Protocol

DNA-Based Testing for Adolescent Idiopathic Scoliosis

(20474)

Medical Benefit		**Effective Date**: 01/01/18	**Next Review Date**: 09/18
Preauthorization	No	**Review Dates**: 01/12, 09/12, 09/13, 09/14, 09/15, 09/16, 09/17	

This protocol considers this test or procedure investigational. If the physician feels this service is medically necessary, preauthorization is recommended.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: • With adolescent idiopathic scoliosis	Interventions of interest are: • Clinical management with prognostic testing with an algorithm incorporating single-nucleotide variants-based testing	Comparators of interest are: • Routine clinical management (radiologic and clinical follow-up)	Relevant outcomes include: • Symptoms • Morbid events • Change in disease status

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, once diagnosed, patients are frequently closely followed. 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, one to 200), which can be used qualitatively or quantitatively to predict the likelihood of spinal curve progression.

Summary of Evidence

For individuals with AIS who receive clinical management with prognostic testing with an algorithm incorporating single-nucleotide variant (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 between 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 through 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 is unknown. The evidence is insufficient to determine the effects of the technology on health outcomes.

Policy

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

Policy Guidelines

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.

Medicare Advantage

For Medicare Advantage DNA-based prognostic testing for adolescent idiopathic scoliosis is unlikely to impact therapeutic decision-making in the clinical management of the patient and is considered **not medically necessary.**

Background

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 rotates 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 and not supporting this practice.

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, by Lonstein and Carlson (1984)[3] 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 using 30° as an end point, initial Cobb angle magnitude produces the best prediction of progression outcome.[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 at Axial Diagnostics published a study evaluating an algorithm using 53 single-nucleotide variant (SNV) 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 was reported in a 2010 retrospective case-control cohort study using this algorithm.[2]

ScoliScore AIS

The ScoliScore AIS prognostic DNA-based test (Transgenomic), which 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, one to 200), can be used qualitatively or quantitatively to predict the likelihood of spinal curve progression. The test is intended for white (Caucasian) patients, ages nine 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.[2] 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 one 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.[8]

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.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced

procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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23. National Government Services, Inc. (Primary Geographic Jurisdiction - Illinois, New York - Entire State, Connecticut, Massachusetts, Maine, New Hampshire, Rhode Island, Vermont, Wisconsin, Minnesota) Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000), Revision Effective Date for services performed on or after 06/01/2017.