Evidence-based Practice Center Systematic Review Protocol

Project Title: Diagnosis of Gout

I. Background and Objectives for the Systematic Review

Gout is a form of inflammatory arthritis characterized by acute intermittent episodes of synovitis presenting with joint swelling and pain (referred to as acute gouty arthritis) that may progress to a chronic intermittent condition, which may progress further to development of tophi (solid deposits of monosodium urate [MSU] crystals in joints, cartilage, and bones), a condition called chronic tophaceous gout.

Based on data from the 2007-2008 National Health and Nutrition Examination Survey (NHANES), the prevalence of gout among adults in the United States was estimated to be 3.9 percent (8.3 million individuals), ranging from 2.0 percent in women to 5.9 percent in men.[1] Comparing the most recent figures for the prevalence of gout to those of previous cycles of NHANES shows that the prevalence of gout appears to be increasing. The rise in the prevalence of gout has paralleled the increase in prevalence of conditions associated with hyperuricemia, including obesity, hypertension, hypertriglyceridemia, hypercholesterolemia, type 2 diabetes and metabolic syndrome, chronic kidney disease, and renal insufficiency. Certain medications also may increase the risk for developing gout (e.g., thiazide diuretics).

A 2013 study estimated the annual costs of gout to be $933 million (in 2008 figures), with the annual ambulatory care costs associated with gout potentially reaching $1 billion. Some 32 percent of the costs were attributed to gouty arthritis attacks, and drug expenditures accounted for 61 percent of the total costs.[2]

Etiology of Gout. The driving force behind acute episodes of gout is hyperuricemia (defined as a serum uric acid (strictly, urate, sUA) concentration greater than 6.8 mg per deciliter [dl] in men and greater than 6.0 in women). Hyperuricemia can be the result of either inadequate renal excretion of UA or, less commonly, UA overproduction (UA is a breakdown product of dietary or endogenous purines, which are among the building blocks of nucleic acids); and is associated with the formation and deposition of the UA crystals, which preferentially dissolve, in joints, tendons, and bursa spaces. Despite the prevalence of hyperuricemia, for reasons that remain unclear, only a small proportion of individuals with hyperuricemia go on to develop gout; in the rest, hyperuricemia remains asymptomatic.[3] The prevalence of hyperuricemia ranges from 21.2 percent in men to 21.6 percent in women, four- to ten-fold higher than the prevalence of gout.

The causes of gout are multifactorial, including a combination of genetic, hormonal, metabolic, pharmacologic, renal disease, and dietary factors. Family history, advancing age, male sex, or, in women, early menopause have been associated with a higher risk of gout and/or gout flares.[4] Dietary risk factors for gout appear to include alcohol consumption, as well as consumption of meat, seafood, sugar sweetened soft drinks, and foods high in fructose, whereas dairy foods and coffee have been associated with a lower

risk of incident gout and in some cases a lower rate of gout flares. However, the role of diet in the etiology and treatment of gout is a topic of considerable research and will be reviewed in a separate systematic review.

Diagnosis of Gout: Definitive diagnosis of gout requires laboratory confirmation of joint/synovial fluid MSU in the setting of an acute inflammatory arthritis.[5] In 2006, the European League Against Rheumatism (EULAR) issued guidelines for diagnosis of gout based on a systematic review of the evidence and a modified Delphi approach: the factors with the strongest evidence to confirm the diagnosis of gout included the presence of needle-like MSU crystals, showing strong negative birefringence by polarized microscopy in synovial fluid; whereas a clinical diagnosis, hyperuricemia, or radiological evidence alone were not considered definitive, they did document high likelihood of gout.[6] Newer diagnostic methods are under evaluation, including dual-energy computed tomography (DECT), and high resolution ultrasound.[7]

The majority of individuals with gout are initially seen, diagnosed, and treated in primary and urgent care settings. Therefore primary care physicians (PCPs) and emergency medicine physicians are well-positioned to diagnose early-stage gout and implement management strategies. However, use of the gold standard synovial fluid analysis for diagnosis of gout is difficult and seldom performed in the primary care setting.[8] Instead, PCPs and emergency medicine physicians may tend to rely on a combination of clinical signs and symptoms to diagnose an acute episode of gout. In fact, evidence from a 2011 survey of rheumatologists suggests that SF analysis is underused in the rheumatology setting as well.[9] Ultrasound and dual-energy computed tomography (DECT) are just beginning to be used to diagnose gout in some settings.

Therefore a systematic review delineating the accuracy of tests used to diagnose gout, including physical findings, serum UA, ultrasound (US), plain radiography, and dual-energy computed tomography (DECT), compared with synovial fluid UA can be used to inform clinical decision-making for patients and providers and improve the quality of care for patients with gout in the primary and acute care setting. A question of interest is whether any combination of clinical signs and symptoms and laboratory tests accessible in the primary or acute care setting will have good predictive value compared with tests such as joint aspiration and synovial fluid analysis and how the newer methods compare with joint aspiration and synovial fluid analysis in their predictive value. A simultaneous review is being conducted on the management of acute and chronic gout.

A set of draft key questions encompassing both diagnosis and treatment of gout were posted for public comment from 1/22/14 to 2/11/14. The remainder of this protocol considers only the questions pertaining to diagnosis. There will be a separate protocol and systematic review related to management of gout.. The revisions to this question based on the public comments and our rationale for the changes are presented in the next section, below.

II. The Key Questions

The original key question on diagnosis of gout was divided into two questions. In response to the public comments and input from the Technical Expert Panel (TEP) for the review on diagnosis of gout, the testing of urinary uric acid was removed and "plain X-

ray" was added. Several public and TEP comments noted that urinary uric acid is not commonly used and plain x-ray is sometimes used in primary care settings. Symptom duration was identified as an important factor to consider; therefore an additional subquestion was added to address this issue. The role of the affected joint site on diagnostic accuracy was also combined with KQ1.

1. Question segments:
   a. What is the accuracy of clinical signs and symptoms and other diagnostic tests (such as serum uric acid, ultrasound, CT scan, DECT, and plain x-ray), alone or in combination, compared to synovial fluid analysis in the diagnosis of acute gouty arthritis, and how does the accuracy affect clinical decision making, clinical outcomes and complications, and patient centered outcomes?
   b. How does the diagnostic accuracy of clinical signs and symptoms and other tests vary by affected joint site and number of joints?
   c. Does the accuracy of diagnostic tests for gout vary by duration of symptoms (i.e., time from the beginning of a flare)
   d. Does the accuracy of synovial fluid aspiration and crystal analysis differ by i) the type of practitioner who is performing the aspiration and ii) the type of practitioner who is performing the crystal analysis?
2. What are the adverse effects associated with each diagnostic test (including pain, infection at the aspiration site, radiation exposure) or harms (related to false positives, false negatives, indeterminate results) associated with tests used to diagnose gout?

PICOTs

- **Population(s) (KQ1 and 2):**
  - Adults (18 years and over) presenting with symptoms (e.g., an acute episode of joint inflammation) suggestive of gout, including the following subgroups:
    - Male and female patients
    - Older (65 and over) and younger patients
    - Patients with comorbidities including hypertension, type 2 diabetes, kidney disease (renal insufficiency)
    - Patients with osteoarthritis, septic arthritis, or previous joint trauma
    - Individuals with a family history of gout
- **Interventions (KQ1, 2):**
  - Clinical history and physical exam
  - Serum uric acid assessment
  - US
  - DECT
  - Plain x-ray
  - Joint aspiration by physicians and synovial fluid analysis using polarizing microscopy (by physicians or laboratory personnel)

- Combinations of these tests as identified in the literature

- **Comparators:**
  - Joint synovial fluid aspiration and microscopic assessment for monosodium urate crystals (KQ1a-c, 2)
  - Joint synovial fluid aspiration and microscopic assessment for monosodium urate crystals as performed by a practitioner with a different level of expertise or experience, e.g. rheumatologist, laboratory personnel (KQ1d)

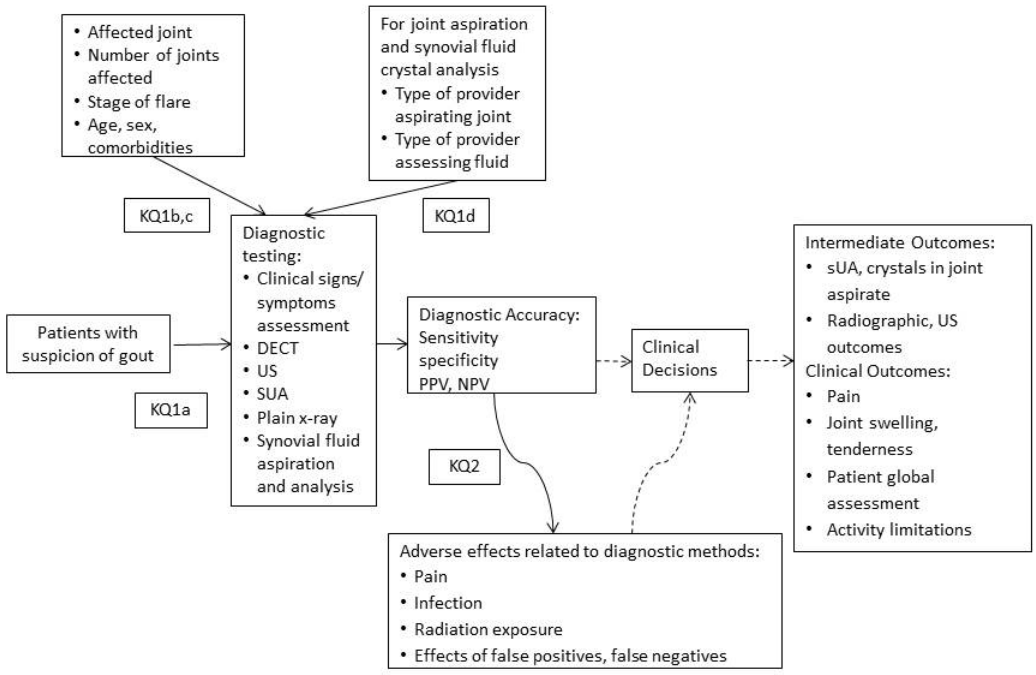
- **Outcomes**
  - Diagnostic accuracy of clinical signs and symptoms, US, DECT, plain radiographs compared with joint aspiration and synovial fluid analysis (KQ1)
    - sensitivity/specificity, true positives/true negatives, area under the curve
    - positive, negative predictive value, positive/negative likelihood ratios (if prevalence known)
  - Clinical decisionmaking
    - Additional testing
    - Pharmacologic/dietary management
  - Intermediate outcomes
    - sUA
    - Synovial fluid crystals
    - radiographic or US changes
  - Clinical outcomes:
    - pain, joint swelling and tenderness,
    - patient global assessment, and activity limitations (KQ1,2)[10]
  - Adverse effects of the tests, including
    - pain, infection, radiation exposure and
    - effects of false positive or false negative (KQ2)

- **Timing:**
  - For clinical outcomes of symptom relief: 1-2 days minimum (KQ1)
  - Early in a flare vs. later or post-flare (KQ1c)
  - For adverse events: immediate

- **Settings:**
  - Primary care (outpatient) or acute care setting, preferentially;
  - Outpatient rheumatology practices/academic medical centers

III. Analytic Framework

Figure 1. Analytic framework for diagnosis of gout



IV. Methods

In general, this systematic review will follow the procedures of the Methods Guide for Medical Test Reviews.

Criteria for Inclusion/Exclusion of Studies in the Review - Included studies will be limited to those that fit the PICOTs described above, namely those that compare the sensitivity and specificity of a proposed diagnostic test (see list below) or clinical criterion, or a combination of tests and clinical criteria for diagnosing gout, with that of joint aspiration and microscopic synovial fluid analysis for monosodium urate crystals in adults 18 years of age and over, with suspicion of gout. Studies will also be included if they compare the accuracy of synovial fluid aspiration and analysis between types of providers. Tests to be included are clinical examination for physical signs, symptoms, and history; ultrasonography; DECT; and plain radiography. Comparators will be microscopic synovial fluid analysis. Outcomes will be the accuracy of the test results (the sensitivity and specificity or the positive and negative predictive value of the test in question), intermediate outcomes such as lab and radiographic test results, clinical decision making, short term clinical (patient-centered) outcomes such as pain and joint

swelling, and any adverse events (including adverse patient experiences such as pain or infection at the aspiration site, effects of radiation exposure, and the results of a false positive or negative) associated with the test. We will also include high quality systematic reviews that address accuracy of the included diagnostic methods.

The results of the report are intended for primary care and acute care settings; however it is understood that the studies of interest might be conducted in academic and other specialty medical settings.

Studies that measure sensitivity and specificity for a test or combination of tests to diagnose gout or report the area under the curve (receiver operator characteristics [ROC]) compared with joint aspiration and synovial fluid analysis will be included for KQ 1. Randomized controlled trials as well as prospective cohort and case control studies that compare outcomes based on the lag between the onset of symptoms and diagnosis (commencement of treatment) will be included for KQ2. Prospective cohort, case control, and case series of any size, as well as case reports of rare adverse events will be included for key question 2, in anticipation that few studies will address the question of adverse outcomes or patient satisfaction with diagnostic procedures. The search will commence with the year 1945, the initial search date for the 2006 EULAR guidelines, which were based on a systematic review; we will also cross-check the references of the 2006 review to ensure the reported references are included in our search results and modify the searches if they are not. Searches will not be limited by language of publication; non-English studies that meet the inclusion/exclusion criteria based on English abstracts will be screened further in full text if translators can be identified with reasonable effort.

Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions – The search strategy was designed by our reference librarian in collaboration with our local content expert, who has participated in two systematic reviews on gout; the search strategy appears in an appendix at the end of this protocol. As recommended by the Methods Guide for Medical Test Reviews,[11] the searches will not use filters specific for diagnostic tests but instead will use the terms "gout" combined with the terms for the diagnostic tests. We will search PubMed (1946 to the present), EMBASE (1972 to the present), the Cochrane Collection (1945 to the present), and the Web of Science (from 1949 to the present). We will search Clinicaltrials.gov for recently completed studies and will also conduct a search for grey literature. Manufacturers of diagnostic equipment (polarizing microscopes) will be contacted for unpublished data specific to their use for gout diagnosis. Any relevant studies identified for the searches we are conducting for a simultaneous review on management of gout will also be included if not identified in the searches for this review. Finally, we will ask the TEP to assess our included studies and to provide references for any studies they believe should also be included. An update search will be conducted after submission of the draft report for peer review.

The DistillerSR software package will be used to manage the search outputs, screening, and data abstraction. Titles and abstracts identified by the searches will be dually screened by the literature reviewers, and all selected by either reviewer will be accepted without reconciliation for further, full-text review. Full-text review will also be

conducted by dual reviewers. Disagreements regarding inclusion at the full-text stage will be reconciled, with the input of the project lead if necessary. Included studies will go on for dual abstraction of study-level details and outcomes and for assessment of risk of bias. Studies identified in the update searches, provided in scientific information packets, or suggested by peer reviewers will undergo the same process.

Data Abstraction and Data Management – Data abstraction will follow the procedures described above. Data collection forms will be designed by the project team in Distiller SR, piloted by the reviewers, further modified, and then the final forms piloted with a random selection of included studies to ensure agreement of interpretation. Studies based on large prospective cohorts will be identified in their Distiller records to allow comparison to ensure data are not duplicated. Study-level data will include PICOTs, inclusion/exclusion criteria, study design, comorbidities, other potential effect modifiers (such as prior history of similar symptoms and joints involved), analytic methods, and characteristics necessary to assess risk of bias, including recruitment, blinding, allocation concealment, description of completeness of final dataset, funding source, and other potential conflicts of interest. Data abstracted from SRs will include the inclusion and exclusion criteria of the reviews, total numbers of participants included in analyses, conclusions with strength of evidence grades and domains, and the included original studies[12]; if multiple SRs address the same question and are included, we will construct a matrix to compare included studies to help address any differences in conclusions. At the end of the project, abstracted data will be uploaded to the Systematic Review Data Repository.

Assessment of Methodological Risk of Bias of Individual Studies - Risk of bias of individual included studies will be assessed using QUADAS-2, the tool recommended in the Methods Guide for Medical Test Reviews (chapter 5).[13, 14] In particular we will focus on assessment of systematic error that could affect the sensitivity and specificity measures. We will use AMSTAR to assess the quality of existing systematic reviews that we include.[15]

Data Synthesis –For the key question pertaining to test accuracy, studies that report the sensitivity, specificity, positive and negative predictive value, or receiver-operating characteristics, or provide the data to perform such calculations, may be potentially included in a synthesis. If three or more studies are deemed sufficiently homogeneous with respect to outcome measures, participants, and tests, we will consider pooling outcomes. For studies that assess the validity of an alternative diagnostic method against that of analysis of monosodium urate crystals in synovial fluid, we will pool sensitivities, specificities, and overall area under the curve.. If sufficient numbers of studies report positive and negative predictive value or if we can estimate these values, we will pool them. Synovial fluid analysis is used as the reference standard in many studies of gout diagnosis, but its identity as the gold standard remains controversial; therefore, we will consider these outcomes as naïve estimates and interpret study findings accordingly. If we are able to identify a sufficient number of studies that use similar relevant long-term outcomes (such as development of tophi, repeated flares that respond to urate lowering therapies) as the reference, we will consider pooling these studies. If

appropriate, sensitivity analysis will be conducted by age group and particular comorbidities, such as hypertension, type 2 DM, or renal insufficiency.

Summary Receiver Operating Characteristic (ROC) curves will be estimated by plotting sensitivity versus 1-specificity and "area under the curve" will be calculated. Studies will be weighted by sample size.

For studies where pooling is clearly not an option, outcomes will be described narratively, stratified by test comparisons of interest and study design, and presented in summary tables. For key questions 1b-d , which assess the validity of diagnostic tests and the potential influence of patient- and provider-level factors including affected joints, only within-study comparisons may be included.

If any prior SRs are identified that we deem of high enough quality to include, we will determine whether any subsequent (or contemporaneous) original studies are sufficiently homogeneous with the review to consider conducting new quantitative synthesis for a particular outcome: this decision will be based on whether the new study represents a potential pivotal finding in terms of size and effect size and the availability of the needed data. Alternatively, we will conduct a qualitative synthesis.

Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes We will assess the overall strength of evidence by using guidance suggested by AHRQ for its Effective Health Care Program.[16] This method is based loosely on one developed by the GRADE Working Group and classifies the grade of evidence as High, Moderate, Low. or Insufficient. The evidence grade is based on five required domains: study limitations, consistency, directness, precision, and publication bias. Publication bias will be assessed using the Begg adjusted rank correlation test[17] and Egger regression asymmetry test[18]; selective outcome reporting bias will also be assessed as part of the risk of bias assessment for individual studies. Three additional domains (plausible confounding, dose-response, and magnitude of effect) can also be included if appropriate. Assessing the SOE of diagnostic test studies is challenging because of the difficulty in identifying studies that include long-term, clinical outcomes and in applying standards of precision to these studies. Assessing the SOE of the body of literature on gout diagnostic methods may be especially challenging, given the limitations of the oldest, gold standard method, the newness of most methods that rely on imaging, and the heterogeneity of studies that employ clinical signs and symptoms (algorithms). To the extent possible, we will focus on risk of bias and consistency among studies and will narratively describe particular strengths and limitations.

Assessing Applicability –Applicability assessment will be based on the PICOTS and include the study population age, sex, and health profiles (including comorbidities as well as duration of symptoms and number of affected joints, when relevant), the interventions, and gold standards used. Study settings and provider types will also be considered, as the focus of this report is on diagnosis in primary and acute care settings. Our methods will reflect the most recent AHRQ guidance on the topic.[19]

V. References

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VI. Definition of Terms

DECT: dual-energy computed tomography

FN: false negative

FP: false positive

MSU: monosodium urate

NPV: negative predictive value

PPV: positive predictive value

sUA: serum uric acid

US: ultrasound

VII. Summary of Protocol Amendments

If we need to amend this protocol, we will give the date of each amendment, describe the change and give the rationale in this section. Changes will not be incorporated into the protocol. Example table below:

Date	Section	Original Protocol	Revised Protocol	Rationale
This should be the effective date of the change in protocol	Specify where the change would be found in the protocol	Describe the language of the original protocol.	Describe the change in protocol.	Justify why the change will improve the report. If necessary, describe why the change does not introduce bias. Do not use justification as "because the AE/TOO/TEP/Peer reviewer told us to" but explain what the change hopes to accomplish.

VIII. Review of Key Questions

AHRQ posted the key questions on the Effective Health Care Website for public comment. The EPC refined and finalized the key questions after review of the public comments, and input from Key Informants and the Technical Expert Panel (TEP). This input is intended to ensure that the key questions are specific and relevant.

IX. Key Informants

Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform healthcare decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor do they contribute to the writing of the report. They have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparation of the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published three months after the publication of the evidence report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XII. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than $1,000 will usually disqualify EPC core team investigators.

XIII. Role of the Funder

This project was funded under Contract No. xxx-xxx from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

Appendix A. Search Strategy

–gout OR gouty

AND

X-ray* OR radiograph* OR erosion OR diagnostic imaging[mh] OR radiography [Subheading] OR Computed tomography OR Computer tomography OR dual energy CT OR DECT OR Radiography, Dual-Energy Scanned Projection[mh] OR Ultrasound OR Ultrasonography[mh] OR Ultrasonography[sh] OR double contour OR radionuclide imaging [Subheading] OR (polariz* AND microscop*) OR Joint aspiration OR Serum urate OR Uric acid OR Crystal* OR Tophi OR tophus OR tophaceous OR Synovial fluid OR Urate OR kidney stones OR Kidney Calculi[mh] OR urate stones OR gouty nephropathy OR Hyperuricemia OR clinical symptom*AND Accura* OR Sensitivity and specificity[mh] OR Sensitivity[tiab] OR Specificity[tiab] OR False positive reactions[mh] OR false positive* OR False negative reactions[mh] OR False negative* OR Predictive value OR predictive value of tests[mh] OR Distinguish* OR Differential* OR Identif* OR Detect* OR valid* OR reliab* OR reproducibility of results

Publication date from 1945/01/01 to present