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REVIEW ARTICLE

Precision medicine for rheumatologists: lessons from the pharmacogenomics of azathioprine

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Abstract

Precision medicine aims to personalize treatment for both effectiveness and safety. As a critical component of this emerging initiative, pharmacogenomics seeks to guide drug treatment based on genetics. In this review article, we give an overview of pharmacogenomics in the setting of an immunosuppressant frequently prescribed by rheumatologists, azathioprine. Azathioprine has a narrow therapeutic index and a high risk of adverse events. By applying candidate gene analysis and unbiased approaches, researchers have identified multiple variants associated with an increased risk for adverse events associated with azathioprine, particularly bone marrow suppression. Variants in two genes, *TPMT* and *NUDT15*, are widely recognized, leading drug regulatory agencies and professional organizations to adopt recommendations for testing before initiation of azathioprine therapy. As more gene-drug interactions are discovered, our field will continue to face the challenge of balancing benefits and costs associated with genetic testing. However, novel approaches in genomics and the integration of clinical and genetic factors into risk scores offer unprecedented opportunities for the application of pharmacogenomics in routine practice.

Key Points

- *Pharmacogenomics can help us understand how individuals' genetics impact their response to medications.*
- *Azathioprine is a success story for the clinical implementation of pharmacogenomics, particularly the effects of TPMT and NUDT15 variants on myelosuppression.*
- *As our knowledge advances, testing and dosing recommendations will continue to evolve, with our field striving to balance costs and benefits to patients.*
- *As we aim toward the goals of precision medicine, future research may integrate increasingly individualized traits—including clinical and genetic characteristics—to predict the safety and efficacy of particular medications for individual patients.*

Keywords Azathioprine · NUDT15 · Personalized medicine · Pharmacogenomics · TPMT

Precision medicine seeks to identify effective approaches for patients based on a combination of personal factors, including genetics and lifestyle. As part of precision medicine, pharmacogenomics examines how genes impact patients' responses to drugs and provides that information to clinicians so they can personalize treatments that maximize drug response and minimize adverse drug reactions [1–3]. Interpersonal variability in drug response is often unpredictable; therefore, identifying the mechanisms underlying this variability remains one of the most complex therapeutic challenges in internal medicine [4]. In rheumatology, many of our current practices include the prescription of drugs that were efficacious in only ~ 50% of patients during randomized clinical trials (e.g., mycophenolate treatment for lupus nephritis or anti-TNF agents treatment for rheumatoid arthritis) [5–9] or of drugs that have a high rate of adverse events (e.g., azathioprine) [10–18].

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Genes and drug metabolism

Based on drug metabolism, genetic variation can affect individual drug response in two key steps: activation and elimination. First, a functional variant in a gene which encodes an enzyme responsible for activating a prodrug can affect concentrations of the active drug. If there is a loss-of-function variant or a variant that decreases the function of the activating enzyme, then the drug might have null or reduced efficacy. Conversely, gain-of-function variants can result in excessive drug activation and increase the risks of adverse events [19]. In either case, changes in drug dosing or drug choice might be necessary. The second way genes can have a large effect on drug action is due to loss-of-function variants in enzymes that are responsible for eliminating the active drug from the body. The resulting increased concentration of the active drug can lead to adverse events. This risk for adverse events is particularly concerning for drugs with a narrow therapeutic window (i.e., a small difference between a dose causing side effects and the therapeutic dose).

Pharmacogenomics approaches

The goal of pharmacogenomics is to use an individual's genetics to guide prescribing decisions. Pharmacogenomics has used two broad methods: (1) the study of candidate gene(s) association studies and (2) unbiased approaches to identify functionally important variants. Candidate gene association studies have focused on variations in genes that encode enzymes, drug transporters, or drug receptors. The genes are chosen based on foreknowledge of drug metabolic pathways. The advantage to this approach is that fewer cases are required to have sufficient power to detect difference [4]. In contrast, unbiased approaches—predominantly, genome-wide association studies (GWAS), exome sequencing, and whole genome sequencing—interrogate millions of variants [20]. GWAS are more costly and complex, and they may obscure causative variants because they adjust the significance threshold for multiple comparisons; however, the unbiased approach offers the opportunity to discover unexpected mechanisms or pathways [21].

Despite pharmacogenomics being a relatively new field, the research derived from using biased and unbiased approaches has yielded substantive information regarding the links between genetic variants and drug response. As of December 2019, the Food and Drug Administration's (FDA) Table of Pharmacogenomic Biomarkers in Drug Labeling includes 404 pharmacogenomic biomarkers for 282 drugs [22]. Indeed, numerous rheumatological medications and their associated recommendations (e.g., testing and concurrent prescription warnings) appear on this table: azathioprine, celecoxib, flurbiprofen, lesinurad, pegloticase, piroxicam, probenecid, and upadacitinib.

Although these discoveries can and should contribute to therapeutic decision-making, implementing pharmacogenomics into clinical practice still faces many challenges. The first challenge is to identify clinically relevant drug response phenotypes. Technology has brought the resources to manage and interrogate genome data robustly [23], but determining clinically important phenotypes may not be feasible or may be too costly in time or labor, particularly if the standard for clinical relevance demands a randomized controlled trial showing the benefit of genotyping [24]. Consequently, real-world data obtained in routine clinical care are an attractive resource. However, the use of real-world data to define the clinical relevance of pharmacogenomics variants also has challenges. For example, the clinical variables used to define response in clinical trials (e.g., DAS28, SLEDAI) may not be recorded routinely in clinical practice. Moreover, accurate collection of data still requires review of individual medical records in many cases, which is labor intensive. The next challenge is to determine which gene-drug pairs are actionable [23]—in other words, identifying a particular genotype leads to either a change in the recommended dose of a drug or the substitution of an alternative drug, ideally implemented at the point of care. Finally, we must consider the potential costs of incorporating genetic testing in the clinical environment (e.g., financial or privacy-related) and carefully balance them with the potential benefits to patients (e.g. improved disease treatment). Overcoming these challenges is crucial as we move forward into the precision medicine era.

Pharmacogenomics applied in rheumatology: the example of azathioprine

Azathioprine and its associated side effects mark the most successful application of pharmacogenomics to rheumatology clinical practice and one of the most successful cases in internal medicine more broadly. In this review, we describe some of the concepts and history related to azathioprine and present the rationale supporting current guidelines to illustrate the current status and the potential direction of pharmacogenomics in general.

Thiopurine drugs (azathioprine and its metabolite 6-mercaptopurine) are immunosuppressants that are used widely for treating autoimmune conditions (e.g., systemic lupus erythematosus and ulcerative colitis), forms of cancer, and preventing organ transplant rejection. Azathioprine is rapidly converted to 6-mercaptopurine (6-MP) outside of the cell; 6-MP is then transported inside the cell where it is converted into thioinosine monophosphate (TIMP). Through a series of reactions, TIMP is converted, in part, to active metabolites for treatment, 6-thioguanine nucleotides (6-TGNs: deoxy-

thioguanosine monophosphate, deoxy-thioguanosine triphosphate, thioguanosine diphosphate, thioguanosine monophosphate, and thioguanosine triphosphate). 6-TGNs suppress the immune system by incorporating into DNA that is replicating and RNA that is translating as well as blocking the de novo pathway of purine synthesis (Fig. 1) [25, 26]. However, as first discovered in 1983, excessive 6-TGNs' concentrations are toxic and can cause bone marrow suppression [27, 28] and certain types of cancers [29, 30].

Variants in *TPMT* can predict leukopenia

The first link between phenotypic variations in the enzyme thiopurine methyltransferase (*TPMT*) and variability in 6-TGNs concentrations was observed in 1987 [31]. We now know that TPMT inactivates intermediate compounds during the metabolism of thiopurine drugs, thereby reducing the final concentration of 6-TGNs at a given dose of the drug (Fig. 1). With this knowledge, geneticists used candidate gene association studies to identify variants in TPMT responsible for reduced activity. Now, they have identified dozens of single nucleotide polymorphisms (SNPs) on the *TPMT* gene that reduce or eliminate its function, which results in an increased likelihood of myelosuppression for patients taking azathioprine. Three of these variants account for 90% of low activity phenotypes in individuals of European descent: *2, *3A, and *3C (found in 0.2%, 3.4%, and 0.4%, respectively) [32–34]. Accordingly, due to the high level of risk, potential users are now routinely tested for this genetic variation before receiving a prescription.

Despite this real-world application, preemptive *TPMT* testing does not eliminate the risk of myelosuppression for most patients who use azathioprine; indeed, known *TPMT* variants appear to account for only 25% of cases of myelosuppression [35–38]. As such, researchers have focused on using unbiased approaches to find additional genetic variants causing adverse events with azathioprine use.

Variants in *NUDT15* can predict leukopenia

The limitations of testing for known *TPMT* variants are particularly relevant to Asian populations. Asians have a much lower frequency of *TPMT* variants identified with azathioprine-associated leukopenia compared to Caucasians (~2% among South/Central Asians versus ~12% of Caucasians); nevertheless, the rate of leukopenia is higher among Asians (31–40% among Asians with Crohn's disease versus ~5% among Caucasians with inflammatory bowel disease). This points to the limitations of using *TPMT* alone to predict azathioprine toxicity [39–42]. Suspecting genes outside *TPMT* played a role in leukopenia, researchers utilized an unbiased approach to identify additional genetic variants causing leukopenia in individuals of Asian descent.

In 2014, Yang et al. found that a missense SNP, rs116855232, in nudix hydrolase 15 (*NUDT15*) was strongly

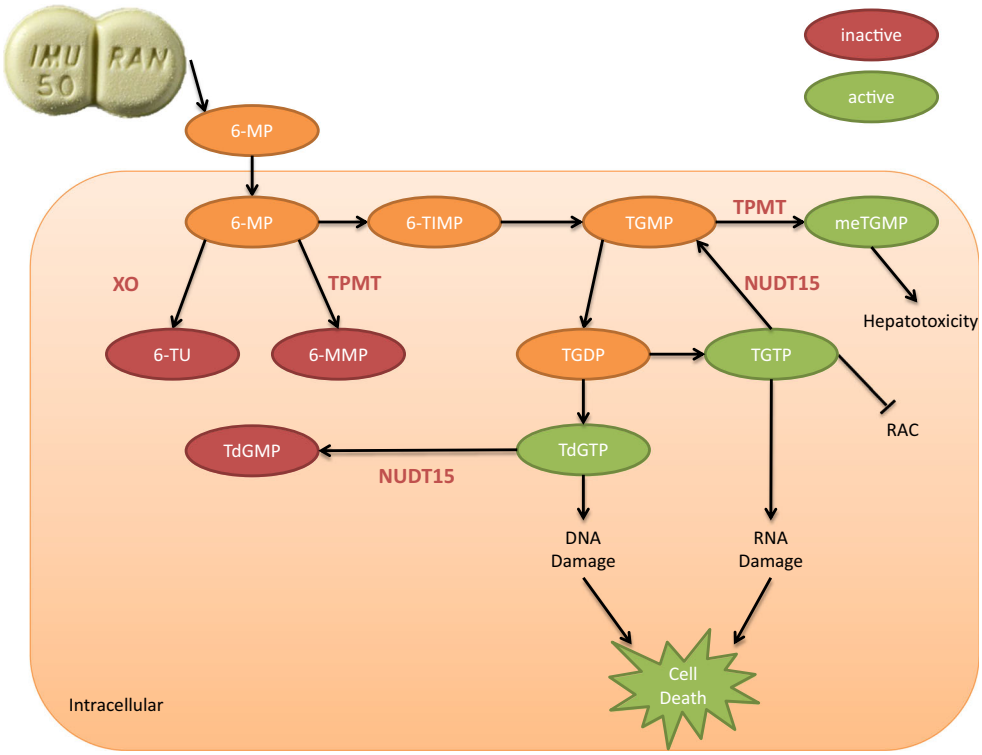

Fig. 1 Azathioprine metabolism. *6-Mercaptopurine (6-MP), 6-methyl-mercaptopurine (6-MMP), 6-thioinosine monophosphate (TIMP), 6-thiouracil (6-TU), deoxy-thioguanosine monophosphate (TdGMP), deoxy-thioguanosine triphosphate (TdGTP), nudix hydrolase 15 (NUDT15), thioguanosine diphosphate (TGDP), thioguanosine monophosphate (TGMP), thioguanosine triphosphate (TGTP), thiopurine methyltransferase (TPMT), xanthine oxidase (XO)

associated with increased risk for leukopenia among Koreans (OR = 35.6; $p = 4.88 \times 10^{-94}$) [43]. The same *NUDT15* SNP was later found to cause azathioprine-associated leukopenia in individuals of Chinese descent [44–46]. While this particular SNP is rare in Caucasians, researchers have found other *NUDT15* variants associated with azathioprine-induced myelosuppression in Caucasians [47, 48]. Indeed, Schaeffeler et al. observed that *NUDT15* variants contributed to 13% of azathioprine-associated leukopenia among Caucasians; further, they observed that *TPMT* and *NUDT15* variants combined to explain ~ 50% of hematotoxicity among azathioprine users of European descent [47]. Having identified the significance of certain *NUDT15* variants, researchers have since been able to identify the mechanisms by which NUDT15 impacts thiopurine metabolism. Similar to TPMT, NUDT15 inactivates thiopurine metabolites, ultimately leading to reduced concentrations of cytotoxic 6-TGNs (Fig. 1). [49]

A variant in *HLA* can predict pancreatitis

Leukopenia is not the only serious side effect associated with azathioprine use. Approximately 4% of patients develop pancreatitis after the initiation of azathioprine; notably, unlike leukopenia, pancreatitis is not dose related [50]. Heap et al. conducted a GWAS to identify potential genetic predictors of pancreatitis among a cohort of European patients who developed pancreatitis after thiopurine treatment for Crohn's disease or ulcerative colitis; notably, these patients had no additional risk factors for pancreatitis, including their concurrent medications. The group found a SNP, rs2647087 (occurring in ~ 30% of individuals with European ancestry), within the human leukocyte antigen (HLA) complex (fine-mapping revealed this SNP was associated with *HLADQA1*02:01-HLA-DRB1*07:01* haplotype) significant for the development of pancreatitis among azathioprine users; they were able to replicate their results in a group of patients with inflammatory bowel disease (IBD). The study found no association between *TPMT* variants (*3A, *3C, *2, *4, and *8) and pancreatitis [51]. A separate study confirmed the association between *HLA* SNP rs2647087 and pancreatitis in a second, independent cohort of patients with IBD taking azathioprine (OR = 0.53% for wild-type, 4.25% for heterozygous, and 14.63% homozygous) [52].

Cost-effectiveness evaluation

Alongside the focus on safety, we must consider cost-effectiveness when considering implementation of genetic testing for patients. Identifying potential side effects and efficacy through genetic testing may ultimately save more money, despite upfront costs. [53]

Analysis of the cost-effectiveness of genetic testing for azathioprine use has brought some controversy, but the results of most studies favor genotyping. Studies in several healthcare systems around the world have demonstrated that the aggregate costs associated with testing tend to be lower compared with the aggregate costs of treatment for patients who are heterozygous (approximately 1 in 10) or homozygous (approximately 1 in 300) for *TPMT* loss-of-function variants [54, 55]. For example, in the USA, one study compared *TPMT* testing, metabolite monitoring, and community care. *TPMT* testing was the least costly strategy at year one ($7142 for community care versus $3861 for testing) [56]. Of course, results are not always so definitive. Several studies in Canada's single payer system have found only small differences in the costs associated with screening versus not [57, 58]. Despite the lack of "savings," these results promisingly show that patients at the greatest risk may be identified for relatively neutral costs.

Gene-drug pairs with the strongest evidence to support the necessity of genetic testing and proven cost-effectiveness of preemptive genotyping are more likely to be reimbursed by Medicare (and similar systems in other countries); accordingly, Medicare reimburses testing for *TPMT* variants before prescribing azathioprine. [59]

Clinical recommendations and guidelines

The success in identifying genetic predictors for drug-associated side effects has led several groups to provide therapeutic guidelines for these drugs. As noted above, the FDA now requires labeling with guidelines for individuals who have variants in *TPMT* and *NUDT15*. Additionally, the Clinical Pharmacogenetics Implementation Consortium (CPIC) and Dutch Pharmacogenetics Working Group (DPWG) both provide evidence-based recommendations for dosing or alternative medication options [27, 60]. The most recent CPIC publication includes dosing guidelines based on TPMT and NUDT15 metabolizer status (Table 1) [34]. For example, for patients who are considered TPMT or NUDT15 poor metabolizers (two nonfunctional alleles), CPIC recommends against using azathioprine to treat non-malignant conditions. CPIC also has guidelines for treating patients with various combinations of TPMT and NUDT15 phenotypes. Creating these types of evidence-based recommendations are not only imperative to improving healthcare but also for reducing healthcare costs and encouraging healthcare reimbursement from insurance companies and healthcare programs like Medicare and Medicaid.

Future opportunities: more genes and the potential role of risk scores

Along with the widely recognized genetic variants described above, numerous additional variants may play a

Table 1 Dosing recommendations for azathioprine

Gene	Haplotype	Examples of diplotypes	Likely phenotype	General dosing recommendation
TPMT	Two normal function alleles	*1/*1	Normal metabolizer	• Start with normal dose • Titrate 2 weeks • Monitor
	One normal function PLUS one no function allele	*1/*2, *1/*3A, *1/*3B, *1/3C, *1/*4	Intermediate metabolizer	• Start with reduced dose (30–80%) • Titrate 2–4 weeks • Monitor
	Two no function alleles	*3A/*3A, *2/*3A, *3A/*3C, *3A/*4	Poor metabolizer	• Consider alternative for non-malignant condition • Start with highly reduced dose (10% and/or alternating days) • Titrate 4–6 weeks • Monitor
NUDT15	Two normal function alleles	*1/*1	Normal metabolizer	• Start with normal dose • Titrate 2 weeks • Monitor
	One normal function PLUS one no function allele	*1/*2, *1/*3	Intermediate metabolizer	• Start with reduced dose (30–80%) • Titrate 2–4 weeks • Monitor
	Two no function alleles	*2/*2, *2/*3, *3/*3	Poor metabolizer	• Consider alternative for non-malignant condition • Start with highly reduced dose (10% and/or alternating days) • Titrate 4–6 weeks • Monitor

Adapted from Clinical Pharmacogenetics Implementation Consortium Guideline for Thiopurine Dosing Based on *TPMT* and *NUDT15* Genotypes: 2018 Update

role in myelosuppression or other adverse effects associated with azathioprine use. Researchers are continuing to examine the potential links between side effects and proteins known to be involved in the metabolic pathway of azathioprine. For example, xanthine oxidase/dehydrogenase (XDH), aldehyde oxidase (AOX1), and molybdenum cofactor sulfurase (MOCOS) are enzymes involved in the metabolism of azathioprine. MOCOS is an enzyme that sulfurates the molybdenum cofactor for AOX1 and XDH, which compete with TPMT to inactivate certain azathioprine metabolites [61, 62]. Initial studies have shown that variants in *AOX1* and *MOCOS* can impact effective dosage among transplant candidates; however, additional studies are required to determine if these variants in these genes play a role in azathioprine-associated side effects. Additional studies have noted the potential for variants in the genes *ABCC4*, *ITPA*, *GST*, *IMPDH1*, *IL6*, and *FTO* [43, 49, 51, 62–92] to impact azathioprine metabolism and its side effects. Nevertheless, more research is needed to determine whether they should be tested in clinical practice.

Because of the interaction between genetics and environment, the most useful information for clinicians and patients may lie in risk scores that consider genetic, clinical, and environmental characteristics. As a proof-of-concept, we recently published a pilot study that generated such a score for azathioprine-associated leukopenia [93]. As discussed above, genetic testing to determine TPMT metabolizer status has become the standard of care for patients initiating azathioprine; however, even with the addition of *NUDT15* testing, almost half of leukopenia cases remain unexplained [47, 94, 95]. We hypothesized that a risk score composed of multiple clinical factors and additional candidate genes could improve the prediction of azathioprine-associated leukopenia. The risk score included demographic characteristics, medications that interact pharmacokinetically or pharmacodynamically with azathioprine, leukopenia-associated comorbid conditions, and genetic variants coding for enzymes involved in azathioprine metabolism (including *TPMT* and *NUDT15*). We generated multiple models using information from electronic health records, including patients with a wide range of indications, and/or the results of genetic testing. The model that included all clinical variables and genetic information performed the best in both the discovery and replication phases of the study. These results indicate that a multivariable score that incorporates important clinical variables and genetic data outperforms scores based on traditional genetic testing (e.g., TPMT metabolizer status).

Many steps are required before implementing risk scores in clinical practice; these include larger studies and GWAS analysis for additional genetic information. Also, while we have determined some of the genetic variants that lead to azathioprine adverse events, further research is needed to examine whether additional genetic information, as well as proteomic

and metabolomic approaches, could improve prediction of adverse events in real-world clinical practice. Although these efforts require an investment of time and resources, we can look forward to risks scores—based on complex clinical and genetic information—that can more effectively determine rheumatology patients' risk for serious side effects.

Conclusion and future directions

Along with this focus on safety, we also anticipate more studies regarding the impact of genetics on the efficacy of medications. As we work toward the goal of precision medicine, future research ultimately may combine genetic and clinical data into a generalized recommendation score that accounts for the efficacy and risk of individual drugs for individual patients. In closing, we see promise, in particular for the multiple drugs with complex metabolism and narrow therapeutic indices that are strong candidates for applied pharmacogenomics in rheumatology.

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Compliance with ethical standards

Disclosures None.

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