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 180 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; 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 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 other 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.

Greenwood Genetic Center

Where Compassion Inspires Progress

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

Conditions with Strong Signatures	Related Region or Gene(s)
Secondary signatures are used to supplement some of the heterogeneous disorder groups, including BAFopathy1, Cornelia de Lange, and Kabuki syndromes. Patients who are positive for the more general, or primary episignature, will also be analyzed for the associated secondary signature. This approach will facilitate a more targeted downstream testing strategy when a genetic variant has not yet been identified.	
Alpha-thalassemia/X-linked impaired intellectual development syndrome • Affected males only.	*ATRX*
Ankylosing spondylitis	*ILI2B*
ARID1A duplication-related syndrome	*ARID1A* (Chr1:26,637,711-26,772,999)
Autosomal dominant intellectual developmental disorder, type 7	*DYRK1A*
Autosomal dominant intellectual developmental disorder, type 21	*CTCF*
Autosomal recessive intellectual disability disorder, type 65/*KDM5B*-related neurodevelopmental disorder • Recessive and dominant forms are detected	*KDM5B*
BAFopathy 1: including Coffin-Siris syndromes & Nicolaides-Baraitser	*ARID1B, ARID1A, SMARCB1, SMARCA4, SMARCE1, DPF2, SMARCA2*
Secondary signatures :	
Coffin-Siris syndrome 1	*ARID1B*
Coffin-Siris syndrome 2	*ARID1A*
Coffin-Siris syndrome 3	*SMARCB1*
Coffin-Siris syndrome 4	*SMARCA4*
Coffin-Siris syndrome 5	*SMARCE1*
Coffin-Siris syndrome 7	*DPF2*
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. • Variants impacting amino acid 37 in SMARCB1 may also be detected.	*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*
CHD6-related syndrome • Missense variants impacting amino acids p.986 and p.987 have a distinct episignature.	*CHD6*
Chromosome 1p36 deletion syndrome	1p36 deletion (Chr1:1,084,373-2,951,396)
Chromosome 8p inverted duplication/deletion syndrome	Chr8p invdel
Chromosome 19p13.13 deletion syndrome • *NFIX* sequence variants are not detected.	Chr19p13.13del (Chr19:13,091,169-13,102,330)
Coffin-Siris syndrome 4 • Only for variants near c.2656. • Secondary episignature; sample must also be positive for BAFopathy 1.	*SMARCA4* c.2656
Coffin-Siris syndrome 6	*ARID2*
Congenital heart defects, dysmorphic facial features, and intellectual developmental disorder/Intellectual developmental disorder with hypertelorism and distinctive facies	*CCNK, CDK13*
CDK13-related syndrome • Defined with truncating variants only. • Reduced specificity may be observed.	*CDK13*

Cornelia de Lange syndromes 1-7	*NIPBL, SMC1A, SMC3, RAD21, MAU2*
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*
Cornelia de Lange syndrome 7	*MAU2*
• Secondary signature analysis when abnormal with reduced sensitivity.	
DEGCAGS	*ZNF699*
• Heterozygotes not detected.	
DeSanto-Shinawi syndrome	*WAC*
Developmental and epileptic encephalopathy 54	*HNRNPU*
Developmental and epileptic encephalopathy 94	*CHD2*
Developmental delay, dysmorphic facies, and brain anomalies	*U2AF2*
Developmental delay, hypotonia, musculoskeletal defects, and behavioral abnormalities	*SRCAP*
• Defined from truncating variants outside the Floating-Harbor syndrome region.	
Diamond-Blackfan anemia types 1, 4, 5-7, 10	*RPS19, RPS17, RPL35A, RPL5, RPL11, RPS26*
• Episignature may detect other Diamond-Blackfan anemia types. • Shwachman-Diamond cases shown to match epigenetic signature.	
Diets-Jongmans syndrome	*KDM3B*
Down syndrome	Trisomy 21
Dystonia 28, childhood-onset/Autosomal dominant intellectual developmental disorder, type 68	*KMT2B*
EHMT2-related syndrome	*EHMT2*
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*
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. • Variants impacting amino acid 497 cluster distinctly from other *ADNP* variants.	
Helsmoortel-Van der Aa syndrome/Sifrim-Hitz-Weiss syndrome	*ADNP, CHD4*
• Variants outside c.2054-2340 can be detected.	
Hunter-McAlpine craniosynostosis syndrome	5q35 duplication (Chr5:176,412,680-177,477,797) involving *NSD1*
Immunodeficiency 31C, autosomal dominant chronic mucocutaneous candidiasis	*STAT1*
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 seizures and language delay	*SETD1B*
Jacobs syndrome	ChrY duplication

Genes/conditions and notes listed in blue are new to EpiSign v6.
All coordinates are based on human genome build GRCh38.

GGC's diagnostic lab was the first lab to offer EpiSign as a clinical test and has more than six years of experience.

Strong Signatures, continued

Kabuki syndrome 1 & 2	*KMT2D, KDM6A*
Secondary signatures :	
Kabuki syndrome 1	*KMT2D*
Kabuki syndrome 2	*KDM6A*
• Secondary signature analysis when abnormal with reduced sensitivity.	
Karayol-Borroto-Haghshenas neurodevelopmental syndrome	*MSL2*
Kleefstra syndrome 1	*EHMT1*
Klinefelter syndrome	47, *XXY*
• XXX and XYY cases may also 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)
MORC2-related syndrome	*MORC2*
Mowat-Wilson syndrome	*ZEB2*
Myhre syndrome	*SMAD4*
Neurodevelopmental-craniofacial syndrome with variable renal and cardiac abnormalities	*ZMYM2*
Neurodevelopmental disorder with congenital cardiac defects and variable renal and ocular abnormalities	*KDM2B*
Neurodevelopmental disorder with hypotonia, stereotypic hand movements, and impaired language	*MEF2C*
Neurodevelopmental disorder with speech impairment and dysmorphic facies/Early-onset epilepsy with or without developmental delay, type 2	*SETD1A*
NSD2 duplication-related syndrome	*NSD2* duplication (Chr4:1,831,006-1,973,304)
Phelan-McDermid syndrome	22q13.3 deletion (Chr22:48,842,456-49,855,259)
• *SHANK3* sequence variants are not detected.	
Pitt-Hopkins syndrome	*TCF4*
Pitt-Hopkins syndrome/Craniosynostosis, type 3	*TCF4, TCF12*
PRC2 complex disorders: Weaver, Cohen-Gibson & Imagawa-Matsumoto syndromes	*EZH2, EED, SUZ12*
Rahman syndrome	*H1-4 (HIST1H1E)*
ReNU syndrome	*RNU4-2*
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.	
Schuurs-Hoeijmakers syndrome	*PACS1*
Sifrim-Hitz-Weiss syndrome/*CHD4*-related syndrome	*CHD4*
• Distinct episignatures for missense and truncating variants.	

SMARCA5-related syndrome	*SMARCA5*
SMARCA5-related syndrome/Neurodevelopmental disorder with dysmorphic facies and distal limb anomalies	*SMARCA5, BPTF*
Smith Magenis syndrome • *RAI1* sequence variants are not detected.	17p11.2 deletion (Chr17:17,419,599-18,612,456)
Sotos syndrome	*NSD1*
Turner syndrome	45, X
Tatton-Brown-Rahman syndrome	*DNMT3A*
Trisomy X	ChrX triplication
Velocardiofacial syndrome	22q11.2 deletion (Chr22:19,510,547-20,285,090)
White-Sutton syndrome/Neurodevelopmental disorder with hypotonia, impaired language, and dysmorphic features	*POGZ, CHAMP1*
Wiedemann-Steiner syndrome	*KMT2A*
Williams-Beuren region duplication syndrome	7q11.23 duplication (Chr7:74,539,188-74,724,126)
Williams-Beuren syndrome	7q11.23 deletion
Witteveen-Kolk syndrome	*SIN3A*
Wolf-Hirschhorn syndrome & Rauch-Steindl syndrome • *NSD2* sequence variants have been detected.	4p16.3 deletion (Chr4:685,926-2,167,274) involving *NSD2*
Xia-Gibbs syndrome	*AHDC1*
X-linked intellectual developmental disorder, type 97 • Heterozygotes are not detected.	*ZNF711*
X-linked intellectual developmental disorder, type 112 • Defined from male cases only.	*ZMYM3*
X-linked syndromic intellectual developmental disorder, Claes-Jensen type • Healthy carriers and those with incomplete penetrance are detectable. • Heterozygotes have a distinct profile from hemizygotes.	*KDM5C*
X-linked intellectual developmental disorder, Lubs type	*MECP2* duplication
X-linked intellectual developmental disorder, Siderius type • Defined from male cases only.	*PHF8*

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EpiSign Expert

Dr. Matthew Tedder believes in the technology behind EpiSign and is committed to expanding its impact. Dr. Tedder has been involved in the test development and data review of EpiSign since its launch and is our EpiSign Expert at GGC. He works closely with our team of laboratory directors and genetic counselors. Clinical teams find his 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 for EpiSign questions or to schedule an educational talk for your team.

*A 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.**

Conditions with Moderate Signatures	Related Region or Gene(s)
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.	
Arboleda-Tham syndrome • Combined signature with *KAT6B*. • Secondary signature analysis when abnormal with reduced sensitivity.	*KAT6A*
Au-Kline syndrome	*HNRNPK*
Branchial arch abnormalities, choanal atresia, athelia, hearing loss, and hypothyroidism syndrome • Defined with missense variants in exons 38-39	*KMT2D*
Autosomal dominant cerebellar ataxia, deafness, narcolepsy	*DNMT1*
Autosomal dominant intellectual developmental disorder type 23, KBG syndrome Secondary signatures : Autosomal dominant intellectual developmental disorder, type 23 KBG syndrome • Secondary signature analysis when abnormal with reduced sensitivity.	*SETD5, ANKRD11* *SETD5* *ANKRD11*
Autosomal dominant intellectual developmental disorder, type 29 • Defined from truncating variants only.	*SETBP1*
Autosomal dominant intellectual developmental disorder, type 51 • Healthy carriers and those with incomplete penetrance are detectable.	*KMT5B*
CHARGE syndrome	*CHD7*
Chromosome Xp11.22 duplication syndrome	Xp.11.22 (ChrX:53,532,096-53,627,567)
Clark-Baraitser syndrome	*TRIP12*
Coffin-Siris syndrome 12	*BICRA*
Developmental delay with or without dysmorphic facies and autism • Defined from missense variants within the range of p.960-1159.	*TRRAP*
Developmental delay with variable intellectual disability and dysmorphic facies	*JARID2*
Diamond-Blackfan anemia, types 6 & 7 • Reduced sensitivity against other Diamond-Blackfan anemia disorders may be observed.	*RPL5, RPL11*
Diamond-Blackfan anemia type 11 • Reduced sensitivity against other Diamond-Blackfan anemia disorders may be observed.	*RPS26*
DMAP1-related syndrome	*DMAP1*
EHMT1 duplicated-related syndrome	*EHMT1* duplication
Fascioscapulohumeral muscular dystrophy, type 2	*SMCHD1*
Fetal valproate syndrome • Included as an opt-in analysis by targeted request.	
Gabrielle-de Vries syndrome	*YY1*
Genitopatellar syndrome • Combined signature with *KAT6A*.	*KAT6B*
Hypermethioninemia with deficiency of S-adenosylhomocysteine hydrolase	*AHCY*
Intellectual developmental disorder with autism and macrocephaly	*CHD8*
Intellectual developmental disorder with dysmorphic facies and behavioral abnormalities	*FBXO11*
Intellectual developmental disorder with microcephaly and with or without ocular malformations or hypogonadotropic hypogonadism	*SOX11*
Intellectual developmental disorder with dysmorphic facies, speech delay, and T-cell abnormalities	*BCL11B*
Karayol-Borroto-Haghshenas neurodevelopmental syndrome	*MSL2*
MACROH2A1-related syndrome	*MACROH2A1*
Neuroocular syndrome • Healthy carriers and those with incomplete penetrance may be detected.	*PRR12*

Neurodevelopmental disorder with dysmorphic facies and behavioral abnormalities	*SRSF1*
Neurodevelopmental disorder with microcephaly, cerebral atrophy and visual impairment	*DOHH*
Neurodevelopmental disorder with or without autism or seizures	*CUL3*
NOTCH1-related syndrome	*NOTCH1*
Ohdo syndrome, SBBYS variant • Combined signature with *KAT6A*.	*KAT6B*
PHF12-related syndrome	*PHF12*
Potocki-Lupski syndrome	17p11.2 duplication (Chr17:16,876,098-20,328,066)
Recurrent constellations of embryonic malformations: VATER/VACTERL association, Oculoauriculovertebral syndrome	
Renpenning syndrome • Heterozygotes are not detected.	*PQBP1*
Schinzel-Giedion midface retraction syndrome • Defined from missense variants impacting amino acids p.868-871.	*SETBP1*
Smith-Kingsmore syndrome	*MTOR*
Tessadori-Bicknell-van Haaften neurodevelopmental syndrome 1-4; *H4C4*-related syndrome; *H4C6*-related syndrome	*H4C3, H4C4, H4C5, H4C9, H4C11*
WAPL-associated syndrome; *PDS5B*-related syndrome • Defined from truncating variants.	*WAPL, PDS5B*
Wieacker-Wolff syndrome • Heterozygotes are not detected.	*ZC4H2*
X-linked intellectual developmental disorder, type 93 • Healthy carriers and those with incomplete penetrance may be detected.	*BRWD3*
X-linked syndromic intellectual developmental disorder, Armfield type • Heterozygotes are not detected.	*FAM50A*
X-linked syndromic intellectual developmental disorder, Nascimento type • Heterozygotes are not detected.	*UBE2A*
X-linked syndromic intellectual developmental disorder, Snyder-Robinson type • Heterozygotes are not detected.	*SMS*

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All coordinates are based on human genome build GRCh38.

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

+1 800.473.9411

Turnaround Time: 4 weeks

labgc@ggc.org

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

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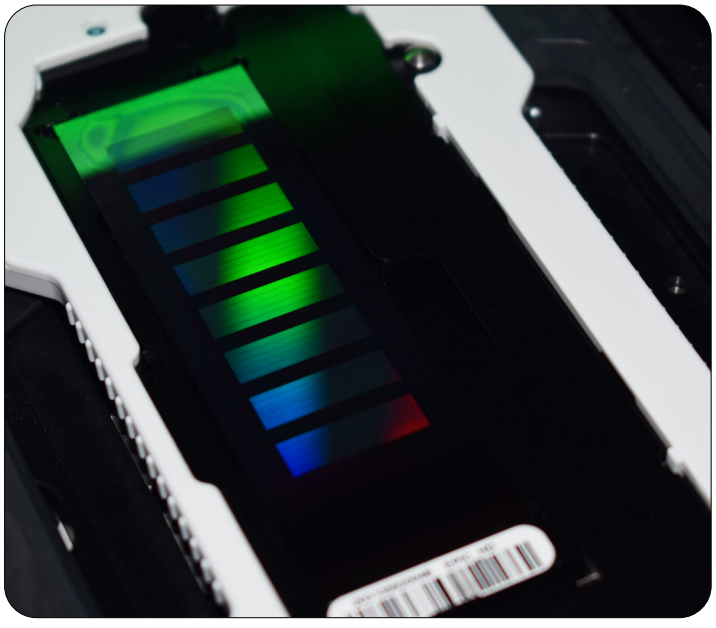

Giving Greater Care

Greenwood Genetic Center

Localized Methylation Analyses	Related Region or Gene(s)
Angelman syndrome • Methylation of *SNURF* and *SNRPN* are reviewed. • *UBE3A* sequence variants are not detected.	15q11.2 imprinting abnormality
BCLAF3-related syndrome • Applicable to male cases only. • *BCLAF* sequence variants are not detected. • Promoter assessment only.	*BCLAF3* promotor
Beckwith-Wiedemann syndrome • CDKN1C sequence variants are not detected.	11p15 imprinting abnormality
Diabetes Mellitus, transient neonatal 1	*PLAGL1* imprinting abnormality
Fragile X syndrome • Heterozygotes are not detected.	*FMR1* promoter
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* is reviewed.	UPD 7 imprinting abnormality
Temple syndrome	*MEG3* imprinting abnormality
Uniparental disomy of chromosome 16	Chr16
Multi-locus Imprinting Disturbance	All imprinting regions listed above

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

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