Precision medicine through patient-level prediction of adverse events

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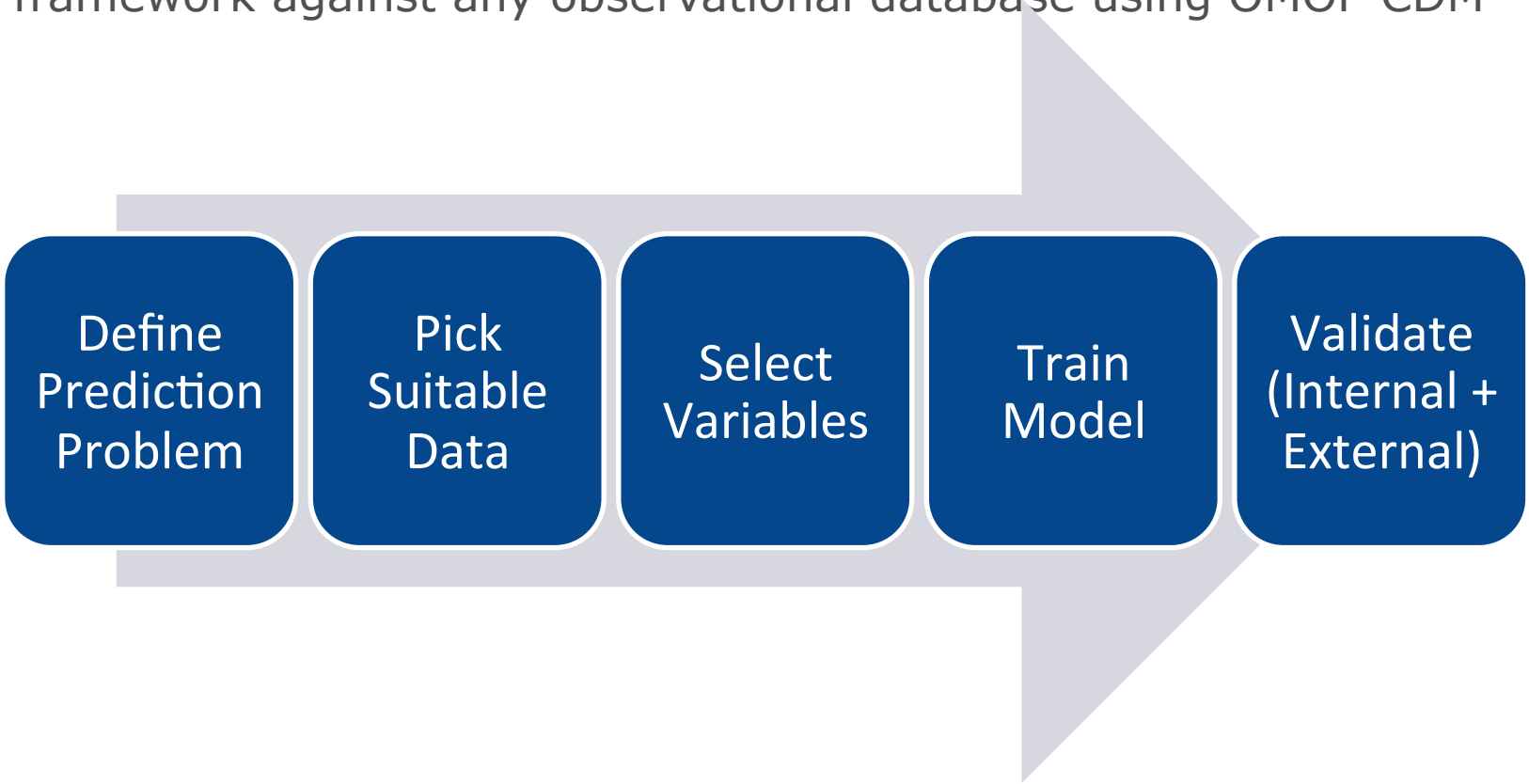
An OHDSI to Patient-Level Prediction

OHDSI established a 5-step standardized framework for developing and evaluating patient-level prediction models, and has released an open-source R package (PatientLevelPrediction) to implement the framework against any observational database using OMOP CDM



Types of prediction problems in healthcare

Amongst **<insert your target population>,** which patients will experience **<insert your outcome>** within **<time at risk>**?

Type	Structure	Example
Disease onset and progression	Amongst patients who are newly diagnosed with **<insert disease>**, which patients will go on to have **<another disease or related complication>** within **<time horizon from diagnosis>**?	Among newly diagnosed **depression** patients, which will go onto to have **suicide** in **next 1 years**?
Treatment choice	Amongst patients with **<indicated disease> who are treated with either <treatment 1> or <treatment 2>**, which patients were treated with **<treatment 1>** (**on day 0**)?	Among **MDD patients who took either sertraline or bupropion**, which patients got **sertraline**? (as defined for propensity score model)
Treatment response	Amongst patients who are new users of **<insert chronically-used drug>**, which patients will **<insert desired effect>** in **<time window>**?	Which patients with **depression who start on sertraline do not require a different antidepressant after 1 years**?
Treatment safety	Amongst patients who are new users of **<insert drug>,** which patients will experience **<insert potential adverse event of the drug>** within **<time horizon following**	Among new users of **sertraline**, which patients will have **sexual dysfunction** in **1 year**?

Note: If you want to determine if a variable **causes** the outcome (e.g., a causal risk factor), then you require population-level effect estimation…

NOT Patient-Level Prediction

ZOLOFT- sertraline hydrochloride tablet, film coated
ZOLOFT- sertraline hydrochloride solution, concentrate
Roerig

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZOLOFT safely and effectively. See full prescribing information for ZOLOFT.

ZOLOFT (sertraline hydrochloride) tablets, for oral use
ZOLOFT (sertraline hydrochloride) oral concentrate
ZOLOFT (sertraline hydrochloride) oral solution
Initial U.S. Approval: 1991

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

See full prescribing information for complete boxed warning.

- **Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric and young adult patients (5.1)**
- **Closely monitor for clinical worsening and emergence of suicidal thoughts and behaviors (5.1)**

RECENT MAJOR CHANGES

Warnings and Precautions, QTc Prolongation/Torsade de Pointes (5.10) 6/2017

INDICATIONS AND USAGE

ZOLOFT is a selective serotonin reuptake inhibitor (SSRI) indicated for the treatment of (1):

- Major depressive disorder (MDD)
- Obsessive-compulsive disorder (OCD)
- Panic disorder (PD)
- Post-traumatic stress disorder (PTSD)
- Social anxiety disorder (SAD)
- Premenstrual dysphoric disorder (PMDD)

https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=fe9e8b7d-61ea-409d-84aa-3ebd79a046b5

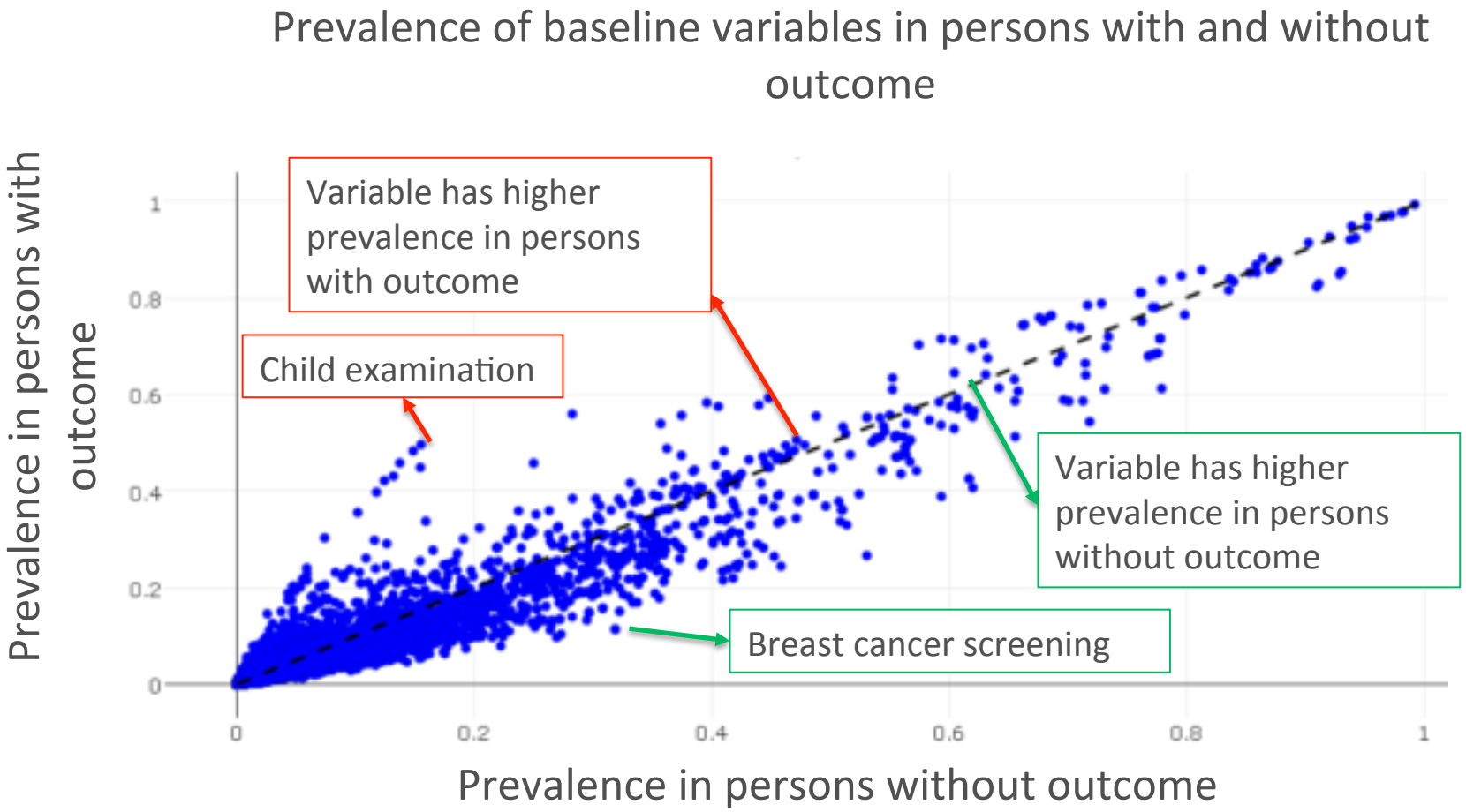
Among patients who initiate sertraline, based on the label, 30 in 1000 will have Suicidal thoughts and behaviors within 1 year after exposure

Define the patient-level prediction problem:

Amongst patients who are new users of **sertraline,** *which* patients will experience **Suicidal thoughts and behaviors** within **1 year after exposure start**?

Prediction step	Design choice
Pick suitable data	OptumInsight Clinformatics™ Data Mart Database: private-payer claims database with inpatient/outpatient medical services, outpatient pharmacy dispensings, and select lab tests T = 67,720 new users of sertraline (>3yr history) with major depressive disorder O = 2,050 persons with suicidal thoughts or behaviors in 1 year after exposure start
Select the variables	• Demographics (age, sex, index month) • All conditions in 1 year and all-time pre-exposure • All drugs in 1 year and all-time pre-exposure • All procedures in 1 year and all-time pre-exposure • All measurements in 1 year and all-time pre-exposure • Risk scores: Charlson, DCSI, CHADS2 • Concept counts: # visits, drugs, conditions, procedures
Train the model	LASSO logistic regression 75% training / 25% test set person-split (test set used for internal validation)

Clinical characterization can be used to descriptively explore the univariate association with all baseline variables

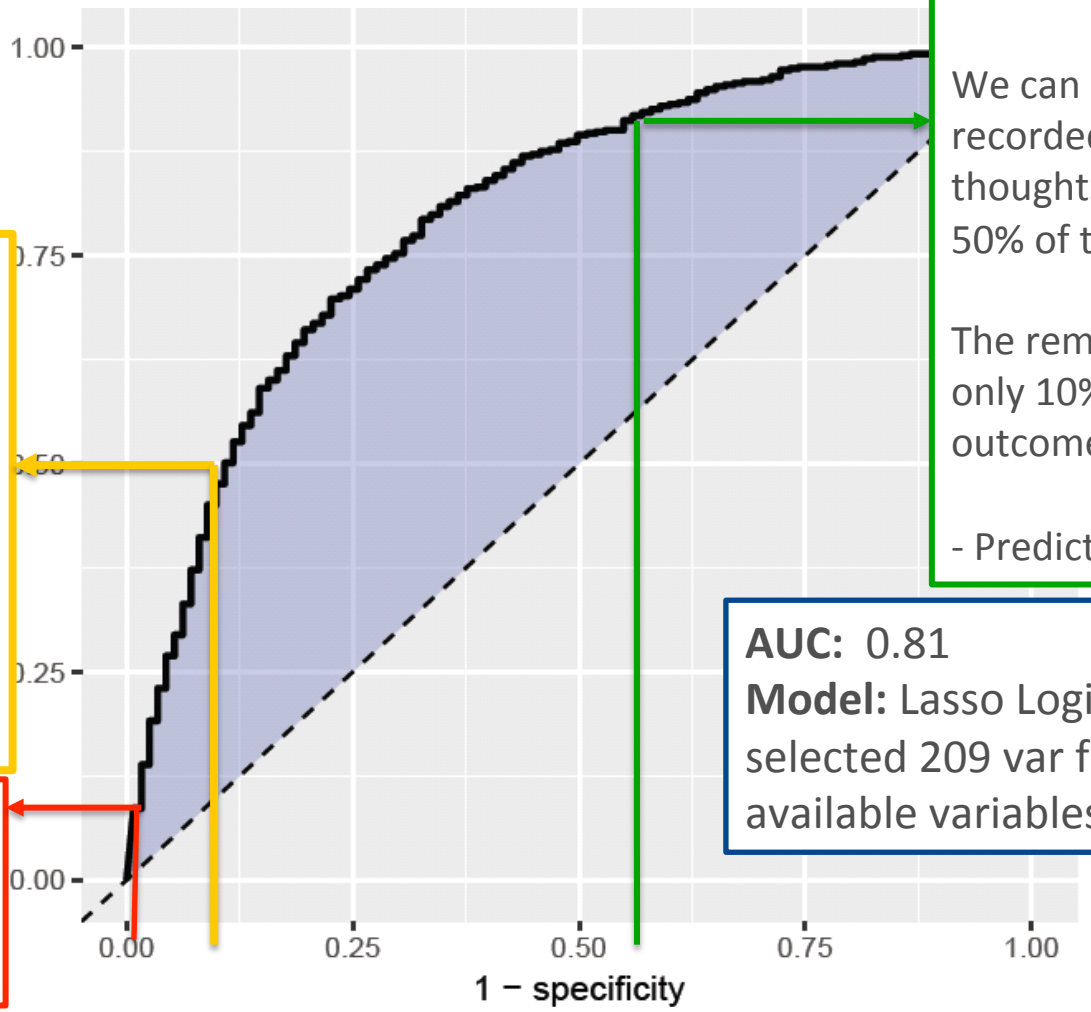


Internal validation on test set: Model shows good discrimination

At-risk threshold = 6%:
Sensitivity = 50%
Specificity = 89%
+ Predictive Value = 12%

We can predict half of all recorded suicidal thoughts and behaviors using only 12% of the population

At-risk threshold = 20%:
Sensitivity = 9%
Specificity = 99%
+ Predictive Value = 26%



At-risk threshold = 1.5%:

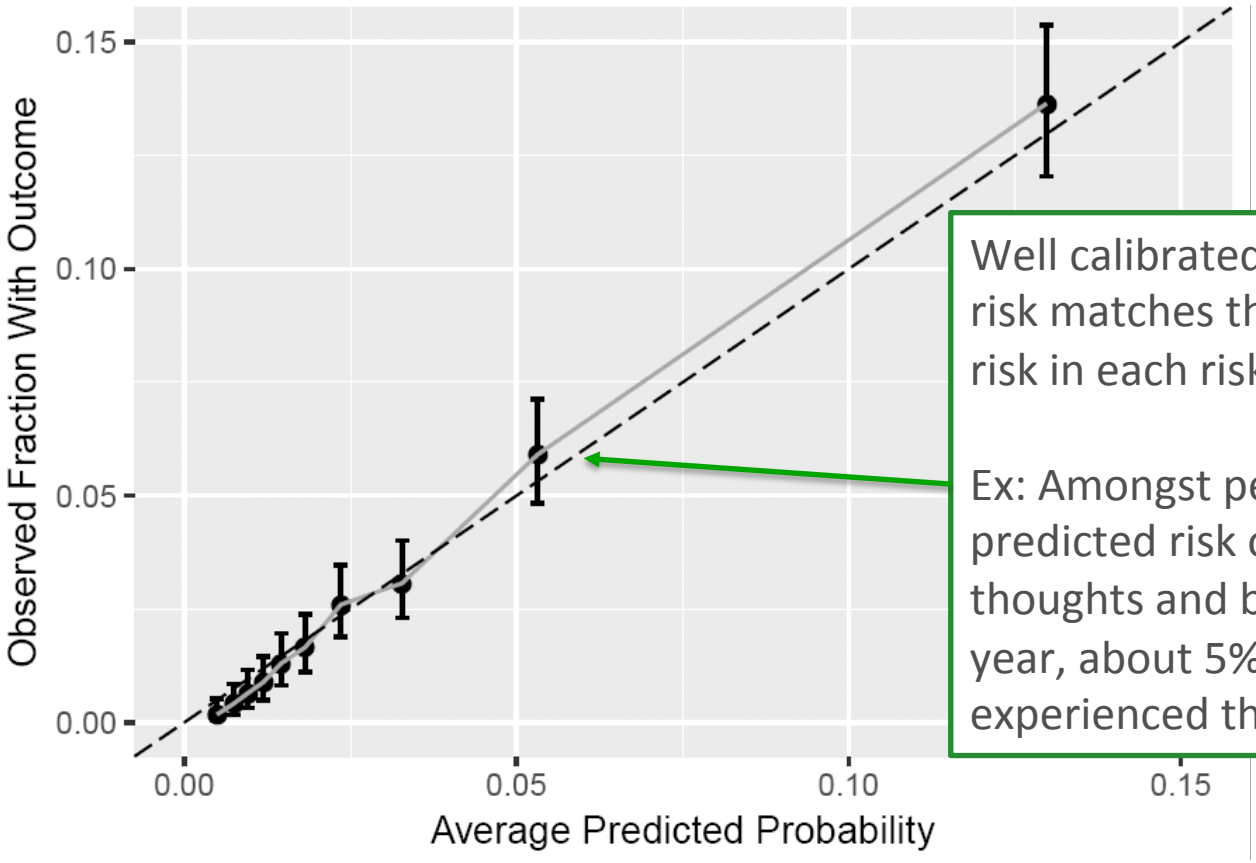
We can predict 90% of all recorded suicidal thoughts and behaviors in 50% of the population.

The remaining 50% have only 10% of the outcomes.

- Predictive Value = 99.3%

AUC: 0.81
Model: Lasso Logistic regression selected 209 var from 53k available variables

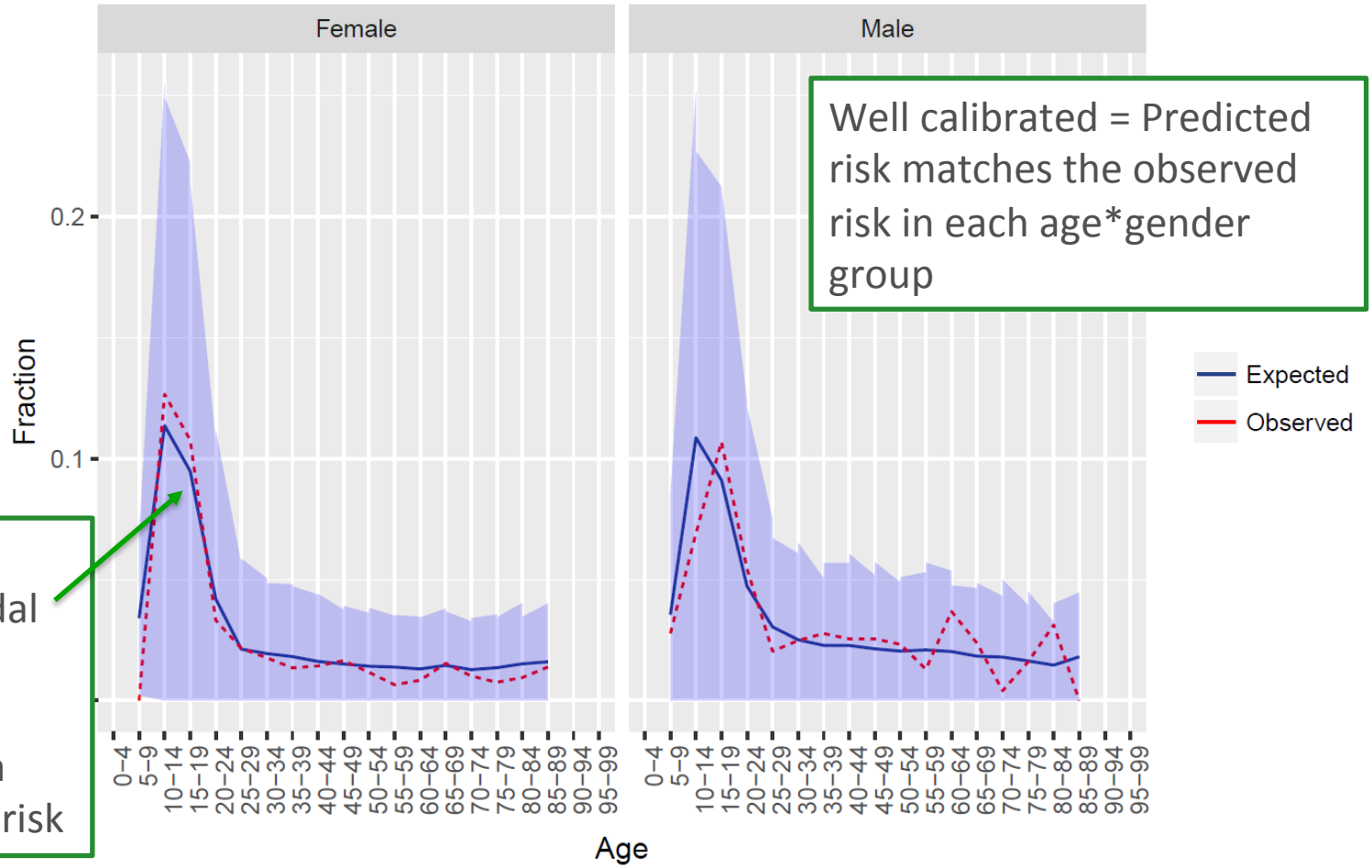
Internal validation on test set: Model shows good calibration across risk profiles



Well calibrated = Predicted risk matches the observed risk in each risk strata

Ex: Amongst people with 5% predicted risk of Suicidal thoughts and behaviors in a year, about 5% actually experienced the event

Internal validation: Model shows good calibration across demographic subgroups



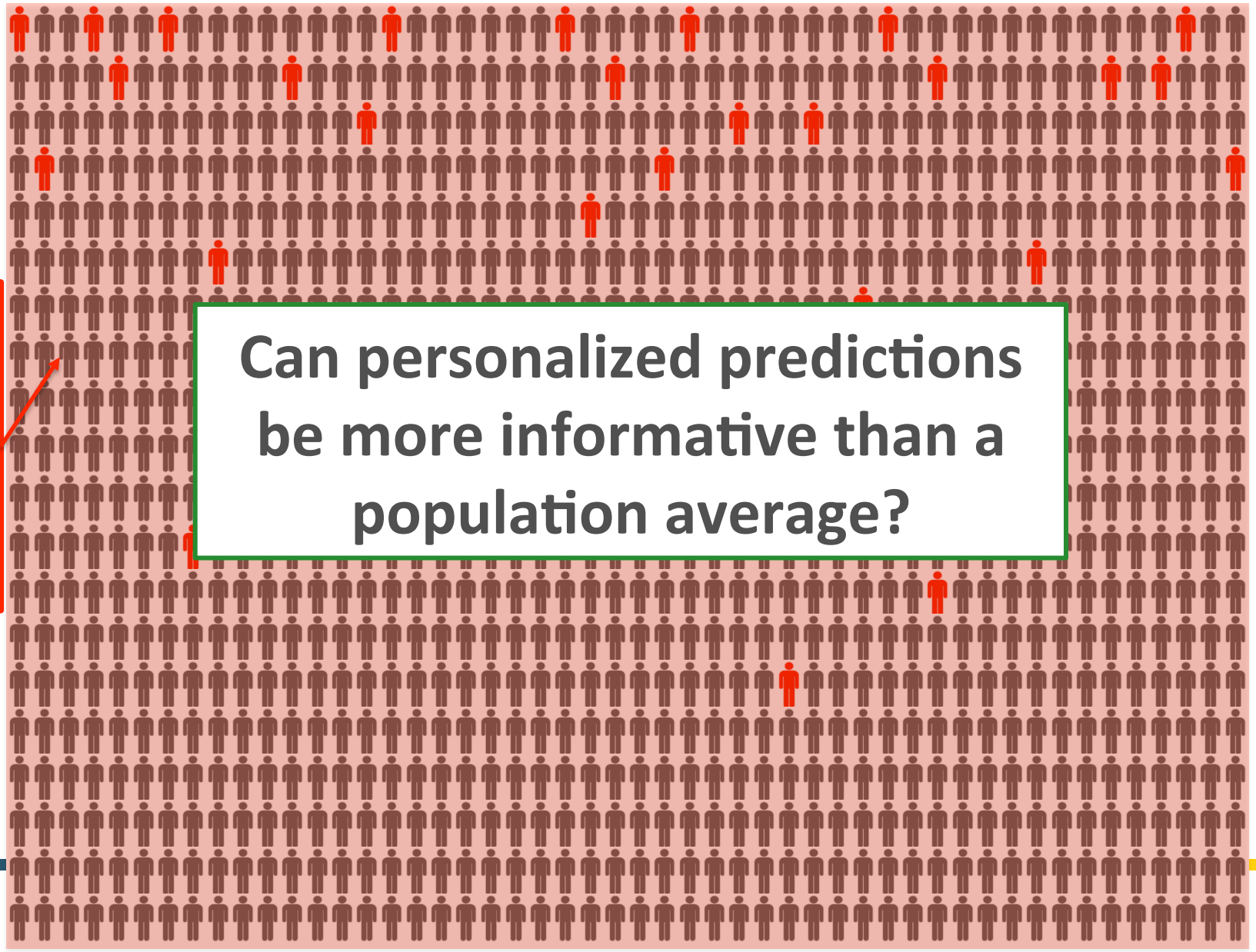
Well calibrated = Predicted risk matches the observed risk in each age*gender group

Young people experience Suicidal thoughts and behaviors more often, and have a higher predicted risk

External validation: Model shows consistent discrimination when applied to other populations

Data type	AUC
Optum (reference)	0.81
US private-payer claims (Truven MarketScan)	0.78
US Medicaid claims	0.70
US Medicare supplemental beneficiary claims	0.70
US electronic health records	0.78
UK electronic health records	0.69

Among patients who initiate sertraline, 30 in 1000 will have Suicidal thoughts and behaviors within 1 year after exposure



If all patients are treated equally, the average probability of event is 'Common' for all patients (p = 3%)

Can personalized predictions be more informative than a population average?

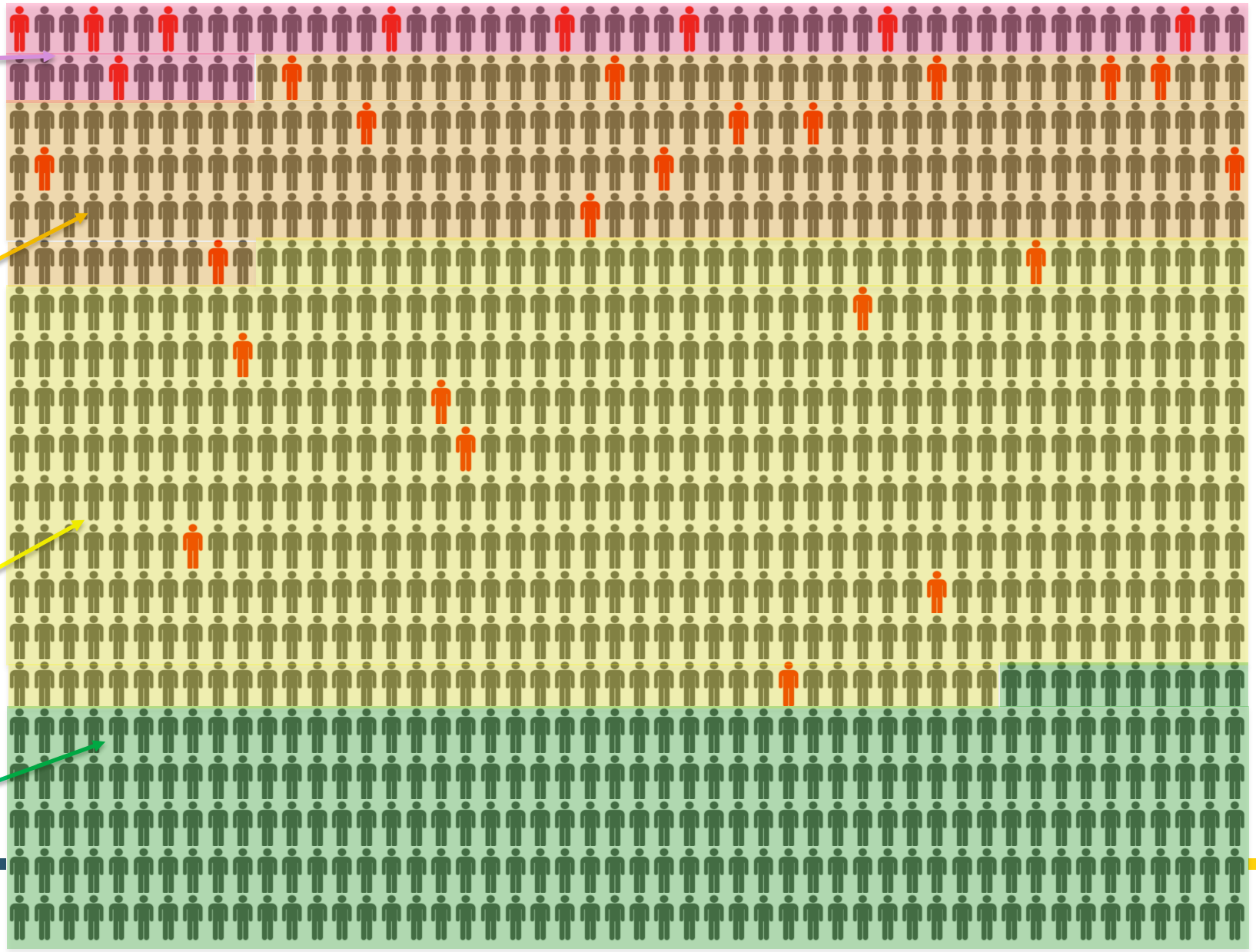
Among patients who initiate sertraline, 30 in 1000 will have Suicidal thoughts and behaviors within 1 year after exposure

6% predicted to have 'Very common' risk (p >= 10%)

20% predicted to have 'Common' and higher than average risk (3%<= p <10%)

47% predicted to have 'Common' and lower than average risk (1%<= p <3%)

26% predicted to have 'Uncommon' (0 .1%<= p <1%)



A drug may have multiple side effects of potential interest to any particular patient

5 WARNINGS AND PRECAUTIONS

5.1 Suicidal Thoughts and Behaviors in Pediatric and Young Adult Patients

5.3 Increased Risk of Bleeding

5.6 Seizures

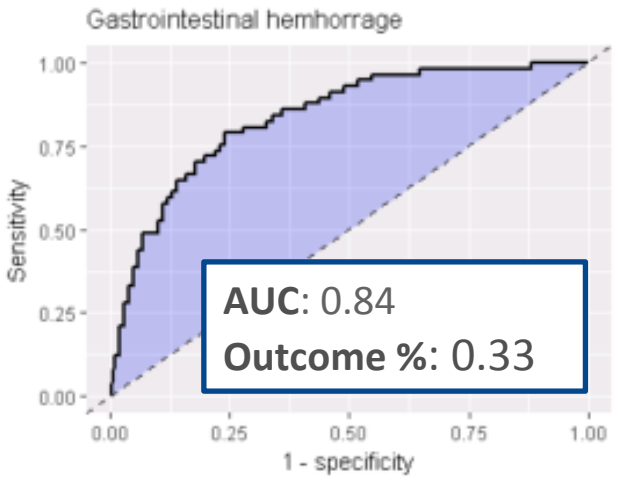
Male and Female Sexual Dysfunction

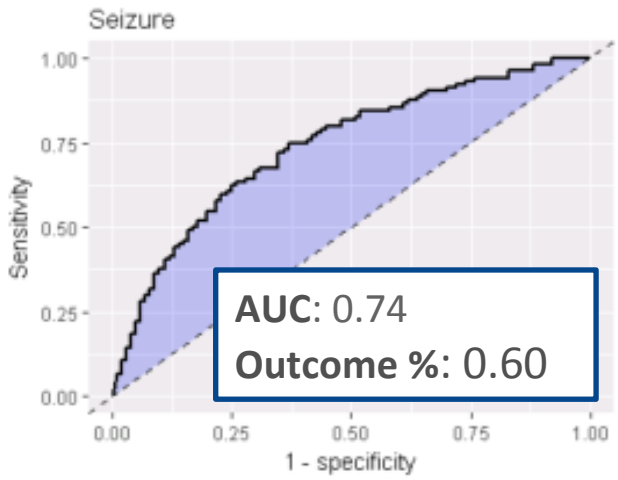
Other Adverse Reactions Observed During the Premarketing Evaluation of ZOLOFT

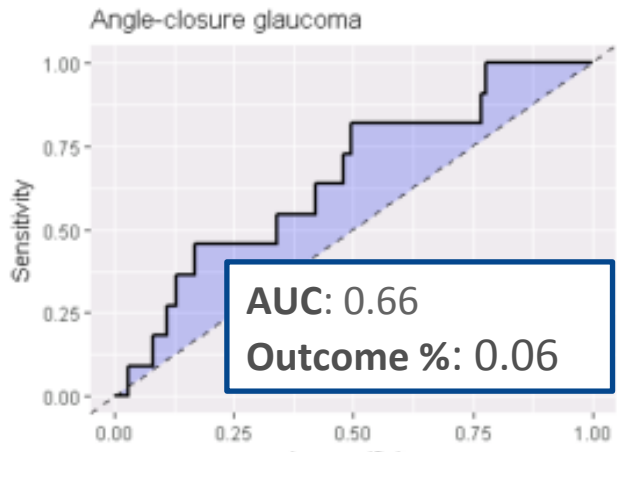
Other infrequent adverse reactions, not described elsewhere in the prescribing information, occurring at an incidence of < 2% in patients treated with ZOLOFT were:

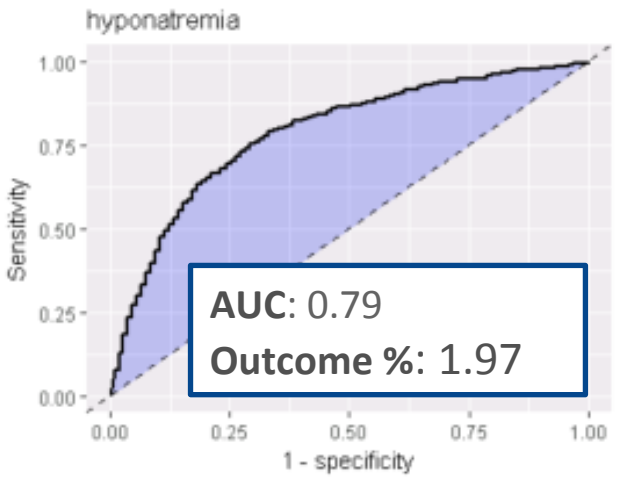
Cardiac disorders – tachycardia
Ear and labyrinth disorders – tinnitus
Endocrine disorders - hypothyroidism
Eye disorders - mydriasis, blurred vision
Gastrointestinal disorders - hematochezia, melena, rectal hemorrhage
General disorders and administration site conditions - edema, gait disturbance, irritability, pyrexia
Hepatobiliary disorders - elevated liver enzymes
Immune system disorders - anaphylaxis
Metabolism and nutrition disorders - diabetes mellitus, hypercholesterolemia, hypoglycemia, increased appetite
Musculoskeletal and connective tissue disorders - arthralgia, muscle spasms, tightness, or twitching
Nervous system disorders - ataxia, coma, convulsion, decreased alertness, hypoesthesia, lethargy,

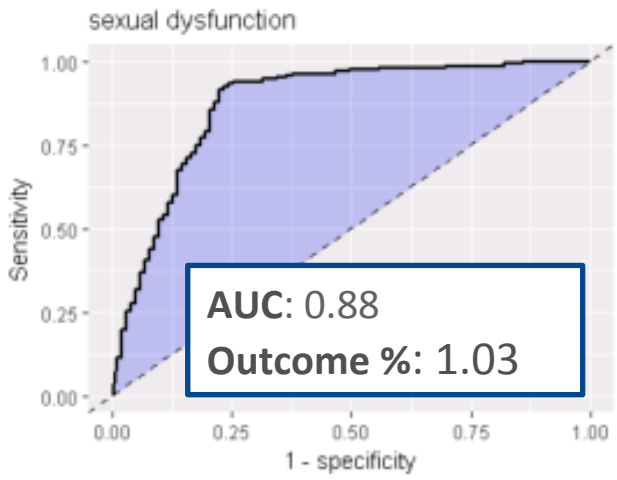
The Patient-Level Prediction framework can be consistently applied to each outcome of interest

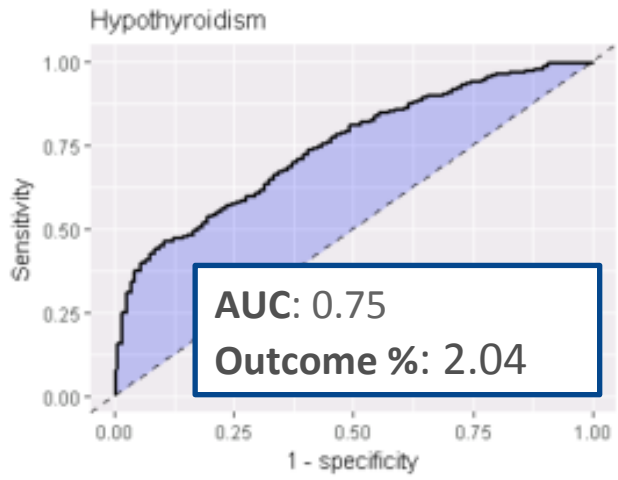












How can these models be useful to a patient?

Outcome of interest	Population average
Suicidal thoughts and behaviors	3.0%
Hypothyroidism	2.0%
Hyponatremia	1.9%
Sexual dysfunction	1.0%
Seizure	0.60%
Gastrointestinal hemhorrage	0.33%
Angle-closure glaucoma	0.06%

Rare: 0.01% <= p <0.1%

Uncommon: 0.1% <= p <1%

Common: 1% <= p <10%

Very common: p >= 10%

How can these models be useful to a patient?

Outcome of interest	Population average	Patient story	Personalized risk
Suicidal thoughts and behaviors	3.0%	18 year-old female with history of skin cancer and recurrent bouts of anxiety requiring psychotherapy	↑ 14.6%
Hypothyroidism	2.0%		↓ 0.76%
Hyponatremia	1.9%		↓ 0.93%
Sexual dysfunction	1.0%		↓ 0.05%
Seizure	0.60%		0.28%
Gastrointestinal hemhorrage	0.33%		↓ 0.07%
Angle-closure glaucoma	0.06%		0.03%

Rare: 0.01% <= p <0.1%

Uncommon: 0.1% <= p <1%

Common: 1% <= p <10%

Very common: p >= 10%

How can these models be useful to a patient?

Outcome of interest	Population average	Patient story	Personalized risk
Suicidal thoughts and behaviors	3.0%	76 year-old male with liver disease, gout, diverticulitis, who was recently diagnosed with pancreatic cancer	5.18%
Hypothyroidism	2.0%		2.28%
Hyponatremia	1.9%		23.97%
Sexual dysfunction	1.0%		6.75%
Seizure	0.60%		10.06%
Gastrointestinal hemhorrage	0.33%		2.42%
Angle-closure glaucoma	0.06%		0.15%

Rare: 0.01% <= p <0.1%

Uncommon: 0.1% <= p <1%

Common: 1% <= p <10%

Very common: p >= 10%

How can these models be useful to a patient?

Outcome of interest	Population average	Patient story	Personalized risk
Suicidal thoughts and behaviors	3.0%	79 year-old female with comorbid obesity, Type 2 diabetes mellitus, atrial fibrillation, congestive heart failure, and prior usage of NSAIDs	0.77%
Hypothyroidism	2.0%		31.67%
Hyponatremia	1.9%		6.65%
Sexual dysfunction	1.0%		0.15%
Seizure	0.60%		0.40%
Gastrointestinal hemhorrage	0.33%		0.64%
Angle-closure glaucoma	0.06%		0.07%

Rare: 0.01% <= p <0.1%

Uncommon: 0.1% <= p <1%

Common: 1% <= p <10%

Very common: p >= 10%

How can these models be useful to a patient?

Outcome of interest	Population average	Patient story	Personalized risk
Suicidal thoughts and behaviors	3.0%	75 year-old female with multiple comorbidities (hypertension, GERD, hyperlipidemia) Multiple ER visits and hospital admissions in the prior year, including recent admission for heart failure and renal failure	3.75%
Hypothyroidism	2.0%		6.52%
Hyponatremia	1.9%		↑ 10.34%
Sexual dysfunction	1.0%		↓ 0.12%
Seizure	0.60%		↑ 2.64%
Gastrointestinal hemhorrage	0.33%		↑ 4.65%
Angle-closure glaucoma	0.06%		↑ 0.17%

Rare: 0.01% <= p <0.1%

Uncommon: 0.1% <= p <1%

Common: 1% <= p <10%

Very common: p >= 10%

Who is the population average helpful for?

Outcome of interest	Population average
Suicidal thoughts and behaviors	3.0%
Hypothyroidism	2.0%
Hyponatremia	1.9%
Sexual dysfunction	1.0%
Seizure	0.60%
Gastrointestinal hemhorrage	0.33%
Angle-closure glaucoma	0.06%

In absence of any other information, the incidence of outcomes can be useful to prioritize risks when evaluating benefit-risk profile

However, at best, the 'population average' only applies to 6% of the population…

94% of patients have at least one outcome with a personalized risk that is at least an order-of-magnitude different from the population average

Rare: 0.01% <= p <0.1%

Uncommon: 0.1% <= p <1%

Common: 1% <= p <10%

Very common: p >= 10%

Conclusions

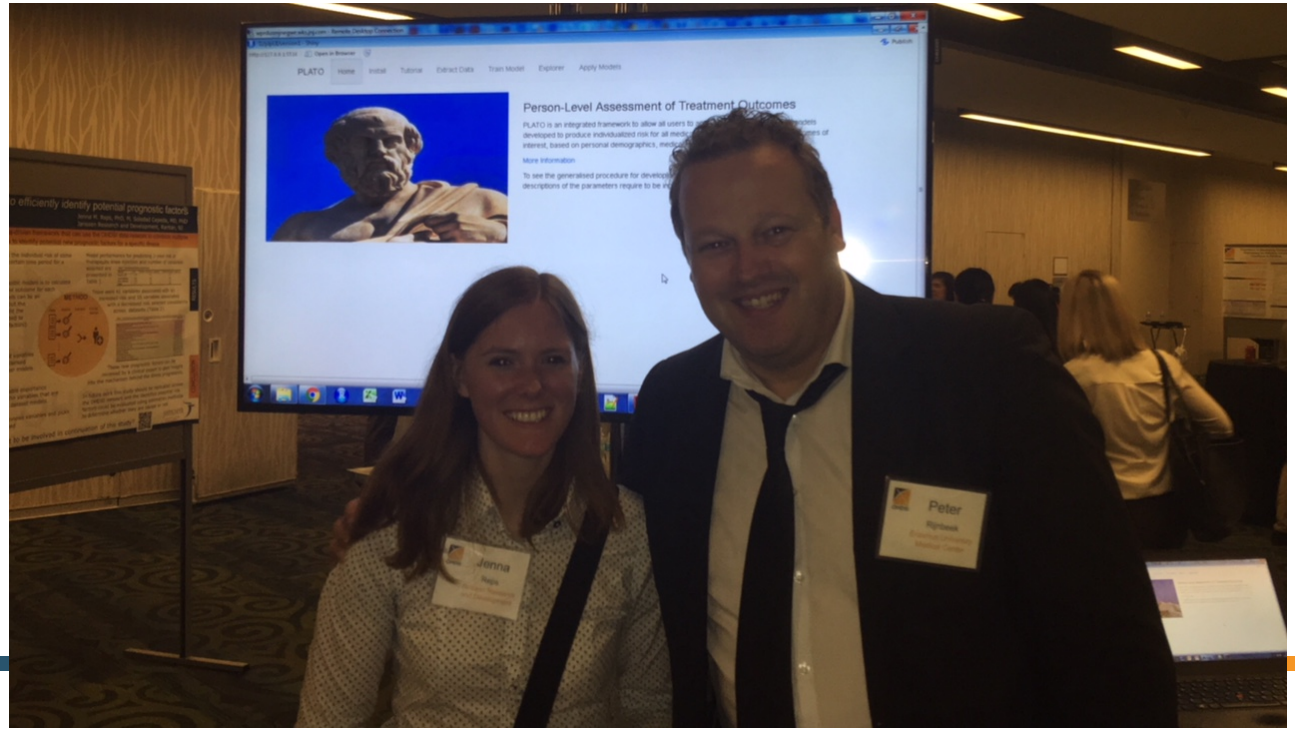
- Patient-level prediction can complement our existing work in clinical characterization and population-level estimation to better understand the potential risk of potential side effects in patients with depression

- Patient-level prediction can advance the notion of ‘precision medicine’ by identifying the subpopulations at high and low risk and managing treatment decisions accordingly

- This does not have to be a ‘post hoc’ research endeavor but could be integrated into the healthcare delivery system itself

OHDSI PatientLevelPrediction Workgroup

- We need contributions from *many* disciplines: clinicians, statisticians, machine learning experts, data custodians, etc.
- Join the PatientLevelPrediction workgroup



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