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“To Biologic or Not to Biologic?: The Question of Cost-Effectiveness”

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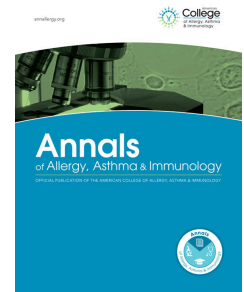
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Title: “To Biologic or Not to Biologic?: The Question of Cost-Effectiveness”

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1 **Introduction**

2 As of 2018, the FDA had approved five biologics for the treatment of asthma –
3 omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab. All five of these
4 biologics are designated for the treatment of severe asthma in patients with a T_H2-driven
5 phenotype, either allergic or eosinophilic. In clinical trials, biologics have demonstrated efficacy
6 to decrease the frequency of asthma exacerbations, unplanned health utilization including ED
7 visits and hospitalizations, and chronic oral steroid use in severe asthmatic patients¹.

8 While these medications may be the answer for patients struggling with severe
9 persistent asthma, their implementation in practice remains a question for many clinicians.
10 Which biologic should they chose for their patient, especially when they target similar
11 pathways? Are there predictors of which patient will respond best to each therapy? How to
12 define a responder? At what point should a switch be considered? How long should a biologic
13 be continued? What are the long-term adverse effects?

14 A common impediment for the use of these medications is the cost, for patients,
15 providers, and insurers including government supported insurance. According to data provided
16 by pharmaceutical manufacturers, the wholesale acquisition cost of an individual unit of these
17 biologics can range from \$879 to over \$4750² (2018 dollars) (**Table 1**). These costs do not
18 capture the associated fees by providers for administration and indirect costs to patients for
19 administration time.

20 In this review, the most current data on the cost-effectiveness of the available biologics
21 for asthma is reviewed, including insights into any comparative efficacy between biologics and

evidence to direct their use in practice. Throughout this review, all prices from cited publications are in United States dollars and with the year of the value denoted .

Burden of Asthma in the United States

The burden of asthma in the United States remains high, with 38.4% of children and 50% of adults with current asthma reporting their asthma as uncontrolled as defined by EPR-3 guidelines according to the Centers for Disease Control and Prevention³. Poor control results in 1.7 million ED visits, 11 million physician office visits for a primary diagnosis of asthma, and 1.3 million hospital outpatient department visits for asthma yearly⁴. As of 2013, this cost the United States \$50.1 billion per year in direct medical costs and \$3.8 billion per year in loss of productivity⁵.

A retrospective analysis of school-aged children in the 2007-2013 Medical Expenditure Panel Survey demonstrated health care resource use and health care expenditure was higher in children with asthma as opposed to those without asthma, with an estimated total nationwide annual health care expenditure of \$5.92 billion (2015 dollars)⁶. Pharmacy and outpatient costs represented the largest proportion of total expenditures⁶. Accompanying this health care utilization is school absenteeism, with children 5-17 years old with asthma missing 13.8 million school days secondary to asthma in 2013³.

Severe asthmatics, who are the primary target for biologic therapies, represent at most 10% of asthmatic patients⁷. Severe uncontrolled asthma represents approximately 1% of all asthma, 29.9% of all uncontrolled asthma, and 19.9% of all severe asthma in the United States, per EPR-3 guidelines⁸. Severe uncontrolled asthma is associated with 3-times the cost than

severe controlled asthma⁸. An observational study of severe uncontrolled asthma patients 12 years and older in a managed care population found the average annual adjusted asthma-related direct costs were \$1,056 (2013 dollars) more per patient compared to those without severe uncontrolled asthma, with hospitalizations, ED visits, outpatient visits, and medications contributing to the difference⁹. A multivariable analysis found that asthma drugs accounted for the majority of this difference, with an annual incremental cost of \$848 (2013 dollars) more per patient with severe uncontrolled asthma⁹. Of note, this evaluation did not address biologic use.

Comparative Biologic Effectiveness

Despite differences in their targeted patient phenotypes and divergent mechanisms of action, including anti-IgE, anti-IL-5, anti-IL-5 receptor, and anti-IL-4 α receptor subunit, all five currently approved biologics have relatively comparable efficacy with each other broadly when compared to placebo². In their respective individual studies, all five biologics reduce the rate of asthma exacerbations requiring steroid therapy by approximately 50%². Omalizumab, reslizumab, benralizumab, and dupilumab (data for mepolizumab not reported) similarly statistically improved AQLQ scores, and mepolizumab, reslizumab, benralizumab, and dupilumab (data for omalizumab data not reported) similarly statistically improved ACQ scores, all compared to placebo². However, the magnitude of both the AQLQ and ACQ scores changes did not meet the minimally important difference².

This information is limited in its application, as clinicians are comparing the benefits of the biologics to each other, not placebo, when choosing which is best for their patient. GINA has recently published a pocket guide to help clinicians choose between anti-IgE and an anti-IL-

5 or anti-IL5 receptor biologic, but this does not discuss their comparable efficacy¹⁰. There are no randomized trials to date directly comparing the biologics to each other in terms of clinical effectiveness. The closest comparison between biologics comes from network meta-analyses, which combine direct evidence from head-to-head trials with indirect evidence from comparator trials¹¹. Given that a network meta-analysis combines two different trial types, an assumption of consistency is necessary to make the indirect and direct evidence congruent, but it is not possible to objectively assess the consistency assumption¹¹. Utilization of a PICOS framework which compares the population, interventions, comparators, outcomes, and study type can assess whether the component studies are sufficiently similar¹¹.

For example, ICER reported a network meta-analysis examining rates of asthma exacerbations for all five biologics specifically for patients with a blood eosinophil count of ≥ 300 cells/ μ L, ≥ 2 exacerbations in the prior year, and an ACQ ≥ 1.5 , in an attempt to represent a more homogenous population². In this analysis, only dupilumab and mepolizumab were better than placebo, which was attributed to the small number of patients who met the requirements of this subgroup in studies involving the other biologics². While dupilumab had the largest reduction in exacerbations and benralizumab had the smallest, none of the inter-drug comparisons were statistically significant².

An area recently explored is a comparison of those biologics that target eosinophils – mepolizumab, reslizumab, and benralizumab. Three recent network meta-analyses utilized a PICOS format to compare these biologics in various combinations¹²⁻¹⁴. A comparison of mepolizumab and reslizumab found no significant difference in any of the predefined clinical outcomes including FEV₁, ACQ, AQLQ, annual exacerbations, and serious adverse events¹². The

authors noted that the quality of evidence was very low concerning inter-drug difference comparison as there was substantial variability between the studies, including key differences in asthma severity and blood eosinophil level cut offs¹². The mepolizumab studies included patients with severe asthma based on GINA guidelines and a cut off of ≥ 150 -300 eosinophils/ μL ¹², while the reslizumab studies included patients with moderate asthma per GINA guidelines and a cut off of ≥ 400 eosinophils/ μL ¹².

Unlike the aforementioned study, a separate network meta-analysis controlled for the heterogeneity between benralizumab and reslizumab studies by only selecting a benralizumab subgroup with ≥ 300 blood eosinophils/ μL and a reslizumab subgroup with GINA step 4/5 or ≥ 2 previous exacerbations and ≥ 400 eosinophils/ μL ¹³. Reslizumab was found to significantly improve ACQ and AQLQ scores compared to benralizumab administered every 4 weeks, but the magnitude of these changes did not meet the minimal important difference¹³. Though not statistically significant, reslizumab had a higher posterior probability of superiority over benralizumab administered every 8 weeks for ACQ scores, AQLQ scores, FEV₁, and clinical asthma exacerbations¹³. With regards to the change in FEV₁, the authors note heterogeneity existed between the studies with a greater improvement seen in the placebo groups in the benralizumab studies versus the reslizumab studies¹³.

A final network meta-analysis made an indirect comparison with mepolizumab, benralizumab, and reslizumab stratified by baseline eosinophil counts and asthma exacerbations¹⁴. Mepolizumab significantly reduced the rate of clinically significant exacerbations and improved ACQ scores compared to benralizumab and reslizumab among patients with a baseline blood eosinophil count of ≥ 400 eosinophils/ μL , without any difference

in exacerbation rates or ACQ score improvements between reslizumab and benralizumab at this eosinophil count¹⁴. Mepolizumab also reduced the rate of clinically significant exacerbations and improved ACQ scores compared with benralizumab at both ≥ 150 and ≥ 300 eosinophils/ μ L (reslizumab was not included in analyses at this eosinophil count). With regards to FEV₁, there was no difference in change in pre-bronchodilator FEV₁ between mepolizumab and benralizumab at all eosinophil thresholds¹⁴. At ≥ 400 eosinophils/ μ L, there were no changes observed between mepolizumab and reslizumab, but benralizumab improved FEV₁ compared to reslizumab¹⁴.

Approach to Cost-Effectiveness

Cost-effectiveness analyses in medicine have encountered barriers, including Medicare not considering cost-effectiveness when determining coverage of most new therapies and the Affordable Care Act forbidding the Patient Centered Outcomes Research Institute from considering QALYs when establishing recommended health care services¹⁵. However, it is now being increasingly utilized to measure the value of new therapies, especially given those with a high cost such as biologics, and incorporated into clinical practice guidelines¹⁵. While cost alone should not be the primary driver when choosing a biologic, clinicians often are limited in their selection by insurance coverage, which may be increasingly driven by such cost-effective evaluations.

Four main categories of economic evaluations exist – cost-benefit, cost-minimization, cost-effectiveness, and cost-quality – all of which share the same cost, expressed in monetary units, but differ in their outcomes^{16,17}. A cost-effectiveness analysis is measured as a ratio of

the net change in costs between two interventions divided by the net change in outcomes, which are natural health-related units^{16,17}. The net change in costs reflects the additional cost to achieve the outcome, and the ratio is expressed as the cost per outcome gained^{16,17}. A cost-utility analysis is a specific form of cost-effectiveness, in which the benefits are measured in healthy year equivalents^{16,17}. These are expressed most commonly as QALYs, which assign a weight to each period of time, ranging from 0 to 1, in which 1 corresponds to optimal health and 0 corresponds to a health state judged to be equivalent to death¹⁸. QALY was not initially developed to aid in individual patient decision-making, but rather across a population subject to resource constraints; although over time it has been extended into clinical decision making¹⁹.

In their 2016 update, the Panel on Cost-Effectiveness in Health and Medicine recommended extending beyond the idea of a traditional health care sector perspective for cost-effectiveness analyses, which is most relevant to third-party payers, to include a societal reference case^{18,20}. This societal reference case includes an impact inventory, encompassing both the health and non-health effects of an intervention, to ensure all consequences of an intervention are included, irrespective of who pays the cost or derives the benefits^{18,20}. Such sectors would include current and future medical costs borne both by third-party payers and out-of-pocket by patients, time costs both by patients to seek and receive care and by unpaid caregivers, transportation costs, effects on future productivity, and social services costs, to name a few¹⁸.

Modelers of cost-effectiveness studies should review country-specific guidelines for decisions on choosing an appropriate perspective, along with indirect and direct cost measures to include in their analyses²¹. Modelers should pay careful attention to inclusion of

administration costs and any additional fees related to administration, as these indirect costs may vary dramatically depending on route of administration²¹.

Limitations exist when utilizing clinical studies to determine biologic cost-effectiveness, including validity being limited to individual trials, generalizability from a relatively small number of patients or from a single study, and lack of long-term data on adverse events and clinical benefits, as well as duration of treatment. Drug prices in these models are often based on wholesale acquisition cost which may not be representative of the actual transaction price given that payers often negotiate a price.

Biologic Cost-Effectiveness

In 2018, the Midwest Comparative Effectiveness Public Advisory Council, a core program of ICER, assessed the comparative cost-effectiveness of omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab². ICER is an independent nonprofit organization that takes a societal perspective to provide transparent, systematic, scientifically rigorous clinical and cost-effectiveness analyses of healthcare treatments, including a budget impact threshold above which a drug would likely contribute to significantly to excessive growth in healthcare costs²².

In ICER's long-term cost-effectiveness model, each asthma biologic was compared to the standard of care for the treatment of moderate to severe uncontrolled asthma with evidence of type 2 inflammation in patients six years of age and older². For the economic inputs, the five manufacturers submitted net price data; treatment-related costs included administration and office visits; and costs of lost productivity associated with treatment were included for the modified societal perspective scenario². The ICER base-case incremental cost-effectiveness

ratio analysis found the biologics falling between \$325,000 to \$391,000 (2018 dollars) per QALY gained² (**Table 1**). ICER defines a value-based benchmark for a drug as the price that would achieve incremental cost-effectiveness ratios between \$100,000 and \$150,000 per QALY gained². No biologic achieved a greater than zero likelihood of meeting this threshold². The ICER report recommended that biologic costs would need to be reduced 62-80% from their 2018 wholesale acquisition cost, depending on the biologic, to meet this threshold².

ICER cost-effective scenarios improved with utilization in select patient populations, specifically treatment responders or patients on chronic oral steroid controller therapy². Restricting the treated population to only those who are on chronic oral corticosteroids decreased the incremental cost-effectiveness ratio to \$174,000 per QALY gained². When adding the responder scenario assuming favorable clinical and cost inputs, the incremental lifetime findings are \$156,000 per QALY gained, which is closer to the accepted cost-effectiveness threshold². Sensitivity analysis suggested that non-exacerbation health state utility improvements are potentially the most influential benefit from the five biologics on lifetime discounted cost-effectiveness, followed by exacerbation reductions and chronic oral steroid reductions, respectively².

Consistent throughout these studies, the individual biologics examined did not meet established cost-effectiveness ratios^{21,23,24}. Lower incremental cost-effectiveness ratios estimates have been associated with higher asthma-related mortality and increased risk of hospitalization in the population; improved health-related quality of life in those treated with a biologic; decreased acquisition prices; longer time horizons; and targeting therapy only to

197 responders²¹. Most studies recommended carefully targeting biological therapy to responders
198 or discounting acquisition price to further improve value^{2,21,23,24}.

199 **Omalizumab.** A systematic review identified 19 studies from 2000-2018 analyzing the
200 cost-effectiveness of omalizumab in patients with moderate-to-severe allergic asthma²¹. The
201 majority of these studies focused on adults, with one being exclusively pediatrics and two
202 included children and adults²¹. Seventeen of the studies compared omalizumab to standard
203 therapy, with one comparing omalizumab to bronchial thermoplasty and another to
204 tiotropium²¹. Approximately two-thirds of the articles analyzed cost-effectiveness from a
205 health system or payer perspective, with 6 using a societal or community perspective²¹. The
206 incremental cost-effectiveness ratio ranged from \$287,200/QALY gained (2008 dollars) to
207 \$821,000/QALY gained (2005 dollars) over a lifetime horizon²¹. Across these studies, 10
208 showed omalizumab was cost-effective in base-case scenarios, 5 showed it was not cost-
209 effective, and the remaining showed omalizumab was only cost-effective when targeted to
210 specific severe subgroups, such as severe persistent allergic asthma, difficult-to-treat asthma,
211 or lack of response to other controller therapies, or given considerable price discounts²¹. The
212 authors concluded that while omalizumab improves clinical outcomes and quality of life to
213 make it cost-effective it should only be utilized in patients with difficult-to-treat persistent
214 allergic asthma who respond to the therapy and the acquisition price should be significantly
215 discounted²¹.

216 **Mepolizumab.** A single study modeled the cost-effectiveness of mepolizumab add-on
217 therapy in adult patients with severe uncontrolled eosinophilic asthma compared to standard
218 of care utilizing from a payer perspective, focusing on direct healthcare costs²³. Over a lifetime

treatment horizon, mepolizumab add-on therapy to standard of care averted almost 24 exacerbations at an incremental cost saved of \$24,626, with a gain of 1.53 QALYs²³. However, costs increased by more than \$600,000 (2014 dollars) from the addition of mepolizumab resulting in a cost-effectiveness estimate of \$385,546/QALY gained (2014 dollars), exceeding threshold values²³. To achieve closer to the \$150,000/QALY gained threshold, the authors suggested mepolizumab would require a 63% price discount in the wholesale acquisition cost at the time of treating only a responder cohort, which would yield cost-effectiveness estimates as low as \$160,000/QALY gained (2014 dollars)²³.

Reslizumab. A single study modeled the cost-effectiveness of reslizumab in adult patients with moderate-to-severe eosinophilic asthma from a United States societal perspective, with direct costs including the costs for reslizumab treatment and management, including adverse events, while indirect costs included infusion time, post-infusion surveillance time, and time to travel to clinic²⁴. Base-case results suggested a potential gain of 0.04 QALYs per patient per year on reslizumab, but this was counterbalanced by an increase of \$24,404 (2017 dollars) in direct and indirect costs, resulting in an incremental cost-effectiveness ratio of \$697,403 (2017 dollars) per QALY gained²⁴. The cost-effectiveness of reslizumab in this study was most impacted by improvement in quality of life scores, with models showing a 20% improvement in quality of life would decrease the incremental cost-effectiveness ratio to \$154,352/QALY gained²⁴. Reslizumab approached cost-effectiveness if the direct cost was decreased by 70%²⁴. The authors concluded that the improvement in quality of life and exacerbation rates with reslizumab are associated with high costs, making reslizumab unlikely to be cost-effective²⁴.

Benralizumab and dupilumab. At the time of this publication, there were no United States dollar-based studies available evaluating their individual cost-effectiveness.

Predictors of Response to Select Biologics

To improve cost-effectiveness by limiting biologic treatment to responders, clinicians should utilize readily available biomarkers to increase the probability that their patients would respond to therapy. The GINA Pocketbook on difficult-to-treat asthma guides clinicians that patients with blood eosinophils ≥ 260 cells/ μ l, exhaled nitric oxide ≥ 20 ppb, allergen-driven symptoms, or childhood-onset asthma are more likely to respond to omalizumab¹⁰. The PROSE study indicated that pediatric patients with fall asthma exacerbations on EPR-3 step 5 therapy are most likely to have a reduction in exacerbations with the addition of omalizumab proceeding the viral season²⁵. Such an intervention may also be cost saving by both targeting responders and limiting the duration of therapy. For the anti-IL5/anti-IL5 receptor directed biologics, the GINA pocketbook indicates a good response is predicted with higher blood eosinophils, more exacerbations in previous year, adult-onset asthma, or nasal polyposis¹⁰. GINA did not discuss dupilumab since it was not approved at the time, but one recent study suggests that a reduction in asthma exacerbations is greater in patients higher blood eosinophils or higher exhaled nitric oxide²⁶. To date, most studies examining biomarker predictors to biologic response have been in adults, limiting interpretation in adolescents and especially those younger than 12 years of age.

Considerations When Selecting a Biologic

Over the last 2 years, four new medications in the biologic category, including mepolizumab, benralizumab, reslizumab, and most recently dupilumab, were approved by the FDA. Those four, combined with omalizumab, leaves the clinician with a decision on which medication to select for initial therapy for a patient with severe asthma. The two very recent documents from GINA and ICER can assist the clinician with these decisions, by providing a step-wise process on decision making on starting a biologic and data on the comparative- and cost-effectiveness of the biologics^{2,10}.

Before starting a biologic, it is most important to address basic measures such as ensuring the correct diagnosis, confirming adherence to the management plan, and assessing proper inhalation technique for inhaled medications¹⁰. The next step in the process addresses the following questions unique to each biologic: What is the dosing frequency? What is the delivery route, subcutaneous or intravenous? Where can the drug be administered? What is the patient preference¹⁰? In addition to the previous questions, the age of the patient and available safety data on the specific biologic must be considered for the pediatric patient.

Cost must be considered when choosing a biologic, including the ability to satisfy local payer eligibility criteria and the responsibility of the patient will bear as well as the payer, including society for those on government insurance support. The ICER report reveals that the major effect explored in clinical trials, impact on exacerbations, is relatively comparable among the available agents². However, a greater contribution to the cost-effectiveness of biologics is on quality of life, where biologics provide a comparable but modest impact². In order to be cost-effective, all of the biologics would have to reduce their cost by about 60 to 80%². Therefore, certain variables would have to be considered that can impact cost-effectiveness

assuming prices are not reduced. First, can one reduce risk by reducing or eliminating systemic steroid dosing? The biologics can be effective in these areas, so this is a priority for selection. Second, can one predict who will respond to certain agents? More insight is needed to adequately predict who will respond aside from blood and sputum eosinophils as an indicator.

The next important feature would be to determine what is an adequate response to consider the biologic effective and what period of time should be allowed to determine that a certain biologic is not effective? It would appear that an optimal response would be one that results in an elimination of exacerbations and a substantial reduction of systemic steroid dosing to a range that dramatically reduces risk of long-term adverse effects, preferably elimination. Currently, GINA recommends an initial trial of on average 4 months and then reassessment¹⁰.

The final important area would be the duration of treatment before considering discontinuation of the biologic. As indicated in the ICER Report, this information is lacking since most trials are only 24 months with a few reaching 15 months². Long-term risks will need to be identified with continued treatment and likely depend on adverse effect reporting.

Conclusion

With the introduction of the new biologics there is optimism that we can radically change the course of asthma not only for severe asthma in adults, where the majority of information exists but also potentially in adolescents and young children for an alteration in the course of the disease. The benefit of these biologics must be weighed against their costs, not just for individual patients, but for us as a society, especially in the setting of expanding health care expenditures. The ability of biologics to be administered at home may impact the societal

306 costs by reducing lost wages and time ascribed to in office administration and monitoring. Each
307 stakeholder, including manufacturers, clinicians, researchers, and patients, must work together
308 to address these challenges (**Table 2**). Hopefully by better targeting the use of these
309 medications using precision medicine accompanied by a reduction in their cost, the cost-
310 effectiveness of these medications will match the increasing potential benefits they can offer.

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References

1. Manka LA, Wechsler ME. Selecting the right biologic for your patients with severe asthma. *Ann Allergy Asthma Immunol* 2018;121:406-13.
2. Institute for Clinical and Economic Review. Biologic therapies for treatment of asthma associated with type 2 inflammation: effectiveness, value, and value-based price benchmarks. Final Evidence Report. December 20, 2018. <https://icer-review.org/material/asthma-final-evidence-report/> Accessed December 22, 2018.
3. Centers for Disease Control and Prevention. Asthma Stats. Last updated September 15, 2014. Available from https://www.cdc.gov/asthma/asthma_stats/ . Accessed on December 31, 2018.
4. Centers for Disease Control and Prevention. Asthma Surveillance Data. Last updated May 2018. Available from https://www.cdc.gov/asthma/most_recent_data.htm . Accessed December 31, 2018.
5. Centers for Disease Control and Prevention. Asthma Facts: CDC's National Asthma Control Program Grantees. Updated July 2013. Available at: https://www.cdc.gov/asthma/pdfs/asthma_facts_program_grantees.pdf . Accessed December 31, 2018.
6. Sullivan PW, Ghushchyan V, Navaratnam P, et al. The national cost of asthma among school-aged children in the United States. *Ann Allergy Asthma Immunol* 2017;119:246-52 e1.
7. Wenzel SE, Busse WW, National Heart L, Blood Institute's Severe Asthma Research P. Severe asthma: lessons from the Severe Asthma Research Program. *J Allergy Clin Immunol* 2007;119:14-21; quiz 2-3.
8. Chen S, Golam S, Myers J, Bly C, Smolen H, Xu X. Systematic literature review of the clinical, humanistic, and economic burden associated with asthma uncontrolled by GINA Steps 4 or 5 treatment. *Curr Med Res Opin* 2018;34:2075-88.
9. Zeiger RS, Schatz M, Dalal AA, et al. Utilization and Costs of Severe Uncontrolled Asthma in a Managed-Care Setting. *J Allergy Clin Immunol Pract* 2016;4:120-9 e3.
10. Global Initiative for Asthma. Pocket guide for asthma management and prevention (for adults and children older than 5 years). Updated November 2018. Available from <https://ginasthma.org/2018-pocket-guide-for-asthma-management-and-prevention/> . Accessed January 7, 2019.
11. Mauger D, Apter AJ. Indirect Treatment Comparisons and Biologics. *J Allergy Clin Immunol Pract* 2019;7:131-3.
12. Henriksen DP, Bodtger U, Sidenius K, et al. Efficacy, adverse events, and inter-drug comparison of mepolizumab and reslizumab anti-IL-5 treatments of severe asthma - a systematic review and meta-analysis. *Eur Clin Respir J* 2018;5:1536097.
13. Casale TB, Pacou M, Mesana L, Farge G, Sun SX, Castro M. Reslizumab Compared with Benralizumab in Patients with Eosinophilic Asthma: A Systematic Literature Review and Network Meta-Analysis. *The Journal of Allergy and Clinical Immunology: In Practice* 2019;7:122-30.e1.
14. Busse W, Chupp G, Nagase H, et al. Anti-IL-5 treatments in patients with severe asthma by blood eosinophil thresholds: Indirect treatment comparison. *J Allergy Clin Immunol* 2018.

15. Neumann PJ, Sanders GD. Cost effectiveness analysis 2.0. *N Engl J Med* 2017;376:203-5.
16. Higgins AM, Harris AH. Health economic methods: cost-minimization, cost-effectiveness, cost-utility, and cost-benefit evaluations. *Crit Care Clin* 2012;28:11-24, v.
17. Bukstein DA, Luskin AT. Pharmacoeconomics of Biologic Therapy. *Immunol Allergy Clin North Am* 2017;37:413-30.
18. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine. *JAMA* 2016;316:1093-103.
19. Weinstein MC, Torrance G, McGuire A. QALY: the basics. *Value in Health* 2009;12:S5-S9.
20. Roberts MS. The next chapter in cost effectiveness analysis. *JAMA* 2016;316:1049-50.
21. McQueen RB, Sheehan DN, Whittington MD, van Boven JFM, Campbell JD. Cost-Effectiveness of Biological Asthma Treatments: A Systematic Review and Recommendations for Future Economic Evaluations. *Pharmacoeconomics* 2018.
22. Pizzi LT. The Institute for Clinical and Economic Review and its growing influence on the US healthcare. *American Health and Drug Benefits* 2016;9:9-10.
23. Whittington MD, McQueen RB, Ollendorf DA, et al. Assessing the value of mepolizumab for severe eosinophilic asthma: a cost-effectiveness analysis. *Ann Allergy Asthma Immunol* 2017;118:220-5.
24. Lam J, Hay JW, Salcedo J, Kenyon NJ. A cost-effectiveness analysis of reslizumab in the treatment of poorly controlled eosinophilic asthma. *J Asthma* 2018:1-10.
25. Teach SJ, Gill MA, Togias A, et al. Preseasonal treatment with either omalizumab or an inhaled corticosteroid boost to prevent fall asthma exacerbations. *J Allergy Clin Immunol* 2015;136:1476-85.
26. Castro M, Corren J, Pavord ID, et al. Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma. *N Engl J Med* 2018;378:2486-96.

Table 1: FDA Approved Biologics Target, Cost, and Cost-Effectiveness Ratio Estimates²

Biologic	Target	Annual WAC	Base-Case Incremental Cost-Effectiveness Ratio*	Discount from WAC Required to Achieve Cost-Effectiveness Threshold Prices [^]
Omalizumab	Anti-IgE	\$39,048	\$325,000	66-77%
Mepolizumab	Anti-IL-5	\$37,293	\$344,000	64-75%
Reslizumab	Anti-IL-5	\$31,637	\$391,000	67-80%
Benralizumab	Anti-IL-5 receptor	\$30,889	\$371,000	62-73%
Dupilumab	anti-IL-4 α receptor subunit	\$38,110	\$351,000	62-73%

WAC: wholesale acquisition cost

*Annual price excluding loading dose in 1 year of a treatment and excluding administration costs; measured in cost in 2018 US dollars per QALY gained

[^]Threshold to achieve an incremental cost-effectiveness ratio between \$100,000 and \$150,000 per QALY gained

Table 2: Key Policy Recommendations for Biologics by Stakeholders²

Stakeholder	Recommendation
Manufacturers	Lower price of biologic therapies
Plan Sponsors	Develop coverage that provides access to biologic treatments
Payers	- Develop prior authorization criteria to ensure coverage for appropriate patients and prudent use - Do not deny coverage of biologics if their use has been found to be clinically beneficial to the patient
Specialty Societies/Providers	- Develop a definition of response to biologic therapy - Advocate for prices better tied to clinical benefits
Researchers	Develop head-to-head comparison trials
Regulators	Update guidelines to assess outcomes to include standardization of patient populations and instruments to assess outcomes

Key Messages

- Biologic therapy for asthma is not considered cost-effective based on current pricing structures.
- Manufactures must seriously consider price reduction to provide fair value for biologic therapy.
- Providers should direct therapy only to responders to improve cost-effectiveness, including using biomarkers before initiating treatment and monitoring for response to treatment.
- A recent publication by the Global Initiative for Asthma provides an algorithmic approach to identifying adolescent and adult patients who can be considered candidates for biologic therapy.
- A recent Institute for Clinical and Economic Review report provides detailed information on available cost-effectiveness data and what is needed to improve cost-effectiveness of these treatment.
- Direct head-to-head studies between biologics are needed to adequately assess their comparative-effectiveness.