Time in Range: A Fourth Domain in Glycemic Control or a Glucose Variability Alternative?

To the Editor: The outcome of glucose control in critically ill patients has received significant attention. Krinsley[1] has stated that hyperglycemia, hypoglycemia, and high glucose variability (GV) are the 3 domains that are independently associated with high mortality in critically ill patients. Moving away from tight to safe glucose control provides an optimum goal.[2] The interest in measuring GV has been raised after multiple studies demonstrated its association with mortality in intensive care units (ICUs).[1,3] Multiple approaches had to be used to measure GV, including average daily risk range[3]; however, these measures seem to be too sophisticated to be implemented in each ICU. *Time in range* (TIR), defined as a measure of time where the blood glucose remains within the proposed target range, has been investigated by Omar et al.[4] Our group found it to be a simple parameter that could be measured without specific requirements; therefore, it could be simply applied in any ICU. We[4] calculated the whole time of insulin infusion (*A*) and the time being within the proposed target range (*B*) during insulin infusion, and expressed TIR as TIR = (*B*/*A*) × 100. We found that patients with more than 80% TIR, whether or not they had diabetes, had better outcomes than those with less than 80% TIR, as determined by wound infection, lengths of ventilation, and ICU stay. In addition, they were not subject to frequent hypoglycemic events.[4]

Interestingly, Krinsley and Preiser[5] followed the same technique in stratifying mortality in critically ill patients without diabetes in a retrospective descriptive study. The authors concluded that survival in critically ill patients without diabetes is strongly associated with a TIR 70 to 140 mg/dL value of more than 80%, independent of the ICU length of stay and severity of the individual's illness.[5] Individualized algorithms for patients with and without diabetes, as mentioned by Tafelski et al,[6] could replace published working guidelines. Therefore, management of blood glucose in the ICU by a single target looks unnecessarily restrictive. The clinical settings could mandate a target to fit, as in cardiac surgery where 6.0 to 8.1 mmol/L seems to be an acceptable goal.[4]

In the view of the reports relating the TIR value to mortality and morbidity in those with and without diabetes, TIR value emerges. In addition to its simplicity, TIR could provide a possible alternative to GV measurements. Even if TIR and GV are mathematically and conceptually linked, they are not interchangeable. Research in ICU glucose control could move a step forward considering the proper intervention in intensive insulin therapy.

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Gene Expression Profiling in Cutaneous Melanoma: Caveats for Clinicians

To the Editor: Despite intensive research, differentiating the lethal cutaneous melanomas from the vast majority of biologically indolent lesions remains challenging. Gene expression profiling (GEP) has recently gained momentum, aiming for more accurate staging, guiding the need for adjuvant therapy, and possibly replacing sentinel lymph node biopsies in the future. Several GEP-based tests have been developed,[1-4] some sold commercially as potential tools for clinical decision making.[1,2] On the basis of our own experience with melanoma GEP,[3] there is a clear need to highlight important aspects of GEP-based test development and share our own experience with technical aspects of GEP. Hopefully, this communication will facilitate a critical review and discussion of published data by clinicians and researchers.

Whereas a developmental biomarker study often uses retrospectively collected samples, it should nevertheless be designed to simulate a prospectively controlled study,[5] ie, the composition of the development cohort should resemble a real-life prospective cohort. For example, if a GEP-based test is intended to identify patients at risk for development of metastasis, it should not be developed from data that includes in situ melanomas. A test to predict metastasis will not be applicable to in situ melanomas because there is no clinical need. Developing tests from sample types that will not be tested in clinically

relevant circumstances makes it uncertain that these tests will perform as predicted for future patients at risk. It is important to define the type of melanoma for which a test is developed because melanoma gene expression is not just a function of malignant potential. It is affected by many other factors, including histologic type, anatomic structure, spatial context, patient immune status, and age, among many additional variables. Technical limitations also interfere with GEP. For example, one typically retrieves less genetic material from thin vs thick melanomas. Sample cross-contamination by keratinocytes and other cell types is often greater when processing thin melanomas.

Problems in GEP-based test development also originate from the inclusion of partial tumor samples. Melanoma is known to have intertumor and intratumor heterogeneity. Clones of cells within a tumor can behave differently, expressing different genetic profiles. Keeping this in mind, a test should be developed from tissue samples that contain the majority of the tumor. Performing tests on partial samples, ie, as obtained by wide reexcision surgical procedures, is inappropriate for multiple reasons. First, an unknown amount of tumor will have been removed by the preceding biopsy, including an unknown number of high-risk tumor cells (Figure). Second, the diagnostic biopsy induces a wound healing reaction that can lead to changes in gene expression akin to what is observed in cancer ("tumors are wounds that do not heal").

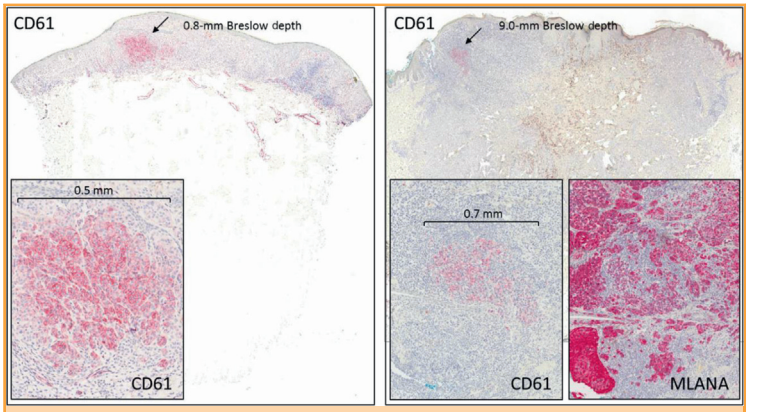

FIGURE. Foci of CD61 (β3 integrin)—positive cells (arrow) in diagnostic biopsy samples of a thin (left) and a thick (right) melanoma. CD61 is believed to facilitate cell adhesion, thereby promoting metastasis. MLANA = Melan-A, a melanocyte marker.

Finally, the RNA that is used for GEP is invariably degraded and fragmented because it is derived from formalin-fixed, paraffin-embedded tissue. Poor-quality RNA may go unrecognized and lead to inaccurate results. We therefore believe that treatment decisions should not be based on GEP alone. Rather, more robust multivariate models should be developed that incorporate molecular data in addition to histopathologic findings, regional lymph node tumor status, and clinical data.

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