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LESS IS MORE IN INTENSIVE CARE

Biomarkers in the ICU: less is more? Yes

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In 1900, Dr. Camac wrote in the Journal of the American Medical Association "Rarely in our science is that any one finding is the open sesame to the secrets of the disease" [1]. In 2020, these words remain relevant, as a reminder that the complexities of both pathophysiology and patient care have always rendered any one test only a part of the puzzle. Regarding biomarkers, definitions vary, with most broad and encompassing many test types [2]. We focus on laboratory-based biomarkers, and contend that before widespread adoption of a given biomarker, we should ask four questions—what is the pretest probability for the diagnosis we are considering, are factors present that interfere with interpretation of the result, will I change management based on the result, and what will the outcome benefit be (Table 1)? We further contend that for many biomarkers, robust answers to these questions are lacking and support this position with illustrative examples of novel and commonly used biomarkers in the ICU.

Procalcitonin: *What is the pretest probability for the diagnosis we are considering?*

Procalcitonin is a biomarker generally elevated in bacterial but not viral infection, and there is much interest in its potential to decrease antibiotic use. Like any test, procalcitonin is best used in cases of diagnostic uncertainty, as low or high pretest probability alone can guide decisions and will heavily affect posttest probability. Procalcitonin also generally correlates with severity of illness and signs of infection and thus may provide only modest additional information to guide decisions. As such, though multiple randomized trials have shown procalcitonin-guided antibiotic de-escalation can reduce antibiotics in the ICU and other areas [3], the average reduction in ICU trials is only 1–1.5 days, and not all trials have shown reduction [4, 5]. Use in select patients where etiology is in doubt and the clinician is prepared to follow procalcitonin guidance could be the most impactful.

Brain natriuretic peptide (BNP): *Are factors present that interfere with interpretation of the result?*

BNP and its N-terminal fragment (NT-proBNP) are excellent markers of cardiac stress and loading. However, in the critical patient the heart is rarely the sole affected organ and the predictive ability of BNP for outcome in non-cardiac pulmonary conditions remains unclear. For example, although BNP has ~ 90% specificity to diagnose transfusion-associated circulatory overload, in severe ICU cases, sensitivity and specificity drop to < 60% [6]. Natriuretic peptides are also elevated in severe transfusion-related acute lung injury [7] and in critically ill patients without acute heart failure and correlate poorly with pulmonary capillary wedge pressure [8]. BNP levels are also generally lower in obesity, and patients with pulmonary disease, renal dysfunction, and atrial fibrillation can have high BNP levels without heart failure. Lastly, although sequential BNP measurement to guide fluid and diuretics in cardiac ICU patients is common, American Heart Association guidelines state the usefulness of BNP- or NT-proBNP-guided therapy for acutely decompensated heart failure is not well established.

Troponin: *Will I change management based on the biomarker result?*

Troponin became the dominant cardiac biomarker due to three key factors—the existence of a clinical gold standard for acute coronary syndromes, specificity to myocardial injury and ischemia, and extensive observational and interventional studies showing troponin provided incremental diagnostic value and outcome benefit. However,

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Table 1 Questions to consider before ordering biomarker testing in the ICU

Question	Example	Comments
What is the pretest probability for the diagnosis we are considering?	Procalcitonin	Low or high pretest probability alone can guide decisions and will heavily affect posttest probability If used, best used in cases of diagnostic uncertainty, and commitment to act on result
Are factors present that interfere with interpretation of the biomarker result?	Brain natriuretic peptide	Limited sensitivity and specificity for heart failure in critically ill patients Levels affected by common conditions such as obesity, renal dysfunction, and atrial fibrillation
Will I change management based on the biomarker result?	Troponin	Established utility for acute coronary syndromes was due to key factors that do not exist in general critical care Higher levels of troponin are associated with worse outcome, but this fact is not actionable
Will the outcome be benefited by biomarker guided decisions?	suPAR	Although higher levels of suPAR are associated with higher rates of death and acute kidney injury, provision of suPAR risk stratification information to clinicians had minimal impact on decisions and no impact on outcome, in a randomized trial

in critical care there is no gold standard for many conditions, multiple organs and pathophysiologic pathways are affected, and much biomarker research demonstrates only correlation. For example, higher levels of troponin itself are associated with worse outcome in critical illness, but this association is not actionable [9]. Prominent troponin investigators have warned clinicians should take care when deciding even when to order a novel test to avoid "erosion of the importance of the clinical findings [and basic tests]," it is "easy to show prognosis…[yet] difficult to show prognostic value," and that even now "integration of troponin…with clinical decision pathways…remains an area of active investigation" [10]. Thus, the history of troponin suggests we be thoughtful about when to order a novel test and how to interpret it, be specific in what we want a biomarker to do, and be cautious in our expectations.

Soluble urokinase-type plasminogen activator receptor (suPAR): *Will the outcome be benefited by biomarker guided decisions?*

suPAR is expressed on immunologically active cells, and an elevated serum level reflects immune system activation. From stem cell transplantation to asymptomatic aortic stenosis, patients with higher suPAR levels have higher mortality [11, 12], and a recent study found high suPAR levels associated with acute kidney injury [13]. What to do with these findings however remains unclear. An emergent department trial used suPAR to aid risk stratification, but found provision to physicians of suPAR levels and instructions on interpretation did not improve outcomes. Notably, 79.4% of physicians stated suPAR influenced their decision making in < 10% of cases or never [14].

In summary, though many biomarkers are clearly associated with disease and outcomes, actionability and incremental value beyond clinical judgment and basic tools are often lacking. This pattern is seen with many novel diagnostics in every field of medicine. For example, despite intense interest in genetic testing, two recent studies found polygenic risk scores provided minimal incremental predictive value for coronary artery disease [15]. Even for established tools such as mammograms and troponin, debate still exists on their optimal use, and we should not lose sight of the additional cost of widespread biomarker use.

Our intent is not to wholly devalue biomarkers, nor discourage research. In oncology, success has been achieved, with novel biomarkers allowing some patients to avoid chemotherapy, and others to have more targeted treatment. We simply recommend that clinically, biomarkers be used only when doubt exists despite sound clinical judgment and traditional tools, and clinicians are prepared to act on the result. We agree with the Choosing Wisely Campaign, which urges thoughtful consideration of when to order and how to use tests. Academically, we recognize how to "test a test" is challenging, and that a test by itself cures nothing, and must be tied to treatment. We agree with the biomarker qualification work by the European Medicines Agency and U.S. Food and Drug Administration, which categorize biomarkers based on their specific purposes, and highlight the need to develop evidentiary standards for their intended use.

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Authors contribution
Drs. Huang and Ramirez jointly conceived, wrote, and approved the manuscript.

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Compliance with ethical standards

Conflicts of interest
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