Hyperinsulinism Status Report

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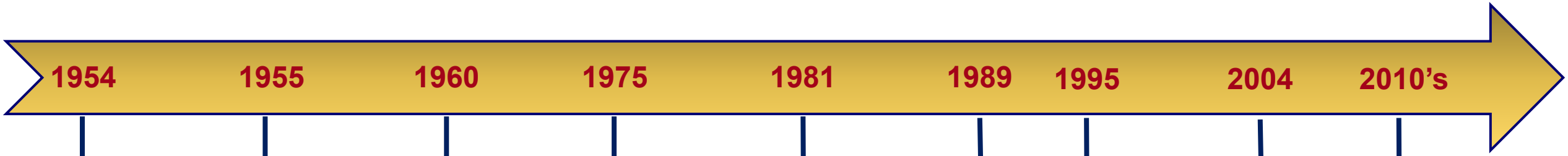
Definition and Diagnosis



1954 Idiopathic spontaneously occurring hypoglycemia in infants. McQuarrie. *Am J Dis Child.*

1955 Familial hypoglycemia precipitated by amino acids. Cochrane, et al. *J Clin Invest.*

1960 Immunoassay of endogenous plasma insulin in man. Yalow and Berson. *J Clin Invest.*

1975 "Congenital hiperinsulinism" replaces "idiopathic hypoglycemia". Haymond & Pagliara; Stanley & Baker; Aynsley-Greene.

Criteria for clinical diagnosis:

1. Hyper-insulinemia
2. Hypo-ketonemia
3. Hypo-FFA-emia
4. Hyper-glycemic response to glucagon

1981 Hyperinsulinism is not a disorder of embriogenesis. Haffe, Hashida, Yunis. *Lab Invest.* Rahier, Wallon, Henquin, *Diabetologia*

1989 Two types of hyperinsulinism: diffuse and focal. Brunelle, et al. *Pediatr Radiol*

1995 *Genetic era:* discovery of SUR1 mutations. Thomas, at al. *Science.*

2004 ^{18}F-DOPA PET imaging for focal hyperinsulinism. Otonkoski, et al. *Diabetes*

2010's *Genetic era:* Expanded availability of genetic testing – multiple genes in one panel

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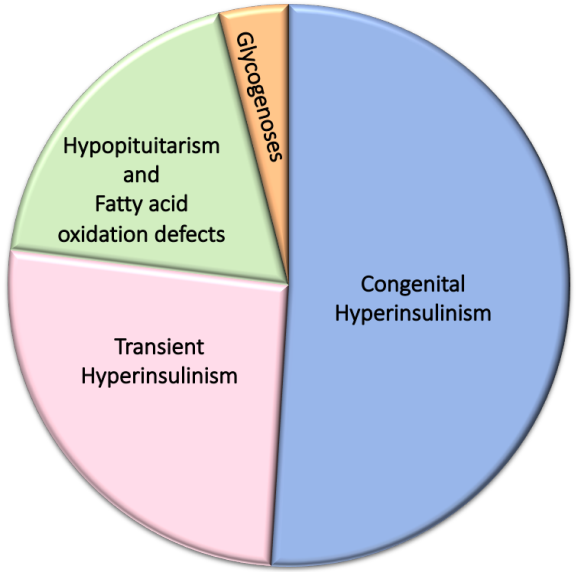
Definition and Diagnosis

- Most common cause of persistent hypoglycemia in children:
  - Rare disease ~ 1:20,000 - 50,000 in USA and Europe
    - **80** new cases in the US every year
- Clinical diagnosis:
  - High glucose requirement
  - Hyper-insulinemia – 82% sensitivity; 100% specificity
  - **Hypo-ketonemia – 100% sensitivity and specificity**
  - Hypo-FFA-emia – 87% sensitivity; 100% specificity
  - Hyper-glycemic response to glucagon – 89% sensitivity: 100% specificity
- Challenges and opportunities:
  - Atypical presentations - late diagnosis/inappropriate treatment
  - Access to biochemical assays

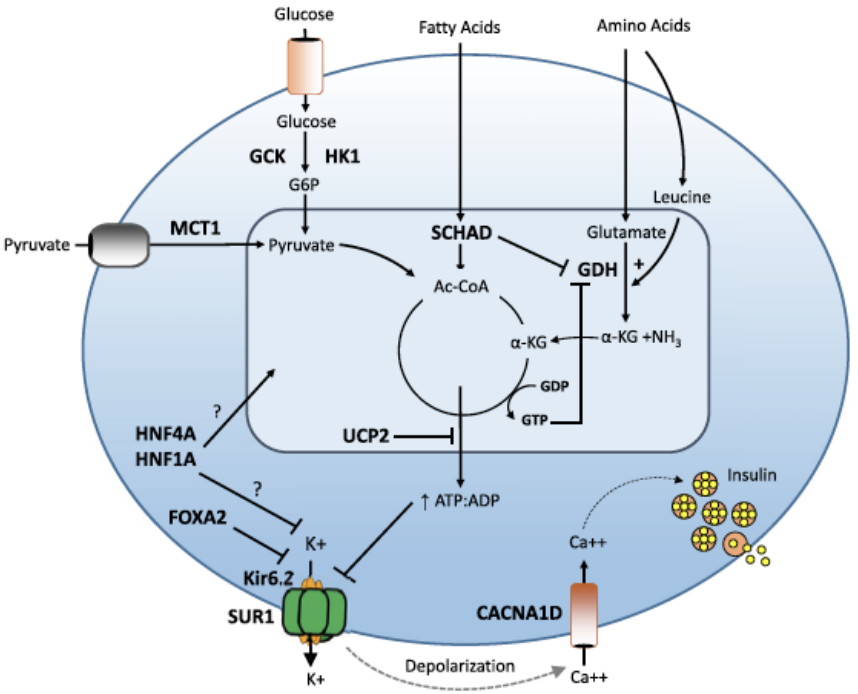


Causes of persistent hypoglycemia in neonates

Ferrara, et al. *J Pediatr,* 2015
Lord & De Leon. *Clin Perinatol*, 2018

Definition and Diagnosis

- Molecular diagnosis:
  - 12+ causative genes identified
  - Next generation sequencing panels include 9-11 genes
  - Two-tier testing with rapid turn around for *ABCC8*/*KCNJ11*
  - Testing available for syndromic causes
- Challenges and opportunities:
  - Access to molecular testing (cost, availability)
  - Interpretation of results (variants of unknown significance)
  - Negative results: **64%** diazoxide-responsive; **10%** diazoxid unresponsive



Molecular causes of hyperinsulinism

Flanagan, Boodhansingh, Lalonde, Ganguly. In Congenital Hyperinsulinism: A practical guide to diagnosis and management; 2019
Rosenfeld, Ganguly & De Leon. *Am J Med Gen C*, 2019

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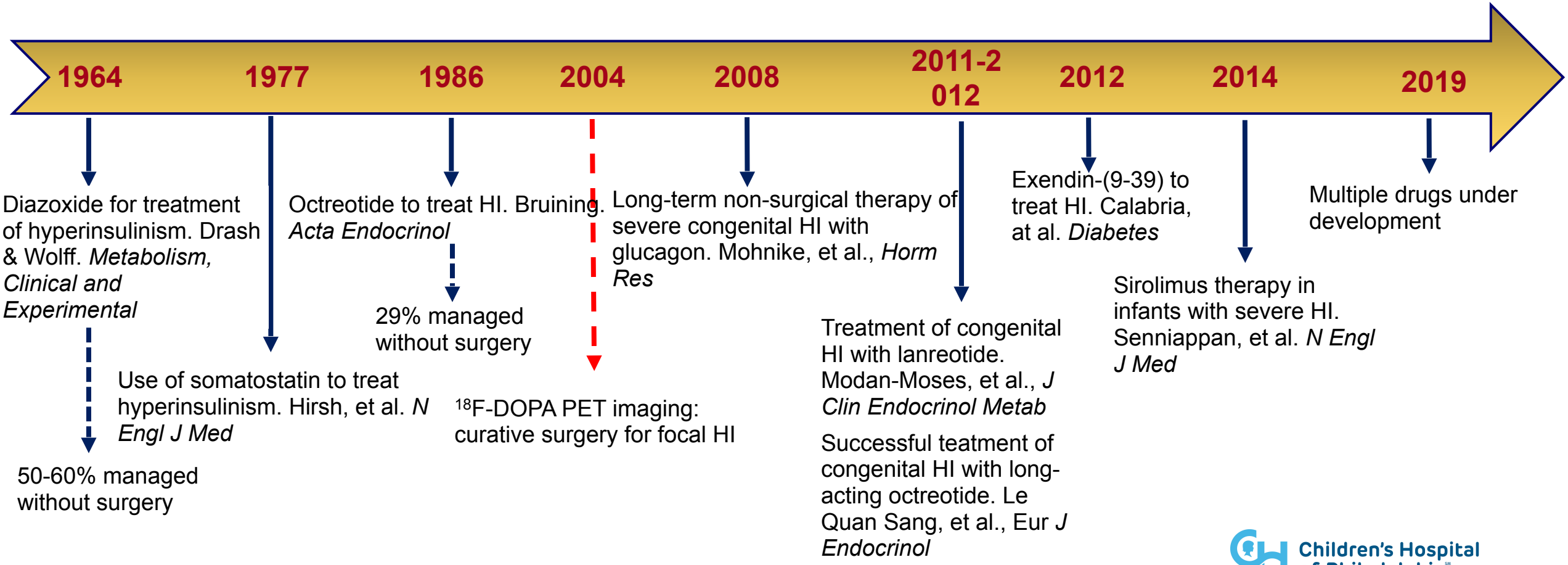
Treatment



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Goals of therapy

- **Immediate:**
  - To promptly restore plasma glucose to normal range [>70 mg/dL(3.9 mmol/L)]
- **Mid-term:**
  - To identify optimal treatment regimens according to type of hyperinsulinism
  - To maintain normal plasma glucose concentrations while encouraging normal feeding/diet
- **Long-term:**
  - To prevent brain damage
  - To promote normal life and development

Precision Medicine

Individualized treatment plan:

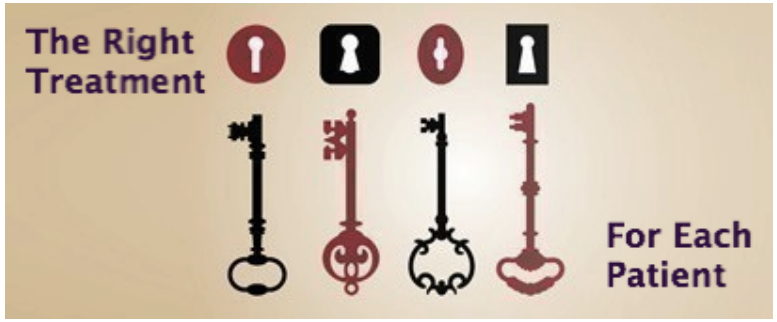
- According to genotype (genetic testing results)
- According to the phenotype (clinical manifestations)

Requires:

- Comprehensive investigations to understand all aspects of the condition
- Different treatment options – one treatment modality may “not fit all”

Is it possible for HI?

- Yes – for focal HI
- Sort of – for non-focal HI



Treatment

- Challenges and opportunities
  - Diazoxide - only FDA-approved drug to treat hyperinsulinism
    - **60%** of cases are unresponsive
    - Not available in many areas of the world: ~ **60%** of respondents to CHI global access survey
  - Ongoing monitoring
    - For side effects of therapy
    - Glycemic control:
      - ✓ Glucose meter vs. CGMS
      - ✓ Inpatient evaluations
    - Growth and development

CGMS for monitoring glycemic control in HI

- 14 children (age 15-67 m) with persistent hypoglycemia due to HI
  - Dexcom G5 for 2 weeks
- Limitations:
  - **High frequency** of false positive lows
  - Helpful for children with glycemic variability, not helpful for children who are well controlled
  - **Cost** – off-label, not covered by insurance

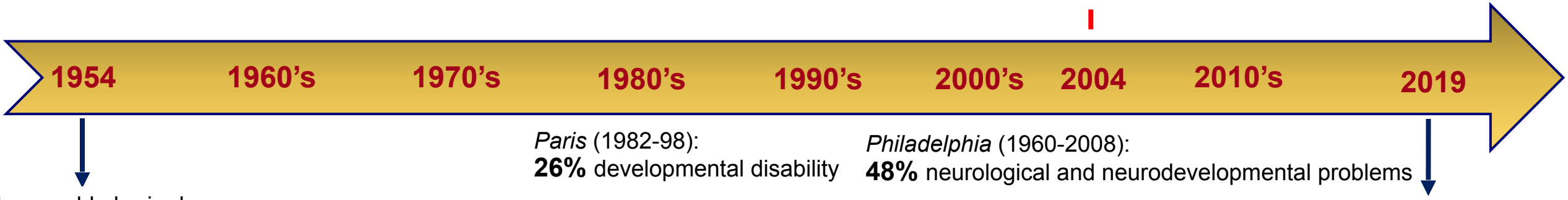
	POSITIVE PREDICTIVE VALUE	NEGATIVE PREDICTIVE VALUE
HYPOGLYCEMIA (<70 MG/DL)	50%	96%
HYPOGLYCEMIA (<54 MG/DL)	15%	99%

Rayannavar, elci, Mitteer, De León. *Horm Res Paediatr,* 2020.

Treatment

- Challenges and opportunities
  - Development of new therapies:
    - Lack of longitudinal natural history data
    - Limited number of patients for clinical trials
    - Heterogeneity of patient population
    - Medical vulnerability of patient population
    - Complex path to approval

Outcomes



^{18}F-DOPA PET imaging

Irreparable brain damage from severe hypoglycemia. McQuarrie. *Am J Dis Child.*

Australia (1972-98):
45% neurological damage

Israel (1975-97):
29% learning problems

Philadelphia (1963-98):
23% developmental disability

Paris (1982-98):
26% developmental disability

Germany (1982-98):
44% developmental disability

Philadelphia (1980-2000):
31% developmental delays

Philadelphia (1960-2008):
48% neurological and neurodevelopmental problems

97% cure for focal HI
CHOP HI Center

Germany (2008-2013):
47% developmental disability

UK (2013):
39% developmental disability

Denmark (2013-2016):
47% developmental disability

Mazor-Aronovitch, *Eur J Endocrinol*, 2007; Lovvorn, *J Pediatr Surg*, 1999; Meissner, *Eur J Endocrinol*, 2003; Menni, *Pediatrics*, 2001; Steinkrauss, *J Pediatr Nurs*, 2005; Avatapalle, *Front Endocrinol,* 2013; Jack, *Clin Endocrinol*, 2003; Adzick, *J Ped Surg*,

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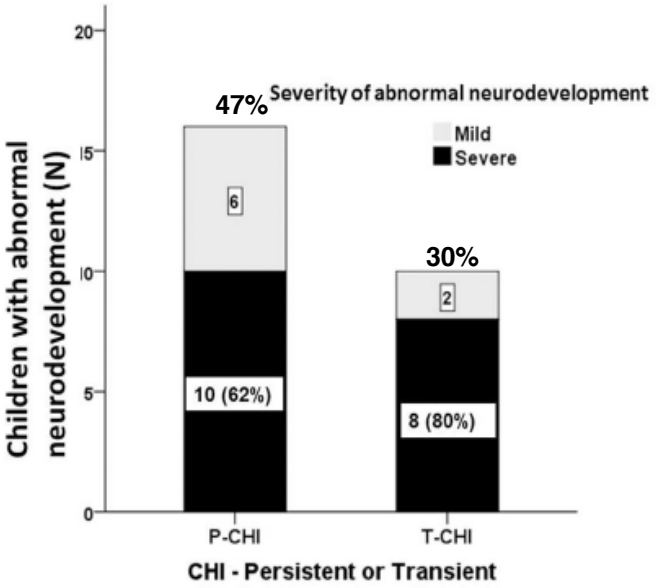
Outcomes

- Neurodevelopmental deficits are common
  - 48% reported problems
  - Children with focal and transient disease equally affected
- Challenges and opportunities:
  - Identification and screening of infants at risk
  - Early diagnosis and treatment with close monitoring of glycemic control
  - **Better treatment options**

Prevalence of Reported Neurobehavioral Problems

Type	Individuals with HI (%) [16]	USA population (%) [20–22]
Psychiatric/behavioral	21	13
Speech delay	18	8
Learning disability	16	8
Seizures	13	1
Physical disability	11	5
ADHD	10	7
Autism	2	0.5



Lord, De León, *J Clin Endocrinol Metab,* 2015
Avatapalle, *Front Endocrinol,* 2013

Research/Clinical Priorities

- Early diagnosis:
  - Novel biomarkers to make newborn screening a reality
- Precise diagnosis:
  - Improved access to molecular testing
  - Better tools for molecular testing and interpretation of results
- Personalized approach to treatment:
  - Natural history and longitudinal data --→ CHI Global Registry
  - *Centers of Excellence*: Specialized Center with Multidisciplinary Team
  - Treatment guidelines ---→ under development (PES/ESPE/SLEP/APPES)
  - Improved tools for monitoring glycemic control
  - *New effective* therapies -→several preclinical and clinical studies ongoing
  - Better access to medications

Thank you

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