



Rare Autoinflammatory
Disease Manifesto

Knowledge is Power: Raising Awareness to Improve Lives

**A manifesto for people living with
rare autoinflammatory diseases**

*“The future is exciting and we must
never stop believing it”*



1.

Acknowledgements

Novartis would like to thank all groups and individuals involved in the manifesto for their input and collaboration:

Individuals

| | | |
|-----------------|----------------|-----------------|
| Saskya Angevare | Wendy Costello | Nacho Llorca |
| Irina Bakradze | Atar Dvir | Michal Nudel |
| Linda Bergamini | Gabi Erbis | Norma O'Keefe |
| Gabriele Bona | Anton Gruss | Malena Vetterli |

Organisations

AIFP – Italy

<http://www.febrriperiodiche.it>

AMRI Onlus – Italy

<http://www.amri.it>

Aspanijer – Spain

www.aspanijer.org

ENCA – International Association

<https://www.enca.org>

FMF & AID Global Association –

International Association

www.fmfandaid.org

KAISZ – Netherlands

<http://www.kaisz.nl>

Kourir – France

<https://www.kourir.org>

Mifrakim Tz'eirim – Israel

<https://mifrakim.org.il>

Sunflower Foundation – Russia

<https://www.fondpodsolnuh.ru>



Individual participants

Professor Miloš Jeseňák

Specialist in Rare Immunological Diseases, Centre for Periodic Fever Syndromes
Department of Paediatrics and Department of Pulmonology and Phthysiology, Jessenius
Faculty of Medicine in Martin, Comenius University in Bratislava, University Hospital
in Martin, Slovakia

Foreword

The Rare Autoinflammatory Disease Manifesto

Novartis has developed the Rare Autoinflammatory Disease Manifesto in collaboration with a group of patients, healthcare professionals and patient organisations that are part of the rare autoinflammatory disease community internationally. The manifesto aims to raise awareness of these rare conditions to drive change and improve lives. It highlights calls to action for key aspects of the patient journey that require urgent attention from various stakeholders, including healthcare professionals, patient organisations, patients and policymakers.

A rare and evolving global challenge

Rare autoinflammatory diseases are an emerging and rapidly evolving group of rare conditions characterised by spontaneous, unprovoked and disabling attacks of systemic inflammation, including recurring fevers, rashes and severe fatigue.²⁻⁷ In most cases, rare autoinflammatory diseases are inherited and start in childhood, persisting throughout adult life.^{6,8-11} Due to the non-specific symptoms of rare autoinflammatory diseases, identification and diagnosis of a condition is often delayed, leading to substantial delays in patients receiving appropriate treatment and care.

The multifaceted burden of rare autoinflammatory diseases

The symptoms and consequences of rare autoinflammatory diseases impose significant physical, emotional, social and financial impact on patients, their families and healthcare providers, that affect all areas of life, from education to relationships.^{2,12-14} The rarity and low level of awareness about these conditions results in a significant lack of understanding and support from their social environment, further adding to the disease burden.² The life-long nature of rare autoinflammatory diseases means these burdens are constant, continuing from childhood to adolescence and adulthood, which gradually impairs patients quality of life, while placing long-term and substantial financial strain on healthcare systems. Paediatric patients are especially impacted by their disease as symptoms disrupt physical, educational and social development, and the transition to adult care is one of the most challenging periods.^{2,14-16}

The need to improve lifelong care and support

Through greater scientific understanding and improvements in technology, there have been significant improvements in the diagnosis and treatment of rare autoinflammatory diseases. However, patients still encounter barriers throughout their journey towards optimal management and care. Awareness and deep knowledge of rare autoinflammatory diseases remains limited amongst healthcare professionals and patients. Coupled with symptoms that overlap with other diseases, this means an accurate diagnosis is challenging and can be very delayed; some patients wait for many years or even decades for an accurate diagnosis.^{2,17-19}

Additionally, although current treatment options for rare autoinflammatory diseases can provide symptomatic control,²⁰⁻²² some patients may struggle to be prescribed an effective medication that they can also tolerate well.^{10,20,22,23} Diagnostic delays, difficulties in accessing specialist care and ineffective management can impede optimal care and can have a substantial impact on long-term health and quality of life.^{17,24} To prevent complications and improve outcomes, there is a need for a more accurate and timely diagnosis, appropriate selection of existing therapies tailored to individual patients and more treatment options that can potentially address the underlying causes of rare autoinflammatory diseases.²⁵

Together, Novartis, the patients, experts and patient organizations that have collaborated to create the manifesto are committed to addressing the needs and advocating for the rights of those impacted by rare autoinflammatory diseases, including the patients, their families and the healthcare providers involved in their care. These aims are being achieved through collaborations with various organisations and healthcare experts.

The manifesto aims to unify stakeholders to help raise awareness and education of rare autoinflammatory diseases and improve the lives of people living with rare autoinflammatory diseases.

Rare Autoinflammatory Disease Manifesto



Vision:

To raise awareness and education of rare autoinflammatory diseases.



Mission:

To improve the lives of people living with rare autoinflammatory diseases.

By identifying key unmet needs mapped against the patient journey, this manifesto proposes key asks that can help overcome the barriers to optimal care, towards the long-term goal of **improving the lives of people living with rare autoinflammatory diseases across the world.**

Rare autoinflammatory diseases:

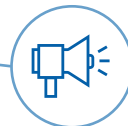
A call to action

Together, patients, carers, healthcare professionals, patient organisations and policymakers must address the unmet needs and lessen the disease burden of people living with rare autoinflammatory diseases and their families. It is vital that key stakeholders, including the entire rare autoinflammatory disease community and beyond, take crucial steps towards **improving the day-to-day lives of all people living with rare autoinflammatory diseases. We call on:**



Healthcare professionals and policymakers to:

- Ensure continuous improvement of diagnostic processes and access to innovative treatment, disease management and specialist healthcare services.



Patient advocacy groups to:

- Empower patients to be at the centre of care-making decisions.
- Promote the development of collaborative, holistic and long-term relationships and effective communication between patients and healthcare professionals.
- Advocate for improved care and health outcomes.



All stakeholders to:

- Increase awareness and recognition of the extensive impact that rare autoinflammatory diseases have on individual lives, healthcare systems and societies at large.
- Engage patients to actively participate in scientific research and development.

Contents

| Chapter | Page |
|--|------|
| 1. Acknowledgements | 1 |
| 2. Foreword | 3 |
| 3. Contents | 5 |
| 4. Understanding rare autoinflammatory diseases | 6 |
| 5. The multifaceted burden of rare autoinflammatory diseases | 8 |
| 6. Identifying barriers to optimal care across the patient journey | 11 |
| 7. Evidence and the need for urgent action | 13 |
| 8. Appendices | 15 |
| 9. References | 19 |

Abbreviations

| | |
|-------------------------|--|
| AID | Autoinflammatory disease |
| AOSD | Adult onset Still's disease |
| CAPS | Cryopyrin-associated periodic syndrome |
| FMF | Familial Mediterranean fever |
| HIDS | Hyper IgD syndrome |
| JIA | Juvenile idiopathic arthritis |
| PFAPA | Periodic fever, aphthous stomatitis, pharyngitis, adenitis |
| PFS | Periodic fever syndrome |
| SAID | Systemic autoinflammatory disease |
| SJIA | Systemic juvenile idiopathic arthritis |
| SURFS | Systemic undifferentiated recurring fever syndrome |
| TRAPS | Tumour necrosis factor receptor-associated periodic syndrome |
| UNC-SAID / uSAID | Unclassified systemic autoinflammatory disease |

3.

Understanding rare autoinflammatory diseases

The International Congress of Familial Mediterranean Fever and Systemic Autoinflammatory Diseases defines rare autoinflammatory diseases as “conditions caused by an exaggerated innate immune system response, resulting in episodes of spontaneous inflammation affecting multiple organs”.²⁶

Rare autoinflammatory diseases are a large number of different rare conditions, which involve an abnormal activation of the body’s first line of defence against infection (the innate immune system), which then triggers the second line of defence (the adaptive immune system).²⁷ In most cases rare autoinflammatory diseases are inherited and start in childhood. Patients spontaneously experience a range of **signs and symptoms** related to fever and inflammation, which can affect multiple organs, including the abdomen, chest, joints, skin and eyes.^{8,11,27,28} These symptoms often flare up suddenly and can be very disabling, having a **major impact** on every aspect of patients’ life.^{2,4,5} Clinical features (symptoms and their severity) can vary greatly from one individual to another and between conditions.^{8,11,15,29}

Key facts and figures

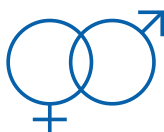


The most common and well known genetic rare autoinflammatory disease is **Familial Mediterranean fever (FMF)**.²¹



FMF affects about **150,000 people worldwide**.³⁰

The frequency of other rare autoinflammatory diseases is lower than this and, for many conditions, is not yet quantified,²³ which may be due to the fact that these conditions remain unrecognised and underdiagnosed, and therefore underreported in a significant proportion of patients.^{29,31,32}



Rare autoinflammatory diseases affect **both genders equally**.²³

In most cases rare autoinflammatory diseases are **inherited** and start in **childhood**, persisting throughout adult life. Other rare autoinflammatory diseases are **acquired**, presenting at any time during adulthood.^{6,8,10,11}



Over **30** genes associated with rare autoinflammatory diseases have been identified.⁶



25% of people with rare diseases wait **5–30 years** from when their symptoms begin to receiving a diagnosis and **40%** receive an incorrect initial diagnosis.³³


Rare autoinflammatory diseases are caused by defects in genes that regulate innate immunity, resulting in excessive production of pro-inflammatory proteins called cytokines, such as IL-1, IL-6 and TNF. Disease pathogenesis can be complex and is likely influenced by the presence of multiple modifying genetic alleles, epigenetic modifications and environmental factors.^{29,34} In most cases, autoinflammatory conditions have an established clinical diagnosis but a complex genetic background; known as complex, polygenic or multifactorial rare autoinflammatory diseases.^{6,11,26,35,36} However, no mutation is found in at least 50% of patients; in such cases the diagnosis can be made based on the typical clinical features.^{15,17}

Most rare autoinflammatory diseases have a complex clinical picture with overlapping signs and symptoms, making classification challenging.³⁷⁻³⁹ Since 1990, more than 40 different conditions have been categorised as rare autoinflammatory diseases.^{6,15,40} The most common and well-characterised group of rare autoinflammatory diseases are periodic fever syndromes (PFS).⁴¹ As the disease spectrum broadens to include new conditions influenced by multiple genetic and environmental factors, it adds complexity to the clinical picture, with overlap between rare autoinflammatory diseases and autoimmune diseases.^{29,34,42} There is often a lack of distinct diagnostic or classification criteria,^{24,43,44} but the conditions can be broadly defined into three categories:^{19,24}


| Type | Monogenic | Polygenic, complex or multifactorial | Undifferentiated |
|-----------------|---|--|---|
| Cause | Changes or mutations to a single gene. ⁶ | Changes to multiple genes which independently have a low risk but combined together, or with external risk factors, can cause disease. ^{6,14} | Undifferentiated or undefined rare autoinflammatory diseases are conditions considered to be rare autoinflammatory diseases clinically, but often have a clinical picture that does not correspond to any specific diagnosis. ^{6,45-47} They can be caused by change(s) in one gene or be multifactorial. ⁴⁶ |
| Examples | FMF , a relatively common rare autoinflammatory disease. TNF-receptor associated periodic syndrome (TRAPS) Cryopyrin-associated periodic syndromes (CAPS). ⁴¹ | Systemic juvenile idiopathic arthritis (SJIA) – the childhood form of Still’s disease, a rare autoinflammatory disease affecting 10–15% of children with juvenile idiopathic arthritis (JIA) in the US and Europe. Adult onset Stills disease (AOSD) – the adult form of }Still’s disease. Behçet’s disease. Periodic fever, aphthous stomatitis, pharyngitis, adenitis (PFAPA). Schnitzler syndrome. ^{36,48,49} | No examples of conditions available – patients who do not fit a specific condition are mostly commonly diagnosed as ‘undifferentiated rare autoinflammatory diseases’ or ‘general PFS’. Other terms used to clinically describe this category include: ⁵⁰ <ul style="list-style-type: none"> • Undifferentiated PFS. • Systemic autoinflammatory disease (SAID). • Systemic undifferentiated recurring fever syndrome (SURFS). • Undifferentiated autoinflammatory disorder. • Unclassified systemic autoinflammatory disease (UNC-SAID or uSAID). • Autoinflammation of unknown cause. |

This table is not representative of all autoinflammatory diseases but simply provides an overview of the main conditions described in this manifesto. For a comprehensive chart please see: [Autoinflammatory Alliance Comparative Chart](#).


Possible symptoms in people with rare autoinflammatory diseases*^{2,9,11,27,51}




Skin symptoms, such as a rash, are a key symptom.




Recurring fever is the most common symptom.




Inflammation / fluid collection / pain in the chest and abdomen.




Severe fatigue.



Inflamed / enlarged internal organs.



Joint swelling / aches / pain.



Muscle pain.

* To search for possible symptoms associated with rare autoinflammatory diseases please see: [The Autoinflammatory disease Database \(http://www.autoinflammatory-search.org\)](http://www.autoinflammatory-search.org).

4.

The multifaceted burden of rare autoinflammatory diseases

Unpredictable and insidious symptoms place severe physical, emotional, social and financial burdens on rare autoinflammatory disease patients, their families and those who treat them.

The symptoms of rare autoinflammatory diseases present a lifelong burden for patients

- Inflammatory symptoms usually occur spontaneously and last for days to weeks, often separated by intervals of symptom-free periods and overall good health for weeks to months,⁸ with patients often suffering considerably during flare-ups.⁵²
- However, some individuals may exhibit a continuous acute phase response, sometimes with worsening of symptoms.¹⁵
- In severe cases, long-term and persistent symptoms may develop into irreversible health conditions, such as loss of organ function and disability, potentially resulting in a poorer quality of life or death.^{8, 15, 53-55}

“The fatigue is so hard in the morning... and then it impacts the rest of the day”⁵⁶

Children and young people are disproportionately affected by the burden of rare autoinflammatory diseases

- Rare autoinflammatory diseases have been shown to impact personal relationships, school, employment and social participation.^{2, 57} As a result, quality of life in patients with rare autoinflammatory diseases is significantly lower than that of the general population, with children being affected the most.^{58, 59}
- Children with rare autoinflammatory diseases often miss school due to symptom flare-ups and medical appointments, implicating their performance.^{2, 16} In a study, missed school days were documented in 78% of patients.²
- Additionally, because the disease is largely “invisible” outside of acute episodes, patients may not always look obviously unwell all the time and so can be misjudged.^{2, 16}
- Patients report a lack of understanding and support from teachers and peers as well as bullying.^{2, 60}
- There is a misconception among teachers that rare autoinflammatory diseases are contagious and children feel they are treated differently to their peers as a result.⁶¹
- Disrupted primary education can prolong a patient’s school career, with negative consequences for higher education and employment later in life. In a quality of life study, 46% of patients indicate that their disease delayed their education and in 17% this made high school graduation unachievable.¹⁴

“Children in school are often judged incorrectly, we are so tired. The teachers think they are not motivated, and they don’t want to learn. The extreme fatigue is part of their illness”²

The transition from childhood to adulthood is one of the most challenging periods for patients

- Symptoms of rare autoinflammatory diseases can disrupt children's physical, educational and social development and, as adults, they face the challenge of holding sole responsibility for managing their disease.^{2,16,62}
- For these reasons, transitioning from childhood to adolescence and to adulthood is one of the most challenging periods for patients; the process should be gradual and requires an appropriate level of medical care and support.^{16,63}

The burden of rare autoinflammatory diseases extends beyond patients to their families and caregivers

- Symptoms associated with rare autoinflammatory diseases, such as fatigue and chronic pain, can be physically debilitating and constant flare ups can make performing seemingly simple day-to-day tasks, challenging and nearly impossible.^{1,2,59,64,65}
- This restriction to daily activities and unpredictability of symptoms can negatively affect the emotional well-being and everyday lives of patients, their families and those who care for them.^{2,16,59,66}

Social exclusion is a key challenge for people living with a rare autoinflammatory disease and their caregivers

- The disease often limits social activities of patients and their families.²
- Social exclusion was reported by 78% of patients in a survey study.²

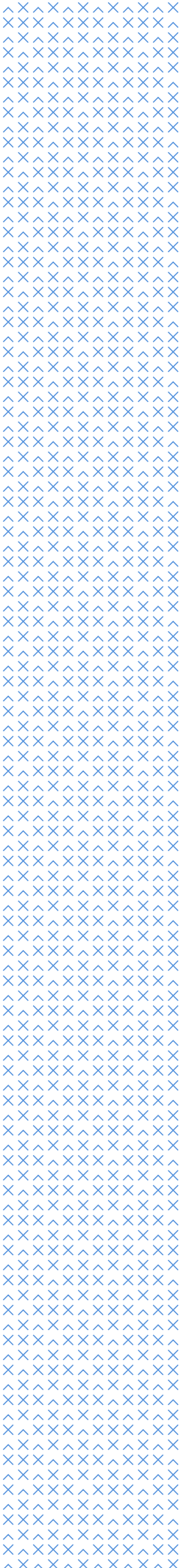
“We often have to cancel social gatherings, because our child has a disease flare...and our friends don't understand: why are they cancelling again? We don't really get invited anymore”

Patients and their families often experience emotional and psychological stress

- Emotional stress on parents and their family members is significant due to the unpredictable nature of rare autoinflammatory diseases.²
- The genetic risk associated with the disease causes concerns around family planning and relationships.²
- Psychological conditions, including anxiety and depression, are associated with rare autoinflammatory diseases, adding to the overall emotional disease burden.^{2,67}
- In addition to the educational/employment and social limitations, the stress of daily living magnifies and contributes to feelings of anxiety, isolation, loneliness, guilt and sadness in patients and caregivers.^{2,66}

“The hardest part is isolation. I'm 28 years old and I just haven't had the same experiences as my peers”¹⁷

“The psychological pressure...is much higher for parents with sick children. Everything comes with a huge time commitment”



“We wanted to get a life insurance for our child when she was 4 or 5 years old...[but] we were told it would be of little benefit given her illness and [so] she [did] not get one²”

Around one in four patients with rare autoinflammatory diseases is unemployed and many face financial difficulties

- Work disruption and absence for patients and their caregivers due to the disease can negatively influence work productivity, job security and career / workplace options.^{2,14,68}
- Adult patients frequently miss work and 26% of patients are unemployed.^{2,14,68}
- Indirect costs, including an inability to work as a patient coping with symptoms, or as a parent caring for a child with a rare autoinflammatory disease, place a significant financial burden on patients and their families.^{13,14,33}
- The direct costs of accessing care and treatment, including travel costs, further adds to the financial impact.^{13,33}

“He got really sick...the constant pressure of his employer [made] him unstable and liable²”

Management of rare autoinflammatory diseases impacts healthcare systems and social care systems

- Rare autoinflammatory diseases generate substantial costs and use of resources, including healthcare professional visits, diagnostic tests, insurance coverage and sick leave.^{12,13}
- Recently, the total treatment cost for a patient living with SJIA to healthcare systems was estimated to be £1,929 in the first year after diagnosis.¹²
- Care costs for long-term complications, such as organ damage, that occur due to long diagnosis delays and inadequate disease management may contribute further to the economic burden on healthcare systems.^{2,14,24,55,69}
- Patients require care from childhood to adulthood, placing a long-term economic burden on national health systems and private payors.^{2,12,58}

5.

Identifying barriers to optimal care across the patient journey

To begin to address the unmet needs of people living with rare autoinflammatory diseases, barriers faced at each stage of the patient journey must be identified.

Making a diagnosis as quickly as possible is vital so patients can receive the most appropriate treatment and care.¹⁶ However, diagnosis of autoinflammatory conditions can be challenging and patients often endure severe delays to diagnosis and subsequently treatment, lasting many years or even decades, due to repeated testing, multiple medical visits and misdiagnosis.^{17,19,70,71} This can have a substantial impact on long-term health and quality of life.^{24,71}

“When we received the diagnosis I was pleased to hear at last they had found what was wrong with me”⁷²”

David

SJIA patient now in remission

The lack of familiarity of rare autoinflammatory diseases amongst primary care healthcare professionals means that final diagnoses are often made by specialists with expertise in rare autoinflammatory diseases at tertiary care centres.^{2,18,73} Additionally, these specialists are essential members of the multidisciplinary team involved in the ongoing management and monitoring of patients with rare autoinflammatory diseases.⁴³ However, accessing appropriate specialist care can be challenging and is a major barrier that can prolong treatment initiation time.⁷³

“It’s more than just an appointment with a doctor for me. It’s a day on which I can talk about myself and my health with someone who really listens to me and also has answers for me. That’s why I’m lucky to have met these doctors who are so amazing”⁷²”

Emma

Muckle Wells patient at the Centre for Autoinflammatory Diseases in Tübingen, Germany

After long periods of uncertainty, finding the appropriate treatment, care and support is vital. In recent years, significant advancements in rare autoinflammatory diseases knowledge has led to more therapy options and improvements in care.²⁰ When patients find treatment regimens that are well-tolerated and effective for them, they are able to lead full and productive lives.⁷⁴ However, treatment and ongoing management still comes with its own set of challenges:

“Availability of novel and effective treatment modalities should be the most important driving tool allowing the patients with rare autoinflammatory diseases to live lives of a full quality and without any limitations, since the innovative therapies showed clear capacity for that. On the other hand, the treatment of rare autoinflammatory diseases has to be in the hands of skilled physicians with experiences with management of such particular diseases. Experiences are able to secure the correct indications of therapy with its full clinical capacity which is a miracle for the majority of the autoinflammatory diseases patients⁷²”

Prof. Milos Jeseňák

Specialist in Rare Childhood Diseases, based at the Centre for Periodic Fever, Department of Paediatrics and Department of Pulmonology, Jessenius Faculty of Medicine in Martine, Comenius University Bratislava, University Hospital (Martin)

| Barriers to achieving timely diagnosis | Barriers to accessing specialist care | Barriers to receiving appropriate treatment and care |
|--|---|---|
| <p>Low awareness of rare autoinflammatory diseases amongst general practitioners causes diagnostic delays.⁵</p> <ul style="list-style-type: none"> The rarity of these conditions makes it difficult for general practitioners to identify them.² The high number of identified rare autoinflammatory diseases (more than 30)⁷⁵ and rare diseases (approximately 7,000),⁷⁶ make it difficult for primary care healthcare professionals to be aware of every condition and therefore, correctly diagnose them.² | <p>There is a shortage of specialists worldwide resulting in access challenges or long waiting times.</p> <ul style="list-style-type: none"> Healthcare professionals specialised in rare autoinflammatory diseases are limited or not available in some countries, with only a few experts and reference centres available in Europe and beyond.⁷⁴⁻⁷⁸ As a result, patients and their families often face long waiting lists and times for appointments.⁷⁴⁻⁷⁸ | <p>Finding optimal treatment can be a lengthy and challenging process.</p> <ul style="list-style-type: none"> Current treatment options can provide symptomatic control,²⁷⁻²⁹ however, tolerability can be a challenge for some patients.^{10,18,27,29} Patients may require trials of numerous therapies before finding an appropriate option.^{10,81} |
| <p>Lack of clear diagnostic criteria and definitive testing means achieving a diagnosis is a complicated process.^{24,43,44}</p> <ul style="list-style-type: none"> Due to a lack of diagnostic criteria for rare autoinflammatory diseases, diagnosis is mostly based on clinical clues.^{16,23,24} Achieving an accurate diagnosis may require clinicians to eliminate a number of possible causes or diseases – this can be a long and challenging process.¹⁶ Although genetic analyses have improved diagnosis times, they are expensive and don't always give clear answers, with only 50% of affected patients having positive results.^{16,23,24} | <p>Patients may have to travel far to access specialised care.</p> <ul style="list-style-type: none"> Due to the lack of specialists, patients often have to travel to other regions or even countries in order to access specialised services, which can lead to substantial personal costs.^{24,39,75} | <p>Access to effective therapies varies by country and can be challenging.</p> <ul style="list-style-type: none"> Physical barriers, such as the need to travel long distances for appropriate care and management are particularly relevant and challenging especially for young patients, for whom the journey must often be made with their family.^{13,39} |
| <p>Low awareness of rare autoinflammatory diseases amongst general practitioners causes diagnostic delays.⁵</p> <ul style="list-style-type: none"> The rarity of these conditions makes it difficult for general practitioners to identify them.² The high number of identified rare autoinflammatory diseases (more than 30)⁷⁵ and rare diseases (approximately 7,000),⁷⁶ make it difficult for primary care healthcare professionals to be aware of every condition and therefore, correctly diagnose them.² | <p>Lack of awareness of specialist centres.</p> <ul style="list-style-type: none"> Many patients are unaware of specialised care facilities in the first place.⁷⁷ | <p>Patients are not always equipped to effectively manage their long-term condition.</p> <ul style="list-style-type: none"> Patients, particularly at a younger age, may not naturally possess the self-management skills to successfully manage their condition into adulthood.^{63,78} Adherence and compliance issues, particularly given the long-term nature of rare autoinflammatory diseases, may result in less favourable patient outcomes,^{18,83} demonstrating the need for improved self-management and more treatment options. |

Evidence and the need for urgent action

Taking appropriate action at each stage of the patient journey can create change and overcome barriers to achieving optimal care.

Analysis of the care pathway shows that the patient journey remains complex and patients, families and healthcare professionals are endlessly faced with **multiple barriers** that impede optimal care. To improve the patient journey, it is essential to identify appropriate actions at each stage, from both a healthcare professional and patient perspective, that can overcome these obstacles.

Actions for improving diagnosis

- Providing primary healthcare professionals with education and knowledge of rare autoinflammatory diseases, including early signs and symptoms, and more well-defined diagnostic criteria may be the first steps to enable primary healthcare professionals to distinguish and accurately diagnose rare autoinflammatory diseases earlier in the patient journey.⁷⁹
- Implementing and educating healthcare professionals on a structured, stepwise approach to refer a patient with a suspected rare autoinflammatory disease is crucial to ensuring accelerated specialist referral and ongoing care management.

Actions for improving access to specialist healthcare teams

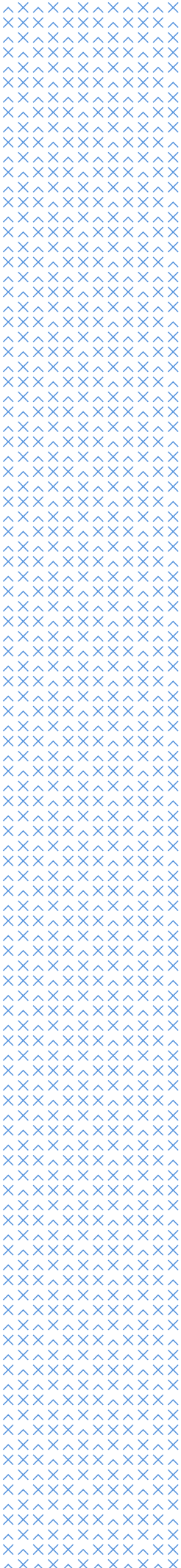
- Facilitating linking of centres of excellence with other expert centres to create centre networks for groups of rare autoinflammatory diseases with similar needs will help improve access to specialised care for patients.
- Implementing reimbursement schemes for costs incurred to patients when travelling will lessen the burden on patients and improve access to specialist care.
- Providing information and resources to raise healthcare professional and patient awareness about local specialised facilities, including centres of excellence, will help improve access high-level support and care.⁷⁷

Actions for improving treatment and care

- All healthcare professionals (nurses, primary care physicians and specialists) should be educated on treatment and management best practice, which will allow them to harmonise treatment strategies and ensure patients receive the best possible care.²⁴
- More research to improve the understanding of disease mechanisms may enable the development of novel therapy options that can potentially address the underlying causes of rare autoinflammatory diseases.²³
- Improved awareness amongst specialist healthcare professionals may also prompt greater research and innovation with regards to clinical trials and academic studies, facilitating the designing of trials and studies around patients living with rare autoinflammatory diseases.

Actions for increasing patient empowerment

- Improving scientific understanding around rare autoinflammatory diseases and providing appropriate tools will help patients recognise their condition early and understand the care they require at different stages of their disease.

- 
- Additionally, greater disease awareness from a societal point of view will help remove stigma and will autoinflammatory disease the implementation of support services within academic and workplace environments.²
 - Importantly, creating and building an environment of trust where patients, caregivers and healthcare professionals can work collaboratively is vital to optimise care.¹⁷
 - Providing patients with the appropriate self-management skills and support to help them participate in decision-making and self-manage their symptoms will ensure a smooth transition process from child to adult care.^{63,78}

Early detection and a precise diagnosis, increasing therapy options, optimising disease management and facilitating patient engagement and empowerment will ensure patients receive effective treatment and care that is right for them as individuals.

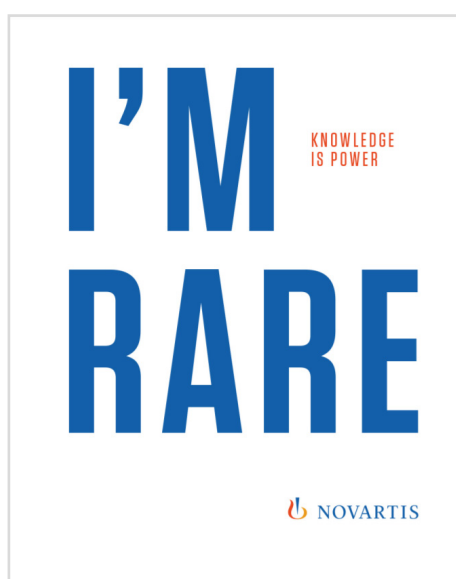
Appendices

Appendix A: Previous activities

The collaboration between Novartis and Patients, healthcare professionals and Patient advocates has resulted in educational programmes, including:

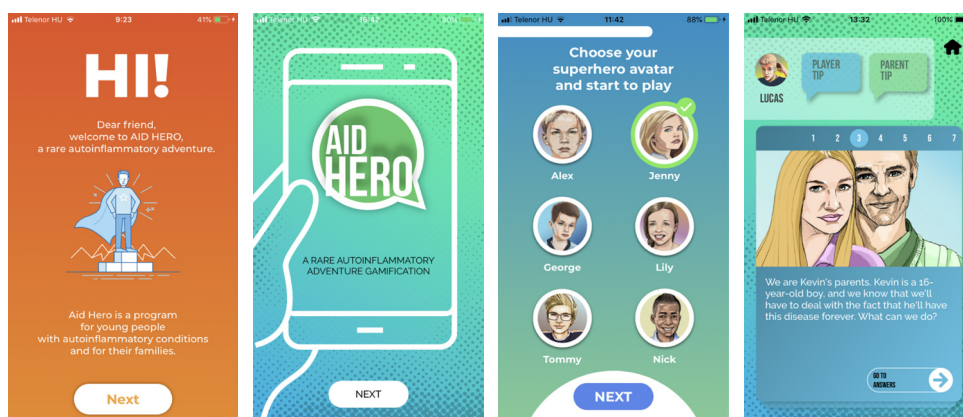
I'm Rare

an [eBook](#) created to raise awareness and develop patient networks, through sharing of personal stories and experiences.¹



AID Hero app

an educational program for young people with autoinflammatory conditions and for their families, to raise awareness of rare autoinflammatory diseases.



Appendix B: Useful links

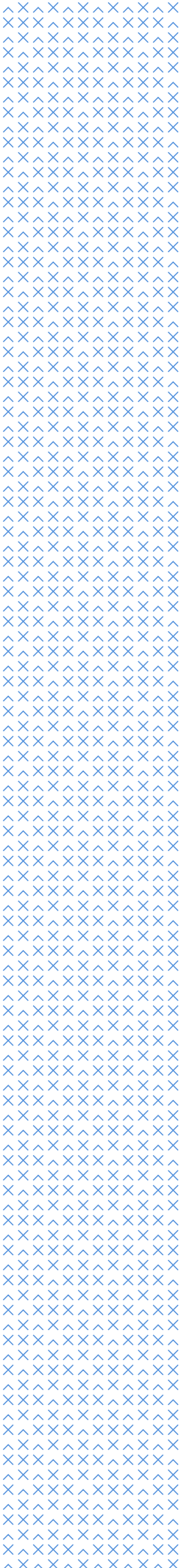
There are a number of organisations that advocate for and support the rare autoinflammatory disease community worldwide. These groups can provide specialised information and support to people worldwide. We have provided a short list of relevant organisations below, however this list is not exhaustive and many other groups exist across the globe. In addition, Novartis have created a website (<http://www.periodicfevers.com>) to provide up-to-date information and resources for people and their families affected by rare autoinflammatory diseases.

| Organisation (Website) | Location | Description | Useful Materials / Resources |
|---|---------------|--|---|
| AIFP http://www.febbriperiodiche.it | Italy | The Italian Association for Periodic Fevers (AIFP) association. AIFP's main aims is to sensitise doctors to Periodic Fevers through events, and to support patients and their families by providing information (publications, website) and support group details. | |
| AMRI Onlus http://www.amri.it | Italy | The Italian Association for Paediatric Rheumatoid Diseases (AMRI, Associazione Italiana per le Malattie Reumatiche Infantili) is a non-profit organisation that supports children affected by paediatric rheumatoid diseases. | |
| Aspanijer http://aspanijer.org/wordpress/?page_id=154 | Spain | Aspanijer is the Association of Parents of Children and Young People with Rheumatic Diseases of the Valencian Community. | |
| Autoinflammatory Alliance – previously known as The NOMID Alliance http://www.nomidalliance.org | International | The Autoinflammatory Alliance is a non-profit public charity dedicated to promoting awareness, proper diagnosis and treatment, and improved care for people with autoinflammatory diseases. | <p>Autoinflammatory disease Classification and Nomenclature Chart</p> <p>A comparison chart of various rare autoinflammatory conditions and key characteristics of each.</p> <p>General Information Brochure</p> <p>A brochure that includes key information about rare autoinflammatory diseases and the Autoinflammatory Alliance, a patient organisation focused on rare autoinflammatory diseases.</p> <p>SAID Database</p> <p>A database to search and learn more about rare autoinflammatory disease symptoms and findings, and to help increase awareness of these conditions.</p> <p>SAID Support: TRAPS Infographic</p> <p>An infographic that presents key information about TRAPS concisely.</p> |
| ENCA https://www.enca.org | International | The European Network for Children with Arthritis and Autoinflammatory Diseases (ENCA) is an international network for national associations working with children and young people with paediatric rheumatic diseases and their families. | |

| Organisation (Website) | Location | Description | Useful Materials / Resources |
|--|---------------|---|------------------------------|
| FMF & AID https://www.fmfandaid.org | International | FMF & AID is a worldwide non-profit umbrella organisation, dedicated to helping patients and their families obtain a quick diagnosis and correct treatment, as well as advocating for them and raising awareness. | |
| ICAN https://icanireland.ie | Ireland | The main aim of the Irish Children's Arthritis Network (ICAN) is to provide a national support network for children with arthritis and their families through the provision of factual, practical and emotional support. | |
| KAISZ http://www.kaisz.nl | Netherlands | KAISZ is an organisation active in raising awareness and providing support to those living and / or coping with an autoinflammatory disease. | |
| KOURIR https://www.kourir.org | France | KOURIR is the French parent association for JIA and other paediatric rheumatic diseases; their mission is to support parents and children, increase paediatric rheumatic diseases awareness at a local, national and international level, and promote research on these diseases. | |
| Mifrakim Tz'eirim https://mifrakim.org.il | Israel | The Israeli Association for rheumatoid arthritis patients Mifrakim Tze'irim provides patients with support and tools. It aims to increase public awareness of the disease and its daily effect on patients, expand knowledge and spread information about the illness, patients' rights, and treatment innovations. | |
| Sunflower Foundation http://www.fondpodsolnuh.com | Russia | The SUNFLOWER Charity Foundation is an organisation supporting patients with immune system disorders that works to save lives of children and adults who are suffering from primary immunodeficiency and autoimmune diseases. | |
| Versus Arthritis https://www.versusarthritis.org | UK | The website for Versus Arthritis; a UK based patient advocacy group focused on campaigning to challenge the misconceptions around arthritis and to ensure that arthritis is recognised as priority in the UK. | |

1. Novartis. I'm Rare 2019 [Available from: https://www.periodicfevers.com/globalassets/periodicfevers/lifestyle/01_im-rare.pdf].
2. Erbis G, Schmidt K, Hansmann S, Sergiichuk T, Michler C, Kuemmerle-Deschner JB, et al. Living with autoinflammatory diseases: identifying unmet needs of children, adolescents and adults. *Pediatr Rheumatol Online J*. 2018;16(1):81.
3. Savic S, Wood P. Does this patient have periodic fever syndrome? *Clinical Medicine*. 2011;11(4):396–401.
4. Gurcay E, Akinci A. Autoinflammatory Diseases and Physical Therapy. *Mediterr J Rheumatol*. 2017;28(4):183–91.
5. Toutou I, Galeotti C, Rossi-Semerano L, Hentgen V, Piram M, Kone-Paut I, et al. The expanding spectrum of rare monogenic autoinflammatory diseases. *Orphanet J Rare Dis*. 2013;8:162.
6. Krainer J, Siebenhandl S, Weinhausel A. Systemic autoinflammatory diseases. *J Autoimmun*. 2020;109:102421.
7. McDermott MF, Aksentijevich I, Galon J, McDermott EM, Ogunkolade BW, Centola M, et al. Germline mutations in the extracellular domains of the 55 kDa TNF receptor, TNFR1, define a family of dominantly inherited autoinflammatory syndromes. *Cell*. 1999;97(1):133–44.
8. Cancer Therapy Advisor. Periodic Fever Syndromes. 2017 [Available from: <https://www.cancertherapyadvisor.com/home/decision-support-in-medicine/pediatrics/periodic-fever-syndromes/>].
9. Beth Israel Deaconess Medical Center. Treatment for Autoinflammatory Diseases [Available from: <https://www.bidmc.org/centers-and-departments/rheumatology/autoinflammatory-disease-center>].
10. Hoffman HM. Therapy of autoinflammatory syndromes. *J Allergy Clin Immunol*. 2009;124(6):1129–38.
11. National Institute of Arthritis and Musculoskeletal and Skin Diseases. Autoinflammatory Diseases 2017 [Available from: <https://www.niams.nih.gov/health-topics/autoinflammatory-diseases>].
12. Thornton J, Lunt M, Ashcroft DM, Baildam E, Foster H, Davidson J, et al. Costing juvenile idiopathic arthritis: examining patient-based costs during the first year after diagnosis. *Rheumatology (Oxford)*. 2008;47(7):985–90.
13. Minden K, Niewerth M, Listing J, Biedermann T, Schontube M, Zink A. Burden and cost of illness in patients with juvenile idiopathic arthritis. *Ann Rheum Dis*. 2004;63(7):836–42.
14. van der Hilst JC, Bodar EJ, Barron KS, Frenkel J, Drenth JPH, van der Meer JWM, et al. Long-term follow-up, clinical features, and quality of life in a series of 103 patients with hyperimmunoglobulinemia D syndrome. *Medicine (Baltimore)*. 2008;87(6):301–10.
15. Russo RA, Brogan PA. Monogenic autoinflammatory diseases. *Rheumatology (Oxford)*. 2014;53(11):1927–39.
16. Novartis. Rare autoinflammatory conditions 2017 [Available from: <https://www.periodicfevers.com/specialists/rare-autoinflammatory-conditions/>].
17. Hausmann JS, Lomax KG, Shapiro A, Durrant K. The patient journey to diagnosis and treatment of autoinflammatory diseases. *Orphanet J Rare Dis*. 2018;13(1):156.
18. Novartis. Determining the presence of periodic fever syndromes 2017 [Available from: <https://www.periodicfevers.com/specialists/doctors-advice-on-diagnosis/>].
19. Bonnekoh H, Krause K. How to Diagnose and Manage Systemic Autoinflammatory Diseases in Childhood. *Current Treatment Options in Allergy*. 2015;2(3):235–45.
20. Soriano A, Soriano M, Espinosa G, Manna R, Emmi G, Cantarini L, et al. Current Therapeutic Options for the Main Monogenic Autoinflammatory Diseases and PFAPA Syndrome: Evidence-Based Approach and Proposal of a Practical Guide. *Front Immunol*. 2020;11:865.
21. Ciccarelli F, De Martinis M, Ginaldi L. An update on autoinflammatory diseases. *Curr Med Chem*. 2014;21(3):261–9.
22. Cleveland Clinic. Periodic Fever Syndrome [Available from: <https://my.clevelandclinic.org/health/articles/17354-periodic-fever-syndrome>].
23. De Sanctis S, Nozzi M, Del Torto M, Scardapane A, Gaspari S, de Michele G, et al. Autoinflammatory syndromes: diagnosis and management. *Ital J Pediatr*. 2010;36:57.
24. Chuamanochan M, Weller K, Feist E, Kallinich T, Maurer M, Kummerle-Deschner J, et al. State of care for patients with systemic autoinflammatory diseases - Results of a tertiary care survey. *World Allergy Organ J*. 2019;12(3):100019.
25. Ostrov BE. Immunotherapeutic Biologic Agents in Autoimmune and Autoinflammatory Diseases. *Immunol Invest*. 2015;44(8):777–802.
26. Miyamae T, Kawamoto M, Kawaguchi Y, Yamanaka H. Prevalence of polymorphisms of the genes responsible for autoinflammatory diseases among 236 patients with recurrent fever in a rheumatology institute in Japan. *Pediatr Rheumatol Online J*. 2015;13:163.
27. The Walter and Eliza Hall Institute of Medical Research. Autoinflammatory diseases 2020 [Available from: <https://www.wehi.edu.au/research-diseases/immune-health-and-infection/autoinflammatory-diseases>].
28. University College London. Autoinflammatory Syndromes [Available from: <https://www.ucl.ac.uk/amyloidosis/national-amyloidosis-centre/autoinflammatory-syndromes>].
29. Schnappauf O, Aksentijevich I. Current and future advances in genetic testing in systemic autoinflammatory diseases. *Rheumatology (Oxford)*. 2019;58(Suppl 6):44–55.
30. Wang D, Bonfrate L, de Bari O, Wang T, Portincasa P. Familial Mediterranean Fever: From Pathogenesis to Treatment. *Journal of Genetic Syndromes & Gene Therapy*. 2014;5(5):1–11.
31. Kenealy S, Creagh EM. Autoinflammatory diseases: Consequences of uncontrolled inflammasome activation. *EMJ Allergy Immunol*. 2018;3(1):106–13.
32. Toplak N, Dolezalova P, Constantin T, Sediva A, Pasic S, Ciznar P, et al. Periodic fever syndromes in Eastern and Central European countries: results of a pediatric multinational survey. *Pediatr Rheumatol Online J*. 2010;8:29.
33. EURODIS. The Voice of 12,000 patients - Experiences and Expectations of Rare Disease Patients on Diagnosis and Care in Europe 2009 [Available from: https://www.eurordis.org/IMG/pdf/voice_12000_patients/EURORDISCARE_FULLBOOK.pdf].
34. Alvarez-Errico D, Vento-Tormo R, Ballestar E. Genetic and Epigenetic Determinants in Autoinflammatory Diseases. *Front Immunol*. 2017;8:318.

35. Wekell P, Karlsson A, Berg S, Fasth A. Review of autoinflammatory diseases, with a special focus on periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis syndrome. *Acta Paediatr.* 2016;105(10):1140–51.
36. Ombrello MJ. Advances in the genetically complex autoinflammatory diseases. *Semin Immunopathol.* 2015;37(4):403–6.
37. Moghaddas F. Monogenic autoinflammatory disorders: beyond the periodic fever. *Intern Med J.* 2020;50(2):151–64.
38. Pathak S, McDermott MF, Savic S. Autoinflammatory diseases: update on classification diagnosis and management. *J Clin Pathol.* 2017;70(1):1–8.
39. Galozzi P, Punzi L, Sfriso P. Clinical Overlapping in Autoinflammatory Diseases: The Role of Gene Duplication. *Front Immunol.* 2017;8:392.
40. Rowczenio D, Shinar Y, Ceccherini I, Sheils K, Van Gijn M, Patton SJ, et al. Current practices for the genetic diagnosis of autoinflammatory diseases: results of a European Molecular Genetics Quality Network Survey. *Eur J Hum Genet.* 2019;27(10):1502–8.
41. Ozen S, Demir S. Monogenic Periodic Fever Syndromes: Treatment Options for the Pediatric Patient. *Paediatr Drugs.* 2017;19(4):303–11.
42. Martorana D, Bonatti F, Mozzoni P, Vaglio A, Percesepe A. Monogenic Autoinflammatory Diseases with Mendelian Inheritance: Genes, Mutations, and Genotype/Phenotype Correlations. *Front Immunol.* 2017;8:344.
43. Hansmann S, Lainka E, Horneff G, Holzinger D, Rieber N, Jansson AF, et al. Consensus protocols for the diagnosis and management of the hereditary autoinflammatory syndromes CAPS, TRAPS and MKD/HIDS: a German PRO-KIND initiative. *Pediatr Rheumatol Online J.* 2020;18(1):17.
44. Lainka E, Bielak M, Hilger V, Basu O, Neudorf U, Wittkowski H, et al. Translational research network and patient registry for auto-inflammatory diseases. *Rheumatology (Oxford).* 2011;50(1):237–42.
45. Tucker LB, Lamot L, Niemietz I, Chung BK, Cabral DA, Houghton K, et al. Complexity in unclassified auto-inflammatory disease: a case report illustrating the potential for disease arising from the allelic burden of multiple variants. *Pediatr Rheumatol Online J.* 2019;17(1):70.
46. De Pieri C, Vuch J, De Martino E, Bianco AM, Ronfani L, Athanasakis E, et al. Genetic profiling of autoinflammatory disorders in patients with periodic fever: a prospective study. *Pediatr Rheumatol Online J.* 2015;13:11.
47. Garg S, Wynne K, Omoyinmi E, Eleftheriou D, Brogan P. Efficacy and safety of anakinra for undifferentiated autoinflammatory diseases in children: a retrospective case review. *Rheumatol Adv Pract.* 2019;3(1):1–7.
48. Modica RF, Lomax KG, Batzel P, Cassanas A. Impact of systemic juvenile idiopathic arthritis/Still's disease on adolescents as evidenced through social media posts. *Open Access Rheumatol.* 2018;10:73–81.
49. Goldbach-Mansky R, Kastner DL. Autoinflammation: The prominent role of IL-1 in monogenic autoinflammatory diseases and implications for common illnesses. *J Allergy Clin Immunol.* 2009;124(6):1141–9.
50. SAutoinflammatory disease Support. What are Undifferentiated Autoinflammatory Diseases?
51. Novartis. SJIA: Systemic juvenile idiopathic arthritis [Available from: <https://www.periodicfevers.ca/en/the-science/sjia/>].
52. Soon GS, Laxer RM. Approach to recurrent fever in childhood. *Can Fam Physician.* 2017;63(10):756–62.
53. de Jesus AA, Goldbach-Mansky R. Genetically defined autoinflammatory diseases. *Oral Dis.* 2016;22(7):591–604.
54. Koga T, Kawakami A. Diagnosis and treatment of autoinflammatory diseases in adults: a clinical approach from rheumatologists. *Immunol Med.* 2018;41(4):177–80.
55. Scarpioni R, Ricardi M, Albertazzi V. Secondary amyloidosis in autoinflammatory diseases and the role of inflammation in renal damage. *World J Nephrol.* 2016;5(1):66–75.
56. Novartis. Data on file.
57. Kone-Paut I, Lachmann HJ, Kuemmerle-Deschner JB, Hachulla E, Leslie KS, Mouy R, et al. Sustained remission of symptoms and improved health-related quality of life in patients with cryopyrin-associated periodic syndrome treated with canakinumab: results of a double-blind placebo-controlled randomized withdrawal study. *Arthritis Res Ther.* 2011;13(6):1–9.
58. Angelis A, Kanavos P, Lopez-Bastida J, Linertova R, Serrano-Aguilar P, Network B-RR. Socioeconomic costs and health-related quality of life in juvenile idiopathic arthritis: a cost-of-illness study in the United Kingdom. *BMC Musculoskelet Disord.* 2016;17:321.
59. Alayli G, Durmus D, Ozkaya O, Sen HE, Nalcacioglu H, Bilgici A, et al. Functional capacity, strength, and quality of life in children and youth with familial Mediterranean fever. *Pediatr Phys Ther.* 2014;26(3):347–52.
60. SAutoinflammatory disease Support. Impact of Familial Mediterranean Fever, MKD/HIDS, and TRAPS on Patients and Families 2016 [Available from: <http://sautoinflammatorydiseasesupport.org/impact-of-familial-mediterranean-fever-mkdhids-and-traps-on-patients-and-families/>].
61. SAutoinflammatory disease Support. Are the Periodic Fever Syndrome Symptoms Contagious? 2013 [Available from: <http://sautoinflammatorydiseasesupport.org/are-the-periodic-fever-syndrome-symptoms-contagious/>].
62. Hausmann JS, Dedeoglu F. Autoinflammatory diseases in pediatrics. *Dermatol Clin.* 2013;31(3):481–94.
63. Pratsidou-Gertsis P. Transition of pediatric patients with an Auto-inflammatory Disease: an alternative version of the Daedalus and Icarus myth. *Mediterr J Rheumatol.* 2018;29(3):156–62.
64. Grimwood C, Kone-Paut I, Piram M, Rossi-Semerano L, Hentgen V. Health-related quality of life in children with PFAPA syndrome. *Orphanet J Rare Dis.* 2018;13(1):132.
65. ter Haar NM, Oswald M, Jeyaratnam J, Anton J, Barron KS, Brogan PA, et al. Recommendations for the management of autoinflammatory diseases. *Ann Rheum Dis.* 2015;74(9):1636–44.
66. Marques MC, Tennermann N, Lapidus S, Schulert G, Tousseau J, Sinha R, et al. Patients Perspectives on Living with a Systemic Autoinflammatory Disease: Impact on Quality of Life [abstract]. *Arthritis Rheumatology.* 2020;72.
67. Chi H, Jin H, Wang Z, Feng T, Zeng T, Shi H, et al. Anxiety and depression in adult-onset Still's disease patients and associations with health-related quality of life. *Clinical Rheumatology.* 2020.
68. Dandekar P, Gregson J, Campbell R, Bourhis F. Hyper Immunoglobulin D syndrome (HIDS): understanding what it is like to live with this rare condition. *Pediatric Rheumatology.* 2015;13(1):P24.
69. Aksu K, Dokuyucu O, Ertenli AI, Gul A, Karaaslan Y, Kasapcopur O, et al. Cost of Familial Mediterranean Fever (FMF) Disease In Turkey [abstract]. 2015.
70. Hausmann JS, Lomax KG, Shapiro A, Durrant K. Impact of Familial Mediterranean Fever, MKD/HIDS, and TRAPS on Patients and Families, Data From Patient Interviews. Poster presented at PReS 2016, September 28–October 1, Genoa, Italy [P235].
71. Krause K, Grattan CE, Bindslev-Jensen C, Gattorno M, Kallinich T, de Koning HD, et al. How not to miss autoinflammatory diseases masquerading as urticaria. *Allergy.* 2012;67(12):1465–74.
72. Novartis. Real life stories [Available from: <https://www.periodicfevers.com/lifewithperiodicfevers/real-life-stories/>].
73. Williams R, Hawkins P, Lane T. Recognising and understanding cryopyrin-associated periodic syndrome in adults. *Br J Nurs.* 2019;28(18):1180–6.

- 
74. Pharmaceutical Research and Manufacturers of America. A Decade of Innovation in Rare Diseases 2015 [Available from: <http://phrma-docs.phrma.org/sites/default/files/pdf/PhRMA-Decade-of-Innovation-Rare-Diseases.pdf>].
 75. National Institutes of Health. Rare autoinflammatory diseases research: Saving lives, giving hope to families [Available from: <https://www.nih.gov/sites/default/files/about-nih/impact/rare-autoinflammatory-diseases-case-study.pdf>].
 76. Boulanger V, Schlemmer M, Rossov S, Seebald A, Gavin P. Establishing Patient Registries for Rare Diseases: Rationale and Challenges. *Pharmaceut Med.* 2020;34(3):185–90.
 77. Rare Disease UK. Centres of Excellence for Rare Diseases 2013 [Available from: <https://www.raredisease.org.uk/media/1601/centres-of-excellence.pdf>].
 78. Hausmann JS, O'Hare K. Improving the Transition from Pediatric to Adult Care for Adolescents and Young Adults with Autoinflammatory Diseases. In: Efthimiou P, editor. *Auto-Inflammatory Syndromes: Pathophysiology, Diagnosis, and Management*: Springer.
 79. MedPage Today. Cutaneous Manifestations of Autoinflammatory Diseases 2017 [Available from: <https://www.medpagetoday.com/resource-centers/advances-in-dermatology/cutaneous-manifestations-autoinflammatory-diseases/1374>].