

Genes Tested:

ACD, ACP5, ACTB, ADA, ADA2, ADAMI7, ADAR, AICDA, AIRE, AK2, AP1S3, AP3B1, AP3D1, APOL1, ARPC1B, ATM, ATP6API, B2M, BACH2, BCL10, BCL11B, BLM, BLNK, BRCA2, BRIPI, BTK, CIQA, CIQB, CIQC, CIR, CIS, C2, C3, C4A, C4B, C4BPA, C5, C6, C7, C8A, C8B, C8G, C9, CARD11, CARD14, CARD9, CARMIL2, CASP10, CASP8, CCBE1, CD19, CD247, CD27, CD3D, CD3E, CD3G, CD40, CD40LG, CD46, CD55, CD59, CD70, CD79A, CD79B, CD81, CD8A, CDCA7, CEBPE, CFB, CFD, CFH, CFHR1, CFHR2, CFHR3, CFHR5, CFI, CFP, CFTR, CHD7, CIITA, CLCN7, CLPB, COG6, COPA, CORO1A, CR2, CREBBP, CSF2RA, CSF2RB, CSF3R, CTC1, CTLA4, CTPSI, CTSC, CXCR4, CYBA, CYBB, DCLRE1B, DCLRE1C, DDX58, DGKE, DKC1, DNAJC21, DNASE1L3, DNASE2, DNMT3B, DOCK2, DOCK8, ELANE, EPG5, ERCC2, ERCC3, ERCC4, ERCC6L2, EXTL3, FAAP24, FADD, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAS, FASLG, FAT4, FCGR3A, FCN3, FERMT3, FOXN1, FOXP3, FPRI, G6PC, G6PC3, G6PD, GATA1, GATA2, GFII1, GINS1, GTF2H5, HAX1, HELLS, HMOX1, HYOU1, ICOS, IFIH1, IFNAR2, IFNGR1, IFNGR2, IGLL1, IKBKB, IKZF1, IL10, IL10RA, IL10RB, IL12B, IL12RB1, IL17F, IL17RA, IL17RC, IL1RN, IL21, IL21R, IL2RA, IL2RG, IL36RN, IL7R, INO80, INSR, IRAK1, IRAK4, IRF2BP2, IRF3, IRF7, IRF8, ISG15, ITCH, ITGAM, ITGB2, ITK, JAGN1, JAK1, JAK3, KDM6A, KMT2D, KRAS, LAMTOR2, LAT, LCK, LIG1, LIG4, LPIN2, LRBA, LRRC8A, LYST, MAGT1, MALT1, MAN2B1, MAP3K14, MASP2, MBL2, MCM4, MEFV, MKL1, MPO, MOGS, MRE11, MS4A1, MSH6, MSN, MTHFD1, MVK, MYD88, MYH9, MYO5A, MYSM1, NBAS, NBN, NCF1, NCF2, NCF4, NCSTN, NFAT5, NFKB1, NFKB2, NFKBIA, NHEJ1, NHP2, NLRC4, NLRP1, NLRP2, NLRP3, NOD2, NOP10, NRAS, NSMCE3, OSTM1, ORAI1, OTULIN, PALB2, PARN, PCCA, PCCB, PEPD, PGM3, PIGA, PIK3CD, PIK3R1, PLCG2, PLEKHM1, PNP, POLA1, POLE, POLE2, PRF1, PRKCD, PRKDC, PSENI, PSENN, PSMA3, PSMB4, PSMB8, PSTPIP1, PTEN, PTPRC, RAB27A, RAC2, RAD50, RAD51C, RAG1, RAG2, RANBP2, RASGRP1, RBCK1, RBM8A, RELB, RFX5, RFXANK, RFXAP, RHOH, RNASEH2A, RNASEH2B, RNASEH2C, RNF31, RNF168, RORC, RPL11, RPL15, RPL26, RPL35A, RPL36, RPL5, RPS10, RPS15, RPS15A, RPS17, RPS19, RPS24, RPS26, RPS27A, RPS28, RPS29, RPS7, RPSA, RTEL1, RUNX1, SAMD9, SAMD9L, SAMHD1, SBDS, SEMA3E, SH2D1A, SH3BP2, SKIV2L, SLC29A3, SLC35A1, SLC35C1, SLC37A4, SLC39A4, SLC46A1, SLC7A7, SLX4, SMARCAL1, SMARCD2, SNX10, SPI10, SPINK5, SRP54, SRP72, STAT1, STAT2, STAT3, STAT5B, STIM1, STK4, STN1, STX11, STXBP2, TAP1, TAP2, TAPBP, TAZ, TBK1, TBX1, TCF3, TCIRG1, TCN2, TERC, TERT, TFRC, THBD, TICAM1, TNF2, TIRAP, TLR3, TMC6, TMC8, TMEM173, TNFAIP3, TNFRSF1A, TNFRSF11A, TNFSF11, TNFRSF13B, TNFRSF13C, TNFRSF4, TNFSF12, TPP2, TRADD, TRAF3, TRAF3IP2, TREX1, TRNT1, TTC37, TTC7A, TYK2, UNC13D, UNC93B1, UNG, USB1, USP18, VPS13B, VPS45, WAS, WDR1, WIPF1, WRAP53, XIAP, XK, ZAP70, ZBTB24

Description:

Our Immunology Exome utilizes Whole Exome Sequencing (WES) technology but focuses on a predefined list of 394 genes that are associated with immune system defects or related disorders. The genes included in this test are associated with susceptibility to recurrent or unusual infections, antibody deficiencies, immune dysregulation, malignancy, allergy, autoimmunity, and auto-inflammatory

disorders. Our extensive gene list was developed through careful review of available evidence and collaboration with clinical immunologists and researchers. Compared to WES, this targeted approach results in a shorter turnaround time and decreased cost. This test will be performed on the proband only and will not include the identification of ACMG recommended actionable incidental findings.

Indications:

- Immunodeficiencies affecting cellular and humoral immunity
- Combined immunodeficiencies with associated or syndromic features
- Predominantly antibody deficiencies
- Diseases of immune dysregulation
- Congenital defects of phagocyte number or function
- Defects in intrinsic and innate immunity
- Autoinflammatory disorders
- Complement deficiencies
- Phenocopies of inborn errors of immunity

Over 325 out of the 394 genes in our Immunology Exome have been classified in the International Union of Immunological Societies: 2017 Primary Immunodeficiency Diseases Committee Report on Inborn Errors of Immunity. Their phenotypic classifications (published in Picard (2018) JClin Immunol. 38(1):96-128.) are outlined below:

2017 IUIS Table 1: Immunodeficiencies affecting cellular and humoral immunity

ADA, AK2, B2M, BCL10, BCL11B, CARD11, CD247, CD3D, CD3E, CD3G, CD40, CD40LG, CD8A, CIITA, CORO1A, DCLRE1C, DOCK2, DOCK8, ICOS, IKBKB, IL21, IL21R, IL2RG, IL7R, JAK3, LAT, LCK, LIG4, MALT1, MAP3K14, MSN, NHEJ1, PRKDC, PTPRC, RAG1, RAG2, RELB, RFX5, RFXANK, RFXAP, RHOH, STK4, TAP1, TAP2, TAPBP, TFRC, TNFRSF4, ZAP70

2017 IUIS Table 2: Combined immunodeficiencies with associated or syndromic features

ACD, ARPC1B, ATM, BLM, CCBE1, CDCA7, CHD7, CTC1, DCLRE1B, DKC1, DNMT3B, EPG5, ERCC6L2, EXTL3, FAT4, FOXP1, GINS1, HELLS, KDM6A, KMT2D, LIG1, MCM4, MTHFD1, MYSM1, NBN, NFKB1A, NHP2, NOP10, NSMCE3, ORAI1, PARN, PGM3, PNP, POLE, POLE2, RBCK1, RNF168, RNF31, RTEL1, SAMD9, SAMD9L, SEMA3E, SLC46A1, SMARCAL1, SP110, SPINK5, STAT3, STAT5B, STIM1, STN1, TBX1, TCN2, TERC, TERT, TINF2, TTC7A, WAS, WIPF1, WRAP53, ZBTB24

2017 IUIS Table 3: Predominantly antibody deficiencies

AICDA, ATP6AP1, BLNK, BTK, CARD11, CD19, CD79A, CD79B, CD81, CR2, IGLL1, IKZF1, INO80, IRF2BP2, MOGS, MS4A1, MSH6, NFKB1, NFKB2, PIK3CD, PIK3R1, PTEN, TCF3, TNFRSF13B, TNFRSF13C, TNFSF12, TRNT1, TTC37, UNG

2017 IUIS Table 4: Diseases of immune dysregulation

AIRE, AP3B1, AP3D1, BACH2, CARMIL2, CASP10, CASP8, CD27, CD70, CTLA4, CTPS1, FAAP24, FADD, FAS, FASLG, FOXP3, IL10, IL10RA, IL10RB, IL2RA, ITCH, ITK, JAK1, LRBA, LYST, MAGT1, NFAT5, PEPD, PRF1, PRKCD, RAB27A, RASGRP1, SH2D1A, STAT3, STX11, STXBP2, TPP2, UNC13D, XIAP, ZAP70

2017 IUIS Table 5: Congenital defects of phagocyte number or function

ACTB, CEBPE, CFTR, CLPB, CSF2RA, CSF2RB, CSF3R, CTSC, CYBA, CYBB, DNAJC21, ELANE, FERMT3, FPR1, G6PC, G6PC3, G6PD, GATA2, GF11, HAX1, HYOU1, ITGB2, JAGN1, LAMTOR2, MKL1, NCF1, NCF2, NCF4, RAC2, SBDS, SLC35C1, SLC37A4, SMARCD2, TAZ, USB1, VPS13B, VPS45, WAS, WDR1

2017 IUIS Table 6: Defects in intrinsic and innate immunity

APOL1, CARD9, CLCN7, CXCR4, CYBB, FCGR3A, HMOX1, IFIH1, IFNAR2, IFNGR1, IFNGR2, IL12B, IL12RB1, IL17F, IL17RA, IL17RC, IRAK1, IRAK4, IRF3, IRF7, IRF8, ISG15, JAK1, MYD88, NBAS, NCSTN, OSTM1, PLEKHM1, PSEN1, PSENE1, RANBP2, RORC, RPSA, SNX10, STAT1, STAT2, TBK1, TCIRG1, TICAM1, TIRAP, TLR3, TMC6, TMC8, TNFRSF11A, TNFSF11, TRAF3, TRAF3IP2, TYK2, UNC93B1

2017 IUIS Table 7: Autoinflammatory disorders

ACP5, ADA2, ADAM17, ADAR, AP1S3, CARD14, COPA, DDX58, IFIH1, IL1RN, IL36RN, LPIN2, MEFV, MVK, NLRC4, NLRP1, NLRP12, NLRP3, NOD2, OTULIN, PLCG2, POLA1, PSMA3, PSMB4, PSMB8, PSTPIP1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, SH3BP2, SLC29A3, TMEM173, TNFAIP3, TNFRSF1A, TREX1, USP18

2017 IUIS Table 8: Complement deficiencies

C1QA, C1QB, C1QC, C1R, C1S, C2, C3, C4A, C4B, C5, C6, C7, C8A, C8B, C8G, C9, CD46, CD55, CD59, CFB, CFD, CFH, CFHR1, CFHR2, CFHR3, CFHR5, CFI, CFP, FCN3, MASP2, THBD

2017 IUIS Table 9: Phenocopies of inborn errors of immunity

AIRE, KRAS, NLRP3, NRAS, STAT3, STAT5B

Additional 66 genes related to inherited immunodeficiencies are also analyzed in our Immunology Exome:

Additional clinically relevant genes

BRCA2, BRIP1, C4BPA, COG6, CREBBP, DGKE, DNASE1L3, DNASE2, ERCC2, ERCC3, ERCC4, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, GATA1, GTF2H5, INSR, ITGAM, LRR8A, MAN2B1, MBL2, MPO, MRE11, MYH9, MYO5A, PALB2, PCCA, PCCB, PIGA, RAD50, RAD51C, RBM8A, RPL11, RPL15, RPL26, RPL35A, RPL36, RPL5, RPS10, RPS15, RPS15A, RPS17, RPS19, RPS24, RPS26, RPS27A, RPS28, RPS29, RPS7, RUNX1, SKIV2L, SLC35A1, SLC39A4, SLC7A7, SLX4, SRP54, SRP72, TRADD, XK

What Is Reported?

Variants that will be discussed in detail in the report:

- **Pathogenic/likely pathogenic variants:** Variants that are known to be pathogenic or for which the laboratory has sufficient evidence suggesting pathogenicity.

Variants that will be listed in the report:

- Variants of uncertain clinical significance.

What is not reported?

- Variants in genes not included in the predefined gene list
- Variants where there is currently no evidence of association with the disease and that are identified in healthy individuals (benign or likely benign variants)
- Variants that predict an increased risk of diseases, but do not cause a disease by themselves (risk alleles).

Methodology:

Procedure: Immunology Exome uses the Agilent SureSelect CRE V1 kit to capture the exonic regions of genes from the genomic DNA extracted from the patient. Targeted regions are sequenced using the Illumina HiSeq 2500 sequencing system with 125 base pair (bp) paired-end reads. Sequence reads are mapped and compared to human genome build UCSC hg19. Variants within exons and flanking sequences of +/- 5bps are identified and evaluated by a validated in-house developed bioinformatics analysis pipeline that includes the usage of GATK 3.5 and Alamut Batch 1.4.4 software packages.

Allele specific analysis for the 253kb inversion as well as targeted analysis of the c.118-308 region in *UNC13D* are performed. Data quality is assessed to confirm it has a minimum coverage of 20X for >95% of targets of interest.

Technical Limitations:

- Pathogenic variants may be present in a portion of the genes not covered by this test and therefore would not be identified. Thus, the absence of reportable findings for any gene does not mean there are no pathogenic variants.
- Certain types of mutations are not detected. Only single base pair changes or small insertions or deletions of DNA are detected. Large deletions, duplications, or rearrangements, mitochondrial genome mutations, repeat expansions, genes with pseudogenes, mutations in tri-allelic inheritance, low level mosaicism and many epigenetic defects may not be detected by this test.

Note: Targeted deletion and duplication analysis of every gene on this panel except *ACD, ACP5, ACTB, ADA, ADAR, AP1S3, AP3D1, APOL1, ARPC1B, ATP6API, B2M, BACH2, BCL10, BCL11B, C4A, C4B, C8G, CARMIL2, CAVIN1, CCBE1, CD46, CD70, CFH, CFHR1, CFHR2, CFHR3, CFHR5, CLCN7, CLPB, COPA, CORO1A, CSF2RA, CSF2RB, CTC1, CTPS1, DCLRE1B, DCLRE1C, DDX58, DHFR, DNAJC21, DNASE1L3, DNASE2, DOCK2, EPG5, ERCC6L2, ETV6, EXTL3, FAAP24, FANCD2, FAT4, FCGR3A, FERMT3, GINS1, GTF2H5, HELLS, HMOX1, HYOU1, IFIH1, IFNAR2, IGLL1, IKBKB, IL17RC, IL2, INO80, IRAK1, IRF2BP2, IRF3, IRF7, ITGAM, JAGN1, JAK1, KMT2D, LAT, MAP3K14, MC2R, MKL1, MOGS, MRE11, MSH6, MSN, MYSM1, NBAS, NCF1, NCSTN, NFAT5, NFKB1, NFKB2, NLRC4, NLRP1, NSMCE3, OSTM1, OTULIN, PARN, PEPD, PGM3, PI4KA, PIGA, PLEKHM1, POLA1, POLE, POLE2, PRKCD, PROS1, PSEN1, PSENEN, PSMA3, PSMB4, RANBP2, RASGRP1, RELB, RNF31, RORC, RPL15, RPL36, RPS15, RPS15A, RPS17, RPS28, RPS29, RPSA, RUNX1, SAMD9, SAMD9L, SBDS, SEMA3E, SKIV2L, SLC29A3, SLC39A4, SMARCD2, SNX10, SRP54, STAT2, STAT5B, STN1, TCF3, TFRC, TIRAP, TMEM173, TNFRSF1A, TNFRSF4, TNFSF11, TNFSF12, TPP2, TRADD, TRAF3IP2, TRNT1, UNC93B1, USP18, and WDR1* is clinically available at an additional charge.

Turn-Around Time:

56 days (8 weeks)

Specimen:

At least 3 mls whole blood in a lavender top (EDTA) tube. Label the tube with the patient's name, birth date, and date of collection. Alternatively, 10 mcg of high quality DNA may be submitted.

CPT Codes:

- **Immunology Exome:** 81415
- **Deletion and duplication analysis of any single Gene on the Immunology Exome except AIRE, ATM, BRCA2, BTK, CD40LG, CHD7, CFTR, CREBBP, G6PC, G6PD, IL2RG, KRAS, MEFV, PALB2, PCCA, PCCB, PTEN, RPS19, SLC37A4, STAT3, TAZ, VPS13B, and WAS:** 81479
- **Deletion and duplication analysis of CD40LG, and MEFV:** 81404
- **Deletion and duplication analysis of IL2RG, KRAS, RPS19, and STAT3:** 81405
- **Deletion and duplication analysis of AIRE, BTK, PALB2, PCCA, PCCB, SLC37A4, TAZ, and WAS:** 81406
- **Deletion and duplication analysis of CHD7 and CREBBP:** 81407
- **Deletion and duplication analysis of ATM and VPS13B:** 81408
- **Deletion and duplication analysis of BRCA2:** 81216
- **Deletion and duplication analysis of CFTR:** 81222
- **Deletion and duplication analysis of G6PD:** 81249
- **Deletion and duplication analysis of G6PC:** 81250
- **Deletion and duplication analysis of PTEN:** 81323

Shipping Instructions:

Please enclose **test requisition** with sample.

All information must be completed before sample can be processed.

Place samples in styrofoam mailer and ship at room temperature by overnight Federal Express to arrive Monday through Friday.

Ship to:

Cytogenetics and Molecular Genetics Laboratories
3333 Burnet Avenue NRB 1042
Cincinnati, OH 45229
513-636-4474

References:

- Picard et al. (2018) International Union of Immunological Societies: 2017 Primary Immunodeficiency Diseases Committee Report on Inborn Errors of Immunity. J Clin Immunol. 38(1):96-128*
- Raje & Dinakar (2015) Overview of Immunodeficiency Disorders. Immunol Allergy Clin North Am. 35(4):599-623*
- Schmidt et al. (2017) Autoimmunity and primary immunodeficiency: two sides of the same coin? Nat Rev Rheumatol. 14(1):7-18*