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Comment on Keeney et al.'s "Delphi Analysis of Relevant Comparators in a Cost-Effectiveness Model of Prostate Cancer Screening"

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Keeney et al. recently published a Delphi analysis on identifying strategies for simulation in a cost-effectiveness analysis (CEA) of prostate cancer screening [1]. The research usefully elucidates the screening strategies experts consider the priority for assessment. This commentary addresses three points, the first two relate specifically to Keeney et al. regarding: (1) the questions asked of experts and (2) the sample of experts consulted. The third relates to the more general issue of how best to specify strategies in cancer screening CEAs.

First, some background regarding strategy selection in cancer screening. As Keeney et al. note, CEAs should ideally include all possible comparators. This is to ensure the analysis does not omit the optimal strategy and thus bias incremental cost-effectiveness estimates of the strategies simulated. An important practical constraint in most cancer screening programmes is that the set of possible strategies is large, making it infeasible to model completely. Constraints on data and analytical capacity mean modellers must attempt to anticipate what finite set of strategies might approximate the efficient set among all possible alternatives. Importantly, when restricting the set of strategies to investigate, analysts should avoid doing so in a way that leads to systematic bias.

Respondents in Keeney et al.'s Delphi analysis were asked what strategies they thought should be provided. This may not be the most relevant question. A CEA should include both candidate strategies (corresponding to what the respondents suggest should be provided) and comparator

strategies against which these candidate strategies should be compared. If experts are asked only what should be provided, then we may elicit many candidate strategies and too few comparator strategies. Good comparator strategies are those likely to be less costly and less effective than the strategies of interest, thereby providing a basis for appropriate incremental analysis. Regarding the screening interval for instance, while respondents might suggest a particular interval, the analysis should also include longer intervals for the purpose of incremental comparison. Similar considerations apply to alternative screening age ranges, combinations of tests and risk thresholds.

The choice of relevant strategies can be linked to the choice of experts consulted in Keeney et al. The panel primarily included clinicians. It also included two screening modellers who have published prostate screening CEAs. Accordingly, experts with health economic experience appear the minority on the panel, which is a limitation in my view. While my own experience of clinicians regarding strategy specification is limited, I perceive a tendency to prioritise clinical effectiveness rather than accepting the trade-offs required to achieve cost effectiveness. I have observed an unwillingness to contemplate lower intensity strategies, even as comparators against which to assess the primary strategies of interest. I also perceive a tendency for close adherence to strategies in clinical guidelines, again limiting the willingness to contemplate potentially relevant but less effective alternatives. In sum, I expect a Delphi panel constituted primarily of clinicians to be biased towards higher intensity strategies and likely to nominate an insufficient range of comparators.

I should caveat my comments by noting that issues of appropriate strategy choice often appear neglected by health economists themselves. Examples from the cervical screening CEA literature frequently feature inadequate comparators [2]. Furthermore, there is considerable heterogeneity in the prostate screening CEA literature regarding the strategies and subgroups assessed [3]. Accordingly,

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increased representation of health economists in the Delphi panel might not necessarily lead to a more comprehensive comparator selection.

My comments on strategy selection assume the objective of a CEA is to identify the optimally cost-effective strategy. This, however, is at odds with Keeney et al.'s statement that "The aim of any future CEA should be to determine, not which screening strategy is most cost effective, but rather if any of the identified screening strategies have the potential to be more cost effective than current practice (i.e. opportunistic PSA-based screening)." [1]. Analyses of opportunistic screening in other cancers indicate it can be cost ineffective relative to appropriately optimised population screening [4, 5], as it typically combines frequent screening for low-risk individuals with low overall population coverage. Unless current opportunistic prostate screening is already a well-judged, risked-based practice, which it probably is not, then I suspect it is also inefficient.

If the objective is only to improve on the status quo, then the potential problems of biased strategy selection are likely less pressing. Accordingly, Keeney et al.'s Delphi analysis might be suitable for their stated objective. In reply, I then question whether attempting only to improve on current practice is a suitable objective, as it does not fully align with the CEA's overarching goal of maximising population health from scarce resources.

Moving to the more general point regarding strategy selection. The following is not a critique of Keeney et al. per se but uses their analysis to illustrate a broader issue. I question whether expert elicitation is a meaningful way to identify relevant strategies for comparison and consider alternative methods. As described above, any cancer screening CEA needs to limit the set of strategies assessed before the analysis is conducted. Without prior costs and effects estimates of screening strategies, it is difficult to anticipate which are most likely to be efficient. In the absence of any prior information, analysts must simply start by simulating strategies and see which emerges.

A pragmatic starting point for simulation therefore seems currently recommended strategies (presuming guidelines exist) and some variation around these in terms of intensity. If no guidelines exist, then an analysis such as Keeney et al.'s offers a good alternative starting point from which to vary screening intensity. Ideally, this intensity variation should include some de-intensification of age ranges, intervals and test positivity cut-offs.

Where prior CEAs exist, analysts can infer from what variation of screening intensity could be relevance to explore further. For example, Heijnsdijk et al. [6] found the stopping age a key determinant of cost effectiveness, therefore subsequent analyses might prioritise variation in screening stop age in their simulations. This, of course,

relies on some inductive reasoning that what was found to be relevant in one simulation will be relevant in the next.

The approach suggested here does not recommend a full ex-ante specification of the relevant set of strategies, rather it advocates an iterative approach whereby analysts examine their initial results to determine the likely benefit of further extending the strategy set. While such an iterative approach contradicts current research guidelines that recommend establishing a fixed analysis plan at the outset, the rationale for alternative methods is hopefully clear.

In conclusion, we should not dismiss the work of Keeney et al. as irrelevant to the specification of screening strategies for comparison. Rather, it seems appropriate to reframe their Delphi analysis as a useful starting point for the strategies we initially judge most relevant, but that this ought to be coupled with careful efforts to expand the comparison set to those strategies most likely to be cost effective.

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