The Royal College of Pathologists
Pathology: the science behind the cure

NICE Multiple Technology Appraisal (MTA)
Assessment Report - Cetuximab, bevacizumab and panitumumab monotherapy for the treatment of metastatic colorectal cancer that has progressed after first line chemotherapy (review of technology appraisal 150 and part-review of technology appraisal 118)

Comments on behalf of the Royal College of Pathologists:

This assessment undertaken by PenTAG is a thorough and comprehensive review of the evidence (both independently obtained and submitted by the manufacturers) regarding the clinical and cost effectiveness of these technologies. It seems that the evidence is fairly limited necessitating some assumptions and it is concluded that whilst the clinical effectiveness of the anti-EGFR therapies (cetuximab and panitumumab) is undoubted, they fall outside the NICE limits of acceptable cost effectiveness. I have a couple of comments:

(1) The cost effectiveness figures submitted by Merck-Serono for Cetuximab were different from those calculated by PenTAG. It seems that the majority of this difference arose from differences in the length of treatment assumed by each party. The PenTAG calculations were based on an assumption of continuous treatment until disease progression (which was the protocol adopted in the two trials which provide most of the evidence). I wonder whether this would fit with activity in the "real world" – the study cited in this document by Annemans et al. suggests that the treatments may be more cost effective the they are stopped when there is no evidence of cost effectiveness.

(2) Mutation analysis for Kras was done retrospectively in both trials and there was some concern about the sensitivity of the laboratory test. Only the codon12/13 hotspot was tested whilst mutations in Kras can occur in codons 64 and 146 and this may be an important confounder. More importantly, there was no mention in document of mutational analysis of Braf. This gene lies downstream of Kras and is mutated in approximately 10% of all colorectal cancers. Braf and Kras mutations ares mutually exclusive and thus a proportion of the Kras WT tumours may harbour Braf mutation. Furthermore, Braf is reported to be a poor prognostic factor and it is possible that the metastatic CRCs may thus be comparatively enriched for these mutations. It is reported that Braf mutations may confer resistance to anti-EGFR therapies and thus the proposed studies delineated in the research recommendations should include an analysis of Braf mutation (as well as the other Kras mutation hotspots and mutational analysis of PIK3CA).

[redacted]