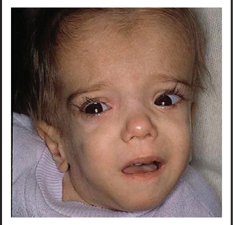
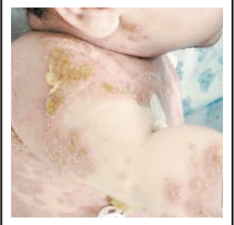
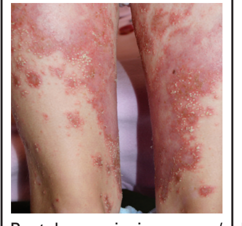
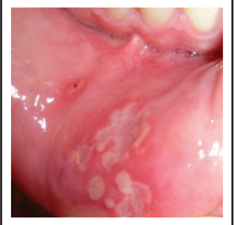
Comparison Chart of Systemic Autoinflammatory Diseases (SAID) Involving Periodic Fevers

	Cryopyrin-Associated Periodic Syndromes (CAPS)				Pyrin	Protein Folding
	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 Sydrome —aka Familial Hibernian Fever
ACRONYM	FCAS	MWS	NOMID/CINCA	SCHNITZLER	FMF	TRAPS
GENE	*NLRP3*	*NLRP3*	*NLRP3*	Currently unknown.	*MEFV*	*TNFRSF1A*
INHERITANCE	Autosomal Dominant. Large familial groups, some spontaneous mutations.[1]	Autosomal Dominant. Spontaneous mutations, some familial groups.[1]	Autosomal Dominant. Spontaneous mutations, few familial cases.[1]	Unknown.	Autosomal Recessive. Some cases are gene-dosage-dependent autosomal dominant.[10]	Autosomal Dominant. Spontaneous mutations, some familial groups.[1]
ETHNICITY	Affects all races, but many are of European descent.[1]	Affects all races, but many are of European descent.[1]	Any–present in all races.[1]	Affects all races, but most cases are in Europe.[13] More men than women are affected.	Turk, Armenian, Arab, Sephardic Jew, Italian.[1] Most common inherited periodic fever syndrome.	Affects all races. 2nd most common inherited SAID (after FMF.)[1]
FREQUENCY IN THE WORLD	1:1 million, or more. In USA 300+ diagnosed–most cases are from large family groups.[2,5]	1:1 million, maybe more. Some large family groups.[5] Frequency of CAPS in France is 1:360,000.[55]	Estimated frequency 1:1 million, mostly due to spontaneous genetic mutations.[5]	Unknown. Over 150 known cases, mostly in Europe.[13]	In specific ethnic groups, the carrier frequency of *MEFV* variants is up to 1:5 people.[1]	Unknown. TRAPS affects 0.01:10,000 people in the European Union.[51] >1000 pts. worldwide.[52]
TIMING OF SYMPTOMS OR ATTACKS	12-24 hours, or longer. Onset of fever & flares is often 1-3 hours after exposure to cold or cooling temperatures.[1]	Often lasts 2-3 days. Random onset–flares of fever & symptoms are often triggered by cold or cooling temperature.[1]	Continuous w/increased symptoms & fever during flares.[1] Chronic inflammation noted between flares.	12-36 hours. Rash is present first. Intermittent fevers, that often occur separately from the rash.[13]	12-72 hours.[1,9] Recurrent fever & flares can occur weekly, or only a few times a year.	Days to weeks. Average flare is 3 weeks.[1,9]
AGE OF ONSET	Infancy, but a few present with symptoms later in childhood or adolescence.[1]	Infancy, but a few present with symptoms later in childhood or adolescence.[1]	Neonatal/early infancy. Rash, symptoms, & abnormal labs are often present at birth.[1,6]	Most cases start in middle age, over 35-50 yrs. Youngest pt. was 13 yrs old. Symptoms start w/the rash.[13]	Infancy, to under 20 years of age for the first symptoms.[9]	Most first attacks by 3 yrs, & almost all begin by 20 yrs. of age; a few start later in life.[9]
SYSTEMIC FINDINGS:						
SKIN/ CUTANEOUS	Cold induced urticaria-like rash with increased neutrophils at the eccrine coils.[4] Almost daily rash–increases w/flares.[1]	Urticaria-like rash with increased neutrophils at the eccrine coils.[4] Most w/daily rash that increases w/flares.[1]	Ever-present[1] Urticaria-like rash with increased neutrophils at the eccrine coils. Rash increases with flares.[4]	Maculopapular rash, & plaques (sometimes itchy) on the chest & limbs. Dermis has neutrophillic infiltrate. Dermographism.[13]	Erysipeloid erythema on the ankle–foot–below knee region–lasts 2-3 days during flares of symptoms.[1]	Migrating rash w/deep pain under rash areas. Severe pain follows the rash path from the trunk out to the limbs.[9]
NEUROLOGIC	Some have headaches, fatigue w/fever after cold exposure. Unknown if there are notable CNS affects at this time.[1]	Some have headaches, fatigue w/fever & flares. Uncommon to have many other CNS symptoms.[1]	Headaches, fever, fatigue. chronic aseptic meningitis, & high CNS pressure (ICP). Many with mental &/or cognitive impairments. Papilledema is common.[6]	Intermittent fevers can rise > 40°C. Chills are uncommon. Fatigue & headaches are common w/fevers. Temperature changes, stress & exercise can trigger flares.[13]	Fevers. Acute aseptic meningitis is rare and can occur during flares, but is never chronic.[1] Other neurological involvement is very rarely seen in FMF.	Fevers lasting >3 days at over 38°C w/flares. Some have headaches w/flares of symptoms.[1,9]
AUDITORY	Some pts have mild hearing loss–not currently known if it's from CAPS inflammation.[1]	Many have increased sensorineural hearing loss, starting in adolescence.[1]	Many have increased sensorineural hearing loss, from infancy/childhood.[1,6]	Uncommon.[13]	Uncommon–not believed to be caused by a FMF disorder.[1]	Uncommon–not believed to be caused by TRAPS.[1]
OPTHALMIC	Conjunctivitis (non-infectious) during flares.[1]	Conjunctivitis (non-infectious) during flares,[1] or corneal haze.[26]	Papilledema, uveitis, iritis, conjunctivitis. Some w/retinal scarring, corneal haze or vision loss.[6,26]	Not noted.[13]	Very rare to uncommon.[1]	Conjunctivitis, & periorbital edema during flares.[1,9]
CARDIO-PULMONARY	Not noted.[1]	Rare.[1]	Some have clubbing of fingers. Some cases of pericardial effusions, or pericarditis.[1]	Not noted.[13]	45% have pleuritis, painful respiration, w/flares. Some w/pericarditis.[1]	Common, including pleurisy.[1]
ABDOMINAL	Uncommon.[1]	Some have abdominal pain w/flares or other gastrointestinal issues.[1]	Nausea, vomiting & abdominal pain with flares, or with high CNS pressure.[6]	GI symptoms are uncommon. Enlarged liver &/or spleen is common.[13]	Sterile peritonitis, pain, and/or constipation with flares.[1]	Peritonitis, diarrhea, & constipation w/flares.[1]
LYMPHATIC	Not noted.[1]	Rarely noted.[1]	Some pts. with enlarged liver and/or spleen, many have large lymph nodes.[1]	<20% w/lymphoma, IgM myeloma, or Waldenströms. >45% w/enlarged lymph nodes.[13]	Enlarged spleen is common, some have enlarged lymph nodes.[1]	Enlarged spleen common, some have enlarged lymph nodes.[1]
JOINTS/BONES MUSCLES & CARTILAGE	Arthralgias, stiffness & swelling with flares.[1]	Arthralgias, recurrent arthritis, stiffness & swelling with flares.[1]	Joint pain, knee valgus or varus. Some w/frontal bossing, saddleback nose, contractures, clubbing.[1] <50% of patients knees have bony overgrowth. Short stature, growth delays failure to thrive, arthritis, osteopenia noted.[1,26]	80% have muscle, bone &/or joint pain; arthritis. Bone pain is most common in the iliac and tibia. <40% have bone lesions. Some w/ osteocondensation & sclerotic bone marrow involvement in the legs.[13]	Mono/Polyarthritis, oligoarthritis & clubbing are common. Ankle arthralgias are common. Severe arthritis of the hip or ankle is rare.[1]	Intermittent or chronic arthritis in large joints w/muscle pain & swelling.[1]
VASCULITIS	Not noted.[1]	Not noted.[1]	Vasculitis rarely develops.[1]	Vasculitis noted in 20% of patients.[13]	HSP, polyarteritis nodosa.[1]	HSP, lymphocytic vasculitis.[1]
AMYLOIDOSIS	Elevated serum amyloid (SAA). Secondary amyloidosis in some patients.[1,9]	Elevated SAA >25 % w/secondary amyloidosis.[1,9]	Elevated SAA. Secondary amyloidosis in <2% pts.[1,6]	A few patients have developed secondary amyloidosis.[13]	Common >50% in untreated patients, it depends on genotype.[9]	10-20% occurrence–higher risk w/cysteine mutation.[9]
ABNORMAL LABS	High: ESR, CRP, SAA. Leukocytosis with flares.[1]	High: ESR, CRP, SAA. Leukocytosis,with flares.[1]	Chronically high: ESR, CRP, SAA, anemia, granulocyte leukocytosis.[1,6]	Monoclonal IgM &/or IgG gammopathy. High: ESR, CRP. Leukocytosis. Complement normal to elevated. 50% w/inflammatory anemia.[13]	High: ESR, CRP, SAA between flares. Fibrinogen, Leukocytosis present with flares.[1]	High: ESR, CRP, SAA. Elevated PMNs, polyclonal gammopathy, leukocytosis.[1]
	 The rash can vary in size, & intensity in all forms of CAPS. (NOMID Alliance pt. image)	 The CAPS rash is often more pronounced during flares. (NOMID Alliance pt. image)	 NOMID pt. w/rash, frontal bossing, & saddleback nose. (NOMID Alliance pt. image)	 Schnitzler syndrome: Urticarial skin rash on the arm. (cri-net.com Schnitzler image 6)	 FMF: Erysipelas-like erythema around the ankle. (Arthritis Research & Therapy 2009 11:212)	 TRAPS rash on the chest of a child. (Swiss Med Wkly. 2012;142:w13602)

	Mevalonate Kinase Deficiencies		Inflammatory Bone Diseases		
	Hyperimmunoglobulinemia D with Periodic Fever Syndrome —aka Mevalonate Kinase Deficiency	Mevalonate Aciduria Syndrome	Deficiency of Interleukin-1ß (IL-1ß) Receptor Antagonist	Majeed Syndrome	Chronic Recurrent Multifocal Osteomyelitis–aka Synovitis, Acne, Pustulosis, Hyperostosis, Osteitis Syndrome
ACRONYM	HIDS/MKD	MA	DIRA	MAJEED	CRMO/SAPHO
GENE	*MVK*	*MVK*	*IL1RN*	*LPIN2*	Currently unknown.
INHERITANCE	Autosomal recessive. Some cases with only one mutation found.[33]	Autosomal recessive.	Autosomal recessive.	Autosomal recessive.	Currently unknown.
ETHNICITY	Mostly of Dutch descent, or Northern European.[1]	Mostly of Dutch descent, or Northern European.[1]	Carriers in 0.2% population of Newfoundland & 1.3% in Puerto Rico. Also Dutch Brazilian & Lebanese pts.[16]	Currently, the only documented cases are of Middle Eastern ancestry.[18]	Affects all races, but the majority of patients have European ancestry; more female pts. than males.[21,22]
FREQUENCY IN THE WORLD	Unknown, but very rare. >200-300 known patients worldwide, (>300, when suspected cases are also included.)[12]	Unknown, but very rare. <100 known patients worldwide.[11]	Unknown, but very rare. In some regions of Aricibo, Puerto Rico w/ more DIRA carriers, DIRA may occur 1:6300.[16]	Unknown, but very rare. Very few documented cases at this time.[18,53]	Unknown, but rare.
TIMING OF SYMPTOMS OR ATTACKS	3-7 days. Recurrent bouts of fever & flares every 2-12 weeks.[1,9] Some flares occur after vaccines.[9]	4-5 days. Recurrent flares & fever every 2-3 weeks. Patients have chronic inflammation noted between flares.[11]	Continuous inflammation from birth/fetal development. Untreated DIRA can lead to death in infancy–childhood.[16]	Flares last for a few days, with 1-4 exacerbations a month of high fevers, severe pain, & joint swelling.[18,53]	At least 6 months w/ chronic/relapsing symptoms. Often 7-25 yrs. of symptoms. Many bone lesions heal completely.[19,22]
AGE OF ONSET	>90% present with symptoms in infancy.[9]	Most present with symptoms at birth, or in early infancy. Most have facial features noted at birth.[11]	Most have symptoms at birth, or as a neonate: pustular rash, bone pain, swollen joints, oral ulcers.[16]	Most present with symptoms in infancy to early childhood, between 3 weeks to 2 years of age.[18]	Mostly affects children–some adult onset. Peak incidence of flares is around 10 years of age.[22]
SYSTEMIC FINDINGS:					
SKIN/ CUTANEOUS	Diffuse maculopapular rash. Some w/petechiae or purpura present. A few w/apthous ulcers.[1,9]	Diffuse maculopapular or morbilliform rash. Some w/petechiae or purpura present. A few w/apthous ulcers.[1,9,11]	Epidermal neutrophilic pustules at hair folicles. Oral ulcers, pathergy, hyperkeratosis, acanthosis; high neutrophil infiltrate of dermis.[16,26]	Most patients have inflammatory dermatosis, Sweet's syndrome, pustular skin lesions, psoriasis. Intra-epidermal neutrophils.[18,53]	Some patients have acne, &/or pustulosis on the palms &/or soles of their extremities (w/ SAPHO). 23% w/psoriasis.[19,22,54]
NEUROLOGIC	Headaches & fevers w/flares of symptoms are common.[1,9] More severe neurological symptoms are rarely present in HIDS.[9]	Fevers w/flares. Microcephaly, dolichocephaly, mental retardation, developmental delays, cerebellar ataxia, cerebellar atrophy & epilepsy often develop over time.[11]	High fevers are not common, or noted in the neonatal period. Neurological complications are not common. A few cases of cerebral vasculitis noted.[16,26]	High fevers last for a few days w/flares & severe pain. Other neurological symptoms are not noted. Growth delays in height, & chronic pain are common.[18,53]	Fevers affect a number of patients during flares of CRMO. Other neurological symptoms are not noted. Some w/impaired bone growth, or overall impaired growth.[19,22,54]
AUDITORY	Uncommon–not believed to be caused by HIDS.[1,9]	Uncommon–not believed to be caused by MA.[1,9,11]	Not noted.[15,16]	Not noted.[18,53]	Not noted.[19,21,22,54]
OPTHALMIC	Very rare to uncommon.[9]	Uveitis, central cataracts, blue sclerae & tapetoretinal degeneration are often present, even in less severe cases.[11]	Eye issues are rare. Non-infectious conjunctivitis can be caused by DIRA.[15,16]	Not noted.[18,53]	Some cases of uveitis.[19]
CARDIO-PULMONARY	Rare.[1]	Rare.[1,11]	Some with resp. distress. 1 case: Pulmonary hemosiderosis & progressive interstitial fibrosis.[15,16,17]	Not noted.[18,53]	Not common–some patients also have ANCA+ Vasculitis that can affect the lungs.[18,54]
ABDOMINAL	Extreme pain, vomiting & diarrhea w/flares.[1,9]	Enlarged liver &/or spleen. Cholestatic liver disease. Pain, vomiting & diarrhea w/flares.[1,9,11]	Rarely have GI issues. Mouth ulcers, stomatitis, & failure to thrive are common.[16]	Enlarged liver & cholestatic jaundice in the neonatal period, but it is transient.[18,53]	Some patients also have inflammatory bowel diseases.[19]
LYMPHATIC	Enlarged cervical lymph nodes are common in children.[1] Some have enlarged spleens.	Enlarged spleen, &/or lymph nodes are common.[1,11]	Enlarged liver and/or spleen is common. Risk of organ failure if untreated.[16]	Neonates: enlarged liver & neutropenia; anemia is common–can be severe.[18]	Some cases of ANCA+ Vasculitis that can affect the kidneys.[19]
JOINTS/BONES MUSCLES & CARTILAGE	Arthralgias common, symmetric polyarthritis frequently noted.[1]	Congenital defects are often noted: microcephaly, dolichocephaly, wide irregular fontanels, low set and posteriorly rotated ears, downslanted palpebral fissures. Hypotonia, myopathy, & failure to thrive are common.[11]	Joint swelling, severe bone pain. Bone biopsy shows no infection. Common: Balloon-like widening of the anterior rib ends, periosteal elevation along multiple long bones, multifocal osteolytic lesions. Other bones affected.[16]	Periarticular tender soft tissue swelling. Bone biopsy shows no infection. Early-onset Chronic Recurrent Multifocal Osteomyelitis (CRMO), periarticular tender soft tissue swelling, short stature, delayed bone age, contractures.[18]	Joint swelling, limp, severe bone pain over affected bones (mostly long bones). 2-18 bone lesions are commonly found. Earlier age of onset & many bone lesions=more severe disease. Bone biopsy/cultures show no infection. [19,22]
VASCULITIS	Cutaneous vasculitis common, HSP is rare.[1]	Not noted.[11]	A few w/localized or cerebral vasculitis.[16]	Not noted.[18,53]	Some w/Takayasu arteritis, or ANCA+ Vasculitis.[54]
AMYLOIDOSIS	<5-10%–uncommon.[9]	Not noted-unknown.[9,11]	Not noted.[15,16,17]	Not noted.[18,53]	Not noted.[19,22,54]
ABNORMAL LABS	High: ESR, CRP, SAA w/ flares. High IgD w/IgA in 80% pts. Mevalonate aciduria noted during flares.[1]	Anemia, leukocytosis, thrombocytopenia. High: ESR, CRP, SAA, CK, IgD, IgA. IgE & chronicly high Mevalonate aciduria.[1,11]	High: ESR, CRP, leukocytosis, chronic anemia.[16,56]	Congenital dyserythropoietic anemia (CDA). High ESR. WBC can be normal, or elevated–neutropenia in infancy. Cultures negative.[18]	Whole body MRI can reveal multifocal bone lesions.[20] Normal or elevated WBC, ESR, CRP.[19,22,54]
	 HIDS: Maculopapular rash on the hand. (cri-net.com Auto Inflammatory Diseases image 23)	 MA: 21 month old pt. w/ facial dysmorphism. (Orphanet Journal of Rare Diseases 2006 1:13)	 DIRA: Generalized pustulosis. (N Engl J Med 2009; 360:2426-2437June 4, 2009)	 Sweet's Syndrome is often present w/Majeed. (pbase. com/leobarco/image/69914524)	 Palmar pustulosis SAPHO (CRMO). (cri-net.com SAPHO Syndrome image 29: Spondylarthropathies)

	Pyogenic Diseases		Granulomatous	Monarch-1	Proteasome
	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 Familal Cold Autoinflammatory Syndrome 2, orGuadaloupe Periodic Fever	Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy & Elevated Temperature–aka Nakajo-Nishimura Syndrome
ACRONYM	CAMPS/PSORS2	PAPA	Blau/PGA/EOS	NLRP12/FCAS2	CANDLE/JMP
GENE	*CARD14*	*CD2BP1*	*NOD2*	*NLRP12*	*PSMB8* and some other Proteasome genes.
INHERITANCE	Autosomal Dominant. Spontaneous mutations, some familial groups.[23]	Autosomal Dominant. Spontaneous mutations, some familial groups.[29,30]	Autosomal Dominant.	Autosomal Dominant. Spontaneous mutations, some familial groups.[29,30]	Autosomal recessive.
ETHNICITY	Most w/European or Asian ancestry. Pts. in US, EU, Canada (Newfoundland), Haiti, & Taiwan.[23]	Currently, the only documented cases are from Europe, New Zealand & the USA.[30]	Affects all races.	Unknown. Current cases from Guadeloupe, Italy, Armenia [38,39]	Caucasian, Hispanic & Japanese.[27]
FREQUENCY IN THE WORLD	Unknown, but rare.	Unknown, but rare.	Unknown, but rare.	Unknown, but rare.	Unknown, but rare.
TIMING OF SYMPTOMS OR ATTACKS	Continuous chronic pustular or plaque psoriasis, triggered by inflammatory stimuli. Some cases w/psoriatic arthritis.[23,24.]	Early-onset, destructive, recurrent inflammation of the joints, skin & muscle. Flares often occur after mild injury, or injections.[29]	Intermittent-persistent daily fevers, rash & arthritis.	1-3, to up to 7-15 days of fevers 39–40°C, rash and pain. Onset after exposure to cold or cooling temperatures.[38,39]	Frequent fevers w/disease flares. Inflammatory flares & symptoms are often present before the age of 6 months.[26,27]
AGE OF ONSET	Variable age of onset from infancy–childhood to adulthood w/pustular psoriasis.[23,24]	First symptoms of arthritis develop by 1-10 yrs old, & skin lesions develop during adolescence.[29,32]	Rash often develops by 4 months of age, fevers and other symptoms present by 4 yrs. of age.[34]	Neonatal/early infancy. Rash, fevers, symptoms, may be present at birth.[38,39]	Onset at birth or in infancy. Progressive damage from chronic inflammation noted as the child grows.[26,27]
SYSTEMIC FINDINGS:					
SKIN/ CUTANEOUS	Generalized pustular psoriasis (can be severe), &/or plaque psoriasis. Sometimes nails are affected w/ psoriasis.[23, 24]	Pathergy. Pyoderma gangrenosum ulcerative lesions, &/or severe cystic acne. Affected tissues w/high neutrophil infiltration.[29]	First symptom: scaly plaques. The rash starts on face, then on torso. Biopsies w/ non-caseating granulomatous dermatitis.[34]	Present during flares: Urticarial or malar rash[39] noted in some patients; some with buccal aphthosis.[38,39]	Annular cutaneous plaques w/residual purpura. Lipodsystrophy: first on face & around joints. Lips swell w/flares. Purple-red eyelids.[26,27]
NEUROLOGIC	Not seen.[23, 24]	Fevers can accompany flares of joint inflammation and pain. Other neurological symptoms are not noted.[31]	Intermittent-persistent daily fevers. Some have-cranial neuropathies. 80% have vision damage & joint deformities if untreated. Some cases have peripheral nerves affected.[34]	Fevers 39–40°C myalgia, headaches with flares. Other neurological symptoms are not noted.[31]	Aseptic meningitis & systemic inflammation. Growth delays–low height & weight. Developmental delays.[26,27]
AUDITORY	Not seen.[23, 24]	Not noted.[29,30,31]	Not noted.[34]	Many have increased sensorineural hearing loss.[38,39]	Some have frequent otitis &/or recurrent sinusitis.[27]
OPTHALMIC	Not seen.[23, 24]	Not noted.[29,30,31]	Uveitis (some w/blindness) 50% w/cataracts, 1:3 pts. get 2° glaucoma, inflamed conjunctiva, lacrimal glands, retina & optic nerves.[34]	Not noted.[38,39]	Nodular episcleritis (inflammation on the eye.) Conjunctivitis. Keratitis. Periorbital edema. Purple-red eyelids.[26,27]
CARDIO-PULMONARY	Not noted.[23, 24]	Not noted.[29,30,31]	Some have atrial hypertension &/or pericarditis. Some cases with lung involvement.[34,35]	Not noted.[38,39]	Clubbing of the fingers &/or toes. At risk for cardiac arrythmias & dilated cardiomyopathy.[26,27]
ABDOMINAL	Not noted.[23,24]	Some patients also have irritable bowel syndrome.[29]	Enlarged liver &/or spleen. Some w/ GI pain, higher risk for kidney &/ or liver issues.[34,35,36]	Some patients have abdominal pain with flares.[39]	Loose bowels with flares. Enlarged liver & abdomen. Delayed or slow growth.[26,27]
LYMPHATIC	Not seen.[23, 24]	Not noted.[29,30,31]	Enlarged liver &/or spleen, enlarged lymph nodes.[34,35,36]	Some patients with adenopathy.[39]	Enlarged liver, with elevated liver enzymes; enlarged lymph nodes.[26,27]
JOINTS/BONES MUSCLES & CARTILAGE	Intermittent joint pain, psoriatic arthritis. 30% of affected patients in one European family w/ PSORS2 also had psoriatic arthritis.[24]	Episodic inflammatory arthritis, often to one joint at a time that doesn't resolve on it's own. Intermittent sterile pauciarticular, peripheral erosive arthritis. Joint damage & destruction can often develop from the arthritis.[29,30,31,32,55]	Symmetrical chronic polyarthritis or oligoarthritis of the wrists, knees, ankles w/a boggy appearance is usually caused by an exuberant tenosynovitis.[34,35,36]	Myalgia, arthralgia, fatigue & malaise w/flares. Permanent bone or joint damage not noted.[39]	Joint Contractures, muscle atrophy, panniculitis induced lipodystrophy, myositis, fatigue and malaise. Inflammed nose & ear cartilage (chondritis). Growth delays–low height & weight.[26,27]
VASCULITIS	Not seen.[23, 24]	Not noted.[29]	Some w/vasculitis, leukocytoclastic vasculitis.[34]	Not noted.[38,39]	Not noted.[26,27]
AMYLOIDOSIS	Not noted.[23, 24]	Not noted.[29]	Not noted.[34]	Not noted.[39]	Not noted.[26,27]
ABNORMAL LABS	Mildly elevated WBC, CRP & ESR rarely elevated–only during flares of symptoms.[56]	Cultures of bone & skin are negative. Purulent synovial fluid full of neutrophils. High w/flares: CRP, ESR, WBC.[29,30,32]	High CRP & ESR, ACE, immunoglobulins. Anemia, leukopenia, eosinophilia, hematuria, proteinuria, pyuria, abnormal LFTs (LF).[34,36]	Elevated CRP during flares.[39]	Hypochromic or normocytic anemia. High CRP, ESR, triglycerides. Some w/elevated platelets, TSH, &/or LDL.[26,27]
	 Pustular psoriasis–seen w/ CAMPS. (dermatlas.med.jhmi.edu/image/pustular_psoriasis_1_061124)	 PAPA: Pyoderma gangrenosum. (dermatlas.med.jhmi.edu/image/pyoderma_gangrenosum_1_020918)	 Blau syndrome: Reddish-brown papules. (Dermatology Online Journal 15 (12): 5)	No image available Please contact nomidalliance.org if you can share an image of NLRP12.	 CANDLE: Child w/facial lipodystrophy, rash & swollen lips. (NOMID Alliance pt. image)

	Idiopathic Periodic Fever Syndromes			Macrophage Activation Diseases	
	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 Stills Disease–aka Adult Still's, Wissler-Fanconi Syndrome	(Primary) Familial Hemophagocytic Lymphohistiocytosis–aka Familial Erythrophagocytic Lymphohistiocytosis
ACRONYM	BEHÇETS	PFAPA	soJIA/sJIA	AOSD	1° HLH/ FHL
GENE	*ERAP1 (with HLA-B51);* also variants near: *CCR1, KLRC4, STAT4*[42]	Currently unknown.	Currently unknown. *HLA-DRB1* in some pts. w/European ancestry[57]	Currently unknown.	*PRF1, STX11, STXBP2, MUNC13-4 , RAB27A X link: SH2D1A, BIRC4*
INHERITANCE	Complex.	Currently unknown.	Complex.	Currently unknown.	Autosomal recessive, but if X-linked: inheritance is dominant.
ETHNICITY	Rare in the USA. More common in the Middle East, Asia & Japan. (Silk Road Route.)[42,43]	Affects all races.[40]	Affects all races. soJIA accounts for 10% of all JIA.[45]	Rare. Affects all races.[44]	Affects all races. 80% of African Americans, & 20% of pts. w/European decent have *PRF1* mutations.[47,48]
FREQUENCY IN THE WORLD	Prevalence is 80-370:100,000 people in Turkey, 10:100,000 in Japan & 0.6:100,000 in Yorkshire, UK.[3]	Unknown. Most common non-infectious recurrent fever disorder.[40]	Uncommon. 0.4–0.9 cases per 100,000 people, per year.[46]	France: estimated that 0.16:100,000 people have AOSD. AOSD affects more women than men.[44]	1° HLH affects 1:50,000 people worldwide.[48]
TIMING OF SYMPTOMS OR ATTACKS	Mouth ulcers are present in almost all patients during flares for around 10 days w/inflamation in the eye, & arthritis.[42,43]	Periodic fevers & symptoms lasting 3-6 days, recurring every 21-28 days. Pts. are symptom-free between flares.[40]	Fevers often > 39°C 1-2 times/day for >2 weeks, most often occuring in the evening w/arthralgia, rash & other symptoms.[45,46]	High fevers > 39°C that last for <4 hours, recurring more than once a week, w/a maculopapular rash & arthralgia.[44]	Fevers often > 39°C 1-2 times/day for >2 weeks, most often occurring in the evening w/arthralgia, rash & other symptoms.[47,48]
AGE OF ONSET	Most show symptoms in early adulthood (20's-30's) but the onset can be in childhood, or any age.[42,43]	Early childhood, usually between 2-5 years of age. A few adult-onset cases. Many teens outgrow it.[40]	Onset before the age of 16–most often by 2 years of age, or between 0-5 yrs. of age.[46]	First onset of symptoms occurs between 16-35 yrs. of age. Affects all ages.[44]	Onset <1yr: often by 6 months–early childhood. Some in utero or late childhood. A few adult-onset cases.[47,48,49]
SYSTEMIC FINDINGS:					
SKIN/ CUTANEOUS	Pathergy. Pseudofolliculitis, erythema nodosum-like &/or acneiform nodules. 98% w/mouth ulcers, & 65% have genital ulcers.[43]	Some have a rash with flares. Aphthous stomatitis, & pharygitis with exudate, (but no infection) is a classic finding.[40,41]	Rash: Fleeting, evanescent, migratory, bright salmon-pink, morbilliform, macular rash often presents w/onset of fevers.[45,46]	Evanescent, salmon-pink, mildly pruritic maculopapular rash on the proximal limbs and trunk.[44]	40% w/transient maculopapular, nodular or purpuric skin rashes during bouts of high fever. Jaundice.[47,48]
NEUROLOGIC	20-40% have Neuro-Behçets w/headaches, aseptic meningitis or meningoencephalitis, seizures, hemiplegia, or cranial nerve palsies. Cerebral venous thrombosis w/high ICP noted.[43]	High fevers for 3-6 days, with chills & malaise. Some patients have headaches with flares. Other neurological symptoms are not noted.[41]	High fevers > 39°C 1-2 times/day for >2 weeks. Other neurological symptoms are rare. A few cases w/seizures, meningismus, irritability & decreased level of consciousness.[46]	>95% have high, spiking fevers, fatigue and myalgia with flares. Other neurological symptoms are very rarely seen.[44]	High fevers. Increased CSF protein. High ICP. Multifocal inflammation of the gray & white matter, intracranial bleeding, generalized atrophy or brain edema, seizures or coma.[47]
AUDITORY	Not noted.[42,43]	Not noted.[40,41]	Not noted to be from soJIA.[45,46]	Not noted.[44]	Not noted.[47,48,49]
OPTHALMIC	Frequent anterior &/or posterior uveitis. Cataract, retinal vasculitis <30% risk for blindness. Papilledema w/CNS involvement.[43]	Not noted.[40,41]	Uveitis can be a complication from soJIA.[46]	Not noted.[44]	Blindness due to CNS inflammation.[48]
CARDIO-PULMONARY	Myocarditis, endocarditis w/aortic or mitral insufficiency, arterial aneurysm, pulmonary embolism.[43]	Flares of fevers, stomatitis & pharygitis are not associated with respiratory illness.[40,41]	Serositis (especially pericarditis) is often seen. Pleuritis, pleural effusions can occur. Risk for MAS.[46]	<25% have pleuritis, pericarditis (a few w/ tamponade.) Some myocarditis, pleural effusions, ARDS[44]	High risk for respiratory infections triggering fevers, systemic inflammation & MAS. Edema.[49]
ABDOMINAL	Ulcers from mouth to anus. Nausea, abdominal pain, anorexia, diarrhea, (may be bloody).[43]	Abdominal pain, diarrhea often present with flares.[40,41]	Peritonitis rarely occurs. 50% have an enlarged spleen, some w/an enlarged liver.[46]	50-75% w/enlarged liver, abnormal LFTs. 43% w/ enlarged spleen. Renal disease is rare.[44]	Liver disease is common. High risk of death from multi-organ failure in 2+ months if untreated.[49]
LYMPHATIC	Some w/enlarged liver &/or spleen; enlarged lymph nodes.[43]	Cervical adenopathy during flares.[40,41]	Many w/generalized lymphadenopathy. Some w/mesenteric adenitis.[45,46]	Lymphadenopathy is common. Many w/ enlarged liver &/or spleen.[44]	Lymphoma. Hemophagocytosis–spleen/lymph nodes. Large liver/ spleen.[49]
JOINTS/BONES MUSCLES & CARTILAGE	45% have arthralgias &/or arthritis–often the knees &/or ankles, but other joints can be affected. May be the first sign of Behçets. X ray is normal but synovium often has high neutrophils or mononuclear cells & a vasculitis process.[43]	Arthralgias, fatigue and malaise. No permanent joint or bone issues noted, and patients are symptom-free between PFAPA flares.[40,41]	Arthralgias may come before the arthritis. 88% have polyarticular or oligoarticular arthritis, most often in the wrists, knees, &/or ankles. Some w/cervical spine, hip, temporomandibular joint arthritis or synovial cysts.[45,46]	Myalgias, arthralgias &/ or arthritis are common. Wrist changes after 6 months. 41% develop intercarpal and carpometacarpal joint space narrowing a few yrs. after onset of AOSD–25% then develop pericapitate ankylosis.[44]	Hemophagocytosis in the bone marrow. Delayed closure of the bones of the skull in infants, bulging fontanel often noted. Neck stiffness, abnormal muscle tone, impaired muscle coordination, paralysis.[48,49]
VASCULITIS	Extensive vasculits. 30% w/venous thrombosis.[43]	Not noted.[40,41]	Not noted.[45,46]	Not noted.[44]	Not noted.[47,48,49]
AMYLOIDOSIS	Not noted.[42,43]	Not noted.[40,41]	Amyloidosis occurs in 7.4% of pts. in the USA, and 16% in Turkey.[46]	Very rare.[44]	Not noted.[47,48,49]
ABNORMAL LABS	Leukocytosis common. Normal–rarely elevated ESR or CRP. Some cryoglobulinemia, elevated factor VIII, fibrinolysis.[43]	High: ESR, CRP, WBC during flares–normal levels when not flaring.[40,41]	High: ESR, CRP, WBC, SAA, ferritin, aldolase. Elevated LFT's. Leukocytosis, thrombocytosis Anemia.[45,46]	High: ESR, CRP, LFTs, ferritin. Low glycosylated ferritin. Leukocytosis, anemia common w/flares. Prolonged PTT (DIC risk.)[44]	High: ESR, CRP, triglycerides, LFTs, soluble CD25, ferritin. Low: platelets, fibrinogen. Low NK cell cytotoxic function, neutropenia, anemia.[49]
	 Behçet's Disease: Oral ulcers. (dermis.net/dermisroot/en/17101/image.htm Behçet's disease)	 PFAPA: Aphthous stomatitis. (drpaulose.com; blog.timesunion.com/mdtobe Mystery Monday 125)	 soJIA: Salmon-pink rash on abdomen. (Joint Bone Spine, Volume 74, Issue 5, Pages 500-503)	 AOSD: Salmon trunk eruption on a young adult pt. (cri-net.com AOSD image 1)	No image available Please contact nomidalliance.org if you can share an image of Familial HLH.

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List of abbreviations:

ACE: Angiotensin-converting enzyme (lab test)
ANCA+ Vasculitis: Granulomatosis w/polyangiitis (GPA); Wegener's
ARDS: Acute Respiratory Distress Syndrome
CD25: Soluble interleukin-2-receptor
CNS: Central Nervous System (involving the brain, spinal cord)
CRP: C-reactive protein (lab test);
DIC: Disseminated intravascular coagulation
ESR: Erythrocyte sedimentation rate (lab test); Westergren ESR
GI: Gastrointestinal (organs in the abdomen)
HSP: Henoch–Schönlein purpura, anaphylactoid purpura
ICP: Intracranial pressure
LFTs: Liver function tests (lab test): AST, ALT, GGT, ALK Phos, Bilirubin
NK cells: Natural killer cells
PMNs: Polymorphonuclear leukocytes (on lab tests w/ WBC count)
pt.: abbreviation for the word "patient"
PTT: Partial thromboplastin time (lab test)
SAA: Serum amyloid A protein (lab test)
TSH: Thyroid-stimulating hormone (lab test); thyrotropin
w/: abbreviation for the word "with"
WBC: White Blood Count (lab test)

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This chart is an educational reference to increase awareness about autoinflammatory diseases. This document is not intended to replace professional medical care, diagnosis and/or treatment by a qualified specialist. It is to be used only for non-commercial purposes.

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