Primary Antibody Deficiency Panel

**Indications for Ordering**

Confirm suspected primary antibody deficiency in individual with clinical symptoms

**Test Description**

- Targeted capture of all coding exons and intron/exon boundaries followed by massively parallel sequencing
  - Reported variants are confirmed by Sanger sequencing
- Deletion/duplication analysis by tiled, custom-designed comparative genomic hybridization (CGH) array

**Tests to Consider**

**Primary test**

*Primary Antibody Deficiency Panel, Sequencing (35 Genes) and Deletion/Duplication (26 Genes) 2011156*

- Preferred test for individuals with clinical phenotype of
  - Primary antibody deficiency
  - Agammaglobulinemia
  - Hyper IgM syndrome
  - Common variable immunodeficiency (CVID)
  - Atypical severe combined immunodeficiency
  - Other related immunodeficiency disorder

**Related tests**

Initial screening for immunodeficiency

- CBC with Platelet Count and Automated Differential 0040003
- Lymphocyte Subset Panel 7 - Congenital Immunodeficiencies 0095899
- B-Cell Memory and Naive Panel 2008901
- Lymphocyte Antigen and Mitogen Proliferation Panel with Cytokine Response 2013117
- Immunoglobulins (IgA, IgG, IgM), Quantitative 0050630
- Immunoglobulin G Subclasses (1, 2, 3, 4) 0050577
- Familial Mutation, Targeted Sequencing 2001961

**Disease Overview**

**Incidence/prevalence** – see table

**Age of onset**

- Agammaglobulinemia and hyper IgM syndrome – usually within first two years of life
- CVID – across all ages, but mostly in the second and third decade

**Symptoms**

- Unusual, opportunistic, or severe infections
  - Most common organisms
    - *Histoplasma capsulatum*
    - *Candida spp*
    - *Cryptococcus neoformans*
  - Common sites
    - Respiratory – pneumonia/empyema
    - Gastrointestinal
      - Diarrhea – intermittent or chronic
    - Skin
    - Head and neck
      - Oral ulcers/gingivitis/stomatitis
      - Conjunctivitis
      - Otitis media
      - Lymphadenopathy
    - CNS
  - Other symptoms
    - Sepsis
    - Failure to thrive
    - Splenomegaly
    - Autoimmune conditions
    - Neutropenia
    - Granulomatous disease
    - Associated with increased risk of lymphoid and nonlymphoid malignancies

**Genetics**

**Genes** – see table

**Mutations**

- Mutations in multiple genes appear to cause overlapping phenotypes
- Other genetic and/or environmental factors may influence severity of clinical phenotype

**Test Interpretation**

**Clinical sensitivity**

- CVID – 20%
- Hyper IgM syndrome – 75-80%
- Agammaglobulinemia – 90%
Results

- **Positive**
  - Two pathogenic mutations on opposite chromosomes detected in a gene with autosomal recessive (AR) inheritance
    - Confirms diagnosis of primary antibody deficiency
  - One pathogenic mutation in an X-linked gene detected in males, or one pathogenic mutation in an autosomal dominant gene detected in males or females
    - Confirms diagnosis of primary antibody deficiency
  - One pathogenic mutation detected in an AR gene
    - Individual is a carrier
  - One pathogenic mutation detected in an X-linked gene in females
    - Individual is a carrier

- **Negative**
  - No pathogenic mutation detected
    - Reduces, but does not exclude, a diagnosis of primary antibody deficiency

- **Inconclusive**
  - Variants of uncertain clinical significance may be identified

Limitations

- Not determined or evaluated
  - Mutations in genes not included on the panel
  - Deep intronic and regulatory region mutations
  - Breakpoints for large deletions/duplications
  - Translocations
  - Deletions/duplications will not be detected in
    - **IKBKG**, **LRBA**, **LRRC8A**, **PIK3CD**, **PIK3R1**, **PLCG2**, **PRKCD**, **SH2D1A**, or **XIAP/BIRC4** gene
  - Small deletions or insertions may not be detected
  - Diagnostic errors can occur due to rare sequence variations
  - Lack of a detectable gene mutation does not exclude a diagnosis of primary antibody deficiency

### Gene Symbol | Gene Name | NM # | OMIM # | Phenotype/Disorder | Inh.* | Incidence/Prevalence |
<table>
<thead>
<tr>
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<tr>
<td>ADA</td>
<td>Adenosine deaminase</td>
<td>NM_000022</td>
<td>608958</td>
<td>SCID T-cell/B-cell/NK-cell negative, due to ADA deficiency</td>
<td>AR</td>
<td>1-9/million live births Higher in populations with high degree of consanguinity</td>
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<td>AICDA</td>
<td>Activation-induced cytidine deaminase</td>
<td>NM_020661</td>
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<td>Immunodeficiency with hyper IgM, type 2</td>
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<td>ATM</td>
<td>Ataxia telangiectasia mutated (includes complementation groups A, C and D)</td>
<td>NM_000051</td>
<td>607585</td>
<td>Ataxia telangiectasia</td>
<td>AR</td>
<td>1/40,000 – 100,000 Varies with degree of consanguinity</td>
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<td>B-cell linker</td>
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<td>Agammaglobulinemia</td>
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<td>BTK</td>
<td>Bruton agammaglobulinemia tyrosine kinase</td>
<td>NM_000061</td>
<td>300300</td>
<td>Agammaglobulinemia and isolated growth hormone deficiency X-linked agammaglobulinemia</td>
<td>XL</td>
<td>1-9/million</td>
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<td>CD19</td>
<td>CD19 antigen</td>
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<td>CVID</td>
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<td>CD40LG</td>
<td>CD40 ligand (TNF superfamily, member 5, hyper IgM syndrome, TNFSF5)</td>
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<td>2/million males</td>
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<td>CD79A</td>
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<td>CR2</td>
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<td>IKBKG</td>
<td>Inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase gamma, NEMO</td>
<td>NM_001099857</td>
<td>300248</td>
<td>Hypohidrotic ectodermal dysplasia with immune deficiency Anhidrotic ectodermal, dysplasia, lymphedema, and immunodeficiency Immunodeficiency 33 syndrome Incontinentia pigmenti Recurrent isolated invasive pneumococcal disease</td>
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<tr>
<td>Gene Symbol</td>
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<td>LRBA</td>
<td>LPS-responsive vesicle trafficking, beach and anchor containing</td>
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<td>CVID with autoimmunity</td>
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<td>LRRC8A</td>
<td>Leucine rich repeat containing 8 family, member A</td>
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<td>MRE11A</td>
<td>Meiotic recombination 11 homologue A</td>
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<td>MS4A1</td>
<td>Membrane-spanning 4-domains, subfamily A, member 1</td>
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<td>CVID</td>
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<td>NBN/NBS1</td>
<td>Nibrin</td>
<td>NM_002485</td>
<td>602667</td>
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<td>NM_020529</td>
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<td>PIK3CD</td>
<td>Phosphoinositide-3-kinase, catalytic, delta polypeptide</td>
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<td>PIK3R1</td>
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<td>Agammaglobulinemia</td>
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<td>PLCG2</td>
<td>Phospholipase C gamma 2</td>
<td>NM_002661</td>
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<td>Autoinflammation, antibody deficiency, and immune dysregulation syndrome</td>
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<td>PRKCD</td>
<td>Protein kinase C, delta</td>
<td>NM_006254</td>
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<td>PTPRC</td>
<td>Protein tyrosine phosphatase, receptor type C</td>
<td>NM_002838</td>
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<td>RAG2</td>
<td>Recombination activating gene 2</td>
<td>NM_000536</td>
<td>179616</td>
<td>SCID, T-cell/B-cell negative, NK-cell positive, Omenn syndrome, Combined cellular and humoral immune defects with granulomas</td>
<td>AR</td>
<td>~1/100,000 live births</td>
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<td>SH2D1A</td>
<td>SH2 domain protein 1A, Duncan’s disease (lymphoproliferative syndrome)</td>
<td>NM_002351</td>
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<td>X-linked lymphoproliferative syndrome</td>
<td>XL</td>
<td>1/million males</td>
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<td>TNFRSF13B</td>
<td>Tumour necrosis factor receptor superfamily, member 13b, TACI</td>
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<td>CVID, immunoglobulin A deficiency</td>
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<td>TNFRSF13C</td>
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<td>XIAP/BIRC4</td>
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<td>X-linked lymphoproliferative syndrome</td>
<td>XL</td>
<td>1/million males</td>
</tr>
</tbody>
</table>

*Inh. = inheritance, AD = autosomal dominant, AR = autosomal recessive, XL = X-linked*