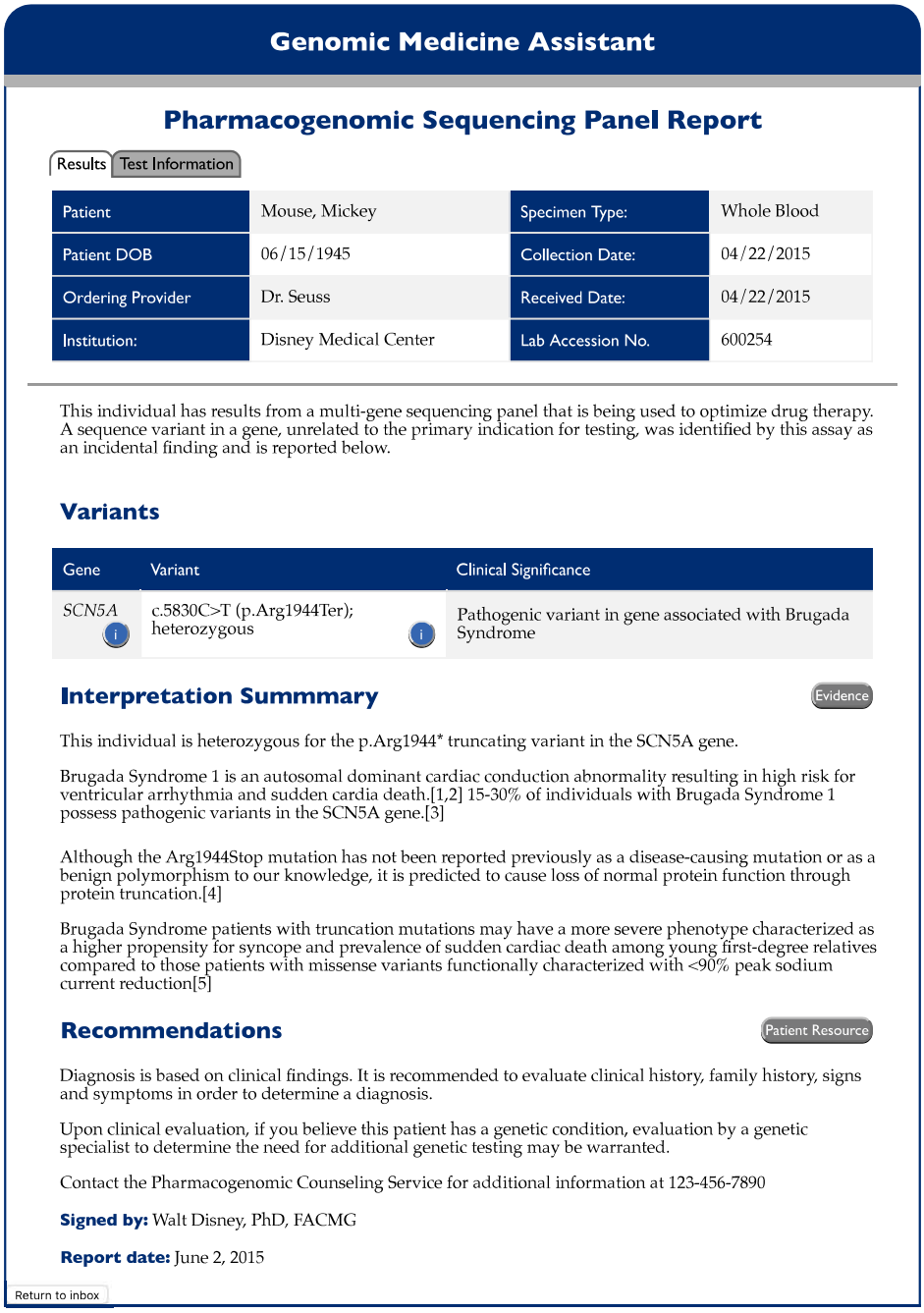
Figure C.3 Pharmacogenomic Sequencing Panel Report - Results Page (*SCN5A*)



Genomic Medicine Assistant

Pharmacogenomic Sequencing Panel Report

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

This individual has results from a multi-gene sequencing panel that is being used to optimize drug therapy. A sequence variant in a gene, unrelated to the primary indication for testing, was identified by this assay as an incidental finding and is reported below.

Variants

Gene	Variant	Clinical Significance
SCN5A	c.5830C>T (p.Arg1944Ter); heterozygous	Pathogenic variant in gene associated with Brugada Syndrome

Interpretation Summmary

Evidence

This individual is heterozygous for the p.Arg1944* truncating variant in the SCN5A gene.

Brugada Syndrome 1 is an autosomal dominant cardiac conduction abnormality resulting in high risk for ventricular arrhythmia and sudden cardia death.[1,2] 15-30% of individuals with Brugada Syndrome 1 possess pathogenic variants in the SCN5A gene.[3]

Although the Arg1944Stop mutation has not been reported previously as a disease-causing mutation or as a benign polymorphism to our knowledge, it is predicted to cause loss of normal protein function through protein truncation.[4]

Brugada Syndrome patients with truncation mutations may have a more severe phenotype characterized as a higher propensity for syncope and prevalence of sudden cardiac death among young first-degree relatives compared to those patients with missense variants functionally characterized with <90% peak sodium current reduction[5]

Recommendations

Patient Resource

Diagnosis is based on clinical findings. It is recommended to evaluate clinical history, family history, signs and symptoms in order to determine a diagnosis.

Upon clinical evaluation, if you believe this patient has a genetic condition, evaluation by a genetic specialist to determine the need for additional genetic testing may be warranted.

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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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.

Figure C.4 Pharmacogenomic Sequencing Panel Report - Test Information Page (*SCN5A*)

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Pharmacogenomic Sequencing Panel Report

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

Pharmacogenomic Sequencing Panel

MPS was performed to screen 84 pharmacogenes for DNA sequence variants relevant for drug therapy decisions. Sequence variations in a set of genes related to 'actionable genes' were also identified by this assay as incidental findings. These actionable genes were chosen based on their association with adult onset conditions for which there is a recommended screening and/or treatment.

Only pathogenic variants are reported for incidental findings - variants of uncertain significance are not returned. Positive findings were validated to clinical standards in a CLIA compliant laboratory; however, the performance characteristics of MPS for negative results (the absence of mutations) were not validated to clinical standards in a CLIA compliant laboratory. This laboratory test was developed and its performance characteristics determined by the University of Maryland Translational Genomics Laboratory (CLIA-certified). Consistent with laboratory-developed tests, this test has not been cleared or approved by the U.S. Food and Drug Administration.

Procedure:

I. Pharmacogenomic Sequencing Panel
Genomic DNA was extracted from blood using standard procedures. A library of DNA fragments was constructured and enriched for protein and RNA coding portions of the human genome using the PGRNseq custom capture reagent. Sequence captured from each gene includes the complete coding regions plus 2 kb upstream and 1kb downstream to assess variation within nearby regulatory regions. Paired-end sequencing of the enriched library was performed using standard TruSeq v3.0 (Illumina) chemistry on a HiSeq 2000 (Illumina) sequencer. Resulting sequences were aligned to the human genome reference (hg19) using the Burrows_Wheeler Aligner (BWA) and variants identified with the Genome Analysis Tool Kit (GATK). A modified version of the SeattleSeq tool was used to annotate variants found within a defined set of actionable genes.

II. Validation of Sequence Variants (CLIA-accredited)
Primers based on the hg19 (February 2009) version of the human genome sequence, were used to amplify standard dye-terminator chemistry.

Limitations

1. This assay does not detect large deletions or duplications and has limited ability to identify small insertions and deletions. This test also has limited ability to detect mosaicism.

2. This assay does not detect variants located: a) outside of 84 pharmacogenes, b) in regions of insuffienct coverage, c) in regions containing paralogous genes or pseudogenes, or d) where the reference genome is inaccurate or contains gaps and insertions.

3. Variants of uncertain significance are not reported.

4. Genes not associated with treatable genetic conditions at the time this test was performed were not analyzed.

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
12345 Fantasy Road
Orlando, FL 56789
123-234-3456

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