I. POLICY

DNA-based prognostic testing for adolescent idiopathic scoliosis is considered investigational. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

Cross-references:

MP-1.120 Interventions for Progressive Scoliosis

II. PRODUCT VARIATIONS

This policy is applicable to all programs and products administered by Capital BlueCross unless otherwise indicated below.

FEP PPO*

*Refer to FEP Medical Policy Manual MP-2.04.74, DNA-Based Testing for Adolescent Idiopathic Scoliosis. The FEP Medical Policy Manual can be found at: www.fepblue.org
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 becomes rotated axially. Deviation can occur anteriorly (a lordotic deviation) or posteriorly (a kyphotic deviation). 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 this practice or alternatively suggesting insufficient evidence for this.

Diagnosis is established by radiologic observation in adolescents (age 10 years until the age of skeletal maturity) of a lateral spine curvature of 10 degrees 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 (less than 25º), moderate (25º to 40º), or severe (more than 40º) in an individual 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 have been published by Lonstein and Carlson(1984) and Peterson and Nachemson (1995) to help in triage and treatment decision making about patients with AIS. Tan et al. have recently compared a broad array of factors and concluded that using 30 degrees 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 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 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 single-nucleotide variant (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 genome-wide association study (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 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 numerical 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.

**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). 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. Food and Drug Administration has chosen not to require any regulatory review of this test.

**IV. RATIONALE**

**Clinical Context and Test Purpose**

The purpose of the ScoliScore AIS prognostic DNA-based test and other individual single-nucleotide variant (SNV) –based test 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.

Validation of genotyping to improve treatment outcomes is a multistep process. In general, important steps in the validation process address the following:

- **Analytic validity**: measures technical performance (i.e., whether the test accurately and reproducibly detects the gene markers of interest**
- **Clinical validity**: measures the strength of the associations between the selected genetic markers and clinical status
- **Clinical utility**: determines whether the use of genotyping for specific genetic markers to guide treatment decisions improves patient outcomes such as survival or adverse event rate compared with standard treatment without

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

**Patients**
The relevant population(s) of interest are individuals with a diagnosis of AIS that is not yet severe enough to undergo 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 undergo bracing or surgery: routine radiographic or clinical follow-up, at an interval that is generally determined by individual patient and physician 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.

**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 analytical performance of the ScoliScore test were identified. It is offered by a Clinical Laboratory Improvement Amendments (CLIA)–accredited laboratory and requirements for analytical 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 Single-Nucleotide Variant–Based Testing
The development of the ScoliScore algorithm is described 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 prevalence of disease by severity according to that expected from review of the literature or survey of clinical practices. There is minimal information provided 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 patients (n=277) 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 patients (n=257) 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 is 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 be 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 and with skeletal immaturity. ScoliScore results were provided as continuous and categorical 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 to >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 in 91 patients evaluated using ScoliScore. Although authors 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. Authors contacted 25 patients with AIS treated at a single institution who 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) evaluated the association between the 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 were 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 non-white 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 from a time period, which overlapped with that for the patients in the 2015 Xu et al study, but it is not specified if 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 is not specified. At 2 loci, allele frequencies differed between groups: the progression group had higher frequency of allele A significantly at rs9945359 (25.7% vs 19.5%; OR=1.42; 95% CI, 1.09 to 1.88; \( p=0.01 \)) and lower frequency of allele 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 of associations between various SNV 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, the review included 25 studies, across a range of physiologic measures. Reviewers included 2 studies that evaluated ScoliScore, Ward et al (2010)² and Bohl et al (2016).¹¹ Pooled results are presented; however, given the differences in intervention in the studies (Bohl et al evaluating response to bracing), the results are more appropriately considered as individual studies, which are described above in the Clinical Validity of ScoliScore Single-Nucleotide Variant–Based Testing section. Studies evaluating 6 additional SNVs in multiple genes, including \textit{CALM1}, \textit{ER1}, \textit{TPH1}, \textit{IGF1}, \textit{NTF3}, \textit{IL17RC}, and \textit{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 results of a GWAS 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.\textsuperscript{17}

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.\textsuperscript{18} 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., \textit{HOXB8}, \textit{HOXB2}, \textit{MEOX2}, \textit{PITX1}), cellular signaling (i.e., \textit{HOXA11}, \textit{BARX1}), connecting structural integrity of the extracellular matrix to the structural integrity of a bone or a muscle fiber (i.e., \textit{COMP}, \textit{HOXA2}, \textit{HOXA11}), and cellular signaling and cartilage damage (\textit{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.\textsuperscript{19,20} Replication of these genetic associations is needed.

\textbf{Section Summary: Clinical Validity}

Four retrospective case-control studies report on the clinical validity of the marketed ScoliScore test; 2 of these allow a determination of the association of the test with curve progression, and these have conflicting results and are limited by their retrospective design. A number of additional studies report on the association of scoliosis progression or presence with various other SNVs, with inconsistent results. The evidence is insufficient to draw conclusions on clinical validity.

\textbf{Clinical Utility}

No studies examining the impact of DNA-based predictive testing for scoliosis on health care 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 an indirect chain of evidence for clinical utility due to the lack of clinical validity.

\textbf{Summary of Evidence}

For individuals with AIS who receive 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 with 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 disorder 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 is unknown, and whether laboratory testing improves disease identification beyond clinical evaluation. The evidence is insufficient to determine the effects of the technology on health outcomes.

**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 (AIS; ScoliScore) should be considered investigational.

**Practice Guidelines and Position Statements**
In 2011, the International Scientific Society on Scoliosis Orthopaedic and Rehabilitation Treatment issued guidelines on the conservative treatment of idiopathic scoliosis. These guidelines did not address the role of DNA-based prognostic testing.

**U.S. Preventive Services Task Force Recommendations**
In 2004, the U.S. Preventive Services Task Force (USPSTF) recommended against the routine screening of asymptomatic adolescents for idiopathic scoliosis (grade D recommendation). No USPSTF recommendations for DNA-based testing for AIS were identified.

**Medicare National Coverage**
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

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

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<th>Table 1. Summary of Key Trials</th>
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<td>Unpublished</td>
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NCT: national clinical trial.
V. DEFINITIONS

N/A

VI. BENEFIT VARIATIONS

The existence of this medical policy does not mean that this service is a covered benefit under the member’s contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member’s individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member’s benefit information or contact Capital for benefit information.

VII. DISCLAIMER

Capital’s medical policies are developed to assist in administering a member’s benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member’s benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Investigational and therefore not covered when used to report DNA-based testing for adolescent idiopathic scoliosis as outlined in policy section above:

<table>
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<th>CPT Codes®</th>
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IX. REFERENCES


DNA-BASED TESTING FOR ADOLESCENT IDIOPATHIC SCOLIOSIS

| POLICY NUMBER | MP-2.244 |

X. POLICY HISTORY

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<thead>
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<td>New policy. Adopted BCBSA. DNA-based testing for adolescent idiopathic scoliosis is investigational.</td>
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