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Review

Detecting Blood-Based Biomarkers in Metastatic Breast Cancer: A Systematic Review of Their Current Status and Clinical Utility

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Abstract: Reviews on circulating biomarkers in breast cancer usually focus on one single biomarker or a selective group of biomarkers. An overview summarizing the discovery and evaluation of all blood-based biomarkers in metastatic breast cancer is lacking. This systematic review aims to identify the available evidence of known blood-based biomarkers in metastatic breast cancer, regarding their clinical utility and state-of-the-art position in the validation process. The initial search yielded 1078 original studies, of which 420 were assessed for eligibility. A total of 320 studies were included in the final synthesis. A Development, Evaluation and Application Chart (DEAC) of all biomarkers was developed. Most studies focus on identifying new biomarkers and search for relations between these biomarkers and traditional molecular characteristics. Biomarkers are usually investigated in only one study (68.8%). Only 9.8% of all biomarkers was investigated in more than five studies. Circulating tumor cells, gene expression within tumor cells and the concentration of secreted proteins are the most frequently investigated biomarkers in liquid biopsies. However, there is a lack of studies focusing on identifying the clinical utility of these biomarkers, by which the additional value still seems to be limited according to the investigated evidence.

Keywords: metastatic breast cancer; liquid biopsy; circulating biomarkers; blood-based biomarkers; circulating tumor cells (CTCs); utility; developmental stages; development evaluation and application chart (DEAC)

1. Introduction

1.1. Breast Cancer Survival

Globally, breast cancer is the most commonly diagnosed form of cancer among women. Clinical management has improved over the last years, and the development of genetic tests such as Mammaprint and OncoTypeDX have proven to guide treatment in early stage breast cancer. Although the current 5-year survival for primary breast cancer is relatively high (ranging from 80% to 92% in different populations) [1], survival rates decrease to less than 25% when the disease becomes metastatic [1,2]. The most important factor to increase survival for those suffering from metastatic breast cancer, is to prescribe a treatment that has the most likelihood of being effective, guided by the tumor cell characteristics [3,4]. To select the most effective treatment once the metastatic lesions have

been detected, it is essential to obtain accurate information on the characteristics of the tumor cells at the time therapy is to be initiated [5].

1.2. Detection and Treatment of Metastatic Lesions

Technical advances in the molecular characterization of cells has already lead to accurate predictions of survival and treatment efficacy. However, these molecular characterizations require high-quality biopsies, which cannot always be obtained from the primary tumor [6]. Alternatively, taking a biopsy of the metastatic lesion is either difficult or even impossible, for example, due to its location, or the inability to visualize that location with the currently used imaging techniques [6–8]. Furthermore, previous research has shown that molecular aberrations of the primary tumor may differ from that of the metastatic lesion and different metastatic lesions can have different characteristics [9]. Therefore, there remains a need for new tests which are sufficiently sensitive and reflect the composition of the tumor at all sites to guide treatment of metastatic disease.

1.3. The Use of Blood-Based Biomarkers

A possible way of enabling better treatment response monitoring or treatment guidance is the use of blood-based biomarkers or liquid biopsies [10]. A large number of single blood-based biomarkers can be distinguished in the blood, of which the most commonly known soluble proteins are Human Epidermal Growth Factor Receptor 2 (HER2), Cancer Antigen 15-3 (CA 15-3), Carcinoembryonic Antigen (CEA) and MUC1 [11]. Furthermore, all kinds of gene expression patterns or mutations can be extracted from circulating mRNA or circulating free DNA [8,12]. However, not only proteins or gene expression patterns yield prognostic or predictive information, even complete cells found in the blood—such as Circulating Tumor Cells (CTCs) or Cancer Associated Fibroblasts (CAF)—provide this type of information.

Although a range of different biomarkers is known, it is far more difficult to evaluate their usefulness for treatment targeting or prognosis of disease. It therefore is required to develop a classification, both to determine biomarkers with clinical utility and to prioritize future research. For clinical decision making, there are different ways of classifying diagnostic information [10]. Classifications focus, for example, on prognostic or predictive ability, or on a classification according to specific hallmarks of cancer [12].

1.4. Evidence on the Utility of Biomarkers

Up to now, the literature is not clear about the clinical utility of biomarkers in breast cancer. Several systematic reviews on blood-based biomarkers have been published yet [10,13]. However, these studies usually focus on one single biomarker or a selective group of biomarkers. These reviews are helpful to understand specific molecular pathways of oncogenesis, on specific prognostic information and all other outcomes they are related to, or on both.

An overview summarizing the discovery and evaluation of blood-based biomarkers for metastatic disease, in terms of their current status and future potential for clinical application, is still lacking. Therefore, this systematic review focusses on identifying known biomarkers, the available evidence regarding their clinical utility and exploring the current state-of-the-art in the validation process of all blood-based biomarkers in metastatic breast cancer. The review aims to identify a set of blood-based biomarkers that may have substantial future potential. Whereas it is common to focus on outcomes in terms of effectiveness, this review instead focusses on the developmental stage as the primary outcome measure of the included studies. First, all blood-based biomarkers will be identified and classified according to their developmental stage (e.g., from discovery to clinical utility). Second, the set of biomarkers with the highest future potential for clinical application will be identified by the number of studies that have been performed in each of the developmental stages.

1.5. Conclusions

The main aim of research on blood-based biomarkers in metastatic breast cancer is the identification of new biomarkers or relations of these biomarkers with other original molecular tumor characteristics. Especially gene expression within CTCs is investigated frequently. However, there still is a lack of studies identifying the clinical utility of these biomarkers. Thereby, the additional value for these biomarkers seems to be still limited according to the investigated evidence.

2. Results

2.1. Search Results

The initial search resulted in a total of 1249 studies from all databases searched. After screening all abstracts, 410 studies were further assessed for eligibility. During the assessment for eligibility, 91 studies were excluded. A total of 320 studies were included in this review. The full list of all studies that were included is presented in Appendix C. Most studies were excluded because the biomarkers investigated were not extracted from metastatic breast cancer patients (n = 22; 24.4%), because the blood used in the detection of the biomarker was non-human or was injected with a cell line that had just metastatic potential (n = 19; 21.1%) or because the study investigated multiple stages of breast cancer but had not reported conclusions for metastatic breast cancer separately (n = 17; 18.9%). The flow diagram of the search is presented in Figure 1.

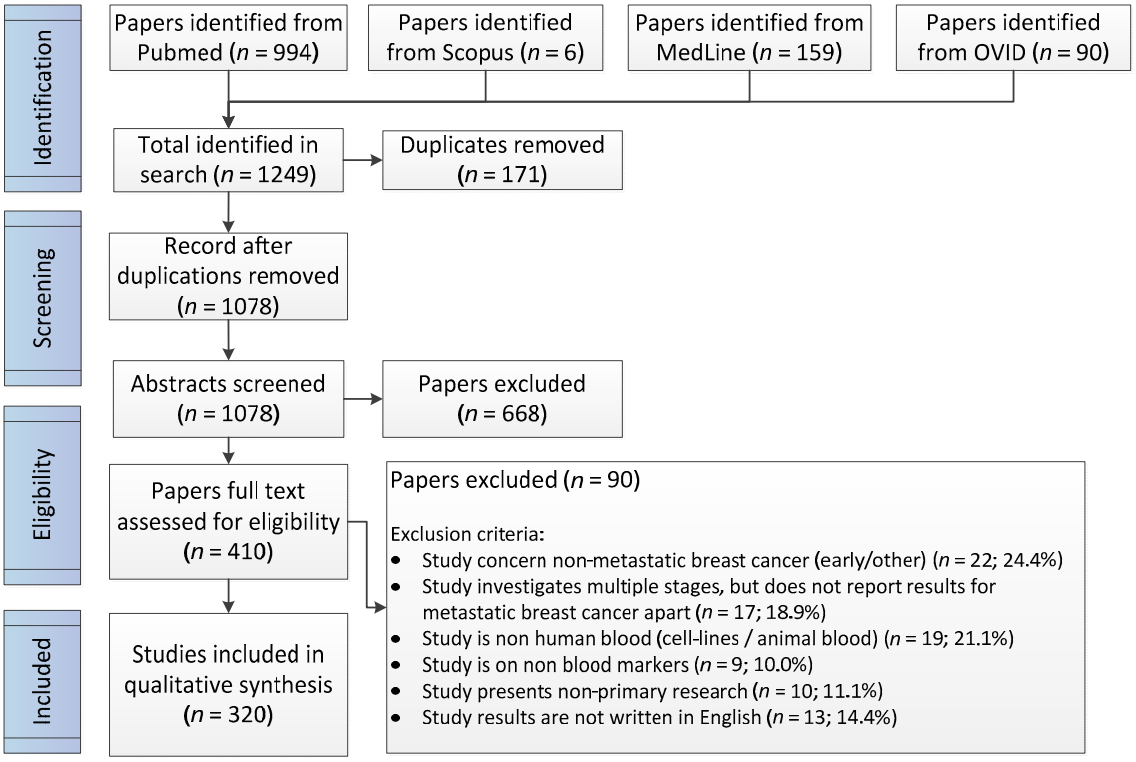

Figure 1. PRISMA Flow Diagram.

2.2. Study Characteristics

For each study, the data were extracted and two classifications were made. First, the biomarkers were classified in one of the four general categories. Second, studies were classified in one of the pre-defined developmental stage categories, as defined in Figure 2. To illustrate the classification more clearly, citations of those studies which were classified as being in one of these phases are given in the right column of Figure 2.

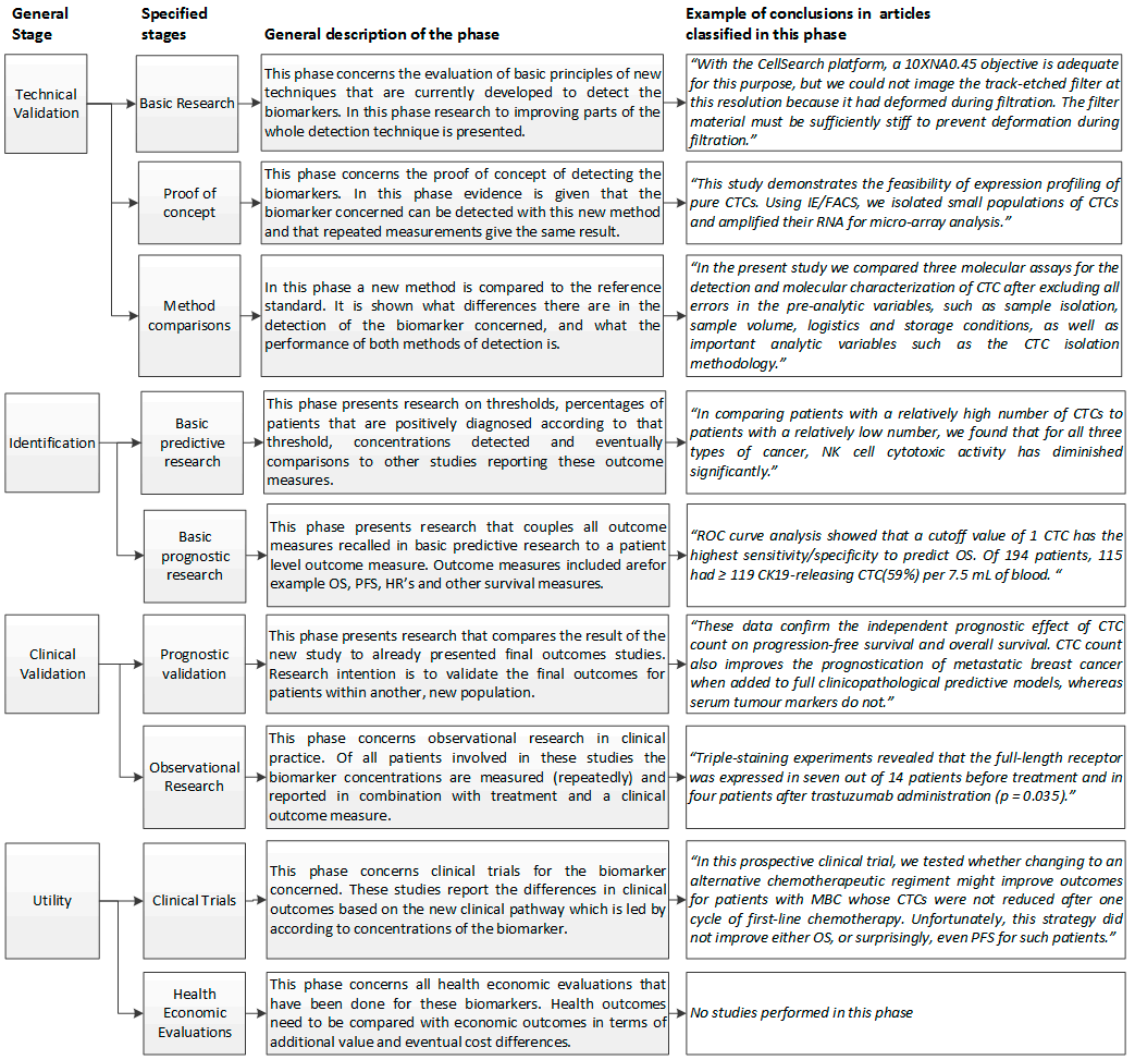

Figure 2. Stages of clinical translation in biomarker discovery [14–21].

2.3. Results According to Developmental Phase

Figure 3 presents the DEAC with the distribution of studies over developmental phases. From this figure it is apparent that most studies focused on the identification phase. This means that most studies focus on finding relationships between the concentration of the biomarker, in relation to a new or existing threshold and furthermore, try to evaluate this against an outcome measure in terms of survival (e.g., Overall Survival (OS), Progression Free Survival (PFS) or survival in months). This phase is split up over two sub phases, namely basic predictive and basic prognostic research. For predictive research, only the concentrations in a subgroup of metastatic breast cancer patients were reported. For prognostic research, these concentrations were linked to an outcome measure related to survival (OS or PFS).

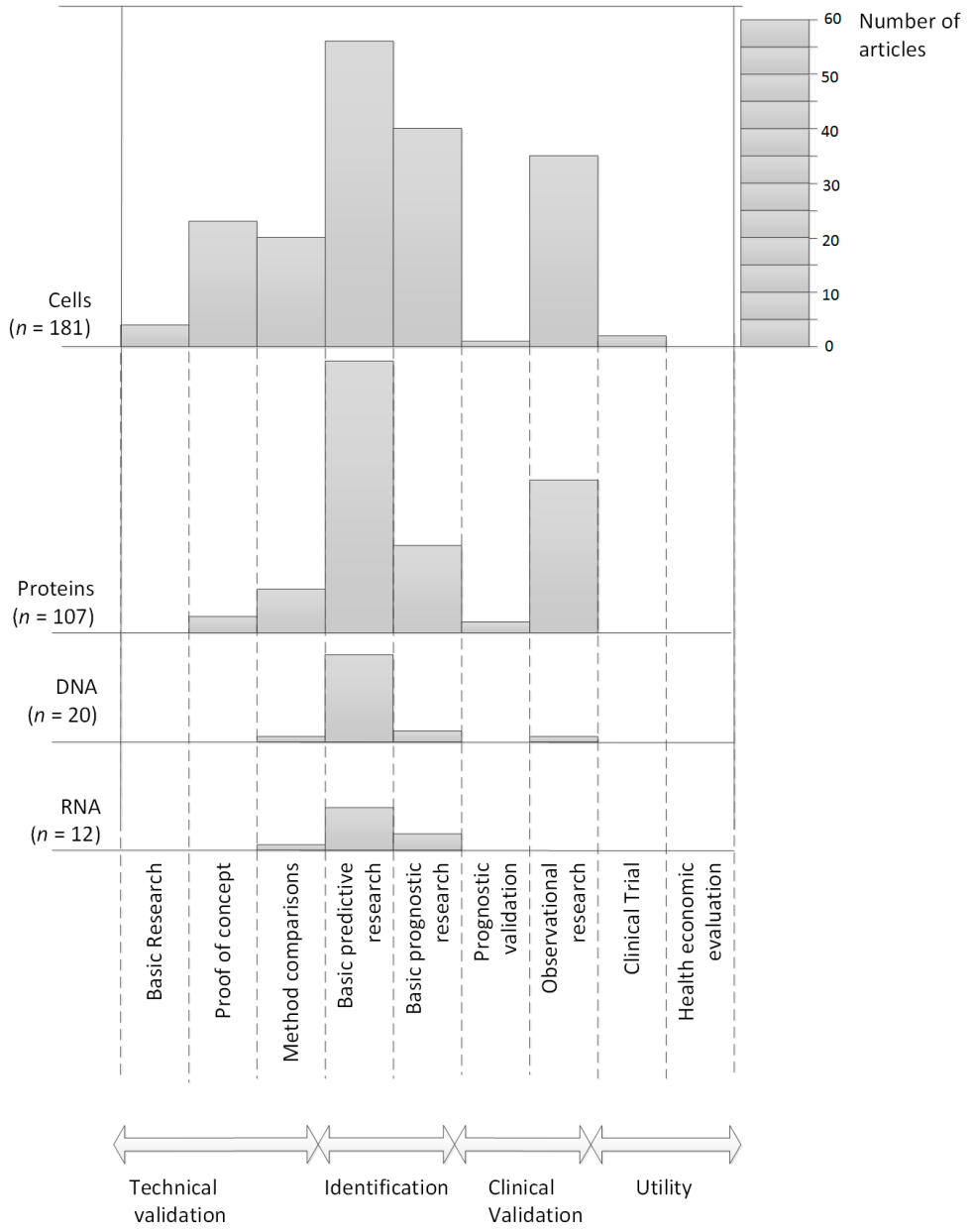

Figure 3. Development, Evaluation and Application Chart.

2.4. Results per Biomarker

The general biomarker category in which most studies were performed on blood-based biomarkers in metastatic breast cancer, concerned whole cells in the blood (n = 181; 56.6%). CTCs made up a large part of this. In 85.1% (n = 154) of all included studies CTC enumeration was performed. In 42.5% of all included studies (n = 136), also genetic profiling for these cells had been done. The markers most frequently investigated are presented in Table 1.

Only those biomarkers for which 5 or more studies have been performed are included in the table. This cut-off had been chosen because these markers represent the most frequently investigated biomarkers. The frequency by which biomarkers are investigated is presented in Table 2, which presents that only 9.8% of all biomarkers is investigated in more than 5 studies. A detailed overview presenting the amount of studies performed for each single biomarker, including an overview of the amount of studies in each developmental stage is presented in Appendix D.

Table 1. Most frequently investigated biomarkers of all studies included.

Biomarker *	Number of Articles	% of Included Studies	End Stage	Number of Studies at End Stage
ALDH1	5	1.6%	Observational	1
CA15-3	51	15.9%	Observational	6
CEA	19	5.9%	Observational	1
CK19	6	1.9%	Observational	1
CTC enumeration	154	48.1%	Clinical trial	29
EGFR	15	4.7%	Observational	6
ER	13	4.1%	Basic prognostic	3
HER2	61	19.1%	Observational	15
PIK3CA	13	4.1%	Observational	1
PR	7	2.2%	Basic prognostic	2
RASSF1A	6	1. 9%	Basic predictive	5
THBS-1	9	2.8%	Observational	5
TP53	5	1.6%	Basic prognostic	1
TWIST	7	2.2%	Observational	2
VEGF	22	6.9%	Observational	15
VEGFR	13	4.1%	Observational	12
Vimentin	6	1.9%	Basic prognostic	1

* The abbreviations used are standard abbreviations. Corresponding gene identities encoding for these biomarkers are presented in Appendix D.

Table 2. Number of studies in which single biomarkers are investigated.

Number of Studies that Investigated a Specific Biomarker	Frequency	% of All Included Studies
1	190	68.8%
2	38	13.8%
3	12	4.3%
4	9	3.3%
5–10	19	6.9%
>10	8	2.9%

The percentages shown in Table 1 present the percentage of total studies that investigated that single marker. The second general biomarker category on which a relatively large amount of studies have been performed (n = 107; 33.4%) are proteins. Within this category most research has been focusing on 4 proteins, which are: CA15-3 (n = 22; 20.5%), soluble HER2 (n = 19; 17.8%), Vascular Endothelial Growth Factor (VEGF) (n = 18; 16.8%) and Vascular Endothelial Growth Factor Receptor (VEGFR) (n = 14; 13.1%). As discussed before, frequently studies are focusing on investigating multiple biomarkers instead of single biomarkers. As presented in Table 1, a total of 51 studies have investigated CA15-3. This means that also research which mainly focuses on one of the other biomarker categories investigates CA15-3. The same differences in the amount of studies performed were seen for HER2 and VEGF.

2.5. Results on the Number of Studies Performed

Summarized over all general biomarker categories, the total amount of studies included in the results synthesis is 320 as presented in Figure 2. In these studies a total of 275 single biomarkers have been investigated. The average number of studies performed on one single biomarker is 2.6 (range 1–154 studies). In Table 2 results are presented for frequency by which the study investigated a number of biomarkers. Table 2 shows that for 68.8% of all the biomarkers only one study has investigated that particular biomarker. For 13.8% of all biomarkers two studies have investigated that biomarker.

3. Discussion

In this paper we present a broad overview of research on blood-based biomarkers in metastatic breast cancer, performed since 2006. Of the included studies, most focused on detecting whole cells in the blood, with a focus on the enumeration or genetic characterization of circulating tumor cells. Considering the classification into developmental stages, the identification stage is the stage during which most research has been performed. Most studies focus on the identification phase, in which they investigate the ability to detect particular biomarkers in the blood and are trying to find connections between these concentrations and potential outcome measures in terms of survival. For proteins CA15-3, soluble HER2, VEGF and VEGFR have been investigated most frequently. However, for CTCs there have been clinical trials, but not for one of these proteins since 2006.

In terms of developmental stages, we expected that the amount of research performed would follow some kind of trend over time. It was expected that per biomarker there would be a substantial amount of studies focusing on the early developmental stages (technical validation), with decreasing numbers of studies the further the research for that particular biomarker proceeded in the developmental process. However, the DEAC shows that this trend does not exist for blood-based biomarkers in metastatic breast cancer. The DEAC shows that the number of studies performed increase until they reach the identification phase, and decrease afterwards. Therefore, it seems that the technical validation and clinical validation phase are currently less performed than research in the identification phase. Another observation from the DEAC is the low amount of research performed in the prognostic validation phase, suggesting this phase is not receiving sufficient attention. However, this may well be due to the fact that the initial search was limited to articles published since 2006, so that a limited amount of studies concerning some of the developmental phases were found. It might have been that specific phases which seemed to have had insufficient attention for several biomarkers were investigated before 2006. In addition, some information might have been missed, as publication bias may have occurred due to excluding non-English studies.

Furthermore, biomarker research may have been performed in a commercial setting or for stakeholders intent to guide internal research and development decisions. As such, selective reporting may occur by which not all findings might have been published. The same holds for studies with negative findings on (some subset) of investigated biomarkers, as it is known that such results are harder to publish than positive findings. As we did not investigate a single outcome measure, no standard methods are available to assess the ensuing risk of bias in our results. Even though the intention of reports might be to inform about recent developments, other stakeholders might use this information differently. Therefore, it seems valuable for future research to be able to have access to all information that was, or can possibly be extracted from the blood samples. Future research should pay attention to selective reporting before publishing, or ensure that samples are publicly available via biobanks.

4. Materials and Methods

This systematic review of blood-based biomarkers in metastatic breast cancer was performed according to the PRISMA guidelines [22]. A review protocol was used and is presented in Appendix A. This review was not registered in the PROSPERO database. All types of studies were included in the initial review, as the aim of this review is to identify the best available evidence exploring the position in the development process of all blood-based biomarkers in metastatic breast cancer. Since all types of primary research studies were included, it was not required that the intervention, control or specific outcome measure was reported in the initial search. Therefore, no specific study characteristics or PICO-statement for inclusion criteria was used. The only restriction applied to the search concerned a time constraint, as studies published since 1 January 2006 were included. Databases that were searched are PubMed, Scopus and OVID. Additionally, articles found by cross-referencing or hand search were included in the initial search. The initial search was performed in June 2016 and updated on 1 December 2016. The detailed search terms applied are presented in Appendix B.

After the initial search and removal of duplicate papers, abstracts were scanned for relevance. Abstracts of articles that either did not present non-primary research data or concerned topics not of interest here (such as, other cancer types, only other stages of breast cancer, and non-blood-based biomarkers—e.g., biomarkers that can be found in other body fluids) were excluded from the full-text review. All abstracts were processed by one reviewer (A. M. Sofie Berghuis) and were discussedwith a second reviewer (Hendrik Koffijberg) if necessary.

Full texts of all included papers were assessed for eligibility by one reviewer (A. M. Sofie Berghuis). All studies were then categorized according to the 10 pre-defined developmental stage and per general biomarker type. Four general developmental stages were identified, namely technical validation, identification, clinical validation and clinical utility. A full description of all pre-defined developmental stages is presented in Figure 1. Data was then classified in four general types of biomarkers, namely cells, proteins, circulating DNA and circulating RNA. Final classification of studies was discussed with a second reviewer (Hendrik Koffijberg) if classification in either one of the categories was unclear to the first reviewer (A. M. Sofie Berghuis). For studies on which there was no consensus between these two reviewers, a third reviewer reclassified the study (Maarten J. IJzerman).

4.1. Article Processing

Quantitative and qualitative data was manually extracted from the included studies and structured in Excel (version 2013) in pre-defined and labeled columns. The following information was extracted from all the included studies:

- General biomarker classification (classification in one of the four categories: cells, proteins, circulating DNA or circulating RNA)
- Developmental stage (classification according to the stages and general descriptions of these stages shown in Figure 1)
- Specific biomarker name
- Type of test used to quantify or detect biomarker (e.g., ELISA, CellSearch, etc.)
- Whether—and if so, which—survival data was presented (Overall Survival, Progression Free Survival, survival in months)

Given the focus on the translation of biomarkers to clinical practice, the results of all included studies were summarized according to the number of studies performed per developmental stage for each general biomarker category. Results for all single biomarkers were summarized per general biomarker category as studies might investigate more than one biomarker. For all single biomarkers it was determined how many studies investigated that biomarker and in which stage of translation the biomarker was identified. For each general biomarker category it was investigated how many studies presented results on the full range of single biomarkers found.

4.2. Synthesis of Results

Results were presented in a Development, Evaluation and Application Chart (DEAC) that was developed specifically for this review. This figure gives a broad overview of the development of biomarkers in each of the predefined stages of clinical translation. Specifically, the figure shows four bar diagrams above each other, one diagram for each of the general biomarker categories. Each vertical bar, per diagram, represents a developmental stage. The bars are displayed to represent the different stages in the translation, starting with the most basic (developmental) research on the left side and more advanced (evaluation) research (such as clinical trials or health economic evaluations) presented on the right side. The height of the bars reflects the number of included studies. This figure therefore gives an overview of the number of studies published on each of the general biomarker categories according to the developmental stage timeline.

5. Conclusions

Since 2006, a substantial amount of research has been done to investigate the potential role of blood-based biomarkers in metastatic breast cancer. There seems to be a focus on research toward the use of CTCs, as most studies investigate these, whether in combination with other markers or as a single marker. The current emphasis of investigating these biomarkers seems to be on developing new techniques or finding new biomarkers that might have predictive or prognostic value, as most studies focus on the identification phase. There is a lack of studies focusing on clinical utility of these biomarkers. This might be because these studies have not yet been performed or suffer from publication bias. However, the lack of studies investigating the utility of blood-based biomarkers causes the additional value in terms of clinical utility, health outcomes or health care efficiency to still be limited according to the investigated evidence.

Author Contributions: The initial search was performed by A. M. Sofie Berghuis. Classification into developmental stages of the articles was discussed with Hendrik Koffijberg and Maarten J. IJzerman. Classification of the general biomarker categories was discussed with Jai Prakash and Leon W. M. M. Terstappen. All authors were involved in writing and revising the manuscript.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

CA15-3	Cancer Antigen 15-3
CTC	Circulating Tumor Cell
DEAC	Development, Evaluation and Application Chart
PFS	Progression Free Survival
HER2	Human Epidermal Growth Factor Receptor 2
OS	Overall Survival
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor

Appendix A. Review Protocol

The steps described in Figure A1 were used as a review protocol.

In the abstract, screening the abstracts were only excluded when they explicitly presented that they contained information on one of the five exclusion criteria. If it was doubted whether results for blood-based biomarkers could have been presented in the text due to vague descriptions, the article was included for full text review. An example of this is the use of "Advanced breast cancer" as study population. For advanced often stage IIIB/IIIC and stage IV is meant. However, several abstracts did not present which stages they exactly investigated. These abstracts therefore were included.

Non-primary research that was excluded from further synthesis was saved in a separate folder, so these can be easily accessed after the complete search. Thereby, comparisons between the results found and the results that were already presented could easily be made.

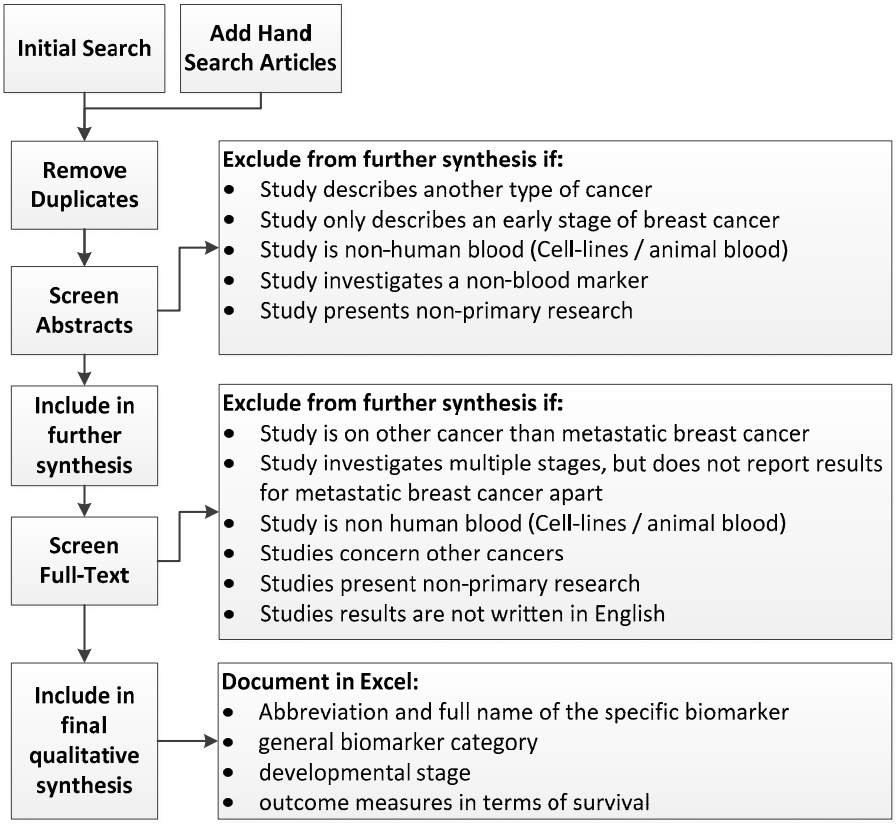

Figure A1. Review Protocol.

Appendix B. Search Terms

Below the full electronic search strategy is presented, i updated until 1 December 2016.

Appendix B.1. Final Search Term PubMed (n = 994)

(((Metastatic[tiab] OR Advanced [tiab] OR Late stage[tiab] OR Malign*[tiab] OR Stage IV[tiab] OR Secondary[tiab]) AND (Breast cancer[majr] OR Breast neoplasm[majr] OR Breast carcinoma[majr] OR Mamma carcinoma[majr] OR Breast tumor[majr] OR Breast tumour[majr] OR "breast neoplasms"[Mesh])) AND ((Blood based[tw] OR Circulating[tw] OR Plasma[tw] OR Liquid[tw] OR Serum[tw] OR Serum based[tw] OR Extracellular[tw]) AND (blood[tw] AND (Marker*[tw] OR Biomarker*[tw] OR Biops*[tw] OR Tumor Cell*[tw] OR Tumor micro particle*[tw] OR Tumor particle*[tw] OR Tumor vesicle*[tw] OR Tumour Cell*[tw] OR Tumour micro particle*[tw] OR Tumour particle*[tw] OR Tumour vesicle*[tw] OR Tumor marker*[tw] OR Tumour marker*[tw] OR Tumor cell cluster*[tw] OR Tumour cell cluster*))))

Appendix B.2. Final Search Term Scopus (n = 6)

(((ALL(blood based OR circulating OR plasma OR liquid OR serum OR serum based OR extracellular)) AND (ALL (marker OR biomarker OR biops OR tumor cell OR tumor micro particle OR tumor particle OR tumor vesicle OR tumour cell OR tumour micro particle OR tumour particle OR tumour vesicle OR tumor marker OR tumour marker OR tumor cell cluster OR tumour cell cluster))) AND (ALL (blood))) AND ((ABS (metastatic OR advanced OR late stage OR malign OR stage iv OR secondary)) AND (ALL (breast cancer OR breast neoplasm OR breast carcinoma OR mamma carcinoma OR breast tumor OR breast tumour)))

Appendix B.3. Final Search Terms OVID (n = 90)

(((ALL (blood based OR circulating OR plasma OR liquid OR serum OR serum based OR extracellular)) AND (ALL (marker OR biomarker OR biops OR tumor cell OR tumor micro particle OR tumor particle OR tumor vesicle OR tumour cell OR tumour micro particle OR tumour particle OR tumour vesicle OR tumor marker OR tumour marker OR tumor cell cluster OR tumour cell cluster))) AND (ALL (blood))) AND ((ABS (metastatic OR advanced OR late stage OR malign OR stage iv OR secondary)) AND (ALL (breast cancer OR breast neoplasm OR breast carcinoma OR mamma carcinoma OR breast tumor OR breast tumour)))

Appendix B.4. Final Search Terms Medline (n = 159)

(((TI = (metastatic OR advanced OR late stage OR malign OR stage iv OR secondary)) AND (TI = (breast cancer OR breast neoplasm OR breast carcinoma OR mamma carcinoma OR breast tumor OR breast tumour))) AND ((TI = (blood based OR circulating OR plasma OR liquid OR serum OR serum based OR extracellular)) AND (TI = (marker OR biomarker OR biops OR tumor cell OR tumor micro particle OR tumor particle OR tumor vesicle OR tumour cell OR tumour micro particle OR tumour particle OR tumour vesicle OR tumor marker OR tumour marker OR tumor cell cluster OR tumour cell cluster)))) AND LANGUAGE: (English) AND DOCUMENT TYPES: (Article)
Indexes = SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan = 2006–2016

Appendix C. Overview of All Included Studies

1. Zhang SH, Li L, Wang T, Bian L, Hu HX, Xu CH, et al. Real-time HER2 status detected on circulating tumor cells predicts different outcomes of anti-HER2 therapy in histologically HER2-positive metastatic breast cancer patients. BMC cancer. 2016;16.
2. Windrichova J, Fuchsova R, Kucera R, Topolcan O, Fiala O, Finek J, et al. Testing of a Novel Cancer Metastatic Multiplex Panel for the Detection of Bone-metastatic Disease—A Pilot Study. Anticancer research. 2016;36(4):1973-8.
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14. Hainsworth JD, Murphy PB, Alemar JR, Daniel BR, Young RR, Yardley DA. Use of a multiplexed immunoassay (PRO Onc assay) to detect HER2 abnormalities in circulating tumor cells of women with HER2-negative metastatic breast cancer: Lack of response to HER2-targeted therapy. Breast cancer research and treatment. 2016;160(1):41-9.
15. Gogoi P, Sepehri S, Zhou Y, Gorin MA, Paolillo C, Capoluongo E, et al. Development of an Automated and Sensitive Microfluidic Device for Capturing and Characterizing Circulating Tumor Cells (CTCs) from Clinical Blood Samples. PloS one. 2016;11(1):e0147400.
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Appendix D. Detailed Overview of All Biomarkers per Developmental Stage

For all biomarkers an overview was created of the number of studies that investigated the biomarker and the translational stages in which these studies have been performed. Some studies focused on biomarkers from multiple categories (e.g., they focused on cells and proteins at the same time). All biomarkers investigated in these studies were categorized according to their main research subject. If the article for example mainly studied CTCs but also measured the concentration of CA15-3, then this study was classified in the cells category. In the following sections an overview of all biomarkers that were classified in the four general biomarker categories is presented.

Appendix D.1. Cells

Several types of research on cells as blood-based biomarkers have been performed. Studies enumerated cells, investigated the expression of proteins on their membrane or investigated the expression of genes that extracted from DNA or mRNA of the cell. The first type of studies are those investigating the enumeration of whole cells or cell clusters. All cells or cell clusters that have been investigated are presented in Table A1.

The second type of studies that investigated cells are those studies that investigate the proteins that are expressed on the membranes of the cells. Table A2 presents the proteins that have been investigated on the membranes of cells. The fourth column "Gene" presents the abbreviations of the genes that encode for these proteins. The fifth column "Gene ID" presents the gene ID of the gene that encodes for the membrane protein.

The third type of studies included in the cells category presented research on the gene expression within these cells. Table A3 presents the genes have been investigated, after DNA or mRNA was extracted from cells.

Studies that mainly focus on cells have also investigated a couple of proteins parallel to their research on the enumeration of cells, membrane expression of proteins on those cells or gene expression within those cells. Table A4 presents the proteins that have been investigated in studies that mainly focused on cells.

Besides the above presented blood-based biomarkers, in one study microRNA 10b had been investigated in parallel with research on CTCs (basic predictive research). In five other studies DNA from cells was extracted and whole genome amplification was performed (all 5 studies were categorized as basic predictive research).

Appendix D.2. Proteins

Several types of proteins have been investigated. Table A5 presents an overview of all proteins that have been investigated in studies which mainly focus on proteins as blood-based biomarkers.

In these studies the main research aim is on proteins as blood-based biomarkers. However, also a couple of other biomarkers have been investigated. In two studies they simultaneously investigated the enumeration of CTCs. In eight studies they looked at gene expression patterns within DNA or mRNA. The genes investigated in these studies were *OPG*, *RANKL*, *eNOS*, and *THBS-1*.

Appendix D.3. DNA

Table A6 presents al genes that have been investigated in studies that mainly focus on circulating DNA.

Besides DNA investigated, several articles investigated proteins or cells in parallel. Two studies enumerated CTCs in parallel (basic prognostic research). In 13 studies proteins were investigated in parallel. Seven studies focused on CA15-3, five on CEA and 1 on the plasminogen activator.

Appendix D.4. RNA

Table A7 presents al circulating micro RNAs that have been studied.

Studies that mainly focused on microRNAs investigated the enumeration of CTCs in parallel in two studies, and the concentration of secreted Mammaglobin in one study.

Table A1. Translational stages of research on the enumeration of whole cells or cell clusters.

Biomarker Abbreviation	Biomarker	Total Number of Articles	Basic Research	Proof of Concept	Comparison of Methods	Basic Predictive Research	Basic Prognostic Research	Prognostic Validation	Observational Trials	Health Economic Analyses
CAMLs	Cancer associated macrophage like cells	1				1				
CAFs	Cancer associated fibroblasts	1		1						
Monocyte CD63	Type of white blood cell CD63	1				1				
Monocyte CD64	Type of white blood cell CD64	1				1				
CECs	Circulating epithelial cells	2							2	
CEPs	Circulating epithelial progenitor cells	2							2	
CETC	Circulating epithelial tumor cells	2				1			1	
aCTCs	Apoptotic circulating tumor cells	1					1			
CSCs	Cancer Stem Cells	2				1			1	
CTC	Circulating tumor cells	156	4	19	20	46	35	1	29 2	
CTC Cluster	Circulating tumor cell clusters	3		1		1			1	
NKs	Natural Killer Cells	2				2				

Table A2. Translational stages of research on the membrane expression of proteins.

Biomarker Abbreviation	Biomarker	Cell *	Gene	Gene ID	Total Number of Articles	Basic Research	Proof of Concept	Comparison of Methods	Basic Predictive Research	Basic Prognostic Research	Prognostic Validation	Observational Trials	Health Economic Analyses
Akt2	AKT serine theronine kinase 2	CTC	*AKT2*	208	4			1	1	1		1	
CD133	Prominin 1	CTC	*PROM1*	8842	1			1					
CD44	CD44 molecule	CTC	*CD44*	960	1		1						
ER	Estrogen	CTC	*ESR1*	2099	13	1	2	1	6	3			
Fibronectin	Fibronectin	CTC	*FN1*	2335	1				1				
HER 2	Human epidermal growth factor receptor 2	CTC	*ERBB2*	2064	25	1	1	3	8	4	0	8	
N-Cadherin	Cadherin 2	CTC	*CDH2*	1000	3			1	2				
PR	Progesteron	CTC	*PGR*	5241	7	1			4	2			
VEGF	Vascular endothelial growth factor	CTC	*VEGFA*	7422	4				2			2	
VEGFR2	Vascular endothelial growth factor receptor 2	CTC	*KDR*	3791	1							1	
Vimentin	Vimentin	CTC	*VIM*	7431	6			1	4	1			
CD24	CD24 molecule	Granulocytes	*CD24*	100133941	1		1						
TLR2	Toll Like Receptor 2	Lymphocytes	*TLR2*	7097	1				1				
TLR4	Toll Like Receptor 4	Lymphocytes	*TLR4*	7099	1				1				

* Cells given in this column represent the cells in which these biomarkers were found.

Table A3. Translational stages of research on gene expression within cell DNA or mRNA.

Biomarker Abbreviation	Biomarker	Cell *	Gene	Gene ID	Total Number of Articles	Basic Research	Proof of Concept	Comparison of Methods	Basic Predictive Research	Basic Prognostic Research	Prognostic Validation	Observational Trials	Health Economic Analyses
CD34	CD34 Molecule	CSCs	*CD34*	947	1				1				
Nanog	NANOG	CSCs	*NANOG*	79923	1				1				
Nestin	Nestin	CSCs	*NES*	10763	1				1				
Oct3/4	POU class 5 homeobox 1	CSCs	*POU5F1*	5460	1				1				
Sox2	SRY Box 2	CSCs	*SOX2*	6657	1				1				
ACTA1	Actin/α 1, skeletal muscle	CTC	*ACTA1*	58	1				1				
AGR2	Anterior gradient 2 protein disulphide isomerase family member	CTC	*AGR2*	10551	1				1				
ALDH1	Aldehyde dehydrogenase 1 family member A1	CTC	*ALDH1A1*	216	5		1	1		2		1	
AURKA	Aurora Kinase A	CTC	*AURKA*	6790	1					1			
BCL2	BCL2 apoptosis regulator	CTC	*BCL2*	596	1		1						
BIRC5	baculoviral IAP repeat containing 5	CTC	*BIRC5*	332	1				1				
CCND1	Cyclin D1	CTC	*CCND1*	595	1				1				
CDC6	Cell Division Cycle 6	CTC	*CDC6*	990	1		1						
CENPF	Centromere protein F	CTC	*CENPF*	1063	1		1						
CEP55	Centrosomal protein 55	CTC	*CEP55*	55165	2		1		1				
CK19	Keratin type I cytoskeletal 19	CTC	*KRT19*	3880	6				4	1		1	
CK8	Cytokeratin 8	CTC	*KRT8*	3856	1				1				
CRABP2	Cellular retinoic acid binding protein 2	CTC	*CRABP2*	1382	1				1				
CSt6 promotor	Cystatin E/M	CTC	*CST6*	1474	1				1				
CXCL14	CXC motif chemokine ligand 14	CTC	*CXCL14*	9547	2				2				
CXXC5	CXXC finger protein 5	CTC	*CXXC5*	51523	1		1						
DTX3	Deltex E3 ubiquitin ligase 3	CTC	*DTX3*	196403	1				1				
DUSP4	Dual specificity phosphatase 4	CTC	*DUSP4*	1846	1				1				
EEF1A2	Eukaryotic translation elongation factor 1 α 2	CTC	*EEF1A2*	1917	2				2				
EGFR	Epidermal growth factor receptor	CTC	*EGFR*	1956	6		1		2	1		2	
ERBB3	ERB-b2 receptor tyrosine kinase 3	CTC	*ERBB3*	2065	2				1	1			
ERBB4	ERB-b2 receptor tyrosine kinase 4	CTC	*ERBB4*	2066	1				1				
ERCC1	ERCC excision repair 1, endonuclease non-catalytic subunit	CTC	*ERCC1*	2067	1					1			

Table A3. *Cont.*

Biomarker Abbreviation	Biomarker	Cell *	Gene	Gene ID	Total Number of Articles	Basic Research	Proof of Concept	Comparison of Methods	Basic Predictive Research	Basic Prognostic Research	Prognostic Validation	Observational Trials	Health Economic Analyses
ESR1	Estrogen Receptor 1	CTC	*ESR1*	2099	3		1		2				
FGFR4	Fibroblast gorwth factor receptor 4	CTC	*FGFR4*	2264	2		1		1				
FKBP10	FK506 binding protein 10	CTC	*FKBP10*	60681	1				1				
FOX A1	Forkhead box A1	CTC	*FOX A1*	3169	1				1				
FOXC1	Forkhead box C1	CTC	*FOXC1*	2296	1		1						
GAPDH	Glyceraldehyde-3-phosphate dehydrogenase	CTC	*GAPDH*	2507	1							1	
HER2	Human epidermal growth factor receptor 2	CTC	*ERBB2*	2064	17	1	3	2	9	1		1	
HIF-1a	hypoxia inducible factor-1 α	CTC	*HIF1A*	3091	1				1				
IGFBP2	Insulin like growth factor binding protein 2	CTC	*IGFBP2*	3485	1				1				
IGFBP4	Insulin like growth factor binding protein 4	CTC	*IGFBP4*	3487	1				1				
IL17 BR	Interleukin 17 receptor B	CTC	*IL17RB*	55540	1				1				
ITGA6	Integrin subunit α	CTC	*ITGA6*	3655	1				1				
Ki67	(proliferation marker)	CTC	*MKI67*	4288	1				1				
KRT14	Keratin 14	CTC	*KRT14*	3861	1		1						
KRT17	Keratin 17	CTC	*KRT17*	3872	1				1				
KRT19	Keratin 19	CTC	*KRT19*	3880	2				2				
KRT20	Keratin type I cytoskeletal 20	CTC	*KRT20*	54474	1		1						
KRT7	Keratin 7	CTC	*KRT7*	3855	1				1				
KRT81	Keratin 81	CTC	*KRT81*	3887	1				1				
LAD1	Ladinin 1	CTC	*LAD1*	3898	1				1				
Mamma-globin	Secretoglobin family 2a member 2	CTC	*SCGB2A2*	4250	3		1		2				
MELK	Maternal embryonic leucine zipper kinase	CTC	*MELK*	9833	1				1				
MUC1	CA15-3	CTC	*MUC1*	4582	5	1	1		2			1	
MYBL2	MYB proto-oncogene like 2	CTC	*MYBL2*	4605	1		1						
NDC80	NDC80 Kinetochore complex component	CTC	*NDC80*	10403	1		1						
NUF2	NUF2, NDC80 kinetochore complex component	CTC	*NUF2*	83540	1		1						

Table A3. *Cont.*

Biomarker Abbreviation	Biomarker	Cell *	Gene	Gene ID	Total Number of Articles	Basic Research	Proof of Concept	Comparison of Methods	Basic Predictive Research	Basic Prognostic Research	Prognostic Validation	Observational Trials	Health Economic Analyses
PIK3CA	Phosphalidylinositol-4,5-bisphosphate 3 kinase catalytic subunit α	CTC	*PIK3CA*	5290	7		1		4	1		1	
PIP	Prolactin induced protein	CTC	*PIP*	5304	1				1				
PKP3	Plakophilin 3	CTC	*PKP3*	11187	1				1				
PTPRK	Protein tyrosine phosphatase, receptor type K	CTC	*PTPRK*	5796	1				1				
PTRF	Polymerase I and transcript release factor	CTC	*PTRF*	284119	2				2				
PTTG1	Pituitary tumor transforming 1	CTC	*PTTG1*	9232	1		1						
RRM2	Ribonucleotide reductase regulatory subunit M2	CTC	*RRM2*	6241	1		1						
S100A7	S100 calcium binding protein A7	CTC	*S100A7*	6278	1				1				
SCGB1D2	Secretoglobin family 1D member 2	CTC	*SCGB1D2*	10647	1				1				
SLUG	Snail family transcriptional repressor 2	CTC	*SNAI2*	6591	1							1	
SNAIL1	Snail family transcriptional repressor 1	CTC	*SNAI1*	6615	1							1	
SPDEF	SAM Pointed domain containing ETS transcription factor	CTC	*SPDEF*	25803	1				1				
TFF3	Trefoil factor 3	CTC	*TFF3*	7033	2		1		1				
TMEM45B	Transmembrane protein 45B	CTC	*TMEM45B*	120224	1		1						
TSPAN13	Tetraspanin 13	CTC	*TSPAN13*	27075	1				1				
TWIST	TWIST	CTC	*TWIST1*	7291	7			3	2			2	
TYMS	Thymidylate synthesase	CTC	*TYMS*	7298	1		1						
UBE2C	Ubiquitin conjugating enzyme E2 C	CTC	*UBE2C*	11065	1		1						
UBE2T	Ubiquitin conjugating enzyme E2 T	CTC	*UBE2T*	29089	1		1						
uPAR	Tyrokinase plasminogen activator receptor	CTC	*PLAU*	5328	2				2				
TP53	Tumor Protein P53	CTC	*TP53*	7157	1				1				
MRP1	ATP binding cassette subfamily C member 1	CTC	*ABCC1*	4363	1				1				
MRP2	ATP binding cassette subfamily C member 2	CTC	*ABCC2*	1244	1				1				
CK18	Cytokeratin 18	CTC	*KRT18*	3875	1				1				
TFF1	Trefoil factor 1	CTC	*TFF1*	7031	2		1		1				
BMS1	BMS1 ribosome biogenesis factor	CTC	*BMS1*	9790	1				1				
SOX 17	SRY Box 17	CTC	*SOX17*	64321	1				1				

* Cells given in this column represent the cells in which these biomarkers were found.

Table A4. Translational stages of research on proteins investigated in parallel in studies which mainly focus on cells.

Biomarker Abbreviation	Biomarker	Membrane or Secreted Protein	Gene	Gene ID	Total Number of Articles	Basic Research	Proof of Concept	Comparison of Methods	Basic Predictive Research	Basic Prognostic Research	Prognostic Validation	Observational Trials	Health Economic Analyses
HER2	Human epidermal growth factor receptor 2	Membrane	*MUC1*	4582	3				2	1			
pFAK	phosphorylated-focal adhesion kinase	Membrane	*PTK2*	5747	1				1				
CA15-3	CA15-3 , produced by MUC1	Secreted	*MUC1*	4582	17	1		2	4	4	1	5	
CAIX	Carbonic anhydrase IX	Secreted	*CA9*	768	1					1			
CEA	Carcinoembryonic antigen related cell adhesion molecule	Secreted	*CEACAM5*	1048	6	1		1	1	1	1	1	
CXCL1	chemokine (C-X-C Motif) Ligand-1	Secreted	*CXCL1*	2919	1					1			
Fibrinogen	Fibrinogen	Secreted	*FGA*	2243	1				1				
LDHA	Lactate dehydrogenase	Secreted	*LDHA*	3939	2				1			1	
M30	Cytokeratin 18 fragments	Secreted	*KRT18*	3875	3				1			2	
P53	Tumor Protein P53	Secreted	*TP53*	7157	1							1	
TGF-B	Transcription Growth Factor Beta 1	Secreted	*TGFB1*	7040	1					1			
TIMP-1	TIMP metallopeptidase inhibitor 1	Secreted	*TIMP1*	7076	1					1			
Bcl-2	BCL2 apoptosis regulator	Secreted	*BCL2*	596	1							1	

Table A5. Translational stages of proteins.

Biomarker Abbreviation	Biomarker	Type of Biomarker	Gene	Gene ID	Total Number of Articles	Basic Research	Proof of Concept	Comparison of Methods	Basic Predictive Research	Basic Prognostic Research	Prognostic Validation	Observational Trials	Health Economic Analyses
EGFR	Epidermal growth factor receptor	Membrane	*EGFR*	1956	9			1	2	2		4	
ENDO180	Mannose Receptor, C type 2 (Endo 180)	Membrane	*MRC2*	9902	1				1				
Endoglin	Glycoprotein co-receptor for peptides in the TGF family	Membrane	*ENG*	2022	1							1	
E-selectin	Selectin E (SELE)	Membrane	*SELE*	6401	2				1			1	
HER2	Soluble Human epidermal growth factor receptor 2	Membrane	*ERBB2*	2064	19				5	8		6	
Jagged 1	Jagged 1	Membrane	*NOTCH1*	4851	1					1			
PDGFR-α	Platelet derived growth factor receptor α	Membrane	*PDGFRA*	5156	1							1	
RAGE	soluble receptor for advanced glycation end products (sRAGE)	Membrane	*AGER*	177	1				1				
RCF	Red Cell Folate	Membrane	*FOLR1*	2348	1				1				

Table A5. *Cont.*

Biomarker Abbreviation	Biomarker	Type of Biomarker	Gene	Gene ID	Total Number of Articles	Basic Research	Proof of Concept	Comparison of Methods	Basic Predictive Research	Basic Prognostic Research	Prognostic Validation	Observational Trials	Health Economic Analyses
sKIT	Stem cell factor receptor/KIT proto-oncogene receptor tyrosine kinase	Membrane	*KIT*	3815	1							1	
VEGFR-1	Vascular Endothelial Growth Factor Receptor 1	Membrane	*FLT1*	2321	1				1				
VEGFR-1	Vascular Endothelial Growth Factor Receptor 1	Membrane	*FLT1*	2321	2							2	
VEGFR-1	Vascular Endothelial Growth Factor Receptor 1	Membrane	*FLT1*	2321	2							2	
VEGFR-2	Vascular Endothelial Growth Factor Receptor 2	Membrane	*KDR*	3791	1				1				
VEGFR-2	Vascular Endothelial Growth Factor Receptor 2	Membrane	*KDR*	3791	3							3	
VEGFR-2	Vascular Endothelial Growth Factor Receptor 2	Membrane	*KDR*	3791	4				1			3	
VEGFR-3	Vascular endothelial growth factor receptor 3	Membrane	*FLT4*	2324	1							1	
a2-HS-glyco-protein	fetuin-A	Secreted	*AHSG*	197	1				1				
Activin A	Inhibin beta A subunit	Secreted	*INHBA*	3624	1				1				
ALP	serum Alkaline Phosphatase	Secreted	*ALPL*	249	4			1	2			1	
bFGF	Fibroblast growth factor 2	Secreted	*FGF2*	2247	1				1				
big ET-1	big endothelin 1-growth factor	Secreted	*EDN1*	1906	1				1				
CA19-9	Carbohydrate antigen	Secreted			2			1	1				
CAIX	Carbonic anhydrase IX	Secreted	*CA9*	768	2					1		1	
CEA	Carcinoembryonic antigen (CEA)	Secreted	*CEACAM5*	1084	8			1	7				
CML	Carboxymethyllysine	Secreted	*BCR*	613	1				1				
CRP	C-reactive protein	Secreted	*CRP*	1401	1					1			
CTX	C-terminal telopeptide	secreted	*CYP27A1*	1593	3				1			2	
CYFRA21-1	Cytokeratin 19 Fragment	Secreted	*KRT19*	3880	1				1				
Cyst C	inhibitor of IL-6	Secreted			1				1				
DKK-1	Dickkopf-1 (DKK1)	Secreted	*DKK1*	22943	2			1	1				
ENO1 ABS	Antibodies against human α enolase	Secreted	*ENO1*	2023	1				1				
ES	Endostatin	Secreted	*COL18A1*	80781	1							1	
FASN	Fatty acid synthase	Secreted	*FASN*	2194	2		1		1				

Table A5. *Cont.*

Biomarker Abbreviation	Biomarker	Type of Biomarker	Gene	Gene ID	Total Number of Articles	Basic Research	Proof of Concept	Comparison of Methods	Basic Predictive Research	Basic Prognostic Research	Prognostic Validation	Observational Trials	Health Economic Analyses
FSIP1	Fibrous sheath interacting protein	Secreted	*FSIP1*	161835	2				2				
Galectin-1	Galectin-1	Secreted	*LGALS1*	3956	1				1				
Galectin-8	Galectin-8	Secreted	*LGALS8*	3964	1				1				
GASP-1	G-protein coupled receptor associated sorting protein 1	Secreted	*GPRASP1*	9737	1				1				
G-CSF	Granulyte colony stimulating factor	Secreted	*CSF3R*	1441	1				1				
GDF15	Growth factor differentiation factor 15	Secreted	*GDF15*	9518	1				1				
GGT	Gamma-Glutamyltransferase	Secreted	*GGT1*	2678	1					1			
HMGB1	soluble high mobility group box 1 (HMGB1)	Secreted	*HMGB1*	3146	1				1				
HSP70	Heat shock protein 70	Secreted	*HSPA4*	3308	1							1	
IFN-y	Interferon gamma	Secreted	*IFNG*	3458	1					1			
IL-10	Interleukin 10	Secreted	*IL10*	3586	1					1			
IL-18	Interleukin 18	Secreted	*IL18*	3606	1			1					
IL-2	Interleukin 2	Secreted	*IL2*	3558	1					1			
IL-4	Interleukin 4	Secreted	*IL4*	3505	1					1			
IL-6	Interleukin 6	Secreted	*IL6*	3569	4				2	2			
IL-7	Interleukin 7	Secreted	*IL7*	3574	1				1				
IL-8	CXC motif chemokine ligand 8	Secreted	*CXCL8*	3576	1							1	
LDHA	Lactate dehydrogenase	Secreted	*LDHA*	3939	1				1				
M30	Cytokeratin 18 fragments	Secreted	*KRT18*	3875	1				1				
Midkine	Growth factor	Secreted	*MDK*	4192	1			1					
MMP2	Matrix Metallopeptidase 2	Secreted	*MMP2*	4313	1				1				
MMP7	Matrix Metallopeptidase 7	Secreted	*MMP7*	4316	1							1	
MMP9	Matrix Metalloproteinase 9	Secreted	*MMP9*	4318	2				1			1	
MUC1	Cancer Antigen 15-3	Secreted	*MUC1*	4582	21		1	4	13	2		1	
MUC1	Antigen	Secreted	*MUC1*	4582	1			1					
MUC16	Mucin 16 or Cancer antigen 125 or	Secreted	*MUC16*	94025	3				3				
Nectin-4	Nectin Cell Adhesion molecule 4	Secreted	*NECTIN4*	81607	1				1				
NSE	Neuron specific enolase	Secreted	*ENO2*	2026	1				1				

Table A5. *Cont.*

Biomarker Abbreviation	Biomarker	Type of Biomarker	Gene	Gene ID	Total Number of Articles	Basic Research	Proof of Concept	Comparison of Methods	Basic Predictive Research	Basic Prognostic Research	Prognostic Validation	Observational Trials	Health Economic Analyses
OC	Osteocalcin (bone gamma-carboxylglutamate) protein	Secreted	*BGLAP*	632	3				2			1	
OPG	Osteoprotegerin	Secreted	*TNFRSF11B*	4982	1				1				
PAI-1	Plasminogen activator inhibitor 1	Secreted	*SERPINE1*	5054	1							1	
Pik3CA	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α	Secreted	*PIK3CA*	5290	1							1	
PLG	Plasminogen	Secreted	*PLG*	5340	1				1				
Prothrombin	Coagulation factor II	Secreted	*F2*	2147	1				1				
PTH	Parathyroid hormone	Secreted	*PTH*	5741	1							1	
RANKL	Receptor activator of nuclear factor kappa-B ligand	Secreted	*TNFSF11*	8600	1				1				
Survivin	baculoviral IAP repeat containing 5	Secreted	*BIRC5*	332	1				1				
TATI	Tumor associated trypsin inhibitor	Secreted	*SPINK*	6690	1			1					
TGF-B1	Transcription Growth Factor Beta 1	Secreted	*TGFB1*	7040	4				1	1		2	
THBS-1	Thrombospondin (TSP-1)	Secreted	*THBS1*	7057	5				2			3	
TIMP1	Tissue inhibitor of metalloproteinase 1	Secreted	*TIMP1*	7076	3				2			1	
TK1	Thymidine kinase1	Secreted	*TK1*	7083	2				1	1			
TNC	Tenascin-C	Secreted	*TNC*	3371	1				1				
TPA	Tissue polypeptide antigen Plasminogen activator, tissue type	Secreted	*PLAT*	5327	1				1				
TRACP5a	Tartrate resistant acid phosphatase 5a	Secreted	*ACP5*	54	2				1	1			
TSH	Thyroid stimulating hormone	Secreted	*TSHB*	7252	1							1	
TWEAK	Tumor necrosis factor related weak inducer of apoptosis	Secreted	*TNFSF12*	8742	1				1				
u-PAR	Urokinase-type plasminogen activator	Secreted	*PLAU*	5328	1				1				
VEGF	Vascular Endothelial Growth Factor	Secreted	*VEGFA*	7422	11				4			7	
VEGF-A	Vascular Endothelial Growth Factor A	Secreted	*VEGFA*	7422	5							5	
VEGF-C	Vascular Endothelial Growth Factor C	Secreted	*VEGFC*	7424	2				1			1	
YKL-40	Chitinase-3-like protein 1	Secreted	*CHI3L1*	1116	2				2				
1CTP	C-terminal telopeptide of collagen type I	Secreted	*CYP27A1*	1593	1				1				
Fibrin α	fibrin alfa	Secreted	*FGA*	2243	1				1				
OPN	Osteopontin (Secreted phosphoprotein 1)	Secreted	*SPP1*	6696	2			1	1				
Osteonectin	Osteonectin	Secreted	*SPARC*	6678	1				1				
Periostin	Periostin	Secreted	*POSTN*	10631	1				1				
Phosphocholine	lipoprotein	Secreted	*PCYT1A*	5130	1		1						
VCAM1	Vascular endothelial adhesion molecule	Secreted	*VCAM1*	7412	1				1				

Table A6. Translational stage of genes investigated in studies that focus on circulating DNA.

Biomarker Abbreviation	Biomarker	Gene	Gene ID	Total Number of Articles	Basic Research	Proof of Concept	Comparison of Methods	Basic Predictive Research	Basic Prognostic Research	Prognostic Validation	Observational	Trials	Health Economic Analyses
AKR1B1	Aldo-keto reductase family 1	*AKR1B1*	231	1				1					
AKT1	AKT serine threonine kinase 1	*AKT1*	207	1				1					
APC	APC, WNT signaling pathway	*APC*	324	1				1					
ARHGEF7	Rho guanine nucleotide exchange factor 7	*ARHGEF7*	8874	1				1					
COL6A2	Collagen type VI α 2 chain	*COL6A2*	1292	1				1					
ESR1	Estrogen Receptor 1	*ESR1*	2099	4				4					
FGFR1	Fibroblast growth factor receptor 1	*FGFR1*	2260	1				1					
FGFR2	Fibroblast growth factor receptor 2	*FGFR2*	2263	1				1					
GPX7	Glutathione peroxidase 7	*GPX7*	2882	1				1					
GSTP1	Glutathione S-transferase pi1	*GSTP1*	2950	1			1						
HER2	Human epidermal growth factor receptor 2	*ERBB2*	2064	2				2					
HIST1H3C	Histone cluster 1 H3 family member C	*HIST1H3C*	8352	1				1					
HOXB4	Homeobox B4	*HOXB4*	3214	1				1					
IDH2	Isocitrate dehydrogenase 2	*IDH2*	3418	1				1					
KU86	X-ray repair cross complementin 5	*XRCC5*	7520	1						1			
PIK3CA	Phosphalidylinositol-4,5-bisphosphate 3 kinase catalytic subunit α	*PIK3CA*	5290	6				6					
PTEN	Phosphatase and tensin homolog	*PTEN*	5728	1				1					
RARβ2 gene	Retinoic acid receoptor beta	*RARB*	5915	1			1						
RASGRF2	Ras protein specific guanine nucleotide-releasing factor 2	*RASGRF2*	5924	1				1					
RASSF1A	Ras association domain family member 1	*RASSF1*	11186	6			1	5					
Stratifin	Stratifin	*SFN*	2810	1				1					
TM6SF1	Transmembrane 6 superfamily member 1	*TM6F1*	53346	1				1					
TMEFF2	Transmembrane protein with EGF like and two follistatin like domains 2	*TMEFF2*	23671	1				1					
TP53	Tumor Protein P53	*TP53*	7157	5				4	1				
WGA	Whole genome amplification	*	*	1				1					

* Whole genome amplification has been performed once. No specific gene or gene ID has been reported as multiple genes can be identified. However, in the study that presented whole genome amplification, no further gene information has been presented.

Table A7. Translational stages of microRNAs.

Biomarker	Total Number of Articles	Basic Research	Proof of Concept	Comparison of Methods	Basic Predictive Research	Basic Prognostic Research	Prognostic Validation	Observational	Trials	Health Economic Analyses
miR-10b	4				3	1				
miR-1260	1				1					
miR-1280	1				1					
miR-141	2				1	1				
miR-155	3				3					
miR-16	2				2					
miR-17	1				1					
miR-197	1				1					
miR-19a	1					1				
miR-200a	1					1				
miR-200b	1					1				
miR-200c	2					2				
miR-2015	1				1					
miR-203	1					1				
miR-21	1					1				
miR-21	1				1					
miR-29b2	1				1					
miR-34a	2				2					
miR-373	1				1					
miR-41	1					1				
miR-720	1				1					
miR-93	1				1					
Profiling 65 miRs	1			1						
U6/SNORD44	1				1					

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