Understanding your results:

Inherited metabolic conditions and pseudodeficiency alleles

What are inherited metabolic conditions?

Inherited metabolic disorders are a family of medical conditions caused by genetic changes that interfere with the body's metabolism. The metabolism is a system of chemical reactions that allow the body to get and make energy from the food we eat (substrates) by breaking it down into subparts like sugars and acids (products). The metabolism also helps the body eliminate toxic waste.

Metabolic chemicals are called enzymes. If these enzymes are absent, unstable, or malfunctioning, a metabolic disease can occur. Usually, this happens when the body is unable to produce the critical fuel it needs, or when substances build up to toxic levels in a person's body.

People with inherited metabolic disorders inherit two copies of the affected gene—one from each carrier parent, who both have one normal copy and one affected copy of the gene. Carriers usually do not have any symptoms because they have one normal gene that makes up for the malfunctioning gene.

Testing can help determine if someone has an inherited metabolic disease, or if they are a carrier.

How is a metabolic condition detected?

For certain types of inherited metabolic conditions, there are multiple ways of testing to determine if someone has the disease or may be a carrier. Two of the most common are DNA testing and biochemical testing. Some inherited metabolic conditions, called inborn errors of metabolism, are tested for at birth through statewide newborn screening programs.

What is DNA testing?

DNA testing looks for changes or variants in the gene that could lead to impaired or reduced biochemical activity.

What is biochemical testing?

Biochemical tests are sometimes called enzyme studies. These studies measure enzyme activity and determine whether an enzyme is working properly. Tests detect metabolic disease when an enzyme is unable (or has reduced ability) to change the tested substrate into the appropriate product.

Enzyme studies cannot differentiate between true pathogenic variants and pseudodeficiency alleles. These must be determined by DNA testing.

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Understanding your results: *(continued)*

Inherited metabolic conditions and pseudodeficiency alleles

What is a pseudodeficiency allele and how is it related to biochemical testing?

Pseudodeficiency alleles are DNA variants that can lead to false positive results on biochemical enzyme studies but are not known to cause clinical symptoms or lead to disease.

In a laboratory enzyme assay, synthetic substrates are commonly used instead of the substrate naturally found in the body. Pseudodeficiency alleles are known to impair an enzyme's ability to convert this artificial substrate to product, which can lead to a false positive result on enzyme tests.

What does this mean for me and my offspring?

Pseudodeficiency alleles are inherited just like any other genetic variant and can be passed to offspring.

The presence of a pseudodeficiency allele does not increase your chance of having a child affected with any of the metabolic conditions that were screened for.

Pseudodeficiency alleles are reported to you so that you are aware of potential false positive results on a biochemical test, such as newborn screening. You may wish to share your test results with your healthcare providers.