**Immunology Exome**

**Genes Tested:**

ACD, ACP5, ACTB, ADA, ADA2, ADAM17, ADAR, AICDA, AIRE, AK2, ALPI, APIS3, AP3B1, AP3D1, APOL1, ARHGEF1, ARPC1B, ATM, ATP6AP1, B2M, BACH2, BCL10, BCL11B, BLM, BLNK, BRCA1, BRCA2, BRIP1, BTK, C1QA, C1QB, C1QC, C1R, C1S, C2, C3, 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, CDC42, CDA7, CEBSA, CFB, CFD, CFH, CFHR1, CFHR2, CFHR3, CFHR5, CFI, CFp, CFR, CHD7, CIITA, CLCN5, CLPB, COG6, COPA, CORO1A, CR2, CREBBP, CSF2RA, CSF2RB, CSF3R, CTC1, CTLA4, CTSS, CTSC, CXCR4, CYBA, CYBB, DBR1, DCLRE1B, DCLRE1C, DDX58, DEFB6, DGKE, DKE, DKCI, DNAJC21, DNASE1L3, DNASE2, DNMT3B, DOCK2, DOCK8, DSG1, DPP4, EFL1, ELANE, EP300, ERBB1, ERCC3, ERCC4, ERCC6L2, EXTL3, FAAP24, FADD, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FAS, FASLG, FAT4, FCGR3A, FCHO1, FCN3, FERMT1, FERMT3, FOXN1, FOXP3, FPR1, G6PC, G6PC3, GATA1, GATA2, GFI1, GINS1, GTF2H5, HAVCR2, HAX1, HELLs, HMOX1, HYOU1, ICS1, ICOS, ICOSLG, IFIH1, IFNA1, IFNAR1, IFNGRI, IFNGR2, IGLL1, IKBKB, IKZF1, IL10, IL10RA, IL10RB, IL12B1, IL12RB1, IL12RB2, IL17F, IL17RA, IL17RC, IL18BP, IL1RN, IL2, IL21R, IL23R, IL2RA, IL2RB, IL2RG, IL36RN, IL6R, IL6ST, IL7R, INO80, INS, IRAK1, IRAK4, IRF2BP2, IRF3, IRF7, IRF4, IRF8, ISG5, ITCH, ITGAM, ITGB2, ITK, JAG1, JAK1, JAK3, KDM6A, KMT2A, KMT2D, KRAS, LAMTOR2, LAT, LCK, LIG1, LIG4, LPIN2, LRBA, LRRC8A, LYST, MAD2L2, MAGT1, MALT1, MAN2B1, MAP3K14, MASP2, MBL2, MCM4, MEFV, MKL1, MOGS, MPO, MRE11, MS4A1, MSH6, MSN, MTHFD1, MVK, MYD88, MYH9, MYOSA, NBS1, NBR1, NCF2, NCF4, GCSTN, NFAT5, NFE2L2, NFkB1, NFkB2, NFkBIA, NHEJ1, NHP2, NLRCA4, NLRP1, NLRP12, NLRP3, NOD2, NOP10, NRS, NSMCE3, OAS1, ODF1, Orai1, OTULIN, PALB2, PARN, PCCA, PCCB, PEPD, PGM3, PIGA, PIK3CD, PIK3R1, PLCG2, PLEKHMI, PNP, POLA1, POLD1, POLD2, POLE, POLE2, POLR3A, POLR3C, POLR3F, PRF1, PRKCD, PRKDC, PSENEN, PSMA3, PSMB4, PSMB8, PSMG2, PSTPIP1, PTPR, RAB27A, RAC2, RAD50, RAD51, RAD51C, RAG1, RAG2, RASGRF1, RBCK1, RBM8A, RECL4L, REL, RELA, RELB, RFWD3, RFX5, RFXANK, RFXAP, RHOD, RIPK1, RNASEH2A, RNASEH2B, RNASEH2C, RNFI68, RNFL31, RORC, RPL11, RPL26, RPL35A, RPL36, RPL5, RPS10, RPS15, RPS15A, RPS19, RPS24, RPS26, RPS27A, RPS28, RPS29, RPS7, RPSA, RETL1, RUNX1, SAMD9, SAMD9L, SAMHD1, SBD5, SEC61A1, SEMA3E, SERPING1, SH2D1A, SH3BP2, SH3KBP1, SKIV2L, SLC29A3, SLC35A1, SLC35C1, SLC37A4, SLC39A4, SLC46A1, SLC7A7, SLX4, SMARCAL1, SMARCD2, SNX10, SP110, SPINKS, SPL1A2, SRP54, SRP72, STAT1, STAT2, STAT3, STAT5B, STIM1, STK4, STN1, STX11, STXBP2, TAPI, TAP2, TAPBP, TAZ, TBK1, TBX1, TCF3, TCIIRG1, TCN2, TERT, TFRC, TGFB1, TGFB2, THBD, TICAM1, TINF2, TIRAP, TLR3, TLR8, TMC6, TMC8, TMEM173, TNFAIP3, TNFRSF11A, TNFRSF13B, TNFRSF13C, TNFRSF1A, TNFRSF4, TNFRSF9, TNFRSF13, TNFRSF12, TOP2B, TP53, TPP2, TRADD, TRAF3, TRF3IP2, TREX1, TRIM22, TRNT1, TTC7A, TYK2, UBE2T, UNC13D, UNC93B1, UNG, USB1, VPS13B, VPS45, WAS, WDR1, WIPF1, WRAP53, XIAP, XK, XRCC2, XRCC4, ZAP70, ZBTB24, ZNF341

**Note:** C4A, C4B, NCF1, IKBKG (NEMO), RANBP2, USP18, RPS17, TERC are not analyzed in the immunology exome due to high homology or lack of coverage.
Description:

Our Immunology Exome utilizes Whole Exome Sequencing (WES) technology but focuses on a predefined list of 44 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:

- Immune deficiencies 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
- Bone marrow failure

Over 370 of the 442 genes in our Immunology Exome have been classified in the Human Inborn Errors of Immunity: 2019 Update on the Classification from the International Union of Immunological Societies Expert Committee. Their phenotypic classifications (published in J Clin Immunol. 40(1): 24–64.) are outlined below:

2019 IUIS Table 1: Immunodeficiencies affecting cellular and humoral immunity

| ADA, AK2, B2M, BCL10, BCL11B, CARD11, CD247, CD3D, CD3E, CD3G, CD40, CD40LG, CD8A, CDC42, CIITA, CORO1A, DCLRE1C, DCK1, DOCK2, DOCK8, FCHO1, ICOS, ICOSLG, IKBKB, IL21, IL2R, IL36, IL7R, JAK3, LAT, LCK, LIG4, MALT1, MAP3K14, MSN, NHEJ1, POLD1, POLD2, PRKDC, PTTP, RAG1, RAG2, REL, RELA, RELB, RFX5, RFXANK, RFXAP, RHOH, STK4, TAP1, TAP2, TAPBP, TFRC, TLR8, TNFRSF4, ZAP70 |

2019 IUIS Table 2: Combined immunodeficiencies with associated or syndromic features

| ACD, ARPC1B, ATM, BLM, CCB1E, CDCA7, CHD7, CTC1, DCLRE1B, DCK1, DNM33B, EPG5, ERCC6L2, ERF, EXT, FAT4, FOXL1, GINS1, HELL, IL6R, IL6ST, KDM6A, KMT2A, KMT2D, LIG1, MCM4, MTHFD1, MYST1, NBN, NFE2L2, NFKBIA, NHP2, NOSMCE3, ORAI1, PARN, PGM3, PNIP, POLE, POLE2, RBCK1, RNFL68, RNFL3, RTNL1, SAMD9, SAMD9L1, SEMA3E, SLC46A1, SMARCA1, SP110, SPINK5, STAT3, STAT5B, STIM1, STIP1, TBX1, TCN2, TERT, TFGBR1, TFGBR2, TINF2, TTCT, WAS, WIF1P, WRAP53, ZBTB24, ZNF341 |

2019 IUIS Table 3: Predominantly antibody deficiencies

| CDA, ARHGFI1, ATP6AP1, BLNK, BTK, CARD11, CD19, CD79A, CD79B, CD81, CR2, IGL1, IKZF1, INO80, IRF2BP2, MOG, MS4A1, MSH6, NFKB1, NFKB2, PAK3, PAK3, PTK, PTN, SEC61A1, SH3KBP1, SLC39A7, TCFC, TNFRSF13B, TNFRSF13C, TNFRSF12, TOP2B, TRNT1, TTCT, UNG |

2019 IUIS Table 4: Diseases of immune dysregulation

| AIRE, AP3B1, AP3D1, BAC2, CARML2, CASP10, CASP5, CD27, CD70, CTLA4, CTPS1, FAAP24, FADD, FAS, FASLG, FERMT1, FOXP3, IL10, IL10RA, IL12, IL2RA, IL2RB, ITCH, ITK, JAK1, LRBA, LYST, MAGT1, NFAT5, PEPD, PRF1, PRKCD, RAB27A, RASGRP1, RIPK1, RSH2D1A, STAT3, STX11, STXBP2, TFGB1, TNFRSF9, TOP2, UCNC3D, XIAP, ZAP70 |

2019 IUIS Table 5: Congenital defects of phagocyte number or function

| ACTB, CEBPE, CFT, CLB, CSF2RA, CSF2RB, CSF3R, CTSC, CYBA, CYBB, DNAJC21, EFL1, ELANE, FERMT3, FPR1, G6PC, G6PC3, G6PD, GATA2, GFN1, HAX1, HYOU1, ITGB2, JAG1, LAMTOR2, MKL1, NCF2, NCF4, RAC2, SBDS, SLC35C1, SLC37A4, SMARCD2, TAZ, USB1, VPS13B, VPS45, WAS, WDR1 |

2019 IUIS Table 6: Defects in intrinsic and innate immunity

| ACP1, CARD9, CLCN7, CIB1, CXCR4, CYBB, DBR1, FDGR3A, HMOX1, IFIH1, IFNAR1, IFNAR2, IFNAR, IFNGR2, IL12B, IL12B1, IL12B2, IL17, IL17A, IL17C, IL18BP, IL123R, IRAK1, IRAK4, IRF4, IRF3, IRF7, IRF8, IRF9, ISG15, JAK1, MYD88, NBAS, NCSTN, OSTM1, PLEKH1M1, POLR3A, POLR3C, POLR3F, PSENEN, RORC, RPSA, SNX10, SPP2, STA1, STAT2, TBK1, TICR1, TICAM1, TIRAP, TLR3, TMC6, TMC8, TNFRSF11A, TNFRSF11B, TRAF3, TRAF3IP2, TYK2, UNC93B1 |

2019 IUIS Table 7: Autoinflammatory disorders

| ACPS, ADA2, ADAM17, ADAR, ALPI, APIS, CARD14, CDP, DDYSX, DAVCR2, IFIH1, IL1RN, IL1RN, LPP12, MEFV, MVK, NLR4, NLRP1, NLRP12, NLRP3, NOD2, OAS1, OTULIN, PCLG2, POLA1, PSMA3, PSMB4, PSMB8, PSMB9, PSTP11, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, SH3BP2, SLC29A3, SLC17A7, SNFD, TNFRSF1A, TREX1, TRIM22 |
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:

Immunology Exome uses the Human Comprehensive Exome kit to capture the exonic regions of genes from the genomic DNA extracted from the patient. Targeted regions are sequenced using an Illumina sequencing system with paired-end reads. Sequence reads are aligned to the human reference genome (build UCSC hg19). Variants within exons and flanking sequences are identified and evaluated by a validated in-house developed bioinformatics analysis pipeline and Fabric Genomic Analysis platform. 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 or in regions with suboptimal data due to homologous issue, polynucleotides, or nucleotide repeats, and therefore may not be identified. Thus, the absence of identified pathogenic variants does not exclude the possibility of a genetic etiology for the patient’s symptoms.**
- **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, 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, ADAM17, ADAR, AICDA, AIRE, ALPI, APOL1, ARHGEF1, ATP6AP1, B2M, BACH2, BCL10, BLNK, BTK, C1QA, C1QB, C1QC, CIR, CIS, C2, C6, C7, C8A, C8B, C8G, C9, CARD11, CARD14, CARD9, CARMIL2, CCBE1, CD19, CD3G, CD40, CD70, CD79A, CD79B, CD81, CD8A, CDC42, CDCA7, CEBPE, CFHR1, CFHR2, CFHR3, CFTR, CIB1, CLCN7, COG6, COPA, CORO1A, CR2, CREBBP, CSF2RA, CSF2RB, CTSC, CYBA, CYBB, DBR1, DCLRE1B, DDX58, DEF6, DNASEL1, DNAS2, DNMT3B, DOCK2, DSG1, EFL1, EPG5, ERBIN, ERCC2, ERCC3, EXTL3, FAAP24, FAT4, FCGRA3A, FCHI, FCN2, FERMT3, FPR1, GINS1, GTF2H5, HAVCR2, HELLS, HOX11, ICOS, ICOSLG, PIH1, IFNAR1, IFNAR2, IFNGR1, IFNGR2, IGL1, IKKβ, IKZF1, IL10, IL10RA, IL10RB, IL12B, IL12RB1, IL12RB2, IL17F, IL17RA, IL17RC, IL18BP, IL1RN, IL21, IL2R, IL23R, IL2RA, IL2RB, IL26RN, IL6R, IL6ST, INO80, INSR, IRAK1, IRAK4, IRF2BP2, IRF3, IRF4, IRF7, IRF8, IRF9, ISG15, ITCH, ITGAM, ITGB2, JAK1, KDM6A, KMT2A, KMT2D, LCK, LIG1, LIG4, LRFCA, MAD2L2, MALT1, MAN2B1, MAP3K14, MAP2K, MBL2, MCM4, MEFV, MKL1, MOGS, MPO, MREI1, MS4A1, MSH6, MTHFD1, MVK, MYD88, MYO5A, NAB1, NCAF, NCF4, NCSNT, NFAT5, NFE2L2, NFKB1, NFKB2, NFKBIA, NHEJ1, NHP2, NLRCA, NLRP1, NLRP12, NLRP3, NOD2, NOP10, OAS1, OFD1, OST1, OTULIN, PCCA, PCCB, PEPD, PGM3, PIGA, PIK3R1, PLCG2, PLEKHM1, POLA1, POLD1, POLD2, POLE, POLE2, POLR3A, POLR3C, PRKCD, PSENEN, PSMA3, PSMB4, PSMB8, PSMG2, PSTPIP1, PTEN, RAD50, RBCK1, RECQL4, REL, RELA, RELB, RFID3, RHOH, RIPK1, RNASEH2A, RNASEH2B, RNASEH2C, RNFS1, RORC, RPL15, RPL36, RPS15A, RPS24, RPS28, RPS29, RPS2A, SAMD9, SAMD9L, SAMHD1, SEC61A1, SEMA3E, SERPING1, SH3BP2, SH3BP1, SKIV2L, SLC29A3, SLC35A1, SLC35C1, SLC37A4, SLC39A4, SLC39A7, SLC46A1, SMACALI, SMARD2, SNX10, SPINK5, SPPL2A, SRP54, STAT1, STAT2, TAPBP, TBK1, TCF3, TFRC, TGFBI, TGFBR1, TGFBR2, TICAM1, TINF2, TRAP, TLR3, TLR8, TMC6, TMC8, TMEM173, TNFAIP3, TNFRSF11A, TNFRSF13B, TNFRSF13C, TNFRSF1A, TNFRSF4, TNFRSF9, TNF, TNF12, TOP2B, TP2, TRADD, TRAF3,  TRAF31P2, TRED1, TRIM22, TRIM24, TSC37, TYK2, UNC93BI, UNG, XRCC4, ZBTB24, and ZNF341 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 or saliva in an Oragene saliva kit. Please call 513-636-4474 for a free saliva collection kit. 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, BRCA1, BRCA2, BTK, CD40LG, CHD7, CFTR, CREBBP, G6PC, G6PD, IL2RG, KRAS, MEFV, PALB2, PCCA, PCCB, PTEN, RPS19, SLC37A4, STAT3, TAZ, TGFBR1, TGFBR2, TP53 VPS13B, and WAS: **81479**
- Deletion and duplication analysis of **CD40LG** and **MEFV**: **81404**
- Deletion and duplication analysis of **IL2RG**, **KRAS**, **RPS19**, **STAT3**, **TGFBR1**, **TGFBR2**, and **TP53**: **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 BRCA1: 81165
• 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 Saturday.

Ship to:
Laboratory of Genetics and Genomics
3333 Burnet Avenue NRB 1042
Cincinnati, OH 45229
513-636-4474

References:

