Impact and applicability of pharmacogenomics in rheumatology: an integrated analysis

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Abstract

Objective

Rheumatology medications are often associated with adverse drug reactions (ADRs) or inadequate response (IR). Pharmacogenomics may be a solution, but there is limited knowledge of its potential utility within rheumatology.

Methods

We analysed medication changes and pharmacogenomically actionable prescriptions for all adult rheumatology outpatient encounters at our medical centre between 10/2012-12/2018. Three sources defined pharmacogenomic actionability: FDA labels, Clinical Pharmacogenetics Implementation Consortium guidelines, and our institutionally-deliverable pharmacogenomic clinical decision support (CDS) summaries. A subset of patients (validation cohort) had previously undergone broad, preemptive pharmacogenomic testing within other clinics but results were unavailable within rheumatology. We assessed the occurrence of specific pharmacogenomic ADRs/IRs in this group.

Results

From 174,834 prescribing events, 6300/7761 patients (81%) had clinically actionable pharmacogenomic drug prescriptions (i.e. institutional CDS summaries would have been deployable if testing had been done). Using more conservative standards (pharmacogenomically actionable by ≥2 guidance bodies), 4158/7761 (54%) patient prescriptions could have been impacted. The greatest proportions of potentially impacted rheumatologic prescriptions were for tramadol (47%), allopurinol (21%), azathioprine (17%) and celecoxib (8%). Among our validation cohort (94 previously-genotyped patients), 29 (31%) patients had a pharmacogenomic genotype that would have cautioned possible ADRs/IRs for ≥1 medication. Four patients actually suffered ADRs/IRs that would have been predicted by preemptive genotyping.

Conclusion

Pharmacogenomic genotyping could inform prescribing for the majority of rheumatology patients and may prevent a subset of ADRs/IRs. These findings justify prospective evaluation of pharmacogenomic testing including assessment of cost-effectiveness in selected rheumatology populations to further understand impact on therapy-related toxicities and treatment outcomes.

Key words

pharmacogenomics, pharmacogenetics, disease-modifying anti-rheumatic drugs (DMARDs), non-steroidal anti-inflammatory drugs (NSAIDs), adverse drug reactions

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Introduction

Rheumatologic diseases carry significant burden of disability, mortality and morbidity (1). The management of rheumatic diseases has progressed since the advent of disease-modifying anti-rheumatic drugs (DMARDs), but rheumatologic therapies still lead to considerable toxicity and often have unpredictable efficacy (2, 3). Drug levels and aspects of a patient's history and comorbidities, among other factors, can help guide choice of the right medication, but there is still significant room to improve precision medicine in rheumatology (4, 5).

Pharmacogenomics is the study of how genetic variances affect medication response or toxicity. Technological progress has facilitated the increasingly widespread implementation of pharmacogenomics within clinical practice in other disciplines (6-10). Within rheumatology, use of pharmacogenomic information is common when prescribing azathioprine and allopurinol for some high-risk populations. However, it is not yet commonplace to genotype all patients prior to therapy decision-making for the vast majority of medications in rheumatology (11-14).

Barriers to more widespread implementation of pharmacogenomics include uncertainty about when testing might be indicated because of a rapidly-evolving evidence base, lack of available test platforms, insurance or reimbursement constraints, and lack of institutional resources to facilitate widespread decision support even when testing can be performed. Perhaps most notably, there is also skepticism regarding the potential utility or potential clinical value of pharmacogenomic implementation approaches within rheumatology (15, 16). To address this final point, we sought to evaluate the potential impact of comprehensive pharmacogenomic genotyping within a large real-world cohort to elucidate its clinical relevance to rheumatologic prescribing and patient care. We hypothesised that a significant porportion of patients receive medication prescriptions where there is robust pharmacogenomic evidence to potentially impact prescribing. We also aimed to examine this potential impact by applying our analysis to a preemptively-genotyped patient cohort (whose results were unavailable to Rheumatology providers) to identify specific rheumatologic pharmacogenomic adverse drug reactions (ADRs) or inadequate responses (IRs) that might have been preventable had genotypes been known.

Patients and methods

We carried out our investigation via two integrated analyses, using a study design that is depicted in Figure 1. Of note, all procedures within this research study were in accordance with the institutional and national ethical standards of human and animal rights and approved in advance by the institutional review board of The University of Chicago.

For our primary analysis, we first identified all adult rheumatology outpatients assessed at the University of Chicago Medical Center between October 1, 2012 and December 31, 2018. To identify patients who received longitudinal, coordinated rheumatologic care at our institution (as opposed to one-time consultations), we restricted our analysis to patients with at least two outpatient rheumatology clinic visits during the study period. We evaluated all outpatient encounters wherein a provider initiated, discontinued or changed the dosing or frequency of any medication and designated them as "drug-encounters." To focus our evaluation on rheumatology-specific medications, we then identified the encounters wherein at least one of 73 commonly prescribed rheumatologic-specific medications was initiated/changed/discontinued (Supplementary Table S1). This resulted in a set of unique evaluable patients associated with rheumatology drug-encounters (*i.e.* receiving the most commonly prescribed rheumatology medications).

Pharmacogenomic guidance and clinical actionability

We next distinguished the drug-encounters that corresponded to medications where pharmacogenomic evidence could have assisted in predicting ADRs/IRs had testing been performed. To determine pharmacogenomic clinical actionability or relevance for a med-

ication, three evidence standards were applied and integrated. The University of Chicago's genomic prescribing system (GPS) is an interactive web-based portal that delivers patient-specific pharmacogenomic guidance via clinical decision support (CDS) summaries to physicians in real time during patient care (17, 18). Secondly, the Clinical Pharmacogenetics Implementation Consortium (CPIC) publishes consensus guidelines describing actionable pharmacogenomic medications as determined by panels of experts; currently six such drug-gene guidelines are designated as "clinically actionable" (levels A and B) by CPIC (19). Third, we utilised the individual medication Food and Drug Administration (FDA) labels and identified those wherein specific pharmacogenomic guidance is included (20). We first individually applied each of these evidence-actionability standards to the evaluable cohort.

Next, acknowledging that the three standards (GPS, CPIC, and FDA) have some differences among their defined lists of pharmacogenomically actionable medications, and in order to be most conservative in our analysis, we repeated the above analysis of evaluable encounters using only those medications that were defined as pharmacogenomically actionable by two or more of the three sources (consensus actionable).

Validation cohort and preemptive genotyping

To further assess impact, we next identified a cohort of patients who had been preemptively genotyped via a separate prior institutional pharmacogenomic study known as The 1200 Patients Project (clinicaltrials.gov identifier NCT01280825) (21). The 1200 Patients Project had enrolled individuals receiving routine outpatient care in selected primary care and subspecialty clinics (cardiology, nephrology, gastroenterology, hepatology, oncology, pulmonology, and executive health) at our institution starting in 2011. All enrolled patients were preemptively genotyped across two custom panels (described below), with return of results to treating providers for the purpose of investigating feasibility of this institutional model and assessment of adoption of pharmacogenomic information during prescribing.

From this study we identified nearly 1000 patients who had undergone broad preemptive pharmacogenomic genotyping (22). These patients' genotypes had been made available to inform clinical care to providers in the selected clinical departments at our institution, but they had not been available within rheumatology. From among this cohort, we examined the treatment records of any patients who had also been seen in our rheumatology outpatient clinic or by our inpatient rheumatology consult team and we obtained the patient-specific genotype data for the resulting patients.

The patient population from The 1200 Patient Project had been genotyped across two comprehensive, custom pharmacogenomic panels, described at length elsewhere (22). In short, Sequenom custom MassARRAYs (Agena Bioscience, San Diego, CA) were used prior to May 5, 2015, while custom OpenArrays from Life Technologies (ThermoFisher, Waltham, MA) were used thereafter. Additionally, a unique *CYP2D6* panel was developed in conjunction with Hologic with supplemental *CYP2D6* Taqman copy number for all patients. All genotyping was conducted in Clinical Laboratory Improvement Amendments-certified and College of American Pathologists-accredited laboratories.

The results from the above preemptive testing had been made available since October 1, 2012 to treating providers in the selected enrolling clinics within our medical center. However, Rheumatology clinics (and Rheumatology providers) were not included in this initial roll-out. Therefore, for patients (even patients enrolled in The 1200 Patients Project) seen in our Rheumatology clinics since 2012, or for those seen during inpatient Rheumatology consultations, pharmacogenomics results from The 1200 Patients Project (and attendant CDS summaries) were unavailable.

This fact enabled us to examine, retroactively, the actual real-world impact of known patient genotypes on rheumatologic ADRs/IRs among this cohort. With available pharmacogenomic information, only GPS actionable drug/gene pairs were utilised. The goal was to identify specific pharmacogenomic ADRs/IRs for prescribed medications among these patients which could have been avoided had genotypes been available during prescribing. To characterise this, our GPS depicts pharmacogenomic recommendations utilising a colored traffic signal graphic to relay to providers the pharmacogenomic risk levels for each drug: red light signifies drugs with high risk of undesirable outcomes whereas yellow drug reflects a cautionary signal and green light indicates favourable outcome (21). Medication prescriptions were noted to be "at-risk" if they corresponded to high risk or cautionary prescriptions, namely red or yellow light prescriptions. Manual, detailed chart analysis was conducted on all patients in this validation cohort. Each patient was evaluated for any rheumatologic medication received (from Suppl. Table S1) that has GPS CDS summaries. For those receiving such prescriptions, we integrated these patients' actual genotypes (and GPS light signals) with specific patient outcomes that occurred. For any patients carrying risk alleles that would have conferred a yellow or red GPS light, we correlated clinical outcomes with the specific pharmacogenomic warnings to determine whether the corresponding ADRs/IRs might have been preventable.

Results

Clinical demographics of the studied rheumatology patients

Our analysis yielded 575,575 total outpatient drug-encounters for adult rheumatology patients over a span of about six years (Fig. 1). Of these, we distinguished 174,834 drug-encounters wherein at least one rheumatologic medication was initiated/modified/discontinued. After excluding a small percentage of encounters comprised by only topical rheumatologic medications or rheumatologic supplements or medications that are not primarily the purview of rheumatology care, we focused the remainder of the primary analysis on the 173,616 drug-encoun-

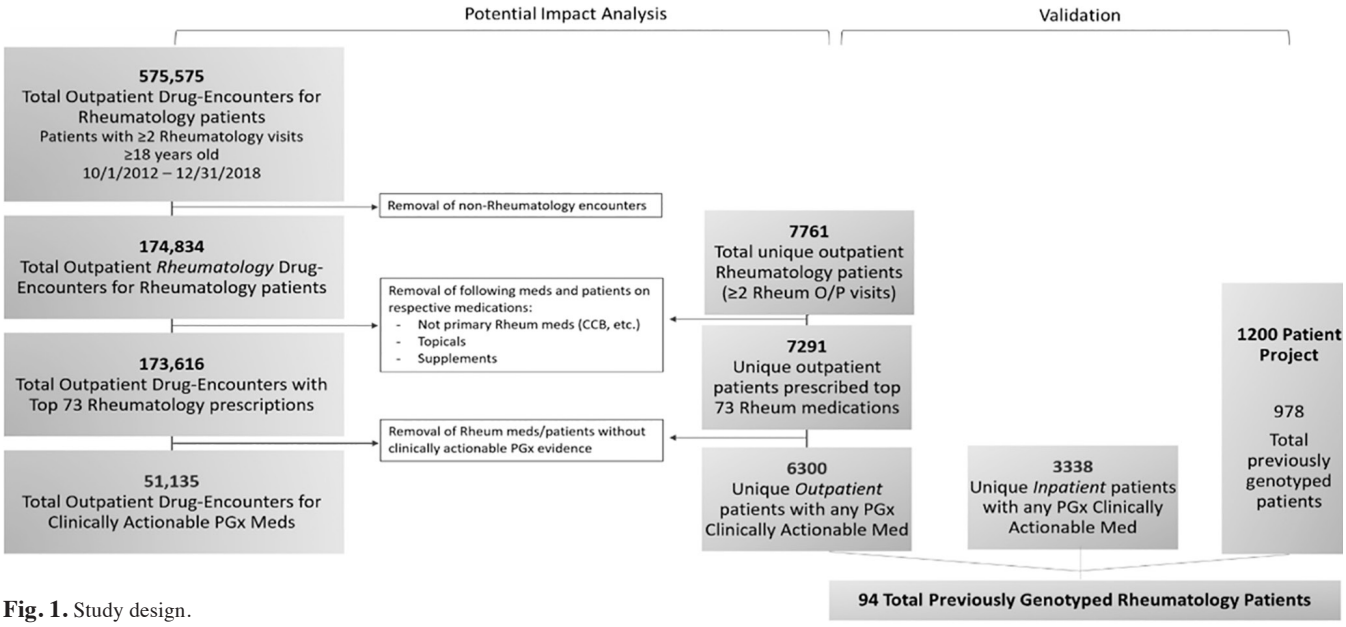

Fig. 1. Study design.

ters that involved the initiation/modification/discontinuation of one or more of the 73 most commonly prescribed rheumatology medications (see Suppl. Table S1 for full list).

These drug-encounters represented 7,291 unique rheumatology patients whose demographics are delineated in Table I. The cohort consisted primarily of women (74.6%) while the racial distribution was comprised of significant proportions of both White (51.4%) and Black/African American patients (42.0%).

Table I. Patients' demographic characteristics.

	Potential impact cohort n (%)	Validation cohort n (%)
Total	7291 (100%)	94 (100%)
Gender		
Female	5437 (74.6%)	67 (71.3%)
Male	1782 (24.4%)	27 (28.7%)
Race		
White	3751 (51.4%)	35 (37.2%)
Black/African-American	3060 (42.0%)	55 (58.5%)
Asian/Mideast Indian	164 (2.2%)	2 (2.1%)
American Indian or Alaska Native	16 (0.2%)	0 (0%)
Native Hawaiian/Other Pacific Islander	9 (0.1%)	0 (0%)
More than one Race	90 (1.2%)	1 (1.1%)
Patient Declined	108 (1.5%)	1 (1.1%)
Unknown	20 0.3%)	0 (0%)
Ethnicity		
Hispanic or Latino	418 (5.7%)	1 (1.1%)
Not Hispanic or Latino	6725 (92.2%)	92 (97.8%)
Patient declined	67 (0.9%)	1 (1.1%)
Unknown	9 0.1%)	0 (0%)

Potential pharmacogenomic impact

To understand how many of these patients were prescribed medications with potential pharmacogenomic relevance, we next applied each of three separate "pharmacogenomic actionability" standards, plus a composite standard, in order to analyse the evaluable rheumatologic drug-encounters. First, our GPS includes guidelines for 14 (of the 73) medications of interest (see Figure 2). Using this standard among our evaluable rheumatology population, 51,135 outpatient drug-encounters could have been impacted by pharmacogenomic information, comprising 6,300 of the 7,761 rheumatology patients. This means that pharmacogenomic information could have had potential impact on almost one-third of all outpatient rheumatology drug-encounters and, more notably, over 80% of all outpatient rheumatology patients.

We then performed the same analysis using two external standards that have defined pharmacogenomically actionable medications using slightly different rubrics. Using the six medications defined as actionable by CPIC (depicted in Fig. 2), pharmacogenomic information could have potentially impacted 23,308 drug-encounters and 3,953 rheumatology patients (Table II). Alternatively, using the seven medications with pharmacogenomic biomarker information in drug labels defined by the FDA (also reflected in Fig. 2), pharmacogenomic information could have potentially impacted 19,754 drug-encounters and 3,807 rheumatology patients in our cohort (Table II).

Finally, given that some variability exists among different expert panels in defining the medications that are currently pharmacogenomically actionable, we applied a consensus standard as a final analysis. The consensus standard defined a pharmacogenomically actionable medication as one agreed upon as actionable by two or more of the above independent standards, thus

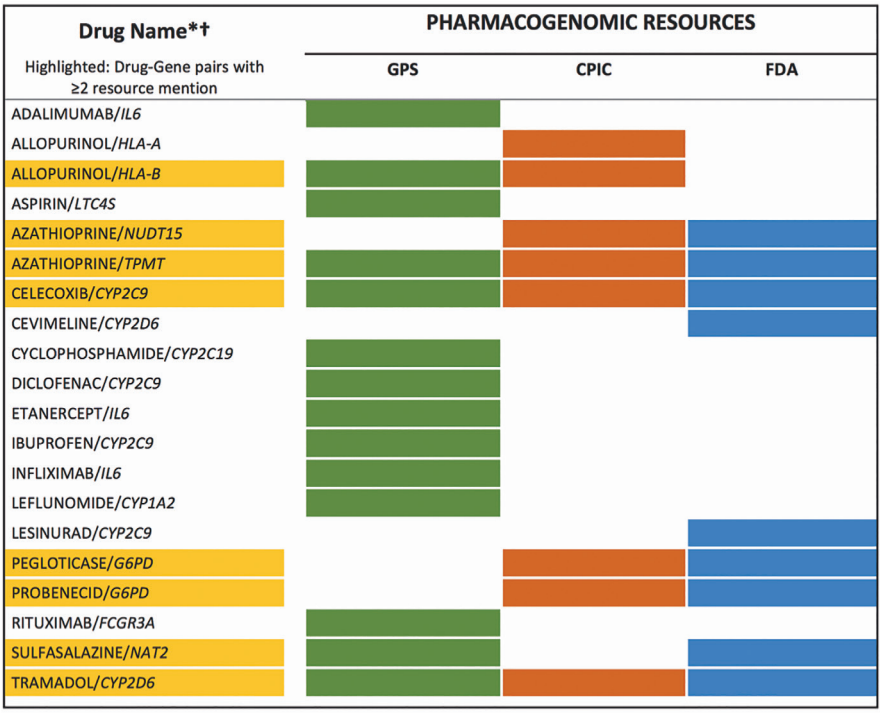

Fig. 2. Clinical actionability by different pharmacogenomic standards.
*List excludes supplements (calcium, folic acid, folinic acid) and IVIg; †Drugs are ordered alphabetically. PGx: pharmacogenomic; Rheum: rheumatology; GPS: Genomic Prescribing System designed at University of Chicago Medical Center; CPIC: Clinical Pharmacogenetics Implementation Consortium; FDA: Food and Drug Administration; ABCB1: Adenosine triphosphate binding cassette Subfamily B Member 1; ATIC: 5-Aminoimidazole-4-Carboxamide Ribonucleotide Formyltransferase/IMP Cyclohydrolase; CYP1A2: Cytochrome P450 Family 1 Subfamily A Member 2; CYP2C19: Cytochrome P450 Family 2 Subfamily C Member 19; CYP2C9: Cytochrome P450 Family 2 Subfamily C Member 9; CYP2D6: Cytochrome P450 Family 2 Subfamily D Member 6; FCGR3A: Fc fragment of immunoglobulin G receptor IIIa; G6PD: Glucose-6-phosphate dehydrogenase; GP1BA: Glycoprotein 1b Platelet Subunit Alpha; HLA-B: Major histocompatibility complex; HLA-DPB1: Major Histocompatibility Complex Class II DP Beta 1; IL6: Interleukin 6; LTC4S: Leukotriene C4 Synthase; NAT2: N-Acetryltransferase2; NUDT15: Nudix hydrolase; OPRM1: Opioid Receptor Mu 1; PTGS1: Prostaglandin-Endoperoxide Synthase 1; class 1; B; TNF: Tumour necrosis factor; TPMT: Thiopurine methyltransferase.

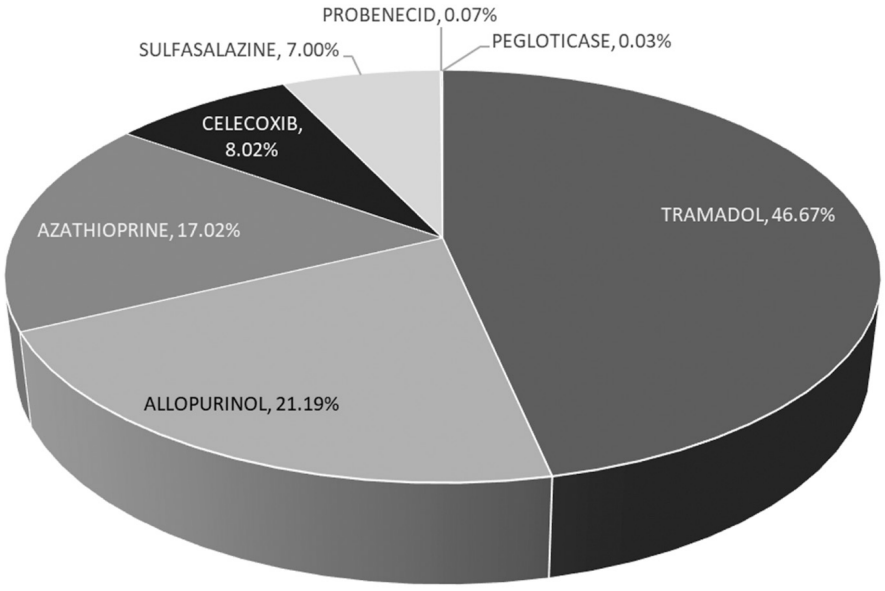

Fig. 3. Proportion of drug-encounters for medications deemed clinical actionable by ≥2 pharmacogenomic sources.

this represented the most conservative analysis measure. This resulted in 7 key consensus medications and 8 different drug-gene pairs being defined as actionable (Fig. 2). This standard resulted in 25,063 of the 174,834 evaluable drug-encounters (14%) potentially informed by pharmacogenomic information, comprising 54% of unique patients (4,158 of 7,761) as reported in Table II. Figure 3 fully summarises the three independent standard and consensus standard results.

High impact medications

We further investigated the 174,834 rheumatology drug-encounters to identify numeric proportions of prescriptions that corresponded to the 7 key consensus medications that had robust evidence for clinical actionability (allopurinol, azathioprine, celecoxib, pegloticase, probenecid, sulfasalazine and tramadol). The highest proportion of prescriptions corresponded to tramadol, with almost half of the drug-encounters (n=11,696; 46.67%) impacted by this medication alone. This was followed by allopurinol (n=5,310; 21.19%). Notably, only rarely did outpatient encounters include prescriptions for probenecid (n=18; 0.01%). The relative proportions of drug-encounters impacted by the top 7 consensus pharmacogenomically-actionable medications are shown in Figure 3.

Validation of clinical impact in genotyped patients

Our second analysis aimed to further explore and validate the potential impact of pharmacogenomic results on rheumatology care by examining a real-life cohort of rheumatology patients who had been previously broadly genotyped. As aforementioned, this cohort of patients had pharmacogenomic information made available to inform clinical care in a myriad of clinics at our institution, but rheumatology was not one of them. By identifying preemptively genotyped rheumatology patients from this cohort, we were able to assess which ADRs or IRs could have been predicted had pharmacogenomic information been available to rheumatologists at time of patient care. Of note,

POTENTIAL PHARMACOGENOMIC IMPACT BY DRUG RESPONSE OR TOXICITY

Pharmacogenomic Sources	Our institutional (University of Chicago's) Genomic Prescribing System (GPS)		Clinical Pharmacogenetics Implementation Consortium (CPIC)*		United States Food and Drug Administration (FDA)		Counts for Drugs which have at least one Drug-Gene pair with >=2 PGx Source mention within its use *in Rheumatology*	
Generic Drug Name	Drug-encounters†	Patients affected‡	Drug-encounters†	Patients affected‡	Drug-encounters†	Patients affected‡	Drug-encounters†	Patients affected‡
PHENOTYPE: INADEQUATE RESPONSE (IRs)								
Adalimumab	3479	724						
Etanercept	3178	607						
Infliximab	371	226						
Rituximab	114	105						
Tramadol	11696	2740	11696	2740	11696	2740	11696	2740
Total with PGx mentions	**15359**	**3735‡**	**11696**	**2740‡**	**11696**	**2740‡**	**11696**	**2740‡**
Percentage§ with potentially actionable PGx	**9%**	**48%**	**7%**	**35%**	**7%**	**35%**	**7%**	**35%**
PHENOTYPE: ADVERSE DRUG REACTIONS (ADRs)								
Allopurinol	5310	831	5310	831			5310	831
Aspirin	6589	2989						
Azathioprine	4266	810	4266	810	4266	810	4266	810
Celecoxib	2011	632	2011	632	2011	632	2011	632
Cevimeline					338	98		
Cyclophosphamide	97	50						
Diclofenac	4119	1915						
Ibuprofen	5557	2240						
Leflunomide	2593	528						
Lesinurad					1	1		
Methotrexate								
Pegloticase			7	5	7	5	7	5
Probenecid			18	11	18	11	18	11
Sulfasalazine	1755	449			1755	449	1755	449
Total with PGx mentions	**32297**	**5216**	**11612**	**2229**	**8058**	**1861**	**13367**	**2563**
Percentage§ with potentially actionable PGx	**19%**	**67%**	**7%**	**29%**	**5%**	**24%**	**8%**	**33%**
Total IRs+ADRs with PGx mention	**51135**	**6300**	**23308**	**3953**	**19754**	**3807**	**25063**	**4158**
Total percentage PGx Actionable (IRs+ADRs)	**29%**	**81%**	**13%**	**51%**	**11%**	**49%**	**14%**	**54%**

PGx information for drug response could have had potential impact on ~35% of all outpatient Rheumatology patients

PGx information for drug toxicity could have had potential impact on ~33% of all outpatient Rheumatology patients

PGx information could have had potential impact on ~14% of all outpatient Rheumatology drug-encounters

PGx information could have had potential impact on ~54% of all outpatient Rheumatology patients

Table II. Herewith is a tabulation of the total number of drug-encounters† or unique patients affected‡ for which pharmacogenomics (PGx) guidance has been annotated by three different PGx sources (columns titled at the top). The right most columns reflect counts for drugs which have at least one drug-gene pair with multiple PGx mentions in the context of drug use within Rheumatology setting. The final row delineates percentage§ of total outpatient rheumatology encounters (of which there were 174,834 drug-encounters for 7,761 unique patients) where there could have been potential pharmacogenomic impact. IP: inpatient, OP: outpatient, PGx: pharmacogenomics, Rheum: rheumatology

*Only CPIC A and B designations notable for clinical actionability and only medications with CPIC A or B designation for use within rheumatology included in analysis here.

† "Drug encounters" represent all encounters in which a provider initiated, discontinued or changed the dosing or frequency of respective drug.

‡ "Patients affected" reflects unique patients affected: duplicate patients with ≥1 clinically actionable drug prescriptions are deleted and *Total* patients affected count is the number after consolidating these duplicates to reflect a list of only unique patients.

§ Percentage is Total with PGx out of total outpatient rheumatology encounters, calculated for drug-encounters as well as for patients affected.

by our study design, we are not able to quantify in real-life to what extent potential adverse events are transient, severe or led to drug discontinuation. In total, 94 patients comprised this validation cohort (Fig. 1). Demographics are as described in Table I.

Our investigation revealed 32 of 219 total drug-encounters (15%) involving at-risk (red or yellow light) medication prescriptions for 29 (of the 94) unique patients. Separating the IR encounters from those of ADRs, we see that while there were 4 drug-encounters associated with pharmacogenomic potential for IR, the pharmacogenomic potential for ADRs is as high as 27 drug-encounters. Table II displays the patient-level results. A detailed examination of clinical records revealed that 4 of these 29 patients actually suffered from an unfavorable treatment outcome (2 from treatment-related adverse event (ADRs) and 2 from suboptimal disease response) that could have been predicted by pharmacogenomics had preemptive genotype results been available to

PATIENT	PRIMARY RHEUM DISEASE	DRUG NAME	PATIENT-SPECIFIC GENOTYPE OR PHENOTYPE	CDS LIGHT*	PGx CLINICAL CONCERN (IR: Inadequate response or ADR: Adverse drug reaction)	ACTUAL CLINICAL OUTCOME†	NOTABLE CLINICAL ANNOTATIONS
1	RA	TRAMADOL	*CYP2D6*, UM	2	Enhanced pain alleviation	IR	"Tramadol not controlling [muscle] pain"
2	SLE	ASPIRIN	*LTC4S*-AC	2	ADR: Urticaria	No ADRs	
3	Gout, OA	IBUPROFEN	*CYP2C9**1/*3	2	ADR: GI bleeding	ADR: GI bleeding	Hematemesis with ibuprofen three-times-per-day use
4	OA	ASPIRIN	*LTC4S*-AC	2	ADR: Urticaria	Unclear	Unclear if patient's urticaria reflects true ADR: history of urticaria noted in 1991, started aspirin in 2008: patient reported lifetime of intermittent urticaria
5	DM	LEFLUNOMIDE	*CYP1A2*-AC	3	ADR: GI, weight loss, lab abnormalities	No ADRs	
6	GCA	ASPIRIN	*LTC4S*-AC	2	ADR: Urticaria	No ADRs	
7	SLE	DICLOFENAC	*CYP2C9**1/*3	2	ADR: GI bleeding	No ADRs	Patient reported history of gastric ulcer, but esophagogastroduodenoscopies negative for ulcers r signs of GI bleeding - diclofenac and ibuprofen tolerated
		IBUPROFEN	*CYP2C9**1/*3	2	ADR: GI bleeding	No ADRs	
8	Gout	ASPIRIN	*LTC4S*-CC	2	ADR: Urticaria	No ADRs	Notable hives after chlorhexadine use perioperatively - no issues with aspirin use
9	SS, SSc, OA	ASPIRIN	*LTC4S*-AC	2	ADR: Urticaria	No ADRs	
10	UCTD	TRAMADOL	*CYP2D6*, IM	2	IR in alleviating pain	IR: frequency increase needed	Requiring higher tramadol frequency for pain relief: first, noted 1-3 times per day use, then notes state patient requiring 3 times per day dosing
11	CD, Arthritis	ADALIMUMAB	*IL6*-CC	3	IR for immunosuppression	Unknown	Unknown clinical response because adalimumab taken for too short of duration due to development of infection, unable to evaluate for response to medication
12	Sarcoidosis	ASPIRIN	*LTC4S*-AC	2	ADR: Urticaria	No ADRs	
13	JIA	ASPIRIN	*LTC4S*-AC	2	ADR: Urticaria	No ADRs	
		LEFLUNOMIDE	*CYP1A2*-AC	3	ADR: GI, weight loss, lab abnormalities	No ADRs	
14	RA	LEFLUNOMIDE	*CYP1A2*-AC	3	ADR: GI, weight loss, lab abnormalities	No ADRs	Leflunomide cessation due to pseudomonas infection
15	IBD, SpA	ADALIMUMAB	*IL6*-CG	3	IR for immunosuppression	IR: dose and frequency increase needed	Poor response initially for IBD-associated SpA, so cessation. Upon retrial, needed dose increase from 40mg to 80mg every 14 days and then required increased frequency to every 7 days.
16	AAV	ASPIRIN	*LTC4S*-AC	2	ADR: Urticaria	No ADRs	
17	SS, OA	ASPIRIN	*LTC4S*-AC	2	ADR: Urticaria	No ADRs	
18	OA	ASPIRIN	*LTC4S*-AC	2	ADR: Urticaria	No ADRs	
19	MCTD	RITUXIMAB	*FCGR3A*-AA	3	IR for immunosuppression	Adequate Response	Sustained benefit to rituximab after only 1 cycle: rituximab used for TTP
20	OA	DICLOFENAC	*CYP2C9**1/*3	2	ADR: GI bleeding	No ADR	
21	SS	IBUPROFEN	*CYP2C9**1/*3	2	ADR: GI bleeding	No ADR	
22	RA	DICLOFENAC	*CYP2C9**1/*3	2	ADR: GI bleeding	No ADR	
		IBUPROFEN	*CYP2C9**1/*3	2	ADR: GI bleeding	No ADR	
23	Gout	IBUPROFEN	*CYP2C9**1/*3	2	ADR: GI bleeding	No ADR	
24	MCTD	IBUPROFEN	*CYP2C9**1/*3	2	ADR: GI bleeding	No ADR	
25	Sarcoidosis Gout	ASPIRIN	*LTC4S*-AC	2	ADR: Urticaria	No ADR	
26	RA, OA	ASPIRIN	*LTC4S*-AC	2	ADR: Urticaria	No ADR	
27	UCTD, ILD	IBUPROFEN	*CYP2C9**1/*3	2	ADR: GI bleeding	No ADR	
28	ANA positive	IBUPROFEN	*CYP2C9**1/*3	2	ADR: GI bleeding	ADR: GI irritation	Ibuprofen cessation due to gastric irritation and nausea without gross bleeding
29	PsA	ASPIRIN	*LTC4S*-AC	2	ADR: Urticaria	No ADR	Developed hives after gadolinium administration

Table III. Clinical annotations for at-risk pharmacogenomic medications.
AAV: antineutrophil cytoplasmic antibody associated vasculitis; ADR: adverse drug reaction; ANA: antinuclear antibody; CD: Crohn's disease; CDS: Clinical Decision Support; CYP1A2: cytochrome P450 family 1 subfamily A member 2; CYP2C9: cytochrome P450 family 2 subfamily C member 9; CYP2D6: cytochrome P450 family 2 subfamily D member 6; DM: dermatomyositis; FCGR3A: Fc fragment of immunoglobulin G receptor IIIa; GCA: giant cell arteritis; GI: gastrointestinal; IBD: inflammatory bowel disease; IL6: interleukin 6; IM: intermediate metaboliser; IR: inadequate response; JIA: juvenile idiopathic arthritis; LTC4S: leukotriene C4 synthase; MCTD: mixed connective tissue disease; OA: osteoarthritis; RA: rheumatoid arthritis; SLE: Systemic lupus erythematosus; SS: Sjögren's syndrome; SSc: systemic scleroderma; SpA: spondyloarthropathy; UCTD: undifferentiated connective tissue disease; UM: ultrarapid metaboliser.
*Colour reflective of light colour and level of evidence (number within circle) as designated by University of Chicago's Genomic Prescribing System CDS, described in detail by Danahey and colleagues (Danahey *et al*., 2017).
†Reflects clinical outcome as associated with respective medication.

the rheumatology providers at time of prescribing. In contrast, from the 187 medication prescriptions associated with pharmacogenomic green lights (genomically favourable), eleven patients suffered unfavourable outcomes. These results reflect a number needed to test of about 57 in order to identify one patient where preemptive genotyping could have warned of an adverse drug reaction.

Discussion

In this study, we found that a substantial percentage of outpatient rheumatology visits and the majority of rheumatology patients could be impacted by the availability of pharmacogenomic information, especially for the management of common rheumatological pain syndromes. Even when applying multiple external standards for defining clinical actionability of medications, these findings held true, with the

most frequently-impacted medications being tramadol, allopurinol, azathioprine, celecoxib, and sulfasalazine. We then corroborated this potential impact in a validation cohort of patients who had been previously genotyped, revealing genotypically at-risk prescriptions in nearly 1 out of every 5 patients. These findings justify future prospective examination of the impact of broad preemptive pharmacogenomic testing to improve clinical outcomes in rheumatology care.

The idea that pharmacogenomics could have an important impact on rheumatology patients resonates with the increasing adoption of genomically-guided care within other fields of medicine. There are already examples of how rheumatology uses personalised medicine methodologies to guide drug therapies, including relatively standard use of TPMT enzymatic testing, drug level testing (*e.g.* hydroxychloroquine, mycophenolate) and the consideration of other non-genomic factors like methotrexate polyglutamation. However, as some have suggested, rheumatology may be lagging behind in the genomic precision medicine movement (13, 15, 23-25). Despite these limited examples, broad implementation of pharmacogenomic testing or return of results is not yet standard practice for most institutions. Also, it is acknowledged that not all ADRs would be preventable by PGx and alternative medications could have their own potential toxicities.

The percentage of rheumatology patients that could stand to potentially benefit is similar to the proportions found in other medical subspecialties. For example, in a recent study looking at in-hospital (hospitalist) prescribing, our group identified about 55% of hospitalised patient cohort with at least one new pharmacogenomic medication prescription, similar to the 54% of our outpatient cohort who could have been impacted by one or more of the seven medications with robust evidence for clinical actionability (26). In a separate study within cardiology that detailed projected impact of pharmacogenetic testing for patients undergoing cardiac catheterisation, the authors found 26 of 122 cases (21%) where pharmacogenomic intervention could have occurred for medications with clinical actionability by CPIC or FDA (27).

We understand that routine pharmacogenomic testing within the clinic faces challenges including availability and comprehensiveness of genotyping, development of standardised decision-support within the electronic medical record, establishment of clinical workflows and clinical champions, and cost or reimbursement hurdles. The estimation of the benefit of pharmacogenomic testing should be weighed against the costs, feasibility, and the potentially high number needed to test. We therefore propose that institutions with limited resources (which include most) should first aim to tackle pharmacogenomic implementation for the highest potential impact medications and their respective genetic variants/genes. Tramadol, with prescribing based on variation in the gene *CYP2D6*, may be an attractive and viable early target. There is recent randomised evidence to support such an implementation in patients with chronic pain (28). Moreover, the American College of Rheumatology conditionally recommends tramadol as one of the first line oral therapies for hand osteoarthritis and knee osteoarthritis (29). This is critical because a 2019 publication in the Journal of the American Medical Association found that in patients over 50 years of age with osteoarthritis, tramadol was associated with a significantly higher concern for toxicity compared to various NSAIDs, with a higher number of deaths compared to naproxen, higher mortality compared to diclofenac, and higher all-cause mortality compared to celecoxib and etoricoxib (30). Yet, NSAIDs are not without risks either, and we have chosen to implement *CYP2C9*-guided pharmacogenomic decision-support at our institution based on sound pharmacokinetic associations as well as clinical outcome studies associating genotypes with NSAID-induced gastrointestinal bleeding risk (31-34). Finally, pharmacogenomic testing to guide gout therapy could potentially have high clinical yield (35), since three medications used for the long-term management of gout were in the medications with consensus pharmacogenomic clinical actionability (allopurinol, probenecid and pegloticase).

Our study is not without limitations. First, the large cohort analyses were focused on potential (or projected/estimated) pharmacogenomic impact, since only a small number of the >7000 patients actually underwent genotyping. Nevertheless, these impact analyses suggest a profound potential significance, and we utilised three independent actionability standards and a consensus standard in order to reduce over-inflation of the estimated impact. If anything, our consensus estimates are likely conservative estimates of the true potential effect of pharmacogenomics for rheumatology care. Separately, in our validation cohort the clinical outcomes that were attributed to various treatment approaches are, admittedly, only associations. We made every attempt to carefully assign the associations based on temporal relatedness and a lack of alternative explanations. However, we are unable to assign true causation since this was a retrospective analysis of the clinical courses for the examined patients, and since prospective randomisation was not performed. Finally, pharmacogenomics information is likely to be most impactful at drug initiation, and in our analysis, we treated drug initiation, dose changes and discontinuations equally. Future implementations should focus on PGx result availability at medication initiation. These limitations further underscore the need and importance of future randomised trials to formally test the potential risk-reductions of pharmacogenomically-guided care. Future prospective studies should also examine questions of cost-effectiveness.

In conclusion, we present the first study to evaluate the potential impact of pharmacogenomics in a rheumatology cohort. With the high risks of toxicity and concern for significant nonresponse associated with rheumatologic medications, the field of rheumatology could potentially benefit from pharmacogenomic technologies and broader preemptive testing to advance models of precision medicine. Our group is

indeed preparing to launch a prospective study to evaluate how preemptive pharmacogenomic testing might inform prescribing behaviours and improve clinical outcomes within rheumatology clinical practice.

References

1. GABRIEL SE, MICHAUD K: Epidemiological studies in incidence, prevalence, mortality, and comorbidity of the rheumatic diseases. *Arthritis Res Ther* 2009; 11: 229.
2. GROVE ML, HASSEL AB, HAY EM, SHADFORTH MF: Adverse reactions to disease-modifying anti-rheumatic drugs in clinical practice. *QJM* 2001; 94: 309-19.
3. KIELY PD: Biologic efficacy optimization--a step towards personalized medicine. *Rheumatology* (Oxford) 2016; 55: 780-8.
4. CANTINI F, NICCOLI L, NANNINI C *et al*.: Tailored first-line biologic therapy in patients with rheumatoid arthritis, spondyloarthritis, and psoriatic arthritis. *Semin Arthritis Rheum* 2016; 45: 519-32.
5. SILVAGNI E, DI BATTISTI M, BONIFACIO AF, ZUCCHI D, GOVERNATO G, SCIRÈ CA: One year in review 2019: novelties in the treatment of rheumatoid arthritis. *Clin Exp Rheumatol* 2019; 37: 519-34.
6. RELLING MV, EVANS WE: Pharmacogenomics in the clinic. *Nature* 2015; 526: 343-50.
7. MANOLIO TA, CHISHOLM RL, OZENBERGER B *et al*.: Implementing genomic medicine in the clinic: the future is here. *Genet Med* 2013; 15: 258-67.
8. RODEN DM, VAN DIEST SL, MOSLEY JD *et al*.: Benefit of preemptive pharmacogenetic information on clinical outcome. *Clin Pharmacol Ther* 2018: 103: 787-94.
9. KLEIN ME, PARVEZ MM, SHIN JG: Clinical implementation of pharmacogenomics for personalized precision medicine: barriers and solutions. *J Pharm Sci* 2017; 106: 2368-79.
10. MOYER AM, CARABALLO PJ: The challenges of implementing pharmacogenomic testing in the clinic. *Expert Rev Pharmacoecon Outcomes Res* 2017; 17: 567-77.
11. ACOSTA-HERRERA M, GONZALEZ-SERNA D, MARTIN J: The potential role of genomic medicine in the therapeutic management of rheumatoid arthritis. *J Clin Med* 2019; 8: 826.
12. SEN D, PAUL JR, RANGANATHAN P: Pharmacogenetics in rheumatoid arthritis. *Methods Mol Biol* 2014; 1175: 625-60.
13. SZEKANECZ Z, MESKÓ B, POLISKA S *et al*.: Pharmacogenetics and pharmacogenomics in rheumatology. *Immunol Res* 2013; 56: 325-33.
14. UMICEVIC MIRKOV M, COENEN MJ: Pharmacogenetics of disease-modifying antirheumatic drugs in rheumatoid arthritis: towards personalized medicine. *Pharmacogenomics* 2013; 14: 425-44.
15. PONCHEL F, BURSKA AN, VITAL EM: Pharmacogenomics in rheumatoid arthritis: how close are we to the clinic? *Pharmacogenomics* 2014; 15: 1275-9.
16. DAVILA L, RANGANATHAN P: Pharmacogenetics: implications for therapy in rheumatic diseases. *Nat Rev Rheumatol* 2011; 7: 537-50.
17. DANAHEY K, BORDEN BA, FURNER B *et al*.: Simplifying the use of pharmacogenomics in clinical practice: Building the genomic prescribing system. *J Biomed Inform* 2017; 75: 110-21.
18. KAUFMAN AL, SPTIZ J, JACOBS M *et al*.: Evidence for clinical implementation of pharmacogenomics in cardiac drugs. *Mayo Clin Proc* 2015; 90: 716-29.
19. RELLING MV, KLEIN TE: CPIC: Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network. *Clin Pharmacol Ther* 2011; 89: 464-7.
20. (FDA) UF a DA: Table of Pharmacogenomic Biomarkers in Drug Labeling. 2018: Silver Spring, MD.
21. O'DONNELL PH, DANAHEY K, JACOBS M *et al*.: Adoption of a clinical pharmacogenomics implementation program during outpatient care--initial results of the University of Chicago "1,200 Patients Project". *Am J Med Genet C Semin Med Genet* 2014; 166C: 68-75.
22. O'DONNELL PH, WADHWA N, DANAHEY K *et al*.: Pharmacogenomics-Based Point-of-Care clinical decision support significantly alters drug prescribing. *Clin Pharmacol Ther* 2017; 102: 859-69.
23. STOLK JN, BOERBOOMS AM, DE ABREU RA *et al*.: Reduced thiopurine methyltransferase activity and development of side effects of azathioprine treatment in patients with rheumatoid arthritis. *Arthritis Rheum* 1998; 41: 1858-66.
24. HUNG SI, CHUNG WH, LIOU LB *et al*.: HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. *Proc Natl Acad Sci USA* 2005; 102: 4134-9.
25. TANIGUCHI A, URANO W, TANAKI E *et al*.: Validation of the associations between single nucleotide polymorphisms or haplotypes and responses to disease-modifying antirheumatic drugs in patients with rheumatoid arthritis: a proposal for prospective pharmacogenomic study in clinical practice. *Pharmacogenet Genomics* 2007; 17: 383-90.
26. LEE YM, DANAHEY K, KNOEBEL RW, RATAIN MJ, MELTZER DO, O'DONNELL PH: Analysis of comprehensive pharmacogenomic profiling to impact in-hospital prescribing. *Pharmacogenet Genomics* 2019; 29: 23-30.
27. DONG OM, LI A, SUZUKI O *et al*.: Projected impact of a multigene pharmacogenetic test to optimize medication prescribing in cardiovascular patients. *Pharmacogenomics* 2018; 19: 771-82.
28. SMITH DM, WEITZEL KW, ELSEY AR *et al*.: CYP2D6-guided opioid therapy improves pain control in CYP2D6 intermediate and poor metabolizers: a pragmatic clinical trial. *Genet Med* 2019; 21: 1842-50.
29. HOCHBERG MC, ALTMAN RD, TOUPIN APRIL K *et al*.: American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res* (Hoboken) 2012; 64: 465-74.
30. FELSON D: Tramadol and mortality in patients with osteoarthritis. *JAMA* 2019; 322: 465-6.
31. CASTELLSAGUE J, RIERA-GUARDIA N, CALINGAERT B *et al*.: Individual NSAIDs and upper gastrointestinal complications: a systematic review and meta-analysis of observational studies (the SOS project). *Drug Saf* 2012; 35: 1127-46.
32. GUNTER BR, BUTLER KA, WALLACE RL, SMITH SM, HARIRFOROOSH S: Non-steroidal anti-inflammatory drug-induced cardiovascular adverse events: a meta-analysis. *J Clin Pharm Ther* 2017; 42: 27-38.
33. CARBONELL N, VERSTUYFT C, MASSARD J *et al*.: CYP2C9*3 loss-of-function allele is associated with acute upper gastrointestinal bleeding related to the use of NSAIDs other than aspirin. *Clin Pharmacol Ther* 2010; 87: 693-8.
34. GARCÍA-MARTÍN E, MARTÍNEZ C, TABARÉS B, FRÍAS J, AGÚNDEZ JA: Interindividual variability in ibuprofen pharmacokinetics is related to interaction of cytochrome P450 2C8 and 2C9 amino acid polymorphisms. *Clin Pharmacol Ther* 2004; 76: 119-27.
35. WHITE WB, SAAG KG, BECKER MA *et al*.: Cardiovascular safety of febuxostat or allopurinol in patients with gout. *N Engl J Med* 2018; 378: 1200-10.