

# Diagnosing autoinflammatory diseases: Insights from an interim analysis of the PRO-AID study

T. Welzel<sup>1-3</sup>, J. Kuemmerle-Deschner<sup>4</sup>, K. Tenbrock<sup>5</sup>, G. Horneff<sup>6,7</sup>, D. Föll<sup>8</sup>, J. Klotsche<sup>1</sup>, M. Niewerth<sup>1</sup>, Ö. Satirer<sup>4</sup>, R. Berendes<sup>10</sup>, H. Lausmann<sup>10</sup>, P. Oommen<sup>11</sup>, M. Lieber<sup>9</sup>, T. Krickau<sup>12</sup>, F. Dressler<sup>13</sup>, N. Brück<sup>14</sup>, D. Windschall<sup>15</sup>, M. Hufnagel<sup>16</sup>, T. Kallinich<sup>1,9</sup>, K. Minden<sup>1,9</sup>

<sup>1</sup> Deutsches Rheuma-Forschungszentrum Berlin (DRFZ), ein Leibniz Institut, Berlin, <sup>2</sup> Pädiatrisches Forschungszentrum und <sup>3</sup> Pädiatrische Rheumatologie, Universitäts-Kinderspital beider Basel, Universität Basel, Basel, <sup>4</sup> Universitätsklinikum Tübingen, Klinik für Kinder- und Jugendmedizin, Pädiatrische Rheumatologie, Autoinflammation reference center Tuebingen (arcT), Tübingen, <sup>5</sup> Pädiatrische Rheumatologie, Klinik für Kinder und Jugendmedizin, Uniklinik RWTH Aachen, Aachen, <sup>6</sup> Zentrum für Allgemeine Pädiatrie und Neonatologie, Asklepios Klinik Sankt Augustin, Sankt Augustin, <sup>7</sup> Universitätsklinik für Kinder- und Jugendmedizin, Medizinische Fakultät, Universität zu Köln, Köln, <sup>8</sup> Universitätsklinikum Münster, Klinik für pädiatrische Rheumatologie und Immunologie, Münster, <sup>9</sup> Charité Universitätsmedizin Berlin, Klinik für Pädiatrie mit SP Pneumologie, Immunologie und Intensivmedizin, Berlin, <sup>10</sup> Kinderkrankenhaus St. Marien, Landshut, <sup>11</sup> Universitätsklinikum Düsseldorf, Klinik für Kinder-Onkologie, Hämatologie und Klinische Immunologie, Düsseldorf, <sup>12</sup> Uniklinikum Erlangen, Klinik für Kinder und Jugendliche, Erlangen, <sup>13</sup> Medizinische Hochschule Hannover, Kinderklinik, Hannover, <sup>14</sup> Universitätsklinikum Carl Gustav Carus Dresden, Klinik und Poliklinik für Kinder- und Jugendmedizin, Dresden, <sup>15</sup> St. Josef-Stift, Klinik für Kinder- und Jugendrheumatologie, Sendenhorst, <sup>16</sup> Universitätsklinikum Freiburg, Kinder- und Jugendklinik, Freiburg

## Background and Objectives

- Uncontrolled disease activity in autoinflammatory diseases (AID) can cause morbidity and mortality. Familial Mediterranean Fever (FMF), NOD-like receptor protein 3 (NLRP3)-AID, Tumor Necrosis Factor Receptor-Associated Periodic Syndrome (TRAPS) and Mevalonate Kinase Deficiency (MKD) are effectively treatable after diagnosis is made. Early diagnosis is critical to mitigate disease burden and to improve patient outcomes.
- This study characterizes the diagnostic journey of children and adolescents with FMF, NLRP-3-AID, TRAPS and MKD.

## Methods

- Multicenter, prospective PRO-AID cohort study, embedded in the National Pediatric Rheumatologic Database
- Inclusion criteria
  - Children and adolescents ≤18 years
  - Diagnosis: FMF, NLRP3-AID, TRAPS, or MKD
  - Informed consent
- Time to diagnosis was defined as the interval between symptom onset and confirmed diagnosis.

### Data obtained by questionnaire at enrollment

Parents:  
Demographics +  
journey data<sup>1</sup>

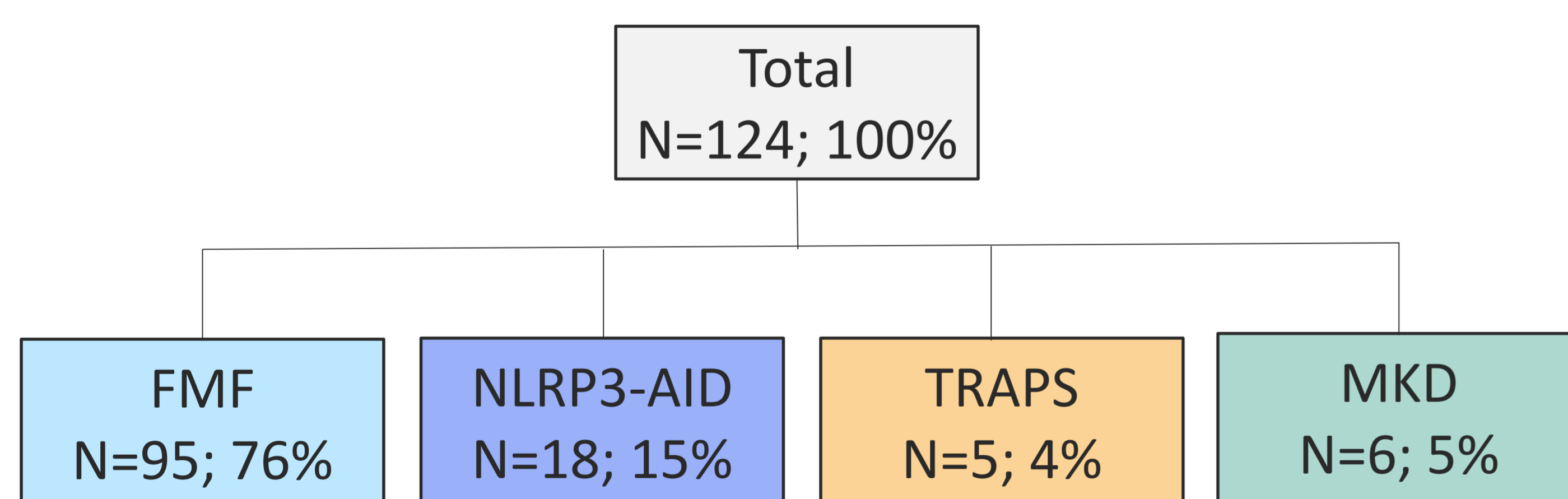
Parents/  
Adolescents:  
PPGA

Physicians:  
Diagnosis<sup>2</sup>  
+ PGA

**Figure 1:** PGA (physician) and PPGA (patient/parent) global assessment (VAS 0 to 10 cm); <sup>1</sup> journey data: number of physicians consulted, antibiotic treatment prior to diagnosis, symptom onset, diagnosis date <sup>2</sup> diagnosis and confirmed diagnosis date

## Results

- In total 124 children and adolescents (45% females) were included. Diagnosis distribution is shown in **figure 2**.



**Figure 2:** FMF Familial Mediterranean Fever, NLRP3-AID NOD-like receptor protein 3- autoinflammatory disease, TRAPS Tumor Necrosis Factor Receptor-Associated Periodic Syndrome, MKD Mevalonate Kinase Deficiency

- Median disease duration: 7.0 (IQR 4.0, 11.0) years
- Mean age at symptom onset: 2.0 (IQR 1.0, 4.0) years
- In median, 2 clinicians (IQR 1.0, 3.0) were consulted until diagnosis was made
  - Diagnosis was made mostly by pediatric rheumatologists (59%)
  - FMF was frequently recognized by pediatricians prior to referral (44%)

- Median time to diagnosis was 12.5 (IQR 4, 23) months
  - Almost 50% of all patients were diagnosed with a delay of ≥12 months
- ↑ Time to diagnosis ↔ ↑ physician (PGA) and patients/parents (PPGA) global assessment of disease activity
  - Median PGA ≥ 12 months versus < 12 months: 1 (IQR 0, 3) vs. 0 (IQR 0, 2)
  - Median PPGA ≥ 12 months versus < 12 months: 3 (IQR 0, 6) vs. 0.5 (IQR 0, 2)

	FMF	NLRP3-AID	MKD	TRAPS
Median time to diagnosis, months (IQR)	12 (4, 20)	21 (8, 24)	5 (4, 12)	26.5 (24, 29)
Hospitalization before diagnosis, % (N)	29 (28/95)	56 (9/16)	50 (3/6)	50 (2/4)

**Table 1:** IQR Interquartile ranges, FMF Familial Mediterranean Fever, NLRP3-AID NOD-like receptor protein 3- autoinflammatory Disease, TRAPS Tumor Necrosis Factor Receptor-Associated Periodic Syndrome, MKD Mevalonate Kinase Deficiency

## Conclusion

- The time to diagnosis in FMF, NLRP3-AID, TRAPS and MKD remains still significant.
- Diagnostic delay hinders timely access to effective treatment and may increase the risk of organ damage and psychosocial impairment.
- Raising awareness and promoting early referral to pediatric rheumatologists in case of recurrent fevers are critical for optimizing care.

### Acknowledgment.

- All recruiting centers supporting Pro-AID
- All patients/ parents being part of the study

- Kindness for Kids for study support

