Clinical Features
Heterozygous inactivating mutations in GCK [OMIM#138079] have been described in patients with maturity onset diabetes of the young type 2 (GCK-MODY) [OMIM#125851], which is characterized by mild fasting hyperglycemia (1). Hyperglycemia is present at birth but often only detected later in life, when individuals undergo routine screening tests (1). Affected individuals rarely, if ever, show progression of disease, or develop the microvascular or macrovascular complications typically associated with diabetes (1). These patients typically therefore can be managed by diet alone, and treatment with oral medications or insulin can actually cause poorer outcomes as patients have an altered counter-regulatory response to hypoglycemia (2). Homozygous inactivating GCK mutations are associated with permanent neonatal diabetes mellitus (PNDM) (1). In addition, heterozygous activating mutations in GCK have also been observed, which lead to hypoglycemia (1).

Molecular Genetics
GCK encodes for the enzyme glucokinase, which has a central role in the regulation of blood glucose and acts as a “glucose sensor” in pancreatic β-cells (3). Mutations in GCK associated with GCK-MODY typically result in a modest decrease in glucokinase activity, which in turn leads to mild fasting hyperglycemia (4).

Inheritance
GCK-MODY is inherited in an autosomal dominant manner. The majority of mutations are inherited, although de novo mutations have also been described. Recurrence risk for children of an affected individual is 50%.

Test methods
Comprehensive sequence coverage of the coding regions and splice junctions of the GCK gene is performed. Targets of interests are captured and amplified using Agilent HaloPlex target enrichment system. The constructed genomic DNA library is sequenced using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All novel and/or potentially pathogenic variants are 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. Deletion/duplication analysis of the GCK gene by oligonucleotide array-CGH identifies copy number changes involving one or more exons. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Array-CGH will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of this assay may be reduced when DNA is extracted by an outside laboratory.

GCK sequencing
Sample specifications: 3 to10 cc of blood in a purple top (EDTA) tube
Cost: $2,200
CPT codes: 81405
Turn-around time: 4 - 6 weeks

GCK deletion/duplication analysis
Sample specifications: 3 to10 cc of blood in a purple top (EDTA) tube
Cost: $1000
CPT codes: 81404
Turn-around time: 4 weeks

Note: The sensitivity of our assay may be reduced when DNA is extracted by an outside laboratory.

Testing for a known mutation in additional family members by sequence analysis
Sample specifications: 3 to10 cc of blood in a purple top (EDTA) tube
Cost: $390
CPT codes: 81403
Turn-around time: 3-4 weeks

Prenatal testing for a known mutation by sequence analysis
Sample specifications: 2 T25 flasks of cultured cells from amniocentesis or CVS or 10 mL of amniotic fluid
Cost: $540
CPT codes: 81403
Turn-around time: 1-2 weeks

Results
Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.
References