Establishing cost-effectiveness of genetic targeting of cancer therapies

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The clinical benefit of a new genomic instrument, the 70-gene signature for breast cancer patients, is being evaluated in a randomised clinical trial. The early, controlled implementation process is supported by a Constructive Technology Assessment to help decision-making in an uncertain time of development.

Treatment for patients with cancer has shifted from administering broadly toxic drugs towards fine-tuning of therapies that are targeted to the personal characteristics of specific tumours. An example of this development is the possibility to base the decision of adjuvant systemic therapy for breast cancer on the results of a genomic prognostic profile. The majority of early stage breast cancer patients, particular with lymph node-negative disease (60-70%), have a fairly good 10-year overall survival with locoregional treatment alone, with only 30-40% developing distant metastasis [1]. Nevertheless, according to current guidelines, most lymph node negative breast cancer patients are offered chemotherapy, causing an important percentage of over-treatment [2]. In 2002, researchers at the Netherlands Cancer Institute (NKI, Amsterdam, the Netherlands) identified a 70-gene prognosis signature (MammaPrint™), using microarray analysis for lymph node-negative breast cancer patients [3]. Using the 70-gene signature, the selection of patients that will benefit most from adjuvant systemic treatment could be more accurate. The signature has been validated in three independent retrospective patient series [4-6]. A prospective feasibility study, the MicroarRAy PrognoSTics in Breast CanER (RASTER)-study was started in 2004 [7].

Coverage decisions regarding new technologies often have to be made at a time when the data on the most relevant variables and adequate comparisons are not yet available from high-quality studies. Especially when the promising new technology is in its early development phase and certain stakeholders find reason to speed up implementation in clinical practice, health policy challenges arise.

Health Technology Assessment (HTA) is widely adopted to help manage the introduction and appropriate use of new technologies [8]. However, a HTA generally starts after the technology is stabilised and proved to be valid in clinical trials. During this time many changes in available treatments can occur, which results in a HTA subsequently answering, at least partly, outdated questions [9]. Genomic knowledge leads to the introduction of new and increasingly personalised diagnostics and treatments, which lead to even more complex evaluation designs when following common and accepted assessment practices. Thus, it would take at least 8-10 years to bring the 70-gene signature into clinical practice, via the usual path of prospective trials. For these reasons, we chose to carry out a controlled introduction of the 70-gene signature, supported with a comprehensive technology assessment, which takes technology dynamics into account, and decided to perform a Constructive Technology Assessment (CTA). CTA is based on the idea that during the course of technology development, choices are constantly being made about the form, the function, and the use of that technology [10]. This assessment method is a possible answer to the (economic) evaluation challenges that new genomic technologies pose.

MINDACT-trial

After the results of the controlled introduction trial were known [7], in the Netherlands a discussion was started whether Coverage with Evidence Development (CED) would be appropriate. CED represents a specific approach to coverage for promising technologies for which the evidence is uncertain yet [8]. Parallel additional prospective evidence on the validity of the prognostic use was needed for which the MINDACT-trial Microarray In Node-negative Disease may Avoid ChemoTherapy) was organised. The MINDACT-trial evaluates whether use of the 70-gene signature is associated with clinical benefit. The randomised controlled design allows a defined group of patients (age 18-70, node negative, operable breast cancer) to have their treatment determined on the basis of either the 70-gene signature or standard practice guidelines. Patients with discordant risk profiles will be randomised to

chemotherapy treatment according to either the clinicopathological criteria (using the Adjuvant! Online software [11]) or according to the 70-gene signature [12]. The trial plans to prospectively recruit 6,000 patients. A follow up of at least ten years will be required before the results are available [13]. At this time, the trial is currently running in eight European countries.

Constructive Technology Assessment

The CTA is related to a Health Technology Assessment (HTA), which predominantly implies a cost-effectiveness analysis (CEA) or economic evaluation. CTA also takes technology dynamics into account and has developed from just assessing the impact of a new technology to the analysis of design, development, implementation and interaction of that new technology with its environment. Only a few publications are available describing the application of CTA in health care [9, 14, 15]. The aspects studied in this CTA on the 70-gene signature so far were: patient-related aspects (understanding of the 70-gene signature and psychological impact), organisational efficiency (logistics and team functioning) and diffusion scenarios [15]. Partially based on these data, a dynamic economic evaluation will be conducted.

Scenarios

Scenario drafting can be used as a tool in forecasting of new, still dynamic technologies and is commonly applied in industry to anticipate future development and diffusion of their products. Scenarios can be used to monitor the implementation process through the various diffusion phases and can support and identify the need for evaluation or even interfere through formal decision making. In the case of the 70-gene signature, the scenarios were written using the timeline of diffusion phases as described by Rogers' theory, 2003 [16], see Figure 1. These phases reflect the degree of spreading throughout the (medical) society. In the *innovation phase*, the prognosis signature technique is developed and the first organisations adopt (introduce) the technology in their daily practice. The first scenario was written before the prognosis signature was introduced in the Netherlands (mid-2004). The *early adoption phase* describes the implementation in 10-15 hospitals. The second, revised scenario was drafted based on the first experiences in the feasibility study (RASTER) in the Netherlands (mid-2005). The *early majority phase* describes the implementation in a gradually increasing number of hospitals and is ongoing. The most recent scenario written at the beginning of the MINDACT trial (mid-2008), incorporating ten alternatives, was first checked by genomic experts and breast cancer specialists, and validated in a recent workshop among 50 European breast cancer experts.

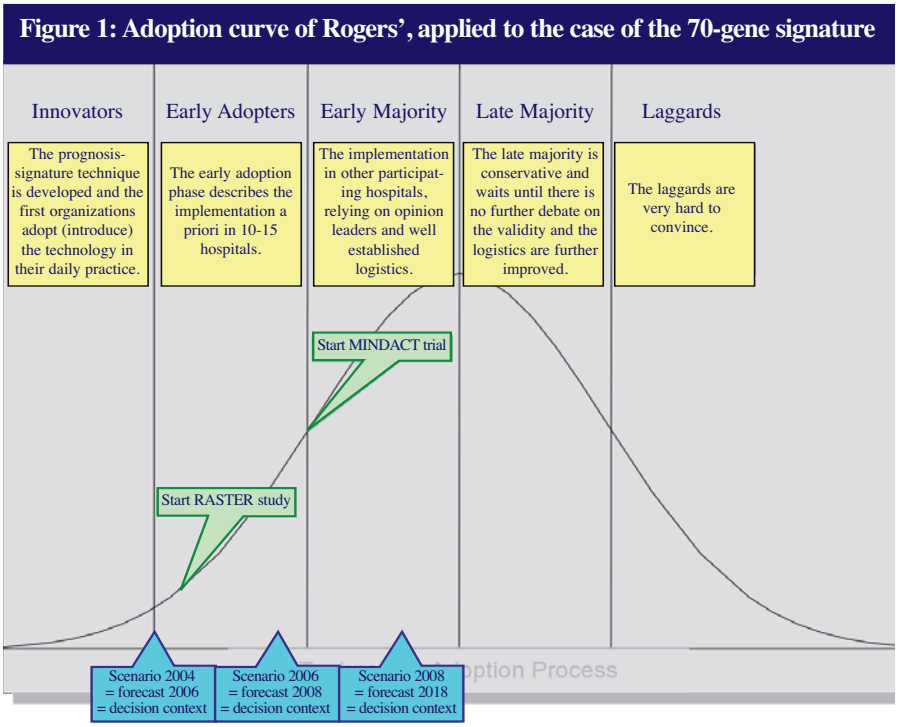
Dynamic Economic Evaluation

The scenarios drafted on the subsequent phases of diffusion describe possible "future worlds" of the use of the 70-gene signature. Probabilistic decision modelling will be used to estimate the cost-effectiveness of the 70-gene signature in these worlds, which may alter as time progresses and more information becomes available. The various alternatives, barriers or facilitators that influence the diffusion of the 70-gene signature will be incorporated into the model as stochastic parameters. Parameters will be updated as soon as new information becomes available. At each moment in time, the decision to adopt or reject the new technology based on existing knowledge, and the decision whether more evidence is required can be informed by the results of the model [17]. Cost-effectiveness Acceptability Curves (CEACs) will reflect the degree of decision uncertainty and Value of Information Analyses (VOI) implies whether additional evidence to further inform the decision is worth gathering, and what kind of information is of the greatest value [18]. VOI is the amount a decision maker would be willing to pay for information prior to making a decision.

Conclusions

Establishing the cost-effectiveness of genetic targeting of cancer therapies is increasingly desirable in an early stage when "traditional" prospective randomised controlled data are not within reach. In the MINDACT-trial that would take another 8-10 years and future tech-

Figure 1: Adoption curve of Rogers', applied to the case of the 70-gene signature



nologies with further personalised differentiation might even lead to conclusions that more qualitative trials will be conducted. However, the challenge is still to inform policy makers about possible advantages or disadvantages and, ultimately, to aid a decision on usage and coverage. A CTA evaluates a new technology in an early and unstable stage of development. Scenarios help to monitor the controlled introduction process and can even assist in anticipating on future developments. Dynamic economic evaluation can support the decision making, by taking the several scenarios per diffusion phase into account in a decision model. We expect that these methods will prove valuable in combination with more "traditional" cost-effectiveness analysis approaches.

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What makes NICE tick?

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The National Institute for Health and Clinical Excellence (NICE), issues mandatory guidance on the use of health technologies within the UK National Health Service. This paper reviews a study involving a model developed to identify which factors influence NICE's technology appraisal decisions.

The National Institute for Clinical Excellence (NICE), subsequently renamed the National Institute for Health and Clinical Excellence, was established by the UK government in 1999 as an independent organisation to provide guidance to the National Health Service (NHS) in England and Wales on the clinical and cost-effectiveness of new and existing clinical interventions. Since January 2002, NHS organisations in England and Wales have been required to provide mandatory funding for medicines and treatments recommended by NICE in its technology appraisals guidance [1]. NICE's technology appraisal decisions are based on a range of factors, including the strength of clinical-effectiveness evidence, cost-effectiveness, the availability of alternative treatments, and the potential for long-term benefits to the NHS from innovation [2, 3]. However, the decision-making criteria other than cost-effectiveness have not been codified by NICE and remain enigmatic [4].