Successful integration of newborn genetic testing into UK routine screening using prospective consent to determine eligibility for clinical trials

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ABSTRACT
Objective INGR1D (INInvestigating Genetic Risk for type 1 Diabetes) was a type 1 diabetes (T1D) genetic study established to identify participants for a primary prevention trial (POInT, Primary Oral Insulin Trial).

Methods The majority of participants were recruited by research midwives in antenatal clinics from 18 weeks’ gestation. Using the NHS Newborn Bloodspot Screening Programme (NBSP) infrastructure, participants enrolled in INGR1D had an extra sample taken from their day 5 bloodspot card sent for T1D genetic screening. Those at an increased risk of T1D were informed of the result, given education about T1D and the opportunity to take part in POInT.

Results Between April 2018 and November 2020, 66% of women approached about INGR1D chose to participate. 15 660 babies were enrolled into INGR1D and 14 731 blood samples were processed. Of the processed samples, 157 (1%) had confirmed positive results, indicating an increased risk of T1D, of whom a third (n=49) enrolled into POInT (20 families were unable to participate in POInT due to COVID-19 lockdown restrictions).

Conclusion The use of prospective consent to perform personalised genetic testing on samples obtained through the routine NBSP represents a novel mechanism for clinical genetic research in the UK and provides a model for further population-based genetic studies in the newborn.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Pre-symptomatic type 1 diabetes (T1D) is marked by the presence of ≥2 diabetes-associated autoantibodies, with a peak age of onset at 2 years.

⇒ T1D primary prevention trials aiming to intervene prior to seroconversion would therefore need to target children <1 year of age.

⇒ A genetic risk score has been developed to identify individuals with a 10% risk of developing pre-symptomatic T1D by 6 years of age by using a combination of 47 single-nucleotide polymorphisms and a family history of a first-degree relative with T1D.

WHAT THIS STUDY ADDS

⇒ The novel methodology used by INGR1D (INInvestigating Genetic Risk for type 1 Diabetes) demonstrates how a successful research trial tool can be integrated into a national screening programme without altering the screening pathway.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This research tool could be expanded to antenatal interventions and exploration of the mother–baby dyad, and represents the cutting edge of clinically relevant genetic research.

INTRODUCTION
Type 1 diabetes (T1D) is an autoimmune condition that leads to significant mortality and morbidity, with a reduced life expectancy of 12 years in 20-year-old diabetics. In 2017, the UK had the world’s fifth highest incidence of T1D in those younger than 15 years of age, equating to 3300 new cases per year. Moreover, the incidence of T1D has been increasing by 3% year-on-year. Pre-existing autoantibodies, with a peak age of 2 years. In addition, the presence of two or more IA is predictive of T1D, with 80% of individuals developing symptoms over the following 10 years. Individuals with multiple IA can therefore be thought of having an early stage of T1D known as asymptomatic or pre-diabetes.

Achieving self-tolerance is facilitated by T-cell exposure of self-antigens in the thymus or secondary lymphoid tissues (such as lymph nodes, gut or spleen), leading to induction of regulatory T cells.
Based on estimates that 1% of the population would screen positive, and that one-third would agree to take part in POInT, GPPAD's aim was to screen 300,000 participants across seven study sites in Europe to recruit 1040 individuals to POInT. The latter would provide 80% power to detect a 50% risk reduction in the incidence of beta-cell autoantibodies using a two-sided test at the 0.05 level after 7.0 years of study duration.

In the UK, recruitment to INGR1D ran from April 2018 to November 2020. The majority of participants were recruited by research midwives in antenatal clinics from 18 weeks' gestation onwards. Consent was received electronically to allow for (a) completion of a maternal questionnaire and (b) prospective consent to use surplus blood from the newborn bloodspot screening card (NBSC) for genetic screening.

All neonates undergoing NBSC whose card had surplus blood were eligible. Neonates for whom consent had been received to participate in the study were considered enrolled when their NBSC was received in the NBSC laboratory.

Bloodspot sampling and analysis

For participants within the Thames Valley area, genetic analysis was undertaken on surplus blood punched from the NBSC after routine screening had been performed. No extra blood was collected on the cards.

For participants from outside Thames Valley, or infants who had already had their NBSC test performed, a bloodspot was taken on an additional NBSC which was clearly labelled as a ‘GPPAD only’ sample. This pathway therefore did not interfere with the child’s routine NBSC which was undertaken at their regional screening laboratory.

Genotyping was conducted by LGC Biosearch Technologies (Milton Keynes, UK) and the results forwarded to Helmholtz Zentrum München, the coordinating centre in Munich. Helmholtz integrated the genotyping data, routine information collected by the screening laboratory and responses to the maternal questionnaire to generate a genetic risk score which was then conveyed to the local study team.

Relaying results

 Mothers were informed of positive results within 16 weeks of sample analysis and subsequently offered a face-to-face appointment to be informed about the implications of the result and POInT. Negative results were not relayed but were told at the time of consent that a negative result could be inferred if the study team did not contact them by 16 weeks. If parents remained anxious about the result, they could also contact the study team directly. Parents could withdraw their consent at any time.

RESULTS

From April 2018 to November 2020, 66% of women approached about INGR1D chose to participate, leading to a total of 15,660 babies being enrolled in the study, of whom 637 (4%) had a first-degree relative with T1D. During this period, 14,731 blood samples were processed, of whom 137 had confirmed positive results (>10% risk of multiple IA). Of these families, 34 declined formal counselling about the positive result, and of the 124 families who undertook this counselling, 49 agreed to take part in POInT. It is of note that 20 families were unable to participate in POInT due to COVID-19 lockdown restrictions. In total, 107 (0.68%) of INGR1D’s 15,660 participants were withdrawn from the study. The most common reasons for withdrawal were...
the NBSP in the UK is widely acceptable to families and provides research purposes. With an average national coverage of 96.5%, potential for other screening tests to be added, including for with positive, borderline or inconclusive results, without redundancy if samples need to be re-analysed for any patient the NBSC can yield approximately 16 blood samples, providing

**DISCUSSION**

The success of the INGR1D study demonstrates the ability of the NBS to facilitate large-scale early screening for research studies without interfering with the newborn bloodspot screening programme (NBSP).

The NBSP can be used in this way as the four bloodspots on the NBSC can yield approximately 16 blood samples, providing redundancy if samples need to be re-analysed for any patient with positive, borderline or inconclusive results, without needing to re-bleed the infant. This redundancy provides the potential for other screening tests to be added, including for research purposes. With an average national coverage of 96.5%, the NBSP in the UK is widely acceptable to families and provides an ideal platform to assist in identifying appropriate cohorts for recruitment into research studies. Despite its vast potential, as far as the authors are aware, this has never previously been used prospectively on a large scale.

Thanks to this novel research screening methodology, it has already started to yield significant advances in our knowledge surrounding the early changes in glycaemic control for infants entering pre-diabetes. Having developed and established this methodology, the GPPAD consortium has built on and expanded this approach to enrol to an international T1D primary prevention randomised trial using probiotics that will be initiated in Newcastle and Cambridge. The new study includes four additional SNPs in the GRS that reflects the continuous advances being made in our understanding of T1D genetic risk. However, this methodology does not need to be solely restricted to T1D, genetic screening or interventions in the newborn. This model also lends itself to exploring the impact of antenatal interventions, interrogation of the mother–fetus dyad and screening for at-risk population groups to offer postnatal primary interventions (eg, to children born to mothers with gestational diabetes or pre-eclampsia, who have increased lifetime risks of diabetes, obesity and hypertension).

In addition, these programmes have the potential to allow for early interventions prior to disease onset or progression. The initiatives that enabled INGR1D have facilitated an Oxford pilot programme of neonatal screening for spinal muscular atrophy (SMA), an example of a condition with a prognosis that can be dramatically improved through prompt identification and treatment, and already forms, or will soon form, part of the screening programme in several countries. Although SMA represents a single gene disorder with a recognised treatment, this approach to enrol to an international T1D primary prevention randomised trial using probiotics that will be initiated in Newcastle and Cambridge. The new study includes four additional SNPs in the GRS that reflects the continuous advances being made in our understanding of T1D genetic risk. However, this methodology does not need to be solely restricted to T1D, genetic screening or interventions in the newborn. This model also lends itself to exploring the impact of antenatal interventions, interrogation of the mother–fetus dyad and screening for at-risk population groups to offer postnatal primary interventions (eg, to children born to mothers with gestational diabetes or pre-eclampsia, who have increased lifetime risks of diabetes, obesity and hypertension).

It is striking that two out of three women approached agreed to take part in this research project, despite the low likelihood of their child testing positive (1%), positive predictive value for T1D (10%) and sensitivity of the GRS (with three-quarters of individuals who will likely develop T1D screening negative), all of which mothers were counselled on and advised not to be falsely reassured by a negative result. It is also notable that the majority of families of babies with an elevated risk for T1D declined to take part in the clinical trial (POInT) that was the *raison d’etre* for the screening programme. Although a substantial proportion of these were for pragmatic reasons (eg, the time commitment required for POInT or a temporary suspension of study recruitment for the COVID-19 lockdown), some families informally reported during consent that the result would give them additional information—however imperfect—about their child’s health, and as such perceived the test as having value even without enrolment into POInT. Furthermore, given that for families there was no financial cost and minimal time commitment to participation in INGR1D, this could be seen as a rationale decision, even if INGR1D would not meet NHS criteria for a clinical screening programme.

As regards to the one-third of women who did not consent to INGR1D, improved counselling about the aetiology of T1D may have increased enrolment as many women felt reassured by the lack of family history of the disease. In addition, the environment in which women were approached about the study also impacted recruitment which was more successful in the antenatal scanning department compared with the postnatal wards where many reported a lack of time and energy to consider the study properly.
Future NBSPs

The model used by GPPAD described earlier demonstrates that genomic screening can be integrated into the NBSP. Indeed, in 2021, NHS England published a vision for the Newborn Genomes Programme, including a pilot study examining the potential for using whole-genome sequencing as part of the NBSP to detect and treat rare but actionable genetic diseases. Findings of a public dialogue undertaken by the UK NSC and Genomics England in 2020 demonstrate the acceptability of this proposal under specific conditions, including limiting genetic analysis to treatable conditions.

The experience garnered from GPPAD suggests such a shift towards a much broader approach to newborn blood-spot screening, which is in alignment with the UK’s intention to becoming a world leader in genomic medicine, is possible. This, however, should still be handled with caution. As illustrated by the informal feedback received during consent, there is a tendency to fear the use of genetic testing and therefore clear boundaries would need to be established to provide reassurance that samples would not be misused. Without such safeguards, there is a risk the acceptability of the NBSP could be affected and lead to a reduced uptake of the NBSP that would be counterproductive.

CONCLUSION

INGRID1 used a novel methodology to recruit and identify newborns at increased genetic risk of T1D by using antenatal consent and genetic analysis of surplus blood from the NBSP. Over 66% of mothers approached agreed to take part, enabling enrolment of over 15,500 babies in just over two-and-a-half years. This demonstrates that not only is use of the NBSP for genetic research both feasible and acceptable in a UK setting, but also that it does not interfere with the routine NBSP pathway. The INGRID1 platform provides a model for future studies of this kind, with the potential to be expanded to antenatal interventions and exploration of the mother–baby dyad, and represents the cutting edge of clinically relevant genetic research.

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19 Winkler C, Haupt F, Heigermoser M, Ziegler AG, Achenbach P, Berner R, Ziegler AG, Danne T, Dunger DB, Barratt BJ, Payne F, Lowe CE, Dayan CM, Besser REJ, Oram RA, Mayer-Davis EJ, Lawrence JM, Dabelea D, Patterson CC, Dahlquist GG, Gyürüs E, Egro FM. Why is type 1 diabetes increasing?

2 International Diabetes Federation. Diabetes Epidemiology Research International Group. Secular trends in incidence of type 1 diabetes among youths, 2002–2012. N Engl J Med 2017;376:1419–29.

3 Diabetes Epidemiology Research International Group. Secular trends in incidence of childhood IDDM in 10 countries. Diabetes 1990;39:585–64.

4 Diabetes Epidemiology Research International Group. The environmental determinants of diabetes in the young (TEDDY) Study: 2018 update. Curr Diab Rep 2018;18:136.

5 TEDDY Study Group. The environmental determinants of diabetes in the young (TEDDY) study. Ann N Y Acad Sci 2008;1150:1–13.

6 TEDDY Study Group. The environmental determinants of diabetes in the young (TEDDY) Study: 2018 update. Curr Diab Rep 2018;18:136.

7 Ziegler A-G, Bonifacio E, BABYDIAB-BABYDIET Study Group. Age-related islet autoimmunity in offspring of patients with type 1 diabetes. Diabetologia 2012;55:1937–43.

8 Ziegler A-G, Bonifacio E, BABYDIAB-BABYDIET Study Group. Age-related islet autoimmunity in offspring of patients with type 1 diabetes. Diabetologia 2012;55:1937–43.

9 Parikka V, Närntö-Salonen K, Saarinen M, et al. Early seroconversion and rapidly increasing autoantibody concentrations predict prepubertal manifestation of type 1 diabetes in children at genetic risk. Diabetologia 2012;55:1926–36.

10 Kritsch JP, Lynch KE, Schatz DA, et al. The 6 year incidence of diabetes-associated autoantibodies in genetically at-risk children: the TEDDY study. Diabetes 2015;64:899–905.

11 Dayan CM, Besser REJ, Gram RA, et al. Preventing type 1 diabetes in childhood. Science 2021;373:506–10.

12 Voß F, Bernet ST, Todd JA, et al. Insulin expression in human thymus is modulated by INS VNTR alleles at the IDDM2 locus. Nat Genet 1997;15:289–92.

13 Fouladi N, Ziegler AG, Bokemeyer A, et al. Oral insulin therapy for primary prevention of type 1 diabetes following islet autoimmunity: the GPPAD-SINT1A randomised controlled trial protocol. BMJ Open 2019;9:e028578.

14 Ahmed Delli J, Jarsonsson S-A, RICKARD HOLT IG, Ake Lernmark Autoimmune type 1 diabetes. In: Textbook of diabetes. 4th edition. Oxford: Wiley-Blackwell, 2010.

15 Winkler C, Haupt F, Heigermoser M, et al. Identification of infants with increased type 1 diabetes genetic risk for enrollment into Primary Prevention Trials—GPPAD-02 study design and first results. Pediatr Diabetes 2019;20:720–7.

16 Bonifacio E. Predicting type 1 diabetes using biomarkers. Diabetes Care 2015;38:989–96.

17 Cooper JD, Smyth DJ, Smiles AM, et al. Meta-Analysis of genome-wide association study data identifies additional type 1 diabetes risk loci. Nat Genet 2008;40:1399–401.

18 Lambert AP, Gillespie KM, Thomson G, et al. Absolute risk of childhood-onset type 1 diabetes defined by human leukocyte antigen class II genotype: a population-based study in the United Kingdom. J Clin Endocrinol Metab 2004;89:4037–43.

19 Valdes AM, Erlich HA, Carlson J, et al. Use of class I and class II HLA loci for predicting age at onset of type 1 diabetes in multiple populations. Diabetologia 2012;55:2394–401.

20 Winkler C, Krumsiek J, Bummert F, et al. Feature ranking of type 1 diabetes susceptibility genes improves prediction of type 1 diabetes. Diabetologia 2014;57:2521–9.

21 Bonifacio E, Beyerlein A, Hippich M, et al. Genetic scores to stratify risk of developing multiple islet autoantibodies and type 1 diabetes: a prospective study in children. PLoS Med 2018;15:e1002548.

22 Public Health England. Newborn blood spot screening programme in the UK. data collection and performance analysis report 2016 to 2017, 2018.

23 Warnke K, Weiss A, Achenbach P. Elevations in blood glucose before and after the appearance of islet autoantibodies in children. JCI.

24 Ziegler A-G, Arnold S, Kåller A, et al. Supplementation with Bifidobacterium longum subspecies infantis ECC001 for mitigation of type 1 diabetes autoimmunity: the GPPAD-SINT1A randomised controlled trial protocol. BMJ Open 2021;11:e052449.

25 Dangouloff T, Servais L. Clinical evidence supporting early treatment of patients with spinal muscular atrophy: current perspectives. Ther Clin Risk Manag 2019;15:1153–61.

26 De Vivo DC, Bertini E, Svoboda KJ, et al. Nusinersen initiated in infants during the presymptomatic stage of type 1 diabetes and type 2 diabetes: a proof of concept study. JAMA 2017;318:110–11.

27 Kay DM, Stevens CF, Parker A, et al. Implementation of population-based newborn screening for spinal muscular atrophy (SMA) in the Netherlands. Neuromuscul Disord 2020;30:93–103.

28 Vill K, Köllin A, et al. Supplementation with Bifidobacterium longum subspecies infantis ECC001 for mitigation of type 1 diabetes autoimmunity: the GPPAD-SINT1A randomised controlled trial protocol. BMJ Open 2021;11:e052449.

29 Dangouloff T, Servais L. Clinical evidence supporting early treatment of patients with spinal muscular atrophy: current perspectives. Ther Clin Risk Manag 2019;15:1153–61.

30 De Vivo DC, Bertini E, Svoboda KJ, et al. Nusinersen initiated in infants during the presymptomatic stage of type 1 diabetes and type 2 diabetes: a proof of concept study. JAMA 2017;318:110–11.

31 De Vivo DC, Bertini E, Svoboda KJ, et al. Nusinersen initiated in infants during the presymptomatic stage of type 1 diabetes and type 2 diabetes: a proof of concept study. JAMA 2017;318:110–11.

32 Dangouloff T, Vrščaj E, Servais L, et al. Supplementation with Bifidobacterium longum subspecies infantis ECC001 for mitigation of type 1 diabetes autoimmunity: the GPPAD-SINT1A randomised controlled trial protocol. BMJ Open 2021;11:e052449.

33 Dangouloff T, Vrščaj E, Servais L, et al. Supplementation with Bifidobacterium longum subspecies infantis ECC001 for mitigation of type 1 diabetes autoimmunity: the GPPAD-SINT1A randomised controlled trial protocol. BMJ Open 2021;11:e052449.

34 Kay DM, Stevens CF, Parker A, et al. Implementation of population-based newborn screening for spinal muscular atrophy (SMA) launched in Oxford, 2022. Available: https://www.paediatics.ox.ac.uk/news/first-uk-pilot-study-of-newborn-screening-for-spinal-muscular-atrophy-sma-launched-in-oxford [Accessed Available from 6 Mar 2022].

35 De Vivo DC, Bertini E, Svoboda KJ, et al. Nusinersen initiated in infants during the presymptomatic stage of type 1 diabetes and type 2 diabetes: a proof of concept study. JAMA 2017;318:110–11.

36 Dangouloff T, Servais L. Clinical evidence supporting early treatment of patients with spinal muscular atrophy: current perspectives. Ther Clin Risk Manag 2019;15:1153–61.

37 Kay DM, Stevens CF, Parker A, et al. Implementation of population-based newborn screening for spinal muscular atrophy (SMA) in the Netherlands. Neuromuscul Disord 2020;30:93–103.

38 Vill K, Köllin A, et al. Supplementation with Bifidobacterium longum subspecies infantis ECC001 for mitigation of type 1 diabetes autoimmunity: the GPPAD-SINT1A randomised controlled trial protocol. BMJ Open 2021;11:e052449.

39 Dangouloff T, Vrščaj E, Servais L, et al. Supplementation with Bifidobacterium longum subspecies infantis ECC001 for mitigation of type 1 diabetes autoimmunity: the GPPAD-SINT1A randomised controlled trial protocol. BMJ Open 2021;11:e052449.

40 Bonifacio E. Predicting type 1 diabetes using biomarkers. Diabetes Care 2015;38:989–96.