Investor Day

February 3, 2026

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.

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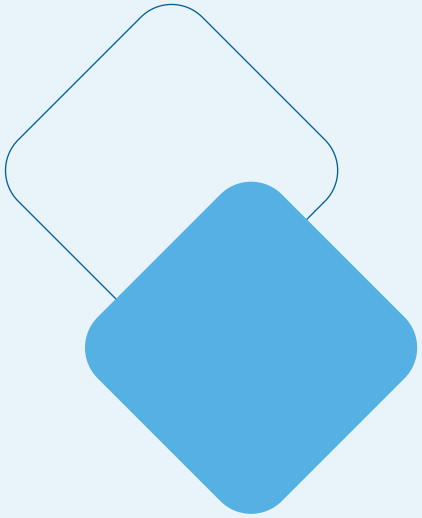
Nothing in this presentation is intended to constitute advertising, promotion, or solicitation for any pharmaceutical product or for any off-label use of any approved product. This presentation is not intended for healthcare professionals or patients.

Agenda

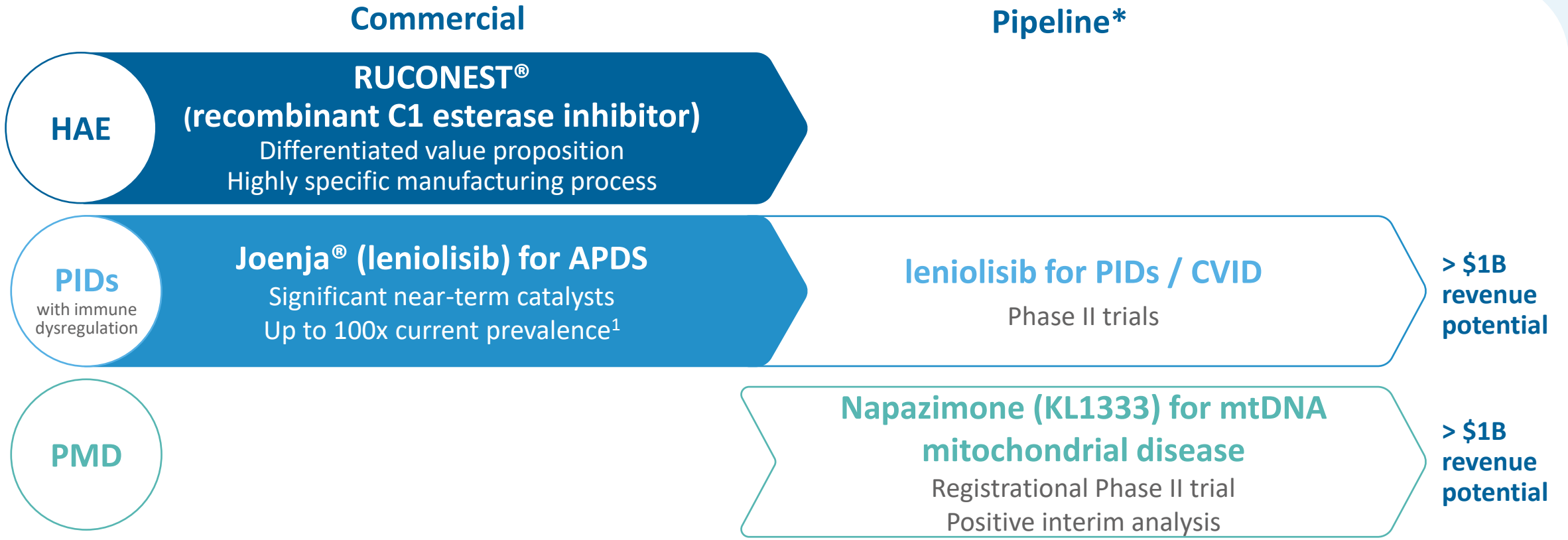
Welcome and introduction	Fabrice Chouraqui, CEO
Financial outlook 2026	Kenneth Lynard, CFO
Q&A	
R&D overview: Pipeline and programs	Anurag Relan, CMO
Program 1: **leniolisib for primary immunodeficiencies (PIDs) with immune dysregulation**	Jocelyn Farmer, MD, PhD. Lahey Hospital & Medical Center Rebecca Marsh, MD. Medical Director
Q&A	
Program 2: **napazimone (KL1333) for primary mitochondrial disease**	Amel Karaa, MD. Massachusetts General Hospital Magnus Hansson, MD, PhD. Executive Medical Director
Q&A	
Closing remarks	Fabrice Chouraqui, CEO

Company overview

Fabrice Chouraqui, CEO



Combination of commercial and pipeline assets poised to deliver strong value creation



*These product candidates are under investigation, and their safety and efficacy have not been established. There is no guarantee that these products will receive health authority approval or become commercially available for the uses being investigated

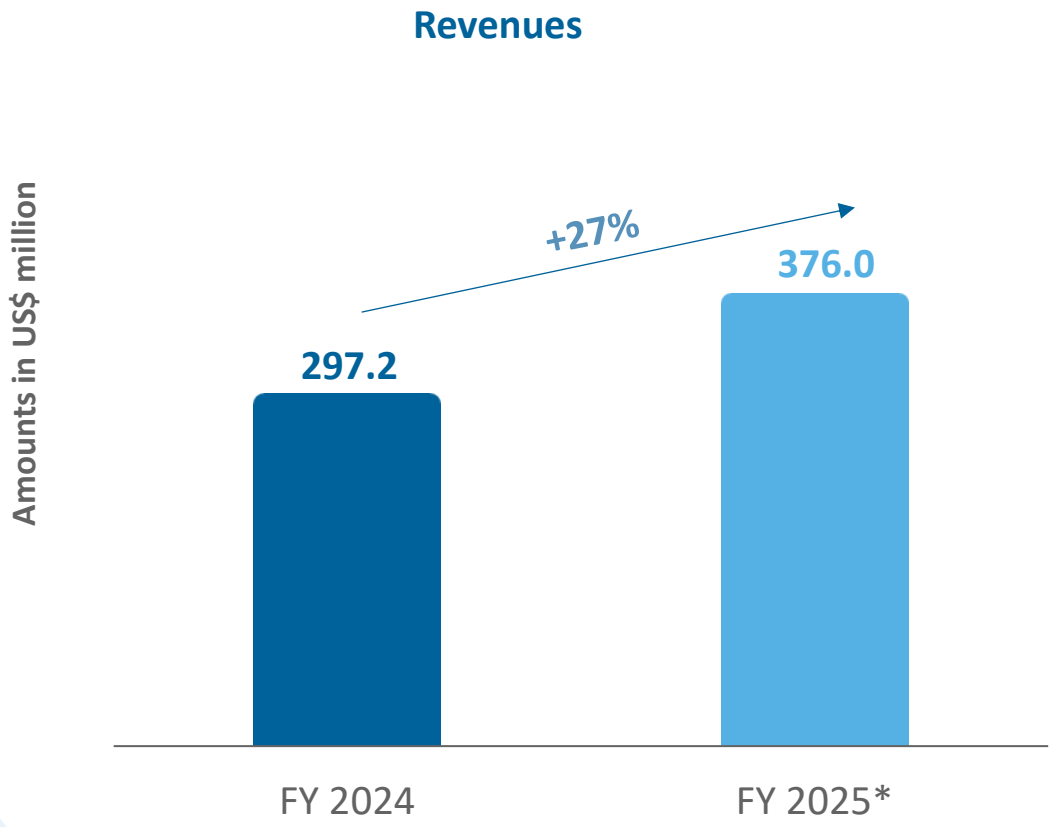
HAE: Hereditary Angioedema, **PIDs:** Primary Immunodeficiencies, **PMD**: Primary Mitochondrial Disease, **CVID:** Common Variable Immunodeficiency

1. Walsh et al., Scalable generation and functional classification of genetic variants in inborn errors of immunity to accelerate clinical diagnosis and treatment, Cell (2025), https://doi.org/10.1016/j.cell.2025.05.037

Vision for the future

Develop a leading global rare disease company with a diverse portfolio and presence in large markets, leveraging proven and efficient clinical development, supply chain, and commercial infrastructure

Strong commercial and financial momentum

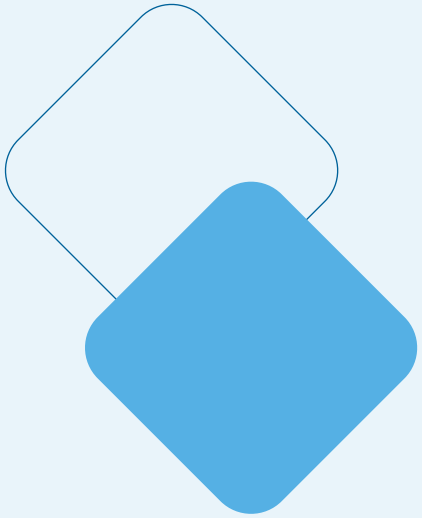


- Announced preliminary 2025 revenues* of $376M (+ 27%) – above latest guidance
- Results reflect continued growth of RUCONEST® and acceleration in Joenja® APDS uptake
- Significant operating profit $30M and operating cash flow $44M in 9M 2025
- Reiterated $304-308M operating expense guidance for 2025 – committed to cost discipline and deploying capital to high growth initiatives

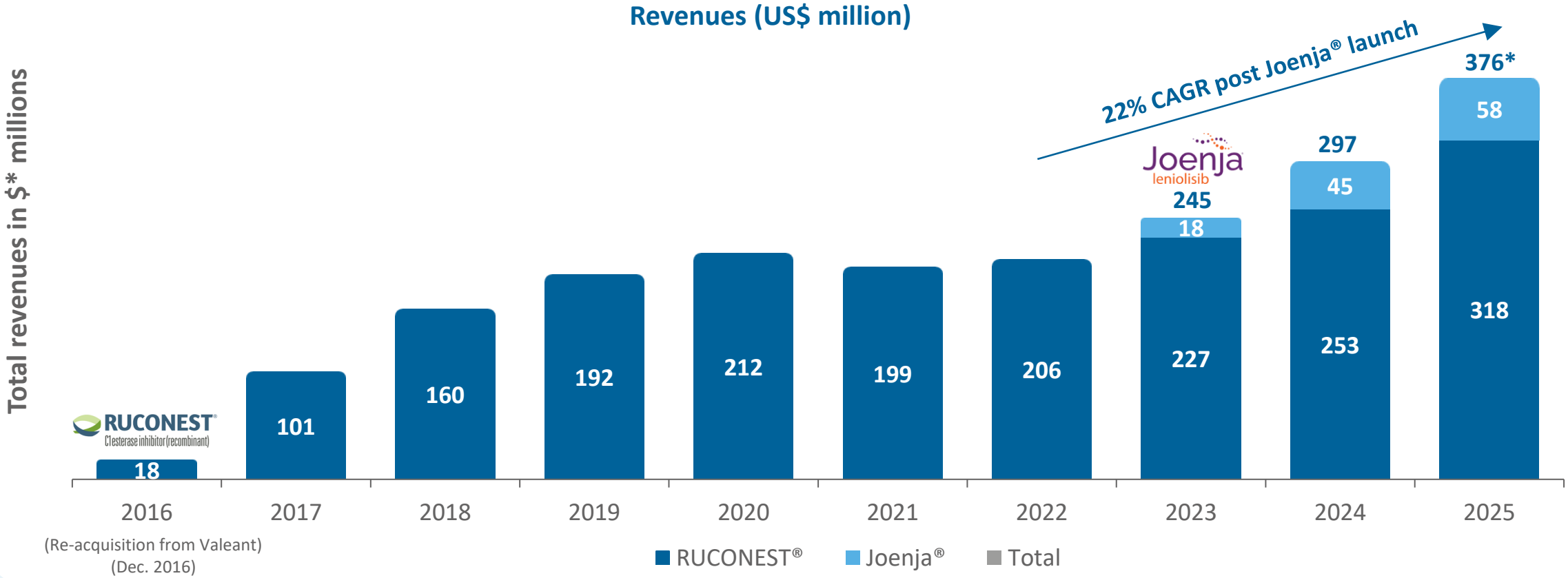
* 2025 revenues are preliminary and unaudited. Final results may differ and will be reported in the financial results for the fourth quarter and full year 2025, to be published in March 2026.

Financial outlook 2026

Kenneth Lynard, CFO



Growth acceleration across the commercial portfolio
27% YoY, 22% CAGR (2022-25)



From FY 2016 – FY 2020 Pharming Group reported earnings in EUR. Revenues during this time frame have been converted to USD. In 2021, Pharming Group began reporting earnings in USD.
4Q 2020 and 1Q 2021 quarterly fluctuations and volatility from COVID-19.
* 2025 revenues are preliminary and unaudited. Final results may differ and will be reported in the financial results for the fourth quarter and full year 2025, to be published in March 2026.

2026 financial guidance and long-term capital outlook

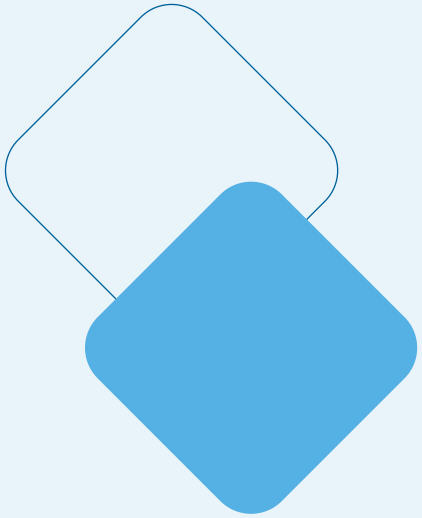
- Revenue and operating expenses (in constant currency):

	FY 2026 Guidance	Notes
Total Revenues	**US$405 - 425 million**	• 8 - 13% growth
Operating Expenses	**US$330 - 335 million**	• US$60 million incremental R&D investments to advance pipeline • US$9 million structural G&A cost reductions (as announced in October 2025)

- Continued RUCONEST® growth, and significant and accelerating Joenja® growth
- Strong financial discipline, and prioritized investments to drive value creation
- Available cash and future cash flows expected to cover current pipeline and pre-launch costs

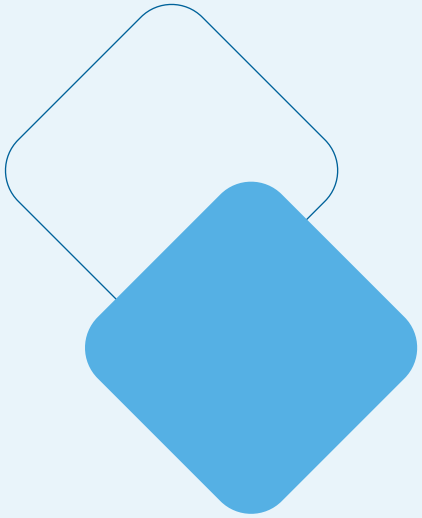
Thank You

Questions and Conversations

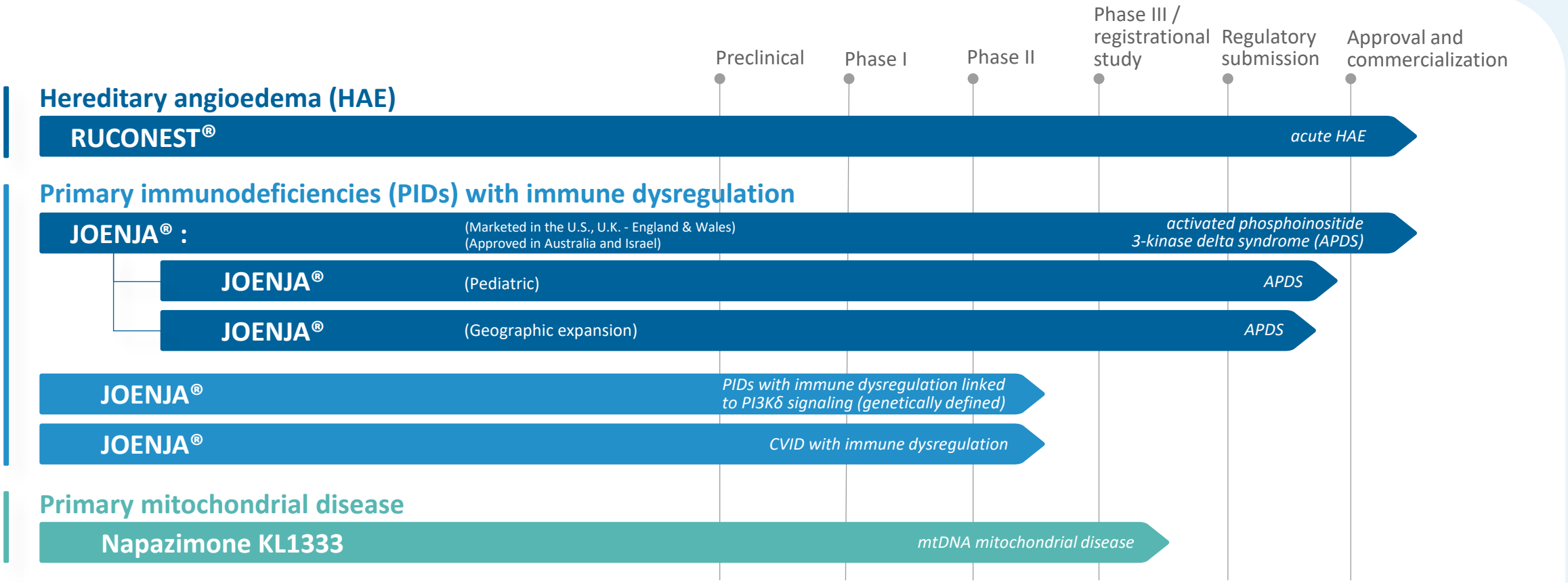


R&D overview: pipeline and programs

Anurag Relan, CMO



Diverse rare disease portfolio and pipeline



Executing on high value rare disease pipeline

APDS

Leniolisib sNDA for 4-11 yo APDS patients – requesting Type A meeting
Responded to CHMP (EMA) outstanding questions – potential 1H 2026 approval
Japan and other regulatory reviews on track for 2026 approvals

PIDs
with immune dysregulation

Genetic PID and CVID phase II POC trials
on track for 2H 2026 read-outs

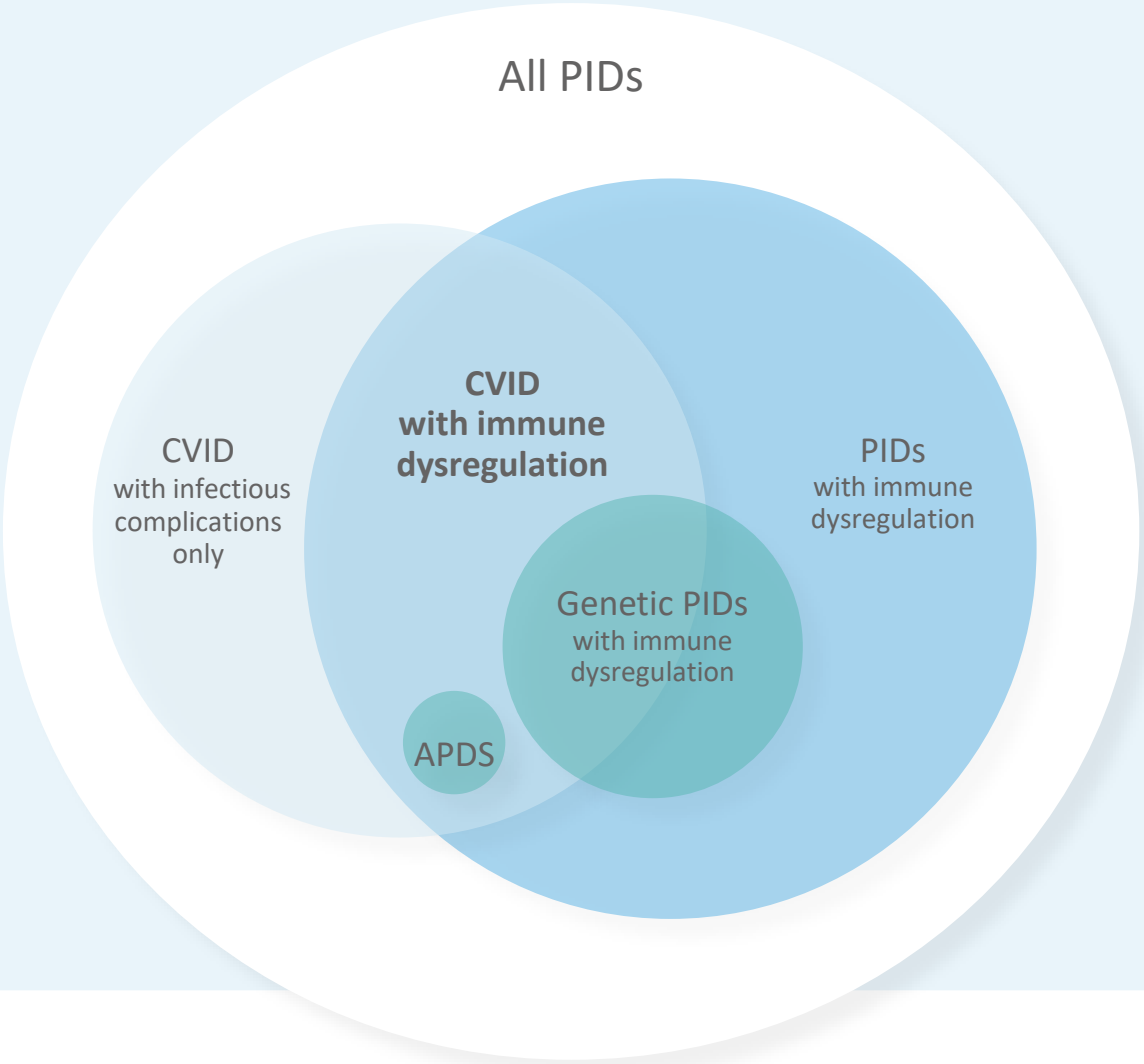
PMD

Napazimone (KL1333) pivotal trial
Over 20 sites actively recruiting – site footprint expanding during 1H 2026
on track for late 2027 read-out

Agenda: leniolisib for PIDs with immune dysregulation

- PIDs with immune dysregulation have a considerable unmet need with large treatable population
- PI3Kδ is a master regulator of the immune system
- Leniolisib targets PI3Kδ and can modulate underlying immune dysregulation in PIDs
- Two multinational phase II clinical studies underway - top line data expected 2H26

The combined targeted population of the 2 phase II studies plus APDS is ~44/million



APDS is a PI3Kδ driven monogenic disease within the IUIS CVID classification acting as proof of concept for **CVID with Immune Dysregulation**

Diagram for illustrative purposes and not to scale
IUIS: International Union of Immunological Societies

Agenda: Napazimone (KL1333)

- Primary mitochondrial diseases – rare disorders with significant unmet medical need
- Napazimone (KL13330 positioned to become first standard of care in mitochondrial DNA (mtDNA) disease
- Pivotal study ongoing with positive interim analysis confirming FDA-agreed primary endpoints
- Significant value creation potential for Pharming and patients

Disclaimer

The information and views presented by Dr. Jocelyn Farmer during this session are solely her own, derived from her clinical expertise and professional judgment. They do not necessarily represent or reflect the positions, perspectives, or official guidance of Pharming Group N.V. or any of its affiliates. This presentation is provided for educational purposes only and should not be interpreted as company-endorsed direction or policy.

Beth Israel Lahey Health
Lahey Hospital & Medical Center

UMASS MEDICAL SCHOOL

Leniolisib:

Transforming Treatment of Immune Dysregulation in Primary Immunodeficiencies

Jocelyn Farmer, MD/PhD
Associate Professor of Medicine, UMass Chan Medical School
Director, Clinical Immunodeficiency Program, Beth Israel Lahey Health

Beth Israel Lahey Health
Lahey Hospital & Medical Center

UMASS MEDICAL SCHOOL

Disclosures

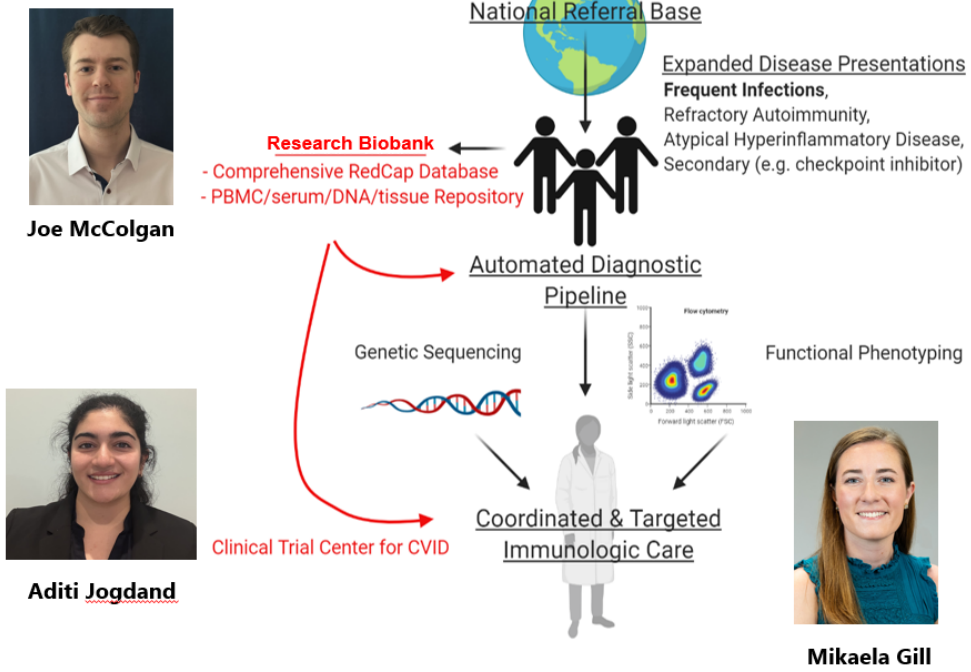
- Consulting: Pharming
- Investigator-initiated research grants:
  - Pharming
  - Bristol Myers Squibb
  - Pfizer

Why am I speaking to you today?

About Me (Dr. Jocelyn Farmer):

- MD/PhD *in microbiology & immunology* (University of Michigan)
- Board-Certified Allergist/Immunologist (A/I Fellowship at Mass General)
- Post-Doc at Ragon Institute *in PI3K signaling impacting B cell biology* (MIT, Harvard, Mass General)
- Hired on at Beth Israel Lahey Health in 2023 as Director, Clinical Immunodeficiency Program
- Founded the New England Immune Deficiency Consortia in 2023
- Invited member of national and international guideline committees that define immunodeficiency (CVID) patient diagnosis & care
- ***I approached Pharming in 2022 with a potential new clinical application for their drug – leniolisib – based on my research.***

BILH Clinical Immunodeficiency Program



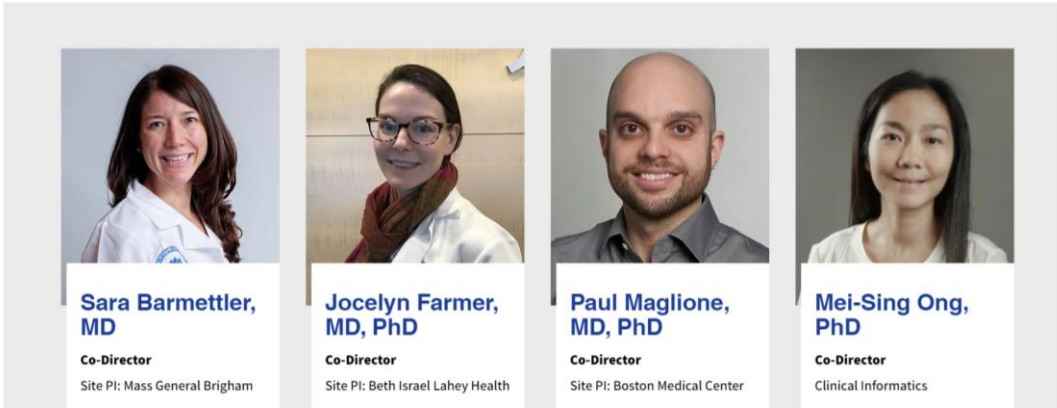
Joe McColgan

Aditi Jogdand

Mikaela Gill

New England Immune Deficiency Consortium

Meet The Team



Beth Israel Lahey Health
Lahey Hospital & Medical Center

What is PID?

Why should you care about PID?

Primary Immunodeficiency (PID)

Primary Immunodeficiency = Unbalanced Immunity

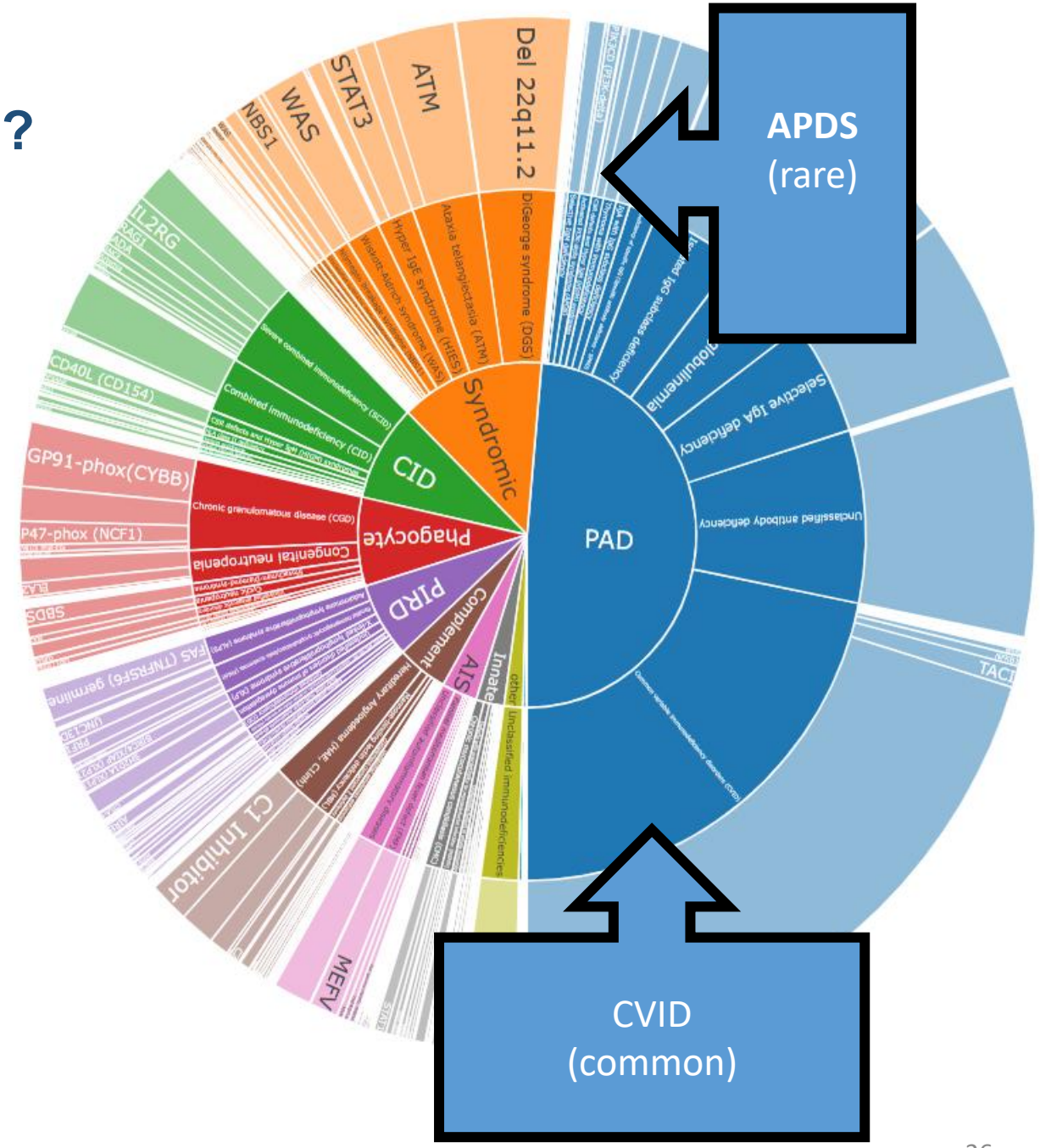
Figure prompted by Farmer, JR; generated by ChatGPT 5.2, January 18, 2026, OpenAI, https://chat.openai.com

Which PID patients do we see in the clinic?

Most common PID =
predominantly antibody deficiency (PAD)

- **APDS** (activated PI3K-delta syndrome)
  rare PAD
  has FDA therapy (leniolisib)

- **CVID** (common variable immunodeficiency)
  common PAD
  NO FDA therapy
  for immune dysregulation
  disease control



Kindle G, Alligon M, Albert MH, Buckland M, Edgar JD, Gathmann B, Ghosh S, Gkantaras A, Nieters A, Pignata C, Robinson P, Rusch S, Schuetz C, Sharapova S, Shillitoe B, Candotti F, Cant AJ, Casanova JL, Etzioni A, Fischer A, Meyts I, Notarangelo LD, Pergent M, Smith CIE; ESID Registry Working Party; Hammarström L, Grimbacher B, Seppänen M, Mahlaoui N, Ehl S, Seidel MG. Inborn errors of immunity: manifestation, treatment, and outcome - an ESID registry 1994-2024 report on 30,628 patients. medRxiv [Preprint]. 2025 Apr 16:2025.02.20.25322586. doi: 10.1101/2025.02.20.25322586. Update in: J Hum Immun. 2025 Sep;1(3):e20250007. doi: 10.70962/jhi.20250007. PMID: 40568655; PMCID: PMC12191083.

What is PID?

Why should you care about PID?

Primary Immunodeficiency (PID)

No FDA-approved therapies to treat immune dysregulation in CVID

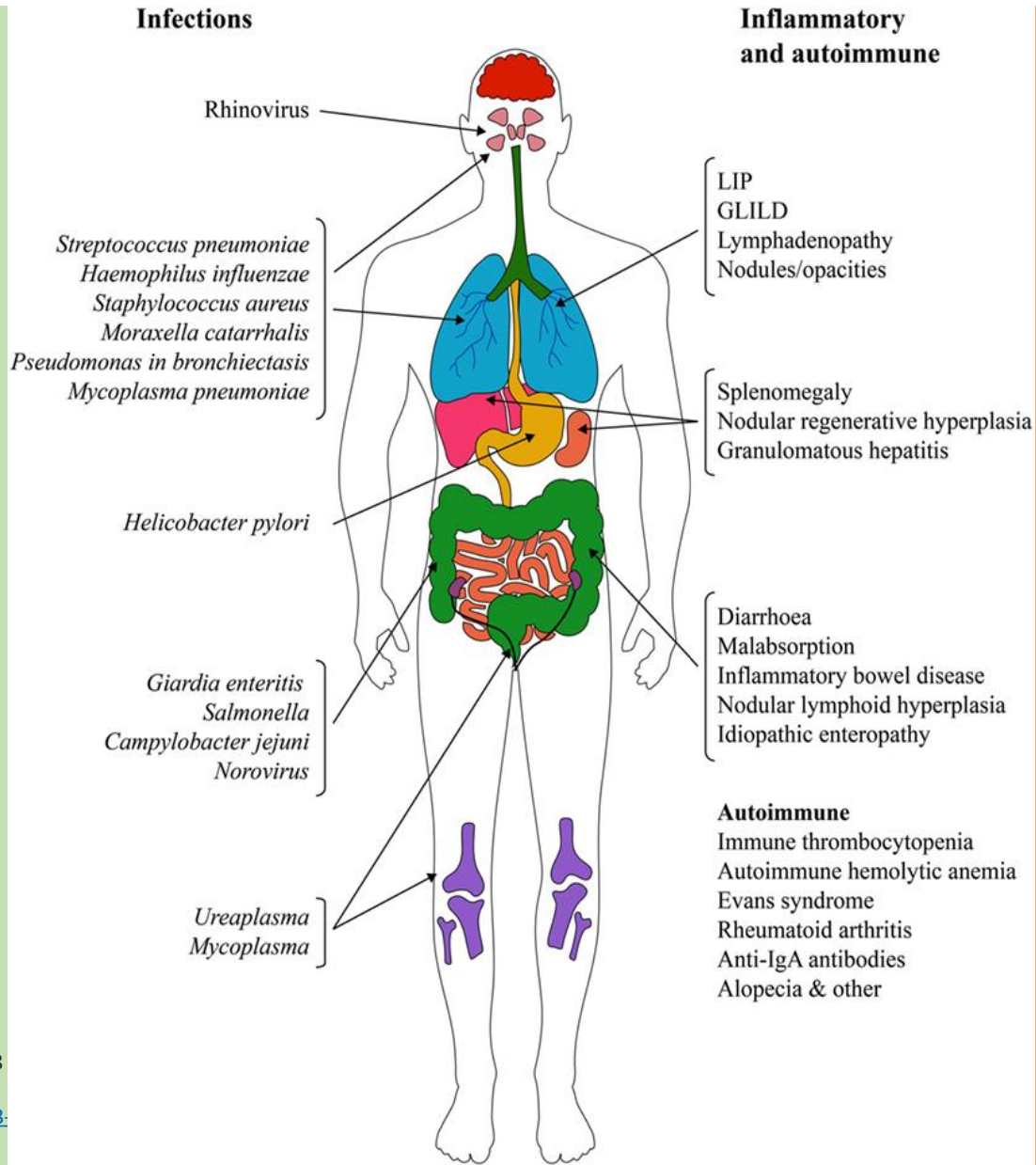
(No products currently in development except for leniolisib)

Infections

Due to Antibody Deficiency

Adequate control of infectious complications achieved through

- Immunoglubulin replacement therapy (IRT)
- Antibiotics



Immune Dysregulation

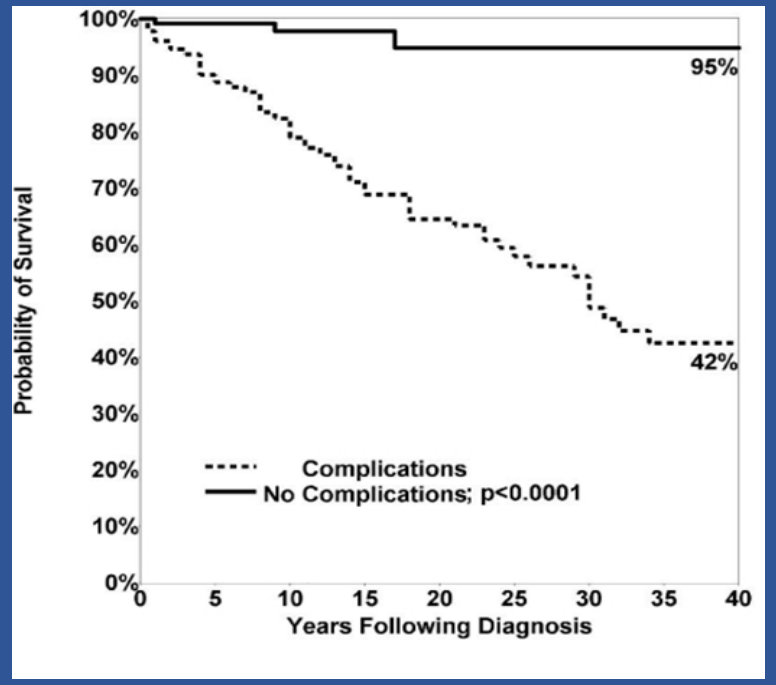
Due to Immune Cell Auto-Reactivity

- No regulatory agency approved treatments
- Adequate control not achieved with standard-of-care

Diagram Adapted from Baumann et. Al. Front. Immunol. August 2018
Blood (2012) 119 (7): 1650–1657.
3 *Orphanet J Rare Dis* **13**, 201 (2018). https://doi.org/10.1186/s13023-018-0941-0

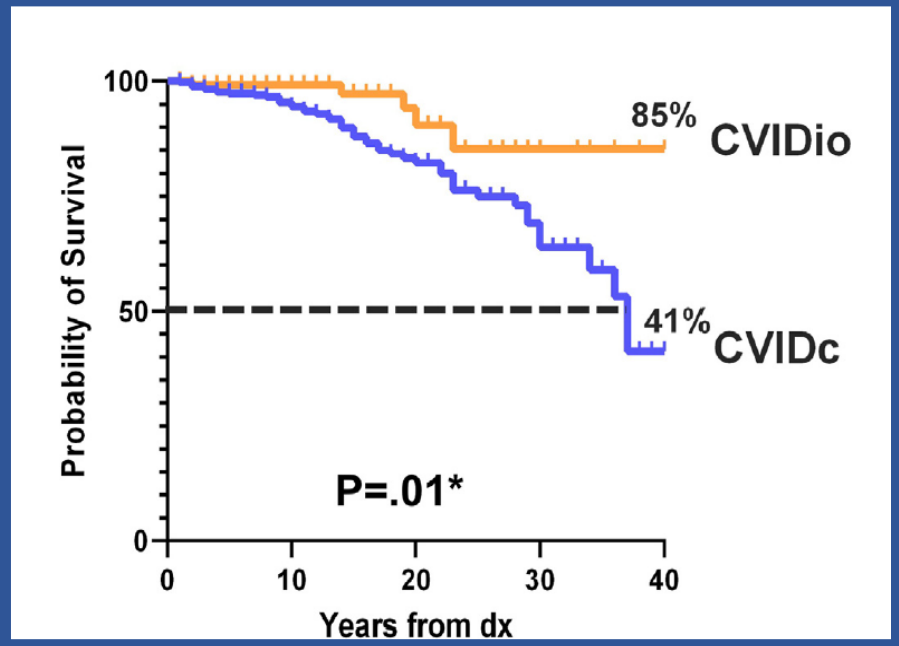
Patients with CVID are dying from immune dysregulation (11-fold higher risk of death with noninfectious complications)

New York's CVID cohort



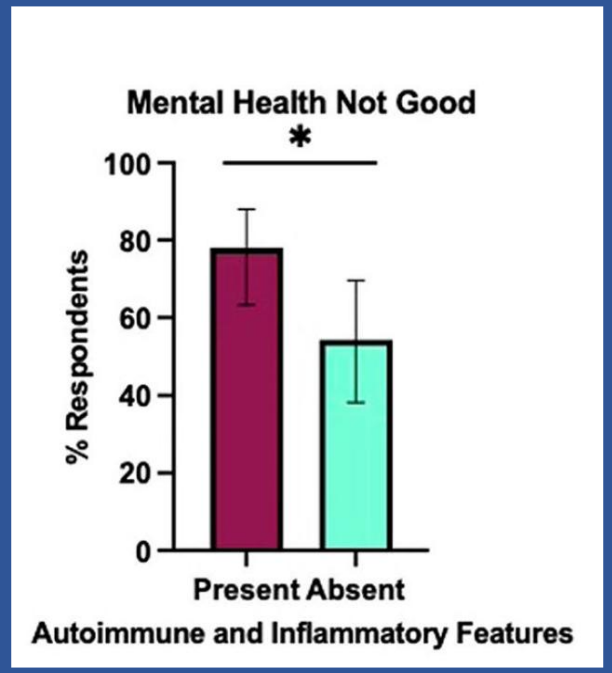
Resnick ES, Moshier EL, Godbold JH, Cunningham-Rundles C. Blood. 2012 Feb 16;119(7):1650-7.

Germany's CVID cohort



Bez P, Smits B, Geier C, Hirsch A, Caballero de Oyteza A, Proietti M, Grimbacher B, Wolkewitz M, Goldacker S, Warnatz K. Uncovering Risk Factors of Premature Mortality in Common Variable Immunodeficiency. J Allergy Clin Immunol Pract. 2025 Mar 14:S2213-2198(25)00256-9. doi: 10.1016/j.jaip.2025.03.009. Epub ahead of print. PMID: 40090481.

Boston's PAD cohort



Elmoursi A, Zhou B, Ong MS, Hong JS, Pak A, Tandon M, Sutherland N, DiGiacomo DV, Farmer JR, Barmettler S. A Cross-Sectional Study of Health-Related Quality of Life in Patients with Predominantly Antibody Deficiency. J Clin Immunol. 2024 Aug 7;44(8):173. doi: 10.1007/s10875-024-01781-y. PMID: 39110257; PMCID: PMC11658799.

What do Patients with CVID Say?

"For decades I faced the systemic complexities of CVID without the benefit of any approved therapeutic treatment. It was a lonely and depressing predicament, knowing that my organs would never last long enough for me to see my sons grow up, and perhaps make me a grandmother."

Direct quote from patient diagnosed with CVID and being managed by Dr. Farmer, provided 01-18-2026

Can we apply clinical lessons from

APDS (rare)

to help the most patients with

CVID (common)?

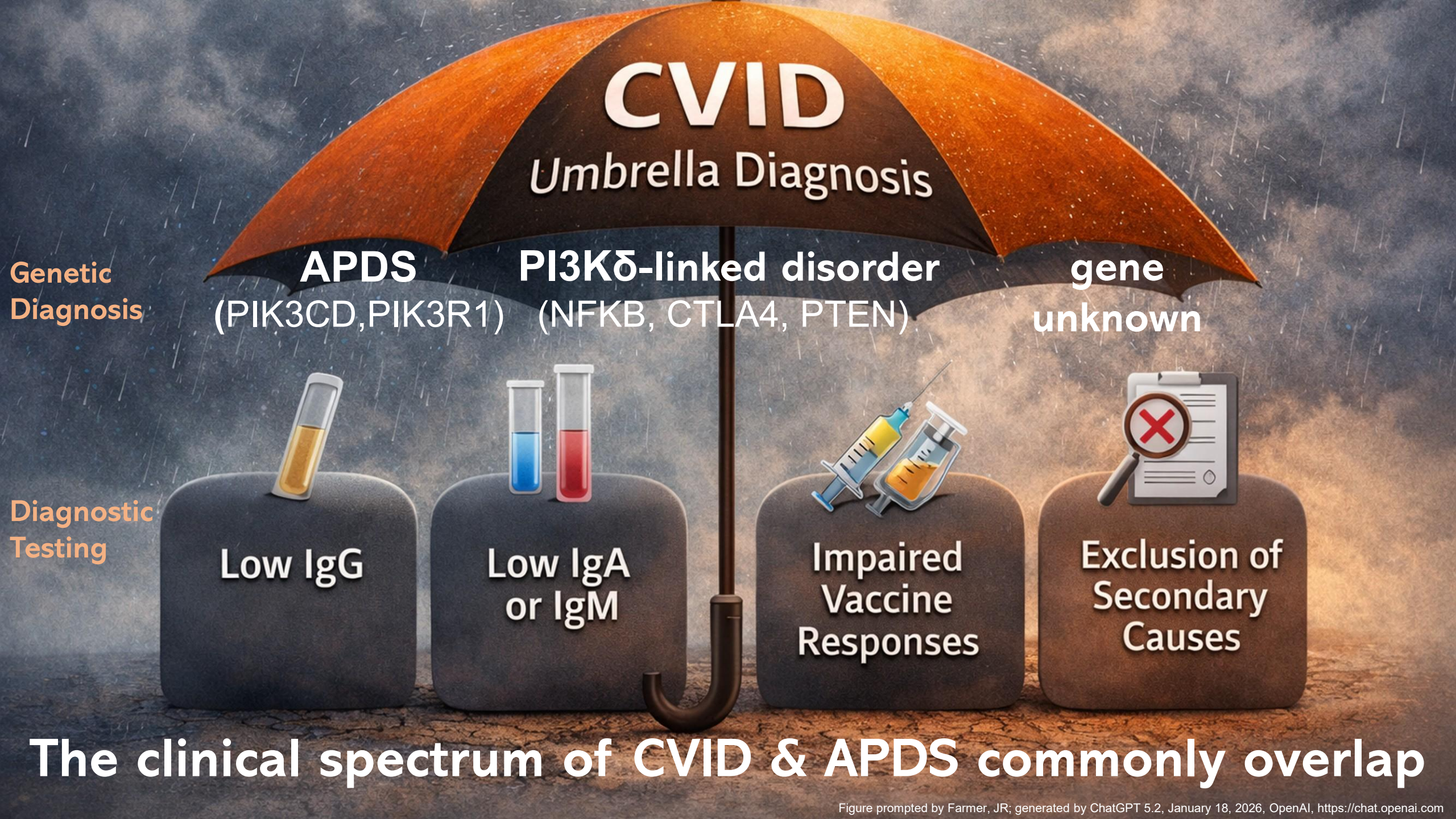


Figure prompted by Farmer, JR; generated by ChatGPT 5.2, January 18, 2026, OpenAI, https://chat.openai.com

CVID = many underlying single genetic conditions

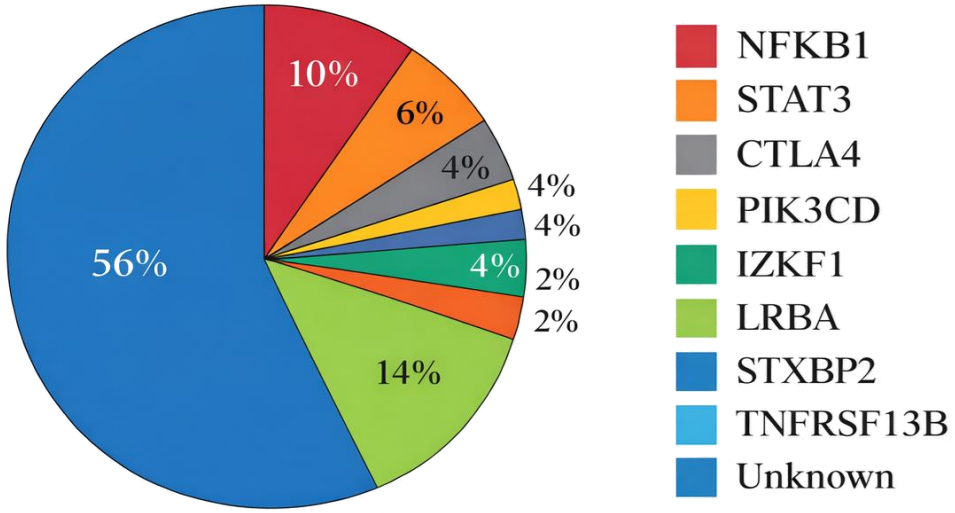
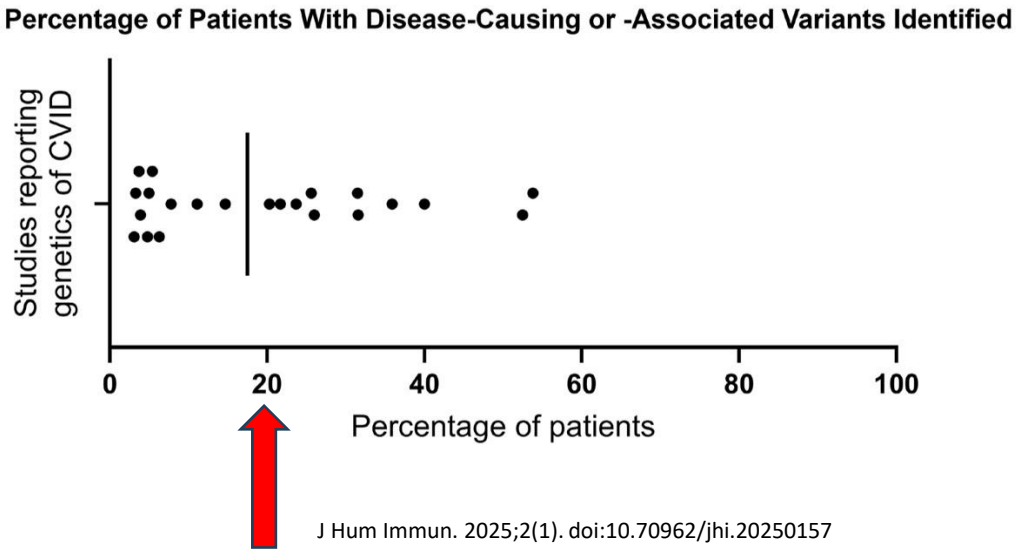


FIGURE 2 | Percentages of patients with likely disease-causing or -associated mutations. One patient had mutations in both *PIK3CD* and *TNFRSF13B* but was only included in the *PIK3CD* category. The Unknown category contains both patients for whom no variations in PID-associated genes were found ($n = 12$) and those who were found only to have a mutation reported in Table S5 in Supplementary Material ($n = 16$).

Within genotyped CVID cohorts we find….

- APDS = rare in CVID
- PI3Kδ-linked disorders = less rare in CVID (e.g., NFKB, CTLA4)
- **unknown gene = most patients with CVID**



J Hum Immun. 2025;2(1). doi:10.70962/jhi.20250157

Maffucci P, Filion CA, Boisson B, Itan Y, Shang L, Casanova JL, Cunningham-Rundles C. Genetic Diagnosis Using Whole Exome Sequencing in Common Variable Immunodeficiency. Front Immunol. 2016 Jun 13;7:220. doi: 10.3389/fimmu.2016.00220. PMID: 27379089; PMCID: PMC4903998.

The Clinical Presentations are Similar

CVID

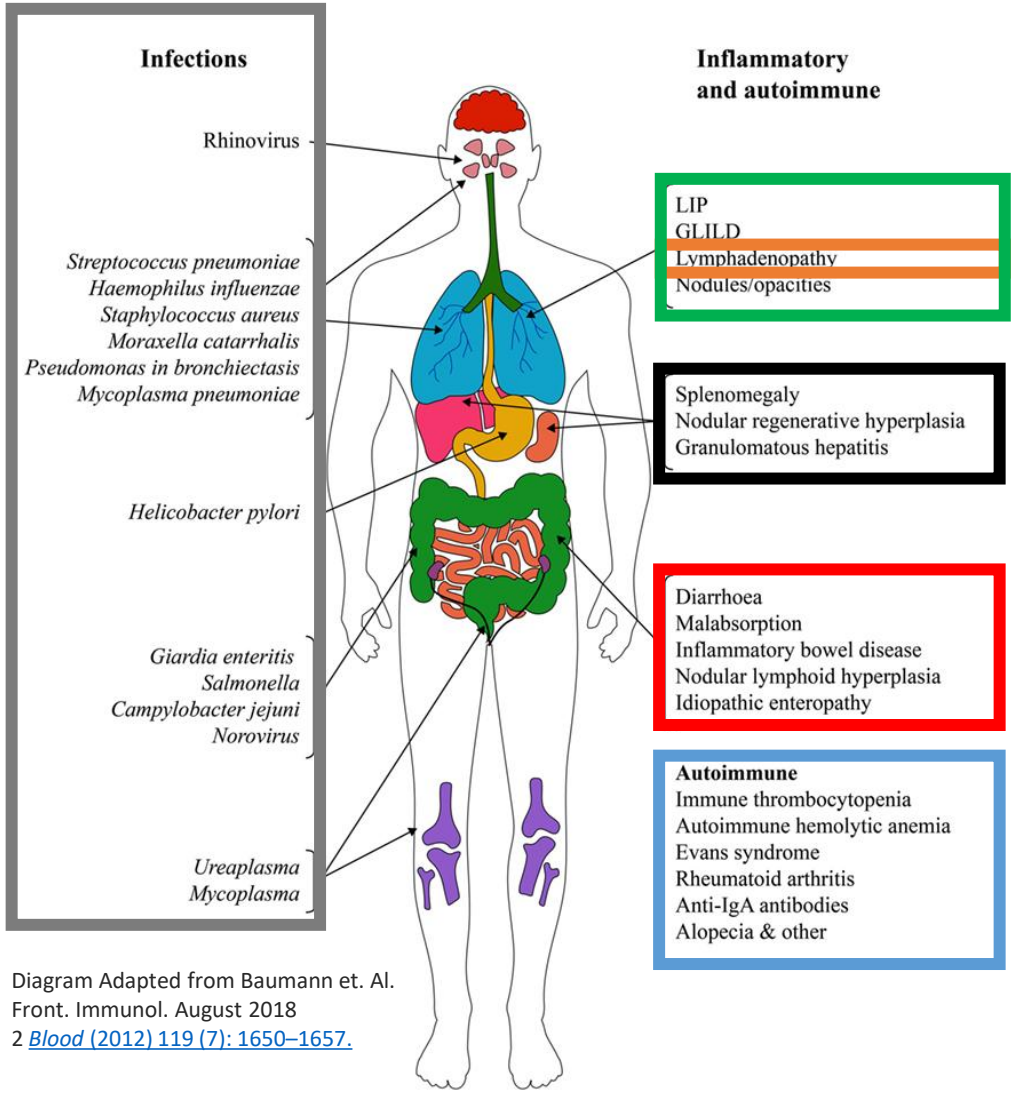


Diagram Adapted from Baumann et. Al. Front. Immunol. August 2018
2 *Blood* (2012) 119 (7): 1650–1657.

APDS

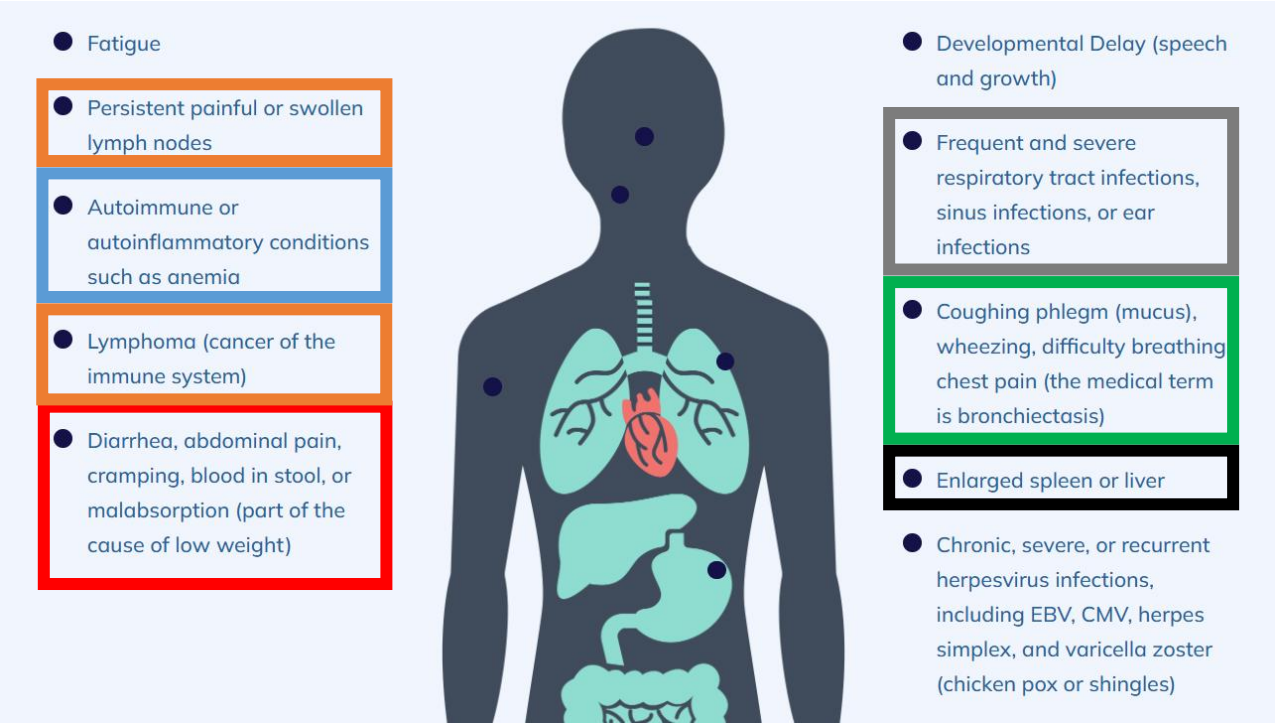
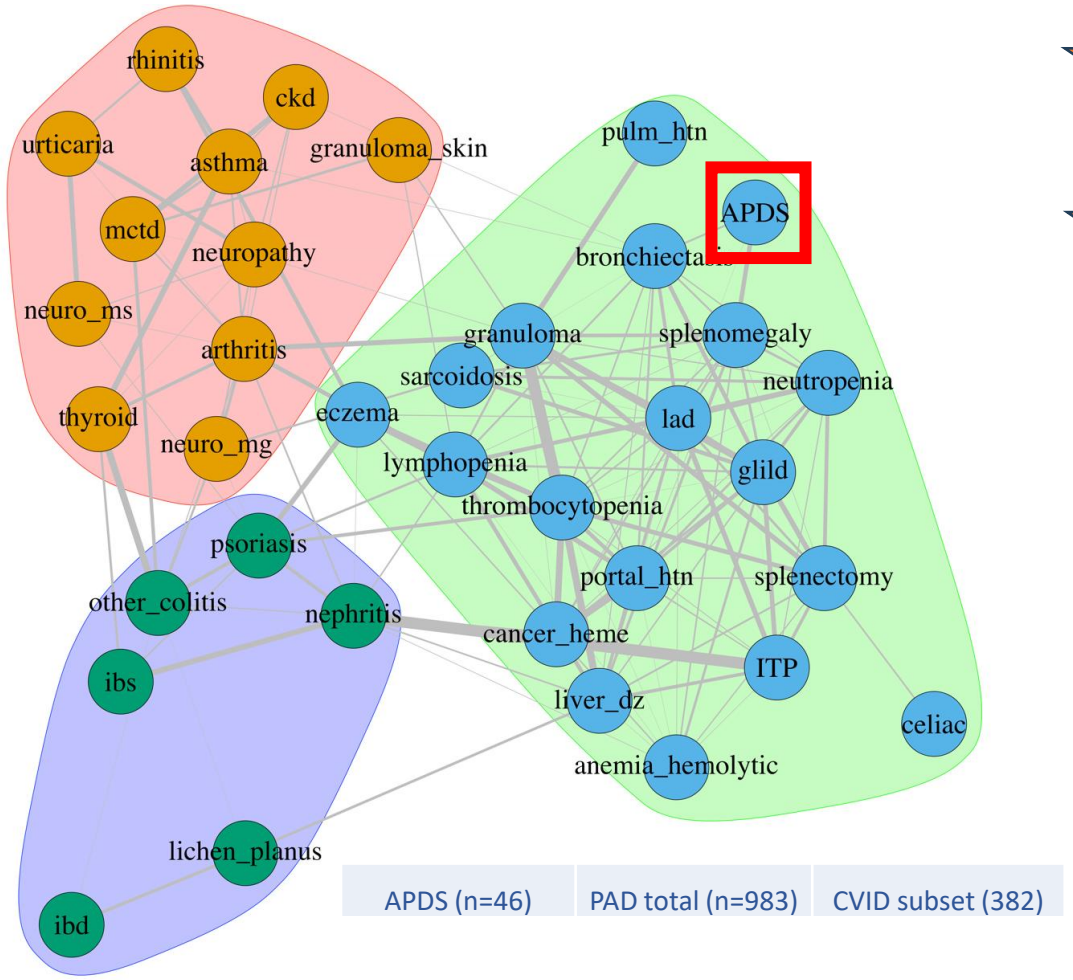


Diagram Adapted from APDS Symptoms | All about APDS

The Clinical Presentations Cluster

Unbiased Network Clustering of Noninfectious Disease Complications



75% **of** CVID Patients with Immune Dysregulation Exhibit **an 'APDS-like'** Endotype

- APDS disease spectrum overlaps significantly with CVID disease spectrum
- We have defined clinical complications within CVID that are APDS-like, setting up for appropriate clinical trial endpoints in CVID:
  - splenomegaly, lymphadenopathy
  - cytopenias
  - inflammatory lung disease
  - inflammatory liver disease

Association between APDS-cluster and clinical diagnoses among patients with PAD

	OR (95% CI)	p-value
Hypogammaglobulinemia	0.90 (0.59 – 1.34)	0.5754
SAD	0.60 (0.30 – 1.15)	0.1227
IgGSD	0.63 (0.31 – 1.29)	0.2060
CVID	5.53 (4.09 – 7.49)	<0.0001
Hyper IgM	0.00 (0.00 – Inf)	0.9755

Abstract was presented in May 2025

Clinical Immunology Society

New England Immune Deficiency Consortium

Can we apply biology learned from

APDS (rare)

to help the most patients with

CVID (common)?

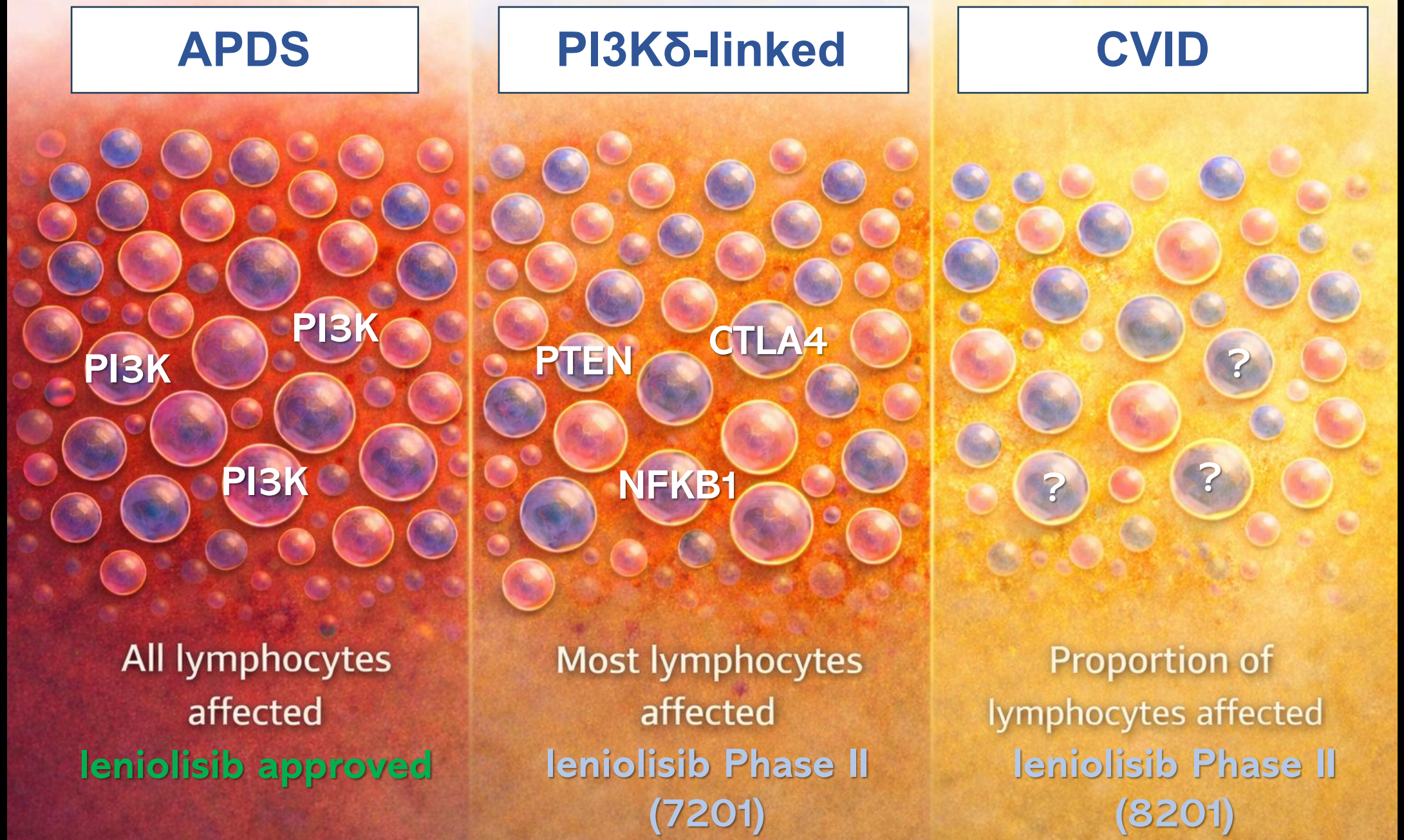
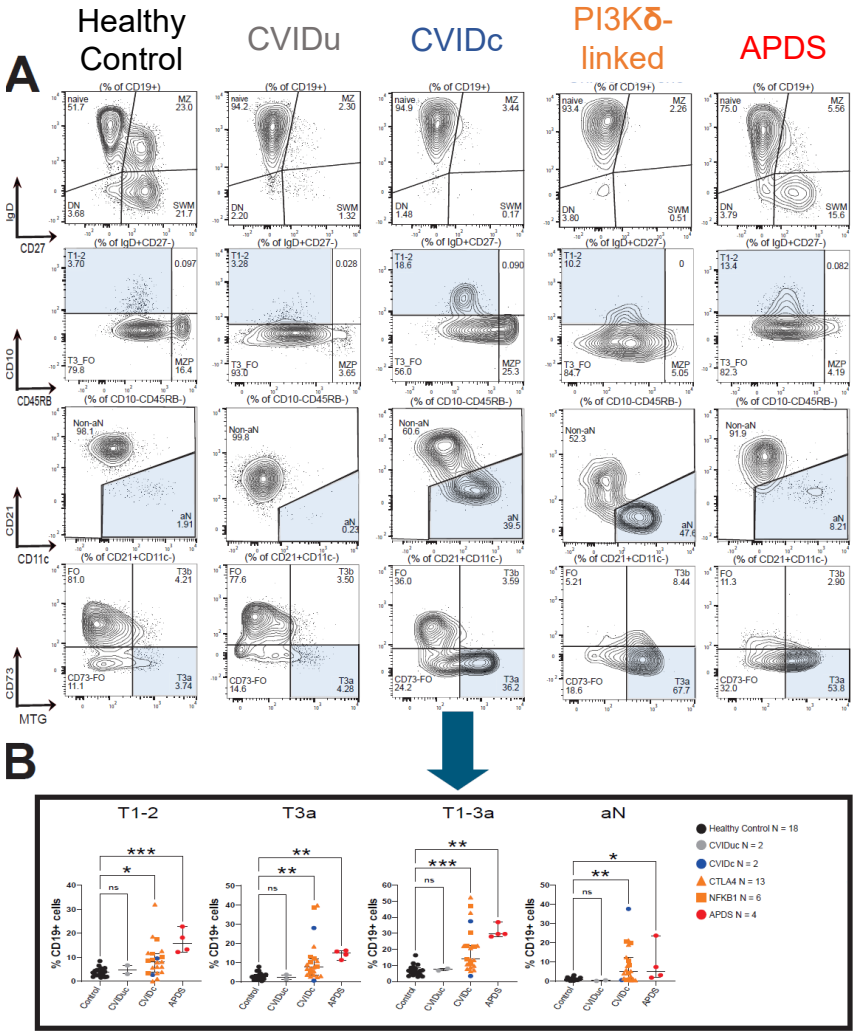
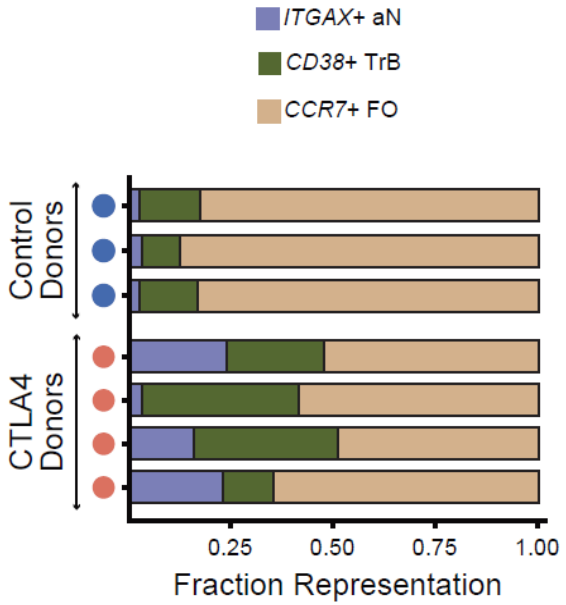


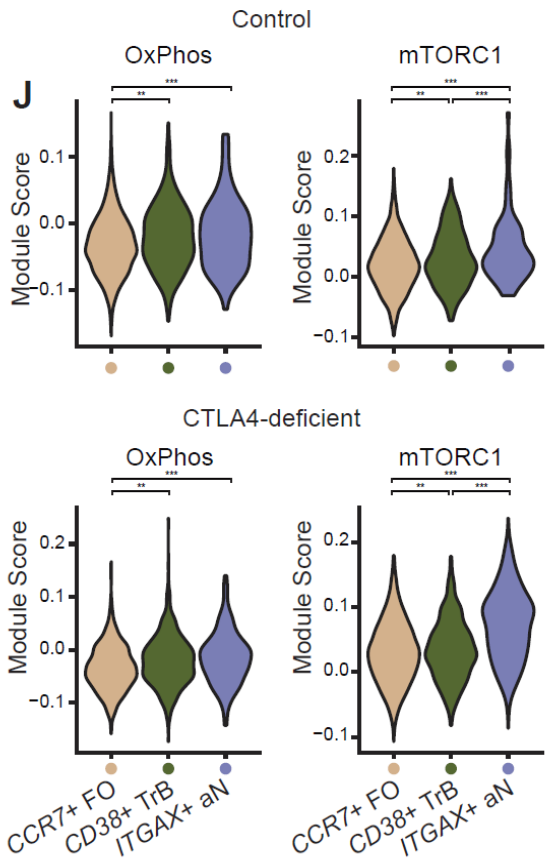
Figure prompted by Farmer, JR; generated by ChatGPT 5.2, January 18, 2026, OpenAI, https://chat.openai.com

Shared in APDS, PI3Kδ-linked, and CVID disease:

Expansion of pathologic B cells (CD21(lo), PI3K/mTOR(hi))





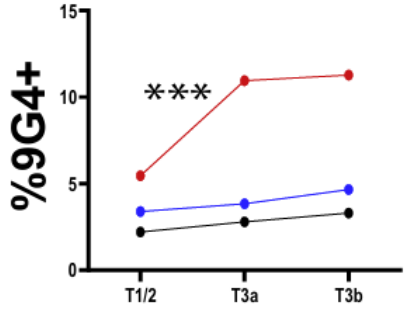


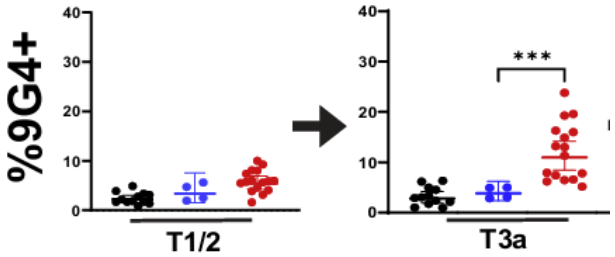
Adapted from:
Loss of B cell tolerance at the T2/T3a B cell transition is a convergent pathogenic mechanism in common variable immunodeficiency
Kirsty Hillier, Grace Yuen, Anson Hui, Suparna Kumar, Priyamvada Guha Roy, Joseph T. McColgan, Kimberly Zaldana, Hugues Allard-Chamard, Katie Premo, Naoki Kaneko, Nicole Ingram, Sara Barmettler, Musie Ghebremichael, Jolan E. Walter, Cory A. Perugino, Jishnu Das, Jocelyn R. Farmer, Shiv Pillai
bioRxiv 2025.06.07.658167; doi: https://doi.org/10.1101/2025.06.07.658167

Allard-Chamard H, Hillier K, Ramseier ML, Bertocchi A, Kaneko N, Premo K, Yuen G, Karpel M, Mahajan VS, Tsekeri C, Hong JS, Vencic J, Crotty R, Sharda AV, Barmettler S, Westermann-Clark E, Walter JE, Ghebremichael M, Shalek AK, Farmer JR, Pillai S. Congenital T-cell activation impairs transitional-to-follicular B-cell maturation in humans. Blood Adv. 2025 Feb 11;9(3):520-532. doi: 10.1182/bloodadvances.2024013267. PMID: 39626280; PMCID: PMC11814514.

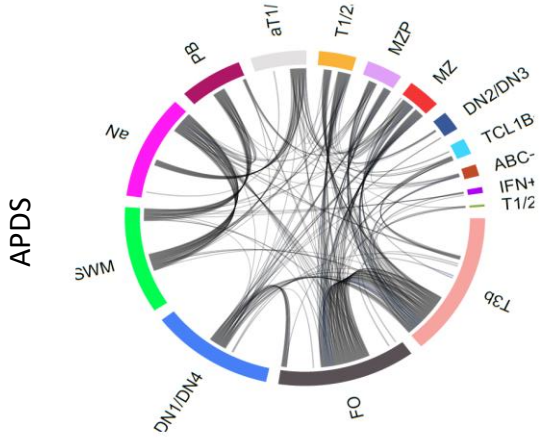
Shared in APDS, PI3Kδ-linked, and CVID disease:

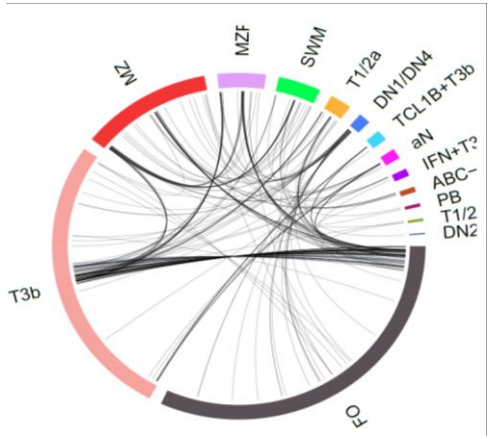
Convergent break in B cell tolerance causing end-organ disease

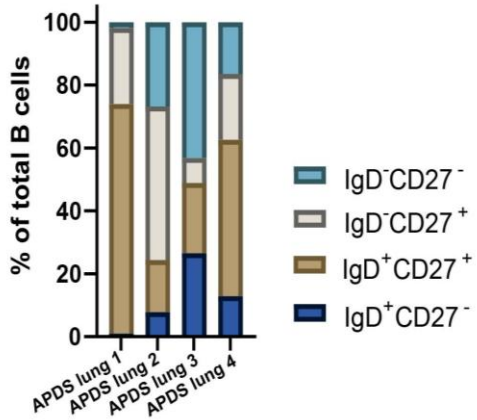


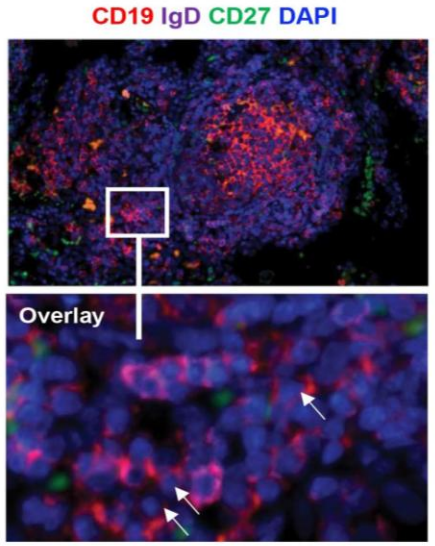


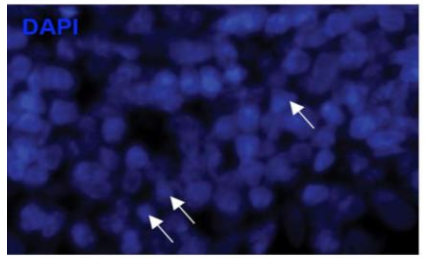
- Healthy control (n=12)
- CVID without autoimmunity (n=4)
- CVID with autoimmunity (n=16)

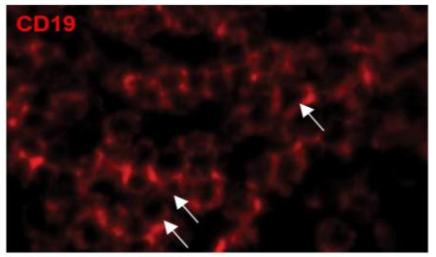


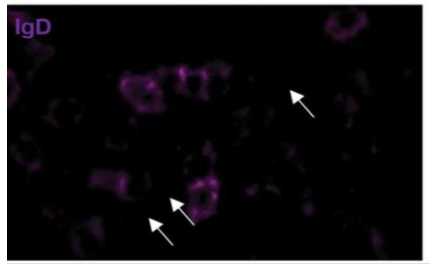


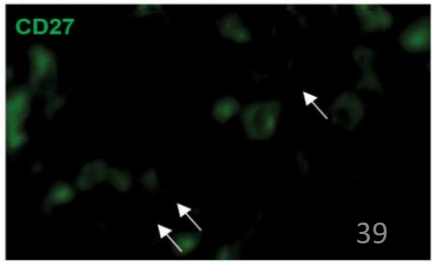












Loss of B cell tolerance at the T2/T3a B cell transition is a convergent pathogenic mechanism in common variable immunodeficiency
Kirsty Hillier, Grace Yuen, Anson Hui, Suparna Kumar, Priyamvada Guha Roy, Joseph T. McColgan, Kimberly Zaldana, Hugues Allard-Chamard, Katie Premo, Naoki Kaneko, Nicole Ingram, Sara Barmettler, Musie Ghebremichael, Jolan E. Walter, Cory A. Perugino, Jishnu Das, Jocelyn R. Farmer, Shiv Pillai
bioRxiv 2025.06.07.658167; doi: https://doi.org/10.1101/2025.06.07.658167

Can we apply treatment from

APDS (rare)

to help the most patients with

CVID (common)?

Single Patient IND Experience in CVID

Demographics: 64-year-old female
Immune Diagnosis: CVID (with unknown genetic cause)

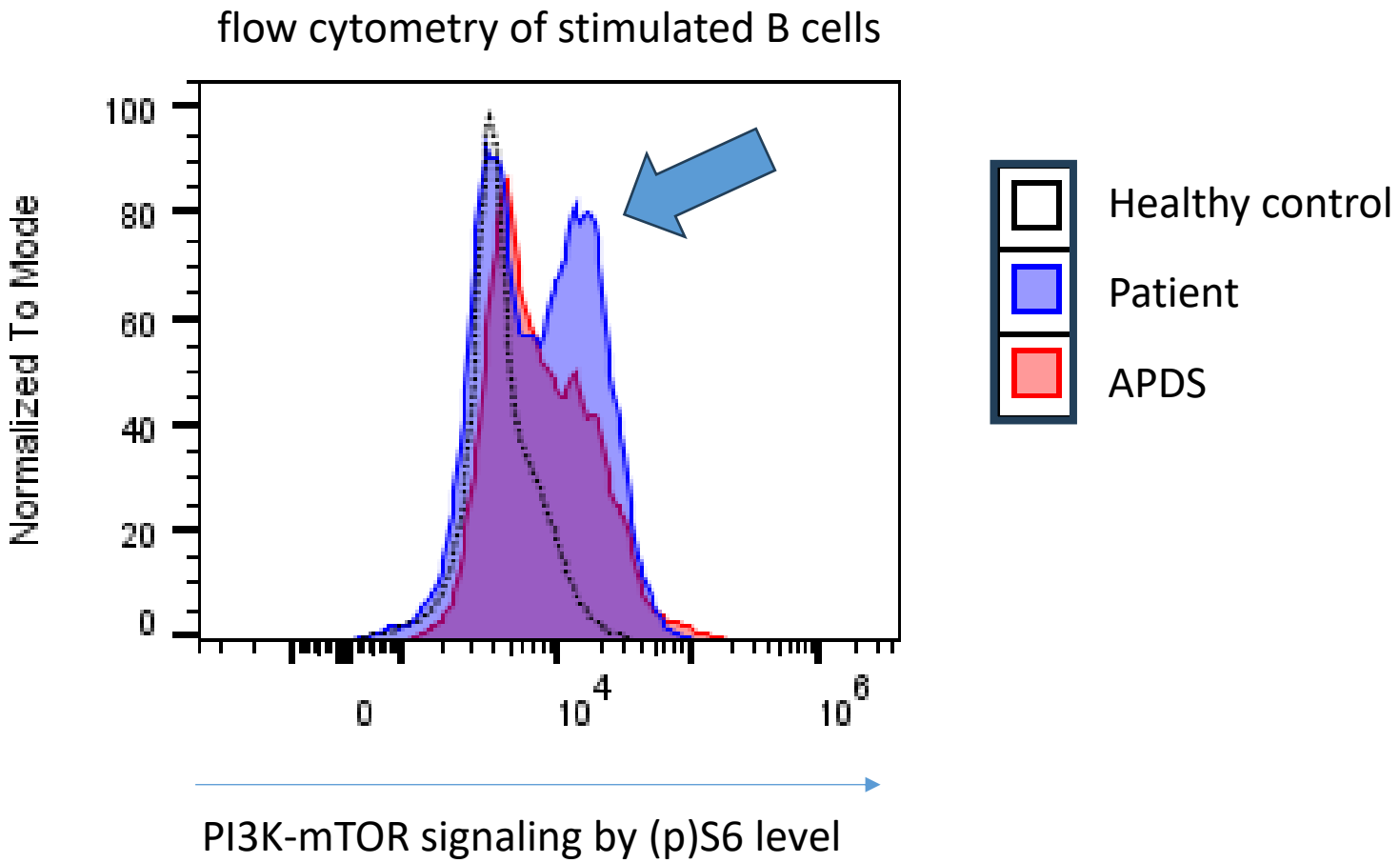
Life-threatening co-morbidities from CVID: chronic infections (sinus, lungs, skin), nodular regenerative hyperplasia (NRH) of liver, granulomatous and interstitial (GLILD) disease of lung, neutropenia, splenomegaly, lymphocytopenia, small fiber polyneuropathy, mastocytosis (in current remission)

Prior therapies without adequate auto-inflammatory disease control:
- high dose IVIG (partial response only)
- rituximab (serum sickness on dose 2)
- anakinra (partial response only)
- tofacitinib (non-responder)
- avapritinab (responder but concern for progression to immune suppression with COVID persistence)

Alternatives for immune modulation not aligned with goals of care at this time: b cell depletion (serum sickness with rituximab); limited data that B cell targeting in isolation ameliorates NRH; cellcept (too risky with CD4+ T cell count ~ 200 cells/uL); abatacept (limited data that ameliorates NRH); sirolimus (not preferred in the setting of ongoing neutropenia)

IND, Investigational New Drug

Single Patient IND Experience in CVID



IND, Investigational New Drug

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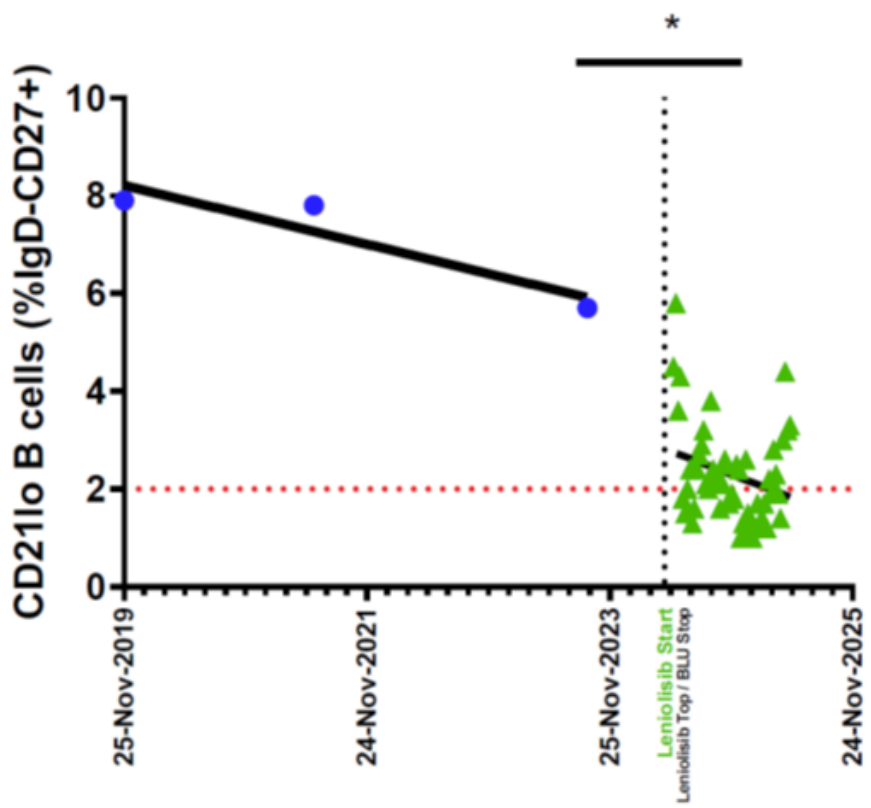


CD21lo B (pre)
CD21lo B (post)

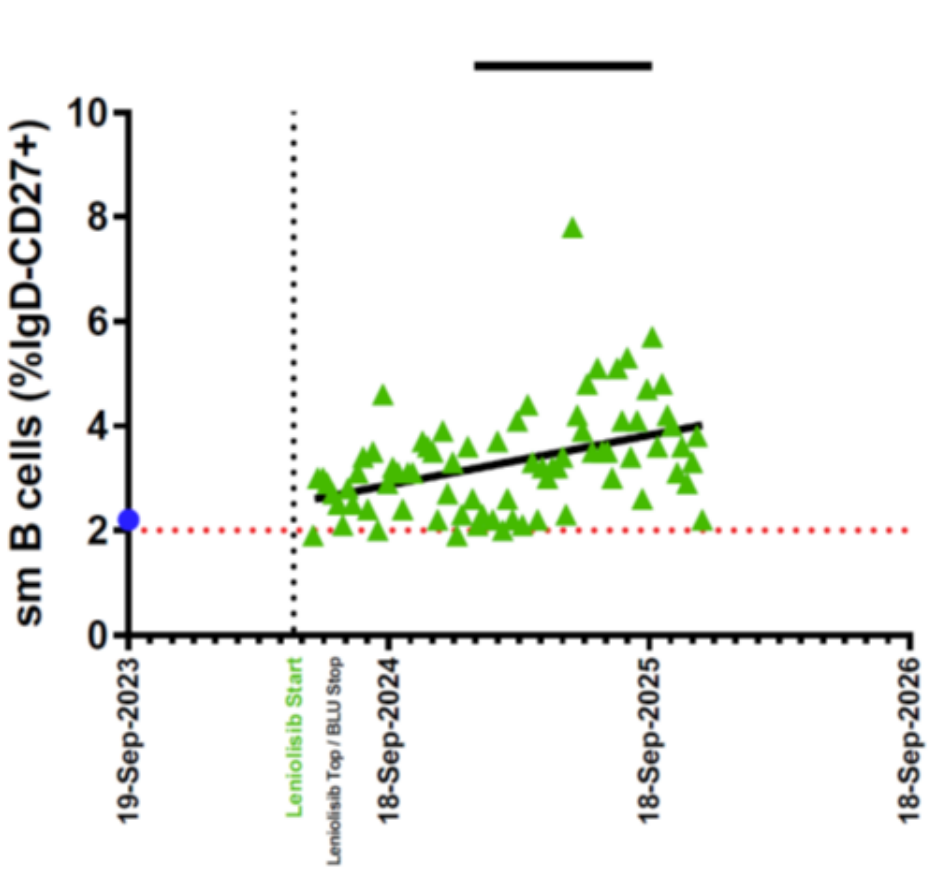
	CD21lo B (pre)	CD21lo B (post)
R square	0.8629	0.07367
Sy.x	0.6506	0.9731
Is slope significantly non-zero?		
F	6.292	3.897
DFn, DFd	1, 1	1, 49
P value	0.2415	0.0540
Deviation from zero?	Not Significant	Not Significant

	CD21lo B (pre)	CD21lo B (post)
Mean	7.133	2.298

Reduction in pathologic CD21(lo) B cells on leniolisib therapy over one year.

IND, Investigational New Drug

Single Patient IND Experience in CVID



sm B (pre)
sm B (post)

	sm B (pre)	sm B (post)
R square		0.1713
Sy.x		0.9334
Is slope significantly non-zero?		
F		15.5
DFn, DFd		1, 75
P value		0.0002
Deviation from zero?		Significant

	sm B (pre)	sm B (post)
Mean	2.2	3.309

Restoration of antibody-making switched memory (sm) B cells on leniolisib therapy over one year.

IND, Investigational New Drug

Single Patient IND Experience in CVID: Patient Perspective

"Leniolisib has given me hope that my immunological deficits can be stabilized and ultimately repaired. Dr. Farmer and her zealousness to obtain compassionate release of leniolisib has renewed my hope for the future and my longevity. Dreams can come true."

IND, Investigational New Drug

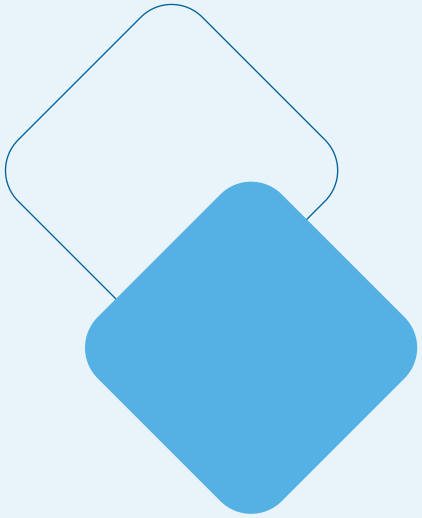
Direct quote from patient diagnosed with CVID and being managed by Dr. Farmer, provided 01-18-2026

Acting With Urgency

Unlocking the potential of leniolisib to transform care for immune dysregulation in PIDs

Rebecca Marsh, MD

Medical Director



Disclaimer

Leniolisib is being investigated for a new indication that has not been approved by the FDA or any other regulatory authorities. The safety, efficacy, and appropriate use of leniolisib have not been established for this indication. There is no guarantee that this product will successfully complete clinical development or receive regulatory approval for any new indication.

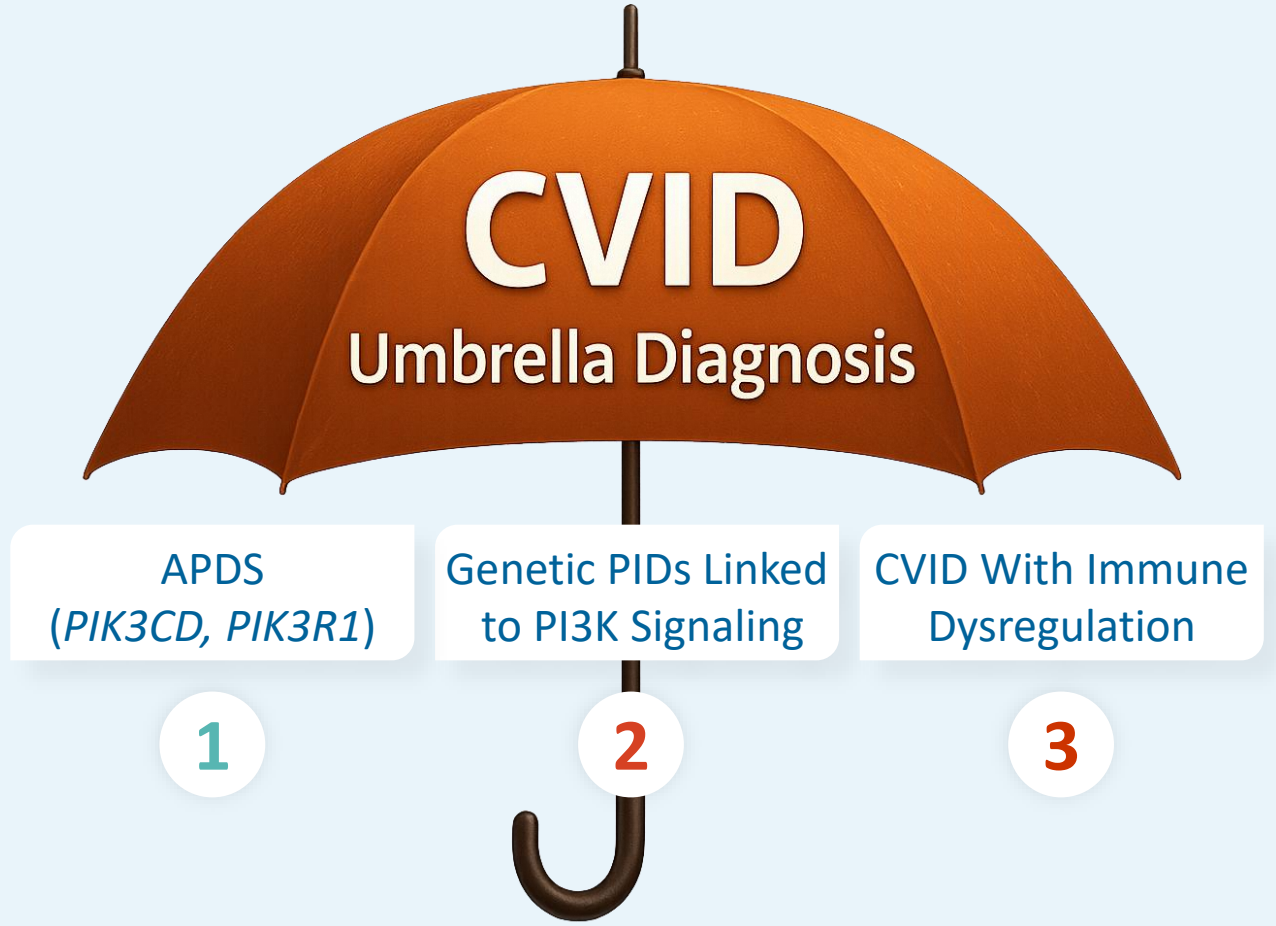
Our mission is to transform the care of additional PID patients with immune dysregulation

This mission is well-founded, supported by:

- Clear and significant patient need
- Strong scientific rationale
- Clinical experience from HCP-requested single patient IND treatment (N=6, 5 CVID)*

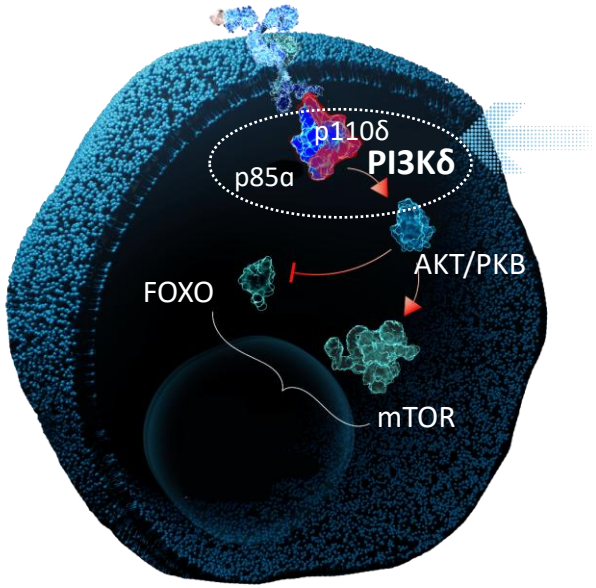
*Abstract submitted for potential presentation at the 2026 annual meeting of the Clinical Immunology Society.

Pharming has developed clinical trials targeting PID disorders with immune dysregulation under the influence of PI3Kδ



PI3Kδ is a master regulator of the immune system and imbalance contributes to immune dysregulation

PI3Kδ is a master regulator of the immune system and influences



Cell trafficking · Cell Growth · Cell proliferation
Cell Differentiation · Apoptosis inhibition/survival

Immune dysregulation pathology

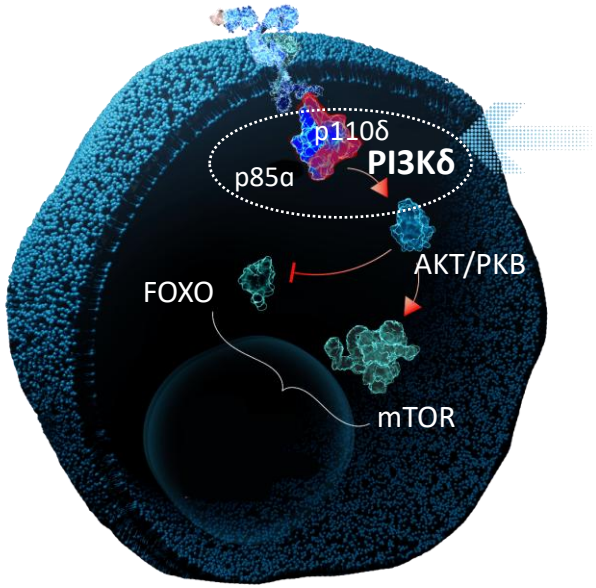
- Lymphoproliferation
- Autoimmunity
- GI Disease
- Pulmonary Disease

Shared pathology under the influence of PI3Kδ

- APDS
- Genetic PIDs linked to PI3Kδ
- CVID with immune dysregulation

Pharming successfully completed a phase III study in APDS which led to the approval of leniolisib in APDS patients 12 years of age and older

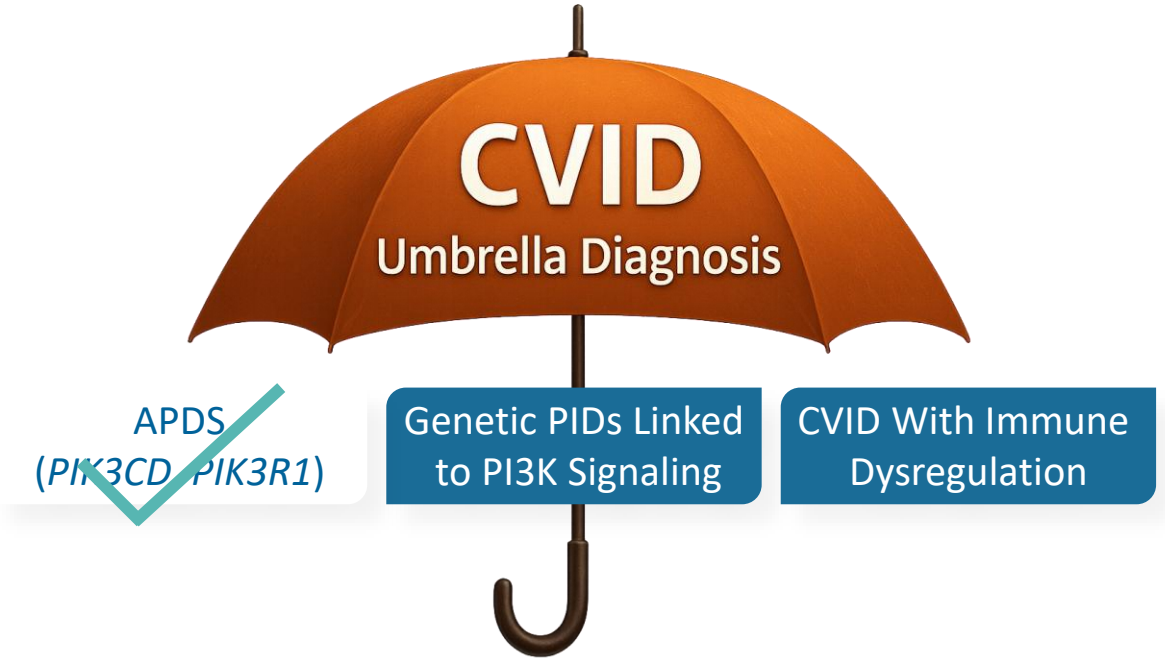
PI3Kδ is a master regulator of the immune system and influences



Cell trafficking Cell Growth Cell proliferation

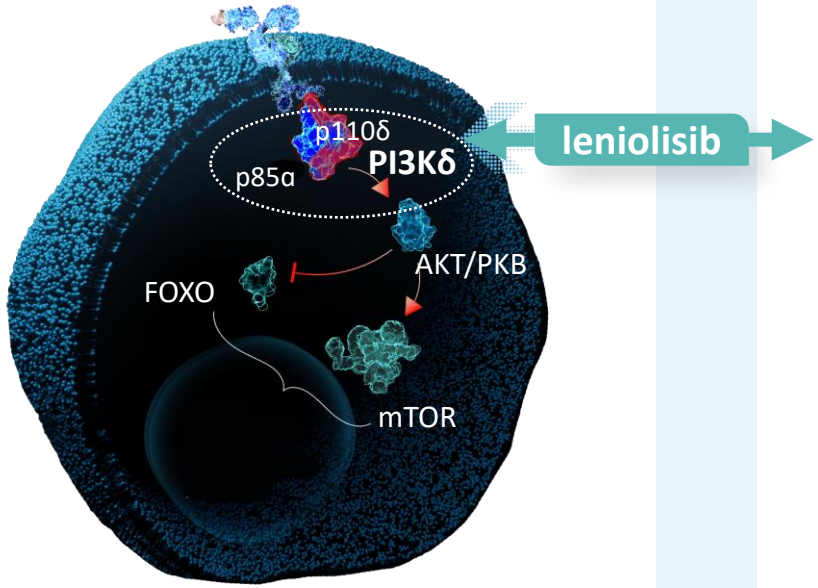
Cell Differentiation Apoptosis inhibition/survival

APDS exemplifies a PID characterized by immune dysregulation and serves as a proof-of-concept model for understanding related disorders being studied by Pharming



Leniolisib is a first-in-class medicine in APDS and acts by modulating PI3Kδ and consequently immune dysregulation

PI3Kδ is a master regulator of the immune system and influences



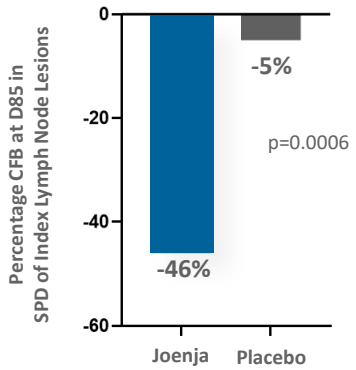
Cell trafficking **Cell Growth** **Cell proliferation**

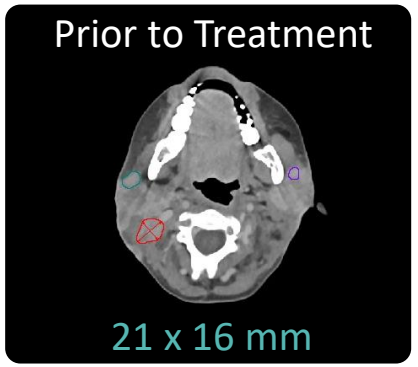
Cell Differentiation **Apoptosis inhibition/survival**

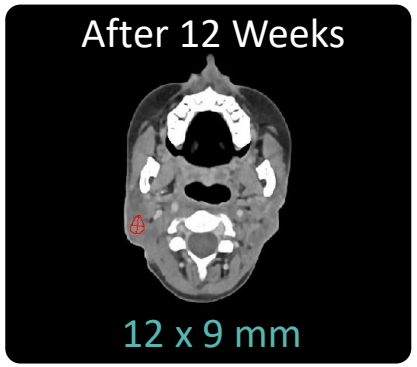
Pivotal study leading to multiple regulatory approvals showed leniolisib has a significant impact on lymphadenopathy*

Change from baseline in index nodes*

Log_{10}-transformed SPD of index lesions	Joenja (n=18)	Placebo (n=8)
Baseline mean (SD)	3.03 (0.42)	3.05 (0.39)
Change from baseline, LS mean (SE)	-0.27 (0.04)	-0.02 (0.05)
Difference vs placebo (95% CI)		-0.25 (-0.38, -0.12)



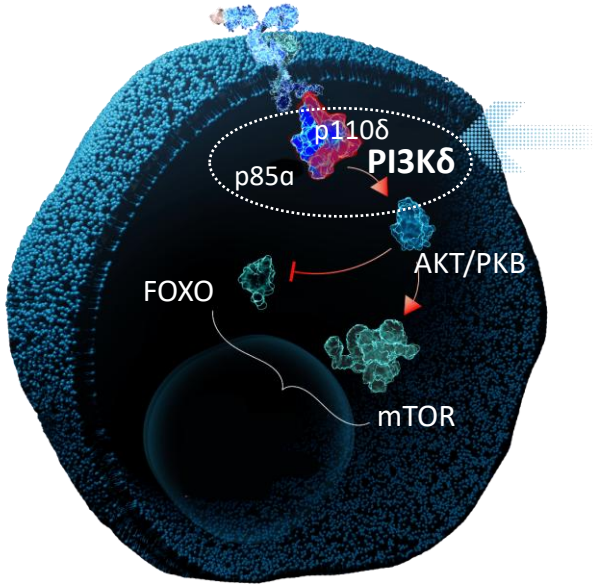




*Rao VK, Webster S, Šedivá A, et al. A randomized, placebo-controlled phase 3 trial of the PI3Kδ inhibitor leniolisib for activated PI3Kδ syndrome. Blood 2023; 141 (9): 971–983.

We believe leniolisib may be a transformative medicine in additional PIDs with immune dysregulation under the influence of PI3Kδ

PI3Kδ is a master regulator of the immune system and influences



Cell trafficking **Cell Growth** **Cell proliferation**

Cell Differentiation **Apoptosis inhibition/survival**

Immune dysregulation pathology

Lymphoproliferation

Autoimmunity

GI Disease

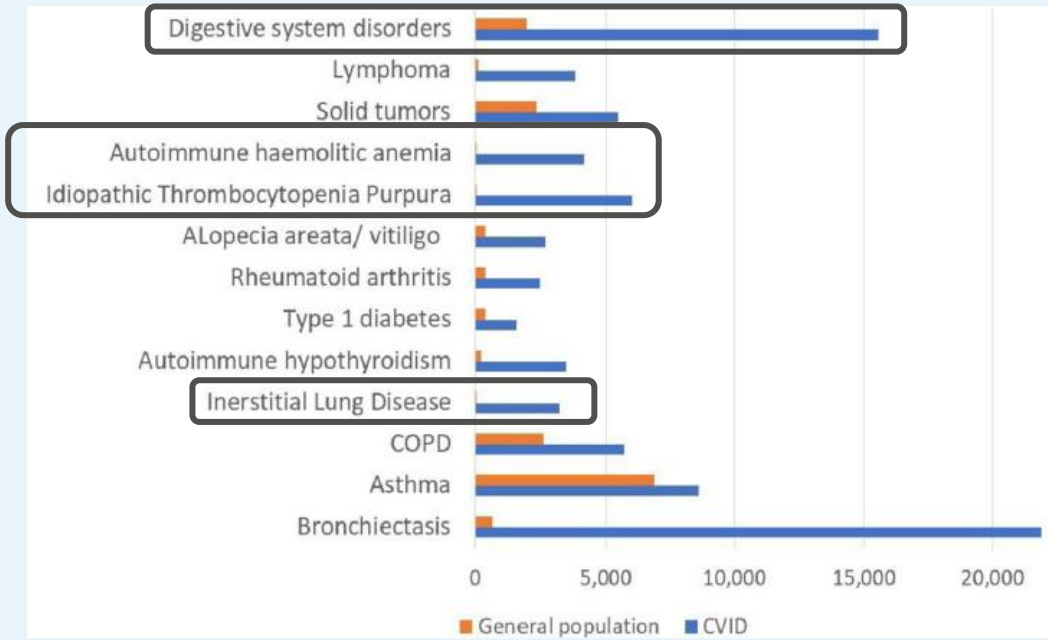
Pulmonary Disease

Shared pathology under the influence of PI3Kδ

- [x] APDS
- [ ] **Genetic PIDs linked to PI3Kδ**
- [ ] **CVID with immune dysregulation**

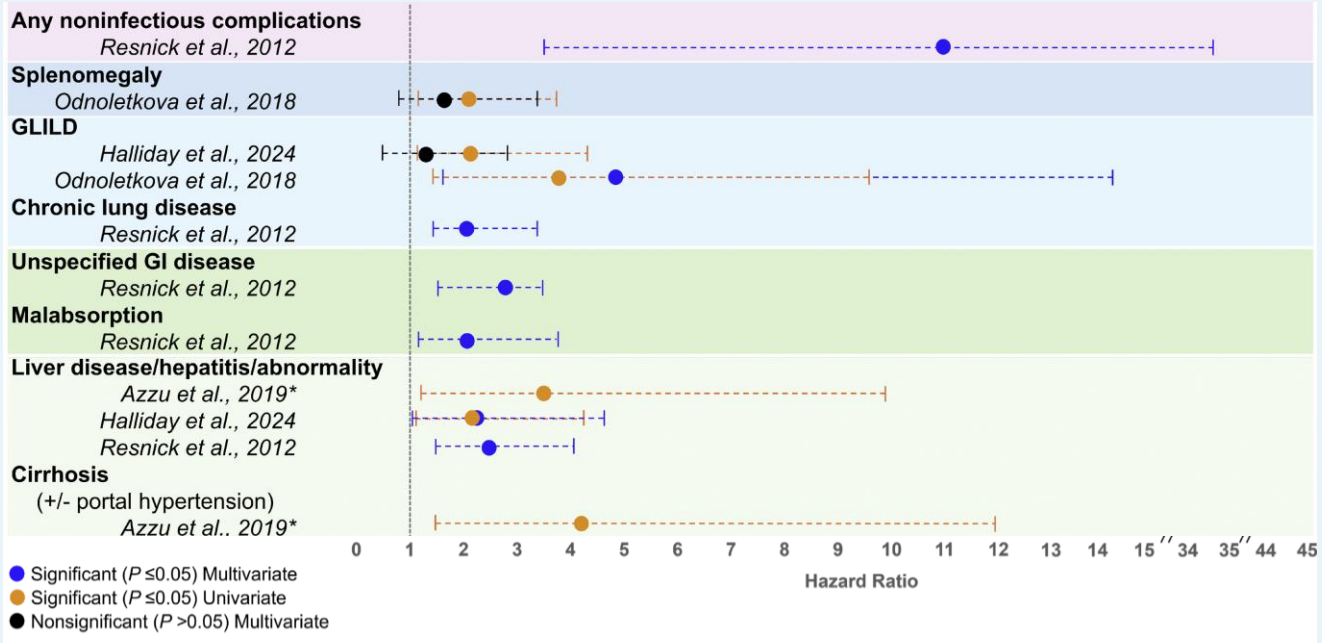
Our phase II trials are designed to evaluate safety, optimal dosing, and the impact of leniolisib on common/serious clinical manifestations

Rates of Complications



Average annual prevalence rate per 100,000 over the period 2004–2014.

Impact of Complications on Mortality

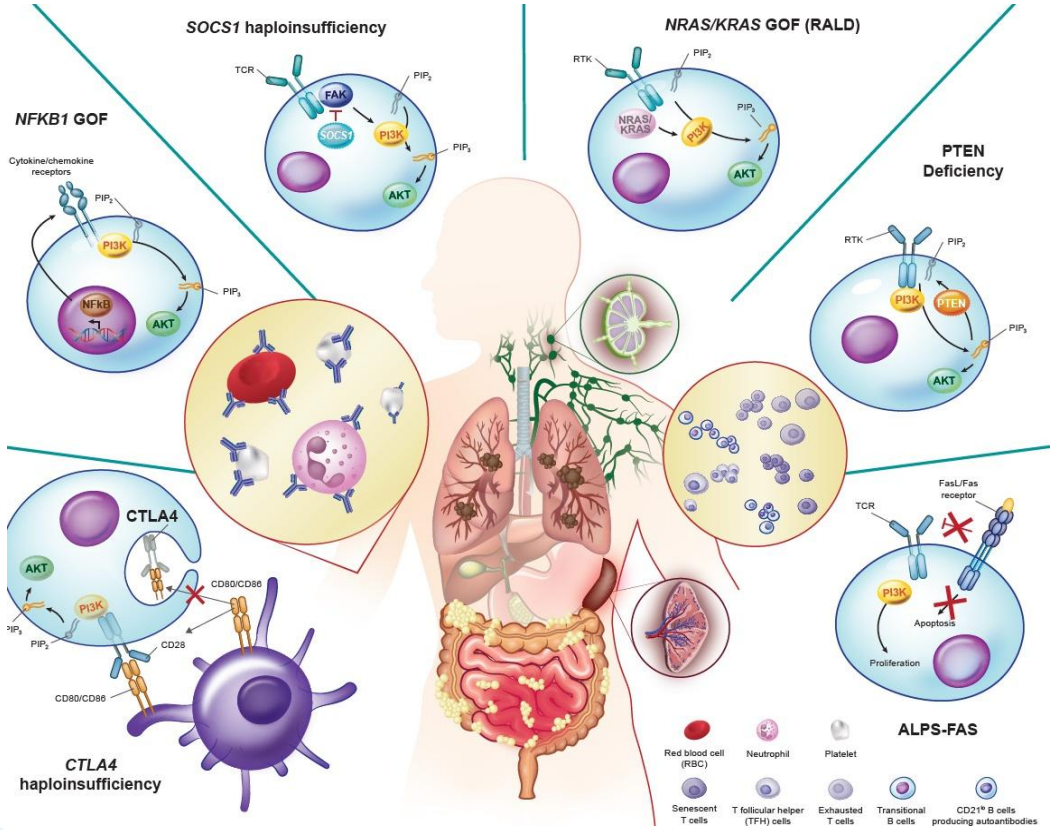


Odnoletkova I, Kindle G, Quinti I, et al . The burden of common variable immunodeficiency disorders: a retrospective analysis of the European Society for Immunodeficiency (ESID) registry data. Orphanet J Rare Dis. 2018 Nov 12;13(1):201.
Ducasa M, Marsh RA, Mojebi A, et al. A systematic literature review of CVID reveals pervasive detrimental noninfectious manifestations. J Hum Immun 5 January 2026; 2 (1): e20250157.

Phase II proof of concept trial in ‘genetic PIDs linked to PI3K signaling’

Developed in collaboration with Dr. Gulbu Uzel, National Institutes of Health

- **PTEN deficiency** reduces PIP3 degradation, mimicking APDS-like PI3K activation (Tsujita et al., 2016).
- **ALPS-*FAS*** involves impaired apoptosis and enhanced PI3K signaling (Völkl 2016; Bride & Teachey 2017; Fajqenbaum 2019).
- ***NRAS/KRAS*** mutations directly increase PI3K activity (Castellano et al., 2011).
- **SOCS1 and CTLA-4 haploinsufficiency** amplify PI3K signaling through altered receptor interactions (Reif 2003; Xia 2004; Körholz 2021; Verma 2017; Rowshanravan 2018).
- ***NFKB1* variants** promote PI3K-linked inflammatory signaling (unpublished data).
- **Of note:** additional disorders alter signaling (*PRKCD*, *LRBA*, *DEF6*, *CARD11* GOF...)



Tsujita Y, Mitsui-Sekinaka K, Imai K, et al. Phosphatase and tensin homolog (PTEN) mutation can cause activated phosphatidylinositol 3-kinase δ syndrome-like immunodeficiency. J Allergy Clin Immunol. 2016 Dec;138(6):1672-1680.e10.
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Bride K, Teachey D. Autoimmune lymphoproliferative syndrome: more than a FAScinating disease. F1000Res. 2017 Nov 1;6:1928.
Fajgenbaum DC, Langan RA, Japp AS, et al. Identifying and targeting pathogenic PI3K/AKT/mTOR signaling in IL-6-blockade-refractory idiopathic multicentric Castleman disease. J Clin Invest. 2019 Aug 13;129(10):4451-4463.
Castellano E, Downward J. RAS Interaction with PI3K: More Than Just Another Effector Pathway. Genes Cancer. 2011 Mar;2(3):261-74.
Reif S, Lang A, Lindquist JN. The role of focal adhesion kinase-phosphatidylinositol 3-kinase-akt signaling in hepatic stellate cell proliferation and type I collagen expression. J Biol Chem. 2003 Mar 7;278(10):8083-90.
.

GOF, gain of function; **RALD**, RAS-associated autoimmune leukoproliferative disorder; ***SOCS1***, suppressor of Cytokine Signaling 1.

Xia H, Nho RS, Kahm J, et al. Focal adhesion kinase is upstream of phosphatidylinositol 3-kinase/Akt in regulating fibroblast survival in response to contraction of type I collagen matrices via a beta 1 integrin viability signaling pathway. J Biol Chem. 2004 Jul 30;279(31):33024-34.
Körholz J, Gabrielyan A, Sowerby JM, et al. One Gene, Many Facets: Multiple Immune Pathway Dysregulation in SOCS1 Haploinsufficiency. Front Immunol. 2021 Aug 5;12:680334.
Verma N, Burns SO, Walker LSK, Sansom DM. Immune deficiency and autoimmunity in patients with CTLA-4 (CD152) mutations. Clin Exp Immunol. 2017 Oct;190(1):1-7.
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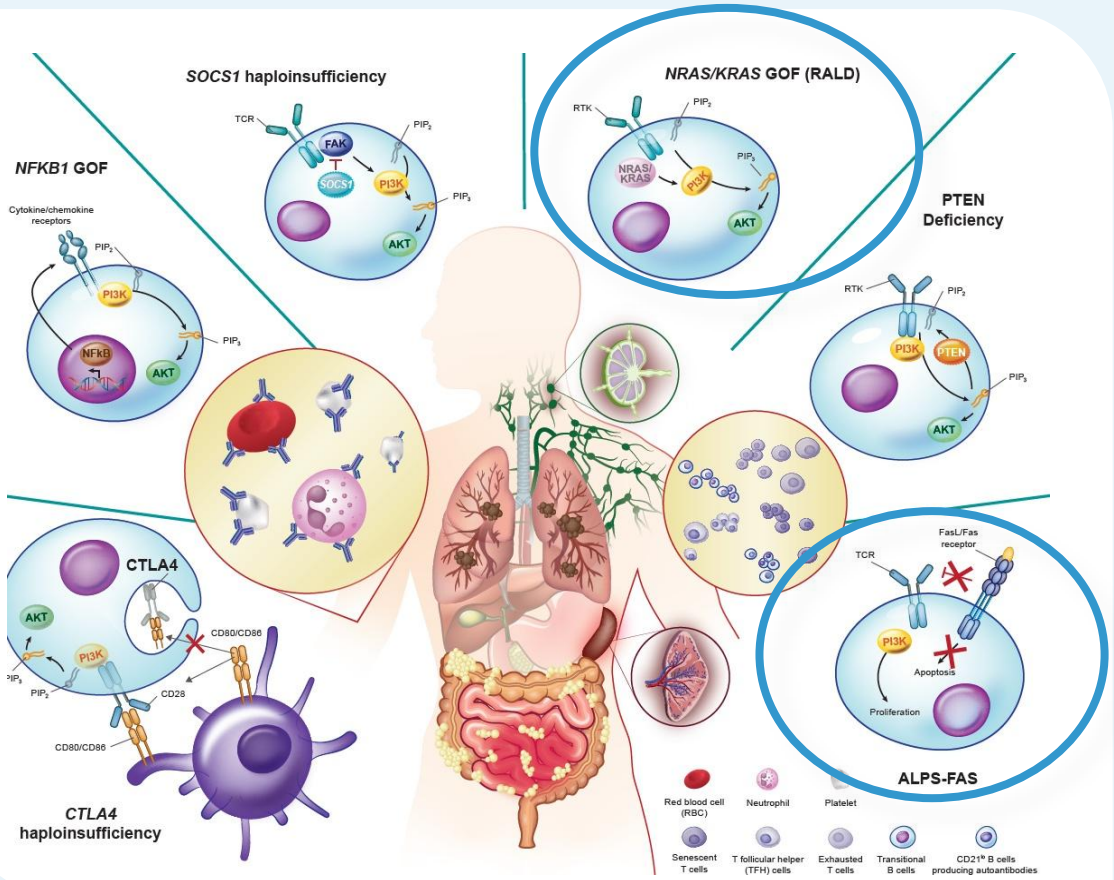

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GOF, gain of function; **RALD**, RAS-associated autoimmune leukoproliferative disorder; ***SOCS1***, suppressor of Cytokine Signaling 1.

Phase II proof of concept trial in ‘genetic PIDs linked to PI3K signaling’

Developed in collaboration with Dr. Gulbu Uzel

- Single arm, open-label, dose range-finding single center study at NIH (N=12)
- Dosing: 10/30/70 mg BID: 4/4/12 weeks treatment, respectively

Key inclusions:

- 12 to 75 years of age
- Pathogenic/likely pathogenic variant: *CTLA4, NFKB1, SOCS1, PTEN, FAS* (germline or somatic) **or** somatic RALD-associated variants in *NRAS* or *KRAS*
- Cytopenia, splenomegaly, lymphadenopathy or GLILD

Key exclusions:

- Hematopoietic stem cell transplant
- Immunosuppressive medications: mTOR inhibitor, rituximab, steroids >25 mg/day prednisone equiv., others

All patients with option to continue to separate 3 yr leniolisib open label extension

BID, twice daily; GLILD, granulomatous-lymphocytic interstitial lung disease; mTOR, mammalian target of rapamycin; OLE, open-label extension.
RALD, RAS-Associated Autoimmune Leukoproliferative Disorder.

Phase II proof of concept trial in ‘CVID with Immune Dysregulation’

Developed in collaboration with Dr. Jocelyn Farmer

- Single arm, open-label, dose confirmation multi-center study (N=20)
- Dosing: 10/30/70 mg BID: 4/4/16 weeks treatment, respectively

Key inclusions:

- 12 to 75 years of age
- Clinical CVID diagnosis (genetic diagnosis not required)
- Splenomegaly or lymphadenopathy PLUS ONE OF: symptoms of splenomegaly or lymphadenopathy, cytopenias, interstitial lung disease, autoimmune enteropathy

Key exclusions:

- Hematopoietic stem cell transplant
- Immunosuppressive medications: mTOR inhibitor, rituximab, steroids >25 mg/day prednisone equiv., others
- Significant T cell deficiency including CD4+ T cells <200/µL
- Significant NK cell deficiency including NK cells <1% or <50/µL
- Clinical history of opportunistic infections

All patients have option to continue to 3 yr leniolisib open label extension (OLE) study

Shared phase II objectives and endpoints support pivotal trial design

Objective: To assess safety and tolerability of leniolisib; confirm dosing strategy

- **Endpoints:** AEs; PK/PD

Objective: To estimate the clinical efficacy of leniolisib for immune dysregulation

- **Endpoints:** Changes in imaging, laboratory, and functional measurements including:
  - Lymph node and spleen size
  - Blood cell counts
  - CT-scored lung disease, pulmonary function tests
  - Others

Objective: To evaluate the mechanistic impact of leniolisib

- **Endpoints:** Phenotypic readouts of B cell maturation and other subset changes

Objective: To pilot correlative biomarker assessments

- **Endpoints:** CXCL13, IFNγ, soluble IL-2Rα, others

Objective: To pilot a modified scoring system used in PIDs

- **Endpoints:** mIDDA scoring

Objective: To pilot standard and custom* PRO tools

- **Endpoints:** PRO scores

*Custom PROs developed through structured discussions with clinical experts (n=4) and formal interview studies with CVID patients (n=20)

Epidemiology of genetic PIDs linked to PI3K signaling*

	Genetic PID type	Prevalence references	Current/future[9] prevalence estimate (per million)	% Targeted for leniolisib treatment	Diagnosed targeted population (per million)
	ALPS-FAS	ESID registry (236 patients): 6 /mill.[1] PID KOLs – 4 /mill[2]	5/10	30%[3]	3
Included in CVID Programme Epidemiology	***CTLA4***	ESID registry (38 patients): 1 /mill.[4] USIDNET registry (28 patients): 2 /mill.[5] Pharming lit review: 1.5/mill.[13] PID KOLs – 10 /mill.[2]	2/4	50%[6]	2
	NFKB1	ESID registry (25 patients): 0.75 /mill.[10] USIDNET registry (6 patients): 0.4 /mill. [11] Pharming lit review: 2/mill.[12] PID KOLs – 10 /mill.[2]	2/4	50%[14]	2
	PTEN	All PTEN patients NORD: 5/ mill.[7] PID KOLs – 4 /mill.[2]	5/10	5%[8]	0.5
				TOTAL Population (includes future patient diagnosis)	**7.5****

*some of these genetic disorders are classified by IUIS as CVID

** SOCS1 and NRAS/KRAS patient pools also included in the phase 2 study provide some additional, however limited, contributions to the estimated prevalence

References on file at Pharming Group

Epidemiology of CVID with immune dysregulation: CVID patients numbering ~39/million may be APDS-like

Prevalence references	Total CVID (p/mill; median)	CVID with immune dysregulation (p/mill)	Targeted APDS-like endotype population (p/mill)
ESID registry (4228 patients): 100 p/mill.[1] USIDNET registry (1823 patients): 125 p/mill.[2] PID KOL views – 40 p/mill.[3] Immunodeficiency Foundation - 40 p/mill.[4] PID US Health Survey – 290 p/mill.[5] CVID global review of registries & literature – 34 p/mill.[6] US Symphony Claims Data – 113 p/mill.[7] US PharMetrics Claims Data – 185 p/mill.[8]	106[9]	53[11,12,13]	39[10]

Note: overall prevalence includes patients with both unknown & known genetic drivers (including CTLA4, NFKB1, PTEN)

Assumptions:

- ~50% of CVID patients present with immune dysregulation (53 patients/million); the other 50% with infectious phenotype only are well-treated with Ig therapy & anti-microbials [11,12,13]
- 74% of CVID with immune dysregulation patients present with an 'APDS-like' endotype[10]
- Market research and KOL discussions indicate 50-60%[14,15] of diagnosed targeted patients may be treated with leniolisib

References on file at Pharming Group

Leniolisib: we have the potential to transform care for ~44/million PID patients with immune dysregulation

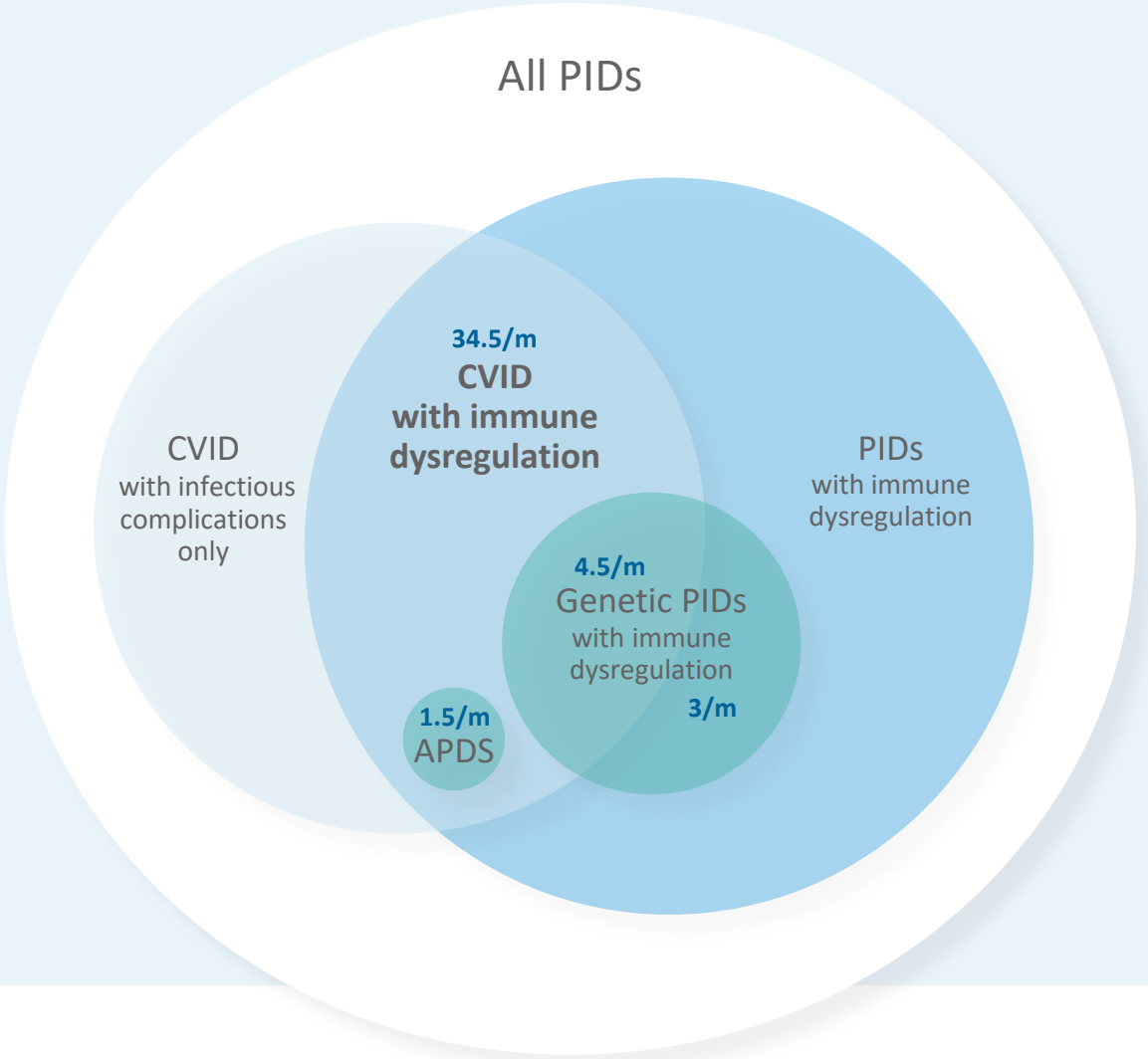


Diagram for illustrative purposes and not to scale

Summary: leniolisib for PIDs with immune dysregulation

PIDs with immune dysregulation have a considerable unmet need with large treatable population

- High mortality, no approved treatments or other products in development
- Combined target population ~44/million, significantly broader than APDS prevalence of 1.5/million

PI3Kδ is a master regulator of the immune system

- PI3Kδ pathway imbalances contribute to immune dysregulation
- Dysregulation contributes to lymphoproliferation, autoimmunity, GI disease and pulmonary disease

Leniolisib targets PI3Kδ and can modulate underlying immune dysregulation in PIDs

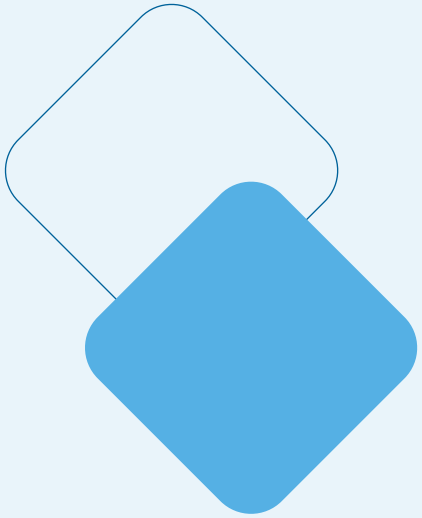
- APDS clinical trials and real-world experience
- HCP-requested individual IND case experience in CVID

Two multinational phase II clinical studies underway - top line data expected 2H26

- Genetic PIDS with immune dysregulation linked to PI3Kδ
- CVID with immune dysregulation

Thank You

Questions and Conversations



Agenda: Napazimone (KL1333)

- Primary mitochondrial diseases – rare disorders with significant unmet medical need
- Napazimone (KL1333) positioned to become first standard of care in mitochondrial DNA (mtDNA) disease
- Pivotal study ongoing with positive interim analysis confirming FDA-agreed primary endpoints
- Significant value creation potential for Pharming and patients

Disclaimer

The information and views presented by Dr. Amel Karaa during this session are solely her own, derived from her clinical expertise and professional judgment. They do not necessarily represent or reflect the positions, perspectives, or official guidance of Pharming Group N.V. or any of its affiliates. This presentation is provided for educational purposes only and should not be interpreted as company-endorsed direction or policy.

MASSACHUSETTS GENERAL HOSPITAL
HARVARD UNIVERSITY

Primary Mitochondrial Diseases

Amel Karaa, MD
Director of the Mito Clinic
Massachusetts General Hospital
Harvard Medical School

Disclaimer:

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- The information presented are my own professional **insights & considerations and not those** of my employer, organization, committee or other group or individual I work with.

Mitochondrial disease is a distinct set of genetic metabolic disorders

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- International classification of inherited metabolic disorders

Mitochondrial disease is a distinct set of genetic metabolic disorders

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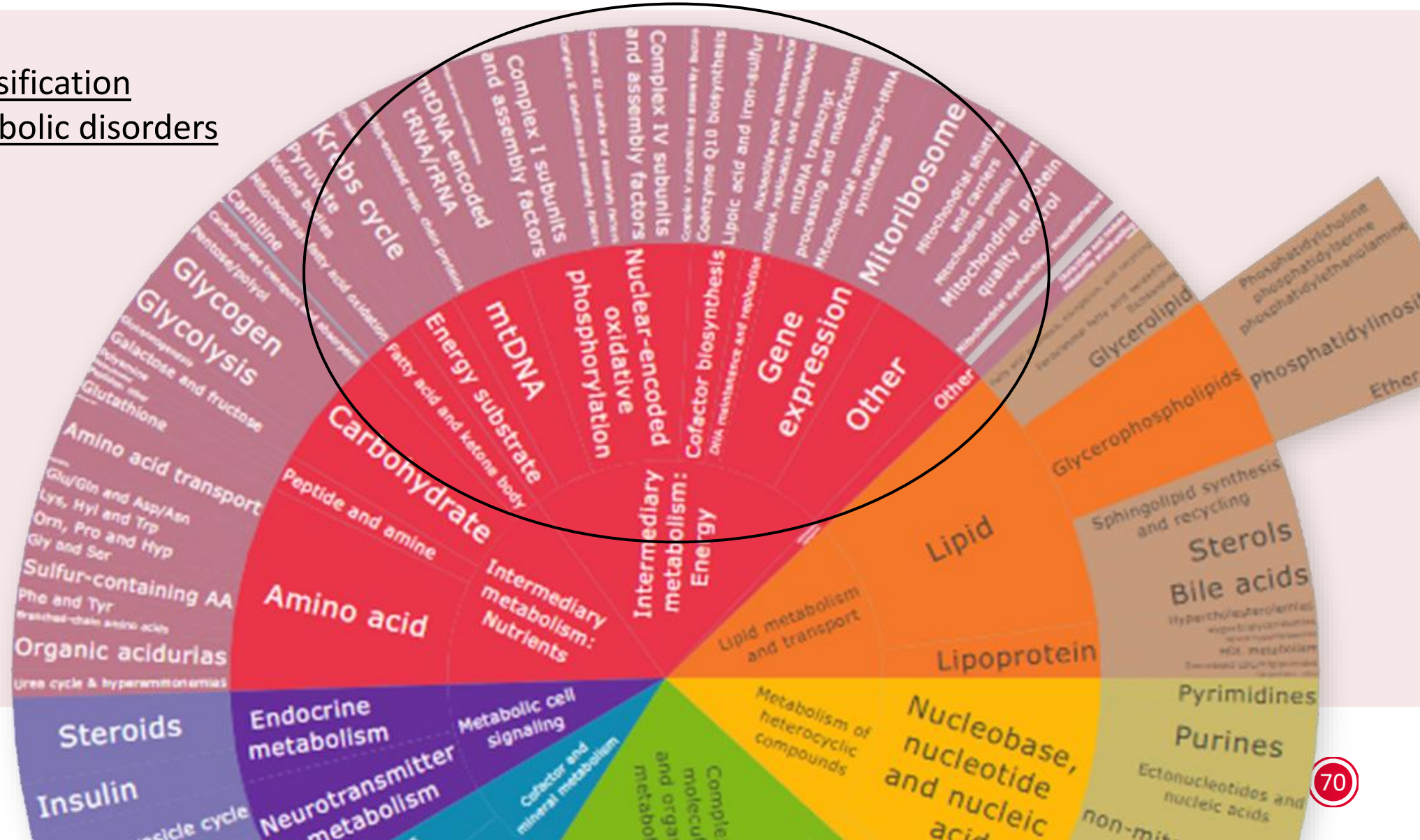
- International classification of inherited metabolic disorders



Mitochondrial disease is caused by mutations in either mitochondrial or nuclear DNA

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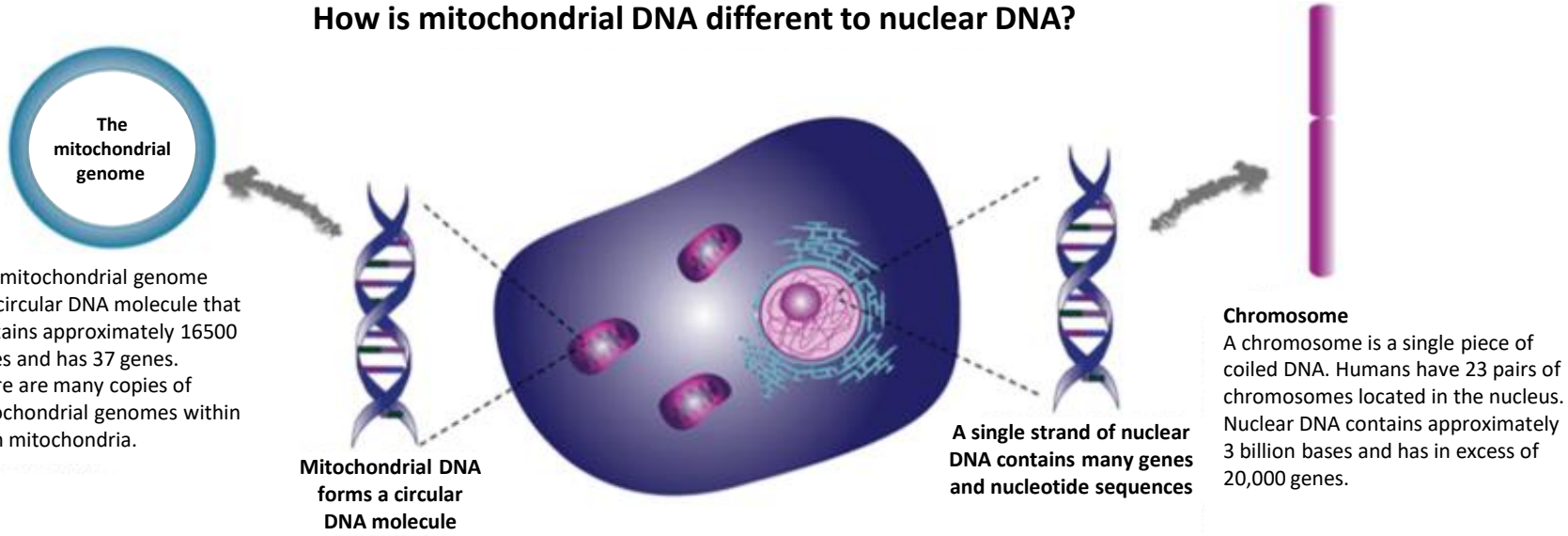
How is mitochondrial DNA different to nuclear DNA?



The mitochondrial genome is a circular DNA molecule that contains approximately 16500 bases and has 37 genes. There are many copies of mitochondrial genomes within each mitochondria.

Mitochondrial DNA forms a circular DNA molecule

A single strand of nuclear DNA contains many genes and nucleotide sequences

Chromosome
A chromosome is a single piece of coiled DNA. Humans have 23 pairs of chromosomes located in the nucleus. Nuclear DNA contains approximately 3 billion bases and has in excess of 20,000 genes.

mtDNA disorders:

- Typically adult onset (~50–70% mtDNA)

Recessive nuclear DNA disorders

- Typically pediatric onset (~75–90% nDNA)

Regina’s story

- **Diagnosis:** mitochondrial DNA myopathy (m.8344A>G)
- **Family history:** Brother and son with a very similar presentation. Daughter with a milder phenotype
- **Symptoms:** SNHL (using hearing aids), myoclonus, ataxia, dysarthria, ptosis, proximal myopathy, lipomatosis
- **Treatments:** exercise, dietary supplements
- **Impacts on daily life:** decreased mobility, inability to work, inability to do house chores, inability to socialize

Path to mitochondrial disease diagnosis (video 1)

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The videos featured can be viewed in the recording of the live event,
which can be accessed here: https://www.pharming.com/pharming-investor-day-2026

Impact of mitochondrial disease (video 2)

The videos featured can be viewed in the recording of the live event,
which can be accessed here: https://www.pharming.com/pharming-investor-day-2026

Multifactorial diagnostic evaluation centered around genetic testing

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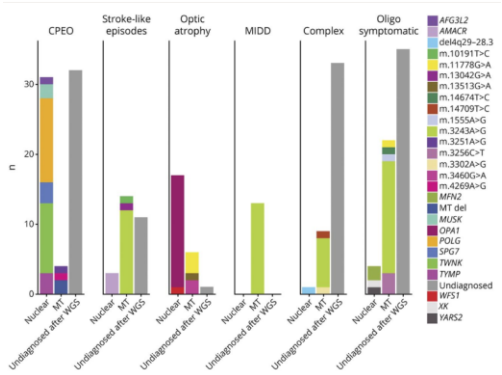
Genetic Testing

- mtDNA sequencing
- Nuclear panels
- WES
- WGS



Davis et al. Neurology. 2022 Aug 16;99(7)

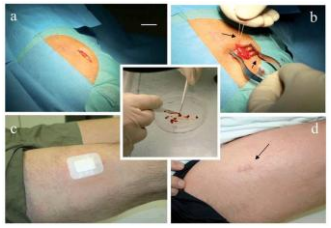
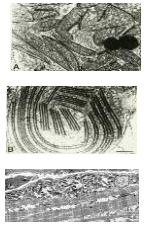
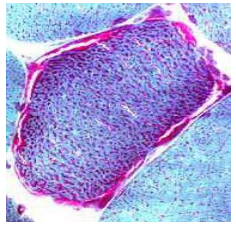
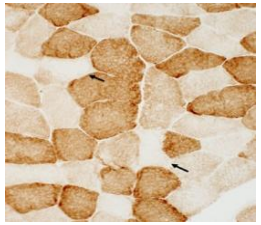
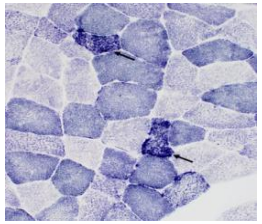
Biochemistry

- Lactate, pyruvate
- CPK, aldolase
- GDF-15/FGF-21
- Metabolic profiling



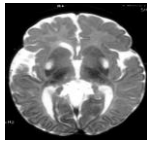
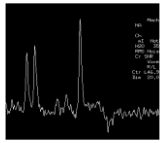
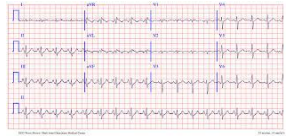
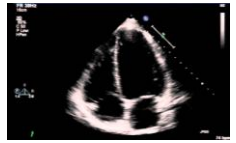
Tissue pathology

- RRF
- COX (-)/SDH (+) fibers
- CoQ10 levels

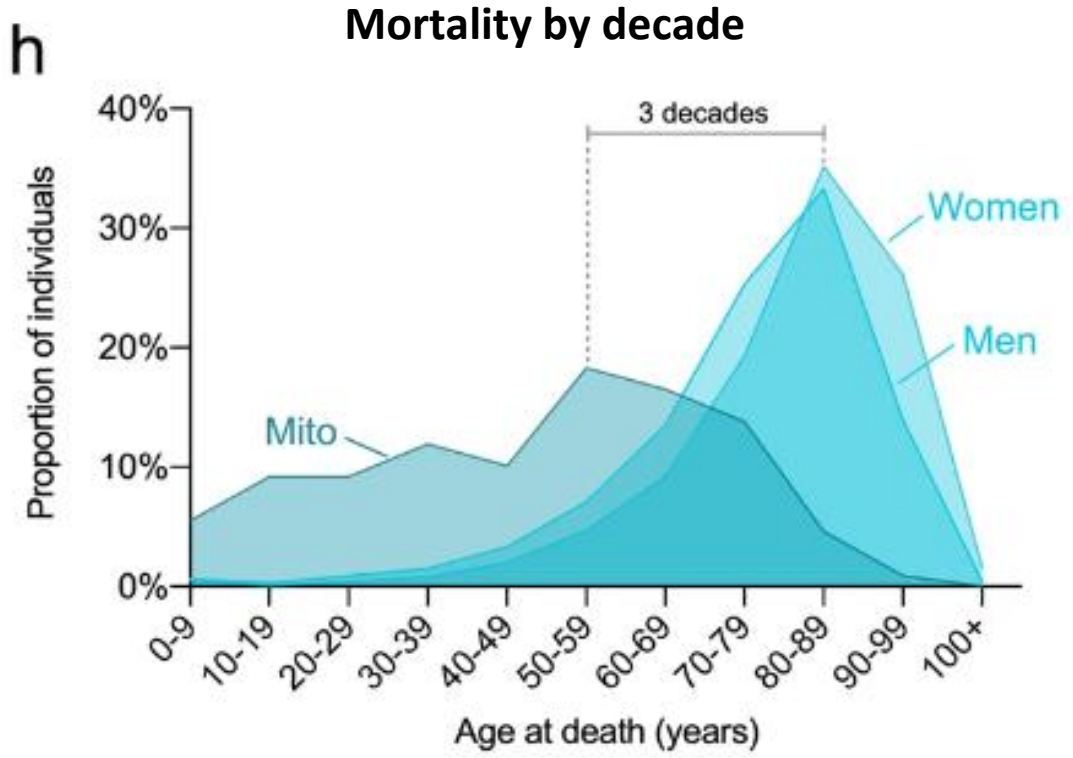






End-Organ Assessments

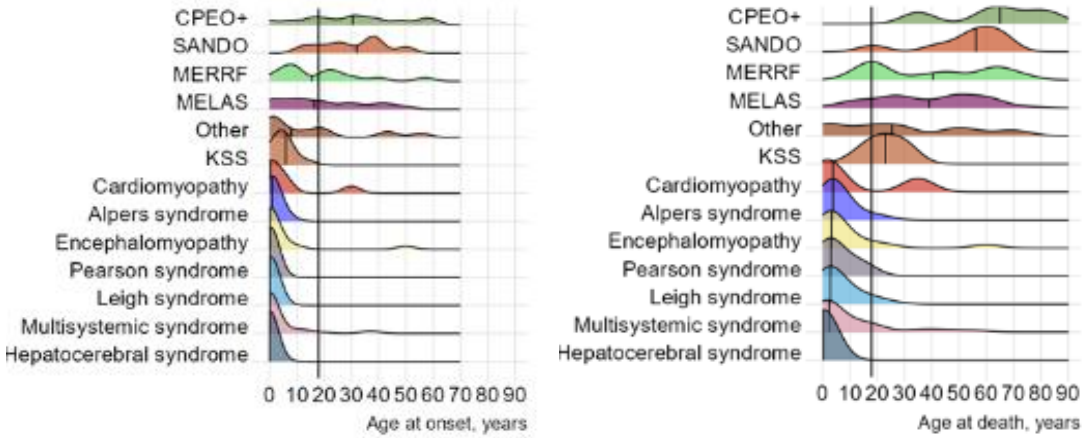
- Heart
- Kidney
- Brain, eye…


Mitochondrial disease is progressive and impacts mortality over the course of life

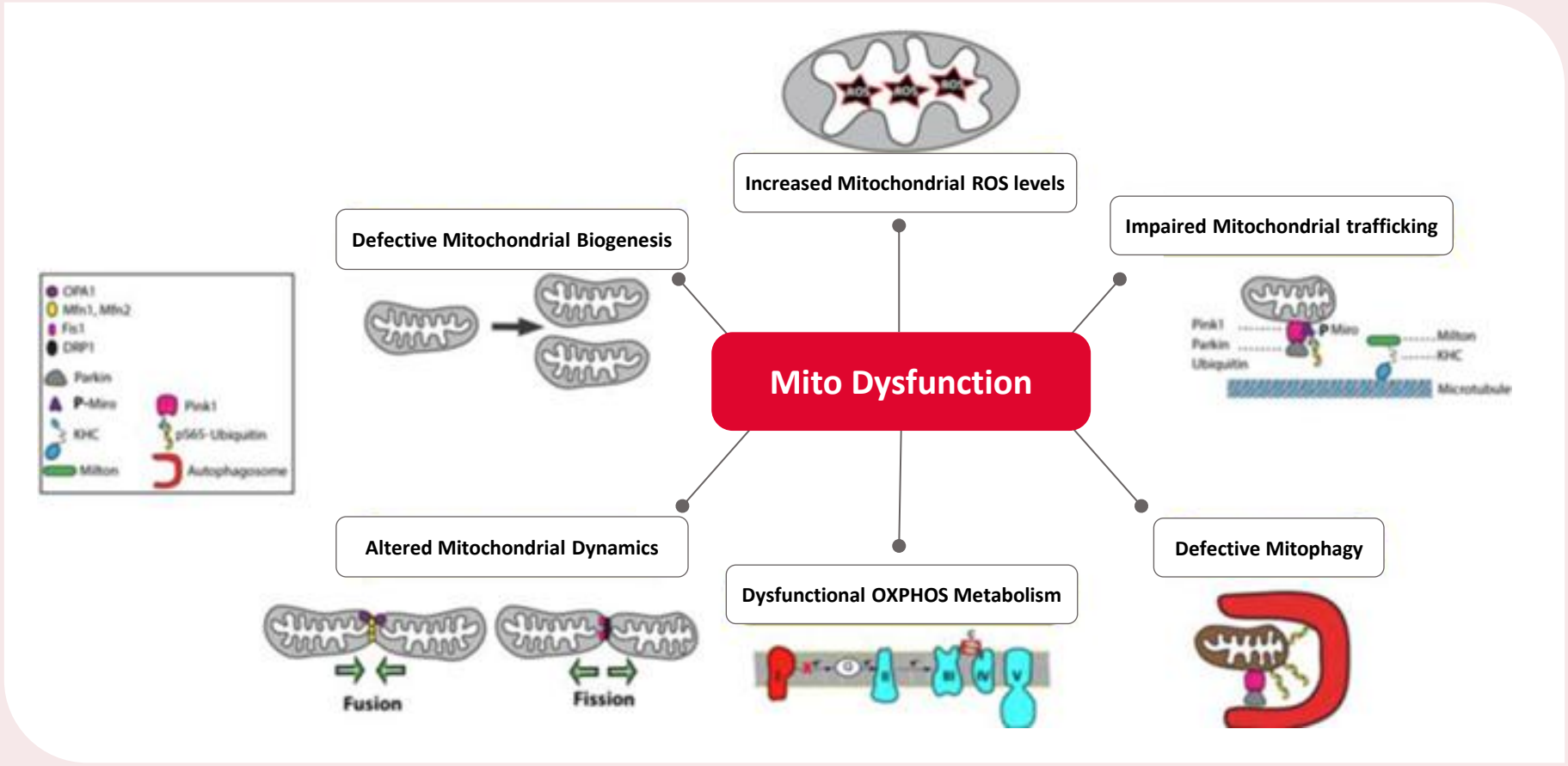


Commun Biol 6, 22 (2023)



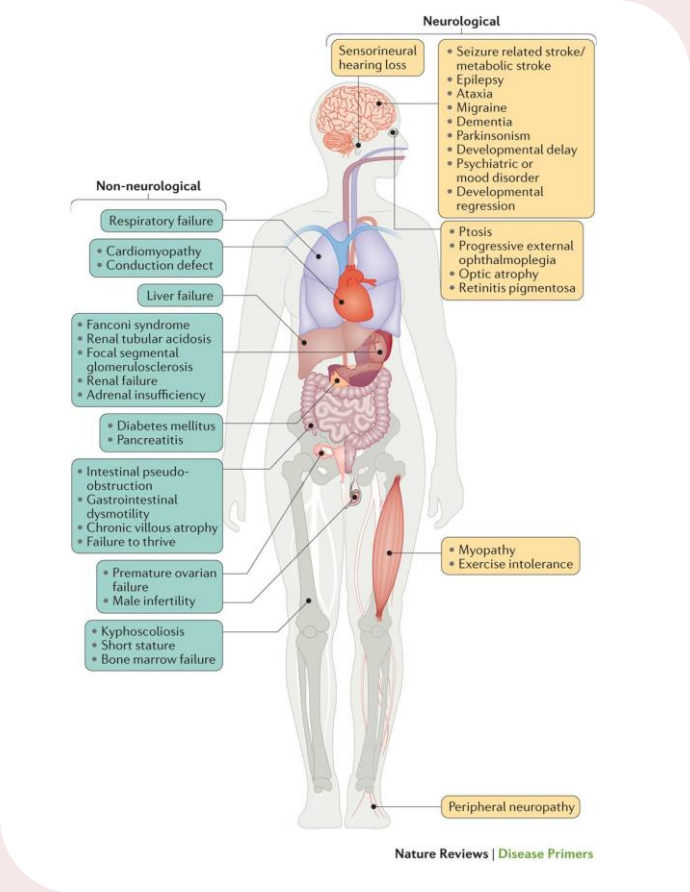
Ivaniuk et al. Neurology 2025 Feb 25;104(4):e209779

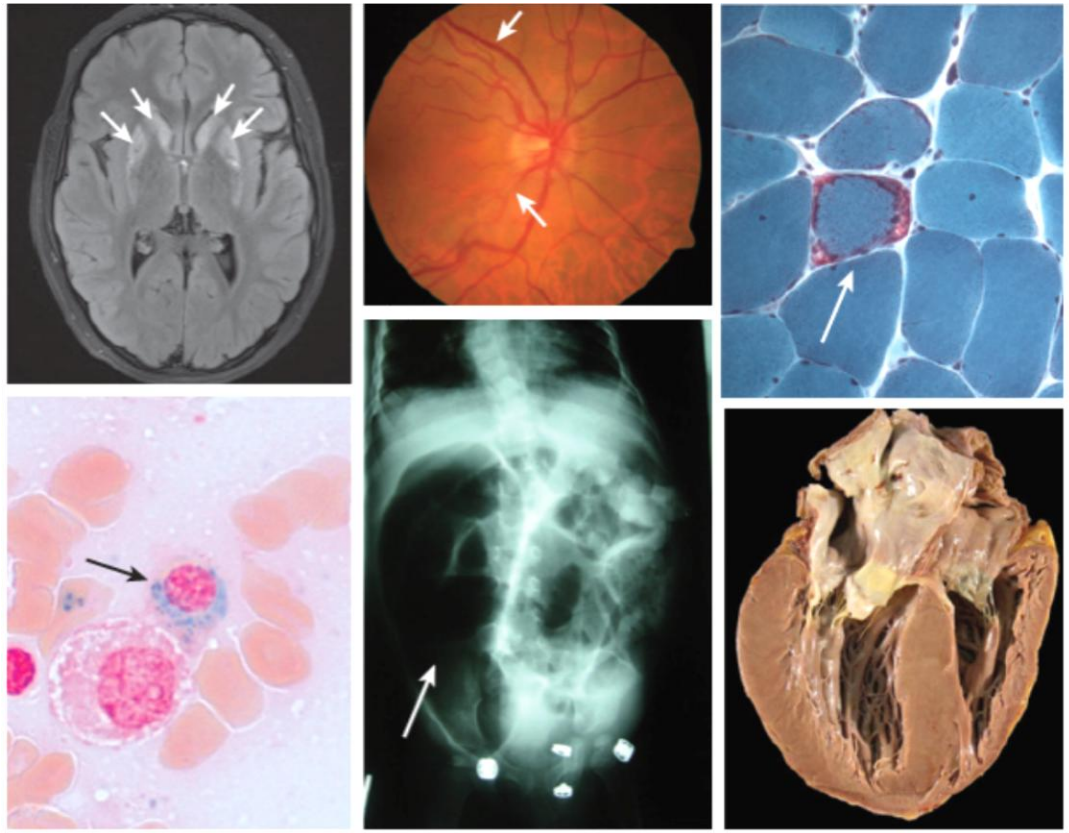
Mitochondrial disease impairs mitochondrial function



Li et al. Metabolites. 2021 Apr 10;11(4):233. PMID: 33920115

Mitochondrial diseases have diverse clinical implications





Vafai and Mootha, Nature 2012

Mitochondrial disease symptoms

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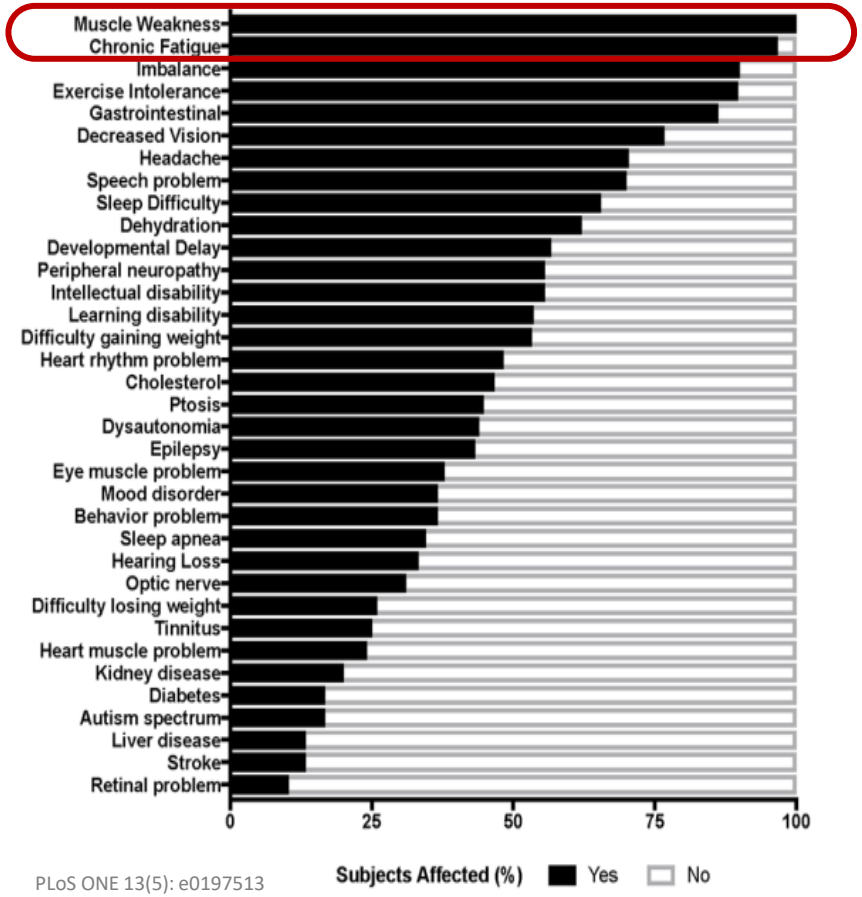
- **Muscle weakness and debilitating fatigue** are among the most frequently reported mitochondrial disease symptoms in adults across studies
  - Two of the highest frequency symptoms in the North American Disease Consortium (NAMDC) registry*
  - Two most frequent and prioritized symptoms by patients for trial participation in the NIH Rare Disease Clinical Research Network (RDCRN) PMD cohort**



PLoS ONE 13(5): e0197513

*A. Karaa et al. / Molecular Genetics and Metabolism 119 (2016) 100–108
**Zolkipli-Cunningham et al. PLoS ONE 13(5): e0197513

Fatigue in mitochondrial disease has a high impact on quality of life and functional abilities

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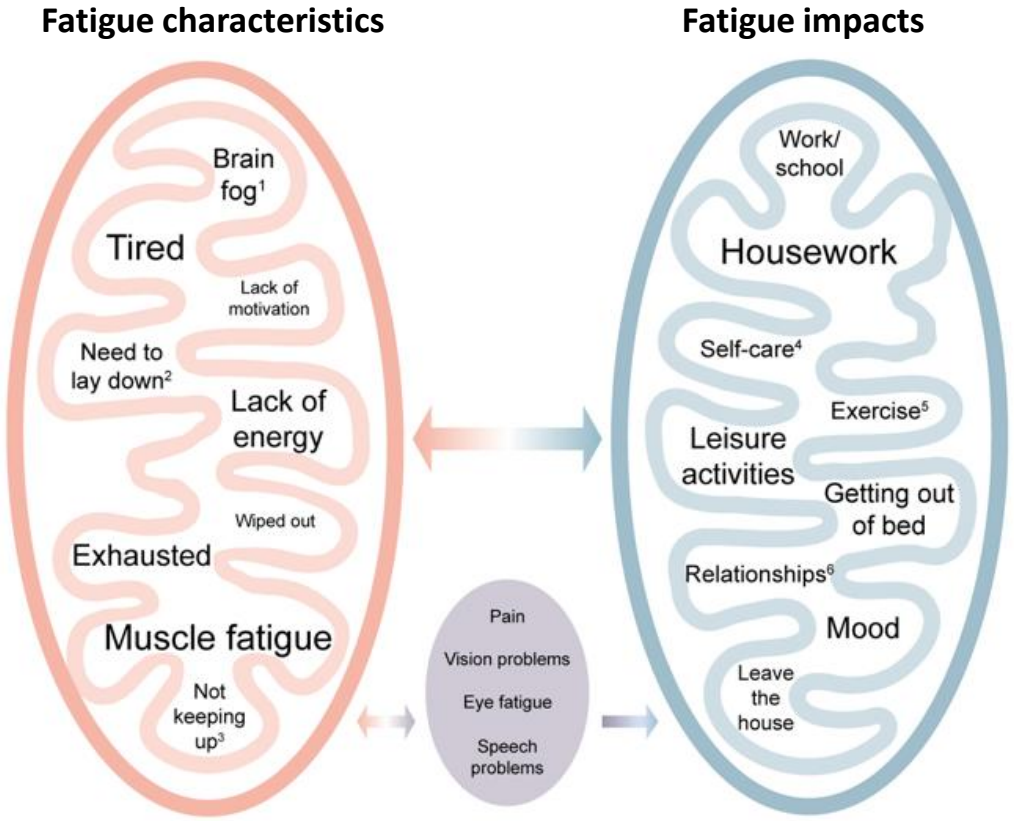

PROMIS® Fatigue Mitochondrial Disease Short Form

- Validated scale to assess mitochondrial disease fatigue symptoms and impacts on daily life

In the past 7 days…	Never	Rarely	Some times	Often	Always
How often did you experience extreme exhaustion?	☐	☐	☐	☐	☐
How often did you run out of energy?	☐	☐	☐	☐	☐
How often did you feel tired?	☐	☐	☐	☐	☐
How often were you too tired to enjoy life?	☐	☐	☐	☐	☐
How often did you have to push yourself to get things done because of your fatigue?	☐	☐	☐	☐	☐
How often were you too tired to do your household chores?	☐	☐	☐	☐	☐
How often were you too tired to take a bath or shower?	☐	☐	☐	☐	☐
How often were you too tired to leave the house?	☐	☐	☐	☐	☐
How often were you too tired to think clearly?	☐	☐	☐	☐	☐

S. Clifford… A. Karaa. Molecular Genetics and Metabolism, 145(4) 2025, 109153.

Mitochondrial disease is a common uncommon disease

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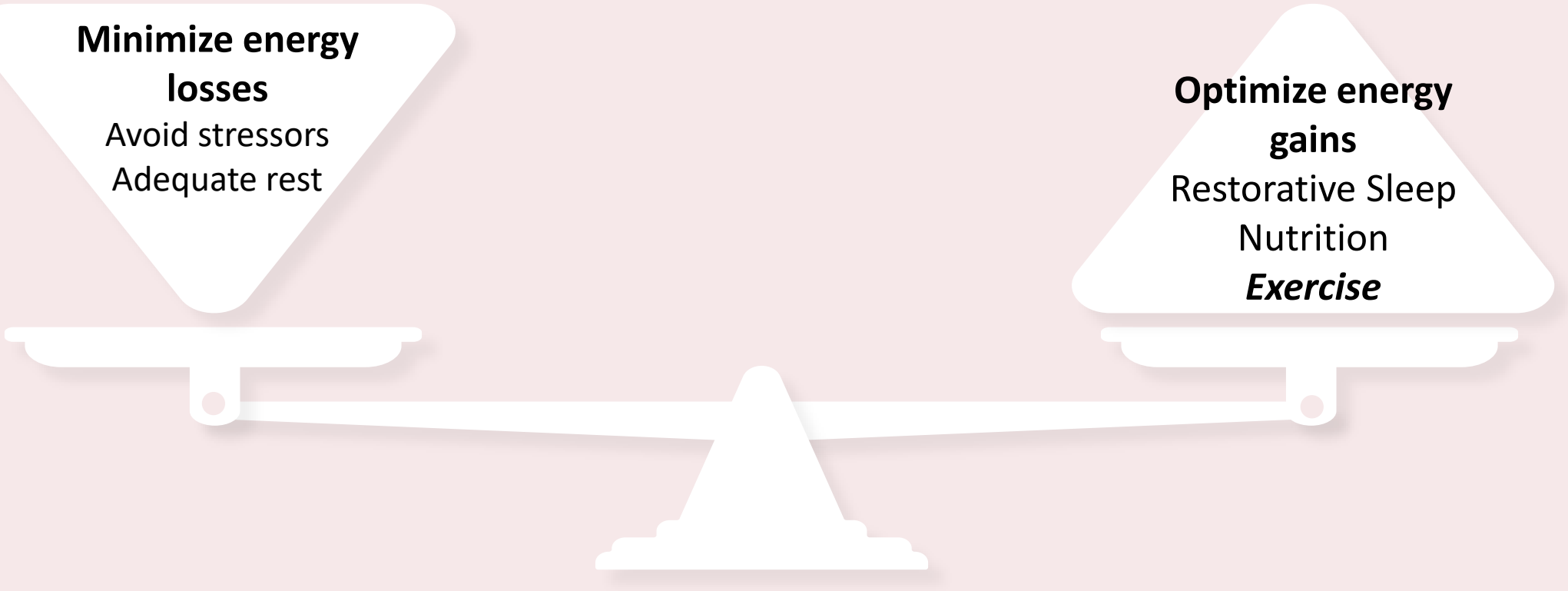
Category	Estimated Worldwide Count
Pathogenic mtDNA variant carriers (genetic)	~32–40 million
Clinically manifest mtDNA disease (all variants)	~0.8–1.6 million
Clinically manifest m.3243A>G disease	~300,000–400,000
Clinically manifest single large-scale deletion disease	~100,000–150,000

Disease prevalence studies:
1. Mitochondrion, 2007; (7), Issue 3:230-233. 2. ANN NEUROL. 2015;77:753–759. 3. PLOS ONE. 2022; 17(4): e0265744. 4. Orphanet J Rare Dis. 2023; 18, 43.
5. J Epidemiol. 2023; 5;33(2):68-75. 6. BMJ Neurology Open. 2024;6:e000546. 7. Internal Medicine Journal. 2024; 54:388–397

Limited treatment and management options



A range of potential therapeutic approaches

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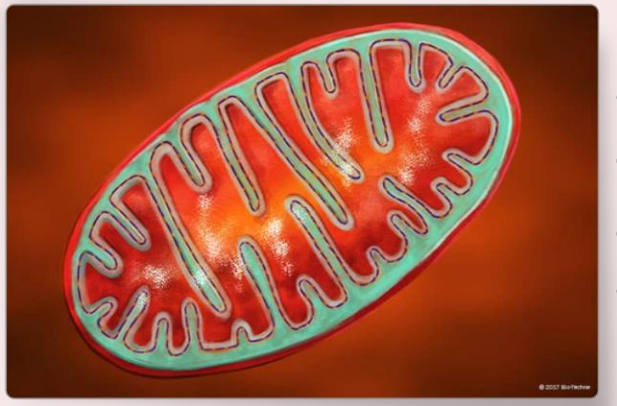
Antioxidants/RedOx
Idebenone
PTC743 (EPI734)
Sonlicromanol
OMT-28

Nitric Oxide modulators
L-citrulline
L-arginine
IW-6463
Sildenafil

Targets of Mitophagy
API-009
Rapamycin

Membrane stabilizers
Elamipretide



Targets of Biogenesis
NAD⁺/NADH ratio modulation
KL1333
Resveretrol
Nicotinic acid, Nicotinamide
Nicotinamide riboside
Acipimox

Gene transcription
Omaveloxolone
REN001
ASP0367
Bezafibrates
AICAR

Miscellaneous
Dichloroacetate
Sodium Phenylbutyrate
CD34+ MNV-BLD
Mitochondrial transplant

Enzyme Bypass
MT-1621 (dC+dT)

Gene Therapy
Lenti-TYMP
AAV2/8-ETHE1
AAV2/8-MPV17
AAV2/9-NDUFS4
AAVPhP.B-Scl25a46
AAV9-ndufs3

rAAV2/2-ND4
scAAV2-P1ND4
AAV9-ZnF (m.5024C>T)
AAV9-MITOTALEN (m.5024C>T)
MitoArcus

Two recent approvals in ultra rare subsets of mitochondrial disease

An official website of the United States government Here's how you know

U.S. FOOD & DRUG ADMINISTRATION

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Home / News & Events / FDA Newsroom / Press Announcements / FDA Grants Accelerated Approval to First Treatment for Barth Syndrome

FDA NEWS RELEASE

FDA Grants Accelerated Approval to First Treatment for Barth Syndrome

New Treatment for Barth Syndrome Showcases FDA's Commitment to Bringing Effective and Safe Medications to Patients in Need

More Press Announcements

For Immediate Release: September 19, 2025

Today, the U.S. Food and Drug Administration granted accelerated approval to Forzinity (elamipretide) injection as the first treatment for Barth syndrome, in patients weighing at least 30 kg. Barth syndrome is a rare, serious and life-threatening disease of the mitochondria (the energy-producing parts of cells).

An official website of the United States government Here's how you know

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Home / Drugs / News & Events for Human Drugs / FDA approves 1st drug for thymidine kinase 2 deficiency, a very rare mitochondrial disease

FDA approves 1st drug for thymidine kinase 2 deficiency, a very rare mitochondrial disease

News & Events for Human Drugs

Meetings, Conferences, & Workshops

Q&A with FDA Podcast

CDER Conversations

From Our Perspective

Spotlight on CDER Science

Action

The U.S. Food and Drug Administration (FDA) approved Kygevvi (doxecitine and doxribtimine) powder to treat thymidine kinase 2 deficiency (TK2d) in adults and pediatric patients who start to show symptoms when they are 12 years old or younger. Kygevvi received Breakthrough Therapy Designation for this indication.

Disease or Condition

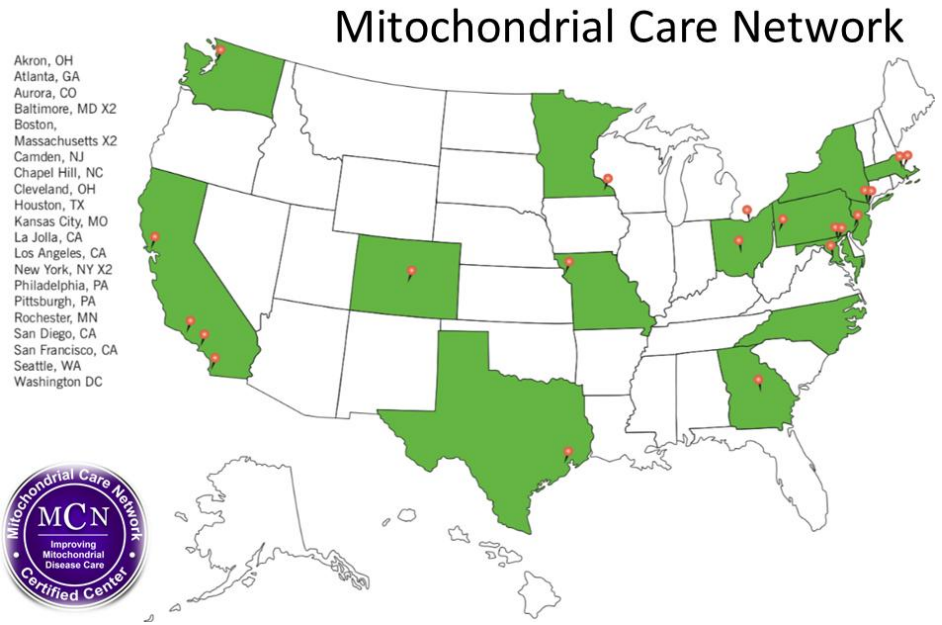
TK2d is a rare, inherited genetic disorder that affects the body's ability to produce and repair mitochondrial DNA (mtDNA). Conditions that cause low levels of mtDNA, including TK2d, can be called mitochondrial depletion syndromes. Symptoms of TK2d can include muscle weakness and respiratory (breathing) failure. While the exact frequency of TKd2 is not known, it is considered very rare. Approximately 120 patients have been described in the medical literature, although the condition may be underdiagnosed.

Content current as of: 11/03/2025

Regulated Product(s) Drugs

Feedback

Established US mitochondrial community



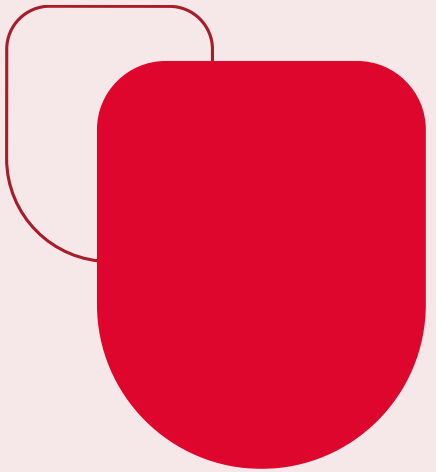
Centers of excellence and expert networks in US

- Mitochondrial Care network
- Mitochondrial Medicine Society
- North American Mitochondrial Disease Consortium
- TREAT MITO

US Patient Organizations

- Driving awareness, research, educations and support
- Patients, health care professionals and research audiences
- Annual disease conferences – Monthly education series
- Disease registries - Natural history studies
- Patient support programs
- Research funding
- Sponsored genetic testing programs

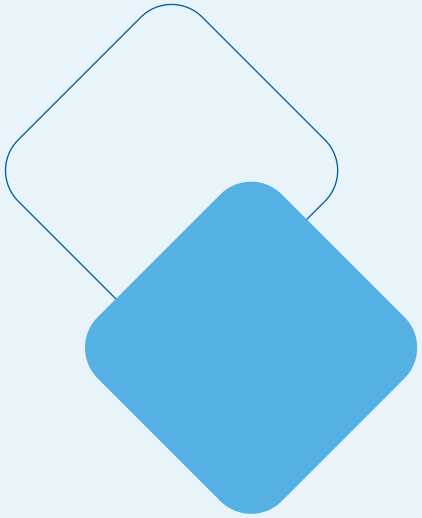
Thank you



Napazimone (KL1333) for primary mitochondrial disease

Magnus Hansson, MD, PhD

Executive Medical Director



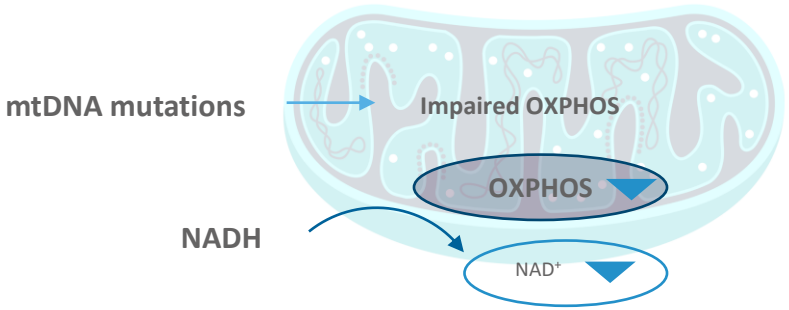
Disclaimer

Napazimone (KL1333) is investigational drug and has not been approved for use by any regulatory authority. Its safety and efficacy have not been established, and it is currently under clinical evaluation.

There is no guarantee that this drug will receive regulatory approval or become commercially available.

Napazimone (KL1333) designed to target the underlying pathology in mtDNA mitochondrial disease

Dysfunctional mitochondria

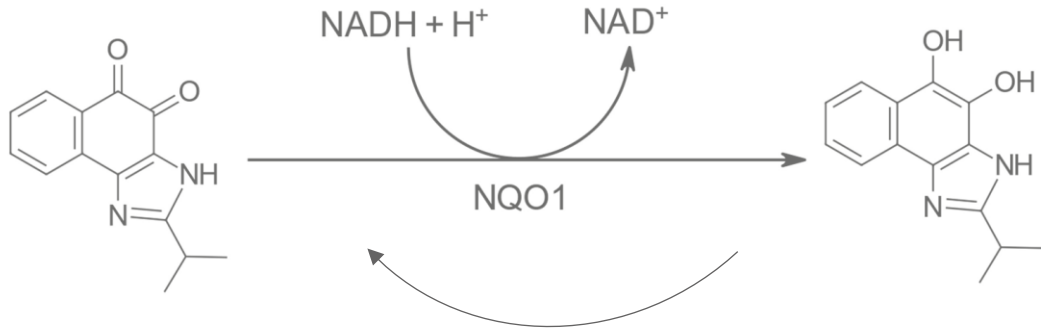


Low NAD^+/NADH ratio

Decreased energy production and decreased mitochondrial biogenesis

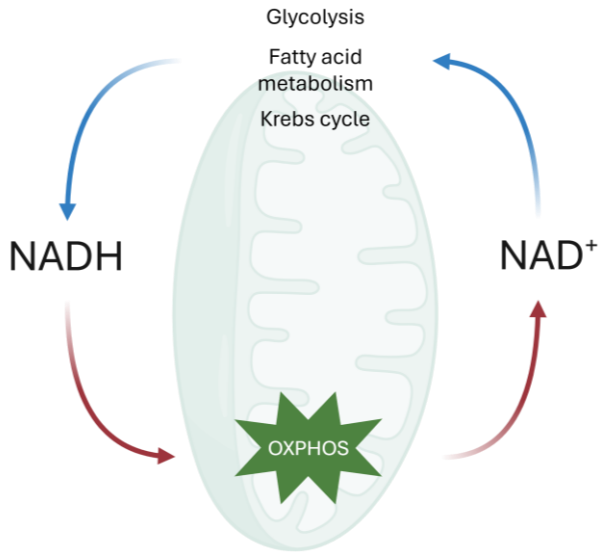
Debilitating symptoms such as fatigue and muscle weakness significantly impairing activities of daily living

Napazimone (KL1333) is designed to target the underlying pathology by restoring NAD+/NADH ratio:

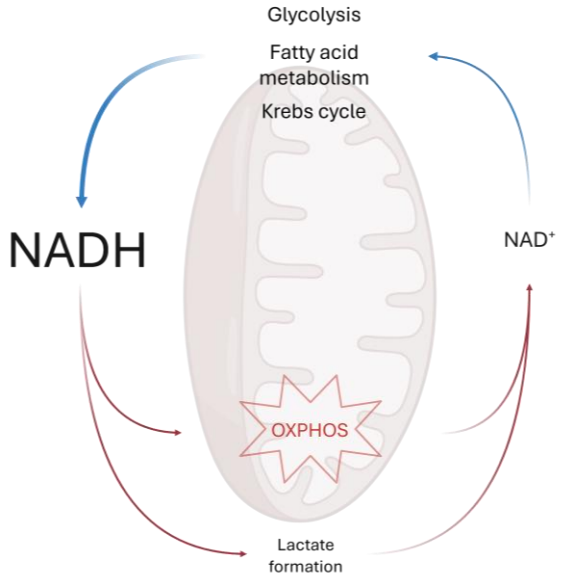


Napazimone (KL1333) is designed to restore NAD+/NADH ratio and energy production

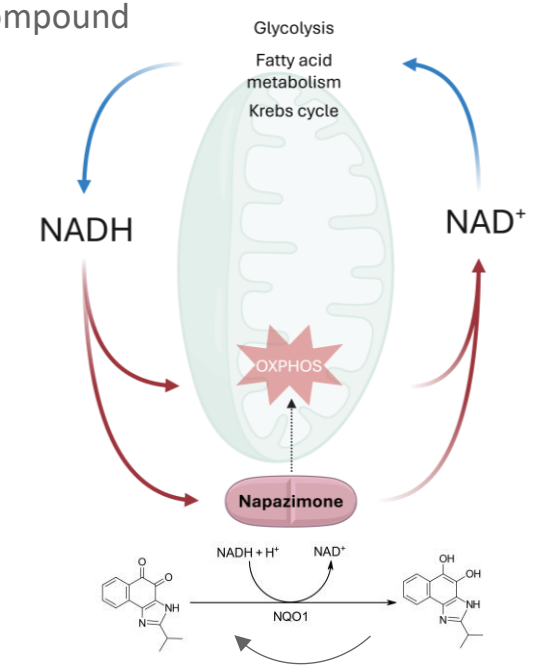
Normal cellular energy production is regulated by the balance of NAD^+/NADH



In **mitochondrial disease**, pathogenic variants in mtDNA impact OXPHOS complex synthesis and function, leading to altered NAD^+/NADH ratio and reduced energy production

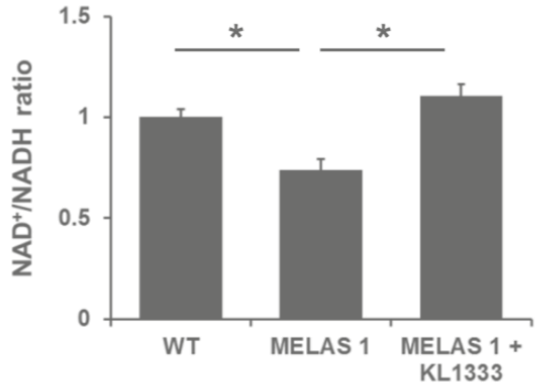


Napazimone (KL1333) is designed to restore energy production via facilitating the conversion of NADH to NAD^+ and stimulating ATP synthesis through a redox cycling of the compound



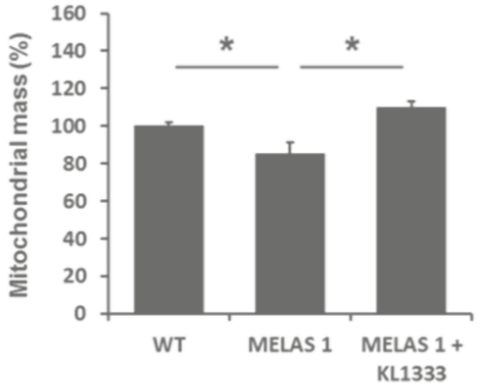
1. Seo et al. 2018. KL1333, a Novel NAD+ Modulator, Improves Energy Metabolism and Mitochondrial Dysfunction in MELAS Fibroblasts (https://www.frontiersin.org/articles/10.3389/fneur.2018.00552/)

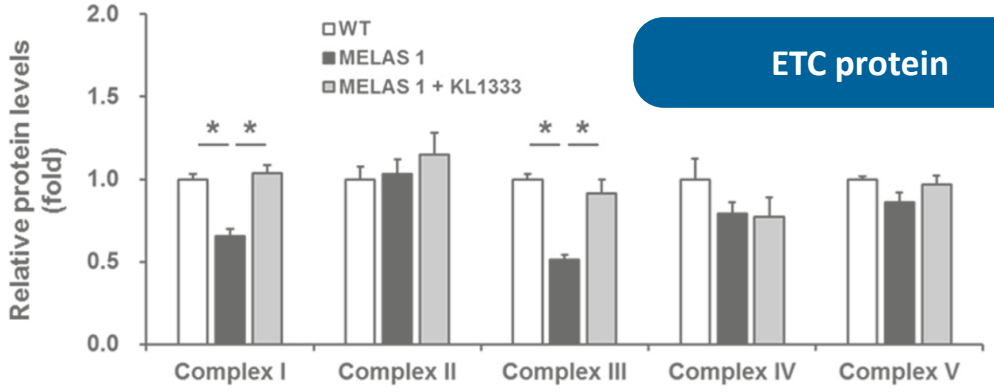
In vitro, napazimone (KL1333) restores NAD+/NADH ratio and mitochondrial biogenesis in MELAS patient fibroblasts



NAD+/NADH ↑

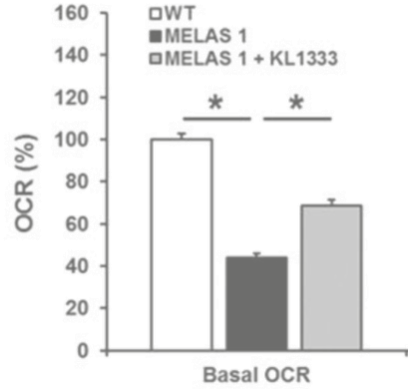
Mitochondrial mass ↑





ETC protein ↑

ETC activity ↑

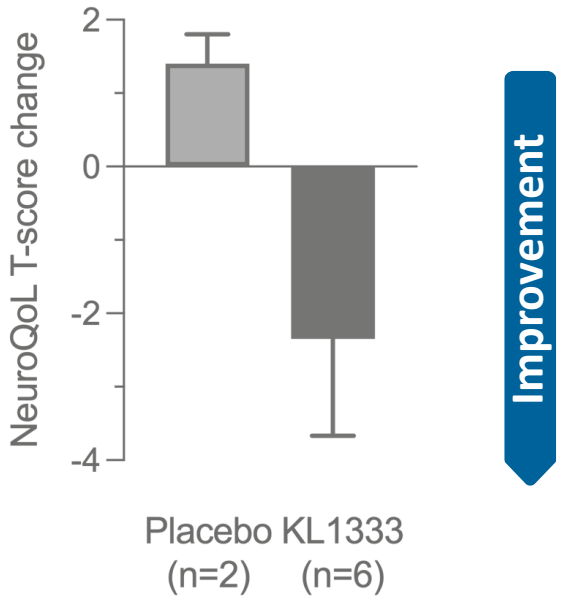


Seo et al. 2018. KL1333, a Novel NAD+ Modulator, Improves Energy Metabolism and Mitochondrial Dysfunction in MELAS Fibroblasts (https://www.frontiersin.org/articles/10.3389/fneur.2018.00552/)

In a phase Ia/b study, napazimone (KL1333) demonstrated positive changes in outcome measures

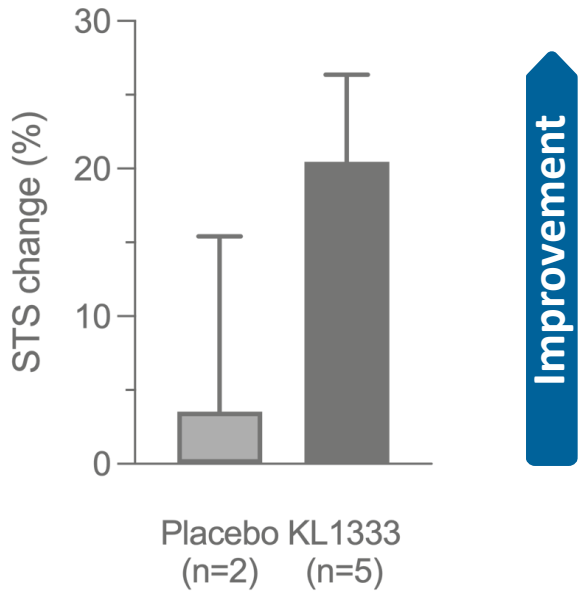
Reduction of fatigue

Changes from baseline to day 10[1]



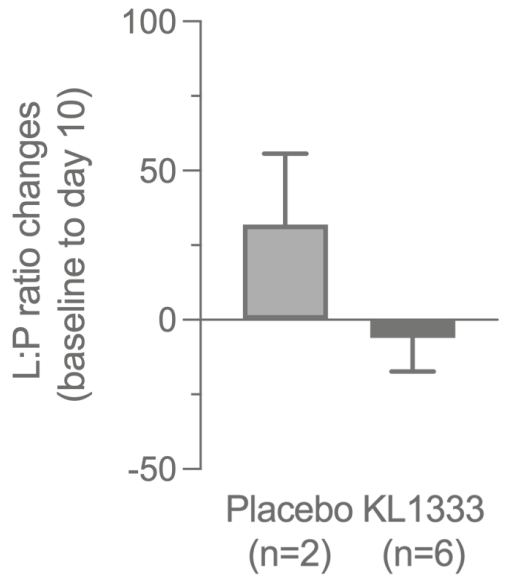
Improvement in muscle function

Changes from baseline to day 10[1]



Biomarker changes

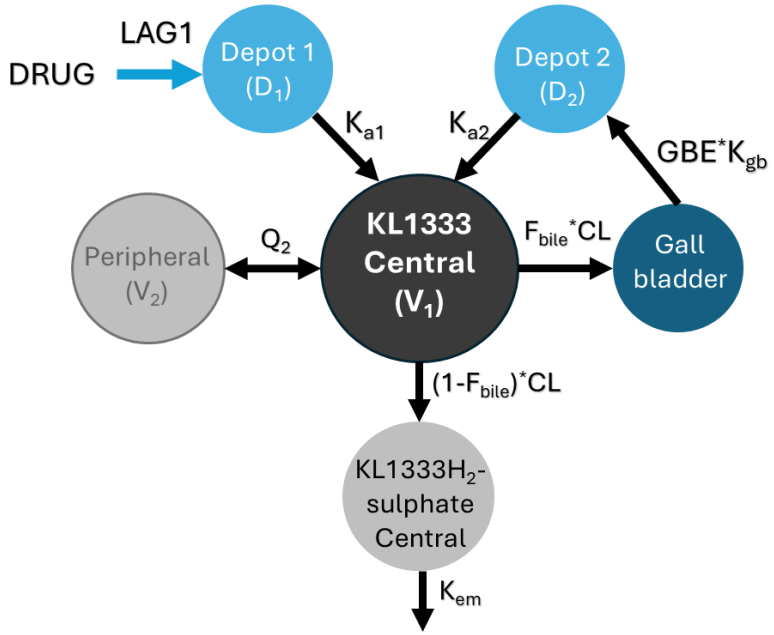
Lactate: Pyruvate ratio[1]



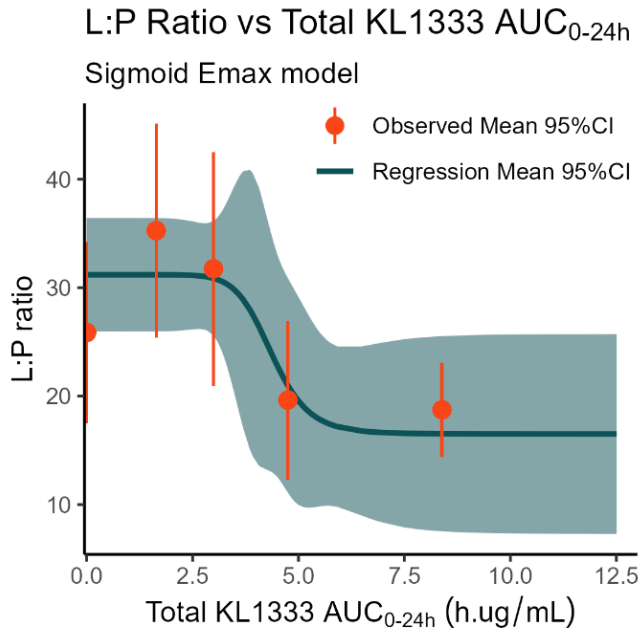
1. Pizzamiglio C et al., Optimizing rare disorder trials: a phase 1a/1b randomized study of KL1333 in adults with mitochondrial disease, Brain 2025;148(1):39-46 https://pmc.ncbi.nlm.nih.gov/articles/pmid/39657714/

Napazimone (KL1333) effects on disease biomarkers demonstrate target engagement at anticipated exposure levels

A PopPK model was developed from 3033 observations in 42 healthy participants and 6 patients with PMD in phase 1a/b study KL1333-2018-102



KL1333 Exposure and changes in lactate and lactate: pyruvate ratio had a clear exposure-response relationship



Ching et al. PoP-PK and exposure response analysis, presented at Mitochondrial Disease Conference, Pisa, Italy Jan 23-25 2026

Napazimone (KL1333) MoA has the potential to address high unmet need of mtDNA mitochondrial disease

HCPs n=16 (US)

"Most patients, unfortunately, don't have a cure. They have **a way of dealing with the issue** but not necessarily reversing the problem. It affects patients both physically, but also cognitively and psychologically."

- Endocrinologist

Napazimone (KL1333) pivotal study program targets a specific but common subset of adult Mitochondrial Disease which can be diagnosed with a genetic test

International Classification of Inborn Metabolic Disorders (ICIMD)	
ICIMD category	**Category 6 – Mitochondrial DNA-related disorders** • Impairs OXPHOS function
mtDNA mutations causing multisystemic disease include	• m.3243A>G • single large-scale mtDNA deletions, • m.8344A>G • similar pathogenic point mutations in mtDNA

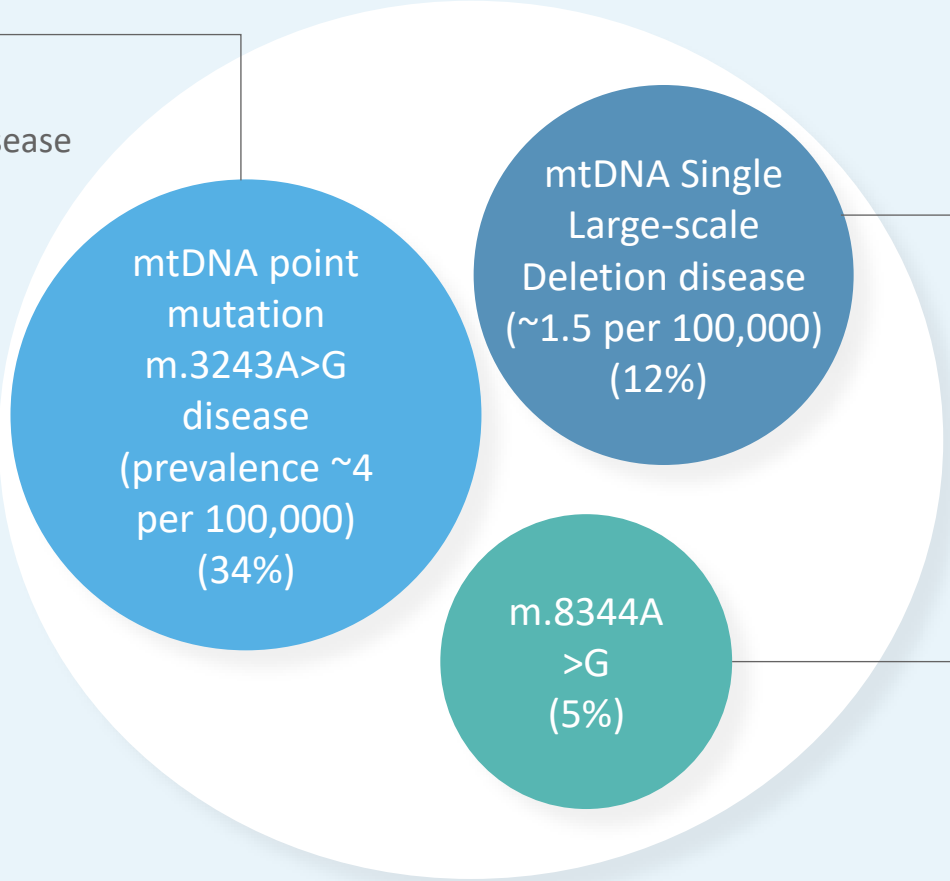
http://www.icimd.org/

mtDNA variants targeted in pivotal program cause the majority of adult disease

Three pathogenic variants of mtDNA causes >50% of adult mitochondrial disease

m.3243A>G caused disease accounts for about 35% of all adult mitochondrial disease

- Most patients have mixed phenotypes, with myopathy and fatigue
- A small proportion of patients have stroke-like episodes (=MELAS syndrome)
- Mitochondrial diabetes and hearing loss are also common symptoms (=MIDD)



The **Single Large-Scale Deletion** of mtDNA is the second most common genetic cause for adult disease

- Typically causes the CPEO-KSS spectrum of disease
- Myopathy and fatigue are common symptoms

m.8344A>G is typically the cause of

- MERFF (Myoclonal Epilepsy with Ragged Red Fibers)
- Myopathy and fatigue are common

Abstract presented at:

Mitochondrial Medicine – Therapeutic Development

21 -23 November 2022

Wellcome Genome Campus, UK and Virtual

1. MitoCohort registry study – Collaboration with Newcastle University. Over 500 adults with active entries over the past 3 years were analyzed

Napazimone (KL1333) clinical trial design to enable first-in-class treatment

Phase I a/b study[1]

- Randomized, blinded, placebo-controlled patient cohort
- 8 patients with genetically confirmed PMD
- 10 days
- 50 mg qd
- Target engagement and notable improvements on exploratory Myopathy and Fatigue assessments

Pivotal FALCON Trial - Efficacy & safety evaluation[2]

- Randomized, blinded, placebo-controlled
- 180 patients with mtDNA-caused PMD (60% KL1333, 40% placebo)
- 48 weeks
- 25-50 mg bid
- Two alternate primary efficacy end points
  - Change from baseline in PROMIS Fatigue (validated for PMD3)
  - 30 Second Sit-to-Stand test
- Interim analysis by IDMC
  - Positive outcome - both primary endpoints passed futility, acceptable safety and tolerability profile

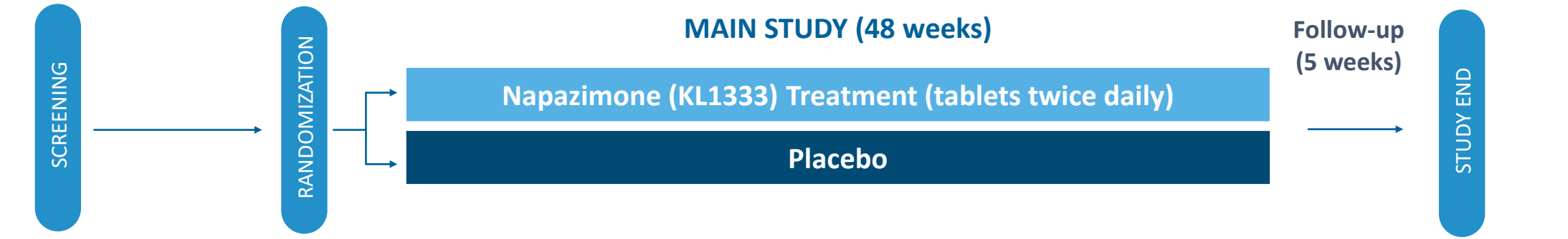
Open-label extension study

- Nonrandomized, open-label, long-term study
- Open to all patients completing FALCON pivotal study
- Potential expansion following completed FALCON recruitment
- Initiating Q2 2026
- 25-50 mg bid
- Long-term safety, tolerability, and efficacy

qd, once a day; bid, twice a day; PMD, primaphosphoinositide 3-kinase delta; SPD, sum of product diameters

1. Pizzamiglio C et al. Optimizing rare disorder trials: a phase 1a/1b randomized study of KL1333 in adults with mitochondrial disease, Brain, 2025, 148(1):39-46. 2. ClinicalTrials.gov https://clinicaltrials.gov/study/NCT05650229 3. Clifford et al. Qualitative study of fatigue in adults with primary mitochondrial disease: Development of the PROMIS Fatigue Mitochondrial Disease Short Form. Molecular Genetics and Metabolism, 2025, 145(4):109153.

Pivotal FALCON study design de-risks program



1. Extended run-in period during patient screening to ensure symptom severity and stability

2. Evaluate the safety profile and the potential of both primary endpoints to be successful of after 24 weeks of dosing

3. Two alternative primary endpoints:
Study is positive if either, or both, demonstrate benefit**

- **PARTICIPANTS:** Adult Primary Mitochondrial Disease patients **(mtDNA mutations*)** with **myopathy** and **fatigue**
- **DESIGN:** Randomized, double-blind, parallel-group, placebo-controlled (40% placebo, 60% active)
- **ALTERNATIVE PRIMARY ENDPOINTS:** PROMIS® Fatigue Mitochondrial Disease Short Form, 30 Second Sit-to-Stand test

*Including **m.3243A>G** associated spectrum disease, **single large scale mtDNA deletion** disorders, **m.8344A>G** and other multisystemic mitochondrial DNA-related disease.
**Hochberg step-up procedure – statistical method for multiple hypotheses

Interim analysis results further de-risked pivotal study

Positive outcome achieved, with both primary endpoints having passed futility

- Promising differences favoring the active arm vs. placebo for both primary efficacy endpoints; if trends continue consistently, we expect a successful result at the completion of this trial

- Data monitoring committee (DMC) recommended continuing with wave 2:
  - Safety and tolerability profile acceptable
    - No safety signals in labs, vital signs or ECGs
    - Adverse Event (AE) profile consistent with benign profile seen in phase 1 studies
    - No drug-related Serious Adverse Events (SAEs) to date
  - No changes to study design
  - 180 total patients confirmed in the study

Napazimone (KL1333) has demonstrated a benign safety profile in phase 1 studies and FALCON wave 1

Phase 1 Single Ascending Dose study (101)

- No Serious Adverse Events (SAEs)
- Mild dose-dependent gastrointestinal (GI) AEs at high doses

Phase 1 Drug-Drug Interaction study (103)

- Weak inhibitor of CYP1A2
- Negligible effects on other CYP450 substrates

Phase 1 a/b Multiple Ascending Dose study (102)

- Healthy volunteers and patients – similar PK and safety profile
- No Serious Adverse Events; No safety signals
- Tolerability at higher doses limited by mild-moderate GI-related side effects – improved by dividing the dose

Pivotal FALCON study (104A) Wave 1 (w48)

- No safety signals in labs, vital signs or ECGs
- No drug-related SAEs
- Adverse Event (AE) profile consistent with benign profile seen in phase 1 studies

Incorporating lessons learned from previous programs

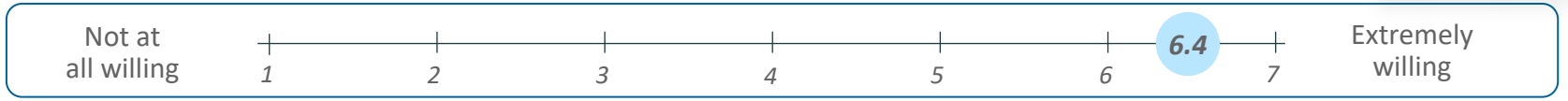
Previous studies likely failed due to mechanism of action not targeting a critical underlying cause of disease, using a mixed patient population (e.g., mtDNA + nDNA) or using insensitive endpoints

	Napazimone (KL1333)	Boicedelpar	Mavodelpar	Sonlicromanol	Elamipretide
	Pharming	Astellas	Reneo	Khondrion	Stealth Biotherapeutics
Current status	Pivotal Phase 2 FALCON study (NCT05650229)	Program terminated at Phase 2 (NCT04641962)	Program terminated at Phase III (NCT05267574)	Phase IIb trial failed (NCT04165239)	Phase III failed (NCT03323749)
MOA	NAD^+/NADH modulator	PPARδ agonist	PPARα agonist	Oxidative Stress modulator, Prostaglandin Synthase inhibitor	Cardiolipin stabilizer
Patient population	180 mtDNA disease patients with myopathy and debilitating fatigue	Adults with nuclear DNA and mtDNA mutations with myopathy	200 adult mtDNA patients with myopathy	27 adults with m.3243A>G MELAS spectrum disease	218 adults with nuclear DNA and mtDNA mutations with myopathy
End point(s)	30s Sit-to-Stand (PE) PROMIS Fatigue (PE)	6-minute walk test (PE) Neuro QoL, 5XSTS, MFIS (SE)	12-minute walk test (PE) FACIT Fatigue (SE)	Cognitive function (PE) multiple SE	6 Minute Walk Test (MWT), fatigue score on mitochondrial myopathy symptom assessment
Potential Reasons for failure	**N/A**	• **MoA may not impact underlying disease** • **Mixed population of nuclear and mitochondrial DNA mutations** • **Safety concerns**	• **MoA may not impact underlying disease** • **12-minute walk test was not the right endpoint for patients who have mobility issues and fatigue**	• **Primary endpoint strategy changed between several PoC trials**	• **MoA is not fully clear** • **Mixed population of patients with both nuclear and mitochondrial DNA mutations**
		Terminated	Terminated	Phase 3 study changed endpoint strategy (now similar to FALCON)	Follow-up study with refined patient population – results not reported

Napazimone (KL1333) Target Product Profile based on FALCON study attractive to HCPs and patients

Willingness to prescribe product X

HCPs n=16



- HCPs see **mechanism** as rational and likely to be **efficacious** because of the nicotinamide adenine dinucleotide's role in the respiratory chain
- Perceived as **disease modifying** as a "**mitochondrial supplementation**" to increase function of mitochondria

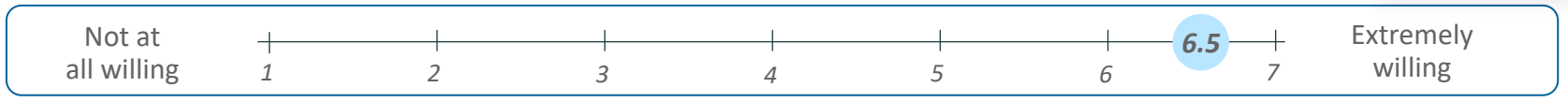
- **Efficacy data is promising for multiple reasons:**
  - **Fatigue** and **myopathy / muscle weakness** are key symptoms for patients, so improvements in those metrics are critical to improve **patient QOL and function**
  - **Lack of approved therapies** increases **enthusiasm** for any option that will improve patient symptoms and / or reduce progression
- Based on level of unmet need in indication, HCPs report **willingness to prescribe with FDA approval**, even with **only one** statistically significant primary endpoint

*"I think it is a **very promising mechanism of action;** it deals with the pathophysiology of the disease. I am impressed with the route of administration.*
I would have expected infusion therapy, which could be a problem."

- Metabolic Disorders Pediatrician

Willingness to speak to HCP about KL1333

Patients n=10



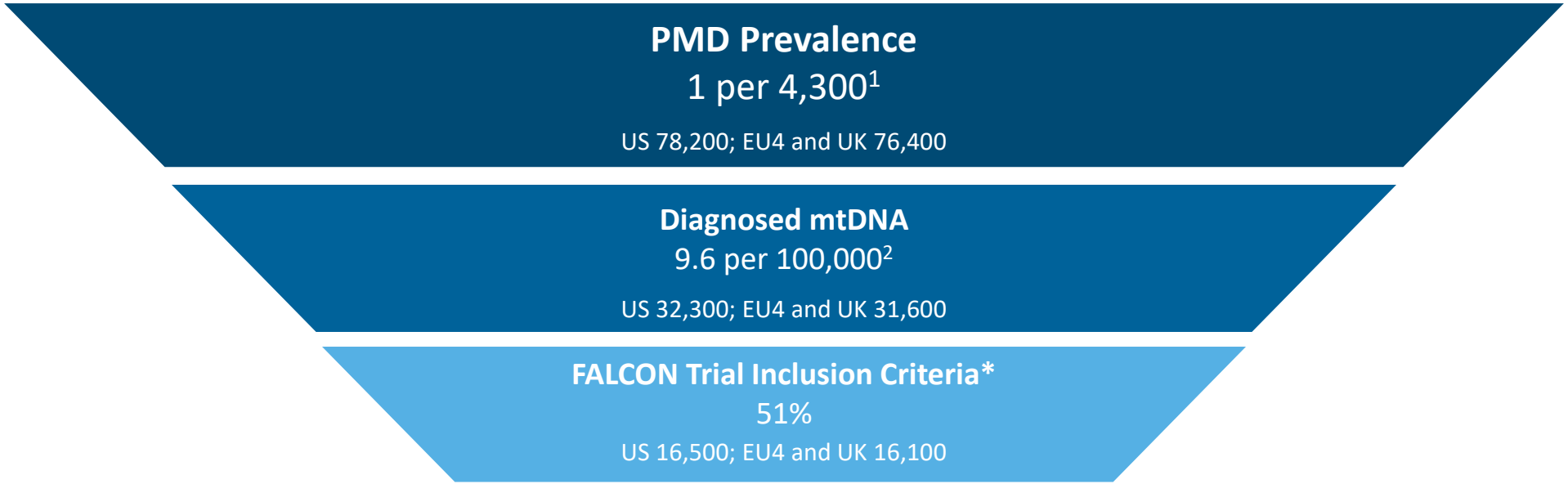
- **Efficacy data is promising for multiple reasons:**
  - **Fatigue** and **myopathy / muscle weakness** are key symptoms for patients, and **fatigue reduction is therefore viewed as a major benefit** and quality of life improvement by N=7 patients
  - **Improved daily functioning and physical activity** is also cited by N=4 patients as a key factor driving the decision to speak to their HCP about KL1333

*"My initial impression of [KL1333] is that it would be amazing. Any**thing that helps with fatigue** to get through the day to make it less overwhelming …*
the underlier is the constant fatigue."

- MELAS Patient

N=10 Patients (US)
MELAS- Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-like episodes

Significant addressable patient population for napazimone (KL1333)



>30,000 diagnosed mtDNA mitochondrial disease patients addressable in the US, EU4 and UK

*mtDNA mutations including m.8344A>G MELAS-MIDD, MERRF, KSS-CEPO, large scale mtDNA deletions

1 Gorman, G.S. et al. Prevalence of nuclear and mitochondrial DNA mutations related to adult mitochondrial disease. Ann Neurol 2015 May;77(5):753-9.
2 Gorman, G.S. et al. Mitochondrial Diseases. Nat. Rev. Vol 2, 1-22 (2016).

Summary: Napazimone (KL1333)

Primary mitochondrial diseases – rare disorders with significant unmet medical need

- Severe fatigue, myopathy (muscle weakness), and reduced life expectancy
- Poor quality of life (e.g., loss of job, social isolation, depression)

Napazimone (KL1333) positioned to become first standard of care in mitochondrial DNA (mtDNA) disease

- Novel mechanism of action addresses the underlying disorder
- >30,000 patients*

Pivotal study ongoing with positive interim analysis confirming FDA-agreed primary endpoints

- Patient recruitment for second wave of pivotal FALCON clinical trial ongoing
- Read-out anticipated in 2027 with launch in early 2029

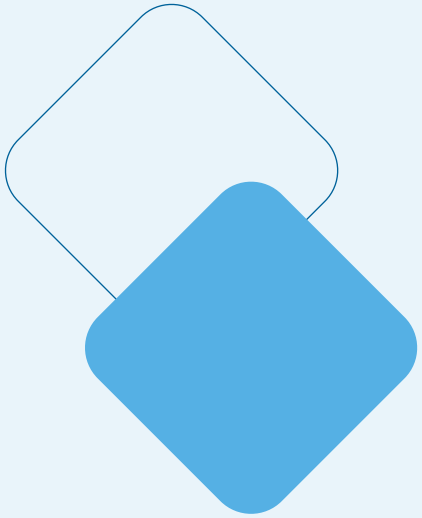
Significant value creation potential for Pharming and patients

- Builds on Pharming's existing rare disease expertise and infrastructure
- Concentrated centers of excellence and strong advocacy groups

*in US, EU4 and UK

Thank You

Questions and Conversations



Building momentum across commercial, financial and pipeline

Strong growth momentum

- 2025 revenue ~$376M:
  - High dbl-digit growth for RUCONEST® and Joenja®
- Significant operating profit and operating cash flow (9M 2025)
- 2026 revenue guidance: $405-425M:
  - Continued RUCONEST® growth, significant and accelerating Joenja® growth

Strategic growth priorities

- Sustained growth of commercial portfolio
- Significant Joenja® APDS growth catalysts:
  - Pediatric label, VUSs, targeted geo expansion, prevalence expansion
- Enhanced capital allocation driving growth

High value pipeline

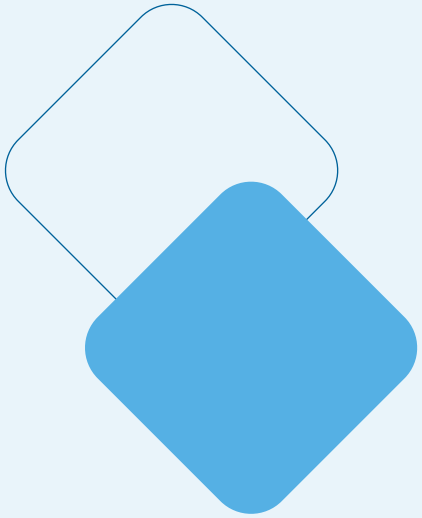
- Joenja® (leniolisib) for PIDs/CVID with immune dysregulation
  - Phase II readouts (2026)
- Napazimone KL1333 for mtDNA mitochondrial disease
  - Pivotal study readout (2027)

Building a leading rare disease company

- Growth-oriented leadership team
- Proven commercial and development capabilities
- Scalable organization

Thank You

Questions and Conversations



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Epidemiology of genetic PIDs linked to PI3K signaling

References:

1. Based on 1.4% of PID patients reported as ALPS in the ESID registry & overall PID prevalence of 1/2500.
2. Median from survey of 7 PID KOL opinions.
3. Most ALPS-FAS patients are well treated, with 30% in need of better treatment (KOL opinions including Konneti Rao/David Teachey – leading global KOLs).
4. Based on 0.2% of PID patients reported as CTLA4 in the ESID registry & overall PID prevalence of 1/2500.
5. Based on 0.5% of PID patients reported as CTLA4 in the USIDnet registry (5489 patients usidnet.org) & overall PID prevalence of 1/2500.
6. 1/3 of CTLA4 patients are considered asymptomatic, others well treated (Hao & Cook. Front Immunol. 2022 12:806043).
7. Overall PTEN Hamartoma Tumor Syndrome prevalence (NORD).
8. Based on Pharming literature review, KOL feedback and PTEN Foundation registry review (>500 patients) identifying PTEN patients with an immune dysregulation phenotype.
9. 2x scaling for additional undiagnosed patients to be identified through future patient finding activities and VUS resolution. This is based on Pharming APDS experience.
10. Based on 0.15% of PID patients reported as NFKB1 in the ESID registry & overall prevalence of 1/2500.
11. Based on 0.11% of PID patients reported as NFKB1 in the USIDnet registry (5489 patients usidnet.org) & overall PID prevalence of 1/2500.
12. Pharming literature review (6 NFKB1 pubs): of all CVID patients with genetic drivers 6% were NFKB1; CVID prevalence ~100 /mill., 30% with genetic drivers (30 /mill.), 30*0.06 = 2/mill
13. Pharming literature review (7 CTLA4 pubs): of all CVID patients with genetic drivers 5% were CTLA4; CVID prevalence ~100 /mill., 30% with genetic drivers (30 /mill.), 30*0.05 = 1.5/mill
14. KOL opinions approx. half of NFKB1 patients need better therapy

- Prevalence calculations for target PID subgroups is based on IUIS reported ‘all PID’ prevalence of 1/2500 (Tangye et al J Clin Immunol. 2020; 40(1): 24–64).
- ESID registry publication includes total PID patients 16486 (Thalhammer et al Allergy Clin Immunol 2021;148:1332-41).

Epidemiology of CVID with immune dysregulation
CVID patients numbering ~39/million may be APDS-like

References:

1. Based on overall PID prevalence of 1/2500, with 26% of PID patients reported as CVID in the ESID registry
2. Based on overall PID prevalence of 1/2500 with 33% of PID patients reported as CVID in the USIDnet 5489 patient registry (usidnet.org)
3. Median from survey of 7 PID KOL opinions
4. Immunodeficiency Foundation - https://primaryimmune.org/
5. PID US health survey – Boyle & Buckley 2007 J Clin Immunol
6. CVID global epi review article – Weifenback et al 2020 J Immunol Res
7. Pharming Symphony Claims Data CVID search
8. Jordan et al 2023 IPIC abstract
9. Median of sources on CVID prevalence
10. Defining an activated PI3K-delta syndrome-like endotype within broader common variable immunodeficiency. Daniel V. DiGiacomo, Sara Barmettler, Paul J. Maglione, Aditi Jogdand, Joseph S. Hong, Rebecca A. Marsh, Kevin S. Thorneloe, Karen Gilbert, Mei-Sing Ong*, Jocelyn R. Farmer*NEIDC CVID cohort (N=423): APDS-like endotype analysis of CVID with immune dysregulation cohort indicates 74% as APDS-like
11. Resnick ES, et al. Blood. 2012 119(7): 1650-1657.
12. Boileau J, et al. J Autoimmun. 2011 36(1): 25-32.
13. Ramirez NJ, et al. Curr Opin Immunol. 2021 72: 176-185.
14. Data on file KOL interviews (50%)

#Based on:

- current unmet medical need in APDS-like CVID with immune dysregulation population
- anticipated benefit/risk profile of leniolisib
- value delivered by currently utilized off label therapies

15. Data on file from Market research conducted by Trinity Life Sciences (60%)