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The time to PREPARE is over; the time to improve diversity in asthma studies is now

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The benefits of inhaled corticosteroids (ICS) in treating asthma were first described by Gelfand in 1951,[1] and their utility in preventing the severest of asthma complications is well-substantiated.[2] However, when one combines a disease characterized by waxing and waning symptoms (i.e., asthma) with a treatment that successfully addresses inflammation but provides little immediate symptomatic relief (i.e., glucocorticoids), and then mix in high treatment costs, multiple prescribed doses per day, and a unique means of administration (i.e., inhalation), it is not surprising that the result is often poor treatment adherence. Research from our group and others suggests that less than half of prescribed ICS medication is actually taken.[3] Moreover, interventions focused on improving asthma medication adherence have been largely unsuccessful despite considerable time and resources invested.[4]

Nevertheless, recent approaches to increase ICS use demonstrate the effectiveness of simplifying regimens to better accord with patterns of use. In 2020, single maintenance and reliever therapy (SMART) was added to U.S. asthma management guidelines for the treatment of moderate-to-severe persistent asthma in individuals age 4 years and older.[5] Unlike earlier approaches using separate inhaled medications for asthma control and symptom relief, SMART involves a single combination inhaler containing formoterol, a quick-onset long-acting beta-agonist, and an ICS medication for both maintenance and rescue use. Clinical trials have found that SMART consistently reduces the occurrence of severe asthma exacerbations when compared with combined regular ICS dosing and as needed short-acting beta-agonist (SABA) use.[5]

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CONFLICT OF INTEREST STATEMENT

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In the recently published Person Empowered Asthma Relief (PREPARE) trial, Israel and colleagues provide another elegantly simple intervention to increase ICS use.[6] Their approach employs a patient-activated, reliever-triggered inhaled glucocorticoid strategy (PARTICS). PARTICS allows individuals to continue their usual maintenance controller therapy, but rescue medication use is a prompt to take additional ICS doses of beclomethasone dipropionate (80 μg per metered dose). Specifically, patients in the intervention arm were instructed to take additional ICS doses at a 1:1 ratio with rescue inhaler use or at a 5:1 ratio with rescue nebulizer use (i.e., 5 inhalations of ICS per one nebulization). A total of 1,201 adults (603 black and 598 Latinx) with moderate-to-severe asthma were randomized to either PARTICS (n=600) or usual-care (n=601); participants were followed for 15 months. The primary outcome, severe asthma exacerbations, was 15% lower in the intervention group when compared with usual care (hazard ratio 0.85, 95% confidence intervals [CI] 0.72-0.99, P-value 0.048). Intervention group participants also reported significantly greater improvements in both patient-reported asthma control (a 0.9 point difference in composite Asthma Control Test score, 95% CI 0.5-1.2) and asthma-related quality of life (a 0.4 point difference in Asthma Symptom Utility Index score, 95% CI 0.02-0.05), as well as lower numbers of days missed from work, school, or usual activities (13.4 vs. 16.8 annualized days missed among intervention and usual care group participants, respectively).

Potential benefits of PARTICS over SMART were the continuance of existing maintenance therapy, the ability to administer additional ICS therapy without concern for added beta-agonist exposure, and its validation in populations of color. Regarding the last point, the unfortunate truth is that the PREPARE trial is one of the rare exceptions of racial and ethnic diversity in asthma clinical trials. Nearly one third of U.S. citizens identify as black and/or Latinx, yet most clinical studies do not meet this mark of inclusiveness. Moreover, even if these percentages are achieved in a given study, the numbers are often too small for sufficiently powered subgroup analyses. Even with the laudable diversity of PREPARE, the trial still may have been underpowered to identify significant effects within the two population groups studied (particularly among Latinos).[6] Among these Census-define groups, we also know that there is substantial heterogeneity. For example, Puerto Rican and Mexican individuals have very different prevalence rates for asthma (being much higher in the former), as well as observed differences in asthma treatment response.[7]

PREPARE was designed as a pragmatic clinical trial. Its permissive inclusion criteria (e.g., including active smokers), limited exclusion criteria, and hands-off approach with respect to patient interaction and monitoring were intended to more closely measure real-world effectiveness. Nevertheless, study patients had an established record of care in their respective health systems and received monthly study surveys; intervention group patients also received free add-on ICS medication. Hence, study results may not reflect actual real-world effectiveness where barriers, such as poor access to care, ineffective physician-patient communication, clinical inertia, high out-of-pocket medication costs, and quantity limits on refills, could adversely affect faithful adherence to PARTICS.

SMART has been estimated to reduce overall corticosteroid exposure when compared to usual care, whereas individuals in the PARTICS arm of PREPARE reported increased ICS

inhalers dispensing over usual care (8.9 vs 7.8 reported ICS inhalers received, respectively).[6] However, these differences in ICS exposure between approaches must be interpreted cautiously. Patient reported measures of ICS use may be a poor proxy for actual use and exposure, even among participants enrolled in clinical trials.[8]

By increasing ICS use in concert with rescue medication, both PARTICS and SMART provide a tailored approach to care that appears to be both simple and effective. In an ideal world, patients would escalate ICS use in advance of requiring reliever medication; however, apart from rescue medication use and past history, clinically practical biomarkers of impending exacerbations don't exist. Perhaps "-omics" (e.g., genomics, transcriptomics, metabolomics, or proteomics) will identify better predictors of asthma severity and treatment responsiveness that can be used to guide both timely and appropriate controller medication dosing. Genetic risk scores for other conditions have already been shown to predict disease susceptibility not identified through traditional risk factors,[9] and these scores may identify patients who can benefit from early prevention. However, these tools rely on data from existing genome-wide association studies, and this is where the conversation again pivots toward diversity and inclusiveness. Populations of color are vastly unrepresented in extant genomic studies, and genetic risk scores developed in one population group often do not predict well in other groups.[10] Therefore, even if scientific advances in predictive genomics come to fruition in terms of clinical implementation, blacks and Latinos will be among the last to benefit unless research inclusiveness radically departs from its current trajectory to fill the existing void.

Given heightened interest in precision medicine, it is also necessary that we learn the important lesson imparted by both PARTICS and SMART – that is, effective medicine must support the *individual* goals of the patient. As clinicians, we should strive to find treatment regimens which complement the routines of our patients, rather than drastically impose new ones and expect that they will be followed. Arguably, the approaches implemented by PARTICS and SMART transcend usually defined patient-centered care. The key insight was not only addressing patient-desired outcomes but also synchronizing controller treatment to pattern the manner in which patients naturally take their asthma medication. Lastly, as we have repeatedly observed, findings within one group or setting often do not generalize to another. Therefore, if an ultimate goal of medicine is tailored treatment, we first need studies which reflect the diversity of the patients we serve. This means pressing grant funding agencies and the pharmaceutical industry to prioritize diversity and to design studies that are sufficient powered to analyze outcomes both across and within population groups. The time is long overdue to close the knowledge gap which has resulted from a lack of diversity in research; kudos to trials, such as PREPARE, which remind us of its importance.

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Abbreviations:

CI	confidence interval
ICS	inhaled corticosteroid
PARTICS	patient-activated, reliever-triggered inhaled glucocorticoid strategy
PREPARE	person empowered asthma relief
SABA	short-acting beta-agonist
SMART	single maintenance and reliever therapy

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