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Perspective

Health Economic Impact of Liquid Biopsies in Cancer Management

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Abstract

Introduction

Liquid biopsies (LBs) are referred to as the sampling and analysis of non-solid tissue, primarily blood, as a diagnostic and monitoring tool for cancer. Because LBs are largely non-invasive, they are a less-costly alternative for serial analysis of tumor progression and heterogeneity to facilitate clinical management. Although a variety of tumor markers are proposed (e.g. free-circulating DNA), the clinical evidence for Circulating Tumor Cells (CTCs) is currently the most developed.

Areas covered

This paper presents a health economic perspective of LBs in cancer management. We first briefly introduce the requirements in biomarker development and validation, illustrated for CTCs. Second, we discuss the state-of-art on the clinical utility of LBs in breast cancer in more detail. We conclude with a future perspective on the clinical use and reimbursement of LBs

Expert commentary

A significant increase in clinical research on LBs can be observed and the results suggest a rapid change of cancer management. In addition to studies evaluating clinical utility of LBs, a smooth translation into clinical practice requires systematic assessment of the health economic benefits. This paper argues that (early stage) health economic research is required to facilitate its clinical use and to prioritize further evidence development.

Keywords

Liquid biopsies, cancer, circulating tumor cells, ctDNA, health economics, biomarker, diagnostic

1. Introduction

There is a growing consensus that the cost of cancer care is exploding, particularly due to new targeted agents. While the total cost of cancer is between 4-6 % of the healthcare spending, cancer drugs account for approximately one third of the costs and this spending is expected to grow even further (1). Several initiatives aim at controlling drug prices directly, such as the negotiation of drug purchasing rebates based on the results of cost-effectiveness studies and the demand for price transparency (2) (3). Another mechanism to provide affordable cancer care, is to effectively prescribe drugs guided by value frameworks such as the ASCO scale (4) and the ESMO magnitude of clinical benefit scale (MCBS) (5) and by better targeting of expensive medicines using biomarkers and genomic profiling (6).

Staging and targeting of treatment is currently done by combining information from tissue biopsies and the use of imaging modalities or combinations of those. However, an emerging and promising technology is the use of liquid biopsies (LBs), which allow for the early detection of cancer (7) and/or the analysis of tumor progression and profiling, by sampling and isolating tumor markers from body fluids, mainly blood (8). Several traditional blood tumor marker proteins, such CA15-3, CA19-9 and PSA markers, are used in the management of respectively breast, colorectal and prostate cancer. However, with the advances of new detection technologies the molecular composition of the cancer can be studied through circulating tumor DNA (ctDNA), tumor derived extra-cellular vesicles (td-EV), micro-RNA (miRNA) and circulating tumor cells (CTCs). Although substantial effort is invested in the isolation and validation of different tumor markers (ctDNA, td-EV, miRNA) from blood, CTCs are most likely to mirror the tumor and represent a true surrogate for a tissue biopsy. CTCs, however, need to be present, isolated and characterized for this to be materialized. At this

time CTC are still the most frequently studied LBs in clinical trials and we will therefore mainly focus on the utility and potential of CTCs to change patient management (9).

The presence of tumor cells in blood was first observed in 1869 (10); a validated assay for reliable CTC measurement was introduced in 2004 (11) and results from multicenter prospective studies in metastatic breast and prostate cancer, showing their prognostic validity and ability to predict response to therapy, were reported from 2004 to 2008 (12-14). The FDA cleared Cellsearch® is based on the immunomagnetic enrichment of cells which express EpCAM and Cytokeratins, but lack CD45. Since the introduction of CellSearch®, many studies have confirmed the early findings (15,16) have expanded it to other cancers (17,18), showed promise in early disease settings (19,20) and moved efforts to the characterization of CTCs by showing their potential for personalized medicine by detecting protein expression and gene aberrations or amplifications (21) .

In particular, the non-invasiveness of sampling LBs (7.5 mL blood sample) makes this technology very useful for frequent therapy monitoring and for deciphering tumor heterogeneity and mechanisms of drug resistance. Particularly in tumors where it is hard to take biopsies from the primary tumor, such as lung-cancer, LBs have substantial potential (22).

2. Biomarker Development and Validation: the Clinical use of CTCs in Cancer Management

Biomarker development follows a known pathway, from technical and clinical validation to the assessment of clinical utility (23). Such distinction is also relevant for LBs, in particular when the health economic benefits are to be discussed (24). Khoury *et al* present an

adapted model for evidence generation distinguishing between four types of evaluation domains (25). First, the assessment of technical validity of an assay, which includes the estimation of common metrics such as sensitivity and specificity, and analyzes the performance of the assay against a known test standard. Second, the clinical validity, which correlates the test findings to a disease process or disease state, for instance in diagnostic or prognostic studies. Third, the clinical utility, is referred to as whether the test implementation will either change an health outcome, or will improve the process of delivering those outcomes including the resources utilized to achieve these health outcomes. Finally, ethical and legal considerations of diagnostic test use are considered. Broadly speaking, health economists are mainly interested in the clinical utility of diagnostic testing, i.e. the added value of a test for society and thus implicitly the additional life-years of QALYs gained. This added value can then be off-set against the additional costs to determine cost-effectiveness. However, in addition to changes in health outcomes or changes in the care process to deliver those outcomes, a discussion amongst health economists revealed that other value components from diagnostic testing may also be relevant for society such as planning value and psychic value, sometimes referred to as value-of-knowing (26).

To follow the biomarker development pathway, multiple clinical trials were performed to address the clinical validity or prognostic value of CTCs. Different studies showed that the presence of >5 CTCs was shown to have prognostic value in metastatic breast cancer (mBC) and metastatic castration resistant prostate cancer (mCRPC). The presence of >3 CTCs was found to be prognostic in colorectal cancer in terms of overall survival before initiation of a new line of therapy and could predict the response to therapy already after the first cycles

of therapy (27). In addition to several prognostic studies, the predictive value of CTC enumeration has also been investigated to guide decisions on the start of systemic therapy. For instance, in a phase II study, Krebs *et al* found that colorectal cancer patients with elevated baseline CTC counts (≥3 CTCs/7.5 ml) could benefit from an intensive chemotherapy regimen, unlike patients with low CTC counts. This study can be considered to be one of the first studies showing the predictive validity of CTCs (28). The interpretation of CTC results is still subject of study, and the use of cut-offs (less or more than 5 CTC) is an oversimplification, and complicates the evaluation of change in CTC as a response marker as the number of CTCs are low (<10 CTCs) anyway in the majority of cases (29)
(30).

Evaluation of CTCs as a response marker was evaluated by a 30% decline of CTCs (initial 5 CTCs/7.5 mL), as this change was associated with treatment response in mCRPC as early as three weeks within the start of therapy (31). This was confirmed in a recent systematic review presenting the evidence for the use of CTC number as a response measure in metastatic prostate cancer. They defined several measures of response based on CTC counts at baseline and at 13 weeks, and concluded that CTC0 (change from >1 CTC at baseline to 0 CTC at 13 weeks) and CTC conversion (change from >5 CTC at baseline to < 4 CTC at week 13) had the highest discriminative power for overall survival (32). These findings imply that CTCs potentially allow for the determination of treatment response 7-8 weeks earlier than using standard RECIST criteria and Prostate Specific Antigen (PSA) with a substantial cost-saving and prevention of toxicity. Although the clinical evidence for this hypothesis is subject of the ongoing CTC-STOP trial, an early stage simulation model

populated with existing clinical trial data confirmed that CTC enumeration may guide early discontinuation and treatment switching reducing cost of over-treatment (33).

Another example of the predictive validity of CTCs, is the expression of the AR-V7 splice variant on CTCs. Recent studies have shown that the expression of the AR-V7 splice variant on CTCs impacts clinical management because this can guide the selection of either hormonal treatment (AHT, Abiraterone or Enzalutamide both around 28,000 US$ per patient 2) or chemotherapy in naïve patients (e.g. Docetaxel at 9,000 US$ or Cabazitaxel at 65,000 US$ per patient). This stratification may therefore result in substantial cost savings in patients with AHT drug resistance (34). Although these examples provide preliminary evidence of health economic benefits, they also require further research on their potential to gain more efficient use of resources.

3. Clinical Validation and the Clinical Utility of Liquid Biopsies in Breast Cancer

In primary breast cancer (BC), several studies provide evidence on the prognostic value of LBs. The German SUCCESS trial showed the independent prognostic relevance of CTCs before and after adjuvant chemotherapy (35). Also, a recently published pooled analysis of 3,173 patients confirmed that the presence of CTCs was an independent predictor of poor disease-free survival, overall survival, and BC specific survival (19).

The first study in metastatic breast cancer (mBC) reported on 177 mBC patients in which CTCs were enumerated before, and at 4 discrete time-intervals after the initiation of therapy (36-38). From this study it was concluded that CTC detection before the start of treatment is highly predictive for overall survival and may be used for patient stratification

(37). Also repeated assessment of CTCs in mBC show that elevated levels of CTCs over time are associated with progression-free and overall survival (36). These findings were confirmed in a pooled analysis with data from 1944 patients included in trials at 17 different European sites (38). The same study also showed that serum tumor markers did not add any significance to the model.

A recent paper, which reviewed the use of LBs in mBC, showed that LBs still focus mostly on the enumeration of tumor derived particles or the characterization of the most common gene specific abnormalities (39). From this review was concluded that most research is basic research in early phases of the development phases of medical tests, with only very few studies presenting the clinical validation of prognostic and predictive value of LBs. They conclude that more efforts are required to clinically validate LBs.

Another question to address is whether liquid biopsies add value compared to routine clinical assessment of progression using CT imaging. Budd *et al* performed CT scans in 138 mBC patients before and after initiation of therapy and compared the results with CTC counts obtained at baseline and 4 weeks after the start of therapy. Both, CT imaging and CTCs are then used to determine progression. They found that there is concordance between radiology and CTCs in about 76% of the patients after four weeks in the assessment of either stable disease/partial response or progressive disease. In addition, they also correlated radiology and CTC assessment at the first follow up with overall survival for all patients and for patients receiving either first or second line systemic therapy. Reported hazard ratios were 4.08 for prediction of response to first-line therapy using CTCs and 5.37 for radiology. Hazard ratios for prediction of response for second line therapy were

2.79 and 1.44 for CTCs and radiology respectively. From their results, Budd *et al* concluded that CTCs are more reproducible than radiologic response, and that CTCs are an early and reliable indication of disease status and suggest that CTCs are a superior surrogate endpoint (40).

As discussed previously, the clinical utility or the ability of LBs to change clinical management ultimately is required to being used in clinical practice. This implies that new prospective randomized controlled trials have to be designed that include a therapeutic decision based on the assessment of CTCs with known predictive validity. Several studies that do evaluate clinical utility are in the final stages of data collection and analysis and results will be available soon (41).

One of the first studies which aimed to evaluate whether CTCs can change clinical management and outcomes, was the SWOG S0500 trial. The SWOG S0500 trial was a randomized controlled design, including patients with mBC after previous lines of non-chemotherapy treatment such as with hormone therapy or selected targeted agents (42). Patients initially having <5 CTCs were treated at the physician's discretion but were not followed for CTC changes. Patients initially having >5 CTCs started a first line of chemotherapy underwent a repeated follow-up examination of CTCs at 21 days. Patients persistently having >5 CTCs at the follow-up test at 21 days, were randomized to either maintain therapy or change therapy. The SWOG S0500 trial has not been able to find a difference in survival for patients stratified based on CTC counts. The SWOG S0500 has been criticized because the negative findings were merely a failure of the study design than a failure of the CTC test (43). In particular, patients included in the SWOG S0500 had

advanced disease and were not likely to have any therapeutic benefit at all at the time of inclusion.

While the SWOG0500 actually guided the clinical decision to switch or maintain therapy by randomizing a subgroup of patients based on CTCs, clinical trials with such LB guided treatment decisions are still scarce but essential to establish real-world clinical utility. An example is the DETECT trial, which aims for improvements in survival by phenotyping CTCs to guide targeted therapy (44). The DETECT trials have included the largest mBC population that is currently investigated. However, the therapeutic decision is still left by the discretion of the physician, based on the characterization of discordance between the primary tumor, metastases and LBs. The premise of the DETECT IV is that patients with a HER2-negative primary tumor can develop HER2-positive CTCs during disease progression, thereby requiring a different therapeutic approach. Such discordance has been shown in about 19% of patients with metastatic breast cancer and does impact clinical management (45). Dagogo-Jack and Shaw only recently published a review showing both spatial (between primary tumor and metastatic sites) and temporal tumor heterogeneity (tumor dynamics over time) and have suggested liquid biopsies may be the appropriate platform for determining the full extent of tumor heterogeneity (46) or can help in identifying new molecular targets in case of drug resistance (47).

The French STIC trial is an study which is designed to address the clinical potential of using CTC counts to prescribe either hormonal (<5 CTCs) or chemotherapy (>5 CTCs) as first-line treatment in hormone-receptor positive mBC (41). The hypothesis of the trial is that the CTC based approach is non-inferior to the physicians' choice in terms of survival, while a reduction of intensive chemotherapy regimens may be possible by prescribing

chemotherapy only to those patients with high CTC numbers. Although the final results are to be published, a presentation at ESMO (2016) of the inclusion and randomization results in the STIC trial suggests that treatment decisions changed in 38% of the patients based on CTCs. Final results of the trial will be available in 2018.

4. Potential Health Economic Benefits of Liquid Biopsies in Cancer Management

Personalized medicine undoubtedly creates health economic potential as treatment decisions can be better targeted, thereby avoiding over- and under treatment and improving health outcomes. However, several authors also identified the many challenges associated with health economic modeling of personalized medicine applications, which is no different for LBs, where clinical utility remains an essential requirement. Utility in this respect refers to the ability of a diagnostic test to change clinical management and/or to improve clinical outcomes (48). This definition also evokes another question, i.e. how to distinguish between predictive validity and utility. In health economics, the utility of a test refers to the benefits and risks of (not) taking the test while anticipating on future health consequences (49). However, before a test can be considered for its clinical utility, it should at least have demonstrated its predictive validity. I.e. the test should be able to distinguish a favorable from a non-favorable outcome if treatment commences. More importantly, to evaluate clinical utility in the real-world, clinical decisions should be made according to the test result and deviations from that (for whatever reason) will directly influence the utility of a test. In other words, if a specific biomarker assay or LB indicates either non-response or therapy resistance the actual utility of a test only can be shown if clinical decisions are solely based on the test outcome, thereby maximizing outcomes based on predictive validity of

the test. The physician attitude or preference towards the use of LBs is often neglected but plays a key-role in translating LBs to clinical practice.

There are several potential applications of LBs with an opportunity to improve clinical outcomes and control healthcare costs, in addition to those applications where it is simply not possible to implement solid tissue biopsies. Screening and early detection of cancer have been suggested, e.g. by detecting hypermethylated DNA in urine or blood (50) or circulating proteins and cell-free DNA (7). Unfortunately, clinical research on LBs for screening is scarce and there is not a lot of evidence for use in screening to date. Instead, at least three other potentially valuable applications are hypothesized to impact clinical management (51), i.e. 1: improved tumor staging by providing evidence on micro-metastasis and thereby guiding systemic therapy, 2: response monitoring, e.g. a change in CTC count as an early sign of progression or stable disease and 3: treatment targeting by determining a complete profile of targets for targeted drugs, tumor heterogeneity and mechanisms of resistance following single-cell sequencing and genomic profiling. In particular, the value of LBs for single-cell or ctDNA sequencing to determine tumor heterogeneity is promising and challenging and therefore requires further (health economic) research.

5. Challenges with the Reimbursement of Liquid Biopsies

While the evidence for using LBs in cancer management is emerging, more clinical research and more evidence on health economic benefits is required. As illustrated, several studies are ongoing to evaluate the potential of using LBs in clinical practice in an attempt to address whether additional diagnostic information from LBs changes clinical management and thereby health outcomes. Such evidence is also essential to populate and update health

economic decision models, as currently existing basic predictive models still have substantial uncertainty in estimating the health economic potential of LBs.

While clinical trials are currently ongoing, health economic modelling may already support the prioritization and design of LBs trials. Early stage health economic models are proposed to prioritize further development and to identify biomarkers that potentially can make it to the clinic (52) (53). For instance, early stage models for LBs are developed for mCRCP, supporting an early switch to Cabazitaxel following Docetaxel treatment (33), and useful to identify model parameters that do change outcome. Furthermore, early models may help distinguishing between and prioritizing different types of LBs, e.g. CTCs, ct-DNA or td-EV.

The health economic evaluation of LBs is not a panacea for its ultimate use. In order to implement molecular (companion) diagnostic testing in clinical practice, several challenges have to be faced (54). First, implementing a (companion) diagnostic to stratify patients after full approval and reimbursement of a cancer medicine is challenging, because a companion diagnostic may influence the market share of a pharmaceutical (55,56)(57). Second, evidence development for diagnostics is difficult as multiple combinations of test outcomes cannot be easily investigated in a clinical trial (58)(59). According to Towse and Garrison, "we need to be conscious about the difficulty of developing the evidence base for diagnostics in personalized medicine". Furthermore, although this certainly applies to LBs, evidence development for biomarkers is difficult in general. There have been many biomarkers that have been published and claimed to be therapeutically useful, but few become part of the clinical decision-making process due to technical, validation and market

access issues (59). Schneider *et al* request policy makers to be aware of this implementation barrier, and urge for defining specific requirements for the introduction of biomarkers (59).

6. Expert commentary

A significant increase in clinical research on LBs, covering all aspects from isolation to validation of tumor markers in blood, can be observed in the last decade. Also, several expert commentaries in medical oncology journals (60) (61-63) as well as the inclusion of liquid biopsies in the Cleveland top-10 medical innovations (64), suggest a promising future and a rapid change of cancer management using liquid biopsies, and ct-DNA in particular. Nevertheless, the actual clinical utilization of liquid biopsies has been slow. Part of this can be explained by the known challenges of bringing personalized medicine to the clinic.

Awareness amongst medical oncologists about increasing drug prices and associated financial toxicity has also brought a new perspective for the further development of LBs as they may improve cost-effective drug prescription. For this to happen, health economists may find ways to share expertise in the process of early discovery, clinical validation and the (early) assessment of health economic benefits (65). In particular, health economists' expertise is warranted in the evaluation of the clinical and economic consequences of implementing LBs using (early stage) decision models, the prioritization of LBs evidence development using a value-of-information framework, and a more detailed analysis of the cost of implementing biomarker assays and LBs. Previous authors have already identified the complexity of health economic modelling in personalized medicine (66) (67), and this certainly applies to the use of LBs with the complexity and uncertainties associated with the

serial assessment of LBs, and the large amount and different targeted treatments and immunotherapy in different lines of treatment.

7. Five-year view

As illustrated, the use of LBs is emerging and basic scientists and clinical researchers have put considerable effort in the identification and analysis to further improve cancer management. Liquid biopsies may change cancer management substantially, allowing for a fully personalized treatment strategy based on the molecular characterization of LBs. While most of the current studies focus at the identification and technical and clinical validation of LBs, there is a need for health economists to be involved and to identify and prioritize further development of LBs and to smoothen the path to implementation and reimbursement of LBs in the management of cancer patients.

In this view, we do see the potential of LBs for clinical management and encourage the design of clinical trials providing the evidence on clinical utility required for trial based economic evaluations to characterize therapeutic potential and health economic benefits of using LBs in clinical management. However, we also emphasize that the clinical utility of LBs is not only about the predictive validity of a test. Physician attitudes and preferences towards the use of LBs for patient management plays a key-role in the process of translating LBs into clinical practice, and thus in the attempts to achieve clinical and societal benefits.

8. Key issues

- A significant research effort is invested in the isolation, molecular characterization and validation of various blood-based tumor markers, known as liquid biopsies.
- Clinical research in the last 2 decades has shown the prognostic and predictive value of CTCs to determine response and overall survival in breast cancer, prostate cancer and colorectal cancer.
- Studies exploring clinical utility of liquid biopsies to change cancer management are ongoing and their results are expected to support implementation and reimbursement of liquid biopsies
- Liquid biopsies have health economic potential if used to initiate and serially monitor treatment response to inform decisions to discontinue inactive treatment, or to switch treatment to agents that target other molecular mechanisms in case of resistance.

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Declaration of Interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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* Of interest

** Of considerable interest

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