Perspective

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Perspectives on the imperatives, opportunities and challenges for point-of-care diagnostics in systemic lupus erythematosus

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Point-of-care diagnostics (POCD) are designed to make diagnostic tests immediately accessible at sites of patient care, are simple to use, economical, of high specificity, and enable rapid clinical decisions. Systemic lupus erythematosus is a disease that is a suitable target for such devices because it can present with a variety of rapid onset and life-threatening features. The development of POCD in systemic lupus erythematosus would be facilitated by evidence-based use of a number of well-defined, disease-specific biomarkers. Rapid initiation of interventions in patients presenting with life-threatening features are of paramount importance. The features of POCD of the future are based on advanced diagnostic platforms such as multiplexed bead-based technologies, lateral flow, novel nanomaterials and lab-on-a-chip microfluidics.

Keywords: autoantibodies • biomarkers • diagnostics • health services • point of care • systemic lupus erythematosus

Background

Point-of-care diagnostics (POCD) is one of the most rapidly growing global medical diagnostic markets with world revenue forecast to reach US$17.2 billion in 2014 [1]. Contemporary POCD market targets are typically aimed at measuring or detecting blood glucose levels, coagulation components, cardiac performance and disease markers, cholesterol levels, infectious diseases, and pregnancy. For overviews on the broad spectrum of advances and issues relating to POCD refer to excellent publications by Konstantinov, Tzamaloukas and Rubin [2], and for 'actionable' and 'mechanistic' diagnostic biomarkers and related considerations to Robinson, Utz and colleagues [3,4]. This overview will focus on autoantibody detection, recognizing that this only one class of biomarkers among proteomics, genomics, ribonomics and metabolomics that could have a prominent place in POCD. Autoantibodies were chosen as the focus for this article because detection of serum autoantibodies is standard practice for the diagnosis and classification of organ-specific [5] and systemic autoimmune rheumatic diseases [6] and has been increasingly used for detection of neoplastic [7–9], paraneoplastic [10–12] and neurological disorders [13–17], and occupational exposures [18,19]. For the most part, autoantibody tests are currently done in large, centralized, high-throughput laboratories where turnaround times are measured in days, not in hours as may be required in some emergent POCD settings.

A wide spectrum of more than 100 autoantibodies directed to intracellular and intercellular macromolecules is a characteristic feature of systemic lupus erythematosus (SLE) [20,21]. Of these, only three, anti-dsDNA, anti-Smith (Sm) and antiphospholipid antibodies, are included in established classification criteria for SLE [22]. SLE can present acutely or with rapid onset disease flares that are attended by significant morbidity and mortality [23,24]. In an emergency setting, where the SLE patient may present for the first time, the diagnosis of SLE can be a particular challenge because many of the clinical features are also seen in acute infections, vascular diseases, malignancies and allergic conditions. Meeting the challenge of making a prompt and accurate

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diagnosis is important because of the risk of rapid progression of the disease to organ failure and even death. In this setting, POCD have obvious clinical value. In addition, patients who are seen in remote geographic locations that do not have access to what is considered standard diagnostic platforms and laboratories is another obvious niche for POCD [25].

Case report

A 15-year-old female was brought to the Emergency Department of a children's hospital because of rapid onset lethargy that rapidly progressed to somnolence and grand mal seizures. She had a past history of tuberculosis that was treated while she was still living in a third-world country. Prior to the onset of this illness, she developed a high fever and complained of chest pain and painful joints. Physical examination established a prepubertal, normotensive female in apparent good nutritional and hydration status and no evidence of trauma. During the examination she had a grand mal seizure and remained icteric. She had a nonscarring bimalar rash, but no evidence of oral ulceration or ocular inflammation. A fundiscopic examination was normal. Examination of the chest revealed a pericardial friction rub, but heart sounds were otherwise normal and the lung fields were clear. Examination of the abdomen was unremarkable and there was no pitting edema of the extremities. The patient did not respond to verbal questions or commands, but there was withdrawal of limbs to painful stimuli. She was judged to have nuchal rigidity but a screening of exam of the cranial nerves and deep tendon reflexes were unremarkable. A stat complete blood count revealed a normocytic, normochromic anemia (Hgb 9.8) and a mild neutrophilia. The urinalysis showed no reds cells, white cells or casts but there was 1+ protein.

This case presentation is an actual case where a prompt and accurate diagnosis is required to differentiate acute infections (i.e., viral, bacterial, reactivation of tuberculosis with CNS involvement), from other causes of acute onset neurological disease in a young female. While a number of investigations are required, the availability of POCD to exclude diagnoses such as SLE and/or infectious [26] or metabolic syndrome(s) [27] would be most helpful in this setting. As a summation of the case report, the patient had high titer anti-Sm antibodies, a highly specific biomarker for the diagnosis of SLE [21]. Based on this and numerous other clinical presentations, there is a need for devices that are can be accessed or easily operated in an acute care environment. Accordingly, portable and relatively inexpensive biosensors capable of detecting multiple serological parameters are becoming one of the fastest growing technological developments in diagnostic medicine [2,25,28].

Box 1. Clinical scenarios where point-of-care diagnostics would benefit the management of acute onset or flares of systemic lupus erythematosus.

- CNS lupus (psychosis, encephalitis, stroke, seizures)
- Transverse myelitis
- Renal failure
- Pulmonary hemorrhage, pneumonitis
- Cytopenias: thrombocytopenia, anemia, neutropenia, leukopenia
- Catastrophic secondary anti-phospholipid syndrome
- Cardiac infarction and tamponade
- Fetal heart block
- Mesenteric vasculitis
- Pancreatitis

Clinical uses of POCD in SLE

In general, the settings where POCD would be of highest value in the initial diagnosis and management of SLE include a specialist's office, in emergency or intensive care situations or in remote geographic settings where there is limited access to diagnostic laboratories. Since any organ system can be involved in SLE, in these settings, there are number of potential clinical scenarios where POCD would be of value in the rapid and accurate diagnosis and then appropriate and effective management (Box 1). These include acute neurological presentations such as coma, encephalitis, seizures, and stroke; thrombotic and hemorrhagic events such as acute pulmonary embolus or hemorrhage; acute abdominal pain attended by pancreatitis or bowel infarction; cardiac infarction or tamponade; acute onset bullous cutaneous disease. In this context, multiplexed POCD that differentiate various systemic autoimmune rheumatic diseases by including anti-dsDNA, anti-Sm, anti-citrullinated peptides, anti-phospholipid and other disease-related biomarkers should be considered (Table 1).

There is a wealth of published information on the critical care of SLE; two studies are highlighted here to emphasize the importance of rapid diagnosis in this setting. In a study of healthcare resource utilization and associated costs over a 2-year audit period, it was found that >45% of SLE patients were seen in an emergency room setting and 26.4% required hospitalization [29]. In a Canadian 3-year follow-up study, 68/665 (10.4%) of SLE patients reported hospitalization related to a SLE flare and an average annual hospitalization rate of 7.6% (range: 6.6–8.9%) [30]. The most common reasons for hospitalization were disease flares as attended by hematologic (22.1%), serositis (20.6%), musculoskeletal (16.2%), and renal (14.7%) parameters.

One key question in the management of SLE is whether a more effective healthcare system [31], particu-

Table 1. Autoantibody biomarkers that would benefit rapid diagnosis and early intervention in systemic lupus erythematosus.

Autoantibody	Clinical association	Ref.
dsDNA	Active SLE	[65–68]
Nucleosome/chromatin	Active SLE progressing to renal failure	[69,70]
Ribosomal P	Active SLE, psychosis, NPSLE	[71–73]
NMDA receptor (NR2)	Encephalitis, NPSLE	[74–76]
Phospholipids, β2 glycoprotein 1, phosphatidyl serine/prothrombin complex	Catastrophic antiphospholipid syndrome	[77–79]
ADAMTS13†	Thrombocytopenia purpura, atypical hemolytic uremic syndrome	[80–84]
Anti-C1q	Progressive renal disease	[20,85,86]

†Autoantibodies directed to ADAMTS13 and also ADMATS13 levels.
NPSLE: Neuropsychiatric systemic lupus erythematosus; SLE: Systemic lupus erythematosus.

larly for those living in medically underserviced areas [32] can prevent unnecessary clinical and/or hospital visits and thus improve outcomes and moderate the costs of healthcare for this condition [33]. With home care services on the rise, POCD devices might have a role in this setting by providing a more immediate access to relevant laboratory diagnostic parameters and results. Digital electronic medical records [34,35], vital sign technologies that employ conventional hand-held devices such as smartphones [36–38], as well as increased variety of POCD [25,39], should decrease costs because fewer medical personnel visits to the home, and accordingly fewer unnecessary trips to emergency rooms.

A pilot study conducted at a home healthcare agency in New York (USA) revealed that 7.3% of home visits offered POCD testing [40]. However, the same study also documented a 10% return visit to the home to recollect another sample because of specimen problems. To alleviate the costs associated with these return visits requires POCD device manufacturers to ensure that they are robust and at least rival the popular take home pregnancy test kit. Of note, telemedicine technology affords the opportunity to send POCD results to a laboratory for review [40] and to the patient's electronic medical record [33,41], allowing both the attending healthcare team and the laboratory in charge of POCD to take control of and ensure quality assurance of such procedures.

Spectrum of POCD

The spectrum of POCD is wide and continues to advance as new technologies are developed. To some, POCD simply refers to the availability of a diagnostic test or device that can provide 'stat' results. This likely requires '24–7' access to fairly conventional devices and diagnostic platforms that are available in many laboratory settings. Whether qualified manpower, cost-containment and other logistical issues can provide this level of access is uncertain. To accommodate a true POCD paradigm, the specimens submitted for diagnostic purposes (blood/serum/plasma, urine, fluid aspirates; i.e., thoracentesis, pericardiocentesis or synovial fluid) must be transported very quickly (i.e., within minutes) to the testing laboratory where a POCD platform is able to provide turnaround time results in minutes, but certainly in less than 1–2 h. This may require dedicated specimen couriers, pneumatic tube systems or other logistical support within acute care settings. Of course, the implied requirement for these systems to work properly is the 24–7 availability of trained, competent and/or certified staff to receive and process the specimen(s), perform the test, generate a report and then ensure that the test results are promptly delivered back to the bedside. In these settings, some diagnostic technologies such as multiplexed bead-based platforms (addressable laser beads or chemiluminescence) [42–44] are able to provide the rapid turnaround times for test performance required. While these approaches may meet the demands for POCD, there is a rapid development of technologies and platforms that provide interesting alternatives. These include devices that utilize lateral flow [39,45] and lab-on-a-chip technologies employing electro-chemical and electro-inferometry [25,46–48].

Lateral flow devices are best known because they use techniques that have been in use for well over a decade in applications such as take home pregnancy tests. Lateral flow devices have been developed for use at the 'bedside' to assist in the diagnosis of bee allergy [49] and life-threatening vasculopathies, such as granulomatosis with polyangiitis [39]. A similar device for detecting anti-dsDNA is in beta testing (Figure 1) and shows promise when compared with conventional techniques of detection anti-dsDNA using the *Crithidia lucilliae* immunofluorescence test [50,51]. One of the advantages of lateral flow devices is that it is possible to detect more than one

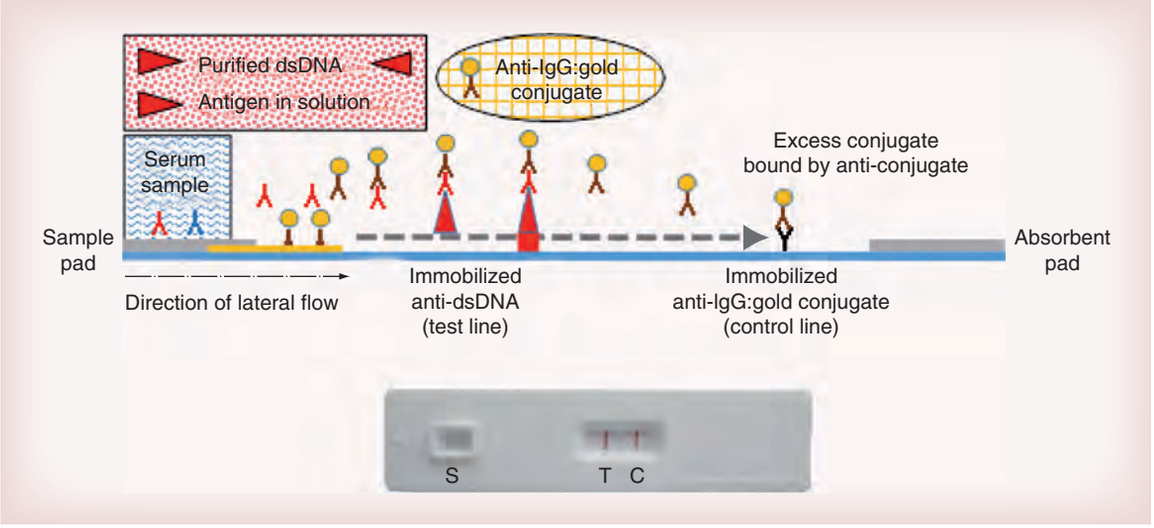

Figure 1. Schematic and image of a lateral flow device. Solutions containing an anti-human IgG conjugated to gold, the test serum sample and purified dsDNA (autoantigen: red triangle) are applied in the sample port (S) of the device. The fluid phase containing the human anti-dsDNA (red Y) binds to the anti-IgG:gold conjugate and moves by diffusion to the right. When the immune complex (anti-dsDNA:anti-human IgG/gold conjugate) encounters the immobilized dsDNA ligand at the test line, it is retained and is visualized as a visible line. Excess conjugate continues to flow toward the immobilized anti-IgG control where it is retained and serves as a visible line, thereby serve as a baseline of test completion and to ensure the device is working. The rest of the fluid is taken up by the absorbent pad at the left extremity of the device. The resulting reaction can be quantitated in a small densitometry device. More than one autoantibody can be detected with such devices at one time. Adapted with permission from [39] © Elsevier (2014).

biomarker (i.e., anti-Sm or anti-phospholipid antibodies) at a time [39].

In many POCD settings, disposable, bioelectrodes have emerged as devices that provide accurate, relatively low cost systems which are attended by minimal technologist involvement [52] and reviewed in [25]. Devices employing this technology include determination of markers for tumors [53], liver disease [54,55], IgG antibodies directed to West Nile Virus [56] and the quantitative measurement of antibodies in human serum [57]. A variety of devices employing surface plasmon resonance and nanoparticles could also find uses in lab on a chip POCD [58–60].

Challenges in development & adoption of POCD

The development, production and adoption of POCD in SLE are attended by a number of challenges (Box 2). First, technological challenges, many of which are not unique to POCD, include discriminatory capacity, reliability, sensitivity and specificity of the devices. In assays where a desired sensitivity has not been achieved, the device developers may opt for antigen capture approaches utilizing highly specific and avid antibodies bound to a solid phase matrix. Undesirable interactions based on physicochemical properties (cationic, anionic or hydrophobic) of the target autoantigens, the cognate autoantibodies and the device matrix are a persistent challenge that require a variety of manipulations and adaptations (i.e., blocking agents, adjusting pH and/or salt concentrations) that are best addressed in the domain of the diagnostic industry that is familiar with and has expertise in dealing with these problems. In devices that rely on miniaturized and nanotechnologies, the purity of the biological fluid is important because serum and other biological fluid-containing particulates, lipids and hemolysis products may require filtration or other pretreatments. If such pretest treatments are required, it could limit the acceptance of a true point-of-care application. In addition, the shelf life of some POCD devices may be a challenge [25].

Second, there are pragmatic and logistic challenges. The lack of demand for POCD in SLE is primarily due to insufficient evidence demonstrating the value of such approaches and wide availability of devices to warrant their adoption. As in the implementation of personalized medicine, there must be a willingness of payers to reimburse for the POCD testing that is based on clinical value [61], not simply the cost of the devices alone. Therefore, there is a need to demonstrate realistic expectations around the standards for evidence of clinical value [62,63]. A simplistic expression of the clinical value proposition of POCD is conceptually expressed as a quotient of the favourable clinical outcomes divided by costs of the devices and performing the test itself. Reimbursement for value that ensures cost–effectiveness for

innovative health systems [64], must also take into consideration a return on the investment to the industry that manufactures and markets the devices [61].

Another significant challenge relates to standardization of tests and quality assurance and control that meets with the approval and certification of the devices by various jurisdictional authorities. In addition, the acceptance of risk and legal responsibility for devices that are used in an acute care setting has to be recognized. An incorrect diagnosis leading to inappropriate and possible risky intervention is one concern. In the development of any diagnostic devices, there is typically a balance between sensitivity and specificity in the diagnostic performance of the devices. In the case of POCD, the bias should obviously be to specificity, perhaps at the expense of sensitivity. Last, there must be attention to developing approaches to the seamless transfer of the results of POCD test to the patient's medical record.

Box 2. Challenges and barriers to point-of-care diagnostics testing in systemic lupus erythematosus.

- Standardization and accuracy of devices
- Specificity must be very high to avoid misdiagnosis
- Results must be readily interpreted and linked to patient's medical record
- Acceptance by health payers and care providers: cost must be balanced by the clinical value proposition

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Executive summary

Background

- Systemic lupus erythematosus (SLE) is a relatively rare, multisystem disease that can present with a spectrum of organ involvement and impending failure where a prompt diagnosis would alleviate significant morbidity, mortality and global burden of disease.
- A significant proportion of SLE patients make their way to emergency and intensive care settings either at initial presentation or during a flare of the disease.

Clinical uses of point-of-care diagnostics in SLE

- There are a number of specific clinical scenarios where point-of-care diagnostics (POCD) based on autoantibody biomarkers could provide a new level of personalized or prescriptive care and management for SLE patients. Most commonly this is likely to be at the time of initial diagnosis but the use of POCD may also find uses in longitudinal management of SLE but this requires stringent evidence based approaches.
- An important approach will be to adapt these technologies to POCD that can be used in emergency, intensive care and other locations where timely diagnosis is of utmost importance.

Spectrum of POCD

- The development of novel diagnostic technologies such as lateral flow and lab-on-a-chip technologies, opens up the opportunity to make inroads into the morbidity and mortality that is currently a challenge in the early and accurate diagnosis of SLE and also managing flares of the disease.

Challenges in development & adoption of POCD

- Challenges to adopting and implementing POCD in SLE include:
  - Availability of the POCD devices;
  - Evidence showing that POCD in SLE are accurate (high specificity is most desirable), cost effective and that they provide a favorable clinical value in terms of patient outcomes;
  - Legislation, regulations and reimbursement that take into account the value of the devices.

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