EpiSign

Methylation Understood

EpiSign is an assay designed to readily identify proven and reproducible *epigenetic signatures* by assessing genome-wide methylation. EpiSign has multiple applications in the clinical setting by providing an additional diagnostic tool beyond the current sequencing and copy number technology paradigm.

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.

Abnormalities detected using this initial screen may require additional targeted testing to confirm and further characterize the underlying genomic abnormality.

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 a useful screening tool for these disorders in the diagnostic work-up or can be applied in a more targeted fashion to help resolve variants of uncertain clinical significance.

Imprinting Abnormalities	Related Region or Gene(s)
Angelman syndrome	15q11.2 methylation abnormality
Beckwith-Wiedemann syndrome	11p15 imprinting abnormality
Diabetes Mellitus, transient neonatal 1	*PLAGL1* imprinting abnormality
Fragile X syndrome	*FMR1* methylation abnormality
Kagami-Ogata syndrome	*MEG3* imprinting abnormality
Mulchandani-Bhoj-Conlin syndrome	20q11-q13 imprinting abnormality involving *GNAS* complex locus
Prader-Willi syndrome	15q11.2 methylation abnormality
Pseudohypoparathyroidism, Type 1A-1C	20q13.32 imprinting abnormality involving *GNAS* complex locus
Russell-Silver syndrome 1	11p15 imprinting abnormality
Russell-Silver syndrome 2	UPD 7 imprinting abnormality
Temple syndrome	*MEG3* imprinting abnormality

Greenwood Diagnostic Labs
Giving Greater Care

in partnership with

London Health Sciences Centre
St Joseph's Health Care London
Pathology and Laboratory Medicine

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

Conditions with Strong Signatures	Related Region or Gene(s)
7q11.23 duplication	7q11.23 duplication (Chr7:72,745,0470-74,138,460)
AD Cerebellar Ataxia. Deafness, Narcolepsy (ADCADN)	*DNMT1*
Alpha-thalassemia X-linked Intellectual Disability	*ATRX*
BAFopathy 1: including Coffin-Siris syndrome & Nicolaides-Baraitser [1]	*ARID1A, ARID1B, SMARCB1, SMARCA4, SMARCA2*
BAFopathy 2: Coffin-Siris syndrome 1 & 2	*ARID1A* (c.6133-c.6254), *ARID1B* (c.6133-c.6254)
Beck-Fahrner syndrome [3,4]	*TET3*
Blepharophimosis Intellectual Disability *SMARCA2* syndrome	*SMARCA2*
CHARGE syndrome	*CHD7*
Coffin-Siris syndrome-4	*SMARCA4* (c.2656)
Cornelia de Lange syndrome [2]	*NIPBL, RAD21, SMC3, SMC1A*
Down syndrome	Trisomy 21
Dystonia-28	*KMT2B*
Epileptic Encephalopathy, childhood-onset	*CHD2*
Floating-Harbor syndrome	*SRCAP*
Gabriele-de Vries syndrome	*YY1*
Helsmoortel-Van der Aa syndrome	*ADNP*
Hunter-McAlpine syndrome	5q35.2q35.3 duplication (Chr5:175,728,979-177,047,793) involving *NSD1*
Intellectual development disorder with seizures and language delay	*SETD1B*
Intellectual Disability, X-linked syndromic, Claes-Jensen type [3]	*KDM5C*
Intellectual Disability, X-linked syndromic, Nascimento-type	*UBE2A*
Kabuki syndrome 1 & 2	*KDM6A, KMT2D*
KDM2B-related syndrome	*KDM2B*
Kleefstra syndrome	*EHMT1*
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)
Myopathy, lactic acidosis, and sideroblastic anemia-2	*YARS2*
Phelan-McDermid syndrome	22q13.3 deletion (Chr22:45,277,036-51,244,566)
PRC2 complex disorders: Weaver & Cohen-Gibson syndromes	*EZH2, EED*
Rahman syndrome	*HIST1H1E*
Rubinstein-Taybi syndrome 1	*CREBBP*
Rubinstein-Taybi syndrome 2	*EP300*
Sotos syndrome 1	*NSD1*
Velocardiofacial syndrome	22q11.2 deletion (Chr22: 16,888,899-21,915,509)
Wiedemann-Steiner syndrome	*KMT2A*
Williams-Beuren syndrome	7q11.23 deletion (Chr7:72,744,455-74,142,510)
Wolf-Hirschhorn syndrome	4p16.3 deletion (Chr4:331,568-2,010,962) involving *NSD2*

Genes/conditions listed in blue are new signatures for EpiSign version 3.

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

Conditions with Moderate Signatures	Related Region or Gene(s)
Arboleda-Tham syndrome	*KAT6A*
Austism, susceptibility to, 18	*CHD8*
Borjeson-Forssman-Lehmann syndrome	*PHF6*
Coffin-Siris syndrome 9	*SOX11*
Genitopatellar syndrome	*KAT6B*
Immunodeficiency-centromeric instability-facial anomalies syndrome, type 1	*DNMT3B*
Immunodeficiency-centromeric instability-facial anomalies syndrome, types 2-4	*CDCA7, ZBTB24, HELLS*
Intellectual Developmental Disorder, autosomal dominant 65	*KDM4B*
Intellectual Developmental Disorder, X-linked, syndromic, Armfield type	*FAM50A*
Intellectual Disability, autosomal dominant 23	*SETD5*
Intellectual Disability, autosomal dominant 51 [3]	*KMT5B*
Intellectual Disability, X-linked 93 [3]	*BRWD3*
Intellectual Disability, X-linked 97	*ZNF711*
Renpenning syndrome	*PQBP1*
SBBYS syndrome	*KAT6B*
Snyder-Robinson syndrome	*SMS*
Tatton-Brown-Rahman syndrome	*DNMT3A*

[1] Patients with variants in other BAFopathy genes may be detected, but this finding has not been confirmed.
[2] *HDAC8* for males may also be detected, but this finding has not been confirmed.
[3] Healthy carriers and those with incomplete penetrance are detectable.
[4] Patients with biallelic variants are distinguishable from those with monoallelic variants.

Note: All coordinates are based on human genome build hg19.

Disclaimer: The listed genes and conditions have undergone a detailed review by Greenwood Diagnostic Labs, and EpiSign has been validated for clinical use. *Please note that some conditions/genes have been classified as having more moderate signatures based on signature strength, small cohort size, or types of mutations.* Females tested for X-linked conditions may have a moderate signature or a potentially false negative result. As with many clinical tests, uncertain results are possible. Please note that a normal result does not rule out the possibility that the patient is affected with one of these conditions. In some case, specific follow-up testing may be suggested to confirm or rule out a diagnosis.

METHYLATION UNDERSTOOD

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 over 50 conditions. This test may be a useful screening tool for patients with developmental delay or with one or more overlapping features suggestive of one of the represented epigenetic signature conditions or imprinting disorders.

EpiSign Variant is a targeted review of the methylation data intended to resolve variants of uncertain clinical significance in genes with a known epigenetic signature. Pathogenic variants in these genes have an established unique signature. When present, this signature can be used to provide a supporting level of evidence for pathogenicity during variant classification.

EpiSign Complete : $1500 (81479)
EpiSign Variant : $1200 (81479)

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

Turnaround time : 4 weeks

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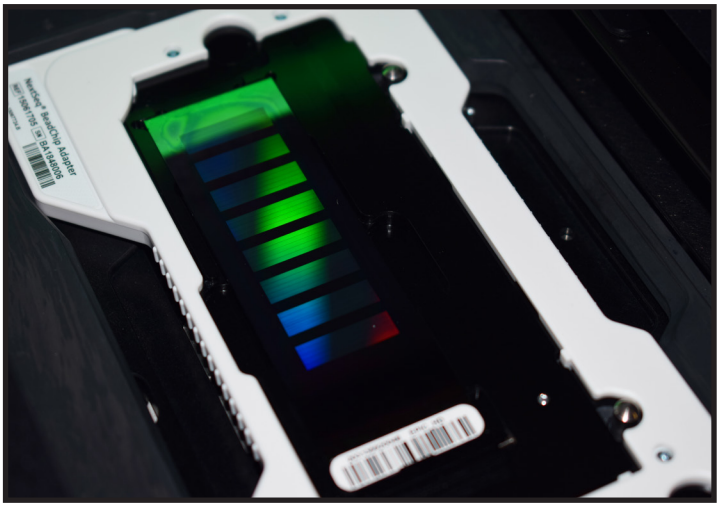

About Greenwood Genetic Center

The Greenwood Genetic Center is a nonprofit institute organized to provide clinical genetic services, diagnostic laboratory testing, educational programs and resources and research in the field of medical genetics.

About London Health Science Centre

Pathology and Laboratory Medicine is an integrated and collaborative team of faculty, staff and learners achieving excellence in knowledge sharing, knowledge creation and patient care; meeting the diverse needs of patients, students and communities we serve and partner with; and pushing the boundaries of quality improvement and innovation in diagnostics to advance health outcomes.