

Title: The 2023 American College of Rheumatology/European Alliance of Associations for Rheumatology Classification Criteria for Calcium Pyrophosphate Deposition (CPPD) Disease

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This criteria set has been approved by the American College of Rheumatology (ACR) Board of Directors and the European Alliance of Associations for Rheumatology (EULAR) Executive Committee. This signifies that the criteria set has been quantitatively validated using patient data, and it has undergone validation based on an independent data set. All ACR/EULAR-approved criteria sets are expected to undergo intermittent updates.

Classification criteria are essential in clinical and basic science research because they allow investigators to study relatively homogeneous populations of patients recruited from a single or multiple research sites. Diagnoses are made by health care professionals evaluating an individual patient's symptoms, signs, and results of laboratory and imaging studies in order to guide therapeutic recommendations. Patients diagnosed with a particular disease may or may not fulfill classification criteria for that disease. Improperly applied classification criteria can lead to misdiagnosis.

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ABSTRACT

Objective: Calcium pyrophosphate deposition (CPPD) disease is prevalent and has diverse presentations, but there are no classification criteria for this symptomatic arthritis. We developed the first ever validated classification criteria for symptomatic CPPD disease.

Methods: Supported by the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR), a multinational group of investigators followed established methodology to develop these criteria. We generated lists of candidate items and refined their definitions, collected de-identified patient profiles, evaluated strengths of associations between candidate items and CPPD disease, developed a classification criteria framework, and used multi-criterion decision analysis to define criteria weights and a classification threshold score. We validated the criteria in an independent cohort.

Results:

Among patients with pain, swelling or tenderness at a peripheral or axial joint(entry criterion) whose symptoms are not fully explained by an alternative disease (exclusion criterion), the presence of crowned dens syndrome or CPP crystals in synovial fluid are sufficient to classify as CPPD disease. In the absence of these findings, a score >56 points using weighted criteria comprised of clinical features, associated metabolic disorders, and results of laboratory and imaging investigations can be used to classify as CPPD disease. These criteria had a sensitivity of 92.2% and specificity of 87.9% in the derivation cohort (190 CPPD cases, 148 mimickers), whereas sensitivity was 99.2% and specificity was 92.5% in the validation cohort (251 CPPD cases, 162 mimickers).

Conclusion: The first ACR/EULAR CPPD disease classification criteria have excellent performance characteristics and will facilitate research in this field.

INTRODUCTION Calcium pyrophosphate deposition (CPPD) disease is a common symptomatic arthritis characterised by the deposition of calcium pyrophosphate (CPP) crystals (1). The prevalence of radiographic chondrocalcinosis, often used as a proxy for CPPD disease, ranges from 4% to $\geq 10\%$ among older adults, though the prevalence of symptomatic CPPD disease remains incompletely defined (2-5). Research in CPPD disease has lagged behind other types of arthritis due, in part, to absence of validated classification criteria. Variable reliance on synovial fluid (SF) polarised light microscopy for diagnosis, and a diversity of presentations that include acute CPP crystal arthritis, chronic CPP crystal inflammatory arthritis, osteoarthritis with CPPD, and crowned dens syndrome (CDS) makes it hard to compare studies (1). The only published diagnostic criteria for CPPD disease were developed in the 1960s by Ryan and McCarty(6). For definite diagnosis, they required evidence of crystals by presence of both typical calcification on radiography and findings consistent with CPP crystals on SF polarised light microscopy, or alternatively by research laboratory techniques that are not widely available (7). These diagnostic criteria have since been recognized to be problematic, because conventional radiography (CR) has low sensitivity for CPPD (8-10), advanced imaging modalities such as ultrasonography and dual energy CT (DECT) were not available in the 1960s, and SF analysis for CPP crystals has a high false negative rate and high inter-observer variability (11-14).

To develop validated classification criteria to facilitate research in CPPD disease, an international collaborative working group was convened with the support of the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR). The goal was to develop a framework enabling investigators to identify people with CPPD disease for entry into research studies, including clinical trials and observational studies. Such criteria are not intended to capture *all* possible cases, but rather to capture the majority of people with symptomatic CPPD disease.

METHODS These classification criteria were developed in four sequential phases (**Figure 1**) following previously established methodology (15-19). A 9-member Steering Committee oversaw the process and a 22-member Combined Expert Committee (CEC) contributed throughout. **Phases-1 and -2** were described previously (20). Briefly, in **Phase 1** we developed a comprehensive list of potential classification criteria items based on a scoping literature review and input from the CEC and two patient research partners and in **Phase 2** we reduced and refined the list of potential items to those considered most specific for CPPD disease. These potential items were included in the case report form (CRF) that was used to collect patient profiles in the derivation and validation cohorts. **Phase 3** involved the multiple steps described below (**Figure 1**).

a. Derivation cohort recruitment.

De-identified information on people with different likelihood of CPPD disease was collected using a standardized CRF aided by item definitions for imaging features adopted from the literature or specifically developed for this project (21-24). Data were collected retrospectively using medical record review with approval of Health Research Authority (Research Ethics Committee reference: 20/SC/0243) and the local Ethics Committee. In addition to reporting clinical manifestations, risk factors for CPPD, and results of imaging and laboratory tests, the submitting clinician rated their clinical impression of the likelihood that the individual had CPPD disease on a seven-point Likert scale, from +3=highly likely to -3=highly unlikely.

Each patient profile was categorized as definite CPPD (case), definite mimicker (control), or uncertain using the submitted information. Profiles rated as +3 or +2 by the submitting clinician with CPPD crystals confirmed by synovial fluid analysis were considered definite CPPD. Profiles rated -3 or -2 by the submitting clinician were considered definite mimickers. All others underwent adjudication by two blinded independent experts from institutions that did not submit that patient

profile. After adjudication, profiles rated +2 or more by both adjudicators were considered definite CPPD and profiles rated -1 or less by both adjudicators were considered definite mimickers (**Table S1**). Profiles that adjudicators did not both rate +2 or higher, or -1 or lower, and those without SF CPP crystals that were rated -1, 0, or +1 by the submitting clinician were considered uncertain. The adjudicators did not discuss the patient profiles among themselves.

b. Patient profile ranking by CEC.

Among the derivation cohort, 30 patient profiles representing the full spectrum of likelihood of CPPD disease were selected. Seven with clinician rating of -2 or -3; 15 with clinician rating -1, 0, or +1; and eight with clinician rating of +2 or +3. These patient profiles were purposefully selected so that all candidate items were present in at least one of the profiles. CEC members then ranked the profiles individually from 1 to 30 according to their perceived likelihood of CPPD disease.

c. Association between potential classification criteria items and CPPD disease.

Data from definite cases and definite mimickers (controls) in the whole derivation cohort were used to calculate the odds of CPPD disease given the presence of each of the potential classification criteria in univariate analyses. Unadjusted logistic regression models estimated odds ratios (OR) and 95% confidence intervals. Uncertain cases were excluded since their true case/control status was unclear.

d. Classification criteria framework.

The CEC convened four videoconferences to review results of the ranking exercise and the odds ratios (ORs) calculated for candidate items. Based on these discussions, the CEC decided to include entry criteria (required to be considered for CPPD classification), exclusion criteria (if present, classification as CPPD should not proceed), and developed the initial draft of classification criteria framework. The framework consisted of domains comprising similar items. The goal was to order items within each domain into mutually exclusive levels from least influential to most influential when considering the likelihood of classifying a person as having CPPD disease. Decisions regarding

domains, their levels, and the relative ordering of the levels within domains were guided by expert opinion and supported by the ORs from derivation cohort data. The Steering Committee iteratively refined the classification criteria framework between and after the CEC videoconferences.

e. Assigning relative weights

Using a multi-criterion decision analysis (MCDA) approach, members of the CEC undertook a discrete-choice conjoint analysis exercise using 1000Minds Potentially All Pairwise Rankings of all possible Alternatives (PAPRIKA) software (<http://www.1000minds.com>), guided by an experienced facilitator (Alison Hendry) over four 2-hour virtual meetings; see **Supplementary Methods** for details (25).-During the virtual meetings, the CEC was presented with paired CPPD clinical scenarios that included items from two different domains; all other patient features were assumed to be equivalent. CEC members were asked to decide which clinical scenario was more likely to have CPPD, for instance, a patient with acute inflammatory arthritis in a peripheral joint other than knee, wrist, or 1st metatarsophalangeal (MTP) joint and evidence of calcification on imaging of one peripheral joint (regardless of symptoms), versus a patient with acute inflammatory arthritis in the 1st MTP joint and evidence of calcification in four peripheral joints (regardless of symptoms). The facilitator encouraged discussion until consensus was reached on each pairwise decision. 1000Minds software used these decisions to determine weights that were automatically scaled so that the sum across all domains ranged from 0 to 100 (see Supplementary Methods).

Early in this process it became apparent that two items dominated decision making and it was decided to make them sufficient criteria, meaning that if either was present then proceeding to score the other criteria was not necessary. The CEC then re-voted on a series of pairwise decisions with those two items removed to update the weights for the remaining criteria.

Upon completing the MCDA exercise, some domains were re-centred to maintain the face validity of item weights. Levels in a domain with a weight difference <1% were merged as a difference of <1% was considered unlikely to improve discrimination on a 100-point scale. Item weights were

rounded to integers for consistency with published classification criteria (15-19). These steps were undertaken by the Steering Committee and approved by the CEC.

f. Threshold determination

Steering Committee members were asked to individually decide whether they would feel comfortable classifying each of the 30 patient profiles used in the ranking exercise as CPPD disease for enrolling them into a research study. The percentage of the Steering Committee classifying each case as CPPD disease was plotted against the total additive criteria score to visualize where the threshold may fall. Classification criteria additive scores were then calculated for the whole derivation cohort, receiver operator characteristic (ROC) curves were plotted, and tables of sensitivity and specificity inspected to select a preliminary threshold score that maximised specificity while retaining high sensitivity. This was done first for definite cases and definite mimickers that were eligible for scoring (i.e., those who had no exclusion criteria nor sufficient criteria). Next, the sensitivity and specificity of the entire classification criteria system – including sufficient criteria and scored criteria – were calculated at the proposed threshold score among all definite cases and definite mimickers. After this, the percentage classified as CPPD disease according to the submitting clinician's rating of likelihood of CPPD disease was examined using the entire derivation cohort.

Phase-4, Validation of the CPPD classification criteria. An independent validation cohort was concurrently recruited from centres that were not contributing cases to the derivation cohort. Investigators contributing to the validation cohort were unaware of the classification criteria framework, relative item weights, and the threshold score. Recruitment, definition of cases and mimickers (controls), and blinded case adjudication were performed as for the derivation cohort. ROC curves were developed and sensitivity and specificity of the threshold score calculated among validation cohort definite cases eligible for scoring and definite mimickers. Then, the sensitivity and specificity of the entire classification criteria system at the proposed threshold score were calculated

among all definite cases and definite mimickers. Finally, using the entire validation cohort, we examined the distribution of the percentage classified as CPPD disease per the submitting clinician's rating of likelihood of CPPD disease.

RESULTS Rheumatologists from 13 sites in six countries submitted 418 patient profiles forming the derivation cohort: 190 definite cases, 148 definite mimickers and 80 uncertain (62 rated -1, 0, or +1 likelihood of CPPD disease by the submitting clinician and 18 judged uncertain by two adjudicators). Primary diagnoses among the 148 definite mimickers included gout (n=43), rheumatoid arthritis (RA, n=38), osteoarthritis (n=27), psoriatic arthritis (PsA, n=12), other inflammatory arthritis (n=11), polymyalgia rheumatica (n=6), others (n=5), and not specified (n=6). Rheumatologists from 12 sites in six countries submitted 617 patient profiles forming the validation cohort: 251 definite cases, 162 definite mimickers and 204 uncertain. Among 162 definite mimickers, primary diagnoses were gout (n=45), RA (n=40), osteoarthritis (n=21), PsA (n=19), other inflammatory arthritis (n=19), septic arthritis (n=5), polymyalgia rheumatica (n=1), others (n=12). **Table 1** summarizes demographic and clinical characteristics of the derivation and validation cohorts.

The CEC comprised 22 experts (20 rheumatologists, one radiologist, one methodologist). Thirteen members were from Europe, six from the USA, and three from New Zealand; 41% were women. Results of the rank-ordering exercise by individual CEC members are presented in **Figure S1**. The CEC identified key factors important for distinguishing CPPD disease from mimickers by reviewing ranking results and ORs (**Tables S2-9**). These were: presence of CPP crystals in SF (or tissue biopsy), CDS, symptom onset after age 60 years, persistent inflammatory arthritis, typical episode(s) of acute inflammatory arthritis defined by acute onset or acute worsening of joint pain with joint swelling and/or warmth that resolves irrespective of treatment, location of typical episode(s) (knee, wrist, 1st MTP joint, other peripheral joints), metabolic conditions that predispose to CPPD (hereditary hemochromatosis, primary hyperparathyroidism, hypomagnesemia, Gitelman syndrome, hypophosphatasia, or familial history of CPPD disease), radiographic osteoarthritis of specific hand joints (scaphotrapezotrapezoidal (STT) joint without 1st carpometacarpal (CMC) joint involvement, radio-carpal joint, 2nd metacarpophalangeal (MCP) joint, 3rd MCP joint), and imaging evidence of

CPPD (linear or punctate calcification in the hyaline cartilage or fibrocartilage) in peripheral joints. Imaging item definitions and example images were developed in parallel to this endeavour and have been previously published (21). Onset of symptoms after 60 years of age was included as a domain even though it was not associated with CPPD disease in the case-mimicker analysis. This decision was based on expert opinion and demographics of CPPD patients in the published literature. Additionally, the lack of association with age was thought to be due to recruitment of potential mimickers that were older adults, i.e., the age group where CPPD disease was a possibility.

Entry, exclusion, and sufficient criteria. The CPPD disease classification framework must be applied in the following sequence (**Figure 2**): (1) entry criteria must be fulfilled; (2) exclusion criteria must be absent, (3) sufficient criteria are evaluated (present vs. absent), 4) if sufficient criteria are absent then proceed with scoring of domains.

CEC members agreed that to be classified as CPPD disease, an individual must have had at least one episode of joint pain, swelling or tenderness at a peripheral joint or axial joint (entry criteria). Symptomatic CPPD disease is required for classification since the intention of classification criteria is to enable enrolment into clinical trials that would focus on symptomatic individuals.

Exclusion criteria were intended to identify individuals in whom *all* musculoskeletal symptoms potentially attributable to CPPD disease were more likely explained by an alternate condition such as RA, gout, PsA or osteoarthritis, to whom the classification criteria should not be further applied. The CEC noted that symptom attribution can be difficult and if at least some symptoms are attributable to CPPD disease, then the classification criteria can be applied. It was also agreed that the classification criteria would apply to CPPD disease as a whole, and development of separate classification criteria for each clinical presentation would not be attempted within this endeavour.

Two sufficient criteria were agreed upon: CDS and SF analysis demonstrating CPP crystals in a joint with swelling, tenderness, or pain (any quantity of intra- and/or extra-cellular crystals). In the initial MCDA exercise, presence of SF CPP crystals and CDS accounted for >40% of the weighting and cases with SF CPP crystals or CDS had consistently been ranked most likely to have CPPD disease in the ranking exercise. Sufficient criteria are also met if CPP crystals are demonstrated in histopathology of joint tissue, provided the patient does not meet exclusion criteria. For instance, articular cartilage CPPD in patients with end-stage osteoarthritis cannot be used to classify the patient as CPPD disease when all symptoms are better explained by osteoarthritis (26).

Domains and categories. The final framework included four clinical, one laboratory, and three imaging domains (**Table 2**). The levels within each domain are scored based on a patient's disease experience to date, such that if a higher and a lower weighted level were fulfilled at different points in time, the higher one is scored.

Assigning relative weights to domains and categories. All weights were initially zero or positive. Domains C (site of typical episodes of inflammatory arthritis), E (synovial fluid analysis) and G (imaging of a symptomatic joint) were re-zeroed such that the level least likely to be present in a person with CPPD disease was assigned negative weight to maintain face validity (see Supplementary Results and **Table S10** for details).

In domain G (imaging of a symptomatic joint), advanced imaging modalities were initially considered separately from CR in this domain; however, item weights differed by <1% so advanced imaging and CR were combined. Item weights, re-zeroing, merging of levels and rounding-off are reported in **Table S10**.

The final ACR/EULAR CPPD classification criteria and weights are presented in **Table 2**. The CEC agreed that imaging of at least one symptomatic peripheral joint is required for scoring when sufficient criteria are not fulfilled, given the important role of imaging when considering the likelihood of CPPD disease. A web-based calculator is accessible at [website-to-be-inserted]. A plot of percent agreement for Steering Committee voting “yes” for enrolling in a research study versus the final additive classification criteria score suggested a threshold between 53 and 57 (**Figure 3**).

Classification criteria performance in derivation and validation cohorts. Among the 190 definite cases in the derivation cohort, 130 fulfilled sufficient criteria and were ineligible for scoring. The classification criteria score separated the remaining 60 definite cases from 148 mimickers with area under curve (AUC) (95% CI) 0.95 (0.93-0.98) (**Figure 4**). A threshold score of >56 was chosen as that maximised specificity at 87.9% while retaining a high sensitivity of 92.2% in this subgroup (**Table S11**). When the entire classification criteria system (i.e., entry, exclusion, sufficient, and scored criteria) was applied to all definite cases and definite mimickers in the derivation cohort, the threshold score of >56 had a specificity of 87.9% and sensitivity of 97.8%.

The face validity of a threshold score of >56 was assessed. Examples of patient profiles just below the threshold included: (A) single typical episode of acute inflammatory arthritis involving the wrist with symptom onset after age 60 and chondrocalcinosis only at that wrist (score: 56), (B) single typical episode of acute inflammatory arthritis involving the knee with symptom onset at age <60 years and chondrocalcinosis in that knee only (score: 53), (C) joint pain without inflammatory arthritis, age >60 at onset, osteoarthritis of bilateral radiocarpal joints and 2nd metacarpophalangeal joints, and chondrocalcinosis of bilateral wrists (score: 50). The CEC reviewed these cases and agreed that they should not be classified as CPPD disease, as sufficient clinical uncertainty existed.

Among the 251 definite cases in the validation cohort, 186 fulfilled sufficient criteria and were ineligible for scoring. The threshold of >56 separated the remaining 65 definite cases from 162 mimickers with AUC (95% CI) 0.98 (0.96-0.99) (**Figure 4**) and had sensitivity and specificity of 96.5% and 92.5% in this subgroup of the validation cohort. Assessment of the entire classification criteria framework (entry, exclusion, and sufficient criteria and the threshold score of >56) among the 413 definite cases and definite mimickers in the validation cohort demonstrated a sensitivity of 99.2% and specificity of 92.5%. The percentage of patient profiles classified as CPPD disease increased with the submitting clinician's rating of CPPD disease in both the derivation and validation cohorts (**Table S12**).

DISCUSSION These are the first ever classification criteria for CPPD disease and we believe they will facilitate future observational studies and clinical trials in CPPD disease. These classification criteria were derived and validated using established methodology relying on data from 751 patient profiles and expert consensus. The classification criteria demonstrated high sensitivity and specificity in an independent validation cohort. Presence of CDS (imaging plus clinical features) or the identification of CPP crystals in synovial fluid from a symptomatic joint were sufficient for classification as CPPD as long as exclusion criteria were not met (e.g. another condition did not explain the entire presentation). Patients without those features can be classified by scoring the remaining imaging and clinical criteria.

Among the scored criteria, imaging features and recurrent typical episodes of acute inflammatory arthritis carried the greatest weight. This reflects consensus among the multidisciplinary CEC that imaging evidence of CPP crystal deposition and acute inflammatory arthritis are central constructs in CPPD disease when laboratory evidence of SF CPP crystals is lacking. An imaging study of at least one symptomatic joint is required in patients not meeting sufficient criteria. No additional imaging is absolutely required; however, the more peripheral joints imaged the greater the potential score as may be the case for centres that routinely image bilateral joints. The Steering Committee considered requiring mandatory imaging of a standardized set of joints (e.g., bilateral knees and wrists) when considering patients for classification but decided against this due to concerns about practical feasibility of this approach especially in low-middle income countries, in institutions with less availability of imaging facilities and/or funding for research. Such a requirement could potentially reduce the uptake of this classification criteria especially for observational research studies. This approach is also consistent with other classification criteria where imaging of a core set of joints is not an absolute requirement. Requiring imaging of at least one symptomatic peripheral joint was

considered a reasonable compromise that would permit widespread, more equitable application of these classification criteria in all potential CPPD disease patients internationally.

The criteria highlight the importance of imaging evidence of CPPD, as its absence prevents classification if an individual does not meet sufficient criteria. The highest levels of two imaging domains account for nearly half of the weighting: evidence of CPPD in a symptomatic joint, and evidence of CPPD in ≥ 4 peripheral joints. While imaging features alone in a patient with joint pain would not be sufficient for classification, they were weighted heavily in the MCDA exercise such that they became a necessary component in the scored criteria. The CEC discussed at length the high sensitivity of ultrasound and CT, particularly in early CPPD disease, compared to CR (10, 27). This higher sensitivity is reflected in negative points assigned if no evidence of CPPD is found on advanced imaging. Because advanced techniques demonstrate high, yet imperfect specificity for CPPD, the group did not reach agreement for evidence of CPPD on advanced imaging as sufficient to classify CPPD disease. Imaging evidence of CPPD on advanced imaging modalities and evidence on CR received nearly equal weight (<1% difference), given high specificity associated with both modalities, resulting in their being grouped together and reflecting expert consensus that imaging evidence of CPPD on any modality is equally convincing. Although only a few studies have been published on the use of DECT in CPPD, it was included as an imaging modality using which CPPD could be detected as it has high specificity and higher sensitivity than plain radiography and comparable sensitivity to ultrasonography (28, 29).

A practical gold-standard for CPPD disease does not exist in clinical settings, as SF CPP crystal positivity on polarized light microscopy is specific but has high false-negative rate and significant interobserver variability (11-14). Challenges of CPP crystal identification include small crystal size and absent or weak positive birefringence (11). Furthermore, feasibility of CPP crystal identification may be limited by difficulty of joint aspiration, particularly from small joints. Thus, although the

CEC determined that presence of any quantity of CPP crystals in a symptomatic joint can lead to classifying an individual as having CPPD disease, requiring presence of SF CPP crystals in all cases is not practical for classification. To that end, the proposed criteria are intended to enable accurate classification of CPPD disease, regardless of whether joint aspiration was performed. Nevertheless, joint aspiration remains important for a clinical diagnosis of CPPD disease in practice and to exclude mimicking conditions including gout and septic arthritis.

Attribution of symptoms to CPPD disease can be challenging, particularly in patients with osteoarthritis, or in those with RA, which can co-exist with CPPD disease and/or be mis-diagnosed initially (30-32). The classification criteria acknowledge the frequent co-existence of CPPD disease with other rheumatic and musculoskeletal diseases (RMDs) by only excluding from classification those patients for whom *all* symptoms are better explained by another condition, and allowing investigators to attempt classification if they suspect that at least some symptoms are due to CPPD disease. Distinguishing between CPPD and basic calcium phosphate (BCP) deposition on imaging can be challenging, although imaging definitions for CPPD developed as part of this project may mitigate this issue (21).

We did not specify a minimum time-limit on the duration of symptoms before which inflammatory arthritis may be considered to be persistent. This was because most patients with symptoms and signs of inflammatory arthritis (of any aetiology) are offered treatment e.g. with corticosteroids, which can shorten the duration of symptoms and make it difficult to apply classification criteria. Additionally, while other inflammatory conditions such as RA are well-defined and well-understood, the same is not true for chronic CPP crystal inflammatory arthritis. Specifying a minimum time for inflammatory arthritis may result in selection bias when recruiting cohorts studying the natural history and clinical presentation of chronic CPP crystal inflammatory arthritis, and in clinical trials. In practice, a

clinician may consider someone to have persistent inflammatory arthritis when the duration of symptoms exceeds that of acute crystal arthritis.

The current endeavour has strengths. First, the criteria establish the clinical picture of CPPD disease as an inflammatory arthritis among older adults typically manifesting with acute inflammatory features (and occasionally with chronic inflammation) and a predilection for knee and wrist joints. Discussions about the threshold made clear that requiring joint inflammation provided superior specificity for CPPD classification while maintaining >90% sensitivity in patients that lack evidence of CDS or SF CPP crystals. Inflammatory arthritis is not absolutely required; individuals with osteoarthritis and SF CPP crystals could be classified by sufficient criteria if not all symptoms are explained by osteoarthritis. Critically, the classification criteria must be applied in the order presented in **Figure 2** and **Table 2** so that individuals in whom *all* symptoms are attributable to osteoarthritis and have SF CPP crystals would not be classified as CPPD disease. Second, patient profiles in the derivation and validation cohorts were collected from a large international pool, supporting generalizability. Nevertheless, further testing of the criteria in other populations would be valuable. Third, we followed well-established methodology for classification criteria development, supporting the validity of the process and final product. Fourth, the criteria allow people with CPPD disease and another RMD to be classified as CPPD disease.

Several limitations deserve mention. Given the absence of a pathologic gold standard for CPPD diagnosis, expert opinion was used to label cases and mimickers. We excluded a significant number of uncertain patient profiles from ROC analyses and sensitivity/specificity calculations as their true case/control status could not be reliably determined. The heterogeneous nature of CPPD disease can lead to differences in clinical opinion about whether particular features are attributable to CPPD, reflected in the clinician's rating of -1 to +1 for likelihood of CPPD and/or lack of agreement among adjudicators. Together with its heterogeneous nature, different rheumatologists' perceptions of the

clinical phenotype that may be attributed to CPPD disease vary substantially. To minimise the possibility that differences in opinion would affect threshold determination, we adopted stringent case and mimicker definitions – often requiring unequivocal evidence of CPPD or agreement between the submitting clinician and two experts. The inclusion of only definite cases and definite mimickers may have contributed to the classification criteria’s high sensitivity and specificity in our validation cohort. Nevertheless, the proportion classified as CPPD disease increased progressively across the submitting clinician’s rating, including among cases deemed uncertain (rated -1/0/+1) by submitting clinicians, further supporting the internal validity of this approach. Moreover, only 16.5% of the combined derivation and validation cohort had non-White ethnicity. Therefore, we recommend that the performance of these criteria be evaluated in other cohorts especially among people with non-White ethnicities. Similarly, the number of cases and mimickers were relatively modest in derivation and validation cohorts and further validation in larger cohorts is recommended. Despite challenges with attribution, the CPPD classification criteria enable identification of a relatively homogenous group of patients with a preponderance of evidence for CPP deposition and characteristic clinical symptoms, for whom *all* features are not better explained by another disease. We did not address asymptomatic CPPD since the purpose of classification criteria is to identify individuals with symptomatic disease to be included in clinical studies. The current criteria represent an endeavour to identify patients with symptomatic CPPD disease with maximal sensitivity and specificity for inclusion in prospective studies, including clinical trials and observational studies.

In conclusion, the 2022 ACR/EULAR classification criteria for CPPD disease represent the first for the condition, with robustly validated performance characteristics. Future studies of CPPD disease may employ these as inclusion criteria for participant screening and enrolment.

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FIGURE LEGENDS

Figure 1: Overview of CPPD Classification Criteria development process across the four phases.

Figure 2: Conceptual schematic for applying the CPPD disease classification criteria.

Figure 3: Plot of Steering Committee percentage agreement on classifying patient profiles as CPPD disease for inclusion in a research study (n=8 participating Steering Committee members). The patient profiles were given pseudonyms.

Figure 4: Receiver Operating Characteristic (ROC) curves in derivation cohort (left panel) and validation cohort (right panel) for the patients that were eligible to be scored. In the derivation cohort, data for 60 definite cases and 148 definite mimickers were included. In the validation cohort, data for 65 definite cases and 162 definite mimickers were included.

Table 1. Characteristics of derivation and validation cohorts

	Derivation cohort			Validation cohort		
	Definite case (n=190)	Uncertain (n=80)	Mimicker (n=148)	Definite case (n=251)	Uncertain (n=204)	Mimicker (n=162)
Symptom onset \geq 60-year age, n (%)	144 (75.8)	63 (78.7)	76 (51.4)	201 (80.1)	147 (72.1)	81 (50.0)
Female, n (%)	113 (59.5)	48 (60.0)	88 (59.5)	141 (56.2)	104 (51.0)	63 (38.9)
Inflammatory arthritis ¹						
Acute	175(92.1)	56 (70.0)	116 (78.4)	244 (97.2)	161 (78.9)	138 (85.2)
Persistent	44 (23.2)	29 (36.3)	66 (44.6)	51 (20.3)	53 (26.0)	50 (30.9)
None	9 (4.7)	14 (17.5)	19 (12.8)	5 (2.0)	31 (15.2)	9 (5.6)
Ethnicity ^{2, 3}	(n=189)	(n=80)	(n=148)	(n=212)	(n=186)	(n=155)
White, n (%)	164 (86.8)	72 (90.0)	136 (91.9)	175 (82.5)	139 (74.7)	124 (80.0)
Other ⁴ , n (%)	25 (13.2)	8 (10.0)	12 (8.1)	37 (17.5)	47 (25.3)	31 (20.0)
Regions						
USA, n (%)	50 (26.3)	19 (23.8)	43 (29.1)	120 (47.8)	113 (55.4)	54 (33.3)
Europe, n (%)	131 (68.9)	54 (67.5)	91 (61.5)	117 (46.6)	76 (37.3)	92 (56.8)
New Zealand, n (%)	9 (4.7)	7 (8.8)	14 (0.5)	14 (5.6)	15 (7.4)	16 (9.9)

¹Patients could have more than one type of inflammatory arthritis. ²Data on ethnicity were missing for 1 case in derivation cohort. ³Data on ethnicity were not available due to restrictions on sharing ethnicity data for 39 definite cases, 18 uncertain and 7 mimicker patient profiles in the validation cohort. ⁴Due to a number of ethnicities with few patient profiles each, the ethnicity data are presented aggregated to maintain confidentiality.

Table 2: ACR/EULAR classification criteria for Calcium Pyrophosphate Deposition (CPPD) disease.

The CPPD classification criteria should be applied in the following order:		
1. Entry criterion: Ever had at least one episode of joint pain, swelling, or tenderness. ⁺		
2. Absolute exclusion criteria: All symptoms are more likely explained by an alternate condition (such as rheumatoid arthritis, gout, psoriatic arthritis, osteoarthritis, etc.)		
3. Sufficient criteria: 1. Crowned dens syndrome* or 2. Synovial fluid analysis demonstrating CPP crystals in a joint with swelling, tenderness or pain.**		
An individual is classified as CPPD if the entry criterion is met, exclusion criteria are not met, and at least one sufficient criterion is fulfilled. If none of the sufficient criteria are present, an individual is classified as CPPD disease if the sum of the criteria below is >56 points.		
Items can be scored if they were ever present during a patient's lifetime. If a patient fulfills >1 item in a given domain, only the highest weighted item will be scored. Imaging of at least one symptomatic joint by CR, US, CT, or DECT is required.		
Domains and levels		Points
A	Age at onset of joint symptoms (pain, swelling, and/or tenderness)	
	≤60 years	0
	>60 years	4
B	Time-course and symptoms of inflammatory arthritis	
	No persistent ¹ or typical ² inflammatory arthritis	0
	Persistent inflammatory arthritis ¹	9
	1 typical acute arthritis episode ²	12
	More than 1 typical acute arthritis episode ²	16
C	Sites of typical episode(s) ² of inflammatory arthritis in peripheral joints	
	1st MTPJ	-6
	No typical episode(s)	0
	Joint(s) other than wrist, knee or 1 st MTPJ	5
	Wrist	8
	Knee	9
D	Related metabolic diseases ³	
	None	0
	Present	6
E	Synovial fluid crystal analysis ⁴ from a symptomatic joint	
	CPP crystals absent on ≥2 occasions	-7
	CPP crystals absent on 1 occasion	-1
	Not performed	0
F	OA of hand/wrist on imaging (defined as present if the Kellgren and Lawrence score is ≥ 2)	
	None of the following findings or no wrist/hand imaging performed	0
	Bilateral radio-carpal joints	2
	≥2 of the following: STTJ OA without 1 st CM CJ OA; 2 nd MCPJ OA; 3 rd MCPJ OA	7
G	Imaging evidence of CPPD in symptomatic peripheral joint(s) ⁵	
	None on US, CT, or DECT (and absent on CR or CR not performed)	-4

	None on CR (and US, CT, DECT not performed)	0
	Present on either CR, US, CT, or DECT	16
H	Number of peripheral joints with evidence of CPPD on any imaging modality ⁵ regardless of symptoms	
	None	0
	1	16
	2-3	23
	≥4	25

⁺ In a peripheral joint or axial joint such as C1/C2 in the case of crowned dens syndrome

* Crowned dens syndrome is defined by the following (A) clinical and (B) imaging features. Both (A) and (B) must be present.

(A) Clinical features: Acute or sub-acute onset of severe pain localized to the upper neck with elevated inflammatory markers, limited rotation, and often fever. Mimicking conditions such as polymyalgia rheumatica and meningitis should be excluded.

(B) Imaging features: Conventional CT with calcific deposits, typically linear and less dense than cortical bone, in the transverse retro-odontoid ligament (transverse ligament of the atlas), often with an appearance of two parallel lines in axial views. Calcifications at the atlanto-axial joint, alar ligament, and/or in pannus adjacent to the tip of the dens are also characteristic. DECT features include a dual-energy index (DEI) between 0.016-0.036(21).

** Sufficient criteria are also met if CPP crystals are demonstrated in histopathology of joint tissue, provided the patient is eligible for classification i.e. does not already meet the exclusion criteria. For instance, articular cartilage CPPD in patients with end-stage osteoarthritis cannot be used to classify the patient as CPPD disease when *all* symptoms are better explained by osteoarthritis (exclusion criteria)

¹Persistent inflammatory arthritis was defined as ongoing joint swelling with pain and/or warmth in ≥1 joint(s).

²Typical episode was defined as an episode with acute onset or acute worsening of joint pain with swelling and/or warmth that resolves irrespective of treatment.

³Hereditary hemochromatosis, primary hyperparathyroidism, hypomagnesemia, Gitelman syndrome, hypophosphatasia, or familial history of CPPD disease.

⁴Synovial fluid analysis should be performed by an individual trained in the use of compensated polarized light microscopy for crystal identification.

⁵Imaging of at least one symptomatic peripheral joint by CR, US, CT, or DECT is required to be considered for classification if sufficient criteria are not met. Imaging evidence of CPPD refers to calcification of the fibrocartilage or hyaline cartilage. Do not score calcification of the synovial membrane, joint capsule, or tendon. Imaging definitions are published elsewhere (21). Only consider involvement of peripheral joints.

Abbreviations: MTPJ metatarsophalangeal joint; CPP calcium pyrophosphate; STTJ scaphotrapeziotrapezoid joint; CMCJ carpometacarpal joint; OA, osteoarthritis; MCPJ metacarpophalangeal joint. US ultrasound; CT computed tomography; DECT dual-energy computed tomography; CR conventional radiography.

Figure 1 Overview of CPPD Classification Criteria development process across the four phases.

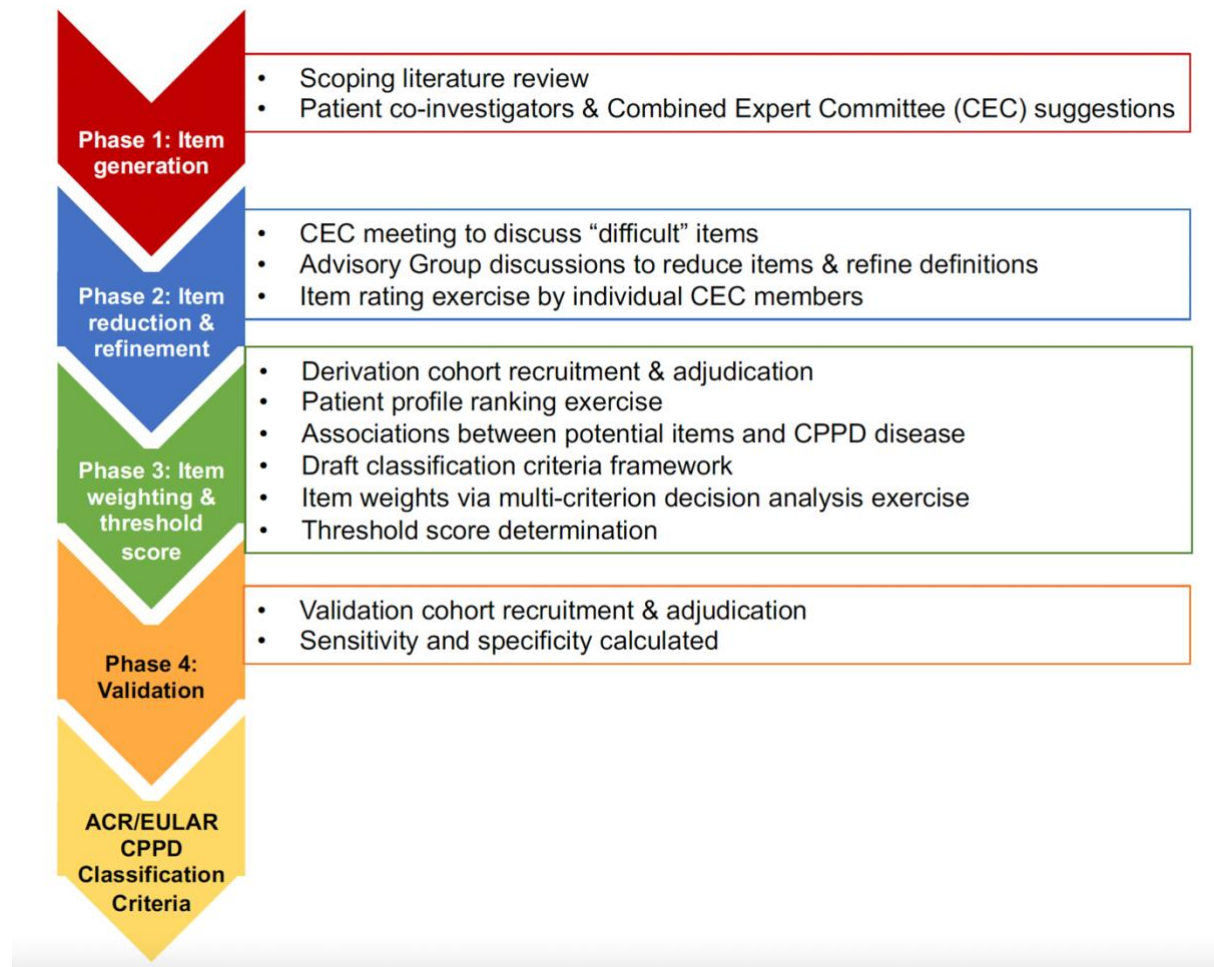


Figure 2: Schematic for applying the CPPD disease classification criteria

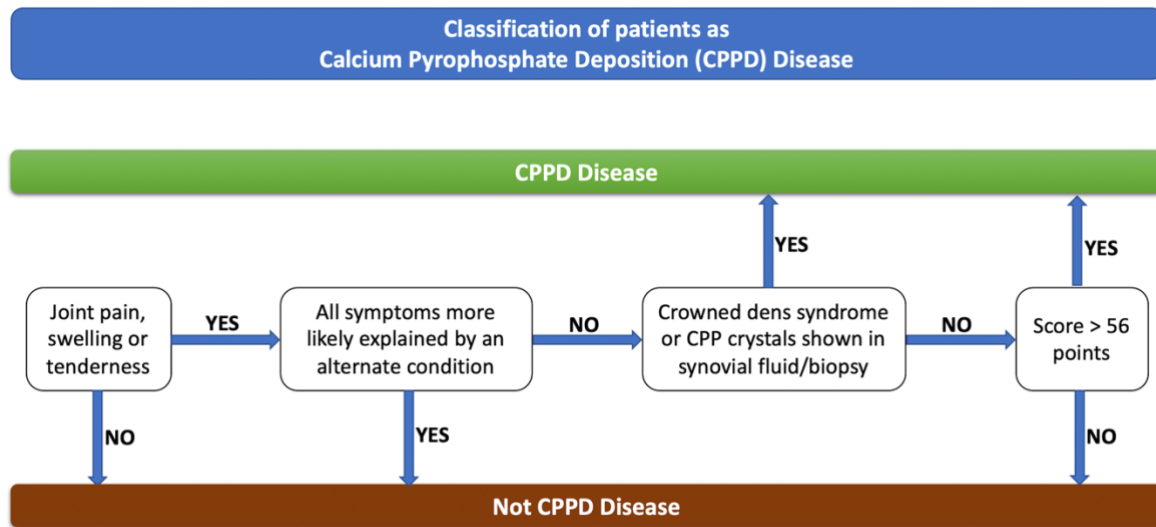


Figure 3 Plot of Steering Committee percentage agreement on classifying patient profiles as CPPD disease for inclusion in a research study (n=8 participating steering committee members). The patient profiles were given pseudonyms.

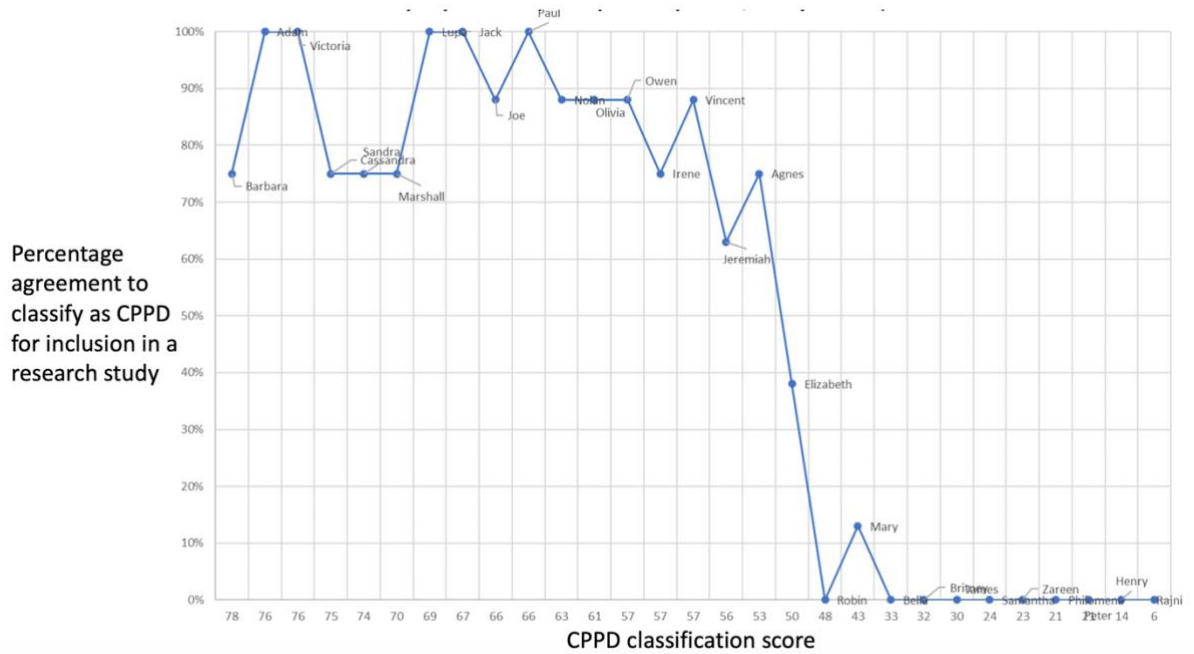
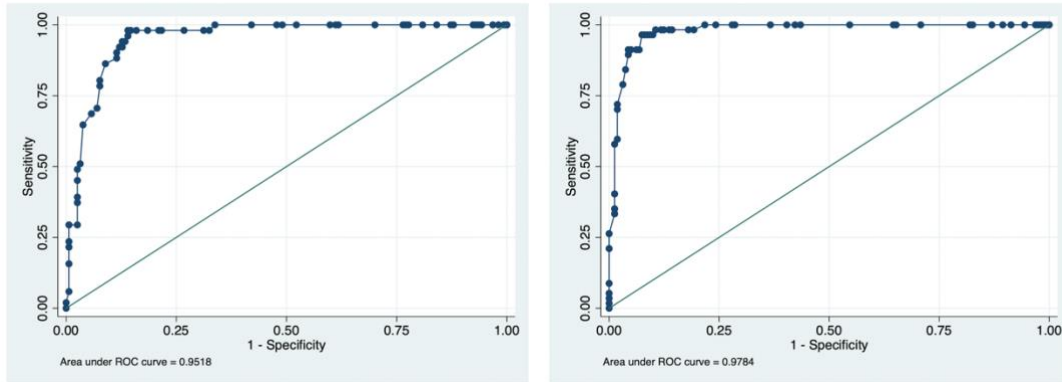


Figure 4 Receiver Operating Characteristic (ROC) curves in derivation cohort (left panel) and validation cohort (right panel) for the patients that were eligible to be scored. In the derivation cohort, data for 60 definite cases and 148 definite mimickers were included. In the validation cohort, data for 65 definite cases and 162 definite mimickers were included.



Supplementary Materials

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Supplementary Methods

Discrete-choice conjoint analysis exercise: Using a multi-criterion decision analysis (MCDA) approach, members of the Combined Expert Committee undertook a discrete-choice conjoint analysis exercise using 1000Minds (<http://www.1000minds.com>) Potentially All Pairwise Rankings of all possible Alternatives (PAPRIKA) software, guided by an experienced facilitator (AH) over four 2-hour virtual meetings. This process involves decision science theory and computer adaptive technology to enable forced-choice trade-offs using pairwise rankings based on 'partial-profiles' of two criteria at a time. Results from pairwise rankings are extended using transitivity principles to reduce cognitive burden from an excessive number of decisions. Using the pairwise ranking results, mathematical methods are used to calculate item weights, representing their relative importance (1).

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Supplementary Results

Assigning relative weights to domains and categories. The Steering Committee reviewed initial item weights for face validity. All weights were initially zero or positive. Domain C (site of typical episodes of inflammatory arthritis) was re-zeroed to maintain face validity such that absence of typical episode(s) scores 0 points rather than 6 points; 6 points were subtracted from all other items in that domain (**Table S10**). This method of subtracting a constant from all values in a domain preserves the relative weight within a domain and does not affect the relative ordering of one patient versus another in terms of likelihood of CPPD disease. Similarly, domain E (synovial fluid analysis) was re-zeroed such that absence of arthrocentesis was re-assigned 0 points and absence of CPP crystals once or twice were re-assigned with -1 and -7 points respectively.

For the domain regarding imaging of a symptomatic joint (domain G), the Steering Committee agreed that absence of imaging evidence of CPPD on advanced imaging modalities (US, CT, or DECT) influences negatively on the likelihood of CPPD given that these modalities are more sensitive than CR and should be able to detect early CPPD. Given concerns about the low sensitivity of CR for CPPD, it was agreed that absence of CPPD on CR should carry no weight. Consequently, the absence of CPPD on advanced imaging was weighted -4 points. Advanced imaging modalities were initially considered separately from CR in this domain; however, item weights differed by <1% so advanced imaging and CR were combined.

Figure S1: Distribution of median rank of 30 patient profiles by 22 members of the Combined Expert Committee (CEC). Patient profile pseudonyms are listed in the first column; each patient profile is represented by one row of data. Within a given row, numbers in the orange shaded boxes indicate the number of CEC members that ranked the patient profile with that particular rank (e.g., 15 CEC members ranked “Charlotte” as most likely to have CPPD disease; 5 CEC members ranked “Charlotte” as 2nd most likely to have CPPD disease; 1 CEC member ranked “Charlotte” as 3rd most likely to have CPPD disease; etc.) Rank 1 indicates most likely to have CPPD disease; rank 30 is least likely.

Patient vs Median Rank	Range	Rank	Difference																																	
				Median	Mean	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	
Charlotte	7	1	2	15	5	1																														
John	12	4	5	2	1	7	6	1	1			2	1		1																					
Benjamin	18	3	5	3	6	3	4	2			1				1	1							1													
Jennifer	17	5	5	2	4	2	1	6	3	2					1																					
Paul	14	4	6	4	3	5	1	2	1	1	2			2		2		1																		
Sandra	17	7	7	1	3	1	2	3	3	4	1	1			1								1		1											
Lupa	13	8	9				3	3	4	4	2	1		1		1	1					1	1													
Jack	15	9	9	1	1		4	1	1	4	4	1		1		3						1														
Nolan	11	12		1	2	1	4	2	1			1	1	1	1	1	1	1	1	1	1	1	2	1	1											
Barbara	24	14	13		1	1		1	2		2	2		2	4		2	1		1	1						2									
Olivia	21	12	13						2	2		2	1	2	4	1	3		1	1				1				1		1						
Joe	21	14	14				1	2		1	1	2	2	1		2	1	3	1		1	2	1						1							
Victoria	20	12	14		1	1		2	3	1	3		1		1	2		1	2		1	2	1		2	1	2	1								
Irene	24	17	15		1	1	2			1	3				2		1	4	1	2	1						2							1		
Vincent	22	16	15		1	1	3						1	1	1	3	3	1	1	1				2		2		2		1						
Marshall	17	16	16				2						2	2	3	2	1	2	1				3	3	1											
Adam	23	18	16		1	1						1	3	1	1		2	1					2	4	1	1		2		1						
Mary	22	16	17				2		2	1	2	2	1		2		4												2	1				2		1
Elizabeth	19	18	18						2	1	1	2	1	1	1	1	1	1	1	1	1			1	2	2	1	2		1						
Cassandra	19	19	18								1				2		1	3	1	2	5	1	2	1	2			1								
Janet	23	20	19				1				1	1	1	1				1	1	4		5	1											1		
Arthur	19	20	19								1	1			2		2				1	3	2	5	2	2		1								
Robin	14	20	19								1	2	1	2	1		2	1	1	2		1	6					2								
Bella	17	21	20								1		1	1	2			1	1	2			3			4	2	1	3							
Philomena	8	25	24																			1		3	4	3	6	2	2	1						
James	13	26	25																			1	1	2	2	1	3	2	5	2	2	2	1			
Peter	11	26	26																			1		1												
Britney	12	27	27																			1		1				2	6	4	4	2	2			
Henry	10	29	28																				1					1	1	3	11	5				
Samantha	6	30	29																								1						2	7	12	

Kendall's W of patient rankings = 0.721, from which the mean Spearman rank correlation can be calculated as approximately 0.711

- # Experts Rank 1
- # Experts Rank 2
- # Experts Rank 3
- # Experts Rank 4
- # Experts Rank 5
- # Experts Rank 6
- # Experts Rank 7
- # Experts Rank 8
- # Experts Rank 9
- # Experts Rank 10
- # Experts Rank 11
- # Experts Rank 12
- # Experts Rank 13
- # Experts Rank 14
- # Experts Rank 15
- # Experts Rank 16
- # Experts Rank 17
- # Experts Rank 18
- # Experts Rank 19
- # Experts Rank 20
- # Experts Rank 21
- # Experts Rank 22
- # Experts Rank 23
- # Experts Rank 24
- # Experts Rank 25
- # Experts Rank 26
- # Experts Rank 27
- # Experts Rank 28
- # Experts Rank 29
- # Experts Rank 30

Table S1: Schematic for patient profile adjudication in the derivation and validation cohorts.

Synovial fluid CPP crystal status	Submitting clinician's rating of likelihood of CPPD disease	Ratings of two blinded adjudicators	Final case-control status (case, control, or uncertain)
Absent, or not done, or not available	-2 or -3	Not adjudicated	Control
	-1, 0, or +1	Not adjudicated	Uncertain
	+2 or +3	Both ≤ -1	Control
		Both $\geq +2$	Case
		Otherwise	Uncertain
Present	$\leq +1$	Both ≤ -1	Control
		Both $\geq +2$	Case
		Otherwise	Uncertain
	+2 or +3	Not adjudicated	Case

Table S2: Case control study of association between candidate clinical and laboratory items and Calcium Pyrophosphate Deposition (CPPD) disease status.

	CPPD disease n=172	Controls n=141	Odds Ratio (95% Confidence Interval)
Age of onset of symptoms			
≤50 years	14 (8.1)	31 (22.1)	1
51-60 years	31 (18.0)	33 (23.6)	2.08 (0.94-4.63)
61-70 years	33 (19.2)	45 (32.1)	1.62 (0.75-3.52)
71-80 years	58 (33.7)	17 (12.1)	7.55 (3.29-17.34)
≥81 years	36 (20.9)	14 (10.0)	5.69 (2.36-13.77)
Acute inflammatory arthritis at the knee (ever)			
No	56 (32.7)	84 (59.6)	1
Yes	115 (67.3)	57 (40.4)	3.03 (1.90-4.81)
Acute inflammatory arthritis at the wrist (ever)			
No	92 (54.1)	76 (54.3)	1
Yes	78 (45.9)	64 (45.7)	1.0 (0.64-1.58)
Acute inflammatory arthritis at the 1 st MTP ¹ joint (ever)			
No	157 (91.8)	99 (70.2)	1
Yes	14 (8.2)	42 (29.8)	0.21 (0.11-0.40)
Episodes of acute inflammatory arthritis			
<i>One typical episode</i>			
No	134 (80.7)	123 (89.1)	1
Yes	32 (19.3)	15 (10.9)	1.96 (1.01-3.79)
<i>More than one typical episode</i>			
No	79 (47.0)	108 (78.3)	1
Yes	89 (53.0)	30 (21.7)	4.06 (2.45-6.72)
Persistent inflammatory polyarthritis			
No	131 (77.1)	80 (57.1)	1
Yes	39 (22.9)	60 (42.9)	0.40 (0.24-0.65)
Metabolic or inherited risk factors			
No	133 (77.3)	129 (91.5)	1
Yes	39 (22.7)	12 (8.5)	3.15 (1.53-6.90)
Synovial fluid crystal analysis negative for intracellular and/or extracellular Calcium Pyrophosphate (CPP) crystals*	n=6	n=58	
Absent once	5 (83.3)	49 (72.1)	1
Absent twice	1 (16.7)	19 (27.9)	0.52 (0.01-5.11)

Data are presented as n (%). Data from the first 313 cases and controls were used in this analysis.¹MTPJ: metatarsophalangeal joint
 *All patients with crowned dens syndrome and/or synovial fluid CPP crystals were classified as cases. This row only includes patient profiles for which joint aspiration was performed and CPP crystals were not seen.

Table S3: Case control study of association between radiographic osteoarthritis in hands and Calcium Pyrophosphate Deposition (CPPD) disease in patients that had imaging of at least one hand.

	CPPD disease	Controls	Odds Ratio (95% Confidence Interval)
Number of MCP ¹ joints affected	n=104	n=80	
0	58 (55.7)	54 (67.5)	1
1	13 (12.5)	7 (8.8)	1.73 (0.64-4.66)
2	9 (8.7)	9 (11.3)	0.93 (0.34-2.52)
3	2 (1.9)	2 (2.5)	0.93 (0.13-6.84)
4	22 (21.2)	8 (10)	2.56 (1.05-6.23)
Number of Scapho-trapezium joints affected	n=105	n=81	
0	52 (49.5)	48 (59.3)	1
1	9 (8.6)	12 (14.8)	0.69 (0.27-1.79)
2	44 (41.9)	21 (25.9)	1.93 (1.01-3.71)
Number of wrists affected	n=105	n=81	
0	62 (59.0)	52 (64.2)	1
1	10 (9.5)	7 (8.6)	1.20 (0.43-3.37)
2	33 (31.4)	22 (27.2)	1.26 (0.65-2.42)
Number of SLAC ² wrists	n=108	n=82	
0	96 (88.9)	77 (93.9)	1
1	9 (8.3)	3 (3.7)	2.41 (0.63-9.20)
2	3 (2.8)	2 (2.4)	1.20 (0.20-7.38)

¹MCPJ: metacarpophalangeal; ²SLAC: scapho-lunate advanced collapse; Data are presented as n (%). Data from the first 313 cases and controls were used in this analysis. The number of cases and controls with imaging data reported for each radiographic finding are noted in each column.

Table S4: Case control study of association between right knee calcification and Calcium Pyrophosphate Deposition Disease (CPPD) disease in patients that had imaging of the right knee.

	CPPD disease	Controls	Odds Ratio (95% Confidence Interval)
<i>Plain radiographs</i>			
Calcification in fibro or hyaline cartilage	n=132	n=90	
<i>No</i>	34 (25.8)	81 (90.0)	1
<i>Yes</i>	98 (74.2)	9 (10.0)	25.94 (11.75-57.24)
Calcification of synovial membrane/capsule/tendon	n=130	n=90	
<i>No</i>	82 (63.1)	83 (92.2)	1
<i>Yes</i>	48 (36.9)	7 (7.8)	6.94 (2.97-16.23)
<i>Computerised Tomography (CT)</i>			
Calcification in fibro or hyaline cartilage	n=28	n=25	
<i>No</i>	5 (17.9)	14 (56.0)	1
<i>Yes</i>	23 (82.1)	11 (44.0)	5.85 (1.68-20.41)
Calcification of synovial membrane/capsule/tendon (n=27)	(n=27)	(n=25)	
<i>No</i>	7 (25.9)	19 (76.0)	1
<i>Yes</i>	20 (74.1)	6 (24.0)	9.05 (2.57-31.84)
<i>Ultrasonography</i>			
Calcification in fibro or hyaline cartilage	n=41	n=30	
<i>No</i>	9 (22.0)	27 (90.0)	1
<i>Yes</i>	32 (78.0)	3 (10.0)	32.0 (7.86-130.21)
Calcification of synovial membrane/capsule/tendon	n=41	n=29	
<i>No</i>	31 (75.6)	29 (100.0)	1
<i>Yes</i>	10 (24.4)	0 (0.0)	-/-
<i>Magnetic Resonance Imaging</i>			
Calcification in fibro or hyaline cartilage	n=8	n=6	
<i>No</i>	4 (50.0)	6 (100.0)	1
<i>Yes</i>	4 (50.0)	0 (0.0)	-/-
<i>Dual-energy CT</i>			
Calcification in fibro or hyaline cartilage	n=16	n=18	
<i>No</i>	2 (12.5)	14 (77.8)	1
<i>Yes</i>	14 (87.5)	4 (22.2)	24.5 (3.84-156.13)
Calcification of synovial membrane/capsule/tendon	n=16	n=18	
<i>No</i>	3 (18.8)	15 (83.3)	1
<i>Yes</i>	13 (81.2)	3 (16.7)	21.67 (3.71-126.47)
Calcification of right knee using any imaging modality	n=146	n=105	
<i>No</i>	33 (22.6)	85 (81.0)	1
<i>Yes</i>	113 (77.4)	20 (19.0)	14.55 (7.81-27.12)

Data are presented as n (%). Data from the first 313 cases and controls were used in this analysis. The number of cases and controls with imaging data reported for each radiographic finding are noted in each column.

Table S5: Case control study of association between left knee calcification and Calcium Pyrophosphate Deposition (CPPD) disease in patients that had imaging of the left knee.

	CPPD disease	Controls	Odds Ratio (95% Confidence Interval)
<i>Plain radiographs</i>			
Calcification in fibro or hyaline cartilage	n=123	n=87	
<i>No</i>	31 (25.2)	81 (93.1)	1
<i>Yes</i>	92 (74.8)	6 (6.9)	40.06 (15.91-100.91)
Calcification of synovial membrane/capsule/tendon	n=122	n=87	
<i>No</i>	78 (63.9)	80 (92.0)	1
<i>Yes</i>	44 (36.1)	7 (8.0)	6.45 (2.74-15.18)
<i>Computerised Tomography (CT)</i>			
Calcification in fibro or hyaline cartilage	n=29	n=26	
<i>No</i>	6 (20.7)	17 (65.4)	1
<i>Yes</i>	23 (79.3)	9 (34.6)	7.24 (2.16-24.24)
Calcification of synovial membrane/capsule/tendon	n=29	n=26	
<i>No</i>	11 (37.9)	20 (76.9)	1
<i>Yes</i>	18 (62.1)	6 (23.1)	5.45 (1.67-17.77)
<i>Ultrasonography</i>			
Calcification in fibro or hyaline cartilage	n=48	n=30	
<i>No</i>	13 (27.1)	28 (93.3)	1
<i>Yes</i>	35 (72.9)	2 (6.7)	37.69 (7.85-181.07)
Calcification of synovial membrane/capsule/tendon	n=46	n=30	
<i>No</i>	37 (80.4)	30 (100.0)	1
<i>Yes</i>	9 (19.6)	0 (0.0)	-/-
<i>Magnetic Resonance Imaging</i>			
Calcification in fibro or hyaline cartilage	n=11	n=10	
<i>No</i>	9 (81.8)	10 (100.0)	1
<i>Yes</i>	2 (18.2)	0 (0.0)	-/-
<i>Dual-energy CT</i>			
Calcification in fibro or hyaline cartilage	n=19	n=20	
<i>No</i>	4 (21.1)	16 (80.0)	1
<i>Yes</i>	15 (78.9)	4 (20.0)	15.0 (3.17-71.0)
Calcification of synovial membrane/capsule/tendon	n=19	n=20	
<i>No</i>	5 (26.3)	16 (80.0)	1
<i>Yes</i>	14 (73.7)	4 (20.0)	11.2 (2.50-50.08)
<i>Calcification of left knee using any imaging modality</i>			
<i>No</i>	26 (19.0)	87 (84.5)	1
<i>Yes</i>	111 (81.0)	16 (15.5)	23.2 (11.72-45.96)

Data are presented as n (%). Data from the first 313 cases and controls were used in this analysis.

The number of cases and controls with imaging data reported for each radiographic finding are noted in each column.

Table S6: Case control study of association between right wrist calcification and Calcium Pyrophosphate Deposition (CPPD) disease in patients that had imaging of right wrist.

	CPPD disease	Controls	Odds Ratio (95% Confidence Interval)
<i>Plain radiographs</i>			
Calcification in fibro or hyaline cartilage	n=118	n=87	
<i>No</i>	45 (38.1)	84 (96.6)	1
<i>Yes</i>	73 (61.9)	3 (3.4)	45.42 (13.5-152.3)
Calcification of synovial membrane/capsule/tendon	n=118	n=87	
<i>No</i>	79 (66.9)	82 (94.3)	1
<i>Yes</i>	39 (33.1)	5 (5.7)	8.10 (3.34-21.59)
<i>Computerised Tomography (CT)</i>			
Calcification in fibro or hyaline cartilage	n=19	n=11	
<i>No</i>	8 (42.1)	8 (72.7)	1
<i>Yes</i>	11 (57.9)	3 (27.3)	3.67 (0.73-18.33)
Calcification of synovial membrane/capsule/tendon	n=19	n=11	
<i>No</i>	12 (63.2)	8 (72.7)	1
<i>Yes</i>	7 (36.8)	3 (27.3)	1.56 (0.31-7.87)
<i>Ultrasonography</i>			
Calcification in fibro or hyaline cartilage	n=39	n=42	
<i>No</i>	5 (12.8)	38 (90.5)	1
<i>Yes</i>	34 (87.2)	4 (9.5)	64.6 (16.03-260.35)
Calcification of synovial membrane/capsule/tendon	n=37	n=42	
<i>No</i>	22 (59.5)	41 (97.6)	1
<i>Yes</i>	15 (40.5)	1 (2.4)	27.95 (3.46-225.88)
<i>Magnetic Resonance Imaging</i>			
Calcification in fibro or hyaline cartilage	n=3	n=3	
<i>No</i>	2 (66.7)	3 (100.0)	1
<i>Yes</i>	1 (33.3)	0 (0.0)	-/-
<i>Dual-energy CT</i>			
Calcification in fibro or hyaline cartilage	n=12	n=5	
<i>No</i>	4 (33.3)	3 (60.0)	1
<i>Yes</i>	8 (66.7)	2 (40.0)	3.0 (0.35-25.87)
Calcification of synovial membrane/capsule/tendon	n=12	n=5	
<i>No</i>	8 (66.7)	3 (60.0)	1
<i>Yes</i>	4 (33.3)	2 (40.0)	0.75 (0.09-6.47)
<i>Calcification of right wrist using any imaging modality</i>			
<i>No</i>	n=128	n=101	1
<i>Yes</i>	30 (23.4)	92 (91.1)	
	98 (76.6)	9 (8.9)	33.39 (15.04-74.12)

Data are presented as n (%). Data from the first 313 cases and controls were used in this analysis. The number of cases and controls with imaging data reported for each radiographic finding are noted in each column.

Table S7: Case control study of association between left wrist calcification and Calcium Pyrophosphate Deposition (CPPD) disease in patients that had imaging of left wrist.

	CPPD disease	Controls	Odds Ratio (95% Confidence Interval)
<i>Plain radiographs</i>			
Calcification in fibro or hyaline cartilage	n=113	n=86	
<i>No</i>	40 (35.4)	80 (93.0)	1
<i>Yes</i>	73 (64.6)	6 (7.0)	24.33 (9.75-60.74)
Calcification of synovial membrane/capsule/tendon	n=112	n=86	
<i>No</i>	73 (65.2)	82 (95.3)	1
<i>Yes</i>	39 (34.8)	4 (4.7)	10.95 (3.73-32.13)
<i>Computerised Tomography (CT)</i>			
Calcification in fibro or hyaline cartilage	n=16	n=9	
<i>No</i>	4 (25.0)	6 (66.7)	1
<i>Yes</i>	12 (75.0)	3 (33.3)	6.0 (1.0-35.91)
Calcification of synovial membrane/capsule/tendon	n=17	n=9	
<i>No</i>	10 (58.8)	6 (66.7)	1
<i>Yes</i>	7 (41.2)	3 (33.3)	1.4 (0.26-7.58)
<i>Ultrasonography</i>			
Calcification in fibro or hyaline cartilage	n=39	n=41	
<i>No</i>	8 (20.5)	37 (90.2)	1
<i>Yes</i>	31 (79.5)	4 (9.8)	35.84 (9.85-130.42)
Calcification of synovial membrane/capsule/tendon	n=37	n=41	
<i>No</i>	21 (56.8)	40 (97.6)	30.48 (3.78-245.95)
<i>Yes</i>	16 (43.2)	1 (2.4)	
<i>Magnetic Resonance Imaging</i>			
Calcification in fibro or hyaline cartilage	n=5	n=1	
<i>No</i>	3 (60.0)	1 (100.0)	1
<i>Yes</i>	2 (40.0)	0 (0.0)	-/-
<i>Dual-energy CT</i>			
Calcification in fibro or hyaline cartilage	n=10	n=3	
<i>No</i>	4 (40.0)	1 (33.3)	1
<i>Yes</i>	6 (60.0)	2 (66.7)	0.75 (0.05-11.31)
Calcification of synovial membrane/capsule/tendon	n=10	n=3	
<i>No</i>	5 (50.0)	1 (33.3)	1
<i>Yes</i>	5 (50.0)	2 (66.7)	0.50 (0.33-7.45)
<i>Calcification of left wrist using any imaging modality</i>			
	n=127	n=100	
<i>No</i>	25 (19.7)	90 (90.0)	1
<i>Yes</i>	102 (80.3)	10 (10.0)	36.72 (16.73-80.60)

Data are presented as n (%). Data from the first 313 cases and controls were used in this analysis. The number of cases and controls with imaging data reported for each radiographic finding are noted in each column.

Table S8: Case control study of association between calcification at other affected site and Calcium Pyrophosphate Deposition (CPPD) disease.

	CPPD	Controls	Odds Ratio (95% Confidence Interval)
<i>Plain radiographs</i>			
Calcification in fibro or hyaline cartilage	n=55	n=47	
<i>No</i>	31 (56.4)	47 (100.0)	1
<i>Yes</i>	24 (43.6)	0 (0.0)	-/-
Calcification of synovial membrane/capsule/tendon	n=54	n=47	
<i>No</i>	37 (68.5)	42 (89.4)	1
<i>Yes</i>	17 (31.5)	5 (10.6)	3.86 (1.30-11.50)
<i>Computerised Tomography (CT)</i>			
Calcification in fibro or hyaline cartilage	n=26	n=19	
<i>No</i>	7 (26.9)	17 (89.5)	1
<i>Yes</i>	19 (73.1)	2 (10.5)	23.07 (4.21-126.6)
Calcification of synovial membrane/capsule/tendon	n=27	n=19	
<i>No</i>	8 (29.6)	17 (89.5)	1
<i>Yes</i>	19 (70.4)	2 (10.5)	20.19 (3.75-108.53)
<i>Ultrasonography</i>			
Calcification in fibro or hyaline cartilage	n=26	n=19	
<i>No</i>	10 (38.5)	19 (100.0)	1
<i>Yes</i>	16 (61.5)	0 (0.0)	-/-
Calcification of synovial membrane/capsule/tendon	n=25	n=19	
<i>No</i>	16 (64.0)	16 (84.2)	1
<i>Yes</i>	9 (36.0)	3 (15.8)	3.0 (0.68-13.17)
<i>Magnetic Resonance Imaging</i>			
Calcification in fibro or hyaline cartilage	n=3	n=0	
<i>No</i>	3 (100.0)	0 (0.0)	1
<i>Yes</i>	0 (0.0)	0 (0.0)	-/-
<i>Dual-energy CT</i>			
Calcification in fibro or hyaline cartilage	n=4	n=5	
<i>No</i>	2 (50.0)	5 (100.0)	1
<i>Yes</i>	2 (50.0)	0 (0.0)	-/-
Calcification of synovial membrane/capsule/tendon	n=5	n=5	
<i>No</i>	3 (60.0)	5 (100.0)	1
<i>Yes</i>	2 (40.0)	0 (0.0)	-/-
<i>Any imaging modality</i>			
	n=76	n=55	
<i>No</i>	14 (18.4)	46 (83.6)	1
<i>Yes</i>	62 (81.6)	9 (16.4)	22.63 (9.02-56.81)

Data are presented as n (%). Data from the first 313 cases and controls were used in this analysis. The number of cases and controls with imaging data reported for each radiographic finding are noted in each column.

Table S9: Number of affected sites with Calcium Pyrophosphate Deposition (CPPD) disease on imaging among patient profiles that had at-least one joint imaged

Number	CPPD n=172	Controls n=141	Odds Ratio (95% Confidence Interval)
0	15 (8.7)	108 (76.6)	1
1	30 (17.4)	14 (9.9)	15.43 (6.71-35.49)
2	25 (14.5)	11 (7.8)	16.36 (6.71-39.90)
3	30 (17.4)	4 (2.8)	54.0 (16.68-174.82)
4	44 (25.6)	4 (2.8)	79.20 (24.90-251.96)
5	28 (16.3)	0 (0.0)	-/-

Data are presented as n (%). Data from the first 313 cases and controls were used in this analysis. The number of cases and controls with imaging data reported for each radiographic finding are noted in each column.

Table S10: Evolution of Calcium Pyrophosphate Deposition (CPPD) disease classification criteria items and weights

Domains and levels		Raw weights	Re-zeroed weights	Adjust items with diff. <1	Final weights
A	Age at onset of joint symptoms				
	≤60 years	0	0	0	0
	>60 years	4	4	4	4
B	Time-course and symptoms of inflammatory arthritis				
	No persistent or typical inflammatory arthritis	0	0	0	0
	Persistent inflammatory arthritis	9	9	9	9
	1 typical episode	12.4	12.4	12.4	12
	More than 1 typical episode	15.8	15.8	15.8	16
C	Sites of typical episode(s) of inflammatory arthritis				
	1 st MTPJ	0	-5.9	-5.9	-6
	No typical episode(s)	5.9	0	0	0
	Joint(s) other than wrist, knee or 1 st MTPJ	10.6	4.7	4.7	5
	Wrist	13.5	7.6	7.6	8
	Knee	15.2	9.3	9.3	9
D	Related metabolic diseases¹				
	None	0	0	0	0
	Present	6.5	6.5	6.5	6
E	Synovial fluid crystal analysis from a symptomatic joint				
	CPP crystals absent on ≥2 occasions	0	-7.1	-7.1	-7
	CPP crystals absent on 1 occasion	5.9	-1.2	-1.2	-1
	Not performed	7.1	0	0	0
F	OA of hand/wrist on imaging				
	None of the following findings	0	0	0	0
	No wrist/hand imaging performed	0.6	0.6		
	Bilateral radio-carpal joints	2.2	2.2	2.2	2
	≥2 of following: STTJ OA without 1 st CMCJ OA; 2 nd or 3 rd MCPJ OA	6.5	6.5	6.5	7
G	Imaging evidence of CPPD in symptomatic joint(s)				
	None on US, CT, or DECT (and absent on CR or CR not performed)	0	-3.7	-3.7	-4
	None on CR (and US, CT, DECT not performed)	3.7	0	0	0
	Present on US, CT, or DECT	19.3	15.6	16.2	16
	Present on CR	19.9	16.2		
H	Number of peripheral joints with evidence of CPPD on any imaging modality regardless of symptoms				
	None	0	0	0	0
	1	16.1	16.1	16.1	16
	2-3	23.3	23.3	23.3	23
	≥4	24.8	24.8	24.8	25

¹ These included hereditary hemochromatosis, primary hyperparathyroidism, hypomagnesemia, Gitelman syndrome, hypophosphatasia, or familial history of CPPD disease. Abbreviations: MTPJ metatarsophalangeal joint; CPP calcium pyrophosphate; STTJ scaphotrapezio-trapezoid joint; CMCJ carpometacarpal joint; OA, osteoarthritis; MCPJ metacarpophalangeal joint. US ultrasound; CT computed tomography; DECT dual-energy computed tomography; CR conventional radiography.

Table S11: Performance characteristics in the derivation cohort (n=60 definite cases and n=148 mimickers) around the preliminary threshold score of >56.

Threshold score	Sensitivity	Specificity
>49	94.1	87.3
>55	92.2	87.3
>56	92.2	87.9
>61	90.2	88.5
>62	88.2	88.5

Table S12: Performance characteristics across submitting expert’s rating for likelihood of Calcium Pyrophosphate Deposition (CPPD) disease.

Submitting expert’s rating for likelihood of CPPD disease							
	-3	-2	-1	0	+1	+2	+3
Derivation cohort							
Number of cases	99	50	16	26	20	60	147
N (%) classified as CPPD	9 (9.1%)	5 (10.0%)	6 (37.5%)	15 (57.8%)	15 (75.0%)	46 (76.7%)	145 (98.7%)
Validation cohort							
Number of cases	71	90	37	43	105	116	155
N (%) classified as CPPD	2 (2.8%)	11 (12.2%)	9 (24.3%)	25 (58.1%)	79 (75.2%)	102 (88.0%)	149 (96.1%)