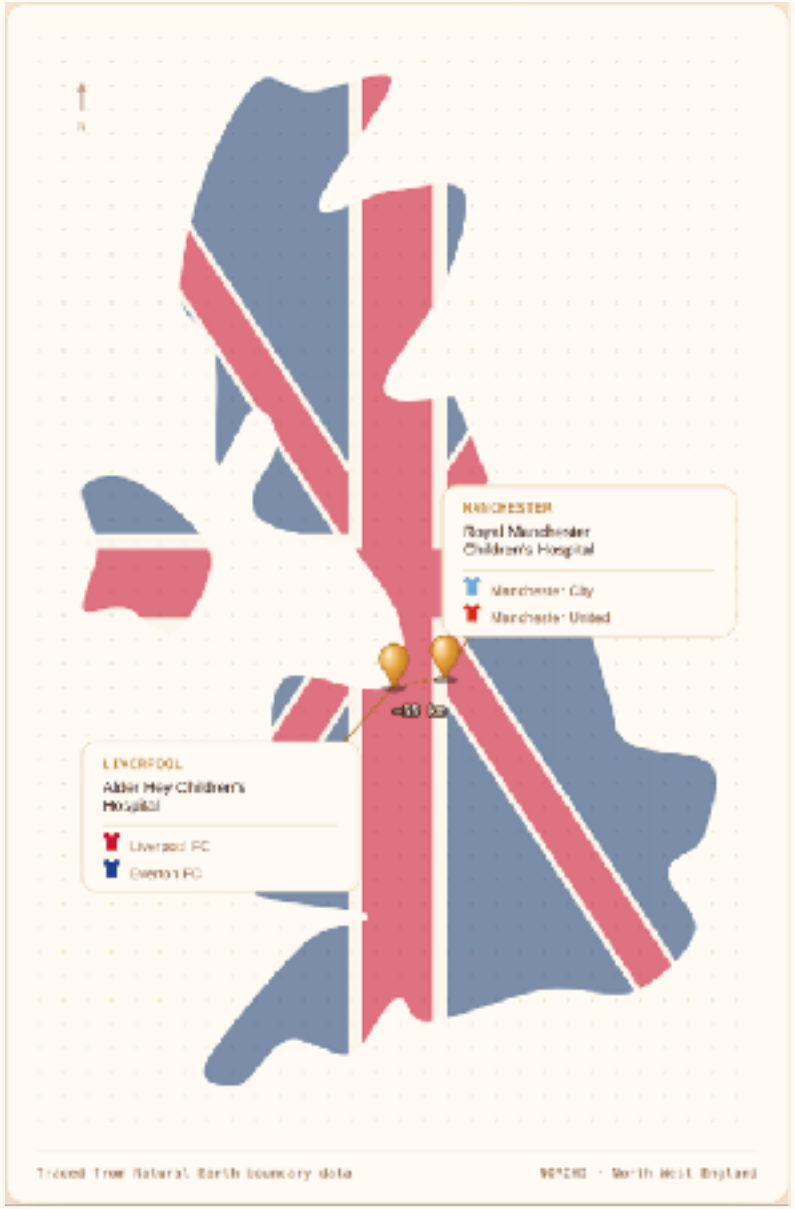
Current Directions in Research in Hyperinsulinism

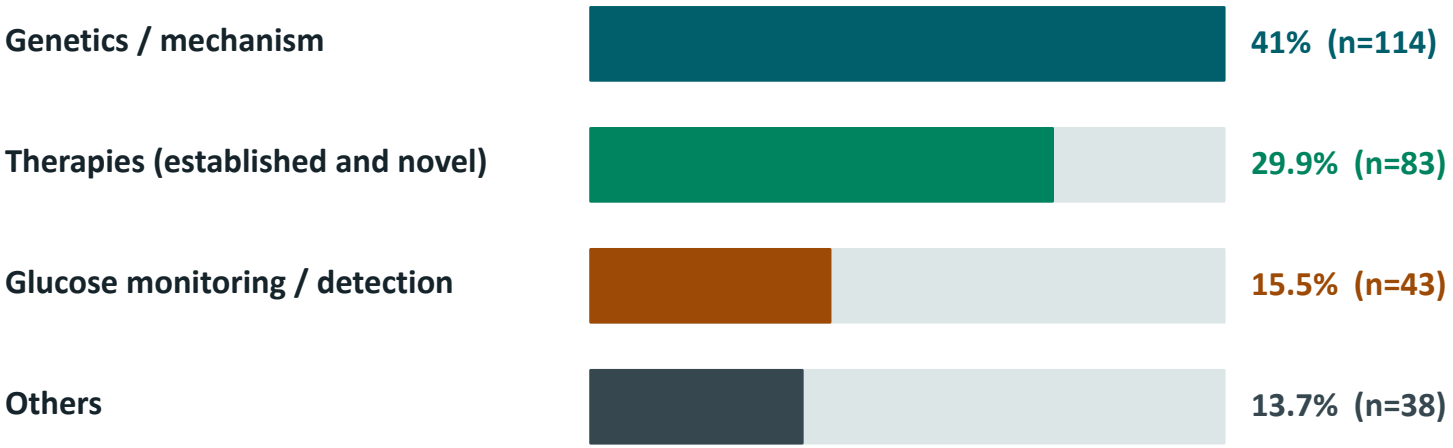
Indi Banerjee



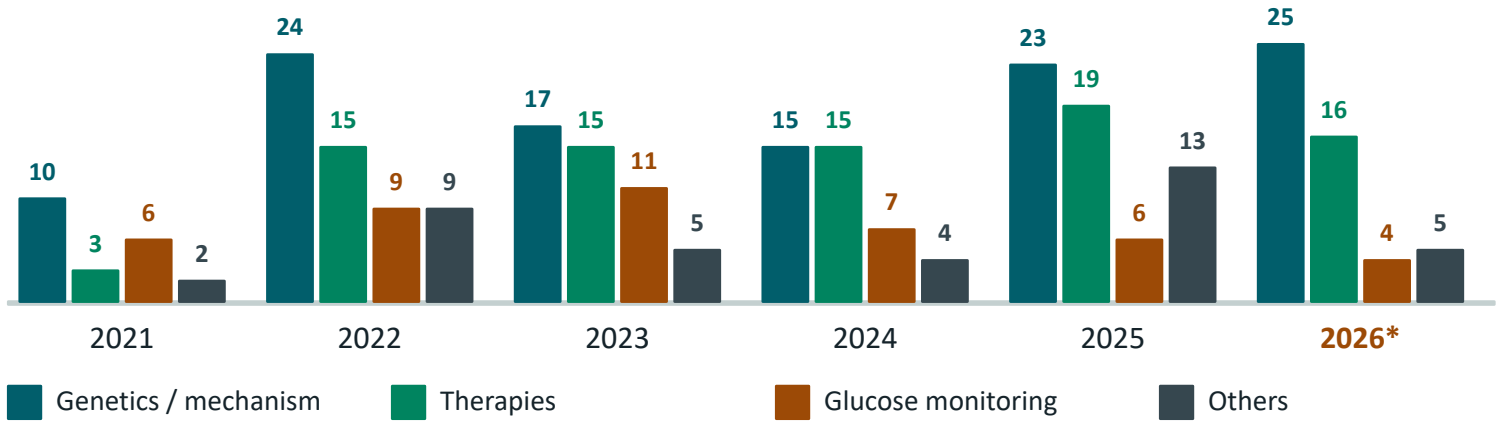
Congenital Hyperinsulinism Research Output, 2021-2026

Distribution of 278 PubMed-indexed publications by primary research focus

SHARE OF PUBLICATIONS BY CATEGORY



PUBLICATIONS PER YEAR BY CATEGORY



WHAT THE DATA SHOW

- Genetics and mechanism is the largest category in every year, never below 35% of annual output.
- Therapy output rose sharply after 2021 (3 → 15–19/year), tracking the dasiglucagon, ersodetug and efpegerglucagon trial programmes.
- Monitoring and detection is the smallest defined category and has declined since 2023 (11 → 4).
- The residual bucket is mostly epidemiology, national cohorts, registries and quality-of-life studies.

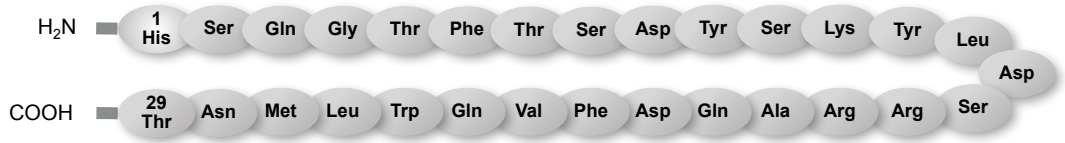
**2026 is a partial year (records to August 2026). Categories are mutually exclusive, assigned by priority: genetics → therapies → monitoring → others.*

Discussion Topics

- Clinical Trials
- Genetics
- Glucose monitoring

Dasiglucagon

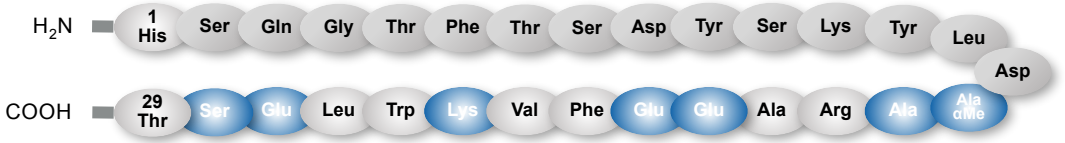
Native glucagon



- **Native human glucagon is effective as an anti-hypoglycemic agent**
  - Lacks stability and fibrillates in aqueous solutions
  - Limits clinical utility

Dasiglucagon – a novel glucagon analog

Amino acid substitution



- **Dasiglucagon is a glucagon analog with 7 amino acid substitutions improving:**
  - Aqueous solubility and enhanced physical stability
  - Suitability for longer term continuous or intermittent infusion

Plasma glucose with dasiglucagon and glucagon

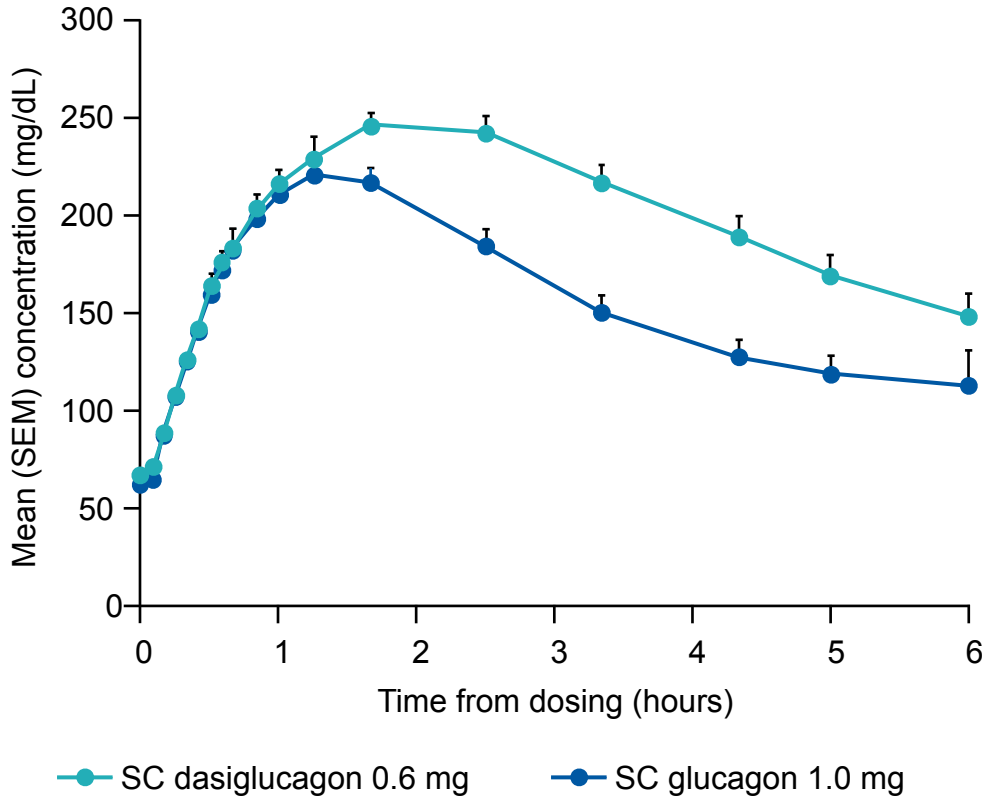
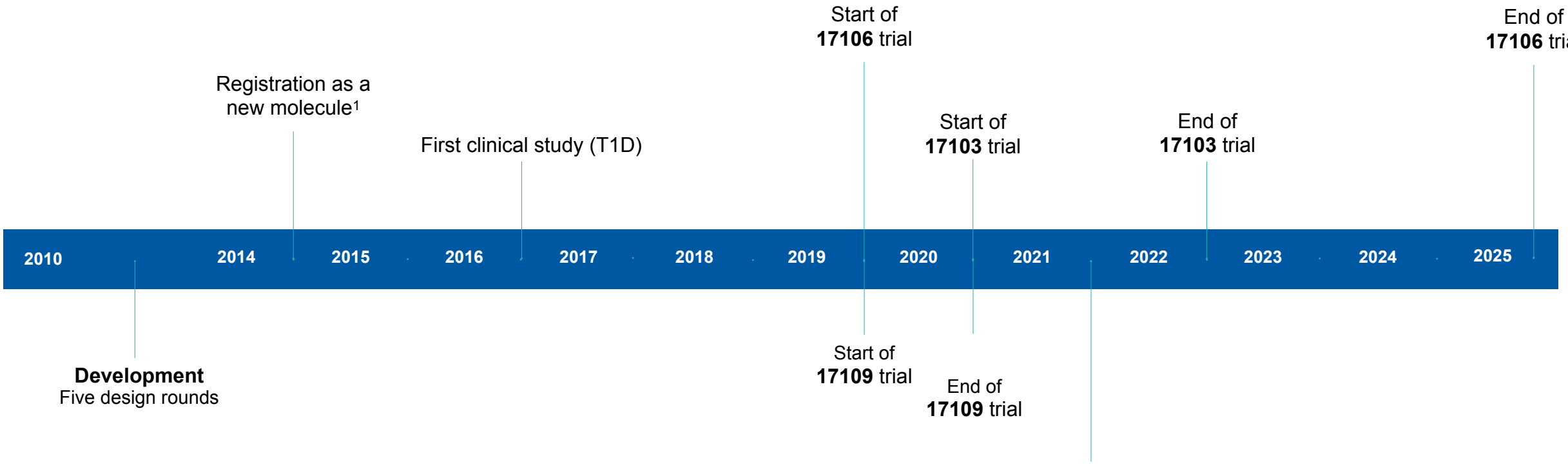


Figure adapted from Hövelmann et al. Diabetes Care 2018;41(3):531–537

Source: Hövelmann et al. Diabetes Care 2018;41(3):531–537.
SC=subcutaneous; SEM=standard error of the mean.

Timeline of Dasiglucagon



1: WO2014016300 GLUCAGON ANALOGUES

Dasiglucagon Phase 3 Program: The Largest Completed Clinical Trial Program in CHI

Completed

Study 17103[1,2] (N=12)

- 4-day (2 x 48 h) placebo-controlled crossover + 3-week open-label treatment
- Patients aged ≥7 days to <12 months dependent on IV glucose
- **Primary endpoint:** Mean IV GIR in the last 12 hours of each treatment period in Part 1

Completed

Study 17106[3] (N=42)

- Long-term, open-label safety study
- Patients aged 6 weeks-13 years from trials 17109 and 17103 with ongoing positive risk-benefit assessment
- **Primary endpoint:** Incidence of adverse events

Completed

Study 17109[4,5] (N=32)

- 4-week crossover with SOC + 4-week open-label treatment
- Patients aged 3 months-12 years with persistent hypoglycemia and receiving maximum therapy including pancreatectomy
- **Primary endpoint:** Rate of SMPG-detected hypoglycemia (plasma glucose <3.9 mmol/L) during Weeks 2-4 of Part 1

Safety was evaluated by assessing type, frequency and severity of adverse events, along with ECG, labs & vital signs (baseline, every 3 months, end-of-treatment) as well as echocardiography (baseline, yearly & end-of-treatment). Safety analysis comprised all treated participants

CHI, congenital hyperinsulinism; GIR, glucose infusion rate; IV, intravenous; SMPG, self-monitored plasma glucose; SOC, standard of care.

1. Clinical Trials Register (EU). Study 17103. https://www.clinicaltrialsregister.eu/ctr-search/trial/2017-004545-24/GB, Accessed June 26, 2026. 2. Clinicaltrials.gov (NCT04172441). https://clinicaltrials.gov/study/NCT04172441, Accessed June 26, 2026. 3. Clinicaltrials.gov (NCT03941236). https://clinicaltrials.gov/study/NCT03941236. Accessed June 26, 2026. 4. Clinicaltrials.gov (NCT03777176). https://clinicaltrials.gov/study/NCT03777176. Accessed June 26, 2026. 5. Clinical Trials Register (EU). Study 17109. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2017-004547-21/GB, accessed February 2024.

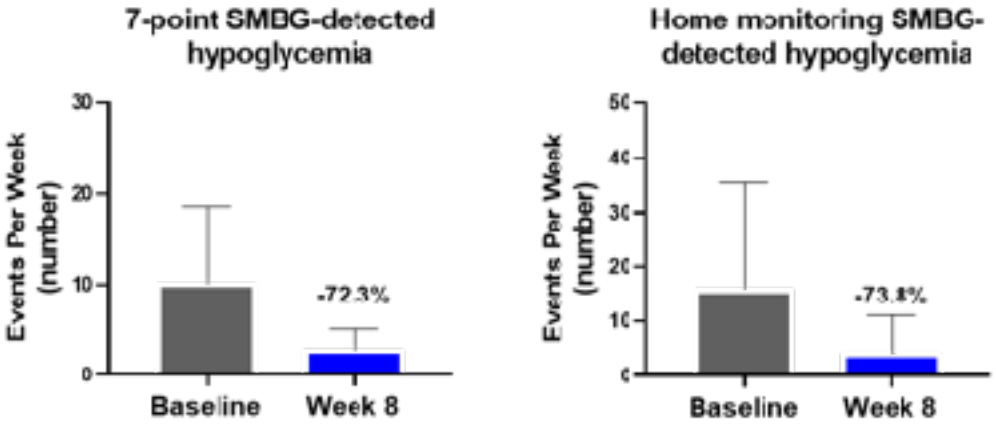
[RC3.2] An Ongoing Phase 2 Study of Efpegerglucagon: Promising Results on Safety and Efficacy in Subjects with Congenital Hyperinsulinism

A. Dastamani[1], I. Banerjee[2], S. Empting[3], M. Puri[4], E. Gwak[5], S. Kang[5], J. Byeon[5], M. Lee[5] and D. De León[6]*
[1]Great Ormond Street Hospital for Children, London, NA, UK; [2]Central Manchester University Hospitals, Royal Manchester Children's Hospital, Manchester, NA, UK; [3]Otto-von-Guericke-Universität Magdeburg, Magdeburg, NA, Germany; [4]Fortrea Inc., Durham, NC, USA; [5]Hanmi Pharm. Co., Ltd, Seoul, Korea; [6]The Children's Hospital of Philadelphia and the Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA, *Corresponding Author

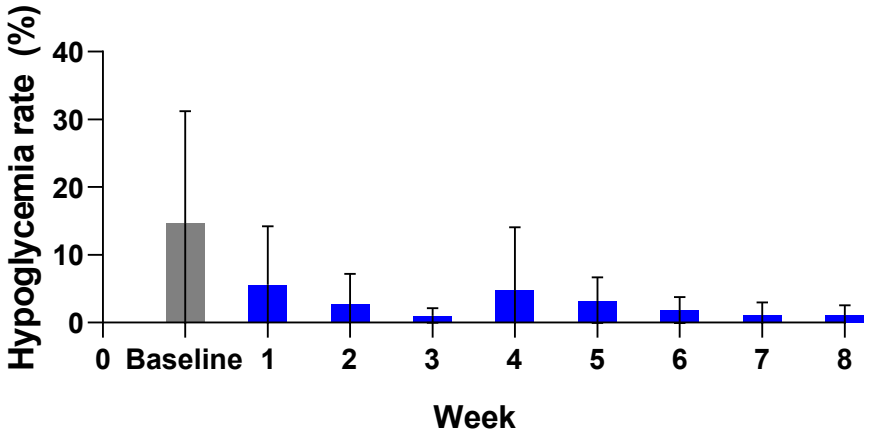
Connecting Endocrinology Across the Life Course

Hanmi pharmaceutical

SMBG Detected Level 1 or Level 2 Hypoglycemia Event/Week



Time in Level 1 or Level 2 Hypoglycemia by CGMS (%)



Level 1 hypoglycaemia: glucose < 3.9 mmol/L (70 mg/dL)
Level 2 hypoglycaemia: glucose < 3 mmol/L (54 mg/dL)

Note: Preliminary data from Cohort 1 (N=8) are presented. Analyses are based on a data snapshot date of 21 January 2024.

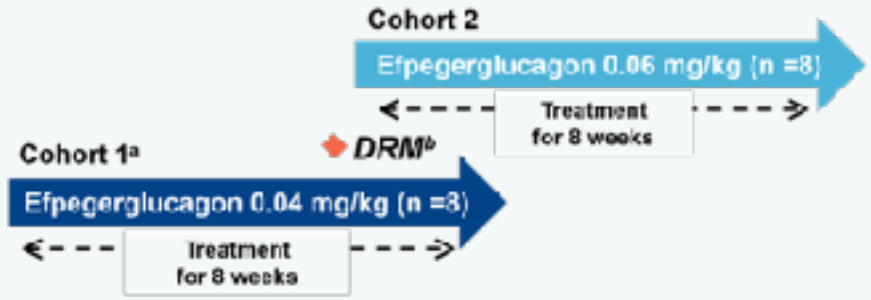
Efpegerglucagon in Congenital Hyperinsulinism

Preliminary Patient Baseline and Demographic Characteristics from the ACHIEVE Phase 2 Study | Planned for ESPE 2026 (September)

NCT04732416 • EU CT 2024-515290-98-00 • Phase 2, multicenter, multiple ascending dose, open-label proof-of-concept

STUDY DESIGN

- **Age ≥2 years, ≥3 hypoglycemia events/week despite stable standard of care**
- **Once-weekly subcutaneous efpegerglucagon: 8-week core period + 44-week optional extension**
- **Two sequential dose cohorts — 0.04 mg/kg (n=8) and 0.06 mg/kg (n=9); enrollment complete in both**



a: The enrollment of subjects in Cohort 1 (n = 8) preceded the enrollment in Cohort 2, with no overlapping enrollment between the two cohorts.
b: After the sixth subject completed the 8-week treatment period in Cohort 1, a data review meeting (DRM) was held to determine dose escalation to Cohort 2.

DEMOGRAPHIC CHARACTERISTICS (N=17)

Parameter	Cohort 1 (N=8)	Cohort 2 (N=9)	Total (N=17)
Age (years), mean (SD)	17.6 (13.8)	5.1 (2.8)	11.0 (11.3)
Sex, n (%)			
Male	4 (50)	5 (56)	9 (53)
Female	4 (50)	4 (44)	8 (47)

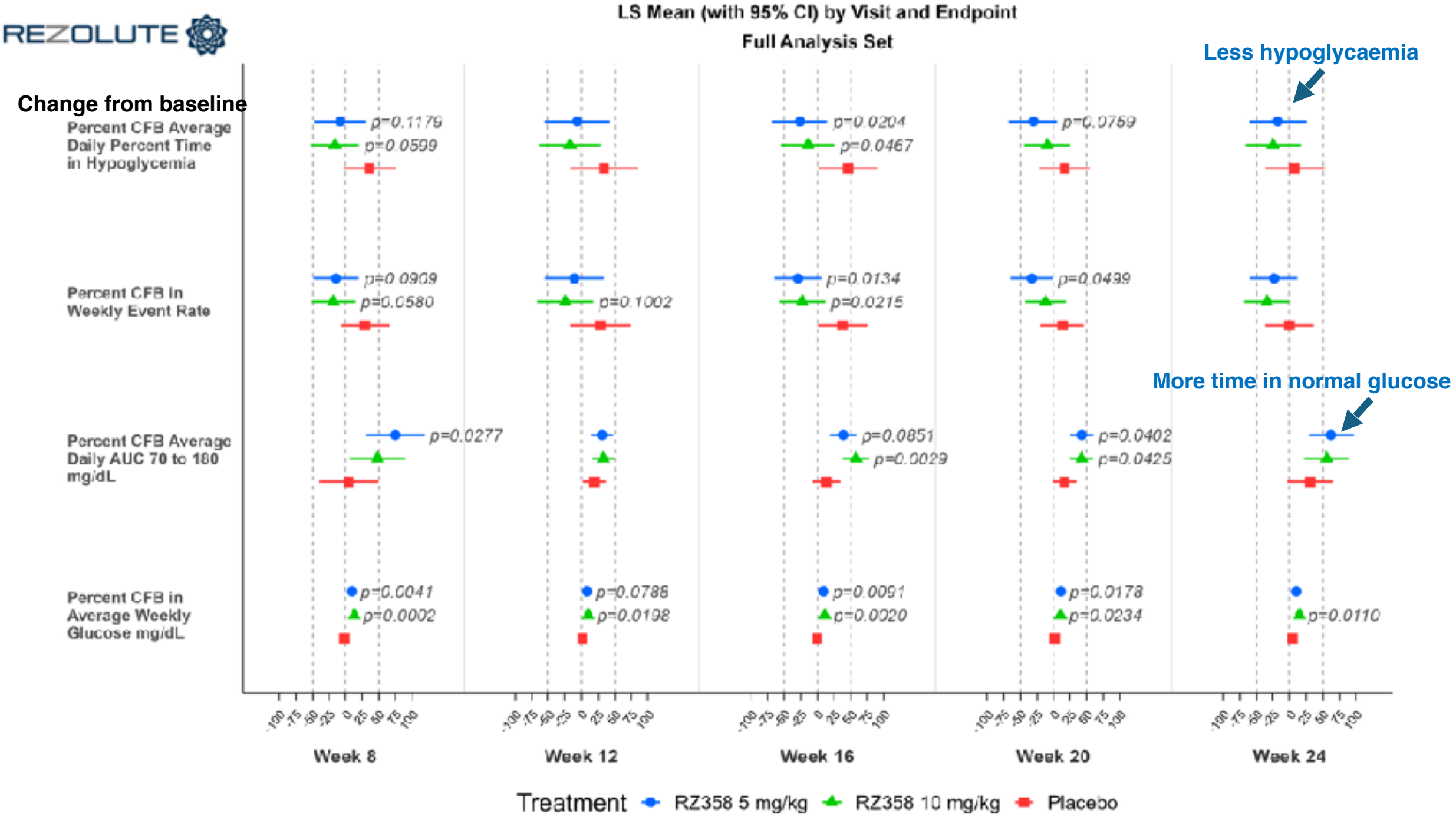
Abbreviations: SD, standard deviation

BASELINE DISEASE CHARACTERISTICS (N=17)

- Genetic etiology: identified in 10 subjects, with KATP channel mutations representing the most common cause
- Pancreatic histology type: diffuse type was documented in 6 subjects (2 subjects had undergone prior pancreatectomy)
- All on concomitant SoC — diazoxide (65%), lanreotide (24%) and octreotide (12%)

Interim data — *study ongoing, subjects at differing stages of core or extension treatment. Primary analysis follows completion of the 8-week core period by all subjects.*

REZOLUTE

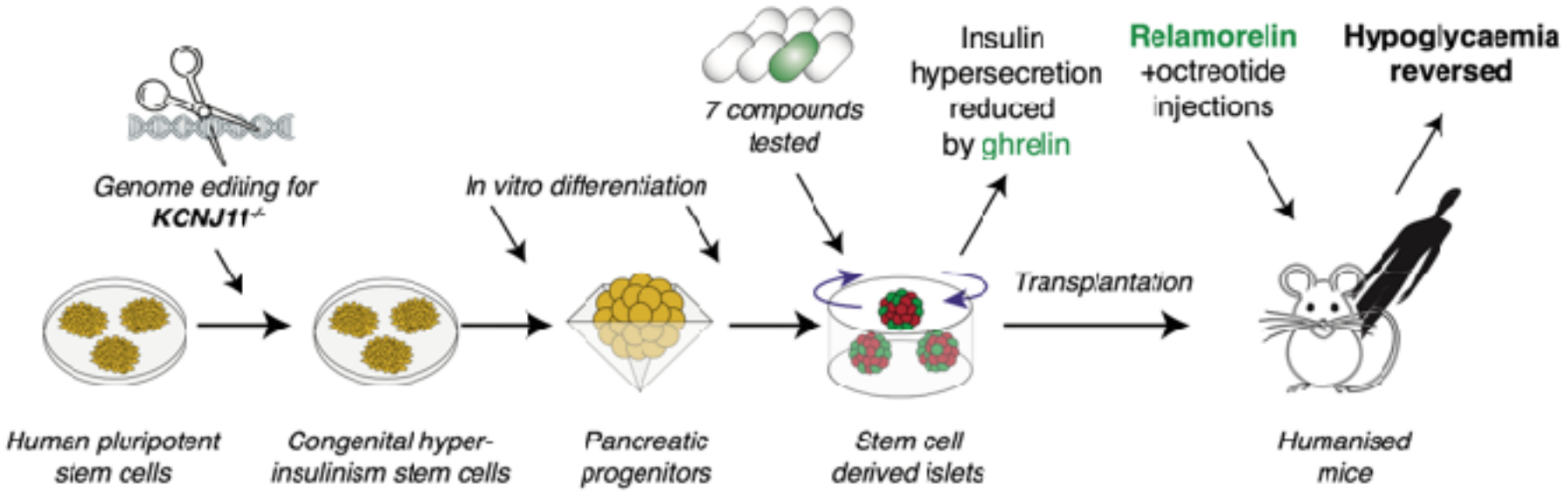

LS Mean (with 95% CI) by Visit and Endpoint
Full Analysis Set
Less hypoglycaemia
More time in normal glucose
Change from baseline
Percent CFB Average Daily Percent Time in Hypoglycemia
p=0.1179
p=0.0599
p=0.0204
p=0.0467
p=0.0759
Percent CFB In Weekly Event Rate
p=0.0909
p=0.0580
p=0.1002
p=0.0134
p=0.0215
p=0.0439
Percent CFB Average Daily AUC 70 to 180 mg/dL
p=0.0277
p=0.0851
p=0.0029
p=0.0402
p=0.0425
Percent CFB in Average Weekly Glucose mg/dL
p=0.0041
p=0.0002
p=0.0788
p=0.0198
p=0.0091
p=0.0020
p=0.0178
p=0.0234
p=0.0110
-100 -75 -50 -25 0 25 50 75 100
Week 8
Week 12
Week 16
Week 20
Week 24
Treatment
RZ358 5 mg/kg
RZ358 10 mg/kg
Placebo

Timo Otonkoski
Vaino Lithovius

Ghrelin and relamorelin counteract hypoglycemia in mice engrafted with congenital hyperinsulinism stem cell-derived islets

Väinö Lithovius[1,*,‡], Hossam Montaser[1,‡], Jonna Saarimäki-Vire[1,‡], Hazem Ibrahim [1], Tom Barsby[1], Diego Balboa[1], Timo Otonkoski[1,2,*]

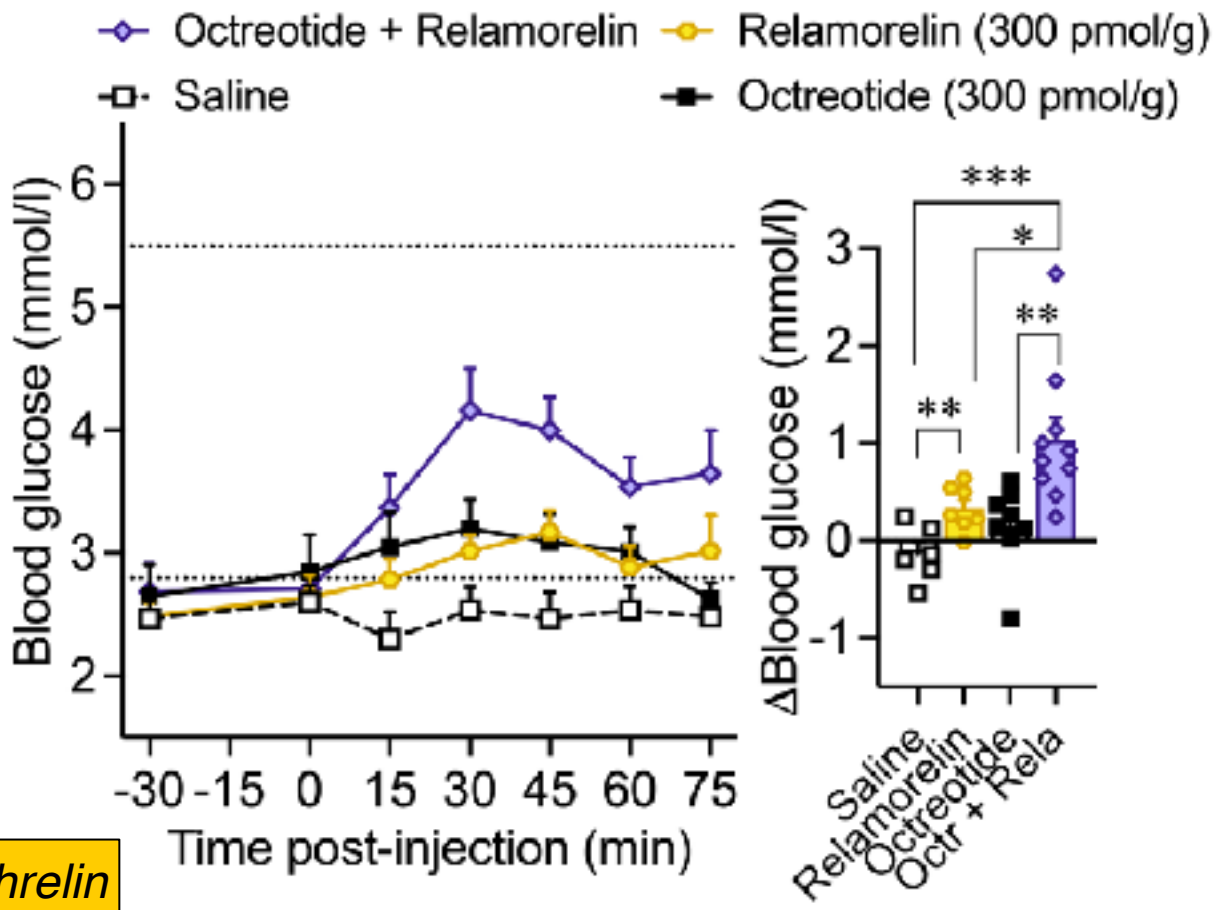
[1]Stem Cells and Metabolism Research Program of the Faculty of Medicine, University of Helsinki, Helsinki, 00290, Finland
[2]Children's Hospital, Helsinki University Hospital, Helsinki, 00290, Finland
[#]Present address: Institute of Diabetes and Regeneration Research, Helmholtz Munich, Germany
[‡]These authors contributed equally to this work
*Corresponding authors: Väinö Lithovius, Biomedicum Helsinki 1, Haartmaninkatu 8, 00290 Helsinki, Finland. E-mail: vaino.lithovius@helsinki.fi; Timo Otonkoski, Biomedicum Helsinki 1, Haartmaninkatu 8, 00290 Helsinki, Finland. E-mail: timo.otonkoski@helsinki.fi.



Relamorelin –

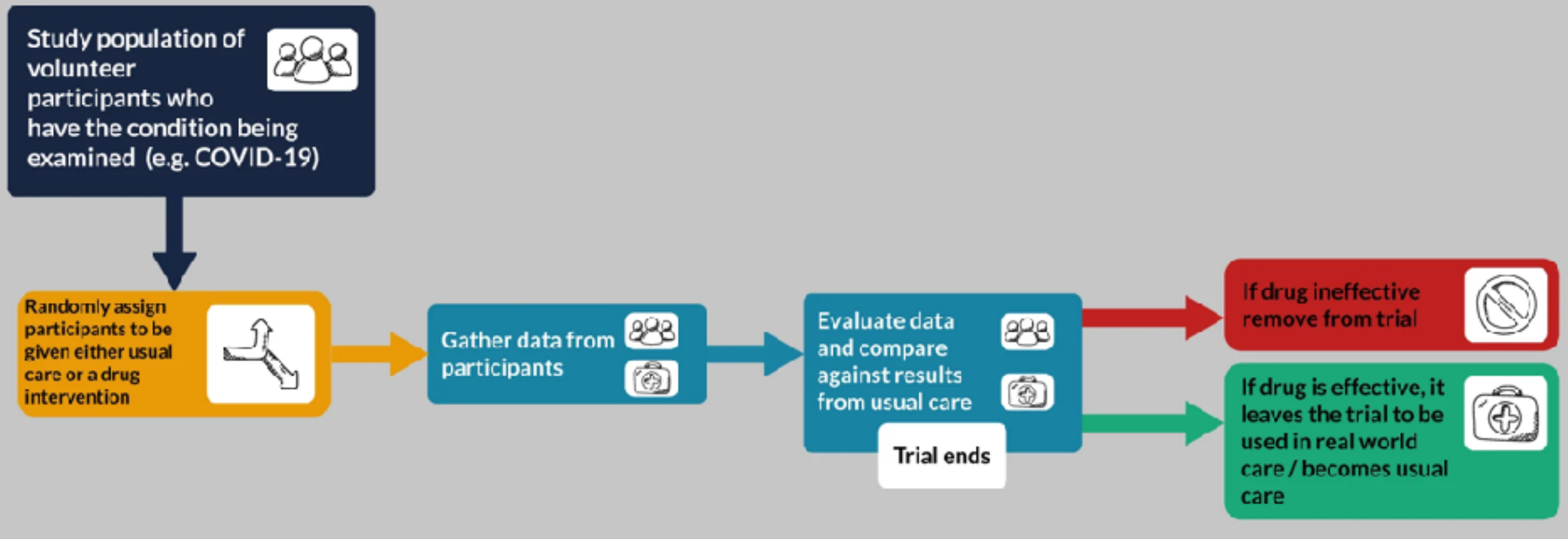
- Appetite hormone
- Improves stomach movement

- Activates ghrelin receptors to stop insulin secretion



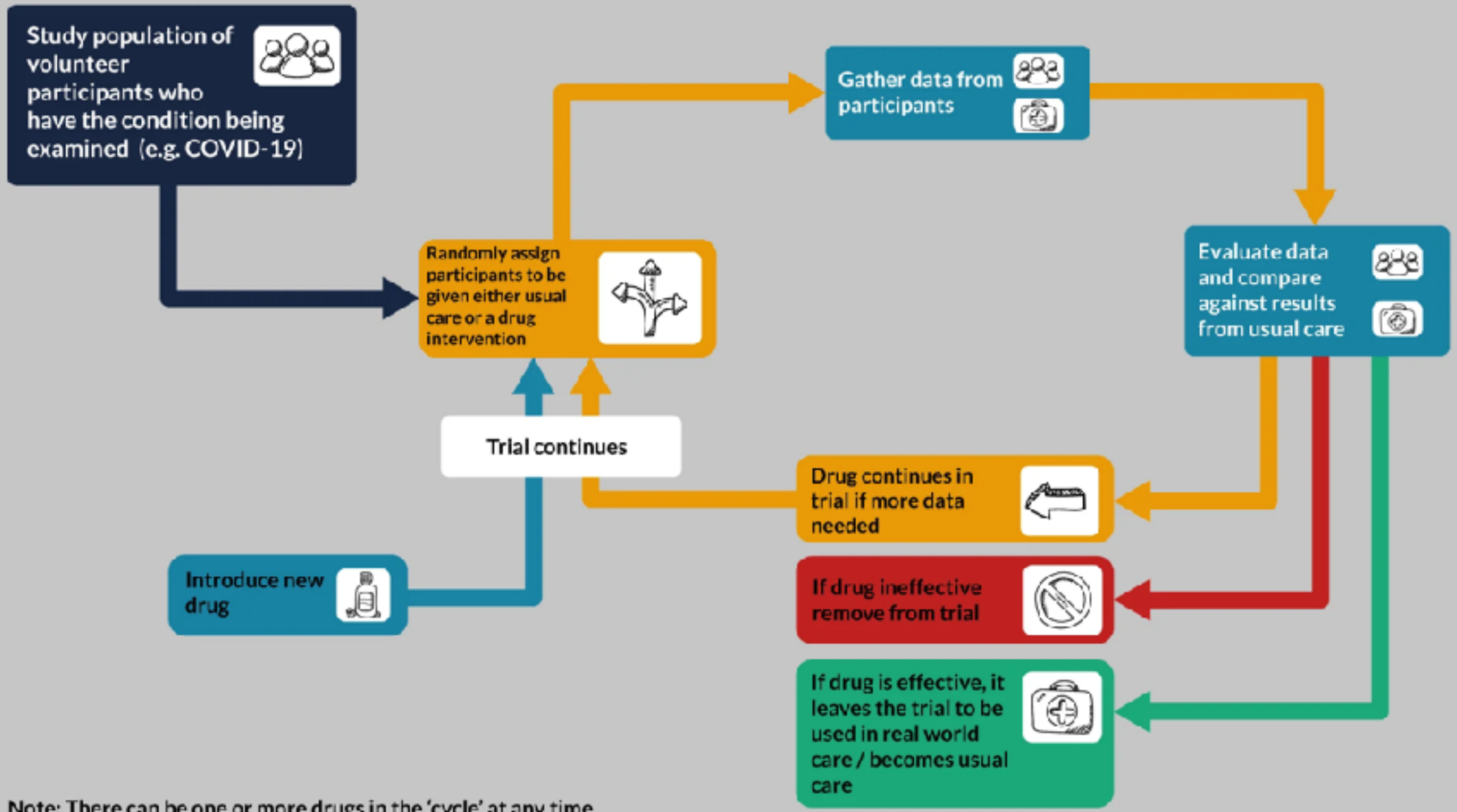
Relamorelin is a long-acting analogue of ghrelin

Traditional clinical trial



UNIVERSITY OF OXFORD
NUFFIELD DEPARTMENT OF PRIMARY CARE HEALTH SCIENCES

Platform trial



Note: There can be one or more drugs in the 'cycle' at any time.

Increasing Clinical Trial Efficiency

LifeArc Centre
Acceleration of Rare Disease Trials

To overcome -

- Small number of participants
- Heterogeneous groups
- Not individualised
- Rigid (not adaptive), often single arm studies
- Yes/No outcomes, not probabilities (Bayesian)

Collaboration

The LifeArc Centre for Acceleration of Rare Disease Trials (ARDT) includes a specialist trial management and statistics team dedicated to running trials in rare diseases. We welcome proposals for clinical trials to be supported by the ARDT team, and the affiliated Clinical Trials Units:

- Cancer Research UK Clinical Trials Unit (CRCTU), University of Birmingham
- Newcastle Clinical Trials Unit, Newcastle University
- Northern Ireland Clinical Trials Unit (NICTU), Belfast

News in Brief | Published: 14 July 2026

MHRA's radical rare disease proposal

Nature Biotechnology **44**, 1070 (2026) | Cite this article

Medicines & Healthcare products Regulatory Agency

- Adaptive trial designs (Bayesian)
- Real-world data
- Patient engagement
- Early engagement with MHRA
- Flexible licensing model
- Predictive knowledge – digital model simulation
- Continued data collection

Rare Disease Clinical Trials can be attractive to Biotech/Pharma

- Orphan Drug Designation
- Small numbers of patients – may be relatively inexpensive compared to large drug trials e.g. diabetes
- Longer time to generic designation (market exclusivity)
- A strong patient voice!

CHI Congenital Hyperinsulinism International
When too little sugar hurts, we help.™

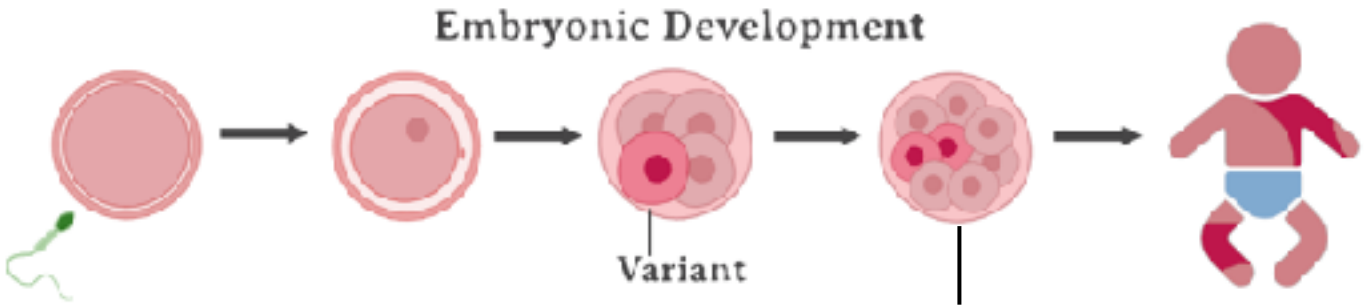
E:RDERA European Rare Diseases Research Alliance

FDA U.S. FOOD & DRUG ADMINISTRATION

ORPHAN PRODUCTS GRANTS PROGRAM FDA

E:RDERA
Clinical Trial Call pre-announcement is now out!

Mosaicism is the presence of two or more populations of genetically distinct cells in an individual



Arise during DNA replication

Two distinct populations of cells

Differences in the level of the variant observed across tissues

Eur J Endocrinol. 2022 August 01; 187(2): 301–313. doi:10.1530/EJE-21-1095.

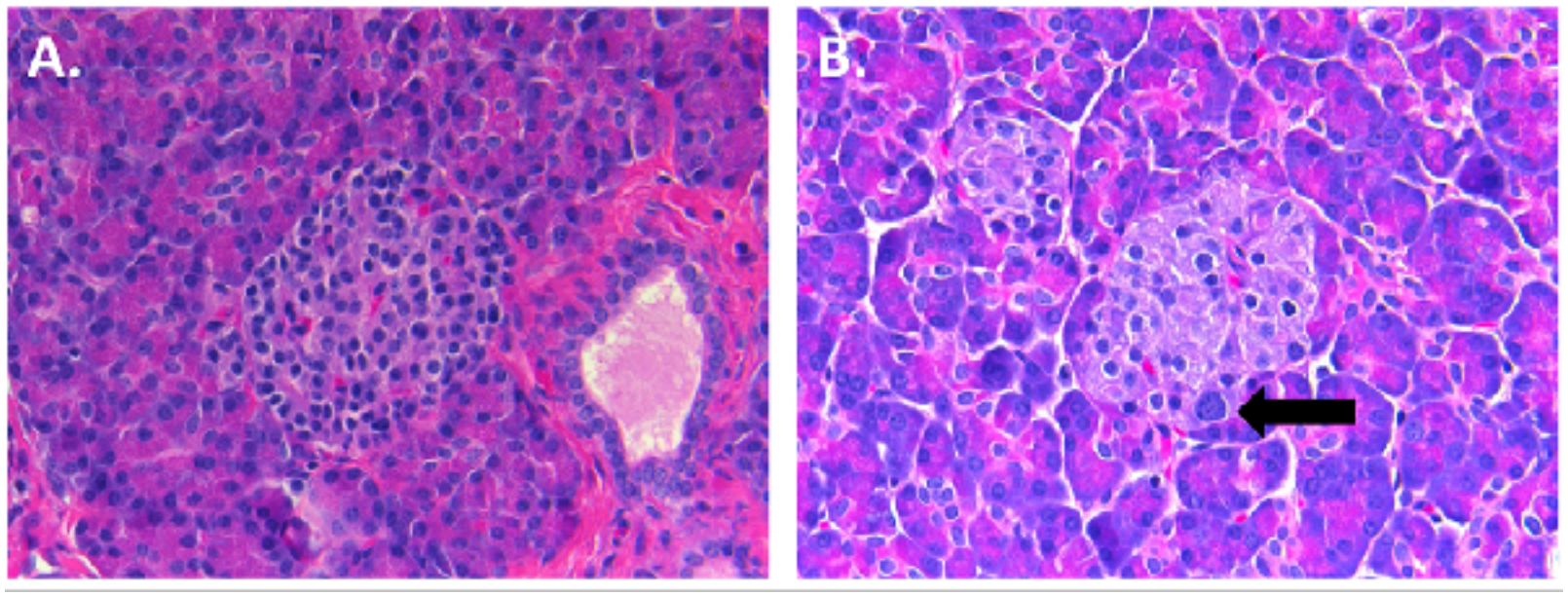
Localized Islet Nuclear Enlargement Hyperinsulinism (LINE-HI) due to *ABCC8* and *GCK* Mosaic Mutations

Kara E. Boodhansingh[1], Zhongying Yang[2], Changhong Li[1], Pan Chen[1], Katherine Lord[1], Susan A. Becker[4], Lisa J. States[4,5], N. Scott Adzick[6], Tricia Bhatti[7,8], Show-Ling Shyng[2], Arupa Ganguly[9], Charles A. Stanley[1,3], Diva D. De Leon[1,3]

The Journal of Clinical Endocrinology & Metabolism, 2025, 110, 1923–1928
https://doi.org/10.1210/clinem/dgae813
Advance access publication 9 October 2024
Clinical Research Article

Low-Level Mosaic *GCK* Mutations in Children With Diazoxide-Unresponsive Congenital Hyperinsulinism

Kara E. Boodhansingh,[1] Katherine Lord,[1,2] N. Scott Adzick,[3] Tricia Bhatti,[4] Arupa Ganguly,[5] Charles A. Stanley,[1,2] and Diva D. De Leon[1,2]



Low level mosaic variants in HI causing genes (dominantly inherited) can be detected in blood by next generation sequencing but require validation

Variants in
10 *ABCC8* variants in 12 individuals, 5 *GCK* variants in 7 individuals, 8 *GLUD1* variants in 16 individuals, and 2 *HK1* variants in 5 individuals. One individual with genetically unsolved CHI had a low-level mosaic variant called in both *ABCC8* and *HK1*

eBioMedicine
Part of THE LANCET Discovery Science

Low-level mosaic variants causing the pancreatic disease congenital hyperinsulinism can be detected from blood DNA

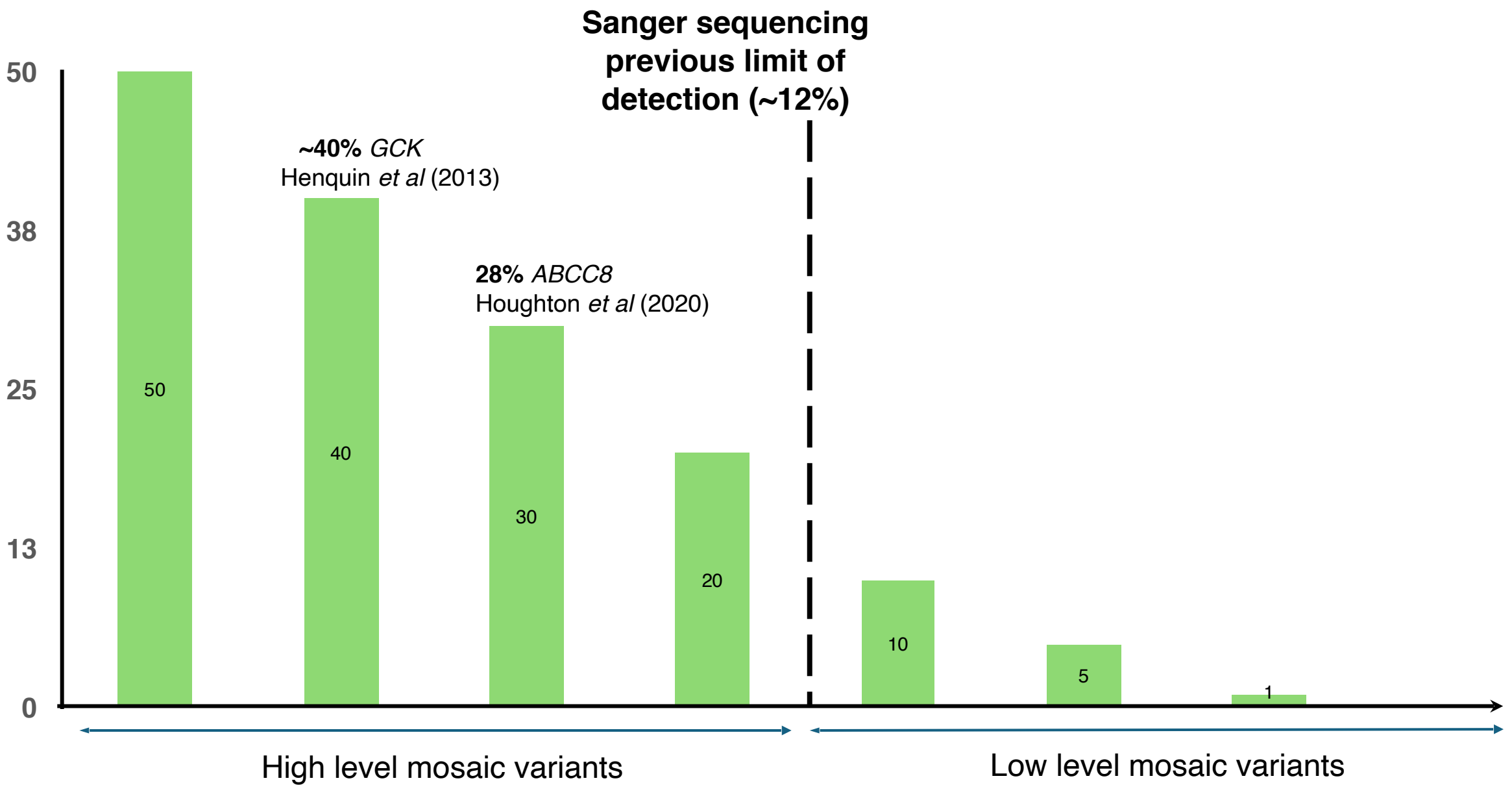
Jasmin J. Bennett,[a,j] Thomas W. Laver,[a,j] Jonna M. E. Männistö,[a,b] Jayne A. L. Houghton,[a,c] Elisa De Franco,[a] Oguzhan Kalyon,[a] Sabrina Wright,[a] Anna-Marie Johnson,[a,c] Diva D. De Leon,[d,e] Evgenia Globa,[f] Sebastian Kummer,[g] Indraneel Banerjee,[h] Antonia Dastamani,[i] International Congenital Hyperinsulinism Consortium, Matthew N. Wakeling,[a] Matthew B. Johnson,[a,j] and Sarah E. Flanagan[a,*,j]

Pushes genetic frontiers

- ~50% genetic causes are unknown
- May provide a greater genetic yield for some dominant HI genes
- Pancreatectomy not needed
- Should this be more mainstream? – needs specialised validation techniques (risk that laboratories without experience may call pathogenic variants incorrectly)

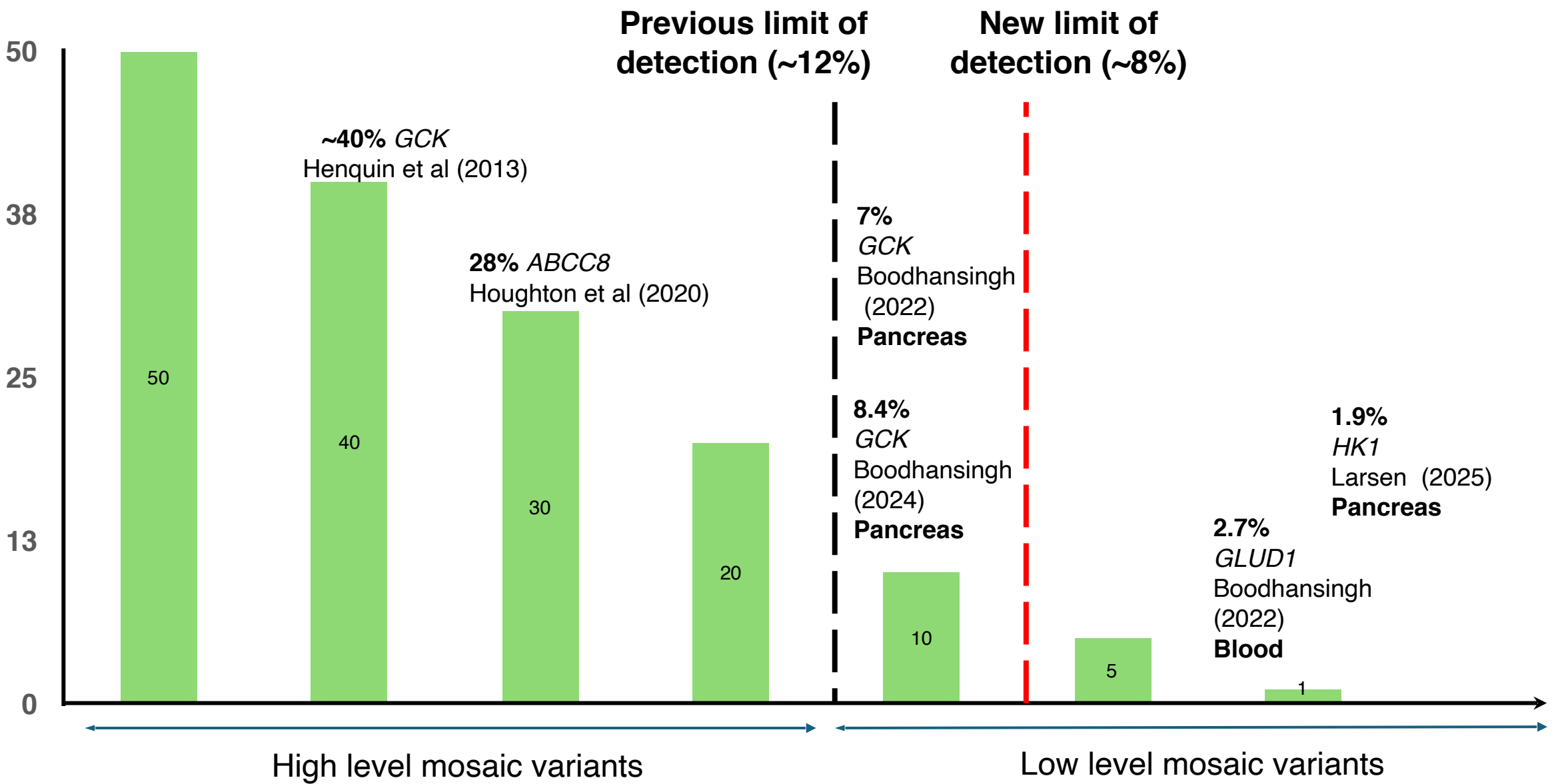
High level mosaic variants: well reported in congenital hyperinsulinism

University of Exeter, Sarah Flanagan 2026



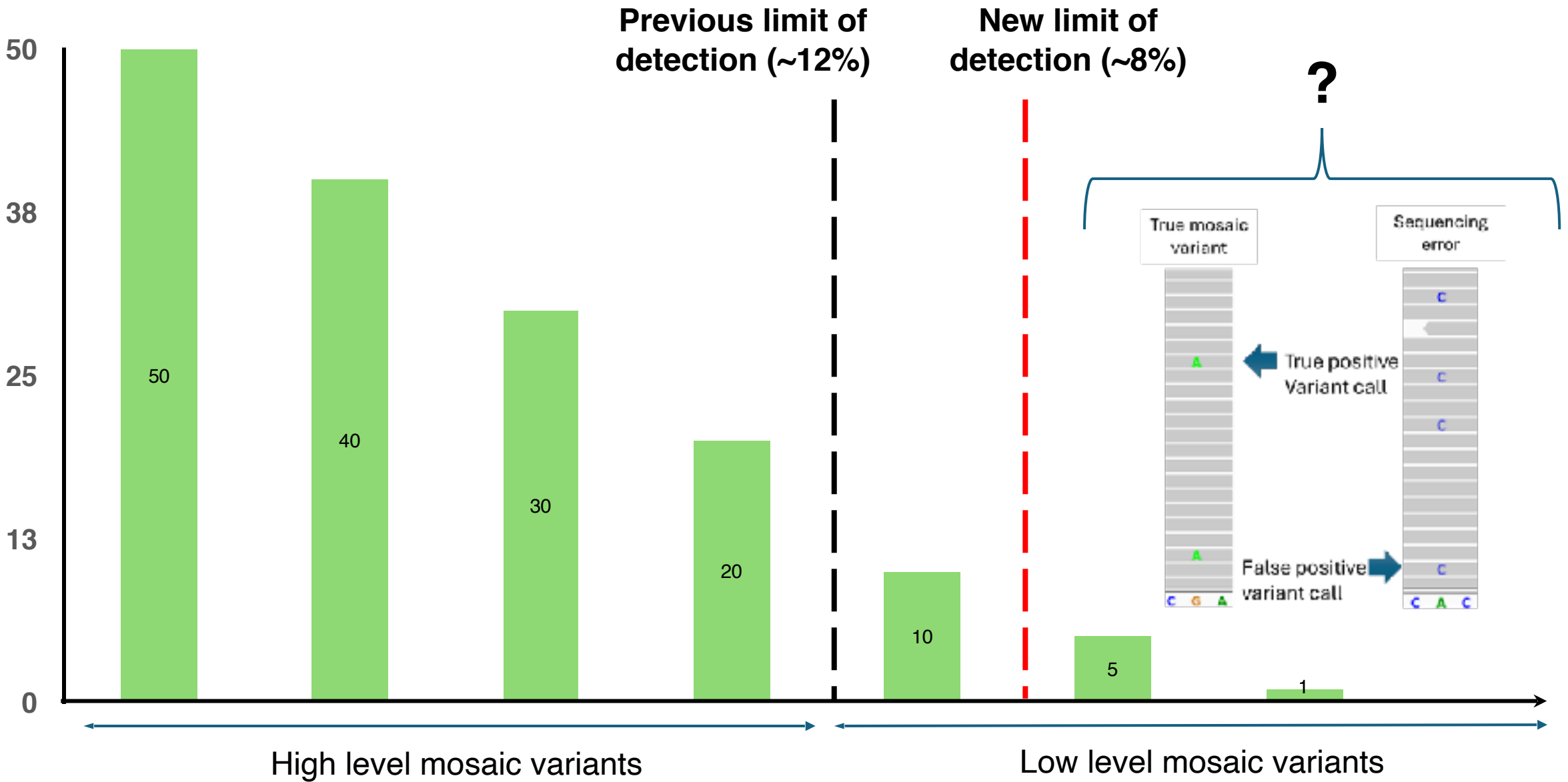
High-depth next generation sequencing allows for detection of low-level mosaic variants

University of Exeter, Sarah Flanagan 202



Can we accurately detect ‘extremely’ low level mosaic variants in routinely sequenced blood samples?

University of Exeter, Sarah Flanagan 2026



Journal of the Endocrine Society, 2026, 10, bvag047
https://doi.org/10.1210/jendso/bvag047
Published: 3 March 2026
Clinical Research Article

Comprehensive genetic rescreening improves diagnostic yield in congenital hyperinsulinism

Jonna M. E. Männistö [1,2], Jayne A. L. Houghton [1,3], Jasmin J. Bennett[1], Päivi Keskinen[4,5], Tiinamaija Tuomi[6,7,8], Heli Ruuskanen[9], Liisa A. Viikari[10], Antti Jokiniitty[11], Jyrki Lähde[5], Joose Raivo[12,13], Timo Otonkoski[14,15], Hanna Huopio[5,16], and Sarah E. Flanagan[1]

Genetic rescreening was informative in 22% (6 of 27) of cases

- non-coding variants in the *ABCC8*, *HK1*
- *SLC16A1* gene
- *GCK* mosaic variant

Value of rescreening with HI gene panel, even after disease resolution
- resources
- centralised activity- e.g. HI Global Registry
- implications for genetic counselling

ENDOCRINE SOCIETY JCEM THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

J Clin Endocrinol Metab. 2026 Mar 10;111(8):2242–2250. doi: 10.1210/clinem/dgag108

Noncoding Variants in Intron 2 of *HK1* Associated With Hyperinsulinism With Variable Clinical Phenotype

Kara E Boodhansingh [1], Katherine Lord [2,3], Winnie Sigal [4,5], Joshua E Benjet [6], Pan Chen [7], Christine A Juliana [8], Lauren Mitteer [9], Tricia Bhatti [10,11], Charles A Stanley [12,13], Diva D De Leon [14,15], Arupa Ganguly [16]

- Intron changes not previously investigated
  - Labs without research insight may miss variants
- Variable presentation
  - Challenge to understand why presentation is different

Sarah Flanagan, U o Exeter

Nuances in genetic interpretation – they do matter!

- Parent of origin is important for *MAGEL2* mutation (Schaaf Young syndrome) – needs to be paternally expressed
  - Required improved methods of analysis (older methods may give incorrect results)

J Med Genet 2026 T Laver et al

- A 94-bp Deletion in the Promoter of the Beta-Cell Disallowed gene *SLC16A1* causing Exercise Induced Hyperinsulinism

  - *SCLC16A1* codes for mono carboxylase transporter 1 (*MCT1*)
  - *SCLC16A1* – another “Disallowed” gene (like *HK1*)
  - Non coding variants in the gene promoter, not previously recognised

Poster

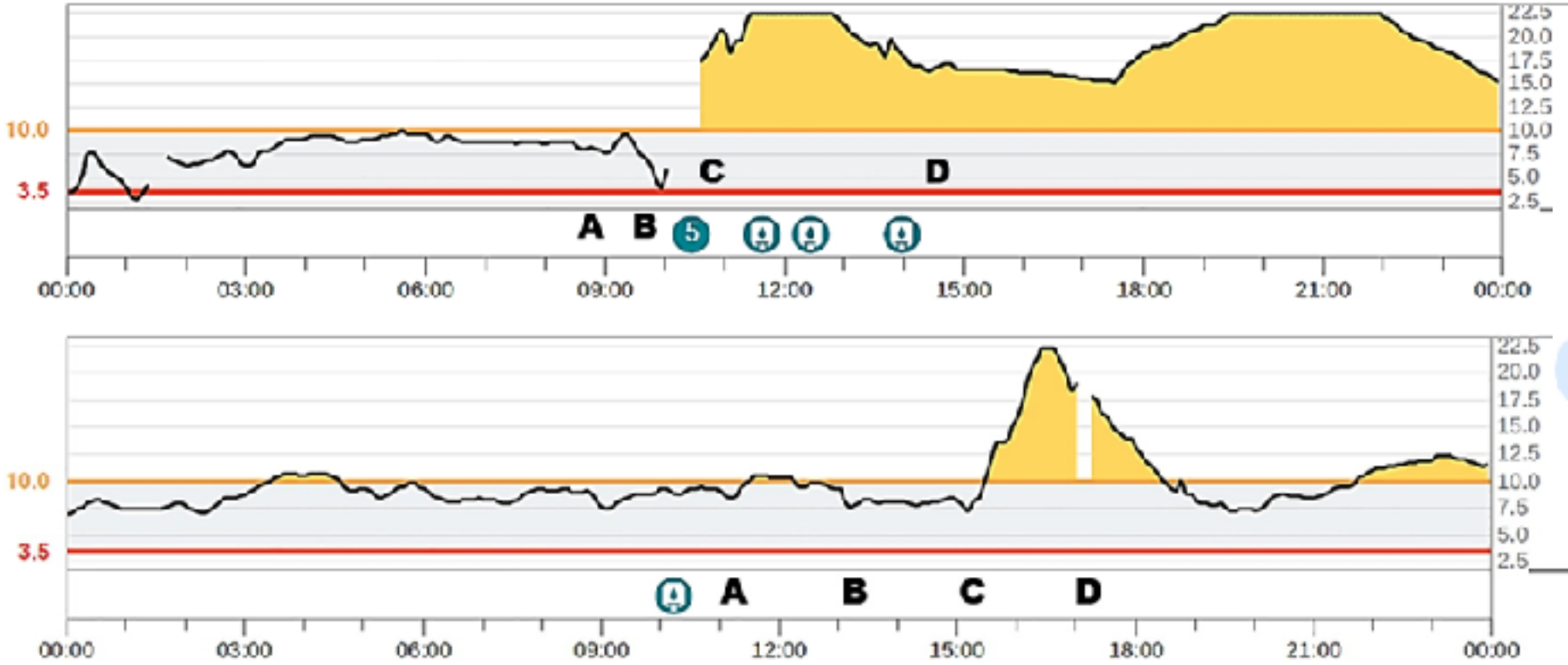
Demand Breastfeeding is Safe in Infants using Diazoxide to manage Hyperinsulinism

Sarah Worthington et al, ESPE 2026

NHS
Manchester University
NHS Foundation Trust

CGM utility in Surgery in HI

Sarah Worthington et al, Front Endocrinol 2026



https://doi.org/10.1038/s44360-026-00119-9

The Open Hyperinsulinism Genes Project bridges global disparities in access to genomic medicine

Julie Raskin[1,4], Jayne A. L. Houghton[2,3,4], Jonna M. E. Männistö[3], Rachel Van Heugten[2], Amy S. Llewellyn[2], Andrew T. Hattersley[3], Tai L. S. Pasquini[1] & Sarah E. Flanagan[3]

[1]Congenital Hyperinsulinism International, Glen Ridge, NJ, USA. [2]Exeter Genomics Laboratory, Royal Devon University Healthcare NHS Foundation Trust, Exeter, UK. [3]Department of Clinical and Biomedical Science, University of Exeter, Exeter, UK. [4]These authors contributed equally: Julie Raskin, Jayne A. L. Houghton.
e-mail: s.flanagan@exeter.ac.uk

- Addressing inequalities of access to reliable genetic testing
- Enhances genetic understanding
- Supports HI Global Registry
- Foundation for natural history phenotyping studies

Home | JAMA Network Open | Vol. 9, No. 4

Original Investigation | Pediatrics

Umbilical Cord Blood Glucose Concentrations and Transitional Neonatal Hypoglycemia

Marcia Roeper, MD[1]; Thomas Melsner, MD[1]; Lisa Friesl[1]; et al

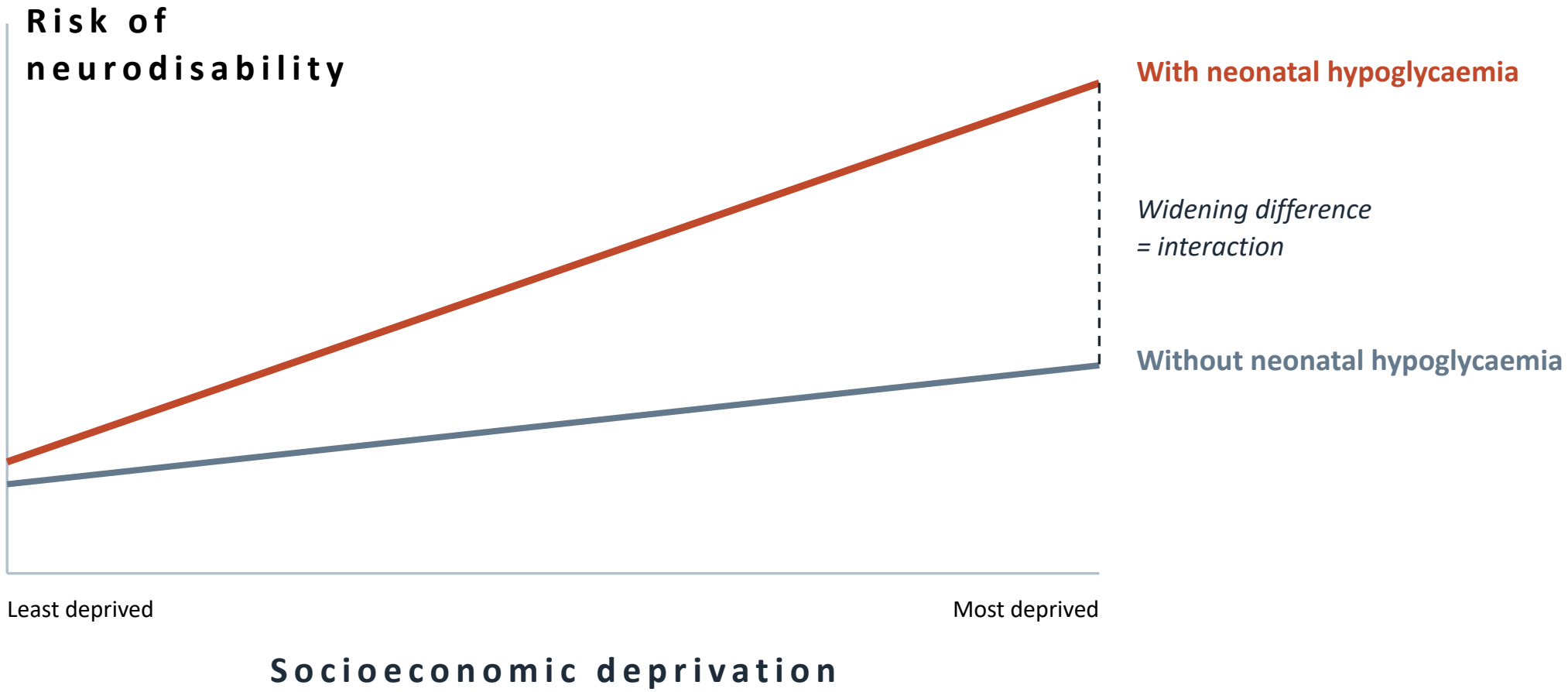
Author Affiliations | Article Information

- Neonatal blood glucose testing -2-3 hours, 36-72 hour after birth or if clinically indicated
- Of 598 neonates, 31% developed hypoglycaemia <2.5 mmol/L (45 mg/dL)
- Umbilical cord blood parameters (arterial/venous glucose, extraction rate were not associated with later hypoglycaemia – single early newborn screening not useful
- Testing association with Transitional Neonatal Hypoglycaemia, not strictly HI

Towards Neonatal Screening of HI…

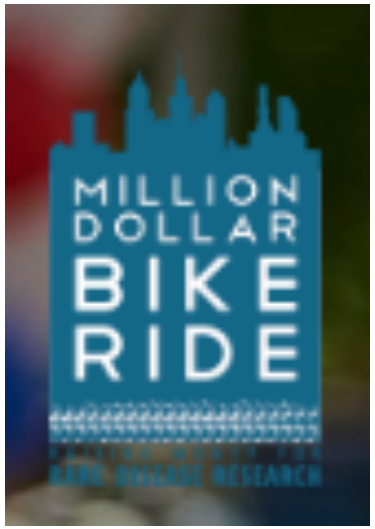
- Theoretical constructs for metabolite-based screening
- Evidence not yet proven
- Need better understanding of mechanisms of neonatal hypoglycaemia

Need to investigate neonatal hypoglycaemia beyond HI – neonatal hypoglycaemia widens the deprivation-neurodisability curve



Children's HYPERINSULINISM Charity

CHI Congenital Hyperinsulinism International
When too little sugar hurts, we help.



MANCHESTER 1824
The University of Manchester

norchi
northern congenital hyperinsulinism service

Thanks to children, families,

CHI CRN Congenital Hyperinsulinism International Collaborative Research Network

CHI as a HI Research Community

NHS National Institute for Health Research

NHS Manchester University NHS Foundation Trust