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Research review paper

Clinically relevant analytical techniques, organizational concepts for application and future perspectives of point-of-care testing

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ABSTRACT

Applications of near-patient testing have developed rapidly during the last years. It offers quick test results and minimal preanalytical interference, having the potential to improve patient outcomes, even when still under scrutiny by laboratory and healthcare professionals. Near-patient diagnostics are currently also used increasingly in developing countries, due to the burden of inadequate healthcare services in resource-constrained settings. This review describes the underlying emerging techniques that are based on advanced microfluidics and nanomaterials, device miniaturization, and multiplexing the detection mode. The organizational concepts for reasonable applications, contributing significantly to the future perspectives of this nascent diagnostic modality, are supplementary portrayed.

Contents

Abbreviations: ACS, acute coronary syndrome; ACT, activated clotting time; AKI, acute kidney injury; AMI, acute myocardial infarction; BE, base excess; BGA, blood gas analysis; BNP, Brain-type Natriuretic Peptide; $paCO_2$, carbon dioxide tension; CAD, coronary artery disease; cBASS, Compact Bead Array Sensor System; CBC, complete blood cell count; CE, Conformité Européenne; CGM, continuous glucose monitoring; CK, creatine kinase; CKD, chronic kidney disease; CKMB, Creatine Kinase Myocardial Band; CLSI, Clinical and Laboratory Standards Institute; CNT, carbon nanotubes; CPA, Cone and Plate(let) Analyzer; CTC, circulating tumor cells; cTnI, cardiac troponins I; cTnT, cardiac troponins T; CVD, cardiovascular disease; DCT, direct-to-consumer testing; ED, emergency department; EQAS, external quality assessment schemes; FDA, Food & Drug Administration; FET, field-effect transistor; FGF-23, fibroblast growth factor 23; FRET, Förster resonance energy transfer; FSH, follicle stimulating hormone; GFR, glomerular filtration rate; Hb, hemoglobin; HbA1c, hemoglobin A1c; HDA, Helicase Dependent Amplification; HCG, human chorionic gonadotrophin; HIV, human immunodeficiency virus; HL7, Health Level 7; hPOCT, hospital POCT; ICU, intensive care unit; IDT, interdigital transducer; IL-18, interleukin 18; IGFBP7, Growth Factor Binding Protein 7; INR, International Normalized Ratio; ISFET, ion-selective field-effect transistor; ISO, International Standards Organization; IT, information technology; IVD, in vitro diagnostics; KIM-1, kidney injury molecule-1; LAMP, Loop Mediated Isothermal Amplification; LOC, Lab-on-a Chip; LDH, L-lactate dehydrogenase; LED, Light emitting diodes; LFA, lateral-flow assay; L-FABP, Liver Fatty Acid Binding Protein; LOD, lower limit of detections; LW-SAW, Love wave surface acoustic wave; LH, luteinizing hormone; MCHC, mean corpuscular Hb concentration; MEMS, micro-electromechanical systems; μ-PAD, microfluidic paper-based analytical device; μ-TAS, micro-total analysis systems; mHealth, mobile health; MIOX, myo-inositol oxygenase; MRSA, methicillin-resistant *Staphylococcus aureus*; NACB, National Academy for Clinical Biochemistry; NADH, Nicotinamide Adenine Dinucleotide plus Hydrogen; NASBA, Nucleic Acid Sequence Base Amplification; NAT, nucleic acid testing; NGAL, Neutrophil Gelatinase-Associated Lipocalin; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; saO_2, oxygen saturation (arterial); paO_2, oxygen tension (arterial); PCR, polymerase chain reaction; POCT, point-of-care-testing; PSA, prostate-specific antigen; PT, prothrombin time; QCM, quartz crystal microbalance; QD, quantum dots; RALS, Remote Automated Laboratory System; RCA, Rolling Circle Amplification; RI, refractive index; ROTEM, Rotation Thrombelastometry; RPA, Recombinase Polymerase Amplification; SAW, surface acoustic wave; sCD40, Soluble Cluster of Differentiation 40; STAT, Statim (abbrev. of the Latin word); SDA, Strand Displacement Amplification; SERS, surface-enhanced Raman scattering; SMBG, self-monitoring of blood glucose; SP, surface plasmon; SPR, surface plasmon resonance; TAT, turn-around-time; TEG, Thrombelastography; TGC, tight glycemic control; TIMP-2, Tissue Inhibitor of Metallo-proteinase 2; TIRF, Total Internal Reflection Fluorescence; WBSs, Wireless Biosensors; WGM, whispering-gallery mode; WHO, World Health Organization.

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1. Introduction

The name point-of-care testing (POCT) refers to the performance of biochemical, hematological, coagulation or molecular diagnostic tests at or near a patient. Applications of POCT in healthcare have been rapidly increasing during the last two decades. Patient-near testing is now implemented in various settings, from self-testing to outpatient clinics and, finally, to the intensive care unit. Near-patient testing offers the clinical advantage of quick test results and minimal preanalytical interference, having the potential to improve patient outcomes, although this is generally less well documented in clinical studies.

POCT is also being used more extensively in countries with limited resources, particularly for diagnostic purposes (Plebani and Lippi, 2014).

The POCT process is truly innovative in healthcare, since it offers new possibilities for prevention, diagnosis, and monitoring of diseased subjects. As Price and St. John (Price and St. John, 2014) pointed out, while underlying analytical technologies hold some clever inventions, "genuine innovation can only come about if the invention is applied in a useful way" within the healthcare system to deliver an enhanced value for the patient. But it should be recognized that for POCT an additional principal catalyst for the innovation process is the patient himself, which reinforces the importance of POCT (Omachonu and Einspruch, 2010).

Consequently, the benefits of a POCT process management are only to be reaped if cooperation with the core competences of the central laboratory exists (Bietenbeck et al., 2015). If there is complementary understanding between POCT specialists and laboratory experts, a reconfiguration of clinical pathways can significantly improve the overall patient outcome. A good example of this improvement is the self-testing of glucose or prothrombin time (PT)/International Normalized Ratio (INR) by diabetics or patients under anticoagulation. These subjects use the self-monitoring to adjust treatment. There are already many studies available (as discussed in Section 3.3.8.), which show that a better disease management improves outcomes in a way that has not been possible before the advent of the respective POCT technologies (O'Kane, 2014).

Innovation in healthcare means novel ways for care, being delivered to the patient. In the context of many health challenges in developing countries, it becomes apparent that POCT most likely offers such changes. The transforming effect of POCT can be verified by the fact that the increasing number of malaria tests has already reduced significantly inappropriate anti-malaria treatment during the last decade (Jani and Peter, 2013).

The role of the central laboratory, however, is still very important, even when POCT is applied. Test results alone are useless (St. John and Price, 2014a, 2014b), as laboratory experts play an important clinical role for the support of the physicians as consultants in hospitals and for outpatient areas. They provide helpful advice for the interpretation of results, comment on pre- or postanalytical errors, recommend follow-up tests, and provide as POCT coordinators the quality management of the patient-near testing (Schimke et al., 2006; Huckle, 2008) (see also Section 4.1.).

What makes POCT so attractive globally, is that there has been a two-step paradigm shift occurring in the last decade:

1. POCT was originally a supplement of the central laboratory and defined as hospital bedside biochemical testing with a limited test portfolio. Now, POCT is often used as the sole diagnostic approach in developing countries without a central laboratory infrastructure.
2. An additional shift arises from the insight that until today laboratory medicine focused on measuring a high number of parameters in the human body with sophisticated methodologies, whereas POCT analysis has a restricted number of parameters with robust devices for many subjects that are self-determined customers or indigent patients in developing countries.

The World Health Organization (WHO) demands that newly established POCT devices implicitly should meet the "ASSURED" criteria:

Affordable, **S**ensitive, **S**pecific, **U**ser-friendly, **R**apid and **R**obust, **E**quipment-free, and **D**elivered (to the enduser) (Peeling and Mabey, 2010; Pai et al., 2012).