

CHAPTER 3

The practice of pharmacoeconomics

For personal use only. Not to be reproduced without permission of the publisher (copyright@ppme.eu).



Valesca P Retèl
MSc



Professor EJTh
Rutgers
MD



MA Joore
PhD



Professor WH
van Harten
MD

ESTABLISHING COST-EFFECTIVENESS OF GENETIC TARGETING OF CANCER THERAPIES

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, particularly with lymph node-negative disease (60–70%), have a fairly good 10-year overall survival with loco-regional 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 overtreatment [2]. Overtreatment is associated with adverse effects and high costs, however, is understandable with the lack of a fully accurate method to select high risk patients needing chemotherapy. 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 four independent retrospective patient series [4–7]. A prospective feasibility study, the MicroarRAY PrognOSTics in Breast CancER (RASTER)-study was started in 2004 to investigate whether the collection of good quality tumour tissue from community hospitals and the analysis of the 70-gene signature was feasible [8].

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, supporting the RASTER-study 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 [9]. This assessment method is a possible answer to the economic evaluation challenges that new genomic technologies pose.

MINDACT-TRIAL

After the feasibility study the MINDACT-trial (Microarray In Node-negative Disease may Avoid ChemoTherapy) was designed. The MINDACT-trial will evaluate whether use of the 70-gene signature is associated with clinical benefit. It will provide findings on the exact prognostic and predictive value of the 70-gene signature. 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 (see Figure 1). Patients with discordant risk profiles will be randomised to chemotherapy treatment according to either the clinicopathological criteria (using the Adjuvant Online software [10]) or according to the 70-gene signature [11]. 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 [12]. The trial started

Figure 1: MINDACT-trial design

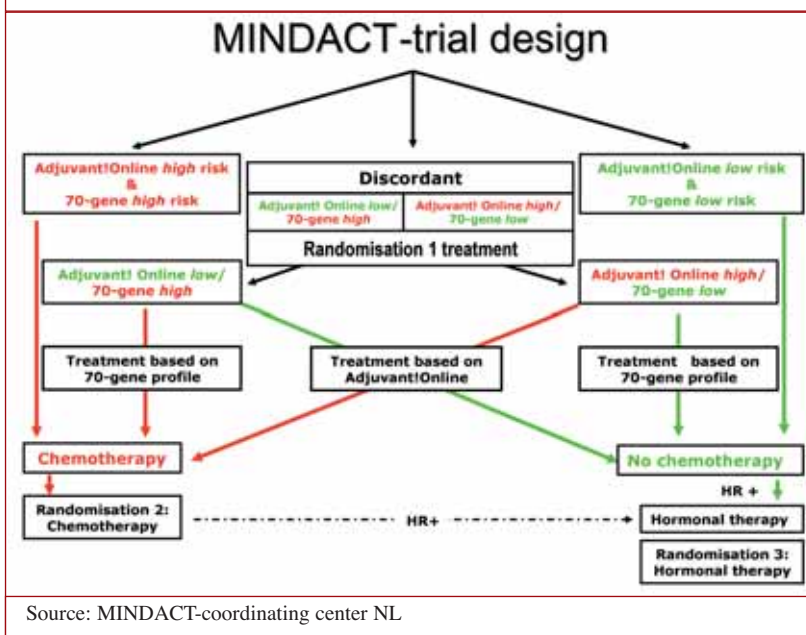


Figure 2: Timeline implementation 70-gene signature

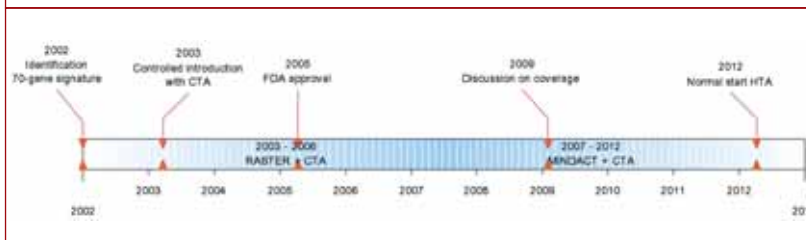
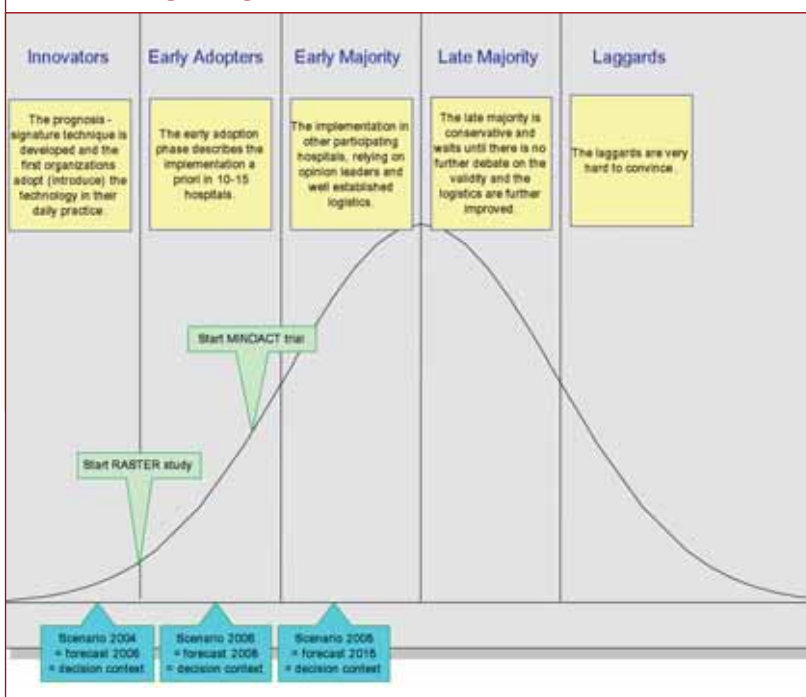


Figure 3: Adoption curve of Rogers', applied to the case of the 70-gene signature



recruiting in 2007 and is expected to finish in 2012. The feasibility of the MINDACT-trial has been proven [13], and the recruitment rate is as planned. The trial is currently ongoing in 10 European countries with 68 participating hospitals.

CONSTRUCTIVE TECHNOLOGY ASSESSMENT

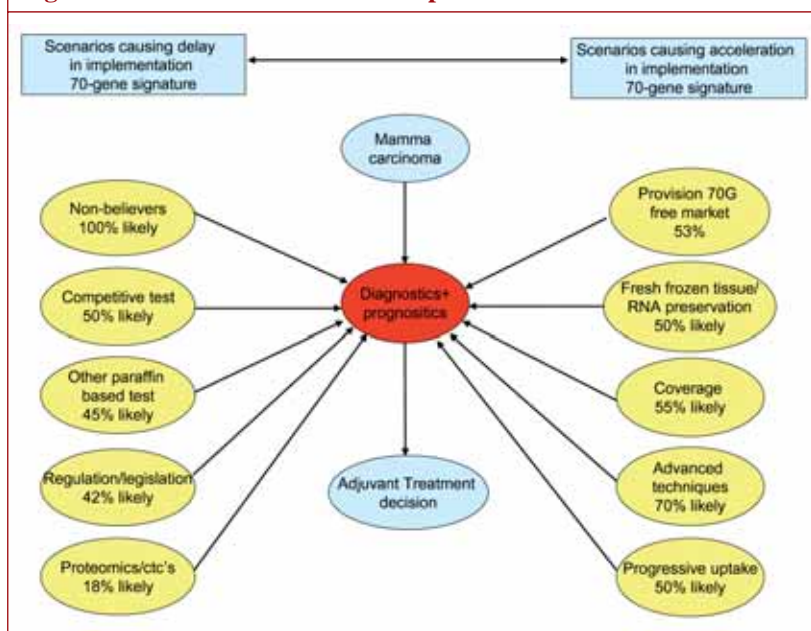
Coverage decisions regarding new technologies often have to be made at a time when the data on most relevant variables and adequate comparisons are not available yet from high-quality studies. Especially when the promising new technology is in its early development phase and certain stakeholders find reason to speed up implementation in clinical practice, health policy challenges arise. Health Technology Assessment (HTA) is widely adopted to help to manage the introduction and appropriate use of new technologies [14]. 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 [15]. The CTA is related to a 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 [15-17]. 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 [17]. After the results of the controlled introduction trial were known [8], in The Netherlands a discussion was started as to 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 [14] (Figure 2).

For this purpose, first a 'conventional' cost-effectiveness analysis was conducted. A Markov decision model was used to simulate the 10-year costs and outcomes (survival and quality-adjusted life years (QALYs)) based on a pooled database of three retrospective validation series. When deciding upon the cost-effectiveness of the prognostic tests, the 70-gene signature has a high potential to improve QALY and has the highest probability of being cost-effective.

CHAPTER 3

The practice of pharmacoeconomics

Figure 4: Result consensus workshop on 10 alternative scenarios



SCENARIOS

Scenario drafting can be used as a tool in forecasting of new, still dynamic technologies. They are commonly applied in industry to anticipate on 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 [18], see Figure 3. These phases reflect the degree of spreading throughout the (medical) society. In the CTA-study, we applied scenario drafting in the case of the 70-gene signature. In the *innovation phase*, the prognosis signature technique was developed and the first organisations adopted (introduced) 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-2006). The *early majority phase* describes the implementation in a gradually increasing

number of hospitals and is ongoing. The 70-gene signature has now been implemented in 25 hospitals in Europe. The third scenario was written at the beginning of the MINDACT trial (mid 2008), in the late early minority/early majority phase. The third draft was written with professional feedback. We designed questionnaires which were sent to 100 European breast cancer experts and organised a consensus workshop in Bordeaux. The questionnaires and consensus workshop looked at six patient cases to investigate the compliance with the prognosis profile and ten different alternatives for the third scenario. The result of the consensus workshop was several probabilities (% of likeliness to happen within the coming 10 years) for the ten different scenarios (Figure 4).

DYNAMIC ECONOMIC EVALUATION

The scenarios drafted on the subsequent phases of diffusion reflect possible 'future worlds' of the use of the 70-gene signature. Probabilistic decision modeling 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 [19]. Cost-effectiveness Acceptability Curves will reflect the degree of decision uncertainty and Value of Information (VOI) analyses implies whether additional evidence to further inform the decision is worth gathering, and what kind of information is of the greatest value [20]. VOI is the amount a decision maker would be willing to pay for information prior to making a decision. Finally, the integrated scenarios and VOI analysis reveals factors that warrant intervention in the implementation process in case of the 70-gene signature [21].

CONCLUSION

Establishing the cost-effectiveness of genetic targeting of cancer therapies is increasingly desirable in an early stage

Constructive Technology Assessment is a possible answer to the (economic) evaluation challenges that new genomic technologies pose.

when 'traditional' prospective randomised controlled data are not within reach. In the MINDACT-trial that would take another 8–10 years and future technologies 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 even can 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.

REFERENCES

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet*. 2005;365:1687-717.
2. Mook S, Van't Veer LJ, Rutgers EJ, Piccart-Gebhart MJ, Cardoso F. Individualization of therapy using MammaPrint: from development to the MINDACT Trial. *Cancer Genomics Proteomics*. 2007;4:147-55.
3. Van't Veer LJ, Dai H, van de Vijver MJ, et al. Gene expression profiling predicts clinical outcome of breast cancer. *Nature*. 2002;415:530-6.
4. van de Vijver MJ, He YD, Van't Veer LJ, et al. A gene-expression signature as a predictor of survival in breast cancer. *N Eng J Med* 2002;347:1999-2009.
5. Buyse M, Loi S, Van't Veer L, et al. Validation and clinical utility of a 70-gene prognostic signature for women with node-negative breast cancer. *J Natl Cancer Inst*. 2006;98:1183-92.
6. Bueno-de-Mesquita JM, Linn SC, Keijzer R, et al. Validation of 70-gene prognosis signature in node-negative breast cancer. *Breast Cancer Res Treat*. 2009;117(3):483-95.
7. Mook S, Schmidt MK, Viale G, et al. The 70-gene prognosis-signature predicts disease outcome in breast cancer patients with 1-3 positive lymph nodes in an independent validation study. *Breast Cancer Res Treat*. 2009;116(2):295-302.
8. Bueno-de-Mesquita JM, van Harten W, Retel V, et al. Use of 70-gene signature to predict prognosis of patients with node-negative breast cancer: a prospective community-based feasibility study (RASTER). *Lancet Oncol*. 2007;8:1079-87.
9. Schot JW. Constructive Technology Assessment and Technology Dynamics: The case of clean technologies. *Sci, Technol & Human Values*. 1992;17:36-56.
10. Ravdin PM, Siminoff LA, Davis GJ, et al. Computer program to assist in making decisions about adjuvant therapy for women with early breast cancer. *J Clin Oncol*. 2001;19:980-91.
11. Bogaerts J, Cardoso F, Buyse M, et al. Gene signature evaluation as a prognostic tool: challenges in the design of the MINDACT trial. *Nat Clin Pract Oncol*. 2006;3(10):540-51.
12. Cardoso F, Van't Veer L, Rutgers E, et al. Clinical application of the 70-gene profile: the MINDACT trial. *J Clin Oncol*. 2008;26:729-35.
13. Mook S, Bonnefoi H, Pruneri G et al. Daily clinical practice of fresh tumour tissue freezing and gene expression profiling; logistics pilot study preceding the MINDACT trial. *Eur J Cancer*. 2009;45:1201-8.
14. Hutton J, Trueman P, Henshall C. Coverage with evidence development: an examination of conceptual and policy issues. *Int J Technol Assess Health Care*. 2007;23:425-32.
15. Douma KF, Karsenberg K, Hummel MJ, et al. Methodology of constructive technology assessment in health care. *Int J Technol Assess Health Care*. 2007;23:162-8.
16. Retel VP, Hummel MJ, van Harten WH. Early phase Technology Assessment of nanotechnology in oncology. *Tumori*. 2008;94:284-90.
17. Retel VP, Bueno-de-Mesquita JM, Hummel MJ et al. Constructive Technology Assessment (CTA) as a tool in coverage with evidence development: the case of the 70-gene prognosis signature for breast cancer diagnostics. *Int J Technol Assess Health Care* 2009;25:73-83.
18. Rogers EM. *Diffusion of Innovations*. 5th ed. New York: Free Press; 2003.
19. Briggs A, Claxton K, Sculpher M. *Decision Modelling for Health Economic Evaluation*. Oxford University Press; 2006.
20. Claxton K, Cohen JT, Neumann PJ. When is evidence sufficient? *Health Aff (Millwood)* 2005;24:93-101.
21. Retel VP, Joore MA, van Harten WH. Conference proceeding. Scenario drafting as a tool to perform early cost-effectiveness analysis: the case of the 70-gene signature in breast cancer. *International Health Economic Association*, 2009; Beijing, China.