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Cost-Effectiveness of a Multi-Stage School-Based Asthma Case Detection Program in an Urban School System

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ABSTRACT

Asthma is a common chronic condition of childhood that results in frequent exacerbations associated with school absences, emergency department visits, and hospitalizations. School-based case detection to identify children with undiagnosed or poorly controlled asthma may reduce asthma morbidity; however, it is uncertain whether the resources consumed by case detection are justified by the expected improvements in health outcomes.

Cost-effectiveness analysis using a decision tree with multiple Markov models to simulate asthma-related costs and outcomes in primarily urban, low-income, African-American, elementary-age school children is performed. Modeled health states include symptom free, symptomatic, and exacerbation recovery days, as well as emergency department visits and hospitalizations. The time horizon is one year divided into 365 cycles. Two questionnaire only and two multi-stage interventions incorporating spirometry only or spirometry and exercise testing are evaluated. The analysis is performed from the societal perspective and is reported in 2006 dollars per quality adjusted life year (QALY) gained.

The multi-stage with spirometry and exercise testing (MSwET) intervention is the most cost-effective intervention, with an incremental cost-effectiveness ratio (ICER) of $107,200 per QALY. Probabilistic sampling demonstrates that 90% of the observed ICERs fall between $47,400 and $155,500 per QALY. Ninety-five percent of the

uncertainty observed in sensitivity analysis is due to the estimation of the quality of life preference weight for the symptomatic health state and asthma prevalence. In its most favorable valuation, the symptomatic state preference weight yields an ICER of $40,900 per QALY.

School-based asthma case detection in the modeled population is unlikely to be cost-effective at $50,000 per QALY; however, if the symptomatic state preference weight is significantly lower or the asthma prevalence is significantly higher than estimated, this finding may not hold. The MSwET intervention, which incorporates spirometry and exercise testing with a symptom-based questionnaire, maximizes true positive results, minimizes false positive results, and is consistently the most cost-effective intervention. Limitations include reliance on secondary data, uncertainty regarding quality of life weights for clinically relevant asthma health states, and limited knowledge of actual health outcomes experienced by children newly diagnosed with asthma by case detection.

DEDICATION

This work is dedicated to my wife, Lynn. Without fail, she was a steadfast supporter, confidant, editor, mentor, and friend. Without her, this work would not have been possible.

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LIST OF ABBREVIATIONS

ACT	Asthma Control Test
ASFD	asthma symptom free day
ATS	American Thoracic Society
AWP	average wholesale price
BQ	Broad Questionnaire
CAMP	Childhood Asthma Management Program Research Group
CDC	Centers for Disease Control and Prevention
CEA	cost-effectiveness analysis
CPI	consumer price index
DWAS	days without asthma
ED	emergency department
FTE	full-time equivalent
ICER	incremental cost-effectiveness ratio
ICS	inhaled corticosteroids
LABA	long-acting beta-agonist
LOS	length of stay
LTRA	leukotriene receptor antagonist
MCO	medical care organization
MDI	metered dose inhaler
MSwET	Multi-stage with Exercise Testing

MSwS	Multi-stage with Spirometry
NAEPP	National Asthma Education and Prevention Program
NHIS	National Health Information Survey
NHLBI	National Heart, Lung and Blood Institute
NMB	net monetary benefits
NQ	Narrow Questionnaire
PAHOM	Pediatric Asthma Health Outcome Measure
PEFR	peak expiratory flow rate
QALD	quality-adjusted life days
QALY	quality-adjusted life year
RCT	randomized controlled trial
ROC	receiver operating characteristics
SABA	short-acting beta-agonist
SAD	school absence day
WTP	willingness-to-pay

INTRODUCTION

Asthma is an inflammatory disease of the small and medium airways that leads to episodic exacerbations characterized by shortness of breath, coughing, and wheezing. There is no cure for asthma, but appropriate treatment allows most patients to achieve excellent symptom control and to reduce the frequency of exacerbations.[1] Approximately 20 million Americans including 6.5 million children (8.9% of all children 0-17 years) have a current diagnosis of asthma.[2] In the U.S., asthma-related expenditures for school-age children exceed two billion dollars a year and are almost equally divided between direct and indirect costs. The majority of indirect costs are attributable to lost caregiver income related to approximately 6 million asthma-related school absence days (SAD) annually. Optimizing asthma care in school-age children could potentially reduce direct and indirect medical expenditures by 20% and 50%, respectively.[3]

The adoption of widespread school-based asthma screening to identify children with undiagnosed and poorly controlled asthma is one proposal to improve care for children with asthma. Numerous investigators report that a significant proportion of children with asthma in urban school systems are undiagnosed[4-12] or poorly controlled.[5] These reports are based on successful demonstrations of limited school-based asthma screening via questionnaire alone[4,5, 9-11,13] or questionnaire augmented by spirometry and/or exercise testing.[6-8,12] These localized successes lead some asthma experts to recommend widespread adoption of school-based asthma screening as one step to reduce asthma-

related morbidity. Important screening proponents include the American College of Asthma, Allergy, and Immunology and the Allergy and Asthma Network Mothers of Asthmatics.[14]

The widespread adoption of school-based asthma screening is not universally supported. Opponents contend that the lack of a pre-clinical phase of asthma, the limitations of available screening programs, and the lack of universal access to high quality asthma care are likely to offset any potential benefits realized from screening. The lack of a pre-clinical, asymptomatic phase and the inability of early treatment to modify the natural history of disease make asthma screening inconsistent with previously established principals of population-based screening outlined by the World Health Organization (as cited by Boss).[15] Because of these factors, "screening" is really "case detection[1]" where the goal is to identify disease that is already manifest and perhaps even previously diagnosed. In addition, opponents assert that barriers within the U.S. health care system limit access to and adherence with guideline-concordant asthma care and these barriers are likely to preclude improved asthma outcomes for children identified by screening.[16,17] A recent report prepared by the Behavioral Science and Pediatric Assemblies of the American Thoracic Society (ATS)[16] unequivocally states, "At this time, the wide scale adoption of asthma case detection programs is unwarranted given the lack of evidence of improvement in health outcomes as a result of case detection" (p.139). This recommendation echoes a similar conclusion reached by the Centers for Disease Control and Prevention (CDC).[15]

[1] For the reader, the terms screening and case detection are considered synonymous unless specifically noted otherwise.

However, the ATS report[16] notes, "Limited case detection programs may be appropriate in areas where there is a high prevalence of undiagnosed/under-treated asthma and where newly identified patients have access to consistent, high-quality asthma care" (p. 139). This allows for a potential compromise between the two positions. If these factors can be identified and estimated, cost-effectiveness analysis (CEA) is one methodology that can make a summary judgment regarding the circumstances where the benefits of screening outweigh its costs. Torrance et al[18] state, "Broadly speaking, the goal of cost-effectiveness analysis is ... to inform a policy maker or others involved in health care decisions about the value of a particular health care program" (p.55). CEA "can investigate the magnitude of costs that an intervention can generate and/or the level of effects that are necessary in order … [to] determine the thresholds with regard to costs and effects that the intervention must achieve to be acceptable" (p.56). The acceptability of CEA to evaluate asthma screening is reflected by the ATS report[16] which states, "Before this panel can recommend wide-scale case detection … The cost-effectiveness of asthma case detection programs must be examined" (p.139).

The underlying theory that supports the use of CEA in this manner is *welfare economics,* which provides a means by which resource allocation decisions can be made to maximize societal well-being by maximizing the aggregated individual preferences for goods, services, and health states.[19] Given this framework, CEA can help decision makers determine when the benefits of a specific health initiative outweigh its costs. Hunick et al[20] note that CEA assumes that resources are constrained, such that "it is not possible to provide all beneficial health services to all people" (p.249). Weinstein and Stason, as cited by Garber et al[19], add that "for any given level of resources available, society …

wishes to maximize the total aggregate health benefits conferred" (p.27). CEA can consider the benefits gained from the screening and also the opportunity costs of foregoing some other initiative. Therefore, CEA is well-suited to inform the decision regarding the adoption of school-based screening.

Even though CEA is recommended by the ATS report[16], there are several other closely related economic analytic techniques that might also be appropriate, including cost-minimization, cost-consequence, and cost-benefit analysis. A brief mention of their strengths and weakness is provided to justify the selection of CEA. It should also be noted that these techniques are not mutually exclusive, but rather are often performed in tandem at little marginal cost to provide a broader and richer package of information.[18] Each type of analysis relies on the basic principle that all relevant costs and benefits of asthma screening should be considered.

Cost-minimization analysis deviates from this principle somewhat because it only compares the costs associated with various programs. It does not explicitly compare outcomes (benefits) because it assumes that health outcomes are equivalent across the compared programs.[18] Because of this assumption, the preferred program is simply the one associated with the least costs. The advantage of cost-minimization is its simplicity, but its usefulness is limited because most comparisons involve programs that are expected to produce differential health outcomes (eg newer, more effective, and more costly programs versus older, less effective and less costly programs).[20] Because asthma screening is expected *a priori* to result in improved health outcomes versus no screening, and because more extensive versus less extensive screening is expected to result in improved

health outcomes, the cost-minimization technique is not well-suited to inform this decision.

Cost-consequence analysis considers both costs and health outcomes but does so in a disaggregated manner, such that direct summary comparisons across programs cannot be made. Instead, Torrance et al[18] write, "the costs and [health outcomes] of the program compared to one or more relevant alternatives are computed separately and listed" (p. 59). The advantage of this analysis is that it allows decision makers to "make the value judgment tradeoffs necessary to integrate a disparate list of pros and cons … to reach a final decision" (p. 59). This approach places a great cognitive burden on the decision makers, does not allow for the explicit summary valuation of costs and health outcomes, and permits inconsistency in the decision-making process. Because of these reasons, cost-consequence analysis is not well-suited to inform this decision.

Unlike the two previous techniques, cost-benefit and cost-effectiveness analysis directly compare programs based upon the expected differences in both costs and health outcomes using a single summary measure. Cost-benefit analysis is unique in that it values both costs and health outcomes in monetary terms, allowing programs to be compared solely in dollar amounts. Torrance et al[18] conclude, "A positive net social benefit [positive dollars] indicates … that the program is worthwhile" (p.60). The strength of cost-benefit analysis is the ability to compare vastly different programs using a common metric, dollars. However, ethical and practical objections to placing dollar values on health outcomes, such as years of life saved, limit its acceptability. Cost-benefit analysis is suitable to inform the decision, but valuing health outcomes in dollars is controversial.

CEA values costs in dollars and health outcomes in non-monetary units, such as cases prevented, life years saved, or quality-adjusted life years (QALY) gained. Programs are compared based on a single summary measure, the cost-effectiveness ratio which is as Garber et al state[19], "the difference in their costs divided by the differences in their effectiveness" (p. 27). Lower cost-effectiveness ratios are preferred, and they can be used to compare any two programs or multiple non-competing programs.[20] Noncompeting programs are those in which choosing one program does not preclude choosing the other (eg asthma screening and cancer screening) whereas competing programs are those where choosing one precludes another (eg different intensities of asthma screening).

Hunick et al[20] suggest that the *incremental* cost-effectiveness ratio (ICER) is preferred to compare multiple competing programs because "by definition, one of [the] choices is more effective but more costly than the other, and the decision between the two depends on whether the extra benefit is worth the extra cost" (p. 281). Instead of comparing all levels of an intervention against the *status quo*, the ICER is calculated by comparing each level of intervention against the next less expensive intervention. This difference in calculating the ICER results in a measure that reveals "the true ratio of cost-effectiveness for mutually exclusive programs, allowing us to 'see' the relative worth of programs … [in terms] of *additional* cost per unit of *additional* benefit" (p. 282). The resulting ICER can be used to directly compare programs, but it can also be compared against a standard referent (eg $50,000 per life year saved). The differing intensities of asthma screening are competing programs, and the ICER is the preferred summary measure to compare them. These considerations favor CEA as the most appropriate technique for this analysis.

One potential limitation of CEA may be pertinent to the evaluation of asthma screening. If asthma screening cannot be shown to improve health, then by definition CEA cannot be used.[20] If screening is not effective, then the denominator of the ICER would be zero, making the ICER un-interpretable. As mentioned previously, screening opponents argue that screening has not been proven effective by large randomized controlled trials (RCT).[16] This implies that a zero denominator is possible. Despite this possibility, Torrance et al[18] state that it is reasonable to proceed because "some [CEA] studies must be undertaken well before good data are available if they are to address relevant policy questions in a timely manner" (p. 56).

The potential problem of a zero denominator is addressed with the following logical argument: (1) Children with undiagnosed and poorly controlled asthma exist; (2) school-based asthma screening programs can identify at least some of these children; (3) at least some children identified by screening will seek treatment; and (4) asthma treatment improves health outcomes. Therefore, asthma screening improves health outcomes by some non-zero amount. The next question regarding cost can be addressed using CEA. The resulting ICER may still be difficult to interpret if the effect is near zero, but it does support proceeding with CEA in order to inform the decision.

Torrance et al[18] indicate that the steps needed to conduct a successful CEA are to "develop a conceptual model describing the intervention and its effects on health outcomes … determine how to collect the data, [and] … develop the analytic methods to combine the information appropriately" (p. 69). Prior to taking these steps, it is important to clearly articulate the question under consideration. The simple question is, "Is school based asthma screening cost-effective?" However, a more specific question is

needed. In order to frame the specific question, one must "consider how the intervention is used and the manner in which it affects the course of the disease of interest, its treatment, and the health status of the target population and other affected individuals" (p. 69). The integration of these aspects is needed to "make it clear to the consumers of the analysis whether or not the cost-effectiveness results will apply to specific real-world programs" (p. 62). The basic underlying assumptions of how the screening programs are expected to work are outlined in the 4 steps of the argument already presented; however, several additional considerations need to be addressed before the full conceptual model can be described. The first of these is the specific screening program to be evaluated, and the second is the target population.

Given the assumptions of how asthma screening is expected to improve health outcomes, the chosen screening program must be able to detect both new cases of asthma and poorly controlled disease in children already diagnosed. In addition, specific properties of the screening program must be available, including sensitivity, specificity, and expected costs. Several screening programs are reported in the literature; however, one validated by Gerald et al (2004)[7] is selected to represent the generic screening intervention. Two primary considerations support this choice. First, this particular screening program has 4 levels of intensity: 2 questionnaire-only versions and 2 multi-stage versions, one questionnaire with spirometry, and one questionnaire with spirometry and exercise testing. These 4 intensity options essentially encompass all of the possible screening choices, thereby allowing a comprehensive and generalizable comparison of "real world" screening options. Second, the sensitivity, specificity, and expected costs for all

intensity levels are available in the literature[6,7] and from Gerald (personal communication, June 17, 2007).

The multi-stage procedures are limited by their inability to detect poorly controlled asthma in children with previously diagnosed asthma.[7] This limitation is addressed by adding a second screening intervention, the Asthma Control Test (ACT), which is specifically designed for this purpose. The sensitivity and specificity of the ACT are reported.[21] The ACT, combined with the four mutually exclusive interventions validated by Gerald et al (2004)[7], comprise the screening methodology evaluated in this study.

The second consideration is the selection of the target population. Torrance et al[18] state, "given age and sex, individuals living in a particular region, those with a specific disease, those with a certain risk profile, or groups defined by combinations of these characteristics … can have a dramatic effect on the cost-effectiveness of an intervention" (p. 62). Rothman[22] notes that this is particularly true for screening because screening effectiveness "is highly dependent on the prevalence of disease in the population" (p. 201). Screening in high-prevalence populations improves screening effectiveness. It is well established that the prevalence of asthma is highest in children, particularly minority children in urban settings.[2] In addition, much is known about health care utilization, treatment, and treatment barriers in this setting. Lastly, the screening intervention chosen for this CEA is validated in an urban, primarily minority elementary school system.[7] These considerations support the choice of urban elementary school children as the population of interest.

With these elements decided, a more specific research question can be posed: "Is asthma screening using a multi-stage screening procedure to detect new asthma cases supplemented by the ACT to detect poorly controlled asthma in a typical population of urban, primarily minority elementary school children cost-effective?" This more specific question is answerable by CEA, but data is required. The design of the CEA influences the sources of data to be used. This particular CEA is one that fits the description provided by Torrance et al[18], "where the model, as opposed to a specific study, is the primary feature of the analysis … Modeling designs draw heavily on existing literature as a source of secondary data on costs and intervention effects relevant to the subject of study" (p. 75). Accordingly, this CEA will use secondary data derived from the published literature to estimate costs, health effects, and preference weights.

With the primary question more specifically framed and the sources of data generally identified, the last step is to operationalize the conceptual model. For this CEA, the model of choice is the decision-analytic model because it can adequately portray clinical realities and the associated decision-making needed to conduct asthma screening. The strength of the decision-analytic model as noted by TreeAge[23] is its "systematic approach to *decision making under uncertainty* … where a complex problem can be disaggregated into smaller problems and elements … incorporating into the decision making process both what is known about a problem, and also what is uncertain" (p. 8). The proposed elements that link asthma screening with improved outcomes are explicitly diagramed in what is termed a decision tree, which is a "branching structure in which various … symbols are used to represent different kinds of events, including decisions, uncertainties, and … the outcomes or alternatives associated with [them]" (p. 8). In this

CEA, the decision tree is augmented by a Markov model, which is designed to represent events that reoccur over time.[23] The Markov model allows this CEA to represent the clinical course of asthma over time, including transitions between well-controlled asthma, poorly controlled asthma, and asthma exacerbations. By doing so, it is possible to account for the primary drivers of asthma-related morbidity and health care utilization.

Now that the general model has been explained it is important to consider the choice of appropriate units for the numerator and denominator of the ICER. The numerator reflects the differences in costs between comparison interventions. The choice of units for the numerator, dollars, is straightforward; however, the choice of unit for the denominator is more difficult because it is not clear what a *meaningful* asthma outcome is for children with asthma. In CEA, the denominator represents the differences in health outcomes between two groups (e.g. *status quo* versus screening) and is a measure of *effectiveness*. Effectiveness in CEA quantifies the gains or improvements in overall health status realized from the adoption of one intervention as compared to another. Ideally, this measure captures elements of quality and quantity such that comparisons across dissimilar conditions can be made. For example, the resulting measure should allow comparisons between prostate cancer treatment and asthma screening.

When one is considering the units of measurement, it is also important to consider from what perspective the analysis is to be performed because as Torrance et al[18] state "it determines what costs and effects to count and how to value them" (p. 61). Generally, the societal perspective that considers "all costs and all effects … no matter who pays the costs or who receives the effects" (p. 61) is preferred, as it is the broadest perspective one can have when evaluating programs that involve allocation of limited public resources.

This analysis is conducted from the societal perspective, as it is assumed that asthma screening will be conducted in the public domain.

Currently, the unit of choice in CEA to measure effectiveness is the QALY. The underlying premise of the QALY is that an individual exists at any given point in time in a discrete health state that can be assigned a numerical weight (preference) that values the desirability of that health state. Gold et al[24] note, "In the conventional approach to QALYs the quality adjustment weight for each health state is multiplied by the time in the state … and then summed to calculate the number of quality-adjusted life years. The advantage of the QALY as a measure of health output is that it can simultaneously capture gains from reduced morbidity (quality gains) and reduced mortality (quantity gains), and integrate these into a single measure" (p. 91).

Unfortunately, using QALYs as an outcome measure in children is problematic. The problems are of such a magnitude that Griebsch et al[25] conclude that "the estimation of QALYs in pediatric studies should not yet be regarded as standardized. Griebsch et al[25] further state, "Comparisons of the relative cost-effectiveness reported as cost per QALY gained across interventions from different diseases and populations should be treated with extreme caution" (p. e606). The situation is equally problematic for other potential measures that have tried to assess clinical, humanistic, and economic outcomes,[26,27] such as asthma symptom free days (ASFD),[28,29] days without asthma symptoms (DWAS),[27] asthma quality of life,[30,31] controlled weeks per patient,[32] and SADs.[33] Gandhi and Blaiss[26] state, "In conclusion, there is no ideal measure for asthma control" (p.109). Without an ideal outcome measure, any choice is subject to limitations. Nevertheless, a choice must be made.

In this analysis, two separate outcome measures will be used. The first is the QALY. As mentioned previously, the preferred outcome measure is the QALY, because it incorporates both gains in quality and quantity of life and is a generic measure that can compare interventions that target dissimilar diseases. New research in asthma allows the opportunity to avoid the problems with QALYs in children brought up by Griebsch et al.[25] Chiou et al[34] report on the findings from the development of the multi-attribute Pediatric Asthma Health Outcome Measure (PAHOM), which allows the calculation of preference weights for various asthma health states in children. The strengths of this measure are its development for use in children and its use of a community-based sample and expected utility theory to derive preference weights. Its primary limitation is a small sample size. The ICER that results from using QALYs as an effectiveness measure will be reported as 2006 dollars per QALY gained.

The second effectiveness measure is the SAD. The use of the SAD is a relatively novel outcome measure for CEA and provides a unit of measurement that has a definable social value. School attendance for elementary school children is mandatory, and public school funding is financed by the taxpayer. This allows the calculation of a per pupil per day cost that represents society's willingness-to-pay (WTP) for a day of school attendance. This measure is readily available or calculable for almost all school districts. Moonie et al[33] and Wang et al[3] report excess SADs are experienced by children with asthma and others have linked SADs and school performance.[35-38] Therefore, preventing SADs is likely to benefit children with asthma. These factors make the SAD a reasonable outcome measure for children with asthma. The summary ICER using prevented SADs from the school system perspective is reported as 2006 dollars per prevented SAD.

In summary, asthma is an important disease of childhood that is associated with significant economic and health burden. Identifying children with undiagnosed or poorly controlled asthma via school-based screening offers a potential intervention to improve health; however, it is not clear whether the costs of doing so are worth the potential gains. CEA, a methodology that can inform this decision, will be conducted using a hypothetical cohort of primarily low-income, minority, and urban elementary school children. All costs and outcomes related to asthma screening are considered from the societal perspective to provide a summary measure of the value of school-based asthma screening.

LITERATURE REVIEW

Etiology and Pathogenesis

Asthma is a common chronic condition of childhood. The underlying etiology and pathogenesis remain uncertain, as evidenced by the primarily descriptive definition found in the 2007 Guidelines for the Diagnosis and Management of Asthma report prepared by the National Heart, Lung, and Blood Institute (NHLBI) and the National Asthma Education and Prevention Program (NAEPP)[1]:

> Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role: in particular, mast cells, eosinophils, neutrophils (especially in sudden onset, fatal exacerbations, occupational asthma, and patients who smoke), T lymphocytes, macrophages, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of coughing (particularly at night or in the early morning), wheezing, breathlessness, and chest tightness. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment (p. 9).

Two primary components of this definition are chronic airway inflammation and bronchial hyperresponsiveness. These derangements are responsible for the clinical hallmark of asthma, the asthma exacerbation. Exacerbations are typically triggered by exposure to environmental allergens, irritants, or upper respiratory viruses. The prominent features of acute exacerbations include shortness of breath, wheezing, and cough, which are caused by acute bronchospasm; however, the underlying, but difficult to observe, airway inflammation is thought to be the most influential determinant of exacerbation frequency

and severity.[1] The absence of a readily identifiable pathophysiologic abnormality means that asthma screening must rely on identifying the secondary manifestations resulting from bronchospasm. This requirement makes it difficult for asthma screening to have high sensitivity and high specificity. Instead, gains in sensitivity occur at the expense of lower specificity. Depending on the costs of false positive results, this can have a dramatic impact.

The etiology of asthma is unclear, but it begins early in life for most individuals and is thought to result from an early gene-environment interaction that affects the development of the immune system. The major environmental factors are airborne allergens and viral respiratory infections.[1] There is evidence to suggest that the pattern of lung function is established by age six.[39] This finding is consistent with epidemiological data that shows that the prevalence of current asthma in children 5-10 years of age is similar to that in children 11-17 years of age.[2] This supports the decision to evaluate asthma screening in a population of elementary-age school children.

The natural history of asthma is correlated with the degree of underlying airway inflammation. The degree of inflammation appears to occur over a continuum, such that some children have relatively mild manifestations while others have more severe manifestations. In some patients with severe and persistent chronic airway inflammation, permanent changes in lung structure and function occur. Unfortunately, there is little to no evidence to suggest that early treatment with anti-inflammatory medications can prevent these permanent changes.[1] This means that any benefits derived from screening are real-

ized by reducing the secondary manifestations of the disease over the course of a patient's lifetime via sustained behavioral and therapeutic interventions.

Diagnosis

The diagnosis of asthma is established clinically by eliciting a history of symptoms consistent with episodic airflow obstruction, observing evidence of reversible airway obstruction, and eliminating alternative diagnoses. The medical history, physical exam, and spirometry serve as the "gold standard" to confirm the diagnosis. The medical history reveals symptoms of episodic airflow obstruction, the physical exam may reveal wheezing or evidence of atopy, and spirometry measures airway obstruction and its reversibility. Key symptoms to elicit include recurrent wheeze, cough (particularly nighttime), difficulty breathing, and chest tightness, which is often precipitated by such triggering factors as exercise, viral infection, allergies, and tobacco smoke. Patients often underreport or misinterpret symptoms related to airflow obstruction; therefore, pulmonary function testing (spirometry) is used to obtain an objective measure of airway obstruction.[1] The 2007 NAEPP guidelines[1] recommend using spirometry in children older than 4 years of age. The need to elicit symptoms and to obtain spirometry to establish the diagnosis of asthma suggests that asthma screening is likely to require some combination of questionnaire and pulmonary function testing.

Establishing a diagnosis of asthma is a necessary but not sufficient step to reduce asthma-related morbidity. Once the diagnosis is confirmed, appropriate treatment that is consistent with the initial estimated severity of disease must be instituted. The response

to treatment must then be evaluated over time to ensure that control of symptoms is achieved. The 2007 NAEPP guidelines[1] emphasize the distinction between asthma severity and control. Asthma severity represents "the intrinsic intensity of the disease process … [and] control [is] the degree to which the manifestations of asthma are minimized by therapeutic intervention and the goals of therapy are met" (p.15). Severity is best assessed prior to initiating treatment, and control can only be assessed after. The concepts of asthma severity and control are linked by their common purpose, which is to match the most appropriate treatment to the level of symptoms and risk for future exacerbations. Ideally, children with well-controlled asthma of any initial severity can, with appropriate treatment, achieve similar levels of impairment (minimal to none) and risk of future exacerbations (< 1-2 per year).[1]

The distinction between these concepts is subtle but important to the screening question. Historically, screening individuals with a known disease status departs from the traditional screening and case detection methodology; however, the concept of asthma control justifies extending the screening paradigm to include children with known asthma status, even to those who are already being treated. It does so by establishing a conceptual framework whereby children with previously diagnosed asthma, but poor disease control, can benefit from screening if it leads to treatment intensification. Because this is a plausible scenario, the screening benefits in this analysis are expected to extend to identification of both new asthma cases and previously diagnosed cases with not well-controlled disease.

The assessment of severity and control relies on elements from the same 4 domains: interference with normal activity, nighttime awakenings, frequency of use of short-acting beta-agonists (SABA), and lung function. Severity is classified into 4 categories (intermittent, mild persistent, moderate persistent, and severe persistent) based on the most severe manifestation in any single domain. Control is similarly classified into 3 categories (well-controlled, not well-controlled, and poorly controlled) based on the most severe manifestation in any single domain. The distinction between severity and control allows a third concept, responsiveness. The NAEEP guidelines[1] define responsiveness as "the ease with which asthma control is achieved by therapy" (p.15). This concept helps distinguish between patients who have similar symptoms and lung function but different levels of treatment. Because of the newness of this emphasis, the literature primarily contains references to severity and not control; however, the two are correlated, so much of the prior information remains useful.

Treatment

The assessment of severity and control has the goal of matching treatment to symptoms, lung function, and risk of future exacerbations. Severity is used to choose the most appropriate initial treatment, and control is used to adjust treatment once begun. The mainstay of asthma treatment involves pharmacotherapy with two general classes of medications, relievers and controllers. Reliever medications such as albuterol, which is a SABA, act to quickly reduce the symptoms associated with bronchospasm. Controller medications such as budesonide, which is an inhaled corticosteroid (ICS), require daily

dosing over a period of weeks to months to reduce the underlying airway inflammation. Other controller medications exist, such as long-acting bronchodilators (LABA), leukotriene receptor antagonists (LTRA), chromolyn, necrodomil, and theophylline. While all of these medications are commonly used, the 2007 NAEPP guidelines[1] recommend medications from one of three classes as preferred treatment: SABA, ICS, and LABA.

The 2007 NAEPP guidelines[1] recommend 6 steps of therapy. Step 1 is the least intensive and requires only a SABA. The only patients who would initially qualify for Step 1 would be those with intermittent asthma. All other severity classifications require both relievers (SABA) and controllers (ICS). Following treatment initiation, future change should be based on level of control. If asthma is not well-controlled or is poorly controlled, the 2007 NAEPP guidelines[1] recommend stepping up one or more steps, respectively. Conversely, if patients are well controlled for at least 3 months, clinicians can consider stepping down treatment. The goal is to match the medications to the level of control by adjusting therapy until the patients' symptoms, lung function, and risk of exacerbations are consistent with well-controlled asthma. Stepping up and down treatment is an ongoing, continuous process that requires close monitoring over time. Generally speaking, the use of a SABA, LABA, and/or ICS is safe and is associated with only minor, self-limited side-effects. The NAEPP guidelines[1] note that ICSs effect childhood growth; however, "The effect on growth velocity appears to occur in the first several months of treatment and is generally small and not progressive" (p. 30).

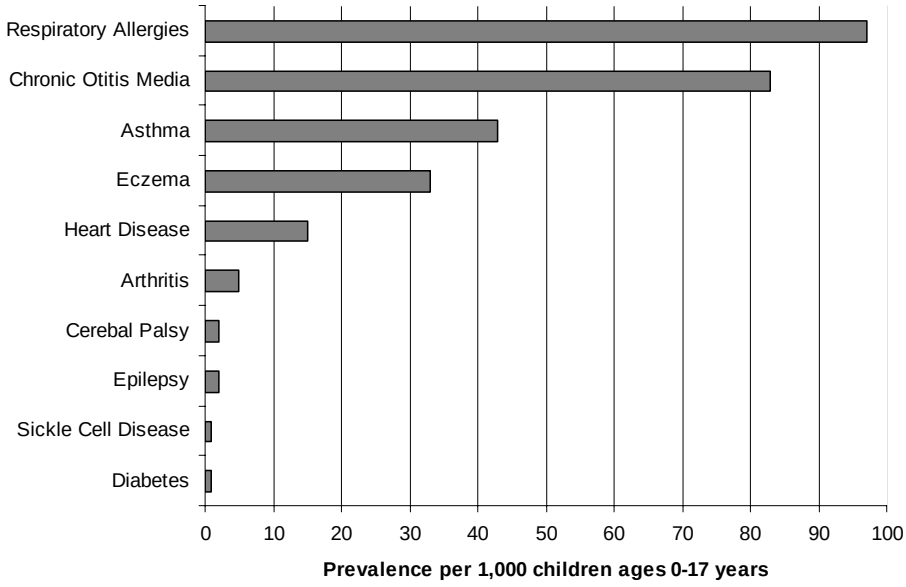
In addition to the long-term management of asthma, additional and/or more intensive treatment is required to manage acute exacerbations. Acute exacerbations often re-

quire treatment in the emergency department (ED) or hospital. Additionally, parental and/or oral corticosteroids are frequently substituted for an ICS. These differences in treatment setting and intensity lead to significantly higher costs.

Epidemiology of Childhood Asthma

Data from the 1988 National Health Information Survey (NHIS) suggests that asthma is the third most common chronic condition of childhood behind respiratory allergies and chronic/frequent otitis media (Fig. 1).[37]

FIGURE 1. Prevalence (per 1,000) of selected medical conditions in children ages 0-17 years.



Akinbami[2] reports that an estimated 9 million (12%) children in the U.S. ages 0-17 years have a diagnosis of asthma, based on responses to the 2004 NHIS question, "Has a doctor or other health professional ever told you that [child's name] had asthma?" Forty-five

percent of those who report having asthma also report having had at least one asthma exacerbation in the year prior to the survey. Prevalence estimates for asthma diagnosis and previous exacerbations in elementary-age school children (5-11 years) are slightly higher, 13% and 6%, respectively.[2] The prevalence of asthma is estimated to have increased 108% between 1980 and 1996; however, a 1997 redesign of the NHIS instrument makes it difficult to compare pre- and post-1997 data.[40] One attempt to reconcile pre- and post-1997 data suggests that asthma prevalence peaked in 1996 and has since declined by 5-10%.[41] Even so, asthma remains one of the most common chronic childhood ailments.

The twofold difference in these prevalence estimates highlights how influential the choice of asthma definition is to the prevalence calculation, even within same source data. This problem is magnified further when comparing data from different sources that use different methodologies and populations. The subsequent variation in reported asthma prevalence has important implications. The practical interpretation of screening results (predictive value) depends on the interaction between sensitivity (percentage of children with asthma who test positive for asthma), specificity (percentage of children without asthma who test negative for asthma), and prevalence. For example, screening low prevalence populations with a screening method with high sensitivity may still result in more false positives than true positives (low predictive value). However, in high prevalence populations, screening tests with relatively low sensitivity may yield more true positives than false positives (high predictive value). Therefore, evaluating screening effectiveness relies not only on the intrinsic test characteristics of sensitivity and specificity, but also on accurate estimates of the prevalence of disease in the population.[22]

For this study, there are 2 important questions related to selecting the definition that best represents the "true" prevalence of asthma. The first is, "Which definition of asthma has the greatest validity?" For the purpose of screening for asthma, the definition should include all children who are reasonably at risk of experiencing adverse asthma-related health outcomes that impact quality of life or health care utilization. These children could potentially benefit from improved treatment if identified by screening.

The second important question is, "What is the prevalence of asthma in the population of interest?" If asthma is not uniformly distributed in the population, then national estimates might not be representative. There is evidence to suggest this is a valid concern in asthma. The 2004 NHIS survey reports that the prevalence of asthma is substantially higher in Black and poor children as compared to White or not poor children.[2] Studies undertaken in urban school settings where Hispanic or Black enrollment is typically high corroborate this finding.[4-8,10-13] However, the association between race and asthma is complex, as demonstrated by Smith et al,[42] who provide evidence that the increased risk of asthma in Black (vs. White) children is present only in families at less than one-half the federal poverty line. Mediating factors of social and environmental exposure may be more important than genetic susceptibility.[42] To minimize the potential impact of these confounders, the prevalence estimates (along with other relevant data) will be derived where possible from studies performed in urban school populations.

Four asthma definitions commonly appear in the literature: asthma attack prevalence, current asthma, lifetime asthma, and probable asthma. These definitions can lead to confusion if they are not consistently used or clearly reported. It is important to under-

stand their strengths and weaknesses before choosing one to represent the "true" asthma prevalence in this analysis. All of these definitions have in common the parental proxy self-report that the child has ever been told by a health care professional they have asthma; however, each definition except lifetime asthma includes at least one additional qualifier that either reduces or expands the prevalence estimate.

The asthma attack rate adds the qualifier that children, via parental proxy, must report having at least one episode of asthma or asthma attack during the past 12 months. The overall asthma attack rate for elementary school-age children is 6%.[2] Using the asthma attack rate definition produces lower prevalence estimates than if one of the other definitions were used. The asthma attack rate is reported by the NHIS survey but is rarely used by others. The definition of current asthma adds the qualifier that children, via parental proxy, must report having asthma during the past 12 months.[2] Some studies go one step further and limit current asthma to those children with diagnosed asthma who also report taking prescription asthma medications, which results in lower prevalence estimates.[5-7] Estimates of current asthma in elementary-age school children range from 8% to 18%.[2,4-8,10,13] Neither of these definitions is well suited for this study's purpose, because they likely underestimate the "true" burden of asthma in the population.

Lifetime asthma is defined simply as all children who report ever being given a diagnosis of asthma by a physician or healthcare provider.[2] This definition is not ideal either because it does not consider children with undiagnosed asthma, while at the same time it considers children with a previous diagnosis who are no longer have asthma. De-

pending on the relative magnitudes of these 2 groups, the lifetime asthma definition may over- or under-estimate prevalence.

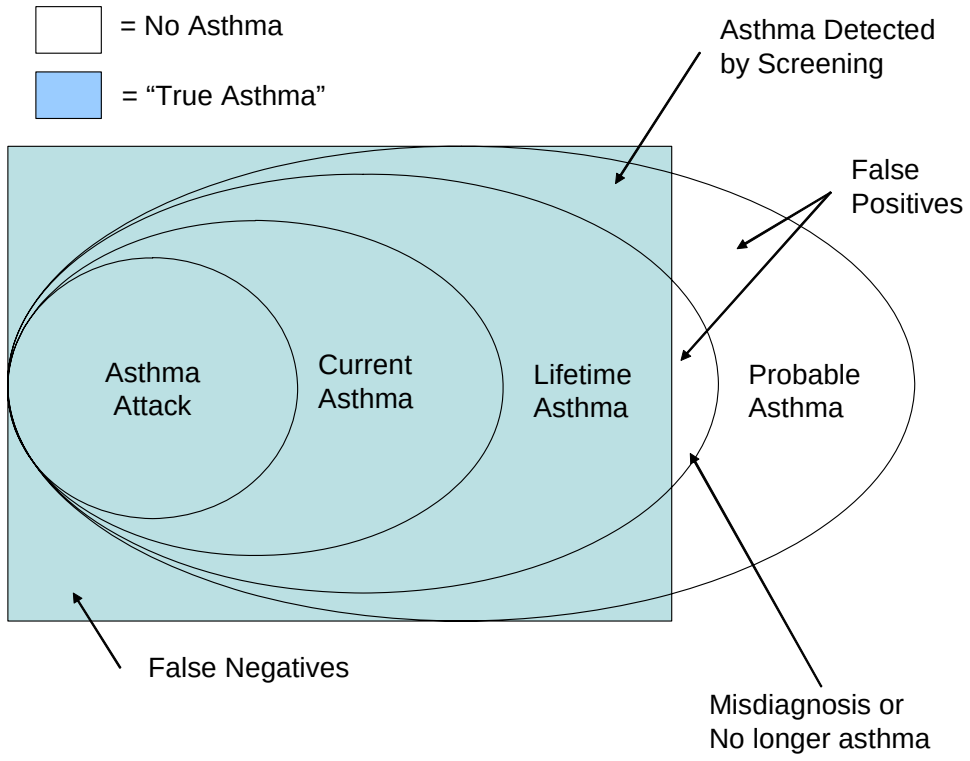
Probable asthma is an oft-used but inconsistently defined concept that is typically encountered in the literature. It is used to report the results of asthma screening initiatives in specific populations. The definition includes children who screen positive for asthma and those who report a previous diagnosis. Screening may be accomplished by questionnaire only[4,5,10,13] or by questionnaire plus pulmonary function testing. [6-8,11,12] False positive results are often significant and result in overestimates of prevalence, particularly when questionnaire-only procedures are used. The advantage of this definition is that it captures children who might have undiagnosed asthma; however, its disadvantage is that many of these children do not actually have asthma. On balance, these children are so numerous that their inclusion results in higher prevalence estimates than the other definitions.

In summary, multiple definitions have been used to define asthma prevalence. The asthma attack rate and current asthma definitions are likely to underestimate asthma prevalence and probable asthma is likely to overestimate it. While not perfect, lifetime asthma is chosen as the definition that best characterize asthma prevalence (Fig. 2).

However, its choice as the most appropriate definition does not completely solve the problem of accurately defining the prevalence asthma in the population of interest. This is because lifetime asthma prevalence estimates vary significantly depending on the specific population in question. For example, the national estimate of lifetime asthma in school-age children is 13%,[2] but estimates for urban elementary school populations are

often much higher, 14-28%.[4-8,10-13] In urban elementary school populations, the lifetime asthma prevalence estimates are likely to best represent the "true" prevalence asthma, including adjustments needed to account for children with undiagnosed asthma and those who no longer have asthma. Estimates suggest that the percent of all elementary-age children who have undiagnosed asthma could be as low as 2% or as high as 14%.[5,6,8,10,11,13] Estimates also suggest that the percent of children who have a diagnosis of asthma but who no longer have asthma is approximately 4-6%.[4, 7,10]

FIGURE 2. Conceptualization of commonly reported asthma definitions.



Among children with asthma, it is also important to consider the distribution of asthma severity because severity influences quality of life, treatment, exacerbation risk, and health care utilization in children with asthma.[1] A number of sources characterize this distribution in children;[5,7,43-47] however, one by Clark et al[5] and one by Gerald et al (2004)[7] are particularly relevant. These 2 reports describe the distribution of asthma severity in a population of urban elementary school children by diagnosis status (previously diagnosed or newly diagnosed by screening). This is particularly important because they observe that the distribution of severity is on average lower in children who are found to have asthma by screening versus those with a previous diagnosis.

Clark et al report findings from a questionnaire-based screening of 4,653 predominately Black children ages 7-10 in Detroit, Michigan. Follow-up telephone interviews with caregivers of children who screened positive were used to estimate severity. Gerald et al (2004) report findings from a multi-stage screening program of 3,539 predominately Black elementary-age school children in Birmingham, Alabama. Follow-up visits with a pediatric pulmonologist for both screen negative and screen positive children were used to estimate severity. The results of both studies are strikingly similar and indicate that children with undiagnosed asthma who are identified by screening have less severe disease than children who have previously diagnosed asthma. Estimates of severity in undiagnosed children by Clark et al and Gerald et al (2004) are intermittent 60 and 57%, mild persistent 24 and 23%, moderate persistent 12 and 17%, and severe persistent 3 and 0%, respectively. Estimates of disease severity in previously diagnosed children by Clark et al and Gerald et al are intermittent 45 and 36%, mild persistent 31 and 35%,

moderate persistent 18 and 29%, and severe persistent 6 and 1%, respectively. These findings indicate that the distribution of severity by diagnosis status should be considered.

Description of Proposed Case Detection Interventions

The specific case detection program being evaluated in this analysis is a multi-stage case detection program validated by Gerald et al (2004)[7] who note that the procedure "was designed to mimic the process through which a diagnosis of asthma is made in a clinical setting, using symptom histories, tests such as spirometry, and tests for [bronchial hyper-responsiveness]" (p. e460). The program has three specific components: questionnaire, spirometry, and submaximal exercise testing. The program can consist of the questionnaire alone or the questionnaire combined with either spirometry or spirometry and exercise testing.

Gerald et al (2004) find that implementing the full version of the case detection program in elementary-age, urban school children is feasible. Their findings indicate that only 2% of children are unable to complete spirometry and exercise step testing. In the development study, Gerald et al (2002)[6] report that the questionnaire response rate was 83%, the testing consent rate was 60% for children with suspected asthma, and the testing completion rate was 98%.[6] In the validation study, Gerald et al (2004)[7] report the questionnaire response rate was 98%, the testing consent rate was 84%, the spirometry completion rate was 96%, and the exercise testing completion rate was 99%.

Two modifications to the program are required for this analysis. The first is the addition of a second questionnaire to identify not well-controlled asthma in children who report a previous physician diagnosis of asthma. This modification allows evaluating the added potential benefit of identifying children with diagnosed, but not well-controlled asthma, in addition to the benefit of identifying children with newly diagnosed asthma. The ACT is used to evaluate asthma control status in children with previously diagnosed asthma. Depending on the cut-points chosen, the sensitivity of the ACT ranges from 9 to 95%, and the specificity ranges from 15 to 99%; however, results of the receiver operating characteristics (ROC) of the ACT demonstrates a maximum area under the curve, 0.727, at a cut point score of < 20. At this cut point, the sensitivity and specificity of the ACT are 69% and 76%, respectively.[21]

The second modification is the extension of response tracking and teacher incentives to ensure maximal parental notification of case detection results for children who screen positive. Gerald et al (2004)[7] demonstrate that tracking combined with teacher and child incentives can yield a questionnaire response rate as high as 98%. This modification ensures that all children complete case detection and all parents receive results. This increases the case detection completion rate and eliminates the need to consider non-response bias; however, this decision also increases the costs of case detection, as the costs of the tracking and parental notification procedures must be considered.

There is one important assumption regarding the administration of the case detection program that requires explicit mention. This analysis assumes that the school system contracts asthma case detection to an outside vendor that has the experience, personnel,

and equipment to implement the case detection program. This assumption is favored over developing the case detection infrastructure within the school system itself. First, the case detection program requires personnel with specific credentials and qualifications who are unlikely to be found in the public school systems (eg respiratory therapists). Secondly the equipment necessary to conduct the case detection (eg spirometry) is not readily available to the schools. Third, specific elements of the incentive system (teacher and student incentives) may be difficult to implement given existing school system policies regarding teacher remuneration. Fourth, some economy-of-scale efficiencies may be realized with a single organization performing case detection versus individual school systems duplicating case detection services.

Implementation of the case detection program by a contract agency requires administrative costs related to the oversight of agency staff and activities assigned to the case detection program. These activities may include but are not necessarily limited to interactions with the system school board, superintendent, school principals, and key school staff to obtain permission, schedule case detection, and provide results. The agency must hire, credential, and supervise the case detection staff. The agency must also provide physical space and equipment. However, the fixed costs associated with these activities are not considered, as recommended by Luce et al,[43] "Most input costs that are fixed in the short run will in fact be variable in the long run.... In these cases, the prices used in the CEA should be the costs that would prevail in the longer run" (p. 194). Therefore, only the variable costs of program administration are considered.

The full case detection procedure consists of three phases: completing the case detection questionnaire, including the ACT; performing spirometry, and if needed, performing submaximal exercise testing. The goal of the parental questionnaire is to identify cases of suspected asthma based on reported symptom history and to estimate asthma control in those children with a previous diagnosis. The 5 item case detection questionnaire and the 22 item ACT, along with the description of the case detection program, is simple and short enough to be easily sent home with children. Each time the child takes home a questionnaire is considered a single attempt. One attempt is made per week, and each weekly attempt requires 2 agency school visits per week, one to distribute questionnaires and one to track responses. This analysis estimates that, on average, 3 attempts per child will be needed to achieve the desired response rate of at least 98%. Similar procedures are used to notify parents of case detection results. Classroom teachers are provided $20 gift cards as an incentive to assist with collection and return of questionnaires. Trivial toy incentives (ie pencil, crayons, or stickers) are also provided to the children to encourage returns. Once the case detection team documents an 80% response rate and scores the questionnaires, the school is eligible to begin the second phase of case detection.

The second phase begins with scheduling a date for the case detection team to come to the school to conduct pulmonary function testing. To perform spirometry alone, the case detection team consists of one certified respiratory therapist proficient with pediatric spirometry and 2 non-professional support staff. To perform both spirometry and exercise testing, the team consists of one certified respiratory therapist and 4 non-

professional support staff. At these staffing levels, approximately 60 children per school day (8:30 – 2:30 PM) can be tested by a single case detection team using either case detection methodology (Gerald, personal communication June 2007).

This full case detection procedure can be modified to create 4 distinct case detection programs. Two are questionnaire only procedures. The 5-item case detection questionnaire[7] can be divided into the Narrow Questionnaire (NQ) and the Broad Questionniare (BQ). The NQ is comprised of two primary questions, the first being, "Has your child ever been diagnosed with asthma?" The second is a follow-up question: "Has your child taken asthma medication in the past 12 months?" These 2 questions identify children with previously diagnosed asthma. By definition, these two questions cannot be used to identify new cases of asthma. Once children with previously diagnosed asthma are identified, the ACT questionnaire is used to identify asthma control status. The goal of the NQ case detection procedure is to identify children with previously diagnosed asthma who have not well-controlled asthma. By identifying these children, they might benefit from medical evaluation and appropriate adjustments of their medical regimen to achieve better control, experience improved quality of life, and experience fewer exacerbations.

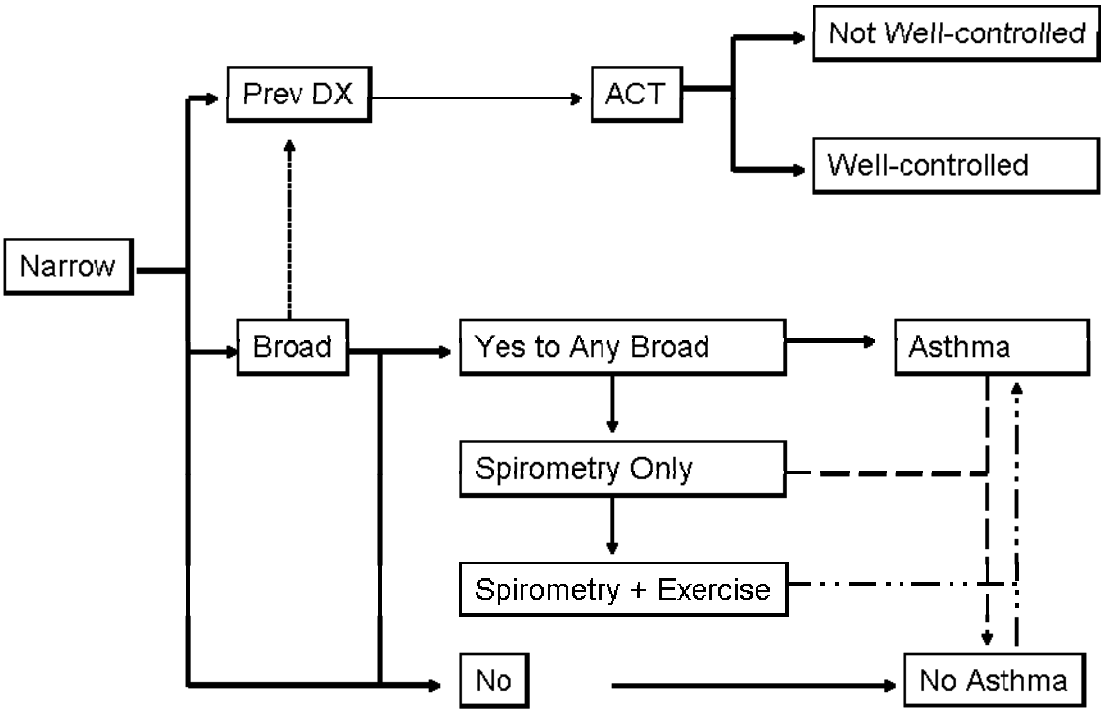
The BQ includes these two questions and 3 additional symptom-based questions to identify both children who have previously diagnosed asthma and those who might have undiagnosed asthma. The symptom-based questions investigate the presence of wheezing, early morning coughing or shortness of breath, and nighttime awakenings. Children with any of these symptoms are considered to have possible asthma and would

be urged to seek medical evaluation to confirm the diagnosis. Children identified with previously diagnosed asthma are also subject to the ACT.

The multi-stage interventions include the BQ as the first stage, and children who are identified as having previously diagnosed asthma are given the ACT. Children identified as having asthma-like symptoms but not previous diagnosis of asthma are subject to either spirometry alone or spirometry plus exercise testing. In the Multi-Stage with Spirometry (MSwS) intervention, children identified with asthma-like symptoms undergo simple spirometry. Children who demonstrate evidence of airway obstruction on spirometry are considered to have asthma and are urged to seek medical evaluation to confirm the diagnosis. In the Multi-Stage with Spirometry and Exercise Testing (MSwET) intervention, children who do not demonstrate evidence of airway obstruction with simple spirometry are subject to submaximal exercise testing. This test consists of timed exercise to achieve a target heart rate. Once the timed event is completed, children undergo a second spirometry. If there is evidence of airway obstruction, they are considered to have asthma and are urged to seek medical evaluation to confirm the diagnosis.

These activities comprise the 4 case detection procedures. Medical confirmation of the screening results is independent of the case detection procedures. Parents of children identified with possible not well-controlled or newly diagnosed asthma are expected to seek physician evaluation in the private sector. The costs associated with medical evaluation are considered separately from the case detection interventions. The structure and relationships between the 4 interventions are graphically presented in Figure 3.

FIGURE 3. Structure of four case detection interventions.



Starting at the left, the NQ identifies children with previously diagnosed asthma. Children who report a previous diagnosis are then subject to the ACT, which screens for not well-controlled asthma. Children identified as having not well-controlled asthma are urged to seek medical evaluation to confirm their status. This sequence of events represents the most basic intervention, the NQ. The NQ only identifies not well-controlled asthma among those with previously diagnosed asthma and does not identify children with undiagnosed asthma. The NQ serves as the first step in each of the 3 remaining procedures.

The next intervention is the BQ, which attempts to identify undiagnosed asthma by asking about asthma-like symptoms. Children who report any asthma-like symptoms are urged to seek further medical evaluation to confirm the diagnosis. As expected, the BQ identifies a significant number of children who have asthma-like symptoms but do not have asthma. The multi-stage procedures attempt to address this possibility by subjecting children who report asthma-like symptoms to additional screening via pulmonary function testing.

The MSwS intervention adds screening with basic spirometry to identify evidence of airway obstruction in children who report asthma-like symptoms. Those with evidence of obstruction are urged to seek medical confirmation of the diagnosis. Those without evidence of obstruction are considered to not have asthma. The result is to reduce the number of children who are considered to have asthma. The MSwET intervention uses submaximal exercise testing in addition to basic spirometry. Children who screen negative on simple spirometry undergo submaximal exercise testing to identify previously unobserved evidence of airway obstruction. Submaximal exercise testing works to identify possible asthma that is missed by simple spirometry. The result is to add some children back into the group that is considered to have possible asthma.

METHODS

Introduction

This study performs a CEA of school-based asthma case detection. There are 4 specific, mutually exclusive case detection interventions under consideration: the NQ, BQ, MSwS, and MSwET. These interventions are compared to the *status quo* condition of no case detection. The primary goal of the analysis is to estimate the short-term (one-year) cost-effectiveness of case detection in a population of low-income, minority elementary school students in an urban setting. The Birmingham City School System in Birmingham, Alabama, serves as the reference source for the hypothetical population of elementary school students.

The reference case analysis is undertaken from the societal perspective and accounts for all costs associated with case detection, disease confirmation, daily treatment, and asthma-related health care utilization. Costs are adjusted to 2006 dollars using the U.S. city average medical care services component of the Consumer Price Index (CPI).[49] The primary health outcome is quality adjusted life days (QALDs), which are converted to QALYs for reporting. Given the one-year time horizon, no discounting of costs or outcomes is required. All data are derived from the literature. Analyses are performed using version 1.4 of TreeAge Pro 2006 software.[50] A secondary analysis is performed from the school system's perspective. In the secondary analysis, the outcome of interest is 2006 dollars per new case of asthma or not well-controlled asthma identified by case

detection. This outcome allows the calculation of the number of prevented SADs needed for the school system to be indifferent to the costs of case detection.

Torrance et al[18] note that "The basic core of any cost-effectiveness analysis is an incremental comparison of an intervention with a comparison program" (p.78). As such, the primary outcome measure in this analysis is the ICER. This measure is preferred to the simple cost-effectiveness ratio when comparing mutually exclusive interventions.[20,51] The basic form of the cost-effectiveness ratio places costs in the numerator and outcomes in the denominator. The numerator represents the total costs incurred by intervention A, and the denominator represents the total QALYs generated. The resulting ratio represents the average cost per QALY generated by intervention A. A cost-effectiveness ratio for each case detection intervention is calculated; however, the simple cost-effectiveness ratio is not the appropriate measure to compare the cost-effectiveness of interventions when they are mutually exclusive.

The ICER is instead used to compare interventions. To calculate the ICER, interventions are first ordered by cost (eg A-D). The next step (assuming the lowest cost option is the *status quo*) is to compare the lowest cost intervention (eg A) with the *status quo*. This calculation produces the first ICER. The next calculation compares the next most costly intervention (eg B) with intervention A (Fig. 4). These steps are repeated until all interventions have been compared to the next lowest cost intervention. Hunick et al[20] state that this provides "the added cost per unit of added benefit of an option, relative to the next less expensive choice ... permitting the decision maker to account for the fact that there was a less expensive option" (p. 280). The resulting ICER represents the average *incremental* cost of gaining one additional QALY using intervention B instead of inter-

vention A. Comparing intervention B with the *status quo* is not appropriate, because there is another less costly option, intervention A.[51]

FIGURE 4. Incremental cost-effectiveness ratio.

$$\frac{\text{Total Costs Intervention B - Total Costs Intervention A}}{\text{Total QALYs Intervention B – Total QALYs Intervention A}}$$

Three outcomes are possible when using the ICER to compare interventions. Intervention B could cost more and generate more QALYs than intervention A. In this case, the ICER represents the average additional cost of gaining one additional QALY using intervention B instead of intervention A. This is a traditional result where spending more gains more. If intervention B costs more but creates fewer QALYs, then intervention B is said to be *dominated*. By convention, the ICER of a dominated intervention is not shown, because it is assumed that no reasonable person would choose a program that costs more but provides less benefit. If intervention A is found to have a higher ICER than another more effective program then it is said to be *weakly dominated*.[46] Perhaps the best layman's analogy is that the program offers "less bang for the buck." The ICER of an intervention that is weakly dominated is also not reported, and the intervention itself is not used for further comparisons. This process is continued until all interventions have

been compared to the next less costly intervention that is not dominated or weakly dominated.

QALYs are chosen as the primary health outcome measure for the reference case analysis instead of other possible measures, including spirometry, markers of airway inflammation, subjective measures of symptoms, or asthma-related quality of life, because these measures are not ideal outcomes for either asthma or CEA.[26,27] The most useful outcome measure is one that combines quantity and quality of life into a single measure and one that allows comparisons of interventions impacting different health conditions. The outcome measure of choice to accomplish these 2 objectives is the QALY.[24]

The QALY is an interval-scaled measure bounded by 0.0 and 1.0 that can be added and multiplied without changing the underlying properties of the scale.[20,24] Gold et al[24] state that "In the conventional approach to QALYs the quality-adjustment weight for each health state is multiplied by the time in the state … and then summed to calculate the number of quality-adjusted life years …[which] can simultaneously capture gains from reduced morbidity (quality gains) and reduced mortality (quantity gains)" (p. 91). Ideally, QALYs are derived from instruments that are preference-based, whereby individuals "make judgments regarding the value of particular health states and use these judgments to produce a score" (p. 97). In addition, the preferences should come "from the general population rather than …[from] particular subgroups" (p.102).

For the secondary analysis from the school system's perspective, the health outcome measure is the SAD. The advantage of using the SAD is that a real-world valuation can be assigned to this measure. For example, the Birmingham City School Schools spent $7,798 per student for 175 instructional days in 2005-2006.[52] This is equivalent to

approximately $45 per child per day of attendance. This represents the school system's financial valuation of a SAD. Children with asthma experience in general, and particularly those who are less adherent to treatment, more SADS on average than children without asthma.[33,53] It is reasonable to conclude that school systems might be willing to pay for asthma case detection if it resulted in fewer SADs. This makes SADs a useful outcome measure from the school system's perspective.

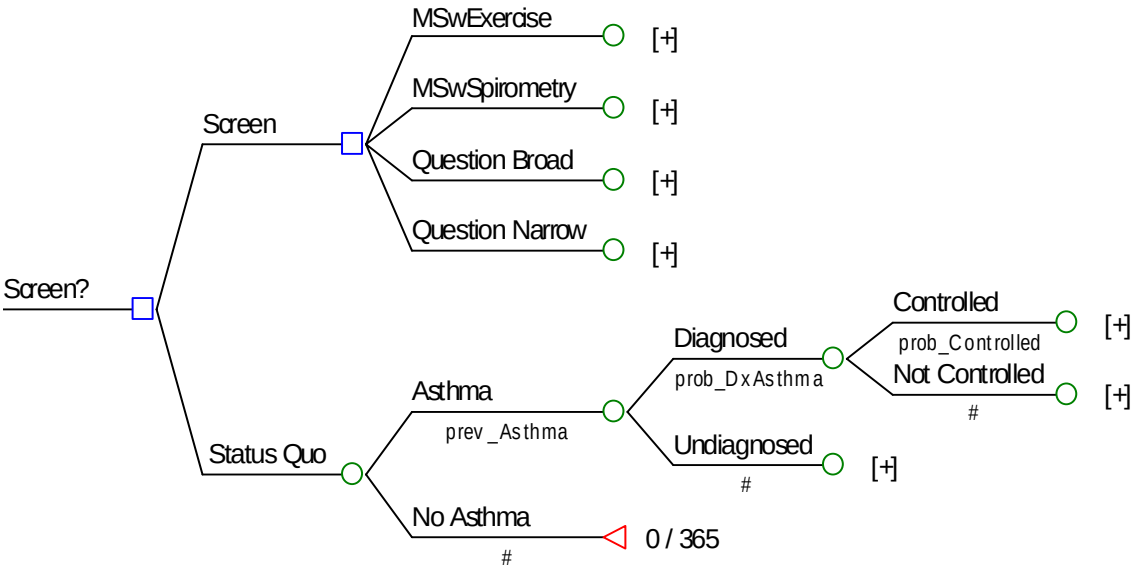
Model Specifications

General Structure of Decision Tree

The decision analytic model for this analysis is a decision tree with attached Markov models. The decision tree provides the structure to compare the 4 case detection interventions against the *status quo*. Inputs within the decision tree modify the probability that a child will be sorted into one of 4 possible end states: children without asthma or children with asthma who receive full, partial, or no treatment. The costs and QALYs of children without asthma are accounted for within the decision tree. The calculation of costs and QALYs for children with asthma is undertaken in 12 Markov models that adjust for asthma severity (intermittent and mild, moderate, and severe persistent) and expected treatment (none, partial, or full). Markov models are needed because asthma is characterized by frequent changes in health status that are associated with vastly different costs and outcomes. Markov models can account for changes in health status, disease severity, and expected treatment by tracking daily costs and outcomes for each individual over the course of a year.

The decision tree is comprised of a number of branches that sort children into one of the 4 end states. A reduced form of the decision tree is shown in Figure 5.

FIGURE 5. Truncated decision tree with the s*tatus quo* branch.



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The decision tree can be "read" from left to right, and each branch represents a sorting opportunity. The intersection of multiple branches is termed a node. There are 4 node types that represent one of 3 events: a decision, a chance, or a terminus. Decision nodes (squares) represent choices to be made between competing elements (eg case detection interventions). Chance nodes (circles) represent decisions made with uncertainty (eg asthma or no asthma). Terminal nodes (triangles or Ms) represent end states.[23] In Figure 5, triangles represent the no-asthma end state where the costs and outcomes of children without asthma are assigned. Ms (not shown) represent Markov models that account for the costs and outcomes of children with asthma. A [+] symbol represents hid-

den branches, and the # symbol represents a complement probability (e.g. 1-prev_asthma).

The first decision node represents the choice of adopting case detection or maintaining the *status quo*. The second represents the choice between competing case detection interventions if adoption is favored. Each intervention has its own branch that is comprised of additional branches (not shown) which incorporate the necessary inputs that determine the final assignment of children into specific end states. To the right of the decision nodes lie chance nodes that contain the specified model inputs (probabilities) that result in the assignment of children into specific end states where costs and outcomes are determined. These determinations ultimately inform the choices to be made at the 2 decision nodes, "Is the adoption of school-based asthma case detection cost-effective? If so, which intervention is most cost-effective?"

The answers to these questions are derived from calculations performed in the decision tree and Markov models based on specific inputs representing one of three information types: probabilities, costs, or outcomes. Probability inputs are associated with chance nodes and represent simple questions such as, "How many children have asthma?" This question is answered probabilistically by the input variable, asthma prevalence. This probability input is used to "sort" children into those with and without asthma. In this analysis, probability inputs are defined globally and take on the same value throughout the decision tree, ensuring that parameters common to all branches have the same value.

Terminal nodes represent specific end states that are defined in terms of total costs (2006 dollars) and outcomes (QALYs). These costs and outcomes can either be

defined at the terminal node itself or within the Markov models (not shown). A cost and outcome pair defined at a terminal node is found at the "no asthma" terminal node. It is associated with zero costs and 365 QALDs (one full QALY). This end state represents children under the *status quo* condition who do not have asthma. No costs are assigned because these children by definition do not undergo case detection and experience no asthma-related costs. They are assigned a full QALY because children without asthma are assumed to have perfect health.

In summary, the decision tree is made up of numerous branches and nodes. The left-most part of the decision tree is bound by the 2 decision nodes that represent the 2 primary questions of this analysis. The right-most part of the decision tree is bound by terminal nodes or Markov models which determine the total and outcomes of each possible end states. Between them lie chance nodes that sort children into one of the possible end states based on estimated probabilities. TreeAge performs the calculations for each branch independently from right-to-left until a decision node is reached. At the decision node, a final summary value of costs and outcomes is reported.[23] These cost and outcomes pairs are used to calculate the primary outcome measure, the ICER, for each intervention.

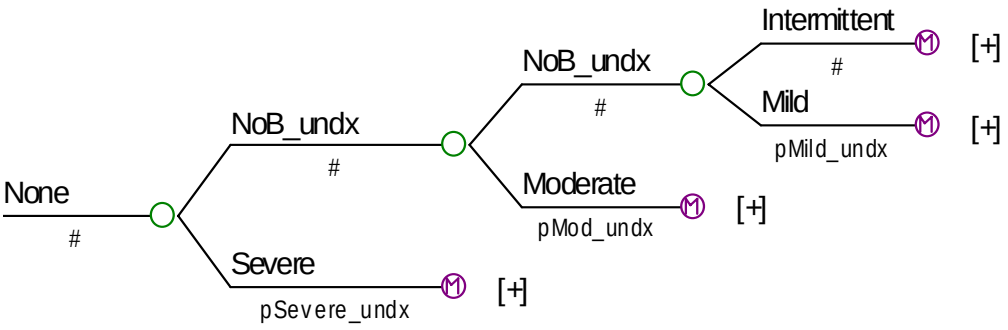
Structure of Status Quo Branch

The no screening branch calculates the total costs and outcomes expected under the *status quo* condition. The first chance node uses the probability input, asthma prevalence, to sort children into those with and without asthma. Since asthma prevalence is not known with certainty, the input is comprised of a point estimate and a range of possi-

ble alternative values.[54] The estimated asthma prevalence is 20% (range 10-30%).[4-13] Range values are used in sensitivity analysis to estimate how influential the uncertainty in the estimated variable influences the final ICER calculation. The probability of not having asthma is the complement of asthma prevalence, 80% (range 65-90%), and is represented by the # symbol.

Children with asthma are sorted into those with previously diagnosed and undiagnosed asthma. The probability of previously diagnosed asthma among those with asthma is 70% (range 50 – 90).[4-13] Children with undiagnosed asthma represent a possible end-state where costs and outcomes are calculated in specific Markov models that account for asthma severity and expected treatment. Children with undiagnosed asthma are assigned to no-treatment Markov models. Multiple Markov models are needed because treatment costs, health care utilization, and health outcomes are expected to vary by both asthma severity and treatment.[1] Asthma severity is also important to consider because it has been found to vary by diagnosis status, such that children with undiagnosed asthma have on average less severe asthma than children with previously diagnosed asthma.[5,7] The branches that sort children by severity are shown in Figure 6.

FIGURE 6. Asthma severity branches for the undiagnosed, no-treatment end state.



These branches are arranged as a series of complement decisions that ultimately sort children with undiagnosed asthma into one of 4 severity classifications. The probability that a child with undiagnosed asthma has severe asthma is 2% (range 1-4%), and the complement represents the probability of not having severe asthma. The advantage of this structure is the ability to perform sensitivity testing on these inputs, but it requires additional mathematical manipulation of the remaining probabilities. For example, the complement of severe asthma, 98%, is carried forward to the next chance node, where the probability of moderate persistent asthma is 20% (range 11-26%).[5,7] This probability must be divided by 1 minus the probability of severe asthma in order to ensure that the sorting into severity classes maintains the proportional representation seen in the reference population. These adjustments are repeated for the remaining nodes to estimate the proportion of children with intermittent and mild persistent asthma. A similar strategy is used to account for asthma severity in children with previously diagnosed asthma (Table 1).

TABLE 1. Probability of Asthma Severity (Low, High) by Diagnosis Status

Asthma Severity	Previously Diagnosed	Newly Diagnosed
Intermittent	.28 (.44, .34)	.47 (.60, .50)
Mild Persistent	.47 (.40, .30)	.31 (.28, .20)
Moderate Persistent	.21 (.14, .28)	.20 (.11, .26)
Severe Persistent	.04 (.02, .08)	.02 (.01, .04)

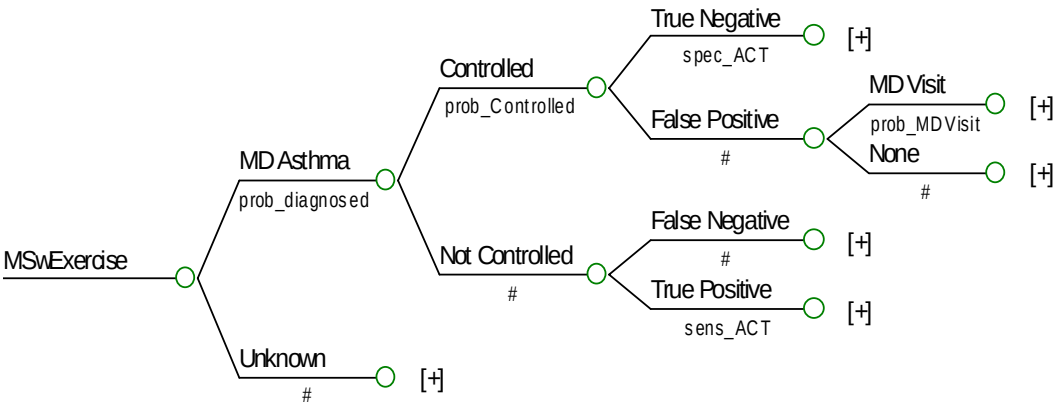
To complete the sorting, the probability that children with previously diagnosed asthma have well-controlled asthma is 60% (range 45-75%).[21,55,56] Children with well-controlled asthma are assigned to full treatment because their well-controlled status is

assumed to be due to adherence to guideline-concordant care. Children with previously diagnosed asthma who do not have well-controlled asthma are assigned to partial treatment benefit, as it is assumed that they are not well-controlled because of some combination of lack of guideline-concordant care and non-adherence.

Structure of Case Detection Intervention Branches

The branches associated with the specific case detection interventions model the factors that influence the accuracy of case detection and the probability that the identification of asthma status will lead to improved treatment. The first set of factors (sensitivity, specificity, and prevalence) influence the ability of the screening program to accurately sort children into the correct health state (eg asthma or no asthma). The second set of factors influence the probability that the new knowledge of the disease state or control status provided by the case detection intervention will lead to future treatment benefit. These factors include the probability that children identified with possible undiagnosed or not well-controlled asthma will seek medical confirmation, the probability that they will receive appropriate treatment, and the probability that they will be adherent to treatment. The structure for each of the case detection interventions is identical but where appropriate, the modeled inputs vary to account for differences between them. Because the tree structures are identical, only the MSwET branches are described (Fig. 7).

FIGURE 7. Decision tree for previously diagnosed asthma.



The first chance node sorts children into those with previously diagnosed asthma and those with unknown asthma status. The probability input at this node is the product of asthma prevalence and the probability of previously diagnosed asthma. This structure allows sensitivity analysis of both inputs. In all of the interventions, children with previously diagnosed asthma are identified by parental response to the question, "Has your doctor ever told you that [your child] has asthma?" Parents of children with previously diagnosed asthma are then asked to complete the ACT to determine the child's control status. Therefore, the only case detection costs children with previously diagnosed asthma incur are those associated with questionnaire administration, as they are not subject to spirometry or exercise testing.

The next node encountered in the "MD Asthma" branch reflects the ability of the ACT to identify children with not well-controlled asthma. The sensitivity and specificity of the ACT are 70% (range 67-73%) and 73% (range 70-76%), respectively.[21,56] The probability that children with previously diagnosed asthma will have well-controlled asthma is 60% (range 45-75%).[21,55,56] This is enough information to sort children into one

of 4 possible case detection outcomes: true positives, false positives, true negatives, or false negatives. A true positive result is the product of ACT sensitivity and the complement of the probability of well-controlled asthma. The remaining three possible case detection outcomes can be calculated in a similar manner.

Children correctly identified as having well-controlled asthma (true negatives) are sorted by severity and assigned to the corresponding full-treatment Markov models. These children are assumed to be well-controlled due to full adherence to an appropriate treatment regimen. Children identified as having well-controlled asthma who actually have not well-controlled asthma (false negatives) are sorted by severity and assigned to the corresponding partial-treatment Markov model. These children are assumed to be receiving at least some asthma care, as they have a previous diagnosis. The partial treatment status is modeled to account for some combination of inadequate adherence, non-guideline-concordant treatment, or environmental exposure as a reason for not well-controlled asthma. Children identified as true or false negatives only incur the case detection costs associated with questionnaire administration.

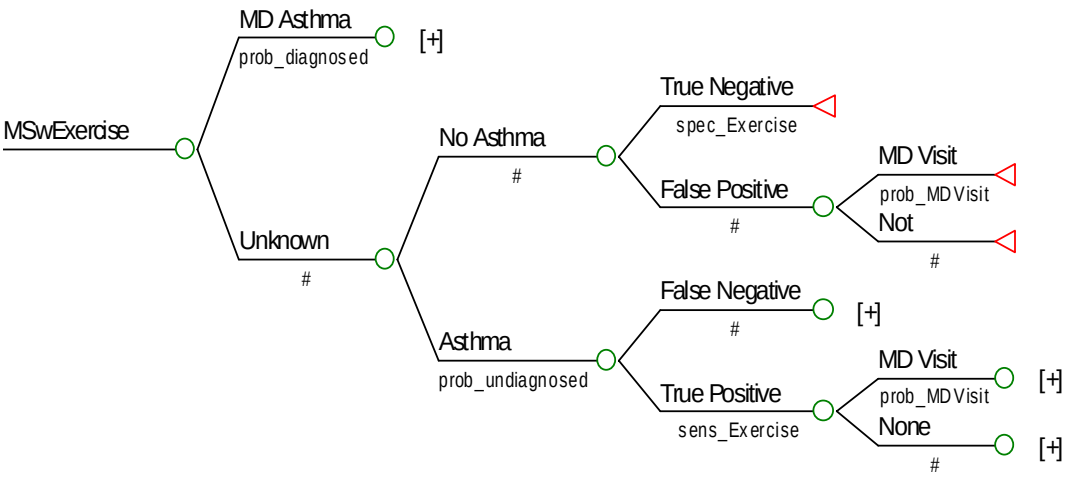
Children identified as having not well-controlled asthma who actually have well-controlled asthma (false positives) are asked to seek medical evaluation to confirm their control status. Yawn et al (2002)[17] report that approximately 50% of children's guardians report intention to seek medical care; however, only 12% of children had a documented asthma-related encounter in a physician office, emergency department, or hospital following case detection. Yawn et al (2003)[57] report that 33% of children with previously diagnosed asthma whose parents were given letters indicating that their children were at risk of not well-controlled asthma due to screening results had a physician visit in the

next 6 months. Based on this information, the probability of a physician visit is 33% (range 15-45%). Children who seek medical evaluation incur both questionnaire administration costs and costs associated with the medical evaluation. Those that do not seek medical evaluation only incur questionnaire costs. Costs associated with possible adjustments in treatment that occur due to the physician visit are not considered. All children identified as false positives are sorted by severity and assigned to the corresponding full-treatment Markov chain.

Children correctly identified as having not well-controlled asthma (true positives) are also asked to seek medical evaluation in order to confirm their control status and to adjust their treatment regimen. Like children identified as having not well-controlled, only one third of children identified as having undiagnosed asthma are expected to seek care. Children who seek medical evaluation incur questionnaire and medical evaluation costs. Before these children are sorted by asthma severity into Markov models they are subject to additional chance nodes that determine their ultimate assignment to treatment condition. This concludes the discussion of children with previously diagnosed asthma.

At the beginning of the "MSwExercise" branch, the proportion of children whose asthma status is unknown is the complement of the product of asthma prevalence and the probability of previously diagnosed asthma. Children with an unknown asthma status are evaluated differently than those with previously diagnosed asthma. Instead of being subject to the ACT, they are subject to case detection via questionnaire, spirometry, and exercise testing (Fig. 8).

FIGURE 8. Decision tree for unknown asthma status.



Again, children are classified into one of the 4 traditional case detection outcomes. While asthma prevalence is constant throughout the tree, it cannot be used here to directly determine case detection outcomes, because children with previously diagnosed asthma have been removed from the population. Therefore, the prevalence estimate must be divided by 1 minus the probability of previously diagnosed asthma before proceeding. The sensitivity and specificity of the MSwET intervention are 45% (range 40-50%) and 97% (range 95-99%), respectively.[7] These values differ from the published results because they are adjusted to exclude children who report a previous diagnosis of asthma. This is necessary because the model requires the sensitivity and specificity of screening when applied to children with an unknown asthma status. The test parameters can be adjusted to reflect this requirement, because Gerald et al (2004)[7] report the screening results both by previous diagnosis and new diagnosis. To calculate the adjusted sensitivity and specificity, children with previously diagnosed asthma are subtracted from the total

number of true and false positives for each of the interventions. The adjusted test characteristics are provided in Table 2. The sensitivity and specificity of the NQ is not shown because by definition the NQ cannot identify children with undiagnosed asthma. The NQ only identifies children with previously diagnosed asthma. In this role, it is assumed to have 100% sensitivity and specificity.

TABLE 2. Sensitivity and Specificity Estimates and Ranges for Asthma Control Test and Case Detection Interventions

Methodology		Point Estimate	Range
Asthma Control Test	Sensitivity	.70	.67-.73
	Specificity	.73	.70-.76
Multi-Stage w/ Spirometry	Sensitivity	.36	.31-.41
	Specificity	.97	.95-.99
Multi-Stage w/ Exercise	Sensitivity	.45	.40-.50
	Specificity	.97	.95-.99
Broad Questionnaire	Sensitivity	.64	.59-.69
	Specificity	.60	.55-.65

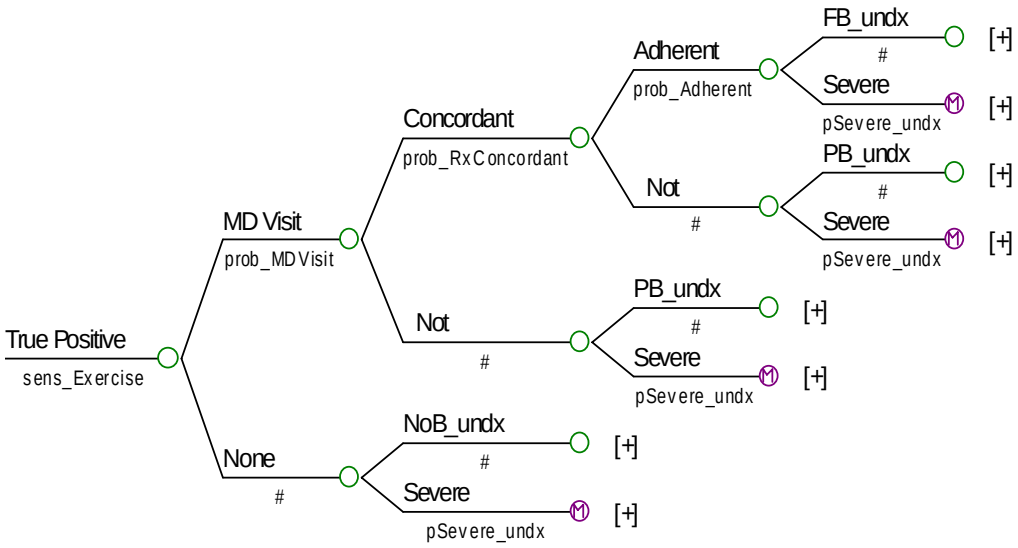
Children who are correctly identified as not having asthma (true negatives) are assigned case detection costs (questionnaire administration, spirometry, and exercise testing) and 365 QALDs. Children who are incorrectly identified as having asthma (false positives) are also assigned case detection costs and 365 QALDs, but 33% are also assigned costs associated with medical evaluation.

Children who are incorrectly identified as not having asthma (false negatives) actually have asthma. Because these children are erroneously classified, they are not expected to seek medical evaluation and only incur costs associated with case detection. Because these children do not have the opportunity to benefit from treatment, they are assigned by severity to the corresponding Markov chain that models the no-treatment

condition. Children who are correctly classified as having asthma (true positives) may benefit from case detection if this knowledge results in treatment. All children classified as true positives incur case detection costs, and only those who seek medical evaluation incur medical costs. Like false negatives, children identified as true positives who do not seek medical evaluation are assigned by severity to the corresponding Markov chain that models no treatment.

Children classified as true positives with either newly diagnosed or not well-controlled asthma who seek medical evaluation are subsequently evaluated in the same manner (Fig. 9). These children are subject to several additional chance nodes that model the probability of their assignment to treatment condition. The first chance node models the probability that they will receive guideline-concordant care. The probability of prescribing ICS to children with persistent asthma is used as a proxy measure of guideline-concordant care, even though there are other acceptable options.[1] Estimates of ICS prescribing are available from physician self-report,[58,59] which likely overestimates prescribing, and from medical claims data[60,61] which likely underestimate prescribing. The model input for the probability of guideline-concordant care is 60% (range 40-80%). No additional costs are associated with this chance node, as daily treatment costs are determined in the Markov models. Children sorted into the guideline-concordant care branch have the possibility of receiving the full treatment benefit, but children assigned to the not-concordant branch are assigned by severity to the corresponding Markov chain that models partial treatment.

FIGURE 9. Decision tree for true positives.



Children assigned to the guideline-concordant branch encounter a second chance node that represents the likelihood of treatment adherence. Again, adherence to ICS is used as a proxy measure for treatment adherence. Finkelstein et al[62] report that 50% of Medicaid-insured children ages 2-16 with persistent asthma do not take a controller medication at all and another 25% take their controller medication less than daily. David[63] reports that only 20% of Florida Medicaid-insured children with persistent asthma who received at least one controller prescription had enough controller refills to cover at least half of the year. Bauman et al[53] reports that parental self-report of adherence results in much lower estimates of underuse as only 20% of parents of inner city children ages 4-9 years report not adhering to 1 or more treatment recommendations. Like ICS prescribing, self-report likely overestimates and claims data underestimates ICS adherence; accordingly, the model input for the probability of adherence to ICS is 60% (range 40 – 80%). Children who are sorted into the "adherent" and "non-adherent" branches are assigned to

the full- and partial-treatment Markov chain, respectively. There are no costs directly attributable to this chance node.

In summary, the decision tree incorporates factors that influence the diagnostic accuracy of the screening program (prevalence, sensitivity, and specificity) and factors that influence the probability of treatment benefit (evaluation rate, guideline concordance, and adherence) given new knowledge from case detection. The end result of the decision tree is to sort children into one of 12 end states (Markov models) that reflect both their disease severity (intermittent and mild, moderate, and severe persistent) and expected treatment (full, partial, or none). Case detection costs and QALDs for children without asthma are assigned within the decision tree. Costs and QALDs for children with asthma are assigned in the Markov models. Table 3 summarizes the variables used in the decision tree.

TABLE 3. Point Estimates and Ranges for Parameters in Decision Tree

	Point Estimate	Range	Reference
Asthma Prevalence	.20	.10 – .30	
Well-Controlled Asthma	.60	.45 – .75	
Previously Diagnosed Asthma	.70	.50 – .90	
Physician Visit	.33	.15 – .45	
Guideline-concordant Care	.60	.40 – .80	
Full Adherence	.60	.40 – .80	

Case Detection Costs

Questionnaire Costs

All children incur questionnaire administration costs which, include program administration, personnel time and travel, variable equipment costs, and missed class time.

Costs related to case detection are estimated using the micro-costing technique. Additionally, cost estimates are developed based on the structure and size of the Birmingham City Schools system, where there are approximately 2500 students per grade level in 42 elementary schools.[52] Case detection is planned for only one grade level occurring annually. Total costs are divided by 2500 to yield a per child cost. Questionnaire costs are summarized in Table 4.

TABLE 4. Questionnaire Administration Costs in 2006 Dollars

Item	Cost ($)
Materials and Supplies	273
Transportation	2,444
Incentives	3,340
Program Administration	19,593
Personnel Time	8,019
Total	33,669
	(24,408-43,144)

The major components include a 0.25 full-time equivalent (FTE) program administrator valued at $19,593 (range $14,694-24,490), based on a annual mean wage estimate of $78,370 for a health services manager in Birmingham, Alabama,[64] 378 hours of a respiratory therapist time valued at $7,896 (range $5,922-9,868), based on a mean hourly wage estimate of $20.89,[64] $20.00 incentives to teachers to achieve a 100% response rate valued at $3,340 (range $1,667-5,000); and transportation costs to and from the schools valued at $2,444 (range $1,865-3,074). The estimated total cost of questionnaire administration (NQ or BQ plus ACT) is $33,669 (range $24,408-43,144). Total cost divided by 2500 children yields a per child cost of $13.49 (range $9.76-$17.25).

Two decisions with regard to questionnaire costs warrant further explanation. The decision to include costs associated with a program administrator is deemed necessary for oversight of case detection personnel and the necessary and frequent communication with local school board members, system administrators, and principals to maintain an effective working collaboration with the schools. Monetary incentives are provided to teachers in order achieve a 100% response rate. This decision is based on the experience of Gerald et al (2004)[7] who demonstrated a near 100% response rate with the use of incentives. The decision avoids the uncertainty of having to adjust for nonresponse bias from a lower response rate. These two decisions create a higher cost estimate for questionnaire administration than might otherwise be expected but are deemed reasonable and necessary.

Spirometry Costs

Spirometry costs are only incurred by children who have unknown an asthma status after questionnaire administration; therefore, the spirometry costs are estimated with the expectation of having to screen approximately 2000 children. Because children screened by one of the multi-stage procedures must first undergo questionnaire administration, spirometry costs are reported as incremental costs. Total costs for spirometry are summarized in Table 5.

TABLE 5. Spirometry Costs in 2006 Dollars

Item	Cost ($)
Spirometer Depreciation and Maintenance	975
Disposable Supplies	6,400
Personnel Time	8,990
School Absence Time	12,857
Total	29,222
	(19,530-38,680)

The major cost of spirometry is missed school time for children to attend. Children are estimated to miss approximately 1 hour of instruction to complete spirometry valued at $6.43 per hour based on a 7 hour school day and the funding rate of $45 per pupil per day in the Birmingham City Schools.[52] Transportation to and from the school is considered in the questionnaire costs. No additional trips for spirometry are needed. Personnel time includes 200 hours for one certified respiratory therapist and 2 medical assistants. The wage cost of the medical assistants is estimated at approximately $12 per hour, based on the hourly wage estimate for a medical assistant in the Birmingham metropolitan area.[64] Miscellaneous supplies required include mouthpieces, nose clips, albuterol rescue medication, and other miscellaneous items valued at approximately $3 per child. Maintenance costs and 10% spirometer depreciation per year are also considered. The physical space for conducting screening is assumed to be provided by the school at no cost. The estimated incremental per child costs of spirometry are $14.61 ($9.77-19.34).

Fixed start-up costs for major equipment, including as many as 4 spirometers are not considered; however, their purchase costs are amortized over a 10-year period to represent depreciation. A single spirometer with ancillary equipment costs approximately

1,500-3,000 dollars.[65-69] Purchasing 4 would equal approximately 15-30% of the total costs of the multi-stage procedures. The decision not to include spirometer start-up costs is consistent with the recommendation of Luce et al[48] who state, "Most input costs that are fixed in the short run will in fact be variable in the long run. Examples are the cost of the equipment used for … screening. In these cases the prices used in the CEA should be the costs that would prevail in the longer run" (p.194).

Exercise Testing Costs

Submaximal exercise testing represents an incremental cost over that of spirometry. All children who are negative on spirometry undergo submaximal exercise testing. This procedure requires minimal fixed costs, and these are not included. The major cost of exercise testing is associated with additional personnel, namely 2 extra medical assistants. This added personnel time yields an incremental per child cost of exercise testing of $2.41 (range $1.20-3.61).

Medical Evaluation Costs

Medical evaluation costs differ based on case identification result. Children identified with possible newly diagnosed asthma are expected to undergo more extensive medical evaluation than those identified with possible not well-controlled asthma. Children with newly diagnosed asthma are expected to incur direct medical costs associated with a physician visit. The direct medical costs are obtained from the Alabama Medicaid Agency (Table 6).[70]

TABLE 6. Diagnosis Confirmation Costs (Range) in 2006 Dollars for Children Identified with Possible Asthma

Procedure	Unit Cost ($)	Units Consumed	Total Cost ($)
Physician Visit	60.00	1.0	60.00
Spirometry	24.00	.35	8.40
Plain Radiography	20.00	.35	7.00
Skin Testing	2.48	.15	0.37
Sinus Radiographs	20.00	.10	2.00
Albuterol MDI	20.49	1.0	20.49
Caregiver Wage	100.98	.50	50.49
Caregiver Transportation	4.90	1.0	4.90
SAD	45.00	.50	22.50
Total			175.93 (125.95-219.91)

Half of the children are estimated to incur costs of a new, low complexity visit valued at $78 and the other half an established, low complexity visit valued at $42. Approximately one third are predicted to undergo basic spirometry ($24) plain chest radiography ($20). Fifteen percent are expected to obtain skin testing ($2.48) and 10% a sinus radiograph ($20).[58,59] A presumptive diagnosis of asthma is commonly followed by a trial of albuterol; so, the cost of a single albuterol metered dose inhaler (MDI) valued at $20.49 is also considered.[59] The albuterol medication cost estimates the costs incurred by Alabama Medicaid. The total direct medical cost per child of medical evaluation for newly diagnosed asthma is $98.

Indirect costs associated with medical evaluation are also considered, including one-half day of caregiver wages valued at $50.49, transportation costs for a 5-mile round-trip valued at $4.90, and one-half SAD valued at $22.50. The daily caregiver wage estimate is $100.98 and is derived from the median annual wage of a female between the

ages of 35 and 44 of all races ($25,435), as published in the 2005 Consumer Population Survey.[71] This wage estimate is divided by 260 working days and converted to 2006 dollars to yield the daily wage estimate.[49] Transportation costs are $0.49 per mile, based on the 2006 Internal Revenue Service allowance for mileage.[72] The total cost of medical evaluation for newly diagnosed asthma is $176 (range $126-220).

Children who are evaluated because of possible not well-controlled asthma are expected to incur costs related to an established, low complexity office visit. Half are expected to obtain basic spirometry. Indirect medical costs are also considered. The total estimated cost for medical evaluation of possible not well-controlled asthma is $132 (range $99-165) (Table 7).

TABLE 7. Total Costs (Range) in 2006 Dollars for Medical Confirmation of Asthma Control Status

Procedure	Unit Cost ($)	Units Consumed	Total Cost ($)
Physician Visit	42.00	1.0	42.00
Spirometry	24.00	.50	12.00
Caregiver Wage	100.98	.50	50.49
Caregiver Transportation	4.90	1.0	4.90
SAD	44.56	.50	22.28
Total			131.67 (98.75-164.59)

Markov Models

Introduction

Markov models represent discrete-time state-transition models that simulate both short- and long-term processes. Markov models have a number of basic characteristics.

They represent a time period that is divided into equal intervals. At the very start of the model, probabilities are used to determine the initial starting state for each member of the cohort. As time progresses from one interval to the next, individuals within the model transition from one mutually exclusive state to another based upon a set of transition probabilities. During any one interval, an individual can be in one and only one state. TreeAge[23] reports that "To calculate an expected value for the model, different cost and/or utility rewards/tolls are accumulated for each interval spent in a particular state" (p.434).

Because asthma is a chronic disease characterized by relatively long periods of "normal" health punctuated by infrequent, but abrupt, exacerbations resulting in a number of adverse outcomes, including SADs, ED visits, and hospitalizations, Markov models are an ideal method to evaluate the benefit and costs of asthma-related interventions. Each of these outcomes can be represented as discrete health states that encompass a single day's time; therefore, the cycle length used in this analysis is the single day, and the total time period of evaluation is a single year.

Torrance et al[18] recommend that the choice of a time period "for a cost-effectiveness study should extend far enough into the future to capture the major health and economic outcomes–both intended effects and unintended side effects" (p.68). Extending the time horizon long enough to capture potential lifesaving effects is also important; however, case detection is not expected to reduce mortality, so a one-year horizon should be sufficient to capture the major health and economic outcomes. This decision is supported by fact that asthma-related deaths are rare in children. In 2004, there were only 186 recorded asthma deaths in children 0-17 years of age, which is equivalent to a

rate of 2.5 asthma deaths per 1 million children.[2] To put this rate into the perspective, a single cohort of children in this analysis is only 2500 children. Another consideration supporting the choice of a single year as the time horizon is the belief that the short-term impacts of greater certainty offer more compelling evidence for the cost-effectiveness of case detection, particularly for important stakeholders, such as the school system. If case detection is cost-effective at one-year, then it is highly probable to be so over longer time horizons, given that the major costs are upfront.

With the time horizon and cycle length determined, there are 4 additional factors to model: health states, transition probabilities, costs, and health outcomes. Before discussing these factors, it is necessary to reiterate the influence of asthma severity and treatment. Children with asthma are sorted in the decision tree into one of 4 severity levels that correspond to one of the 4 severity classifications identified in the most recent asthma treatment guidelines: intermittent and mild, moderate, and severe persistent asthma.[1] Costs, health care utilization, and health outcomes are expected to vary significantly by severity; so, the Markov models must take this into account.

The costs and outcomes are also expected to vary significantly based on treatment. In this analysis, there are 3 treatment levels. They approximate guideline-concordant-care (full treatment), guideline-discordant care (partial treatment), and no asthma care (no treatment). The NHLBI guidelines[1] recognize 7 discrete levels of care. These levels are intended to guide physicians to mach treatment intensity with asthma severity and control status. Guideline concordance in this analysis is defined as Step 1 for intermittent asthma, and Steps 2 to 4 for mild, moderate, and severe asthma, respectively.[1] While it is recognized that some children may require more intense treatment

(eg Step 5), especially during exacerbations, these additional treatment steps are not modeled. To account for treatment intensification with exacerbations, the use of oral corticosteroids in the post-exacerbation period is modeled. Guideline concordance is also defined as concordance with the preferred, and not alternative, treatment recommendations. Although frequently used in practice, alternative therapies such as LTRAs, cromolyn, and nedocromil are not modeled. This decision biases toward lower daily asthma treatment costs. Given that the population of interest likely consists of a large proportion of Medicaid recipients, the extent of the bias depends on the degree of restriction of the state Medicaid formulary for asthma controller medications.

Under the full-treatment condition, children are expected to receive all recommended routine asthma-related medical care, to obtain guideline-concordant treatment consistent with their assigned severity, and to maintain full-treatment adherence. Adherence within the full-treatment condition is modeled as 90% adherence to daily ICS treatment and routine asthma-related care. The implication is that costs associated with these activities are discounted by 10%. No similar discounting of treatment effects is performed. Children assigned to the partial- and no-treatment conditions are expected to experience even less asthma-related care (eg guideline concordance and adherence). To account for this, costs in the partial- and no- treatment conditions are discounted 45% and 10%, respectively. Expected treatment outcomes in the partial- and no-treatment condition are also discounted.

The interaction between asthma severity and treatment condition also influences the expected health outcomes within the Markov models. For example, children with more discordant care and/or more severe asthma are expected to experience more fre-

quent exacerbations and worse overall health outcomes than children with more concordant care and/or less severe disease. Modeling the interaction of severity and treatment condition on expected health outcomes is complex. The impact on health outcomes is modeled as the change in the expected number of specific health outcomes, such ASFDs, ED visits, and hospitalizations. These changes are modeled individually by assigning unique transition probabilities by severity and treatment condition. The specific adjustments are discussed with the corresponding health states.

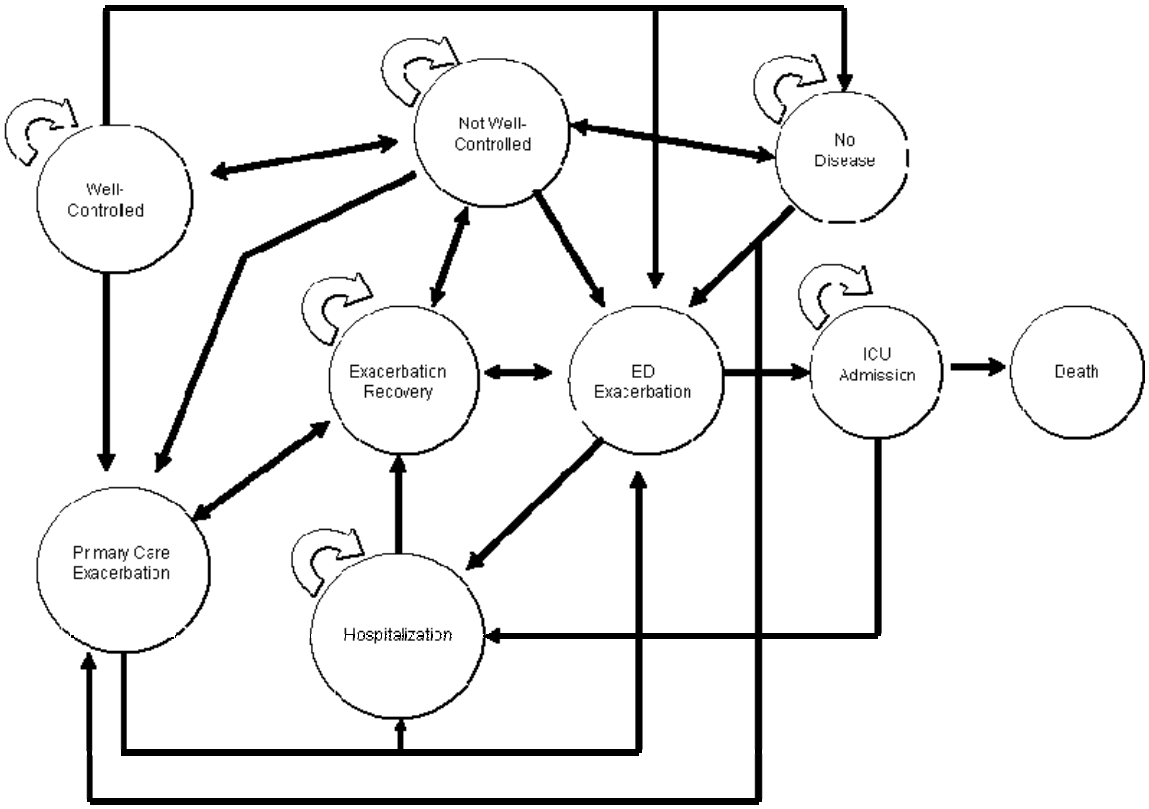
Markov models estimate the impact of case detection on health outcomes by modeling the increased probability that children exposed to case detection will obtain more guideline-concordant care controlling for level of severity. Children with greater treatment concordance have a lower probability of experiencing a negative asthma health outcome and, therefore, experience an overall improvement in health as measured by QALDs. At the same time, treatment costs and exacerbation costs are also followed. Depending on the balance between increased daily treatment costs due to case detection and avoided exacerbation costs, case detection may be more costly, cost-saving, or balanced.

Asthma Health States

Children with asthma can experience a number of discrete health states that are mutually exclusive and exhaustive (Fig. 10). The enumerated health states are important, as Mandelbaltt et al[73] state, because "to estimate the net effect of an intervention, the analyst needs to know the health states that may occur as a consequence of the intervention and the alternative, the probability that each state will occur, when each is likely to occur, and

how long each will last. … It is critical that the analysis consider all events that change the health of the patient or that generate costs" (p.135).

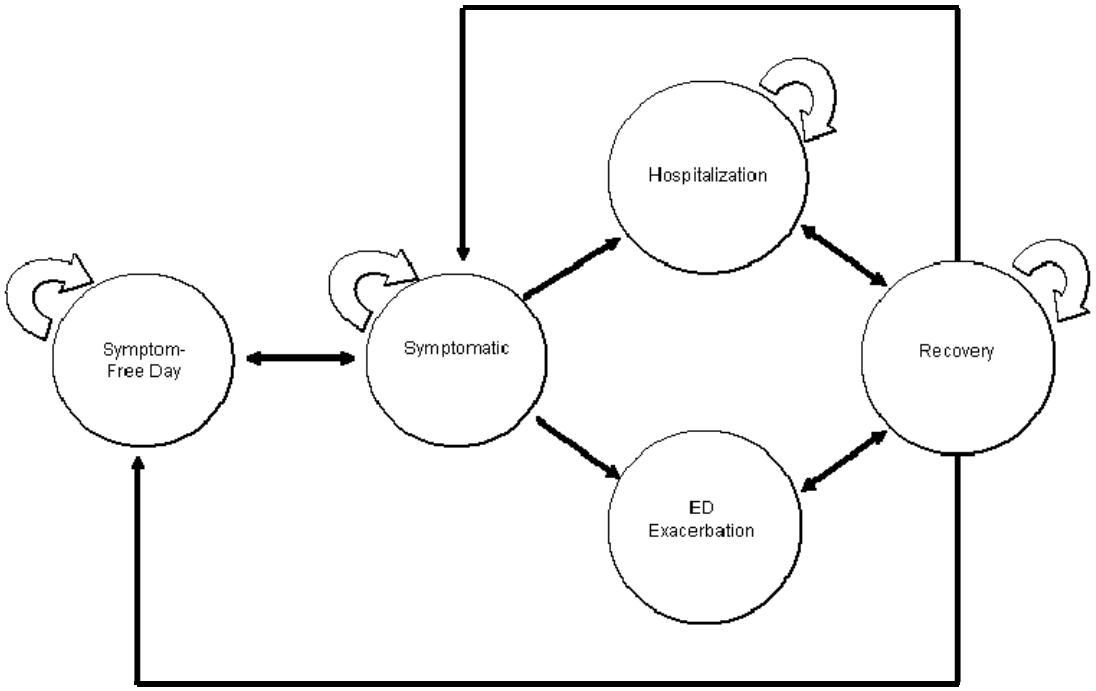
FIGURE 10. Comprehensive asthma health states.



The need for completeness must be balanced by real-world constraints; however, the number of health states and possible transitions in the comprehensive model are too numerous to model practically. A more parsimonious model is needed that captures all relevant costs and outcomes, is reliably supported by literature, and is readily programmable. The comprehensive model can be reduced to 5 basic asthma health states: the

ASFD, symptomatic asthma day, ED exacerbations, hospitalization, and exacerbation recovery days (Fig. 11).

FIGURE 11. Reduced asthma health states.



The reduced model is similar to another 5-health-state model developed by Price and Briggs.[32] The 5 health states in their model include successfully controlled, suboptimal control, primary-care-managed exacerbation, hospital-managed exacerbation, and treatment failure. The treatment failure health state is designed as an absorbing state from which patients cannot exit. Other than this exception, transitions are allowed between all health states. The cycle length for their model was one week. This model is not ideal for the evaluation of asthma screening. One reason for is the inclusion of an absorbing state. To simulate "real world" conditions, children with asthma must be able

to transition from different health states throughout the simulation. The inclusion of an absorbing state would prevent this. Another limitation is that too many allowable transition paths exist in the Price and Briggs model. While the transitions may be modeled with data from a concurrent study, secondary data does not exist to model some of the allowed transition with accuracy. For these reasons, a more parsimonious model without an absorbing state is used.

The health states classify children with asthma into distinct groups that predict the likelihood of asthma-related symptoms and health care utilization. For each of the 365 days in the model, a child with asthma exists in one and only one of the 5 mutually exclusive health states. As time progresses, children have the opportunity to move from one health state to another, based on a defined set of pathways with unique transition probabilities. These transition probabilities vary based on previously determined assignment to asthma severity level and expected treatment condition. Ultimately, following the costs and outcomes for each day's time in a health state allows the calculation of the primary outcome, 2006 dollars per QALY gained.

ASFD

The ASFD represents the "best" health state that children with asthma can experience. In this state, children do not have cough, chest tightness, shortness of breath, activity limitations, or nighttime awakenings. Their SABA use is infrequent, and exacerbation risk is low. This definition is consistent with the definition of well-controlled asthma found in the 2007 NHLBI guidelines.[1] An ASFD does not imply treatment concordance, but rather represents a period of asthma remission that is the result of some combination

of treatment effect, disease severity, environmental exposure, and airway inflammation. Therefore, children with severe asthma in the no-treatment condition experience ASFDs, but they do so less frequently than children in the full-treatment condition or those with less severe asthma.

The ASFD health state, like all health states, is associated with 4 critical pieces of information: the cost associated with a single day in the health state, the assignment of a QALD preference weight for a day in the health state, the probability of starting day 1 of analysis in the health state and the probability of transitioning to other health states, on subsequent days.

ASFD costs. Daily costs for the ASFD health state include only asthma-related costs. Direct costs include medication costs and costs of routine physician visits for asthma monitoring. Indirect costs are patient costs incurred due to routine monitoring (eg lost wages and SADs). Daily medication costs are based on guideline recommendations for the preferred treatment of asthma by initial disease severity and level of control.[1] Preferred treatment proscribes medication classes from which individual medications can be chosen. For simplification only a single medication from each of the preferred medication classes is chosen. The medication classes (single medication) used to calculate medication costs include SABAs (Proventil HFA), LABas (Serevent), ICSs (Pulmicort), and oral corticosteroids (prednisone). All of these medications, except Pulmicort, are on the preferred drug list and are readily available via Alabama Medicaid.[74] The decision to use Pulmicort even though it is not on the preferred drug list is based on the desire to be

able to model ICS and LABA separately. The impact on cost between Pulmicort and the preferred ICS is minimal and should not impact the results.

This analysis defines the preferred treatment of children with intermittent asthma as Step I care using only a SABA. The preferred treatment for children with mild persistent asthma is Step II treatment using a SABA and low-dose ICS (200 mcg/day, Pulmicort). The preferred treatment for moderate asthma is Step III treatment using a SABA and low-range, medium-dose ICS (400 mcg/day, Pulmicort). Preferred treatment for severe asthma is Step IV treatment with a SABA, LABA (100 mcg/day, Serevent), and high-range medium-dose ICS (800 mcg/day, Pulmicort).

Medication costs are calculated by discounting the average wholesale drug price (AWP) to obtain an estimate of the true cost to Alabama Medicaid.[75] The discounting formula is (0.9 discount * 0.7 Medicaid rebate * $AWP) + $5.40 dispensing fee + $1.75 co-payment.[76,77] The 10% discount is the estimated Medicaid discount price for initial purchase. The 30% Medicaid rebate is the end-of-year drug manufacturer rebate back to Alabama Medicaid. The dispensing fee is paid by Medicaid to the pharmacy for preparation. The co-payment is paid by the patient at time of dispensing. The medication acquisition costs including dispensing fee are shown in Table 8.

TABLE 8. Medication Unit Costs in 2006 Dollars Including Dispensing Fee

Medication	Unit Cost ($)
Budesnonide (Pulmicort)	103.26
Salmeterol (Serevent)	82.92
Albuterol (Proventil HFA)	26.32
Prednisone (generic)	9.67

The cost assigned for one routine asthma-related monitoring visit including the cost of one established patient, low complexity physician visit, a 50% chance of undergoing basic spirometry charge, one-half day's lost caregiver wage, one-half day school absence, and a single 10-mile round-trip personal transportation is $131.89. This amount is discounted in the full-(10%), partial-(55%), and no-treatment condition (90%) to yield $118.70, $59.35, and $13.19, respectively. These annual costs are divided by 365 to yield daily estimates and are added to the daily medication cost to yield the total costs for a day in the ASFD state (Table 9).

TABLE 9. Daily Treatment Costs (Annualized) in 2006 Dollars for Asthma Symptom Free Day by Severity and Treatment Effect

Severity	Full Treatment	Partial Treatment	No Treatment
Severe Persistent	5.39 (1,967)	2.73 (995)	0.60 (218)
Moderate Persistent	1.65 (601)	0.86 (312)	0.18 (66)
Mild Persistent	0.86 (312)	0.46 (168)	0.10 (34)
Intermittent	0.23 (83)	0.15 (54)	0.03 (9)

The rate of physician visits for routine, asthma-related monitoring is consistent with the 2007 NHLBI Guidelines[1] that recommend routine monitoring of asthma control and medications at 1- to 6-month intervals, depending on the level of control. The rate of routine, asthma-related services is also adjusted for asthma severity by a factor such that children with intermittent and mild, moderate, and severe asthma experience on average 0.5, 1, 2 and 3 asthma-related office visits per year for routine monitoring. These visits

are in addition to annual routine well-child visits for all children recommended by the American Academy of Pediatrics.[78]

QALD Assignment. Gold et al[24] state, "The ideal system for use in a Reference Case analysis should meet the criteria of: (1) derivation from a theory-based method on which empirical data have been collected; (2) availability of weights from a representative, community-based sample of the U.S. population; (3) low burden of administration in clinical and population-based settings; and (4) ability to furnish weights for health states, as well as for illnesses and conditions" (p.120). In this analysis, the preference weights for specific health states are derived from the development of the PAHOM about which Chiou et al[34] state it is a "multi-attribute, asthma-specific outcome measure for children with asthma that allows for the calculation of QALYs …[and] can be used to assess the daily impact of asthma with a health classification system … and assign preference weights to various asthma-related health states based on community preferences" (p.24). These preference weights are based on visual analog scale and standard gamble techniques, which represent the 2 preferred methods of preference weight development from expected utility and psychological scaling theory, respectively.[24]

The health states in the PAHOM contain attributes from three domains: symptoms (none, moderate, and severe), emotional disturbance (present or absent), and activity limitations (present or absent). Chiou et al[34] state, "The 3 X 2 X 2 classification system results in 12 unique health states. However, we removed the two health states (s3, e1, a1) and (s3, e2, a2) because we believed children hospitalized due to severe breathing problems would experience activity limitations" (p. 25). The remaining 10 health states en-

compass all of the possible health states for a child with asthma. Each of these states is associated with a specific weight that values the relative worth of spending a day in that health state compared to a day in optimal health. Gold et al[24] state, "To satisfy the QALY concept, the quality weights must be preference-based, interval scaled, and measured or transformed onto an interval scale where the reference point 'death' has a score of 0.0 and the reference point 'optimal health' has a scale of 1.0….Community preferences for health states are the most appropriate ones for use in a Reference Case analysis" (p.122). Again, the PAHOM-derived preference weights satisfy these conditions, as they have interval scale properties and are derived from a community-based sample of adults in the Seattle, Washington, metropolitan area.[34]

However, the PAHOM weights cannot be used directly in this analysis because the PAHOM health states do not map exactly on the 5 asthma health states of this analysis. The 10 PAHOM health states are ranked by preference weight and then grouped to form 5 categories that are then mapped onto the 5 health states in this analysis. The preference weight point estimates for the health states in this analysis are calculated as the mean preference weight of the PAHOM health states (e.g. s1, e1, a1) that are grouped together to form the analysis health state (e.g. ASFD). The grouping of PAHOM health states to map onto the analysis health states is potentially controversial, as there is no clear right or wrong answer. To account for this, relatively large sensitivity ranges are used to estimate the impact of the preference weight assignment on the ICER. The upper and lower ranges are created using the lowest and highest PAHOM preference weights, respectively, from the adjacent analysis heath states (Table 10).

TABLE 10. Preference Weight Conversions for Asthma Health States Derived from the Pediatric Asthma Health Outcomes Measure (PAHOM)

Dissertation Health State	PAHOM Equivalent	PAHOM Utility	CEA Utility	Sensitivity Range
ASFD	(s1, e1, a1)	1	1	0.96 - 1
	(s2, e1, a1)	.96		
Symptomatic	(s1, e2, a1)	.89	0.9	0.76 – 0.96
	(s1, e1, a2)	.85		
	(s2, e2, a1)	.76		
Recovery	(s2, e1, a2)	.71	0.70	0.49 – 0.85
	(s1, e2, a2)	.64		
ED Exacerbation	(s3, e1, a2)	.49	0.43	0.06 – 0.64
	(s2, e2, a2)	.37		
Hospitalization	(s3, e2, a2)	.06	0.06	0.01 – 0.37

The ASFD health state is assigned a preference weight of 1 (range 0.96-1) and corresponds to the (s1, e1, a1) PAHOM health state. This health state is defined as no symptoms, emotional problems, or activity limitations. Children in the ASFD health state are assigned QALD at a rate equivalent to children without asthma.

Transition Probabilities. It is necessary to estimate the likelihood that a child with asthma will experience the ASFD health state versus any other health state. Graphically, the possibility of transitioning from the ASFD state to another is represented by arrows that exit the ASFD health state in Figure 8. This figure shows that once a child is in the ASFD state, it is possible to remain there or transition to the symptomatic, ED exacerbation or hospitalization states. The absence of an arrow leading to the exacerbation recovery state indicates that this transition is not allowed. This graphical representation demonstrates what is possible, but not what is probable. The probability of transitioning

to another health state is represented by individual variables within the Markov model termed transition probabilities.

There are 2 specific transition probabilities needed to complete the Markov model. The first is the probability of starting day 1 of the analysis in a specific health state. The second is the probability of remaining in a health state or transitioning to another on subsequent days. In this analysis, rates are used as the underlying data element and are subsequently converted into probabilities to derive the actual transition probabilities. There are a number of reasons for this. One is that population-based rates are readily available in the literature; however, these average rates cannot be used directly, because this analysis requires rates that reflect differences by asthma severity and treatment effect. It is possible to disentangle these relationships by choosing a reference group against which all others are compared. For this analysis, children with mild persistent asthma experiencing full treatment are chosen as the reference point for determining ASFD rates by severity and treatment effect. This group is chosen because good evidence from 2 RCTs exists.[79,80]

This approach is advantageous because rates, and not probabilities, have mathematical properties that allow addition, subtraction, multiplication, and division. Once a base rate of ASFDs is defined, the rates of ASFDs in other groups are calculated using conversion factors for severity and treatment effect. After these rates have been calculated, they are converted to transition probabilities using the formula, $p = 1 - e^{-rt}$, where r equals rate and t equals the time period of 1 year. The annualized rates of ASFDs by severity and treatment condition are shown in Table 11.

TABLE 11. Rate of Asthma Symptom Free Days (ASFDs) per Year by Asthma Severity and Treatment Effect

Severity	Full Treatment	Partial Treatment	No Treatment
Intermittent	346	277	225
Mild Persistent	260	208	169
Moderate Persistent	195	156	127
Severe Persistent	130	104	85

The base ASFD rate for children with mild persistent asthma experiencing full treatment is 260 (range 210-300) ASFDs per year. This estimate is derived from a RCT of daily ICS treatment in children with mild persistent asthma.[79] The conversion factor to adjust the ASFD rate from full to partial treatment is 0.8 (range .7-.9), which results in 208 ASFDs per year for children with mild persistent asthma experiencing partial treatment benefit. This point estimate is also derived from Boushey[79], as it is reported that children treated with either intermittent ICS or daily LTRAs experienced 20% fewer ASFD than children treated with daily ICS (full treatment). This choice is also supported by a similar reduction in ASFD (25% fewer) from another RCT of daily ICS versus LRTA or placebo in a population of children with mild and moderate persistent asthma.[80]

Data to support the choice of a conversion factor to adjust ASFDs from the full- to no-treatment benefit are not readily available. One reason for this is that the no-treatment group has by definition undiagnosed asthma; therefore, data from RCT data are not available because to be eligible for such a RCT a subject would have to have previously diagnosed asthma. Second, the no-treatment condition is defined as no daily controller therapy for children with persistent asthma. RCTs are unable to create a "true" no-treatment arm, as this would be unethical. The RCT placebo group is not an acceptable

substitute for the no treatment condition because these children are diagnosed, because placebo treatment is associated with at least some interventions (ie education and monitoring), and because RCTs select for highly motivated patients. These limitations mean that the placebo group is unlikely to be representative of the hypothetical no-treatment group. Therefore, the choice of 0.65 (range .55-.75) as the conversion factor for adjusting full to no treatment is made with the assumption that the magnitude of effect is similar to that seen moving from full to partial treatment. This conversion factor results in 169 ASFDs per year for children with mild persistent asthma experiencing no treatment. The magnitude of its impact is identifiable by sensitivity analysis.

The conversion of the ASFD rate from mild persistent to other asthma severity levels is based on reports of ASFD rates by severity in a cohort of adults recruited from specialized asthma centers in Italy.[81] The use of an adult, non-U.S. reference population for severity conversion factors is not ideal, but it is the only complete source of ASFD rates by severity. With the ASFD rate for mild persistent asthma as a reference, the conversion factors for intermittent, moderate persistent, and severe persistent asthma are 1.33, 0.75, and 0.5, respectively. This corresponds to annual ASFD rates of 346, 195, and 330, respectively, in children with mild persistent asthma experiencing full treatment. The individual conversion factors for the rate of ASFDs by severity and treatment are shown in Table 12.

TABLE 12. Conversion Factors for Rate of Asthma Symptom Free Days (ASFDs) per Year by Asthma Severity and Treatment Effect

Severity	Full Treatment	Partial Treatment	No Treatment
Intermittent	1.33	1.06	.86
Mild Persistent	1	.80	.65
Moderate Persistent	.75	.60	.49
Severe Persistent	.50	.40	.33

The annualized rate of ASFDs in the entire cohort of children with previously diagnosed asthma in the full-, partial-, and no-treatment groups is 276, 221, and 179, respectively. To put this in perspective, children with previously diagnosed asthma who move from the partial-treatment condition to the full-treatment condition due to case detection experience 55 days more days a year (4.6 per month) in the ASFD state. Children with undiagnosed asthma who by definition begin in the no-treatment condition and who then move to the partial- or full-treatment conditions due to case detection gain 32 days a year (2.7 per month) or 87 days a year (7.3 per month), respectively. These 3 annualized ASFD gains represent one of several possible mechanisms by which case detection improves health outcomes.

Taken together, these estimates represent the probability of experiencing an ASFD on any given day, accounting for severity and treatment effect for children who spent the previous cycle in either the ASFD or symptomatic health state. All children who transition from the recovery state to the ASFD state do so at a probability of 0.75.[84] No other transitions to the ASFD health state are allowed. In this analysis, children are only allowed to start day 1 in the ASFD or symptomatic health states. These transition

probability estimates above are also used as day 1 starting probabilities for the ASFD health state. The complement of the ASFD probability is the probability that a child will start in the symptomatic health state.

Symptomatic health state

The symptomatic health state represents a period of increased disease activity marked by more frequent and severe symptoms, more frequent SABA use, and greater risk of exacerbations leading to greater health care utilization. In this state, children experience frequent cough, chest tightness, shortness of breath, activity limitations, and/or nighttime awakenings. This health care state is consistent with the 2007 NHLBI guideline[1] definition of not well-controlled or poorly controlled asthma. As before, the symptomatic health state does not imply a lack of treatment concordance, but children with less treatment concordance and/or more severe asthma are more likely to transition to and remain in this less desirable health state. Exacerbations that do not result in ED visits or hospitalizations are also included in this health state.

Costs. Daily costs for the symptomatic health state are calculated similarly to those of the ASFD health state. Costs include only asthma-related costs of direct medical care (daily medications and routine physician monitoring) and indirect patient costs incurred due to routine monitoring (eg lost wages and SADs). Costs are adjusted to account for asthma severity and treatment condition as they are for the ASFD state. The only difference in the total daily cost calculation for the symptomatic versus ASFD health state is a 4-fold increase in SABA costs. This represents an increase of approximately

$0.20 per day (2 inhalations twice a week to 2 inhalations a day). The specific cost inputs, daily totals, and annualized totals for the symptomatic health state are presented in Table 13.

TABLE 13. Daily Treatment Costs (Annualized) in 2006 Dollars for a Symptomatic Day by Severity and Treatment Effect

Severity	Full Treatment	Partial Treatment	No Treatment
Severe Persistent	5.59 (2,039)	2.92 (1,067)	0.62 (226)
Moderate Persistent	1.84 (673)	1.05 (384)	0.20 (74)
Mild Persistent	1.05 (384)	0.66 (240)	0.12 (43)
Intermittent	0.43 (155)	0.34 (126)	0.05 (17)

QALD Assignment. Mapping PAHOM health states onto the symptomatic state is difficult, as some combination of the 9 remaining PAHOM states must selected. The symptomatic health state is deemed to be less desirable than the ASFD health state but more desirable than the exacerbation recovery health state. The rationale for being preferred to the recovery state is that children in the recovery state take oral corticosteroids with potential side effects, experience daily symptoms throughout most of the recovery period, and experience impairments that result in multiple SADs.[82]

The preference weight point estimate for the symptomatic health state is the mean preference weight of the 3 PAHOM health states that are grouped to form the symptomatic health state. The symptomatic health state is assigned a preference weight of 0.9 (range 0.76-0.96) and corresponds to three PAHOM health states: (s1, e2, a1); (s1, e1, a2)

and (s2, e1, a1). These three PAHOM states represent either moderate symptoms without emotional problem or activity limitation or no symptoms with either emotion problem or activity limitation. The upper range estimate is bounded by the lowest PAHOM preference weight from the group above (s1, e1, a1), and the lower range estimate is bounded by the highest PAHOM preference weight from the group below (s2, e2, a1). This grouping of PAHOM health states is associated with significant uncertainty. To account for this, a relatively large sensitivity range is used to estimate the impact of the preference weight assignment on the ICER.

Transition Probabilities. Once in the symptomatic health state, it is possible to remain there or transition to the ASFD, ED exacerbation, or hospitalization health states. Transition to the ASFD state represents improvement resulting from some combination of treatment and/or underlying disease activity. Transition to the ED exacerbation or hospitalization state represents exacerbations severe enough to warrant medical attention. Transition to the recovery state is not allowed. The probability of starting day 1 in the symptomatic state is the complement of the probability of starting in the ASFD state after adjusting for asthma severity and treatment effect. Complement probabilities are used as specific transition probabilities to other health states from the symptomatic state because the other transition probabilities are better supported by the literature. Because the transition probabilities to the symptomatic state are complement probabilities, they are not specifically presented. The probability of remaining in the symptomatic state once in it is the remainder of 1 minus the probability of transitioning to the ASFD, ED, or hospitalization states from the symptomatic state. The probability of transitioning to the sympto-

matic state from the recovery state is the complement of the probability of transitioning to the ASFD state from the recovery state.

ED Exacerbation State

The ED exacerbation state represents an exacerbation that is severe enough to warrant medical care, but not severe enough to require hospitalization. Exacerbations that result in urgent outpatient care visits are not modeled, because appropriate data on outpatient use is not available. A wealth of data document that children with asthma use outpatient services frequently; however, no distinction is made between outpatient visits for routine monitoring versus urgent care.[81,83-87] In this analysis, outpatient visits for routing monitoring are accounted for in the daily costs associated with the ASFD and symptomatic health states, but outpatient visits due to urgent care are not. This decision biases the results away from demonstrating cost-effectiveness to the extent that case detection and subsequent treatment reduce exacerbations; however, the bias should be minimal, due to the fact that outpatient costs are much lower than ED or hospitalization costs.

Costs. The costs associated with the ED exacerbation state include direct medical service costs related to the ED visit itself and indirect costs related to patient and caregiver costs. Data on the direct medical costs of ED services are available from Hayward,[88] and Pawar and Smith,[85] and Piecoro et al.[89] Piecoro et al report the average amount paid by Kentucky Medicaid in fiscal year 1996 for ED visits for children and adults with asthma as $368.61 in 2006 dollars. Hayward reports the average amount paid

by Rhode Island Medicaid in 2002 for ED visits for children and adults with asthma as $366.81 in 2006 dollars. Pawar and Smith report the average amount paid by West Virginia Medicaid in 2002 for an ED visit for Blacks less than 65 years of age with asthma as $178.78 in 2006 dollars. This significantly lower estimate is acknowledged but is not specifically incorporated into the point estimate for the costs of ED visit direct medical services, $350 (range $275-425).

Indirect costs associated with an ED visit include 2.5 days lost caregiver wages, 2.5 SADs, and one 5-mile round trip transportation cost. One-half day's caregiver wage, one-half SAD, and one transportation cost are directly attributable to the ED visit itself. The remaining 2 day's caregiver wage loss and SADs represent costs incurred during convalescence supported by data from Stevens and Gorelick[82] who report on a population of urban children who experienced an asthma-related ED visit in 1996-1997. The median number of SADs is 2 per child following an ED visit and 50% of caretakers working outside the home report at least one lost day of work, and 20% missed 3 or more days. The point estimate for indirect costs of an ED visit is $369 (range $277-461). The point estimate for total costs of an ED visit is $719 (range $539-898).

QALD. Mapping PAHOM health states onto the ED exacerbation state is difficult, as well. This health state is deemed to be less desirable than the recovery state, but more desirable than the hospitalization state. The preference weight point estimate for the ED exacerbation state is the mean preference weight of the two PAHOM health states that comprise the ED exacerbation state. The ED exacerbation state is assigned a preference weight of 0.43 (range 0.06-0.64) and corresponds to two PAHOM health states: (s3,

e1, a2) and (s2, e2, a2). These 3 PAHOM states represent either moderate symptoms with both emotional problems and activity limitations or severe symptoms with only activity limitations. The s3 state is intended to represent symptoms significant enough to warrant medical intervention.[34] The upper range estimate is bounded by the lowest PAHOM preference weight from the recovery group (s1, e2, a2), and the lower range estimate is bounded by the highest PAHOM preference weight for the hospitalization state (s3, e2, a2). To account for uncertainty, a relatively large sensitivity range is used to estimate the impact of the preference weight assignment on the ICER.

Transition Probabilities. The ED exacerbation state can be reached only from the symptomatic state. The decision not to allow ED visits from the ASFD state represents a simplification of the model. While it is possible to experience a sudden exacerbation due to a specific exposure or infection in the ASFD state, requiring a 24-hour transition to the symptomatic state first is reasonable. It is not possible to remain in the ED exacerbation state for more than one cycle. From the ED exacerbation state, all children exit to the exacerbation recovery health state. The decision is supported by the fact that utilization data and costs resulting from ED visits that result a hospitalization are often subsumed in hospitalization data and costs;[85] therefore, ED exacerbations in this analysis represent independent visits that never lead to hospitalizations.

Transition probabilities to the ED exacerbation health state are adjusted for severity and treatment effect, much like ASFD probabilities. In order to create the necessary conversion factors, ED exacerbations are manipulated as rates then converted to probabilities. Because of the effect of the interrelationship between severity, treatment effect,

age, race, income, and other factors on ED utilization rates, establishing a base rate for ED exacerbations in children with asthma is difficult. The literature contains reports of ED utilization rates that vary by a factor of approximately 10.[83-86,88-93]

One particular study by Donahue et al[93] demonstrates the variability in ED utilization that can be observed. Donahue et al used claims data to describe health care utilization of children with asthma in 3 large medical care organizations (MCO) in Seattle, Chicago, and eastern Massachusetts from July 1996 to June 1997. A low annual estimate of 40 ED visits per 1,000 children ages 6-8 with previously diagnosed asthma is observed in one MCO (the MCO locations are not revealed), and a high annual estimate of 120 per 1,000 is observed in another. An even larger difference is observed in children ages 9-11. In this group, the observed range is 20-140 ED visits per 1,000 per year, a 7-fold difference. Treatment patterns are similar among the groups, but the MCO with the highest proportion of children receiving Medicaid benefits (19%) also has the highest ED utilization rates.

The finding of increased ED utilization among children with Medicaid is supported by Ortega et al[90] who report 50% increase in the relative risk of ED visit for children with Medicaid versus private insurance. Among children with Medicaid, higher ED utilization is observed in Black children versus White children.[84,86,95] ED utilization rates in Blacks ages 6-64 with asthma receiving Medicaid in Texas in the year 2000 is reported as 227 per 1,000.[82] ED utilization rates of Blackchildren ages 0-20 in West Virginia receiving Medicaid are reported as 400 per 1,000.[85] Given this data, the ED utilization rate for children with previously diagnosed asthma is expected to be approximately 250 per 1,000 (range 100-400).

This population estimate represents the target ED utilization rate for the analysis population based on the utilization rates for individual children adjusted for severity and treatment effect. Dolan et al[92] report on ED utilization by asthma severity for children with difficult to treat asthma. The ratios of ED visits by severity for mild, moderate, and severe persistent asthma are 1, 2, and 4, respectively. Diette et al[96] report on ED utilization by severity for adult patients with asthma. The ratios of ED visits by severity for mild, moderate, and severe persistent asthma are 1, 1.5, and 2, respectively. Antonicelli et al[81] reports on ED utilization among adults with asthma in Italy. The ratio of ED visits by severity for mild, moderate, and severe persistent asthma are 1, 1.2, and 3.2, respectively. Antonicelli also reports on the ratio between intermittent and mild persistent asthma of approximately 0.25. Given this information, the conversion factors to adjust for severity of intermittent and mild, moderate, and severe persistent asthma are 1, 4 (range 2.5-5.5), 6 (range 4-8), and 12 (range 9-15), respectively. The ED utilization rate for intermittent asthma is used as the reference group.

Data to support conversion factors for treatment effect are provided by the Childhood Asthma Management Program Research Group[80] (CAMP). This RCT compares daily ICS with daily LTRA and placebo. The observed treatment effect of daily ICS is a 45% and 25% reduction in urgent care visits versus the placebo and nedocromil treatment groups, respectively. Supporting evidence from an observational study indicates a 50% decrease in ED utilization in patients ages 5-60 with asthma among users of ICS versus non-users.[97] Adams et al[90] report that children ages 3-15 with asthma who were prescribed any controller (including ICS) medication experienced a 70% reduction in ED visits, and children prescribed ICS experienced a 50% reduction compared to those with

no controller prescriptions. Smith et al(2004) [98] and Camargo et al[91] report similar findings in Medicaid populations. Given this data the conversion factors for full, partial and no treatment effect are 1, 2, and 2.5, respectively.

With intermittent asthma as the reference group, an annual ED utilization rate of 36 per 1,000 combined with the conversion factors yield an annual ED utilization rate of 250 per 1,000 in children with previously diagnosed asthma. Varying this rate between 22 and 50 per 1,000 yields the desired population range of 150-350 annual ED visits per 1,000 children. The annualized ED utilization rates and conversion factors by severity and treatment effect are listed in Tables 14 and 15, respectively.

TABLE 14. Rate of Emergency Department Visits per Year by Asthma Severity and Treatment Effect

Severity	Full Treatment	Partial Treatment	No Treatment
Intermittent	36	72	90
Mild Persistent	144	288	360
Moderate Persistent	216	432	540
Severe Persistent	432	864	1080

TABLE 15. Conversion Factors for Rate of Emergency Department Visits per Year by Asthma Severity and Treatment Effect

Severity	Full Treatment	Partial Treatment	No Treatment
Intermittent	1	2	2.5
Mild Persistent	4	8	10
Moderate Persistent	6	12	15
Severe Persistent	8	24	30

Hospitalization Health State

The hospitalization state represents the most severe manifestation of an exacerbation. Intensive care days are considered to be included in the hospitalization state and are not modeled independently. Asthma deaths are also not modeled, because they are rare events at this scale.[2]

Costs. The costs associated with the hospitalization state include direct medical service costs related to the hospitalization itself and indirect costs related to patient and caregiver costs. Hayward[88] reports the average amount paid per day of hospitalization by Rhode Island Medicaid in 2002 for children and adults with asthma as $1,239 in 2006 dollars. The average length of stay (LOS) is reported as 3.02 days. Pawar and Smith[85] report the average amount paid by West Virginia Medicaid in 2002 for a hospitalization for Blacks less than 65 years of age with asthma as $4,080 in 2006 dollars. No length of stay data is provided. Gupta et al[99] report median hospital charges for children admitted for asthma as $5,280 in 2006 dollars. Charges are reported as significantly higher for children who are Black, who receive Medicaid, and who are admitted to children's hospitals after adjusting for LOS; however, the specific LOS figures are not available. Hospital charges overestimate costs by a significant factor and cannot be used directly. Given this data, the point estimate for daily hospitalization costs is $1,200 (range $900-1500). The mean LOS is 2.5 days.

Indirect costs associated with hospitalization include one day's lost caregiver wages, 1 SAD, and one 5-mile round trip transportation cost per hospital day. Two additional days of lost caregiver wages and SADs are added to the recovery period immedi-

ately following hospitalization to represent convalescence. This is supported by data from Stevens and Gorelick.[82] The point estimate for total costs of a day's hospitalization is $1350 (range $1,013-1,688).

QALD. Mapping PAHOM health states onto the hospitalization state is comparatively straightforward. This health state is deemed to be the least desirable. It is assigned a preference weight of 0.06 (range 0.01-0.37) and corresponds to the (s3, e2, a2) PAHOM health state. This PAHOM state represents severe symptoms, with both emotional problems and activity limitations. The upper range estimate is bounded by the lowest PAHOM preference weight from the ED exacerbation group (s2, e2, a2), and the lower range estimate is arbitrarily chosen.[34] The relatively large range is used to estimate the impact on the ICER of the uncertainty surrounding the preference weight point estimate.

Transition Probabilities. It is possible to transition from the hospitalization state to the exacerbation recovery state or to remain in the hospitalization health state. The decision not to allow hospitalizations from the ASFD state represents a simplification of the model, like that of ED exacerbations. It is possible to remain in the hospitalization state for up to 7 days. To allow this, the hospitalization health state is a tunnel state with a length of 7 days. From the hospitalization state it is only possible to transition to the recovery state. The probability of transitioning to the recovery state is 0.39 for days 1-6 and 1.0 on day 7. This yields a hospitalization LOS estimate of 2.48 days.

The hospitalization state can be reached only from the symptomatic and recovery states. Transition probabilities to the hospitalization state are adjusted for severity and treatment effects much like ED exacerbation and ASFD probabilities. In order to create the necessary conversion factors, hospitalizations are manipulated as rates then converted to probabilities. Because of the effect of the interrelationship between severity, treatment effect, age, race, income, and other factors on hospitalization rates, a base rate for hospitalizations in children with asthma is challenging. Fortunately, the literature regarding hospitalization rates do not vary as wildly as those of ED visits.[83-86,88-93]

As a comparison to ED visit utilization, Donahue et al[93] also report on the variability of hospitalization rates in a population of children with asthma in 3 large MCOs in Seattle, Chicago, and eastern Massachusetts from July 1996 to June 1997. A low annual estimate of 15 hospitalizations per 1,000 children ages 6-8 with previously diagnosed asthma is observed in one MCO (the MCO locations are not revealed), and a high annual estimate of 30 per 1,000 is observed in another. Again, treatment patterns are similar among the groups but, in an unexpected outcome, the MCO with the highest proportion of children receiving Medicaid benefits (19%) had the lowest hospitalization rate, unlike the pattern observed for ED utilization.

This finding of decreased hospitalization among children with Medicaid is not supported by Ortega et al[94] who report an increased relative risk of hospitalization for children with Medicaid (1.2, 95% CI: 1.0, 1.5) versus private insurance, particularly among Black children (3.3, 95% CI: 0.8, 14.4). Higher hospitalization rates among Black children with Medicaid are also observed by Lieu et al,[84] Lozano et al,[95] and Smith et al (2005).[86] Hospitalization rates in Blacks ages 6-64 with asthma receiving Medicaid in

Texas in the year 2000 is reported as 53 per 1,000.[86] The hospitalization rates of Black children ages 0-20 in West Virginia receiving Medicaid are reported as 150 per 1,000.[85] Given this data, the target annual hospitalization rate for children with previously diagnosed asthma is approximately 100 per 1,000 (range 50-150).

These individual hospitalization estimates for severity and treatment effect are created in a similar way to those of ED visit rates. For hospitalization, the reference group is children with mild persistent asthma. Dolan et al[92] report on hospitalization by asthma severity for children with difficult to treat asthma. The ratios of hospitalizations by severity for mild, moderate, and severe persistent asthma are 1, 3, and 10, respectively. Diette et al[96] report on hospitalization rates by severity for adult patients with asthma. The ratio of hospitalization rates by severity for mild, moderate, and severe persistent asthma are 1, 2.3, and 3.9, respectively. Antonicelli et al[81] report on hospitalization rates among adults with asthma in Italy. The ratios of hospitalization visits by severity for mild, moderate, and severe persistent asthma are 1, 0.75, and 3, respectively. Antonicelli et al also report on the ratio between intermittent and mild persistent asthma of approximately 0.2. Given this information, the conversion factors to adjust for severity of intermittent and mild, moderate, and severe persistent asthma are 0.25 (range 0.2-.33), 1, 2 (range 1.5-3), and 4 (range 2-8), respectively.

Data to support conversion factors for treatment effect are provided by CAMP.[80] This RCT compares daily ICS with daily LTRA and placebo. The observed treatment effect of daily ICS is a 75% reduction in hospitalizations versus both the placebo and LTRA treatment groups. Supporting evidence from an observational report of children ages 3-15 with asthma who were prescribed any controller (including ICS) medication or

just ICS experienced 60% fewer hospitalizations compared to those with no controller prescriptions.[90] Smith et al (2004)[98] and Carmargo et al[91] report similar findings in Medicaid populations. Given this data, the conversion factors for full-, partial- and no-treatment effect are 1, 2, and 2.5, respectively. This is the same magnitude of effect seen for ED utilization.

Children with mild persistent asthma serve as the reference group. An annual hospitalization rate of 50 per 1,000 combined with the conversion factors yields an annual hospitalization rate of 100 per 1,000 in the analysis population of children with previously diagnosed asthma. Varying this rate between 25 and 75 hospitalizations per 1,000 yields the desired range of 50-150 annual hospitalizations per 1,000 children. The annualized hospitalization rates and conversion factors by severity and treatment effect are listed in Tables 16 and 17, respectively.

TABLE 16. Rate of Hospitalizations per Year by Asthma Severity and Treatment Effect

Severity	Full Treatment	Partial Treatment	No Treatment
Intermittent	13	25	31
Mild Persistent	50	100	125
Moderate Persistent	100	200	250
Severe Persistent	200	400	500

TABLE 17. Conversion Factors for Rate of Hospitalizations per Year by Asthma Severity and Treatment Effect

Severity	Full Treatment	Partial Treatment	No Treatment
Intermittent	.25	.50	.625
Mild Persistent	1	2	2.5
Moderate Persistent	2	4	5
Severe Persistent	4	8	10

Exacerbation Recovery Health State

The exacerbation recovery health state represents the final common pathway between exacerbation resolution and a child's "typical" health state (e.g. ASFD or symptomatic health states). The exacerbation recovery period is associated with more frequent and severe symptoms, greater treatment intensity, and greater risk of exacerbation than either of the other 2 health states.[82]

Costs. The costs associated with the recovery state are calculated in a similar fashion to those of the ASFD and symptomatic health states, such that direct medical service costs are related to daily medications and recommended physician monitoring and indirect costs related to patient and caregiver costs. Costs are adjusted to account for asthma severity and treatment benefit assignment. Adjustments for severity include assigning only medication costs specific to severity level according to guideline recommended treatment. Adjustment for the full-, partial- and no-treatment benefit conditions include cost modifiers for daily controller medications and routine monitoring of 0.9, 0.45, and 0.1, respectively. These modifiers account for decreased adherence to controller therapies and recommended physician monitoring. SABA use is 8 times that seen in the ASFD state, reflecting an average of 4 inhalations per day, and is constant across severity levels. The only other difference in the total daily cost calculation for the recovery state versus the ASFD state is the addition of a oral corticosteroid burst of 30 mg/day for 5 days estimated to cost $6.09. Transition to the recovery state also incurs a one-time cost of 1 outpatient visit and associated indirect costs to reflect recommended follow-up

after hospitalization or ED visits. The daily and 2 week totals for the symptomatic health state are presented in Table 18.

TABLE 18. Daily Treatment Costs (2 Week Costs) in 2006 Dollars for Exacerbation Recovery Day by Severity and Treatment Effect

Severity	Full Treatment	Partial Treatment	No Treatment
Severe Persistent	14.04 (197)	7.63 (107)	2.64 (37)
Moderate Persistent	10.62 (149)	5.92 (83)	2.26 (32)
Mild Persistent	10.16 (142)	5.69 (80)	2.21 (31)
Intermittent	9.70 (136)	5.46 (76)	2.16 (30)

QALD. Mapping PAHOM health states onto the recovery state is difficult as well. This health state is deemed to be less desirable than the symptomatic state but more desirable than the ED exacerbation state. The preference weight point estimate for the recovery state is the mean preference weight of the 3 PAHOM health states that comprise the recovery state. The symptomatic health state is assigned a preference weight of 0.70 (range 0.49-0.85) and corresponds to 3 PAHOM health states: (s2, e2, a1), (s2, e1, a2) and (s1, e2, a2). These 3 PAHOM states represent either moderate symptoms, with either emotional problems or activity limitations or no symptoms, with both emotional problems and activity limitations. The upper range estimate is bounded by the lowest PAHOM preference weight from the symptomatic state (s1, e1, a2), and the lower range estimate is bounded by the highest PAHOM preference weight for the ED exacerbation

state (s3, e1, a2).[34] To account for uncertainty, a relatively large sensitivity range is used to estimate the impact of the preference weight assignment on the ICER.

Transition Probabilities. From the exacerbation recovery state it is possible to transition to 4 other health states: minimally symptomatic, symptomatic, ASFD, and ED exacerbation. Like the hospitalization health state, the exacerbation recovery state is modeled as a tunnel state with a fixed duration (14 days). At anytime during the 14 days, children can exit into either the ED exacerbation or hospitalization state. The probability of doing so is much higher than in either the ASFD or symptomatic states representing the high risk of re-visit during the recovery period.[82] The annualized hospitalization rate is 780 per 1,000, and the annualized ED visit rate is 3,400 per 1,000. These are constant by severity and treatment effect. On the 14th day, children in this health state that do not exit into the ED exacerbation or hospitalization state exit into the ASFD state ($p = 0.75$) or symptomatic state ($p = 0.25$).

School Absence Days

National estimates of SADs indicated that children with asthma experience approximately twice as many SADs per year as children without asthma, 6 and 3, respectively. The excess number of SADs in children with asthma is estimated to be 2.5 absences.[3] A study of inner city children with asthma by Moonie et al[33] demonstrates more SADs in elementary-age school children with asthma (mean = 8, 95% CI = 7.3, 8.5), but a smaller differential when compared with children without asthma (mean = 6.9, 95% CI = 6.7, 7.1). Absences due to asthma only accounted for 31% of all absences, and those

due to another illness, including asthma, accounted for another 45% of absences. Children with intermittent asthma (8.5 SADs) experienced significantly fewer absences than those with persistent asthma (11.5 SADs). For this study, the estimated number of excess asthma-related SADS in children with asthma is 2 (range 1-3).

RESULTS

Decision Tree Analysis: Case Detection Results

Any evaluation of a case detection methodology must consider the impact of the underlying epidemiological factors of sensitivity, specificity, and prevalence. These factors are important components of the decision tree, and their potential impact on the overall results are examined. There are 2 distinct case detection methodologies employed. The first is the ACT, which identifies not well-controlled asthma in the population of children with previously diagnosed asthma. This methodology is common to all 4 of the case detection interventions. Because of this, it does not distinguish one intervention from another, but it does influence each intervention's overall cost-effectiveness.

A hypothetical cohort of 2500 children are subjected to ACT case detection, given the base assumptions of asthma prevalence, probability of previously diagnosed asthma, probability of well-controlled asthma, and ACT sensitivity and specificity. Under these conditions, 500 children are expected to have asthma, including 350 predicted to have previously diagnosed asthma. Among these 350 children, 140 are expected to have not well-controlled asthma. Using this information, it is possible to evaluate the efficiency of the ACT (Table 19).

TABLE 19. Case Detection Results of Asthma Control Test (ACT) under Base Assumptions

	Not Well-Controlled	Well-Controlled	Total
ACT (+)	98	57	155
ACT (−)	42	153	195
Total	140	210	350

The ACT correctly identifies 98 of the 140 (70%) children who have not well-controlled asthma and incorrectly identifies 57 of the 210 (27%) children who have well-controlled asthma. This is consistent with the sensitivity and specificity estimates for the ACT. The 98 children who are correctly identified with not well-controlled asthma are the only children who can potentially benefit from case detection; however, to do so they must also seek medical evaluation, obtain ICS, and be adherent to treatment. In this analysis, achieving these additional requirements is not certain but is instead based on the input probabilities of 33%, 60%, and 60%, respectively. Under these additional assumptions, the number of children who could potentially benefit from case detection is reduced from 98 to 12, representing a substantial loss of efficiency. The benefits accrued by these 12 children must be weighed against the costs incurred by 19 of the 57 children incorrectly identified as having not well-controlled asthma who are predicted to seek medical evaluation unnecessarily. This scenario describes the costs and benefits of the NQ intervention, as the only children who benefit from this intervention are those with previously diagnosed asthma who are not well-controlled.

The second case detection methodology combines the identification of not well-controlled asthma using the ACT with the identification of new asthma cases using one of the 3 other mutually exclusive interventions. The same epidemiological and behavioral assumptions made for the ACT apply to these interventions as well. From the previous cohort of 2500 children, 2,150 children with unknown asthma status remain, including 150 who are predicted to have undiagnosed asthma. The efficiency of the 3 interventions is evaluated (Table 20).

TABLE 20. Case Detection Results (Incremental Results) of Identification of New Asthma Cases

Methodology	True Positive	False Positive	True Negative	False Negative
Multi-Stage with Spirometry	54	60	1940	96
	(-)	(-)	(-)	(-)
Multi-Stage with Exercise	68	60	1940	82
	(14)	(0)	(0)	(-14)
Broad Questionnaire	96	800	1200	54
	(28)	(740)	(-740)	(-28)

The BQ correctly identifies the greatest number of new asthma cases, 96 out of 150 children (64%) with asthma, and incorrectly identifies the greatest number of "normal" children as having asthma. When the 96 children are subject to the additional requirements of seeking medical evaluation, obtaining ICS, and being adherent to treatment, the number of children predicted to receive at least some benefit from case detection is reduced to 32, 11 who receive full benefit and 21 who receive partial benefit. These benefits are counter-balanced by the costs incurred by the 267 of the 800

incorrectly diagnosed children who seek medical evaluation unnecessarily, but an evaluation of the incremental changes reveals a truer picture of the cost-benefit structure of the BQ. Compared to the MSwET intervention, the BQ identifies only 28 additional new asthma cases but does so at the cost of an additional 740 misidentified cases.

There are 3 important findings that have implications for the final analysis. The first is the substantial loss of case detection efficiency due to the modeled behavioral factors. This loss of efficiency reduces the number of children predicted to benefit from case detection and subsequently make the interventions less cost-effective than if they were not considered. The second is the large number of false positive results obtained by the BQ relative to the other interventions. The costs incurred by these children have the potential to dramatically influence the results. Finally, the ACT contributes to the absolute, but not relative, ranking of case detection cost-effectiveness, as it is common to all 4 interventions. Another implication of this is that the cost-effectiveness of the NQ reflects only the impact of identifying not well-controlled asthma in children with previously diagnosed asthma.

Reference Case Results

For the reference case analysis, costs are reported in 2006 dollars per child and health outcomes are reported as QALDs gained per child. QALDs are converted to QALYs, so that ICERs are reported as 2006 dollars per QALY. Only 2 interventions are not dominated, the MSwET intervention and the BQ. The MSwET intervention has an ICER of $107,168 per QALY gained, and the BQ has an ICER of $398,300 per QALY gained (Table 21).

TABLE 21. Reference Case Cost-Effectiveness Results

Intervention	Total Costs† ($)	Total Effect† (QALD)	Incr. Costs ($)	Incr. Effect (QALD)	ICER ($/QALY)
Status Quo	148.86	360.821	-	-	-
Narrow Questionnaire	161.05	360.841	12.19	.020	dom.
Multi-stage with Spirometry	164.40	360.867	3.35	.026	dom.
Multi-stage with Exercise	164.60	360.875	0.20	.008	107,168
Broad Questionnaire	181.37	360.890	16.76	.015	398,300

† Costs and Effects are per child screened.

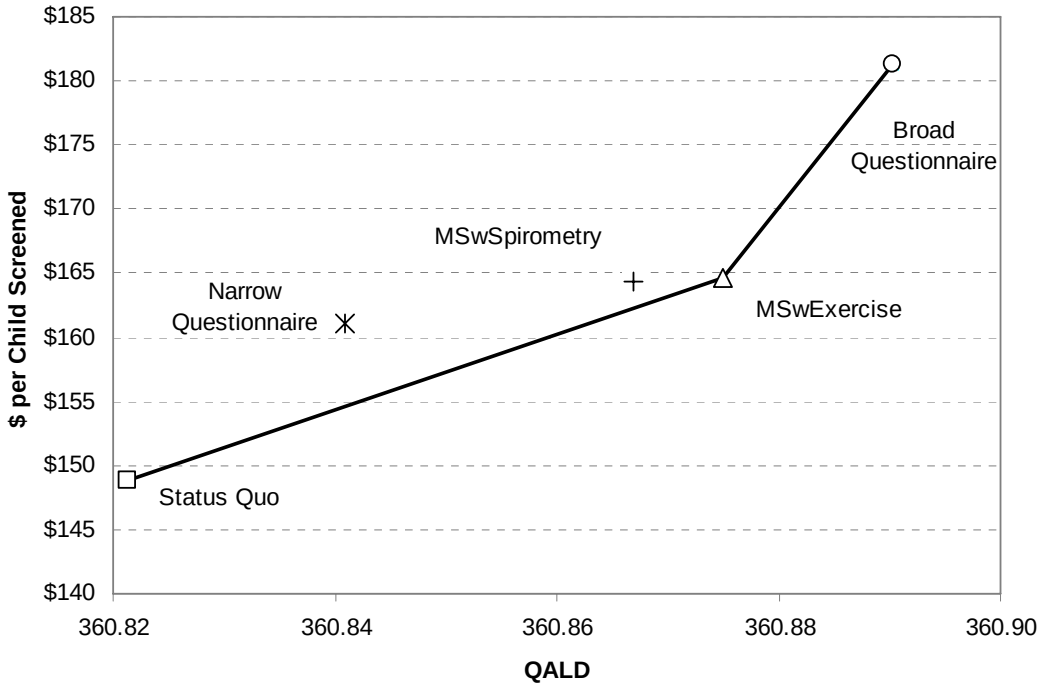
The *status quo* condition is least costly at $149 per child screened. Among the case detection interventions, the least expensive is the NQ, followed by the MSwS, MSwET, and BQ interventions. The large difference observed in total costs between the NQ and BQ despite having identical questionnaire administration costs occurs because the BQ identifies large numbers of false positives relative to the NQ. These children incur additional costs related to diagnosis confirmation.

The *status quo* condition is associated with the least QALDs, but all interventions yield very similar QALDs. These results are difficult to interpret directly, as QALDs are generated by all children and not just those with asthma; however, only children with asthma can experience gains in QALDs. The magnitude of the increase in QALDs gained by the average child with asthma can be calculated. For example, the difference in QALDs between the *status quo* and the BQ is 0.07 QALD per child screened per year.

In our hypothetical cohort, this gain represents approximately 175 days, concentrated in the 500 children with asthma who on average gain one-third QALD per year.

The NQ and MSwS interventions are weakly dominated interventions because they cost more per additional unit of benefit than the MSwET. This is why their ICERs are not reported and their costs and effects are not considered in subsequent ICER calculations.[20] The concept of dominance can be graphically presented. Hunick et al[20] note that dominated programs are identified by being above "the line of optimal programs (also known as the efficiency frontier) and the graph demonstrates the diminishing marginal returns of programs as you go up the efficiency frontier" (p. 284) (Fig. 12).

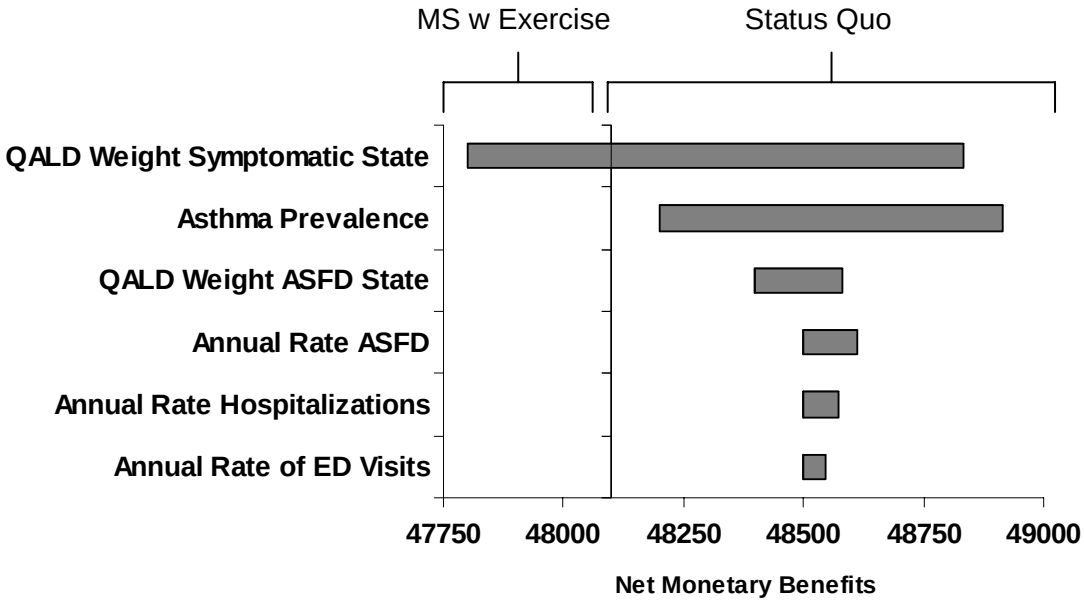
FIGURE 12. Reference case cost-effectiveness graph.



Sensitivity Analysis

Manning et al[54] suggest that sensitivity analysis be conducted on all nonformulaic variables to investigate "how sensitive the results might be to a substantial but not implausible change in that parameter" (p. 249). The sensitivity analysis is undertaken using two different outcome measures: net monetary benefits (NMB) and the ICER. NMB is the product of total effectiveness and WTP minus total costs. TreeAge[23] notes that using it is advantageous when comparing multiple interventions as "the most cost-effective comparator is simply the one with the highest net benefit, given the same threshold ICER" (p. 396). This strategy is also useful in identifying variables that over the course of their range are associated with different preferred strategies (see Fig.13).

FIGURE 13. Reference case tornado diagram of most influential variables.



Five variables account for 99% of the total uncertainty, and two account for 95%. The vertical line at NMB= 48,100 represents a WTP of $50,000 per QALY gained. To the left of the line, the MSwET intervention is preferred, and to the right the *status quo* is preferred. Only one variable, the QALD preference weight for the symptomatic health state, has a NMB range that crosses the $50,000 QALY line. The point estimate (range) of the QALD preference weight is 0.9 (0.76-0.96). The asthma prevalence estimate is the second-most influential variable, but it does not have an outcome range that crosses the cost-effective line. The point estimate (range) for asthma prevalence is 0.2 (0.1-0.3). In their most favorable positions, the corresponding ICERs for the MSwET intervention are $40,850 and $59,107 per QALY, respectively (Tables 22 and 23). These effects are also graphically presented (Figs. 14 and 15).

TABLE 22. One-Way Sensitivity Analysis of the Symptomatic Health State Preference Weight

Range Estimate	Intervention	Cost ($)	QALD	Incr. Cost	Incr. QALD	ICER ($/QALY)
0.76	*Status quo*	149	355.424	-	-	-
	MS w/Exercise	166	355.571	16.48	.147	40,850
	Broad Questionnaire	182	355.603	16.77	.032	193,535
0.96	*Status quo*	149	363.113	-	-	-
	MS w/Exercise	166	363.149	16.48	.036	166,925
	Broad Questionnaire	182	363.156	16.77	.007	835,741

TABLE 23. One-Way Sensitivity Analysis of Asthma Prevalence

Range Estimate	Intervention	Cost ($)	QALD	Incr. Cost	Incr. QALD	ICER ($/QALY)
0.10	*Status quo*	74.60	362.903	-	-	-
	MS w/Exercise	90.70	362.938	16.10	.035	169,375
	Broad Questionnaire	109.44	362.945	18.75	.007	936,540
0.30	*Status quo*	223.78	358.709	-	-	-
	MS w/Exercise	240.64	358.813	18.86	.104	59,107
	Broad Questionnaire	255.43	358.835	14.79	.022	246,241

FIGURE 14. One-way sensitivity analysis of the symptomatic health state preference weight

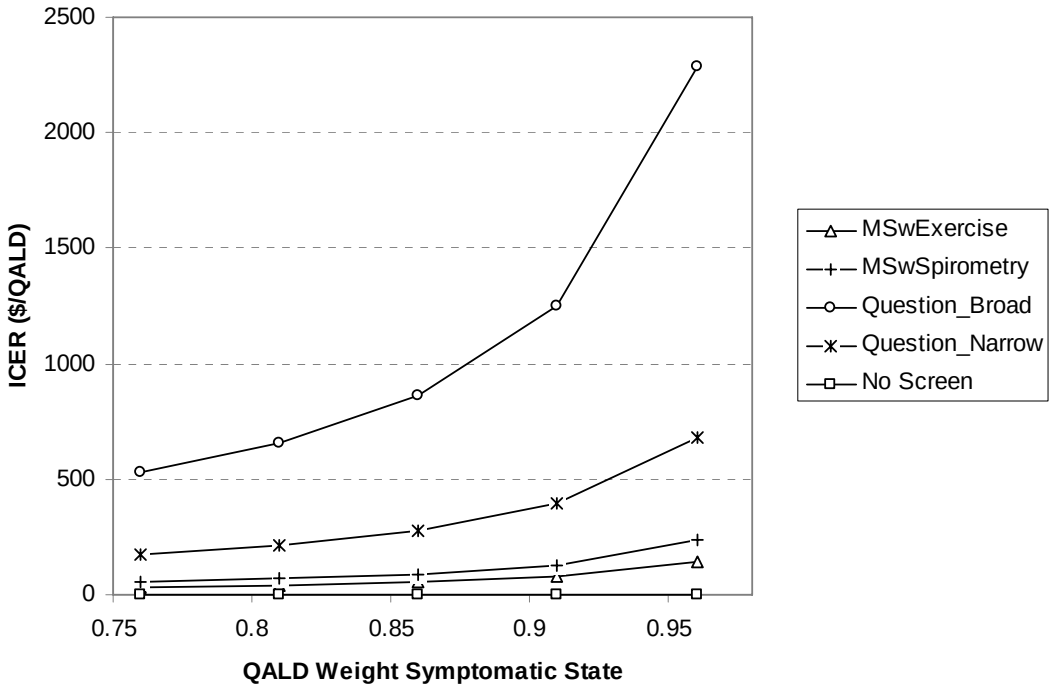


FIGURE 15. One-way sensitivity analysis of asthma prevalence

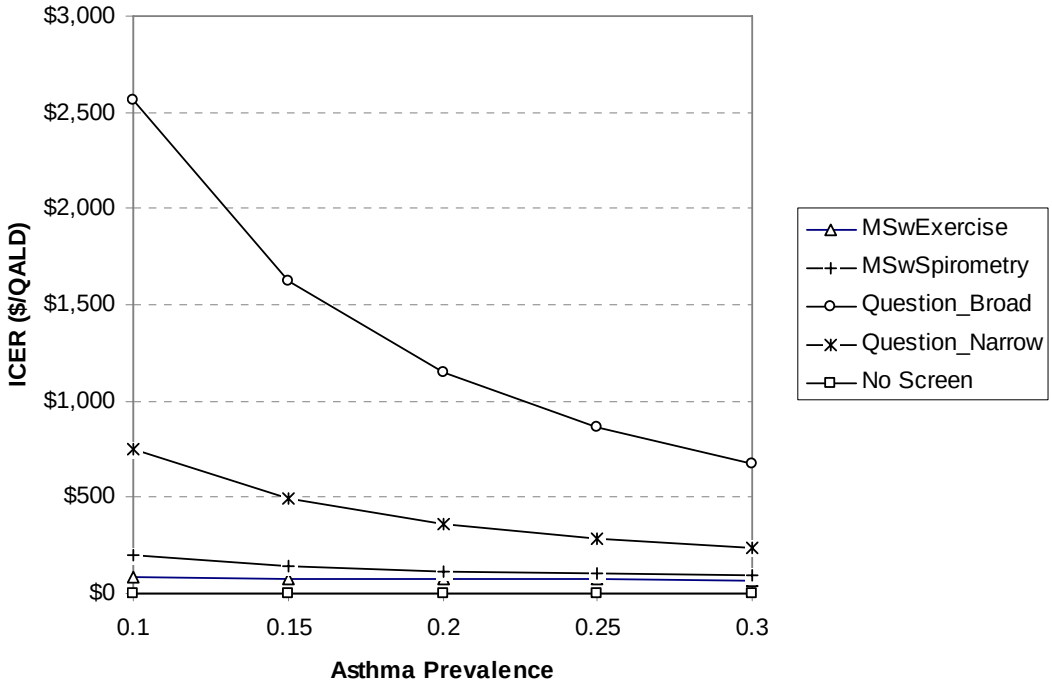
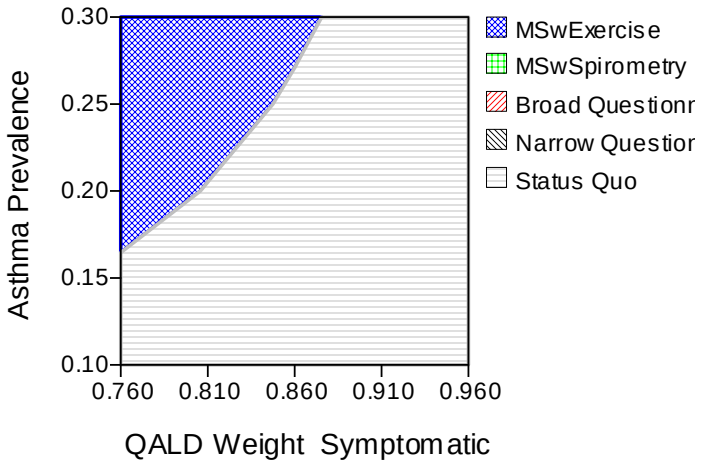


Figure 14 demonstrates that all interventions become more cost-effective as the symptomatic state QALD preference weight decreases. The impact is greatest on the BQ, but the curves demonstrate that BQ will not overtake the MSwET intervention over the range of plausible values. When the preference weight is less than 0.81, the MSwET intervention becomes cost-effective at a threshold of $50,000 per QALY. Lower values of the preference weight are associated with improved cost-effectiveness, because treatment results in greater gains in quality of life. Figure 15 demonstrates that all interventions become more cost-effective as asthma prevalence increases. Higher prevalence results in improved cost-effectiveness because, as prevalence increases, there are more children who benefit from case detection. These results demonstrate the

robustness of the model and provide strong evidence that the MSwET intervention is the most likely intervention to be cost-effective.

A 2-way sensitivity analysis that allows both variables (QALD Weight for Symptomatic State and Asthma Prevalence) to vary simultaneously while all others are held constant is performed. The 2-way sensitivity analysis demonstrates that, as asthma prevalence increases, the QALD preference weight for the symptomatic state can rise and the MSwET intervention can remain cost-effective. This information can be useful to determine what the asthma prevalence needs to be in order for case detection to be cost-effective given a specified preference weight or *vice versa*. Therefore, over certain ranges greater certainty in one variable can offset less certainty in another (Fig. 16).

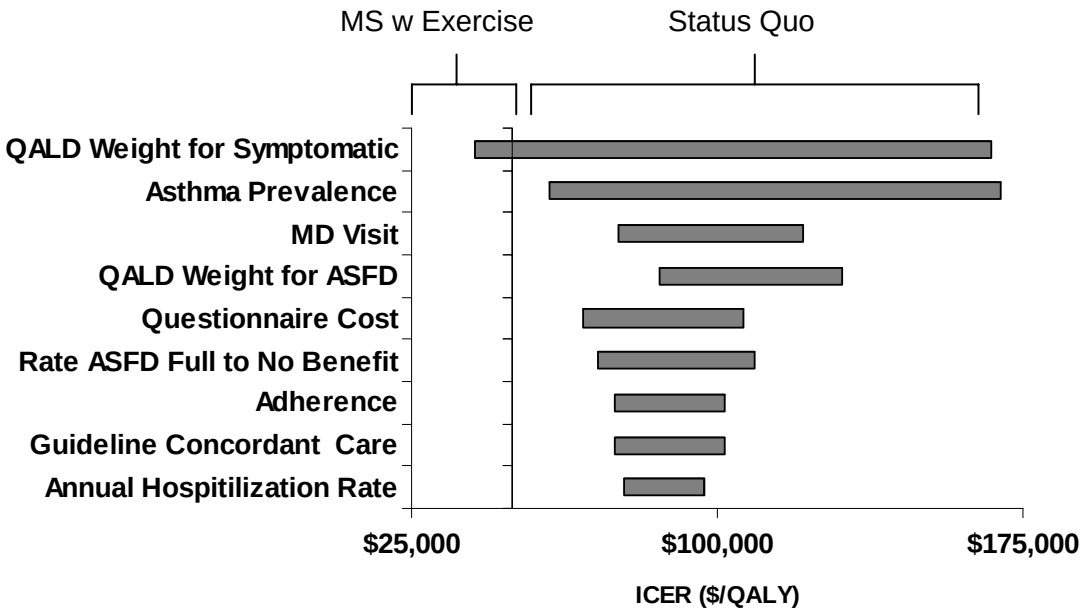
FIGURE 16. Two-way sensitivity analysis of the symptomatic state preference weight and asthma prevalence.



The results so far have demonstrated how the total uncertainty in the modeled variables influences the preferred case detection strategy. From this, it is clear that if any

case detection strategy is going to be cost-effective it is going to be the MSwET. Additional insight into what variables are important in influencing the cost-effectiveness of the MSwET intervention when compared to the *status quo* can be gained by sensitivity analysis using the ICER as the outcome measure instead of NMB. The symptomatic health state QALD preference weight and asthma prevalence are the 2 most influential variables accounting for over 70% of the total uncertainty; however, 7 additional variables account for another 25% of the uncertainty (Fig. 17).

FIGURE 17. Tornado diagram of give most influential variables comparing the Multi-Stage with Exercise Testing intervention and the s*tatus quo.*



Again, only one of these variables, the QALD preference weight for the symptomatic state, when assigned its most favorable estimate, results in cost-

effectiveness at a threshold of $50,000 per QALY. The sensitivity ranges are reported below for the variables that account for 99% of the uncertainty in the model (Table 24).

TABLE 24. Selected Sensitivity Results Comparing the Multi-Stage with Exercise Testing Intervention and the *Status Quo*

Variable	Range Estimate	Low ICER ($/QALY)	High ICER ($/QALY)
QALD Weight Symptomatic State	.76-.96	40,844	166,915
Asthma Prevalence	.30-.10	59,094	169,360
Probability of MD Visit	.45-.15	75,844	120,779
QALD Weight ASFD State	.96-1	85,921	130,524
Questionnaire Cost	$9.76-17.25	67,051	106,507
ASFD Rate Full to No Benefit	.55-.75	70,920	108,916
Probability Guideline Concordance	.8-.4	75,008	101,835
Probability Adherence	.8-.4	75,008	101,835
Annual Rate of Hospitalizations	150-50	77,344	96,652
ASFD Rate Mild Persistent to Intermittent	1.53-1.13	79,132	97,966
Prob. Previously Diagnosed Asthma	.5-.9	79,716	96,871
QALD Weight Recovery State	.49-.85	77,818	94,353
Annual Rate of ED Visits	350-150	80,410	93,586
Specificity of MS w/Exercise Intervention	.99-95	80,410	92,929
Annual Rate ASFD	300-210	83,512	93,440
Hospitalizations Rate Full to No Treatment	3-2	81,797	91,688
Specificity of Asthma Control Test	.77-.69	82,016	91,725
ED Rate Full to No Treatment	2-3	82,381	91,250

Best-Case Scenario

The best case scenario represents a special type of sensitivity analysis where all of the inputs are set to the extreme of their range of plausible values in the direction that is most favorable to case detection (i.e. lowest cost-effectiveness ratio).[54] This is another way to evaluate the robustness of the model. If under the ideal conditions, case detection is not cost-effective then that is strong evidence that it is not cost-effective in practice. If

it is found to be cost-effective under ideal conditions, then the model results are not definitive. The best case scenario must be interpreted cautiously, as it is unlikely that all of the variables will align in such a way in real life. Results are presented in Table 25.

TABLE 25. Best Case Scenario Reference Case Analysis

Intervention	Total Costs† ($)	Total Effect† (QALD)	Incr. Costs ($)	Incr. Effect (QALD)	ICER ($/QALY)
Multi-stage with Exercise	500.17	350.83	-	-	-
Multi-stage with Spirometry	502.76	350.73	2.58	-.10	dom.
Broad Questionnaire	506.81	351.03	6.63	.21	11,798
Narrow Questionnaire	516.82	350.27	10.01	-.77	dom.
Status Quo	521.70	350.03	14.89	-1.01	dom.

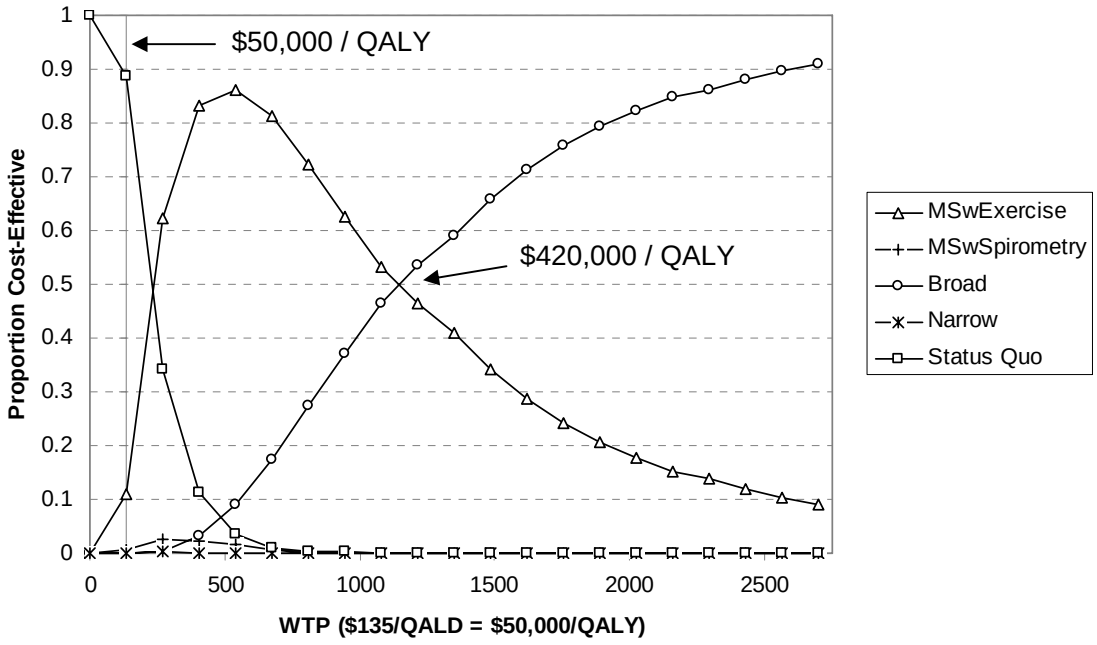
The best case analysis demonstrates that the MSwET intervention is cost-saving $21.53 per child screened or $53,825 in our hypothetical cohort of 2,500 children. The BQ has an ICER of $11,798 per QALY gained, which is below the threshold of $50,000 per QALY gained.

Acceptability Curve

Hunick et al[20] state that the acceptability curve "plots the relative frequency or probability that the strategy is cost-effective compared to the alternative for varying threshold values of the CE ratio" (p. 358). In this analysis, the acceptability curve is generative via a probabilistic sampling of the modeled inputs over their range of possible values. This differs from the base analysis, which is derived solely from a large number of microsimulation trials undertaken without sampling from the range distributions. The

2 techniques generate very similar results but are interpreted slightly different. The microsimulation results are interpreted as the cost-effectiveness of the average child screened given the modeled variables as fixed without uncertainty. The probabilistic results are interpreted as the most likely cost-effectiveness given the uncertainty surrounding the point estimates of the modeled variables. This approach allows one to see how changes in WTP affect the probability that any one strategy is cost-effective relative to others (Fig. 18).[20]

FIGURE 18. Acceptability curve for reference case analysis.



At a WTP of $0, the *status quo* is the preferred option, as it is the least costly option. As WTP increases, the MSwET intervention becomes more likely to be the most effective option. At a WTP of $50,000 per QALY, the probability that the MSwET

intervention is the most effective is approximately 10%. At a WTP of $83,000 per QALY, the MSwET intervention is more likely to be the most effective condition. At a WTP of approximately $420,000 per QALY, the BQ is more likely to be the most effective intervention.

Probabilistic sampling also allows one to estimate the likely range of ICERs, given the inherent uncertainty regarding the modeled variables. The resulting interpretation is similar to a 90% confidence interval (Fig. 19).

FIGURE 19. Probability distribution of incremental cost-effectiveness ratio.

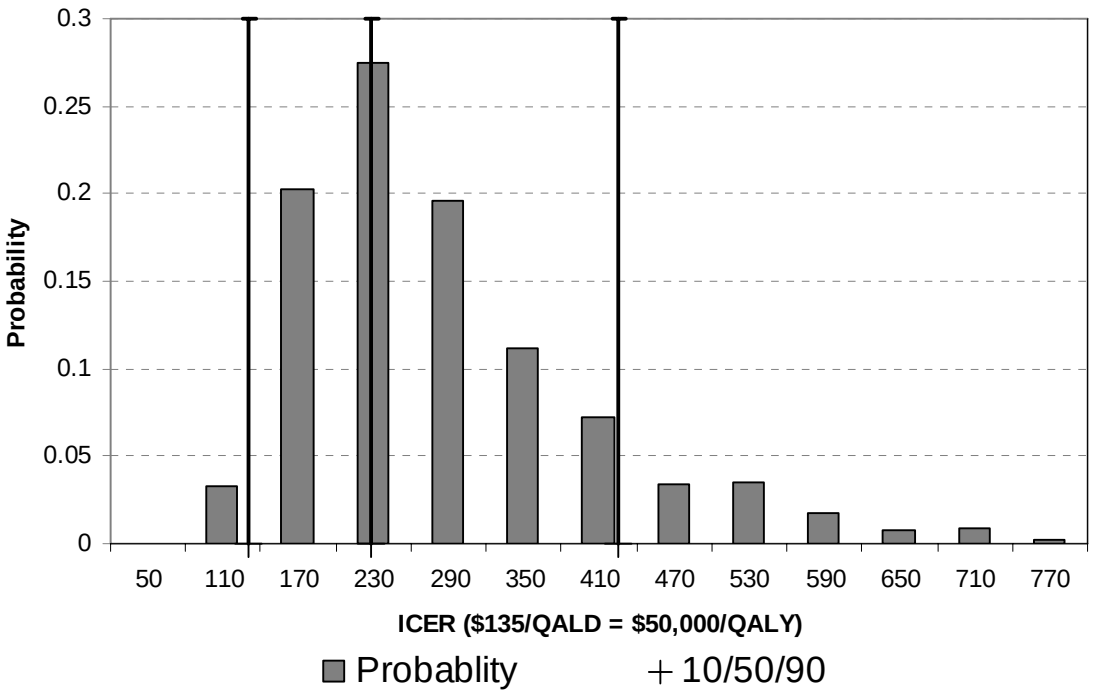


Figure 19 shows the distribution of ICER values generated from the comparison of the MSwET intervention and the *status quo*. The 50% percentile ICER is $83,100 per QALY, with 90% of values falling between $47,400 and $155,500 per QALY. The

distribution shows skewness, which is reflected by the mean ICER, $93,400 per QALY, being higher than the median ICER, $$83,300 per QALY. The minimum ICER observed from the probabilistic sampling methodology is $20,500 per QALY. These results assist interpretation of the best-case findings, which demonstrate that the MSwET intervention is cost-saving. From sampling alone, it is extremely unlikely to observe cost-savings from case detection. The best-case scenario forces the simultaneous alignment of all parameter estimates to their most favorable position. Given that there are 143 variables modeled, the probability that this occurs due to chance alone is infinitesimally small.

School System Perspective

For the analysis from the school system perspective, costs are valued in 2006 dollars per child screened and effects are valued as true positives (newly diagnosed or not well-controlled asthma cases) identified per child screened. The ICER is reported as 2006 dollars per true positive gained. Dividing this ICER by the cost of a SAD ($45) yields the number of prevented SADs needed for the school system to be indifferent to the costs of case detection.

From the school system perspective, only the direct costs of case detection are relevant. Costs associated with confirming the case detection findings, with asthma treatment and with asthma-related health care utilization, are not considered because these costs are paid by others. Because the BQ and NQ interventions have the exact same administration cost, $0.01 is added per child to case detection costs of the BQ strategy to

allow the calculation of dominance. As in the reference case analysis, only the ICERs for interventions that are not dominated or weakly dominated are presented (Table 26).

TABLE 26. Cost-Effectiveness Results from School System Perspective

Intervention	Total Costs† ($)	Total Effect† (QALD)	Incr. Costs ($)	Incr. Effect (QALD)	ICER ($/QALY)
Status Quo	$0	0	-	-	-
Narrow Questionnaire	$13.47	.005	$ 13.47	.005	dom.
Broad Questionnaire	$13.47	.009	$ 0.00	.005	$1,462
Multi-Stage with Spirometry	$28.08	.007	$ 14.61	-.002	dom.
Multi-Stage with Exercise	$30.49	.008	$ 17.02	-.001	dom.

† Costs and Effects are per child screened.

The *status quo* condition by definition is least costly and results in no new cases being identified. All interventions except the BQ are dominated. The ICER of the BQ is $1,462 per case identified. The number of prevented SADs needed for the school system to be indifferent to the costs of case detection is $1,462 divided by $45, which equals 33.

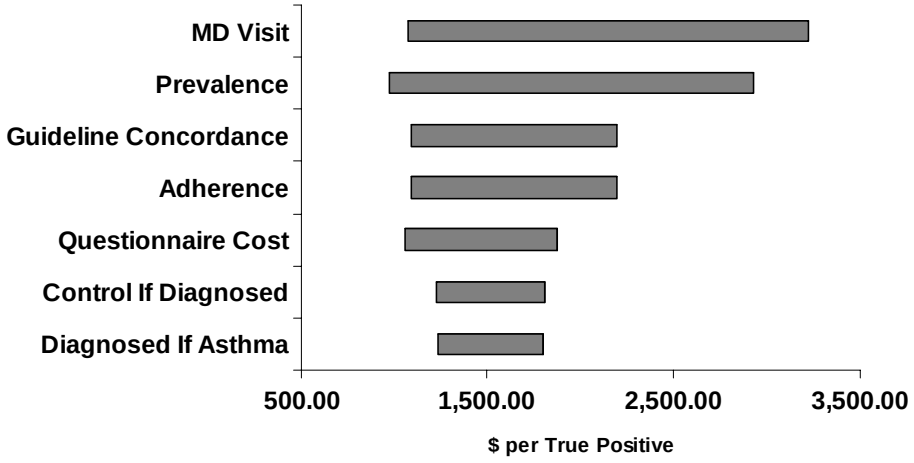
Sensitivity Analysis

One-way sensitivity analysis is performed to identify influential variables comparing the BQ to the *status quo*. The ICER range and number of prevented SADs needed for indifference are presented for the variables accounting for 99% of the total uncertainty. These results demonstrate that even in their most favorable position, a large numbers of prevented SADs are needed for indifference (Table 27). These results are presented graphically in Figure 20.

TABLE 27. Sensitivity Analysis of Selected Variables and Corresponding Minimum Number of School Absence Days Needed for Indifference

Variable	Range Estimate	Low ICER ($/TP)	High ICER ($/TP)	Min. SADs for Indifference
MD Visit	.45-.15	1,072	3,216	24
Prevalence	.30-.10	974	2,923	22
Guideline Concordance	.80-.40	1,096	2,193	25
Adherence	.80-.40	1,096	2,193	25
Questionnaire Cost	$9.76-17.25	1,059	1,872	24
Control if Diagnosed	.45-.75	1,229	1,803	28
Diagnosed if Asthma	.5-.9	1,233	1,795	28

FIGURE 20. Tornado diagram of influential variables from school system perspective.



Best Case Scenario

The best-case scenario for the analysis from the school system perspective yields an ICER of $206 per true positive identified for the BQ. The corresponding number of

prevented SADs needed for indifference is 5. All other case detection methodologies are dominated and thus not considered (Table 28).

TABLE 28. Best Case Scenario Results from School System Perspective

Intervention	Total Costs† ($)	Total Effect† (QALD)	Incr. Costs ($)	Incr. Effect (QALD)	ICER ($/QALY)
Status Quo	0	0	-	-	-
Narrow Questionnaire	9.76	.018	9.76	.018	dom.
Broad Questionnaire	9.76	.047	0.00	.030	206
Multi-Stage with Spirometry	19.53	.035	9.77	-.012	dom.
Multi-Stage with Exercise	20.73	.039	10.97	-.008	dom.

† Costs and Effects are per child screened.

DISCUSSION

Cost-Effectiveness of School Based Asthma Case Detection

The reference case results demonstrate that the MSwET program is the most cost-effective case detection intervention, at $63,361 per QALY. This value is higher than the traditional threshold of $50,000 per QALY. However Siegal et al[100] caution, "The simple conclusion that an intervention is 'cost-effective' or 'not cost-effective' should be used with caution" (p.295). Within the cost-effectiveness literature, support can be found for a lower,[101] higher,[102] or no[103] cost-effectiveness threshold. Ultimately, the cost-effectiveness of school-based asthma case detection depends on society's WTP. Prior to this analysis, no data was available to inform this decision. It is now possible to state with a reasonable degree of certainty that asthma case detection under the conditions proposed costs between $47,400 and $155,500 per QALY gained. With this information, more informed decisions regarding the allocation of limited resources amongst competing demands can be made.

A more definitive conclusion can be reached about which case detection intervention is likely to be the most cost-effective. Over a range of scenarios, the MSwET intervention is consistently found to be the most cost-effective. The NQ and the MSwS interventions are consistently dominated, and the BQ results in a ICER that is four times that of the MswET. Given these findings, it is clear that MSwET intervention is the

preferred case detection strategy. The MSwET intervention outperforms the others because it has the most efficient combination of sensitivity and specificity.

Compared to the other interventions, the MSwET intervention maximizes the detection of children with newly diagnosed asthma while minimizing false positive results. While the BQ identifies more new asthma cases than the MSwET intervention, this gain is more than offset by additional false positive results. These additional false positive results generate significant costs that account for the significantly higher ICER observed for the BQ. This finding is surprising given the pre-analysis assumption that the expense and effort of conducting spirometry and exercise testing would be prohibitively expensive, especially at a lower sensitivity. However, this analysis indicates that over the range of available sensitivities, the specificities of the various procedures are more important. The MSwET intervention takes advantage of the sensitivity of the BQ to identify most children at risk, then it uses the specificity provided by spirometry to cull the children least likely to have asthma from the at risk population. This illustrates how important epidemiological principles are to the cost-effectiveness of case detection.

Additional evidence to support the importance of underlying epidemiological principles is found in the sensitivity results. Two variables account for the preponderance of the observed uncertainty in the model: asthma prevalence and the quality of life preference weight for the symptomatic health state. Prevalence is an important determinant of case detection efficiency and accuracy.[22] In general, if the asthma prevalence is lower than estimated, then case detection is less cost-effective. If it is higher, then case detection is more cost-effective. For example, if the asthma prevalence

is 10% instead of 20%, then the ICER of the MswET intervention is $169,400 per QALY. At 30% prevalence, the ICER is $59,100. This finding underscores the importance of knowing the actual prevalence with a high degree of certainty.

There are two important determinants of asthma prevalence. One is the population of interest and the other is the definition of asthma used. At 10%, the prevalence estimate remains slightly higher than the estimated 8% of the national population of children ages 0-17 years who have current asthma.[2] The national average obscures the higher prevalence found in Black children, and the definition of current asthma on average yields lower prevalence estimates than the other definitions (lifetime and probable asthma). The combined impact of these two factors is to make the national estimate a likely underestimation of asthma burden. On the other hand, using the definition of probable asthma from a population of low-income, urban, primarily minority children yields prevalence estimates greater than 30%.[6,7,10,11,13] The difference in magnitude between these estimates is approximately three-fold. As seen in the sensitivity results, this difference results in highly variable cost-effectiveness estimates.

Achieving greater precision and agreement on the actual prevalence of asthma will greatly improve the reliability of the cost-effectiveness estimate. One way to achieve a more precise estimate is to select identifiable subpopulations with a relatively homogenous asthma risk. This consideration supports the examination of case detection cost-effectiveness in a population of low income, urban, primarily minority school children. While some heterogeneity remains, children within this population exhibit characteristics that are distinct from a higher income, suburban, primarily White population. These patterns extend beyond prevalence and also encompass patterns

related to ED visits, hospitalizations, and ICS use. Taken together, these factors act to make case detection more cost-effective. If case detection is not cost-effective in this population, then it is not going to be cost-effective in another with lower asthma prevalence, lower health care utilization, and higher ICS use.

A second action that would improve the precision of the prevalence estimate is to standardize the definition of asthma. Ideally, the definition will yield a prevalence estimate that accurately reflects the asthma burden in the population, including children with undiagnosed asthma and excluding children with asthma-like symptoms but no asthma. The importance of doing so is hinted at in the findings of Clark et al[5] and Gerald et al (2004),[7] who note that children with newly diagnosed asthma identified by case detection have on average less severe asthma. This finding is considered in the analysis; however, the assumption is also made that children who are newly identified by case detection exhibit the same pattern of health care utilization as children who have a previous diagnosis. If these children actually have lower rates of asthma-related health care utilization, then case detection is less cost-effective than estimated. One possible reason these children might be undiagnosed at the time of case detection is that their asthma is characterized by low symptomatic burden and, correspondingly, less health care utilization. If this is true, then this analysis overestimates the potential benefits of case detection.

It is also important to better characterize the asthma burden in children with intermittent asthma. Several reports shed considerable light on the asthma burden in children with mild persistent asthma.[79,80,104] Less is known about symptoms, health care utilization, and treatment effect in children with intermittent asthma. This analysis

considers children with intermittent asthma to express these factors in a relatively linear fashion with respect to children with persistent asthma. This modeling decision likely results in an overestimation of the health care utilization and treatment effect for children with intermittent asthma. Greater knowledge regarding the relationship between severity, treatment, and outcomes would be useful.

Behavioral factors are also important to consider in the discussion of case detection cost-effectiveness. There are 3 important behavioral "A's" that should be considered: action, access, and adherence. Caregivers of children identified by case detection must take action for benefits to be obtained. These children must have access to high-quality asthma care and low-cost medications. These children must be adherent to treatment recommendations. Any break in this chain will reduce the cost-effectiveness of case detection. Sensitivity analysis indicates that addressing these factors will have a greater impact on case detection cost-effectiveness than developing a better case detection methodology.

Interestingly, the costs of asthma case detection are not found to strongly influence the final cost-effectiveness estimate. Of all the case detection costs, only the cost of questionnaire administration has observable influence across its range of possible values. In their most and least favorable position, questionnaire costs are associated with an ICER of $67,000 and $106,500, respectively. A more costly questionnaire administration process than could be theoretically achieved was modeled in order to maximize the response rate by minimizing the impact of nonresponse and subsequent nonresponse bias. This was done because little is known about nonresponse bias in asthma case detection. The impact on the final results is likely to be minimal, because

questionnaire costs are minimally influential in the sensitivity analysis. In addition, costs saved by using a less expensive process would likely be offset by fewer health gains due to nonresponse. The impact of nonresponse and nonresponse bias must be considered if a substantially less expensive questionnaire administration process is to be modeled.

In summary, this analysis evaluates asthma case detection in a setting where it is most likely to be cost-effective and is not meant to be generalizable to other populations. In addition, when decisions regarding point estimates and ranges for individual variables were made under conditions of uncertainty, the "benefit of the doubt" was given to case detection. For these reasons, the results should be interpreted cautiously. This analysis evaluates asthma case detection in a setting most favorable to case detection. Extending these findings to any other population is likely to significantly overestimate the cost-effectiveness of school-based asthma case detection.

Preference-Based Utility Weights for Asthma Health States

One of the strengths of this analysis is the use of community-based preference weights for childhood asthma health states derived from Chiou et al.[34] These preference weights allow QALYs to be used as an outcome measure of effectiveness. The advantage of using QALYs is the subsequent ability to compare the ICER of asthma case detection with ICERs from analyses of other health interventions. However, there are several reasons why using these preference weights could be problematic. First, it is not clear how generalizable these weights are because they were derived from a relatively small sample of adults from the Pacific Northwest. They may not be representative of how these health states are valued by the unique population considered in this analysis.

More importantly, it is not clear how precisely the PAHOM health states map onto the asthma health states used in this analysis. To derive the preference weights for the analytic health states, multiple PAHOM health states had to be aggregated and their preference weights averaged. This crude mapping strategy is susceptible to possible misclassification errors. To minimize this possibility, relatively large ranges were created around each health state, but that accommodation introduces significant uncertainty around each of the health state preference weights.

The importance of this uncertainty to the primary analysis result is reflected in the secondary sensitivity results. The quality of life preference weight for the symptomatic health state is the most influential variable in the sensitivity analysis. In addition, it is the only variable that results in an ICER below $50,000 per QALY when allowed to vary over its range of possible values. When the preference weight for the symptomatic state is less than 0.80, the MSwET intervention is cost-effective at a threshold of $50,000 per QALY. This finding illustrates the importance of the uncertainty surrounding the symptomatic heath state preference weight.

The symptomatic state preference weight is the most influential preference weight because it is associated with one of the most common health states and because it is known with relatively little certainty. The relative frequency of the symptomatic state means that many opportunities exist for case detection to improve the quality of life of children with asthma. For every day spent in the ASFD state instead of the symptomatic state, children experience gains in quality of life. When the preference weight is lower, the gain in quality of life is bigger. Therefore, a lower weight makes case detection more cost-effective because the intervention generates more QALYs. Therefore, the less

desirable society views a day spent in the symptomatic state to be the more likely case detection is to be cost-effective.

Clearly, greater knowledge regarding the true composition and value of the symptomatic health state would yield a more precise estimate. To obtain this knowledge, it is important to better understand how the PAHOM states map onto the symptomatic state. It is also important to revalidate the preference weights for the PAHOM health states in a larger, more diverse sample of community-dwelling adults. Of course these steps would lead to a better understanding of all of the health states, but obtaining a more accurate estimate of the true cost-effectiveness of asthma case detection lies in knowing more about the symptomatic state preference weight.

School System Perspective

A more definitive statement about the cost-effectiveness of case detection can be made from the school system perspective. From this perspective, case detection is not cost-effective, even under ideal conditions. One important explanation for this finding is the small number of excess asthma-related SADs experienced by children with asthma. The estimated number of excess SADs in children with asthma is 1 to 3 days per school year.[33] The results from the school system perspective demonstrate that, even under ideal conditions, at least 5 SADs must be prevented in order for the school system to be indifferent to the costs of case detection. The estimated number of prevented SADs needed for indifference under real-world conditions is 33. This provides robust evidence that school-based asthma case detection is not cost-effective from the narrow perspective

of the school system. This finding is unfortunate as the school system is a well-defined stakeholder for advocacy.

The other implication of this finding is that SADs are not a useful outcome measure for cost-effectiveness analyses of school based asthma interventions. The paucity of excess asthma-related SADs means that there are not enough SADs to offset intervention costs. This is also partly due to the low estimated economic value of SADs, $45 dollars. If other factors (eg academic performance) can be incorporated into the economic valuation of SADs it would increase their usefulness as outcome measures for asthma-related interventions. Unfortunately, these factors are likely to be difficult to value economically.

Limitations

The most significant limitation is the reliance on secondary data. The ability to find estimates appropriate to the specific population under consideration is challenging. It is not possible to know with certainty which estimates are generalizable to the analytic population and which are not. Ideally, CEA should be performed prospectively as part of a RCT; however, the need to follow children over a significant period of time and capture large amounts of data regarding health care utilization and quality of life likely makes such a trial economically unfeasible. In the absence of a large RCT, reliance on secondary analyses is inevitable.

As mentioned previously, use of the PAHOM health states to develop QALY estimates is potentially problematic. The two major issues are their generalizability to the analytic population and the uncertainty with regard to their mapping onto the analytic

health states. The fact that the preference weight for the symptomatic health state is the most influential variable in the model underscores the importance of addressing these concerns in future work. Having such a significant portion of the outcome effect dependent on this one measure is a concern. Additional work to validate this measure should be a research priority.

Lastly, the results of the analysis are in large part driven by gains in quality of life and reductions in ED visits and hospitalizations in children with relatively mild asthma. As mentioned, the real-world health burden, health care utilization, and treatment effect may not match the estimates used in this analysis. If these children experience an asthma burden that is lower than estimated, then the cost-effectiveness of asthma case detection is overestimated. Greater knowledge about the asthma burden experienced by children newly diagnosed by case detection and children with intermittent asthma is needed. Closely related to this issue is the need to have a better understanding of asthma burden and treatment effect by asthma severity. This analysis likely overestimates the distinctions between severity classifications. While this represents an improvement over considering children with asthma as one homogenous group, it is still crude.

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