Commentary

How Useful Are Early Economic Models?
Comment on “Problems and Promises of Health Technologies: The Role of Early Health Economic Modelling”

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Abstract
Early economic modelling has long been recommended to aid research and development (R&D) decisions in medical innovation, although they are less frequently published and critically appraised. A review of 30 innovations by Grutters et al provides an opportunity to evaluate how early models are used in practice. The evidence of early models can be used to inform two types of decision: to continue development (‘stop or go’) or to alter future R&D activities. I argue that early models have limited use in stop or go decisions, as less resource and data undermine the reliability of the models’ indicative estimates of cost-effectiveness. Whilst they are far more useful for informing future R&D directions, the best techniques available from statistical decision science, such as value of information analysis, are not regularly used. It is highly recommended that early models adopt these methods to best deal with uncertainty, quantify the potential value of further research, identify areas of study with the greatest potential benefit and generate recommendations on study design and sample size.

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Introduction
The development of innovative healthcare products such as pharmaceuticals and medical devices is highly resource intensive, involving billions of dollars.1 Public purchasers are the most common procurers of these products, with more than half of global health expenditure publicly funded.2 Manufacturers therefore have an obvious interest in trying to identify the social value of potential investments as early as possible in order to maximize revenue. Early health economic modelling is often proposed to aid investment decisions by estimating the expected costs and health benefits generated by an innovation, compared with current standards of care.

Early modelling has been recommended for at least 20 years.3,4 However, compared with more typical, later-stage decision models that are developed to inform adoption and reimbursement decisions (hereafter ‘late-stage models’), the details of early models are less frequently published. The recent retrospective analysis of 32 early models by Grutters and colleagues is therefore a welcome addition to this relatively under researched area.5 Their sample covers a variety of product development stages and clinical areas, with the vast majority commissioned by medical device companies. There is explicit focus on the early economic models themselves, rather than a broader early health technology assessment (HTA) process in which additional factors such as regulatory environment and safety profile are deliberated.6 ‘Early’ is defined as being any point before healthcare payers are making decisions about whether or not to adopt the intervention – the traditional point at which decision models are developed.

Grutters set out to address two questions relating to early models: (i) how useful the models were in establishing potential cost-effectiveness and (ii) exploring how the results affected the subsequent design or implementation of the intervention. Another way of framing these questions is whether the early model informed decisions about whether to (i) continue development (‘stop or go’) or (ii) alter future research and development (R&D) activities (ie, by focusing additional research on promising patient groups). Since the principal motivation for decision modelling is to inform decisions, I agree that these are the principal justifications for developing early models. I argue that early models are far better at answering (ii) than (i).

Stop or Go?
“Potential” cost-effectiveness is a low bar that a vast majority of early models clear. Every intervention in Grutters’ sample demonstrated some scenario in which it was cost-effective, as did an earlier smaller review by Markiewicz and colleagues.7 This is not surprising. First, compared with late-stage models, early models are programmed with less complete data of lower quality and higher uncertainty. Being built at an earlier phase of product development means that fewer trials will have been conducted, fewer patients treated and fewer outcomes monitored. Exploratory analyses of cost-effectiveness that

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The lack of probabilistic analysis is acknowledged by Grutters et al and justified on the basis that it “is difficult to quantify the (non-statistical) uncertainty… in [terms of probability] distributions,” favouring the likes of tornado plots when assessing the impacts of the model parameters on results. However, deterministic sensitivity analysis and tornado plots still require a range of values that each parameter is to be varied over. If this range is not specified according to uncertainty (ie, through a probability distribution), then the influence of that parameter on cost-effectiveness will also be a function of a potentially *ad hoc* range selection. A solution to this issue is to estimate parameter values and/or probability distributions using structured expert elicitation methods, a number of which can be used depending upon the type of intervention or parameter under consideration.\(^7\) The use of structured expert elicitation would not only improve the validity of deterministic sensitivity analysis; it will also facilitate analytically preferable probabilistic methods and value of information analysis. Using these techniques will require more resource for early models, however, which may not be forthcoming due to the incentive problems noted above.

### Concluding Remarks
Grutters et al are right to conclude that their early models provide insight into the potential cost-effectiveness and associated uncertainty of their sample of innovations. However, this support comes with several caveats. The insights into potential cost-effectiveness are rather limited due to the exploratory nature of the analysis and may really only be truly useful when development decisions involve selecting a limited number of innovations from a portfolio, such as in a real options model.\(^18\) The insights into the drivers of cost-effectiveness and uncertainty, although much more worthwhile for R&D decision-making, could be greatly enhanced by using the best techniques available from statistical decision science. Similar conclusions have been reached by Abel et al during a review of early models of diagnostics.\(^19\)

The focus of Grutters and of this article has been on how the outputs of early models can be used in R&D decisions. A related empirical question that should be the subject of future inquiry is whether those outputs should be used. One way of approaching this question is to compare the results of an early model with those of a late-stage model produced with greater resource and populated with better data. Such comparisons would be possible using an iterative Bayesian modelling process advocated by many in the literature,\(^5,11,14\) in which a model is regularly updated throughout the product development cycle. However, there is little evidence suggesting that this approach is being implemented, leaving this validation question around early models more challenging to address. Given the scarcity of published research on early models, Grutters et al deserve credit for at least shedding some light on this frequently private and internal process.

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**Author’s contribution**
JLK is the single author of the paper.

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