INTRODUCTION
Mutations in the cyclin dependent kinase inhibitor genes; CDKN1A, CDKN1B, CDKN2B and CDKN2C have been identified in a few patients with an MEN1-like phenotype and no mutation identified in the MEN1 gene. They are therefore implicated in an inherited susceptibility to endocrine neoplasia. Clinical overlap with HPT-JT syndrome is also seen in these patients. The symptoms seen include primary hyperparathyroidism, pituitary tumour, parathyroid tumour, prolactinoma, gastrinoma, and acromegaly.
Germline mutations in CDKN1A, CDKN2B and CDKN2C cause an MEN1-like phenotype. Mutations in CDKN1B cause MEN4; a novel form of MEN characterised by parathyroid involvement, and less typically with pituitary adenomas and other endocrine features.

TESTING AND REFERRALS
All samples should be accompanied by a completed pre-referral form (click here)
Clinical guidance is available from Professor Rajesh Thakker, Professor of Medicine, OCDEM, Churchill Hospital (rajesh.thakker@ndm.ox.ac.uk).

- Diagnostic:
  - Clinically affected patients.
  - UK diagnostic referrals are accepted from Clinical Genetics, Endocrinology and consultants from other relevant specialties.

- Carrier/presymptomatic/test for familial mutation:
  - Individuals at risk of developing the condition. Relatives of clinically affected patients in whom a pathogenic mutation has been identified.
  - Presymptomatic referrals should ideally be referred through/in collaboration with Clinical Genetics departments.

- Prenatal:
  - Prenatal testing is not generally requested but if required must be discussed with the laboratory and arranged in advance, and referrals are only accepted from Clinical Genetics.

STRATEGY
Molecular analysis of CDKN1A, CDKN1B, CDKN2B and CDKN2C is recommended for patients who have previously tested negative for MEN1 mutations or as part of the familial isolated hyperparathyroidism panel (FIHP). Once a pathogenic mutation has been identified in an individual, molecular testing for that variant is available to at-risk or affected family members.

TECHNICAL INFORMATION
Sanger sequencing analysis of the coding regions and exon intron boundaries of:
- CDKN1A (p21) (exons 2-3)
- CDKN1B (p27) (exons 1-2 and also analysis of a uORF in the 5' UTR)
- CDKN2B (p15) (exons 1-2)
- CDKN2C (p18) (exons 2-3)

Clinical Sensitivity: Intragenic mutations in the CDKN1A, CDKN1B, CDKN2B and CDKN2C genes have so far been reported in only a few patients and the number of cases accounted for by these mutations is as yet unknown. Literature to date suggests that these genes may account for 2-4% of MEN1 like phenotypes in patients who have screened negative for mutations in MEN1.

TARGET REPORTING TIMES
Diagnostic: 40 days
Carrier/presymptomatic/familial mutation test: 10 days

N.B. Details are correct for the date of printing only – last updated 15/07/2015