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Medical Policy Manual Genetic Testing, Policy No. 45

DNA-Based Testing for Adolescent Idiopathic Scoliosis

Effective: February 1, 2019

Next Review: December 2019
Last Review: January 2019

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

DNA-based testing for adolescent idiopathic scoliosis is intended to help determine the risk of spinal curve progression to facilitate the treatment plan.

MEDICAL POLICY CRITERIA

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

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

None

BACKGROUND

Adolescent idiopathic scoliosis (AIS) is a disease of unknown etiology that causes mild to severe spinal deformity in approximately 1% to 3% of adolescents.[1] Diagnosis of AIS 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 (spinal curve).[2] Curvature is considered mild (less than 25º), moderate (25º to 40º), or severe (more than 40º) in an individual still growing. While there is controversy about the value of both screening and treatment, 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.

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.[3,4] A recent testing algorithm has been developed to identify patients unlikely to exhibit severe progression in curvature versus those at considerable risk for severe progression.[5] The ScoliScore™ AIS (adolescent idiopathic scoliosis) prognostic DNA-based test that uses an algorithm incorporating results from 53 single nucleotide variants (SNVs), along with the patient's presenting spinal curve (Cobb angle) generate a risk score (range, 1-200), which can be used to predict the likelihood of spinal curve progression to triage patients who would benefit from individualized treatment regimens based upon their given risk score. The test is intended for Caucasian patients with a primary diagnosis of AIS between the ages of nine and thirteen years with a mild scoliotic curve (defined as <25º).

REGULATORY STATUS

The ScoliScore™ AIS (adolescent idiopathic scoliosis) prognostic DNA-based test (Originally developed by Axial Biotech, Salt Lake City, UT; test rights acquired by Transgenomic in 2013) 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 (CMS) under the Clinical Laboratory Improvement Amendments of 1988 (CLIA).

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017.[6] According to this nomenclature, the term "variant" is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as "mutation." Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

Validation of the clinical use of any genetic test focuses on three main principles:

1. The analytic validity of the test, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent;
2. The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. The clinical utility of the test, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

The focus of the following literature appraisal is on evidence related to the clinical utility of testing.

ANALYTIC 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

In 2015, Noshchenko published results from a systematic review with meta-analysis that spanned both ScoliScore single-nucleotide polymorphism-based testing, and other single-nucleotide polymorphism associations with scoliosis prognosis.[7] The review included 25 studies, and all showed statistically significant or borderline association between the severity or progression of AIS with the following characteristics:

- An increase of the Cobb angel or axial rotation during brace treatment;
- Decrease of the rib-vertebral angle at the apical level of the convex side during brace treatment;
- Initial Cobb angle severity (>25^{o});
- Osteopenia;
- Patient less than 13 years of age at diagnosis;
- Premenarche status;
- Skeletal immaturity;
- Thoracic deformity;
- Brain stem vestibular dysfunction; and
- Multiple indices combining radiographic, demographic, and psychological characteristics.

The predictive value of all findings were limited, and the levels of evidence were low. The pooled results of brace treatment outcomes demonstrated that around 27% of patients with AIS experiences exacerbation of the spine deformity during or after brace treatment, and 15% required surgical correction. However, the level of evidence is again low due to the limitation of the studies included in the systematic review. The authors concluded that the review did not reveal any methods for the prediction of progression in AIS that could be recommended for clinical use as diagnostic criteria.

Clinical Validity of ScoliScore Single-Nucleotide Variant-Based Testing

The development and validation of the ScoliScore single-nucleotide variant (SNV) –based prognostic algorithm were described by Ward 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 genome-wide association study (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 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 numerical 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 algorithm was validated in a group of patients who had a diagnosis of adolescent idiopathic scoliosis (AIS) but who had not been previously involved in any AIS/genotype-related studies. These subjects were preselected by curvature severity (mild, moderate, or severe) and assigned into three 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 three independent scoliosis experts.

The screening cohort was composed of patients (n=277) 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 interval [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=257) 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 (NPV) after testing was 97% (95% CI, 93.3% to 99%).

Although there is a description of positive predictive value calculations using a risk score cutoff of 190 or more, recruitment of patients into this category appears to be derived from patients pooled from different and undescribed sources, making interpretation difficult.

In 2016, Bohl evaluated 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.[8] Eleven 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 eight patients whose curves progressed to greater than 45 degrees 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 45degrees. The interpretation of these results is unclear due to the study’s small size and potential for selective response bias.

In 2015, Roye evaluated an independent validation of the ScoliScore algorithm in a sample of 126 patients with AIS who were enrolled at two centers using a retrospective cohort design. Nine eligible patients had AIS with an initial Cobb angle of 10° to 25° and were white and with skeletal immaturity.[9] ScoliScore results were provided as continuous and categorical

variables; categories were low (1-50 points), intermediate (51-179 points), or high (180-200 points) risk for progression. Outcomes were defined as progression (curve progression to >40 degrees or requirement for spinal fusion) or nonprogression (reached skeletal maturity without curve progression to >40 degrees). The mean ScoliScore overall was 103 (SD=60). In unadjusted analysis, the continuous ScoliScore value was not significantly associated with curve progression (odds ratio [OR], 0.999; 95% CI, 0.991 to 1.006; p=0.664). The proportion of patients with curve progression did not differ significantly by ScoliScore risk group. The ScoliScore test PPV and NPV were 0.27 (95% CI, 0.09 to 0.55) and 0.87 (95% CI, 0.69 to 0.96), respectively.

In 2012, Roye reported results in 91 patients evaluated using ScoliScore.[10] Although they noted a positive correlation between the 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.

Clinical Validity of Other Single-Nucleotide Variant Associations with Scoliosis Prognosis

In addition to studies evaluating the clinical validity of the ScoliScore algorithm specifically, a number of other studies have reported results of associations between various SNVs and scoliosis progression.

In 2016, Xu evaluated on the association between the 53 SNVs in the ScoliScore panel with scoliosis progression in a retrospective case-control study of 670 female Han Chinese patients with AIS.[11] Fourteen patients were identified from a set of patients who visited trialists' scoliosis center from a time period, which overlapped with that for the patients in the 2015 Xu study, but it is not specified if the data overlap. Of the 670 patients, 313 were assigned to the nonprogression group (defined as a Cobb angle <25 degrees at final follow-up) and 357 were assigned to the progression group (defined as a Cobb angle of >40 degrees at final follow-up). The overall follow-up duration is not specified. At two loci, allele frequencies differed between groups: the progression group had higher frequency of allele A significantly at rs9945359 (25.7% vs 19.5%; OR=1.42; 95% CI, 1.09 to 1.88; p=0.01) and lower frequency of allele at rs17044552 (11.5% vs 16.4%; OR=0.65; 95% CI, 0.47 to 0.91; p=0.01). There was no association between the 53 SNPs SNVs in the ScoliScore panel and curve progression in an earlier study of 2117 Japanese patients with AIS.[12]

In 2015, Xu evaluated the association between the 53 SNVs in the ScoliScore panel with scoliosis in a retrospective case-control study of 990 female Han Chinese patients with AIS and 1188 age-matched healthy controls.[13] At four loci, patients with AIS differed from controls: they had had higher frequency of alleles G at rs12618119 (46.5% vs 40.2%, OR=1.29; 95% CI, 1.15 to 1.46; p<0.001) and A at rs9945359 (22.6% vs 18.4%; OR=1.29; 95% CI, 1.12 to 1.50; p<0.001), and lower frequency of alleles T at rs4661748 (15.6% vs 19.4%; OR=0.77, 95% CI, 0.66 to 0.90; p<0.001) and C at rs4782809 (42.4% vs 47.4%; OR=0.82, 95% CI, 0.72 to 0.92; p<0.001). The authors concluded that further studies are needed to determine the correlation of gene testing and AIS.

A number of genome-wide association studies (GWAS) have attempted to identify genetic loci with associations with AIS progression. Sharma reported results of a GWAS evaluating 327,000 SNVs in 419 families with AIS that found three loci significantly associated with

scoliosis progression, which did not include any of the 53 SNVs included in the Ward study previously described.[14] Tang evaluated the association between the 53 SNVs used in the Ward study previously described and severe scoliosis in a case control study involving 450 AIS patients of French-Canadian background.[15]

In 2013, Fendri reported results from a case-control GWAS of 6 AIS patients and six non-AIS controls evaluating differential gene expression profiling in AIS.[16] 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 five groups based on molecular function and biological process that fell into four pathways: developmental/growth differentiation of skeletal elements (ie, HOXB8, HOXB2, MEOX2, PITX1), cellular signaling (ie, HOXA11, BARX1), connecting structural integrity of the extracellular matrix to the structural integrity of a bone or a muscle fiber (ie, COMP, HOXA2, HOXA11), and cellular signaling and cartilage damage (GDF15).

Studies have also associated variants in the promoter regions of tissue inhibitor of metalloproteinase-2 and neurotrophin 3 with AIS severity in Chinese populations.[17] Replication of these genetic associations is needed.

CLINICAL UTILITY

No studies have been conducted that examine the impact of DNA-based predictive testing for scoliosis 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 severe curvature. Test-induced changes in outcome will provide insight into the clinical utility of the test. Because treatment outcomes are used as the end point of interest in characterizing the test, changes in outcomes may also produce changes in the test's clinical validity

PRACTICE GUIDELINE SUMMARY

UNITED STATES PREVENTIVE SERVICES TASK FORCE

In 2018, the US Preventive Services Task Force (USPSTF) published an evidence based guideline for screening for adolescent idiopathic scoliosis. In asymptomatic children and adolescents aged 10 to 18 years, the USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening. DNA-based tests were not specifically addressed in the guideline evidence summary.

SUMMARY

There is not enough research to show that performing DNA-based testing improves health outcomes in patients with adolescent idiopathic scoliosis (AIS). In addition, no clinical guidelines recommend testing in patients with AIS. Therefore, DNA-based testing for AIS is considered investigational.

REFERENCES

1. Weinstein, SL, Dolan, LA, Cheng, JC, Danielsson, A, Morcuende, JA. Adolescent idiopathic scoliosis. *Lancet*. 2008 May 3;371(9623):1527-37. PMID: 18456103
2. Ward, K, Ogilvie, JW, Singleton, MV, Chettier, R, Engler, G, Nelson, LM. Validation of DNA-based prognostic testing to predict spinal curve progression in adolescent idiopathic scoliosis. *Spine*. 2010 Dec 1;35(25):E1455-64. PMID: 21102273
3. Lonstein, JE, Carlson, JM. The prediction of curve progression in untreated idiopathic scoliosis during growth. *The Journal of bone and joint surgery American volume*. 1984 Sep;66(7):1061-71. PMID: 6480635
4. Peterson, LE, Nachemson, AL. Prediction of progression of the curve in girls who have adolescent idiopathic scoliosis of moderate severity. Logistic regression analysis based on data from The Brace Study of the Scoliosis Research Society. *The Journal of bone and joint surgery American volume*. 1995 Jun;77(6):823-7. PMID: 7782354
5. Ogilvie, J. Adolescent idiopathic scoliosis and genetic testing. *Current opinion in pediatrics*. 2010 Feb;22(1):67-70. PMID: 19949338
6. den Dunnen, JT, Dalgleish, R, Maglott, DR, et al. HGVS Recommendations for the Description of Sequence Variants: 2016 Update. *Human mutation*. 2016 Jun;37(6):564-9. PMID: 26931183
7. Noshchenko, A, Hoffecker, L, Lindley, EM, et al. Predictors of spine deformity progression in adolescent idiopathic scoliosis: A systematic review with meta-analysis. *World journal of orthopedics*. 2015 Aug 18;6(7):537-58. PMID: 26301183
8. Bohl, DD, Telles, CJ, Ruiz, FK, Badrinath, R, DeLuca, PA, Grauer, JN. A Genetic Test Predicts Providence Brace Success for Adolescent Idiopathic Scoliosis When Failure Is Defined as Progression to >45 Degrees. *Clin Spine Surg*. 2016;29:E146-50. PMID: 27007790
9. Roye, BD, Wright, ML, Matsumoto, H, et al. An Independent Evaluation of the Validity of a DNA-Based Prognostic Test for Adolescent Idiopathic Scoliosis. *The Journal of bone and joint surgery American volume*. 2015;97:1994-8. PMID: 26677232
10. Roye, BD, Wright, ML, Williams, BA, et al. Does ScoliScore Provide More Information Than Traditional Clinical Estimates Of Curve Progression? *Spine*. 2012 May 18. PMID: 22614798
11. Xu, L, Qin, X, Sun, W, Qiao, J, Qiu, Y, Zhu, Z. Replication of Association Between 53 Single-Nucleotide Polymorphisms in a DNA-Based Diagnostic Test and AIS Progression in Chinese Han Population. *Spine*. 2016 Feb;41(4):306-10. PMID: 26579958
12. Ogura, Y, Takahashi, Y, Kou, I, et al. A replication study for association of 53 single nucleotide polymorphisms in a scoliosis prognostic test with progression of adolescent idiopathic scoliosis in Japanese. *Spine*. 2013 Jul 15;38(16):1375-9. PMID: 23591653
13. Xu, L, Huang, S, Qin, X, et al. Investigation of the 53 Markers in a DNA-Based Prognostic Test Revealing New Predisposition Genes for Adolescent Idiopathic Scoliosis. *Spine*. 2015 Jul 15;40(14):1086-91. PMID: 25811265
14. Sharma, S, Gao, X, Londono, D, et al. Genome-wide association studies of adolescent idiopathic scoliosis suggest candidate susceptibility genes. *Human molecular genetics*. 2011 Apr 1;20(7):1456-66. PMID: 21216876
15. Tang, QL, Julien, C, Eveleigh, R, et al. A replication study for association of 53 single nucleotide polymorphisms in ScoliScore test with adolescent idiopathic scoliosis in French-Canadian population. *Spine*. 2015 Apr 15;40(8):537-43. PMID: 25646748

16. Fendri, K, Patten, SA, Kaufman, GN, et al. Microarray expression profiling identifies genes with altered expression in Adolescent Idiopathic Scoliosis. *European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society*. 2013 Jun;22(6):1300-11. PMID: 23467837
17. Jiang, J, Qian, B, Mao, S, et al. A promoter polymorphism of tissue inhibitor of metalloproteinase-2 gene is associated with severity of thoracic adolescent idiopathic scoliosis. *Spine*. 2012 Jan 1;37(1):41-7. PMID: 21228746
18. BlueCross BlueShield Association Medical Policy Reference Manual "DNA-Based Testing for Adolescent Idiopathic Scoliosis." 2.04.74

CODES

Codes	Number	Description
CPT	0004M	Scoliosis, DNA analysis of 53 single nucleotide polymorphisms (SNPs), using saliva, prognostic algorithm reported as a risk score
	81599	Unlisted multianalyte assay with algorithmic analysis
HCPCS	None	

Date of Origin: *November 2012*