Prior Authorization Review Panel
MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review.
Policies submitted without this form will not be considered for review.

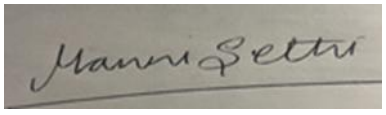
Plan: AmeriHealth Caritas Pennsylvania & Keystone First	Submission Date:1/1/2026
Policy Number: CCP.1553	Effective Date:1/1/2026 Revision Date:
Policy Name: EpiSign Testing for DNA Methylation Analysis	

Type of Submission:

☒ New Policy	☒ Prior Authorization Policy
☐ Revised Policy*	☐ Base Policy
☐ Annual Review- no revisions	☒ Experimental/Investigational Policy
	☐ Statewide PDL
	☐ Other:

*All revisions to the policy must be highlighted using track changes throughout the document.

Please provide any clarifying information for the policy below:

Name of Authorized Individual (Please type or print): Manni Sethi, MD, MBA, CHCQM	Signature of Authorized Individual: 

EpiSign Testing for DNA Methylation Analysis

Clinical Policy ID: CCP.1553

Recent review date: 12/1/2025

Next review date: 4/1/2027

Policy contains: Constitutional disorder; DNA methylation, EpiSign, epivariant; episignature.

AmeriHealth Caritas Pennsylvania has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas Pennsylvania clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by AmeriHealth Caritas Pennsylvania on a case by case basis when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. AmeriHealth Caritas Pennsylvania clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. AmeriHealth Caritas Pennsylvania clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas Pennsylvania will update its clinical policies as necessary. AmeriHealth Caritas Pennsylvania clinical policies are not guarantees of payment.

Coverage policy

Use of EpiSign Variant or EpiSign Complete testing (Greenwood Genetic Center, Florence, South Carolina) for dioxyribonucleic acid (DNA) methylation analysis is investigational/not clinically proven and, therefore, not medically necessary for genetic diagnosis.

Limitations

No limitations were identified during the writing of this policy.

Alternative covered services

- Clinical microarray testing.
- Targeted gene panels.
- Exome sequencing.
- Methylation tests on specific gene loci or regions.

Background

Constitutional conditions are diseases or health problems that are genetic or epigenetic in origin and have a systemic effect on the body's general health and strength. They are either inherited (genetic) or associated with complex, overlapping clinical features that cause genetic changes without altering the DNA sequence (epigenetic). Epigenetic regions of the genome contain information, other than the DNA sequence itself, that is involved in regulating gene expression. These regions are maintained during cell division, are influenced by the

environment, cause stable changes in gene expression, and, in some cases, can be passed down to future generations. Epigenetic changes can be a cause or a consequence of disease, and both genome-wide and epigenome-wide association studies may be needed to assess the association between exposures, epigenetic changes, and their connection with disease phenotypes (Feinberg, 2018).

DNA methylation is the most well-understood form of epigenetic information. DNA methylation is a chemical modification involving the attachment of a methyl group to the nucleotide cytosine at the 5′ position. DNA methylation occurs after DNA replication and can activate or inactivate a gene and alter protein synthesis without changing the underlying DNA sequence. DNA methylation is heritable during cell division and essential for normal cell development, tissue differentiation, and many other cellular processes (Feinberg, 2018). DNA methylation defects may occur at a single locus (called “epivariants”) or across multiple loci (called “episignatures”) and are linked to many health conditions, such as cancer, heart disease, and genetic disorders associated with a loss of genomic imprinting (i.e., inappropriate expression of genes inherited from one parent) (Jin, 2018).

Traditional genetic testing for constitutional conditions involves clinical microarray testing, next-generation sequencing of targeted gene panels, and exome sequencing. Methylation tests on specific gene loci or regions have been used primarily for the diagnosis of imprinting disorders. However, these approaches are limited in their ability to assess complex genomic rearrangements and structural variations, deep intronic and noncoding sequences, and variants of uncertain significance. As a result, only half of these cases, at best, are genetically resolved (Clark, 2018; Chung, 2023).

Genome-wide DNA methylation episignatures are developed by computational machine learning models, primarily using methylation microarray data from peripheral blood samples in individuals with common genetic or environmental etiology. The ability to detect these episignatures will depend on the intensity (effect size) and extent of the observed DNA methylation changes (van Karnebeek, 2024).

EpiSign is a proprietary assay that can detect genome-wide, unique, reproducible DNA methylation patterns or epigenetic signatures in peripheral blood. EpiSign is offered as two different tests. EpiSign Complete can detect unique epigenetic signatures and methylation abnormalities, either in a targeted region or genome-wide, for more than 90 rare disorders, including fragile X and imprinting conditions. EpiSign Variant provides a targeted review of the methylation data intended to resolve variants of uncertain clinical significance in genes with a known epigenetic signature, or when the provider has a strong clinical suspicion for a condition on the list of disorders EpiSign can detect. The manufacturer states that a previous molecular finding is not required to order testing, and if EpiSign Variant is negative, EpiSign Complete is a follow-up option (Greenwood Genetic Center, 2025).

Findings

The evidence suggests a potential role for genome-wide DNA methylation analysis for individuals with constitutional disorders whose phenotypes overlap with conditions that have known episignatures, individuals with variants of unknown significance in genes linked to episignatures, or for individuals for whom other genetic tests have been uninformative. The purported advantage of genome-wide EpiSign testing is the ability to improve the diagnostic yield (i.e., to achieve a definitive genetic diagnosis) above that of available genetic testing, which may improve the diagnostic rate and quality of life and health care of patients and their families. New genetic discoveries continue to influence the incremental diagnostic yield of EpiSign testing, as evidenced by several updated versions of the tests, but its impact on clinical care has not been established.

Guidelines

The American College of Medical Genetics and Genomics recommends targeted exome or genome testing as the initial test for patients with clinical presentations highly suggestive of a specific genetic diagnosis. This may

include patients with suspicion of a chromosomal disorder, a known family history of a chromosomal disorder, or a strong clinical suspicion of a diagnosis in which sequencing may not be diagnostic, such as the methylation abnormality related to Prader–Willi syndrome and Angelman syndrome, or fragile X syndrome (Manickam, 2021).

The American College of Medical Genetics and Genomics (2022) has a document in progress that will address the implementation of DNA methylation arrays for clinical diagnostics. The College states that while several DNA methylation arrays have been adopted and clinically validated for the diagnosis of both constitutional and neoplastic disorders, there is a lack of standardization regarding validation and implementation of this technology in the clinical setting. There is an absence of standards or recommendations for clinical laboratories to interpret the findings of DNA methylation arrays.

The International Rare Diseases Research Consortium states that application of DNA methylation episignature technology to broader patient populations will depend on the rate of discovery of gene and disorder-specific episignatures. Larger-scale studies are necessary to assess the diagnostic yield and health system impact as either a first-line test or in cases still unresolved after genomic assessment. Development of clinical recommendations and guidelines for the use and application of DNA methylation episignature analysis is ongoing (van Karnebeek, 2024).

Evidence review

The evidence supporting EpiSign testing consists of test validation studies and diagnostic utility studies. An international working group representing the EpiSign Clinical Testing Network has published several studies of EpiSign DNA methylation testing. Validation studies continue to define new DNA methylation episignatures as biomarkers for rare disorders along with interpretation of genetic variants of unknown clinical significance (Haghshenas, 2024; Rooney, 2023; Trajkova, 2024; van der Laan, 2024; Verberne, 2022; Vos, 2024).

Diagnostic utility studies analyzed the test's incremental diagnostic yield, defined as a positive EpiSign result, in individuals who were lacking a genetic diagnosis (Kerkhof, 2024; LaFlamme, 2024). The largest study analyzed 2,399 peripheral blood samples of individuals who were referred for EpiSign testing (versions 1 through 3) between May 2019 and January 2023. A total of 1,667 referrals underwent EpiSign comprehensive screening of validated episignatures, imprinting, and promoter regions. The remaining 732 referrals underwent EpiSign targeted analysis for assessment of sequence or copy-number variants of uncertain significance or for assessment of clinical diagnoses without confirmed molecular findings. The diagnostic yields of Episign targeted and complete analyses were 32.4% (237/732) and 18.7% (312/1,667), respectively (Kerkhof, 2024). In a smaller cohort of 582 blood samples from individuals with developmental and epileptic encephalopathies, the diagnostic yield of EpiSign was 2% (12/582) (LaFlamme, 2024).

While DNA methylation analysis of episignatures, imprinting, and promoter regions may improve the diagnostic yield in select cohorts, it does not establish clinical utility. The clinical utility of genome-wide DNA methylation analysis can be challenging to quantify for several reasons. A positive result may include false-positive cases, and a negative episignature finding alone is not sufficient to rule out pathogenicity, although it may be useful as supporting evidence in combination with other clinical and diagnostic findings. The low prevalence of rare disorders often requires collaboration among several sites to achieve sufficient numbers for a reference cohort. The diversity of conditions and genetic variants within the source data and the magnitude of methylation changes can lead to inconclusive findings. Analytical processes need to account for other factors such as age, gender, and environmental exposures. Episignature analysis is limited to peripheral blood DNA, and a number of rare diseases studied thus far do not show changes in peripheral blood (Kerkhof, 2022, 2024; Sadikovic, 2021; van Karnebeek, 2024).

A large-scale population study called EpiSign-CAN is underway in Canada to compare the impact of DNA methylation analysis as a first-line versus a second-line test in 4,000 individuals with suspected rare disorders,

while increasing the numbers of disorders it can detect to 100 additional genetic conditions. Outcomes will assess changes to quality of life for patients and families, time to genetic diagnosis, and cost benefits to the health system (Genome Canada, 2022; Sadikovic, 2021).

References

On 10/21/2025, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were “DNA methylation (MeSH)”, “DNA methylation,” “Epigenetics,” and “Episign.” We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

American College of Medical Genetics and Genomics. “ACMG documents in development. Points to consider for the implementation of DNA methylation arrays for clinical diagnostics.” https://www.acmg.net/ACMG/Medical-Genetics-Practice-Resources/Documents_in_Development/ACMG/Medical-Genetics-Practice-Resources/Documents_in_Development.aspx?hkey=620bd72b-8b8d-427d-9660-67f7d04b3d4a. Published 2024.

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Policy updates

12/2/2025 initial review date and clinical policy effective date: 1/1/2026