DNA-Based Testing for Adolescent Idiopathic Scoliosis

Policy # 00314
Original Effective Date: 09/14/2011
Current Effective Date: 12/20/2017

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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.*

Background/Overview
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. 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 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 angulation 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. 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 end point, 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 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 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 identify patients unlikely to exhibit severe progression in curvature versus 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 in 2010 by Ward et al in an industry-sponsored study. 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.

As of December 2016, the Transgenomic website did not include any information about the ScoliScore test.

**DA 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 (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). The ScoliScore AIS prognostic DNA-based test (originally developed by Axial Biotech; test rights acquired by Transgenomic in 2013) is available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. FDA has chosen not to require any regulatory review of this test.

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.
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Rationale/Source

CLINICAL CONTEXT AND TEST PURPOSE

The purpose of the ScoliScore AIS prognostic DNA-based test and other individual 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 evaluation of a prognostic genetic test focuses on 3 main principles: (1) analytic validity (technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent); (2) clinical validity (prognostic performance of the test [sensitivity, specificity, positive and negative predictive values] in predicting course of clinical disease); and (3) clinical utility (ie, a demonstration that the prognostic information can be used to improve patient health outcomes).

The following PICOTS were used to select literature to inform this review.

 Patients
The relevant population of interest is individuals with a diagnosis of 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.

 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 (ie, progression in scoliosis curve), morbid events (ie, 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.
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Time
The relevant follow-up period depends on the timing of presentation relative to cessation of growth; however, it is generally over the course of 2 to 3 years.

Setting
Outpatient.

ANALYTICAL VALIDITY
Analytic validity is the ability of a test to accurately and reliably measure the marker of interest. Measures of analytic validity include sensitivity (detection rate), specificity (1 – false-positive rate), reliability (repeatability of test results), and assay robustness (resistance to small changes in preanalytic or analytic variables).

No published reports on analytic performance of the ScoliScore test were identified. It is offered by a CLIA–accredited laboratory and requirements for analytic performance and quality control are components of the CLIA accreditation process.

CLINICAL VALIDITY
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
The development of the ScoliScore algorithm is discussed briefly in the Background section (Ward et al, 2010).

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. 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. 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 nonprogression (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 retrospective results for 91 patients evaluated using ScoliScore. 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 a standard risk score, with a marked increase in low-risk patients and a decrease in high-risk patients. However, no clinical end points were examined in association with classification results, and so 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. Authors contacted 25 patients with AIS treated at a single institution who
underwent nighttime bracing; 16 subjects provided saliva samples to allow ScoliScore testing. Authors reported 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) 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. 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. 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 is not specified whether the data overlap. 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 of 2117 Japanese patients with AIS.

**Clinical Validity of Other SNV Associations With Scoliosis Prognosis**
In addition to studies evaluating the clinical validity of the ScoliScore algorithm specifically, other studies have reported results for associations between SNVs 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. In total, reviewers included 25 studies, across a range of physiologic measures. Reviewers selected 2 studies that evaluated ScoliScore—Ward et al (2010) and Bohl et al (2016). 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.

In 2013, Fendri et al reported results from a case-control study 6 AIS patients and 6 non-AIS controls evaluating differential gene expression profiling in AIS. 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 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 biologic process that fell into 4 pathways: developmental/growth differentiation of skeletal elements (ie, HOXB8, HOXB2, MEOX2, PITX1), cellular signaling (ie, HOXA11, BARX1), connecting structural integrity of the extracellular matrix to the structural integrity of a bone or a muscle fiber (ie, COMP, HOXA2, HOXA11), and cellular signaling and cartilage damage (GDF15).

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

Section Summary: Clinical Validity
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 draw conclusions on clinical validity.
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CLINICAL UTILITY
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 AIS who receive clinical management with prognostic testing with 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. 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.

References

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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
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
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes

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12/07/2017 Medical Policy Committee review
12/20/2017 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
Next Scheduled Review Date: 12/2018

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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:

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2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.
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