DNA-Based Testing for Adolescent Idiopathic Scoliosis

**Section**
2.0 Medicine

**Effective Date**
August 29, 2014

**Subsection**
2.04 Pathology/Laboratory

**Original Policy Date**
August 29, 2014

**Next Review Date**
August 2015

**Description**

The ScoliScore™ AIS (adolescent idiopathic scoliosis) 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°).

**Related Policies**

None

**Policy**

DNA-based prognostic testing for adolescent idiopathic scoliosis is considered investigational.

**Policy Guidelines**

The ScoliScore™ AIS (adolescent idiopathic scoliosis) prognostic DNA-based test has a specific CPT code:

- **0004M**: Scoliosis, DNA analysis of 53 single nucleotide polymorphisms (SNPs), using saliva, prognostic algorithm reported as a risk score

These pathology tests are commercially available only at a single reference laboratory, Axial Biotech (Salt Lake City, UT). The sputum specimen is mailed to Axial Biotech for analysis.

**Benefit Application**

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.
Some state or federal mandates (e.g., Federal Employee Program (FEP)) prohibit Plans from denying Food and Drug Administration (FDA) - approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Rationale

Background

Adolescent idiopathic scoliosis (AIS) is the most common pediatric spinal deformity, affecting 1% to 3% of adolescents.(1) This disease, of unknown etiology, occurs in otherwise healthy children with the onset of, and highly correlated with, the adolescent growth spurt. The vertebrae become misaligned such that the spine deviates from the midline laterally and becomes rotated axially. Deviation can occur anteriorly (a lordotic deviation), posteriorly (a kyphotic deviation), or laterally. Although AIS affects females and males in a nearly 1:1 ratio, progression to severe deformity occurs more often in females. Because the disease can have rapid onset and produce considerable morbidity, school screenings have been recommended. However, screening remains somewhat controversial, with conflicting guidelines supporting this practice or alternatively suggesting an insufficiency of 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° or more, as measured using the Cobb angle.(2) 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 have been published by Lonstein and Carlson(3) and Peterson and Nachemson(4) to help in triage and treatment decision making about patients with AIS. Tan et al.(5) recently compared a broad array of factors and concluded that using 30° as an end point, initial Cobb angle magnitude produces the best prediction of progression outcome.

The familial nature of this disease was noted as early as 1968.(6) About one-quarter of patients report a positive family history of disease, and twin studies have consistently supported shared genetic factors.(1) Genome-wide linkage studies have reported multiple chromosomal regions of interest, often not replicated. Ogilvie has recently suggested AIS is a complex polygenic trait.(7) He et al. at Axial Diagnostics have published a study evaluating an algorithm using 53 single nucleotide polymorphisms (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.(2)

Regulatory Status

The ScoliScore™ AIS prognostic DNA-based test (Axial Biotech, Salt Lake City, UT) has not been approved or cleared by the U.S Food and Drug Administration (FDA) 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.

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.

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 with standard treatment

Literature Review

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.

Clinical Validity

**Clinical validity of ScoliScore SNP-based testing**: In 2010, Ward et al.(2) 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 genome-wide association studies (GWAS) study of 2,750 patients. The GWAS was used to develop a 1 to 200 scoring system. A cutpoint of 40 or less was selected during the GWAS to identify patients at low risk (<1%) of developing severe curvatures 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(2) was performed in a retrospective analysis of cases 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=176) 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 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 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 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=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.

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 genetic testing for scoliosis prognosis: In 2013, Fendri et al. reported results from a case-control GWAS study 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 (i.e., HOXB8, HOXB2, MEOX2, PITX1), cellular signaling (i.e., HOXA11, BARX1), connecting structural integrity of the extracellular matrix to the structural integrity of a bone or a muscle fiber (i.e., COMP, HOXA2, HOXA11), and cellular signaling and cartilage damage (GDF15).

Studies have also associated polymorphisms in the promoter regions of tissue inhibitor of metalloproteinase-2 and neurotrophin 3 with AIS severity in Chinese populations. 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. Currently, 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

A search of online database ClinicalTrials.gov in August 2014 identified the following studies that use DNA-based testing in the evaluation of scoliosis:

- Genetic Evaluation for the Scoliosis Gene(s) in Patients With Neurofibromatosis 1 and Scoliosis (NCT01776125): This is a retrospective observational cohort study designed to compare genetic profiles on the ScoliScore among patients with neurofibromatosis with dystrophic scoliosis with those with nondystrophic scoliosis. Enrollment is planned for 100 subjects; the study completion date is listed as August 2013, but no published results were identified.

Summary

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.

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 genome-wide association 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. Studies have identified additional SNPs that may be associated with AIS severity, but these associations have not been reliably replicated. The clinical utility of the DNA-based predictive testing for scoliosis is 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 intervention(s) for people 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.

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.

Medicare National Coverage

There is no national coverage determination (NCD).

References


**Documentation Required for Clinical Review**

- No records required

**Coding**

This Policy relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

IE

**The following services are considered investigational and therefore not covered for any indication.**

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<thead>
<tr>
<th>Type</th>
<th>Code</th>
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<td>0004M</td>
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<td>ICD-10 Procedure</td>
<td>For dates of service on or after 10/01/2015</td>
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**Medical Policy**

**ICD-10 Diagnosis**

For dates of service on or after 10/01/2015

M41.122 - M41.129  
Adolescent idiopathic scoliosis, code range

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**Policy History**

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

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<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
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<tr>
<td>8/29/2014</td>
<td>BCBSA Medical Policy adoption</td>
<td>Medical Policy Committee</td>
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**Definitions of Decision Determinations**

**Medically Necessary:** A treatment, procedure or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California / Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a Split Evaluation, where a treatment, procedure or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

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**Prior Authorization Requirements**

This service (or procedure) is considered **medically necessary** in certain instances and **investigational** in others (refer to policy for details).

For instances when the indication is **medically necessary**, clinical evidence is required to determine **medical necessity**.

For instances when the indication is **investigational**, you may submit additional information to the Prior Authorization Department.

Within five days before the actual date of service, the Provider MUST confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should also be directed to the Prior Authorization Department. Please call 1-800-541-6652 or visit the Provider Portal www.blueshieldca.com/provider.
The materials provided to you are guidelines used by this plan to authorize, modify, or deny care for persons with similar illness or conditions. Specific care and treatment may vary depending on individual need and the benefits covered under your contract. These Policies are subject to change as new information becomes available.