1º JORNADA DE LA ESTRATEGIA DE ENFERMEDADES MINORITARIAS DE LES ILLES BALEARS

La Fe Hospital Universitari i Politècnic

SINDROMES AUTOINFLAMATORIOS E INMUNODEFICIENCIAS

4-5 Noviembre 2021


LIVE
P E
SOCIEDAD ESPAÑOLA DE
REUMATOLOGÍA PEDIÁTRICA
Dra. Inmaculada Calvo


NORTH
AMERICA
EUROPE
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Pacific
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AUSTRALIA
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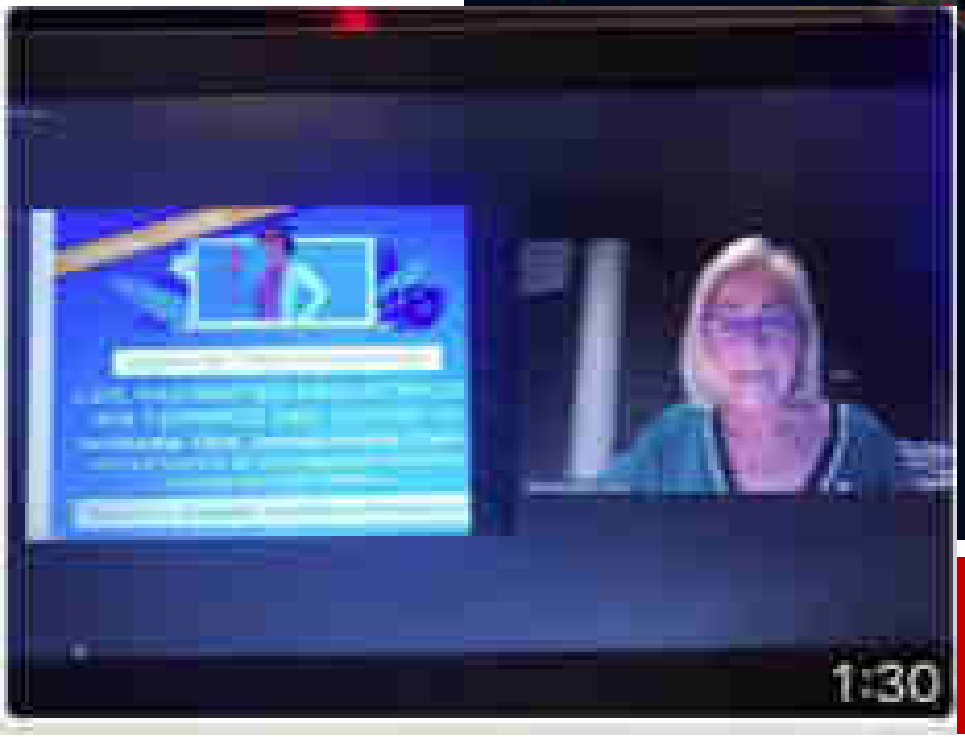
Ocean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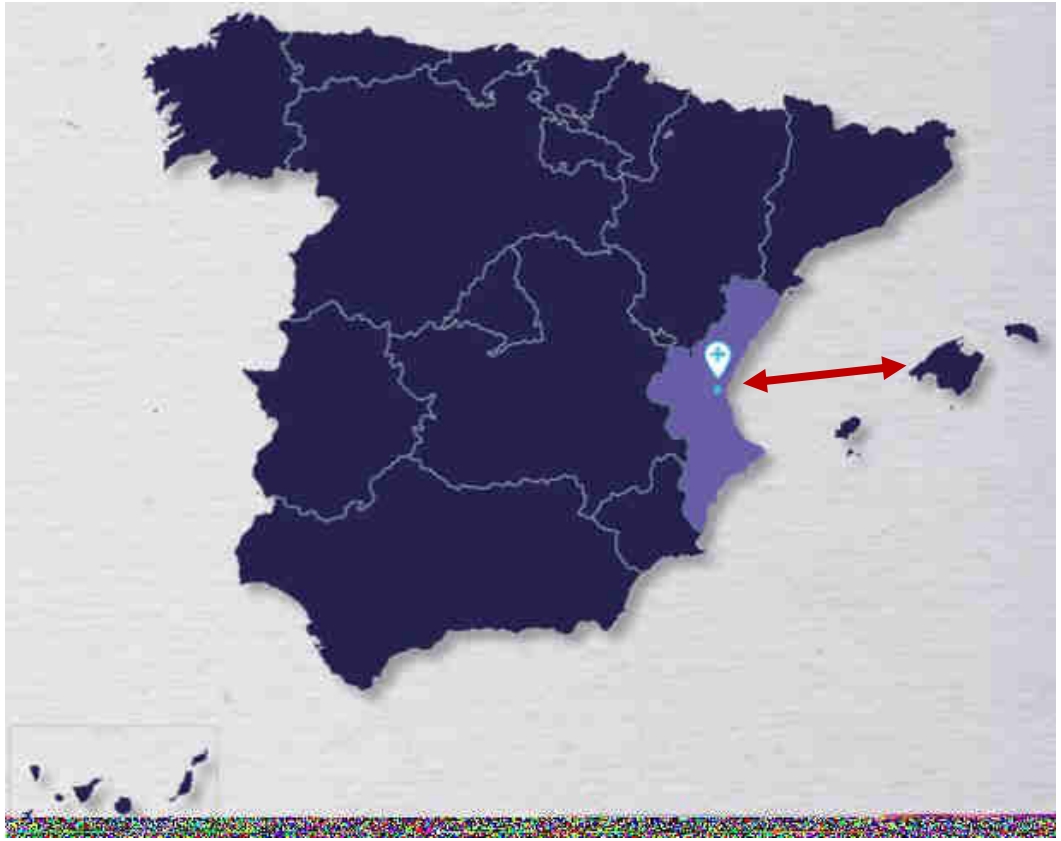


Inmaculada Calvo

Unidad de Reumatología Pediátrica
Valencia

Fiebre Mediterránea Familiar nuevas perspectivas

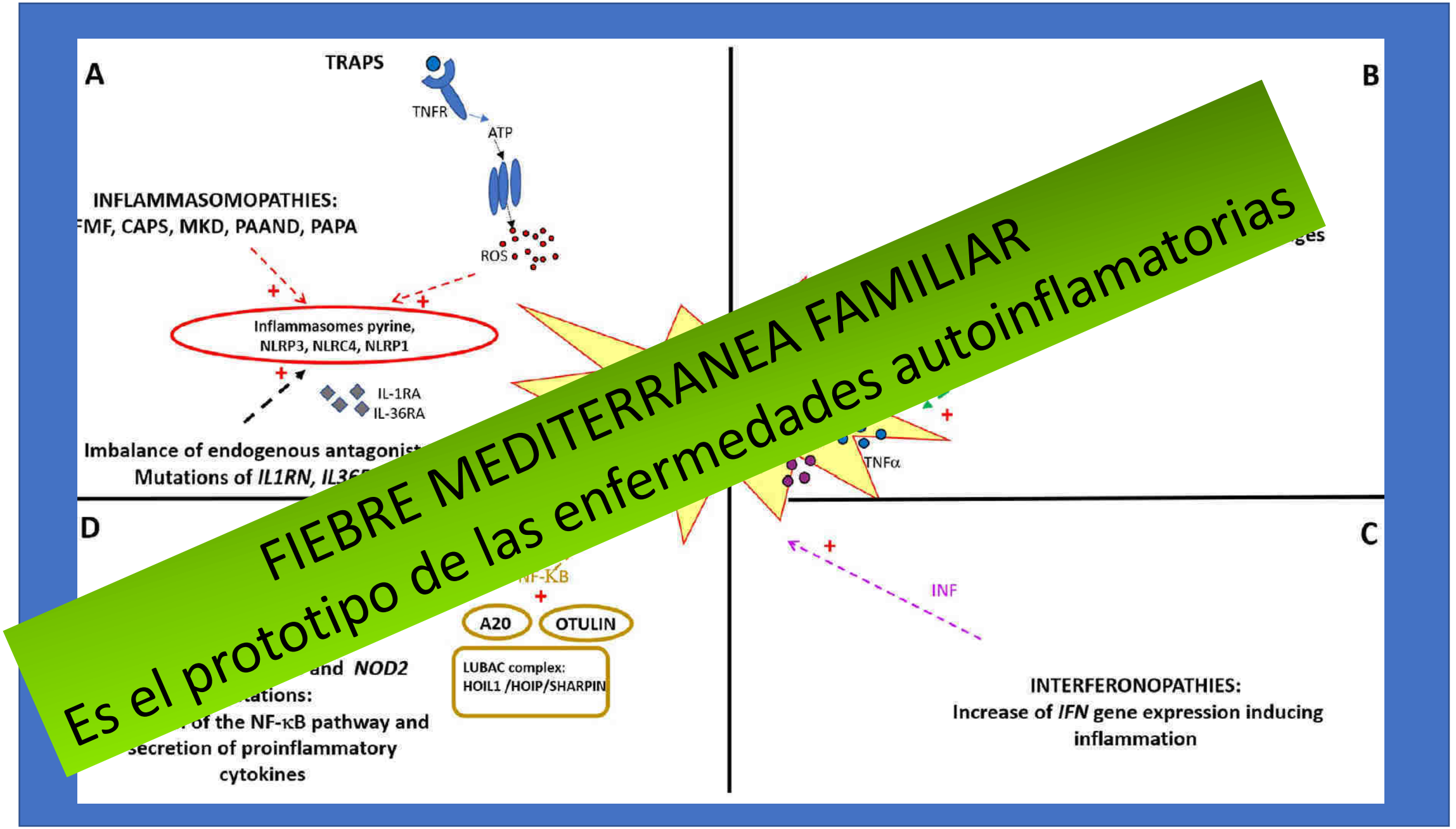
FMF

Monogénicas

- **Inflamasomopatías (fiebres periódicas)**
- Mediadas vía de NF-κB. Immuno-proteinopathias
- Immuno-actinopatihas
- Defectos receptores señal IL-10/IL36
- Relopatias
- Interferonopatías tipo I
- Otras: déficit ADA2

Poligénicas

- AIJ sistémica/Still
- Enfermedad de Behçet
- OCMR



FIEBRE MEDITERRANEA FAMILIAR
Es el prototipo de las enfermedades autoinflamatorias

Georgin-Lavialle S, et al. Autoinflammatory diseases: State of the art. Presse Med. (2019), https://doi.org/ 10.1016/j.lpm.2018.12.003

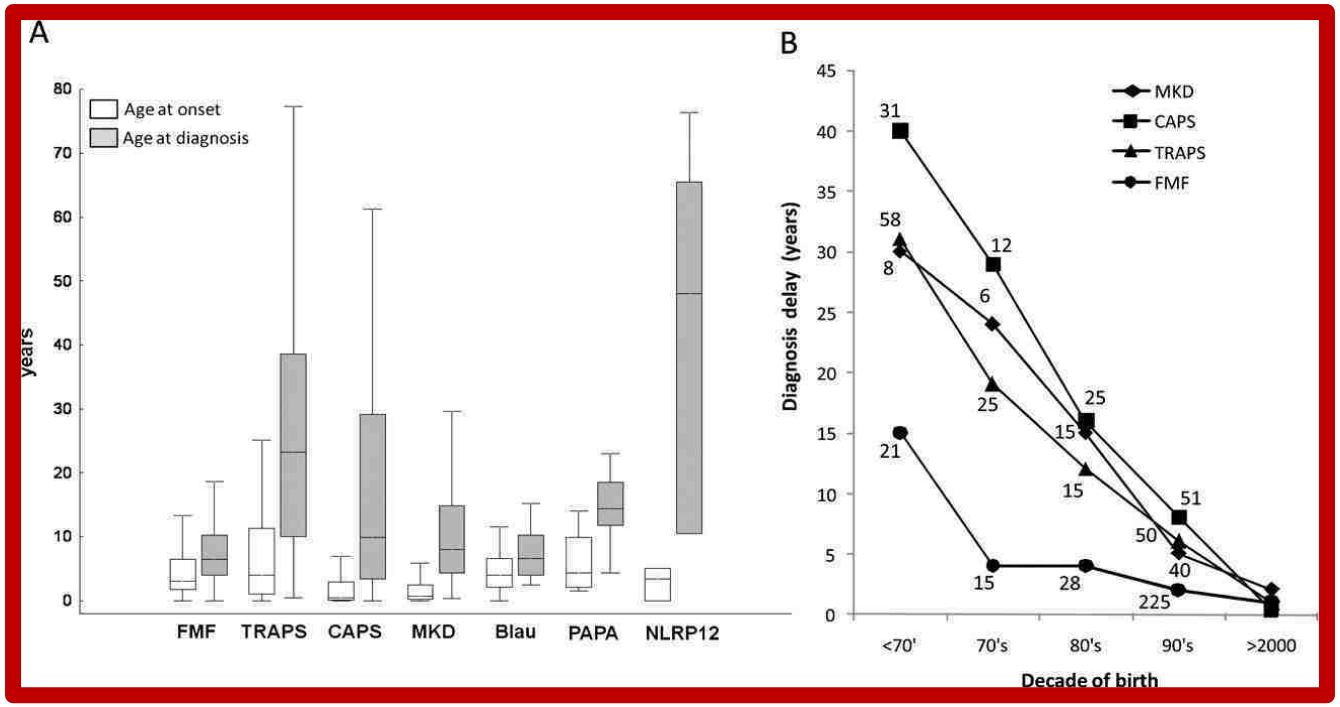
Enfermedades autoinflamatorias (EAI) raras

Las EAI raras afectan tanto a pacientes muy jóvenes como a adultos[1]

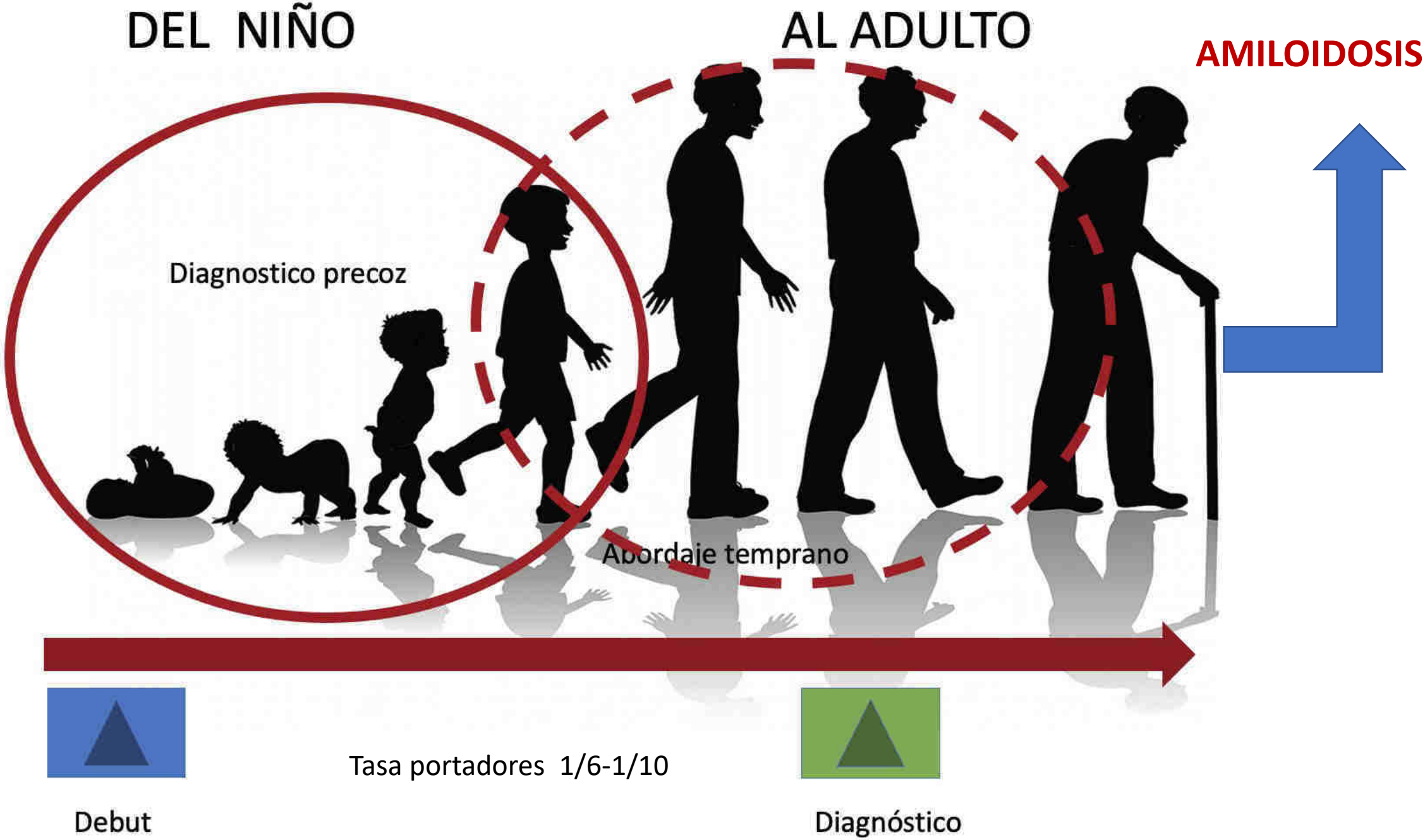
Hasta 8.500 pacientes reciben un tratamiento inadecuado en Europa

En un **30%** de los pacientes no se ha identificado la enfermedad o no han recibido un diagnóstico adecuado[2]

5-10 años: tiempo de diagnóstico[2]



1. http://www.orpha.net/consor/cgi-bin/index.php?lng=IT; 2. Toplak N, et al. Ann Rheum Dis. 2012; 71: 1.177-1.182.


DEL NIÑO
AL ADULTO
AMILOIDOSIS
Diagnostico precoz
Abordaje temprano
Tasa portadores 1/6-1/10
Debut
Diagnóstico

2020-2021

CONCEPTOS CLAVES

DIAGNOSTICAR A LOS PACIENTES CON FMF

REVIEW

CURRENT OPINION

Update in familial Mediterranean fever

Seza Ozen

Septiembre 2021

The NEW ENGLAND JOURNAL of MEDICINE

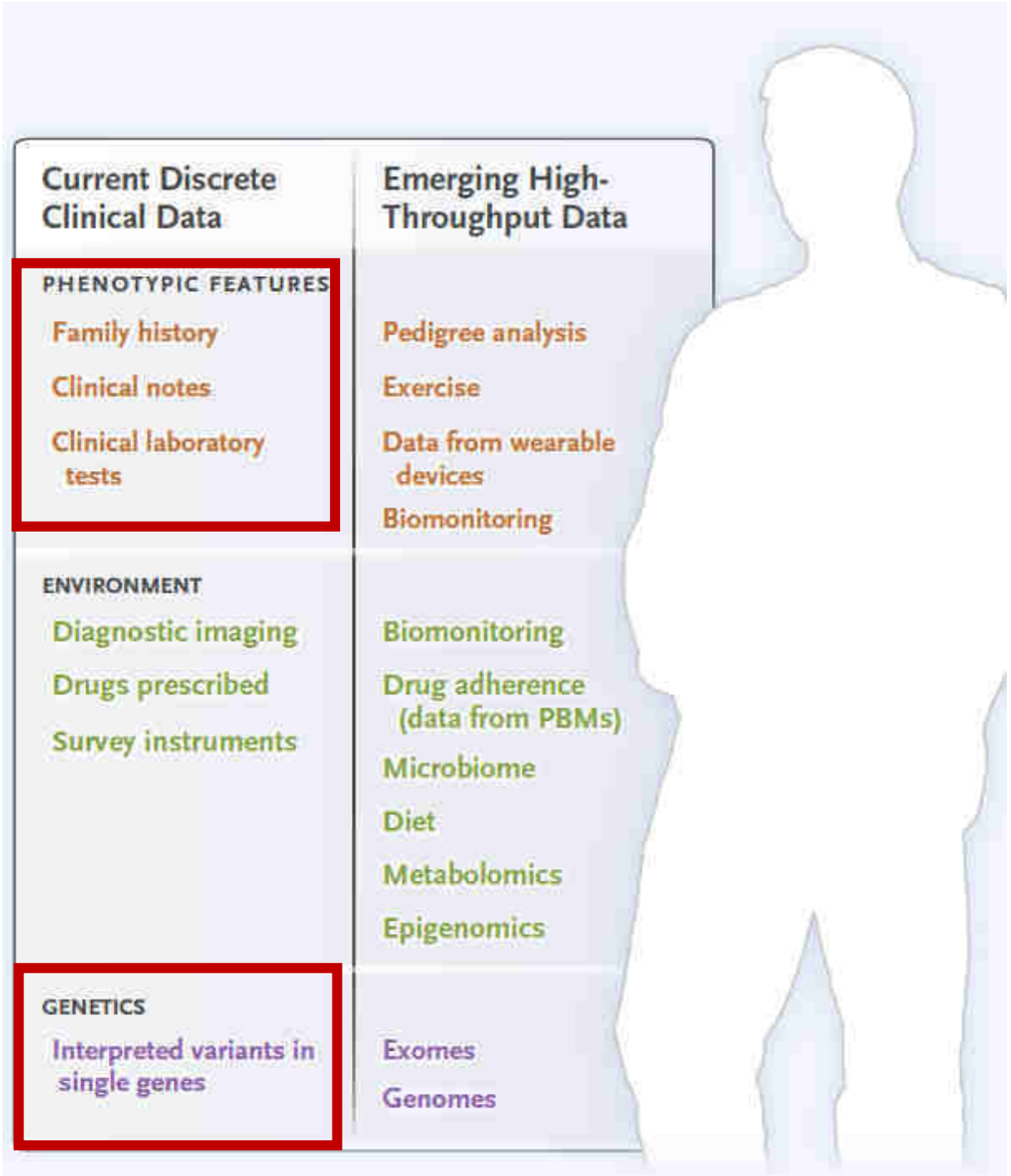
REVIEW ARTICLE

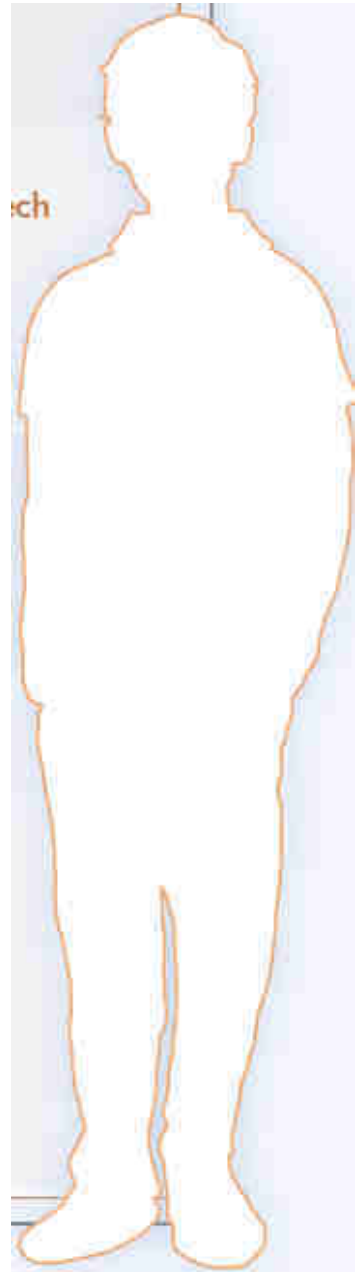
Elizabeth G. Phimister, Ph.D., *Editor*

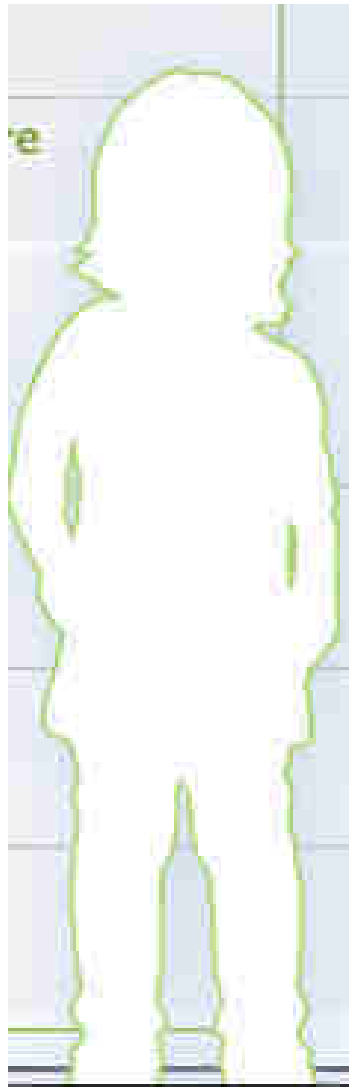
Classification, Ontology, and Precision Medicine

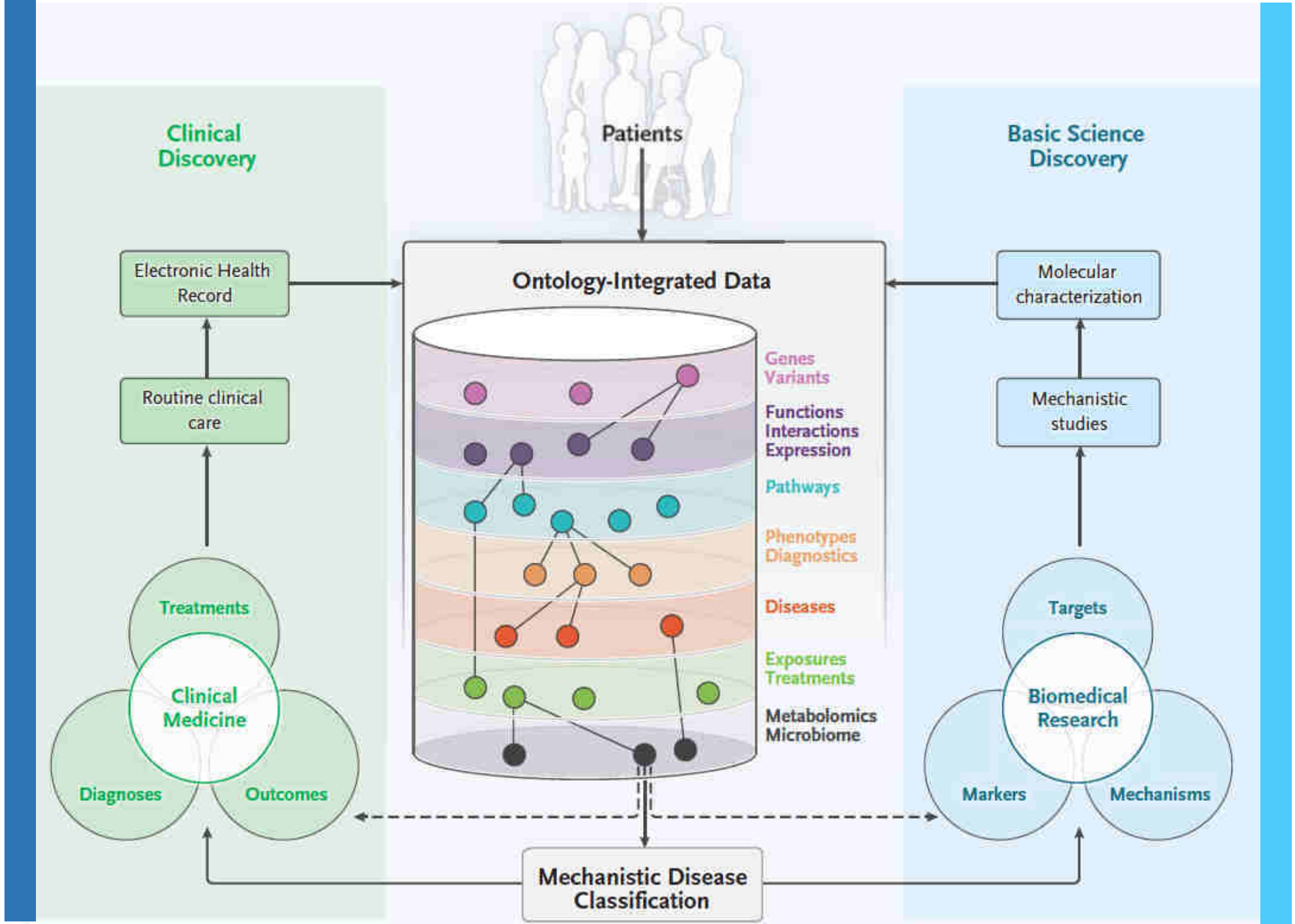
Melissa A. Haendel, Ph.D., Christopher G. Chute, M.D., Dr.P.H., and Peter N. Robinson, M.D.

N ENGL J MED 379;15 NEJM.ORG OCTOBER 11, 2018


Current Discrete Clinical Data
Emerging High-Throughput Data
PHENOTYPIC FEATURES
Family history
Clinical notes
Clinical laboratory tests
Pedigree analysis
Exercise
Data from wearable devices
Biomonitoring
ENVIRONMENT
Diagnostic imaging
Drugs prescribed
Survey instruments
Biomonitoring
Drug adherence (data from PBMs)
Microbiome
Diet
Metabolomics
Epigenomics
GENETICS
Interpreted variants in single genes
Exomes
Genomes






Clinical Discovery
Patients
Basic Science Discovery
Electronic Health Record
Ontology-Integrated Data
Molecular characterization
Routine clinical care
Genes
Variants
Functions
Interactions
Expression
Pathways
Phenotypes
Diagnostics
Diseases
Exposures
Treatments
Metabolomics
Microbiome
Mechanistic studies
Treatments
Clinical Medicine
Diagnoses
Outcomes
Targets
Biomedical Research
Markers
Mechanisms
Mechanistic Disease Classification

DIAGNOSTICAR A LOS PACIENTES CON FMF

LEUKEMIA & LYMPHOMA
2019, VOL. 60, NO. 8, 2091–2093
https://doi.org/10.1080/10428194.2019.1571204

Taylor & Francis
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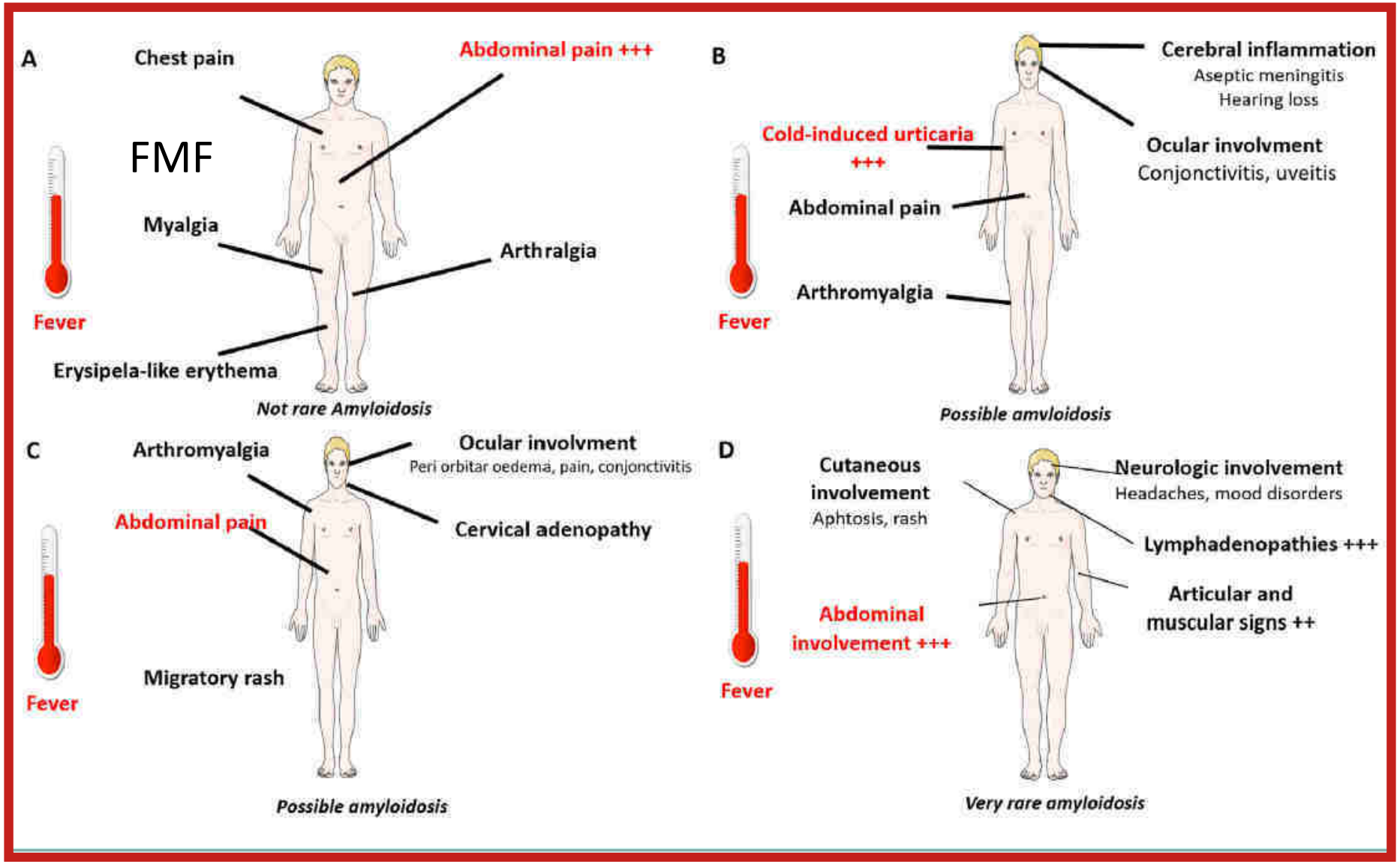
LETTER TO THE EDITOR

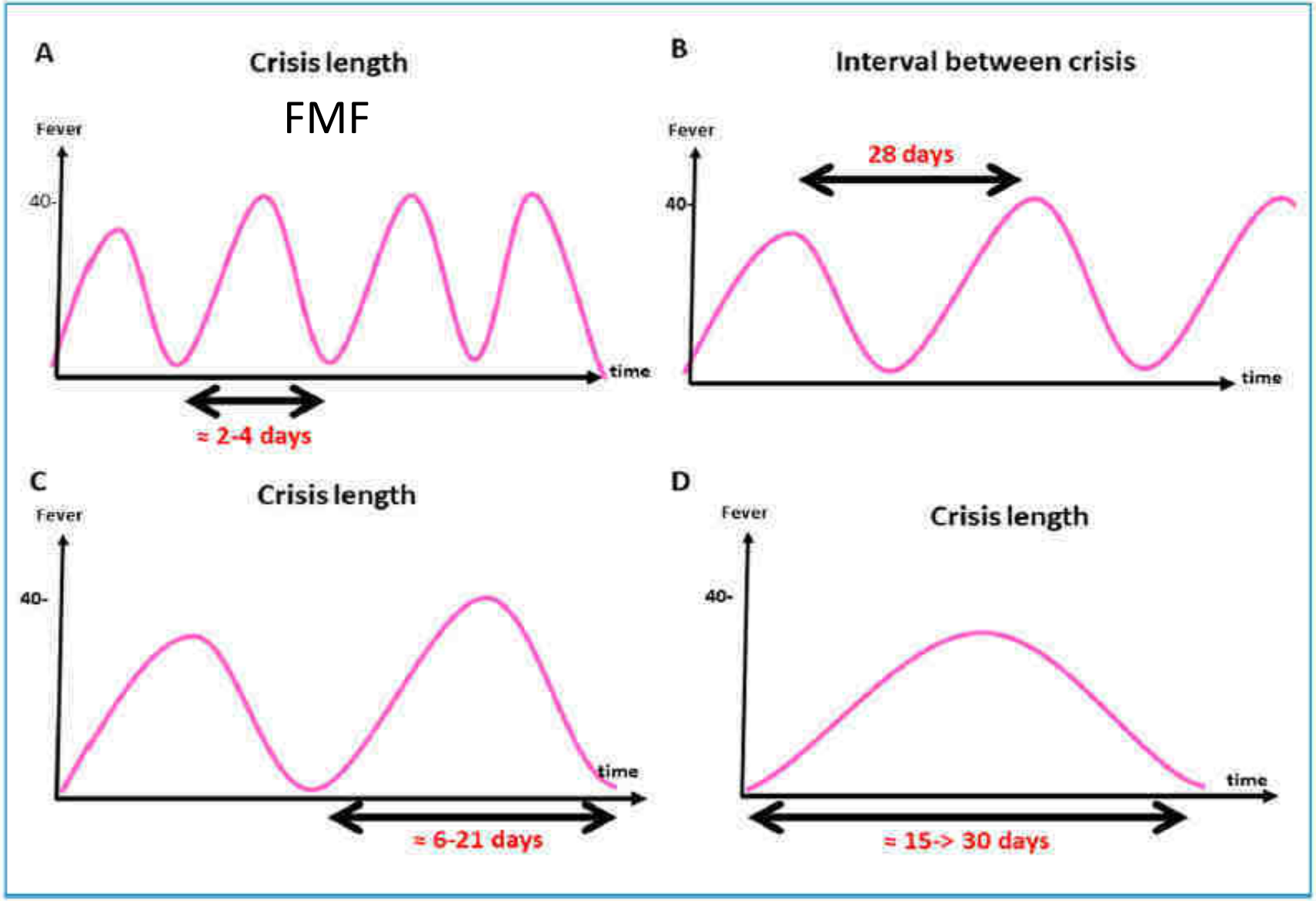
The application of precision medicine in diagnosing familial Mediterranean fever

Shannon Glynn[a], Steven Lipkin[a], Tuo Zhang[b,c], Andrea Sboner[b,d,e], Olivier Elemento[b], Koen Van Besien[a]* and Himisha Beltran[a,b,f]*

[a]Department of Medicine, Weill Cornell Medicine, New York, NY, USA; [b]Caryl and Israel Englander Institute for Precision Medicine, New York, NY, USA; [c]Department of Microbiology and Immunology, New York, NY, USA; [d]Department of Pathology and Laboratory Medicine, Weill Cornell Medicine, New York, NY, USA; [e]Institute for Computational Biomedicine, Weill Cornell Medicine, New York, NY, USA; [f]Department of Medical Oncology, Dana Farber Cancer Institute, Boston, MA, USA



Georgin-Lavialle S, et al. Autoinflammatory diseases: State of the art. Presse Med. (2019), https://doi.org/ 10.1016/j.lpm.2018.12.003



Georgin-Lavialle S, et al. Autoinflammatory diseases: State of the art. Presse Med. (2019), https://doi.org/ 10.1016/j.lpm.2018.12.003

Clinical Science (2018) 132 1901–1924
https://doi.org/10.1042/CS20171498

PORTLAND PRESS

Review Article

The classification, genetic diagnosis and modelling of monogenic autoinflammatory disorders

Fiona Moghaddas[1,2] and Seth L. Masters[1,2]

[1]Inflammation Division, The Walter and Eliza Hall Institute of Medical Research, Parkville, Australia; [2]Department of Medical Biology, The University of Melbourne, Parkville, Australia

Correspondence: Fiona Moghaddas (moghaddas.f@wehi.edu.au)

Tel-Hashomer criteria	Yalcinkaya-Ozen criteria
Major criteria 1- Recurrent febrile episodes with serositis (peritonitis, synovitis or pleuritis) 2- Amyloidosis of AA type without a predisposing disease 3- Favorable response to regular colchicine treatment **Minor criteria** 1- Recurrent febrile episodes 2- FMF in a first-degree relative 3- Erysipelas-like erythema	1- Fever (Axillary temperature of >38 °C, 6–72 h of duration, ≥3 attacks) 2- Abdominal pain (6–72 h of duration, ≥3 attacks) 3- Chest pain (6–72 h of duration, ≥3 attacks) 4- Arthritis (6–72 h of duration, ≥3 attacks, oligoarthritis) 5- Family history of FMF
≥2 major or 1 major+2 minor criteria	≥2 criteria

Pras M. Scand J Rheumatol 1998;27:92^7

Yalcinkaya F, et al. Rheumatology2009;48(4):395–8.

CRITERIOS DE CLASIFICACION EN LA FMF

Performance of the new 'Eurofever/PRINTO classification criteria' in FMF patients

Erdal Sag[a,1], Dilara Demirel[b,1], Selcan Demir[a], Erdal Atalay[a], Ummusen Akca[a], Yelda Bilginer[a], Seza Ozen[a,*]

[a] *Division of Pediatric Rheumatology, Department of Pediatrics, Hacettepe University, Ankara, Turkey*
[b] *Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey*

Seminars in Arthritis and Rheumatism 2019

Eurofever/PRINTO clinical + genetic criteria

1. **Confirmación** de presencia de **genotipo MEFV** y **al menos 1** de los siguientes síntomas:

o bien

2. **NO confirmación** de presencia de **genotipo MEFV** y **al menos 2** de los siguientes síntomas:

+

- **Episodios de 1-3 días**
- **Artritis**
- **Dolor toracico**
- **Dolor abdominal**

Eurofever/PRINTO clinical only criteria

3. Que se cumplan los siguientes criterios, **al menos 6 de 9:**

Presencia:

- Etnia mediterránea oriental
- Episodios de 1-3 días
- Artritis
- Dolor en el pecho
- Dolor abdominal

Ausencia:

- Estomatitis aftosa
- Erupción tipo urticaria
- Erupción maculopapular
- Ganglios linfáticos dolorosos

Gattorno M et al. AnnRheum Dis 2019;78:1025–32.

Sensibilidad y especificidad en los diferentes criterios de clasificación

	Sensitivity	Spesificity	Misclassified cases (number)
Eurofever/PRINTO criteria	145/151 (96%)	59/82 (73.1%)	29
Tel Hashomer criteria	134/151 (88.7%)	76/82 (92.6%)	23
Yalcinkaya–Ozen criteria	141/151 (93.4%)	69/82 (84.1%)	23

Sensibilidad y especificidad en los diferentes criterios basado en los diferentes genotipos

	Eurofever/PRINTO criteria	Tel Hashomer criteria	Yalcinkaya–Ozen criteria
Biallelic exon 10 mutations ($n = 87$)	87/87 (100%)	76/87 (87.4%)	82 (94.2%)
Heterozygote exon 10 mutations ($n = 34$)	30/34 (88.2%)	32/34 (94.1%)	32/34 (94.1%)

Datos clínicos a tener en cuenta para el diagnostico FMF

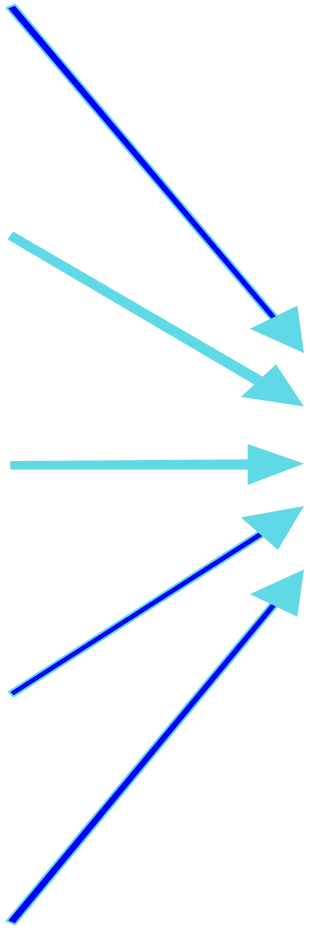
Historia clínica / Historia familiar / Etnia

Diario de fiebre/síntomas–
AIDAI, VAS del paciente

Exploración física, VAS del médico

Exámenes de laboratorio: Hemograma, Estudio hepático, renal, VSG, PCR, SAA,

Exámenes orientados a los síntomas:
Audiogramas, Oftalmolgía, MRI, Rx, Ultrasonidos



Patrón síntomas clínicos

Marcadores inflamatorios

¿COMO DE DICISIVO ES EL ESTUDIO GENETICO EN LA FMF?

¿Y LA EXPRESION DEL FENOTIPO ?

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

FRONTIERS IN MEDICINE

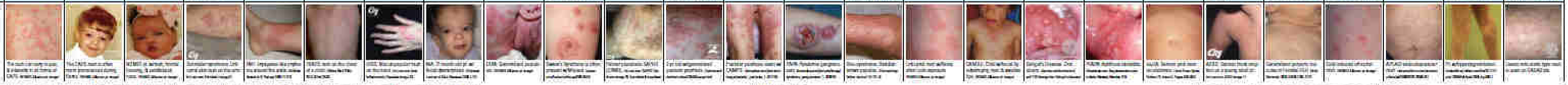
Next-Generation Sequencing to Diagnose Suspected Genetic Disorders

David R. Adams, M.D., Ph.D., and Christine M. Eng, M.D.

N ENGL J MED 379;14 NEJM.ORG OCTOBER 4, 2018

Comparison Chart of Systemic Autoinflammatory Diseases (SAID)

	Cryopyrin-Associated Periodic Syndromes (CAPS)				Pyrin	Protein Folding	Mevalonate Kinase Deficiencies		Inflammatory Bone Diseases			Pyogenic Diseases			Granulomatous	Monarch-1	Proteasomal	Idiopathic		Macrophage Activation Diseases			PLCG2-associated		SLC29A3 related	ADA2 deficiency
	Familial Cold Autoinflammatory Syndrome*	Muckle-Wells Syndrome*	Neonatal-Onset Multisystem Autoinflammatory Disease—aka Chronic Infantile Neurological Cutaneous Articular Syndrome (CINCA)*	Schnitzler Syndrome	Familial Mediterranean Fever*	Tumour Necrosis Factor (TNF)-Associated Periodic Syndrome—aka Familial Hibernian Fever*	Hyperimmunoglobulinemia D with Periodic Fever Syndrome (HIDS)*	Mevalonic Aciduria (MA) (Mevalonate Kinase Deficiencies, such as HIDS & MA are also referred to as MKD)	Deficiency of Interleukin-1β (IL-1β) Receptor Antagonist (DIRA)—aka Osteomyelitis, Sterile Multifocal w/Periostitis Pustulosis	Majeed Syndrome—aka Chronic Recurrent Multifocal Osteomyelitis, Congenital Dyserythropoietic Anemia, & Neutrophilic Dermatosis	Chronic Recurrent Multifocal Osteomyelitis—aka Synovitis, Acne, Pustulosis, Hyperostosis, Osteitis Syndrome	Deficiency of Interleukin-36-Receptor Antagonist (DITRA)—aka Generalized Pustular Psoriasis (GPP)	Familial Psoriasis (PSORS2)—aka CARD14 Mediated Pustular Psoriasis	Pyogenic Sterile Arthritis, Pyoderma Gangrenosum, & Acne Syndrome	Juvenile Systemic Granulomatosis—aka Blau Syndrome, Pediatric Granulomatous Arthritis (PGA), Early Onset Sarcoidosis, or Jabs Syndrome	NLRP12-Associated Periodic Fever Syndrome—aka Familial Cold Autoinflammatory Syndrome 2, or Guadeloupe Periodic Fever	Chronic Atypical Neutrophilic Dermatosis w/ Lipodystrophy & Elevated Temperature—aka Nakajo-Nishimura Syndrome	Behçets Disease	Periodic Fever, Aphthous Stomatitis, Pharyngitis, & Cervical Adenitis (PFAPA)—aka Marshall Syndrome	Systemic-Onset Juvenile Idiopathic Arthritis—aka still's, Systemic Juvenile Idiopathic Arthritis	Adult-Onset Still's Disease—aka Adult Still's, Wissler Fanconi Syndrome	(Primary) Familial Hemophagocytic Lymphohistiocytosis—aka Familial Erythrophagocytic Lymphohistiocytosis	PLCG2-associated Antibody Deficiency & Immune Dysregulation (PLAID)—aka Familial Atypical Cold Urticaria (FACU) or FCAS3	Autoinflammation & PLCG2-associated Antibody Deficiency & Immune Dysregulation (APLAID)	SLC29A3 Spectrum Disorder—aka [illegible]	Deficiency of Adenosine Deaminase 2 (DADA2)—aka Fever w/Early Onset Stroke (FEOS)
ACRONYM	**FCAS**	**MWS**	**NOMID/CINCA**	**SCHNITZLER**	**FMF**	**TRAPS**	**HIDS**	**MA**	**DIRA/OMPP**	**MAJEED**	**CRMO/SAPHO**	**DITRA/PSORP**	**CAMPS/PSORS2**	**PAPA**	**BLAU/PGA/EOS**	**NLRP12/FCAS2**	**CANDLE/PRAAS**	**BEHÇETS/BD**	**PFAPA**	**soJIA/sJIA**	**AOSD**	**1° HLH/FHL**	**PLAID/FCAS3**	**APLAID**	**SLC29A3**	**DADA2**
GENE	NLRP3	NLRP3	NLRP3	Currently unknown. [illegible] NLRP3 mutations	MEFV	TNFRSF1A	MVK	MVK	IL1RN	LPIN2	Currently unknown	IL36RN	CARD14	PSTPIP1	NOD2	NLRP12	PSMB8 [illegible]	[illegible]	Currently unknown	Currently unknown. [illegible]	Currently unknown	[illegible]	[illegible]	PLCG2 mutation	SLC29A3	CECR1
INHERITANCE	[illegible]	[illegible]	[illegible]	Unknown	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	Currently unknown	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	Complex	Currently unknown	Complex	Currently unknown	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
ETHNICITY	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	Unknown	[illegible]	Unknown
FREQUENCY IN THE WORLD	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
TIMING OF SYMPTOMS OR ATTACKS	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
AGE OF ONSET	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
SYSTEMIC FINDINGS:																										
SKIN/CUTANEOUS	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
NEUROLOGIC	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
AUDITORY	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
OPHTHALMIC	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
CARDIO-PULMONARY	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
ABDOMINAL	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
LYMPHATIC	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
JOINTS/BONES MUSCLES & CARTILAGE	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
VASCULITIS	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
AMYLOIDOSIS	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
ABNORMAL LABS	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]



List of abbreviations:

*These noted diseases are also referred to as "Classic" Hereditary Periodic Fever Syndromes (CAPS, FMF, HIDS & TRAPS)

NOMID ALLIANCE

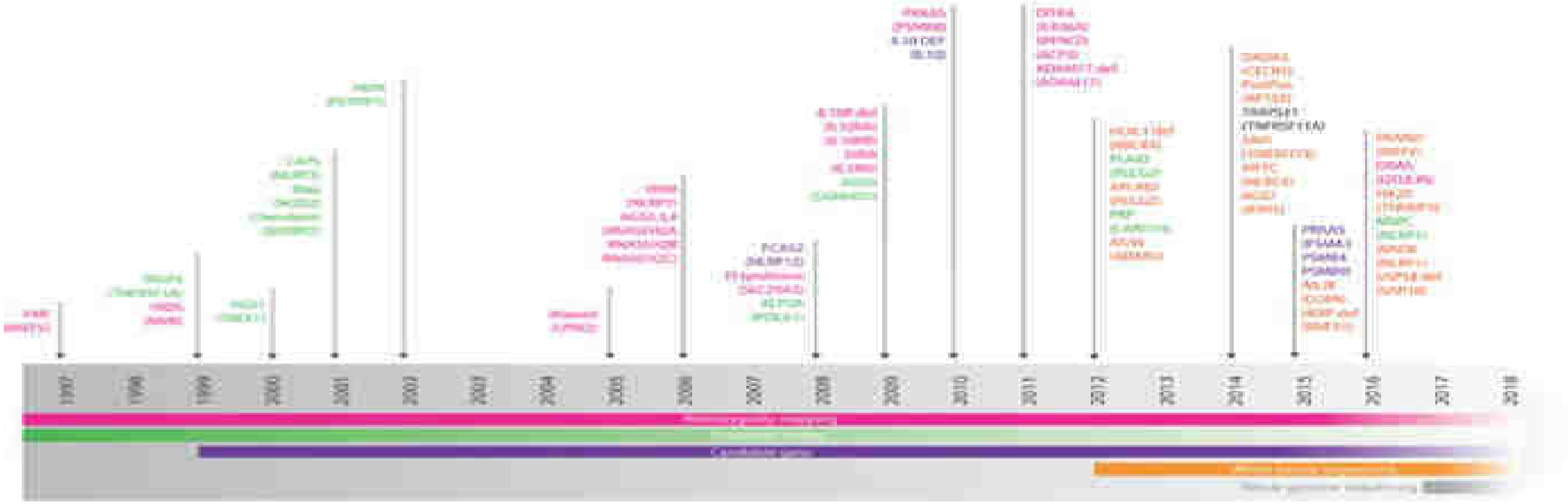
https://www.nomidalliance.org/downloads/comparative_chart_front.pdf. Último acceso: 06/05/21.

The expanding pathways of autoinflammation: a lesson from the first 100 genes related to autoinflammatory manifestations

Riccardo Papa[a,*], **Paolo Picco**[a] **and Marco Gattorno**[a]

[a]Autoinflammatory Diseases and Immunodeficiencies Centre, IRCCS Istituto Giannina Gaslini, Genova, GE, Italy

Advances in Protein Chemistre and Structural Biology 2020

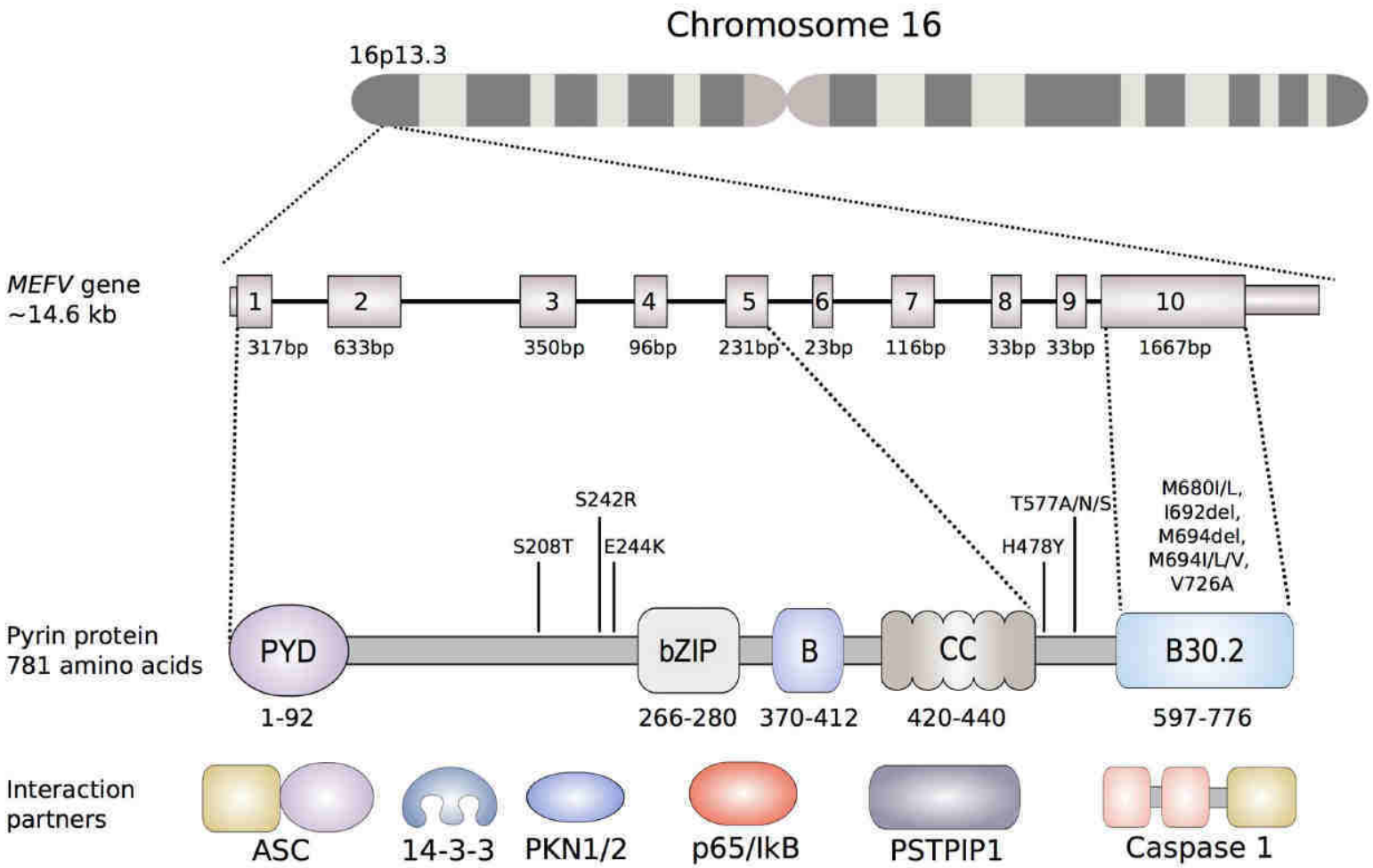


Timeline of monogenic autoinflammatory disorder discovery and genetic sequencing technique used

Assessment Categories Used by the American College of Medical Genetics and Genomics:

1. Pathogenic
2. Likely pathogenic
3. Variant of unknown significance
4. Likely benign
5. Benign

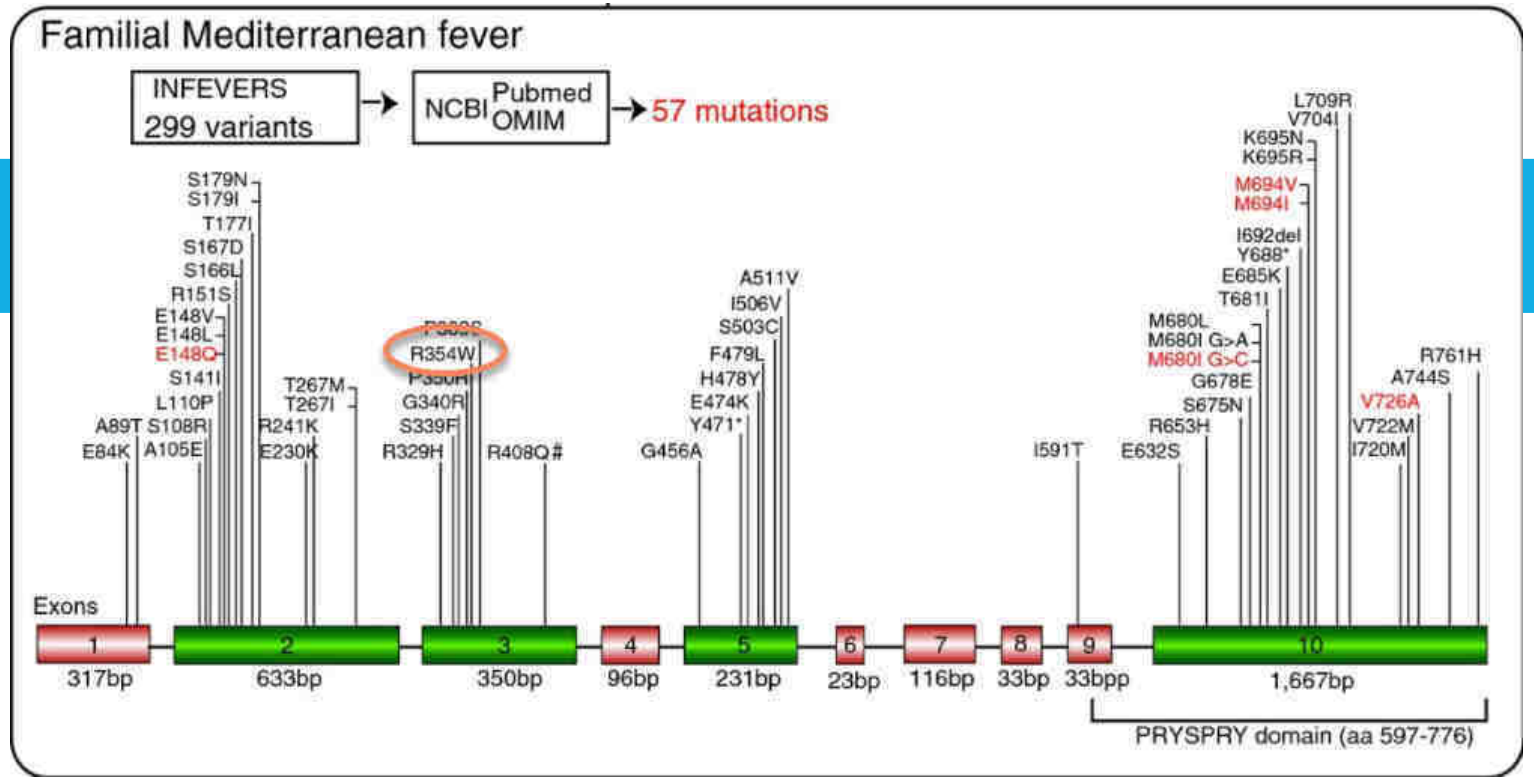
GEN MEFV



El gen MEFV tiene 10 exones y hay más de 370 variantes identificadas hasta la fecha

Schnappauf et al. Frontiers in Immunology 2019

1997



2021

Patogénesis de la inflamación

Variación del fenotipo

Cambios en la compresión genética y ambiental

Cambios en los criterios de clasificación

RECOMENDACIONES PARA EL DIAGNOSTICO GENETICO PARA LA FMF

1. FMF is a clinical diagnosis, which can be supported but not excluded by genetic testing
2. Consider patients homozygous for M694V at risk of developing, with very high probability, a severe phenotype
3. FMF patients carrying two of the common mutated alleles (homozygotes or compound heterozygotes), especially for M694V mutation or mutations at position 680 to 694 on exon 10, must be considered at risk of having a more severe disease
4. The E148Q variant is common, of unknown pathogenic significance and, as the only MEFV variant, does not support the diagnosis of FMF
5. Patients homozygous for M694V mutation are at risk of early onset disease
6. Individuals homozygous for M694V who are not reporting symptoms should be evaluated and followed closely in order to consider therapy
7. For individuals with two pathogenic mutations for FMF who do not report symptoms, if there are risk factors for AA amyloidosis (such as the country, family history and persistently elevated inflammatory markers, particularly serum amyloid A protein), close follow-up should be started and treatment considered
8. Consultation with an autoinflammatory disease specialist may be helpful in order to aid in the indication and interpretation of the genetic testing and diagnosis

Giancane G, et al. Ann Rheum Dis 2015;74:635–641.

VARIANTES DEL GEN MEFV

Benign	Likely benign	VUS	Likely pathogenic	Pathogenic
D102D	R75Q	E148Q	S208T	M680IG>C
G138G	P115T	P369S	F479L	M680I G>A
R202Q	G304R	H478Y	M680L	M694V
R314R	A317T	G678E	I692DEL	M694I
E474E	A457V	T681I	M694L	V726A
D510D	I591M	I720M	K695R	R761H
P588P	V690L	V722M	K695N	F497L
S675N	I772V	A744S	R761H	K695R

[1] Infevers (2020). MEFV sequence variants [online]. Website https://infevers.umai-montpellier.fr/web/search.php?n=1 [accessed 30 May 2020].

Sólo el 60% de los pacientes tienen 2 mutaciones (30% tienen 1 y 10% tienen 0)

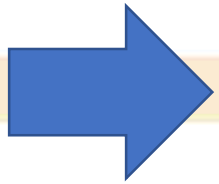
Bilge Y, et al. J Medical Sciences 2019

Abdurrahman T, Lachmann H. J Medical Sciences 2020

Recomendaciones para el escrining e interpretación de las variantes del gen MEFV

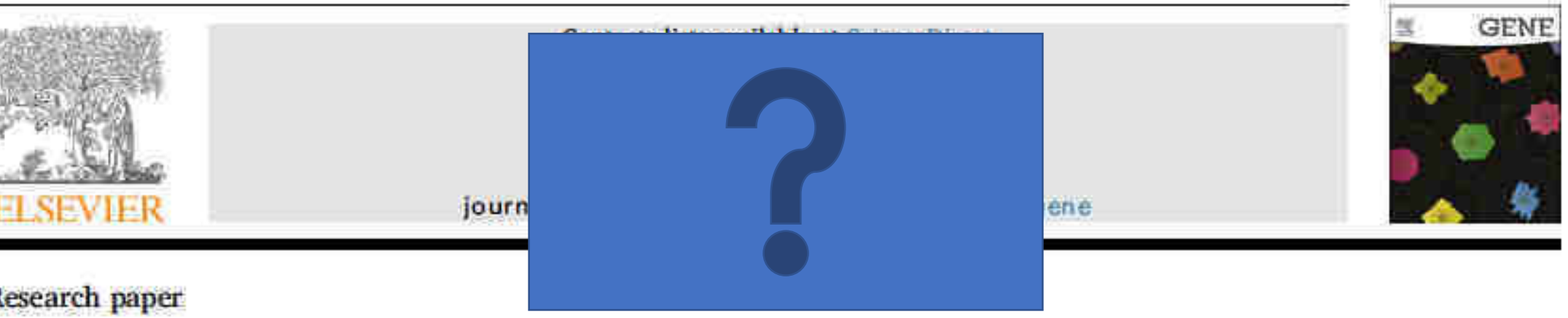
Pathogenic mutations in exon 10	Classical FMF
p.E148Q, p.L110P, p.P369S	Frequent VUS, often allelic (complex alleles)
p.P373L, p.H478Y, p.M694del, p.T577	Sometimes associated with dominant FMF-like transmission
p.P373L, p.H478Y, p.M694del, p.T577	Associated with dominant transmission (neutrophilic dermatosis

Modified with permission from [4▪]. FMF, familial Mediterranean fever; VUS, variant of unknown significance.



Ozen S. Curr Opin Rheumatol 2021, 33:398–402;2021

Gene 641 (2018) 279–286



Research paper

Genotype-phenotype correlation in FMF patients: A "non classic" recessive autosomal or "atypical" dominant autosomal inheritance?

V. Procopio[a,1], S. Manti[a,*,1], G. Bianco[a], G. Conti[b], A. Romeo[a], F. Maimone[a], T. Arrigo[a], M.C. Cutrupi[a], C. Salpietro[a], C. Cuppari[a]

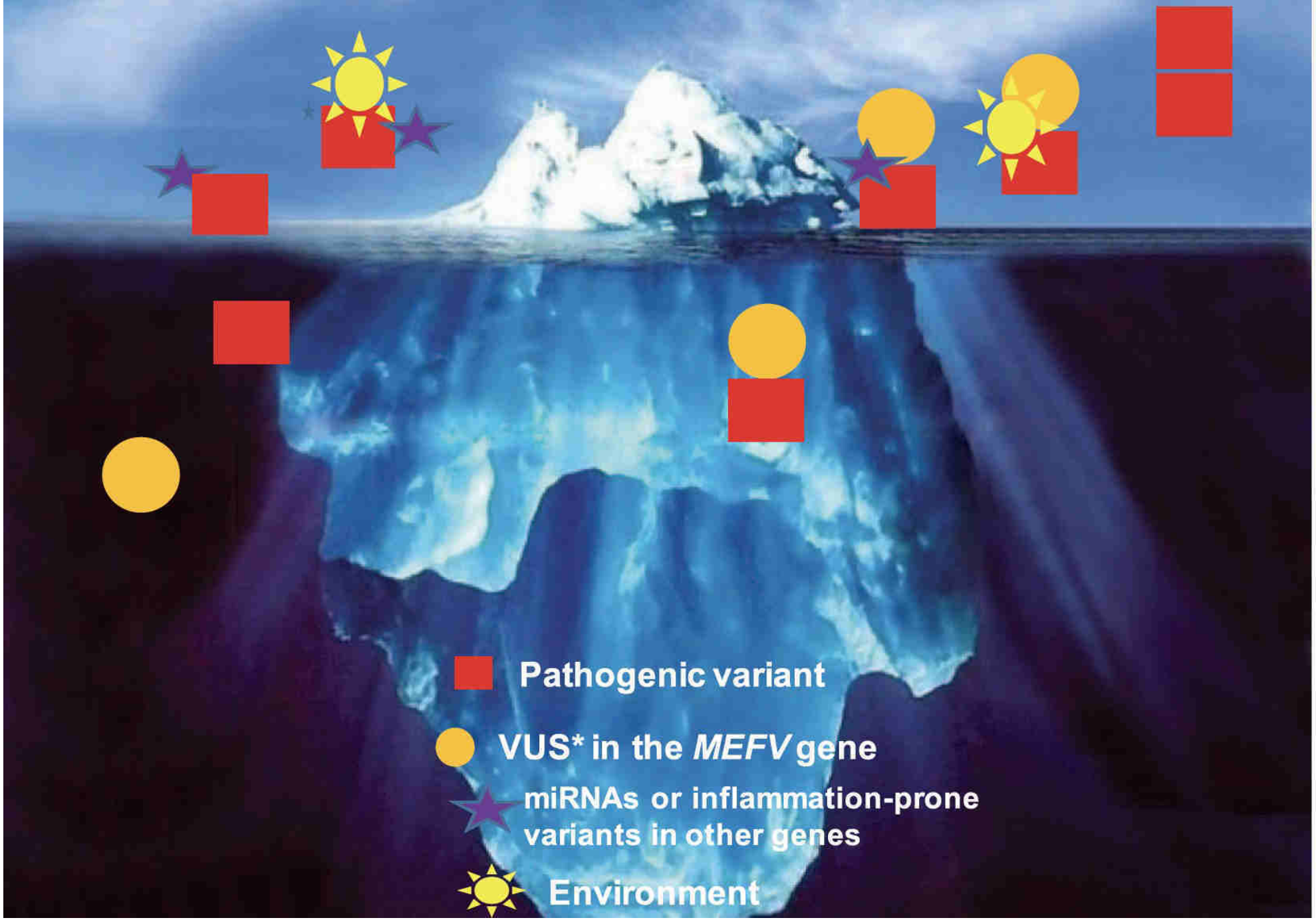
[a] Department of Pediatrics, Unit of Pediatric Genetics and Immunology, University of Messina, Messina, Italy
[b] Department of Pediatric Sciences, Unit of Pediatric Nephrology and Rheumatology, University of Messina, Messina, Italy

Lack of clear and univocal genotype-phenotype correlation in Familial Mediterranean Fever

La FMF UNA ENFERMEDAD MONOGENICA CON DISTINTAS EXPRESIONES

- Heter medad
- Pacie notipo pero grave sin penetrancia
- Varia ierto
- Entor

Ozen S. Curr Opin Rheumatol 2021, 33:398–402;2021



Ozen S. Curr Opin Rheumatol 2021, 33:398–402;2021

FACTORES DE RIESGO inflamatorios o específicos de la enfermedad

LA EPIGENETICA EN LA FMF

- Los ARNmi
  - ¿Podemo… …entificar sus dianas genéticas
  - ¿Pueden … …áficas?
  - ¿Pueden … …gotos manifiestan la enfermed…
  - ¿Pueden … …cientes con un cuadro moderad…

Sesa Ozen. ISSAID 2019

LA EPIGENETICA EN LA FMF

Rheumatology International
https://doi.org/10.1007/s00296-020-04541-4

Rheumatology
INTERNATIONAL

OBSERVATIONAL RESEARCH

Check for updates

Altered expression of apoptosis-related, circulating cell-free miRNAs in children with familial Mediterranean fever: a cross-sectional study

Emin Murat Karpuzoglu[1] · Rabia Miray Kisla Ekinci[2] · Sibel Balci[2] · Atil Bisgin[3] · Mustafa Yilmaz[2]

Received: 24 December 2019 / Accepted: 23 February 2020

Received: 20 March 2020 | Revised: 9 July 2020 | Accepted: 14 July 2020
DOI: 10.1111/jcmm.15701

ORIGINAL ARTICLE

WILEY

Genome sequencing unveils mutational landscape of the familial Mediterranean fever: Potential implications of IL33/ST2 signalling

Meenakshi Umar[1] | Andre Megarbane[2,3] | Jingxuan Shan[4,5] | Najeeb Syed[6] | Eliane Chouery[7] | Elbay Aliyev[8] | Puthen Jithesh[6] | Ramzi Temanni[6] | Issam Mansour[9] | Lotfi Chouchane[4,5,10] | Aouatef Ismail Chouchane[1]

Check for updates

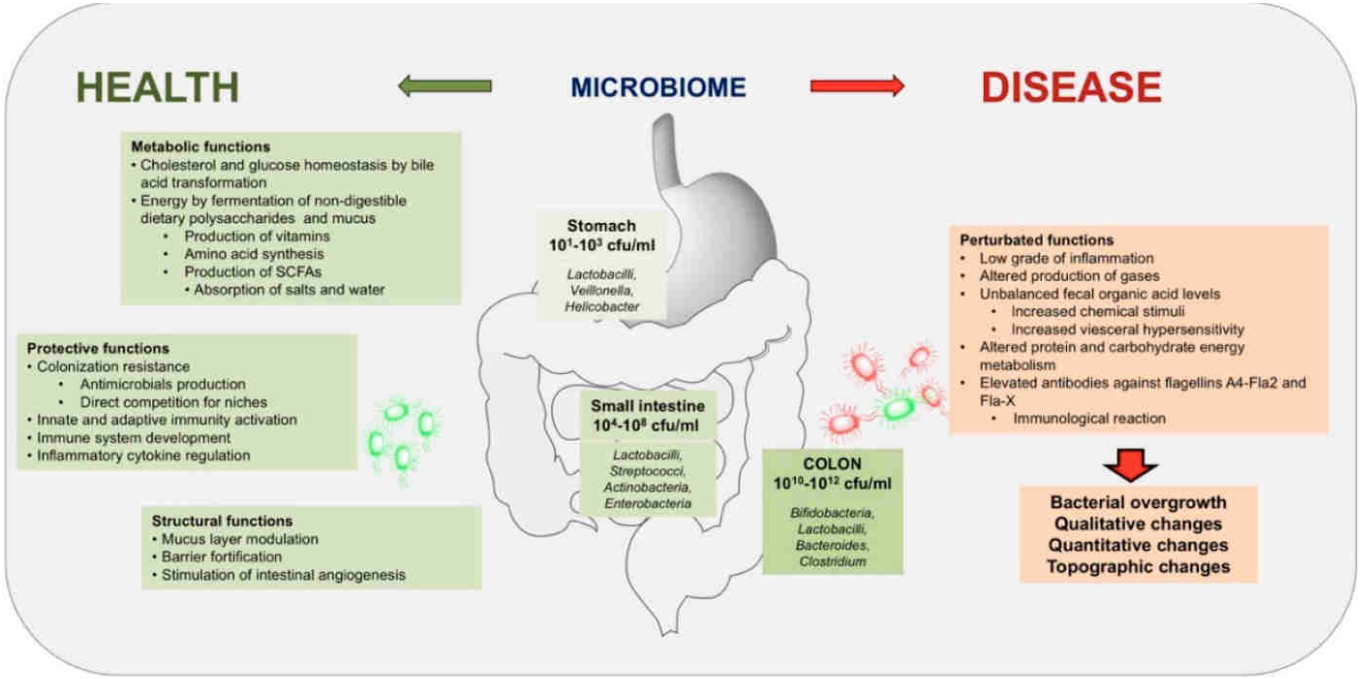
OPEN

Familial Mediterranean fever-related miR-197-3p targets *IL1R1* gene and modulates inflammation in monocytes and synovial fibroblasts

Yeliz Z. Akkaya-Ulum[1,2], Tayfun Hilmi Akbaba[1], Zeynep Tavukcuoglu[1], Jae Jin Chae[2], Engin Yilmaz[1], Seza Ozen[3] & Banu Balci-Peynircioglu[1]✉

(2021) 11:685 | https://doi.org/10.1038/s41598-020-80097-4. nature research

MICROBIOTA Y ACTIVIDAD CLINICA DE LA FMF



genes

MDPI

Review

Gut Microbiota between Environment and Genetic Background in Familial Mediterranean Fever (FMF)

Agostino Di Ciaula [1,†], Alessandro Stella [2,†], Leonilde Bonfrate [1], David Q. H. Wang [3] and Piero Portincasa [1,*]

Genes 2020, 11, 1041; doi:10.3390/genes11091041

› Clin Exp Rheumatol. 2021 Jul 5. Online ahead of print.

Microbiome is not linked to clinical disease severity of familial Mediterranean fever in an international cohort of children

Seza Ozen [1], Holly L Lutz [2], Vanessa M Rivera [3], Andreas Reiff [3], Ezgi Deniz Batu [4], Edwin Anderson [5], Mariana Salas Garcia [6], Grace Aldrovandi [3], Tayfun Hilmi Akbaba [7], İlker Pazarbasi [8], Yelda Bilginer [4], Ayse Balat [9], Banu Balci-Peynircioglu [7], Jack A Gilbert [6], Fatma Dedeoglu [5], Jonathan S Hausmann [10]

Maggio and Corsello *Italian Journal of Pediatrics* (2020) 46:7
https://doi.org/10.1186/s13052-019-0766-z

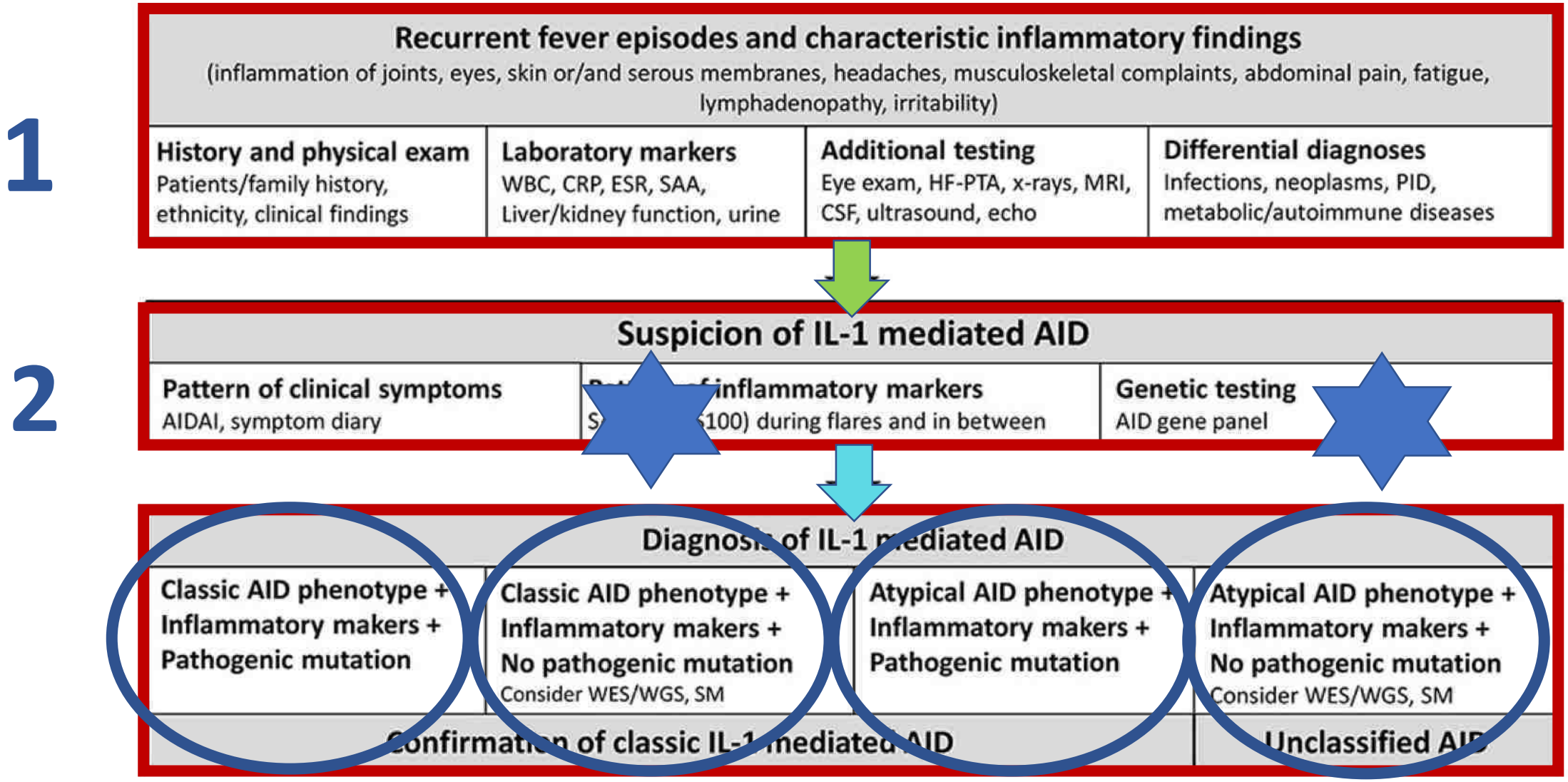
Italian Journal of Pediatrics

REVIEW Open Access

FMF is not always "fever": from clinical presentation to "treat to target"

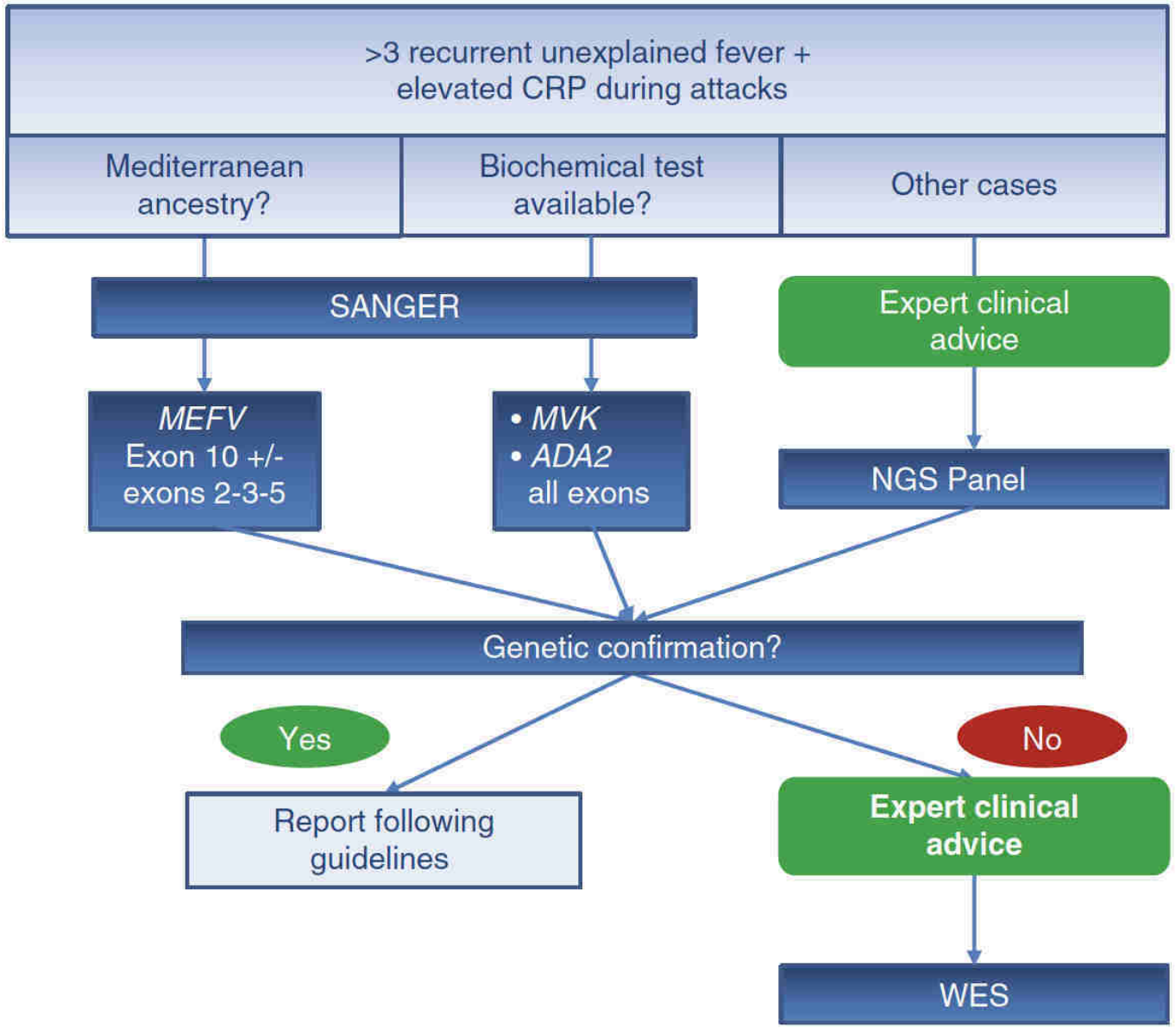
Maria Cristina Maggio* and Giovanni Corsello

DIAGRAMA DE FLUJO DE LOS PASOS EN EL DIAGNOSTICO FMF

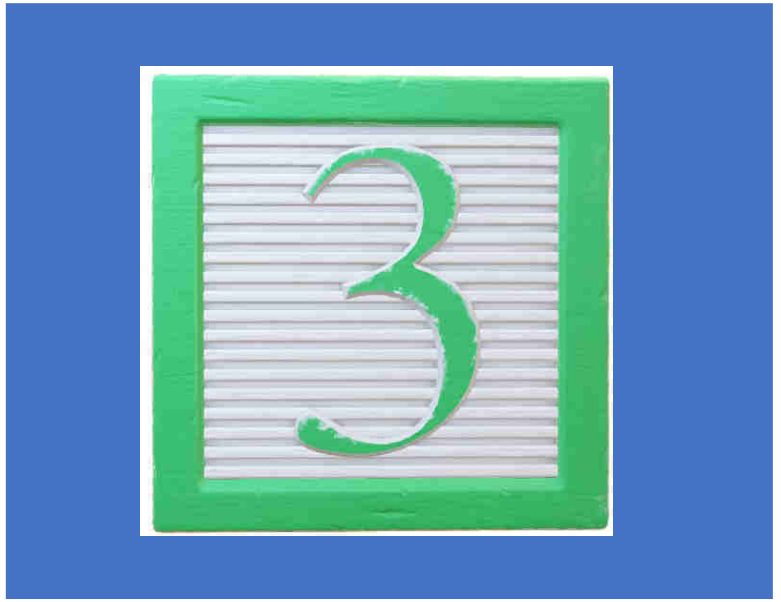


Welzel T at cols. Frontiers Inmunology 2021

ESTRATEGIA OPTIMA PARA EL DIAGNOSTICO GENETICO



Touitou I, Aksentijevic I Textbook of Autoinflammation, https://doi.org/10.1007/978-3-319-98605-0_12



SEGUIMIENTO

Monitorización de la actividad y daño de órganos FMF

Monitorización de la actividad y daño de órganos FMF

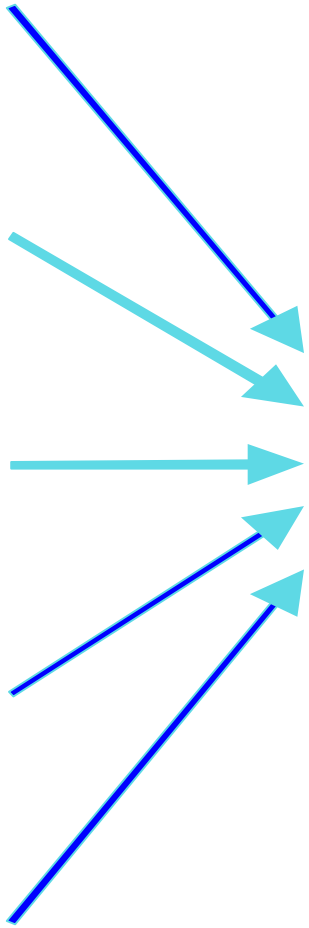
Examen Físico
Marcadores inflamatorios: PCR y Amiloide

Diario de fiebre/síntomas:
AIDAI, VAS del paciente

Instrumentos específicos:
FMF-50, VAS médico

Monitorización función órgano: Hepático, renal, proteinuria, Oftalm, RM, ecografia, Test cognitivo

Instrumento específico: ADDI



Actividad de la enfermedad

Daño de órganos

Clinical Rheumatology
https://doi.org/10.1007/s10067-019-04765-1

ORIGINAL ARTICLE

Serum amyloid A as a biomarker in differentiating attacks of familial Mediterranean fever from acute febrile infections

Mustafa Çakan[1] · Nuray Aktay Ayaz[1] · Gonca Keskindemirci[2] · Şerife Gül Karadağ[1] · Ayşe Tanatar[1] · Hafize Emine Sönmez[1]

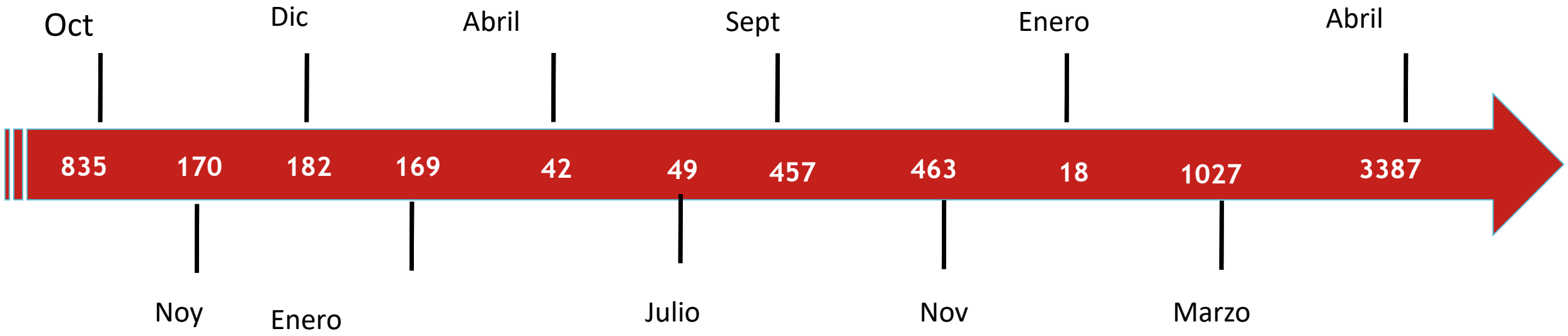
Received: 10 April 2019 / Revised: 22 August 2019 / Accepted: 26 August 2019

The Value of Serum Amyloid A Levels in Familial Mediterranean Fever to Identify Occult Inflammation During Asymptomatic Periods

Mustafa Çakan, MD, Şerife Gül Karadağ, MD, Ayşe Tanatar, MD, Hafize Emine Sönmez, MD, and Nuray Aktay Ayaz, MD

Journal of Clinical Rheumatology 2019

EVOLUCION AMILOIDE



PRS 2021

SERUM CALPROTECTIN (MRP8/14) AS A MARKER OF DISEASE ACTIVITY IN THE ASSESSMENT OF THE PAEDIATRIC PATIENT WITH AUTOINFLAMMATORY DISEASE: A CROSS-SECTIONAL STUDY

Miguel Martí Masanet, María Isabel González Fernández, Amparo Alba Redondo, Berta López Montesinos, Lucía Lacruz Pérez, Inmaculada Calvo Penadés.

Paediatric Rheumatology Unit, Hospital Universitari i Politècnic La Fe, Valencia (Spain)

TÜBİTAK

Turkish Journal of Medical Sciences

http://journals.tubitak.gov.tr/medical/

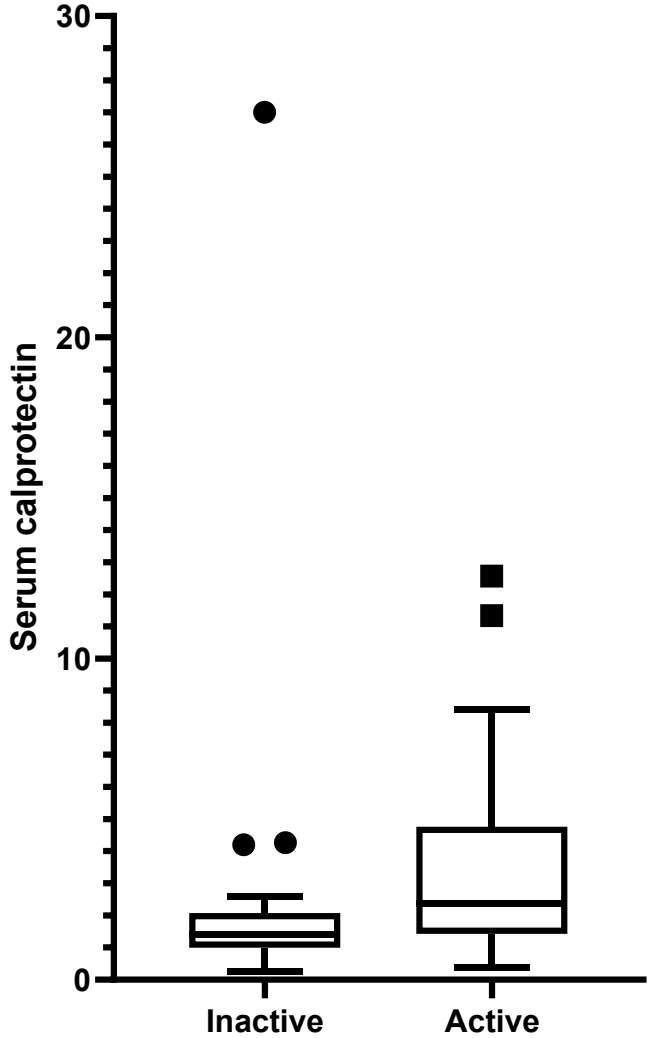
Research Article

Turk J Med Sci
(2021) 51: 1396-1405
© TÜBİTAK
doi:10.3906/sag-2009-187

Evaluation of S100A12 protein levels in children with familial Mediterranean fever

Yelda TÜRKMENOĞLU[1,*], Elif GÜNEY[1], Diğdem BEZEN[2], Ahmet İRDEM[3], Biray ERTÜRK[4], Hasan DURSUN[5]

[1]Department of Pediatrics, Okmeydanı Training and Medical Research Hospital, University of Health Science, İstanbul, Turkey
[2]Department of Pediatric Endocrinology, Okmeydanı Training and Medical Research Hospital, University of Health Science, İstanbul, Turkey
[3]Department of Pediatric Cardiology, Okmeydanı Training and Medical Research Hospital, University of Health Science, İstanbul, Turkey
[4]Department of Medical Genetic, Okmeydanı Training and Medical Research Hospital, University of Health Science, İstanbul, Turkey
[5]Department of Pediatric Nephrology, Okmeydanı Training and Medical Research Hospital, University of Health Science, İstanbul, Turkey



94 patients AD

Validation of the Auto-Inflammatory Diseases Activity Index (AIDAI) for hereditary recurrent fever syndromes

Maryam Piram,[1] Isabelle Koné-Paut,[1] Helen J Lachmann,[2] Joost Frenkel,[3] Seza Ozen,[4] Jasmin Kuemmerle-Deschner,[5] Silvia Stojanov,[6] Anna Simon,[7] Martina Finetti,[8] Maria Pia Sormani,[9] Alberto Martini,[8,10] Marco Gattorno,[8] Nicolino Ruperto,[8] on the behalf of EUROFEVER, EUROTRAPS and the Paediatric Rheumatology International Trials Organisation (PRINTO) networks

Ann Rheum Dis published online September 11, 2013
doi: 10.1136/annrheumdis-2013-203666

Control de la actividad de la enfermedad: valoraciones de pacientes

Name:	Age:	Month:	Year:

Auto-inflammatory diseases related symptoms today													
Days	**Fever ≥38°C (100.4°F) (a)**	**Overall symptoms (b)**	**Abdominal pain (c)**	**Nausea /vomiting (d)**	**Diarrhoea (e)**	**Headaches (f)**	**Chest pain (g)**	**Painful glands/ lymph nodes (h)**	**Aching in limbs or joints (i)**	**Swollen or red joints (j)**	**Eyes manifestations (k)**	**Skin rash (l)**	**Pain relief taken**
Scored as:	0 or 1	0 to 3	0 to 3	0 to 3	0 to 3	0 to 3	0 to 3	0 to 3	0 to 3	0 to 3	0 to 3	0 to 3	0 or 1
1													
2													
3													
4													
5													
6													
7													
8													
9													
10													
11													
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29													
30													
31													

Please complete the diary **during the time of the attacks** and score symptoms according to their severity.

Scoring system:

- Fever ≥38°C (100.4°F) and Pain relief taken: 0=no 1=yes
- Others variables: 0=none 1: minor 2: mild 3: severe

Use a different diary for each month. If you have no flair, bring back the diary empty.

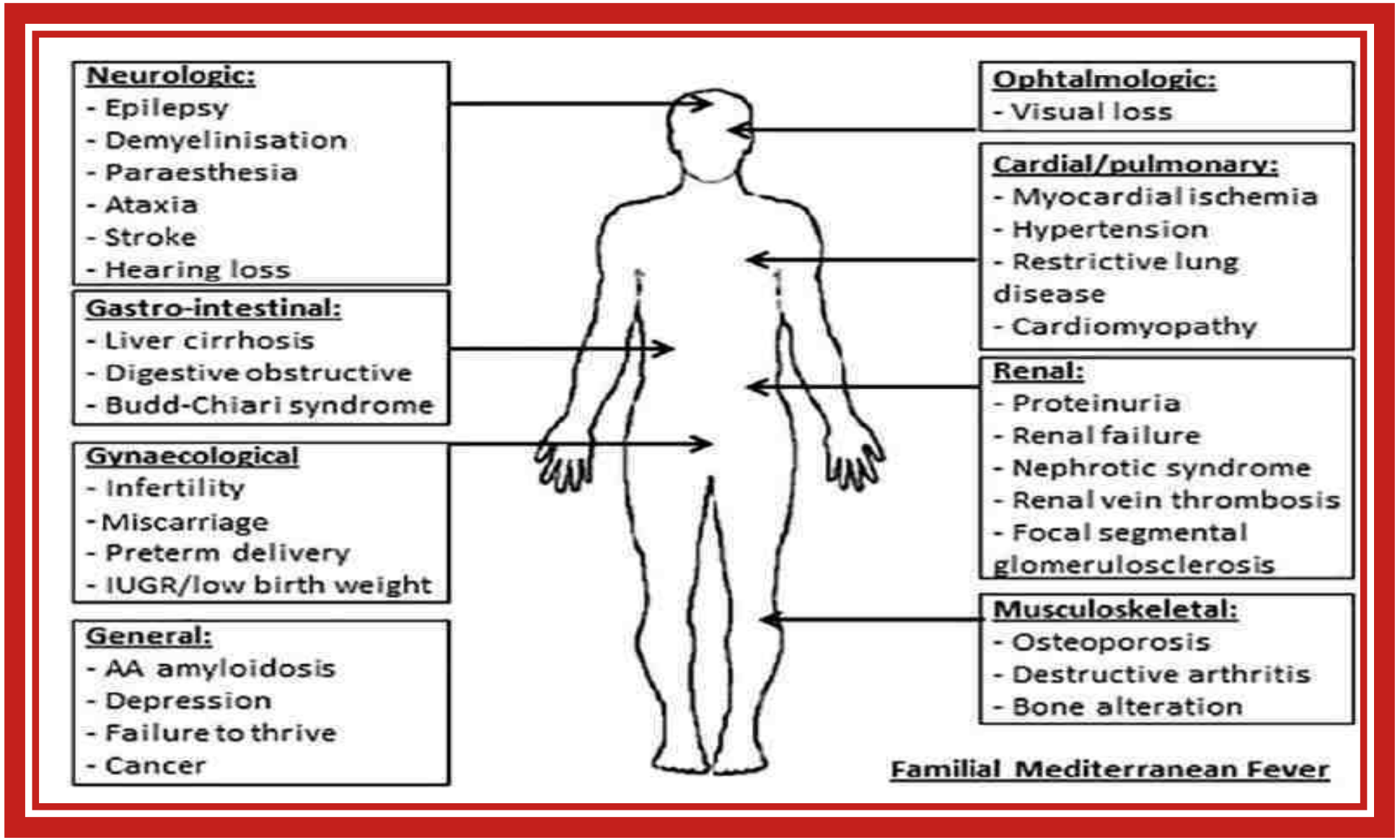
Only record symptoms due to your fever syndrome.

EXTENDED REPORT

Development of the autoinflammatory disease damage index (ADDI)

Nienke M ter Haar,[1,2] Kim V Annink,[3] Sulaiman M Al-Mayouf,[4] Gayane Amaryan,[5] Jordi Anton,[6] Karyl S Barron,[7] Susanne M Benseler,[8] Paul A Brogan,[9] Luca Cantarini,[10] Marco Cattalini,[11] Alexis-Virgil Cochino,[12] Fabrizio De Benedetti,[13] Fatma Dedeoglu,[14] Adriana A De Jesus,[15] Ornella Della Casa Alberighi,[16] Erkan Demirkaya,[17] Pavla Dolezalova,[18] Karen L Durrant,[19] Giovanna Fabio,[20] Romina Gallizzi,[21] Raphaela Goldbach-Mansky,[15] Eric Hachulla,[22] Veronique Hentgen,[23] Troels Herlin,[24] Michaël Hofer,[25,26] Hal M Hoffman,[27] Antonella Insalaco,[28] Annette F Jansson,[29] Tilmann Kallinich,[30] Isabelle Koné-Paut,[31] Anna Kozlova,[32] Jasmin B Kuemmerle-Deschner,[33] Helen J Lachmann,[34] Ronald M Laxer,[35] Alberto Martini,[36] Susan Nielsen,[37] Irina Nikishina,[38] Amanda K Ombrello,[39] Seza Ozen,[40] Efimia Papadopoulou-Alataki,[41] Pierre Quartier,[42] Donato Rigante,[43] Ricardo Russo,[44] Anna Simon,[45] Maria Trachana,[46] Yosef Uziel,[47] Angelo Ravelli,[48] Marco Gattorno,[49] Joost Frenkel[3]

ter Haar NM, et al. Ann Rheum Dis 2017;76:821–830


Neurologic:
- Epilepsy
- Demyelinisation
- Paraesthesia
- Ataxia
- Stroke
- Hearing loss
Gastro-intestinal:
- Liver cirrhosis
- Digestive obstructive
- Budd-Chiari syndrome
Gynaecological
- Infertility
- Miscarriage
- Preterm delivery
- IUGR/low birth weight
General:
- AA amyloidosis
- Depression
- Failure to thrive
- Cancer
Ophtalmologic:
- Visual loss
Cardial/pulmonary:
- Myocardial ischemia
- Hypertension
- Restrictive lung disease
- Cardiomyopathy
Renal:
- Proteinuria
- Renal failure
- Nephrotic syndrome
- Renal vein thrombosis
- Focal segmental glomerulosclerosis
Musculoskeletal:
- Osteoporosis
- Destructive arthritis
- Bone alteration
Familial Mediterranean Fever

Examen físico general

VAS Médico

LABORATORIO

3 meses

PCR

AMILOIDE

Examen ocular

Proteinuria

Score de daño ADDI

6 meses

ACTIVIDAD DE LA ENFERMEDAD

EVALUACIÓN DEL GRADO DE SEVERIDAD DE LA FMF

Development and initial validation of international severity scoring system for familial Mediterranean fever (ISSF)

Criterios de gravedad de la enfermedad	Puntos
Secuelas crónicas (incluidas amiloidosis, retraso del crecimiento, anemia, esplenomegalia)	1
Disfunción orgánica (proteinuria en intervalo nefrótico, relacionado con la FMF)	1
Fallo orgánico (corazón, riñón, etc., relacionado con la FMF)	1
Frecuencia de las crisis (promedio de crisis entre 1 y 2 al mes)	1
Frecuencia de las crisis (promedio de crisis >2 al mes)	2
Aumento de reactantes de fase aguda (cualquiera entre PCR, AAS, ESR, fibrinógeno) durante el periodo sin crisis, ≥2 semanas tras la última crisis (al menos dos veces con una diferencia de 1 mes)	1
Más de dos sitios involucrados durante una crisis aguda individual (pericarditis, pleuritis, peritonitis, sinovitis, ELE, afectación testicular, mialgia, etc.)	1
Más de dos tipos de crisis durante el curso de la enfermedad (fiebre aislada, pericarditis, pleuritis, peritonitis, sinovitis, ELE, afectación testicular, mialgia, etc.)	1
Duración de las crisis (más de 72 h en tres crisis al año como mínimo)	1
Dolor de piernas durante el ejercicio (dolor tras estar de pie durante un periodo prolongado o hacer ejercicio, después de excluir otras causas)	1
Puntuación total	**10**


MODERN RHEUMATOLOGY
https://doi.org/10.1080/14397595.2020.1719594

MODERN RHEUMATOLOGY

Taylor & Francis

ORIGINAL ARTICLE

Check for updates

Age of onset as an influencing factor for disease severity in children with familial Mediterranean fever

Ayşe Tanatar, Şerife Gül Karadağ, Mustafa Çakan, Hafize Emine Sönmez and Nuray Aktay Ayaz

Department of Pediatric Rheumatology, Kanuni Sultan Süleyman Research and Training Hospital, University of Health Sciences, Istanbul, Turkey

Demirkaya E, et al. Ann Rheum Dis. 2016; 75(6): 1.051-1.056. doi:10.1136/annrheumdis-2015-208671.

FMF50: a score for assessing outcome in Familial Mediterranean Fever

Responders to treatment are defined as those with at least 50% improvement in five of six criteria, without worsening in any

1. Percentage change in the frequency of attacks with treatment
2. Percentage change in the duration of attacks with treatment
3. Percentage change in the patients/parents global assessment of disease severity with treatment (10 cm visual analog scale)
4. Percentage change in the physicians' global assessment of disease severity with treatment (10 cm visual analog scale)
5. Percentage change in the frequency of arthritis attacks with treatment
6. Percentage change in levels of acute-phase reactants with treatment (the best of C-reactive protein, erythrocyte sedimentation rate, or serum amyloid A obtained at least 2 weeks after the last attack).

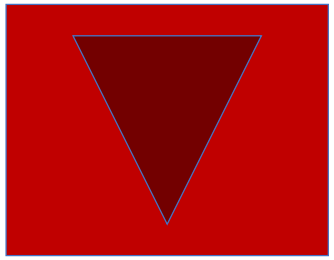
Ozen S, et al. Ann Rheum Dis 2014;73:897–901

TREAT TO TARGET

A LARGO PLAZO

TREAT - TO - TARGET

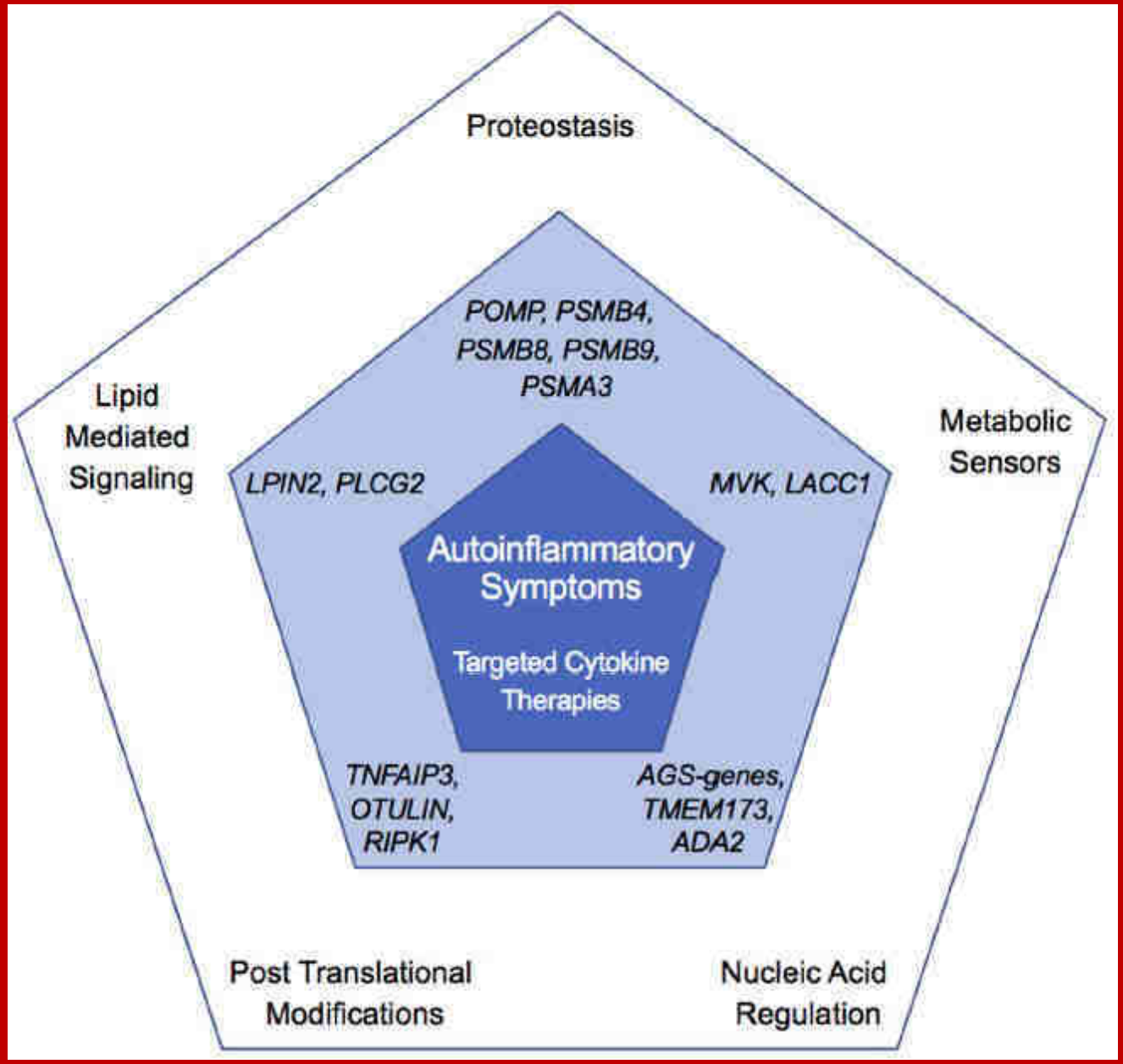
Remisión completa o enfermedad activa mínima



No actividad clínica
No síntomas

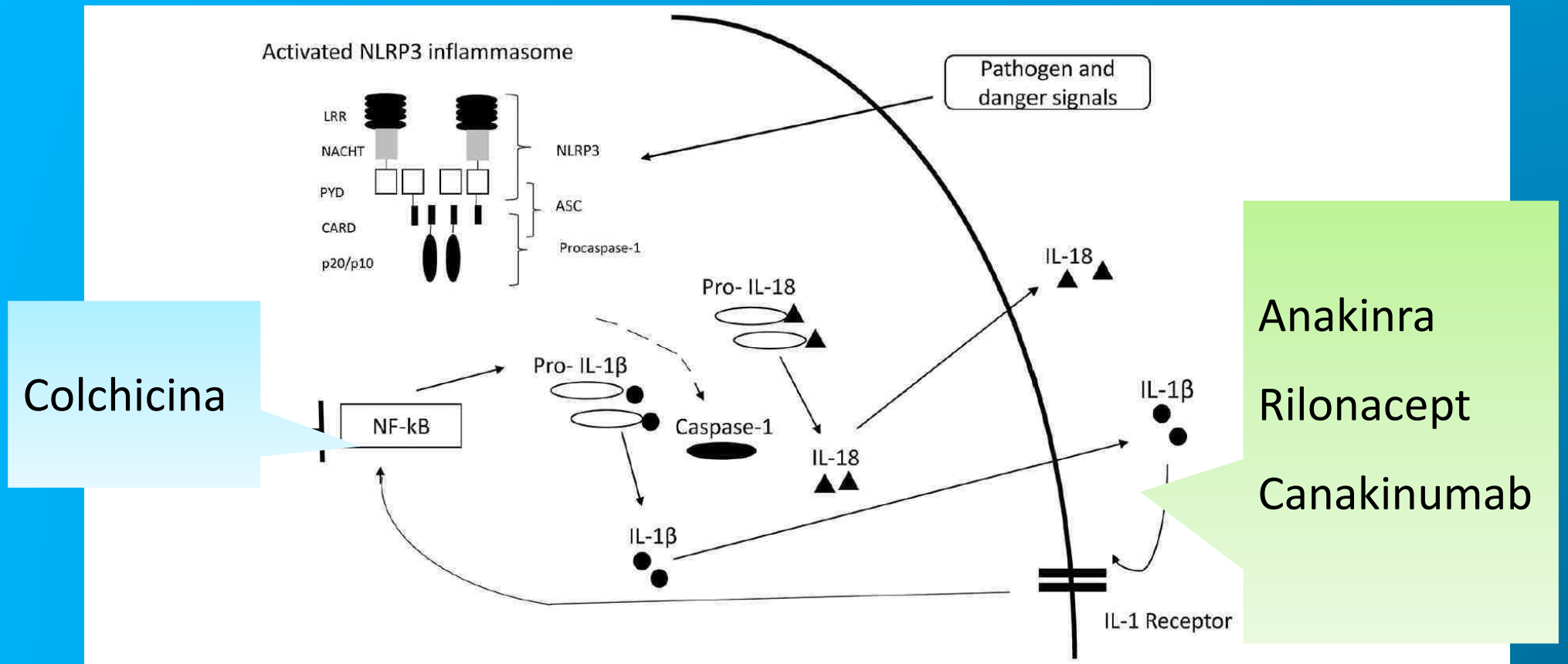
Normalización Marcadores inflamatorios PCR y Amiloide

Prevenir las complicaciones a medio y largo plazo



David B Beckand and Ivona Aksentijevich. Frontiers Inmunology 31 January 2019

IL-1 inflammasome structure, cytokine release, and treatment target



Tatjana Welzel et al. Frontiers in Immunology 2021

ALGORITMO TERAPEUTICO

1º línea

1º línea

Colchicina

- <5 años de edad, 0.5-1.0 mg / día
- Niños de 5-10 años de edad, 1.0-1.5 mg / día
- Niños > 10 años de edad y en adultos de 2 hasta 3 mg.

Adecuado control FMF

Insuficiente controL

Intolerante

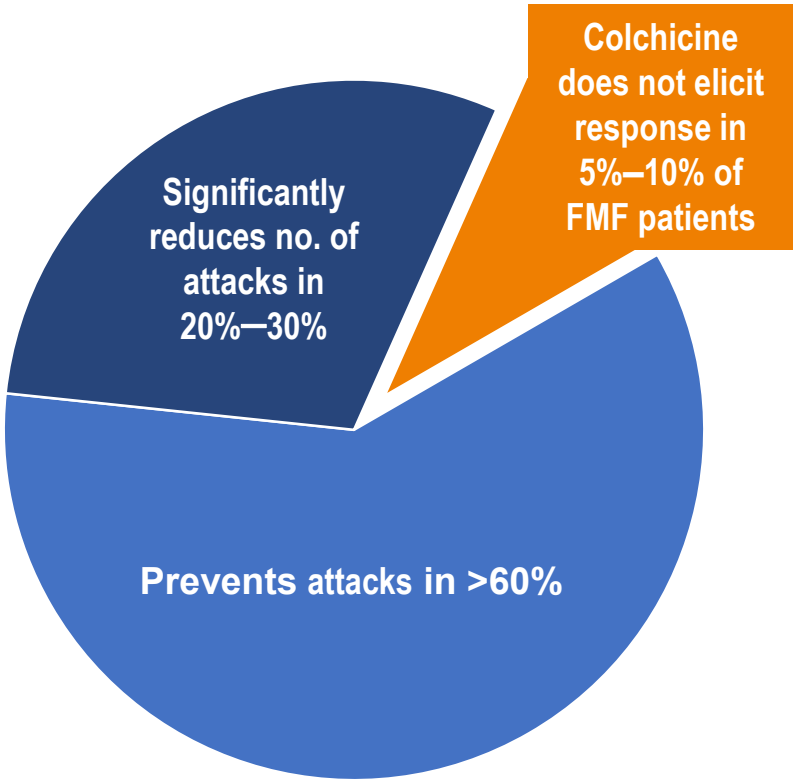
Recomendaciones de la EULAR para el tratamiento de la FMF

Recommendation	A	LoE	GR
01. Ideally, FMF should be diagnosed and initially treated by a physician with experience in FMF	7.6	5	D
02. The ultimate goal of treatment in FMF is to reach complete control of unprovoked attacks and minimising subclinical inflammation in between attacks	9.3	4	C
03. Treatment with colchicine should start as soon as a clinical diagnosis is made	8.9	1b	A
04. Dosing can be in single or divided doses, depending on tolerance and compliance	9.4	5	D
05. The persistence of attacks or of subclinical inflammation represents an indication to increase the colchicine dose	9.7	3	C
06. Compliant patients not responding to the maximum tolerated dose of colchicine can be considered non-respondent or resistant; alternative biological treatments are indicated in these patients	9.8	2b	B
07. FMF treatment needs to be intensified in AA amyloidosis using the maximal tolerated dose of colchicine and supplemented with biologics as required	9.5	2b	C
08. Periods of physical or emotional stress can trigger FMF attacks, and it may be appropriate to increase the dose of colchicine temporarily	7.6	5	D
09. Response, toxicity and compliance should be monitored every 6 months	8.6	5	D
10. Liver enzymes should be monitored regularly in patients with FMF treated with colchicine; if liver enzymes are elevated greater than twofold the upper limit of normal, colchicine should be reduced and the cause further investigated	8.4	5	D
11. In patients with decreased renal function, the risk of toxicity is very high, and therefore signs of colchicine toxicity, as well as CPK, should be carefully monitored and colchicine dose reduced accordingly	9.3	4	C
12. Colchicine toxicity is a serious complication and should be adequately suspected and prevented	9.4	4	C
13. When suspecting an attack, always consider other possible causes. During the attacks, continue the usual dose of colchicine and use NSAID	9.5	2b	C
14. Colchicine should not be discontinued during conception, pregnancy or lactation; current evidence does not justify amniocentesis	9.3	3	C
15. In general, men do not need to stop colchicine prior to conception; in the rare case of azoospermia or oligospermia proven to be related to colchicine, temporary dose reduction or discontinuation may be needed	8.2	3	C
16. Chronic arthritis in a patient with FMF might need additional medications, such as DMARDs, intra-articular steroid injections or biologics	9.5	2b	C
17. In protracted febrile myalgia, glucocorticoids lead to the resolution of symptoms; NSAID and IL-1-blockade might also be a treatment option; NSAIDs are suggested for the treatment of exertional leg pain	9.3	2b	C
18. If a patient is stable with no attacks for more than 5 years and no elevated APR, dose reduction could be considered after expert consultation and with continued monitoring	8.0	5	D
A, agreement (/10); APR, acute phase reactants; CPK, creatinine phosphokinase; DMARDs, disease modifying antirheumatic drugs; EULAR, European League Against Rheumatism; FMF, familial Mediterranean fever; IL-1, interleukin 1; LoE, level of evidence; NSAID, non steroidal anti inflammatory drugs.			

Ann Rheum Dis 2016;75:644–651

Colchicina es el principal tratamiento para evitar ataques repentinos en la FMF

Colchicine Response in FMF Patients[1-3]

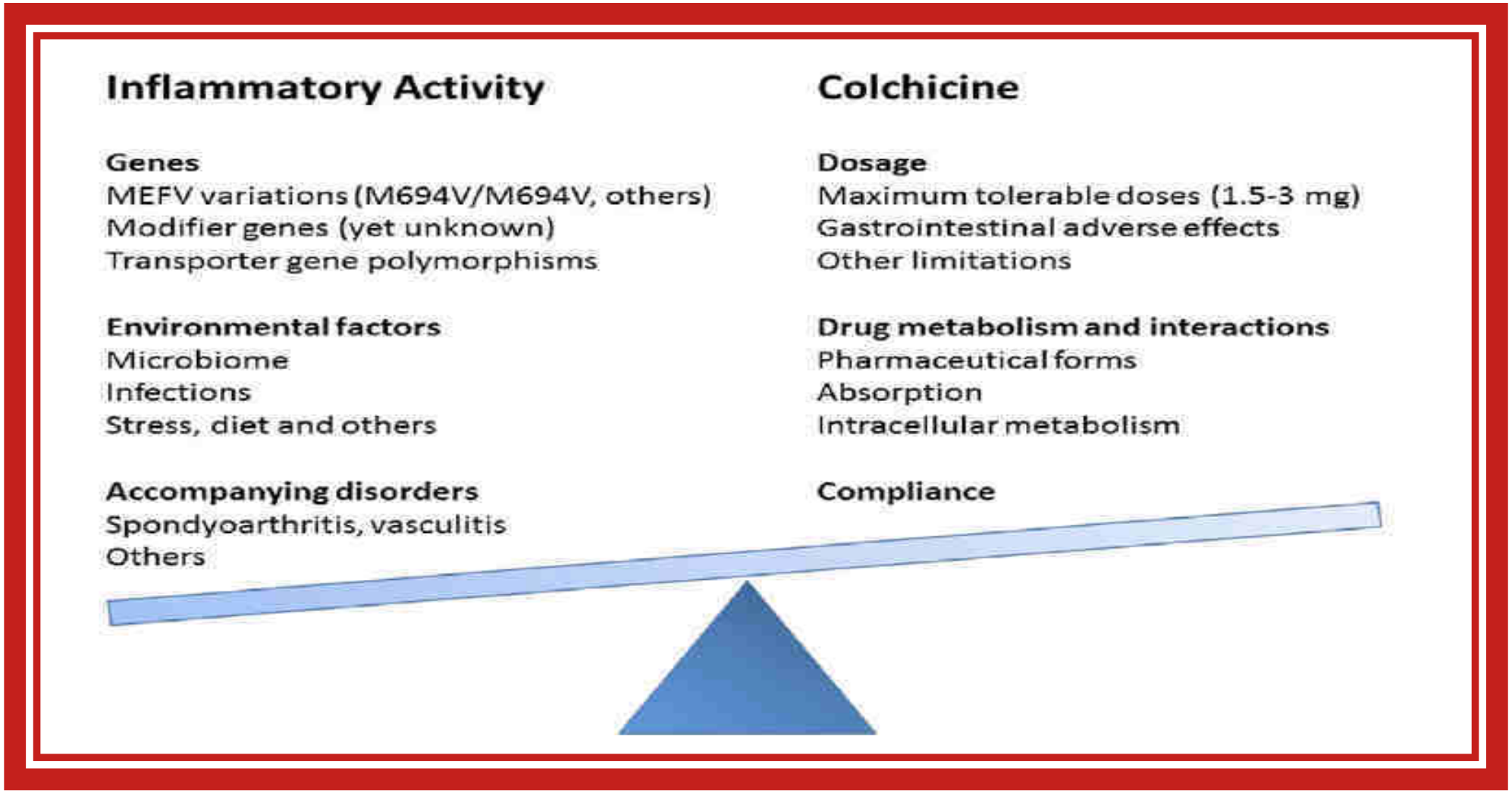


- Colchicina es el principal tratamiento para evitar ataques agudos en la mayoría de los pacientes con FMF[1]
  - Reduce la frecuencia de los ataques, disminuye la gravedad y acorta la duración de los ataques
  - Previene, detiene o incluso revierte la amiloidosis renal
- La mayoría de los pacientes que no tienen respuesta a colchicina es a causa de incumplimientos[1-3]

Includes those patients who can not tolerate colchicine, those who can tolerate it but whose attacks don't stop or don't reduce sufficiently, and those who are contraindicated to taking colchicine. Colchicine resistant is not well understood by HCPs and not well accepted in the literature, which is why we are moving away for using the term.

1. Ozturk MA, et al. Clin Exp Rheumatol. 2011; 29(Suppl. 67): S77-86; 2. Ben-Chetrit E, et al. Clin Exp Rheumatol. 2009; 27(Suppl. 53): S1-3;
3. Ben-Chetrit E, et al. Lancet. 1998; 351: 659-664.

FACTORES QUE CONTRIBUYEN A LA RESPUESTA INADECUADA DE COLCHICINA



Seminars in Arthritis and Rheumatism 2017;47:115–120

COLCHICINA.... ”VALOR REAL 2021”

OPTIMIZACIÓN DE DOSIS.

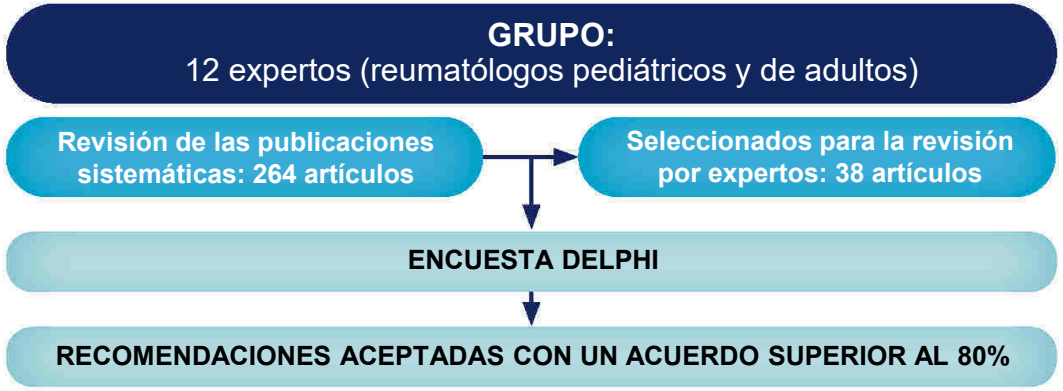
MONITORIZACIÓN. HÍGADO.RIÑÓN

CONCEPTOS:

- TOLERANCIA
- INTERACCIONES....ADULTOS CON MULTIFARMACIA
- RESPUESTA OBJETIVA
- RESISTENCIA

Consenso de un grupo de expertos sobre la resistencia a colchicina, la intolerancia y el cumplimiento en pacientes con FMF

- Se organizó una **reunión de consenso** con 12 expertos (reumatólogos pediátricos y de adultos) en la que se trabajó en la revisión de publicaciones sistemáticas (264 artículos seleccionados). Se alcanzó un consenso y se definieron unas recomendaciones siguiendo el método Delphi. Se aceptaron las recomendaciones con un acuerdo superior al 80%
- **Objetivos del grupo de expertos:** elaborar recomendaciones a partir de las evidencias en la administración de colchicina y en la definición de resistencia a colchicina, la intolerancia o el cumplimiento

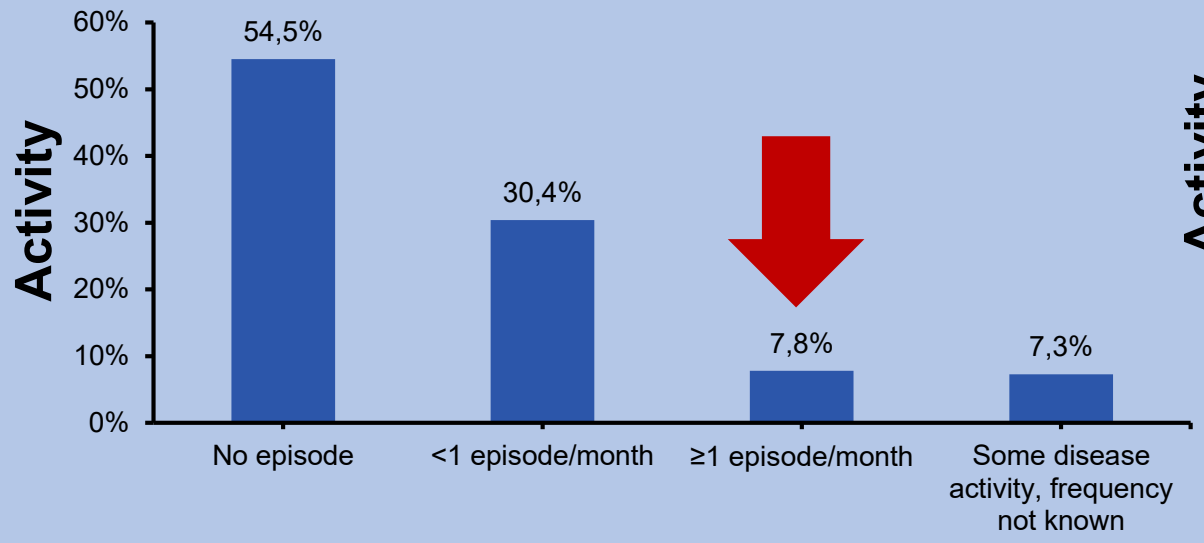


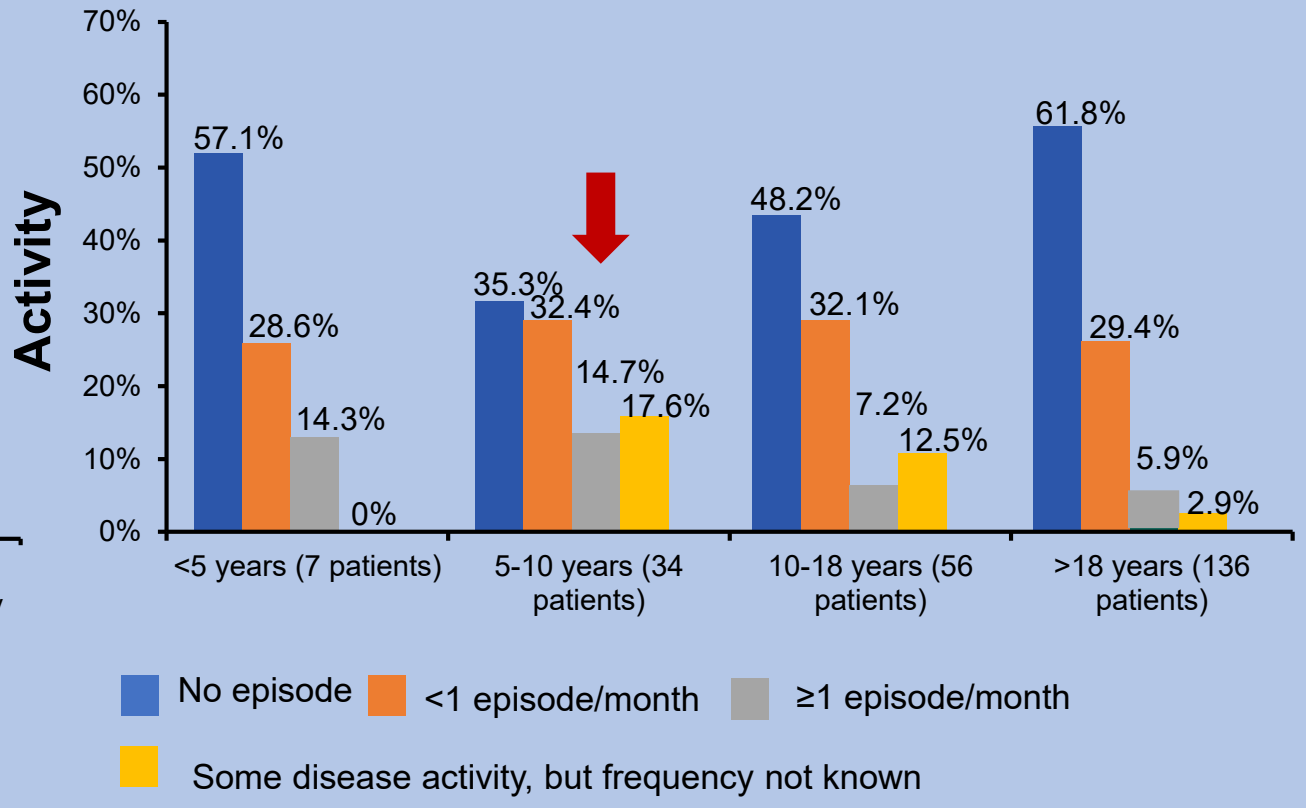
Recomendaciones

1. Colchicina es el fármaco de referencia
2. Se debe ajustar la dosis en función de la actividad de la enfermedad
3. La dosis máxima recomendada de colchicina es 1-3 mg/día
4. Se define la resistencia a colchicina como la actividad persistente de la enfermedad (media de 1 o más episodios al mes durante un periodo no inferior a 3 meses) o la presencia continua de valores de PCR o SAA elevados entre crisis
5. La amiloidosis AA se desarrolla como consecuencia de la inflamación persistente
6. La intolerancia a colchicina puede limitar la capacidad para conseguir o mantener la dosis efectiva
7. La enfermedad activa y la intolerancia a colchicina afectan a la calidad de vida
8. Se deben usar los resultados notificados por el paciente para orientar el tratamiento de la FMF

Ozen S, et al. ISSAID Congress 2019. Genoa, March 31-April 3 2019; Abstract D08.

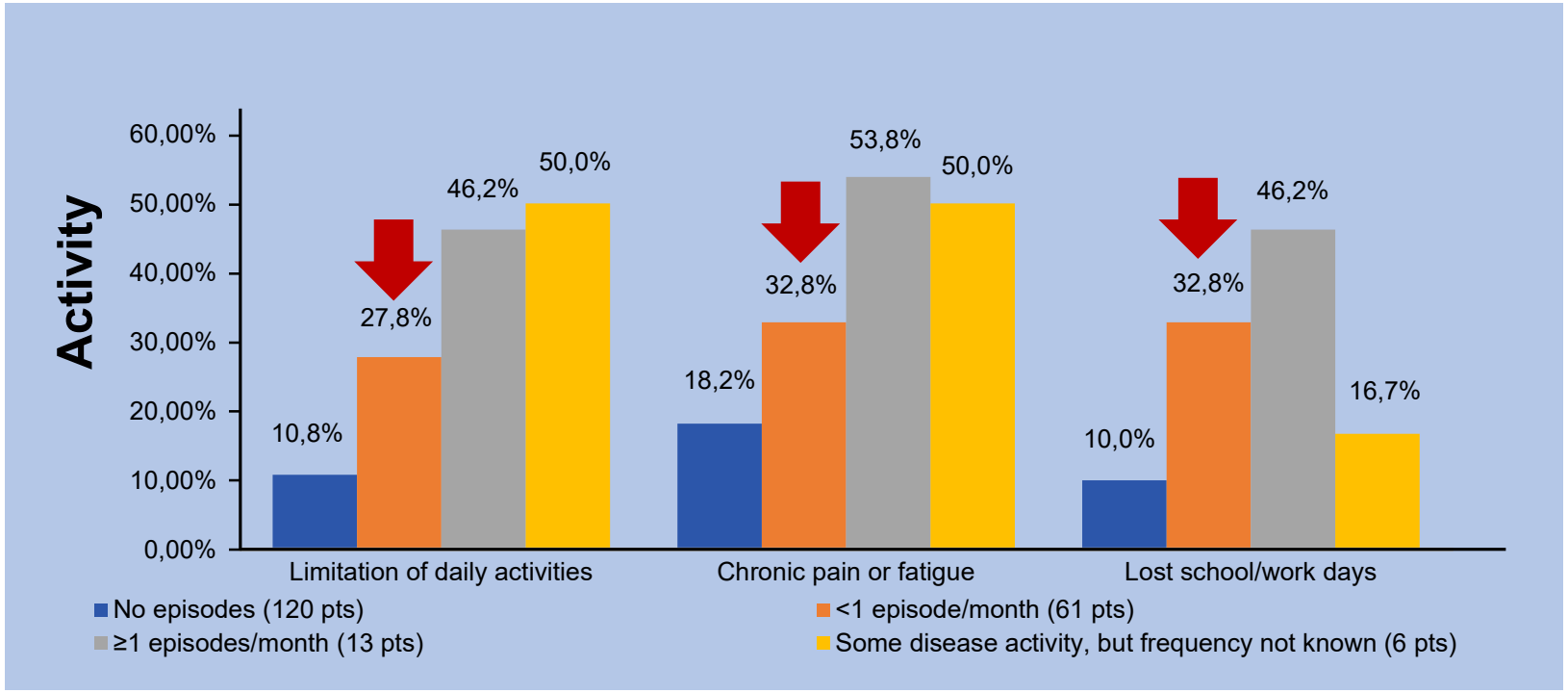
Actividad de la enfermedad durante el tratamiento con colchicina según la edad





Bustaffa M et al. EULAR 2020. Presentation OP0273; Bustaffa et al J Allergy Clin Immunol Pract 2021 Apr 20;S2213-2198(21)00434-7

Calidad de vida y respuesta al tratamiento

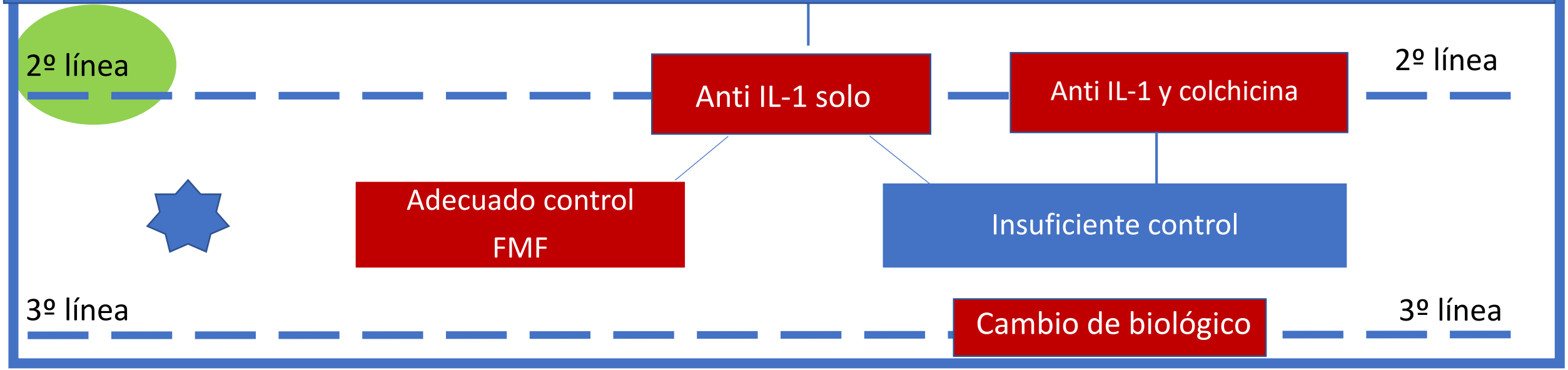


Conclusiones:

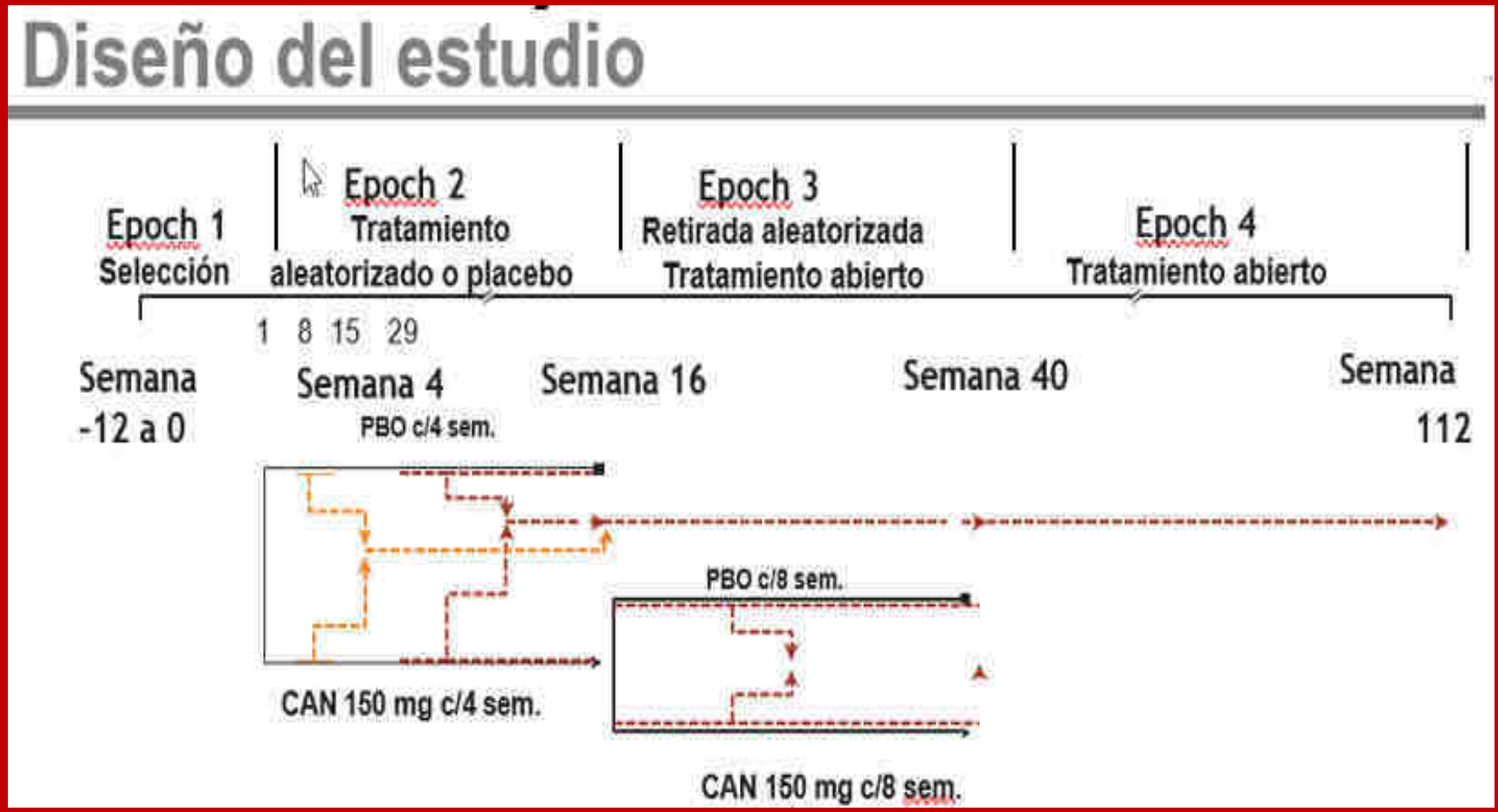
- Casi el 46% de los pacientes con FMF mostraron algún tipo de actividad de la enfermedad a pesar del tratamiento con colchicina
- En el 20% de los pacientes con actividad leve de la enfermedad, colchicina se administró de forma insuficiente
- La actividad de la enfermedad tiene una repercusión significativa en la calidad de vida, incluso en pacientes con una actividad de la enfermedad baja (<1 episodio/mes)

Bustaffa M et al. EULAR 2020. Presentation OP0273; Bustaffa et al J Allergy Clin Immunol Pract 2021 Apr 20;S2213-2198(21)00434-7

CANAKINUMAB

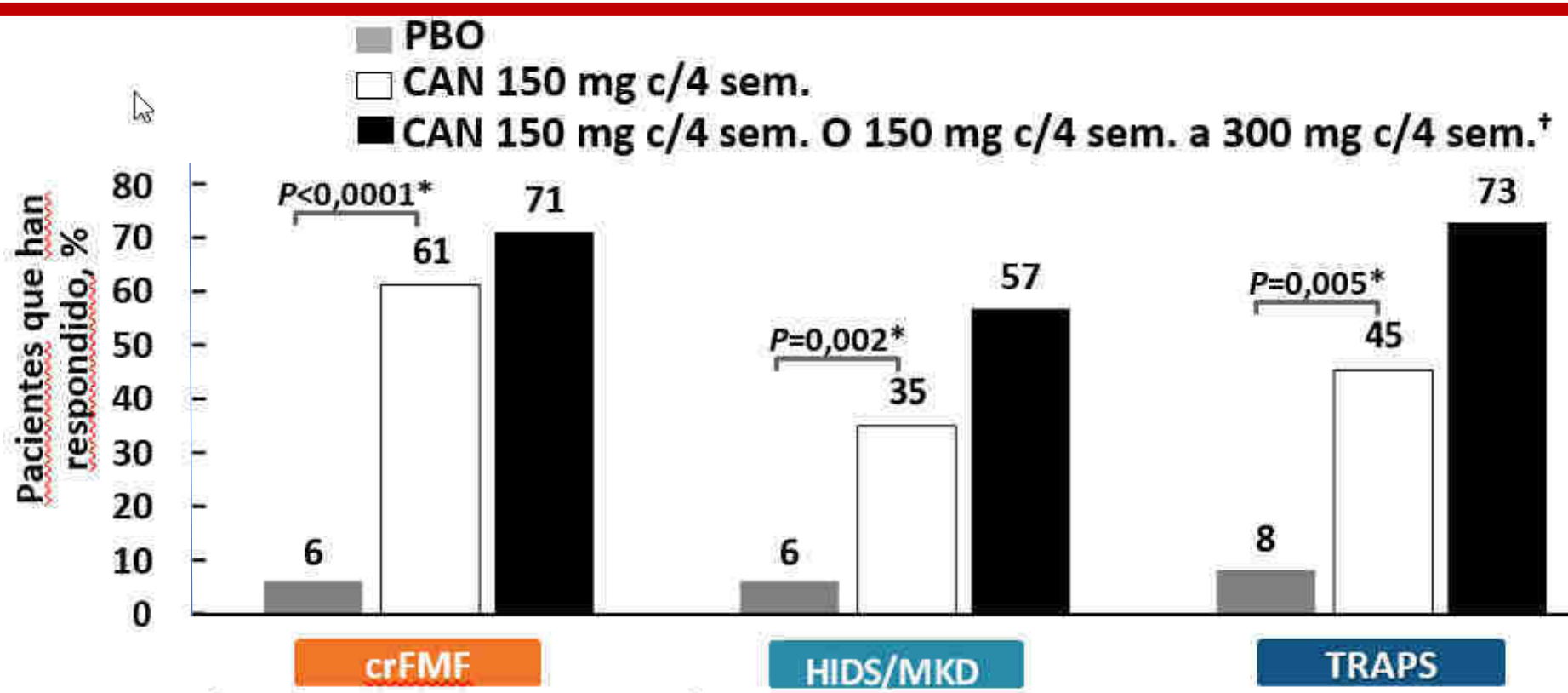


CLUSTER: canakinumab in recurrent fever syndromes: FMF, HIDS/MKD and TRAPS



De Benedetti F, et al. NEJM. 2018; 378: 1.908-1.919.

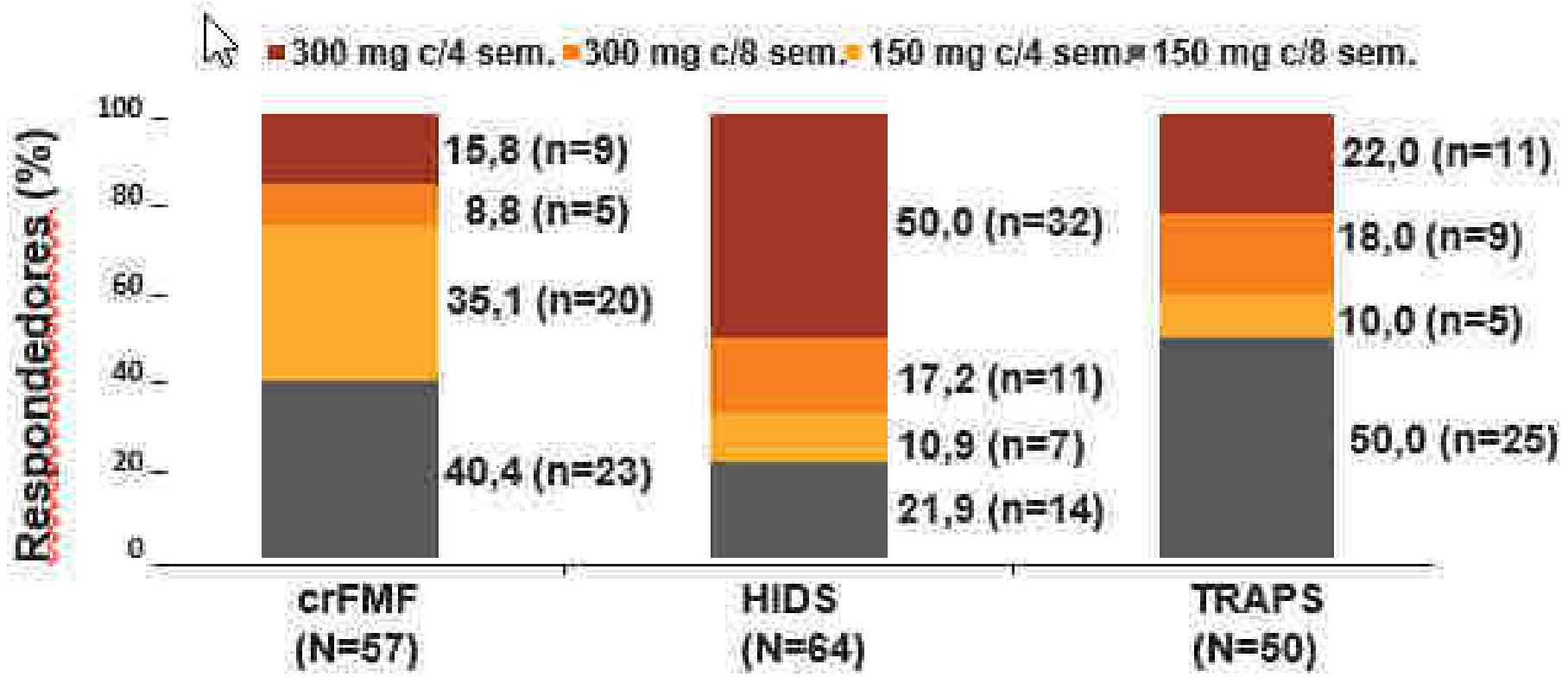
Resultado principal: Análisis post-hoc con inclusión de pacientes que aumentaron la dosis hasta 300 mg c/4 sem. antes del día 29



*Indica significación estadística (unilateral) al nivel de 0,025 según la prueba exacta de Fisher.
†Incluye a pacientes con un aumento de dosificación con ocultación de 150 mg a 300 mg c/4 sem. antes del día 29
CAN, canakinumab; PBO, placebo; PGA, Evaluación global del médico; c/4 sem., cada 4 semanas

De Benedetti F, et al. NEJM. 2018; 378: 1.908-1.919.

Proporción de pacientes que respondieron por dosis y mantuvieron el control optimo de actividad de la enfermedad al final de Epoch 4

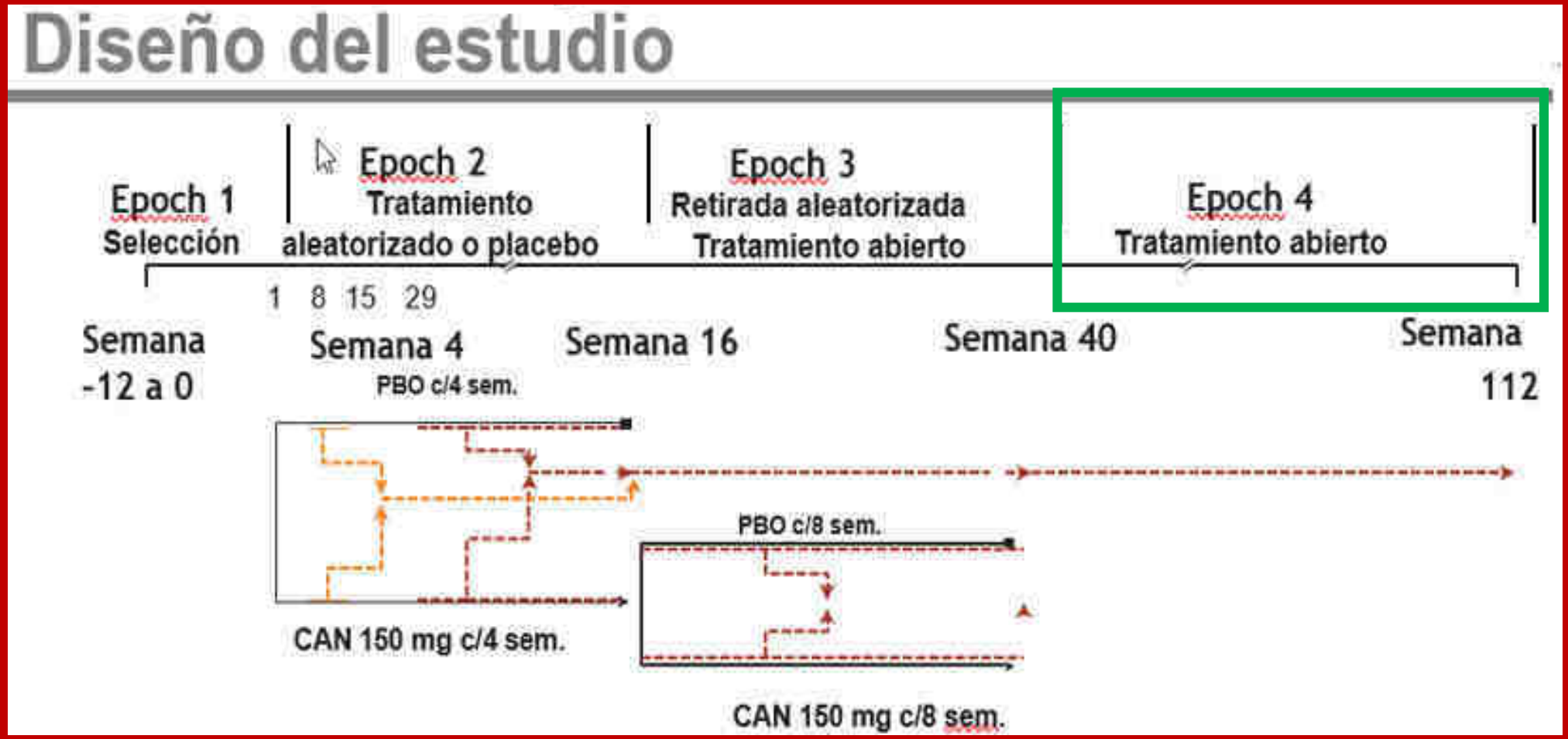


De Benedetti F et al. *N Engl J Med.* 2018;378:1908-1919

*Resolución del brote del índice el día 15, sin nuevos brotes de enfermedad durante 15 semanas de tratamiento.

N= número total de pacientes en la cohorte; n = número de pacientes que mantuvieron el control óptimo de la actividad de la enfermedad. c/4 sem., cada 4 semanas; c/8 sem., cada 8 semanas; TRAPS, síndrome periódico asociado al receptor del factor de necrosis tumoral

CLUSTER: canakinumab in recurrent fever syndromes: FMF, HIDS/MKD and TRAPS



De Benedetti F, et al. NEJM. 2018; 378: 1.908-1.919.

Características basales

Characteristics	Patients (N=60)
Median age, years (Q1, Q3)	18.0 (14.0, 29.5)
Female, n (%)	28 (46.7)
Median duration of disease, years (Q1, Q3)	13.8 (9.3, 24.2)
Median number of flares per year (Q1, Q3)	17.5 (12.0, 27.5)
Active disease at maximum colchicine dose, n (%)	59 (98.3)
CRP (mg/L), median (Q1, Q3)	102 (56.7, 202.6)
SAA (mg/L), median (Q1, Q3)	618 (265.5, 1266.0)
PGA score (disease activity), n (%)	None: 0; minimal: 0; mild: 9 (15.0); moderate: 34 (56.7); severe 17 (28.3)

Ozen S, et al. Ann Rheum Dis. 2020; 0: 1-8.

Long-term efficacy and safety of canakinumab in patients with colchicine-resistant familial Mediterranean fever: results from the randomised phase III CLUSTER trial

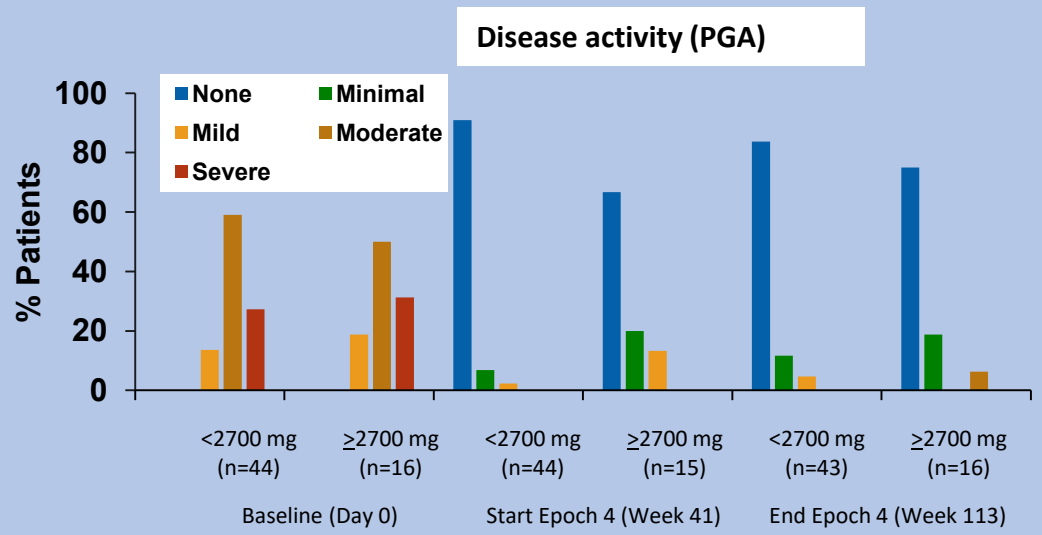
Seza Ozen [1], Eldad Ben-Cherit [2], Ivan Foeldvari [3], Gil Amarilyo [4,5], Huri Ozdogan [6], Steven Vanderschueren [7], Katherine Marzan [8], J Michelle Kahlenberg [9], Elise Dekker [10], Fabrizio De Benedetti [11], Isabelle Koné-Paut [12,13]

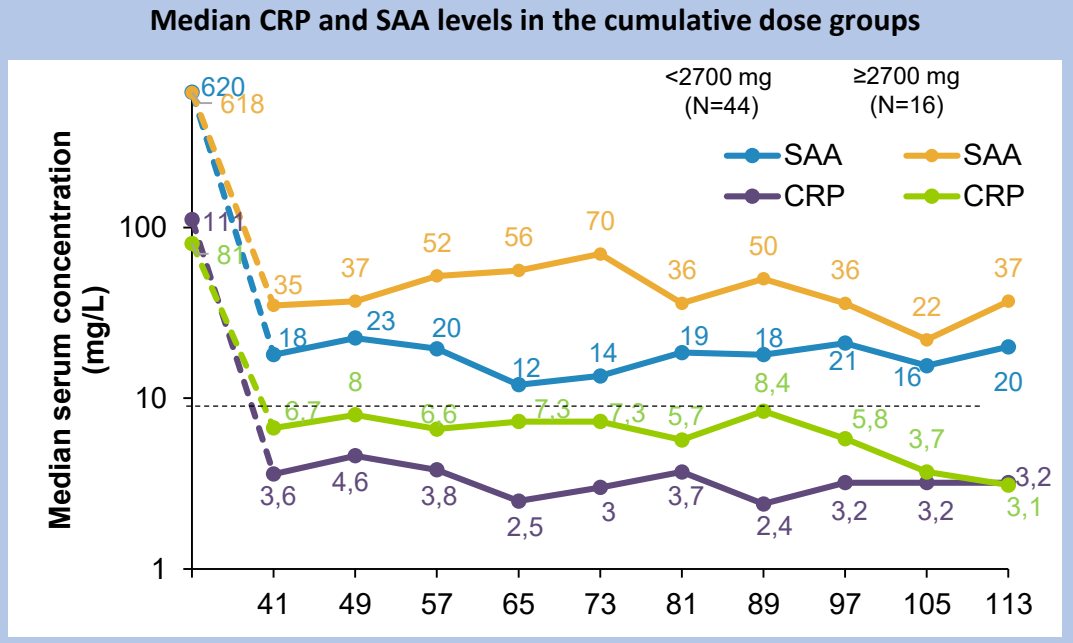
Characteristics	Patients (N=60)
***MEFV* genotype, n (%)**	
M694V/M694V	**42 (70.0)**
M694V/M694I	**3 (5.0)**
Other genotypes with mutations in exon 10	**13 (21.7)**
No mutations in exon 10	**2 (3.3)**
Prior use of biologics, n (%)	**16 (26.7)**
Anakinra	**15 (25.0)**

Actividad de la enfermedad a lo largo del tiempo

Durante el periodo de 72 semanas:

- La mayoría de los pacientes no tuvieron brotes (58%).
- Una minoría tuvieron entre 1 y 3 brotes (38% un brote, y dos pacientes comunicaron 2 y 3 brotes, respectivamente).
- La incidencia de brotes fue similar en ambos grupos de dosis acumuladas.
- Se normalizaron los parámetros clínicos de manera sostenida.
- Aparentemente, no existe ninguna asociación entre las infecciones graves, u otros AAG, y el aumento de las dosis acumuladas de canakinumab.





Ozen S, et al. Ann Rheum Dis. 2020; 0: 1-8.

FMF /EII

Amiloide sérico A

PCR

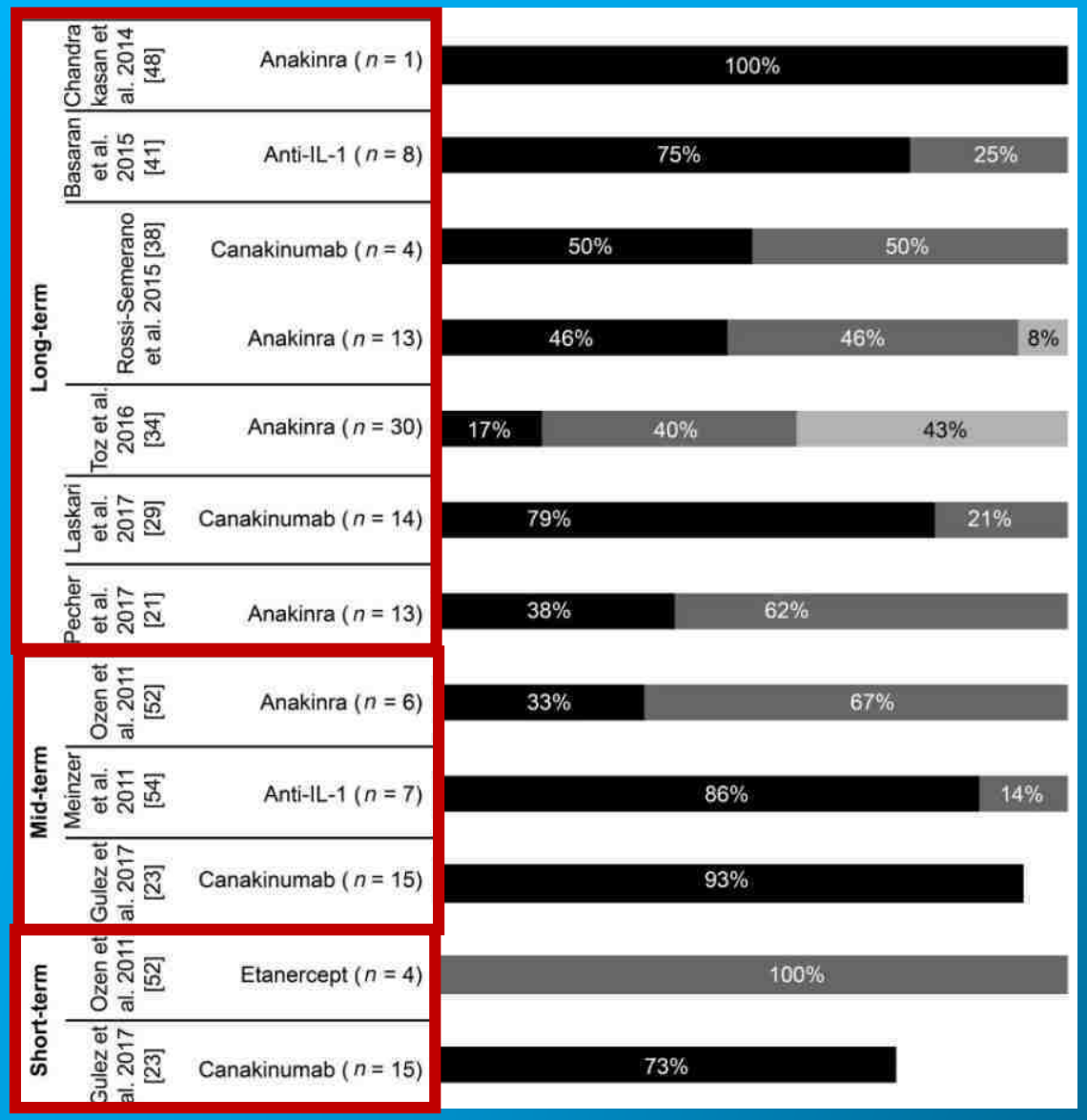
Calprotectina fecal

Mejoría de los niveles séricos después del tratamiento con canakinumab

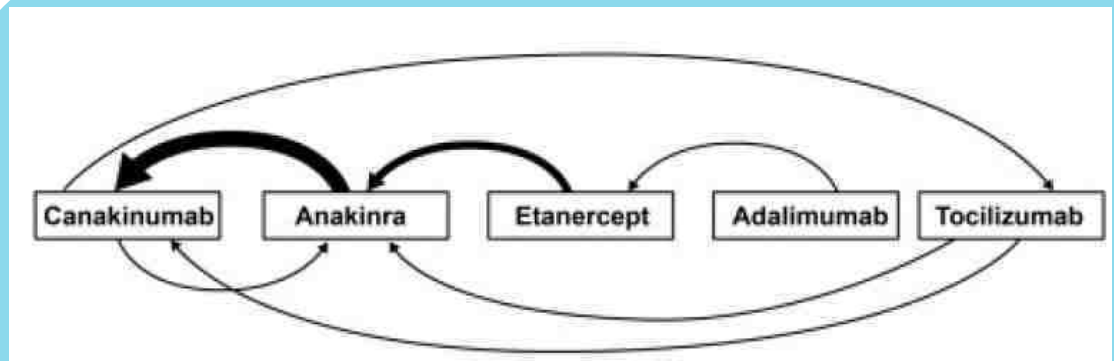
Inicio o aumento de colchicina

Inicio o aumento de canakinumab

Estudios observacionales de fiebre mediterránea familiar a corto, medio y largo plazo



Treatment Switch



Estudios observacionales

RHEUMATOLOGY
Rheumatology 2020;0:1–14
doi:10.1093/rheumatology/keaa205

Systematic Review and Meta Analysis

A systematic literature review of efficacy, effectiveness and safety of biologic therapies for treatment of familial Mediterranean fever

Jasmin B. Kuemmerle-Deschner[1], Raju Gautam[2], Aneesh T. George[2], Syed Raza[2], Kathleen G. Lomax[3] and Peter Hur[4]

Terapia a demanda

Terapia continua → Considerar ajustes de dosis

Leve actividad enfermedad

Moderada actividad enfermedad

Severa actividad enfermedad

frontiers in Immunology

MINI REVIEW
published: 18 March 2021
doi: 10.3389/fimmu.2021.616427

Management of Monogenic IL-1 Mediated Autoinflammatory Diseases in Childhood

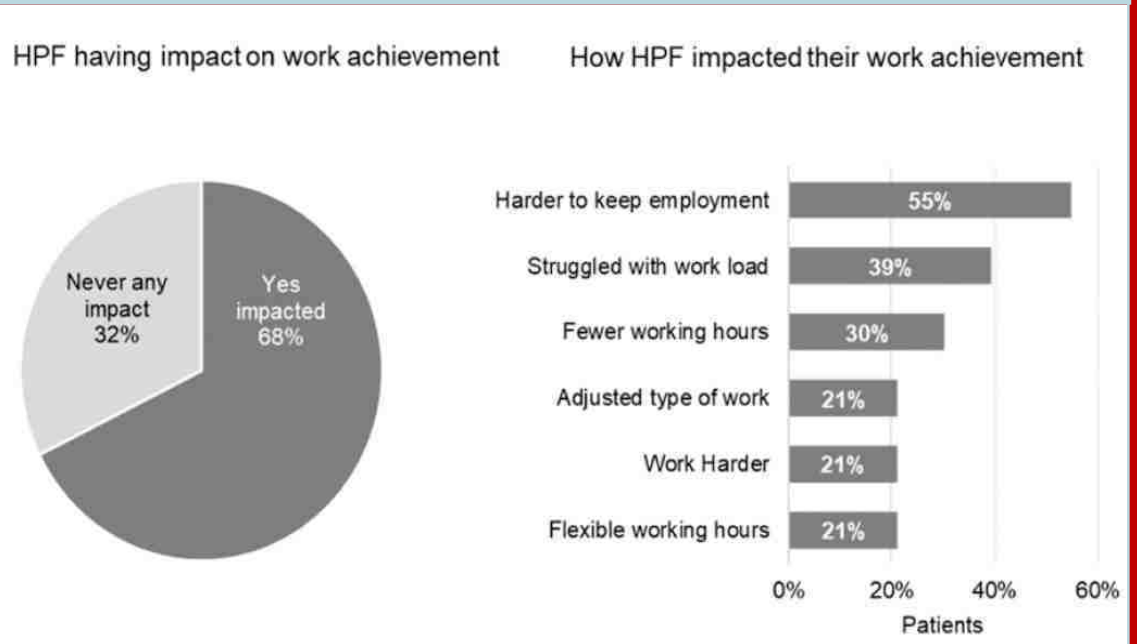
*Tatjana Welzel[1,2], Susanne M. Benseler[3] and Jasmin B. Kuemmerle-Deschner[1]**

[1] Autoinflammation Reference Center Tuebingen (arcT) and Division of Pediatric Rheumatology, Department of Pediatrics, University Hospital Tuebingen, Tuebingen, Germany, [2] Pediatric Pharmacology and Pharmacometrics, University Children's Hospital Basel (UKBB), University Basel, Basel, Switzerland, [3] Rheumatology, Department of Pediatrics, Alberta Children's Hospital (ACH), ACH Research Institute, University of Calgary, Calgary, AB, Canada

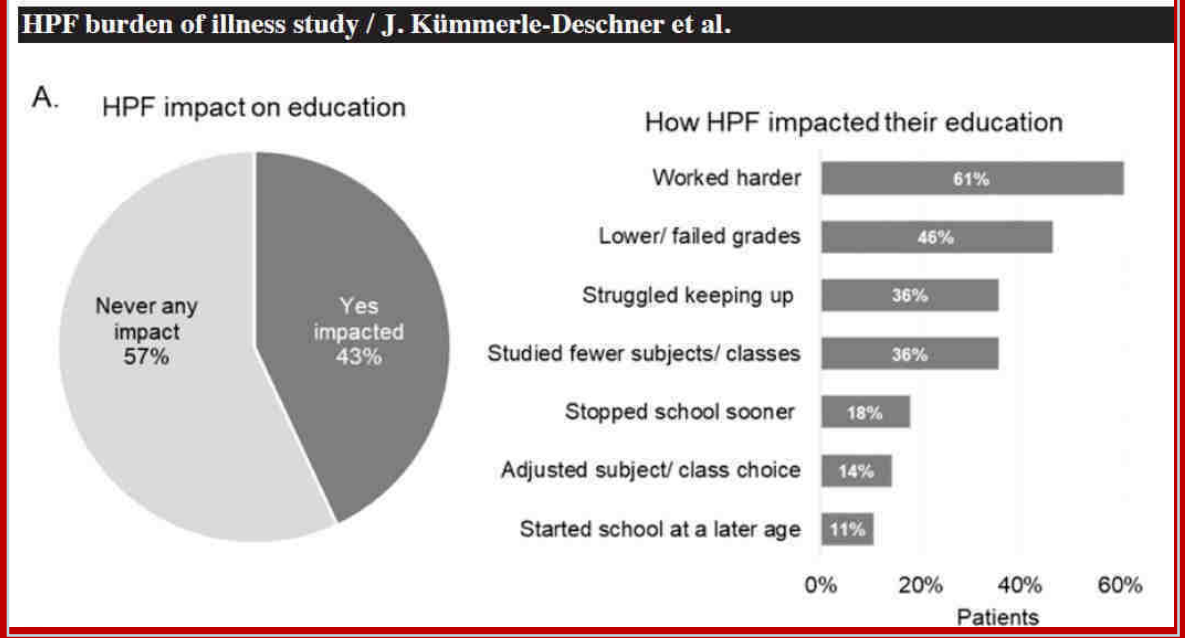
Calidad de vida

LA CALIDAD DE VIDA DE LOS PACIENTES QUE PADECEN SFP SE VE AFECTADA NEGATIVAMENTE – EDUCACIÓN Y TRABAJO

El impacto de los SHFP en el empleo de los pacientes[1]



El impacto de los SHFP en la escolarización de los pacientes[1]



J.B. Kuemmerle-Deschner et al. Clinical and Experimental Rheumatology 2020

North Clin Istanb 2021;8(3):255–260
doi: 10.14744/nci.2020.90093

ORIGINAL ARTICLE PEDIATRICS

Evaluation of quality of life and its associations with clinical parameters in pediatric patients with familial Mediterranean fever

Deniz Gezgin Yildirim,[1] Sevcan Azime Bakkaloglu,[2] A. Sebnem Soysal Acar,[3] Bulent Celik,[4] Necla Buyan[2]

FMF patients have significantly QoL

MODERN RHEUMATOLOGY
2018, VOL. 28, NO. 6, 1016–1020
https://doi.org/10.1080/14397595.2018.1427459

Japan College of Rheumatology MODERN RHEUMATOLOGY

Taylor & Francis
Taylor & Francis Group

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ORIGINAL ARTICLE

Fatigue in pediatric patients with familial Mediterranean fever

Semanur Özdel[a], Z. Birsin Özçakar[a], Nilgün Cakar[a], Fatma Aydın[a], Elif Çelikel[a], Atilla H. Elhan[b] and Fatoş Yalçınkaya[a]

[a]Department of Pediatrics, Division of Pediatric Rheumatology, Ankara University School of Medicine, Ankara, Turkey; [b]Department of Biostatistics, Ankara University School of Medicine, Ankara, Turkey

Comorbilidades

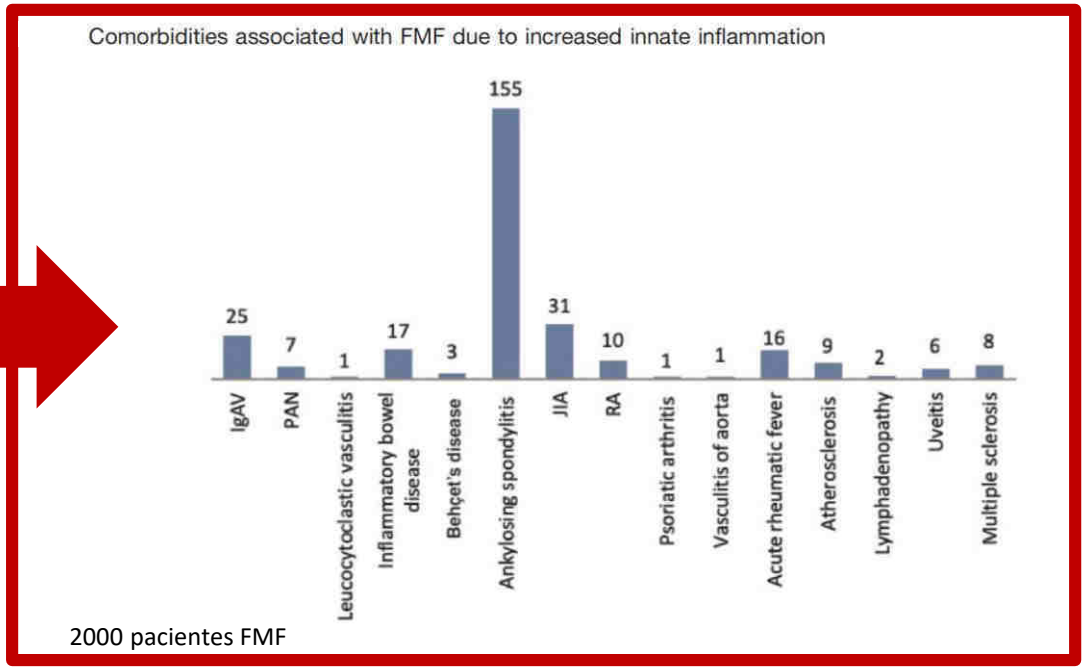
RHEUMATOLOGY

Original article

doi:10.1093/rheumatology/kez410

Comorbidities in familial Mediterranean fever: analysis of 2000 genetically confirmed patients

Banu Balcı-Peynircioğlu[1,*], Ümmüşen Kaya-Akça[2,*], Zehra Serap Arıcı[2], Edibe Avcı[1], Z. Yeliz Akkaya-Ulum[1], Ömer Karadağ[3], Umut Kalyoncu[3], Yelda Bilginer[2], Engin Yılmaz[1] and Seza Özen[2]



2000 pacientes FMF

Rheumatology International
https://doi.org/10.1007/s00296-020-04592-7

Rheumatology INTERNATIONAL

OBSERVATIONAL RESEARCH

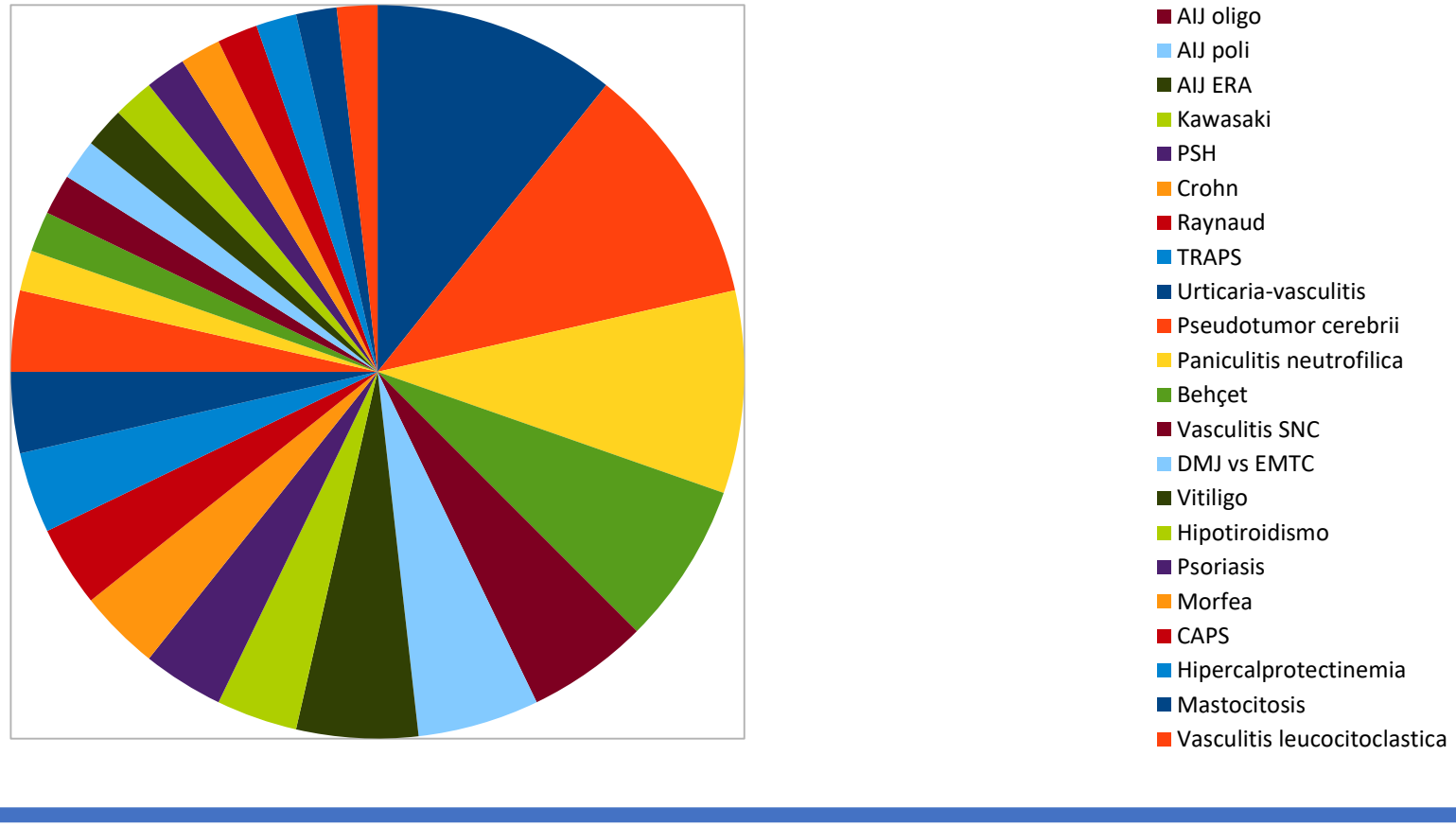
Comorbidities and phenotype–genotype correlation in children with familial Mediterranean fever

Nuray Aktay Ayaz[1] · Ayşe Tanatar[1] · Şerife Gül Karadağ[2] · Mustafa Çakan[3] · Gonca Keskindemirci[4] · Hafize Emine Sönmez[2]

Received: 16 March 2020 / Accepted: 18 April 2020

Comorbid diseases	*n* (%)	*MEFV* mutations	*n* (%)
Juvenile idiopathic arthritis	63 (53.3%)	*M694V/M694V*	49 (41.5%)
Immunoglobulin A vasculitis	35 (29.6%)	*M694V/-*	14 (11.8%)
Hashimoto thyroiditis	8 (6.7%)	*M694V/ M680I*	10 (8.4%)
Inflammatory bowel disease	4 (3.3%)	*M694V/ V726A*	8 (6.8%)
Psoriasis	3 (2.5%)	*M694V/E148Q*	2 (1.7%)
Nutcracker syndrome	3 (2.5%)	*M694V/R761H*	2 (1.7%)
enile SLE	2 (1.7%)	*M680I/V726A*	6 (5.1%)
mune thrombocytopenic purpura	2 (1.7%)	*M680I/-*	8 (6.7%)
Behçet's disease	1 (0.9%)	*M680I/E148Q*	4 (3.3%)
Polyarteritis nodosa	1 (0.9%)	*V726A/E148Q*	5 (4.3%)
Pan-hypopituitarism	1 (0.9%)	*V726A/-*	3 (2.5%)
Addison's disease	1 (0.9%)	*E148Q/-*	5 (4.3%)
Type 1 diabetes mellitus	1 (0.9%)	*E148Q/E148Q*	1 (0.9%)
Congenital adrenal hyperplasia	1 (0.9%)	*A744S/-*	1 (0.9%)
Diffuse proliferative glomerulonephritis	1 (0.9%)		
TINU	1 (0.9%)		

110 PACIENTES CON MUTACIONES FMF



Calvo I et al. PRES 2019

- Enfermedades poco frecuentes donde el diagnóstico precoz implica conocer sus manifestaciones clínicas y complicaciones.
- La asociación de estos genes con enfermedades multifactoriales es posible, por lo tanto conocer el fenotipo es de gran importancia.
- Conceptos claves como la resistencia a la colchicina y la indicación de IL-1 serán relevantes en el manejo de estas enfermedades.
- Actividad de enfermedad y calidad de vida también serán puntos a considerar en el tratamiento.

GRACIAS