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# 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 (INvestigating Genetic Risk for type 1 Diabetes) was a type 1 diabetes (T1D) genetic screening 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 (INvestigating 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.

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## 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.[1] 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.[2] Moreover, the incidence of T1D has been increasing by 3% year-on-year.[3–6]

Beta cells in the islets of Langerhans, responsible for insulin production, are destroyed through an immune-mediated process that can be identified by circulating islet autoantibodies (IA). Through several T1D observational cohort studies, it has

become apparent that the break in immune self-tolerance, marked by the presence of IA, can occur as early as 3–6 months of age and peaks at the 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.[7–12]

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

and deletion of autoreactive effector T cells. The risk of T1D is known to be influenced by polymorphisms in the *INSULIN* (*INS*) gene that affect insulin expression in the thymus and hence disturb the self-tolerance pathway.[13][14] This therefore raises the question as to whether such a process could be influenced by inducing self-tolerance through regular oral mucosal exposure of insulin in infancy when immune mechanisms driving tolerance are fully active. In support of this hypothesis, the LEAP trial successfully demonstrated that early and repeated exposure to peanuts can induce tolerance and lead to a sevenfold reduction in the risk of peanut allergy.[15] The Global Platform for the Prevention of Autoimmune Diabetes (GPPAD) is now undertaking a T1D primary prevention trial,[16] called Primary Oral Insulin Trial (POInT, NCT03364868),[17] aiming to emulate the success of the LEAP study with early exposure to oral insulin prior to IA seroconversion.

Conducting primary prevention clinical trials in T1D has historically been difficult to carry out due to the inability to identify an at-risk population large enough to be approached for recruitment. Having a first-degree relative (FDR) increases the risk of T1D to 1-in-20; however, 85% of newly diagnosed diabetics do not have a family history of the disease.[18] Solely targeting FDRs would therefore miss a large proportion of prospective cases and would require a large geographical footprint to yield an adequate sample size. This problem was resolved by using a genetic risk score (GRS) based on 47 single-nucleotide polymorphisms (SNPs) that enables stratifying T1D risk (see online supplemental appendix 1). The scoring system was generated by amalgamating two GRS that were developed by the Type 1 Diabetes Genetic Consortium and Wellcome Trust Case Control Consortium, known as the Winkler and Oram score, respectively, and was analysed to identify HLA class II genotypes and 40 non-HLA SNPs associated with T1D risk.[19] Individuals can therefore now be identified as having a 10% risk of developing asymptomatic T1D by 6 years of age by solely using HLA typing in those with a T1D FDR, or the GRS in conjunction with HLA type in those without a T1D FDR.[17][20–25]

Accordingly, the aim of the INGR1D study (INvestigating Genetic Risk for type 1 Diabetes) was to implement a novel large-scale genetic research screening tool to identify a cohort of infants at an increased risk of early-onset T1D large enough to serve recruitment into the POInT trial.

## METHODS
### Study design
INGR1D was a population screening study primarily recruiting infants prior to their day 5 newborn bloodspot screening (NBS) from four NHS trusts across the Thames Valley, UK:
► Oxford University Hospital NHS Foundation Trust (FT)
► Buckinghamshire Healthcare NHS Trust
► Royal Berkshire NHS FT.
► Milton Keynes University Hospital NHS FT.

The recruiting hospitals within these trusts represented the busiest delivery units in the Thames Valley and, crucially, shared the same NHS NBS laboratory at Oxford University Hospitals NHS trust.

In addition, to allow enrolment of families from outside the Thames Valley area, or those whose infants had already had their NBS test performed before their parents became aware of the study, recruitment of babies up to 3 months of age was allowed if parents were willing to travel to the Oxford study centre.

### Recruitment
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 NBS 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 NBS 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 NBS 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 NBS which was undertaken at their regional screening laboratory.
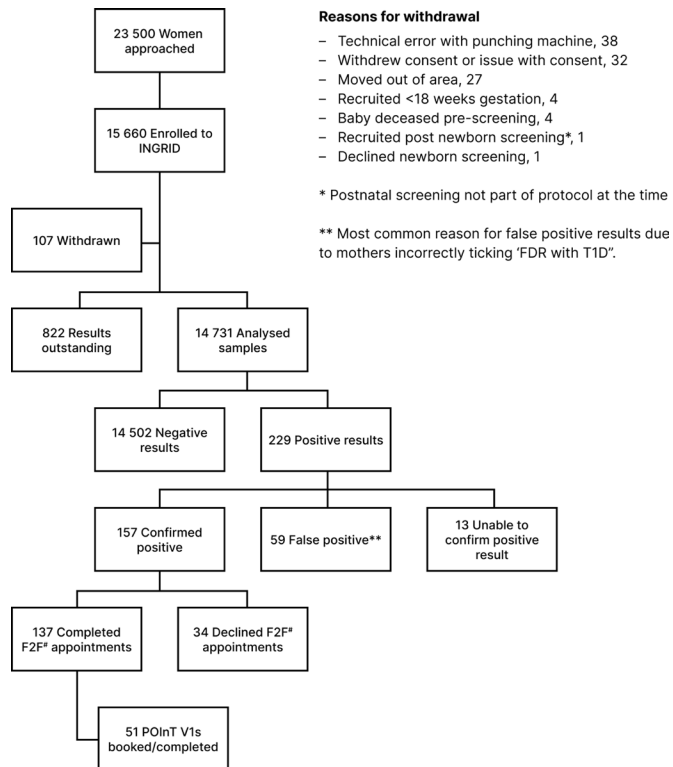
Genotyping was conducted by LGC Biosearch Technologies (Milton Keynes, UK) and the results forwarded to Helmholtz Zentrum München, the coordinating centre in Munich. Helmholtz integrated the genotyping data, routine information collected by the screening laboratory and responses to the maternal questionnaire 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 157 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

**Reasons for withdrawal**
– Technical error with punching machine, 38
– Withdrew consent or issue with consent, 32
– Moved out of area, 27
– Recruited <18 weeks gestation, 4
– Baby deceased pre-screening, 4
– Recruited post newborn screening*, 1
– Declined newborn screening, 1

\* Postnatal screening not part of protocol at the time

\*\* Most common reason for false positive results due to mothers incorrectly ticking 'FDR with T1D'.

**Figure 1**  INGR1D and POInT accrual (#F2F—face-to-face).

a technical error with the sampling machine (36 participants), withdrawing consent or issues with recording consent (32 participants), and being out-of-area at the time the newborn bloodspots were taken (27) (figure 1).

In the process of recruitment, many families verbally relayed their reasons for accepting or declining participation in INGR1D to the study team. Women reported that a principal reason for the successful recruitment to the screening study was the absence of any additional interventions. Of those women who declined screening, many had concerns regarding data protection. Some women feared their baby's entire genome would be sequenced and its genetic data exploited by, for example, being sold to pharmaceutical companies. Others who declined did so based on the test's accuracy; with a sensitivity of 25%, some women worried about the value of a negative result. In addition, some stated that a predictive value of 10% meant that a high-risk result could lead to unwarranted anxiety. Another barrier to women consenting to the study centred on understanding of disease risk. Many were falsely reassured by the fact they had no family history of T1D and therefore felt their baby would be low risk.

## 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.[26] 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.[27] 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.[28] 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,[29–31] and already forms, or will soon form, part of the screening programme in several countries.[32–36] Although SMA represents a single gene disorder with a recognised treatment, rather than a screening for a clinical trial as in INGR1D, both programmes demonstrate the potential for novel use of the NBSP to progress novel interventions within the NHS.

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 rational decision, even if INGR1D would not meet NHS criteria for a clinical screening programme.[37]

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,[38] 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.[39]

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 NBS could be affected and lead to a reduced uptake of the NBS that would be counterproductive.

## CONCLUSION

INGR1D 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 NBS pathway. The INGR1D 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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List of single nucleotide polymorphisms (SNP) used in the GPPAD-02 study

| | SNP | Gene, Allele, Haplotype# | Merged Score Weight |
|---|---|---|---|
| | **HLA class II** | | |
| 1 | rs17426593 | HLA DR4-DQ8/DR4-DQ8 | 3.15 |
| 2 | rs2187668 | | 3.98 |
| 3 | rs7454108 | HLA DR3/DR4-DQ8 | |
| 4 | rs3129889 | DRB1*1501 | Exclusion criteria for first degree relative |
| 5 | rs1794265 | DQB1*0503 | Exclusion criteria for first degree relative |
| | **HLA class I** | | |
| 6 | rs1264813 | HLA A 24 | 0.43 |
| 7 | rs2395029 | HLA B 5701 | 0.92 |
| | **Non-HLA SNPs** | | |
| 8 | rs2476601 | PTPN22 | 0.76 |
| 9 | rs2816316 | RGS1 | 0.16 |
| 10 | rs3024505 | IL10 | 0.22 |
| 11 | rs1990760 | IFIH1 | 0.16 |
| 12 | rs3087243 | CTLA4 | 0.16 |
| 13 | rs10517086 | | 0.19 |
| 14 | rs2069763 | IL2 | 0.11 |
| 15 | rs6897932 | IL7R | 0.19 |
| 16 | rs3757247 | BACH2 | 0.19 |
| 17 | rs9388489 | C6orf173 | 0.14 |
| 18 | rs6920220 | TNFAIP3 | 0.15 |
| 19 | rs1738074 | TAGAP | 0.05 |
| 20 | rs7804356 | SCAP2 | 0.15 |
| 21 | rs4948088 | COBL | 0.17 |
| 22 | rs7020673 | GLIS3 | 0.23 |

Supplemental material

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| 23 | rs12722495 | IL2RA | 0.47 |
|----|------------|-------|------|
| 24 | rs947474 | PRKCQ | 0.15 |
| 25 | rs10509540 | RNLS/C10orf59 | 0.25 |
| 26 | rs689 | INS | 0.65 |
| 27 | rs4763879 | CD69 | 0.06 |
| 28 | rs2292239 | ERBB3 | 0.36 |
| 29 | rs3184504 | SH2B3 | 0.24 |
| 30 | rs1465788 | ZFP36L1 | 0.13 |
| 31 | rs17574546 | | 0.13 |
| 32 | rs3825932 | CTSH | 0.15 |
| 33 | rs12708716 | CLEC16A | 0.15 |
| 34 | rs4788084 | IL27 | 0.20 |
| 35 | rs7202877 | | 0.19 |
| 36 | rs2290400 | ORMDL3 | 0.25 |
| 37 | rs7221109 | | 0.15 |
| 38 | rs45450798 | PTPN2 | 0.09 |
| 39 | rs763361 | CD226 | 0.12 |
| 40 | rs425105 | PRKD2 | 0.21 |
| 41 | rs2281808 | SIRPG | 0.07 |
| 42 | rs3788013 | UBASH3a | 0.16 |
| 43 | rs5753037 | | 0.15 |
| 44 | rs229541 | IL2B | 0.18 |
| 45 | rs5979785 | TLR8 | 0.09 |
| 46 | rs2664170 | GAB3 | 0.14 |
| 47 | rs917997* | IL18RAP* | 0.14* |

#gene listed may be the nearest protein-coding gene