A Diagnostic Rule for Acute Gouty Arthritis in Primary Care Without Joint Fluid Analysis

Hein J. E. M. Janssens, MD; Jaap Fransen, PhD; Eloy H. van de Lisdonk, MD, PhD; Piet L. C. M. van Riel, MD, PhD; Chris van Weel, MD, PhD; Matthijs Janssen, MD, PhD

Background: Most cases of acute gouty arthritis are diagnosed in primary care and without joint fluid analysis in many instances. Our objectives were to estimate the validity of this diagnosis by family physicians and to develop a diagnostic rule.

Methods: Patients with monoarthritis recruited in an open Dutch population with gout by family physician diagnosis were enrolled in a diagnostic study (March 24, 2004, through July 14, 2007). Validity variables were estimated using $2 \times 2$ tables, with the presence of synovial monosodium urate crystals as the reference test. For development of the diagnostic rule, clinical variables (including the presence of synovial monosodium urate crystals) were collected within 24 hours. Statistically significant variables and predefined variables were separately entered in multivariate logistic regression models to predict the presence of synovial monosodium urate crystals. Diagnostic performance of the models was tested by receiver operating characteristic curve analysis. The most appropriate model was transformed to a clinically useful diagnostic rule.

Results: Three hundred twenty-eight patients were included in the study. The positive and negative predictive values of family physician diagnosis of gout were 0.64 and 0.87, respectively. The most appropriate model contained the following predefined variables: male sex, previous patient-reported arthritis attack, onset within 1 day, joint redness, first metatarsophalangeal joint (MTP1) involvement, hypertension or 1 or more cardiovascular diseases, and serum uric acid level exceeding 5.88 mg/dL (to convert serum uric acid level to micromoles per liter, multiply by 59.485). The area under the receiver operating characteristic curve for this model was 0.85 (95% confidence interval, 0.81-0.90). Performance did not change after transforming the regression coefficients to easy-to-use scores and was almost equal to that of the statistically optimal model (area under the receiver operating characteristic curve, 0.87; 95% confidence interval, 0.83-0.91).

Conclusions: The validity of family physician diagnosis of acute gouty arthritis was moderate in this study. An easy-to-use diagnostic rule without joint fluid analysis was developed for their use.

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Gout is a common medical problem affecting many patients worldwide. The annual incidence ranges from 62 to 180 cases per 100 000 and the annual prevalence from 940 to 1400 cases per 100 000, and approximately 0.1 million US adults 20 years or older have had gout. Primary care physicians diagnose and manage most patients with gout. Less than 10% of patients diagnosed as having gout are referred to rheumatologists. In primary care, this diagnosis is based on clinical signs and symptoms, usually without synovial fluid analysis for the presence of monosodium urate (MSU) crystals, which is the reference test for the diagnosis. We found no evidence to suggest that joint aspiration is unnecessary for diagnosis of gout in primary care.

The number of patients involved renders it more than a theoretical issue to gain greater insight into the validity of gout diagnosed by physicians in primary care. Failure to diagnose gout and incorrect diagnosis of gout may have adverse consequences (equivalent to withholding appropriate management) for many patients.

Therefore, we studied the validity of acute gouty arthritis diagnosed by family physicians, with the presence of synovial MSU crystals as the reference test. From the signs and symptoms of patients, we developed and internally validated prediction models with the objective to develop a diagnostic rule without need for joint fluid analysis.

Author Affiliations: Departments of Primary and Community Care (Drs Janssens, van de Lisdonk, and van Weel) and Rheumatology (Drs Fransen and van Riel), Radboud University Nijmegen Medical Center, Nijmegen, and Department of Rheumatology, Rijnstate Hospital, Arnhem (Dr Janssen), the Netherlands.

METHODS
DESIGN, DOMAIN, AND CONTEXT

We performed a prospective diagnostic study of patients in primary care with a high priori probability of acute gouty arthritis. These in-
cluded patients seen with signs and symptoms of a monoa-
thritis by Dutch family physicians (FPs) irrespective of whether this was an index case of arthritis or a recurrent episode or whether a previous episode was considered gout. Within 24 hours of presentation to the FP, the affected joint was aspi-
rated, and synovial fluid was analyzed for the presence of MSU
crystals. In all eligible patients, gout diagnosis by participat-
ing FPs was evaluated using 2 × 2 tables, with the presence of
MSU crystals as the reference test. After this, prediction mod-
els were developed and validated in patients with gout by FP
diagnosis using multivariate logistic regression analysis by link-
ing the presence of MSU crystals to clinical variables. The ra-
tionale was that further diagnostic procedures for detecting gout
would generally only be pursued in patients who were sus-
pected by physicians of having the disease.

The study was conducted in the eastern part of the Nether-
lands among a population of about 330,000 inhabitants (March
24, 2004, through July 14, 2007). The FP practices that eventu-
ally participated in the study covered 180,000 to 200,000 of
this population. In the Netherlands, all inhabitants are regis-
tered with a personal FP who provides primary care for about
2000 to 3000 people and who refers patients for secondary
medical care to a hospital if needed. After study inclusion, patients
with the presence of MSU crystals were also invited to partici-
pate in a randomized clinical trial (Trial Registration: www.
controlled-trials.com Identifier: ISRCTN14648181) on the ef-
effectiveness of prednisolone; the trial was approved by the regional
ethics review committee (Arnhem-Nijmegen).9

PROCEDURES

We invited FPs to participate in the study personally and at re-
gional educational meetings. We asked participating FPs to re-
cruit consecutive patients with monoarthritis who were en-
countered and diagnosed in the setting of primary care during
regular office hours (Monday through Friday, 8 AM to 6 PM).
The FPs sent recruited patients to our regional hospital re-
search center (Department of Rheumatology, Rijnstate Hospi-
tal, Arnhem, the Netherlands) with concealed information about
their diagnosis.

To obtain clinical variables at the time of study inclusion,
patients were evaluated in the research center by one of us (M.J.,
substituted in a few instances by a rheumatologist colleague)
using a standard interview, physical examination, and labora-
tory testing within 24 hours of visiting the FP. The clinical vari-
ables were not collected by the FPs to avoid interference with
their daily work. For practical reasons, the evaluation was com-
tinuous within the clinical care of a hospital if needed. After study inclusion, patients
with the presence of MSU crystals were also invited to partici-
pate in a randomized clinical trial (Trial Registration: www.
controlled-trials.com Identifier: ISRCTN14648181) on the ef-
effectiveness of prednisolone; the trial was approved by the regional
ethics review committee (Arnhem-Nijmegen).9

**Table 1**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSU crystals</td>
<td>Presence of MSU crystals in synovial fluid.</td>
</tr>
<tr>
<td>Joint pain</td>
<td>Intensity and duration of joint pain.</td>
</tr>
<tr>
<td>Joint swelling</td>
<td>Size and tenderness of the affected joint.</td>
</tr>
<tr>
<td>Temperature</td>
<td>Joint swelling and tenderness.</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Presence of synovial inflammation.</td>
</tr>
</tbody>
</table>

**Data analysis**

Data were analyzed from all patients with signs and symptoms
of monoarthritis. Family physician gout diagnosis (index test)
was related to the presence of synovial MSU crystals (refer-
ence test) to evaluate diagnostic test characteristics (sensitiv-
ity, specificity, positive and negative predictive values, and posi-
tive and negative likelihood ratios) using 2 × 2 tables.

In patients with gout by FP diagnosis, signs and symptoms
were analyzed using descriptive statistics (mean [SD] num-erries and percentages) and univariate logistic regression (odds
ratios, 95% confidence intervals, and P values), with the pres-
ence of MSU crystals as the dependent variable. The occur-
ance of missing values was evaluated. The following 3 multi-
ivariate logistic regression models, with the presence of MSU
crystals as the dependent variable, were fitted to the data set
of the sample: a statistically optimal model (model 1) and 2 pre-
defined models (model 2 and model 3). In model 1, selection
of predictor variables was based on statistical significance. In
models 2 and 3, selection of predictor variables was based on
external knowledge and on practical availability during regu-
lar patient care.

Model 1, the best model given the data, was used to gauge
the performance of models 2 and 3, which were developed for
convenient clinical use. Between models 2 and 3, the most ap-
propriate regression model was chosen.

For model 1, all variables with P < .20 in the univariate logistic
regression analysis and a plausible direction of the regression
coefficient (based on generally accepted knowledge) were se-
lected for inclusion in the full multivariate logistic regression model.

The full model was subsequently reduced by stepwise exclu-
sion of all variables with P > .10. For model 2, the following vari-
ables were selected: male sex, previous patient-reported arthritis
attack, onset within 1 day, joint redness, first metatarsophalan-
geal joint (MTP1) involvement, and hypertension or 1 or more
cardiovascular diseases. Model 3 included the same variables as
model 2 but also included the laboratory variable of serum uric
acid level exceeding 5.88 mg/dL (to convert serum uric acid level
to micromoles per liter, multiply by 59.485).

Diagnostic performance of the 3 models was evaluated using
receiver operating characteristic (ROC) curve analysis (area un-
der the curve), the fraction of variance by the model was ex-
plained (Nagelkerke R²), and the model fit (with respect to the
data) was assessed according to Hosmer-Lemeshow good-
ness-of-fit, P value, and calibration slope. The calibration slope
is a measure of “extremeness” of the predictions: a slope of 1.0
indicates complete agreement between observed and pre-
dicted probabilities. Calibration plots compared observed fre-
frequencies vs predicted probabilities of the presence of MSU
crystals in deciles of the risk score.

The most appropriate model was then chosen between model
2 and model 3. The bootstrap method (ie, repeated sampling with
replacement) with 300 repetitions without variable selection
was used to determine the shrinkage factor. Variable selection
was not included in the bootstrap procedure because we used a predefined model. The regression coefficients of the final model were multiplied by the shrinkage factor to reduce model
overoptimism of the model in new patients. The final model
was then transformed to an easy-to-use diagnostic rule by res-
caling the regression coefficients of the variables. The perfor-
mance of this diagnostic rule was evaluated, and the preva-
ience of gout confirmed by the presence of MSU crystals was
assessed at several cutoff points.

In secondary analyses, models were tested in all patients with
monoarthritis, including those judged by FPs as having nongouty

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## Table 1. Potentially Diagnostic Variables in Patients With Presumed Gout in Primary Care

<table>
<thead>
<tr>
<th>Variable</th>
<th>Present (n=209)</th>
<th>Absent (n=119)</th>
<th>P Value&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Odds Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSU Crystals</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>58.8 (12.9)</td>
<td>56.6 (14.4)</td>
<td>.15</td>
<td>0.99 (0.97-1.00)</td>
</tr>
<tr>
<td>Male sex, No. (%)</td>
<td>187 (89.5)</td>
<td>74 (62.2)</td>
<td>&lt;.001</td>
<td>5.17 (2.90-9.20)</td>
</tr>
<tr>
<td>Onset, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within hours</td>
<td>78 (37.3)</td>
<td>52 (43.7)</td>
<td>.26</td>
<td>0.77 (0.49-1.21)</td>
</tr>
<tr>
<td>Within 1 d</td>
<td>166 (79.4)</td>
<td>90 (75.6)</td>
<td>.42</td>
<td>1.24 (0.73-2.13)</td>
</tr>
<tr>
<td>Patient history, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient-reported arthritis attack</td>
<td>156 (74.6)</td>
<td>53 (44.5)</td>
<td>&lt;.001</td>
<td>3.67 (2.27-5.91)</td>
</tr>
<tr>
<td>Arthritis always in the same joint</td>
<td>51 (24.6)</td>
<td>25 (47.2)</td>
<td>&lt;.001</td>
<td>0.54 (0.29-1.03)</td>
</tr>
<tr>
<td>Patient-reported gout</td>
<td>128 (61.2)</td>
<td>44 (37.0)</td>
<td>&lt;.001</td>
<td>2.69 (1.69-4.29)</td>
</tr>
<tr>
<td>Medication use, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>65 (31.1)</td>
<td>22 (18.5)</td>
<td>.01</td>
<td>1.99 (1.15-3.44)</td>
</tr>
<tr>
<td>Antiplatelet agents, acetylsalicylic acid</td>
<td>17 (8.1)</td>
<td>5 (4.2)</td>
<td>.27</td>
<td>1.24 (0.85-1.81)</td>
</tr>
<tr>
<td>Cardiovascular or antihypertensive drugs</td>
<td>128 (61.2)</td>
<td>44 (37.0)</td>
<td>&lt;.001</td>
<td>2.64 (1.65-3.93)</td>
</tr>
<tr>
<td>Family history of gout, No. (%)</td>
<td>53 (25.9)</td>
<td>32 (27.4)</td>
<td>.77</td>
<td>0.93 (0.56-1.55)</td>
</tr>
<tr>
<td>Alcohol consumption, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>132 (63.2)</td>
<td>65 (55.1)</td>
<td>.26</td>
<td>1.31 (0.82-2.07)</td>
</tr>
<tr>
<td>Beer</td>
<td>95 (45.5)</td>
<td>25 (21.2)</td>
<td>&lt;.001</td>
<td>3.10 (1.85-5.21)</td>
</tr>
<tr>
<td>Wine</td>
<td>28 (13.4)</td>
<td>32 (27.1)</td>
<td>.002</td>
<td>0.42 (0.24-0.73)</td>
</tr>
<tr>
<td>Liquor</td>
<td>26 (12.4)</td>
<td>14 (11.9)</td>
<td>.88</td>
<td>1.06 (0.53-2.11)</td>
</tr>
<tr>
<td>Location of affected joint, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First metatarsophalangeal joint</td>
<td>120 (57.4)</td>
<td>35 (29.4)</td>
<td>&lt;.001</td>
<td>3.24 (2.05-5.33)</td>
</tr>
<tr>
<td>Foot or ankle</td>
<td>161 (77.0)</td>
<td>75 (63.0)</td>
<td>.007</td>
<td>1.97 (1.20-3.22)</td>
</tr>
<tr>
<td>Lower leg</td>
<td>179 (85.6)</td>
<td>94 (79.0)</td>
<td>.12</td>
<td>1.59 (0.88-2.85)</td>
</tr>
<tr>
<td>Tophus, No. (%)</td>
<td>27 (12.9)</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Body mass index&lt;sup&gt;g&lt;/sup&gt; (n=118)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>29.7 (4.4)</td>
<td>28.7 (5.6)</td>
<td>.08</td>
<td>0.96 (0.91-1.00)</td>
</tr>
<tr>
<td>&gt;30, No. (%)</td>
<td>85 (40.7)</td>
<td>38 (32.2)</td>
<td>.13</td>
<td>1.44 (1.90-2.32)</td>
</tr>
<tr>
<td>&gt;50, No. (%)</td>
<td>187 (89.5)</td>
<td>89 (75.4)</td>
<td>.001</td>
<td>2.77 (1.51-5.09)</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic (mean, SD)</td>
<td>144.3 (22.6)</td>
<td>143.6 (22.1)</td>
<td>.78</td>
<td>1.00 (0.99-1.01)</td>
</tr>
<tr>
<td>Systolic &gt;140, No. (%)</td>
<td>91 (43.5)</td>
<td>53 (44.5)</td>
<td>.86</td>
<td>0.96 (0.61-1.51)</td>
</tr>
<tr>
<td>Diastolic (mean, SD)</td>
<td>84.1 (12.7)</td>
<td>83.6 (14.7)</td>
<td>.73</td>
<td>1.00 (0.98-1.01)</td>
</tr>
<tr>
<td>Diastolic &gt;90, No. (%)</td>
<td>57 (27.3)</td>
<td>31 (26.1)</td>
<td>.81</td>
<td>1.07 (0.84-1.37)</td>
</tr>
<tr>
<td>Serum uric acid level, mg/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>8.24 (1.51)</td>
<td>6.05 (2.01)</td>
<td>&lt;.001</td>
<td>0.00 (0.00-0.00)</td>
</tr>
<tr>
<td>&gt;7.06 For men or &gt;5.72 for women, No. (%)</td>
<td>161 (77.0)</td>
<td>38 (32.2)</td>
<td>&lt;.001</td>
<td>7.06 (4.27-11.68)</td>
</tr>
<tr>
<td>&gt;5.88, No. (%)</td>
<td>199 (95.2)</td>
<td>55 (46.6)</td>
<td>&lt;.001</td>
<td>22.80 (10.98-47.35)</td>
</tr>
<tr>
<td>Creatinine level, mg/dL</td>
<td>(n=207)</td>
<td>(n=117)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>1.12 (0.43)</td>
<td>0.91 (0.31)</td>
<td>&lt;.001</td>
<td>0.98 (0.97-0.99)</td>
</tr>
<tr>
<td>&gt;1.19, No. (%)</td>
<td>133 (65.2)</td>
<td>56 (49.1)</td>
<td>.002</td>
<td>2.82 (1.47-5.43)</td>
</tr>
<tr>
<td>Glomerular filtration rate, mL/min/1.73 m²</td>
<td>(n=207)</td>
<td>(n=117)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>7.44 (24.4)</td>
<td>85.0 (21.9)</td>
<td>&lt;.001</td>
<td>1.02 (1.01-1.03)</td>
</tr>
<tr>
<td>&lt;90, No. (%)</td>
<td>148 (71.5)</td>
<td>61 (52.1)</td>
<td>.001</td>
<td>2.30 (1.44-3.69)</td>
</tr>
<tr>
<td>&lt;60, No. (%)</td>
<td>54 (26.1)</td>
<td>13 (11.1)</td>
<td>.002</td>
<td>2.82 (1.47-5.43)</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate, mm/h</td>
<td>(n=206)</td>
<td>(n=117)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>23.6 (20.3)</td>
<td>20.4 (16.5)</td>
<td>.16</td>
<td>0.99 (0.98-1.00)</td>
</tr>
<tr>
<td>&gt;20 For men or &gt;30 for women, No. (%)</td>
<td>88 (42.7)</td>
<td>38 (32.5)</td>
<td>.07</td>
<td>1.55 (0.96-2.49)</td>
</tr>
<tr>
<td>C-reactive protein level, mg/dL</td>
<td>(n=204)</td>
<td>(n=114)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>27.0 (33.1)</td>
<td>20.6 (29.7)</td>
<td>.09</td>
<td>0.99 (0.99-1.00)</td>
</tr>
<tr>
<td>&gt;1, No. (%)</td>
<td>133 (65.2)</td>
<td>56 (49.1)</td>
<td>.005</td>
<td>1.94 (1.22-3.09)</td>
</tr>
</tbody>
</table>

**Abbreviations:** MSU, monosodium urate; NA, not applicable because tophus presence completely coincided with MSU presence.

SI conversion factors: To convert serum uric acid level to micromoles per liter, multiply by 59.485; creatinine level to micromoles per liter, multiply by 88.4; C-reactive protein level to nanomoles per liter, multiply by 9.524.

<sup>a</sup> Between-group differences after univariate logistic regression analysis.

<sup>b</sup> n=156.

<sup>c</sup> n=53.

<sup>d</sup> n=205.

<sup>e</sup> n=117.

<sup>f</sup> n=118.

<sup>g</sup> Calculated as weight in kilograms divided by height in meters squared.
Patients with MSU crystals

Figure 1 shows the study profile. Ninety-three FPs recruited 381 patients with monoarthritis. Their mean age was 57.7 (13.6) years, and 285 patients (74.8%) were male. The presence of MSU crystals was identified in 216 patients (56.7%), 209 at the initial investigation and 7 during the follow-up period. A total of 328 patients (86.1%) had an index test diagnosis of gout. The reference test demonstrated index test sensitivity of 0.97 (209 of 216), specificity of 0.28 (46 of 165), positive predictive value of 0.64 (209 of 328), and negative predictive value of 0.87 (46 of 53). The derived positive likelihood ratio was 1.3, with a negative likelihood ratio 0.1.

Of 328 patients with an index test diagnosis of gout (included in the regression models), the mean age was 58.0 (13.5) years, 261 (79.6%) were male, and hypertension, 1 or more cardiovascular diseases, and diabetes were present in 146 (44.5%), 81 (24.7%), and 25 (7.6%), respectively. The presence of MSU crystals was identified in 209 patients (63.7%). Of 53 patients excluded from the regression models (with an index test diagnosis of nongouty arthritis), 24 (45.3%) were male, the mean age was 55.8 (14.2) years, and hypertension, 1 or more cardiovascular diseases, and diabetes were present in 16 (30.2%), 9 (17.0%), and 3 (5.7%), respectively. The presence of MSU crystals was identified in 7 nongouty patients (13.2%).

Table 1 summarizes findings of the descriptive statistics and univariate logistic regression analyses of diagnostic indicators and risk factors for the presence of MSU crystals among 328 patients who were included in the regression models. The number of missing values was low; therefore, missing values were not replaced.

After the univariate procedure and the multivariate logistic regression procedure that included stepwise exclusion of all variables with P ≥ 10, model 1 (the statistically optimal model) consisted of 8 variables (including 2 laboratory values) that were independently predictive in multivariate logistic regression analysis. The equation for model 1 is as follows:

$$-4.66 \text{ (intercept)} + (0.92 \times \text{male sex}) + (1.02 \times \text{previous patient-reported arthritis attack}) + (1.83 \times \text{MT1 involvement}) + (1.01 \times \text{hypertension or } \geq 1 \text{ cardiovascular diseases}) + (1.15 \times \text{beer consumption}) + (2.44 \times \text{serum uric acid level} > 5.88 \text{ mg/dL}) + (0.68 \times \text{erythrocyte sedimentation rate} > 20 \text{ mm/h for men or } > 30 \text{ mm/h for women})$$

The eighth variable was the presence of tophus, which was 100% specific for the presence of MSU crystals in synovial joint fluid analysis. Therefore, a regression coefficient for this variable could not be calculated, but the variable was kept in the model by awarding the maximum risk score for patients with tophus.

Results of the multivariate logistic regression analysis in the predefined models (models 2 and 3) are given in Table 2. Except for onset within 1 day and joint redness, all other variables (male sex, previous patient-reported arthritis attack, hypertension or at least 1 cardiovascular diseases, MTP1 involvement, and serum uric acid level > 5.88 mg/dL) were independently predictive in multivariate regression analysis based on their respective P values.

Performance of the 3 models is summarized in Table 3. The area under the ROC curve for the statistically optimal model (model 1) was high, with the areas under the ROC curve for models 2 and 3 being slightly lower. Compared with model 2, the performance of model 3 was better based on area under the ROC curve, Nagelkerke $R^2$, Hosmer-Lemeshow goodness-of-fit test, and calibration slope. Accordingly, model 3 was chosen as the final model. The areas under the ROC curve for models 1 and 3 are shown in Figure 2.

The regression coefficients of variables included in model 3 were first multiplied by a shrinkage factor of 0.81, and the regression coefficients were then rescaled to easy-to-use scores (Table 4). The area under the ROC curve for this diagnostic rule was 0.85 (95% confidence interval, 0.81-0.90). Figure 3 shows the calibration plot of the rule. As confirmed by the presence of MSU crystals, the prevalences of gout at 3 cutoff scores (≤4, >4 to <8, and ≥8 points) on the final diagnostic rule were 2.2% (1 of 45), 31.2% (15 of 48), and 82.5% (193 of 234), respectively.

Among all patients with monoarthritis, including those judged by FPs as having nongouty arthritis, the area under the ROC curve for the diagnostic rule was 0.87 (95% CI, 0.84-0.91). As confirmed by the presence of MSU crystals, the prevalences of gout at the 3 cutoff scores (≤4, >4 to <8, and ≥8 points) on the final diagnostic rule were (2.2%, 31.2%, and 82.5%, respectively).
To our knowledge, this diagnostic study is the first to develop a clinical prediction model for the diagnosis of acute gouty arthritis in primary care. We present a model that showed a good internal validity and performed nearly equally as well as the statistically optimal model even after the correction for overoptimism of the model in new patients and the transformation of the regression coefficient to easy-to-use scores. The model contains a limited number of signs and symptoms and 1 laboratory test (serum uric acid level), predefined based on prior knowledge of their association with gout and their availability to primary care physicians in routine daily practice. This yielded a diagnostic rule that could discriminate patients with gout using scores for the following 7 variables that are easily ascertainable in primary care: male sex, previous patient-reported arthritis attack, onset within 1 day, joint redness, MTP1 involvement, hypertension or 1 or more cardiovascular diseases, and serum uric acid level exceeding 5.88 mg/dL. The positive and negative predictive values of FP diagnosis of gout were moderate in our study. The presented diagnostic rule helps FPs to select patients with high vs low probability of gout and to restrict the use of joint fluid aspiration to test for the presence of MSU crystals for patients with remaining uncertainty about the diagnosis. On the diagnostic rule, a score of 4 or less ruled out gout in almost 100% of patients. Diagnoses such as rheumatoid arthritis, pseudogout, psoriatic arthritis, and reactive arthritis must be considered in these patients. Among patients with a score of 8 or higher, gout was confirmed in more than 80%, indicating gout-specific management options such as systemic corticosteroid use (instead of nonsteroidal anti-inflammatory drugs), uric acid–lowering therapies.

Table 2. Results of Multivariate Logistic Regression Analysis of the Predefined Models (Model 2 Without Laboratory Testing and Model 3 With Laboratory Testing)\textsuperscript{a}

| Variable | Model 2 | | | Model 3 | | |
|----------|---------| | |----------| | |
|          | Regression Coefficient | OR (95% CI) | P Value | Regression Coefficient | OR (95% CI) | P Value |
| Male sex | 1.90 | 6.67 (3.26-13.67) | .<.001 | 1.25 | 3.50 (1.54-8.00) | .003 |
| Previous patient-reported arthritis attack | 1.42 | 4.13 (2.20-7.78) | .<.001 | 1.17 | 3.24 (1.63-6.43) | .001 |
| Onset within 1 d | 0.30 | 1.35 (0.69-2.63) | .38 | 0.03 | 1.03 (0.50-2.14) | .93 |
| Joint redness | 0.45 | 1.57 (0.73-3.39) | .25 | 0.50 | 1.64 (0.73-3.72) | .23 |
| MTP1 involvement | 1.87 | 6.48 (3.37-12.46) | .<.001 | 1.54 | 4.68 (2.34-9.35) | .<.001 |
| Hypertension or \( \geq 1 \) cardiovascular diseases\textsuperscript{b} | 1.16 | 3.21 (1.81-5.69) | .<.001 | 0.88 | 2.42 (1.30-4.50) | .005 |
| Serum uric acid level \( >5.88 \text{mg/dL} \) | . . . | . . . | . . . | 2.28 | 9.81 (4.32-22.31) | .<.001 |

Abbreviations: CI, confidence interval; ellipsis, not applicable; MTP1, metatarsophalangeal joint; OR, odds ratio.
SI conversion factor: To convert serum uric acid level to micromoles per liter, multiply by 59.485.
\textsuperscript{a}The intercept of model 2 is \(-3.78\), and the intercept of model 3 is \(-4.49\).
\textsuperscript{b}Angina pectoris, myocardial infarction, heart failure, cerebrovascular accident, transient ischemic attack, or peripheral vascular disease.

Table 3. Performance of the 3 Models Before Shrinkage by the Bootstrap Method

<table>
<thead>
<tr>
<th>Model</th>
<th>Description</th>
<th>Area (95% Confidence Interval) under the ROC Curve</th>
<th>Nagelkerke ( R^2 )</th>
<th>Hosmer-Lemeshow Goodness-of-Fit P Value</th>
<th>Calibration Slope (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1\textsuperscript{a}</td>
<td>Statistically optimal model</td>
<td>0.89 (0.85-0.92)</td>
<td>0.57</td>
<td>.52</td>
<td>0.98 (0.11)</td>
</tr>
<tr>
<td>2</td>
<td>Predefined model without laboratory testing</td>
<td>0.82 (0.77-0.87)</td>
<td>0.41</td>
<td>.44</td>
<td>1.00 (0.12)</td>
</tr>
<tr>
<td>3</td>
<td>Predefined model with laboratory testing</td>
<td>0.85 (0.81-0.90)</td>
<td>0.51</td>
<td>.46</td>
<td>1.00 (0.11)</td>
</tr>
</tbody>
</table>

Abbreviation: ROC, receiver operating characteristic.
\textsuperscript{a}Includes the variable of tophus, which was 100% specific for the presence of monosodium urate crystals in synovial joint fluid analysis.
therapy if indicated, and evaluation of gout-associated cardiovascular and renal diseases. At this score range, a false-positive diagnosis of gout was found in 17% of patients, which is better than the FP false-positive diagnosis rate of 36.3%. However, the risk of missing other important conditions remains. Thirty-two patients with false-positive results according to the diagnostic rule were classified as having arthritis of unknown cause, and only 1 patient was classified as having a possible prestige of rheumatoid arthritis. None had septic arthritis (data not shown). This implies that the false-positive outcomes only occasionally missed important diagnoses at a cutoff score of 8 or higher on the diagnostic rule. In addition, development of another disease over time must be noted if the arthritis continues, deteriorates, or recurs. A midrange score (>4 to <8) leaves uncertainty about the diagnosis (with gout confirmed in about 30%). In these patients, analysis of synovial fluid from the affected joint for the presence of MSU crystals should be considered if necessary for future management. With the help of a computer program or calculator, the original untransformed (shrunk) regression coefficients of the final model can be applied to more accurately predict gout diagnosis for an individual patient compared with the simple scores of the diagnostic rule.

We used a model with predefined variables rather than a data-derived model. Fitting such an optimal model using variables based on statistical significance in small data sets such as ours has the following risks: a few patients can alter the model (unstable selection), variables may be nonsignificant due to chance processes, standard errors and P values are underestimated, and power to select important variables is limited. Our strategy to fit a model with predefined variables (based on external knowledge independent of statistical significance and shrink by the bootstrap method to correct for overoptimism of the model in new patients) is considered the most obvious choice in this situation. Despite this, overoptimism of the model may occur among new patients. Therefore, our diagnostic rule needs to be validated in other primary care populations before definitive implementation in daily practice, as the application in a single data set may not indicate its performance among future patients.

Because most patients with gout are diagnosed (and subsequently managed) in primary care, the setting of our study was relevant for investigating gout. The included patients had a high priori probability of physician-diagnosed gout in the general population. There are several limitations of the study. The clinical variables were not assessed by the participating FPs but by one of us (M.J.) according to the study protocol. Although this may have limited the generalizability of our results, we believe that the variables in the proposed diagnostic rule can be reliably assessed by FPs as well.

Because the diagnostic rule was developed in a population of patients with monoarthritis seen by FPs, its application pertains to them and not to patients with oligoarticular and polyarticular arthritis. However, the prevalence of oligoarticular and polyarticular (gout) arthritis is low among primary care patients. Because monoarthritis was the inclusion criterion, the probability of gout was raised among the studied patients. Rather than (possible) selection bias, this reflects the population of interest in whom FPs diagnose acute gouty arthritis. As a consequence, there is little risk that this aspect of patient recruitment biased our findings. Bias at the testing stage (e.g., verification bias) was another risk of our study. However, participating FPs were invited to send all patients with presumed monoarthritis even when referral was not needed from the perspective of regular primary care. There were no exclusion criteria, and all patient data were evaluated without delay, which could have diluted the association between presenting signs and symptoms and MSU crystal identification.

Aspirated joint fluid was thoroughly searched for MSU crystals (sensitive detection), and detected crystals were specifically identified by rheumatologists (M.J. and colleague) with experience in synovial fluid analysis. The sensitivity of crystal detection is estimated to be higher than 95%, with a specificity higher than

### Table 4. Clinical Scores of the Final Diagnostic Rule After Transforming the Regression Coefficients Shrunk by the Bootstrap Method

<table>
<thead>
<tr>
<th>Predefined Variable</th>
<th>Regression Coefficient</th>
<th>After Shrinkage</th>
<th>Clinical Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>1.01</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>Previous patient-reported arthritis attack</td>
<td>0.95</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>Onset within 1 d</td>
<td>0.03</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Joint redness</td>
<td>0.40</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>MTP1 involvement</td>
<td>1.25</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>Hypertension or ( \geq 1 ) cardiovascular diseases</td>
<td>0.72</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>Serum uric acid level ( &gt;5.88 ) mg/dL</td>
<td>1.85</td>
<td>3.5</td>
<td></td>
</tr>
<tr>
<td>Maximum score</td>
<td>6.21</td>
<td>13.0</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: MTP1, metatarsophalangeal joint.

SI conversion factor: To convert serum uric acid level to micromoles per liter, multiply by 59.485.

*Angina pectoris, myocardial infarction, heart failure, cerebrovascular accident, transient ischemic attack, or peripheral vascular disease.*
97%, even by trained observers who had no previous experience in synovial fluid analysis.\textsuperscript{20} In addition, study patients in synovial fluid were eligible to participate in a randomized clinical trial accompanying the present study.\textsuperscript{9}

However, in 63 patients (19.2%), no MSU crystals were detected and no other joint diagnosis established. Our study findings would have differed if patients with arthritis of unknown cause had turned out to have true gout diagnoses after our follow-up period of 1 to 3 years. Most gouty reattacks would have occurred within the follow-up period, and (as expected) this did not happen frequently. In addition, the proportion of patients with arthritis of unknown cause in our study was low compared with the proportion of patients with undifferentiated arthritis reported in population surveys or investigations among patients at early-arthritis clinics.\textsuperscript{21,22}

Although it is not difficult to obtain the variables to compute the diagnostic rule score, time constraints in busy practices and perceived complexity may prevent the use of the model. To alleviate this, an online calculator is available on the Internet (http://www.umcn.nl/goutcalc). In conclusion, our study using an unequivocal reference test for the presence of synovial MSU crystals elucidates the validity of clinical signs and symptoms for diagnosing acute gouty arthritis in primary care. We developed and validated a diagnostic rule without joint fluid analysis for use by FPs. The rule may also be helpful in defining eligible patients with gout for participation in research settings vs other clinical criteria such as those of the American College of Rheumatology,\textsuperscript{23} which appear recently to have limited validity.\textsuperscript{24,25}

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Correspondence: Hein J. E. M. Janssens, MD, Department of Primary and Community Care, Radboud University Nijmegen Medical Center, PO Box 9101, 6500 HB Nijmegen, the Netherlands (h.janssens@elg.umcn.nl).  

Author Contributions: Study concept and design: Janssens, Fransen, van de Lisdonk, van Riel, van Weel, and Janssen. Acquisition of data: Janssens and Janssen. Analysis and interpretation of data: Janssens and Fransen. Drafting of the manuscript: Janssens, Fransen, and van de Lisdonk. Critical revision of the manuscript for important intellectual content: Fransen, van de Lisdonk, van Riel, van Weel, and Janssen. Statistical analysis: Fransen. Administrative, technical, and material support: Janssens and van de Lisdonk. Study supervision: Janssens, van de Lisdonk, van Riel, van Weel, and Janssen.

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