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Commentary

Moving Molecular Profiling to Routine Clinical Practice: A Way Forward?

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Abstract

Molecular profiling of a patient's tumor to guide targeted treatment selection offers the potential to advance patient care by improving outcomes and minimizing toxicity (by avoiding ineffective treatments). However, current development of molecular profile (MP) panels is often based on applying institution-specific or subjective algorithms to nonrandomized patient cohorts. Consequently, obtaining reliable evidence that molecular profiling is offering clinical benefit and is ready for routine clinical practice is challenging. In particular, we discuss here the problems with interpreting for clinical utility nonrandomized studies that compare outcomes in patients treated based on their MP vs those treated with standard of care, studies that compare the progression-free survival (PFS) seen on a MP-directed treatment to the PFS seen for the same patient on a previous standard treatment (PFS ratio), and multibasket trials that evaluate the response rates of targeted therapies in specific molecularly defined subpopulations (regardless of histology). We also consider some limitations of randomized trial designs. A two-step strategy is proposed in which multiple mutation-agent pairs are tested for activity in one or more multibasket trials in the first step. The results of the first step are then used to identify promising mutation-agent pairs that are combined in a molecular panel that is then tested in the step-two strategy-design randomized clinical trial (the molecular panel–guided treatment for the selected mutations vs standard of care). This two-step strategy should allow rigorous evidence-driven identification of mutation-agent pairs that can be moved into routine clinical practice.

Precision medicine has the potential for greatly improving the treatment of patients with cancer whose tumor molecular profile (MP) suggests targeted treatments that are highly effective. However, realizing this potential will require a thorough evidence-driven development process. Over the last few years, a considerable number of studies explicitly designed to evaluate the outcomes of patients treated according to their MP have been published (see 1,2), with the nonrandomized studies consistently reporting benefit from the molecular profiling. However, the one reported randomized trial comparing MP-directed treatments to standard treatments, SHIVA (3), was negative, suggesting that caution is needed in accepting the purported benefits seen in the nonrandomized studies.

In this commentary, we discuss some problems with interpreting nonrandomized studies as providing evidence of the utility of molecular profiling as a routine treatment strategy. In statistical nomenclature, this corresponds to establishing an MP as a predictive biomarker: a biomarker that can effectively identify patients that benefit from a specific treatment vs those who do not (as opposed to a prognostic biomarker, which indicates a patient's overall prognosis). We consider study designs comparing outcomes in MP-treated vs non-MP-treated patients, study designs comparing the progression-free survival (PFS) seen on an MP-directed treatment to the PFS seen for the same patient on a previous standard treatment (PFS ratio), and multi basket trials that evaluate the response rates of targeted therapies in specific molecularly defined subpopulations (regardless of histology). We also consider some limitations of randomized strategy designs (like SHIVA), followed by a suggestion for a path to strengthen the evidence for routinely using molecular profiling in clinical practice.

Comparison of Outcomes in MP-Treated vs Non-MP-Treated Patients

These nonrandomized study designs separate the study population into the subgroup treated with an MP-selected therapy vs

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the subgroup not treated with MP-selected therapy and then suggest that observing better outcomes in the MP-selected subgroup than in the non-MP-selected subgroup demonstrates that molecular profiling benefited the patients. There are three major interpretational issues with this approach. First, the two study subgroups are likely to differ with respect to important clinical characteristics. Even though some studies (4,5) use multivariate analyses or match patients based on known prognostic factors (eg, number of previous lines of therapy) (6), this is unlikely to remove all the confounding. In fact, the very mechanism by which some patients are separated into the two groups is likely to introduce bias. For example, patients who were treated with MP therapy were selected into that group based on their willingness to accept additional (possibly invasive) MP testing; their willingness to wait for results to come back (and the tumor board to issue a recommendation, if there was one); and their willingness to accept a potentially more aggressive, prolonged, and/or logistically challenging treatment course. Ultimately, the treatment selection decision is made by the treating physician and the patient, inevitably introducing differences between the subgroups.

A second issue is that patients who have a particular molecular mutation may have a better prognosis than patients who do not, regardless of therapy (ie, the mutation may be a prognostic biomarker). For example, p16 is an important biomarker in head and neck cancer, with better prognosis for p16-positive vs p16-negative populations (7,8) (similar prognostic results have been reported in Non-Small Cell Lung Cancer) (9). For example, in RTOG 0129, a randomized trial that compared standard chemoradiation with accelerated chemoradiation in oropharyngeal cancer, 30% of patients were p16 positive and the PFS hazard ratio of p16-positive vs p16-negative subgroups was 0.33 (7). Consider a hypothetical study evaluating an MP panel that assigns new or additional therapy for p16-positive patients (while p16-negative patents are treated with a standard treatment). Suppose 50% of the study patients are treated with MP-selected treatment (including 30% with p16-directed treatment) and 50% of the study patients with the standard of care. Then, even if none of the MP-directed treatments are better than the standard treatment, a comparison of the MP-treated vs non-MP–treated patients on the study would yield a PFS hazard ratio of 0.51 simply because the MP-treated group included all of the better prognosis p16-positive patients and, therefore, incorrectly imply that the molecular profiling benefited patients. In general, multiple MP-directed studies at an institution may result in the control standard-of-care population having the worst prognosis patients.

Finally, another potential problem with interpreting results of trials with this design is that the agent(s) assigned to the MP-treated patients could be beneficial to all study patients regardless of their MP. As an example, Haslem et al. (6) concluded that "precision cancer medicine can be applied to the community setting with measurable patient benefit" after reporting a PFS hazard ratio of 0.47 in 36 patients who received genomic-testing-determined targeted treatment compared with 36 patients who received standard chemotherapy. However, 12 of the 36 MP-treated patients received everolimus (six of the 12 had metastatic breast cancer). Given that everolimus is beneficial in breast cancer regardless of biomarkers with an overall PFS hazard ratio of 0.45 (10), it is quite plausible that a substantial portion of the observed difference between the MP-treated and chemotherapy-treated populations in this study could be attributed to the MP arm receiving better treatments that do not require MP screening to be deployed (ie, challenging the benefit of the molecular profiling). In the very special situation where the MP-directed agents are also used in standard practice, it may be possible to stratify the comparisons by agent, avoiding this potential problem (11).

PFS Ratio as the Study Endpoint

Von Hoff (12) suggested using the ratio of a patient's time to progression on an experimental agent to that patient's time to progression on the preceding treatment. If this ratio was larger than 1.3, this would suggest that the new agent was affecting the tumor in a beneficial way for that patient. Typically, the time to progression on the preceding drug (usually a standard therapy) is compared with the PFS of the experimental regimen, which we refer to as PFS1 and PFS2, respectively. Originally intended solely for cytostatic experimental agents (where a single-arm historically controlled trial would not be appropriate) (13), the use of the PFS ratio was extended to molecularly profiled targeted agents, for example, using a null hypothesis that 15% or less of the patients would have a PFS ratio greater than 1.3 (4,5,14–19). The attraction of using the PFS ratio as the primary endpoint of a study is that it does not require a randomized trial, resulting in a possibly smaller required sample size and avoiding the need for a standard treatment arm.

There are several problems with using the PFS ratio (1,20–22). The first is that it depends critically on knowing what proportion of patients would have a PFS ratio greater than 1.3 if they had been given second a standard treatment rather than a molecularly profiled targeted therapy. It is not inconceivable that the *rate* of growth may naturally slow down with time for some tumors, yielding PFS ratios greater than 1.3 even if treated with minimally active agents. This leads to questions concerning what proportion of patients with PFS ratios greater than 1.3 should be considered an appropriate null hypothesis rate and whether 1.3 is the appropriate cut off for suggesting an active targeted agent (23).

The second issue with the PFS ratio is that patients selected for the molecularly profiled targeted therapy may represent a special subset of the patients progressing on the previous treatment, leading to the potential for overestimating the benefits of the targeted therapy if patients with short PFS1 (on the previous therapy) are preferentially included in the study; this overestimation is an example of the statistical phenomenon known as regression to the mean. To demonstrate how this overestimation could happen, consider the PFS1 and PFS2 data from a group of 73 advanced colon cancer patients who were treated with FOLFIRI followed by FOLFOX6 (Figure 1A) (24); the horizontal and vertical axes give the PFS1 and PFS2 values for each patient, respectively. These patients were from the first arm of a randomized trial of the sequence FOLFIRI→FOLFOX6 vs the sequence FOLFOX6→FOLFIRI; the sequences had similar efficacy (25). The points in Figure 1A above the diagonal line represent patients with PFS ratios greater than 1.3; there were 14 such patients. Thus, the percentage of patients with a PFS ratio greater than 1.3 was 19.2% (14 of 73), close to a null value of 15%, suggesting that there is no evidence that FOLFOX6 is better than FOLFIRI. Now hypothetically suppose patients with short PFS1 were preferentially included in a retrospective study evaluating FOLFOX6 after progression on FOLFIRI; for example, only patients with PFS1 less than or equal to 5 months were enrolled in the study. The PFS data would then appear as in Figure 1B, which are the same as Figure 1A except only including patients with PFS1 less than or equal to 5 months. There are 18 patients

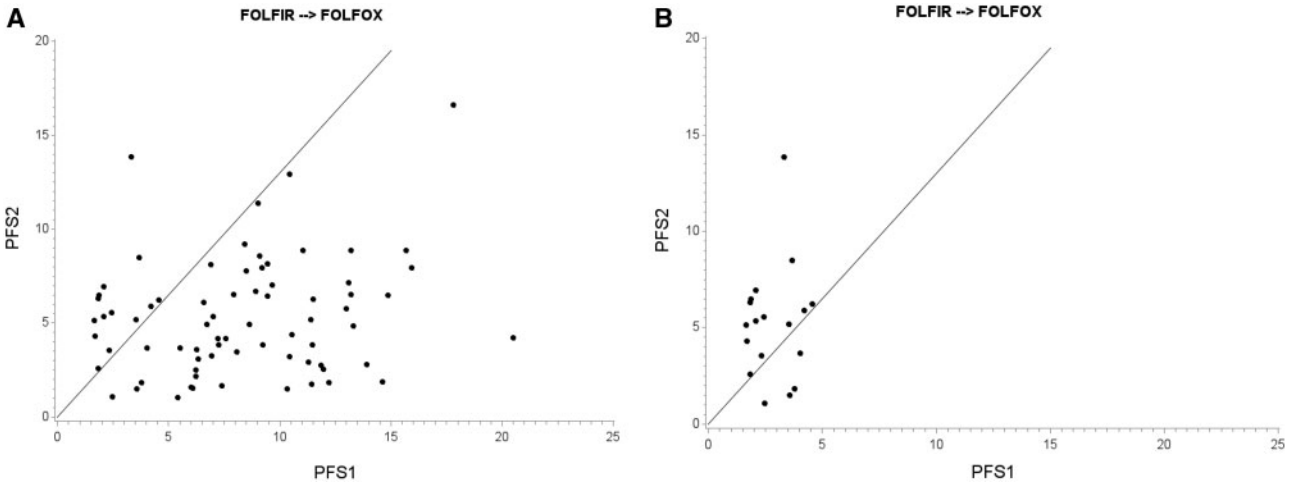

Figure 1. Progression-free survival data (PFS2 vs PFS1) for patients treated with FOLFIRI followed by FOLFOX6 from the arm of a randomized trial of the sequencing of the two regimens (24). **A)** All the data. **B)** Reduced data by omitting patients with PFS1 greater than 1.5. **Points above the diagonal lines** represent patients with a PFS ratio greater than 1.3.

included in Figure 1B, 14 (77.8%) of which have a PFS ratio greater than 1.3. Because 77.8% is much larger than the null value of 15%, this suggests incorrectly that FOLFOX6 is better than FOLFIRI.

A third potential limitation of using the PFS ratio is the necessity of having the same intensity of follow-up when measuring PFS1 as when measuring PFS2 (21), which is of special concern when PFS1 is very short. For example, in a study (18) of 101 patients who received matched treatment based on molecular profiling, the authors noted that a large proportion of patients with a PFS ratio greater than 1.3 had progressive disease at the first evaluation with the targeted treatment, suggesting the possibility that a more intensive follow-up with the targeted treatment would have yielded a lower value of PFS2 and a ratio less than 1.3 and that there was no benefit for these patients even though their ratio was greater than 1.3. The authors concluded, "Overall, our study adds to the shortcomings of using PFS ratio as surrogate for clinical benefit" (18). Furthermore, in addition to the differences in the follow-up intensity, different response criteria (eg, other than RECIST) are often used for patients whose PFS1 was determined outside clinical trials.

Finally, consider the SHIVA trial that randomly assigned patients with one of three study-specified molecular pathways (hormone receptor, PI3K/AKT/mTOR, RAF/MEK) between the MP arm (receiving the pathway-specific targeted agent) and the physician's choice standard therapy arm (3). In a secondary analysis of the crossover data from this trial (26), the PFS ratio was greater than 1.3 for 36.8% of the patients (25 of 68) crossing over from the physician's choice arm to a molecularly profiled targeted treatment, suggesting a benefit of the molecular profiling (in contradiction to the results of the primary randomized comparison of the trial). In particular, even in the hormone receptor pathway (where the randomized evidence of the trial clearly showed no benefit of molecular profiling), 35.5% of the patients (11 of 31) who crossed over from the physician's choice arm to a molecularly profiled hormone receptors–pathway agent had a PFS ratio greater than 1.3. This analysis provides empirical evidence that use of the PFS ratio can lead to incorrect conclusions about the benefits of treatments directed by molecularly profiling.

Multibasket Trials With Response Rate Endpoints

In a basket trial, patients with specific molecular alterations are treated with an agent (or a combination of agents) that targets those alterations, regardless of histology (ie, the trial includes a "basket" of histologies). In a multibasket trial, molecular profiling of the patient's tumor leads to the assignment of the patient to a specific basket (and agent) if their tumor has the alteration associated with that basket (27). For example, NCI-MATCH (28) currently has 35 histology-agnostic alteration-agent baskets. In each basket, 5% vs 25% response rates are targeted with a targeted sample size of 31 eligible patients.

There are a number of assumptions and limitations underlying the utility of basket trials. First, it is assumed that if a targeted agent is going to be effective in a basket, it should be effective for all, or almost all, histologies in the basket (otherwise one could miss a target-agent pair that is effective only for some histologies). If there are sufficient numbers of patients with each molecular target, one can have a separate basket for each target-histology combination. This approach was used in the MyPathway study (29). An alternative approach for settings with a limited number of histologies, which was used in the NCI-COG Pediatric MATCH trial (30), is to expand the number of patients with a specific histology in a basket if a sufficient number of responses are seen in that basket with that histology. To further improve histology-specific representation and evaluation, a basket design may limit the maximum number of patients with specific histologies.

Historical control comparisons with time-to-event endpoints (eg, PFS) are unreliable because of the potential selection bias due to which patients enter the trial and their molecular attributes, similarly to issues outlined in the previous section. Therefore, in a basket trial the primary analysis for each basket should be targeting a response rate (limiting its application to agents that are expected to yield responses if active). Note, however, that a basket with responses that are few and not durable may not be demonstrating any clinical benefit for that target-agent pair even though a formal activity threshold has been met. Furthermore, it should be noted that basket designs are most appropriate for clinical settings where responses with standard (nontargeted) therapies would be extremely unlikely

(eg, patients who progressed on available standard therapies) and where the experimental agent (or agent combination) would unlikely yield responses in an unselected patient population; otherwise, one could not attribute the responses to the targeted molecular alteration.

Finally, although the targeted treatment in a basket can be a combination therapy, if each patient's profile suggests a unique combination of several agents (based on having multiple alterations), it is likely that there may not be enough patients to fill baskets for some of the alteration-agent permutations. This problem will increase exponentially as the number of agents in the combinations increases. It may still be possible to use a multibasket trial in this situation, but combinations will need to be grouped together (eg, by similar molecular pathways involved in a combination) to form baskets that can be filled in a reasonable amount of time. In addition, it may be reasonable to increase the target response rate from 25% to higher values (eg, 40%) if combinations of many drugs (eg, three or more) are being used, thus lowering the required sample size for each basket (eg, to nine). The inability to evaluate multi agent combinations may not be a major practical limitation, because such combinations may be too toxic or require counterproductive dose reductions of the individual agents (31).

Randomized Strategy Designs

In a randomized biomarker-strategy design, patients are randomly assigned to receive a standard treatment (the control arm) or a treatment determined by the biomarker(s) (the experimental MP strategy arm). In the case of a single (binary) biomarker determining treatment, the design is known to be inefficient compared with a biomarker-stratified design (used to establish the predictive value of a biomarker, in which both biomarker-positive and biomarker-negative patients are randomly assigned to either the targeted therapy or a standard therapy). This is because in the strategy design many patients may receive the same treatment on both arms (32,33). For establishing the predictive value of biomarkers with strong credentials, instead of a biomarker-stratified design, one can use a randomized enrichment design that limits eligibility to the patients positive for the biomarker, who are then randomly assigned to receive either the targeted or a standard therapy (34). With molecular profiling, it is usually impractical to perform a biomarker-stratified design or enrichment designs because of the insufficient numbers of patients in the individual MP subgroups. Therefore, a randomized MP strategy design becomes a more attractive option. An example of a completed randomized MP strategy design is SHIVA (3). Ongoing randomized MP strategy designs include SAFIR2 (35) and IMPACT 2 (NCT02152254).

With an MP strategy design, the randomization avoids the confounding due to differences in the patients treated on the arms that is inherent in nonrandomized studies that compare the outcomes of MP-treated and non-MP-treated patients. In addition, because all patients are on the trial at the same time, there is less concern about follow-up schedules that can bias single-arm trials that use the PFS ratio. Therefore, randomized strategy trials can accommodate time-to-event endpoints, which are problematic for multibasket trials.

Randomized MP strategy designs do have some drawbacks. Participation in the trial may appear less attractive because of the control arm. A second drawback is that patients without an actionable mutation will receive the same standard treatment on both arms, leading to inefficiency; this problem can be avoided by only randomizing patients who have a MP that suggests a specific targeted treatment. A final drawback is that the MP strategy design (evaluating multi component profiles) mixes results from target or agent combinations that work with those that do not. This problem is also present in nonrandomized studies. For example, it has been suggested that the SHIVA trial results were not positive overall because of the negative results from the subset of patients with molecular alterations in the hormone receptor pathway (3). Besides leading to a potentially muddled trial conclusion, this mixing of trial results means that even a positive trial may not lead directly to future treatment recommendations, because one would not know which target-agent combinations to recommend. We return to this issue in the next section.

A Way Forward?

A major concern often leveled at current oncology practice recommendations is that they are driven by large randomized clinical trials of unselected populations and thus ignore disease heterogeneity and expose many patients to treatments that do not benefit them (36). Although this is a valid concern, there is a real danger that without a reliable vetting of MP-based treatment strategies, we are replacing an admittedly imperfect system with a much more complex and expensive system that will expose even more patients to treatments that do not benefit them.

We suggest that the following two-step strategy may be a way to provide a reliable approach for moving molecular profiling forward from hypothesis-generating or exploratory studies to use in the routine clinical practice (Figure 2). First, identify mutation-targeted-treatment pairs where activity is seen using multibasket trials. Treatments should be included in these multibasket trials only if they are known to not have broad activity (regardless of presence of molecular alterations) for eligible histologies (although this determination could be challenging early in drug development). Otherwise, positive results from a basket may be due to just having a generally effective treatment for those histologies rather than effective molecular profiling. For example, inclusion of neuroendocrine pancreatic tumor patients in a basket trial of the mTOR inhibitor everolimus would be suboptimal because for this histology everolimus is effective in patients with or without an mTOR mutation (37).

After step 1, active mutation-treatment pairs that involve sufficiently large populations would be directed to evaluation in individual randomized enrichment trials (blue box in Figure 2) or possibly a master protocol containing multiple randomized enrichment trial components. Step 2 of the proposed approach is a randomized MP strategy trial (based on one or several basket trials described in step 1). The trial incorporates the identified active mutation-targeted-treatment pairs ("Step 2" boxes in Figure 2) but excludes those pairs that are already accepted into clinical practice because of extremely good activity seen in the multibasket trial or in other studies (green check marks in Figure 2) and also excludes inactive mutation-agent pairs (red Xs in Figure 2). For example, the basket in NCI-MATCH for palbociclib for tumors with CCND1, 2, or 3 amplification (excluding breast cancer patients) observed zero responses out of 36 patients (38), so this mutation-treatment pair would not be included in a future randomized MP strategy trial. On the other hand, the basket in NCI-MATCH for nivolumab for patients with

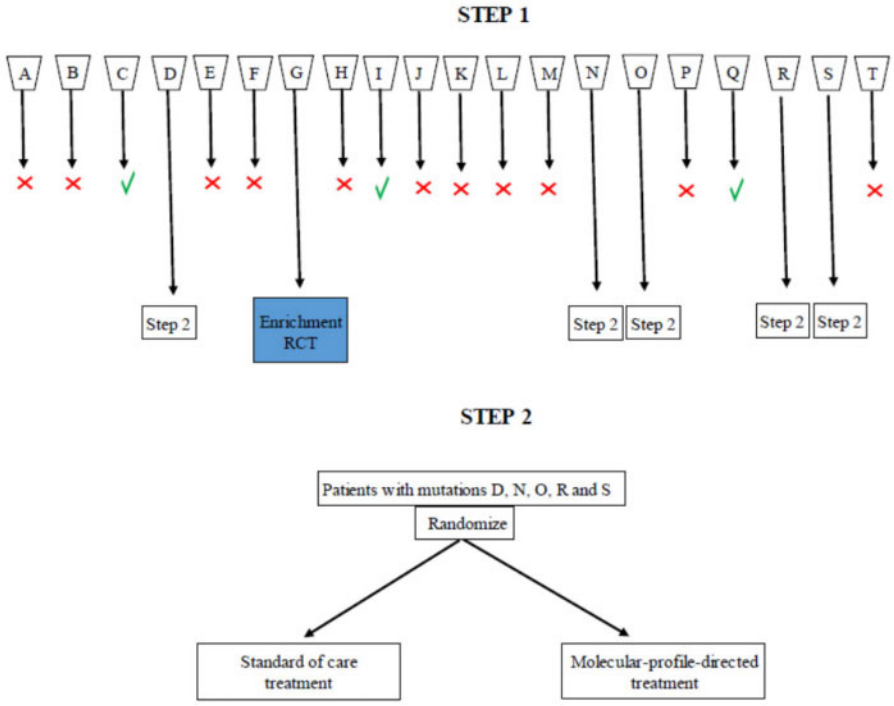

Figure 2. Proposed two-step strategy for moving molecular profiling to clinical practice. Step 1: Multi basket trial with some baskets showing no or minimal response rate activity (**red Xs**) or exceptional activity (**green check marks**); other mutation-agent baskets require further testing in their own enrichment randomized clinical trial (**blue box**) or in step 2. Step 2: Patients with mutation-agent pairs identified in step 1 are included in a randomized strategy design using a survival endpoint with a standard-of-care control arm and a molecular profile (MP)-directed treatment experimental arm. RCT = randomized clinical trial.

mismatch repair-deficient tumors (excluding colorectal cancer) had a response rate of 24% (39), demonstrating activity, and thus would theoretically qualify for inclusion into a randomized MP strategy trial. However, because this therapy for these patients has already become generally accepted, it would not be included in a future randomized MP strategy trial. Furthermore, note that in transitioning the active mutation-targeted-treatment pairs from step 1 to step 2, one could refine the set of mutational alterations or histologies included in the pair based on results observed in step 1 (eg, dropping histologies or specific alterations for which step 1 was clearly negative).

The randomized MP strategy design of the identified mutation-treatment pairs should use a primary outcome that directly measures patient benefit, for example, overall survival for a metastatic disease trial or disease-free survival for an adjuvant trial. A relatively small overall sample size may be adequate, as a large treatment effect could be targeted for the molecular profiling because all the mutation-agent pairs have already shown activity in step 1. Finally, it is important that the trial use a reproducible platform for determining mutation status that is locked down with automated procedures (rather than tumor boards) so that positive results can be expected to be generalizable to routine use in general practice. (The platform can be finalized when going from step 1 to step 2.)

Our two-step proposal is not a panacea for developing and evaluating molecular profiling. A positive randomized MP strategy trial still leaves open the possibility that some of the mutation-agent pairs are not offering a meaningful amount of clinical benefit (even though they have all shown activity previously), and the sample sizes for individual mutation-agent pairs will generally not be large enough to determine this. However, a positive randomized MP strategy trial will provide strong evidence that the molecular profiling is beneficial for the group as a whole, which may be enough to recommend it for routine clinical practice.

Notes

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The authors are solely responsible for the study design; the collection, analysis, and interpretation of the data; the writing of the manuscript; and the decision to submit the manuscript for publication.

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