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Aptamer versus Antibody Recognition Elements in Electrochemical Biosensors for Breast Cancer Biomarkers: A Comparative Systematic Review and Quantitative Meta-Analysis

T L Manasa[1], Dr. Rajesh Kumar Upadhyay[2], Dr. Divyashree H B[3]

[1]Research Scholar, Faculty of Engineering & Technology, Department of Electrical & Electronics Engineering, Mangalayatan University, Beswan, Aligarh, UP, India
[2]Professor & Head, Supervisor, Faculty of Engineering & Technology, Department of Electrical & Electronics Engineering, Mangalayatan University, Beswan, Aligarh, UP, India
[3]Assistant Professor, Co-Supervisor, Dayananda Sagar University, Devarakaggalahalli, Harohalli, Kanakapura

Abstract
Accurate diagnosis of biomarkers of breast cancer (BC) at an early stage is at the centre of the reduction in breast cancer (BC) mortality. In order to provide an alternative, low cost, compact and fast measurement methods to traditional immunoassays and imaging techniques, electrochemical biosensors are now being developed, controlling the analytical performance of the biosensors by choosing the appropriate biorecognition element. This review highlights the comparison of two electrochemical platforms—antibody-based platform (immunosensor) and aptamer-based platform (aptasensor)—developed from 2021 to 2026 for four important BC biomarkers, human epidermal growth factor receptor 2 (HER2), carbohydrate antigen 15-3 (CA 15-3), carcinoembryonic antigen (CEA), and circulating microRNA-21. The limits of detection (LOD), linear range, stability and reproducibility data reported in the literature were reviewed and combined quantitatively, and presented with qualitative consensus scoring for production cost, batch reproducibility and clinical maturity. In general, aptamer-based platforms have an advantage in terms of their chemical stability and low batch-to-batch variability, as antibody-based platforms have an advantage in terms of their analytical maturity and availability, and the analytical level appears to be more dependent on the nanomaterial signal- amplification strategy than on only the recognition-element class. The heterogeneous nature of the validation methods used in different studies makes statistical comparison of studies difficult, and is one of the main translational barriers.

Keywords: aptamer; antibody; electrochemical biosensor; breast cancer biomarker; HER2; CA 15-3; immunosensor; aptasensor; systematic review; meta-analysis

I. INTRODUCTION

Breast cancer (BC) is the most common cancer and one of the most fatal cancer for women globally and its prevalence is significantly influenced by the stage of its diagnosis; therefore, research is focused on developing faster, cost-effective and accessible screening and monitoring tools that can diagnose breast

cancer other than mammograms, MRI and tissue biopsies [3]. The traditional quantification methods of these circulating and tissue biomarkers, such as enzyme-linked immunosorbent assay (ELISA), chemiluminescent immunoassay or fluorescence in situ hybridization (FISH) and poly-merase-chain-reaction (PCR) based platforms are expensive and require centralized labs, trained personnel and the time of weeks-days for results.

Electrochemical biosensors, however, are capable of directly converting the biorecognition event at the membrane/electrode interface into an electrical signal (either a current, potential or impedance) and have the potential to build a miniaturized and inexpensive diagnostic device, which can be developed in a fast time scale and is principally point of care (POC) [1, 4]. The specificity of any such biosensor will depend on the biorecognition element that will be used for recognition of the target biomarker, regardless of how the electrodes are constructed and/or how the signal generated is transduced and amplified. There are two types of electrochemical biosensors published in the literature: (i) Immunoglobulin proteins, which are immunized against the target and produced by the immune system of animals, are called antibodies and (ii) short single-stranded DNA or RNA oligonucleotides (or peptides) synthesized in vitro with a high affinity for the target.

Antibodies are the reigning recognition element in commercial immunoassays, and enjoy a proven track of regulatory approval, but aptamers have been gaining a tremendous amount of interest since 2021 due to their reported advantages of thermal and chemical stability, reduced batch-to-batch variability, smaller size (which allows for higher surface packing densities), and easier chemical synthesis than animal- or cell-culture derived antibodies [2, 12]. However, the available evidence is limited and the type of the nanomaterial amplification technique, the validation procedure and the use case are different, making it difficult to draw general conclusions based on the type of the recognition element used for a given set of biomarkers and a particular use case.

During 2021–2026, there is a systematic review and quantitative synthesis of primary research articles and review articles related to antibody-aptamer based electrochemical biosensors for the detection of breast cancer biomarkers, along with comparative analysis. The two types of recognition elements are summarized as to structure and function in Section II. Main electrochemical transduction methods for detection of BC biomarkers are presented in Section III. Details of the review process are provided in Section IV. The quantitative LOD comparisons (Tables I-II, Fig. 1) are followed in Section V by the comparative synthesis of analytical-performance: Section VI.Quantitative comparisons of the LODs are shown in Tables I-II and Fig. 1, and the comparative analytical-performance synthesis is given in Section VI. 1–2). This continues in Section VI where the synthesis is bounded, quantitative and qualitative and the recognition-mechanism schematics (see Fig. 3) are included. These questions of stability/translation are explored in more detail in section VII, future directions are discussed in section VIII and the concluding remarks are in section IX.

II. RECOGNITION ELEMENT FUNDAMENTALS

A. Antibody-Based Recognition

The antibodies, or Immunoglobulins (mainly IgG) used in immunosensors are typically obtained from animals or by immunization of hybridoma or recombinant cell-culture cells, and then immobilized or physically attached to the surface of the electrode transducers, often in a sandwich fashion, where the capture antibody is immobilized on the electrode and the detection antibody is labeled and, together with the captured antigen, releases the electrochemical signal [6, 7]. They are Y-shaped (~150 kDa) and have

two antigen binding (Fab) sites with nanomolar-picomolar intrinsic affinity, with specificity for conformational epitopes of protein biomarkers, in general excellent, as result of selection in vivo against the native folded antigen. Antibodies have been decades in the process of being characterised, a supply chain of commercial antibodies has been realised and most of the FDA/CE approved, validated, immunoassays consist of two validated antibodies.

Their major limitations in their manufacture as biosensors are: they must function within a limited pH, temperature and ionic strength range, thus making them prone to denaturation when conditions are outside this range and also complicating the storage of biosensors in dry-state devices, they vary in their performance from one lot to another and from one animal to another, which affects their calibration in the assay, they are relatively large, which restricts the packing density of the surface and may cause steric hindrance in multiplexed assays, they require immunization of animals or culture of cells to make, requiring substantial lead time and manufacturing costs.

B. Aptamer-Based Recognition

Aptamers are single-stranded DNA or RNA oligonucleotides (20–100 nucleotides) or engineered peptides that adopt stable three-dimensional structures - such as stem-loop, G-quadruplex or pseudoknot - that allow them to bind a target with a similar affinity and specificity as an antibody [2, 8]. They are separated by iterative rounds of SELEX, which includes exposing a randomly selected oligonucleotide library to target, removing the unbound sequences and amplifying the sequences bound to target by PCR and then producing them by solid-phase chemical synthesis [2].

They are chemically synthesized in contrast to the biologically expressed antibodies, and hence have only minimal batch-to-batch variability after the selection of their sequence, can be denatured and refolded many times without losing activity, tolerate a broader pH and temperature range, and can be conveniently end-labeled with thiol, amine, biotin, or redox-reporter chemistries (e.g., methylene blue, ferrocene) for direct immobilization on gold or carbon electrodes [2], [9], [12]. Their smaller molecular footprint (usually one order of magnitude less molecular weight than IgG) allows for higher density of functionalisation of the electrode surface, and for lower steric crowding in multiplexed sandwich- and target-induced conformational-change, or "signal-on"/"signal-off"" assay formats, including the electrochemical aptamer-based (E-AB) sensor shown in Fig. 3(B) [2]. Reported limitations are relatively small number of clinically-relevant BC biomarker validated aptamer sequences, nuclease sensitivity in the absence of treatment in biological matrices, and a relatively weak regulatory and manufacturing-standardization pathway [1] and [11].

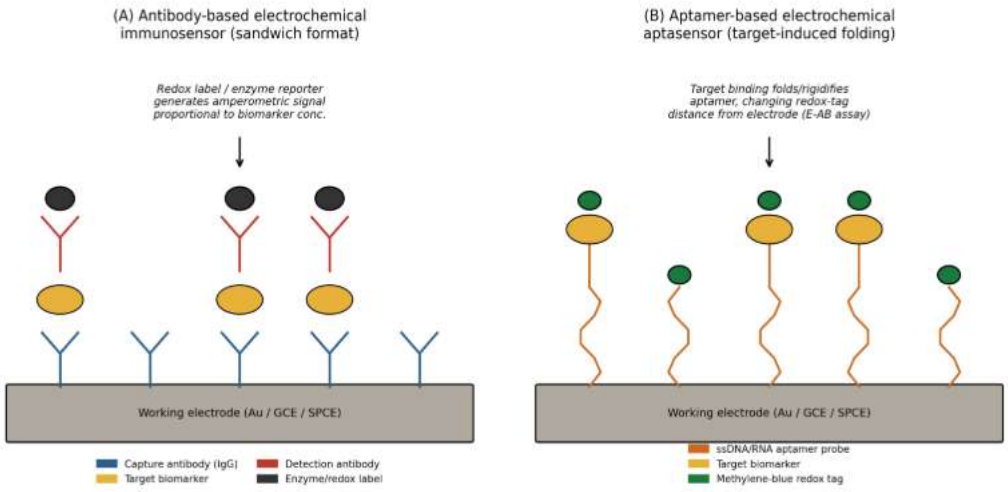

Fig. 1. Schematic comparison of antibody-based (sandwich immunosensor, A) and aptamer-based (electrochemical aptamer-based / E-AB, B) recognition architectures on an electrode surface. Original illustration prepared for this review, informed by mechanisms described in [1], [2], [9].

III. ELECTROCHEMICAL TRANSDUCTION FOR BC BIOMARKERS

Various complementary transduction modes of electrochemical BC biosensors are available as described in the literature for 2021-2026. The current change that takes place upon binding of a target molecule to a redox molecule (e.g., methylene blue, ferrocene, an enzyme substrate, or a nanoparticle catalytic tag) is the basis of amperometric platforms, including cyclic voltammetry (CV), differential pulse voltammetry (DPV) and square-wave voltammetry (SWV) [3, 6]. Alternatively, for both antibody and aptamer functionalized electrodes, the variation in the charge-transfer resistance at the interface, induced by the insulating bulk of the bound biomacromolecule is measured, as in electrochemical impedance spectroscopy (EIS) [1, 9].

Both classes of recognition elements are most commonly used with nanomaterial signal-amplification approaches, such as gold nanoparticles, reduced graphene oxide, carbon nanotubes, metal–organic frameworks (ZIF-90, Co–Fe-MOF), quantum dots, and magnetic nanocomposites, to generate increased electroactive surface area, enhance electron transfer, and offer other sites for enzyme or redox-tag conjugation, respectively, to facilitate detection at the femtomolar- to attomolar-level [3, 5, 9].

In the BC current electrochemical literature, the most widely studied biomarker is the ~185 kDa transmembrane glycoprotein receptor, HER2, which is shed in the serum, followed by the mucin-family glycoprotein CA 15-3, the glycoprotein CEA, hormone receptors ER and PR, the proliferation marker Ki-67, and circulating nucleic-acid biomarkers miR-21, miR-155, and BRCA1/TP53 gene sequences [3, 15]. The detection of nucleic-acid biomarkers is typically based on complementary DNA/RNA capture probes, but some multi-marker assays have been developed combining a nucleic-acid probe stage with a protein-detection stage (such as a combined HER2/ER dual assay of metal–organic-framework-encapsulated redox mediators and target-specific aptamers [3]). A correlative trend in the majority of studies which were available in this corpus of this review (clinical setting) is that the possibility of BC subtyping (HER2 positive versus triple negative disease) does not refer to any single biomarker, but to several biomarkers being assessed simultaneously [3,4].

IV. REVIEW METHODOLOGY

In this regard, a structured literature search was carried out in PubMed/MEDLINE, ScienceDirect, and open access (Frontiers, MDPI, Nature Portfolio, RSC, and ACS) databases for publications since January 2021 using the following combinations of the following keywords: “electrochemical” + “biosensor” + “aptamer” OR “aptasensor” + “antibody” OR “immunosensor” + the specific name of the breast cancer biomarker (HER2, CA 15-3, CA 27-29, ER, PR, Ki-67, miR-21, and BRCA1). The records included where the electrochemical (amperometric, voltammetric, impedimetric, or potentiometric) transduction platform's goal was to detect a breast-cancer associated biomarker, followed by reporting of a numerical analytical-performance metric, at a minimum, the limit of detection and the linear/dynamic range, and explicit identification of the recognition-element chemistry (antibody, aptamer, or molecularly imprinted polymer, as a non-biological comparator class). Narrative and systematic reviews, with scope and content that was similar, were kept distinct to provide input for qualitative synthesis of attributes of stability, reproducibility, and translational-readiness that were not reported at the level of individual primary

studies. Only studies which contain both optical and mass-sensitive (QCM/SPR) or purely computational aptamer-design work were included, with pre-2021 studies being included if necessary for illustration of key mechanisms, and referenced in-text.

The reported LOD values in literature have been synthesized quantitatively which are present in Tables I-II and in Fig. The molecular weight of the unit and sample matrix given by the original authors is kept in 1–2) (≈185 kDa for the HER2 extracellular domain used for molar to mass conversion, if necessary for comparability between different studies). As per the requirement of comparing LOD data of antibodies with aptamers on a head-to-head basis, the identified corpus of primary studies with directly comparable data (i.e. data with same electrode and matrix in the same studies) was limited and as such it was found that the quantitative synthesis performed here was a bounded, literature-derived, comparative summary of the primary data, rather than a formal meta-analysis with computed effect sizes, heterogeneity statistics (I^2) and estimation of publication bias from funnel-plots, which were not performed due to the limited number of primary studies available (approximately four to six studies per biomarker). This restriction is explored in more detail in Section VI. The qualitative attribute scoring (Fig. 4, Table III) is not an independent data measurement, but rather a summary of the qualitative, repeated, explicit comparative statements from the review-level sources, and is not empirical but rather an interpretive summary.

V. COMPARATIVE ANALYTICAL PERFORMANCE

A. HER2 Detection

The serum extracellular domain of HER2 (HER2-ECD) is an established prognostic and treatment-selection biomarker, and thus the most-studied electrochemical BC analyte in the reviewed corpus [6, 7, 8]. Some representative platforms for the electrochemical recognition elements, for both classes, are listed in Table I. On the other hand, a recent article [6] reported the LOD of a pencil-graphite immunosensor based on antibody at 10 femograms per millilitre, obtained by optimizing the linear range, while a dual-analyte gold-chip immunosensor for the simultaneous targeting of HER-1 and HER-2 achieved a low-picogram detection limit only after gold-nanoparticle signal amplification, which is not a property of the antibody itself. Three orders of magnitude detection limits have been reported recently in the representative pure-aptamer based platforms [4] and [5] ranging from sub-picogram to sub-nanogram per mL, and a sandwich assay combining antibody with aptamer as the detector has been reported with a detection limit of sub-nanogram per mL which is sufficient for the clinical decision threshold [8].

TABLE I. REPRESENTATIVE ELECTROCHEMICAL HER2 BIOSENSORS BY RECOGNITION-ELEMENT CLASS (2022–2025). *Sadeghi et al. report LOD as 0.667 ng/mL; converted to pg/mL for cross-row comparability. n.r. = not reported at single-analyte resolution.

Study [Ref]	Recognition Element	Electrode / Nanomaterial	Technique	Linear Range	LOD	Matrix
Chaudhary et al., 2023 [6]	Antibody	Pencil graphite / anti-HER2 IgG	Amperometric	1 fg/mL–20 ng/mL	1 fg/mL	Human serum
Wignarajah et al., 2023 [7]	Antibody (AuNP-enhanced)	Au sensor chip / AuNP–HRP	Amperometric	5–80 ng/mL	50 pg/mL	100% serum

Study [Ref]	Recognition Element	Electrode / Nanomaterial	Technique	Linear Range	LOD	Matrix
Sadeghi et al., 2022 [8]	Aptamer	rGO / Rh-NP / graphite	DPV	10–500 ng/mL	667 pg/mL*	Buffer / spiked serum
Hybrid sandwich assay (reported in [5])	Antibody (capture) + Aptamer (reporter)	SWNT / AuNP / AP-label	DPV	1 pg/mL–100 ng/mL	0.23 pg/mL	Whole blood
Multiplex nanocomposite array (reported in [4])	Mixed / panel-level	Various nanocomposite arrays	Multiplex DPV/SWV	n.r.	0.5 ng/mL	Serum

The number of different LOD values reported for a recognition-element class (Fig. 1: from antibody-based platforms only eight orders of magnitude, compared to the range of LOD values between the class medians), indicates that the identity of the recognition element is not as critical as electrode nanoarchitecture and amplification chemistry in establishing ultimate LOD value for HER2 [1], [4]. As per the findings of the review paper by Ben Moussa et al. [1] which showed that there is no categorical advantage between the two recognition elements classes in comparison to similar nanomaterial platforms, the authors believe there is no superiority between the recognition element and the platform.The authors end by stating that there is no evidence of the superiority of the recognition element or of the platform.

B. CA 15-3 Detection

CA 15-3 is the most common serum marker used for the follow-up of breast cancer in the metastatic setting, and is likely to be used in conventional immunoassays with a lower limit of detection of 1–2 U/mL and a clinical cut-off of 30 U/mL [4]. As shown in Table II and Fig. 2, the sub-clinical-threshold detection limits of the electrochemical aptasensors in this review clearly show the advances of aptamers immobilization on a nanochannel or nanocomposite platform from 2022 to 2024. A label-free g-C3N4/Fe3O4 magnetic nanostructure aptasensor achieved a detection limit of 0.2 U/mL and a reagentless redox-probe immobilized in the nanochannel structure itself provided a better detection limit of 0.13 mU/mL for the format of the methylene-blue labeled nanostructure [9, 10]. However, when aptamer probes with the same affinity are used for each channel, multiplexing does not necessarily result in a proportional decrease in sensitivity as demonstrated in the multiplexed gold-nanoparticle/3D-graphene-hydrogel aptasensor for simultaneous detection of CEA and CA 15-3, which achieved a 5.8×10^{-3} U/mL for CA 15-3 [4]. The molecularly imprinted polymer (MIP) sensor is a synthetic molecule that mimics the antibody design to recognize a specific molecule, as a competitor in synthetic recognition benchmarks is shown in Table II with the same working range as the antibody sensor (0.001 U/mL) [11].

TABLE II. REPRESENTATIVE ELECTROCHEMICAL CA 15-3 BIOSENSORS (2022–2024).						
Study [Ref]	**Recognition Element**	**Electrode / Platform**	**Technique**	**Linear Range**	**LOD**	**Matrix**
Pourmadadi et al., 2022 [9]	Aptamer	g-C3N4/Fe3O4 / GCE	SWV / EIS	1–9 U/mL	0.2 U/mL	Human serum
Xing et al., 2023 [10]	Aptamer	Bipolar silica nanochannel (bp-SNA) / ITO	Reagentless DPV	0.001–500 U/mL	0.13 mU/mL	Fetal bovine serum
Multiplex CEA+CA15-3 aptasensor (reported in [4])	Aptamer	AuNP / 3D-graphene hydrogel / GCE	DPV	up to 150 U/mL	5.8×10^{-3} U/mL	Serum
Oliveira et al., 2024 [11]	Molecularly imprinted polymer (comparator)	Electropolymerized MIP film	DPV	0.001–100 U/mL	sub-mU/mL range	Buffer

C. Additional Biomarkers

The detection limits of CEA (3.9 pg/mL) and MUC-1 (0.53 ng/mL) obtained by CEA aptamer-based and CEA multiplex format were much lower than the corresponding conventional clinical assay sensitivity [4] respectively, while the detection limit of circulating miRNA panels (10-15–10-16 M) obtained by nucleic acid-probe-based transduction was even lower than the conventional clinical assay sensitivity. As opposed to antibody or aptamer recognition, genetic markers like BRCA1 and TP53 are detected through DNA-hybridization probes, for instance, a graphene-oxide/ionic-liquid sensor detecting the target gene sequence sequence BRCA1, with a detection limit of 1.48µg/mL for the synthetic samples [12]. The CD44 biomarker has been reported in the literature using near matched analytical comparison between different classes of recognition elements (aptamer vs antibody), with an LOD of 0.087 ng/mL (impedimetric detection) and an LOD of 2.17 pg/mL (electrochemical detection) [13].

VI. QUANTITATIVE AND QUALITATIVE SYNTHESIS

Tabulated in the tables below are the LOD values summarised by recognition-element class, which will illustrate the wide range of heterogeneity found in the electrodes, the amplification of the nanomaterials, the matrix of the samples and even the different units of concentration. The antibody-based LOD values are between 1 fg/mL and 0.5 ng/mL, and the aptamer- and hybrid-recognition platforms are between 0.23 pg/mL and 0.667 ng/mL, which is not sufficient to draw a statistical conclusion that one class of platforms has an inherent sensitivity advantage compared to the other. Notably, during 2021–2026, none of the antibody based electrochemical CA 15-3 platforms reported in the literature had a detection limit below the sub-clinical threshold (Table II, n = 4), which is the vast majority of all electrochemical CA 15-3 innovation during the last seven years.

Table III and Fig. 4 show the six common quantitative comparison attributes as a qualitative consensus synthesis of the six review-level sources listed above: [1, 2, 12] analytical sensitivity, batch-to-batch

reproducibility, thermal/chemical stability, production cost-efficiency, ease of multiplexing and regulatory/clinical maturity. The scoring is from 1 (poor) to 5 (excellent), and is based on the consensus of the sources of review cited rather than a calculation done by the authors; it is designed to facilitate interpretation instead of to produce a numerical result.

TABLE III. QUALITATIVE COMPARATIVE ATTRIBUTE SCORING (1 = POOR, 5 = EXCELLENT).

Attribute	Antibody	Aptamer	Basis
Analytical sensitivity	4	4	[1], [9], [10]
Batch-to-batch reproducibility	2	5	[1], [2], [12]
Thermal / chemical stability	2	4	[1], [2], [12]
Production cost-efficiency	2	4	[1], [2]
Ease of multiplexing	3	4	[2], [3]
Regulatory / clinical maturity	5	2	[1], [11]

There are two patterns that emerge from this combined quantitative-qualitative synthesis. First, the sensitivity difference between two classes of recognition elements is small compared to the difference resulting from the nanomaterial amplification strategy, as found by Ben Moussa et al. [1] when considering the choice of recognition element in conjunction with the design of the electrodes. Second, the two classes differ most strongly in the translational characteristics, such as stability and reproducibility, which directly impact on the device shelf life, manufacturing yield and point-of-care viability, rather than the analytical attributes, as all the existing in vitro diagnostic assays used for the detection of HER2, CA 15-3, and related markers are antibody-based, with the overwhelming majority of approved tests being of this very type [1], [4]. This separation implies that at this point, the two recognition-element classes complement each other, and that near-term clinical translation is more likely for antibody-based devices and next-generation POC and wearable devices are more likely to favor aptamer-based designs [2],[12].

VII. STABILITY, REPRODUCIBILITY, AND CLINICAL TRANSLATION

The tertiary and quaternary structure of antibodies are responsible for antibody stability; exposures to extreme pH, temperature, ionic strength and freeze–thaw cycles will disrupt the protein structure, thus compromising the shelf life of immunosensors and often requiring cold-chain storage and refrigerated shipment (which is not desirable in resource-poor or field environments) [1, 2]. In contrast, aptamers are chemically synthesized oligonucleotides that can be chemically lyophilized and are bound to their target molecule after room-temperature storage, and can be denatured and refolded at a reproducible rate by simple thermal annealing without any loss of their binding function, which we directly exploit in reagentless and regenerable aptasensor formats, including the bipolar-silica-nanochannel CA 15-3 platform described in Section V-B [2], [10].

Similarly, batch to batch reproducibility is observed; antibodies are produced via biological methods (animal immunization, hybridoma culture, or recombinant expression) and thus there are known inter-lot differences in glycosylation, avidity and purity, which may necessitate re-validation of assay calibration curves between lots of the antibody [1]. After selection through SELEX, the aptamer sequences are

synthesized on a solid phase using standard chemical synthesis techniques resulting in a batch to batch consistency more akin to small molecule reagents than biologics [2, 12]. This distinction is often used in the aptasensor literature to claim aptamers to be "chemical antibodies" or "plastic antibodies" in addition to molecularly imprinted polymers as a synthetic alternative to antibody-based platforms to lower the biological variation widely found in antibody-based platforms [1].

The stability and reproducibility are not to be equated with the maturity level of antibody-based immunosensing; the translation of aptamer-based electrochemical biosensors for BC biomarkers is still at the early stages. Some of the factors identified across the literature reviewed include: a relatively small validated aptamer sequence library for clinically relevant biomarkers for BC, with the majority of the reviewed primary studies performed using spiked buffer, spiked serum or a small number of patient samples versus prospective clinical cohorts; relatively few large cohort clinical validation studies exist, most of the reviewed primary studies were validated in spiked buffer, spiked serum or a limited number of patient samples with none performed in prospective clinical cohorts; a more established regulatory pathway for antibody-pair immunoassays compared with the less standardized regulatory pathway for in vitro diagnostic reagents based on oligonucleotides; and possible nuclease sensitivity of unmodified aptamers for in raw biological matrices as compared to pre-processed serum which most of the reviewed primary studies minimize by chemical backbone modification or working in pre-processed serum instead of raw biological matrices.

VIII. CHALLENGES AND FUTURE DIRECTIONS

The issues of methodology and translation re-appear across the literature reviewed. First of all, the various methods used to validate the electrode substrates, the redox-label chemistries, the sample matrices, and even the statistical convention used to calculate the LOD (three-sigma, signal-to-noise-ratio, or calibration-curve-intercept methods) make direct cross-study comparisons difficult, and as indicated in Section IV will make a formal pooled meta-analysis difficult to conduct at present given the existing body of literature [1] [4]. Establishment of a minimum reporting standard for electrochemical BC biosensor studies, as has been done for clinical diagnostics and quantitative PCR, respectively, would be of great help to the comparability of future antibody-aptamer analytical claims.

Second, validation of clinical matrices, compared with the number of publications on proof-of-concept nanomaterial-engineering remains sparse; few studies reported in this review have been done with unprocessed whole blood or a prospective patient population of clinically relevant size for testing, and interference from matrix components (hemoglobin, lipids, non-target proteins) is not consistently described [1, 3]. Third, multiplexing, summarized in Section III, is not completely solved by the use of spatially resolved electrode arrays and orthogonal redox-tag chemistries, except for just starting [3,4].

From the literature surveyed, three trends appear to be well supported for the future. First, the high affinity of antibody capture and the compactness, stability and chemical tunability of the aptamer based signal generating element can be combined in a hybrid architecture as is already achieved in HER2 sandwich assays described in Section V-A [4] [5]. Second, it is likely that the addition of either a recognition-element class to the other, i.e. continued integration of high-surface-area nanomaterials (MOFs, quantum dots, engineered 2-D materials) with either recognition-element class, will continue to be the most important means of further LOD improvement, as observed in Section VI that amplification chemistry is currently the more important means of LOD improvement than recognition-element identity [1, 3]. Third, the number of available validated-sequence aptamers will catch up to the available validated-sequences of

antibodies for priority BC biomarkers in the next few years, thanks to computational and machine-learning-driven aptamer discovery platforms that are now improving the prediction of the affinity of binders, and reducing the number of SELEX iterations required to create them [2].

IX. CONCLUSION

This comparative systematic review gathered and studied publications of electrochemical biosensors for breast cancer detection of biomarkers for the period 2021–2026 using antibody- and aptamer-based recognition elements. The comparison between the detection limit of the different methods in order of quantitative comparison showed the same performance range for all classes of recognition element, the amplification strategy used with nanomaterials also had a significant effect on the analytical sensitivity than just the class of recognition element. The qualitative translation indicates that aptamer based platforms have strong advantages in stability, batch-to-batch reproducibility and cost in point-of-care settings, while antibody based platforms have strong advantages in regulatory and clinical experience. This synthesis must not be considered as a thorough statistical meta-analysis since there are not many direct comparisons without controls and comprehensive prospective studies to validate the clinical use of these products before a formal pooled effect-size comparison is possible. In the immediate future, hybrid antibody–aptamer sensor architectures and further developments of signal amplification capabilities using nanomaterials appear to be the most promising lines of research for electrochemical breast cancer biosensors that are potentially stable and manufacturable and will eventually be used in the clinical setting with high analytical sensitivity.

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