PATIENTS RISING NOW

June 11, 2021

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 "JAK Inhibitors and Monoclonal Antibodies for the Treatment of Atopic Dermatitis"

Dear Dr. Pearson:

Patients Rising Now advocates for patients with serious and chronic conditions to have access to life-improving and life-saving therapies and services. Access to such treatments and services is essential, and it spans affordability, insurance coverage, and physical access. To support improved access, we are committed to engaging patients, caregivers, clinicians, media, health policy experts, payers, providers, and others to foster people-centered discussions about the entire U.S. health care system. That is, our goal is a balanced dialogue that illuminates the truth about health care innovations and advancements in a just and equitable way.

We appreciate the opportunity to provide our comments on ICER's May 14th Draft Evidence Report, "JAK Inhibitors and Monoclonal Antibodies for the Treatment of Atopic Dermatitis." Our comments about the draft report are organized below into sections about People-Centered Perspectives; Data, Modeling, Assumptions and Uncertainties; and Additional Points.

People-Centered Perspectives

Atopic dermatitis – commonly known as eczema – is a complex immune disorder affecting the skin. The draft report does a reasonably good job of describing many of the clinical and personal challenges faced by people with atopic dermatitis. But it is also clear that better treatments for atopic dermatitis are needed because of great variability in how the condition affects individuals and people who have various co-morbidities. As the draft report states:

- "Despite available treatments, many individuals do not respond to multiple different topical and systemic therapies supporting the need for new treatment options."[i]
- "There was broad recognition that current therapies do not address all of the needs of patients with atopic dermatitis."[ii]

Better treatments are needed not just to improve clinical outcomes, but perhaps more important, to improve patients' productivity and quality of life. As described in the draft report: "For students it can affect school attendance and lead to distraction when in class, negatively impacting developmental milestones. Similarly, atopic dermatitis can affect work through missed days, decreased work performance (presenteeism), missed promotions, limited career options, and even disability from one's chosen profession. The net result is a financial impact on individuals and families over the course of one's life in terms of educational and work advancement opportunities delayed or lost."[iii] Unfortunately, that reality is minimally recognized in the draft report's analyses and conclusions.

There are similar important aspects of how atopic dermatitis affects people and their treatment choices that the draft report fails to acknowledge or incorporate into its analysis and conclusions.

First, a key data point cited in the draft report highlights the personal financial toll of atopic dermatitis: "The overall costs associated with atopic dermatitis are estimated to be $5.3 billion in the US, including over $1 billion in health care costs."[iv] This means that the personal (i.e., non-health care costs) are about 400% greater than the health care costs. This four-to-one ratio quantifies the serious limitations of the draft report, its analyses, and its conclusions since it focuses almost exclusively on the costs that are less than 20% of the actual impact of the disease.

Second, although the draft report discusses how atopic dermatitis significantly impairs an individual's work and life activities, it fails to capture the full consequences of the "social embarrassment and isolation"[v] resulting from a person's skin appearance, and how that leads to "psychological distress including loss of self-esteem, anxiety, depression, and suicidal ideation."[vi] Specifically, the draft report does not explore research about atopic dermatitis leading to greater suicide attempts (although it is unclear if the condition causes an increase in deaths from suicide) or other mental, emotional, or behavioral health issues.[vii]

Third, while the draft report – like much of ICER's work – focuses on a small group of treatments, for people with atopic dermatitis and their clinicians, the actual range of treatment options is much wider and more complex. This discrepancy is apparent when comparing the draft report's scope with that of the two actual systemic reviews and technology assessments summarized and referenced in Section D5 of the Supplemental Material.[viii] One of those reviews evaluated "20 different medications," and the other "13 different approved treatments in Europe," in contrast with only six treatments included in the draft report. For clinicians, patients, policy makers, and others concerned with improving the quality and efficiency of health care within the populations of their purview (e.g., the management of Medicare, state Medicaid programs, private health insurance, Veterans Affairs' health care, Department of Defense health care, or the Indian Health Service), the question is not about evaluating small subsets of treatment options, but rather how to develop and implement appropriate policies for ensuring quality and efficient health care for the population for whom they are either paying for their health care or actually delivering their health care services and treatments. In contrast – as we've noted before – ICER's work is illusionary in that it assumes a unified, single health care system, and it assumes that there is a single health care budget for that "system."

And lastly, in the subgroup analysis, the only differentiators are age and disease severity. However, there are some indications that women and Black Americans are more likely to have severe atopic dermatitis.[ix] Even though the available data may be limited or not definitive, given the inherent underrepresentation of women and people of color in clinical trials, and the disparities and inequities they continue to experience in access to health care in the U.S., we strongly believe that the draft report should at least address the important issues for those subgroups, namely potential issues related to the need for new treatments, and challenges accessing them. And in this area, we note that the draft report states, "Given the large impact of atopic dermatitis in African-Americans and the importance of skin appearance on outcomes of treatment more broadly, few trials included a sizable number of patients with darker skin complexions, and we are not aware of any trial that has reported outcomes among those with darker

skin complexion."[x] So while ICER appears to be aware of this issue, we suggest that it be more explicitly stated in the draft report, and that the need for better and more extensive data collection on those subgroups, and greater inclusion of people of color in future research, be stressed by ICER.

Data, Modeling, Assumptions, and Uncertainties

Because the draft report does a deep numerical dive into the available research for six different medicines, it contains an extensive amount of data. However, just because there are numbers, and those numbers are compared and plugged into formulas for evaluative purposes, does not make the resulting "output" insightful, useful, or even correct. We are reminded of the old adage: "Not everything that counts can be counted, and not everything that can be counted counts."[xi] Breaking this down into its two parts, we see that the first part relates to the reality that patient concerns and perspectives are often hard to measure and are often not robustly evaluated in clinical research. For atopic dermatitis treatments, we are gratified that there are so many different patient-focused metrics as described in the draft report's Supplemental Materials Definition section.[xii] However, of those 11 different outcome measures, the draft report focuses on two that are investigator-measured (i.e., EASI and IGA), rather than patient-reported or primarily related to quality of life. This selection of measures may be because of the structure and compatibility of data across trials, but it underscores that the way data is collected and chosen for evaluation drives both thinking and conclusions.

To that point, we appreciate that uncertainties about metrics such as EASI are discussed in the draft report, e.g., "…we assumed that levels of EASI response are associated with differences in health-related quality of life." However, there may be differential effects of the treatments modeled on conditions such as itch and sleep that are not completely captured by generic quality of life instruments. However, available data did not support the use of treatment-specific utilities. Additionally, there may be incremental effects of some of these treatments on quality of life in sub-populations of people with atopic dermatitis, such as those with co-occurring asthma or chronic rhinosinusitis, which are not explicitly captured in the current model."[xiii] Because of the importance of those uncertainties, they should have been explored in greater depth and earlier in the draft report, particularly since one researcher stated that the use of such measures "in clinical practice is not recommended," and that "both objective and subjective assessments of disease severity are important to assess, consideration of clinical characteristics such as disease recurrence or persistence, as well as location of the affected areas, should be considered in the overall judgement of disease severity and consideration of therapy choice."[xiv]

And more generally concerning ICER's assessment approach, a recent review of books on the topic of evaluation metrics[xv] produced the following insights and quotes that are very illuminating:

- "Seduced by their seeming precision and objectivity, we can feel betrayed when the numbers fail to capture the unruliness of reality."
- "As Tim Harford writes, data 'may be a pretty decent proxy for something that really matters,' but there's a critical gap between even the best proxies and the real thing—between what we're able to measure and what we actually care about."
- "To simplify the world enough that it can be captured with numbers means throwing away a lot of detail. The inevitable omissions can bias the data against certain groups."
- "Numbers are a poor substitute for the richness and color of the real world."

- **"Numbers don't lie, except when they do."** [emphasis added]

Another problematic assumption in the draft report is the relationship between atopic dermatitis and mortality. The draft report states, "We assumed that atopic dermatitis disease and treatment did not affect mortality,"[xvi] and one of the Long-Term Cost Effectiveness analysis' assumptions is "Atopic dermatitis disease and treatments do not affect mortality."[xvii] However, research indicates higher rates of suicide attempts, and overall higher mortality, i.e., one analysis "found that patients with atopic eczema had an 8-14 percent increased risk of death due to infectious, digestive, and genitourinary causes. They noted that increased mortality risk was mainly in those with the most severe or more active atopic eczema. Patients with severe atopic eczema had 62 percent higher overall risk of death. These findings are consistent with previous studies."[xviii]

The draft report also primarily compared trial data that looked at monotherapy, but advancement and actual practice may include a combination of treatments, including systemic and topical. Once again ICER may be looking at the theoretical that does not reflect reality. As the report itself describes in discussing its modeling, "the NMA analyses that informed our effectiveness estimates in the model were derived from phase II and III RCTs that compared the treatments of interest to placebo with only the added use of topical emollients at 16 weeks. Therefore, the incremental value of these treatments may not be generalizable to patients using topical steroids and/or calcineurin inhibitors."[xix]

Overall, the extensive data, charts, graphs, and comparative analytics across six different treatment options contained in the document made the draft report very user unfriendly. In other words, for unsophisticated readers, the content is probably indecipherable, leaving those individuals to look at the conclusions and assume that ICER's internal and external teams got everything correct. And for sophisticated readers and analysts – such as those who decide clinical care, formulary placement or reimbursement policies – there remains the question about how the information in the draft report fits in with the much larger array of treatment options for atopic dermatitis (including possible combinations of treatments), or the much larger issue of managing access and coverage for immunomodulator medicines. On both points, the draft report clearly fails usability tests in multiple and different ways.

<u>Additional Points</u>

- Please explain how the New England CEPAC is both a "core program of ICER" and "an independent committee."[xx]
- The draft report states that "ICER does not provide health benefit price benchmarks as part of draft reports because results may change with revision following receipt of public comments," however, <u>that is not true</u>. Health Benefit Price Benchmarks <u>were</u> included in ICER's recent draft report about Alzheimer's treatments.[xxi] And further – as we pointed out in comments to that draft report – ICER's draft reports should absolutely include benefits price benchmarks from a societal perspective, particularly in this draft report because (as noted above), there is a 4:1 ratio in societal to health care costs. To add to the draft report's inconsistencies in this area, the Long-term Cost Effectiveness Supplemental Information goes into some detail about analyzing the situation from a societal perspective,[xxii] but here too the draft report ignores the evidence about increased mortality related to atopic

dermatitis. This is another example of ICER making up its own arbitrary rules but only following them when it sees fit to do so.

- The draft report states that as part of building the comparative clinical effectiveness model the assumption was made "that background topical medication is not an important effect modifier."[xxiii] Does this mean that ICER believes that topical medications are ineffective? We would appreciate ICER specifically responding to this point and to the clinical logic behind that assumption as it relates to ICER's modeling in the draft report and hence the draft report's conclusions.
- There is no discussion about the biological mechanism of action of atopic dermatitis, aside from it being related to "problems with the body's immune system"[xxiv] or as an "allergic condition,"[xxv] while also noting that people with atopic dermatitis also commonly have allergies and asthma. Such general and imprecise language does a disservice to readers. According to Mt. Sinai Medical Center, atopic dermatitis is an autoimmune disease at the molecular level,[xxvi] and the Immune Deficiency Foundation also discusses atopic dermatitis within the spectrum of autoimmune skin diseases.[xxvii] The draft report should include more discussion about the underlying cause of atopic dermatitis, and if the draft report's writers and reviewers disagree with the conclusions noted above, then those disagreements should be explained.
- Given the extensive data density in the draft report, it is critical that the language be crisp, clear, and correct. However, there are several places in the draft report where words are missing, the meaning is unclear, or the text is complex and hard to decipher. Such poor writing (or faulty proofreading or copyediting) does a severe disservice to readers and ultimately to anyone who might use ICER's reports for anything substantive. For example:
  - In this sentence, we believe the word "report" is missing: "Concerns about lack of long-term data for dupilumab, noted in ICER's 2017, have been alleviated over time based on published data and widespread use in clinical practice."[xxviii]
  - And this sentence is misleading: "Non-pharmacologic treatments are recommended to maintain and prevent flares." That is, we do not believe that treatments are recommended to maintain flares.
- In the draft report, the acronym AD is used to refer to Atopic Dermatitis, but it is not in the list of acronyms on page vii of the draft report nor could we find it specified in the text of the draft report. While that may seem obvious, in the previous draft report AD was used for Alzheimer's Disease, and that abbreviation was noted in on page viii of that draft report.

Conclusions

Patients Rising Now is pleased that people with atopic dermatitis have many treatment options. Like many complex health conditions that have very different presentations and courses for different people, and where there are multiple types of treatment options, individualization of care and close coordination with clinicians is important. Unfortunately, we see the draft report as thwarting that goal. Indeed, we are concerned (once again) that through ICER's myopic cost-fixated lens, the draft report will serve to reduce access and impair patient-clinician care planning and coordination.

Sincerely,

Terry M. Wilcox

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

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[i] Draft report, p. 12
[ii] Draft report, p. 14
[iii] Draft report, pp. 13-14
[iv] Draft report, p. viii
[v] Draft report, p. 11
[vi] Draft report, p. 13
[vii] "[P]atients with AD were 44% more likely to exhibit suicidal ideation (pooled odds ratio, 1.44; 95% CI, 1.25-1.65) and 36% more likely to attempt suicide (pooled odds ratio, 1.36; 95% CI, 1.09-1.70) compared with patients without AD. Studies investigating completed suicides in patients with AD had inconsistent results." https://pubmed.ncbi.nlm.nih.gov/30540348/
[viii] Draft report, p. 301
[ix] https://atopicdermatitis.net/eczema-statistics; https://nationaleczema.org/research/eczema-facts/, and https://link.springer.com/chapter/10.1007/978-3-319-72156-9_19#:~:text=The%20increase%20was%20higher%20in,gender%20did%20not%20influence%20prevalence
[x] Draft report, pp. 29-30
[xi] Often attributed to Albert Einstein, but more likely originating with William Bruce Cameron, https://quoteinvestigator.com/2010/05/26/everything-counts-einstein/
[xii] Draft report, pp. 70-72
[xiii] Draft report, p. 51
[xiv] "Approach to the Assessment and Management of Adult Patients With Atopic Dermatitis: A Consensus Document. Section II: Tools for Assessing the Severity of Atopic Dermatitis," Gooderham et al., Journal of Cutaneous Medicine and Surgery, 2018, Vol 22(IS)10S-16S
[xv] "What Data Can't Do: When it comes to people – and policy – numbers are both powerful and perilous," Hannah Fry, New Yorker, March 29, 2021, pp 70-73
[xvi] Draft report, p. 37
[xvii] Draft report, p. 40
[xviii] https://practicaldermatology.com/news/people-with-severe-atopic-dermatitis-may-have-increased-risk-of-death-from-several-causes
[xix] Draft report, p. 52
[xx] Draft report, p. iii
[xxi] https://icer.org/wp-content/uploads/2020/10/ICER_ALZ_Draft_Evidence_Report_050521.pdf
[xxii] Draft report, pp. 312-13
[xxiii] Draft report, p. 106
[xxiv] Draft report, p. 11
[xxv] Draft report, p. 13
[xxvi] https://www.mountsinai.org/about/newsroom/2014/atopic-dermatitis-found-to-be-an-immunedriven-disease
[xxvii] https://primaryimmune.org/about-primary-immunodeficiencies/relevant-info/autoimmunity
[xxviii] Draft report, p. 8