The world is changing – are we ready?

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EDITORIAL

It is clear that there is an ongoing revolution in medicine as cost and regulatory pressures begin to intersect with our clinical responsibilities for the care of patients. In the past, particularly in the area of in vitro diagnostics, all that was required for approval for clinical use of biomarkers was an analytically robust measuring system, a reasonable analytic validation, a modicum of clinical validation and resources to market the testing. It was then often left to clinicians to figure out how and where any particular assay happened to fit. Publications indicating a rationale or enthusiasm for those markers were often more than was necessary to get clinicians to utilize these assays. From the point of view of developers this was a very facile process that was lucrative because even if an assay failed to work it took a large amount of time and multiple test runs for the field to understand the difficulties.

Our present environment challenges this previous paradigm. We have now progressed to the point where assays can no longer be used without some understanding of their clinical utility (1,2). Thus, clinical validation has become an essential part of assay validation in addition to a reasonable analytic validation of the accuracy of the assay. Unfortunately,

or fortunately, as the case may be, it used to be that a speculative utilization plan was adequate. One would argue that a given new marker probably should work based on interesting data about the biomarker. Often, the incremental prognostic value of the marker could be shown, which was a way of acknowledging that the marker was capable of identifying something that had important pathophysiologic relationship. However, it is no longer adequate to show incremental prognostic risk stratification. Knowing that a patient is at higher or lower risk than originally thought is often not helpful clinically. If one is high risk, knowing he/she is at still higher risk often does not result in a change in therapeutic response (2). And if the marker suggests the patient is at lower than low risk, are we willing to not treat as we had intended. Often that is now what occurs (2).

It now is deemed important and this author would suggest correct that the proper use of a given biomarker requires an answer to what one might do to respond to any given marker value and the efficacy of that response should be understood. Specifically, one needs to understand whether or not one has a specific action to implement in response to a given elevation of a biomarker. Absent that information, even if there are prognostic implications, the uptake in the use of the biomarker is unlikely to be extensive because in a cost sensitive environment having actionable data that informs clinicians about something important about his or her patient has become important criteria for test implementation. This is the evolving nature of the biomarker field. Thus, one ought to be cynical about using biomarkers when one does not know what to do in response to the data. High sensitivity troponin is a good example of this. We have exciting information about the possible utility of this marker and many are ready to implement this long before there is robust clinical validation of how one might proceed to use

the data associated with the applications (2,3). This has the potential to put patients at risk because although most often the suggestions for use are reasonable, that does not always mean they are correct, nor does it imply that they are generically or consistently cost effective. Therefore, the bar is much higher today than it was in the past.

Thus, we take the opportunity in this addition of the Journal to review the analytic and clinical substrate for some attractive biomarkers. Some such as natriuretic peptides have already been approved for clinical use for a variety of indications but not necessarily the ones we will discuss. Similarly, high sensitivity troponin is in use throughout much of the world save the United States and is being used to great advantage. However, the ability to implement their use in an optimal manner that will improve patients care has been problematic. Indeed, some of the algorithms proposed have been criticized because of an inadequate data substrate (4,5). In addition, we will discuss new more novel markers as well, both analytically and clinically. These markers have potential to substantially improve our ability to triage patients who have heart failure in particularly. They carry tremendous promise because of the way in which they interdigitate with the pathophysiology of heart failure.

However, in order to use these markers intelligently, one must understand the analytic issues related to the assays. There are often problem areas or areas of that are unknown to clinicians where eventually refinements are very likely to change our understanding of their clinic use. It is one thing to speculate how they might work and another to prove it. As indicated above, we are in a time when proving value and not just speculating about it is the mantra. From that perspective the articles included on natriuretic peptides, ST2 and Glaectin-3 are of particular importance. The articles on the use

of these markers and how to implement high sensitivity cardiac troponin begin to probe what is necessary from the evidence base and from the implementation perspective before we can initiate specific interventions based of the results from these assays. Some will require more clinical data predominately to define actionable information that tells clinicians what to do as opposed to simply recapitulating the idea of increased risk. On the other hand, some assays such as high sensitivity troponin have an adequate data sense to start implementation but it is the steps to optimize operationalization that are key. That does not mean that all the answers are in or that there are no controversies. That is far from the case. However, as when one starts a new major paradigm, coordination of those efforts become key and how we coordinate these efforts such that all members of the care teams responsible for patients are pulling together to implement this successfully is not clear. This desperately needs to be emphasized, followed, appreciated, and finally in the interest of patient care.

Finally, there are new insights into some of the older markers whose use we understand but they could influence markedly our ability to utilize these markers in a way that will intelligently allow for appropriate utilizing and improvements in patient care. What is critical to appreciate about all of these articles is that they present the state-of-the-art as it is today and that state-of-the-art no longer recapitulates what it used to be. It is a new era with new metrics that as you read the articles in this themed issue, you will be clearly sensitized to.

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