INTRODUCTION
Prader-Willi syndrome (PWS) is a common syndromal cause of obesity, affecting 1/15,000 to 1/20,000 individuals. It is characterised by hypotonia and poor feeding (early infancy), hyperphagia, obesity, hypogonadism, developmental delay, short stature and small hands and feet. The PWS phenotype results from the lack of a paternal contribution at 15q11-q13. This can be caused by a deletion (~75-80%), maternal uniparental disomy (UPD) (~20-25%), microdeletions of the imprinting centre (10-15% of patients with an imprinting defect) or rarely a sporadic imprinting defect in the 15q region (~1%). All of these disease mechanisms can be detected by studying methylation patterns within in the 15q11-q13 region.

Determining the disease mechanism is important as it enables recurrence risks to be given to the family.
- Deletions and UPD are usually de novo events; therefore the recurrence risk is low (unless there is a paternal chromosomal rearrangement predisposing to UPD15).
- The vast majority of imprinting defects are sporadic methylation defects; therefore the recurrence risk is low. 10-15% of imprinting defects are due to imprinting centre mutations (microdeletions) and these may be de novo (with a low recurrence risk) or inherited with a recurrence risk of up to 50%.

TESTING
Diagnostic
- Clinically affected patients
Prenatal
- Available to couples at risk of having a child affected with PWS

REFERRALS
- From Clinical Genetics, paediatricians and psychiatrists.
- Prenatal referrals are only accepted from Clinical Genetics and, where possible, arranged in advance.

STRATEGY AND TECHNICAL INFORMATION
- Methylation-sensitive multiplex ligation probe amplification (MS-MLPA) analysis
  - Determines copy number and methylation status within the PWS/AS critical region
  - Can distinguish between large deletions (copy number and methylation changes), microdeletions of the imprinting centre and UPD/sporadic imprinting defects (methylation changes only)
  - Can not distinguish between UPD and sporadic imprinting defects
- Microsatellite marker analysis
  - Performed to distinguish between UPD and sporadic imprinting defects in order to provide families with recurrence risks
  - Provides a second independent test for prenatal diagnosis
- Cytogenetic analysis can identify deletions and parental chromosomal rearrangements
- Cytogenetic analysis requires a separate blood sample, in lithium heparin. Samples should be sent to the Cytogenetics Laboratory at the address below.

NB: Similar analysis is undertaken for Angelman syndrome (AS)

TARGET REPORTING TIMES
Diagnostic: 10 days
Prenatal testing (includes maternal contamination check): 3 days

N.B Details are correct for the date of printing only – last updated 07/09/2015