



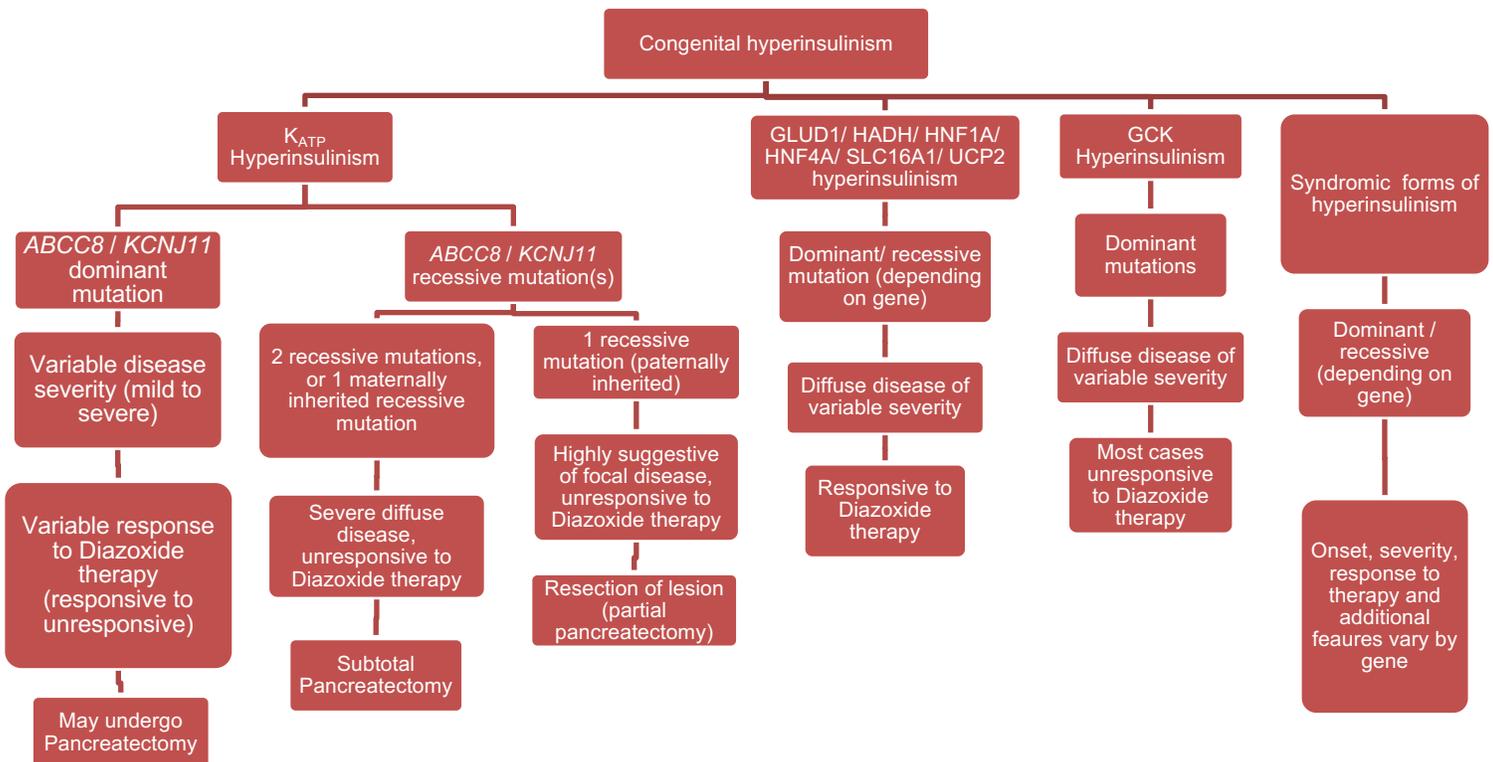
Congenital Hyperinsulinism Testing

Clinical Features:

Congenital hyperinsulinism (CHI) is the most frequent cause of severe persistent hypoglycemia in early infancy. CHI is characterized by unregulated insulin secretion from pancreatic beta-cells... The incidence is estimated at 1/50,000 live births, but it may be as high as 1/2,500 in countries where consanguinity is common. Untreated hypoglycemia due to hyperinsulinism in infants can lead to seizures, developmental delay, and permanent brain injury. Hyperinsulinism can be caused by diffuse disease affecting the whole pancreas, or by a focal lesion.

Mutations in several genes have been identified in congenital forms of hyperinsulinism. Inactivating mutations in the genes encoding the two subunits of the beta-cell ATP-sensitive potassium channel (KATP channel), ABCC8 and KCNJ11, cause the most common and severe form of hyperinsulinism, although mutations in ABCC8 are more common... The second most common form of CHI is due to activating mutations of glutamate dehydrogenase (GDH), encoded by GLUD1, leading to hyperinsulinism/hyperammonemia syndrome (HI/HA)...

The following diagram illustrates the predictions that can be made based on genotype regarding disease extent and severity, and the associated predictions regarding appropriate therapy.



Some genes associated with multisystem syndromes may be associated with hyperinsulinism in a subset of patients.

- Kabuki syndrome is a variable congenital malformation syndrome associated with mutations in *KDM6A* and *KMT2D*, and is characterized by a range of findings including characteristic facial features, minor skeletal anomalies, persistent fetal fingertip pads, intellectual disability, and postnatal growth deficiency²⁶. Additional anomalies including congenital heart defects and cleft lip/palate may also be observed. Hyperinsulinism has been reported as a rare manifestation of Kabuki syndrome, and may be one of the first presenting findings²⁶.
- Biallelic mutations in *PMM2* are associated with congenital disorder of glycosylation 1A (CDG1A), which is variable disorder that can be associated with findings including failure to thrive, developmental delay, epilepsy, ataxia, inverted nipples and abnormal subcutaneous fat patterns²⁷. Some patients with CDG1A may have endocrine abnormalities including hyperinsulinemic hypoglycemia, and for some affected individuals that may be one of the presenting features of the condition in early infancy²⁷.
- Biallelic mutations in *PGM1* are associated with phosphoglucomutase 1 deficiency, a congenital disorder of glycosylation. Common clinical features in affected individuals include hepatopathy, bifid uvula, growth retardation, myopathy, hypoglycemia, and dilated cardiomyopathy²⁸. Affected individuals can have postprandial hyperinsulinemic hypoglycemia, in addition to hyperketotic hypoglycemia²⁹.

Testing options for Congenital Hyperinsulinism

1. Tier 1 Panel: Diazoxide-Unresponsive Hyperinsulinism

This panel is most suited to patients who need rapid results to assist with management decisions. Whenever possible, we recommend sending blood samples on both parents in addition to the patient. There is no charge for parental testing, if performed.

Testing includes:	1. <i>ABCC8</i>, <i>KCNJ11</i>, <i>GCK</i> sequencing 2. Deletion/duplication analysis of <i>ABCC8</i> 3. Sequencing of deep intronic splicing mutations: c.3989-9G>A and c.1333-1013A>G in <i>ABCC8</i>
Turn-around time:	7 days
Sample specifications:	3 to 10 cc of blood in a purple top (EDTA) tube
Cost:	\$3,000
CPT codes:	81407

Test methods:

We offer full gene sequencing of all coding exons and intron/exon boundaries of *ABCC8*, *KCNJ11* and *GCK* by direct sequencing of amplification products in both the forward and reverse directions. This panel also includes testing for 2 deep intronic splicing mutations: c.3989-9G>A and c.1333-1013A>G in *ABCC8*^{30,31}. Deletion/duplication analysis of the *ABCC8* gene is performed by MLPA using a pre-designed kit that contains probes for each for exons 1-38 of the *ABCC8* gene. The sensitivity of our deletion/duplication assay may be reduced when DNA is extracted by an outside laboratory.

2. Comprehensive Congenital Hyperinsulinism Panel:

This test is the most comprehensive available on the market for determining the genetic etiology of hyperinsulinism in patients who do not need results urgently for management reasons. Whenever possible, we recommend sending blood samples on both parents in addition to the patient. There is no charge for parental testing, if performed.

Testing includes:	1. <i>ABCC8</i>, <i>KCNJ11</i>, <i>HADH</i>, <i>HNF1A</i>, <i>HNF4A</i>, <i>INSR</i>, <i>GCK</i>, <i>GLUD1</i>, <i>KDM6A</i>, <i>KMT2D</i>, <i>PGM1</i>, <i>PMM2</i>, <i>SLC16A1</i>, <i>TRMT10A</i>, <i>AKT2</i>, <i>CACNA1D</i>, <i>FOXA2</i> and <i>UCP2</i> Sequencing 2. <i>ABCC8</i>, <i>KCNJ11</i>, <i>HADH</i>, <i>HNF1A</i>, <i>HNF4A</i>, <i>INSR</i>, <i>GCK</i>, <i>GLUD1</i>, <i>KDM6A</i>, <i>KMT2D</i>, <i>PGM1</i>, <i>PMM2</i>, <i>SLC16A1</i>, <i>UCP2</i>, <i>TRMT10A</i>, <i>AKT2</i> Deletion/Duplication 3. Sequencing for 3 deep intronic splicing mutations: c.3989-9G>A and c.1333-1013A>G in <i>ABCC8</i>, and c.636+471G>T in <i>HADH</i>
Turn-around time:	4 weeks
Sample specifications:	3 to 10 cc of blood in a purple top (EDTA) tube
Cost:	\$3000
CPT codes:	81406, 81407

Test methods:

Comprehensive sequence coverage of the coding regions and splice junctions of all genes in this panel will be performed. Targets of interests will be captured and amplified using Agilent SureSelect system. This panel also includes testing for 3 deep intronic splicing mutations: c.3989-9G>A and c.1333-1013A>G in *ABCC8*, and c.636+471G>T in *HADH* – which are founder FHI mutations in the Ashkenazi Jewish, Irish and Turkish populations^{30,31}. The constructed genomic DNA library will be sequenced using Illumina technology and reads will be aligned to the reference sequence. Variants will be identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All pathogenic and likely pathogenic variants will be confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20bp. Our CNV detection algorithm was developed and its performance determined for the sole purpose of identifying deletions and duplications within the coding region of the gene(s) tested. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Regions of high homology and repetitive regions may not

be analyzed. This methodology will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of our deletion/duplication assay may be reduced when DNA extracted by an outside laboratory is provided.

Results:

Results, along with an interpretive report, are faxed to the referring physician as soon as they are completed. All abnormal results are reported by telephone.

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.

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