



BlueCross BlueShield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association.

DNA-Based Testing for Adolescent Idiopathic Scoliosis

Policy # 00314

Original Effective Date: 09/14/2011

Current Effective Date: 10/16/2013

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

The ScoliScore™[†] AIS prognostic DNA-based test (Axial Biotech, Salt Lake City, UT) is a saliva-based genetic test designed to predict the risk of progression of scoliosis in patients with AIS. The test 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 (ranging from 1 to 200), which can be used qualitatively or quantitatively to predict the likelihood of spinal curve progression. The test is intended for white (Caucasian) patients with a primary diagnosis of AIS between the ages of 9 and 13 years with a mild scoliotic curve (defined as < 25°).

Adolescent idiopathic scoliosis 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 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.

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.

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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 (Axial Biotech, Salt Lake City, UT) has not been approved or cleared by the FDA but is being offered as a laboratory-developed test. The laboratory performing this test is accredited by the Centers for Medicare and Medicaid (CMS) under the Clinical Laboratory Improvement Amendments of 1988 (CLIA).

The FDA has indicated an interest in changing its policy for use of enforcement discretion in the oversight of laboratory-developed tests, but the status of this proposed change in policy and the impact of any particular laboratory-developed test are currently unknown.

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

Literature Review

Analytical Validity:

There are no published reports on analytical performance of this test. It is offered by a CLIA-accredited laboratory and requirements for analytical performance and quality control are components of this process.

Clinical Validity:

Ward et al. recently described a company-sponsored clinical validation study of a DNA-based prognostic test to predict spinal curve progression in AIS. This test involves use of a proprietary algorithm to integrate information from 53 SNPs identified as exhibiting an association with AIS in a case-controlled GWAS study of 2,750 patients. The GWAS was used to develop a 1 to 200 scoring system. A cut-point of 40 or less was selected during the GWAS to identify patients at low risk (less than 1%) of developing severe curvatures



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requiring surgical intervention. Following generation of data, an analysis of patients with scores of 190 or greater was performed to determine risk for developing severe curves.

Clinical validation of this test was performed in a retrospective analysis of cases preselected by curvature severity (mild, moderate, or 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 = 176) recruited to ensure 85% exhibited mild or improved curves, 12% moderate curve progression, and 3% severe curve progression. Using a risk score cut-off of 41 or less, the predictive value of a negative test (defined as identification of patients without severe curve progression) was 100% (95% confidence intervals [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 = 133) recruited to ensure 68% exhibited mild or improved curves, 21% moderate curve progression, and 11% severe curve progression. Using the risk score cut-off 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 after testing was 97% (95% CI: 93.3 to 99%).

Although there is a description of positive predictive value in patients exhibiting high-risk score values, recruitment of patients into this category appears to be derived from patients pooled from different and undescribed sources, making interpretation difficult.

A subsequent GWAS evaluating 327,000 SNPs in 419 families with AIS failed to duplicate the associations reported in the study by Ward et al. There was no association between the 53 SNPs and curve progression in a study of 2,117 Japanese patients with AIS.

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 ($r = .581$, $p < 0.001$), ScoliScore appeared to be providing information very different from that observed using standard risk score with a marked increase



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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.

Clinical Utility:

No studies have been performed examining the impact of testing 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 gold standard endpoint 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 endpoint of interest in characterizing the test, changes in outcome may also produce changes in the test's clinical validity.

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 two specialty societies and four 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

Idiopathic adolescent scoliosis 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.

Investigators affiliated with the manufacturer of the test have recently reported on use of an algorithm incorporating results of 53 SNPs along with the Cobb angle to predict progression of scoliosis. Preliminary clinical validity results for the ScoliScore AIS prognostic DNA-based test are available, indicating 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 provided by testing is statistically or clinically meaningful. A similar GWAS study failed to identify overlapping SNPs for identification of disease progression (prognosis). No association was found between the 53 SNPs and curve progression in Japanese patients with AIS.

The clinical utility of the test remains unknown. 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

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intervention(s) for individuals at risk for progression of disease is unclear. As a result, DNA-based testing for AIS is considered investigational until results of further research on both clinical validity and utility have been reported.

References

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11. Roye BD, Wright ML, Williams BA et al. Does ScoliScore provide more information than traditional clinical estimates of curve progression? Spine (Phila Pa 1976) 2012 [Epub ahead of print].

Coding

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

Code Type	Code
CPT	81599, 0004M
HCPSCS	No code
ICD-9 Diagnosis	737.30 thru 737.39
ICD-9 Procedure	No code

Policy History

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09/01/2011 Medical Policy Committee review

09/14/2011 Medical Policy Implementation Committee approval. New policy.

10/11/2012 Medical Policy Committee review

10/31/2012 Medical Policy Implementation Committee approval.

02/19/2013 Coding updated

04/01/2013 Coding update

10/03/2013 Medical Policy Committee review

10/16/2013 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 10/2014

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

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

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