Immune Deficiency Foundation

Lunch & Learn: APDS

August 24th, 2022

IDF MISSION

Improving the diagnosis, treatment, and quality of life of people affected by primary immunodeficiency through fostering a community empowered by advocacy, education and research.

Immune Deficiency Foundation

Thank you to our Sponsor!

HOUSEKEEPING

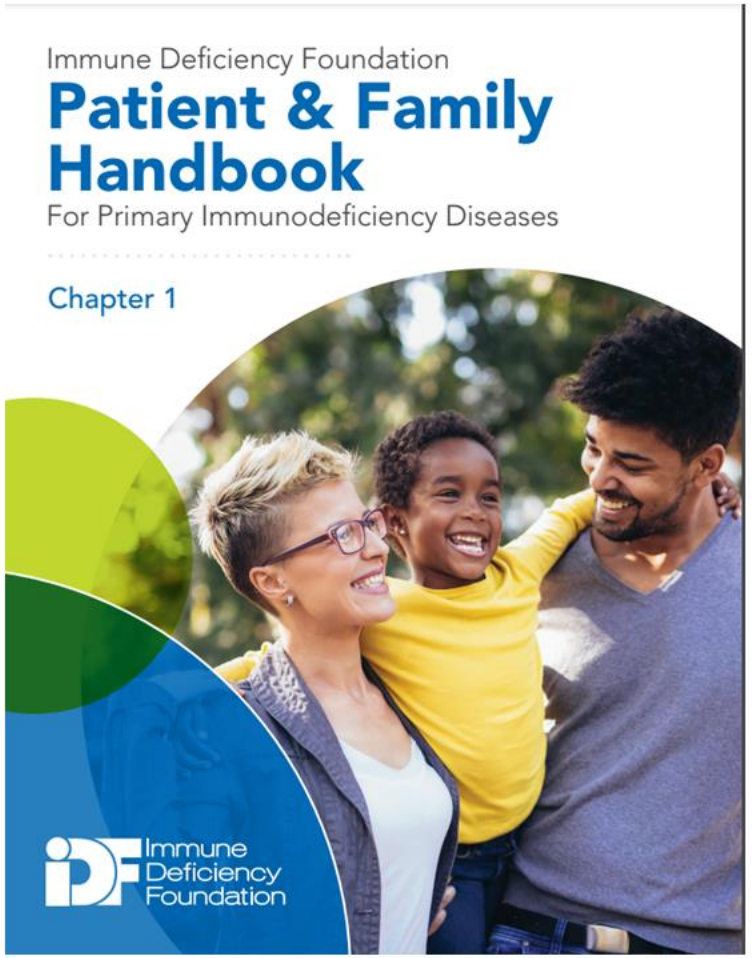
- Attendees will not have access to their microphone or webcam throughout the event.
- To see the full slides, you can adjust the settings on the speaker view panel on the top of the Zoom screen and select "side-by-side" in the dropdown option.
- Please submit all questions for the presenter via the Q&A box

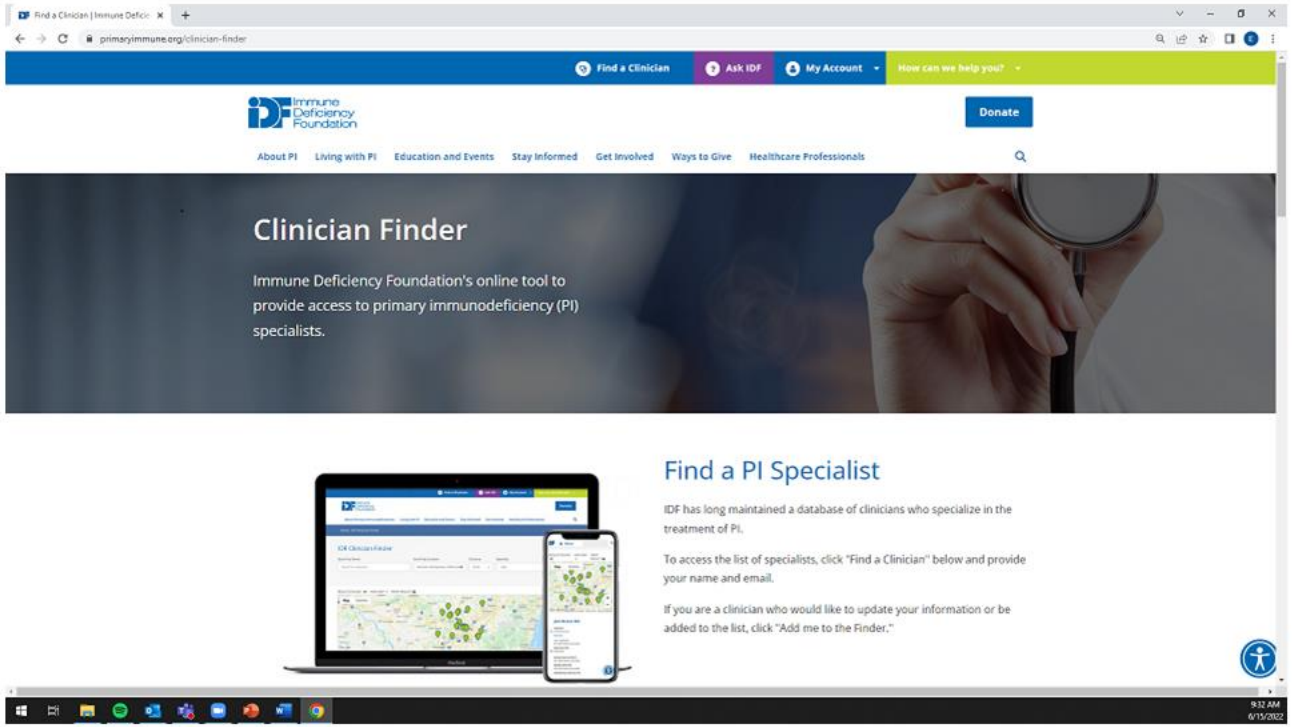
DISCLAIMER

Immune Deficiency (IDF) education events offer a wide array of educational presentations, including presentations developed by healthcare and life management professionals invited to serve as presenters. The views and opinions expressed by guest speakers do not necessarily reflect the views and opinions of IDF.

The information presented during this event is not medical advice, nor is it intended to be a substitute for medical advice, diagnosis or treatment. Always seek the advice of a physician or other qualified health provider with questions concerning a medical condition. Never disregard professional medical advice, or delay seeking it based on information presented during the event.

IDF Website: www.primaryimmune.org

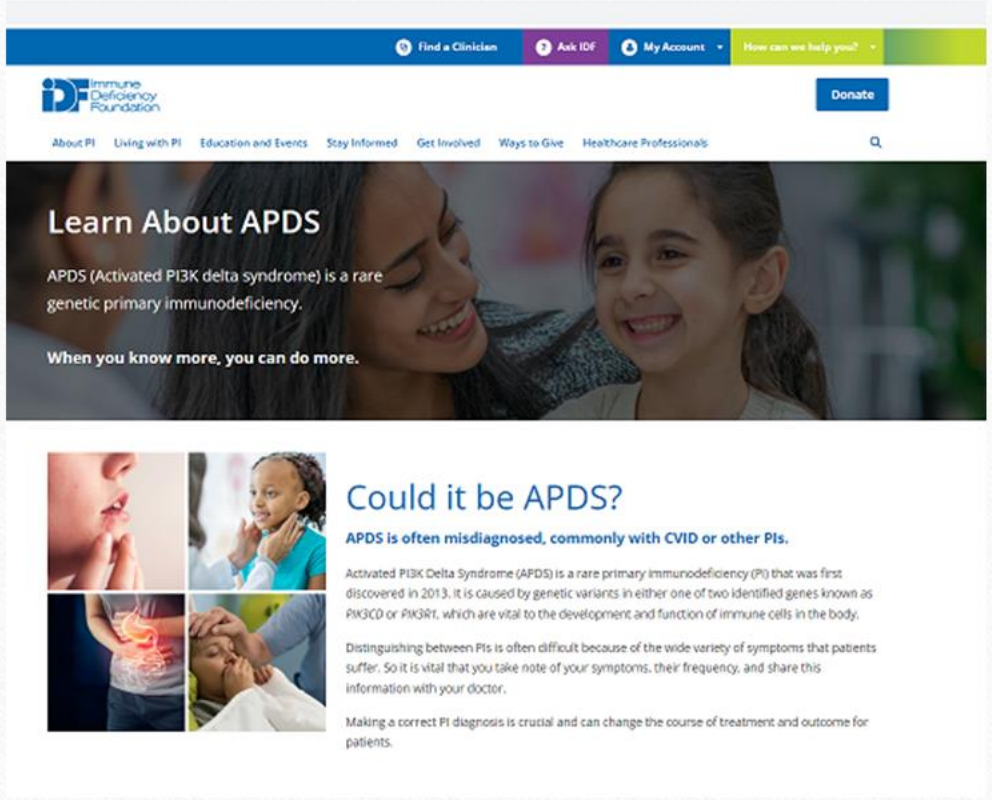


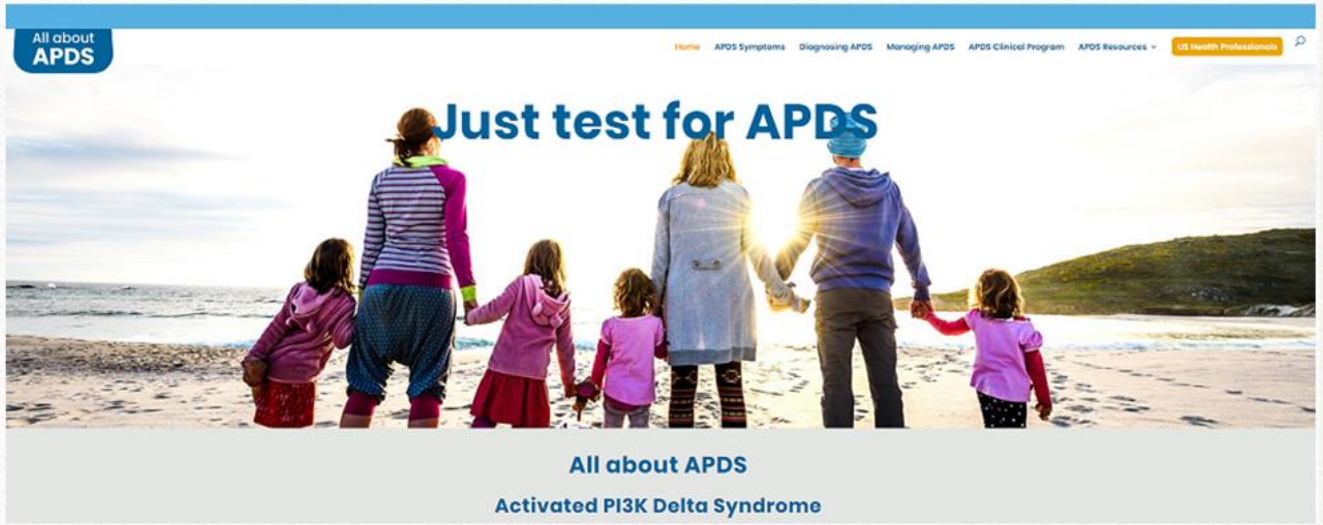


Immune Deficiency Foundation

To view all APDS Resources and Materials, visit:

https://primaryimmune.org/apds





https://allaboutapds.com/about-apds/

PI COMMUNITY SERVICES

- Monthly Lunch & Learns- medical experts present on various diagnosis-specific topics
- Get Connected Groups: share experiences, receive information, and gain support
- IDF Forums
- Ask IDF
- Annual PI Conference

To view a list of all upcoming IDF events, visit: https://community.primaryimmune.org/s/events?language=en_US

REGISTRATION IS OPEN: www.primaryimmune.org/conference

WELCOME!

Eveline Wu, MD, MSCR
Assistant Professor of Pediatrics
Allergy & Immunology, Pediatric Rheumatology
University of North Carolina, Chapel Hill

IDF Lunch & Learn: All About APDS!

Eveline Wu, MD, MSCR

Associate Professor of Pediatrics

Allergy & Immunology, Pediatric Rheumatology

University of North Carolina, Chapel Hill

Disclosure

- Dr. Wu has received consulting fees from Pharming Healthcare, Inc.
- Dr. Wu has received grants as an investigator from AstraZeneca, Bristol-Myers Squibb, Enzyvant, and Janssen.
- Pharming Healthcare, Inc. supported the creation of this content.

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

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.

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

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

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

Activated PI3Kδ Syndrome (APDS) Is A PIRD

APDS = **A**ctivated **P**I3K **D**elta **S**yndrome[1,2]
(previously known as PASLI)

Discovered in 2013[1,2]
Rare: Estimated 1-2 people per million[3]

Doctors are still learning about and becoming aware of the disease

Caused by variants in one of two genes: *PIK3CD* and *PIK3R1*[1,4]
These variants cause the immune system to not work properly[1,4]

APDS, activated phosphoinositide 3-kinase delta syndrome; PASLI, p110δ-activating mutation causing senescent T cells, lymphadenopathy, and immunodeficiency.

1. Angulo I, et al. *Science*. 2013;342(6160):866-871. 2. Lucas CL, et al. *Nat Immunol*. 2014;15(1):88-97. 3. Activated PI3K-delta syndrome. Orphanet website. Accessed May 14, 2021. https://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=EN&Expert=397596. 4. Lucas CL, et al. *J Exp Med*. 2014;211(13):2537-2547.

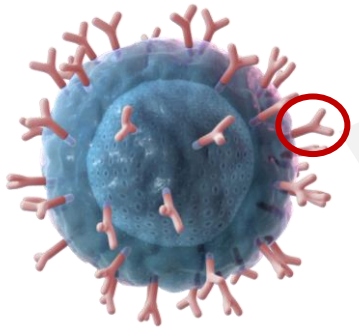
What Causes APDS?

The Immune System Is Made of T Cells and B Cells That Work Together To Protect the Body

T cell

Destroys specific germs or helps regulate the immune system, depending on the type of T cell[1]

B cell



Makes antibodies to target specific germs for destruction[1]

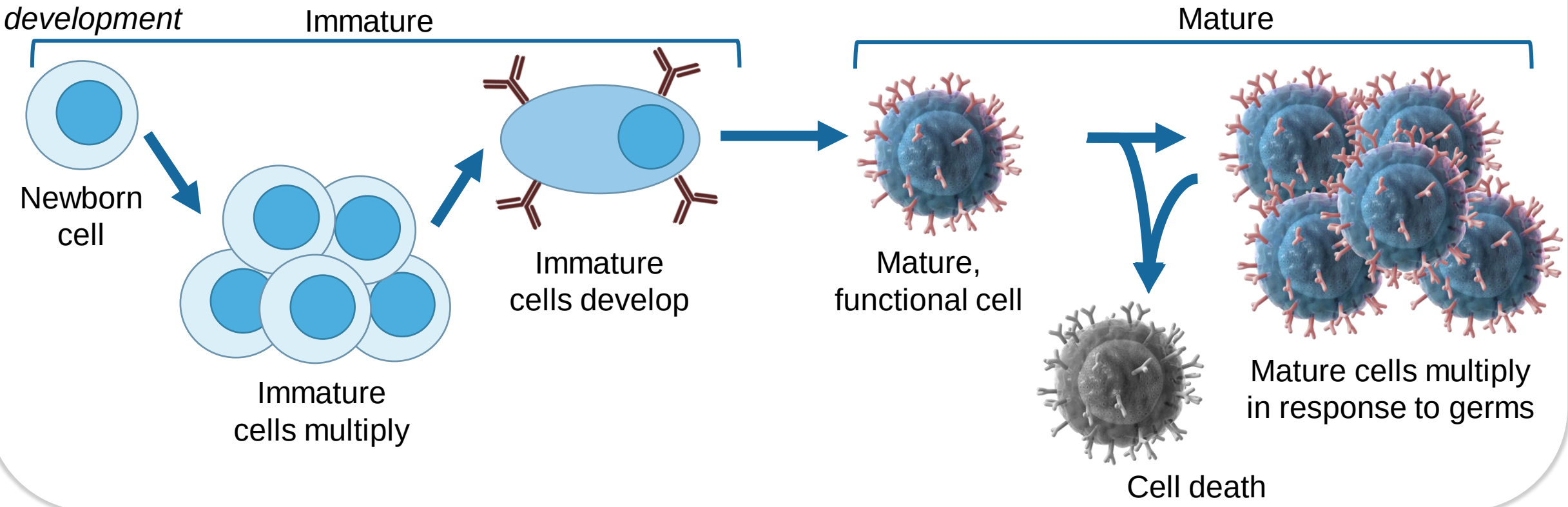
Antibodies:
Special shaped proteins that attach to specific germs

Too much or too little T and B cell activity causes problems—it needs to be just right[2]

1. Janeway CA Jr, et al. *Immunobiology: The Immune System in Health and Disease*. 5th ed. New York, NY: Garland Science; 2001. Accessed May 14, 2021. https://www.ncbi.nlm.nih.gov/books/NBK27092/. 2. Tangye SG, et al. *J Clin Immunol*. 2019;39(2):148-158.

B Cells and T Cells Must Follow Specific Steps To Mature or They Will Not Become Functional

Strangely, B and T cells do not start out functional They must go through a series of specific steps[1,2]



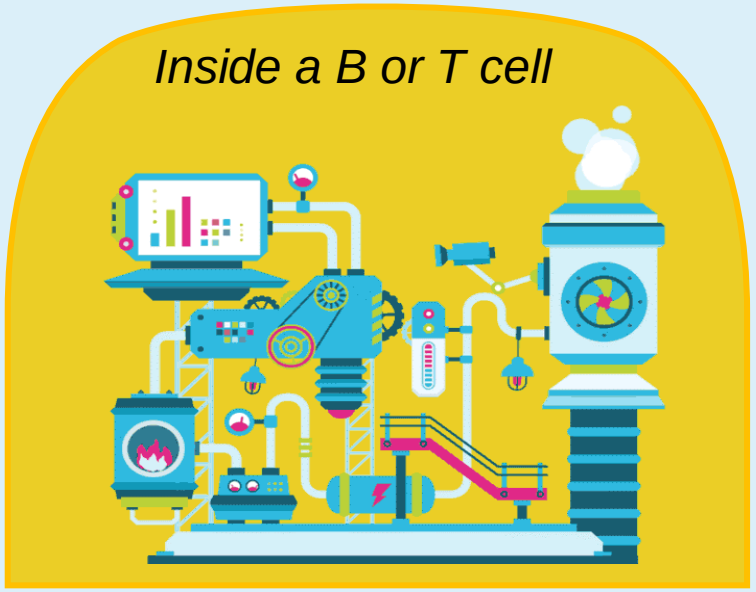
1. Janeway CA Jr, et al. *Immunobiology: The Immune System in Health and Disease*. 5th ed. New York, NY: Garland Science; 2001. Accessed May 14, 2021. https://www.ncbi.nlm.nih.gov/books/NBK27092/. 2. Okkenhaug K, Vanhaesebroeck B. *Nat Rev Immunol*. 2003;3(4):317-330.

Pathways INSIDE of Each B and T Cell Instruct the Cell Precisely How to Mature

The only way for B cells and T cells to become functional is if they mature using specific pathways

Immature Mature

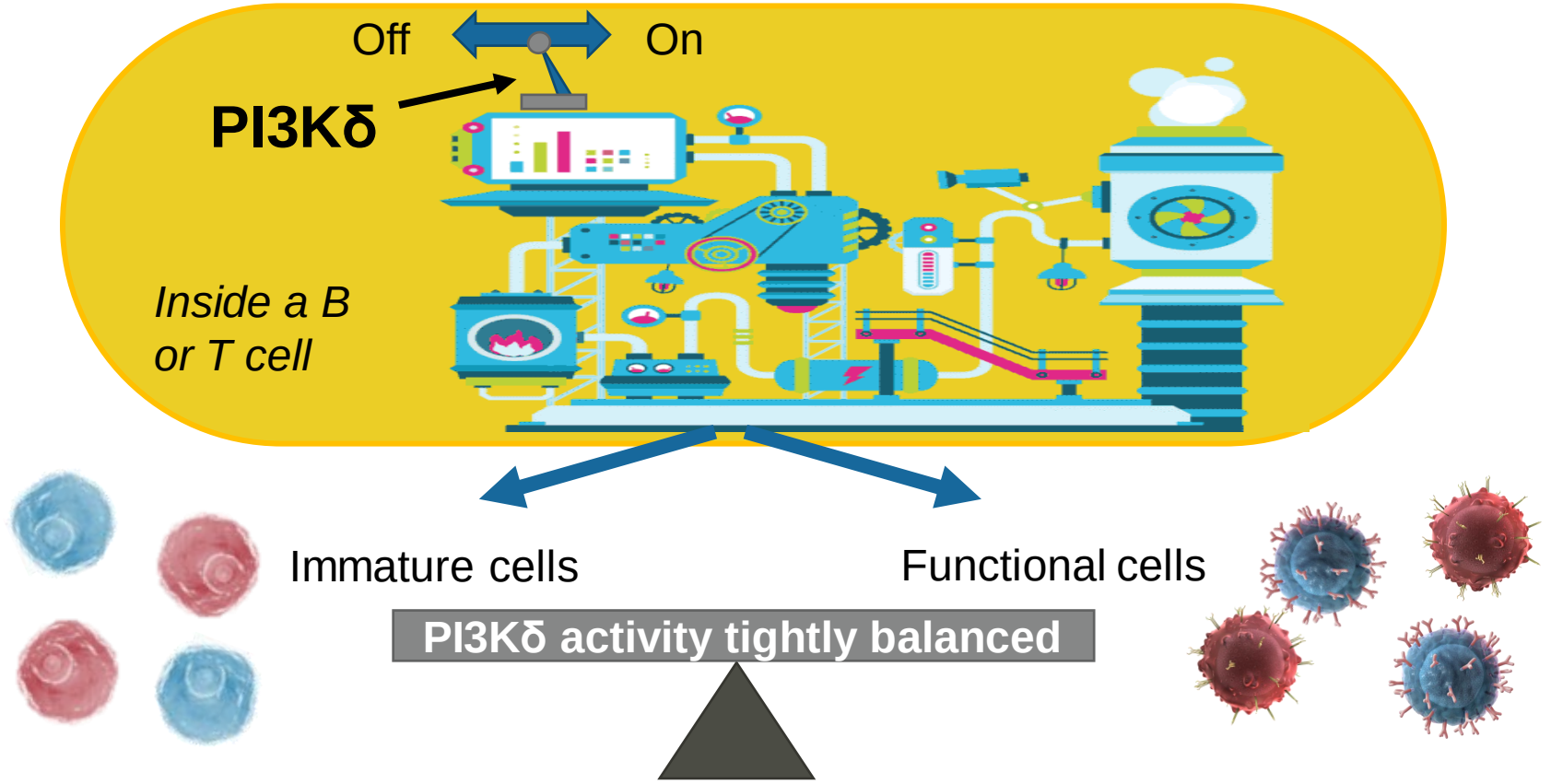
Some pathways are like this machine: a series of steps or cascades of events inside the cell that produce an effect



Janeway CA Jr, et al. *Immunobiology: The Immune System in Health and Disease*. 5th ed. New York, NY: Garland Science; 2001. Accessed May 14, 2021. https://www.ncbi.nlm.nih.gov/books/NBK27092/.

The PI3Kδ Pathway Controls How B and T cells Mature and Function

PI3Kδ activity kick-starts cascades that instruct B and T cells to multiply, mature, or even die

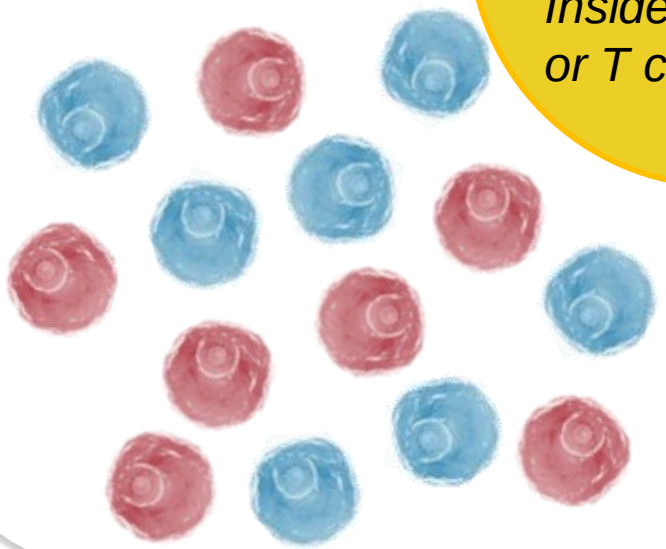


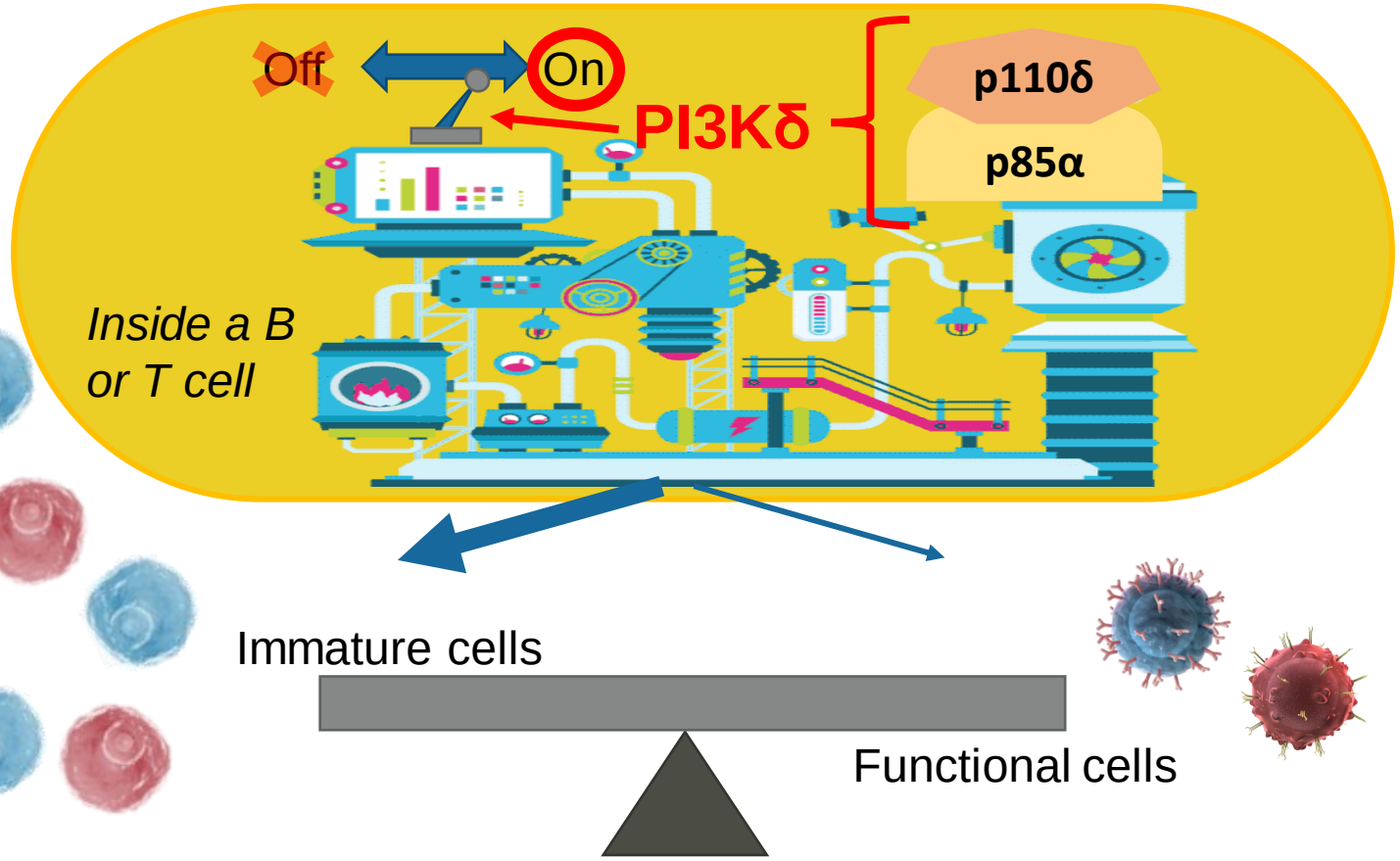
PI3Kδ, phosphoinositide 3-kinase delta.

Fruman DA, et al. *Cell*. 2017;170(4):605-635.

Unbalanced PI3Kδ Pathway Activity Alters B and T Cells

In APDS, PI3Kδ is overactive





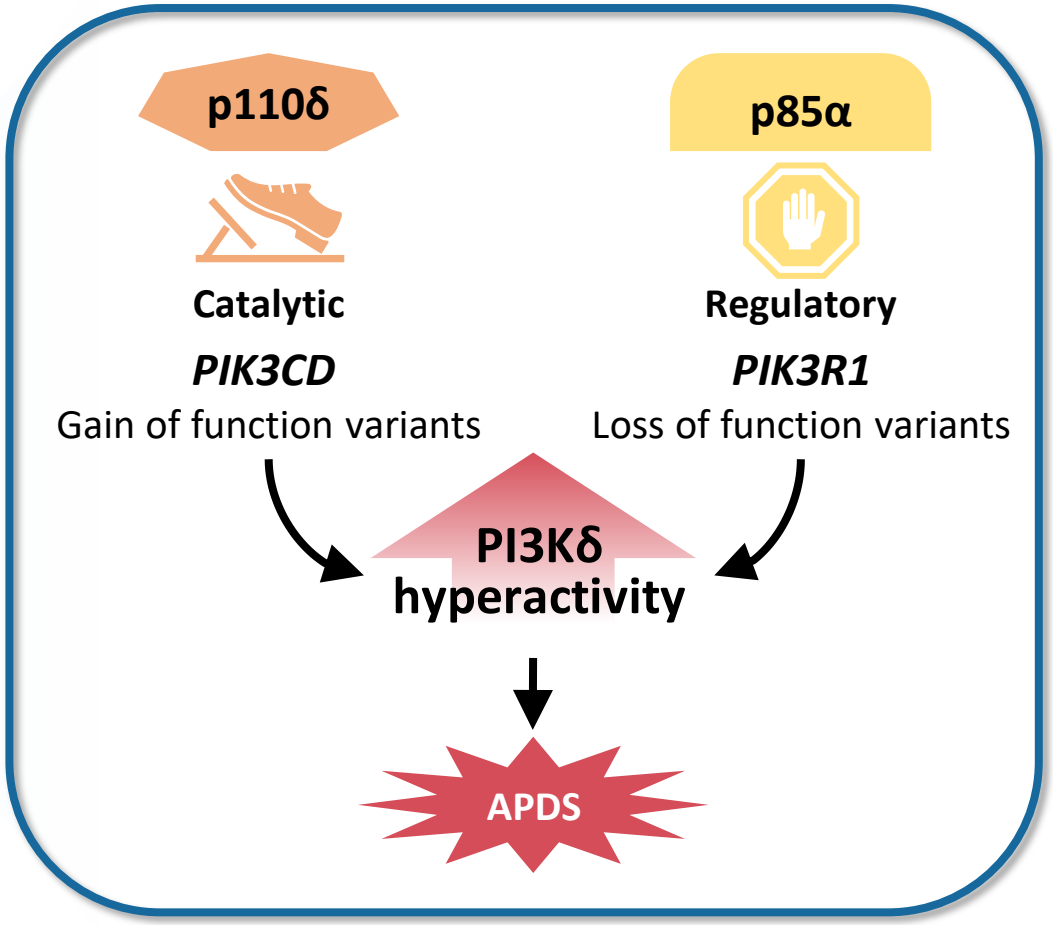
PI3Kδ activity is unbalanced, leading to altered B and T cell development and function

APDS, activated phosphoinositide 3-kinase delta syndrome; PI3Kδ, phosphoinositide 3-kinase delta.

Lucas CL, et al. *Nat Immunol*. 2014;15(1):88-97.

Variants In PI3Kδ Genes Can Cause APDS

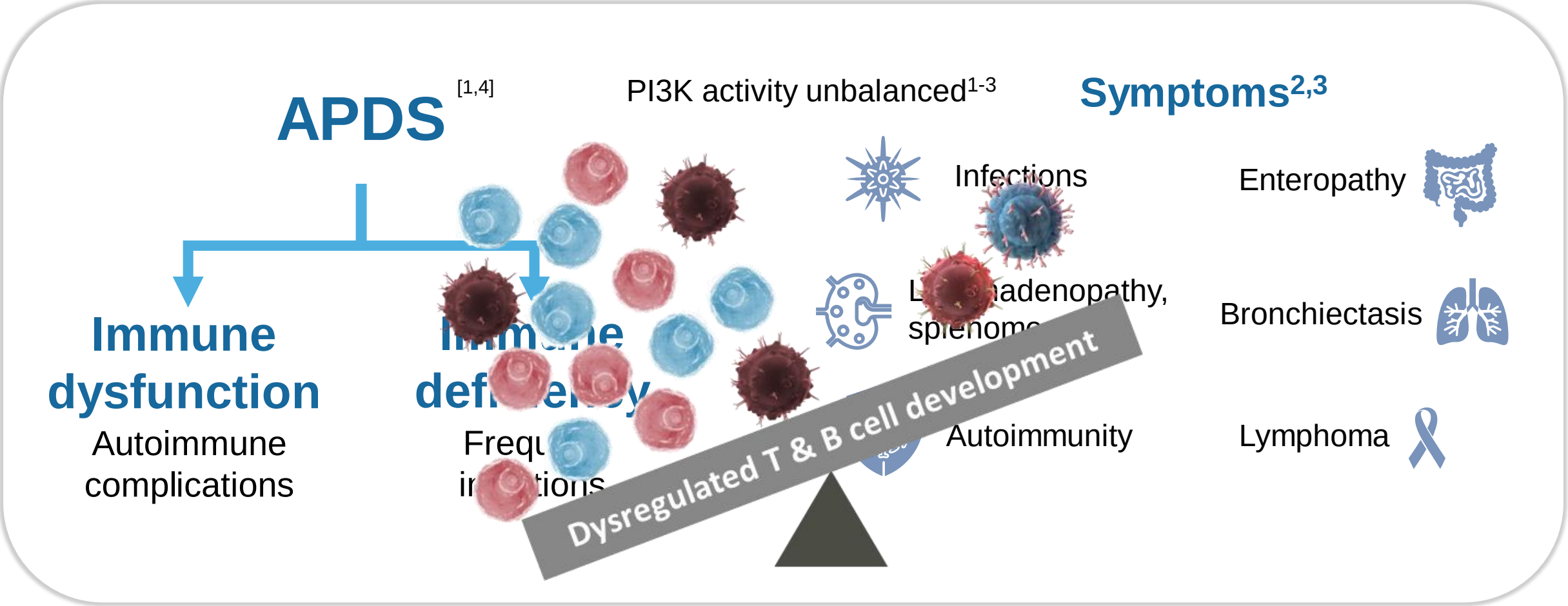
Genetic variants in either PI3Kδ subunit that result in enzyme hyperactivity cause APDS[1-4]



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.

Altered B And T Cells Lead To Many APDS Symptoms



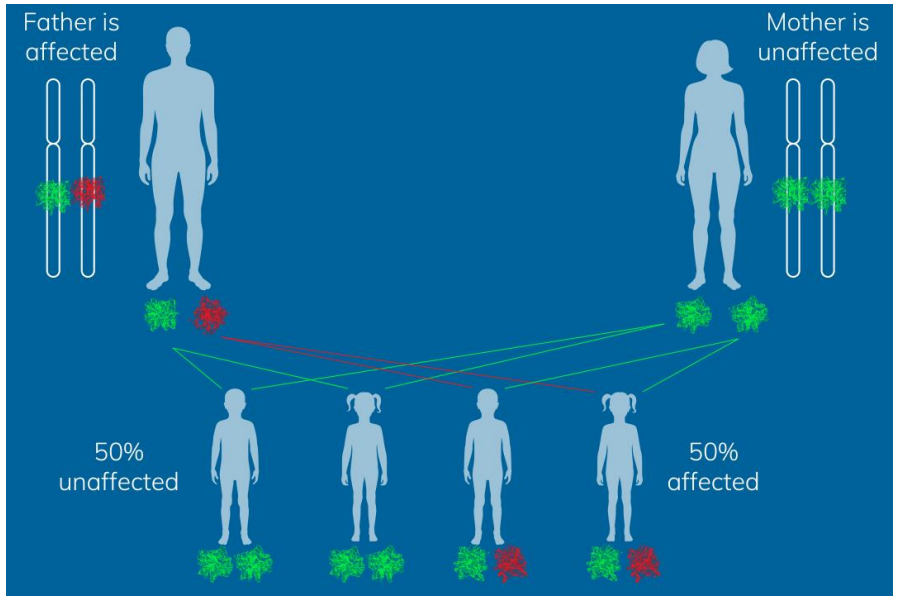
APDS, activated phosphoinositide 3-kinase δ syndrome; PI3Kδ, phosphoinositide 3-kinase δ.

1. Lucas CL, et al. *Nat Immunol.* 2014;15(1):88-97. 2. Coulter TI, et al. *J Allergy Clin Immunol*. 2017;139(2):597-606. 3. Elkaim E, et al. *J Allergy Clin Immunol*. 2016;138(1):210-218. 4. Angulo I, et al. *Science*. 2013;342(6160):866-871.

APDS May Be Present in Multiple Members of a Family

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

- APDS can be passed down from a person's mother *or* father[2]
- It can also spontaneously appear in a person with no family history[2]



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

Even within the same family, one person's APDS symptoms may look different than another's symptoms[4]

APDS, activated phosphoinositide 3-kinase delta syndrome.

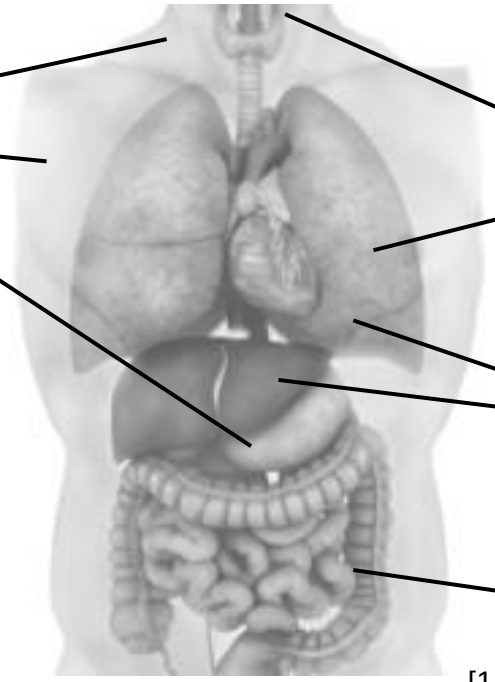
1. Chinn IK, et al. *J Allergy Clin Immunol*. 2020;145(1): 46-69. 2. Lucas CL, et al. *Nat Immunol*. 2014;15(1):88-97. 3. Autosomal dominant. National Human Genome Research Institute website. https://www.genome.gov/genetics-glossary/Autosomal-Dominant. Accessed May 14, 2021. 4. Genetic Alliance; The 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.

What Are The Symptoms of APDS?

APDS Has A Wide Range Of Clinical Manifestations

Developmental delay
Failure to thrive

Chronic lymphadenopathy
Nodular lymphoid hyperplasia
Lymphoma
Premature mortality



Recurrent sinopulmonary infections
Pneumonia
Bronchiectasis

Persistent, severe, or recurrent herpesvirus infections, particularly EBV and CMV

Splenomegaly
Hepatomegaly

Autoimmune cytopenias and autoinflammatory diseases

Enteropathy

[1,2]

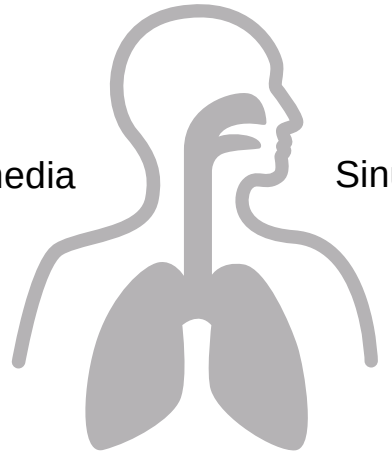
APDS, activated phosphoinositide 3-kinase δ syndrome; CMV, cytomegalovirus; EBV, Epstein-Barr virus.

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.

Recurrent Sinopulmonary Infections Are The Initial Hallmark Of APDS

Include[1-4]

Upper respiratory tract infections



Otitis media

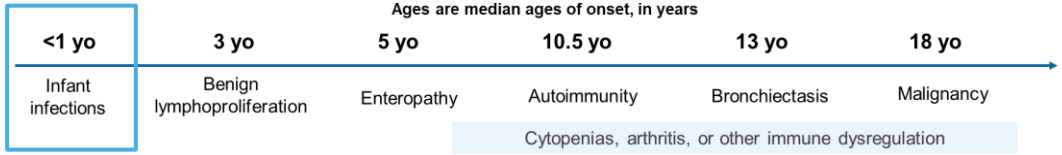
Sinusitis

Pneumonia

Bronchitis

Allergy/asthma are also common[6]

Timeline of the Most Common Pathologies Seen in APDS



APDS, activated phosphoinositide 3-kinase δ syndrome; yo, years old.

1. Maccari ME, et al. *Front Immunol*. 2018;9:543. 2. Coulter TI, et al. *J Allergy Clin Immunol*. 2017;139(2):597-606. 3. Elkaim E, et al. *J Allergy Clin Immunol*. 2016;138(1):210-218. 4. Carpier JM, Lucas CL. *Front Immunol*. 2018;8:2005.
5. Jamee M, et al. *Clin Rev Allergy Immunol*. 2020;59(3):323-333. 6. Kubala SA, et al. Poster presented at: CIS 2021 Annual Meeting; April 14-17, 2021. 7. Takeda AJ, et al. *J Allergy Clin Immunol*. 2017;140(4):1152-1156.

Patients With APDS Are Particularly Vulnerable To Herpesviruses

Acute and chronic viral infections reported in

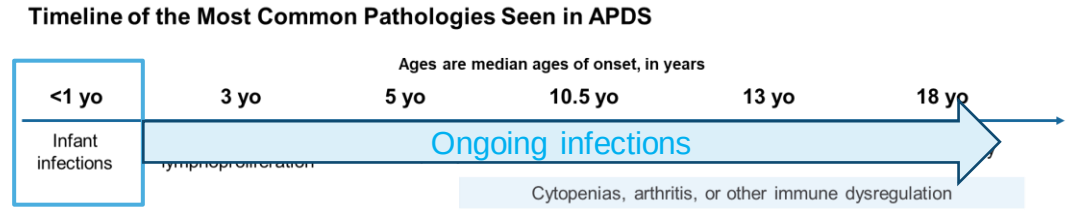
36-49%

of patients[1,2]

CMV[1-3] 15-17%

EBV[1-5] 24-30%

Genetic testing for APDS should be considered in patients with unexplained EBV or CMV viremia[6]



APDS, activated phosphoinositide 3-kinase δ syndrome; CMV, cytomegalovirus; EBV, Epstein-Barr virus; yo, years old.

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. Jamee M, et al. *Clin Rev Allergy Immunol.* 2020;59(3):323-333. 4. Maccari ME, et al. *Front Immunol.* 2018;9:543. 5. Carpier JM, Lucas CL. *Front Immunol.* 2018;8:2005. 6. Cohen JI. *Front Immunol.* 2018;9:237.

Lymphoproliferation Can Be A Manifestation Of Immune Dysregulation

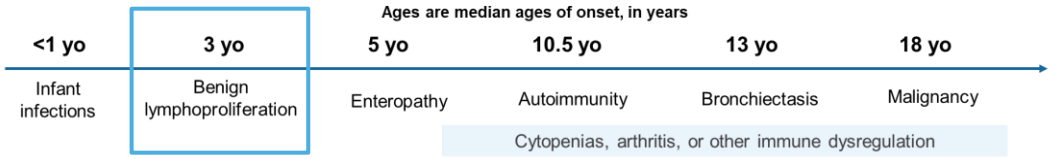
71-89%

of patients have been shown to be affected by **lymphadenopathy, splenomegaly, hepatomegaly and/or nodular lymphoid hyperplasia**[1-5]

Manifests early

Median onset reported at 3 years of age (range, 1-6 years)[4]

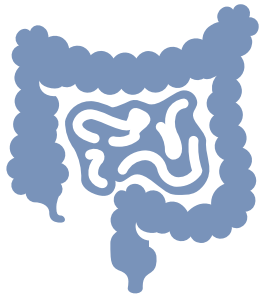
Timeline of the Most Common Pathologies Seen in APDS



*Open arrows indicate lymphadenopathy as imaged using positron emission tomography. Closed arrows indicate hepatosplenomegaly.
APDS, activated phosphoinositide 3-kinase δ syndrome; yo, years old.

1. Maccari ME, et al. *Front Immunol*. 2018;9:543. 2. Coulter TI, et al. *J Allergy Clin Immunol*. 2017;139(2):597-606. 3. Elkaim E, et al. *J Allergy Clin Immunol*. 2016;138(1):210-218. 4. Jamee M, et al. *Clin Rev Allergy Immunol*. 2020;59(3):323-333. 5. Carpier JM, Lucas CL. *Front Immunol*. 2018;8:2005. 6. Kang, JM et al. *Yonsei Med J*. 2020;61(6):542-546. 7. Binesh F, et al. *Iran J Ped Hematol Oncol*. 2013;3(4):173-175.

Lymphoproliferation Can Result In Enteropathy



51% of patients reported experiencing **gastrointestinal manifestations**[1]

- Includes bowel inflammation, chronic diarrhea, and malabsorption[1-3]
- Can indicate nodular mucosal lymphoid hyperplasia in the GI tract[2,3]

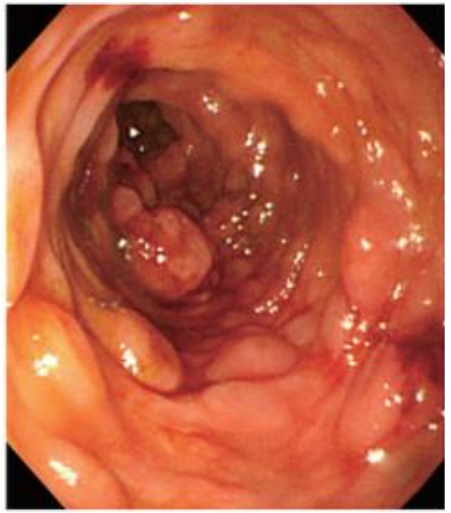
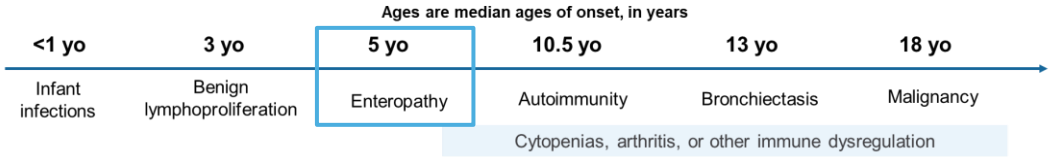


Image reproduced from Kang, JM et al. *Yonsei Med J*. 2020;61(6):542-546.

Gastrointestinal endoscopy reveals lymphoid nodules in a 4-year-old patient with APDS[4]

Timeline of the Most Common Pathologies Seen in APDS



APDS, activated phosphoinositide 3-kinase δ syndrome; GI, gastrointestinal; yo, years old.

1. Maccari ME, et al. *Front Immunol*. 2018;9:543. 2. Coulter TI, et al. *J Allergy Clin Immunol*. 2017;139(2):597-606. 3. Elkaim E, et al. *J Allergy Clin Immunol*. 2016;138(1):210-218.
4. Kang, JM et al. *Yonsei Med J*. 2020;61(6):542-546.

Patients With APDS May Fail To Thrive

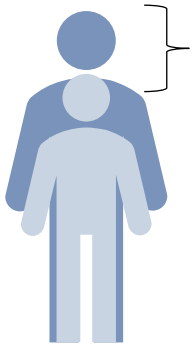
Failure to thrive reported in

45-62%

of patients with **APDS2** (variants in *PIK3R1*)[1-3]

Encompasses[1,3-5]

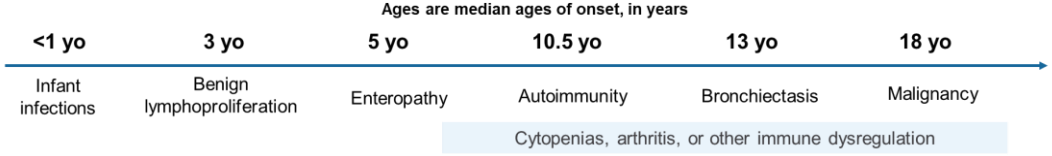
Short stature



Low weight

May be partially due to enteropathy[3]

Timeline of the Most Common Pathologies Seen in APDS



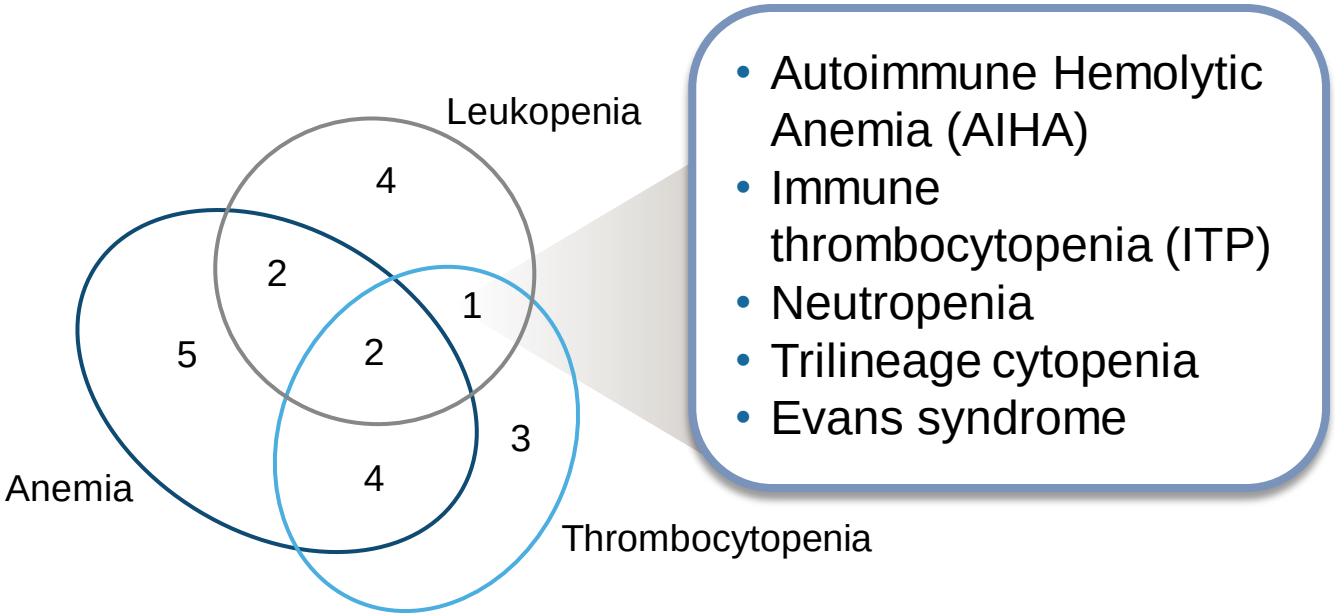
APDS, activated phosphoinositide 3-kinase δ syndrome; *PIK3R1*, phosphoinositide 3-kinase regulatory subunit 1 gene; SD, standard deviation; yo, years old.

1. Maccari ME, et al. *Front Immunol*. 2018;9:543. 2. Jamee M, et al. *Clin Rev Allergy Immunol*. 2020;59(3):323-333. 3. Elkaim E, et al. *J Allergy Clin Immunol*. 2016;138(1):210-218.
4. Kang JM, et al. *Yonsei Med J*. 2020;61(6):542-546. 5. Petrovski S, et al. *J Clin Immunol*. 2016;36(5):462-471.

Patients With APDS May Present With Autoimmunity In Addition To Immune Deficiency

Autoimmune cytopenias reported in around 30% of patients with APDS[1-3]

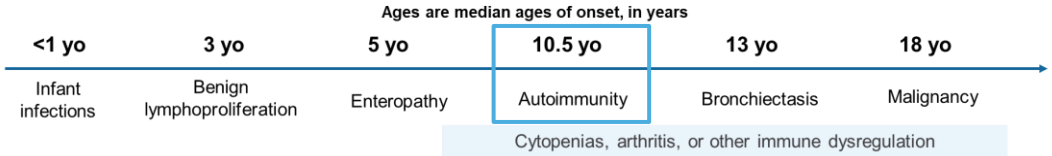
Multiple blood lineages may be affected[1-4]



- Autoimmune Hemolytic Anemia (AIHA)
- Immune thrombocytopenia (ITP)
- Neutropenia
- Trilineage cytopenia
- Evans syndrome

Image reproduced from Maccari ME, et al. *Front Immunol*. 2018;9:543.

Timeline of the Most Common Pathologies Seen in APDS



AIHA, autoimmune hemolytic anemia; APDS, activated phosphoinositide 3-kinase δ syndrome; ITP, immune thrombocytopenic purpura; yo, years old.

1. Maccari ME, et al. *Front Immunol*. 2018;9:543. 2. Coulter TI, et al. *J Allergy Clin Immunol*. 2017;139(2):597-606. 3. Jamee M, et al. *Clin Rev Allergy Immunol*. 2020;59(3):323-333.
4. Elkaim E, et al. *J Allergy Clin Immunol*. 2016;138(1):210-218.

Neurological Deficits May Occur In Patients With APDS

Neurodevelopmental delay reported in

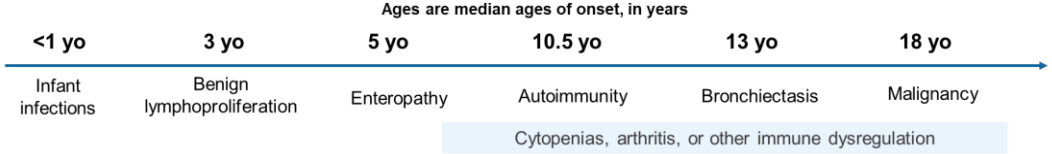
10-19%
of patients with **APDS1** (variants in *PIK3CD*)[1-3]

27-31%
of patients with **APDS2** (variants in *PIK3R1*)[3,4]

Includes[1-5]

- Global developmental delay
- Speech delay
- Learning disabilities
- Autism spectrum disorders
- Anxiety and depression disorders
- Behavioral disorders

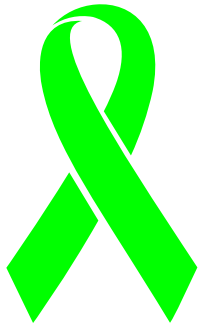
Timeline of the Most Common Pathologies Seen in APDS



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

1. Coulter TI, et al. *J Allergy Clin Immunol*. 2017;139(2):597-606. 2. Wang Y, et al. *J Clin Immunol*. 2018;38(8):854-863. 3. Jamee M, et al. *Clin Rev Allergy Immunol*. 2020;59(3):323-333. 4. Elkaim E, et al. *J Allergy Clin Immunol*. 2016;138(1):210-218. 5. Maccari ME, et al. *Front Immunol*. 2018;9:543.

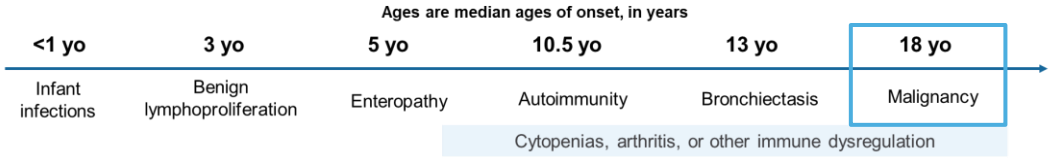
Benign Lymphoproliferation May Progress To Malignancy In Patients With APDS



Lymphomas are most common[1,2]

Multiple lymphomas are not unusual[3,4]

Leukemias and solid organ malignancies may also affect patients with APDS, though less frequently than lymphoma[1,3]



*In a cohort of patients with variants in *PIK3R1*.
APDS, activated phosphoinositide 3-kinase δ syndrome; *PIK3R1*, phosphoinositide 3-kinase regulatory subunit 1 gene ; yo, years old.

1. Maccari ME, et al. *Front Immunol*. 2018;9:543. 2. Coulter TI, et al. *J Allergy Clin Immunol*. 2017;139(2):597-606. 3. Elkaim E, et al. *J Allergy Clin Immunol*. 2016;138(1):210-218.
4. Jamee M, et al. *Clin Rev Allergy Immunol*. 2020;59(3):323-333. 5. Carpier JM, Lucas CL. *Front Immunol*. 2018;8:2005.

APDS Can Alter Immunoglobulin Levels In Complex Ways

Patients with APDS frequently have all or some of the below immunoglobulin characteristics[1,2]

- Low to normal IgG levels
- Low to normal IgA levels
- High IgM levels

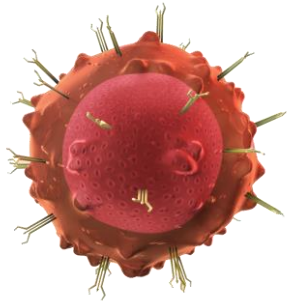
- Poor antibody responses to vaccine challenges

APDS, activated phosphoinositide 3-kinase δ syndrome; Ig, immunoglobulin.

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.

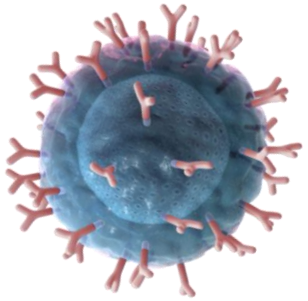
Hyperactive PI3Kδ Alters Immune Cell Phenotypes

T cells[1-4]



- ↓ CD4+
- ↑ CD8+
- → ↑ Effector memory CD8+
- ↻ Inverted CD4+/CD8+ ratio
- ↑ Follicular T helper
- Total CD8+ skewed to T_{EM}/T_{EMRA} (senescent)
- → ↓ NK cells

B cells[1-4]



- ↓ B cells (CD19+)
- ↑ Transitional B cells
- ↓ Memory B cells
- Defects in class-switch recombination

Common Symptoms of APDS[2,3]

Severe, Recurrent, Persistent Infections:
- Sinopulmonary
- Herpesvirus (especially EBV and CMV)

Lymphoproliferation:
- Lymphadenopathy
- Splenomegaly/hepatomegaly
- Nodular lymphoid hyperplasia

Enteropathy

Autoimmunity:
- Cytopenias
- Autoimmune disorders
- Autoinflammatory disorders

Bronchiectasis

Lymphoma

CMV, cytomegalovirus; EBV, Epstein-Barr virus; NK, natural killer; PI3Kδ, phosphoinositide 3-kinase δ; T_{EM}, T effector memory cell; T_{EMRA}, T effector memory cells re-expressing CD45RA.

1. Lucas CL, et al. *Nat Immunol.* 2014;15(1):88-97. 2. Coulter TI, et al. *J Allergy Clin Immunol.* 2017;139(2):597-606. 3. Elkaim E, et al. *J Allergy Clin Immunol.* 2016;138(1):210-218.
4. Jamee M, et al. *Clin Rev Allergy Immunol.* 2020;59(3):323-333.

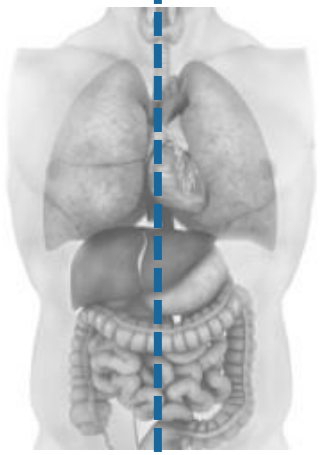
How Do You Treat APDS?

Current Management For APDS

Current APDS Management[1,2]

Immune Deficiency

- Antimicrobial prophylaxis
- Immunoglobulin replacement therapy

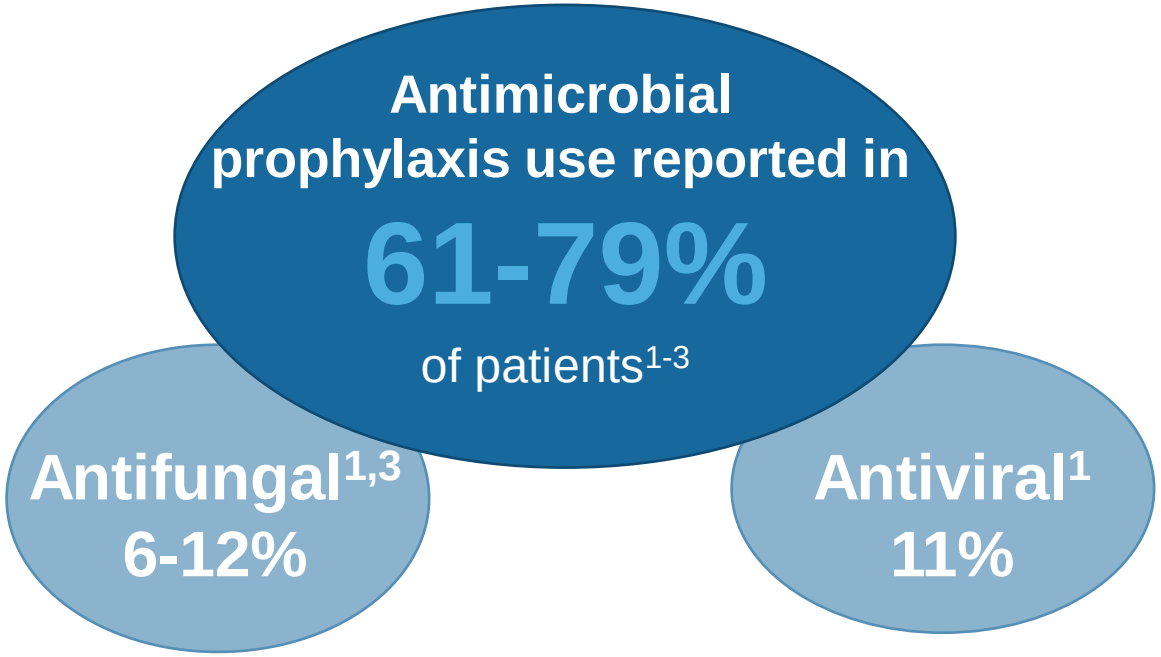


None of these therapies are FDA-approved for APDS treatment

APDS, activated phosphatidylinositol 3-kinase δ syndrome.

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.

Antimicrobial Prophylaxis May Only Address A Small Subset Of APDS Disease Manifestations



Limitations

- **Does not address immune dysregulation** aspects of APDS such as lymphoproliferation[5]

Antimicrobial prophylaxis is used to prevent infections, which are pervasive among patients with APDS[1,2,6]

Not FDA-approved for APDS treatment

APDS, activated phosphatidylinositol 3-kinase δ syndrome.

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. Maccari ME, et al. *Front Immunol*. 2018;9:543. 4. Kannan JA, et al. *Ann Allergy Asthma Immunol*. 2015;115(5):452-454. 5. Elgizouli M, et al. *Clin Exp Immunol*. 2016;183(2):221-229. 6. Sandman Z, Iqbal OA. In: *StatPearls Internet*. Treasure Island, FL: StatPearls Publishing; 2021-.

Immunoglobulin Replacement Therapy Can Be Used To Address Sinopulmonary Infections Or Autoimmune Cytopenias

IRT use reported in

63-89%

of patients[1-4]

Reported median age of IRT initiation - 5 years of age (range, 1-35 years)[3]

Outcomes

May reduce infections[2]

Well-tolerated[1]

Limitations

Does not prevent **herpes virus infections**[5,6]
May not be effective for all sinopulmonary infections[6,7]

Bronchiectasis can still progress[5,7]

Does not address immune dysregulation aspects of APDS such as lymphoproliferation, autoimmunity, and lymphoma[5,6,8]

Immunoglobulins administered intravenously (IVIg) or subcutaneously (SCIg) may prevent infections by correcting secondary antibody deficiencies present in patients with APDS[2,3,5,7]

Not FDA-approved for APDS treatment

APDS, activated phosphatidylinositol 3-kinase δ syndrome; IRT, immunoglobulin replacement therapy.

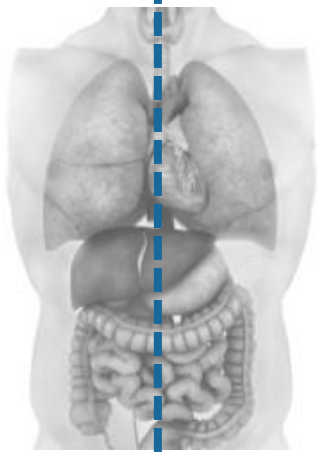
1. Maccari ME, et al. *Front Immunol*. 2018;9:543. 2. Coulter TI, et al. *J Allergy Clin Immunol*. 2017;139(2):597-606. 3. Elkaim E, et al. *J Allergy Clin Immunol*. 2016;138(1):210-218. 4. Jamee M, et al. *Clin Rev Allergy Immunol*. 2020;59(3):323-333. 5. Elgizouli M, et al. *Clin Exp Immunol*. 2016;183(2):221-229. 6. Crank MC, et al. *J Clin Immunol*. 2014;34(3):272-276. 7. Kannan JA, et al. *Ann Allergy Asthma Immunol*. 2015;115(5):452-454. 8. Kracker S, et al. *J Allergy Clin Immunol*. 2014;134(1):233-236.

Current Management For APDS

Current APDS Management[1,2]

Immune Deficiency

- Antimicrobial prophylaxis
- Immunoglobulin replacement therapy



Immune Dysregulation

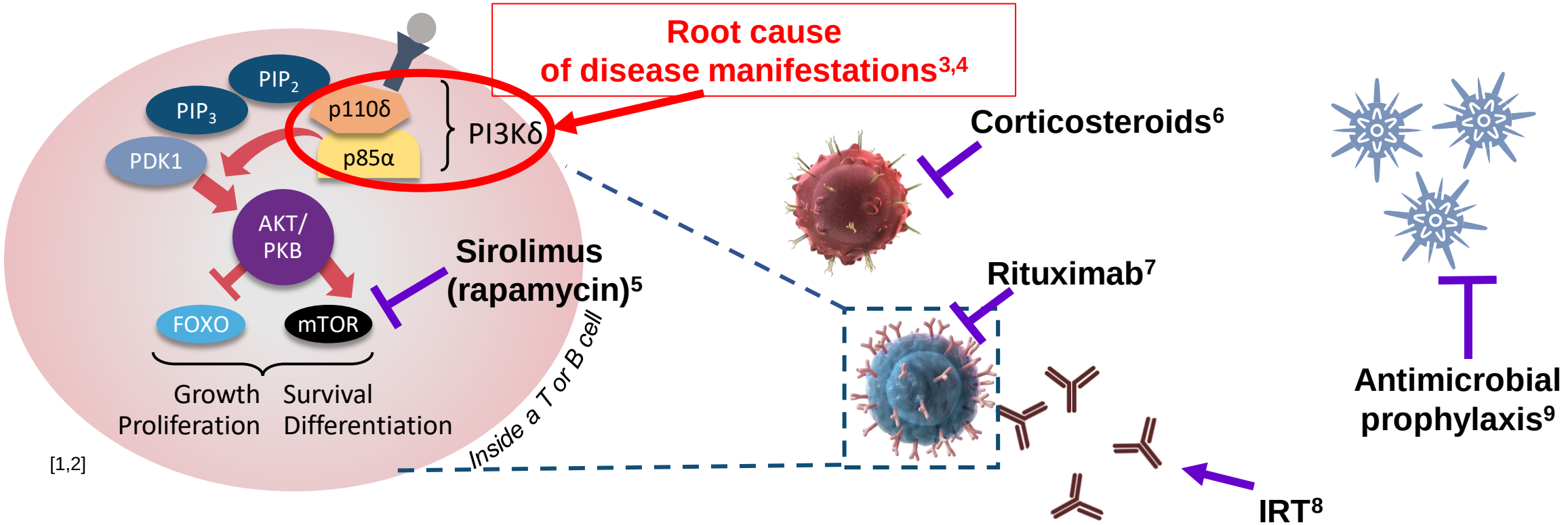
- Corticosteroids
- mTOR inhibitors
- Other immunosuppressants

None of these therapies are FDA-approved for APDS treatment

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. Chan AY, et al. *Front Immunol*. 2020;11:239. 4. Chinn IK, et al. *J Allergy Clin Immunol*. 2020;145(1):46-69.

Current Management Options Address Individual Symptoms Of APDS But Not The Root Cause: PI3Kδ Hyperactivation



Normalization of the PI3Kδ pathway may mitigate both immunodeficiency and immune dysregulation[10]

APDS, activated phosphatidylinositol 3-kinase δ syndrome; FOXO, forkhead box O; IRT, immunoglobulin replacement therapy; mTOR, mammalian target of rapamycin; PDK1, phosphoinositide-dependent protein kinase 1; PI3Kδ, phosphoinositide 3-kinase δ; PIP2, phosphatidylinositol 4,5-bisphosphate; PIP3, phosphatidylinositol 3,4,5-trisphosphate; PKB, protein kinase B.

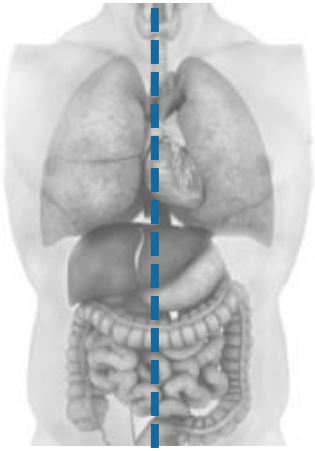
1. Fruman DA, et al. *Cell*. 2017;170(4):605-635. 2. Okkenhaug K, Vanhaesebroeck B. *Nat Rev Immunol*. 2003;3(4):317-330. 3. Lucas CL, et al. *Nat Immunol.* 2014;15(1):88-97. 4. Lucas CL, et al. *J Exp Med*. 2014;211(13):2537-2547. 5. Rapamune [package insert]. Philadelphia, PA: Pfizer; 2021. 6. McKay LI, Cidlowski JA. In: Kufe DW, et al, eds. *Holland-Frei Cancer Medicine*. 6th ed. Hamilton, Ontario, Canada: BC Decker; 2003. 7. Rituxan [package insert]. South San Francisco, CA: Genentech Inc; 2021. 8. Food and Drug Administration. Guidance for industry: safety, efficacy, and pharmacokinetic studies to support marketing of immune globulin intravenous (human) as replacement therapy for primary humoral immunodeficiency. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-efficacy-and-pharmacokinetic-studies-support-marketing-immune-globulin-intravenous-human. Published June 2008. Accessed July 8, 2021. 9. Sandman Z, Iqbal OA. In: *StatPearls Internet*. Treasure Island, FL: StatPearls Publishing; 2021-. 10. Nunes-Santos CJ, et al. *J Allergy Clin Immunol*. 2019;143(5):1676-1687.

Current Management For APDS

Current APDS Management[1,2]

Immune Deficiency

- Antimicrobial prophylaxis
- Immunoglobulin replacement therapy



Immune Dysregulation

- Corticosteroids
- mTOR inhibitors
- Other immunosuppressants

Hematopoietic stem cell transplant

None of these therapies are FDA-approved for APDS treatment

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. Chan AY, et al. *Front Immunol*. 2020;11:239. 4. Chinn IK, et al. *J Allergy Clin Immunol*. 2020;145(1):46-69.

Take Home Points

- APDS is a rare disorder characterized by **immune deficiency** and **immune dysregulation.**
- Common manifestations of APDS include recurrent respiratory infections, infections with herpes viruses, lymphoproliferation, autoimmunity, and lymphoma.
- Treatment currently consists of antimicrobial prophylaxis, immunoglobulin replacement therapy, and therapies for immune dysregulation and autoimmune features.
- APDS is due to variants in the *PIK3CD* and *PIK3R1* genes, and a genetic confirmation can direct treatment and care.

Resources Available To You!

Looking for more information on primary immunodeficiencies like APDS?

Primary Immune Deficiency Treatment Consortium

Jeffrey Modell Foundation

Immune Deficiency Foundation

IPOPI INTERNATIONAL PATIENT ORGANISATION FOR PRIMARY IMMUNODEFICIENCIES

Want insight on genetic testing and genetic disease?

GeneMatters™
Genetics Care. Reimagined.
A Genome Medical Company

Want additional information on APDS?

All about APDS

You can find more APDS information and resources at **AllaboutAPDS.com.**

YouTube

Detailed videos from APDS experts are also available on the **All about APDS YouTube page.**

Genetic Testing – Definitive Diagnosis May Change Treatment

navigateAPDS by Pharming

Pharming partnership with Invitae

- **NO CHARGE 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** – Choice of either 429-gene Primary Immunodeficiency Panel or 574-gene Inborn Errors of Immunity and Cytopenias 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

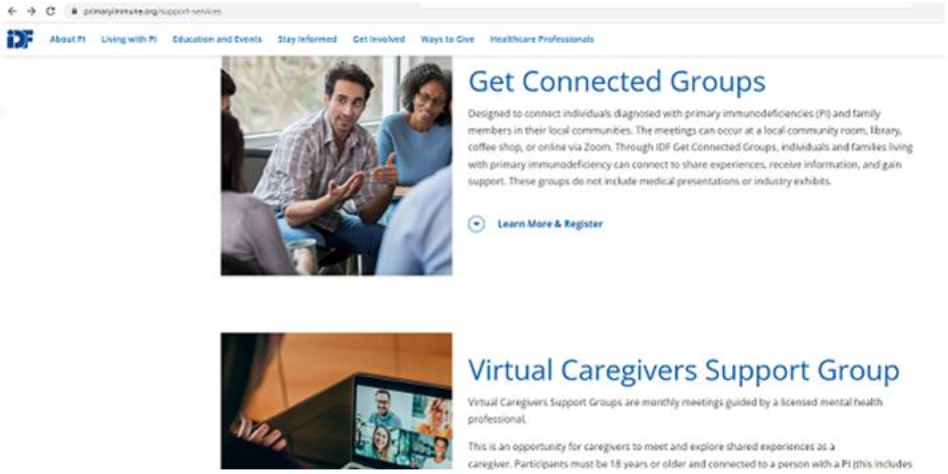
Questions?

THANK YOU!

Eveline Wu, MD, MSCR
Assistant Professor of Pediatrics
Allergy & Immunology, Pediatric Rheumatology
University of North Carolina, Chapel Hill

Additional Resources

- **Read about the brand-new diagnostic code for APDS:** https://primaryimmune.org/news/new-diagnostic-code-ultrarare-primary-immunodeficiency-promises-multiple-benefits
- **Learn about APDS:** https://primaryimmune.org/apds
- **IDF Resource Center:** https://primaryimmune.org/resource-center
- **IDF Support Services:** https://primaryimmune.org/support-services



Have more Questions?

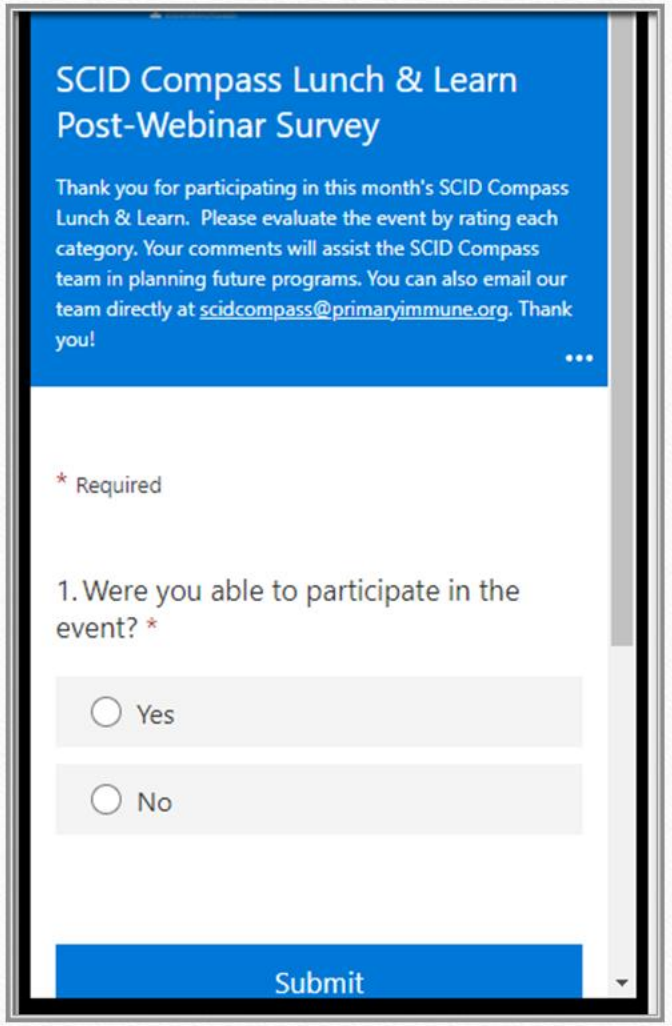
www.Primaryimmune.org/ask-idf

800-296-4433

Immune Deficiency Foundation

WE VALUE YOUR FEEDBACK…

Please take a moment to complete our Evaluation Survey after the Program!



Upcoming Lunch & Learns

B Cell Reconstitution and IgG Infusion

Wednesday, 8/31/22

11:00 AM ET

Manish Butte, MD, PhD

Victoria Dimitriades, MD

ADA SCID Gene Therapy Update

Wednesday, 9/14/22

2:00 PM ET

Donald Kohn, MD

For a list of all upcoming IDF Events, visit:

https://community.primaryimmune.org/s/events?language=en_US

Pharming Healthcare, Inc.

Brian Hartline, MD

Senior Director, Medical Affairs

Introduction to Pharming Healthcare

- A global, commercial stage biopharmaceutical company developing innovative protein replacement therapies and precision medicines for the treatment of rare diseases and unmet medical needs.
- Pharming's main product candidate portfolio is focused on the rare diseases of hereditary angioedema (HAE), activated PI3Kδ syndrome (APDS) and Pompe disease.

What is activated PI3Kδ syndrome (APDS)?

APDS*

Is a Primary Immune Regulatory Disorder (PIRD)

Caused by variants in the genes (*PIK3CD* or *PIK3R1*) encoding subunits of PI3Kδ enzyme complex and affects both B and T cells

Immune deficiency
Frequent infections

Immune dysregulation
Autoimmune complications

Wide Range of Clinical Manifestations

Severe infections, **permanent lung damage**

Severe **swollen lymph nodes, spleen and liver**

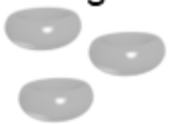
Developmental delay failure to thrive

Severe, chronic **herpes virus infections**

Enteropathy

Lymphoma

Autoimmunity including **anemias** & bleeding disorders



*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. Lucas CL et al. *J Exp Med*. 2014;211(13):2537-2547. 4. Coulter TI et al. *J Allergy Clin Immunol*. 2017;139(2):597-606. 5. Elkaim E et al. J Allergy Clin Immunol. 2016;138(1):210-218. 6. Chan A, et al. Front Immunol. 2020:11:239.

Definitive diagnosis through genetic testing may change treatment

Pharming

Pharming partnership with Invitae & Gene Matters

- **SPONSORED, NO-CHARGE GENETIC TESTING** – no cost to qualified patients in the USA and Canada
- **FAST** – results 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** – choice of 429-gene Primary Immunodeficiency Panel, or 574-gene Inborn Errors or Immunity and Cytopenias Panel
- **SUPPORTED** – option for sponsored, no-charge genetic counseling provided by GeneMatters
- **FAMILY TESTING** – sponsored, no-charge genetic testing for blood relatives of patients with pathologic or likely pathologic variants

GeneMatters™

navigateAPDS by Pharming