Assessment of Patient Medication Adherence, Medical Record Accuracy, and Medication Blood Concentrations for Prescription and Over-the-Counter Medications

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Abstract

**IMPORTANCE** Inaccurate medication records and poor medication adherence result in incomplete knowledge of therapy for patients.

**OBJECTIVE** To study accuracy of medical records and patient adherence by measuring blood concentrations of medications.

**DESIGN, SETTING, AND PARTICIPANTS** This cross-sectional study validated a serum-based liquid chromatography–tandem mass spectrometry assay to simultaneously quantify 263 medications used for acute and chronic conditions. The assay panel was applied to 3 clinical patient cohorts: residual serum from 1000 randomly selected samples sent for routine clinical chemistry testing between April 8 and October 6, 2015 (residuals cohort), 50 prospectively enrolled patients in a gastroenterology clinic between March 1 and March 15, 2016, who were prescribed more than 5 medications (gastroenterology care cohort), and a convenience cohort of 296 patients with hypertension who sought care in an emergency department (ED care cohort) between July 1, 2012, and April 25, 2013. Integrated data analysis of the cohorts was performed from August 22 to November 29, 2017.

**MAIN OUTCOMES AND MEASURES** Medication serum concentrations, electronic health record medication lists, and predicted drug interactions.

**RESULTS** Of the 1346 total samples, 1000 came from the residuals cohort (640 women and 360 men; median age, 60 years [interquartile range (IQR), 44-71 years]), 50 from the gastroenterology care cohort (30 women and 20 men; median age, 66 years [IQR, 62-70 years]), and 296 from the ED care cohort (160 women and 136 men; median age, 59 years [IQR, 52-66 years]). Median medication adherence, defined as the subset of detected medications from the prescription record, was 83% (IQR, 50%-100%) in the residuals cohort, 100% (IQR, 84%-100%) in the gastroenterology care cohort, and 78% (IQR, 57%-100%) in the ED care cohort. Patients adherent to 1 medication were more often adherent to other medications. Among patients prescribed 3 medications or more, there were no significant associations between medication adherence and sex or number of prescribed medications, and there was a modest association between adherence and age. By comparing detected vs prescribed medications, we detected a median of 0 (IQR, 0-2) medications per patient that were not listed in the electronic health record in the residuals cohort, 1 (IQR, 0-2) medication per patient that was not listed in the electronic health record in the gastroenterology care cohort, and 1 (IQR, 0-2) medication per patient that was not listed in the electronic health record in the ED care cohort. A total of 435 patients (43.5%) in the residuals cohort had no discrepancy between the electronic health record and detected medication lists, 22 patients (44.0%) in the gastroenterology care cohort, and 28 patients (9.5%) in the ED care cohort.

**Key Points**

**Question** What is the agreement between prescribed medications in the electronic health record and empirically measured drug concentrations for 263 frequently prescribed and coprescribed medications?

**Findings** In this cross-sectional study of 1346 patients in 3 different health care settings, 78% to 100% of medications were detected as prescribed in the electronic health record medication list. In addition, medications not included in electronic health record medication lists were detected and were more frequently associated with alerts for potential adverse drug reactions.

**Meaning** Medication lists in the electronic health record are often inaccurate; a method for comprehensive medication monitoring offers promise to improve adherence, reconcile medical records, and address safety and effectiveness concerns associated with the choice of medication for patients who are prescribed multiple medications.

(continued)
Abstract (continued)

care cohort had no discrepancy between the electronic health record and detected medication lists, and 41 patients (13.9%) in the ED care cohort had no discrepancy between the electronic health record and detected medication lists. Half of adverse drug reaction alerts occurred among medications detected without prescription.

CONCLUSIONS AND RELEVANCE  Comprehensive medication monitoring offers promise to improve adherence, the accuracy of medical records, and the safety for patients with polypharmacy.

Introduction

Measurement of medication concentrations has been used to determine dosing paradigms in drug development, 1,2 to detect misuse of abused medications, 3 to investigate pharmacogenomic differences in drug-metabolizing status among patients, 4,5 and as the primary measure in clinical therapeutic drug monitoring. 6 These applications have focused on one or a small number of medications at a time to answer questions about individual components of a patient’s medication regimen. This approach to medication monitoring does not meet the needs of patients with comorbid conditions who are prescribed multiple medications and who drive a disproportionate share of health care use. Identifying and quantifying all medications that a patient takes would provide information vital to optimizing treatment for each patient, including an accurate assessment of medication adherence, of ingested medications relative to the medical record, and of medication concentrations relative to target reference ranges. Recent pilot medication measurement studies have unearthed problematic trends in medication therapy for real-world patients prescribed multiple medications using small, focused medication panels. 7,8 These evidence-based studies of nonadherence, medication record inaccuracies, and subtherapeutic and/or supratherapeutic dosing found costly and potentially dangerous issues affecting both patients and the health care system. 9,10

Measuring all medications using individual assays is impractical: the probability of 2 patients prescribed 5 or more medications being on the same medication regimen is less than 1%. 11 Technical advances in liquid chromatography-tandem mass spectrometry (LC/MS/MS) technology have made possible the simultaneous measurement of hundreds of analytes in a single complex biological sample, offering a practical way of assessing most prescribed medications in a single test. The ingestion of medications by patients frequently does not match the prescription records, 7,12 and this would be valuable information that can be used to improve medication therapy and safety. If the concentration of each medication in a patient was known, then medication adherence and the discordance between the medications taken and those listed in the patient’s health record could be shown at both the individual level and the population level, and it could also be shown which drug interactions, genetic polymorphisms, and environmental factors manifest as altered drug concentrations.

Therefore, we describe a 263-medication serum assay panel that detects 91% of small-molecule oral drug prescriptions for US patients, using serum or plasma samples. Medications were selected based on prescribing frequency, drug interaction potential, pharmacogenetic influence, and route of administration. To use this comprehensive therapeutic drug monitoring test to address medication therapy as outlined, 3 cohorts totaling 1346 clinical samples were examined. This novel approach of comprehensively comparing measured medication concentrations with patient medical records could be used to optimize medication efficacy and safety and tailor drug therapy.
Methods

Clinical Samples
Serum samples were obtained at the Cleveland Clinic, Cleveland, Ohio; the Vanderbilt University Medical Center (VUMC), Nashville, Tennessee; and the Associates in Gastroenterology, Nashville, Tennessee. Patient enrollment, sample acquisition, and data collection were performed by the Cleveland Clinic, VUMC, and Associates in Gastroenterology personnel. Quantitative sample analysis was performed by using an assay developed and validated under College of American Pathologists/Clinical Laboratory Improvement Amendments guidelines by Precera Bioscience. Study designs at all 3 organizations were approved by the respective organizations’ institutional review board. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Residuals Cohort
A random selection of 1000 serum samples remaining after routine vitamin D testing between April 8 and October 6, 2015, at the Cleveland Clinic was used as the residuals cohort. Residual samples after vitamin D testing were chosen because vitamin D is a high-volume test routinely ordered by multiple clinicians in otherwise generally healthy outpatients. The Cleveland Clinic Institutional Review Board granted a waiver of informed consent on the basis that residual material was used from preexisting laboratory specimens to measure medication concentrations, and there would be no patient contact that would affect patient care. The Cleveland Clinic central electronic health record (EHR) database was used to match medication lists with residual serum samples from all 1000 individuals.

Gastroenterology Care Cohort
A convenience cohort of 50 patients seeking treatment at a gastroenterological clinic between March 1 and March 15, 2016, was used as the gastroenterology care cohort. These patients were prospectively approached and provided written informed consent to participate in a medication monitoring study. Patients were eligible if they were prescribed 5 or more medications on their primary EHR medication record, at least 1 of which was from the statin medication class. Not all prescribed medications were included in the test panel; as such, some patients have fewer than 5 medications listed. A final medication list was obtained through medication reconciliation by comparing patient-reported medications and dosing time with the electronic medical record at the time of enrollment.

Emergency Department Care Cohort
A convenience cohort of patients with hypertension who were treated by a VUMC primary care professional and who sought medical care in the VUMC adult emergency department (ED) between July 1, 2012, and April 25, 2013, was used as the ED care cohort, and these patients were approached for enrollment. A full description of the inclusion criteria and the patient cohort is available elsewhere; in brief, patients prescribed at least 1 of 14 antihypertensive medications for hypertension and a functioning peripheral intravenous line were approached for consent. Of the 300 individuals who provided written informed consent to participate, 296 had serum samples available for secondary exploratory analyses. Reconciled medication lists were obtained from the EHR and reviewed for accuracy with the patients at the time the blood samples were obtained. Medications prescribed outside the VUMC system and not mentioned by patients would be omitted from the medication list.

Sample Collection, Assay, and Data Analysis
Samples were collected by study personnel at the investigation site and processed by blinded laboratory personnel. Assay validation and individual medication performance characteristics are
contained in the eMethods in the Supplement. Integrated data analysis of the 3 cohorts was performed from August 22 to November 29, 2017.

**Multiplex Drug Panel Composition**

A multiplex assay for the assessment of drug concentrations in serum or plasma samples was developed for studying medication exposure in humans that consisted of 277 analytes, corresponding to 263 drugs covering more than 30 drug classes. Of these, 179 analytes corresponding to 173 drugs met performance criteria allowing quantitative assessment. The remainder were measured qualitatively and reported as “detected” or “not detected.” The complete panel is listed in eTable 1 in the Supplement, with details including biological half-lives in eTable 2 in the Supplement. The panel covers 91% of prescription drug use among US adults with polypharmacy when compared against the 2013-2014 National Health and Nutrition Examination Survey of prescription drug use (eMethods in the Supplement).

**Statistical Analysis**

Summary statistics were presented as frequencies and proportions, as appropriate. Univariate analyses exploring patient factors associated with adherence within each cohort were performed with box plots (2-sample t tests) and 1-way analysis of variance. The association between medication half-life and proportion of prescribed medications detected was examined with a scatterplot and a locally weighted smoothing line with 95% CIs. A multivariable linear regression model (percent adherence = cohort [3-level] + sex [sex] + age [years] + prescribed drug count) was used to explore factors associated with greater adherence among the 640 patients from the 3 clinical cohorts who were 20 years or older, had nonmissing data on sex, and were prescribed 3 or more drugs from the subset of 189 medications described in the eMethods in the Supplement. Examination of the Q-Q plot revealed moderately nonnormal model residuals. Repeating the analysis with nonlinear modeling (glm, family = γ) gave significant coefficients for the gastroenterology care cohort (P = 4 × 10⁻⁵) and age (P = .02), similar to the results from linear modeling. As such, linear modeling is discussed in the Results.

We also explored whether the proportion of detected medications differed by medication class. Only medications from the subset of 189 medications were considered. For these analyses, we excluded medications that were prescribed as needed and/or were detected but not included in the medication list (ie, detected, not prescribed [DNP]). Adherence by drug class was calculated by tabulating the percentage of all prescriptions in the class in which the drug was detected.

Logistic regression was performed with drug class as a 23-level categorical variable (drug detected [yes or no] = cohort [3-level] + sex [age] + adherence to other medications [continuous] + drug class). Adherence to other medications ranged from 0% to 100% (number of medications detected/number of medications prescribed) and excluded the medication used as the dependent variable. The exponentiated coefficients from the model represent the adjusted odds of being adherent. Statistical analyses were performed using R, version 3.3.2 (R Foundation for Statistical Computing). All P values were from 2-sided tests and results were deemed statistically significant at P < .05.

**Results**

**Clinical Samples**

A total of 1346 samples were analyzed among the 3 cohort populations (Table 1). For the residuals cohort, the median age was 60 years (interquartile range [IQR], 44-71 years), 640 were women, and 360 were men. These patients were prescribed a median of 2 medications (IQR, 0-5 medications). For the gastroenterology care cohort, the median age was 66 years (IQR, 62-70 years), 30 were women, and 20 were men. These patients were prescribed a median of 6 medications (IQR, 5-8 medications). For the ED care cohort, the median age was 59 years (IQR, 52-66 years), 160 were
women, and 136 were men. These patients were prescribed a median of 7 medications (IQR, 5-9 medications).

Analysis using the validated mass spectrometry–based 263-drug serum assay revealed a median number of detected medications per patient of 2.5 (IQR, 1-5) in the residuals cohort, 6 (IQR, 5-9) in the gastroenterology care cohort, and 6 (IQR, 4-7) in the ED care cohort. Inconsistencies between detected and listed medications consisted of both missing medications that were prescribed but not detected and additional medications that were DNP according to the patient EHR. More medications were detected in serum samples from the gastroenterology care cohort and ED care cohort (patients seeking treatment) than from the residuals cohort (patients randomly selected), similar to previous results using a smaller assay panel.7 To discern trends within categories of medications, we compared the overall detection rate among patients in the ED care cohort relative to those in the residuals cohort (eFigure 1 in the Supplement). The detection rates of individual medications were correlated between the 2 large cohorts. Narcotic analgesics were overdetected in patients in the ED care cohort, out of proportion to their prescription rate (eFigure 2 in the Supplement).

Medication Adherence
To minimize the role of technical factors when assessing overall adherence to prescribed medications, we defined a subset of medications that were usually administered orally and had a half-life greater than 4 hours or an empirical detection rate of 70% or more (eMethods in the Supplement; Figure 1). The resulting subset of 189 detected drugs was used to calculate the percentage of all prescribed medications to which a patient was adherent. Using this measure, we found that the median adherence rate for samples was 83% (IQR, 50%-100%) in the residuals cohort, 100% (IQR, 84%-100%) in the gastroenterology care cohort, and 78% (IQR, 57%-100%) in the ED care cohort (Table 1). We found no association between adherence and sex (eFigure 3B in the Supplement), although univariate linear regression suggested an association with age in the residuals cohort (β = 0.36; 95% CI, 0.15-0.57; P < .001) and ED cohort (β = 0.36; 95% CI, 0.06-0.66; P = .02). There was no such detectible trend among patients in the gastroenterology care cohort, all of whom were 40 years or older. The association between the number of prescribed medications and overall adherence was variable and inconsistent among the 3 cohorts (eFigure 3D in the Supplement). To corroborate these trends, we modeled percent adherence for each patient with polypharmacy using multivariate linear regression. Only being in the gastroenterology care cohort (β = 19.6; 95% CI, 11.1-28.2; P < .001) and having an older age (β = 0.35; 95% CI, 0.19-0.52; P < .001) were associated with greater adherence.

When measured by medication class, adherence ranged from 50.0% (25 of 50) for leukotriene modifiers (ie, montelukast) to 86.7% (72 of 83) for anticoagulants (eTable 3 in the Supplement). Among the classes with the lowest adherence were nonsteroidal anti-inflammatory drugs.

### Table 1. Clinical Characteristics of Patient Cohorts

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Residuals Cohort (n = 1000)</th>
<th>Gastroenterology Care Cohort (n = 50)</th>
<th>ED Care Cohort (n = 296)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, No. (%)</td>
<td>640 (64.0)</td>
<td>30 (60.0)</td>
<td>160 (54.1)</td>
</tr>
<tr>
<td>Age, median (IQR), y</td>
<td>60 (44-71)</td>
<td>66 (62-70)</td>
<td>59 (52-66)</td>
</tr>
<tr>
<td>No. of medications per patient, median (IQR)a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prescribed</td>
<td>2 (0-5)</td>
<td>6 (5-8)</td>
<td>7 (5-9)</td>
</tr>
<tr>
<td>PAD</td>
<td>1 (0-3)</td>
<td>5.5 (4-7)</td>
<td>4 (2-6)</td>
</tr>
<tr>
<td>Detected</td>
<td>2.5 (1-5)</td>
<td>6 (5-9)</td>
<td>6 (4-7)</td>
</tr>
<tr>
<td>DNPb</td>
<td>0 (0-2)</td>
<td>1 (0-2)</td>
<td>1 (0-2)</td>
</tr>
<tr>
<td>Adherence, median (IQR), %a</td>
<td>83 (50-100)</td>
<td>100 (84-100)</td>
<td>78 (57-100)</td>
</tr>
<tr>
<td>Accurate EHR medication list, No. (%)a</td>
<td>435 (43.5)</td>
<td>22 (44.0)</td>
<td>41 (13.9)</td>
</tr>
</tbody>
</table>

Abbreviations: DNP, detected, not prescribed; ED, emergency department; EHR, electronic health record; IQR, interquartile range; PAD, prescribed and detected.

a Only prescription drugs tested in the assay.

b Number of detected medications that were not prescribed (ie, not listed in the EHR).

c Percentage of prescribed medications detected, of the 189-drug subset for assessing overall adherence (see Methods).

d The percentage of patients for which there are no discrepancies between the EHR and detected medication list: no prescribed, nondetected medications from the 189-drug subset and no DNP medications, excluding over-the-counter drugs.
antihistamines, antiemetics, and muscle relaxants; the latter 2 classes are combined in the “other central nervous system agents” group and represent 83.2% of all class prescriptions (149 of 179). We found no clear patterns in adherence by medication class. For example, among cardiovascular agents, adherence to calcium channel blockers was low, at 65.9% (143 of 217), while adherence to antiarrhythmics was higher, at 81.8% (45 of 55). Because this naive analysis may have been confounded, we modeled individual medication adherence by medication class with the inclusion of covariates for cohort, age, and adherence to other medications. Coefficients for the drug classes, which reflect increased or decreased probability of adherence within the model, were highly correlated with the naive estimates ($R^2 = 0.9$; eFigure 4 in the Supplement). Adherence to 1 medication was associated with adherence to other medications (odds ratio for a 1% increase in adherence to other drugs, 1.03; 95% CI, 1.02-1.03; $P < .001$), indicating that the best estimate of whether patients are taking a given medication is whether or not they took their concomitant medications.

Medical Record Inaccuracies

The median number of DNP medications per patient was 0 (IQR, 0-2) in the residuals cohort, 1 (IQR, 0-2) in the gastroenterology care cohort, and 1 (IQR, 0-2) in the ED care cohort (Table 1). The top 10% of patients exceeded 3.5 such medications per patient. As anticipated, over-the-counter drugs made up the largest proportion of DNP medication classes (eTable 4 in the Supplement), narcotic analgesics were the prescription class with highest DNP proportion, and within the benzodiazepine class, diazepam was not prescribed in 61.4% of samples (27 of 44) in which it was detected. For the ED care cohort, however, patients may have received medications as part of care in the ED prior to having blood obtained for tests. The rate of DNP detections by drug class was correlated in the residuals cohort and ED care cohort (eFigure 5 in the Supplement).

We evaluated prescription and detection data on an individual patient basis by determining the percentage of patients with any unexpected finding relative to the EHR medication list. Electronic health record medication lists were classified as accurate if there were no prescribed but nondetected medications from the subset of 189 drugs used for assessing adherence and no DNP medications (excluding over-the-counter medications). The percentage of patients with accurate EHR medication lists was 43.5% for the residuals cohort (n = 435), 44.0% for the gastroenterology care cohort (n = 22), and 13.9% for the ED care cohort (n = 41) (Table 1).

Figure 1. Detection Rate of Prescribed Oral Medications vs Biological Half-life

Percentage of all prescribed oral medications that are detected in the assay vs literature-reported biological half-life in hours; drugs with a half-life greater than 36 hours are shown at 36 hours. Only drugs with 20 or more prescriptions were retained, after combining results from the present 3 cohorts and additional cohorts from prior work (eMethods in the Supplement). The gray shaded area represents the 95% CIs on the trend as determined with locally weighted smoothing (LOESS). For medications that are often used nonorally, such as clonidine and prednisone, only prescriptions for which the electronic health record explicitly listed an oral formulation were retained. These detection rates are not adjusted for dosing frequency, time since ingestion, as needed usage (ie, nonsteroidal anti-inflammatory drugs), or topical administration where the electronic health record indicated otherwise.


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Drug-Drug Interactions

We examined the frequency and severity of drug-drug interaction alerts among patients and found a total of 1245 unique moderate, major, or severe drug-drug interactions as defined in the Elsevier Gold Standard database across the 1346 samples (Table 2). The most common interaction, involving lisinopril and hydrochlorothiazide, was observed 53 times. These medications are, however, recommended for the treatment of hypertension and are often combined in a single pill for a synergistic antihypertensive effect and to increase adherence. By combining the 3 cohorts, 318 of 601 (52.9%) major or severe drug-drug interactions involved DNP medications, out of proportion to the 1510 of 4608 (32.8%) detected medications not in the EHR (Figure 2).

Discussion

We describe a laboratory-developed assay that measured 263 prescription and over-the-counter medications to comprehensively assess medication treatment for patients with complex medical conditions across multiple health care settings. Medications in the panel were selected based on a variety of factors, including prescription prevalence, potential for drug-drug or drug-gene interactions, analytical performance, and route of administration, to determine how these elements manifested when measured in real-world patients. In samples collected from 3 distinct clinical populations, the results revealed the following: (1) medications are frequently detected despite lack of prescription evidence in the EHR, (2) patient adherence varies by health care setting, (3) being

<table>
<thead>
<tr>
<th>Cohort (No. of Patients)</th>
<th>Alert Severitya</th>
<th>Severe</th>
<th>Major</th>
<th>Moderate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Residuals (n = 500)</td>
<td></td>
<td>12</td>
<td>172</td>
<td>619</td>
</tr>
<tr>
<td>Primary care (n = 48)</td>
<td></td>
<td>3</td>
<td>37</td>
<td>154</td>
</tr>
<tr>
<td>ED care (n = 261)</td>
<td></td>
<td>8</td>
<td>140</td>
<td>541</td>
</tr>
<tr>
<td>Totalc</td>
<td></td>
<td>20</td>
<td>273</td>
<td>952</td>
</tr>
</tbody>
</table>

| No. of DDIs/patient with ≥3 drugs detected | Residuals (n = 500) | 0.03 | 0.6 | 2.7 |
| Primary care (n = 48)                  | 0.06 | 0.9 | 4.8 |
| ED care (n = 261)                       | 0.03 | 1.0 | 4.3 |
| Total                                    | 0.03 | 0.7 | 3.3 |

Abbreviation: DDI, drug-drug interaction; ED, emergency department.

a Severe: contraindicated. Major: may be contraindicated in a select group of patients; monitor patient. Moderate: may result in unintended clinical effects; monitor patient.
b Each pair of drugs involved in a DDI is considered a unique DDI.
c The number of unique DDIs involving detected drugs was obtained by pooling the 3 cohorts; not the sum from the 3 cohorts because many DDIs were observed in multiple cohorts.

Across each cohort, detected medications were classified as detected, not prescribed (DNP) when not listed in the electronic health record; DDIs were similarly classified if 1 or both drugs involved were DNP. Only individuals with 3 or more detected drugs were included in the analysis. The proportion of interactions involving DNP drugs was greater than the corresponding proportion of detections in all 3 cohorts: residuals cohort, gastrointestinal care cohort, and emergency department (ED) cohort (all \(P < .001\) by \(\chi^2\) tests). Error bars represent SEs of proportions calculated using the normal approximation.
adherent to 1 medication is a positive determinant of adherence to other medications, and (4) drug-
drug interactions were common and occurred more frequently among patients with medications
that were DNP.

A recent study has shown that LC/MS/MS technology can be used qualitatively as a medication
therapy optimization tool to address patient adherence and reconcile medical records using a subset
of the medications tested in this panel. As individual patient data are amassed, drug exposure data
relative to health parameters are being produced, offering a novel insight into patient behaviors,
medication errors, and biological determinants of medication therapy. Collectively, we demonstrated
that 63.0% of patients (848 of 1346) have a discrepancy between the medical record and detected
medications, illustrating the extent to which adherence and medical record inaccuracies manifest at
the patient level.

Medication use depends on many factors, with patients typically consuming more medications
as they age. Using a 189-drug subset of orally prescribed medications to assess adherence, we
found that adherence was higher in samples obtained from prospectively enrolled patients
(gastroenterology care cohort) than in samples obtained from retrospectively tested patients
(residuals cohort and ED care cohort).

Many medications detected using the comprehensive LC/MS/MS panel were not listed in the
medical records of patients. Opioids and diazepam were the most common medications that were
detected despite lack of evident prescription. The medications used to treat cardiovascular and other
chronic diseases were, however, frequently found in patients who were not expected to be taking
them. Because the latter medications have low potential for abuse, the medical record itself may be
incomplete and not accurately reflect what patients are prescribed or taking. More important, a
disproportionate number of potentially interacting medications were noted among patients without
evidence of a prescription, suggesting that health care professionals may be prescribing and making
clinical care decisions with incomplete information. As an example, 429 of 1678 (25.6%) medications
detected in patients in the ED care cohort were not listed in the prescription record; however, 131 of
265 (49.4%) predicted drug-drug interactions came from these medications. This finding indicates
that medications unknown to the health care professional triggered more drug-drug
interaction alerts.

Limitations
There are several limitations to this study. First, the time of dosing was not obtained (except for the
gastroenterology care cohort), and patients take medications at different times of the day, so
individual medications were not consistently measured at trough level. Second, medications with a
short half-life or medications taken as needed that do not reach steady state concentrations in serum
may have skewed adherence estimates, although our adherence estimates exclude short half-life
medications with low empirical detection rates. Third, persistence, or adherence over time, is an
important measure to consider in future studies. Fourth, the incompleteness or presence of multiple
medication records with different clinicians, and the uniqueness of medication combinations in
patients with complex medical conditions, are caveats that must be considered when using such a
test to optimize therapy. To be leveraged quantitatively, larger cohorts with consistent recruitment
strategies will be necessary to contextualize medication measures with patient information if they
are to prove valuable clinical decision support.

Conclusions
We have developed a test capable of accurately measuring 263 prescribed and over-the-counter
medications in a single blood sample. Applied clinically, this exploratory analysis showed that
nonadherence is common and that the EHR medication list often did not agree with detected
medications. The best determinant of whether patients take their medication is whether they take
concomitant medications, demonstrating that behavior is one important parameter underlying
variability in response to treatment. Comprehensive medication monitoring has merit and will require further data comparing measured drug concentrations with outcomes to verify published reference ranges and future clinical decision support algorithms.

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Author Contributions: Drs Sutherland and Ryan had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Morrison, Milne, Daniels, Ryan.

Acquisition, analysis, or interpretation of data: Sutherland, Morrison, McNaughton, Daly, Milne, Daniels.

Drafting of the manuscript: Sutherland, Morrison, McNaughton, Daniels.

Critical revision of the manuscript for important intellectual content: McNaughton, Daly, Milne, Ryan.

Statistical analysis: Sutherland.

Obtained funding: Ryan.

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Supervision: Morrison, Ryan.

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