EpiSign

Methylation Understood

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.

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

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.

50TH Anniversary
Greenwood Genetic Center
Leading the Way Since 1974

London Health Sciences Centre
St JOSEPH's HEALTH CARE LONDON
Pathology and Laboratory Medicine

Giving Greater Care

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 • *NFIX* sequence variants are not detected.	19p13.13p13.2 deletion (Chr19:13,201,983-13,213,144)
Alpha-thalassemia/X-linked impaired intellectual development syndrome • Affected males only.	*ATRX*
Autosomal dominant intellectual developmental disorder, type 7	*DYRK1A*
Autosomal dominant intellectual developmental disorder, type 21	*CTCF*
BAFopathy 1: including Coffin-Siris syndromes & Nicolaides-Baraitser	*ARID1B, ARID1A, SMARCB1, SMARCA4, SMARCA2*
Secondary signatures :	
Coffin-Siris syndrome 1	*ARID1B*
Coffin-Siris syndrome 2	*ARID1A*
Coffin-Siris syndrome 3	*SMARCB1*
Coffin-Siris syndrome 4	*SMARCA4*
Nicholaides-Baraitser	*SMARCA2*
• Secondary signature analysis when abnormal with reduced sensitivity.	
BAFopathy 2: Coffin-Siris syndrome 1 & 2 • Only for variants within the indicated nucleotide range.	*ARID1B* (c.6133-c.6254), *ARID1A*
Beck-Fahrner syndrome • Healthy carriers and those with incomplete penetrance are detectable. • Patients with biallelic variants are distinguishable from those with monoallelic variants.	*TET3*
Blepharophimosis-impaired intellectual development syndrome	*SMARCA2*
Borjeson-Forssman-Lehmann, Chung-Jansen, White-Kernohan syndromes • Borjeson-Forssman-Lehmann syndrome analysis was only validated in males. • Secondary signature analysis when abnormal with reduced sensitivity.	*PHF6, PHIP, DDB1*
CHARGE syndrome	*CHD7*
Clark-Baraitser syndrome	*TRIP12*
Coffin-Siris syndrome 4 • Variants near c.2656 may cluster separately from BAFopathy 1.	*SMARCA4*
Coffin-Siris syndrome 6	*ARID2*
Cornelia de Lange syndromes 1-4	*NIPBL, SMC1A, SMC3, RAD21*
Secondary signatures :	
Cornelia de Lange syndrome 1	*NIPBL*
Cornelia de Lange syndrome 2	*SMC1A*
Cornelia de Lange syndrome 3	*SMC3*
Cornelia de Lange syndrome 4	*RAD21*
• Secondary signature analysis when abnormal with reduced sensitivity.	
DEGCAGS • Heterozygotes are not detected.	*ZNF699*
Developmental and epileptic encephalopathy 54	*HNRNPU*
Developmental and epileptic encephalopathy 94	*CHD2*
Diets-Jongmans syndrome	*KDM3B*
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*
• Autosomal dominant intellectual development disorder, type 68 phenotype is not detected.	
Fanconi anemia	*FANCA, FANCC, FANCD2, FANCG, FANCI, FANCL*
• Heterozygotes are not detected.	
Fetal Valproate syndrome	
• Included as an opt-in analysis by targeted request.	
Floating-Harbor syndrome	*SRCAP* (c.6925-c.9690)
• Only truncating variants within exons 33 and 34 are detected.	
Hao-Fountain syndrome	*USP7*
Helsmoortel-Van der Aa syndrome	*ADNP*
• Includes analysis of central (variants within c.2054-2340) and terminal (variants outside c.2054) episignatures.	
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*
• Secondary signature analysis when abnormal with reduced sensitivity.	
KDM2B-related syndrome	*KDM2B*
Kleefstra syndrome 1	*EHMT1*
Klinefelter syndrome	47, *XXY*
• 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)
• *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	*CREBBP, EP300*
Secondary signatures :	
Rubinstein-Taybi syndrome 1	*CREBBP*
Rubinstein-Taybi syndrome 2	*EP300*
• Secondary signature analysis when abnormal with reduced sensitivity.	
Sifrim-Hitz-Weiss syndrome	*CHD4*
Smith-Magenis syndrome • *RAI1* sequence variants are not detected.	17p11.2 deletion (Chr17:17,322,913-18,515,769)
Sotos syndrome	*NSD1*
Turner syndrome	45,X
Velocardiofacial syndrome	22q11.2 deletion (Chr22:19,510,547-20,285,090)
White-Sutton syndrome	*POGZ*
Wiedemann-Steiner syndrome	*KMT2A*
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 • *NSD2* sequence variants have been detected.	4p16.3 deletion (Chr4:679,715-2,169,001) involving *NSD2*
X-linked syndromic intellectual developmental disorder, Claes-Jensen type	*KDM5C*

- Healthy carriers and those with incomplete penetrance are detectable.
- Heterozygotes have a distinct profile from hemizygotes.

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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	*SETD5*
KBG syndrome	*ANKRD11*
• Secondary signature analysis when abnormal with reduced sensitivity.	
Autosomal dominant intellectual developmental disorder, type 51	*KMT5B*
• 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*
Genitopatellar syndrome	*KAT6B*
• 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*
• Healthy carriers and those with incomplete penetrance may be detected.	
Ohdo syndrome, SBBYS variant	*KAT6B*
• Analysis for Genitopateller syndrome is also recommended.	
Potocki-Lupski syndrome	17p11.2 duplication (Chr17:16,779,412-20,231,379)
Renpenning syndrome	*PQBP1*
• Heterozygotes are not detected.	
SLC32A1-related disorder	*SLC32A1*
Tatton-Brown-Rahman syndrome	*DNMT3A*
Wieacker-Wolff syndrome	*ZC4H2*
• Heterozygotes are not detected.	
Witteveen-Kolk syndrome	*SIN3A*
X-linked intellectual developmental disorder, type 93	*BRWD3*
• Healthy carriers and those with incomplete penetrance may be detected.	
X-linked intellectual developmental disorder, type 97	*ZNF711*
• Heterozygotes may be detected	
X-linked syndromic intellectual developmental disorder, Armfield type	*FAM50A*
• Heterozygotes are not detected.	
X-linked syndromic intellectual developmental disorder, Nascimento type	*UBE2A*
• Heterozygotes are not detected.	
X-linked syndromic intellectual developmental disorder, Snyder-Robinson type	*SMS*
• Heterozygotes are not detected.	
Xp11.22 duplication syndrome	Xp11.22 (ChrX:53,559,057-53-6546-518)
• Females are not detected.	

METHYLATION UNDERSTOOD

Imprinting Abnormalities	Related Region or Gene(s)
Angelman syndrome • Methylation of *SNURF* and *SNRPN* are reviewed. • *UBE3A* sequence variants are not detected.	15q11.2 imprinting abnormality
Beckwith-Wiedemann syndrome	11p15 imprinting abnormality
Diabetes Mellitus, transient neonatal 1	*PLAGL1* imprinting abnormality
Fragile X syndrome • Heterozygotes are not detected.	*FMR1* methylation abnormality
Kagami-Ogata syndrome	*MEG3* imprinting abnormality
Mulchandani-Bhoj-Conlin syndrome	20q13.32 imprinting abnormality involving *GNAS* complex locus
Prader-Willi syndrome • Methylation of *SNURF* and *SNRPN* are reviewed.	15q11.2 imprinting abnormality
Pseudohypoparathyroidism, Type 1A, 1B • GNAS sequence variants are not detected.	20q13.32 imprinting abnormality involving *GNAS* complex locus
Russell-Silver syndrome 1	11p15 imprinting abnormality
Russell-Silver syndrome 2 • Methylation of *MEST, GRB10, PEG10, SVOPL, and HTR5A* are reviewed.	UPD 7 imprinting abnormality
Temple syndrome	*MEG3* imprinting abnormality
Multi-locus Imprinting Disturbance	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)

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