Letter to the Editor

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A word of caution on using tumor biomarker reference change values to guide medical decisions and the need for alternatives

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To the Editor,

A word of caution on using biomarker reference change values (RCV) to guide medical decisions: In a recent study from the EFLM working group on biological variation, the biological variation of tumor markers has been investigated and estimates of the within and between subject biological variations were obtained [1]. The authors very much appreciate the efforts of this working group and acknowledge the relevance of this work for obtaining analytical performance specifications for these tumor biomarkers. However, based on their results the authors make recommendations on the use of RCV for follow-up and clinical decision-making in patients. The authors have however some significant objections to this recommendation that is presented as a major outcome of the study.

Biological variation studies are by design based on healthy volunteers and on the assumption of a steady “clinical” state. Furthermore, they are considered most useful for measurands under strict homeostatic control

[2–4]. Cancers and especially the advanced malignancies for which the tumor markers studied are generally used, are often instable as they have a progressive nature. Also, cancer treatment itself has a significant effect on the tumor and therefore tumor biomarker dynamics. The tumor marker dynamics are highly dependent on the type of tumor, stage of the tumor and the used treatment; surgery, radiotherapy or the various systemic treatments can all significantly differ in the expected response-time and duration that can all result in different tumor marker dynamics. Other factors of relevance for interpreting tumor biomarker results include the biomarker half-life e.g., in surgically removed tumor, tumor heterogeneity; some tumors express different tumor biomarkers or the same tumor marker at significantly different circulating concentrations. These tumor marker concentrations can be multiple times (10–100 times) the concentrations observed in “normals”, and can have a different anatomical origin and molecular structure as the tumor markers observed in healthy volunteers. Also, tumor marker increases can also origin from other benign causes such as renal failure, liver failure, etc. [5]. Finally, the tumor marker dynamics are also affected by the clinical response or non-response to treatment. However, all of the previously mentioned biological, pathological and clinical factors are ignored when using RCV for clinical decision-making on the latter.

Another limitation of using RCV values is that, by design, it is based on the statistical probability that determines a significant increase, not caused by change, in the reference “normal” population. Basically, this corresponds to a fixed specificity based on the z-value used, generally selected to be 95%. This cut-off does not provide any information on the sensitivity for a specific clinical condition, since no clinical cases are involved and studied! In addition, the reference population used for obtaining RCV might significantly differ from the reference population in clinical practice [6]. Furthermore, a physician is not interested a significant change in a tumor marker based on a standard 95% probability, but rather in medical decision levels or the probability of a patient having or not having a

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relevant clinical event in a specific clinical setting. Examples of these are the probability of having a response or non-response to treatment, probability of cancer recurrence after curative treatment or probability of treatment resistance after initial response. Additionally, the clinical requirements for diagnostic tests to be relevant and result in clinical utility in a specific setting might differ from the 95% specificity generally used for RCVs. In some situations, tests with a lower or higher specificity might be more relevant or test sensitivity is essential e.g., to rule out certain events. No information of any of these factors is provided by RCV. These presented arguments illustrate why RCV should not be blindly used in clinical decision-making from a statistical and clinical need perspective.

Finally, from an evidence-based medicine perspective when biomarkers are used for making important medical decisions and guiding medical interventions potentially affecting clinical outcomes, a proper clinical validation study is necessary to support such a practice. This should at least be done in an independent, clinically relevant and statistically powered validation cohort. Also, the clinical value must be demonstrated [7]. Here, the false positives

and negatives resulting in limited positive or negative predictive values might compromise the clinical utility of the RCV and can potentially even worsen the clinical outcomes when RCV are used for clinical decision-making.

A call for methods to support the clinical interpretation and use of consecutive tumor marker results as diagnostic tests: The many listed limitations of using RCV for guiding the interpretation of consecutive tumor marker results complicates and limits the clinical use of this metric. However, there is a clear clinical need for a more objective interpretation of consecutive tumor markers for a large range of oncological settings. The recent revolutions in systematic cancer treatments by targeted and immunotherapy, for many types of cancer, have further triggered the interest in and needs for diagnostics that enable an early detection of response or non-response to treatment or disease recurrence after initial response [8]. With new next in-line treatments being available, an early detection of progressive disease will enable an early switch to next line treatments when patients are still eligible for these, avoid unnecessary toxicity and reduce clinical expenses. Unfortunately, often the use of the “classical”

Figure 1: Biomarker response characteristic plot for CEA in NSCLC.

Based on a cohort of 344 advanced NSCLC patients treated with immunotherapy the CEA change between base-line and six weeks of follow-up is plotted against a clinical responses observed at six months [10].

tumor markers is neglected in current cancer biomarker research, while these tumor markers are rather well characterized, (pre-) analytically validated and widely available. Consequently, the clinical meaning of consecutive tumor marker results is often rather unknown, not studied for the modern treatments and if so with an inferior experimental design. The latter limits the adoption in clinical guidelines. When clinical guidelines recommend against the use of tumor markers this is often based on historical and outdated studies that have become largely irrelevant for today's practice [9]. When the use of tumor markers is suggested, this is not supported by clear guidance on the interpretation. Therefore, often the application and interpretation of tumor markers is highly variable between physicians and generally based on their personal experiences.

When investigating new tumor biomarker applications it is essential to take the limitations, previously listed for the RCV, into account. Therefore, studies investigating the clinical application of consecutive tumor markers and design decision algorithms should be based on the relevant patient population in terms of clinical presentation, treatment, cancer type and stage, etc. in order to be meaningful. Furthermore, a clear understanding of the clinical application is required such as the following diagnostic decision or consecutive intervention triggered by the test and the required diagnostic performance specifications (sensitivity, specificity, PPV, NPV) that are expected for clinical utility of the test. New data-driven approaches have been developed that enable to study the relation of an early change in tumor marker result with relevant clinical events later in time, see Figure 1 [10]. Recent developments in data and computer sciences such as artificial intelligence and the cloud might provide new valuable methods and systems that enable a better understanding of consecutive tumor biomarker results and clinical application thereof. We very much encourage laboratory specialists, oncologist and other researchers' to work on this. Till then, be careful with using RCV and include the knowledge and experience of the other factors mentioned for interpretation and clinical decision-making.

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