Introduction

Scoliosis is a condition in which the spine abnormally curves to the side. The abnormal curving starts for no known reason (it is “idiopathic”), and usually begins in adolescence. The curve may be mild or severe, but most of the time it is not painful and does not cause any problems. However, if the curve becomes severe it can put pressure on the lungs and heart. This can make it harder to breathe and affect how well the heart can pump blood. Severe curvature may need to be corrected with surgery.

A genetic test (ScoliScore™) has been developed that is supposed to predict whether a child’s mild to moderate scoliosis will become severe. Medical studies have not shown that this test is effective or helpful in managing patients. For this reason, genetic testing for idiopathic scoliosis is considered to be unproven (investigational).

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
Policy Coverage Criteria

<table>
<thead>
<tr>
<th>Testing</th>
<th>Investigational</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testing for adolescent idiopathic scoliosis</td>
<td>DNA-based prognostic testing for adolescent idiopathic scoliosis is considered investigational.</td>
</tr>
</tbody>
</table>

Coding

Note: The ScoliScore™ AIS (adolescent idiopathic scoliosis) prognostic DNA-based test is a saliva-based genetic test designed to predict the risk of progression of scoliosis in patients with AIS. The provider is Axial Biotech, Salt Lake City, UT (aka, Transgenomic, Omaha, NE).

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>CPT</td>
<td></td>
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<tr>
<td>0004M</td>
<td>Scoliosis, DNA analysis of 53 single nucleotide polymorphisms (SNPs), using saliva, prognostic algorithm reported as a risk score</td>
</tr>
<tr>
<td>81599</td>
<td>Unlisted multianalyte assay with algorithmic analysis</td>
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</tbody>
</table>

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Related Information

Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients. Genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.
Benefit Application

These pathology tests are commercially available only at a single reference laboratory, Transgenomic.

Evidence Review

Description

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 screening and treatment, patients are frequently closely followed once they have been diagnosed. In cases with significant progression of curvature, both medical (bracing) and surgical (spinal fusion) interventions are considered. The ScoliScore AIS prognostic DNA-based test uses an algorithm incorporating results of testing for 53 single-nucleotide variants (SNVs), along with the patient’s presenting spinal curve (Cobb angle), to generate a risk score (range, 1-200). This score can be used qualitatively or quantitatively to predict the likelihood of spinal curve progression.

Background

Adolescent Idiopathic Scoliosis

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 laterally in a “C” or “S” shape. 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 a 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**

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 angle measured between the maximally tilted proximal and distal vertebrae of the curve. The curvature is considered mild (<25°), moderate (25°-40°), or severe (>40°) in a patient who is still growing. Once diagnosed, patients must be monitored over several years, usually with serial radiographs, for curve progression.

**Treatment**

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)¹ and Peterson and Nachemson (1995)⁴, help in triage and treatment decision making about patients with AIS. Tan et al. (2009) compared a broad array of factors and concluded that “Initial Cobb angle magnitude is the most important predictor of long-term curve progression and behavior past skeletal maturity.” Additionally, they suggest that “…an initial Cobb angle of 25° (was) an important threshold magnitude for long-term curve progression.”⁵

**Genetic Associations and Scoliosis**

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 (2010) has suggested AIS is a complex polygenic trait.⁷ Ogilvie et al published a study evaluating an algorithm using 53 single-nucleotide variants (SNV) markers identified from unpublished genome-wide association studies (GWAS) in order to differentiate patients unlikely to exhibit severe progression in curvature from those at considerable risk for severe progression. The clinical validity of this assay has recently been reported in a 2010 retrospective case-control cohort study using this algorithm.²
**ScoliScore AIS**

The ScoliScore AIS prognostic DNA-based test (Transgenomic), 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) that can be used qualitatively or quantitatively to predict the likelihood of spinal curve progression. The test is intended for Caucasian patients, aged 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 the industry-sponsored study discussed above. 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 studies 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.

The ScoliScore™ AIS Prognostic Test was originally developed by Axial Biotech with test rights acquired by Transgenomic in 2013. In 2015, Transgenomic divested its Genetic Assays & Platforms Business Unit to ADSTEC Corp. In June 2017, Transgenomic was acquired by Precipio Diagnostics in a reverse merger transaction. It does appear that the test remains commercially available.

**Summary of Evidence**

For individuals with AIS who receive clinical management with prognostic testing using 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 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 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 are unknown. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Ongoing and Unpublished 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>
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<tr>
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<tr>
<td>NCT01776125</td>
<td>Genetic Evaluation for the Scoliosis Gene(s) in Patients With Neurofibromatosis 1 and Scoliosis</td>
<td>100</td>
<td>Aug 2015 (completed)</td>
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**Clinical Input Received from Physician Specialty Societies and Academic Medical Centers**

While the various physician specialty societies and academic medical centers may provide appropriate reviewers who collaborate with and make recommendations during this process, 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.
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 do 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). This recommendation is currently being updated. 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.

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). 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.

References


<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>10/11/11</td>
<td>New Policy – Add to Pathology/Laboratory section. Policy created with literature search through June 2011; considered investigational.</td>
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<td>05/24/12</td>
<td>Policy renumbered to 12.04.74 (previously 2.04.74) and reassigned to new Genetic Testing category.</td>
</tr>
<tr>
<td>10/26/12</td>
<td>Replace policy. Rationale section revised based on literature review through June 2012 and results of clinical vetting. Reference 9 added. ICD-10 codes are now effective 10/01/2014. Code 83912 added. Policy statement unchanged.</td>
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<td>01/14/13</td>
<td>Coding update. CPT codes 83890 – 83913 deleted as of 12/31/12; CPT codes 81200 – 81479 and 81599, effective 1/1/13, are added to the policy.</td>
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<td>05/14/13</td>
<td>Update Related Policies. Add 12.04.91.</td>
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<td>07/12/13</td>
<td>Coding update. MAAA code 0004M added to the policy.</td>
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<tr>
<td>09/27/13</td>
<td>Replace policy. Policy updated with literature review through 6/18/13; reference 9 added; policy statement unchanged.</td>
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<tr>
<td>09/08/14</td>
<td>Annual Review. Policy updated with literature review through June 6, 2014; references 11-15 added. No change to policy statement.</td>
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<td>09/08/15</td>
<td>Annual Review. Added to the Appendix, Table 1. Categories of Genetic Testing Addressed in This Policy. Policy updated with literature review through June 1, 2015; reference 11 added. Policy statement unchanged.</td>
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<tr>
<td>11/01/16</td>
<td>Annual Review, approved October 11, 2016. Policy updated with literature review through September 15, 2016; reference 18 added. No change to policy statement.</td>
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<tr>
<td>09/22/17</td>
<td>Policy moved into new format. No changes to policy statements.</td>
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Italiano (Italian):
