Issue 06 – 2026

AUTOINFLAMMATORY MAGAZINE

INSIDE OUR HELPLINE

How We Support Patients Around the World

FMF VIRTUAL SCHOOL

Empowering Armenian Patients Through Knowledge

PATIENT JOURNEYS

Stories From Our Community

This magazine is presented by the FMF & AID Global Association.

For more information visit fmfandaid.org

In this edition

Editorial Team

Dear Readers,

Welcome to the 6th edition of the FMF & AID Magazine! Last year's theme of 'Navigating the Medical Maze Together', highlighted the main obstacles and challenges faced by autoinflammatory patients as they made their way through medical systems around the globe.

FMF & AID remained committed to assisting patients. We continued to provide access to knowledgeable rheumatologists who diagnose, monitor, and prescribe appropriate treatments. We collaborated with health authorities to ensure colchicine availability due to shortage in France. We offered genetic testing to patients in critical need, who were suspected of having an autoinflammatory condition. We provided ongoing multilingual support through our 24/7 helpline. We also developed a training course on common autoinflammatory diseases for physicians in collaboration with the Center for Periodic Systemic Autoinflammatory Diseases, University Hospital Erlangen in Germany.

Our Medical Assistance Program continued to provide travel and accommodation costs for those in need requiring specialists, supplied Buzzy devices for children on biological shots, and offered targeted help in urgent cases. In addition, we produced new awareness and educational resources in several languages and strengthened collaborations with international experts and organizations to improve care and understanding of autoinflammatory conditions.

Diagnostic delays, lack of medical awareness, and inequitable access to biological treatment remain a daily reality for many patients globally. FMF & AID will continue to address these and other key issues impacting autoinflammatory patients.

With warm regards,

Malena Vetterli
Founder & Executive Director
FMF & AID Global Association

Inside the FMF & AID Helpline: Supporting Autoinflammatory Patients Around the World

Introduction

The FMF & AID Helpline provides international support to patients and families affected by autoinflammatory diseases. It offers guidance on diagnosis, treatment access information, specialist referrals and disease management for conditions including FMF, MKD/HIDS, CAPS, TRAPS, uSAID, Yao Syndrome/NOD2, Still's disease, etc. Many individuals who contact the helpline have experienced long diagnostic delays, misdiagnosis, or lack of access to knowledgeable specialists.

Helpline Reach

FMF & AID receives messages daily through WhatsApp, Facebook Messenger, email, direct phone calls and the website.

On average, FMF & AID assists 600–700 patients each month, and approximately 7,000 individuals yearly. The helpline supports patients in English, German, French, Spanish, Italian, and Portuguese. Additional language translation is offered via our volunteers.

Countries of Origin

The helpline supports patients from all regions of the world. Countries represented include:

Argentina, Armenia, Australia, Austria, Afghanistan, Belgium, Brazil, Canada, Chile, Colombia, Czech Republic, El Salvador, France, Gambia, Georgia, Germany, Israel, Italy, Jordan, Lebanon, Morocco, Netherlands, New Zealand, Poland, Romania, Russia, Saudi Arabia, South Africa, Spain, Sweden, Switzerland, Syria, Turkey, Ukraine, United Kingdom, United States and Uzbekistan.

The patient diversity reflects the lack of global expertise to treat autoinflammatory conditions and the urgent need for expanded medical awareness and training.

Diseases Reported

The individuals who contacted the helpline in 2025 presented with: FMF, MKD/HIDS, CAPS (incl. NOMID/ CINCA), FCAS2, TRAPS, Yao Syndrome/ NOD2, PFAPA, Behçet's disease, PAMI Syndrome, DADA2, Still's disease, Pericarditis, and uSAID (Undifferentiated systemic autoinflammatory disease).

Cont. Inside the FMF & AID Helpline

Reasons for Contact

Patients contacted the helpline for a variety of inquiries. Themes included:

1. Diagnostic uncertainty

- doctors refusing or delaying genetic testing
- patients misdiagnosed for years (sometimes decades)
- clinical confusion between FMF, PFAPA, BD, uSAID, TRAPS and NOD2
- families seeking interpretation of benign genetic variants or VUS

2. Treatment issues

- colchicine intolerance, resistance or incorrect dosing
- colchicine side effects (hair loss, gastrointestinal issues, infections, pregnancy and fertility questions)
- biologic therapy questions (Kineret, Ilaris, Rilonacept, etc.)
- treatment failure or incomplete response to biologics
- concerns about switching biological medication unnecessarily (dosing escalation)
- use of steroids concurrent with biologics & antibiotics during an infection (concurrent use with colchicine)

3. Access to care

- request for knowledgeable paediatric or adult specialists (concentrated in USA and Germany – concern for lack of expert centers in various countries)

4. Medication shortages and quality concerns

- lack of colchicine availability in certain regions
- concerns about colchicine brands efficacy and intolerance
- difficulties accessing biologics due to insurance or availability

5. Severe or complex medical situations

- pericarditis not controlled by Kineret
- uncontrolled inflammation despite colchicine and biologics
- children with inflammatory asthma and recurring infections due to medication underdosing
- flare-ups while travelling without medication

6. Emotional support and education

- families distressed by lack of medical recognition
- parents falsely accused of Munchhausen by Proxy
- adult patients frustrated by years of medical dismissal (gaslighting)
- families needing reassurance, scientific information, and help navigating their medical system

Cont. Inside the FMF & AID Helpline

Observed Trends

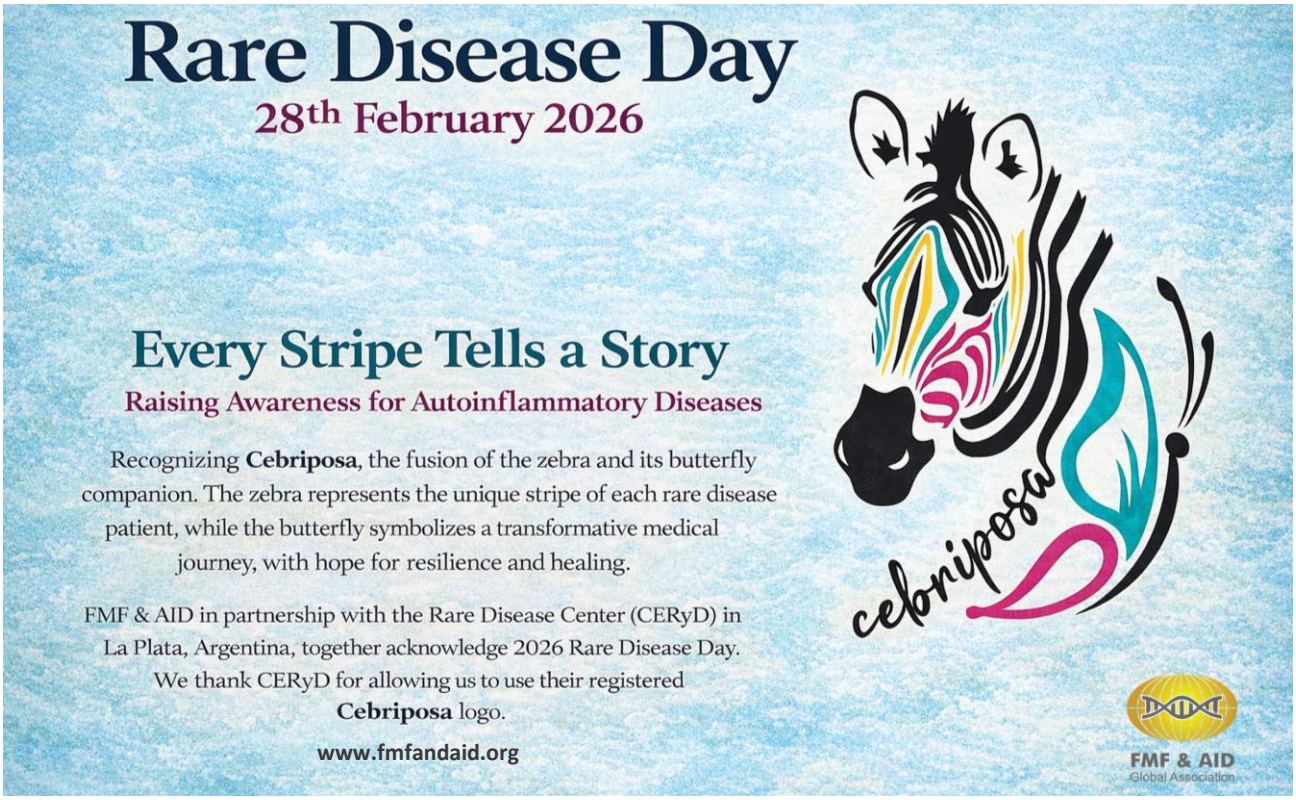
2025 revealed several consistent inquiry patterns:

- diagnostic delay remains a major global problem
- symptomatic heterozygous patients are frequently medically dismissed or left untreated
- children are often labelled “psychosomatic” or “anxious,” delaying care
- access to biologics and colchicine is inconsistent
- patients often rely on FMF & AID to locate specialists
- misinterpretation of genetics is widespread

Conclusion

The FMF & AID Helpline remains an essential support system for patients with rare autoinflammatory diseases worldwide. The volume and complexity of cases demonstrate the urgent need for improved physician education, specialist access and treatment availability.

With more than 7,000 patients supported each year, the helpline plays a crucial role in closing gaps in care and providing a reliable source of expert-informed guidance for parents and patients who otherwise have nowhere else to turn.



A Comprehensive AID Educational Course for Physicians

FMF & AID Global Association, in collaboration with Prof. Dr. Jürgen Rech, Head of the Center for Autoinflammatory Diseases at the University Hospital Erlangen, has developed an extensive educational course designed to support physicians in recognizing and treating autoinflammatory diseases. The course link is available on the FMF & AID website (www.fmfandaid.org). This project was supported by an Educational Grant from Swedish Orphan Biovitrum GmbH. None of the authors received remuneration or compensation for their involvement.

Autoinflammatory diseases remain significantly underdiagnosed, and many patients continue to face years of uncertainty and inappropriate treatments before receiving a correct diagnosis. With this course, FMF & AID aims to provide physicians with practical and clinically relevant information that can support earlier disease recognition, faster referral, and better treatment outcomes. The course is divided into three comprehensive modules:

Module 1: Fundamentals of Autoinflammation

This introductory section explains the mechanisms of the innate immune system, the concept of autoinflammation, key inflammatory pathways, and how autoinflammatory diseases differ from autoimmune conditions. Biomarkers, recurrent fever patterns, and clinical red flags are presented in a clear and structured manner.

Module 2: Disease-Specific Chapters

This section provides detailed information on FMF, CAPS, MKD/HIDS, TRAPS, uSAID, Still's Disease, and other autoinflammatory conditions. It covers clinical presentations, genetics, complications, differential diagnoses, and treatments. Photographs of aim to help physicians recognize typical autoinflammatory dermatological patterns. Treatment guidance includes information on colchicine, IL-1 inhibitors, and other biological therapies.

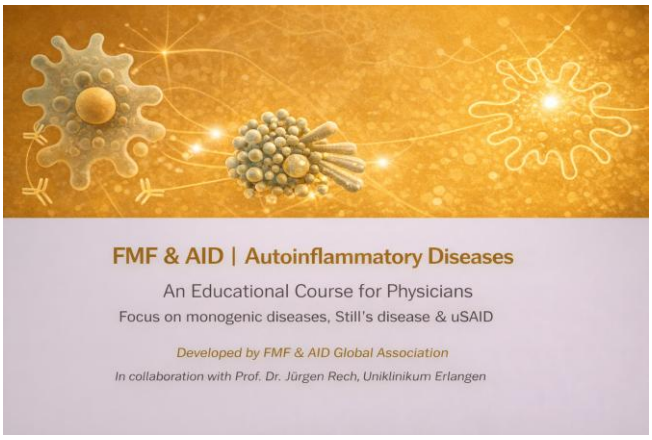
Cont. A Comprehensive AID Educational Course for Physicians

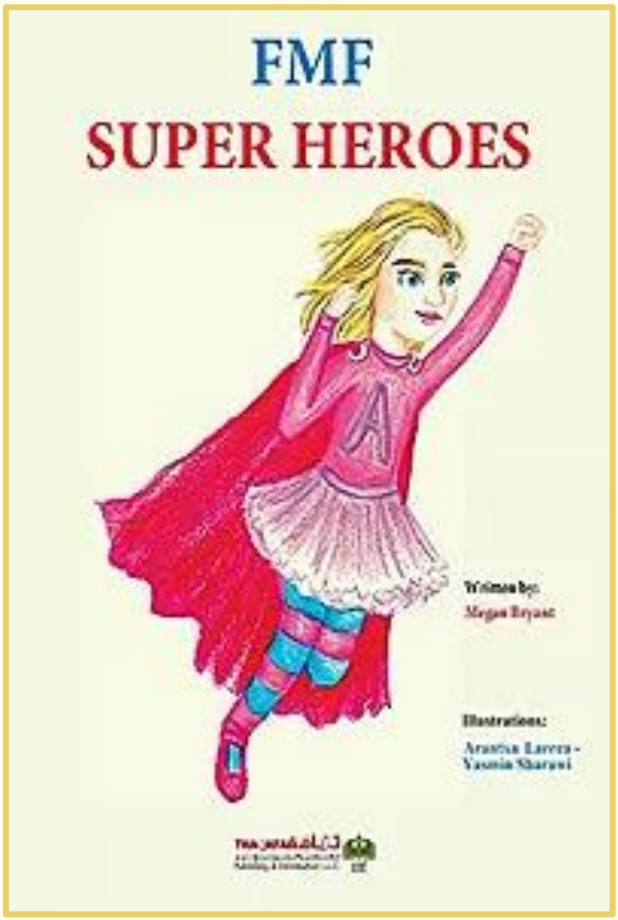
Module 3: The Physician's Role

This final section focuses on diagnosis, patient evaluation, and common challenges in everyday practice. Topics include interpreting genetic testing, distinguishing between psychosomatic assumptions and genuine autoinflammatory symptoms, understanding variants of uncertain significance, and avoiding frequent diagnostic pitfalls. Practical case examples illustrate how early recognition can prevent long-term complications.

The course will be made available online at no cost. Additional resources will be available in the future to assist medical professionals across all specialties treating autoinflammatory conditions with the goal to have an accessible, centralized source of reliable information.

By providing physician resources, FMF & AID continues its mission to support the medical community and enhance the quality of life for individuals living with autoinflammatory diseases.





The educational children's e-book "FMF Superheroes" is available in English, German, and Arabic.

It is designed to help children of all ages better understand Familial Mediterranean Fever in an age-appropriate, reassuring, and empowering manner. The book can be read independently or together with parents, caregivers, or healthcare professionals.

"FMF Superheroes" is available on Amazon, and purchasing a copy directly supports the work of the FMF & AID Global Association in raising awareness, educating families, and improving support for autoinflammatory patients worldwide.

A Journey That Began With a Voice — And a Parrot

By Tatevik Grigoryan, MD, Rheumatologist, Center of Medical Genetics and Primary Health Care, Yerevan, Armenia.

It was June 3, 2020, a day I remember clearly. My first online FMF patient meeting consisted of many questions, sincere faces on the screen — and a parrot sitting beside me in my brother's home. I was worried he might interrupt the 1.5-hour session with an unexpected sound, but he remained silent, and everything went remarkably well. When the meeting ended, messages of gratitude began to arrive. Patients were engaged, curious, and hopeful. Something changed inside me that day.

After the session, my father called. His voice was proud, yet cautious. "You spoke beautifully," he said. "But be careful with saying you love FMF. It is a hereditary disease that has changed many lives. People suffer, they feel pain, they face uncertainty about their future. If you say you love FMF, they might misunderstand you." I listened calmly… Then I spent days thinking, searching inside myself. And I understood: I truly do love FMF — not as a disease, but for the meaning it holds. It challenges the mind and touches the heart. Because behind every gene mutation there is a human story — a family, a future, a life. My feelings were not about the disease itself, but about the people living with it.

Finding My Purpose

I began reading more, joining online/offline courses, and immersing myself in autoinflammatory medicine. With every new fact, my passion grew stronger. Soon after, I began working at the Center of Medical Genetics and Primary Health Care, where I am grateful to work alongside experts who have deeply shaped FMF science in Armenia and globally. I meet patients who carry myths, fears, silence, and stigma. Many did not know what FMF was, doubted colchicine, and felt ashamed of their diagnosis.

Cont. A Journey That Began With a Voice — And a Parrot

I realized as a practicing physician that knowledge is medicine and awareness saves lives. Due to these patients' interactions, I began creating short videos to explain FMF in a simple, clear, and kind manner. The videos bring FMF education into a patient accessible space, where they can learn about their disease without fear.

A Missing Flag — And a Call to Action

During my research, I discovered the FMF & AID Global Association — a global network connected with more than 22 affiliated patient associations worldwide. Yet Armenia with a high concentration of FMF patients, is often under-acknowledged globally.

I felt a call to action. I wrote to the organization immediately and received a warm response from the Director, who has since become a partner and a friend — Malena Vetterli. Our first Zoom meeting was full of ideas and mutual enthusiasm, and I felt a sense of deep connection. It was clear that together, we could build something meaningful for Armenian patients.

The Birth of the FMF Virtual School of Armenia

On September 17 — World FMF Day — the FMF Virtual School of Armenia was born. A place where patients and families could learn, ask questions, and stop feeling alone. Our first session took place online, and like my former June meeting, it gave me strength, joy, and direction.

One patient's message has remained in my heart: "Your videos helped us see FMF not with fear, but with hope and confidence. We realized that life, dreams, and plans are still ahead — and everything began to change."

More Than a Disease — A Mission

For me, FMF is not just a disease, it is a path, a responsibility, and a promise. This journey is still in its beginning stages and I believe Armenia, with our history, patients, scientists, and heart, has much to share with the world. My work continues with every lecture, consultation, and shared story, with the goal to ensure that patients are heard, understood, and educated. Sometimes, all it takes is one voice — and yes, even a little parrot — to begin a movement.

ERN RITA: Patient Journey for Familial Mediterranean Fever (FMF)

Patient journeys encompass the various stages, interactions, and experiences encountered by individuals who are navigating the healthcare system. Understanding how patients traverse these complex networks is critical for healthcare providers, policymakers, and researchers to learn how improved care delivery can enhance diagnostic and treatment outcomes and to also promote patient-centered management.

Within the context of rare and chronic diseases, patient journeys are often far more complicated. A lack of awareness and expertise can lead to delayed diagnosis, misdiagnosis, treatment, and suboptimal oversight, significantly affecting patients' quality of life.

The establishment of the European Reference Networks (ERNs) in 2017 marked an important step toward improving care for people living with rare diseases. These networks connect healthcare professionals, researchers, and patient representatives across Europe in an effort to share expertise and ensure that rare patients are not disadvantaged due to their location.

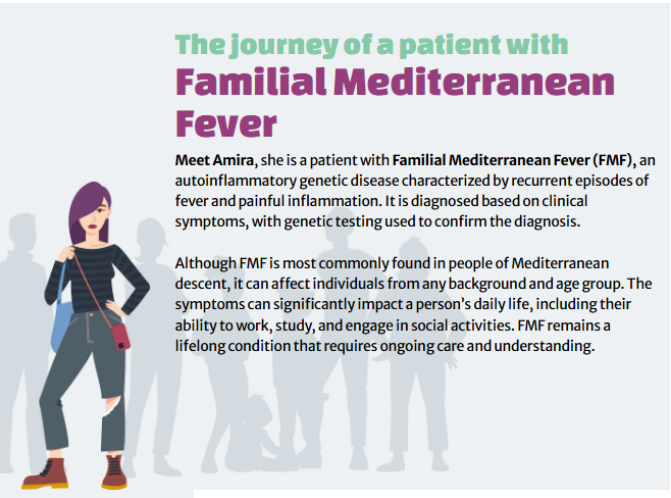
Developing the FMF Patient Journey

Under the leadership of Martine Pergent, ERN RITA's Communication Working Group Lead, a Patient Journey Handbook was developed to guide the process across all RITA disease groups.

The Familial Mediterranean Fever (FMF) journey was developed by ERN RITA in collaboration with Malena Vetterli, who represents patients with autoinflammatory diseases. As the RIPAG Stream Lead for Autoinflammatory Diseases, she also serves on the Communication Working Group. Clinicians' input was sought throughout the entire process to validate all data collected.

As the lead organization for autoinflammatory diseases, FMF & AID coordinated the focus groups that formed the foundation of this project. These patient focus groups met regularly and were conducted in several languages and various countries to ensure diverse and inclusive participation.

The goal was to map out real-life experiences of FMF patients, from initial symptoms onward detailing their medical odyssey, including diagnosis, treatment, management, and psychosocial impact. This process allowed both patient representatives and clinicians to identify unmet needs and potential areas for improvement within the healthcare pathway.



Cont. Patient Journey for FMF

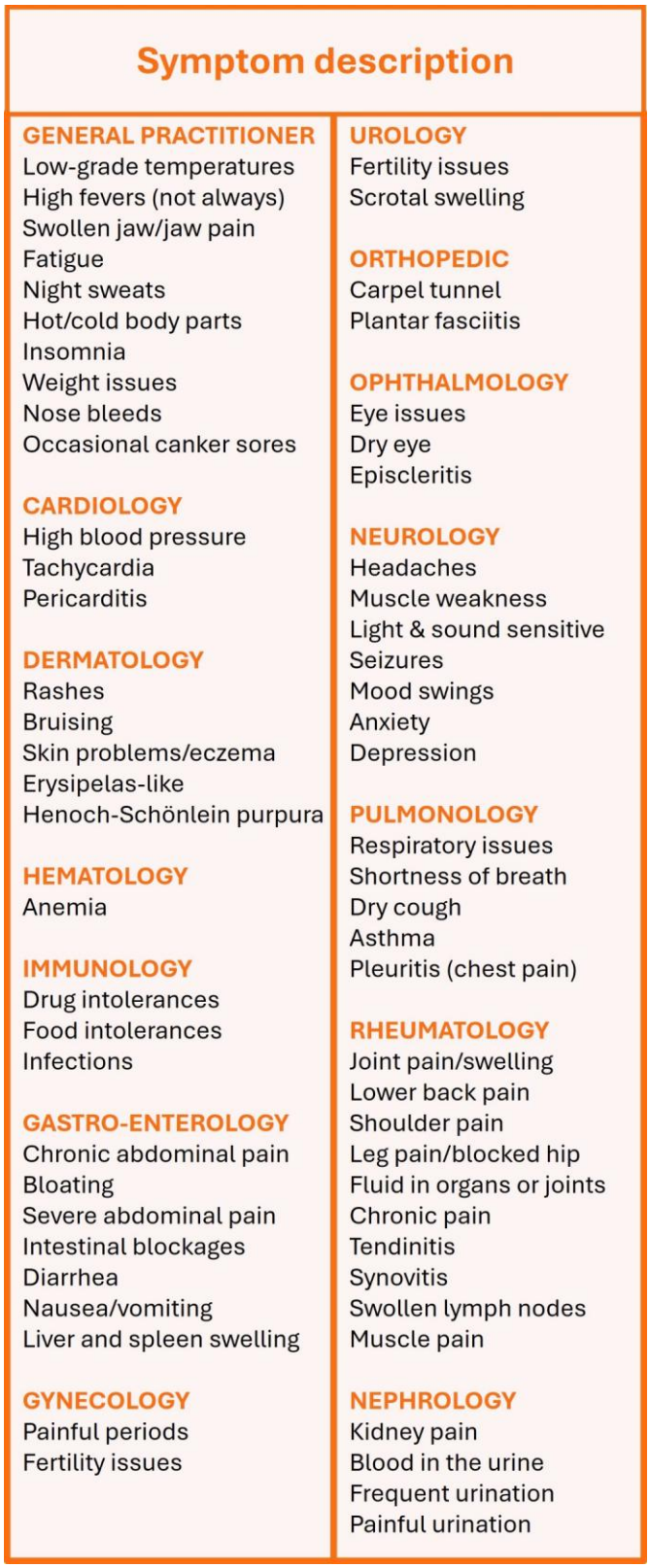
Collaboration and Validation

Once the patient journey was drafted, it underwent review and validation by a multidisciplinary team of experts, ensuring that it accurately reflected both clinical practices and patient experiences. The final version of the FMF Patient Journey has now been published on the ERN RITA website, serving as a valuable tool for healthcare professionals, patients, and policymakers alike. Read the full FMF Patient Journey here: https://ern-rita.org/jop3-2/

Acknowledgements

FMF & AID Global Association extends its sincere appreciation to everyone involved in this project. This includes ERN RITA for their unwavering support to the autoinflammatory community, the patients who participated by sharing their experiences, and FMF & AID volunteers (Janine Tschan, Audrey Zagouri, and Ellen Cohen), who played key roles in moderating focus groups, collecting valuable input from patients and parents, and writing key documentation for the patient journeys.

Through this collaborative effort between clinicians, patient representatives, and communication experts, ERN RITA continues to strengthen its mission of improving the lives of people affected by rare immune and autoinflammatory diseases.



The Search for a Knowledgeable Physician

For individuals and families living with rare autoinflammatory diseases, the journey to diagnosis is often long, frustrating, and emotionally challenging.

Why are Rare Diseases Difficult to Diagnose?

Rare diseases are not widely well known. Many general practitioners and even specialists may have little to no experience with autoinflammatory conditions such as FMF, PFAPA, CAPS, TRAPS, MKD/HIDS, and others. Lack of medical training leads to misinterpretation of symptoms, insufficient or incorrect treatment, and limited awareness regarding treatment guidelines and available therapies.

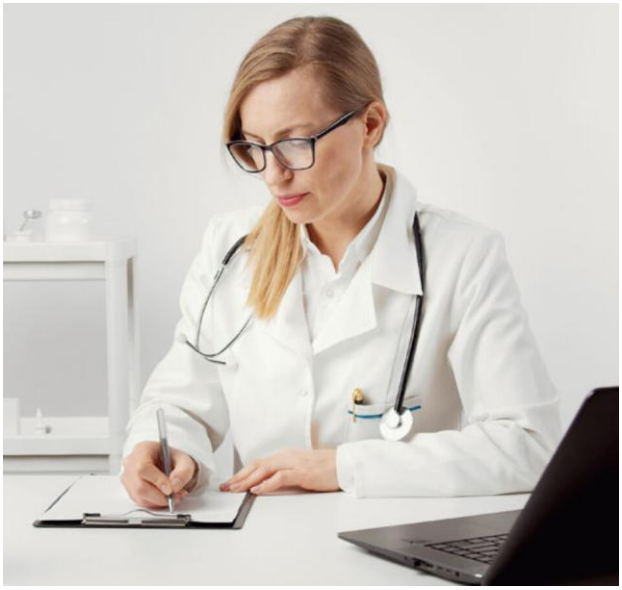
Even when a diagnosis has been made, patients often feel like they have to advocate for themselves. It is not uncommon for patients to request testing, asking for medication dose adjustments, and explaining their condition repeatedly to various medical providers.

Criteria for Selecting a Physician

- willing to learn and stay up-to-date on autoinflammatory diseases, medication dosing, and treatment guidelines.
- listening to the patient experiences and input.
- collaborative, not dismissive and believes in shared decision-making.
- connected to networks of specialists, research centers, and rare disease organizations.

How to Begin a Physician Search

- make contact with a national or international patient organization. FMF & AID maintains contacts with expert centers and physicians around the world.
- check for referral networks, such as the ERN RITA network in Europe, which brings together expert centers in rare immunological and autoinflammatory diseases.
- join patient groups and forums. These communities often share personal experiences, which can be helpful in locating a medical specialist.
- review published research. Many physicians in active research may take new patient cases.



Cont. The Search for a Knowledgeable Physician

Lack of Local Expertise

Many patients do not live near a major medical center and are dependent upon receiving care from regional or local doctors. Should a physician be unfamiliar with autoinflammatory conditions, it may be relevant to:

- share educational materials. FMF & AID provides brochures and training documents that can be shared with doctors.
- request a second opinion. Certain hospitals may offer a second-opinion consultation with specialists.
- encourage the treating physician to consult with an autoinflammatory expert or center.
- stay informed. Patients are encouraged to read about autoinflammatory diseases to better help guide care and recognize red flags.

Patients Deserve Better

Too often patient issues are dismissed, especially if lab results appear normal or if disease is not visibly active. Symptoms that are invisible are not imagined. Ongoing problems such as fatigue and flare-ups take a toll on daily life. All patients deserve a doctor who addresses concerns, offers treatment options, and works to improve quality of life parameters.

For more information, visit our website: https://www.fmfandaid.org/publications

Recommended Centers for Autoinflammatory Diseases

FMF & AID collaborates with a broad network of adult and pediatric rheumatologists and immunologists worldwide.

If you are looking for a knowledgeable physician or a center for autoinflammatory diseases, please contact FMF & AID directly at info@fmfandaid.org. Recommendations are made based on consistent positive feedback from patients and parents within our community.

Local Collaborative Centers for adult patients

Center for Periodic Systemic Autoinflammatory Diseases, University Hospital Erlangen, Germany

SCAIA – Swiss Center for Systemic Autoinflammatory Diseases, Zurich, Switzerland

Hirslanden – Immunology, Lucerne, Switzerland

Local Collaborative Centers for pediatric patients

UKBB - Pediatric Rheumatology, Basel, Switzerland

Should you require assistance making appointments with specialists at these centers, please contact us.

Challenges Faced by Patients with NOD2/Yao's syndrome

Autoinflammatory patients carrying the intron plus other mutations in the NOD2 gene (Yao's) face numerous diagnostic and therapeutic challenges. NOD2/Yao's disease has multiple questions regarding clinical aspects, of which many, are undefined by medical research and literature.

As with other autoinflammatory conditions, patients' C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) often remain normal, leading to under-recognition of this innate inflammatory-driven disease. Patient's constellation of clinical symptoms are often ignored or attributed to other conditions, leading to a delayed or missed diagnosis.

Per the medical literature, there is extensive overlap of the NOD2-gene pathways impacting allergic disorders, autoimmunity, primary immunodeficiency (PID), IBD, and autoinflammation, yet these intersections remain poorly acknowledged or understood. The absence of standardized clinical criteria leaves many navigating fragmented care systems with little clarity regarding their condition.

A significant gap also exists in understanding why NOD2 patients react severely to certain foods, medications, and environmental triggers. Many are treated with anti-IL-1, anti-IL-6, or other biologics, which often work only temporarily before losing effectiveness. This results in the need for multiple concurrent therapies, which insurance providers frequently refuse to cover.

Gastrointestinal involvement is common and diverse, including vomiting, food impaction, abdominal swelling, gastroparesis, constipation, and diarrhea. Some patients also experience cyclical vomiting syndrome, raising the question of whether it may be part of the disease spectrum. There appears to be an overlap with eosinophilic esophagitis (EOE) and other inflammatory gastrointestinal disorders, emphasizing the need for further investigation. Potential vascular implications have also been observed but remain insufficiently explored.

The epidemiological data on NOD2/Yao's disease is weak. Claims that only white women are affected, for example, fail to reflect the real diversity seen in the global patient community. Moreover, patients are often told that intron mutations are irrelevant, despite emerging evidence suggesting otherwise. Misdiagnoses are also frequent in Yao patients — as some are labeled with lupus or other autoimmune disorders — and in certain cases, NOD2-associated disease may mimic PLCG2 autoinflammatory disease.

Brain and CNS issues are another underrecognized aspect, with many patients reporting chronic neurological symptoms alongside recurrent respiratory infections.

Cont. Challenges Faced by Patients with NOD2/Yao's Syndrome

A notable proportion also present with hypogammaglobulinemia and other immune deficiencies, highlighting the need for further investigation into these types of dysregulation.

FMF & AID is currently working on a NOD2-educational brochure that will be available in 2026. An interview with a NOD2 patient was recorded during 2025 September autoinflammatory awareness month and can be found on the FMF & AID YouTube channel.

https://www.youtube.com/watch?v=U_33_dYc7PQ&t=2s

Overall, NOD2/Yao's disease often remains poorly understood, misdiagnosed, and under-treated.

Global collaboration is urgently needed to research patient symptoms, identify meaningful biomarkers to ensure timely diagnosis, update clinical guidelines with treatment protocols, and facilitate access to concurrent treatments.

Yao Syndrome
(NOD2-associated autoinflammatory disease)

- Rare systemic autoinflammatory disease

Key clinical features

- Recurrent flares
- Fever
- Skin rashes
- Joint pain and swelling, especially in the lower limbs
- Swelling of ankles, legs, and eyelids
- Gastrointestinal symptoms (abdominal pain, diarrhea)
- Sicca-like symptoms (dry eyes, dry mouth)
- Chest pain related to pleuritis or pericarditis
- Food and medication intolerances

Genetics & epidemiology

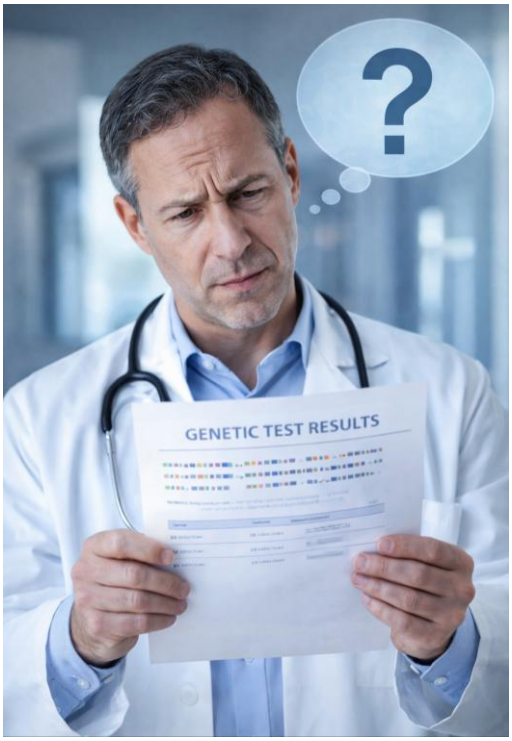
- Associated with variants in the NOD2 gene plus others
- Polygenic condition
- Estimated prevalence: approximately 1 in 100,000
- Often diagnosed in adulthood due to delayed recognition

When Genetic Testing does not Tell the Full Story

Potential autoinflammatory patients and their physicians often place high diagnostic value on genetic testing results to pinpoint a named disease to match symptoms of fevers, joint pain, serositis, rashes, GI manifestations, eye problems, etc. Results may confirm FMF, CAPS or one of 50+ autoinflammatory diseases currently identified. However, in many cases, these results may be incomplete due to limited testing or provide no genetic data (negative genetics) correlating to patient's clinical presentation. It is critical that physicians understand that 60% percent of all autoinflammatory patients do NOT have any identifiable variants. Research indicates that these patients should be diagnosed with uSAID (undifferentiated systemic autoinflammatory disorder) and prescribed treatment to prevent inflammatory damage and to control inflammasome over-activation.

Modern genetic testing has revolutionized the rare autoinflammatory diagnosis space, yet even with advanced sequencing methods, there are limitations and issues. Discrepancies across populations and ethnicities regarding mutation pathogenicity can be variable, compounded heterozygosity is often under-considered, benign mutations that appear symptom causing are not reviewed or dismissed due to lack of research, or findings may only reflect VUS (variant of uncertain significance) and raise more questions regarding a patient's innate immune function.

When a pathogenic variant is identified, its impact can vary widely from one patient to another, even within the same family of carriers. Those who express the same mutation will often have differences in symptoms, disease severity, flare patterns, onset age, or in treatment responses. This variability highlights the unique influence of epigenetics, adaptive/innate immune system pathways, microbiome, and other inherited traits impacting the cellular function within each patient. Finally, environmental triggers, infections, hormonal fluctuations, diet, vaccines, allergies, aging, and sleep patterns also influence how DNA functions. These factors all contribute to how an autoinflammatory disease is uniquely expressed.



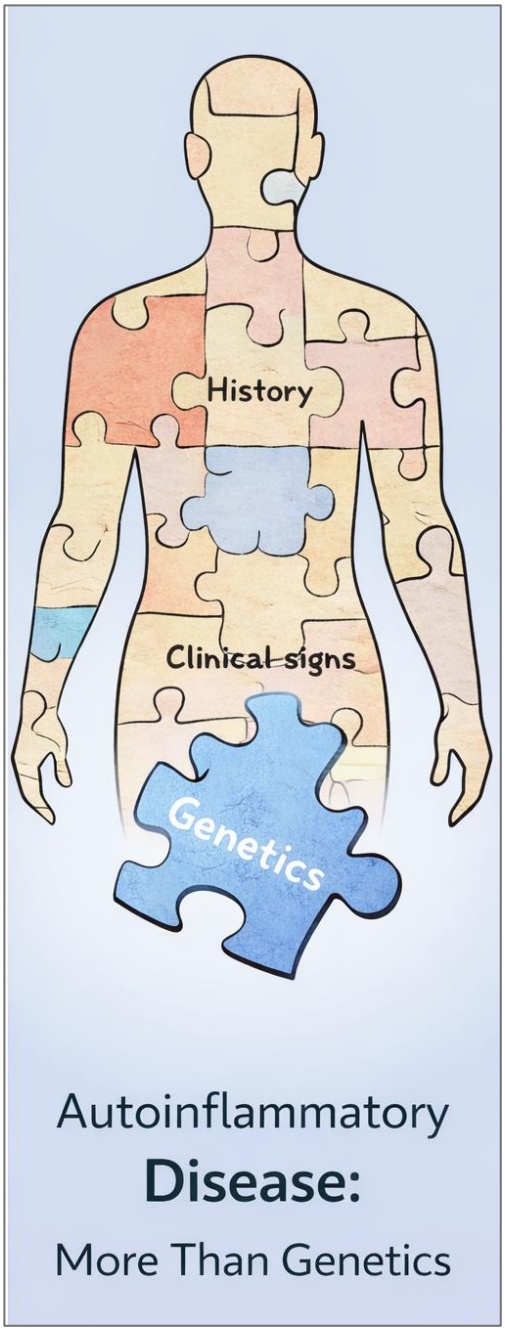
Cont. When Genetic Testing does not Tell the Full Story

Autoinflammatory conditions are not all monogenic (caused by a single mutated gene such as FMF or MVK). Several diseases such as PFAPA, Behçet's, SJIA/Stills, NOD2 (Yao's) and uSAIDs are considered to be undefined polygenic or multifactorial — meaning several genes along with adaptive immunity, mitochondrial function, and microbial response are likely co-contributing players in disease development. Thus, a broader investigation of the patient's clinical presentation, family history, and treatment response are all essential.

The Importance of a Clinical Diagnosis

A knowledgeable physician who recognizes patterns of autoinflammation should be able to make a clinical diagnosis based upon a patient's extensive medical documentation. It is important for patients to be prescribed treatment immediately upon diagnosis, regardless of genetic confirmation, to avoid complications. Standard treatment typically consists of colchicine, anti-IL-1, or other biological medications. Steroids may also be required.

Research is advancing rapidly. Whole-exome and whole-genome sequencing, transcriptomics, and advanced immunophenotyping will reveal new pathways and uncover links between autoinflammation, immunity, and metabolism. Each discovery brings new understanding to these complex disorders. It is essential for both doctors and patients to remember that genetic test results do not define the reality of autoinflammatory diseases, nor do they confirm the absence of illness. Patients must be taken seriously, listened to, and treated with compassion, while physicians should use shared decision-making strategies to ensure patient-centric care.



PFAPA Syndrome: Diagnosis, Genetic Testing, and Treatment Protocols

Diagnosis Journey

PFAPA (Marshall syndrome) is an autoinflammatory disease referred to as a Periodic Fever Syndrome (PFS). The PFAPA journey begins when the child gets recurrent monthly fever episodes accompanied by sore throat, mouth ulcers, swollen lymph nodes, fatigue, and sometimes abdominal pain or headache. These unexplained flares appear like clockwork every few weeks. Parents will take their child to the pediatrician, who, after an examination, will suspect bacterial or viral infections, leading to repeated rounds of antibiotics that are ineffective.

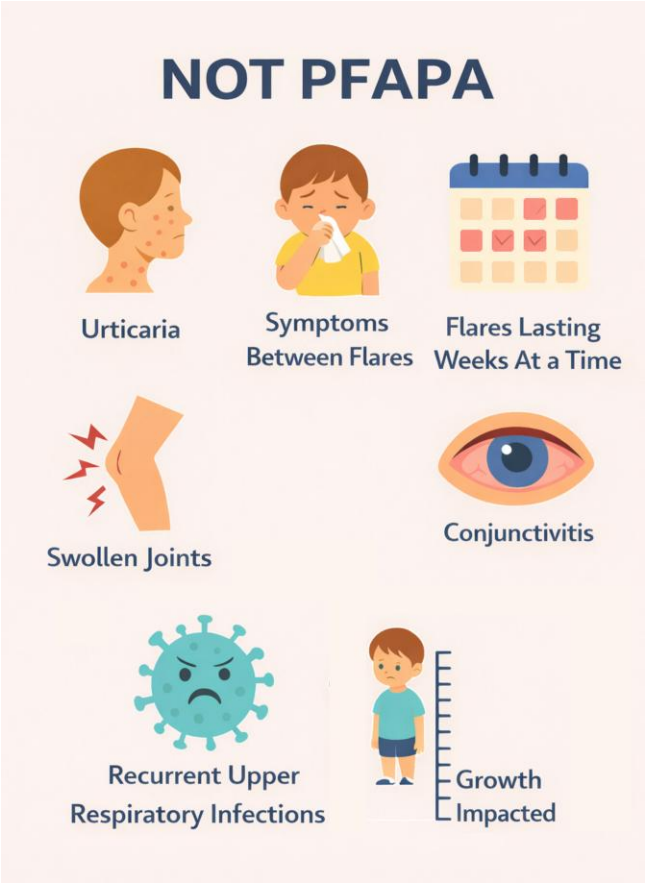
Usually after parents begin researching, often through support groups (FMF & AID's PFAPA group), that they learn about this disease and the need to consult a specialist — typically a rheumatologist, immunologist, or infectious disease expert (in the US). These types of physicians may be familiar with autoinflammatory diseases. However, it is important to note that not all physicians in these fields are knowledgeable about these conditions.

Once PFAPA is suspected, careful documentation and testing become essential. Parents are encouraged to keep a fever and symptom diary and bring it to every appointment — even if a symptom seems unrelated, it may be important to note. The length of the flare is very important to record, as it provides a valuable clue for diagnosis.

Doctors should request the following blood tests during and between flare times for appropriate diagnosis:

- CBC (Complete Blood Count)
- CRP (C-reactive protein)
- ESR (Erythrocyte Sedimentation Rate)
- SAA (Serum Amyloid A)

Monitoring elevations of acute phase reactants between and during flares will help the doctor to identify patterns of inflammation, rule out other disorders that can mimic PFAPA, and provide valuable diagnostic insight.



Cont. PFAPA Syndrome: Diagnosis, Genetic Testing, and Treatment Protocols

🧬 When Genetic Tests Come Back Negative

It is often recommended that the child expressing these symptoms be genetically tested for autoinflammatory diseases. A key point often misunderstood by many physicians is that negative genetic results do not confirm PFAPA — nor do they rule out other autoinflammatory conditions.

PFAPA is a clinical diagnosis, based on symptoms, disease course, and response to treatment. Some red flags that warrant further investigation include children who present with issues outside the typical flare timeframes. Symptoms such as rashes, anemia, respiratory or lung issues, unusually long or short flares, or flares severe enough to require hospitalization are NOT seen in PFAPA.

Unfortunately, many children are diagnosed with PFAPA, as it is the most well-known autoinflammatory condition. In such cases, valuable time may be lost while the actual underlying disease remains untreated. Thus, it is critical for these young patients to be followed closely and that data regarding their flares be collected monthly and evaluated to ensure that a misdiagnosis has not been made.

According to recent research and clinical guidelines, adult PFAPA cases are now being reclassified as uSAID (undifferentiated systemic autoinflammatory disease), therefore leaving PFAPA as a diagnosis reserved for pediatric cases.

💊 Understanding PFAPA Treatments

PFAPA treatment aims to relieve the symptoms of the flare as it is typically self-limiting and has no long-term consequences. Parents may opt for a variety of treatment options: symptomatic, abortive, prophylaxis, and surgical.

Symptomatic treatment options include NSAIDs Ibuprofen (Advil, Motrin) and/or Tylenol (paracetamol) to control fevers and other issues.

Abortive treatment options include corticosteroids to stop the flares. The typical PFAPA treatment consists of a single dose of corticosteroids (e.g. prednisone) given at the onset of a flare. In some cases, a second dose may be required the following day. The drug response can take between one to four hours, after which the fever subsides and the child recovers. The limited use of prednisone is considered safe and effective for all ages. It is often believed that steroids can increase the frequency of flares, but this is not always the case. It is imperative to contact the provider immediately, should a PFAPA child given steroids expresses severe behavioral problems or mood swings.

Cont. PFAPA Syndrome: Diagnosis, Genetic Testing, and Treatment Protocols

Diagnostically, a common misconception persists, that if prednisone stops the fever, it must be PFAPA. This is not medically accurate, as corticosteroids are powerful anti-inflammatory drugs that are also effective for other autoinflammatory conditions, including FMF (Familial Mediterranean Fever), TRAPS, MKD, etc. Steroid efficacy in aborting the flare demonstrates that inflammation is present, but it does not confirm a PFAPA diagnosis.

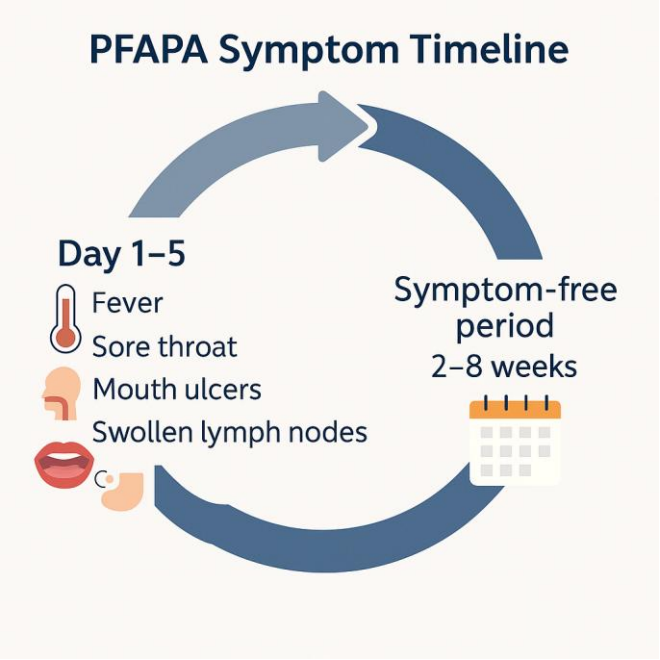
A prophylactic treatment approach to prevent flares would be the daily use of colchicine or cimetidine. However, not all patients respond to either of these medications. It is important to work with a treating physician to determine either drug's efficacy.

Additionally, another option to control PFAPA flares include T&A (tonsillectomy and adenoidectomy) surgical removal. This procedure is recommended only if all other treatment options have failed. All pros and cons should be weighed for the best decision and outcome. It is important to note that if the tonsils & adenoids are enlarged or blocking the airway, then patients should be separately evaluated for removal.

🌿 In Summary

PFAPA is the most common recurrent fever syndrome, but it remains frequently misunderstood.

A thoughtful diagnostic process, guided by specialists, symptom presentation and patient diary and observation over time is essential. Genetic testing can support but not replace clinical judgment. While prednisone remains an effective tool, its use and resolution of symptoms should not be mistaken for a PFAPA diagnosis. It is important that every child with unexplained and recurrent inflammation receives a proper medical investigation to prevent unnecessary suffering and long-term consequences.



Navigating the Medical Maze – Obstacles

The theme for the 2025 Autoinflammatory Awareness campaign was Navigating the Medical Maze. Highlighted below are the main obstacles or challenges faced by patients.

Finding a Knowledgeable Physician

Accessing a doctor with expertise in autoinflammatory diseases can be challenging due to limited local availability, long wait times for appointments, the need (and cost) to travel — sometimes internationally — and out-of-pocket expenses not always covered by insurance.

Accessing Treatment

Accessing treatment after diagnosis can be difficult — due to lack of insurance coverage, medication availability, and the need for multiple drugs. Additionally, long waiting periods for medication approval may delay starting therapy.

Treatments are NOT a cure

There is no cure for autoinflammatory diseases, and to date, there have never been drugs developed specifically targeting autoinflammation. As a result, anti-IL-1, anti-IL-6 and other medications are not always effective. Even when treatment is successful, it may only improve certain symptoms without eliminating them entirely, and it may not provide efficacy for specific clinical issues.

Myths and misconceptions

Patients often defy textbook definitions or standard diagnostic criteria in these autoinflammatory diseases. Each case is unique — even among members of the same family. Open-minded physicians, who think out the box and listen to their patients are needed.

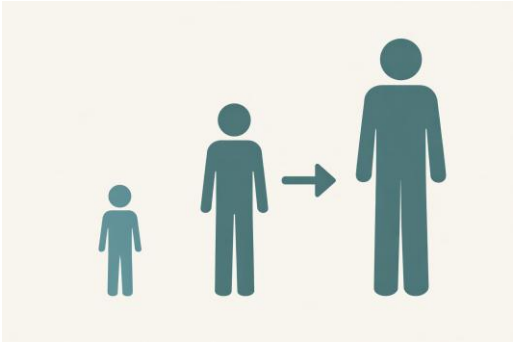
Negative Genetic Findings

Medical professionals often rely too heavily on genetic test results for diagnosis. However, up to 60% of patients with autoinflammatory diseases have no identifiable variants, underscoring the need for clinical evaluation to remain the primary diagnostic tool. The clinical presentation should guide doctors to treat symptomatic patients regardless of genetic status.

Transitioning Care from Childhood to Adulthood

Young patients may face challenges when moving into adult care. Issues may include: advocating for themselves, finding a knowledgeable physician, managing gaps in care & treatment, transferring medical records, navigating delays in medication approval, coping with emotional stress, disputing insurance or healthcare coverage changes.

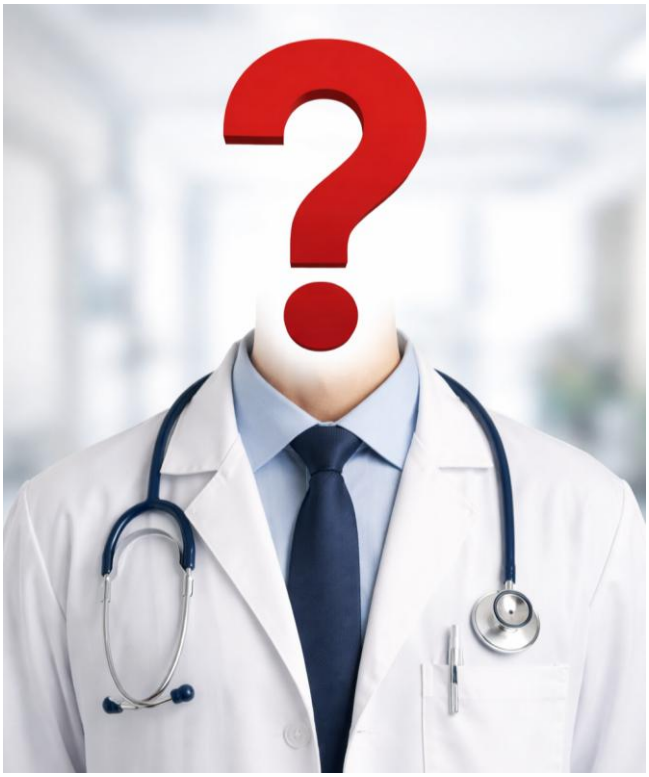
.



Cont. Navigating the Medical Maze – Obstacles

Global Lack of Experienced Rheumatologists

Few physicians have the necessary expertise to diagnose and treat autoinflammatory diseases. Many top specialists are concentrated in major cities or located at research centers, making access difficult for patients.



Accessing Disability Support

Patients may have limited access to support services and compensation due to their disease rarity, as national health systems are not designed to accommodate rare disease patients.

Parents Accused of Munchausen Syndrome

Parents often encounter disbelief or wrongful accusations regarding their child's symptoms. These confrontations may lead to false allegations of Munchausen syndrome and negatively impact the timeframe to diagnosis and treatment.

Gaslighting by Family and Friends

Family and friends often suggest that eating a healthier diet, losing weight, or being more active will cure the disease, dismissing or not understanding the medical complexity of autoinflammatory conditions.

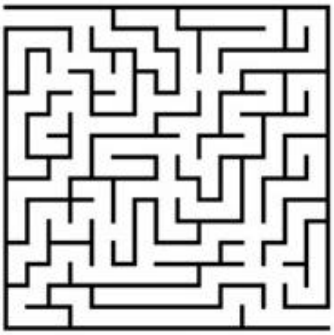
Obstacles Navigating the Medical Autoinflammatory Maze

Finding a Knowledgeable Physician
Accessing a doctor with expertise in autoinflammatory diseases can be challenging due to long wait times, limited local availability, the need (and cost) to travel — sometimes internationally — and out-of-pocket expenses not covered by insurance.

Accessing Treatment
Even after diagnosis, accessing treatment can be difficult due to lack of insurance coverage, medication availability, the need for multiple drugs, and long drug approval waiting periods.

Treatments are NOT a cure
There have never been drugs developed specifically for autoinflammatory diseases. As a result, anti-IL-1/IL-6 and other medications are not always effective for patients. Even when treatment is successful, it may only alleviate certain symptoms and not eliminate them entirely. In many cases, treatment alone is not enough to restore a normal quality of life.

Myths and misconceptions
Autoinflammatory diseases are rare, and patients often defy textbook definitions or standard diagnostic criteria. Each case is unique — even among members of the same family. Open-minded physicians, who will think out the box and listen to their patients are required.



Global Lack of Experienced Rheumatologists
Few specialists have the necessary expertise in autoinflammatory diseases, and most are concentrated in major cities or research centers, making access difficult for many patients.

Transitioning Care from Childhood to Adulthood
Young patients may face challenges: advocating for themselves, finding a knowledgeable physician, managing gaps in care and treatment, transferring medical records, navigating delays in medication approval, coping with emotional stress, disputing insurance or healthcare coverage changes.

Accessing Disability Support
May be difficult due to disease rarity, lack of specific medical codes, and the invisible nature of many symptoms.

No Genetic Findings
Medical professionals often rely too heavily on genetic test results for diagnosis. However, up to 60% of patients with autoinflammatory diseases have no identifiable variants, underscoring the need for clinical evaluation to remain the primary diagnostic tool.

Accused of Munchausen Syndrome
Physicians lack of knowledge on autoinflammatory diseases, leads to disbelief of patient symptoms and wrongful accusations against parents.

Gaslighting by Family and Friends
Often suggest that eating healthier, losing weight, or being more active will cure the disease, dismissing or not understanding the medical complexity of autoinflammatory conditions.

“Listen to Wisdom”: A book on Rare Diseases by Dr. Crespi and Diana Szarazgat

Introducing Dr. César Crespi

FMF & AID has had the pleasure of working with Dr. César Crespi and collaborating on his new book with a chapter dedicated to patient associations written by Malena Vetterli, Executive Director of FMF & AID Global Association. Dr. Crespi is not only a friend but is currently helping our Argentinean autoinflammatory patient community.

César Crespi is a physician specialist in Clinical Medicine and Hepatology. He is also the Founder and Coordinator of the Reference Center for Rare and Difficult-to-Diagnose Diseases at the Hospital San Juan de Dios. In addition, he is a lecturer at the Faculty of Medical Sciences at the National University of La Plata (UNLP). He taught for twenty years in the Department of Pathology and is currently teaching in Internal Medicine and Rare Diseases. He also holds a position as a representative for the Rare Disease Program at the Ministry of Health.

In his insightful book Listen to Wisdom, Dr. César Crespi tackles the many challenges faced by those living with rare diseases. Drawing on both medical expertise and years of experience, he explores the long and painful diagnostic odysseys patients often endure and offers a call to action for the medical community.

The book is co-authored by Diana Szarazgat, who is an Educator with an advanced degree in Education and Psychology. She works as a teacher, literacy instructor, and educational advisor. She also volunteers as a human rights advocate.

Rare diseases are frequently misdiagnosed or remain unidentified for years, causing unavoidable patient suffering. Dr. Crespi stresses that special, coordinated efforts are needed to improve early recognition and effective treatment. In many cases, the first symptoms mimic those of more common conditions, leading to delays and inappropriate therapies. This is compounded by the lack of awareness in the medical field—a reality that results in late diagnoses and greater harm.

One of the most important messages in his book is the value of listening to patients, to their experience, and to what is not immediately obvious. Dr. Crespi encourages a shift toward patient-centered care, a model that prioritizes continuous and timely support, alleviates suffering, and promotes shared decision-making between the patient and their physician.

Cont. “Listen to Wisdom”

He emphasizes that listening to patients’ issues, their lived experience, and their own reasoning, can guide the doctor to make a more effective use of their medical knowledge. A collaborative doctor-patient relationship can lead to a faster more accurate diagnosis, and better outcomes. The book also highlights the role of expert patients and patient associations, recognizing their growing contribution to medical understanding. These voices are not only important—they are essential. Their knowledge, resilience, and collective advocacy play a key role in advancing research and improving care. Dr. Crespi doesn’t shy away from the systemic challenges either, as he acknowledges the difficulty of conducting clinical studies on low-prevalence diseases, the need for specialized centers, and the importance of including rare diseases in medical training curriculum. Argentina serves as an inspiring example: since 2021, the country has introduced university-level courses on rare diseases for medical students, demonstrating a proactive commitment to improve education and to achieve more timely diagnoses.

To meet the urgent needs of this population, Dr. Crespi founded the CERyD (Reference Center for Rare and Difficult-to-Diagnose Diseases) located at the HIEA and San Juan de Dios in La Plata, Buenos Aires - Argentina. His work through this center has become a beacon of hope for many, proving that with the right structures and attitudes, change is possible.

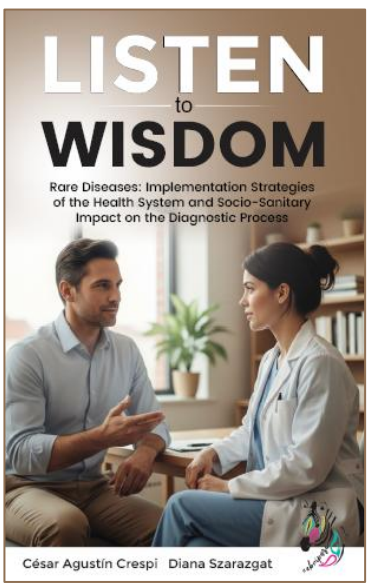
The book includes reflections and quotes that linger long after reading. Among them:

“If you hear hoofbeats, think of horses; but please don’t forget that all these other things also exist—and they can gallop too.”

“You can’t diagnose what you don’t think about, and you don’t think about what you don’t know.”

“You don’t know what hasn’t been studied, is being studied, or will be explored in the future.”

“The truth is, I don’t know what’s going on—but we are going to investigate it.” And a quote from Claude Bernard: “The one who does not know what he is looking for, does not understand what he finds.” These words invite us to stay humble, curious, and open—to both knowledge and to each other. This book is highly recommended to doctors and patients. It reminds us that medical wisdom comes not only from textbooks or test results, but also from shared experiences, communication, and the willingness to listen. Link to Amazon: https://amzn.eu/d/7LZH0MZ



Patient journey: Facundo with FMF (Argentina)

My name is Juan Facundo from Buenos Aires, Argentina. My whole adult life I have lived with symptoms that no doctor could explain. Migratory pain, inflammatory flare-ups without logic, low-grade fevers, rashes, deep weakness, cold intolerance, swelling, gastrointestinal crises, and relentless fatigue that was always present. I grew up adapting to these discomforts that for decades remained elusive.

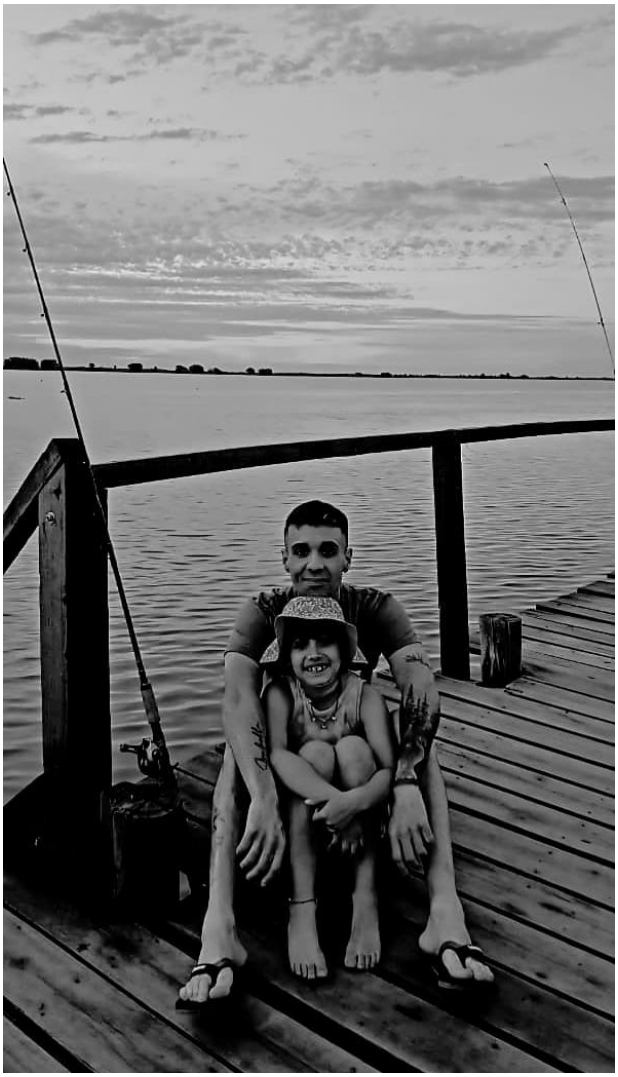
A few years ago, my symptoms became more intense. The hypoglycemia episodes were more frequent, and I began to lose weight. The pain also multiplied as I was diagnosed with having a brain tumor, followed by the suspicion that I had a neuroendocrine tumor in my pancreas. These diagnoses opened the door to hospitalizations, invasive tests, and surgeries meant to “rule things out,” but never to explain anything.

After the COVID-19 vaccine, my symptoms — present since childhood — exploded.

Inflammatory flare-ups became longer and more painful. My skin reacted for no reason. Swelling appeared in my abdomen, legs, buttocks, face. My sleep was severely affected and my body lived in a constant state of misery. Nothing made sense and each specialist saw only one piece of the puzzle.

In addition to the hypoglycemia, I developed bradycardia, that required a procedure, which nearly destroyed my life. The recommendation to treat this bradycardia led to the recommendation that I have a cardiac ablation, which would have resulted in me getting a pacemaker that I did not need. Luckily, a doctor intervened who understood my situation.

I met Dr. Guillermo Scasso, a cardiologist at Hospital Posadas and he was the first physician to fully review my case history. He noted my L-carnitine deficiency, understood that my symptoms did not fit a primary cardiac issue, and cancelled the cardiac ablation procedure that could have ruined my life.



Cont. Patient journey: Facundo with FMF (Argentina)

Thanks to him, I was able to have genetic test that revealed my accurate diagnosis of Familial Mediterranean Fever.

For the first time, a single explanation brought all the pieces together: the flares, pain, inflammation, swelling, low-grade fevers, gastrointestinal episodes, skin manifestations, episodes of extreme fatigue, and secondary cardiac symptoms. All these symptoms resulted in a diagnosis of atypical multisystemic, adult-onset, Familial Mediterranean Fever (FMF).

Under the care of my new doctor, César Agustín Crespi, a specialist in autoinflammatory diseases, I started a monthly biological treatment. The medication began to slow the deep inflammation and, above all, reduce the most feared risk: amyloidosis, a potentially fatal complication of FMF. My body began to stabilize, my labs improved, and the flare-ups decreased in intensity. However, the disease is not curable.

Along this journey, someone else fundamental appeared: Malena Vetterli, who lives, works, and breathes for patients with autoinflammatory diseases. She brings knowledge, but above all humanity. Her empathy, constant presence, and emotional support — with no personal interest, only love and deep understanding — were a lifeline that words cannot fully capture. I thank her infinitely, and on behalf of my entire family, especially my little daughter for understanding our struggle.

In every step forward, every setback, and every doubt — she was there. This is something one does not forget.

I continue with my treatment, facing unpredictable flare-ups, and fighting monthly the healthcare system to access my medication, which prevents organ damage. The emotional and physical struggle is part of the treatment process that no one talks about.

I know my hope must coexist with reality as I continue believing that science will find a simpler, more accessible treatment to control this disease. I hope that my story will help others avoid going through the same ordeal getting diagnosed with FMF.

Patient journey: Olivia with NOD2/Yao syndrome (USA)

My name is Olivia from the USA and when I was 18, I had my first fever and pain episode. I was taken to the ER, where I saw several doctors, who ultimately decided to remove my appendix. After a short recovery, I began getting sick again, and the vomiting was so severe that I could not eat or drink for many days and became very dehydrated. I eventually returned to the hospital, where it was decided to remove my gallbladder despite my feeling better after receiving IV fluids.

This periodic cycle of feeling unwell repeated over several years. I was continuously told I had some type of virus but would test negative for everything. I was told, it must be a false negative and when asked repeatedly why each fever episode was so similar, the response was that I did not fully heal from the previous illness. I was told that my job working with children was the trigger for my getting sick and it could not be that bad since I was still able to work.

Doctors would tell me I was complaining or asking too many questions, and eventually, when I was 24, my flares became so significant that I began having febrile seizures with my temperature reaching 104°F/40°C every 5 days. I was also having episodes of pericarditis and my neck hurt so badly I could not move during flares, which were also accompanied by gastrointestinal symptoms.

This pattern continued for months, where I would feel better for only 3 to 5 days between episodes.

It was during the COVID shutdown, when the doctor finally realized my repeated symptoms were not sickness. I had been to rheumatology, cardiology, orthopedics, neurology, genetics, and was beginning to think they would never figure out had I had.

Eventually, I was referred back to the geneticist who prescribed colchicine even though my FMF test came back negative. My fevers went down to 102°F/39°C during flares and I was ordered additional genetic testing for autoinflammatory diseases. The results indicated that I carried a NOD2 genetic variant. However, my doctor indicated it was an insignificant finding. I called my mom when I received the results and we began researching this mutation and found information relating it to NOD2/Yao syndrome.

Cont. Patient journey: Olivia with NOD2/Yao syndrome (USA)

My symptoms appeared to match and I emailed my doctor asking if Yao Syndrome had been ruled out. Unfortunately, he didn't know what this disease was and was unwilling to help me.

I went to a NOD2 provider who confirmed that I did have Yao's syndrome, and was then diagnosed by a different provider, that I also have concurrent Still's disease. Despite having two confirmed diagnoses, another provider told me I should be thankful that I was no longer having febrile seizures. It was about that time that I reached out to FMF & AID, where I connected with Malena, who offered me support and medical information to help me determine how to advocate for myself.

I was put on an anti-IL-1 biologic that was helping, but wore off too quickly. I am now on a different biologic that helps me feel much better. It has been a 12-year process finding the correct diagnosis and treatment. Thankfully, the medication has allowed me to restart hobbies I used to love. I can now do things that I was previously unable to do in my adult life. It has been a blessing.

Malena has helped me tremendously. Before my contact with her and FMF & AID, I had never spoken with any other patient who had an autoinflammatory disease. I was able to join support groups and meet other people struggling like myself.

The support I have received gave me hope and has facilitated my diagnosis and care. Additionally, she was able to translate several key medical documents in case of emergency situations for my travels. She also offered compassion, when my family was not always accepting my having a chronic illness. I now have my whole family wearing the FMF & AID merch and telling everyone about the website to educate others about autoinflammatory conditions.

FMF & AID Merch

Every purchase of FMF & AID merch directly supports our advocacy work and helps raise awareness for autoinflammatory diseases worldwide. By wearing or sharing our merch, you are helping make our rare diseases more visible.

Shop our merch here:
www.zazzle.ch/kollektionen/rare_disease_awareness-119156308160487760

KIDS CORNER

FMF & AID's mascott JJ

FIND YOUR WAY THROUGH THE MEDICAL MAZE!

Disease Terminology and Awareness Dates

Disease	Autoinflammatory Syndromes	Gene	Awareness Day
TRAPS	Tumor necrosis factor- associated Periodic Fever Syndrome	TNFRSF1A	2nd September
NOD2	Blau/Yao Syndrome	NOD2 (CARD15)	3rd September
PFAPA	Periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis	N/A	4th September
HA20	A20 haploinsufficiency	TNFAIP3	5th Sepember
HIDS / MKD	Hyper IgD / Mevalonate Kinase Deficiency	MVK	6th September
AOSD sJIA	Adult-onset Still's disease Systemic Juvenile Idiopathic Arthritis	N/A	7th September
CAPS	Cryopyrin-associated periodic fever syndromes (CAPS):	NLRP3	9th September
	Muckle Wells Syndrome (MWS)		
	Familial cold Autoinflammatory Syndrome (FCAS)		
	Neonatal onset multisystem inflammatory disease (NOMID) Chronic infantile neurologic cutaneous and articular syndrome (CINCA)		
FCAS2	Familial cold Autoinflammatory syndrome 2	NLRP12	10th September
PAPA	Pyogenic Arthritis, Pyoderma gangrenosum and Acne	PSTPIP1	11th September
DADA2	Deficiency of Adenosine Deaminase 2	ADA2	15th September
FMF	Familial Mediterranean Fever	MEFV	17th September
SAPHO	Synovitis-acne-pustulosis-hyperostosis-osteitis syndrome	N/A	19th September
IRAP	Idiopathic recurring acute pericarditis	N/A	25th September
uSAID	Undefined systemic autoinflammatory disease	N/A	29th September
Other autoinflammatory diseases			
HS	Hidradenitis Suppurativa	N/A	6th – 12th June
BD	Behcet's disease	N/A	20th May
CRMO CNO	Chronic recurrent multifocal osteomyelitis Chronic nonbacterial osteomyelitis	N/A	October

FMF & AID Partner Associations

Italy Spain Georgia Czech Republic Turkey United Kingdom Italy Spain

Italy Italy Chile Argentina El Salvador Israel Germany

Brazil Thailand Morocco Italy Spain Middle East France