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The economics of precision health: preventing air pollution-induced exacerbation in asthma

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Take home message:

Glutathione-s-transferase genotyping to determine the use of preventive asthma medication in the face of air pollution is cost-effective in our model. Precision prevention in the setting of common environmental exposures may be used in other contexts.

ABSTRACT

Background: The demonstrable value of precision medicine, in the context of common environmental exposures, has scarcely been explored. This study evaluated the cost-effectiveness of a preventive personalized intervention to reduce the adverse effect of air pollution in the context of asthma.

Methods: A decision-analytic model was used to conduct a cost-utility analysis of prevention interventions in case of acute exposure to air pollution in mild asthma. Three different strategies, as follows, were compared: no preventive intervention, precision health strategy based on information from genotype testing – followed with treating high-risk patients, and prescribing additional medication to all mild asthmatics as a preventive intervention. The costs and quality-adjusted life years (QALYs) in the base case and alternative scenarios were obtained through probabilistic analysis.

Results: The results showed that the precision prevention intervention (anticipatory intervention for asthmatics, guided by relevant genetic abnormality, in the face of acute air pollution) is a cost-effective strategy compared to no such intervention, with an incremental cost-effectiveness ratio of \$49,555 per QALY. Furthermore, this strategy is a dominant strategy compared to an intervention that prescribes medication indiscriminately to all asthmatics.

Conclusion: The incorporation of genomic testing, to stratify risk of asthmatics to pollution-driven exacerbations, and then tailoring a preventive intervention accordingly, may be cost-effective relative to untailored methods. These results lend plausibility to the use of precision medicine for limiting asthma exacerbation in the context of air pollution and, potentially, other exposures.

INTRODUCTION

Precision medicine, or more broadly precision health, is the approach in which preventive measures and/or health care interventions are personalized and tailored to each individual's characteristics. These traits are believed to reflect risks and/or response to interventions, and effectively harnessing this model has long been a goal of health care. Indeed, over recent years, development in pharmacogenomics has made such targeted medicine more available. However, evidence for the value of such approaches, particularly in the context of common environmental exposures[1], is required to support their implementation. Also, in the face of limited health care resources, the decision to allocate resources to an intervention is associated with 'opportunity costs' of not being able to allocate resources to other ones. As such, in addition to clinical benefit, economic evaluation needs to be considered to determine when personalized medicine can be applied[2]. A comprehensive analysis demonstrating the 'value for money' potential of using pharmacogenomics methods to guide health care interventions can support informed decision-making in the adaptation of these technologies in clinical practice and prioritizing research. This study proposes a modelling framework for predicting the costs and effectiveness of personalized health in the context of genotyping for the prevention of asthmatics exposed to air pollution.

Asthma is one of the most common chronic diseases worldwide, including in Canada and British Columbia (BC), where it poses a significant economic burden[3, 4]. Asthma is a multifactorial disease whose risk and burden is a complex function of both genetic and environmental factors. Multiple studies have shown that exposure to air pollution can impact lung function and worsen asthma symptoms[5–7].

In recent years, BC has experienced longer and more severe fire seasons and more frequent forest fires, which severely impact air quality. The effect of forest-fire-generated smoke exposures in BC and its adverse effect on public health, including an increase in physician visits and hospital admissions for respiratory and cardiovascular diseases, has been demonstrated[8–12]. However, not all asthmatics have a similar risk of being affected by such exposures. For example, there is evidence showing that glutathione S-transferases (GSTs) genes can modify the impact of air pollution on lung function as well as the risk and severity of asthma and allergy[13–17].

In this context, designing personalized preventive therapy for those exposed to air pollution, based on genotyping, can potentially improve quality of life and save costs. To inform such personalizing of care, we conducted a cost-effectiveness analysis to predict the costs and benefits of proposed preventive strategies including personalized preventive intervention to reduce the adverse effect of known air pollution events such as a forest fire in asthmatics with mild disease. While the modelling framework developed and utilized in this study was based on data from BC, it can be used in other settings to analyze cost-utility of personalized preventive intervention in settings of acute air pollution and, with model adaptation, other exposures.

METHODS

In reporting the results of this study, we have adhered to Consolidated Health Economic Evaluation Reporting Standards (CHEERS)[18].

Model Overview

A decision-analytic model was used to conduct a cost-utility analysis of prevention interventions in case of acute exposure to air pollution, such as wildfire smoke in seasonal forest fires, in mild

asthma. The schematic diagram of the simulation model is illustrated in Figure 1. Key parameters of the model, including unit costs, utility weights, and main parameters for risk and prevalence of the asthma cohort are presented in Table 1.

Table 1. Model inputs.

Parameter	Mean	Distribution	Reference
Probabilities			
Prevalence of asthma	323,500	Fixed	[19]
Percentage of mild asthma	67.1%	Fixed	[4]
Prevalence of genetic abnormality (GSTT1 null or GSTM1 null or GSTP1 Ile105)	25%	Fixed	[20, 21]
Risk of additional exacerbation in asthmatics with GA, without preventive intervention	55%	Beta (42.7, 34.9)	[22, 23]
Risk of additional exacerbation in asthmatics with GA, with preventive intervention	5%	Beta (91.2, 1732.5)	[22, 23]
Risk of additional exacerbation in asthmatics without GA (with or without preventive intervention)	0	Fixed	
Unit Costs			
Advair 500/50 BID (per month)	\$74.7	Fixed	[19]
Exacerbation without hospitalization	\$126	Gamma (96.04, 0.76)	[24] (Converted to 2018 CAD)
Exacerbation requiring emergency room visits	\$575	Gamma (96, 0.17)	[24] (Converted to 2018 CAD)
Exacerbation requiring hospitalizations	\$6440	Gamma (96, 0.014)	[24] (Converted to 2018 CAD)
Genetic testing	109.43	Fixed	[25] (Converted to 2018 CAD)
Utilities			
Exacerbation without hospitalization	0.57	Beta (0.51, 0.38)	[26]

Exacerbation requiring emergency room visits	0.45	Beta (0.36, 0.45)	[26]
Exacerbation requiring hospitalizations	0.33	Beta (0.15, 0.30)	[26]

We employed a probabilistic analysis to predict costs and QALYs associated with each decision, and incorporated uncertainty in the evidence base. The model was developed using R statistical software version 3.4[27]. The analysis was from a Canadian public health care payer perspective with a one-year time horizon. Due to the one-year horizon, discounting was not applied to either costs or benefits.

The target population comprised patients with mild asthma which, according to the Global Initiative for Asthma (GINA) guidelines, is defined as asthma that is well controlled with as-needed reliever medication alone, or with low-intensity controller intervention such as low-dose ICS, leukotriene receptor antagonists, or cromolyn[28].

The model was developed based on the following assumptions: a) exposure to air pollution can lead to an asthma exacerbation (including those requiring an emergency room visit) in asthmatics with a genetic abnormality (GA); b) prescribing additional medication as a prevention therapy decreases the risk of such exacerbation; c) asthmatics with mild asthma who are identified as normal genotype will carry no extra risk of exacerbation due to air pollution.

The modelled intervention is prescribing additional Inhaled Corticosteroids (ICS) + Long-Acting Beta-Agonists (LABA) (Advair 500/50 BID) for two months each summer. The intervention model begins at the start of the fire season (July 1st). Genetic abnormality was defined as having one of the following genotypes: GSTT1 null or GSTM1 null or GSTP1 Ile105Val. These were chosen based on their well-established influence on clinically relevant respiratory responses to

air pollution, including acute decrements in lung function and associated disease exacerbations[6, 7, 29, 14, 30].

We modeled and compared three different strategies:

- The first strategy is no preventive intervention (standard of care).
- The second strategy is the precision health strategy based on information from genotype testing. In this strategy, the preventive intervention (Advair 500/50 BID) is prescribed only to asthmatics with mild asthma who are identified as having a genetic abnormality in the genotype test.
- The third strategy includes prescribing additional medication (Advair 500/50 BID) to all mild asthmatics as a preventive intervention.

Unit costs

The costs of an asthma exacerbation were derived from a previous study[24]. We used a weighted average of the cost of exacerbation without hospitalization and exacerbation requiring emergency room visits. The cost of genotyping was based on published data[25]. Canadian costs were used directly where available. Otherwise, available US costs were converted to Canadian costs using a two-step approach: first, we applied the ratio of health care expenditure in US and Canada[31]; second, the consumer price index for health care was used to adjust costs to 2018 Canadian dollars (CAD).

Utility weights

Utility weights for different levels of exacerbation severity came from a study conducted in the UK[26]. A weighted average of utility weights for exacerbation without hospitalization and

exacerbation requiring emergency room visits was used in the model. Effectiveness was measured in terms of change in QALY loss.

Sensitivity and uncertainty analysis

In addition to the base case analysis, we conducted scenario analyses considering different modelling assumptions and investigated the effects of these assumptions. To address uncertainty around the value of input parameters included in the model and examine the impact of this uncertainty on the outcomes, we adopted a probabilistic approach in the base case and scenario analyses. In probabilistic analysis, input parameters are represented as distributions that reflect the level of uncertainty (e.g., constructed from the point estimate and confidence intervals from original studies). Monte Carlo simulation was then applied to propagate the uncertainty through the model. This technique uses random numbers to sample from the input data probability distributions. As such, this method of analysis allows quantifying the level of confidence in the output of the model. Following standard practice, gamma distributions were assigned to the costs, and the probabilities were drawn from beta distributions[32] .

Analysis

The expected values of costs and QALYs in the base case and all scenario analyses were obtained through probabilistic analysis from the Monte Carlo simulation. We ran the analysis 10,000 times, and each time different random values were selected for the inputs of the model, resulting in 10,000 sets of results from which the statistical output data are derived. Finally, we extrapolated these results to the entire population of BC to estimate the number of exacerbations that can be avoided using a preventive intervention was derived.

RESULTS

Base Case Analysis

The results of a sequential cost-utility analysis of comparing three strategies, including 1) No intervention, 2) preventive intervention only for asthmatics with GA, and 3) preventive intervention for all asthmatics, are presented in Table 2.

Table 2. The expected value of costs, QALY and incremental cost per QALY (base case) per one patient with mild asthma

Strategy	Costs (\$)	QALY loss	Sequential Incremental costs	Sequential Incremental QALY loss	Sequential Incremental Cost per QALY Gained
No intervention	42.13	0.0024			
Preventive intervention only for asthmatics with GA	150.58	0.00021	108.45	-0.00219	\$49,555
Preventive intervention for all asthmatics	153.2	0.00021	2.61	0	Dominated

*All the numbers are per asthmatic. QALY: quality-adjusted life-year.

No intervention compared to preventive intervention only for asthmatics with GA

Comparing no intervention with targeted therapy shows that using a preventive intervention only for the ones with GA is expected to cost more than no intervention (\$150.5 vs \$42) but it causes QALY gain (decrease in QALY loss from 0.0024 to 0.00021). The incremental cost-effectiveness ratio (ICER) was \$49,555 per QALY. At a willingness-to-pay threshold of \$50,000 per QALY, the personalized intervention is considered cost-effective (Table 2).

Results of comparing no intervention and treating only the asthmatics with GA are also presented in the cost-effectiveness acceptability curve (CEAC). CEAC shows the probability of the targeted intervention being cost-effective compared with no intervention across a range of willingness-to-pay thresholds.

As shown in CEAC (Figure 2) there is a 50% probability that the ICER would be less than \$50,000 per QALY and a 75% probability of the ICER being less than \$100,000 per QALY.

Preventive intervention for asthmatics with GA compared with preventive intervention for all asthmatics

As shown in Table 2, preventive intervention only for asthmatics with GA compared with preventive intervention for all asthmatics lowered cost for healthcare system (\$150 vs \$153) while the change in QALY was the same. As such, preventive intervention only for the ones with GA is a dominant strategy.

Population-level outcome

Considering the estimate of mild asthmatics in BC and the average prevalence of genetic abnormality (Table 1), we project that 27,093 extra pollution-induced exacerbations can be avoided in one year by using additional medication as a preventive intervention.

Scenario Analyses

We also conducted a series of scenario and sensitivity analyses to explore the impact of uncertainty around the value of the model's parameters and alternative assumptions on the outcomes of the model. To simplify reporting, for the scenario / sensitivity analyses, we compared the preventive intervention (intervention only for the asthmatics with GA) with no

intervention. The results are presented in Supplementary Table 1 and Figure 3 (tornado diagram). Tornado diagram illustrates graphically how variations in each input or assumption affect the outcome.

The sensitivity analysis that varied the prevalence of the genetic abnormality showed that results are sensitive to this parameter. When the prevalence of GA was increased to 45%, costs and QALY loss of both strategies went higher compared to the base case but ICER decreased to \$27,330 per QALY, which again indicates that preventive intervention for asthmatics with GA is cost-effective. However, with the lower prevalence of GA at 15%, costs and QALY loss were lower for both strategies, but the ratio of cost and effectiveness changed to \$82,894 per QALY and at a willingness-to-pay threshold of \$50,000 per QALY, it is not cost-effective to prescribe intervention for the asthmatics with GA compared to no intervention.

Results of analysis are also sensitive to the estimated risk of pollution-induced exacerbation in asthmatics with GA (without preventive intervention). We assumed this risk may vary based on some factors like level of exposure to air pollution. When the risk was increased to 65%, costs and QALY loss of no intervention strategy went higher compared to the base case, such that the suggested intervention remained cost effective (ICER of 38,528 per QALY). On the other hand, when the risk of exacerbation was assumed lower than the base case (45%), ICER was higher than the threshold (\$66,844 per QALY) and the suggested intervention was no longer cost-effective.

The cost of genetic identification also affects the results. When the cost of genetic testing is lower than the base case value, expected cost of the suggested strategy is decreased, which results in a lower ICER, thus the suggested intervention remains cost-effective. With the assumed cost of \$0 for the cost of genetic testing, the suggested intervention becomes a dominant

strategy compared to no intervention as the cost is lower and efficiency is increased (Supplementary Table 1). Similarly, the higher cost of genetic identification will increase ICER. Next, as is demonstrated in Supplementary Table 1, when the mean cost of exacerbation was lower compared to the base case, the ICER was higher and with the higher mean cost of exacerbation, and the ICER was lower compared to the base case which means the suggested intervention remains cost-effective (Supplementary Table 1).

DISCUSSION

To our knowledge, this study is the first to perform an economic evaluation of a specific application of precision health to preventing exacerbations of asthma. Importantly, we framed the analysis around a common scenario (exposure to air pollution in asthmatics) with broad public health relevance. The decision-analysis model employed in the current study provides a framework for the cost-effectiveness of preventing pollution-induced asthma exacerbations based on genotype testing. The model assessed the incremental cost-effectiveness ratio of preventive intervention strategies and compared these with the current standard of care (no personalized preventive intervention). The findings show that the suggested intervention (anticipatory intervention for the asthmatics with relevant genetic abnormality facing acute air pollution) is a cost-effective strategy compared to no such intervention. Furthermore, this strategy is a dominant strategy compared to an intervention that prescribes medication indiscriminately (without regard to genotype) to all asthmatics. A series of scenario analyses showed that these outcomes are most sensitive to the prevalence of genetic abnormality among asthmatics, risk of exacerbation in asthmatics with GA, and to the cost of genetic testing.

Our study has some limitations, which generally lead to a tendency to underestimate the benefits of a precision approach to prevention in our example. First, in the model we considered the risk

of one additional exacerbation in the context of increased air pollution exposure whereas in reality, pollution-related exacerbations can happen more than once in a year. Since effectiveness of the preventive intervention will increase along with the risk of multiple exacerbations, our method has therefore generated conservative results that may underestimate the benefits. Second, there is uncertainty around some of the key parameters of the model, such as the prevalence of genetic abnormality in the exposure population. In order to overcome this issue, we used probabilistic analyses and a series of scenario analyses to support the generalizability of our results. Even so, this approach still likely leads further to an underestimation of the benefit of preventive pharmacotherapy, because the true population includes those with more than one of the genetic abnormalities assessed. Multiple such abnormalities lead to increased susceptibility to pollution[6] and, accordingly, likely addition benefits from the preventive intervention, but we did not have sufficient data on population prevalence therein for modelling. Third, in the model, we have assumed that our target group of mild asthmatics don't develop an exacerbation requiring hospitalization; although exacerbations even in mild asthmatics can sometimes lead to hospitalization, we have again taken a conservative approach based on the likelihood that if a mild asthmatic were to develop an exacerbation requiring hospitalization, he/she would no longer fit the definition of mild asthma. Furthermore, as genotyping is inherently stable and so needs be done once, for subsequent years the ICER will be even more favorable. Finally, we have used July 1 as the start of the fire season, whereas it often starts considerably earlier (in which case the benefit of precision intervention would be enhanced). Collectively, this suggests that the precision health approach modeled may confer considerable cost-effectiveness benefit even beyond that shown in our primary analysis. That said, our analysis represents a proof-of-

principle that is not intended for direct decision-making without further work to refine and update the parameters inputted into the model.

CONCLUSION

Our findings provide evidence that the incorporation of genomic testing, to stratify risk level of asthmatics to pollution-driven exacerbations, and tailoring a preventive intervention accordingly, may be cost-effective relative to usual care. The results inform and motivate the design of programs that use a precision health framework to limit asthma exacerbation in the context of acute air pollution excursions and, furthermore, serve as a model of other genotype-driven preventive strategies for a range of common exposures.

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FIGURE LEGENDS

Figure 1. Schematic diagram of the model. GA: Genetic Abnormality.

Figure 2. Cost-effectiveness acceptability curve comparing no intervention with targeted intervention.

Figure 3. Scenario analysis (tornado diagram). ICER: Incremental Cost-Effectiveness Ratio.
QALY: Quality-Adjusted Life-Year.

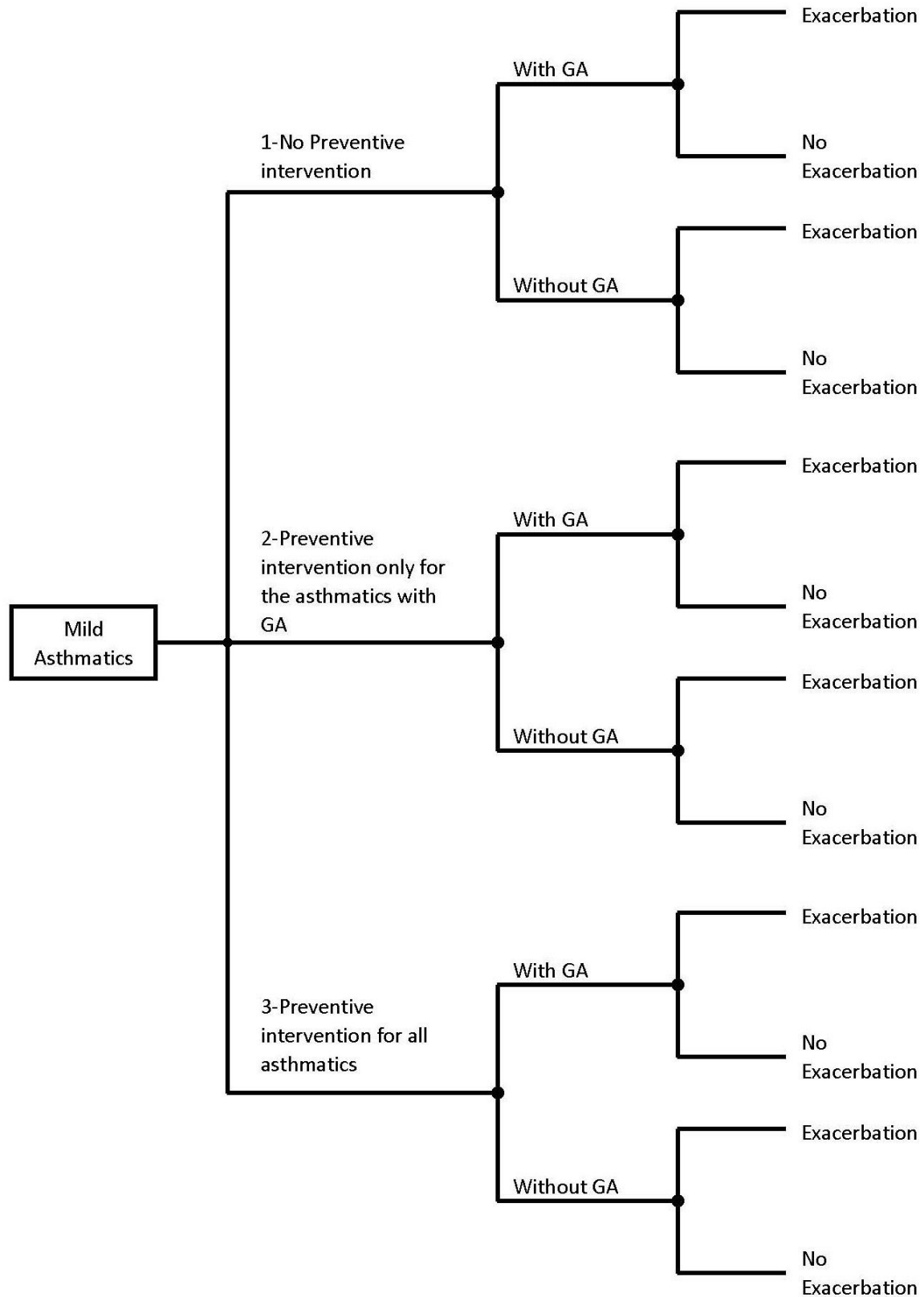


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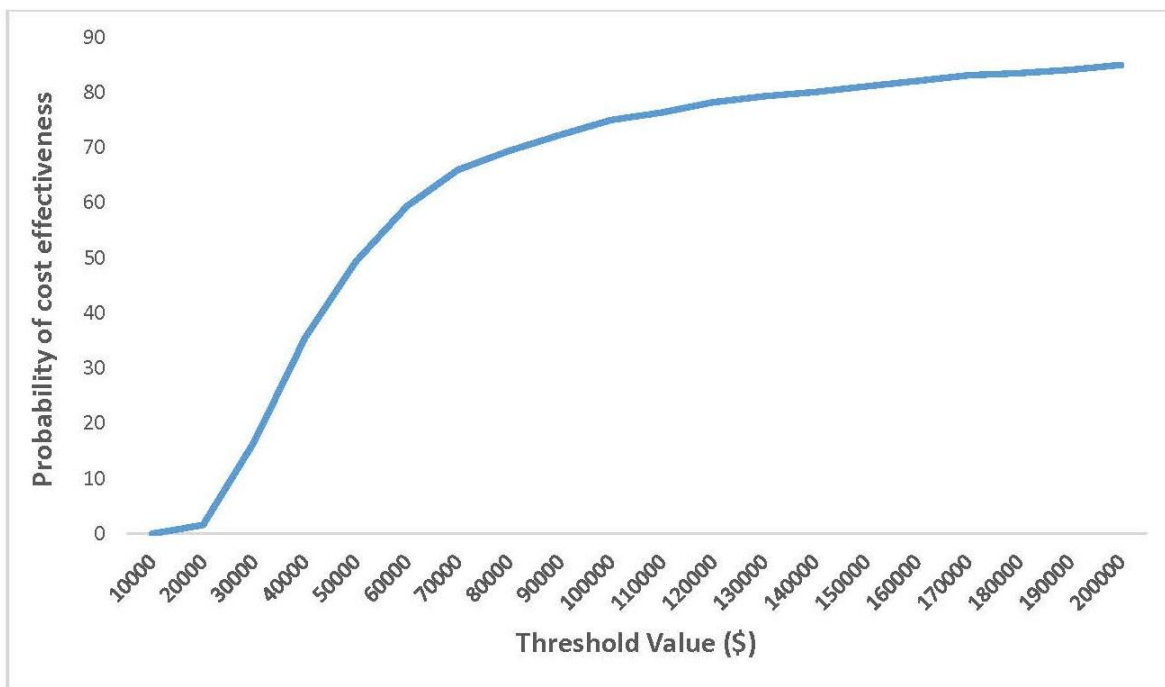


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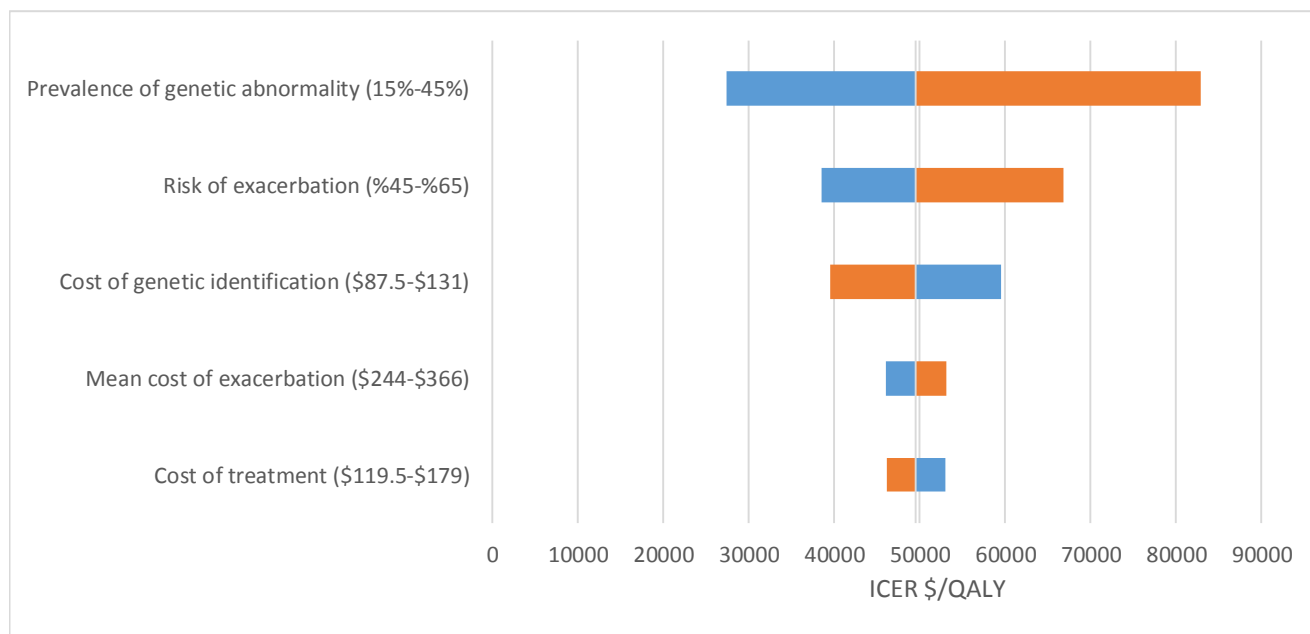


Figure 3. Scenario analysis (tornado diagram). ICER: Incremental Cost-Effectiveness Ratio. QALY: Quality-Adjusted Life-Year.

Scenario	No intervention		Preventive intervention only for GA		Incremental Cost per QALY (\$/QALY)
	Cost (\$)	QALY loss	Cost (\$)	QALY loss	
Prevalence of genetic abnormality: %15	25	0.0014	134	0.00013	82,894
Prevalence of genetic abnormality: %45	76	0.0043	183.5	0.00039	27,330
Cost of genetic identification: \$0	42	0.0024	41	0.00021	Dominant Strategy
Cost of genetic identification: \$50	42	0.0024	91	0.00021	22,396
Risk of exacerbation in asthmatics with GA, without preventive intervention: %65	50	0.0028	151	0.00021	38,528
Risk of exacerbation in asthmatics with GA, without preventive intervention: %45	34	0.0020	151	0.00021	66,844
Cost of genetic identification: \$87.5	42	0.0024	129	0.00021	39,554
Cost of genetic identification: \$131	42	0.0024	172	0.00021	59,557
Mean cost of exacerbation : \$244	34	0.0024	150	0.00021	53,060
Mean cost of exacerbation : \$366	50.5	0.0024	151	0.00021	46,052
Cost of treatment: \$119.5	42	0.0024	143	0.00021	46,142
Cost of treatment: \$179	42	0.0024	158	0.00021	52,969

Supplementary Table 1: Results of scenario analyses