News and Perspectives

CRISPR Diagnostics, in Your Pocket

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Key Takeaways

- CRISPR-on-a-chip platforms combine nanoscale engineering with microfluidic chemistry to develop portable, high-sensitivity diagnostic assays.
- Different assays, including fluorescent reporting systems and graphene-based sensors, have distinct but potentially complementary strengths.

When it comes to clinical diagnostic devices, three variables must be carefully considered—speed, cost, and sensitivity. The catch: you can only pick two [1]. Now, a new generation of artificial intelligence (AI)–powered technology could allow doctors of the future to have it all—fast, affordable, sensitive devices right at the patient's bedside. Thanks to CRISPR-Cas technology and microfluidic engineering, the concept is beginning to look more like science and less like fiction. It's called CRISPR-on-a-chip—and yes, it could possibly talk to your smartphone.

To understand what this could mean in practice, imagine a patient of the future checking into their doctor's office. They press their finger onto a disposable cartridge attached to a tabletop reader. A few microliters of blood wicks its way through microscopic channels, where it encounters cocktails of CRISPR enzymes and guide RNAs. The guide RNAs direct the enzymes to specific genetic sequences, and the enzymes analyze the content, scanning for pathogens, genetic point mutations, and early biomarkers of cancer. Within the hour, the results populate the patient's health record and an alert is sent to their smartphone.

No lab required—just a chip, a drop of blood, and a layer of AI.

The Evolution of Point-of-Care Diagnostics

Point of care diagnostic devices, such as pregnancy tests and SARS-CoV-2 rapid antigen tests, are economical and easy to use [2]. All they require is the application of a sample onto a plastic lateral flow device. As the sample travels along the device, it interacts with antibodies and, if positive, produces a color reaction. They work well for low-sensitivity applications but tend to miss rare DNA or RNA species present in the sample that could otherwise be detected in analytical laboratories. Wouldn't it be wonderful to shrink those high-tech labs and provide accurate diagnoses with the convenience of a portable device?

Biomedical engineers are attempting to do just this by downsizing state-of-the-art lab assays and running them on a microchip [3]. To do this, they have turned to microfluidics, the science of reducing assays into minute reaction volumes. Early successes involved small plates and cartridges, but these approaches often still required bulky equipment to analyze the results [4].

True portability demands that the assay be independent of specialist equipment and the skilled technicians who operate them. Attention has now focused on running these assays in microchannels etched onto microchips. It's a tall order—the microchips would need to do it all, including analyzing the sample and reporting the results directly to a small detector, possibly a smartphone.

How does this work? How can state-of-the-art analytical equipment possibly be replicated on a microchip, some of which are as small as a fingernail?

CRISPR-on-a-Chip Unpacked

CRISPR-Cas, the Nobel Prize–winning technology associated with gene editing, has been adapted to these miniaturized microfluidic platforms [5,6]. Under the control of its guide RNA, the CRISPR-Cas complex binds to the target sequences and produces a detectable fluorescent signal.

Rachel Tinker-Kulberg, PhD, is the Director of Research and Development and Professional Track Faculty at the University of North Carolina, Greensboro. Tinker-Kulberg and colleagues work on microfluidic-based CRISPR technologies to detect and potentially suppress infectious diseases such as SARS-CoV-2 [7,8]. For Tinker-Kulberg, there have been two key advances that have made these "portable diagnostics more sensitive and feasible"—the non–polymerase chain reaction (PCR) amplification of the target DNA/RNA and an unanticipated signal boost by the activated Cas enzyme.

The signal amplification magic begins when enzymes capable of amplifying the target nucleic acid sequence recognize DNA/RNA in the sample. Typically, this kind of amplification is done in the lab using the PCR technique, which involves making many copies of the DNA by repeatedly heating and cooling the sample. In CRISPR-based systems, the trick is that Cas enzymes get activated when they find their target, triggering a strong fluorescent signal at a steady temperature, foregoing the need for bulky thermal cycling equipment.

A second sensitivity boost is provided by an enzymatic quirk in the Cas12 and Cas13 endonucleases that are a crucial part of CRISPR diagnostic systems [9,10]. In what Tinker-Kulberg calls a "key biochemical discovery," these enzymes, once bound and activated to their targets, become nonspecific nucleases, meaning they cut DNA or RNA nonselectively, producing thousands of fluorescent signals and better detection. Tinker-Kulberg writes that this CRISPR-Cas12/13 anomaly has "allowed sequence-specific nucleic acid recognition to be converted into a strong detectable fluorescent signal," providing clinically useful levels of sensitivity.

How sensitive is it? Between 10 and 100 times more sensitive than cutting-edge PCR assays [11]. Leading CRISPR-on-a-chip technologies like SHERLOCK and DETECTR (after amplification) can detect as few as 10 particles of the SARS-CoV-2, influenza, and parainfluenza viruses in a sample under controlled laboratory conditions [12].

From Fluorescence to Hypersensitive Graphene Chips

Are you looking for just one molecule in your sample? Graphene chip technology with its zeptomolar (single molecule) sensitivity might be for you. The new platform called graphene field-effect transistor (gFET) technology currently holds much promise in the single molecule detection game [13].

gFET biosensors trade the adaptability of microfluidic chips for extreme assay sensitivity. Silicon microchips are covered with an ultrasensitive layer of carbon (graphene) just one atom thick [14]. When a target nucleic acid sequence binds to the CRISPR guide RNA, a change in electrical potential is registered and reported to the machine learning–assisted detection software. A potential advantage of gFET technology is that it has fewer moving parts than fluorescent reporters—with no amplification step or fluorescent reporter system needed.

gFET assay sensitivity is ideally suited to CRISPR diagnostics and is being deployed in the early diagnosis of cancer [15,16]. Many cancers present clinically at an advanced stage with a corresponding poor prognosis for the patient. Circulating tumor DNA (ctDNA) and microRNA (miRNA) are relatively scarce molecular tumor fingerprints that can be detected in the bloodstream shortly after tumor formation [17]. Point-of-care gFET technology can detect these pathological sequences in otherwise symptom-free individuals and, if approved, is well-positioned to replace PCR amplification in detecting early tumor formation.

The Road Ahead

Each approach is in early development and each has its unique strengths and limitations. Fluorescent reporting systems are less sensitive than gFET, but offer the flexibility of multiplexing—the ability to detect multiple fluorophores in a single sample. By contrast, the high sensitivity of the gFET approach promises greater portability but is currently limited by surface chemistry constraints. Both remain, for now, works in progress.

Which of these technologies will ultimately prevail? The answer may well be both. Tinker-Kulberg notes that "Both assays are equally valuable" for different reasons. She foresees a future that may "involve hybrid systems exploiting their individual advantages in sensitivity, speed, and integration into portable devices."

The early detection of infection, antimicrobial resistance, and cancer means earlier treatment and ultimately better patient outcomes. If these portable diagnostic devices are approved, and arrive in our clinics and homes, they could become a key component of the proactive management of our future health.

Keywords: CRISPR-Cas systems; microfluidic; point-of-care testing; fluorescence; biosensing techniques; nucleic acid amplification techniques; disease surveillance

Conflicts of Interest

None declared.

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