

Porphyria Panel

Test code: ME0101

Is a 9 gene panel that includes assessment of non-coding variants.

Is ideal for patients with a clinical suspicion of porphyria. This panel is included in the Comprehensive Metabolism Panel.

About Porphyria

Porphyrias are a group of metabolic disorders that are characterized by abnormalities in the production of heme and result in the accumulation of heme precursors in the liver or in the bone marrow and blood cells. Porphyrias present with neuro-visceral symptoms, skin problems, or both. Acute porphyrias usually have nerve symptoms and episodic crises resulting in nausea, vomiting, abdominal pain and hypertension. Non-acute porphyrias seldom have acute attacks but rather cause skin problems after exposure to light as these molecules react with light. The prevalence of different porphyria types varies significantly. Porphyria cutanea tarda is the most common (1:10,000; not all cases are genetic), while some other types have a prevalence of 1:1,000,000 or even less.

Availability

4 weeks

Gene Set Description

Genes in the Porphyria Panel and their clinical significance

| Gene | Associated phenotypes | Inheritance | ClinVar | HGMD |
|-------|--|-------------|---------|------|
| ALAD | Porphyria, acute hepatic | AR | 6 | 11 |
| ALAS2 | Anemia, sideroblastic, Protoporphyrinemia, erythropoietic | XL | 27 | 103 |
| CPOX | Coproporphyrinemia, Harderoporphyria | AD/AR | 15 | 70 |
| FECH | Protoporphyrinemia, erythropoietic | AD/AR | 14 | 193 |
| HFE | Hemochromatosis | AR/Digenic | 11 | 56 |
| HMBS | Porphyria, acute intermittent, Hydroxymethylbilane synthase deficiency | AD/AR | 55 | 419 |
| PPOX | Porphyria variegata | AD/AR | 16 | 183 |
| UROD | Porphyria cutanea tarda, Porphyria, hepatoerythropoietic | AD/AR | 15 | 122 |
| UROS | Porphyria, congenital erythropoietic | AR | 22 | 49 |

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Some, or all, of the gene is duplicated in the genome. [Read more.](#)

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The gene has suboptimal coverage (means <90% of the gene's target nucleotides are covered at >20x with mapping quality score (MQ>20) reads), and/or the gene has exons listed under Test limitations section that are not included in the panel as they are not sufficiently covered with high quality sequence reads.

The sensitivity to detect variants may be limited in genes marked with an asterisk (*) or number sign (#). Due to possible limitations these genes may not be available as single gene tests.

Gene refers to the HGNC approved gene symbol; Inheritance refers to inheritance patterns such as autosomal dominant (AD), autosomal recessive (AR), mitochondrial (mi), X-linked (XL), X-linked dominant (XLD) and X-linked recessive (XLR); ClinVar refers to the number of variants in the gene classified as pathogenic or likely pathogenic in this database ([ClinVar](#)); HGMD refers to the number of variants with possible disease association in the gene listed in Human Gene Mutation Database ([HGMD](#)). The list of associated, gene specific phenotypes are generated from [CGD](#) or Mitomap databases.

Non-coding disease causing variants covered by the panel

| Gene | Genomic location HG19 | HGVS | RefSeq | RS-number |
|-------|-----------------------|---------------|----------------|-------------|
| ALAD | Chr9:116153914 | c.165-11C>T | NM_000031.5 | rs749066913 |
| ALAD | Chr9:116153914 | c.165-11C>A | NM_000031.5 | |
| ALAS2 | ChrX:55054634 | c.-15-2186C>G | NM_000032.4 | |
| ALAS2 | ChrX:55054635 | c.-15-2187T>C | NM_000032.4 | |
| ALAS2 | ChrX:55054636 | c.-15-2188A>G | NM_000032.4 | |
| ALAS2 | ChrX:55057393 | c.-34C>T | NM_000032.4 | rs780642606 |
| ALAS2 | ChrX:55057617 | c.-258C>G | NM_000032.4 | rs140772352 |
| CPOX | Chr3:98300369 | c.1173-14T>G | NM_000097.5 | |
| CPOX | Chr3:98310014 | c.557-15C>G | NM_000097.5 | |
| FECH | Chr18:55238820 | c.315-48T>C | NM_000140.3 | rs2272783 |
| FECH | Chr18:55238839 | c.333-67G>A | NM_001012515.2 | |
| FECH | Chr18:55254103 | c.-251G>C | NM_000140.3 | |
| HFE | Chr6:26087649 | c.-20G>A | NM_000410.3 | rs138378000 |
| HMBS | Chr11:118955302 | | NM_000190.3 | rs782669452 |
| HMBS | Chr11:118955413 | c.-331C>T | NM_000190.3 | |
| HMBS | Chr11:118955474 | c.-270G>A | NM_000190.3 | |
| HMBS | Chr11:118955588 | c.-154delG | NM_000190.3 | |
| HMBS | Chr11:118955622 | c.-122T>A | NM_000190.3 | |
| HMBS | Chr11:118956445 | c.33+669A>G | NM_000190.3 | |
| HMBS | Chr11:118958944 | c.34-21A>G | NM_000190.3 | |
| HMBS | Chr11:118959325 | c.88-20A>C | NM_000190.3 | |

| | | | | |
|------|-----------------|-----------------------------|----------------|-------------|
| PPOX | Chr1:161135755 | c.-655G>C | NM_000309.3 | |
| PPOX | Chr1:161136225 | c.-185G>T | NM_000309.3 | rs114493458 |
| PPOX | Chr1:161136462 | c.-9G>A | NM_001122764.1 | rs999497211 |
| PPOX | Chr1:161138197 | c.472-24_472-16delCTTAGTCCT | NM_000309.3 | |
| PPOX | Chr1:161140686 | c.1249-11T>G | NM_000309.3 | rs780277900 |
| UROD | Chr1:45481229 | c.*62_*63delAA | NM_000374.4 | |
| UROS | Chr10:127477605 | c.661-31T>G | NM_000375.2 | rs750180293 |
| UROS | Chr10:127505271 | c.-26-177T>C | NM_000375.2 | rs397515348 |
| UROS | Chr10:127505271 | c.-26-177T>A | NM_000375.2 | |
| UROS | Chr10:127505277 | c.-26-183G>A | NM_000375.2 | rs397515349 |
| UROS | Chr10:127505287 | c.-26-193C>A | NM_000375.2 | rs397515350 |
| UROS | Chr10:127505287 | c.-26-193C>G | NM_000375.2 | |
| UROS | Chr10:127505291 | c.-26-197C>A | NM_000375.2 | rs397515351 |
| UROS | Chr10:127511774 | c.-203T>C | NM_000375.2 | rs869320670 |

Test Strengths

The strengths of this test include:

- CAP accredited laboratory
- CLIA-certified personnel performing clinical testing in a CLIA-certified laboratory
- Powerful sequencing technologies, advanced target enrichment methods and precision bioinformatics pipelines ensure superior analytical performance
- Careful construction of clinically effective and scientifically justified gene panels
- Some of the panels include the whole mitochondrial genome (please see the Panel Content section)
- Our Nucleus online portal providing transparent and easy access to quality and performance data at the patient level
- Our publicly available analytic validation demonstrating complete details of test performance
- ~2,000 non-coding disease causing variants in our clinical grade NGS assay for panels (please see 'Non-coding disease causing variants covered by this panel' in the Panel Content section)
- Our rigorous variant classification scheme
- Our systematic clinical interpretation workflow using proprietary software enabling accurate and traceable processing of NGS data
- Our comprehensive clinical statements

Test Limitations

This test does not detect the following:

- Complex inversions
- Gene conversions
- Balanced translocations
- Some of the panels include the whole mitochondrial genome but not all (please see the Panel Content section)
- Repeat expansion disorders unless specifically mentioned
- Non-coding variants deeper than ±20 base pairs from exon-intron boundary unless otherwise indicated (please see

above Panel Content / non-coding variants covered by the panel).

This test may not reliably detect the following:

- Low level mosaicism in nuclear genes (variant with a minor allele fraction of 14.6% is detected with 90% probability)
- Stretches of mononucleotide repeats
- Low level heteroplasmy in mtDNA (>90% are detected at 5% level)
- Indels larger than 50bp
- Single exon deletions or duplications
- Variants within pseudogene regions/duplicated segments
- Some disease causing variants present in mtDNA are not detectable from blood, thus post-mitotic tissue such as skeletal muscle may be required for establishing molecular diagnosis.

The sensitivity of this test may be reduced if DNA is extracted by a laboratory other than Blueprint Genetics.

For additional information, please refer to the Test performance section and see our Analytic Validation.

Test Performance

The genes on the panel have been carefully selected based on scientific literature, mutation databases and our experience.

Our panels are sectioned from our high-quality, clinical grade NGS assay. Please see our sequencing and detection performance table for details regarding our ability to detect different types of alterations (Table).

Assays have been validated for various sample types including EDTA-blood, isolated DNA (excluding from formalin fixed paraffin embedded tissue), saliva and dry blood spots (filter cards). These sample types were selected in order to maximize the likelihood for high-quality DNA yield. The diagnostic yield varies depending on the assay used, referring healthcare professional, hospital and country. Plus analysis increases the likelihood of finding a genetic diagnosis for your patient, as large deletions and duplications cannot be detected using sequence analysis alone. Blueprint Genetics' Plus Analysis is a combination of both sequencing and deletion/duplication (copy number variant (CNV)) analysis.

The performance metrics listed below are from an initial validation performed at our main laboratory in Finland. The performance metrics of our laboratory in Seattle, WA, are equivalent.

Performance of Blueprint Genetics high-quality, clinical grade NGS sequencing assay for panels.

| | Sensitivity % (TP/(TP+FN)) | Specificity % |
|---|----------------------------|---------------|
| Single nucleotide variants | 99.89% (99,153/99,266) | >99.9999% |
| Insertions, deletions and indels by sequence analysis | | |
| 1-10 bps | 99.2% (7,745/7,806) | >99.9999% |
| 11-50 bps | 99.13% (2,524/2,546) | >99.9999% |
| Copy number variants (exon level dels/dups) | | |
| 1 exon level deletion (heterozygous) | 100% (20/20) | NA |
| 1 exon level deletion (homozygous) | 100% (5/5) | NA |
| 1 exon level deletion (het or homo) | 100% (25/25) | NA |
| 2-7 exon level deletion (het or homo) | 100% (44/44) | NA |
| 1-9 exon level duplication (het or homo) | 75% (6/8) | NA |
| Simulated CNV detection | | |



| | | |
|--|--------------|---------|
| 5 exons level deletion/duplication | 98.7% | 100.00% |
| Microdeletion/-duplication sdrs (large CNVs, n=37) | | |
| Size range (0.1-47 Mb) | 100% (25/25) | |

The performance presented above reached by Blueprint Genetics high-quality, clinical grade NGS sequencing assay with the following coverage metrics

| | |
|---|--------|
| Mean sequencing depth | 143X |
| Nucleotides with >20x sequencing coverage (%) | 99.86% |

Performance of Blueprint Genetics Mitochondrial Sequencing Assay.

| | Sensitivity % | Specificity % |
|---|--------------------|---------------|
| ANALYTIC VALIDATION (NA samples; n=4) | | |
| Single nucleotide variants | | |
| Heteroplasmic (45-100%) | 100.0% (50/50) | 100.0% |
| Heteroplasmic (35-45%) | 100.0% (87/87) | 100.0% |
| Heteroplasmic (25-35%) | 100.0% (73/73) | 100.0% |
| Heteroplasmic (15-25%) | 100.0% (77/77) | 100.0% |
| Heteroplasmic (10-15%) | 100.0% (74/74) | 100.0% |
| Heteroplasmic (5-10%) | 100.0% (3/3) | 100.0% |
| Heteroplasmic (<5%) | 50.0% (2/4) | 100.0% |
| CLINICAL VALIDATION (n=76 samples) | | |
| All types | | |
| Single nucleotide variants n=2026 SNVs | | |
| Heteroplasmic (45-100%) | 100.0% (1940/1940) | 100.0% |
| Heteroplasmic (35-45%) | 100.0% (4/4) | 100.0% |
| Heteroplasmic (25-35%) | 100.0% (3/3) | 100.0% |
| Heteroplasmic (15-25%) | 100.0% (3/3) | 100.0% |
| Heteroplasmic (10-15%) | 100.0% (9/9) | 100.0% |
| Heteroplasmic (5-10%) | 92.3% (12/13) | 99.98% |
| Heteroplasmic (<5%) | 88.9% (48/54) | 99.93% |
| Insertions and deletions by sequence analysis n=40 indels | | |



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| | | |
|---|-----------------|-------------------|
| Heteroplasmic (45-100%) 1-10bp | 100.0% (32/32) | 100.0% |
| Heteroplasmic (5-45%) 1-10bp | 100.0% (3/3) | 100.0% |
| Heteroplasmic (<5%) 1-10bp | 100.0% (5/5) | 99,997% |
| SIMULATION DATA /(mitomap mutations) | | |
| Insertions, and deletions 1-24 bps by sequence analysis; n=17 | | |
| Homoplasmic (100%) 1-24bp | 100.0% (17/17) | 99.98% |
| Heteroplasmic (50%) | 100.0% (17/17) | 99.99% |
| Heteroplasmic (25%) | 100.0% (17/17) | 100.0% |
| Heteroplasmic (20%) | 100.0% (17/17) | 100.0% |
| Heteroplasmic (15%) | 100.0% (17/17) | 100.0% |
| Heteroplasmic (10%) | 94.1% (16/17) | 100.0% |
| Heteroplasmic (5%) | 94.1% (16/17) | 100.0% |
| Copy number variants (separate artificial mutations; n=1500) | | |
| Homoplasmic (100%) 500 bp, 1kb, 5 kb | 100.0% | 100.0% |
| Heteroplasmic (50%) 500 bp, 1kb, 5 kb | 100.0% | 100.0% |
| Heteroplasmic (30%) 500 bp, 1kb, 5 kb | 100.0% | 100.0% |
| Heteroplasmic (20%) 500 bp, 1kb, 5 kb | 99.7% | 100.0% |
| Heteroplasmic (10%) 500 bp, 1kb, 5 kb | 99.0% | 100.0% |
| The performance presented above reached by following coverage metrics at assay level (n=66) | | |
| | Mean of medians | Median of medians |
| Mean sequencing depth MQ0 (clinical) | 18224X | 17366X |
| Nucleotides with >1000x MQ0 sequencing coverage (%) (clinical) | 100% | |
| rho zero cell line (=no mtDNA), mean sequencing depth | 12X | |

Bioinformatics

The target region for each gene includes coding exons and ± 20 base pairs from the exon-intron boundary. In addition, the panel includes non-coding and regulatory variants if listed above (Non-coding variants covered by the panel). Some regions of the gene(s) may be removed from the panel if specifically mentioned in the "Test limitations" section above. If the test includes the mitochondrial genome the target region gene list contains the mitochondrial genes. The sequencing data generated in our laboratory is analyzed with our proprietary data analysis and annotation pipeline, integrating state-of-the-art algorithms and industry-standard software solutions. Incorporation of rigorous quality control steps throughout the workflow of the pipeline ensures the consistency, validity and accuracy of results. Our pipeline is streamlined to maximize sensitivity without sacrificing specificity. We have incorporated a number of reference population databases and mutation databases including, but not limited, to [1000 Genomes Project](#), [gnomAD](#), [ClinVar](#) and [HGMD](#) into our clinical interpretation software to make the process effective and efficient. For missense variants, *in silico* variant prediction tools such as [SIFT](#), [PolyPhen](#), [MutationTaster](#)

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are used to assist with variant classification. Through our online ordering and statement reporting system, Nucleus, ordering providers have access to the details of the analysis, including patient specific sequencing metrics, a gene level coverage plot and a list of regions with suboptimal coverage (<20X for nuclear genes and <1000X for mtDNA) if applicable. This reflects our mission to build fully transparent diagnostics where ordering providers can easily visualize the crucial details of the analysis process.

Clinical Interpretation

We provide customers with the most comprehensive clinical report available on the market. Clinical interpretation requires a fundamental understanding of clinical genetics and genetic principles. At Blueprint Genetics, our PhD molecular geneticists, medical geneticists and clinical consultants prepare the clinical statement together by evaluating the identified variants in the context of the phenotypic information provided in the requisition form. Our goal is to provide clinically meaningful statements that are understandable for all medical professionals regardless of whether they have formal training in genetics.

Variant classification is the corner stone of clinical interpretation and resulting patient management decisions. Our classifications follow the [ACMG guideline 2015](#).

The final step in the analysis is orthogonal confirmation. Sequence and copy number variants classified as pathogenic, likely pathogenic and variants of uncertain significance (VUS) are confirmed using bi-directional Sanger sequencing or by orthogonal methods such as qPCR/ddPCR when they do not meet our stringent NGS quality metrics for a true positive call.

Our clinical statement includes tables for sequencing and copy number variants that include basic variant information (genomic coordinates, HGVS nomenclature, zygosity, allele frequencies, in silico predictions, OMIM phenotypes and classification of the variant). In addition, the statement includes detailed descriptions of the variant, gene and phenotype(s) including the role of the specific gene in human disease, the mutation profile, information about the gene's variation in population cohorts and detailed information about related phenotypes. We also provide links to the references, abstracts and variant databases used to help ordering providers further evaluate the reported findings if desired. The conclusion summarizes all of the existing information and provides our rationale for the classification of the variant.

Identification of pathogenic or likely pathogenic variants in dominant disorders or their combinations in different alleles in recessive disorders are considered molecular confirmation of the clinical diagnosis. In these cases, family member testing can be used for risk stratification. We do not recommend using variants of uncertain significance (VUS) for family member risk stratification or patient management. Genetic counseling is recommended.

Our interpretation team analyzes millions of variants from thousands of individuals with rare diseases. Our internal database and our understanding of variants and related phenotypes increases with every case analyzed. Our laboratory is therefore well-positioned to re-classify previously reported variants as new information becomes available. If a variant previously reported by Blueprint Genetics is re-classified, our laboratory will issue a follow-up statement to the original ordering health care provider at no additional cost.

CPT code(s) *

81405(1), 81406(2), 81479(1)

* The CPT codes provided are based on AMA guidelines and are for informational purposes only. CPT coding is the sole responsibility of the billing party. Please direct any questions regarding coding to the payer being billed.

ICD Codes

Refer to the most current version of ICD-10-CM manual for a complete list of ICD-10 codes.

Sample Requirements

- Blood (min. 1ml) in an EDTA tube
- Extracted DNA, min. 2 µg in TE buffer or equivalent
- Saliva (Please see [Sample Requirements](#) for accepted saliva kits)

Label the sample tube with your patient's name, date of birth and the date of sample collection.

We do not accept DNA samples isolated from formalin-fixed paraffin-embedded (FFPE) tissue. In addition, if the patient is affected with a hematological malignancy, DNA extracted from a non-hematological source (e.g. skin fibroblasts) is strongly recommended.

Please note that, in rare cases, mitochondrial genome (mtDNA) variants may not be detectable in blood or saliva in which case DNA extracted from post-mitotic tissue such as skeletal muscle may be a better option.

Read more about our sample requirements [here](#).

For Patients

Other

- [American Porphyria Foundation](#)
- [British Porphyria Association](#)
- [Canadian Association for Porphyria](#)
- [GeneReviews - Acute Intermittent Porphyria](#)
- [GeneReviews - Congenital Erythropoietic Porphyria](#)
- [GeneReviews - Hepatoerythropoietic Porphyria](#)
- [GeneReviews - Hereditary Coproporphyrinuria](#)
- [GeneReviews - Porphyria Cutanea Tarda](#)
- [GeneReviews - Variegate Porphyria](#)
- [GeneReviews - X-Linked Protoporphyrinuria](#)
- [GeneReviews- Acute Intermittent Porphyria](#)
- [GeneReviews- Congenital Erythropoietic Porphyria](#)
- [GeneReviews- Hepatoerythropoietic Porphyria](#)
- [GeneReviews- Hereditary Coproporphyrinuria](#)
- [GeneReviews- Variegate Porphyria](#)
- [GeneReviews- X-Linked Protoporphyrinuria](#)
- [GeneReviewsFamilial Porphyria Cutanea Tarda](#)
- [NORD - ALAD Porphyria](#)
- [NORD - Erythropoietic Protoporphyrinuria](#)
- [NORD - Porphyria](#)