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15th Anniversary Essay: Point-of-Care Testing

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15th Anniversary Essay: Point-of-Care Testing

Examining the changes and developments in point-of-care testing technologies during the past 15 years.

By: Steve Ross

The catch-all term point-of-care (POC) testing covers an enormous range of tests in a diverse range of settings (e.g., home, doctor's office, bedside, developing world). The main focus of this article will be the technologies behind POC testing, primarily those technologies used for immunoassay tests.

Most IVD industry experts would agree that POC testing will slowly gain greater market share and that, in particular, this is a one-way street. Tests rarely migrate back to the central lab once they have a foothold at the point-of-care. The real success stories in POC testing so far have been the low-hanging fruit in terms of developing robust tests that have strong market demand. Such tests include glucose, HbA1C, coagulation, blood gas, and pregnancy/fertility testing.¹

Requirements for POC Devices

Developing novel POC testing technologies, achieving regulatory approval, and getting the technologies on the market are big challenges. To gain competitive advantages, the ideal POC system should meet all or most of the following requirements and surpass current technologies in at least one category: sample volume and type (less than 30 μ L of whole blood), time to result (ideally 5-10 minutes), ease-of-use (for a CLIA waiver), performance (e.g., detection limit, precision, accuracy, and dynamic range), no quality control requirements, instrument cost (ideally no cost to end user), cartridge cost (around \$1 in manufacturing costs), and ability to measure multiple parameters from one sample (i.e., multiplexing).

The last requirement is probably the most contentious. The benefit of a master chip that can measure anything is that an IVD company only needs to manufacture one cartridge for all tests. But the downside is that users often require only one test, so they do not want to pay for the additional tests that the cartridge may offer.

Technologies Used at the POC

POC tests can be broadly split into two categories: technologies that are miniaturized versions of hospital lab analyzers, and those that are specifically designed solely for the POC. Most lab analyzers are complex, automated variants of ELISA methods. There is a capture medium (usually solid phase), a sample (usually serum/plasma) is incubated, a reporter is added in combination with a number of wash steps, and a final measurement is made, usually using an optical method (e.g., absorption, fluorescence, chemiluminescence, electrochemiluminescence).

Chemiluminescent methods have the strong benefit of having no other interfering optical signals due to non-specific binding of the label.

Miniaturized versions of lab analyzers for POC testing include the Abaxis Piccolo Chemistry Analyzer, which uses a centrifugal disc system, and the Qualigen Fastpack IP system, which offers a number of immunoassay tests on self-contained cartridges with reagents onboard. Other examples include the Siemens Stratus CS (see Figure 1) and the Roche Cobas b221.

Tests that are specifically tailored to POC settings are conceptually different from lab analyzers (e.g., lateral-flow strips and glucose meters). The actual test device is invariably in the form of a disposable cartridge and is often read with a small instrument. Apart for glucose, HbA1c, and coagulation, red cell separation in a cartridge is common, which places demands on sample volume, since separating red cells from whole blood in a small volume is not a trivial task. Examples of POC-specific devices are the Roche Cobas h232, which is a quantitative lateral-flow device, the Abbott i-Stat device, the Biosite Triage, and the Axis-Shield Afinion. Most of the major IVD manufacturers have developed numerous POC devices for blood glucose testing.



[5]

Figure 1. The Siemens Stratus CS mini lab analyser for cardiac markers.

Although by no means the only company, Inverness Medical Innovations is one of the key players developing POC testing that is geared toward the doctor's office and home use. Inverness offers tests in fertility and pregnancy (through SPD, a joint venture with Procter and Gamble), cholesterol (through Cholestech), and coagulation (through Hemosense).

R&D in POC Testing

What new technologies have emerged in the POC setting in recent years? While a lot has been promised, not much has been delivered in terms of commercialization. Each year, many large conferences on biosensors discuss novel transduction methodologies, but they often use simple systems (e.g., streptavidin, biotin, protein G, IgG, etc.) in buffer and exhibit sensitivity that is no better compared with existing technologies. When the methods do show promise, they invariably still have to overcome the problems inherent with any measurements made in complex media: non-specific binding, cross-reactivity, and matrix effects.

While magnetic particles make ideal substrates for capture and separation steps, what about magnetic detection methods? Some IVD companies such as Magnisense and MagnaBiosciences have been actively involved in this area. Philips has also reported developing technologies in this area, but it is focussing on magnetic transport mechanisms to drive reactions to faster endpoints. But overall, magnetic detection technologies have seen little market penetration, so whether they can achieve the necessary cost/performance attributes required is difficult to assess.

Fluorescent in-situ hybridization (FISH) has started to make progress in the field of

microbiology. Miacom has a range of test kits that can identify a number of pathogens directly from specimens in 30 minutes.

The BioFlash CANARY (Cellular Analysis and Notification of Antigen Risks and Yields) system relies on the binding of analytes to membrane-bound antibodies, leading to elevated levels of calcium, which enable light emission.² Innovative Biosensors has commercialized this system as a frontline defense system against biological warfare agents. A benefit of this technology is that it is a label-free system. However, it still remains to be proven as a robust

POC device for clinical diagnostics

One of the important areas for POC technologies is cardiac troponin I, the key marker for myocardial infarction and one of the most difficult analytes to measure reproducibly. None of the current POC troponin I tests can meet the recommended performance of 10% CV at the 99th percentile of the normal reference range, as specified by the European Society of Cardiology and the American College of Cardiology.³

Two research-use only methods that do meet this criterion are tests developed by Nanosphere and Singulex. Although neither of these tests are true POC methods, and both are still for research use only, their performances are currently driving the expectations for the next generation of POC troponin tests. The Nanosphere technology uses a signal amplification technique based on the release of oligonucleotides and has applications in molecular diagnostics. The Singulex technology uses a single-molecule fluorescence detection system. Both systems have detection limits in the femtomolar range.^{4,5}

Other areas of interest that have yet to make inroads into POC devices include quantum dots as fluorescent labels, whispering-gallery methods for non-labelled detection, which are similar to surface plasmon resonance, and surface-enhanced resonance Raman methods.⁶ In the area of molecular recognition, there has been much work in the areas of aptamers and molecularly imprinted polymers.⁷ However, monoclonal antibodies still reign supreme in the majority of immunoassay POC devices.

Lab-on-a-Chip

At the beginning of the 1990s, lab-on-a-chip (LOC) promised to be the next big revolution in POC technology. Lithography-based techniques would be used to make LOC devices the same way that PC chips are made. Small sample volumes would be analyzed in devices that had all of the functionality of laboratory analyzers but were a fraction of the size. Such self-contained devices with all the necessary reagents would give lab results in minutes, if not seconds.

The big question is why the LOC revolution has not happened yet. It is not due to lack of interest in the scientific community, considering that thousands of journal pages and entire journals are dedicated to the topic, as well as regular conferences. The difficulty seems to be taking experimental work that is carried out once in a research lab, turning it into a manufacturable product that actually works over and over again with real patient samples, and doing so at a reasonable cost.

Integrating instrumentation with chemical/biological systems is another stumbling block. Integrated circuits and application-specific integrated circuits (ASIC) can be reliably manufactured in large volumes at low cost. Lateral-flow strips can also be reliably manufactured in large volumes at low cost. However, putting together something that combines the biology, chemistry, fluidics, and electronics, and making it cost prohibitive, is not a simple task.

Molecular POC Diagnostics

The challenges in developing POC molecular tests are different than immunoassays or

clinical chemistry. Sample preparation, the avoidance of inhibitor carry-over into the amplification reaction (e.g., hemoglobin), and contamination by either or both the primary target and the amplicons are critical factors in molecular assay and consumables design, particularly in the case of polymerase chain reaction (PCR). Areas for market growth in molecular POC tests include pharmacogenetics (e.g., screening for adverse reactions to Warfarin or Abacovir) and testing for infectious diseases in which rapid results close to patients has high added value. Two recent examples of such tests include multi-drug resistant Staph. aureus (MRSA) testing of patients prior to admission for treatment and rapid tests for Clostridium difficile in feces by real-time PCR.⁸

One of the key areas of recent research in molecular POC testing has been isothermal amplification methods as an alternative to PCR. Isothermal methods include smart amplification processes (SMAP) by the Riken Institute, plus a range of different methods including transcription mediated amplification (TMA), signal mediated amplification of RNA (SMART), loop-mediated isothermal amplification (LAMP), and helicase-dependent amplification (HDA).^{9,10} Cepheid has been a pioneer in the POC market with their self-contained sample-in/result-out GeneXpert system that includes a range of tests, including enterovirus and MRSA.

POC Product Lifecycle

Developing a novel diagnostic device or technology is a lengthy task. The seeds of new technologies come from research and development labs, either in academia or industry. The academic spin-out or industry start-up company has a long path to get from concept to marketable product. The initial stage of feasibility and proof-of-principle is often the quickest, proving that a protein or small molecule can be measured to some degree of accuracy and precision at a clinically relevant concentration, often in buffer to start with.

The key tasks in developing a POC device (assumed to be an instrument and disposable cartridge) are the following: user needs/market analysis, instrument development (breadboard, prototype, final instrument, user interface, cartridge interface, risk analysis, human factors), cartridge (sample entry, reagent stability), assay optimization (performance across patient populations, interfering factors), cartridge manufacturing (transfer from R&D, validation, scale-up), quality system, internal evaluation, clinical trials (ethics approval), regulatory submission, regulatory approval for CLIA waiver, shelf-life studies (9-12 months minimum shelf life is normally required), beta trials, product launch, and resolution of user issues

The POC development life cycle for this process is commonly 5-10 years. Once POC products are established on the market, they can easily maintain sales for 5-10 years, even 20 years. They are often repackaged to look more up-to-date, but the core technology remains the same. For example, the Biosite Triage system was first launched in 1992, the Cholestech LDX in 1990, the Abbott i-Stat in 1992, and the Unipath range of Clearblue pregnancy tests in 1985; all of these products are still going strong.

POC Tests for the Developing World

Developing nations usually get little attention from the IVD industry, due to the economics of developing and marketing tests for those regions. Ironically, settings like the developing world are critically in need of POC diagnostics, places where there is no central testing lab and often no access to electricity. In recent years, a number of charitable organizations have been at the forefront of a strong impetus to fund research in IVDs for the developing world. Such organizations include the Foundation for Innovative New Diagnostics, the Program for Appropriate Technology in Health, and the Gates Foundation CD4 initiative. While their efforts in these areas are laudable, it is not clear whether these organizations have the capabilities to drive new IVD technologies or whether they must piggy-back on more mainstream technologies. One exception may be the novel CD4 test being developed by

Zyomyx for the Gates Foundation.

Novel POC Technologies

Four POC technologies that are close to market launch are highlighted below. These four products were chosen because their underlying technologies offer something unique compared to similar tests that are already in the marketplace, and they are projects being developed for commercialization, rather than research projects.

Philips Handheld Immunoassays (Magnotech). The use of superparamagnetic particles as the capture surface in immunoassay lab systems to allow efficient washing steps is not new. However, the Philips Magnotech system, which is in development, uses magnetic particles as the actual label and drives the label on and off the sensor surface using an oscillating magnetic field. This process drives the assay rapidly to an endpoint, rather than relying on diffusion processes. Bound particles are then determined by an optical method. The system is being developed as a POC device, and product launch, in collaboration with bioMérieux, is scheduled for 2013.



[6]

Figure 2. The Vivacta PzoDx system (in development).

Vivacta. The Vivacta technology has a number of key benefits that make it unique in POC testing (see Figure 2).¹¹ Light energy is pulsed into the system from an LED source, causing localized microheating, which is converted directly into an electrical output using a pyroelectric polymer sensor. Interrogation of this signal allows carbon particles at the surface of the polymer to be distinguished from those in the bulk, and measurements can be made in whole blood without red-cell separation.

Zyomyx. Zyomyx has worked with the Gates Foundation to develop a novel cell-counting method that could revolutionize POC testing, particularly in the field of CD4 cell-counting to monitor the progression of HIV infection. The system is simple, utilizing the density of colloidal gold particles to rapidly label and sediment CD4 leukocytes, making them fall into a narrow capillary. The CD4 level is then read visually like a thermometer (see Figure 3).

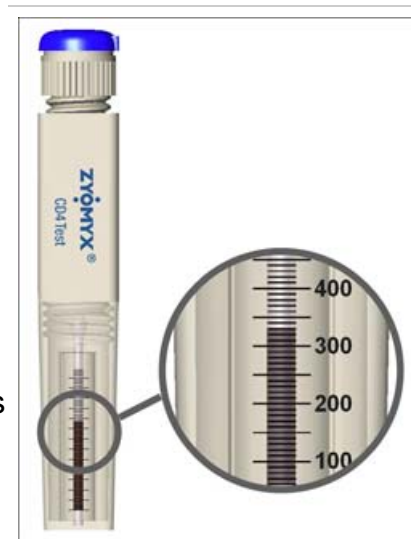
Oxford Nanopore. While Oxford Nanopore's primary focus has been nucleic acid sequencing, its technology also has potential in the area of high sensitivity immunoassays. The core technology works by detecting differences in current flow across ion channels in a lipid bilayer. A number of methods have been described ranging from DNA sequencing to protein and small molecule detection. From an outsider's viewpoint, the key question is, how reliable and robust will the technology be in the long term?

Conclusion

The lengthy development and product life cycles, coupled with regulatory hurdles and technological challenges, prevent the IVD industry from matching the fast-paced advances in other industries. A lot of exciting and novel work is being carried out in academic and industry research and development labs, but very few novel technologies are actually launched each year. Miniaturization is not always the answer; rather, truly novel methods that can satisfy the needs of POC testing are required, particularly in terms of cost. Finally, the true test of a novel POC technology is when it starts making sizeable inroads to the marketplace.

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