October 22, 2018

Steven D. Pearson, MD, MSc, FRCP
President, Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, MA 02109 USA

RE: Draft Evidence Report "Biologic Therapies for Treatment of Asthma Associated with Type 2 Inflammation: Effectiveness, Value, and Value-Based Price Benchmarks"

Dear Dr. Pearson:

Patients Rising Now advocates on behalf of patients with serious, chronic, and life-threatening conditions and diseases for them to have access to vital therapies and services. Access to treatments enables those patients to have better, more productive, and longer lives. We believe access spans affordability, insurance coverage, and physical access. We are committed to engaging patients, caregivers, physicians, the media, health policy experts, payers, providers and other health professionals to foster realistic, patient-centered, solution-oriented discussions so that people facing critical medical needs can amplify their collective voice to create lasting improvements for health care in the United States. That is, our goal is to advance a balanced dialogue that illuminates the truth about health care in a just and equitable manner.

We appreciate the opportunity to provide our comments on the September 24th draft report, "Biologic Therapies for Treatment of Asthma Associated with Type 2 Inflammation: Effectiveness, Value, and Value-Based Price Benchmarks." At the outset, we want to raise a question about the title, which unlike recent draft reports includes "Value-Based Price Benchmarks." ICER states that value-based price benchmarks "are related solely to the long-term cost-effectiveness results."[i] Therefore, putting Value Based Price Benchmarks in the report seems to tilt ICER's analytical prejudice towards economic rather than clinical outcomes. Additionally, since ICER also states that such value-based benchmarks "are being used by the pharmaceutical and insurance industries to develop pricing and coverage policies,"[ii] we are concerned that this also indicates that ICER's goal is to support the economic well-being of those companies rather than the clinical (or economic) well-being of individual patients.

This problematic anti-patient perspective is further reinforced by ICER's explanation of its methodology for value-based price benchmarks that states "the $100,000-$150,000 range for the ICER value-based price benchmark will not be shifted according to votes on 'other benefits or disadvantages' and 'contextual considerations' or on 'long-term value for money' by the independent appraisal committees"[iii] which in ICER's procedural scheme provide "clinical and policy expertise,"[iv] but unfortunately, not those of patients.

Other, specific areas of patient-focused concern with the draft report are below in sections pertaining to: Complexity of Controlling and Treating Asthma; Patient-Oriented Information and Perspectives; Uncertainties about Data and Resulting Conclusions; and Additional Points.

Complexity of Controlling and Treating Asthma
Asthma is a complex disease with many causes and triggers leading to exacerbations or worse disease. As the draft report notes, "Asthma has been divided into different phenotypes with some overlap. Allergic asthma, which is associated with allergic rhinitis, atopy, and elevated IgE levels, is characteristic of approximately half of all patients with asthma. About half of individuals with severe asthma exhibit the type 2 phenotype with increases in T helper 2 cells."[v]

The complexity of treating asthma is also explored in the NHLBI's clinical guidelines that lists the four components of care for people with asthma as "assessment and monitoring, education, controlling environmental factors and comorbid conditions, and medications."[vi] However, the draft report only focuses on a narrow subset of medications. Similarly, the NICE clinical guidelines note that biologics "are one piece of a comprehensive treatment plan that includes close clinician monitoring and assessment, control of patient's environment and comorbidities, and patient engagement and adherence to his/her full treatment plan."[vii]

By not fully encompassing all the treatment components of care that could improve clinical outcomes, the draft report fails to explore all the real-world concerns of patients and their care team. This is important because the "standard of care" patients are receiving needs to address all the factors that can make patient's asthma worse, cause additional exacerbations (and the need for rescue medications, including oral steroids), or prevent them from decreasing their maintenance medicines.

The draft report (and apparently the clinical trials) assume that all patients are receiving standard of care. This is important since with a great diversity of patients with asthma, we are concerned that there is also a wide diversity of what is called standard of care. Specifically, without exploring whether that care is not just "standard," but actually optimized for the individual patient, raises questions about the data. We realize that clinical improvement through overall therapeutic optimization – whether in standard of care or with a new treatment option – is not the goal of ICER's work, but we think it is important to recognize that uncertainty so that the conclusions and analytics of ICER's draft reports are not taken out of context as a way to justify anyone making clinical, access, or payment decisions for individual patients.

Patient-Oriented Information and Perspectives
As you know, Patients Rising Now is concerned with individual patient care and outcomes, as well as overall population and society issues and outcomes. And since the Asthma and Allergy Foundation of America has noted that "**there is no 'one size fits all' approach to managing asthma,"**[viii] we are very happy that the draft report recognizes what is truly important for patients: "The reduction in exacerbation rates is often the focus of the clinical trials, but patients only have one or two exacerbations per year (rate in the placebo group of the clinical trials). Their quality of life when they are not having exacerbations is even more important to patients. They want to be able to go to work and school, exercise, and sleep through the night."[ix] But then we are very disappointed that those same clinical trial data points – that patients so clearly indicated are <u>not</u> the most important things to them – are what the draft report uses for the vast majority of its analysis and conclusions. And similarly, even though the draft report clearly illuminates patient perspectives about the balance between clinical and economic outcomes – "The two most important factors for choosing a therapy for both groups were effectiveness and

then cost. However, effectiveness was the far more important factor for patients surveyed"[x] – the report weighs the economic analytics much more heavily than patient's clinical concerns.

In addition, to better capture the breadth of patient perspectives concerning asthma treatments, we suggest that the draft report expand upon the serious consequences of long-term use of oral steroids, which are not only very serious clinically, but for patients often lead to dramatic and real life-altering adverse events.[xi] And with approximately one-third of the people in one Severe Asthma Research Program regularly using oral steroids,[xii] we would urge the draft report to highlight those consequences in greater detail, and weigh more heavily the benefits of reducing or avoiding long-term oral steroids for people with asthma.

Patients' Actual Costs

A related area of patient perspectives is actual costs to patients versus payer, insurance company or nationally aggregated costs. Asthma, like most serious diseases with a range of presentations, results in 5-10% of patients with severe asthma representing 50% of costs,[xiii] which is similar to data on the distribution of national health spending.[xiv] This range of costs translates into very different individual patient costs. This is an issue we have raised before, but we continue to find ICER's justification that it uses "a health system third party payer perspective in our base case analysis since this perspective is most relevant for decision-making by public and private payers, provider groups, and policy makers"[xv] to be a contradiction for the United States since the terms "health system" and "third party payer" cannot be joined in a meaningful way in the U.S. where multiple third party payers each have their own patient populations, coverage rules, and payment mechanisms. And those differences are very significant for patient's actual costs irrespective of the seriousness of their disease. For example, while people with Medicaid have low costs for medicines, they are not insignificant for the low-income people who are eligible for Medicaid. And for middle-income people who have high-deductible health plans those costs can be very significant. (HDHPs are increasingly common in the individual and employer-based insurance segments of the U.S. insurance markets, with 29% of employees now having high-deductible health plans.[xvi]) In contrast, for veterans' non-service connected conditions, through the VA they have a fixed-dollar co-payments of $11 per 30 day prescription, (with a $700 annual cap),[xvii] and Medicare Part D plans, which has within its complicated benefit structure the requirement that enrollees only pay 5% after reaching $5,000 in spending in the year (for 2018).[xviii] Thus, ICER continuing to treat the United States as having a singular and homogenous health care financing system – or even one that operates under a uniform set of rules is fictional or delusional.

We appreciate ICER requesting that Patients Rising Now provide them with information about "methods or estimates of patients' financial burden for different health technologies,"[xix] but the Federal government and others have conducted and published those types of analyses for years for technologies and populations concerning Medicare, Medicaid, and the VA health system. And others have conducted analyses of the costs to patients with private insurance for specific instances. Of course every disease and technology is a unique situation, which is precisely why ICER – since it presents itself as an analytical organization – should at least try to conduct this type of analysis. Just because it is challenging, does not mean it shouldn't be attempted.

Therefore, we continue to urge that ICER use a more appropriate patient-focused perspective and analytical framework that considers the pluralistic system of private and public payers in the U.S. – with rebates, discounts, and other factors that influence patient costs and access.

Uncertainties about Data and QALYs, and Resulting Conclusions

We are concerned about the extensive uncertainty of the data the draft report relies upon. For example, in the draft report there is this very telling sentence: "Because of the residual heterogeneity of the underlying patient populations and the definitions of exacerbations used across trials, we consider this to be an **exploratory analysis**. We hope to have more homogenous data from the manufacturers prior to the final report."[xx] [emphasis added] While we appreciate the candor in this statement, we think it is very, very important that this illumination not be buried in the middle of the report, but made explicit from the beginning.

Other part of the draft report concerning the systemic uncertainty of the data used in the draft report's analysis – and thus the potential significant imprecision of the draft report's conclusions – that we found troubling include:

- "There is significant heterogeneity in the FDA indications for the five drugs: allergic versus eosinophilic asthma and starting ages of 6, 12, or 18 years." (Draft report - page 17)
- "[T]here were no head to head randomized or observational trials of the five monoclonal antibodies." (page 19)
- "[A]ll five of the drugs reduced the annual exacerbation rate by about 50% with overlapping confidence intervals despite both the differences in the patient populations studied and the different mechanisms of action of the drugs. These estimates are specific to the populations in which each drug was studied and likely vary by patient characteristics." (page 19)
- "If the drugs were compared in identical patient populations the differences in rate ratios between each pair of the drugs might be larger or smaller than the ones observed in Table 3.3." (page 19)
- "When comparing the effect sizes from the meta-analyses of the individual drugs compared with placebo, the improvements in exacerbation rates and quality of life appear qualitatively similar, but this may be misleading." (page 31)

We are also concerned about ICER's use of QALY's. As noted above, because of insufficient inclusion of patient perspectives, data uncertainties, and analytical problems resulting from the data uncertainty, there is great concern that there is a significant disconnect between the analysis and conclusions. In addition, as ICER has stated, QALYs are a "widely used metric in cost-effectiveness analyses"[xxi] and that is precisely the point – the draft report presenting them as a component of clinical analysis is misleading, and we want to reiterate the conclusion of Garrison et al. that "QALYs may not always fully capture the health (or well-being) of patients, or incorporate individual or community preferences about the weight to be given to health gain - for example, about disease severity, equity of access, or unmet need."[xxii]

Additional Points

- In the draft report, clinical guidelines, and published literature, the terms "Quick Relief" and "Rescue" are used to refer to medicines for treating acute exacerbations of asthma. However, for patients with moderate or severe asthma, since acute exacerbations can lead to very

serious consequences – including death – we believe that the draft report should use the term "rescue" rather than "quick relief."

- We are puzzled by the characterization of Wellcare IL, and Aetna Better Health IL as "commercial plans" since their websites indicate that their business is only with government insurance programs, i.e., Medicare and Medicaid.[xxiii] We consider commercial insurance to be that which is paid for through premiums by individuals or companies, or which administers health benefit plans for self-insured companies operating under ERISA. We believe that this distinction should be clarified in the draft report.
- Another area of concern is the draft report's discussion of coverage policies for a medicine that is provided solely through by intravenous injection (such as Reslizumab) since it would be covered under an insurance plan's medical benefit, while the self-administrable medicines would typically be covered under a plan's drug benefit – and those differences in coverage can dramatically influence patient costs. This too should be explained in the report.
- We are confused by the opening sentence in the Clinical Guidelines section: "The U.S. Department of Health and Human Services, National Institutes of Health, and National Heart, Lung, and Blood Institute jointly release clinical guidelines for the diagnosis and treatment of Asthma." [xxiv] First, shouldn't it be "released" rather than "release" since it is something they have done in the past, and it is not an ongoing or necessarily repetitive activity? And second, these are three connected (i.e., not separate) government organizations, so stating that they jointly release[d] guidelines is misleading. Their relationships and the tense should be corrected.

Conclusions & Recommendations

Patients Rising Now believes that ICER's draft report on some treatments for people with moderate and serious asthma inadequately reflects patients' perspectives about the complexity of treatment regimens, quality of life, clinical versus economic concerns, and actual patient costs – including non-medical interventions. The continuing over-representation of medical and payer perspectives at the expense of patient perspectives in ICER's reports is an ongoing concern.

We believe patients' voices need to be a greater part of defining and assessing the value of their treatment plans along with the cost of all aspects of their care within the pluralistic U.S. health care system. Minimizing patient perspectives and concerns continue to be a barrier to more value-based care, and movement toward a more just and equitable health care system in the United States. Removing such barriers – and addressing gender, and socioeconomic disparities in access to care and outcomes – is something that the United States can and should do better. Since some of those barriers are perpetuated by siloed or homogeneous thinking, we would hope that ICER would be part of that solution rather than continuing to be part of the problem by reinforcing payer and provider privileges for making decisions that are clearly determinantal to specific groups of individuals – particularly individuals with more serious conditions.

Sincerely,

Terry M. Wilcox

Terry Wilcox
Co-Founder & Executive Director, Patients Rising Now

[i] https://icer-review.org/blog/icer-addresses-misrepresentation-of-methods/
[ii] https://icer-review.org/announcements/price-increase-reports/
[iii] https://icer-review.org/final-vaf-2017-2019/
[iv] https://icer-review.org/about/independent-voting-committees/
[v] Draft report "Biologic Therapies for Treatment of Asthma Associated with Type 2 Inflammation: Effectiveness, Value, and Value-Based Price Benchmarks" p. 2.
[vi] Draft report Op. cit., p. 12.
[vii] Draft report Op. cit., p 14.
[viii] "My Life With Asthma: Survey Overview," Asthma and Allergy Foundation of America, 2017
[ix] Draft report Op. cit., p. 20.
[x] Draft report Op. cit., p. 8.
[xi] http://www.asthma.partners.org/NewFiles/OralSteroids.html
[xii] "International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma," Eur Respir J 2014; 43, p 361.
[xiii] Draft report Op. cit., p. 1.
[xiv] https://www.healthsystemtracker.org/chart-collection/health-expenditures-vary-across-population/#item-discussion-health-spending-often-focus-averages-spending-varies-considerably-across-population_2015
[xv] https://icer-review.org/material/cgrp-response-to-comments/
[xvi] https://www.kff.org/health-costs/press-release/employer-sponsored-family-coverage-premiums-rise-5-percent-in-2018/
[xvii] https://www.va.gov/HEALTHBENEFITS/cost/copay_rates.asp
[xviii] https://www.kff.org/medicare/fact-sheet/the-medicare-prescription-drug-benefit-fact-sheet/
[xix] https://icer-review.org/material/cgrp-response-to-comments/
[xx] Draft report Op. cit., p. 28.
[xxi] https://icer-review.org/material/cgrp-response-to-comments/
[xxii] Garrison et al., Value in Health (21) 2018, 161-165.
[xxiii] https://www.wellcare.com/Illinois/Corporate/About-Us, https://www.aetnabetterhealth.com/illinois/become-a-member/,
[xxiv] Draft report Op. cit., p. 12.