Title **Genetic testing for hereditary mutations in the *VHL* gene that cause von Hippel-Lindau syndrome**

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Aim

To conduct a systematic review on genetic testing for hereditary mutations in the von Hippel-Lindau (*VHL*) gene that cause VHL syndrome for (i) patients with symptoms of VHL syndrome, and (ii) family members of a patient with a confirmed diagnosis of VHL syndrome.

Conclusions and results

Patients suspected of having VHL syndrome, who are tested for VHL-mutation status, are only likely to have a clinical benefit from being tested, if they are presenting with their first neoplasm and have no family history of VHL syndrome. VHL mutation testing in this scenario would mean that routine screening would be offered earlier, leading to better long term patient outcomes. No comparative evidence was identified to support these conclusions. VHL genetic testing in asymptomatic relatives is expected to change management when used as a triage test for lifelong screening. Relatives with a negative genetic test result would not require lifelong screening, which would otherwise be recommended.

The most accurate method of genetic testing for VHL mutations was a combination of direct DNA sequencing plus a deletion detection method. Even with this method, VHL genetic testing has a median false negative rate of 10.2%, suggesting that detection of germline mutations is not possible in all patients with VHL syndrome. These patients may have mutations or epigenetic changes affecting gene regulation and/or protein expression, or somatic mosaicism, where a VHL mutation occurred during embryonic development involving affected organs but may not be present in peripheral blood cells. It is likely that the median false positive rate of 4.2% reflects those patients with the first manifestations of VHL syndrome, where their disease has not yet progressed sufficiently to obtain a positive clinical diagnosis. High positive predictive values and negative predictive values (median 100% and 100%) signal that there is a high likelihood of the test results corresponding to the clinical diagnosis. In family members, the sensitivity of testing was perfect. The specificity depended on the age of the relatives, as the younger they were, the more likely that genetic testing occurred before any signs of VHL syndrome could be detected.

An overall cost saving (through avoided inappropriate monitoring) was calculated per single index case and their family over their lifetimes as $7,749 in discounted costs and $20,783 in undiscounted costs. Assuming usage patterns remain at an estimated 80 tests per year, the total cost of genetic counseling and listing VHL testing on the Medicare Benefits Schedule was calculated to be $86,100 per year (or $154,400 if usage doubles).

Recommendations

After considering the strength of the available evidence in relation to the safety, effectiveness and cost-effectiveness of genetic testing to evaluate VHL disease, the Medical Services Advisory Committee (MSAC) supported public funding for listing three tests on the MBS, as follows:

- Diagnostic test for heritable mutation in affected patient;
- Predictive test for heritable mutation in relative of person with a heritable mutation; and
- Diagnostic test for somatic mutations in patient with VHL syndrome and normal germline study.

Methods

A systematic review was performed on the safety, effectiveness, cost-comparison and ethical considerations of VHL genetic testing. Medline, Embase, The Cochrane Library, and several other biomedical databases, HTA and other internet sites were searched (1995- June 2007). Specific journals were hand searched and reference lists pearled. Studies were included in the review using pre-determined PICO selection criteria and reasons for exclusion were documented. Study quality was appraised, data extracted in a standardised manner, and findings synthesised narratively.

No comparative evidence was identified providing health outcomes after VHL genetic testing, in comparison to no VHL genetic testing. A linked evidence approach was therefore taken, including 71 level III-2 diagnostic accuracy studies, 21 level IV case series providing diagnostic yield, and 5 case series providing non-comparative data on patient management following VHL genetic testing.

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Methods

Further research/reviews required

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