Editorial

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The Theranos phenomenon, scientific transparency and freedom of speech

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Since July 2015 *Clinical Chemistry and Laboratory Medicine* (*CCLM*) has published a series of four articles on the up-and-coming laboratory diagnostics enterprise Theranos, (co)authored by one of the members of our editorial board, Eleftherios Diamandis [1–4]. There were two opinion papers and two letters to the editor. All dealt with the novel technology of Theranos and the company's innovative or perhaps unorthodox approach to laboratory testing in general, which proposes that the availability of self-testing will contribute to overall improved public health. The most recent letter to the editor dealt with the invited lecture of Elizabeth Holmes, the founder and CEO of Theranos, at the upcoming annual conference in 2016 of the American Association for Clinical Chemistry (AACC). Apparently triggered by this last paper in the series, one of our readers suggested to us that Dr. Diamandis may have violated *CCLM*'s conflict of interest policy. This was based on the fact that Dr. Diamandis serves as scientific advisor of another clinical laboratory that performs "analysis on small volume blood collections". The case in question was labeled as being "particularly egregious given his position on the journal's board of editors". This was followed by the request to retract the articles or publish corrections, indicating the alleged conflict of interest. The Editor-in-Chief and the Associate Editors of *CCLM* have taken this issue very seriously and examined carefully the relevant question, i.e. if the author(s) of the four papers had indeed withheld "relevant competing interests" which would require corrective action. Before going into details, we would like to draw attention to the term "relevant" in our guidelines. We are firmly convinced that any conflict of interest policy concerning the authors of submitted manuscripts must focus on conflicts relevant to the issue raised in the manuscript that might constitute an embarrassment to any of the authors were it not declared and emerged after publication. This applies in particular to conflicts which may really affect the way scientific data are collected, selected, presented and discussed. Otherwise, we would swamp our readers with a tsunami of irrelevant disclosures among which the relevant conflicts of interest will go unnoticed.

Examining the issue, it turned out that things are more complicated than they were portrayed. First of all, what is a relevant conflict of interest? The guidelines on good publication practices, issued by the Committee on Publication Ethics (COPE) in 1999 [5] provide a practical and still valid description: "*They (conflicts of interest) have been described as those which, when revealed later, would make a reasonable reader feel misled or deceived*". It is obvious from the whole guidelines that they are focused on original research, review articles and practice guidelines. This is also apparent if the COPE guidelines for retracting articles are studied. Again, they deal with "reliability of findings", "redundant publication" and "plagiarism". But can or should the COPE guidelines be always and fully applied to appropriately labeled opinion papers as the four articles in question? We believe not.

In general, an opinion is a judgment, viewpoint, or statement that is not conclusive [6]. There are many examples that opinions may not be changed by arguments and evidence, because they are shaped by many other factors. Accordingly, opinion is not evidence, even though it may be influenced by evidence. Opinion is perhaps the integral of personal expertise, experience, bias, interests and other factors. Thus, a reasonable reader could perhaps disagree with an opinion but "not feel misled or deceived" by the opinion itself, as long as it is appropriately labeled as such. If this is true, it is difficult to construct a relevant conflict of interest in the case of an opinion. Paradoxically, would any of us publish conflict of interests of being a laboratory professional in the effort of publishing data about innovative biomarkers or techniques, just because these tests will expectedly become standard practice and thereby increase the activity (and income) of our lab?

Conversely, expert opinion is regarded as a level of evidence in medicine, even though the lowest level. This is related to the fact that expert opinions are generally perceived to be supported by some evidence and

broad personal experience. Thus, the distinction between opinion and evidence may not always be easy, especially when an opinion is presented by an expert in the field. Furthermore, we all know that experts sometimes confuse opinion with evidence. Accordingly, expert opinion has influenced and still influences medical practice significantly, sometimes more so than other evidence. Therefore, knowledge about relevant competing interests is important to identify potential sources of bias in cases of expert opinion, in particular in cases where expert opinion is taken as (low level) evidence and will likely determine medical practice.

We would like to reemphasize here that *CCLM* requires "all contributors to disclose relevant competing interests". As outlined above, "relevant competing interests" rarely apply to papers presenting obviously personal opinions of the author(s) on scientific issues, in particular when such opinions will not immediately influence medical practice. This is part of the regular scientific discourse. Furthermore, we strongly believe that disclosures must be limited to relevant issues to prevent blunting of this instrument.

Let us come back to the four publications in question. The complaint was apparently triggered by the last paper [4]. In this letter, the author outspokenly argues that the invitation of Ms. Holmes to present a lecture at the AACC annual conference 2016 was inappropriate. This is quite obviously his personal view and he presents his arguments. Every laboratory scientist interested in this issue can decide, for him- or herself, to agree or disagree with this view. Disclosures by the author would not make this decision any easier than disclosures by the persons who decided to invite Ms. Holmes.

What about the three other papers [1–3]? The first and most detailed paper in the series deals with several facets of Theranos, including the fact that the methodology developed by the company had never been presented to the scientific community and therefore could not be judged. Next, the author analyzed the claims of shorter turn-around times of the new technology and lower costs, and the claim that finger pricks are much better tolerated than conventional blood drawings. The largest part of the article deals with the authors view on marketing lab tests directly to the public. This is an ongoing controversial debate in laboratory medicine with many facets, including (genetic) lifestyle diagnostics [7–10], with an outspoken position of the author [11]. However, the opinion presented by the author that the potential harms outweigh the potential benefits is shared by many if not most professionals in the field [7]. He concludes with the statement *"An open discussion of the merits and shortcomings of the Theranos and similar approaches should take place in the scientific literature and other public forums, so that the benefits and harms are better understood by the public."* This does not sound like an attempt to manipulate the readers, driven by strong competing interests. It rather describes an urgent need to assure the safety of our patients and the lay public. Again, we have checked whether the knowledge of current and past involvement of the author with companies could be regarded as a relevant competing interest and would make a reasonable reader feel misled or deceived, when revealed later. We are absolutely convinced that the present and past involvements of the author with industry do not fulfill these criteria and that the author had no reason to disclose them.

The second paper deals almost completely with self-testing and self-interpretation of laboratory tests [2]. Again, the bottom line is that the authors are convinced that healthy persons are not able to adequately interpret laboratory results and that laboratory tests without proper indication will lead to numerous false positive results. Consequently, they propose that the overall effect on public health and health expenses of such practices will be most likely detrimental. However, they admit that additional studies are perhaps needed to prove this view. Also with this article, we agree with the author that there was no relevant conflict of interest to disclose.

The third paper is an update on Theranos that summarizes some of the events in late 2015 and early 2016 [3]. All the facts presented are in the public domain. This is complemented by the personal opinion of the authors on the actual developments broadly covered in the US lay press. This is in our view a typical example of a personal opinion which cannot be subject to the simple conflict of interest concepts very much like the last letter in this series.

In summary, we consider the alleged violation of *CCLM*'s conflict of interest rules by the authors as not sufficiently substantiated. When disclosures are mostly meaningless, because they are listed automatically, independent of their relevance, they would be worthless, because the awareness would be lost in a deluge of irrelevant disclosures. In fact, we cannot help but suspect that the major motivation of this accusation may be an attempt to silence a critical voice in the laboratory medicine community. *CCLM* will hold up its practice to publish opinion papers and letters on laboratory medicine issues. As long as such articles are as well balanced as the four articles discussed here, we do not see an advantage for our readers in uncovering all potential motives for preparing a manuscript. *CCLM* is also an "open forum", and anyone is welcome to reply to something we publish. We have done

this many times in the past, and we are willing to do this in the future. We are convinced that our readership can distinguish facts from opinions, and can judge opinions on their own.

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References

1. Diamandis EP. Theranos phenomenon: promises and fallacies. Clin Chem Lab Med 2015;53:989–93.
2. Li M, Diamandis EP. Theranos phenomenon – part 2. Clin Chem Lab Med 2015;53:1911–2.
3. Li M, Diamandis EP. Theranos phenomenon – part 3. Clin Chem Lab Med 2016;54:e145–6.
4. Diamandis EP. Theranos phenomenon – part 4: Theranos at an International Conference. Clin Chem Lab Med 2016;54: e243–4.
5. Committee on publication ethics (COPE) Guidelines on good publication practice. Available at: http://publicationethics.org/files/u7141/1999pdf13.pdf. Accessed 9 June 2016.
6. Wikipedia. The free Enzyclopedia. Available at: https://en.wikipedia.org/wiki/Opinion. Accessed 8 June 2016.
7. Lippi G, Favaloro EJ, Plebani M. Direct-to-consumer testing: more risks than opportunities. Int J Clin Pract 2011;65:1221–9.
8. Chung R. Telehealth physician oversight over direct to consumer testing: doctors working with patients towards patient empowerment. Telemed J E Health 2012;18:354–9.
9. Campbell B, Linzer G, Dufour DR. Lab Tests Online and consumer understanding of laboratory testing. Clin Chim Acta 2014;432:162–5.
10. Webborn N, Williams A, McNamee M, Bouchard C, Pitsiladis Y, Ahmetov I et al. Direct-to-consumer genetic testing for predicting sports performance and talent identification: Consensus statement. Br J Sports Med 2015;49:1486–91.
11. Diamandis EP. The Hundred Person Wellness Project and Google's Baseline Study: medical revolution or unnecessary and potentially harmful over-testing? BMC Med 2015;13:5.

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