EpiSign

Methylation Understood

Frequently Asked Questions

How does EpiSign work?

EpiSign is performed as a genome-wide methylation array analyzing 935,000 methylation sites across the genome. Each recognized episignature includes an average of 150 unique probes that were selected to distinguish between healthy controls and individuals known to be affected with that particular condition.

What is the difference between strong signatures and moderate signatures?

Generally, training cohorts for EpiSign are comprised of alterations consistent with the reported disease mechanism such as loss of function or haploinsufficiency. 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 have reduced sensitivity/specificity and a lower negative predictive value than the other "strong signatures."

Why are imprinting disorders listed separately?

The imprinting disorders do not involve specific episignatures across the genome. Instead, we are analyzing only the associated gene or region known to be differentially methylated for that condition. If you have a strong clinical suspicion for one of these conditions, we suggest a standard test such as pyrosequencing or MS-MLPA. However, if your differential includes multiple conditions such as Russell-Silver and Temple syndrome, or if parents are not available for UPD testing, EpiSign can provide a comprehensive analysis of the imprinting disorders. Please note that EpiSign Variant can be requested to include all imprinting disorders if multiple conditions are in the patient's differential or if you suspect multilocus imprinting disturbance (MLID).

Do I order EpiSign Complete or EpiSign Variant?

EpiSign Variant is typically used to clarify the significance of a VUS in a specific gene or when the patient has a presentation consistent with one of the included conditions. A previous molecular finding is not required to order testing. Since the full methylation array data is captured, we can reflex to EpiSign Complete for the cost difference if Variant is negative. However, you are welcome to start with EpiSign Complete if desired, even if none of the included conditions are in your differential.

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What billing options are available?

The laboratory can only bill insurance for patients that reside in South Carolina. We offer institutional billing or a 40%, upfront, self-pay discount for patients and families payable by check or credit card. If preauthorization is obtained prior to testing, then the family may be able to submit the payment as a claim to their insurance company. The current CPT codes are 0318U for EpiSign Complete and 81479 for EpiSign Variant. Please check with the patient's insurance to ensure that these codes are on their fee schedule.

What samples are accepted for EpiSign?

New blood samples and previously isolated DNA from blood from patients are accepted. Due to global hypomethylation, please contact the lab when considering EpiSign for a patient less than one year old. Please note that DNA from saliva or tissue is not accepted.

How much DNA is needed if sending isolated DNA?

If you are sending blood-derived DNA, we ask for 2-3 micrograms at a concentration of ~100 ng/µl. If you have a limited amount of DNA available the lab would recommend sending at least 1 µg of DNA for EpiSign testing.

Can EpiSign be ordered on infants?

Newborns tend to have global hypomethylation which can make data interpretation difficult for the conditions with moderate signatures. The imprinting disorders and the strong signatures are usually not impacted by this issue. We are willing to accept samples from infants, and our current policy for uninterpretable cases due to global hypomethylation is to offer repeat testing at no additional charge on a new sample collected after one year of age.

Should I provide a copy of previous outside genetic testing results?

We like to have as much phenotype/genotype information as possible. Providers will often send recent clinic notes as well as previous genetic testing results. This information helps in the current analysis as well as with signature refinement/development going forward.

What about reanalysis?

EpiSign is an evolving test as episignatures become more refined and new signatures are added to the condition list. We will attempt to reach out to the original referring provider for any previously run patient who matches a new signature to inquire if an updated report is needed.

Do you work with any external sites to assist with methylation signatures in genes not currently included on EpiSign?

We do collaborate with clinicians for episignature discovery work. If there is a specific gene/condition you are interested in, please contact the lab to see if a cohort is in progress or if it is likely to be included on an upcoming version. This episignature discovery work is usually performed on an investigational or research basis. If a signature is established, a report would be issued stating that the patient's sample matches a signature. If we are unable to establish a signature for that gene/condition, then we would be unable to issue a report.

The most recent list of genes/conditions included on EpiSign is located on the EpiSign webpage: www.GGC.org/EpiSign.

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