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Measuring High-Risk Patients' Preferences for Pharmacogenetic Testing to Reduce Severe Adverse Drug Reaction: A Discrete Choice Experiment

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ABSTRACT

Objectives: To investigate patient preferences and willingness to pay (WTP) for a genetic test that can reduce the risk of life-threatening adverse drug reactions (ADRs). We hypothesize that test features (risk of developing the adverse reaction with and without testing, test cost, and treatment cost) and the choice context (physician recommendation and the most common choice made by peer patients) will influence choices. **Methods:** A discrete choice experiment was conducted in which 189 patients at high risk for gout were asked to choose between treatment options that varied along key attributes. A latent class logit model was used to analyze the choice data and test the hypotheses. **Results:** We identified two classes of patients: the risk-averse class and the cost-conscious class. The WTP to reduce the risk of life-threatening ADRs from 1 out of 600 to 1 out of 1 million was SGD1215 in the risk-averse class. In contrast, in the cost-conscious class, the WTP was insensitive to the extent of risk reduction. Overall, the predicted take-up rate for the test is 65% at a price of SGD400. If the test was recommended by a physician or was chosen by most of the patients, the take-up rate for the test would increase by 8.5 and 1.5 percentage points, respectively. **Conclusions:** There is a potentially large demand for genetic tests that could reduce the risk of life-threatening ADRs. Physician recommendations and providing information on the choices of others are powerful influences on demand, even more so than moderate price reductions.

Keywords: discrete choice experiment, patients' preferences, pharmacogenetics, willingness to pay.

Introduction

Serious adverse drug reactions (ADRs) associated with some commonly used drugs have long been a medical and public health concern. The risk of severe ADRs results not only in increased morbidity, mortality, and health care costs but also in the withdrawal or decreased use of some potentially effective medications [1]. With the discovery of genetic risk factors underlying ADRs, pharmacogenetic testing and test-guided treatment is a promising strategy to reduce the risk of ADRs.

Allopurinol is the first-line and the most commonly used urate-lowering therapy drug for the management of chronic gout [2]. Gout is a common form of inflammatory arthritis affecting around 4% of the population in the United States and Singapore, with its prevalence among men at least three times that of women [3]. Despite allopurinol's effectiveness and low cost, it may induce life-threatening skin conditions such as the Stevens-Johnson syndrome (SJS) [4–8], which is characterized by the detachment of the epidermis from the dermis. The incidence of allopurinol-induced SJS is 0.2% among Han Chinese patients initiating allopurinol [9]. The fatality rate of SJS and related conditions ranges between 5% and 30% [10,11].

An association between the genetic risk factor HLA-B*5801 allele and allopurinol-induced SJS has been established in various populations [9,12–16]. With HLA-B*5801 testing results, clinicians can avoid allopurinol in at-risk patients. There is no consensus, however, on the appropriate use of the HLA-B*5801 testing. The clinical guideline by the American College of Rheumatology recommends HLA-B*5801 genotyping for at-risk populations [2], whereas the European Medicines Agency cautions against routine HLA-B*5801 testing because of unproven clinical utility [17].

The HLA-B*5801 risk allele is more prevalent among Han Chinese, Southeast Asian, and Korean populations than among whites. In Singapore, the prevalence of HLA-B*5801 carriers is 22.3%, 7.3%, and 3.5% among Chinese, Malays, and Indians, respectively [18]. In Han Chinese in Taiwan, the HLA-B*5801

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genetic test has a negative predictive value close to 100% but a positive predictive value of only 1.52% for SJS [9], which implies that a negative test result almost guarantees no SJS; nevertheless, 98.48% of individuals with a positive test result would not develop SJS even if receiving allopurinol. Moreover, other than allopurinol, there are limited choices of alternative drugs for chronic gout treatment [2,19] and these are significantly more expensive than allopurinol. The lack of consensus results because it is unclear whether the risk reduction due to HLA-B*5801 genetic testing outweighs the additional long-term treatment cost and potential negative impact on gout outcomes arising from avoiding the use of allopurinol. Taking all these factors into account, a cost-effectiveness analysis of HLA-B*5801 genetic testing over a 30-year period suggested that routine testing is at present not cost-effective for the Singapore population on the basis of established thresholds for cost-effectiveness [18,20]. Specifically, if HLA-B*5801 testing was used to avoid allopurinol among test-positive patients, the strategy increased the cost by $1030 USD, but resulted in lower quality-adjusted life-years (QALYs) compared with the standard allopurinol treatment; if, however, allopurinol was used as the second-line drug after the failure of alternative drugs among patients with HLA-B*5801, the test-guided treatment strategy increased the QALYs by 0.0054 at the incremental cost of $457, resulting in an incremental cost-effectiveness ratio of $84,629/QALY compared with the standard allopurinol treatment.

At present, the HLA-B*5801 test is not available in Singapore. After the HLA-B*1502 genetic testing for carbamazepine became the standard of care in Singapore, the fear for life-threatening SJS and the increased awareness of pharmacogenetic testing among physicians and patients call for the provision of HLA-B*5801 testing services. In the clinician community, there is also need for guidance on the appropriate use of HLA-B*5801 genetic testing in gout management and for patient communication strategies on pharmacogenetic information.

To inform testing policy and clinician's decision making, we estimate the demand for HLA-B*5801 testing and quantify how different factors influence patients' uptake. Cost-effectiveness evidence suggests that HLA-B*5801 testing is not cost-effective from a health system perspective; many patients, however, might opt to take the test for risk reduction if it were available, even at a significant cost to them. To test this hypothesis, we quantify the take-up rate of candidate genetic tests that vary along various dimensions including the risk of developing SJS, the cost of genetic test, and the cost of gout treatment. We hypothesize that patients are more likely to test with lower risk of developing SJS after testing, lower cost of genetic test, and lower long-term gout treatment cost. We further hypothesize that there is heterogeneity in patients' preferences. Some patients may consider the risk of SJS as the most important factor in decision making, whereas others may care more about cost. Moreover, medical decisions are not made in isolation. Patients often seek advice from physicians, family members, and peers, especially for services that are new or unfamiliar. Physician recommendations have been shown to influence the use of preventive services and treatments [21–27]. In addition, several studies demonstrate that many patients "follow the herd" in the sense that they prefer to opt for the popular choice [23,28–32]. Therefore, we further hypothesize that providing the information that an alternative is recommended by a physician or is the most common choice leads to a higher take-up rate for this alternative. To explore the relative strength and interaction of the two types of information, we hypothesize that information on a physician's recommendation has a stronger impact than information on the most common choice. We test these hypotheses using a discrete choice experiment (DCE), a method to elicit stated preferences that is commonly used to assess the value of new medical technologies [33, 34]. The results will inform policymakers and clinicians on patients' preferences, so that services could be provided in alignment with patients' preferences, and information related to HLA-B*5801 could be effectively communicated.

Methods

Survey Development

A DCE survey was developed following the procedures recommended by the International Society for Pharmacoeconomics and Outcomes Research Good Research Practices for Conjoint Analysis Task Force [35,36]. The survey included a general introduction to SJS and genetic testing, an introduction to DCE attributes and levels, nine DCE choice tasks, and a background section with questions on demographic characteristics, medical history related to gout and ADRs, and socioeconomic factors. Because SJS is a technical medical term, we simply referred to it as "the severe side effect" in the choice tasks, and described the symptoms of SJS with a photo before the choice tasks.

Attributes influencing patients' genetic testing decisions were selected on the basis of a literature review and in-depth interviews with 10 patients. Attributes included genetic test features (risk of developing the severe side effect SJS with and without a genetic test, cost of genetic test, cost of test-guided long-term gout treatment) and other information (whether a treatment option is physician-recommended or the most common choice).

In determining attribute levels, realistic levels and policy-relevant levels were included. For numerical variables, more extreme levels were also included to identify the level of an attribute at which a respondent would switch choices. Attribute levels and framing were systematically tested and fine-tuned using cognitive interviews with 50 patients, during which respondents were encouraged to "think aloud" and explain their decision-making process and rationale to interviewers [37]. The final sets of attributes and levels are presented in Table 1. The risk of developing the severe side effect was "1 out of 500 patients" without test, and ranged from "1 out of 1 million patients" to "1 out of 600 patients" for test-guided treatments. The cost of genetic test ranged from SGD20 to SGD1000. The cost of long-term gout treatment (over 2 years) is a complex attribute with a probability component, because the appropriate treatment a patient needs depends on test results. We displayed the probability of testing positive and the treatment costs associated with positive or negative test results. The cost of gout treatment over 2 years was SGD200 if tested negative (8 in 10 chance), and ranged from SGD250 to SGD4000 if tested positive (2 in 10 chance). To reduce hypothetical bias, a budget reminder was included when introducing the cost attributes, which encouraged respondents to think carefully on how the specified monetary value would influence their daily consumption [38]. Verbal recommendation by a physician is more salient than receiving it in writing. Although we could not replicate a verbal recommendation in the survey, we increased saliency by including a graphical display with the physician's recommendation written in a flag-shaped banner (Fig. 1). A treatment option was assigned one of the following three levels: "the physician-recommended" (with the recommendation banner), "not the physician-recommended" (without the recommendation banner), or "no information on physician recommendation" (with written information that no information is available).

To explore how the most common choice influences patients' decisions, we displayed the most common choice (herd effect) graphically using a check mark (Fig. 1). A treatment option was labeled "the most common choice" (with a check mark), "not the most common choice" (no check mark), or "no information on the