### Condition Description

Mutations in the *PRPS1* gene (Xq22-q24) can result in one of four X-linked syndromes: phosphoribosylpyrophosphate synthetase-1 (PRPS1) superactivity, Charcot-Marie-Tooth disease-5 (CMTX5), Arts syndrome, and X-linked nonsyndromic sensorineural deafness (DFN2). Affected individuals may have neurological, hematopoietic and/or purine overproduction symptoms. Neurological symptoms can include ataxia, hypotonia, optic atrophy, hearing impairment, and neuropathy. The main hematopoietic symptom can be susceptibility to infection. Purine overproduction symptoms manifest primarily as uric acid stones, hyperuricemia, and gout. Phenotype may vary both between and within families.

**PRPS1 Superactivity**
The clinical presentation of PRPS1 superactivity is variable. Individuals may present in early adulthood with hyperuricemia and hyperuricosuria. Uric acid overproduction may be accompanied by intellectual disability, ataxia, hypotonia, and hearing impairment. Some female carriers have been reported to be symptomatic, with hyperuricemia, gout, and hearing impairment.

**Charcot-Marie-Tooth Disease-5**
Charcot-Marie-Tooth disease-5 (CMTX5) is defined by peripheral neuropathy, early-onset sensorineural hearing impairment, and optic atrophy. Hypotonia, gait disturbances, and loss of deep tendon reflexes develop around age 10 to 12 years, likely due to peripheral demyelination and axonal loss. Intellectual disability is not a feature of CMTX5. Some carrier females have been reported to have hearing impairment while others are unaffected.

**Arts Syndrome**
Arts syndrome is characterized by intellectual disability, early-onset hypotonia, ataxia, delayed motor development, profound congenital sensorineural hearing impairment, and optic atrophy. Susceptibility to infections, especially of the upper respiratory tract, can result in early death. Carrier females may show isolated and milder symptoms.

**X-Linked Nonsyndromic Sensorineural Deafness**
Individuals with X-linked nonsyndromic sensorineural deafness (DFNX1 or DFN2) generally present with postlingual progressive nonsyndromic hearing loss, although one family has been reported with congenital profound nonsyndromic hearing loss. Female carriers are reported to have mild to moderate hearing loss.

### References:

### Genes

**PRPS1**

### Indications

This test is indicated for:
- Confirmation of a clinical diagnosis of *PRPS1*-related disorders
- Carrier testing in adult females with a family history of *PRPS1*-related disorders

### Methodology

PCR amplification of 7 coding exons contained in the *PRPS1* gene is performed on the patient's genomic DNA. Direct sequencing of amplification products is performed in both forward and reverse directions, using automated fluorescence dideoxy sequencing methods. The patient's gene sequences are then compared to a normal reference sequence. Sequence variations are classified as mutations, benign variants unrelated to disease, or variations of unknown clinical significance. Variants of unknown clinical significance may require further studies of the patient and/or family members. This assay does not interrogate the promoter region, deep intronic regions, or other regulatory elements, and does not detect large deletions.
Clinical Sensitivity: Unknown. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Large deletions will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's biochemical phenotype.

Analytical Sensitivity: ~99%

**Specimen Requirements**

Submit only 1 of the following specimen types

* Preferred specimen type: Whole Blood

**Type: Whole Blood**

Specimen Requirements:

In EDTA (purple top) tube:
- Infants (2 years): 3-5 ml
- Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Type: Saliva**

Specimen Requirements:

Oragene™ Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Special Instructions**

Submit copies of diagnostic biochemical test results with the sample, if appropriate. Contact the laboratory if further information is needed.

Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of EGL Genetics, please submit a copy of the sequencing report with the test requisition.

**Related Tests**

- Deletion/duplication analysis of the PRPS1 gene by CGH array is available for those individuals in whom sequence analysis is negative.
- A next-generation sequence analysis panel of 90+ XLID genes is available.
- A CGH array-based test for deletion/duplication analysis of 90+ XLID genes is available.
- Custom diagnostic mutation analysis (KIM) is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.
- Prenatal testing is available to couples who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.