

Hyperlipidemia Panel

Test code: CA1101

Is ideal for patients with a clinical suspicion of inherited dyslipidemia including familial hypercholesterolemia due to LDL receptor mutation or ligand-defective apoB, any type of hypertriglyceridemia and sitosterolemia. The genes on the Hyperlipidemia Core Panel are included on this panel.

Familial lipid disorders are inherited in an autosomal dominant and recessive manner. Genetic diagnostics can confirm or modify the clinical diagnosis in lipid disorders. It also enables effective identification of individuals carrying genetic defects that predispose to these diseases. Proband's genetic diagnosis forms the basis for familial screening, which is especially useful for recognizing individuals whose disease has not yet manifested as abnormal lipid levels. Genetic diagnosis helps in adopting a healthy lifestyle at young age, allows early pharmacological treatment, and makes it possible to select patients with homozygous FH (HoFH) or equivalent disease (compound heterozygous or digenic heterozygous) for more aggressive treatment. Mutation detection may affect the therapy related compensation given for patients from government or insurance companies. Hyperlipidemia Panel includes the Hyperlipidemia- Core Panel.

About Hyperlipidemia

Familial lipid disorders such as familial hypercholesterolemia (FH) are inborn errors of metabolism that result in high levels of blood cholesterol and predispose to myocardial infarctions at an early age. In addition to lethal cardiovascular complications, inherited forms of hypercholesterolemia can also cause health problems related to the buildup of excess cholesterol in other tissues. If cholesterol accumulates in tendons, it causes characteristic growths called tendon xanthomas. These growths most often affect the Achilles tendons and tendons in the hands and fingers. Yellowish cholesterol deposits under the skin of the eyelids are known as xanthelasmata. Cholesterol can also accumulate at the edges of the clear, front surface of the eye (the cornea), leading to a gray-colored ring called an arcus cornealis. Familial hypercholesterolemia is usually an autosomal dominant/recessive disorder caused by mutations in LDLR, APOB, PCSK9 or LDLRAP1. Both APOB and PCSK9 related FH are clinically indistinguishable from heterozygous FH (HeFH) caused by LDLR mutations. Recessive forms of hypercholesterolemia are rare. Of these, FH associated with LDLRAP1 is clinically similar to HeFHs. On the contrary, sitosterolemia, which is caused by ABCG5 and ABCG8 mutations, is a specific form of hyperlipidemia that manifests as hypercholesterolemia and high levels (30-100x normal) of plant sterols (phytosterols) in blood and other tissues. Clinical presentation of sitosterolemia includes xanthomas and coronary artery disease at an early age with conflict between the standard risk factor profile and the disease presentation. The familial lipoprotein lipase (LPL) deficiency (also called type 1 hyperlipoproteinemia) is an autosomal recessive condition distinct from other hyperlipidemias. It usually presents in childhood with very severe hypertriglyceridemia and episodic abdominal pain, recurrent acute pancreatitis, eruptive cutaneous xanthomata, and hepatosplenomegaly.

Availability

Results in 3-4 weeks

Gene set description

Genes in the Hyperlipidemia Panel and their clinical significance

| Gene | Associated phenotypes | Inheritance | ClinVar | HGMD |
|-------------------------------|--|-------------|---------|------|
| ABCA1 | Tangier disease, ABCA1 deficiency, HDL deficiency, Familial hypoalphalipoproteinemia | AD/AR | 25 | 218 |
| ABCG5 | Sitosterolemia | AR | 13 | 42 |
| ABCG8 | Sitosterolemia | AR | 18 | 44 |
| <u>ALMS1*</u> | Alström syndrome | AR | 197 | 302 |

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|---------|--|-------|------|------|
| APOA1 | Amyloidosis, systemic nonneuronopathic, Hypoalphalipoproteinemia | AD/AR | 28 | 71 |
| APOA5 | Hyperchylomicronemia | AD/AR | 3 | 61 |
| APOB | Hypobetalipoproteinemia, Hypercholesterolemia | AD/AR | 69 | 306 |
| APOC2 | Hyperlipoproteinemia, type Ib | AR | 13 | 22 |
| APOC3 | Apolipoprotein C-III deficiency | AD | 6 | 8 |
| APOE | Sea-blue histiocyte disease, Dysbetalipoproteinemia, familial (Hyperlipoproteinemia), Lipoprotein glomerulopathy | AD/AR | 31 | 55 |
| CREB3L3 | Hypertriglyceridaemia | AD | | 9 |
| GPIHBP1 | Hyperlipoproteinemia, type ID | AR | 10 | 31 |
| LDLR | Hypercholesterolemia | AD/AR | 1719 | 2180 |
| LDLRAP1 | Hypercholesterolemia | AR | 10 | 23 |
| LIPA | Wolman disease, Cholesterol ester storage disease | AR | 27 | 93 |
| LMF1 | Combined lipase deficiency | AR | 4 | 14 |
| LPL | Lipoprotein lipase deficiency, Hyperlipoproteinemia, Combined hyperlipidemia, familial | AD/AR | 44 | 209 |
| PCSK9 | Hypercholesterolemia | AD | 29 | 89 |

*Some regions of the gene are duplicated in the genome. [Read more.](#)

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 (#)

Gene refers to the HGNC approved gene symbol; Inheritance refers to inheritance patterns such as autosomal dominant (AD), autosomal recessive (AR), 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 [Orphanet](#) databases.

Non-coding disease causing variants covered by the panel

| Gene | Genomic location HG19 | HGVS | RefSeq | RS-number |
|-------|-----------------------|---------------|-------------|-------------|
| ABCA1 | Chr9:107549295 | c.6205-39delT | NM_005502.3 | rs572405590 |
| ABCA1 | Chr9:107567035 | c.4465-34A>G | NM_005502.3 | |
| ABCA1 | Chr9:107571856 | c.4176-11T>G | NM_005502.3 | |
| ABCA1 | Chr9:107599404 | c.1195-27G>A | NM_005502.3 | rs200563809 |
| ABCA1 | Chr9:107690213 | c.-93+2dupT | NM_005502.3 | |

| | | | |
|-------|-----------------|------------------------------------|--------------------------|
| APOA1 | Chr11:116708299 | c.-21+22G>A | NM_000039.1 |
| APOA1 | Chr11:116708365 | c.-65A>C | NM_000039.1 |
| APOC3 | Chr11:116701284 | c.-13-2A>C | NM_000040.1 |
| LDLR | Chr19:11199939 | | NM_000527.4 |
| LDLR | Chr19:11199958 | c.-267A>G | NM_000527.4 |
| LDLR | Chr19:11199997 | c.-228G>C | NM_000527.4 rs376713337 |
| LDLR | Chr19:11200000 | | NM_000527.4 |
| LDLR | Chr19:11200019 | c.-206C>T | NM_000527.4 rs549995837 |
| LDLR | Chr19:11200031 | | NM_000527.4 rs1270618112 |
| LDLR | Chr19:11200032 | | NM_000527.4 rs879254362 |
| LDLR | Chr19:11200032 | | NM_000527.4 |
| LDLR | Chr19:11200034 | c.-191C>A | NM_000527.4 |
| LDLR | Chr19:11200037 | c.-188C>T | NM_000527.4 |
| LDLR | Chr19:11200038 | c.-185_-183delCTT | NM_000527.4 |
| LDLR | Chr19:11200053 | c.-172G>A | NM_000527.4 |
| LDLR | Chr19:11200057 | c.-168A>G | NM_000527.4 |
| LDLR | Chr19:11200062 | c.-163T>C | NM_000527.4 |
| LDLR | Chr19:11200064 | c.-161A>C | NM_000527.4 |
| LDLR | Chr19:11200069 | c.-156C>T | NM_000527.4 |
| LDLR | Chr19:11200069 | c.-155_-154delACinsTTCTGCAAACCTCCT | NM_000527.4 |
| LDLR | Chr19:11200069 | c.-155_-150delACCCCA | NM_000527.4 |
| LDLR | Chr19:11200070 | c.-155_-154delACinsTTCTGCAAACCTCCT | NM_000527.4 rs879254365 |
| LDLR | Chr19:11200070 | c.-155_-150delACCCCAinsTT | NM_000527.4 |
| LDLR | Chr19:11200071 | c.-154C>T | NM_000527.4 |
| LDLR | Chr19:11200072 | c.-153C>T | NM_000527.4 |
| LDLR | Chr19:11200073 | c.-152C>T | NM_000527.4 |
| LDLR | Chr19:11200074 | c.-151C>G | NM_000527.4 |
| LDLR | Chr19:11200075 | c.-150A>G | NM_000527.4 |
| LDLR | Chr19:11200076 | c.-149C>A | NM_000527.4 |
| LDLR | Chr19:11200079 | c.-146C>A | NM_000527.4 |
| LDLR | Chr19:11200083 | c.-142C>G/T | NM_000527.4 |

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|---------|----------------|---------------------------------------|-------------|-------------|
| LDLR | Chr19:11200084 | c.-139_-130delCTCCCCCTGC | NM_000527.4 | |
| LDLR | Chr19:11200086 | c.-139C>A/G | NM_000527.4 | |
| LDLR | Chr19:11200086 | c.-138delT | NM_000527.4 | rs387906307 |
| LDLR | Chr19:11200087 | c.-138T>C | NM_000527.4 | |
| LDLR | Chr19:11200088 | c.-137C>T | NM_000527.4 | |
| LDLR | Chr19:11200089 | c.-136C>G/T | NM_000527.4 | |
| LDLR | Chr19:11200089 | c.-136C>G | NM_000527.4 | rs879254374 |
| LDLR | Chr19:11200089 | c.-136C>T | NM_000527.4 | |
| LDLR | Chr19:11200090 | c.-135C>G | NM_000527.4 | |
| LDLR | Chr19:11200091 | c.-134C>T | NM_000527.4 | |
| LDLR | Chr19:11200098 | c.-124dupA | NM_000527.4 | |
| LDLR | Chr19:11200105 | c.-120C>T | NM_000527.4 | rs875989886 |
| LDLR | Chr19:11200124 | c.-101T>C | NM_000527.4 | rs747068848 |
| LDLR | Chr19:11200126 | c.-99A>G | NM_000527.4 | |
| LDLR | Chr19:11200127 | c.-98C>T | NM_000527.4 | |
| LDLR | Chr19:11200202 | c.-23A>C | NM_000527.4 | rs763282380 |
| LDLR | Chr19:11200202 | c.-22delC | NM_000527.4 | rs879254379 |
| LDLR | Chr19:11200211 | c.-14C>A | NM_000527.4 | |
| LDLR | Chr19:11218203 | c.940+14delC | NM_000527.4 | rs879254730 |
| LDLR | Chr19:11221315 | c.941-13T>A | NM_000527.4 | |
| LDLR | Chr19:11224179 | c.1359-31_1359-23delGCGCTGATGinsCGGCT | NM_000527.4 | |
| LDLR | Chr19:11224186 | c.1359-25A>G | NM_000527.4 | |
| LDLR | Chr19:11227685 | c.1845+11C>G | NM_000527.4 | |
| LDLR | Chr19:11227689 | c.1845+15C>A | NM_000527.4 | |
| LDLR | Chr19:11231284 | c.2140+86C>G | NM_000527.4 | |
| LDLR | Chr19:11231301 | c.2140+103G>T | NM_000527.4 | |
| LDLR | Chr19:11242035 | c.*43G>A | NM_000527.4 | rs879254527 |
| LDLRAP1 | Chr1:25870164 | c.-17_-12dupGGCGGC | NM_015627.2 | |
| LDLRAP1 | Chr1:25891056 | c.748-608G>A | NM_015627.2 | |
| LPL | Chr8:19796711 | c.-241G>C | NM_000237.2 | rs540525285 |
| LPL | Chr8:19796725 | c.-227T>C | NM_000237.2 | |

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
- 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

Genes with partial, or whole gene, segmental duplications in the human genome are marked with an asterisk (*) if they overlap with the UCSC pseudogene regions. The technology may have limited sensitivity to detect variants in genes marked with these symbols (please see the Panel content table above).

This test does not detect the following:

- Complex inversions
- Gene conversions
- Balanced translocations
- Mitochondrial DNA variants
- 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 (variant with a minor allele fraction of 14.6% is detected with 90% probability)
- Stretches of mononucleotide repeats
- Indels larger than 50bp
- Single exon deletions or duplications
- Variants within pseudogene regions/duplicated segments

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

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).¹

Assays have been validated for various sample types including EDTA-blood, isolated DNA (excluding from formalin fixed

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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.

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% |
| 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% |

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. 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

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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](#) 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 <20X sequencing depth 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 [Blueprint Genetics Variant Classification Schemes](#) based on the [ACMG guideline 2015](#). Minor modifications were made to increase reproducibility of the variant classification and improve the clinical validity of the report. Our experience with tens of thousands of clinical cases analyzed at our laboratory allowed us to further develop the industry standard.

The final step in the analysis is orthogonal confirmation. Sequence variants classified as pathogenic, likely pathogenic and variants of uncertain significance (VUS) are confirmed using bi-directional Sanger sequencing when they do not meet our stringent NGS quality metrics for a true positive call. □ Reported heterozygous and homo/hemizygous copy number variations with a size <10 and <3 target exons are confirmed by orthogonal methods such as qPCR if the specific CNV has been seen and confirmed less than three times at Blueprint Genetics.

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.

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ICD codes

Commonly used ICD-10 codes when ordering the Hyperlipidemia Panel

| ICD-10 | Disease |
|--------|---------|
|--------|---------|

| | |
|--------|---|
| E78.01 | Familial hypercholesterolemia |
| E78.2 | Mixed hyperlipidaemia |
| E78.4 | Other hyperlipidaemia |
| E78.6 | Lipoprotein deficiency |
| E78.9 | Disorder of lipoprotein metabolism, unspecified |
| Z83.42 | Family history of familial hypercholesterolemia |

Accepted sample types

- EDTA blood, min. 1 ml
- Purified DNA, min. 3µg*
- Saliva (Oragene DNA OG-500 kit)

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

Note that we do not accept DNA samples isolated from formalin-fixed paraffin-embedded (FFPE) tissue.

Resources

- [FH Foundation](#)
- [FH diagnosis and treatment - The FH Foundation](#)
- [Familial Hypercholesterolemia Foundation](#)
- [Familial hypercholesterolaemia: identification and management by National Institute for Health and Care Excellence](#)
- [GeneReviews - Familial Hypercholesterolemia](#)
- [GeneReviews - Lipoprotein Lipase Deficiency](#)
- [GeneReviews - Sitosterolemia](#)
- [Genest J et al. Canadian Cardiovascular Society position statement on familial hypercholesterolemia. Can J Cardiol. 2014 Dec;30\(12\):1471-81.](#)
- [NORD - Familial Hypercholesterolemia](#)
- [NORD - Lipoprotein Lipase Deficiency](#)