Letter to the Editor

Farshid Dayyani* and David Morgenstern

Letter in response to: Identifying risk in the use of tumor markers to improve patient safety

DOI 10.1515/cclm-2016-0335
Received April 20, 2016; accepted June 28, 2016; previously published online July 28, 2016

Keywords: cancer antigen 125 (CA 125); cancer antigen 15-3 (CA 15-3); carcinoembryonic antigen (CEA); cancer antigen 19-9 (CA 19-9); cancer antigen 50 (CA 50); cancer antigen 72-4 (CA 72-4); human epididymis protein (HE4); prostate-specific antigen (PSA); tumor marker.

To the Editor,

The manuscript by Drs. Moreno-Campoy et al. [1] described the usage of tumor markers (TMs) in a retrospective cohort of 14,728 patients over a 2-year period (2011–2013) at the University Hospital of Padua. The authors assert that only 40% of TM requests are appropriate, increasing patient anxiety and the risk of patient harm through unnecessary complementary tests. While we applaud the authors for the effort to summarize and provide an overview on the number of selected TMs ordered at a large urban hospital, we feel some comments are warranted with regards to the authors' analysis and interpretation of their study results.

1. Their characterization of TMs as belonging to two discrete groups, i.e. TMs used after a cancer is diagnosed [group 1: carcinoembryonic antigen (CEA), cancer antigen 15-3 (CA 15-3), cancer antigen 19-9 (CA 19-9), cancer antigen 125 (CA 125), cancer antigen 50 (CA 50) and human epididymis protein (HE4)] and TMs used for screening [group 2: alpha-fetoprotein (AFP) and prostate-specific antigen (PSA)] is overly simplistic. The European Group on Tumor Markers (EGTM) guidelines include monitoring of primary hepatocellular carcinoma among the primary uses of AFP [2], the use of PSA is still recommended in select populations for prostate cancer screening [3], it is prognostic in localized disease and after initiation of hormone-ablative treatment for advanced cancer, and it can be used for treatment monitoring or active surveillance [4]. Given that prostate and liver cancer accounted for over 50,000 cancer diagnoses in Italy in 2012 [5], excluding orders for disease monitoring with these two commonly used TMs (all of which would be 'appropriate' by the authors' definition) fails to capture a large number of appropriate and non-controversial TM uses.
2. Characterizing the use of group 1 TMs prior to pathologic diagnosis of cancer as 'inappropriate' fails to consider uses recommended by guidelines and also based on published data in large cohorts for the differential diagnosis of a pelvic mass [6] CEA in the work-up of suspected colorectal carcinoma [7], and appropriate work-up and triage of suspicious pulmonary nodules [8]. These examples are all indications done in individuals without a diagnosis of malignancy. In addition, a TM such as CA 125 is more sensitive for peritoneal carcinomatosis than most imaging modalities. It might also be ordered to detect micrometastatic omental spread of a gastrointestinal malignancy [9]. In this case, a negative result is not an inappropriate test, but informative and useful for the further treatment planning of the patient.
3. The authors note that in over 26% of cases, four or more TMs are ordered, suggesting inappropriate usage of the group 1 TMs for screening of undiagnosed tumors. However, the number of multiple TMs determined for a single patient reflects the actual biology of these markers as also conceded by the authors in the introduction: none have 100% sensitivity. Thus, for a given condition (e.g. gastric carcinoma), no single TM will cover all patients, whereas a combination, e.g. CEA, CA 19-9, cancer antigen 72-4 (CA 72-4), CA 15-3, and CA 125, might identify a higher proportion of patients with at least one elevated TM which can then be followed [10].

***Corresponding author: Farshid Dayyani,** Roche Diagnostics International, Forrenstr. 2, Rotkreuz 6343, Switzerland, Phone: +41 41 792 4051, E-mail: dayyani@gmx.net
David Morgenstern: Roche Diagnostics, Indianapolis, IN, USA.
http://orcid.org/0000-0003-0554-3947

4. The authors assert that inappropriate TM usage promotes the unnecessary ordering of harmful complementary tests. Although this risk no doubt exists, the risk cannot be quantified as the authors did not evaluate the number of follow-up tests associated with appropriate vs. inappropriate TM orders or adverse events associated with those tests. It is certainly likely that some of these tests would have been ordered in any case as part of the routine work-up of these patients and some complementary tests would not have been ordered despite a positive biomarker result if an explanation for the TM elevation, such as renal dysfunction or evidence of inflammatory disease, became evident. Furthermore, the authors fail to consider or evaluate the possibility of benefit based on TM ordered, i.e. avoided tests and invasive procedures based on the TM result. The retrospective nature of the study, the lack of in-depth knowledge of the individual patient or respective clinical scenario when the TM was ordered, missing information on any ancillary diagnostic or therapeutic measures undertaken based on the TM, and the missing documentation of any resulting change in patient management preclude any conclusive statement regarding the appropriateness of TM usage in this cohort.

While it has become fashionable to dismiss traditional TMs, we believe few other diagnostic tools are as inexpensive, easy to obtain, and as safe to use. We disagree with the authors' conclusion that protocols for the safe use of TMs are needed, as we are unaware of any data demonstrating that their current usage is unsafe. Rather, what is needed is better education and familiarization of physicians with the correct use and interpretation of TMs so that their value as an additional tool in the diagnostic armamentarium can be improved. The crude classification of appropriateness of TM ordering based on non-granular groups 1 and 2 is akin to assuming most drivers on a busy highway are lost just because one does not know their actual destination.

Acknowledgments: Editorial support was provided by Kim Brown of Roche Diagnostics International Ltd.

Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Research funding: None declared.

Employment or leadership: F.D. and D.M. are employees of Roche Diagnostics.

Honorarium: None declared.

Competing interests: The authors' employment 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.

References

1. Moreno-Campoy EE, Mérida-De la Torre FJ, Martos-Crespo F, Plebani M. Identifying risk in the use of tumor markers to improve patient safety. Clin Chem Lab Med 2016;54:1947–53.
2. European Group on Tumor Markers (EGTM). General information on tumor markers. Available at: http://www.egtm.eu/professionals/general_info_tumor_markers. Accessed 6 Apr 2016.
3. Carter HB, Albertsen PC, Barry MJ, Etzioni R, Freedland SJ, Greene KL, et al. Early detection of prostate cancer: AUA guideline. J Urol 2013;190:419–26.
4. Heidenreich A, Aus G, Bolla M, Joniau S, Matveev VB, Schmid HP, et al. EAU guidelines on prostate cancer. Eur Urol 2008;53:68–80.
5. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11. Available at: http://globocan.iarc.fr. Accessed 6 Apr 2016.
6. Moore RG, McMeekin DS, Brown AK, DiSilvestro P, Miller MC, Allard WJ, et al. A novel multiple marker bioassay utilizing HE4 and CA125 for the prediction of ovarian cancer in patients with a pelvic mass. Gynecol Oncol 2009;112:40–6.
7. National Comprehensive Cancer Network (NCCN). Colon cancer: Version 2.2016. Available at: http://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed 4 Apr 2016.
8. Molina R, Marrades RM, Auge JM, Escudero JM, Vinolas N, Reguart N, et al. Assessment of a combined panel of six serum tumor markers for lung cancer. Am J Respir Crit Care Med 2016;193:427–37.
9. Nakata B, Hirakawa YS, Kato Y, Yamashita Y, Maeda K, Onoda N, et al. Serum CA 125 level as a predictor of peritoneal dissemination in patients with gastric carcinoma. Cancer 1998;83:2488–92.
10. Goral V, Yesilbagdan H, Kaplan A, Sit D. Evaluation of CA 72-4 as a new tumor marker in patients with gastric cancer. Hepatogastroenterology 2007;54:1272–5.