Prader-Willi Syndrome Testing

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

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What is Prader-Willi syndrome

Definition

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.\(^1,2\)

- Prader-Willi syndrome (PWS) is characterized by:\(^1\)
  - Decreased muscle tone (hypotonia) and feeding difficulties in early infancy
  - Insatiable appetite in childhood that often results in obesity
  - Developmental delay
Lab Management Guidelines

Test information

- **SNRPN Methylation Analysis**: This test is typically the first test in the evaluation of both Angelman syndrome and Prader-Willi syndrome. It will detect about 80% of patients with Angelman syndrome and >99% of patients with Prader-Willi syndrome. 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 Angelman (AS) or Prader-Willi syndrome (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 next may be appropriate for evaluation of both Angelman (AS) and Prader-Willi syndrome (PWS). About 28% of PWS cases are due maternal UPD (both chromosome 15s are inherited from the mother). Both parents must be tested to diagnose UPD.

- **Imprinting Center Defect Analysis**: This test may be considered in the evaluation of Angelman syndrome (AS) and Prader-Willi syndrome (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%.

- **Imprinting Center Known Familial Mutation Analysis**: If a mutation in the imprinting center has been identified in an affected family member, testing for just the known familial mutation in the imprinting center can be performed for at-risk relatives, including at-risk pregnancies.
Guidelines and evidence

- The Prader-Willi Syndrome Association (2016) recommends the following test strategy when physical exam and family history suggest the diagnosis of PWS.2
  - 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.1,3
- The 2017 Gene Reviews article on Prader-Willi Syndrome states: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

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:
o Developmental delay or intellectual disability, and
o 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:
  o Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

• Previous Testing:
  o No previous 15q11-q13 deletion analysis, and
  o No previous chromosomal microarray, AND

• Diagnostic Testing for Symptomatic Individuals:
  o Developmental delay or intellectual disability, and
  o 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

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Chromosome 15 Uniparental Disomy

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

• Previous Testing:
  o SNRPN methylation analysis results are abnormal, and
  o 15q11-q13 deletion analysis is negative, and
  o No previous chromosome 15 UPD studies, AND

• Diagnostic Testing for Symptomatic Individuals:
  o Developmental delay or intellectual disability, and
  o 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

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Imprinting Center Defect Analysis

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

• Previous Testing:
  o SNRPN methylation analysis results are abnormal, and
  o 15q11-q13 deletion analysis is negative, and
  o Previous chromosome 15 UPD studies negative, and
  o No previous imprinting center (IC) analysis, AND

• Diagnostic Testing for Symptomatic Individuals:
  o Developmental delay or intellectual disability, and
  o 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

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

**References**