NASDAQ: **PHAR** | EURONEXT Amsterdam: **PHARM**

Pharming®

Webcast

New study published in *Cell* advancing functional classication of VUSs

June 30, 2025 at 16:30 CEST / 10:30 EDT

Joshua Milner, MD
Columbia University
Irving Medical Center

Anurag Relan
Chief Medical Officer
Pharming Group N.V.

Forward-looking statements

This presentation may contain forward-looking statements. Forward-looking statements are statements of future expectations that are based on management's current expectations and assumptions and involve known and unknown risks and uncertainties that could cause actual results, performance, or events to differ materially from those expressed or implied in these statements. These forward-looking statements are identified by their use of terms and phrases such as "aim", "ambition", ''anticipate'', ''believe'', ''could'', ''estimate'', ''expect'', ''goals'', ''intend'', ''may'', "milestones", ''objectives'', ''outlook'', ''plan'', ''probably'', ''project'', ''risks'', "schedule", ''seek'', ''should'', ''target'', ''will'' and similar terms and phrases. Examples of forward-looking statements may include statements with respect to timing and progress of Pharming's preclinical studies and clinical trials of its product candidates, Pharming's clinical and commercial prospects, and Pharming's expectations regarding its projected working capital requirements and cash resources, which statements are subject to a number of risks, uncertainties and assumptions, including, but not limited to the scope, progress and expansion of Pharming's clinical trials and ramifications for the cost thereof; and clinical, scientific, regulatory, commercial, competitive and technical developments. In light of these risks and uncertainties, and other risks and uncertainties that are described in Pharming's 2024 Annual Report and the Annual Report on Form 20-F for the year ended December 31, 2024, filed with the U.S. Securities and Exchange Commission, the events and circumstances discussed in such forward-looking statements may not occur, and Pharming's actual results could differ materially and adversely from those anticipated or implied thereby. All forward-looking statements contained in this presentation are expressly qualified in their entirety by the cautionary statements contained or referred to in this section. Readers should not place undue reliance on forward-looking statements. Any forward-looking statements speak only as of the date of this presentation and are based on information available to Pharming as of the date of this presentation. Pharming does not undertake any obligation to publicly update or revise any forward-looking statement as a result of new information, future events or other information.

Agenda

- Dr. Joshua Milner will:
  - Present findings of a new study published in *Cell* titled “Scalable generation and functional classification of genetic variants in inborn errors of immunity to accelerate clinical diagnosis and treatment”
  - Discuss how this study advances variant of uncertain significance (VUS) resolution, improves APDS diagnosis, and informs its true prevalence

- Q&A with Dr. Anurag Relan, Chief Medical Officer

Large-scale functional classification of *PIK3CD* and *PIK3R1* variants to improve APDS diagnosis

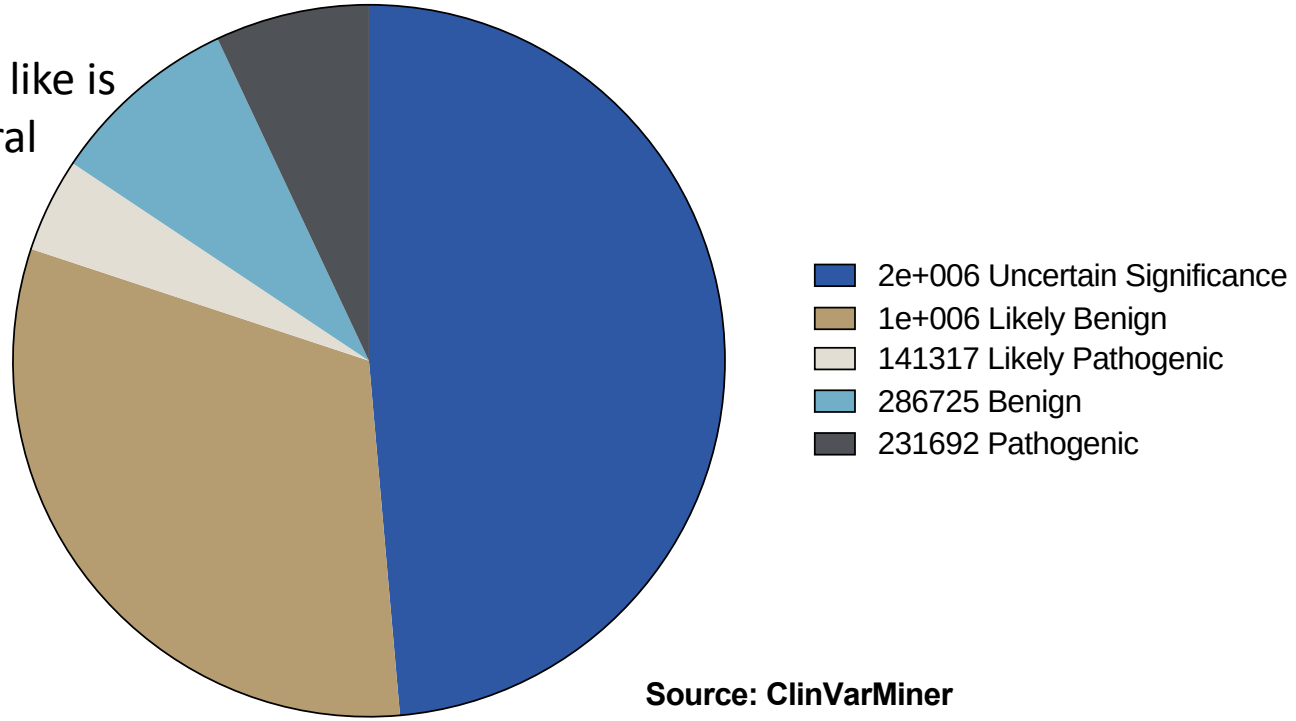
Joshua Milner, MD
Director, Division of Pediatric Allergy, Immunology and Rheumatology
Chief, Allergy, Immunology and Rheumatology Services New York-Presbyterian
Morgan Stanley Children Hospital
Columbia University
New York, NY

Two major rate-limiting steps in genetic-based precision medicine

We often don't know that there is a genetic disease of the immune system right in front of us

Our concept of what a genetic syndrome looks like is largely the result of referral bias and extreme clinical presentations

If genetic testing is performed and a variant is found in a particular gene, there's a 50/50 chance we won't know how to interpret it



Source: ClinVarMiner

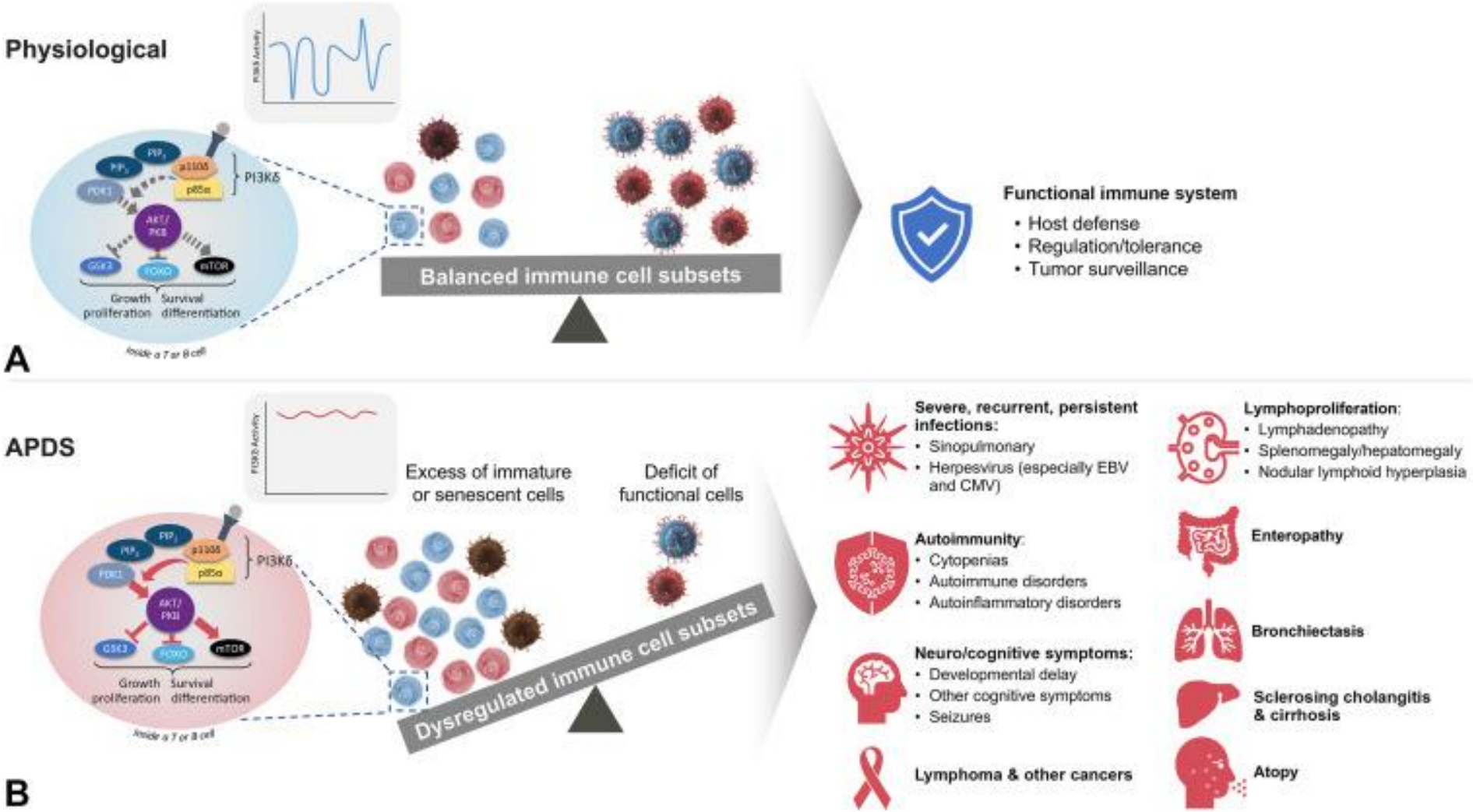
Multiplexed functional assays

Clinically-relevant, high-throughput methods are required to resolve the VUS problem at scale

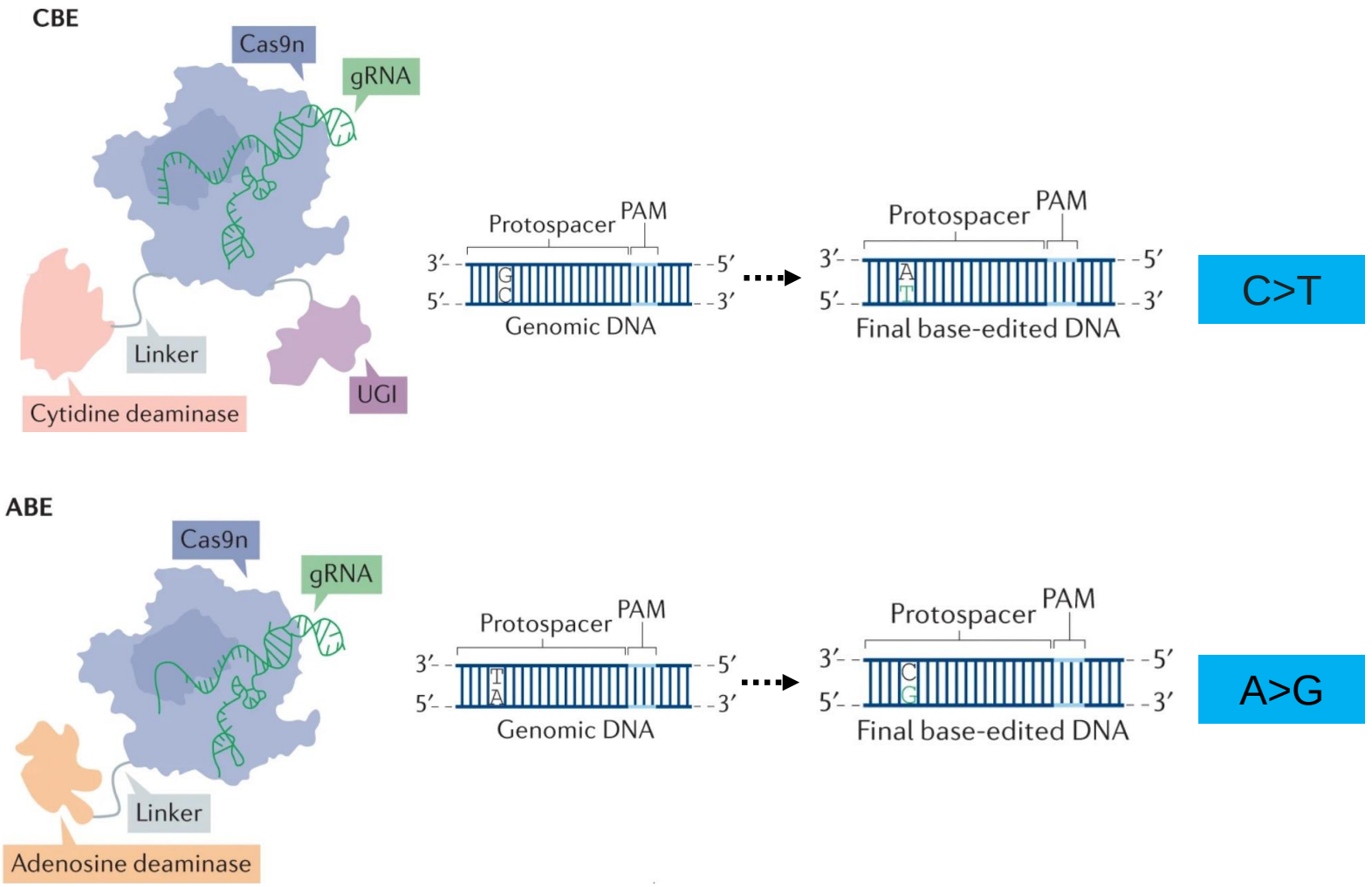
Multiplexed functional assays simultaneously evaluate the biological effect of thousands of different genetic variants by generating quantitative, functional data on how each variant affects gene activity, protein function, or cellular signaling

Data from validated multiplexed studies are considered strong functional evidence for variant interpretation by the American College of Medical Genetics and Genomics (ACMG) / Association for Molecular Pathology (AMP) guidelines

Activated PI3Kδ syndrome (APDS): a genetic disorder of immune dysregulation caused by gain of PI3Kδ function (GOF)



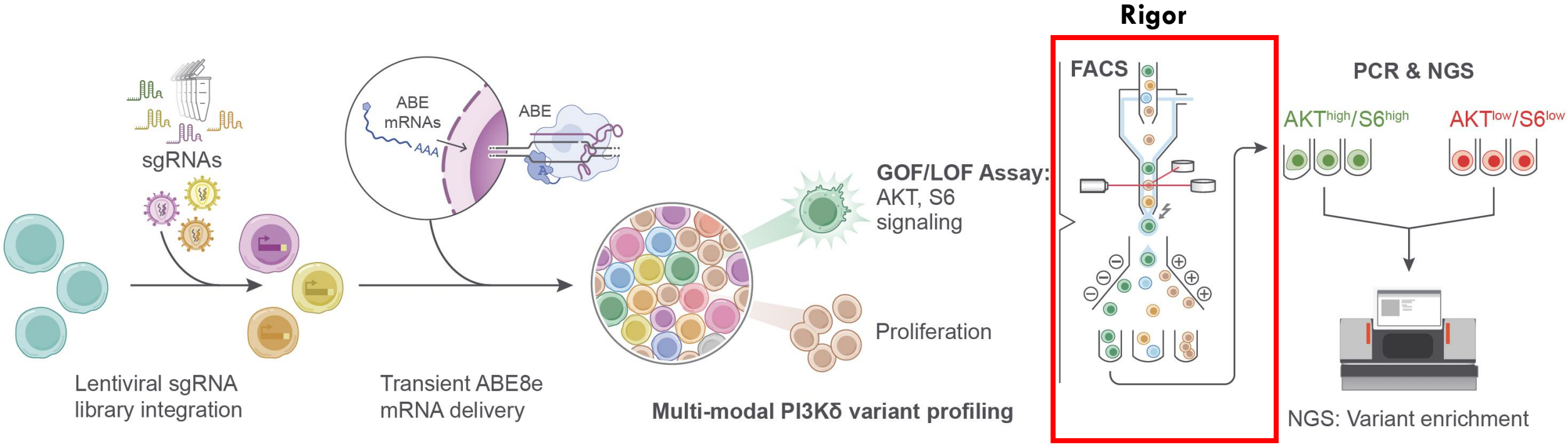
Introducing precise variants directly in primary human T cells using CRISPR-dependent base editing



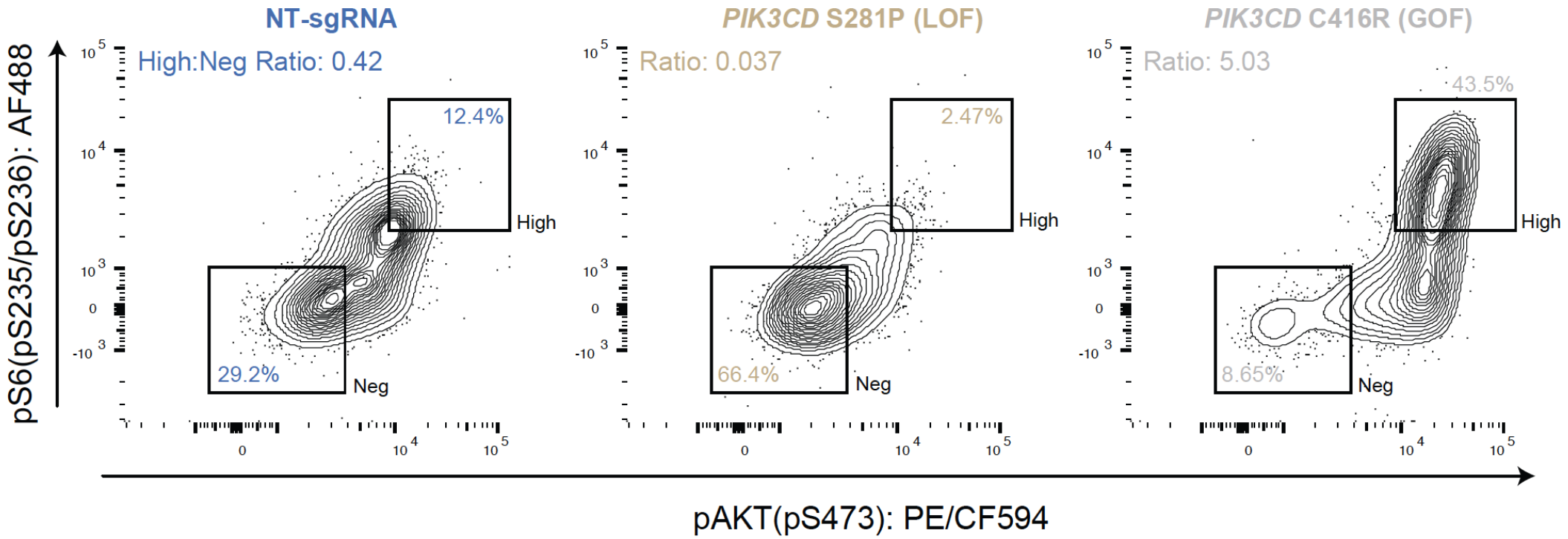
Porto et al., Nat Rev Drug Disc, 2020

Walsh*, Shah* et al., Nature Biotechnology, 2024

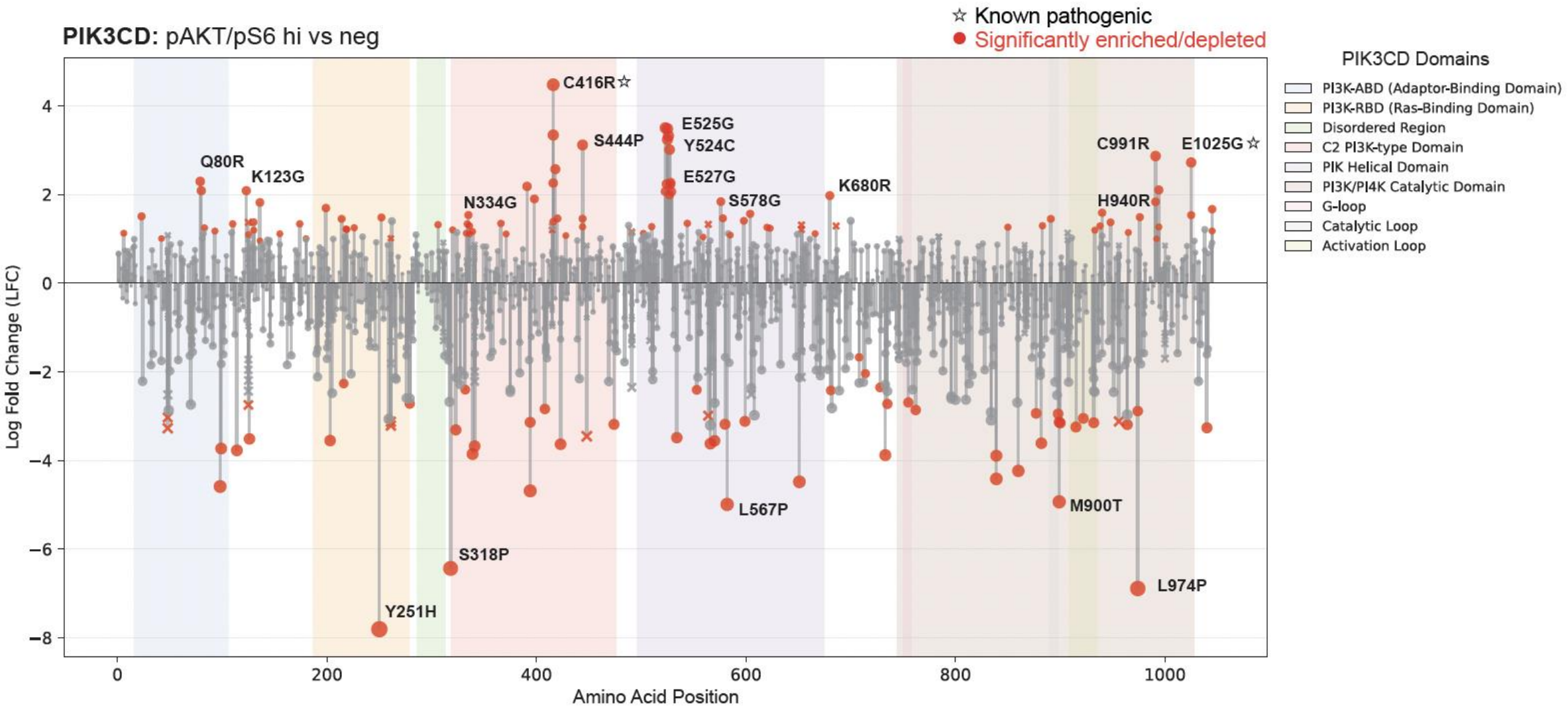
Massively paralleled generation and functional mapping of APDS gene (*PIK3CD/PIK3R1)* variants



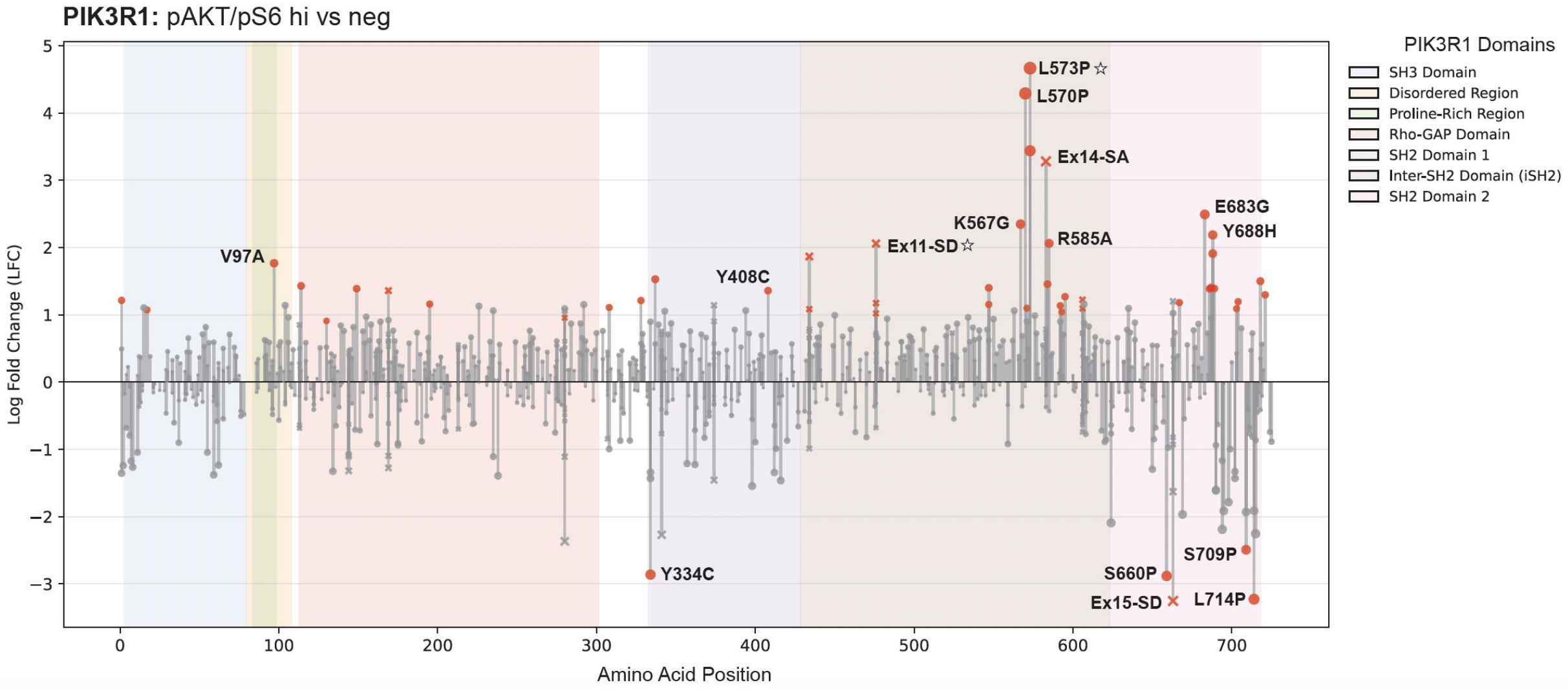
Clinically-relevant assay discriminates between PI3Kδ gain-of-function (GOF) and loss-of-function (LOF)



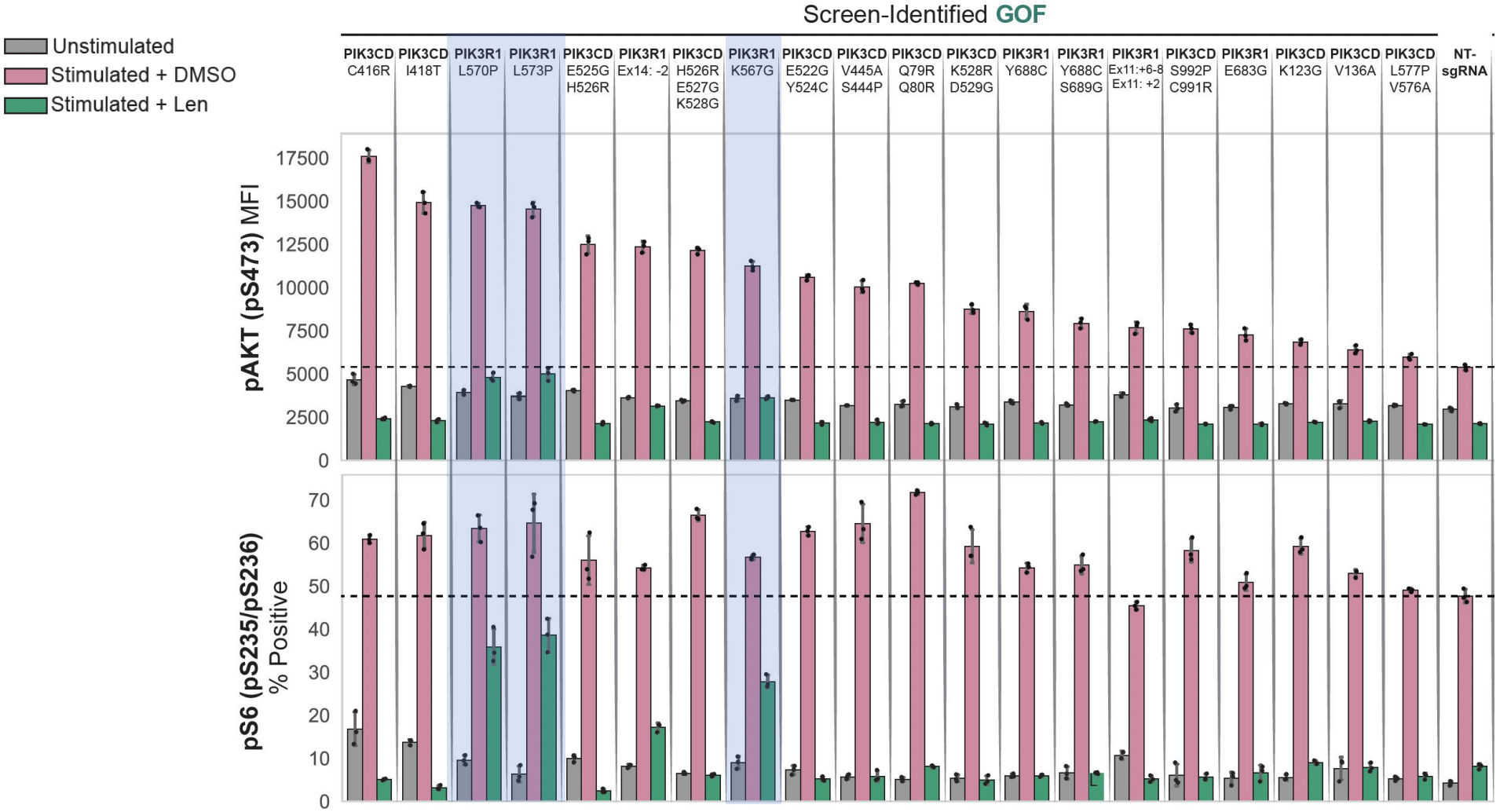
Assay confirms known *PIK3CD* APDS-causing variants and uncovers new GOF variants



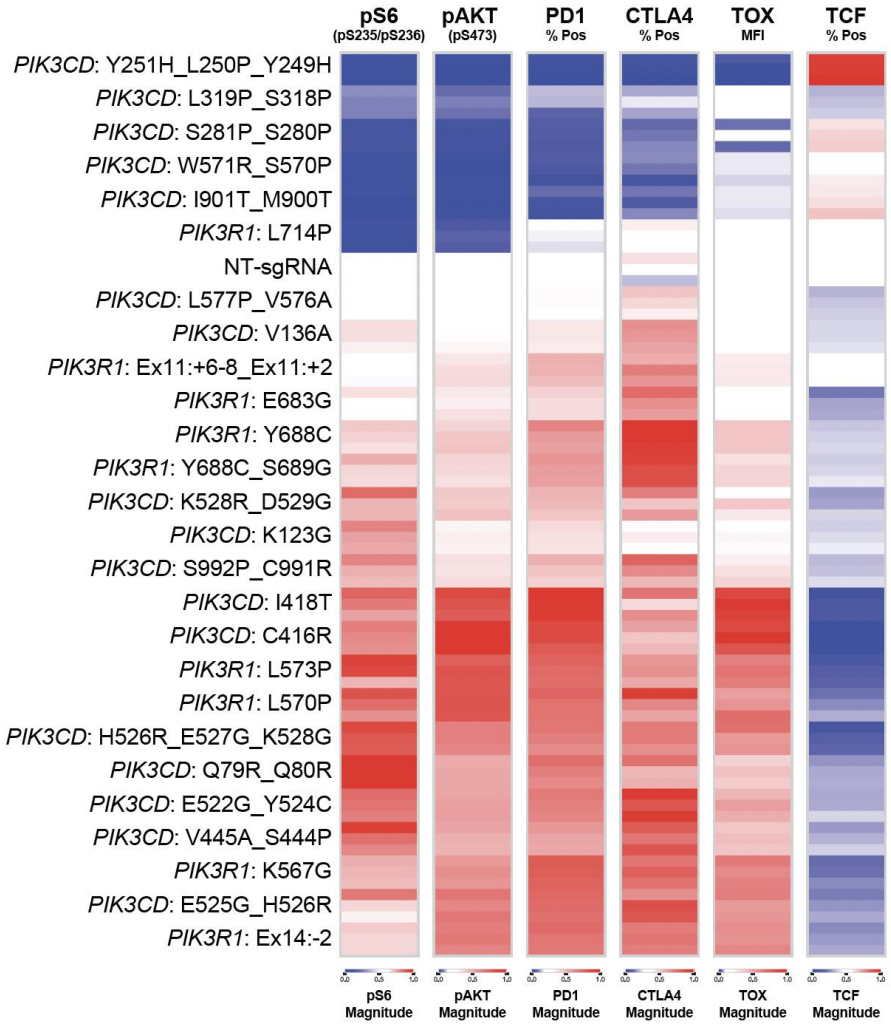
Assay confirms known *PIK3R1* APDS-causing variants and uncovers new GOF variants

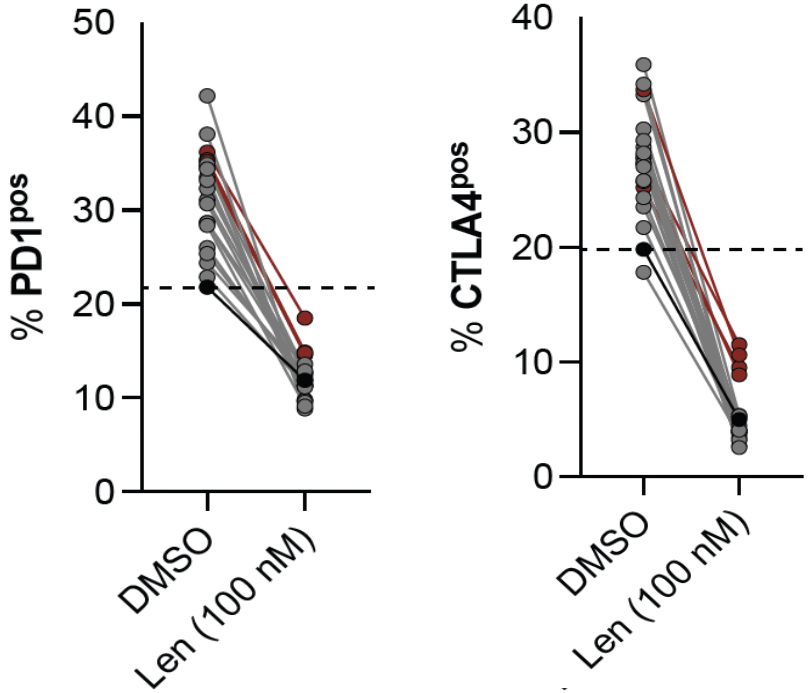


Leniolisib normalizes PI3Kδ hyperactivity in human T-cells and provides validation of study results



Leniolisib normalizes APDS-associated T-cell abnormalities caused by GOF variants





REVIEW ARTICLE · Articles in Press, June 17, 2025

T follicular helper cells in primary immune regulatory disorders

Sarah Chamseddine, MD [1] ✉ · Emily M. Harris, MD [2] · Janet Chou, MD [1]

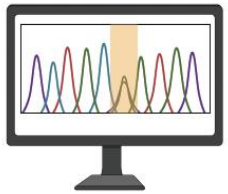
Finding patients with GOF variants identified in this study

1. Patients who underwent genetic testing for IEIs
   - Data can be utilized by clinical laboratories to reclassify VUS results as APDS

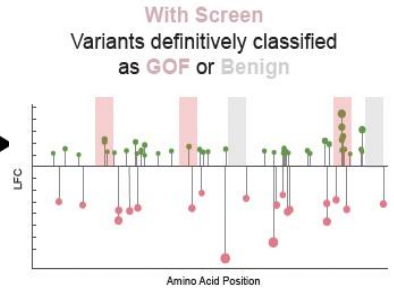
2. General population
   - Since the study identified many novel unannotated variants, we searched large-scale population databases to better understand the prevalence and full phenotypic spectrum of APDS

GOF variants identified in the study are found in patients with VUS test results who have APDS symptoms

Cohort of undiagnosed patients
with APDS-like symptoms

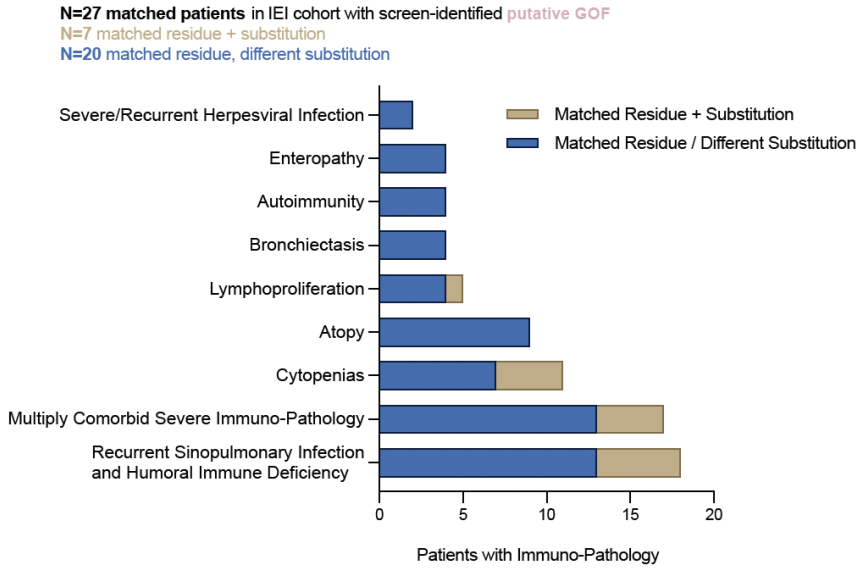


Clinical NGS reveals
VUS profiled in screens
in *PIK3R1* or *PIK3CD*



benign

pathogenic



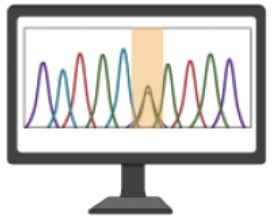
Harnessing population databases to estimate genetic prevalence

The **UK Biobank** is a large-scale biomedical database and research resource containing in-depth genetic, health, and lifestyle information from participants aged 40–69 at recruitment across the United Kingdom.

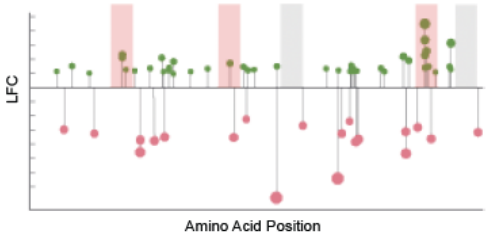
The **All of Us Research Program** is a U.S.-based initiative led by the **National Institutes of Health (NIH)** that aims to collect health data from people across the United States to advance precision medicine.

Review of population databases suggests APDS may be significantly more prevalent than previously described

Cohort of 633,540 individuals from population database



NGS reveals *PIK3CD* or *PIK3R1* variant



Screen variant effect provides evidence to functional classification

Variant scores as non-significant: decreased suspicion for APDS

Variant scores as significant GOF: increased suspicion for APDS

n=123

12% of these patients had multiple comorbid severe immunopathologic diagnoses

Approximately 1/5,000 volunteers in large public databases carry one of the newly found GOF variants

GOF carriers in population databases more likely to exhibit GI, lymphoproliferative, and inflammatory phenotypes

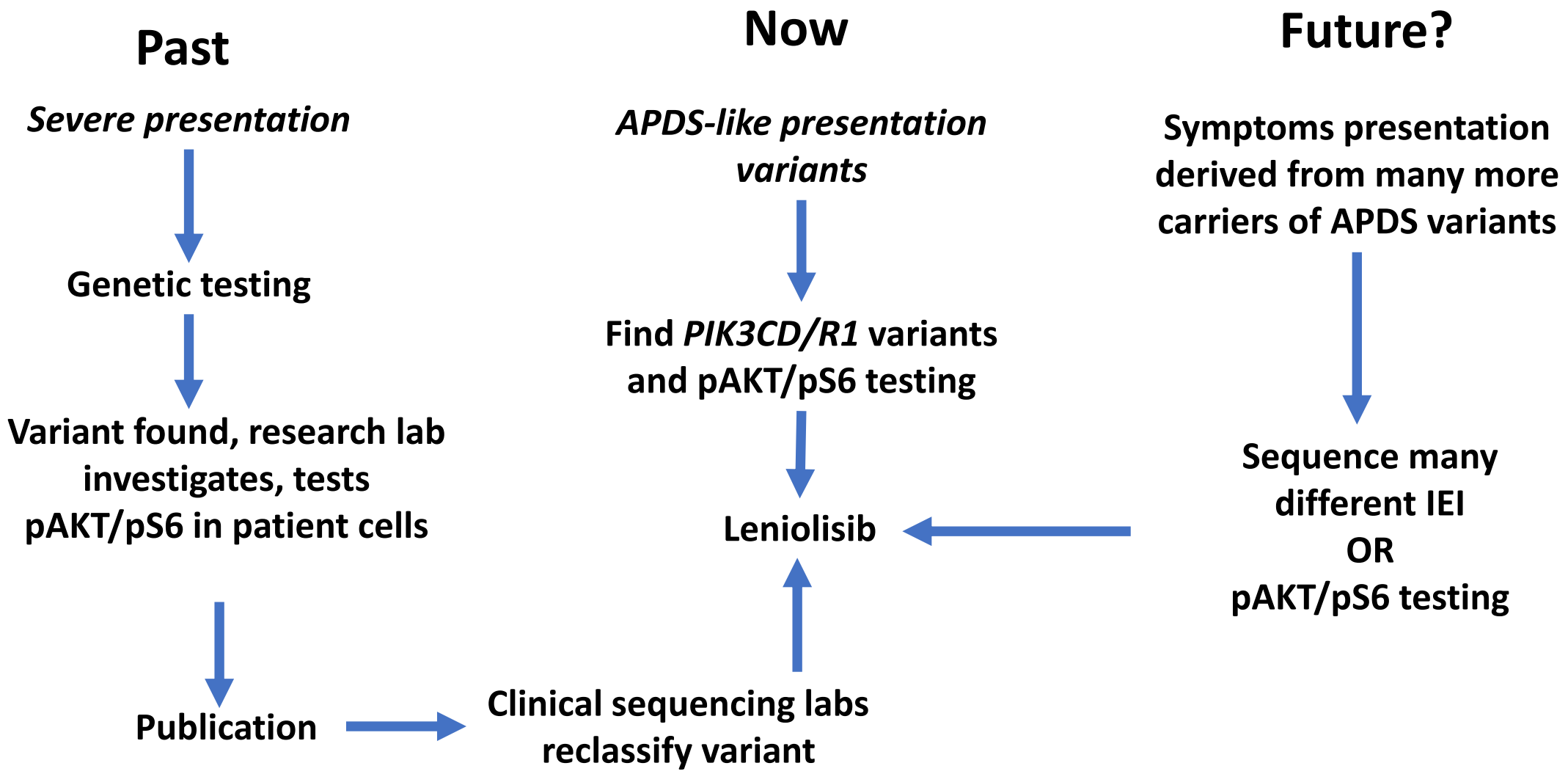
All of Us cohort (US)

System	Diagnosis	Odds Ratio	p value (raw)
Gastrointestinal	Biliary cirrhosis	inf	1.040E-06
	Cirrhosis - non-alcoholic	5.37	1.201E-03
	Persistent vomiting	9.43	7.930E-06
	Autoimmune hepatitis	14.75	5.053E-03
	Abscess of perineum	11.06	0.0134
	Primary biliary cholangitis	inf	0.0257
Respiratory	Chronic ethmoidal sinusitis	6.65	2.144E-04
Infectious	Osteomyelitis	4.87	7.132E-04
	Digitate wart		0.0257
	Orbital cellulitis	8.85	0.0272

UK Biobank

System	Diagnosis	Odds ratio	p-value (raw)
Lymphoproliferative neoplasm	non-Hodgkin lymphoma	15.08	0.0084
Neoplasm	Basal cell carcinoma	2.12	0.0094
inflammatory	Sarcoidosis unspecified	118.38	0.0086
Gastrointestinal	irritable bowel syndrome	3.53	0.0019
	bowel problem	2.66	0.0006101
	gastrointestinal|abdominal	1.90	0.003
	Peritonitis	46.69	0.0009313
Inflammatory	Gout	113.29	0.0092

Toward pathway specific drug indications



Summary

- MAVE study provides functional classification (e.g., GOF or LOF) for >2,000 *PIK3CD/PIK3R1* variants
- Assay confirmed known *PIK3CD/PIK3R1* APDS-causing variants and uncovered many new GOF variants
- Leniolisib can restore or improve PI3Kδ signaling defects and immune abnormalities caused by the new GOF variants
- APDS is a continuum of GOF magnitude, disease severity and population prevalence
  - **APDS may be orders of magnitude more prevalent than previously estimated**
  - **The clinical heterogeneity of APDS may be much broader than previously described.**
- There are many more immune-mediated symptoms– alone or in combination with other immune symptoms-- driven by these newly discovered variants which can be treated by leniolisib. This necessitates new ways of defining genetic diseases of the immune system

Acknowledgements

Izar lab

Zach Walsh
Chris Frangieh
Neeha Kothapalli
Johannes Melms
Clarissa Heck
Parin Shah
Lindsay Caprio
Somnath Tagore
Amit Dipak Amin
Karan Luthria
Michael Mu
Sean Chen

Karan Luthria
Edridge D'Souza
Luke Cai
Hsiang-Hsi Ling
Ron Gejman
Azzurra Cottarelli
Dev Biswas
Jared Pollard
Akul Naik
Sumali Jayakody
Devinak Biswas
Leon Ebel

Milner Lab

Josh Milner
Jay Levy
Lei Haley Huang
Ashley Lee

Pharming Group

Anurag Relan
Heather McLaughlin

Dusan Bogunovic

Columbia NY ROYAL

HTI^3 - Human Tissue Immunology and Immunotherapy Initiative

R37CA258829
R01CA266446
R01CA280414
U54CA274506

HTI^3 - Human Tissue Immunology and Immunotherapy Initiative

Patients & Families

Next steps

- Clinical genetic laboratories will utilize this data to independently re-assess *PIK3CD/R1* VUSs
  - These data may impact both patients with exact matches and patients with different genetic changes affecting the same amino acid as a known GOF variant
  - Expect reassessments to be completed in 2H 2025
- Additional multiplexed studies to functionally assess the remainder of all possible *PIK3CD/R1* variants
- Additional studies to refine the genetic prevalence and the full spectrum of clinical manifestations of APDS using biobanks that link genomic data with longitudinal EHR records

Pharming®

Q&A