Cancer Treatment Reviews 52 (2017) 117–127

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Anti-Tumour Treatment

(Very) Early technology assessment and translation of predictive biomarkers in breast cancer

Anna Miquel-Cases [a,1], Philip C. Schouten [b,1], Lotte M.G. Steuten [c], Valesca P. Retèl [a,d], Sabine C. Linn [b,e,f], Wim H. van Harten [a,d,*]

[a] Department of Psychosocial Research and Epidemiology, Netherlands Cancer Institute, Plesmanlaan 121, 1066CX Amsterdam, The Netherlands
[b] Department of Molecular Pathology, Netherlands Cancer Institute, Plesmanlaan 121, 1066CX Amsterdam, The Netherlands
[c] Hutchinson Institute for Cancer Outcomes Research, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave. N., P.O. Box 19024, Seattle, USA
[d] Department of Healthcare Technology and Services Research, University of Twente, Drienerlolaan 5, 7522 NB, Enschede, The Netherlands
[e] Department of Pathology, Utrecht University Medical Center, Heidelberglaan 100, 3584CX Utrecht, The Netherlands
[f] Division of Medical Oncology, Antoni van Leeuwenhoek Hospital – Netherlands Cancer Institute, Plesmanlaan 121, 1066CX Amsterdam, The Netherlands

ARTICLE INFO

Article history:
Received 29 July 2016
Received in revised form 20 November 2016
Accepted 21 November 2016

Keywords:
Health Technology Assessment
Predictive biomarkers
Breast cancer

ABSTRACT

Predictive biomarkers can guide treatment decisions in breast cancer. Many studies are undertaken to discover and translate these biomarkers, yet few biomarkers make it to practice. Before use in clinical decision making, predictive biomarkers need to demonstrate analytical validity, clinical validity and clinical utility. While attaining analytical and clinical validity is relatively straightforward, by following methodological recommendations, the achievement of clinical utility is extremely challenging. It requires demonstrating three associations: the biomarker with the outcome (prognostic association), the effect of treatment independent of the biomarker, and the differential treatment effect between the prognostic and the predictive biomarker (predictive association). In addition, economical, ethical, regulatory, organizational and patient/doctor-related aspects are hampering the translational process. Traditionally, these aspects do not receive much attention until formal approval or reimbursement of a biomarker test (informed by Health Technology Assessment (HTA)) is at stake, at which point the clinical utility and sometimes price of the test can hardly be influenced anymore. When HTA analyses are performed earlier, during biomarker research and development, they may prevent further development of those biomarkers unlikely to ever provide sufficient added value to society, and rather facilitate translation of the promising ones. Early HTA is particularly relevant for the predictive biomarker field, as expensive medicines are under pressure and the need for biomarkers to guide their appropriate use is huge. Closer interaction between clinical researchers and HTA experts throughout the translational research process will ensure that available data and methodologies will be used most efficiently to facilitate biomarker translation.

Introduction

Biomarkers are measurements of biological processes or disease that represent their state or activity. Since biomarkers signify a level of biological understanding, they can be exploited to improve research and clinical decision-making. For cancer treatment outcome, two types of biomarkers exist. Prognostic biomarkers associate with outcome and can help identify whether a patient should be treated. Predictive biomarkers, associate with outcome after a specific treatment and can guide the choice of treatment for an individual patient [1].

The neo-adjuvant (NACT) setting provides an in vivo research setting to identify predictive biomarkers. In this setting the expression of biomarkers can be characterized prior to systemic treatment and the response to the therapy can subsequently be measured in the surgical specimen. Significant amounts of effort and money have been put in identifying predictive biomarkers to systemic NACT [2]. However, despite many studies being undertaken, few of these biomarkers are actually used for clinical decision making [3]. Several reasons may prevent more effective translation. Statistically, studies are often poorly designed. Clinically they lack a relevant use, and biologically they underestimate the complexity of a drug's mechanism of action and signaling pathways that confer sensitivity and resistance. Furthermore, econom-

* Corresponding author at: Division of Psychosocial Research and Epidemiology, The Netherlands Cancer Institute, Plesmanlaan 121, 1066CX Amsterdam, The Netherlands.
E-mail address: w.v.harten@nki.nl (W.H. van Harten).
[1] First shared authorship.

http://dx.doi.org/10.1016/j.ctrv.2016.11.008
0305-7372/

ical, ethical, regulatory, organizational and patient/doctor-related aspects can affect translation as well.

Health Technology Assessment (HTA) is a multidisciplinary process that scientifically evaluates the medical, health economic, social and ethical aspects related to the adoption, implementation and use of a new technology or intervention. It aims to inform decisions on safe and effective health policies by seeking best value for money [4]. Traditionally, HTA does not receive much attention until the formal approval or reimbursement of a biomarker test is at stake. Early HTA refers to assessing these aspects alongside the basic, translational and clinical research process [5,6]. Early HTA can thus improve biomarker translation by preventing the further development of those biomarkers unlikely to ever provide sufficient added value to society, while facilitating the translation of promising ones [7]. Furthermore, it can be used to prevent late unfavorable assessments at the time the technology is being evaluated for cost-effectiveness and after big investments are done [8]. Common early HTA methods include literature reviews, evidence synthesis, decision analysis and health economic modeling as well as formal qualitative methods to elicit expert opinions and perform multi-criteria assessments for example in focus group discussions [5,9].

In this manuscript, we discuss the clinical challenges in the translation of predictive biomarkers for NACT in breast cancer and provide concrete guidance on how the use of early HTA methods can support this process.

Types of treatment biomarkers

For treatment outcomes two types of biomarkers exist. Prognostic biomarkers inform on who to treat and predictive biomarkers inform on how to treat. The investigations of predictive biomarkers have to take into account three associations: the biomarker with the outcome (prognostic association), the effect of treatment independent of the biomarker, and the differential treatment effect between the prognostic and the predictive biomarker group (predictive association) [10–17]. Understanding these relations is important to choose the proper clinical action: to treat or not to treat in situations of good or very poor prognosis (prognostic biomarker), or to apply a treatment that is effective only in a subgroup of patients (predictive biomarker). For a hypothetical biomarker, survival curves that demonstrate prognostic value, treatment effects and predictive value are shown in Fig. 1. The overall landscape of the use of biomarkers for a particular population of patients can be illustrated by the therapeutic response surface [18], as shown in Fig. 2. This figure describes the relationship between treatment (drug and/or doses), sorted by prognostic characteristics, and clinical benefit of adding the treatment of a biologically homogeneous group of cancers. Through that figure one can identify patients for whom treatment should be spared, due to their exceptional prognosis or due to their increased risk of suffering from toxicities, and patients for whom additional treatment is likely to be beneficial, due to their poor prognosis in combination with on target treatment.

If we describe the figure from the easiest to the most complex concepts, the easiest area to see is that of ineffective treatment i.e., the treatment does not add any benefit, despite the fact that some patients may seem to do well due to the good prognosis of their tumor. Some early stage tumors may have such good outcome that treatment is not advised, prognostic markers or characteristics should be used to identify these and spare patients the treatment. If one would use a predictive biomarker in this group, it could select patients and the therapy could seem efficacious given the good outcome. The extra benefit however would be smaller or non-existent due to the good prognosis from the outset. Predictive biomarkers can be identified as those markers that find groups of patients that benefit especially from a specific treatment (or dose). Suppose that the figure describes a homogenous group that can be identified by one biomarker. There would be one treatment option that adds benefit to all patients except those with good prognosis. This is illustrated by the ridge halfway the treatment axis in the figure. Additionally, some treatments may only add benefit to patients with intermediate prognostic characteristics and not those with poor characteristics. This may describe treatment burden-toxicity considerations. For example, in the case of two patients; one being young and without comorbidities, and one being older with many comorbidities, a treatment associated with high toxicity may only benefit the first, as shown in the figure by benefit decreasing in the area representing characteristics associated with poor prognosis.

Translating predictive biomarkers

To translate a biomarker from bench to bedside evidence should demonstrate that the test is reliable (analytical validity), that it separates a population in clinically relevant subgroups (clinical validity), and that applying the test results in improvement of clinical outcomes compared to not applying the test (clinical utility) [19–22,17]. To address these criteria, predictive biomarker investigations typically involve multiple, often overlapping stages [19,23–25,1,12,26,27] (see Fig. 3). After discovery, investigations range from laboratory experiments, to data mining exercises or clinical studies that aim to understand biological and/or clinical outcomes. Subsequently, the test may be improved. This can be done sequentially or in parallel with demonstrating its use in clinical studies [1,12,28]. The amount of evidence needed to demonstrate clinical utility will be weighed on a per-biomarker basis. The process may consist of differing combinations of studies [1]. Multiple rounds of testing may be performed until sufficient quality of the test and validation has been reached for regulatory approval. This differs between countries. For instance in the US, approval is granted countrywide by the FDA, while in Europe this is the responsibility of national certified bodies. Furthermore, as commercialized biomarker tests are considered high risk medical devices [29,30], they need to demonstrated safety and performance in Europe (to get a CE-mark [31]) and safety and effectiveness in the US (to get premarket approval [30]). If biomarkers tests are, on the other hand, developed as in-house tests and performed in specific health care institutions, the situation differs. In the US one will require a lab certification according to the Clinical Laboratory Improvement Amendments (CLIA)[32], while in Europe there is no applicable regulation yet (although the medical device directive is currently being revised [33]). Subsequently after having demonstrated clinical utility and being formally approval, one would expect that the test is fastly adopted in clinical practice. However this is not often the case. In most countries, the achievement of reimbursement is a key step for wide spread use of the biomarker test, and without it, adoption is limited. Even with reimbursement, adoption is can be slowed down by the financial, human and knowledge –barriers of implementing the biomarker to the hospital.

Studies on predictive biomarkers do not reach a high level of evidence

Case study: predictive biomarkers for NACT in breast cancer

We performed a systematic search to identify tumor biomarkers that predict NACT response in breast cancer ($n = 134$, specific methods are described in the annex). Based on the type and quality

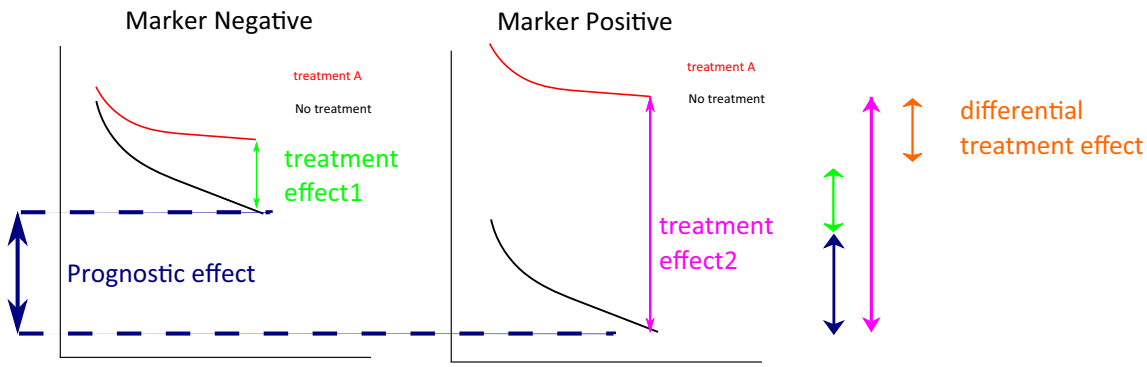

Fig. 1. Prognostic, treatment and predictive effect. In this figure, hypothetical Kaplan–Meier curves resulting from biomarker-negative and -positive cases are shown. Patients have been treated with a specific treatment (A) or nothing. Two treatment effects can be observed (1 and 2), the prognostic effect is the difference between the non-treated biomarker-positive and negative patients. A differential treatment effect gives the predictive value.

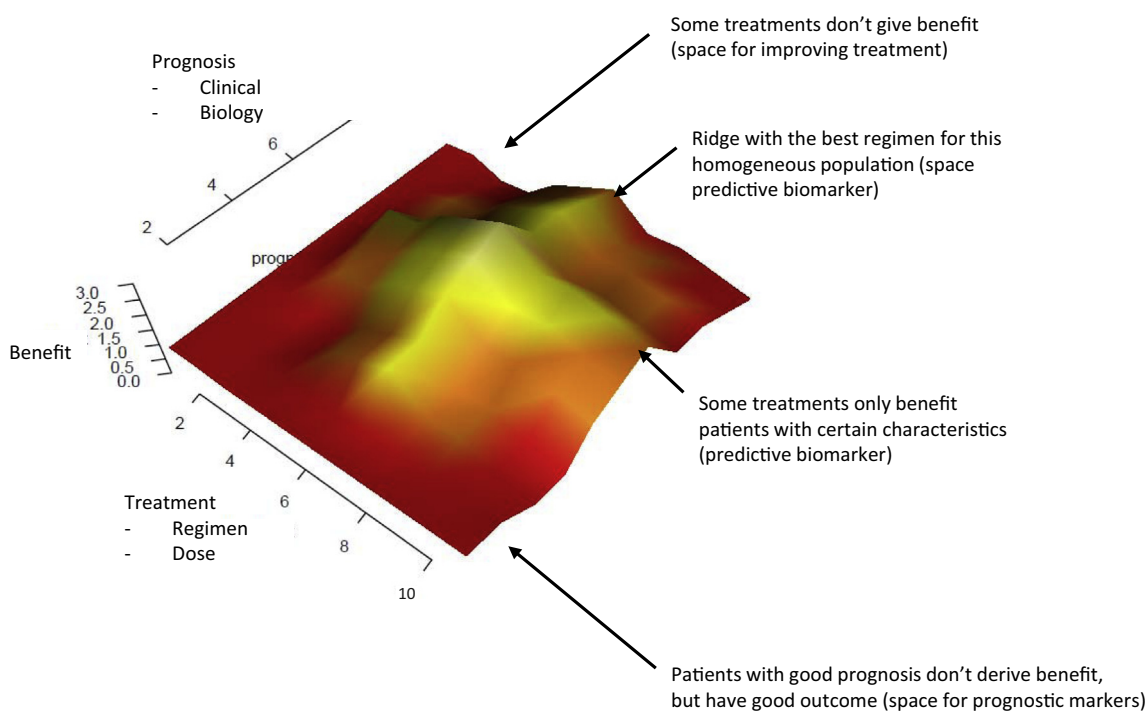

Fig. 2. Therapeutic response surface plotting clinical prognostic characteristics on the *x*-axis, treatment regimen and dose on the *y*-axis and clinical benefit on the *z*-axis. Several important regions are signaled: prognostic marker area, predictive biomarker area, the overlap between prognostically poor and predictive biomarker area (in which a predictive biomarker adds benefit), the areas in which treatments are not working, and the area in which treatments may work but do not give benefit due to for example high toxicity.

of the identified studies, we concluded that biomarkers of NACT for breast cancer are in early stage evaluation. The characteristics of the identified studies are summarized in Fig. 4. We found that drugs involved were generally standard NACT (regimens), that few genes have been investigated more than once (either in different studies or with different tests) and that all studies had a control for biomarker negative patients. On the other hand, only 8% (11/134) of the studies used control groups without the treatment of interest, and even those that had options for controlling did not. Based on the reported analysis interpretation, many studies found that the marker under investigation could be predictive. In those without control groups the amount of 'positive' studies was about 69% (85/123) versus 60% (6/10) in those with control groups. These conclusions can be misleading in the absence of control groups.

Challenges in translating predictive biomarkers

Our review showed that biomarkers of NACT for breast cancer are in early stage evaluation. The underlying success in the translation of a predictive biomarker is the final demonstration of clinical utility. This requires the right choice of biomarker, treatment and outcome and application, as well as subsequent validation.

With regards to the biomarker, in principle, any biomarker/mechanism or biological entity can be investigated. Similarly any single drug or drug regimen can be investigated in relation to the biomarker. It is likely that resistance and sensitivity mechanisms are drug specific. Hence for the dissection of such mechanisms, ideally, only one treatment variable should be tested in the study design. The design could be drug A versus nothing, drug A versus

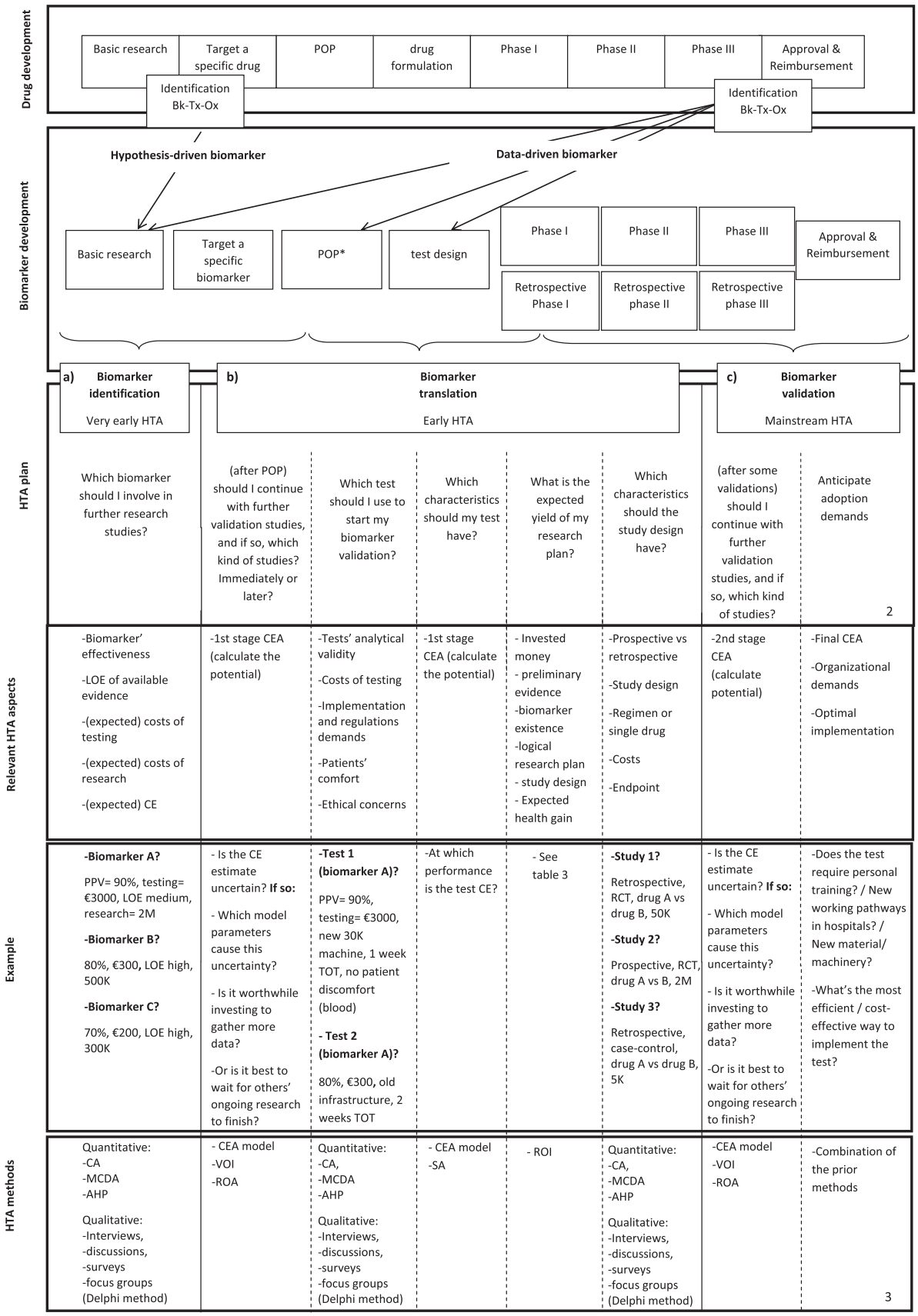

Fig. 3. Moment and type of decisions that (very) early and mainstream HTA can inform along the predictive biomarker research continuum. *POP = proof of principle study, refers to the first in-human study. From an HTA perspective it is important to discern this because it provides the first. Abbreviations: CE = cost-effectiveness analysis (CEA); CA = Conjoint analysis; MCDA = Multi criteria decision analysis; AHP = hierarchical analytical process; VOI = value of information analysis; ROA = real options analysis; RCT = randomized clinical trial; TOT = turnaround time ; ROI = return on investment; LOE = level of evidence; PPV = positive predictive value;, SA = sensitivity analysis; Bk-Tx-Ox = Biomarker-treatment-outcome; HTA = Health Technology Assessment.

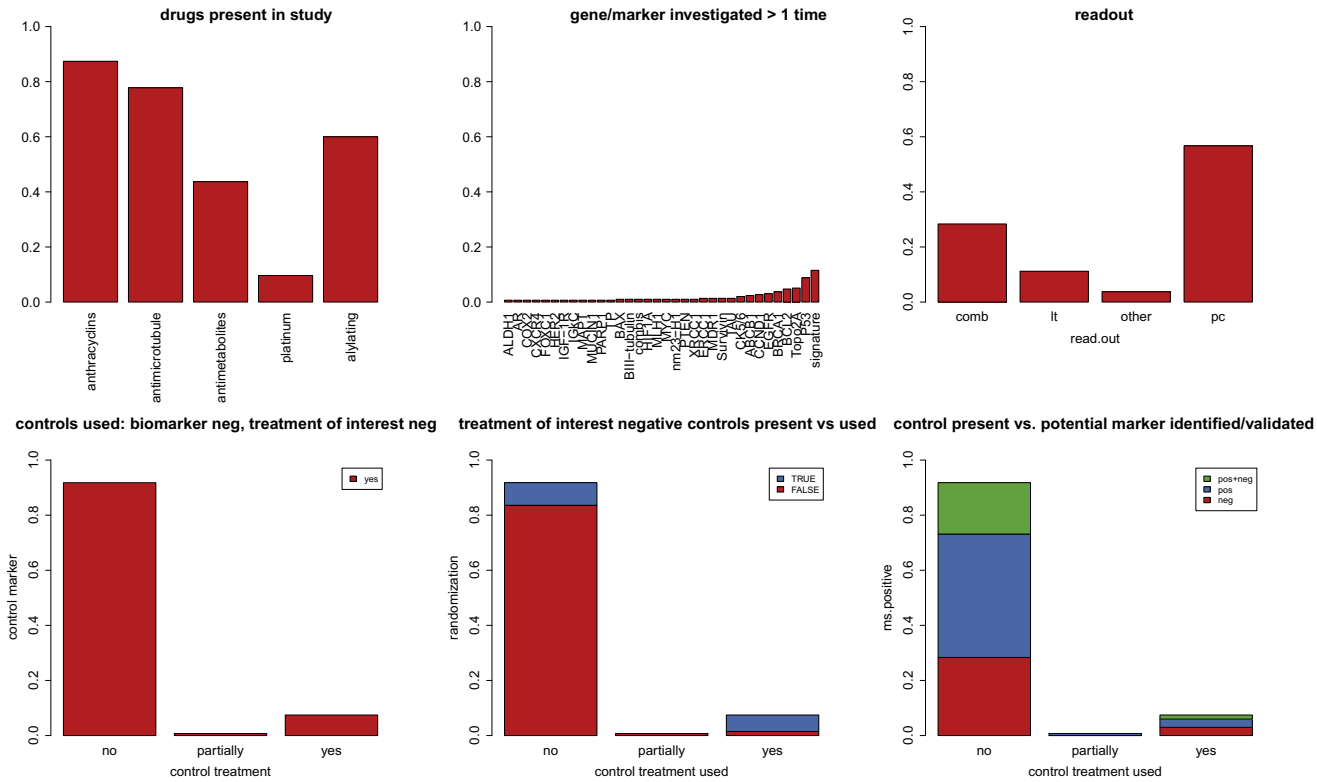

Fig. 4. Summary of the study characteristics of literature review. Top left: percentage of studies with a particular class of drugs. Top middle: genes investigated more than 1 time. Note signatures is a summary, individual signatures have been investigated very little. Top right: percentage of outcomes, cmb = combined long term and pCR, pc = pCR, lt = long term, other = none of the other. Bottom left: percentage of biomarker negative controls used and non-treatment-of-interest controls. Bottom middle: percentage of studies that could have used a control treatment but that did not do so. On the *y*-axis is plotted whether control treatment was used, the colors represent whether the control treatment was present (blue = present, red = absent). Bottom right: percentages of positive (pos), negative (neg), and mixed (pos + neg) results plotted by whether a control treatment of interest was used. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

AB, or combo AB versus ABC, etc. Instead, if drug A is compared to drug B, or combo ABC with combo CDE, it won't be possible to dissect single drug resistance or drug sensitivity mechanisms anymore. However, treatment in the NACT setting is in principle curative, therefore, it is ethically impossible to withhold proven or administer only unproven treatments, thus many studies have mixed effects. That is why trying to identify biomarkers in these studies could be heavily confounded. Knowing this, it is important to include control groups for the biomarker (negative and positive) and for the treatment (treatment of interest and a comparator) and derive the treatment effect, prognostic effect and predictive effect of the biomarker [10–17]. If the theoretically best control is not available, resorting to a control group with the current clinical best practice is essential as it sets the minimal expected performance.

Regarding the clinical outcome, it remains important to carefully choose the endpoint that fits with the intended application and aim. The NACT setting provides rapid assessment of biomarker effectiveness by means of pathologic complete response (pCR), a surrogate endpoint of long-term survival [34,35]. Although pCR has gained acceptance in research and in the clinics, its association with long-term survival is not straightforward [36–38]. While pCR is a measure of local treatment effect, which measures tumor shrinkage, long-term survival is a measure of systemic treatment effect, which measures the presence or absence of events as consequence of the presence or absence of micro-metastasis. The outcome measure should give insight into the sensitivity of the cancer cell population (e.g. (a clone of the) primary lesion, metastatic lesion, a stem-cell population, etc.) that determines the overall prognosis. Differences between the measured population and this population will lead to unexpected results, i.e., bad outcome where expected a good one, or vice versa. The interpretations that may derive from the use of pCR to predict survival are summarized in Table 1. In some cases the early response measured by pCR translates well into improved patient survival, this is the case of patients in the case mix in the grey row. However in most of the cases it does not, as shown in the white rows. The majority of breast cancer subtypes in the case mix where pCR does not translate into improved breast cancer specific survival i.e., luminal B/HER2-positive or luminal A tumors probably fall in these last categories. Hard endpoints like relapse free survival (RFS), distant metastasis free interval (DMFI) or overall survival (OS) are measures of systemic treatment effect. Their downside is the confounding due to additional adjuvant and/or metastatic treatment and due to competing risks, next to the lengthy time required for its measurement.

The combination of a specific biomarker, treatment and outcome sets the stage for the envisioned application and investigations needed. This combination needs to show analytical validity, clinical validity and clinical utility. While many problems that can arise during the analytical validity and clinical validity phases i.e., using correct study designs or analytical robustness, can be tackled by strictly following known methodological recommendations or guidelines [1,10,21,39], demonstrating clinical utility is rather difficult. This is the consequence of the majority of clinical datasets not providing high levels of evidence (LOE), for example due to missing control groups. Furthermore, for some applications, no suitable clinical dataset may be available. For example, biomarker-drug combinations that were identified in modeling

Table 1
Interpretations that derive from the use of pCR to predict survival.

Measured outcomes		Interpretation	Underlying research question
Surrogate outcome	Long term outcome	Can treatment downsize tumour for breast conserving surgery?	Can treatment eliminate micrometastases that would otherwise grow into macrometastases using pCR as a read-out?
pCR – at diagnosis no micrometastases present that could turn into macrometastases	Favourable	Yes	Incorrect interpretation that treatment can eliminate micrometastases that could turn into macrometastases
No pCR – at diagnosis no micrometastases present that could turn into macrometastases	Favourable	Depends on amount of downsizing achieved, tumour size at diagnosis, and breast size	Confounder in 'poor' prognosis distant-recurrence free interval curve – since no pCR was achieved
pCR – at diagnosis micrometastases present that could turn into macrometastases	Favourable	Yes	Correct interpretation that treatment can eliminate micrometastases that could turn into macrometastases
pCR – at diagnosis micrometastases present that could turn into macrometastases	Distant recurrence	Yes	Incorrect interpretation that treatment can eliminate micrometastases that could turn into macrometastases; primary tumor is eliminated, but not micrometastatic tumor cells
No pCR – at diagnosis micrometastases present that could turn into macrometastases	Favourable	Depends on amount of downsizing achieved, tumour size at diagnosis, and breast size	Incorrect interpretation that treatment cannot eliminate micrometastases that could turn into macrometastases; primary tumor is not completely eliminated, but micrometastatic tumor cells are
No pCR – at diagnosis micrometastases present that could turn into macrometastases	Distant recurrence	Depends on amount of downsizing achieved, tumour size at diagnosis, and breast size	Correct interpretation that treatment cannot eliminate micrometastases that could turn into macrometastases, since primary tumor cells cannot be eliminated completely either

systems may not have a clinical dataset in the neoadjuvant setting. Additionally, many neoadjuvant biomarker studies do not use a control treatment since it is thought that pCR is a direct proof of *specific* treatment efficacy. When data-mining is performed in such cohorts it is easy to identify confounded associations as interesting. These are examples that show that identifying and establishing the predictive value of a biomarker may be jeopardized by design limitations [17].

Concluding, for any biomarker-treatment-outcome analysis intended for implementation, the application is a specific case for which high LOE needs to be gathered. This is important because from this application a particular clinical decision will follow i.e., withholding or giving a specific treatment. Any non-high-level, circumstantial evidence or evidence that fits another application should thus be considered too early. Randomized trials provide the most optimal setting in which this interaction can be investigated properly.

The role of early Health Technology Assessment

While medicine and biology form the basis for predictive biomarker research, economical, ethical, regulatory, organizational and patient/doctor-related aspects influence biomarkers' translation and adoption as well. These aspects are often assessed nearing decisions on coverage or reimbursement. However, if HTA analyses were performed earlier ((very) early HTA), during biomarker research and development, it could prevent the further development of those biomarkers unlikely to ever provide sufficient added value to society and rather facilitate translation of the promising ones. Furthermore, it could help appraising other relevant aspects timely, as the trade-offs with alternate approaches or the performance requirements for a specific technology to reach cost-effectiveness [7].

In Fig. 3, we present the moment and the type of decisions that (very) early and mainstream HTA can inform along the predictive biomarker research continuum. The difference between very early and early HTA mainly lies on the availability of evidence from the assessed technology (very limited at the time of using very early HTA), and the methodology used (more use of modeling methods and assumptions in very early HTA). Furthermore, in Fig. 3 we provide a sample of common HTA methods used to inform these decisions. This does not provide all existing HTA methods (most of them can be found in references [5,9,40]), but highlights those that seem specifically useful for predictive biomarker research. Descriptions of the technical methods are provided in Supplementary Table 2.

(Very) early HTA is not yet used to assess predictive biomarkers

Case study: predictive biomarkers for NACT in breast cancer

We performed a systematic search to identify the current use of early HTA methods during the research and translation process of predictive biomarkers for NACT treatment in breast cancer ($n = 31$, specific methods are described in the Supplementary material). These studies were classified on being on very early, early or mainstream HTA according to Fig. 3, and on whether they described clinical, economic, ethical, organizational and patient/doctor related aspects. The identified studies were classified either as early or mainstream HTA, but none as very early HTA. Almost all early HTA articles reported on the comparative effectiveness of testing techniques [41–45]. Only one article presented an early stage cost-effectiveness analysis [46]. Another article presented an organizational and/or implementation aspect; the increase in uptake of a biomarker test as a consequence of new potential clinical applications [47]. Opinion leaders attitudes were used to gather potential issues arising from 'treatment-focused' genetic testing in one article [48].

The findings of our exploratory review on early HTA were similar to those of a 2014 review on early HTA for medical devices [9], where no studies for predictive biomarkers for breast cancer were found.

Improving the translation of predictive biomarkers from an HTA perspective

Our systematic review found that (very) early HTA is not applied along the research process of predictive biomarkers for

NACT treatment in breast cancer. Different HTA aspects are relevant to address different type of decisions during the research process and can facilitate translation (Fig. 3 contains all references to methods).

Biomarker identification (a, Fig. 3)

At this stage, the presence of limited budgets and/or time can force researchers into decisions on which biomarker to involve in further investigations i.e., biomarker A (90% positive predictive value (PPV), medium LOE, €3000 expected testing costs and 2 M expected validation costs), biomarker B (80%, high LOE, €300 and 500 K) or biomarker C (70%, high LOE, €2000 and 300 K)? As illustrated, aspects likely to play a role on this decision are the biomarker's PPV, the LOE of this evidence, the expected costs of testing and the expected costs for its validation. The conjoint analysis (CA), the multi criteria decision analysis (MCDA) and the analytical hierarchical process (AHP) are methods that can be used to prioritize these biomarkers, in a step-wise approach by using the aforementioned relevant aspects to compare and judge them. These judgments are made by a selected group of doctors, patients, developers, payers and/or policymakers. They are all decision-makers along the development process and can provide useful knowledge to the decision. In some situations, the evidence to characterize the aspects of the biomarkers will not yet be there i.e., the PPV of the test is not clear. In such cases, prior to starting the CA, MDCA or AHP process, estimates for these aspects can be derived by means of expert elicitation methods (via CA, MCDA, AHP or other elicitation methods) or by extrapolation from similar biomarker-drug cases (see methods of Supplementary Table 2 with references to case studies). In other situations, a quantitative-driven decision may not seem applicable yet. In this case, biomarker selection can be made via (semi) qualitative methods such as interviews, discussions, survey or focus groups (Delphi method). These methods allow a more flexible decision-making process and they are already common practice.

Biomarker translation (b, Fig. 3)

After biomarker selection has been made and the first proof of principle (POP) study has been conducted (refers to the first in-human study), the researcher questions whether more research towards biomarker validation should be continued. Assuming the endpoint of research is maximizing health outcomes with the resources available to society, this question can be answered by using the value of information analysis (VOI) method. VOI execution requires a prior construction of a CE model (with the POP data) and a first stage CEA. VOI analysis will translate the magnitude of uncertainty around this first cost-effectiveness estimate into a monetary value that could lead to full certainty on the biomarkers' CE. This value (the expected value of perfect information (EVPI)) is subsequently compared to the expected costs of conducting further research, and if these are lower, it suggests that conducting further research is worthwhile. Further calculations of the VOI analysis can help determining for which data type is most beneficial to conduct research i.e., PPV of the test or quality of life of the administered treatment (the expected value of partial perfect information (EVPPI)), and which type and magnitude of study designs should be conducted (Expected value of sampling information (EVSI)). A next relevant question is the timing to start these studies. The real option analysis (ROA) method helps deciding when it is most worthwhile to undertake this research. Whether it is best to invest on further research immediately or whether it is best to wait for current ongoing studies to be finished before investing. Maybe these studies already provide some evidence that can increase the CE uncertainty without needing investment. This option takes into account the costs of withholding the use of the biomarker and thus the possibility of giving suboptimal treatment to patients in the meantime. ROA is especially useful at these stages of development, when large investments are still expected.

Upon the decision of starting further biomarker validations, a biomarker test needs to be chosen. Available tests to measure one biomarker may have very different characteristics i.e. test 1 (PPV 90%, €3000 expected testing costs, new 30 K machine, 1 week turnaround time (TOT), patient comfort (blood)) or test 2 (80%, €300, old infrastructure, 2 weeks TOT)? As illustrated, aspects likely to play a role on this decision are the tests' analytical validity, the expected costs of testing, its implementation and regulatory demands, the patients' comfort, and ethical concerns. This choice can be made by using the same methods described in the biomarker identification stage. Yet in the case evidence to define the biomarkers' aspects is lacking, other methods than the previously described are useful. For instance, usability testing to determine patients' comfort during the usage of a specific test, or the multi-path mapping tool to forecast the implementation demands of the test (see Supplementary Table 1).

Biomarker tests performance has traditionally been guided by effectiveness. By accounting for the costs associated to false cases, a more realistic minimum performance that can warrant the tests' clinical application can be determined. This can be achieved by using the (likely) already built CE model together with the one-way sensitivity analysis (SA) method. This means varying model parameter values that represent performance in the model to determine the minimum performance values where cost-effectiveness remains and to see which parameters drive the cost-effectiveness. The SA method can be used any time during biomarker development to explore how new features of the test affect CE. It is essential that this goes along with updates on clinical and economic evidence in the CE model.

Another consideration that may be relevant at this point is to anticipate the expected yield of future investigations and its associated investments. Its evaluation can be done by using the concept of returns on investment (ROI). By drawing a likely research plan for the specific biomarker and considering the amount of money invested and the expected health outcomes gained in return. Hypothetical scenarios on possible 'research plans' for predictive biomarker development and its economic and health consequences are explained in Table 2. The scenarios show that opting for the speedy solutions with wrong study designs (scenario 1) or basing research on unreliable preliminary evidence (scenario 2) can lead to futile expenditures. On the other hand, investing in basic research endeavors or prospective validation studies, that seem more costly at the onset, is likely to lead to improved health outcomes (scenario 3). Using this line of reasoning one can build other scenarios in which to assess the economic and health consequences of a desired research plan.

While ROI type of analysis can provide an overview of the consequences of a specific research plan, the use of CA, MCDA or AHP methods can help optimally designing each validation study. The basis is to consider the high costs of setting up new studies with the optimal features these can offer versus the of use already available data which is less costly but comes with limitations (retrospective, presence/absence control group, availability of hard endpoints or drug administered alone) i.e., choice between study 1 (retrospective, RCT, drug A vs drug B, 50 K), study 2 (prospective, RCT, drug A vs B, 2 M) or study 3 (retrospective, case-control, drug A vs drug B, 5 K)? This choice will be driven by the timing of the study (prospective vs retrospective), the understanding of the underlying biological mechanism, the study design, the presence of a drug regimen or single drug, the costs of the study and the

Table 2
Hypothetical scenarios on possible 'research plans' for predictive biomarker development and its economic and health consequences. These scenarios are composed of four characteristics: (1) whether a consistent path of investigations for the aim is followed, (2) whether the studies are designed properly; (3) whether the preliminary evidence is strong and reliable; and (4) whether the biomarker under investigation actually exists. Based on those, we hypothesized discovery paths that a biomarker may follow and whether approval and reimbursement of the biomarker test can be obtained.

	Reliable preliminary evidence	Biomarker exists or test is reliable	Logical steps for the plan/all evidence is contributing	Proper study designs	Basic research/ retrospective trials	POP/ First in Human	Prospective Trials	Evidence sufficient for approval and use	Sufficiently cost-effective for reimbursement	Total investment compared to best case scenario	Economic outcome	Health outcomes
Scenario 1	Yes	No	No	No	Yes	Yes	Yes	No	N/a	Equal to reference	High loss (invested money)	High loss (not improved)
Scenario 2	No	Yes	Yes	Yes	Yes	Maybe	No	No	N/a	Lower	Low loss (based on wrong evidence)	High loss (not improved)
Scenario 3	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	Reference	Well invested	Improved

Health: high loss = something that is not used.
Costs: high loss = many studies vs early stop.

endpoint. In this case, the execution of CA, MCDA or AHP methods should include other specialized experts, such as statisticians, molecular biologists and/or epidemiologists. The final choice can be further investigated by using clinical trial simulations (CTS) that can explore the effects of specific design assumptions to the expected outcomes.

Biomarker validation (c, Fig. 3)

Prior to each validation study, one will reflect upon the need for a further study, the nature of the study and the timing of such study. By updating the CE model with the newly generated evidence and using the CEA, VOI and ROA methods, as explained in the biomarker translation phase, these questions can be answered taking the broader health economic perspective. Furthermore, decisions on study design characteristics can be assessed at any time as explained in the biomarker translation phase.

Finally, once biomarker clinical utility is almost demonstrated, questions on future adoption and implementation demands become relevant. For instance, does the test require personnel training, the generation of new working pathways or the purchase of machinery? It is likely that during prior stages of the biomarker development process these questions have already been addressed (via previously mentioned methods like interviews, discussions or MCDA type of methods). Additional issues to address at this stage are the availability of resources for immediate implementation of the biomarker. A quantitative method specially formulated to anticipate and quantify demands is resource-modeling analysis. Also important is to determine the optimal implementation scenario for the test. This can be determined by using the SA method together with the final updated version CE model. For instance, it can determine the optimal turn-around time for the test by varying the parameter values that represent material and personnel requirements. Last, the final cost-effectiveness of the test can be determined. Recently, Coverage with Evidence Development (CED) programs were initiated throughout Europe and the US. These programs contain a (randomized) controlled trial including a broad Health Technology Assessment, where the new technology/drug is already being reimbursed. This program seems to be highly applicable for this setting. A first example has recently started in the Netherlands ('BRCA1-like biomarker for stage III breast cancer).

Important to highlight is that integration of HTA into the biomarker development process requires communication between researchers, clinicians, health-economists and decision-makers. This cooperation is necessary to ensure that all the relevant questions to move forward the biomarker translation process are answered and that appropriate data and methods are used. Partnerships like the Canter for Translational Molecular Medicine (CTMM) in the Netherlands [49] or the INterdisciplinary HEalth Research International Team on BReast CAncer susceptibility (INHERIT BRCAs) in Canada [50] have demonstrated that collaborations result in solid scientific impact and accelerated translational research.

As explained before, whether a biomarker will be useful depends on a lot of factors. The available information may differ per biomarker and therefore HTA methods can be used to assess the expected performance and whether it's worthwhile to continue validation of a particular biomarker. Examples of a biomarker that could likely be useful in the short-term and one that is doubtful are *BRCA1*-like status and *Xist* expression [46,51]. Summarizing the extensive analysis described in the respective manuscripts, the BRCA1-like status could be useful because its current performance is nearly at the minimum level required for the test to achieve cost-effectiveness (as shown in an early CEA). On the contrary, the amount of data required to validate whether the Xist expression

biomarker is cost-effective is so high that it becomes doubtful whether it is worthwhile to continue with its research (as shown in an early CEA and VOI analysis).

Box 1 provides a summary of the review in 7 key points.

Box 1

- Our investigations concluded that predictive biomarkers for neo-adjuvant treatment of breast cancer are in early stage evaluation and that (very) early HTA is hardly being used.
- There is no best investigational nor HTA framework for predictive biomarkers, and it is likely best to keep analyses case-specific.
- Predictive biomarker research requires specific study design choices to characterize the treatment effect, prognostic effect and predictive effect in a biomarker-treatment-outcome combination.
- Predictive biomarker research could be planned based on current evidence but taking into account future required investigations and associated investments that go with it.
- Use the HTA and study design methodology appropriate for the current investigational stage critically, to make explicit why or how a certain study contributes to reaching a specific target.
- Consider early on research and during development the regulatory, organizational, patient-related and economic requirements of biomarker development and involve expert help.
- Different HTA methods can inform different decisions during biomarker research. While multiple choice decisions can be informed by using CA, AHP and MCDA methods, decisions on the continuity and design of further research can be informed by using the CE model together with CEA VOI, ROA methods.

Outlook

It is likely that the use of predictive biomarkers will become more prevalent. We will describe the advances in this field by using the previously mentioned components of a successful predictive biomarker: the biomarker, the treatments, the outcome and the relation between these three parameters. Regarding the biomarker, our understanding of tumor biology has greatly expanded due to the use of high throughput methods, allowing for simultaneous assessment of tumors at DNA, RNA and protein level [52]. In combination with experimental data, discovering mechanisms of action should improve the chances of finding predictive biomarkers. However, it has also become clear that tumors are more heterogeneous than often described before [53]. Evolutionary pressure exists both intrinsically as well as extrinsically, by applying selection through therapies. Under these pressures, multiple resistance mechanisms may be present or develop [53]. This heterogeneity should be taken into account for predictive biomarkers. For example, it could be that differential sensitivity between the primary tumor and occult systemic disease exists, especially when NACT is used in presence of occult systemic disease. Measuring biomarkers in the tumor is an invasive procedure and the development of bloodstream biomarkers is promising. Yet it has to be proven, first, whether the ease of assaying outweighs the uncertainty on which lesion is being investigated, and second, whether the bloodstream ("liquid biopsies") can be used sufficiently reliable to forego tumor sampling [54,55]. Focusing outside of the tumor, host factors can affect the sensitivity of these, as they contribute significantly to varying drug responses. For instance, drug metabolism (pharmacodynamics) has been recognized to result in different levels of drugs exposure. The dose of drug (regimens) administered is widely optimized to be as high as possible while having acceptable toxicity for a large population. This results in the under-treatment of some patients, whereas other patients develop unacceptable toxicity [56–59]. Another host factor currently being investigated is the immune/tumor microenvironment system, which also seems to contribute or shape drug response [60]. First, the immune system may be sensitized to attack tumor cells or already work to keep the tumor from expanding in a balance between tumor growth and immune cell killing. Contrary to this tumor-suppressing role, the immune system's tumor promoting role may be important. Both the immune system and microenvironment may act as protective factors against therapy. The compromised or tumor-recruited microenvironment could therefore be predictive for response [61].

Regarding the drugs a range of new drugs targeted at specific proteins are being developed aiming for a more specific killing of tumor cells [62,63]. With this increased target specificity, developing companion diagnostic may become more straightforward or even already available from outset. These targeted therapies are increasingly added to drug regimens used in the NACT setting [64]. Although currently used chemotherapy drugs were identified in screening efforts the identification of its mechanism of action to improve efficacy, reduce toxicity, and predict their resistance/sensitivity is an ongoing effort [65–70]. This knowledge and new biomarkers could make 'untargeted' drugs similar to newly mechanistically developed targeted drugs. Both old and new drugs may have unexpected efficacy in certain subsets of tumors that was previously overlooked due to the then current standard of developing drugs for the whole tumor populations rather than a more targeted approach. Linking the improved tumor characterizations to better characterized cohorts likely will improve understanding of reliable endpoints [71,37,72–74]. It will also facilitate the translation to clinical practice of biomarker-drug combinations that meaningfully improve treatment outcomes.

Although the overall recommendations for the statistical analysis and study design remain in place [1], the introduction of genomic measurements in clinical trials has yielded new study designs. Umbrella and basket, in which respectively one experimental platform is used to find actionable alterations for a variety of drugs and a heterogeneous group of tumor types or alterations to be investigated for a response to a single drug (regimen) in one trial [75,76]. Furthermore, clinical trials can be of adaptive design, which allows statistically valid modification of the clinical trial course based on the results that are being accumulated in the same trial [77,78]. Although, new types of trials also contain their particular characteristics [75], they'll likely lead to some improvement of efficiency in the identification and validation of biomarker-drug combinations.

The use of early HTA is still not incorporated into routine practice, yet it is expected to become more common [79]. Especially in the predictive biomarker field, as expensive medicines like nivolumab are increasingly used for the total population and the urge for biomarkers is huge. Early HTA can help making the biomarker research process more efficient, so as to prevent futile investments and delays in patient access. With the raise of multiple testing, the use of panels and whole genome testing, the construction of CEA models will become more complex, the amount of effectiveness data originating from studies that are not RCTs (e.g., practice based studies) will increase and we will be facing so far unaddressed ethical and organizational concerns. This will require the development of innovative evaluation frameworks outside the traditional model-based CEA, where the remaining HTA aspects have more weight in decision-making. Furthermore, these assessments will

be required to be more iterative, rapidly incorporating new evidence and re-calculating outcomes.

Concluding, we found that research on biomarkers (in NACT) is methodologically weak and provided suggestions for improvement that are of a rather basic methodological nature. Early stage HTA can be more fully exploited in assisting in- and preparing for bringing the findings to the next translational development stage (or falsifying developments in a timely way). Closer interaction between clinical researchers and HTA experts may smoothen these processes. With the lessons from the past, the current possibilities of techniques, exciting times are ahead that may improve therapy choices for patients by optimizing existing applications and discovery of new options.

Declarations of interest

LMGS, VPR, SCL and WHV declare no conflict of interest. AMC declares that she is currently an employee of AstraZeneca SA, while this publication was prepared before this employment status. PCS declares that a direct family member is currently an employee of AstraZeneca SA, while this publication was prepared before this employment status.

Submission declaration

This work has not been published previously and it is not under consideration for publication elsewhere.

Its publication is approved by all authors, and if accepted it will not be published elsewhere including electronically in the same form, in English or in any other language, without the written consent of the copyright-holder.

Contributors

AMC and PCS have contributed to conception and design, data acquisition, data analysis, data interpretation, and manuscript writing. LMGS and SCL have contributed data interpretation and manuscript adaptations for important intellectual content. WVH and VPR contributed to conception and design, data interpretation, and manuscript writing. All authors have read and approve of the final version of the manuscript.

Role of the funding source

This work was supported by the Center for Translational Molecular Medicine [CTMM project Breast CARE, Grant No. 03O-104].

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ctrv.2016.11.008.

References

[1] Hayes DF. Biomarker validation and testing. Mol Oncol 2015;9:960–6. http://dx.doi.org/10.1016/j.molonc.2014.10.004.
[2] Ptolemy AS, Rifai N. What is a biomarker? Research investments and lack of clinical integration necessitate a review of biomarker terminology and validation schema. Scand J Clin Lab Investig Suppl 2010;242:6–14. http://dx.doi.org/10.3109/00365513.2010.493354.
[3] Poste G. Bring on the biomarkers. Nature 2011;469:156–7. http://dx.doi.org/10.1038/469156a.
[4] European Network for Health technology Assessment (eunethta). What is Health Technology Assessment (HTA) n.d. http://www.eunethta.eu/about-us/faq#t287n73.
[5] Ijzerman MJ, Steuten LMG. Early assessment of medical technologies to inform product development and market access: a review of methods and applications. Appl Health Econ Health Policy 2011;9:331–47. http://dx.doi.org/10.2165/11593380-000000000-00000.
[6] Claxton K, Griffin S, Koffijberg H, McKenna C. How to estimate the health benefits of additional research and changing clinical practice. BMJ 2015;351:h5987.
[7] Şardaş S, Endrenyi L, Gürsoy UK, Hutz M, Lin B, Patrinos GP, et al. A call for pharmacogenovigilance and rapid falsification in the age of big data: why not first road test your biomarker? Omics J Integr Biol 2014;18:663–5. http://dx.doi.org/10.1089/omi.2014.0132.
[8] Steuten LM, Ramsey SD. Improving early cycle economic evaluation of diagnostic technologies. Expert Rev Pharmacoecon Outcomes Res 2014;14:491–8. http://dx.doi.org/10.1586/14737167.2014.914435.
[9] Markiewicz K, van Til JA, IJzerman MJ. Medical devices early assessment methods: systematic literature review. Int J Technol Assess Health Care 2014;30:137–46. http://dx.doi.org/10.1017/S0266462314000026.
[10] Simon R. Clinical trial designs for evaluating the medical utility of prognostic and predictive biomarkers in oncology. Pers Med 2010;7:33–47. http://dx.doi.org/10.2217/pme.09.49.
[11] Simon R. Sensitivity, specificity, PPV, and NPV for predictive biomarkers. J Natl Cancer Inst 2015;107. http://dx.doi.org/10.1093/jnci/djv153.
[12] Simon RM, Paik S, Hayes DF. Use of archived specimens in evaluation of prognostic and predictive biomarkers. J Natl Cancer Inst 2009;101:1446–52. http://dx.doi.org/10.1093/jnci/djp335.
[13] Mandrekar SJ, Sargent DJ. Clinical trial designs for predictive biomarker validation: theoretical considerations and practical challenges. J Clin Oncol Off J Am Soc Clin Oncol 2009;27:4027–34. http://dx.doi.org/10.1200/JCO.2009.22.3701.
[14] Sargent DJ, Conley BA, Allegra C, Collette L. Clinical trial designs for predictive marker validation in cancer treatment trials. J Clin Oncol Off J Am Soc Clin Oncol 2005;23:2020–7. http://dx.doi.org/10.1200/JCO.2005.01.112.
[15] Janes H, Pepe MS, McShane LM, Sargent DJ, Heagerty PJ. The fundamental difficulty with evaluating the accuracy of biomarkers for guiding treatment. J Natl Cancer Inst 2015;107. http://dx.doi.org/10.1093/jnci/djv157.
[16] Fine JP, Pencina M. On the quantitative assessment of predictive biomarkers. J Natl Cancer Inst 2015;107. http://dx.doi.org/10.1093/jnci/djv187.
[17] Henry NL, Hayes DF. Uses and abuses of tumor markers in the diagnosis, monitoring, and treatment of primary and metastatic breast cancer. Oncologist 2006;11:541–52. http://dx.doi.org/10.1634/theoncologist.11-6-541.
[18] Sheiner LB. Learning versus confirming in clinical drug development. Clin Pharmacol Ther 1997;61:275–91. http://dx.doi.org/10.1016/S0009-9236(97)90160-0.
[19] Parkinson DR, McCormack RT, Keating SM, Gutman SI, Hamilton SR, Mansfield EA, et al. Evidence of clinical utility: an unmet need in molecular diagnostics for patients with cancer. Clin Cancer Res Off J Am Assoc Cancer Res 2014;20:1428–44. http://dx.doi.org/10.1158/1078-0432.CCR-13-2961.
[20] Duffy MJ, Sturgeon CM, Sölétormos G, Barak V, Molina R, Hayes DF, et al. Validation of new cancer biomarkers: a position statement from the European group on tumor markers. Clin Chem 2015;61:809–20. http://dx.doi.org/10.1373/clinchem.2015.239863.
[21] Polley M-YC, Freidlin B, Korn EL, Conley BA, Abrams JS, McShane LM. Statistical and practical considerations for clinical evaluation of predictive biomarkers. J Natl Cancer Inst 2013;105:1677–83. http://dx.doi.org/10.1093/jnci/dit282.
[22] Simon R. Lost in translation: problems and pitfalls in translating laboratory observations to clinical utility. Eur J Cancer Oxf Engl 1990;2008(44):2707–13. http://dx.doi.org/10.1016/j.ejca.2008.09.009.
[23] Simon R. Clinical trials for predictive medicine: new challenges and paradigms. Clin Trials Lond Engl 2010;7:516–24. http://dx.doi.org/10.1177/1740774510366454.
[24] Kelloff GJ, Sigman CC. Cancer biomarkers: selecting the right drug for the right patient. Nat Rev Drug Discov 2012;11:201–14. http://dx.doi.org/10.1038/nrd3651.
[25] Schully SD, Carrick DM, Mechanic LE, Srivastava S, Anderson GL, Baron JA, et al. Leveraging biospecimen resources for discovery or validation of markers for early cancer detection. JNCI J Natl Cancer Inst 2015;107. http://dx.doi.org/10.1093/jnci/djv012. djv012-djv012.
[26] McShane LM, Cavenagh MM, Lively TG, Eberhard DA, Bigbee WL, Williams PM, et al. Criteria for the use of omics-based predictors in clinical trials. Nature 2013;502:317–20. http://dx.doi.org/10.1038/nature12564.
[27] Simon R, Roychowdhury S. Implementing personalized cancer genomics in clinical trials. Nat Rev Drug Discov 2013;12:358–69. http://dx.doi.org/10.1038/nrd3979.
[28] Beelen K, Zwart W, Linn SC. Can predictive biomarkers in breast cancer guide adjuvant endocrine therapy? Nat Rev Clin Oncol 2012;9:529–41. http://dx.doi.org/10.1038/nrclinonc.2012.121.
[29] European Commission. Regulation of the European Parliament and of the Council on medical devices, and amending directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009. n.d.
[30] U.S. Food and Drug Administration. Premarket Approval (PMA) n.d. http://www.fda.gov/Medicaldevices/Deviceregulationandguidance/%20Howtomarketyourdevice/Premarketsubmissions/Premarketapprovalpma/.
[31] Annex IX of the EU Directive 93/42/EEC. n.d.
[32] U.S. Food and Drug Administration. Clinical Laboratory Improvement Amendments (CLIA) n.d. http://www.fda.gov/medicaldevices/deviceregulationandguidance/ivdregulatoryassistance/ucm124105.htm.

[33] European Commission. Revisions of Medical Device Directives n.d. http://ec.europa.eu/growth/sectors/medical-devices/regulatory-framework/revision/index_en.htm.
[34] Fisher B, Bryant J, Wolmark N, Mamounas E, Brown A, Fisher ER, et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol Off J Am Soc Clin Oncol 1998;16:2672–85.
[35] Kuerer HM, Newman LA, Smith TL, Ames FC, Hunt KK, Dhingra K, et al. Clinical course of breast cancer patients with complete pathologic primary tumor and axillary lymph node response to doxorubicin-based neoadjuvant chemotherapy. J Clin Oncol Off J Am Soc Clin Oncol 1999;17:460–9.
[36] von Minckwitz G, Untch M, Blohmer J-U, Costa SD, Eidtmann H, Fasching PA, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol Off J Am Soc Clin Oncol 2012;30:1796–804. http://dx.doi.org/10.1200/JCO.2011.38.8595.
[37] von Minckwitz G, Fontanella C. Comprehensive review on the surrogate endpoints of efficacy proposed or hypothesized in the scientific community today. J Natl Cancer Inst Monogr 2015;2015:29–31. http://dx.doi.org/10.1093/jncimonographs/lgv007.
[38] Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014;384:164–72. http://dx.doi.org/10.1016/S0140-6736(13)62422-8.
[39] McShane LM, Hayes DF. Publication of tumor marker research results: the necessity for complete and transparent reporting. J Clin Oncol Off J Am Soc Clin Oncol 2012;30:4223–32. http://dx.doi.org/10.1200/JCO.2012.42.6858.
[40] Martin JL, Murphy E, Crowe JA, Norris BJ. Capturing user requirements in medical device development: the role of ergonomics. Physiol Meas 2006;27:R49–62. http://dx.doi.org/10.1088/0967-3334/27/8/R01.
[41] Cockburn A, Yan J, Rahardja D, Euhus D, Peng Y, Fang Y, et al. Modulatory effect of neoadjuvant chemotherapy on biomarkers expression; assessment by digital image analysis and relationship to residual cancer burden in patients with invasive breast cancer. Hum Pathol 2014;45:249–58. http://dx.doi.org/10.1016/j.humpath.2013.09.002.
[42] García-Caballero T, Prieto O, Vázquez-Boquete A, Gude F, Viaño P, Otero M, et al. Dual-colour CISH is a reliable alternative to FISH for assessment of topoisomerase 2-alpha amplification in breast carcinomas. Breast Cancer Res Treat 2014;143:81–9. http://dx.doi.org/10.1007/s10549-013-2791-8.
[43] Castle J, Shaker H, Morris K, Tugwood JD, Kirwan CC. The significance of circulating tumour cells in breast cancer: a review. Breast Edinb Scotl 2014;23:552–60. http://dx.doi.org/10.1016/j.breast.2014.07.002.
[44] Kuo S-J, Wang BB-T, Chang C-S, Chen T-H, Yeh K-T, Lee D-J, et al. Comparison of immunohistochemical and fluorescence in situ hybridization assessment for HER-2/neu status in Taiwanese breast cancer patients. Taiwan J Obstet Gynecol 2007;46:146–51. http://dx.doi.org/10.1016/S1028-4559(07)60008-4.
[45] Logullo AF, de Moura RP, Nonogaki S, Kowalski LP, Nagai MA, Simpson AJ. A proposal for the integration of immunohistochemical staining and DNA-based techniques for the determination of TP53 mutations in human carcinomas. Diagn Mol Pathol Am J Surg Pathol Part B 2000;9:35–40.
[46] Miquel-Cases A, Steuten LMG, Retèl VP, van Harten WH. Early stage cost-effectiveness analysis of a BRCA1-like test to detect triple negative breast cancers responsive to high dose alkylating chemotherapy. Breast Edinb Scotl 2015;24:397–405. http://dx.doi.org/10.1016/j.breast.2015.03.002.
[47] Moreno L, Linossi C, Esteban I, Gadea N, Carrasco E, Bonache S, et al. Germline BRCA testing is moving from cancer risk assessment to a predictive biomarker for targeting cancer therapeutics. Clin Transl Oncol Off Publ Fed Span Oncol Soc Natl Cancer Inst Mex 2016. http://dx.doi.org/10.1007/s12094-015-1470-0.
[48] Lobb EA, Barlow-Stewart K, Suthers G, Hallowell N. Treatment-focused DNA testing for newly diagnosed breast cancer patients: some implications for clinical practice. Clin Genet 2010;77:350–4. http://dx.doi.org/10.1111/j.1399-0004.2009.01307.x.
[49] Steuten LMG, Schutten M, Kip M, IJzerman MJ. Assessing the impact of a multi-million public-private partnership for translational research: the centre for translational molecular medicine (Ctmm). Value Health 2014;17:A31. http://dx.doi.org/10.1016/j.jval.2014.03.192.
[50] Avard D, Bridge P, Bucci LM, Chiquette J, Dorval M, Durocher F, et al. Partnering in oncogenetic research–the INHERIT BRCAs experience: opportunities and challenges. Fam Cancer 2006;5:3–13. http://dx.doi.org/10.1007/s10689-005-2570-8.
[51] Miquel-Cases A, Retèl VP, van Harten WH, Steuten LMG. Decisions on further research for predictive biomarkers of high-dose alkylating chemotherapy in triple-negative breast cancer: a value of information analysis. Value Health 2016;19:419–30. http://dx.doi.org/10.1016/j.jval.2016.01.015.
[52] Network Cancer Genome Atlas. Comprehensive molecular portraits of human breast tumours. Nature 2012;490:61–70. http://dx.doi.org/10.1038/nature11412.
[53] Zardavas D, Irrthum A, Swanton C, Piccart M. Clinical management of breast cancer heterogeneity. Nat Rev Clin Oncol 2015;12:381–94. http://dx.doi.org/10.1038/nrclinonc.2015.73.
[54] Beije N, Jager A, Sleijfer S. Circulating tumor cell enumeration by the Cell Search system: the clinician's guide to breast cancer treatment? Cancer Treat Rev 2015;41:144–50. http://dx.doi.org/10.1016/j.ctrv.2014.12.008.
[55] Patel KM, Tsui DWY. The translational potential of circulating tumour DNA in oncology. Clin Biochem 2015;48:957–61. http://dx.doi.org/10.1016/j.clinbiochem.2015.04.005.
[56] Deenen MJ, Cats A, Beijnen JH, Schellens JHM. Part 4: pharmacogenetic variability in anticancer pharmacodynamic drug effects. Oncologist 2011;16:1006–20. http://dx.doi.org/10.1634/theoncologist.2010-0261.
[57] Deenen MJ, Cats A, Beijnen JH, Schellens JHM. Part 3: pharmacogenetic variability in phase II anticancer drug metabolism. Oncologist 2011;16:992–1005. http://dx.doi.org/10.1634/theoncologist.2010-0260.
[58] Deenen MJ, Cats A, Beijnen JH, Schellens JHM. Part 2: pharmacogenetic variability in drug transport and phase I anticancer drug metabolism. Oncologist 2011;16:820–34. http://dx.doi.org/10.1634/theoncologist.2010-0259.
[59] Deenen MJ, Cats A, Beijnen JH, Schellens JHM. Part 1: background, methodology, and clinical adoption of pharmacogenetics. Oncologist 2011;16:811–9. http://dx.doi.org/10.1634/theoncologist.2010-0258.
[60] Galluzzi L, Vacchelli E, Bravo-San Pedro J-M, Buqué A, Senovilla L, Baracco EE, et al. Classification of current anticancer immunotherapies. Oncotarget 2014;5:12472–508.
[61] Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;144:646–74. http://dx.doi.org/10.1016/j.cell.2011.02.013.
[62] Zardavas D, Baselga J, Piccart M. Emerging targeted agents in metastatic breast cancer. Nat Rev Clin Oncol 2013;10:191–210. http://dx.doi.org/10.1038/nrclinonc.2013.29.
[63] Arnedos M, Vicier C, Loi S, Lefebvre C, Michiels S, Bonnefoi H, et al. Precision medicine for metastatic breast cancer-limitations and solutions. Nat Rev Clin Oncol 2015;12:693–704. http://dx.doi.org/10.1038/nrclinonc.2015.123.
[64] Barker AD, Sigman CC, Kelloff GJ, Hylton NM, Berry DA, Esserman LJ. I-SPY 2: an adaptive breast cancer trial design in the setting of neoadjuvant chemotherapy. Clin Pharmacol Ther 2009;86:97–100. http://dx.doi.org/10.1038/clpt.2009.68.
[65] Prota AE, Bargsten K, Zurwerra D, Field JJ, Díaz JF, Altmann K-H, et al. Molecular mechanism of action of microtubule-stabilizing anticancer agents. Science 2013;339:587–90. http://dx.doi.org/10.1126/science.1230582.
[66] Dumontet C, Jordan MA. Microtubule-binding agents: a dynamic field of cancer therapeutics. Nat Rev Drug Discov 2010;9:790–803. http://dx.doi.org/10.1038/nrd3253.
[67] Minotti G, Menna P, Salvatorelli E, Cairo G, Gianni L. Anthracyclines: molecular advances and pharmacologic developments in antitumor activity and cardiotoxicity. Pharmacol Rev 2004;56:185–229. http://dx.doi.org/10.1124/pr.56.2.6.
[68] Pang B, Qiao X, Janssen L, Velds A, Groothuis T, Kerkhoven R, et al. Drug-induced histone eviction from open chromatin contributes to the chemotherapeutic effects of doxorubicin. Nat Commun 2013;4:1908. http://dx.doi.org/10.1038/ncomms2921.
[69] Rottenberg S, Nygren AOH, Pajic M, van Leeuwen FWB, van der Heijden I, van de Wetering K, et al. Selective induction of chemotherapy resistance of mammary tumors in a conditional mouse model for hereditary breast cancer. Proc Natl Acad Sci USA 2007;104:12117–22. http://dx.doi.org/10.1073/pnas.0702955104.
[70] Borst P, Wessels L. Do predictive signatures really predict response to cancer chemotherapy? Cell Cycle Georget Tex 2010;9:4836–40.
[71] Fontanella C, Loibl S, von Minckwitz G. Clinical usefulness and relevance of intermediate endpoints for cytotoxic neoadjuvant therapy. Breast Edinb Scotl 2015;24(Suppl 2):S84–7. http://dx.doi.org/10.1016/j.breast.2015.07.020.
[72] Hudis CA, Barlow WE, Costantino JP, Gray RJ, Pritchard KI, Chapman J-AW, et al. Proposal for standardized definitions for efficacy end points in adjuvant breast cancer trials: the STEEP system. J Clin Oncol Off J Am Soc Clin Oncol 2007;25:2127–32. http://dx.doi.org/10.1200/JCO.2006.10.3523.
[73] Gourgou-Bourgade S, Cameron D, Poortmans P, Asselain B, Azria D, Cardoso F, et al. Guidelines for time-to-event end point definitions in breast cancer trials: results of the DATECAN initiative (Definition for the Assessment of Time-to-event Endpoints in CANcer trials)†. Ann Oncol Off J Eur Soc Med Oncol ESMO 2015;26:873–9. http://dx.doi.org/10.1093/annonc/mdv106.
[74] Berruti A, Amoroso V, Gallo F, Bertaglia V, Simoncini E, Pedersini R, et al. Pathologic complete response as a potential surrogate for the clinical outcome in patients with breast cancer after neoadjuvant therapy: a meta-regression of 29 randomized prospective studies. J Clin Oncol Off J Am Soc Clin Oncol 2014;32:3883–91. http://dx.doi.org/10.1200/JCO.2014.55.2836.
[75] Renfro LA, Sargent DJ. Statistical controversies in clinical research: basket trials, umbrella trials, and other master protocols: a review and examples. Ann Oncol Off J Eur Soc Med Oncol 2016. http://dx.doi.org/10.1093/annonc/mdw413.
[76] Menis J, Hasan B, Besse B. New clinical research strategies in thoracic oncology: clinical trial design, adaptive, basket and umbrella trials, new end-points and new evaluations of response. Eur Respir Rev Off J Eur Respir Soc 2014;23:367–78. http://dx.doi.org/10.1183/09059180.00004214.
[77] Rugo HS, Olopade OI, DeMichele A, Yau C, van 't Veer LJ, Buxton MB, et al. Adaptive randomization of veliparib-carboplatin treatment in breast cancer. N Engl J Med 2016;375:23–34. http://dx.doi.org/10.1056/NEJMoa1513749.
[78] Berry DA. Adaptive clinical trials in oncology. Nat Rev Clin Oncol 2011;9:199–207. http://dx.doi.org/10.1038/nrclinonc.2011.165.
[79] Buchanan J, Wordsworth S, Schuh A. Issues surrounding the health economic evaluation of genomic technologies. Pharmacogenomics 2013;14:1833–47. http://dx.doi.org/10.2217/pgs.13.183.