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Putting value in biomarker research and reporting

With the turn of the millenium, biological mass spectrometry emerged as a quantitative discipline, extending the application of proteomics research beyond the merely qualitative identification of proteins. The ability to compare in a single shotgun experiment the relative abundances of thousands of proteins between different sets of samples, aroused the old aspiration to discover the holy grail of disease-specific biomarkers that would bring benefits, whether applied to early diagnosis, prognosis or therapeutic monitoring. However, after intensive labor in hundreds of laboratories around the world, the field has yet to deliver on its aspirations envisaged some ten to fifteen years ago. The poor performance of many biomarker hunters may have to do with the stochastic nature of MS-based shotgun proteomics, but also with the intrinsic individual variability of biological samples. Each of these factors can potentially confound the statistical analysis, and represents a major difficulty in the interpretation of causes and effects. However, it can also be indicating that the existence of biomarkers, which is often given for granted, is only a hypothesis that needs to be tested. Paradoxically, the number of manuscripts reporting on proteomic biomarkers is constantly increasing (see Fig. 1), although many of the so-called clinical biomarkers reported so far in quite different pathological conditions comprise one and again the same set of proteins, suggesting that the diseased organism is under some kind of stress but lacking any clinically useful distinction among various diseases. Hence, as has been outlined in several articles [1–3], these claimed findings have generally not resulted in the implementation of the reported biomarkers in the clinic [4,5].

Even though biomarker implementation undoubtedly includes multiple challenges extending well beyond scientific issues [5], substantial room for improvement in the scientific process of biomarker research exist. Several potential shortcomings observed relate to practices applied during the early stages of biomarkers discovery. These include: 1) too low sample size (sometimes claims are even made based on a single observation), 2) failure to verify the results in an independent test-set, 3) lack of expected utility and clinical value and 4) data over-interpretation for the presented evidence. This development is reflected by, on the one hand, a plethora of reported biomarkers, while, on the other hand, a paucity (or total lack) of their translation in clinically used tools. The assumption that (pharmaceutical) companies will pick up on all these reported biomarkers and translate them into products is naïve and unsubstantiated, also as a result of the frequently low validity of the findings. Nevertheless, an ever increasing number of manuscripts is constantly generated (see Fig. 1), driven to some degree by the need to publish, or perish.

In a time when many scientists are indeed under great bibliometric pressure and publishing has changed from being a way of communicating the results of an investigation to representing the primary objective of a research project, the peer-review system should not contribute to this absurd and dangerous game, preventing the publication of scientific papers whose relevance does not go beyond a personal curriculum. To counteract this situation and the negative impact on quality, new and clear guidelines for publication of reports on clinical biomarkers appear to be required.

The Journal of Proteomics has decided to move one step ahead and support shaping the field in a constructive way, by implementing such simple, yet effective requirements for the publication of a proteomics biomarker study. These (requirements) aim at alerting biomarker researchers on the aforementioned issues and prompting them to reconsider claims on biomarker value of their findings in the lack of sufficient evidence. They will also help authors to shape their projects in a way that their results will truly be meaningful, and have higher chances of ultimately being of value in medicine and patients care. On the other hand, the new requirements also provide editors and reviewers of J. Proteomics a conceptual framework for helping them to develop more efficiently their task of separating the wheat from the chaff.

The first requirement refers to placing the biomarker in the context of a clear clinical need. If the latter is not existent, then obviously there is no justification for developing a biomarker. It is well accepted by now that pathological changes will result in proteomic changes and a further demonstration of this fact is of no added value, neither in general, nor specifically to the clinical management of the disease. The clinical situation and the current state of the art in assessing patients, as well as the aim for improvement has to form the basis of any clinical proteomics biomarker study. In general, biomarkers/indicators for specific pathological situations exist and they are currently used with known and described accuracies. To be of any potential use, a novel biomarker has to ultimately result in a significant improvement (e.g. higher accuracy, lower cost, etc.) of the current practice. As exemplified in Fig. 2, the detection of, for

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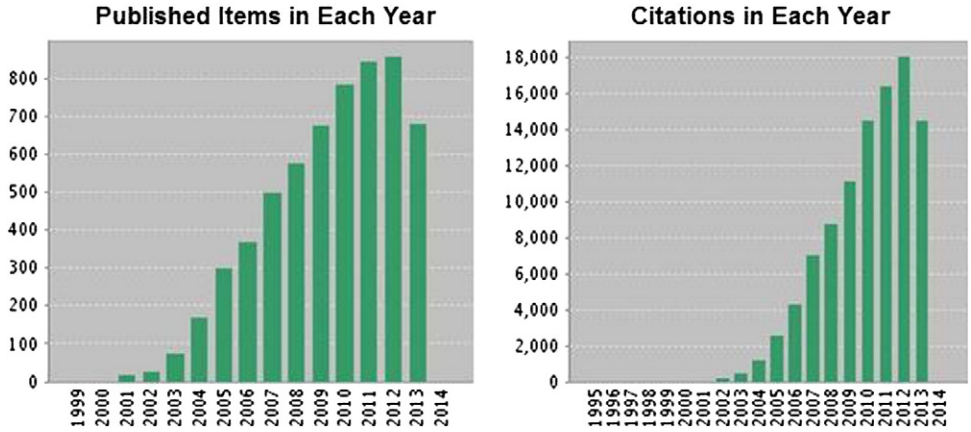

Fig. 1 – Number of manuscripts published and citations received when searching the Web of Science for the topics "proteom*" and "biomarker".

example, a possible critical condition in a patients in the Intensive Care Unit, often even with moderate confidence, is of no use.

It is therefore suggested that in biomarker discovery reports the specific proposed context of use must be given, as well as the current state of the art. This includes specific information on the target population. For example, the requirements for a biomarker to predict bladder cancer in a population-wide screening are very different from the requirements of a biomarker detecting the cancer patients suspected of harbouring a disease relapse. We are aware of the fact that the demonstration of e.g. prognostic value of a biomarker (resulting in improvement of the current state of the art) may be a substantial challenge and hence may not be possible in the initial study. However, as a minimum requirement, credible evidence has to be presented that the biomarker has a good chance to fulfil these requirements, and the aimed context of use has to be given. For example, the authors could outline a planned future study that would demonstrate the utility of the biomarker, based on the current state of the art and the estimated performance of the proposed biomarker, based on the data presented.

The second requirement refers to the problem that findings from discovery studies can generally not be reproduced [6–8]. Assessment of performance and expressing claims on biomarker value based on results from a discovery set

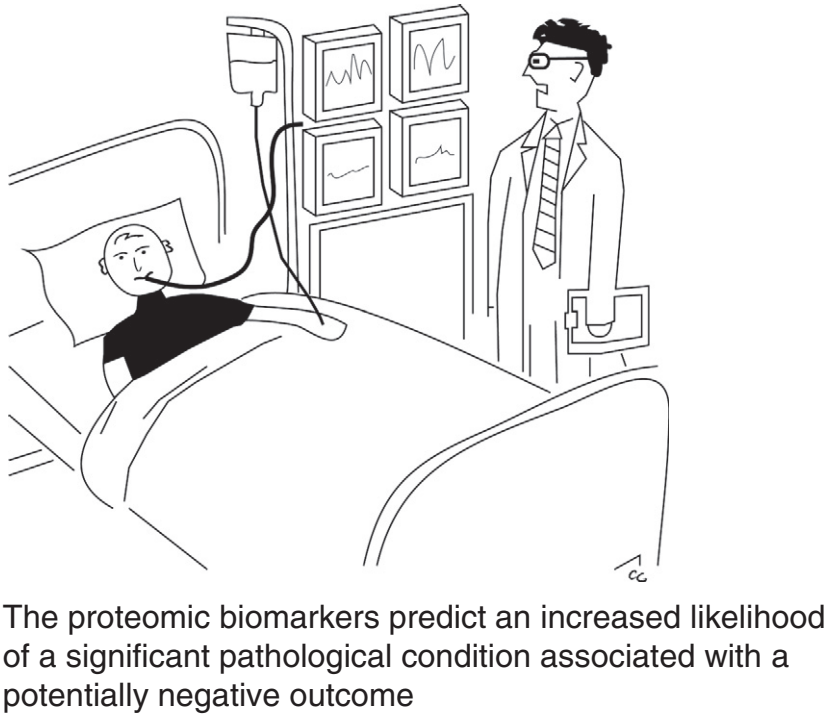

Fig. 2 – Sad example of a biomarker of questionable quality. The value of a biomarker indicating the obvious, often even with moderate confidence, does not exist.

are inappropriate. A biomarker can only be assessed in an independent (ideally blinded) test-set, containing sufficient samples to demonstrate significant value. Ideally, performance should be assessed in samples that reflect the typical clinical situation. However, as also outlined above, this requirement may frequently be difficult to fulfil, as a result of lack of appropriate samples. Along the same lines, we anticipate that most relevant biomarkers will have prognostic value, hence they should ideally be tested in a prospective study. The implication here –and as a result of the overinflated number of reports on biomarkers-, is that it is very difficult to secure funding for the appropriate prospective study in the absence of published preliminary data. Biobanks could be a valid solution to this problem, however, efficient procedures for sample accessibility are still not well developed. To avoid the implementation of rules that are just too restrictive and would effectively block clinical biomarker research, a compromise is that independent samples from independent crossectional studies, reflecting the typical clinical situation (young healthy controls are frequently used, but inappropriate, typical patients, frequently also with similar disease, must be employed as controls) are being employed for the first validation studies. The study must be designed in a way that the value of the biomarker in the actually proposed context of use, if it can not be proven with the study, can at least be credibly claimed as being valid.

Further issues that should be taken into account are that a biomarker must have a demonstrated potential to improve the current state of the art, either based on its sole performance, or by being of added value to the current standard. Along the same lines, the application of the biomarker must have a potential (therapeutic) consequence. To clearly highlight the value of a biomarker, the practical consequence of its application must be discussed. E.g. a biomarker predicting poor outcome for renal cell carcinoma patients, without any therapeutic option to improve the situation, does not appear to be of any practical use.

In conclusion, the proposed requirements aim at inciting consciousness and implementation-focused orientation (which per definition applies in biomarker research, nevertheless is frequently overlooked) to biomarker discovery. Irrespective of the aim of the study, the mere possible association of a protein or peptide with a disease is generally not worth to be published, and certainly does by no means justify baptising this change a "biomarker".

We need to stress that these considerations only are valid for clinical biomarker research. If the research is e.g. targeted towards understanding molecular pathology, then other considerations apply. The point of these recommendations is that biomarker research can with no doubt confer major impact on patient care and this exact fact should be the driving force and determining factor for the experimental strategy.

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