DNA-Based Testing for Adolescent Idiopathic Scoliosis

Policy # 00314
Original Effective Date: 09/14/2011
Current Effective Date: 01/11/2021

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers deoxyribonucleic acid (DNA)-based prognostic testing for adolescent idiopathic scoliosis (AIS) to be **investigational.***

Policy Guidelines

Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Background/Overview

Adolescent Idiopathic Scoliosis

AIS is the most common pediatric spinal deformity, affecting 1% to 3% of adolescents. This disease, of unknown etiology, occurs in otherwise healthy children with the onset of, and highly correlated with, the adolescent growth spurt. The vertebrae become misaligned such that the spine deviates from the midline laterally and rotates axially. The deviation can occur anteriorly (a lordotic deviation), posteriorly (a kyphotic deviation), or laterally. Although AIS affects females and males in a nearly 1:1 ratio, progression to severe deformity occurs more often in females. Because the disease can have a rapid onset and produce considerable morbidity, school screenings have been

recommended. However, screening remains somewhat controversial, with conflicting guidelines supporting and not supporting this practice.

Diagnosis
Diagnosis is established by radiologic observation in adolescents (age 10 years until the age of skeletal maturity) of a lateral spine curvature of 10° or more, as measured using the Cobb angle. The Cobb angle is defined as the angle measured between the maximally tilted proximal and distal vertebrae of the curve. The curvature is considered mild (<25°), moderate (25°-40°), or severe (>40°) in a patient still growing. Once diagnosed, patients must be monitored over several years, usually with serial radiographs for curve progression.

Treatment
If the curve progresses, spinal bracing is the generally accepted first-line treatment. If the curve progresses in spite of bracing, spinal fusion may be recommended.

Curve progression has been linked to a number of factors, including sex, curve magnitude, patient age, and skeletal maturity. Risk tables, by Lonstein and Carlson (1984) and Peterson and Nachemson (1995), help in triage and treatment decision making about patients with AIS. Tan et al (2009) compared a broad array of factors and concluded that using 30° as an endpoint, initial Cobb angle magnitude produces the best prediction of progression outcome.

Genetic Associations and Scoliosis
The familial nature of this disease was noted as early as 1968. About one-quarter of patients report a positive family history of the disease, and twin studies have consistently supported shared genetic factors. Genome-wide linkage studies have reported multiple chromosomal regions of interest, often not replicated. Ogilvie (2010) has suggested AIS is a complex polygenic trait. Ogilvie et al (2010) at Axial Diagnostics published a study evaluating an algorithm using 53 single nucleotide variant (SNV) markers identified from unpublished genome-wide association studies to differentiate patients unlikely to exhibit severe progression in curvature from those at considerable risk for severe progression. The clinical validity of this assay was reported in a 2010 retrospective case-control cohort study using this algorithm.

ScoliScore AIS
The ScoliScore AIS prognostic DNA-based test (Transgenomic), which uses an algorithm incorporating results of testing for 53 SNVs, along with the patient's presenting spinal curve (Cobb angle), to generate a risk score (range, 1-200), can be used qualitatively or quantitatively to predict the likelihood of spinal curve progression. The test is intended for white (Caucasian) patients, ages 9 to 13 years, with a primary diagnosis of AIS with a mild scoliotic curve (defined as <25°).

The development and validation of the ScoliScore SNV-based prognostic algorithm were described by Ward et al (2010) in the industry-sponsored study discussed above. The prognostic algorithm was developed in a cohort of 2192 female patients from prior studies. Candidate genes were selected based on previous genome-wide association studies data from the same investigators. The independent effect of each SNV and clinical factors (initial Cobb angle) and all gene-gene interaction terms were tested in a stepwise logistic regression using a backward-selection procedure and then using a forward-selection procedure. The final predictive model included 53 SNV markers, multiple gene-gene interaction terms, and the patient's initial Cobb angle. Prediction probabilities were converted to a numeric score ranging from 1 to 200. A priori, low-risk of progression was determined to be less than 1%; from the generation cohort, a score of less than 41 was selected as an initial cutoff.

The ScoliScore™‡ AIS Prognostic Test was originally developed by Axial Biotech with test rights acquired by Transgenomic in 2013. In 2015, Transgenomic divested its Genetic Assays & Platforms Business Unit to ADSTEC Corp. In June 2017, Transgenomic was acquired by Precipio Diagnostics in a reverse merger transaction. It does appear that the test remains commercially available.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the FDA has chosen not to require any regulatory review of this test.

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Rationale/Source

Adolescent idiopathic scoliosis (AIS) is a disease of unknown etiology that causes mild-to-severe spinal deformity in approximately 1% to 3% of adolescents. While there is controversy about the value of screening and treatment, once diagnosed, patients are frequently closely followed. In cases with significant progression of curvature, both medical (bracing) and surgical (spinal fusion) interventions are considered. The ScoliScore AIS prognostic DNA-based test uses an algorithm incorporating results of testing for 53 SNVs, along with the patient's presenting spinal curve (Cobb angle), to generate a risk score (range, 1-200), which can be used qualitatively or quantitatively to predict the likelihood of spinal curve progression.

For individuals with AIS who receive clinical management with prognostic testing using an algorithm incorporating SNV-based testing, the evidence includes cross-sectional studies reporting on the clinical validity of the ScoliScore test, along with cross-sectional studies reporting on the association between SNVs in various genes and scoliosis progression. The relevant outcomes are symptoms, morbid events, and change in disease status. A single study on the clinical validity for the ScoliScore AIS prognostic DNA-based test has reported a high negative predictive value for ruling out the possibility of progression to severe curvature in a population with a low baseline likelihood of progression. It is not clear if the increase in predictive accuracy provided by testing is statistically or clinically meaningful. Other genetic studies have not demonstrated significant associations between the SNVs used in the ScoliScore and scoliosis progression. Studies have identified additional SNVs that may be associated with AIS severity, but these associations have not been reliably replicated. The clinical validity of DNA-based testing (either through testing of individual SNVs or an algorithm incorporating SNV results) for predicting scoliosis progression in patients with AIS has not been established. There is no direct evidence demonstrating that use of this test results in changes in management that improve outcomes. The value of early identification and intervention(s) for people at risk for progression of the disease and whether laboratory testing improves disease identification beyond clinical evaluation are unknown. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers,

input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 2 specialty societies and 4 academic medical centers while this policy was under review in 2012. All agreed with this policy and indicated that DNA-based prognostic testing for adolescent idiopathic scoliosis (ScoliScore) should be considered investigational.

Practice Guidelines and Position Statements
The Scientific Society on Scoliosis Orthopaedic and Rehabilitation Treatment (2011) issued guidelines on the conservative treatment of idiopathic scoliosis. These guidelines did not address the role of DNA-based prognostic testing. A 2016 guideline update mentions a single prognostic genetic test (ScoliScore) and states that, while initial results have been promising, the generalizability is considered uncertain.

U.S. Preventive Services Task Force Recommendations
The U.S. Preventative Services Task Force (2018) concluded that "the current evidence is insufficient to assess the balance of benefits and harms of screening for adolescent idiopathic scoliosis in children and adolescents aged 10 to 18 years."

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Unpublished			

NCT01776125	Genetic Evaluation for the Scoliosis Gene(s) in Patients With Neurofibromatosis 1 and Scoliosis	59	Aug 2015 (completed)

NCT: national clinical trial.

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Policy History

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09/01/2011	Medical Policy Committee review
09/14/2011	Medical Policy Implementation Committee approval. New policy.
10/11/2012	Medical Policy Committee review
10/31/2012	Medical Policy Implementation Committee approval.
02/19/2013	Coding updated
04/01/2013	Coding update
10/03/2013	Medical Policy Committee review
10/16/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/04/2014	Medical Policy Committee review
12/17/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
12/03/2015	Medical Policy Committee review
12/16/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/01/2016	Medical Policy Committee review
12/21/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
12/07/2017	Medical Policy Committee review

12/20/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/06/2018	Medical Policy Committee review
12/19/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/05/2019	Medical Policy Committee review
12/11/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/03/2020	Medical Policy Committee review
12/09/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 12/2021

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2019 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	0004M, 81599
HCPCS	No codes
ICD-10 Diagnosis	M41.00-M41.08, M41.112-M41.119, M41.1122-M41.1129, M41.20-M41.27, M41.30, M41.34-M41.35, M41.80-M41.87, M41.9, M96.5

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.