Using aggregated, de-identified electronic health record data for multivariate pharmacosurveillance: A case study of azathioprine

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A B S T R A C T

Objective: To demonstrate the use of aggregated and de-identified electronic health record (EHR) data for multivariate post-marketing pharmacosurveillance in a case study of azathioprine (AZA).

Methods: Using aggregated, standardized, normalized, and de-identified, population-level data from the Explore platform (Explorys, Inc.) we searched over 10 million individuals, of which 14,580 were prescribed AZA based on RxNorm drug orders. Based on logical observation identifiers names and codes (LOINC) and vital sign data, we examined the following side effects: anemia, cell lysis, fever, hepatotoxicity, hypertension, nephrotoxicity, neutropenia, and neutrophilia. Patients prescribed AZA were compared to patients prescribed one of 11 other anti-rheumatologic drugs to determine the relative risk of side effect pairs.

Results: Compared to AZA case report trends, hepatotoxicity (marked by elevated transaminases or elevated bilirubin) did not occur as an isolated event more frequently in patients prescribed AZA than other anti-rheumatic agents. While neutropenia occurred in 24% of patients (RR 1.15, 95% CI 1.07–1.23), neutrophilia was also frequent (45%) and increased in patients prescribed AZA (RR 1.28, 95% CI 1.22–1.34). After constructing a pairwise side effect network, neutropenia had no dependencies. A reduced risk of neutropenia was found in patients with co-existing elevations in total bilirubin or liver transaminases, supporting classic clinical knowledge that agranulocytosis is a largely unpredictable phenomenon. Rounding errors propagated in the statistically de-identified datasets for cohorts as small as 40 patients only contributed marginally to the calculated risk.

Conclusion: Our work demonstrates that aggregated, standardized, normalized and de-identified population level EHR data can provide both sufficient insight and statistical power to detect potential patterns of medication side effect associations, serving as a multivariate and generalizable approach to post-marketing drug surveillance.

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1. Introduction

Azathioprine (AZA), a purine analog widely used in solid organ transplants and autoimmune disorders, is known to induce a spectrum of toxicities. While bone marrow suppression [1,2] and hepatotoxicity [3] – thought to be dose-dependent effects due to the accumulation of 6-thioguanine metabolites – are the most widely recognized side effects, dermatologic [4] and renal effects [5] have also been reported. Predictions of adverse reactions can be guided by thiomercaptopurine methyltransferase (TPMT) activity [6,7], though TPMT activity has poor sensitivity as a test for toxicity [8]. As a supplement to measuring TPMT activity, case reports of AZA’s toxicities help document the clinical course of side effects, yet the likelihood of a particular organ system’s involvement is often established on an ad hoc basis from a survey of the literature. Consequently, side effects with a poor showing in the literature are presumed to be rare, though they may, in fact, be common. More generally, tracking side effects via case reports or reporting databases provides inaccurate and incomplete estimates of incidence.

While case reports and TPMT activity help to substratify patients into cohorts likely to develop adverse reactions, clinical
awareness can be further heightened by assembling the frequent sets of clinical patterns that arise in patients prescribed AZA. Studying multivariate side effects allows for a synergistic approach to identifying adverse drug reactions, which can point to clinical patterns for gauging a subgroup’s risk of developing complications. While knowledge of disease presentations and syndromes was classically acquired through prolonged clinical observations, the emergence of electronic health data sources now allow for the possibility of mining such information through retrospective data analysis, based on data captured as part of routine clinical care. In particular, network models have proven useful in mining and organizing patterns of clinical phenomena, with recent applications in the assembly of disease comorbidity networks based on frequencies of ICD-9 (International Classification of Diseases, ninth revision) code co-occurrence [9,10]. These networks of side effects provide a global overview of disease–disease associations and may be useful for lifetime risk calculations, though they have limited utility in informing clinical practice as they lack temporal associations and specific clinical variables. Additionally, there may be significant issues with the accuracy of ICD-9 codes. In the area of pharmacovigilance, research has classically focused on signal detection from voluntary reporting databases, which are limited by the biases inherent in voluntary submissions of adverse drug event [11]. Methodologically, pharmacovigilance has largely focused on the extraction of bivariate – i.e. drug-event – signals [11,12], though studies have recently emerged that focus on detecting multivariate patterns through association rule mining [13,14].

In this work, we aim to (1) quantify the incidence of size effects associated with AZA, (2) compare the incidence of side effects associated with AZA to other similar drugs, and (3) combine network-based approaches with traditional pharmacovigilance signal detection methods to discover patterns of multiple events associated with AZA that can be clinically informative. As opposed to discovering events in reporting databases, we used a database of aggregated, standardized, normalized, and de-identified population level EHR data from over 10 million patients. Rather than using ICD-9 codes, we use laboratory and vital sign measurements – reliable fields in most EHR systems [15] – to assess the presence of side effects. The use of laboratory and vital sign values from aggregated EHR data avoids the biases of spontaneous reporting systems and the problems with provider-entered ICD-9 codes, while simultaneously increasing our power to detect rare event associations.

2. Materials and methods

2.1. Database description

De-identified data was obtained using the Explore application of the Explorys platform (Explorys, Inc.), which places a health data gateway (HDG) server behind the firewall of each participating healthcare organization. After collecting data from a variety of health information systems – electronic health records (EHRs), billing systems, laboratory systems, etc. – the HDG maps the data to informatics ontologies, standardizing and normalizing measurements. Next, the data from each participating healthcare organization is passed into a data grid. A web application allows each healthcare organization to search and analyze the aggregated, standardized, normalized, and de-identified population level data.

At the time of this study, the aggregated data grid contained information on more than 10 million patients from multiple, distinct healthcare systems with different EHRs; the EHR serves as the primary medical record within participating institutions. All data used were de-identified to meet Health Insurance Portability and Accountability Act (HIPAA) and Health Information Technology for Economic and Clinical Health (HITECH) Act standards. Therefore, this work was deemed not to be human studies research by the Institutional Review Board of the MetroHealth System. Business affiliation agreements were in place between all participating healthcare systems and Explorys Inc. regarding contribution of EHR data to facilitate searching and indexing. Diagnoses, findings, and procedures were mapped into the systematized nomenclature of medicine–clinical terms (SNOMED-CT) hierarchy [16]. Prescription medication orders were mapped to RxNorm [17]. Laboratory test observations were mapped to logical observation identifiers names and codes (LOINC), established by the Regenstrief Institute [18]. At the time of analysis, the application contained 14,580 records of patients who had ever been prescribed AZA.

2.2. Side effect network analysis

Our analysis focused on end-organ dysfunction known to be implicated with AZA, as well as non-specific side effects, such as hypertension, fever, and cell lysis. To study side effect patterns of AZA associated with particular organ systems, we used key reference ranges for lab values as proxies of organ function (Table 1) [19].

Patients were selected who had normal lab values within 90 days prior to being prescribed AZA, and an abnormal measurement within 90 days after being prescribed AZA. As the actual administration or consumption of a medication is often not recorded in EHRs, especially for outpatient medications, we used medication orders as a proxy for drug administration (i.e. the term “prescribed” refers to the date at which the order for “azathio-prine” appeared in the patient’s EHR). For neutropenia and neutrophilia, we extended the selection window to patients with a normal neutrophil count within 365 days prior to AZA prescription. To avoid inflating the significance of creatinine measurements due to subgroup effects from pre-existing renal dysfunction, we excluded all patients with an ICD-9 or American Medical Association Common Procedural Terminology (CPT) code mapped to any of the following SNOMED terms: renal impairment, renal failure syndrome, history of kidney transplant, or renal transplant (procedure).

2.3. Control cohort

Identification of patients suffering from various side effects is subject to the myriad biases of dealing with EHR data. For instance, an elevation in blood pressure observed after prescribing AZA may be due to external factors (e.g. environment, other drugs) or errors in measurement. Similarly, an elevation in liver enzymes may simply be a phenomenon associated with the underlying autoimmune disease rather than AZA. To address these issues and to calculate the significance of AZA-induced side effects, we assembled a control cohort of patients who experienced abnormal values when administer one of 11 other anti-rheumatic drugs (Table 2). The control drugs were identified by first selecting those drugs tagged with the SNOMED (Systemized Nomenclature of Medicine) code “anti-rheumatic agents.” This unfiltered list of 42 drugs contains agents with both frequent and infrequent side effect profiles, and the inclusion of drugs with infrequent side effects would artificially inflate the significance of side effects associated with AZA. From identifying statistically significant side effects, we also sought to identify clinically relevant side effects. In this regard, it was important to account for the prevalence of “common” side effects, e.g. headache, to judge the relevance of side effects associated with AZA. Thus, to avoid statistical bias and produce clinically relevant
results, we focused on those drugs most likely to produce side effects. Namely, we selected the subset of anti-rheumatic drugs for which at least 5% of all patients prescribed the drug were tagged with the SNOMED code “Adverse Reaction to Drug” and at least 50% were tagged with a SNOMED “Allergy to Drug” code. This approach does not guarantee that a particular drug was responsible for an adverse reaction or a drug allergy; rather, it serves to increase the likelihood of a drug-event association. We also included sulfasalazine, for whom 49.4% of patients prescribed the drug had an “Allergy to Drug” code. Through this process, we arrived at a concise list of 12 anti-rheumatic agents that are prone to inducing toxicity. After manual inspection of this list, homatropine was excluded because it is applied topically, rather than taken orally, to treat rheumatologic sequelae (i.e. uveitis). Overlap is evident between the “AZA” and “non-AZA” cohorts since controlling the AZA cohort for the absence of the other 11 drugs was computationally intractable and yielded cohorts of near-null size, as most patients prescribed AZA have also been prescribed other anti-rheumatic agents at some point.

We performed database searches for subsets of patients experiencing each of the 9 individual side effects (Table 1) and the 36 non-redundant side effect pairs. As over-constraining the search resulted in too few patients, searches were not designed to be mutually exclusive, i.e. a search for patients with abnormal creatinine and abnormal bilirubin was not controlled to rule out those patients with abnormal hemoglobin, abnormal blood pressure, etc. The total number of patients experiencing each individual side effect and each side effect pair is shown in Supplemental Table 1. For the AZA group experiencing two side effects, cohort sizes ranged from 10 to 310 patients. Control cohort sizes ranged from 70 to 1400 patients. We also calculated the number of patients with normal laboratory and vital sign values before and after drug prescription. This value was used in calculating the total number of patients in whom the value was measured, which was necessary for estimating the proportion of patients experiencing a single side effect.

2.4. Side effect network

As with previous network models of disease co-occurrence [9,10], we began construction of our network by compiling the frequencies of side effect pairs. To help identify causal relationships between side effects, we then calculated the conditional probability of developing a side effect, as per Bayes’ theorem:

\[
P(A|B) = \frac{P(A \cap B)}{P(B)}
\]

where \(A\) and \(B\) represent two abnormal values for two side effects. To reduce the number of pairwise searches required, we simplified the probability as follows:

\[
P(A|B) = \frac{\#(A \cap B)}{\#(A \cup B)} \approx \frac{\#(A \cap B)}{\#B}
\]

where \(\#(A \cap B)\) represents the number of patients with abnormal values for both \(A\) and \(B\), and \(\#(A \cup B)\) represents the total number of patients with either an abnormal or normal value for \(B\). The right-hand side approximation is possible if the total number of patients with either an abnormal or normal value for \(B\) is similar to the total number for the numerator, \(P(A \cap B)\). We found this to be true for our data, where both denominators were of similar order. To normalize the probability of AZA event associations by an appropriate background, we calculated the relative risk of a side effect association in the AZA cohort relative to the control cohort, assessing significance using the 95% confidence interval. This approach is akin to the proportional reporting ratio commonly used in pharmacovigilance [11]. Cells in Table 3 are color-coded according to the relative risk induced by AZA relative to the control drugs.

2.5. Error propagation analysis

Since cohort numbers reported were rounded to the nearest ten (for full statistical de-identification), we calculated the uncertainty propagated by this rounding error. Since the relative risk is based on divisions of proportions, we estimated the error carried forth in division (or multiplication) of two proportions, \(z = x/y\), as:

\[
\left(\frac{\Delta z}{z} \right)^2 = \left(\frac{\Delta x}{x} \right)^2 + \left(\frac{\Delta y}{y} \right)^2
\]

where \(\Delta x\) and \(\Delta y\) are the uncertainty in the proportions \(x\) and \(y\), respectively, and \(\Delta z\) is the uncertainty in the relative risk [20]. The uncertainties of \(x\) and \(y\) are both equal to 5 in this case (as cohort sizes were rounded to the nearest 10). The contribution of rounding error to the relative risk is reported in Table 4.

3. Results

3.1. Incidence of individual side effects

The proportion of patients experiencing side effects 90 days after prescription of AZA appears in Table 3. Side effect pairs with an increased risk of co-occurrence under AZA are highlighted, with

### Table 1 Side effects assessed after AZA prescription.

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Lab value</th>
<th>Abnormal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>Hemoglobin (Hgb)</td>
<td>&lt;11 g/dL</td>
</tr>
<tr>
<td>Cell lysis</td>
<td>Lactate dehydrogenase (LDH)</td>
<td>&gt;190 IU/L</td>
</tr>
<tr>
<td>Fever</td>
<td>Temperature</td>
<td>&gt;37.8 °F</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>Aspartate aminotransferase (AST)</td>
<td>AST &gt; 40 IU/L</td>
</tr>
<tr>
<td></td>
<td>Alanine aminotransferase (ALT)</td>
<td>ALT &gt; 40 IU/L</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>Total bilirubin (Bili)</td>
<td>&gt;1 mg/dL</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Blood pressure (BP)</td>
<td>Systolic &gt; 140 mm Hg or Diastolic &gt; 90 mm Hg</td>
</tr>
<tr>
<td>Nephrotoxicity</td>
<td>Creatinine (Cr)</td>
<td>&gt;1.5 mg/dL</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Neutrophil count</td>
<td>Count &gt; 57% or &lt;2.5 cells/µL</td>
</tr>
<tr>
<td>Neutrophilia</td>
<td>Neutrophil count</td>
<td>Count &gt; 70%</td>
</tr>
</tbody>
</table>

### Table 2 Distribution of anti-rheumatic agents among the control and AZA cohorts.

<table>
<thead>
<tr>
<th>Drug name (RxCUI)</th>
<th>Control cohort (% Total)</th>
<th>AZA cohort (% Total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abatacept (614391)</td>
<td>180 (0.2%)</td>
<td>80 (0.5%)</td>
</tr>
<tr>
<td>Adalimumab (327361)</td>
<td>3100 (4.3%)</td>
<td>750 (5.1%)</td>
</tr>
<tr>
<td>Azathioprine (1256)</td>
<td>3330 (4.6%)</td>
<td>14,270 (97.9%)</td>
</tr>
<tr>
<td>Clioquinol (5942)</td>
<td>100 (0.1%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Etanercept (214555)</td>
<td>2920 (4.0%)</td>
<td>280 (1.9%)</td>
</tr>
<tr>
<td>Hydroxychloroquine (5521)</td>
<td>27,670 (38.3%)</td>
<td>2120 (14.5%)</td>
</tr>
<tr>
<td>Infliximab (191831)</td>
<td>3100 (4.3%)</td>
<td>1320 (9.1%)</td>
</tr>
<tr>
<td>Iodoquinol (3435)</td>
<td>5510 (7.6%)</td>
<td>50 (0.3%)</td>
</tr>
<tr>
<td>Leflunomide (27169)</td>
<td>1620 (2.2%)</td>
<td>520 (3.6%)</td>
</tr>
<tr>
<td>Methotrexate (6851)</td>
<td>21,080 (29.0%)</td>
<td>1880 (12.9%)</td>
</tr>
<tr>
<td>Oxyquinoline (110)</td>
<td>280 (0.4%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Sulfasalazine (9524)</td>
<td>6230 (8.6%)</td>
<td>630 (4.3%)</td>
</tr>
<tr>
<td>Total</td>
<td>72,290</td>
<td>14,580</td>
</tr>
</tbody>
</table>

* The fraction of patients in the AZA cohort prescribed AZA is not 100% since this analysis was performed at a different time than the side effect network analysis. The analysis tool maps patients to the most current instantiation of the patient database, and a discrepancy indicates a change in the underlying database between analyses.
the risk calculated relative to the proportion of patients prescribed one of the 11 other anti-rheumatic drugs. Proportions were calculated relative to the side effect on the row, \( P(\text{column}|\text{row}) \). For each row, the proportion of AZA patients suffering from that individual side effect (along the diagonal) is calculated relative to the total number of patients given AZA that had this particular laboratory or vital sign value measured, i.e. normal and abnormal combined. While a single laboratory or vital sign measurement may not have been identified as occurring more frequently in AZA patients, the frequency may be increased when viewed in conjunction with other laboratory or vital sign values, and these pairings are found in the off-diagonal elements of Table 3.

Among isolated lab or vital sign values along the diagonal of Table 3, we first note that renal dysfunction (measured by elevated creatinine) is infrequent, with only 7.9% of patients developing a measured creatinine having an abnormal value (i.e. >1.5 mg/dL). The relative risk of nephroxicity in patients prescribed AZA was not statistically significantly greater than patients prescribed other anti-rheumatic agents in our data. AZA-associated fever, defined in our study as a temperature >37.8°C, occurred at a rate of 13.1% of AZA patients (RR 1.31, CI 1.18–1.44), more than three times the previously reported incidence of fever of 4.2% [21].

Given AZA's well-known side effect of bone marrow suppression, we successfully identified the significantly increased risk of neutropenia in 24% of AZA users (RR 1.15, CI 1.07–1.23). Anemia is highly prevalent (28%) in our cohort, but AZA does not demonstrate an increased risk relative to other anti-rheumatic drugs (RR 0.97, CI 0.90–1.05).

Neutrophilia, thought to arise either in direct response to the drug or from bone marrow stimulation due to excessive hemolysis [4], was also frequent (45.2%) and significant (RR 1.28, CI 1.22–1.34). Among the non-specific laboratory and vital sign values (temperature, blood pressure, and lactate dehydrogenase), over a quarter (30%) of patients experienced a spike in blood pressure after being prescribed AZA, equivalent to controls (RR 1.01, CI

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Frequencies and conditional probabilities of side effects induced by AZA.</th>
</tr>
</thead>
</table>

\[ \begin{array}{cccccccc}
\text{Primary Effect} & \text{Secondary Effect} & \text{Cr} & \text{AST, ALT} & \text{Bil} & \text{Neutropenia} & \text{Neutrophilia} & \text{Temp} & \text{BP} & \text{Hgb} & \text{LDH} \\
\hline
\text{Cr} & 7.9\%^a & 30.8\% & 7.7\% & 15.4\% & 38.5\% & 53.8\% & 53.8\% & 69.2\% & 39.8\% \\
\text{AST, ALT} & 19.0\% & 14.1\% & 33.3\% & 9.5\% & 23.8\% & 33.3\% & 14.3\% & 47.6\% & 19.0\% \\
\text{Bil} & 4.5\% & 31.8\% & 14.1\% & 9.1\% & 45.5\% & 27.3\% & 36.4\% & 45.5\% & 13.6\% \\
\text{Neutropenia} & 2.4\% & 2.4\% & 2.4\% & 24.3\% & 0.0% & 4.7% & 8.2% & 7.1% & 0.0% \\
\text{Neutrophilia} & 3.6\% & 3.6\% & 7.3\% & 0.0\% & 45.2\% & 7.3\% & 13.9\% & 18.2\% & 7.3\% \\
\text{Temp} & 15.6\% & 15.6\% & 13.3\% & 8.9\% & 22.2\% & 13.1\% & 60.0\% & 55.6\% & 4.4\% \\
\text{BP} & 4.6\% & 2.0\% & 5.3\% & 4.6\% & 12.5\% & 17.8\% & 29.5\% & 20.4\% & 2.0\% \\
\text{Hgb} & 16.1\% & 17.9\% & 17.9\% & 10.7\% & 44.6\% & 44.6\% & 55.4\% & 28.4\% & 19.6\% \\
\text{LDH} & 50.8\% & 30.8\% & 23.1\% & 0.0\% & 70.9\% & 15.4\% & 21.3\% & 84.6\% & 59.1\% \\
\end{array} \]

\[ ^a \text{The diagonal represents the proportion of patients experiencing a single side effect. The off-diagonal elements represent the conditional probability, } P(\text{column}|\text{row}). \]

\[ ^b \text{The relative risk of developing a side effect pair (relative to any one of 12 anti-rheumatic drugs) is indicated by the cell color; only those side effect pairs with a statistically significant (95\% confidence interval) increased risk are highlighted.} \]

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Contribution of rounding error to uncertainty in relative risk.</th>
</tr>
</thead>
</table>

\[ \begin{array}{cccccccc}
\text{Cr} & \text{AST, ALT} & \text{Bil} & \text{Neutropenia} & \text{Neutrophilia} & \text{Temp} & \text{BP} & \text{Hgb} & \text{LDH} \\
\hline
\text{Cr} & 0.05 & 0.14^a & 0.11 & 0.19 & 0.16 & 0.07 & 0.05 & 0.07 & 0.28 \\
\text{AST, ALT} & 0.14 & 0.02 & 0.05 & 0.08 & 0.05 & 0.05 & 0.10 & 0.04 & 0.10 \\
\text{Bil} & 0.12 & 0.05 & 0.02 & 0.08 & 0.11 & 0.05 & 0.05 & 0.04 & 0.10 \\
\text{Neutropenia} & 0.13 & 0.05 & 0.05 & 0.01 & -- & 0.04 & 0.03 & 0.02 & \text{NaN}^b \\
\text{Neutrophilia} & 0.10 & 0.03 & 0.07 & -- & 0.01 & 0.04 & 0.02 & 0.02 & 0.12 \\
\text{Temp} & 0.07 & 0.05 & 0.05 & 0.07 & 0.07 & 0.01 & 0.02 & 0.02 & 0.11 \\
\text{BP} & 0.07 & 0.13 & 0.06 & 0.05 & 0.04 & 0.02 & 0.00 & 0.02 & 0.16 \\
\text{Hgb} & 0.07 & 0.04 & 0.04 & 0.04 & 0.04 & 0.02 & 0.02 & 0.01 & 0.18 \\
\text{LDH} & 0.18 & 0.06 & 0.07 & \text{NaN}^b & 0.16 & 0.06 & 0.07 & 0.05 & 0.05 \\
\end{array} \]

\[ ^a \text{Uncertainties greater than 0.10 are highlighted in gray; this cutoff was chosen because the smallest cohort size was two significant digits.} \]

\[ ^b \text{Two cells marked as “not a number” (NaN) had cohorts too small to report and were estimated as zero.} \]

\[ ^c \text{Neutrophilia and neutropenia are mutually exclusive.} \]
anti-rheumatic agents (RR 1.15, CI 1.00–1.34). (59%) of patients prescribed AZA experience a rise in LDH, for elevated transaminases (RR 0.34, CI 0.22–0.52); elevated bilirubin (RR 0.33, CI 0.21–0.51); fever (RR 0.54, CI 0.39–0.74); elevated transaminases are both disconnected from the other side effects in the network, indicating that, by this approach, these two side effects have no reliable priors upon which clinical predictions can be made. In particular, neutropenia and elevated transaminases are no more frequent in patients prescribed AZA (14.1%) than in patients prescribed other anti-rheumatologic agents studied. We also found that our estimated rate of neutropenia is comparable to the rate reported by Salix Pharmaceuticals, Inc. for leukopenia (28%) in rheumatoid arthritis [23]. Neutropenia and/or leukopenia have been previously reported at much lower rates, from 2.9% [24] to 5.5% [25] to 10.5% [21], and the higher incidence of this side effect in our study may be due, in part, to the conservative cutoff used to define the clinical event. In addition, the total number of patients (i.e. the denominator) used for our calculations is based upon patients in whom neutrophils were measured but were found to be normal. Since a neutrophil count was ordered in these patients as part of routine clinical care, the clinician may have been suspecting an abnormality of this laboratory value, and, thus, this subgroup of patients with a “normal” neutrophil count may artifically underestimate the true proportion of patients whose neutrophils were unaffected by AZA.

An elevated neutrophil fraction in AZA has received mixed attention over the years, playing a prominent role in a recent dermatologic review [4], while receiving no mention in other case reports [5,26,27]. As a downstream clinical phenomenon, or sink, this finding may have received scant attention [28] for its lack of specificity andambiguous biological role. However, our findings clearly show that both neutrophilia and neutropenia are relatively frequent entities with distinct patterns uniquely associated with AZA prescriptions.

As we also found that elevated liver transaminases are no more frequent in patients prescribed AZA (14.1%) than in patients prescribed other anti-rheumatic agents, contrary to reporting trends [26], this is similar to the rate (13.7%) reported in a pediatric population based on an AST greater than twice normal limits [21], though our incidence is much greater than the rate (5.2%) found by Hindorf et al. [25].

The use of a side effect network allowed us to examine the interplay between organ systems that show differential involvement in the process of AZA toxicity. In particular, we recapitulated the classic clinical knowledge that neutropenia is, indeed, an unpredictable event, as it has no dependencies in our side effect network. Though a lack of statistically significant associations alone does not prove the absence of such associations, neutropenia also had a decreased and statistically significant relative risk of association with several side effects, supporting our claim that patterns of neutropenia are isolated and distinct from other variables examined in our study. Thus, our analysis has the power to segregate side effects by our ability to predict and prevent them. In the future analysis of drug side effects, our work would allow biomedical researchers to limit their scope to clinically unpredictable side effects in order to identify molecular bases for prevention and therapy (e.g. the role of TPMT in predicting bone marrow toxicity in AZA).

As mentioned, there may be confounders in the underlying data set that may systematically bias our AZA results. Importantly, the
analysis of individual edges – i.e. pairwise side effect associations – must proceed with caution, as such correlations are significantly influenced by selection bias. For instance, we found that inclusion of renal transplant patients in our analysis – approximately 10% of our AZA cohort – produced a significant interaction between creatinine elevation and anemia in our side effect network, which may be attributable to hemolytic uremic syndrome following renal transplant [29] rather than AZA prescription per se. These kinds of issues reflect underlying clinical heterogeneities that may be difficult to deduce at the aggregate level [30]. In another example, LDH is not a routine laboratory order; it is more frequently ordered in intensive care units and by physicians who suspect a hemolytic process. Consequently, patient cohorts exhibiting correlations between LDH and other side effects may significantly differ in their clinical characteristics from patient cohorts exhibiting correlations between routine measurements (e.g. blood pressure and temperature). While individual correlations, or edges, are prone to such selection bias, the global structure of the side effect network reflects generalizable processes, reflected in the network’s ability to recapitulate classic clinical knowledge. Our careful choice of controls based on patients’ prescribed medications of the same pharmacological class also serves to minimize concerns of selection bias. The appropriate selection of controls and the reduction of cohort heterogeneity remain open questions in the analysis of aggregated, de-identified, population-level data. Additionally, we recognize that there is cross-contamination between the AZA and control cohorts. While this cross-contamination biases the results toward the null hypothesis, we continued to find statistically significant results between the two groups. Finally, while the rounding error introduced for statistical de-identification appears formidable, we show that the error introduced for cohorts as small as 40 patients is often only a marginal contribution to the calculated relative risk (Table 4).

Our work lays the foundation for future explorations of side effect networks using pooled, standardized, normalized, and de-identified population level EHR data. As opposed to the “global” networks assembled in recent studies [9,10] from ICD-9 codes, we illustrate the power of “local” networks focusing on a few, well-defined clinical parameters, based on LOINC or vital sign data. Using the methodology outlined herein, we show that side effect networks can be leveraged to increase post-marketing surveillance of drugs and associated side effects. While this work examined the effects of AZA retrospectively over more than a decade, periodic assessments of EHR data would allow the AZA side effect network (or side effect networks for other drugs) to proactively track clinical phenomena, with increasing statistical power as more EHR data becomes available. The approach presented here identifies associations between prescribed medications and side effects and points to areas to investigate further to understand if true cause and effect exist. The tools and methodologies used here are also very scalable to many other medications and side effects that could be explored for post-market drug surveillance.

This case study of AZA demonstrates the growing potential of clinical research informatics tools and methodologies to address important clinical questions. As digital clinical data becomes increasingly available through the proliferation of EHRs, the possibilities for the secondary use of such data are numerous, though contingent upon the development of new tools and methods. Our example for post-marketing drug surveillance demonstrates that clinical research informatics combining the right clinical data (large aggregated, standardized, normalized, and de-identified EHR data), the right tools (a fast, easy-to-use, and HIPAA/HITECH compliant interface), and the right methods (side effect analyses driven by case reports and biological hypotheses) has the ability to transform certain types of clinical research, in this case post-marketing drug surveillance.

Conflict of Interest

Neither DCK or VNP or the MetroHealth System have any direct financial ties to Explorys Inc. In exchange for contributing de-identified data to the Explorys network, the MetroHealth System received access to the Explorys Population Explorer tool, which was used to conduct this study.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jbi.2013.10.009.

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