Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

Oncogenetic testing for persons with von Hippel-Lindau (VHL) syndrome

The von Hippel-Lindau (VHL) syndrome is associated with a variety of benign and malignant tumours, in particular haemangioblastomas of the retina and central nervous system, endolymphatic sac tumours, phaeochromocytomas, renal cell carcinomas and cysts in various organs including the kidney, pancreas and liver. The VHL syndrome is inherited, and caused by germline mutations in the VHL tumour suppressor gene.

Epidemiological data are not available for Belgium, but the disease prevalence is estimated to be around 1 in 90 000 people.

Criteria for clinical diagnosis of VHL

An individual with **no known family history of VHL disease** presenting with two or more characteristic lesions:

- Two or more hemangioblastomas of the retina, spine, or brain or a single hemangioblastoma in association with a visceral manifestation (e.g., multiple kidney or pancreatic cysts)
- Renal cell carcinoma (typically of the clear cell subtype)
- Adrenal or extra-adrenal phaeochromocytoma
- Less commonly, endolymphatic sac tumour, papillary cystadenoma of the epididymis or broad ligament, or neuroendocrine tumour of the pancreas

An individual with **a positive family history of VHL disease** in whom one or more of the following disease manifestations is present:

- Retinal angioma
- Spinal or cerebellar hemangioblastoma
- Adrenal or extra-adrenal phaeochromocytoma
- Renal cell carcinoma (typically of the clear cell subtype)
- Multiple renal and pancreatic cysts

Criteria for clinical suspicion of VHL

- Isolated central nervous system hemangioblastoma
- Isolated endolymphatic sac tumour
- Isolated renal cell carcinoma (typically of the clear cell subtype) at an age < 40 years
- Multiple renal cell carcinomas (typically of the clear cell subtype)
- Renal cell carcinoma (typically of the clear cell subtype) and a first- or second-degree relative with a typical VHL tumour
- Phaeochromocytoma or paraganglioma (if no Succinate Dehydrogenase mutation)
- Isolated papillary cystadenoma of the epididymis
- Bilateral epididymal cysts
- Two or more pancreatic serous cystadenomas
- Two or more pancreatic neuroendocrine tumours
- Pancreatic serous cystadenoma or neuroendocrine tumour, and first- or second-degree relative with a typical VHL tumour
- Multiple pancreatic cysts and another typical VHL tumour

Clinical Recommendations

- Pre- and post-test genetic counselling should be offered to all patients with a clinical diagnosis or suspicion of VHL (strong recommendation)
- All patients with a clinical diagnosis of VHL should be offered VHL genetic testing (strong recommendation)
- In patients with a suspected phenotype of VHL, VHL genetic testing may be considered (weak recommendation)
- Once a germline VHL mutation has been identified in a proband, VHL mutation analysis should be offered to all first-degree relatives as soon as possible* (strong recommendation)

** Or first-degree relatives of patients with clinical VHL who died before genetic testing was carried out.*

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