The primary limitation of our study is its cross-sectional design, which did not allow us to measure temporal changes in outcome. Participants with preexisting respiratory conditions are more likely to remember adverse events than participants without these conditions, which may lead to recall bias and overestimation of the risk of adverse events. Future studies would benefit from a cohort design, which would overcome these limitations. Nonetheless, the chance of participants without respiratory conditions not recalling these events is partially mitigated by the fact that the 2019–2020 bushfire was a major natural disaster and the adverse effects surveyed were relatively uncommon.

In conclusion, smoke exposure was significantly associated with adverse health effects during the Australian bushfire season in 2019/2020 not only among people with respiratory conditions but also among healthy people. Surprisingly, older age (65 yr and above) was associated with a significantly lower risk of adverse health effects. Our data suggest older people may be more cautious and less mobile in outdoor settings than younger people during bushfires. Younger people (<65 yr) may benefit from public health messaging about outdoor air avoidance and respirator use. Adverse health effects due to smoke exposure also impacted people without respiratory conditions. However, people with respiratory conditions are at greater risk and should be a priority for mitigation measures into the future. ■

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Optimism with Caution: Elexacaftor–Tezacaftor–Ivacaftor in Patients with Advanced Pulmonary Disease

To the Editor:

We read with great interest the article by Burgel and colleagues, which described significant and rapid improvements in outcomes of patients

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with severe cystic fibrosis (CF)-related lung disease after commencing elexacaftor–tezacaftor–ivacaftor (1). We congratulate the authors on capturing real-world population data in this key group of patients with FEV_1 <40% who have significant potential to benefit from these treatments but were excluded from the pivotal phase 3 trials. The authors demonstrated significant and rapid improvements in lung function, nutritional parameters, and treatment burden in line with previous studies (2–4). Importantly, they are the first to describe a significant reduction in the need for lung transplantation, with 11 of 16 patients removed from the lung transplant waiting list and a remarkable 36 of 37 removed from consideration of transplant within the next 3 months.

Therefore, at a population level, there are many reasons to be optimistic, but clinicians must remain cautious in their expectations and not prematurely alter their practice, which is a message that was not highlighted in the manuscript. Our own experience and that of others (2–4) suggests that not every patient will experience such a dramatic improvement in lung function, because of either lack of response or medication intolerance. For example, in one phase 3 trial of triple therapy, 1% of subjects had to cease the medication because of adverse events, 11.6% developed elevated liver enzymes, and 10.9% developed a rash (3). In addition, nonresponding cases may not be reported as frequently because of publication bias. Enthusiasm for this class of medications may also be heightened because of the widespread involvement of CF care teams (including the authors of this letter) in the clinical trials and the frequent conflict of interests that have developed consequently through associations with manufacturers. As clinicians we must remain alert to all possible outcomes and continue to follow existing standards of care, which currently include early referral for consideration of lung transplantation.

The importance of continuing to consider lung transplantation is a key aspect of management, as early engagement with transplant services leads to better outcomes (5). In addition, early involvement with palliative care services can benefit patients with severe, end-stage lung disease considerably. The Cystic Fibrosis Foundation recommends that discussions about lung transplantation should occur when FEV_1 declines below 50%, and lung transplant referral should occur for those with advanced but not end-stage lung disease (5). Lung transplantation is a major undertaking, and consideration includes significant education, support, and joint decision-making over time. Although CFTR modulator therapies such as elexacaftor–tezacaftor–ivacaftor now play an important role in discussions about disease trajectory and treatment options, we suggest that the practice of early transplant discussion and referral should continue.

Despite the remarkable outcomes described in this paper and the optimistic promise of future CFTR modulator therapies, we must remain cautious about changing our practice and continue to prepare and offer options for those who do not tolerate or respond to triple therapy. ■

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Reply to Kuek *et al.*

From the Authors:

We thank Dr. Kuek and colleagues for their letter in reference to our recent publication (1). They suggest that our manuscript contains many reasons to be optimistic but that it does not highlight that clinicians must remain cautious with their expectations and should not prematurely alter their practice standards. As stated in our original manuscript, our study provided the first data describing the effects of initiating elexacaftor–tezacaftor–ivacaftor in a large cohort

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