and treatment regimens have patients experienced before being effectively diagnosed? • How are patients diagnosed? What diagnostic modalities are available and what is their use (e.g., MRI, CT)?
Role of Con-Meds, Co-morbidities	• What is the prevalence of various comorbidities? • What is the prevalence of con-meds for comorbidities? • What is the prevalence of con-meds for this disease?

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RWE Use Cases at AbbVie – **Population Identification (Cont'd)**

Issue	RWE Support
Enrolling patients	• Which patients meet inclusion/exclusion criteria? • Are they willing to participate, e.g., social medial?
Indication calibration	• Are unmet medical needs consistent across the targeted population? • What is the most appropriate population in which to assess the value of the treatment being investigated?

RWE Use Cases at AbbVie – **Choice of Comparator and Outcome Measure Assessment**

Issue	RWE Support
Outcome measure identification and planning	• Expected background event rate in disease? Varies by duration? Severity?
Safety event planning	• How common are CV events? Infections? Malignancy? Liver disease? • Variation by geography and patients' characteristics?
Rare safety events	• How many events of cancer do we expect in our development program?
Understand disease and treatment Pattern	• What medications are used in population of interest? By country? In what sequence and what are the associated outcomes?

RWE Use Cases at AbbVie **– Product Safety Follow-up**

Issue	RWE Support
Fulfil regulatory safety commitment	• Design patient registries to fulfil regulatory commitment on AEs of special interests, rare side effects and in uncommon population, e.g., Humira LEGACY registry in moderate to severe UC patients. It also serves as data platform for scientific communication

RWE Use Cases at AbbVie – **Improving Study Design and Execution**

Issue	RWE Support
Hybrid retrospective / prospective study design	• Enroll patients at point of care, leverage EHR to retrieve historic information and long-term follow-up
Use of synthetic control	• Single-arm venetoclax overall response rates was compared with historic standard rate in R/R CLL with 17p-deletion • Radiographic progression in the spines of patients with ankylosing spondylitis treated with adalimumab vs. historic anti-TNF naïve patients

RWE Use Cases at AbbVie – **Value Demonstration and Care Quality Improvement**

Issue	RWE Support
Change of treatment paradigm	• Real-world studies demonstrating cure rates and safety of next-gen HCV treatment, innovative care pathway to diagnose HCV patients and initiate appropriate treatments for cure
Raise standard of care	• Identify gaps in SOC and understand long-term implication for patients with a disease condition • Designed cohort studies to show that patients with a disease condition experienced better outcomes by switching to an innovative product after failing SOC and thus impact treatment guideline

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3. Applying quantitative approaches in RW research
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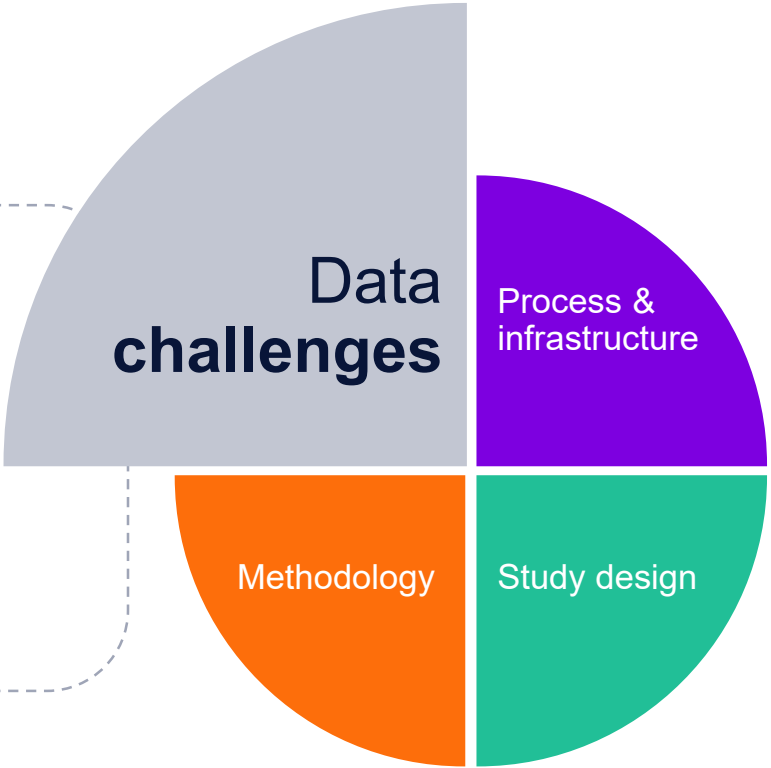
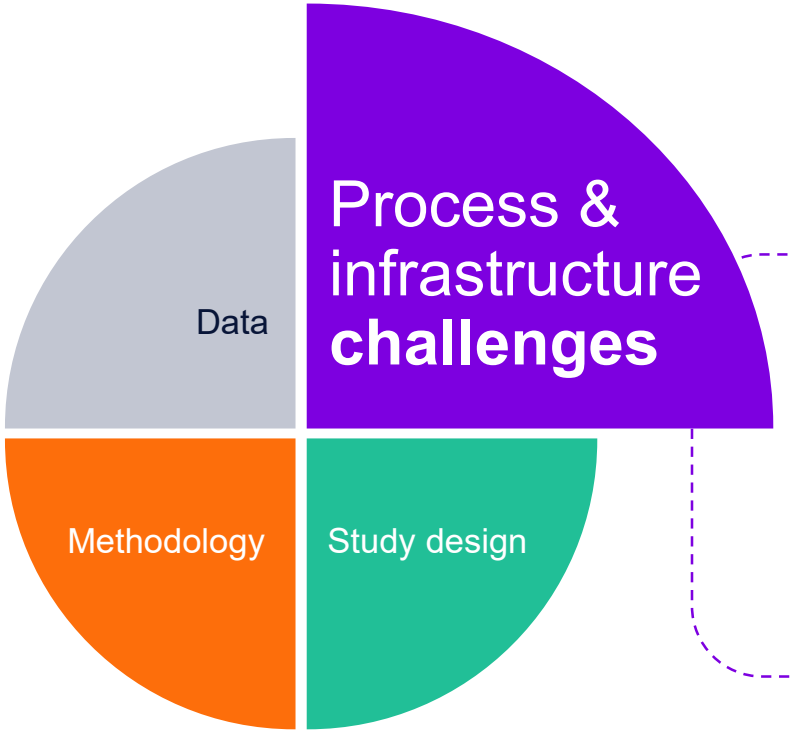
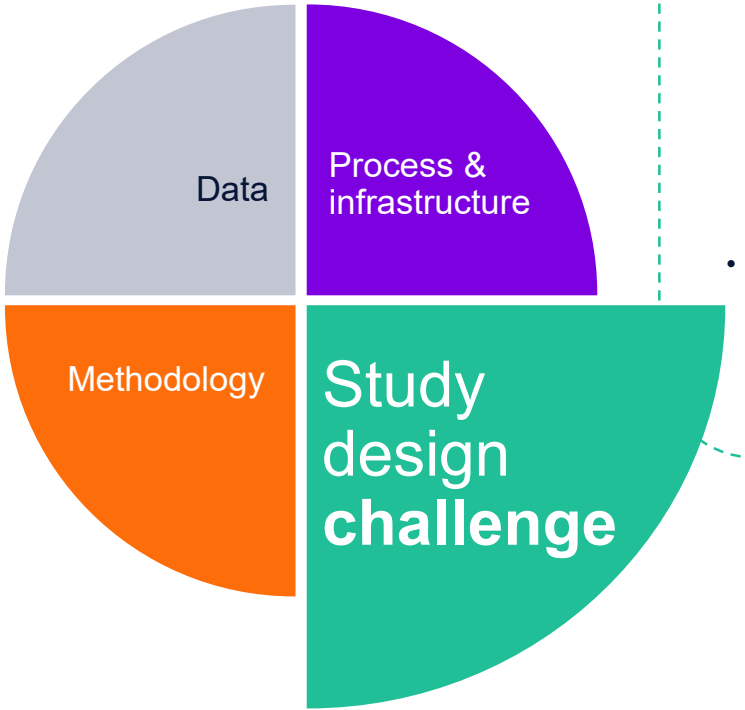
- Availability of data and gaps in data collection
- Data standards, definition, and methodologies for data collection
- Interoperability of databases
- Data quality and representativeness
- Methods for linking data sources

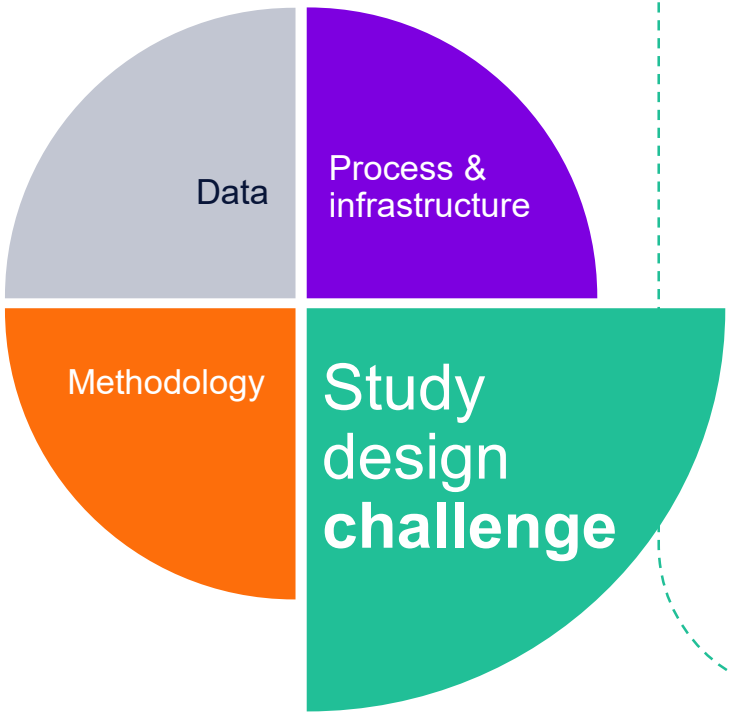




- IT infrastructure and standard operating procedures to facilitate RWD/RWE research
- Transparency, consistency, and reproducibility
- Verifiability and robustness of RWE results/conclusions
- Re-useable tools development, e.g., advanced analytics



- Substantial variabilities in study designs and lack of consensus when conducting RW study to address specific type of research questions, e.g., comparative effectiveness, non-medial switch of biologic products, patient journey, disease progression, path to diagnosis, biomarkers and subgroup identification, etc.
- Some of the above design challenges are recognizable and remediable, but some others may defy solely analytic solutions due to misalignment of study goals with study characteristics and/or unmeasured confounding factors



- Other design challenges*
  - Establish causal relationship
  - Design matches research questions
  - Control for bias and confounding at both design stage and analytic stage
  - Sufficient statistical precision and consideration of multiplicity adjustment
  - Statistical significance and clinical important effect size
  - Completeness of data and not intervening with routine clinical practice
  - Address unobserved confounders
  - Ascertainment of target population and key outcomes, e.g., may not be definable and need approximation
  - Different needs of key stakeholders

***** *Goodman, Schneeweiss,* Baiocchi M. *Using design thinking to differentiate useful from misleading evidence in observational research. JAMA, 2017*

- Existing analysis methodologies require deeper understanding of practical usages and appropriate applications, e.g.

  Propensity score based methods, multivariate regression or G-methods for confounding control and quantification of unobserved confounders

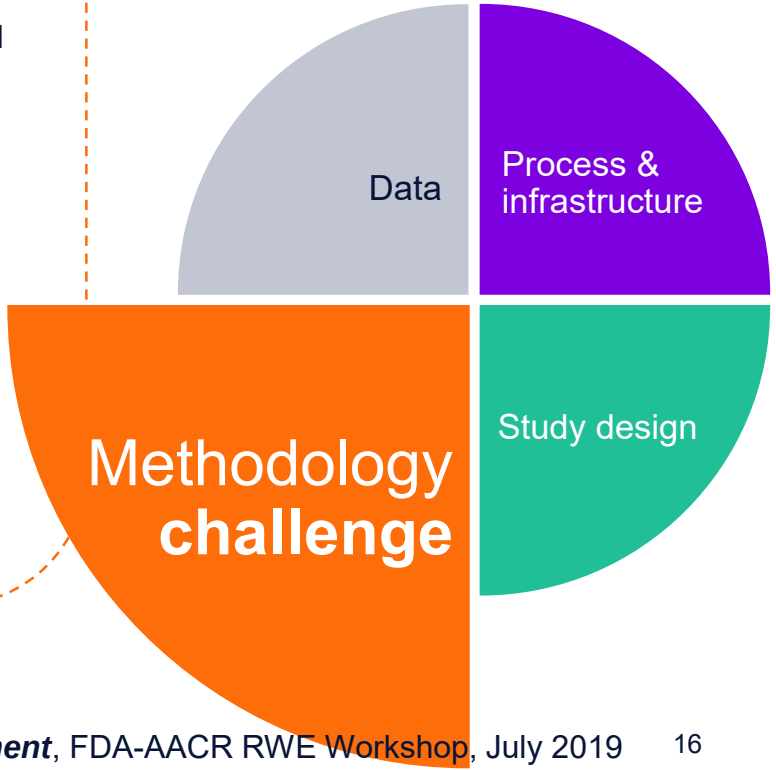
  Network meta-analysis / Indirect treatment comparison

  Machine learning and Predicative modeling

  Natural language processing for unstructured data

- Statistical techniques suffer from the same limitation that they cannot overcome unquantifiable or poorly recorded confounders

- Model fit, sensitivity analysis, Internal validity, external validity, reproducibility, pre-specification



1. A few RWE use cases at AbbVie
2. Key challenges
3. **Applying quantitative approaches in RW research**
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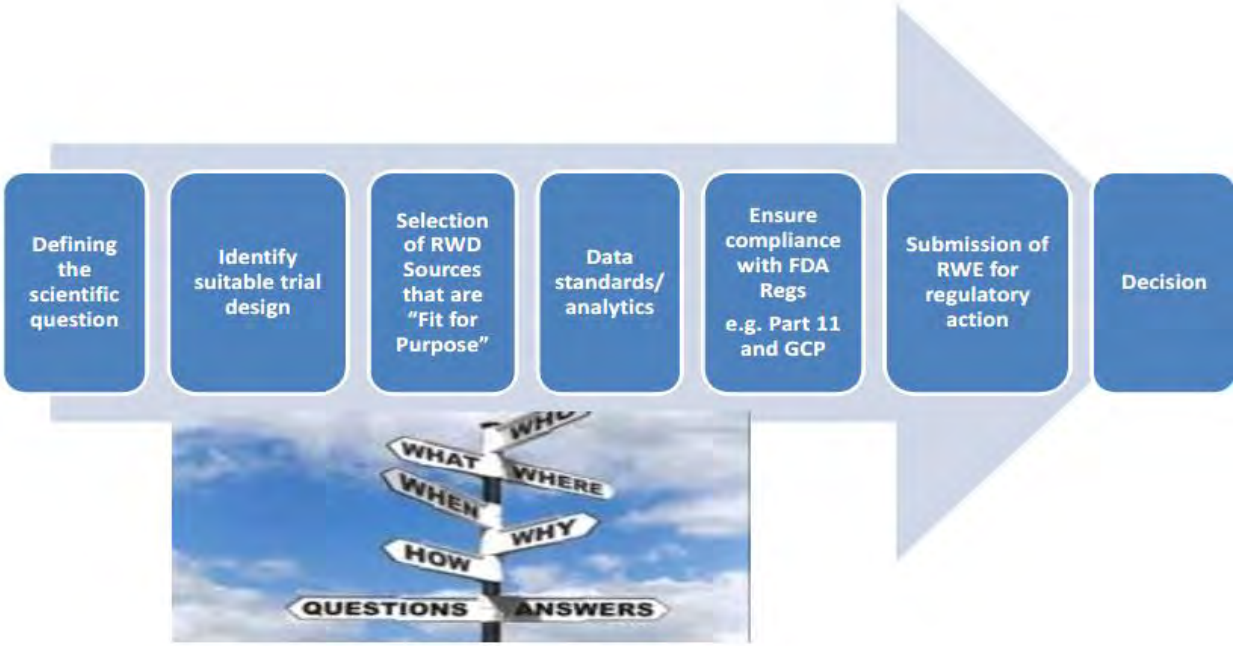
Putting Key Elements Together



* Source: Corrigan-Curay. Real World Evidence A Path Forward. FDA RWE Public Meeting, Sept. 13, 2017

Applying quantitative in RW research **– Assessment of Data Aspect**

Data sources, quality, and accuracy

- Feasibility assessment and availability of key data elements
- Longitudinal nature of the data source
- Data elements, measure of exposure, outcome, potential confounding factors
- Accuracy of data being captured (e.g. diagnosis, intervention, outcome)
- Data allowing for comparative analysis
- Generalizability of the results (spectrum between RCTs and RW setting

Outcome measures

- Outcomes/Endpoints in RW setting may be different from RCTs
- Need to validate routine care RWD endpoints in given indication
- Need to develop algorithm for endpoints that are not captured in precise way and/or in different places in medical records
- Use of machine learning and text analytics to augment key outcomes or variables

Applying quantitative in RW research – **Assessment of Data Aspect (Cont'd)**

Missing data

Assess level of missing data, including whether certain data fields are not designed to capture or level/magnitude of missing data for key data elements at patients' level

Methods for missing data imputation and sensitivity analysis to assess robustness

Missing at random assumption may not hold, e.g., survival effect

Linking or pooling different databases

Use appropriate approaches for linking different databases, accounting for differences in coding and reporting and using suitable and adequate patient identifiers

For pooling, use appropriate methods to prevent double-counting of patients across different data sources

Relatively small proportion of patients may be linkable and heterogeneity may exist when pooling

Applying quantitative in RW research – **Assessment of study design and methodology aspects**

Causal evidence

Design studies that establish causal evidence

Working within constrains of data source, cohort entry criteria, operational definition of data elements, temporal anchors, exposures, methodological approaches to avoid selection biases, outcomes, follow up, covariates

Understand strengths and limitations of studies

Different analytic frameworks available to account for confounding and reduce biases

Propensity score-based method: matching, weighting, stratification, adjustment – marginal effect model

G-methods including double-robust methods

Multivariate regression – conditional effect model

Special cases: rare events, impact of unobserved confounders

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Remarks

- RWD/RWE research is evolving rapidly and is playing an increasingly important role in clinical development
- Use cases are increasing available and the sharing of lessons learned and best practices essential
- Quantitative approaches play a critical role in the conduct of RWE research from conceptualization, design, analyses, interpretation to communication
- With growing knowledge and evolving regulatory landscape, quantitative scientists should be in the forefront in shaping up RWE research strategy, leading methodologic development and execution

Key References, Citation of examples

- Goodman, Schneeweiss, Baiocchi M. Using design thinking to differentiate useful from misleading evidence in observational research. JAMA, 2017; Vol 317 (7) 705-707
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The webcast will resume shortly.

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SESSION III:

Postmarket Use Cases

Session Moderator: Pallavi Mishra-Kalyani, PhD

Speakers:

Albert L. Kraus, PhD

Ruthanna Davi, PhD

Jeff Allen, PhD

Postmarket Real World Data Perspectives: Oncology Registration Use Cases

Albert L. Kraus PhD

FDA/AACR workshop
19 July 2019

Pfizer Innovative Health

Pfizer Oncology

This presentation shares my views and not necessarily those of Pfizer

Disclosures

- I am a full time Pfizer employee
- I own stock and/or options in Pfizer and other pharmaceutical Companies

Why is RWE especially appealing today?

1 Regulators are implementing programs to drive the application of Real World Evidence

Sentinel Initiative — Proactive monitoring of product safety

21st Century Cures Act

PDUFA VI

Draft guidance on how RWE can contribute to safety and effectiveness assessment in regulatory submissions by 2021

2 Increase in the availability of data

- **Clinical data**
- **Biological data**
- **Real world: structured data**
- **Real world: unstructured data**
- **Other data**

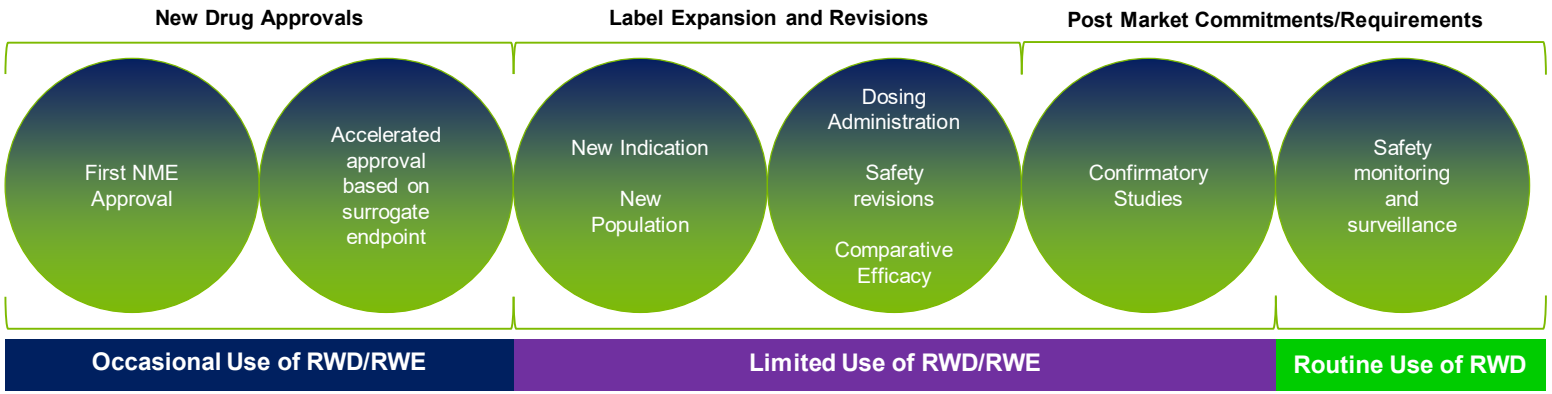
3 Significant advancements in data analysis capabilities

Level of insight ← *High* — *Low* →

- **Artificial Intelligence-enabled data science**
- **Traditional prediction and simulation**
- **Learning and monitoring**

FDA routinely uses RWE for post-approval safety, effectiveness decisions limited to rare diseases

Experience Utilizing RWD and RWE for Regulatory Purposes:



Source: Berger et al., 2017

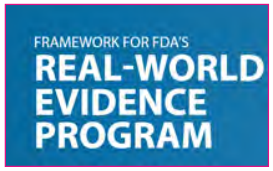
CDER Director Janet Woodcock on RWE in a 2017 Public Workshop*:

- RWE is "currently used extensively for evaluation of safety of marketed products," but there is **"very little historical use of real world experience in drug regulatory decisions about effectiveness."**
- Most of those efficacy decisions have come for therapies for very rare diseases. Woodcock identified two sets of circumstances:
  1. Approvals "based on data from registry-like case series"
  2. Approvals where "we have used registry data as external controls."

*2017 RWE workshop at the National Academies of Sciences, Engineering, and Medicine

Expansion of FDA use of RWE is anticipated

Recent Key FDA Initiatives and Communications regarding RWE:



FRAMEWORK

December 18, 2018

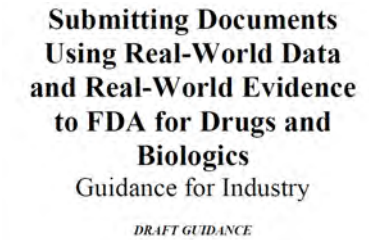
- Intended for drug and biological products
- Outlines FDA's plan to implement the RWE program
- Multifaceted program
  - Internal processes
  - Guidance development
  - Stakeholder engagement
  - Demonstration projects.

HARVARD MEDICAL SCHOOL

AETION

April 10, 2019

- Expansion of their demonstration project, RCT DUPLICATE, using real-world evidence to predict the results of seven ongoing Phase IV trials.


Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics
Guidance for Industry
DRAFT GUIDANCE

May 8, 2019

- This guidance is intended to encourage sponsors and applicants who are using RWD to generate RWE as part of a regulatory submission to FDA to provide information on their use of RWE in a simple, uniform format.

Early FDA consultation recommended to assess if RWD 'fit for purpose'

FRAMEWORK FOR FDA'S REAL-WORLD EVIDENCE PROGRAM

RELEVANCE: the relevance assessment considers whether the data are fit for purpose
Are there sufficient details on exposure, covariates, outcomes to address pre-specified questions?

RELIABILITY of RWD via data accrual and data quality control (data assurance)
Do the codes or combinations of codes adequately represent the underlying medical concepts they are intended to represent?

COMMON DATA MODEL with common terminologies, vocabularies, coding schemes is needed to work with RWD across multiple sources
RWD sources should follow **REPORTING STANDARDS** and document data elements and definitions,
data aggregation methodology and data collection time windows

ADDRESSING RWD GAPS requires a variety of RWD sources including wearable, biosensors to illustrate the patient journey and account for relevant endpoints

TRANSPARENT source verification and auditing procedures for completeness and consistency

* "Framework for FDA's Real World Evidence Program" 2018

RWE Oncology Use Cases: Registration Precedents

Pfizer Oncology

Product & disease considerations

- Patient population size: **Small/ rare**
- Therapeutic options: **No adequate options**
- Disease urgency: **Serious and life threatening**
- Drug effect size: **Large/ easily measured**

Past precedents with EHR or other RWE data generally

- Safety monitoring
- 'External control' to clarify patient prognosis with best available therapy
- usually not for effectiveness or included in label

Endpoints of Benefit Important: Palbociclib

San Antonio Breast Cancer Symposium 2017

Pfizer Oncology

RWD/RWE vs P3 data control arm (endocrine therapy – letrozole; Paloma-2 control arm)

- endpoint relation to traditional study outcomes

- front line advanced/ metastatic breast cancer

- **Tumor Progression**: propensity score–matched median PFS was similar between the letrozole-treated cohorts:
  - 18.5 months (95% CI, 13.7–24.1) for the Flatiron RW group
  - 19.2 months (95% CI, 13.7–not estimable) for the PALOMA-2 RCT group.
- **Tumor Response:** using matched data
  - 39.2% rwTR in the Flatiron RW cohort
  - 36.7% ORR via RECIST in the PALOMA-2 RCT cohort
  - odds ratio: 0.90 [95% CI, 0.45–1.80]

* SABCS 2017: Concordance of Real-World Progression-Free Survival (PFS) on Endocrine Therapy as First Line Treatment for Metastatic Breast Cancer Using Electronic Health Records With Proper Quality Control vs Conventional PFS From a Phase 3 Trial

In the past two years, some regulatory decisions on effectiveness have been informed by RWE

				FDA		EMA	
				Approval	Label Expansion	Conditional Approval	Approval
Pragmatic	janssen	INVEGA SUSTENNA	Schizophrenia		✓(2018)		
External Comparators	Pfizer	BAVENCIO avelumab	Metastatic merkel cell carcinoma (RW Benchmark)	✓(2017) Accelerated*		✓(2017)	
	BIOMARIN	Brineura (cerliponase alfa)	Infantile batten disease (RW Comparator)	✓(2017) Full			✓(2017)
	GILEAD Kite	YESCARTA (axicabtagene ciloleucel)	Diffuse large B-cell lymphoma (RW Benchmark)	✓(2017) Full			✓(2018)
	FRESENIUS KABI	Omegaven	Parenteral nutrition-associated cholestasis (RW Comparator)	✓(2018) Full			
	AMGEN	BLINCYTO (blinatumomab)	B-cell precursor acute lymphoblastic leukemia in 1st / 2nd complete remission with MRD ≥ 0.1% (RW Comparator)		✓(2018) Accelerated		✓(2019)
Observational	amneal	TEPADINA	Reduce the risk of graft rejection in pediatric class 3 beta-thalassemia		✓(2017) Full		
	NOVARTIS		Somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs)	✓(2018) Full			✓ (2017)
	Pfizer	IBRANCE	HR+, HER2- advanced /metastatic breast cancer in males		✓ (2019)		

MRD = minimal residual disease
SSTR = Somatostatin receptor
GEP-NETs = gastroenteropancreatic neuroendocrine tumors
HER2 = human epidermal growth factor receptor 2
HR = hormone receptor

Regulators asked for post-approval clinical trial

RWE included in the label

Blinatumomab in ALL

Surrogate control arms: Accelerated Approvals

- Relapsed/ refractory acute lymphoblastic leukemia (ALL): 2014
- Front line/ relapsed MRD+ ALL: 2018

Front line/ MRD+ Accelerated Approval by US FDA

- Phase 2 strong objective response data in MRD+ ALL patients and totality of RWE external control and other information
- Existing positive P3 data in relapsed/ refractory ALL patients
  - Ongoing P3 in front line/ relapsed MRD+ ALL patient population
- Strong drug effect in ALL
- Rare disease with poor prognosis (expected death from disease)
- Current treatment options are effective but not curative

Blinatumomab in ALL

RWE results and new drug effect

- Careful patient matching:
  - Perfect matching of traditional trial I/E and RWE is difficult
- Blinatumomab effect large vs external control response findings

ODAC review

My Observations

- Nice job by Amgen and FDA to deliver an important new medicine to poor prognosis ALL patients some years before a traditional P3 will read out
- Many of the current patients will have died by the time the P3 trial reads out

Real-World Evidence of Male Breast Cancer Patients Treated With Palbociclib in Combination With Endocrine Therapy

Cynthia Huang Bartlett,[1] Jack Mardekian,[2] Michelle Yu-Kite,[3] Matthew J. Cotter,[2] Sindy Kim,[3] Jaclyn Decembrino,[4] Tamara Snow,[5] Kenneth R. Carson,[5] Jillian Motyl Rockland,[5] Albert L. Kraus,[6] Keith Wilner,[2] Norihiko Oharu,[6] Patrick Schnell,[2] Dongrui Ray Lu,[3] Jennifer Tursi[7]

[1]Pfizer Inc, Collegeville, PA, USA; [2]Pfizer Inc, New York, NY, USA; [3]Pfizer Inc, San Diego, CA, USA; [4]IQVIA Inc., Plymouth Meeting, PA, USA; [5]Flatiron Health, New York, NY, USA; [6]Pfizer Inc, Groton, CT, USA; [7]Pfizer Srl, Milan, Italy

Presented at the American Society of Clinical Oncology (ASCO) Annual Meeting, May 31–June 4, 2019, Chicago, IL, USA

Pfizer Innovative Health

Pfizer Oncology

Background: Breast Cancer in Men

- 2670 new cases of invasive breast cancer and 500 deaths from metastatic breast cancer (MBC) in men in the United States in 2019 (estimated).[2]
  - MBC remains an incurable disease with a 5-year survival rate of only 16% in men.[3]
- In male patients with breast cancer, most tumors express hormone receptors[4]; men are more likely to be diagnosed at an older age and with a more advanced stage of disease, and are more likely to have lymph node involvement.[5]
- USA National Comprehensive Cancer Network guidelines indicate that male patients with MBC should receive similar treatment as postmenopausal women with MBC.[6]

1. Losurdo A, et al. *Crit Rev Oncol Hematol*. 2017;113:283-291.
2. American Cancer Society. Key statistics for breast cancer in men. Available at: https://www.cancer.org/cancer/breast-cancer-in-men/about/key-statistics.html. Accessed April 12, 2019.
3. Giordano SH. *N Engl J Med*. 2018;378(24):2311-2320.
4. Chavez-Macgregor M, et al. *Cancer*. 2013;119(9):1611-1617.
5. Giordano SH, et al. *Cancer*. 2004;101(1):51-57.
6. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Breast Cancer Version 1.2019. Plymouth Meeting, PA: National Comprehensive Cancer Network; 2019.

Background: Breast Cancer in Men

- Palbociclib, a CDK4/6 inhibitor, is approved for the treatment of HR+/HER2– MBC in women and has been incorporated into treatment for men with MBC in real-world clinical practice.

- Due to the rarity of breast cancer in men, it is not feasible to conduct large and adequately powered randomized clinical trials.[1]

1. Losurdo A, et al. *Crit Rev Oncol Hematol.* 2017;113:283-291.

Fit of RWE into Totality of Evidence

- Biology of breast cancer in men similar to women
  - Preclinical cellular/ molecular/ animal model Information
- Clinical Information:
  - Palbociclib has a large and consistent treatment effect
  - Palbociclib has a well defined and manageable safety profile (mainly hematological AEs)
- Clinical information: other CDK4,6 inhibitors
- NCCN assessment

RWD/RWE Objective

Evaluate real-world treatment patterns of palbociclib, including clinical activity and safety data, in order to assess the benefits and risks of palbociclib plus ET for the treatment of men with HR+/HER2– MBC

IBRANCE Males – 3 Real World Data Sources

Source 1 (US only) :
Flatiron Health Electronic Health Records

Key Output used in messaging :
Tumor response

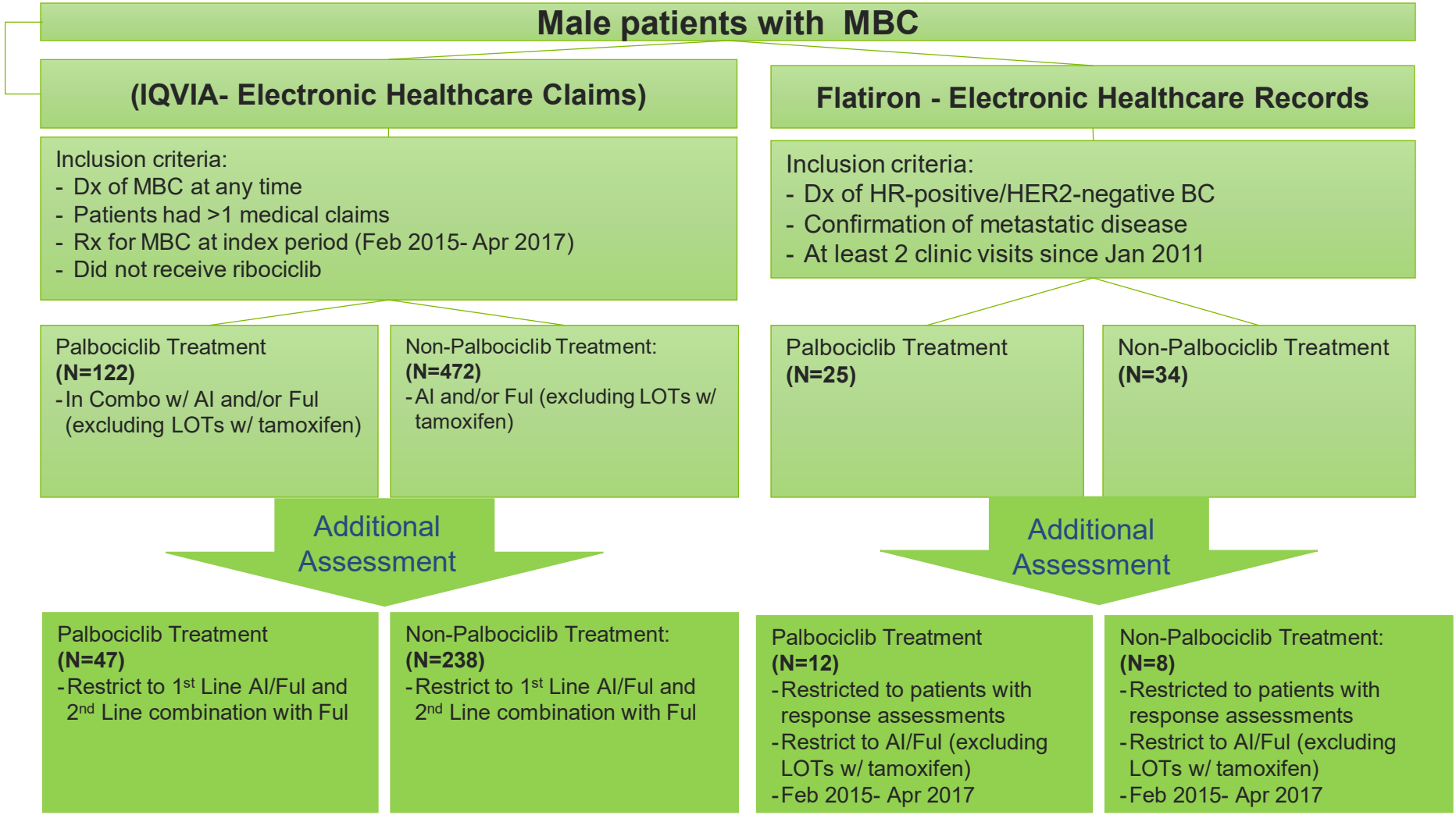
Source 2 (US only) :
IQVIA Pharmacy and Medical Claims Databases

Key Output used in messaging: DOT, unmet medical need, frequency of prescriptions

Source 3 (Global):
PFE global safety database [ARGUS]

Key Output used in messaging:
Spontaneous reports in male patients with metastatic BC treated with palbociclib, review of AE and outcome

IQVIA and Flatiron Data Sources: Male Patients with MBC

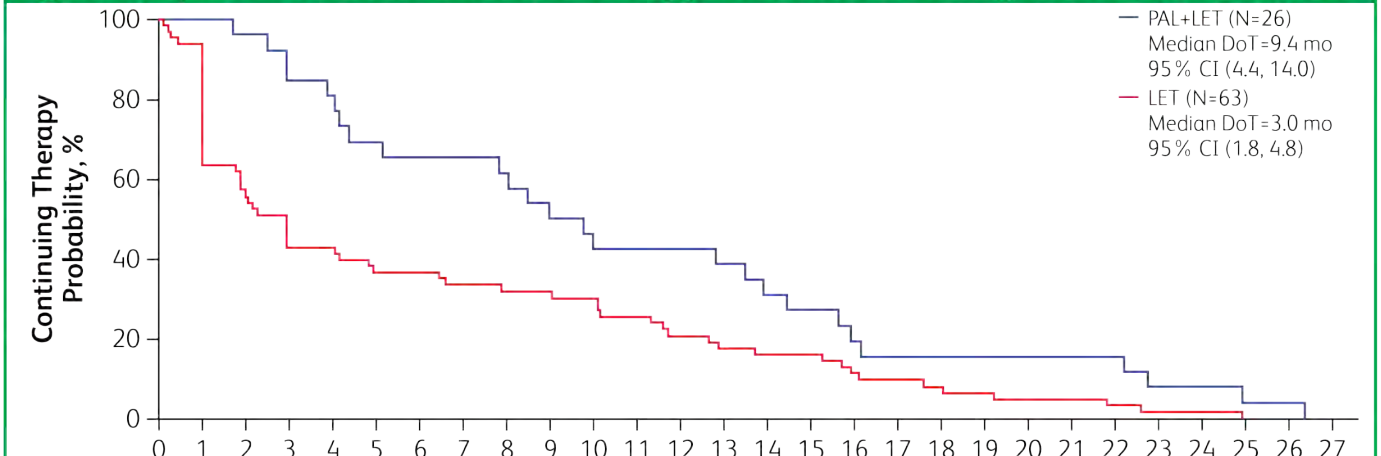


Results

IQVIA Data Source

- Median duration of treatment in the first-line setting was longer with palbociclib plus letrozole compared to letrozole alone (9.4 vs 3.0 months)
- Median duration of treatment in the second-line setting was longer with palbociclib plus fulvestrant vs fulvestrant alone (2.7 vs 1.8 months)

Figure 1. Kaplan-Meier Plot of Duration of Therapy in the First-Line Setting in the IQVIA Data Source



DoT=duration of therapy; LET=letrozole; PAL=palbociclib.

Results

Flatiron Health EHR-Derived Data Source

- real-world maximum response rate (partial response [PR] plus complete response [CR]) in palbociclib plus AI/FUL cohort across all lines of therapy in the metastatic setting was 33.3% (4 of 12 patients).
- AI/FUL alone rate was 12.5% (1/8 patients)
- during an expanded timeframe, the real-world maximum response rate in the AI/FUL alone cohort was also 12.5% (2 of 16 patients).

Figure 2. Response Assessments in the Flatiron Health EHR-Derived Data Source

A. Real-world maximum tumor response

Response	Palbociclib + AI/FUL Cohort* N=12 n (%)	AI/FUL Alone Cohort† N=8 n (%)
Complete response	2 (16.7)	0
Partial response	2 (16.7)	1 (12.5)
Stable disease	5 (41.7)	4 (50.0)
Progressive disease	3 (25.0)	3 (37.5)
Response (CR+PR) rate	**4 (33.3)**	**1 (12.5)**

Results

Safety

- Using the Flatiron Health EHR-derived database, a targeted safety review of 5 prespecified AEs of interest (ie, neutropenia, febrile neutropenia, fatigue, pulmonary embolism, and stomatitis) in the 25 palbociclib-treated patients showed no unexpected safety signals; there were no reports of febrile neutropenia or pulmonary embolism.
- A review of the reported AEs from the Pfizer global safety database suggests that the AE profile of male patients with MBC treated with palbociclib was generally consistent with the known AE profile of palbociclib with no new major safety signals identified.

US FDA elements

- Multiple meetings on several RWE designs, approaches and issues, including palbociclib males effort
- Thorough review with many questions and FDA queries on data elements and interpretation
- Multiple inspections on RWE work involved to evaluate and ensure data quality
  - Pfizer, Flatiron, and IQVIA

RWD/RWE Specific Conclusions

- The real-world data sources used in this analysis support
  - men with MBC derive clinical benefit from the addition of palbociclib to ET
  - safety profile in men was consistent with previous observations in women treated with palbociclib plus ET
- Noninterventional, real-world evidence from multiple sources was useful to delineate the benefit of therapies in this setting.
- A limitation of this retrospective analysis is the small dataset given the rarity of men with breast cancer.
- An expanded indication was granted by the US Food and Drug Administration in April 2019 for palbociclib plus AI or FUL for the treatment of men with HR+/HER2– MBC.[1]
- These findings highlight a new path to expand product labels and increase patient access based on real-world evidence in rare tumors, where rarity makes large randomized trials unfeasible.

1. Pfizer. US FDA approves IBRANCE® (palbociclib) for the treatment of men with HR+, HER2- metastatic breast cancer. Available at: https://www.pfizer.com/news/press-release/press-release-detail/u_s_fda_ approves_ibrance_palbociclib_for_the_treatment_of_men_with_hr_her2_metastatic_breast_cancer. Accessed April 15, 2019.

APPROVAL

- USPI:
  - Indication:

"IBRANCE is indicated for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with:

- an aromatase inhibitor as initial endocrine-based therapy in postmenopausal women or in men; or
- fulvestrant in patients with disease progression following endocrine therapy."

- Section 2.1 Recommended Dose and Schedule
  - "For men treated with combination IBRANCE plus aromatase inhibitor therapy, consider treatment with an LHRH agonist according to current clinical practice standards."
- Section 6.2 Postmarketing Experience

"Male patients with HR-positive, HER2-negative advanced or metastatic breast cancer

Based on postmarketing reports and electronic health records the safety profile for men treated with IBRANCE is consistent with the safety profile in women treated with IBRANCE."

Where are we now…my views

- Retrospective and Prospective RWD/RWE Approaches
  - Careful considerations and ‘fit for purpose’
  - Totality of evidence and fit in overall drug development important
- Retrospective RWD/E: Key focus areas include
  - Patient matching
  - Endpoint considerations
  - Bias reduction approaches
  - Pre-specified approaches
  - Integrated assessment with totality of biological and medical information
- Prospective ‘pragmatic’ RWD/E: Key focus areas include
  - Need more case examples
  - Randomization, added data to EHR methods
  - Endpoints

Regulators have signaled receptivity to RWE-RCT hybrid studies to RWE-RCT hybrid studies

	EXTERNAL CONTROL	PRAGMATIC	INNOVATIVE EXTENSION
FDA	"In appropriate cases, [the FDA has] accepted RWE -- using data from registries, natural history studies and chart reviews -- to **establish a comparison arm** in single arm trials" Scott Gottlieb, M.D., former FDA commissioner	"FDA sees promise in the **opportunities created by pragmatic clinical trials**, including broader inclusion/ exclusion criteria and streamlined data collection" Framework for FDA's RWE Program	"**Decentralized** trials that are conducted at the point of care – and that **incorporate real world evidence** (RWE) -- can help clinical trials become more agile and efficient" Scott Gottlieb, M.D., former FDA commissioner
EMA	"RWE can be used to better understand **single arm data** when RCTs are not/less feasible" EMA Joint Big Data Taskforce	"It is in the interest of public health to fully explore the potential **added value of pragmatic trials** in the context of regulatory decisions" Guido Rasi, Executive Director EMA	"…data collection via **mobile phones, tablets and other telemedicine services** enable patients to participate in clinical trials from home, regardless of geographical location" EMA Joint Big Data Taskforce

"RWD can come from a number of sources, for example: electronic health records, claims and billing activities, product and disease registries, patient-generated data including in home-use settings, data gathered from other sources that can inform on health status, such as mobile devices." – *FDA, February 2019*

Conclusions: Work to Do - "*The Road Less Traveled*"

- "***The Road Less Traveled***" by M Scott Peck MD, psychiatrist and author
  - Book begins with the statement "Life is difficult" and is a series of problems to be solved or ignored
  - By analogy: the RWE road less traveled has similarities and will be more traveled and result in important information for patients and providers around drug effectiveness and safety in the real world

In *The Road Less Traveled*, Peck wrote of the importance of discipline. He described four aspects of discipline*:

- **Delaying gratification**: Sacrificing present comfort for future gains
- **Acceptance of responsibility**
- **Dedication to truth**
- **Balancing**: the problem of reconciling multiple, complex, possibly conflicting factors that impact on an important decision

- **We have work to do on many levels. More precedent case examples will help frame RWD/E use and 'fit for purpose' considerations**

PATIENTS FIRST

*borrowed from Wikipedia

THANK YOU

Questions? Comments?

medidata

Case Study Illustrating that a Synthetic Control Arm derived from Historical Clinical Trials and Matching of Baseline Characteristics can Replicate the Overall Survival of a Randomized Control

Case Study in Non-Small Cell Lung Cancer

Working Group

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Daiichi Sankyo

The Challenge: Recruitment, Retention, and Compliance in Randomized Control

- Maintaining a concurrent control arm can be difficult due to rarity of the disease or availability of the investigational agent outside the study
- BRAVO study in BRCA+ breast cancer[1]
  - Unusually high rate of censoring in the control arm likely associated with increased availability of PARP inhibitors
  - Unlikely to produce data that is interpretable
- Sunitinib Malate in gastrointestinal stromal tumor[2]
  - Large effect on progression free survival (HR 0.33, 95% CI (0.24, 0.47))
  - After 84% of placebo patients elected to receive sunitinib malate, effect on overall survival was not observed (HR 0.88, 95% CI (0.68, 1.1))

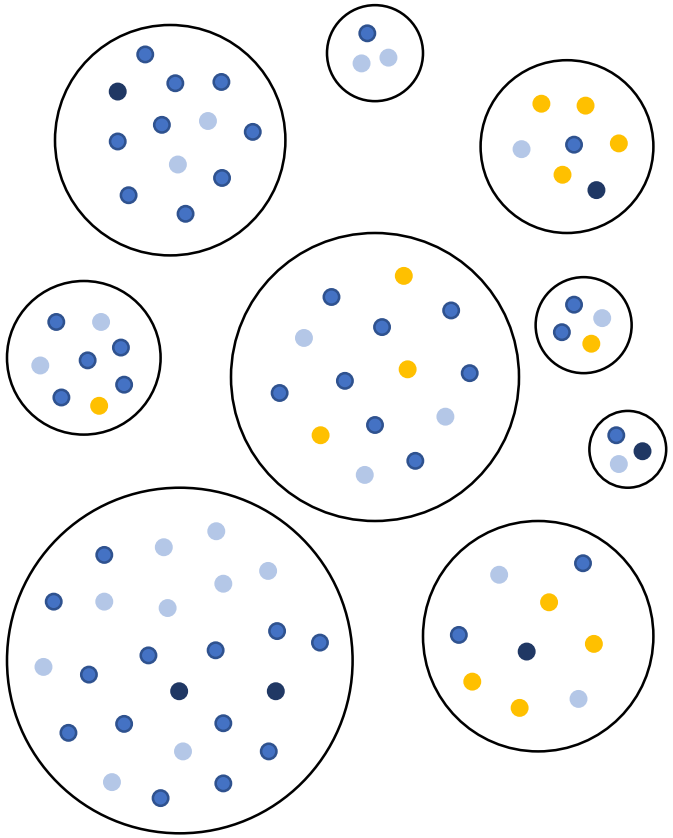
1. Tesaro press release (2017)
2. Sunitinib malate capsule prescribing information (2006)

A Possible Solution – Synthetic Control Arm

A Synthetic Control Arm is

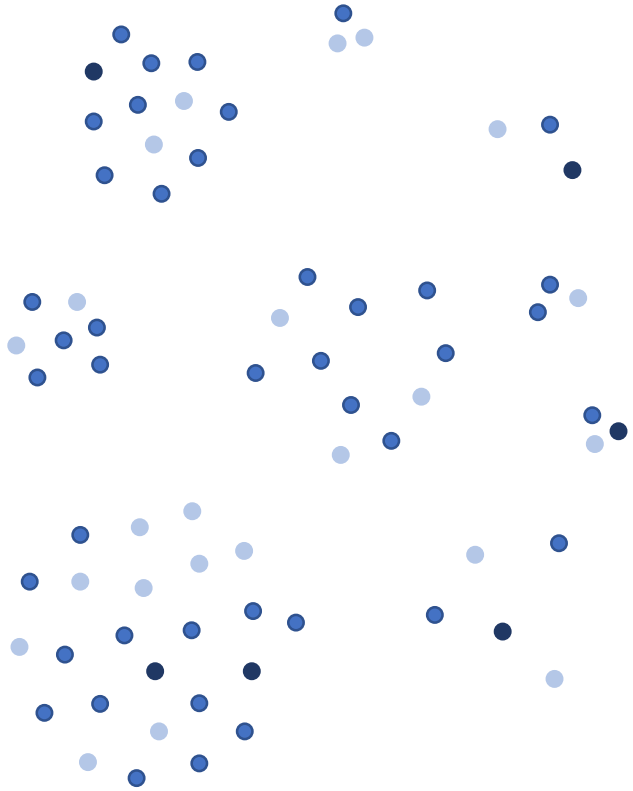
- *Patient level data from multiple historical clinical trials in the same indication*
- *Carefully selected historical patients*
  - Who meet eligibility criteria and were assigned to receive the appropriate standard of care
  - With baseline characteristics that statistically match those in the current-day experimental arm
- *For a setting where a randomized control is problematic*

Historical Clinical Trials Data

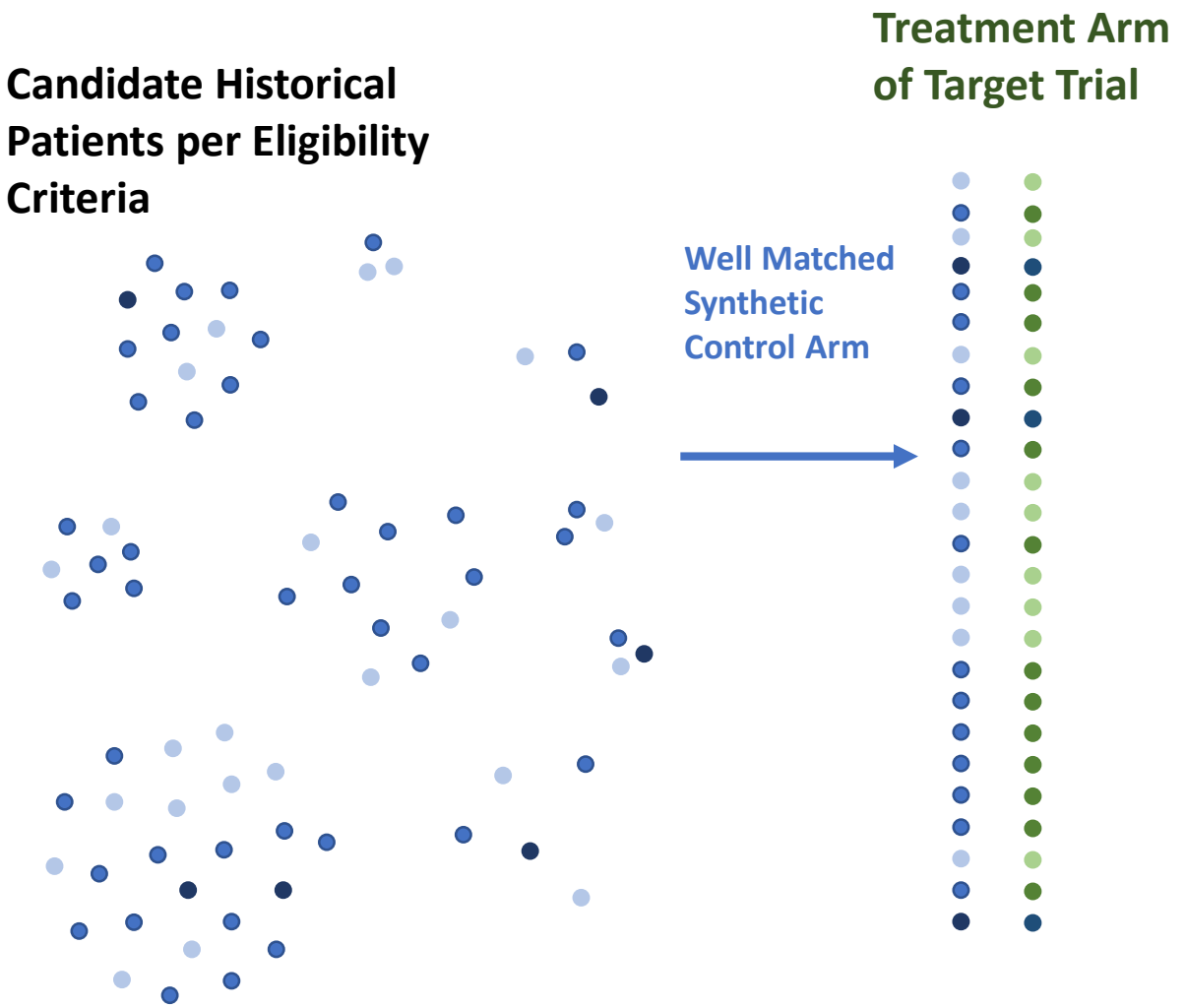


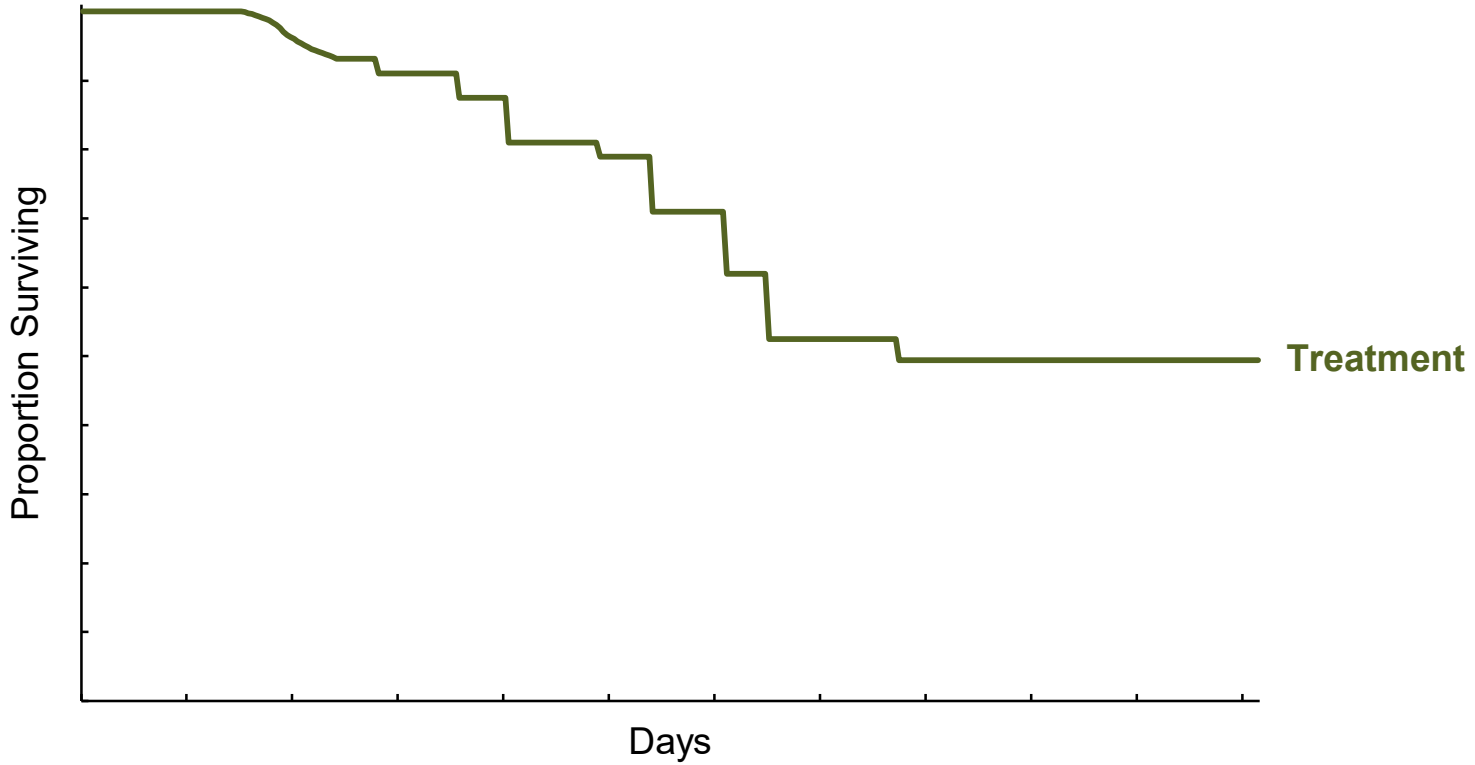
Treatment Arm of Target Trial

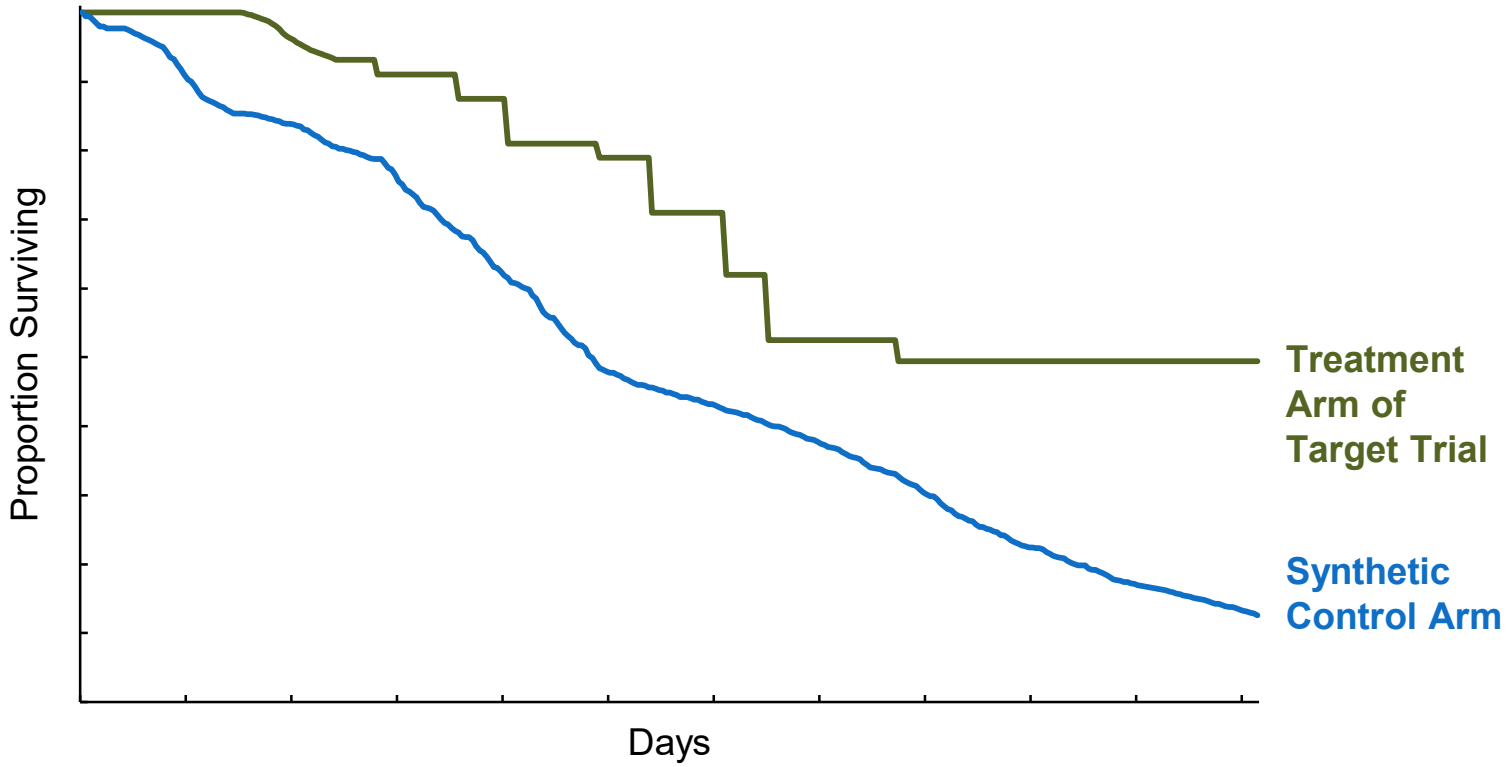
Candidate Historical Patients per Eligibility Criteria

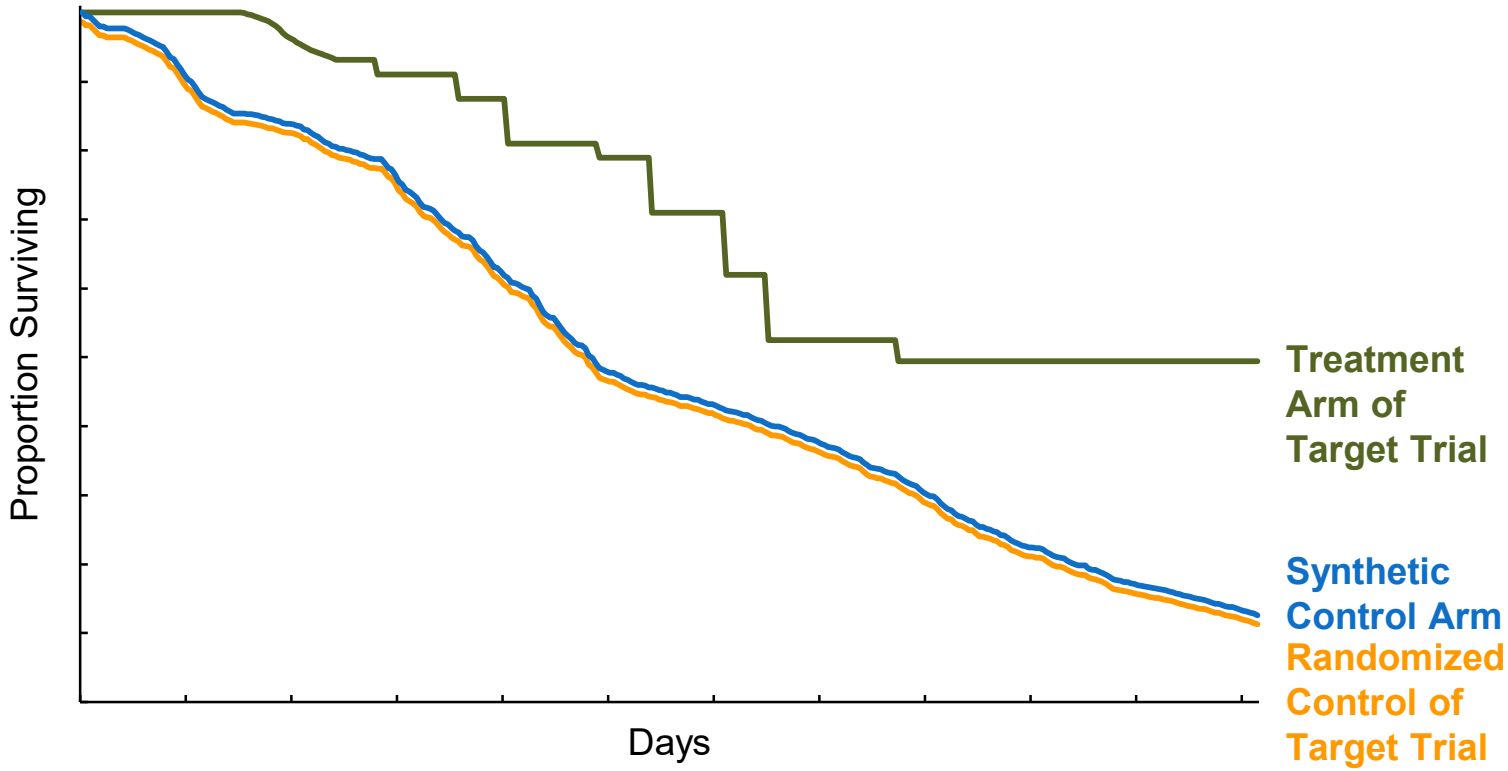


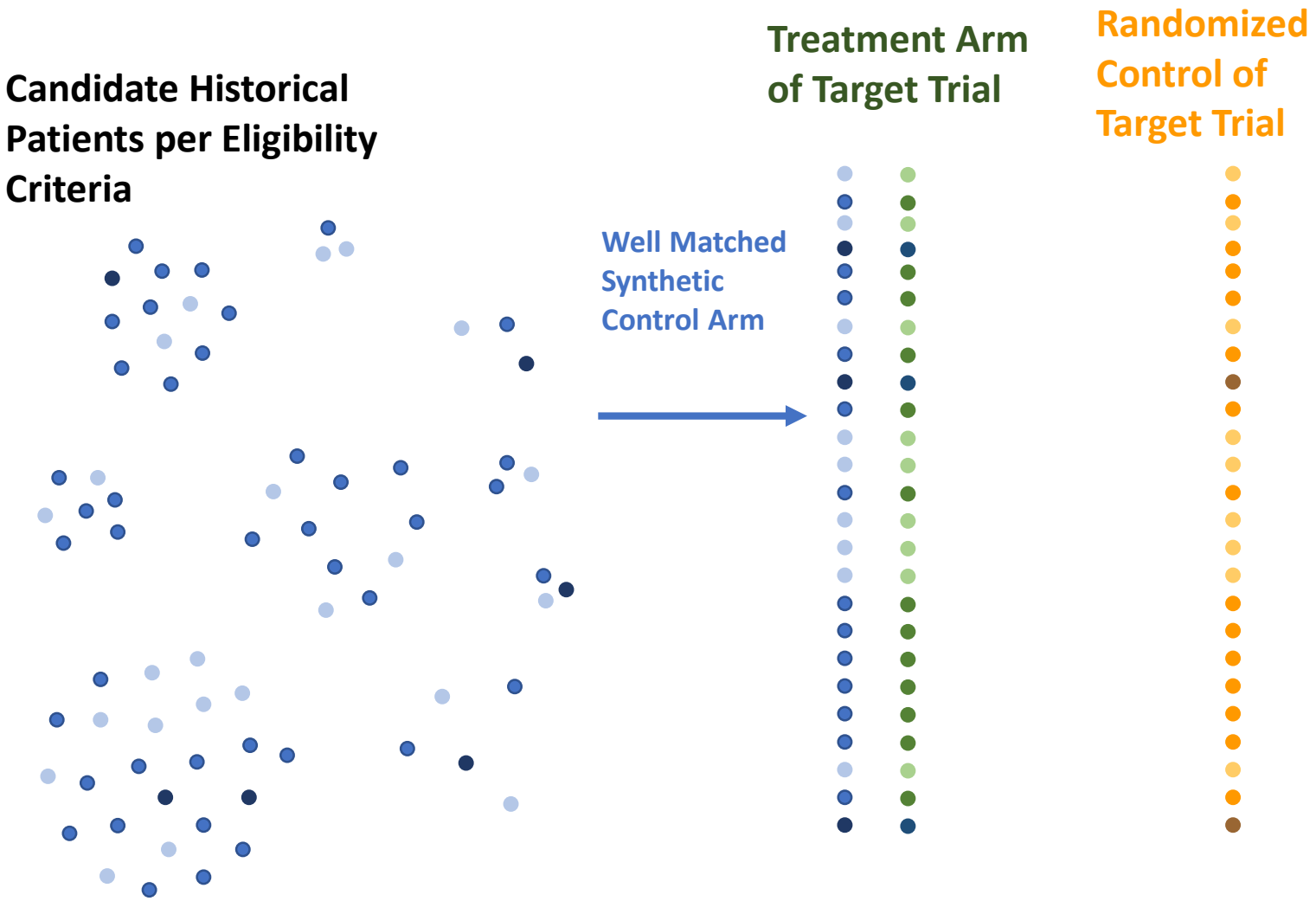
Treatment Arm of Target Trial



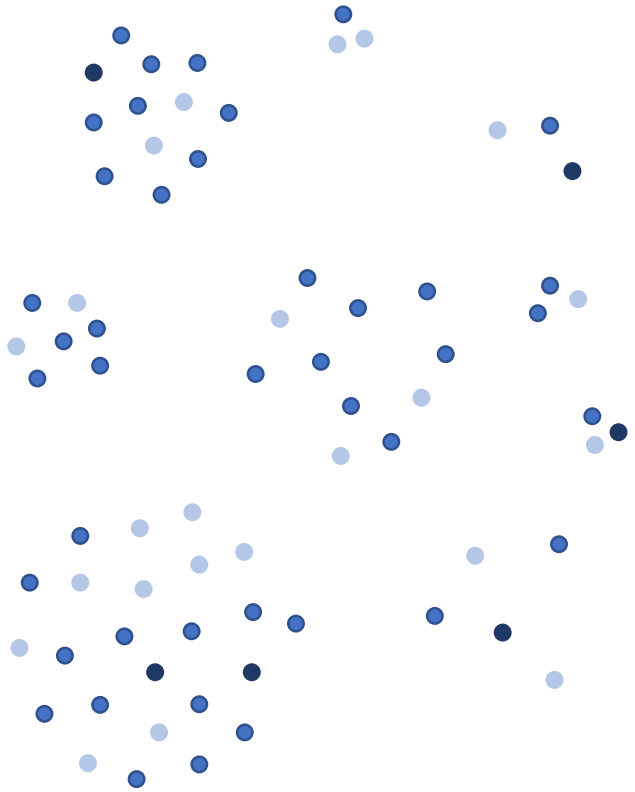






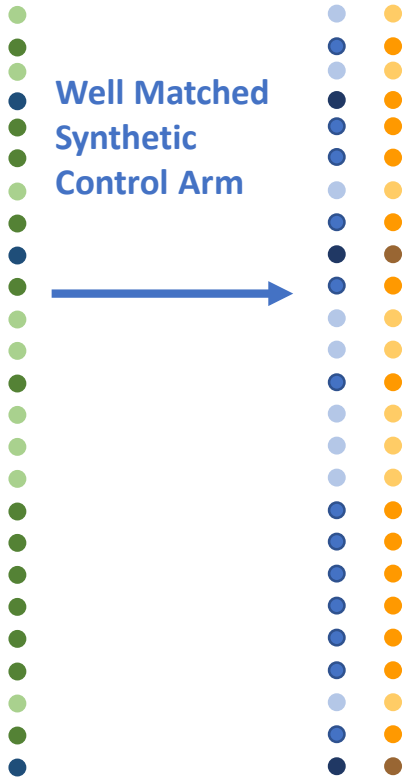


Candidate Historical Patients per Eligibility Criteria

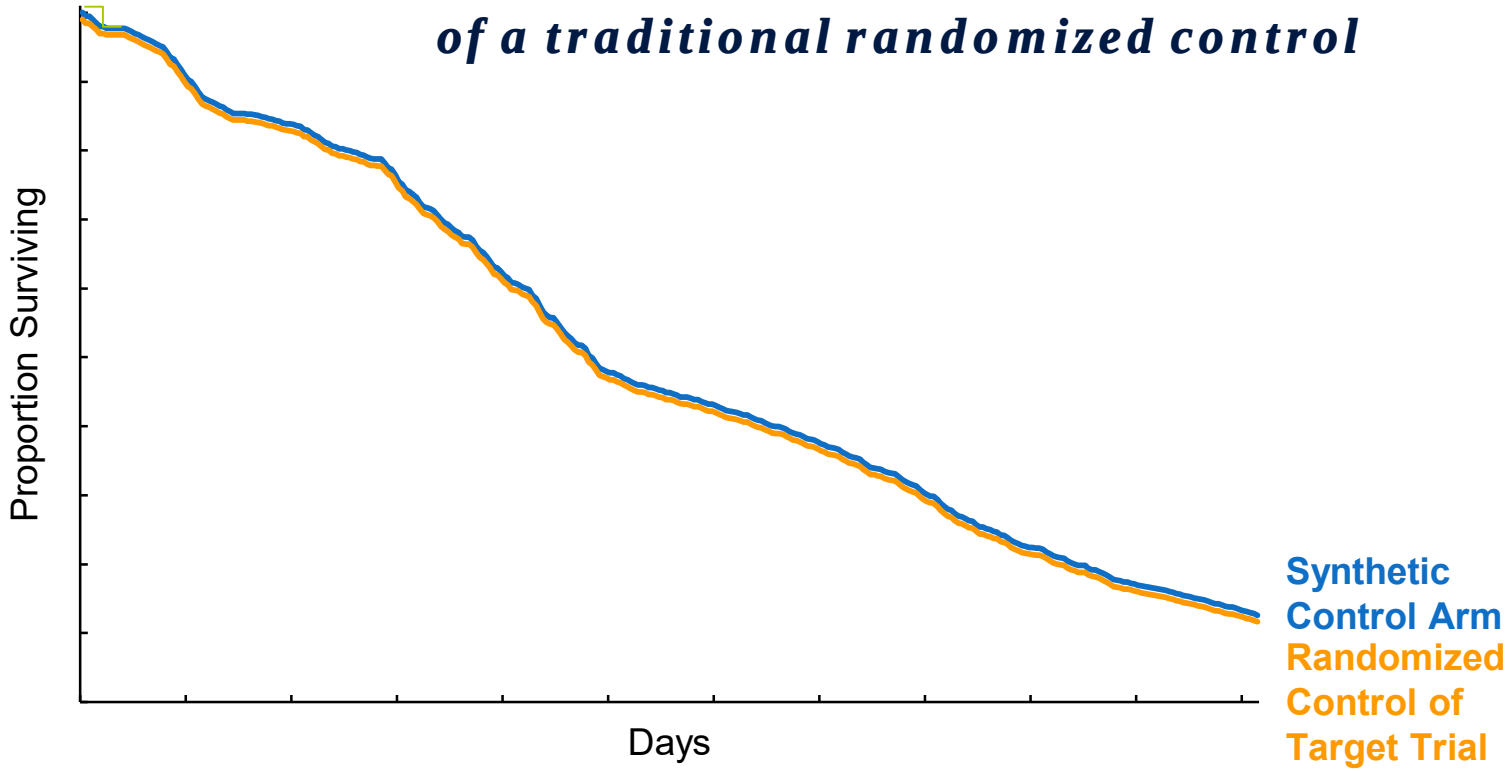


Treatment Arm of Target Trial

Randomized Control of Target Trial



Case Study Objective: Assess whether a Synthetic Control Arm can be created to replicate the outcomes of a traditional randomized control



Non-Small Cell Lung Cancer Case Study

Building the SCA

Propensity Score Matching

Patient level data from multiple previous NSCLC trials

Data Sources

- Project Data Sphere[1]
- Medidata Enterprise Data Store (MEDS)[2]

Trial Characteristics

- Open label and blinded phase 2 & 3 trials
- Multinational
- Timespan of starts of trials (2004 to 2013)
- Overall survival measured

SCA Patient Eligibility Criteria

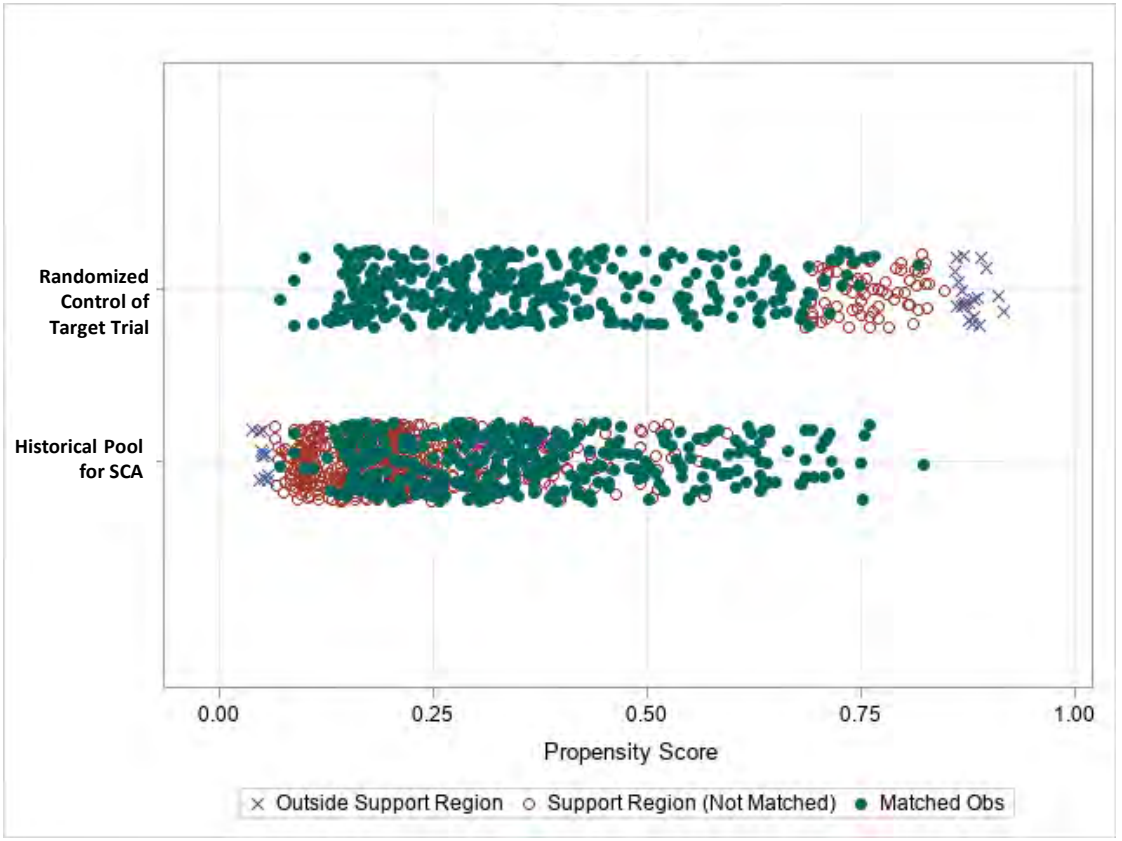
- Inclusion in a historical clinical trial accessible within this project
- NSCLC at stage III or IV
- Received prior platinum-based chemotherapy
- Men and women ≥ 18 years of age
- ECOG performance status of ≤ 2
- Measurable disease
- Received treatment with docetaxel

1. These analyses are based on research using information obtained from www.projectdatasphere.org, which is maintained by Project Data Sphere, LLC. Neither Project Data Sphere, LLC nor the owner(s) of any information from the web site have contributed to, approved or are in any way responsible for the contents of this work.
2. Includes thousands of previous clinical trials conducted by the pharmaceutical industry for drug or medical product development with patient level data recorded through the Medidata electronic data capture system. Legal agreements permit use in deidentified (i.e., patients and original sponsor of the trial cannot be identified) and aggregated (i.e., every analysis must include data from two or more sponsors) form.

Prespecified Propensity Score Matching

Baseline Characteristics for Matching

- Age at baseline (continuous)
- Years from cancer diagnosis (continuous)
- Race (White vs Others)
- Sex (Female vs Male)
- Smoking (Current vs Former vs Never)
- Histology (Squamous vs Non-squamous)
- Stage (III vs IV)
- ECOG (0 vs 1 vs 2)
- Prior surgery (Yes/Maybe vs No)
- EGFR/KRAS mutation (Positive vs No/Unknown)

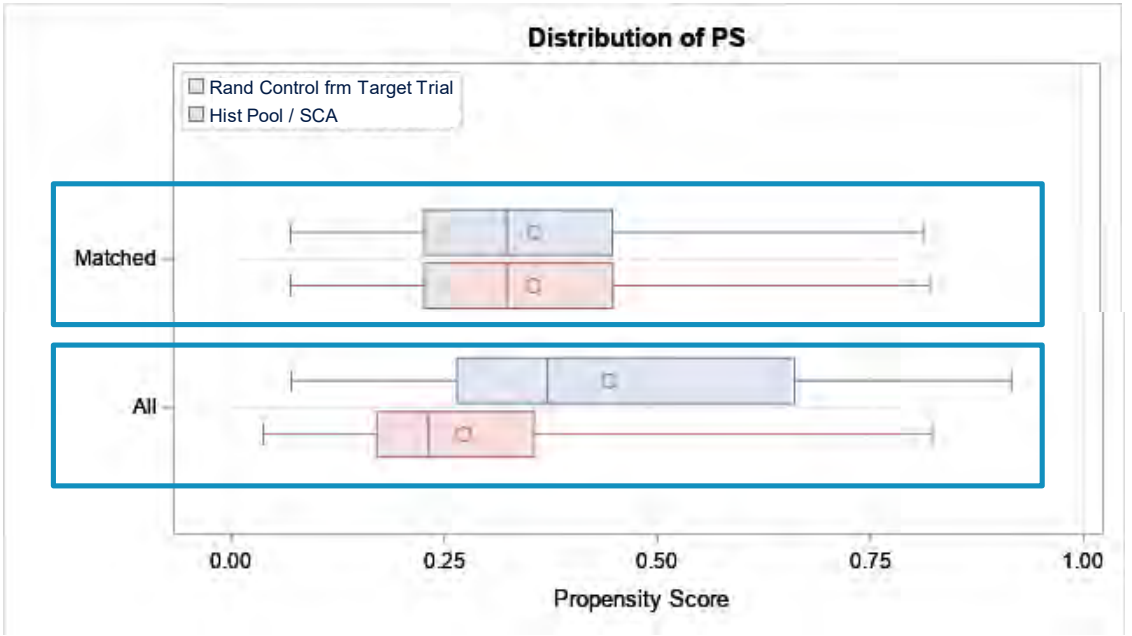


Matching Performance

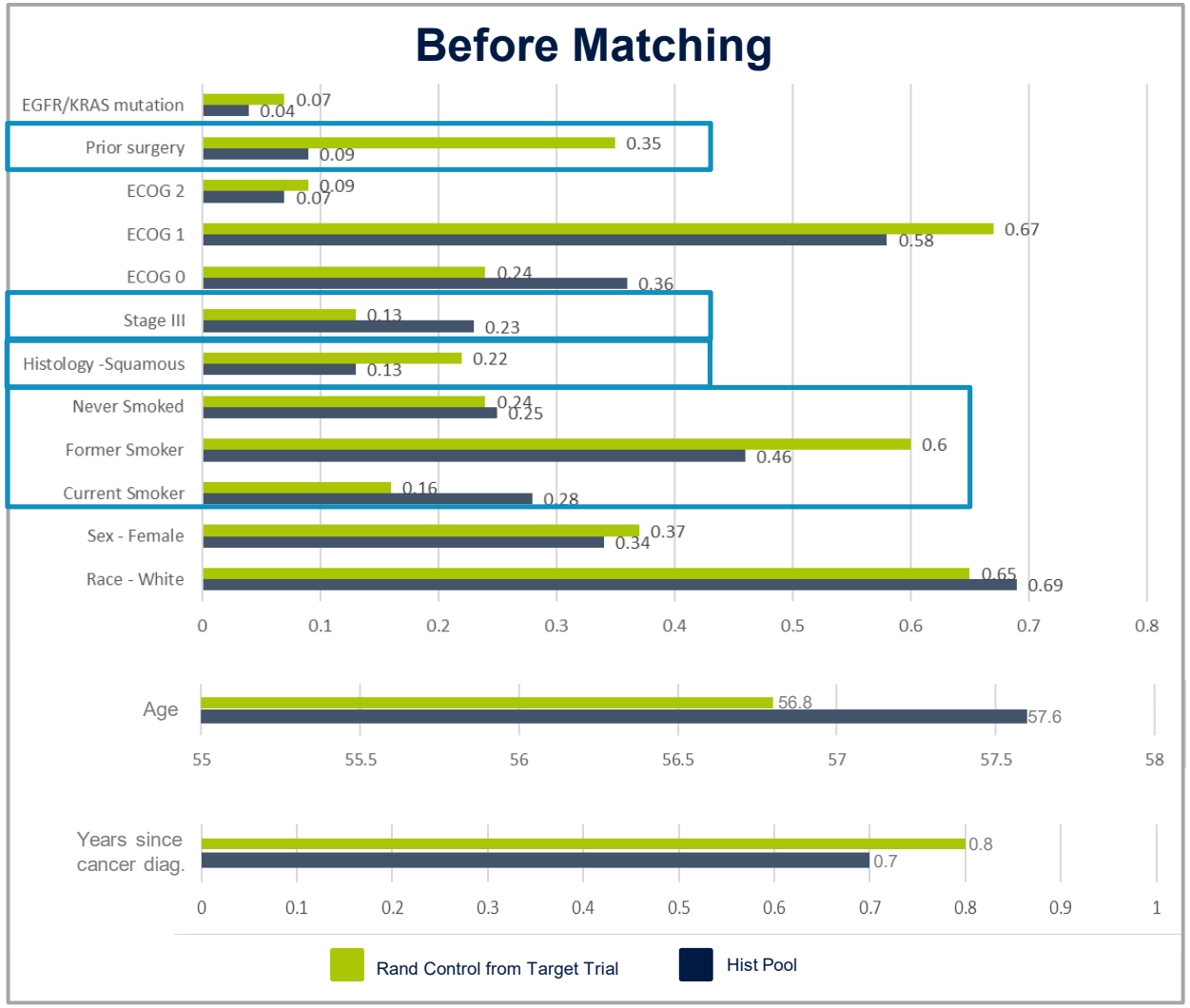
Baseline Comparability

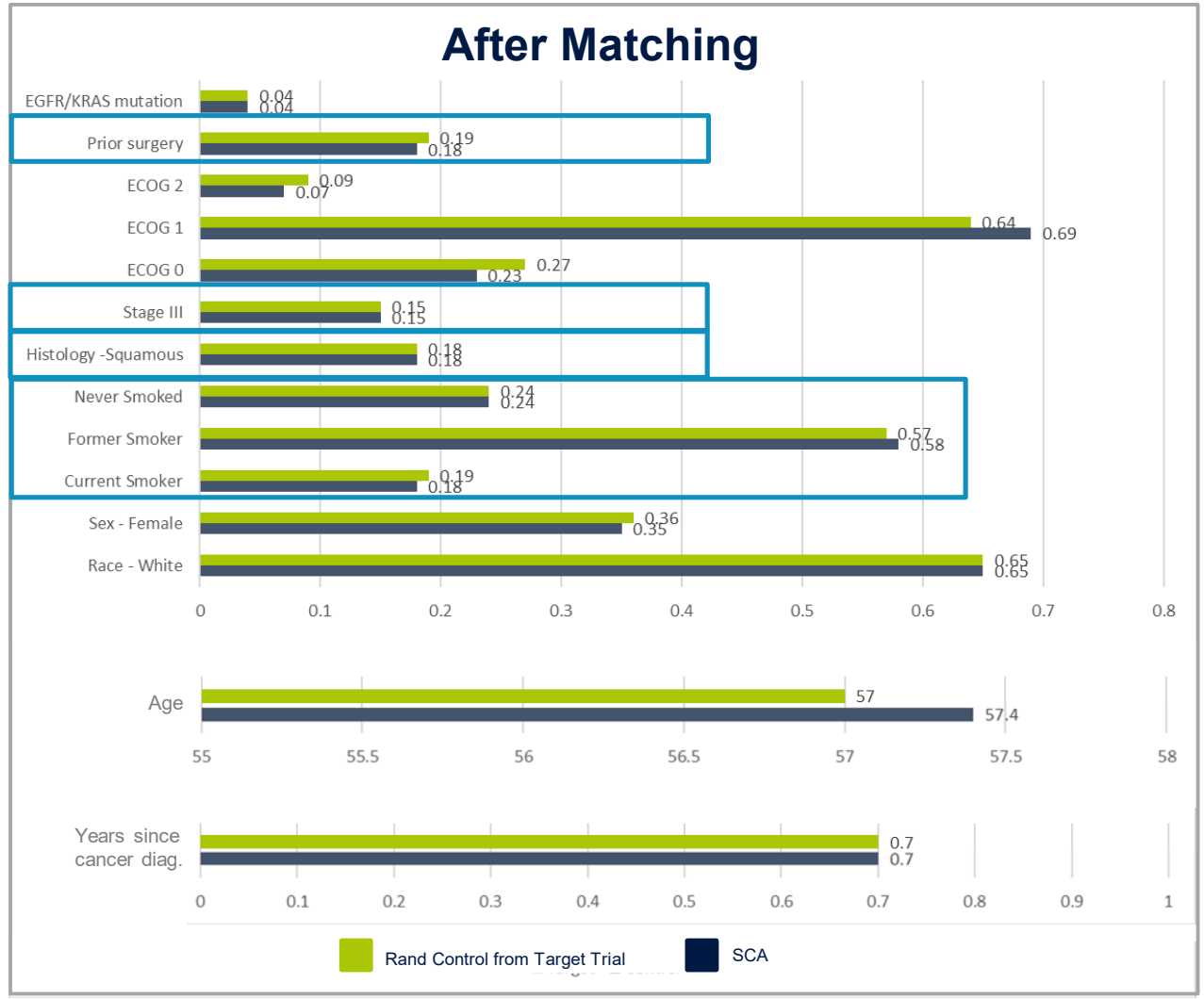
Comparability of SCA & Target Control

- *Considerable mismatch of propensity scores before matching*
- *After matching, SCA and Randomized Control from Target Trial have similar propensity score distributions*

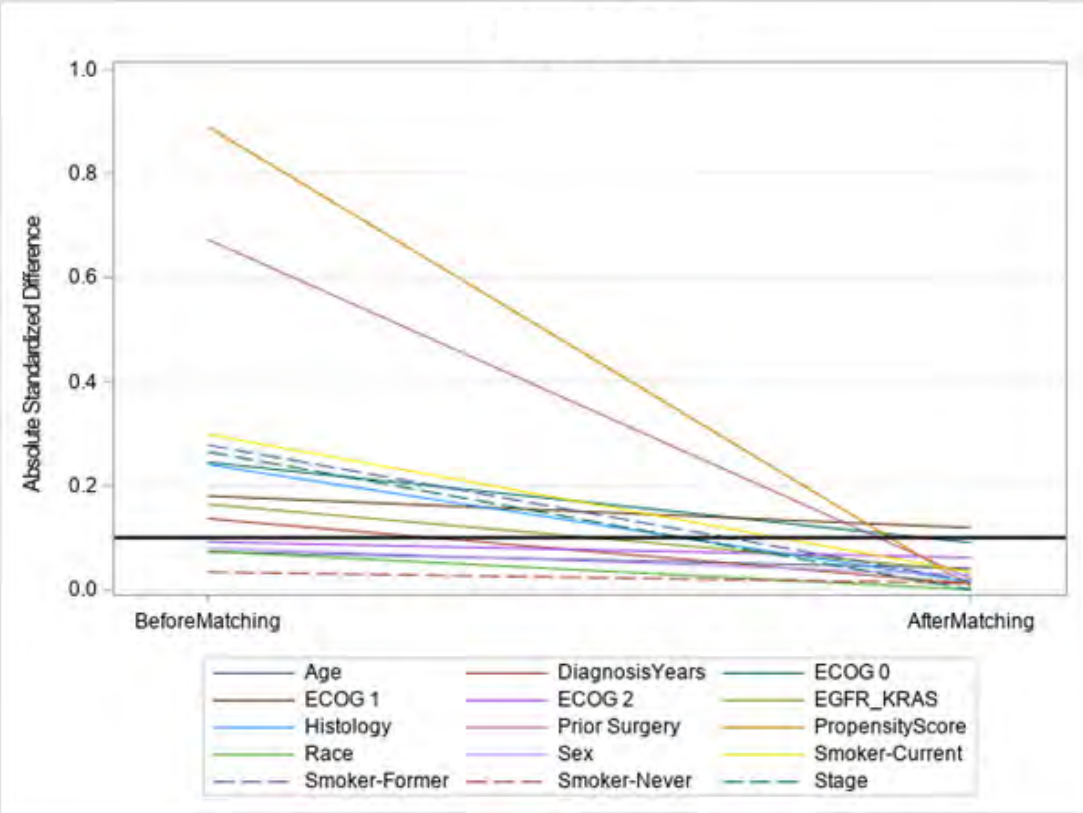


Baseline Characteristics Well Balanced After Matching





Absolute Standardized Differences in Baseline Characteristics are Small/Negligible After Matching



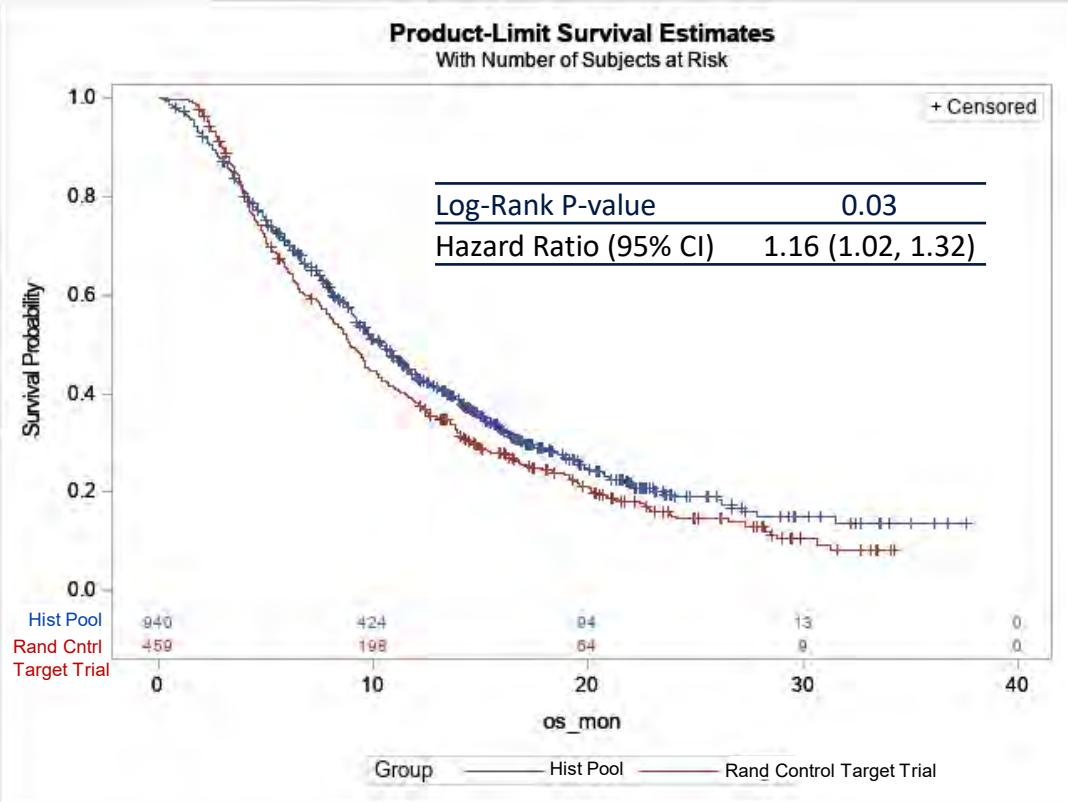
Propensity score matching has achieved good balance of baseline characteristics between the SCA and the randomized control from target trial.

SCA Validation

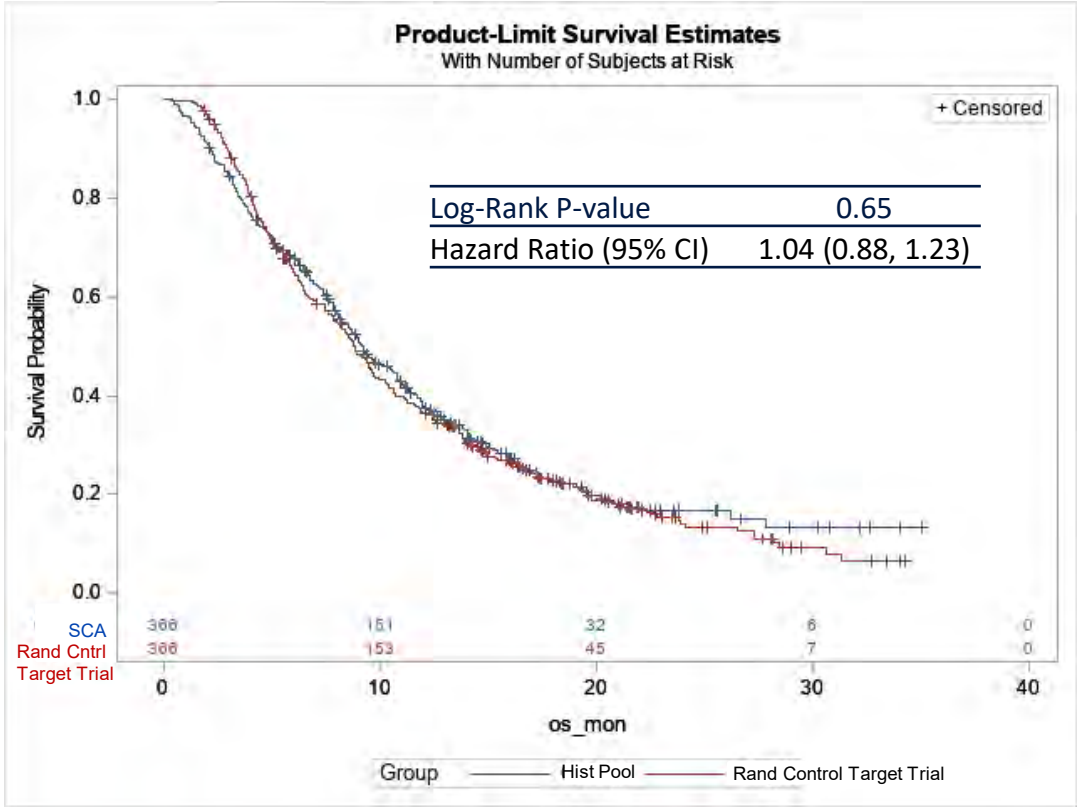
Overall Survival

Overall Survival

Before Matching



After Matching

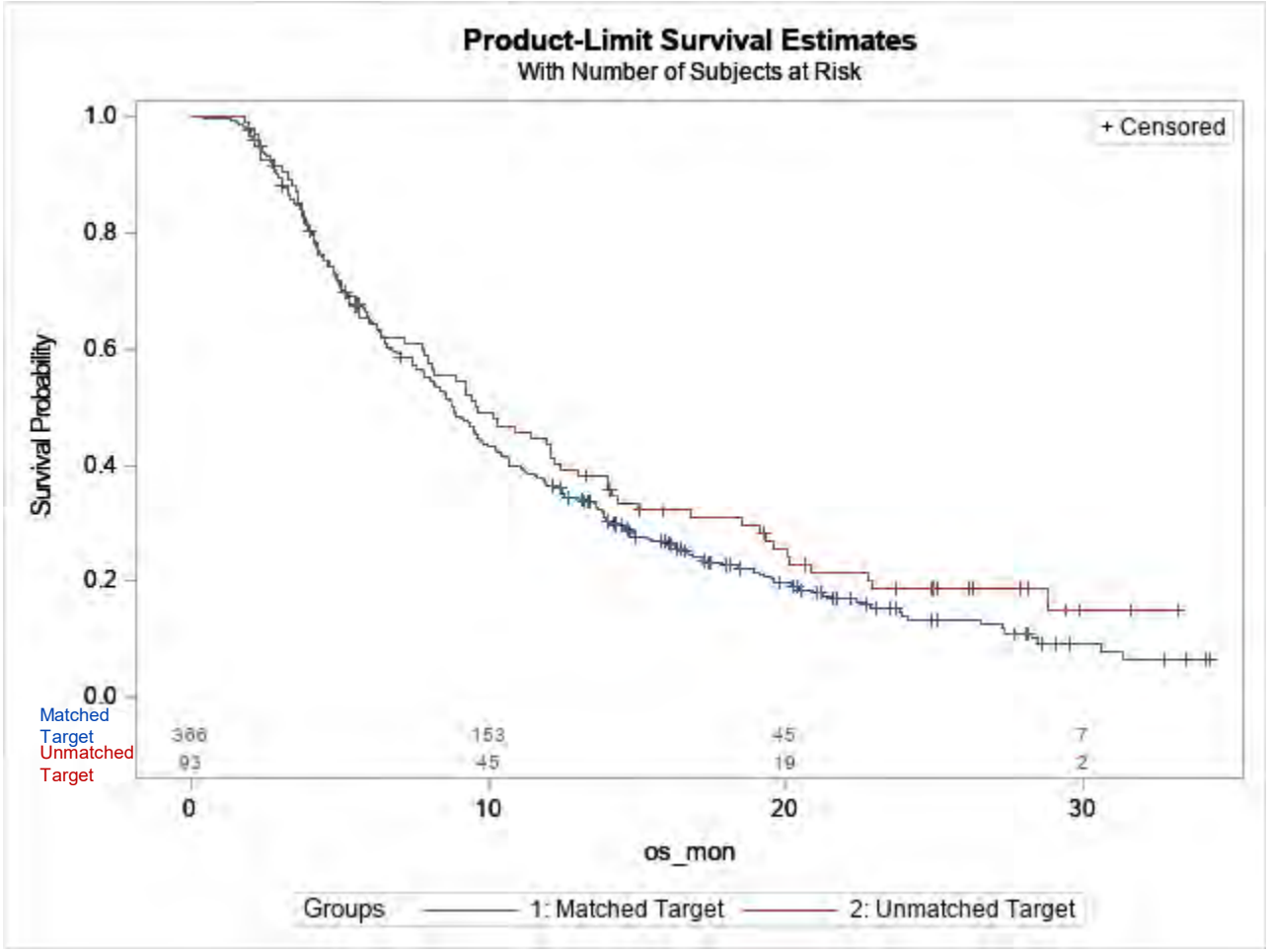


Summary

- *In this NSCLC case study, **SCA successfully replicated the control arm** of the target trial*
- *Important step in understanding how **SCA may mitigate challenges faced with a concurrent control arm** in difficult-to-study indications*
- *Future work*
  - Assessment of whether the treatment effect can be replicated with the use of SCA
  - Exploration of tweaks to the matching methods to reduce the proportion of patients who are not matched
  - Expand to additional indications

Thank you.

Overall Survival – Matched versus Unmatched Patients from Randomized Control



RWE Pilot Project Data: Characterization of Real-World Endpoints to Assess Long-Term Benefit

Jeff Allen, PhD
Friends of Cancer Research

Correlation of real-world endpoints to overall survival among immune checkpoint inhibitor-treated aNSCLC patients

Project Goals: Explore potential endpoints that may be fit for regulatory purposes as well as assessing long term benefits of a product

Project Focus	Evaluate the performance of real-world endpoints across multiple data sets by focusing on a common question: ***What outcomes can be evaluated for advanced NSCLC (aNSCLC) patients treated with immune checkpoint inhibitors?***
Research Objectives	Objective 1: Characterize the demographic and clinical characteristics of aNSCLC patients treated with immune checkpoint inhibitors Objective 2: Assess ability to generate real-world endpoints (OS, PFS, TTP, TTNT, TTD) in aNSCLC patients treated with immune checkpoint inhibitors, and segmented by clinical and demographic characteristics Objective 3: Assess performance of real-world endpoints (PFS, TTP, TTNT, TTD) as surrogate endpoints for overall survival (OS)
Study Design	This is a retrospective observational analysis of data derived from electronic health record (EHR) and claims based databases. The datasets generated for the study will include all relevant, retrospective patient-level data available for eligible individuals up to the data cutoff date, pending approval by a third-party de-identification.
Data Partners	**Cota, Flatiron Health, IQVIA, Kaiser Permanente/CRN, Mayo Clinic/OptumLabs®, and PCORnet/University of Iowa**

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Characteristics of Participating Data Sources

	Cancer Research Network	Cota Healthcare	Flatiron Health	IQVIA™	OptumLabs® Data Warehouse	PCORnet
Data Source	Virtual Data Warehouse (VDW)[1]	De-identified, longitudinal data source comprised of abstracted patient-level EHR data from contributing provider sites including academic medical centers, community practices and hospital systems	De-identified patient-level clinical data from OncoEMR, Flatiron's oncology-specific EHR, and integrations with academic EHRs (e.g., Epic); data includes a complete copy of the medical record as well as patient-level linkages to other datasets to fill gaps (e.g., mortality)	Diversified oncology EHRs, including EHRs from TransMed, that are de-identified at the patient level	Medical claims data and enrollment information for commercial and Medicare Advantage enrollees in a large US health plan	Pooled dataset from 11 medical centers participating in a PCORnet Rapid Cycle Project –PCORnet Common Data Model linked with tumor registries
Setting	Community-based healthcare systems	Predominantly community practices (90%+) in this project	Predominately Community Oncology practices (80% of patients) and Academic Medical Centers (20% of patients)	Predominantly community oncology practices (90%+)	Paid claims from provider, which include enrollees treated in both community practice and the academic settings (or both)	Ten academic medical centers and one multi-hospital healthcare system
Region	Across the U.S.	Northeast and Mid-Atlantic regions in this project	800+ sites of care at 280+ clinics across the U.S.	Sources from sites across the U.S.	Geographically diverse across the U.S.	Eleven states - Great Plains/Midwest, Mid-South, and Florida
Single Source or Linked	Linked	Multi-sourced EHR data linked for supplementation (e.g. mortality data sources)	Linked to resolve data gaps (e.g., SSDI and commercial death data)	EHR from several sources, including multiple EHR software systems and networks integrate at a patient level	Linked data. For this project, race and SES information, and death information from the SSA DMF is linked to health plan enrollees (note: SSA DMF results are not reported)	Linked
Data Processing	Structured EHR and other clinical and administrative data only	Structured and unstructured EHR data collected through Cota's software platform and subject to a rigorous quality control process	Structured EHR data and unstructured EHR and document data curated by clinical experts using a single software interface and PHI controls	Structured EHR elements included. Custom abstractions of unstructured elements were excluded for this analysis	Structured files included in this analysis	Structured EHR and other clinical and administrative data only

Real-World Endpoint Assessment

Real-world derived endpoint definitions

Overall survival (OS)

- *Data definition / computation*: length of time from the date the patient initiates the PD-(L)1 regimen to the date of death. Patients without a date of death will be censored at their last known activity.

Time to Next Treatment (TTNT)

- *Data definition / computation*: length of time from the date the patient initiates the PD-(L)1 regimen to the date the patient initiates their next systemic treatment. When subsequent treatment is not received (e.g., continuing on current treatment), patients will be censored at their last known activity.

Time to Treatment Discontinuation (TTD)

- *Data definition / computation*: length of time from the date the patient initiates the PD-(L)1 regimen to the date the patient discontinues treatment. Patients still on treatment will be censored at their last known activity.

Definition of progression in aNSCLC as evident in the EHR

A **progression event** is a distinct episode in which the treating clinician concludes that there has been growth or worsening in the aNSCLC. The progression event (and date) is based on review of the patient chart.

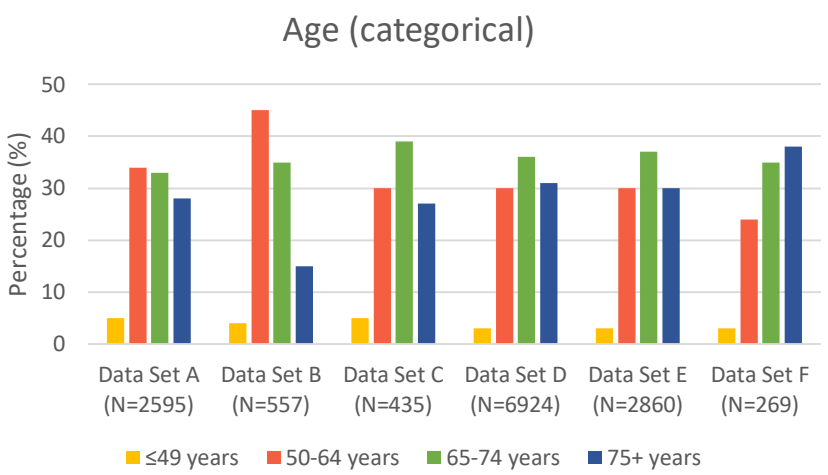
Progression Free Survival (PFS)

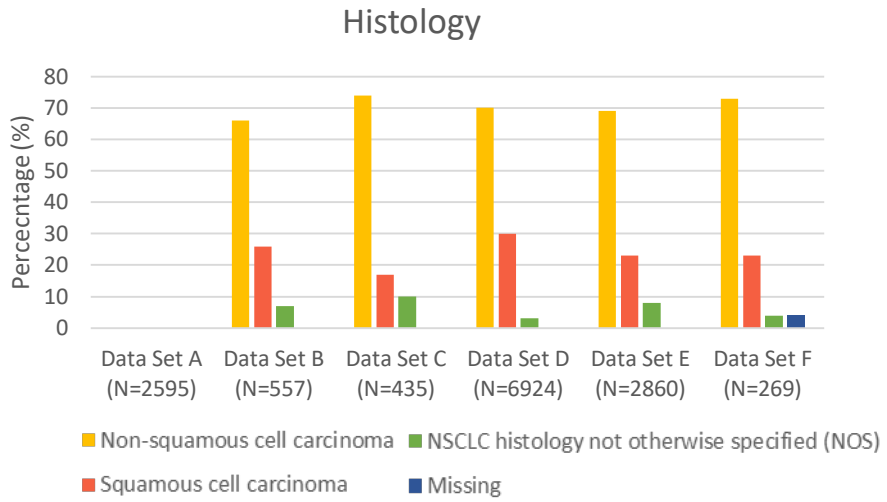
- *Data definition / computation*: length of time from the date the patient initiates the PD-(L)1 regimen to the date that a progression event as evident in the EHR is documented in the patient's chart or the patient passes away. Patients without a progression event or date of death will be censored at the end of the patient's chart.

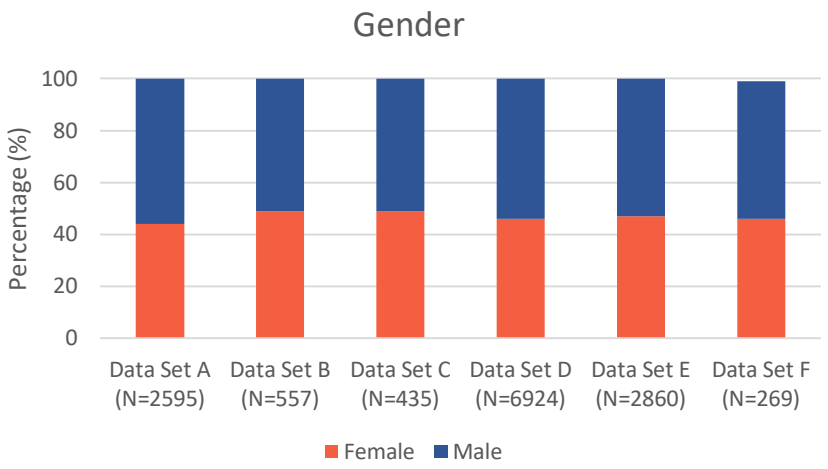
Time to Progression (TTP)

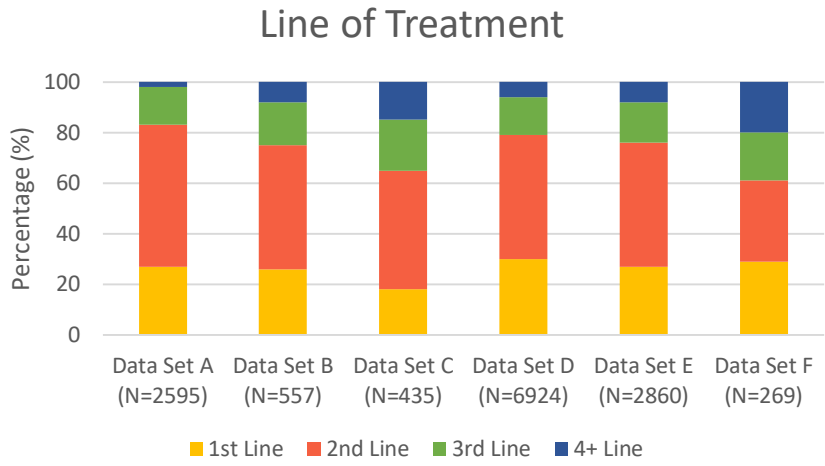
- *Data definition / computation*: length of time from the date the patient initiated the PD-(L)1 regimen to the date that a progression event as evident in the EHR is documented in the patient's chart (excludes death as an event). Patients without a progression event will be censored at the end of the patient's chart.

Shared demographic and clinical characteristics among data sets









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Median Time and 95% CI for Real-World Extracted Endpoints

Data Set	rwOS	rwTTD	rwTTNT	1-Year rwOS Landmark Analysis
A	13.50 [12.80, 14.50] #	7.03 [6.27, 9.97]	22.50 [NA]	0.57 [0.52, 0.57]
B	15.78 [12.2, 24.59]; 8.58 [7.56, 10.26] *	3.25 [2.76, 3.75]	12.95 [10.29, 14.73]	0.54 [0.48, 0.59]; 0.41 [0.32,0.49]
C	8.67 [6.83, 10.02]	4.70 [3.68, 5.52]	11.60 [8.80, 16.10]	0.40 [0.35, 0.46]
D	9.15 [8.82, 9.51]	3.21 [3.21, 3.44]	14.03 [12.89, 15.15]	0.42 [0.41, 0.43]
E	12.69 [11.7, 13.87]	3.63 [3.40, 3.87]	12.07 [11.24, 13.48]	0.51 [0.49, 0.53]
F	12.30 [9.61, 16.94]	4.60 [3.71, 6.32]	12.50 [9.29, NA]	0.40 [0.34, 0.48]

OS was calculated as months between I/O initiation and disenrollment.

* Sites with social security or state death data, censored at estimated earliest date such data should be available if no death was observed

Correlation between rwOS and real-world extracted endpoints

	rwOS vs rwTTNT		rwOS vs rwTTD	
Data Set	N	Correlation [95% CI]	N	Correlation [95% CI]
A	83	0.36 [0.15, 0.53]	254	0.63 [0.55, 0.70]
B	86	0.77 [0.67, 0.85]	254	0.62 [0.54, 0.69]
C	96	0.70 [0.58, 0.79]	295	0.89 [0.86, 0.91]
D	1203	0.61 [0.57, 0.64]	4337	0.80 [0.79, 0.81]
E	358	0.62 [0.54, 0.68]	1456	0.77 [0.75, 0.79]
F	39	0.46 [0.33, 0.81]	142	0.80 [0.66, 0.85]

	rwOS vs rwPFS		rwOS vs rwTTP	
Data Set	N	Correlation [95% CI]	N	Correlation [95% CI]
D	4337	0.75 [0.74, 0.76]	2286	0.60 [0.57, 0.63]
F	142	0.84 [0.62, 0.86]	55	0.56 [0.21, 0.71]

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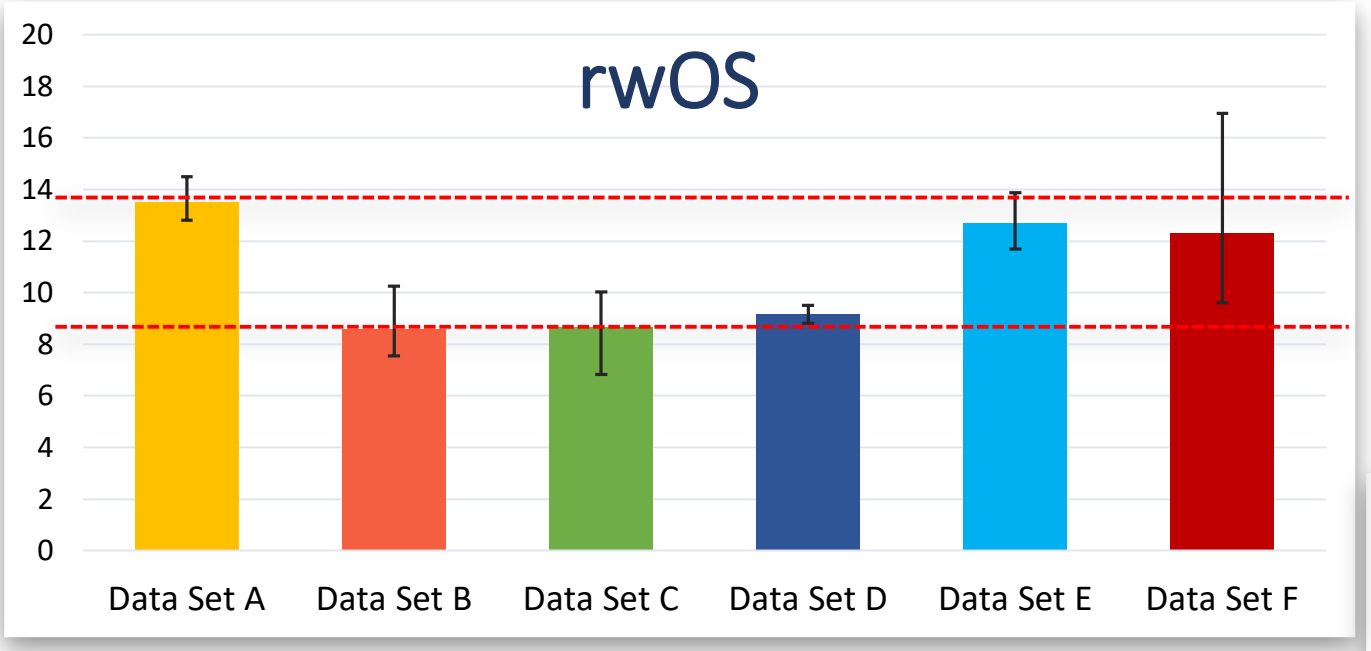
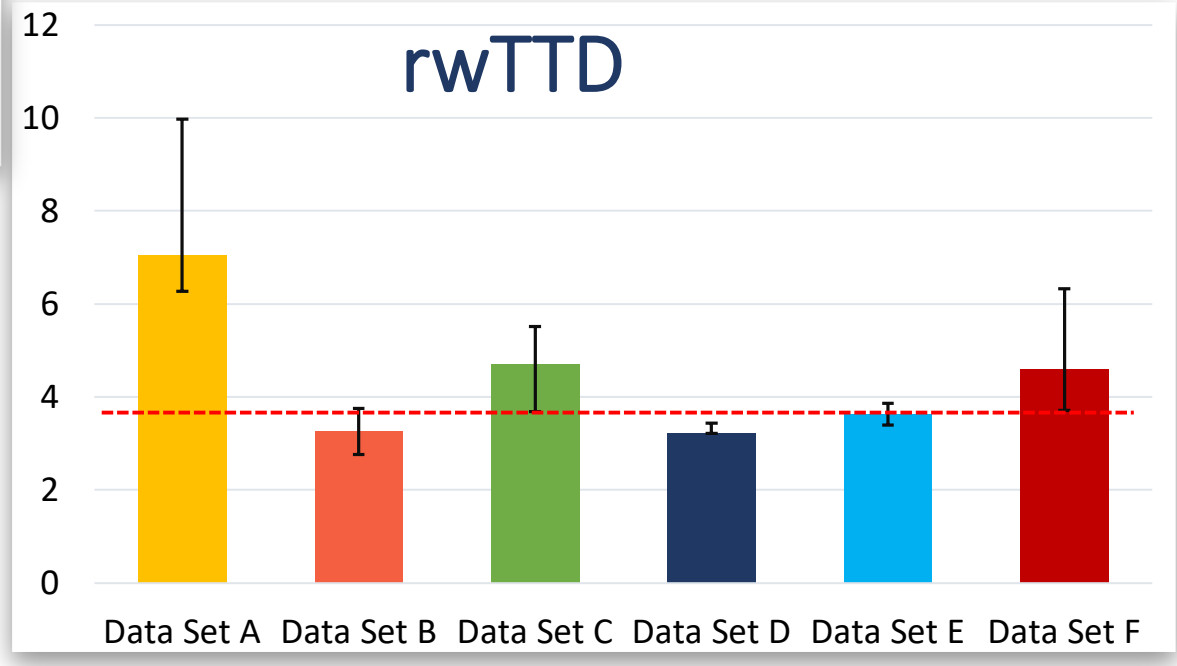


G *Huang*, et al. Oncotarget. (2018) 9(3) 4239-4248.

-------- = range of median OS measured in RCTs

-------- = TTD measured in RCTs



Y Gong, et al. JCO. (May 2018) 36 no.15 suppl; 9064.

Conclusions

1. There is a high level of shared characteristics among the varying data sets despite varying sample sizes, data capture processes, and data sources demonstrating the feasibility of identifying aNSCLC patients treated with immune checkpoint inhibitors from diverse RWD sources.

2. Assessment of extracted endpoints from EHR and claims data demonstrate that efficacy of immune checkpoint inhibitors is relatively consistent across a variety of patient characteristics, such as age and sex.

3. The pilot project demonstrated that several extractable endpoints from EHR and claims data correlate with OS. Further validation is required to determine whether these endpoints are reliable proxies for OS outside of a RCT and whether they can support regulatory and payer decision-making.

4. Survival among patients as assessed through EHR and claims data fall within the range of median OS values observed in several immune checkpoint inhibitor trials, however data regarding dates of death varied by data source

Next Steps

- RWE is not posed here as a solution to every problem, but rather a cost effective and relatively reliable tool for understanding cancer treatment heterogeneity and effectiveness

- RWD provides the opportunity to:
  - Investigate populations and/or drug combinations not studies in clinical trials
  - Supplement studies for effectiveness and long-term surveillance
  - Provide insights for scare populations or when loss of clinical equipoise may make randomization difficult

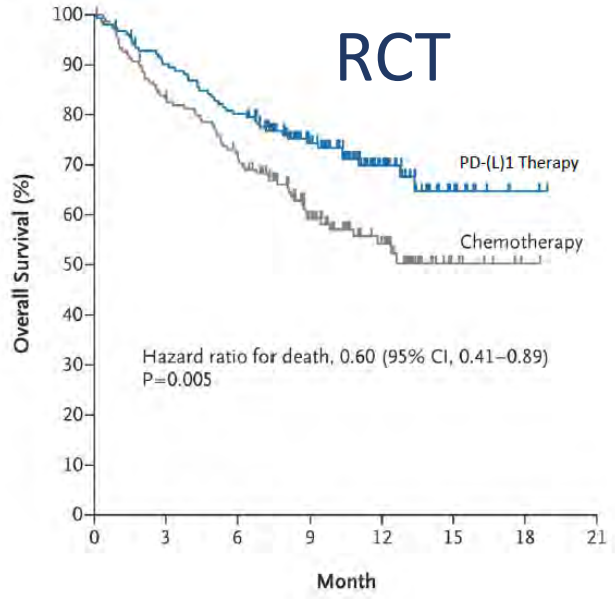
- RWD may have missing common data elements, will almost always have nonstandard timepoints at which data are collected, and reflect variability in types of diagnostic tests and data quality

- *Question*: Despite the inherent variability (as compared to protocol-driven data), is RWD sufficient to differentiate between different treatment options?

Next Steps – Pilot 2.0

- Can real-world endpoints be used to accurately characterize differences between available interventions?

RCT



RWE

?

- Can further alignment on data quality and standards be used to develop an analytic framework to evaluate real world endpoints?

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Pilot 2.0: Establishing a Framework to Evaluate Real-World Endpoints

Project Goals: Explore potential endpoints that may be fit for assessing long term benefits of a product compared to an existing alternative	
Project Focus	What is the ability of different real-world endpoints (rwOS, rwTTD, rwTTNT, rwTTP, and rwPFS) to reflect effectiveness previously observed in clinical trials across two frontline treatment pairs in advanced non-small cell lung cancer (aNSCLC) patients?
Research Objectives	Objective 1: Description of demographic and clinical characteristics of patients with aNSCLC receiving the following frontline treatments: doublet chemotherapy; PD-(L)1 monotherapy; or PD-(L)1 + doublet chemotherapy Objective 2: Evaluate and compare rwOS, rwTTD, rwTTNT, rwTTP, and rwPFS among select frontline therapy pairs in aNSCLC patients: • Doublet chemotherapy versus PD-(L)1 monotherapy • Doublet chemotherapy versus PD-(L)1 + doublet chemotherapy Objective 3: Propose a validation framework to assess performance of real-world endpoints in a given dataset.
Study Design	This is a retrospective observational analysis of data derived from electronic health record (EHR) and claims based databases. The datasets generated for the study will include all relevant, retrospective patient-level data available for eligible individuals up to the data cutoff date, pending approval by a third-party de-identification.
Data Partners	**Cancer LinQ, Cota, Flatiron Health, IQVIA, Kaiser Permanente/CRN, Mayo Clinic/OptumLabs®, McKesson, SEER, Syapse, and Tempus**

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Internal Validation Study

- Pilot analyses will assess all patients that received ICI and/or chemotherapy for each of the data sets
- This will allow comparison of the reproducibility of various real-world endpoints and help to identify factors that may lead to differences between data sets
- An additional analysis will include real-world patients that match eligibility requirements in order to assess comparability to clinical trial populations. Such analyses may:
  - Help identify sources of variability – data source, treatment settings, provider level variation
  - Model methodology for potential data quality control
- Such an approach may help to add details about data elements or parameters that should be reported for datasets to be fit for purpose to be used for comparative real-world endpoint analyses

rwEndpoints Use Case: Assessing Frontline Treatment Regimens in Real-world Patients with Advanced Non-Small Cell Lung Cancer

Results Discussion for RWE Pilot 2.0
Public Meeting

September 18, 2019
Washington, DC

Acknowledgements

Pilot 1.0 Data Partners

- Cota
- Flatiron Health
- IQVIA
- Kaiser Permanente/Cancer Research Network
- Mayo Clinic/OptumLabs®
- University of Iowa/ PCORnet

Project Team

- Mark Stewart, PhD
- Laura Lasiter, PhD
- Diana Merino, PhD
- James Wu, MSc, MPH

Key Collaborators

- FDA
- NCI
- PCORI

Pilot 2.0 Data Partners

- Cancer LinQ
- Cota
- Flatiron Health
- IQVIA
- Kaiser Permanente/Cancer Research Network
- Mayo Clinic/OptumLabs®
- McKesson
- SEER/NCI
- Syapse
- Tempus

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American Association for Cancer Research

FINDING CURES TOGETHER℠

SESSION IV:

Large Genomic Databases & Real-world Evidence

Session Moderator: Deborah Schrag, MD, MPH

Speakers:

Wendy Rubinstein, MD, PhD

Robert Grossman, PhD

William S. Dalton, PhD, MD

Neal J. Meropol, MD

Gary Palmer, MD, JD, MBA, MPH

Jonathan Hirsch

Deborah Schrag, MD, MPH

CancerLinQ and RWE: Accomplishments, Barriers to Opportunity, and a Path toward Shared Success

"Large Genomic Databases and Real World Evidence" session of
FDA-AACR Real World Evidence Workshop

Wendy Rubinstein, MD, PhD, FACP, FACMG

July 19, 2019

ASCO CancerLinQ®

Shaping The Future Of Cancer Care

Creating CancerLinQ: high-level overview

Accomplishments using RWD

- Real-world outcomes of patients with advanced non-small cell lung cancer and autoimmune disease receiving immune checkpoint inhibitors
- Impact of Broadening Clinical Trial Eligibility Criteria from NCI, Friends of Cancer Research, FDA and ASCO

Barriers to opportunity

- Transforming RWD into RWE – methodology, standards gaps
- Curation vs. sourcing structured genomic data from the sequencing spigots

Paths toward shared success

- Genomics
- mCODE

What is CancerLinQ®?

Built by a wholly owned, nonprofit subsidiary of ASCO

Only nonprofit, physician-led big-data platform in cancer

Delivers knowledge back to physicians and researchers

Collects and analyzes real-world cancer care data from multiple healthcare IT systems

Key Milestones

100+ | **Organizations** have signed BAAs

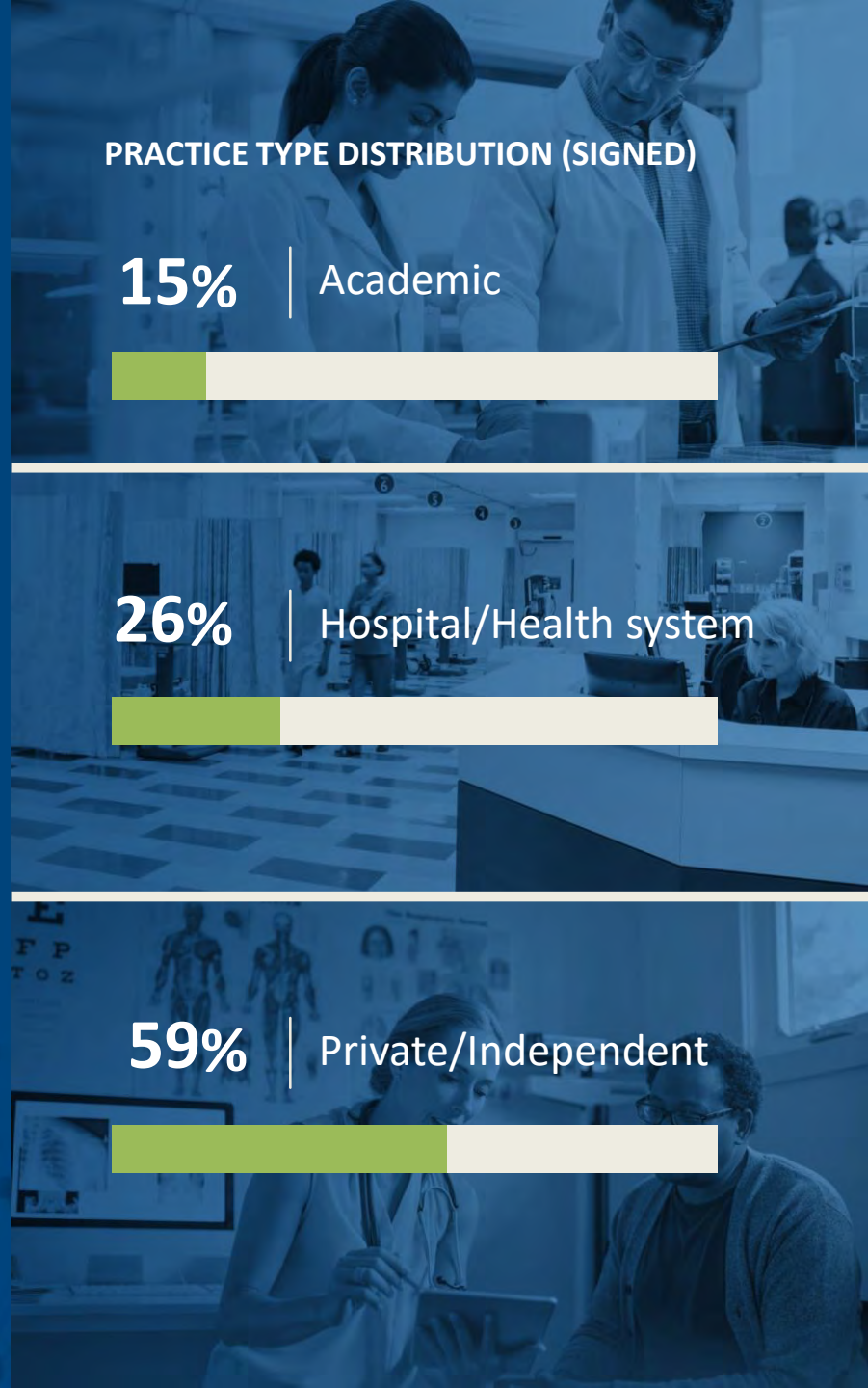
50+ | **Organizations** have been connected to the CancerLinQ® platform

980,000+ | Total number of **patients** with a primary cancer diagnosis in the clinical database

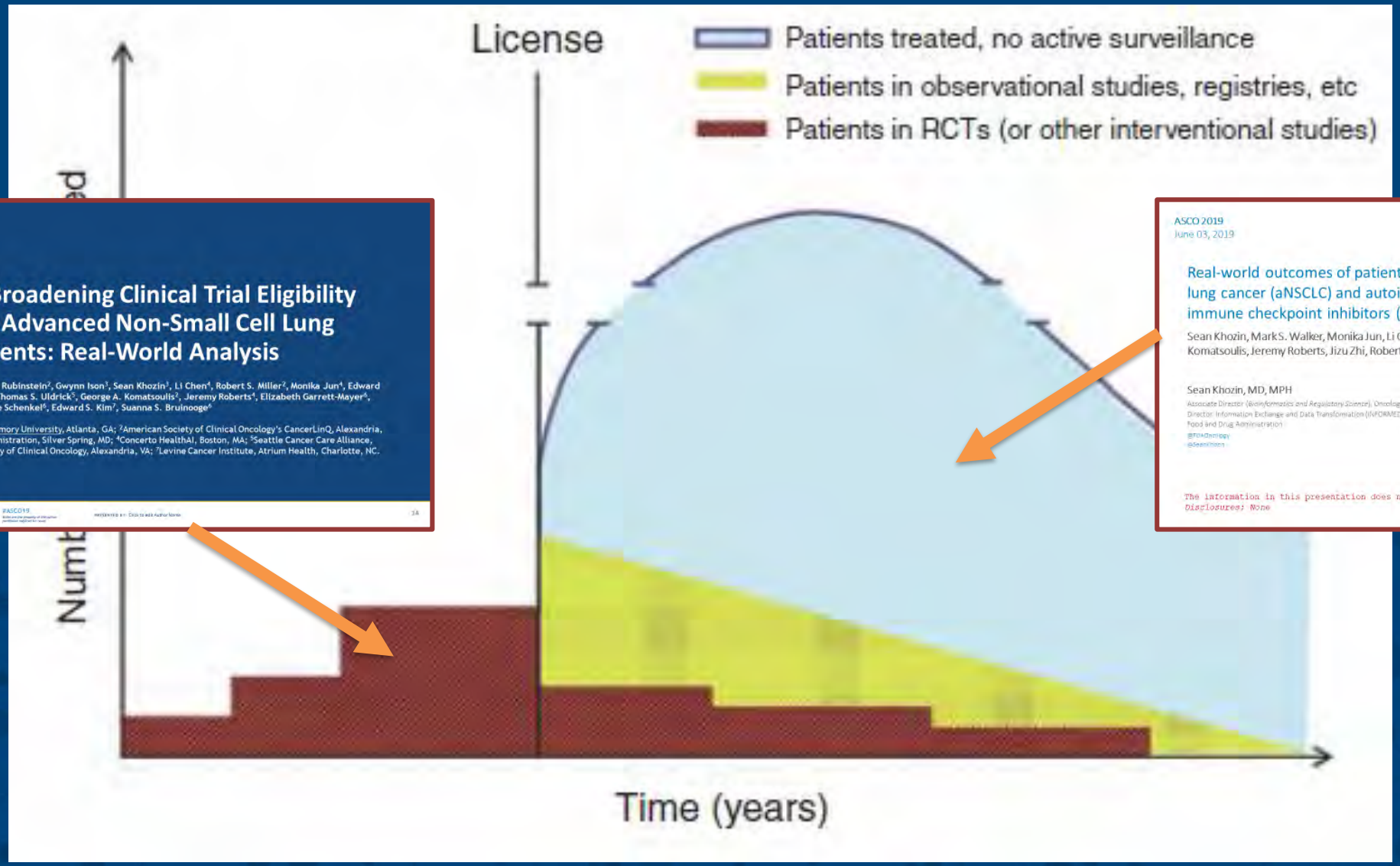
10 | **Supported EMRs:** Epic, MOSAIQ, Allscripts, ARIA, CureMD, OncoEMR, Integra Connect, Centricity, NextGen, IntelliDose

1.5M+ | **Patients** with a cancer or benign heme diagnosis

147,000+ | **Curated records** to date: Lung (NSCLC, SCLC), breast, ovarian, prostate, pancreatic, colorectal and CLL



RCTs drive our understanding and treatment of cancer, but only 3% of adult cancer patients enroll in clinical trials …



Impact of Broadening Clinical Trial Eligibility Criteria for Advanced Non-Small Cell Lung Cancer Patients: Real-World Analysis

R. Donald Harvey[1], Wendy S. Rubinstein[2], Gwynn Ison[3], Sean Khozin[3], Li Chen[4], Robert S. Miller[2], Monika Jun[4], Edward Stepanski[4], Brigham Hyde[4], Thomas S. Uldrick[5], George A. Komatsoulis[2], Jeremy Roberts[4], Elizabeth Garrett-Mayer[6], Richard L. Schilsky[6], Caroline Schenkel[6], Edward S. Kim[7], Suanna S. Bruinooge[6]

[1]Winship Cancer Institute of Emory University, Atlanta, GA; [2]American Society of Clinical Oncology's CancerLinQ, Alexandria, VA; [3]U.S. Food and Drug Administration, Silver Spring, MD; [4]Concerto HealthAI, Boston, MA; [5]Seattle Cancer Care Alliance, Seattle, WA; [6]American Society of Clinical Oncology, Alexandria, VA; [7]Levine Cancer Institute, Atrium Health, Charlotte, NC.

2019 ASCO ANNUAL MEETING

ASCO 2019
June 03, 2019

U.S. FOOD & DRUG ADMINISTRATION

Real-world outcomes of patients with advanced non-small cell lung cancer (aNSCLC) and autoimmune disease receiving immune checkpoint inhibitors (ICIs)

Sean Khozin, Mark S. Walker, Monika Jun, Li Chen, Edward Stepanski, Wendy S. Rubinstein, George Anthony Komatsoulis, Jeremy Roberts, Jizu Zhi, Robert S. Miller, Ryan Fukushima, Denise Lau, Brigham Hyde

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Food and Drug Administration
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@SeanKhozin

The information in this presentation does not necessarily represent the view of the FDA
Disclosures: None

ASCO 2019
June 03, 2019

U.S. FOOD & DRUG ADMINISTRATION

Real-world outcomes of patients with advanced non-small cell lung cancer (aNSCLC) and autoimmune disease receiving immune checkpoint inhibitors (ICIs)

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Director, Information Exchange and Data Transformation (INFORMED)
Food and Drug Administration

@FDAOncology
@SeanKhozin

The information in this presentation does not necessarily represent the view of the FDA
Disclosures: None

Background

- Treatment with appropriate ICIs has been shown to improve overall survival in patients with aNSCLC
- Patients with a history of autoimmune disease are typically excluded in traditional clinical trials
- Anecdotal and early evidence suggest that ICIs are being used at the point of routine care (i.e., “real-world”) in patients with aNSCLC and history of autoimmune disease

Darvin P, et al. Exp Mol Med. 2018
Drugs@FDA: FDA approved drug products. Available at https://www.accessdata.fda.gov/scripts/cder/daf. Accessed on May 1, 2019.

Table 1. Attrition Table

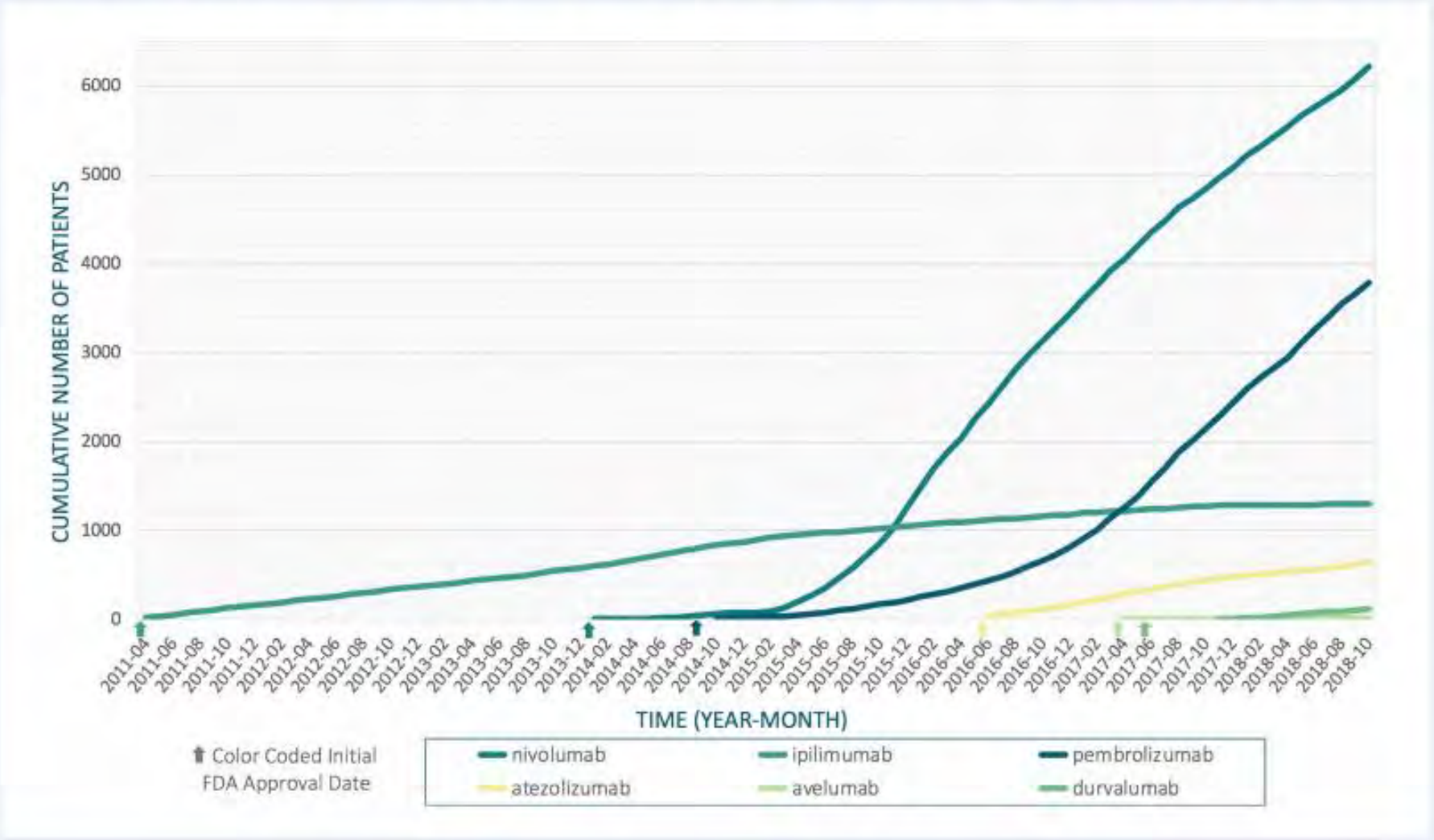
Inclusion or Exclusion Criteria	Sample Size (N)
Complete de-identified dataset*	1,129,679
At least 1 dose of ICI after Jan 1, 2011**	12,905
Patients with ≥2 documented clinical visits***	12,803
Patients who started ICI treatment on or after the FDA approval date	12,712
Total patients included in ICI cohort	12,712

* Patients with a primary diagnosis record of malignant or benign neoplasm or benign heme disorder in EHRs from participating CancerLinQ practices.

** ICI medications defined as the following generic medications or corresponding trade names: atezolizumab, avelumab, durvalumab, ipilimumab, nivolumab, pembrolizumab.

*** Clinical visits defined as at least 2 documented clinical interactions or 2 drug administration events on or after the first administration of an ICI.

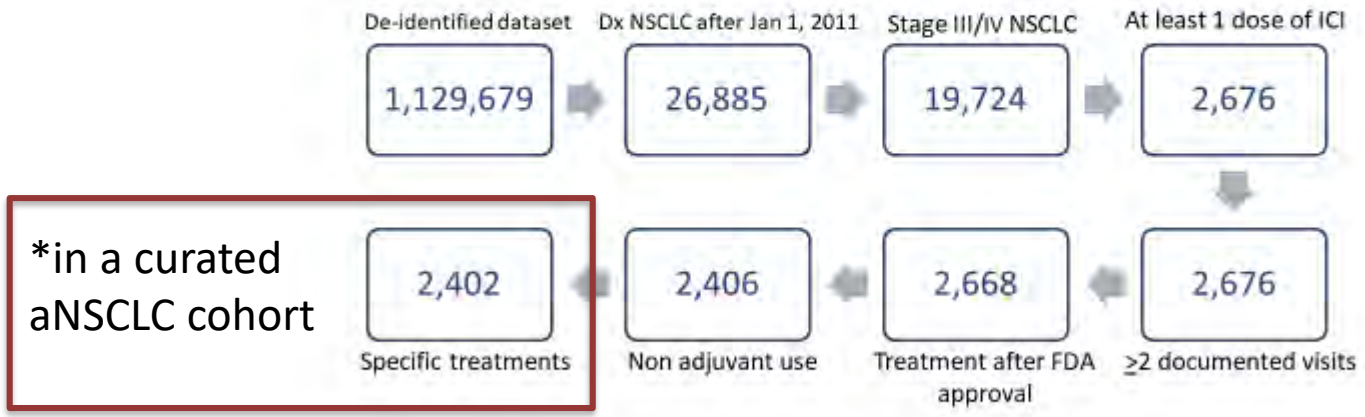
Figure 1. Utilization of ICI Medications (2011-2018)



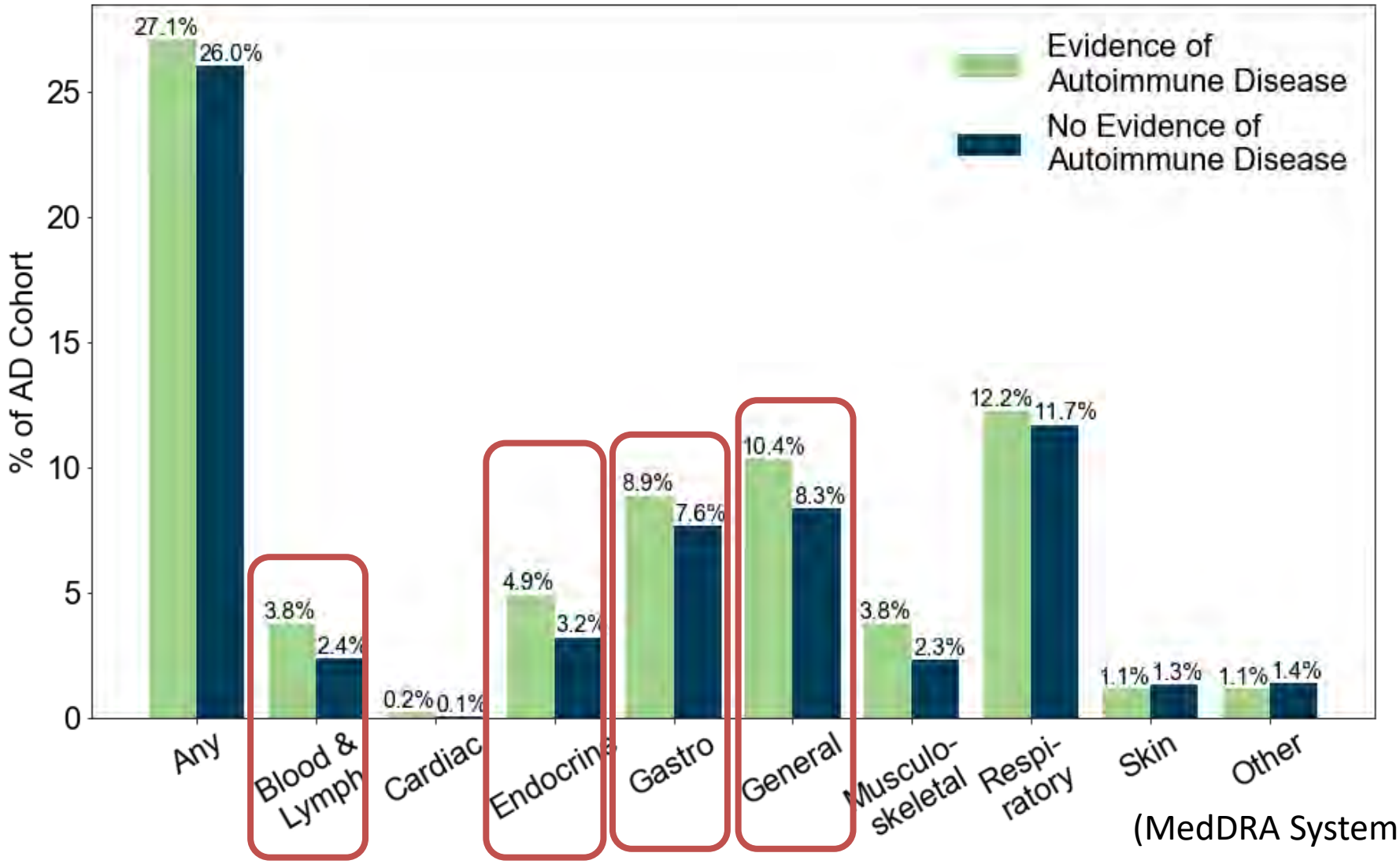
ASCO CancerLinQ
Shaping The Future Of Cancer Care

Study objectives

- To describe the real-world characteristics and outcomes of patients with aNSCLC with and without prior history of autoimmune disease treated with ICIs in community-based oncology practices in the U.S. *
- To explore immune-related adverse events (irAEs) *

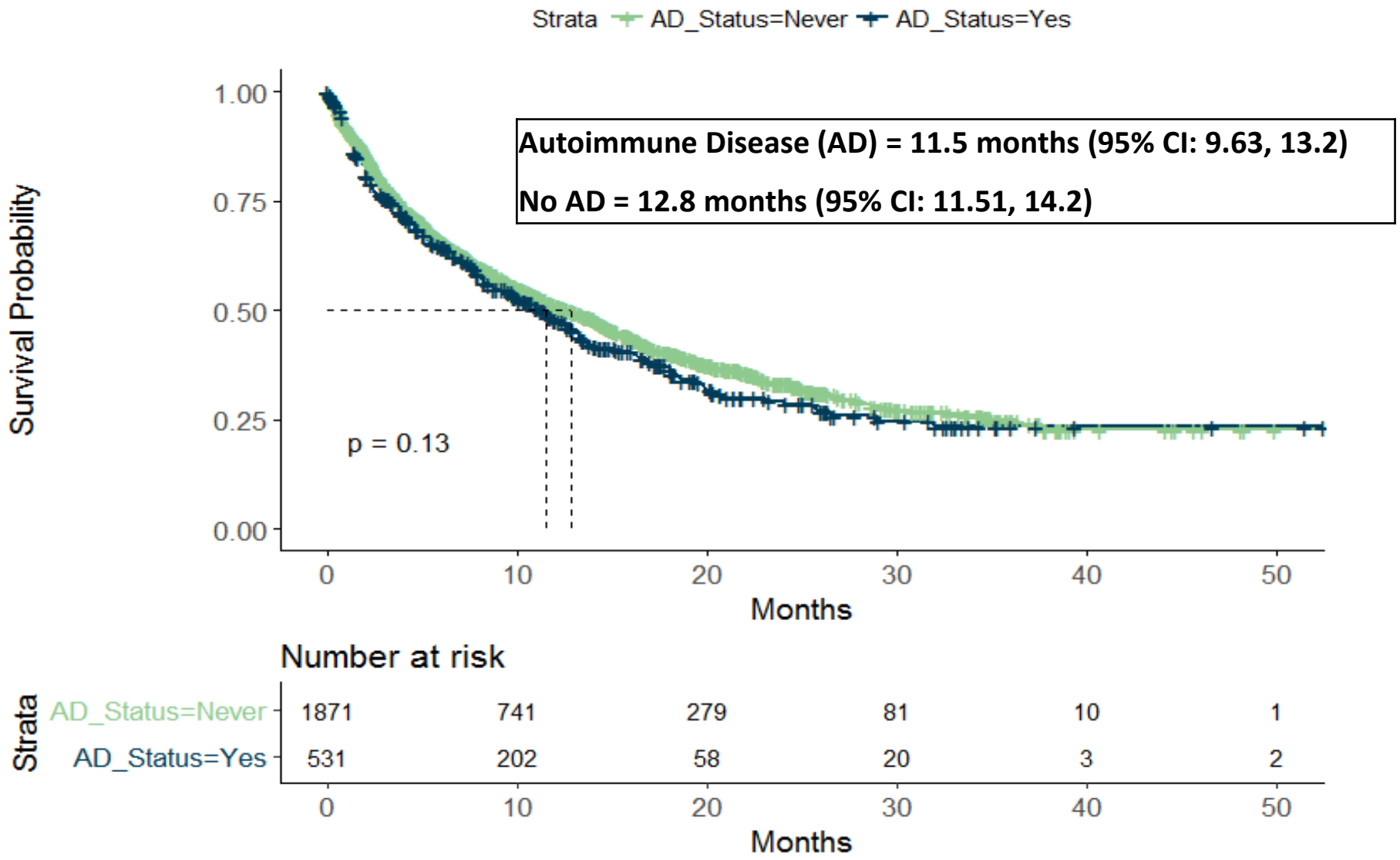


Results: irAEs



(MedDRA System Organ Class)

aNSCLC – Results: OS



Impact of Broadening Clinical Trial Eligibility Criteria for Advanced Non-Small Cell Lung Cancer Patients: Real-World Analysis

R. Donald Harvey[1], Wendy S. Rubinstein[2], Gwynn Ison[3], Sean Khozin[3], Li Chen[4], Robert S. Miller[2], Monika Jun[4], Edward Stepanski[4], Brigham Hyde[4], Thomas S. Uldrick[5], George A. Komatsoulis[2], Jeremy Roberts[4], Elizabeth Garrett-Mayer[6], Richard L. Schilsky[6], Caroline Schenkel[6], Edward S. Kim[7], Suanna S. Bruinooge[6]

[1]Winship Cancer Institute of Emory University, Atlanta, GA; [2]American Society of Clinical Oncology's CancerLinQ, Alexandria, VA; [3]U.S. Food and Drug Administration, Silver Spring, MD; [4]Concerto HealthAI, Boston, MA; [5]Seattle Cancer Care Alliance, Seattle, WA; [6]American Society of Clinical Oncology, Alexandria, VA; [7]Levine Cancer Institute, Atrium Health, Charlotte, NC.

Background

- ASCO and Friends of Cancer Research recommendations for broadening eligibility criteria
  - Included patient advocates, FDA, NCI, investigators, sponsors
- Broadening trial eligibility will:
  - Enable more patients to participate
  - Make trial population more representative and results more generalizable
  - Accelerate accrual

1. Kim ES, Bruinooge SS, Roberts S, et al. *Broadening Eligibility Criteria to Make Clinical Trials More Representative: American Society of Clinical Oncology and Friends of Cancer Research Joint Research Statement*. JCO (2017)
2. Uldrick T, Ison G, Rudek M, et al. *HIV Working Group*. JCO (2017)
3. Lin N, Prowell T, Tan, AR, et al. *Brain Metastases Working Group*. JCO (2017)
4. Lichtman SM, Harvey RD, Smit MAD, et al. *Organ Dysfunction, Prior or Concurrent Malignancy, and Comorbidities Working Group*. JCO (2017)
5. Gore L, Ivy SP, Balis FM, et al. *Minimum Age Working Group*. JCO (2017)

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Broadening Eligibility Criteria to Make Clinical Trials More Representative: American Society of Clinical Oncology and Friends of Cancer Research Joint Research Statement

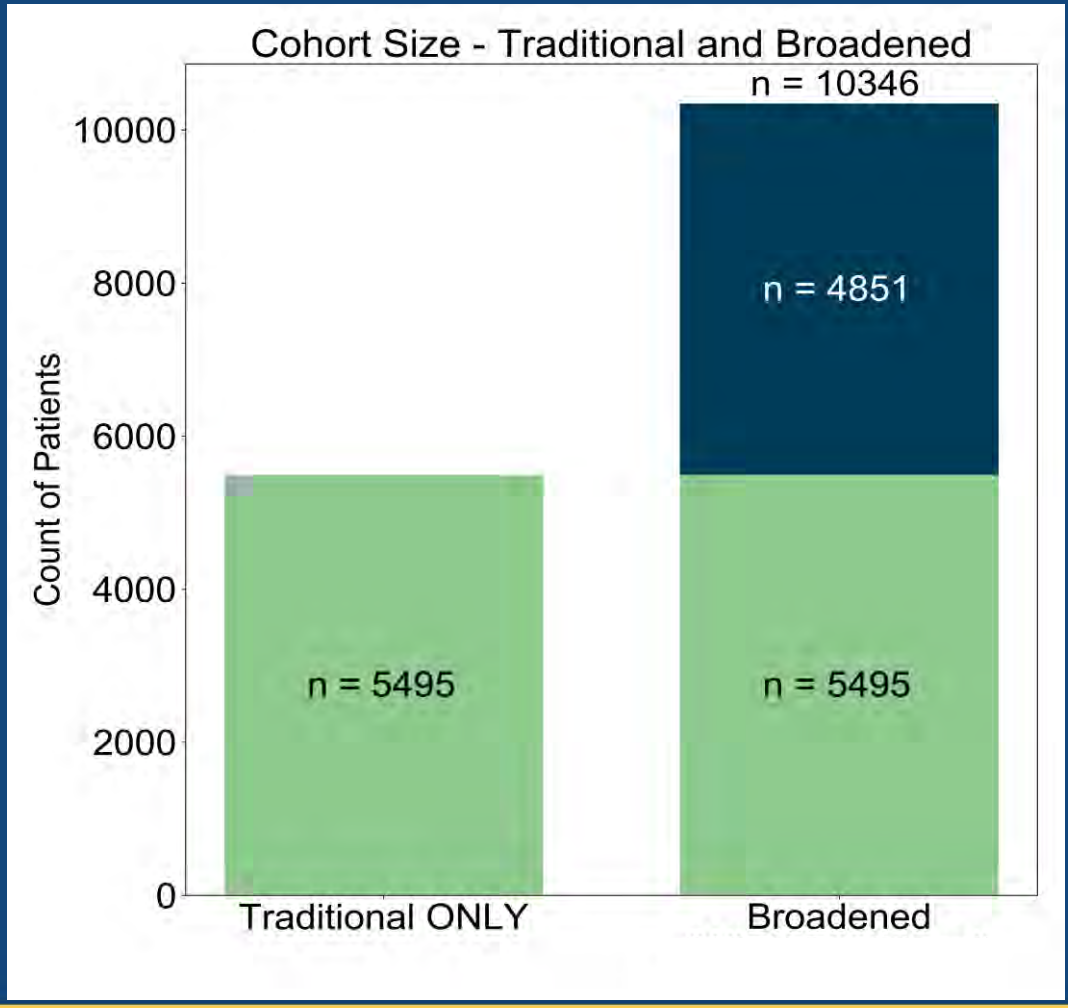
Edward S. Kim, Suanna S. Bruinooge, Samantha Roberts, Gwynn Ison, Nancy U. Lin, Lia Gore, Thomas S. Uldrick, Stuart M. Lichtman, Nancy Roach, Julia A. Beaver, Rajeshwari Sridhara, Paul J. Hesketh, Andrea M. Denicoff, Elizabeth Garrett-Mayer, Eric Rubin, Pratik Multani, Tatiana M. Prowell, Caroline Schenkel, Marina Kozak, Jeff Allen, Ellen Sigal, and Richard L. Schilsky

Study Design, Data Source, and Population

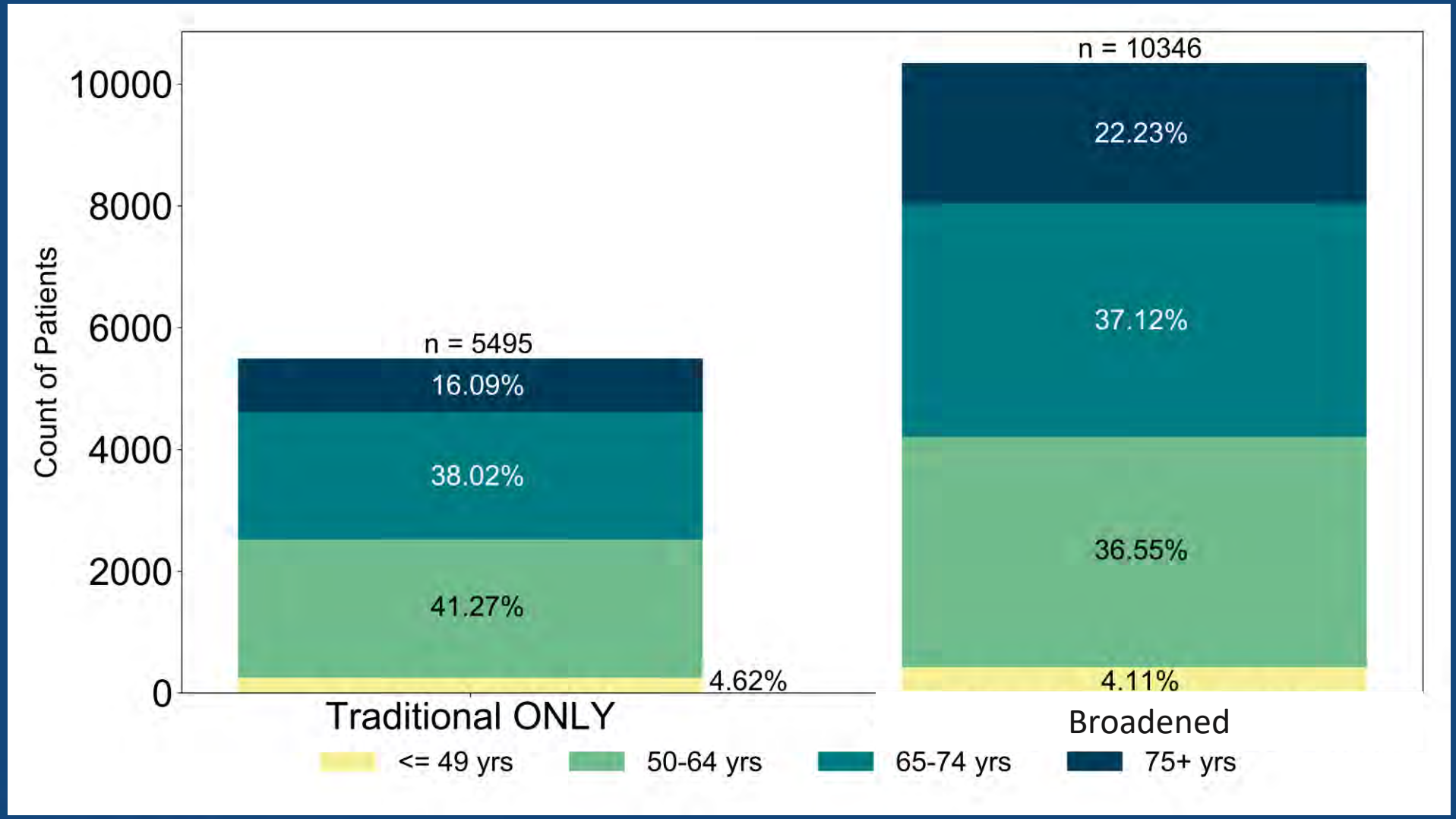
- Retrospective study based on real-world data
  - January 2011-December 2018
- ASCO CancerLinQ Discovery (CLQD) deidentified electronic health record (EHR) data
- Study conducted in NSCLC because
  1. More advanced patients and comorbidities common
  2. Scientific relevance because many trials available
  3. Curated CLQD data
- Inclusion criteria:
  - Patients who received therapy after diagnosis of advanced NSCLC

Impact of Exclusions on Cohort Size

Original Cohort	10,500 (100%)
Traditional Criteria	
Pts excluded due to brain metastases	2,226 (21.2%)
Pts excluded due to prior/concurrent cancers	1,509 (14.4%)
Pts excluded because CrCl ≤ 60 mL/min	2,254 (21.5%)
Pts excluded by one or more of 3 traditional criteria	**5,005 (47.7%)**
ASCO-Friends' Broadened Criteria	
Pts excluded by brain metastases & prior/concurrent cancers	**0 (0%)**
Pts excluded by CrCl cut-off	**154 (1.5%)**



Effect of Broadened Criteria on Age Groups Represented



Large clinico-genomic databases currently exist in 2 forms:

CLINICO – genomic

clinico – **GENOMIC**

Sourcing of genomic content

1. NGS panels are typically brought into the EHR as PDFs or scanned faxes, and therefore are not computable
   Since 2017 CancerLinQ has been extracting high-value genomic information via user interface-assisted data abstraction
2. CancerLinQ has also obtained and processed structured genomic reports in XML format
3. Evaluating automated processes to scan and extract data from reports with standardized formats
4. Exploring solutions with data aggregators

Genomic content

Structured in native EHRs vs. available through curation

EGFR in advanced NSCLC

- structured data in native EHRs: 1.7% (546/32,283) of all aNSCLC records
- curated patient records: 85.3% (6,800/7,967) had *EGFR* tests

Proportion of positive *BRCA1* and *BRCA2* tests in breast cancer (curated)

- *BRCA1* = 8.0% (400/5,004)
- *BRCA2* = 11.5% (485/4235)

The terrible, the bad, and the ugly

Two unique *EGFR* sequence variations with a multiplicity of representations

Standard HGVS representation	
NM_005228.4(EGFR):c.2573T>G (p.Leu858Arg)	
Variant String	**OCR Transformation**
L858R,	
L8S8R	5 → S
L8SSR	5 → S, 8 → S
LB58R	8 → B
LB5BR	8 → B, 8 → B
exon 21 codon L858 mutation L858R	
exon 21 for mutation p.L858R	
exon 21 for mutation, p.L858R	
exon 21 for mutation, p.L858R.	
Exon 21(L858R)	
exon 21, L858R	
exon 21, p. L858R	
exon 21 L05BR	8 → 0, 8 → B
EXON 21 L858R	
Exon 21 L858R	
exon 21 L858R	
EXON 21 L858R.	
Exon 21 L85SR	8 → S

Standard HGVS representation	
NM_005228.4(EGFR):c.2582T>A (p.Leu861Gln)	
Variant String	**OCR Transformation**
L861Q	
1861Q	L → 1
L86lQ	1 → I
L8B1Q	6 → B
L8G1Q	6 → G
exon 21/L861Q	

Paths toward shared success

All NGS data is originally generated as structured data by molecular diagnostics labs

- the data capture of the various chemistries that underlie NGS sequencing
- the components of bioinformatics pipelines (sequence aligners, variant callers)
- even clinical report production

Curation of NGS reports *re-structures* the data

- at a significant cost, along with some erosion of data quality
- the technical solutions CancerLinQ and others have painstakingly developed would not be necessary if the originally-structured data were provided

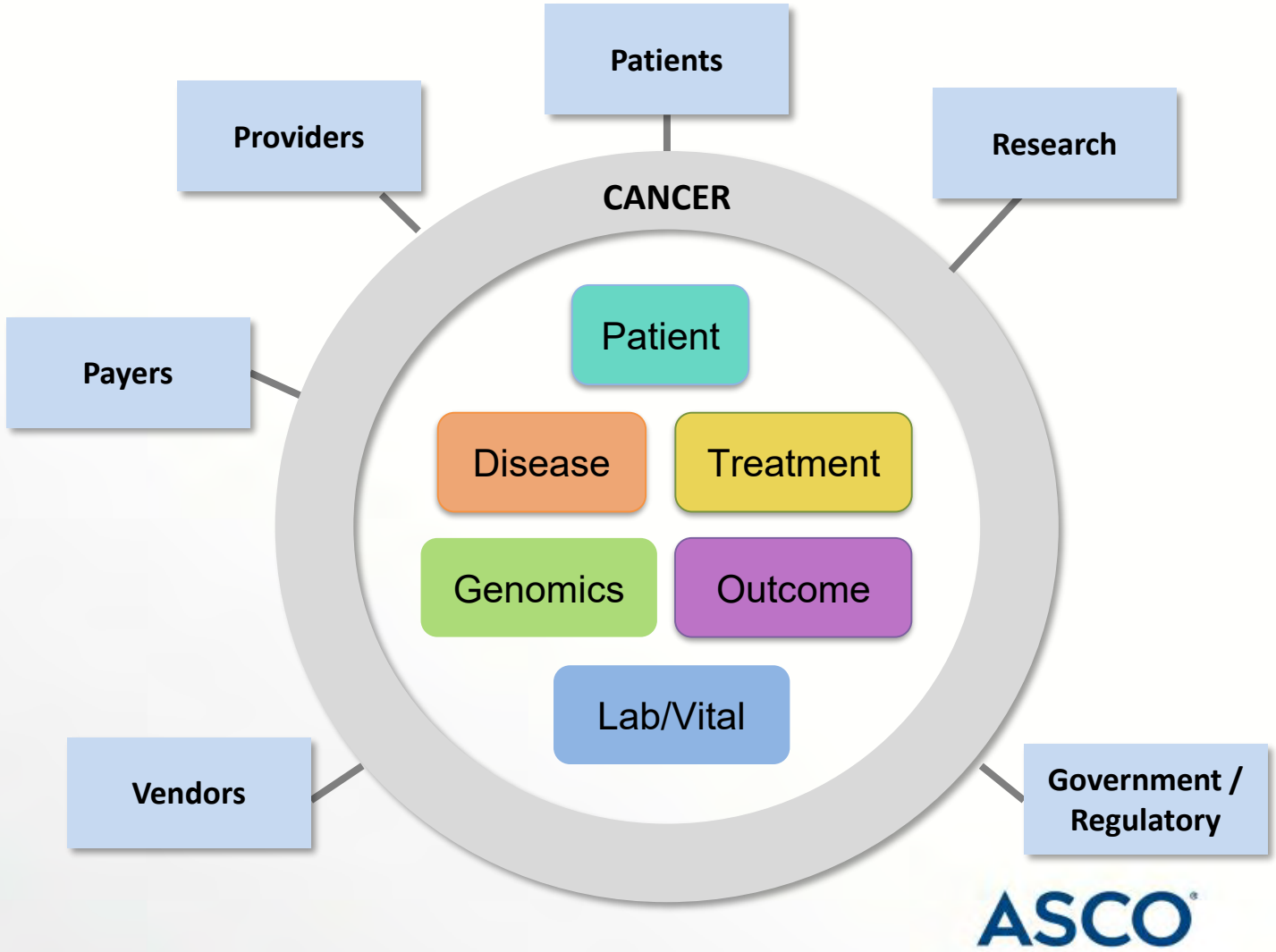
Genomic results were reimbursed through federal and private insurers

but the reporting format impedes its utility to clinicians

- We call for all molecular diagnostics laboratories to provide structured data as part of routine reporting
- This would help laboratories meet the definition of interoperability by the 21st Century Cures Act
  - to facilitate health information exchange without special effort on the part of the user
  - while avoiding the Act's prohibition of information blocking

mCODE™: Minimal Common Oncology Data Elements

- **A data standard for the oncology electronic health record created through a collaborative effort convened by ASCO with input from diverse stakeholders across the oncology ecosystem**
- Minimal set of data elements applicable to all cancers, and collected for:
  - standardized information exchange among oncology information systems
  - use by multiple stakeholders
- Initial data element domains: patient, lab/vital, disease, treatment, genomics, outcome



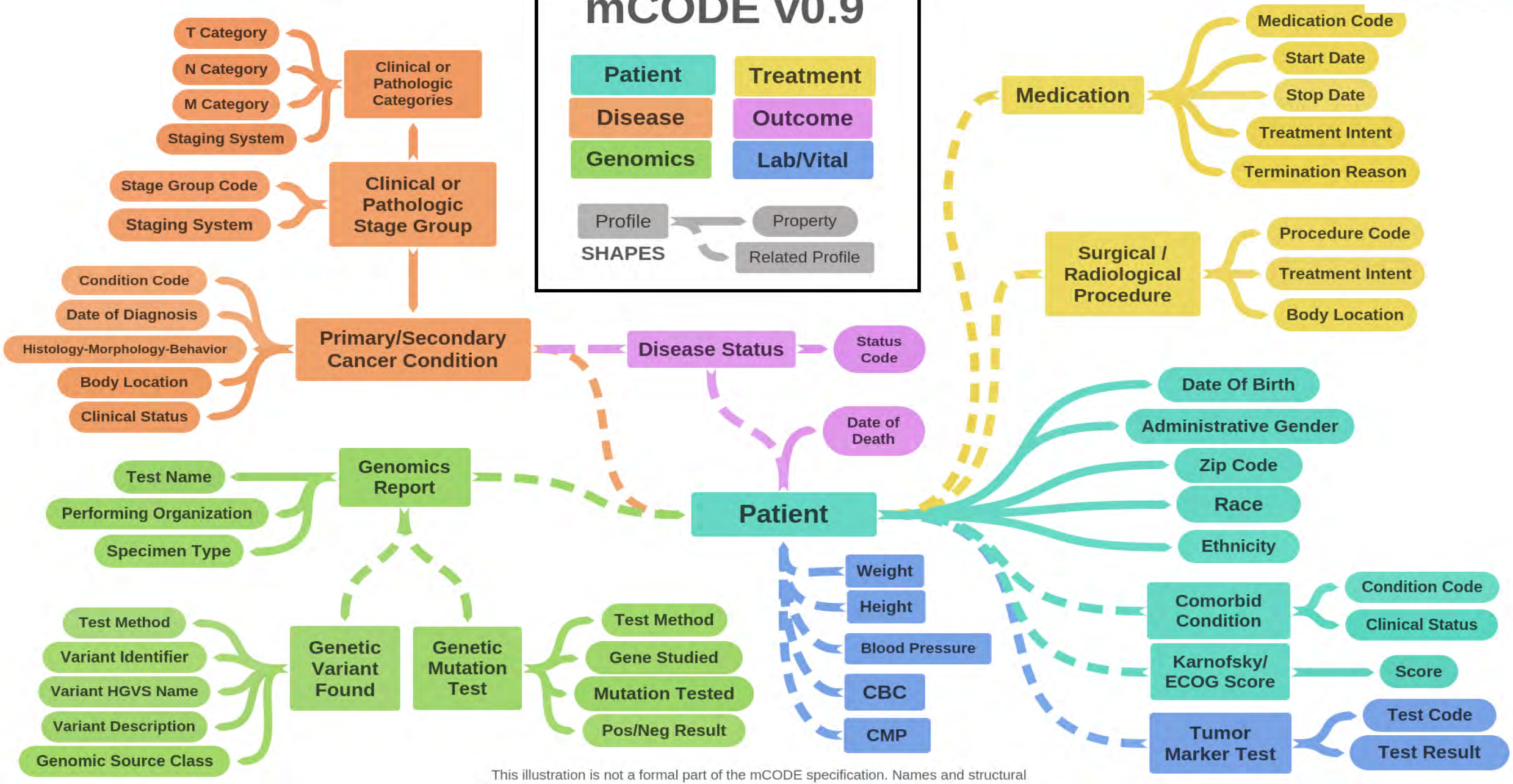
ASCO

mCODE™

mCODE v0.9

Patient | Treatment
Disease | Outcome
Genomics | Lab/Vital

Profile — Property
SHAPES
Related Profile



This illustration is not a formal part of the mCODE specification. Names and structural relationships shown here may not precisely correspond to the data dictionary and FHIR profiles.

Thank you

Wendy.Rubinstein@CancerLinQ.org

The James

The ORIEN Alliance

Mission: Accelerating discovery and delivery through collaborative learning and partnerships

William Dalton Disclosures July 2019

- Chair and Founder of M2GEN, a for-profit organization
- Stock owner in M2GEN
- Inventor of patents licensed to M2Gen

The ORIEN Alliance: Mobilizing the Nation's Leading Cancer Centers

ORIEN consists of 19 of the nation's leading cancer centers to deliver informatics-based solutions to accelerate therapy discovery, development and delivery of personalized medicine.

- Scientific Leadership

  The Network includes some of the nation's leading cancer centers, clinicians and researchers

- Clinical Trials Network

  M2Gen has implemented streamlined site activation protocols, including single IRB and scientific review committee to accelerate activation and enrollment

- Serving Patients

  ORIEN represents a cross section of diverse patients, improving research and clinical trial coverage and health equity

ORIEN

Total Cancer Care Protocol: A Partnership with Patients to Discover and Learn

10+
years of operating history

19
leading cancer centers

250,000+
patients consented to date

Patients who consent to TCC…

1. Donate all of their clinical data for research purposes throughout their lifetime
2. Consent for tissue to be used to generate laboratory data
3. Agree to be re-contacted for future studies, e.g. clinical trials
4. Allow their data to be shared with multiple stakeholders

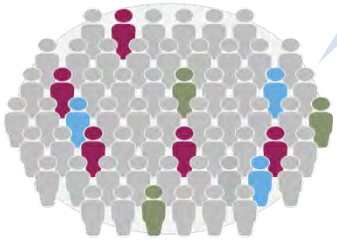
Focus on Improving Clinical Trials

- Meeting the Challenges of Patients with Greatest Need: New Therapy Discovery and Development and Clinical Trials through a System that Anticipates Patient Need

- Moving from Reactive to Proactive Medical Care

ORIEN Avatar:
Power of Cohort Surveillance

Using the TCC Protocol, we can identify patients using both genotypic data as well as phenotypic information to assign patients to an "in silico" community of patients like them….poised for enrollment in studies to investigate the impact of new targeted therapies



Biospecimens

Molecular Data

Longitudinal Data on Clinical Outcomes, Healthcare Utilization, and Patient-Reported Behaviors and Outcomes

…providing a system of continuous learning and ability to anticipate need.

ORIEN Member Access to Data

ORIEN Avatar generates rich molecular data which can be used by scientists. Goal is for ORIEN members to share data for collaboration and cooperative learning

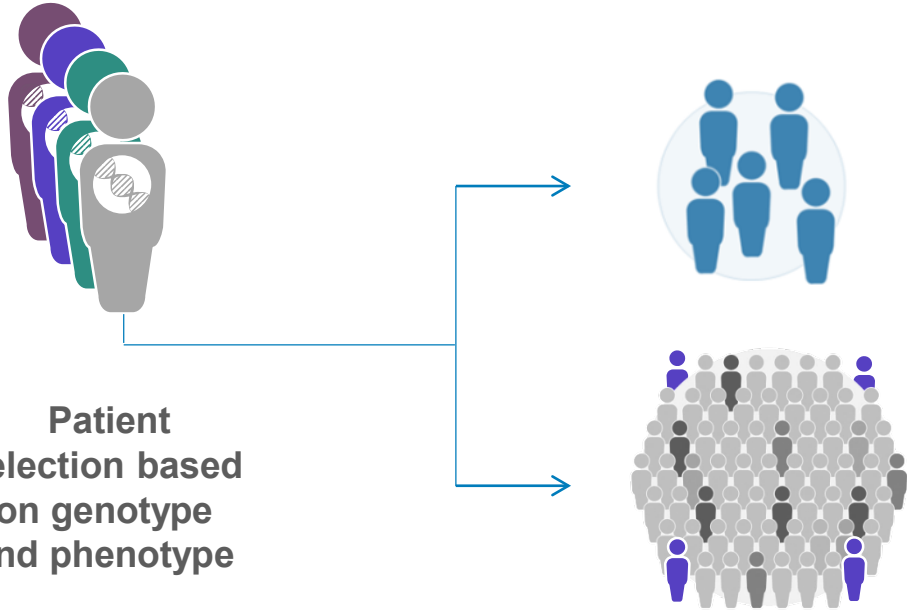
Data Being Generated on High Risk Patients Assigned to ORIEN Avatar

- Whole Exome Sequencing (300x)
- RNA-Sequencing (100 million reads)
- Germline DNA Sequencing (100x) for Somatic Variant-Calling Enrichment
- Abstracted Clinical Data

- Raw data provided to Members
- Processed data available through M2Gen tools
- Data available for research purposes
- Data sharing policies are established by members

Creating a Real-World, Real-Time Comparator Cohort

Because of the TCC Consent, patients who are not enrolled on trial will continue to be followed and serve as a real-world, real-time comparator cohort for the ongoing study



Patient selection based on genotype and phenotype

Eligible patients in Cohort Surveillance can be enrolled on Pharma client's clinical trials…

…or serve as real-world, real-time "comparator cohorts" for those patients enrolled on trial.

Meeting the Challenges of Therapy Development and Clinical Trials

Challenges:

- Trials are too slow and costly
- Individual patients identified for trial at time of need
- High ratio of screening to actual enrollment
- Costs of bringing a drug to market estimated to be $2.6 billion[1] and take 10 – 15 years[2]
- Patients with aggressive disease often have narrow “trial matching window”, making enrollment especially challenging

ORIEN Goals:

- Enroll ***high volume of patients*** in Total Cancer Care (TCC) Protocol through ORIEN
- ***Anticipate need*** of patients enrolled in TCC by understanding patients clinical and molecular properties
- Follow TCC consented patients over time and ***track disease progression/recurrence***
- ***Proactively Identify patients*** that are appropriate for target-based trial
- ***Rapid accrual and data analysis to address patient need***

(1) Tufts Center for the Study of Drug Development
(2) PhRMA

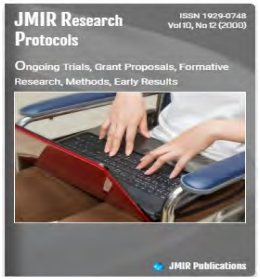
CLINICAL TRIALS NETWORK

ORIEN Members have agreed to develop an efficient, timely and ethical, scientific and contractual review of industry clinical trials brought forward by M2Gen.

Goals:

- Fostering clinical research across ORIEN
- Partnership among member sites and industry sponsors
- Speed
- Quality

Use of TCC in Translation: Partnering with Pharma to Better Design Clinical Trials



Original Paper

Use of the Total Cancer Care System to Enrich Screening for CD30-Positive Solid Tumors for Patient Enrollment Into a Brentuximab Vedotin Clinical Trial: A Pilot Study to Evaluate Feasibility

Bin Li[1], PhD; Steven A Eschrich[2], PhD; Anders Berglund[2], PhD; Melissa Mitchell[3], BA; David Fenstermacher[4], PhD; Hadi Danaee[5], SD; Hongyue Dai[6], PhD; Daniel Sullivan[7], MD; William L Trepicchio[5], PhD; William S Dalton[3], MD

[1]Takeda Pharmaceuticals International Company, Takeda Data Science Institute, Cambridge, MA, United States
[2]H Lee Moffitt Cancer Center and Research Institute, Biostatistics and Bioinformatics, Tampa, FL, United States
[3]M2Gen, Administration, Tampa, FL, United States
[4]MedImmune, LLC, Research Bioinformatics, Gaithersburg, MD, United States
[5]Takeda Pharmaceuticals International Company, Translational and Biomarker Research, Cambridge, MA, United States
[6]M2Gen, Bioinformatics, Tampa, FL, United States
[7]H Lee Moffitt Cancer Center and Research Institute, Blood and Marrow Transplantation, Tampa, FL, United States

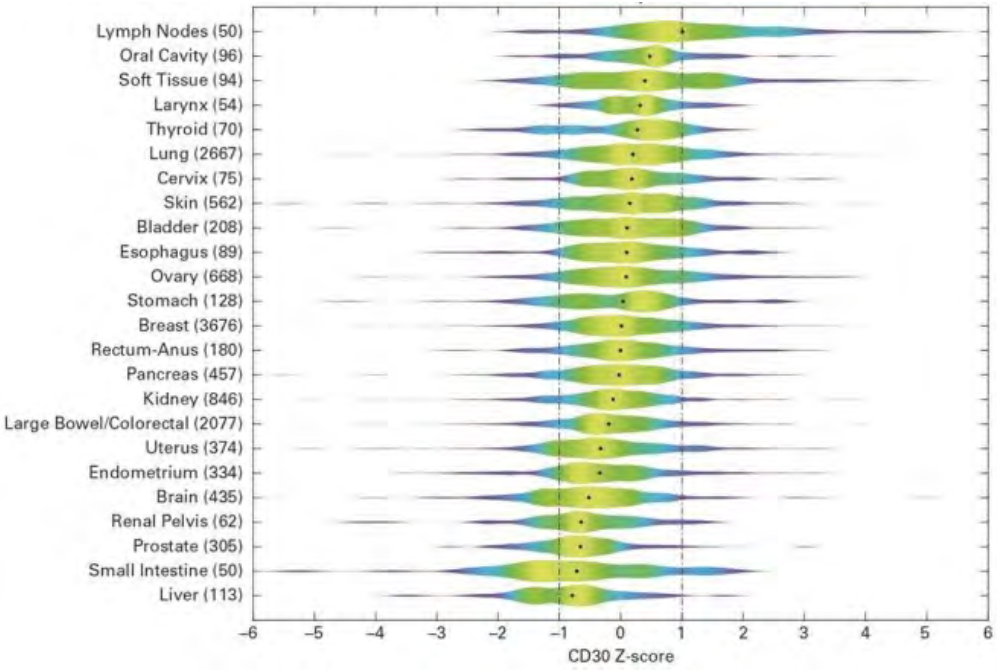


Figure 1. Density plot of CD30 expression Z-score across Total Cancer Care primary tumor types with ≥50 samples. The dots indicate the median value for each tissue type and the dotted lines show the Z-score cut-off.

Use of TCC Protocol in ORIEN Alliance: Challenges in Forming Patient Cohorts to Generate RWD/RWE

Table 1 Challenges associated with forming prospective patient cohorts to improve precision based clinical trials

Challenges	Potential solutions
1. Defining a patient's phenotype relies on accurate and standardized interpretation of unstructured data from diverse health records. Health records are primarily unstructured, making difficult the identification and transference of data that is necessary to match patients to clinical trials.	1. Development of common data dictionaries and automated natural language processing (NLP) technologies are needed.
2. Patient data must be secure, yet shared to achieve collaborative learning. Access and use of the data donated by patients requires a secure environment with sound governance to assure the data are being used in the patients' best interest.	2. Use of honest brokers, limited datasets and deidentification allow compliance with HIPAA and FISMA while not overly restricting data aggregation and analysis. It will be important that regulations not be overly restrictive, making it difficult to access and aggregate data for analysis.
3. Sound scientific oversight and measurements of quality of the data need to be in place to identify and recommend clinical trials for patients in need.	3. Data quality standards must be established and automated so that data from disparate sources can be integrated for analysis and decision making.
4. Communicating with patients who have consented to cohort surveillance and providing information to them in a meaningful and constructive way.	4. Patients who consent to donate data and biospecimens may request results and reports of studies performed and this must be communicated in an understandable format with access to counseling to explain findings.
5. Recognizing that patients' cancers genotypically evolve and are heterogeneous, how do we determine the current genomic state of a patient at the time of clinical trial enrollment?	5. Performance of longitudinal assays, including liquid biopsies, may address the genotypic evolution of a patient's disease. Creating *in silico* communities based on genotype and phenotype with longitudinal clinical follow-up will become the basis for deep learning and pattern recognition to predict events.
6. With advances in technology how do we integrate new "-omic" analysis into the repertoire of studies of patients to better understand the disease?	6. Integrating new "-omic" technologies will enhance systems analysis but will also require prospective validation of new assays to determine the value of each.
7. Creation of a national (global) infrastructure to share data from all networks involved in collecting and studying patient data will enable all stakeholders to access and learn from the data to better meet patient needs, including need for clinical trials.	7. Development of a "network of networks" will require the development of data standards and tools that promote interoperability.

Dalton WS etal. CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 104 NUMBER 1 | JULY 2018

Total Cancer Care: Lessons Learned to Date

Over the course of the last decade, several "lessons learned" have identified challenges and opportunities

Need for Scale	▪ "Scale" is multi-dimensional across the "4-V's": volume, velocity, veracity, and variety.
Anticipate Need	▪ In order to address patient need requires timely reception of high quality patient data to create options for clinical trials (Velocity).
Focus on Data Utilization	▪ Understanding the needs of key stakeholders, including patients, requires tailored design of data aggregation, presentation of information and novel analytics .
Harmonized Approach	▪ Harmonizing all aspects of the TCC Protocol including tissue and data SOPs across multiple sites, centralizing lab functions and utilizing a single consent.

TCC – Ultimate Goal – Evidence-Based Clinical Decision Support at the Point of Care-Using Evidence of Value

Point of Care
Informed Interaction

Physician Portal

Treating physicians and patients have the ability to share information and questions with each other and drive informed interaction

Patient Portal

- EMR Data
- Imaging
- Labs
- Genomic Data

✓ "Best" diagnostic and therapeutic options

✓ Presentation of "best" options in "layman's" terms

- Patient self-reported data
- Patient preferences

Total Cancer Care (TCC) Data Warehouse (DW) and Rapid Knowledge Generation Environment

July 19, 2019

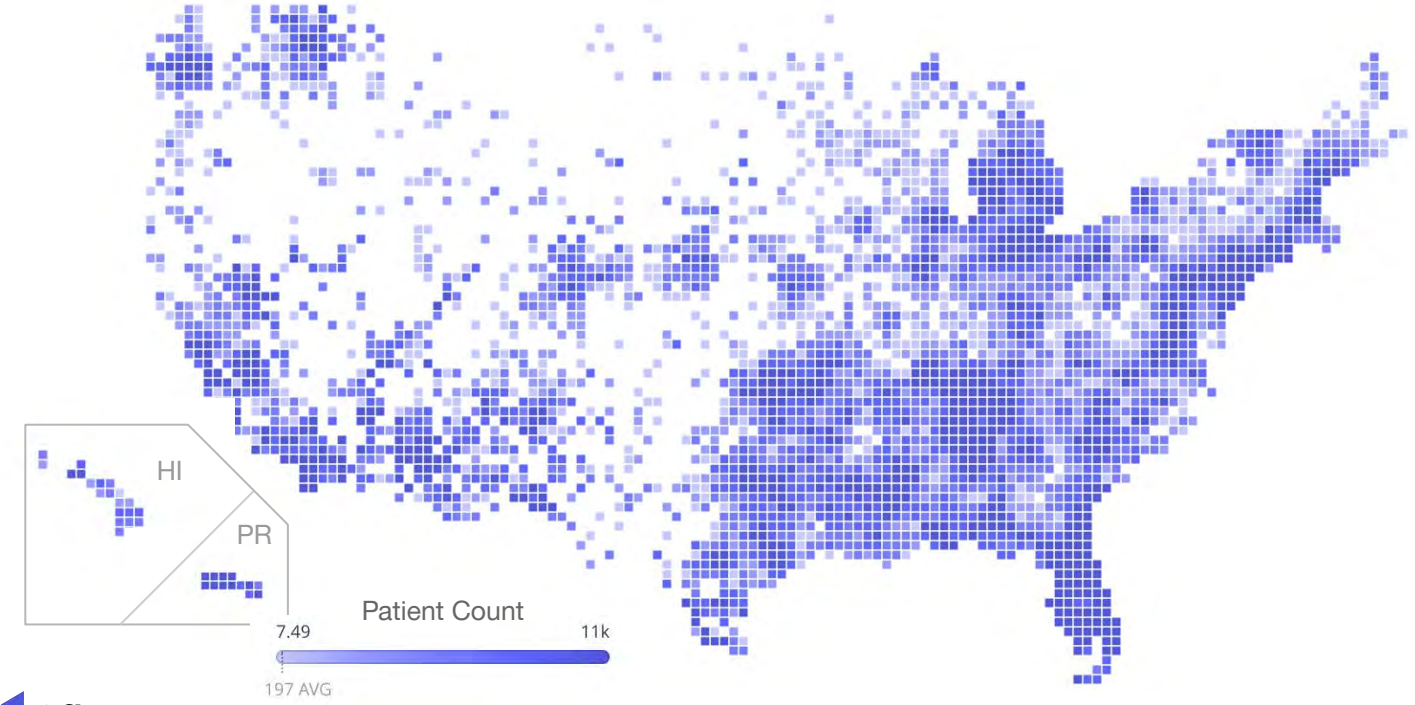
A Real-World Clinico-Genomic Data Platform to Accelerate Research and Development

FDA-AACR RWE Workshop
Bethesda, MD

Neal Meropol, MD
Vice President, Research Oncology
Flatiron Health

flatiron

Data Source: Flatiron network of community and academic practices across the US.



2.2M
Active Patients

2,500+
Clinicians

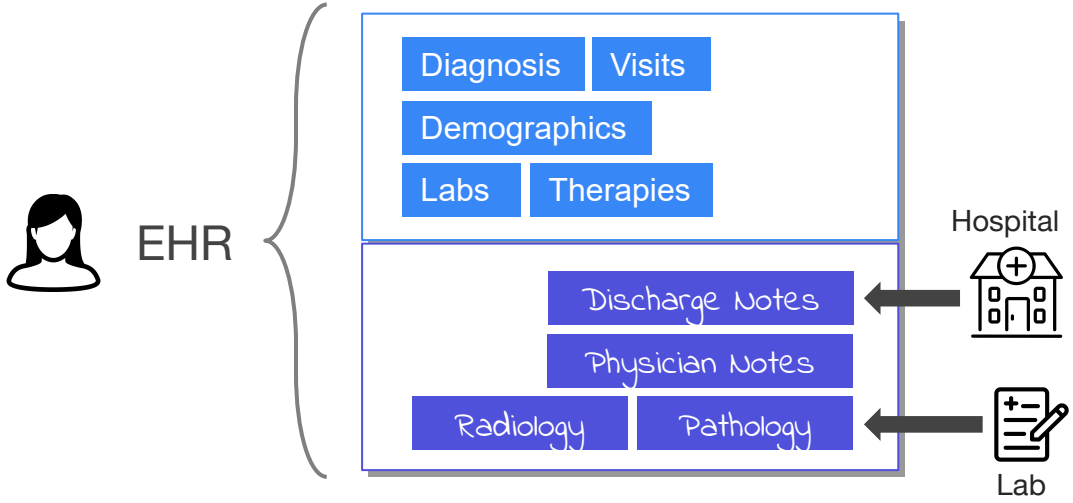
280
Cancer Clinics

800
Unique Sites of Care

flatiron

Getting from *DATA* to *EVIDENCE*

Structured and Unstructured Data in the EHR



flatiron

The promise of precision medicine requires rich clinico-genomic data

flatiron

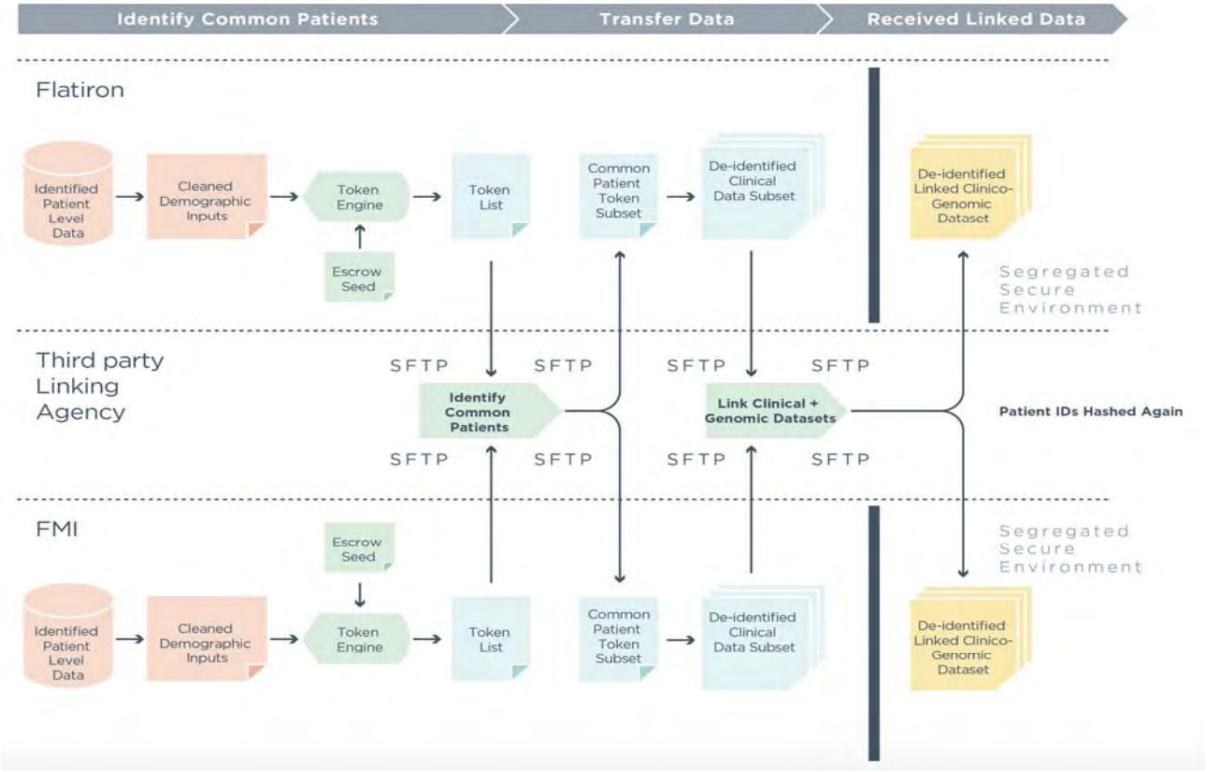
+

FOUNDATION MEDICINE®

Real-World Clinico-Genomic Database

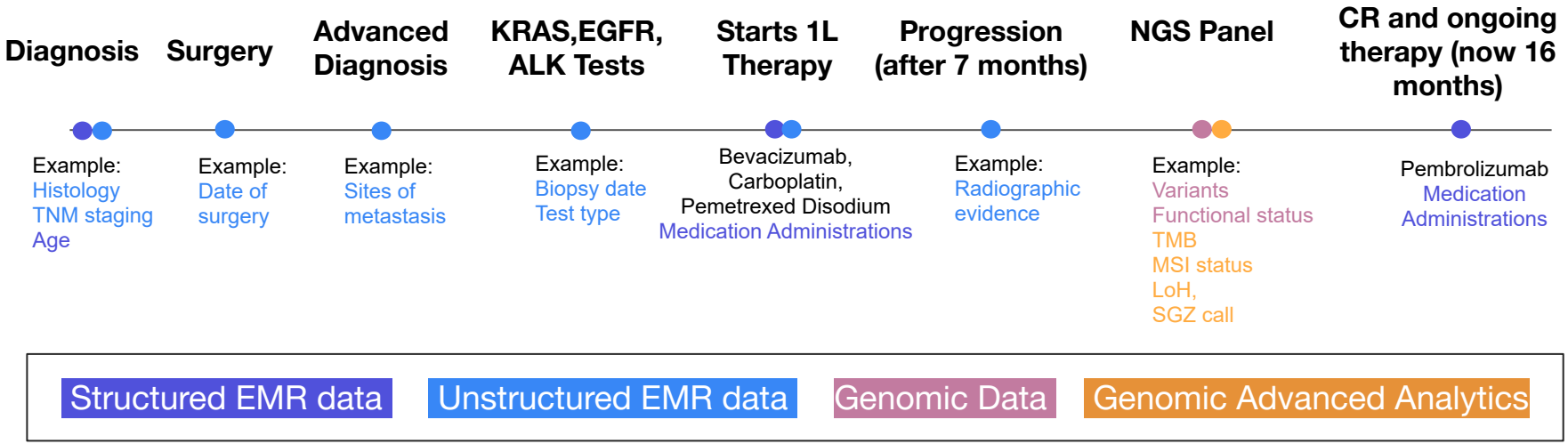
Patient population: >48,000 patients

Linking Clinical and Genomic Data



Singal, Miller, Agarwala, et al. JAMA. 2019.

Illustrative view of the patient journey



How are clinico-genomic data being used?

Commercial Applications

Research and Clinical Applications

Regulatory Applications

Understanding Uptake of New Biomarkers and Treatments

Discovery and Validation of New Predictive Biomarkers

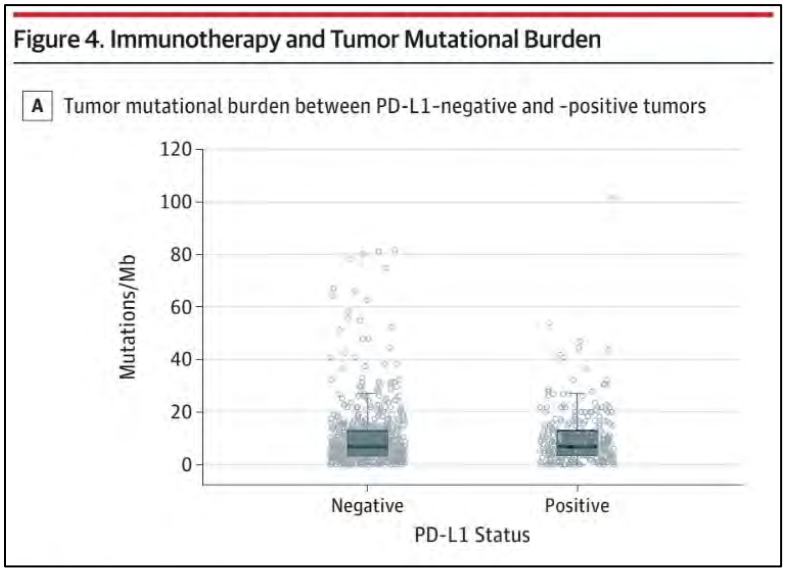
Trial Design

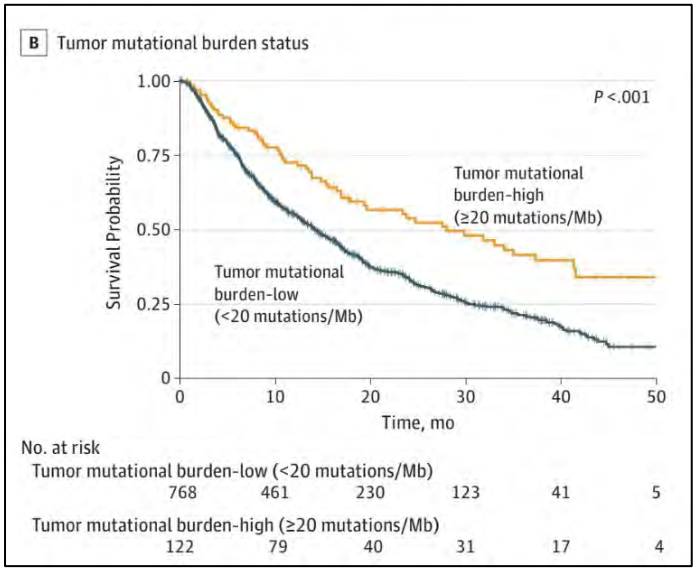
Trial Planning

Submission of Real-World Outcomes for Regulatory Decisions

flatiron

TMB as Predictive Biomarker in NSCLC





Singal, Miller, Agarwala, et al. JAMA. 2019;321(14):1391-1399.

Using TMB and PD-L1 expression to predict response to IO in aNSCLC patients

Predicted Real-World ORR (%) by TMB and PD-L1 Levels in Line 1

TMB Score (mut/mb)	TMB Percentile	Negative PD-L1	Low PD-L1	High PD-L1
1	8.50%	23 (14 - 37)	23 (13 - 38)	38 (26 - 52)
5	26.9%	28 (19 - 40)	28 (18 - 41)	45 (35 - 55)
10	52.8%	36 (25 - 49)	36 (24 - 49)	53 (42 - 63)
15	74.9%	43 (31 - 57)	43 (30 - 58)	61 (50 - 71)
30	94.7%	45 (27 - 65)	45 (26 - 66)	63 (45 - 78)

Castellanos et al. ASCO 2019

Strengths (Challenges to Follow)

- **Scale** permits study of rare cohorts
- **Single lab** with known performance -- can define genomic cohorts uniformly
- **Standardized curation process and longitudinal clinical follow-up** with treatment and outcomes
- **Recency** facilitates rapid insights with new treatment paradigms

Challenges and Analytic Considerations for Real-World Clinico-Genomic Data

- **Challenge: Cross-sectional convenience sample, with long-surviving patients overrepresented**
  - **Mitigation**: Apply left truncation adjustment or landmark analysis; careful cohort selection
- **Challenge: Missing data**
  - **Mitigation**: Apply censoring rules to account for missing data
- **Challenge: Variation in timing of testing relative to diagnosis and treatment**
  - **Mitigation**: Careful cohort selection based on use case
- **Challenge: Analysis across diseases requires data model consistency**
  - **Mitigation**: Develop pan tumor data models and methods to allow for outcomes analyses across heterogeneous populations

Future Directions

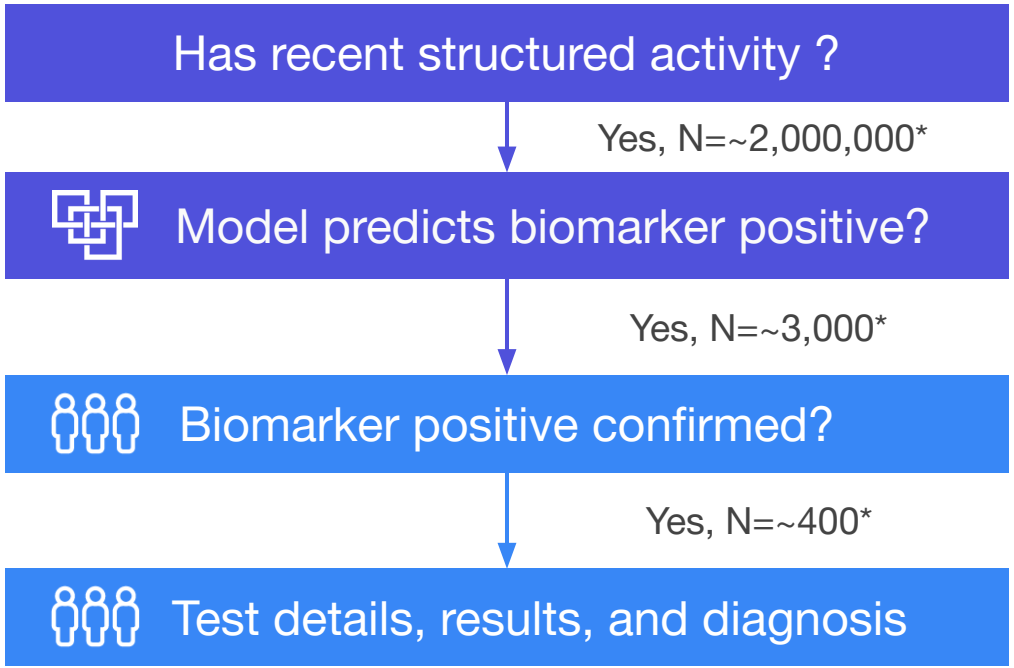
Finding the needle in a haystack in a population-based sample

flatiron

2 million+ patients

100 patients

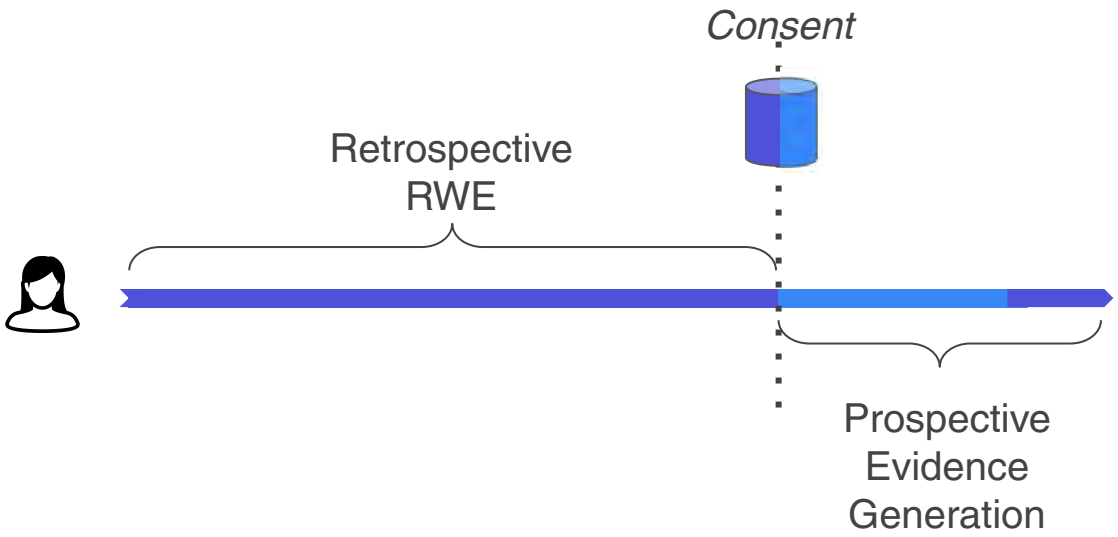
Performance of a Machine Learning Model in an Unselected Population to Create a Tumor-Agnostic Biomarker Dataset



These results may not generalize to all biomarkers in all histologies.

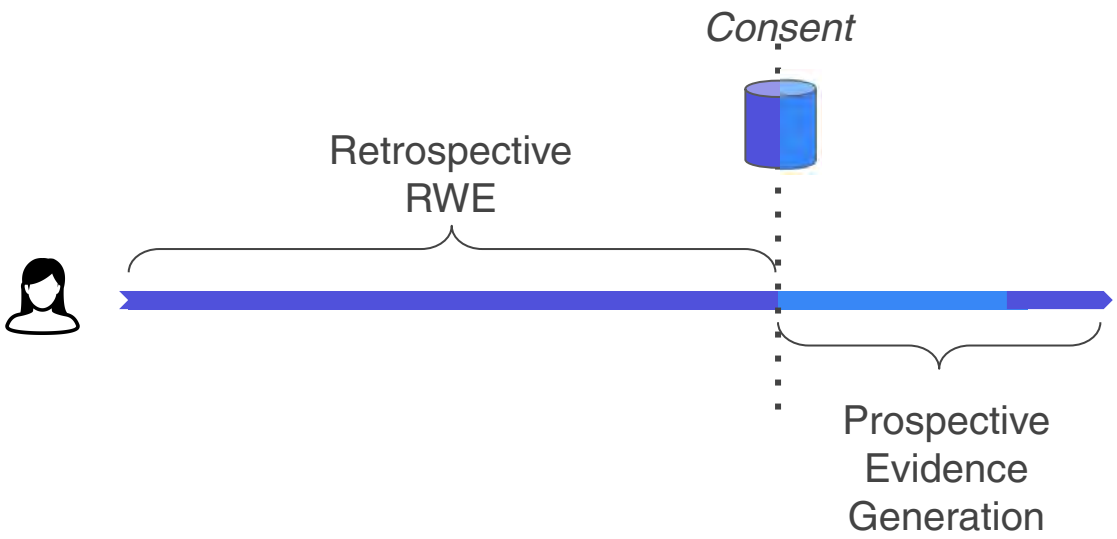
A look to the future - a new paradigm for RWE in drug development

The Continuum of RWE



A look to the future - a new paradigm for RWE in drug development

The Continuum of RWE



- *Use technology to bridge the gap between retrospective RWE and prospective evidence generation*
- *Consent permits performance of supplemental biomarker tests for research in prospective setting:*
  - *hypothesis generation and testing*
  - *Monitoring biomarker status over time*

Thank you

Integrating Genomics and Phenomics: Standards for RWE in AACR's Project Genie

AACR-FDA Workshop on RWD, July 19th 2019

Deb Schrag, MD, MPH, Professor of Medicine

Dana-Farber Cancer Institute and Brigham and Women's Hospital

Harvard Medical School, Boston, MA USA

Disclosures

Research Support:

Funding from AACR for Project GENIE---AACR Receives Funding from Multiple For Profit Entities

Grail, Pfizer, EPIC

Collaborations without Research Support or Fees: Amazon, Microsoft, Google, Proteus, Trip Advisor, Aetna

Personal Fees:

JAMA for Editorial Services, EABs of Multiple Academic Medical Centers

Imedex for Speaking at CME Event, Pfizer for speaking at ESMO

AACR's GENIE Consortium:
Collaboration Among Cancer Centers that Perform NGS

DFCI
GRCC
JHU
MDA
MSK
NKI
UHN
VICC

Clinical Sequencing

A

regular data uploads

Synapse
CONTRIBUTE to the CURE

- Data mapped to common ontology and harmonized
- Limited PHI removed
- Data governance, provenance, and versioning in a secure, HIPAA-compliant environment.

cBioPortal for Cancer Genomics

Institution-only access 6 months

Consortium-only access 6 months

B

clinical queries are posed based on registry content

clinical data required to answer the question are manually abstracted

genomic and clinical data linked

Consortium/sponsor-only access
6 months to time of publication

Achieving Goals of Precision Medicine Requires Integration

Genomic Data

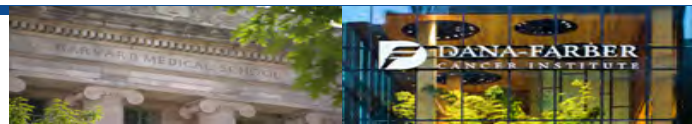
What features?

Therapeutic Data

What Rx interventions?

Outcomes Data

Achieve best results?



Achieving Goals of Precision Medicine Requires Integration

GENOMICS

- Somatic Tumor DNA
- Germline DNA
- cfDNA
- RNA Seq
- Epigenetics

THERAPEUTICS

- Anti-neoplastics:
  - Chemotherapy
  - Immunotherapy
  - Hormonal therapy
  - Vaccines
- Surgery
- Radiation

PHENOMICS

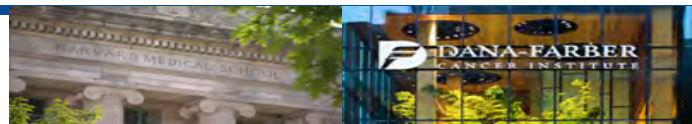
Outcomes:

- Vital status
- Response
- Progression free survival
- Disease free survival
- Toxicity/Complications

Data Reasonably Structured
Data Standards Exist

Data Less Well Structured
Data Standards Do Not Exist

PRISSMM



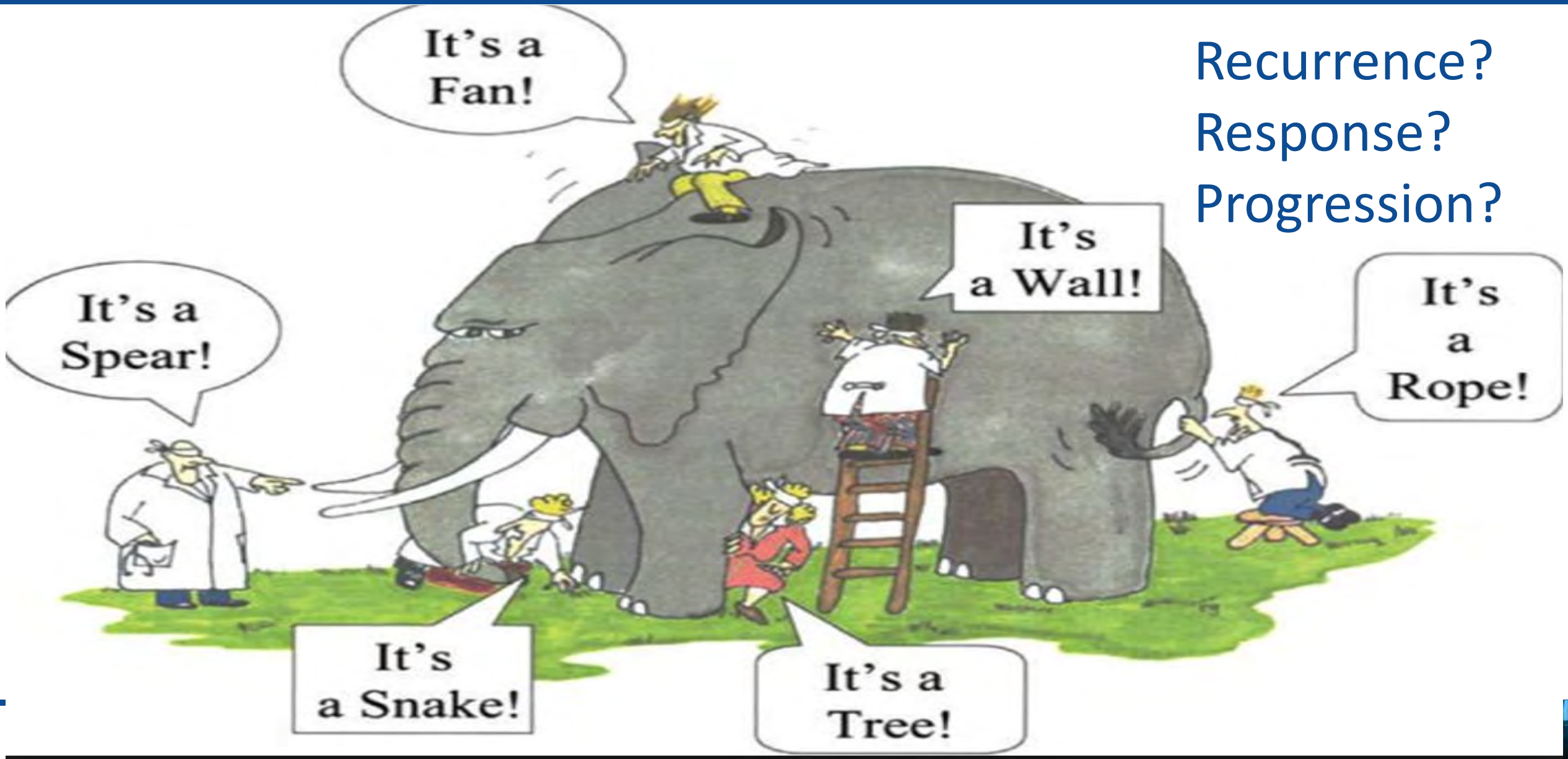
Challenge: How do we define outcomes consistently?

- Overall survival: structured, but not necessarily standardized

- Response to treatment: unstructured in EHR
- Recurrence and Disease Free Survival: unstructured in EHR
- Progression and Progression Free Survival: unstructured in EHR

- Can we develop common approach to curation of these data elements so that data are valid and usable for discovery?

The Parable of the Blind Men:



Recurrence?
Response?
Progression?

Publicly Available Data Standards Enable Progress

Standards Beget Standards…. Beget Better Data

NATIONAL CANCER INSTITUTE
Division of Cancer Control & Population Sciences

Search

Healthcare Delivery Research Program

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Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™)

Deb Schrag MD MPH

RECIST: A Standard for Defining PFS in Clinical Trials

RECIST (Response Evaluation Criteria in Solid Tumours) provides a simple and pragmatic methodology to evaluate the activity and efficacy of new cancer therapeutics in solid tumors, using validated and consistent criteria to assess changes in tumor burden. The RECIST Working Group comprises representatives of the European Organization for Research and Treatment of Cancer (EORTC), National Cancer Institute (NCI) of the United States and Canadian Cancer Trials Group (CCTG), as well as several pharmaceutical companies. Its mission is to ensures that RECIST undergoes continued testing, validation and updating.

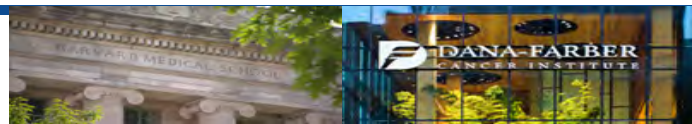
- Real world scan reports do not quantify response according to RECIST
- Requires like scan to like scan comparisons
- Depends on scans performed at pre-defined intervals
- RECIST criteria not captured in text of radiology reports
- Expensive to perform post-hoc

Can Structured Surrogate Endpoints Approximate rwPFS?

- **Administration of anti-neoplastic drugs is captured in structured format**

Metric	Specification
Time to Treatment Discontinuation	First treatment date to last treatment date (breaks >6 weeks count as discontinuation)
Time to new treatment start	First treatment date of drug 1 to first treatment date of drug 2

Challenge: These intervals do not distinguish treatment stops or starts for: progression vs. complete response vs. toxicity and are therefore an imperfect surrogate for rwPFS



Staging Standards in Oncology

cT3N2Mx
yT4N1M0

- Interpretable
- Computable
- Flexible
- Adaptable framework across tumor sites

A PHENOMIC DATA STANDARD: PRISSMM™

- Captures disease status each month
- Cancer site agnostic
- Builds on NAACCR/SEER standards
- Defines rwDFS and rwPFS consistently with high inter-rater reliability
- Method for defining rwDFS and rwPFS consistently in multi-center curation projects
- Tags records with “ground truth” for machine teaching----to enable future automation with machine learning

PRISSMM:

Phenomic Data Standards for Defining Cancer Outcomes from EHR data

Pathologic evidence of tumor

Radiographic evidence of locoregional recurrent tumor

Imaging evidence of distant/disseminated tumor beyond the primary site

Signs of tumor on physical exam

Symptoms attributable to cancer

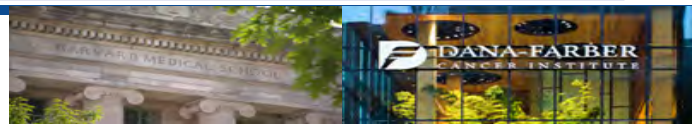
M_k protein marker evidence of recurrent tumor

Medical oncology Provider assessment

Each curation effort may focus on some or all of the PRISSMM components
Signs may be relevant for melanoma outcomes
Markers may not be relevant for lung outcomes

PRISSMM Establishes Standards to Define Cancer Treatment Outcomes from EHR Data

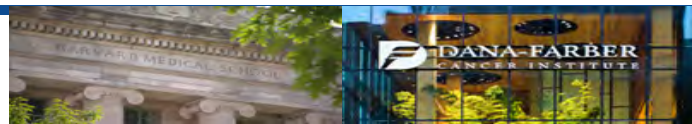
$PRISSM_kM$	Generic Framework and Data Provenance
P	Pathology reports
R	Imaging reports of primary site
I	Imaging reports of distant sites
S_i	Signs on physical exam in oncologist notes
S_y	Symptoms noted in HPI, impression, interval history
M_k	Biomarkers
M	Impression/plan from clinician notes (oncology MD, RN, RNP, PA)



PRISSMM as Communication Tool to Describe RWD Endpoints

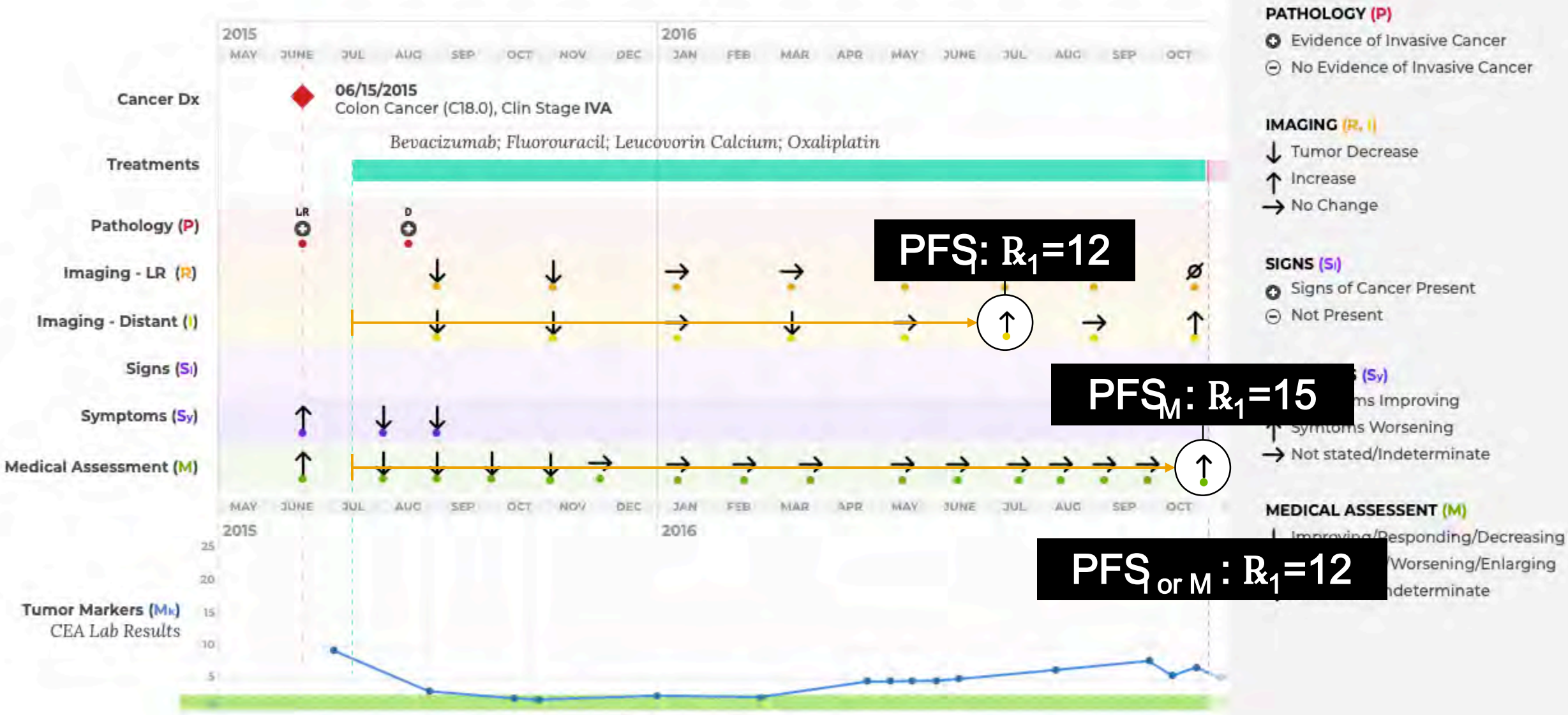
PRISSMM captures disease status and treatment response relative to: 1. Diagnosis and 2. Any treatment event

@48: $P_xR_{\downarrow}ISSM_xM_{\rightarrow}$	FOLFIRI+3	Response after 3 months of FOLFIRI based on imaging Stable after 3 months based on oncologist evaluation
@52: $P_+R_{\rightarrow}ISSMM_{\rightarrow}$	FOLFIRI+7	Stable disease based on imaging and oncologist evaluation
@54: $P_+R_{\uparrow}ISSMM_{\uparrow}$	FOLFIRI+9	Progression based on imaging and oncologist evaluation



PRISSMM: Measuring Real World Outcomes

Real World Progression -Free Survival: Anchored from Treatment [R_1]



PATHOLOGY (P)
- Evidence of Invasive Cancer
- No Evidence of Invasive Cancer

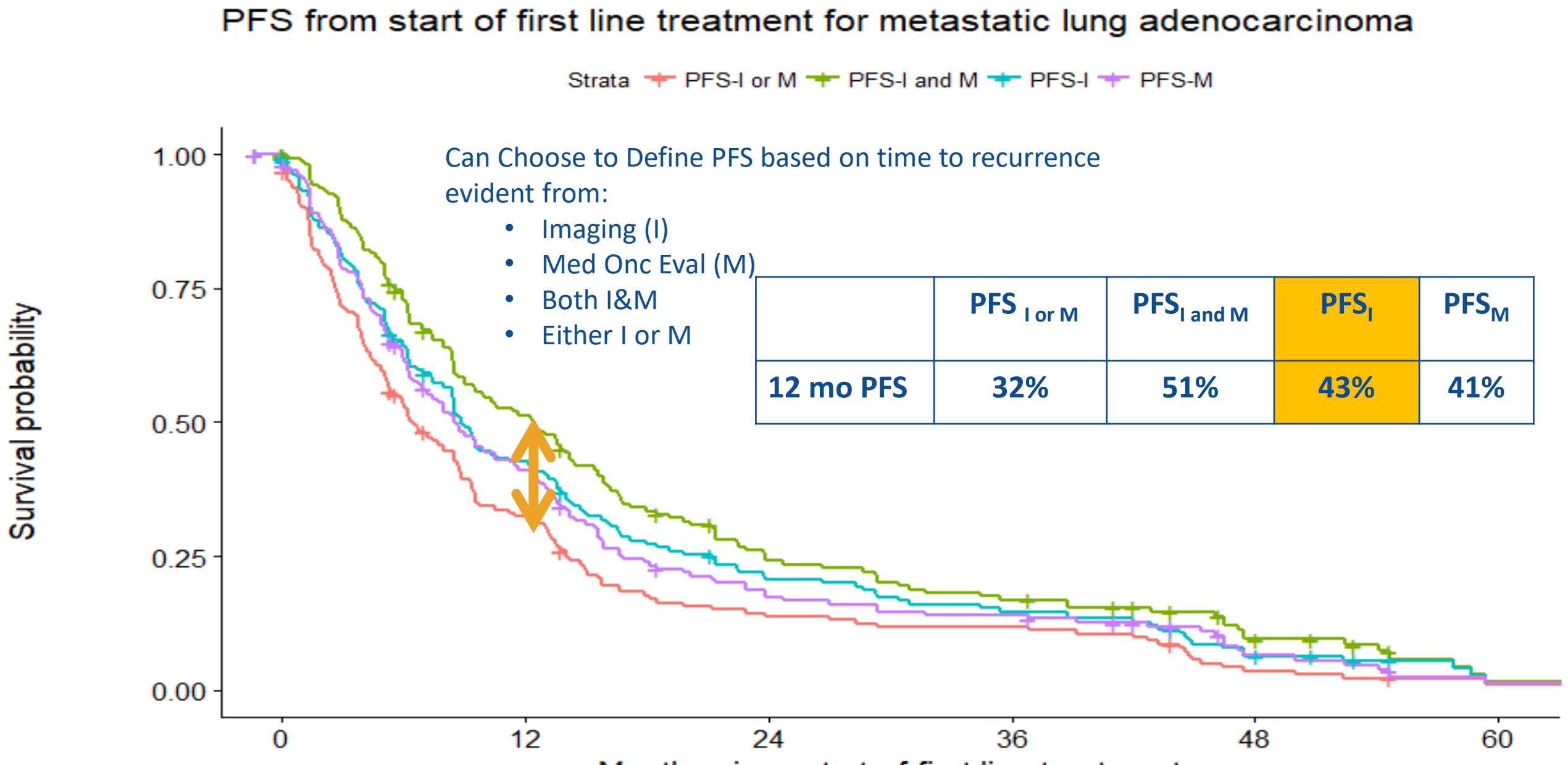
IMAGING (R, I)
- Tumor Decrease
- Increase
- No Change

SIGNS (SI)
- Signs of Cancer Present
- Not Present

(SY)
- ms Improving
- Symptoms Worsening
- Not stated/Indeterminate

MEDICAL ASSESSENT (M)
- Improving/Responding/Decreasing
- /Worsening/Enlarging
- ndeterminate

Define a RW Endpoint Based on PRISSMM



Can Choose to Define PFS based on time to recurrence evident from:

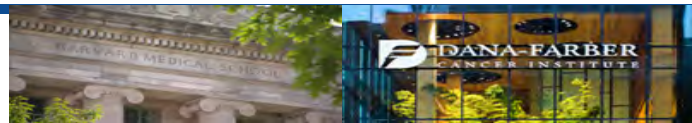
- Imaging (I)
- Med Onc Eval (M)
- Both I&M
- Either I or M

	$PFS_{I\ or\ M}$	$PFS_{I\ and\ M}$	PFS_{I}	PFS_{M}
12 mo PFS	**32%**	**51%**	**43%**	**41%**

PRISSMM is a Data Standard for RWD in Oncology

- **PRISSMM Includes:**
  - **Training materials for EHR curators**
  - **REDCAP databases to extract data from EHRs**
  - **QA methods, manuals and standardized reporting tools**
  - **Flexible model that works across solid tumor types**
  - **Model can be applied retrospectively or prospectively**
  - **Builds on and integrates with existing data standards**

- **PRISSMM:**
  - **Expedites and optimizes human curation of medical records**
  - **Enables patients to track their own outcomes across space and time**
  - **Enables machine curation of medical records**



American Association for Cancer Research

FINDING CURES TOGETHER℠

Oncology needs data standards that define clinical endpoints in transparent reproducible manner to extract knowledge from every cancer patient's journey

Please contact us to learn more about Project GENIE and PRISSMM

shawn.sweeney@aacr.org

Phenomic Data Standards are Critical for RWD Use in Oncology

- Improve ability to communicate “real world” outcomes in consistent manner

- Expedite and optimizes human curation of medical records
- Enables patients to track their own outcomes across space and time
- Enables machine curation of medical records

- Build capacity to create, share and use “Real World” Data
  - Creates a “lingua franca” understood by clinical and research community
  - Allows custom definitions of disease status and dynamic endpoints: TTR/DFS, TTP/DFS
  - Enables interoperability and data sharing

PRISSMM Establishes Standard Directives for Curation of Cancer Treatment Outcomes from EHRs

PRISSMM	Generic Framework
P	Pathology reports
R	Imaging reports of primary site
I	Imaging reports of distant sites
S_i	Signs on physical exam in oncologist notes
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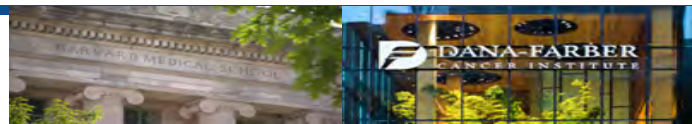


U.S. FOOD & DRUG ADMINISTRATION

American Association for Cancer Research

FINDING CURES TOGETHER℠

SESSION V:

Real-world Evidence – Future Directions

Session Moderator: Andrea Coravos

Speakers:

Andrea Coravos

James Gulley, MD, PhD

Mark Shapiro, MBA, PhD

Algorithms, Connected Technologies and Generating Real-World Evidence

Andy Coravos
CEO, Elektra Labs

FDA-AACR Real-World Evidence Workshop
July 8 19 2019

Disclosures

FDA-AACR Real-World Evidence Workshop
Andy Coravos

I have the following financial relationships to disclose:

- Grant/Research support from the Harvard -MIT Center for Regulatory Science
- Stockholder and employee of Elektra Labs

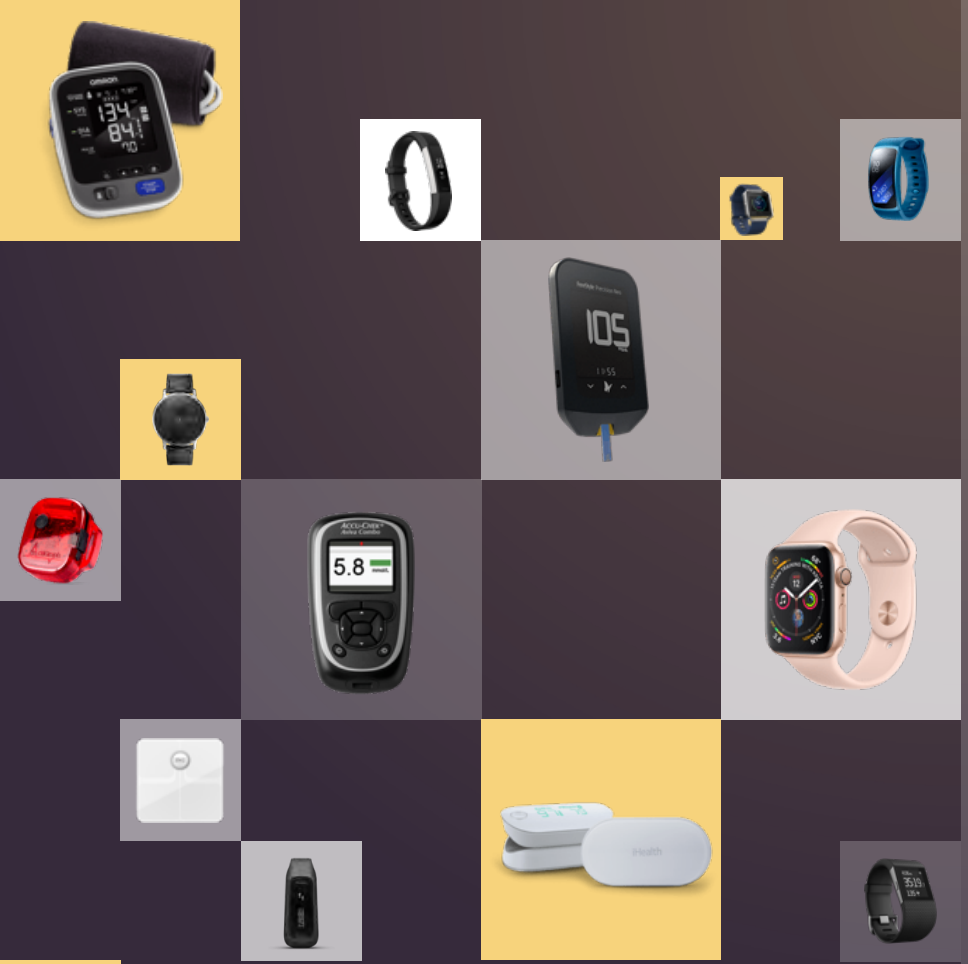
I will not discuss off label use and/or investigational use in my presentation.

```
class Career

        def current_experience
        CEO/co-founder @ Elektra Labs
                Member, Harvard-MIT Center for Regulatory Sciences
        end

        def past_experience
        Entrepreneur in Residence, US Food and Drug Administration (FDA)
        Software Engineer @ Akili Interactive
        Healthcare Private Equity @ KKR
        Management Consultant @ McKinsey & Company
        end

end
```



Overview of today's talk

- **Introduction to digital tools**
  A look at the wearables, ingestibles and biosensors that are collecting digital specimen data.

- **Overview of decentralized clinical trials**
  A framework for "direct-to-patient," "remote," "site-less," and "virtual" clinical research

- **Data rights and governance considerations**
  Ethical and legal considerations when using digital specimen data

What are RWD and where do they come from?

Real world data are the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources. RWD can come from a number of sources, for example:

- Electronic health records (EHRs)
- Claims and billing activities
- Product and disease registries
- Patient-generated data including in home-use settings
- Data gathered from other sources that can inform on health status, such as mobile devices

Source: https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence

Today's focus

What are RWD and where do they come from?

Real world data are the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources. RWD can come from a number of sources, for example:

- Electronic health records (EHRs)
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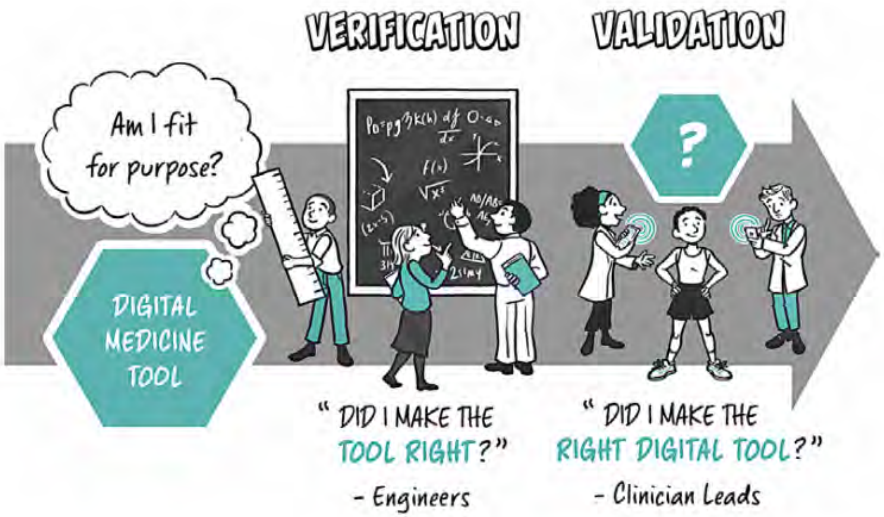
- **Data gathered from other sources that can inform on health status, such as mobile devices**

Source: https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence

Before we start, a few definitions.

New to digital medicine?

We published a book (with cartoons!)



digital biomarkers

Digit Biomark 2019;3:31–71
DOI: 10.1159/000500413
Received: February 22, 2019
Accepted: April 16, 2019
Published online: May 9, 2019

Review Article

Digital Medicine: A Primer on Measurement

Andrea Coravos[a–c] Jennifer C. Goldsack[c, d] Daniel R. Karlin[c, e, f]
Camille Nebeker[g, h] Eric Perakslis[i, j] Noah Zimmerman[k, l] M. Kelley Erb[m]

[a]Elektra Labs, Boston, MA, USA; [b]Harvard-MIT Center for Regulatory Science, Boston, MA, USA; [c]The Digital Medicine Society (DiMe), Boston, MA, USA; [d]monARC Bionetworks, San Francisco, CA, USA; [e]HealthMode, New York, NY, USA; [f]Tufts University School of Medicine, Boston, MA, USA; [g]Department of Family Medicine and Public Health, School of Medicine, University of California, San Diego, La Jolla, CA, USA; [h]Center for Wireless and Population Health Systems, School of Medicine, University of California, San Diego, La Jolla, CA, USA; [i]Rubenstein Fellow – Duke Forge, Durham, NC, USA; [j]Harvard Medical School, Boston, MA, USA; [k]Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [l]Institute for Next Generation Healthcare, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [m]Digital Medicine and Translational Imaging, Worldwide Research, Development, and Medical, Pfizer Inc., Cambridge, MA, USA

Download a copy: https://www.karger.com/Article/Abstract/500413

There are four types of Clinical Outcome Assessments (COAs)

- Patient-reported outcomes (**PRO**)
- Clinician-reported outcome (**ClinRO**)
- Observer-reported outcome (**ObsRO**)
- Performance outcome (**PerfO**)

COAs can become digitized to collect data at home. When referring to digital COAs, it's traditional to include an "e" → *eCOA, ePRO*

But what happens when we use a mobile or connected technology? Are there '**mobileOAs**'?

Source: https://www.fda.gov/about-fda/clinical-outcome-assessments-coa-frequently-asked-questions

A glossary of terminology and uses of biomarkers and endpoints in biomedical research, medical product development and clinical care

- The BEST framework was created in 2016 by an NIH-FDA Working Group
- Seven types of biomarkers:
  - Diagnostic Biomarker
  - Monitoring Biomarker
  - Pharmacodynamic / Response Biomarker
  - Predictive Biomarker
  - Safety Biomarker
  - Susceptibility / Risk Biomarker

Although not explicitly listed in the BEST framework, a **"digital biomarker"** is a biomarker collected through digital means, often used in a remote (at-home) setting

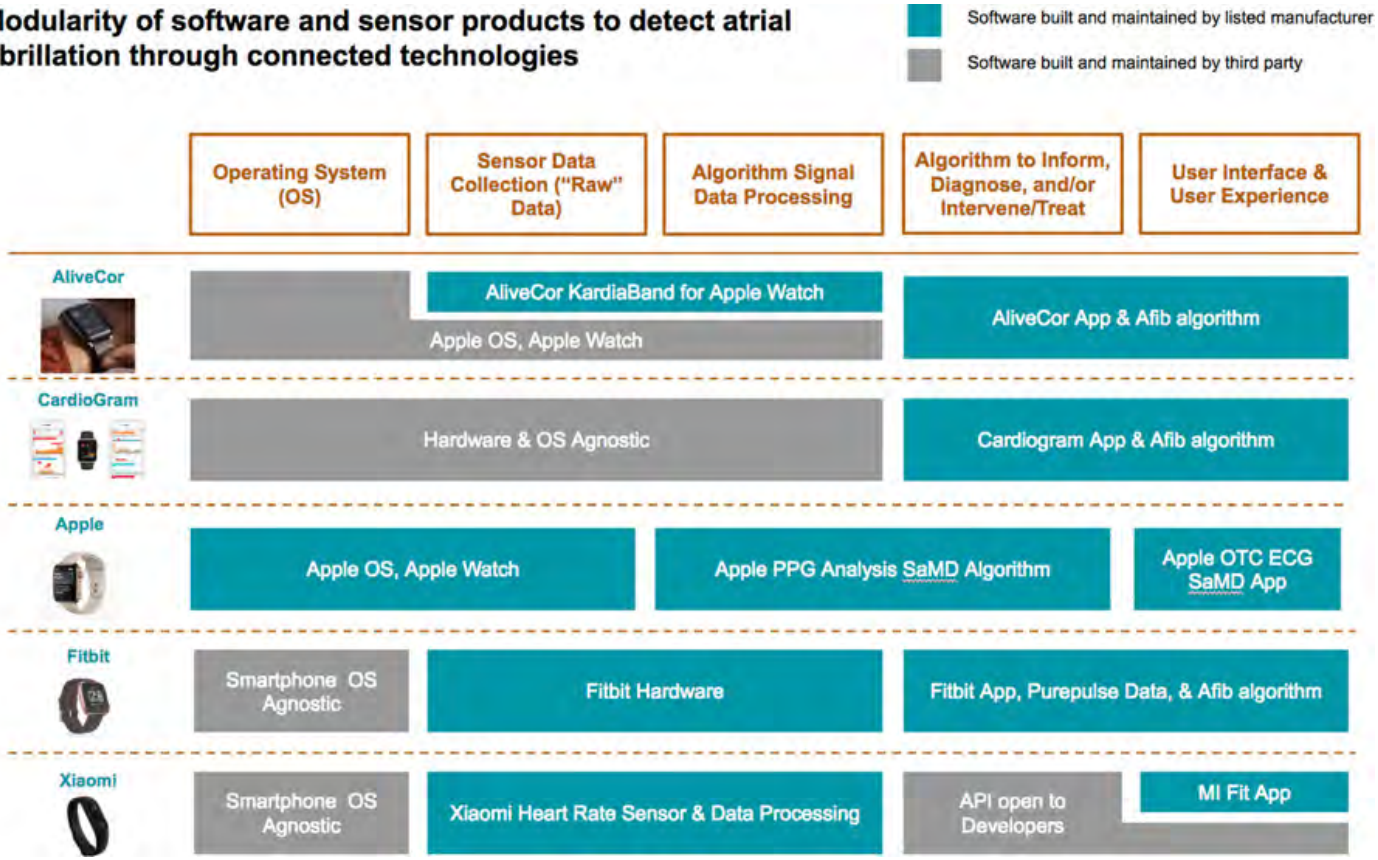
Source: FDA-NIH BEST Framework, https://www.ncbi.nlm.nih.gov/books/NBK326791/

Software and algorithms have a wide range of applications

Measure	Diagnose	Treat
With **sensors + algorithms** to create objective measurements	With **advanced algorithms** to support the clinician	With **novel software-based therapies** that may augment or substitute a drug
E.g., Digital biomarkers, clinical decision support	*Digital diagnostics*	*Digital therapeutics*

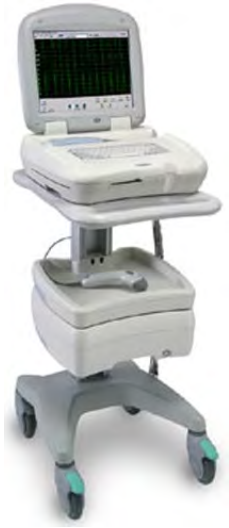
To develop these products, we'll need to build safe and clinically validated algorithms.

Modularity of software and sensor products to detect atrial fibrillation through connected technologies



Source: Coravos A, Khozin S, Mandl KD. Developing and adopting safe and effective digital biomarkers to improve patient outcomes. NPJ Digit Med. 2019;2(1), https://www.nature.com/articles/s41746-019-0090-4

In 2014, AliveCor brought the EKG home...



Philips Pagewriter Touch Interpretive EKG Machine: $15k

Take a medical -grade EKG in just 30 seconds. Results are delivered right to your smartphone.

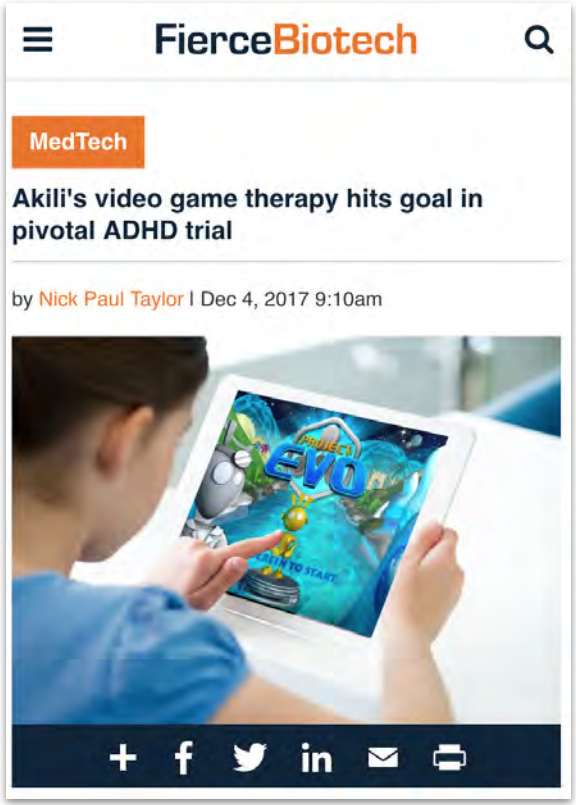
FDA

Meet Kardia Mobile. Your personal EKG: $99. FDA-Cleared.

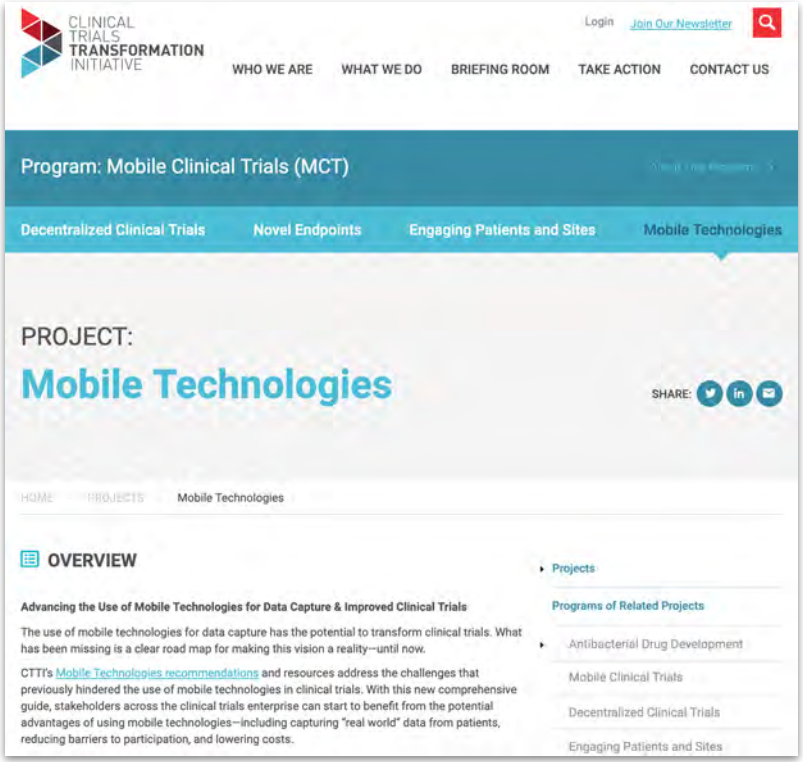
… and since then, the FDA has cleared multiple "software -as -a-medical -device" (SaMDs)

- Developed in a lab at UCSF
- Published in Nature in 2013 and found that video game training enhances cognitive control in older adults
- Technology licensed to Akili Interactive Labs, a start-up, working to commercialize the product

Four Years Later...



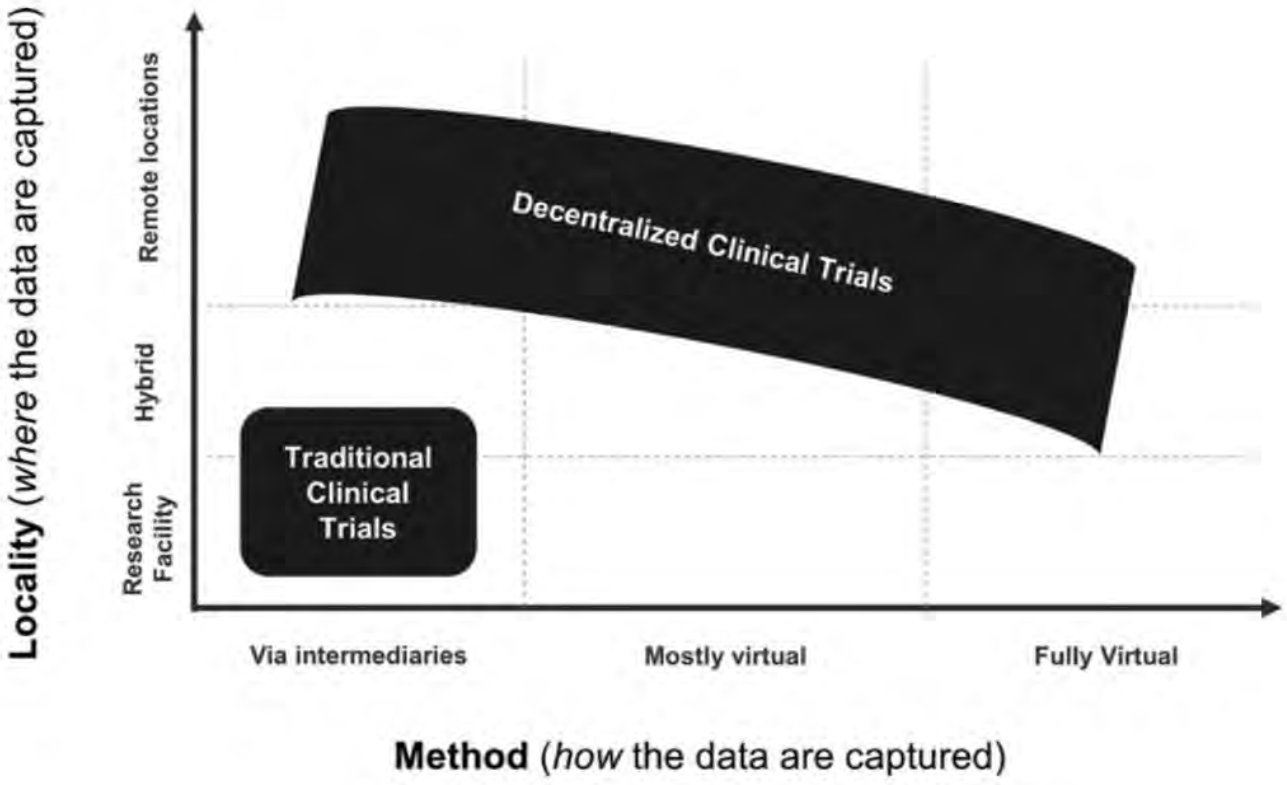
How can I know if these tools are trustworthy?



Source: https://www.ctti-clinicaltrials.org/projects/mobile-technologies

Source: https://www.nature.com/articles/s41746-019-0125-x

So, what can these tools enable?

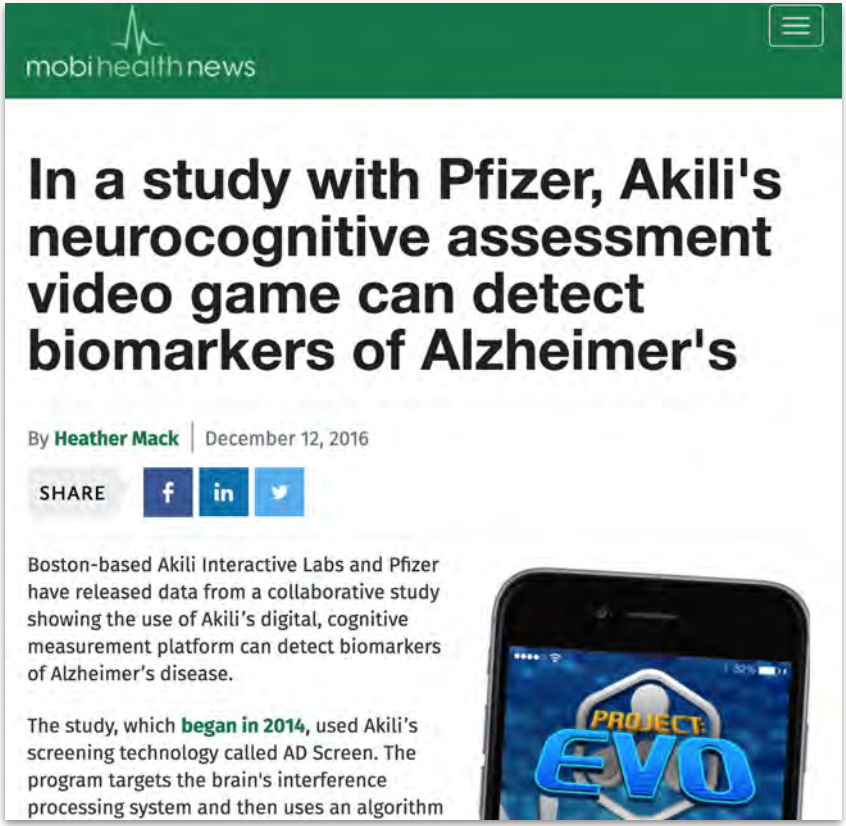


Mobile technologies are enabling new clinical investigation designs like **Decentralized Clinical Trials** (DCTs)

Source: Khozin S, Coravos A. Decentralized Trials in the Age of Real-World Evidence and Inclusivity in Clinical Investigations. Clin Pharmacol Ther. 2019;
https://ascpt.onlinelibrary.wiley.com/doi/full/10.1002/cpt.1441

Two Case Studies: Cognition, Oncology and Digital Performance Outcomes

Still early days!



mobihealthnews

In a study with Pfizer, Akili's neurocognitive assessment video game can detect biomarkers of Alzheimer's

By **Heather Mack** | December 12, 2016

SHARE

Boston-based Akili Interactive Labs and Pfizer have released data from a collaborative study showing the use of Akili's digital, cognitive measurement platform can detect biomarkers of Alzheimer's disease.

The study, which **began in 2014,** used Akili's screening technology called AD Screen. The program targets the brain's interference processing system and then uses an algorithm

AKILI

- Digital biomarkers may have the potential to serve as non-invasive options to screening procedures
- These (adaptive) technologies may be able to collect more sensitive measures / surrogates of cognitive decline
- Potential to develop these types of applications for other therapeutic areas and/or use cases (e.g., impact of a drug on cognitive function)

Source: https://www.mobihealthnews.com/content/study-pfizer-akilis-neurocognitive-assessment-video-game-can-detect-biomarkers-alzheimers

Koneksa Results: Actigraphy as a predictor of imminent hospitalization

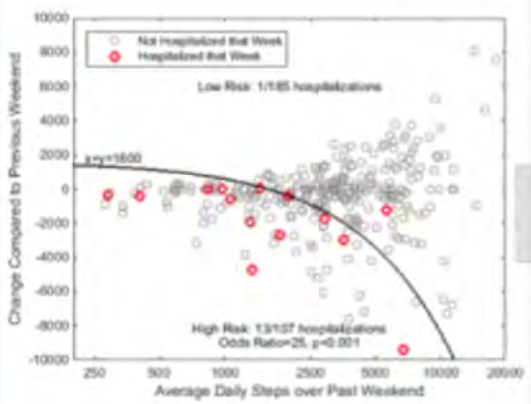
Assessing the ability of actigraphy to predict hospitalization vs. existing measures

Predictive Utility

- Baseline model included:
  - Age
  - Gender
  - ECOG performance status
  - Most recent QoL
  - Tumor location & stage
- Actigraphy model included all of the above and:
  - Average daily steps over past weekend
  - Change in average daily steps from previous weekend
- The Actigraphy model was independently predictive of hospitalization in the current week after accounting for age, ECOG and QoL

Hospitalizations	
Low risk group	1 / 185
High risk group	13 / 107
Odds ratio	25

Continuous activity monitoring enables early detection of imminent hospitalization



Activity over the past weekend is highly predictive of hospitalization in the current week (P < 0.001)

>10X more data than ECOG performance status

Is less subject to rater bias

Passive at-home data collection eases patient burden

Enabled detection of meaningful changes in patient status -- and assessing the impact on a disease/treatment in a clinical trial.

Source: https://www.koneksahealth.com/ocepresentation/

Ok, so the tools are safe and effective, but what about the information collected from the tools?

WSJ

JOURNAL REPORTS: TECHNOLOGY

The 'Internet of Bodies' Is Here. Are Courts and Regulators Ready?

A network of smart devices attached to or implanted in bodies raises a host of legal and policy questions

By Andrea M. Matwyshyn
Nov. 12, 2018 11:19 a.m. ET

We've all heard of the Internet of Things, a network of products ranging from refrigerators to cars to industrial control systems that are connected to the internet.

Now comes the Internet of Bodies—a network of smart devices that are attached to or inside our bodies. But using the human body as a technology platform raises a host of challenging legal and policy questions that regulators and

Our healthcare system has strong protections for patients' biospecimens, like blood or genomic data, but what about our **digital specimens**?

Sources
[1] https://www.wsj.com/articles/the-internet-of-bodies-is-here-are-courts-and-regulators-ready-1542039566
[2] https://www.thelancet.com/journals/landig/article/PIIS2589-7500(19)30001-9/fulltext

GPS

Fitness tracking app Strava gives away location of secret US army bases

Data about exercise routes shared online by soldiers can be used to pinpoint overseas facilities

Latest: Strava suggests military users 'opt out' of heatmap as row deepens

The New York Times

This Thermometer Tells Your Temperature, Then Tells Firms Where to Advertise

REGULATION

There's No Such Thing as Anonymous Data

by Scott Berinato

FEBRUARY 09, 2015

PROPUBLICA Donate

TOPICS ▾ SERIES ▾ ABOUT MORE ▾

HEALTH INSURANCE HUSTLE

Your Medical Devices Are Not Keeping Your Health Data to Themselves

CPAP units, heart monitors, blood glucose meters and lifestyle apps generate information that can be used in ways patients don't necessarily expect. It can be sold for advertising or even shared with insurers, who may use it to deny reimbursement.

PROPUBLICA Donate

Justin Volz, special to ProPublica

HEALTH INSURANCE HUSTLE

You Snooze, You Lose: Insurers Make The Old Adage Literally True

[1] https://www.theguardian.com/world/2018/jan/28/fitness-tracking-app-gives-away-location-of-secret-us-army-bases

[2] https://www.nytimes.com/2018/10/23/business/media/fever-advertisements-medicine-clorox.html

[3] https://www.propublica.com/article/your-medical-devices-are-not-keeping-your-health-data-to-themselves

[4] https://hbr.com/2015/02/theres-no-such-thing-as-anonymous-data


DISOBEY
DEFCON

Learn more about the FDA-led initiative at **WeHeartHackers.org**

[1] https://www.fda.gov/medical-devices/workshops-conferences-medical-devices/public-workshop-content-premarket-submissions-management-cybersecurity-medical-devices-january-29-30
[2] WeHeartHackers.org

JMIR Publications 20

The Case for a Hippocratic Oath for Connected Medical Devices: Viewpoint

Beau Woods; Andrea Coravos; Joshua David Corman

ABSTRACT

Prior to graduating from medical school, soon-to-be physicians take the Hippocratic Oath, a symbolic declaration to provide care in the best interest of patients. As the medical community increasingly deploys connected devices to deliver patient care, a critical question emerges: should the manufacturers and adopters of these connected technologies be governed by the symbolic spirit of the Hippocratic Oath? In 2016, I Am The Cavalry, a grassroots initiative from the cybersecurity research community, published the first Hippocratic Oath for Connected Medical Devices (HOCMD). Over the past three years, the HOCMD has gained broad support and influenced regulatory policy. We introduce five case studies of the HOCMD in practice, leading to a safer and more effective adoption of connected medical technologies.

[1] https://www.jmir.org/2019/3/e12568/
[2] DiMeSociety.org

Clinicians have professional societies to support their development, e.g., the Society for Neuro-Oncology (SNO).

What exists for those who practice and develop digital medicine products?

Members from government agencies have teamed up with software engineers, security researchers and more to launch...

DiME

Learn more about the 501(c)3 Digital Medicine (DiMe) Society at **DiMeSociety.org**.

We're hitting an inflection point in digital medicine. Now's the time to shape the healthcare community.

Let's build an intentional future that we want, and not an accidental one.

Want to continue the conversation? Shoot me your questions via Twitter *@andreacoravos*

Intelligent Health (iHealth), an intramural NCI digital health initiative

NIH NATIONAL CANCER INSTITUTE
James Gulley, MD, PhD

U.S Food and Drug Administration
Sean Khozin MD

A NEW ERA OF SEEKING OUT CARE

Medical grade wearables + predictive diagnostics = proactive health services

Today

Reactive Health

1. Seek health services when feeling ill
2. Consumer sorts through different care options
3. Data is then captured to confirm diagnosis

Tomorrow

Proactive Health

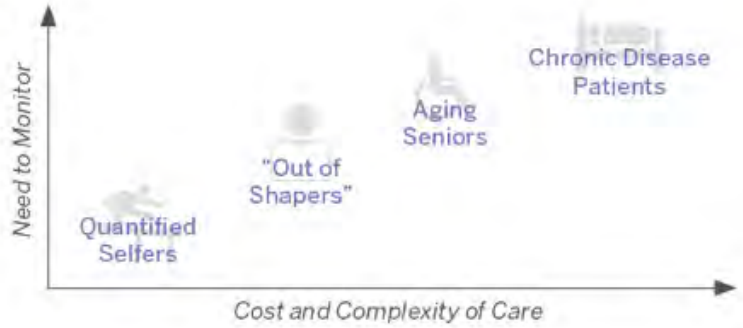
1. Data is captured via medical-grade wearables
2. Care option reaches out if there is an anomaly
3. Provider already has historical dataset of relevant biomarkers and genetic predispositions

Courtesy of Adam Dicker

Is It Technically Feasible?

Technical Considerations

Is It Clinically Relevant?



Clinical Considerations

Is It Cost Effective?

$$ROI = \frac{\text{Outcomes} - \text{Program Cost}}{\text{Program Cost}}$$

Cost Considerations

Example: Remotely Monitoring High Risk Oncology Patients is Technically Feasible, Clinically Relevant and Financially Effective

Patients capture weight, temp, BP, pulse, PROs

Analyzed data is transmitted to providers to monitor

Remote monitoring reduces hospital and ER admissions

Courtesy of Adam Dicker

Patient-Reported Outcomes (PROs)

"Any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else."

Kluetz et al., *Clin Cancer Res* 2016; 22:1553-8.

Courtesy of Adam Dicker

Project #1 (n=60)

Mobile Senor Technology (collaboration with Industry, FDA)

- Determine the feasibility of using an app on a phone alone or in conjunction with a wearable device to collect data relevant for clinical care from patients with cancer.
- Compare with current methodology

Metric: Performance status

Comparison: Medical History

Performance Status Scales

Zubrod Scale		Karnofsky Scale	
0	Normal activity	100	Normal; no evidence of disease
		90	Able to perform normal activities with only minor symptoms
1	Symptomatic and ambulatory; cares for self	80	Normal activity with effort; some symptoms
		70	Able to care for self but unable to do normal activities
2	Ambulatory >50% of time; occasional assistance	60	Requires occasional assistance; cares for most needs
		50	Requires considerable assistance
3	Ambulatory ≤50% of time; nursing care needed	40	Disabled; requires special assistance
		30	Severely disabled
4	Bedridden	20	Very sick; requires active supportive treatment
		10	Moribund

West et al., *JAMA Onc* 2015

Project #1 (n=60)

Mobile Senor Technology (collaboration with Industry, FDA)

- Determine the feasibility of using an app on a phone alone or in conjunction with a wearable device to collect data relevant for clinical care from patients with cancer.
- Compare with current methodology

Fatigue
FACT-G,
CTCAE fatigue

Cognitive Response Time
MMSE

Ototoxicity
Audiometry if indicated

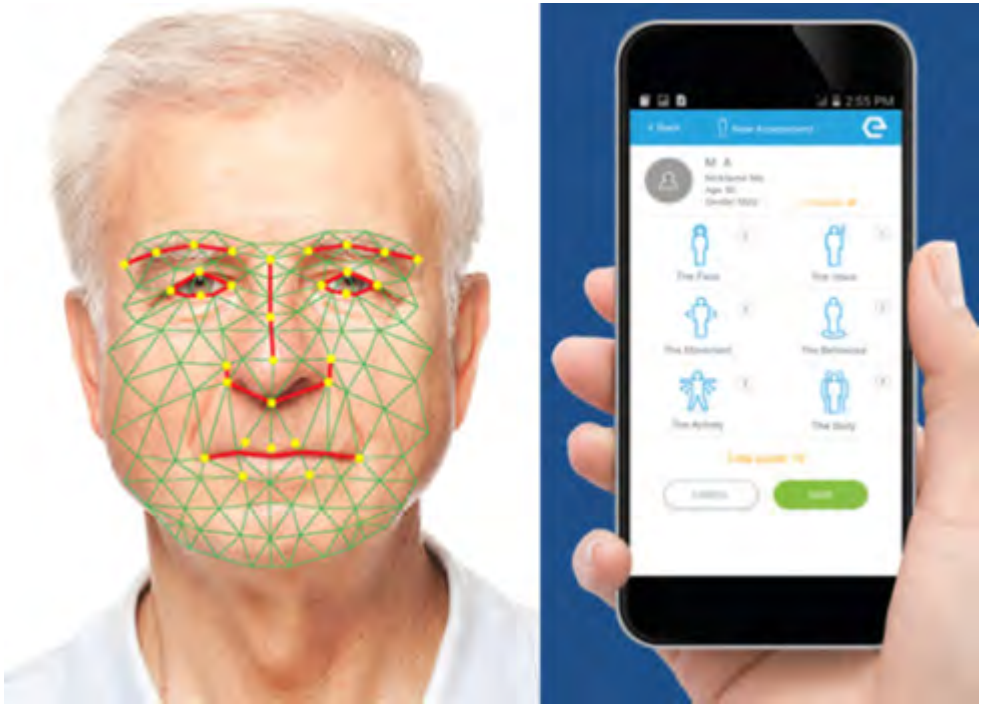
Metric: Performance status
Comparison: Medical History

Trial status: NCI IRB approved. Planned to open in Sept 2019

Project #2

Pain Recognition (collaboration with BAH, FDA)

- Determine the feasibility facial recognition technology (primary) and voice recognition technology (secondary) to detect and classify pain in patients with cancer.
- Compare with current methodology (11 point pain scale)
- Evaluate other facial changes in cancer patients (fear, anxiety, sadness, anger, etc.)



Trial Status: Concept review ongoing. Clinical Trial Agreement Finalized. Projected opening Q4 2019

Project #3

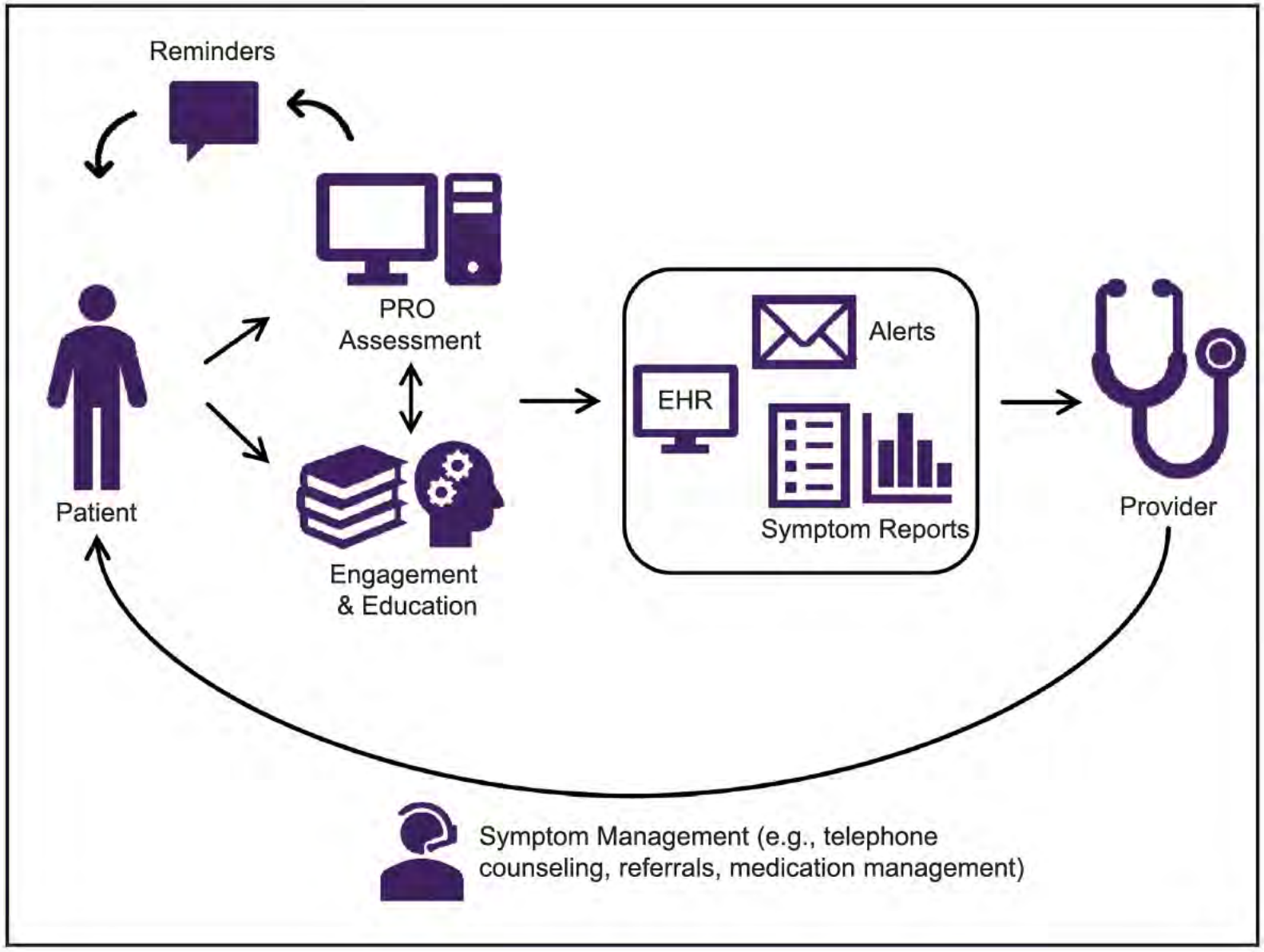
Electronic Patient Reported Outcomes (ePRO) (collaboration with Jefferson, Moffit, and FDA)

- Goal: See if we can identify and triage / treat side effects that may cause serious harm *earlier* thereby improving patient outcomes.
- Planned clinical trial with immunotherapy patients
- Use ePRO along with mobile sensor technology and pain assessment tools (from Projects 1 and 2)

Prevent serious side effects
Allow quicker resumption of effective therapy
Provide clinical safety net
Allow remote assessment more effectively

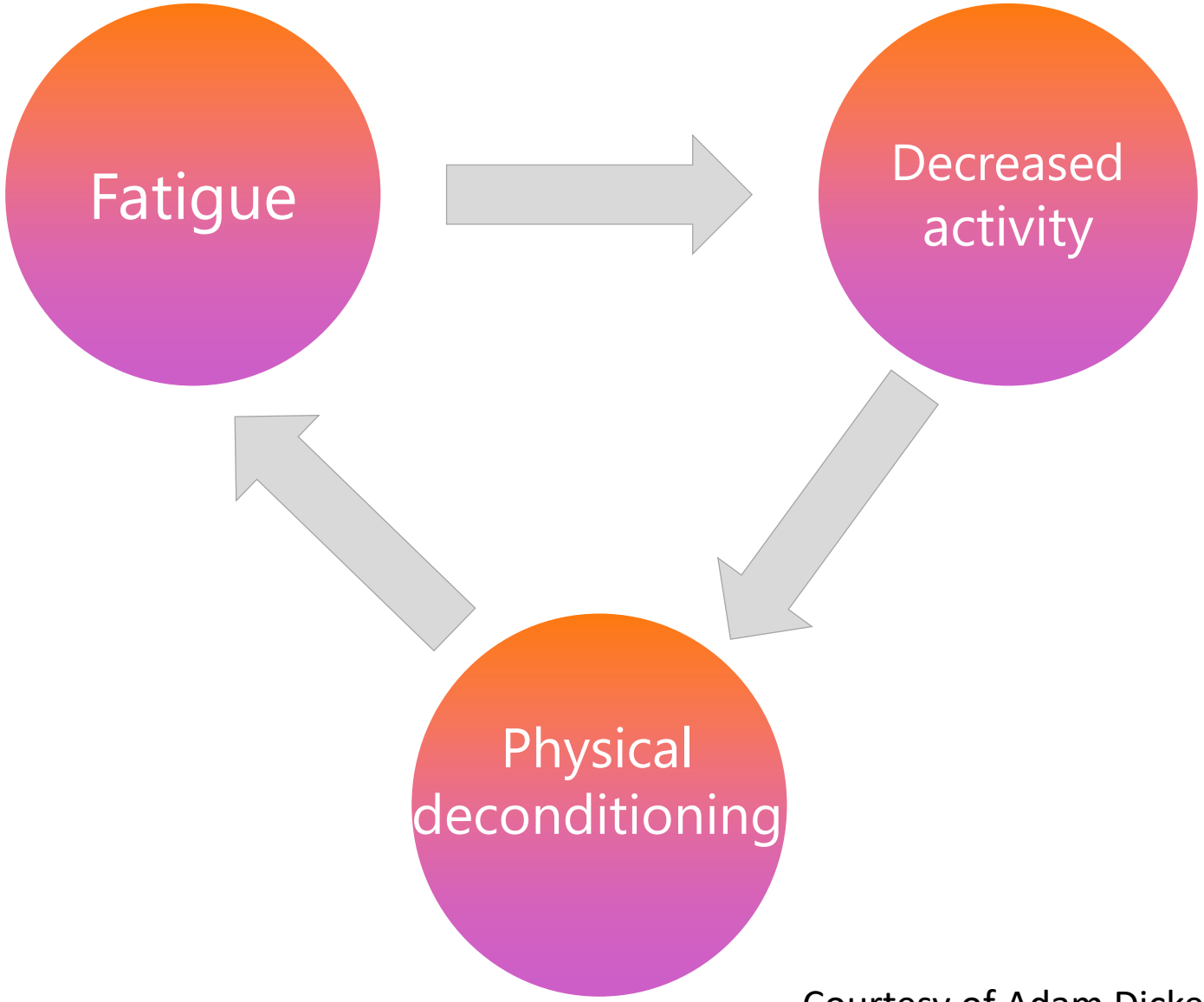
Trial Status: Concept review ongoing.

OncoTool



Courtesy of Adam Dicker

Cancer-Related Fatigue



Courtesy of Adam Dicker

MOFFITT CANCER CENTER

energize

Do What Matters

Heather Jim, PhD
Associate Member
Department of Health Outcomes and Behavior

MOFFITT CANCER CENTER

Courtesy of Adam Dicker

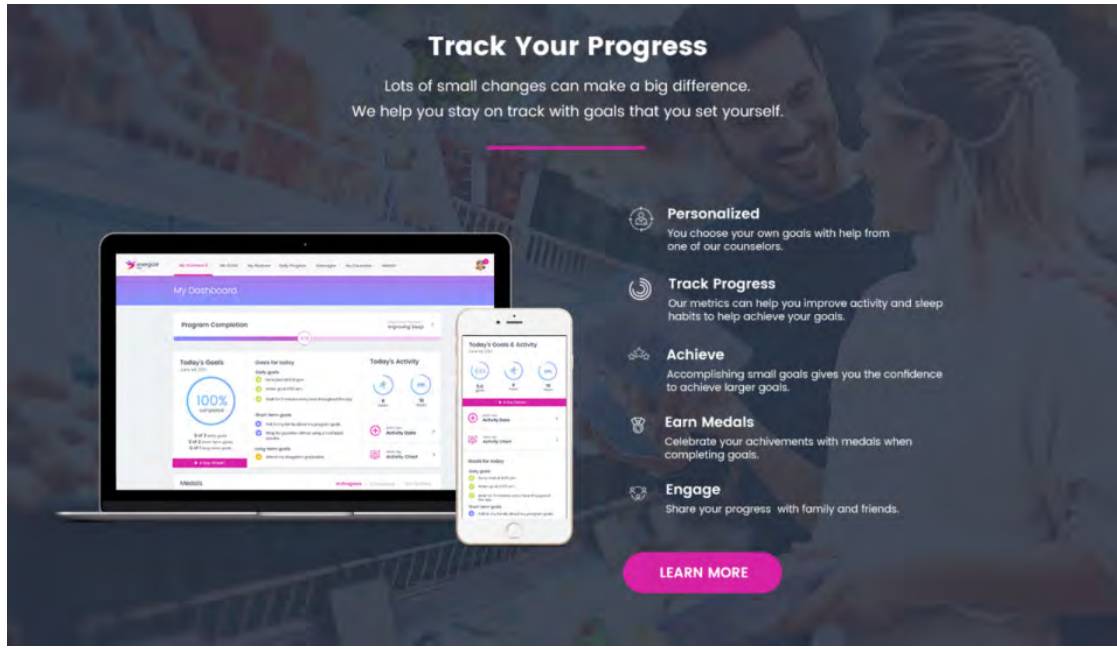
Energize Modules

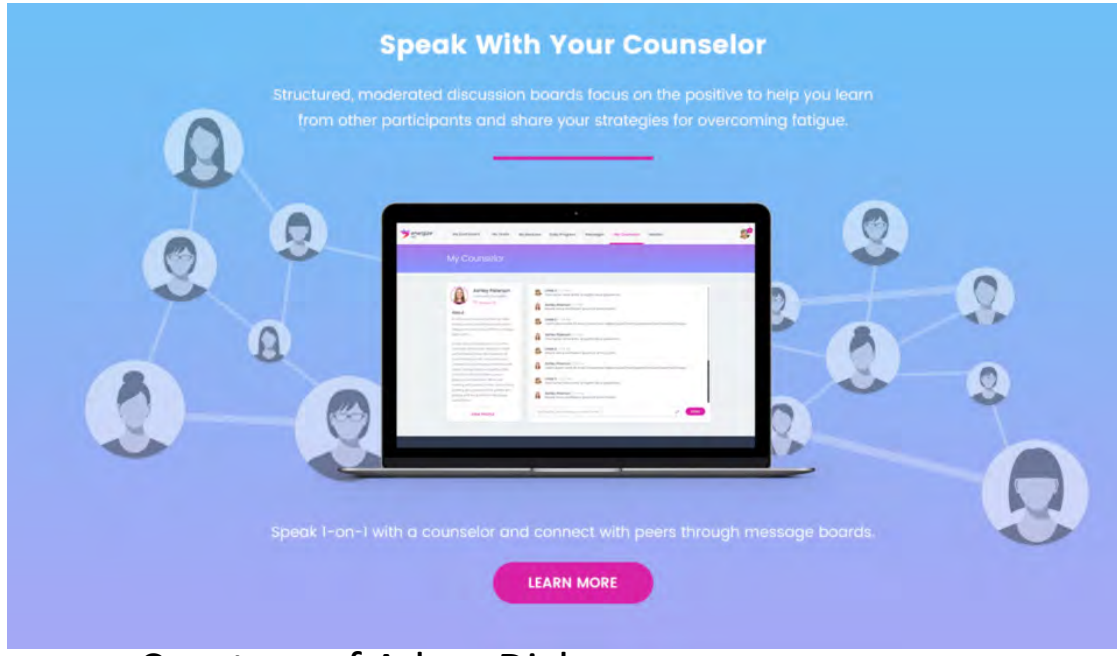
Activity pacing

Sleep hygiene

Thinking differently about fatigue

Plus optional modules

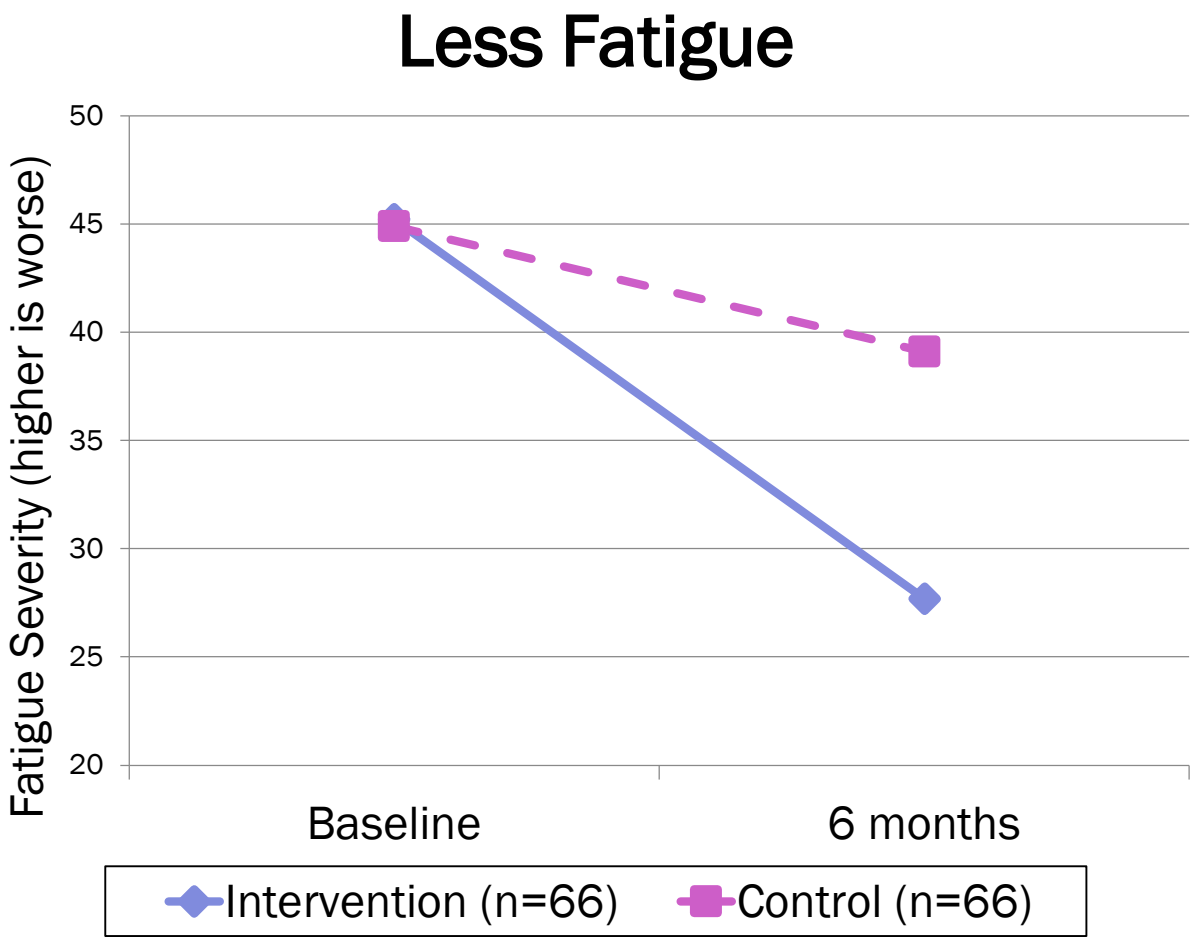


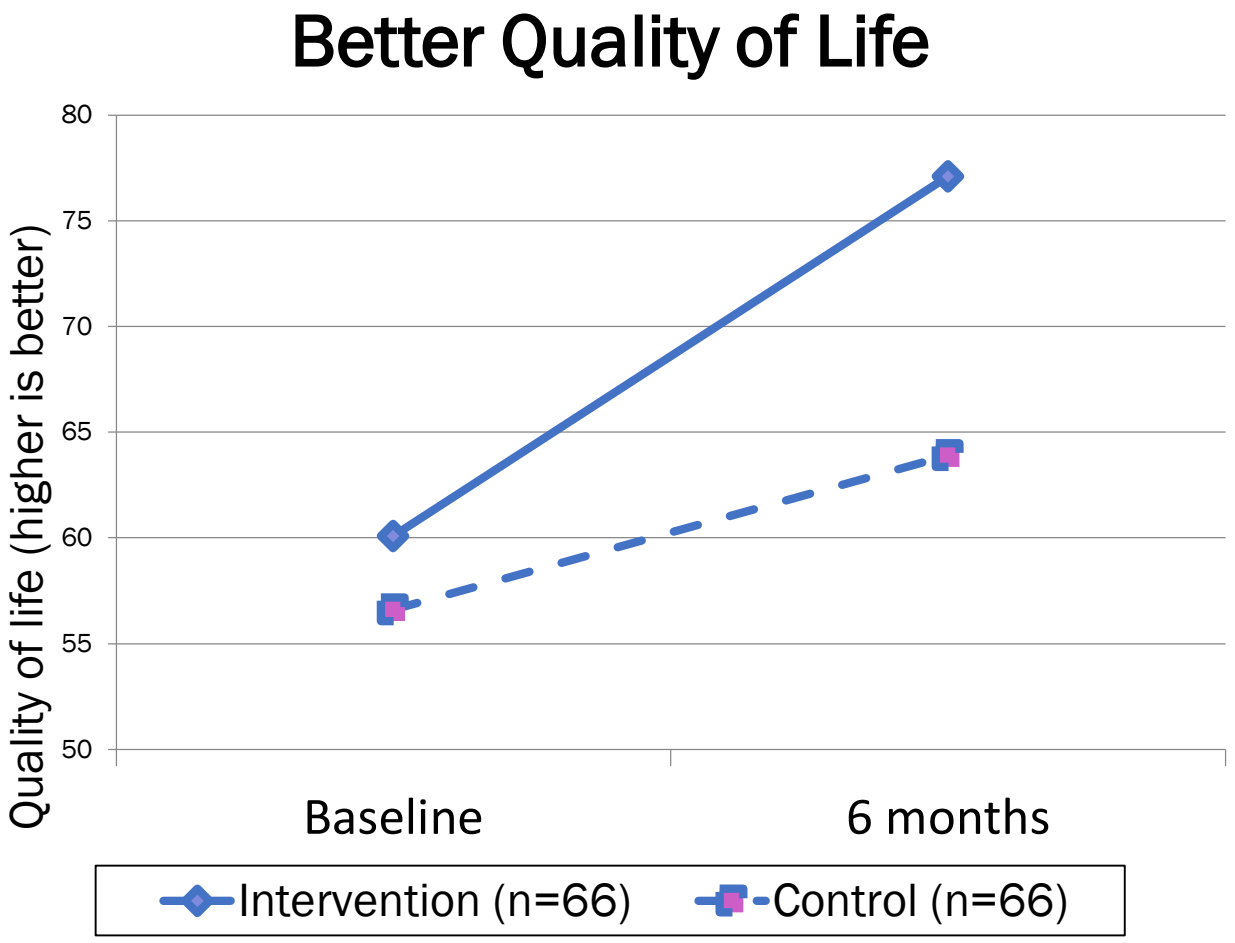


Cognitive Behavioral Therapy

Courtesy of Adam Dicker

Efficacy in Randomized Trials





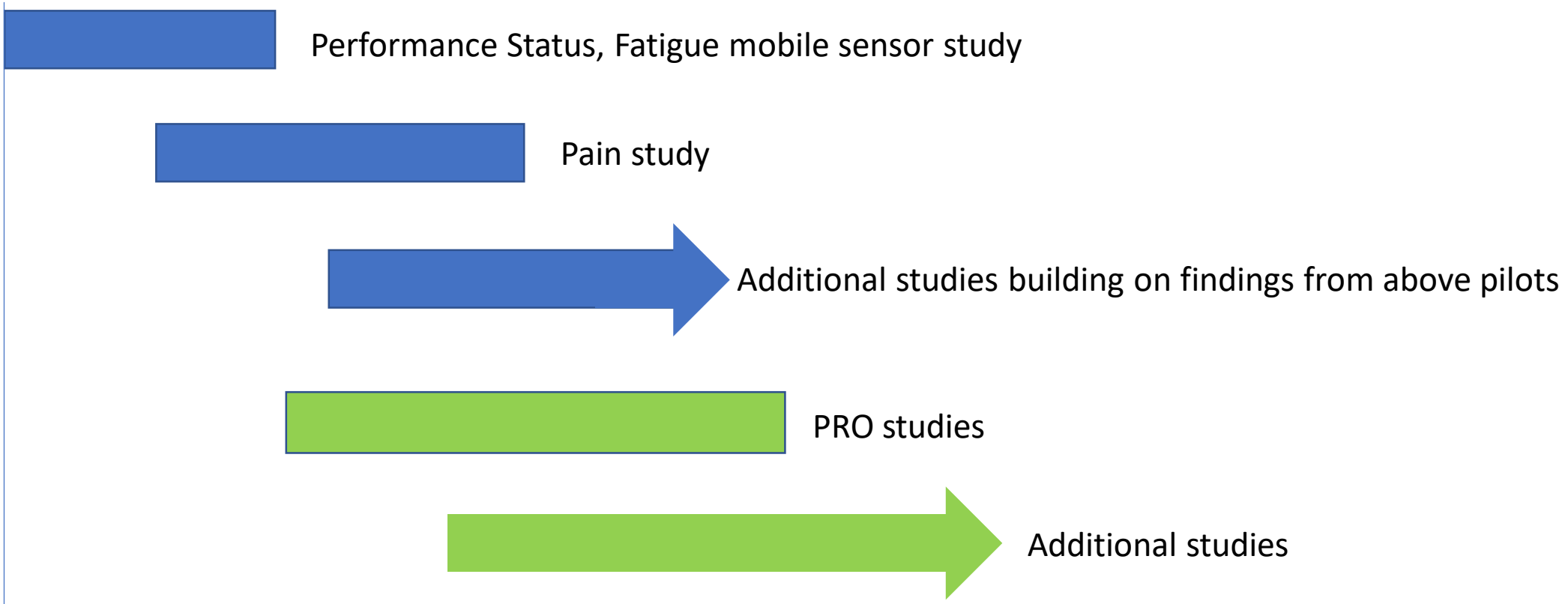
Courtesy of Adam Dicker

MOFFITT CANCER CENTER

NIH Clinical Center

- Largest Clinical Research Center in the World
- 2018 NCI Numbers
  - 2,240 new patients
  - 35,823 outpatient visits
  - All patients on clinical trials

Timelines


Performance Status, Fatigue mobile sensor study
Pain study
Additional studies building on findings from above pilots
PRO studies
Additional studies
FY 20
FY 21
FY 22
FY 23

Immunotherapy

- Rapid, deep, durable responses
- Widely variable response to therapy (some complete response, some progressive disease) even within tumor subtype and biomarker status
- Perhaps driven in part by underlying immune status
- Stress → ↑glucocorticoids
  - Heart Rate
  - Facial recognition
  - ? Impact of intervention

Psychol Bull. 2004 July ; 130(4): 601–630.

Psychological Stress and the Human Immune System: A Meta-Analytic Study of 30 Years of Inquiry

Suzanne C. Segerstrom and
University of Kentucky

Gregory E. Miller
University of British Columbia

Abstract

The present report meta-analyzes more than 300 empirical articles describing a relationship between psychological stress and parameters of the immune system in human participants. Acute stressors (lasting minutes) were associated with potentially adaptive upregulation of some parameters of natural immunity and downregulation of some functions of specific immunity. Brief naturalistic stressors (such as exams) tended to suppress cellular immunity while preserving humoral immunity. Chronic stressors were associated with suppression of both cellular and humoral measures. Effects of event sequences varied according to the kind of event (trauma vs. loss). Subjective reports of stress generally did not associate with immune change. In some cases, physical vulnerability as a function of age or disease also increased vulnerability to immune change during stressors.

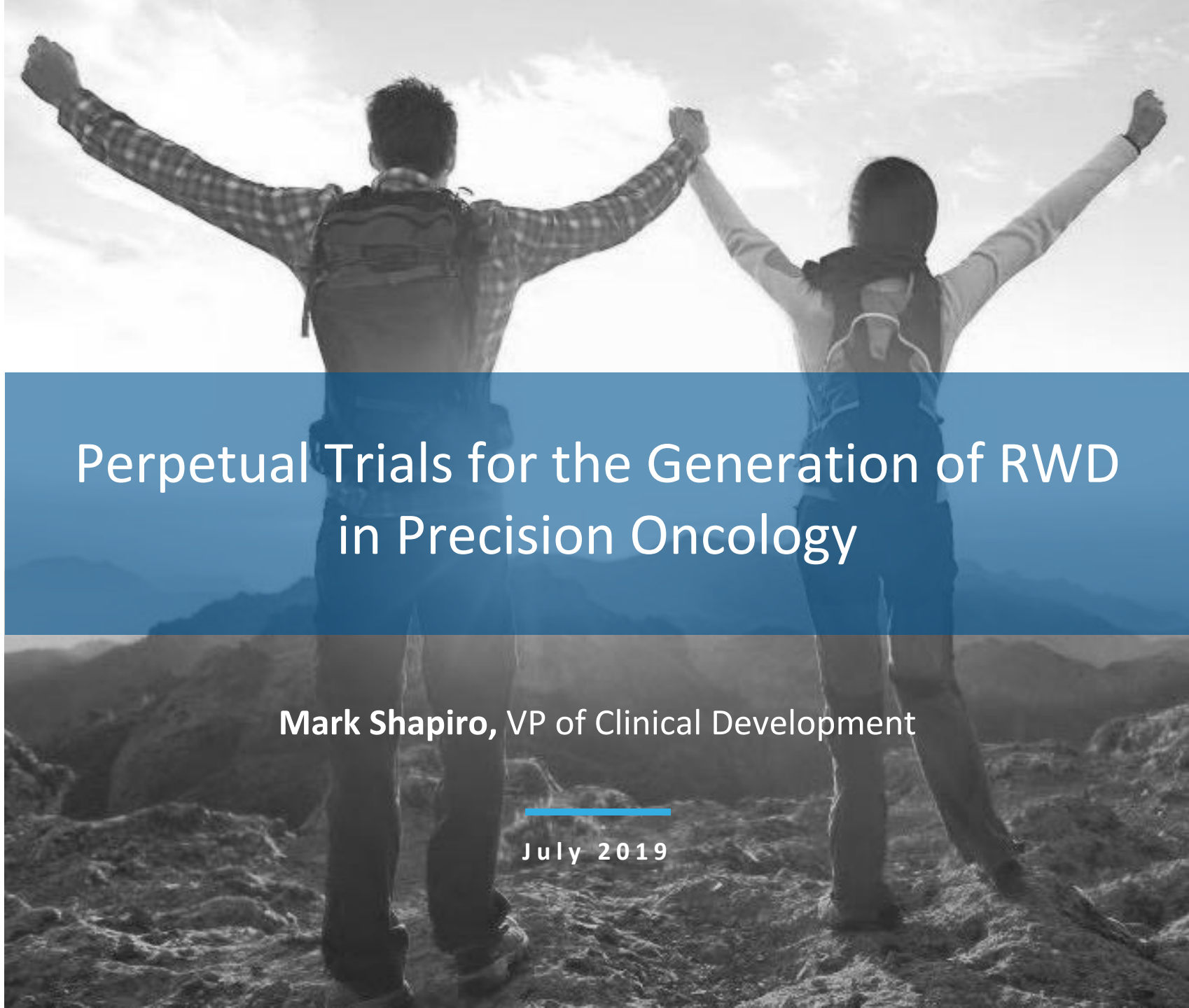
https://www.cancer.gov/about-cancer/coping/feelings/stress-fact-sheet#how-does-psychological-stress-affect-people-who-have-cancer

Maybe not today, but tomorrow…?

“You can’t list your iPhone as your primary-care physician.”

New Yorker

XCURES



Perpetual Trials for the Generation of RWD in Precision Oncology

Mark Shapiro, VP of Clinical Development

July 2019

About us

- Created by Cancer Commons, a non-profit that helps thousands of patients find and assess clinical trials as treatment options each year
- Co-founded by AI researchers hoping to bring new approaches to helping cancer patients
- Team of computer scientists, statisticians, physicists, clinical researchers, and patient advocates
- Multiple partnerships with other non-profit patient advocacy organizations

XCURES

Our goal is to create a global learning system for cancer

What is a perpetual trial?

A patient-centric outcomes registry

Infrastructure for ongoing pragmatic trials

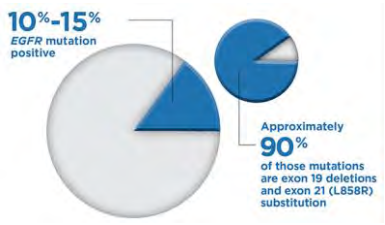
Prospective and retrospective data

- Explicit consent from patients with IRB oversight
- Direct access to medical records under HIPAA (RWD)
- Patient, clinician, caregiver surveys (eCOA/ePRO)
- Integrate patient utility with clinical decision-making
- Infrastructure to support continuous research

Traditional clinical research is already strained by exploding data.

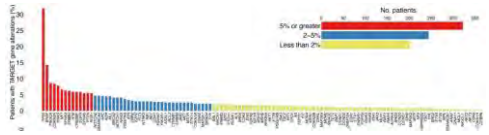
2005

- Targeted Therapy with Companion Diagnostic based on microarray technology
- Example Tarceva (erlotinib) with companion diagnostic



2017

- NGS panels testing hundreds of variants across 10 - 100 of target genes
- 20% of patients with targetable variants identified by NGS
- Basket trials possible



Soon

- More types of data means 1,000s of phenotypes per cancer
- Vast, sparse, high-dimensional space requires new approaches to search

XCURES

Clinical trials are slow, expensive, unsystematic and uncoordinated.

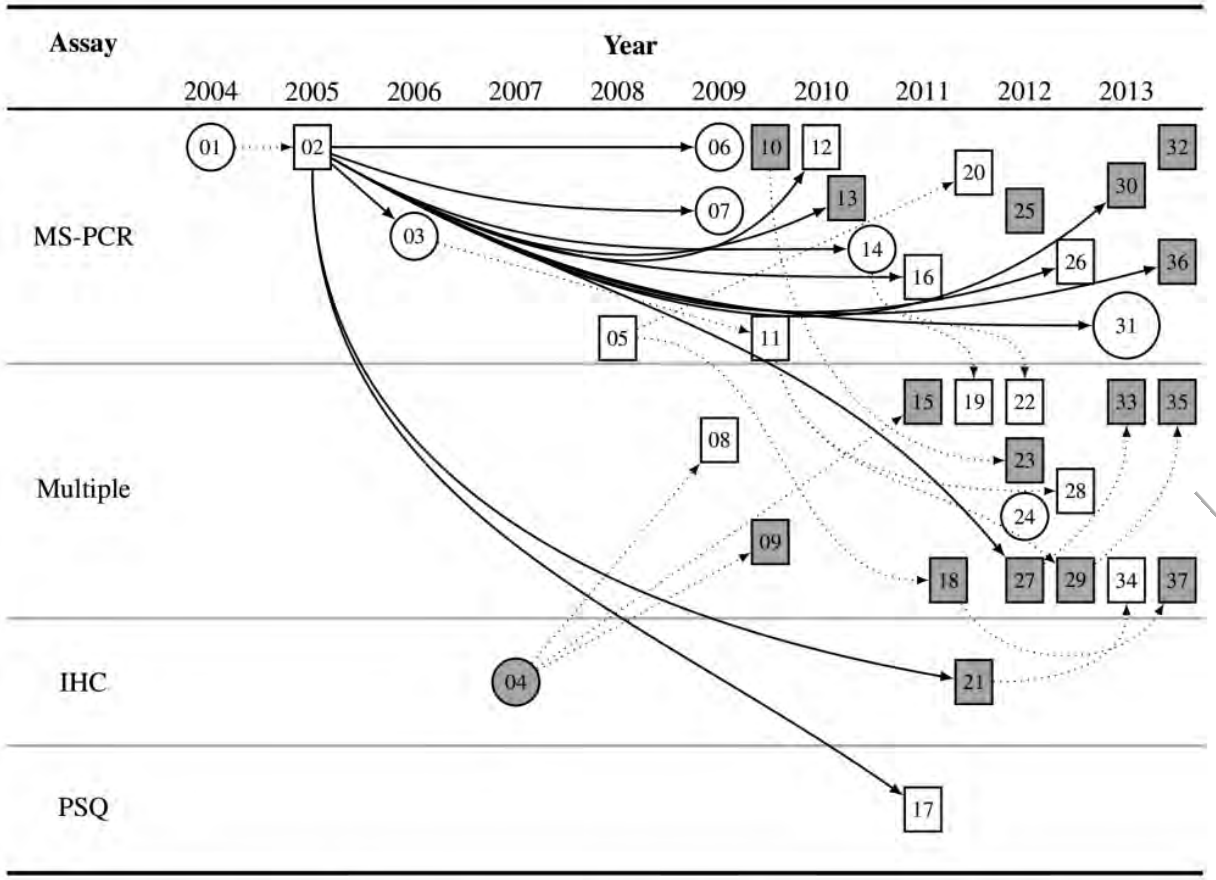
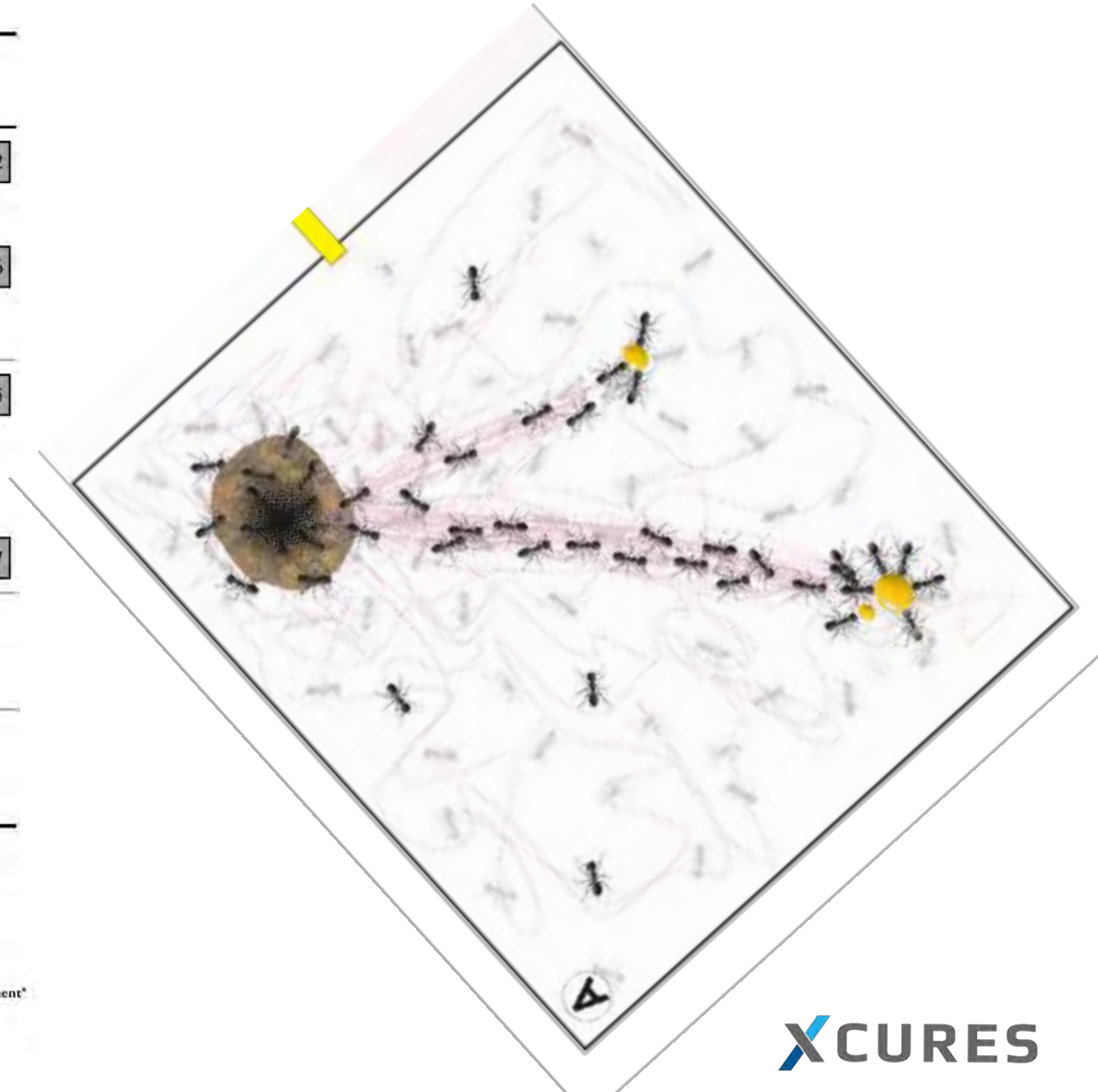


Figure 1. AERO graph for studies investigating MGMT testing as a predictive diagnostic for first-line TMZ therapy in adult GBM patients. Solid arrows are all references to Hegi et al. (2005)—the landmark retrospective study

Judging Quality and Coordination in Biomarker Diagnostic Development*

Spencer Phillips Hey



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Too many trials, too few patients.

~3,500 open IO trials in the US

Require ~600,000 patients

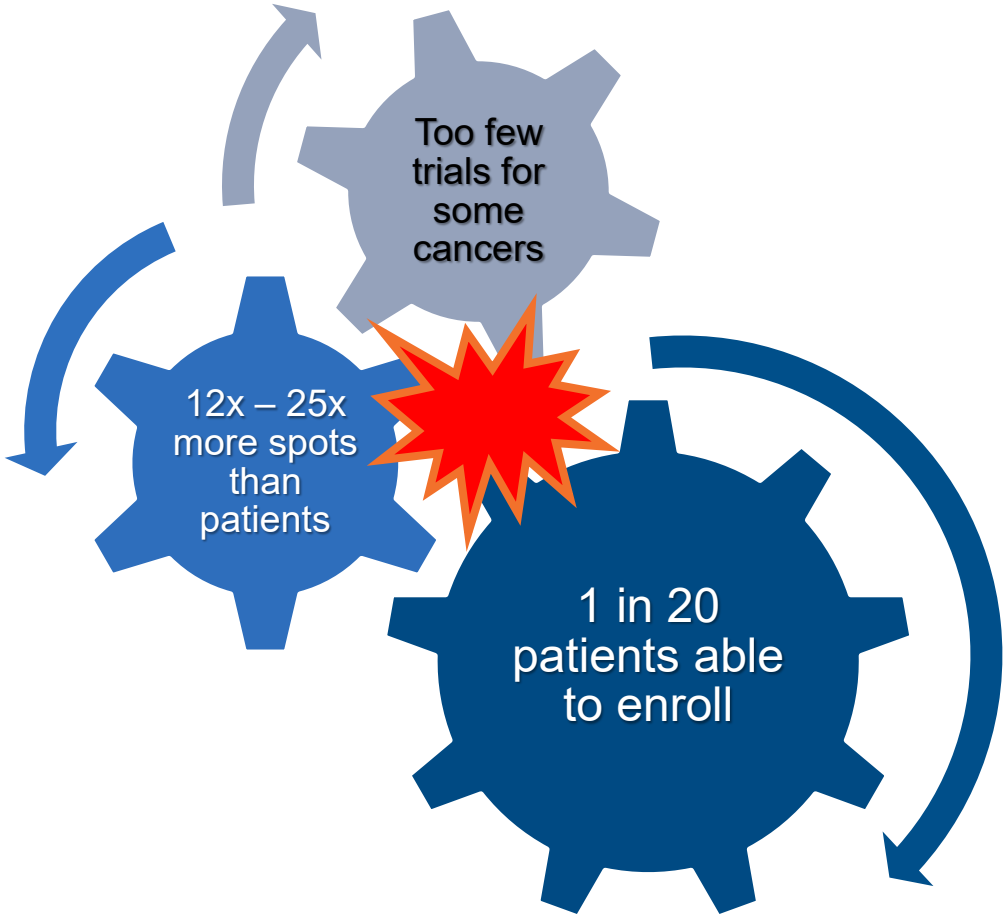
Enroll ~50,000 patients / year

= 20 years!?!

20,000 open spaces in pediatric ALL

700 US diagnoses per year

= 29 years?!?



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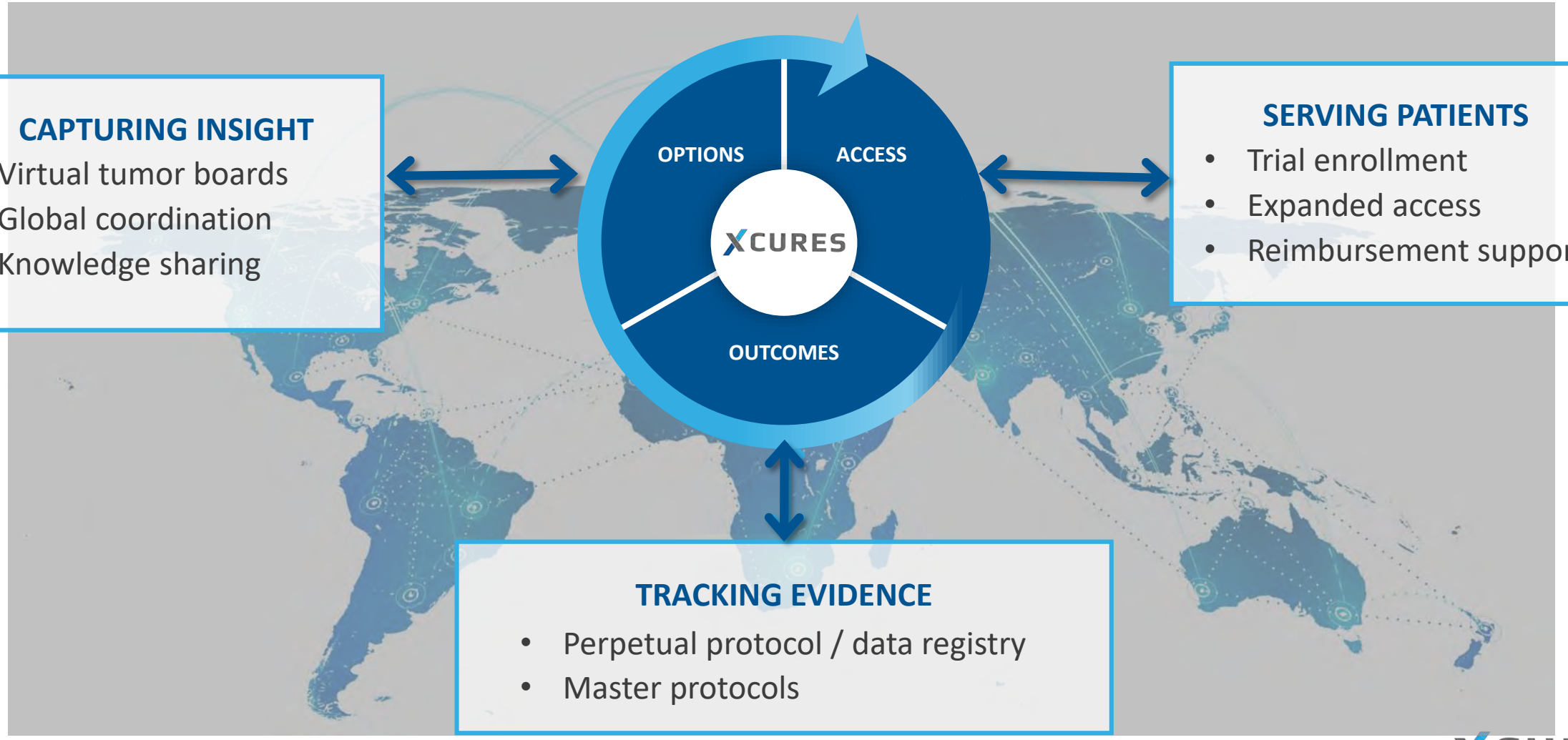
Our Vision for Cancer Research

All doctors. All patients. All the data. All the time.



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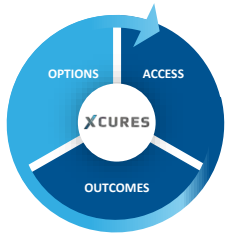
Why Perpetual Trials?

Bridge between RWD based on claims data and other sources…

Options – Using Experts and AI to Optimize Care



AI

Knowledge Sharing

NLP to capture treatment options, recommendations, and rationales from literature, conferences, social media, and real-world evidence

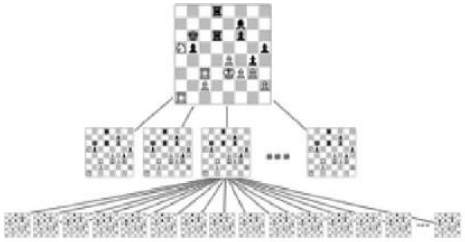
Treatment Planning

Decision support for virtual tumor board recommendations

Community oncologists engage on cases with experts

Treatment Optimization

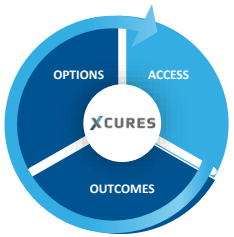
Evaluating patient's treatment longitudinally with multiple drug regimens, to maximize shots on goal while pursuing segmented hypothesis testing across all patients



Source: stanford.edu

XCURES

Access – Getting the Right Drugs to Patients



xCures SERVICES

- Ethical trial matching and enrollment
- Travel assistance partnerships
- Manage expanded access programs
- Build a clearinghouse for EA under a MP
- Assist with coverage determination and pre-approvals for VTB recommendations

BENEFITS

- Patients get access to treatments rapidly
- xCures gets hot drugs on our platform for use by patients in Virtual Trials
- Companies get real world data to accelerate approvals, label extensions, reimbursements

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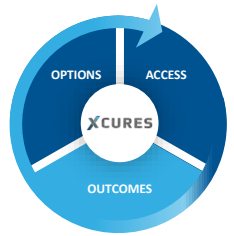
Outcomes – Generating Real World Evidence

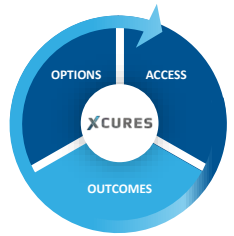


XCELSIOR

- IRB-approved patient-centric outcomes registry
- Always-on: All types of cancer patients, all treatments
- Add new sites, PIs, and drugs in days through amendments, sub-PIs, and subprotocols
- Patient-centric design: minimal inclusion / exclusion criteria; no randomized controls
- Observational registry captures longitudinal, regulatory grade, treatment and outcomes data
- Virtual Tumor boards and Virtual Trials seek to optimize individual outcomes and collective learning
- Innovative statistics for efficient signal generation from small data sets

REDCAP CLOUD

- Unstructured data mapped parsed with NLP/AI and mapped into a 21 CFR Part 11 compliant, HIPAA & FISMA compliant, validated EDC system.
- Source provenance captured and source accessible with permission (DICOM, Claims, EMR, images, etc.) ePRO/eCOA measures via app/email
- Coding to standard ontologies (e.g., NCI Thesaurus) and variable-naming follow CDISC convention
- Standardized data reporting forms support precision oncology studies for most solid tumors
- Flexible, “best-of” approach for solid tumors based on experience with clinical trials, work with KOLs and advocates
- Reporting forms can be quickly customized to capture study-specific fields, if needed



A perpetual protocol can…

Answer new and different questions, or

Answer the same questions more efficiently

- Which drug or combo for each patient and why?
- What to try when there is no guideline?
- How did prior therapy modify response?
- Find signals in small-population cancer phenotypes.
- **Create a learning system across oncology**.

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