Newborn Screening for Type 1 Diabetes Risk Using Genome Sequencing: The Early Check Experience

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Disclosures

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- Breakthrough T1D with support from Janssen Pharmaceuticals
- Sanofi
- Travere Therapeutics
- Orchard Therapeutics

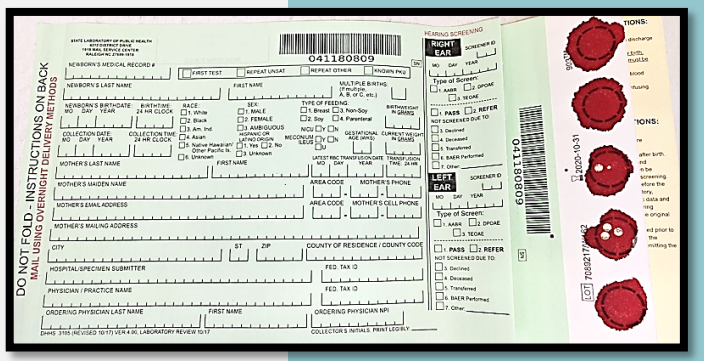
Lab Partner Acknowledgements:

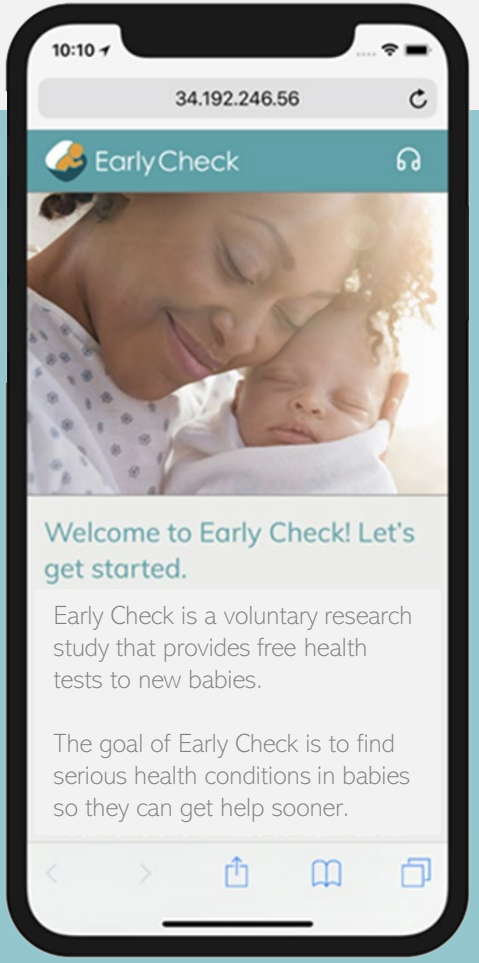
- GeneDx (first 2000 screened)
- Illumina (first 2000 screened)
- Revvity Omics Inc (current)

The findings and conclusions in this presentation are those of the authors and do not necessarily represent the views of the North Carolina Department of Health and Human Services, Division of Public Health.

Early Check – A Newborn Screening Program in North Carolina

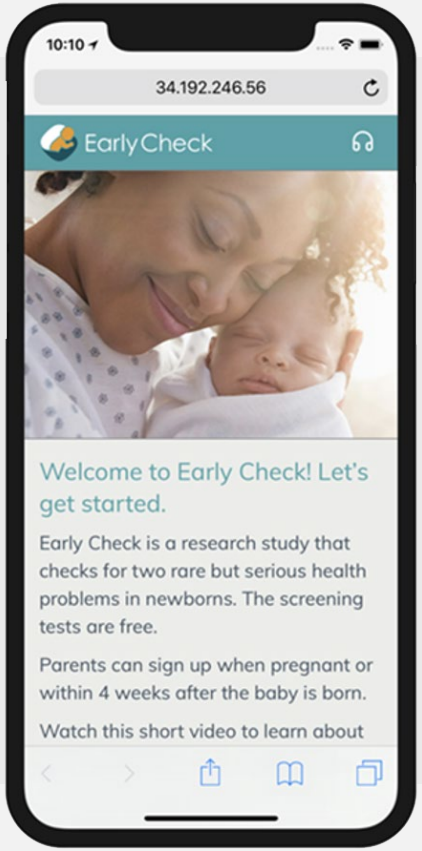
- Researching the feasibility and acceptability of using genome sequencing to screen newborns for monogenic and complex conditions
- Mothers of babies born in North Carolina visit the Early Check website to sign-up
- Uses the state-collected dried blood spot (no additional sample collection needed)

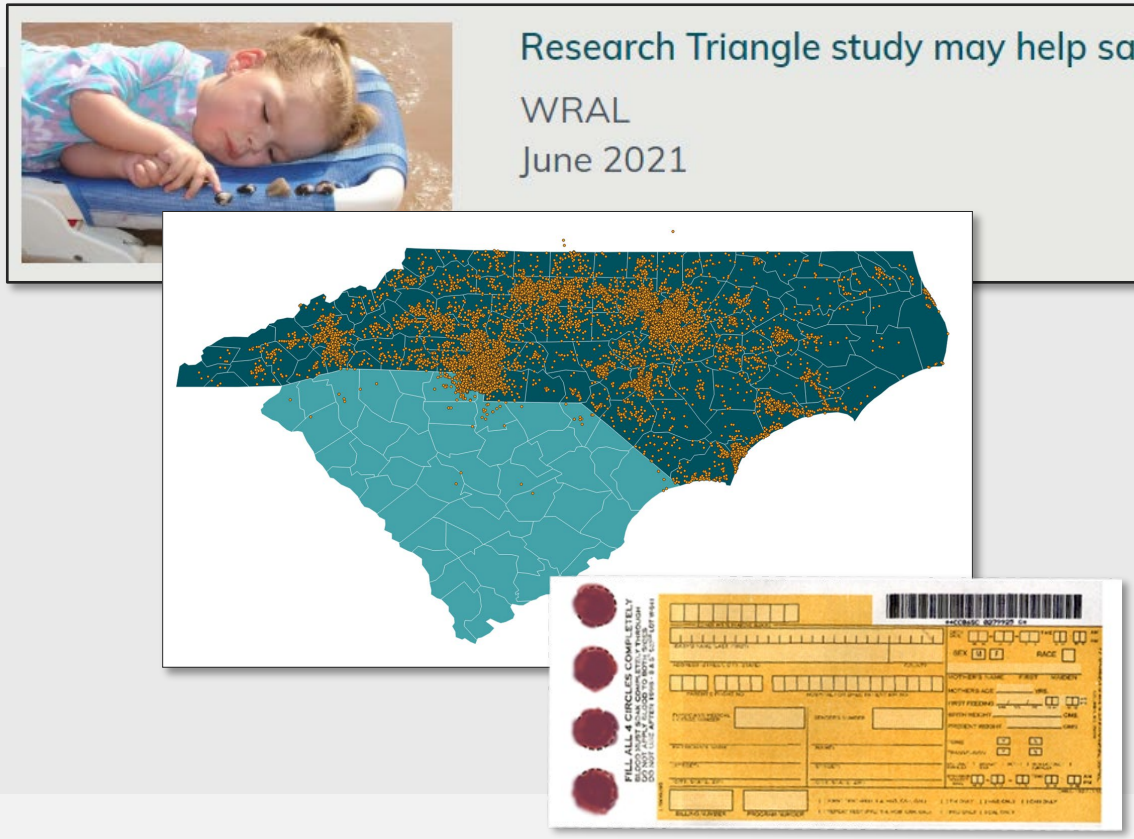




Early Check: A Voluntary Newborn Screening Program

Screened ~ 27,000 newborns in N.C. since 2018

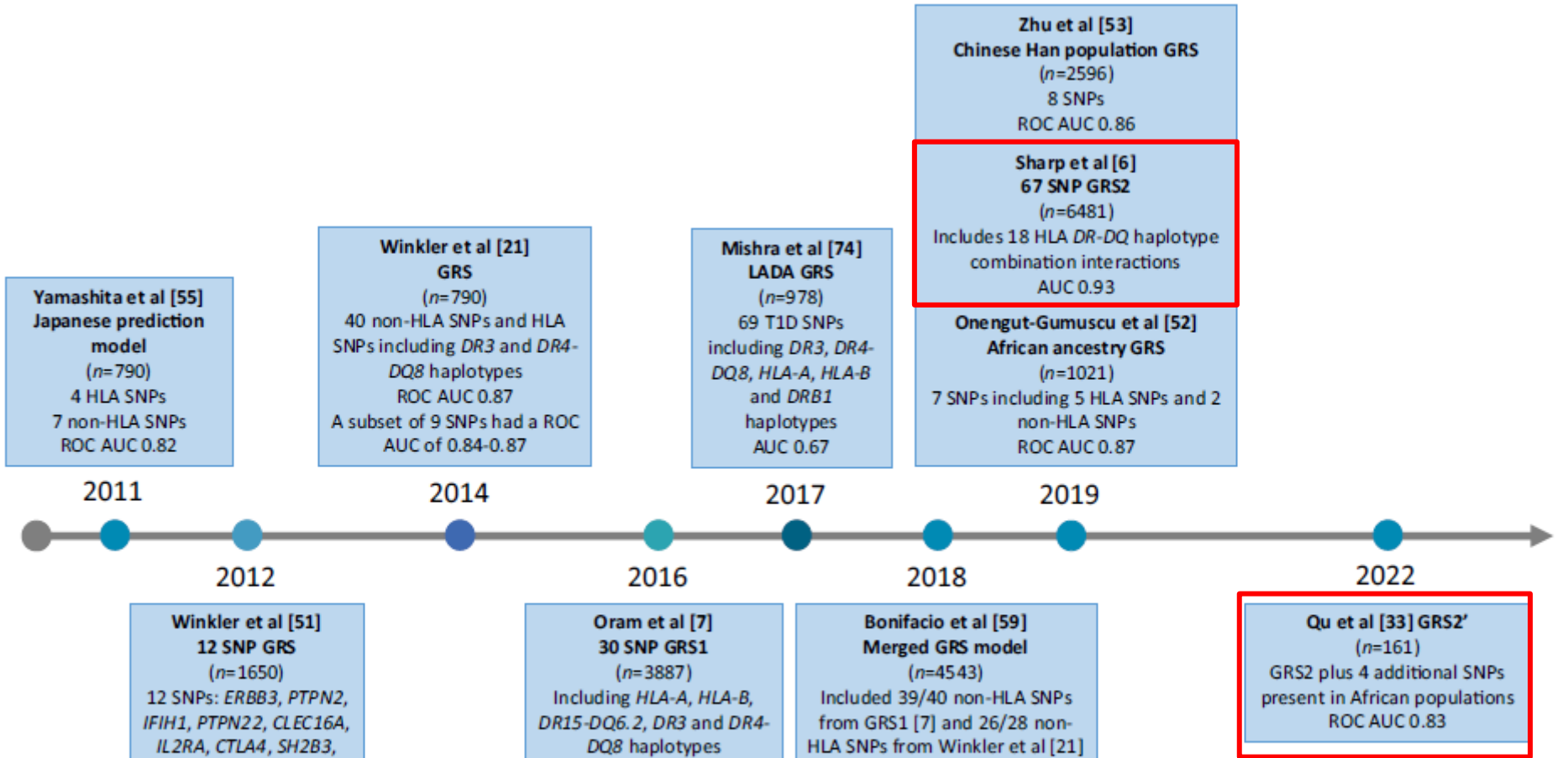




Early Check Panel

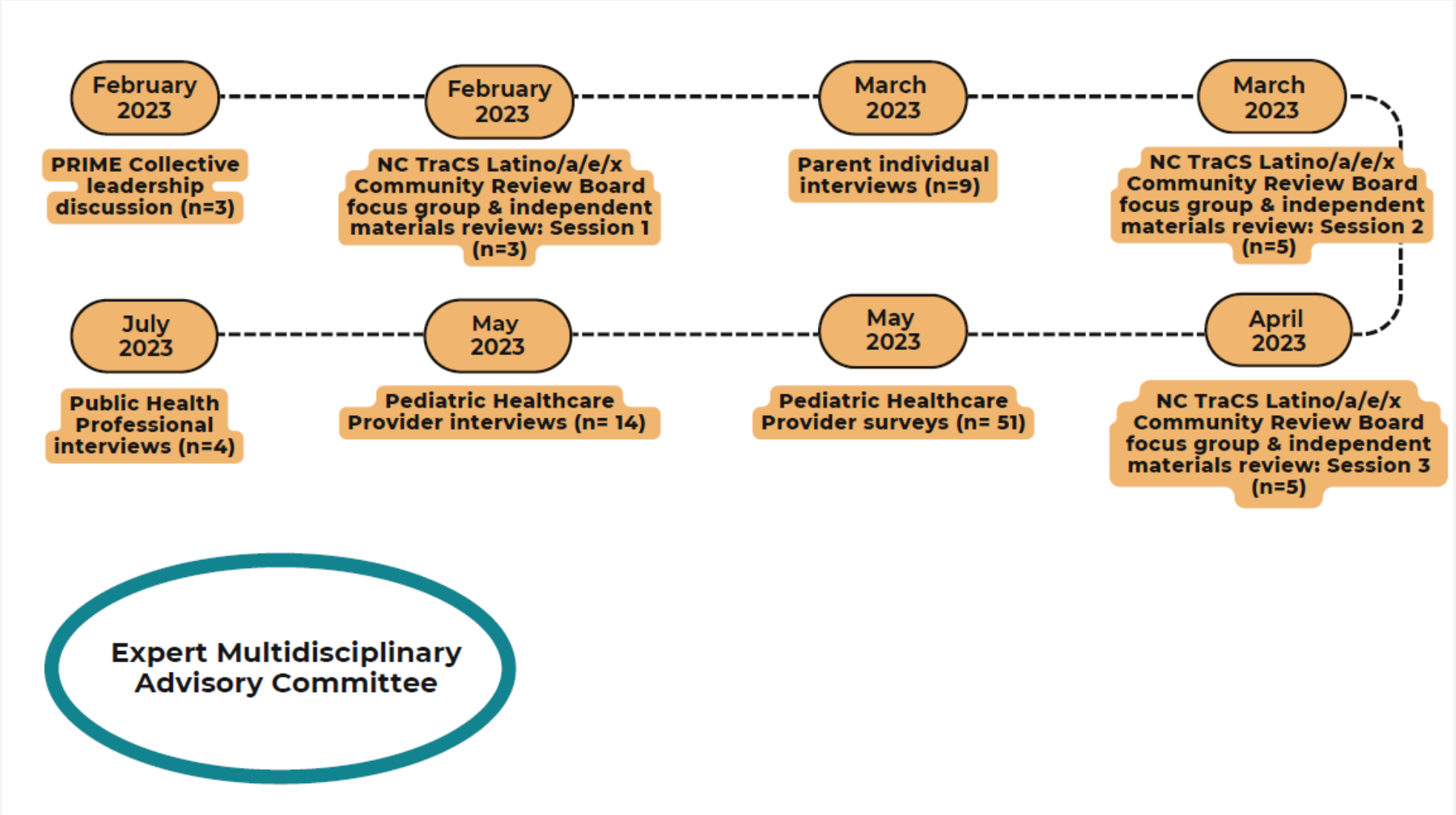
- Duchenne Muscular Dystrophy (DMD) and related conditions
- Fragile X Syndrome (FXS)
- Spinal Muscular Atrophy (SMA)

Selected a Published and Validated GRS



Luckett et al., 2023

Formative Research and Community Engagement Activities



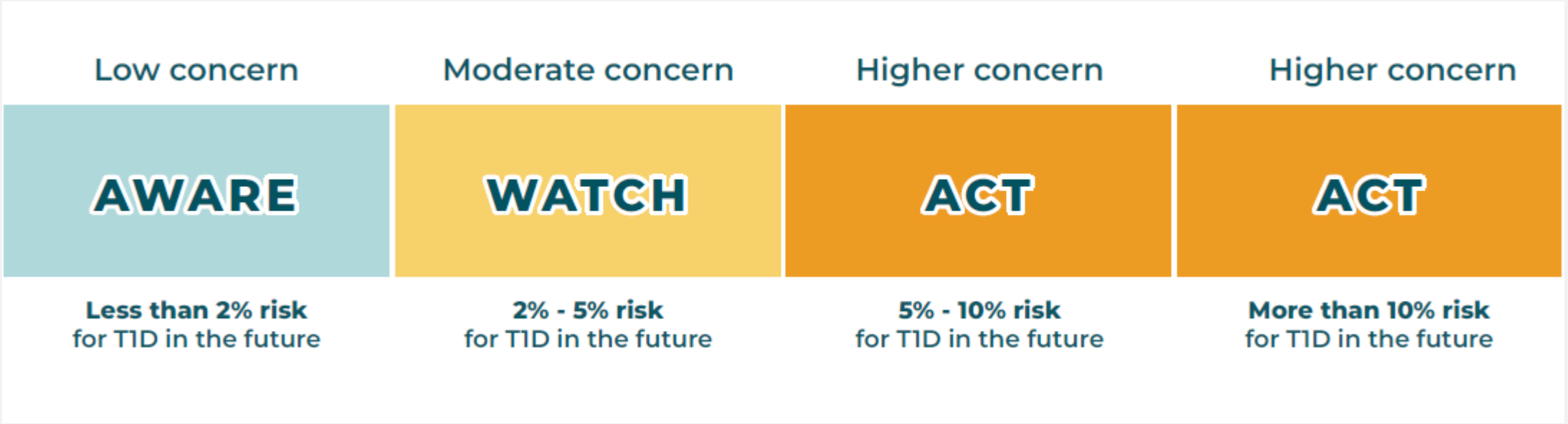
Set GRS Reporting Thresholds

Table 1—Simulated population-based prediction of T1D using HLA screening, the original T1D GRS, and the T1D GRS2

T1D centile*	Population centile**	GRS2	Specificity (%)	Sensitivity (%)	1-Specificity (%)	Youden index (*j*)	T1D risk (%)***
5	70.2	11.68	69.5	94.8	30.5	0.643	0.9
10	79.4	12.36	78.9	89.4	21.1	0.683	1.3
25	90.6	13.45	90.4	77.5	9.6	0.679	2.4
50	96.8	14.60	96.7	53.7	3.3	0.505	4.7
75	99.1	15.65	99.1	30.2	0.9	0.293	9.1
90	99.8	16.54	99.8	13.2	0.2	0.130	15.7
95	99.9	17.06	99.9	7.2	0.1	0.072	22.8

Sharp et al, 2019

Set GRS Reporting Thresholds



T1D Screening Process Overview

Early Check

- Obtain consent in portal
- Match consent to dried blood spot (DBS) specimens at state lab
- Obtain punches from DBS card

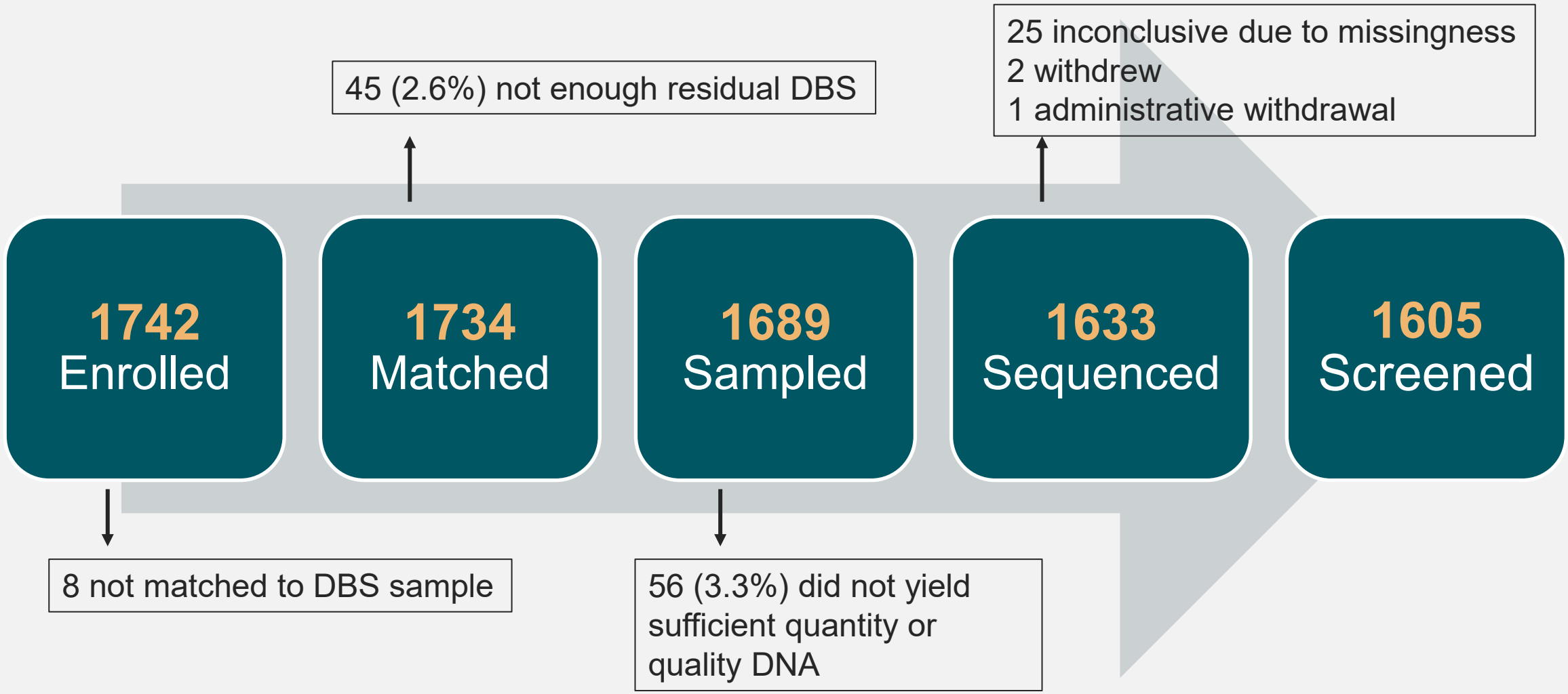
Laboratory Partner

- DNA extraction
- Genome sequencing
- Prepare genome data and send to RTI

Early Check

- Extract SNPs from genome data
- GRS calculation
- Results reported in portal

Screening flow: T1D cohort of first ~ 2,000 babies screened



Characteristics: first ~2,000 babies screened

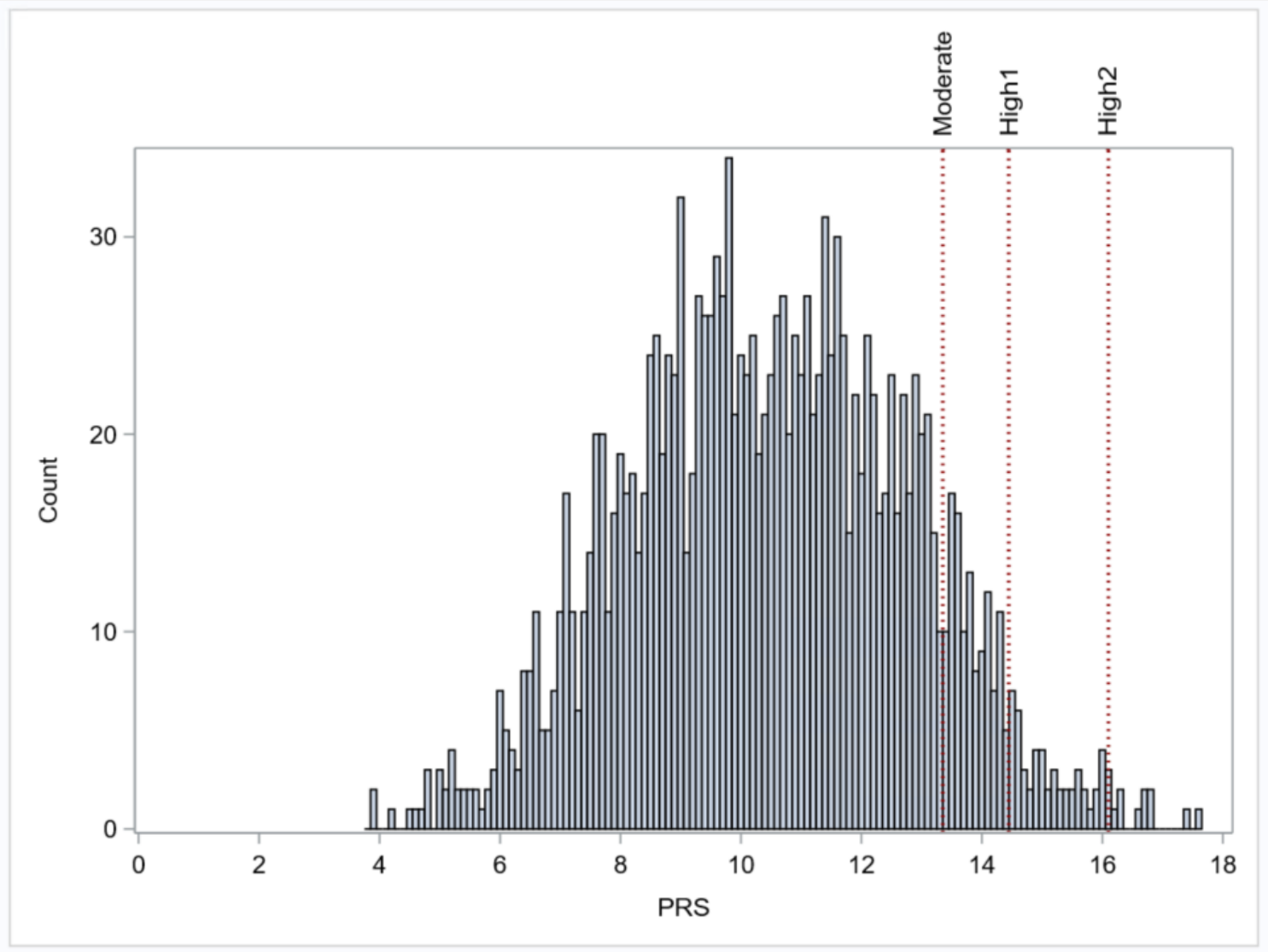
9/2023 – 6/2024

	Screened Newborns (N=1979)	Screened for T1D Risk (N=1605)
Sex		
Girl	1006 (50.8%)	807 (50.3%)
Boy	973 (49.2%)	798 (49.7%)
Group Identity		
American Indian or Alaska Native	4 (0.2%)	2 (0.1%)
Asian	98 (5.0%)	71 (4.4%)
Black, African American or African	145 (7.3%)	99 (6.2%)
Hispanic, Latino, or Spanish	103 (5.2%)	74 (4.6%)
Middle Eastern or North African	5 (0.3%)	5 (0.3%)
Native Hawaiian or Pacific Islander	0 (0.0%)	0 (0.0%)
White	1164 (58.8%)	986 (61.4%)
Two or more groups	438 (22.1%)	355 (22.1%)
Unknown	22 (1.1%)	13 (0.8%)

Genetic risk scores: first T1D cohort (N=1605)

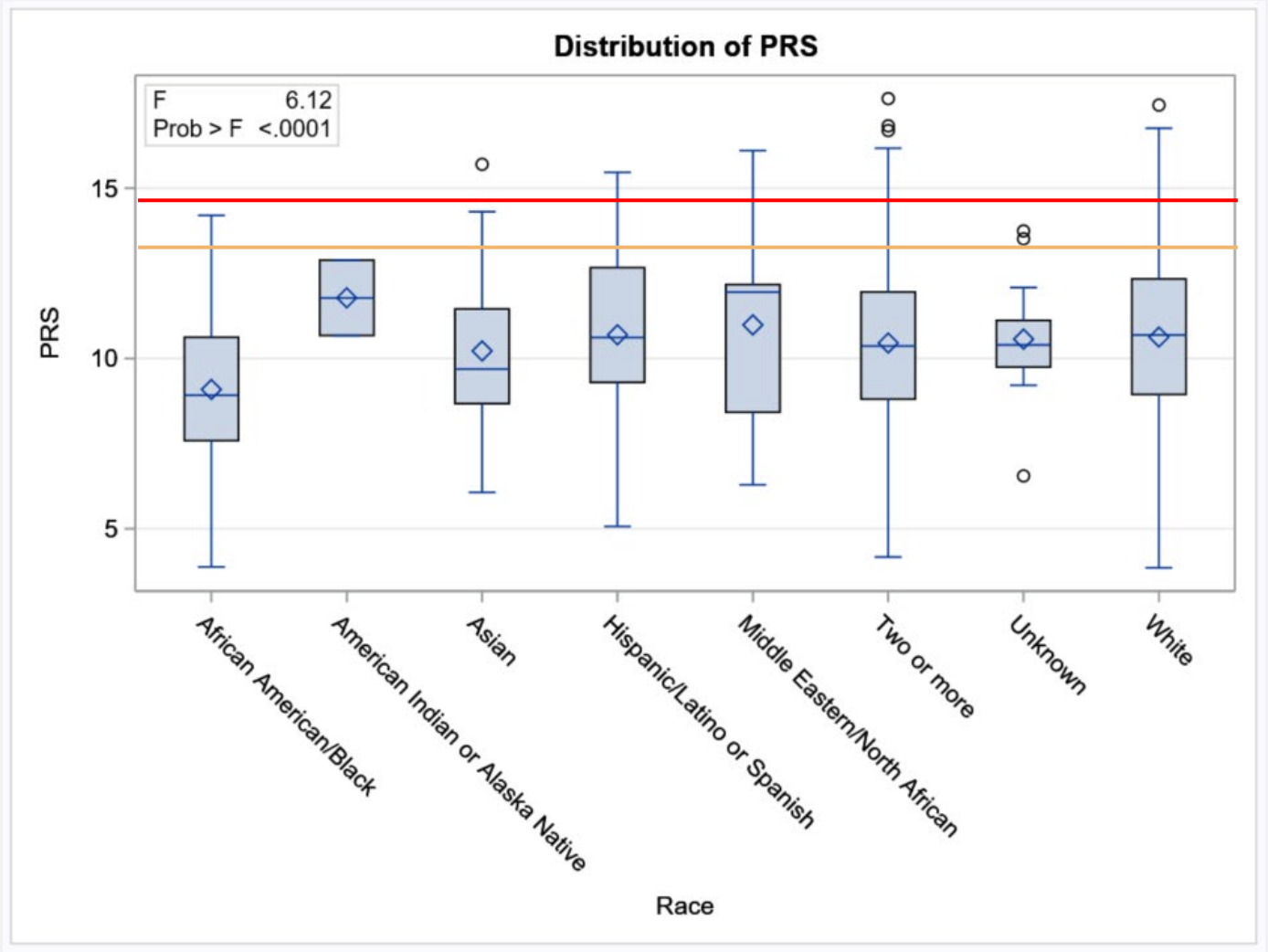
	T1D Results n (%)
Low concern (<2% risk)	1425 (88.8%)
Moderate concern (2-5% risk)	118 (7.4%)
Higher concern (5-10% risk)	51 (3.2%)
Higher concern (>10% risk)	11 (0.7%)
Total	**1605**

Distribution of PRS Scores (N=1605)

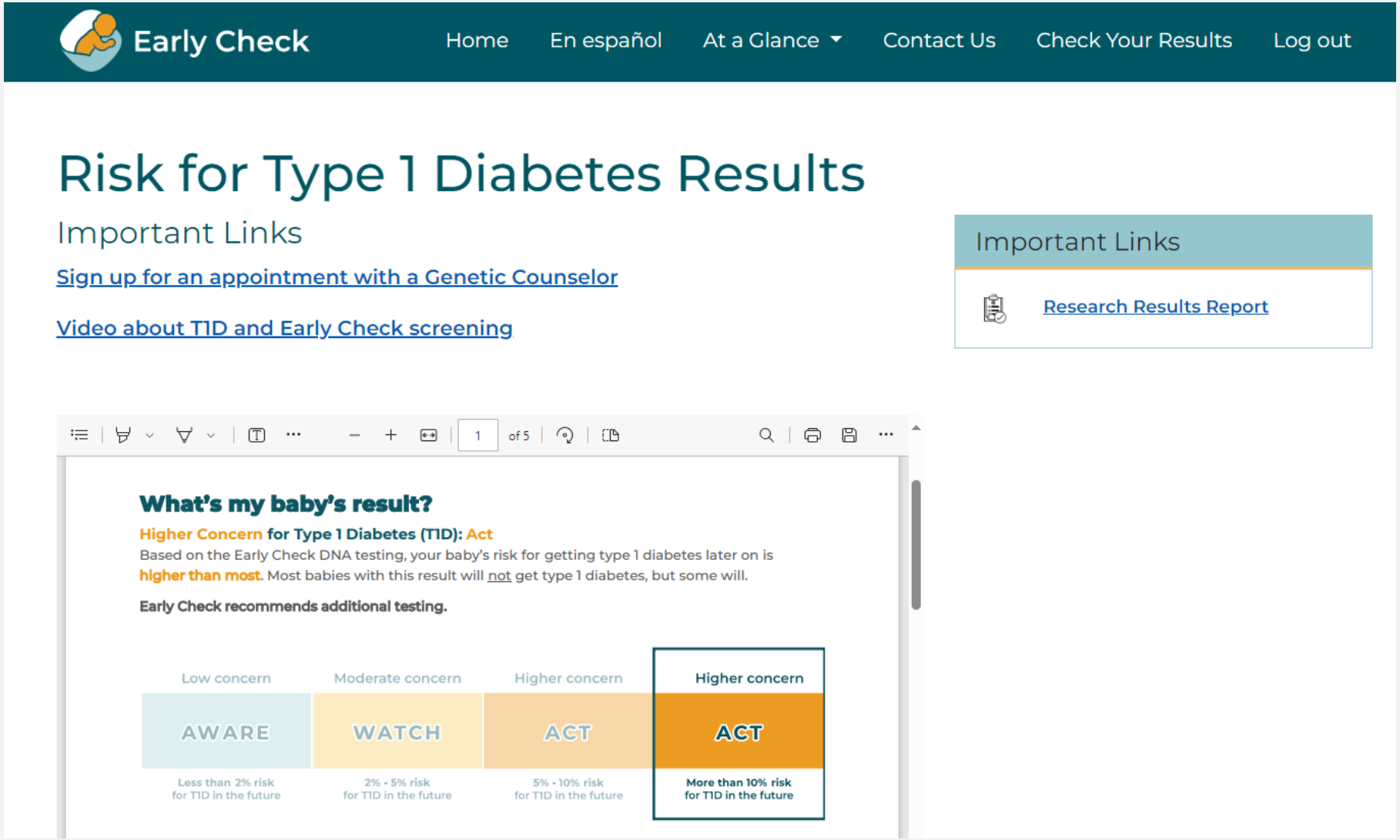


Mean GRS Scores by Self-reported Group Identity (N=1605)

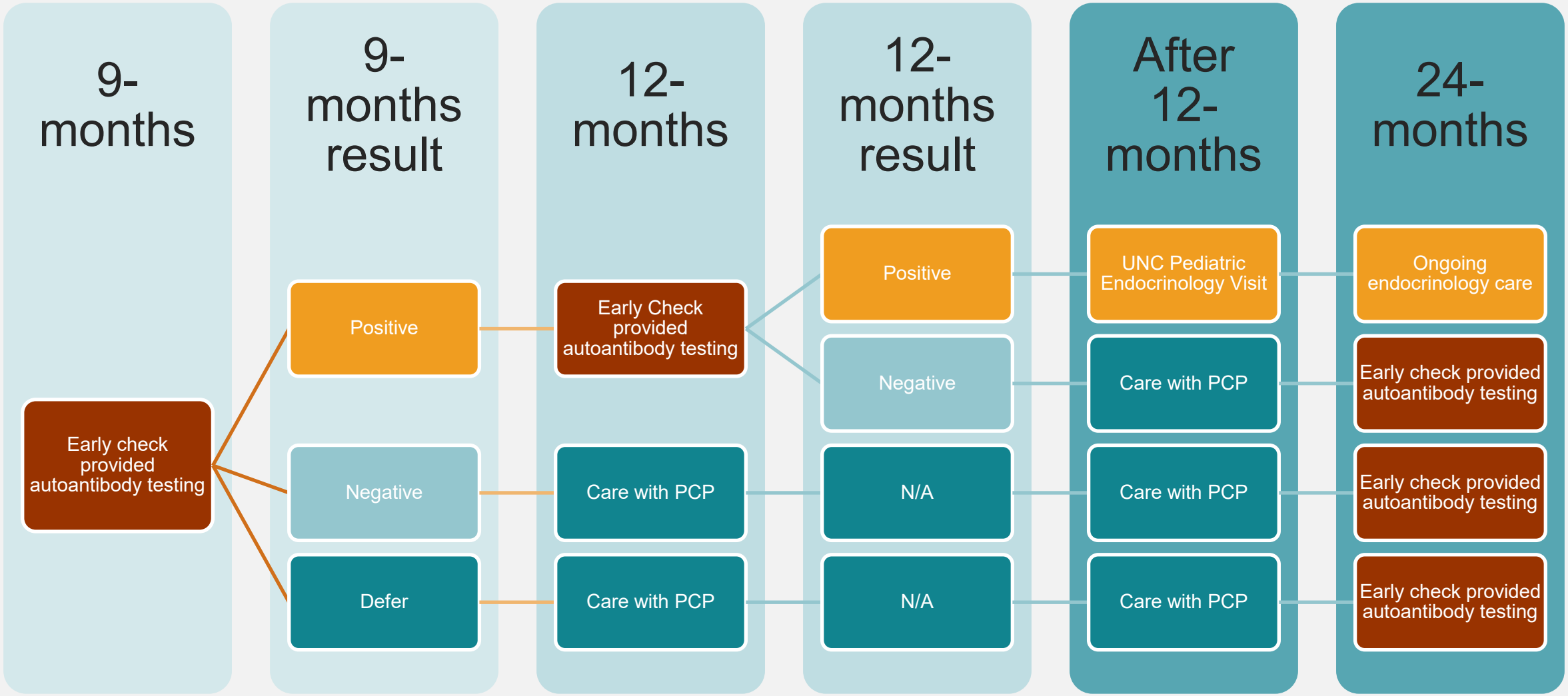
	PRS		
	N	Mean	Std
African American/Black	99	9.09	2.19
American Indian or Alaska Native	2	11.78	1.57
Asian	71	10.22	2.07
Hispanic/Latino or Spanish	74	10.70	2.28
Middle Eastern/North African	5	10.99	3.78
Two or more	355	10.45	2.30
Unknown	13	10.57	1.88
White	986	10.63	2.32



Return of Results in the Portal



Follow-up for Higher Concern or Moderate + 1º relative



Early Check T1D follow-up, to date

5/7/2024 – 11/04/2024

Result Category	Result Returned in Portal	Genetic Counseling	Signed up for Autoantibody Screening	Attempted Autoantibody Screening
Higher concern	62	38	41	19
Moderate concern + 1st degree family history	5	1	0	0

Sign-up is ongoing

11 – Negative
1 – Positive
1 – Pending
6 – No sample

Psychosocial assessments

- Consenting parent for 17 of 27 (63%) newborns completed the Patient Health Questionnaire (PHQ-2) and General Anxiety Disorder (GAD-2) after completion of genetic counseling
- 1 scored above clinical cutoffs and was administered the PHQ-9 and GAD-7
- 1 remained above clinical cutoffs
  - Follow-up by study psychologist
  - Parent was actively in comprehensive treatment

Conclusions

- Demonstrates feasibility of using genome data to screen for complex conditions
- Evaluation surveys and interviews with parents and providers will assess acceptability, clinical utility and psychosocial outcomes

Early Check Team


Sara Andrews


Don Bailey


Vesselina Bakalov


Blythe Crissman


Javan Carter


Emily Cheves

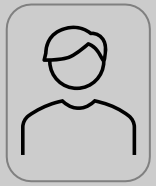

Heidi Cope


Manisha Dass


Jake Dibble


Anne Edwards


Ana Forsythe


Nathan Gaddis


Angela Gwaltney


Jessica Hunter


Kate Kucera


Colin Mathews


Brooke Migliore


Rebecca Moultrie


Casey Okoniewski


Grier Page


Holly Peay


Melissa Raspa


Veronica Robles


Samantha Scott


Anne Wheeler


Becca Wright

UNC


Jonathan Berg


Liz Jalazo


Jennifer Law


Laura Milko


Cindy Powell

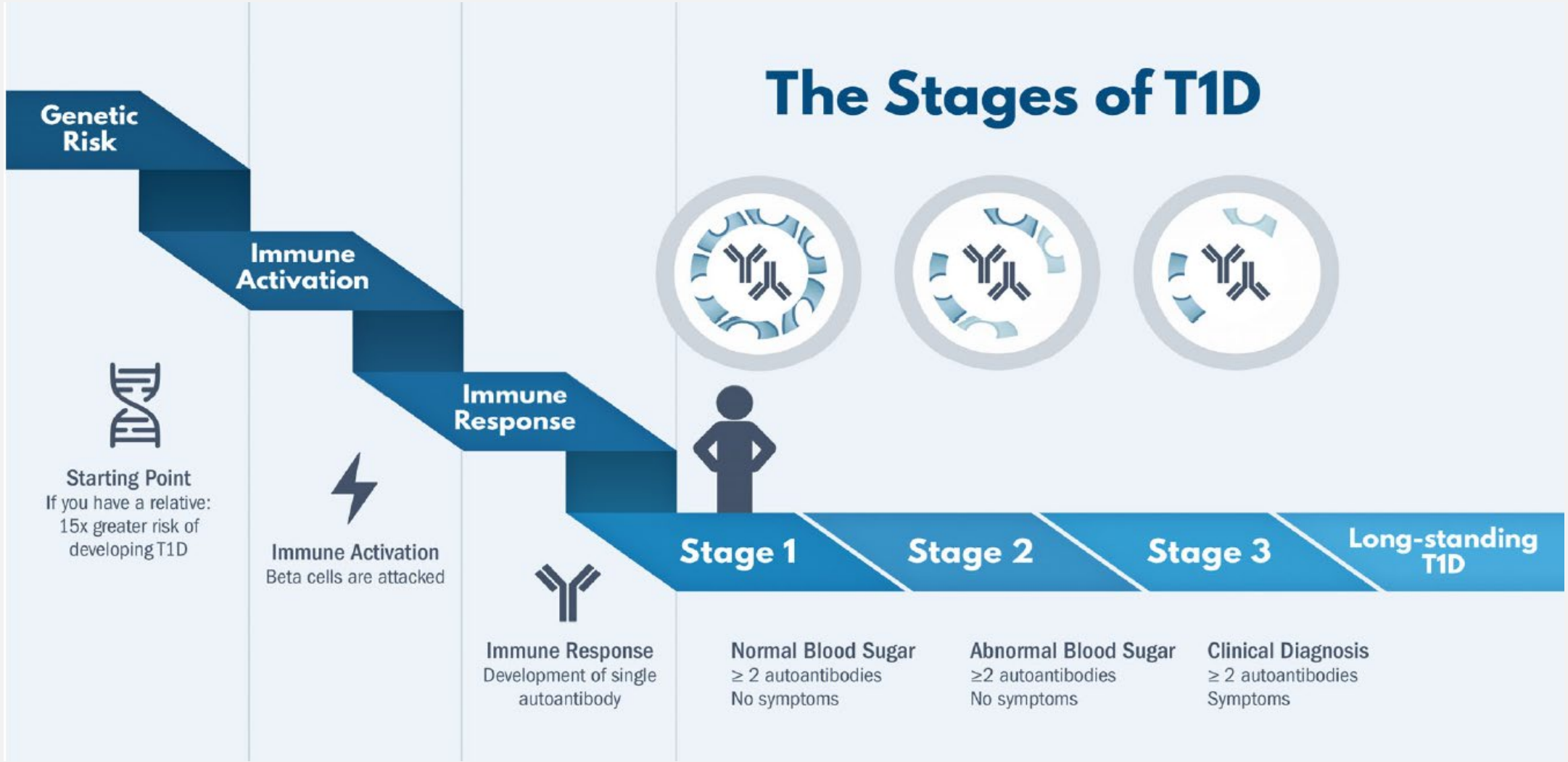

Jennifer Sullivan

NCSLPH


Scott Shone

Thank you

Why Screen for T1D?



Besser et al., 2022

Developed SNP Missingness Thresholds

- SNPs contributing to T1D GRS2 calculation fall into 3 main classes:
  - HLA-DQ (n=14)
  - HLA other (n=21)
  - Non-HLA (n=32)
- Different missingness thresholds used for different classes of SNPs
  - HLA-DQ: No tolerance for missing SNPs
  - Other SNPs: Tolerance for up to 2 missing SNPs