U.S. FOOD & DRUG ADMINISTRATION

Real World Data – Building the Foundation for Regulatory RWE

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Office of Medical Policy
Center for Drug Evaluation and Research
May 8, 2020

FDA Definitions

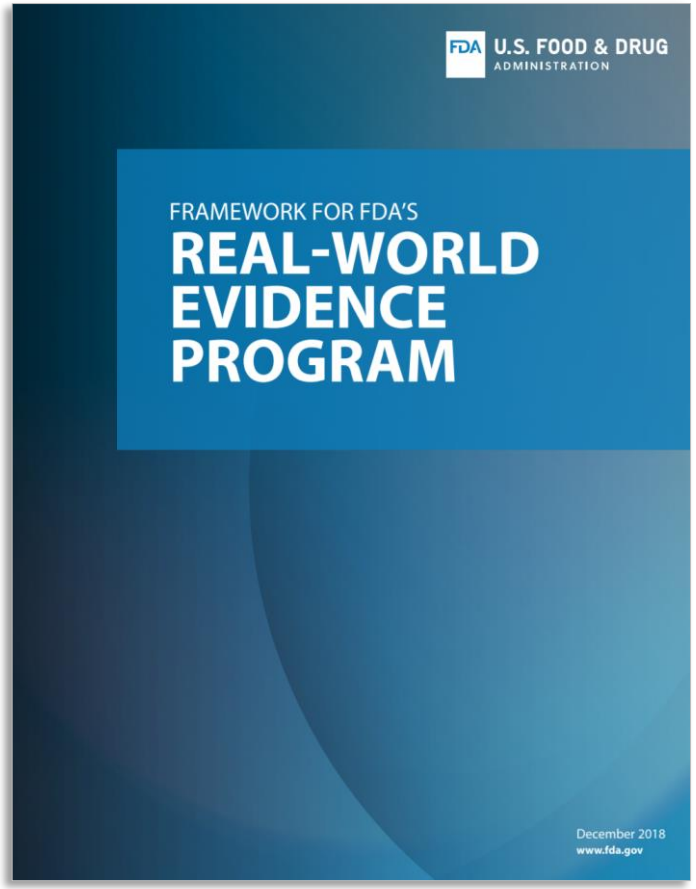
Real World Data (RWD) are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.

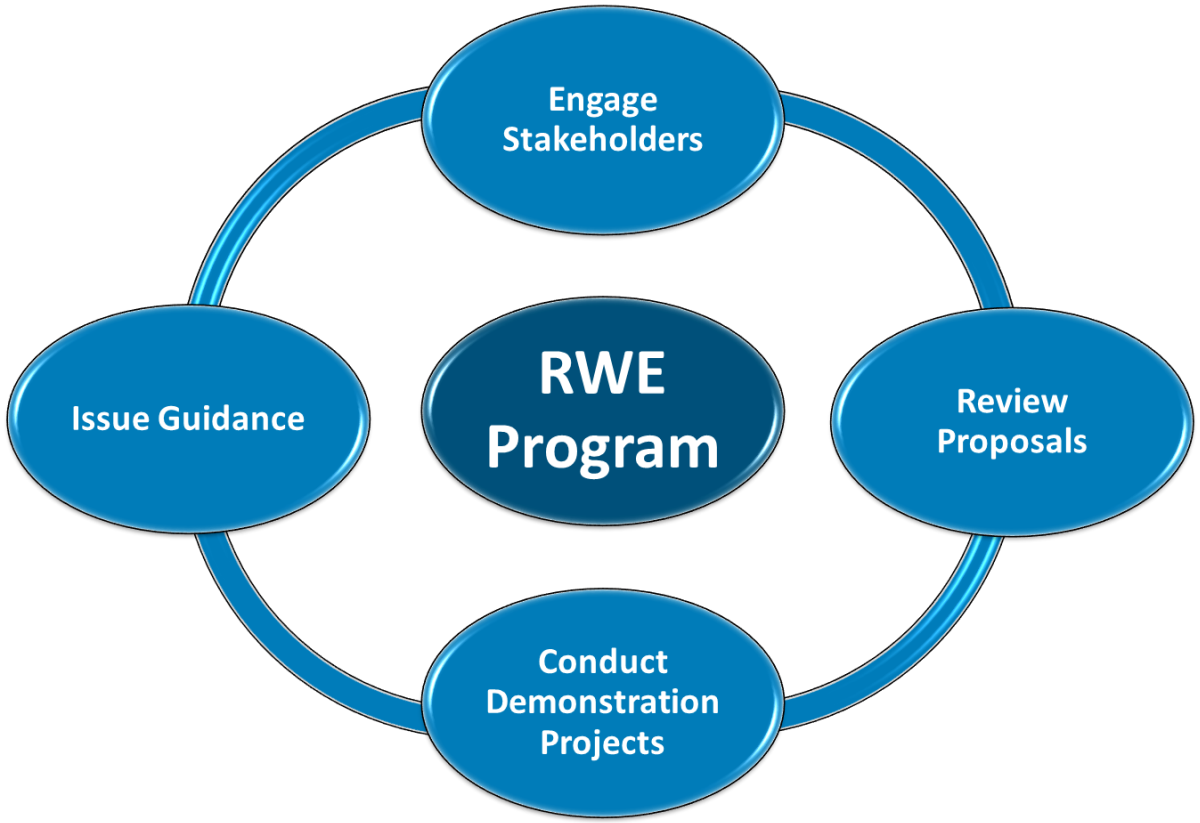
- electronic health records (EHRs)
- claims and billing data
- data from product and disease registries
- patient-generated data including in home-use settings
- data gathered from other sources that can inform on health status, such as mobile devices

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.

Generated using many different study designs, including but not limited to, randomized trials, such as large simple trials, pragmatic clinical trials, and observational studies.

FDA Real-World Evidence Program





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

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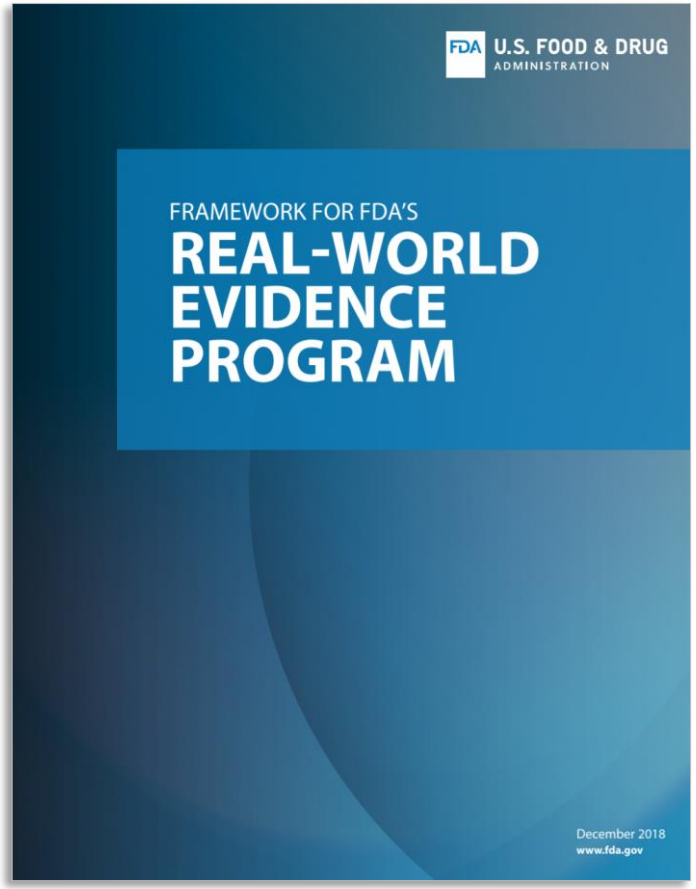

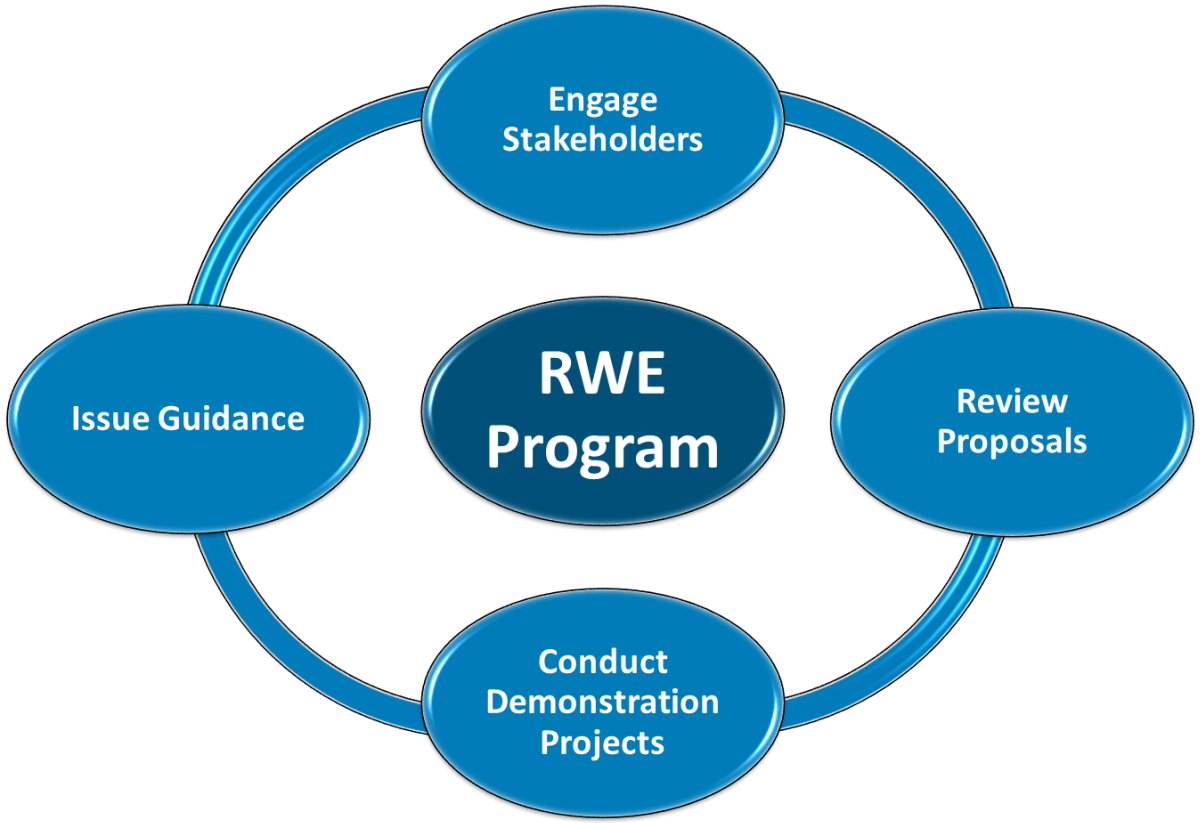

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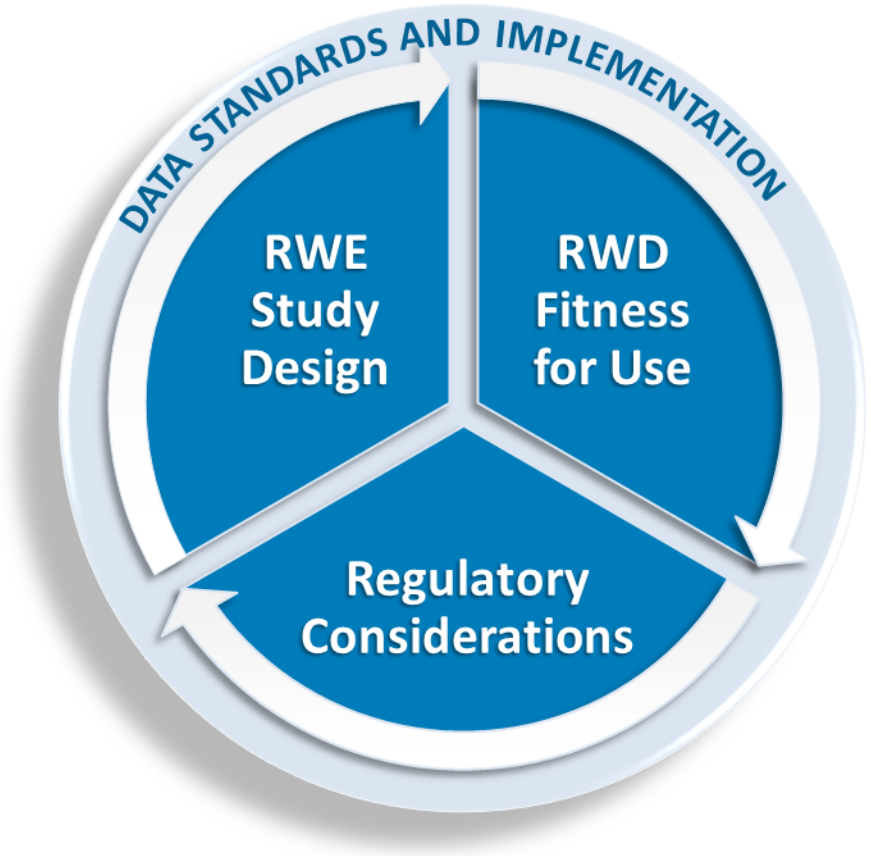
Framework for Evaluating RWD/RWE for Use in Regulatory Decisions



Consider:

- **Whether the RWD are fit for use**
- **Whether the trial or study design used to generate RWE can provide adequate scientific evidence to answer or help answer the regulatory question**
- **Whether the study conduct meets FDA regulatory requirements**

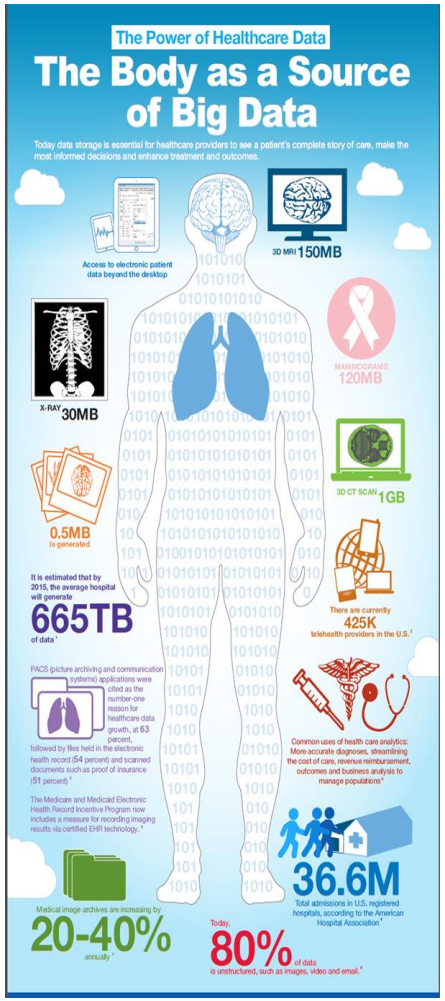
RWD FIT FOR USE

RWD and Clinical Endpoint

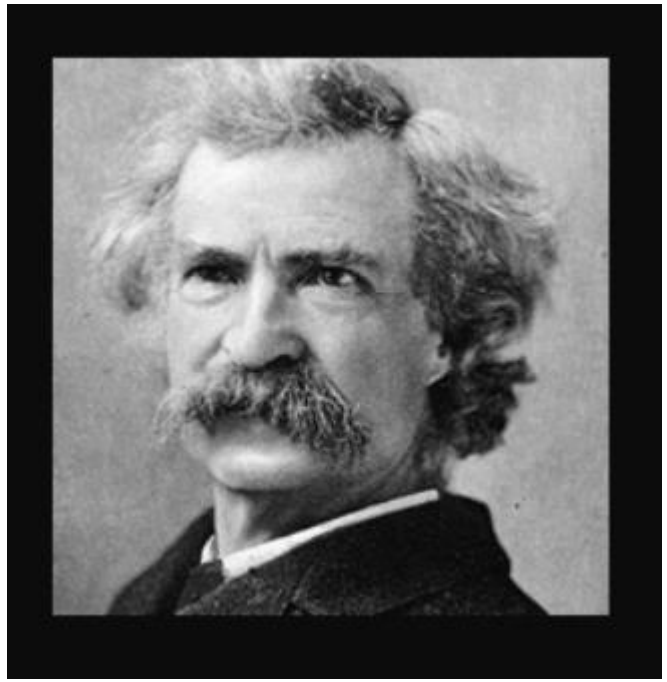
Biomarker

Clinical endpoint

Type of endpoint	Studies %	Examples of endpoints measured
Chemistry	21%	HBA1c, pregnancy test, GFR
Hematology	4%	Severe neutropenia Apheresis yield > 5 million CD34+ cells/kg
Pathology	1%	Increase/decrease of parabasal cells; biopsy proven acute rejection, clearing of anterior chamber cells
Microbiology	9%	Sustained virological response, plasma viral load, conversion to negative sputum
Imaging +/- (survival, clinical signs)	10%	Bone mineral density; vertebral fractures, spleen volume, progression free survival
Physiological/ functional measurement	10%	6 minute walk, normal sinus rhythm, FEV1, sleep studies
Clinical event /clinical sign	13%	Death, hospitalization, MACE, MS relapse, Lice free head
CRO/PRO	31%	Toronto western spasmodic torticollis rating scale, Hamilton depression rating scale, Rheumatology scale ankylosing spondylitis scale, psoriasis severity index, seizures, sleep, prostate symptom score



Real World Data

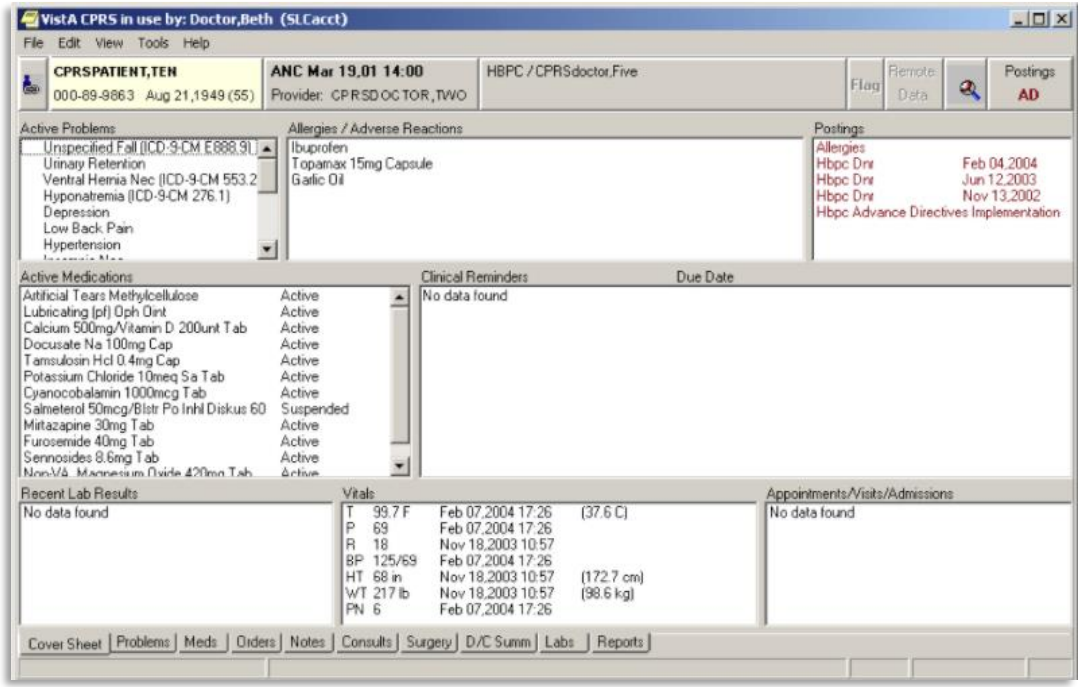


In the real world, nothing happens at the right place at the right time . . .

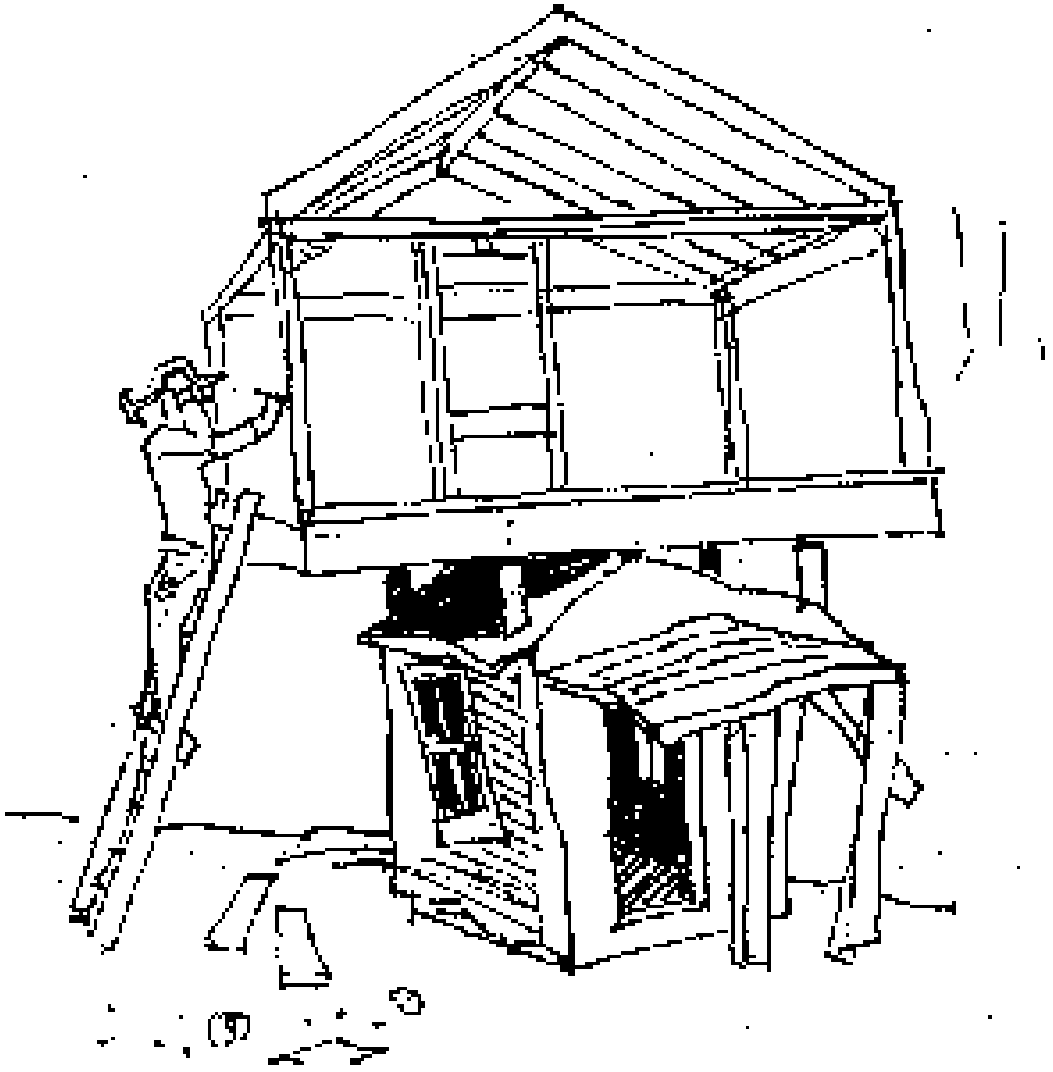
~ Mark Twain

EHRs – Quality and Relevance

- Certain endpoints – labs, pathology, imaging are used in clinical practice and research
  - Challenge is curation of unstructured and inconsistent data format
- Timing of assessment in clinical practice may be variable
  - Only using patients who have sufficient data may create a bias as those who show up for follow up are often different than those who do
- Clinical outcome measures for disease progression may not be used or consistently recorded in practice
- Interoperability will be necessary for studies outside of small populations
  - Including linkage to claims for longitudinal data



Quality RWE can't be Built without Quality RWD



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ONC's Cures Act Final Rule

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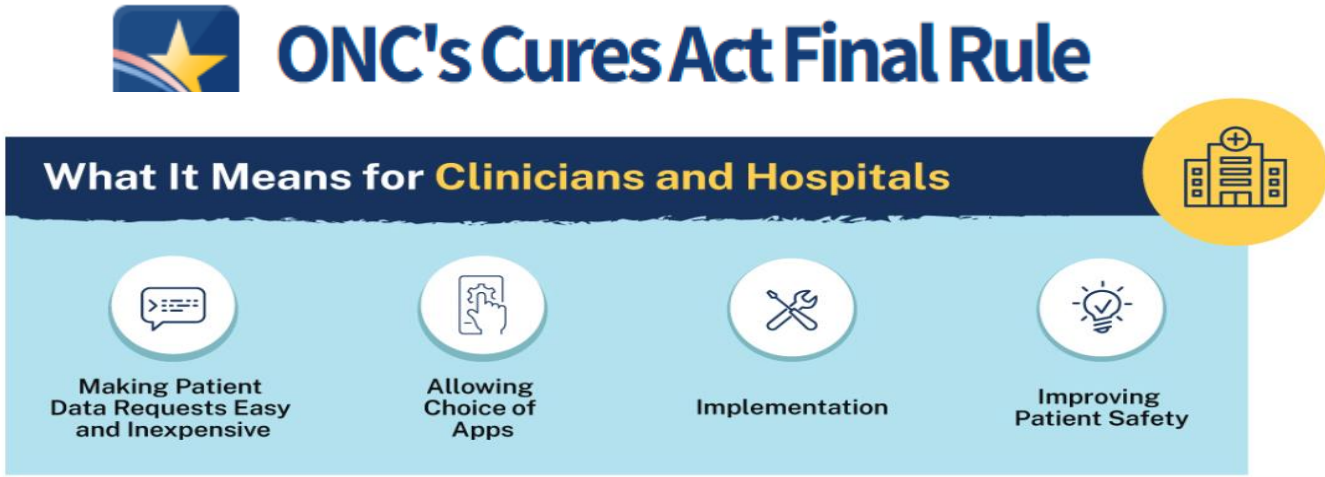

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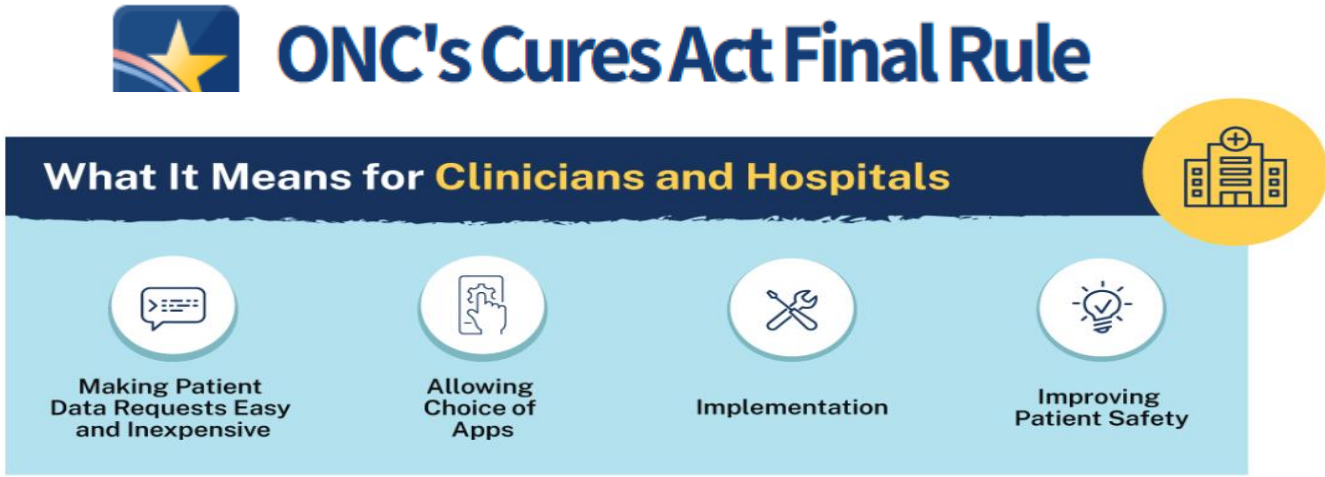
- **Bad news:** The proprietary EHR systems made by more than 700 vendors routinely don't talk to one another, meaning that doctors still resort to transferring medical data via fax and CD-ROM
- EHRs promised to put all of a patient's records in one place
  - Critical or time-sensitive information routinely gets buried in an endless scroll of data . . . — and amid the maze of pulldown menus — it can be missed



Physician Time Spent Using the Electronic Health Record During Outpatient Encounters

A Descriptive Study[1]

J. Marc Overhage, MD, PhD, and David McCallie Jr., MD

- **Study included data from approximately 100 million patient encounters with about 155 000 physicians from 417 health systems**
- **Looked at active time spend in the EHR**
- **Physicians spent an average of 16 minutes and 14 seconds per encounter using EHRs, with chart review (33%), documentation (24%), and ordering (17%) functions accounting for most of the time.**
- **"Chart review stands out as the activity most in need of optimization but with the fewest tools available ….**
  - **Although investments in visualization tools and predictive models or artificial intelligence–enabled tools aim to help identify critical problems that could otherwise be missed, few target the outpatient setting and address common pain points like information synthesis." [2]**

1. Ann Intern Med. 2020;172:169-74
2. Julia Adler-Milstein, Electronic Health Record Time Among Outpatient Physicians: Reflections on the Who, What, and Why Ann Intern Med. 2020;172:212-213

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

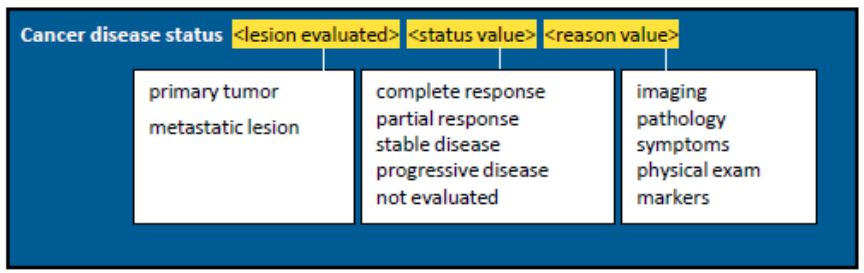
ICARE: Develop and validate mCODE-based outcome measures embedded in the EHR

Disease Status

Clinical Assessment

Based on the data available today (at the time of evaluation), categorize the patient's disease extent.

Question Format

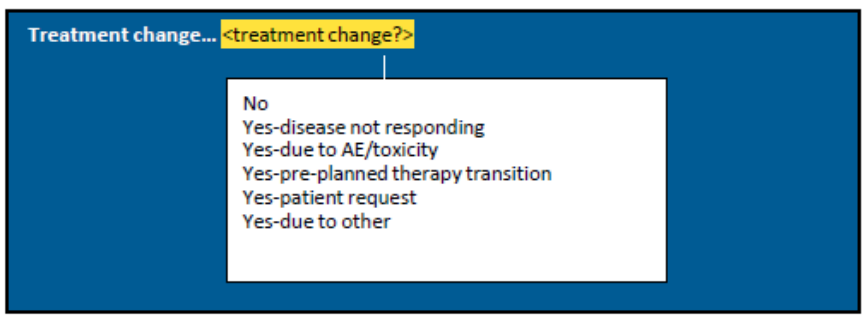


Treatment change

Clinical Assessment

Based on your evaluation today, are you making a change in treatment?

Question Format



ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

MITRE

FDA

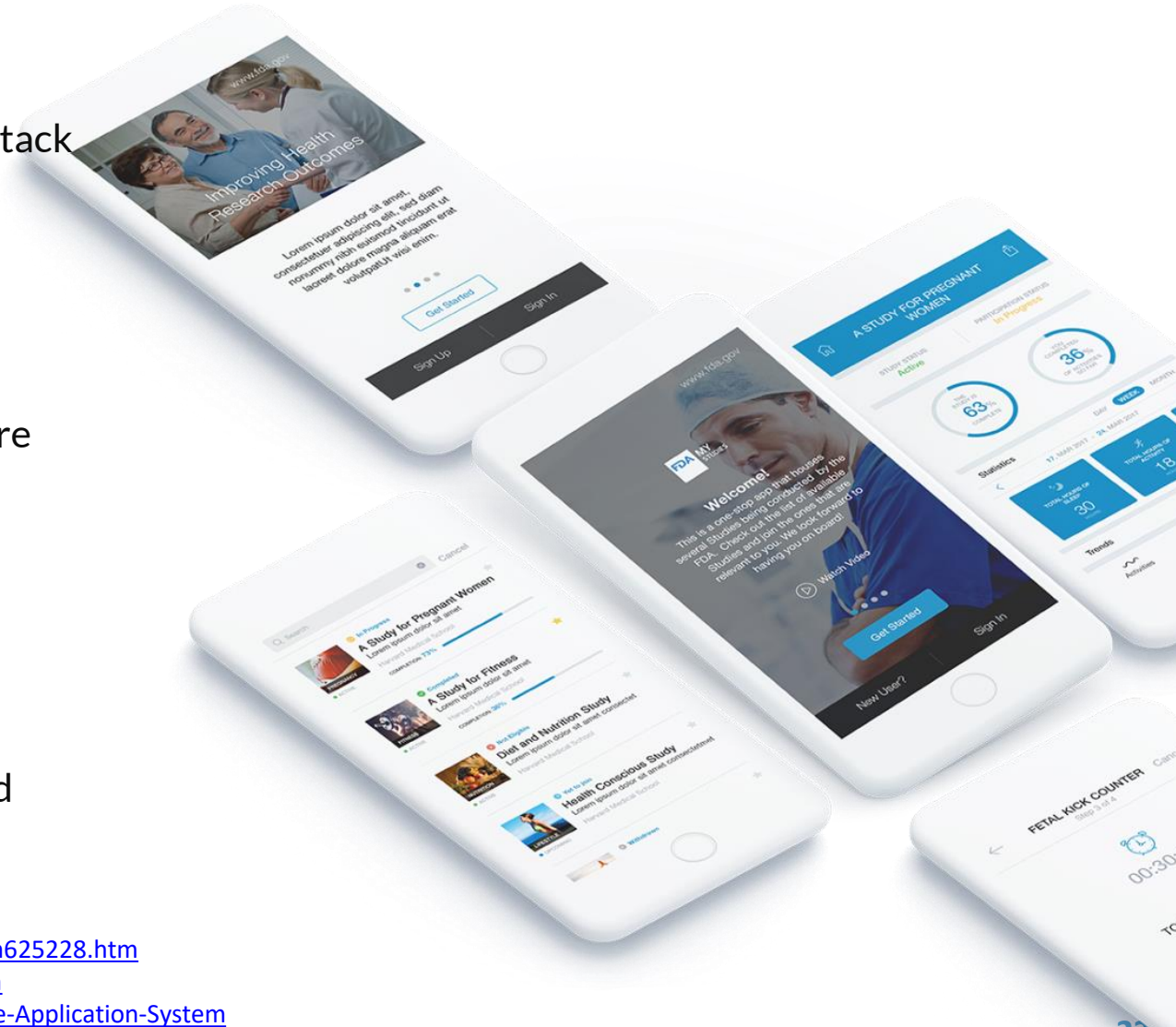
NCI National Clinical Trials Network
a National Cancer Institute program

ASCO
AMERICAN SOCIETY OF CLINICAL ONCOLOGY

Patient-Generated Health Data (Digital Health Tools)

FDA MyStudies

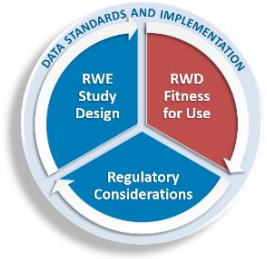
- **Mobile App**
  - Standard frameworks - ResearchKit (iOS), ResearchStack (Android)
- **Web-based Configuration Portal (WCP)**
  - Enables support of multiple types of medical product effectiveness and safety studies with minimal software development
- **Secure Storage Environment**
  - Generates secure tokens
  - Separates registration information and responses
  - Partitioned for multisite, decentralized, or distributed models



https://www.fda.gov/NewsEvents/Newsroom/FDAInBrief/ucm625228.htm
https://www.fda.gov/Drugs/ScienceResearch/ucm624785.htm
https://github.com/PopMedNet-Team/FDA-My-Studies-Mobile-Application-System

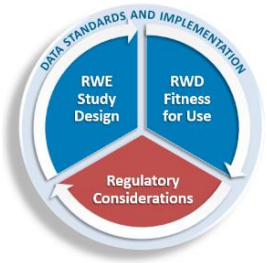
Limit JIA trial

- **Randomized real world trial in patients with Limited Juvenile Idiopathic Arthritis (<=4 joints affected and no uveitis)**
  - Six month course of subcutaneous Abatacept (T cell co-stimulation inhibitor) plus usual care with NSAIDs and intra-articular glucocorticoids vs. usual care alone
  - Outcome: extension to more than 4 joints, new uveitis, and/or need for treatment with systemic medication at 18 months

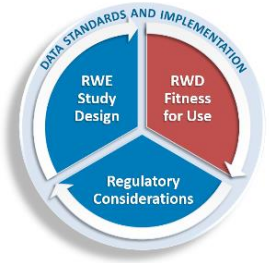


- **FDA-Catalyst is aligning with the trial by providing support from the MyStudies App**
  - First use of FDA-Catalyst to support a pediatric trial – data collection starting in January 2020
  - Potential support for the Childhood Arthritis & Rheumatology Research Alliance (CARRA) Registry
  - Collection of primary outcome (uveitis) from ophthalmology appointments in trial
  - Collection of adherence information/adverse events for study drug with “drug diary”

SPARC Registry



- **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

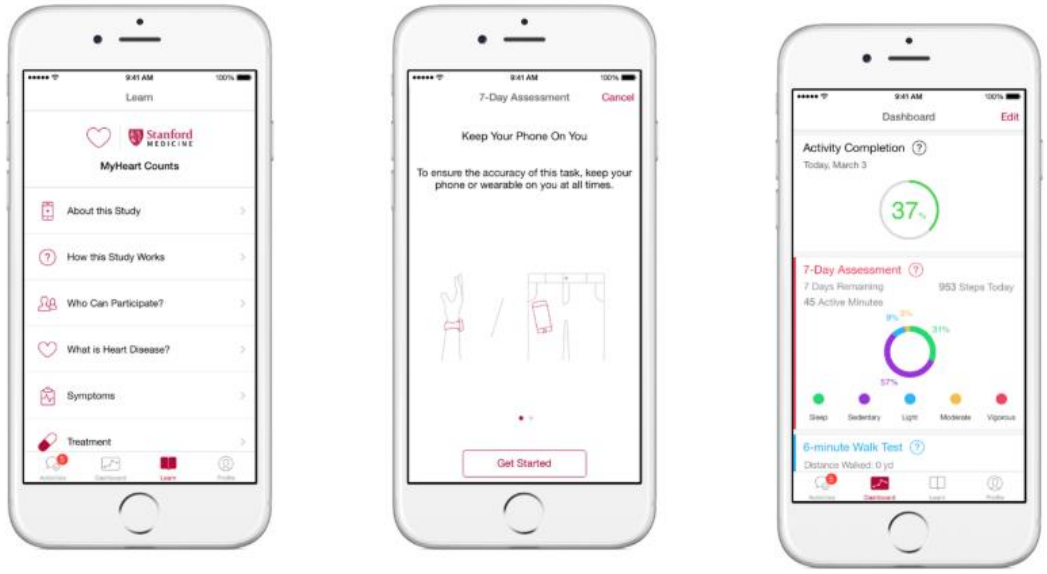


- **FDA-Catalyst is aligning registry by providing support from the My Studies App**
  - **App configured – integration of new "participant properties" feature underway**
  - **Data collection starting in April 2020**

IBD PROdigy

- Plan to include registry responses in the PCORI Comparative Effectiveness of Biologic or Small Molecule Therapies in Inflammatory Bowel Disease study (prospective cohort for patient reported outcomes)

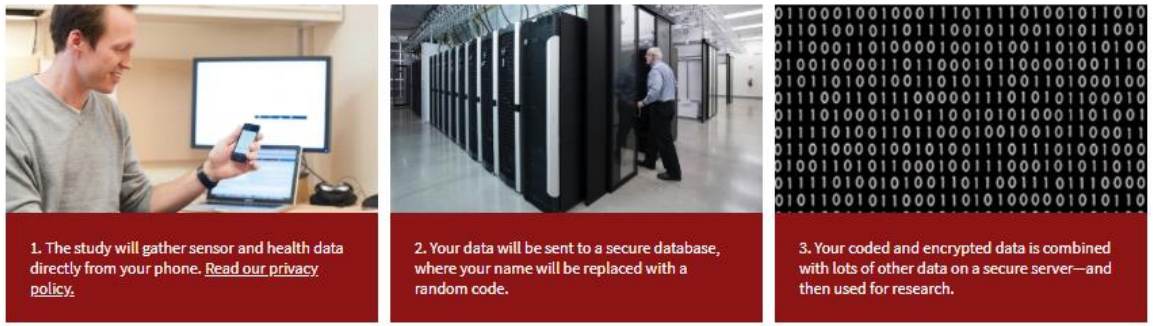
FDA MyStudies and the MY Heart Study



Stanford MEDICINE | MyHeart Counts *iPhone Application*

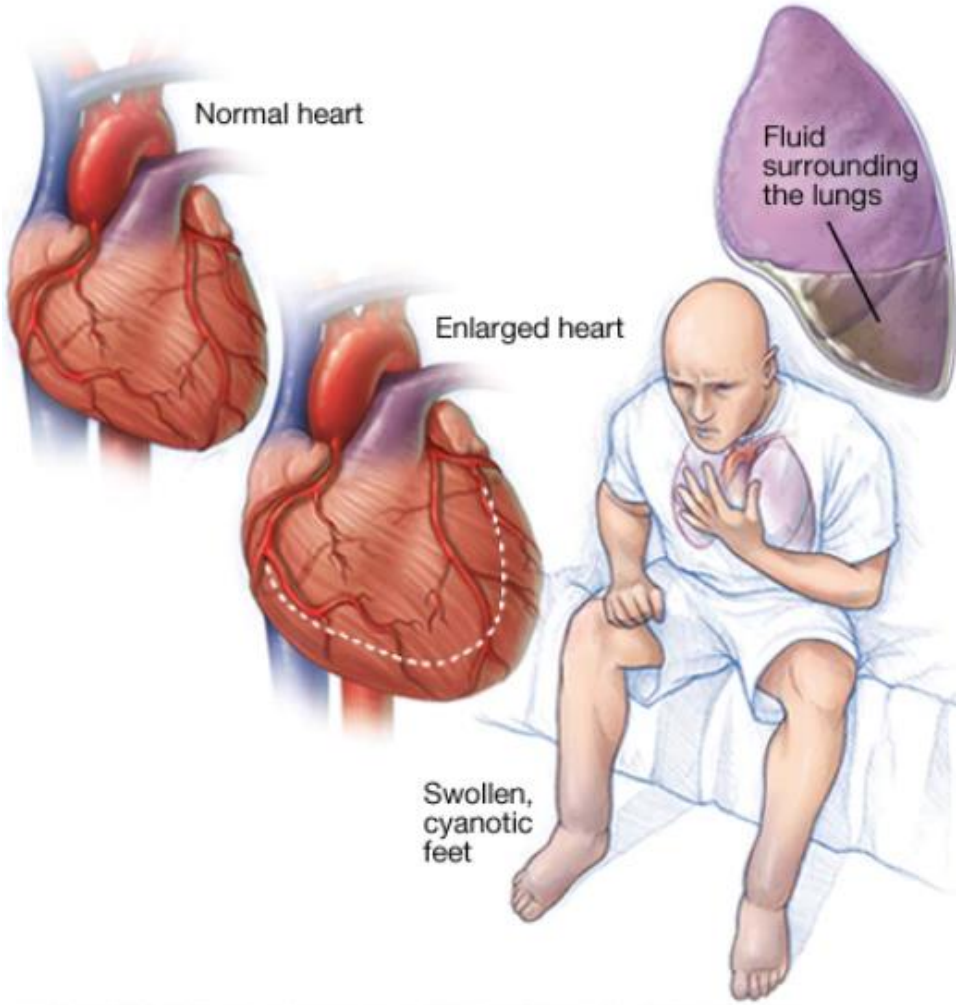
MyHeart Counts + FDA MyStudies on Google Cloud

Further, Google Cloud is providing sponsorship to bring Stanford University's MyHeart Counts cardiovascular research study onto the FDA MyStudies platform, enabling this groundbreaking virtual clinical study to begin enrolling users of both Android and iOS devices. Since it launched as one of the initial iOS research applications, MyHeart Counts has enrolled more than 60,000 participants and driven significant understanding of the feasibility of conducting large-scale, smartphone-based clinical trials.



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



Sponsors Exploring Digital Endpoints

Bellerophon THERAPEUTICS

Press Releases

December 17,2019

- Announced positive top-line results from Cohort 2 of its ongoing Phase 2/3 randomized, double-blind, placebo-controlled clinical study (iNO-PF) of INOpulse® for the treatment of Pulmonary Hypertension associated with Interstitial Lung Disease (PH-ILD).

- Statistically significant improvement in moderate to vigorous physical activity (MVPA), defined as walking, climbing stairs, yard work, and similar activities, versus placebo. The improvements in **MVPA were underscored by benefits shown in other actigraphy parameters**, as well as patient reported outcomes

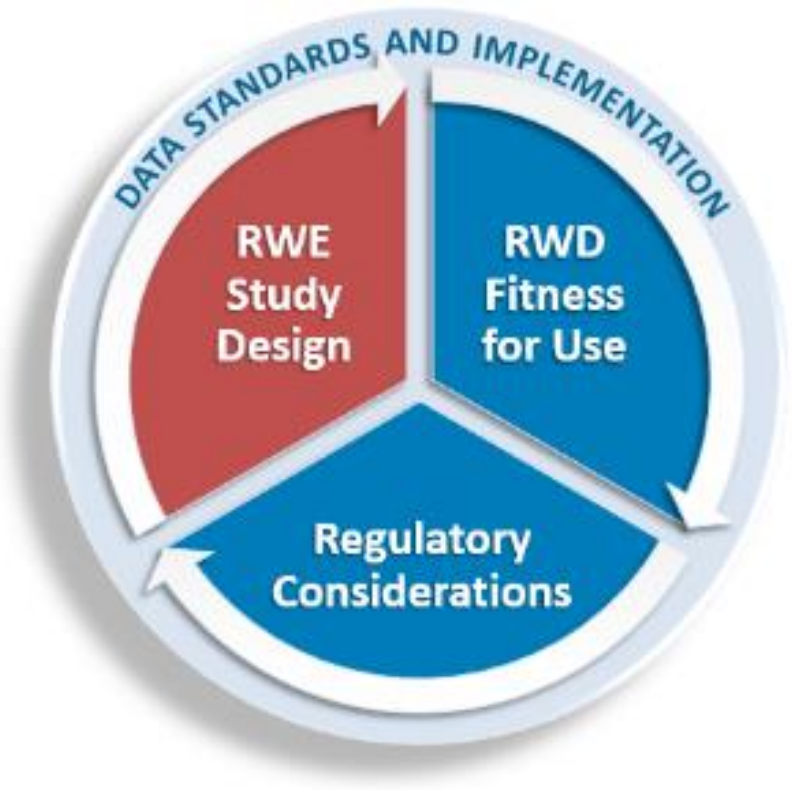
Sponsors Exploring Digital Endpoints

Bellerophon THERAPEUTICS

Press Releases

March 10, 2020

The Company, in consultation with the FDA, has finalized the key elements of its planned pivotal Phase 3 study, including the use of **moderate to vigorous physical activity (MVPA)** as the primary endpoint for approval, the patient population of pulmonary fibrosis subjects at risk of PH, as well as the dose of iNO45 (45 mcg/kg IBW/hr).



RWE STUDY DESIGN

Duke | MARGOLIS CENTER *for* Health Policy

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› Events › Leveraging Randomized Clinical Trials to Generate Real-World Evidence for Regulatory Purposes

Leveraging Randomized Clinical Trials to Generate Real-World Evidence for Regulatory Purposes

July 11, 2019 - 8:30 am to July 12, 2019 - 1:00 pm

Register now

The Westin Washington, D.C. City Center - National Ballroom
1400 M Street NW
Washington, DC 20005

Contact Info

Event Manager
margolisevents@duke.edu

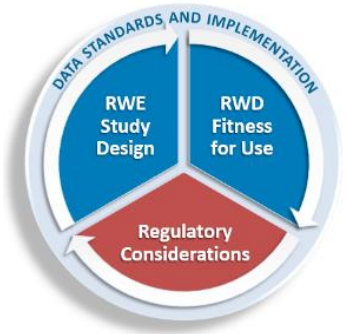
Description

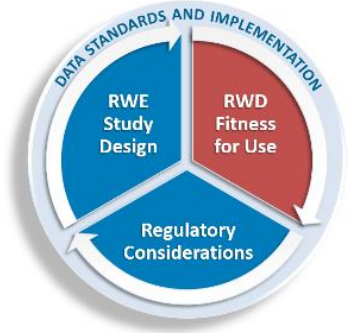
There are emerging opportunities to leverage real world data (RWD) and resultant real-world evidence (RWE) in support of supplemental approval or labeling actions based on substantial evidence of effectiveness as envisioned in 21st Century Cures and PDUFA VI. As part of implementation efforts for this legislation, the U.S. Food and Drug Administration (FDA) published a strategic framework to guide the development of a new program for regulatory uses of RWD and RWE. The Framework suggests the potential integration of clinical trials into the healthcare system by using randomized designs to generate RWE for regulatory submissions.

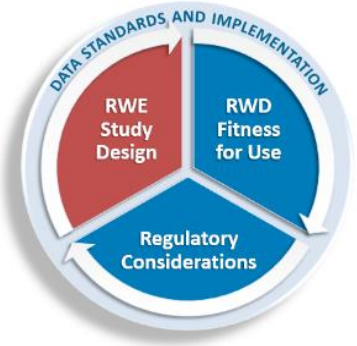
https://healthpolicy.duke.edu/events/leveraging-randomized-clinical-trials-generate-real-world-evidence-regulatory-purposes

RELIANCE Trial

ClinicalTrials.gov Identifier: NCT04069312







- **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
  - Both guideline recommended but Roflumilast is FDA approved for this indication
- **Population**
  - Clinician considering treatment intent to intensify therapy with roflumilast or azithromycin
  - > 40 years with severe COPD or associated chronic bronchitis
  - Current or past smoker – 10 pack/ years
  - Hospitalized with COPD exacerbation in past 12 months
  - Current medications include long acting – muscarinic antagonist, beta agonist or inhaled corticosteroid
  - No contraindications to the medications
- **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

Adopting “Pragmatism” into Regulatory RCTs

- A **well-constructed endpoint** means that the study can determine if the purported effect of the drug is observed, and that effect is meaningful to patients
- **Reliable data**, that accurately collects the patient experience, and is accurately transferred into the analysis datasets supports **reliable conclusions**
- **Adequate monitoring** means complete collection of **important, relevant** efficacy and safety endpoints

Adopting “Pragmatism” into Regulatory RCTs

- **Randomization** supports strong causal inference
- **Blinding** supports strong causal inference vs unblinded
- **Appropriate enrollment criteria** assures patients have the target condition (that the study objective is aimed to address)
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Adopting "Pragmatism" into Regulatory RCTs

- The issue is **reliability – persuasiveness** – of the results, not trial methodology
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- **Blinding** supports strong causal inference vs unblinded
- **Appropriate enrollment criteria** assures patients have the target condition (that the study objective is aimed to address)
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- **Adequate monitoring** means complete collection of **important, relevant** efficacy and safety endpoints

- How do we create a **research infrastructure** that can provide reliable, persuasive results?
- **Randomization methods** adapted to investigational sites
- **If blinding needed** – adapted to practices, such as central dispensing to patients
- **Simpler monitoring** – focused on endpoints that matter, but collected reliably
- **Endpoints utilizing digital tools**, in-home collection
- **Enrollment criteria that are broad** but define properly the patient population
  - The issue isn't the enrollment criteria – it's doing studies in sites that bring in patients across a broader spectrum

Conclusions

- Electronic health care data is ubiquitous
  - Question is what is being collected reliably and consistently
    - Certain endpoints may be more feasible
  - Share need between clinicians and research to have data in the chart be better organized and accessible
    - Opportunities for technology
- Integration of other data streams may be necessary to capture the patient experience
  - Potential of digital technologies are just starting to be realized
- With greater efficiencies in data capture, randomization with RWD provides a pathway for reliable –persuasive - RWE

Acknowledgements

- Khair ElZarrad
- David Martin
- Dianne Paraoan
- Peter Stein
- Robert Temple

U.S. FOOD & DRUG ADMINISTRATION

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Clinical data to advance discovery

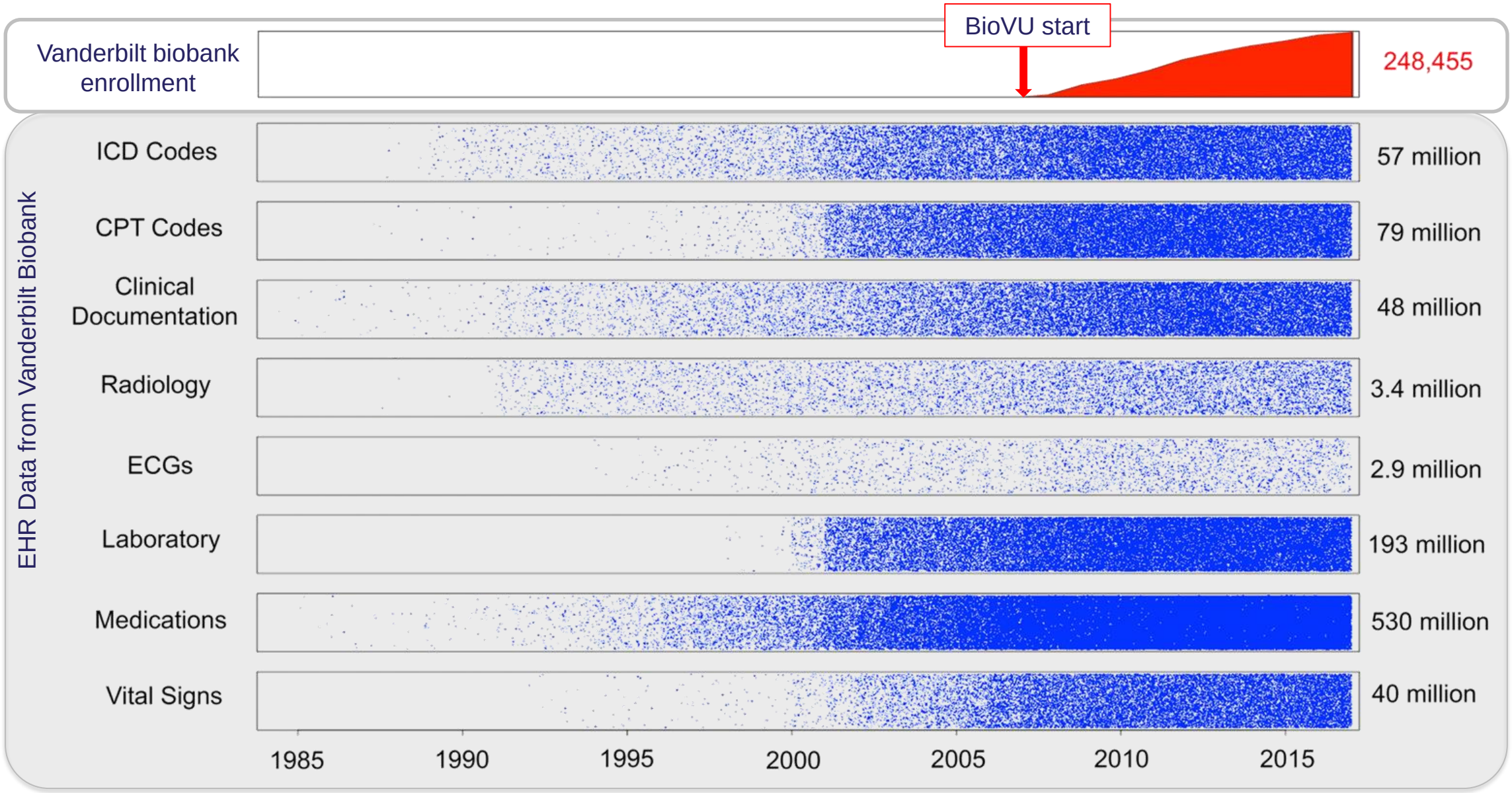
Josh Denny, MD MS

***All of Us* Research Program, NIH**

(formerly, Vanderbilt University Medical Center until 1/2020)

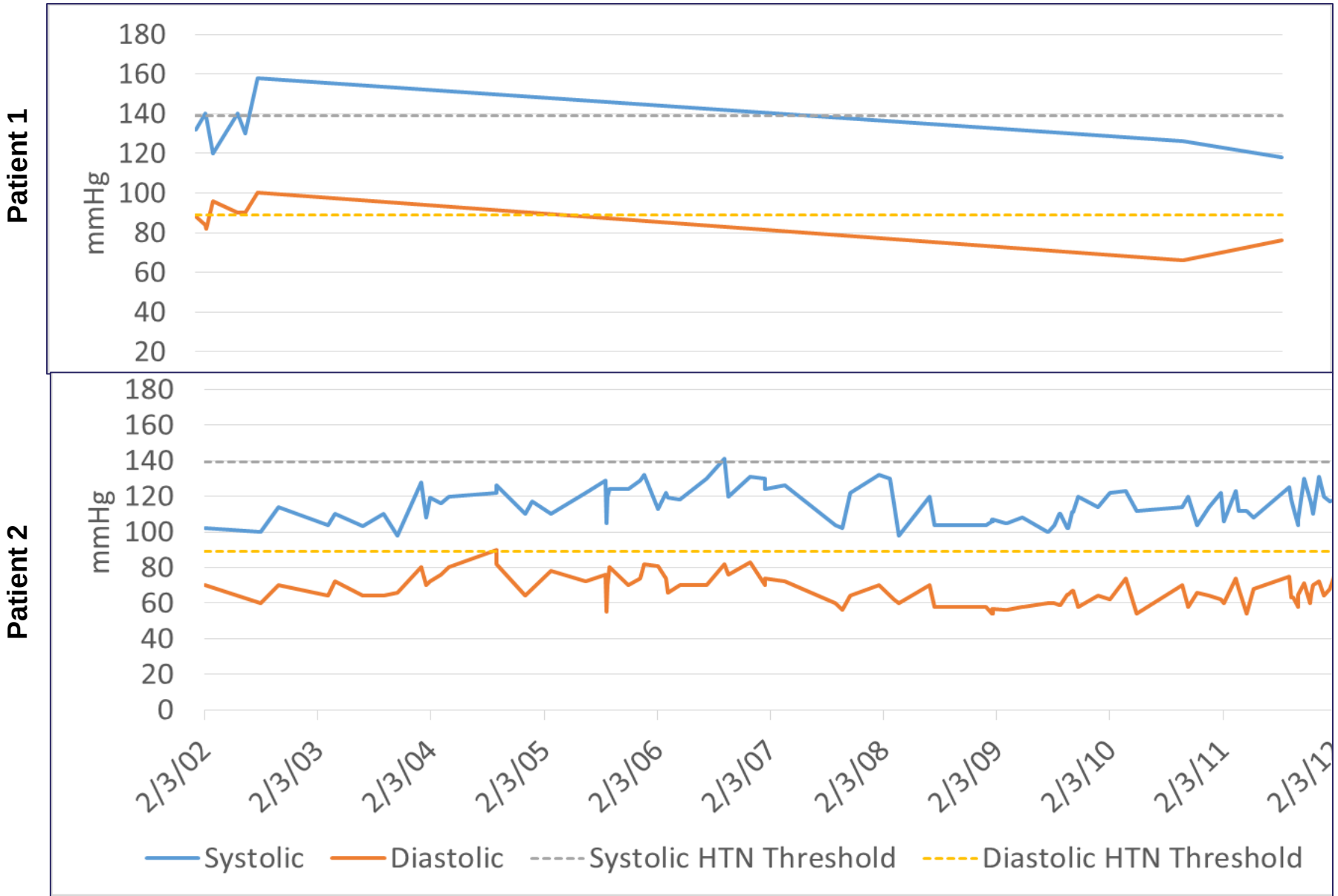
5/8/2020

EHRs provides dense resource for efficient discovery: BioVU's example



Finding a “simple” disease in the EHR: Who has hypertension?

Definition: SBP > 140 or DBP > 90



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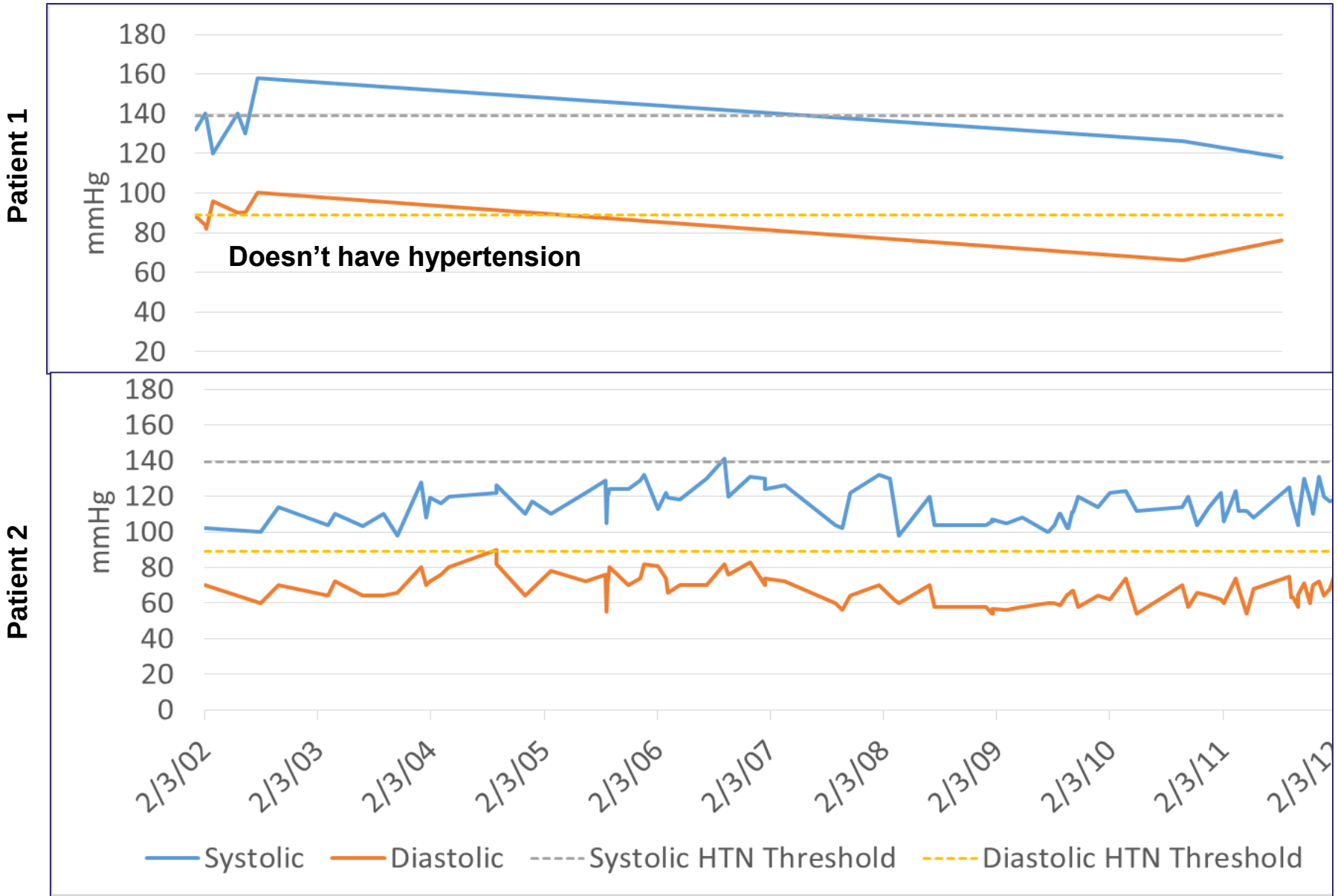

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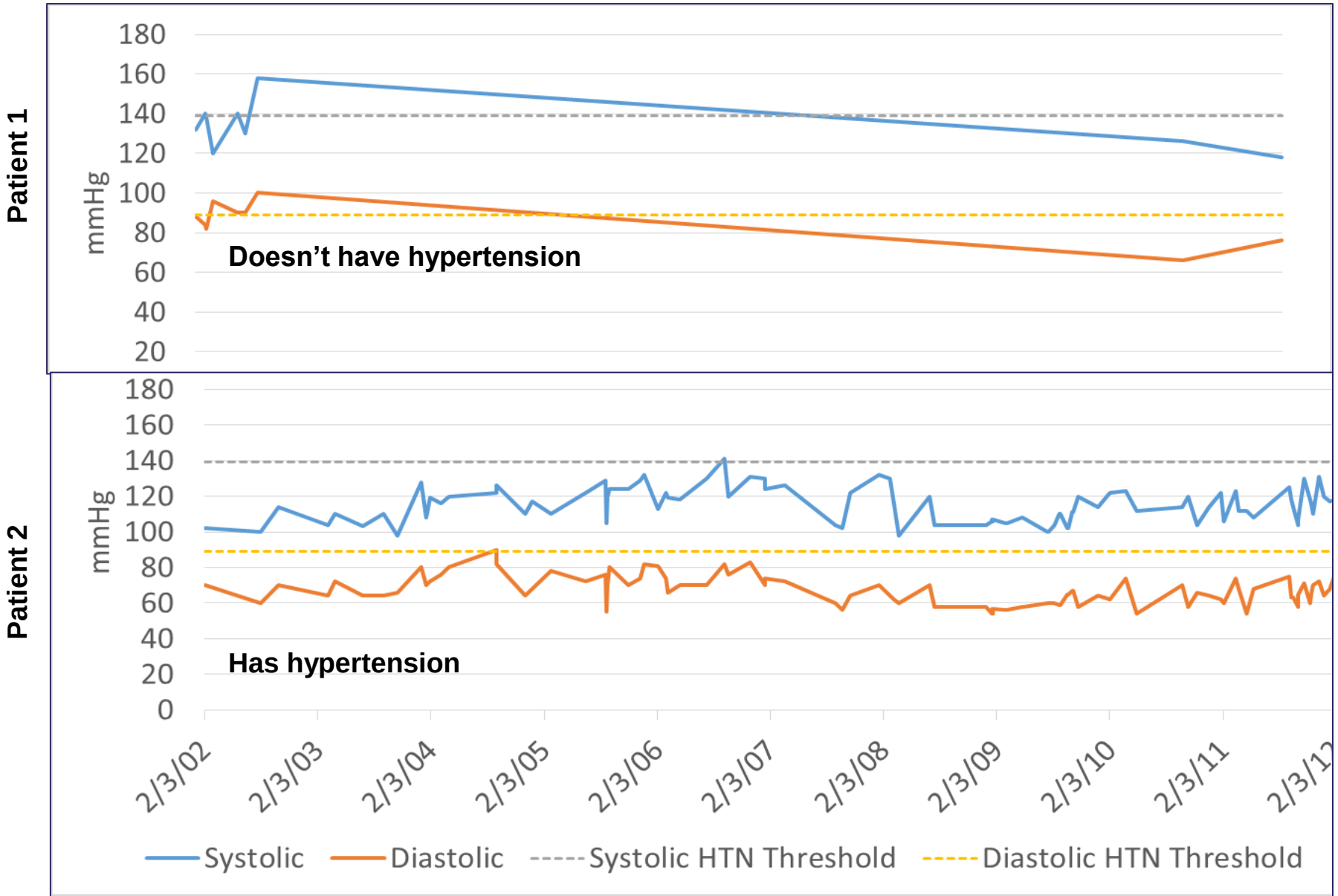
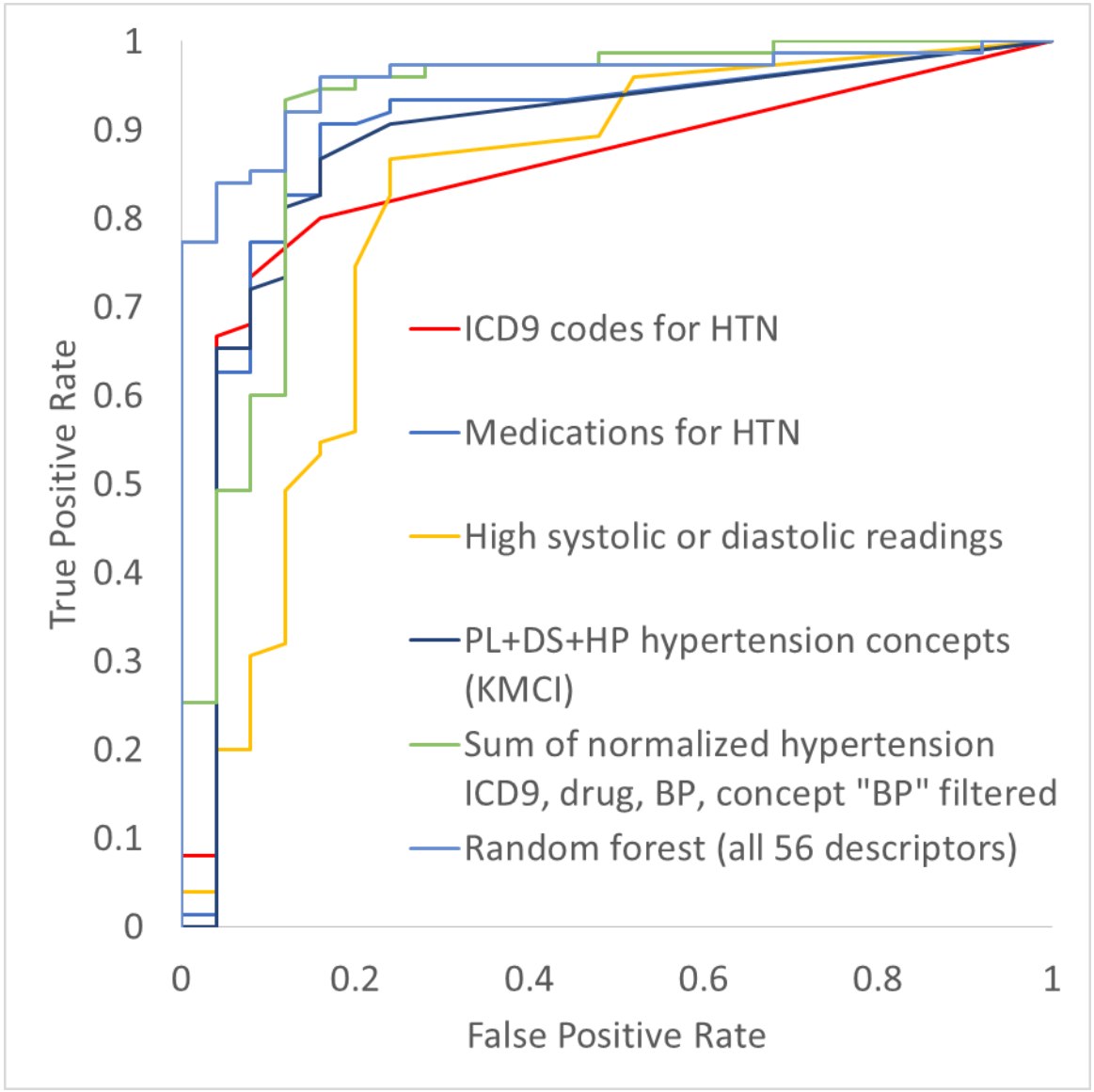


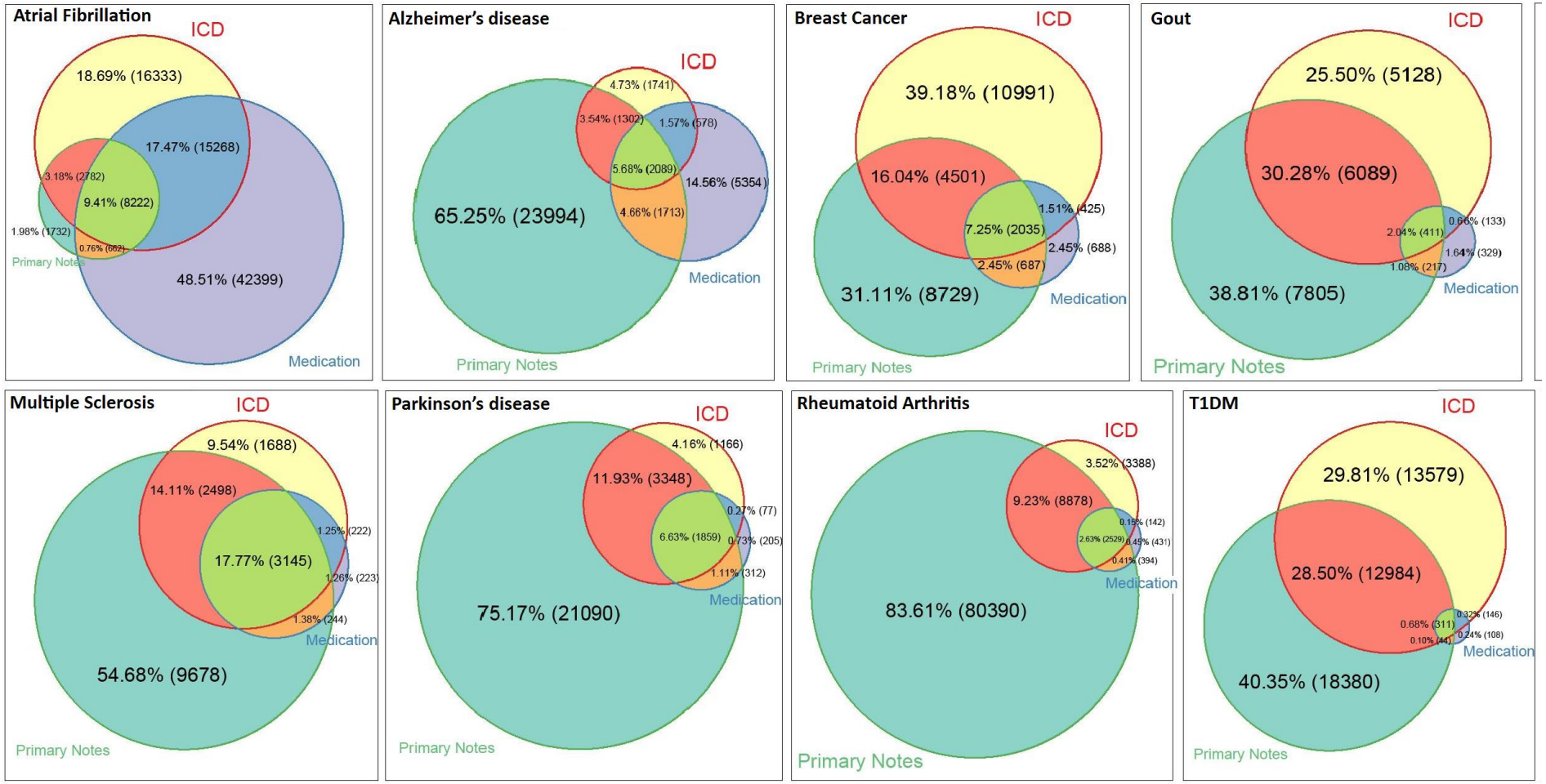
Our “simple” example: Hypertension

Multiple components are better
(and blood pressure is the worst)



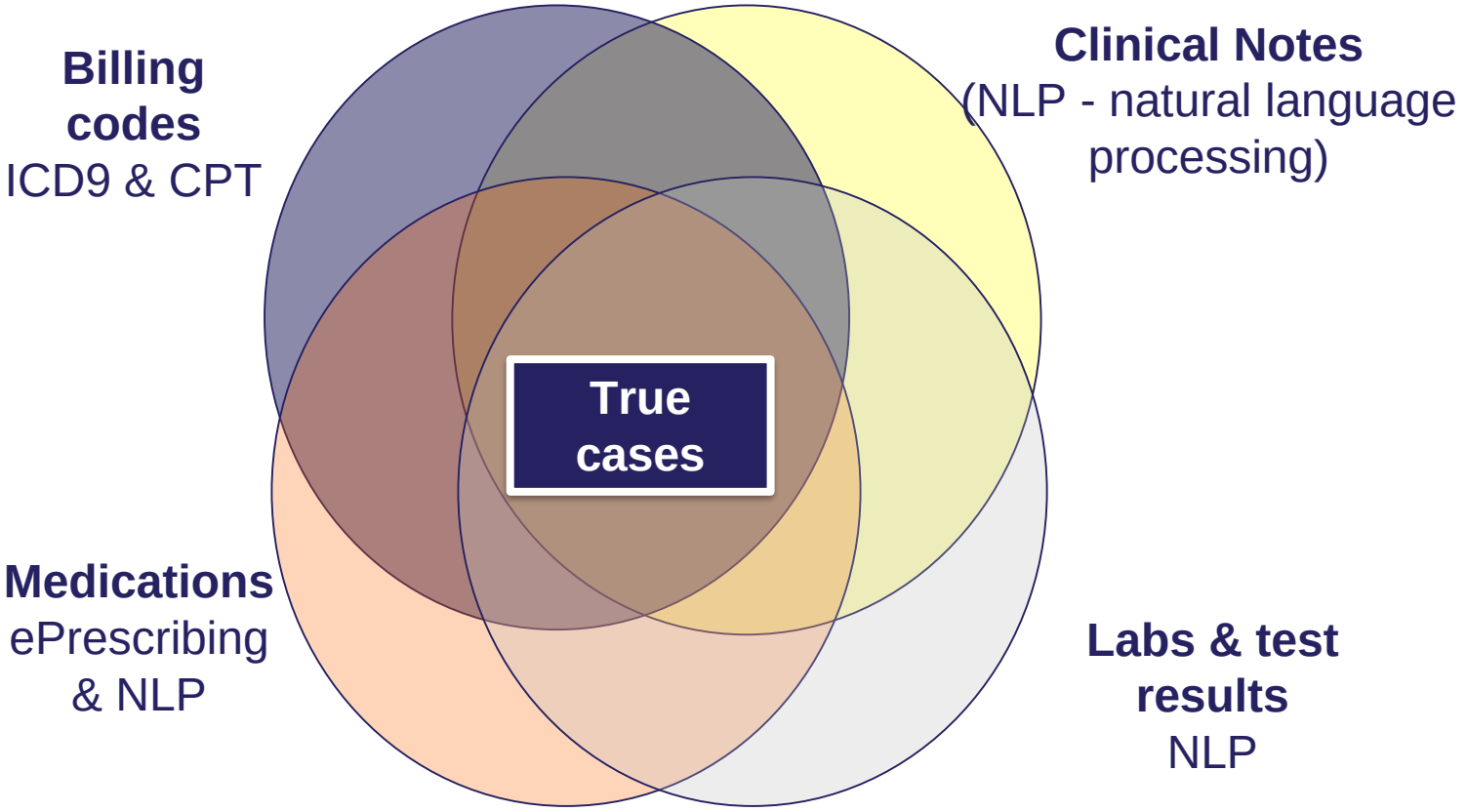
Teixeira, JAMIA 2016

ICD, Meds, and NLP identify different counts of possible cases for different diseases

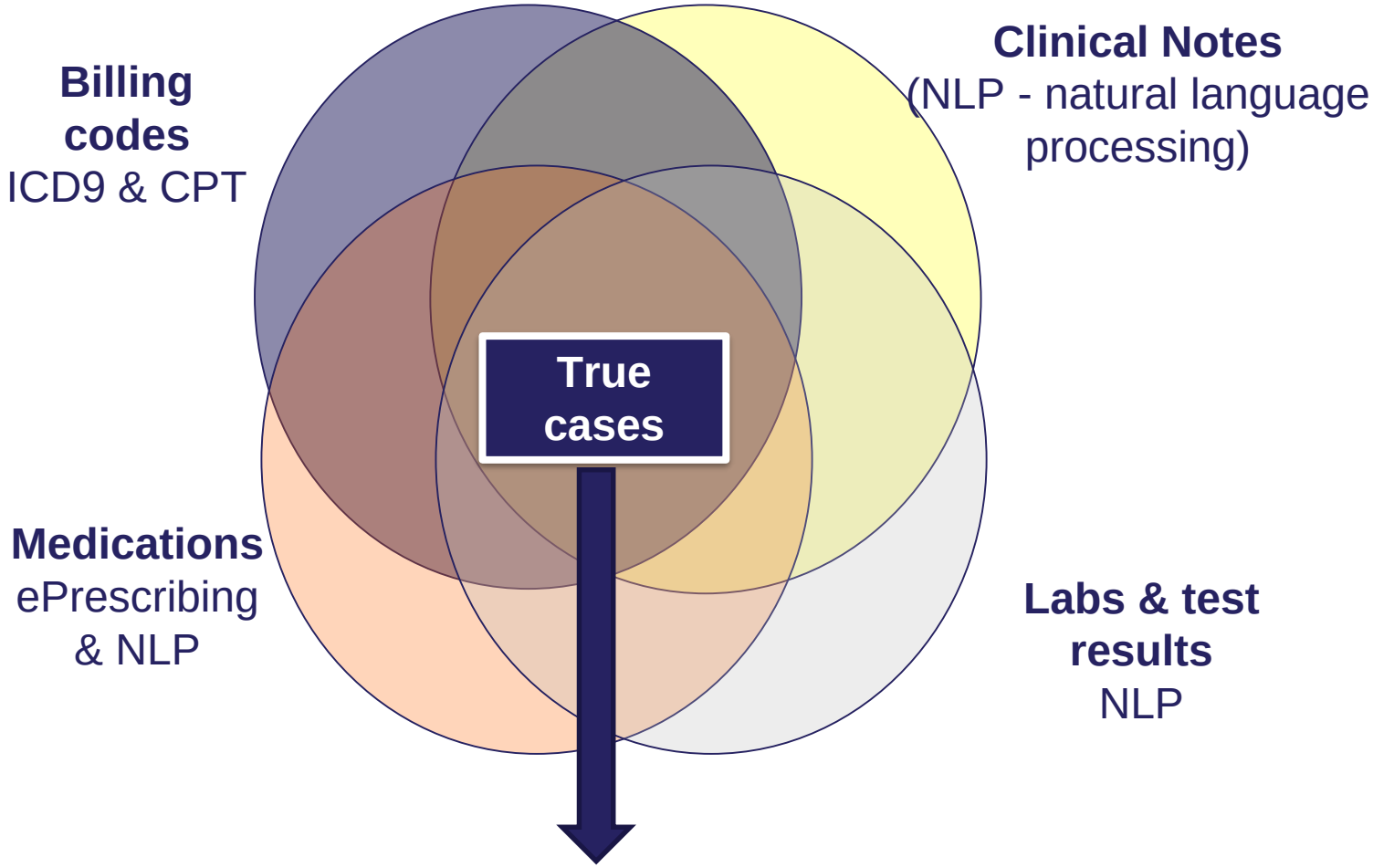


Wei-WQ JAMIA 2015

What we learned - Finding phenotypes in the EHR



What we learned - Finding phenotypes in the EHR



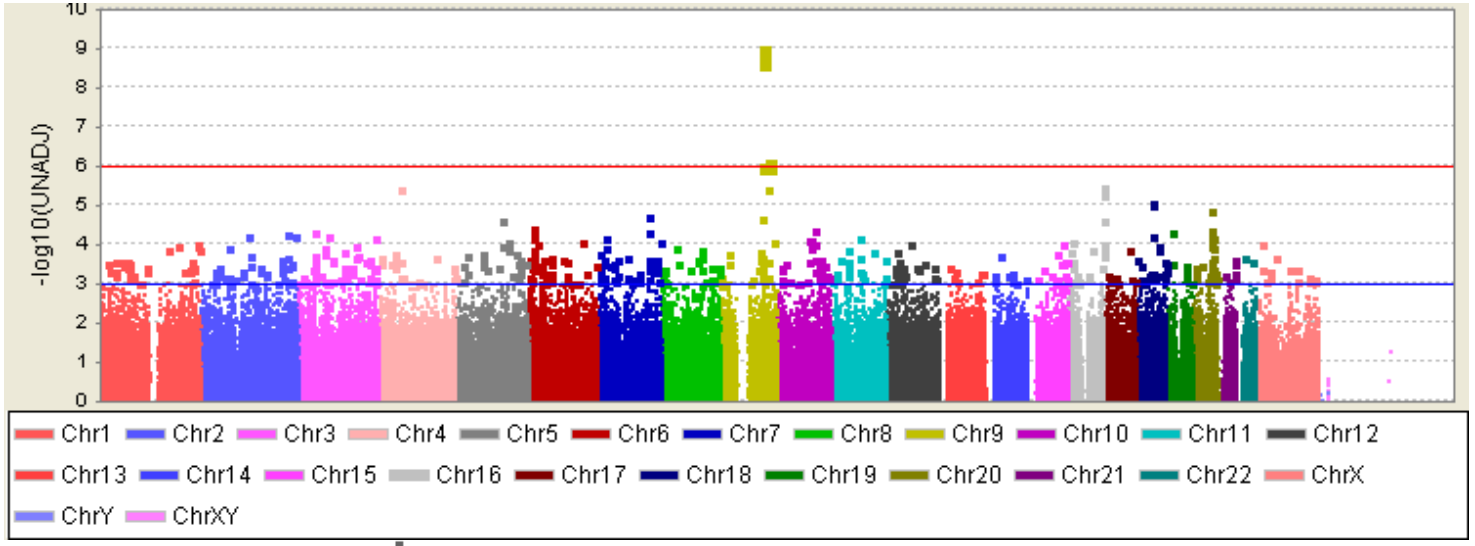
Any combination of rules, logic, machine learning. Can be deterministic (yes/no), probabilistic, or even use ”markers” of disease

Early discovery science in eMERGE –Hypothyroidism

Table 1. Evaluation of Primary Hypothyroidism Algorithm at the Five eMERGE Sites

Site	Primary Phenotype	Total Genotyped Subjects	Primary Hypothyroidism			
			Cases	Controls	Case PPV (%)	Control PPV (%)
Group Health	dementia	2532	397	1,160	98	100
Marshfield	cataracts	4113	514	1,187	91	100
Mayo Clinic	peripheral arterial disease	3043	233	1,884	82	96
Northwestern	type 2 diabetes	1217	92	470	98	100
Vanderbilt	normal cardiac conduction	2712	81	352	98	100
All sites		13,617	1317	5053	92.4[a]	98.5[a]

Genotype counts represent all subjects who were found by the hypothyroidism algorithms at each site and who were genotyped. Counts are limited to those classified as "white" in the electronic medical record of each site. PPV = positive predictive value.
[a] Average weighted for number of samples contributed to the total.



Algorithms can be deployed across multiple EHRs

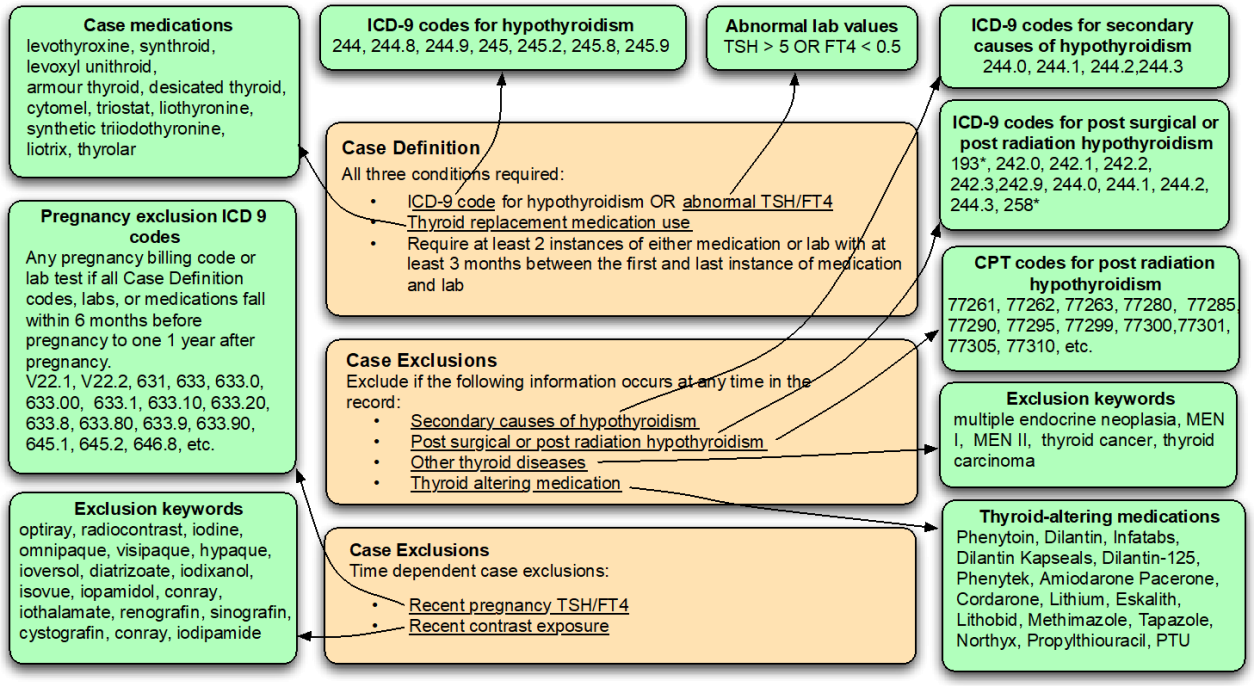
Analyses can be performed using extant data

emerge network
ELECTRONIC MEDICAL RECORDS & GENOMICS

Am J Hum Genet. 2011;89:529-42

Hypothyroidism Algorithm

Hypothyroidism Algorithm



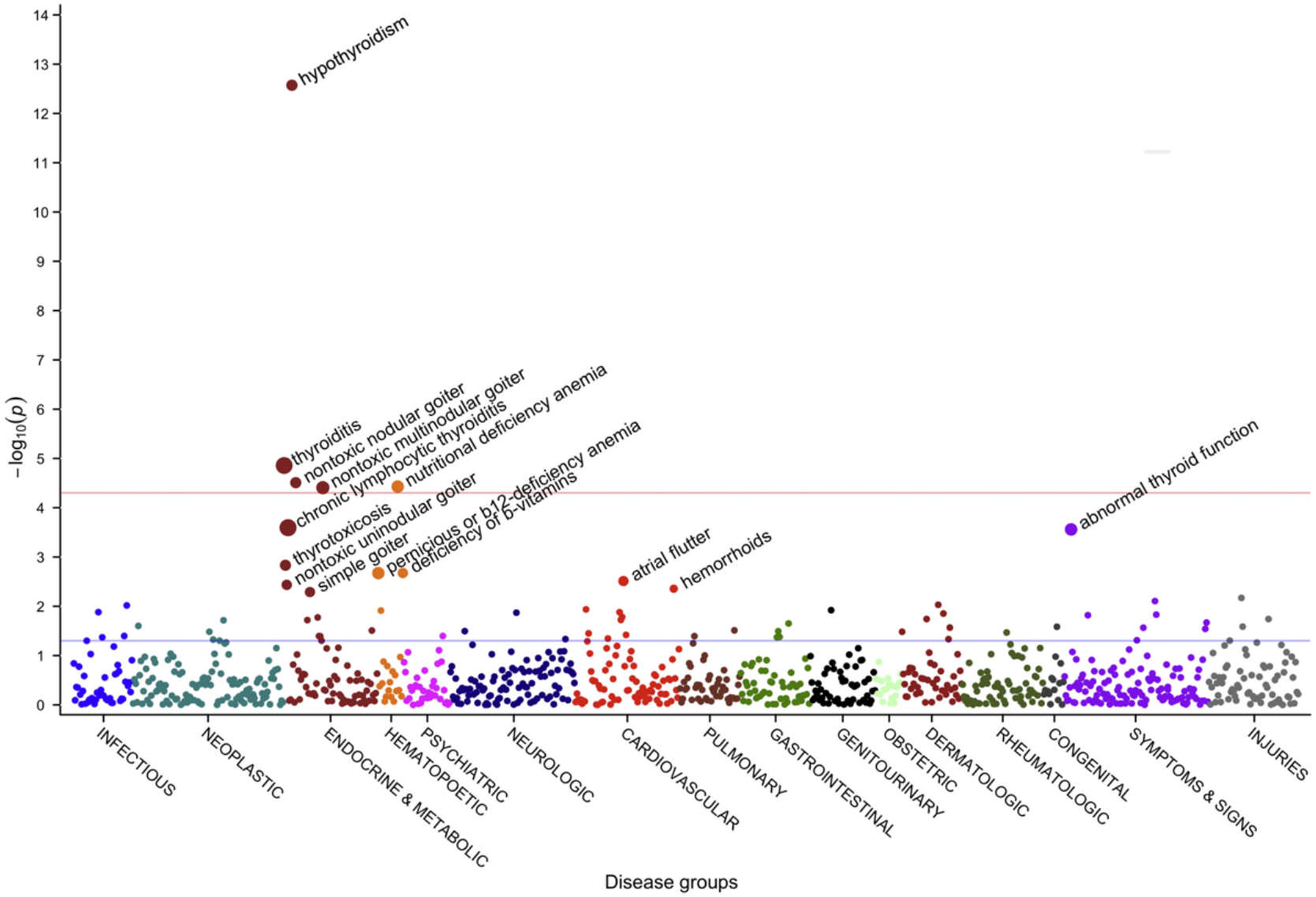
Conway et al. AMIA 2010.

Algorithms in PheKB.org

	Public (n = 44)	Non-public (n = 110)	%
ICD-9 or -10 codes	39	73	73%
Medications	31	51	53%
CPT codes	23	44	44%
NLP	28	36	42%
Laboratory test results	21	37	38%
Vital signs	5	14	12%

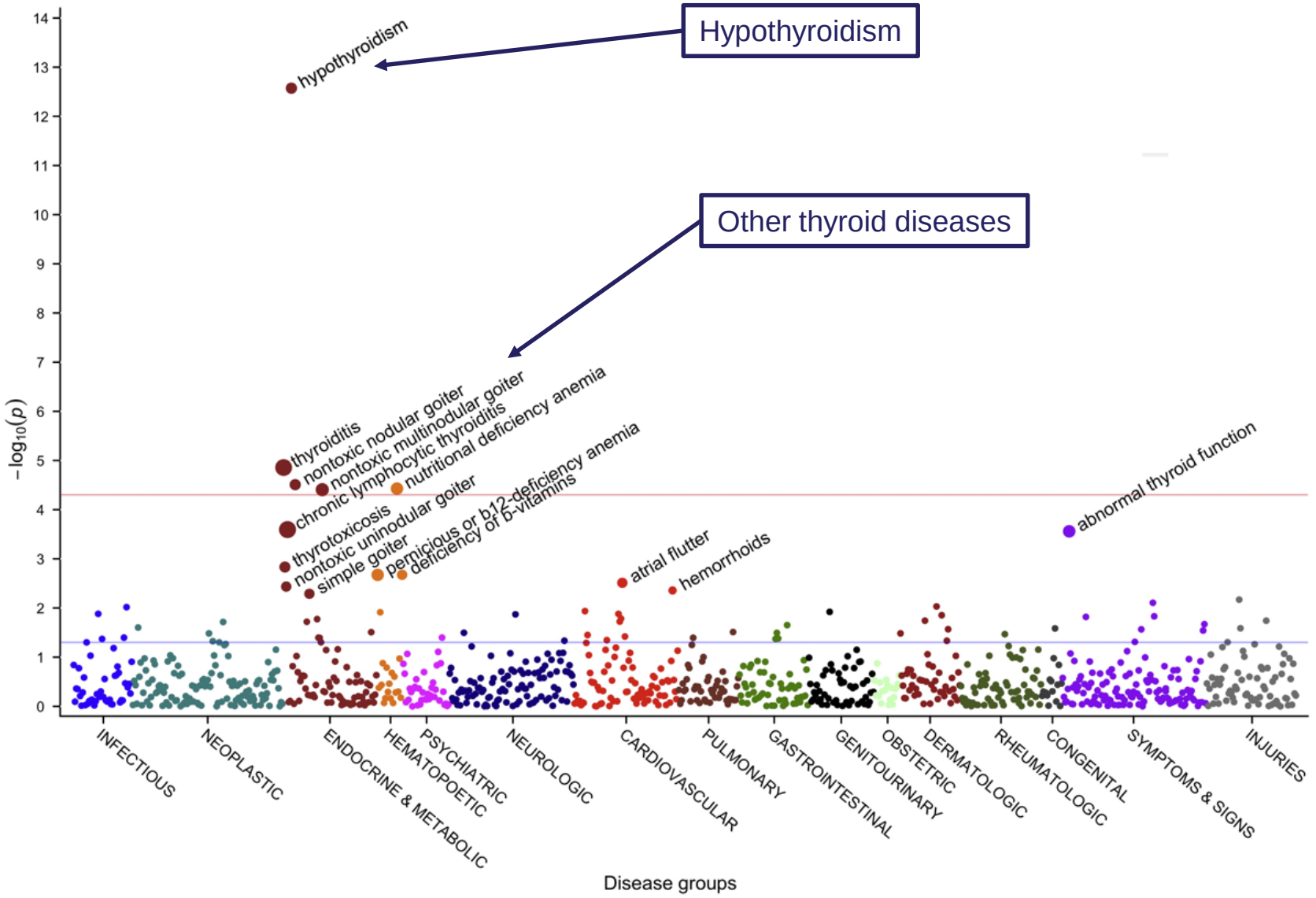
Kirby et al. JAMIA 2015.

PheWAS of the *FOXE1* locus



Denny et al., AJHG 2011

PheWAS of the *FOXE1* locus



Denny et al., AJHG 2011

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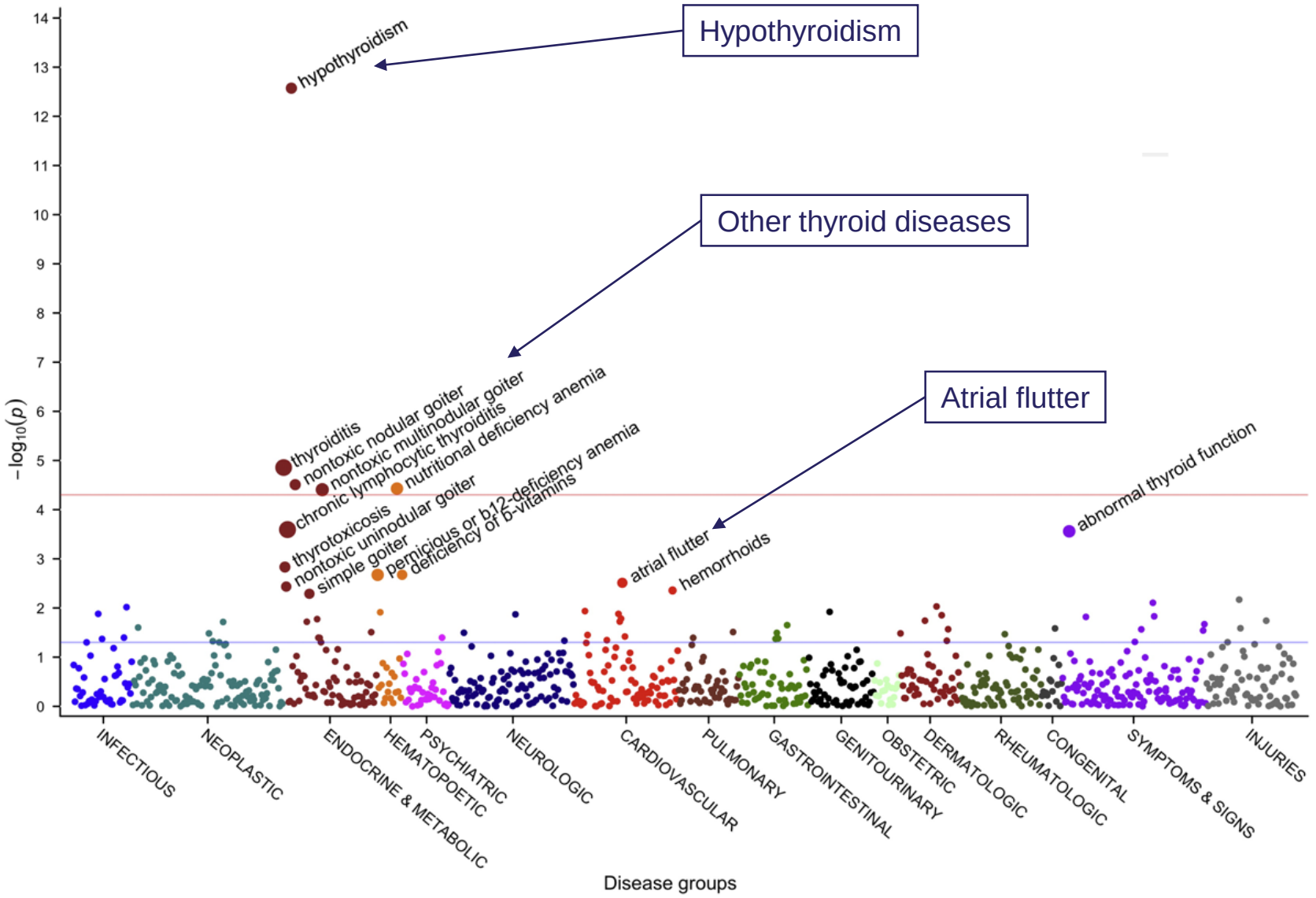
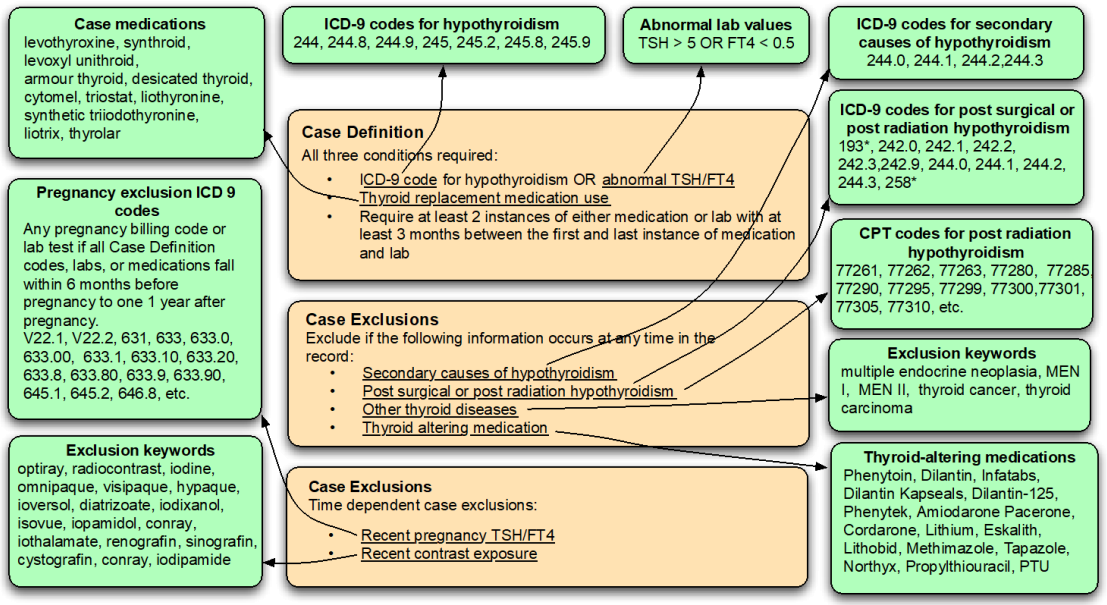


Denny et al., AJHG 2011

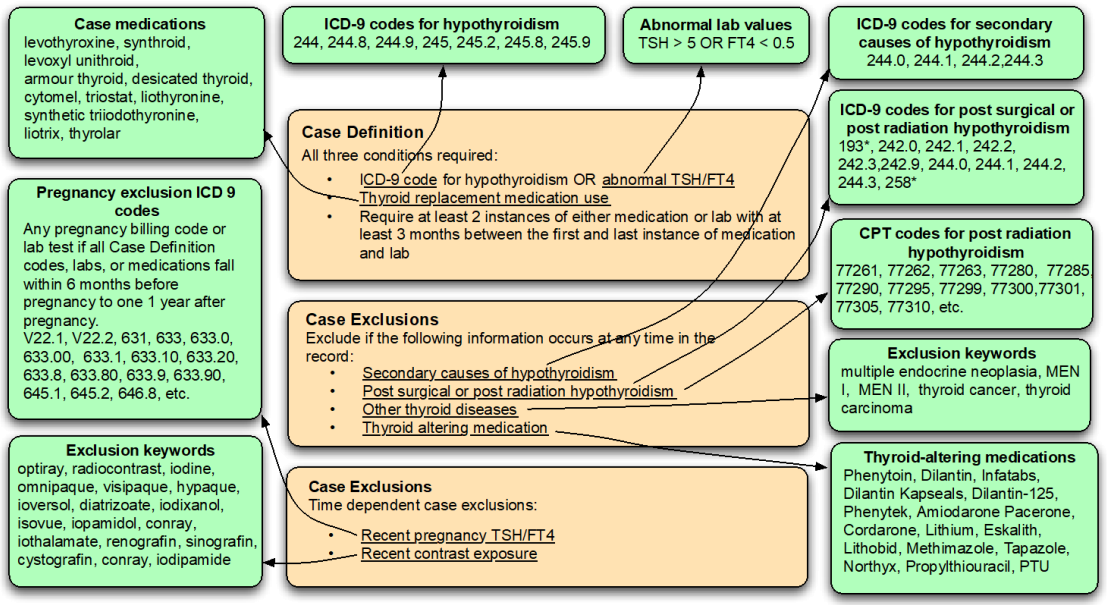
How much does the algorithm help?



versus

Two or more ICD-9 244* codes (phecodes)

How much does the algorithm help?



versus

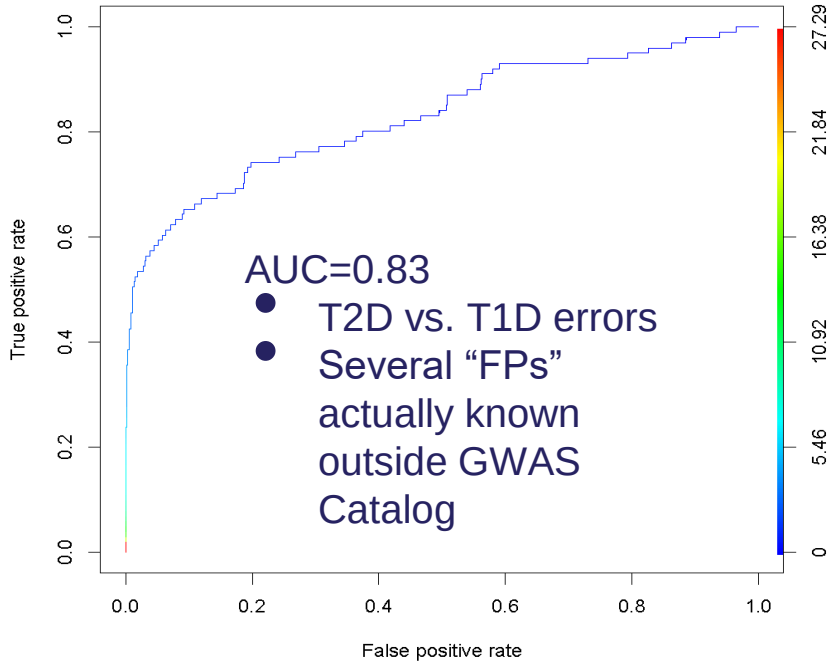
Two or more ICD-9 244* codes (phecodes)

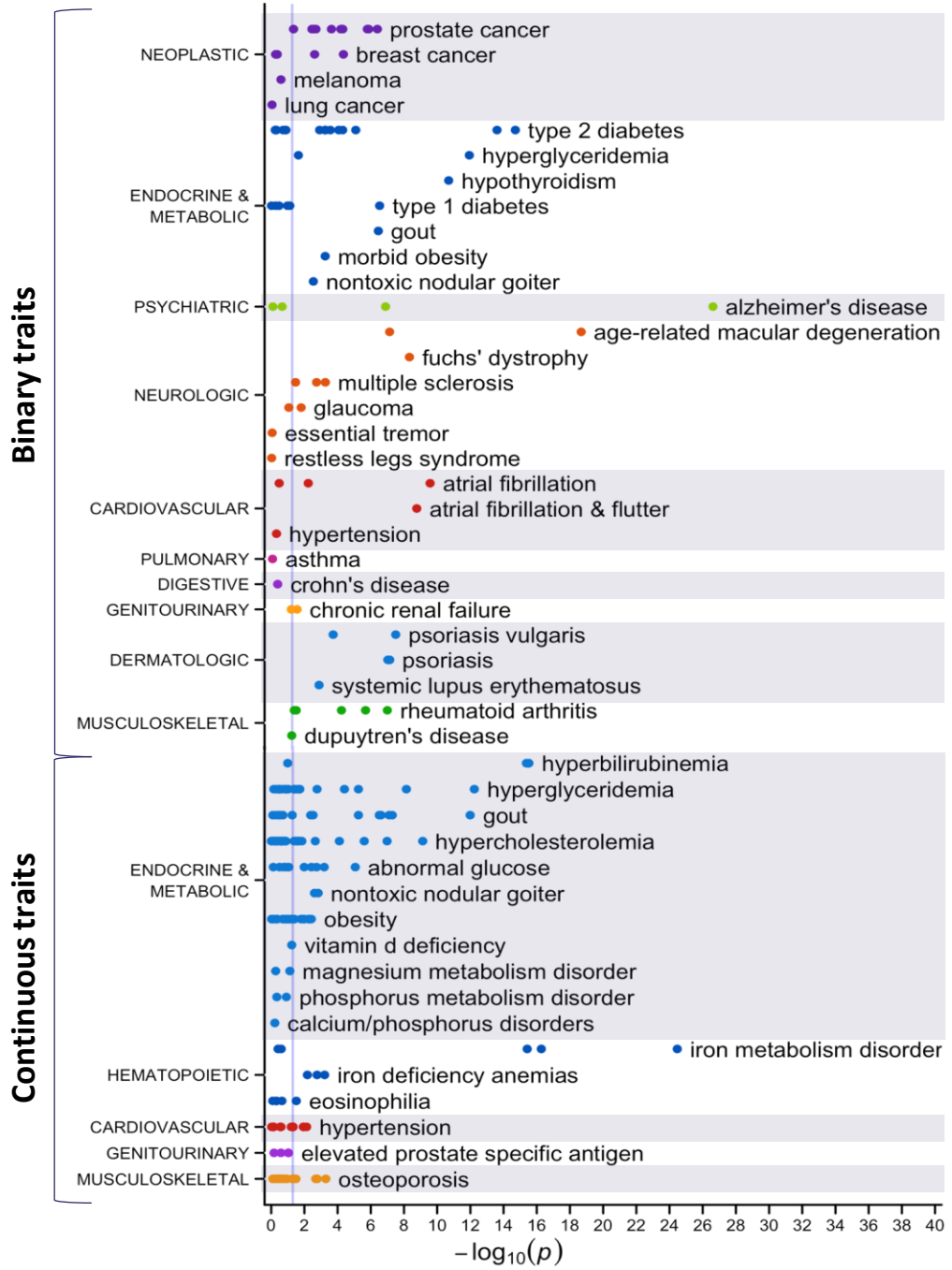
	Cases	Odds ratio	P-value
Super complicated algorithm	1317	0.74 (0.67 – 0.82)	8.2×10^{-9}
2+ phecodes	2108	0.76 (0.70 – 0.81)	2.7×10^{-13}

Replications of GWAS associations via PheWAS

P-value for replication:

- All - 210/751: $2x10^{-98}$
- Powered - 51/77: $3x10^{-47}$

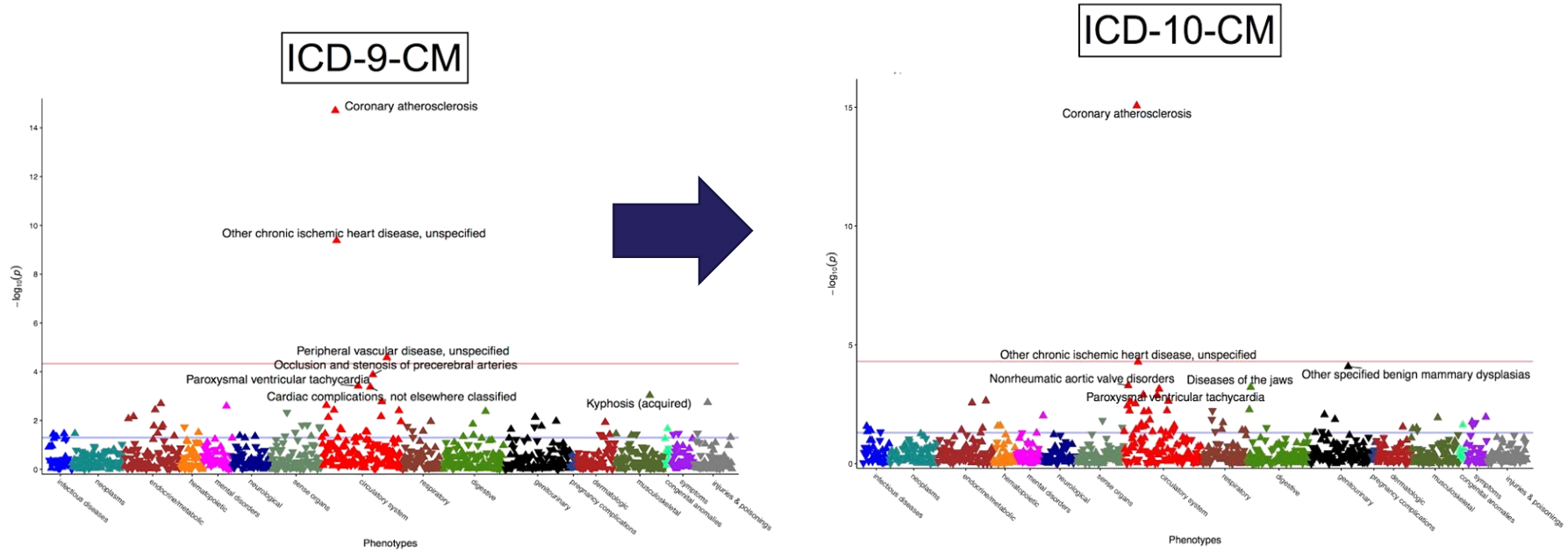




Nat Biotech 2013; 31:1102-1111

Creating PheWAS for ICD10 (UK Biobank) and ICD10-CM (US)

https://github.com/PheWAS/PheWAS / http://phewascatalog.org

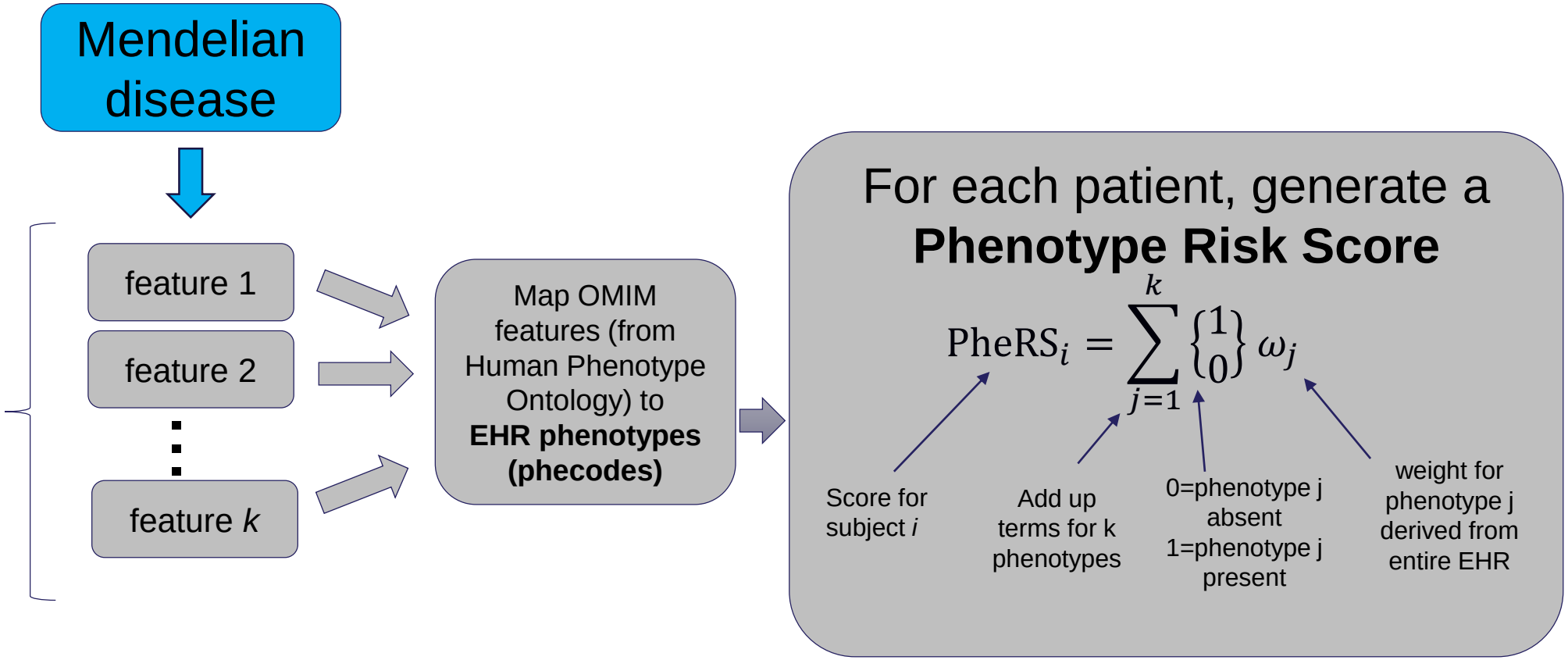


	Odds ratio	
	ICD9 → phecodes	ICD10 → phecodes
Coronary atherosclerosis	1.60	1.60
Ischemic heart disease	1.50	1.47

Wu et al. bioRxiv. doi.org/10.1101/462077

Automating assessments of “phenotype patterns” in the EHR

Extract disease features from OMIM



Bastarache et al, Science 2018

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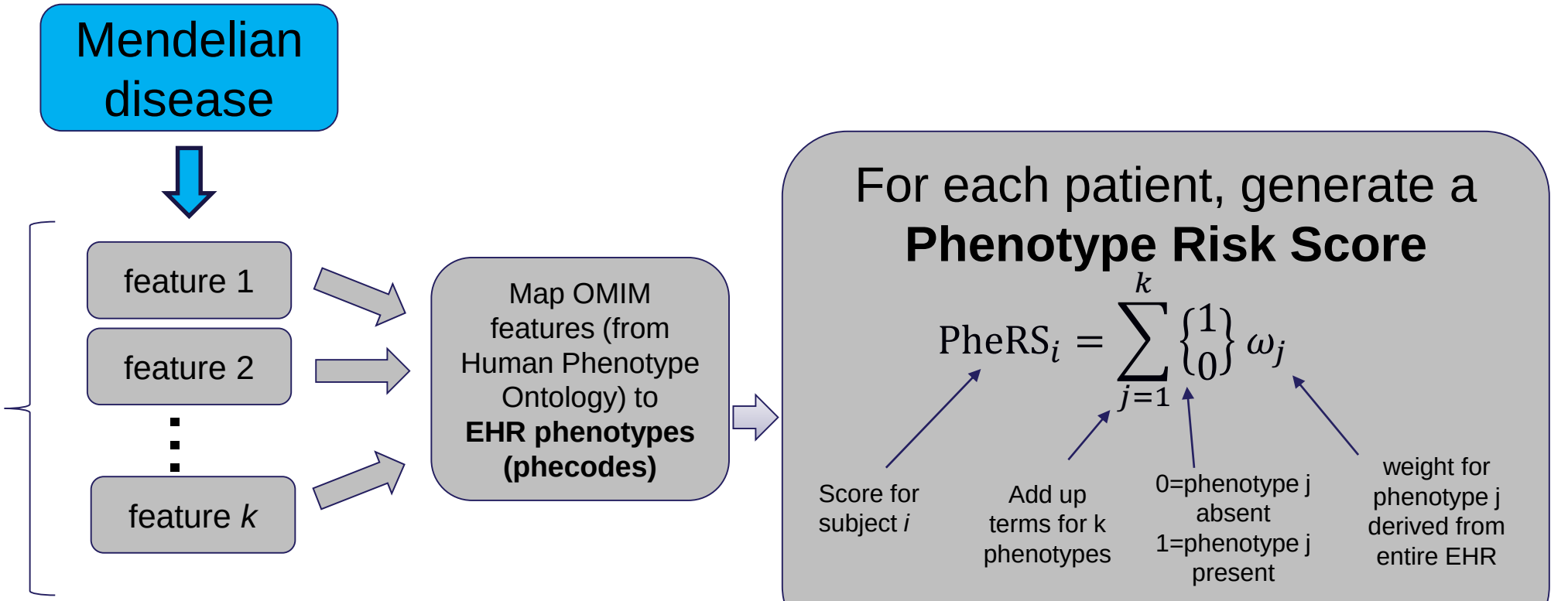
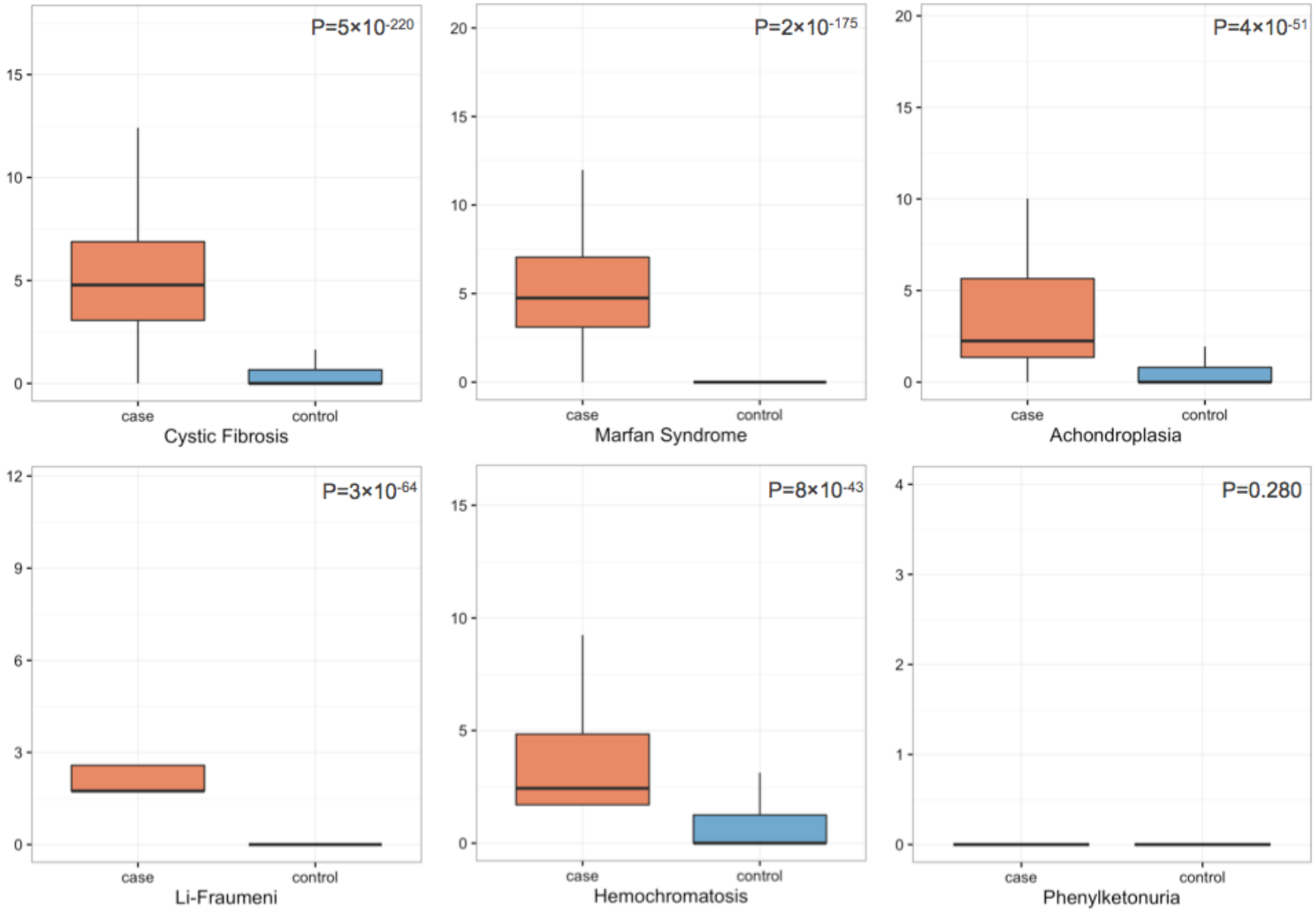


Repeat this for any Mendelian diseases

Bastarache et al, Science 2018

Validating PheRS on diagnosed individuals

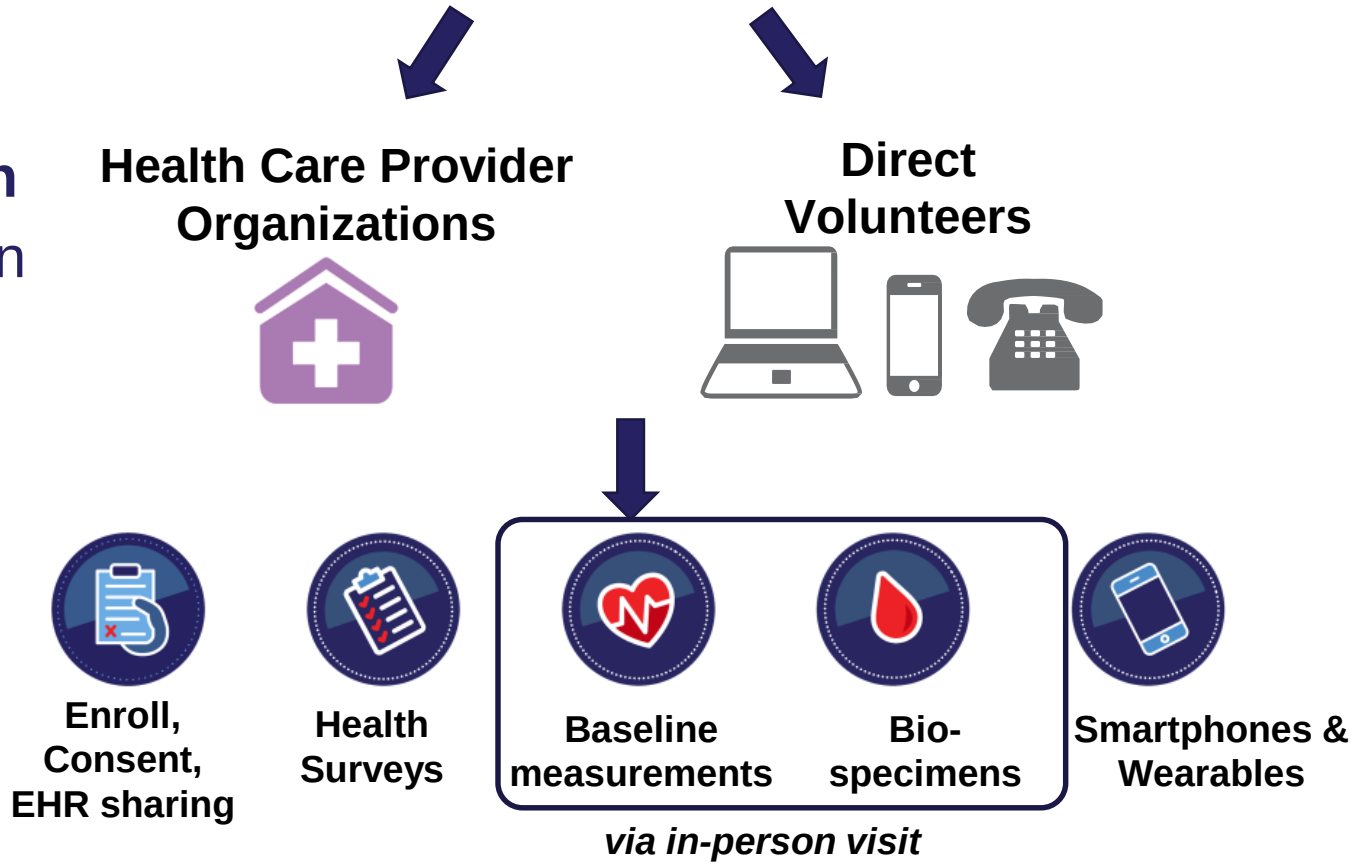


Bastarache et al, Science 2018

All of Us Research Program - Summary

- >340k participants, >271k with biospecimens
- >200k EHRs, goes back to decades
- >75% underrepresented population, >50% non-white
- Cloud-based **researcher workbench beta testing later this month –** open to US academic eRA commons researchers

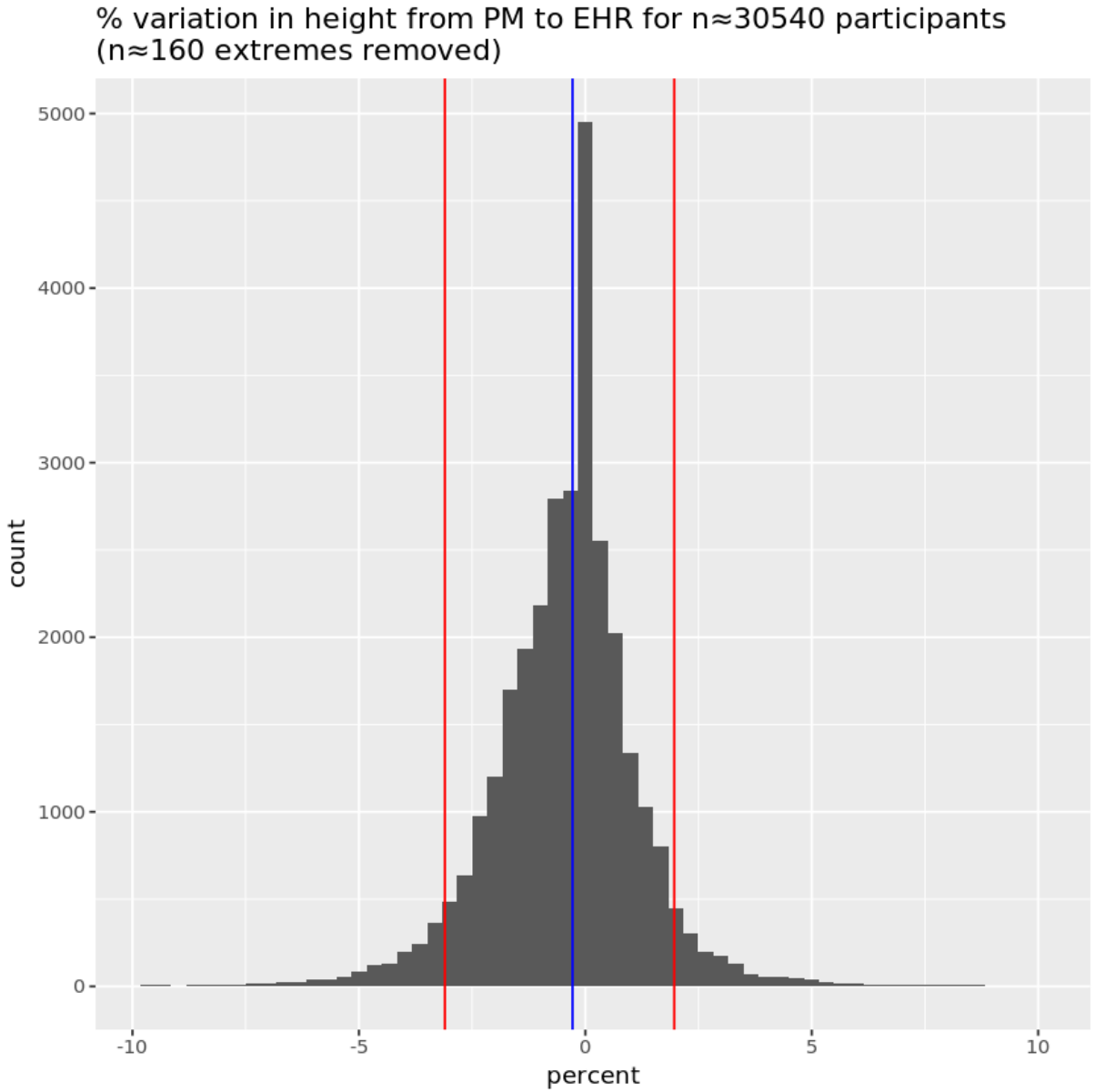
http://researchallofus.org
https://databrowser.researchallofus.org



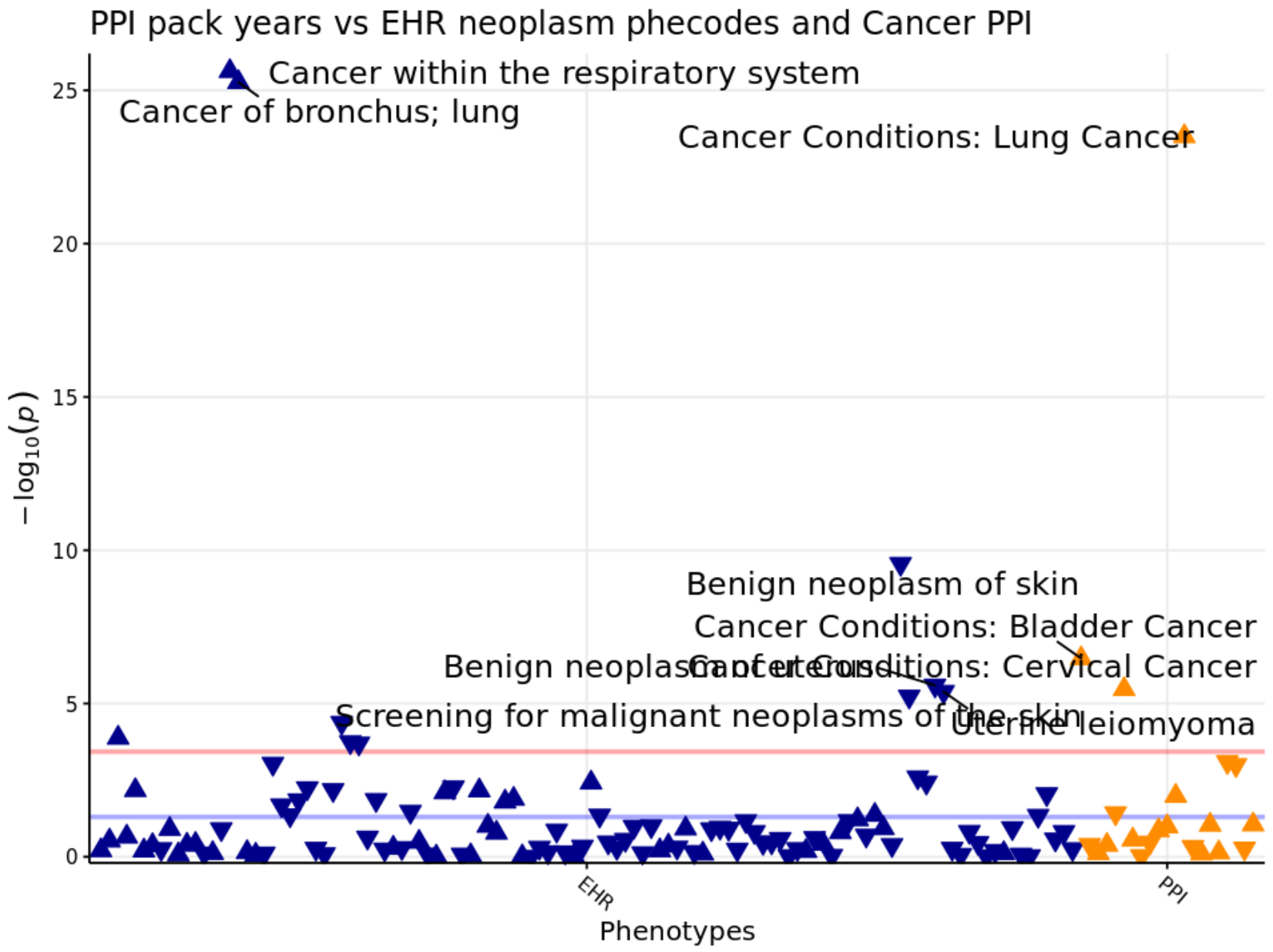
Case Study: Height Comparison (EHR + Physical Measurements)

- Physical Measurements data: height measured in centimeters
- EHR data: most recent height for each individual, normalized to centimeters

- **You are a median of 0.48cm (-0.4%) taller in the EHR!**



AoU smoking Cancer PheWAS comparison (EHR vs. PPI data)



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