

# RESEARCH

## Congenital Hyperinsulinism

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**NHS**

**Great Ormond Street**  
**Hospital for Children**  
NHS Foundation Trust



# Research in Congenital Hyperinsulinism



**Children with CHI  
are at high risk for  
hypoglycaemia &  
irreversible brain  
damage**

**Prevent  
Hypoglycaemia**

**Protect  
the brain**

**Unmask the unknown**

**Improve  
understanding for the  
disease & disease  
progression**

**Discover new  
therapies, more  
efficient, with less  
side-effects**



**what?**

**Mechanism**

**Genes**

**Syndromes**

**Diagnosis**

**Insulin assay**

**Imaging of the pancreas**

**Monitoring**

**Blood glucose levels**

**Treatment**

**New medications**

**Surgical techniques**



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**Centre with expertise & experience in the CHI management**

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**High quality of care through an MDT approach**

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**Access to all required specialties**

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**Deliver research in a safely manner**

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**Careful follow up of the protocol and data collection**

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**Commitment**

# Mechanism

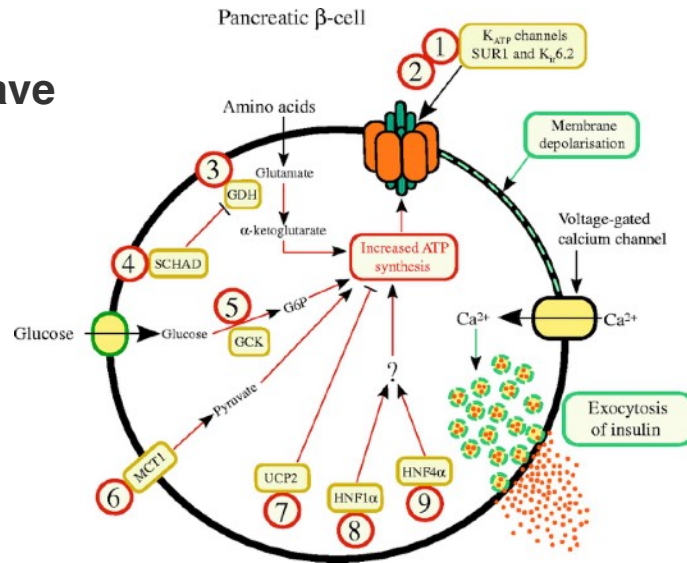
1995

2015- 9 genes

2019- 14 genes

2023- 23 genes

First CHI patients to have a genetic mutation in **ABCC8** gene



S A Rahman et al. J Mol Endocrinol 2015

Gene	Protein	Function	Chromosome
<b>CHI DUE TO DEFECTS IN CHANNEL AND TRANSPORTER PROTEINS</b>			
ABCC8	SUR1	$K_{ATP}$ channel; regulation of channel gating	11p15.1
KCNJ11	Kir6.2		
CACNA1D	CACNA1D	Encodes L-type voltage-gated calcium channels that play a pivotal role in the regulation of insulin secretion	3p21.1
SLC16A1	MCT1	Mediates the transport of lactate and pyruvate across cell membranes	1p13.2
<b>CHI DUE TO ABNORMALITIES IN METABOLIC PATHWAYS</b>			
GLUD1	GDH	Central role in nitrogen metabolism, catalyses the oxidative deamination of L-glutamate to 2-oxoglutarate	10q23.3
GCK	GCK	Important regulatory role in glucose metabolism	7p15-p13
HADH	HADH	Catalyzes the reversible dehydrogenation of 3-hydroxyacyl-CoAs	4q22-q26
UCP2	UCP2	Control of pathway involved in dissipation of the proton electrochemical gradient across the inner mitochondrial membrane	11q13.4
HK1	HK1	Catalyzes the first step in glucose metabolism, using ATP for the phosphorylation of glucose to glucose-6-phosphate	10q22.1
PGM1	PGM1	Catalyzes the transfer of phosphate between the 1 and 6 positions of glucose	1p31.3
PMM2	PMM2	Encodes phosphomannomutase, an enzyme essential for the synthesis of GDP-mannose	16p13.2
<b>CHI DUE TO DEFECTS IN TRANSCRIPTION FACTORS</b>			
HNF4A	HNF4 $\alpha$	Regulates genes largely involved in the hepatic gluconeogenic program and lipid metabolism	20q13.12
HNF1A	HNF1 $\alpha$	Binds to a sequence required for hepatocyte-specific transcription of the genes for the alpha and beta chains of fibrinogen and alpha-1-antitrypsin	12q24.31
FOXA2	HNF 3 $\beta$	Transcription factor required for notochord formation during embryonic development involved in endoderm-derived organ system	20p11.21

Galcheva S et al.. Front. Endocrinol.2019

**ABCC8, AKT2, CACNA1D, CREBBP, EP300, FOXA2, GCK, GLUD1, GPC3, HADH, HNF1A, HNF4A, INSR, KCNJ11, KDM6A, KMT2D, MAFA, NSD1, PHOX2B, PMM2, SLC16A1 and TRMT10A genes and non-coding regulatory region of HK1 by targeted next generation sequencing**



~ 45-50%  
Negative Genetic Testing

If we unmask:

- ✓ Estimate Disease Progression
- ✓ Accurate Genetic Counselling
- ✓ Develop New Therapies

- ✓ Repeat genetic testing every few years to include new genes
- ✓ Exeter Research program
- ✓ [www.exeterlaboratory.com](http://www.exeterlaboratory.com)



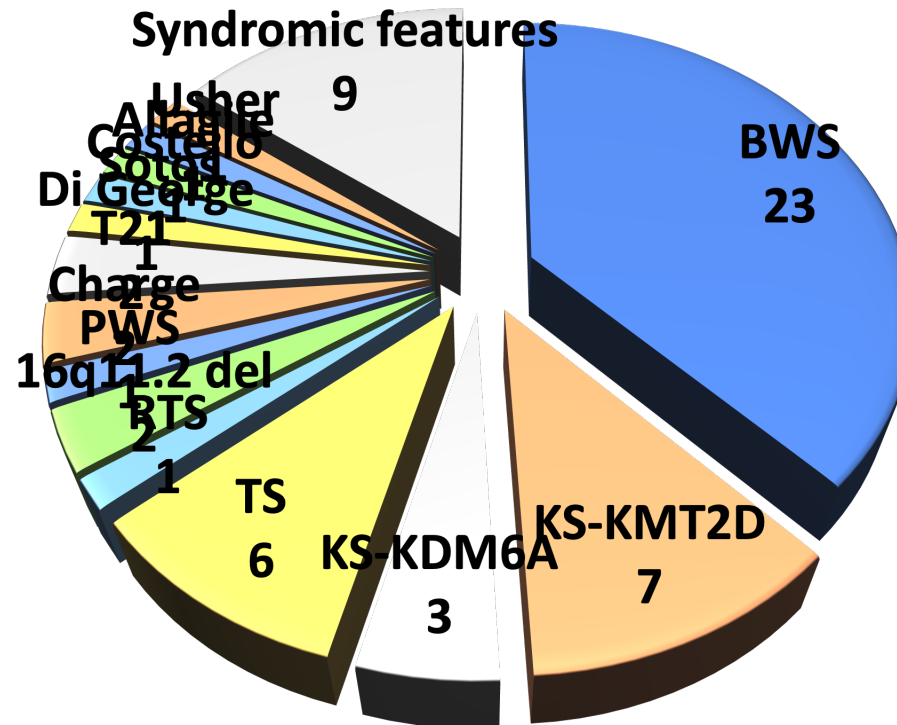
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# Syndromic Forms of Hyperinsulinaemic Hypoglycaemia

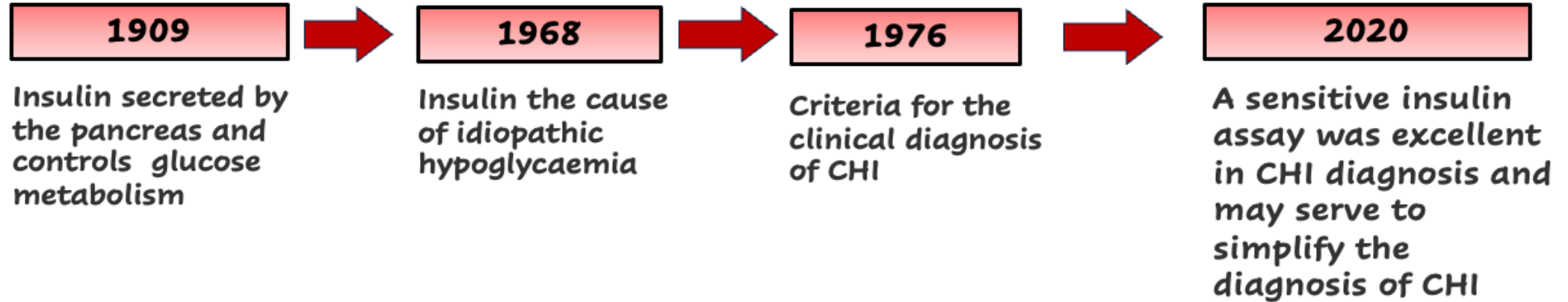
## A 15-year follow-up Study

Clin Endocrinol (Oxf). 2021

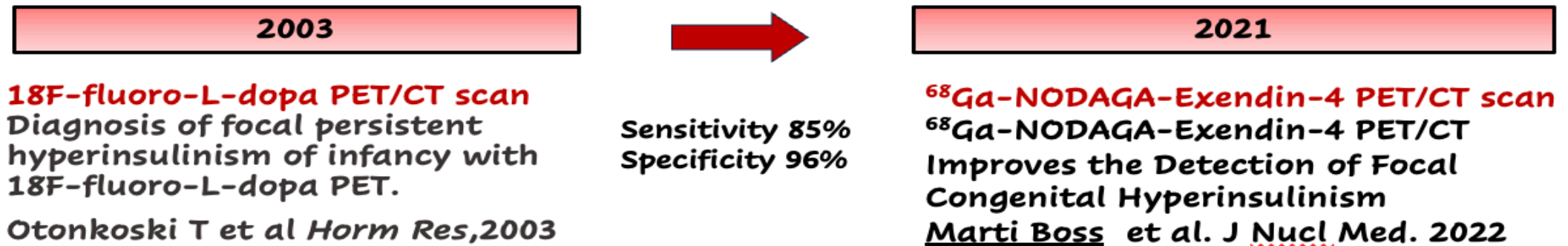


# Diagnosis

## Insulin



## Imaging of the pancreas



Research for new radiotracer to detect focal CHI might provide sufficient image quality for interpretation and improve outcome of lesionectomy



# Monitoring Blood glucose

1980

Glucometers  
available

2004

RT-CGM  
available

2016

Endocrine Society  
recommended CGM  
for T1D adults

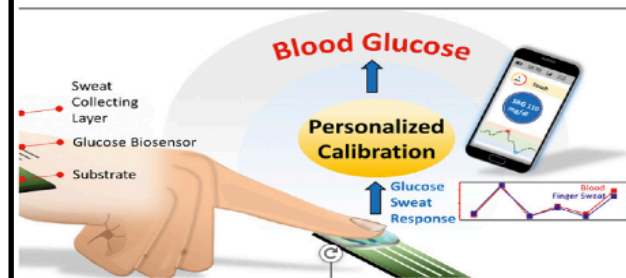
2018

CGM in children with CHI first  
report on accuracy and patient  
experience

2023

No international  
guidelines for CGM use in  
CHI children. CGM used  
on individual basis and as  
per medical team's advice

**Touch-Based Fingertip Blood-Free Reliable Glucose Monitoring: Personalized Data Processing for Predicting Blood Glucose Concentrations**  
Sempionatto J et al. *ACS Sens.* 2021, 6, 5, 1875–1883



- ✓ Different biofluids have been explored recently for replacing current blood finger-stick glucose strips with noninvasive painless sensing devices.
- ✓ There are mixed reports on correlating the sweat results with blood glucose levels.
- ✓ New rapid and reliable approach that combines a simple touch-based fingertip sweat electrochemical sensor with a new algorithm that addresses for personal variations toward the accurate estimate of blood glucose concentrations.

## Noninvasive and CGM

Afon Technology LTD  
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➤ Imagine not being restricted by your finger stick blood glucose monitor.

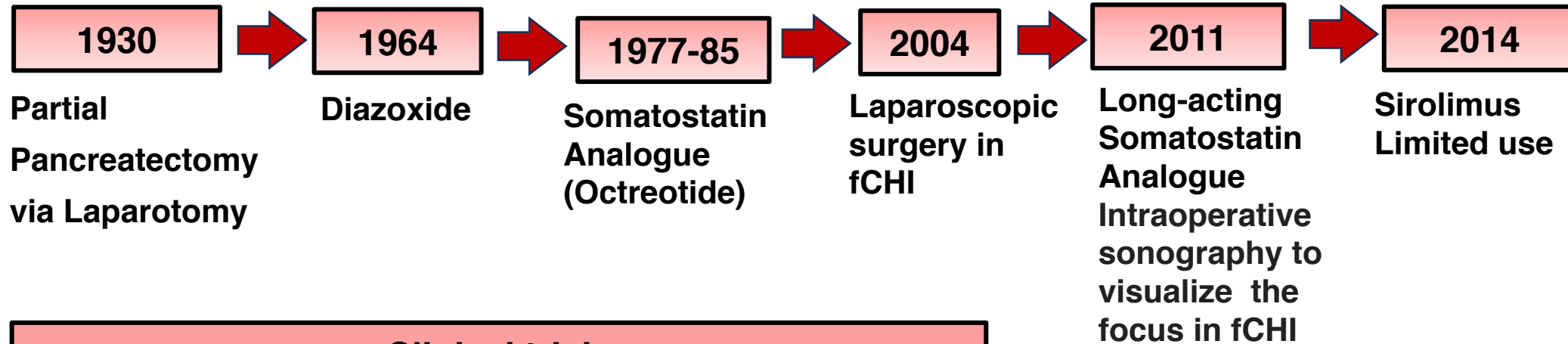
➤ Imagine having a device automatically alerting you when your blood sugar levels are going high or low and all that without taking a single drop of blood.

Watch this space!

RCD No: 008213961-0001



## Treatment



### Clinical trials

- ❑ Dasiglucagon by Zealand Pharma-phase 2,3 studies completed
- ❑ RZ358: Monoclonal Antibody against Insulin receptor by Resolute- phase 2 completed, phase 3 starting
- ❑ HM15136: long-acting glucagon by Hanmi-phase 2 active
- ❑ Avexitide by Eiger: GLP-1 receptor antagonist-phase 2 studies completed
- ❑ CRN04777: SST5 Agonist by Crinetics-phase 1 studies

### Surgery

- ❑ Radio-guided surgery using 68Ga-labelled Exendin in CHI (Charite)
- ❑ Fluorescence-guided surgery with Indocyanine Green dye (GOSH)

## Take home message

**If you are a parent of a CHI child or a CHI patient yourself and interested in what studies are available to you to participate, ask your clinical team about research taking place. They will know if there are any studies available to be offered to you or your child**

**Research in CHI**



**Without Lows**