Immunology Exome

Genes Tested:

ACP5, ACTB, ADA, ADA2, ADAMTS13, ADAR, AICDA, AIRE, AK2, AP3B1, APOL1, ATM, BLM, BLNK, BLOC1S3, BLOC1S6, BRCA2, BRIP1, BTK, C1QA, C1QB, C1QC, C1S, C2, C3, C4BPA, C5, C6, C7, C8A, C8B, C8G, C9, CARD11, CARD14, CARD9, CARMIL2, CASP10, CASP8, CAVIN1, CD19, CD247, CD27, CD3D, CD3E, CD3G, CD40, CD40LG, CD46, CD59, CD70, CD79A, CD79B, CD81, CD8A, CDCA7, CEBPE, CFB, CFD, CFH, CFHR1, CFHR3, CFHR5, CFI, CFP, CHD7, CIITA, CLEC7A, CLPB, COG6, COLEC11, CORO1A, CR2, CREBBP, CSF3R, CTC1, CTLA4, CTPS1, CTSC, CXCR4, CYBA, CYBB, DCLRE1C, DGKE, DHFR, DKC1, DNAJC21, DNMT3B, DOCK8, DTNBP1, ELANE, EPG5, ERCC2, ERCC3, ERCC4, ERCC6L2, ETV6, F11, F13A1, F13B, F5, F7, F8, F9, FADD, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAS, FASLG, FCN3, FERMT3, FGA, FGB, FOXN1, FOXP3, FPR1, G6PC, G6PC3, G6PD, GATA1, GATA2, GFI1, GP1BA, GP1BB, GP9, GTF2H5, HAX1, HELLS, HPS1, HPS3, HPS4, HPS5, HPS6, ICOS, IFIH1, IFNGR1, IFNGR2, IGLL1, IKBKB, IKZF1, IL10, IL10RA, IL10RB, IL12B, IL12RB1, IL17F, IL17RA, IL1RN, IL2, IL21R, IL2RA, IL2RG, IL36RN, IL7R, INSR, IRAK4, IRF8, ISG15, ITCH, ITGAM, ITGB2, ITK, JAGN1, JAK2, JAK3, KMT2D, KRAS, LAMTOR2, LCK, LIG1, LIG4, LPIN2, LRBA, LRRC8A, LYST, MAGT1, MALT1, MAN2B1, MANBA, MASP1, MASP2, MBL2, MC2R, MCM4, MEFV, MLPH, MPL, MPO, MRE11, MS4A1, MTHFD1, MVK, MYD88, MYH9, MYO5A, MYSM1, NBN, NCF2, NCF4, NCSTN, NFKB1, NFKB2, NFKBIA, NHEJ1, NHP2, NKX2-5, NLRC4, NLRP12, NLRP3, NOD2, NOP10, NRAS, ORAI1, PALB2, PARN, PCCA, PCCB, PEPD, PGM3, PI4KA, PIGA, PIK3CD, PIK3R1, PLCG2, PLG, PMM2, PNP, POLE, PRF1, PRKCD, PRKDC, PROC, PROS1, PSENEN, PSMB8, PSTPIP1, PTPRC, RAB27A, RAC2, RAD50, RAD51C, RAG1, RAG2, RBCK1, RBM8A, RFX5, RFXANK, RFXAP, RHOH, RNASEH2A, RNASEH2B, RNASEH2C, RNF168, RPL11, RPL15, RPL26, RPL35A, RPL36, RPL5, RPS10, RPS15, RPS15A, RPS17, RPS19, RPS24, RPS26, RPS27A, RPS28, RPS29, RPS7, RPSA, RTEL1, RUNX1, SAMHD1, SBDS, SEMA3E, SH2D1A, SH3BP2, SKIV2L, SLC29A3, SLC35A1, SLC35C1, SLC37A4, SLC39A4, SLC46A1, SLC7A7, SLX4, SMARCAL1, SP110, SPINK5, SRP72, STAT1, STAT2, STAT3, STAT5B, STIM1, STK4, STX11, STXBP2, TAP1, TAP2, TAPBP, TAZ, TBK1, TBX1, TCIRG1, TCN2, TERC, TERT, THBD, TICAM1, TINF2, TLR3, TMC6, TMC8, TNFAIP3, TNFRSF13B, TNFRSF13C, TNFRSF1A, TNFRSF4, TNFSF12, TRADD, TRAF3, TRAF3IP2, TREX1, TRNT1, TTC37, TTC7A, TYK2, UNC119, UNC13D, UNG, USB1, 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 351 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:

- Combined Immunodeficiencies with or without associated syndromic features
- Predominantly antibody deficiencies
- Diseases of immune dysregulation
- Congenital defects of phagocyte number, function, or both
- Defects in innate immunity
- Autoinflammatory disorders
- Complement deficiencies
- Phenocopies of Primary Immunodeficiency Disease (PID)

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Over 240 out of the 351 genes in our Immunology Exome have been classified in the 2017 IUIS Phenotypic Classification for Primary Immunodeficiencies. Their phenotypic classifications (published in Bousfiha (2018) J Clin Immunol. 38(1):129-143.) are outlined below:

2017 IUIS Figure I: Immunodeficiencies affecting cellular and humoral immunity
a) SCID, defined by CD3 T cell lymphopenia: *ADA, AK2, CD247, CD3D, CD3E, CORO1A, DCLRE1C, FOXN1, IL2RG, IL7R, JAK3, LIG4, NHEJ1, PRKDC, PTPRC, RAG1, RAG2*
b) CID Generally Less Profound than SCID: *CARD11, CD3G, CD40, CD40LG, CD8A, CIITA, DOCK8, ICOS, IKBKB, IL21R, LCK, MAGT1, MALT1, RFX5, RFXANK, RFXAP, RHOH, STK4, TAP1, TAP2, TAPBP, TNFRSF4, UNC119, ZAP70*

2017 IUIS Figure II: CID with associated or syndromic features
a) *ATM, BLM, CDCA7, DNMT3B, ERCC6L2, HELLS, LIG1, MCM4, MYSM1, NBN, POLE, RNF168, SEMA3E, SMARCAL1, TBX1, WAS, WIPF1, ZBTB24*
b) *CTC1, DKC1, EPG5, KMT2D, MTHFD1, NFKBIA, NHP2, NOP10, ORAI1, PARN, PGM3, PNP,RBCK1, RTEL1, SLC46A1, SP110, SPINK5, STAT3, STAT5B, STIM1, TCN2, TERC, TERT, TINF2, TTC7A, WRAP53*

2017 IUIS Figure III: Predominantly Antibody deficiencies
a) Hypergammaglobulinemia: *BLNK, BTK, CD19, CD79A, CD79B, CD81, IGLL1, IKZF1, MS4A1, NFKB1, NFKB2, PIK3CD, PIK3R1, TNFRSF13B, TNFRSF13C, TNFSF12, TRNT1, TTC37*
b) Other Antibody deficiencies: *AICDA, CARD11, UNG*

2017 IUIS Figure IV: Disease of Immune dysregulation
a) Hemaphagocytic Lymphohistiocytosis HLH & EBV susceptibility: *AP3B1, CARMIL2, CD27, CD70, CTPS1, ITK, LYST, MAGT1, PRF1, PRKCD, RAB27A, SH2D1A, STX11, STXBP2, UNC13D, XIAP*
b) Sd with Autoimmunity and Others: *AIRE, CASP10, CASP8, CTLA4, FADD, FAS, FASLG, FOXP3, IL10, IL10RA, IL10RB, IL2RA, ITCH, LRBA, PEPD, STAT3, ZAP70*

2017 IUIS Figure V: Congenital defects of phagocyte number, function or both
a) Neutropenia (without anti-PMN): *CLPB, CSF3R, DNAJC21, ELANE, G6PC3, GFI1, HAX1, JAGN1, LAMTOR2, SBDS, SLC37A4, TAZ, USB1, VPS13B, VPS45, WAS, WDR1*
b) Functional defects: *ACTB, CEBPE, CTSC, CYBA, CYBB, FERMT3, FPR1, G6PD, GATA2, ITGB2, NCF2, NCF4, RAC2, SLC35C1*

2017 IUIS Figure VI: Defects in Intrinsic and Innate immunity
a) Bacterial and Parasitic Infections: *APOL1, CARD9, IL17F, IL17RA, IRAK4, MYD88, NCSTN, PSENEN, RPSA, STAT1, TCIRG1, TRAF3IP2*
b) MSMD and Viral infection: *CXCR4, CYBB, IFIH1, IFIH1, IFNGR1, IFNGR2, IL12B, IL12RB1, IRF8, ISG15, STAT1, STAT2, TBK1, TICAM1, TLR3, TMC6, TMC8, TRAF3, TYK2*

2017 IUIS Figure VII: Auto-Inflammitory disorders
a) *MEFV, MVK, NLRC4, NLRP12, NLRP3, PSMB8, TNFAIP3, TNFRSF1A*
b) *ACP5, ADA2, ADAR, CARD14, IFIH1, IL1RN, IL36RN, LPIN2, NOD2, PSTPIP1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, SH3BP2, SLC29A3, TREX1*

2017 IUIS Figure VIII: Complement deficiencies
C1QA, C1QB, C1QC, C1S, C2, C3, C5, C6, C7, C8A, C8B, C8G, C9, CD46, CD59, CFB, CFD, CFH, CFHR1, CFHR3, CFHR5, CFP, FCN3, MASP2, THBD

2017 IUIS Figure IX: Phenocopies of PID
KRAS, NLRP3, NRAS, STAT5B

Additional 106 genes related to inherited immunodeficiencies are also analyzed in our Immunology Exome

Additional clinically relevant genes
ADAMTS13, BLOC1S3, BLOC1S6, BRCA2, BRIP1, C4BPA, CAVIN1, CFI, CLEC7A, COG6, COLEC11, CR2, CREBBP, DGKE, DHFR, DTNBP1, ERCC2, ERCC3, ERCC4, ETV6, F11, F13A1, F13B, F5, F7, F8, F9, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FGA, FGB, G6PC, GATA1, GP1BA, GP1BB, GP9, GTF2H5, HPS1, HPS3, HPS4, HPS5, HPS6, IL2, INSR, ITGAM, JAK2, LRRC8A, MAN2B1, MANBA, MASP1, MBL2, MC2R, MLPH, MPL, MPO, MRE11, MYH9, MYO5A, NKX2-5, PALB2, PCCA, PCCB, PI4KA, PIGA, PLCG2, PLG, PMM2, PROC, PROS1, 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, 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 mosaism and many epigenetic defects may not be detected by this test.

Note: Targeted deletion and duplication analysis of every gene on this panel except *ACP5, ACTB, ADA, ADAR, APOL1, C8G, CARMIL2, CAVIN1, CD46, CD70, CFH, CFHR1, CFHR3, CFHR5, CLPB, CORO1A, CTC1, CTPS1, DCLRE1C, DHFR, DNAJC21, EPG5, ERCC6L2, ETV6, FANCD2, FERMT3, GTF2H5, HELLS, IFIH1, IGLL1, IKBKB, IL2, ITGAM, JAGN1, KMT2D, MC2R, MRE11, MYSM1, NCSTN, NFKB1, NFKB2, NLRC4, PARN, PEPD, PGM3, PI4KA, PIGA, POLE, PRKCD, PROS1, PSENEN, RPL15, RPL36, RPS15, RPS15A, RPS17, RPS28, RPS29, RPSA, RUNX1, SBDS, SEMA3E, SKIV2L, SLC29A3, SLC39A4, STAT2, STAT5B, TNFRSF4, TNFSF12, TRADD, TRAF3IP2, TRNT1,* 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 , CREBBP, F8, G6PC, G6PD, GP1BB, IL2RG, KRAS, MEFV, PALB2, PCCA, PCCB, RPS19, SLC37A4, STAT3, TAZ, VPS13B,* and *WAS:*** 81479
- **Deletion and duplication analysis of *CD40LG, GP1BB,* 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, CREBBP,* and *F8:*** 81407
- **Deletion and duplication analysis of *ATM* and *VPS13B:*** 81408
- **Deletion and duplication analysis of *BRCA2:*** 81216
- **Deletion and duplication analysis of *G6PD:*** 81249
- **Deletion and duplication analysis of *G6PC:*** 81250

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:

Bousfiha et al. (2018) The 2017 IUIS Phenotypic Classification for Primary Immunodeficiencies. J Clin Immunol. 38(1):129-143

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