Reviewer’s report

Title: Prediction of response to anti-EGFR antibody-based therapies by multigene sequencing in colorectal cancer patients

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Reviewer: Bastiaan Tops

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Lupini, et al present comprehensive data regarding the prediction of response to anti-EGFR therapies by NGS in CRC patients.

The manuscript is well written and makes a strong argument for extensive NGS analysis for patient selection in clinical trials to analyze responses in relation to biomarkers. However, the biological rationale why mutations in e.g. FBXW7 and/or SMAD4 would convey therapy resistance is puzzling.

Major issue:

There is one major concern and that is that population group as it was analyzed is biased and relatively small (with respect to the number of identified mutations). The patient group is strongly selected against KRAS positive tumors (only KRAS wt tumors were included). The comparison is therefore biased. The authors themselves state that 35-45% of wt RAS cases do not respond and that the analyses of several genes by NGS could identify additional genetic changes involved in response (line 15-22). Since the question is therefore if there is additional value for other genetic biomarkers, the KRAS and NRAS positive tumors should be ignored in data-analysis (e.g. Table 2). In my opinion it would be unfair to include the KRAS mutated tumours since these contribute significantly to the correlation between mutational status and response outcome in the presented data.

Minor point:

- the authors state (line 11) that HRAS mutations are a contra-indication for cetuximab therapie. To my knowledge this only applies to NRAS and KRAS. So a specific reference is required or the sentence should be adapted.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:
I declare that I have no competing interests