Pharmacogenomic test that predicts response to inhaled corticosteroids in adults with asthma likely to be cost-saving

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Pharmacogenomic test that predicts response to inhaled corticosteroids in adults with asthma likely to be cost-saving

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Abstract

Aim—To identify the clinical and economic circumstances under which a pharmacogenomic test that predicts response to inhaled corticosteroids might be a cost-effective option for individuals with asthma.

Materials & methods—We synthesized published data on clinical and economic outcomes to project 10-year costs, quality-adjusted life-years and cost-effectiveness of pharmacogenomic testing for inhaled corticosteroid response. We assumed the pharmacogenomic test cost was $500 with a sensitivity and specificity of 84 and 98%, respectively. These were varied in sensitivity analyses.

Results—Both strategies, pharmacogenomic testing for inhaled corticosteroid response and no testing conferred 7.1 quality-adjusted life-years. Compared with no testing, pharmacogenomic testing costs less.

Conclusion—Pharmacogenomic testing for asthma is cost-saving and noninferior in improving health.

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Ethical conduct of research The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.
**Background**

Inhaled corticosteroids (ICS) are the most commonly used controller medication for persistent asthma. It is estimated that 10–30% of asthma patients do not benefit with enhanced asthma control from ICSs yet risk suffering from side effects of corticosteroids [1–5]. ICS response profile shows repeatable inter individual variation, due in part to genetics [6–8]. Given the potential impact of adverse events from ICS, such as diminished linear growth rate in children, decreased bone density and cataract formation, a pharmacogenomic test that predicts poor response to ICS would minimize unnecessary drug exposure and reduce adverse side effects [1,3,9,10]. Additionally, by eliminating the time a patient spends on inappropriate medication, such a test could speed the time to selection of optimal medication for individual sufferers.

Currently, a person with asthma who is empirically started on ICS may be either a responder or nonresponder. In clinical practice, the differentiation of ICS responders and ICS nonresponders is not easy as no guidelines currently exist on ICS response; nevertheless, nonresponse is being recognized in the literature [6–8]. Thus, no data exist on frequency and accuracy of detection of ICS nonresponse. An astute clinician may notice that a patient’s asthma does not improve, despite use of an ICS and the clinician may alter the patient’s medical regimen; however, this is done in a minority of cases. Anecdotal evidence suggests alternative controller medications for asthma such as leukotriene antagonists (LTRAs) are more frequently added to treatment with ICS rather than used as a replacement for failed ICS.

Pharmacogenomic tests to predict response to asthma medications are in early development [11–14]. Evaluating the potential impact on costs and health benefits of a test to identify persons at high risk for nonresponse can help guide development and set pricing. Understanding how test characteristics affect the projected costs and benefits is critical as more pharmacogenomic tests enter clinical practice. To our knowledge, few studies have examined the potential impact of pharmacogenomics on healthcare costs [15], and no studies have been done in conformity with the recommendations of the US Panel on Cost–effectiveness in Health and Medicine [16]. Therefore, we used computer modeling to examine the expected impact of alternative strategies for, formulating and using, asthma pharmacogenomic tests on the health benefits, costs and cost–effectiveness of asthma care. This analysis will help guide clinical policymakers on how to evaluate and use new predictive tests for large populations and understand the key parameters for these tests to be adopted clinically.

**Materials & methods**

This analysis was conducted from a societal perspective and included direct costs. In order to evaluate the cost and effectiveness of the two strategies outlined for identification and
treatment of asthma, based on ICS response, we used the Asthma Policy Model, a Markov state transition model previously developed to evaluate the cost–effectiveness of asthma therapy [17–19]. Details of this model – its underlying assumptions, construction, input data fields and analysis – have been described elsewhere [17–19]. Briefly, this is a model that characterizes the progress of disease as a sequence of transitions through a defined set of ‘health states.’ The model characterizes the natural history of illness as a sequence of transitions into and out of three healthy states: chronic, acute and death. The model assumes that patients in the same health state also share a similar clinical history and prognosis, a common perception of well-being, and a comparable pattern of health utilization.

The following dimensions define the model’s health states: disease status (chronic, acute exacerbation, dead), lung function (FEV₁), prior hospitalizations, patient age and cause of death (asthma related, other). Acute exacerbations are divided into three categories: urgent care visits, emergency department visits and hospitalizations. A hypothetical cohort of individuals with asthma, examined with the model, begin in the chronic state that reflects published distributions of age and pulmonary function. Each month, individuals’ states may worsen or improve, similar to the natural history of asthma. Each transition involves a unique set of mortality risks, clinical consequences, changes in quality of life and economic costs. Exacerbations and hospitalizations from asthma are accounted for when a patient moves from the chronic health state to the acute state. The clinical course of this cohort, ages 18–35 years is tracked for 10 years.

We evaluated two strategies: a clinical detection strategy which models current practice, initiation of ICS therapy without testing and a pharmacogenomic-based strategy that incorporates a one-time pharmacogenomic testing for ICS response prior to initiating a controller medication. Current guidelines for the treatment of asthma recommend ICS as the preferred therapy for patients who meet criteria for persistent asthma [20]; therefore, we chose to focus on a population of asthma patients with persistent asthma. Costs were updated to 2012 US dollars using the medical care component of the Consumer Price Index. Costs and quality-adjusted life-years (QALYs) were discounted at 3%.

**Clinical detection strategy**

Among subjects with persistent asthma under the status quo therapy strategy (Figure 1), we have three subpopulations:

- ICS responders who are prescribed ICS therapy;
- ICS nonresponders who are prescribed ICS therapy and then clinically detected as poor responders and have LTRA added to their ICS regimen. Based on unpublished, de-identified and aggregate data of asthma patients from Harvard Vanguard Medical Associates, we found that 31% of patients have LTRA added on to ICS, suggesting that the providers felt that ICS alone was inadequate. Therefore, we assumed that a third of patients have a poor response to ICS alone and have a second controller (such as a LTRA) added to their regimen;
- ICS nonresponders who are not clinically detected and continue on ICS therapy alone.
Patients in group 2 and 3 continue to have the additional costs for ICS and the potential side effects of their use without improvement in asthma related outcomes associated with ICS use.

**Pharmacogenomic testing strategy**

Among subjects with persistent asthma under a testing strategy (Figure 2), we have four subpopulations:

- **True positives** – ICS responders correctly identified by the pharmacogenomic test and prescribed ICS therapy;
- **False negatives** – ICS responder incorrectly identified by the pharmacogenomic test to be a nonresponder and prescribed LTRA;
- **True negatives** – ICS nonresponders correctly identified via the pharmacogenomic test and prescribed LTRA;
- **False negatives** – ICS nonresponder incorrectly identified and prescribed ICS.

LTRAs are an accepted alternative medication to ICS per the NAEPP guidelines [20], and the alternative therapy used for our modeling analysis. We assume that changing a nonresponder to an alternative treatment (LTRA) is more effective than leaving them on ICS, resulting in better FEV₁, better control of asthma and fewer exacerbations.

The benefit of a testing strategy derives from the identification of nonresponders who would not be clinically detected under the status quo. We assumed that subjects were clinically detected during the first month of ICS treatment.

**Input data**

Baseline input values and parameters for sensitivity analyses are listed in Table 1. Details of the input data for each of the strategies are described in the Supplementary Material (see online at: www.futuremedicine.com/doi/suppl/10.2217/pgs.15.28). We modeled both the clinical detection and pharmacogenomic-based strategies along the following independent dimensions: improvement in FEV₁% predicted, reduction in exacerbation rate and reduction in days and nights with symptoms. We conducted a PubMed search of clinical trials that included both ICS and the alternative controller, LTRA, in order to obtain estimates for the inputs. We assumed all subjects have persistent asthma with a 1% prevalence of a prior history of hospitalization for asthma, that all of the subjects are between the ages of 18 and 35 years, and that 25% of the population are smokers [21]. We chose a young adult population with a 10-year time horizon because healthcare utilization changes for older adults with asthma who may also have coexisting chronic obstructive pulmonary disease.

Estimates suggest that 10–30% of ICS users are nonresponders [4,8]. For our base case analysis, we made the conservative assumption that 10% of asthma patients are ICS nonresponders. Furthermore, because of preliminary data that suggest 31% of patients who are taking an ICS have LTRA added on to ICS, we assumed that in a population of asthmatics, if 10% are ICS nonresponders, 3% (approximately 31% of the 10% of
nonresponders) of the total population, would be clinically detected. Thus, in current practice, very few ICS nonresponders are identified.

**Acute event incidence**

The rate of acute events, including ED visits and hospitalizations were incorporated using retrospective studies. The logistic relationship which was estimated and included in the model has been previously published [18].

**Pharmacogenomic test**

We made conservative assumptions for the pharmacogenomic test using our knowledge of the prototype pharmacogenomic test that has been developed [14]. Although a pharmacogenomic test for response to ICS is under active development, the test is not currently available for clinical use. This pharmacogenomic test is reported to have a sensitivity of 84% and specificity of 98% [30]. In order to estimate the cost of the test, we met with developers of pharmacogenomic tests who estimated the costs of the prototype pharmacogenomic test. The developers determined that the test will range from $500–1000 once it goes into production and this would include the professional or lab cost of actually administering the test [REHM H, FUNKE B, FARWELL L, PERS. COMM.]. For the base case, we assumed a cost of $500 which was on the low range because genomic technologies are decreasing in price.

**Costs**

Using the wholesale price [31], we calculated an overall mean cost for ICS and LTRA. We used unpublished data from Harvard Vanguard Medical Associates in order to determine the percentage of each brand of ICS that is dispensed. While accounting for each brand of ICS, we calculated an overall mean cost per month for ICS of $136.54 by taking into account the percentage of each brand of ICS that is dispensed. The cost of LTRA per month was $124.99, while taking into account what percentage of each brand of LTRA is dispensed.

Baseline monthly chronic care costs (medications, routine office visits, laboratory testing) were drawn from published studies [32–39] and adjusted to reflect US 2012 dollars by using the Consumer Price Index [32]. Acute event costs included $105 for non-ED urgent care visits, $2162 for ED visits and $40,135 for hospitalizations [32].

**Quality of life**

We used published preference weights collected for the Asthma Policy Model via direct utility assessments using the time tradeoff elicitation technique [40]. The relationship between FEV1% predicted and preference scores was estimated using ordinary least squares regression [40].

**Sensitivity analysis**

We conducted threshold analyses of variables, including the sensitivity of the pharmacogenomic test, the effectiveness of treatment with ICS and LTRA on FEV1% predicted and the proportion of the population who are responsive to ICS. To account for uncertainty associated with the data on cost and outcomes, we utilized multivariate probabilistic sensitivity analysis by using Monte Carlo simulation modeling to present
uncertainty ranges for benefits and costs. The Monte Carlo simulation drew values for each input parameter and calculated expected cost and benefits in QALYs for each arm of the model. Input parameters included: proportion of steroid responders, change in probability for outcomes for the medications, cost of the test and sensitivity of the test. This process was repeated 10,000-times to give a range of all expected cost and effectiveness values using @Risk.

Results

Clinical detection strategy

For patients with persistent asthma receiving ICS, the model predicts a population average of 0.0023 hospitalizations, 0.0041 ED visits and 0.0174 urgent care visits per patient per year (undiscounted). Based on our model, over a 10-year horizon, patients age 18–35 years are expected to live an average of 9.47 years (8.20 discounted life-years) with virtually all deaths attributable to nonasthma-related causes. Adjusted for both quality of life and the time value of outcomes, this equates to 7.1 discounted, QALYs. Discounted, asthma-related costs are expected to total $51,900 per patient over 10 years.

Pharmacogenomic testing strategy

Under baseline assumptions, use of pharmacogenomic testing with a similar rate of hospitalizations of 0.0023 per patient per year slightly decreased rate of ED visits to 0.0040 per patient per year, and slightly decreased urgent care visits to 0.0171 per patient per year (undiscounted; Table 2). While the test does not affect life expectancy over the 10-year planning horizon, quality-adjusted survival decreases to 7.1 QALYs. With the addition of pharmacogenomic testing, discounted, asthma-related costs rose to $50,200 per patient over a 10-year time period. For the pharmacogenomic tests characteristics (sensitivity 84% and specificity 98%), testing resulted in lower costs but similar QALYs; net discounted costs of $1735.

Sensitivity analyses

In sensitivity analyses, assumptions of key parameters were varied over plausible ranges (Table 1). The cost and sensitivity of the pharmacogenomic test and the relative effectiveness of the two therapies had the greatest impact on the net discounted costs and QALYs. Regardless of the cost of the test, we found that testing was cost-saving.

At a test sensitivity of 84%, the net benefits were noninferior to no testing while being cost-saving. If the sensitivity of the test was greater than 80% while specificity was 98% or if the specificity of the test was greater than 90% while sensitivity was 84%, testing had positive net benefits while still being cost-saving.

If the proportion of nonresponders increased to 15%, the pharmacogenomic test would be cost-saving at $2500 and the incremental improvement of net discounted QALYs would be 0.0004 for pharmacogenomic testing compared with empiric treatment.
Effectiveness of therapy

Increase in FEV1% predicted for ICS—We conducted sensitivity analyses using the high and low estimates of the improvement in FEV1% predicted for patients using ICS, based on the range of the effectiveness of ICS found in the literature. The testing strategy is cost-saving compared with the status quo when the effectiveness (increase in FEV1% predicted) of ICS was 12–40% while keeping the effectiveness of LTRA therapy constant. If the improvement in FEV1% predicted is 30% or lower, the net discounted QALYs show improvement (QALYs 0.0018 or greater). Threshold analysis suggests that if the medication used in the empiric treatment strategy were less effective such that the increase in FEV1% predicted for treatment with ICS were 30%, compared with our base case assumption of 36%, the pharmacogenomic testing strategy would be cost-saving and confer improved QALYs.

Increase in FEV1% predicted for LTRA—If the effectiveness (increase in FEV1% predicted) for an alternate controller medication was increased to 25% from the baseline of 21%, the CER for the pharmacogenomic testing strategy would continue to be cost-saving but would also confer improvement in QALYs.

Multivariate probabilistic sensitivity analysis

The results of the uncertainty simulations are presented in a cost–effectiveness plane (Figure 3), which shows the quadrants of cost differences plotted against benefit differences (improvement in QALYs). Figure 3 shows that all iterations of the intervention fell in the cost-saving portion, and the net discounted benefits were positive right of the vertical line. Overall, 100% of iterations were cost-saving, 49.4% led to a net gain in health.

Discussion

Our study found that pharmacogenomic testing for asthma is potentially cost-saving and is noninferior in improving health compared with no testing. Future improvements in test performance and the availability of treatment alternatives could make pharmacogenomic testing an attractive and cost-effective option. Pharmacogenomic testing could be considered acceptable in terms of improving benefits if the sensitivity of the pharmacogenomic test is 90% or higher or an alternative medication is developed that has an effectiveness (increase in% predicted FEV1) similar to ICS.

In our analysis, pharmacogenomic testing to predict response to ICS is cost-saving but does not reap significant improved benefits, assuming the pharmacogenomic test costs $500 and the sensitivity of the test is 84% and specificity is 98%. This scenario could be adopted as money saved from the pharmacogenomic testing strategy could be reinvested to improve QALYs, given both strategies resulted in similar QALYs. The increase in quality of life garnered from placing patients on an appropriate controller medication in the testing strategy arm is countered by the decreased quality of life associated with a less than perfect test that causes providers to change patients from ICS to the alternative medicine, LTRA, when the patient could have responded to ICS. Three possibilities could reap improved QALYs and make the pharmacogenomic testing strategy more appealing. First, a test with higher
sensitivity would reap higher QALYs and would still be cost-saving. Secondly, a different medication that has better efficacy than LTRA, would also reap improved QALYs. Third, in real-life populations, LTRA may be just as effective as ICS; under this scenario, pharmacogenomic testing would be both cost-saving and reap higher QALYs [41]. The inputs used in this analysis were all based on randomized clinical trials which report on efficacy.

As pharmacogenomic test developers refine such tests and policy makers decide whether to adopt pharmacogenomic tests, they need to take into account important tradeoffs. Our scenario of a pharmacogenomic test that is cost-saving and reaps similar benefits is likely to be attractive. Even if the pharmacogenomic test scenario resulted in slightly decreased QALYs, it could be accepted because it has been observed that consumers’ willingness to accept monetary compensation to forgo a benefit is greater than the willingness to pay for the same benefit [42,43]. One potential reason that willingness to accept could be higher than willingness to pay could be dependent on availability of substitute commodities [42]. In our case, patients might be willing to accept a lower cost but not having higher benefits with LTRAs at lower cost with the pharmacogenomic testing scenario because many asthma management alternatives exist, including rescue medications such as albuterol, additional controller medications and other self-management methods. Furthermore, adoption of pharmacogenomic testing is plausible as adherence to controller medications could increase if patients feel more confident that they are taking a medication that they respond to.

A few limitations to this study deserve mention. Perhaps most notable is that this analysis is based on a model and is not based on a prospective clinical trial; however, conducting a clinical trial comparing empiric treatment to pharmacogenomic testing would not be feasible because such tests are not yet available. Even if the pharmacogenomic tests were available, the financial cost of a trial would be insurmountable if subjects are followed over a 10-year period. A model-based approach permits the extrapolation of costs and health effects beyond the time horizon of a single clinical study. Also, this type of model-based approach can be used to anticipate the results of new clinical investigations and to help guide developers of pharmacogenomic tests and asthma medications in their efforts. In addition to relating biological and clinical information, this type of model can provide quantitative insight into the relative importance of different components of each strategy and investigate how results will change if values of key parameters are affected. By identifying the most important sources of uncertainty, a model can be used to help prioritize and guide efforts in pharmacogenomic test development. Furthermore, another limitation is that the pharmacogenomic tests for inhaled steroid response are not available currently. Nevertheless, pharmacogenomic tests are under active development [11–14] and conducting such an analysis can help inform the developers that such tests are likely to be cost-saving, but the tests need to have certain levels of sensitivity and specificity. A limitation of the Asthma Policy Model is that there may be concern that FEV1% predicted does not fully predict prognosis. However, based on our previous analyses, we found that FEV1% predicted is associated with symptoms, acute exacerbations, costs and quality of life. Anecdotally, we have seen few providers take their patients off of ICS for suspected non-response; thus we felt this assumption was reasonable. In addition, our analysis did not account for negative adverse events related to use of ICS (e.g., diminished bone mineral
density, cataracts); including these negative adverse events would have made the results more favorable toward pharmacogenomic testing. Our model also did not account for nonresponse to the alternative medication, LTRAs, but previous studies have suggested adherence to LTRAs is higher because it is an oral medication [44].

**Conclusion**

In conclusion, contingent upon future improvements in test performance and/or the availability of treatment alternatives, pharmacogenomic testing for response to ICS in asthma patients can fall within an accepted value range for interventions within the US. Pharmacogenomic testing for inhaled steroid response is potentially cost-saving and is noninferior to no testing.

**Future perspective**

With the active development of controller medications for asthma, we expect that the availability of treatment alternatives will support the need for pharmacogenomic testing. In addition, with the decreasing costs related to technology and genetic testing, we predict that pharmacogenomic testing will become more and more cost-saving.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

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Papers of special note have been highlighted as:

• of interest;

•• of considerable interest


[Compared the relative beneficial and systemic effects for two inhaled corticosteroids and found that significant intersubject variability in response occurred with both inhaled corticosteroids]


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Executive summary

- Pharmacogenomic testing for asthma is potentially cost-saving and reaps similar benefits as no testing.

- Future improvements in test performance and the availability of treatment alternatives could make pharmacogenomic testing an attractive and cost-effective option.

- Pharmacogenomic testing could be considered acceptable in terms of improving benefits if the sensitivity of the pharmacogenomic test is 90% or higher or an alternative medication is developed that has an effectiveness (increase in % predicted FEV1) similar to inhaled corticosteroids.

- A test with higher sensitivity would reap higher quality-adjusted life-years and would still be cost-saving.

- A new asthma medication that has better efficacy than leukotriene antagonists would also reap improved quality-adjusted life-years while being cost-saving.

- As pharmacogenomic test developers refine such tests and policy makers decide whether to adopt pharmacogenomic tests, they need to take into account important tradeoffs. Our scenario of a pharmacogenomic test that is cost-saving and reaps similar benefits is likely to be attractive.
Figure 1. Clinical detection strategy
This figure demonstrates the probabilities related to the status quo empiric treatment strategy. Currently, we estimated that 90% of a population of patients with persistent asthma are ICS responders and are treated with ICS. Of the 10% of the population of patients with persistent asthma who are ICS nonresponders, we estimated that 3.1% are clinically detected and treated with ICS and LTRAs and 6.9% are not clinically detected and continue on ICS. ICS: Inhaled corticosteroids; LTRA: Leukotriene antagonist.
Figure 2. Pharmacogenomic testing strategy
This figure demonstrates the various probabilities related to the proposed pharmacogenomic test. Of the total population of patients with persistent asthma, 75.6% are true positives and are treated with ICS, 14.4% are false negatives and are treated with LTRAs, 0.2% are false positives and are treated with ICS and 9.8% are true negatives and are treated with LTRAs. ICS: Inhaled corticosteroids; LTRA: Leukotriene antagonist; NR: (True) nonresponder; P: Probability; R: (True) responder; TNR: Test nonresponder; TR: Test responder.
Figure 3. Cost–effectiveness plane of multivariate probabilistic sensitivity analyses
All of the iterations were cost-saving. This figure shows the lower two quadrants of cost
differences plotted against benefit differences (improvement in QALYs). Iterations to the
right of the vertical line show improvement in benefit as measured in QALYs. Iterations to
the right of the vertical line represent when pharmacogenomic testing is less costly and more
effective. Iterations on the left of the vertical line represent the number of iterations in which
the intervention is less costly and less effective.
QALY: Quality-adjusted life-year.
### Table 1

Model parameters for base case and sensitivity analysis.

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<th>Attribute</th>
<th>Baseline assumption</th>
<th>Range for sensitivity analysis</th>
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<td>Cost of the pharmacogenomic test ($)</td>
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<td>25-1000</td>
<td>Expert opinion</td>
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<td>Sensitivity of the test (%)</td>
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<td>84-97</td>
<td>[14]</td>
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<tr>
<td>Specificity of the test (%)</td>
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<td>Proportion of population who are nonresponders (%)</td>
<td>10</td>
<td>10-18</td>
<td></td>
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<tr>
<td>Increase in FEV1% predicted for inhaled corticosteroids (ICS) (%)</td>
<td>36</td>
<td>12-40</td>
<td>[22,23]</td>
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<tr>
<td>Increase in FEV1% predicted for alternative medication (LTRA) (%)</td>
<td>21</td>
<td>20-36</td>
<td>[22,23]</td>
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<tr>
<td>Days with symptoms for ICS (%)</td>
<td>61</td>
<td>-</td>
<td>[22-27]</td>
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<td>Days with symptoms for alternative medication (LTRA) (%)</td>
<td>75</td>
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<td>-</td>
<td>[23,26-28]</td>
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<tr>
<td>Nights with symptoms for alternative medication (LTRA) (%)</td>
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<td>-</td>
<td>[23,26-28]</td>
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<td>Adherence to ICS † (%)</td>
<td>100</td>
<td>52-100</td>
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ICS: Inhaled corticosteroids; LTRA: Leukotriene antagonist.

† We assumed LTRA adherence remains at 100%.
Table 2

Base case analysis over 10 year time horizon.

<table>
<thead>
<tr>
<th>Asthma-related events (per 100 person-years)</th>
<th>No test</th>
<th>Pharmacogenomic test</th>
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<tr>
<td>Hospitalizations</td>
<td>0.23</td>
<td>0.23</td>
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<tr>
<td>ED visits</td>
<td>0.41</td>
<td>0.40</td>
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<tr>
<td>Urgent care visits</td>
<td>1.74</td>
<td>1.71</td>
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<tr>
<td>Discounted QALYs</td>
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**Costs, discounted**

| Chronic asthma cost, without drug ($)       | 21,457  | 20,408               |
| Acute asthma cost ($)                       | 924     | 911                  |
| Genetic test cost ($)                       |         | 500                  |
| Total cost ($)                              | 51,942  | 50,208               |

**Cost-effectiveness ratios**

<table>
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<th>Cost per QALY gained ($/QALY)</th>
<th>Dominated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost per SFD gained ($/SFD)</td>
<td>Dominated</td>
</tr>
</tbody>
</table>

ED: Emergency department; QALY: Quality-adjusted life-year; SFD: Symptom-free day.

† All cost-effectiveness ratios are incremental, compared with the next-least-costly, undominated alternative. Reported ratios may not be precisely equal to the ratio of costs and effects due to rounding.