Hereditary leiomyomatosis and renal cell cancer (HLRCC) is an autosomal dominant condition characterized by cutaneous leiomyomata, uterine leiomyomata (fibroids), and/or single renal tumor. The majority (three-quarters) of individuals with HLRCC present with a single or multiple cutaneous leiomyomata. Cutaneous leiomyomata appear as skin-colored to light brown papules or nodules distributed over the trunk and extremities and occasionally on the face and appear at a mean age of 25 years, increasing in size and number with age. Uterine leiomyomata are present in almost all females with HLRCC and tend to be numerous and large; age at diagnosis ranges from 18 to 52 years, with most women experiencing irregular heavy mensturation and pelvic pain. The presence of cutaneous leiomyomata correlates with the presence of uterine fibroids in females. Renal tumors causing hematuria, lower back pain, and a palpable mass are usually unilateral, solitary, and aggressive and range from type 2 papillary to tubulo-papillary to collecting-duct carcinomas. They occur in about 10%-16% of individuals with HLRCC; the median age of detection is 44 years. Disease severity show significant intra- and interfamilial variation.

HLRCC is diagnosed by the presence of multiple cutaneous leiomyomata with at least one histologically confirmed leiomyoma or by a single leiomyoma in the presence of a positive family history of HLRCC. Diagnosis is confirmed by testing fumarate hydratase enzyme activity in cultured skin fibroblasts or lymphoblastoid cells showing reduced activity (≥60%) or by molecular genetic testing. The FH gene (1q42.1) is the only gene known to be associated with HLRCC. Between 80% and 100% of individuals with HLRCC have identifiable sequence variants in FH. No correlation is observed between FH mutations and the occurrence of cutaneous lesions, uterine fibroids, or renal cancer of HLRCC. The proportion of cases caused by de novo mutations is unknown as subtle manifestation in parents has not been evaluated and genetic testing data are insufficient. Early detection of at-risk individuals affects medical management. In the absence of an increased risk of developing childhood malignancy, however, the American Society of Clinical Oncology (ASCO) recommends delaying genetic testing in at-risk individuals during childhood until individuals reach 18 years of age and are able to make informed decisions regarding genetic testing.

Mutations in the FH gene also occur in the autosomal recessive condition fumarase deficiency (FHD), or fumeric aciduria. FHD results from inherited biallelic mutations in FH, and is characterized by rapidly progressive neurologic impairment including hypotonia, seizures, and cerebral atrophy. Homozygous or compound heterozygous germline mutations in FH are found in individuals with FHD. Leiomyomata and renal cancer have not been reported in FHD. Most individuals with FHD, however, survive only a few months; a very few survive to early adulthood. In one report, a parent (heterozygous carrier) of an individual with fumarase deficiency developed cutaneous leiomyomata similar to those observed in HLRCC.

For patients with suspected HLRCC, 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.

**Condition Description**

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**Genes**

FH

**Indications**

This test is indicated for:

- Confirmation of a clinical diagnosis of HLRCC
- Individuals at-risk for HLRCC due to family history

**Methodology**

PCR amplification of 10 exons contained in the FH 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.

**Detection**

Clinical Sensitivity: Between 80% and 100% of individuals with HLRCC have identifiable sequence variants in FH. 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

**Type: Saliva**

Disclaimer: This information is confidential and subject to change without notice. It may not be reproduced in whole or part unless authorized in writing by an authorized EGL representative.
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.

**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.

**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 *FH* gene by CGH array is available for those individuals in whom sequence analysis is negative (VI).
- 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.