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Online Supplementary Material

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Supplemental Appendix 1. *EPR-3*: Non–Evidence-Based Topics

The *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma* (*EPR-3*)[1] did not assign evidence rankings to recommendations pulled through from the *EPR-2* (1997)[2] guidelines on topics for which there was little new published literature. *EPR-3* did not apply its evidence-based methodology to "Section 2. Definition, Pathophysiology and Pathogenesis of Asthma, and Natural History of Asthma." As a consequence, the perspectives of the experts on the panel were emphasized at the expense of a systematic review of the literature. For example:

1. Atopy: *EPR-3* continues its previous emphasis on atopy as a cardinal attribute of asthma by stating that "atopy…is the strongest identifiable predisposing factor for developing asthma,"[1(p11)] but fails to cite 2 systematic epidemiology reviews showing that less than one-half of asthma cases can be attributed to atopy[3] and that allergens have not been proven as a primary cause for asthma.[4] Associations between atopic sensitization and asthma in developing countries are even weaker.[5]

2. Age of onset of asthma: *EPR-3* states that "the onset of asthma for most patients begins early in life with the pattern of disease persistence determined by early, recognizable risk factors including atopic disease, recurrent wheezing, and a parental history of atopy."[1(p12)] This statement is based in part on elegant research conducted in cohorts of children.[6] *EPR-3*, however, fails to review systematically the epidemiologic research on the total population, which reveals a different picture: childhood-onset and adult-onset asthma are equally prevalent[7-12]; adult-onset asthma is more severe,[12] less likely to remit,[7] and is associated with greater mortality[7,14] than childhood-onset asthma.

3. Asthma and chronic obstructive pulmonary disease (COPD): *EPR-3* acknowledges that some patients with asthma develop persistent changes in airway structure ie, COPD[1(p11)] and that anti-inflammatory therapy does not prevent progression of underlying disease severity.[1(p12)] *EPR-3* fails to present available data supporting the logical conclusion from these observations that asthma and COPD may be part of the same natural history.[15-17] To understand the interrelationships of asthma and other obstructive airways diseases, a longitudinal approach over a patient lifespan has been recommended.[17] For example, *EPR-3* did not present results from a large, population-based prospective cohort study of children and adults reporting that asthma was a more significant risk factor for COPD (RR = 12.5) than smoking (RR = 2.5).[15]

4. Classification of obstructive lung disease: *EPR-3* fails to acknowledge that the nosology of asthma and COPD is based on expert opinion. There are (at least) 2 different approaches to classifying obstructive airway diseases: the splitting[18] and the lumping[16] approaches. Splitters (prevalent in North America and Britain) classify asthma and COPD as entirely different diseases, whereas lumpers classify asthma and COPD as points on a continuum, sometimes referred to as the Dutch Hypothesis[16] or as chronic nonspecific lung disease (CNSLD).[17] As a consequence of the existing bias toward the splitting approach, adult asthma research usually includes only atopic, nonsmoking patients who are mainly 30 to 40 years old and excludes asthma patients with smoking and/or COPD.[17] Conversely, COPD research generally includes only smokers and excludes patients with asthma. Research results based on the splitting approach are severely limited in generalizabilty, since many patients have a mixed presentation for obstructive

airways disease and are never studied, as for example, asthmatic smokers with COPD, the group of patients with reactive airways that is difficult to classify,[19] and nonsmokers with COPD, who comprise up to 15% of males and 30% of females with COPD.[20] These conceptual and methodological biases in current asthma research greatly affect the generalizability of the research upon which the guidelines are based.

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Supplemental Appendix 2. *EPR-3*: An Example of Poor-Quality Research

Historically, asthma research has favored surrogate outcomes such as pulmonary function, or inflammatory markers. The *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma* (*EPR-3*)[1] describes a desirable trend toward valuing patient-oriented outcomes, such as symptoms, rescue medication use, exacerbations and quality of life. A currently popular hybrid outcome is "asthma control," which combines asthma symptoms, rescue bronchodilator use, and pulmonary function.[2,3] When patient-oriented outcomes are conflated with surrogate outcomes in asthma research, interpretation can be problematic. For example, clinicians must remain vigilant in interpreting some asthma trials that may not be generalizable and that claim to report patient-oriented outcomes but include surrogate outcomes in the hybrid measure.

OPTIMA[4] randomized 900 mild asthma patients aged >15 years from 198 centers in 14 countries to 1 year of treatment with inhaled budesonide or placebo twice daily for 1 year (group A in the OPTIMA trial). The investigators did not state whether they included or excluded smokers, and they did not present a table of patient characteristics, so it was not possible to understand the relevance of OPTIMA to the general population of asthmatics. The primary outcome was "time to the first severe asthma exacerbation." OPTIMA reported that 33.3% in the placebo group compared with 13.3% in the inhaled corticosteroids (ICS) group had a "severe exacerbation" (NNT = 5; $P<.001$).

Although both START and OPTIMA studied patients with mild disease, the OPTIMA NNT of 5 to prevent a "severe exacerbation" was more than 25-fold greater than the annualized START NNT of 132. What factor(s) might account for this large discrepancy, and which result is more likely to be accurate? The answer probably lies in a closer inspection of OPTIMA's definition for "severe exacerbation."

In addition to hospital admission and emergency treatment, OPTIMA included "a decrease in morning peak expiratory flow rate (PEF) >25% from baseline…on 2 consecutive days" as part of the definition for a "severe exacerbation." Thus, addition of a disease-oriented, surrogate endpoint (PEF) may have vastly inflated the reported clinical effectiveness of ICS treatment in mild asthma. Because PEF changes of this magnitude may not always be perceived, it is even possible that many of these "severe exacerbations" were asymptomatic.

Because OPTIMA did not report separately on results for the endpoints of hospitalization, emergency treatment, and PEF changes, it is unknown whether other factors might also have contributed. OPTIMA justifiably deserves at most a SORT level-2 or possibly a SORT level-3 grade based, in part, on uncertain generalizability and limited use of patient-oriented outcomes. Current practices in asthma research justify careful inspection of asthma trial details to determine the extent to which results are generalizable, internally valid, and patient oriented.

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