nation diet is indeed standard of care. Compliance with the 6-food elimination diet in real-world settings is understandably low. Some recommend repeat EGDs at each step of the elimination diet, for up to 5 EGDs per patient, at an immense burden to patients and expense to the health care system.

My review also revealed that the most common food trigger was dairy. This seemed a perfect situation for an unblinded n-of-1 trial. The condition is chronic. Response to food elimination varies by individual. The symptoms are experienced near daily. And if I was going to eliminate a food from my diet for the rest of my life, I wanted to know for certain that it was the cause of my symptoms.

I eliminated all milk products from my diet for 8 weeks. My symptoms resolved. I then ate bread pudding with ice cream, sweet butter on my corn, and milk in my cereal. My symptoms recurred. I am now off dairy, symptom free, and convinced I know my food trigger. No further EGDs.

At the end of my trial, I read the article by Kravitz and colleagues that demonstrated a lack of effectiveness of patients randomized to n-of-1 trials compared with usual care for treatment of chronic musculoskeletal pain. This was a laudable negative study that advanced the science of n-of-1 trials. Still, my experience suggests there may yet be a role for n-of-1 trials. My hope is that the study by Kravitz and colleagues spurs other researchers and clinicians not to abandon n-of-1 trials, but rather animates us to think creatively about scenarios in which n-of-1 trials might simplify treatment regimens, improve patient compliance, and reduce health care costs.

In Reply The letters from Vohra and Punja and Smith about our recent Original Investigation underscore the same crucial point: patients may vary not only in their response to treatment, but also in their response to n-of-1 trials. Vohra and Punja offer an ardent counterpoint to Mirza and Guyatt’s conclusion that n-of-1 trials are a “beautiful idea being vanquished by cruel and ugly evidence.”2 Smith’s story offers an inspiring example of how n-of-1 trials may be applied informally in the service of better, more patient-centered care.

More generally, we believe that rumors of the demise of n-of-1 trials may be premature for 3 reasons. First, advances in mobile technology and ubiquitous home and environmental sensors will increasingly make tracking and self-experimentation much less demanding of time and effort on the part of both patients and clinicians. Second, n-of-1 trials retain promise not only for evaluating treatment benefits in individual patients, but also (as Vohra and Punja suggest) for comparing treatments of comparable efficacy that may differ in terms of costs or harms. Finally, we believe that n-of-1 trials have not yet been fully appreciated as an instrument for advancing scientific literacy and self-efficacy. Broad deployment of n-of-1 trials evaluating health behaviors such as diet, exercise, medication adherence, and stress reduction may not only show people how to be healthier, they might also teach them about the power of randomization, the importance of systematic outcomes assessment, and the need to minimize bias—concepts that are not only central to science and data literacy, but ultimately fundamental to democracy.
efits of participating in an n-of-1 trial, not to assess the superiority or inferiority of any particular treatment.”

The study by Kravitz and colleagues reported higher incidences of a 5-point pain score reduction, which may have resulted in statistical significance between groups using this as a primary outcome. The study also reported increased discussion from the patients and clinicians for the intervention group, with a P value of .01 for differences discussion scores at 6 months and a P value of .05 for 12-month discussion scores. These results actually suggest that n-of-1 trials show some promise for pain management, which warrants further investigation. Therefore, it is quite premature to conclude so thoroughly, as is done in the accompanying Invited Commentary, that “the results fail to show any benefit of n-of-1 care.”

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To the Editor We read with interest the recent article by Kravitz and colleagues describing a randomized clinical trial comparing n-of-1 trials with standard care for treatment of chronic musculoskeletal pain.

The goal of the study was to establish the “benefits of participating in an n-of-1 trial, not to assess the superiority or inferiority of any particular treatment.” However, there appears to be a disconnect between the study goal and the choice of outcomes, which were focused on pain interference scores across different treatment regimens. Therefore, the null results should be interpreted with respect to treatment efficacy, not design. The n-of-1 participants who demonstrated a better response to 1 of 2 treatments were likely to experience improved pain outcomes as a result of continuing to receive the superior treatment. However, there was a high proportion (>75%) of n-of-1 participants who had no treatment superiority, and this may explain the trial’s findings.

Methodological factors, including the number and length of phases, could have influenced the degree of certainty about treatment superiority. Individual n-of-1 trials were heterogeneous, ranging from 4 to 12 weeks and with phases lasting 1 to 2 weeks. Some n-of-1 trials could have involved few crossovers, which might have affected the identification of a superior treatment and increased the risk of type-2 error. Furthermore, there was a lack of blinding, and the study did not achieve its sample size target, which may have influenced the results.

A total of 48% of n-of-1 participants incorporated nonpharmacological treatment into their n-of-1 trials. Designing phases that are long enough to show an effect (if one exists) is a relatively easy task for n-of-1 pharmacological trials owing to well-known drug half-lives, but this is more difficult in nonpharmacological trials (eg, exercise, acupuncture) where one must hypothesize about the immediacy and duration of effect. As such, 1 to 2 weeks is potentially too short.

Finally, the findings assume that participants adhered to the superior or recommended treatments. Lack of adherence could influence the effectiveness of interventions, and adherence rates may vary across different intervention types; adherence may be better for simple interventions (eg, daily medication) compared with more complex ones (eg, regular exercise). Nonadherence could have influenced the study findings, but this does not appear to have been explored.

Clinically meaningful results favoring the n-of-1 group were underemphasized, and between-subject variability in response to treatment was not reported. This was an ambitious but valuable study, which has illustrated a number of key issues for the field. We should avoid throwing the baby out with the bathwater and instead capitalize on the contribution this study makes to optimize future n-of-1 research.

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Letters

In Reply Many of the questions raised by Chapple and Blackston and by McDonald and colleagues about our recent Original Investigation1 are addressed in Pocock and Stone’s recent review on what to do when the primary outcome fails.2 Certainly, a trial in which the primary outcome fails short of statistical significance can be distressing to investigators. However, as highlighted by Chapple and Blackston, the interpretation of trial results may be colored by undue attention to a single primary outcome and arbitrary P value cut points. These constraints make sense in confirmatory studies of new drugs and devices (where the consequences of false positives can be dire) but not necessarily in more exploratory studies (like the Personalized Research for Monitoring Pain Treatment study).3

Both letters raise a number of other methodological issues, including lack of statistical power, underemphasis of important secondary outcomes, problems with application of the n-of-1 intervention, and potentially poor patient adherence. As we noted in our article,1 the study fell 12% short of enrollment goals, but it is not clear that reaching the planned sample size of 244 would have resulted in a significant P value. Single studies rarely provide definitive estimates of effect size, and for this reason we believe further studies (and subsequent meta-analyses) are warranted.

We agree that statistically significant between-group differences were seen in medication-related shared decision making and in the probability of achieving a 5-point pain interference score reduction. These findings are clinically important and deserving of further study. Likewise, although certain n-of-1 trial design choices (eg, offering nonpharmacologic treatments and relatively short treatment periods) may have contributed to the large proportion of inconclusive n-of-1 trials, our goal was to balance experimental rigor with patient choice and convenience.

Finally, although patients randomized to the n-of-1 arm adhered well to their assigned treatment regimens (averaging 1.4 on a 1-5 scale, with 1 indicating “always” following the directed treatment), we did not track adherence to the “winning” treatment following the trial. If the benefit of n-of-1 trial participation (if any) is mediated purely through the identification of clinically superior treatments, poor adherence to the “winner” in the aftermath of an n-of-1 trial could, as McDonald and colleagues suggest, limit the potential benefit. However, we suspect that other potential mechanisms are operative (eg, creating a more therapeutic physician-patient relationship, enhancing patients’ self-efficacy as autonomous agents) and may deserve more attention than previously recognized.

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Inconsistencies in Reporting Studies of Lactic Acidosis

To the Editor In their recently published Original Investigation regarding metformin use, renal function, and acidosis, Lazarus and colleagues1 explained why their findings were different than ours2 and wrote that our study “was limited by sparse [estimated glomerular filtration rate] data and did not account for changes in [estimated glomerular filtration rate] over time.”3 This is not true. Table 2 in our article summarized that we were able to classify more than 90% of metformin exposure time to renal function. In addition, our methods section clearly stated that we determined renal function during follow-up time and ran our analysis using a time-varying Cox regression analysis in which we modeled both changes in metformin exposure and changes in renal function over calendar time.

Nevertheless, because both studies1-2 used routine health care data, renal function recordings were probably a proxy indicator of the true renal function during the development of lactic acidosis. A more sensible explanation for the differences between the studies is that Lazarus and colleagues1 were more likely to measure metabolic or respiratory acidosis instead of lactic acidosis. The authors used International Classification of Diseases, Ninth Revision, Clinical Modification codes to define their outcome. This coding system, in contrast with UK Read terminology, cannot define lactic acidosis; therefore, we feel that the words lactic acidosis should have been replaced by acidosis. In a recently published follow-up letter, Lazarus and colleagues3 wrote that our study2 evaluated acidosis. This is not true either; we evaluated the risk of lactic acidosis.

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References