

Office of Population Health Genomics

Policy:
Guidelines for patient referral for
genetic testing for Familial
Endocrine Neoplasia

Purpose: Guidelines are intended to assist specialists (predominantly endocrinologists and endocrine surgeons) in selecting patients for referral for genetic testing.

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Guidelines for patient referral for genetic testing for familial endocrine neoplasia

Genetic testing for MEN 1 (menin gene), MEN 2 (ret gene) and Von Hippel Lindau disease (VHL gene) is available through Genetic Services of WA. Testing for mutations in the succinate dehydrogenase subunits B (SDHB) and D (SDHD) genes is currently done by sending samples to Royal North Shore Hospital, Sydney, but may be set up locally.

The following guidelines are intended to assist specialists (who will be predominantly endocrinologists and endocrine surgeons) in selecting patients for referral for genetic testing. They have been drawn up after review of the literature and in consultation with endocrinologists and endocrine surgeons in WA. They are not exhaustive or exclusive, and are for guidance only; liaison with clinical geneticists is encouraged.

Summary: patients who should be referred for genetic testing

Clinical MEN 1 cases: patients with two or more MEN 1 related endocrinopathies (primary hyperparathyroidism, pituitary tumour, enteropancreatic endocrine tumour)

Suspected familial MEN 1 cases: patients with one MEN 1 related endocrinopathy plus a close relative with MEN 1 endocrinopathy

Apparently sporadic primary hyperparathyroidism in patients aged under 30 or with pathological findings of parathyroid hyperplasia

Phaeochromocytoma or paraganglioma: all patients

Medullary thyroid cancer: all patients

Apparently sporadic enteropancreatic endocrine tumour (insulinoma, gastrinoma), bronchial or thymic carcinoid: patients aged under 30

Detailed Recommendations

MEN-1

Clinical MEN-1 cases

A clinical case of MEN-1 is a patient with 2 or more of the 3 main MEN-1 related endocrinopathies (primary hyperparathyroidism, pituitary tumour, entero-pancreatic endocrine tumour). Such patients should be offered testing for menin mutations.

MEN-1 should also be suspected in a patient with 1 of the 3 main MEN-1 related endocrinopathies (primary hyperparathyroidism, pituitary tumour, entero-pancreatic endocrine tumour) plus a close relative with one or more such endocrinopathy. Such patients should be offered testing for menin mutations.

Primary hyperparathyroidism

In a patient with apparently sporadic primary hyperparathyroidism, the chance of MEN 1 is 1-2% and MEN 2 is 0.1%, and genetic testing is generally not indicated. Genetic testing should, however, be considered if the patient is young (<30 yrs) or if the pathological findings are of parathyroid hyperplasia rather than adenoma.

Pituitary tumour

In patients with an apparently sporadic pituitary tumour, the chance of MEN-1 is about 5% and genetic testing is not usually indicated. Biochemical screening (serum calcium, PTH) for primary hyperparathyroidism as a marker of MEN-1 is indicated, since PHPT is the first manifestation of MEN-1 in 90% of cases, and is present by the age of 40 years in 95% of cases.

Enteropancreatic neuroendocrine tumours and carcinoid tumours

In patients with apparently sporadic enteropancreatic neuroendocrine tumours or foregut (bronchial, thymic) carcinoid tumours, biochemical screening for primary hyperparathyroidism as a marker of MEN-1, rather than genetic testing is indicated, based on the reasoning above. It may, however, be reasonable to offer menin mutation analysis for younger patients, eg aged under 30, in case the tumour is the presenting feature of MEN-1 and PHPT has not yet developed.

MEN 2/VHL/SDHB/SDHD

Medullary thyroid cancer

All patients with clinical MEN 2 (MTC plus pheochromocytoma) or familial MTC should be offered testing for mutations in the ret oncogene.

In patients with apparently sporadic MTC, germ line mutations in the ret oncogene are found in 1.5-6% of cases. Despite this relatively low yield, routine testing is widely recommended because of the importance of establishing the diagnosis of MEN-2. Therefore, all patients with MTC should be referred for testing.

Pheochromocytoma and paraganglioma

Approximately 25% of patients with apparently sporadic pheochromocytoma or paraganglioma have a germ line mutation in the ret, VHL, SDHB or SDHD genes. Therefore, all patients with pheochromocytoma or paraganglioma should be referred.

References

1. Learoyd DL, Delbridge LW, Robinson BG. Multiple endocrine neoplasia. *Aust N Z J Med* 2000;30:675-82.
- 2 Brandi ML, Gagel RF, Angeli A et al. Guidelines for diagnosis and therapy of MEN type 1 and type 2. *J Clin Endocrinol Metab* 2001;86:5658-71.
3. Neumann HP, Bausch B, McWhinney SR et al. Germ-line mutations in nonsyndromic pheochromocytoma. *N Engl J Med* 2002;346:1459-66.