



EpiSign is a genome-wide methylation assay designed to readily identify methylation defects due to triplet repeat expansions and imprinting disorders as well as robust, reproducible *epigenetic signatures* for over 90 conditions.

Methylation Defects

EpiSign can detect multiple methylation abnormalities associated with certain imprinting or triplet repeat conditions including Angelman syndrome, Prader-Willi syndrome, and Fragile X syndrome, among others. Analysis of these conditions does not include a specific episignature from across the genome. However, the associated gene or region that is known to be differentially methylated is included in the analysis.

Unique Multi-locus Epigenetic Signatures

EpiSign can also identify disease-specific methylation patterns involving multiple loci across the genome. These unique methylation patterns, or epigenetic signatures, have been associated with a number of disorders. Assessment of distinct methylation patterns can be used in the diagnostic work-up or can be applied in a more targeted fashion to help resolve variants of uncertain clinical significance.

One Assay. Two Options.

EpiSign is offered as two different tests to suit the needs of your patients.

EpiSign Complete is a comprehensive analysis that includes all conditions (over 90) listed. **EpiSign Complete** is a useful diagnostic tool for patients with developmental delay or other clinical features suggestive of a condition with an epigenetic signature and conditions with methylation defects (imprinting disorders).

EpiSign Variant is a targeted review of the methylation data based on a strong clinical suspicion and/or a previously identified variant of uncertain significance. Pathogenic variants in genes associated with these conditions have an established unique signature. When present, this unique signature can provide evidence for variant pathogenicity.



*EpiSign has proven to be a successful diagnostic advancement beyond traditional testing methods.**



Greenwood Diagnostic Laboratories in partnership with London Health Sciences Centre present *EpiSign*.

Secondary signatures are used to supplement some of the heterogeneous disorder groups, including Kabuki, BAFopathy 1, and CdLS syndromes. Patients who are positive for the more general, or primary, episignature will also be analyzed for the associated, secondary signatures. This approach will facilitate a more targeted downstream testing strategy when a genetic variant has not yet been identified.

Conditions with Strong Signatures

Related Region or Gene(s)

19p13.13 deletion syndrome	19p13.13p13.2 deletion (Chr19:13,201,983-13,213,144)
<ul style="list-style-type: none"> <i>NFIX</i> sequence variants are not detected. 	
Alpha-thalassemia/X-linked impaired intellectual development syndrome	<i>ATR</i>
<ul style="list-style-type: none"> Affected males only. 	
Autosomal dominant intellectual developmental disorder, type 7	<i>DYRK1A</i>
Autosomal dominant intellectual developmental disorder, type 21	<i>CTCF</i>
BAFopathy 1: including Coffin-Siris syndromes & Nicolaides-Baraitser	<i>ARID1B, ARID1A, SMARCB1, SMARCA4, SMARCA2</i>
Secondary signatures :	
Coffin-Siris syndrome 1	<i>ARID1B</i>
Coffin-Siris syndrome 2	<i>ARID1A</i>
Coffin-Siris syndrome 3	<i>SMARCB1</i>
Coffin-Siris syndrome 4	<i>SMARCA4</i>
Nicolaides-Baraitser	<i>SMARCA2</i>
<ul style="list-style-type: none"> Secondary signature analysis when abnormal with reduced sensitivity. 	
BAFopathy 2: Coffin-Siris syndrome 1 & 2	<i>ARID1B</i> (c.6133-c.6254), <i>ARID1A</i>
<ul style="list-style-type: none"> Only for variants within the indicated nucleotide range. 	
Beck-Fahrner syndrome	<i>TET3</i>
<ul style="list-style-type: none"> Healthy carriers and those with incomplete penetrance are detectable. Patients with biallelic variants are distinguishable from those with monoallelic variants. 	
Blepharophimosis-impaired intellectual development syndrome	<i>SMARCA2</i>
Borjeson-Forsman-Lehmann, Chung-Jansen, White-Kernohan syndromes	<i>PHF6, PHIP, DDB1</i>
<ul style="list-style-type: none"> Borjeson-Forsman-Lehmann syndrome analysis was only validated in males. Secondary signature analysis when abnormal with reduced sensitivity. 	
CHARGE syndrome	<i>CHD7</i>
Clark-Baraitser syndrome	<i>TRIP12</i>
Coffin-Siris syndrome 4	<i>SMARCA4</i>
<ul style="list-style-type: none"> Variants near c.2656 may cluster separately from BAFopathy 1. 	
Coffin-Siris syndrome 6	<i>ARID2</i>
Cornelia de Lange syndromes 1-4	<i>NIPBL, SMC1A, SMC3, RAD21</i>
Secondary signatures :	
Cornelia de Lange syndrome 1	<i>NIPBL</i>
Cornelia de Lange syndrome 2	<i>SMC1A</i>
Cornelia de Lange syndrome 3	<i>SMC3</i>
Cornelia de Lange syndrome 4	<i>RAD21</i>
<ul style="list-style-type: none"> Secondary signature analysis when abnormal with reduced sensitivity. 	
DEGCAGS	<i>ZNF699</i>
<ul style="list-style-type: none"> Heterozygotes are not detected. 	
Developmental and epileptic encephalopathy 54	<i>HNRNPU</i>
Developmental and epileptic encephalopathy 94	<i>CHD2</i>
Diets-Jongmans syndrome	<i>KDM3B</i>
Down syndrome	Trisomy 21

Genes/conditions and notes listed in blue are new to EpiSign v5.

The first clinical assay validated to detect unique epigenetic signatures and methylation abnormalities for clinically recognized genetic conditions.

Strong Signatures, continued

Dystonia 28, childhood-onset	KMT2B
<ul style="list-style-type: none"> Autosomal dominant intellectual development disorder, type 68 phenotype is not detected. 	
Fanconi anemia	FANCA, FANCC, FANCD2, FANCG, FANCI, FANCL
<ul style="list-style-type: none"> Heterozygotes are not detected. 	
Fetal Valproate syndrome	
<ul style="list-style-type: none"> Included as an opt-in analysis by targeted request. 	
Floating-Harbor syndrome	SRCAP (c.6925-c.9690)
<ul style="list-style-type: none"> Only truncating variants within exons 33 and 34 are detected. 	
Hao-Fountain syndrome	USP7
Helsmoortel-Van der Aa syndrome	ADNP
<ul style="list-style-type: none"> Includes analysis of central (variants within c.2054-2340) and terminal (variants outside c.2054) epesignatures. 	
Hunter-McAlpine craniosynostosis syndrome	5q35 duplication (Chr5:175,839,681-176,904,789) involving NSD1
Intellectual developmental disorder with seizures and language delay	SETD1B
Kabuki syndrome 1 & 2	KMT2D, KDM6A
Secondary signatures :	
Kabuki syndrome 1	KMT2D
Kabuki syndrome 2	KDM6A
<ul style="list-style-type: none"> Secondary signature analysis when abnormal with reduced sensitivity. 	
KDM2B-related syndrome	KDM2B
Kleefstra syndrome 1	EHMT1
Klinefelter syndrome	47, XXY
<ul style="list-style-type: none"> 47, XXX patients may be detected. 	
Koolen-De Vries syndrome	KANSL1
Luscan-Lumish syndrome	SETD2
Menke-Hennekam syndrome 1 & 2 (IDR4 domain only)	CREBBP(c.5563-5614), EP300 (c.5471-5495)
Mowat-Wilson syndrome	ZEB2
Neurodevelopmental disorder with dysmorphic facies and behavioral abnormalities	SRSF1
Neurodevelopmental disorder with hypotonia, stereotypic hand movements, and impaired language	MEF2C
NSD2 duplication-related syndrome	NSD2 duplication (Chr4:1,832,733-1,975,031)
Phelan-McDermid syndrome	22q13.3 deletion (Chr22:49,238,268-50,248,907)
<ul style="list-style-type: none"> SHANK3 sequence variants are not detected. 	
Pitt-Hopkins syndrome	TCF4
PRC2 complex disorders: Weaver & Cohen-Gibson syndromes	EZH2, EED
Rahman syndrome	H1-4 (HIST1H1E)

*A recent publication in Genetics in Medicine that summarized over 2,000 clinical cases reported a diagnostic yield of 19% for patients tested by EpiSign Complete. Additionally, 32% of patients analyzed by EpiSign Variant have a positive result.**

EpiSign offers the potential for a diagnosis when initial results are negative by the continual reanalysis of all unresolved patients as new episignatures are identified.

Strong Signatures, continued

Rubinstein-Taybi syndromes 1 & 2	<i>CREBBP, EP300</i>
Secondary signatures :	
Rubinstein-Taybi syndrome 1	<i>CREBBP</i>
Rubinstein-Taybi syndrome 2	<i>EP300</i>
• Secondary signature analysis when abnormal with reduced sensitivity.	
Sifrim-Hitz-Weiss syndrome	<i>CHD4</i>
Smith-Magenis syndrome	17p11.2 deletion (Chr17:17,322,913-18,515,769)
• <i>RAI1</i> sequence variants are not detected.	
Sotos syndrome	<i>NSD1</i>
Turner syndrome	45,X
Velocardiofacial syndrome	22q11.2 deletion (Chr22:19,510,547-20,285,090)
White-Sutton syndrome	<i>POGZ</i>
Wiedemann-Steiner syndrome	<i>KMT2A</i>
Williams-Beuren region duplication syndrome	7q11.23 duplication (Chr7:73,953,518-74,138,459)
Williams-Beuren syndrome	7q11.23 deletion (Chr7:72,744,455-74,142,510)
Wolf-Hirschhorn syndrome & Rauch-Steindl syndrome	4p16.3 deletion (Chr4:679,715-2,169,001) involving <i>NSD2</i>
• <i>NSD2</i> sequence variants have been detected.	
X-linked syndromic intellectual developmental disorder, Claes-Jensen type	<i>KDM5C</i>
• Healthy carriers and those with incomplete penetrance are detectable.	
• Heterozygotes have a distinct profile from hemizygotes.	



Matthew Tedder, PhD
mtedder@ggc.org



Robin Fletcher, MS, CGC
rfletcher@ggc.org

EpiSign Experts

Dr. Matthew Tedder and laboratory genetic counselor, Robin Fletcher, believe in the technology behind *EpiSign*, and are committed to expanding its impact. Clinical teams find their educational talks an invaluable resource as they offer comprehensive insights and practical guidance for clinicians incorporating *EpiSign* in their diagnostic approach.

Please email Dr. Tedder or Robin for questions on *EpiSign* or to schedule an educational talk for your team.



Some conditions are designated as having a "moderate signature" when the sample size, mutation spectrum, or the methylation differences at CpG sites are smaller than preferred.

Conditions with Moderate Signatures

Related Region or Gene(s)

1p36 deletion syndrome	1p36 deletion (Chr1:1,019,753-2,867,961)
ARID1A duplication-related syndrome	ARID1A
Autosomal dominant cerebellar ataxia, deafness, narcolepsy	DNMT1
Autosomal dominant intellectual developmental disorder type 23, KBG syndrome	SETD5 , ANKRD11
Secondary signatures : Autosomal dominant intellectual developmental disorder, type 23 KBG syndrome	SETD5 ANKRD11
<ul style="list-style-type: none"> Secondary signature analysis when abnormal with reduced sensitivity. 	
Autosomal dominant intellectual developmental disorder, type 51	KMT5B
<ul style="list-style-type: none"> Healthy carriers and those with incomplete penetrance are detectable. 	
Arboleda-Tham syndrome	KAT6A
Coffin-Siris syndrome 9	SOX11
Congenital heart defects, dysmorphic facial features, and intellectual developmental disorder	CCNK , CDK13
Developmental delay with variable intellectual disability and dysmorphic facies	JARID2
Gabriele-de Vries syndrome	YY1
Genitopatellar syndrome	KAT6B
<ul style="list-style-type: none"> Analysis for Ohdo syndrome, SBBYS variant is also recommended. 	
Immunodeficiency-centromeric instability-facial anomalies syndrome, type 1	DNMT3B
Immunodeficiency-centromeric instability-facial anomalies syndrome, types 2-4	CDCA7 , ZBTB24 , HELLS
Intellectual developmental disorder with autism and macrocephaly	CHD8
Intellectual developmental disorder with dysmorphic facies, speech delay, and T-cell abnormalities	BCL11B
KMT2D-related syndrome	KMT2D (c.10307-c.10745)
MSL2-related syndrome	MSL2
Neuroocular syndrome	PRR12
<ul style="list-style-type: none"> Healthy carriers and those with incomplete penetrance may be detected. 	
Ohdo syndrome, SBBYS variant	KAT6B
<ul style="list-style-type: none"> Analysis for Genitopatellar syndrome is also recommended. 	
Potocki-Lupski syndrome	17p11.2 duplication (Chr17:16,779,412-20,231,379)
Renpenning syndrome	PQBP1
<ul style="list-style-type: none"> Heterozygotes are not detected. 	
SLC32A1-related disorder	SLC32A1
Tatton-Brown-Rahman syndrome	DNMT3A
Wieacker-Wolff syndrome	ZC4H2
<ul style="list-style-type: none"> Heterozygotes are not detected. 	
Witteveen-Kolk syndrome	SIN3A
X-linked intellectual developmental disorder, type 93	BRWD3
<ul style="list-style-type: none"> Healthy carriers and those with incomplete penetrance may be detected. 	
X-linked intellectual developmental disorder, type 97	ZNF711
<ul style="list-style-type: none"> Heterozygotes may be detected 	
X-linked syndromic intellectual developmental disorder, Armfield type	FAM50A
<ul style="list-style-type: none"> Heterozygotes are not detected. 	
X-linked syndromic intellectual developmental disorder, Nascimento type	UBE2A
<ul style="list-style-type: none"> Heterozygotes are not detected. 	
X-linked syndromic intellectual developmental disorder, Snyder-Robinson type	SMS
<ul style="list-style-type: none"> Heterozygotes are not detected. 	
Xp11.22 duplication syndrome	Xp11.22 (ChrX:53,559,057-53-654-518)
<ul style="list-style-type: none"> Females are not detected. 	

METHYLATION UNDERSTOOD

Imprinting Abnormalities

Angelman syndrome

- Methylation of *SNURF* and *SNRPN* are reviewed.
- *UBE3A* sequence variants are not detected.

Beckwith-Wiedemann syndrome

- *CDKN1C* sequence variants are not detected.

Diabetes Mellitus, transient neonatal 1

Fragile X syndrome

- Heterozygotes are not detected.

Kagami-Ogata syndrome

Mulchandani-Bhoj-Conlin syndrome

Prader-Willi syndrome

- Methylation of *SNURF* and *SNRPN* are reviewed.

Pseudohypoparathyroidism, Type 1A, 1B

- *GNAS* sequence variants are not detected.

Russell-Silver syndrome 1

Russell-Silver syndrome 2

- Methylation of *MEST*, *GRB10*, *PEG10*, *SVOPL*, and *HTR5A* are reviewed.

Temple syndrome

Multi-locus Imprinting Disturbance

Related Region or Gene(s)

15q11.2 imprinting abnormality

11p15 imprinting abnormality

PLAGL1 imprinting abnormality

FMR1 methylation abnormality

MEG3 imprinting abnormality

20q13.32 imprinting abnormality involving *GNAS* complex locus

15q11.2 imprinting abnormality

20q13.32 imprinting abnormality involving *GNAS* complex locus

11p15 imprinting abnormality

UPD 7 imprinting abnormality

MEG3 imprinting abnormality

All imprinted sites listed above except *FMR1*

Abnormalities detected using EpiSign as a first tier test may require additional targeted testing to confirm and further characterize the underlying genomic abnormality.



EpiSign Complete: 0318U
EpiSign Variant: 81479
(Contact lab for price)



Turnaround Time: 4 weeks



Sample Requirements: 3-5ml of
blood in EDTA tube
(Sample collection kits available upon request)



+1 800.473.9411



106 Gregor Mendel Circle
Greenwood, SC 29646



labgc@ggc.org

*<https://doi.org/10.1016/j.jgm.2024.101075>