The CASCADE Study

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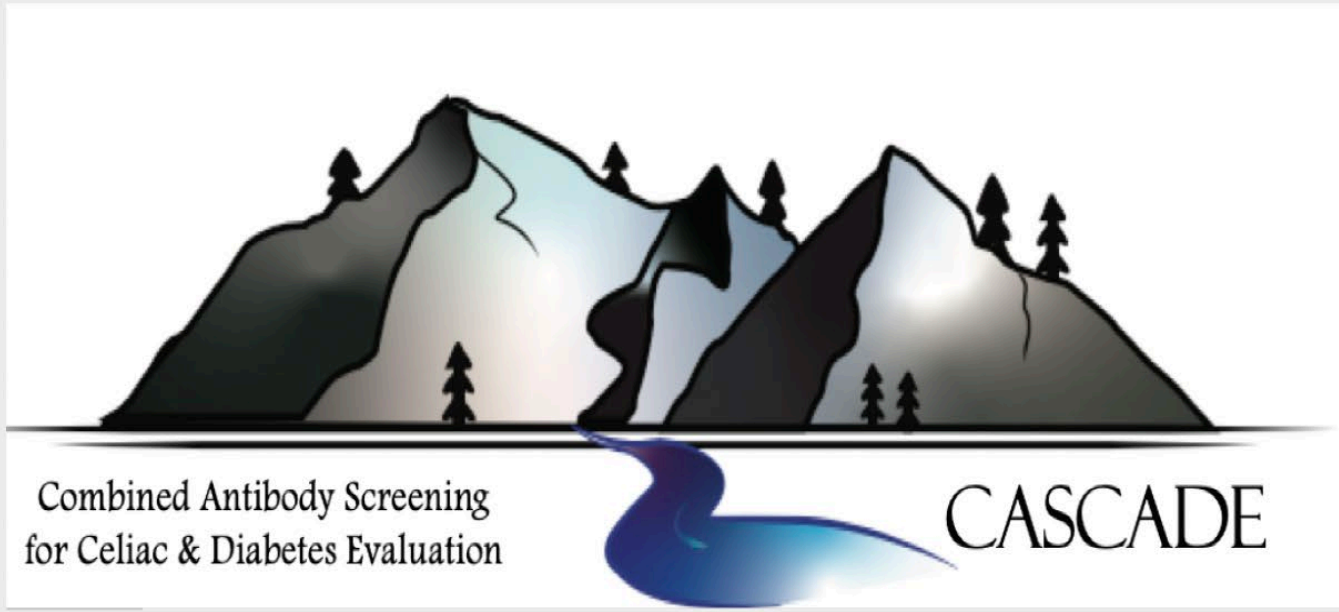

pri Pacific Northwest Research Institute

UW Medicine

Newborn Screening Program
Washington State Department of Health

Disclosures

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Dr. Hagopian serves as consultant to Sanofi and to Randox Health

Combined Antibody Screening for Celiac & Diabetes Evaluation

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How low must Type 1 diabetes prediction costs be to implement in public health settings?

- 1/300 kids get T1D, with a ~35% decrease in DKA by prediction and parent education

- Benefits are lower mortality, lower acute care costs, and lower glycemic and cognitive sequelae

- To precede Stage 3 onset, islet autoantibody screening must occur at multiple ages during childhood

-Doing sampling and autoantibody panels 3 times in all kids incurs costs greater than calculated benefits

- CASCADE explores several ways to decrease prediction costs:
    a- low cost, high performance genetic risk score using already available samples
    b- selection of the least number of antibody sampling ages, optimized by country
    c- mail-based sampling to lower costs and minimize burden to care providers
    d- economical islet antibody screening tests

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Educating parents and providers of children with islet autoantibodies to prevent DKA

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Following Islet autoantibodies in kids consistently prevents DKA at onset

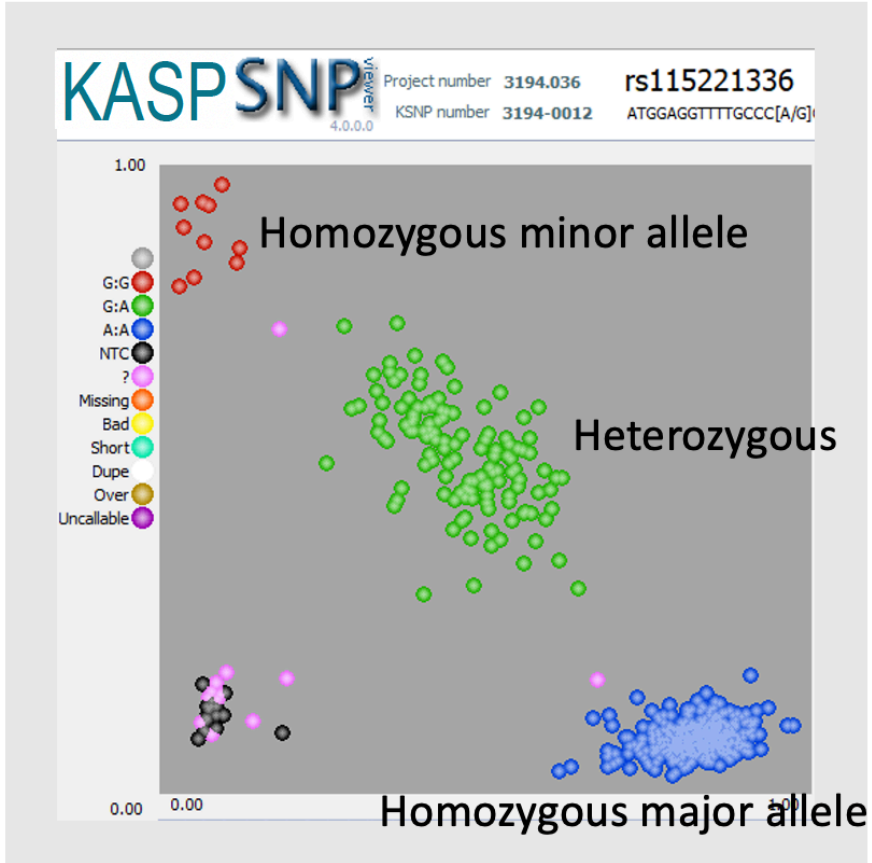
First Author/Journal	Study	Background	With IAb follow-up	p-value
Barker 2004 Diab Care	**DAISY**	44%	3.3%	<0.0001
Larsson 2014 Ped Diab ≤5 yrs old	**TEDDY**	40%-54%	8.0%	<0.0001
Winkler 2012 Ped Diab	**Baby-Diab**	29%	3.3%	<0.001
Hekkala 2017 Ped Diab	**DIPP**	23%	5.0%	<0.001
Nakala 2021 JAMA Pediatrics	**TRIGR**	19-40%	4.6%	<0.001

TEDDY
The Environmental Determinants of Diabetes in the Young

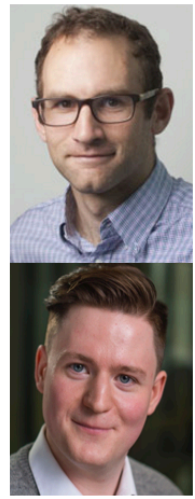
CASCADE 67-SNP T1D and CD combined panel and automated pipeline

Order	Locus or DQA1-DQB1 haplo	alternative DQ haplo names	CASCADE Primary SNP	T1D-GRS2	celiac-GRS	Chr band	Primary SNP Chr location
1	020X-0202	HLA-DQ22	rs17211699	T1D	celiac	6p21	Chr 6
2	0501-0201	HLA-DQ25	rs9273369	T1D	celiac	6p21	Chr 6
3	0401-0402	HLA-DQ42	rs12527228	T1D	celiac	6p21	Chr 6
4	010x-0501	HLA-DQ51	rs10947332	T1D	celiac	6p21	Chr 6
5	010x-0503	HLA-DQ53	rs1794265	T1D	celiac	6p21	Chr 6
6	0103-0601	HLA-DQ61	rs117806464	T1D	celiac	6p21	Chr 6
7	0102-0602	HLA-DQ62	rs17843689	T1D	celiac	6p21	Chr 6
8	0103-0603	HLA-DQ63	rs62406889	T1D	celiac	6p21	Chr 6
9	0102-0609	HLA-DQ69	rs16822632	T1D	celiac	6p21	Chr 6
10	030x-0301	HLA-DQ73	rs1281935	T1D	celiac	6p21	Chr 6
11	0505-0301	HLA-DQ75	rs9469200	T1D	celiac	6p21	Chr 6
12	030x-0302	HLA-DQ81	rs9275490	T1D	celiac	6p21	Chr 6
13	0201-0303	HLA-DQ92	rs28746898	T1D	celiac	6p21	Chr 6
14	0302-0303	HLA-DQ93	rs9405117	T1D	celiac	6p21	Chr 6
15	0601-0301	HLA-DQ76	rs118118976	T1D	celiac	6p21	Chr 6
16	0102-0604	HLA-DQ64	rs114609017	T1D	celiac	6p21	Chr 6
17	0102-0502	HLA-DQ52	rs149929277	T1D	celiac	6p21	Chr 6
23	XL9 Regulatory		rs9271346	T1D		6p21	Chr 6
24	Intergenic DRA1-DRB1 ND3		rs9269173	T1D		6p21	Chr 6
25	BTNL2 Regulatory		rs116522341	T1D		6p21	Chr 6
26	DPB1*0101		rs17214657	T1D		6p21	Chr 6
27	DPB1*0402		rs6934289	T1D		6p21	Chr 6
28	DPB1*1501		rs2567287	T1D		6p21	Chr 6
29	A*0201		rs12153924	T1D		6p21	Chr 6
30	A*0301		rs9259118	T1D		6p21	Chr 6
31	A*2402		rs72848653	T1D		6p21	Chr 6
32	A*2902		rs144530872	T1D		6p21	Chr 6
33	B*3906		rs540653847	T1D		6p21	Chr 6
34	B*4403		rs2524277	T1D		6p21	Chr 6
35	B*5701		rs149663102	T1D		6p21	Chr 6
36	C*0602		rs12189871	T1D		6p21	Chr 6
18	ATXN2/SH2B3		rs653178	T1D	celiac	12q24.12	Chr 12
19	ADAD1-IL21-AS1		rs17388568	T1D	celiac	4q27	Chr 4

Not all SNPs shown. For all SNPs, see Sharp DiabCare 2019 and Sharp APT 2020



A KASP-based T1D-GRS2 and Celiac-GRS from a dried bloodspot punch in CASCADE costs only **$17**



Many ways to genotype SNPs:

- Real Time PCR (e.g.KASP)
- SNP arrays with imputation
- Whole genome sequencing

Combined Antibody Screening for Celiac & Diabetes Evaluation
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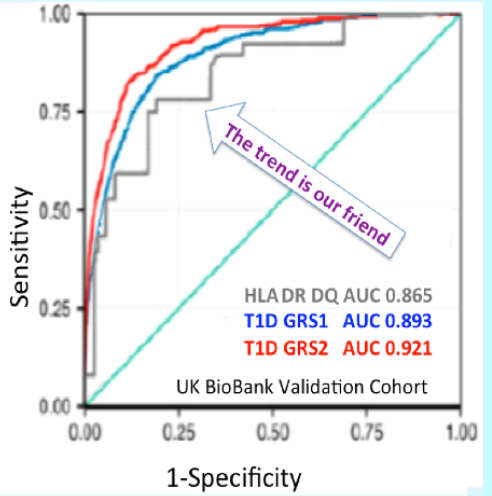
T1D GRS2 improves upon HLA to define high risk children

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	0.67	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

T1D centile*	Risk category	HLA type	Specificity (%)	Sensitivity (%)	1-Specificity (%)	Youden index (*j*)	T1D risk (%)***
—	Background	Other	0.0	100.0	0.0	0.00	0.3
57.0	Moderate	DR3/3, DR4/X	79.1	77.0	23.0	0.561	0.6
81.1	High	DR4/4	96.3	41.3	58.7	0.376	2.5
84.5	Very High	DR3/4	97.2	37.0	63.1	0.342	3.8

Risk of T1D is calculated assuming a 0.3% population prevalence of T1D. *T1D cases in T1DGC. **Centile in UK Biobank European population. ***Risk of T1D is calculated assuming a 0.3% population prevalence of T1D.

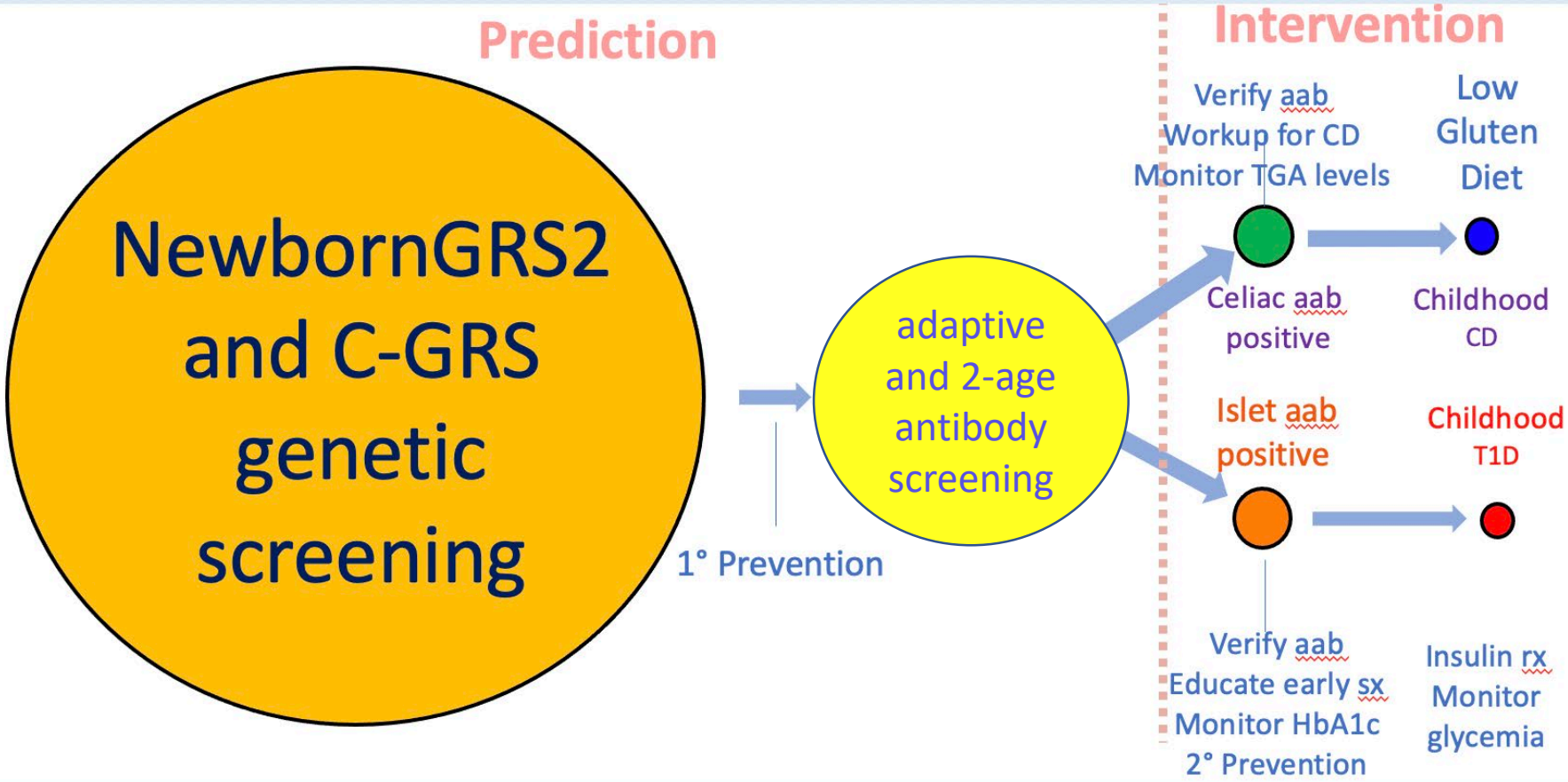


Sharp et al Diabetes Care 2019

TEDDY
The Environmental Determinants of Diabetes in the Young

Genetic then Autoantibody Screening Lowers Prediction Costs

% of All Newborns	100%	24%	1.5%	1.0%

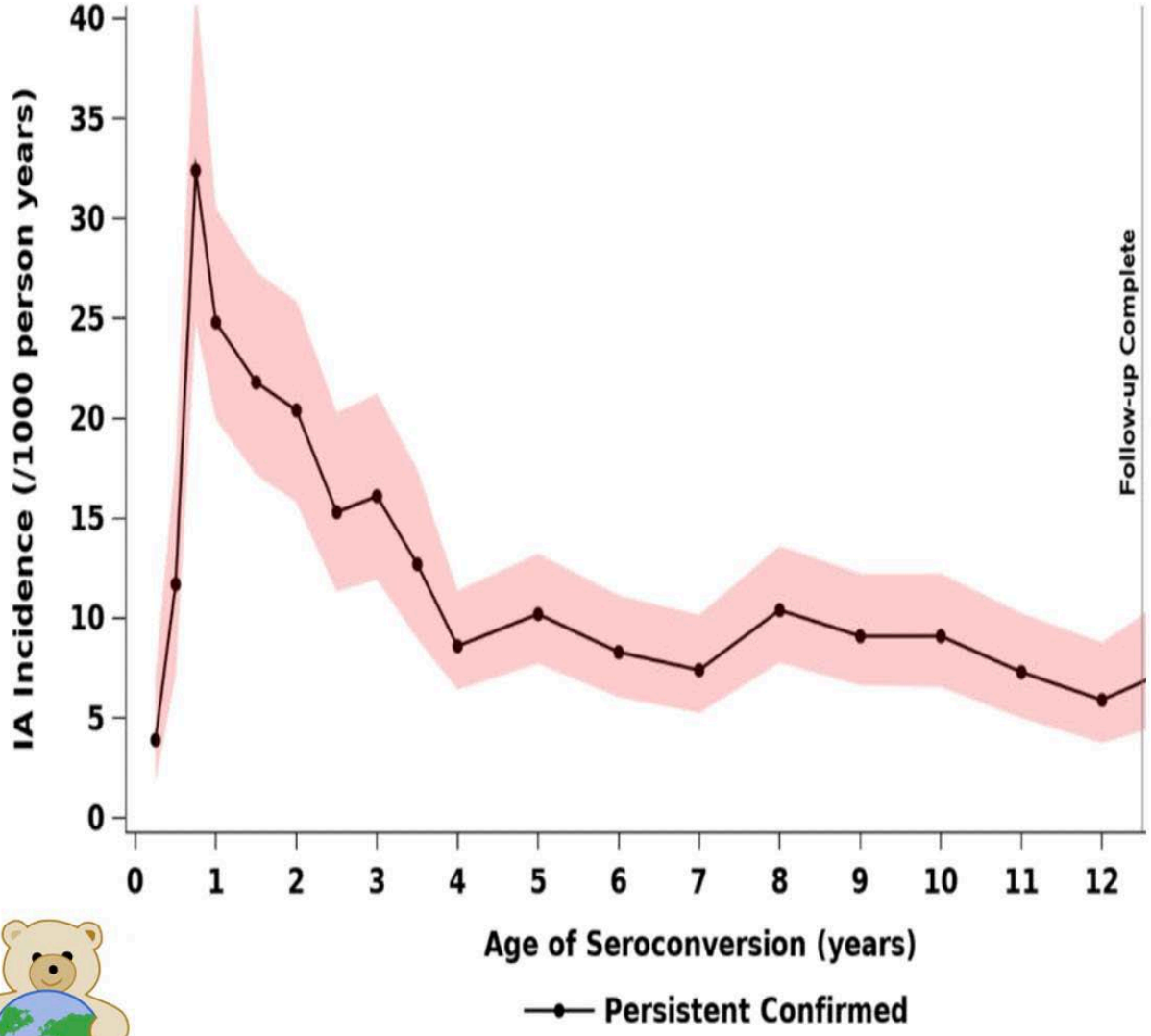


Celiac Disease

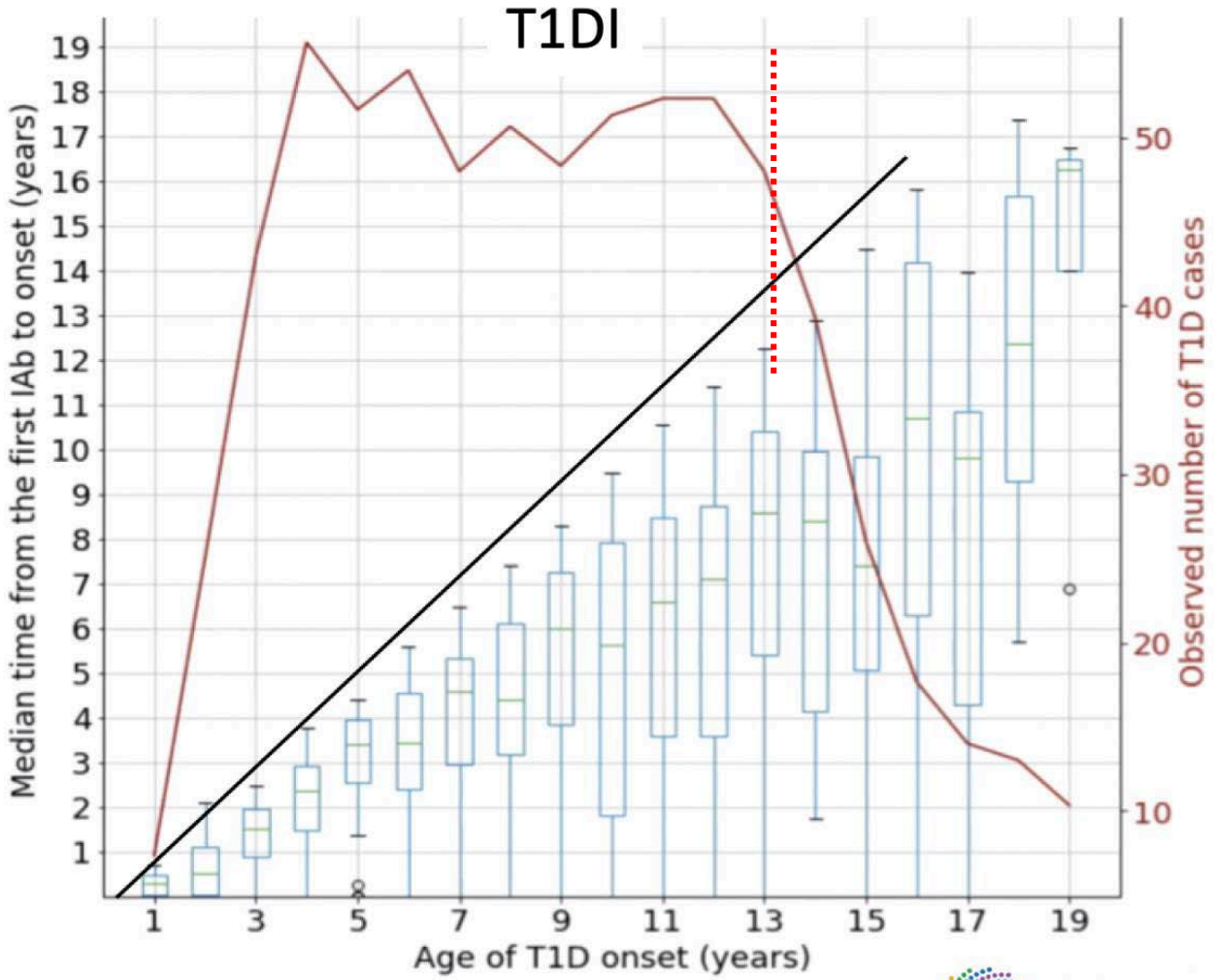
Type 1 diabetes

% of All Newborns	100%	21%	0.6%	0.3%

Islet aab appear at many ages, but later appearance means slower average progression to T1D
Despite this, testing at multiple ages will be necessary, requiring additional steps for efficiency



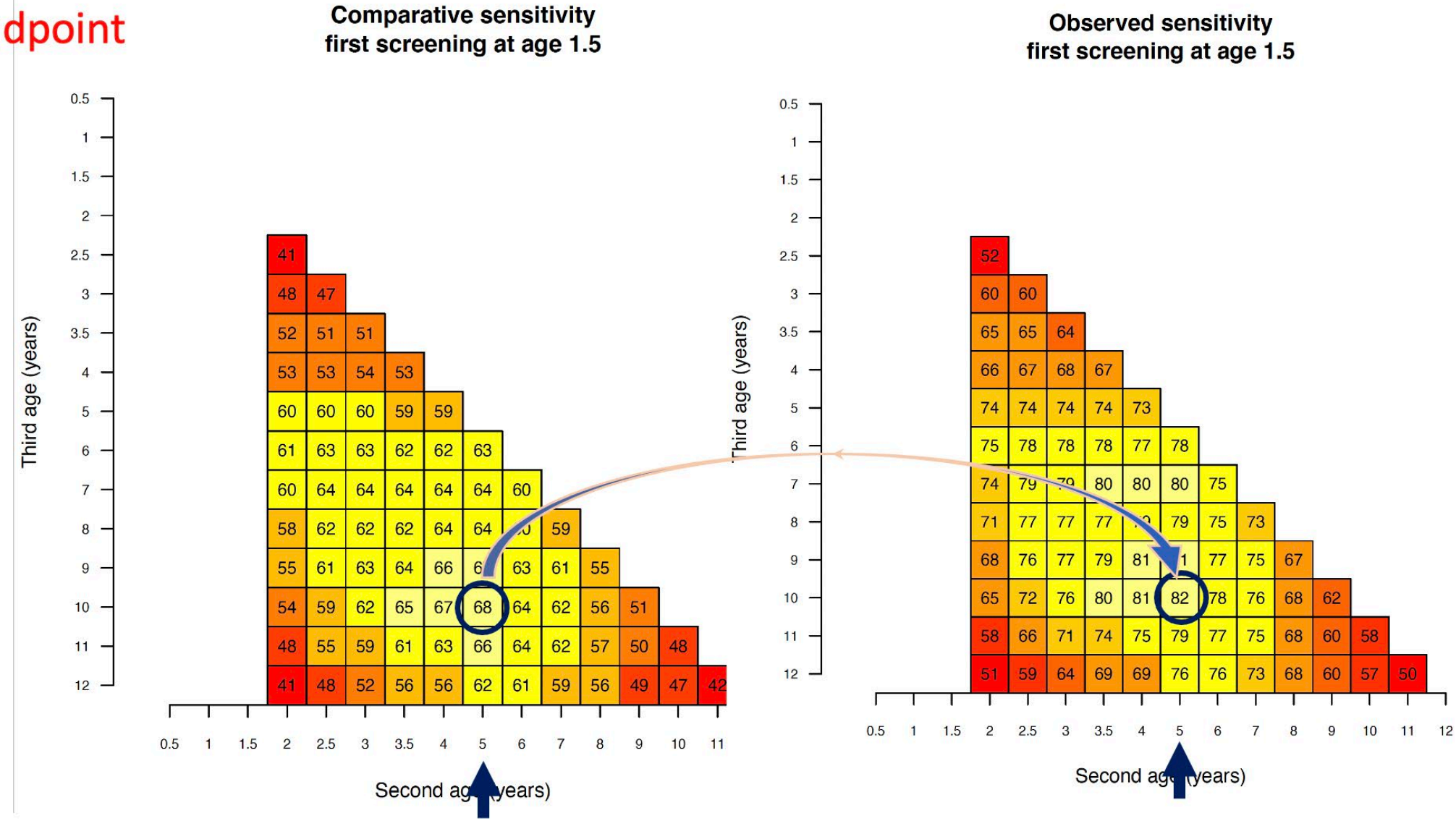
Krischer 2017 Diab Care



Ghalwash 2022 Lancet D+E

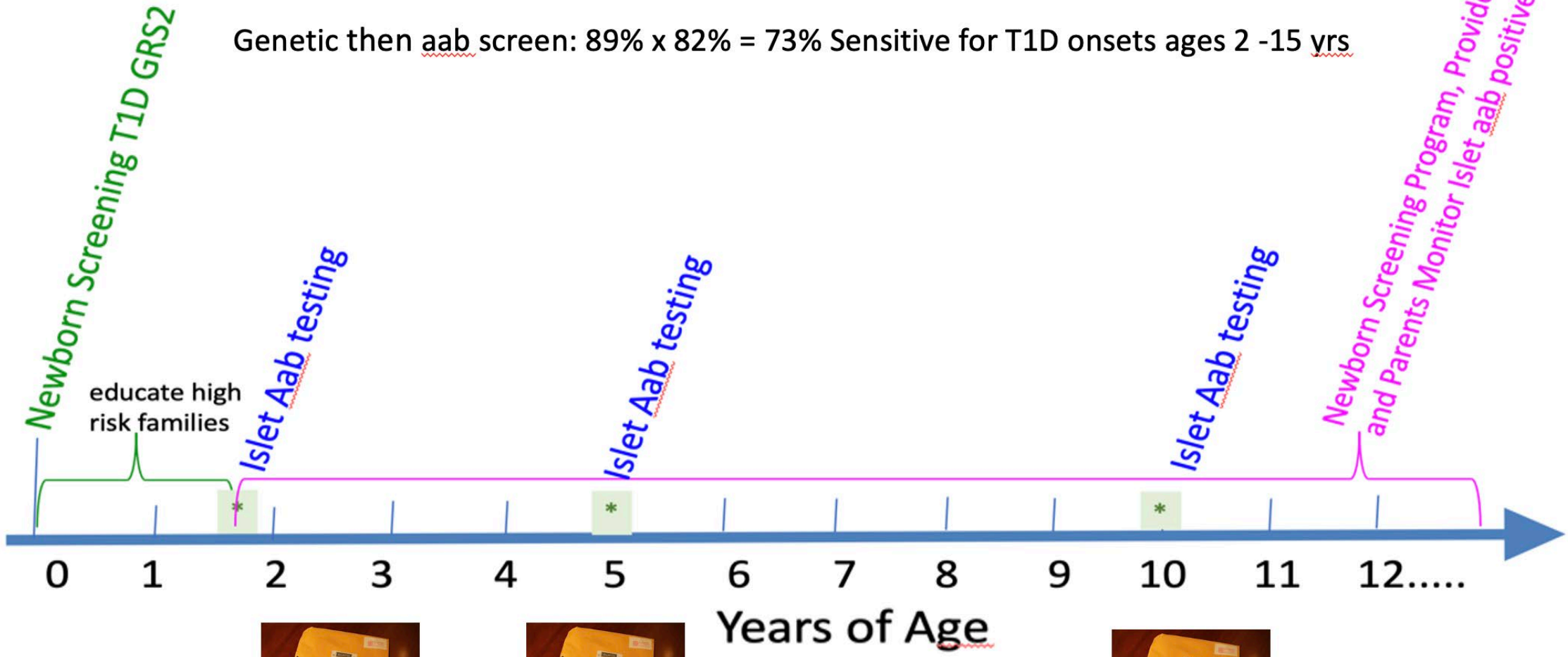
T1DI
type 1 data intelligence

3-age screen
US sites
age 13 endpoint



Scheme for incorporation into Public Health and Medical Care Systems

Genetic then aab screen: 89% x 82% = 73% Sensitive for T1D onsets ages 2 -15 yrs



CASCADE Research Study

Type 1 diabetes and celiac disease screening for children in the state of Washington.

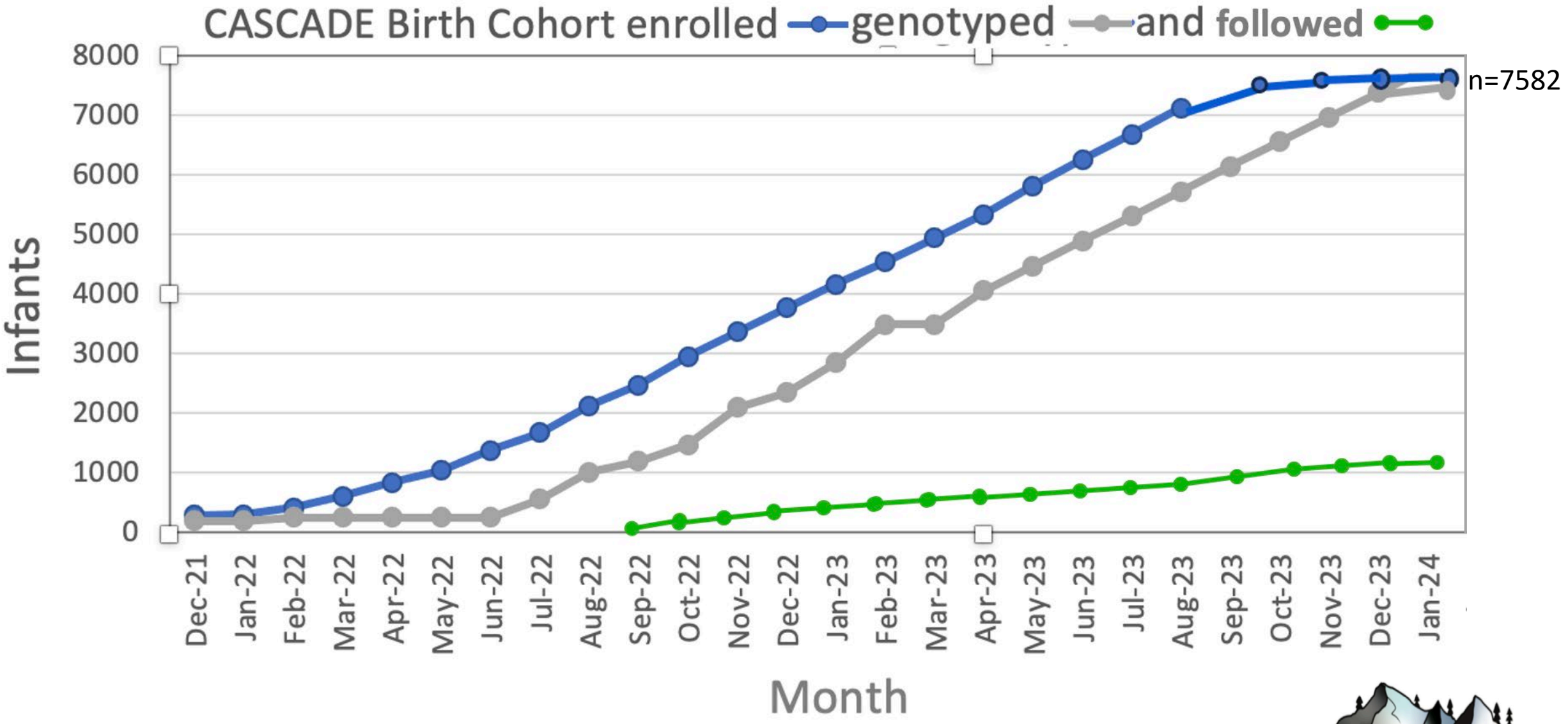
LEARN MORE

SIGN UP

APPROVED
March 03, 2022
WSIRB

www.cascadekids.org

CASCADE Study



Combined Antibody Screening for Celiac & Diabetes Evaluation

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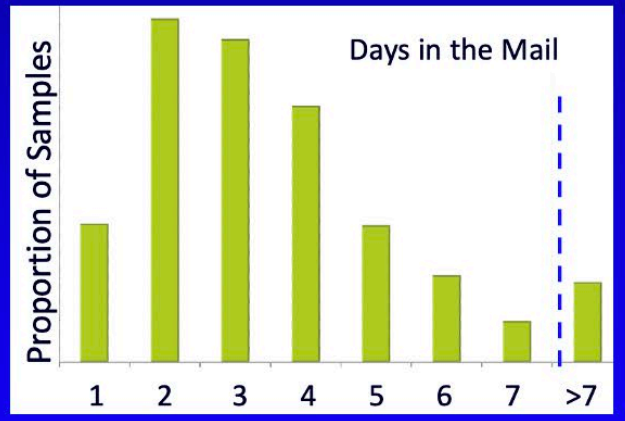
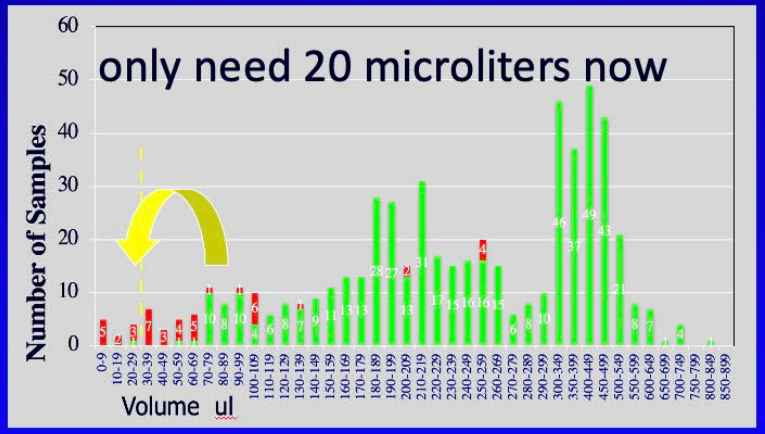
Mail-based CASCADE autoantibody testing

15% of infants containing 84% of T1D cases increases absolute risk from 1/300 to 1/50
First test at age 18 months so CASCADE is just testing now

11% of infants with 65% of celiac cases increases absolute risk from 1/100 to 1/17
First test later at age 3 years so no CASCADE testing yet





Mail-based, home capillary blood sampling is highly cost-effective vs. provider or commercial phelbotomy
Participation Rate was 70% in DEW-IT (Wion et al 1999) and similar experiences elsewhere (eg Sweden)
But unknown if this will be practical in the US in 2023. CASCADE will test this.

Conclusions

- Newborn prescreening via genetic risk scores followed by islet autoantibody screening can detect most childhood type 1 diabetes.
- Requires screening 20% of US children at ages 1.5, 5 and 10 yrs, which may be logistically challenging especially if cost-effective mail-based sampling is used**.
- We expect 73% sensitivity for T1D by age 13, while minimizing costs**.
- Celiac Disease can be efficiently tested at the same time via C-GRS and TGA screening
- Effective T1D interventions available now, with prevention potential in the future

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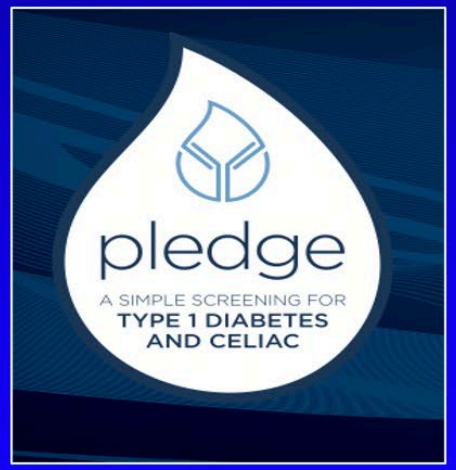
Our approach has also powered several other studies



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Acknowledgements

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