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Title **Genetic testing for hereditary mutations in the RET gene**

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Aim

To conduct a systematic review on genetic testing for hereditary mutations in the RET gene that cause multiple endocrine neoplasia type II (MEN2) for (i) patients with symptoms of MEN2, and (ii) family members of a patient with a confirmed pathological RET mutation.

Conclusions and results

Clinical management with the addition of RET mutation testing would appear to have superior effectiveness and at least non-inferior safety, compared with diagnosis and treatment of MEN2 without knowledge of RET mutation status.

Nine historical controlled studies provided evidence showing that health outcomes are likely to be better for patients diagnosed with the addition of RET mutation testing. Seven historical controlled trials reported on the incidence and severity of medullary thyroid carcinomas (MTC) in patients who underwent total thyroidectomy in the era prior to RET mutation testing, compared with the era subsequent to RET mutation testing. Those diagnosed with the addition of genetic testing had almost half the risk of having an MTC at the time of surgery, compared with the historical cohort (RR=0.53, 95%CI 0.32, 0.90). Age at time of diagnosis and age at time of total thyroidectomy have been significantly reduced since the introduction of RET mutation testing. Age at time of surgery, and severity of MTC at time of total thyroidectomy are significant predictors of the risk of residual or recurrent disease. Six studies reported greatly reduced risk of persistence, recurrence or mortality in those who underwent total thyroidectomy with knowledge of their RET mutation status, compared with total thyroidectomy without this knowledge (RR=0.28, 95%CI 0.17, 0.45). However, this evidence is highly biased, as those in the historical cohort were followed up for longer time periods, allowing a greater chance of disease recurrence simply as a matter of time.

Mutation testing of the RET gene is already standard practice in Australia, however, a cost-minimisation analysis was performed comparing the use of RET mutation testing against a hypothetical scenario in the absence of RET mutation testing. Over the course of 30 years, savings of approximately $535 per MTC patient tested, or $1,458 per phaeochromocytoma patient under 50 years of age tested, would be expected.

The total combined cost to the health system (Medicare and patient co-payments) of RET mutation testing is estimated to be between $82,011 and $175,999 per annum, assuming between 130 and 260 index patients are tested, and between 150 and 359 relatives are tested.

Methods

A systematic review was performed on the safety, effectiveness, cost-comparison and ethical considerations of RET gene mutation testing. Medline, Embase, The Cochrane Library, and several other biomedical databases, HTA and other internet sites were searched (1993- July 2012). Specific journals were handsearched 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, or with meta-analyses where possible.

Written by

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