The CASCADE Study

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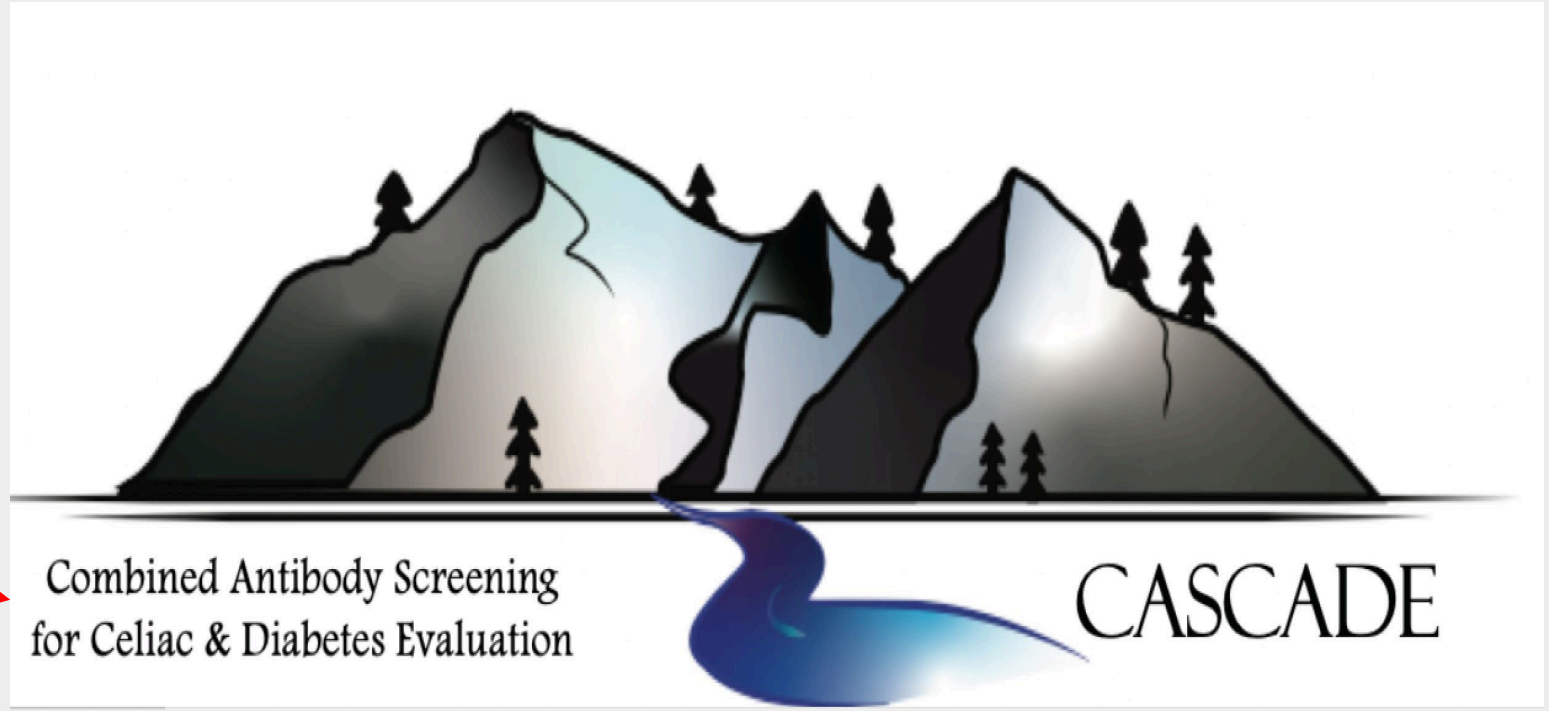

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Dr. Hagopian serves as consultant to Sanofi and to Randox Health

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

- 1/300 kids get T1D, of which more that half get DKA at Stage 3 onset. Prediction and parental education can decrease DKA incidence by threefold or more.

- Benefits are lower acute care costs, lower glycemic sequelae, and rarely lower mortality. There is also an opportunity created to apply FDA-approved intervention therapy.

- However, to allow warning before Stage 3 onset, islet autoantibody (IA) test must occur at several ages during childhood which may cost more than calculated benefits.

- CASCADE explores several ways to decrease these costs:
  A strategy of genetic prescreening before IA screening with only modest sensitivity loss
  Selection of the least number of necessary IA screening ages, optimized for this continent
  Less expensive sampling and testing methods

- CASCADE also explores efficiently combining T1D and celiac disease screening, with added benefits of earlier diagnosis/treatment and increased parental interest

Combined Antibody Screening for Celiac & Diabetes Evaluation
CASCADE

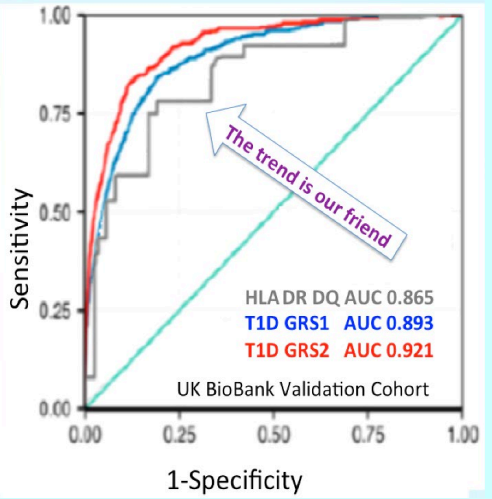
T1D GRS2 improves upon HLA to define high risk children

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[illegible]	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[illegible]	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

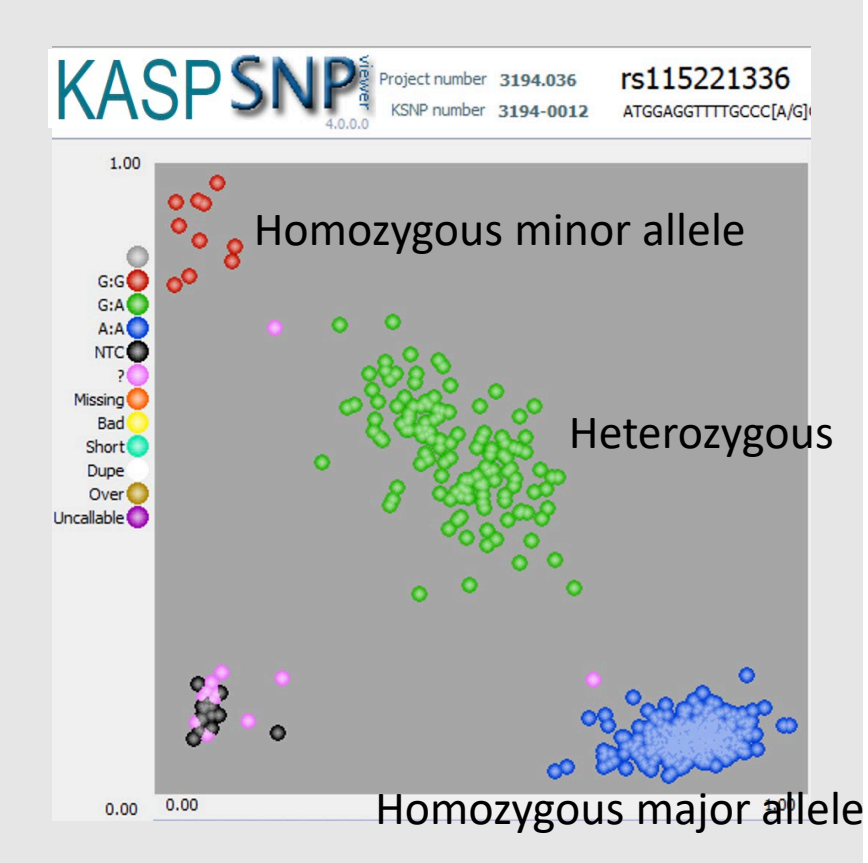
TEDDY

The Environmental Determinants of Diabetes in the Young

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		rs17288568	T1D	celiac	4q27	Chr 4

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



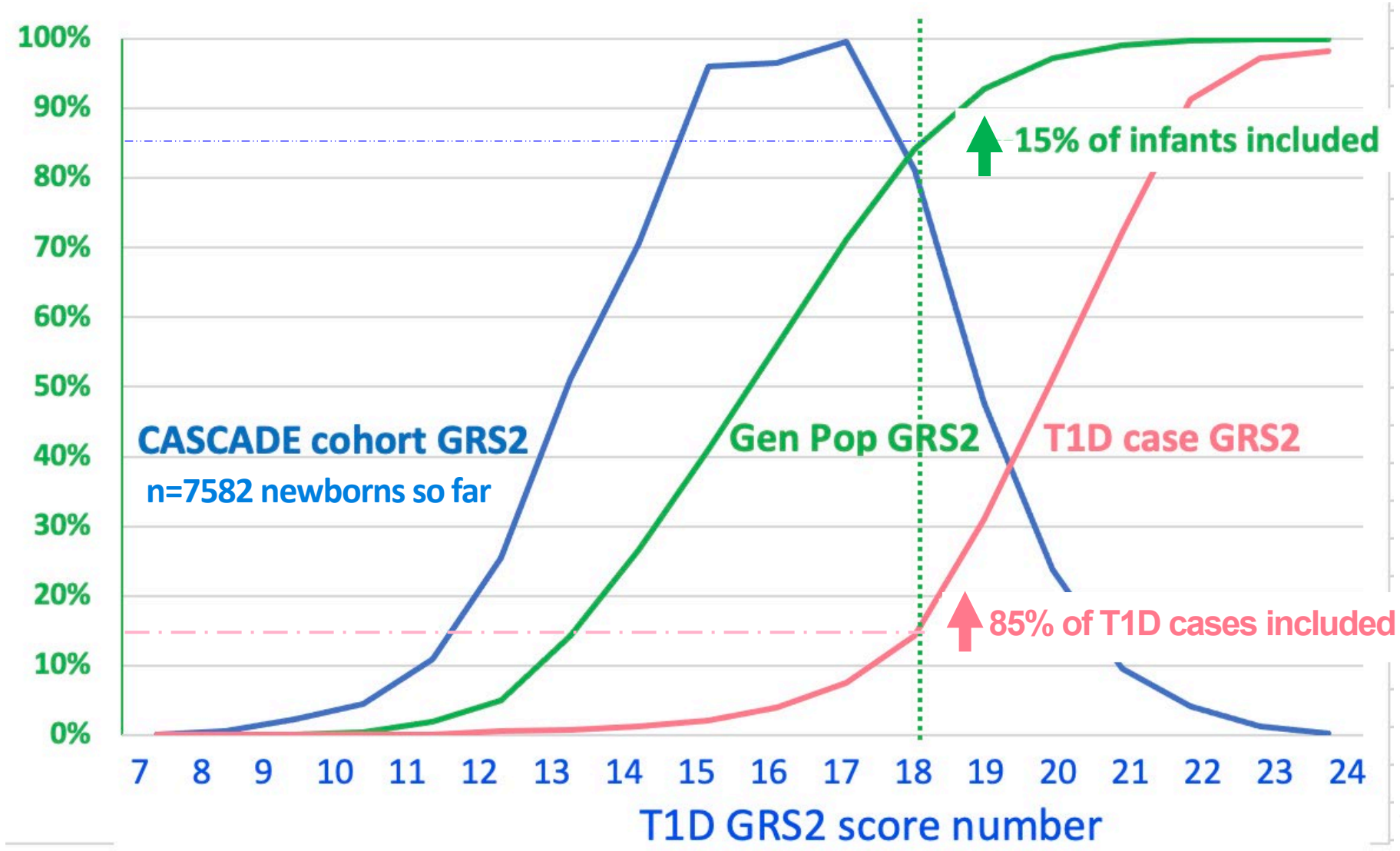
Many ways to genotype SNPs:
- Real Time PCR (e.g. KASP)
- SNP arrays with imputation
- Whole genome sequencing

A KASP-based T1D-GRS2 and Celiac-GRS from a dried bloodspot punch in CASCADE costs under $20

GRS2 works well in multiple US ethnicities

Combined Antibody Screening for Celiac & Diabetes Evaluation CASCADE

T1D GRS2 Results CASCADE cohort



Combined Antibody Screening for Celiac & Diabetes Evaluation
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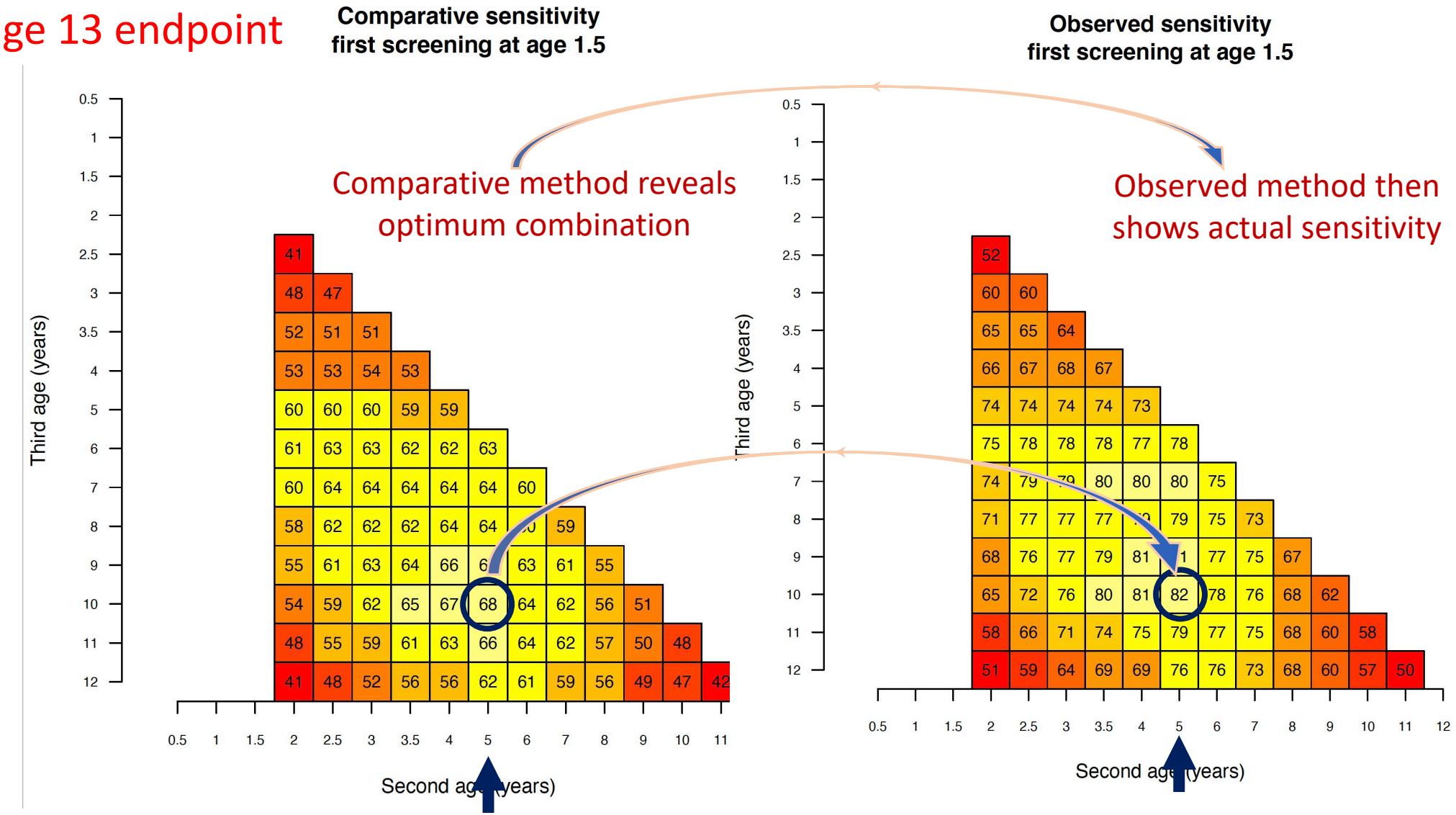
three age islet autoantibody screen US sites age 13 endpoint



Ghalwash et al

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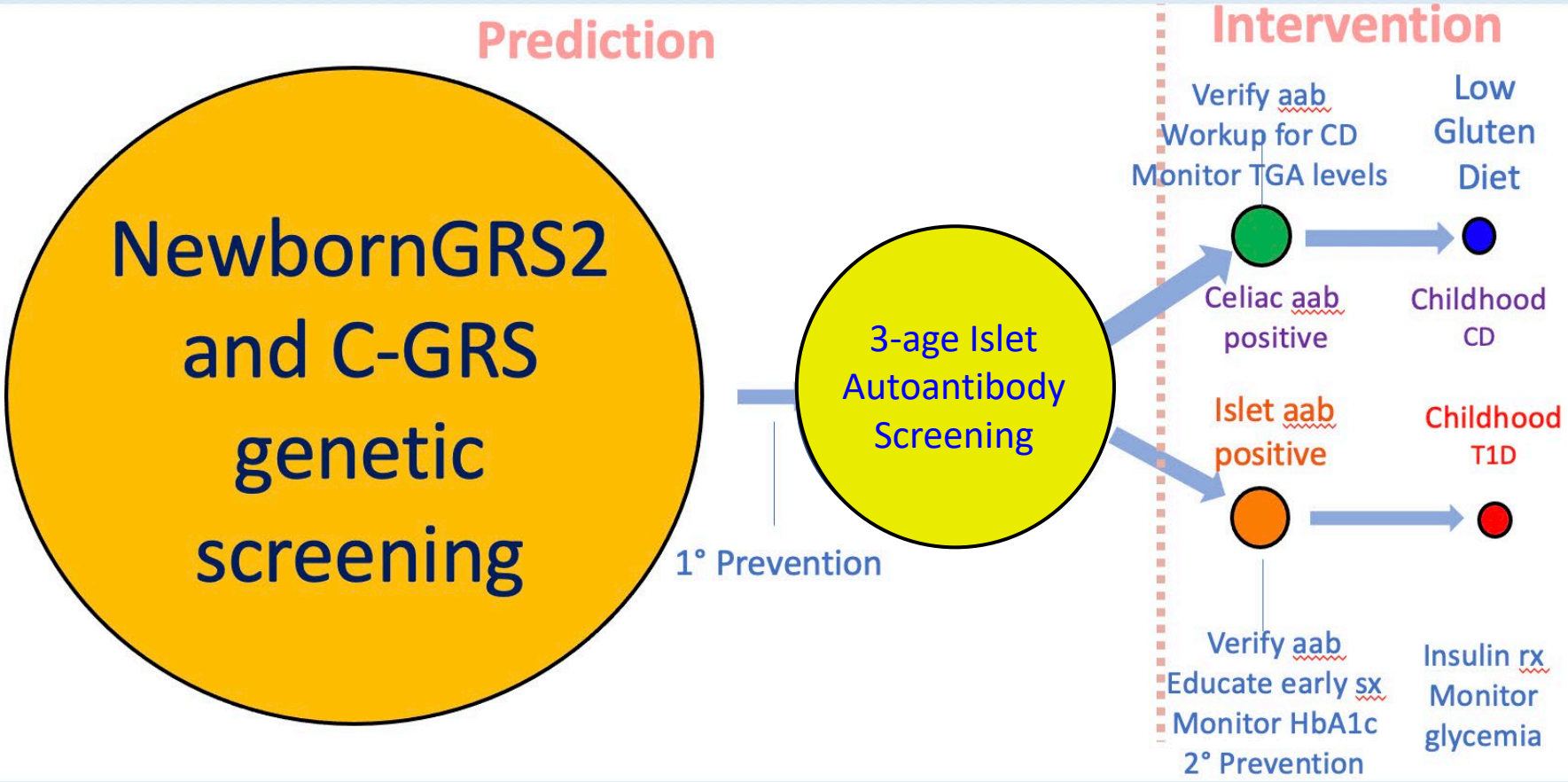
The Environmental Determinants of Diabetes in the Young

Genetic then Autoantibody Screening Lowers Prediction Costs

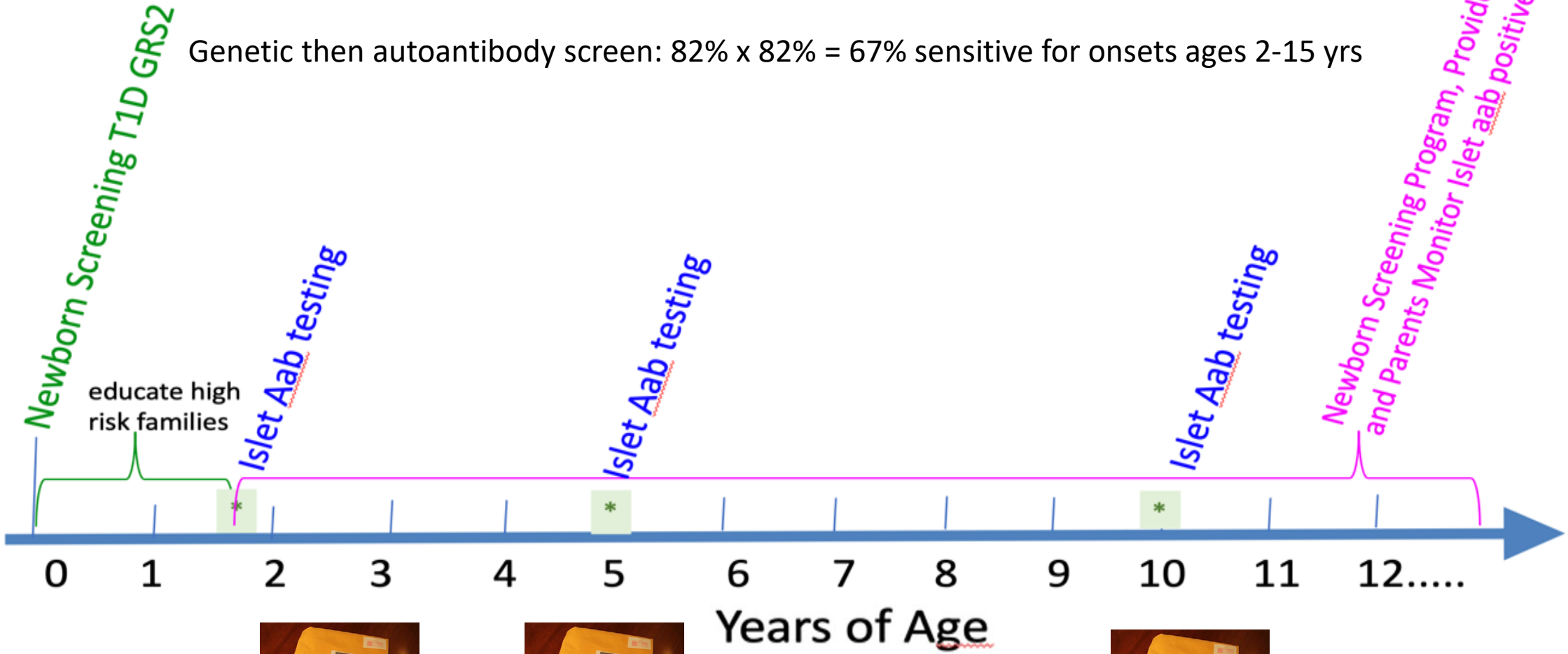
% of All Newborns	100%	24%	1.5%	1.0%



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

Scheme for incorporation into Public Health and Medical Care Systems

Genetic then autoantibody screen: 82% x 82% = 67% sensitive for onsets ages 2-15 yrs



Combined Antibody Screening for Celiac & Diabetes Evaluation

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CASCADE Research Study

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

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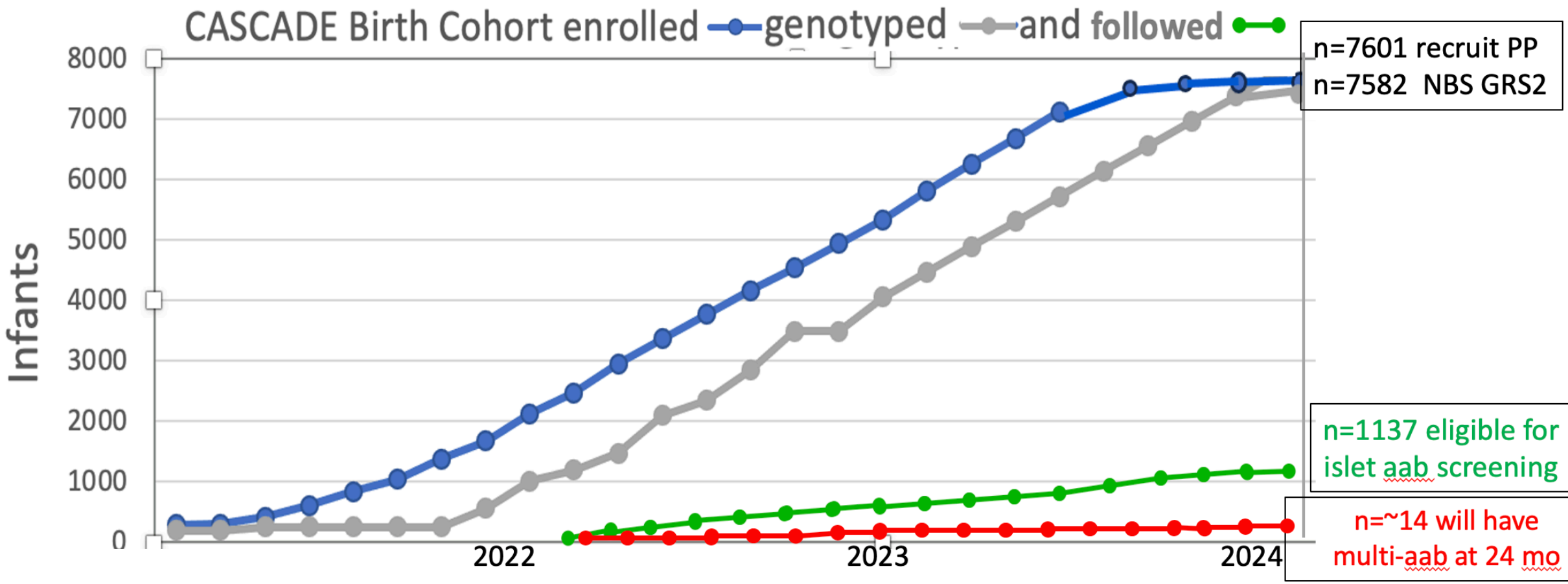
APPROVED
March 03, 2022
WSIRB

www.cascadekids.org

CASCADE Study

Preliminary Islet Autoantibody Screening



6.7% of those with high GRS tested have ≥1 islet aab, most transient, but 2.2% are persistent multiple aab
It's consistent with a priori estimate of 82% of cases in 15% of infants * 0.3% prevalence = 1.6%
But 79% haven't yet reached age 2, and uptake so far is 47% for aab screening (remote kits or in-clinic).
So screening 300-600 children per year for a study recruiting 4000 newborns per year.

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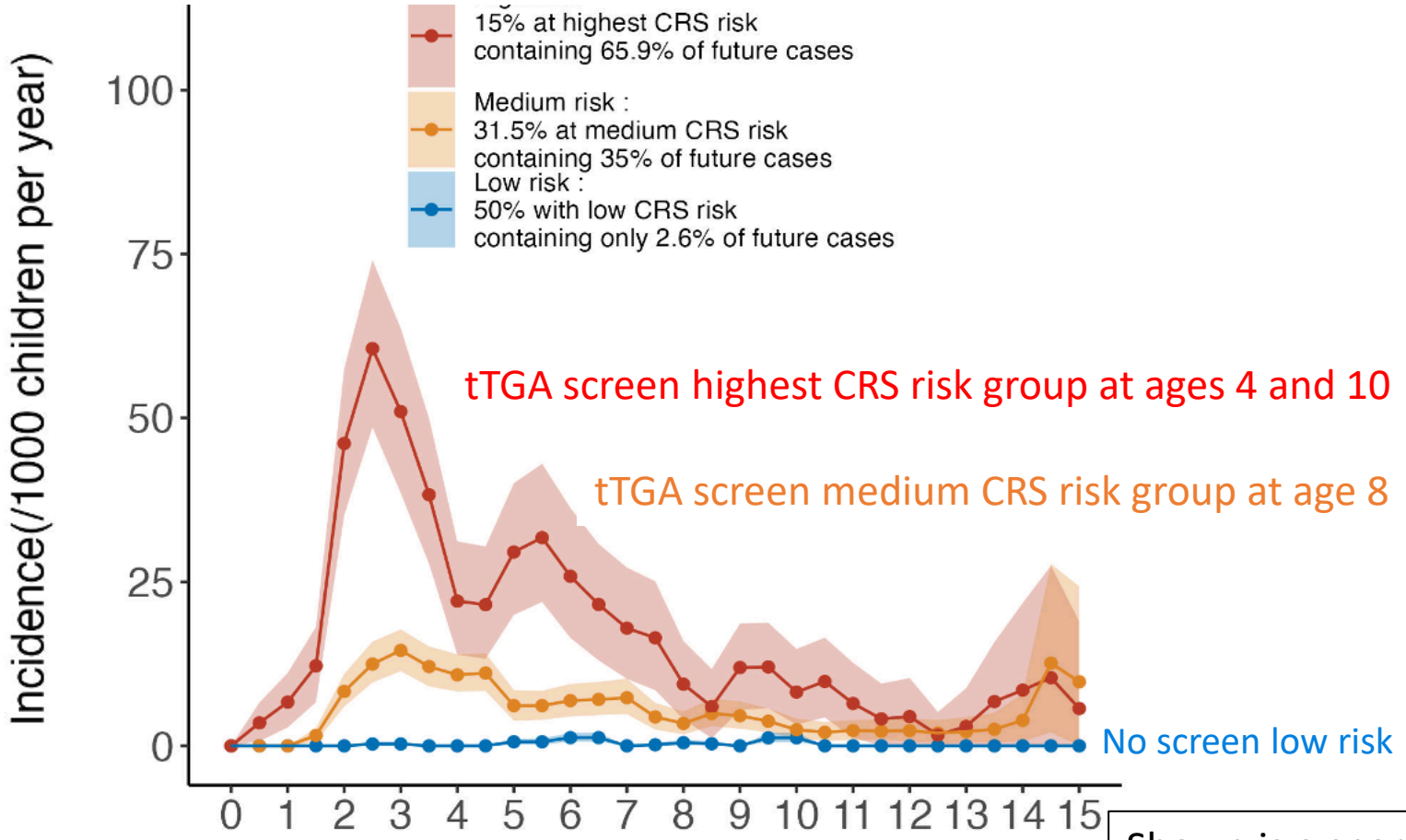
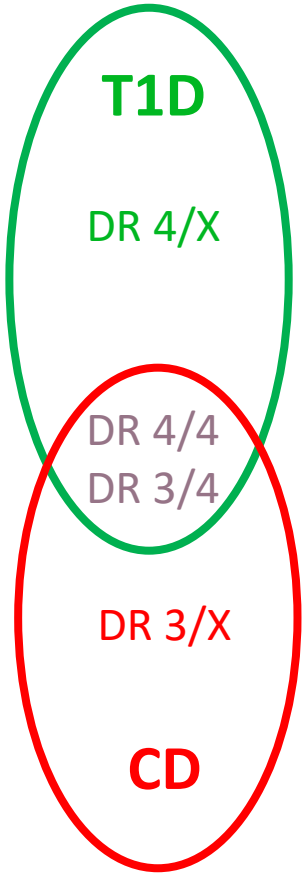
How to add in a Celiac Disease prediction strategy (via combined score using celiac-GRS, FH and sex)

- No added C-GRS cost in those with T1D GRS2
- A CD aab test and treatment exist
- High parental interest





Overall 88% sensitive for childhood CD
Median detection delay 2.2 years
Overall cost 0.65 TGA tests per child

Shown is a sparse tTGA autoantibody test strategy for best cost-benefit

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Monitoring autoantibody screen positives

After confirmation on repeat draw, confirmed early stage T1D follow-up uses consensus guidelines for patient education, immune monitoring and glycemic monitoring.

After confirmation on repeat draw, persistently TGA-positive children are referred to their pediatric primary or specialist provider for further evaluation.

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Criteria for adding a disease to the WA State Newborn Screening Panel

- A good screening test exists
- Diagnostic testing and treatment are available
- Early identification benefits the newborn
- Nature of the condition justifies population-based screening
- The benefits justify the costs of screening

Conclusions

- Newborn prescreening via genetic risk scores followed by islet autoantibody screening is expected to detect most childhood type 1 diabetes. We expect 67% sensitivity for T1D by age 15, while minimizing costs.
- Requires screening 15% of US children at ages 1.5, 5 and 10 yrs, which is logistically challenging especially if cost-effective mail-based sampling is used.
- Celiac Disease can be efficiently tested within the same framework via C-GRS and TGA screening
- Effective T1D interventions are available now to both greatly lessen DKA incidence and intervene with FDA-approved therapy. CD can be treated by diet.
- In the future, genetic information may be part of standard health care and of no cost to autoimmunity prediction programs

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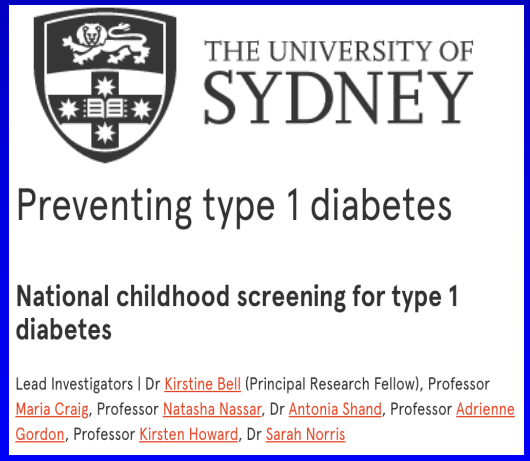
Our approach has also aided several other studies

South Dakota

Doha, Qatar



Sydney, Australia

Acknowledgements

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