### Condition Description

Hermansky-Pudlak syndrome (HPS) is an autosomal recessive, multisystemic disorder. The main clinical features of HPS include oculocutaneous albinism, which presents as hypopigmentation of the skin and hair; reduced iris and retinal pigments; foveal hypoplasia; nystagmus; increased crossing of optic fibers; bleeding diathesis due to a platelet storage pool deficiency; and deposition of lysosomal ceroid, which may cause pulmonary fibrosis (onset in the early thirties), granulomatous colitis (severe presentation in ~15% of all cases), and cardiomyopathy in some cases.

The clinical features of HPS are caused by the disruption of lysosome-related organelles in different tissue types. The incidence of HPS is approximately 1 in 500,000-1,000,000. HPS has an increased incidence, up to 1 in 1800, in Puerto Rico. Locus heterogeneity has been associated with HPS and nine causative genes (HPS1-HPS9) have been identified to date.

Pulmonary fibrosis is a condition in which the lung tissue becomes thickened and scarred over time making the lungs incapable of transporting oxygen into the bloodstream effectively. The most common signs and symptoms of idiopathic pulmonary fibrosis are shortness of breath and a persistent dry, hacking cough. Many affected individuals also experience a loss of appetite and gradual weight loss. It is reported that about 0.5-3.7% of idiopathic pulmonary fibrosis is familial.

### References:
- GeneReviews.
- Wei & Li (2013), Pigm Cell Melanoma R. 26:176-192
- OMIM #203300: HPS.

### Genes

- ABCA3
- AP3B1
- BLOC1S3
- BLOC1S6
- CSF2RA
- DTNBP1
- ELMOD2
- HPS1
- HPS3
- HPS4
- HPS5
- HPS6
- SFTPB
- SFTPC
- SFTPDC
- TERT

### Indications

This test is indicated for:
- Confirmation of a clinical diagnosis of pulmonary fibrosis.
- Confirmation of a clinical diagnosis of Hermansky-Pudlak syndrome.

### Methodology

**Next Generation Sequencing:** In-solution hybridization of all coding exons is performed on the patient's genomic DNA. Although some deep intronic regions may also be analyzed, this assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements, and does not detect single or multi-exon deletions or duplications. Direct sequencing of the captured regions is performed using next generation sequencing. The patient's gene sequences are then compared to a standard reference sequence. Potentially causative variants and areas of low coverage are Sanger-sequenced. Sequence variations are classified as pathogenic, likely pathogenic, benign, likely benign, or variants of unknown significance. Variants of unknown significance may require further studies of the patient and/or family members.

**Copy Number Analysis:** Comparative analysis of the NGS read depth (coverage) of the targeted regions of genes on this panel was performed to detect copy number variants (CNV). The accuracy of the detected variants is highly dependent on the size of the event, the sequence context and the coverage obtained for the targeted region. Due to these variables and limitations a minimum validated CNV size cannot be determined; however, single exon deletions and duplications are expected to be below the detection limit of this analysis.

### Detection

**Next Generation Sequencing:** Clinical Sensitivity: Unknown. Pathogenic variants in the promoter region, some pathogenic variants in the introns and other regulatory element mutations cannot be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's clinical/biochemical phenotype.

Analytical sensitivity for sequence variant detection is ~99%.

**Copy Number Analysis:** The sensitivity and specificity of this method for CNV detection is highly dependent on the size of the event, sequence context and depth of coverage for the region involved. The assay is highly sensitive for CNVs of 500 base pairs or larger and those containing at least 3 exons. Smaller (<500 base pairs) CNVs and those that involving only 1 or 2 exons may or may not be detected depending on the sequence context, size of exon(s) involved and depth of coverage.

### Specimen Requirements

Submit only 1 of the following specimen types
Type: DNA, Isolated

Specimen Requirements:
- Microtainer
- 8µg

Isolation using the Perkin Elmer™Chemagen™ Chemagen™ Automated Extraction method or Qiagen™ Puregene kit for DNA extraction is recommended.

Specimen Collection and Shipping:
Refrigerate until time of shipment in 100 ng/µL in TE buffer. Ship sample at room temperature with overnight delivery.

Type: Saliva

Specimen Requirements:
- Oragene™ Saliva Collection Kit

Oragene™ Saliva Collection Kit used according to manufacturer instructions. Please contact EGL for a Saliva Collection Kit for patients that cannot provide a blood sample.

Specimen Collection and Shipping:
Please do not refrigerate or freeze saliva sample. Please store and ship at room temperature.

Type: Whole Blood (EDTA)

Specimen Requirements:
- EDTA (Purple Top)
  - Infants and Young Children (2 years of age to 10 years old): 3-5 ml
  - Older Children & Adults: 5-10 ml
  - Autopsy: 2-3 ml unclotted cord or cardiac blood

Specimen Collection and Shipping:
Ship sample at room temperature for receipt at EGL within 72 hours of collection. Do not freeze.

Related Tests

- Pulmonary Disease Comprehensive Panel
- Pulmonary Arterial Hypertension Panel
- Bronchiectasis
- Cystic Lung Disease Panel
- Congenital Central Hypoventilation Syndrome Panel
- HPS1 Gene Sequencing
- HPS4 Gene Sequencing
- HPS4 Deletion/Duplication Panel
- Pulmonary Fibrosis and Hermansky-Pudlak Syndrome: Deletion/Duplication Panel

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