Activated Phosphoinositide 3-Kinase δ Syndrome (APDS)

ICD-10 C&M Committee

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Presentation Topics

- **Overview of APDS**
- **Challenges and benefits of accurately diagnosing APDS**
- **Rationale for new ICD-10-CM code**

Primary Immunodeficiencies are an Expanding Group of Rare Genetic Disorders with Variable Manifestations

Primary Immunodeficiencies:

- **400+** genetic disorders known in 2020[1]
- Full or partial lack of immune system function[2]

Appear at any age[2]

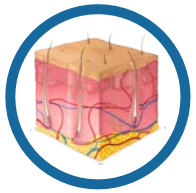
- Severe cases commonly diagnosed in infancy or early childhood

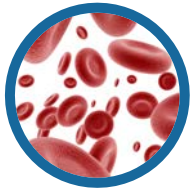
Variable clinical presentations[1]

- Routine or severe infections
- Autoimmune or autoinflammatory complications
- Risk for premature development of cancer

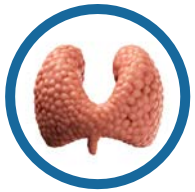
Predominant Locations of Clinical Manifestations[3]


Gastrointestinal

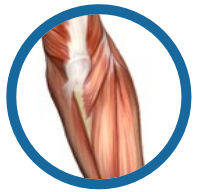

Dermatologic


Hematologic


Pulmonary


Endocrine


Neurological


Musculoskeletal

1. Bousfiha A, et al. *J Clin Immunol*. 2020;40(1):66-81. 2. McCusker C, Warrington R. *Allergy Asthma Clin Immunol*. 2011;7(suppl 1):S11. 3. Chan AY, et al. *Front Immunol*. 2020;11:239.

Activated PI3Kδ Syndrome (APDS) is a Primary Immunodeficiency

APDS

Immune deficiency
Frequent infections

Immune dysregulation
Autoimmune complications[1,2]

Risk for early development of lymphoid malignancies

Fully characterized in 2013[1,2]

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

PI3Kδ is upstream of the **proliferative AKT/mTOR pathway**[3]

Normal B and T cell function requires **balanced** PI3Kδ signaling[3,4]

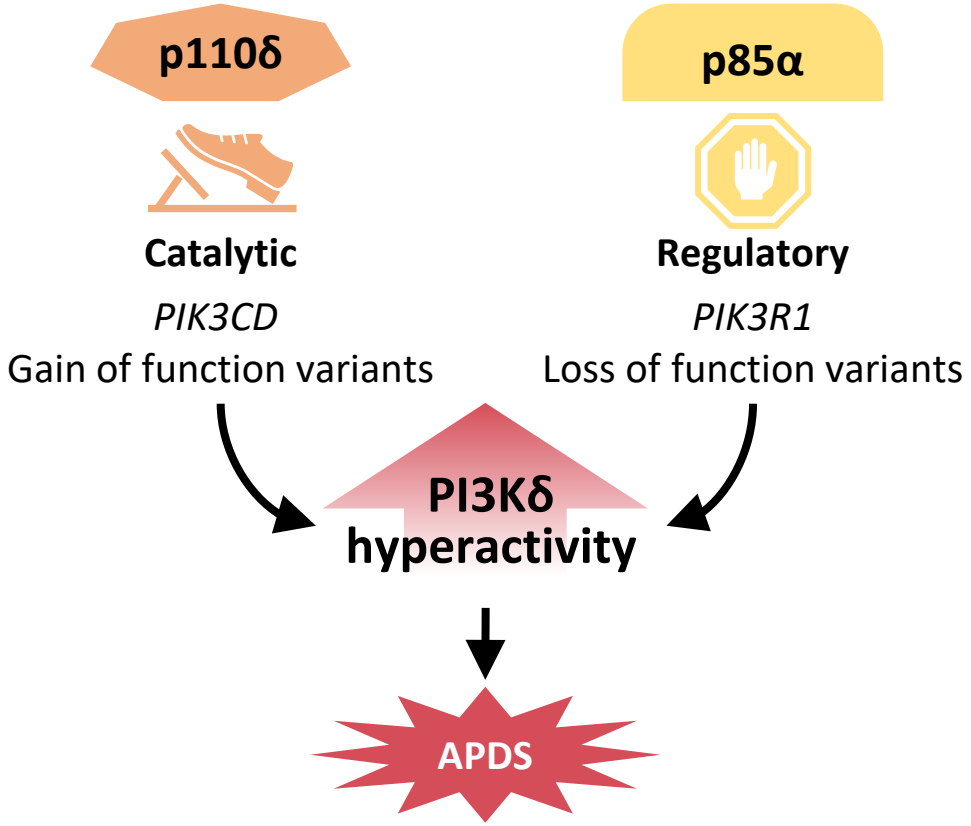
In APDS, **PI3Kδ is hyper-active**[1,2,5,6]

mTOR, mammalian target of rapamycin; PI3Kδ, phosphoinositide 3-kinase δ.

1. Angulo I, et al. *Science*. 2013;342(6160):866-871. 2. Lucas CL, et al. *Nat Immunol.* 2014;15(1):88-97. 3. Fruman DA, et al. *Cell*. 2017;170(4):605-635. 4. Okkenhaug K, Vanhaesebroeck B. *Nat Rev Immunol*. 2003;3(4):317-330. 5. Lucas CL, et al. *J Exp Med*. 2014;211(13):2537-2547. 6. Deau MC, et al. *J Clin Invest*. 2014;124(9):3923-3928.

Variants in PI3Kδ Genes Can Cause APDS

Genetic variants in either PI3Kδ subunit that result in enzyme hyperactivity cause APDS[1-4]



Genetic testing continues to reveal new pathogenic variants[5]

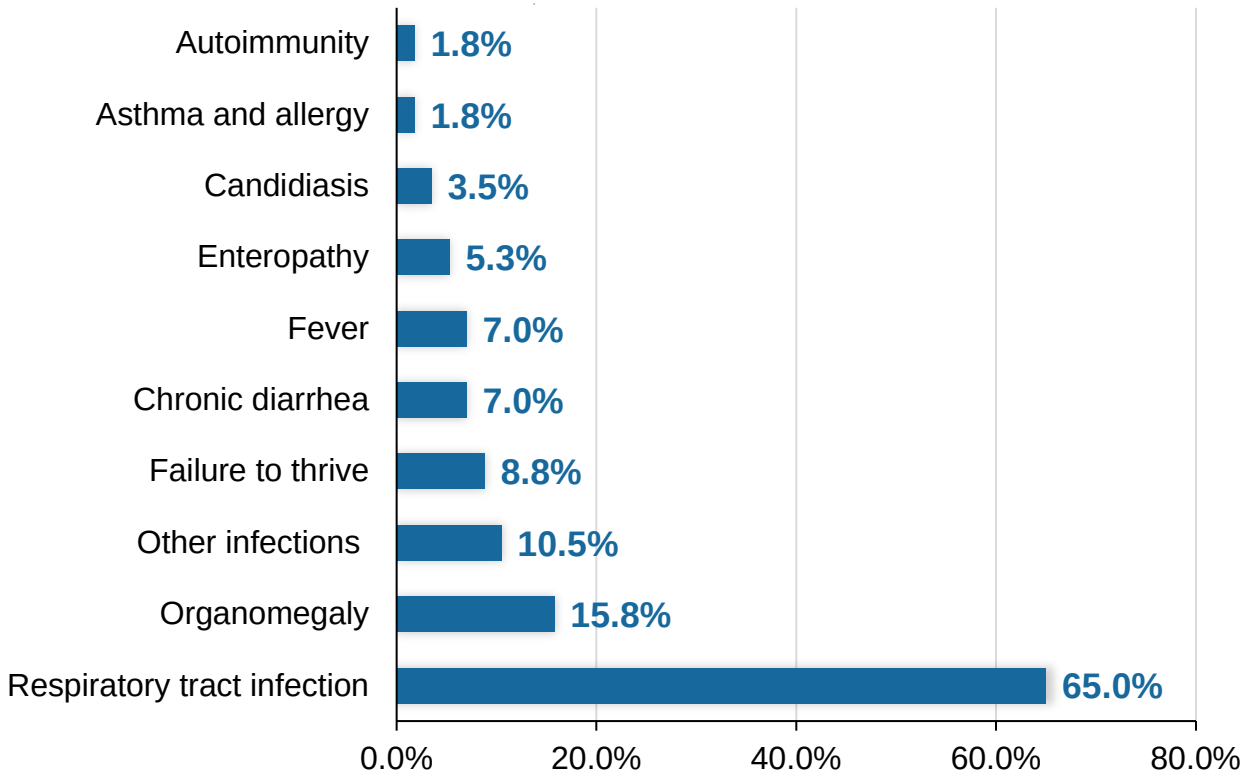
Genetic Testing is the Only Way to Diagnose APDS

APDS, activated phosphoinositide 3-kinase δ syndrome; *PIK3CD*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta; *PIK3R1*, phosphoinositide 3-kinase regulatory subunit 1; PI3Kδ, phosphoinositide 3-kinase δ.

1. Lucas CL, et al. *Nat Immunol.* 2014;15(1):88-97. 2. Angulo I, et al. *Science*. 2013;342(6160):866-871. 3. Lucas CL, et al. *J Exp Med*. 2014;211(13):2537-2547.
4. Deau MC, et al. *J Clin Invest*. 2014;124(9):3923-3928. 5. Heimall JR, et al. *J Clin Immunol*. 2018;38(3):320-329.

Initial APDS Presentation Varies and Can Frequently Be Misdiagnosed

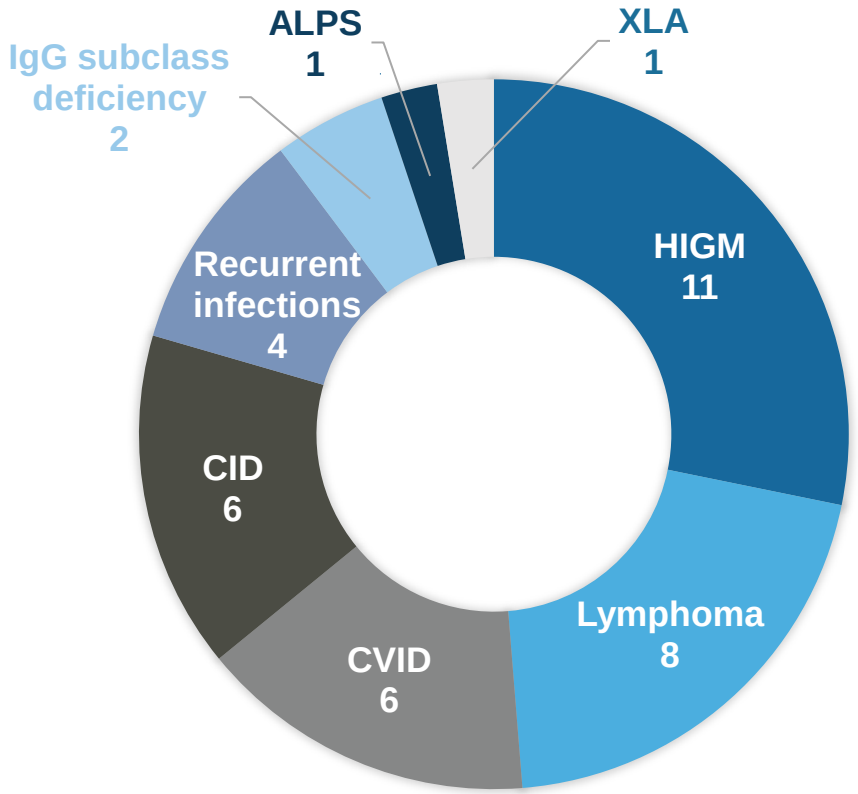
The most common first presentations reported in patients with APDS are **respiratory tract infections** and **organomegaly**[1]



Images adapted from Jamee M, et al. *Clin Rev Allergy Immunol.* 2020;59(3):323-333.

Cases of APDS are often diagnosed as **HIGM** or **lymphoma**[1]

39 patients with APDS had the following initial diagnoses:



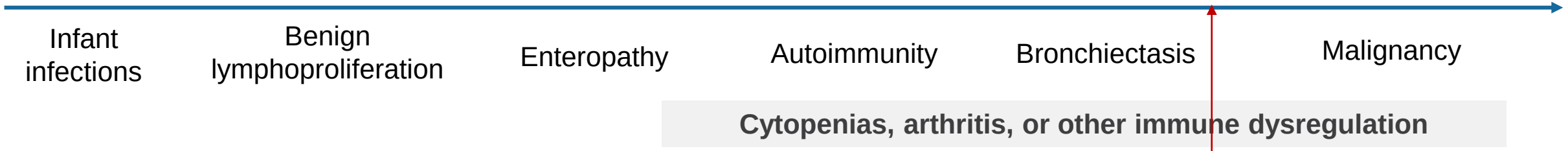
ALPS, autoimmune lymphoproliferative syndrome; APDS, activated phosphoinositide 3-kinase δ syndrome; CID, combined immune deficiency; CVID, common variable immunodeficiency; ESID, European Society for Immunodeficiencies; HIGM, hyperimmunoglobulin M; Ig, immunoglobulin; XLA, X-linked agammaglobulinemia.

1. Jamee M, et al. *Clin Rev Allergy Immunol*. 2020;59(3):323-333. 2. Maccari ME, et al. *Front Immunol*. 2018;9:543. 3. Elkaim E, et al. *J Allergy Clin Immunol*. 2016;138(1):210-218.

APDS Evolves Over Time and may be Underdiagnosed

Timeline of the Most Common Pathologies Seen in APDS

Ages are median ages of onset, in years[1-3]



Depending on their clinical manifestations, patients with PI may see <u>many different specialties</u>

Median age at diagnosis: 12 years
(7-year median diagnostic delay)

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.
APDS, activated phosphoinositide 3-kinase δ syndrome; ESID, European Society for Immunodeficiencies.

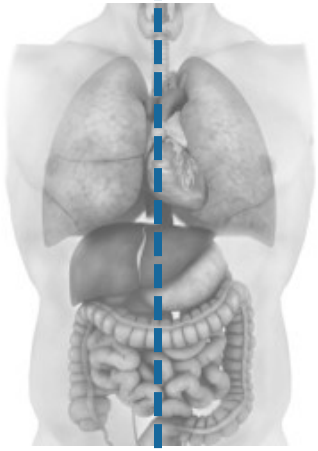
1. Jamee M, et al. *Clin Rev Allergy Immunol*. 2020;59(3):323-333. 2. Maccari ME, et al. *Front Immunol*. 2018;9:543. 3. Elkaim E, et al. *J Allergy Clin Immunol*. 2016;138(1):210-218.e9.
4. Condliffe AM, Chandra A. *Front Immunol*. 2018;9:338.

Current Management for APDS

Current APDS Management[1,2]

Immune Deficiency

- Antimicrobial prophylaxis
- Immunoglobulin replacement therapy



Immune Dysregulation

- Corticosteroids
- Other immunosuppressants
- mTOR inhibitors

Hematopoietic stem cell transplant

- *None of these therapies are approved for APDS treatment*
- *None of the therapies currently being used target the specific underlying molecular mechanism of the disease*

Therapies targeting either immunodeficiency or immune dysregulation do not address the full complexity of APDS[3]

APDS, activated phosphatidylinositol 3-kinase δ syndrome; mTOR, mammalian target of rapamycin.

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. Walter JE, et al. *J Allergy Clin Immunol Pract*. 2016;4(6):1089-1100.

Accurate Primary Immunodeficiency Diagnosis Impacts Treatment & Precision Medicine

Genetic diagnosis with a specific disorder **changed disease management in 25-40%** of patients with PI[1,2] and **altered outcomes in 45%**[1]*

Targeted treatments for specific PIs are becoming available,[3]
highlighting the need for accurate diagnosis and coding

Primary Immunodeficiency	Off-Label Precision Medicine
CTLA-4 haploinsufficiency	Abatacept, belatacept
LRBA deficiency	Abatacept
STAT1 gain of function	Ruxolitinib, tofacitinib, baricitinib
STAT3 gain of function	Ruxolitinib, tofacitinib, tocilizumab
IFNγ receptor deficiency	IFNγ
LAD-1	Ustekinumab

Leniolisib, a PI3Kδ inhibitor under investigation for treatment of APDS, is currently completing Phase III clinical trials, with the potential for approval in 2022[4]

*N=158 patients[1] and n=110 patients[2] with PI.
APDS, activated phosphatidylinositol 3-kinase δ syndrome; CTLA-4, cytotoxic T lymphocyte antigen-4; IFN, interferon; LAD-1, leukocyte adhesion deficiency type 1; LRBA, lipopolysaccharide-responsive beige-like anchor; PI, primary immunodeficiency; STAT, signal transducer and activator of transcription.

1. Quinn J, et al. *Immunol Res*. 2020;68(3):126-134. 2. Stray-Pedersen A, et al. *J Allergy Clin Immunol*. 2017;139(1):232-245. 3. Ballow M, Leiding JW. *Clin Rev Allergy Immunol*. 2021;10.1007/s12016-021-08871-4. 4. Pharming Healthcare, Inc. *Pharming acquires exclusive license to CDZ173, a late-stage drug for the treatment of APDS*.; 2019. Available at: https://www.pharming.com/sites/default/files/imce/Press%20releases/PR%20CDZ173%2013%20August%202019.pdf. Accessed September 1, 2021.

A Wide Range Of ICD-10 Codes are Currently Used for Patients with APDS

In the ESID Registry, HCPs used ICD-10 codes spanning 7 categories for patients with APDS

Infection
Eg, J32.8 other chronic sinusitis, J35.02 chronic adenoiditis, B34.0 adenovirus infection unspecified

Lymphoproliferation
Eg, R59.0 localized enlarged lymph nodes, R16.1 splenomegaly not elsewhere classified

Autoimmunity
Eg, D59.1 other autoimmune hemolytic anemias, J45.909 unspecified asthma uncomplicated, L30.9 dermatitis unspecified

Immunodeficiency*
- Various cytopenias (eg, D69.9, D70.9, D72.810)
- D80.1 nonfamilial hypogammaglobulinemia
- D80.3 selective deficiency of IgG subclasses
- D80.5 immunodeficiency with increased IgM
- D80.8 other immunodeficiencies with predominantly antibody defects
- D81.1 SCID with low T- and B-cell numbers
- D81.8 other CID
- D81.9 CID unspecified
- D83.9 CVID unspecified
- D84.8 other specified immunodeficiencies
- D84.9 immunodeficiency unspecified
- D89.9 disorder involving the immune mechanism unspecified

Bronchiectasis
Eg, J49.0 bronchiectasis with acute lower respiratory infection

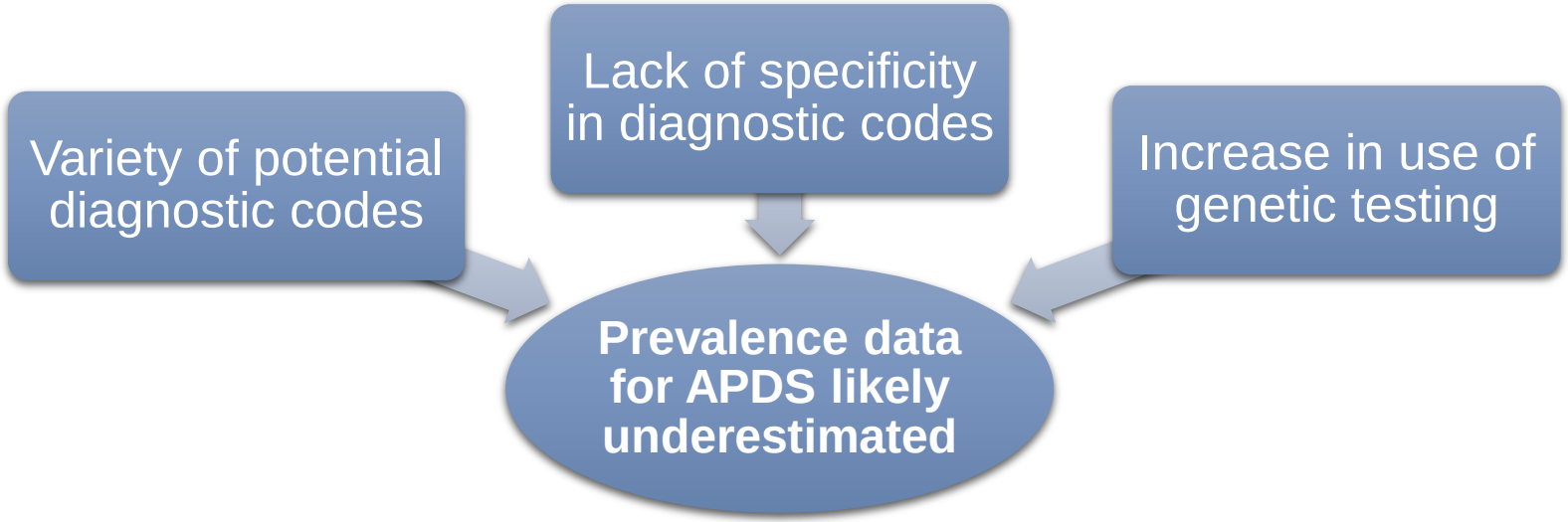
Gastrointestinal
Eg, R19.7 diarrhea unspecified, K29.70 gastritis unspecified without bleeding

Malignancy
Eg, C95.90 leukemia unspecified not having achieved remission

At least 11 different immunodeficiency codes are used to designate APDS

*Includes codes from the ESID registry as well as codes used by 7 American immunologists caring for patients with APDS. DOF, Pharming Inc. 2021.
CID, combined immunodeficiency; CVID, common variable immune deficiency; ESID, European Society for Immunodeficiencies; HCP, healthcare provider; Ig, immunoglobulin; SCID, severe combined immunodeficiency.

Rationale for a New ICD-10-CM Code



APDS can underlie diseases such as lymphoma. Increasingly, it's understood that outcomes for sequalae from PIs may be better managed if the underlying PI is known. An ICD-10 code may possibly contribute to better management

Rationale for a stand-alone code

- Aid in **strengthening research and monitoring** of the disease and its progression
- Enable more **accurate quantification of the prevalence** of APDS
- **Facilitate care** for patients seeking treatment when a targeted therapy is available, to enable specific identification of APDS
  - Leniolisib will be considered 'precision medicine' for the treatment of APDS

PI, primary immunodeficiency

Thank You & Questions