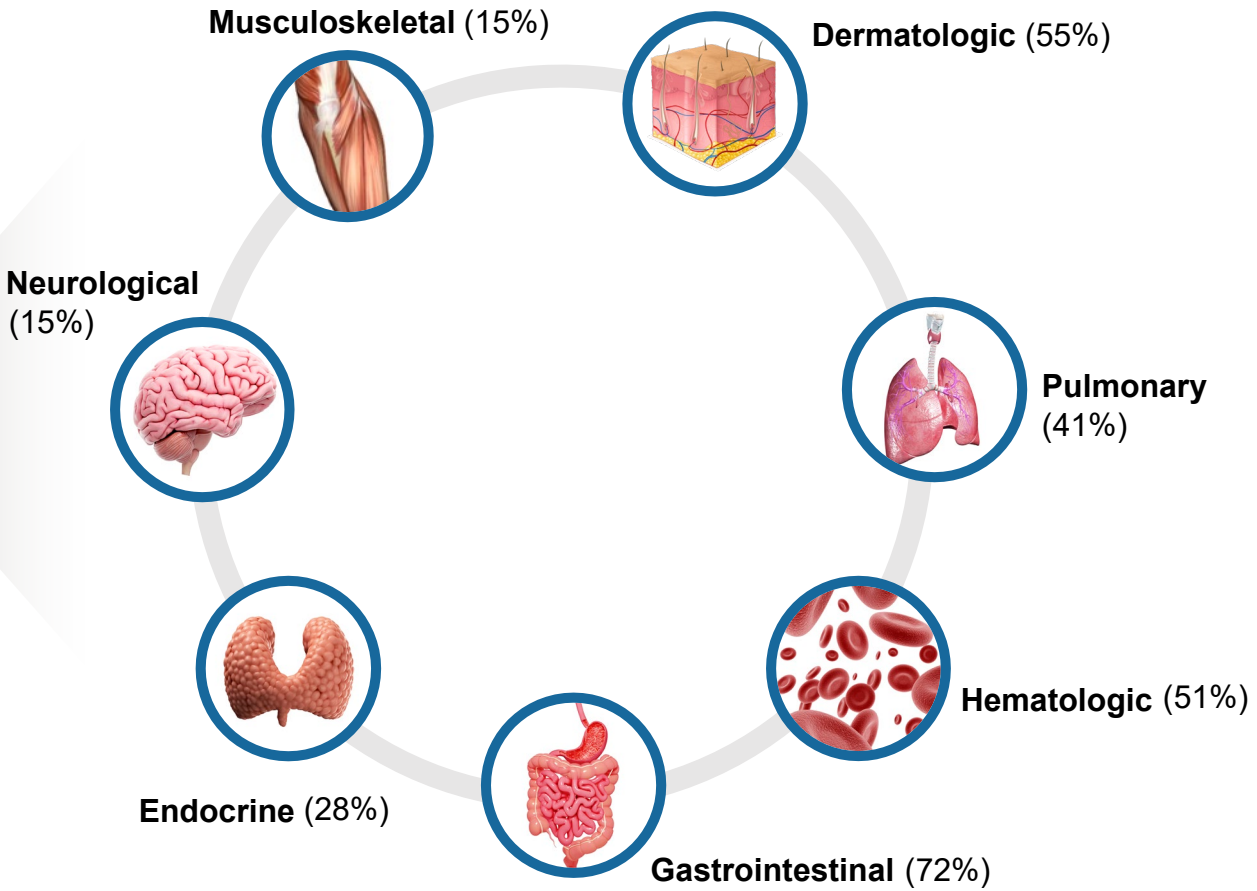
A Brief Look at APDS:
Clinical Manifestations and Diagnostic Testing

Primary Immune Regulatory Disorders (PIRDs)
A Subset of Primary Immunodeficiencies

Patients present with infections (**immunodeficiency**) ***and*** immune-mediated pathology, such as:

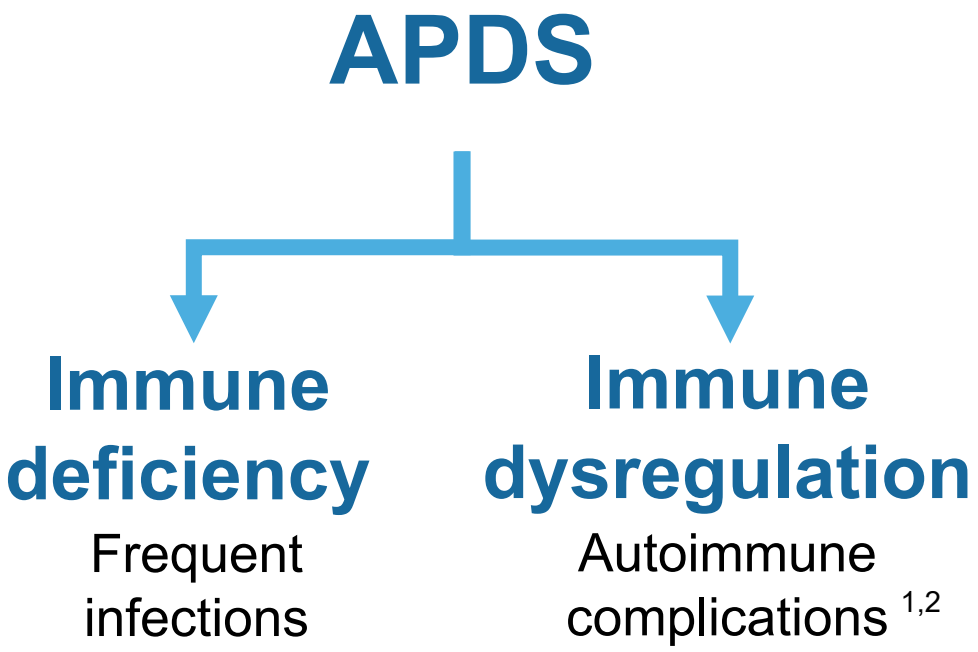
- **Autoimmunity**
- **Autoinflammation**
- **Lymphoproliferation**

Predominant Locations of Clinical Manifestations



Chan A et al. *Front Immunol*. 2020;11: Article 239.

Activated PI3Kδ Syndrome (APDS)* Is A PIRD



Discovered in **2013**[1,2]

Rare: estimated prevalence worldwide is 1-2 per million[3]

Combined immunodeficiency: both B and T cells affected[1,2]

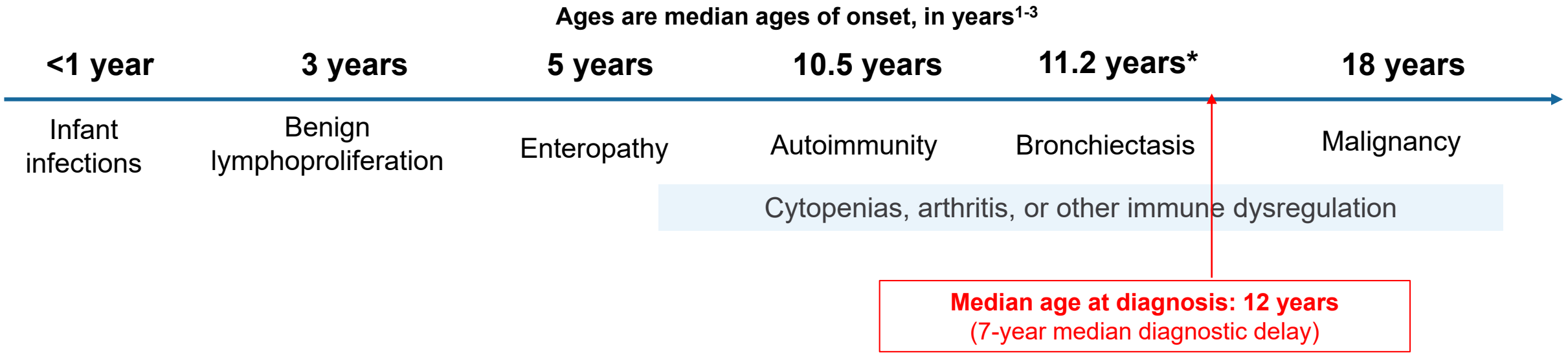
Caused by mutations in the genes encoding subunits of PI3Kδ enzyme complex[1,2,4,5]

*Also known as PASLI (p110δ-activating mutation causing senescent T cells, lymphadenopathy, and immunodeficiency).
APDS, activated phosphatidylinositol 3-kinase δ syndrome; PASLI, p110δ-activating mutation causing senescent T cells, lymphadenopathy, and immunodeficiency; PIRD, primary immune regulatory disorder.

1. Angulo I et al. *Science*. 2013;342(6160):866-871. 2. Lucas CL et al. *Nature Immunology*. 2014;15:88-97. 3. Orphanet. https://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=EN&Expert=397596. Accessed March 1, 2021. 4. Deau MC et al. *J Clin Invest*. 2014;124(9):3923-3928. 5. Lucas CL et al. *J Exp Med*. 2014;211(13):2537-2547.

APDS Evolves Over Time And May Be Underdiagnosed

Timeline of the Most Common Pathologies Seen in APDS



A careful family history may be especially useful in diagnosis. A goal of early diagnosis and treatment is to interrupt the disease evolution[1-4]

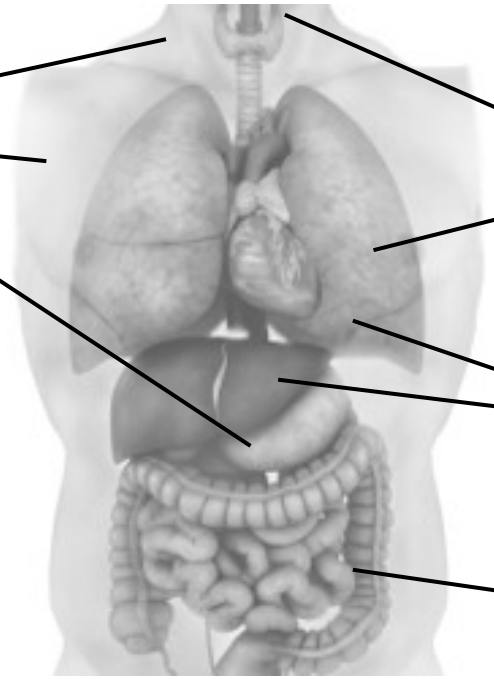
*In Elkaim APDS2 cohort, median age of bronchiectasis is 13, in Maccari ESID cohort median age is 11.2.

1. Jamee M et al. *Clin Rev Allergy Immunol*. 2019 May 21. 2. Maccari ME et al. *Front. Immunol*. 2018;9: Article 543. 3. Elkaim E et al. *J Allergy Clin Immunol*. 2016;138(1):210-218.
4. Condliffe AM & Chandra A. *Front. Immunol*. 2018;9: Article 338.

APDS Has A Wide Range of Clinical Manifestations

Developmental delay[1,2]
Failure to thrive[2]

Chronic lymphadenopathy[1,2]
Nodular lymphoid hyperplasia[1,2]
Lymphoma[1]
Premature mortality[1,2]



Recurrent, severe sinopulmonary infections[1,2]
Pneumonia[1,2]
Bronchiectasis[1,2]

Persistent, severe, or recurrent herpesvirus infections, particularly EBV and CMV[1,2]

Splenomegaly[1,2]
Hepatomegaly[1,2]

Autoimmune cytopenias and autoinflammatory diseases[1,2]

Enteropathy[1,2]

APDS, activated phosphatidylinositol 3-kinase δ syndrome; CMV, cytomegalovirus; EBV, Epstein-Barr virus

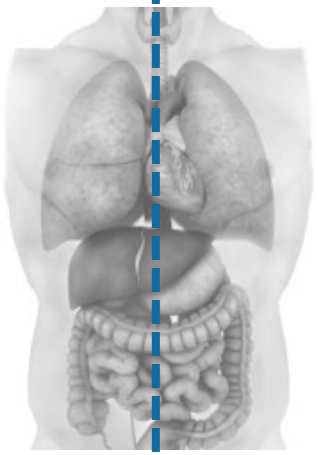
1. Coulter TI et al. *J Allergy Clin Immunol*. 2017;139(2):597-606. 2. Elkaim E et al. *J Allergy Clin Immunol*. 2016;138(1):210-218.

Most Current APDS Treatments Do Not Address Both Immune Deficiency and Dysregulation

Current APDS Treatments[1,2]

Immune Deficiency

- Antimicrobial prophylaxis
- Immunoglobulin replacement therapy



Immune Dysregulation

- Corticosteroids
- Rituximab
- mTOR inhibitors
  - Sirolimus (rapamycin)

Hematopoietic stem cell transplant

If you have patients who need **therapies with opposing effects** (eg, IRT and rituximab), a PIRD may be present[1,3]
A genetic test – particularly a PI panel – may be warranted[4]

IRT, immunoglobulin replacement therapy; mTOR, mammalian target of rapamycin; PIRD, primary immune regulatory disorder.

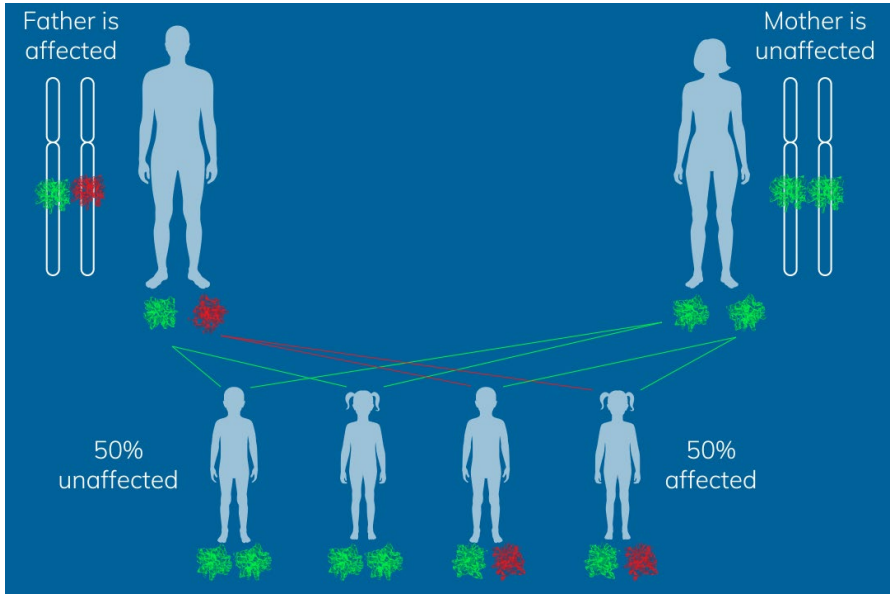
1. Coulter TI et al. *J Allergy Clin Immunol*. 2017;139(2):597-606. 2. Elkaim E et al. *J Allergy Clin Immunol*. 2016;138(1):210-218. 3. Chan AY et al. *Front Immunol*. 2020;11:239. 4. Chinn IK et al. *J Allergy Clin Immunol*. 2020;145(1):46-69.

APDS May Be Present in Multiple Members of a Family

Family members of patients with APDS should undergo genetic testing[1]

APDS has an autosomal dominant inheritance pattern[2]

- *De novo* mutations are also observed



50% chance of APDS being passed down to a patient's children[3]

In a systematic review for APDS, nearly 40% of patients had a family history of PI[4]

- **A careful family history may be especially useful in diagnosis[2,4]**
- Symptoms frequently do not present in the same manner within a family[5]

PI, primary immunodeficiency. 1. Chinn IK et al. *J Allergy Clin Immunol*. 2020; 145(1): 46-69. 2. Lucas CL et al. *Nature Immunology*. 2014;15:88-97. 3. National Human Genome Research Institute website. Autosomal Dominant. https://www.genome.gov/genetics-glossary/Autosomal-Dominant. Accessed March 1, 2021. 4. Jamee M et al. *Clin Rev Allergy Immunol*. 2019 May 21 5. Genetic Alliance; The New York-Mid-Atlantic Consortium for Genetic and Newborn Screening Services. *Understanding Genetics: A New York, Mid-Atlantic Guide for Patients and Health Professionals*. Washington (DC): Genetic Alliance; July 8, 2009.

Genetic Testing – Definitive Diagnosis May Change Treatment

navigateAPDS by Pharming

Pharming partnership with Invitae

- **FREE GENETIC TEST** – no cost to qualified patients in the USA and Canada
- **FAST** – results back to doctor within 2 weeks on average (10-21 days)
- **DESIGNED TO BE EASY FOR PROVIDERS** – online form
- **DESIGNED TO BE EASY FOR PATIENTS** – blood draw kits (preferred), buccal swab kits, saliva kits, or mobile phlebotomy
- **COMPREHENSIVE** – 407-gene primary immunodeficiency panel
- **SUPPORTED** – option for free genetic counseling provided by GeneMatters
- **FAMILY TESTING** – free genetic testing for blood relatives of patients with pathologic or likely pathologic variants

www.invitae.com/navigateAPDS

Genetic Testing Criteria

navigateAPDS by Pharming

Program available to patients in the US and Canada who meet **any two or more** or the following bulleted criteria

Clinical Features

- ◯ Onset of symptoms under 12 years of age
- ◯ Documented severe recurrent sinopulmonary infections (> 2 events within 3 years of each other)
- ◯ Bronchiectasis
- ◯ Lymphadenopathy for greater than one month
- ◯ Any nodular lymphoid hyperplasia
- ◯ Chronic hepatomegaly or chronic splenomegaly
- ◯ Severe, persistent, or recurrent Herpesviridae infections (e.g., EBV, cytomegalovirus)
- ◯ Autoimmune cytopenia
- ◯ Enteropathy
- ◯ Lymphoma

Laboratory

- ◯ Hypogammaglobulinemia
- ◯ Elevated levels of immunoglobulin M
- ◯ Reduced number of CD3+CD4+ T cells; increased number of follicular helper T cells
- ◯ Reduced number of naïve T cells

History

- ◯ Primary Immune Deficiency diagnosis
- ◯ Common Variable Immune Deficiency (CVID) phenotype or direct family member with CVID phenotype
- ◯ Relative with PIK3CD or PIK3R1 genotype (first or second degree)