Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 7/1/21**
(See policy history boxes for previous effective dates)

Title: Genetic Testing – DNA Based Testing for Adolescent Idiopathic Scoliosis

Description/Background

ADOLESCENT IDIOPATHIC SCOLIOSIS

Adolescent idiopathic scoliosis (AIS) is the most common pediatric spinal deformity, affecting 1% to 3% of adolescents.[1] 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 becomes rotated axially. 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 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.[2] The Cobb angle is defined as the angle measured between the maximally tilted proximal and distal vertebrae of the curve. 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 have been published by Lonstein and Carlson (1984)[3] and Peterson and Nachemson (1995)[4] to help in triage and treatment decision making about

patients with AIS. Tan et al (2009) recently compared a broad array of factors and concluded that using 30° as an end point, initial Cobb angle magnitude produces the best prediction of progression outcome.[5]

GENETIC ASSOCIATIONS AND SCOLIOSIS

The familial nature of this disease was noted as early as 1968.[6] About one-quarter of patients report a positive family history of disease, and twin studies have consistently supported shared genetic factors.[1] Genome-wide linkage studies have reported multiple chromosomal regions of interest, often not replicated. Ogilvie (2010) has suggested AIS is a complex polygenic trait.[7] Ogilvie et al at Axial Diagnostics published a study evaluating an algorithm using 53 single-nucleotide variant (SNV) markers identified from unpublished genome-wide association studies (GWAS) to differentiate patients unlikely to exhibit severe progression in curvature versus those at considerable risk for severe progression. The clinical validity of this assay has recently been reported in a retrospective case control cohort study using this algorithm.[2]

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, aged 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 in 2010 by Ward et al in an industry-sponsored study.[2] The prognostic algorithm was developed in a cohort of 2192 female patients from prior studies. Candidate genes were selected based on previous GWAS data from the same investigators. The independent effect of each SNV and of 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.

Since publication of the Ward et al (2010) study, subsequent clinical studies were unable to replicate the association of the 53 genetic markers with progression of AIS.[8,9]

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.[8] It appears that the test is no longer commercially available[11,]; the ScoliScore™ AIS Prognostic Test is not listed as available on the Precipio Diagnostics website.[12]

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the

Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Medical Policy Statement

DNA-based testing for adolescent idiopathic scoliosis is experimental/investigational. The peer reviewed medical literature has not demonstrated the clinical utility of this testing.

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

N/A

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:

N/A

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

0004M

Rationale

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

PROGNOSTIC TESTING FOR ADOLESCENT IDIOPATHIC SCOLIOSIS

Clinical Context and Test Purpose

The purpose of the ScoliScore AIS prognostic DNA-based test and other individual single-nucleotide variant (SNV) based tests for scoliosis prognosis is primarily to determine whether patients with scoliosis are at higher likelihood for curve progression. Such patients could undergo more frequent surveillance than they would without testing. The current standard for

management of patients with scoliosis that is not severe enough to undergo bracing or surgery is observation with routine radiographic or clinical follow-up.

The following **PICOs** were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with a diagnosis of adolescent idiopathic scoliosis (AIS) that is not yet severe enough to require bracing or surgery.

Intervention
The intervention of interest is testing for SNVs, including testing with the specific ScoliScore AIS prognostic test, which uses multiple SNVs along with the Cobb angle in an algorithm.

Patients would be seen in the outpatient setting.

Comparator
The following practices are currently being used to make decisions about follow-up for patients with AIS that is not severe enough to require bracing or surgery: routine radiographic or clinical follow-up, at an interval that is generally determined by the individual patient and physician in shared decision making. The test is an adjunct to existing clinical information and test results.

Outcomes
The general outcomes of interest are change in disease severity (i.e., progression in scoliosis curve), morbid events (i.e., development of severe scoliosis, which is generally considered to be a Cobb angle >40°), or symptoms of back pain.

Beneficial outcomes resulting from a true test result, if a true test result is followed by earlier detection of scoliosis by either clinical or radiologic testing, would be earlier detection and treatment of scoliosis. Potential harms from the test include those from a false positive or a false negative: false-positive results could lead to increased clinical or radiologic surveillance, while false-negative tests could lead to premature stopping of surveillance.

The relevant follow-up period depends on the timing of presentation relative to the cessation of growth; however, it is generally over the course of 2 to 3 years.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Study Selection Criteria
For the evaluation of clinical validity of the ScoliScore and other SNV-related testing for scoliosis progression, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the ScoliScore test OR describes the specific SNVs measured;
- Patient/sample clinical characteristics were described;
- Patient/sample selection criteria were described.

Clinical Validity of ScoliScore SNV–Based Testing

In 2010, Ward et al described the validation of the ScoliScore algorithm in a group of patients who had a diagnosis of AIS but who had not been previously involved in any AIS/genotype-related studies.[2] These subjects were preselected by curvature severity (mild, moderate, severe) and assigned into 3 cohorts identified as: (1) a screening cohort of white females; (2) a spinal surgery practice cohort of white females; and (3) a male cohort. Inclusion/exclusion criteria were cited as being used, but not explicitly provided, although a component of cohort development was matching of disease prevalence by severity according to that expected from review of the literature or survey of clinical practices. Ward provided minimal information about the demographics of patients assigned to each cohort. Assignment of curvature severity was performed using expert opinion of a single orthopedic spine surgeon and was supplemented by external blinded review of the spinal surgery practice patients using an outside panel of 3 independent scoliosis experts.

The screening cohort was composed of 277 patients recruited to ensure 85% exhibited mild or improved curves, 12% moderate curve progression, and 3% severe curve progression. Using a risk score cutoff of 41 or less, the predictive value of a negative test (defined as identification of patients without severe curve progression) was 100% (95% confidence interval [CI], 98.6% to 100%). No analysis was performed to demonstrate whether this was a statistically significant improvement in prediction of negatives, given the low initial prevalence of patients expected to exhibit severe progression.

The spine surgery practice cohort was composed of 257 patients recruited to ensure 68% exhibited mild or improved curves, 21%, moderate curve progression, and 11% severe curve progression. Using the risk score cutoff of 41 or less, the predictive value of a negative test (defined as identification of patients without severe curve progression) was 99% (95% CI, 95.4% to 99.6%). No analysis was performed to demonstrate whether this was a statistically significant improvement in prediction of negatives. In the male cohort (n=163), the prevalence of patients with progression to severe curvature was 11% before testing. The negative predictive value (NPV) after testing was 97% (95% CI, 93.3% to 99%).

Although there is a description of positive predictive value calculations using a risk score cutoff of 190 or more, recruitment of patients into this category appears to have been derived from patients pooled from different and undescribed sources, making interpretation difficult.

In 2015, Roye et al reported on an independent validation of the ScoliScore algorithm in a sample of 126 patients with AIS who were enrolled at 2 centers using a retrospective cohort design.[10] Eligible patients had AIS with an initial Cobb angle of 10° to 25° and were white with skeletal immaturity. ScoliScore results were provided as continuous and categoric variables; categories were low (1-50 points), intermediate (51-179 points), or high (180-200 points) risk for progression. Outcomes were defined as progression (curve progression to >40° or requirement for spinal fusion) or non-progression (reached skeletal maturity without curve progression >40°). The mean ScoliScore overall was 103 (SD=60). In unadjusted analysis, the continuous ScoliScore value was not significantly associated with curve progression (odds

ratio [OR], 0.999; 95% CI, 0.991 to 1.006; p=0.664). The proportion of patients with curve progression did not differ significantly by ScoliScore risk group. The ScoliScore test PPV and NPV were 0.27 (95% CI, 0.09 to 0.55) and 0.87 (95% CI, 0.69 to 0.96), respectively.

In 2012, Roye et al reported results in 91 patients evaluated using ScoliScore.[11] Although they noted a positive correlation between Cobb angle and ScoliScore results (r=0.581, p<0.001), ScoliScore appeared to be providing information very different from that observed using standard risk score with a marked increase in low-risk patients and decrease in high-risk patients. However, no clinical end points were examined in association with classification results, and so the interpretation of results observed remains unclear.

In 2016, Bohl et al reported results from a small retrospective cohort study comparing ScoliScore results among patients with AIS undergoing bracing whose scoliosis progressed to those undergoing bracing who did not have progression.[12] The authors contacted 25 patients with AIS treated at a single institution that underwent nighttime bracing; 16 subjects provided saliva samples to allow ScoliScore testing. The authors report that the 8 patients whose curves progressed to greater than 45° had a higher mean ScoliScore than those whose curves did not progress (176 vs. 112, respectively; p=0.03). No patient with a ScoliScore below 135 progressed to greater than 45°. The interpretation of these results is unclear due to the study's small size and potential for selective response bias.

Studies Using SNV Subsets From ScoliScore

Some studies have evaluated subsets of the SNVs used in the ScoliScore algorithm. Tang et al (2015)[13] evaluated the association between 25 of the 53 SNVs used in the Ward et al study (previously described), along with 27 additional SNVs in high linkage disequilibrium with the other SNVs, and severe scoliosis in a case-control study involving 476 AIS patients of French-Canadian background. None of the SNVs was significantly associated with scoliosis severity.

The ScoliScore algorithm was developed and validated in a sample of white patients. Other studies have evaluated the association of specific SNVs from the algorithm in nonwhite populations. In 2015, Xu et al reported on the association between the 53 SNVs in the ScoliScore panel with scoliosis in a retrospective case-control study of 990 female Han Chinese patients with AIS and 1188 age-matched healthy controls.[14] At 4 loci, patients with AIS differed from controls: they had had higher frequency of alleles G at rs12618119 (46.5% vs. 40.2%, OR=1.29; 95% CI, 1.15 to 1.46; p<0.001) and A at rs9945359 (22.6% vs 18.4%; OR=1.29; 95% CI, 1.12 to 1.50; p<0.001), and lower frequency of alleles T at rs4661748 (15.6% vs 19.4%; OR=0.77, 95% CI, 0.66 to 0.90; p<0.001) and C at rs4782809 (42.4% vs 47.4%; OR=0.82, 95% CI, 0.72 to 0.92; p<0.001).

In 2016, Xu et al reported on the association between the 53 SNVs in the ScoliScore panel with scoliosis progression in a retrospective case-control study of 670 female Han Chinese patients with AIS.[15] Patients were identified from a set of patients who visited trialists' scoliosis center for a time period that overlapped with that for the patients in the 2015 Xu study, but it was not specified whether the data overlapped. Of the 670 patients, 313 were assigned to the nonprogression group (defined as a Cobb angle <25° at final follow-up), and 357 were assigned to the progression group (defined as a Cobb angle of >40° at final follow-up). The overall follow-up duration was not specified. At 2 loci, allele frequencies differed between groups: the progression group had a significantly higher frequency of allele A at rs9945359

(25.7% vs. 19.5%; OR=1.42; 95% CI, 1.09 to 1.88; p=0.01) and a significantly lower frequency of allele A at rs17044552 (11.5% vs. 16.4%; OR=0.65; 95% CI, 0.47 to 0.91; p=0.01).

There was no association between the 53 SNVs in the ScoliScore panel and curve progression in an earlier study (2013) of 2117 Japanese patients with AIS.[16]

Clinical Validity of Other SNV Associations With Scoliosis Prognosis

In addition to studies evaluating the clinical validity of the ScoliScore algorithm specifically, a number of other studies have reported results of associations between various SNPs and scoliosis progression. In 2015, Noshchenko et al reported on a systematic review and meta-analysis of predictors of progression in AIS, which included studies evaluating the association between ScoliScore and SNVs and curve progression.[17] In total, reviewers included 25 studies, across a range of physiologic measures. Reviewers selected 2 studies that evaluated ScoliScore—Ward et al (2010)[2] and Bohl et al (2016).[12] Pooled results were presented; however, given the differences in intervention in the studies (Bohl et al evaluated response to bracing), the results are more appropriately considered as individual studies, which are described above in the Clinical Validity of ScoliScore SNV-Based Testing section. Studies evaluating 6 additional SNVs in multiple genes, including *CALM1*, *ER1*, *TPH1*, *IGF1*, *NTF3*, *IL17RC*, and *MTNR1B* (N=7 studies) were included. The level of evidence based on GRADE for the studies was considered very low or low. Estimates for the pooled odds ratios for the association of the variant with the outcome ranged from 1.5 to 3.3. Reviewers concluded that "the levels of association were relatively low with small predictive capacity. All these findings have very low level of evidence due to the limitations of the studies' design and that fact that only one study reported each finding."

Sharma et al (2011) reported genome-wide association study results evaluating 327,000 SNVs in 419 families with AIS that found 3 loci significantly associated with scoliosis progression, which did not include any of the 53 SNVs included in the Ward et al study previously described.[18]

In 2013, Fendri et al reported results from a case-control GWAS of 6 AIS patients and 6 non-AIS controls evaluating differential gene expression profiling in AIS.[19] Gene expression profiles from primary osteoblasts derived from spinal vertebrae of AIS patients (n=6) were compared with profiles from the same cells collected from age- and sex-matched previously healthy patients who underwent spinal surgery for trauma (n=6). One hundred forty-five genes displayed significant gene expression changes in AIS osteoblasts compared with non-AIS osteoblasts. After hierarchical clustering gene ontology analysis, the authors identified 5 groups based on molecular function and biological process that fell into 4 pathways: developmental/growth differentiation of skeletal elements (i.e., *HOXB8*, *HOXB2*, *MEOX2*, *PITX1*), cellular signaling (i.e., *HOXA11*, *BARX1*), connecting structural integrity of the extracellular matrix to the structural integrity of a bone or a muscle fiber (i.e., *COMP*, *HOXA2*, *HOXA11*), and cellular signaling and cartilage damage (*GDF15*).

Studies have also associated polymorphisms in the promoter regions of tissue inhibitor of metalloproteinase-2 and neurotrophin 3 with AIS severity in Chinese populations.[20,21] Replication of these genetic associations is needed.

Section Summary: Clinically Valid
Four retrospective case-control studies have reported on the clinical validity of the marketed ScoliScore test; 2 of them permitted a determination of the association of the test with curve progression, and they have conflicting results and are limited by their retrospective designs. A number of additional studies have reported on the association between scoliosis progression or presence and various other SNVs, with inconsistent results. The evidence is insufficient to conclude clinical validity.

Clinically Useful
A test is clinically useful if use of the results inform management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or testing.

No studies examining the impact of DNA-based predictive testing for scoliosis on health outcomes were identified. The value of early identification and intervention(s) for people at risk for progression of disease and whether laboratory testing improves disease identification beyond clinical evaluation are unknown. It is not possible to construct a chain of evidence for clinical utility due to the lack of clinical validity.

SUMMARY OF EVIDENCE

For individuals with adolescent idiopathic scoliosis (AIS) who receive clinical management with prognostic testing using an algorithm incorporating single-nucleotide variant (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. 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 through 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 disease and whether laboratory testing improves disease identification beyond clinical evaluation is 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, BCBSA received input 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

In 2011, the Scientific Society on Scoliosis Orthopaedic and Rehabilitation Treatment issued guidelines on the conservative treatment of idiopathic scoliosis.[22] These guidelines did not address the role of DNA-based prognostic testing.

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."[23]

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this policy 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	100	Aug 2015 (completed)

NCT: national clinical trial.

Government Regulations

National:

There are no national or local coverage determinations on this topic. No Medicare fee on file.

(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

N/A

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through February 2021, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
3/1/14	12/10/13	1/6/14	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. Additional references added. No change in policy status.
7/1/18	4/17/18	4/17/18	Routine maintenance, updated references. No change in policy status.
7/1/19	4/16/19		Routine 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. Testing is no longer available, policy is recommended for retirement.

Next Review Date: This policy refers to an obsolete procedure and is no longer subject to routine review.

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENETIC TESTING – DNA BASED TESTING FOR ADOLESCENT IDIOPATHIC SCOLIOSIS

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered.
BCNA (Medicare Advantage)	See government section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

N/A