Global Frequencies of Clinically Important HLA Alleles and Their Implications For the Cost-Effectiveness of Preemptive Pharmacogenetic Testing

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Immune-mediated drug hypersensitivity reactions are an important source of iatrogenic morbidity and mortality. Human leukocyte antigen (HLA)-B*57:01, HLA-B*15:02, HLA-A*31:01, and HLA-B*58:01 constitute established risk factors and preemptive genotyping of these HLA alleles in patients prior to the initiation of abacavir, carbamazepine, and allopurinol-based therapies can prevent toxicity and improve patient outcomes. However, the cost-effectiveness of preemptive HLA testing has only been evaluated in the United States and few countries in Europe and Asia. In this study, we consolidated HLA genotypes from 3.5–6.4 million individuals across up to 74 countries and modeled the country-specific cost-effectiveness of genetic testing. We find major ethnogeographic differences in risk allele prevalence, which translated into pronounced differences in the number of patients needed to test to prevent one case of severe hypersensitivity reactions between countries and populations. At incremental cost-effectiveness ratio thresholds of $40,000, testing of HLA-B*57:01 in patients initiating abacavir was cost-effective in the majority of countries with potential exceptions of East Asia, Saudi Arabia, Ghana, and Zimbabwe. For carbamazepine, preemptive genotyping of HLA-B*15:02 is only cost-effective across most of East and South Asia, whereas HLA-A*31:01 testing is likely to be cost-effective globally. Testing of HLA-B*58:01 is more likely to be cost-effective throughout Africa and Asia compared with Europe and the Americas. We anticipate that this data set can serve as an important resource for clinicians and health economists to guide clinical decision making and inform public healthcare strategies.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑️ Specific human leukocyte antigen (HLA) alleles are well-established biomarkers for abacavir, carbamazepine, and allopurinol hypersensitivity. However, the cost-effectiveness of genotype-guided prescribing of these medications has only been evaluated in the United States and few countries across Europe and South East Asia.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑️ We consolidated genotype data from 6.4 million individuals to map the global distribution of HLA-B*57:01, HLA-B*15:02, HLA-A*31:01, and HLA-B*58:01, and provide country-specific and population-specific cost-effectiveness estimates for preemptive HLA testing to guide prescribing of abacavir, carbamazepine, and allopurinol.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑️ Our analyses quantify the global extent of HLA hypersensitivity allele prevalence on an unprecedented scale and reveal unexpectedly large ethnogeographic differences. We provide global estimates for the cost-effectiveness of preemptive HLA genotyping across 74 countries, the vast majority of which had previously not been evaluated.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
☑️ These data provide an important resource to increase access to the socioeconomic benefits of genotype-informed decision making and facilitate the implementation of precision public health, particularly in previously understudied countries and ethnicities.

Adverse drug reactions (ADRs) are of major concern in pharmacological therapy. Around 80% of ADRs are caused by an unintended magnitude of on-target effects, as a consequence of the pharmacological action of the drug in question, whereas the remaining 20% of ADRs are due to idiosyncratic off-target interactions.1,2 Idiosyncratic ADRs most commonly affect skin, liver,

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and blood, either in isolation or in combination with systemic effects, and are often life-threatening. The majority of idiosyncratic ADRs is immunologically mediated and can be distinguished into B-cell-dependent antibody-mediated reactions and hypersensitivity reactions mediated by T-cells, of which particularly the latter is an important cause of drug-induced morbidity and mortality.

In the past decades, genetic variability in human leukocyte antigen (HLA) genes encoding the major histocompatibility complex has been identified as the major risk factor for multiple immune-mediated ADRs. The clinically most established example is the association between the HLA-B*57:01 allele and abacavir hypersensitivity syndrome (AHS). Preemptive testing of HLA-B*57:01 followed by abacavir initiation only in HLA-B*57:01 negative individuals and treatment of allele carriers with alternative antiretrovirals eliminated all incidences of immunologically confirmed AHS (100% negative predictive value) with a positive predictive value of 47.9%. Consequently, relevant expert groups, such as the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Infectious Diseases Society of America (IDSA) concordantly advocate for preemptive HLA-B*57:01 genotyping to guide abacavir prescribing, and both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have included boxed warnings in the respective labels recommending upfront HLA-B*57:01 screening whereby individuals testing positive for HLA-B*57:01 should not be prescribed abacavir.

In addition to the association between HLA-B*57:01 and AHS, the clinical utility and cost-effectiveness of HLA-B*15:02, HLA-A*31:01, and HLA-B*58:01 testing to predict carbamazepine-induced Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) as well as allopurinol-induced severe cutaneous adverse reactions (SCARs) have been evaluated in the United States, as well as few countries in Europe and Asia. However, implementation of these tests into routine clinical practice is lagging behind.

Importantly, whether to recommend preemptive genetic testing into public health programs critically relies on the prevalence and predictive power of a biomarker in the country or population in question, genotyping costs, the severity, and costs of ADR treatment, as well as safety, cost, and efficacy of substitute therapies. However, although a multitude of studies have provided important information about the frequencies of clinically important HLA alleles in different populations, most studies had a narrow geographic focus and analyzed only one or few selected variants of interest. Furthermore, cost-effectiveness studies for preemptive HLA testing are only available for the United States and few selected countries in Europe and Asia.

Thus, to facilitate informed decision making about the implementation of preemptive HLA testing in previously understudied countries, we consolidated frequency data of 3.5–6.4 million individuals across 74 countries, resulting in global prevalence maps of HLA risk alleles predisposing to severe abacavir, allopurinol, and carbamazepine-related ADRs. Based on these ethnogeographic prevalence data, we calculated the country-specific and population-specific numbers of individuals needed to test (NNT) to prevent one severe ADR, as well as the number of patients who would be unnecessarily denied the drug (NUD). Finally, we developed a global cost-effectiveness model in which we integrate this information with established predictive metrics of the biomarkers in question to estimate country-specific cost-effectiveness thresholds for preemptive genetic testing for abacavir, allopurinol, and carbamazepine. Together, these data provide an important resource for health economists and clinicians and are expected to facilitate the guidance of global precision public health programs.

METHODS

HLA frequency and allele carrier data

Allele frequencies of HLA-B*57:01, HLA-B*15:02, HLA-A*31:01, and HLA-B*58:01 were calculated by consolidating genotype information from 6,488,913 individuals provided by the Allele Frequency Net Database and the Estonian Biobank. The inclusion of country-specific and allele-specific data depended on whether data at the level of HLA protein (i.e., four-digit code) was available and passed quality control. Depending on the data source, subpopulation information was either self-reported or defined based on genetic markers. The number of allele carriers \( F \) for a given country or population was calculated according to the Hardy–Weinberg equation as \( F = 2p^2 - p \) in which \( F \) represents the carrier frequency and \( p \) corresponds to the frequency of the variant allele. National population data was obtained from World Population Prospects 2017, United Nations. In case of countries with heterogeneous population structures, we aggregated subpopulation-specific frequency information based on the national population composition. For countries with no available information on allele frequency, we used the averaged continental allele frequency to calculate the number of carriers per continent.

Calculation of genetic test metrics

The positive predictive value (PPV) and false discovery rate (FDR) of a test was calculated from the number of true positive (TP) and false positive (FP) predictions as $PPV = TP/TP+FP$ and $FDR = FP/TP+FP$. The number of patients needed to test to prevent one case of drug hypersensitivity (NNT) was calculated for every drug and country $c$ as $\text{NNT}_{c} = 1/F_c + PPV$. Correspondingly, the number of patients who would be unnecessarily denied drug $d$ in country $c$ (NUD) per 1,000 genotyped patients is given by $\text{NUD}_{c} = 1,000 	imes F_c 	imes FDR$.

Estimation of incremental cost thresholds for country-specific cost-effectiveness assessments

We compared the cost of two treatment strategies: (i) no genetic test and initiation of treatment with regimen containing an HLA allele associated drug; and (ii) testing for HLA risk alleles and referral of risk allele carriers to an alternative treatment regimen, not containing the risk allele associated drug. In the first strategy, costs are calculated as $\text{COST}_{\text{ALT}} = c_{\text{REF}} + c_{\text{ADR}}$ with $c_{\text{REF}}$ as treatment costs of first line therapy, $c_{\text{ADR}}$ as the average costs caused by the respective ADR (see Table S2), and $f_{\text{ADR}}$ as the incidence of ADRs among patients who initiate a first-line treatment that is associated with an HLA risk allele (Table S3). For the second strategy, costs are calculated as $\text{COST}_{\text{ALT}} = c_{\text{TEST}} + c_{\text{ALT}} + c_{\text{REF}} 	imes (1-F_c)$ with $c_{\text{TEST}}$ as the cost of the genetic test per patient, $c_{\text{ALT}}$ as treatment costs of the alternative therapy among the carriers of a risk allele, $F_c$ as carrier frequency, and $c_{\text{REF}}$ as costs of first-line therapy in risk allele negative ($1-F_c$) patients. For test costs, we assumed $200 based on literature values (Table S4). Based on these equations, the incremental cost of preemptive genotyping is given as $\Delta \text{COST} = \text{COST}_{\text{ALT}} - \text{COST}_{\text{REF}} = F_c \times (T_{\text{ALT}} - T_{\text{REF}}) + c_{\text{TEST}} - c_{\text{REF}}/\text{NNT}$ where NNT is defined as $1/F_c$. To evaluate the cost-effectiveness of preemptive genotyping, we compared the incremental cost-effectiveness ratio of genotyping defined as $\text{ICER} = \Delta \text{COST}/\Delta \text{EFFECT} (F_c)$ against the “willingness-to-pay” threshold (ICER$_{\text{wtp}}$), which varied between $10,000.
and $100,000.10 ΔEFFECT was expressed as a function of $F_c$ and using incremental quality adjusted life years (ΔQALY) as units. To estimate ΔEFFECT ($F_c$), we established linear models for each drug and biomarker based on associations from the available literature (Table S5). The resulting incremental cost threshold for cost-effectiveness (ICT$_{c|s}$), defined as the total cost by which the alternative treatment can exceed the cost of the first-line treatment for the genotype-guided strategy to be cost-effective, is given by ICT$_{c|s} = ((ICER_s * ΔEFFECT ($F_c$)) + (ADR/NNT – TEST)) / $F_c$. Preemptive genotyping was estimated to be cost-effective if the incremental country-specific cost of switching treatment was smaller than ICT$_{c|s}$. Preemptive genotyping was furthermore assumed to be the dominant strategy (i.e., to improve patient outcomes and reduce societal costs), if the incremental country-specific cost of switching, assuming an ICER of 0, was below ICT$_{c|s} = ((ADR/NNT – TEST)) / $F_c$.

RESULTS
Establishing a global cost-effectiveness model for assessing preemptive genotyping of HLA risk alleles
Conventionally, cost-effectiveness analysis (CEA) was established on the basis of socioeconomic metrics provided by national health care systems and with the inclusion of detailed treatment strategies regulated by local policies. Thus, comparing the outcomes and recommendations of CEs across countries can be problematic given the multitude of differences in underlying parameters. In order to increase global comparability, we aimed to establish a globally uniform cost-effectiveness model that could, however, provide country-specific recommendations. As treatment strategies and medication costs can differ drastically between countries, we thus developed a model that could provide the threshold cost by which the alternative treatment regimen that would be prescribed for risk allele-positive patients could exceed the cost of first-line treatment for preemptive HLA genotyping and genotype-informed prescribing to be cost-effective. To this end, the model considered these thresholds (ICT$_{c|s}$) as a function of country-specific HLA allele frequency, predictive values for risk allele associated ADRs, ADR-associated treatment costs, “willingness-to-pay” thresholds, increase in ΔQALY upon genetic testing, and the costs for these tests. Country and population-specific HLA allele frequencies were calculated based on genotypes from 3.5–6.4 million individuals across up to 74 countries. PPVs (Table S1), ADR-specific treatment costs (Table S2), as well as the costs of genetic testing were obtained from the literature (Table S4). These parameters were each found to vary less than fourfold between countries and we, thus, assumed them to be country-invariant. By contrast, ΔQALY differed > 10-fold among countries and subpopulations (Table S5). To accommodate for these differences we considered ΔQALY to be a function of risk allele carrier frequency (i.e., ΔQALY($F_c$)), in important contrast to previous studies.11–16 This relationship is intuitive, as gains in QALYs due to preemptive genotyping should be very low in countries with only very few risk allele carriers, whereas potential benefits should increase with higher numbers of individuals who can benefit from genotype-guided prescribing. We confirmed this hypothesis using available country-specific QALY and carrier frequency data from the literature (Table S5). For abacavir (HLA-B*57:01) and allopurinol (HLA-B*58:01), for which data was available from four and six studies, respectively, we found that ΔQALY correlated linearly with carrier frequency ($F_c$) with Pearson correlation coefficients $r$ of 0.97 and 0.54, respectively, thus strongly supporting the implementation of ΔQALY as a linear function of $F_c$.

Screening of HLA-B*57:01 to guide antiretroviral therapy
Abacavir is a nucleoside analogue reverse transcriptase inhibitor that is used as part of combination antiretroviral therapy for the treatment of HIV infections. Although generally well-tolerated, seminal studies revealed that 2–8% of patients experienced AHS that mandated abacavir discontinuation.17,18 Importantly, AHS shows a highly specific association with the HLA-B*57:01 allele that has been validated in individuals of white and African ancestry.19–21

Analysis of HLA genotype data of 3,586,065 individuals from 56 countries revealed drastic ethnogeographic differences (Figure 1, Table 1). Globally, the highest prevalence of HLA-B*57:01 was identified in Sri Lanka (9.3%), India (6.2%), and the Indian diaspora in South Africa (10.2%). Furthermore, frequencies were high in Western Europe, ranging from 2% in Belgium to 5.8% in Ireland, whereas its prevalence was lower in Scandinavia (1% in Sweden and 1.7% in Finland) and the Eastern Mediterranean coast (1.5% in Turkey and 1.6% in Greece). Allele frequencies were < 0.3% in South Korea, Japan, and Saudi Arabia and HLA-B*57:01 was not detected in Mali and South African Zulus. In the United States, the overall frequency was 2.8% with prevalence in individuals of white (3.6%) and Asian (3.2%) ancestry exceeding the national average, whereas frequencies were lower in Native Americans (0.7%), African Americans (0.9%), and Hispanics (1.4%). Aggregation of national data by major geographic regions reveals that most of the global HLA-B*57:01 carriers are found in South Asia and Europe with an estimated 227.4 million and 44.4 million allele carriers corresponding to 9.3% and 6% carrier frequency, respectively. In contrast, carrier rate was considerably lower in East Asia (1% carrier rate) with a total of 16.2 million allele carriers.

By integrating allele frequency data with established predictive values of HLA-B*57:01 genotyping, we calculated the country-specific NNTs to prevent one case of immunologically confirmed AHS (Table 1). In Sri Lanka and India, only 12 and 18 individuals need to be genotyped to prevent one case of AHS, whereas 461 and 1,351 patients need to be tested in South Korea and Japan, respectively. We furthermore calculated the number of patients who would be unnecessarily referred to an alternative highly active antiretroviral therapy (HAART) regimen based on a positive genotyping result but who would not have developed AHS. In Sri Lanka, this NUD was 92 per 1,000 genotyped patients whereas < 3 per 1,000 genotyped patients would be unnecessarily denied abacavir-based therapy in Japan and South Korea.

To evaluate the cost-effectiveness of preemptive HLA-B*57:01 genotyping, costs and benefits are expressed as the incremental cost per unit of health gain of this intervention. Based on robust clinical trial data we considered abacavir-containing treatment regimens as therapeutically equivalent to regimens without abacavir.22–25 The ICER was then compared with “willingness-to-pay” thresholds determined by national healthcare bodies.25 Specifically, we compared the cost-effectiveness of prescribing abacavir-containing regimens without genetic tests with the preemptive genotyping for HLA-B*57:01 to inform antiretroviral therapy (abacavir-containing regimens for
**HLA-B*57:01 negative individuals and alternative HAART for HLA-B*57:01 allele carriers** across a common range of ICER thresholds from $10,000 to $100,000 (see Method section for details). Incremental cost thresholds for HLA-B*57:01 genotyping were positive across South Asia, Europe, and the Americas. Using the United States as an example, these values indicate that preemptive genotyping is cost-effective until the increase in cost of the alternative HAART per patient exceeds $2,419.80 for a “willingness-to-pay” threshold of $40,000 ($979.80–$5,299.80 for $10,000 to $100,000, respectively). Furthermore, preemptive genotyping constitutes the dominant strategy in the United States if the increase in treatment costs of the alternative HAART is < $499.80. Monthly costs for first-line abacavir-based therapy (abacavir, lamivudine, and efavirenz) in the United States were $1,135, whereas costs of the alternative tenofovir, emtricitabine, and efavirenz treatment regimen were only slightly higher at $1,139 (Table S6). Based on the average life expectancy of patients initiating abacavir treatment, the incremental cost of switching from abacavir-based regimens to non-abacavir containing regimens is $1,485 and, thus, well below the ICTCE of $2,419.80, which corroborates the cost-effectiveness of HLA-B*57:01 testing prior to the initiation of abacavir therapy in the United States.

In contrast, incremental cost thresholds are negative in East Asia and several countries in Africa and West Asia, including Mali, Ghana, Saudi Arabia, China, Japan, and South Korea, which suggest that the cost of the alternative HAART would have to be cheaper than abacavir-based therapy for preemptive genotyping in these countries to be cost-effective. These effects are primarily attributed to the low frequency of HLA-B*57:01 in these populations and the corresponding substantial increase in patients who need to be genotyped to prevent one ADR. As such, these countries could benefit most from reduced genotyping costs.

**HLA-B*15:02 and HLA-A*31:01 as markers for carbamazepine-induced SCARs**

Carbamazepine is an anticonvulsant associated with SCARs, including drug rash with eosinophilia and systemic symptoms, maculopapular eruptions, SJS, and TEN, specifically in carriers of the HLA-B*15:02 and HLA-A*31:01 alleles. Based on data of 3,540,660 individuals, we find that HLA-B*15:02 is common throughout South and East Asian populations with the exception of Japan (< 0.1%), ranging from 22% in the Philippines to 1.5% in South Korea (Figure 2, Table 2). Moreover, HLA-B*15:02 is prevalent in Asian communities in the United States (4.1%) and South Africa (3.1%), as well as in the Roma minority in Spain (1%), which originates from North-West India. In contrast, HLA-B*15:02 is rare (< 1%) in all analyzed non-Asian populations.

**Figure 1.** Global distribution of the abacavir hypersensitivity risk allele human leukocyte antigen (HLA)-B*57:01. Carrier and frequency analyses were based on 3,586,065 individuals across 56 countries. Allele frequencies are color-coded with the highest frequency in red, the average frequency across all countries (\(f\)) in yellow, and the lowest frequency in blue. Countries for which no HLA-B*57:01 frequency information was available are colored white. Subpopulation-specific frequencies are indicated where available. The text boxes provide the total number of allele carriers and allele carrier frequency of the respective continent. Continent and subcontinent were defined according to the United Nations World Population Prospects (see ref. 9 and Table 1).
Table 1 Socioeconomic metrics of HLA-B*57:01 testing for country-specific cost-effectiveness analyses

| Risk allele | HLA-B*57:01 |
|-------------|-------------|
| Associated ADR | Abacavir hypersensitivity syndrome |
| PPV, % | 47.9 |
| NPV, % | 100 |
| ΔEFFECT (F<sub>c</sub>) | 0.048 * F<sub>c</sub> |

| Countries | MAF, % | Allele carriers (in thousands) | NNT | NUD per 1,000 patients | ICT<sub>CE</sub>, $ | ICT<sub>D</sub>, $ |
|-----------|--------|-------------------------------|-----|------------------------|-----------------|-----------------|
| Africa    |        |                               |     |                        |                 |                 |
| Cameroon  | < 1.3  | < 601.8                       | > 79.2 | < 13.7                | < 1,622.2 [182.2, 4,502.2] | < -297.8       |
| Ghana     | 0.4    | 210.3                         | 273.8 | 4                     | -2,105.6 [-3,545.6, 774.4] | -4,025.6       |
| Kenya     | 0.7    | 648.7                         | 152   | 7.2                   | 227.5 [-1,212.5, 3,107.5] | -1,692.5       |
| Mali      | 0      | 0                             | N/A   | 0                     | Not cost-effective |                 |
| Sudan     | 1.5    | 1,150.7                       | 70.1  | 15.5                  | 1,796.6 [356.6, 4,676.6] | -123.4         |
| Tunisia   | 3      | 666.3                         | 35.3  | 30.8                  | 2,463.2 [1,023.2, 5,343.2] | 543.2          |
| Uganda    | 3.1    | 2,450.4                       | 34.2  | 31.8                  | 2,484.7 [1,044.7, 5,364.7] | 564.7          |
| Zambia    | 1.1    | 352.3                         | 95.4  | 11.4                  | 1,311.8 [-128.2, 4,191.8] | -608.2         |
| Zimbabwe  | 0.4    | 126                           | 261.5 | 4.2                   | -1,870 [-3,310, 1,010] | -3,790         |
| East Asia |        |                               |     |                        |                 |                 |
| China     | 0.6    | 15,622.6                      | 186.7 | 5.8                   | -436.9 [-1,876.9, 2,443.1] | -2,356.9       |
| Japan     | < 0.1  | 197.7                         | 1,351.1 | 0.8                  | -22,746.6 [-24,186.6, -19,866.6] | -24,666.6     |
| South Korea | 0.2   | 229.3                         | 460.7 | 2.4                   | -5,686.6 [-7,126.6, -2,806.6] | -7,606.6       |
| South Asia |        |                               |     |                        |                 |                 |
| India     | 6.2    | 156,207.7                     | 17.5  | 62.2                  | 2,804.8 [1,364.8, 5,684.8] | 884.8          |
| Malaysia  | 1.1    | 646.1                         | 99.3  | 11                    | 1,238.1 [-201.9, 4,118.1] | -681.9         |
| Singapore | 1      | 109.2                         | 105.8 | 10.3                  | 1,112.9 [-327.1, 3,992.9] | -807.1         |
| Sri Lanka | 9.3    | 3,673.7                       | 11.8  | 92.4                  | 2,914.5 [1,474.5, 5,794.5] | 994.5          |
| Thailand | 2.1    | 2,898.4                       | 49.5  | 22                    | 2,192.5 [752.5, 5,072.5] | 272.5          |
| Vietnam  | 2.6    | 4,804.6                       | 40.7  | 26.8                  | 2,361 [921, 5,241] | 441            |
| West Asia |        |                               |     |                        |                 |                 |
| Armenia  | 1.5    | 86.9                          | 70.1  | 15.5                  | 1,796.6 [356.6, 4,676.6] | -123.4         |
| Georgia  | 0.9    | 70.8                          | 116.5 | 9.3                   | 907.7 [-532.3, 3,787.7] | -1,012.3       |
| Iran     | 1.5    | 2,347.2                       | 70.6  | 15.4                  | 1,787.6 [347.6, 4,667.6] | -132.4         |
| Israel   | 2.4    | 389.2                         | 43.3  | 25.1                  | 2,311.1 [871.1, 5,191.1] | 391.1          |
| Jordan   | 1      | 182.3                         | 104.9 | 10.4                  | 1,130 [-310, 4,010] | -790           |
| Oman     | 1.3    | 108.5                         | 80.8  | 13.5                  | 1,591.5 [151.5, 4,471.5] | -328.5         |
| Saudi Arabia | 0.2 | 126.1                         | 522.4 | 2.1                   | -6,870 [-8,310, -3,990] | -8,790         |
| Turkey   | 1.5    | 2,330.5                       | 70.1  | 15.5                  | 1,796.6 [356.6, 4,676.6] | -123.4         |
| Europe   |        |                               |     |                        |                 |                 |
| Austria  | 3.7    | 629.4                         | 28.8  | 37.8                  | 2,588.5 [1,148.5, 5,468.5] | 668.5          |
| Belgium  | 2      | 447                           | 52.7  | 20.6                  | 2,129.9 [689.9, 5,009.9] | 209.9          |
| Bosnia and Herzegovina | 3.3 | 229.5                         | 32.2  | 33.8                  | 2,523.8 [1,083.8, 5,403.8] | 603.8          |
| Bulgaria | 4.5    | 631.4                         | 23.7  | 45.8                  | 2,685.3 [1,245.3, 5,565.3] | 765.3          |
| Czech Republic | 3.2 | 668.2                         | 33.1  | 32.8                  | 2,505.2 [1,065.2, 5,385.2] | 585.2          |
| Estonia  | 2.7    | 70.5                          | 38.9  | 27.9                  | 2,393.9 [953.9, 5,273.9] | 473.9          |
| Finland  | 1.7    | 184.8                         | 61.9  | 17.6                  | 1,953.5 [513.5, 4,833.5] | 33.5           |
| France   | 3.2    | 4,090.9                       | 32.9  | 33.1                  | 2,509.8 [1,069.8, 5,389.8] | 589.8          |

(Continued)
Based on these data, we estimate a total of 483.3 million HLA-B*15:02 carriers in South and East Asia corresponding to 1 in 8 individuals. In contrast, only 3 million non-Asian carriers are expected globally.

Less than 130 patients need to be genotyped for HLA-B*15:02 to prevent one case of SJS/TEN in the Philippines, Malaysia, Indonesia, Singapore, and China, whereas > 9,000 individuals need to be tested to prevent one case in Europe (Table 2). The NUD for carbamazepine based on HLA-B*15:02 screening exceeds 100 per 1,000 tested patients in most countries in South Asia, with the exception of India and Sri Lanka where only 40–47 patients would be unnecessarily referred to an alternative anticonvulsant. Similarly, NUDs are very high in China (133 per 1,000 tested patients) but substantially lower in Mongolia (28 per 1,000 tested patients), South Korea (27 per 1,000 tested patients), and Japan (1 per 1,000 tested patients). Accordingly, preemptive genotyping of HLA-B*15:02 in patients initiating carbamazepine is likely to be cost-effective across Southern Asia, whereas it is unlikely to be cost-effective in other populations at test costs of $40 per patient. Additionally, preemptive genotyping of HLA-B*15:02 could become a dominant strategy in China and most countries in Southern Asia if their incremental treatment costs are below the thresholds indicated in Table 2 (ICTD).

In contrast to the Asian-specific HLA-B*15:02 allele, HLA-A*31:01 is prevalent globally. Based on genotype information from 3,578,482 individuals, this allele is most frequent in indigenous populations of the Americas, particularly in Argentina (28.8%), Mexico (10.1%), the United States (7.8%), Nicaragua (6.7%), and Chile (6.6%; Figure 3, Table 2, and Table S7). Further allele hotspots are Japan (5.6%) and China (4.1%). Populations in which HLA-A*31:01 is rare include Ghana (0.4%), Peru (0.5%), and Maori in New Zealand (0.5%). Across Europe allele frequencies range between < 1% in Albania and 5.9% in Sweden. Only limited information was

### Table 1 (Continued)

| Countries | MAF, % | Allele carriers (in thousands) | NNT | NUD per 1,000 patients | ICTCE, $a | ICTD, $b |
|-----------|--------|-------------------------------|-----|------------------------|-----------|----------|
| Germany   | 2.9    | 4,746                         | 35.9| 30.3                   | 2,451.4 [1,011.4, 5,331.4] | 531.4    |
| Greece    | 1.6    | 359                           | 65.2| 16.7                   | 1,890.3 [450.3, 4,770.3]  | −29.7    |
| Ireland   | 5.8    | 529.4                         | 18.5| 58.7                   | 2,784.9 [1,344.9, 5,664.9] | 864.9    |
| Italy     | 2.6    | 3,074                         | 40.4| 26.9                   | 2,365.7 [925.7, 5,245.7]  | 445.7    |
| Macedonia | 1.6    | 66                            | 65.8| 16.5                   | 1,879.9 [439.9, 4,759.9]  | −40.1    |
| Poland    | 3.8    | 2,819.3                       | 28.3| 38.4                   | 2,597.1 [1,157.1, 5,477.1] | 677.1    |
| Portugal  | 2.5    | 519.7                         | 41.9| 26                     | 2,338.1 [898.1, 5,218.1]  | 418.1    |
| Romania   | 1.9    | 766.9                         | 54.1| 20.1                   | 2,103.2 [663.2, 4,983.2]  | 183.2    |
| Russia    | 2.8    | 7,893.2                       | 38.1| 28.6                   | 2,410.8 [970.8, 5,290.8]  | 490.8    |
| Serbia    | 3.4    | 591.7                         | 31.2| 34.8                   | 2,541.6 [1,101.6, 5,421.6] | 621.6    |
| Spain     | 3.2    | 2,879.7                       | 33.6| 32.3                   | 2,495.5 [1,055.5, 5,375.5] | 575.5    |
| Sweden    | 1      | 200.6                         | 101.6| 10.7                   | 1,192.7 [247.3, 4,072.7]  | −727.3   |
| Switzerland | 4.6   | 754.8                         | 23  | 47.3                   | 2,699.1 [1,259.1, 5,579.1] | 779.1    |
| United Kingdom | 4.1 | 5,252.6 | 26  | 41.8                   | 2,642 [1,202, 5,522] | 722 |

**South America**

| Countries | MAF, % | Allele carriers (in thousands) | NNT | NUD per 1,000 patients | ICTCE, $a | ICTD, $b |
|-----------|--------|-------------------------------|-----|------------------------|-----------|----------|
| Bolivia   | < 0.7  | < 149.6                       | > 149.6| < 7.3                 | < 272.8 [−1,167.2, 3,152.8] | < −1,647.2 |
| Chile     | 2.8    | 980.8                         | 37.8| 28.8                   | 2,415.6 [975.6, 5,295.6]  | 495.6    |

**North and Central America**

| Countries | MAF, % | Allele carriers (in thousands) | NNT | NUD per 1,000 patients | ICTCE, $a | ICTD, $b |
|-----------|--------|-------------------------------|-----|------------------------|-----------|----------|
| Cuba      | 2.3    | 510                           | 46.9| 23.2                   | 2,241 [801, 5,121]  | 321 |
| Mexico    | 0.9    | 2,155.6                       | 121.9| 8.9                   | 804 [−636, 3,684]  | −1,116 |
| Nicaragua | 1.2    | 145.1                         | 87.5| 12.4                   | 1,463.3 [23.3, 4,343.3] | −496.7 |
| United States | 2.8 | 17,769.4 | 37.6| 28.9                   | 2,419.8 [979.8, 5,299.8] | 499.8 |

**Oceania**

| Countries | MAF, % | Allele carriers (in thousands) | NNT | NUD per 1,000 patients | ICTCE, $a | ICTD, $b |
|-----------|--------|-------------------------------|-----|------------------------|-----------|----------|
| Australia | 2.7    | 1,288.9                       | 38.5| 28.2                   | 2,401.4 [961.4, 5,281.4] | 481.4 |
| New Zealand | 1     | 92.5                          | 104.1| 10.4                  | 1,145.5 [−294.5, 4,025.5] | −774.5 |

ADR, adverse drug reaction; Fc, carrier frequency; HLA, human leukocyte antigen; ICTCE, incremental cost threshold for cost-effectiveness; ICTD, incremental cost threshold for dominant strategy; MAF, minor allele frequency; N/A, not applicable; NNT, number of patients needed to test to prevent one ADR; NPV, negative predictive value; NUD, number of patients who would be unnecessarily denied the drug; PPV, positive predictive value.

*aICTCE indicates the threshold value for ICERF = $40,000 (see Methods section for calculation details). Square brackets indicate the ICTCE interval for ICERF between $10,000 and $100,000. bICTD indicates the threshold value for ICERF = 0 (see Methods section for calculation details).
available for African populations. However, the available data from Ghana (0.4%), Uganda (0.9%), Sao Tome and Principe (1.5%), and Tunisia (1.6%), as well as for African Americans (1.1%) suggests that the prevalence of HLA-A*31:01 in Africa is overall low. Due to the relatively low predictive power of HLA-A*31:01 testing (Table S1), the NNT to prevent one SCAR exceeds 1,000 individuals in most countries with the exception of Japan (NNT = 493.9), South Korea (NNT = 734.9), Sweden (NNT = 703.9), Chile (NNT = 626.7), and indigenous populations in the Americas (Table 2, Table S7).

Preemptive genotyping of HLA-A*31:01 was likely cost-effective globally, primarily due to the substantial gain in QALY upon switching therapy to alternative anticonvulsants in HLA-A*31:01 carriers. However, genotype-guided carbamazepine prescribing was not found to be the dominant strategy, indicating that the cost thresholds are very sensitive to ICERs.

**Testing for HLA-B*58:01 to guide allopurinol therapy**

The xanthine oxidase inhibitor allopurinol is the first-line treatment for the management of hyperuricemia. Although it is generally well-tolerated, allopurinol can cause SCARs in up to 4.7 per 1,000 new users. HLA-B*58:01 has been consistently identified as genetic risk factor in Asian and European populations and allopurinol is contraindicated in HLA-B*58:01 carriers. In total, we analyzed HLA-B*58:01 genotypes of 6,448,207 individuals across 66 countries. The allele is highly prevalent throughout most of East and South Asia with an estimated 440 million variant carriers and peak frequencies in Mongolia (8.8%), China (7.8%), and Thailand (7.8%), whereas this allele is rare in Japan (0.7%; Figure 4, Table 3). Furthermore, HLA-B*58:01 is common in various African countries, including Kenya (8.2%) and Guinea Bissau (7.8%). In Europe, HLA-B*58:01 frequencies are overall low, ranging from < 0.5% in Belgium and Ireland to 2% in Italy. HLA-B*58:01 frequencies in US populations are reflective of ancestry with the allele being most prevalent in Asian (5.4%) and African Americans (3.5%), whereas frequencies in individuals of Hispanic (1.5%) or white (0.7%) descent or Native Americans (0.3%) were substantially lower (Table S7).

To prevent one case of allopurinol-induced SCARs, 457 to 512 individuals need to be tested in Mongolia and China, respectively, whereas 1,918 to 9,634 need to be screened in Europe (Table 3). In the United States, 727 and 1,108 Asian and African Americans need to be tested for HLA-B*58:01, respectively, to prevent one case of allopurinol-induced SCARs, whereas NNTs are substantially higher for individuals of white (NNT = 5,308), Hispanic (NNT = 2,647), or Native American ancestry (NNT = 11,306; Table S7). Conversely, in South East Asia, preemptive genetic

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Figure 2 Global distribution of human leukocyte antigen (HLA)-B*15:02, predisposing to carbamazepine-induced Stevens-Johnson syndrome/toxic epidermal necrolysis. Carrier and frequency analyses were based on 3,540,660 individuals across 34 countries. Allele frequencies are color-coded with the highest frequency in red, the average frequency across all countries (f) in yellow, and the lowest frequency in blue. Countries for which no HLA-B*15:02 frequency information was available are colored white. Subpopulation-specific frequencies are indicated where available. The text boxes provide the total number of allele carriers and allele carrier frequency of the respective continent. Continent and subcontinent were defined according to the United Nations World Population Prospects (see ref. 9 and Table 2).
Table 2 Socioeconomic metrics of HLA-B*15:02 and HLA-A*31:01 for country-specific cost-effectiveness analysis

| Countries          | MAF, % | Allele carriers (in thousands) NNT | NUD per 1,000 patients | ICTC ($)^a | ICTC ($)^b | MAF, % | Allele carriers (in thousands) NNT | ICTC ($)^a | ICTC ($)^b |
|--------------------|--------|-----------------------------------|------------------------|------------|------------|--------|-----------------------------------|------------|------------|
| Africa             |        |                                   |                        |            |            |        |                                   |            |            |
| Burkina Faso       | 0      | 0                                 | N/A 0                 | Not cost-effective | < 1       | < 352.5 | > 4,110.7 | < 19.2 | < 16,459.7 | [2,728.7, 43,921.7] | < −1,848.3 |
| Cameroon           | N/A    | N/A N/A N/A | N/A                      | < 1.7     | < 755.5 | > 2,417.9 | > 32.7 | < 17,306.1 | [3,575.1, 44,768.1] | < −1,001.9 |
| Ghana              | N/A    | N/A N/A N/A | N/A                      | 0.4       | 210.3   | 10,491.2 | 7.5   | 13,269.5 | [461.5, 40,731.5] | −50,385.5 |
| Morocco            | 0      | 0                                 | N/A 0                 | Not cost-effective | N/A N/A N/A N/A N/A | N/A N/A N/A N/A N/A | N/A |
| Sao Tome and Principe | N/A   | N/A N/A N/A | N/A                      | 1.5       | 6       | 2,602.5  | 30.4  | 17,213.8 | [3,482.5, 44,675.8] | −1,094.2 |
| South Africa       | 0.1    | 128.8 7,668.5 2.2                 | −16,061.9 [−16,205.9, −15,773.9] | −16,253.9 | N/A N/A N/A N/A N/A | N/A N/A N/A N/A N/A | N/A |
| Tunisia            | N/A    | N/A N/A N/A | N/A                      | 1.6       | 357.9   | 2,520.2  | 31.3  | 17,255 | [3,524, 44,717] | −1,053 |
| Uganda             | N/A    | N/A N/A N/A | N/A                      | 0.9       | 719.4   | 4,464.5  | 17.7  | 16,282.8 | [2,551.8, 43,744.8] | −2,025.2 |
| East Asia          |        |                                   |                        |            |          |        |                                   |            |            |
| China              | 7.3    | 197,141.4 126.5 133.2 | 832 [688, 1,120]       | 640       | 2.1     | 57,054.2 | 40.3  | 17,535.6 | [3,804.6, 44,997.6] | −772.4 |
| Japan              | < 0.1  | 118.7 19,253.1 0.9                 | −42,011.4 [−42,155.4, −41,723.4] | −42,203.4 | 8.5     | 20,730.2 | 160   | 18,268.1 | [4,537.1, 45,730.1] | −39.9 |
| Mongolia           | 1.5    | 88.6  599.7 28.1                | −227.9 [−371.9, 60.1] | −419.9 | N/A N/A N/A N/A N/A | N/A N/A N/A N/A N/A | N/A |
| South Korea        | 1.5    | 1,464.4 616.9 27.3                | −266.4 [−410.4, 21.6] | −458.4 | 5.6     | 5,507.8  | 107.5 | 18,147.6 | [4,416.4, 45,609.6] | −160.4 |
| South Asia         |        |                                   |                        |            |          |        |                                   |            |            |
| India              | 2.2    | 56,425.5 414.3 40.7               | 187.5 [43.5, 475.5]    | −4.5      | 4       | 101,927 | 76.9  | 18,001.4 | [4,270.4, 45,463.4] | −306.6 |
| Indonesia          | 11.6   | 56,471.8 81.6 206.5               | 932 [788.6, 2,206.6]   | 740.6     | N/A N/A N/A N/A N/A | N/A N/A N/A N/A N/A | N/A |
| Malaysia           | 11.5   | 6,656.2 82.4 204.5               | 930.9 [786.9, 1,218.9] | 738.9     | 0.6     | 384.1   | 123   | 15,315.9 | [1,584.9, 42,777.9] | −2,992.1 |
| Philippines        | 2.2    | 39,832.1 45.6 369.7               | 1,013.4 [869.4, 1,301.4] | 821.4     | N/A N/A N/A N/A N/A | N/A N/A N/A N/A N/A | N/A |
| Singapore          | 7.8    | 824.8 119.8 140.7                | 847 [703, 1,135]      | 655      | N/A N/A N/A N/A N/A | N/A N/A N/A N/A N/A | N/A |
| Sri Lanka          | 2.5    | 1,022.8 361.7 46.6               | 305.4 [161.4, 593.4]   | 113.4     | 2.2     | 901.4   | 43    | 17,595.9 | [3,864.9, 45,057.9] | −71.21 |
| Thailand           | 8.4    | 11,059.4 110.9 152.1             | 867.2 [723.2, 1,155.2] | 675.2     | 1.3     | 1,773.5 | 25.5  | 16,966.5 | [3,235.5, 44,428.5] | −1,341.5 |
| Vietnam            | 13.8   | 24,041.9 69.5 242.5               | 959.8 [815.8, 1,247.8] | 767.8     | 1.4     | 2,601.7 | 27.5  | 17,076.4 | [3,345.4, 44,338.4] | −1,231.6 |
| West Asia          |        |                                   |                        |            |          |        |                                   |            |            |
| Armenia            | N/A    | N/A N/A N/A | N/A                      | 3.5       | 200.6   | 1,163.2 | 67.9  | 17,933.5 | [4,202.5, 45,395.5] | −374.5 |
| Iran               | 1.5    | 2,363 599.7 28.1                | −227.9 [−371.9, 60.1] | −419.9 | 2.7     | 4,252.8 | 52.9  | 17,768.6 | [4,037.6, 45,230.6] | −539.4 |
| Israel             | < 0.1  | 1.5  94,688.9 0.2               | −210,987.6 [−211,131.6, −210,699.6] | −211,179.6 | 0.8 | 131.4 | 16.1  | 16,060.6 | [2,329.6, 43,522.6] | −2,247.4 |

(Continued)
### Table 2 (Continued)

| Countries                  | MAF, % | Allele carriers (in thousands) NNT | NUD per 1,000 patients | ICTCE ($)a | ICTD ($)b | MAF, % | Allele carriers (in thousands) NNT | NUD per 1,000 patients | ICTCE ($)a | ICTD ($)b |
|----------------------------|--------|-----------------------------------|------------------------|------------|----------|--------|-----------------------------------|------------------------|------------|----------|
| Oman                       | 0      | 0                                 | Not cost-effective     | N/A        | N/A      | N/A    | N/A                               | N/A        | N/A       | N/A      |
| Turkey                     | < 0.1  | 32.9                              | 42,521.5               | 0.4        | 94,132.6 | −94,324.6 | 1.9      | 2,946.1                       | 2,125.5     | 37.2      | 17,452   | −855.7   |
| Europe                     |        |                                   |                        |            |          |         |                                   |                        |            |          |
| Albania                    | N/A    | N/A                               | N/A                    | N/A        | N/A      | N/A    | N/A                               | N/A        | N/A       | N/A      |
| Austria                    | N/A    | N/A                               | N/A                    | N/A        | 2.9      | 496.1   | 1,399.6                           | 56.4       | 17,815.3 | [4,084.3, 45,277.3] |
| Bosnia and Herzegovina     | N/A    | N/A                               | N/A                    | N/A        | 1.6      | 112.2   | 2,520.2                           | 31.3       | 17,255   | [3,524, 44,717] |
| Bulgaria                   | 0      | 0                                 | Not cost-effective     | N/A        | N/A      | N/A    | N/A                               | N/A        | N/A       | N/A      |
| Czech Republic             | < 0.1  | 2.1                               | 91,146.3               | 0.4        | −203,052.2 | −203,196.2 | −203,244.2 | 2.1      | 440.7   | 1,925    | −855.7   |
| Estonia                    | < 0.1  | 0.06                              | 372,028.3              | 0          | −832,227.8 | −832,371.8 | −832,419.8 | 2.5      | 65.7    | 1,601.3  | −936.4   |
| France                     | N/A    | N/A                               | N/A                    | N/A        | 3        | 3,809.4 | 1,353.6                           | 58.4       | 17,838.3 | [4,107.3, 45,300.3] |
| Germany                    | < 0.1  | 154.9                             | 9,421                  | 1.8        | −19,987.6 | −20,131.6 | −19,699.6 | −20,179.6 | 2.3      | 3,759   | 1,738.9  | −662.4   |
| Greece                     | < 0.1  | 11.3                              | 17,796.6               | 0.9        | −38,749.4 | −38,893.4 | −38,461.4 | −38,941.4 | 1.9      | 417     | 2,152    | −868.9   |
| Italy                      | < 0.1  | 47.1                              | 22,578.1               | 0.7        | −49,459.3 | −49,603.3 | −49,171.3 | −49,651.3 | 2.2      | 2,612.5 | 1,822.2  | −704.9    |
| Netherlands                | < 0.1  | 18.9                              | 15,975.8               | 1.1        | −34,670.3 | −34,814.3 | −34,382.3 | −34,862.3 | 3.4      | 1,135.7 | 1,193.2  | −389.5    |
| Poland                     | < 0.1  | 3.1                               | 222,723.6              | 0.1        | −497,785.4 | −497,929.4 | −497,977.4 | 2.4      | 1,784.7 | 1,715.3  | −650.6    |
| Portugal                   | N/A    | N/A                               | N/A                    | N/A        | 1.9      | 398.3   | 2,092.4                           | 37.8       | 17,489.8 | [3,737.9, 45,930.9] |
| Romania                    | 0      | 0                                 | Not cost-effective     | N/A        | 2.9      | 1,136.1 | 1,399.6                           | 56.4       | 17,815.3 | [4,084.3, 45,277.3] |
| Russia                     | N/A    | N/A                               | N/A                    | N/A        | 2.1      | 5,979.8 | 1,925                             | 41         | 17,552.6 | [3,821.6, 45,014.6] |
| Spain                      | N/A    | N/A                               | N/A                    | N/A        | 2.1      | 1,928.2 | 1,925                             | 41         | 17,552.6 | [3,821.6, 45,014.6] |
| Sweden                     | N/A    | N/A                               | N/A                    | N/A        | 5.9      | 1,109.7 | 703.9                             | 112         | 18,163.1 | [4,432.1, 45,625.1] |
| Switzerland                | N/A    | N/A                               | N/A                    | N/A        | 3.9      | 634.9   | 1,048.4                           | 75.4       | 17,990.9 | [4,259.9, 45,452.9] |
| UK                         | N/A    | N/A                               | N/A                    | N/A        | 2.6      | 3,356.4 | 1,558.7                           | 50.7       | 17,735.7 | [4,004.7, 45,197.7] |
| South America              |        |                                   |                        |            |          |         |                                   |                        |            |          |
| Chile                      | N/A    | N/A                               | N/A                    | N/A        | 6.6      | 2,267.3 | 626.7                             | 126        | 18,201.7 | [4,470.7, 45,663.7] |
| Ecuador                    | 0      | 0                                 | Not cost-effective     | N/A        | 2.4      | 765.6   | 1,866.9                           | 46.8       | 17,671.6 | [3,940.6, 45,133.6] |
| Peru                       | N/A    | N/A                               | N/A                    | N/A        | 0.5      | 313     | 8,020.1                           | 9.9        | 14,505   | [774, 41,967] |
| North and Central America  |        |                                   |                        |            |          |         |                                   |                        |            |          |
| Cuba                       | 0      | N/A                               | Not cost-effective     | N/A        | N/A      | N/A    | N/A                               | N/A        | N/A      | N/A      |
| Mexico                     | 0.2    | 381.1                             | 5,898.7                | 2.9        | −12,097.6 | −12,241.6 | −11,809.6 | −12,289.6 | 10.1     | 24,084.8 | 617.7    | −101.8    |

(Continued)
testing for HLA-B*58:01 would result in up to 166 patients per 1,000 tested individuals to be unnecessarily referred to allopurinol alternatives, whereas these numbers are substantially lower in Europe (8–40) and the United States (between 7 in Native Americans and 104 in Asian Americans).

Genotype-informed allopurinol therapy can be cost-effective throughout most of Africa and Asia with incremental thresholds for cost-effectiveness between $929 and $2,130 at an ICERₚ threshold of $40,000, with the exception of Zambia and Japan where HLA-B*58:01 is rare. In contrast, preemptive testing of HLA-B*58:01 is unlikely to be cost-effective in Belgium, the Czech Republic, Estonia, and Ireland, as well as Serbia and the United Kingdom. In the United States, alternative treatment thresholds differ considerably between subpopulations. Here, preemptive HLA-B*58:01 testing is more likely to be cost-effective for African (ICT₉₀ up to $5,019.3) and Asian Americans (ICT₉₀ up to $5,217.1) compared with white and Hispanic Americans (ICT₉₀ up to $2,835.3 and $4,219.1, respectively), in agreement with previous reports. However, HLA-B*58:01 screening is unlikely to be the dominant strategy in any population analyzed.

### DISCUSSION

Cost-effectiveness analyses constitute important health economic evaluation methods that compare treatment alternatives by weighing their incremental costs against their therapeutic benefits, thus constituting essential tools to inform public health care strategies. In pharmacogenetics, CEAs are used to quantitatively assess the costs and outcomes of genotype-guided prescribing for which risk allele frequency constitutes a key parameter, and as such provide the basis for the clinical implementation of the respective strategy. However, determination of the cost-effectiveness of HLA genotyping have so far only been presented for the United States, as well as for few countries in Europe and Southeast Asia, which renders informed decision making in countries in which some data are not available, difficult. Furthermore, the presented studies are nonstandardized and methodologically diverse, comprising both decision tree and Markov models, which reduces comparability.

To overcome these limitations and facilitate informed public health care in, as of yet, understudied countries and populations, we modeled the cost-effectiveness of HLA genotyping across 74 countries by integrating genotype data from a total of 6.4 million individuals, established predictive metrics for the tests in question, as well as data about the effects of both first-line and alternative treatments on life quality. We provide estimates for the maximal incremental cost that the alternative treatment can be more expensive than first-line therapy to justify preemptive genotyping, thus allowing for the incorporation of country-specific medical cost structures. Of note, careful analysis of the available literature showed that the increase in QALY of genotype-guided versus traditional prescribing of abacavir and allopurinol strongly depends on risk allele carrier frequency. Based on these findings, our model considered ΔQALY as a function of Fₚ and we believe that this approach provides a conceptual advancement over previous evaluations.
Importantly, our results align with available CEAs from the literature, supporting model validity (Table S8). Specifically, our model supports the cost-effectiveness of HLA-B*57:01 genotyping to guide abacavir therapy for Germany, Spain, the United Kingdom, and United States, in agreement with previous studies. In contrast, both our model and literature data suggest that genotype-guided prescribing is unlikely to be cost-effective in Singapore and Korea. Similarly, our estimates align with the literature regarding the cost-effectiveness of HLA-B*15:02 and HLA-A*31:01 testing for carbamazepine in South East Asia and the United Kingdom, respectively. Moreover, although our estimates disagree with a previous analysis concluding that HLA-B*58:01 testing is not cost-effective in Singapore due to major discrepancies in genotyping cost estimates ($270 compared with $40 in our model), our predictions corroborate the cost-effectiveness of preemptive testing for HLA-B*58:01 before initiation of allopurinol in Korea, China, and Thailand, as well as Asian and African Americans. In contrast, testing in Portugal, the United Kingdom, as well as white and Hispanic Americans was not found to be cost-effective, in full agreement with available reports.

In addition to country-specific predictions, we provide cost-effectiveness estimates for various understudied populations, such as Native Americans, Roma, and Aboriginal Australians, as well as various diasporas of different ethnicities. Importantly, conscious consideration of these subpopulation-specific differences, particularly in countries with heterogeneous population structures, can refine the allocation of healthcare resources in a precision public health framework.28,29 For instance, preemptive HLA-B*15:02 testing in the United States is reimbursed for all patients with Asian ancestry.30 However, our data show that carrier frequencies in Japan are very low (<0.1%), suggesting that HLA-B*15:02 genotyping in individuals of Japanese descent does not constitute an efficient allocation of healthcare resources. Notably, we anticipate that the increasing availability of ethnogeographic annotated genetic data will allow to further refine allele frequency information and, accordingly, cost-effectiveness estimates, particularly in ethnically heterogeneous countries.

Genotyping costs are one of the key parameters determining the cost-effectiveness of preemptive HLA testing. For our calculations, we assumed a relatively low cost of $40 per genotyping reaction. Although we acknowledge that costs provided in the literature can be considerably higher (Table S4), we motivate our decision by multiple lines of argumentation: (i) costs of genetic testing decreases in parallel to its increasing...
Figure 4 Global distribution of human leukocyte antigen (HLA)-B*58:01, predisposing to cutaneous adverse reactions due to allopurinol. Carrier and frequency analyses were based on 6,448,207 individuals across 66 countries. Allele frequencies are color-coded with the highest frequency in red, the average frequency across all countries (\( f \)) in yellow, and the lowest frequency in blue. Countries for which no HLA-B*58:01 frequency information was available are colored white. Subpopulation-specific frequencies are indicated where available. The text boxes provide the total number of allele carriers and allele carrier frequency of the respective continent. Continent and subcontinent were defined according to the United Nations World Population Prospects (see ref. 9 and Table 3).

Table 3 Socioeconomic metrics of HLA-B*58:01 for country-specific cost-effectiveness analysis

| Risk allele | HLA-B*58:01 |
|-------------|-------------|
| Associated ADR | Allopurinol-induced SJS/TEN/DRESS |
| PPV, % | 1.3 |
| NPV, % | 100 |
| \( \Delta \text{EFFECT (} F_c \text{)} \) | 0.0538 * \( F_c \) |

| Countries          | MAF, % | Allele carriers (in thousands) | NNT | NUD per 1,000 patients | ICT\(_{\text{CE}}\), $^a$ | ICT\(_{\text{CP}}\), $^b$ |
|--------------------|--------|--------------------------------|------|------------------------|--------------------------|--------------------------|
| Africa             |        |                                |      |                        |                          |                          |
| Burkina Faso       | 5.4    | 1,899.7                        | 733.3| 103.5                  | 1,986 [372, 5,214]       | −166                     |
| Cameroon           | 5.0    | 2,238.8                        | 784.6| 96.8                   | 1,959.4 [345.4, 5,187.4] | −192.6                   |
| Cape Verde         | 3.6    | 37.7                           | 1,088| 69.8                   | 1,801.6 [187.6, 5,029.6] | −350.4                   |
| Ghana              | 4.2    | 2,268.3                        | 935.4| 81.2                   | 1,881 [267, 5,109]       | −271                     |
| Guinea Bissau      | 7.8    | 265.4                          | 513.1| 148                    | 2,100.5 [486.5, 5,328.5] | −51.5                    |
| Ivory Coast        | 2.3    | 1,050.8                        | 1,691.7| 44.9                   | 1,487.7 [−126.3, 4,715.7] | −664.3                   |
| Kenya              | 8.2    | 7,446.7                        | 487.9| 155.6                  | 2,113.6 [499.6, 5,341.6] | −38.4                    |
| Mali               | 2.2    | 760.1                          | 1,767.7| 43                     | 1,448.2 [−165.8, 4,676.2] | −703.8                   |
| Sao Tome and Principe | 3.6  | 13.7                           | 1,101.4| 68.9                   | 1,794.6 [180.6, 5,022.6] | −357.4                   |
| Senegal            | 6.9    | 1,995.5                        | 577.3| 131.5                  | 2,067.1 [453.1, 5,295.1] | −84.9                    |

(Continued)
## Table 3 (Continued)

| Countries         | MAF, % | Allele carriers (in thousands) | NNT  | NUD per 1,000 patients | ICT$_{Cr}$ $^a$ | ICT$_{Pr}$ $^b$ |
|-------------------|--------|--------------------------------|------|------------------------|----------------|----------------|
| South Africa      | 6.3    | 6,739.6                        | 631.1| 120.3                  | 2,039.2 [425.2, 5,267.2] | −112.8         |
| Sudan             | 4.5    | 3,400                          | 874.4| 86.8                   | 1,912.7 [298.7, 5,140.7] | −239.3         |
| Tunisia           | 3.2    | 704.1                          | 1,231.6| 61.6                  | 1,726.9 [112.9, 4,954.9] | −425.1         |
| Uganda            | 5      | 3,945.9                        | 782.6| 97                     | 1,960.4 [346.4, 5,188.4] | −191.6         |
| Zambia            | 0      | 0                              | N/A  | 0                      | Not cost-effective |                |
| Zimbabwe          | 4.4    | 1,357.9                        | 893.8| 84.9                   | 1,902.6 [288.6, 5,130.6] | −249.4         |
| **East Asia**     |        |                                |      |                        |                |                |
| China             | 7.8    | 210,007.6                      | 511.7| 148.4                  | 2,101.3 [487.3, 5,329.3] | −50.7          |
| Japan             | 0.7    | 1,727.4                        | 5,699| 13.3                   | −596.1 [−2,210.1, 2,631.9] | −2,748.1       |
| Mongolia          | 8.8    | 500.9                          | 457.2| 166.1                  | 2,129.6 [515.6, 5,357.6] | −22.4          |
| South Korea       | 6.1    | 6,024.1                        | 646  | 117.5                  | 2,031.4 [417.4, 5,259.4] | −120.6         |
| **South Asia**    |        |                                |      |                        |                |                |
| India             | 3.6    | 93,687.6                       | 1,074.8| 70.6                  | 1,808.5 [194.5, 5,036.5] | −343.5         |
| Indonesia         | 5.7    | 28,721.1                       | 691.4| 109.8                  | 2,007.8 [393.8, 5,235.8] | −144.2         |
| Malaysia          | 6.9    | 4,096.1                        | 577  | 131.6                  | 2,067.3 [453.3, 5,295.3] | −84.7          |
| Singapore         | 7.2    | 765.6                          | 556.2| 136.5                  | 2,078.2 [464.2, 5,306.2] | −73.8          |
| Sri Lanka         | 7.2    | 2,875.4                        | 554.1| 137                    | 2,079.2 [465.2, 5,307.2] | −72.8          |
| Thailand          | 7.8    | 10,258.4                       | 514.8| 147.5                  | 2,099.6 [485.6, 5,327.6] | −52.4          |
| Vietnam           | 6.9    | 12,464.7                       | 577.5| 131.5                  | 2,067.1 [453.1, 5,295.1] | −84.9          |
| **West Asia**     |        |                                |      |                        |                |                |
| Armenia           | < 1.8  | < 105.7                        | > 2,123| < 35.8                | < 1,263.4 [−350.6, 4,491.4] | < −888.6       |
| Georgia           | 1.4    | 109.9                          | 2,766.6| 27.4                  | 928.7 [−685.3, 4,156.7] | −1,223.3       |
| Iran              | 3.5    | 5,471.4                        | 1,115.7| 68                    | 1,787.2 [173.2, 5,015.2] | −364.8         |
| Israel            | 1.9    | 307.1                          | 2,019.9| 37.6                  | 1,317 [−297, 4,545] | −835          |
| Jordan            | 1.4    | 254.7                          | 2,766.6| 27.4                  | 928.7 [−685.3, 4,156.7] | −1,223.3       |
| Oman              | 6.8    | 551.8                          | 585.5| 129.7                  | 2,062.9 [448.9, 5,290.9] | −89.1          |
| Saudi Arabia      | 4.6    | 2,836.5                        | 855.8| 88.7                   | 1,922.3 [308.3, 5,150.3] | −229.7         |
| Turkey            | 1.8    | 2,792.4                        | 2,156.2| 35.2                  | 1,246.2 [−367.8, 4,474.2] | −905.8         |
| **Europe**        |        |                                |      |                        |                |                |
| Albania           | < 1.8  | < 105.4                        | > 2,133.3| < 35.6                | < 1,258.1 [−355.9, 4,486.1] | < −893.9       |
| Austria           | 1.2    | 199.8                          | 3,341.1| 22.7                  | 630 [−984, 3,858] | −1,522        |
| Belgium           | < 0.5  | < 112.6                        | > 7,711.6| < 9.8                 | < −1,642.7 [−3,256.7, 1,585.3] | < −3,794.7     |
| Bosnia and Herzegovina | 1 | 68.5 | 3,972.2 | 19.1 | 301.8 [−1,312, 3,529.8] | −1,850.2       |
| Bulgaria          | 1.8    | 256.1                          | 2,156.2| 35.2                  | 1,246.2 [−367.8, 4,474.2] | −905.8         |
| Croatia           | < 1.8  | < 154.9                        | > 2,103.5| < 36.1                | < 1,273.5 [−340.5, 4,501.5] | < −878.5       |
| Czech Republic    | 0.7    | 148                            | 5,509.6| 13.8                  | −497.6 [−2,111.6, 2,730.4] | −2,649.6       |
| Estonia           | 0.6    | 15.2                           | 6,639.4| 11.4                  | −1,085.1 [−2,699.1, 2,142.9] | −3,237.1       |
| France            | 1.4    | 1,834.7                        | 2,702.4| 28.1                  | 962.1 [−651.9, 4,190.1] | −1,189.9       |
| Germany           | 1.1    | 1,807.9                        | 3,476.5| 21.8                  | 559.6 [−1,054.4, 3,787.6] | −1,592.4       |
| Greece            | 1.5    | 342.4                          | 2,520.5| 30.1                  | 1,056.7 [−557.3, 4,284.7] | −1,095.3       |
| Ireland           | 0.4    | 37.5                           | 9,634.7| 7.9                   | −2,642.7 [−4,256.7, 585.3] | −4,794.7       |
| Italy             | 2      | 2,386.3                        | 1,918.1| 39.6                  | 1,369.9 [−244.1, 4,597.9] | −782.1         |
| Macedonia         | 0.9    | 37.3                           | 4,292.8| 17.7                  | 135.1 [−1,478.9, 3,363.1] | −2,016.9       |
| Poland            | 1.3    | 995                            | 2,958.2| 25.7                  | 829.1 [−784.9, 4,057.1] | −1,322.9       |
| Portugal          | 1.6    | 328.3                          | 2,441.1| 31.1                  | 1,098 [−516, 4,326] | −1,054        |

(Continued)
Table 3 (Continued)

| Countries          | MAF, % | Allele carriers (in thousands) | NNT   | ICTCE, $a | ICTD, $b |
|--------------------|--------|--------------------------------|-------|-----------|----------|
| Romania            | 1      | 412.9                          | 3,702.9 | 20.5      | 441.9 [−1,172.1, 3,669.9] | −1,710.1 |
| Russia             | 1.6    | 4,702                          | 2,354  | 32.3      | 1,143.3 [−470.7, 4,371.3] | −1,008.7 |
| Serbia             | 0.5    | 88.3                           | 7,711.6 | 9.8       | −1,642.7 [−3,256.7, 1,585.3] | −3,794.7 |
| Spain              | 1.3    | 1,162.5                        | 3,070  | 24.7      | 770.9 [−843.1, 3,998.9] | −1,381.1 |
| Switzerland        | 1.9    | 312.1                          | 2,050.9 | 37        | 1,300.9 [−313.1, 4,528.9] | −851.1  |
| UK                 | 0.5    | 625                            | 8,048.8 | 9.4       | −1,818 [−3,432, 1,410] | −3,970  |
| South America      |        |                                |        |           |          |
| Chile              | 2.8    | 980.8                          | 3,603.5 | 21.1      | 493.5 [−1,120.5, 3,721.5] | −1,658.5 |
| Ecuador            | < 1.1  | < 344.6                        | 1,393.1 | 54.5      | < 1,642.9 [28.9, 4,870.9] | < −509.1 |
| North and Central America |      |                                |        |           |          |
| Cuba               | 3.6    | 813.1                          | 1,084.3 | 70        | 1,803.5 [189.5, 5,031.5] | −348.5  |
| Guatemala          | 0.7    | 226.7                          | 5,513.8 | 13.8      | −499.8 [−2,113.8, 2,728.2] | −2,651.8 |
| Mexico             | 0.8    | 1,979.8                        | 4,891.4 | 15.5      | −176.2 [−1,790.2, 3,051.8] | −2,328.2 |
| Nicaragua          | 1.8    | 217                            | 2,156.2 | 35.2      | 1,246.2 [−367.8, 4,474.2] | −905.8  |
| United States      | 1.5    | 9,466.5                        | 2,599.7 | 29.2      | 1,015.5 [−598.5, 4,243.5] | −1,136.5 |
| Oceania            |        |                                |        |           |          |
| Australia          | 4.7    | 2,206                          | 829.9  | 91.5      | 1,935.8 [321.8, 5,163.8] | −216.2  |
| New Zealand        | 0.5    | 46                             | 7,711.6 | 9.8       | −1,642.7 [−3,256.7, 1,585.3] | −3,794.7 |

ADR, adverse drug reaction; DRESS, drug rash with eosinophilia and systemic symptoms; HLA, human leukocyte antigen; Fc, carrier frequency; ICTCE, incremental cost threshold for cost-effectiveness; ICTD, incremental cost threshold for dominant strategy; MAF, minor allele frequency; N/A, not applicable; NNT, number of patients needed to test to prevent one ADR; NPV, negative predictive value; NUD, number of patients who would be unnecessarily denied the drug; PPV, positive predictive value; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

*ICTCE indicates the threshold value for ICER T = $40,000 (see Methods section for calculation details). Square brackets indicate the ICTCE interval for ICER T between $10,000 and $100,000. bICTD indicates the threshold value for ICER T = 0 (see Methods section for calculation details).

In summary, this study provides the global and country-specific frequencies of genetic risk alleles that predispose to severe abacavir, carbamazepine, and allopurinol toxicity and reveal significant patterns of both ethnic and geographic diversity. Based on these comprehensive data, we provide cost-effectiveness estimates for preemptive pharmacogenomic testing across 74 countries. We anticipate that these evaluations can inform precision public health care strategies, particularly for understudied countries and ethnicities on a global scale.

SUPPORTING INFORMATION
Supplementary information accompanies this paper on the Clinical Pharmacology & Therapeutics website (www.cpt-journal.com).

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CONFLICT OF INTEREST
The authors declare no conflict of interest according to the ICMJE Uniform Requirements. However, V.M.L. would like to declare the following financial relationship: co-founder and shareholder of HepaPredict AB; consultancy work for Enginzyme AB. All other authors declared no competing interests for this work.
AUTHOR CONTRIBUTIONS
Y.Z. and V.M.L. wrote the manuscript. Y.Z. and V.M.L. designed the research. Y.Z. and K.K. performed the research. Y.Z., K.K. and V.M.L. analyzed the data.

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