MEDICAL POLICY – 12.04.74
DNA-Based Testing for Adolescent Idiopathic Scoliosis

BCBSA Ref. Policy: 2.04.74
Effective Date: April 1, 2017
Last Revised: Sept. 22, 2017
Replaces: 2.04.74

RELATED MEDICAL POLICIES:
None

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | CODING | RELATED INFORMATION
EVIDENCE REVIEW | REFERENCES | HISTORY

∞ Clicking this icon returns you to the hyperlinks menu above.

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 the likelihood of a child’s mild to moderate scoliosis becoming 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

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

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>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td></td>
</tr>
<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>
</tr>
</tbody>
</table>

**Note:** CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing.
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 both 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**

AIS is the most common pediatric spinal deformity, affecting 1% to 3% of adolescents. This disease, of unknown etiology, occurs in otherwise healthy children. Typically, the onset is highly correlated with the adolescent growth spurt. The vertebrae become misaligned such that the spine deviates laterally from the midline and becomes rotated axially. Deviation can also 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 an insufficiency of evidence for this.
Diagnosis in adolescents (age 10 years until the age of skeletal maturity) is established by radiologic documentation of a lateral spine curvature of 10° 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 (<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. 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.

The risk of 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 with making triage and treatment decisions in patients with AIS. Tan et al. (2009) 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.

**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 polymorphism (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.

**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). This score 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°).
The development and validation of the ScoliScore 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 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 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.

As of December 2016, the Transgenomic website did not include any information about the ScoliScore test.

Summary of Evidence

For use of single-nucleotide polymorphisms (SNP)-based testing in the management of patients with existing adolescent idiopathic scoliosis (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 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.
Ongoing and Unpublished Clinical Trials

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

Table 1. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unpublished</td>
<td></td>
<td></td>
<td></td>
</tr>
<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>
</tr>
</tbody>
</table>

NCT: national clinical trial.

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). 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). 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.

References


**History**

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<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>
</tr>
<tr>
<td>Date</td>
<td>Comments</td>
</tr>
<tr>
<td>------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<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>
</tr>
<tr>
<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>
</tr>
<tr>
<td>09/08/15</td>
<td>Update Related Policies. Add 12.04.91.</td>
</tr>
<tr>
<td>11/01/16</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>
</tr>
<tr>
<td>09/22/17</td>
<td>Policy moved into new format. No changes to policy statements.</td>
</tr>
</tbody>
</table>

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.

**Scope:** Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.
Discrimination is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:
• Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  • Qualified sign language interpreters
  • Written information in other formats (large print, audio, accessible electronic formats, other formats)
• Provides free language services to people whose primary language is not English, such as:
  • Qualified interpreters
  • Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:
Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5592. TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can also file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.


Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost. Call 800-722-1471 (TTY: 800-842-5357).

Arabic (Arabic):
لا يمكن للطبيعة أو العاملية أن تحدث الحصول عليه من خلال Premera Blue Cross. حصولك على هذه المعلومات والسريعة في هذا الإشعار. تقدم لنا ترتيبات يمكن أن تتوجع للسُرعة في تأجيل الحصول على هذه المعلومات في استخدامك. يقع عبر التفاضل، يقع على ذلك الحصول على هذه المعلومات والسريعة في تقديم كل تكلفة للحصول على تكلفة عامة. لحول الحصول على تكلفة عامة 800-722-1471 (TTY: 800-842-5357).

Chinese (Chinese):
本通知有重要的訊息。本通知可能有關於您透過 Premera Blue Cross 提交的申請或保單的重要訊息。本通知可能有重要的日期。您可能需要在截止日期之前採取行動，以保留您的健康保險或費用補貼。您有權利免費以您的母語得到本訊息和幫助。請接電話 800-722-1471 (TTY: 800-842-5357).

Français (French):

Kreyòl ayisyen (Creole):

Deutsche (German):

Hmoob (Hmong):
Tsaab ntaww tshaj xo no muaj cov ntsiab lus tseem ceeb. Tej zaum tsab ntaww tshaj xo no muaj cov ntsiab lus tseem ceeb boj koj dain tmaw thov kev pab los yoy koj kvos kev pab cuam los ntawm Premera Blue Cross. Tej zaum muaj cov hnb tseem ceeb uss sau rau hauv daim ntaww no. Tej zaum koj tooy jwav taa uu gya yam uss peb koj us tiis pub dhaus coven cajy ngoy uas teev tseeg rau hauv daim ntawm no. Tej zaum koj jwav taa uu gya yam uss peb koj us tiis pub dhaus coven cajy ngoy uas teev tseeg rau hauv daim ntawm no. Tej zaum koj tooy jwav taa uu gya yam uss peb koj us tiis pub dhaus caij nyoog uas teev tseg rau hauv daim ntawm no. Tej zaum koj tooy jwav taa uu gya yam uss peb koj us tiis pub dhaus caij nyoog uas teev tseg rau hauv daim ntawm no. Tej zaum koj tooy jwav taa uu gya yam uss peb koj us tiis pub dhaus caij nyoog uas teev tseg rau hauv daim ntawm no.

Ilokano (Ilocano):
Daytoy a Pakdaa ket naglaon iti Napateng nga Impomarsion. Daytoy a pakdaa mabalin nga adda ket naglaon iti napateng nga impomarsion maiyanggep iti aplikasyon wenyen coverage babaen iti Premera Blue Cross. Daytoy ket mabalin dagiti importante a pelsa iti daytoy a pakdaa. Mabalin nga adda rumbeng nga araimenedo nga adda sasay dagiti partikular a naituding nga adda alaw tapno mapagtailandeyo ti coverage ti saluy-an wenyen tulong kadagiti gastos. Adda karbenganyo a mangala iti daytoy nga impomarsion ken tulong iti bukodyo a pagasasao nga awan ti bayadanyo. Tumawag ti numero nga 800-722-1471 (TTY: 800-842-5357).

Italiano (Italian):

Oromoo (Cushite):
Premera Blue Cross

This notice contains important information. Premera Blue Cross must provide this notice in a timely fashion for you to benefit from your health care plan. This notice may contain key dates for your plan that you should consider when planning for your health care.

Español (Spanish): Este Aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud o cobertura a través de Premera Blue Cross. Es posible que haya fechas claras en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica y ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).

Tagalog (Tagalog): Ang Paunawa na ito ay naglalarawan ng malahangal impormasyon. Ang paunawa na ito ay naglalarawan ng mga mahalagang impormasyon tungkol sa iyong aplikasyon o pagsakop sa pagsasagamitan ng Premera Blue Cross. Maaaring may mga mahalagang petsa dito sa paunawa. Maaring tumawag ngayon para sa tulong na dapat na makakuha ng ganitong impormasyon.