# Diagnostic Odyssey of Patients with the Rare Immunodeficiency Activated PI3 Kinase Delta Syndrome (APDS): Case Study with Clinician and Patient Interviews

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Fabio Candotti, MD[1], Roman Spelsberg[2], Hermann Maximilian Wolf, MD[3, 4], Georgios Sogkas, MD[5], Hans-Holger Bleß[2], Kirsten H. Herrmann, PhD[6], Fabian Hauck, MD, PhD[7]

[1] Division of Immunology and Allergy, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland
[2] fbeta GmbH, Akazienstraße 31, 10823 Berlin, Germany
[3] Sigmund Freud Private University Vienna (SFU), Faculty of Medicine, Vienna, Campus Prater, Freudplatz 3, 1020 Vienna, Austria
[4] Clinical Immunology Office, Garnisongasse 18/Stiege 11 Tür 10, 1090 Vienna, Austria
[5] Hannover Medical School (MHH), Department of Rheumatology and Immunology, Carl-Neuberg-Straße 1, 30625 Hannover, Germany
[6] Pharming Group NV, 2333 CR Leiden, Darwinweg 24, The Netherlands
[7] Division of Pediatric Immunology and Rheumatology, Department of Pediatrics, Dr. von Hauner Children's University Hospital, Munich Ludwig-Maximilians-Universität München, Germany

## INTRODUCTION

Activated phosphoinositide 3-kinase delta syndrome (APDS) is an ultra-rare inborn error of immunity (prevalence approx. 1-2:1.000.000) first described in 2013.[1,2,3]

Patients present with recurrent infections, poly- to monoclonal lymphoproliferation and immune dysregulation.[3,4,5]

PI3Kδ inhibitors are precision therapeutic options for patients with APDS.[6]

## OBJECTIVE

To explore diagnostic and therapeutic challenges for APDS from both patient and clinician perspectives and to identify opportunities to shorten time to diagnosis and optimize care.

## METHODS

Qualitative case study with semi-structured interviews.[7] Six patients or legal guardians and four clinicians with hands on APDS experience were interviewed. At the end of the clinician interviews, the four participants were asked whether they agreed or disagreed with a set of four hypotheses. Transcripts underwent inductive content analysis to identify recurring themes across diagnosis, treatment and care pathways.[8]

Inclusion criteria: Clinicians were board certified specialists in pediatric/ adult immunology, rheumatology, hematology/ oncology; direct experience with APDS. Patients or legal guardians of children with APDS. Written informed consent.

Countries for recruitment: Austria, Germany and Switzerland.

## CONCLUSIONS

APDS is frequently diagnosed too late, prolonging morbidity and psychological burden. Early genetic testing, structured interdisciplinary care and timely access to targeted therapies can substantially improve outcomes. Health-system interventions that raise awareness and standardize pathways are critical to reducing the diagnostic odyssey.

## RESULTS

For three of the six included patients legal guardians of affected children answered the interview questions. Four experienced clinicians specialized in immunology, rheumatology, hematology, and/or oncology were included.

Patients were included from Austria and Germany; no patient could be included from Switzerland. Physicians were included from Austria, Germany and Switzerland.

Reported time to diagnosis was 3.83 - 73 years (median 11 years).

Challenges for the management of APDS were attributed to the clinical heterogeneity of the disease but also to multiple systemic and structural challenges such as multiple specialists and lack of awareness for APDS and time to diagnosis.

Patients as well as clinicians reported a diagnostic odyssey of patients with APDS (Figure 1 and 2) .

The delayed diagnosis is a heavy burden, especially for children with irreversible developmental setbacks. Main reasons for diagnostic delay are the rarity, low awareness, variable symptoms, and lack of clear patient pathways.

A confirmed diagnosis is considered as a turning point. It enables targeted therapy and social reintegration.

Patients and clinicians call for better education, early use of genetic testing, and stronger interdisciplinary models.

### Patients

"We were in and out of hospitals for years. Nobody thought to check the immune system. Only when our new pediatrician ran more comprehensive tests did things move forward."

"We were lucky to end up at a university center. Without that referral, we might still be waiting."

"It was a fight. Every test result brought new questions. Only when we got the genetic result did things finally make sense."

"After he started the therapy, he was like a different child. He ran, he was full of energy, we realized for the first time that life could be better."

### Clinicians

"We used to wait and rely on substitution therapy. But now, knowing the publications and based on my experience, I would initiate the targeted APDS therapy as early as possible."

"For one patient, there was no perspective before the targeted APDS therapy. He was hospitalized with multiorgan disease, opportunistic infections, colitis and cytopenia. After starting therapy, he returned to work, gained weight, and no longer needed prophylactic medication."

A corresponding overview of the clinicians' agreement with four hypotheses is presented in Figure 2.

### Systemic Challenges

Barriers included limited awareness among non-immunologists, as APDS is not routinely considered.

There is a lack of standardized diagnostic pathways; variable access to and interpretation of genetic testing and fragmented referral structures. Both patients and clinicians emphasized the urgent need for validated APDS-specific disease activity instruments to guide therapeutic decisions.

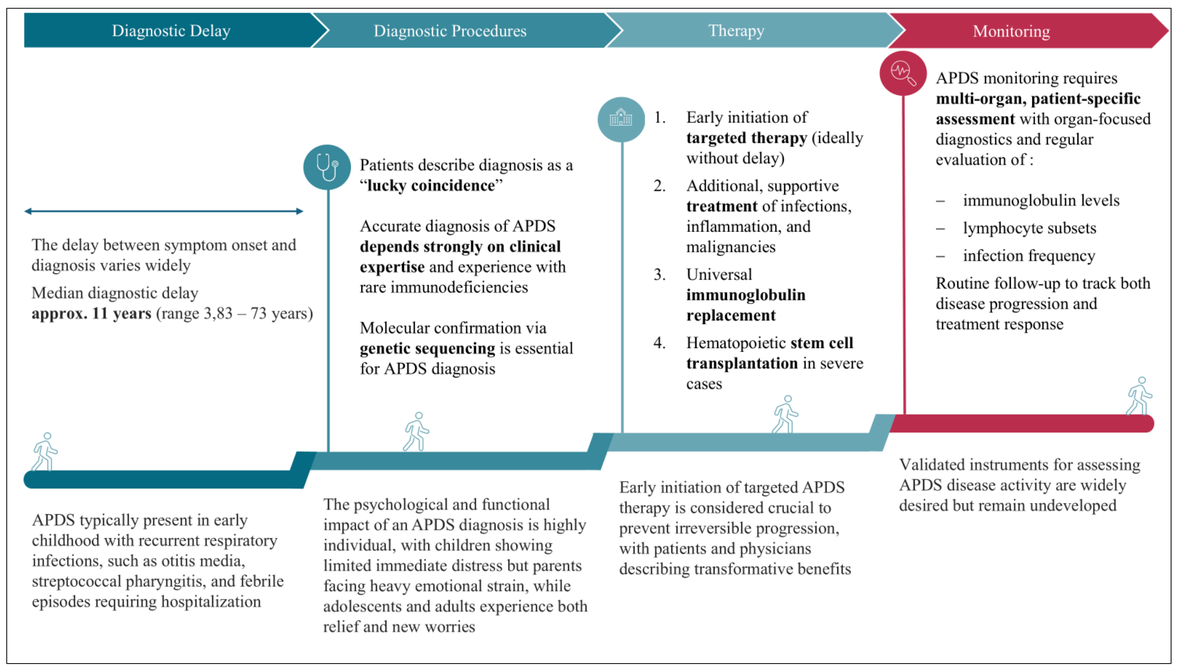


**Figure 1: Summary of diagnostic and therapeutic pathway of patients with APDS.**

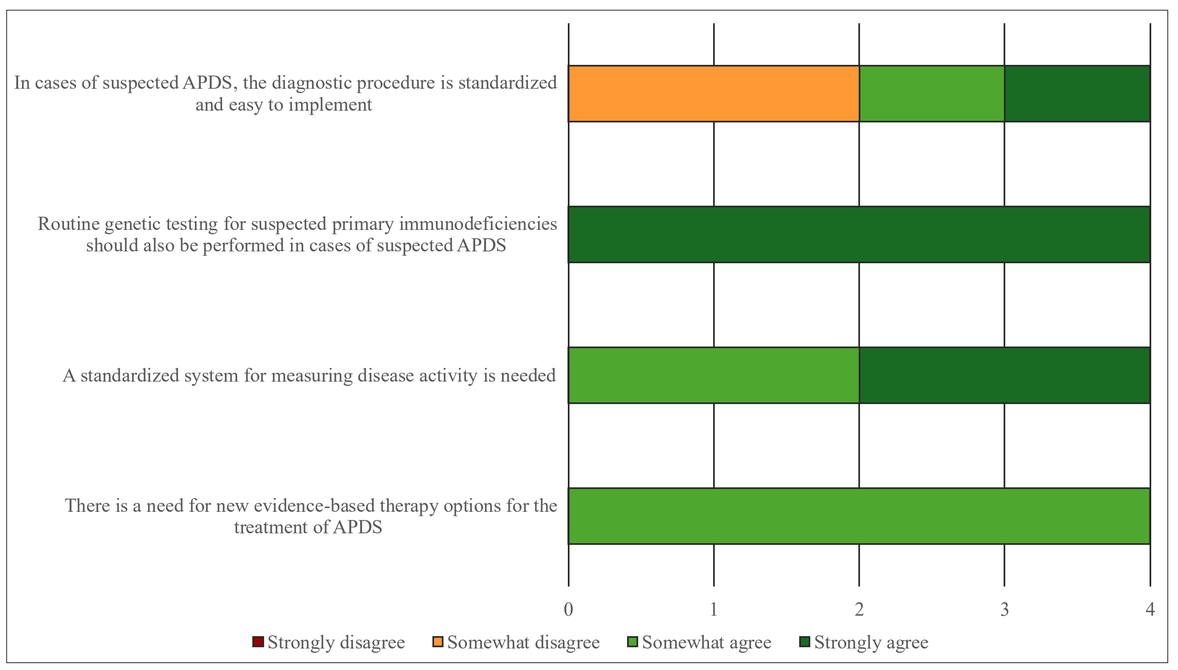


**Figure 2: Statements validated by clinicians during the interviews.**

## DISCUSSION

This study highlights the prolonged diagnostic odyssey faced by APDS patients. Despite advances in genetic testing, diagnostic delays remain common, primarily due to low disease awareness and clinical heterogeneity. Earlier use of genetic testing and structured referral pathways could shorten diagnostic timelines. Targeted therapies, particularly PI3Kδ inhibitors, represent a paradigm shift, yet timely access is hindered by administrative processes. Developing APDS-specific disease activity indices and strengthening multidisciplinary networks will be critical to optimize care and outcomes. Findings are consistent with registry-based analyses and emphasize the importance of patient perspectives in rare diseases management.[3]

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## CONTACT INFORMATION

Kirsten H Herrmann@pharming.com

## Disclosure

This study was sponsored by Pharming Technologies B.V., Leiden, The Netherlands.

## Acknowledgement

The authors would like to thank the dsai (https://www.dsai.de/) for support in the patient recruitment.