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Feasibility of Fast Turnaround Genetic Screening for Type 1 Diabetes Risk in Newborns—Recruiting Infants for the Global Platform for the Prevention of Autoimmune Diabetes Primary Prevention Study Supplementation with *Bifidobacterium infantis* for Mitigation of Type 1 Diabetes Autoimmunity

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ABSTRACT

Screening using polygenic risk scores can identify infants at increased risk for islet autoimmunity and type 1 diabetes. The Supplementation with *Bifidobacterium infantis* (EVC001) for Mitigation of Type 1 Diabetes Autoimmunity study is a primary prevention study that enrolled infants aged between 7 and 42 days with an elevated genetic risk for type 1 diabetes identified through newborn screening. Here, we describe the screening process that enabled timely genetic risk assessment and enrolment into the Supplementation with *B. infantis* (EVC001) for Mitigation of Type 1 Diabetes Autoimmunity clinical intervention study within the required enrolment window. Screening was conducted in Belgium, Germany, Poland, Sweden, and the United Kingdom. Among 257,784 screened newborns included in the analysis, 3,309 newborns (1.3 %) had an eligible genotype associated with a > 10 % risk of developing early-stage type 1 diabetes by 6 years of age. Samples were collected at a median age of 2 days (interquartile range, 0–3), registered at a median age of 9 days (interquartile range, 6–11), and genotyped at a median age of 21 days (interquartile range, 18–24). Study sites received validated genotyping results at a median age of 22 days (interquartile range, 19–25). Consultation visits occurred at a median age of 29 days (interquartile range, 25–34) and enrolment into the Supplementation with *B. infantis* (EVC001) for Mitigation of Type 1 Diabetes Autoimmunity study took place at a median age of 38 days (interquartile range, 35–41). Overall, 1,149 eligible infants were enrolled into the Supplementation with *B. infantis* (EVC001) for Mitigation of Type 1 Diabetes Autoimmunity study (34.7 % of eligible infants). These findings demonstrate the feasibility of accelerated genetic screening programs and show that newborn screening workflows can be completed within the first 6 weeks of life to support timely enrolment into early intervention trials.

Keywords early detection, genetic risk, paediatric diabetes, clinical trial

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Introduction

The Global Platform for the Prevention of Autoimmune Diabetes (GPPAD) was established in 2015 as an international research consortium dedicated to the primary prevention of type 1 diabetes (T1D). Through a coordinated network of academic and clinical partners across Europe, GPPAD aims to use large-scale newborn screening to identify infants at increased genetic risk for T1D and to enable preventive interventions prior to the onset of autoimmune beta-cell destruction.¹ GPPAD employs a genetic risk score (GRS)–based screening strategy to identify newborns with a sub-

stantially elevated risk of developing T1D, defined as an estimated $\geq 10\%$ probability of progressing to early-stage disease by the age of 6 years.^{2,3} This strategy was initially implemented for the Primary Oral Insulin Trial,^{4,5} in which newborns were screened across multiple European centres. Infants exceeding the predefined GRS threshold were invited for enrolment between 4 and 7 months of age, resulting in the screening of 241,977 newborns and the enrolment of 1,050 participants within 3.1 years.

Building on this infrastructure, GPPAD launched subsequent primary prevention studies, including the “Supplementation with

Bifidobacterium infantis for Mitigation of Type 1 Diabetes Autoimmunity (SINT1A)” trial, a randomized, placebo-controlled, double-blind, multicentre study conducted across Belgium, Germany, Poland, Sweden, and the United Kingdom. SINT1A investigates whether daily supplementation with *Bifidobacterium longum* subsp. *infantis* (EVC001) within the first year of life reduces the cumulative incidence of beta-cell autoantibodies in childhood in children with an elevated genetic risk for T1D through early-life modulation of the gut microbiome and the immune response. Eligible participants were identified either through GRS-based screening or family history combined with human leukocyte antigen (HLA) genotyping, corresponding to a predicted > 10 % risk of multiple beta-cell autoantibodies by 6 years of age (Clinicaltrials.gov Identifier: NCT04769037⁶). A defining feature of the SINT1A protocol was the requirement for very early intervention, with enrolment targeted between 7 and 42 days of age. This narrow time window reflects the critical role of early postnatal gut microbiome colonization in immune development and metabolic programming, during which microbial exposures may shape long-term immune tolerance. Consequently, the rapid identification and recruitment of eligible newborns required an optimized, high-throughput genetic screening pipeline with substantially reduced turnaround times.

To meet these demands, the GPPAD screening framework was iteratively refined to accelerate all stages of the process, including sample collection, single nucleotide polymorphism (SNP)-based genotyping, risk calculation, and communication of results to families and study sites. Here, we describe the process that enabled the SINT1A study to achieve full enrolment of 1,149 newborns between March 2021 and February 2024, describe its performance, and thereby demonstrate the feasibility of rapid, population-based genetic screening combined with very early preventive intervention.

Materials and methods

Study design

This study is an analysis of data collected during newborn screening for the genetic risk of T1D conducted by GPPAD between March 2021 and February 2024. GPPAD screening was conducted using a standardized fast turnaround protocol to identify newborns with a high genetic risk of developing T1D with the goal of enrolling them into the SINT1A primary prevention study within the required enrolment age of 7 to 42 days of life (Clinicaltrials.gov Identifier: NCT04769037). For this purpose, the original GPPAD screening protocol published in 2019 was accelerated.⁶ Specifically, the key differences between the two screening procedures were in their timing and frequency: in SINT1A, samples were shipped to the genotyping laboratory on a weekly basis. At the laboratory, genotyping for SINT1A was completed within 1 week, and the results were subsequently validated on a weekly schedule. Screening for SINT1A was performed in Belgium (Leuven), Germany (Dresden, Hannover, and Munich), Poland (Warsaw), Sweden (Malmö) and the United Kingdom (Newcastle).

Participants

Newborns who participated in the genetic screening were tested for their genetic risk of T1D based on risk scores derived from 51 SNPs that define HLA-DR3, HLA-DR4, and HLA-DQ8 alleles as well as SNPs from HLA class I, from non-HLA T1D susceptibility genes, and from HLA class II protective alleles, with a high genetic risk identified using a combination of calculated risk scores and whether or not a newborn had a first degree relative with T1D.^{3,6} Newborns with a > 10 % predicted risk to develop multiple beta-cell autoimmunity by the age of 6 years and who fulfilled the inclusion criteria were eligible to participate in the SINT1A study. Newborns with missing or invalid dates of birth were excluded from further processing because a valid date of birth was required in order to calculate the child’s age at each screening step. For more information about eligibility for the SINT1A study, see ref.⁶

The screening process from blood sample collection to enrolment of eligible children in SINT1A is shown in **Fig. 1**. The following flow and timelines were predefined: (1) Blood samples were to be collected within 7 days after birth on a filter paper card and immediately shipped from participating clinics or paediatricians (screening sites) to their respective local study sites; (2) Local study sites were to process and register the samples; (3) Local study sites were to send the samples to the central genotyping laboratory (LGC Group, Hoddesdon, United Kingdom) on a weekly basis, and, in parallel, transfer the participants’ data to the GPPAD Coordinating Centre (CC) database; (4) The central genotyping laboratory was commissioned to perform the genotyping with a turnaround time of approximately 7 days, before transmitting the results to the GPPAD CC; (5) The GPPAD CC was to validate these genotyping results, calculate the T1D GRSs and determine eligibility; (6) Validated results, risk scores and eligibility were to be transmitted back to the originating local study site; (7) Study sites were asked to contact families of eligible infants and to invite them to participate in a consultation visit; and (8) Upon the confirmation of eligibility and obtaining informed consent, infants were to be enrolled into the SINT1A intervention study. The entire screening-to-enrolment process was designed to be completed within 42 days of birth, with a permissible extension to 56 days under exceptional circumstances, which were pre-defined in the study protocol (illness, COVID-19-related issues or unexpected delay in result reporting).

Ethical approval for genetic screening was obtained from the local ethical committees of the Technische Universität München Medical Faculty (138 / 17 S), the Technische Universität Dresden (EK 151042016), the Medizinische Hochschule Hannover (7578), the Medical University of Warsaw (Instytucie Matki i Dziecka w Warszawie) (48/2020), EC Research UZ Leuven (S60710), the Regionala etikprövningsnämnden i Lund (2017/917) and NHS Health Research Authority (21/NE/0161). Ethical approval for the SINT1A study was approved by the local ethical committees and regulatory authorities of the Technische Universität München, Medical Faculty (715/20 S-SR), the Technische Universität Dresden (SR + BO-44012021), the Medizinische Hochschule Hannover (9589_BO_S_2021), the Medical University of Warsaw (KB/5/2021), EC Research UZ Leuven (S65015), Swedish ethical review authority (Dnr 2021-01210) and the NHS Health Research Authority (21/

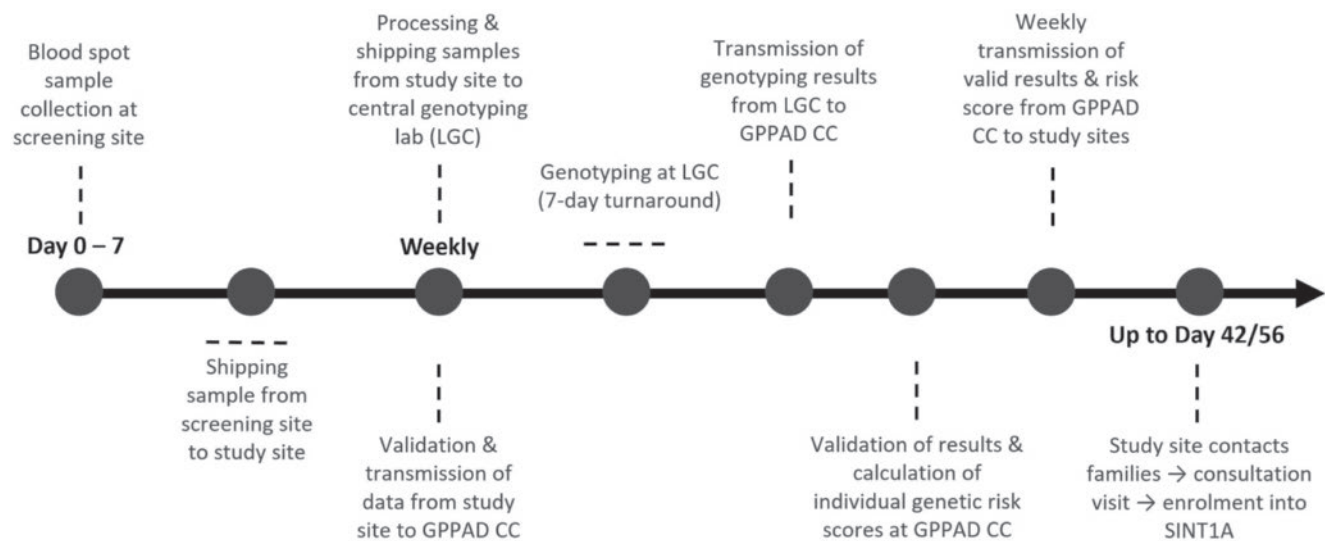


Fig. 1 Fast turnaround newborn screening for type 1 diabetes genetic risk. A diagram showing the accelerated screening and enrolment process used in the GPPAD trial SINT1A. CC, coordinating centre; GPPAD, Global Platform for the Prevention of Autoimmune Diabetes; LGC, LGC Group; SINT1A, Supplementation with *B. infantis* (EVC001) for Mitigation of Type 1 Diabetes Autoimmunity.

NE/0180). The parents or legal representatives of each participant provided written informed consent.

Sample and data flow and processes around screening

All data included in the analysis were collected in one comprehensive database, the GPPAD-02 screening application, a custom-built, web-based system developed by the GPPAD CC. The system's back-end and databases were hosted on secured servers. Each newborn was assigned a unique ID number for pseudonymization, and a separate genotyping ID was generated for analysis at LGC to guarantee data safety. The application also had an audit trail to ensure the traceability of user actions and data changes. Recorded variables included the screening site (location of sample collection), date of birth of the screened newborn, whether a second (retype) sample was required due to an invalid initial genotyping result, and the final eligibility status for participation in SINT1A.

As screening sites used one of three different screening approaches, the screening type was also recorded. In combined newborn screening, samples and data were obtained from an additional blood spot on the national newborn screening card (Newcastle, Warsaw). In attached newborn screening, blood was collected on a separate filter paper card for the GPPAD-02 study, while some data were obtained from the national newborn screening cards (Dresden, Hanover, and Leuven). In independent screening, samples and data were collected separately from the national newborn screening programme using different blood draws and filter paper cards (Malmö and Munich).

In addition to the date of birth, the age of the newborn was recorded at several defined time points to allow the precise tracking of the procedural workflow. This documentation included the sample date (blood draw), registration date at the study site, shipping date of the sample to the central genotyping laboratory, receiving date at the genotyping laboratory, the date of receipt of genotyp-

ing results at the GPPAD CC, the date of validation of the genotyping results and dissemination of results to the participating study sites, the consultation visit date with families of newborns identified as genetically at risk and the enrolment date into the SINT1A study. This comprehensive data collection enabled the detailed analysis of the logistical processes and contributed to quality assurance and the optimization of the screening procedure.

Costs of fast turnaround screening for enrolment in the Supplementation with *Bifidobacterium infantis* (EVC001) for Mitigation of Type 1 Diabetes Autoimmunity

The screening costs of this research project were estimated upfront for each process step based on previous experience and quotes for services. Funding was provided to the partners based on the number of participants screened and the estimated costs. Actual costs are reported in this analysis.

Statistical analyses

Statistical analyses were performed using R software, version 4.4.1.7. Timing variables were compared between study sites and respective screening types using the Kruskal–Wallis test. A Bonferroni-corrected two-tailed *p*-value of <0.05 was considered significant.

Results

Screening and enrolment numbers

The target number of participants to be enrolled in SINT1A was 1,144 newborns within a period of 36 months. Ultimately, 1,149 newborns were enrolled in the SINT1A study over a period of 34 months. In total, 258,567 newborns were screened between March 1, 2021, and February 15, 2024. Of these, 783 newborns (0.28%)

were not considered eligible for genotyping due to missing or invalid data or material (454 with missing or invalid dates of birth and 329 with insufficient sample materials). The remaining 257,784 newborns were processed and included in this analysis data set.

Of the 257,784 included newborns, 131,179 (50.9 %) were male, 124,821 (48.4 %) were female and no sex information was provided for 1,784 (0.7 %). Among the screening sites, 13,241 (5.1 %) were screened by Newcastle (UK), 87,537 (34.0 %) by Warsaw (Poland), 44,147 (17.1 %) by Dresden (Germany), 19,390 (7.5 %) by Hanover (Germany), 59,005 (22.9 %) by Munich (Germany), 19,783 (7.7 %) by Leuven (Belgium), and 14,681 (5.7 %) by Malmö (Sweden). The sample date was missing for 60,897 (23.6 %) samples. Apart from those screened in Dresden, where no samples dates were transmitted, the percentage of missing sample date ranged from 17 (0.02 %) in Warsaw to 13,422 (67.8 %) in Leuven. Overall, 1,796 (0.7 %) samples needed a retype because the first typing did not achieve a valid result. A first degree relative with T1D was recorded for 3,616 (1.4 %) newborns, including 1,582 (43.8 %) mothers with T1D, 1,486 (41.1 %) fathers with T1D, and

346 (9.6 %) siblings with T1D. An unspecified relative status was only recorded in Newcastle for 202 (5.6 %) newborns.

Of screened newborns, 3,309 (1.3 %) had a predicted risk of greater than 10 % to develop two or more islet autoantibodies by 6 years of age based on their genotypes, making them eligible for enrolment in SINT1A. The frequency of eligible newborns ranged from 1.0 % in Warsaw to 2.4 % in Malmö. Overall, 962 (29.1 %) of eligible newborns had a first degree relative with T1D. The parents/guardians of 2,415 (73.0 %) eligible newborns responded to the invitation to attend a consultation visit informing about the SINT1A study, the child's risk for T1D, and T1D in general, with the percentage of consultation visit participation ranging from 37.1 % in Newcastle to 97.6 % in Leuven. This included 718 (74.6 %) of the 962 eligible newborns who had a first degree relative with T1D and 1,594 (67.9 %) of 2,347 who did not have a first degree relative with T1D. The final number of newborns enrolled in SINT1A was 1,149 (34.7 % of eligible) newborns, with enrolment frequencies among those ranging from 29.0 % in Warsaw to 49.3 % in Malmö (Table 1). Enrolment included 415 (43.1 %) of 962 eligible newborns who had first degree relatives with T1D and 734 (31.3 %) of 2,347 eligible newborns who did not have a first degree relative with T1D.

Table 1 Characteristics of newborns included into the data analysis, both overall and per-site. Sites are additionally grouped according to whether screening for type 1 diabetes (T1D) risk was combined, attached, or independent of the newborn screening programme

	Combined with newborn screening						Attached to newborn screening						Independent from newborn screening			
	Overall		Newcastle		Warsaw		Dresden		Hanover		Leuven		Malmö		Munich	
	N	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Screened participants	257,784	100	13,241	5.1	87,537	34.0	44,147	17.1	19,390	7.5	19,783	7.7	14,681	5.7	59,005	22.9
Male	131,179	50.9	6,511	49.2	44,877	51.3	22,575	51.1	9,745	50.3	10,015	50.6	7,306	49.8	30,150	51.1
Female	124,821	48.4	6,218	47.0	42,602	48.7	21,504	48.7	9,189	47.4	9,680	48.9	6,972	47.5	28,656	48.6
Unknown sex	1,784	0.7	512	3.9	58	0.1	68	0.2	456	2.4	88	0.4	403	2.7	199	0.3
No sample date	60,897	23.6	55	0.4	17	0.02	44,147	100	1,356	7.0	13,422	67.8	7	0.05	1,875	3.2
Retyped	1,796	0.7	38	0.3	414	0.5	262	0.6	89	0.5	294	1.5	142	1.0	557	0.9
First-degree relative with T1D (FDR)	3,616	1.4	407	3.1	609	0.7	436	1.0	434	2.2	360	1.8	311	2.1	1,059	1.8
Father	1,486	41.1	110	27.0	292	47.9	148	33.9	168	38.7	160	44.4	170	54.7	438	41.4
Mother	1,582	43.8	73	17.9	243	39.9	233	53.4	230	53.0	175	48.6	122	39.2	506	47.8
Sibling	346	9.6	22	5.4	74	12.2	55	12.6	36	8.3	25	6.9	19	6.1	115	10.9
Unspecified	202	5.6	202	49.6	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Eligible for SINT1A	3,309	1.3	240	1.8	862	1.0	474	1.1	293	1.5	254	1.3	359	2.4	827	1.4
No FDR	2,347	70.9	172	71.7	674	78.2	374	78.9	187	63.8	168	66.1	243	67.7	529	64.0
FDR	962	29.1	68	28.3	188	21.8	100	21.1	106	36.2	86	33.9	116	32.3	298	36.0
Consultation visit	2,415	73.0	89	37.1	772	89.6	326	68.8	171	58.4	248	97.6	298	83.0	511	61.8
No FDR	1,697	70.3	57	64.0	600	77.7	253	77.6	109	63.7	165	66.5	199	66.8	314	61.4
FDR	718	29.7	32	36.0	172	22.3	73	22.4	62	36.3	83	33.5	99	33.2	197	38.6
Enrolled in SINT1A	1,149	34.7	83	34.6	250	29.0	171	36.1	90	30.7	103	40.6	177	49.3	275	33.3
No FDR	734	63.9	52	62.7	182	72.8	123	71.9	51	56.7	68	66.0	110	62.1	148	53.8
FDR	415	36.1	31	37.3	68	27.2	48	28.1	39	43.3	35	34.0	67	37.9	127	46.2

Timing of screening steps

In the conclusion of the screening process, 3,054 (92.3 %) newborns with eligible genotypes were in the 7–42 days age range for enrolment, 121 (3.7 %) newborns were in the extended (<56 days) age range for enrolment and 134 (4.0 %) newborns with an eligible genotype were outside the age range for enrolment (>56 days; **Fig. 2**). While newborns were only enrolled in the SINT1A study if they fell within the age range for enrolment, and all newborns with eligible genotype were invited to consultation visits so that families could be informed about their child's increased risk for developing T1D.

Dried blood spot samples were collected at a median age (interquartile range in d, IQR) of 2 days (0–3 d). Registration of the samples in the GPPAD-02 screening application occurred at a median age of 9 days (6–11 d). Shipment of the samples to the central genotyping laboratory occurred at a median age of 11 days (8–14 d) reflecting the fast turnaround screening process. Samples were received at the central genotyping laboratory at a median age of 15 days (12–18 d). Genotyping results were received at a median age of 21 days (18–24 d). The final step of the screening process, the validation of results and notification of study sites, occurred at a median age of 22 days (19–25 d). Overall, sites received notification about newborns with an eligible genotype a median

of 20 days after sample collection. Following the screening process, participants with an eligible genotype were invited to the consultation visit, which occurred at a median age of 29 days (25–34 d). Finally, the baseline visit, which represented randomization and enrolment into the study, occurred at a median age of 38 days (35–41 d).

Of the 1,796 screened newborns who required retyping, 192 (10.7 %) were found to have an eligible genotype. Of these 192, 90 (46.9 %) were processed within the 7–42 days enrolment age range, 48 (25 %) between 42 days and the extended enrolment age limit (56 days), and 54 (28.1 %) outside the enrolment age range (>56 days). Overall, 21 (10.9 %) retyped newborns with an eligible genotype were enrolled in SINT1A.

Variation between sites

Variations between sites were observed for the age at which the sample was taken, the time from sample collection to registration, the shipment time from the study site to the genotyping lab, the time from the site receiving notification of eligibility ("site notification") to the consultation visit, and the time from the consultation visit to enrolment into SINT1A (**Table 2, Supplementary Fig. S1**, available in the online version only). Samples were taken at a median age of 0 days (IQR, 0–0 d) in Malmö to 5 days (5–5 d) in

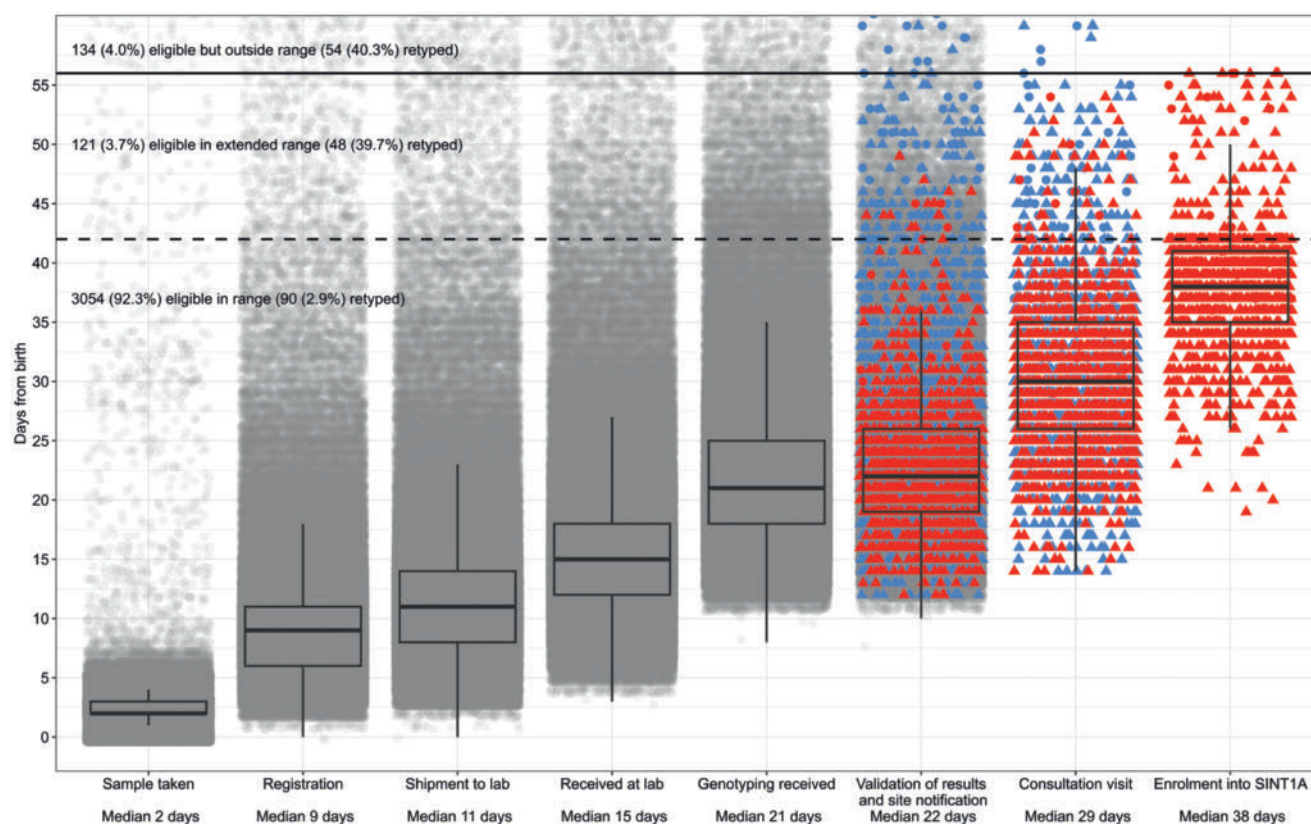


Fig. 2 Screening programme timeline in the GPPAD primary prevention study SINT1A. The graphs depicts newborn age (in days) at completion of each step in the screening and enrolment process for the SINT1A primary prevention study. The median age is indicated at each step. Triangles denote children eligible for enrolment in SINT1A. Circles denote eligible participants whose samples required repeat genotyping. Red points indicate children enrolled in the study. Blue points represent eligible children who were not enrolled. Box plots show the median and interquartile range (IQR) for each column, and the whiskers extend to 1.5 x IQR. GPPAD, Global Platform for the Prevention of Autoimmune Diabetes; SINT1A, Supplementation with *B. infantis* (EVC001) for Mitigation of Type 1 Diabetes Autoimmunity.

Table 2 Age and processing time (median in days) of samples and data from newborns included into the study, overall and per site. Sites are additionally grouped according to whether screening for type 1 diabetes risk was combined, attached, or independent of the newborn screening programme. Interquartile range (IQR), Median (Med.)

	Combined with newborn screening						Attached to newborn screening						Independent from newborn screening			
	Overall		Newcastle		Warsaw		Dresden		Hanover		Leuven		Malmö		Munich	
	Med.	IQR	Med.	IQR	Med.	IQR	Med.	IQR	Med.	IQR	Med.	IQR	Med.	IQR	Med.	IQR
Age at sample taken	2	0–3	5	5–5	3	2–3	NA	NA	2	2–2	3	3–3	0	0–0	2	0–2
Time from sample collection to registration	7	5–9	6	5–8	5	3–7	NA	NA	8	6–10	16	12–21	7	5–9	7	5–11
Shipment time (site to laboratory)	3	2–6	3	2–4	3	3–6	3	2–4	3	2–8	3	2–8	6	5–7	3	2–4
Time from received at lab to genotyping received	6	5–7	6	5–7	6	5–7	6	6–7	6	5–7	6	6–7	6	5–7	6	6–7
Time from genotyping received to validation and site notification	1	0–1	0	0–1	1	0–1	1	0–1	1	0–1	1	0–1	1	0–1	1	0–1
Time from notification to consultation visit	6	4–11	7	5–8	6	4–8	10	6–14	8	6–13	6.5	4–16	3	1–5	7	5–10
Time from consultation visit to enrolment	7	4–11	3	2–7	10	7–14	7	4–9	4	1–7	7	5–9	8	6–11	7	5–9
Age at enrolment into SINT1A	38	35–41	36	33–40	38	35–40	39	37–41	39	36–41	40	37–42	36	34–39	39	35–41

Newcastle and were registered from a median age of 7 days (5–9 d) in Dresden and Malmö to 16 days (13–21 d) in Leuven. Shipment time to the central genotyping laboratory ranged from a median of 3 days from Dresden (2–4 d), Hanover (2–8 d), Leuven (2–8 d), Munich (2–4 d), Newcastle (2–4 d) and Warsaw (3–6 d) to 6 days (5–7 d) from Malmö. The time from site notification to the consultation visit varied from a median of 3 days (1–5 d) in Malmö to 10 days (6–14 d) in Dresden. The time from the consultation visit to enrolment in SINT1A ranged from a median of 3 days (2–7 d) in Newcastle to 10 days (7–14 d) in Warsaw. Despite these variations, the median age of enrolment into SINT1A was relatively similar between sites, ranging from a median of 36 days in Newcastle (33–40 d) and Malmö (34–39 d) to 40 days (37–42 d) in Leuven. Furthermore, no significant differences in the age at enrolment were observed when sites were grouped into those where screening was combined with the national or local newborn screening programme (Newcastle, Warsaw; median age, 38 d; IQR, 34–40 d), attached to the newborn screening programme (Dresden, Hanover, and Leuven; median age, 39 d; IQR, 37–41 d) or independent of the newborn screening programme (Malmö and Munich; medi-

an age, 38 d; IQR, 34–40 d) (**Supplementary Fig. S2**, available in the online version only).

Screening costs

The total programme cost was \$13,986,988 (**Table 3**). The largest cost components were sample collection at clinics and the obtaining of informed consent (\$2,835,624 and \$11.00 per screened newborn), genotyping laboratory services (\$2,651,960 and \$10.29 per screened newborn), study site project staff (\$2,979,613 and \$11.56 per screened newborn), and local laboratory sample processing/data entry (\$1,417,812 and \$5.50 per screened newborn). Additional costs included GPPAD CC management (\$1,342,615 and \$5.21 per screened newborn), site operational expenses (\$744,903 and \$2.89 per screened newborn), software and data management (\$561,579 and \$2.18 per screened newborn), filter paper cards (\$622,533 and \$2.41 per screened newborn), shipping (\$166,224 and \$0.64 per screened newborn), and consultation visits (\$664,125 and \$201 per eligible newborn). Overall, the cost was \$52 per screened newborn, \$4,227 per eligible newborn, and \$12,173 per enrolled newborn.

Table 3 Cost breakdown for the GPPAD-02 newborn screening programme (FTE = full time equivalent)

	Total cost	Per screened newborn	Per high risk T1D newborn	Per enrolled newborn
Clinic: blood collection and consenting	\$2,835,624	\$11.00	\$857	\$2,468
Local laboratory: sample processing and data entry	\$1,417,812	\$5.50	\$428	\$1,234
Shipment to genotyping laboratory	\$166,224	\$0.64	\$50	\$145
Genotyping lab: DNA extraction and genotyping	\$2,651,960	\$10.29	\$801	\$2,308
Study site: 2 FTE staff per site	\$2,979,613	\$11.56	\$900	\$2,593
Study site: project costs (travel allowance, local printing, and public awareness)	\$744,903	\$2.89	\$225	\$648
GPPAD-coordinating centre: 4 FTE staff	\$1,342,615	\$5.21	\$406	\$1,169
GPPAD-02 screening application (development, maintenance, and data management)	\$561,579	\$2.18	\$170	\$489
Filter paper cards	\$622,533	\$2.41	\$188	\$542
Consultation Visits	\$664,125		\$201	\$578
Grand Total	\$13,986,988	\$52	\$4,227	\$12,173

Discussion

Newborn enrolment into the SINT1A study served as a proof of concept for fast turnaround newborn genetic screening, showing that it was feasible to complete blood sampling, shipping, genotyping, and validation of results within a median of 22 days from birth. Screening was performed on over 250,000 newborns from five European countries allowing the enrolment of 1,149 infants to a prevention study within a maximum of 56 days from birth, with 96 % of these infants enrolled within 42 days. This is an important finding for the design of primary prevention trials or trials for therapies that must be conducted early in life and require prior genetic stratification.

Our results are encouraging and indicate strong family interest and engagement in trials such as SINT1A, as previously observed.⁸ Notably, 70 % of families who were notified of an elevated genetic risk for T1D participated in consultation visits and around half of those families enrolled into the trial. There was, however, a substantial variation between locations. Newcastle, for example had a relatively low participation rate in consultation visits, but very high acceptance to participate in the trial among those who attended consultation. In contrast, Leuven had very high participation in the consultation visits, but much less acceptance to partic-

ipate in the trial among those who attended consultation. These differences may reflect the degree of information provided to families prior to screening as this varied between sites. Overall, however, the final recruitment rates from those eligible were similar between locations. These findings demonstrate that rapid follow-up and early trial enrolment are feasible and that the short interval between the notification of elevated genetic risk and the decision to enrol did not appear to deter participation.

Sustaining the rapid workflow over 3 years required substantial efforts from all parties. The process was feasible due to its structured, well-documented and trackable design, and the inclusion of automated steps, where possible. Clinical studies such as SINT1A are not conducted by a single research group, but by multiple centres and organizations working in cooperation.⁹ Thus, it is also important to consider the ways in which fast turnaround genetic screening can be impacted by variations between sites. We observed that while 96 % of children were ultimately screened in time to be enrolled in the study, variability existed between the sites with regard to the amount of time taken to complete several steps. Despite its accelerated pace, our screening process contained enough flexibility to allow sites that lagged behind earlier in the process to catch up in later phases. Variations due to the screening type were largely restricted to the site-dependent steps of the screening process. Some of these differences related to engagement with the national or local newborn screening programmes, while others were related to logistics of arranging visits after notification. In particular, the Swedish model of using cord blood collected at birth independently of the national newborn screening programme shortened the early steps of the process.

An important aspect of screening is costs. The costs presented are those that were calculated for expected workload at sites based on the predicted numbers screened and the actual costs of the services used. The per child screened cost was \$52 (USD). This is the total cost from collection to enrolment and was for the specific needs of the SINT1A study. Costs could be reduced by increasing the shipping intervals to genotyping laboratories and by combining genetic risk screening for T1D with existing programmes so that additional consultation and sample collection can be minimised. Nevertheless, the costs provide a guide to the costs generally expected for genetic screening programmes. Notably, the entire cost for SINT1A genetic screening to enrolment is substantially lower than the unit cost for SNP typing of \$200 used in a recent cost estimate for screening in Canada.¹⁰ Polygenic risk scores for T1D are proposed to identify some 80 % of future cases of T1D from 20 % of the background population.¹¹ In a population that has a 0.4 % disease prevalence, this would approximate to around \$16,000 per individual with T1D identified by the genetic screening.

Conclusion

We conclude that fast turnaround genetic screening is possible, and that screening can feasibly be conducted within a median of 22 days, enabling enrolment into a primary prevention clinical trial within the first 6 weeks of life. Fast turnaround screening can be applied in other infant clinical trials, either to enrol participants at a very early age or to maximize the decision time available for par-

ents and caregivers. However, this must be balanced against its costs and the requirements of the study. Variability between sites and screening programmes did not prevent sites from screening and enrolling enough newborns to meet participation targets, showcasing the adaptability of the genetic screening process, even with an accelerated schedule.

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Statements and Additional Information

Conflict of Interest The authors declare that they have no conflict of interest.

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