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Suggested Reference

Dalbeth, N., Choi, H. K., & Terkeltaub, R. (2017). Gout: A roadmap to approaches for improving global outcomes. *Arthritis and Rheumatology*, *69*(1), 22-34. doi:10.1002/art.39799

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Arthritis & Rheumatology
DOI 10.1002/art.39799

Accepted Article

Gout: A roadmap to approaches for improving global outcomes

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Supported by the Health Research Council of New Zealand (9101-3708025)(ND), NIH (R01AR065944)(HKC), and VA Research Service (RT).

Dr. Dalbeth has received grant support from AstraZeneca. She also has participated on speaker bureaus for Menarini, ARDEA/Astra-Zeneca, Takeda, and as a consultant for Astra-Zeneca, Fonterra, Takeda, Pfizer, CymaBay, and Crealta (all for <$10,000). Dr. Choi has served as consultant for Takeda and ARDEA/Astra-Zeneca (all for <$10,000). Dr. Terkeltaub has served as a consultant for ARDEA/Astra-Zeneca (for >$10,000), and SOBI, Revive, Selecta, Aequus, ProteoThera, Horizon, Relburn, and CymaBay (all for <$10,000).

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Running Head:

Roadmap to improved gout outcomes

Keywords: Hyperuricemia, ABCG2, URAT1, NLRP3 inflammasome, Precision Medicine

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as an 'Accepted Article', doi: 10.1002/art.39799
© 2016 American College of Rheumatology
Received: May 04, 2016; Revised: Jun 06, 2016; Accepted: Jun 21, 2016

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Introduction

Gout is the most common inflammatory arthritis (1) in the USA and in many developed countries worldwide (2), and linked with multiple serious comorbidities (3-5). Acute gout flares (1) are characteristically excruciatingly painful (6), and are associated with poor health-related quality of life, hospitalization, emergency room visits, and increased healthcare costs (7-10). Despite advanced understanding of gout pathogenesis and outcomes, quality of gout care delivered to patients, let alone accepted by them, remains remarkably suboptimal worldwide (11,12). To that effect, gout is well suited for a straightforward quality improvement framework, in that there is a simple measure for quality of care (i.e., serum uric acid (SUA) level), and robust and pragmatic management guidelines have been published (1,13,14). Moreover, via advances in genomics and molecular pathogenesis summarized in this review, gout is well positioned to take advantage of the emerging transformation of medical care by precision medicine by increased employment of genomics and other “omics”.

Key approaches to markedly improve quality of gout care clearly start with provider and patient education, individualized lifestyle and pharmacologic measures, and overcoming therapeutic inertia (i.e., failure to initiate or intensify treatment in a patient not yet at the evidence-based treatment target)(11,15). Such measures, in gout, closely parallel those in other chronic conditions such as diabetes and hypertension, for which, the time recommended to achieve the therapy target, and individualization of the effort to achieve standard therapy targets, have been extensively investigated and reviewed. In this review, we look beyond these charted paths, to propose a roadmap for how we can improve global outcomes of gout patients by venturing beyond the currently established generation of treatment measures and targets (**Table 1**). In doing so, we particularly elaborate on the need to better develop and employ precision medicine approaches and effective implementation

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strategies to achieve these goals.

Step 1. Refining disease stages of gout

Gout has recently been re-classified, with equal weight in diagnostic scoring given to palpable tophi, the ultrasound finding of a double contour sign, and positive dual energy CT (DECT)) for urate crystal deposition (16). In this context, novel studies using advanced imaging (ultrasound and DECT), and compensated polarized light microscopy, have demonstrated that a substantial fraction of hyperuricemic individuals (ie, ~25-40%, depending on degree of hyperuricemia and urate crystal detection approach employed) have evidence of monosodium urate (MSU) crystal deposition without gouty joint symptoms (17-19). These data support the concept that there are pathophysiological stages of hyperuricemia/gout, from (i) asymptomatic hyperuricemia without MSU crystal deposition, to (ii) asymptomatic hyperuricemia and MSU crystal deposition, to (iii) gout (ie, "symptomatic hyperuricemia with MSU crystal deposition"), and to (iv) progressively more advanced gout characterized by tophi, chronic arthritis and joint damage. Rare cases of gout appear to vary from this standard sequence, presumably for idiosyncratic reasons, but it does not obviate the overall value of this new schema.

In conventional models of gout care utilized to date, the decision points to initiate urate lowering therapy (ULT) have been primarily for frequent acute gout flares and for features of advanced chronic gouty arthritis (13). Overall, this disease definition spectrum has been linked to key gout-related outcomes (20) (**Figure 1A**). However, symptomatic gout, and asymptomatic hyperuricemia (with or without MSU crystal deposition in tissues), both appear to have implications well beyond the joint (**Figure 1B**)(21-25). Potential links to hyperuricemia have been raised for worsening of hypertension, for onset and progression of chronic kidney disease (CKD), and for insulin resistance and obesity (21-23). Furthermore, asymptomatic MSU crystal deposition in the joints was recently reported to be strongly associated with moderate-severe coronary artery calcification in patients presenting with

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non-STEMI acute coronary syndrome (24). It is conceivable that gout is part of a larger "crystal-forming" diathesis in extracellular matrices. Also intriguing is detection of negatively birefringent crystals (with features of MSU) in coronary arteries of explanted hearts and in resected prostate tissue (25). Such findings suggest that MSU crystal deposition might directly contribute to focal inflammation at non-articular sites.

It remains unknown if simple presence of tissue MSU crystal deposits predicts ultimate development of clinical gout flares, tophus formation, and joint damage, let alone associated comorbidities (**Figure 1**), or if ULT provides benefits that exceed potential risks, among people with asymptomatic MSU crystal deposition, for prevention of either articular disease or comorbidities. Studies that carefully assess clinical implications of confirmed tissue MSU crystal deposition in asymptomatic hyperuricemia are overdue.

Step 2. Improving Care for Comorbidities of Hyperuricemia and Gout

Hyperuricemia and gout are strongly associated with cardiovascular (CV)-metabolic-renal comorbidities) and their sequelae (e.g., myocardial infarction and premature death (3-5). Causal role of gout and hyperuricemia on these outcomes remains unresolved, but recent expansion of genetic discovery through genome wide association studies (GWAS) has allowed novel modes of testing individual associations for potential causality. Mendelian randomization studies are particularly relevant in the context of the gout-urate-CVD links, since they take advantage of random assignment of alleles of an individual's genotype at meiosis, thereby eliminating bias by confounding variables and reverse causation. To date, most such uric acid Mendelian randomization study findings for comorbidities have been null, suggesting non-causal associations (26,27). However, in two randomized controlled trials (RCTs)(with N=30, and N=60), among adolescents with hyperuricemic prehypertension or stage-1 hypertension, allopurinol or probenecid was associated with lowered blood pressure, with magnitude of effect similar to first line oral anti-hypertensive agent (28,29), whereas a similarly designed trial among adults (N=149) did not find such a benefit (30).

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Importantly, participants in the RCTs did not have gout (28-30); thus, generalizability of the results remains to be clarified.

Regardless of causality questions, the high frequency of major comorbidities and their sequelae in gout requires serious consideration of these issues in gout care, moving beyond choosing appropriate anti-gout therapy, to reducing overall disease burden of gout. For example, observational studies have suggested that allopurinol initiation is associated with lower risk of all-cause mortality (31,32) and CV events (33). Moreover, use of colchicine has been associated with a lower risk of several cardiovascular events (34,35).

Taken together, optimal gout-limiting therapy approaches (pharmacologic, diet, and lifestyle measures) would adopt a personalized treat-to-target paradigm to reduce both SUA and CV-metabolic-renal complications. The low-purine dietary approach to gout is clearly obsolete; it offers limited efficacy, palatability, and sustainability, and promotes increased consumption of refined carbohydrates and saturated fat that can promote insulin resistance and increased plasma glucose, triglycerides, and LDL-Cholesterol (36). In contrast, we need to better apply effective dietary approaches to reduce CV-metabolic conditions (including obesity and insulin resistance) in combination with lowering serum urate and risk of incident gout. For example, the Dietary Approaches To Stop Hypertension (DASH) diet, which was associated with urate-lowering effect of ~1.3 mg/dL among those with SUA >7 mg/dL (37), warrants investigation in gout patients. Diets against the metabolic syndrome and high glycemic index, which showed urate-lowering effects (36,38), merit further examination in gout patients. Several ongoing randomized trials of effects of urate-lowering drugs on CV-renal outcomes may help to clarify the potential role of such medications on these outcomes, via urate-lowering and/or antioxidant effects through xanthine oxidase inhibition (23).

Step 3. Implementing precision urate-lowering therapy and optimizing target urate levels

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FDA-approved drugs for use in ULT in gout patients are allopurinol, probenecid, febuxostat, pegloticase, and, in combination with a xanthine oxidase inhibitor (XOI), the uricosuric lesinurad. Effective implementation of oral ULT may not be easy to achieve in some clinical practices, due to the need for continuously supervised dose titration regimens and/or risk management strategies for allopurinol and certain potent uricosuric agents. This problem is compounded by the high frequencies of both acute flares and nonadherence after starting ULT (1,13).

A number of ULT drugs are in pipeline development (**Table 2**); some have dual mechanisms for urate-lowering, or posses both urate-lowering and anti-inflammatory properties. However, for individual patients, we need to better understand what ULT drug should be used first, at what dose, and the best option if first-line ULT fails. A prime example, with a baseline ULT regimen that is well-tolerated but only partially effective, is the decision to switch patients to a different oral ULT drug of the same class (XOI or uricosuric), or add another oral drug in a different class by combining XOI and uricosuric therapy. Cost-effectiveness of selected agents and strategies will need further, rigorous study.

Precision medicine is defined as “an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person” (http://www.nih.gov/precision-medicine-initiative-cohort-program). An integrated approach for clinical practice is needed that systematically considers both genetic and non-genetic variables. Some elements are now in place or within reach for broader applicability (**Table 3**). For allopurinol, this includes the well-documented association of *HLA-B*5801* with markedly increased risk of severe allopurinol hypersensitivity syndrome (AHS) (13,39,40). The *HLA-B*5801* linkage with AHS is cogent, given impact on ULT risk management strategies in racial and ethnic groups with relatively high allele prevalence and confirmed high predictive value of *HLA-B*5801* (e.g., Han Chinese, Thai, and Korean ancestry)(39,40). It appear likely those of some other Asian ancestries (including East

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Indian) or African-American ancestry (41) could be impacted, due to their several-fold higher *HLA-B*5801* allele frequency as compared to the ~1% in people of European ancestry. In addition to clear, strong *HLA-B*5801* association with risk of AHS (39,40), other HLA haplotypes also predict less severe allopurinol adverse drug reactions, including an *HLA-B*5801* haplotype (CACGAC) with 6 SNPs in those of European ancestry (42). Since the event rate of AHS remained low even in Taiwanese with *HLA-B*5801* in a recent prospective cohort analysis, the frontiers of allopurinol risk management will likely include more precise identification of *HLA-B*5801* variants and other complex genotypes with AHS.

Genome wide association studies (GWAS) have provided new insights into biological bases for hyperuricemia and gout, on a population level, that may be translated to clinical care as whole genome sequencing becomes increasingly available (**Table 3**). Results have highlighted importance of both extra-renal and renal urate transport (43-45). The two genes most strongly associated with gout in GWAS are *ABCG2* and *SLC2A9*. *ABCG2* encodes ABCG2/BCRP, a high capacity plasma membrane urate efflux transporter that acts in part by promoting renal uric acid excretion, and also in part by promoting extra-renal (small intestinal) urate secretion, which consequently promotes uric acid degradation by colonic bacterial uricase (44). *SLC2A9* encodes GLUT9, a transporter that mediates renal urate reabsorption at the proximal tubular cell basolateral membrane (45). GWAS of serum urate regulation have also identified a suite of other renal urate transporters including *SLC22A12* (encoding URAT1, a transporter that regulates renal urate reabsorption on the proximal tubular cell apical membrane), and other pathways, including the inhibins-activins growth factor system and carbohydrate metabolism pathways. Significantly, some genetic variants associated with hyperuricemia and gout interact with BMI, and consumption of alcohol and sugar (46).

For precision medicine, genomic analysis of the root cause of hyperuricemia in a person with gout may allow more selective decision-making about what mechanism of action to target

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(**Table 3**). In particular, it may identify patients who are more likely to respond to uricosuric drugs.

ABCG2 in precision models of hyperuricemia in gout patients

In clinical practice, the efficacy of allopurinol is primarily limited by chronic under-dosing and low adherence. However, some patients are adherent to allopurinol but do not achieve serum urate targets despite adequate allopurinol dosing. Variables such as baseline SUA, kidney function, diuretic use, and body size contribute to allopurinol response (47,48). In addition, at least one common *ABCG2* variant (Q141K, encoded by the single nucleotide polymorphism (SNP) *rs2231142*), plays an important role in allopurinol response (49,50). This risk likely relates to the observation that ABCG2/BCRP transports allopurinol, and its' long-lived active metabolite (49,50). Q141K, which is associated with ~50% loss of urate transport activity compared to wild type ABCG2, may act on drug transport in the liver, and possibly elsewhere, to decrease urate-lowering response to the drug. The allele frequency of ABCG2 rs2231142 appears to be at least ~10% at the population level in Whites, less common in those of African extraction, but several times more common (ie, ~25-30% in several studies) in populations of Japanese, Han Chinese, Korean, and Western Polynesian descent (51). In some cohorts with gout and Southeast Asian descent, ~50% of gout subjects have been reported to carry the Q141K ABCG2 rs2231142. Together with HLA haplotype analysis for allopurinol adverse events, these discoveries of quite common ABCG2 gene variation provide a clear opportunity to develop personalized models for safe and effective allopurinol dosing (**Table 3**).

Impairment of the urate transport function and/or stability or expression of ABCG2 has additional ramifications in gout precision medicine (**Table 3**). Specifically, some *ABCG2* genotypes are associated with several-fold increase in odds ratio for gout in genetic studies, suggesting possible future use to help improve the ability to predict the likelihood of development of incident gout in some with asymptomatic hyperuricemia. Furthermore,

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genotypes that encode for increasing loss of ABCG2 are associated with not only proportionately earlier onset of gout (a potential biomarker for earlier ULT intervention)(52), but also with extra-renal uric acid underexcretion, and consequent “renal uric acid overload, without uric acid overproduction" (44), a phenotype that contraindicates use of primary uricosuric monotherapy due to risk of urolithiasis. In this context, carriage of the ABCG2 variant Q126X (encoded by SNP rs72552713), which is entirely nonfunctional for urate transport, is a particularly strong contributor to the phenotype of intestinal underexcretion of urate with renal uric acid overload (44). Though Q126X has not been reported in Whites or Blacks, it is relatively common in Japanese (2.4%), and, also reported in some cohorts of Han Chinese and Korean descent, but at a lower allele frequency (51).

Collectively, the new *ABCG2* findings also have changed the way we classify causative factors for hyperuricemia in gout, adding renal uric overload due to intestinal ABCG2 dysfunction to uric acid underexcretion and uric acid overproduction (44). Moreover, the ability to pharmacologically increase ABCG2 function potentially provides a rational target for next generation ULT agents (53). Clearly, in the larger gout population, more studies will be needed to integrate genomic effects with acquired effects on urate transport of acquired renal comorbidities (e.g., hypertension, CKD) and environmental exposures via medications, diet, alcohol use, lifestyle, and other factors (**Table 3**). In addition, “omics” approaches other than genomics (e.g., transcriptomics, proteomics, and epigenetic studies [gene methylation, miRNA]), and serum biomarker studies, could be important to help advance translation in gout.

How current "treat-to-target" paradigms are anticipated to evolve

Not all gout patients require pharmacologic ULT. In those that do (13), current “treat-to-target” ULT paradigms advocated by rheumatology guidelines recommend serum urate target <6.0 mg/dL for most with gout, and <5.0mg/dL for “advanced gout", with evidence for a high body tissue burden of uric acid, such as the presence of palpable tophi, or clinical or

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imaging evidence of tophaceous disease with joint damage. Unequivocally, more intensive ULT leads to faster dissolution of MSU crystals and regression of tophi (54,55). As such, there is potential for more precision in SUA targets based on clinical presentation, as proposed in **Table 4,** though exact numerical SUA targets would need more clinical investigation to validate. Going forward, we expect to increasingly employ combination XOI and uricosuric ULT to achieve lower SUA targets in higher proportions of gout patients refractory to simple ULT monotherapy regimens that are appropriately dosed (13). Moreover, we need to better define the proportion of gout patients that are truly refractory to simple ULT monotherapy, as opposed to being nonadherent or receiving inappropriate ULT dosing. One unmet need, for severe, advanced tophaceous gouty arthritis (13), is for development of less immunogenic dosing regimens and other approaches to deliver recombinant PEGylated uricase, particularly with moderate to severe CKD (**Table 2**). Central to progress in the field will be integrative analyses of clinical trials, using both patient-reported outcomes and objective assessments of crystal burden (eg, DECT) as outcome measures. In this way, we can identify optimal serum urate targets for specific clinical presentations, with some potential target levels proposed in **Table 4**. There also is the possibility to adjust an individual patient's serum urate target over time, depending on the initial response to hyperuricemia. Exactly how low to drop the SUA in each patient may involve not only a question of lowering enough for the gout, but also, potentially, a question of not lowering too much to adversely affect other conditions; this is an area that needs substantial further investigation.

Step 4. Novel prognostic markers and disease activity indices beyond SUA.

Currently, SUA, frequent acute gout flare activity, presence of palpable tophi and gouty erosions, definition of a state of uric acid overproduction, urolithiasis, and CKD, are the major features of disease activity that help guide the treatment decisions to initiate or intensify ULT and/or prolonged anti-inflammatory flare prophylaxis (1,13). Higher SUA and longer disease duration are associated with elevated risk of acute gout flares, but there is

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sizable variability of risk determined by other factors. Similarly, aside from CKD and disease duration, factors contributing to presentation with palpable tophi are poorly understood.

The concept of composite disease activity scoring for gout has evolved from early efforts based simply on single clinical and laboratory parameters. In this light, the first gout disease activity scoring system has been recently reported, incorporating a 12-month flare count, serum urate levels, visual analogue scale (VAS) of pain, VAS global activity assessment, swollen and tender joint count, and cumulative measure of palpable tophi (56). However, validation of this type of gout disease activity measure is far behind instruments used for RA and certain other rheumatic diseases. Markers from advanced imaging, such as subclinical (and non-radiographic) synovitis, tophi, and joint damage have substantial potential for advancing identification patients at risk for recurrent flares, tophi, or progressive connective tissue destruction. However, determination of reliable prognostic markers (clinical, laboratory as well as imaging) for flares and development of destructive tophi will require analyses of large-scale, well-characterized prospective follow-up studies of gout.

New opportunities for gout inflammation biomarkers

Rapidly emerging knowledge of the molecular cascade of the acute MSU crystal inflammatory response, as well as priming and master regulatory inhibitory effects for this process, have provided opportunities for several new biomarkers (**Figure 2**). In this context, gouty inflammation is driven by innate immune responses to MSU crystals. Such core responses include "first signal" priming of the NLRP3 inflammasome in macrophage lineage cells by C5a (via cleavage of C5 on the MSU crystal surface), GM-CSF, and a variety toll-like receptor 2 and 4 (TLR2, 4) ligands (including the long chain fatty acid palmitate)(57). MSU crystals provide a "second signal" via NLRP3 inflammasome activation, thereby driving

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maturational processing and secretion of IL-1β (58-60). Local endothelial and mast cell activation, the ingress and activation of monocytes and neutrophils, and multiple additional cytokines and inflammatory mediators, contribute to full phenotypic expression of the acute gouty arthritis cascade (**Figure 2**).

In serum, the most consistent inflammatory cytokine biomarker in both acute flares and intercritical gout (ie, between flares) has been reported to be IL-8/CXCL8, linked to circulating S100A8/A9, a heterodimer robustly released from granules by activated neutrophils (61). New biomarkers for gout arthritis activity and disease progression could be mined from processes mediating constitutive "master" limitation of inflammatory responses to MSU crystals, which also provide potential novel therapy targets, as discussed below for AMPK-activated protein kinase (AMPK) and PPARγ (**Figure 2).** Other biomarkers and/or therapy targets could include kinins (subject to regulation by angiotensin converting enzyme inhibitors)(62), C5/C5a (63), and products of MSU crystal inflammation-associated connective tissue turnover.

Step 5. Novel mechanism-based precision medicine for gouty inflammation

The unmet need is substantial for new, safe and effective anti-inflammatory options to prevent and treat gouty arthritis. First, current anti-inflammatory gout prophylaxis is dated and imperfect; all first line oral pharmacologic approaches (low doses of colchicine, NSAIDs, and corticosteroids) are limited by potential drug toxicities, drug-drug interactions (64), and gaps in therapeutic efficacy (1). These issues contribute to the high frequency of patient and clinician preferences for foregoing the current generation of pharmacologic flare prophylaxis. Second, collective randomized, controlled, double-blind clinical trials of monotherapy for acute gout flares, using the currently FDA-approved oral agent standards for patient self-treatment regimens (1), have indicated substantial unmet need (65). For example, using oral

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high or low dose colchicine for early acute gout flare (defined as within 12 hours of onset), only 32.7% and 37.8% of subjects, respectively, compared to 15.5% given placebo, achieved ≥50% reduction in baseline flare by 24 hours without rescue medication (66). In addition, in trials with NSAIDs and oral corticosteroids for acute gout flare, including recent trials that suggest equivalence of both options (67), only up to ~50% of subjects have a >50% reduction in baseline flare pain by 72 hours (65). Fortunately, combination therapy modality studies for flares, though more difficult to design and perform, retain some promise for improved outcomes (1). Though selective biologic IL-1 inhibition can be effective in preventing and treating gouty joint inflammation (1), it adds substantial cost to treatment regimens, and not currently FDA-approved.

Precision medicine, and associated development of new rational therapeutics for gouty arthritis can mine not only recently identified host processes that limit MSU crystal-induced inflammation, but also exogenous inflammation stimulatory mechanisms (**Figure 2**). In this context, sources of variability in the capacity of MSU crystals to cause inflammation appear to include not only genomic variants of inflammatory mediators (68), but also targetable epigenetic regulatory effects (eg, exerted by micro-RNAs-1461 and 155 (69,70), and by certain class I histone deacetylases (HDACs) (71)). In this context, the gut microbiome in gout patients, compared to controls, has been reported to have not only decreased uric acid-degrading capacity but also decreased potential for generating anti-inflammatory effects via biosynthesis of butyrate (72), which acts partly via HDAC inhibition (71). Moreover, SUA elevation itself may have priming effects on macrophage activation, mediated by suppressing IL-1ra expression via modulation of histone methylation (73).

Constitutive "master" limitation of host inflammatory responses to MSU crystals also is exerted in part by biosensing of changes in nutrition, metabolism, and cellular energy processes, including by PPARγ (74), macrophage autophagy (75) and by AMPK (76).

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First, in this context, signaling by PPARγ, which regulates insulin sensitivity, also limits experimental gouty inflammation, and a partial PPARγ agonist with additional moderate uricosuric activity (via URAT1 inhibition) demonstrated positive effects on gout flare prevention in a phase II clinical trial (74). Second, autophagy, which is promoted under conditions of nutrient deprivation, functions homeostatically in intracellular energy-generating proteostasis by recycling obsolete moieties including damaged long-lived proteins and organelles; autophagy also plays a major role in maintaining balance of innate inflammatory processes (75). Third, constitutive and pharmacologically induced activation of AMPK limits innate inflammation by suppression of NF-κB transcription factor activation (itself a master regulator of inflammation), and effects on macrophage differentiation, including promotion of autophagy and anti-inflammatory M2 macrophage polarization (76). AMPK is activated by factors that increase cellular AMP:ATP ratio (e.g., caloric deprivation, exercise). Conversely, numerous factors that promote gouty inflammation inhibit tissue AMPK activity, exemplified by intake of palmitate (57) or fructose, by other nutritional excesses, by alcohol excess, and also by cell stimulation by IL-1β, TNFα, and MSU crystals.

Tissue AMPK activity is diminished in obesity, type II diabetes, and metabolic syndrome with linked low-grade adipose tissue inflammation. Moreover, decreased tissue AMPK activity can promote certain comorbidities prevalent in gout patients, including hypertension, onset and progression of renal disease and associated fibrosis, NASH, and atherosclerosis and cardiac hypertrophy (77,78). Furthermore, activated AMPK transduces multiple anti-inflammatory effects of colchicine (76). Significantly, systemic activation of AMPK is induced by certain drugs already in the clinic for arthritis and other diseases (e.g., metformin, methotrexate, nonacetylated salicylates, high dose aspirin). It would be of interest to discern the impact on gout flares of such agents, since some are already commonly employed for comorbidities by gout patients.

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Neutrophil activation is both a major driver and pro-resolving component in gouty inflammation, since self-limitation of model gout-like inflammation involves several phagocyte-driven native resolution mechanisms for acute neutrophilic inflammation (58,63,79,80)(**Figure 2**). These pathways include neutrophil microvesicle release, which inhibits C5a (63), phagocyte ingestion of apoptotic neutrophils, which leads to an altered profile of inflammatory and anti-inflammatory mediators released by effector cells (79), and NETosis, which also may promote tophus development (80). As such, new candidates for translation for gouty inflammation could emerge from refinements to currently approved modes of modulation of phagocyte activation (by colchicine, NSAIDs, corticosteroids, ACTH) in gout. In addition, the identification of IL-37 as one of the anti-inflammatory cytokines potentially active in limiting gouty arthritis is noteworthy and merits further investigation (81).

Step 6. Improving gout care in all clinical practices, particularly in the primary care setting

While the exact proportion of gout patients who meet the current indication for urate-lowering drugs is unknown, only 32% of US gout patients have been found to be treated with a urate-lowering drug (12). Further, the majority of those on urate-lowering drugs are not at SUA target levels (12), which promotes poor outcomes (e.g., acute gout flares, including those promoting hospitalization for gout (9), and joint damage). For example, a recent national study found that primary hospitalization rates for gout have doubled over the past two decades in the US, whereas those for RA have declined by 67% owing to improvements in RA care (9). Unequivocally, few patients in the USA receive clear education about the potential for long term remission and, in some, 'curability' of the disease, through long term ULT, as supported by uric acid pathophysiology (82,83) These practices have led to poor medication adherence, with as few as 10% of people with gout adhering to their treatment (84).

Current suboptimal gout care is promoted in part by substantial gaps, between

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rheumatologists and primary care providers (PCPs), in their gout care approaches and guidelines, as reinforced by the recent Agency for Healthcare Research Quality (AHRQ) gout care review for the ACP (85). In particular, the key approach advocated by rheumatology guidelines of ULT "treat-to-target" (to baseline SUA target of <6.0 mg/dL at a minimum), has not been implemented as a standard by PCPs in gout guidelines and care (85). This ideological schism between rheumatologists and PCPs is rendered even more vexing, given that moderate strength evidence supporting ULT of more than 1 year duration was recognized by AHRQ (85). Differences in valuation of long-term ULT in gout may largely be perpetuated by distinct interpretations of relatively short term (ie, 6-12 months) clinical trial results for oral ULT, which do not routinely show reduction of gout flare frequency or resolution of tophi. Since ~90% of gout patients are managed by PCPs, we need innovative efforts to systematically improve gout care outcomes, including by intensively engaging allied health professionals. Results have been impressive for clinical models that share some aspects of broadly employed anticoagulation and hyperlipidemia management and monitoring clinics (86,87). An open-label UK pilot study conducted at a gout specialty clinic provided a proof-of-concept that remarkable success rates (e.g., 92% achieving serum urate <6mg/dL and 85% achieving serum urate <5mg/dL, and with steadily improving gout flare rate) can be achieved by implementing a nurse-guided approach that combines patient education, personalized lifestyle measures, and treat-to-target ULT according to rheumatology guidelines, but with patient preferences driving the option of added anti-inflammatory prophylaxis (86). Of the 101 participants, 21% required an alternative agent for various reasons over one year, including only 8% due to treatment failure (86). Adopting a similar strategy of allopurinol use for the vast majority of gout patients, followed by febuxostat only for those with an inadequate response to allopurinol, was estimated to be cost-effective, compared with accepted willingness-to-pay thresholds, in a USA setting (88). Last, a pharmacist-led pilot study, under rheumatologist guidance for ULT in a USA HMO environment, provided somewhat similar findings (87) to the work of Rees et al in the UK (86). While the emerging pilot data on allied health professional managed gout clinics are

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promising, they are from open studies (86,87). We need more clinical trials, done in a controlled manner, and in different practice environments and with patients of different cultural and socioeconomic backgrounds.

Conclusions

Future precision medicine systems can ultimately lead to improved selection, dosing, safety, efficacy and cost-effectiveness of hyperuricemia based on clinical presentation combined with genomic, environmental and lifestyle data, integrating the SUA target, causes of hyperuricemia, and predictors of safety and efficacy to available therapies. These models need to evolve in step with major upgrades in the number and effectiveness of ULT and anti-inflammatory options and regimens. Fortunately, platforms and roadmaps for new models are provided not only by research advances in gout inflammation biology, including recent identification of gouty inflammation master regulators and biomarkers, but also by the emerging wealth of new genomics and epigenetic findings applicable to clinical bioinformatics. Attention to integrating better outcomes in gout and comorbidities is essential, and achieving tighter control of SUA in more patients will be central to this mission. However, major improvements in gout outcomes at a population level will require much deeper engagement of primary care and affiliated health professionals, and require careful validation, particularly in populations with differing cultural and socioeconomic backgrounds.

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Figure 1. New definitions of gout and expanded key outcomes.

A. Current definitions of gout and key outcomes are restricted to symptomatic MSU crystal deposition with important but limited management outcomes. B. Revised definitions will address disease stages in both asymptomatic and asymptomatic disease, leading the increasing scope for improved outcomes, both for articular and non-articular features of disease.

Figure 2. Some of the recently identified inflammation stimulatory mechanisms, as well as native host processes that limit MSU crystal-induced inflammation, that provide potential biomarkers and rational therapeutic targets in gout. As discussed in the text, and named in the left part of the schematic, constitutive "master" limitation of host inflammatory responses to MSU crystals is exerted partly by genetic and epigenetic effects, and partly by biosensing of changes in nutrition and cellular energy processes (via changes in macrophage autophagy, AMPK activity, and PPARγ signaling). Priming effects of hyperuricemia and the long chain fatty acid palmitate can promote gout inflammatory processes, whereas some of these processes can be suppressed by butyrate (whose generation is partly regulated by gut microbiome content). The middle portion of the schematic mentions several mediators (and biomarkers) involved in the inflammatory cascade of acute gouty arthritis. The right side of the schematic mentions some of the factors, transduced by modulation of phagocyte function and cell fate, which promote spontaneous self-limitation of acute gouty arthritis. Experimentally, these events lead to altered balance of anti-inflammatory vs. inflammatory mediators at the locus for MSU crystals in model acute gout.

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Table 1. A roadmap for improvement upon the current generation of treatment targets and their associated outcomes in gout.

Step	Major Tools and Approaches Include:
1. Refining disease stages of gout	Prospective studies of people with hyperuricemia and gout using advanced techniques such as ultrasound and DECT
2. Improving care for comorbidities of hyperuricemia and gout	Randomized trials of target lifestyle modifications for uric acid levels and CV-metabolic intermediate outcomes
3. Implementing precision ULT and optimizing target urate level	Development of personalized models to guide choice and dose of urate-lowering therapies, including: -HLA-B*5801 for allopurinol hypersensitivity syndrome risk management -*ABCG2* alleles to predict allopurinol response, renal uric overload due to impaired gut urate secretion, and contraindication to uricosuric therapy -Clinical trials that convincingly demonstrate the therapeutic benefits of ULT strategies on clinically relevant endpoints -Better define ULT indications and serum urate targets for comorbidities -Better define true refractoriness to ULT monotherapy, and validate indications for

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	combination XOI and uricosuric therapy - Developing less immunogenic PEGylated uricase regimens, particularly with moderate to severe CKD
4. Novel prognostic markers and gout-specific disease activity indices beyond SUA	Large, well-characterized prospective studies of patients with gout for -Clinical gout disease activity scores -Serum biomarkers for gout flare activity and tophus development other than SUA (eg, inflammation and connective tissue turnover markers) -New applications of advanced imaging (ultrasound, DECT, and potentially MRI)
5. Novel mechanism-based precision medicine for gouty inflammation	-Exploit recently defined natural master regulatory and anti-inflammatory cytokine mechanisms limiting gouty arthritis
6. Improving gout care in all practices, particularly in the primary care setting	-Engage primary care physicians to adapt more effective ambulatory models to initial optimization of ULT and control of gouty inflammation -Broaden use of allied health professional-run gout clinics that apply high level disease education methods for patients

Abbreviations:

DECT: dual energy CT

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Table 2. Examples of urate-lowering and anti-inflammatory agents in development for gout

	Compound Name	**Mechanism of Action/Molecular Target**	**Status**
ULT	Topiroxostat	XOI	Phase III
	Extended release febuxostat	XOI	Phase III
	RDEA3170 (added to xanthine oxidase inhibitor)	URAT1 inhibition	Phase II
	RLBN3010 series KUX-1151	Combined XOI and uricosuric agents (combined mechanism of action)	Phase 0-I Phase II
	Modifications in PEGylated recombinant uricase administration: -- altered initial dosing schedule of pegloticase -- Nanoparticle-encapsulated pegsiticase with the immunomodulator rapamycin to promote immune tolerance	Uricolysis by PEGylated uricase	Various

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ULT and anti-inflammatory flare prophylaxis	Arhalofenate	URAT1 inhibition and PPARɣ agonist	Phase II completed
Anti-inflammatory	Bucillamine	Orally administered inhibition of IL-1beta responsiveness	Phase IIa completed
	Various	Injectable biologic modulation of IL-1 responses	Various

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Table 3. Core applicable elements of precision medicine models for gout management

Treatment Decision	**Current determinant(s) used for medical decision making**	**Within reach: Determinant(s) for gout "Precision Medicine"**	**On the horizon: Determinants for unmet needs in gout "Precision Medicine"**
Initiate oral ULT and/or choose a lower serum urate target (ie, <5 mg/dL, at a minimum), and initiate pharmacologic gout flare prophylaxis	-Extent of crystal burden and/or gout arthritis flare frequency or chronicity -CKD -Urolithiasis -Palpable tophi are detected -Certain heritable and acquired disorders with uric acid overproduction	-Gout disease activity index -Imaging techniques to quantify extend of urate burden to guide dynamic selection of serum urate treatment target -*ABCG2* variants	-Serum biomarkers for prognosis of inflammatory activity and joint destruction (eg, C5/C5a, kinins) - Multiple "omics" approaches including for urate metabolism and transport mediators and inflammation genes
Select or avoid allopurinol	*A-B*5801* (presence or absence), to predict increased risk of allopurinol hypersensitivity syndrome	-*ABCG2* variant *Q141K (*encoded by SNP *rs2231142*), to predict failure to adequantely respond	- *HLA-B*5801* single nucleotide polymorphisms to more accurately predict risk of allopurinol

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	(AHS)	to allopurinol, putatively via altered allopurinol and oxypurinol transport	adverse events (eg, 6 SNP CACGAC haplotype) -Integration of genomic and non-genomic data into validated models that guide selection and dosing of ULT drugs for individual patients
Calibrate a lowered starting dose for allopurinol	Estimated GFR in stage 3-5 CKD	--	
Select or avoid primary uricosuric therapy	-Estimation of renal uric acid excretion -Avoidance uricosuric therapy in those with urolithiasis -Selection of uricosuric therapy if on azathioprine or 6-mercaptopurine	-*ABCG2* variants	
Initiate pegloticase therapy	-Unable to resolve palpable tophi and severe functional impairment due to gouty arthritis, despite optimal oral ULT -Adequate G6PD level	--	--

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Monitor pegloticase therapy	Discontinue therapy if serum urate becomes >6.0 mg/dL during sustained course of treatment	--	--

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Table 4. Model proposed for testing, in order to potentially better individualize serum urate (SUA) targets and improve outcomes

Gout phenotype	**Crystal deposition on advanced imaging, no arthritis or urolithiasis**	**Infrequent acute arthritis flares, no palpable tophi**	**Frequent acute arthritis flares, no palpable tophi**	**Infrequent acute arthritis flares, palpable extra-articular tophi**	**Frequent acute arthritis flares, palpable extra-articular tophi**	**Chronic tophaceous gouty arthritis**
Proposed SUA target	? <7 mg/dL	<6 mg/dL	? <5 or < 6 mg/dL	<5mg/dL	? <4 or <5mg/dL	?<4mg/dL ?<3mg/dL or lower
Goal of treatment	-Prevent first flare -Prevent joint inflammation -Prevent joint damage	-Prevent recurrent flare -Treat joint inflammation -Prevent joint damage	-Prevent recurrent flare -Treat joint inflammation -Prevent joint damage	-Prevent recurrent flare -Treat joint inflammation -Prevent/treat joint damage	-Prevent recurrent flare -Treat joint inflammation -Prevent/treat joint damage	-Prevent recurrent flare -Treat joint inflammation -Treat joint damage
Co-morbidity targets	Hypertension, CKD, coronary artery disease, urolithiasis, obesity, metabolic syndrome and type II diabetes					

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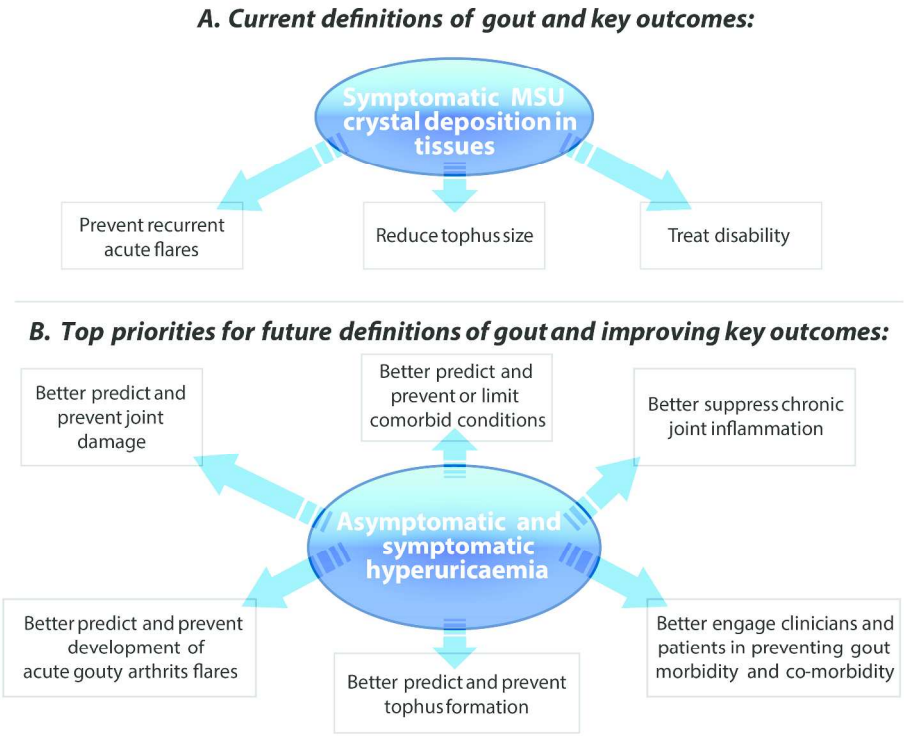

Figure 1
279x215mm (300 x 300 DPI)

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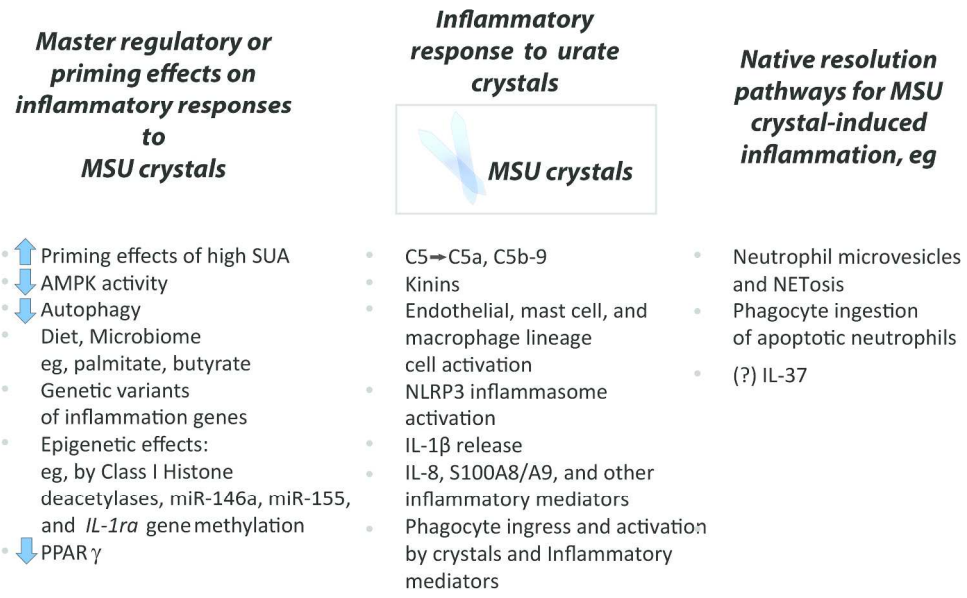

Figure 2
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