Systematic Review of Natural History Models in CEAs of Novel Testing Techniques in Cervical Screening: A Brief Summary

This note provides a brief summary of a systematic review to identify natural history models employed in cost-effectiveness analyses of cervical screening that incorporated novel biomarkers beyond the current use of HPV testing. Knowledge of the natural history of disease progression according to biomarker status is important to the construction of any cost-effectiveness analyses of such novel biomarkers in screening. Therefore, the findings of this review were to help inform how current modelling techniques employed by the CERVIVA team could be adapted to assess new screening tests.

The systematic review adapted a search string used in a systematic review of cervical screening CEAs previously published by the CERVIVA group in 2015 [O'Mahony et al 2015]. The search string was updated to include studies published up to June 2016. The string was also adapted to search for particular search terms relating to the novel tests proposed for use in cervical screening. These specific search terms were p16, INK4a, E6, E7, and mRNA. The titles and abstracts found by the updated string were searched for relevant studies.

The search resulted in 879 unique titles and abstracts for review, of which 43 were selected for further detailed review. Of these, there were only two published studies that considered novel testing techniques beyond the current screening technology of cytology or HPV DNA testing.

One study examined the use of mRNA versus DNA testing using a Markov model in a US context [Ting et al, 2015]. The analysis uses a model to compare the costs and health effects as measured in life year saved of four alternative scenarios, two using the currently recommended test for high risk HPV DNA and the other two using mRNA testing. The models use an existing natural history model that is not disaggregated by HPV type or rate of disease progression according to mRNA status. The difference between the strategies in the model derives primarily from improved specificity of mRNA testing over DNA, as reported in previous trials. Accordingly, this study does not present a marked change from previous modelling approaches regarding the natural history of disease progression. The reported results show that mRNA testing dominates DNA testing, as although the tests are assumed to have similar costs, mRNA testing is overall cost saving due to higher test specificity.

Consequently, this study indicates mRNA is likely to be a highly policy relevant screening tool deserving of further analysis.

The second study examined the use of DNA ploidy analysis versus liquid based cytology using a Markov model in a US context [Nghiem et al, 2015]. This analysis uses a development of the same core model used by Ting et al. Similarly, the model does not contain any changes in simulation of the underlying natural history of disease, rather it addresses differences in test performance between strategies. Accordingly, this model is also comparable to existing natural history models employed in cervical screening cost-effectiveness analyses. The analysis compares DNA ploidy analysis, which is an alternative to the more commonly employed Hybrid Capture II test. DNA ploidy was examined at a number of different sensitivity and specificity values, depending on the number of abnormal cells found per slide. These various configurations of ploidy analysis were compared to liquid based cytology (LBC). The simulation results presented showed ploidy analysis to be less costly but also less effective in terms of quality-adjusted life years gained compared to LBC. The report concludes that ploidy analysis is unlikely to be adopted as a testing strategy due to its inferior performance. However, this conclusion overlooks the fact that ploidy analysis might outperform cytology when increased screening frequency is considered. Accordingly, ploidy appears to remain a policy-relevant alternative that deserves consideration.

A clear finding of this review is that only a very small number of CEAs on screening tests other than cytology or conventional HPV testing methods have been published to date. More specifically, detail reviewing of the two published studies show that both use natural history models that are comparable to the SPCC and adapted MISCAN models currently employed by the CERVIVA project. Accordingly, neither model has any distinct advantages over the approach being taken in CERVIVA. Moreover, neither analysis contained a broad comparison of screening tests over a range of screening intensities to identify the incremental cost-effectiveness over a full efficient frontier. The models currently employed in CERVIVA have such a broad comparison as a key goal and therefore should be able to yield more policy relevant findings. In summary, the existing cost-effectiveness literature does not provide clear guidance on how to best adopt existing models to assess novel biomarkers; nor does it feature models that provide a particular advantage over those currently employed by CERVIVA. Appropriate model specification for the assessment of such new tests will require research that looks beyond the CEA literature and towards epidemiological analysis of such markers in disease progression.

References:

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