

Quo Vadis, Electrochemical DNA Biosensor? Lessons from Three Decades of SNP Sensing

Dalius Ratautas,* Skomantas Serapinas, Deimantė Stakelytė, Simona Guobužaitė, Andrijana Danytė, and Marius Dagys



Cite This: *ACS Sens.* 2026, 11, 5296–5314



Read Online

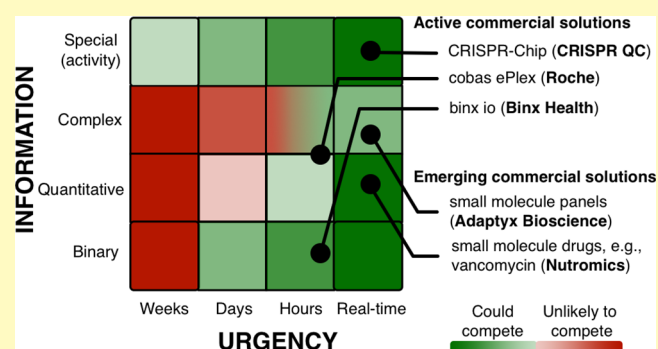
ACCESS |

Metrics & More

Article Recommendations

ABSTRACT: Electrochemical DNA biosensors have been studied for over three decades, producing thousands of publications and a sophisticated engineering toolkit. However, a broad clinical adoption remains limited. The COVID-19 pandemic served as a stress test—global demand, unprecedented funding, accelerated regulatory pathways, and a clearly defined genomic target—yet electrochemical nucleic acid biosensors played no meaningful role in the diagnostic response, indicating that the barriers to translation are structural. Here, rather than cataloging sensing formats, we analyze the field framing progress through three interacting constraints focusing on single-nucleotide polymorphism (SNP) sensing: the biological realities of nucleic acid targets, the physical limits of surface-based hybridization, and the clinical/market environment that governs adoption. We find that many advances optimize analytical performance under laboratory conditions while leaving application complexity largely unresolved. Yet, viable niches emerge at the intersection of low information complexity and operational urgency—rapid pharmacogenomic genotyping, now driven by directive clinical guidelines, and infection diagnostics, where simplicity matters more than sophistication. A broader redirection emerges when DNA acts not as the analyte but as a functional tool: Electrochemical aptamer-based sensors are entering commercial markets; nuclease and enzymatic activity profiling exploits the regime where these sensors perform best; and therapeutic oligonucleotides—invisible to standard sequencing workflows—map naturally onto the platform's strengths. The field's most transferable contribution may not be DNA detection itself, but the programmable molecular interfaces it has developed.

KEYWORDS: electrochemical DNA (E-DNA) biosensors, single-nucleotide polymorphism (SNP) sensing, DNA hybridization, clinical translation, point-of-care diagnostics, genomic diagnostics, electrochemical aptamer-based (E-AB) sensors, pharmacogenomics, nuclease activity detection, therapeutic oligonucleotide monitoring



THE UNDELIVERED PROMISE OF ELECTROCHEMICAL DNA BIOSENSING

Expectations versus Reality: DNA Is Not Glucose

The glucose biosensor, developed from Clark and Lyons' 1962 work,¹ is the most successful electrochemical biosensing technology—specific, rapid, inexpensive, and addressing a massive clinical need. Its success raised a natural expectation: if glucose, why not DNA? Once DNA was shown to be electroactive, the field embraced a vision that electrochemical detection would enable rapid, low-cost DNA analysis: “credit card-sized sensor arrays for clinical applications such as detection of pathogenic bacteria, tumors, and genetic diseases”.² More than 25 years later, that vision has only been partially realized.

In our view, the lack of translation lies in mismatches between expectations and reality across three dimensions—biological, technological, and clinical/market—which we

identified independently nevertheless mirror the framework proposed by Nagata and Sode,³ suggesting that these constraints are structural. Biologically, glucose is present at high, relatively stable concentrations, whereas DNA targets typically occur at orders of magnitude lower and highly variable levels. Technologically, glucose sensing benefits from highly efficient and stable enzymes that provide catalytic signal amplification, while DNA recognition relies mainly on hybridization. Clinically, glucose monitoring addresses an urgent, widespread,

Received: March 23, 2026

Revised: May 12, 2026

Accepted: May 15, 2026

Published: June 29, 2026



life-critical need, whereas electrochemical DNA biosensing has rarely met a similar demand. This does not mean the field lacks a future—unlike glucose sensing, which targets a single metabolite, DNA sensing offers a programmable platform capable of detecting virtually any structure-defined target. This broader potential comes with greater biological and technological complexity, making translation into practical devices significantly more challenging.

This review traces the history of electrochemical DNA biosensing through the lens of single-nucleotide polymorphism (SNP) detection as a key target application, from the field's origins to its current maturity. We examine the biological complexity of nucleic acid targets, the physical limits of surface-based hybridization, and the genuine technological achievements, as well as the remaining hard limits related to translation. We also review the competitive landscape, commercial device history, and clinical trends that define the translation environment. Finally, we identify where electrochemical nucleic acid sensing most credibly belongs, arguing that the field becomes most promising when nucleic acids are viewed not as analytes to be detected but as programmable molecular interfaces and versatile biochemical substrates that enable sensing strategies beyond nucleic acid detection itself.

A brief clarification of the scope is necessary. The term “electrochemical DNA detection” is broad enough to include technologies such as nanopore sequencing. In this review, however, we focus on electrochemical DNA biosensors based on surface hybridization, in which an immobilized oligonucleotide

probe on an electrode transduces target binding into an electrical signal.⁴ Electrochemistry-assisted sequencing technologies are discussed only briefly as part of the broader competitive technological landscape.

A Brief History of Electrochemical DNA Biosensors

DNA sensing can be divided into three periods: before 1990 (foundation), from 1990 to 2019 (COVID-19 pandemic, growth), and the post-COVID-19 period (maturation). These periods differ substantially in dominant contributors, research focus, methodological approaches, and publication output. Due to space constraints, this review highlights selected studies that, in our view, represent cornerstone achievements. We queried the Web of Science using the same keyword strategy as Paleček:⁵ “(polarograph* AND DNA) OR (electrochem* AND DNA) OR (electrochem* AND “nucleic acid*”)”. Paleček reported sustained exponential growth up to 2008. Our analysis shows that publication output plateaued at approximately 1300–1500 papers per year from 2019 (timeline in Figure 1), following approximately three decades of growth.

Foundation (1960–1990). In 1960, Paleček demonstrated that DNA is electroactive: Double-stranded (ds) and single-stranded (ss) DNA show distinct electrochemical behavior on mercury electrodes.⁶ Paleček later reflected on this founding period in his 2009 review, “Fifty Years of Nucleic Acid Electrochemistry”, which is an important historical overview.⁵ Around the same time, Miller (1961) showed that DNA and

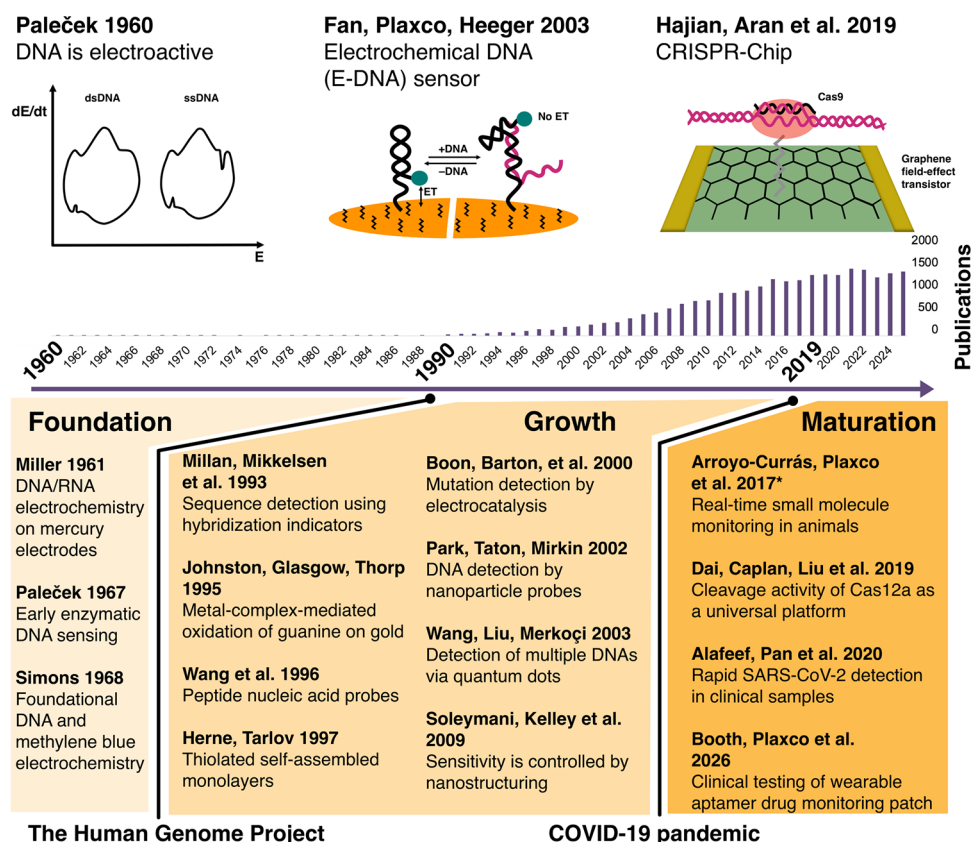


Figure 1. Timeline of the field. The field originates from the discovery of DNA electroactivity by Paleček in 1960 and early DNA electrochemistry studies in the 1960s. The introduction of hybridization-based electrochemical detection in the 1990s triggered rapid growth, followed by the development of diverse sensing architectures, including nanoparticle amplification, E-DNA sensors, and CRISPR-based platforms. The publication rate increased markedly after 1990, plateauing from 2019 to 2020. *Although the work was demonstrated in 2017, we assign it to the maturation period because of a thematic fit.

RNA adsorb onto mercury electrodes and quantified surface coverages, establishing early principles of DNA–electrode interfaces.⁷ Paleček (1967) further demonstrated electrochemical differences between native and nuclease-treated DNA, representing one of the earliest examples of functional DNA-based sensing.⁸ In 1968, Simons presented foundational work on methylene blue–DNA electrochemistry, showing that MB binds DNA primarily through hydrophobic interactions with electrostatic contributions—a property central to many contemporary biosensors.⁹ Between 1960 and 1989, approximately 10 papers per year were published, primarily from the groups of Berg, Miller, Nürnberg, Paleček, and Reynaud,¹⁰ establishing fundamental principles of the field.

Growth (1990–2019). Research output accelerated sharply from 1990, catalyzed by the Human Genome Project.¹¹ The field's key technologies were established: sequence-selective detection using hybridization indicators;^{12,13} peptide nucleic acid probes for SNP discrimination;¹⁴ thiolated DNA/mercaptohexanol self-assembled monolayers (SAMs) on gold, which became the immobilization standard;^{15,16} Ru(bpy)₃²⁺-mediated electrocatalytic guanine oxidation;¹⁷ mutation detection via DNA charge transport;¹⁸ and nanoparticle-based electrical detection using gold nanoparticles with silver enhancement—¹⁹ later shown to quantum-dot reporters via stripping voltammetry.²⁰

In our opinion, the most consequential advance of this era came in 2003, when Fan et al. reported the electrochemical DNA (E-DNA) sensor—a reagentless, reusable, structure-switching sensor using a ferrocene-based reporter loop probe on gold.²¹ This architecture became the foundation for a family of folding-based sensors and was demonstrated with PCR amplicons via signal-off²² and signal-on²³ formats and later extended to protein detection via aptamers (E-AB sensors).²⁴ Willner et al. developed multiple signal amplification strategies, including DNzyme cascades and hemin/G-quadruplex HRP-mimicking systems,²⁵ and Soleymani et al. developed microelectrodes controlling detection limits by surface nanostructuring.²⁶

Maturation (2019–2026). The COVID-19 pandemic catalyzed a surge in electrochemical nucleic acid detection research while simultaneously revealing the field's persistent translational gap—despite many publications describing SARS-CoV-2 biosensors, none achieved significant clinical deployment, with RT-qPCR and lateral flow antigen tests dominating clinical testing.²⁷ Many sensors were reported in 2020–2022, including notable advances such as an AuNP-based chip detecting as few as 6.7 copies/μL in clinical samples.²⁸ However, most were validated only with synthetic or spiked samples, and, to the best of our knowledge, none achieved the true positive/negative performance values required for clinical use.²⁹

This maturation period produced two distinct extensions of electrochemical DNA sensing. One direction integrated CRISPR-Cas recognition with electrochemical transduction. Key examples include the CRISPR-Chip reported by Hajian et al., which coupled catalytically inactive Cas9 with graphene field-effect transistors (FETs) for unamplified genomic DNA,³⁰ Cas12a collateral-cleavage systems integrated with electrochemical readout,³¹ Cas9-graphene FET for SNP detection,³² and Cas13a-based systems coupled to electrochemical platforms.³³ A second trajectory extended E-DNA sensors to electrochemical aptamer-based (E-AB) sensing. Arroyo-Currás et al. demonstrated the measurement of drug concentrations directly in the bloodstream of live animals using structure-switching aptamers³⁴ followed by a landmark pilot clinical study

of real-time vancomycin monitoring in humans.³⁵ Post-COVID work has also increasingly focused on multiplexed detection, integration of isothermal amplification with electrochemical readout in closed cartridge formats,³⁶ or isothermal SNP-discrimination approaches,³⁷ addressing the sample-to-answer gaps.

Box 1. Section highlights

- The glucose biosensor created a natural expectation that DNA could be detected electrochemically under a similar paradigm; more than 25 years later, this vision has only been partially realized.
- Unlike glucose, electrochemical DNA sensing faces structural mismatches across three dimensions: biological, technological, and clinical/market.
- Foundational work by Paleček et al. established DNA electroactivity and DNA–electrode surface principles.
- During the field's growth period, key architectures emerged, including SAM-based probe immobilization, nanoparticle amplification, and reagentless E-DNA sensors.
- Publication output plateaued at ~1300–1500 papers per year after 2019–2020, consistent with a maturing field.
- The COVID-19 pandemic catalyzed a publication surge but also exposed the translational gap: Despite many SARS-CoV-2 biosensor reports, none achieved significant clinical deployment.
- Nevertheless, DNA sensing retains a unique advantage: programmability, enabling recognition of virtually any structure-defined nucleic acid target.

■ BIOLOGICAL REALITY: DNA SENSING IS AGAINST UNFAVORABLE ODDS

In this section, we review the biological targets most frequently proposed for electrochemical DNA biosensors and examine the constraints on their detection. We show that the typical concentration regimes of clinically relevant DNA targets, their molecular forms, and the complexity of biological matrices create gaps with the operating regime of surface-based electrochemical DNA/SNP biosensors. Together with hybridization thermodynamics and transport limitations, these factors define the practical boundaries within which a sensor must operate.

The Dynamic Range Mismatch and Sample Complexity

Concentration reality across clinical targets. In the context of SNP sensing, electrochemical DNA biosensors have primarily targeted (i) cancer-related cell-free DNA (cfDNA), (ii) germ-line variants relevant to pharmacogenetics, and (iii) pathogen-specific targets.

Cancer-related cfDNA circulates in plasma at staggeringly low concentrations (Figure 2a). For example, fewer than two copies per mL of plasma have been reported in stage I, increasing to 20–200 copies at advanced stages and ~2000 copies/mL for metastatic breast cancer³⁸ (molar 10^{−21}–10^{−18} M). For comparison on a logarithmic scale, glucose concentrations are

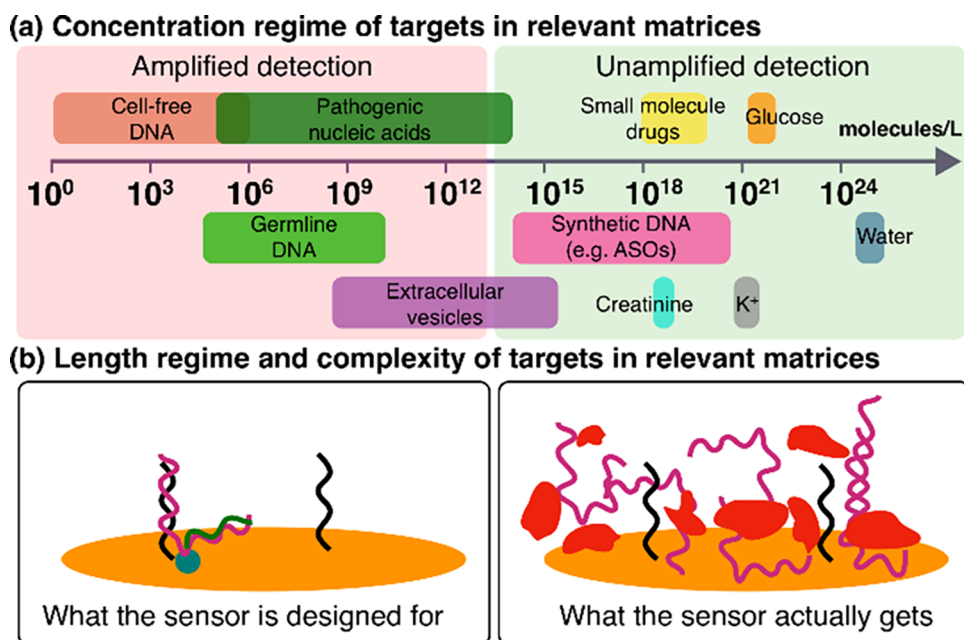


Figure 2. Complexity of biological targets. (a) Concentration regime of targets in relevant matrices. Extracellular vesicles,⁴⁸ creatinine, glucose, K^+ , and water are included for scale comparison. (b) Length regime of targets in clinical samples: a contrast between what a DNA biosensor is typically designed for and what is actually present in clinical samples. Here: ASOs—antisense oligonucleotides.

much closer to water (~ 4 orders of magnitude) than to cfDNA (~ 15 – 18 orders). Furthermore, a specific SNP-bearing allele may constitute only a fraction of this sparse pool: The variant allele frequency can fall below 0.01%, embedding the target in a 99.99% background of competing wild-type sequence—this is not a sensitivity shortfall to be engineered away—it is a fundamental mismatch in the operating regime, where even PCR-based assays and next-generation sequencing (NGS) struggle without pre-enrichment.^{39,40}

Germline targets are more abundant but still orders of magnitude below the typical electrochemical operating range (Figure 2a). Human saliva contains approximately 5.65×10^5 genome copies per mL,⁴¹ while blood provides 4 – 11×10^6 leukocyte-derived genome copies per mL.⁴² Both saliva and blood reflect systemic biomarker status to varying degrees.^{43,44} As a result, the concentration of any specific mutant sequence in clinical samples is extremely low, frequently reaching the fM–aM range, which is accessible to amplification-based methods but remains challenging for direct electrochemical detection.

Pathogenic nucleic acids represent the most favorable concentration regime (Figure 2a). For example, in severe meningococcal disease, blood concentrations reach a median of 8.4×10^6 copies/mL and spike to 1.8×10^9 copies/mL in critical cases.⁴⁵ Pneumococcal bacteremia shows concentrations from 10 to 1.5×10^6 (median 1075) copies/mL with septic shock patients reaching median loads up to 1.3×10^4 copies/mL.⁴⁶ SARS-CoV-2 nasopharyngeal viral loads reached 10^3 – 10^9 copies/mL in critically ill and fatal cases.⁴⁷ These concentrations are orders of magnitude higher than cfDNA and approach the pM–nM range in severe infections—within borderline reach of unamplified electrochemical detection.

Target length mismatch and biofouling. Genomic DNA extracted from samples is double-stranded, ranging from kilobases to tens of kilobases in length (20–50 kb from blood,⁴⁹ 150–300 bp cfDNA),⁵⁰ while a hybridization-based biosensor

requires a short (~ 20 – 40 bp) ssDNA (Figure 2b). Bridging this gap—denaturing the duplex, fragmenting or amplifying to the appropriate length, and isolating—constitutes sample preparation bottlenecks. Almost every reported electrochemical SNP detection from clinical material uses DNA purification with commercial kits and/or amplification with locus-specific primers. From our experience, applying locus-specific primers is not straightforward, as the received amplicon will not be the same length as a synthetic DNA used for sensor development; thus, further optimization may be needed.³⁷ Biofouling is an additional barrier for DNA-modified electrodes (Figure 2b). In E-AB sensors, the best-studied *in vivo* case, exposure to undiluted whole blood causes a signal drift mainly through soluble high-molecular-weight blood proteins, with fouling and degradation both contributing.⁵¹

Hybridization and SNP Discrimination Limits

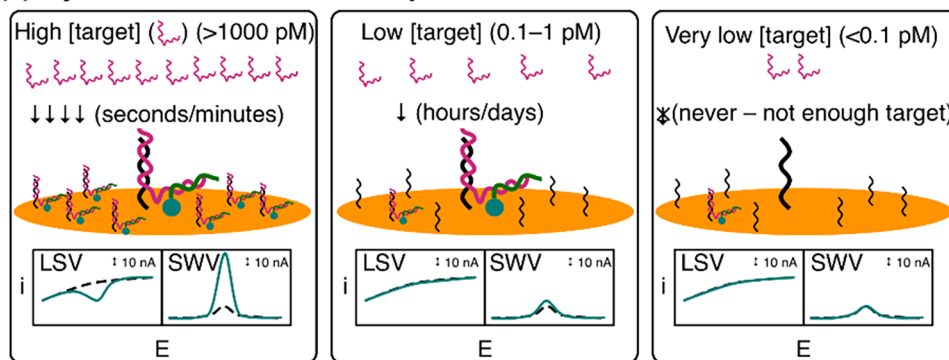
Hybridization limits on surfaces. In this section, we discuss constraints that impose a limit on direct (unamplified) surface-based detection. We show that this limit is in the range of 0.1–1.0 pM when the sensing interface is a macroscopic planar surface (cm^2 scale) exposed to a finite sample volume. For more details, readers are referred to those papers.^{52,53}

For a typical 30 bp duplex, the hybridization free energy (1 M NaCl, pH 7.0, 37°C) is approximately $\Delta G^\circ \sim -45$ kcal/mol.^{54,55} From eq 1, the equilibrium constant (K) is $\sim 10^{32}$. Duplex formation is therefore overwhelmingly favorable: If a target encounters a complementary probe, then hybridization will occur.

$$\Delta G = -RT \ln(K) \quad (1)$$

However, before hybridization can occur, the target must diffuse across the stagnant (Nernst) layer to reach the surface (Figure 3a). For a 2.0 mm-diameter surface (0.0314 cm^2), a diffusion layer thickness of $\sim 100 \mu\text{m}$, and a 30 bp DNA strand with

(a) Hybridization on macroscopic surfaces



(b) SNP discrimination

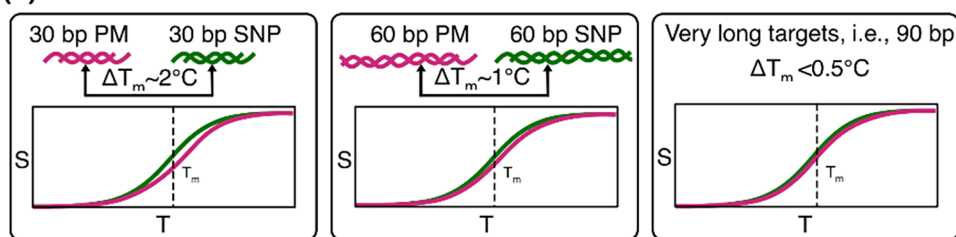


Figure 3. Fundamental constraints on electrochemical DNA hybridization sensors. (a) Effect of target concentration on surface hybridization and electrochemical response. As the target concentration decreases, mass transport becomes limiting—from rapid hybridization at >1000 pM to diffusion-limited capture at 0.1–1 pM, to physically insufficient molecule counts at <0.1 pM. Illustrative LSVs (greenish—after hybridization, black—before) and SWV responses are shown. (b) SNP discrimination narrows with increasing target length. Melting curves for a perfect match (PM, pink) and a single-nucleotide mismatch (MM, greenish) show relative ΔT_m decreasing from $\sim 2^\circ\text{C}$ at 30 bp to $\sim 0.5^\circ\text{C}$ at 90 bp, where PM and SNP become indistinguishable.

$D \sim 10^{-6} \text{ cm}^2/\text{s}$,⁵⁶ the diffusion-limited flux is $\sim 6 \times 10^4$ molecules/ cm^2/s at 1 pM and ~ 60 molecules/ cm^2/s at 1 fM (eq 2). For the 2.0 mm electrode, this yields $\sim 2 \times 10^3$ molecules/s at 1 pM and ~ 2 molecules/s at 1 fM.

$$J = \frac{D[C]}{\delta} \quad (2)$$

The minimum number of detectable molecules is set by the requirement that the resulting current exceeds the instrumental noise. The total charge associated with redox-active reporters is given by Faraday's law. For example, in linear sweep voltammetry (LSV), this charge is distributed over a characteristic timescale, and a theoretically detectable current on the order of ~ 1 pA corresponds to a total charge of $\sim 10^{-11}\text{C}$, representing a minimum of $\sim 10^7$ – 10^8 molecules. In practice, at such low coverages, LSV signals are hidden in the noise; therefore, techniques such as square wave voltammetry (SWV), which concentrate the same charge into higher effective currents allowing detection at the lower end of this range, are required.

Combining this detection requirement with the diffusion-limited arrival rates shows that the accumulation of $\sim 10^7$ – 10^8 molecules requires 1–14 h at 1 pM and impractically long times (months to years) at fM concentrations (Figure 3a). Thus, at low concentrations, mass transport—not hybridization—becomes the limitation. An even more restrictive constraint emerges when finite sample volume is considered. For a 1 mL sample at 0.1 pM, the total number of molecules present is $\sim 6 \times 10^7$. This value is already within the $\sim 10^7$ – 10^8 molecules needed. Thus, below ~ 0.1 – 0.2 pM (for a 1 mL volume), detection becomes molecule-count limited: Even if every molecule in

the sample were captured, the signal would remain below the detection even for SWV.

This analysis predicts a practical detection limit in the ~ 0.1 – 1 pM range for macroscopic, unamplified, surface-based electrochemical sensors. Early work by the Plaxco group provides an excellent demonstration.⁵⁷ Under their conditions (PerfectHyb Plus buffer, 5 h at 37°C), detection of 400 fM (0.4 pM) with a signal change of ~ 3 – 4 nA using alternating current voltammetry (ACV) was reached. Immunoassays used without amplification strategies exhibit similar sensitivities (~ 10 – 100 fM),⁵⁸ reinforcing the conclusion that such limits are governed by fundamental transport and molecule-counting constraints.

Therefore, platforms claiming aM sensitivities without amplification should explicitly address mass transport, single-molecule transduction efficiency, and signal-to-noise limitations. While nanostructured electrodes have been reported to achieve aM detection limits—apparently circumventing mass transport constraints through enhanced probe accessibility at nanoscale features²⁶ the physical basis, in our opinion, remains incompletely resolved. For example, at 10 aM in a typical 100 μL sample, fewer than 1000 target molecules are present, and kinetic demonstration at or near the claimed detection limits is important but is rarely provided in the literature.

Limits of SNP discrimination. Even if target DNA could be delivered to the sensor at adequate concentrations, the fundamental physics of energy differences between perfect match (PM) and mismatch (MM) duplexes imposes a limited detection window for sequence lengths of ~ 15 – 35 bp.

Let us consider three cases: 30, 60, and 90 bp targets (Figure 3b). For a 30 bp target, the parameters per base pair for 50% GC content are $\Delta H^0 \sim -8$ kcal/mol and $\Delta S^0 \sim -22$ cal/(mol K) derived

by the nearest-neighbor model.⁵⁴ Thus, a PM duplex has total $\Delta H^0(\text{PM}) \sim -232$ kcal/mol and $\Delta S^0(\text{PM}) \sim -638$ cal/(mol K). At $C_T = 10^{-6}$ M and under standard conditions, T_m is⁵⁴

$$T_m = \frac{\Delta H^0}{\Delta S^0 + R \ln(C_T/4)} \quad (3)$$

Here, $R = 1.987$ cal/(mol K) and $T_m(\text{PM})$ is calculated at ~ 74 °C. A single MM gives $\Delta H^0(\text{MM}) \sim -223$ kcal/mol and $\Delta S^0(\text{MM}) \sim -616$ cal/(mol K) and, using eq 3, $T_m(\text{MM})$ is ~ 72 °C. This window ($\Delta T_m \sim 2$ °C) provides a measurable signal difference. Extending calculations to 60 bp gives $T_m(\text{PM}) \sim 82$ °C and $T_m(\text{MM}) \sim 81$ °C. At 90 bp, $T_m(\text{PM}) \sim 85$ °C and $T_m(\text{MM}) \sim 84.5$ °C. Thus, at >60 bp, ΔT_m falls in <1 °C differences—the signal difference between PM and MM becomes marginal. This establishes a practical limit on target length for hybridization-based SNP detection of ~ 15 – 35 bp. An important caveat and illustration is that, while fragments of ~ 100 – 300 bp are analyzed by melting analysis in industry, this analysis relies on high-resolution melting techniques capable of very narrow discrimination of T_m values (e.g., ~ 0.25 °C) as well as fine-tuning of reaction conditions (e.g., ionic strength).⁵⁹

This constraint imposes sample-processing limitations. Genomic DNA must first be converted into a usable target, e.g., by PCR with locus-specific primers, adding complex steps and, paradoxically, shifting the technology from a true sensor toward an analytical method.⁶⁰ Alternatively, DNA recognition approaches can be used, such as sandwich formats using short allele-specific reporters to interrogate longer captured amplicons. From our own experience, even after amplification, PCR amplicons behave differently from synthetic oligonucleotides: A portion of the target is “overwritten” by primers, producing overhangs—which repel incoming shorter reporter strands, requiring sensor redesign, e.g., incorporation of spermine-conjugated ZNA probes to neutralize surface charge,³⁷ downward reporter geometry,⁶¹ or introduction of hairpin probes.⁶²

Box 2. Section highlights

- Clinically relevant DNA targets (cfDNA, germline variants, and pathogens) span extreme concentration regimes, with cfDNA in the 10^{-21} – 10^{-18} M range.
- SNP allele fractions can fall below 0.01%, placing targets within a vast excess of near-identical competing sequences.
- Native DNA is long and double-stranded, whereas sensors require short ssDNA, making denaturation, fragmentation, or amplification needed.
- Hybridization is thermodynamically favorable—the true limitation is mass transport and the finite number of molecules reaching the surface.
- For macroscopic, unamplified sensors, these constraints impose a practical detection floor of ~ 0.1 – 1 pM and SNP discrimination window of ~ 15 – 35 bp.
- Biofouling is an additional engineering problem, whereas concentration, transport, and target-format limits are physical constraints.

■ TECHNOLOGICAL REALITY: ACHIEVEMENTS ARE GENUINE, BUT LIMITS ARE HARD

The limitations described above should not downplay genuine and creative technological achievements. The field has developed a sophisticated toolkit for electrochemical DNA sensing. In this section, we discuss genuine progress of surface chemistries, signal transduction innovations, and highlight technological limits, which, in our opinion, are not yet fully resolved.

Genuine Progress

Probe architecture and surface engineering. The transition from mercury drop to solid gold electrodes was enabled by thiol-based SAM protocols: Thiolated DNA probes co-assembled with short-chain alkanethiols (typically mercaptohexanol, MCH), which backfill unoccupied surface sites and reduce non-specific adsorption and parasitic reactions.^{15,16} This became the universal standard for gold electrode DNA sensors. Alternative immobilization strategies include amino-functionalized probes on activated surfaces⁶³ and biotinylated probes bound to streptavidin-modified electrodes,⁶⁴ each offering specific advantages.

The simplest recognition layer employs linear ssDNA probes, typically 20–40 bp nucleotides, where SNP detection relies on analyzing signal differences between PM and MM targets arising from differences in duplex stability.^{65–68} This direct-capture approach works but lacks the discrimination power needed for SNP detection. Sandwich-type architectures represent a significant advance.⁶⁹ By splitting target recognition between a capture probe on the electrode and a reporter carrying the signal element, a second layer of selectivity is introduced. Discrimination can be further enhanced by incorporating ligases or polymerases, as extension occurs only under conditions of perfect complementarity.^{70–72}

An important innovation was the development of structure-switching E-DNA biosensors. In these designs, a stem-loop (molecular beacon) probe bearing a redox reporter is tethered to the electrode surface—target hybridization forces a conformational change that alters the reporter-to-electrode distance, converting a binding event directly into current.^{21,57} Structure-switching probes also provided a natural framework for SNP discrimination, since MM targets induce incomplete or unstable conformational changes that produce measurably different signals from PM.⁶⁸

Three-dimensional (3D) DNA nanostructures have emerged as programmable material for electrode surface engineering. Tetrahedral DNA nanostructures (TDNs) position individual probes at defined heights with controlled spacing, in principle resolving probe orientation and surface crowding. The foundational reports established 250-fold improvements in signal⁷³ as well as up to 20-fold faster hybridization kinetics⁷⁴ over ssDNA/MCH probes. DNA origami has also been used as a programmable target-capturing tile to amplify electrochemical DNA hybridization signals.⁷⁵ DNA nanotweezers and related structures add a further dimension by coupling recognition to a defined open-closed conformational change, as recently demonstrated for drug development,⁷⁶ providing a structural basis for signal-on readouts, although nanotweezer-based hybridization sensors remain almost exclusively tested under controlled conditions.⁷⁷ The demonstrated value of these architectures lies primarily at the mechanistic level—control probe orientation,

spacing, and local steric and electrostatic environment. Their translational value, however, is not yet established. Even the most clinically oriented 3D DNA biosensor works establish performance in buffers but still require complex biological sample pretreatment: purification with commercial kits involving lysis, extraction, and centrifugation.⁷⁸ In our opinion, 3D DNA nanostructures will become compelling for practical sensing only when their added design and synthesis complexity translates into measurable advantages under clinically relevant conditions. An overview of the most important surface innovations is given in Figure 4a.

Signal transduction innovations. After molecular recognition, the hybridization event must be converted into an electrochemically measurable signal. For SNP detection, this conversion must be sensitive enough to resolve the small structural and stability differences between PM and MM.

The earliest reporter-free approaches exploited redox-active intercalators and groove binders—daunomycin, Hoechst 33258, and $[\text{Ru}(\text{NH}_3)_6]^{3+}$, which preferentially associate with dsDNA.⁷⁹ The signal increase upon duplex formation provided a simple readout, though discrimination between PM and MM was often modest. A rapid direct stripping approach has been explored via hybridization to guanine-free probes.⁸⁰ Electrochemical impedance spectroscopy (EIS) offered an alternative reporter-free strategy, detecting hybridization-induced changes in interfacial charge transfer resistance without any redox indicator,⁸¹ but suffered from sensitivity to non-specific adsorption and drift.

Covalently attached redox reporters, i.e., methylene blue (MB) and ferrocene, were introduced and provided greater control—reversible redox chemistry, mild potentials, and relative ease of conjugation to synthetic DNA.⁸² The dominant signal transduction mechanism in E-DNA sensors exploits their conformational dynamics. An alternative mechanism, DNA-mediated charge transport through π -stacked base pairs, treats intact dsDNA as a conductive bridge between the redox

reporter and the electrode; an MM disrupts this pathway, decreasing the signal.¹⁸ Electrochemical molecular beacons for solution-phase sensing have been proposed.⁸³

Approaches were demonstrated to couple detection with catalytic amplification. Redox cycling using MB and ascorbic acid, enabling real-time hybridization monitoring in the nM range with ~ 1 s temporal resolution, was demonstrated.⁸⁴ Enzymatic amplification, e.g., using alkaline phosphatase or horseradish peroxidase, was also demonstrated—such systems achieved performance without PCR pre-amplification using human blood samples.⁸⁵ Nanoparticle-based amplification—particularly using gold nanoparticles (AuNPs)—was used as the dominant amplification approach through the 2000s and 2010s, offering signal gains through more redox-active metal atoms per binding event.^{20,86} Interesting advance is nuclease-assisted target recycling, e.g., exonuclease III cleaves the probe after hybridization and releases the target for repeated binding cycles, pushing detection limits to the aM range, providing sufficient time given for signal accumulation.^{87,88} Electromechanical detection via quartz crystal microbalance utilizing gravimetric reporters⁸⁹ or the binding of a PCR-amplified biotinylated duplex assemblies was also demonstrated.⁹⁰

CRISPR use in biosensor designs is another significant achievement. In these systems, nuclease–gRNA complexes serve as recognition elements whose specificity is determined by the guide sequence and can be adapted to detect different mutations.⁹¹ The most notable achievement is the CRISPR-SNP-Chip, which immobilized a Cas9–gRNA complex on a graphene field-effect transistor, enabling direct SNP detection in unamplified genomic DNA within ~ 40 min at ~ 6.3 fM sensitivity.³² An overview of the most important transduction innovations is given in Figure 4b.

Hard Technological Limits

Another layer of barriers is engineering—even if a sensor demonstrates adequate sensitivity in clinical samples, translating it into a practical device introduces constraints. A common assumption is that practical electrochemical DNA sensors

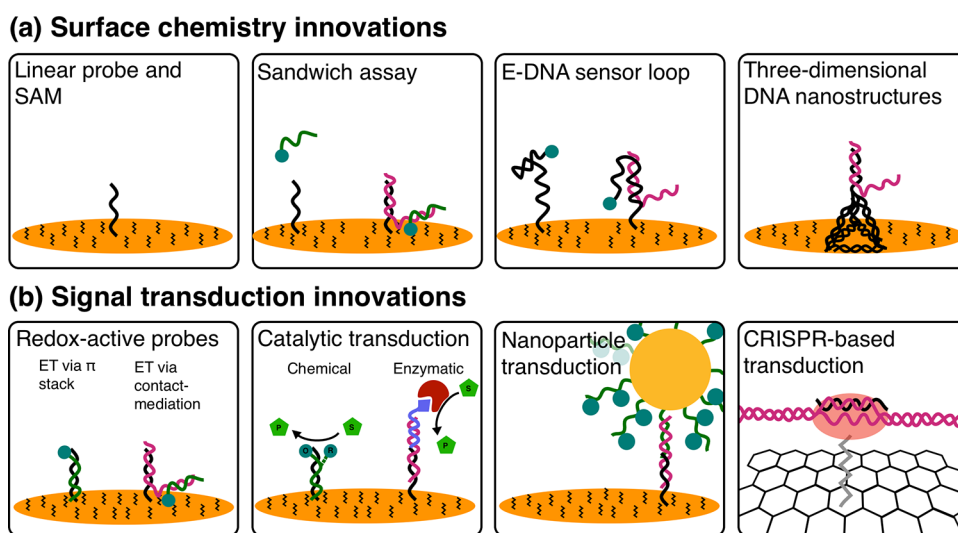


Figure 4. Key technological achievements in electrochemical DNA sensing. (a) Evolution of surface architectures: linear thiolated probes on alkanethiol SAMs; sandwich capture assays; structure-switching E-DNA sensors enabling reagentless detection through conformational change; and three-dimensional DNA nanostructures for controlled probe orientation and spacing. (b) Signal transduction strategies: redox-active probes via DNA-mediated π -stack or contact-mediated electron transfer; catalytic amplification via chemical or enzymatic conversion; nanoparticle-based amplification loading thousands of redox reporters per binding event; and CRISPR-Cas recognition on graphene field-effect transistors enabling amplification-free electronic detection. Each innovation addressed a specific limitation of its predecessor, collectively building a sophisticated toolkit of the field.

resemble the simplicity of glucose meters; however, this analogy is not entirely accurate.

System integration trade-offs in advanced electrochemical readouts. Glucose meters are inexpensive partly because their measurement circuitry is minimal: a fixed-potential amperometric readout implemented with a single op-amp transimpedance stage and a low-cost microcontroller (MCU) with integrated analogue-to-digital converter (ADC).⁹² Most DNA-relevant assays rely on more demanding methods—CV, and especially DPV and SWV, which dominate as readout methods for DNA sensors due to their superior discrimination against capacitive background. These pulse techniques require deterministic timing of digital-to-analogue converter (DAC) updates and ADC sampling on the 10–100 ms scale, multi-bit DAC/ADC resolution, post-acquisition baseline subtraction, and peak fitting. These are not, however, prohibitive barriers. The ongoing commercialization of electrochemical aptamer-based (E-AB) sensors (see in Section 7.7),³⁵ which routinely use SWV in wearable and implantable formats, demonstrates that pulse voltammetry can be implemented. The relevant point is therefore not that the electronics are unattainable but that they are no longer at the simplicity level of a glucose meter—moving from amperometry to SWV introduces system integration trade-offs in cost, power budget, and signal processing that must be justified by the application.

Requirement of multichannel potentiostats. Unlike HRP-type setups, which produce redox mediators that can reliably accumulate in the cell without constant electrode potential control, continuous measurements of adsorbed DNA, such as in T_m -based assays, require constant potential control of the working electrode (WE). Furthermore, clinical utility for SNP panels requires multi-well operation. Although 96-well electrode array formats are commercially available (e.g., Metrohm's DRP-96X110-U4), these arrays are switch-cycled—connected and measured only a few at a time. Fully independent, continuously operated 96-channel potentiostats have been demonstrated,^{93,94} and some designs use 96 WEs that share reference and counter electrodes (RE and CE, respectively),^{95,96} but the physical constraints of connecting 96 or 288 electrical contacts in a compact format remain challenging. Custom complementary metal oxide semiconductor (CMOS) integrated circuits designed for these applications are a logical but costly solution. A practical compromise to reduce the number of components is to use multiplexers controlled by the MCU, cycling through a subset of channels (for example, five at a time), with the switching interval determined by the WE's electric capacity to hold the potential for a short period.

Thermostatic control as the binding constraint for melting-based SNP discrimination. Among the engineering constraints, temperature control is the one most resistant to scaling. As discussed above, ΔT_m between PM and MM duplexes can be ~ 0.5 – 2 °C depending on target and conditions, with the practical SNP-discriminating window concentrated below 35 bp. High-resolution melting platforms in laboratory settings achieve 0.01 °C resolution through Peltier-stabilized blocks and reference-genotype calibration. Disposable point-of-care formats typically achieve 0.05 – 0.2 °C, which compresses the discriminatory margin substantially. Surface-localized thermometry (e.g., thin-film RTDs co-fabricated with the working electrode) and adaptive control algorithms can partially close this gap, as can constant-temperature designs that avoid melting altogether,³⁷ but each adds cost, complexity, or restrictions on the assay format. In our view, this is the most binding engineering constraint specific to hybridization-based SNP

detection. Furthermore, DNA hybridization assays may require high ionic strengths, at around 0.3 – 1 M, to improve kinetics,⁹⁷ which is not problematic in a laboratory but creates challenges for the disposable devices.

Box 3. Section highlights

- The field has developed a sophisticated toolkit: SAM-based gold electrodes, probe architectures including tridimensional structures, as well as diverse transduction strategies.
- These innovations improve selectivity, signal generation, and control of surface chemistry.
- However, performance gains often depend on controlled environments that do not translate to practical applications easily.
- Translation introduces engineering constraints: precise temperature control for SNPs discrimination, high ionic strength requirements, and susceptibility to noise and drift.
- Advanced readouts (e.g., SWV) enhance sensitivity but require more complex electronics and non-trivial signal processing, increasing cost and failure modes.
- Multiplexing remains a bottleneck—scaling demands multichannel potentiostats, dense electrical interconnects, and precise temperature control.

CLINICAL AND MARKET REALITY: THE VALUE PROPOSITION IS NARROWING

The technological and biological barriers described above should be evaluated not in isolation, but against the performance trajectory of competing platforms and the reality of clinical/market demand. The competitive landscape for genetic variant detection has evolved dramatically since the emergence of electrochemical DNA biosensors. In this section, we examine competing technologies, clinical demand—including recent guideline updates relevant to SNP detection—and the commercial technology landscape.

Competing Technologies and Infrastructure

The trajectory of sequencing cost and speed. The cost of whole-genome sequencing (WGS) has fallen by approximately six orders of magnitude since the Human Genome Project, from USD ~ 3 billion to ~ 200 per genome in 2026. More critically, turnaround time—historically the limiting factor—has compressed dramatically. Standard clinical WGS turnaround remains 2–3 weeks, but the technical capabilities have moved far beyond this: In 2025, the Roche sequencing-by-expansion (SBX) platform demonstrated complete genome sequencing and analysis in a scalable newborn intensive care unit workflow, with a fastest sample-to-report time of 6 h 47 min.⁹⁸ A substantial gap remains between this technical frontier and routine clinical practice, but the trajectory is clear and accelerating. Thus, the key argument as the cornerstone advantage for electrochemical DNA biosensors—their fast time-to-result readout—is rapidly shrinking.

Established laboratory infrastructure. SNP genotyping technologies such as microarrays (e.g., Illumina Infinium, Thermo Fisher Axiom), quantitative PCR panels, and targeted next-generation sequencing (NGS) are already integrated into clinical laboratory workflows, supported by established bioinformatic pipelines, trained personnel, and standardized quality control procedures.⁹⁹ These platforms detect not just one SNP but thousands simultaneously, providing a comprehensive pharmacogenomic and disease-risk profile from a single assay.¹⁰⁰ A new electrochemical SNP sensor must not only match these platforms analytically—it must also displace an installed base that has been built over the decades.

Rapid point-of-care competitive set. For rapid molecular testing at or near the patient, the competitive landscape is dominated by integrated cartridge-based optical platforms, for example, GeneXpert (Cepheid), FilmArray (bioMérieux), ID NOW (Abbott), QIAstat-Dx (QIAGEN), and cobas Liat (Roche). These instruments integrate sample preparation, nucleic acid amplification, and fluorescence-based detection into closed disposable cartridges, delivering sample-to-answer times of approximately 15–60 min. Their dominance reflects not primarily analytical superiority but engineering maturity, bioinformatics, and system integration. Three practical advantages have proven decisive: (i) these platforms provide fully integrated sample-to-answer workflows, minimizing manual handling; (ii) they offer broad multiplexed selection, with respiratory and syndromic panels detecting 10–25 pathogens simultaneously; and (iii) they are supported by established hospital procurement channels, regulatory clearances, and installed instrument bases.

The Single Allele Value Problem

The competitive landscape described above would be forgiving if clinical demand were sufficiently strong. For glucose sensing, billions of daily measurements by hundreds of millions of patients have justified decades of engineering investment. For electrochemical SNP detection, the demand picture is different.

SNPs are emerging as clinically important but are rarely urgent. Over the years, the clinical importance of SNPs has become well established, with expanding recognition that SNPs influence disease susceptibility, drug metabolism, treatment response, and prognosis across nearly every area of medicine.^{101,102} SNPs have been associated with susceptibility to neurological and psychiatric disorders, cardiovascular disease risks, cancers and toxicity, acute inflammatory conditions, hepatitis C outcomes, and hereditary pancreatitis, among many others.^{103,104}

SNPs are particularly emerging in pharmacogenomics. An actionable list received from CPIC guidelines, FDA labels, the FDA Pharmacogenomics table, DPWG guidelines, and GSI/PHARMDOG currently identifies 10 genes with consensus recommendations for clinical testing: *CYP2C19*, *CYP2C9*, *CYP2D6*, *DPYD*, *HLA-A*, *HLA-B*, *NUDT15*, *TPMT*, *UGT1A1*, and *VKORC1* (see in <https://www.clinpgx.org/pgxGenes>). The clinical significance of these genes is substantial. *CYP2C19* guides antiplatelet, antidepressant, and antifungal therapy through three key variants (rs4244285, rs4986893, and rs12248560).¹⁰⁵ *CYP2D6* is involved in the metabolism of up to 25% of commonly prescribed drugs, including opioids, antidepressants, and tamoxifen.¹⁰⁶ As of 2026, *DPYD* testing before fluoropyrimidine chemotherapy involves eight tier 1 and six tier 2 variants.¹⁰⁷ *HLA-B* testing for *15:02, *57:01, and *58:01 alleles prevents life-threatening Stevens–Johnson syndrome and toxic epidermal

necrolysis when carbamazepine, abacavir, allopurinol, or anti-epileptic drugs are prescribed.^{108,109}

The regulatory and guideline landscape is evolving rapidly. The DPWG has published new guidelines for *TPMT/NUDT15*–thiopurine¹¹⁰ and *SLCO1B1*–statin/*CYP2C9*–sulfonylurea interactions,¹¹¹ followed by *CYP2D6/CYP2C19*–tricyclic antidepressant guidelines with metabolizer-specific dosing recommendations in 2026.¹¹² The UK released a national guideline in December 2025 recommending *CYP2C19* testing for all patients before clopidogrel prescription, regardless of the underlying indications.¹¹³ This expanding clinical importance creates, at first glance, a growing market for rapid genotyping. However, the implementation model favored by these guidelines systematically undermines the need for urgency. While pretreatment testing is now recommended for several gene–drug pairs—*DPYD* before fluoropyrimidines,¹¹⁴ *HLA-B**57:01 before abacavir,¹¹⁵ *HLA-B**15:02 before carbamazepine,¹⁰⁸ and *CYP2C19* before clopidogrel¹¹³ as far as we know, urgency is recommended only for *CYP2C19* variants.

Even in one of the most time-critical single-SNP scenarios in current clinical practice—neonatal screening for the *MT-RNR1* m.1555A>G variant to prevent aminoglycoside-induced permanent hearing loss—the solution that reached clinical validation was not electrochemical but a miniaturized PCR platform (Genedrive) using fluorescent melt analysis, delivering results in 26 min.¹¹⁶ This illustrates a recurring pattern: When genuine clinical urgency drives demand for rapid genotyping, existing molecular platforms consistently fill the gap before electrochemical alternatives reach the market.

Information asymmetry. Beyond the trajectories of cost and speed, long-read sequencing introduces a qualitative dimension that electrochemical DNA sensors cannot match, e.g., nanopore generates reads exceeding 4 Mb with real-time base identification.¹¹⁷ Adaptive sampling enables computational target enrichment without capture chemistry—a single MinION run can enrich for specific pharmacogenomic loci while simultaneously providing structural variant detection, methylation profiling, and haplotype phasing from native DNA.¹¹⁸ These technologies answer the same clinical question while delivering categorically richer information from the same sample.

Commercial Technologies: Successes, Pivots, and Lessons

Remarkably, despite the challenges described above, several commercially relevant technologies have emerged that directly or indirectly descend from the electrochemical DNA sensing approaches discussed in this review. Their trajectories, including pivots, discontinuations, and technological retreats, are just as instructive as their successes.

Direct descendants: electrochemical hybridization detection. The most comprehensive commercial pipeline in the field belongs to the eSensor lineage (Figure 5).^{119,120} The platform passed through Motorola, and Genmark before reaching its current form as the Roche cobas ePlex. The core technology is composed of in-cartridge PCR amplification, sandwich capture onto gold electrode arrays, with ferrocene-based reporter detection. The platform was originally developed for pharmacogenomic SNP typing, including the *CYP2C19* panel,¹²¹ but later abandoned human SNP genotyping and was repositioned for infectious disease detection.¹²² In its current format, a platform of gold electrodes is combined with electrowetting-on-dielectric sample handling for multiplexed pathogen identification.¹²²

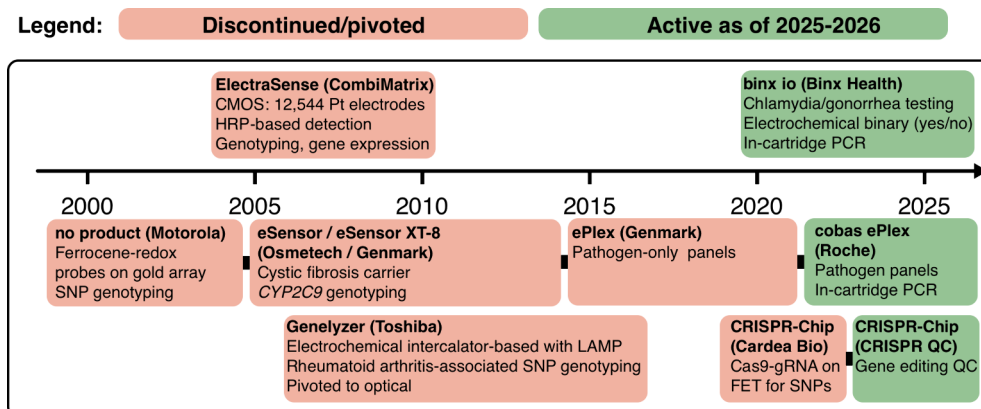


Figure 5. Commercial electrochemical DNA detection devices: timeline and outcomes. Red indicates discontinued or pivoted products; green—commercially active as of 2025–2026. The eSensor lineage—spanning different corporate owners over 25 years—is the field’s longest continuous technology thread; it survives today as cobas ePlex (Roche) after abandoning its original SNP genotyping for pathogen panel detection. The CRISPR-Chip pivoted to gene editing quality control. The only surviving point-of-care device (binx io) performs binary pathogen presence/absence detection.

The binx io (Binx Health) platform is the only other surviving electrochemical DNA detection device for diagnostics.¹²³ Using PCR amplicon hybridization with ferrocene-based reporter detection on a chip, it provides FDA-cleared point-of-care chlamydia and gonorrhea testing with a ~30 min sample-to-answer time. Importantly, binx io operates in a binary pathogen detection niche (yes/no).

The CRISPR-Chip, the third and final commercially available solution, followed a different but equally interesting path. Originally demonstrated for amplification-free mutation detection of Duchenne muscular dystrophy using Cas9 on graphene FETs,³⁰ the technology was positioned for clinical diagnostics. However, the commercial application pivoted: CRISPR-Chip (CRISPR QC) is now focused on quality control services for CRISPR gene editing.¹²⁴ Importantly, the technology found a viable commercial home—just not in diagnostics.

Other direct-descendant platforms we discovered, to the best of our knowledge, were either discontinued or retreated from electrochemical detection. The CombiMatrix ElectraSense combined an impressive amount of 12,544 individual microelectrodes on-chip with PCR-amplified biotin-based ssDNA targets with HRP/TMB signal transduction.¹²⁵ Toshiba developed the Genelyzer electrochemical DNA chip for SNPs associated with rheumatoid arthritis,¹²⁶ which later was named Canon Genelyzer (after Toshiba Medical Systems was acquired by Canon) but eventually switched to fluorescence detection.¹²⁷

The pattern among direct descendants is clear: Of the platforms that used electrochemical transduction for DNA hybridization detection, one survived by pivoting away from human SNPs (eSensor-ePlex), one survived in binary pathogen detection (binx io), and one pivoted from diagnostics to research tools (CRISPR-Chip). To the best of our knowledge, none remains commercially active for only SNP detection by hybridization.

Indirect descendants: electrochemistry in DNA analysis beyond hybridization. While these approaches fall outside the definition of electrochemical DNA biosensors, it is useful to briefly highlight technologies in which electrochemistry is applied to DNA analysis through mechanisms other than surface hybridization. The conceptual framework of these methods is fundamentally different.

In the research device market, an electrochemical PCR quantitation platform DetScan with a complete PCR device Leo has

been developed by Easy Life Science.¹²⁸ Ion Torrent (now Thermo Fisher) detects protons released during sequencing-by-synthesis using ion-sensitive field-effect transistors. In this case, the signal arises from electrical detection of a chemical byproduct rather than from DNA hybridization.¹²⁹ GenapSys (Prayoga Life Sciences) is the newest addition to electrically detected sequencing-by-synthesis (SBS), measuring continuously increasing electrical impedance in steps corresponding to the added nucleotide.¹³⁰ Oxford Nanopore’s MinION and PromethION platforms measure modulation of ionic current as single DNA strands translocate through protein nanopores, enabling direct electrical readout of DNA sequences.¹³¹ Roche’s in-development SBX technology expands target DNA into Xpandomer polymers that are subsequently interrogated through nanopores, recently demonstrating same-day whole-genome sequencing in around 4 h.⁹⁸ Electronic genome mapping via electronic transduction is also offered by Nabsys. DNAe has announced the development of LiDia-SEQ sample-to-result sequencing platform, operating via automated sample preparation and ion-sensitive field-effect transistor detection. Most of these platforms have either achieved commercial success or are progressing toward clinical deployment.

Lessons from the commercial landscape. Electrochemical hybridization detection for human SNPs alone does not have surviving commercial implementations, as the only platform that achieved clinical scale (eSensor) abandoned the application. Other attempts were discontinued, switched detection type, or pivoted away from diagnostics. The existing hybridization-based devices succeeded by avoiding human SNP discrimination—binx io detects pathogen presence, and the cobas ePlex as of today identifies microbial species. Optical detection dominates the hybridization readout: point-of-care molecular diagnostic platforms competing with cobas ePlex—BioFire FilmArray (bioMérieux), BD MAX (Becton Dickinson), QIAstat-Dx (Qiagen), cobas liat (Roche), ID NOW (Abbott), and VERIGENE (DiaSorin)—use fluorescence-based detection. One in-between case is the Elecsys (Roche) platform, which utilizes electrochemiluminescence detection; however, despite being DNA-capable, the technology focuses exclusively on immunoassays. Finally, electrochemistry succeeds in DNA analysis when it avoids hybridization, e.g., Nanopore sequencing and SBX technologies are commercially viable and growing.

Box 4. Section highlights

- The competitive landscape has advanced rapidly: Whole-genome sequencing (WGS) costs have fallen to USD 200 and turnaround times have compressed to hours.
- Established platforms (microarrays, qPCR, and WGS) deliver multiplexed, infrastructure-integrated solutions detecting thousands of SNPs in a single assay.
- Sequencing technologies also provide information richness (long reads, phasing, and epigenetics), far exceeding the single-SNP output of electrochemical biosensors.
- Rapid point-of-care molecular systems already provide fully integrated sample-to-answer workflows in under 1 h.
- Clinical demand for SNPs is growing but rarely time-critical.
- Commercial history shows three commercially active solutions as of 2025–2026, but no electrochemical platform for SNP genotyping by hybridization.
- The most advanced lineage (Roche cobas ePlex) abandoned human SNP detection in favor of infectious disease panels.
- Present electrochemical solutions succeed in narrow specific cases: binary pathogen detection (binx) and quality control (CRISPR-Chip).
- Electrochemistry remains commercially viable in DNA analysis when it avoids hybridization (e.g., nanopore sequencing and SBS platforms).

■ PERSPECTIVES: WHERE ELECTROCHEMICAL DNA SENSING MAY BELONG

The analysis highlights a structural gap between the properties of DNA hybridization at electrode interfaces and the requirements of modern genomic diagnostics. The biological reality of DNA targets is often unfavorable for the operating regime of electrochemical hybridization sensors, while the technological landscape has shifted toward highly integrated molecular diagnostic platforms and rapidly advancing sequencing technologies. At the same time, electrochemical DNA sensing has produced a sophisticated toolbox of molecular interfaces, surface chemistries, and signal transduction strategies. The question facing the field is where the value lies.

Narrow, Time-Critical Niches

As integrated cartridge systems already provide automated and established clinical workflows, viable niches therefore should emerge not from analytical superiority but from operational simplicity and reliability in environments where conventional molecular platforms are impractical. In our opinion, for such scenarios to exist, the following conditions should be met: (a) the genetic variant must be known, specific, and clinically important; (b) the clinical decision must be time-critical (e.g., <30 min); and (c) the electrochemical system must provide a meaningful operational advantage. Two frequently discussed areas are pharmacogenomics and infection diagnostics.

Pharmacogenomics. The pharmacogenomic landscape has undergone a decisive shift. As discussed above, the importance of pharmacogenes has been building for decades, but the critical change is recent: 2025–2026 marks the period when guidelines give directive recommendations.^{111–113} This regulatory momentum means that clinical demand for pharmacogenomic genotyping is driven by a clinical need.

However, this strengthened case simultaneously exposes a structural limitation of single-SNP electrochemical sensors: Guidelines do not ask for only one variant. For example, UK *CYP2C19* guidelines specify a minimum tier 1 panel of three variants,¹¹³ and *DPYD* requires at least four core alleles.¹³² This creates a narrow but genuine design target: a minimally multiplexed sensor array interrogating 3–10 variants from a single sample. Yet even here, existing PCR-based point-of-care devices, e.g., Spartan RX (Spartan Bioscience), already deliver *CYP2C19* results.¹³³ Any electrochemical implementation would need to provide advantages in cost, multiplexing capacity, or workflow simplicity to justify adoption.

It is worth addressing an apparent historical contradiction. Previously, we noted that the eSensor platform was launched for pharmacogenomic genotyping in the early 2000s but abandoned this direction. We believe that this pivot reflects timing rather than incompatibility—eSensor entered a market where pharmacogenomic testing was an academic curiosity. The landscape of 2026 is different. We must also acknowledge that pharmacogenomics is moving toward pre-emptive panel-based genotyping for building profiles into electronic health records,¹³⁴ in principle, eliminating the need for rapid genotyping a biosensor would serve. In practice, healthcare implementation is not straightforward.

Infection diagnostics. A second potential niche is the rapid detection of predefined resistance mutations or genes when immediate therapeutic decisions are required—notably, two out of three commercial electrochemical DNA devices (cobas ePlex and binx io) operate in this space. The strongest example is tuberculosis (TB), where rifampicin resistance—most commonly caused by mutations in the *rpoB* rifampicin-resistance-determining region—can be detected by molecular assays directly from sputum, enabling same-day treatment decisions.¹³⁵ This application aligns reasonably well with the criteria outlined above: The targets are known, the clinical decision is urgent, and infrastructure may be limited. However, TB diagnostics are already dominated by integrated PCR platforms such as GeneXpert, which combine automated sample preparation, amplification, and mutation detection within closed cartridges suitable for low-resource environments.¹³⁶ However, implementation studies in high-burden regions show that the main limitations of GeneXpert include instrument cost, unstable electricity supply, maintenance requirements, cartridge logistics, and the need for centralized laboratory infrastructure.¹³⁷

Similar considerations apply to bloodstream infections, where rapid detection of carbapenemase genes such as *bla_{KPC}*, *bla_{NDM}*, *bla_{VIM}*, and *bla_{IMP}* can guide treatment.¹³⁸ Infection diagnostics represent a narrow and infrastructure-dependent opportunity, where electrochemical DNA sensors would need to offer clear advantages in cost, portability, or workflow simplicity to gain traction.

Beyond Endogenous DNA Detection

Using DNA hybridization to answer the question “*what endogenous DNA is present?*” faces structural limitations. This does not mean that the knowledge accumulated over decades of electrochemical nucleic acid research lacks translational value. On the contrary, that value may become most apparent when redirected

toward analytical problems that are better aligned with the strengths. The following subsections organize these opportunities by evidence level—from platforms already entering commercial markets, through clinically relevant but commercially unrealized applications, to frontier directions where electrochemical DNA expertise offers genuine and largely unrecognized opportunities.

Electrochemical aptamer-based (E-AB) sensors: a clinically validated platform at the threshold of commercialization. E-AB sensors represent the most mature and commercially advanced redirection of electrochemical DNA sensing expertise. These systems retain the core molecular toolkit—thiol-tethered oligonucleotide probes on gold, methylene blue as a redox reporter, and electrochemical readout (e.g., SWV)—but target small molecules and proteins rather than nucleic acids. The approach was pioneered by Plaxco and Soh,¹³⁹ with a demonstration of reversible real-time drug monitoring¹⁴⁰ and subsequent demonstration of E-AB sensors in the bloodstream of awake ambulatory animals.³⁴ Key engineering challenges were solved: biofouling by blood components⁵¹ and aptamer degradation by endogenous nucleases.¹⁴¹ These advances converged in a landmark pilot clinical study published in 2026, demonstrating vancomycin monitoring at 5 min resolution in humans.³⁵

To the best of our knowledge, two companies, as of 2026, are commercializing E-AB platforms: Nutromics Pty Ltd (Australia) are sharply focused on therapeutic drug monitoring (i.e., vancomycin and tobramycin) and Adaptyx Biosciences, Inc. (USA), pursuing a broader panel of electrolytes, cardiac biomarkers, hormones, and metabolites. The technology unquestionably works and, in our view, represents both scientific ingenuity and genuine engineering maturity. However, whether continuous molecular monitoring will provide sufficient value proposition for broad clinical adoption alongside established biochemical parameters remains an open question—one the market will ultimately answer.

Pathogen-relevant, disease-relevant, and commercially relevant nucleases: electrochemically demonstrated. A second direction exploits DNA not as a recognition element for hybridization but as a substrate for enzymatic cleavage—measuring nuclease activity rather than nucleic acid sequence. This niche already has a commercial foothold: CRISPR-Chip operates in this space. The electrochemical implementation for nuclease detection is well established: DNA probes with redox reporters are immobilized on gold electrodes, and nuclease-mediated cleavage releases the reporter. Hybridization still contributes—reporter probes can hybridize to cleavage products—but the analytical step is enzymatic.

The clinical motivation is demonstrated: Bacterial nucleases represent pathogen-specific enzymatic signatures,¹⁴² while cancer-associated nucleases are emerging as diagnostically relevant targets.¹⁴³ A fascinating recent example—a work by Clark et al., which showed that cyclophilin B, a protein oversecreted by pancreatic cancer cells indeed has previously debated nuclease activity detectable using electrochemical DNA sensors.¹⁴⁴ From our own experience, similar sensors achieve measurement of DNases in biological samples such as saliva with high sensitivity and minimal sample preparation.¹⁴⁵ A further compelling opportunity is monitoring DNA repair enzyme activity using defined DNA substrates at electrochemical interfaces. Oxidative lesions such as 8-oxoguanine are among the best-established parameters of genomic damage and are linked to cancer, neurodegeneration, cardiovascular disease, diabetes, and aging.¹⁴⁶ An electrode-bound DNA containing a defined target can be used to directly interrogate repair enzymes such as 8-oxoguanine DNA glycosylase, where the electrochemical signal reports enzymatic processing of the damaged

base at the surface.¹⁴⁷ Compelling proof-of-concept evidence across multiple nuclease classes are presently laying foundations for further development and clinical translation.

Therapeutic oligonucleotide monitoring: sequence-defined targets at favorable concentrations. A third direction preserves hybridization-based recognition but redirects it toward synthetic rather than endogenous nucleic acids. Instead of endogenous genomic DNA or rare mutant alleles, electrochemical sensors can be directed toward known synthetic nucleic acids present at relatively high and analytically accessible concentrations. The most compelling example is the monitoring of therapeutic oligonucleotides.¹⁴⁸ As of 2024, 19 small nucleic acid drugs are approved, representing a rapidly expanding pharmaceutical class,¹⁴⁹ with more candidates in development.¹⁵⁰ Therapeutic oligonucleotides are short (18–30 nt), are sequence defined, and circulate at nM– μ M. These concentrations lie within the practical operating window of electrochemical DNA biosensors, avoiding most of the limitations discussed above. Electrochemical biosensing of therapeutic oligonucleotides remains almost entirely unexplored—to date, only a single study has demonstrated this concept, reporting hybridization-based detection of viltolarsen, a charge-neutral phosphorodiamidate morpholino oligomer used in Duchenne muscular dystrophy.¹⁵¹ In addition, those nucleotides are effectively invisible to standard sequencing workflows, including NGS, and represent a rare analytical niche.

The clinical relevance of dose–response relationships for oligonucleotide drugs is no longer hypothetical: The DEVOTE trial, whose final results were published in February 2026 and which led to FDA approval of a high-dose nusinersen in March 2026, provides direct clinical evidence that dose titration could matter for this drug class.¹⁵² Should this pattern extend across the rapidly growing oligonucleotide therapeutic landscape and move toward personalized dosing, the analytical demand for precise, frequent drug-level measurement will follow—and the electrochemical DNA sensing field is well positioned for this demand.

Electrochemistry as DNA infrastructure: beyond molecular detection. While outside the scope of this review, it is instructive that electrochemical and electronic principles have found durable commercial success in DNA workflows—not as detectors, but as physical infrastructure for sample manipulation. Electrowetting-on-dielectric platforms, in which applied voltages move, merge, and split nanoliter droplets across electrode arrays, are now replacing robotic liquid handlers for sequencing library preparation.¹⁵³ Miro Canvas (Integra Biosciences) and Callisto (Volta Labs) have achieved meaningful market adoption for automated DNA extraction, library construction, and target enrichment. Similarly, the Ionic system (Bionano) uses electric field-driven isotachopheresis to extract high-molecular-weight DNA and RNA from challenging samples without columns or magnetic beads.¹⁵⁴ Isotachopheresis-aided hybridization enhancement has been demonstrated at rates exceeding 10,000-fold in solution with striking results on microarray slides, suggesting possible usefulness in accelerating DNA assays.¹⁵⁵ Dielectrophoresis and AC electrokinetic (micro)devices for preconcentration of cells (CytoChip),¹⁵⁶ extracellular vesicles,¹⁵⁷ and circulating nucleic acids (Verita)¹⁵⁸ are being developed and integrated, showing promising results for low-abundance targets. The pattern is consistent: Electrochemistry has succeeded in the DNA space by exploiting capabilities that optics cannot match—contactless nanoliter fluidics, selective electromigration, and programmable surface wettability—rather than by competing with optical detection on information content. Those advances reinforce

the broader argument of this review: The expertise accumulated in electrochemical DNA sensing is genuinely transferable, provided the target application is chosen to match the platform's strengths.

Box 5. Section highlights

- Viable niches are narrow and conditional: known targets, time-critical decisions, and operational simplicity.
- Pharmacogenomics and infection diagnostics are the most plausible directions, but both face strong competition from established platforms.
- The stronger opportunity lies in redirecting accumulated expertise beyond endogenous DNA detection, toward problems where targets are known and concentrations are favorable.
- Electrochemical aptamer-based sensors targeting small molecules and proteins are already entering markets—Nutromics and Adaptyx—are actively commercializing continuous molecular monitoring platforms.
- Nuclease and enzymatic activity profiling on DNA substrates exploits the regime where electrochemical sensors perform best, with demonstrated relevance in infection and cancer diagnostics.
- Therapeutic oligonucleotides—sequence-defined circulating at nM– μ M—represent an underexplored but analytically favorable target class.
- The field's most transferable contribution may not be nucleic acid detection itself, but programmable molecular interfaces and the use of DNA as a functional substrate.

CONCLUDING REMARKS

Electrochemical DNA biosensors have produced a sophisticated toolkit, yet the broad translational vision once imagined—credit card-sized arrays for routine clinical genetic diagnostics—has not fully materialized.² As discussed throughout this review, this likely reflects structural factors arising from biological constraints, technological realities, and clinical and market demand, rather than a lack of scientific progress.

The field has nonetheless reached genuine maturity. Figure 6 maps competitive landscape of clinically related applications across two dimensions—information complexity and urgency. A boundary appears between domains where sequencing and conventional molecular diagnostics hold a decisive advantage, and those where electrochemical approaches can compete. The commercial record supports this framework: cobas ePlex, binx io, and CRISPR-Chip all occupy viable niches within it. Time-critical pharmacogenomic genotyping—now driven by 2025–2026 regulatory changes—and rapid antimicrobial resistance detection represent realistic near-term targets, demanding not single-SNP sensors but minimally multiplexed arrays of 3–10 targets within a clinically actionable timeframe.

Beyond endogenous DNA detection, the molecular engineering toolkit developed by the field—surface-tethered oligonucleotides, conformational switching, interfacial charge transfer, and catalytic amplification—extends well beyond sequence identification. DNA becomes a molecular material: a substrate for enzymatic activity sensing, a structure for continuous *in vivo* monitoring of small molecules, and a potential recognition element for synthetic nucleic acid therapeutics. Electrochemical aptamer-based sensors, now commercialized by Nutromics and Adaptyx, are the clearest evidence that this redirection is already underway.

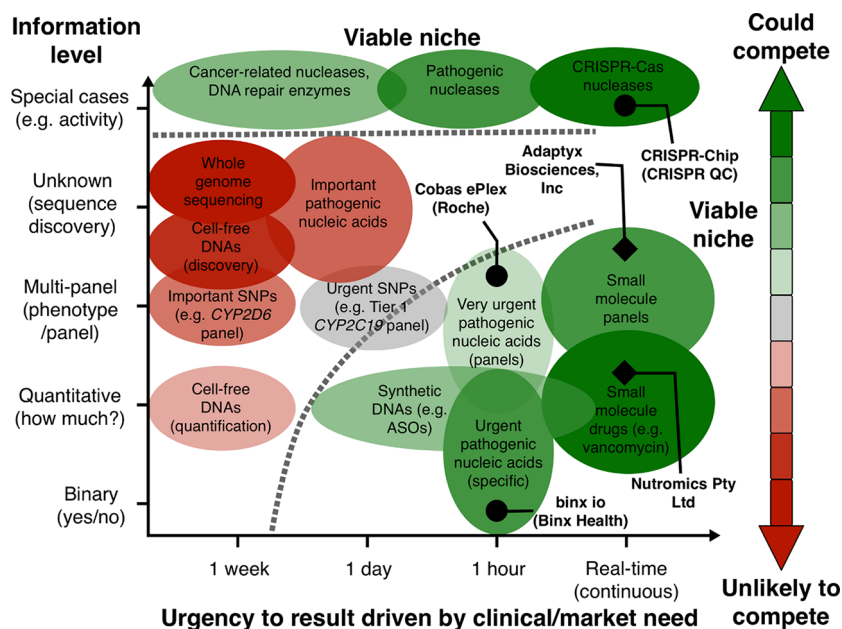


Figure 6. Competitive landscape for electrochemical DNA sensing: information complexity vs urgency. The boundary separates the domain where sequencing and conventional molecular diagnostics dominate. Notably, the established (filled circle) and emerging (filled diamond) commercial electrochemical DNA solutions are all located (or migrated) into viable space. Applications above the diagonal—including cell-free DNA analysis, whole-genome genotyping, and comprehensive pathogen identification—require information density that electrochemical sensors, in our opinion, cannot match. Several applications within the viable space (nuclease activity profiling and small-molecule monitoring) are not DNA detection *per se* but employ the same probe architectures, surface chemistries, and signal transduction strategies developed by the electrochemical DNA sensing field.

The key risk is not that the field lacks potential but that it continues directing creativity toward applications where it is structurally disadvantaged. The strongest case for electrochemical DNA biosensing lies where electrochemistry is uniquely capable: speed, simplicity, high-frequency measurement, and programmable molecular interfaces operating where amplification is unnecessary. This is a different ambition than once imagined—but honest, and arguably more durable.

AUTHOR INFORMATION

Corresponding Author

Dalius Ratautas – Life Sciences Center, Vilnius University, Saulėtekio al. 7, Vilnius LT-10257, Lithuania; orcid.org/0000-0003-3938-3574; Email: dalius.ratautas@gmc.vu.lt

Authors

Skomantas Serapinas – Life Sciences Center, Vilnius University, Saulėtekio al. 7, Vilnius LT-10257, Lithuania; orcid.org/0000-0001-7713-4347

Deimantė Stakelytė – Life Sciences Center, Vilnius University, Saulėtekio al. 7, Vilnius LT-10257, Lithuania; orcid.org/0009-0005-8481-6537

Simona Guobužaitė – Life Sciences Center, Vilnius University, Saulėtekio al. 7, Vilnius LT-10257, Lithuania; orcid.org/0009-0007-3086-8651

Andrijana Danytė – Life Sciences Center, Vilnius University, Saulėtekio al. 7, Vilnius LT-10257, Lithuania; orcid.org/0000-0003-4360-3453

Marius Dagys – Life Sciences Center, Vilnius University, Saulėtekio al. 7, Vilnius LT-10257, Lithuania; orcid.org/0000-0001-7997-2774

Complete contact information is available at:

<https://pubs.acs.org/doi/10.1021/acssensors.6c01221>

Author Contributions

D.R. envisioned the idea and wrote the manuscript. S.S. contributed to Perspectives section. S.S. and D.S. contributed to Clinical and Market reality section. S.G. and M.D. contributed to Technological reality section. A.D. contributed to Biological reality section. All authors performed literature analysis, revised and approved the final version of the manuscript.

Funding

This project has received funding from the Research Council of Lithuania (LMTLT), agreement no. S-LJ-26-02.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We express our sincere gratitude to our dear colleague and friend, Prof. Sergey Shleev, whose article “*Quo Vadis, Implanted Fuel Cell?*”¹⁵⁹ inspired both the title and the spirit of this work.

VOCABULARY

ACV	alternating current voltammetry
ADC	analog-to-digital converter
ASO	antisense oligonucleotide

AuNP(s)	gold nanoparticle(s)
CMOS	complementary metal–oxide–semiconductor
cfDNA	cell-free DNA
DAC	digital-to-analog converter
DPV	differential pulse voltammetry
EIS	electrochemical impedance spectroscopy
E-DNA	electrochemical DNA biosensor
E-AB	electrochemical aptamer-based biosensor
EV	extracellular vesicle
FET	field-effect transistor
HRP	horseradish peroxidase
ITP	isotachopheresis
LSV	linear sweep voltammetry
MB	methylene blue
MCH	mercaptohexanol
MCU	microcontroller unit
MM	mismatch
NGS	next-generation sequencing
PCR	polymerase chain reaction
PM	perfect match
RT-qPCR	reverse transcription quantitative PCR
SAM	self-assembled monolayer
SNP	single-nucleotide polymorphism
SBS	sequencing-by-synthesis
SBX	sequencing-by-expansion
SWV	square wave voltammetry
WGS	whole-genome sequencing

REFERENCES

- (1) Clark, L. C.; Lyons, C. Electrode systems for continuous monitoring in cardiovascular surgery. *Ann. N. Y. Acad. Sci.* **1962**, *102* (1), 29–45.
- (2) Kuhr, W. G. Electrochemical DNA Analysis Comes of Age. *Nat. Biotechnol.* **2000**, *18* (10), 1042–1043.
- (3) Nagata, M.; Sode, K. In-Vivo Continuous Monitoring with Biosensors Based on Engineered Biological Recognition Elements: Opportunities and Challenges. *Front. Sens.* **2025**, *6*, No. 1579359.
- (4) Labuda, J.; Brett, A. M. O.; Evtugyn, G.; Fojta, M.; Mascini, M.; Ozsoz, M.; Palchetti, I.; Paleček, E.; Wang, J. Electrochemical Nucleic Acid-Based Biosensors: Concepts, Terms, and Methodology (IUPAC Technical Report). *Pure Appl. Chem.* **2010**, *82* (5), 1161–1187.
- (5) Paleček, E. Fifty Years of Nucleic Acid Electrochemistry. *Electroanal.* **2009**, *21* (3–5), 239–251.
- (6) Paleček, E. Oscillographic Polarography of Highly Polymerized Deoxyribonucleic Acid. *Nature* **1960**, *188* (4751), 656–657.
- (7) Miller, I. R. The Structure of DNA and RNA in the Water-Mercury Interface. *J. Mol. Biol.* **1961**, *3* (3), 229–240.
- (8) Paleček, E. The Polarographic Behaviour of Double-Helical DNA Containing Single-Strand Breaks. *Biochim. Biophys. Acta Nucleic Acids Protein Synth.* **1967**, *145* (2), 410–417.
- (9) Simons, M. J. Interaction of Methylene Blue with DNA. A Polarographic Study. *Trans. Faraday Soc.* **1968**, *64*, 727–732.
- (10) Paleček, E.; Bartošík, M. Electrochemistry of Nucleic Acids. *Chem. Rev.* **2012**, *112* (6), 3427–3481.
- (11) Watson, J. D. The Human Genome Project: Past, Present, and Future. *Science* **1990**, *248* (4951), 44–49.
- (12) Millan, K. M.; Mikkelsen, S. R. Sequence-Selective Biosensor for DNA Based on Electroactive Hybridization Indicators. *Anal. Chem.* **1993**, *65* (17), 2317–2323.
- (13) Millan, K. M.; Saraullo, Angela; Mikkelsen, S. R. Voltammetric DNA Biosensor for Cystic Fibrosis Based on a Modified Carbon Paste Electrode. *Anal. Chem.* **1994**, *66* (18), 2943–2948.
- (14) Wang, J.; Paleček, E.; Nielsen, P. E.; Rivas, G.; Cai, X.; Shiraishi, H.; Dontha, N.; Luo, D.; Farias, P. A. M. Peptide Nucleic Acid Probes

for Sequence-Specific DNA Biosensors. *J. Am. Chem. Soc.* **1996**, *118* (33), 7667–7670.

(15) Herne, T. M.; Tarlov, M. J. Characterization of DNA Probes Immobilized on Gold Surfaces. *J. Am. Chem. Soc.* **1997**, *119* (38), 8916–8920.

(16) Steel, A. B.; Herne, T. M.; Tarlov, M. J. Electrochemical Quantitation of DNA Immobilized on Gold. *Anal. Chem.* **1998**, *70* (22), 4670–4677.

(17) Johnston, D. H.; Glasgow, K. C.; Thorp, H. H. Electrochemical Measurement of the Solvent Accessibility of Nucleobases Using Electron Transfer between DNA and Metal Complexes. *J. Am. Chem. Soc.* **1995**, *117* (35), 8933–8938.

(18) Boon, E. M.; Ceres, D. M.; Drummond, T. G.; Hill, M. G.; Barton, J. K. Mutation Detection by Electrocatalysis at DNA-Modified Electrodes. *Nat. Biotechnol.* **2000**, *18* (10), 1096–1100.

(19) Park, S.-J.; Taton, T. A.; Mirkin, C. A. Array-Based Electrical Detection of DNA with Nanoparticle Probes. *Science* **2002**, *295* (5559), 1503–1506.

(20) Wang, J.; Liu, G.; Merkoçi, A. Electrochemical Coding Technology for Simultaneous Detection of Multiple DNA Targets. *J. Am. Chem. Soc.* **2003**, *125* (11), 3214–3215.

(21) Fan, C.; Plaxco, K. W.; Heeger, A. J. Electrochemical Interrogation of Conformational Changes as a Reagentless Method for the Sequence-Specific Detection of DNA. *Proc. Natl. Acad. Sci. U. S. A.* **2003**, *100* (16), 9134–9137.

(22) Lai, R. Y.; Lagally, E. T.; Lee, S.-H.; Soh, H. T.; Plaxco, K. W.; Heeger, A. J. Rapid, Sequence-Specific Detection of Unpurified PCR Amplicons via a Reusable, Electrochemical Sensor. *Proc. Natl. Acad. Sci. U. S. A.* **2006**, *103* (11), 4017–4021.

(23) Xiao, Y.; Qu, X.; Plaxco, K. W.; Heeger, A. J. Label-Free Electrochemical Detection of DNA in Blood Serum via Target-Induced Resolution of an Electrode-Bound DNA Pseudoknot. *J. Am. Chem. Soc.* **2007**, *129* (39), 11896–11897.

(24) Xiao, Y.; Lubin, A. A.; Heeger, A. J.; Plaxco, K. W. Label-Free Electronic Detection of Thrombin in Blood Serum by Using an Aptamer-Based Sensor. *Angew. Chem., Int. Ed.* **2005**, *44* (34), 5456–5459.

(25) Willner, I.; Shlyahovsky, B.; Zayats, M.; Willner, B. DNAzymes for Sensing, Nanobiotechnology and Logic Gate Applications. *Chem. Soc. Rev.* **2008**, *37* (6), 1153–1165.

(26) Soleymani, L.; Fang, Z.; Sargent, E. H.; Kelley, S. O. Programming the Detection Limits of Biosensors through Controlled Nanostructuring. *Nat. Nanotech.* **2009**, *4* (12), 844–848.

(27) Vandenberg, O.; Martiny, D.; Rochas, O.; Van Belkum, A.; Kozlakidis, Z. Considerations for Diagnostic COVID-19 Tests. *Nat. Rev. Microbiol.* **2021**, *19* (3), 171–183.

(28) Alafeef, M.; Dighe, K.; Moitra, P.; Pan, D. Rapid, Ultrasensitive, and Quantitative Detection of SARS-CoV-2 Using Antisense Oligonucleotides Directed Electrochemical Biosensor Chip. *ACS Nano* **2020**, *14* (12), 17028–17045.

(29) Antiochia, R. Electrochemical Biosensors for SARS-CoV-2 Detection: Voltametric or Impedimetric Transduction? *Bioelectrochemistry* **2022**, *147*, No. 108190.

(30) Hajian, R.; Balderston, S.; Tran, T.; deBoer, T.; Etienne, J.; Sandhu, M.; Wauford, N. A.; Chung, J.-Y.; Nokes, J.; Athaiya, M.; Paredes, J.; Peytavi, R.; Goldsmith, B.; Murthy, N.; Conboy, I. M.; Aran, K. Detection of Unamplified Target Genes via CRISPR–Cas9 Immobilized on a Graphene Field-Effect Transistor. *Nat. Biomed. Eng.* **2019**, *3* (6), 427–437.

(31) Dai, Y.; Somoza, R. A.; Wang, L.; Welter, J. F.; Li, Y.; Caplan, A. I.; Liu, C. C. Exploring the Trans-Cleavage Activity of CRISPR–Cas12a (Cpf1) for the Development of a Universal Electrochemical Biosensor. *Angew. Chem., Int. Ed.* **2019**, *58* (48), 17399–17405.

(32) Balderston, S.; Taulbee, J. J.; Celaya, E.; Fung, K.; Jiao, A.; Smith, K.; Hajian, R.; Gasiunas, G.; Kutanasovs, S.; Kim, D.; Parkinson, J.; Dickerson, K.; Ripoll, J.-J.; Peytavi, R.; Lu, H.-W.; Barron, F.; Goldsmith, B. R.; Collins, P. G.; Conboy, I. M.; Siksnys, V.; Aran, K. Discrimination of Single-Point Mutations in Unamplified Genomic

DNA via Cas9 Immobilized on a Graphene Field-Effect Transistor. *Nat. Biomed. Eng.* **2021**, *5* (7), 713–725.

(33) Zhou, T.; Huang, R.; Huang, M.; Shen, J.; Shan, Y.; Xing, D. CRISPR/Cas13a Powered Portable Electrochemiluminescence Chip for Ultrasensitive and Specific MiRNA Detection. *Adv. Sci.* **2020**, *7* (13), No. 1903661.

(34) Arroyo-Currás, N.; Somerson, J.; Vieira, P. A.; Ploense, K. L.; Kippin, T. E.; Plaxco, K. W. Real-Time Measurement of Small Molecules Directly in Awake, Ambulatory Animals. *Proc. Natl. Acad. Sci. U. S. A.* **2017**, *114* (4), 645–650.

(35) Booth, M. A.; Erdal, M. K.; Larson, M.; Birthisell, E.; Friedel, M.; Gonçalves, V. R.; Alinezhad, A.; Morawski, F.; Li, J.; Hogan, N.; Teo, S.; Wordsworth, J.; Khanna, S.; Van Eps, J.; Boyd, S.; Dewhirst, L.; Gerson, J.; D'Souza, D.; Yin, W.; Padmanabhan, P. T.; Batchelor, R. H.; Farnkopf, A.; Hodges, A.; Chambers, G.; Braude, M.; Kippin, T. E.; Kirkpatrick, C. M. J.; Justin Gooding, J.; Pianko, S.; Stocker, S. L.; Plaxco, K. W. Pilot Phase Clinical Trial of a Wearable, Electrochemical Aptamer-Based Patch for Continuous Drug Concentration Measurement. *Nat. Biotechnol.*, **2026**.

(36) Yenice, C. P.; Chahin, N.; Jauset-Rubio, M.; Hall, M.; Biggs, P.; Dimai, H.-P.; Obermayer-Pietsch, B.; Ortiz, M.; O'Sullivan, C. K. Semiautomated Electrochemical Melting Curve Analysis Device for the Detection of an Osteoporosis Associated Single Nucleotide Polymorphism in Blood. *Anal. Chem.* **2023**, *95* (38), 14192–14202.

(37) Serapinas, S.; Stakelytė, D.; Tučinskytė, K.; Tomkuvienė, M.; Dagys, M.; Ratautas, D. Constant Temperature Electrochemical Biosensor for SNP Detection in Human Genomic DNA Based on DNA Melting Analysis. *ACS Sens.* **2025**, *10* (9), 6819–6827.

(38) Wan, J. C. M.; Massie, C.; Garcia-Corbacho, J.; Mouliere, F.; Brenton, J. D.; Caldas, C.; Pacey, S.; Baird, R.; Rosenfeld, N. Liquid Biopsies Come of Age: Towards Implementation of Circulating Tumour DNA. *Nat. Rev. Cancer* **2017**, *17* (4), 223–238.

(39) Darbeheshti, F.; Yu, F.; Makrigiorgos, G. M. Pre-PCR Mutation-Enrichment Methods for Liquid Biopsy Applications. *Cancers* **2022**, *14* (13), No. 3143.

(40) Dai, P.; Wu, L. R.; Chen, S. X.; Wang, M. X.; Cheng, L. Y.; Zhang, J. X.; Hao, P.; Yao, W.; Zarka, J.; Issa, G. C.; Kwong, L.; Zhang, D. Y. Calibration-Free NGS Quantitation of Mutations below 0.01% VAF. *Nat. Commun.* **2021**, *12* (1), No. 6123.

(41) Garbieri, T. F.; Brozoski, D. T.; Dionísio, T. J.; Santos, C. F.; Neves, L. T. D. Human DNA Extraction from Whole Saliva That Was Fresh or Stored for 3, 6 or 12 Months Using Five Different Protocols. *J. Appl. Oral Sci.* **2017**, *25* (2), 147–158.

(42) Saidani, O.; Umer, M.; Alturki, N.; Alshardan, A.; Kiran, M.; Alsubai, S.; Kim, T.-H.; Ashraf, I. White Blood Cells Classification Using Multi-Fold Pre-Processing and Optimized CNN Model. *Sci. Rep.* **2024**, *14* (1), No. 3570.

(43) Li, S.; Zhang, H.; Zhu, M.; Kuang, Z.; Li, X.; Xu, F.; Miao, S.; Zhang, Z.; Lou, X.; Li, H.; Xia, F. Electrochemical Biosensors for Whole Blood Analysis: Recent Progress, Challenges, and Future Perspectives. *Chem. Rev.* **2023**, *123* (12), 7953–8039.

(44) Li, Y.; Ou, Y.; Fan, K.; Liu, G. Salivary Diagnostics: Opportunities and Challenges. *Theranostics* **2024**, *14* (18), 6969–6990.

(45) Hackett, S. J. Meningococcal Bacterial DNA Load at Presentation Correlates with Disease Severity. *Arch. Dis. Child.* **2002**, *86* (1), 44–46.

(46) Rello, J.; Lisboa, T.; Lujan, M.; Gallego, M.; Kee, C.; Kay, I.; Lopez, D.; Waterer, G. W. Severity of Pneumococcal Pneumonia Associated With Genomic Bacterial Load. *Chest* **2009**, *136* (3), 832–840.

(47) Kawasaki, H.; Morinaga, Y.; Tani, H.; Yoshida, Y.; Takegoshi, Y.; Kaneda, M.; Murai, Y.; Kimoto, K.; Ueno, A.; Miyajima, Y.; Fukui, Y.; Kimura, M.; Yamada, H.; Sakamaki, I.; Yamamoto, Y. SARS-CoV-2 RNAemia with a Higher Nasopharyngeal Viral Load Is Strongly Associated with Disease Severity and Mortality in Patients with COVID-19. *J. Med. Virol.* **2022**, *94* (1), 147–153.

(48) Nieuwland, R.; Siljander, P. R.-M. A Beginner's Guide to Study Extracellular Vesicles in Human Blood Plasma and Serum. *J. Extracell. Vesicles* **2024**, *13* (1), No. e12400.

- (49) Psifidi, A.; Dovas, C. I.; Bramis, G.; Lazou, T.; Russel, C. L.; Arsenos, G.; Banos, G. Comparison of Eleven Methods for Genomic DNA Extraction Suitable for Large-Scale Whole-Genome Genotyping and Long-Term DNA Banking Using Blood Samples. *PLoS ONE* **2015**, *10* (1), No. e0115960.
- (50) Moulriere, F.; Chandrananda, D.; Piskorz, A. M.; Moore, E. K.; Morris, J.; Ahlborn, L. B.; Mair, R.; Goranova, T.; Marass, F.; Heider, K.; et al. Enhanced Detection of Circulating Tumor DNA by Fragment Size Analysis. *Sci. Transl. Med.* **2018**, *10* (466), No. eaat4921.
- (51) Pham, J. D.; Fetter, L. C.; Gerson, J.; Kippin, T. E.; Plaxco, K. W.; Leung, K. K. On the Blood Components Contributing to the Drift of Electrochemical Aptamer-Based Biosensors. *ACS Sens.* **2025**, *10* (7), 5160–5165.
- (52) Squires, T. M.; Messinger, R. J.; Manalis, S. R. Making It Stick: Convection, Reaction and Diffusion in Surface-Based Biosensors. *Nat. Biotechnol.* **2008**, *26* (4), 417–426.
- (53) Esteban Fernández De Ávila, B.; Watkins, H. M.; Pingarrón, J. M.; Plaxco, K. W.; Pallechi, G.; Ricci, F. Determinants of the Detection Limit and Specificity of Surface-Based Biosensors. *Anal. Chem.* **2013**, *85* (14), 6593–6597.
- (54) SantaLucia, J. A Unified View of Polymer, Dumbbell, and Oligonucleotide DNA Nearest-Neighbor Thermodynamics. *Proc. Natl. Acad. Sci. U. S. A.* **1998**, *95* (4), 1460–1465.
- (55) Owczarzy, R.; You, Y.; Moreira, B. G.; Manthey, J. A.; Huang, L.; Behlke, M. A.; Walder, J. A. Effects of Sodium Ions on DNA Duplex Oligomers: Improved Predictions of Melting Temperatures. *Biochemistry* **2004**, *43* (12), 3537–3554.
- (56) Stellwagen, E.; Lu, Y.; Stellwagen, N. C. Unified Description of Electrophoresis and Diffusion for DNA and Other Polyions. *Biochemistry* **2003**, *42* (40), 11745–11750.
- (57) Xiao, Y.; Lubin, A. A.; Baker, B. R.; Plaxco, K. W.; Heeger, A. J. Single-Step Electronic Detection of Femtomolar DNA by Target-Induced Strand Displacement in an Electrode-Bound Duplex. *Proc. Natl. Acad. Sci. U. S. A.* **2006**, *103* (45), 16677–16680.
- (58) Kusnezow, W.; Sygailo, Y. V.; Rüffer, S.; Baudenstiel, N.; Gauer, C.; Hoheisel, J. D.; Wild, D.; Goychuk, I. Optimal Design of Microarray Immunoassays to Compensate for Kinetic Limitations. *Mol. Cell. Proteomics* **2006**, *5* (9), 1681–1696.
- (59) Wittwer, C. T. High-Resolution DNA Melting Analysis: Advancements and Limitations. *Hum. Mutat.* **2009**, *30* (6), 857–859.
- (60) Bakker, E. Let Us Aim to Develop Sensors, Not Electroanalytical Techniques: The Direct Detection of Dissolved Inorganic Carbon. *ACS Sens.* **2021**, *6* (8), 2785–2786.
- (61) Chahin, N.; Escobar-Nassar, S.; Osmá, J.; Bashammakh, A. S.; AlYoubi, A. O.; Ortiz, M.; O'Sullivan, C. K. Low-Cost Platform for Multiplexed Electrochemical Melting Curve Analysis. *ACS Meas. Sci. Au* **2022**, *2* (2), 147–156.
- (62) Patterson, A. S.; Heithoff, D. M.; Ferguson, B. S.; Soh, H. T.; Mahan, M. J.; Plaxco, K. W. Microfluidic Chip-Based Detection and Intraspecies Strain Discrimination of Salmonella Serovars Derived from Whole Blood of Septic Mice. *Appl. Environ. Microbiol.* **2013**, *79* (7), 2302–2311.
- (63) Fuentes, M.; Mateo, C.; García, L.; Tercero, J. C.; Guisán, J. M.; Fernández-Lafuente, R. Directed Covalent Immobilization of Aminated DNA Probes on Aminated Plates. *Biomacromolecules* **2004**, *5* (3), 883–888.
- (64) Park, J. W.; Lee, H.-Y.; Kim, J. M.; Yamasaki, R.; Kanno, T.; Tanaka, H.; Tanaka, H.; Kawai, T. Electrochemical Detection of Nonlabeled Oligonucleotide DNA Using Biotin-Modified DNA(Ss) on a Streptavidin-Modified Gold Electrode. *J. Biosci. Bioeng.* **2004**, *97* (1), 29–32.
- (65) Petrovykh, D. Y.; Kimura-Suda, H.; Whitman, L. J.; Tarlov, M. J. Quantitative Analysis and Characterization of DNA Immobilized on Gold. *J. Am. Chem. Soc.* **2003**, *125* (17), 5219–5226.
- (66) Inouye, M.; Ikeda, R.; Takase, M.; Tsuru, T.; Chiba, J. Single-Nucleotide Polymorphism Detection with “Wire-like” DNA Probes That Display Quasi “on–off” Digital Action. *Proc. Natl. Acad. Sci. U. S. A.* **2005**, *102* (33), 11606–11610.
- (67) Wong, E. L. S.; Gooding, J. J. Charge Transfer through DNA: A Selective Electrochemical DNA Biosensor. *Anal. Chem.* **2006**, *78* (7), 2138–2144.
- (68) Yang, A. H. J.; Hsieh, K.; Patterson, A. S.; Ferguson, B. S.; Eisenstein, M.; Plaxco, K. W.; Soh, H. T. Accurate Zygote-Specific Discrimination of Single-Nucleotide Polymorphisms Using Microfluidic Electrochemical DNA Melting Curves. *Angew. Chem., Int. Ed.* **2014**, *53* (12), 3163–3167.
- (69) Xu, X.-W.; Weng, X.-H.; Wang, C.-L.; Lin, W.-W.; Liu, A.-L.; Chen, W.; Lin, X.-H. Detection EGFR Exon 19 Status of Lung Cancer Patients by DNA Electrochemical Biosensor. *Biosens. Bioelectron.* **2016**, *80*, 411–417.
- (70) Liu, G.; Lao, R.; Xu, L.; Xu, Q.; Li, L.; Zhang, M.; Song, S.; Fan, C. Single-Nucleotide Polymorphism Genotyping Using a Novel Multiplexed Electrochemical Biosensor with Nonfouling surface. *Biosens. Bioelectron.* **2013**, *42*, 516–521.
- (71) Wan, Y.; Lao, R.; Liu, G.; Song, S.; Wang, L.; Li, D.; Fan, C. Multiplexed Electrochemical DNA Sensor for Single-Nucleotide Polymorphism Typing by Using Oligonucleotide-Incorporated Nonfouling Surfaces. *J. Phys. Chem. B* **2010**, *114* (19), 6703–6706.
- (72) Ortiz, M.; Jauset-Rubio, M.; Kodr, D.; Simonova, A.; Hecsek, M.; O'Sullivan, C. K. Solid-Phase Recombinase Polymerase Amplification Using Ferrocene-Labelled dNTPs for Electrochemical Detection of Single Nucleotide Polymorphisms. *Biosens. Bioelectron.* **2022**, *198*, No. 113825.
- (73) Pei, H.; Lu, N.; Wen, Y.; Song, S.; Liu, Y.; Yan, H.; Fan, C. A DNA Nanostructure-based Biomolecular Probe Carrier Platform for Electrochemical Biosensing. *Adv. Mater.* **2010**, *22* (42), 4754–4758.
- (74) Lin, M.; Wang, J.; Zhou, G.; Wang, J.; Wu, N.; Lu, J.; Gao, J.; Chen, X.; Shi, J.; Zuo, X.; Fan, C. Programmable Engineering of a Biosensing Interface with Tetrahedral DNA Nanostructures for Ultrasensitive DNA Detection. *Angew. Chem., Int. Ed.* **2015**, *54* (7), 2151–2155.
- (75) Williamson, P.; Piskunen, P.; Ijäs, H.; Butterworth, A.; Linko, V.; Corrigan, D. K. Signal Amplification in Electrochemical DNA Biosensors Using Target-Capturing DNA Origami Tiles. *ACS Sens.* **2023**, *8* (4), 1471–1480.
- (76) Ponzo, I.; Soldà, A.; Crowe, C.; Dahl, G.; Jahodová, T.; Heerwig, A.; Geschwindner, S.; Ciulli, A.; Rant, U. Proximity Binding Assay for PROTAC Ternary Complex Analysis. *ACS Sens.* **2026**.
- (77) Liu, S.; Xiang, K.; Wang, C.; Zhang, Y.; Fan, G.-C.; Wang, W.; Han, H. DNA Nanotweezers for Biosensing Applications: Recent Advances and Future Prospects. *ACS Sens.* **2022**, *7* (1), 3–20.
- (78) Zeng, D.; Wang, Z.; Meng, Z.; Wang, P.; San, L.; Wang, W.; Aldabahi, A.; Li, L.; Shen, J.; Mi, X. DNA Tetrahedral Nanostructure-Based Electrochemical miRNA Biosensor for Simultaneous Detection of Multiple miRNAs in Pancreatic Carcinoma. *ACS Appl. Mater. Interfaces* **2017**, *9* (28), 24118–24125.
- (79) Hashimoto, K.; Ito, K.; Ishimori, Y. Sequence-Specific Gene Detection with a Gold Electrode Modified with DNA Probes and an Electrochemically Active Dye. *Anal. Chem.* **1994**, *66* (21), 3830–3833.
- (80) Wang, J.; Rivas, G.; Fernandes, J. R.; Lopez Paz, J. L.; Jiang, M.; Waymire, R. Indicator-Free Electrochemical DNA Hybridization Biosensor. *Anal. Chim. Acta* **1998**, *375* (3), 197–203.
- (81) Lisdat, F.; Schäfer, D. The Use of Electrochemical Impedance Spectroscopy for Biosensing. *Anal. Bioanal. Chem.* **2008**, *391* (5), 1555–1567.
- (82) Kang, D.; Zuo, X.; Yang, R.; Xia, F.; Plaxco, K. W.; White, R. J. Comparing the Properties of Electrochemical-Based DNA Sensors Employing Different Redox Tags. *Anal. Chem.* **2009**, *81* (21), 9109–9113.
- (83) Kitamura, Y.; Mishio, K.; Arslan, P.; Ikeda, B.; Imoto, C.; Katsuda, Y.; Ihara, T. Electrochemical Molecular Beacon for Nucleic Acid Sensing in a Homogeneous Solution. *Anal. Sci.* **2020**, *36* (8), 959–964.
- (84) Gineitytė, J.; Serapinas, S.; Ratautas, D. Electrochemical DNA Hybridization Signal Amplification System Using Methylene Blue and Ascorbic Acid. *Electrochim. Acta* **2024**, *507*, No. 145146.

- (85) Patolsky, F.; Lichtenstein, A.; Willner, I. Detection of Single-Base DNA Mutations by Enzyme-Amplified Electronic Transduction. *Nat. Biotechnol.* **2001**, *19* (3), 253–257.
- (86) Zhang, J.; Song, S.; Wang, L.; Pan, D.; Fan, C. A Gold Nanoparticle-Based Chronocoulometric DNA Sensor for Amplified Detection of DNA. *Nat. Protoc.* **2007**, *2* (11), 2888–2895.
- (87) Zuo, X.; Xia, F.; Xiao, Y.; Plaxco, K. W. Sensitive and Selective Amplified Fluorescence DNA Detection Based on Exonuclease III-Aided Target Recycling. *J. Am. Chem. Soc.* **2010**, *132* (6), 1816–1818.
- (88) Xuan, F.; Luo, X.; Hsing, I.-M. Ultrasensitive Solution-Phase Electrochemical Molecular Beacon-Based DNA Detection with Signal Amplification by Exonuclease III-Assisted Target Recycling. *Anal. Chem.* **2012**, *84* (12), S216–S220.
- (89) Patolsky, F.; Lichtenstein, A.; Willner, I. Amplified Microgravimetric Quartz-Crystal-Microbalance Assay of DNA Using Oligonucleotide-Functionalized Liposomes or Biotinylated Liposomes. *J. Am. Chem. Soc.* **2000**, *122* (2), 418–419.
- (90) Naoumi, N.; Michaelidou, K.; Papadakis, G.; Simaiaki, A. E.; Fernández, R.; Calero, M.; Arnau, A.; Tsortos, A.; Agelaki, S.; Gizeli, E. Acoustic Array Biochip Combined with Allele-Specific PCR for Multiple Cancer Mutation Analysis in Tissue and Liquid Biopsy. *ACS Sens.* **2022**, *7* (2), 495–503.
- (91) Wang, M.; Zhang, R.; Li, J. CRISPR/Cas Systems Redefine Nucleic Acid Detection: Principles and Methods. *Biosens. Bioelectron.* **2020**, *165*, No. 112430.
- (92) Ji, D.; Liu, L.; Li, S.; Chen, C.; Lu, Y.; Wu, J.; Liu, Q. Smartphone-Based Cyclic Voltammetry System with Graphene Modified Screen Printed Electrodes for Glucose Detection. *Biosens. Bioelectron.* **2017**, *98*, 449–456.
- (93) Frank, R.; Prönncke, C.; Azendorf, R.; Jahnke, H.-G.; Beck-Sicking, A. G.; Robitzki, A. A. Advanced 96-Microtiter Plate Based Bioelectrochemical Platform Reveals Molecular Short Cut of Electron Flow in Cytochrome P450 Enzyme. *Lab Chip* **2020**, *20* (8), 1449–1460.
- (94) Nazari, M. H.; Mazhab-Jafari, H.; Lian, Leng; Guenther, A.; Genov, R. CMOS Neurotransmitter Microarray: 96-Channel Integrated Potentiostat With On-Die Microsensors. *IEEE Trans. Biomed. Circuits Syst.* **2013**, *7* (3), 338–348.
- (95) Szydlowski, L.; Ehlich, J.; Goryanin, I.; Pasternak, G. High-Throughput 96-Well Bioelectrochemical Platform for Screening of Electroactive Microbial Consortia. *Chem. Eng. J.* **2022**, *427*, No. 131692.
- (96) Clark, R. B.; Glasscott, M. W.; Verber, M. D.; DeMartino, J. C.; Netchaev, A.; Ray, J. D.; Brown, E. W.; Alberts, E.; Fernando, P. U. A. I.; Moores, L. C.; Dick, J. E. A Generalized Potentiostat Adaptor for Multiplexed Electroanalysis. *Anal. Chem.* **2021**, *93* (20), 7381–7387.
- (97) Khuda, N.; Somasundaram, S.; Urgunde, A. B.; Easley, C. J. Ionic Strength and Hybridization Position near Gold Electrodes Can Significantly Improve Kinetics in DNA-Based Electrochemical Sensors. *ACS Appl. Mater. Interfaces* **2023**, *15* (4), 5019–5027.
- (98) Wojcik, M. H.; Larkin, K.; Cipicchio, M.; Douppnik, A.; Zhao, C.; Cech, C.; Lopez, D.; Chandrasekar, J.; Leadbetter, J.; Mannion, J.; et al. Toward Same-Day Genome Sequencing in the Critical Care Setting. *N. Engl. J. Med.* **2025**, *393* (20), 2063–2065.
- (99) Berry, N. K.; Scott, R. J.; Rowlings, P.; Enjeti, A. K. Clinical Use of SNP-Microarrays for the Detection of Genome-Wide Changes in Haematological Malignancies. *Crit. Rev. Oncol. Hematol.* **2019**, *142*, 58–67.
- (100) Roden, D. M.; McLeod, H. L.; Relling, M. V.; Williams, M. S.; Mensah, G. A.; Peterson, J. F.; Van Driest, S. L. Pharmacogenomics. *Lancet* **2019**, *394* (10197), S21–S32.
- (101) Ahmed, I.; Siddiqui, H. I.; Qureshi, G. S.; Bernhardt, G. V. A Review of Literature on the Pharmacogenomics of Single-Nucleotide Polymorphisms. *Biomed. Biotechnol. Res. J.* **2022**, *6* (1), 14–20.
- (102) Shastri, B. S. SNPs in Disease Gene Mapping, Medicinal Drug Development and Evolution. *J. Hum. Genet.* **2007**, *52* (11), 871–880.
- (103) Cheng, H. H.; Giri, V. N.; Goggins, M.; Yurgelun, M. B.; Karlan, B. Y.; Norquist, B. S.; Daly, M. B.; Pal, T.; AlHilli, Z.; Arun, B.; et al. NCCN Guidelines® Insights: Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate, Version 2.2026: Featured Updates to the NCCN Guidelines. *J. Natl. Compr. Canc. Netw.* **2026**, *24* (2), 2–10.
- (104) Tam, V.; Patel, N.; Turcotte, M.; Bossé, Y.; Paré, G.; Meyre, D. Benefits and Limitations of Genome-Wide Association Studies. *Nat. Rev. Genet.* **2019**, *20* (8), 467–484.
- (105) Lee, C. R.; Luzum, J. A.; Sangkuhl, K.; Gammal, R. S.; Sabatine, M. S.; Stein, C. M.; Kisor, D. F.; Limdi, N. A.; Lee, Y. M.; Scott, S. A.; Hulot, J.; Roden, D. M.; Gaedigk, A.; Caudle, K. E.; Klein, T. E.; Johnson, J. A.; Shuldiner, A. R. Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2C19 Genotype and Clopidogrel Therapy: 2022 Update. *Clin. Pharmacol. Ther.* **2022**, *112* (5), 959–967.
- (106) Ingelman-Sundberg, M. Genetic Polymorphisms of Cytochrome P450 2D6 (CYP2D6): Clinical Consequences, Evolutionary Aspects and Functional Diversity. *Pharmacogenomics J.* **2005**, *5* (1), 6–13.
- (107) El Rouby, N.; Aquilante, C. L.; Bargal, S. A.; Cavallari, L. H.; Duarte, J. D.; Gunderson, K.; Mazhindu, T.; Nagy, M.; Nie, X.; Nguyen, D. G.; Patel, J. N.; Skaar, T. C.; Smith, D. M.; Tuteja, S.; Van Schaik, R. H. N.; Hicks, J. K. The PGRN Implementation Working Group. Global Investigation of Clinical Implementation Strategies for DPYD Testing to Guide Fluoropyrimidine Therapy. *Clin. Transl. Sci.* **2026**, *19* (1), No. e70466.
- (108) Phillips, E. J.; Sukasem, C.; Whirl-Carrillo, M.; Müller, D. J.; Dunnenberger, H. M.; Chantratita, W.; Goldspiel, B.; Chen, Y.; Carleton, B. C.; George, A. L.; Mushiroda, T.; Klein, T.; Gammal, R. S.; Pirmohamed, M. Clinical Pharmacogenetics Implementation Consortium Guideline for HLA Genotype and Use of Carbamazepine and Oxcarbazepine: 2017 Update. *Clin. Pharmacol. Ther.* **2018**, *103* (4), 574–581.
- (109) Mallal, S.; Phillips, E.; Carosi, G.; Molina, J.-M.; Workman, C.; Tomažič, J.; Jägel-Guedes, E.; Rugina, S.; Kozyrev, O.; Cid, J. F.; Hay, P.; Nolan, D.; Hughes, S.; Hughes, A.; Ryan, S.; Fitch, N.; Thorborn, D.; Benbow, A. HLA-B*5701 Screening for Hypersensitivity to Abacavir. *N. Engl. J. Med.* **2008**, *358* (6), S68–S79.
- (110) Coenen, M. J. H.; Nijenhuis, M.; Soree, B.; De Boer-Veger, N. J.; Buunk, A. M.; Guchelaar, H.-J.; Houwink, E. J. F.; Risselada, A.; Rongen, G. A. P. J. M.; Swen, J. J.; Touw, D. J.; Van Westrhenen, R.; Deneer, V. H. M.; Van Schaik, R. H. N. Dutch Pharmacogenetics Working Group (DPWG) Guideline for the Gene-Drug Interaction between TPMT/NUDT15 and Thiopurines. *Eur. J. Hum. Genet.* **2026**, *34* (1), 152–160.
- (111) Wolthuis, D. F. G. J.; Nijenhuis, M.; Soree, B.; De Boer-Veger, N. J.; Buunk, A. M.; Guchelaar, H.-J.; Risselada, A.; Rongen, G. A. P. J. M.; Van Schaik, R. H. N.; Swen, J. J.; Touw, D. J.; Van Westrhenen, R.; Deneer, V. H. M.; Houwink, E. J. F. Dutch Pharmacogenetics Working Group (DPWG) Guideline for the Gene-Drug Interaction between SLCO1B1 and Statins and CYP2C9 and Sulfonylureas. *Eur. J. Hum. Genet.* **2025**, *33* (4), 413–420.
- (112) Kleine Schaars, K.; Nijenhuis, M.; Soree, B.; De Boer-Veger, N. J.; Buunk, A.-M.; Guchelaar, H.-J.; Houwink, E. J. F.; Risselada, A.; Rongen, G. A. P. J. M.; Van Schaik, R. H. N.; Swen, J. J.; Touw, D.; Deneer, V. H. M.; Van Westrhenen, R. Dutch Pharmacogenetics Working Group (DPWG) Guideline for the Gene-Drug Interaction between CYP2D6 and CYP2C19 and Tricyclic Antidepressants. *Eur. J. Hum. Genet.* **2026**, *34* (3), 379–386.
- (113) Dello Russo, C.; Frater, I.; Kuruvilla, R.; Lip, S.; O'Neill, H.; Burke, K.; Chaplin, V.; Doney, A. S. F.; Elyas, S.; Greaves, N.; Harding, S.; Hargroves, D.; Hayward, J.; Hughes, D. A.; Hughes, T. A. T.; Kondapally, S.; Mok, P.; Peace, A.; Rafi, I.; Ray, S.; Stinton, V.; Venetucci, L.; Pirmohamed, M. CYP2C19 Genotype Testing for Clopidogrel: A Guideline Developed by the UK Centre of Excellence in Regulatory Science and Innovation in Pharmacogenomics (CERSI-PGx). *Br. J. Clin. Pharmacol.* **2026**, *92* (2), 329–347.
- (114) Hertz, D. L.; Venook, A. P. Ending the Controversy Around Pretreatment Dihydropyrimidine Dehydrogenase (DPD/ DPYD) Testing Heightens the Controversy Over Appropriate Fluoropyrimidine Dosing. *J. Clin. Oncol.* **2026**, *44* (13), 1182–1185.

- (115) Dean, L.; Kane, M. Abacavir Therapy and HLA-B*57:01 Genotype. In *Medical Genetics Summaries*; Pratt, V. M.; Scott, S. A.; Pirmohamed, M.; Esquivel, B.; Kattman, B. L.; Malheiro, A. J., Eds.; National Center for Biotechnology Information (US): Bethesda (MD), 2012.
- (116) McDermott, J. H.; Mahaveer, A.; James, R. A.; Booth, N.; Turner, M.; Harvey, K. E.; Miele, G.; Beaman, G. M.; Stoddard, D. C.; Tricker, K.; et al. Rapid Point-of-Care Genotyping to Avoid Aminoglycoside-Induced Ototoxicity in Neonatal Intensive Care. *JAMA Pediatr.* **2022**, 176 (5), 486–492.
- (117) Jain, M.; Koren, S.; Miga, K. H.; Quick, J.; Rand, A. C.; Sasani, T. A.; Tyson, J. R.; Beggs, A. D.; Dilthey, A. T.; Fiddes, I. T.; et al. Nanopore Sequencing and Assembly of a Human Genome with Ultra-Long Reads. *Nat. Biotechnol.* **2018**, 36 (4), 338–345.
- (118) Payne, A.; Holmes, N.; Clarke, T.; Munro, R.; Debebe, B. J.; Loose, M. Readfish Enables Targeted Nanopore Sequencing of Gigabase-Sized Genomes. *Nat. Biotechnol.* **2021**, 39 (4), 442–450.
- (119) Yu, C. J.; Wan, Y.; Yowanto, H.; Li, J.; Tao, C.; James, M. D.; Tan, C. L.; Blackburn, G. F.; Meade, T. J. Electronic Detection of Single-Base Mismatches in DNA with Ferrocene-Modified Probes. *J. Am. Chem. Soc.* **2001**, 123 (45), 11155–11161.
- (120) Vernon, S. D.; Farkas, D. H.; Unger, E. R.; Chan, V.; Miller, D. L.; Chen, Y.-P.; Blackburn, G. F.; Reeves, W. C. Bioelectronic DNA Detection of Human Papillomaviruses Using eSensorTM: A Model System for Detection of Multiple Pathogens. *BMC Infect. Dis.* **2003**, 3 (1), 12.
- (121) Lee, C. C.; McMillin, G. A.; Babic, N.; Melis, R.; Yeo, K.-T. J. Evaluation of a CYP2C19 Genotype Panel on the GenMark eSensor[®] Platform and the Comparison to the Autogenomics InfinitiTM and Luminox CYP2C19 Panels. *Clin. Chim. Acta* **2011**, 412 (11–12), 1133–1137.
- (122) Babady, N. E.; England, M. R.; Jurcic Smith, K. L.; He, T.; Wijetunge, D. S.; Tang, Y.-W.; Chamberland, R. R.; Menegus, M.; Swierkosz, E. M.; Jerris, R. C.; Greene, W. Multicenter Evaluation of the ePlex Respiratory Pathogen Panel for the Detection of Viral and Bacterial Respiratory Tract Pathogens in Nasopharyngeal Swabs. *J. Clin. Microbiol.* **2018**, 56 (2), No. e01658–17.
- (123) Van Der Pol, B.; Gaydos, C. A. A Profile of the Binx Health Io[®] Molecular Point-of-Care Test for Chlamydia and Gonorrhea in Women and Men. *Expert Rev. Mol. Diagn.* **2021**, 21 (9), 861–868.
- (124) Aran, K.; Goldsmith, B. R. CRISPR Quality Control on a Chip. *Nat. Rev. Bioeng.* **2024**, 2 (3), 194–195.
- (125) Ghindilis, A. L.; Smith, M. W.; Schwarzkopf, K. R.; Roth, K. M.; Peyvan, K.; Munro, S. B.; Lodes, M. J.; Stöver, A. G.; Bernards, K.; Dill, K.; McShea, A. CombiMatrix Oligonucleotide Arrays: Genotyping and Gene Expression Assays Employing Electrochemical Detection. *Biosens. Bioelectron.* **2007**, 22 (9–10), 1853–1860.
- (126) Hongo, S.; Okada, J.; Hashimoto, K.; Tsuji, K.; Nikaido, M.; Gemma, N. Development of an Automated DNA Detection System Using an Electrochemical DNA Chip Technology. *SICE J. Control Meas. Syst. Integr.* **2008**, 1 (3), 265–270.
- (127) Taki, K.; Yokota, I.; Fukumoto, T.; Iwasaki, S.; Fujisawa, S.; Takahashi, M.; Negishi, S.; Hayasaka, K.; Sato, K.; Oguri, S.; Nishida, M.; Sugita, J.; Konno, S.; Saito, T.; Teshima, T. SARS-CoV-2 Detection by Fluorescence Loop-Mediated Isothermal Amplification with and without RNA Extraction. *J. Infect. Chemother.* **2021**, 27 (2), 410–412.
- (128) Moreau, M.; Delile, S.; Sharma, A.; Fave, C.; Perrier, A.; Limoges, B.; Marchal, D. Detection of a Few DNA Copies by Real-Time Electrochemical Polymerase Chain Reaction. *Analyst* **2017**, 142 (18), 3432–3440.
- (129) Merriman, B.; R&D Team, I. T.; Rothberg, J. M. Progress in Ion Torrent Semiconductor Chip Based Sequencing. *Electrophoresis* **2012**, 33 (23), 3397–3417.
- (130) Browne, T. N.; Freeman, M. Next Generation Sequencing: Forensic Applications and Policy Considerations. *WIREs Forensic Sci.* **2024**, 6 (6), No. e1531.
- (131) Jain, M.; Olsen, H. E.; Paten, B.; Akeson, M. The Oxford Nanopore MinION: Delivery of Nanopore Sequencing to the Genomics Community. *Genome Biol.* **2016**, 17 (1), No. 239.
- (132) Ho, T. T.; Smith, D. M.; Aquilante, C. L.; Cicali, E. J.; El Roubay, N.; Hertz, D. L.; Imanirad, I.; Patel, J. N.; Scott, S. A.; Swain, S. M.; Tuteja, S.; Hicks, J. K. the Pharmacogenomics Global Research Network Publication Committee. A Guide for Implementing *DPYD* Genotyping for Systemic Fluoropyrimidines into Clinical Practice. *Clin. Pharmacol. Ther.* **2025**, 117 (5), 1194–1208.
- (133) Davis, B. H.; DeFrank, G.; Limdi, N. A.; Harada, S. Validation of the Spartan RX CYP2C19 Genotyping Assay Utilizing Blood Samples. *Clin. Transl. Sci.* **2020**, 13 (2), 260–264.
- (134) Duarte, J. D.; Dalton, R.; Elchynski, A. L.; Smith, D. M.; Cicali, E. J.; Lee, J. C.; Duong, B. Q.; Petry, N. J.; Aquilante, C. L.; Beitelshes, A. L.; Empey, P. E.; Johnson, J. A.; Obeng, A. O.; Pasternak, A. L.; Pratt, V. M.; Ramsey, L. B.; Tuteja, S.; Van Driest, S. L.; Wiisanen, K.; Hicks, J. K.; Cavallari, L. H. Multisite Investigation of Strategies for the Clinical Implementation of Pre-Emptive Pharmacogenetic Testing. *Genet. Med.* **2021**, 23 (12), 2335–2341.
- (135) Boehme, C. C.; Nabeta, P.; Hillemann, D.; Nicol, M. P.; Shenai, S.; Krapp, F.; Allen, J.; Tahirli, R.; Blakemore, R.; Rustomjee, R.; Milovic, A.; Jones, M.; O'Brien, S. M.; Persing, D. H.; Ruesch-Gerdes, S.; Gotuzzo, E.; Rodrigues, C.; Alland, D.; Perkins, M. D. Rapid Molecular Detection of Tuberculosis and Rifampin Resistance. *N. Engl. J. Med.* **2010**, 363 (11), 1005–1015.
- (136) Akalu, G. T.; Tessema, B.; Petros, B. High Proportion of RR-TB and Mutations Conferring RR Outside of the RRDR of the *rpoB* Gene Detected in GeneXpert MTB/RIF Assay Positive Pulmonary Tuberculosis Cases, in Addis Ababa, Ethiopia. *PLoS ONE* **2022**, 17 (12), No. e0277145.
- (137) Brown, S.; Leavy, J. E.; Jancey, J. Implementation of GeneXpert for TB Testing in Low- and Middle-Income Countries: A Systematic Review. *Glob. Health Sci. Pract.* **2021**, 9 (3), 698–710.
- (138) Ziad, G. A.; Jalal, D.; Hashem, M.; Sayed, A. A.; Mahfouz, S.; Bayoumi, A.; Lotfi, M.; Hassanain, O.; Tolba, M.; Madney, Y.; Shalaby, L.; Elanany, M. Rapid Identification of Carbapenemase Genes Directly from Blood Culture Samples. *Diagnostics* **2025**, 15 (19), No. 2480.
- (139) Plaxco, K. W.; Soh, H. T. Switch-Based Biosensors: A New Approach towards Real-Time, in Vivo Molecular Detection. *Trends in Biotechnol.* **2011**, 29 (1), 1–5.
- (140) Ferguson, B. S.; Hoggarth, D. A.; Maliniak, D.; Ploense, K.; White, R. J.; Woodward, N.; Hsieh, K.; Bonham, A. J.; Eisenstein, M.; Kippin, T. E.; Plaxco, K. W.; Soh, H. T. Real-Time, Aptamer-Based Tracking of Circulating Therapeutic Agents in Living Animals. *Sci. Transl. Med.* **2013**, 5 (213), No. 213ra165.
- (141) Leung, K. K.; Gerson, J.; Emmons, N.; Heemstra, J. M.; Kippin, T. E.; Plaxco, K. W. The Use of Xenonucleic Acids Significantly Reduces the In Vivo Drift of Electrochemical Aptamer-Based Sensors. *Angew. Chem., Int. Ed.* **2024**, 63 (21), No. e202316678.
- (142) Hernandez, F. J.; Huang, L.; Olson, M. E.; Powers, K. M.; Hernandez, L. I.; Meyerholz, D. K.; Thedens, D. R.; Behlke, M. A.; Horswill, A. R.; McNamara, J. O. Noninvasive Imaging of *Staphylococcus Aureus* Infections with a Nuclease-Activated Probe. *Nat. Med.* **2014**, 20 (3), 301–306.
- (143) Balian, A.; Hernandez, F. J. Nucleases as Molecular Targets for Cancer Diagnosis. *Biomark. Res.* **2021**, 9 (1), No. 86.
- (144) Clark, V.; Waters, K.; Orsburn, B.; Bumpus, N. N.; Kundu, N.; Szczepanski, J. T.; Ray, P.; Arroyo-Currás, N. Human Cyclophilin B Nuclease Activity Revealed via Nucleic Acid-Based Electrochemical Sensors. *Angew. Chem., Int. Ed.* **2022**, 61 (45), No. e202211292.
- (145) Serapinas, S.; Gineitytė, J.; Butkevicius, M.; Danilevicius, R.; Dagys, M.; Ratautas, D. Biosensor Prototype for Rapid Detection and Quantification of DNase Activity. *Biosens. Bioelectron.* **2022**, 213, No. 114475.
- (146) Valavanidis, A.; Vlachogianni, T.; Fiotakis, C. 8-Hydroxy-2'-Deoxyguanosine (8-OHdG): A Critical Biomarker of Oxidative Stress and Carcinogenesis. *J. Environ. Sci. Health C* **2009**, 27 (2), 120–139.
- (147) Zhang, Q.; Zhao, S.; Tian, X.; Qiu, J.-G.; Zhang, C. Development of a CRISPR-Cas-Based Biosensor for Rapid and

Sensitive Detection of 8-Oxoguanine DNA Glycosylase. *Anal. Chem.* **2022**, 94 (4), 2119–2125.

(148) Crooke, S. T.; Liang, X.-H.; Baker, B. F.; Crooke, R. M. Antisense Technology: A Review. *J. Biol. Chem.* **2021**, 296, No. 100416.

(149) Cheng, X.; Wang, Y.; Zhang, T.; Cao, Y.; Cheng, H.; Du, Y.; Ge, X.; Ren, B.; Lu, J.; Li, L. Emergence of Small Nucleic Acids as Drugs in Precision Medicine. *Clin. Pharmacol. Ther.* **2025**, 118 (2), 308–323.

(150) Smith, C. I. E.; Zain, R. Therapeutic Oligonucleotides: State of the Art. *Annu. Rev. Pharmacol. Toxicol.* **2019**, 59 (1), 605–630.

(151) Kanno, Y.; Ino, K.; Son, K.; Fujie, T.; Sato, Y.; Masui, S.; Nisisako, T. Electrochemical Sensing of Charge-Neutral Antisense Oligonucleotides Using Hairpin Probes: A Case Study with Viltolarsen. *ACS Electrochem.* **2026**, 2 (2), 305–315.

(152) Finkel, R. S.; Crawford, T. O.; Mercuri, E.; Sumner, C. J.; Garcia Romero, M. D. M.; Day, J. W.; Montes, J.; Sun, P.; Tichler, B.; Paradis, A. D.; Boesch, E.; Inra, J.; Littauer, R.; Sohn, J.; Monine, M.; Gambino, G.; Foster, R.; Farewell, R.; Fradette, S. High-Dose Nusinersen for Spinal Muscular Atrophy: A Phase 3 Randomized Trial. *Nat. Med.* **2026**, 32 (3), 1095–1104.

(153) Kim, H.; Bartsch, M. S.; Renzi, R. F.; He, J.; Van De Vreugde, J. L.; Claudnic, M. R.; Patel, K. D. Automated Digital Microfluidic Sample Preparation for Next-Generation DNA Sequencing. *JALA* **2011**, 16 (6), 405–414.

(154) Rose, K. A.; Yadav, M.; Zhang, Y.; Nieto, R.; Proskow, C.; Lozar, A.; Eggleston, E.; Patel, S.; Patel, P.; Arin, S.; Sadowski, H. 39: Isotachopheresis (ITP) for High-Throughput Isolation of UHMW gDNA Suitable for Optical Genome Mapping (OGM). *Genet. Med. Open* **2025**, 3, No. 101956.

(155) Bercovici, M.; Han, C. M.; Liao, J. C.; Santiago, J. G. Rapid Hybridization of Nucleic Acids Using Isotachopheresis. *Proc. Natl. Acad. Sci. U. S. A.* **2012**, 109 (28), 11127–11132.

(156) Thomas, D. E.; Kinskie, K. S.; Brown, K. M.; Flanagan, L. A.; Davalos, R. V.; Hyler, A. R. Dielectrophoretic Microfluidic Designs for Precision Cell Enrichments and Highly Viable Label-Free Bacteria Recovery from Blood. *Micromachines* **2025**, 16 (2), No. 236.

(157) Gustafson, K. T.; Huynh, K. T.; Heineck, D.; Bueno, J.; Modestino, A.; Kim, S.; Gower, A.; Armstrong, R.; Schutt, C. E.; Ibsen, S. D. Automated Fluorescence Quantification of Extracellular Vesicles Collected from Blood Plasma Using Dielectrophoresis. *Lab Chip* **2021**, 21 (7), 1318–1332.

(158) Hinestrosa, J. P.; Searson, D. J.; Lewis, J. M.; Kinana, A.; Perrera, O.; Dobrovolskaia, I.; Tran, K.; Turner, R.; Balcer, H. I.; Clark, I.; Bodkin, D.; Hoon, D. S. B.; Krishnan, R. Simultaneous Isolation of Circulating Nucleic Acids and EV-Associated Protein Biomarkers From Unprocessed Plasma Using an AC Electrokinetics-Based Platform. *Front. Bioeng. Biotechnol.* **2020**, 8, No. 581157.

(159) Shleev, S. Quo Vadis, Implanted Fuel Cell? *ChemPlusChem* **2017**, 82 (4), 522–539.