Nephronophthisis, an autosomal recessive cystic kidney disease, is the most frequent monogenic cause of renal failure in childhood. There are four forms of nephronophthisis caused by mutations in four different genes. Clinically, there is a statistically different age at onset at end-stage renal disease: terminal renal failure develops at median ages of 13 years, 1 year, 19 years, and 11-34 years in NPHP1, NPHP2, NPHP3, and NPHP4 respectively. Hallmarks of familial nephronophthisis are tubular basement membrane disruption, interstitial lymphohistiocytic cell infiltration, and development of cysts at the corticomedullary border of the kidneys. The histology in later stages of NPH always merges into a chronic sclerosing tubulointerstitial nephropathy, which is found in chronic renal failure of all origins.

**Nephronophthisis 1**

Clinical features of familial juvenile nephronophthisis (NPHP1) include anemia, polyuria, polydipsia, isosthenuria, and death in uremia. Hypertension and proteinuria are conspicuous in their absence. Excessive urinary loss of sodium accounts for the rarity of hypertension. Symmetrical destruction of the kidneys involving both tubules and glomeruli (which were hyalinized) is observed. The age at death ranges from about 4 to 15 years. This is the second most common cause of childhood chronic renal failure. 65 to 75% of NPHP1 patients exhibit large homozygous deletions in the 2q13 region that includes the NPHP1 gene.

Joubert syndrome is an autosomal recessive multisystem disease characterized by cerebellar vermis hypoplasia with prominent superior cerebellar peduncles (resulting in the 'molar tooth sign,' or MTS, on axial MRI), mental retardation, hypotonia, irregular breathing pattern, and eye movement abnormalities. Some individuals with JS have retinal dystrophy and/or progressive renal failure characterized as nephronophthisis. The disorder in such patients is referred to as cerebellorubralrenal syndrome, or CORS. Individuals with a mild form of JS have been shown to have a homozygous deletion of the NPHP1 gene identical, by mapping, to that in subjects with nephronophthisis alone. Senior-Loken syndrome, the association of nephronophthisis with autosomal recessive retinitis pigmentosa, has been observed in patients with homozygous deletion of the NPHP1 gene.

**Nephronophthisis 2**

In one study, individuals with infantile nephronophthisis (NPHP2) presented within the first months of life with severe renal failure and acidosis, which could be associated with hypertension and/or polyuria and/or severe cholestatic liver disease. A renal biopsy, performed in all patients, showed similar features characterized by a diffuse chronic tubulointerstitial nephritis and particularly by the presence of microcystic dilatation of proximal tubules and Bowman space. Progression of the renal disease was extremely rapid and patients can reach end-stage renal failure before the age of 2 years (11 to 22 months).

In another study, phenotypic presentation ranged from a Potter-like syndrome to hyperechogenic kidneys, renal insufficiency, hypertension, and hyperkalemia. Affected individuals showed rapid deterioration of kidney function, leading to end-stage renal failure within 3 years. The manifestations range from prenatal fetal oliguria and oligohydramnios resulting in postnatal respiratory failure and death to postnatal onset of disease later than 30 months of age. None of the postnatally diagnosed patients had a history of either oligohydramnios or neonatal respiratory symptoms. All affected individuals developed anemia, hyperkalemic metabolic acidosis, and increased serum creatine. None of the affected subjects had polyuria, polydypsia, or associated ocular or hepatic complications.

The specific clinical features of this disease are its early onset and rapid progression to end-stage renal failure. Pathologically, it differs from later-onset nephronophthisis by the absence of medullary cysts and thickened tubular basement membranes and by the presence of cortical microcysts. NPHP2 is caused by mutations in the INVS gene (also known as NPHP2) (9q31). The protein product of the INVS gene, inversion, has been shown to interact with that of the NPHP1 gene, nephrocystin.

**Nephronophthisis 3**

In one study, most individuals with adolescent nephronophthisis (NPHP3) suffered from anemia when they first came to medical attention. Onset of terminal renal failure occurred significantly later (median age, 19 years) than in juvenile nephronophthisis (median age, 13.1 years). Histologic findings in adolescent nephronophthisis are generally not distinguishable from those of juvenile nephronophthisis. Renal pathology in adolescent NPHP is characterized by alterations of tubular basement membranes, tubular atrophy and dilatation, sclerosing tubulointerstitial nephropathy, and renal cyst development predominantly at the corticomedullary junction.

Mutations in the NPHP3 gene (3q22) cause NPHP3. Mutations have been found in NPHP3 in families with isolated nephronophthisis and in families with nephronophthisis with associated hepatic fibrosis or tapetoretinal degeneration. Studies have shown that the protein product of the NPHP3 gene interacts with the protein products of NPHP1 and INVS.

**Nephronophthisis 4**

Mutations in the NPHP4 gene (1p36) cause nephronophthisis 4 (NPHP4), which has also been referred to as juvenile nephronophthisis. In these families, end-stage renal disease commenced within a wide age range, 11 to 34 years. The NPHP4 protein has been shown to interact with the NPHP1 protein. Mutations in NPHP4 have been associated with Senior-Loken syndrome-4, the association of nephronophthisis with autosomal recessive retinitis pigmentosa.

Testing is available for each gene individually or as a panel.

For patients with suspected nephronophthisis, sequence analysis is recommended as the first step in mutation identification. For patients in whom mutations are not identified by full gene sequencing, deletion/duplication analysis is appropriate.
Click here for the OMIM summary on Nephronophthisis 1.

Click here for the OMIM summary on Nephronophthisis 2.

Click here for the OMIM summary on Nephronophthisis 3.

Click here for the OMIM summary on Nephronophthisis 4.

**Genes**

INVS, NPHP1, NPHP3, NPHP4

**Indications**

This test is indicated for:

- Confirmation of a clinical/biochemical diagnosis of nephronophthisis
- Carrier testing in adults with a family history of nephronophthisis

**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**

**Clinical Sensitivity:** Unknown. Mutations in the promoter region, some mutations 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 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: Saliva**

**Specimen Requirements:**
Oragene™ Saliva Collection Kit
Orangene™ 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: 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: 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.

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 NPHP1, INVS, NPHP3, and NPHP4 genes by CGH array is available for those individuals in whom sequence analysis is negative.
- Custom diagnostic mutation analysis 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.