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CPPD disease: an understudied arthritis that's moving forward

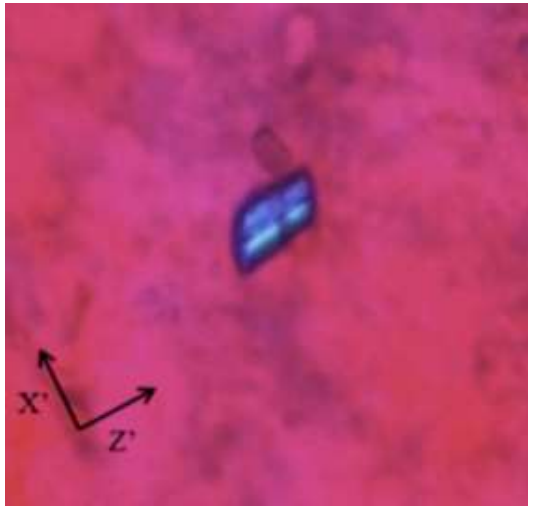
Sara Tedeschi, MD, MPH
Division of Rheumatology, Inflammation and Immunity, Brigham and Women's Hospital
Assistant Professor of Medicine, Harvard Medical School
Head, Crystalline Arthritic Diseases
Director, BWH Giant Cell Arteritis Fast Track Clinic

Disclosures

Consulting fees: Novartis, Avalo Therapeutics, Merck, Alexion, Kyowa Kirin, Fresenius Kabi

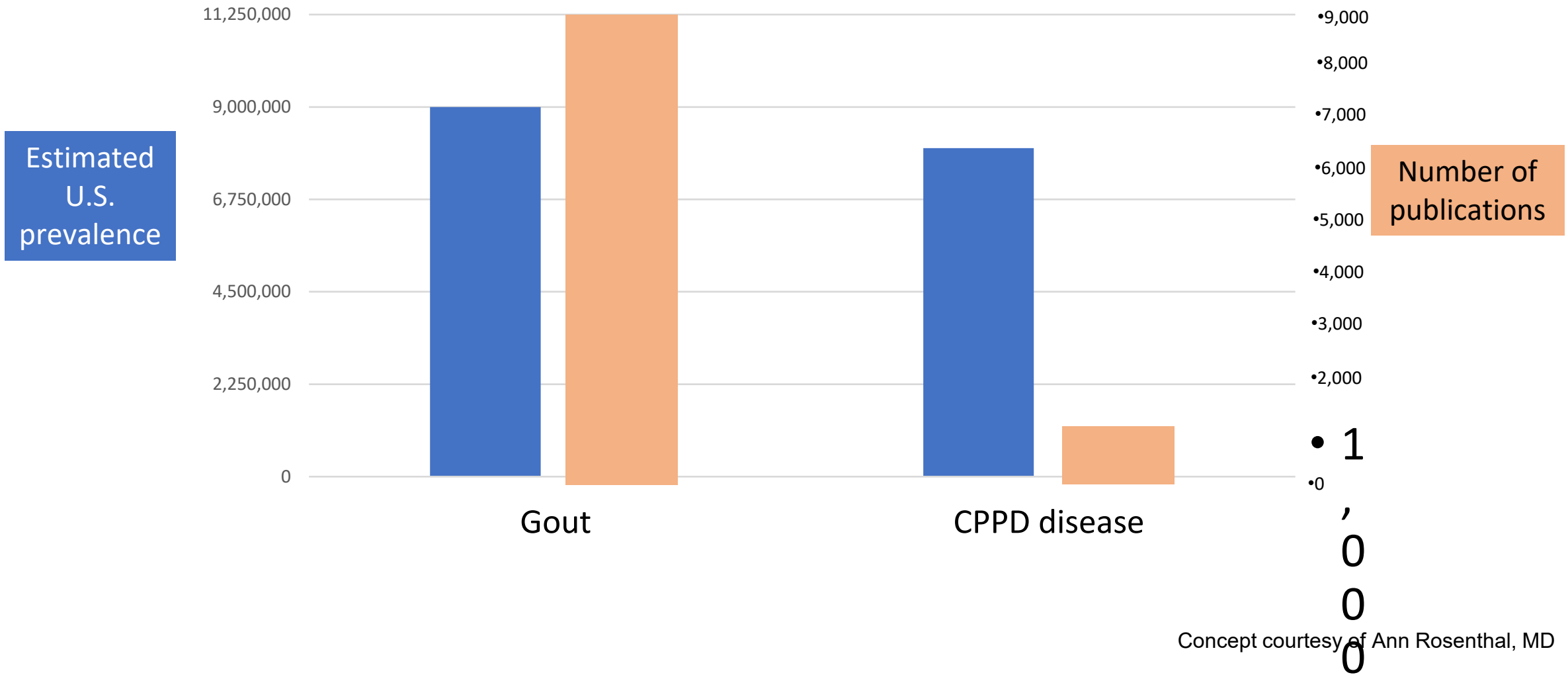
Calcium pyrophosphate deposition (CPPD) disease represents a common crystalline arthritis

- Symptomatic arthritis caused by calcium pyrophosphate (CPP) crystal deposition
- Knee and wrist most common
- Affects 8-10 million U.S. adults
- No targeted therapies currently exist
- Prevalence will increase as the population ages



McCarty et al. *Ann Int Med* 1962
Abhishek et al. *Arthritis Rheum* 2018

Crystalline arthritis prevalence & publications in the past decade



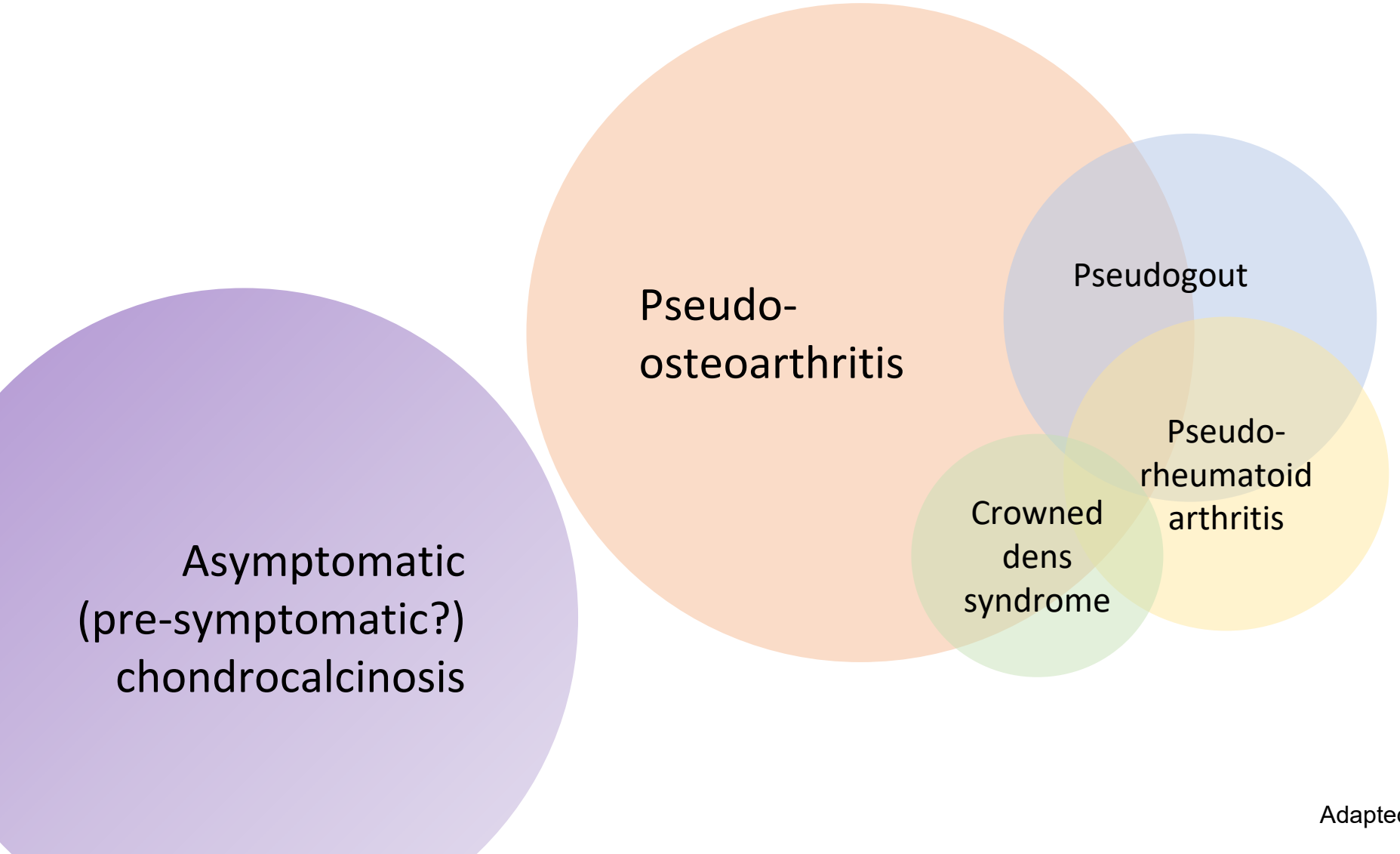
Concept courtesy of Ann Rosenthal, MD

How do we get from here…

…to here in caring for patients with CPPD disease?

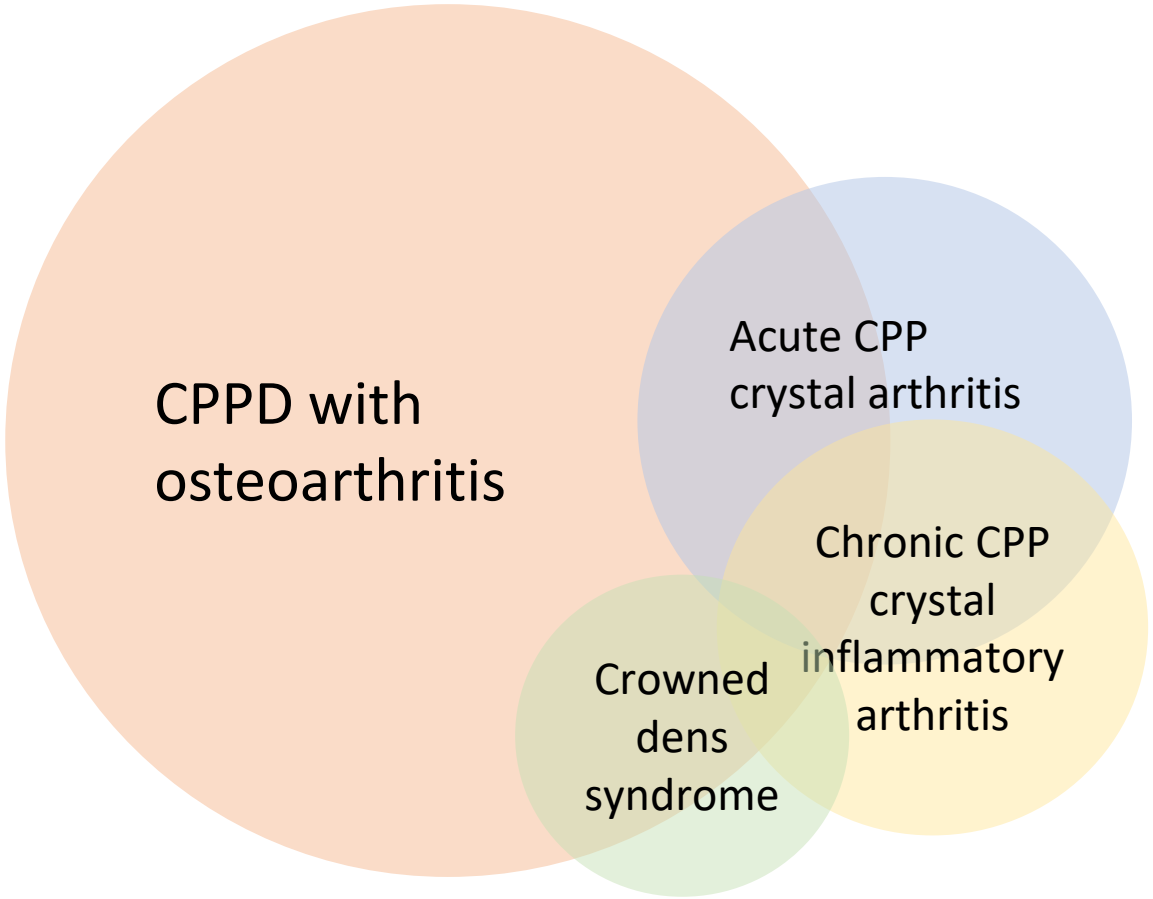
1. Lay the foundation	Clinical experience & epidemiologic studies
2. Install the beams	Basic science
3. Run the plumbing	Classification criteria & outcome domains
4. Install the drywall	Prospective cohorts & biorepositories
5. Paint the house	Develop & test treatments

CPPD disease has multiple clinical manifestations



Adapted from Cai et al. *Semin Arthritis Rheum* 2021

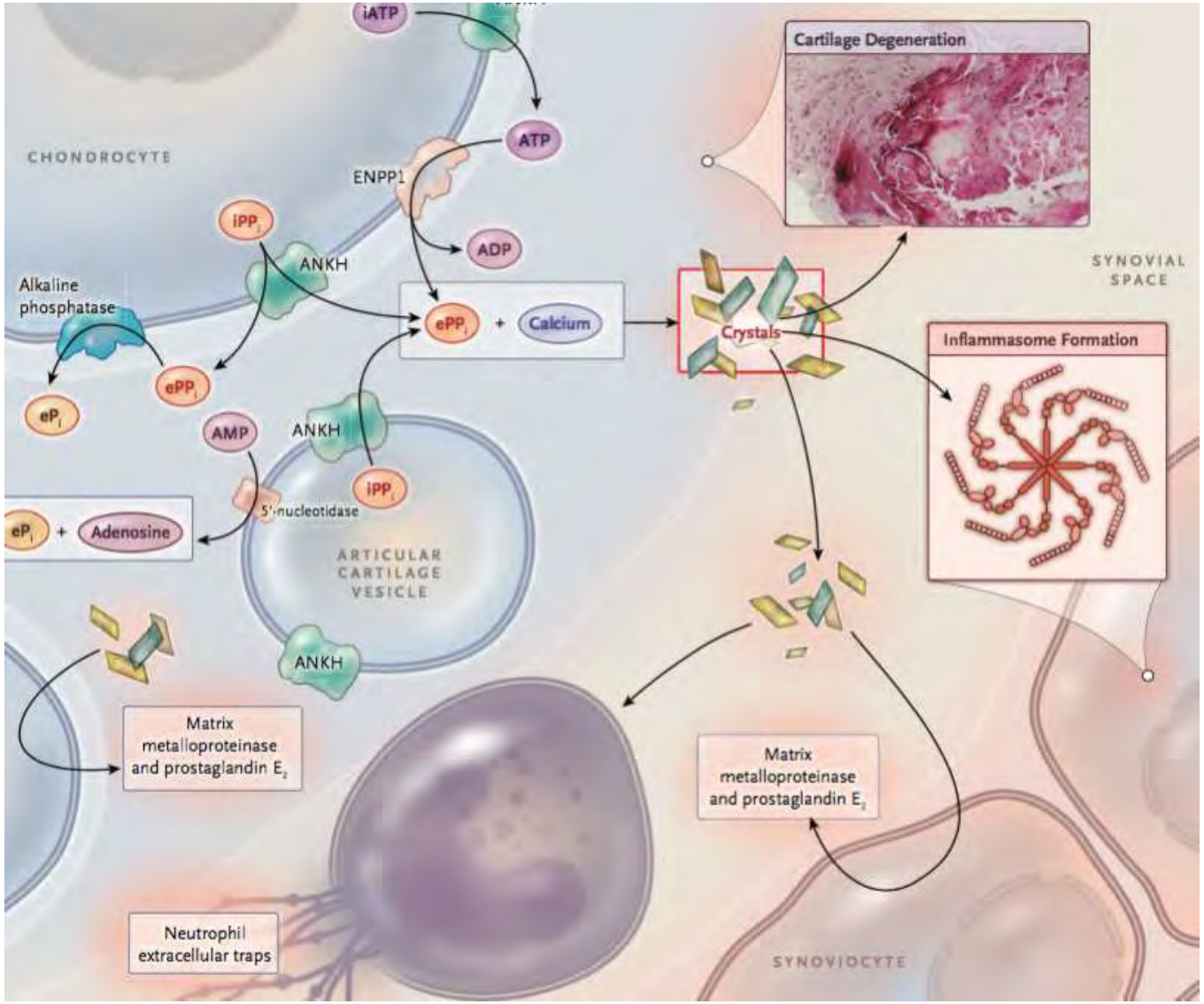
EULAR terminology (2011): not user-friendly



Adapted from Cai et al. *Semin Arthritis Rheum* 2021
Zhang, et al. *Annals Rheum Dis* 2011

Calcium pyrophosphate crystals

- form around chondrocytes
- activate the NLRP3 inflammasome and neutrophil extracellular traps
- deposit in cartilage, which may cause mechanical damage



Rosenthal AK, Ryan LM. *N Engl J Med* 2016

Clinical research in CPPD disease has been challenging

- Difficulty identifying patients in large datasets
  - radiographs ≠ symptoms
  - billing codes vary in accuracy
  - nomenclature varies
  - under-recognition → under-diagnosis

- Lack of classification criteria → heterogeneous study populations

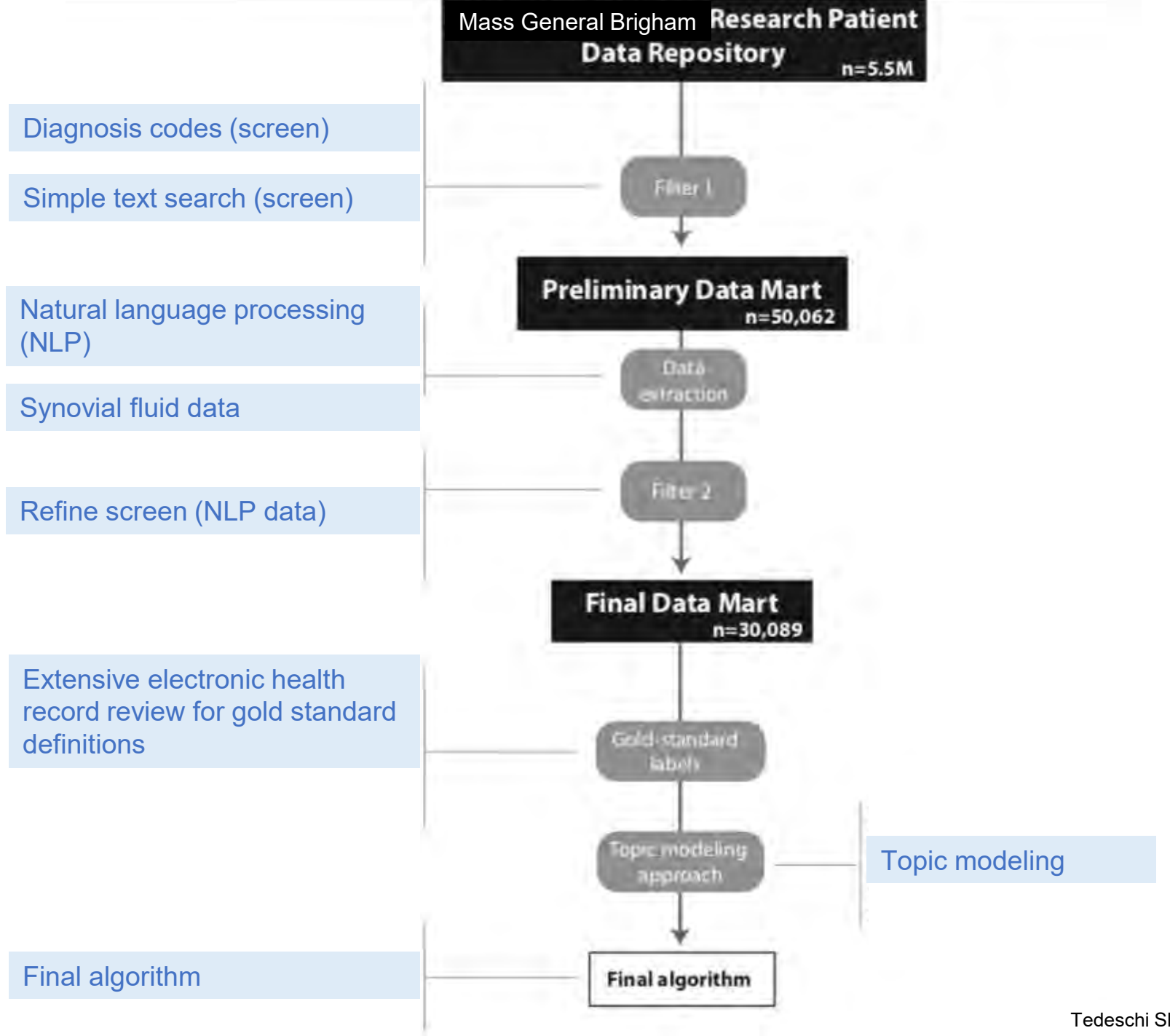
Billing codes have varying accuracy for CPPD

- There are 4 ICD-9 codes (and 5 ICD-10 codes) for CPPD
  - Chondrocalcinosis or “other disorders of calcium metabolism”

- Positive predictive value of ≥1 billing code
  - 91% for “CPPD” @ Milwaukee VA Medical Center
  - 68% for “CPPD” @ Mass General Brigham
  - 24% for “acute pseudogout” @ Mass General Brigham

Bartels CM, et al. *J Clin Rheumatol* 2015
Tedeschi SK et al. *Rheumatol Int* 2018

Machine learning methods improved the accuracy of identifying acute CPP crystal arthritis in electronic health record data



Tedeschi SK et al. *Arthritis Care Res* 2021

Identifying acute CPP crystal arthritis in the Mass General Brigham electronic health record

	Performance among gold-standard labels (N=900)			
Algorithm	**Sensitivity**	**Specificity**	**PPV**	**AUC**
≥1 billing code	0.65	0.63	0.22	0.64

How common is CPPD disease?

8-14 million

"Estimates vary, but CPPD disease appears to affect 4 to 7% of the adult population in Europe and the United States."

Rosenthal AK and Ryan LM. *NEJM* 2016

CPPD prevalence estimates

		Prevalence estimates
Cohort	**Study population**	**Radiographic chondrocalcinosis**
Framingham knee OA study (1980s)	~1400 adults age 63	8% age 63 30% age 85
Italian PROVA study (2000s)	~3000 adults age 65	10% age 65 21% age >85

Symptoms?

Felson et al. *J Rheum* 1989
Ramonda et al. *Clin Exp Rheum* 2009
Hameed et al. *Arthritis Res & Ther* 2019
Rho et al. *Rheumatology* 2012

CPPD prevalence estimates

		Prevalence estimates	
Cohort	**Study population**	**Radiographic chondrocalcinosis**	**Diagnosis codes**
Framingham knee OA study (1980s)	~1400 adults age 63	8% age 63 30% age 85	--
Italian PROVA study (2000s)	~3000 adults age 65	10% age 65 21% age >85	--
Southern Sweden (1998-2014)	>1 million adults	--	"non-gout crystal arthropathy" **0.23%**
UK THIN dataset (1986-2010)	>4 million adults	--	"pseudogout" **0.02%**

Felson et al. *J Rheum* 1989
Ramonda et al. *Clin Exp Rheum* 2009
Hameed et al. *Arthritis Res & Ther* 2019
Rho et al. *Rheumatology* 2012

Clinical factors associated with CPPD/pseudogout

	Strength of supporting data	
	Positive association	**Inverse association**
Older age	+++	
Joint trauma, including joint surgery	++	
Osteoarthritis	+++	
Gout	+++	
Rheumatoid arthritis	++	
Hemochromatosis	+++	
Primary hyperparathyroidism	+++	
Hypomagnesemia (incl. Gitelman syndrome)	+++	
Osteoporosis	++	
Bisphosphonates	++	+
Calcium supplements	+	
Loop diuretics	++	+
Thiazide diuretics	+	+
Proton pump inhibitors	++	+

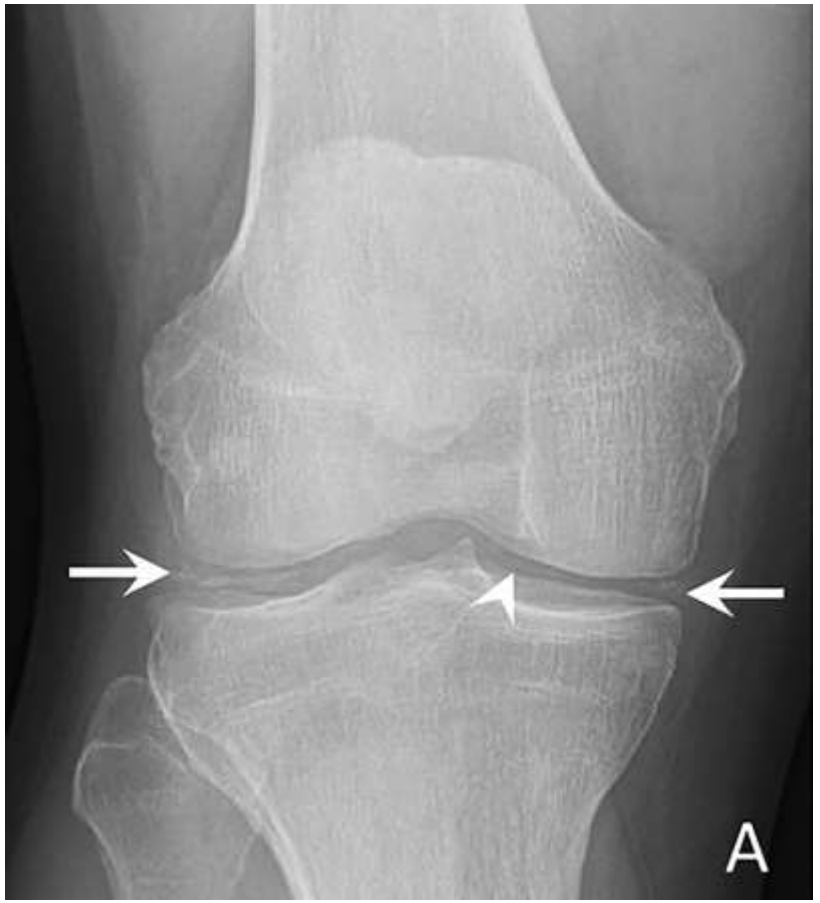
Kleiber-Baldarrama C, et al. *Arthritis Care Res* 2017
Bartels CM, et al. *J Clin Rheumatol* 2015
Roddy E, et al. *Medicine* 2017
Rho YH, et al. *Rheumatology* 2012
Tedeschi SK, et al. *Arthritis Care Res* 2021

What imaging modalities are most useful for identifying CPPD?

Conventional radiography (x-ray)

- Commonly performed and easy to obtain

- High specificity (>90%) but only moderate sensitivity (~50%) for calcium pyrophosphate deposition

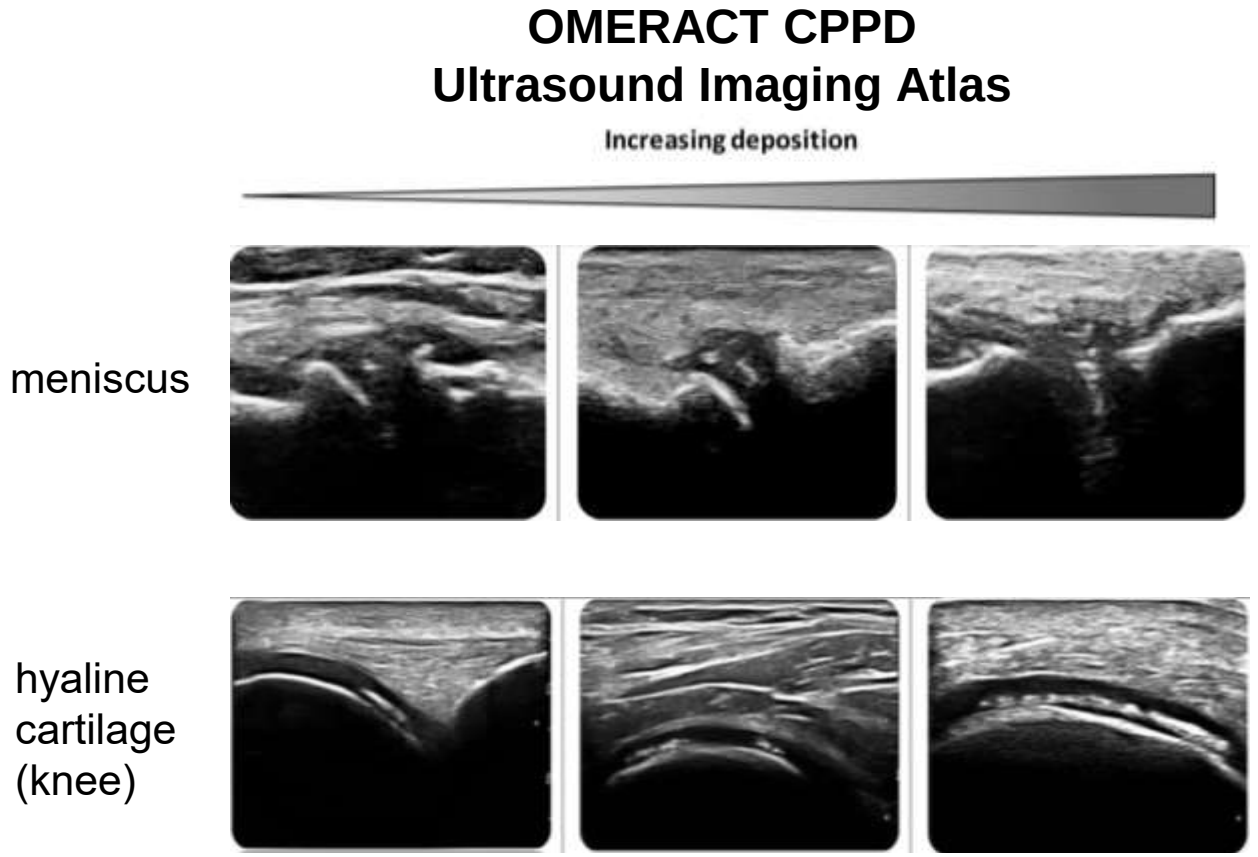


Tedeschi SK, et al. *Arthritis Care Res* 2023
Sirotti S, et al. *Arthritis Rheumatol* 2023

Ultrasound

- Visualizes portions of hyaline and fibrocartilage (e.g., menisci) not obscured by bone

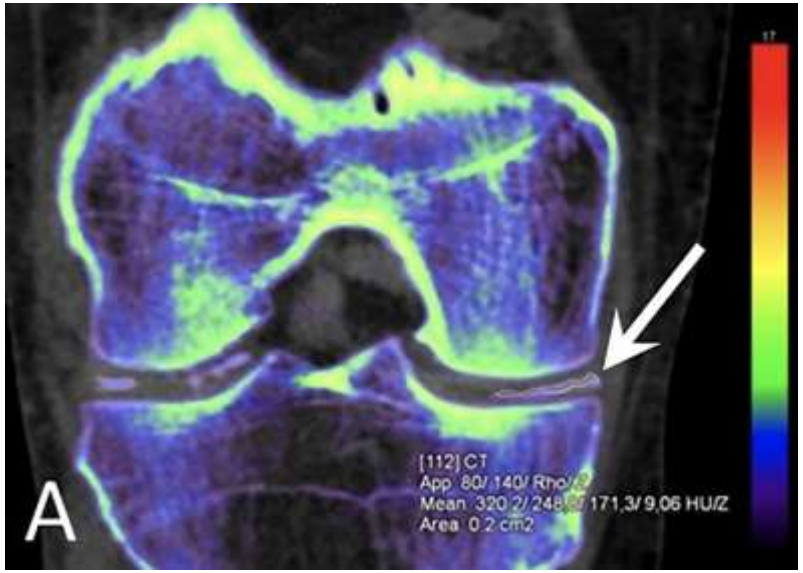
- High specificity (87%) and high sensitivity (85%) for calcium pyrophosphate deposition in meta-analysis of 26 studies



Filippou G, et al. *Ann Rheum Dis* 2018
Cipolletta E, et al. *Osteoarthritis Cartilage* 2021

Computed tomography (CT) and dual-energy CT (DECT)

- Availability, cost, radiation considerations
- DECT sensitivity 63-100%
- DECT is not significantly more accurate than conventional CT for detecting CPPD



Tedeschi SK, et al. *Arthritis Care Res* 2023
Tanikawa, et al. *J Ortho Surg Research* 2018
Tedeschi, et al. *Rheumatology (Oxford)* 2020
Budzik, et al. *Arthritis Rheumatol* 2021

Test performance characteristics of DECT, conventional CT, and x-ray for identifying CPPD (N=50)

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
DECT	1.00 (1.00, 1.00)	0.76 (0.60, 0.91)	0.75 (0.59, 0.91)	1.00 (1.00, 1.00)
Conventional CT	0.90 (0.78, 1.00)	0.83 (0.69, 0.97)	0.79 (0.63, 0.95)	0.92 (0.82, 1.00)
X-ray	0.71 (0.52, 0.91)	0.93 (0.83, 1.00)	0.88 (0.73, 1.00)	0.81 (0.68, 0.95)

Reference standard: synovial fluid crystal analysis for calcium pyrophosphate crystals

manuscript under review

Unanswered questions about the natural history of CPPD

a brief list

- Among people with chondrocalcinosis, what are risk factors for developing joint symptoms?
- Why do some people have several CPPD manifestations in a lifetime, while others only have one?
- What are the long-term extra-articular consequences of CPPD?
- Does CPPD cause OA?

What do we know about the course of acute CPP crystal arthritis (pseudogout) flares?

- Two case-control studies investigated risk factors for flares in patients with an initial episode of pseudogout

- 25% of patients with an initial episode had at least 1 flare

- Higher risk for recurrence associated with:
  - CKD unadjusted HR 2.9 (1.1-7.8)
  - Cancer unadjusted HR 3.0 (1.3-6.7)
  - Chemotherapy adjusted HR 5.6 (1.2-27.2)
  - Proton pump inhib. adjusted HR 5.6 (1.7-18.9)
  - Warfarin adjusted HR 7.3 (1.9-27.6)

Yates KA, et al. *J Rheumatol* 2019
Lee JS, et al. *Clin Exp Rheumatol* 2019

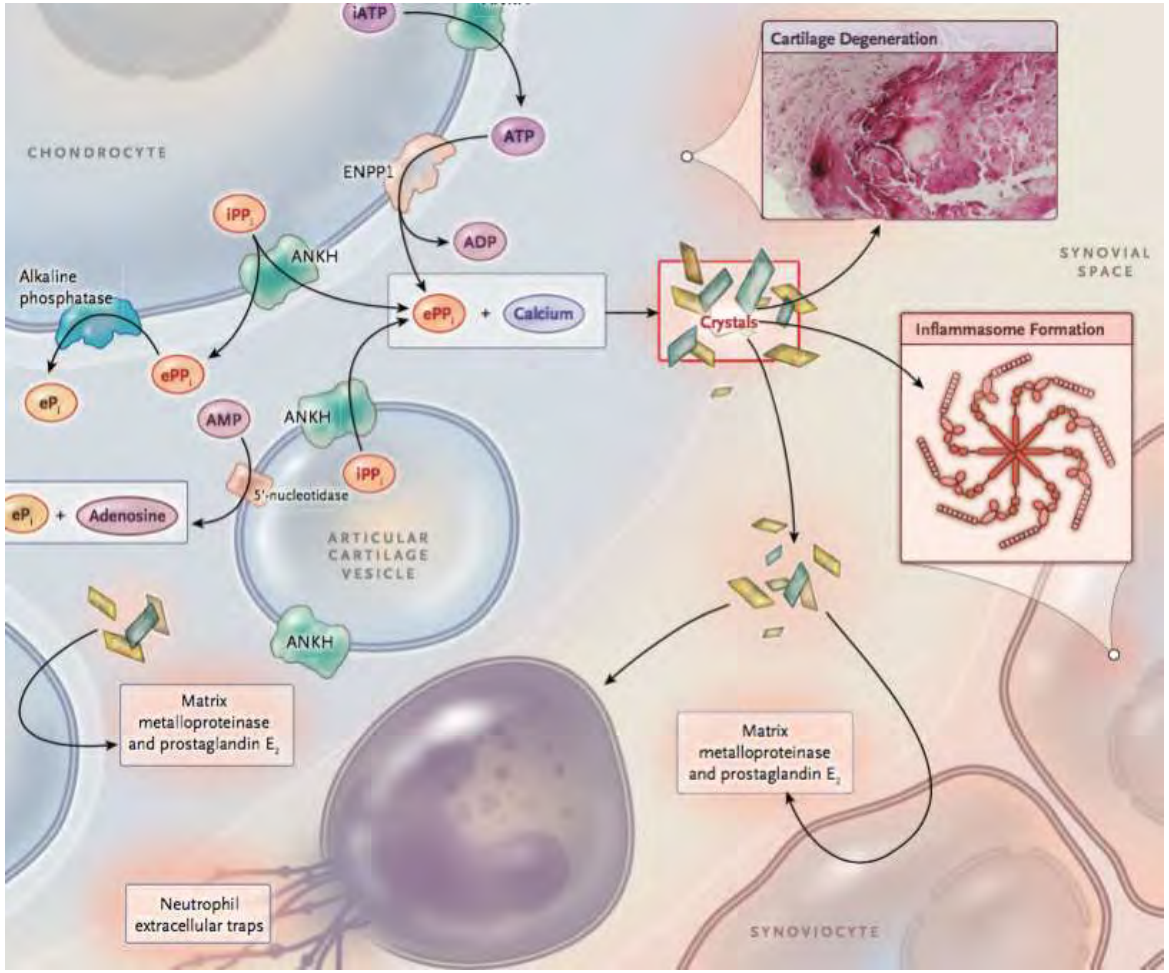
Does CPPD cause OA? Billion-dollar question

“It remains unclear if calcium-containing crystals are the cause or result from OA.”

Foreman SC, et al. *Osteoarthritis and Cartilage* 2020

Does CPPD cause OA? Billion-dollar question

- CPP crystals can induce cartilage damage
- Subchondral bone remodeling in OA may lead to increased CPP crystal formation



Rosenthal AK, Ryan LM. *N Engl J Med* 2016

Osteoarthritis progression in individuals with chondrocalcinosis

- Conflicting results in 4 large cohort studies with 3-5 years follow-up

Cohort study	Study overview	Progressive cartilage loss on MRI
Boston OA Knee Study (BOKS)	265 knees Followed 2.5 years with MRI	**Lower risk** RR 0.4 (0.2, 0.7)
Health, Aging and Body Composition Study (Health ABC)	373 knees Followed 3 years with MRI	**No association** RR 0.9 (0.6, 1.5)
Knee & Hip OA Long-term Assessment cohort (KHOALA)	656 knees Followed 5 years with x-ray	**No association** OR 0.9 (0.4, 1.7)
Osteoarthritis Initiative (OAI)	140 knees Followed 4 years with MRI	**Higher risk** beta coeff >0

- But, 2024 study: chondrocalcinosis associated with progressive cartilage loss in same knee compartment

Neogi T, et al. *Arthritis Rheum* 2006
Latourte A, et al. *Arthritis Rheum* 2020
Foreman SC, et al. *Osteoarthritis Cartilage* 2020
Liew JW, et al. *Arthritis Rheum* 2024

Arthritis & Rheumatology

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American College of Rheumatology

Full Length

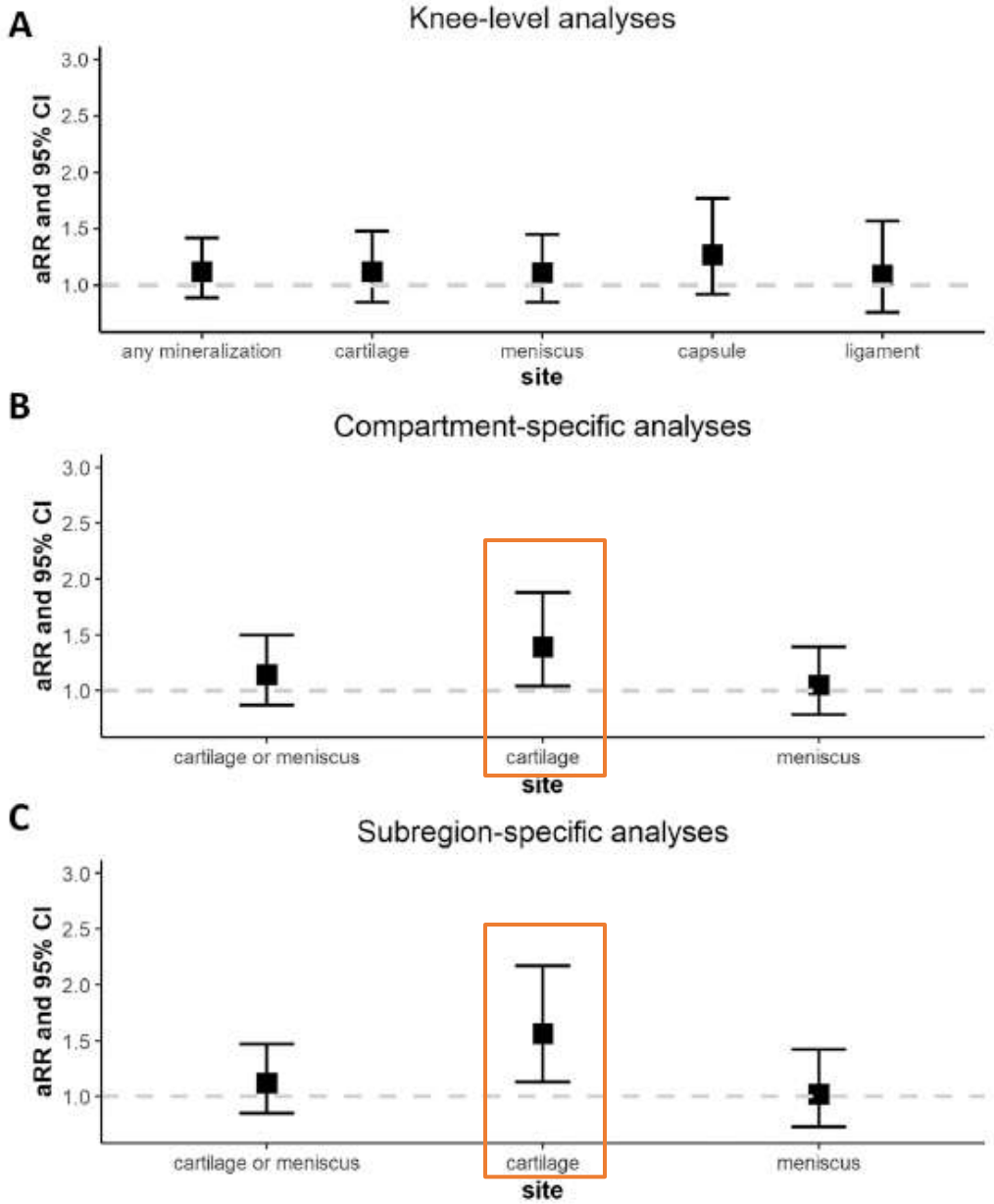
Intra-Articular Mineralization on Computerized Tomography of the Knee and Risk of Cartilage Damage: The Multicenter Osteoarthritis Study

Jean W. Liew, Mohammed Jarraya, Ali Guermazi, John Lynch, David Felson, Michael Nevitt, Cora E. Lewis, James Torner, Frank W. Roemer, Michel D. Crema, Na Wang, Fabio Becce, Gabriela Rabasa, Tristan Pascart, Tuhina Neogi

- 1,673 participants in Multicenter Osteoarthritis (MOST) Study
- Knee CT at baseline: intra-articular mineralization assessment **present in 9%**
  - Location
  - Burden
- Knee MRI at year 2: cartilage worsening **occurred in 47%**

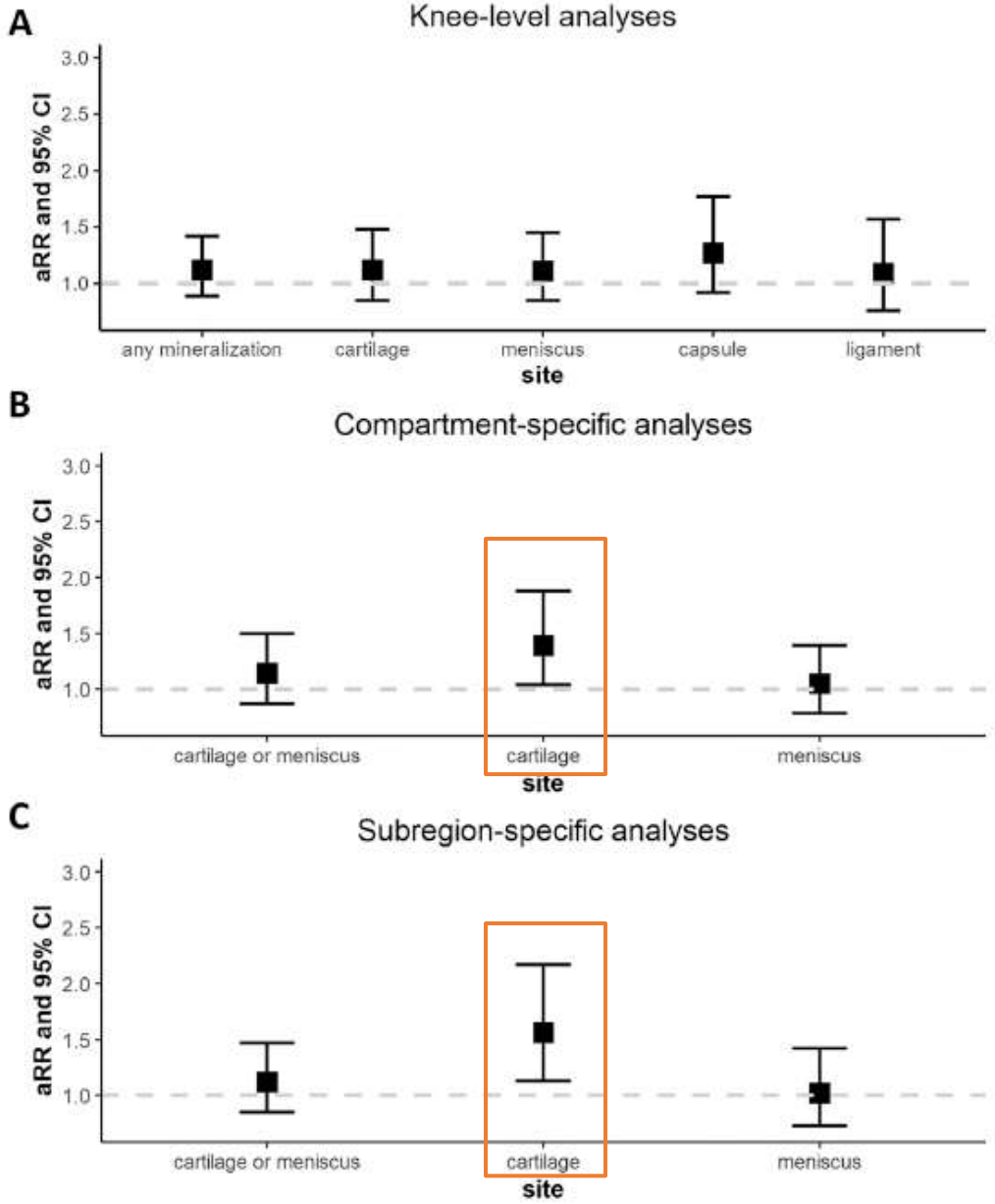
Liew JW, et al. *Arthritis Rheumatol* 2024

Risk of cartilage worsening over 2 years by location of intra-articular (IA) mineralization



Liew JW, et al. *Arthritis Rheumatol* 2024

Risk of cartilage worsening over 2 years by location of intra-articular (IA) mineralization



Hyaline cartilage calcification predicted future cartilage loss in the same compartment & subregion – even if no baseline cartilage damage there

Greater risk for cartilage worsening if younger than 60 years old

Implications

- Localized effect
- Tip scales in controversy over IA calcification & OA progression?
- Therapies to treat IA calcification and/or downstream effects

Liew JW, et al. *Arthritis Rheumatol* 2024

Long-term outcomes in joints of patients with chondrocalcinosis

- **Knee or hip replacement**
  - Not associated with baseline chondrocalcinosis (5 years of follow-up)

- **Joint pain**
  - Chondrocalcinosis at baseline *not* associated with WOMAC pain in KHOALA cohort
  - Intra-articular mineralization on baseline knee CT *was* associated with more frequent, persistent, and worsening knee pain over 2 years in MOST cohort

Latourte A, et al. *Arthritis Rheum* 2020
Liew JW, et al. *Arthritis Rheum* 2023

CPPD disease and conditions beyond the joints

Why focus on cardiovascular disease in CPPD disease?

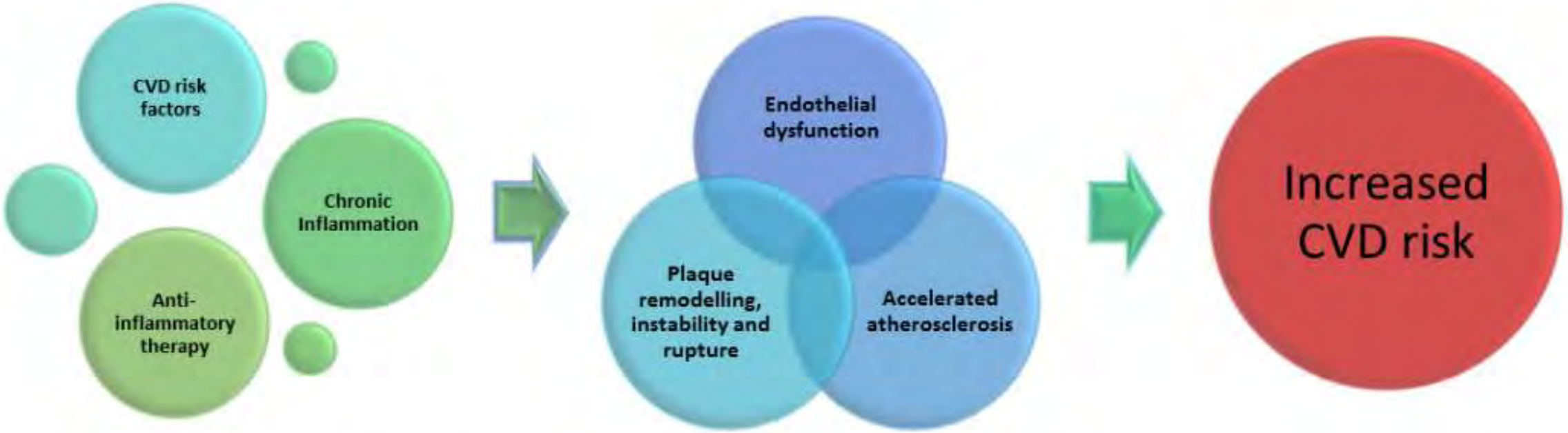
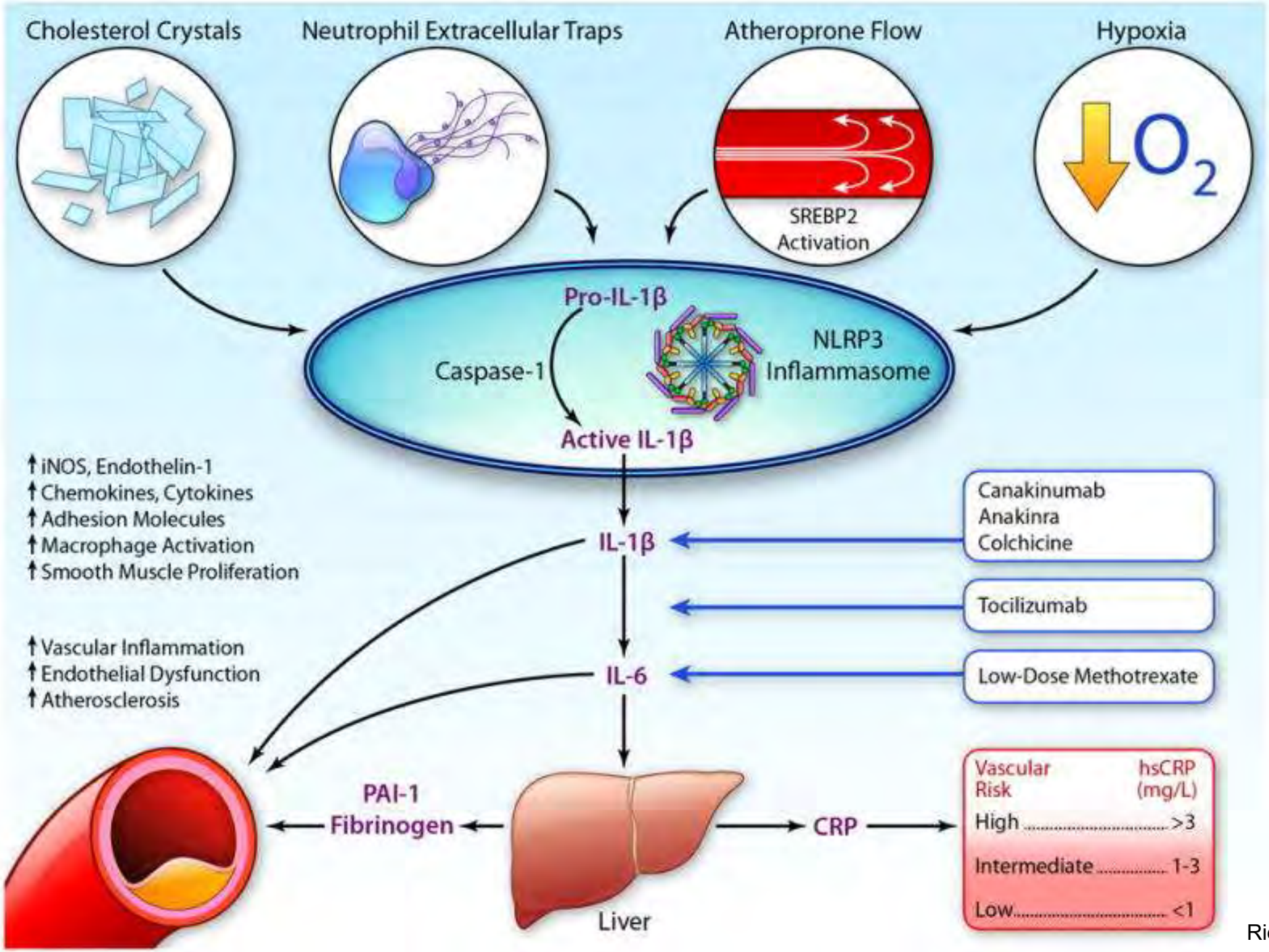


Figure 1 Contributors to cardiovascular disease (CVD) risk in immune-mediated inflammatory diseases.

Agca, et al. *Heart* 2022



Ridker *Circ Res* 2016

CV event risk was significantly elevated in two large CPPD cohorts

CPPD disease (broadly defined) and CV events

- Matched cohort study using Veterans Administration data, 2011-2014
- >23,000 CPPD patients matched to >87,000 comparators
- Index date: date of first CPPD ICD-9 code, or matched encounter
- Primary outcome: any major adverse cardiovascular outcome (MACE)
  - Myocardial infarction (MI)
  - Acute coronary syndrome (ACS)
  - Coronary re-vascularization
  - Stroke
  - Death

Bashir et al. *Arthritis Care Res* 2021

25% greater risk for non-fatal CV event in CPPD cohort versus comparators

Outcome	HR (95% CI)
MACE	0.98 (0.94–1.02)
MI, ACS, coronary revascularization, or stroke	1.25 (1.14–1.38)
MI	1.41 (1.20–1.66)
ACS	1.27 (1.13–1.44)
Coronary revascularization	1.13 (0.95–1.33)
Stroke	1.30 (1.07–1.58)
Death	0.95 (0.91–0.99)

* Adjusted for race, CVE during baseline period, number of outpatient encounters, number of hospitalizations, traditional CV risk factors, medications. Age and sex were matching factors and were not included in the model.

Bashir et al. *Arthritis Care Res* 2021

Acute CPP crystal arthritis and risk of CV events

- Matched cohort study in Mass General Brigham EHR dataset, 1991-2017
- 1200 acute CPP crystal arthritis patients matched to 3810 comparators
- Primary outcome: MACE

Tedeschi SK, et al. *Ann Rheum Dis* 2022

CV event rates were increased in the first 2 years after a pseudogout flare, and up to 10 years later

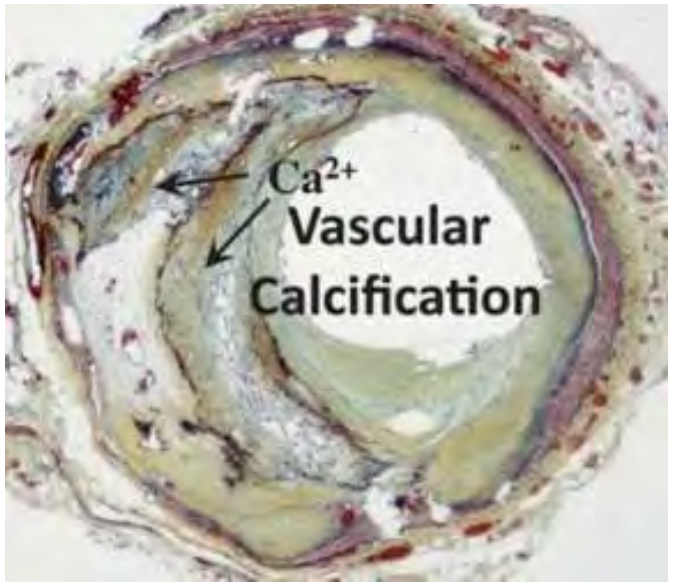
Table 2 Incidence rates (IR), incidence rate ratios (IRR) and HRs for MACE, non-fatal CV event and death

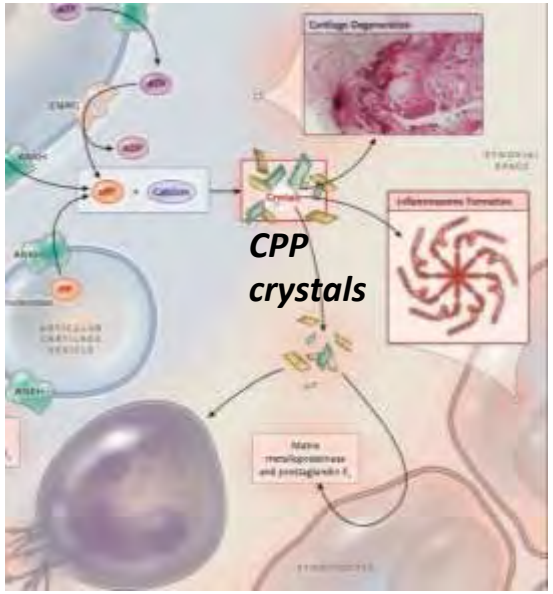
	Acute CPP crystal arthritis cohort		Comparator cohort		Incidence rate ratio	HR (95% CI)
	Events	IR/1000 person-years (95% CI)	Events	IR/1000 person-years (95% CI)	IRR (95% CI)	Multivariable adjusted*
Years 0–2						
MACE	178	90.57 (78.20 to 104.90)	362	59.06 (53.28 to 65.47)	1.53 (1.28 to 1.83)	1.32 (1.01 to 1.73)
Non-fatal CV event	63	32.06 (25.04 to 41.03)	74	12.07 (9.61 to 15.16)	2.65 (1.90 to 3.72)	1.92 (1.12 to 3.28)
Death	131	65.07 (54.83 to 77.22)	312	50.46 (45.16 to 56.38)	1.29 (1.05 to 1.58)	1.19 (0.87 to 1.62)
Years 2–10						
MACE	196	58.30 (50.69 to 67.07)	445	53.15 (48.43 to 58.32)	1.10 (0.93 to 1.30)	1.26 (0.97 to 1.64)
Non-fatal CV event	69	20.53 (16.21 to 25.99)	100	11.94 (9.82 to 14.53)	1.72 (1.26 to 2.34)	2.18 (1.27 to 3.75)
Death	159	43.68 (37.39 to 51.03)	415	45.93 (41.72 to 50.57)	0.95 (0.79 to 1.14)	1.04 (0.78 to 1.39)

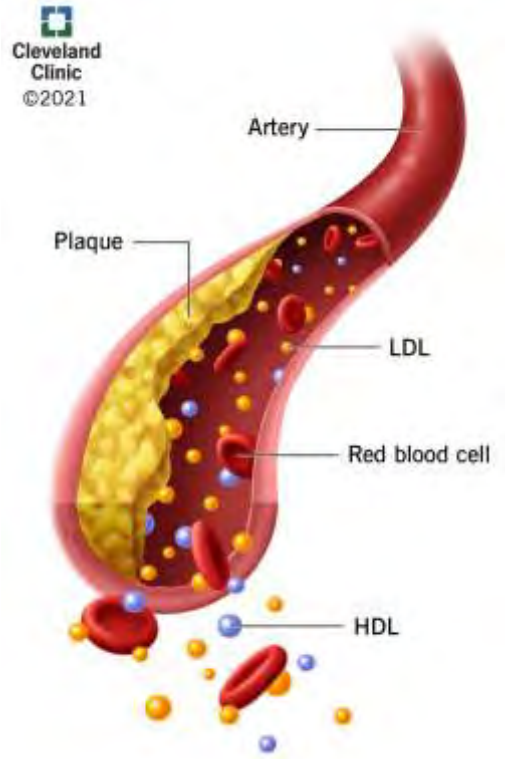
*Adjusted for age, sex, race, BMI, comorbidities, medications, multimorbidity index score, healthcare utilization

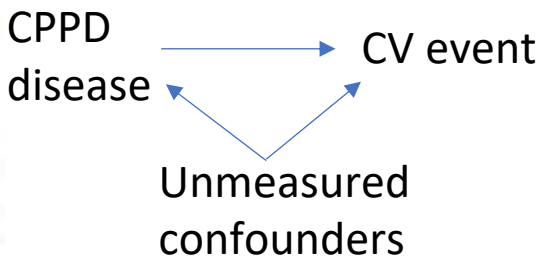
Tedeschi SK, et al. *Ann Rheum Dis* 2022

Potential explanations for elevated risk of CV events in CPPD disease









Vascular calcification

Inflammation

Dyslipidemia

Unmeasured confounders

Coronary artery calcium scores were slightly higher in patients with vs. without chondrocalcinosis

	Chondrocalcinosis	Age & sex-matched comparators	*P* value
	***N* = 606**	***N* = 1108**	
Agatston score, mean (S.D.)	359.1 (737.9)	297.1 (644.9)	0.08
Agatston score category			
None (=0)	164 (27.1%)	312 (28.2%)	0.22
Low/moderate (1–400)	299 (49.3%)	821 (51.4%)	
High (>400)	143 (23.6%)	321 (20.4%)	
10-year ASCVD risk score category			
	***N* = 606**	***N* = 1108**	
Low (<5%)	107 (17.7%)	243 (21.9%)	<0.01
Borderline/intermediate (5–20%)	269 (44.4%)	518 (46.8%)	
High (≥20%)	230 (38.0%)	347 (31.3%)	

Tedeschi SK, et al. *Rheumatology* 2024

Why focus on CPPD disease and bone?

- **Osteopenia and CPPD**
  - Genetics of Osteoarthritis and Lifestyle (GOAL) study
    - Lower cortical bone density on hand x-ray
    - No difference in cancellous bone density in calcaneus
  - VA Medical Center study
    - Osteopenia ICD-9 codes more common in CPPD vs. comparators

- **Biologic plausibility**
  - Inorganic pyrophosphate *strongly inhibits* hydroxyapatite crystal formation
  - Possible low peri-articular bone mineral density in CPPD?

Abhishek, et al. *Ann Rheum Dis* 2014
Kleiber Balderrama, et al. *Arthritis Care Res* 2017

Acute CPP crystal arthritis and fracture risk

- Matched cohort study in Mass General Brigham dataset, 1991-2023
- 1148 patients with acute CPP crystal arthritis, 3730 matched comparators
- Primary outcome: 1st ever fracture of humerus, wrist, hip, pelvis using administrative claims algorithm (PPV >90%)

Tedeschi SK, et al. *Arthritis Rheum* 2024
Ray WA, et al. *J Clin Epidemiol* 1992

Fracture risk was 80% increased in patients with acute CPP crystal arthritis versus comparators

Parameter	Acute CPP crystal arthritis cohort (n = 1,148)		Comparator cohort (n = 3,730)		Fracture IRR[a] (95% CI)	Adjusted HR[b] (95% CI)
	Events, n	IR per 1,000 person-years (95% CI)[a]	Events, n	IR per 1,000 person-years (95% CI)[a]		
Any fracture	100	11.7 (11.0–12.5)	150	5.5 (5.3–5.7)	2.1 (1.0–4.5)	1.8 (1.3–2.3)
Humerus	14	1.5 (1.3–1.8)	24	0.9 (0.8–0.9)	1.8 (0.9–3.7)	1.4 (0.7–2.8)
Wrist	23	2.5 (2.2–2.9)	17	0.6 (0.6–0.7)	4.1 (2.0–8.6)	3.6 (1.8–7.1)
Hip	32	3.6 (3.2–4.0)	61	2.2 (2.1–2.3)	1.7 (0.8–3.5)	1.3 (0.8–2.1)
Pelvis	41	4.6 (4.1–5.0)	71	2.6 (2.5–2.7)	1.8 (0.9–3.8)	1.4 (0.9–2.2)
Excluding patients prescribed glucocorticoids	–	–	–	–	–	1.6 (1.2–2.2)
Excluding patients prescribed osteoporosis treatment	–	–	–	–	–	1.8 (1.4–2.5)
Excluding patients with rheumatoid arthritis	–	–	–	–	–	1.7 (1.3–2.3)

HRs for any fracture

[a] Adjusted for age and sex

[b] Adjusted for age, sex, race, healthcare utilization, BMI, multimorbidity index, smoking, rheumatoid arthritis, hyperparathyroidism, hemochromatosis, hypothyroidism, hyperthyroidism, heart failure, cancer, oral glucocorticoids in 90d before index date, osteoporosis treatment 365d before index date, proton pump inhibitor 365d before index date

Tedeschi SK, et al. *Arthritis Rheum* 2024

1. Lay the foundation	Clinical experience & epidemiologic studies
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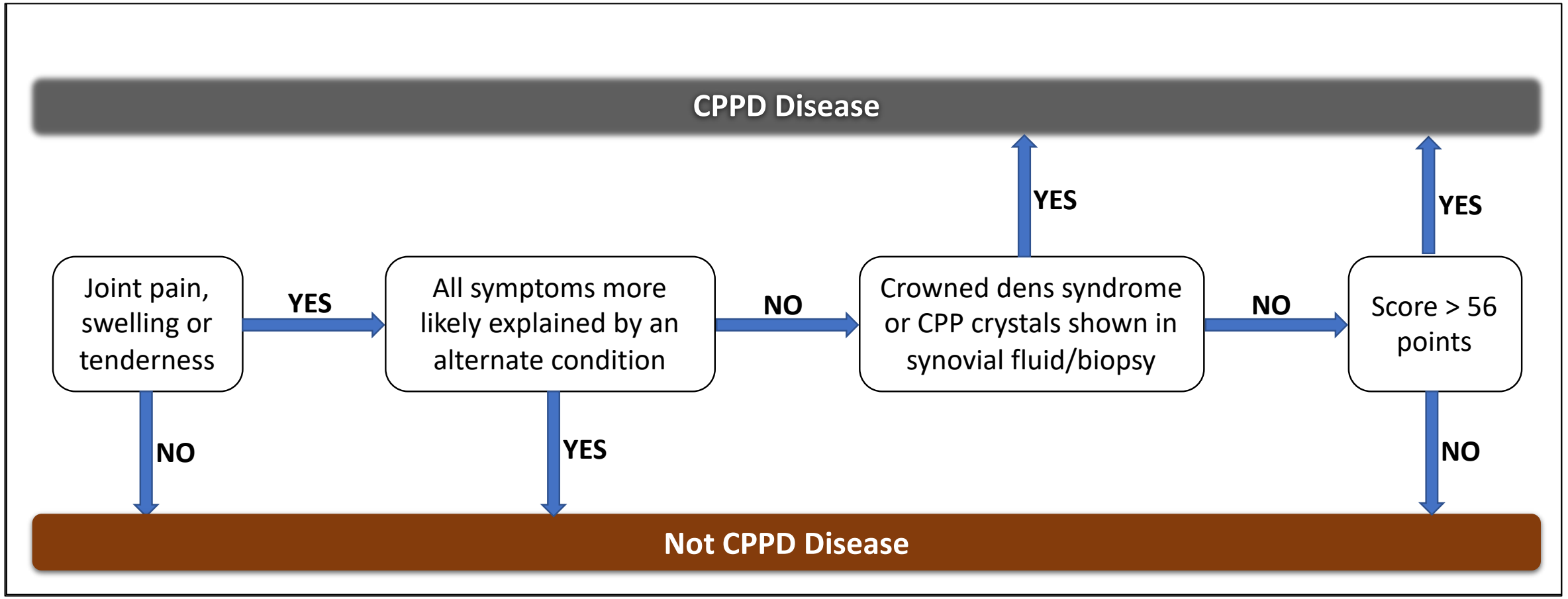
Empowering Rheumatology Professionals

The 2023 ACR/EULAR Classification Criteria for Calcium Pyrophosphate Deposition Disease

Abhishek Abhishek,[1*] Sara K. Tedeschi,[2*] Tristan Pascart,[3] Augustin Latourte,[4] Nicola Dalbeth,[5] Tuhina Neogi,[6] Amy Fuller,[1] Ann Rosenthal,[7] Fabio Becce,[8] Thomas Bardin,[4] Hang Korng Ea,[4] Georgios Filippou,[9] John FitzGerald,[10] AnnaMaria Iagnocco,[11] Frédéric Lioté,[12] Geraldine M. McCarthy,[13] Roberta Ramonda,[14] Pascal Richette,[4] Francisca Sivera,[15] Mariano Andres,[16] Edoardo Cipolletta,[17] Michael Doherty,[1] Eliseo Pascual,[18] Fernando Perez-Ruiz,[19] Alexander So,[20] Tim L. Jansen,[21] Minna J. Kohler,[22] Lisa K. Stamp,[23] Janeth Yinh,[22] Antonella Adinolfi,[24] Uri Arad,[25] Thanda Aung,[26] Eva Benillouche,[27] Alessandra Bortoluzzi,[28] Jonathan Dau,[29] Ernest Maningding,[30] Meika A. Fang,[10] Fabiana A. Figus,[31] Emilio Filippucci,[17] Janine Haslett,[23] Matthijs Janssen,[32] Marian Kaldas,[33] Maryann Kimoto,[33] Kelly Leamy,[34] Geraldine M Navarro,[35] Piercarlo Sarzi-Puttini,[36] Carlo Scirè,[37] Ettore Silvagni,[28] Silvia Sirotti,[38] John R. Stack,[13] Linh Truong,[35] Chen Xie,[35] Chio Yokose,[39] Alison M. Hendry,[40] Robert Terkeltaub,[41] William J. Taylor,[22] and Hyon K. Choi[22]

*co-first authors

Schematic for CPPD Disease Classification



Abhishek A,* Tedeschi SK,* et al. *Ann Rheum Dis* 2023

CPPD Classification Criteria: Points System

Domains and levels	Points
Age at onset of joint symptoms	
≤60 years	0
>60 years	4
Time-course and symptoms of inflammatory arthritis	
No persistent or typical inflammatory arthritis	0
Persistent inflammatory arthritis	9
1 typical episode	12
More than 1 typical episode	16
Sites of typical episode(s) of inflammatory arthritis	
1st MTP joint	-6
No typical episode(s)	0
Joint(s) other than wrist, knee or 1st MTP	5
Wrist	8
Knee	9
Related metabolic diseases	
None	0
Present	6

Domains and levels	Points
Synovial fluid crystal analysis from a symptomatic joint	
CPP crystals absent on ≥2 occasions	-7
CPP crystals absent on 1 occasion	-1
Not performed	0
Osteoarthritis (OA) of hand or wrist on imaging	
None of the following findings or no imaging	0
Bilateral radio-carpal joints	2
≥2 of: STTJ OA without 1st CMCJ OA; 2nd or 3rd MCPJ OA	7
Imaging evidence of CPPD in symptomatic joint(s)	
None on US, CT, or DECT (absent on CR, CR not performed)	-4
None on CR (and US, CT, DECT not performed)	0
Present on either CR, US, CT, or DECT	16
Number of peripheral joints with CPPD on any imaging modality regardless of symptoms	
None	0
1	16
2-3	23
≥4	25

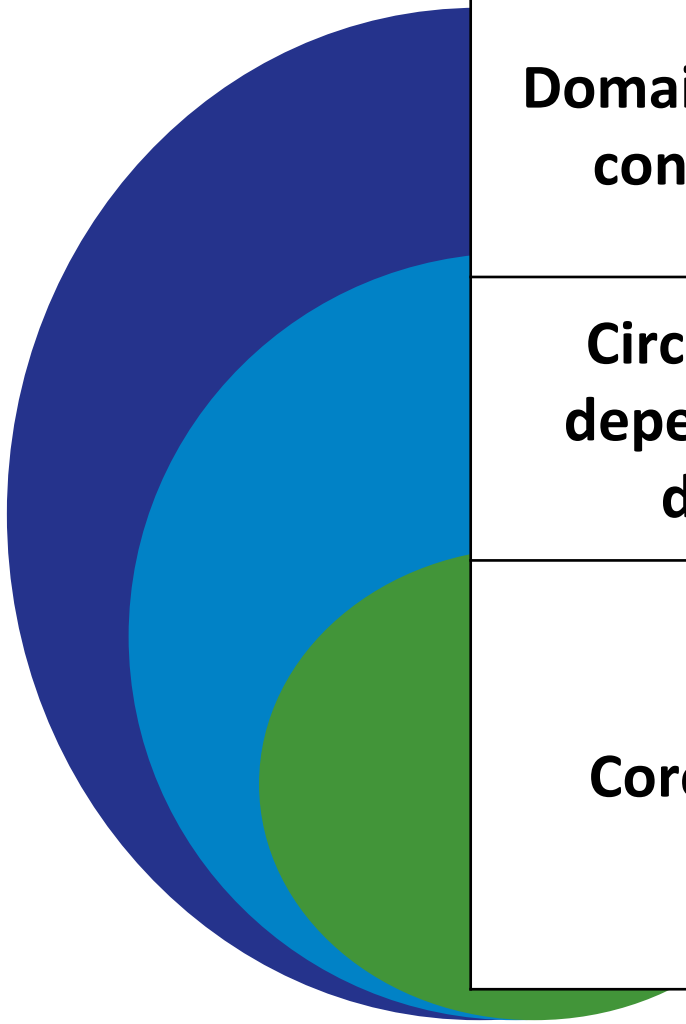
Web-based calculator

https://bblinks.live/acr-classification-criteria-for-cppd-disease

CPPD classification criteria performed very well in validation cohort

Sensitivity: 99.2%
Specificity: 92.5%

OMERACT onion for studies of chronic and/or recurrent manifestations of CPPD Disease



Domains for future consideration	• Joint movement • Joint inflammation on imaging joints • Crystals in joint fluid • Patient satisfaction with treatment • Fatigue • Adapting to physical disability • Health related QoL • Sleep • Use of long-term medications
Circumstance-dependent core domains	• Joint damage on imaging tests • Joint calcification on imaging tests • Patient global assessment of response to treatment
Core Domains	• Pain intensity • Joint tenderness • Joint swelling • Acute CPP crystal arthritis flare • Patient global assessment of disease activity • Physician global assessment of disease activity • Overall function • Adverse events (including death)

Cai, et al. *Semin Arthritis Rheum* 2021
Fuller, et al. *Semin Arthritis Rheum* 2021

1. Lay the foundation	Clinical experience & epidemiologic studies
2. Install the beams	Basic science
3. Run the plumbing	Classification criteria & outcome domains
4. Install the drywall	Prospective cohorts & biorepositories
5. Paint the house	Develop & test treatments

GWAS reveals several causal loci for CPPD

- Familial cases of early-onset CPPD: *ANKH* and *TNFRSF11B*
- Genetic basis of older-onset ("typical") CPPD not established

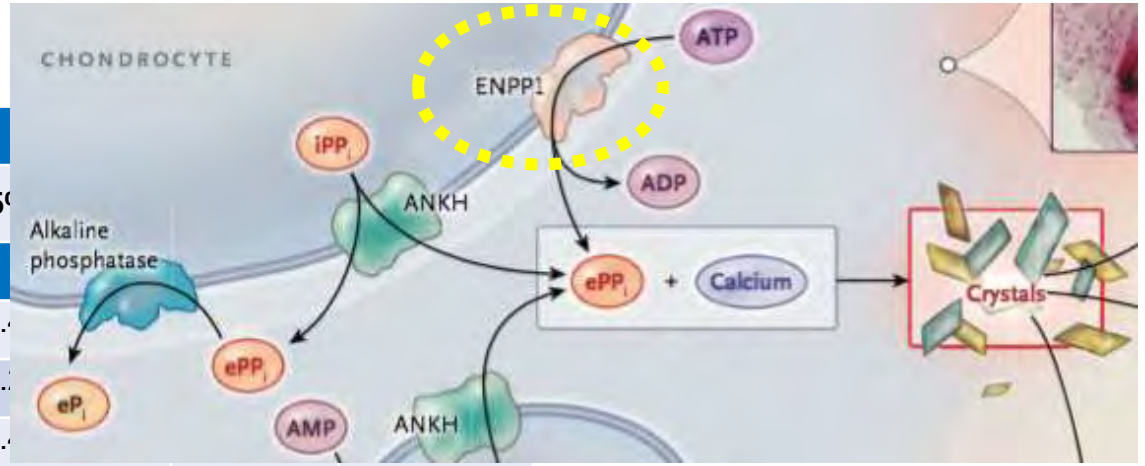
- Genome-wide association study (GWAS) using data from Million Veteran Program
  - 91% male, mean age 62 years
  - African (AFR) genetic ancestry: N=121,177
  - European (EUR) genetic ancestry: N=449,042

- Chondrocalcinosis and (non-gout) crystal arthropathy
  - Chondrocalcinosis: N=3,004 (536 AFR and 2,468 EUR)
  - Crystal arthropathy: N=3,766 (700 AFR and 3,066 EUR)

- Two loci on chromosome 6, within genes for ***ENPP1*** and ***RNF114B***, significant in AFR & EUR cohorts

Takei R, et al. Ann Rheum Dis 2025 (in press)

GWAS reveals several causal loci for CPPD



Genome-Wide Associations with CPPD in the Million Veterans Program						
	SNP	**Chromosome: Base pairs**	**Risk allele: frequency**	**OR [95**		
African (AFR) genetic ancestry*						
Chondrocalcinosis	rs11963689	6:131889538	C:0.80	1.78 [1.		
Chondrocalcinosis	rs9396861	6:18403902	C:0.64	1.49 [1.		
Non-gout crystal arthropathy	rs11963689	6:131889538	C:0.80	1.64 [1.		
European (EUR) genetic ancestry**						
Chondrocalcinosis	rs6939185	6:131818047	G:0.60	1.32 [1.24, 1.40]	3.5×10^{-19}	*ENPP1*
Chondrocalcinosis	rs1886248	6:18403902	C:0.41	1.43 [1.35, 1.51]	4.0×10^{-33}	*RNF144B*
Non-gout crystal arthropathy	rs766592	6:131810461	G:0.60	1.27 [1.20, 1.34]	1.8×10^{-17}	*ENPP1*
Non-gout crystal arthropathy	rs1886248	6:18399163	C:0.41	1.36 [1.28, 1.43]	2.7×10^{-31}	*RNF144B*
Trans-ancestry meta-analysis						
Chondrocalcinosis	rs1409181	6:131828160	G: NR	1.26 [1.19, 1.33]	2.3×10^{-17}	*ENPP1*
Chondrocalcinosis	rs1886248	6:18403902	C: NR	1.43 [1.35, 1.50]	3.6×10^{-40}	*RNF144B*
Non-gout crystal arthropathy	rs1409181	6:131828160	G: NR	1.21 [1.16, 1.27]	3.8×10^{-15}	*ENPP1*
Non-gout crystal arthropathy	rs9396861	6:18403902	C: NR	1.37 [1.30, 1.44]	2.5×10^{-36}	*RNF144B*

*AFR: 536 chondrocalcinosis cases and 120,708 controls; 700 non-gout crystal arthropathy cases and 120,306 controls
**EUR: 2,468 chondrocalcinosis cases and 445,620 controls; 3,066 non-gout crystal arthropathy cases and 444,490 controls
NR: not reported

Takei R, et al. Ann Rheum Dis 2025 (in press)

BRIgham Cppd (BRIC) Registry

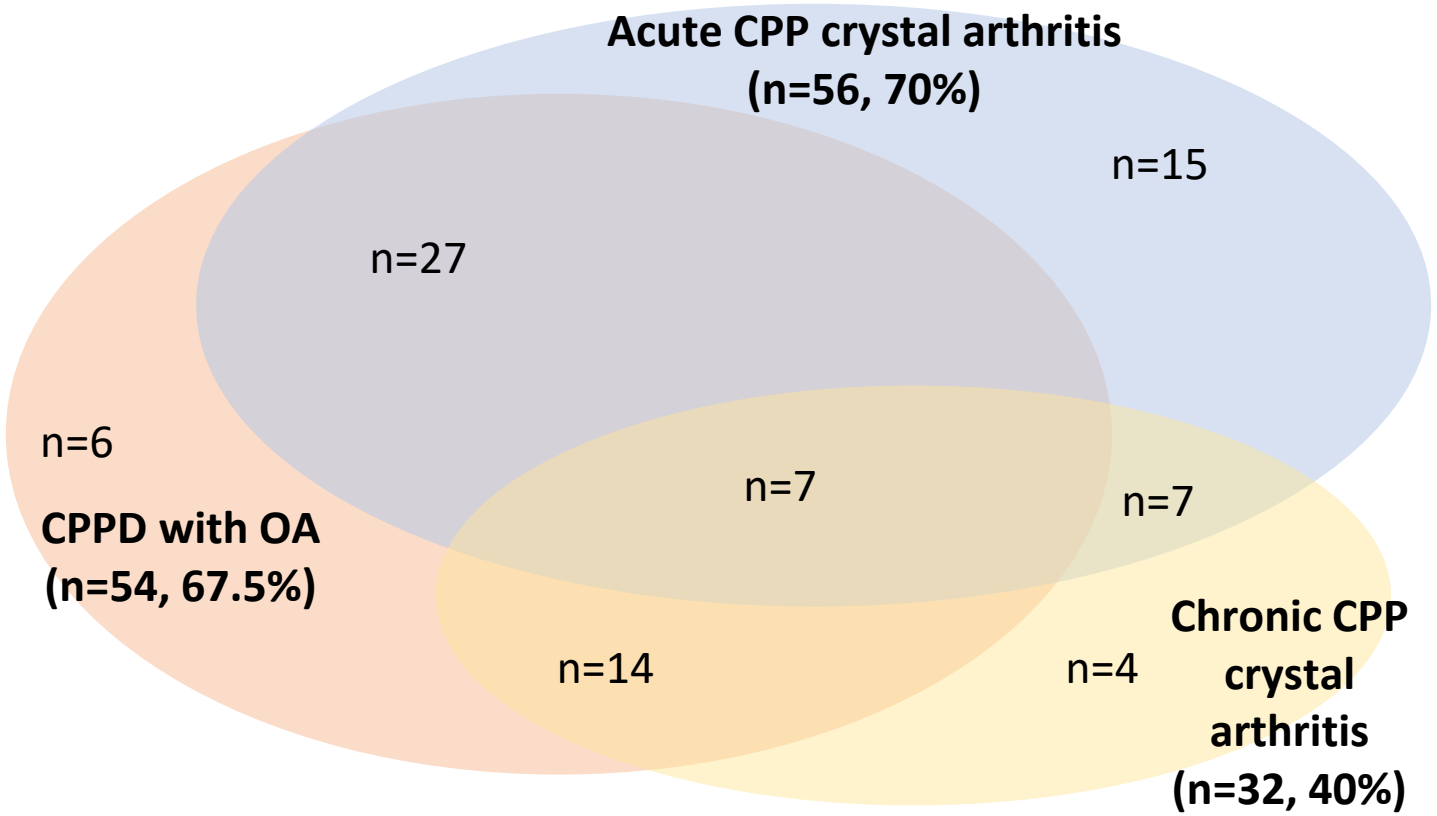
- Prospective registry enrolling patients fulfilling ACR/EULAR 2023 CPPD Classification Criteria, 2022-present

- Questionnaires every 6 months
  - Medications, flares, pain VAS, WOMAC, MDHAQ
  - Additional questionnaires during self-reported flares

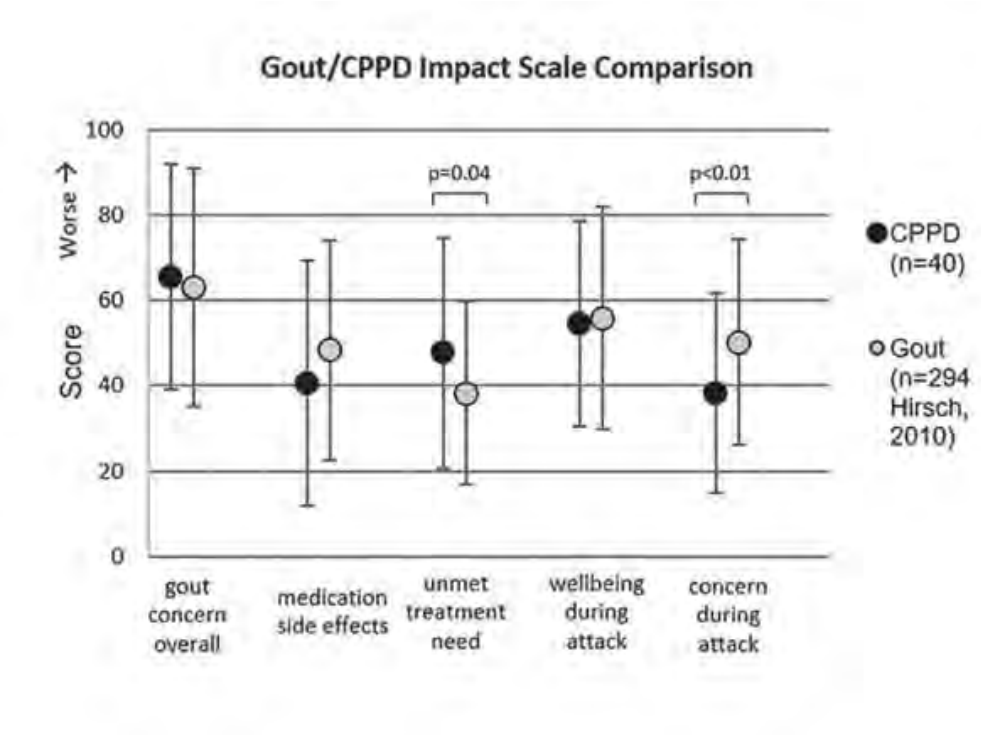
- Annual in-person study visit (optional)
  - Joint examination
  - Musculoskeletal ultrasound
  - Blood samples banked

BRIgham Cppd (BRIC) Registry

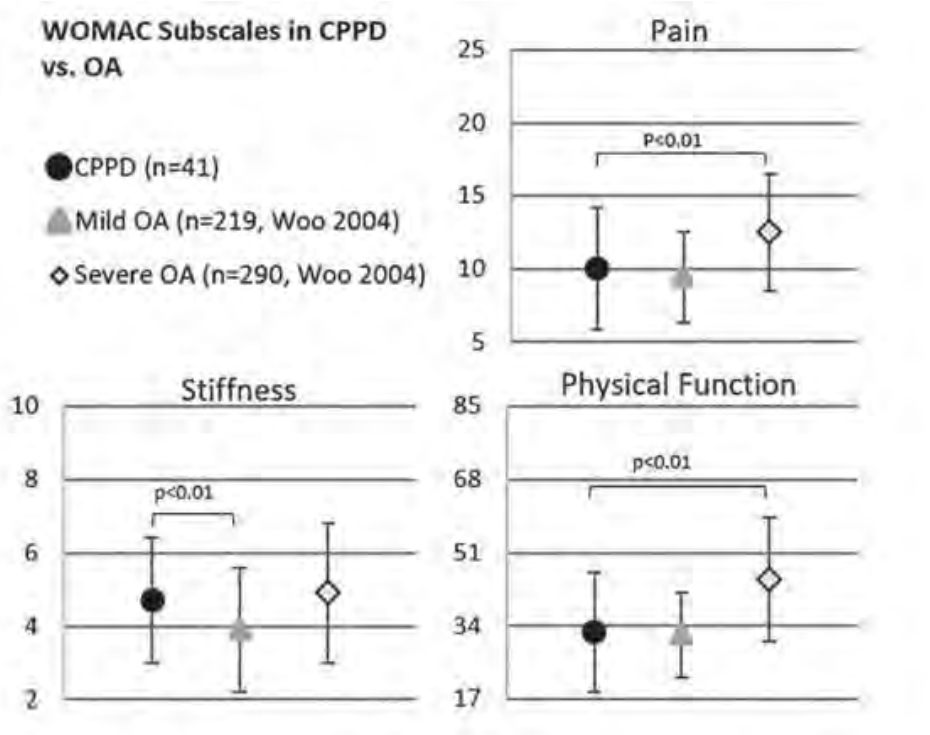
Characteristics of 80 BRIC Registry participants	
Age, mean (SD) years	73.5 (8.0)
Female, n (%)	50 (62.5)
Race, n (%)	
White	73 (84.5)
Black	4 (4.7)
Other	3 (3.5)
Medications ever used for CPPD, n (%)	
Colchicine	52 (65.0)
Oral glucocorticoids	43 (53.8)
NSAID	44 (55.0)
Hydroxychloroquine	12 (15.0)
Methotrexate	9 (11.3)
Anakinra	2 (2.5)
Baseline blood sample, n	44
Month 12 blood sample, n	22 (of 22 due)



Patient-reported outcome measures in CPPD compared to gout and OA: data from BRIC Registry



Significantly greater unmet treatment need in CPPD than gout



Significantly greater joint stiffness in CPPD than mild OA

Whelan, et al. *J Rheumatol* 2023

1. Lay the foundation	Clinical experience & epidemiologic studies
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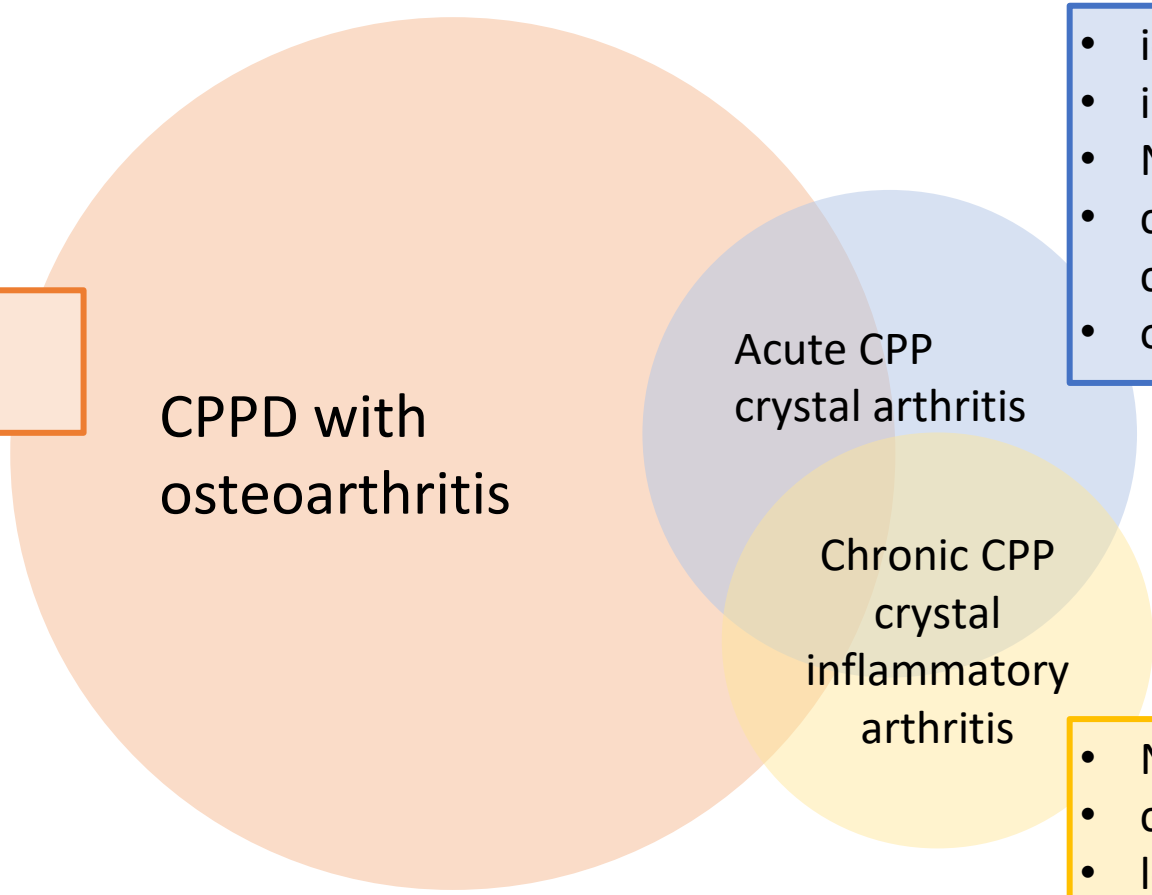
EULAR CPPD treatment recommendations



- treat as osteoarthritis without CPPD

- ice & rest
- intra-articular glucocorticoid
- NSAID
- colchicine (0.5mg 3-4x/day, consider 1mg at start)
- oral glucocorticoid

- NSAID
- colchicine 0.5 to 1mg/day
- low-dose oral glucocorticoid
- methotrexate
- hydroxychloroquine

Zhang, et al. *Ann Rheum Dis* 2011

Data behind methotrexate and hydroxychloroquine for chronic CPP crystal inflammatory arthritis

Methotrexate: Double blind crossover RCT of MTX (7.5-15mg/week) vs. placebo (n=26)

- 3-month intervention
- No difference in outcomes (DAS44 or pain VAS) between study arms

Hydroxycholoroquine: Double-blind RCT of HCQ 400mg/day vs. placebo (n=36)

- 6-month intervention
- Percentage of responders (>30% reduction in tender and/or swollen joint count) significantly higher in hydroxychloroquine arm

Finckh A, et al. *Arthritis Res Ther* 2014
Rothschild, et al. *Compr Ther* 1997

Anakinra as treatment for CPPD

- Growing number of case reports and case series describing benefit for acute & chronic CPP inflammatory arthritis resistant to other therapies
  - Anakinra 100mg SC daily x3d for acute flare
  - Daily chronic therapy may be an option for chronic symptoms

- Double-blind RCT among patients with acute CPP crystal arthritis (n=15)
  - Anakinra 100mg SC daily x3d + PBO, vs. prednisone 30mg daily x3d + PBO
  - No significant difference in change in pain VAS at 72h between arms
  - Recruitment stopped at 3 years (difficult enrollment)

Andres M, et al. *Curr Rheum Reports* 2018
Dumusc A, et al. *Joint Bone Spine* 2021

The latest in CPPD disease treatments

- **Tocilizumab** for acute or chronic CPP inflammatory arthritis
  - Open-label study of tocilizumab IV or SC, N=11
  - All failed/had contraindication to colchicine, NSAID, anakinra, and required daily prednisone at enrollment
  - Patient Global Assessment decreased from median 60 → 15 mm at 3 months
  - 2 patients had flares after >3 months of tocilizumab

- **COLCHICORT** trial

Latourte A, et al. *Ann Rheum Dis* 2020
Pascart T, et al. *Lancet Rheumatol* 2023

Evaluating the safety and short-term equivalence of colchicine versus prednisone in older patients with acute calcium pyrophosphate crystal arthritis (COLCHICORT): an open-label, multicentre, randomised trial

Tristan Pascart, Pierre Robinet, Sébastien Ottaviani, Rémi Leroy, Nicolas Segaud, Aurore Pacaud, Agathe Grandjean, Hélène Luraschi, Thibault Rabin, Xavier Deplanque, Pierre Maciejasz, Fabien Visade, Alexandre Mackowiak, Nicolas Baclet, Sylvestre Maréchaux, Antoine Lefebvre, Jean-François Budzik, Thomas Bardin, Pascal Richette, Laurène Norberciak, Vincent Ducoulombier, Eric Houvenagel

Lancet Rheumatol 2023

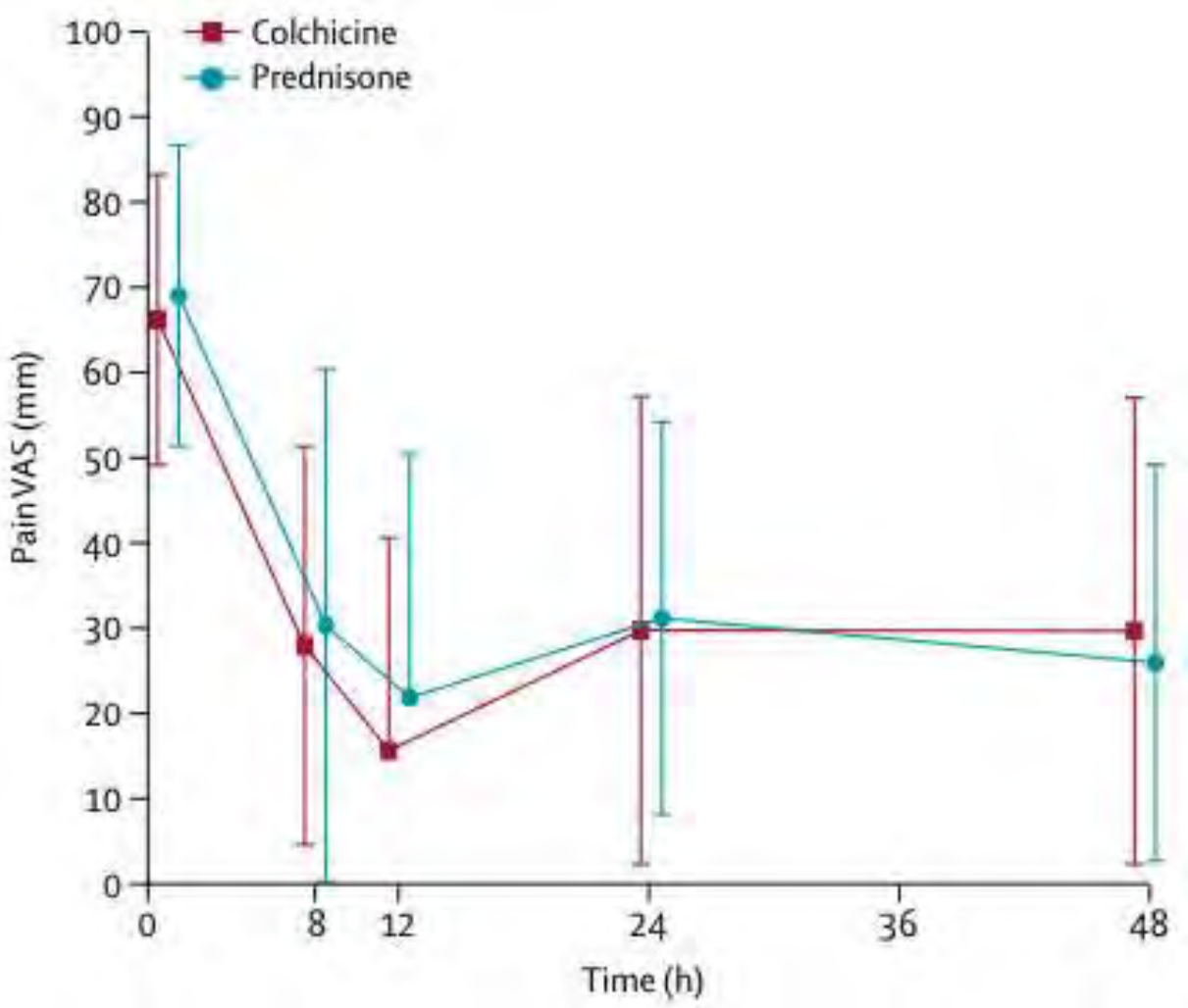
- First RCT among patients with acute CPP crystal arthritis
- Prednisone 30mg x2 days versus colchicine x2 days (1.5mg on day 1, then 1mg on day 2) among adults >65 years old hospitalized with acute CPP crystal arthritis and symptom duration <36h
- Non-inferiority (95% CI of difference in pain VAS at 24h between -13 to +13mm)

Baseline characteristics of COLCHICORT (per-protocol population)

	Prednisone group (n=46)	**Colchicine group (n=49)**
Median age, years	88 (IQR 84-91)	88 (IQR 79-91)
Female	78%	67%
Median BMI, kg/m2	25 (IQR 21-30)	25 (IQR 23-29)
Most painful index joint		
Knee	48%	49%
Wrist	26%	14%
Other	26%	37%
Pain VAS, mm	69 (SD 18)	66 (SD 17)
Prior acute CPP crystal arthritis	28%	24%

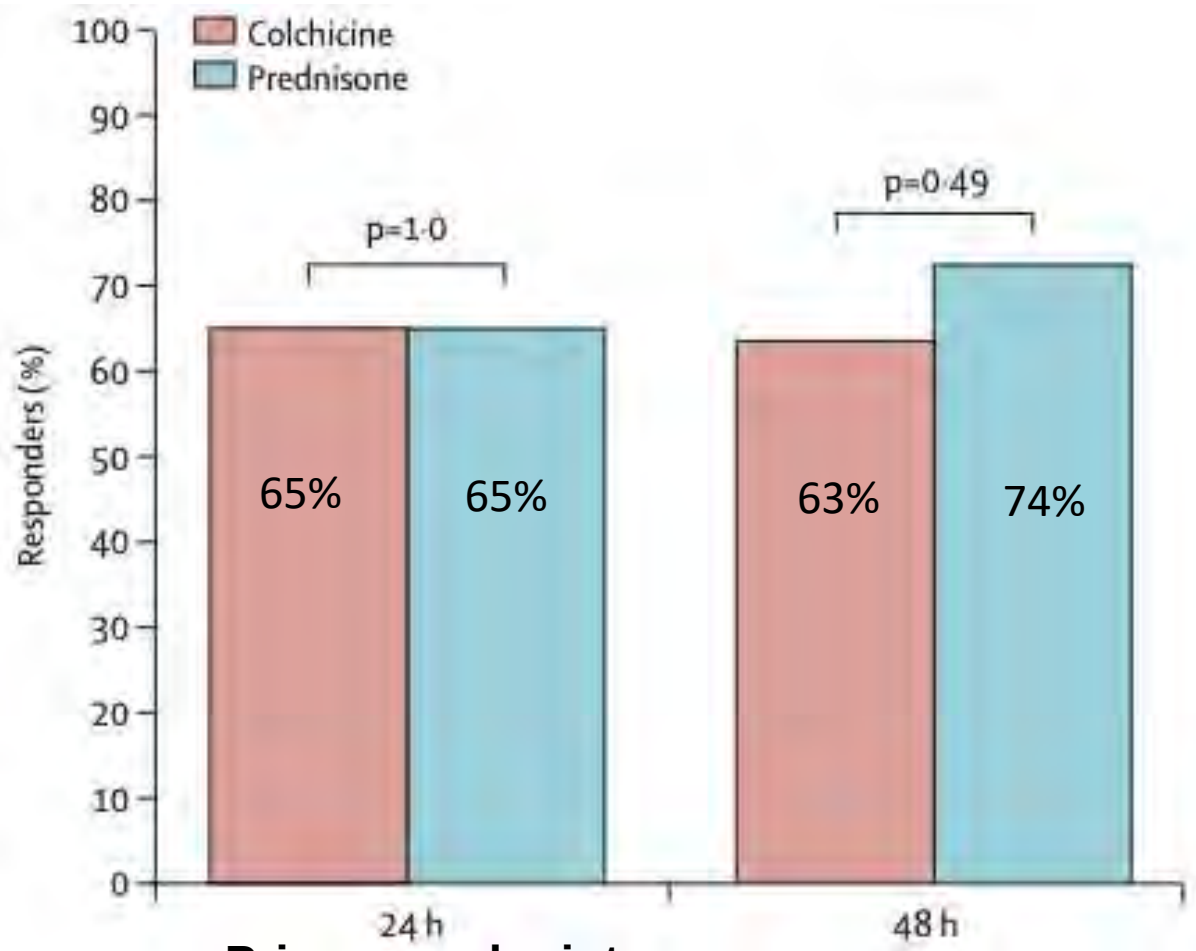
Pascart T, et al. *Lancet Rheumatol* 2023

Pain VAS in the 48h after treatment



Proportion achieving treatment response

>50% reduction in pain VAS, or pain VAS <40 mm



Primary endpoint

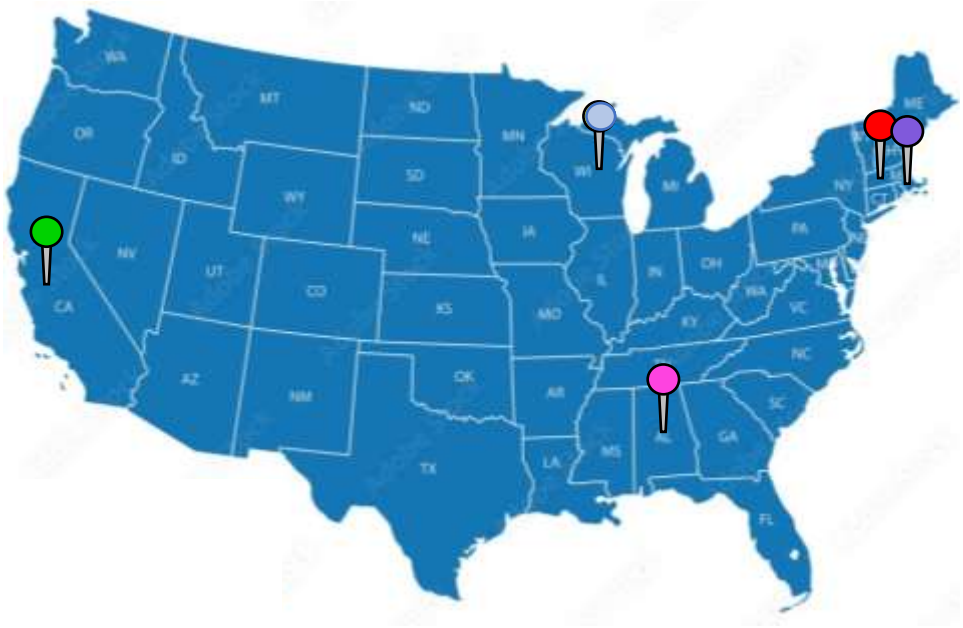
Pascart T, et al. *Lancet Rheumatol* 2023

CRYSTALLIZE Trial

Colchicine to Reduce Your SympToms And Lower Levels of Inflammation, Zeroing in on Effective CPPD disease treatment

- **Design**: Randomized, placebo-controlled, double-blind multi-site trial

- **Study population**: 150 participants randomized across 5 U.S. sites over 4 years
  - Brigham and Women's Hospital (Boston) n=60
  - UCLA (Los Angeles) n=30
  - Boston Medical Center (Boston) n=20
  - Medical College of Wisconsin (Milwaukee) n=20
  - University of Alabama (Birmingham) n=20



- **Intervention**: Colchicine 0.6mg once daily

- **Primary Outcome**: Serum IL-18 at week 24

- **Duration per Participant**: 28 weeks (24 weeks on study drug)

- **Study Duration**: 5 years

Before we choose the paint color….

- Validate definitions
  - Flare
  - Chronic CPP crystal arthritis
- Develop & validate patient-reported outcome measures
- Recruit CPPD disease cohorts
  - Natural history studies
  - Biomarkers to predict flares
- Therapies to prevent or dissolve CPP crystals
- Interventions to reduce extra-articular consequences of CPPD disease

Thank you!

Brigham and Women's Hospital
Dan Solomon, Kat Liao, Karen Costenbader, Stacy Smith, Keigo Hayashi, Weixing Huang, Muneet Gill, Kathleen Vanni, Gracie Whelan, Katie Yates, Brittany Weber, Hongshu Guan

CPPD Classification Criteria Steering Committee
Hyon Choi, Abhishek Abhishek, Bob Terkeltaub, Will Taylor, Nicola Dalbeth, Tristan Pascart, Augustin Latourte, Tuhina Neogi

OMERACT CPPD Co-Chairs and fellows
Nicola Dalbeth, Abhishek Abhishek, Ken Cai, Amy Fuller, Yiling Zhang

CRYSTALLIZE Trial Study Team
Tuhina Neogi, John FitzGerald, Ann Rosenthal, Angelo Gaffo, Muneet Gill, Jackie Stratton, Jamie Collins, Dan Solomon, Nicola Dalbeth, Geraldine McCarthy, Pui Lee

National Institute of Arthritis and Musculoskeletal and Skin Diseases

K23 AR075070 (Tedeschi) R03 AR081309 (Tedeschi)
L30 AR070514 (Tedeschi) P30 AR072577 (Solomon)

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Rheumatology Research Foundation
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