TREACHER COLLINS SYNDROME (TCS)

(TCS1 OMIM 154500; TCS2 OMIM 613717; TCS3 OMIM 248390)

INTRODUCTION
Treacher Collins syndrome (TCS) is a genetically heterogeneous craniofacial disorder characterised by hypoplasia of the mandible and cheek bones, eyelid coloboma, micrognathia, microtia and cleft palate. Approximately 50% of patients have conductive hearing loss. There can be marked phenotypic variability among patients, ranging from perinatal death, due to a compromised airway, to those that go undetected by medical examination.

Mutations in \( TCOF1 \) (TCS1), \( POLR1D \) (TCS2) and \( POLR1C \) (TCS3) have been identified in individuals with this disorder. Mutations in \( TCOF1 \) and \( POLR1D \) are autosomal dominant whereas mutations in \( POLR1C \) are recessive. A majority of cases have mutations in \( TCOF1 \), which encodes a nucleolar phosphoprotein and is localised to chromosome 5q32. \( POLR1D \) and \( POLR1C \) encode proteins that together form the \( \alpha \) subunit of the DNA-dependant RNA polymerases I and III.

TESTING
- **Diagnostic:** Clinically affected patients
- **Carrier/Familial mutation test:** Relatives of clinically affected patients (known mutation(s))
- **Prenatal:** At risk of having an affected child (known mutation(s))

REFERRALS
- From Geneticists, Paediatricians, Antenatal Services, or Dysmorphologists
- Prenatal referrals must be discussed with the laboratory and, where possible, arranged in advance.

STRATEGY AND TECHNICAL INFORMATION
- For new diagnostic cases \( TCOF1 \) will be usually be screened initially, with \( POLR1D/POLR1C \) analysis offered as a reflex test in appropriate cases. The tests consist of bi-directional sequencing analysis and dosage analysis of:
  - 26 coding exons and intron/exon boundaries of \( TCOF1 \) (including 6A – So et al. (2004) Gene 328:49-57)
  - 2 coding exons and intron/exon boundaries of \( POLR1D \) isoform 1, and the 3 coding exons and intron-exon boundaries of isoform 2.
  - 9 coding exons and intron/exon boundaries of \( POLR1C \)

CLINICAL SENSITIVITY
- Our data (Bowman et al. 2012 Eur J Hum Genet 20:769-777) indicate that pathogenic mutations and deletions of \( TCOF1 \) account for around 71% of referrals with a strong clinical suspicion of TCS; and that pathogenic mutations or deletions of \( POLR1D \) or \( POLR1C \) account for at least a further 5% of these cases (with the majority being due to \( POLR1D \)). Failure to detect a mutation cannot therefore exclude a diagnosis of TCS.

TARGET REPORTING TIMES
- **Diagnostic test:** 40 days
- **Familial mutation test:** 10 days
- **Prenatal test (includes maternal contamination check):** 3 days

N.B. Details are correct for the date of printing only – last updated 10/09/2015