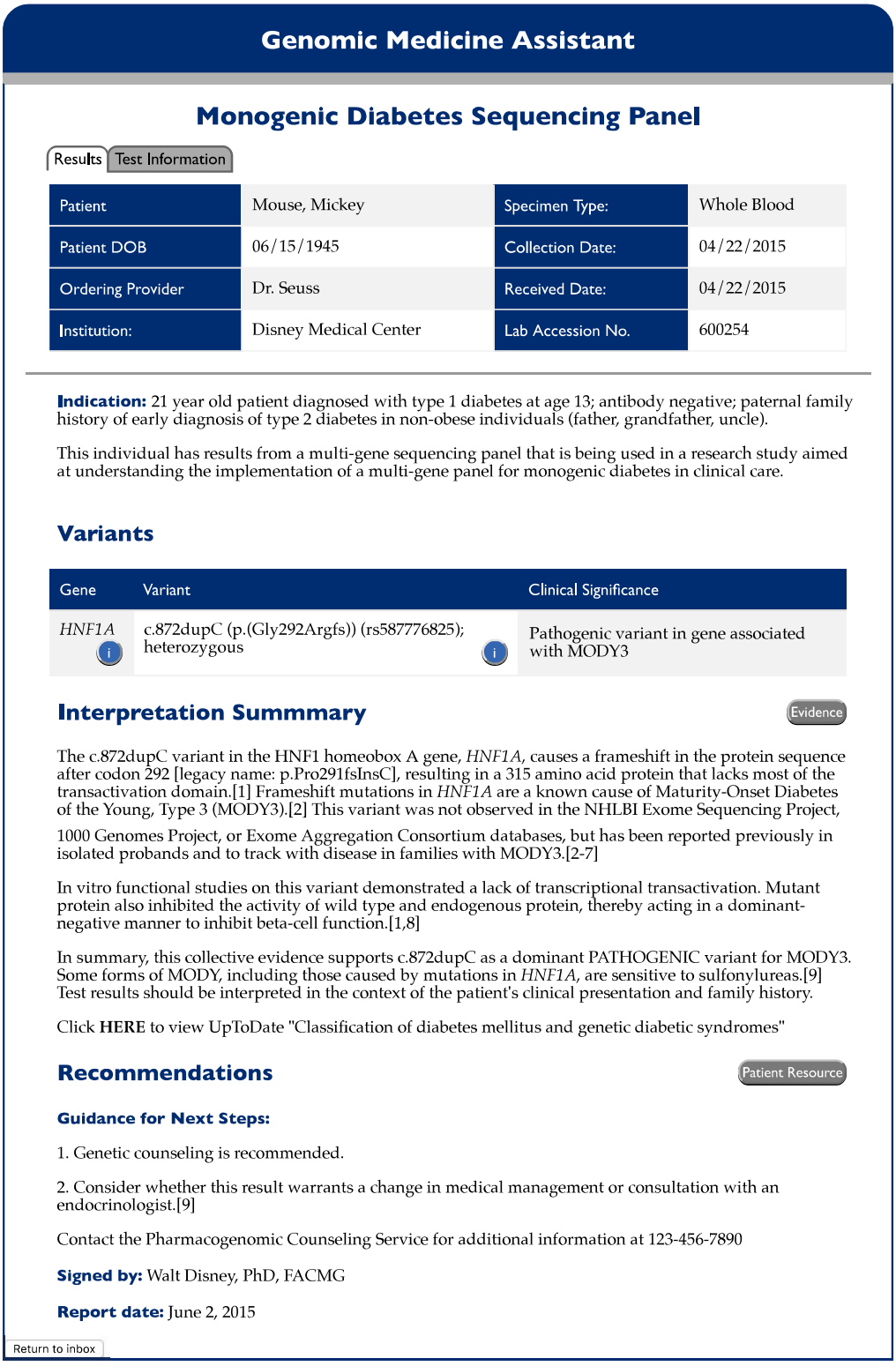
Figure C.5 Monogenic Diabetes Sequencing Panel - Results Page (*HNF1A*)



Genomic Medicine Assistant

Monogenic Diabetes Sequencing Panel

Results | Test Information

Patient	Mouse, Mickey	Specimen Type:	Whole Blood
Patient DOB	06/15/1945	Collection Date:	04/22/2015
Ordering Provider	Dr. Seuss	Received Date:	04/22/2015
Institution:	Disney Medical Center	Lab Accession No.	600254

Indication: 21 year old patient diagnosed with type 1 diabetes at age 13; antibody negative; paternal family history of early diagnosis of type 2 diabetes in non-obese individuals (father, grandfather, uncle).

This individual has results from a multi-gene sequencing panel that is being used in a research study aimed at understanding the implementation of a multi-gene panel for monogenic diabetes in clinical care.

Variants

Gene	Variant	Clinical Significance
HNF1A	c.872dupC (p.(Gly292Argfs)) (rs587776825); heterozygous	Pathogenic variant in gene associated with MODY3

Interpretation Summmary

Evidence

The c.872dupC variant in the HNF1 homeobox A gene, *HNF1A*, causes a frameshift in the protein sequence after codon 292 [legacy name: p.Pro291fsInsC], resulting in a 315 amino acid protein that lacks most of the transactivation domain.[1] Frameshift mutations in *HNF1A* are a known cause of Maturity-Onset Diabetes of the Young, Type 3 (MODY3).[2] This variant was not observed in the NHLBI Exome Sequencing Project, 1000 Genomes Project, or Exome Aggregation Consortium databases, but has been reported previously in isolated probands and to track with disease in families with MODY3.[2-7]

In vitro functional studies on this variant demonstrated a lack of transcriptional transactivation. Mutant protein also inhibited the activity of wild type and endogenous protein, thereby acting in a dominant-negative manner to inhibit beta-cell function.[1,8]

In summary, this collective evidence supports c.872dupC as a dominant PATHOGENIC variant for MODY3. Some forms of MODY, including those caused by mutations in *HNF1A*, are sensitive to sulfonylureas.[9] Test results should be interpreted in the context of the patient's clinical presentation and family history.

Click **HERE** to view UpToDate "Classification of diabetes mellitus and genetic diabetic syndromes"

Recommendations

Patient Resource

Guidance for Next Steps:

1. Genetic counseling is recommended.

2. Consider whether this result warrants a change in medical management or consultation with an endocrinologist.[9]

Contact the Pharmacogenomic Counseling Service for additional information at 123-456-7890

Signed by: Walt Disney, PhD, FACMG

Report date: June 2, 2015

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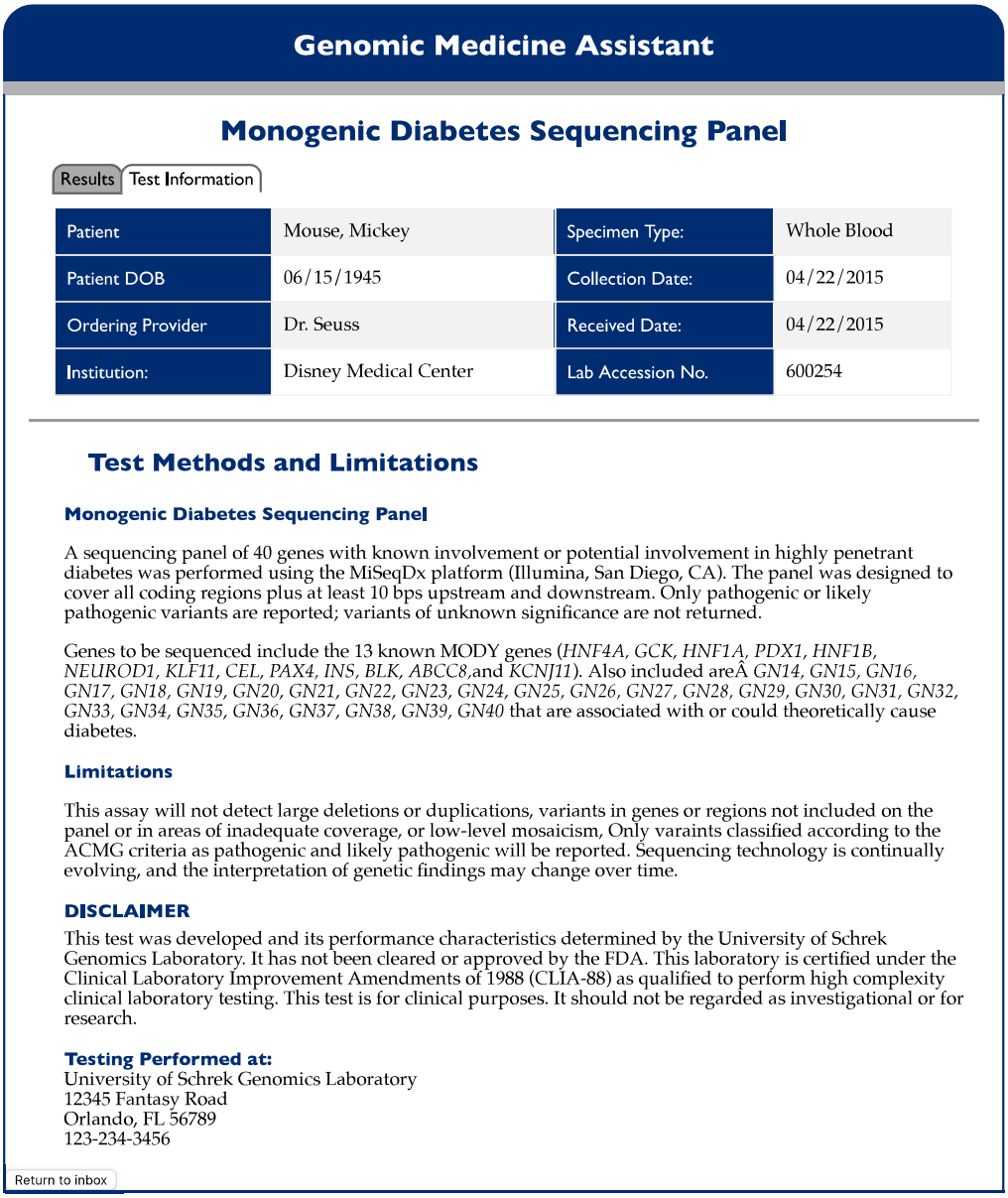
Figure C.6 Monogenic Diabetes Sequencing Panel - Test Information Page (*HNF1A*)



Genomic Medicine Assistant

Monogenic Diabetes Sequencing Panel

Results | Test Information

Patient	Mouse, Mickey	Specimen Type:	Whole Blood
Patient DOB	06/15/1945	Collection Date:	04/22/2015
Ordering Provider	Dr. Seuss	Received Date:	04/22/2015
Institution:	Disney Medical Center	Lab Accession No.	600254

Test Methods and Limitations

Monogenic Diabetes Sequencing Panel

A sequencing panel of 40 genes with known involvement or potential involvement in highly penetrant diabetes was performed using the MiSeqDx platform (Illumina, San Diego, CA). The panel was designed to cover all coding regions plus at least 10 bps upstream and downstream. Only pathogenic or likely pathogenic variants are reported; variants of unknown significance are not returned.

Genes to be sequenced include the 13 known MODY genes (*HNF4A, GCK, HNF1A, PDX1, HNF1B, NEUROD1, KLF11, CEL, PAX4, INS, BLK, ABCC8,*and *KCNJ11*). Also included areÂ *GN14, GN15, GN16, GN17, GN18, GN19, GN20, GN21, GN22, GN23, GN24, GN25, GN26, GN27, GN28, GN29, GN30, GN31, GN32, GN33, GN34, GN35, GN36, GN37, GN38, GN39, GN40* that are associated with or could theoretically cause diabetes.

Limitations

This assay will not detect large deletions or duplications, variants in genes or regions not included on the panel or in areas of inadequate coverage, or low-level mosaicism, Only varaints classified according to the ACMG criteria as pathogenic and likely pathogenic will be reported. Sequencing technology is continually evolving, and the interpretation of genetic findings may change over time.

DISCLAIMER

This test was developed and its performance characteristics determined by the University of Schrek Genomics Laboratory. It has not been cleared or approved by the FDA. This laboratory is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA-88) as qualified to perform high complexity clinical laboratory testing. This test is for clinical purposes. It should not be regarded as investigational or for research.

Testing Performed at:
University of Schrek Genomics Laboratory
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Orlando, FL 56789
123-234-3456

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While the investigators in the study have made every effort to ensure that the information presented is consistent with current practices, all information presented was prepared for simulated conditions and may not reflect all aspects of standard medical care.