The progress in the management of patients with solid tumors has been associated not only with the introduction of new drugs or other therapeutic methods, but also with the advances of biomarkers [1]. The utilization of dozens of different biomarkers is a companion of the patient and the physician on the path from the diagnosis through therapy that includes surgery, radiation therapy, chemotherapy or targeted therapy and then on throughout the lifelong follow-up.

As can be imagined, the requirements for the biomarkers at each step during the path from diagnosis to treatment and then during follow-up vary. Four papers in this issue of *Clinical Chemistry and Laboratory Medicine* cover different aspects of utilization of biomarkers in oncology [2–5]. The role of biomarkers in the diagnosis of cancer may seem to be the most obvious. The report by Trapé et al. [2] illustrates the potential use of circulating biomarkers in this setting. A relatively large cohort of patients presenting with symptoms suggestive of advanced cancer was evaluated using a panel of three circulating biomarkers including carcinoembryonic antigen, carbohydrate antigen (CA) 19-9 and soluble fragments of cytokeratin 19 (CYFRA 21-1). The cohort of patients was enrolled 10 years ago, and is therefore mature as even originally occult tumors would have manifested by the time of writing of the reports. Cut-offs of the concentrations of circulating biomarkers were set to be 100% specific for diagnosis of cancer and were defined separately for patients with or without renal and/or hepatic dysfunction. The sensitivity of tumor marker concentrations above this level was 69% for patients with normal renal and/or liver function and 42% for patients with renal and/or hepatic dysfunction (in whom higher cut-off concentrations were selected). As expected, sensitivity of increased biomarker concentrations was much higher for metastatic compared to localized tumors. The paper shows that the measurement of this panel of biomarkers could aid the diagnosis. However, the sensitivity is highest in patients who have evidence of distant metastases detected by imaging, and for whom also the treatment options are more limited than for patients with early tumors.

With the refinement of therapeutic strategies and improved outcomes, the demands on biomarkers obviously grow. As mentioned above, advanced disease may be evident by physical examination or simple imaging methods, yet therapeutic options and the chance for cure are often limited in patients with advanced metastatic tumors. In contrast, the best chance for cure is present in patients with localized tumors. Early tumors are usually asymptomatic and biomarkers may represent an important aid in precocious diagnosis. Although many biomarkers, e.g., CA 19-9 are increased in a number of non-neoplastic disorders and indiscriminate determination may obscure rather than clarify the diagnosis [6, 7], biomarker measurement could in some other cases aid the diagnosis or be used in early tumor detection.

Prostate cancer represents an example of the role the biomarkers can play in cancer care. In fact, the introduction of prostate-specific antigen (PSA) has virtually transformed the management of patients with prostate cancer throughout the course of the tumor from the screening to the therapy of advanced disease [8, 9]. Although PSA remains a pillar biomarker of prostate cancer, the search for additional biomarkers continues [9–11]. Despite the fact that scores of promising biomarkers have been proposed over the last two decades, only few of these biomarkers have passed the test of time, and none of them has fully replaced PSA-based methods. The paper by Stephan et al. [3] in this issue of the *Clinical Chemistry and Laboratory Medicine* marks an apparent end of the story for one failed biomarker in prostate cancer. The authors of this multicenter study have to be commended for this truly exemplary effort that also involved the authors of the original positive report. Chwatko et al. [12] reported in 2013 in this journal promising results of urinary thiosulfate as a biomarker of prostate cancer. In an editorial that accompanied the publication of the report by Chwatko et al. Jung and Stephan [13] stressed the need for validation studies stating that “this task of the scientists in the biomarker translation process could be supported by the
encouragement of scientific journals to publish also re-evaluation studies that fail to confirm original data”. This is an important point since the whole system of medical publications may be biased towards publication of positive results. Obviously, for the reader positive findings may seem to be more interesting, but selective publication of positive results may distort perception of the topic. As part of its commitment to the advancement of science, Clinical Chemistry and Laboratory Medicine publishes in this issue a report that failed to confirm the original promising data on urinary thiosulfate in prostate cancer. Urinary thiosulfate/creatinine ratio was not different in patients with prostate cancer and controls, and, in contrast to the established biomarkers, thiosulfate/creatinine ratio was not able to discriminate between patients with or without prostate cancer [3]. The issue seems to be closed and there will probably be few, if any additional reports on this topic. Thus, urinary thiosulfate joins the huge and rapidly growing family of failed biomarkers [14].

The perils of the selective publishing approach that highlights positive and neglects negative results may be illustrated in the example of another heavily disputed (in the opinion of many scientists – failed) biomarker in prostate cancer, sarcosine. In a paper that was much highlighted by the media Sreekumar et al. [15] reported that prostate cancer progression is accompanied by increased production of sarcosine, and sarcosine represents a specific biomarker in this tumor. A study that unsuccessfully attempted to replicate the clinical data and essentially refuted the hypothesis that sarcosine could be a clinically useful biomarker of prostate cancer was published rather soon after the original report [16]. This second negative study that focused more on the methodological issues was, unfortunately, not considered for publication in a journal of comparable rank to the paper by Sreekumar et al. that reported the original positive findings. Obviously, a paper in a high ranking journal incites more additional studies and citations, and negative results that are published in journals with lower impact factors are more likely to be overlooked. As the results, dozens of papers continue to be published on this topic that, from a scientific point of view, may seem to be a dead end. Many of these papers are on analytical issues or reviews, perpetuating a controversy that has, apparently, long been resolved. In other instances commercial interests may override insufficient scientific evidence and different biomarkers are marketed based on more or less sophisticated theoretical presumptions [14].

Local therapy and locoregional control are usually not a problem in patients presenting with early cancer. What threatens the life of the patient in the long term is systemic progression. Systemic disease, if present, takes the form of dormant tumor cells and micrometastases that are not detectable by imaging. Moreover, a progression of dormant tumor cells or micrometastases to clinically manifest metastatic disease is observed only in a variable proportion of cancer patients.

Systemic microscopic disease can be treated only by systemic therapies. The administration of any drugs is associated with a risk of side effects, and the administration of agents used in the causal therapy of cancer, including cytotoxic drugs, hormonal or targeted agents, is frequently accompanied by serious, sometimes even life-threatening, toxicity [17–19]. Systemic disease may never manifest in many patients with early cancer, and these patients are already cured by local therapies. However, similarly to patients with advanced disease, systemic therapy may also fail to prevent the metastatic recurrence of the tumor in some cases. Thus, in patients with early tumors, systemic adjuvant therapy may represent an overtreatment in a proportion of cases while in the other cases it fails. At the same time, the administration of this treatment will be accompanied by toxicity that would affect both the patients who would potentially benefit from the systemic treatment as well as those patients in whom the treatment would not improve outcomes. The decision on the therapeutic course can therefore be very difficult in many patients presenting with early cancer. Prognostic and predictive biomarkers may be of considerable help in therapeutic decisions. Predictive biomarkers may predict the likelihood of a response to therapy or the risk of toxicity. Important group of biomarkers are used in the assessment or prediction of toxicity. The toxicity is visible only in some cases, e.g., in the case of skin toxicity [20]. In most instances, the toxicity is not readily assessed clinically. Laboratory methods may be essential here. Laboratory methods are well established in the assessment of hematologic toxicity [21], but for other side effects, e.g., gastrointestinal [17–19] or cardiac toxicity [22], the use of laboratory methods in routine practice is still limited.

In many instances, the routine utilization of prognostic and predictive biomarkers in clinical practice is hampered by the cost or technical complexity. Two papers in the present issue of this journal introduce biomarkers that are based on analytical measurements that have been part of routine laboratory assessment for many decades and could be done in virtually any laboratory [4, 5].

Sarcomas represent a very heterogeneous group of rare tumors. With the exception of few chemosensitive tumors like Ewing sarcoma, or gastrointestinal stromal tumors for which effective targeted therapy is available [23], the therapeutic options for most patients with
advanced sarcoma are limited. Szkandera et al. [4] report on the prognostic significance of uric acid concentrations in patients with sarcoma. In this study, high serum uric acid concentrations were associated with improved survival in both univariate and multivariate analyses. In different tumor types, high circulating uric acid concentrations have been associated with both improved and worse outcomes, and the mechanism(s) behind possible association between prognosis and uric acid levels remain speculative. Based on the primary tumor and stage, different mechanisms may explain differential prognostic significance of circulating uric acid concentrations. Among other mechanisms, high uric acid concentrations may augment immune response.

An important group of biomarkers reflect the host response to neoplasia. It is now well established that the tumor growth stimulates the host immune response resulting in inflammatory reaction and specific immune response directed against the tumor [24]. Depending on other factors, this immune and inflammatory response may either suppress or stimulate the immune response. Evasion of the host response has been defined as one of the hallmarks of cancer [25]. These phenomena may be studied with laboratory methods that assess the immune response both locally [26–28] as well as on the systemic level [29,30]. Most of these methods are demanding and expensive and have not gained widespread use in the clinical practice.

Recently, a number of studies have emerged reporting the use of ratios derived from peripheral blood cell count as prognostic or predictive biomarkers in patients with cancer. Changes in neutrophil/lymphocyte, lymphocyte/monocyte or platelet/lymphocyte ratios have been reported in cancer patients across the spectrum of tumor types with implications for prognosis [31–34]. In fact, most of these changes are not specific to cancer and are reported in a number of other disorders associated with systemic inflammatory response. Similar findings have been reported for the neutrophil/lymphocyte ratio in a spectrum of diseases, including atherosclerosis and its complications [35–37]. This spectrum of disorders is very similar to other biomarkers that have been used for decades, including C-reactive protein (CRP) or neopterin. For example, increased urinary or serum neopterin concentrations have been associated with a number of disorders as different as acute myocardial infarction, cancer or autoimmune disorders [38,39] or have been shown to predict mortality in a general population of elderly subjects [40]. This lack of specificity of prognostic inflammatory biomarkers may be at first glance regarded as a disadvantage, but could also useful since the ultimate goal of the multidisciplinary treatment is to avert the death of the patients, irrespective of the cause.

Stotz et al. [5] report on the prognostic significance of the lymphocyte/monocyte ratio in patients with pancreatic cancer. The prognosis of patients with pancreatic cancer remains extremely poor. Most patients present with inoperable disease, and even among patients in whom radical surgery is attempted, only a fraction will be long-term survivors. Systemic therapy has limited efficacy in patients with metastatic pancreatic cancer, with median survival being <1 year. Improved results have been reported for combination regimens that are, however, associated with high toxicity [41]. The data reported by Stotz et al. demonstrate that, similarly to tumors of other primary locations, the host response to tumor growth is an important prognostic factor in patients with pancreatic cancer. Given the role of the host response, trials with immunotherapeutic agents acting at the immunologic synapse, e.g., ipilimumab or nivolumab, could be considered in metastatic pancreatic cancer.

There is limited information comparing the performance of peripheral blood cell count-derived ratios and more established biomarkers of inflammatory response. The correlation between different biomarkers of systemic inflammatory response, e.g., CRP and neopterin, has been well established. It could be expected that ratios that are based on relative lymphocyte counts may to some extent correlate with CRP or neopterin. It has, for example, been previously reported that relative lymphocyte counts in patients with a history of breast cancer correlate with serum neopterin concentrations [42]. Based on the magnitude of this correlation, peripheral blood cell count-derived ratios could be combined with CRP and neopterin to more complex indices of systemic inflammatory activation. Obviously, peripheral blood cell counts can be evaluated retrospectively in historic patient cohorts and these results are available for virtually every patient presenting for therapy. However, technological advances have resulted in the wide availability of biomarkers like CRP or neopterin. Future research should determine the optimal spectrum and utilization of biomarkers of systemic inflammatory response.

In conclusion, the highs and lows of tumor biomarkers accompany and sometimes compromise successes and failures of new therapies in the management of cancer patients. Despite all the lost illusions, no one would dispute the fact that the utilization of biomarkers currently represents an indispensable part of cancer medicine and that the role of laboratory biomarkers in therapy of malignant disorders has to increase. Both successes and failures need to be published in journals of comparable rank.
**Author contributions:** All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

**Financial support:** None declared.

**Employment or leadership:** None declared.

**Competing interests:** The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

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