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Gene expression biomarkers for kidney transplant rejection-The entire landscape–Author's reply

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We thank Prof Friedewald and his colleagues for highlighting their recently-published study [1]. Reassuringly, they also found a positive biomarker in a quarter of stable patients with a gene-set completely different from our signature.

While microarray-based identification of new genes is clearly beneficial, this approach is untargeted but not necessarily unbiased. Statistical algorithms may favour genes with better analytical performance, may also capture some noise and may derive various similarly-predictive gene-sets [2]. Selection among known genes goes one step further by validating genes in new datasets, thus minimising chance findings.

Gene multiplicity in microarrays is problematic rather than beneficial for missing data imputations, as not all genes are informative for the imputation rules. The newly-developed nearest-neighbour method, recommended in the letter, addresses this "curse of dimensionality" [3], but for our small gene-set the classical K-nearest-neighbour method was acceptable [4]. We based the imputation rules on over 500 longitudinal samples from training patients. Missing data in RT-qPCR (<0.5% in total) arose from expression levels beyond the commonly-used limit of detection 35Ct (cycle threshold) or failed quality control of analytical repeats for isolated genes in isolated samples.

Although creatinine has limitations, the mechanisms affecting its levels are known. Therefore, a clarification of the mechanistic relevance of individual genes to rejection is needed in addition to statistical validation of gene-expression signatures. We agree that a positive biomarker test is "a potentially actionable signal of alloimmune activation" [1], but also fundamentally agree that further studies are warranted to establish the biological specificity and clinical usefulness of gene-expression signatures [5].

Declaration of conflict of interests

SC, MR and PC declare no conflict of interest. MHF is currently an employee of UCB Celltech, a pharmaceutical company based in the UK. Her involvement in this research was solely in her capacity as academic from King's College London.

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