**INTRODUCTION**

The *PTEN* gene is a tumour suppressor gene which is somatically mutated in a large number of tumours. Germline mutations of the *PTEN* gene are associated with several syndromes:

- **PTEN** hamartoma tumour syndromes including Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome and Proteus–like syndrome. Cowden syndrome is characterised by multiple hamartomas and a high risk of tumours of the breast, thyroid and endometrium. Patients usually have macrocephaly. Mucocutaneous lesions, thyroid abnormalities, fibrocystic disease and multiple leiomyoma may also be seen. The lifetime risk of developing cancer is up to 33% for female breast cancer and 9% for endometrial cancer. The lifetime risk for thyroid symptoms is 35% [Tan et al 2011, The American Journal of Human Genetics, 88, 42-56].

- Lhermitte-Duclos disease (LDD) is a rare cerebellar tumour associated with Cowden syndrome.

- Autism spectrum disorder / developmental disorder and macrocephaly are seen in some patients with *PTEN* mutations [McBride et al, Autism Research, 2010, Jun 3(3)]. These patients are at risk of developing further *PTEN* related symptoms.

**TESTING AND REFERRALS**

  
  Referrals are accepted via Clinical Genetics or relevant clinicians such as Consultant Paediatricians.

- Family tests (predictive or diagnostic confirmations): testing for known pathogenic/likely pathogenic *PTEN* variant previously identified in an individual’s family. Requests for presymptomatic testing should either be accompanied by details of the known pathogenic mutation in the family or discussed with the laboratory in advance. Referrals are accepted via Clinical Genetics.

- Prenatal testing: Prenatal testing is not usually requested. Prenatal requests would only be accepted from Clinical Genetics and must be discussed with the laboratory and arranged in advance.

**STRATEGY AND TECHNICAL INFORMATION**

- Sequence and dosage analysis of *PTEN* is undertaken by Next Generation Sequencing using the Custom Hereditary Cancer Solution (HCS) by Sophia Genetics along with the Sophia DDM analytical platform. Data is generated for 38 cancer susceptibility genes; however, analysis is restricted to *PTEN* only. Data reveal and analysis of additional clinically relevant genes is available, if required.

- Regions of interest (ROI) are minimally defined as coding exons +/- 10bp and are guaranteed to be covered to 100% at >50x reads. Analytical sensitivity for single nucleotide substitutions is estimated to be >99%; analytical sensitivity for small insertions/deletions may be slightly lower.

- Putative pathogenic variants detected by NGS are confirmed by Sanger sequencing or Multiplex Ligation-dependent Probe Amplification (MLPA), as appropriate.

- Targeted testing (e.g. family testing) is undertaken by Sanger sequencing of the relevant exon or MLPA, as appropriate.

**CLINICAL SENSITIVITY**

Tan et al 2011, Identified a pathogenic mutation in *PTEN* in 9.5% of patients who met relaxed International Cowden Consortium operational criteria for Cowden syndrome.

**TARGET REPORTING TIMES** (National Target)

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Target Reporting Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic screen</td>
<td>42 calendar days</td>
</tr>
<tr>
<td>Predictive testing for known familial variant</td>
<td>14 calendar days</td>
</tr>
<tr>
<td>Diagnostic testing for known familial variant</td>
<td>42 calendar days</td>
</tr>
<tr>
<td>Prenatal testing</td>
<td>3 calendar days</td>
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</tbody>
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N.B Details are correct for the date of printing only – last updated 03/07/2019