Autosomal Dominant Polycystic Kidney Disease: **PKD2** Gene Sequencing

**Condition Description**

Autosomal dominant polycystic kidney disease (ADPKD) is generally a late-onset multisystem disorder characterized by bilateral renal cysts; cysts in other organs including the liver, seminal vesicles, pancreas, and arachnoid membrane; vascular abnormalities including intracranial aneurysms, dilatation of the aortic root, and dissection of the thoracic aorta; mitral valve prolapse; and abdominal wall hernias. Renal manifestations include hypertension, renal pain, and renal insufficiency. Approximately 50% of individuals with ADPKD have end-stage renal disease (ESRD) by age 60 years.

The prevalence of liver cysts, the most common extrarenal manifestation of ADPKD, increases with age and may have been underestimated by ultrasound and CT studies. The prevalence of intracranial aneurysms is higher in those with a positive family history of aneurysms or subarachnoid hemorrhage (22%) than in those without such a family history (6%). Mitral valve prolapse, the most common valvular abnormality, occurs in up to 25% of affected individuals. Substantial variability in severity of renal disease and other extrarenal manifestations occurs even within the same family.

The diagnosis of ADPKD is established primarily by imaging studies of the kidneys. In 85% of individuals with ADPKD, mutations in the **PKD1** gene are causative; in 15%, mutations in the **PKD2** gene (4q21-q23) are causative. Approximately 4% of ADPKD-causing mutations are larger deletions or duplications. About 95% of individuals with ADPKD have an affected parent and about 5% have a *de novo* mutation. Genetic background and environmental factors account for significant intrafamilial variability in disease severity. **PKD1** mutations are associated with a 20-year earlier onset of ESRD than **PKD2** mutations. In PKD2, males progress to ESRD more rapidly than females; no gender difference is seen in PKD1.

ADPKD is the most common potentially lethal single-gene disorder. Its prevalence at birth is between 1:400 and 1:1,000; and it affects approximately 600,000 persons in the United States.

This testing is ONLY for the **PKD2** gene.

For patients with suspected ADPKD in whom **PKD1** testing is negative, 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.

**Genes**

**PKD2**

**Indications**

This test is indicated for:

- Confirmation of a clinical diagnosis of ADPKD in patients with negative **PKD1** testing
- Individuals at-risk for ADPKD due to family history, in whom **PKD1** testing is negative

**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.

**Detection**

Clinical Sensitivity: In 15% of individuals with ADPKD, mutations in the **PKD2** gene are causative. 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

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* 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 *PKD2* gene by CGH array is available for those individuals in whom sequence analysis is negative (WE).
- Custom diagnostic mutation analysis (KM) is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.
- Prenatal testing is available to individuals who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.