Author's response: Inconsistent results or inconsistent methods? A plea for standardisation of biomarker sampling in mesothelioma studies

Dr Blyth raises some important issues regarding the interpretation of malignant pleural mesothelioma (MPM) biomarker studies. First, the effects of confounders, including healing and/or inflammatory factors on biomarker levels; second, the reproducibility of biomarker results between centres.

In our independent evaluation of the proposed MPM biomarker fibulin-3, we considered some of the confounders he suggests—for instance, body mass index and renal function—which were not significant determinants of the diagnostic use of fibulin-3; and the neutrophil to lymphocyte ratio, which was reported and adjusted for in multivariate models. We agree that timing with respect to talc pleurodesis should be acknowledged in papers because of the potential effects of inflammation. Indeed, given that some biomarkers are increased in inflammatory effusions such as CA125, we agree that this is a good suggestion.

We have not, however, routinely reported on surgical intervention for tumour biopsies or for resection because these are not common in our patients, where the diagnosis is routinely accurately made on cytological samples[1] and surgery is rarely conducted.

We also consider it important to test the earliest possible sample, prior to surgical and chemotherapeutic intervention, as this is what the primary diagnostic aim is: to develop a biomarker for the diagnosis of the disease, which is by definition prior to treatment. We assumed that this was implicit in our statement regarding patient selection, but take the point that this could have been explicitly stated.

With regards to reproducibility, we strongly agree that reproducibility is important, and there is an extensive body of literature highlighting these issues for biomarker discovery and the resulting difficulties involved in translating biomarker research into clinical practice.[2] However, we disagree that discordance is common in MPM biomarker studies. Indeed, since we first published that serum mesothelin is a good biomarker for MPM,[3] there have been over 40 published studies from at least 10 independent centres consistently showing that mesothelin is significantly elevated in patients with MPM relative to

Thorax: first published as 10.1136/thoraxjnl-2014-206564 on 5 December 2014. Downloaded from http://thorax.bmj.com/ on April 18, 2024 by guest. Protected by copyright.

healthy controls, controls with benign disease and patients with lung cancer.[4 5] Results from the assay are consistent in all these studies, although suboptimal for use as a screening tool for the early detection of mesothelioma, hence the search for additional MPM biomarkers. While it is logical for authors reporting such new biomarkers to suggest their clinical applicability, consideration should be given to performing a head-to-head comparison with the recognised mesothelin biomarker before large-scale international prospective studies are undertaken.

Lastly, we need to consider the well-described Prometheus Effect: the situation in which the first published study is often the most biased towards an extreme result, which later studies cannot replicate.[6] Thus, the disparate results found between Professor Pass and ourselves are perhaps not so surprising, regardless of any differences in the patient cohorts studied, but are rather the result of chance and the way in which science is reported. This highlights the need for multiple replications, in geographically and ethnically diverse populations, to validate any biomarker, for any disease, and the need to publish the results from all rigorously conducted studies.

Jenette Creaney,[1,2] Bruce W S Robinson[1,2,3]

[1]National Centre for Asbestos Related Diseases, School of Medicine and Pharmacology, University of Western Australia, Nedlands, Western Australia, Australia
[2]The Australian Mesothelioma Tissue Bank, Sir Charles Gairdner Hospital, Nedlands, Western Australia, Australia
[3]Department of Respiratory Medicine, Sir Charles Gairdner Hospital, Nedlands, Western Australia, Australia

Correspondence to Dr Jenette Creaney, National Centre for Asbestos Related Diseases, School of Medicine and Pharmacology, University of Western Australia, Harry Perkins Building, 5th Floor, QQ Block, 6 Verdun St, Nedlands, WA 6009, Australia; jenette.creaney@uwa.edu.au

Contributors JC and BWSR both drafted and approved the final document.

Competing interests None.

Provenance and peer review Not commissioned; internally peer reviewed.

To cite Creaney J, Robinson BWS. *Thorax* 2015;**70**:374–375.

Received 13 November 2014
Accepted 14 November 2014
Published Online First 5 December 2014

► http://dx.doi.org/10.1136/thoraxjnl-2014-205205
► http://dx.doi.org/10.1136/thoraxjnl-2014-206464

Thorax 2015;**70**:374–375.
doi:10.1136/thoraxjnl-2014-206564

REFERENCES

1 Segal A, Sterrett GF, Frost FA, *et al*. A diagnosis of malignant pleural mesothelioma can be made by effusion cytology: results of a 20 year audit. *Pathology* 2013;45:4–8.
2 Wagner PD, Srivastava S. New paradigms in translational science research in cancer biomarkers. *Transl Res* 2012;159:343–53.
3 Robinson BW, Creaney J, Lake R, *et al*. Mesothelin-family proteins and diagnosis of mesothelioma. *Lancet* 2003;362:1612–16.
4 Hollevoet K, Reitsma JB, Creaney J, *et al*. Serum mesothelin for diagnosing malignant pleural mesothelioma: an individual patient data meta-analysis. *J Clin Oncol* 2012;30:1541–9.
5 Cui A, Jin XG, Zhai K, *et al*. Diagnostic values of soluble mesothelin-related peptides for malignant pleural mesothelioma: updated meta-analysis. *BMJ Open* 2014;4:e004145.
6 Ioannidis JP. Contradicted and initially stronger effects in highly cited clinical research. *JAMA* 2005;294:218–28.

Thorax: first published as 10.1136/thoraxjnl-2014-206564 on 5 December 2014. Downloaded from http://thorax.bmj.com/ on April 18, 2024 by guest. Protected by copyright.