# Test Specific Guidelines

# Prader-Willi Syndrome Testing

**MOL.TS.217.A**
**v1.0.2023**

## Introduction

**Prader-Willi syndrome testing is addressed by this guideline.**

## Procedures Addressed

**The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.**

| Procedures addressed by this guideline | Procedure codes |
|---|---|
| Chromosome 15 Uniparental Disomy | 81402 |
| Chromosomal Microarray [BAC], Constitutional | 81228 |
| Chromosomal Microarray [CGH], Constitutional | S3870 |
| Chromosomal Microarray [SNP], Constitutional | 81229 |
| Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and loss-of-heterozygosity variants, low-pass sequencing analysis | 81349 |
| FISH Probe for 15q11-q13 Deletion | 88271 |
| Imprinting Center Defect Analysis | 81479 |
| Imprinting Center Known Familial Mutation Analysis | 81403 |
| SNRPN/UBE3A Methylation Analysis | 81331 |

## What Is Prader-Willi Syndrome?

### Definition

**Prader-Will syndrome (PWS) is a multi-system genetic disorder that is due to a**

loss of specific genes on chromosome 15. Infants present with low muscle tone (hypotonia) and feeding difficulties which can result in failure to thrive. In the childhood years, children with Prader-Willi syndrome develop an increased appetite with decreased satiety which, without proper management, results in obesity and an increased risk of type 2 diabetes. Cognitive impairment and behavioral problems are usually present in addition to an increased risk for specific medical diagnoses.[1]

**Prevalence**

The prevalence is estimated to be 1/10,000 to 1/30,000.[1]

**Symptoms**

Prader-Willi syndrome is characterized by:[1,2]

Decreased muscle tone (hypotonia) and feeding difficulties in early infancy

Strabismus

Insatiable appetite in childhood that often results in obesity

Developmental delay

Short stature

Behavior problems

Small hands and feet

Underdeveloped genitalia and infertility

**Causes**

The features of Prader-Willi syndrome are caused when the Prader-Willi critical region (PWCR) on chromosome 15 is only inherited from the mother and there is no copy from the father.

Prader-Willi syndrome can be caused by a chromosome deletion, uniparental disomy (two copies of the maternal chromosome), or imprinting defect. There are several genetic tests available that can help diagnose Prader-Willi syndrome.[1-3]

**Diagnosis**

If an individual has all of the clinical findings denoted below at the indicated age, testing by methylation analysis is recommended.[1] Prader-Willi syndrome is established in individuals who have abnormal DNA methylation analysis consistent with absence of the paternal contribution of the PWCR.[1]

Birth to two years

Hypotonia with poor suck

Two to six years

Hypotonia with history of poor suck

Global developmental delay

Six year to 12 years

History of hypotonia with poor suck

Global developmental delay

Excessive eating and, if uncontrolled, central obesity

12 years to adulthood

Cognitive impairment which is most often mild intellectual disability

Excessive eating and, if uncontrolled, central obesity

Hypothalamic hypogonadism and/or typical behavior problems

Treatment

Individuals with Prader-Willi syndrome have age-specific medical needs. Some of the more common treatments and management include: [1]

Infancy

Ensuring adequate nutrition through feeding support

Physical therapy for improved muscle strength

Screening for strabismus

Managing cryptorchidism through hormonal and surgical treatments

Growth hormone treatment may be initiated in infancy

Childhood through adulthood

Monitoring of daily food intake

Determining if calcium and vitamin D supplementation is indicated

Encouraging physical activity

Growth hormone replacement therapy

Evaluating for sleep disturbance

Educational planning

Addressing behavioral concerns with a behavioral management program with firm limit setting

Assessing for hypothyroidism

Assessing for scoliosis

Teenage years

Serotonin reuptake inhibitors may help with behavioral problems

Sex hormone replacement at puberty as indicated

Adulthood

Housing in a group home familiar with the needs of individuals with PWS to regulate behavior and weight management

Growth hormone may help with maintaining muscle bulk

Evaluate for possible osteoporosis every two years

Survival

Obesity and the associated complications contribute to the higher mortality rate in individuals with Prader-Willi syndrome. Initially, the rate of death was estimated to be 3% per year however, a later study showed this to be 1.25% per year. The decrease is attributed to improved management. [1]

## Test Information

### Introduction

Testing for Prader-Willi syndrome may include known familial mutation analysis, SNRPN methylation analysis, chromosomal microarray, FISH analysis for 15q11-q13 deletion, chromosome 15 uniparental disomy (UPD), or imprinting center defect analysis.

Known Familial Mutation Analysis: Known familial mutation analysis is performed when a causative mutation has been identified in a close relative of the individual requesting testing. Analysis for known familial mutations typically includes only the specific mutation identified in the family, but if available, a targeted mutation panel that includes the familial mutation(s) may be performed.

SNRPN/UBE3A Methylation Analysis: This test is typically the first test in the evaluation of both Angelman syndrome (AS) and Prader-Willi syndrome (PWS). It will detect about 80% of patients with AS and greater than 99% of patients with PWS. However, DNA methylation analysis does not identify the underlying cause, which is important for determining the risk to future siblings. This risk ranges from less than 1% to up to 50%, depending on the genetic mechanism. Follow-up testing for these causes may be appropriate.

Chromosomal Microarray or FISH Analysis for 15q11-q13 Deletion: If DNA methylation analysis for AS or PWS is abnormal, deletion analysis is typically the next step. Approximately 70% of cases of both AS and PWS have a deletion in one copy of chromosome 15 involving the 15q11.2-q13 region. When looking specifically for this deletion, FISH (fluorescence in situ hybridization) analysis is most commonly performed. However, chromosomal microarray can also detect

such deletions. If chromosomal microarray (CMA, array CGH) has already been done, FISH is not likely to be necessary.

Chromosome 15 Uniparental Disomy (UPD): If DNA methylation analysis is abnormal but deletion analysis is normal, UPD analysis may be an appropriate next step for evaluation of both AS and PWS. About 28% of PWS cases are due to maternal UPD (both chromosome 15s are inherited from the mother). About 7% of cases of AS are due to paternal UPD (both chromosome 15s are inherited from the father). Both parents must be tested to diagnose UPD.

Imprinting Center Defect Analysis: This test may be considered in the evaluation of AS and PWS when methylation is abnormal, but FISH (or array CGH) and UPD studies are normal. Individuals with such results are presumed to have an imprinting defect. An abnormality in the imprinting process has been described in a minority of cases. However, imprinting center deletions may be familial, and if familial, the recurrence risk can be up to 50%.

## Guidelines and Evidence

### Introduction

This section includes relevant guidelines and evidence pertaining to Prader-Willi syndrome testing.

### Prader-Willi Syndrome Association

The Prader-Willi Syndrome Association (PWSA, 2021) recommended the following test strategy when physical exam and family history suggest the diagnosis of PWS.[3]

Methylation analysis will detect greater than 99% of individuals with PWS including those with deletion, uniparental disomy, or imprinting defect.

If methylation testing is abnormal, it confirms the clinical diagnosis. However, to help determine whether there are risks of PWS in other family members it may be necessary to perform FISH, UPD and/or Imprinting Center testing to determine the exact cause of the abnormal methylation.

Deletion analysis (FISH 15q11-q13 or chromosomal microarray)

If deletion testing is abnormal (70% of individuals with PWS will have a deletion) chromosome analysis may be considered to rule out a familial chromosome rearrangement (rare).

If deletion testing is normal, it is appropriate to consider UPD analysis.

Uniparental Disomy (UPD) analysis of chromosome 15 determines if the patient inherited both copies of chromosome 15 from the mother.

If methylation analysis is abnormal, but FISH and UPD analysis are normal, it is usually assumed there is an imprinting center mutation (which carries a higher recurrence risk than other causes). There is limited clinical testing available.[1,4]

Selected Relevant Publications

An expert-authored review (2017) stated the following regarding testing for Prader-Willi syndrome:[1]

"DNA methylation-specific testing is important to confirm the diagnosis of PWS in all individuals, but especially in those who have atypical findings or are too young to manifest sufficient features to make the diagnosis on clinical grounds."

Abnormal methylation is sufficient to establish clinical diagnosis, but additional testing is needed to establish the mechanism of disease and recurrent risk.

## Criteria

### Introduction

Requests for Prader-Willi syndrome testing are reviewed using these criteria.

Imprinting Center Known Familial Mutation Analysis

Genetic Counseling:

Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

Previous Testing:

No previous imprinting center defect analysis testing, AND

Family History:

Familial imprinting center defect mutation known in blood relative, AND

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SNRPN Methylation Analysis

Genetic Counseling:

Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

**Previous Testing:**

**No previous SNRPN methylation analysis, AND**

**Diagnostic Testing for Symptomatic Individuals:**

**Developmental delay or intellectual disability, and**

**Some combination of the following:**

**Neonatal hypotonia, or**

**Feeding problems (i.e., poor suck) or poor growth in infancy, or**

**Obesity and/or food-related behavior problems (i.e., hyperphagia; obsession with food), or**

**Characteristic facial features, or**

**Hypogonadism AND**

**Rendering laboratory is a qualified provider of service per the Health Plan policy.**

**Deletion Analysis (FISH Analysis for 15q11-q13 Deletion or Chromosomal Microarray)**

**Genetic Counseling:**

**Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND**

**Previous Testing:**

**No previous 15q11-q13 deletion analysis, and**

**No previous chromosomal microarray, AND**

**Diagnostic Testing for Symptomatic Individuals:**

**Developmental delay or intellectual disability, and**

**Some combination of the following:**

**Neonatal hypotonia, or**

**Feeding problems (i.e., poor suck) or poor growth in infancy, or**

**Obesity and/or food-related behavior problems (i.e., hyperphagia; obsession with food) or**

**Characteristic facial features, or**

**Hypogonadism, AND**

**Rendering laboratory is a qualified provider of service per the Health Plan policy.**

**Chromosome 15 Uniparental Disomy**

**Genetic Counseling:**

**Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND**

**Previous Testing:**

**SNRPN methylation analysis results are abnormal, and**

**15q11-q13 deletion analysis is negative, and**

**No previous chromosome 15 UPD studies, AND**

**Diagnostic Testing for Symptomatic Individuals:**

**Developmental delay or intellectual disability, and**

**Some combination of the following:**

**Neonatal hypotonia, or**

**Feeding problems (i.e., poor suck) or poor growth in infancy, or**

**Obesity and/or food-related behavior problems (i.e., hyperphagia; obsession with food), or**

**Characteristic facial features, or**

**Hypogonadism AND**

**Rendering laboratory is a qualified provider of service per the Health Plan policy.**

**Imprinting Center Defect Analysis**

**Genetic Counseling:**

**Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND**

**Previous Testing:**

**SNRPN methylation analysis results are abnormal, and**

**15q11-q13 deletion analysis is negative, and**

**Previous chromosome 15 UPD studies negative, and**

**No previous imprinting center (IC) analysis, AND**

**Diagnostic Testing for Symptomatic Individuals:**

**Developmental delay or intellectual disability, and**

**Some combination of the following:**

**Neonatal hypotonia, or**

**Feeding problems (i.e., poor suck) or growth failure in infancy, or**

**Obesity and/or food-related behavior problems (i.e., hyperphagia; obsession with food), or**

**Characteristic facial features, or**

**Hypogonadism AND**

**Rendering laboratory is a qualified provider of service per the Health Plan policy**

## References

**Introduction**

**This guideline cites the following references.**

**Driscoll DJ, Miller JL, Schwartz S, Cassidy SB. Prader-Willi Syndrome. 6 Oct 1998 [Updated 14 Dec 2017]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021. Available at: http://www.ncbi.nlm.nih.gov/books/NBK1330/**

**Butler MG, Miller JL, Forster JL. Prader-Willi Syndrome - Clinical genetics, diagnosis and treatment approaches: An update. *Curr Pediatr Rev*. 2019;15(4):207-244.**

**Prader-Willi Syndrome Association (USA). Testing and diagnosis. https://www.pwsausa.org/resources/medical-issues-a-z (copyright 2021)**

**Gunay-Aygun M, Schwartz S, Heeger S, O'Riordan MA, Cassidy SB. The changing purpose of Prader-Willi syndrome clinical diagnostic criteria and proposed revised criteria. *Pediatrics.* 2001;108(5):E92.**