Factors Associated With Natriuretic Peptide Testing in Patients Presenting to Emergency Departments With Suspected Heart Failure

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Heart failure (HF) is a major health care problem in Canada and worldwide. It is estimated that there are 500,000 Canadians living with symptomatic HF, with 50,000 new patients diagnosed each year,1 and the global burden of HF is expected to double in the next 1-2 decades.2-4

The majority of patients with dyspnea or suspected HF present through the emergency department (ED), and thus tools to diagnose each year,1 and the global burden of HF is expected to double in the next 1-2 decades.2-4

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See page 7 for disclosure information.

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ABSTRACT

Background: Testing for natriuretic peptides (NPs) such as brain natriuretic peptide (BNP) or N-terminal prohormone brain natriuretic peptide (NT-proBNP) in the emergency department (ED) assists in the evaluation of patients with acute heart failure (HF). The aim of this study was to investigate factors related to the use of NP testing in the ED in a large population-based sample in Canada.

Methods: This was a retrospective cohort study using linked administrative data from Alberta in 2012. Patients were included if they had testing for an NP in the ED; a comparator group with HF but without NP testing was also included.

Results: Of the 16,223 patients in the cohort, 5793 were patients with HF (n = 3148 tested and n = 2645 not tested for NPs) and 10,430 were patients without HF but who were tested for NPs. Patients without HF who were tested for NPs had respiratory disease (34%), non-HF cardiovascular diseases (13%), and other conditions (52%).

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RÉSUMÉ

Introduction : Les tests de dépistage des peptides natriurétiques (NP), comme le peptide natriurétique de type B (BNP) ou le pro-peptide natriurétique de type B N-terminal (NT-proBNP), réalisés aux urgences aigües (IC) aiguë. L’objectif de cette étude était de déterminer quels facteurs contribuent à l’utilisation des tests de dépistage des NP aux urgences. L’étude a été réalisée auprès d’un vaste échantillon de patients canadiens.

Méthodes : Il s’agissait d’une étude de cohorte rétrospective provenant de données administratives interreliées recueillies en Alberta de 2012. Le groupe de patients ayant subi des tests de dépistage des NP aux urgences a été comparé à un groupe de patients atteints d’IC qui n’avait pas été soumis à de tels tests aux urgences.

Résultats : Parmi les 16 223 patients de la cohorte, 5793 patients souffraient d’insuffisance cardiaque (n = 3148 avec dépistage des NP...
Patients with HF who were tested had a higher rate of hospital admission from the ED (78.4% vs 62.2%; P < 0.001) and lower 7-day and 90-day repeated ED visit rates compared with those who were not tested. Among patients with HF, male sex, being an urban resident, being seen by an emergency medicine or cardiology specialist, and being seen in hospitals with medium ED visit volumes were associated with increased likelihood of testing for NPs.

Conclusions: Several factors, including the type of provider and ED clinical volume, influenced the use of NP testing in routine ED practice. Standardization of an NP testing strategy in clinical practice would be useful for health care systems.

Health Services for all Alberta EDs in 2012. However, little is known about the use of this HF biomarker in a wide spectrum of EDs in a publicly funded health care system. The objectives of this study were to describe NP testing in all EDs of Alberta and evaluate the factors related to NP testing.

Methods
In this retrospective cohort study, administrative data were used to capture information on patients who attended any ED in Alberta, Canada between April 1, 2012 and March 31, 2013. Alberta provides universal health care coverage, and all patients and health care facilities provide data. Alberta has approximately 4 million residents, 107 acute-care facility EDs, and an annual ED volume of > 2.3 million visits. This study was approved by the Health Ethics Research Board of the University of Alberta, Edmonton, Alberta, Canada.

Data sources
Data for the study were retrieved from databases described previously and maintained by Alberta Health Services—Analytics.14,15 These databases contain data on all inpatient and outpatient interactions with the health system. The databases are comprehensive and were linked using each individual’s unique lifetime identifier (ULI).

The Alberta version of the National Ambulatory Care Reporting System (NACRS) database includes all visits to any ED in Alberta and captures the most responsible diagnosis and up to 9 other diagnoses per encounter. The NACRS also includes patients brought by ambulance who died before arriving at the hospital. Data from the NACRS was merged with inpatient data from the hospital Discharge Abstract Database to identify the most responsible diagnosis and up to 24 comorbid conditions coded using International Classification of Diseases, 10th revision (ICD-10) codes.16,17 The information in these databases has been demonstrated to be highly accurate for research use.18 Urban/rural residence was determined according to the methodology applied by Statistics Canada, using the second character of the forward sortation address for each patient’s home address as reported in the Alberta Health Care Insurance Plan Registry file.19,20

Our cohort included all patients older than 18 years who presented to the ED and either (1) had an ED most responsible diagnosis of HF or (2) had an NP test done. HF was defined using ICD-10 code I50.x (Supplemental Table S1). NP testing is outlined in Figure 1.

Hospital-specific variables were created by identifying clusters of hospitals based on the average annual ED visits with a main diagnosis of HF, categorizing them into 3 tertiles with small (< 62 HF cases/yr; n = 87 EDs), medium (62-320 cases; n = 15 EDs), and high (> 320 cases; n = 5 EDs) ED visit volumes.21 The 3 largest tertiary care hospitals (2 in Edmonton, 1 in Calgary) were also explored in a secondary analysis given their high patient volume. The cost of each hospitalization was estimated using the Resource Intensity Weight (RIW) methodology.22 An estimate of the expected province-specific, intensity-adjusted resource consumption was calculated and made available for each of the 528 case mix groups (CMGs). CMGs are identified by the Canadian Institute of Health Information, and each is composed of cases with similar characteristics including diagnosis, intervention, and resource use. In Alberta, a physician working in the ED may have a variety of certifications or training, and physician specialty was divided into 5 categories (cardiology and critical care medicine, internal medicine, emergency medicine, general practice, and others), as previously described.23

Laboratory data
The ULI was used to link each patient to the ED and hospital laboratory data from a province-wide laboratory
Repository, similar to a previous study. The following test results were included: sodium, potassium, creatinine, hemoglobin, BNP, and NT-proBNP concentrations. In Alberta, the Alere BNP assay (Alere, San Diego, CA) is used for BNP testing, and the Roche assay (Roche Diagnostics GmbH, Manheim, Germany) is used for NT-proBNP testing. The choice of NP test is dictated by the available laboratory equipment; all hospitals had access to 1 test or the other. Creatinine values were included if obtained within 2 days before the index ED visit, and sodium, potassium, and hemoglobin determinations were included if obtained ± 2 days around the index ED visit. The majority of tests (90%) were performed on the same day as the ED visit, and NP testing was used only if done at the time of the ED visit. If multiple tests were available in these time frames, the one that was closest to the ED presentation time was used.

Comorbidities

Comorbidities were identified using ICD-10 codes for all acute-care hospitalizations in the preceding 3 years. For the purposes of risk adjustment, the Charlson comorbidity index score was calculated using the previous 3 years’ data.

Primary and clinical outcomes

The primary outcome was testing for NPs in EDs. Clinical outcomes of interest included all-cause mortality, hospitalization, rehospitalization, and repeated ED visits in the year after the visit.

Statistical analysis

The continuous variables in each group were presented as mean ± standard deviation or median and interquartile range (IQR), as appropriate, and the categorical variables were provided as frequency and percentage. The patient characteristics were compared between groups using the Wilcoxon test and the χ² test, as appropriate.

A series of logistic regression models were created to estimate the adjusted effects of demographics, comorbidities, laboratory data, and NP testing on the specified outcome variables as well as the likelihood of being tested based on urban/rural split, number of cases at a hospital, and physician speciality. Adjusted models were built using the backward stepwise selection method with a P value of 0.20 for removal. Hosmer-Lemeshow goodness of fit was used to examine the appropriateness of the fitted models. Statistical significance was set at P = 0.05, and all statistical tests were 2-sided. All statistical analysis was done using SAS statistical software, version 9.4 (SAS Institute, Cary, NC).

Results

From April 1, 2012 to March 31, 2013, there were 2.33 million ED visits by 1.15 million Albertans. Of these individuals, 862,805 (74.8%) were > 18 years of age. Five thousand seven hundred ninety-three unique patients (0.7% of all adult patients in the ED) had a most responsible diagnosis of HF, and a total of 13,578 (1.6%) patients had testing for NPs. Of those tested for NPs in the ED, 76.8% (10,430 patients) did not receive a final most responsible diagnosis of HF. Two thousand six hundred forty-five patients were not tested for NPs and received a most responsible diagnosis of HF (Fig. 1).

Mean age was similar between HF groups who were or were not tested for NPs (77.2 ± 12.5 and 77.2 ± 12.7 years, respectively; P = 0.83), and they were older than those without a diagnosis of HF who were tested for NPs (72.3 ± 14.4; P < 0.001) (Table 1). The rate of male sex was higher (53.0% vs 50.2%; P = 0.003) and the rate of rural residence was lower (17.9% vs 27.0%; P < 0.001) among patients with HF who were tested for NPs compared with patients with HF who were not tested. Based on the Charlson comorbidity index score, the patients with HF tested for NPs had a burden of comorbidities similar to that of the patients with HF who were not tested for NPs. There was no difference regarding renal function between HF groups with and without NP testing. The NP testing patterns differed between hospitals with different levels of ED visit volumes (P < 0.001) and between different types of medical care providers (P < 0.001).

NP testing results

A total of 13,578 patients had an NP test: 10,383 (76.4%) patients had a BNP test, and 3195 (23.5%) patients had a NT-proBNP test. The median values for both BNP and NT-proBNP were 6-fold higher than those without the diagnosis of HF: BNP, 649 pg/mL; IQR, 324-1244 and 123 pg/mL; IQR, 44-318, respectively; P < 0.0001 and NT-proBNP, 3408 pg/mL; IQR, 1654-7616 and 605 pg/mL; IQR, 177-2033; P < 0.0001). Other laboratory values are presented in Supplemental Table S2.

Geographic, hospital volume, and specialty variability in NP testing

The proportion of rural residents with HF tested for NPs was lower compared with urban patients with HF (16.9% vs 27.0%; P < 0.001). In hospitals with low, medium, or high
ED visit volume, the rate of testing for NPs among patients with HF was 42.0%, 71.5%, and 52.0%, respectively ($P < 0.001$). The rate of testing for NPs in patients with HF varied from 0% to 100% across different hospitals (Supplemental Fig. S1). The rate of patients with a primary ED diagnosis of HF who were not tested for NPs was higher in Calgary’s tertiary care centre (67.6%) compared with the 2 tertiary care hospitals in Edmonton (8.0% and 11.6%, respectively; $P < 0.001$).

A higher percentage of patients with HF seen by emergency medicine specialists was tested for NPs (62.7%) compared with patients seen by other specialties (total, 54.3%; $P < 0.001$; 50.3% in cardiology and critical care medicine, 56.8% in internal medicine, 50.9% for other specialties, and 45.1% for general practitioners).

The top 3 diagnoses (by ICD-10 code) in the patients without HF who were tested for NPs included diseases of the respiratory system in 34.0%, diseases of the circulatory system other than HF in 13.1%, and signs and symptoms involving the respiratory and circulatory systems but not yet diagnosed in 17.0% of patients (Supplemental Table S3).

### Clinical outcomes

In patients with a diagnosis of HF, 78.4% ($n = 2467$) were admitted to the hospital. The admission rates were lower for those without testing for NPs but with a diagnosis of HF (62.2%) and for patients who had NP testing and a diagnosis other than HF (58.6%; $n = 6097$; $P < 0.001$).

Thirty-eight patients (0.2%) died during their index ED visit, and among patients who were hospitalized, 9.5% ($n = 977$) died during their index hospitalization (Table 2). The rate of death at index hospitalization was numerically higher in those patients with HF who were not tested for NPs. The patients with HF, regardless of testing for NPs, had similar 7-day, 90-day, and 1-year mortality rates (Table 2). Patients with HF who were not tested for NPs had similar 7-day and 90-day rehospitalization rates but higher 7-day and 90-day

### Table 1. Baseline characteristics for patients with suspected HF by different study groups ($N = 16,223$)

<table>
<thead>
<tr>
<th>Variable</th>
<th>HF with NPs tested (n = 3148)</th>
<th>HF without NPs tested (n = 2645)</th>
<th>No HF with NPs tested (n = 10,430)</th>
<th>$P$ value (HF with NPs tested vs HF without NPs tested)</th>
<th>$P$ value (comparison among 3 groups)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td>Age (y), mean (SD)</td>
<td>77.2 (12.5)</td>
<td>77.2 (12.7)</td>
<td>72.3 (14.4)</td>
<td>0.83</td>
</tr>
<tr>
<td></td>
<td>Male sex, %</td>
<td>53.0</td>
<td>50.2</td>
<td>50.3</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>Rural residence, %</td>
<td>17.9</td>
<td>27.0</td>
<td>16.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Comorbidities, %</td>
<td>Hypertension</td>
<td>59.0</td>
<td>57.7</td>
<td>52.4</td>
<td>0.32</td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td>34.3</td>
<td>37.1</td>
<td>29.7</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>Dyslipidemia</td>
<td>24.8</td>
<td>17.5</td>
<td>19.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>CAD</td>
<td>40.3</td>
<td>38.3</td>
<td>27.4</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>Myocardial infarction</td>
<td>21.9</td>
<td>19.1</td>
<td>14.9</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>Previous coronary artery revascularization</td>
<td>5.8</td>
<td>5.9</td>
<td>4.4</td>
<td>0.98</td>
</tr>
<tr>
<td>Hospital and provider characteristics</td>
<td>Previous HF</td>
<td>57.9</td>
<td>51.5</td>
<td>24.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Atrial fibrillation</td>
<td>36.5</td>
<td>34.6</td>
<td>20.0</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>Cerebrovascular disease</td>
<td>11.4</td>
<td>10.9</td>
<td>10.0</td>
<td>0.48</td>
</tr>
<tr>
<td></td>
<td>Peripheral vascular disease</td>
<td>10.1</td>
<td>9.2</td>
<td>7.1</td>
<td>0.26</td>
</tr>
<tr>
<td></td>
<td>COPD</td>
<td>33.6</td>
<td>32.4</td>
<td>38.8</td>
<td>0.34</td>
</tr>
<tr>
<td></td>
<td>Dementia</td>
<td>7.8</td>
<td>8.3</td>
<td>7.4</td>
<td>0.52</td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
<td>22.8</td>
<td>22.0</td>
<td>18.6</td>
<td>0.46</td>
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<tr>
<td></td>
<td>Cancer</td>
<td>9.4</td>
<td>9.3</td>
<td>9.7</td>
<td>0.82</td>
</tr>
<tr>
<td></td>
<td>Charlson score, mean (SD)</td>
<td>2.9 (2.4)</td>
<td>2.8 (2.5)</td>
<td>2.3 (2.4)</td>
<td>0.13</td>
</tr>
<tr>
<td>Hospital and provider characteristics</td>
<td>Hospital, %</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tertiary care in Calgary</td>
<td>20.5</td>
<td>42.9</td>
<td>36.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Tertiary care in Edmonton</td>
<td>17.2</td>
<td>1.5</td>
<td>81.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Tertiary care in Edmonton</td>
<td>19.8</td>
<td>2.6</td>
<td>77.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>All urban</td>
<td>19.5</td>
<td>13.0</td>
<td>67.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ED visit hospital volume, n (%)</td>
<td>Low</td>
<td>767 (19.1)</td>
<td>1058 (26.3)</td>
<td>2201 (54.7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Medium</td>
<td>1165 (18.9)</td>
<td>464 (7.5)</td>
<td>4530 (73.6)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>1216 (20.1)</td>
<td>1123 (18.6)</td>
<td>3699 (61.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Main provider in ED visit, n (%)</td>
<td>Emergency medicine</td>
<td>1701 (54.0)</td>
<td>1009 (38.2)</td>
<td>7579 (72.7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>General practice</td>
<td>1131 (35.9)</td>
<td>1373 (51.9)</td>
<td>2570 (24.7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Internal medicine</td>
<td>211 (6.7)</td>
<td>160 (6.1)</td>
<td>131 (1.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Cardiology/critical care medicine</td>
<td>78 (2.5)</td>
<td>77 (2.9)</td>
<td>19 (0.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Other</td>
<td>Timing of ED visit</td>
<td>27 (0.9)</td>
<td>26 (1.0)</td>
<td>129 (1.2)</td>
<td>0.99</td>
</tr>
<tr>
<td></td>
<td>Weekday, %</td>
<td>75.0</td>
<td>75.0</td>
<td>73.9</td>
<td>0.30</td>
</tr>
<tr>
<td></td>
<td>Weekend, %</td>
<td>25.0</td>
<td>25.0</td>
<td>26.1</td>
<td>0.30</td>
</tr>
</tbody>
</table>

Values are n (%) or mean (SD)/median as appropriate. Comorbidities are defined as being present 3 years before the index ED visit.

CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; ED, emergency department; HF, heart failure; NPs, natriuretic peptides; SD, standard deviation.
repeated ED visit rates compared with patients with HF who were tested for NPs (P < 0.02). These differences remained after adjusting for key patient- and hospital-related variables (Supplemental Table S4).

### Multivariable modelling predicting NP testing

Among patients with a diagnosis of HF, male sex, being an urban resident, and having a previous HF diagnosis were associated with a higher likelihood of being tested for NPs (Fig. 2). The likelihood of being tested for NPs was higher if the care provider was an emergency medicine specialist (odds ratio [OR], 2.29; 95% confidence interval [CI], 1.97-2.66), cardiology/critical care medicine specialist (OR, 1.57; 95% CI, 1.10-2.24), or internal medicine specialist (OR, 1.49; 95% CI, 1.17-1.90) compared with general practitioners. Compared with the hospitals with low volumes of ED visits, the patients treated in hospitals with a medium volume of ED visits had higher odds of NP testing (OR, 2.43; 95% CI, 2.07-2.86). Patients with diabetes or those treated in hospitals with a high volume of ED visits had a lower likelihood of being tested for NPs (adjusted OR, 0.76; 95% CI, 0.68-0.86 and 0.79; 95% CI, 0.66-0.94, respectively).

### Resource use

The RIW related to index ED visit as well as the 90-day RIW were significantly different between HF groups, with higher resources spent for the HF group who was tested for NPs.

### Interpretation

We found that three quarters of patients tested for NPs in the ED did not end up with a diagnosis of HF, which is likely consistent with clinicians’ knowledge of the established high negative predictive value of NP testing. We also identified several factors influencing NP testing patterns, including some comorbidities, geographic location, ED volume, and physician specialty. Finally, patients who had NP testing done were more likely to be admitted to the hospital during their index ED visit.

Urban and rural variations in testing for NPs within Alberta were evident despite a single-payer system and universal availability. In fact, there was even a difference between tertiary care centres in 2 urban settings. These variations in practice, despite strong endorsement in Canadian guidelines since 2007 for the role of NP testing in the ED, suggests a need for better knowledge dissemination efforts to standardize care and thereby optimize patient outcomes.26 All the physicians across the province received the same educational materials developed by AHS Chemistry Laboratory Integration Network in conjunction with a group of cardiologists, internists, and emergency physicians during the provincial implementation of NP testing.27

Our data showed that patients with HF who were tested for NPs were more often admitted to the hospital from the ED compared with patients who were not tested for NPs. Additionally, this group (patients with HF and tested for NPs) had a lower rate of short-term or long-term repeated ED visits compared with their counterparts with HF but who were not tested for NPs, even after adjusting for key patient- and hospital-related variables. In general, the length of stay in patients with HF who were tested for NPs and admitted to the hospital was shorter; the cause for this is uncertain but remained after adjustment. Additionally, the subsequent lower repeated ED visit rate remained even after landmark analyses for the evaluated periods out to 90 days after a hospital or ED visit. Potential explanations include a shorter time to diagnosis...
with fewer tests and initiation of appropriate therapy, unaccounted bias if patients with a higher certainty of HF or who are sicker are tested less often, or improved coordination of care given diagnostic certainty.

Previous randomized studies have demonstrated the cost-effectiveness of NT-proBNP testing in the ED, including a study done in Canada. Although the estimated cost saving by using NP testing varied between studies (from ~ USD$500-1800 cost reduction per case) and with varying time frames, almost all have demonstrated a significant cost-saving by using this biomarker. For example, Moe et al., in the study of Improved Management of Patients with Congestive Heart Failure (IMPROVE-CHF), showed a significant cost reduction ($949) in median costs at 60 days of follow-up but no significant difference in the median costs of the initial ED visit or initial hospitalization between NT-proBNP-guided and usual-care groups.

Compared with previous reports from European, Canadian, and US registries of patients with HF, the study population is similar regarding patient age, sex, and prevalence of comorbidities such as diabetes mellitus and atrial fibrillation. The BNP or NT-proBNP levels were also similar to those reported by registries in which NPs were measured. Considering the similar patient characteristics, we believe our results are generalizable to other regions of Canada and other countries. For regions that are planning to introduce, extend, or standardize their NP testing in the ED, the results of the current study may help them to recognize and address the potential target groups (eg, care providers who are more or less likely to order the test), patient groups that should be targeted for testing in the EDs, and particular hospitals where other services—eg, echocardiography—are not easily available.

Some strengths and limitations are noteworthy. First, and as with all administrative data studies, we lacked clinical details such as blood pressure, heart rate, ejection fraction, or patient-reported outcomes such as dyspnea. However, and unlike previous studies using population-level data, we linked laboratory values (both the testing and the result) and hospital and clinician-level variables together. Second, we did not have individual costing data and therefore used the RIW methodology, which may lack precision, and focused mostly on hospitalization-related costs; however it does provide an overall estimate of costs when available. Third, we did not capture data on physician-level decision making, ie, the probability that a patient having HF may influence the likelihood of NP testing. This study was conducted in the year after the institution of the provincial program in Alberta for the province-wide access to NP testing in EDs; hence, it should be noted that the results may be different than if the study had been done several years after the provincial program was started. Finally, we included sites across varying geographic regions and patient volumes, which may dilute the effect of individual outlier sites. However, by being inclusive across an entire province in a single-payer system, this is likely to enhance the identification of opportunities for further study and knowledge dissemination for the ideal use of NP testing.

In conclusion, several factors, including the type of care provider and ED volume, influenced the use of NPs in routine ED practice. Despite having a single-payer system and the universal availability of NP testing, there was substantial geographic variation in testing for NPs in Alberta EDs. Optimization of an NP testing strategy in clinical practice would be useful for health care systems to potentially improve patient outcomes or cost-efficiency of care, or both.

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Supplementary Material
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