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Volume 8, Number 1

PRESIDENT'S CORNER

Quantitative Interpretation of Sequence Variants

James L. Weber, PhD, President, PreventionGenetics

First of two part series

We're excited to announce that our del/dup menu has doubled. We now offer deletion/duplication testing for over 1500 genes via custom, gene-centric aCGH. Even more exciting is a reduction in the cost of these tests. With our continued exceptional quality and a reduced cost, the value equation of our del/dup testing just got a lot better.

Our new pricing structure is listed below, for more infomattion, visit our website.

Interpretation of sequence variants is certainly one of the greatest current challenges in clinical genetics. Despite the impressive new ACMG interpretation guidelines (Richards et al. 2015 Genet Med 17:405-424), variant interpretation is still a highly subjective exercise. Two highly experienced and skilled geneticists each examining exactly the same evidence will often come up with different interpretations. In an effort to make interpretation more objective, we have been working at PreventionGenetics to develop several simple, quantitative measures of pathogenicity. Our results have been presented at the ACMG and ICHG meetings earlier this year, and will be presented at the ASHG meeting in Vancouver this fall. In this article, I provide rationale and introduction to our approaches. In the second part of this series, I will provide a more detailed description of the two quantitative approaches we have developed along with some of the supporting evidence.

At least in North America, and perhaps gradually throughout the world, sequence variants (defined as differences between patient sequences and reference sequences) are now classified into five groups: Pathogenic, Likely Pathogenic, Uncertain, Likely Benign and Benign. Objective interpretation must begin with quantitative definitions of these group labels. Much more discussion needs to take place before even national consensus about quantitative definitions is reached, but the values currently used at PreventionGenetics are shown in the accompanying Table. These values are the probabilities that the interpretation assignments are incorrect; for example a variant that is classified as Likely Pathogenic should have no more than a 5% chance of being benign. Note that our definitions are conservative. We want only a small chance that our assignments of “pathogenic” or “benign” are incorrect. When there is more than a small chance, we classify the variants as Uncertain.

Our two quantitative approaches involve allele frequency differences between cases and controls,

Number of Genes Ordered	Total Price
1	$690
2	$730
3	$770
4-10	$840
11-30	$1290
31-100	$1670
Over 100	Call for Quote

DR. BLIVEN SPECIALIZES IN MITOCHONDRIAL DISORDERS

Kym Bliven, Ph.D., joined PreventionGenetics in August 2015 as a Clinical Molecular Geneticist. Her portfolio focuses on mitochondrial disorders.
Dr. Bliven received and her Ph.D. in molecular genetics from the Uniformed Services University of Health Sciences. Her doctoral research involved investigation of bacterial antivirulence genes - genes

and the fraction of times a particular variant occurs together with a second plausible pathogenic variant in patients affected with recessive disorders. These approaches have limitations as well as potential pitfalls and therefore must be used with caution. The results of the quantitative approaches should also always be considered together with all available qualitative evidence. Nevertheless, these approaches are important first steps in transforming sequence interpretation from an art to a science. We are cautiously, but steadily applying these quantitative approaches to variant interpretation at PreventionGenetics.

Category	Target Error Rate
Pathogenic	1%
Likely Pathogenic	5%
Uncertain	--
Likely Benign	5%
Benign	1%

Visit us at:

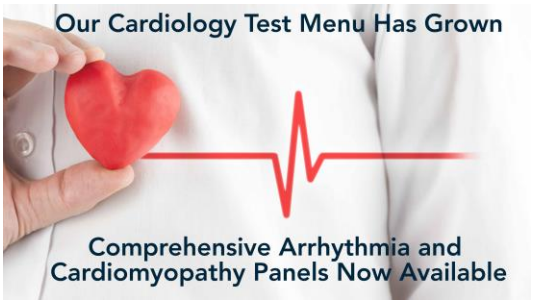
Heart Rhythm Society Meeting - San Francisco, CA
Booth #2239
NERGG GC Meeting - Danvers, MA
ESHG - Barcelona, Spain Booth #245

More Information:

- New Tests
-Tests by Category

that are lost or inactivated by the bacteria during host adaptation to facailitate optimal virulence.

Originally from Marshfield, Dr. Bliven is excited to be back in Central Wisconsin, an area she loves. She was drawn to PreventionGenetics by a fascination with genetics and evolution as well as the opportunity to investigate mitochondrial disorders. She is passionate about quality and effective communication of results so that “healthcare providers can make the best possible decisions for their patients based on the information we provide”.



Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia Panel: 9 genes (Test #1315)
Brugada Syndrome NextGen Sequencing Panel - 16 genes (Test #2603)
Catecholaminergic Polymorphic Ventricular Tachycardia Panel - 8 genes (Test #1311)
Comprehensive Cardiac Arrhythmia Panel - 46 genes (Test #2607)
Dilated Cardiomyopathy Panel - 32 genes (Test #1339)
Hypertrophic Cardiomyopathy Panel - 15 genes (Test #1313)
Left Ventricular Noncompaction Panel - 9 genes (Test #1333)
Long QT Panel - 15 genes (Test #2601)

Upcoming Presentations:

Managing Genetic Test Utilization: Doing the Right Thing for Patients While Supporting

- Requistion Forms
- Billing Policy
- Utilization Management
- Order Testing Kits

Physicians and Managing Costs

Amy Nystrom, MBA - Chief Business Officer, PreventionGenetics

Executive War College - Conference on Laboratory & Pathology Management

Wednesday April 27, 2016 1:10 PM - 2:00 PM

Join us for this presentation via Webinar by registeringhere

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