CellPress

Review

Emerging Technologies for Next-Generation Point-of-Care Testing

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Considerable advances in point-of-care testing (POCT) devices stem from innovations in cellphone (CP)-based technologies, paper-based assays (PBAs), lab-on-a-chip (LOC) platforms, novel assay formats, and strategies for long-term reagent storage. Various commercial CP platforms have emerged to provide cost-effective mobile health care and personalized medicine. Such assay formats, as well as low-cost PBAs and LOC-based assays, are paving the way to robust, automated, simplified, and cost-effective POCT. Strategies have also been devised to stabilize reagent storage and usage at ambient temperature. Nevertheless, successful commercialization and widespread implementation of such clinically viable technologies remain subject to several challenges and pending issues.

Emerging POCT Technologies

POCT – defined as '[biochemical] testing at or near the site of patient care whenever the medical care is needed' [1] – yields immediate acquisition of information on an individual's condition to facilitate treatment decisions or further extensive testing. It offers the advantages of widening accessibility to diagnosis, minimal sample volumes, reduced costs, and rapid analysis times [2]. Moreover, POCT can be performed at the bedside, in a physician's office, at home, or in paramedical support vehicles, as well as in secondary and tertiary care settings. Ideally, POCT devices must provide first results within minutes using a simple protocol with one or two steps for the analysis of whole blood, urine, or other biological samples. They are equipped with single-use test cartridges or strips that provide qualitative or quantitative results with in-built readers, while others are designed for multiple-use cartridges with quantification conducted on bench-top readers. The global market of point-of-care diagnostics will reach US$27.5 billion by 2018 (http://www.marketsandmarkets.com/PressReleases/point-of-care-diagnostic.asp). POCT will especially increase considerably in India and China, which have enormous populations with increased prevalence of chronic and infectious diseases. Therefore, POCT devices must be affordable for those at risk of infection or chronic diseases. They must also be robust and unrefrigerated to provide the desired sensitivity and specificity, minimal steps, and short turnaround time.

The advanced features and massive uptake of CPs (about 7.3 billion users, ~70% of whom reside in developing countries) make them highly suitable for personalized POCT and the decentralization of health-care management, particularly in remote, resource-deficient private and public settings [3,4]. Spatiotemporal data tagging further facilitates real-time monitoring and management of epidemics and emergency situations. Similarly, innovations in PBAs, LOC platforms, novel assay formats, and strategies for prolonged reagent storage are providing increasing sophistication and advanced functionality for POCT and have great

Trends

Recent advances in emerging technologies [i.e., cellphone (CP)-based technologies, paper-based assays (PBAs), and lab-on-a-chip (LOC) platforms] are paving the way for next-generation point-of-care testing (POCT).

Advances in novel assay formats as well as strategies for long-term reagent storage are the prerequisites for emerging POCT technologies.

Current and future analytes for POCT comprise small-molecule metabolites, proteins, cardiac biomarkers, and cells.

One emerging future trend is centered on miniaturized, fully automated, and network-enabled CP-based POCT technologies integrated with PBAs and/or LOC platforms.

Several key challenges that must be addressed are bioanalytical performance, miniaturization of microfluidic devices, material safety and disposal, changing CP specifications, data security and ownership, big data, and health economics feasibility.

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potential (Table 1, Key Table). This review highlights recent advances in this field along with key challenges, opportunities, and future trends.

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Target Analytes for POCT

Small Molecules

Various POCT devices are available, often based on electrochemical or optical detection, for measuring electrolytes and small molecules [5] (Table 2), with blood glucose testing as the predominant test [592 million diabetics worldwide by 2035 (http://www.idf.org/diabetesatlas/update-2014). Considering the lower water content in circulating cells compared with that in plasma (73% vs 93%) [6], the POCT procedure is limited to hematocrit (Hct) extremes such as during the course of hypotensive episodes and coronary artery bypass surgery [7]. Thus, most devices are now calibrated to plasma rather than whole blood. The use of glucose dehydrogenase is oxygen independent and provides accurate results for all blood specimen types [8], although this enzyme is interfered with by maltose, a disaccharide in foodstuffs. Several deaths have been attributed to the malfunction of the glucose test as it provided falsely high results for hypoglycemic subjects [9]. The use of glucose oxidase is oxygen dependent and therefore not recommended during shock, diabetic coma, or dehydration. Electrochemical detection of H_2O_2, a byproduct of this enzymatic oxidation, is also susceptible to interference from several drugs and their metabolites [10]. Among noninvasive glucose measurement techniques [11], of note is contact lens-based glucose sensing [12] and painless glucose monitoring (http://www.freestylelibre.co.uk/). The estimated market for continuous glucose monitoring systems alone will reach US$783.9 million in 2019 (http://www.mdtmag.com/news/2015/01/continuous-glucose-monitoring-market-surging).

Proteins

POCTs are currently available for HIV antibodies (Abs), *Streptococcus*, *Treponema pallidum* (treponemal diseases), *Chlamydia trachomatis* (eye epithelium inflammation), rotavirus (severe diarrhea), influenza virus, *Plasmodium falciparum* (malaria), and *Trichomonas* (vaginitis). Future POCT extends to fibrosis (galectin-3 or β-galactoside-binding protein), myocardial infarction (copeptin), acute renal failure (neutrophil gelatinase-associated lipocalin), and preeclampsia (e.g., endoglin, placental growth factor, tyrosine kinase). The demand for POCT for sexually transmitted infections (STIs) is also strong, with over 1 million people infected each day (http://www.who.int/mediacentre/factsheets/fs110/en/).

Cardiac and Cancer Biomarkers

The early detection of cardiovascular disease (CVD) (17 million cases by 2030) will drive the global cardiology diagnostics market to US$913 million by 2017 (http://www.cdc.gov/heartdisease/facts.htm). On-site POCT for cardiac injury markers [myoglobin, creatinine kinase isoenzyme MB (CKMB; myocardial type)] and the cardiac troponins (cTnI and cTnT) facilitates effective screening, lower hospitalization rates, and cost savings [13]. Direct and indirect biomarkers such as myoglobin, ischemia-modified albumin (IMA), glycogen phosphorylase isoenzyme BB, copeptin (C-terminal proAVP), fatty acid-binding protein (FABP), B-type natriuretic peptide (BNP) (mostly measured as NT-proBNP), and myeloperoxidase have also been identified in acute myocardial infarction (AMI) patients [14,15]. However, at present, cTnI and cTnT are the best validated of all cardiac markers. The global cancer diagnostics market will reach US$168.6 billion by 2020 (http://www.transparencymarketresearch.com/cancer-diagnostics-market.html) for the detection of several protein biomarkers such as prostate-specific antigen, platelet factor 4, and carcinoembryonic antigen.

Cell Count

Cell-based POCT for full blood cell counts provides vital information for the diagnosis and monitoring of conditions such as anemia and HIV/AIDS (e.g., $CD4^+$ lymphocyte count