

Genetic Testing for Adolescent Idiopathic Scoliosis

Policy Number: AHS – M2058 – Genetic Testing for Adolescent Idiopathic Scoliosis	Prior Policy Name and Number, as applicable:
Original Effective Date: 5/15/2022	
Current Effective Date: 1/01/2023	

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I. Policy Description

Scoliosis is a disorder with abnormal rotation and curvature of the spine. In most cases the cause is idiopathic. Adolescent idiopathic scoliosis (AIS) typically occurs after the age of 10, and tends to run in families. Most individuals with scoliosis do not suffer from progression of the curvature, and treatment is needed only for a small percentage of patients (Scherl, 2021).

Genetic markers have been identified related to AIS. The ScoliScore™ Test was the first clinically validated genetic test for AIS.

II. Related Policies

Policy Number	Policy Title
	Not applicable

III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual’s benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in Section VII of this policy document.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of a patient’s illness.

- 1) DNA-based prognostic testing for adolescent idiopathic scoliosis **DOES NOT MEET COVERAGE CRITERIA.**

IV. Table of Terminology

Term	Definition
AAFP	American Academy of Family Physicians
AAOS	American Academy of Orthopaedic Surgeons
AAP	American Academy of Pediatrics
<i>ADAMTSL2</i>	<i>A disintegrin-like and metalloproteinase with thrombospondin-like protein 2 gene</i>
AIS	Adolescent idiopathic scoliosis
<i>BNC2</i>	<i>Basonuclin 2</i>
CMS	Centers for Medicare and Medicaid
<i>COL11A1</i>	<i>Collagen type 11 alpha 1 chain gene</i>
<i>COL11A2</i>	<i>Collagen type 11 alpha 2 chain gene</i>
<i>FBN1</i>	<i>Fibrillin 1 gene</i>
FDA	Food and Drug Administration
<i>GPR126</i>	<i>G protein-coupled receptor 126</i>
GWAS	Genome-wide association study
HCTD	Hereditary connective tissue disorders
<i>HSPG2</i>	<i>Heparan sulfate proteoglycan 2</i>
IS	Idiopathic scoliosis
<i>LBX1</i>	<i>Ladybird homeobox 1 gene</i>
LDT	Laboratory developed test
<i>LTBP4</i>	<i>Latent transforming growth factor-beta-binding protein 4 gene</i>
POSNA	Pediatric Orthopaedic Society of North America
SNP	Single nucleotide polymorphism
SOSORT	International Scientific Society on Scoliosis Orthopaedic and Rehabilitation Treatment
SRS	Scoliosis Research Society
TGF-b	Transforming growth factor beta
<i>TGFBR2</i>	<i>Transforming growth factor-beta receptor 2</i>
UK NSC	United Kingdom National Screening Committee
USPSTF	United States Preventive Services Task Force
VSI	Virginia Spine Institute

V. Scientific Background

Adolescent idiopathic scoliosis (AIS) is the most common spinal deformity, affecting between 2-3% of children worldwide (Grauers, Einarsdottir, & Gerdhem, 2016). However, only 10% of adolescents with AIS progress to more severe curvature requiring treatment. Although males and females are affected equally, females are 10 times more likely to have curve progression (Scherl, 2021).

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The etiology of AIS is uncertain, but a genetic contribution is suggested by familial inheritance (Simony, Carreon, Hjmark, Kyvik, & Andersen, 2016). Increased levels of calmodulin in platelets and an asymmetrical distribution of calmodulin in paraspinal muscles (Acaroglu, Akel, Alanay, Yazici, & Marcucio, 2009), uncoordinated growth of the vertebral bodies in relation to the dorsal elements (Guo, Chau, Chan, & Cheng, 2003), higher growth velocity during puberty (Cheung et al., 2006), and high levels of cartilage oligomeric matrix protein (Gerdmhem et al., 2015), have all been investigated in association with AIS.

Genetic candidates associated with AIS have been identified. Takahashi et al. (2011) performed a large genome-wide association study (GWAS) which found an association with a variant downstream of *LBX1*. Kou et al. (2013) identified *GPR126* mutation in a large Japanese GWAS; *GPR126* was found to be highly expressed in cartilage and cause delayed ossification in zebrafish. Baschal et al. (2014) completed exome sequencing for three members of a multigenerational family with idiopathic scoliosis, resulting in the identification of a variant in the *HSPG2* gene as a potential contributor to the phenotype. Buchan et al. (2014) used genome-wide rare variant burden analysis using exome sequence data to identify fibrillin-1 (*FBNI*) as the most significantly associated gene with AIS and scoliosis severity, suggesting that rare variants may be useful as predictors of curve progression. Ogura et al. (2015) identified a variant of *BNC2*, overexpression of which resulted in body curvature in zebrafish in a dose-dependent manner.

Haller et al. (2016) analyzed exome sequence data of 391 severe AIS cases and 843 controls of European ancestry using a pathway burden analysis. Novel variants in musculoskeletal collagen were found in 32% (126/391) of AIS cases compared to 17% of the control cases (146/843). The authors concluded that the AIS cases “harbor mainly non-glycine missense mutations” but noted that the genetic basis for AIS was complex with a polygenic burden of rare variants (Haller et al., 2016).

Proprietary Testing

Proprietary tests, such as Scoliscore, assess the genetic basis for AIS. Scoliscore was developed by Axial Biotechnology and intended for the prediction of the likelihood of curve progression. This test is noted to be appropriate for Caucasian patients ages nine to 13 with a mild to moderate curve. The test evaluates 53 genetic markers to determine the risk of progression. These markers are combined (along with the Cobb angle) into a risk score from one to 200. The test is claimed to have a 99% negative predictive value for risk of progression (VSI, 2020).

Clinical Utility and Validity

Determination of which spinal curvature will progress is difficult. Prognostic testing for AIS has the potential to reduce psychological trauma, serial exposure to diagnostic radiation, unnecessary treatments, and direct and indirect costs-of-care related to scoliosis monitoring in low-risk patients.

Ward et al. (2010) used logistic regression to develop and validate an algorithm to predict spinal curve progression incorporating genotypes for 53 single nucleotide polymorphisms (SNPs) and the patient's presenting spinal curve, marketed as Scoliscore. The study included 277 low-risk

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females, 257 higher-risk females, and 163 high-risk males. Patients were sequenced and assessed using the ScolioScore algorithm. The risk model of the algorithm was standardized to identify 75% of patients as low-risk (<1% risk of progressing to a surgical curve), 24% as intermediate-risk, and 1% as high-risk. The cutoff scores were listed as <41 for low-risk, 50 for intermediate-risk, and 180 for high-risk. Low-risk scores had negative predictive values of 100% for the low-risk population, 99% for the higher-risk females, and 97% for the high-risk males (Ward et al., 2010).

Although initial results were significant, the association of these variants to progression of scoliosis has not been replicated, including studies on both a Japanese and a French-Canadian cohort (Ogura et al., 2013; Tang et al., 2015). Ogura et al. (2013) assessed the frequency of the 53 SNPs in a 600-sample progression group and a 1114-sample non-progression group and did not find any difference in risk allele frequency between the two groups. Furthermore, the authors did not find any SNPs to correlate with the AIS curve progression (Ogura et al., 2013).

The replication association study by Tang et al. to determine whether the 53 single nucleotide polymorphisms (SNPs) that were previously associated with spinal deformity progression in an American Caucasian cohort are similarly associated in French-Canadian population found that none of the SNPs used in ScolioScore were associated with adolescent idiopathic scoliosis curve progression or curve occurrence in French-Canadian population. No difference in risk allele frequencies between the severe and non-severe groups was observed, as well as no difference between the severe and control groups (Tang et al., 2015).

Roye et al. (2012) compared the risk stratification between ScolioScore and traditional clinical estimates to determine whether ScolioScore provides unique information. The study showed that clinical assessment classified more patients as high-risk (47 versus nine percent), and ScolioScore categorized more patients as low risk (36 versus two percent). The authors found a positive correlation of $r = 0.581$ between the ScolioScore and the Cobb angle. The authors concluded that ScolioScore provides unique information to traditional clinical predictors of curve progression (Roye et al., 2012).

Roye et al. (2015) conducted a dual-center retrospective cohort study of 126 Caucasian patients with AIS and Cobb angle between 10 and 25 degrees to determine if the ScolioScore effectively predicted the risk of curve progression in patients with mild and moderate adolescent idiopathic scoliosis. The study concluded that ScolioScore results did not differ between patients with and without curve progression, and the negative and positive predictive values (0.87 and 0.27, respectively) were lower in the study than in the previously published validation study by the developers of the test. The ScolioScore of the patients with curve progression had a mean of 107 and standard deviation of 55 points, and the ScolioScore of the patients without the curve progression had a mean of 102 and standard deviation of 62 points (Roye et al., 2015).

Noshchenko et al. (2015) performed a meta-analysis to identify possible predictors of spine deformity progression in AIS. The authors analyzed 25 studies. Two of the eight predictors identified as “statistically significant or borderline association between severity or progression of AIS” included polymorphisms of seven genes [(1) calmodulin 1; (2) estrogen receptor 1; (3) tryptophan hydroxylase 1; (3) insulin-like growth factor 1; (5) neurotrophin 3; (6) interleukin-17

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receptor C; (7) melatonin receptor 1B,'] and the ScolioScore test. However, the authors remarked that the “predictive values of all these findings were limited, and the levels of evidence were low,” leading them to conclude that “this review did not reveal any methods for the prediction of progression in AIS that could be recommended for clinical use as diagnostic criteria” (Noshchenko et al., 2015).

Liu et al. (2022) conducted a study among 302 patients with AIS who underwent exome sequencing for genes related to hereditary connective tissue disorders (HCTD), since AIS genes have been related to HCTD previously. They identified nine pathogenic variants “based on a monogenic inheritance” in *FBN1*, *COL11A1*, *COL11A2*, and *TGFBR2*. They also found three unique *ADAMTSL2-LTBP4* variant pairs in three patients, demonstrating a correlation with the AIS phenotype. With this variant pair, the researchers also revealed that they “could affect the interaction between *ADAMTSL2* and *LTBP4* and upregulated the TGF- β signaling pathway in human fibroblasts.” This study supports the continued assessment of genetic testing with AIS patients and how these novel variant pairs can affect patient care (Liu et al., 2022).

VI. Guidelines and Recommendations

International Scientific Society on Scoliosis Orthopaedic and Rehabilitation Treatment (SOSORT)

The SOSORT released revised evidence-based guidelines on conservative treatment of idiopathic scoliosis (IS) that align the guidelines with the new scientific evidence to assure faster knowledge transfer into clinical practice. They state, “Recently developed genetic assessment, with 53 identified loci, can now help predict the risk of IS progression. The determination of the polymorphism of selected genes is meant to facilitate the assignment of a patient to a progressive or stable group. Unfortunately, the data originating from one population often are not confirmed in replication studies involving other populations. A prognostic genetic test, known as ScolioScore, has also been developed. Although these initial results have been promising, their generalizability is still uncertain.” SOSORT recommends prudence in using genetic tools; caution is needed to translate genetic results from research setting to clinical setting (Negrini et al., 2018).

School screening programs are recommended for the early diagnosis of idiopathic scoliosis using the Scoliometer during trunk forward bend (Adam’s test); 5° and 7° of angle of trunk rotation should be used as criteria for referral. Screening is also recommended every time pediatricians, general practitioners, and sports physicians evaluate children aged from eight to 15 years (Negrini et al., 2018).

U.S. Preventive Services Task Force (USPSTF)

The USPSTF issued an updated recommendation that the current evidence is insufficient to assess the balance of benefits and harms of screening for adolescent idiopathic scoliosis in children and adolescents aged 10 to 18 years. No USPSTF recommendations for DNA-based testing for AIS were identified (Grossman et al., 2018).

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American Academy of Family Physicians (AAFP)

The AAFP published a clinical preventative service recommendation which states that “The AAFP supports the U.S. Preventive Services Task Force (USPSTF) clinical preventive service recommendation on this topic” (AAFP, 2018).

The Scoliosis Research Society (SRS), American Academy of Orthopaedic Surgeons (AAOS), Pediatric Orthopaedic Society of North America (POSNA), and American Academy of Pediatrics (AAP)

The AAOS, SRS, POSNA, and AAP issued a statement (Hresko, Talwalkar, & Schwend, 2016) which states:

“The AAOS, SRS, POSNA, and AAP believe that there are documented benefits of earlier detection and non-operative management of AIS, earlier identification of severe deformities that are surgically treated, and incorporation of screening of children for AIS by knowledgeable health care providers as a part of their care... AAOS, SRS, POSNA, and AAP believe that screening examinations for spine deformity should be part of the medical home preventive services visit for females at age 10 and 12 years, and males once at age 13 or 14 years.”

United Kingdom National Screening Committee (NSC)

The United Kingdom (UK) NSC recommends against screening for AIS as there “is not enough evidence to show if detecting the condition earlier through screening results in better health outcomes than waiting until symptoms develop” (UKNSC, 2021).

VII. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: <http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx>. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

VIII. Applicable CPT/HCPCS Procedure Codes

CPT	Code Description
0004M	Scoliosis, dna analysis of 53 single nucleotide polymorphisms (snps), using saliva, prognostic algorithm reported as a risk score

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Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

IX. Evidence-based Scientific References

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X. Review/Revision History

Effective Date	Summary
01/01/2023	Reviewed and Updated: Updated background, guidelines, and evidence-based scientific references. Literature review did not necessitate any modification to the coverage criteria.
05/15/2022	Initial Policy Implementation