DNA-Based Testing for Adolescent Idiopathic Scoliosis

Policy # 00314
Original Effective Date: 09/14/2011
Current Effective Date: 12/21/2016

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.*

Background/Overview
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 both screening and treatment, patients once diagnosed are frequently closely followed. In cases with significant progression of curvature, both medical (bracing) and surgical (spinal fusion) interventions are considered. Classification tables for likelihood of progressive disease have been constructed to assist in managing patients, but these have not proven to be highly reliable and the impact of their use on outcomes is unknown. The ScoliScore™ AIS prognostic DNA-based test (Transgenomic, Omaha, NE) that uses an algorithm incorporating results of testing for 53 single-nucleotide polymorphisms (SNPs), 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. 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°).

Adolescent idiopathic scoliosis is the most common pediatric spinal deformity. 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 25°), moderate (25° to 40°), or severe (more than 40°) 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.

©2016 Blue Cross and Blue Shield of Louisiana
An independent licensee of the Blue Cross and Blue Shield Association
No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.

Page 1 of 8
DNA-Based Testing for Adolescent Idiopathic Scoliosis

Policy # 00314
Original Effective Date: 09/14/2011
Current Effective Date: 12/21/2016

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 and Peterson and Nachemson to help in triage and treatment decision making about patients with AIS. Tan et al. 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.

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 has recently suggested AIS is a complex polygenic trait. He and colleagues at Axial Diagnostics have published a study evaluating an algorithm using 53 SNP 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 has recently been reported in a retrospective case control cohort study using this algorithm.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
The ScoliScore™ AIS prognostic DNA-based test (originally developed by Axial Biotech, Salt Lake City, UT; test rights acquired by Transgenomic in 2013) has not been approved or cleared by the U.S Food and Drug Administration but is being offered as a laboratory-developed test. The laboratory performing this test is accredited by the Centers for Medicare and Medicaid under the Clinical Laboratory Improvement Amendments of 1988.

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.

Rationale/Source

Introduction
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 to standard treatment without

**Analytical Validity:**
There are no published reports on analytical performance of this test. 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.
DNA-Based Testing for Adolescent Idiopathic Scoliosis

Policy # 00314
Original Effective Date: 09/14/2011
Current Effective Date: 12/21/2016

Clinical Validity
Clinical Validity of ScoliScore Single-Nucleotide Polymorphism–Based Testing
The development and validation of the ScoliScore SNP–based prognostic algorithm were described 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 SNP 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 SNP 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.

The algorithm was validated in a group of patients who had a diagnosis of adolescent idiopathic scoliosis (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%).
DNA-Based Testing for Adolescent Idiopathic Scoliosis

Policy #  00314
Original Effective Date:  09/14/2011
Current Effective Date:  12/21/2016

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 2012, Roye et al. reported results in 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 standard risk score with a marked increase in low-risk patients and decrease in high-risk patients. However, no clinical endpoints were examined in association with classification results, and so the interpretation of results observed remains unclear.

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. The 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.

Clinical Validity of Other SNP 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.

A number of GWASs have attempted to identify genetic loci with associations with AIS progression. Sharma et al. reported results of a GWAS evaluating 327,000 SNPs in 419 families with AIS that found 3 loci significantly associated with scoliosis progression, which did not include any of the 53 SNPs included in the Ward et al. study previously described. Tang et al. evaluated the association between the 53 SNPs used in the Ward et al. study previously described and severe scoliosis in a case control study involving 450 AIS patients of French-Canadian background. There was no association between the 53 SNPs and curve progression in a study of 2117 Japanese patients with AIS.

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. 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 (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).
DNA-Based Testing for Adolescent Idiopathic Scoliosis

Policy # 00314
Original Effective Date: 09/14/2011
Current Effective Date: 12/21/2016

Studies have also associated polymorphisms 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.

Clinical utility
No studies have been performed examining the impact of DNA-based predictive testing for scoliosis on health care outcomes.

Current practice includes careful follow-up of patients. Those with progressive disease are frequently treated with bracing, or in severe cases, with surgical intervention. Careful follow-up and treatment of patients with scoliosis would be expected to have an impact on the criterion standard end point being used to evaluate this test in this study—severe curvature. Test-induced changes in outcome will provide insight into the clinical utility of the test. Because treatment outcome is used as the end point of interest in characterizing the test, changes in outcome may also produce changes in the test’s clinical validity.

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

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td>Genetic Evaluation for the Scoliosis Gene(s) in Patients With Neurofibromatosis 1 and Scoliosis</td>
<td>100</td>
<td>Aug 2015</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

Clinical Input Received Through 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 AIS (ScoliScore) should be considered investigational.

Summary
For use of SNP–based testing in the management of patients with existing AIS, the evidence consists of a number of cross-sectional studies reporting on the clinical validity of the ScoliScore test, along with cross-sectional studies reporting on the association with SNPs in various genes and scoliosis progression. Preliminary clinical validity results for the ScoliScore AIS prognostic DNA-based test indicate a high negative predictive value and an uncertain positive predictive value. A single study has been published reporting 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

©2016 Blue Cross and Blue Shield of Louisiana
An independent licensee of the Blue Cross and Blue Shield Association
No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.
DNA-Based Testing for Adolescent Idiopathic Scoliosis

Policy #  00314
Original Effective Date:  09/14/2011
Current Effective Date:  12/21/2016

provided by testing is statistically or clinically meaningful. Other genetic studies have not demonstrated significant associations between the SNPs used in the ScoliScore and scoliosis progression. Studies have identified additional SNPs 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 SNPs or through an algorithm incorporating SNP results) for predicting scoliosis progression disorder in patients with AIS condition has not been established because studies of the association of DNA-based testing and scoliosis progression have had mixed findings.

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 unclear. Therefore, the evidence is insufficient to permit conclusions about the clinical utility of DNA-based predictive testing for scoliosis.

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 adolescent idiopathic scoliosis were identified.

References

DNA-Based Testing for Adolescent Idiopathic Scoliosis

Policy # 00314
Original Effective Date: 09/14/2011
Current Effective Date: 12/21/2016


Policy History
Original Effective Date: 09/14/2011
Current Effective Date: 12/21/2016
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
Next Scheduled Review Date: 12/2017

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 2015 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.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

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:
DNA-Based Testing for Adolescent Idiopathic Scoliosis

Policy # 00314
Original Effective Date: 09/14/2011
Current Effective Date: 12/21/2016

<table>
<thead>
<tr>
<th>Code Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>81599, 0004M</td>
</tr>
<tr>
<td>HCPCS</td>
<td>No codes</td>
</tr>
<tr>
<td>ICD-10 Diagnosis</td>
<td>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</td>
</tr>
</tbody>
</table>

*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. 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: 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.