

Autosomal Recessive Polycystic Kidney Disease via *PKHD1* Gene Sequencing Sequential (Standard) Test – Test #101; Tier 1 Only – Test #102; Tier 2 Only – Test #103

Brief Description of Clinical Features: Autosomal Recessive Kidney Disease (ARPKD) is characterized by enlarged, cystic kidneys and hepatic fibrosis. Diagnosis is often made pre- or neonatally, although some cases are diagnosed in childhood or adult life. Severity varies widely; the most severe cases are often neonatal lethal. Many who survive the newborn period progress to end stage renal disease. A small fraction of cases are initially diagnosed with liver disease. Incidence is roughly 1 in 20,000 births. The carrier frequency in the general population may be as high as 1 in 70. See Dell and Avner Gene Reviews 2008 and www.pkdcure.org for more information.

Genetics: Mutations within the large (470 kb) *PKHD1* gene on 6p are the only known cause of this recessive disease. Over 300 likely causative mutations have been reported (Losekoot et al. Hum Genet 118:185-206, 2005; Sharp et al. J Med Genet 42:336-349, 2005). In the mixed American population, no mutations are predominant. Mutations are missense, nonsense, frameshift and splicing and are located throughout the length of the gene (www.humgen.rwth-aachen.de). Multi-exon deletions occur, but are relatively rare (probably <5% of mutations) (Bergmann et al. J Med Genet 42:e63, 2005). Patients with two protein-truncating mutations usually have the most severe disease.

Description of This Particular Test: Sequencing of *PKHD1* at PreventionGenetics is performed in two tiers. Tier 1 comes first and involves bidirectional sequencing of exons 3, 5, 9, 14, 16, 20, 21, 22, 30, 32, 33, 34, 36, 37, 39, 43, 50, 54, 55, 57, 58, 59 and 62. These 23 exons have been reported to contain roughly 80% of detectable causative mutations (Bergmann et al. Hum Mut 25:225-231, 2005). If zero or one likely causative mutation is found in Tier 1, then sequencing of the remaining exons commences in Tier 2. Although several alternative exons due to splicing variation have been demonstrated for this gene, to our knowledge no causative mutations have yet been reported in these alternative exons. We therefore sequence only the 66 coding exons in the longest open reading frame.

Indications for Test: Candidates for this test are patients with symptoms consistent with a diagnosis of ARPKD. We will sequence one or two exons in the family members of patients with known mutations to determine carrier status. We will also sequence specific exons to confirm research results.

Sensitivity of Test: The full test is likely to reveal $\geq 80\%$ of causative *PKHD1* mutations (Bergmann et al. 2005; Sharp et al. 2005). This means that at least one likely causative mutation will be detected in at least 95% of ARPKD patients, and two likely causative mutations in at least two-thirds of patients.

Turn Around Time: Maximum of 40 days.

Specimen Requirements: See bottom of page 2 of Requisition Form.

Prices:	
Tier 1 (Test #102): Sequencing of <i>PKHD1</i> exons 3,5,9,14,16,20,21,22,30,32,33,34,36,37,39,43,50,54,55,57,58,59,62	\$1,190
Tier 2 only (Test #103): Sequencing of the remaining 43 <i>PKHD1</i> exons	\$2,300
Tiers 1 and 2 Combined (Test #101): Full gene sequencing	\$2,990

CPT Codes:

Codes	Description	Tier 1 Only	Tier 2 Only	Tier 1 + Tier 2
83890	Ascertainment	\$ 30 (x1)	\$ 30 (x1)	\$ 30 (x1)
83891	DNA Isolation	\$ 40 (x1)	\$ 40 (x1)	\$ 40 (x1)
83898	Amplification	\$ 344 (x28)	\$ 360 (x43)	\$ 990 (x71)
83904	Mutation Ident by Sequencing	\$ 516 (x28)	\$1610 (x43)	\$1,670 (x71)
83894	Separation	\$ 90 (x1)	\$ 90 (x1)	\$ 90 (x1)
83912	Interpretation and Report	\$ 170 (x1)	\$ 170 (x1)	\$ 170 (x1)
Totals:		\$1,190	\$2,300	\$2,990

Single exon sequencing is also available for \$190, and two exon sequencing for \$340.

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