

# The Economic Value of Genetic Testing for Tolerance of Allopurinol in Gout



Gout affects around 0.08% of the population globally and is the most common cause of inflammatory arthritis in men<sup>1</sup>. Gout is associated with a considerable economic burden to healthcare systems; gout patients incur substantially greater direct healthcare costs compared to the healthy population<sup>2,3</sup>. The indirect costs to society, such as loss of productive capacity, are also high<sup>2,3</sup>. Notably, measures of disease activity including serum urate acid (SUA) levels, frequency of flares, and the presence of tophi have all been linked to higher costs<sup>2,3</sup>. Evidence demonstrates that health-related quality of life (HRQOL) is lower in the gout population when compared with the healthy population, largely attributed to the painful flares and physical disability associated with the disease<sup>2,4</sup>. The global burden of gout is rising; disability-adjusted life-years increased from 76,000 in 1990 to 114,000 in 2010<sup>1</sup>. The rising burden of gout has led to calls to improve the management of gout across healthcare systems<sup>1</sup>.

Longer-term treatment of chronic gout aims to reduce and maintain target SUA levels, which in turn reduces symptoms and the risk of patients developing painful and debilitating tophi. Urate-lowering therapy (ULT) is indicated for patients with tophi who are experiencing acute attacks and/or with radiographic changes of gout<sup>5</sup>. ULT drugs either increase the rate of the removal of uric acid by the kidneys or block the production of uric acid<sup>5,6</sup>. Allopurinol, a xanthine oxidase inhibitor, is recommended as the first-line treatment for patients with gout requiring a urate-lowering drug<sup>7</sup>. While allopurinol is a preferred treatment, there are issues with toxicity that can result in suboptimal titration, reducing the likelihood of patients receiving the most effective dose<sup>8</sup>. The HLA-B\*5801 allele is linked to an increased risk of allopurinol-induced severe cutaneous adverse drug reactions (SCAR)<sup>9</sup>. Risk factors for SCAR include ethnicity, age, sex (female), higher doses, poor renal function, and cardiovascular disease<sup>9</sup>.

In this issue of *The Journal*, Ke, *et al* present their findings on the cost-effectiveness of HLA-B\*58:01 screening

alongside allopurinol treatment versus the use of alternative urate-lowering drugs<sup>10</sup>. Screening comes with a cost to the healthcare system, not just of the test, but also healthcare practitioner time to administer the test and interpret results. Screening presents an opportunity to prevent patients from being prescribed a treatment that may result in increased healthcare costs and a lower HRQOL as a result of SCAR, and therefore inform a more effective distribution of healthcare resources. There is a need for economic evaluation to compare costs and health benefits to inform decisions about whether such interventions offer value for money overall.

The Ke, *et al* study used a decision analytical model to assess the direct healthcare costs and health benefit, represented by quality-adjusted life-years (QALY), of genetic screening followed by allopurinol for non-carriers of HLA-B\*58:01 compared to commonly used urate-lowering agents: benzbromarone without screening, febuxostat without screening, and allopurinol without screening in Taiwan. The study looked not only at patients with gout requiring ULT, but also at patients with chronic kidney disease. Applying a 1-year time frame and using a third-party cost perspective, probabilistic sensitivity analysis demonstrated that screening prior to allopurinol prescription was cost-effective in 70% of iterations if decision makers are prepared to pay threshold NT\$800,000 (US\$25,600 in 2015) to gain 1 QALY. To prevent 1 SCAR in the allopurinol-using population it was estimated that 461 patients needed to be screened for HLA-B\*58:01. The authors concluded that screening offered good value for money in this population.

A strong association has been identified between the risk of allopurinol-induced SCAR and the presence of HLA-B\*58:01 allele in the Han Chinese, Thai, Indian, and Korean populations<sup>11,12</sup>. There is a paucity of evidence in the European population although limited evidence demonstrates that HLA-B\*58:01 allele is a risk factor for allopurinol-induced SCAR in a European (Portuguese) population. However, because the prevalence of

---

See Cost-effectiveness of genotype screening, page 835

HLA-B\*58:01 is lower, the potential benefits of screening will be more limited<sup>13</sup>. The economic evidence to date seems to support this: cost-effectiveness studies of HLA-B\*58:01 screening in different populations show varied results. A Korean study determined it would be likely to be cost effective and offered value for money<sup>14</sup>. Favorable results were also identified in a Thai population, with screening identified as a potentially dominant intervention (i.e., both cheaper and more effective than the alternative)<sup>15</sup>. Mixed results were found by subgroups in a US-based population, with screening identified as being cost-effective for Asian and African American populations but not for the white or Hispanic ones<sup>16</sup>. Finally, a study focusing on the Singapore population concluded that screening was not cost-effective<sup>17</sup>. No cost-effectiveness studies were found through targeted literature searches that were published on other populations, likely due to a lack of clinical evidence.

The Ke, *et al* study<sup>10</sup> is an example of stratified medicine (also known as personalized or precision medicine). Stratified medicine refers to the use of biomarkers to stratify patient populations into subgroups who are more likely to experience a benefit, or at higher risk of experiencing an adverse reaction to a treatment<sup>18</sup>. A systematic literature review of economic evaluations of pharmacogenetic tests to reduce the incidence of adverse drug reactions found allopurinol was one of a small number of treatments with robust cost-effectiveness evidence available, albeit in a limited number of countries<sup>19</sup>. Stratified medicine is relatively new, and consequently there are still challenges with conducting economic evaluations in this area, such as identifying where in a patient pathway the pharmogenomic test best fits, the use of surrogate endpoints, and identifying robust clinical evidence for all comparators<sup>20</sup>.

Currently only the American College of Rheumatology guidelines recommend HLA-B\*58:01 screening prior to allopurinol prescription, but for a select group of patients (e.g., Koreans, Han Chinese, and Thai regardless of renal function)<sup>7</sup>. European guidelines did not recommend blanket screening because of a recognized lack of cost-effectiveness data to support screening in populations with a lower prevalence of HLA-B\*58:01. Instead they recommend that physicians use their judgment, according to patient characteristics, to decide whether screening may be beneficial<sup>21</sup>.

Future research is needed to determine whether screening is effective in a population with lower allele prevalence. It is important that studies cover a sufficient sample size to accurately estimate the burden and potential benefits in relation to adverse events that may affect only a small subgroup of the population<sup>20</sup>. Once this is available, cost-effectiveness studies can be conducted to determine whether such interventions could be cost-effective uses of healthcare resources. Cost-effectiveness evaluations will also need to be done carefully according to potential variations in screening uptakes and how testing fits into the patient pathway: these differences lead to structural uncertainty in

economic models and without detailed investigation can limit the interpretation of results in economic evaluations<sup>20</sup>. It is also important to remember that healthcare systems (e.g., costs of care and resources used) vary greatly, a condition that limits the generalizability of economic evidence between countries. When additional robust clinical and economic evidence is available, decision makers will be better able to consider whether screening offers value for money for their population. Achieving greater knowledge of efficient and cost-effective treatment options could help to reduce or slow the growing burden of gout.

#### GEMMA ELIZABETH SHIELDS, MPH

Research Fellow,  
Centre for Health Economics,  
Division of Population Health,  
Health Services Research and Primary Care,  
Faculty of Biology, Medicine and Health,  
University of Manchester,  
Oxford Road,  
Manchester M13 9PL, UK.

Address correspondence to G.E. Shields;  
E-mail: gemma.shields@manchester.ac.uk

#### REFERENCES

1. Smith E, Hoy D, Cross M, Merriman T, Vos T. The global burden of gout: estimates from the Global Burden of Disease 2010 study. *Ann Rheum Dis* 2014;73:1470-6.
2. Shields GE, Beard SM. A systematic review of the economic and humanistic burden of gout. *Pharmacoeconomics* 2015;33:1029-47.
3. Rai SK, Burns LC, De Vera MA, Haji A, Giustini D, Choi HK. The economic burden of gout: a systematic review. *Semin Arthritis Rheum* 2015;45:75-80.
4. Chandratne P, Roddy E, Clarson L, Richardson J, Hider SL, Mallen CD. Health-related quality of life in gout: a systematic review. *Rheumatology* 2013;52:2031-40.
5. Zhang W, Doherty M, Bardin T, Pascual E, Barskova V, Conaghan P, et al. EULAR evidence based recommendations for gout. Part II: Management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCSIT). *Ann Rheum Dis* 2006;65:1312-24.
6. Pacher P, Nivorozhkin A, Szabó C. Therapeutic effects of xanthine oxidase inhibitors: renaissance half a century after the discovery of allopurinol. *Pharmacol Rev* 2006;58:87-114.
7. Khanna PP, FitzGerald J. Evolution of management of gout. *Curr Opin Rheumatol* 2015;27:139-46.
8. Jennings CG, Mackenzie IS, Flynn R, Ford I, Nuki G, De Caterina R, et al. Up-titration of allopurinol in patients with gout. *Semin Arthritis Rheum* 2014;44:25-30.
9. Wang C-W, Dao R-L, Chung W-H. Immunopathogenesis and risk factors for allopurinol severe cutaneous adverse reactions. *Curr Opin Allergy Clin Immunol* 2016;16:339-45.
10. Ke CH, Chung WH, Wen YH, Huang YB, Chuang HY, Tain YL, et al. Cost-effectiveness analysis for genotyping before allopurinol treatment to prevent severe cutaneous adverse drug reactions. *J Rheumatol* 2017;44:835-43.
11. Somkruea R, Eickman EE, Saokaew S, Lohitnavy M, Chaiyakunapruk N. Association of HLA-B\*5801 allele and allopurinol-induced Stevens Johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis. *BMC Med Genet* 2011;12:118.
12. Zeng M, Zhang M, Liu F, Yan W, Kong Q, Sang H. Drug eruptions

- induced by allopurinol associated with HLA-B\*5801. *Indian J Dermatol Venereol Leprol* 2015;81:43-5.
13. Gonçalo M, Coutinho I, Teixeira V, Gameiro AR, Brites MM, Nunes R, et al. HLA-B\*58:01 is a risk factor for allopurinol-induced DRESS and Stevens-Johnson syndrome/toxic epidermal necrolysis in a Portuguese population. *Br J Dermatol* 2013;169:660-5.
  14. Park D-J, Kang J-H, Lee J-W, Lee K-E, Wen L, Kim T-J, et al. Cost-effectiveness analysis of HLA-B5801 genotyping in the treatment of gout patients with chronic renal insufficiency in Korea. *Arthritis Care Res* 2015;67:280-7.
  15. Saokaew S, Tassaneeyakul W, Maenthaisong R, Chaiyakunapruk N. Cost-effectiveness analysis of HLA-B\*5801 testing in preventing allopurinol-induced SJS/TEN in Thai population. *PLoS One* 2014;9:e94294.
  16. Jutkowitz E, Dubreuil M, Lu N, Kuntz KM, Choi HK. The cost-effectiveness of HLA-b\*5801 screening to guide initial urate-lowering therapy for gout in the United States. *Semin Arthritis Rheum* 2016 Nov 1 (E-pub ahead of print).
  17. Dong D, Tan-Koi W-C, Teng GG, Finkelstein E, Sung C. Cost-effectiveness analysis of genotyping for HLA-B\*5801 and an enhanced safety program in gout patients starting allopurinol in Singapore. *Pharmacogenomics* 2015;16:1781-93.
  18. Trusheim MR, Berndt ER, Douglas FL. Stratified medicine: strategic and economic implications of combining drugs and clinical biomarkers. *Nat Rev Drug Discov* 2007;6:287-93.
  19. Plumpton CO, Roberts D, Pirmohamed M, Hughes DA. A systematic review of economic evaluations of pharmacogenetic testing for prevention of adverse drug reactions. *Pharmacoeconomics* 2016;34:771-93.
  20. Shabaruddin FH, Fleeman ND, Payne K. Economic evaluations of personalized medicine: existing challenges and current developments. *Pharmgenomics Pers Med* 2015;8:115-26.
  21. Richette P, Doherty M, Pascual E, Barskova V, Becce F, Castañeda-Sanabria J, et al. 2016 updated EULAR evidence-based recommendations for the management of gout. *Ann Rheum Dis* 2017;76:29-42.
- J Rheumatol* 2017;44:717-19; doi:10.3899/jrheum.170200