AI/ML-ENHANCED NEWBORN SCREENING

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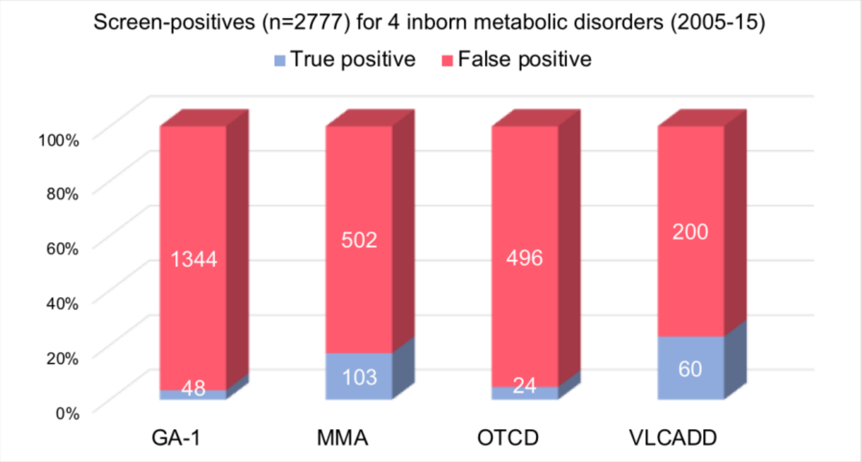
Financial Disclosure

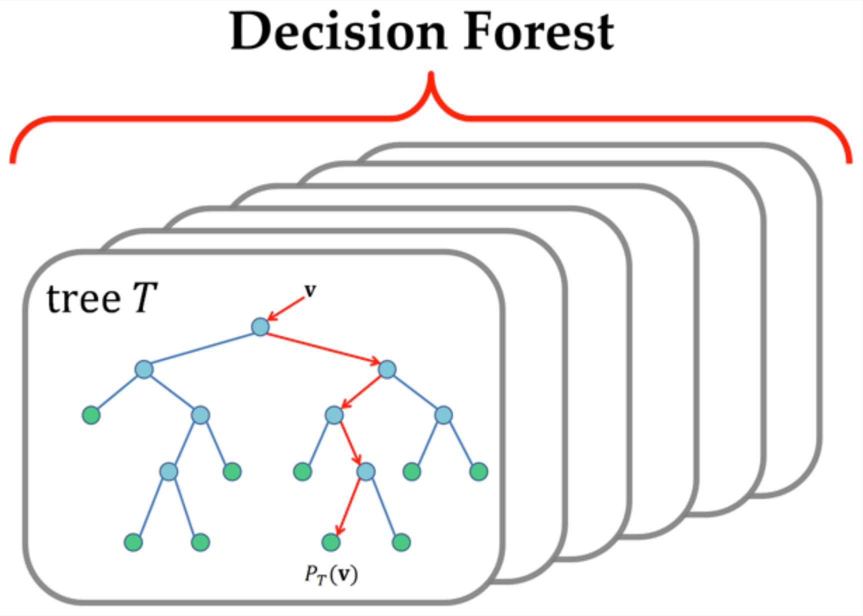
“Nothing to disclose”

Learning objectives

Recognize the inherent metabolic variations among individuals



Review the challenge of false positive results in genetic disease screening



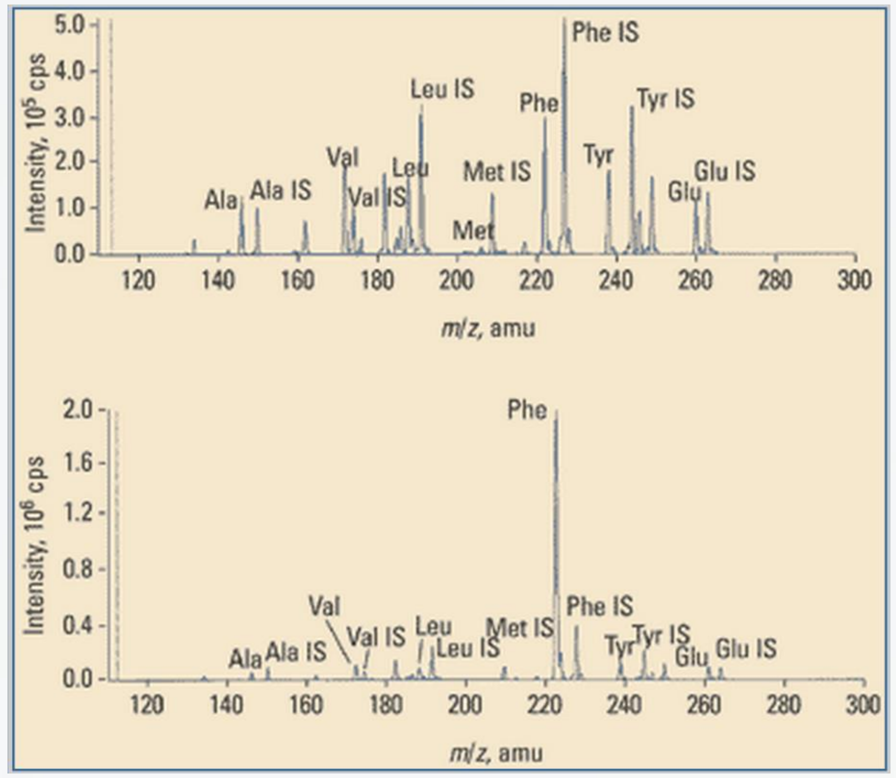
Validate and employ AI/ML-based tools to improve screening accuracy

Newborn screening: The process

Sample collection
Hospital

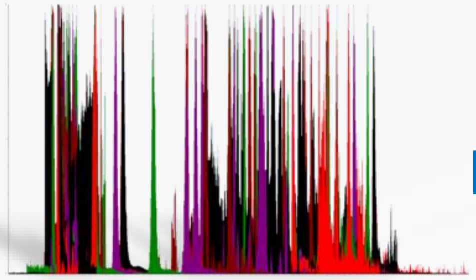
Screening
State NBS lab

Confirmation
Hospital/State



Neg.

Pos.



Neg.

Pos.

Diagnosis
Treatment

Dried blood spot (DBS) card collected 24-48 hrs. after birth

40 metabolites, 60 diseases (Recommended Uniform Screening Panel (**RUSP**)

>90% false positives

Long turnaround time
Diagnostic delays

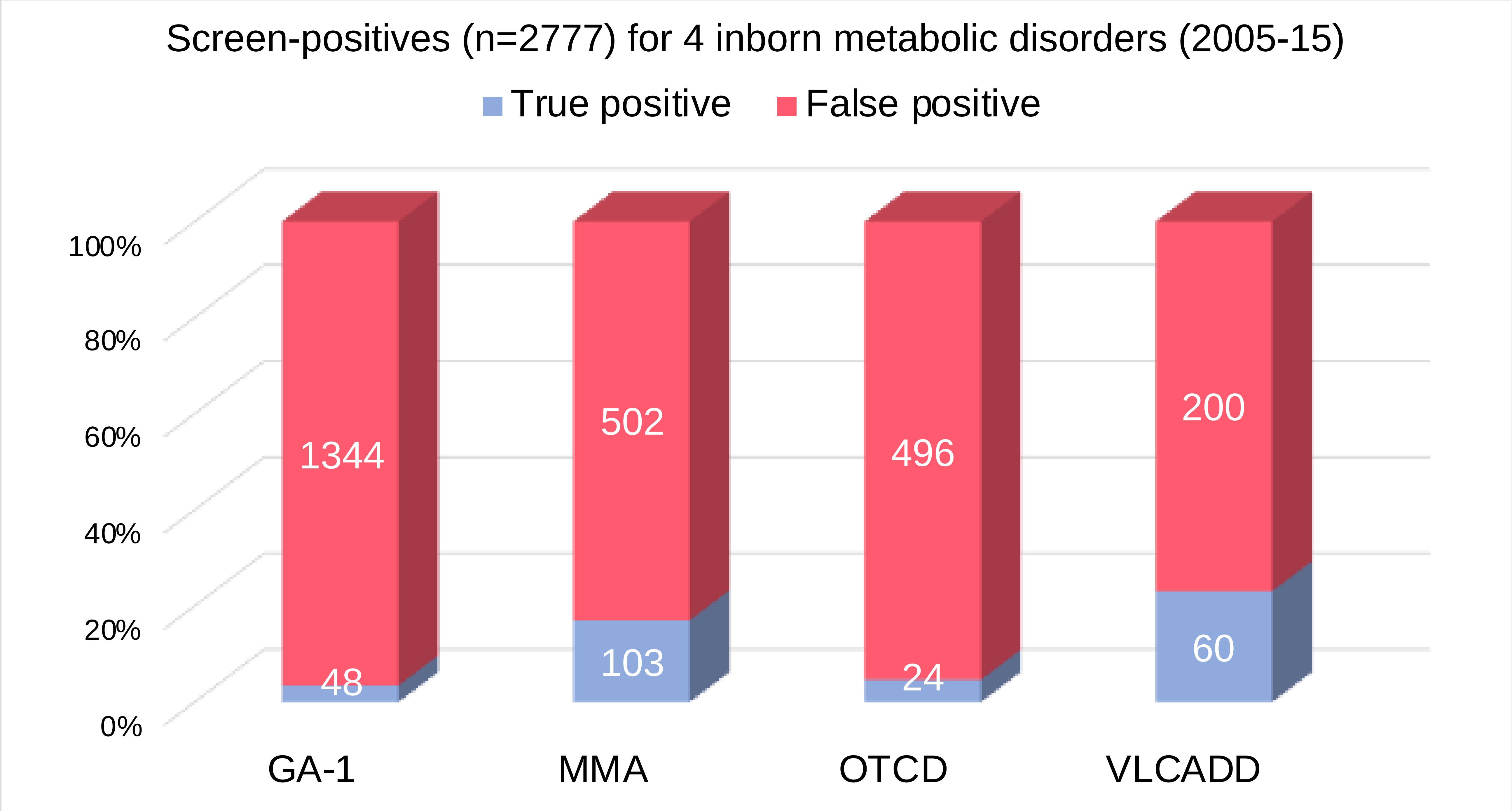
False positives are a major challenge in newborn screening

- >12,000 babies identified each year to receive treatment and longitudinal follow-up
- Most infants identified with a condition in NBS are completely healthy at birth and have no family history of a rare disorder.
- ~50 false-positives for every true-positive in the US (Kwon & Farrell, JAMA 2000)
- Resolving FP cases can take weeks to months, even years in some cases.

Association of Public Health Laboratories (APHL)

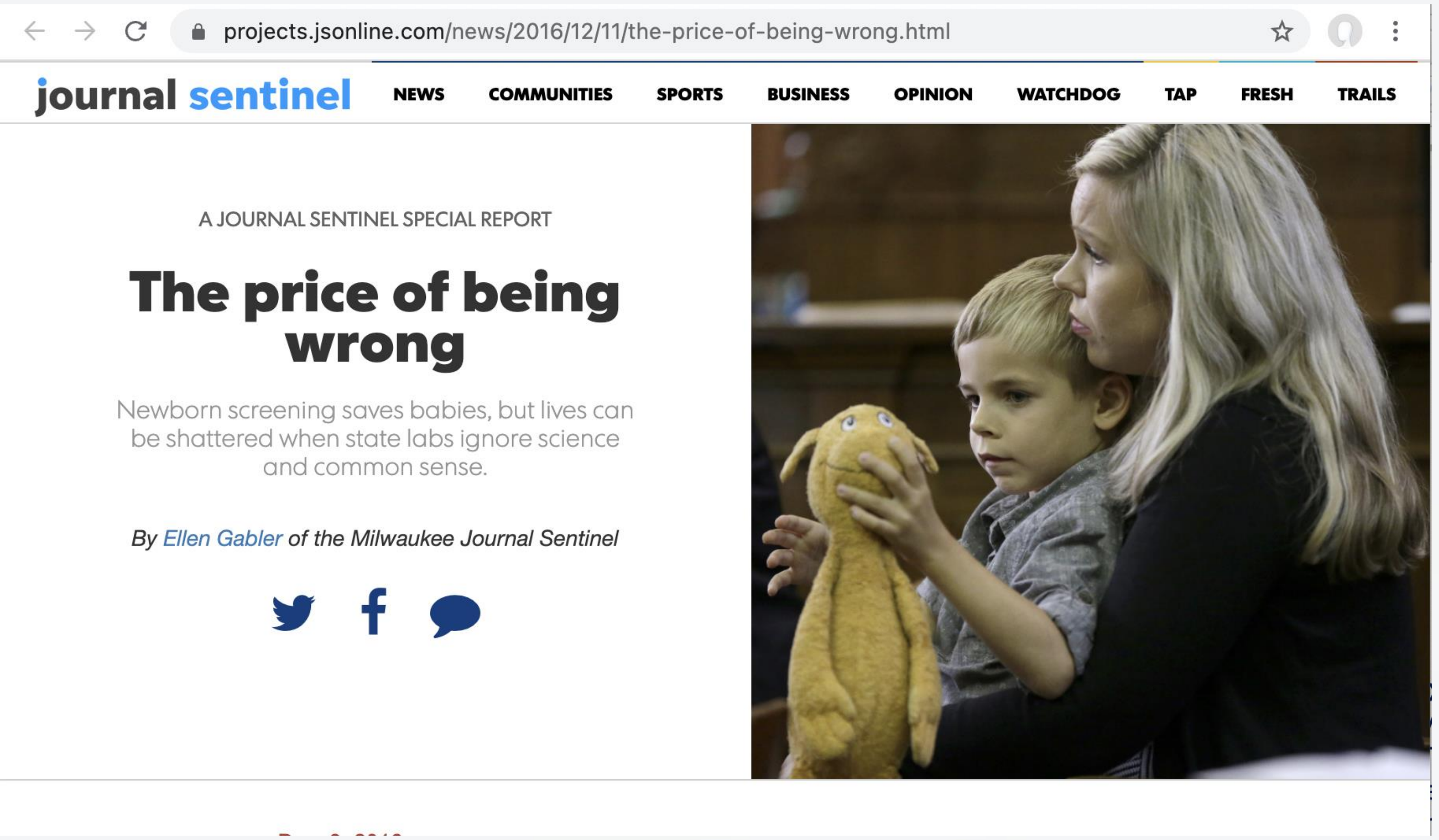
Reduce false positives
Reduce diagnostic delays
Lower cost of screening

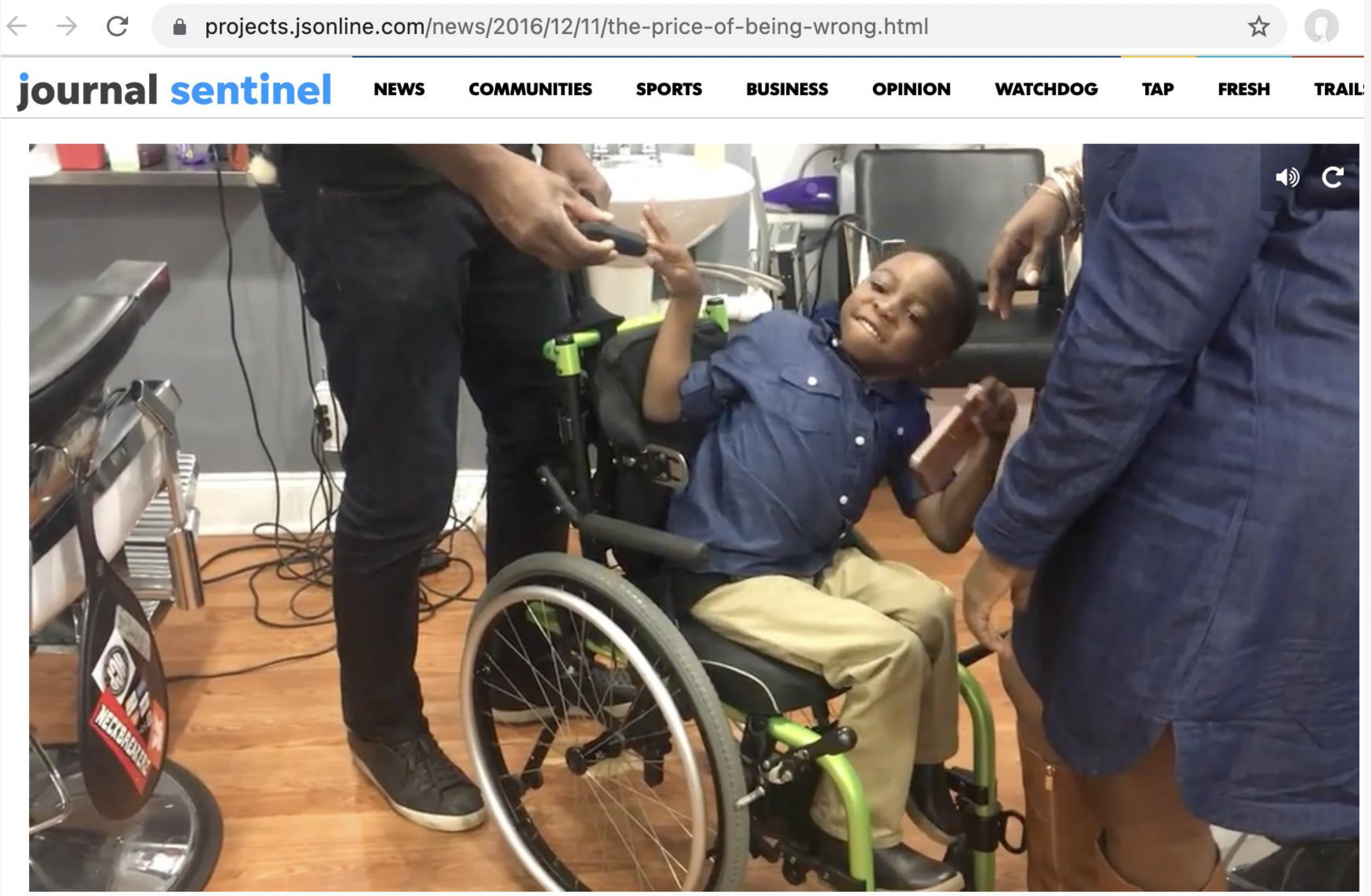
NBS for GA-1 has many false-positives with a ratio of 29 infants without to 1 infant with the disease



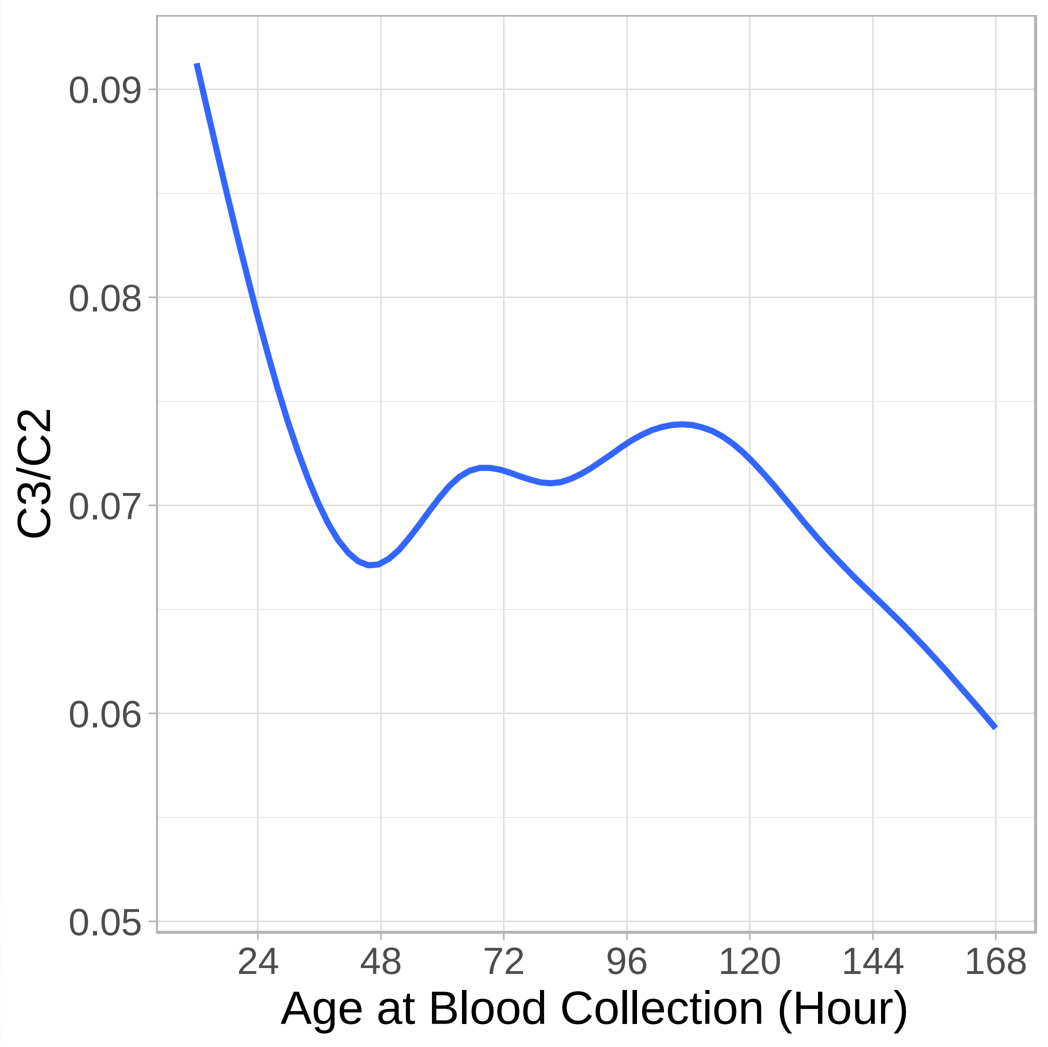
PPV (TP/TP+FP):	3%	17%	5%	23%

False-negative results and time of blood collection



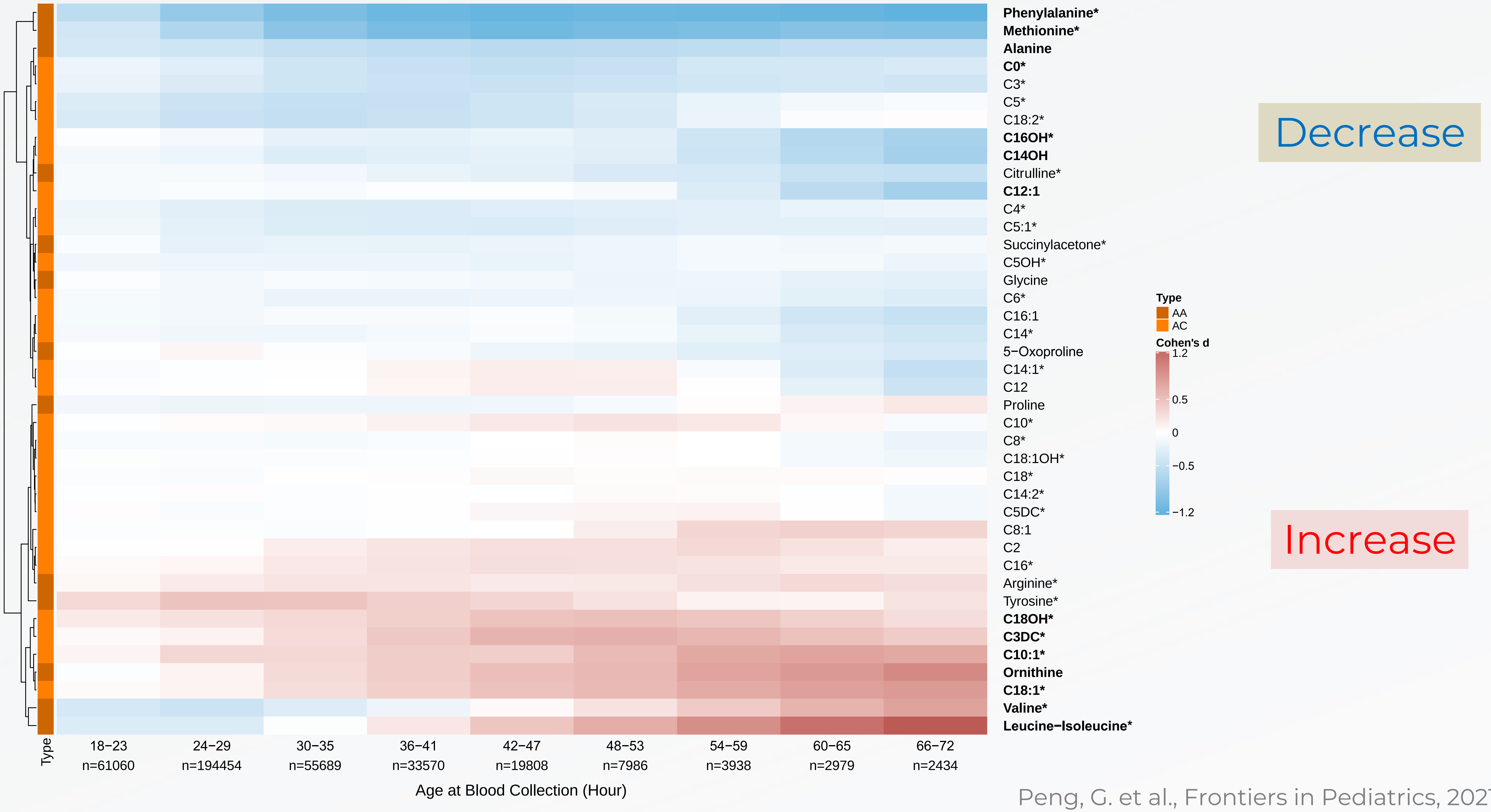


- Two infants tested pos for MMA after birth, but neg in follow-up testing several days later
- It was unknown at that time that the 1st test was a TP while the 2nd test was a FN
- C3/C2 levels (MMA) decrease after birth



Peng, G., et al., Frontiers in Pediatrics, 2021.

Timing of Newborn Blood Collection Alters Metabolic Disease Screening Performance

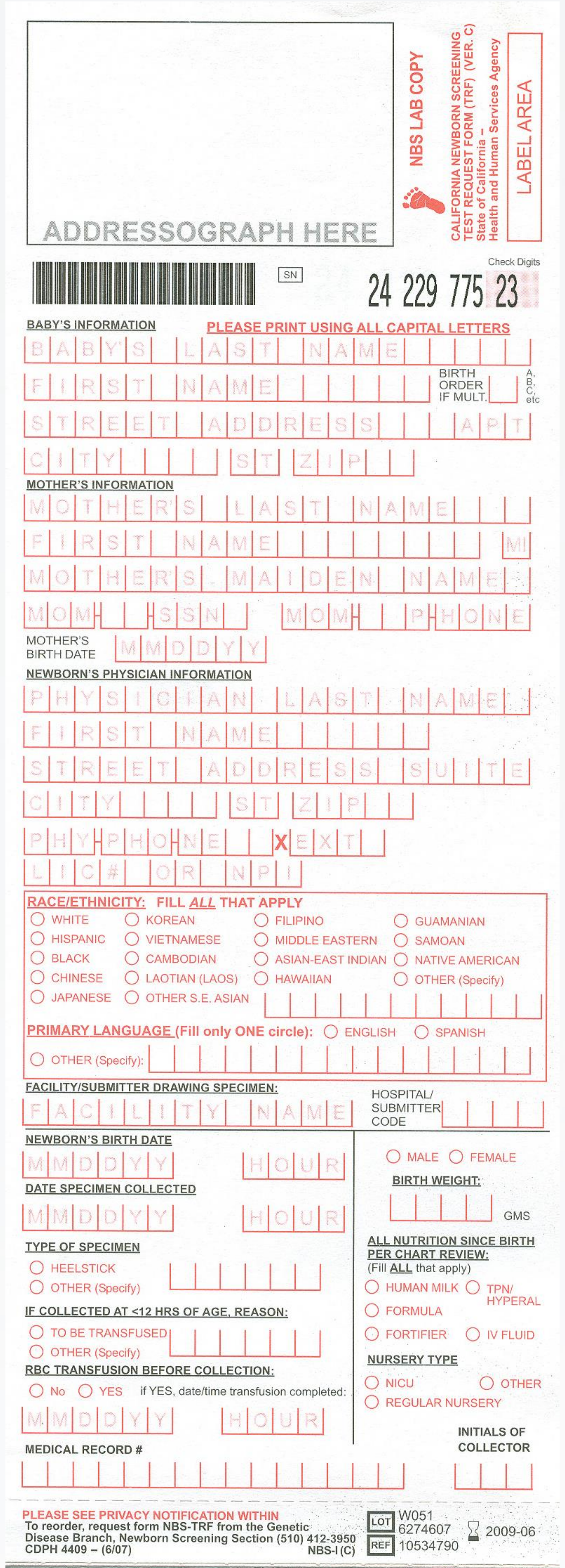


56% (23 of 41 analytes) with AaBC-related differences

Peng, G. et al., Frontiers in Pediatrics, 2021.

Blood metabolite levels are influenced by several clinical variables (covariates). This can lead to FP screens.

- Age at blood collection
- Birth weight
- Gestational age
- Infant sex
- Parent-reported ethnicity
- Maternal age
- Season of birth
- Transfusion status
- Total parenteral nutrition



ADDRESSOGRAPH HERE

NBS LAB COPY

CALIFORNIA NEWBORN SCREENING TEST REQUEST FORM (TRF) (VER. C)
State of California – Health and Human Services Agency

LABEL AREA

SN

Check Digits

24 229 775 23

BABY'S INFORMATION

PLEASE PRINT USING ALL CAPITAL LETTERS

BABY'S LAST NAME

FIRST NAME

BIRTH ORDER IF MULT. A, B, C, etc

STREET ADDRESS APT

CITY ST ZIP

MOTHER'S INFORMATION

MOTHER'S LAST NAME

FIRST NAME MI

MOTHER'S MAIDEN NAME

MOM-SSN MOM-PHONE

MOTHER'S BIRTH DATE MMDDYY

NEWBORN'S PHYSICIAN INFORMATION

PHYSICIAN LAST NAME

FIRST NAME

STREET ADDRESS SUITE

CITY ST ZIP

PHY-PHONE X EXT

LIC# OR NPI

RACE/ETHNICITY: FILL ALL THAT APPLY

WHITE / HISPANIC / BLACK / CHINESE / JAPANESE / KOREAN / VIETNAMESE / CAMBODIAN / LAOTIAN (LAOS) / OTHER S.E. ASIAN / FILIPINO / MIDDLE EASTERN / ASIAN-EAST INDIAN / HAWAIIAN / GUAMANIAN / SAMOAN / NATIVE AMERICAN / OTHER (Specify)

PRIMARY LANGUAGE (Fill only ONE circle): ENGLISH / SPANISH / OTHER (Specify):

FACILITY/SUBMITTER DRAWING SPECIMEN:

FACILITY NAME

HOSPITAL/ SUBMITTER CODE

NEWBORN'S BIRTH DATE MMDDYY HOUR

MALE / FEMALE

BIRTH WEIGHT: GMS

DATE SPECIMEN COLLECTED MMDDYY HOUR

TYPE OF SPECIMEN

HEELSTICK / OTHER (Specify)

ALL NUTRITION SINCE BIRTH PER CHART REVIEW: (Fill ALL that apply)

HUMAN MILK / TPN/ HYPERAL / FORMULA / FORTIFIER / IV FLUID

IF COLLECTED AT <12 HRS OF AGE, REASON:

TO BE TRANSFUSED / OTHER (Specify)

NURSERY TYPE

NICU / OTHER / REGULAR NURSERY

RBC TRANSFUSION BEFORE COLLECTION:

No / YES if YES, date/time transfusion completed: MMDDYY HOUR

MEDICAL RECORD #

INITIALS OF COLLECTOR

PLEASE SEE PRIVACY NOTIFICATION WITHIN
To reorder, request form NBS-TRF from the Genetic Disease Branch, Newborn Screening Section (510) 412-3950
CDPH 4409 – (6/07) NBS-I (C)

LOT W051 6274607 2009-06
REF 10534790

Development of AI/ML-based tools to improve screening accuracy

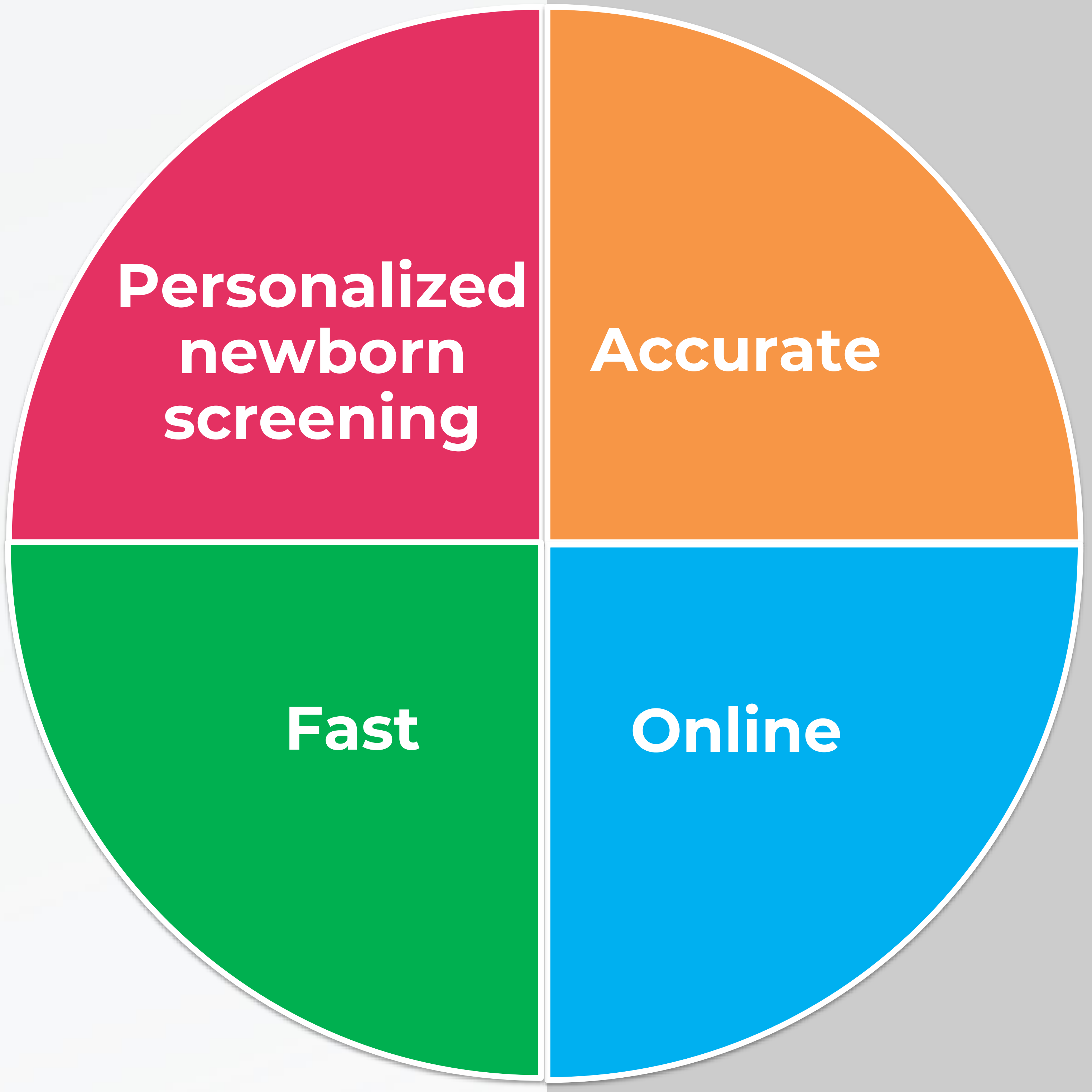
1. Curated Database: dbRUSP

https://rusptools.shinyapps.io/dbRUSP/

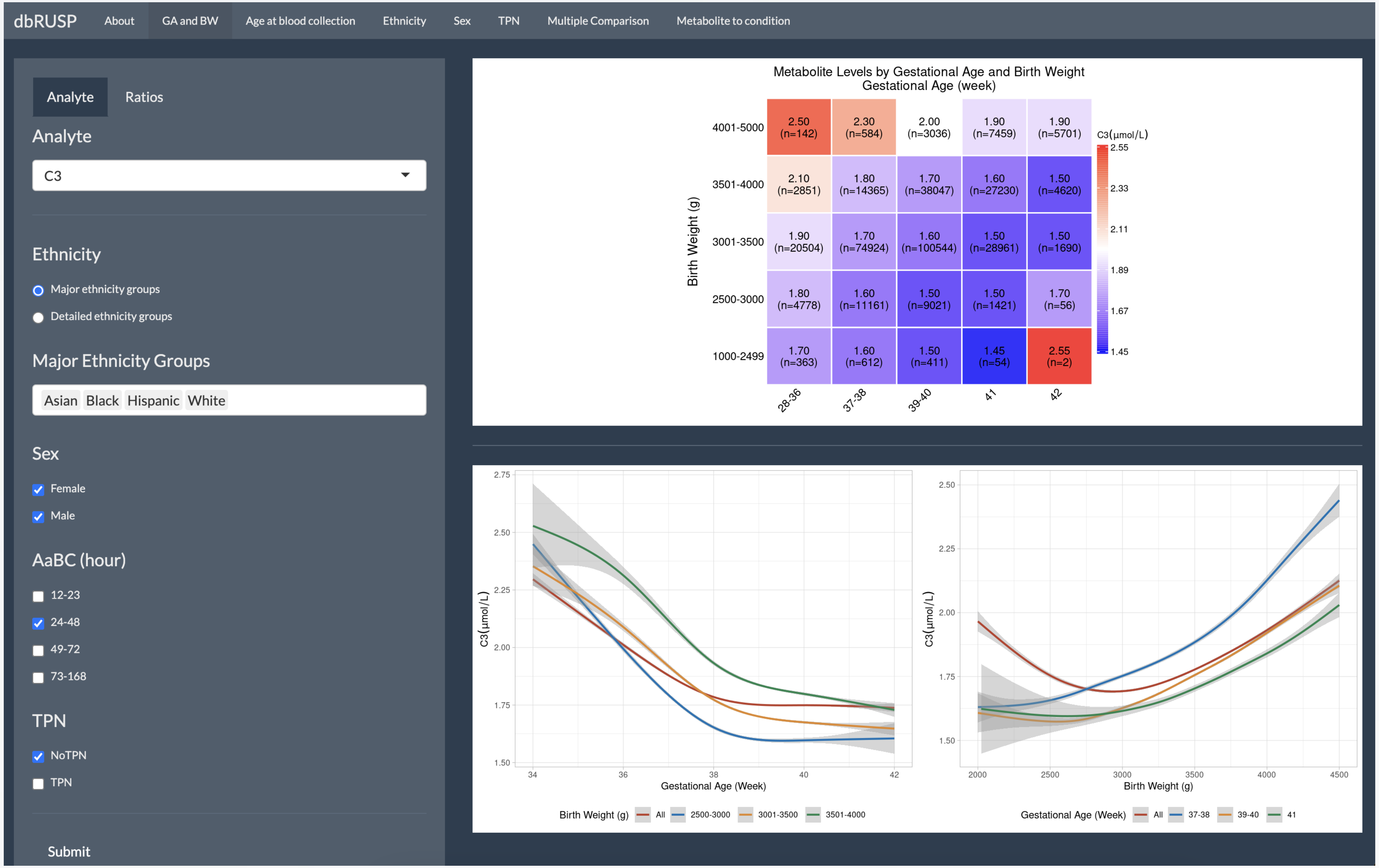
1. >500K screen-negative, healthy newborns
2. >3000 screen-positive cases for IMD
3. Develop in partnership with state NBS programs

2. AI/ML online software: RUSPtools

https://rusptools.shinyapps.io/RandomForest/



dbRUSP: Influence of covariates on metabolite levels



Peng, G. et al., IJNS, 2022

dbRUSP: Analysis of joint effects of multiple variables on metabolite levels

Analyte(s) Ratios

Analyte

Valine Citrulline C3

Birth Weight (g)

3501-4000

Gestational Age (week)

39-40

Ethnicity

- Major ethnicity groups
- Detailed ethnicity groups

Major Ethnicity Groups

Black

Sex

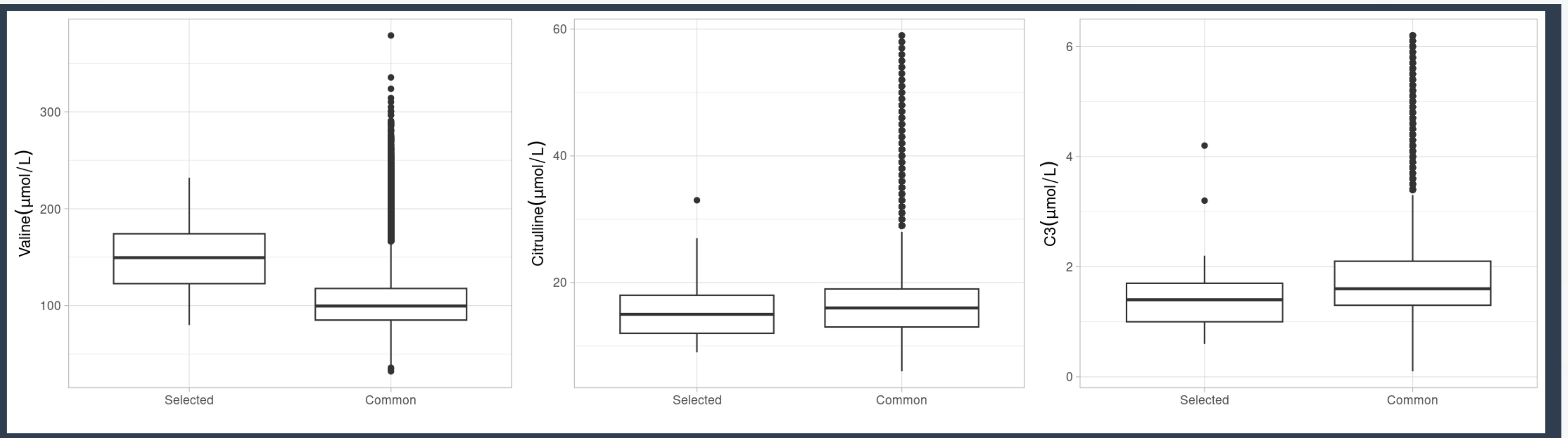
Male

AaBC (hour)

73-168

Status of Total Parenteral Nutrition

NoTPN



Show 10 entries Search:

	Mean		Median			
	Selected	Common	Selected	Common	Cohen's d	95% CI
Valine	152.32	103.74	149.50	99.60	1.84	1.55, 2.12
Citrulline	16.09	16.53	15.00	16.00	-0.10	-0.38, 0.19
C3	1.43	1.74	1.40	1.60	-0.46	-0.75, -0.18

Showing 1 to 3 of 3 entries

Previous 1 Next

Selected group (n=47):
Birth Weight: 3501-4000
Gestational age: 39-40
Ethnicity groups: Black
Age at Blood Collection: 73-168
Sex: Male
Total parenteral nutrition (TPN): NoTPN

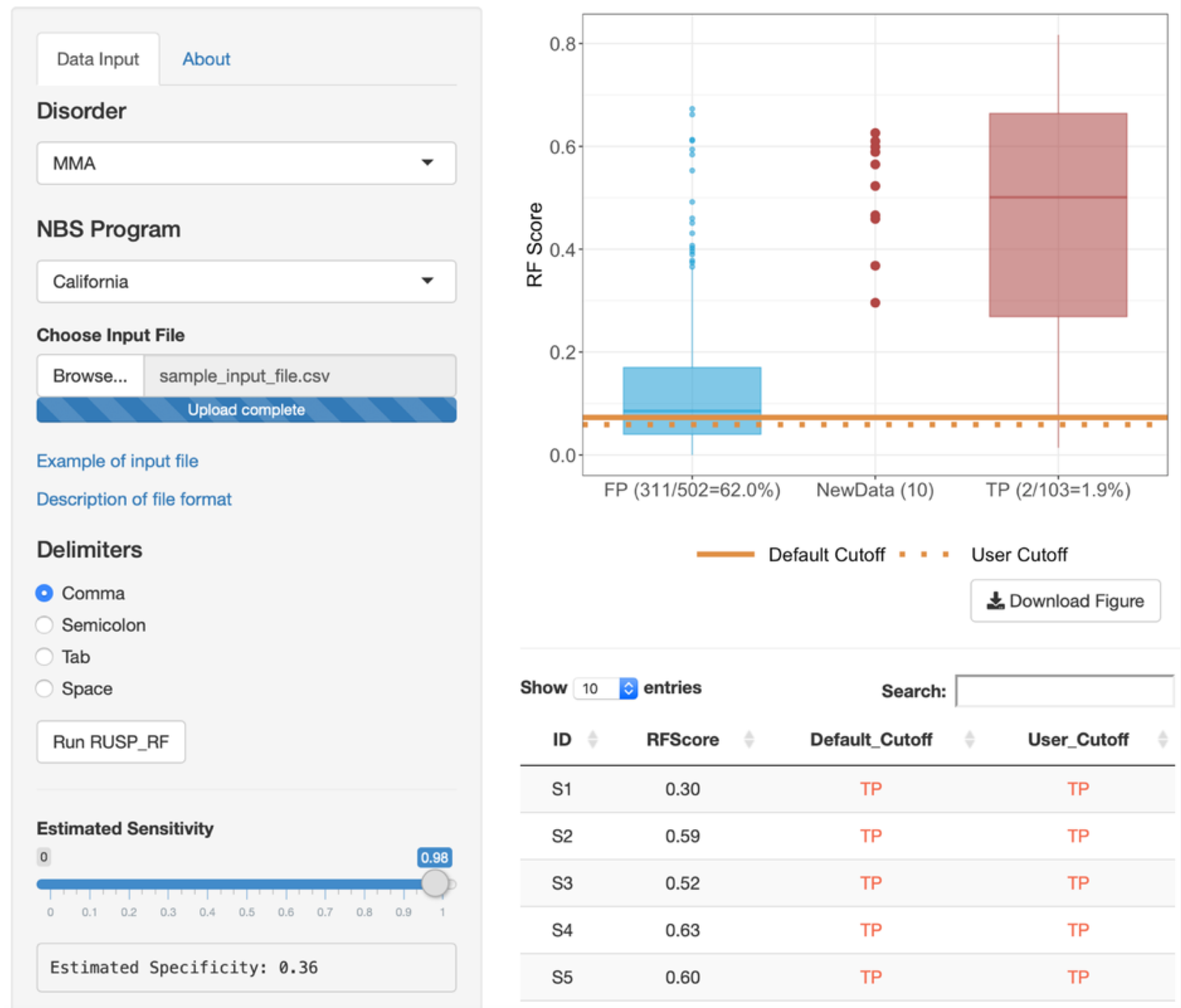
Common group (n=305674):
Birth weight: 2500-4000g
Gestational age: 37-41 weeks
Age at blood collection: 24-48 hours
TPN: NoTPN

https://rusptools.shinyapps.io/dbRUSP/

Peng, G. et al., IJNS, 2022

RUSPtools: Reducing false-positives using AI/ML

- RUSPtools employs a Random Forest (RF) machine learning classifier
- Trained using "*real-world*" NBS data of >3000 screen positives (TP and FP) reported by a public state program
- Incorporate entire metabolic profile (all MS/MS markers and ratios) and variables (e.g., BW, GA, sex, AaBC, etc.)
- RF risk score to predict TP and FP at increased specificity
- User-friendly, flexible, expandable, and fast (real-time)
- Learn from the increasing NBS data to continuously improve predictions



ID	RFScore	Default_Cutoff	User_Cutoff
S1	0.30	TP	TP
S2	0.59	TP	TP
S3	0.52	TP	TP
S4	0.63	TP	TP
S5	0.60	TP	TP

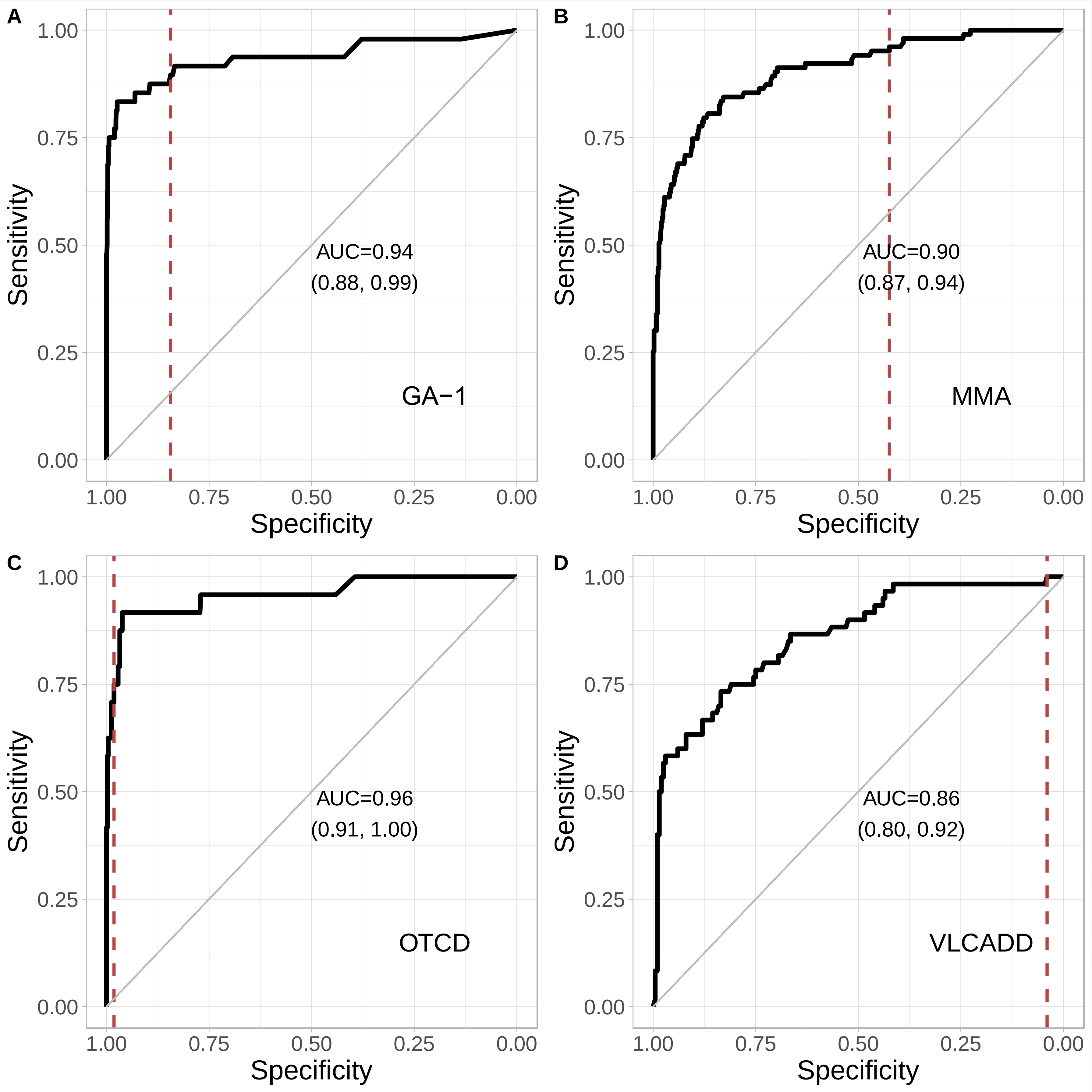
https://rusptools.shinyapps.io/RandomForest/

Peng, G., et al., *IJNS*, 2020.

RUSPtools: Reducing false-positives using AI/ML

89%

45%



98%

2%

Peng, G., et al., *IJNS*, 2020.

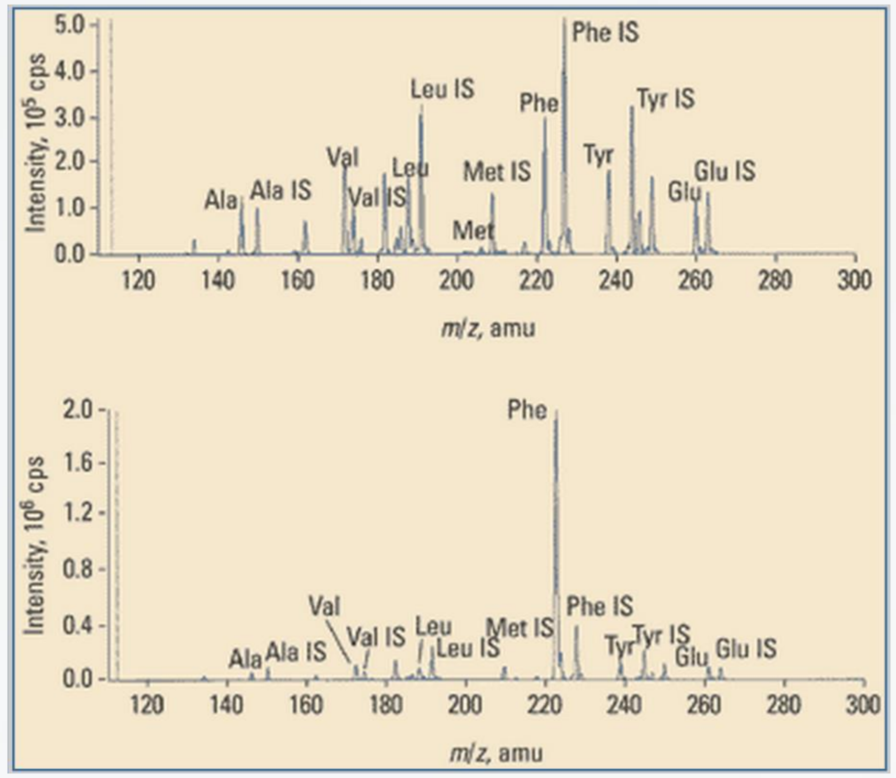
Incorporate AI/ML in newborn screening

RUSPtools (AI/ML)

Sample collection
Hospital

Dried blood spot (DBS) card collected 24-48 hrs. after birth

Screening
State NBS lab

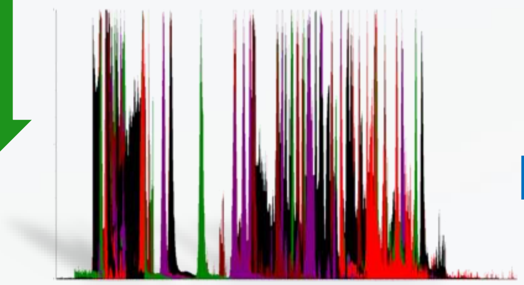


40 metabolites, 60 diseases (Recommended Uniform Screening Panel (**RUSP**)

Neg.

Pos.

Confirmation
Hospital/State



Neg.

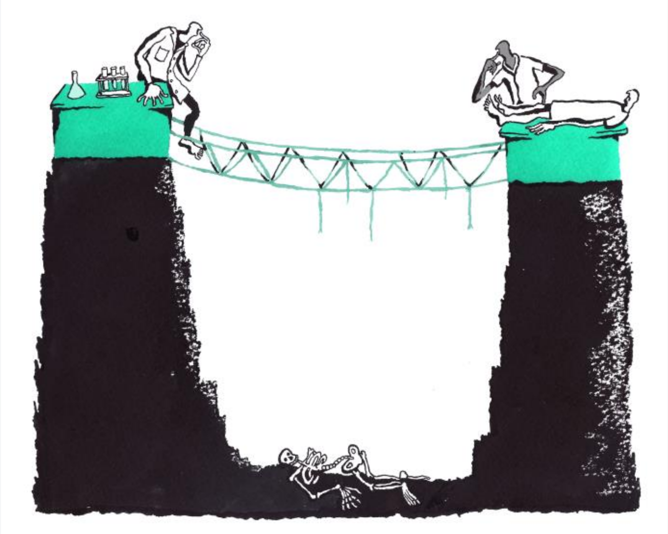
Pos.

Diagnosis
Treatment

Reduce false positives

Reduce TAT and diagnostic delays

Incorporate AI/ML in newborn screening: Challenges and Opportunities



- Metabolism is complex, with nonlinear relation between metabolites and covariates
- Analytical tools used by NBS labs lack capacity to adapt and learn from data
- Finding new links between metabolites and disease risk is difficult for a person, but aligns perfectly for AI/ML algorithms
- Opportunity for AI/ML to augment NBS data analysis in increasingly diverse populations

- To assess the effectiveness of AI/ML tools for NBS requires stages of training, modeling, validation, and ongoing expert supervision post-implementation (unlike self-driving cars)
- Training of AI/ML tools requires large datasets, which presents unique challenges for rare diseases due to their limited sample sizes.
- No current infrastructure allowing states to benchmark their screening performance by comparing program metrics with those of other states.
- Opportunity for cooperation among different state programs to aggregate/share NBS data and expand the datasets for effective training.

- Opportunity to combine AI/ML-enhanced NBS with omics technology (metabolomics, proteomics, sequencing) to improve screening accuracy and risk assessment.