Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 7/1/23**
(See policy history boxes for previous effective dates)

Title: Genetic Testing for Prader-Willi and Angelman Syndromes (Chromosome 15 Abnormalities)

Description/Background

The Prader–Willi (PWS) and Angelman (AS) syndromes are two clinically distinct syndromes which result from the lack of expression of imprinted genes within chromosome 15q11-q13. These two syndromes result from 15q11-q13 deletions, chromosome 15 uniparental disomy (UPD), imprinting centre mutations and, for AS, probable mutations in a single gene. The differential phenotype results from a *paternal* genetic deficiency in PWS patients and a *maternal* genetic deficiency in AS patients.

Within 15q11-q13, four genes (*SNRPN, IPW, ZNF127*, and *FNZ127*) and two expressed sequence tags (*PAR1* and *PAR5*) have been found to be expressed only from the paternally inherited chromosome, and therefore all must be considered candidate genes involved in the pathogenesis of PWS. A candidate AS gene (*UBE3A*) has very recently been identified in Angelman syndrome. The mechanisms of imprinted gene expression are not yet understood, but it is clear that DNA methylation is involved in both somatic cell expression and inheritance of the imprint. The presence of DNA methylation imprints that distinguish the paternally and maternally inherited alleles is a common characteristic of all known imprinted genes which have been studied extensively, including *SNRPN* and *ZNF127*. Recently, several PWS and AS patients have been found that have microdeletions in a region upstream of the *SNRPN* gene referred to as the imprinting center, or IC. Paternal IC deletions in PWS patients and maternal IC deletions in AS patients result in uniparental DNA methylation and uniparental gene expression at biparentally inherited loci. The IC is a novel genetic element which controls initial resetting of the parental imprint in the germline for all imprinted gene expression over a 1.5–2.5 Mb region within chromosome 15q11-q13.

Prader-Willi syndrome

Prader–Willi syndrome (PWS) is a rare, genetic disorder in which seven genes (or some subset thereof) on chromosome 15 (q11-13) are deleted or unexpressed (chromosome 15q partial

deletion) on the paternal chromosome. The incidence of PWS is between 1 in 25,000 and 1 in 10,000 live births. Although Prader-Willi syndrome is genetic, it usually is not inherited and generally develops due to deletions or partial deletions on chromosome 15.

Specific changes to the chromosome can include the following:

- **Deletions**. A section of a chromosome may be lost or deleted, along with the functions that this section supported. About 65% to 75% of Prader-Willi syndrome cases result from the loss of function of several genes in one region of the father's chromosome 15, due to deletion. The corresponding mother's genes on chromosome 15 are always inactive and thus cannot make up for the deletion on the father's chromosome 15. The missing paternal genes normally play a fundamental role in regulating hunger and fullness.
- **Maternal uniparental disomy.**. A cell usually contains one set of chromosomes from the father and another set from the mother. In ordinary cases, a child has two chromosome 15s, one from each parent. In 20% to 30% of Prader-Willi syndrome cases, the child has two chromosome 15s from the mother and none from the father. Because genes located in the PWCR are normally inactive in the chromosome that comes from the mother, the child's lack of active genes in this region leads to Prader-Willi syndrome.
- **An imprinting center defect.** Genes in the PWCR on the chromosome that came from the mother are normally inactivated, due to a process known as "imprinting" that affects whether the cell is able to "read" a gene or not. In less than 5% of Prader-Willi syndrome cases, the chromosome 15 inherited from the father is imprinted in the same way as the mother's. This can be caused by a small deletion in a region of the father's chromosome that controls the imprinting process, called the imprinting center. In these cases, both of the child's copies of chromosome 15 have inactive PWCRs, leading to Prader-Willi syndrome.

The maternal origin of the genetic material that is affected in the syndrome is important because the particular region of chromosome 15 involved is subject to parent of origin imprinting, meaning that for a number of genes in this region, only one copy of the gene is expressed while the other is silenced through imprinting. For the genes affected in PWS, it is the maternal copy that is usually imprinted (and thus is silenced), while the mutated paternal copy is not functional. This means that while most people have a single working copy of these genes, people with PWS have a non-working copy and a silenced copy.

Regardless of genetic subtype, genetic testing for PWS is typically focused on the Small Nuclear Ribonucleoprotein Polypeptide N (SNRPN) gene mapped to 15q11 to q13, an imprinted gene with paternal expression. PWS genotype is determined by assays detecting deletion (chromosome analysis and fluorescence in situ hybridization [FISH]) or maternal methylation patterns (Southern blot analysis, methylation-specific multiplex-ligation-dependent probe amplification assay [MS-MLPA], or methylation-specific melting analysis [MS-MA]) of SNRPN. In 1996, the American Society of Human Genetics/American College of Medical Genetics (ASHG/ACMG) published recommendations for diagnostic testing for PWS.

In order to determine a diagnosis of PWS, specific criteria have been developed:

- **Children younger than 3 years** must have at least four major criteria and at least one minor criterion for a Prader-Willi syndrome diagnosis.
- **Those older than age 3** must have at least five major criteria and at least three minor criteria for a diagnosis of Prader-Willi syndrome.

Major Clinical Criteria of Prader-Willi Syndrome

- Extremely weak muscles in the body's torso
- Difficulty sucking, which improves after the first few months
- Feeding difficulties and/or failure to grow, requiring feeding assistance, such as feeding tubes or special nipples to aid in sucking
- Beginning of rapid weight gain, between ages 1 and 6, resulting in severe obesity
- Excessive, uncontrollable overeating
- Specific facial features, including narrow forehead and downturned mouth
- Reduced development of the genital organs, including small genitalia (vaginal lips and clitoris in females and small scrotum and penis in males); incomplete and delayed puberty; infertility
- Developmental delays, mild-to-moderate intellectual disability, multiple learning disabilities

Minor Clinical Criteria of Prader-Willi Syndrome

- Decreased movement and noticeable fatigue during infancy
- Behavioral problems-specifically, temper tantrums, obsessive-compulsive behavior, stubbornness, rigidity, stealing, and lying (especially related to food)
- Sleep problems, including daytime sleepiness and sleep disruption
- Short stature, compared with other members of the family, noticeable by age 15
- Light color of skin, eyes, and hair
- Small hands and feet in comparison to standards for height and age
- Narrow hands
- Nearsightedness and/or difficulty focusing both eyes at the same time
- Thick saliva
- Poor pronunciation
- Picking of the skin

Additional Findings may include:

- High pain threshold
- Inability to vomit
- Curvature of the spine (scoliosis)
- Earlier-than-usual activity in the adrenal glands, which can lead to early puberty
- Especially brittle bones (osteoporosis)

Genetic testing is the only way to positively confirm the Prader-Willi syndrome diagnosis. More than 99% of individuals with Prader-Willi syndrome have an abnormality within a specific area of chromosome 15. Early diagnosis is best because it enables affected individuals to begin early intervention/special needs programs and treatment specifically for Prader-Willi symptoms.

Genetic testing can confirm the chance that a sibling might be born with Prader-Willi syndrome. Prenatal diagnosis also is available for at-risk pregnancies-that is, pregnancies among women with a family history of Prader-Willi syndrome abnormalities.

Angelman Syndrome

Angelman Syndrome (AS) is a neurodevelopmental disorder with multisystemic effects that include the following characteristics:

- Severe developmental delays
- Absence of speech
- Mental retardation

- Seizures
- Motor dysfunction
- Subtle dysmorphic facial features, and
- An abnormally happy disposition with frequent laughter.

Other symptoms may include:
- Seizures, usually beginning between 2 and 3 years of age
- Stiff or jerky movements
- Small head size with flatness in the back of the head (microbrachycephaly)
- Tongue thrusting
- Light pigmentation in hair, skin and eyes
- Unusual behaviors, such as hand-flapping and arms uplifted while walking

The estimated prevalence of AS is 1 in 10,000 to 1 in 40,000 individuals. Many of the characteristic features of Angelman syndrome result from the loss of function of a gene called *UBE3A*. People normally inherit one copy of the *UBE3A* gene from each parent. Both copies of this gene are turned on (active) in many of the body's tissues. In certain areas of the brain, however, only the copy inherited from a person's mother (the maternal copy) is active. This parent-specific gene activation is caused by a phenomenon called genomic imprinting. If the maternal copy of the *UBE3A* gene is lost because of a chromosomal change or a gene mutation, a person will have no active copies of the gene in some parts of the brain.

There are 4 main causes of AS :
- Maternal deletions involving 15q11.2-q13 (70% of cases);
- Paternal uniparental disomy (UPD) of chromosome 15 (the inheritance of both copies of a homologous pair of chromosomes with no contribution from the other parent; approximately 5% of AS patients);
- Imprinting defect of biparental inheritance with only paternal methylation and expression (approximately 5% of AS)
- Sequence variants in the ubiquitin protein ligase e3a (*UBE3A*) gene imprinting defect of biparental inheritance with only paternal methylation and expression (approximately 5% of AS).

In addition, for approximately 10 to 15% of clinically diagnosed AS patients, molecular defects remain unidentifiable. Most cases of Angelman syndrome are not inherited, particularly those caused by a deletion in the maternal chromosome 15 or by paternal uniparental disomy. These genetic changes occur as random events during the formation of reproductive cells (eggs and sperm) or in early embryonic development. Affected people typically have no history of the disorder in their family.

The United States Angelman Syndrome Foundation (USASF) recommends considering genetic testing for individuals showing consistent and frequently observed clinical features of AS with a defined developmental history that includes the following:
- Absence of major birth defects with normal head circumference, although feeding difficulties may be present in neonate and infant.
- Evident developmental delay by age 6 to 12 months with possible unsteady limb movements and increased smiling.
- Delayed forward progression of development with no overall loss of skills.

- Presence of normal metabolic, hematologic, and chemical profiles.
- Clinical evidence of normal brain structure, although mild cortical atrophy or dysmyelination may be present.

Consistent and frequently observed clinical features of AS include:
- Functionally severe developmental delay.
- Balance disorder with ataxia of gait or limb movement.
- Frequent and inappropriate happy demeanor
- Absence or severe impairment of speech.
- Other AS features frequently observed among more than 80% of individuals with AS:
  - Microcephaly by age 2 years.
  - Seizures by < age 3 years.
  - Abnormal characteristic electroencephalography (EEG).

Genetic testing for AS typically involves testing for abnormal methylation patterns or maternal allele deletions involving the small nuclear ribonucleoprotein polypeptide N (*SNRPN*) gene, paternal UPD for chromosome 15. Among those testing negative for the former, *UBE3A* sequence variants may be investigated. On chromosome 15, bands q11-q13, *SNRPN* partially overlaps *UBE3A* gene in the antisense orientation. Loss of function of *UBE3A* expressed from the maternal chromosome originally implicated *UBE3A* in the etiology of AS, and may be the primary mechanism responsible for AS phenotype associated with deletions, UPD, and imprinting defects.

Some individuals with Angelman Syndrome are misdiagnosed as having autism, pervasive developmental disorder, or cerebral palsy. If an individual fits the diagnostic criteria, testing for AS is recommended as issues, medications, and educational strategies that benefit AS individuals can be drastically different than those recommended for other disorders in spite of seemingly similar characteristics.

The management of patients with PWS or AS is centered providing the appropriate therapies for the physical and neurological problems encountered in this condition and provision for special educational needs, given the very specific cognitive profiles and behavioral features of both conditions.

Regulatory Status

No U.S. Food and Drug Administration (FDA)-cleared genotyping tests were identified. The available commercial genetic tests for Prader-Will syndrome and Angelman syndrome are offered as laboratory-developed tests. Clinical laboratories may develop and validate tests in-house (“home-brew”) and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA) of 1988. ARUP Laboratories, Genzyme Genetics, LabCorp, Mayo Medical Laboratories, and Quest Diagnostics have current CLIA certifications.

Medical Policy Statement

The safety and effectiveness of genetic testing for Prader-Willi syndrome (PWS) and Angelman syndrome (AS) (chromosome 15 abnormalities) have been established. This testing is a useful diagnostic option when indicated.

Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

Inclusions:
Genetic testing for Prader Will or Angelman syndromes may be appropriate for:

- Neonates, infants, children, or adults who display clinical features of Prader-Willi or Angelman syndromes but the diagnosis remains uncertain.
- Prenatal testing in the presence of risk factors.
- Presymptomatic diagnosis of PWS or AS in patients who are direct risk of inheriting the sequence variant in question.

An early diagnosis will directly impact the treatment being delivered to the member.

Exclusions:
When used as a general screening test in the absence of symptoms or risk factors,

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

81331 81402 81406

Other codes (investigational, not medically necessary, etc.):

N/A

Rationale

The Centers for Disease Control and Prevention (CDC) developed the ACCE model to be used in reviewing genomic tests and applications. The ACCE model takes its name from an abbreviation of its main components: Analytical validity; Clinical validity; Clinical utility; and Ethical, legal and social implications. The model is widely used to allow the performance of rapid health technology evaluations of genetic tests.

Prader-Willi Syndrome:
Analytical validity is the ability of a genetic test to measure accurately and reliably the genotype of interest. A variety of commonly used mechanism-specific testing methods for PWS have been reliably used for more than a decade, including microscopic chromosome analysis by karyotyping, submicroscopic detection of DNA abnormalities using FISH, and molecular DNA-based assays such as methylation and microsatellite analysis.

Borelina and colleagues performed multiple commonly used molecular and cytogenetic assays to validate clinically suspected PWS for 27 patients. Complete karyotype analysis was performed to observe microscopic chromosome 15 abnormalities, and FISH was used to detect submicroscopic abnormalities such as paternal allele deletions. Methylation-specific restriction fragment length polymorphism followed by Southern blotting or bisulfite treatment of

methylation-specific PCR followed by gel electrophoresis was used to distinguish between maternal and paternal methylation patterns. Finally, to detect UPD of chromosome 15, microsatellite analysis of 15 polymorphic loci was performed. The authors report genetic validation for only half (14 of 27; 52%) of the clinically suspected PWS patients. Of the 14 genetically confirmed PWS patients, 6 patients had paternal deletions, 1 patient had maternal UPD, and 7 patients had abnormal methylation but no detected deletion or UPD. For the 13 patients with clinically suspected PWS, the authors also evaluated several for possible tissue mosaicism using lymphocytes and buccal mucosa. However, all further tissue-specific evaluations showed biparental inheritance. Therefore, the authors concluded that their failure to genetically validate clinically suspected PWS is likely due to misdiagnosis, especially since clinical diagnoses were based on presenting hypotonia and developmental delay, which is also common to metabolic inborn errors or other disorders.

Procter and colleagues described and validated MS-MA for use by ARUP Laboratories in the determination of the methylation status of PWS patients. A total of 52 DNA samples were tested, including 12 PWS samples previously tested by methylation-specific PCR and 33 normal samples from asymptomatic individuals. An additional 10 normal and 9 PWS samples tested by MS-MA were used to cross-validate MS-MLPA. In MS-MA, PWS amplicons are determined by higher temperature melting curves due to higher guanine-cytosine (GC) contents derived from methylated maternal alleles compared to paternal alleles. The authors concluded that MS-MA may be used for efficient initial diagnosis of PWS, while MS-MLPA may replace FISH for determination of type of variant (e.g., deletion or other).

Bittel and colleagues evaluated the efficacy of the MS-MLPA kit in detecting abnormalities of chromosome 15. Among the 82 subjects tested, 62 had PWS while 10 had Angelman syndrome (AS) and 10 had other abnormalities involving chromosome 15, including terminal deletions of the long arm of chromosome 15 and chromosome ring 15. Another 13 patients had normal cytogenetic findings. The authors concluded that MS-MLPA is a relatively simple and cost-effective technique that is useful and accurate for determining methylation status, copy number, and analysis of genetic subtype (deletion, UPD, or imprinting center defect) in PWS and AS, and is also useful for diagnosing other chromosome 15 abnormalities.

Dikow and colleagues compared sequence-based quantitative methylation analysis (SeQMA) and the MS-MLPA kit for quantification of methylation status using 9 controls and 12 patients with either PWS or AS. The authors reported that both methods were effective at determining correct methylation status for PWS or AS patients. However, MS-MLPA performed superior to SeQMA in the titration curve assessment. More specifically, SeQMA was less sensitive than MS-MLPA for proportions approaching 0% methylation (AS).

Clinical validity is the ability of a genetic test to detect or predict the associated disorder or phenotype. Buiting and colleagues conducted a case-only molecular study of 51 unrelated PWS patients with imprinting defects. DNA samples were also collected from fathers of probands for genotyping to describe origin of grandparental alleles by analysis of microsatellite markers. The authors performed DNA methylation assays and Southern blot analysis to screen for microdeletions. In addition, when no microdeletion was found, the authors performed sequence analysis of the *SNURF-SNRPN* exon 1 region. The authors report that inherited microdeletions may account for 14% (7 of 51) of PWS patients with imprinting defects. An affected sibling was observed among 43% (3 of 7) of those with inherited microdeletions and imprinting defects. In contrast, all PWS patients with no imprinting center microdeletion were

sporadic as no affected siblings were observed. Among the 86% (44 of 51) of patients with no imprinting center microdeletion, mosaic methylation may explain etiology of only 2 patients. Finally, the authors were able to verify grandparental origin of the incorrectly imprinted paternal allele for 19 PWS patients, of which all originated from the paternal grandmother.
Torrado and colleagues conducted a prospective case-only study of 91 children with PWS in Argentina. PWS diagnosis was verified by various molecular methods that included: (1) methylation test by Southern blot to establish initial diagnosis; and (2) FISH and microsatellite analysis to establish etiology of maternal methylation pattern (e.g., deletion, UPD, or imprinting center variant). The authors specifically compared characteristics of 59 patients who had PWS due to deletions versus 32 PWS patients without deletions (30 due to maternal UPD and 2 due to imprinting center variants). The authors reported a significantly increased average maternal age for mothers of the PWS patients without deletions compared to those with deletions (36 years versus 27 years, respectively; $P<0.001$).

Hartley and colleagues conducted a case-only study comparing maladaptive behaviors using the Reiss Screen across genotypes among 65 PWS patients aged 12 to 45 years (mean age, 24 years). High-resolution chromosome analysis, FISH, and microsatellite analysis were used to distinguish between deletions and UPD. Deletions were further subtyped as type I or type II, depending on the proximal breakpoint of the typical 15q11 to q13 deletion, by consideration of specific microsatellite markers and confirmed using quantitative PCR. Several maladaptive behaviors (including aggression, autism, psychosis, paranoia, depression, dependency, avoidance, substance abuse, over activity, self-injury, sexual problems, stealing, and suicidal tendencies) were measured using the Reiss Screen. Of the 65 PWS patients, 40 paternal deletions, 23 maternal UPD, and 2 imprinting defects were observed.

Clinical utility focuses on what needs to be considered when evaluating the risks and benefits of introducing a genetic test into routine practice, and includes studies that seek to determine improvements in health outcomes when using the genetic test in clinical practice.

Monaghan and colleagues compared the cost of genetic testing for PWS using: (1) DNA methylation analysis followed by FISH for positive results (ASHG/ACMG recommended); (2) FISH followed by DNA analysis for negative results (an alternate sequential testing strategy); and (3) simultaneous FISH and DNA analysis. More specifically, the authors totaled hypothetical costs using various testing strategies, assuming $200 for FISH and $300 for DNA testing, based on the results of 136 samples processed (primarily by the ASHG/ACMG strategy) at a single center between July 1998 and March 2002. The added cost of chromosome analysis was not considered, since this is likely to be performed for all patients with suspected PWS. The authors confirmed that, based on patient data in their clinic, the ASHG/ACMG testing strategy is the most cost-effective testing strategy for PWS. However, since simultaneous testing is likely to expedite reporting time and diagnosis, the authors acknowledge instances, such as for hypotonic infants, in which greater cost may be more favorable.

Section Summary
Commonly used laboratory methods for genetic diagnosis of PWS include digestion using methylation-sensitive restriction enzymes followed by Southern blotting or methylation-specific PCR-based methods with detection by gel electrophoresis. Chromosome analysis, FISH, and microsatellite analysis are additional commonly used methods that may help to validate

molecular PWS diagnosis and clarify the genetic mechanism. The cost-effectiveness of PWS testing may be influenced by the testing strategy.

Angelman Syndrome

Analytical Validity

Borelina and colleagues performed multiple commonly used molecular and cytogenetic assays to validate clinically suspected AS for 24 patients. Complete karyotype analysis was performed to observe microscopic chromosome 15 abnormalities, and FISH was used to detect submicroscopic abnormalities such as maternal allele deletions. Methylation-specific restriction fragment length polymorphism followed by Southern blotting or bisulfite treatment of methylation-specific PCR followed by gel electrophoresis was used to distinguish between maternal and paternal methylation patterns. Finally, to detect UPD of chromosome 15, microsatellite analysis of 15 polymorphic loci was performed. The authors report genetic validation for only 7 of the 24 (29%) clinically suspected AS patients. Of these 7 genetically confirmed AS patients, 4 patients had maternal deletions and the remaining 3 had abnormal methylation patterns, while the molecular etiology was undetermined.

Procter and colleagues described and validated methylation-specific melting analysis (MS-MA) for use by ARUP Laboratories in the determination of the methylation status of AS patients. A total of 52 DNA samples were tested, including 7 AS samples previously tested by methylation-specific PCR and 33 normal samples from asymptomatic individuals. The authors concluded that MS-MA may be used for efficient initial diagnosis of AS, while MS-MLPA may replace FISH for determination of type of variant (e.g., deletion or other). However, the relatively high failure rate of MS-MA may preclude its adoption into routine laboratory practice.

Baumer and colleagues screened for *UBE3A* sequence variants among 101 AS patients after excluding patients with typical 15q11-q13 deletion, UPD, or imprinting defects. Standard single strand conformation polymorphism (SSCP) and restriction fragment length polymorphism (RFLP) analysis was performed, as well as long-range PCR and DNA sequencing of the larger exons (8, 9, and 16) and including segments of introns. Of the 101 patients screened, the authors detected a total of 8 variations in *UBE3A*, including 5 novel rare sequence variants and 3 polymorphisms. The authors noted that all 8 variants were observed using standard SSCP and RFLP analysis, while use of long-range PCR and DNA sequencing of larger exons did not reveal any additional variants.

Clinical Validity

Lossie and colleagues assessed 104 AS patients from 93 families for molecular etiology. Patients included in the analysis were ascertained from a single clinical repository and restricted to those with “absolutely classical” or “fairly classical” characteristics of AS. While all included patients fulfilled the 4 main criteria of AS, the “fairly classical” AS patients showed 1 or 2 atypical features, such as mild or absent seizures or obesity. Molecular genotypes were assigned for: (1) deletion at 15q11-q13; (2) UPD; (3) imprinting defect; (4) *UBE3A* sequence variant; and (5) unknown. In addition, for genotype-phenotype comparisons, the authors evaluated clinical variables that included growth parameters, acquisition of motor skills, and history of seizures. Of 104 patients, the authors identified 64 (61%) with deletions at 15q11-13; 7 (7%) with UPD; 7 (7%) with imprinting defects; 15 (14%) with *UBE3A* sequence variants; and 11 (11%) with unknown molecular etiology. The authors assessed phenotypes of patients with UPD, imprinting defects, *UBE3A* variants, and unknown molecular etiology compared to a

random sample of patients with deletions. They reported significant differences by genotype for body mass index (BMI), microcephaly, mean age to walking, onset of seizures, and hypopigmentation.

Varela and colleagues assessed 58 AS patients due to deletions (n=49) and UPD (n=9) for phenotypic variability. Methylation pattern analysis of *SNRPN-SNURF* and microsatellite analysis of 15q11-q13 were previously used to confirm molecular diagnosis of AS. In addition, the authors classified 15q11-q13 deletions by the proximal and distal breakpoints. All but 3 patients were classified within one of two major proximal-distal breakpoint classifications. The authors reported normal karyotypes for all patients. Significant differences were observed in percentage of patients with absence of speech for BP1-BP3 compared to BP2-BP3 deletion patients. Significantly greater percentages of patients with deletions had swallowing difficulties, hypotonia, microencephaly, and seizures.

Hitchins and colleagues screened 45 AS cases for *UBE3A* variants using SSCP analysis and DNA sequencing. All cases previously tested negative for 15q11-q13 deletion, UPD, and imprinting defects. Of the 45 cases tested, 39 were sporadic and 6 were familial in nature. The authors report finding a total of 7 pathogenic *UBE3A* variations, of which 6 were novel. Of the 7 pathogenic variants discovered, 3 were found among familial AS cases and 4 were found among sporadic cases. Therefore, 50% (3 of 6) of familial AS and 10% (4 of 39) of sporadic AS were due to pathogenic *UBE3A* variants among cases previously testing negative for other typical genetic abnormalities.

Clinical Utility
Monaghan and colleagues compared the cost of genetic testing for AS using: (1) DNA methylation analysis followed by FISH for positive results (ASHG/ACMG recommended); (2) FISH followed by DNA analysis for negative results (an alternate sequential testing strategy); and (3) simultaneous FISH and DNA analysis. The authors confirmed that, based on patient data in their clinic, the ASHG/ACMG testing strategy is the most cost-effective testing strategy for AS. However, since simultaneous testing is likely to expedite reporting time and diagnosis, the authors acknowledge instances, such as for hypotonic infants, in which greater cost may be more acceptable in order to promote better patient care.

Section Summary
Commonly used laboratory methods for genetic diagnosis of AS include digestion using methylation-sensitive restriction enzymes, followed by Southern blotting or methylation-specific PCR-based methods with detection by gel electrophoresis. Chromosome analysis, FISH, and microsatellite analysis are additional commonly used methods that may help to validate molecular AS diagnosis and clarify the genetic mechanism. The cost-effectiveness of AS testing may be influenced by the testing strategy.

Government Regulations
National:
There is no national determination for this genetic testing. Requests for such services would be processed on an individual consideration basis.

Local:

There is no specific local coverage determination for genetic testing for Prader Willi and Angelman Syndrome. Requests for such services would be processed on an individual consideration basis.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Genetic Testing and Counseling
- Genetic Testing-Chromosomal Microarray (CMA) Analysis (or Comparative Genomic Hybridization-CGH) for the Genetic Evaluation of Patients with Developmental Delay/Intellectual Disability or Autism Spectrum Disorder

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through March 2023, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
7/1/14	4/8/14	4/15/14	Joint policy established
7/1/15	4/24/15	5/8/15	Routine maintenance. No change in policy status.
7/1/16	4/19/16	4/19/16	Routine maintenance
7/1/17	4/18/17	4/18/17	Routine maintenance. No change in policy status.
7/1/18	4/17/18	4/17/18	Routine policy maintenance.
7/1/19	4/16/19		Routine policy maintenance, no change in policy status.
7/1/20	4/14/20		Routine policy maintenance, no change in policy status.
7/1/21	4/20/21		Routine policy maintenance. No change in policy status.
7/1/22	4/19/22		Routine policy maintenance, no change in policy status.
7/1/23	4/18/23		Routine policy maintenance, no change in policy status. Vendor managed: N/A. (ds)

Next review: 2nd Qtr. 2024

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENETIC TESTING FOR PRADER-WILLI AND ANGELMAN SYNDROMES (CHROMOSOME 15 ABNORMALITIES)

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply.
BCNA (Medicare Advantage)	See government section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.