Technology At Bedside: Are We Crossing The Line?

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Technology At Bedside: Are We Crossing The Line?

ANCC Accredited NCPD Hours: 2.5hrs

Target Audience: RN/APRN

Goal

The goal of this article is to discuss the current trends in point of care testing and monitoring - from ambulatory to critical care settings - and its impact on healthcare. The article also discusses the pros and cons of technology deployment for point of care testing

Objectives

- Describe the importance of point of care testing in present healthcare settings
- Describe Pros and Cons of Technology Deployment for Point of Care Testing
- Identify the definition of point of care testing
- Describe the current trends in point of care testing
- Discuss the Impact of Quantification Tests in POCT

Need Assessment

Point-of-care (POC) diagnostic tests provide an opportunity to get clinically relevant information at the point-of-use, without the need for sample processing or analysis from a remote clinical chemistry laboratory. The review of POCT includes the observations which shows the evidents regarding application of POCT will fill the gap between the funding needed to support the health system and also it reveals evidents of technological advancement of POCT, its application, current trends, pros and cons of POCT, and also information regarding quantification of POCT and its challenges.

> **"Point-of-care (POC) diagnostic tests provide clinically relevant information at the point-of-use, without the need for sample processing or analysis from a remote clinical chemistry laboratory. The blood glucose meter, used for the management of diabetes, and the home pregnancy test (dipstick) are the most popular examples"**

Introduction

Poor health conditions shorten peoples' lives and undermine their quality of life. These conditions also limit economic and social development by reducing 'human capital' and generating health costs. More broadly, long and healthy lives are important indicators for societal well-being.

Within ***industrialized nations there is a challenge of increasing demand, typically arising from an aging population, rising costs and decreasing resources.*** Point-of-care (POC) diagnostic tests provide clinically relevant information at the point-of-use, without the need for sample processing or analysis from a remote clinical chemistry laboratory.

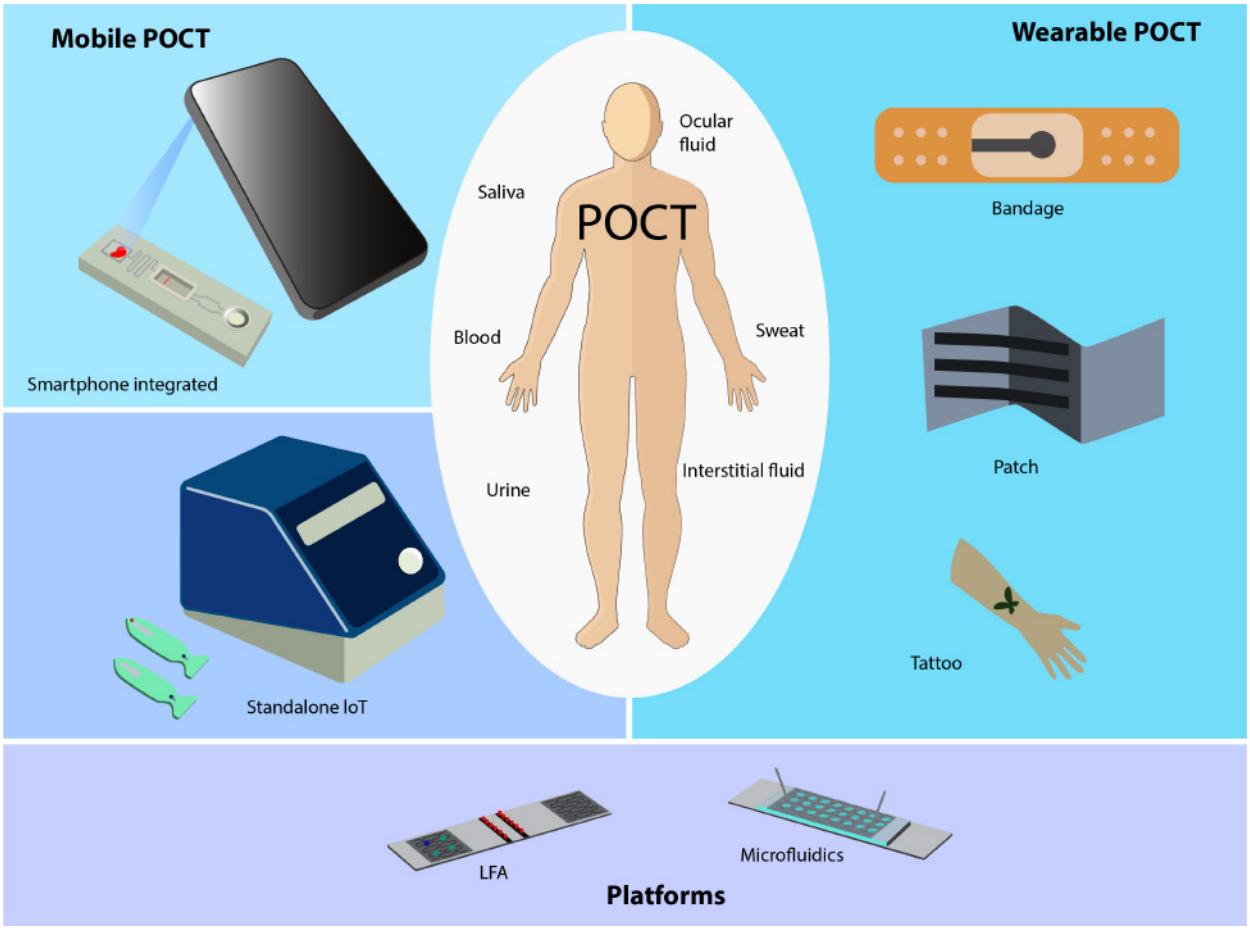

Fig 1: Different types of Point of Care Testing Devises in Use

The blood glucose meter, used for the management of diabetes, and the home pregnancy test (dipstick) are the most popular examples (As shown in fig.2). However, recent advances in microfluidics combined with the decreasing cost and size of advanced electrochemical and optical sensors have broadened the range of applications for POC diagnostics. For example, these advances have made possible the burgeoning field of POC diagnostics for resource-limited settings, such as developing nations. [12, Rank 2]

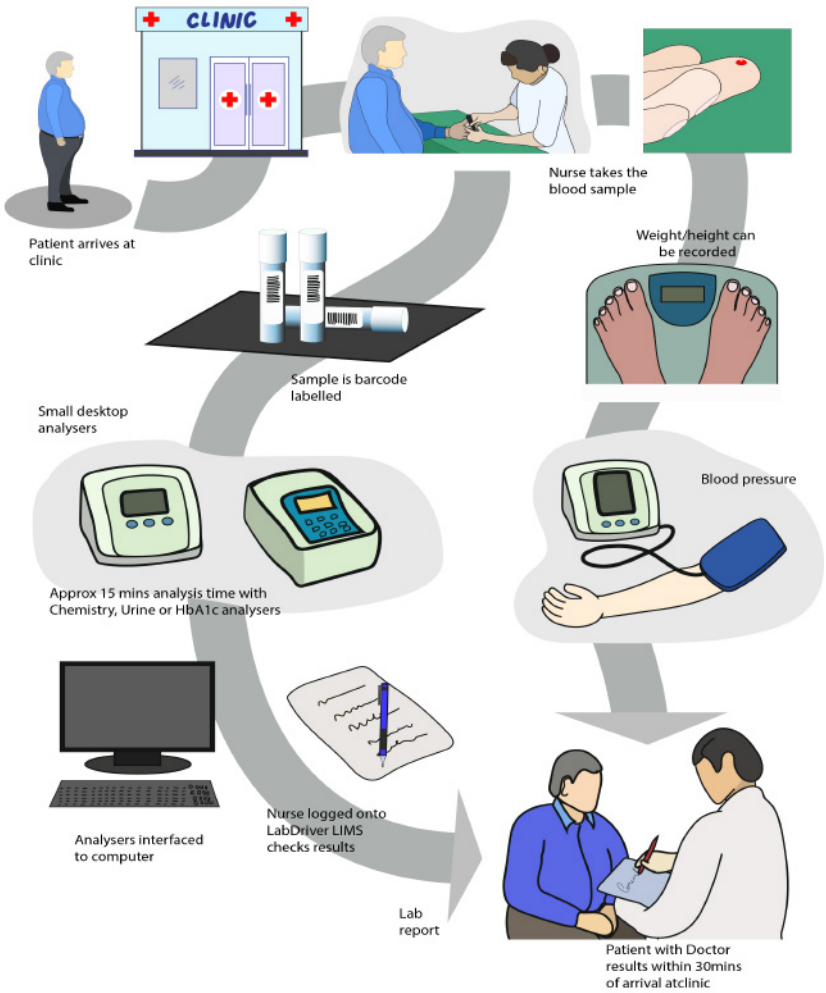

Fig 2: Clinical decision making process of Point of Care Testing

The Importance of Point of Care Testing (POCT)

- Point-of-Care Testing (POCT) that is easy to use and interfaces with medical records or a broader health surveillance system,
- It has the potential to dramatically alter disease burdens through home-testing or self-testing.
- Patients who may avoid seeking medical care for a stigmatized condition could perform testing without having to report to a public health center or physician's office.
- Simple, standard interfaces for POCT results, could overcome some of the traditional barriers to widespread adoption by allowing for testing in the most convenient and medically appropriate location, at the point of need.
- Most chronic disorders—such as cancer, metabolic disease, cardiovascular disease, diabetes and dementia the disease

process starts decades earlier before it appears symptomatically. Identifying individuals at the earliest stage of their disease will completely change the therapeutic paradigm and transform the way that health care is delivered.

- This will help to ensure focused attention on sustaining health rather than treating late stage-patients with symptomatic disease.
- There is also an opportunity of innovation through development of new models of person-centered community-based health delivery.
- This allow decentralization of care from traditional secondary care providers, such as hospitals [5, Rank 4]

Definition of Point of Care Testing

Point-of-care testing (POCT) is defined as laboratory testing conducted close to the site of patient care. Various POCT kits have been used for years (eg, blood glucose, urine ketones, pregnancy). However, new research and discussions about POCT focus on the use of new technologies that can test for blood coagulation times, blood gas composition, cardiac enzyme profiles, standard electrolytes, and the presence of infectious entities including influenza, human immunodeficiency virus (HIV), hepatitis C, and group A streptococcus. ***These tests are increasingly being administered by trained staff in hospitals, clinics, and other professional health-care settings, including pharmacies.*** Rapid advances in testing technology including the development of easy-to-use portable health-monitoring devices means, that such testing can now be done by individuals with little or no training and in virtually any setting, including a patient's home.

With the ongoing evolution in POCT, numerous concerns have arisen about the quality and accuracy of the tests, comparability between multiple tests for the same endpoint. For example, each test may be internally consistent but provide different absolute values, making longitudinal data more difficult to evaluate if the same manufacturer is not used each time. Interpretation of the results, how to use the results for clinical decision-making, and whether and how to include the results in a patient's medical record are some of the other practical concerns. Although performing a point-of-care test may be done in many settings, ***optimal use of the generated data requires appropriate interpretation of the results and communication among the multidisciplinary health-care team and***

with the patient. Communication among these stakeholders with different levels of understanding of human physiology, biochemistry, disease, and test characteristics offers multiple opportunities for misunderstanding, a concern that is compounded when patients are self-testing. In terms of education, it is important that pharmacists become knowledgeable about the mechanics and data of POCT and are able to communicate this information to patients and other health-care providers. [17,Rank 4]

Pros and Cons of Technology Deployment for Point of Care Testing

Based on the increased fidelity of read-out, digital detectors offer the potential to fill the diagnostic gap between ultrasensitive molecular amplification tests and qualitative POC tests, by promising both direct and sensitive measurement of health biomarkers. Key ***challenges in translating from a laboratory instrument requiring manual operation by a skilled operator to an automated tool for diagnostic applications include stringent calibration and characterization requirements.*** [16, Rank 5]

Advanced Technology

Rapid technological improvement in mobile phone connectivity and functionality and increased global market penetration has opened new avenues in biomedical research, education and applications. These improvements have been accompanied by an explosion in new sensing modalities that are enabled by batch-fabrication of complex transducers on a single chip(As shown in fig.3)

> **“Rapid technological improvement in mobile phone connectivity and functionality as well as their increased global market penetration has opened new avenues in biomedical research, education and applications”**

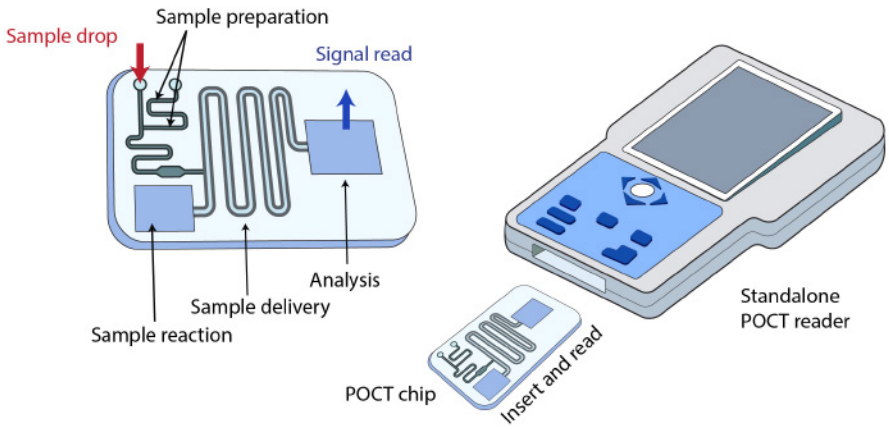

Fig 3: Process of Pont of Care Testing in a single chip

The growth of such complementary technologies has resulted in new and exciting mobile phone-based point-of-care sensors. Mobile phone functions that are key to the development of point-of-care systems include: sensors (camera, microphone, etc.), communication (Bluetooth, Wi-Fi, cellular, etc.), sophisticated multi-touch user interface, enhanced battery, huge data storage and processing capacities.(As shown in figure 4)[19, Rank 3]

Figure 4: Mobile phone functions that are key to the development of Point of Care Testing POCT

Mobile phones house an array of sensors ranging from cameras operating in visible and infrared spectrum to microphones and proximity sensors. Each sensor is a valuable source for collecting information that can be tapped into for point-of-care applications. Practically all newer generations of mobile phones contain built-in high resolution cameras that are capable of detecting amplitude (brightness) and wavelength (shade of color) of incident light with high accuracy. They operate by projecting incident light using a lens on a rectangular array of micron scale photo-sensors that detect light in the visible spectrum. Following data processing and enhancement, information from a single or a group of adjacent photo-sensors is stored as a single pixel in the final image.(As shown in fig.5)

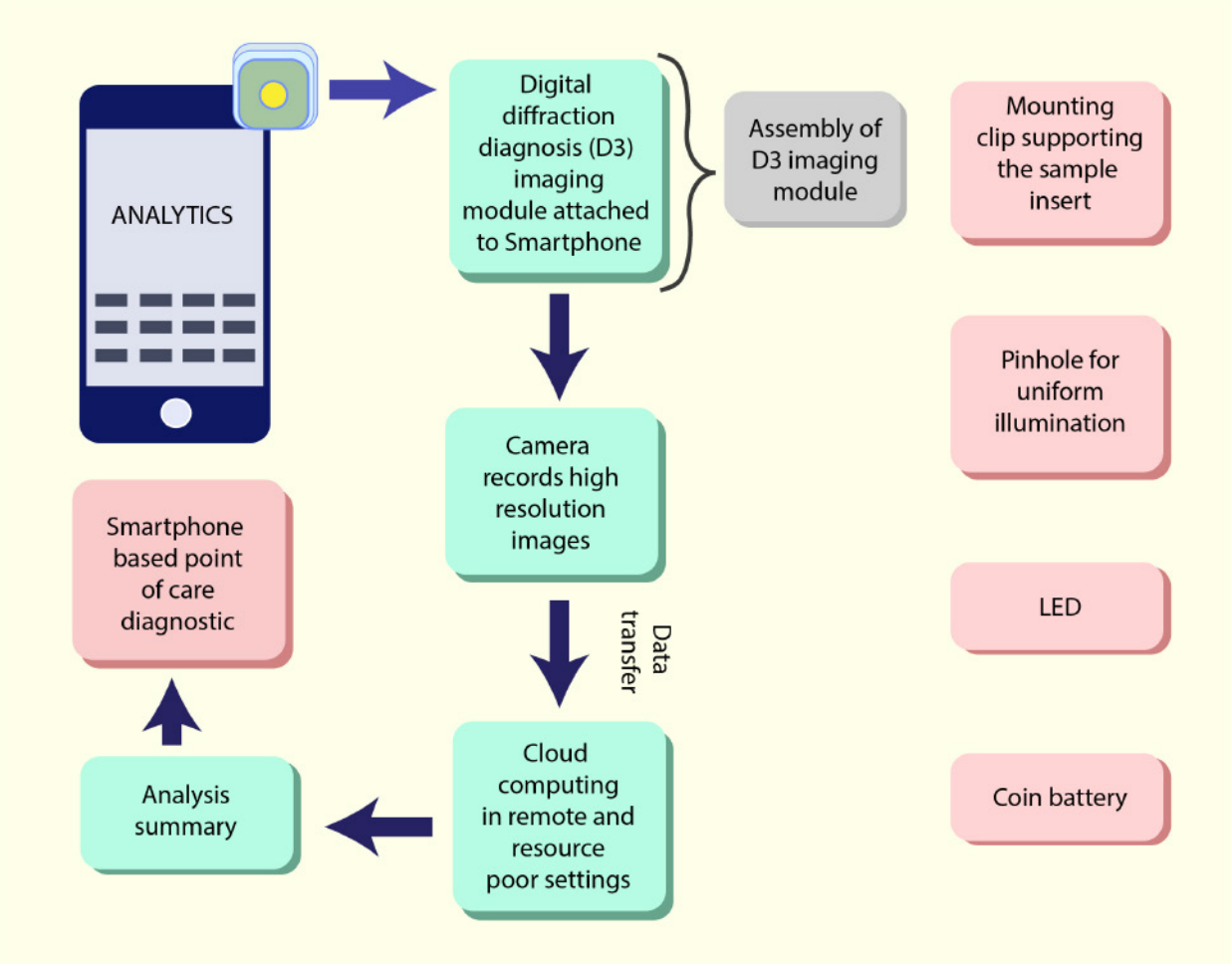

Fig 5: Process of Point of Care Testing using a smartphone

Evidence based

Researchers developed a molecular diagnostic point-of-care system that processed a sample using the mobile phone's flashlight to excite fluorescence dye and consequently the camera was utilized to measure average fluorescence reaction light intensity in real time. The system used a water triggered exothermal reaction to regulate temperature and took advantage of a custom-made microfluidic chip for amplification. This system was reportedly capable of consistently detecting as few as 100 copies of herpes simplex virus type 2 per sample. Infrared cameras operate using the same mechanism as visible light cameras, with the key difference being that the photo-sensors are made sensitive to infrared light (longer wavelength). [22, Rank 2]

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Infrared cameras detect temperature profile of objects and, due to the higher penetration depth of infrared light compared to visible light, they have the capability of visualizing subsurface features. Infected wounds exhibit a characteristic temperature profile even in cases where the infection exists in the underlying tissue of a closed wound. Researchers have developed a non-invasive point-of-care system that analyzes thermal images produced by an auxiliary infrared camera of a mobile phone and successfully diagnosed infected closed wounds.

Presently, microphones used in mobile phones are almost exclusively silicon micro electro mechanical system (MEMS). In MEMS microphones, a suspended micro-structure deflects as a function of the amplitude and frequency (pitch) of incoming acoustic pressure waves. This deflection is then converted to an electric signal using either capacitive or piezoelectric transduction. The airflow into and out of the respiratory system generates acoustic waves that can be detected by mobile phone microphones making the respiratory track a test subject for this class of point-of-care systems. An example of such a system correlates the spectrum of respiration sound to flow rate of air, which can then be used for diagnosis of respiratory conditions, including asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis. [23, Rank 3]

Improved communication technology and infrastructure

Improved mobile phone communication technology and infrastructure has made it possible for fast, reliable, secure, accessible data transfer between mobile phone-based point-of-care systems and the network (As shown in fig.6
). At its most basic form, communication between mobile phone-based point-of-care systems and the network, enables transmission of the findings. However, given the reality of current 4G and Long-Term Evolution (LTE) technology and next generation 5G connectivity, mobile phone-based point-of-care systems are no longer limited to the in-built mobile phone data processing and storage capabilities. They have near real-time access to the significantly larger computational and data storage capacity of remote servers. In addition to the above functionalities, mobile phones offer researchers a sophisticated and accessible hardware platform for software implementation, user interaction and an energy source for low power point-of-care systems. [26, Rank 5]

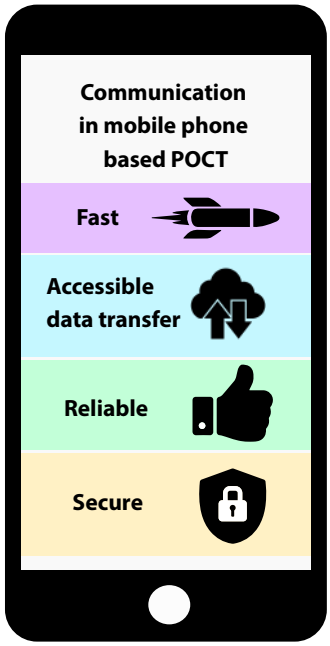

Figure 6 : Benefit of communication in mobile phone based Point of Care Testing (POCT)

User Convenience

User convenience is an important advantage of mobile phone-based biosensors. A mobile laboratory-based ELISA that fully replicates the functions of a benchtop ELISA was tested in the field. The mobile ELISA collects whole blood by pricking a finger and simultaneously detects HIV antibodies, treponemal antibodies for syphilis, and non-treponemal antibodies for active syphilis infections(As shown in fig.7).

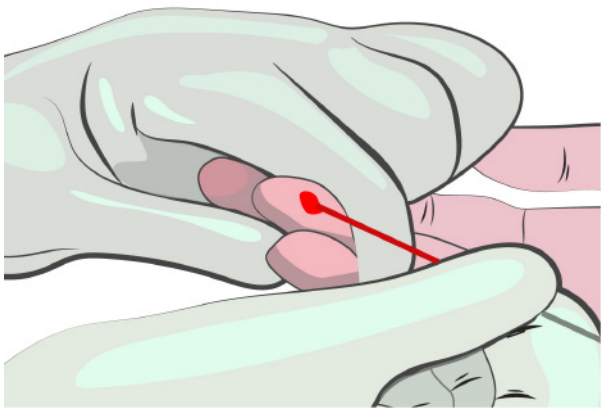

Figure 7: Sample collection for mobile ELISA

A sample of individuals was tested, with 97% stating a preference for the mobile phone-based sensor compared to the conventional testing method. Additionally, 95% preferred finger-prick blood collection over the typical venipuncture method.

Fulfils the demands

In addition to detection of infectious diseases, responders to outbreaks require access to standard medical tests in the field. To fulfil this demand a paper-based blood type detector is developed. In this sensor, hydrophobic channels treated with Anti-A, -B, and -D antibodies were printed on a paper substrate. Blood reacts differently in each channel according to its blood type. A visible difference of the different reactions is the eluting lengths of blood in each channel. An accompanying app, installed on a smartphone, photographs the paper sensor and, in a similar way to that of a bar code, analyses the lengths of the bars to detect the blood type. The blood type is reported to the user in the form of a text message. It was reported that all 8 ABO/RhD blood types were detectable. [6, Rank 4]

Diversity

Information from diverse sensors can be most easily integrated if the sensors interface has a common platform such as a smartphone. Recent sensor advances have either used smartphones as a platform for sensor development or included developed technology to rapidly transfer results to a smartphone. Additionally, larger portable systems (that could be deployed in a public health emergency) have wireless communi-

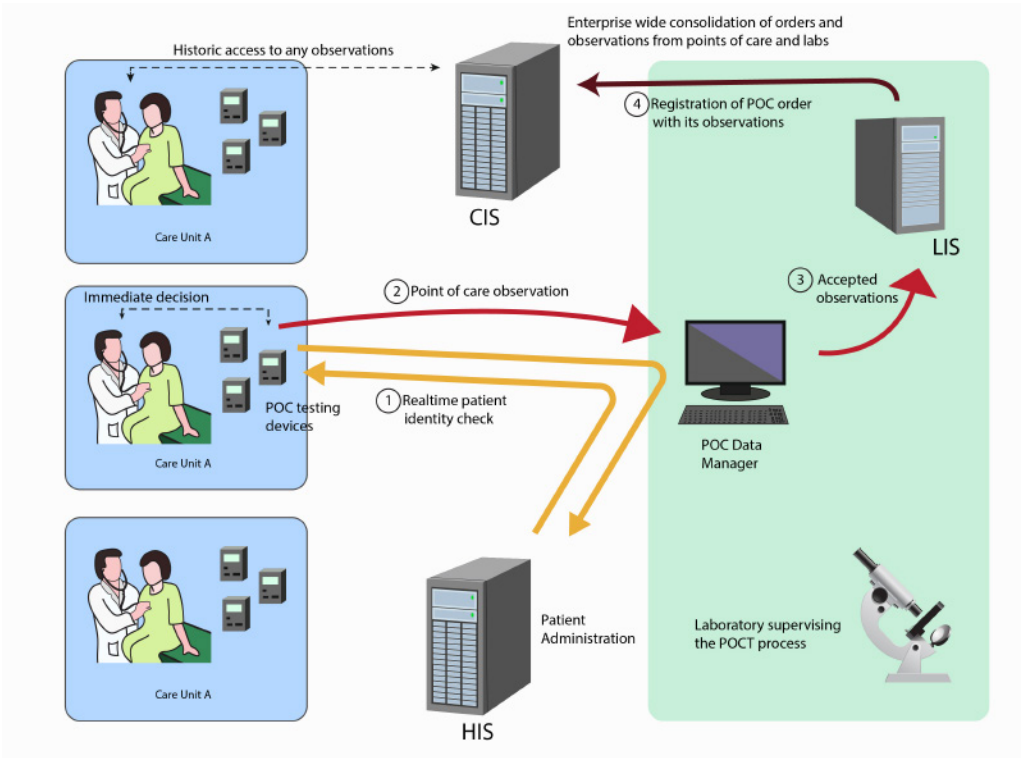

Figure 8: Data communication in Point of Care Testing network

cation abilities already integrated and could communicate directly with sensor networks.

The data collected from various sensors may be diverse and will not necessarily translate easily across platforms. However, even simple reporting of qualitative identification (species present or not present) along with geospatial information could provide a wealth of information about epidemic outbreak and containment when collected across a large number of sensors. In addition to hand-held strategies, the network could also include autonomous sensors (such as continuous air-sampling from drone-mounted mass-spec, or stationary surveillance systems) (As shown in fig.8)[10, Rank 5]

Current Trends in Point of Care Testing

POCT Kits

In the early days of western medicine, health care was delivered primarily in the patient's home and what limited testing available was provided directly at this local point of care. As the science and technology of medicine developed rapidly in the mid- to late twentieth century, care shifted to hospitals with an emphasis on treating injuries and curing acute disease. At this time, centralized laboratories were established for the analysis of numerous patient samples using standardized techniques and complex equipment. As technology improved, automation was added, further standardizing the results.

Today, ongoing research is identifying an increasing number of disease biomarkers, and additional tests for these biomarkers are continually being developed. Furthermore, there is an increased emphasis on wellness and preventive activities as evidenced by the rapid expansion of fitness trackers, which are effectively point-of-care tests, and some of these have the ability to measure rather sophisticated clinical endpoints. This potential is being exploited by the development of smart phone apps designed to collect data to promote healthier behaviors. Despite the extensive marketing and use of such devises, research continues to be inconclusive regarding the health and economic value of such advancements. [2, Rank 3]

Technological drivers of POCT for consumer medicine(As shown In fig.9) include advances in assay automation, low cost sensors, and instrument miniaturization, as well as access to cloud computing. However, while many routine laboratory tests provide critical information about a patient's health status, tests are sometimes ordered just because they are available, and new

tests are sometimes implemented without adequate justification for their prognostic or economic value. Nevertheless, as the technology advances, opportunities are being seized by manufacturers to make POCT available directly to consumers, a scenario that will undoubtedly affect care providers through patient purchases, questions, and requests for clinical services. [1, Rank 1]

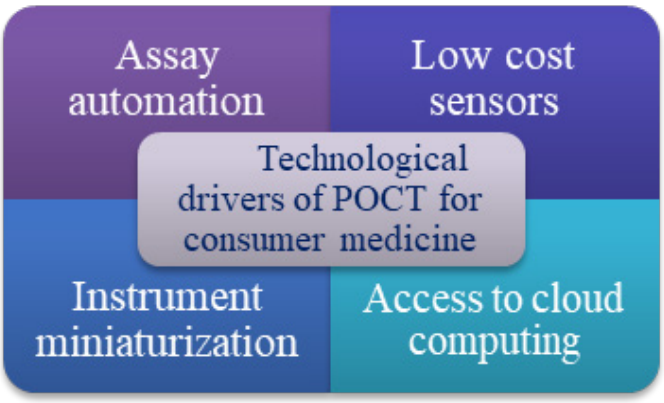

Figure 9 : Technological drivers of POCT for consumer medicine

POCT Devices

Point-of-care devices have been used for several decades, but until recently on a limited basis in the hospital or other acute care settings when rapid analysis is sometimes needed (eg, in intensive care units for methicillin-resistant Staphylococcus aureus, procalcitonin, and rapid diagnostic testing for bacteria) and for simple home testing such as diabetes and pregnancy. In the intensive care environment, POCT can improve patient care. For example, serial analyses of arterial blood lactate with a handheld analyzer, coupled with a specific management protocol, resulted in a marked reduction in mortality for infants and neonates undergoing heart surgery. It also has value in diagnosing and treating HIV infection in resource-constrained countries. Recently, the potential advantages of POCT for international normalized ratio (INR) monitoring led to the development of guidelines for its use in patients on oral anticoagulant therapy.

POCT alone is often insufficient to achieve health benefits and that changes in care processes are also required. However, the advances in POCT over the past six years indicate a need for additional research to address the clinical and economic impact of new technologies. Of note, the POCT kits used most frequently in the primary care setting (blood glucose, urine pregnancy, and urine leucocytes/nitrites) only partially correspond with the conditions for which these physicians would like immediate diagnoses. Although there were differences across countries, there appeared to be a need for POCT kits to assist clinicians with immediate decisions regarding urgent referrals or treatment. What is not yet clear is whether the range of POCT kits becoming

available – from infectious disease to cholesterol and INR tests – should be performed by health care professionals in various settings and what demand individuals will have for self-testing and monitoring of acute or chronic conditions. [6, Rank 4]

An increasing number of POCT kits and devices are available for general use. These allow patient diagnoses in a pharmacy (eg, streptococcal and influenza tests), a physician's office, an ambulance, at home, or a hospital. The tests may give results directly for testing that require sending a sample to a central laboratory for analysis with results returned to the patient or health-care provider, often within 24 hours. Assuming the results are accurate and interpreted appropriately, care can then occur in a timely manner.

Health-care Related Diagnostic Tests

Healthcare-related diagnostic tests are an integral component of healthcare delivery in the US as they currently have a direct impact on up to 70% of healthcare-related decisions. This impact has been driven by the advances in science and technology of the 20th century. Prior to these advances, decision making was primarily based on patient history and physical examination. When these tests were first used in diagnosis, the individual practitioner had a significant amount of easiness in timely intervention for the patient. However, the variability in quality of these tests ultimately led to regulation that mandated how these tests were to be performed [24, Rank 5]

Clinical Laboratory Improvement Amendment (CLIA) Regulation

This regulation was primarily enforced by the Clinical Laboratory Improvement Amendment (CLIA), which established regulatory standards for all human-related laboratories testing for diagnostic purposes. This was, specifically, in response to an alarmingly high number of false negative results from in-house laboratories. Since its enactment, CLIA has required that all labs performing diagnostic tests of human samples must register with the Centers for Medicare and Medicaid Services (CMS). The process of registration is based on the type of testing that is to be performed, and a set of compliance standards are required for the given lab classification. This lab classification is determined by the complexity and clinical significance of the testing to be performed. The resulting CLIA requirements are more stringent for more compli-

cated tests.

The diagnostic tests are scored by the FDA using seven independent criteria. These scores are then summed to determine the risk associated with the test. Diagnostic tests with scores of 12 or less are in the moderate-complexity category. Scores higher than that are deemed high-complexity. CLIA defines waived-tests to be "simple laboratory examinations and procedures that have an insignificant risk of an erroneous result." Sites that only perform waived tests must still have a CLIA certificate and follow the instructions from the manufacturer. [27, Rank 4]

Identifying Patient Needs for POCT

Infectious Diseases

POCT can play an important role in both the diagnosis and management of specific diseases. POCT for the rapid identification of specific pathogens is ongoing. The need for POCT for the early identification and management of sepsis is particularly important since this is difficult to diagnose and the mortality increases by an average of 8% for every undiagnosed hour. In the hospital setting, various tests and investigations are undertaken when suspecting sepsis in both adults and children: these include vital signs checks (observations of temperature, blood pressure, respiratory rate, pulse oximetry oxygen saturation, heart rate and responsiveness).

A full set of routine blood tests can include blood count, a chemistry profile including urea and electrolytes, C-Reactive Protein (CRP), and glucose, and a coagulation screen. More than 170 biomarkers have been reported in the literature for the diagnosis of sepsis. However, only the most common biomarkers, such as CRP or procalcitonine, can typically be analysed within centralised hospital laboratories. The testing of the other biomarkers typically requires more specialised laboratories. Other tests can include arterial or venous blood gas samples, urine output recorded and urine sample dipstick test and microbiological culture, aerobic and anaerobic microbiological blood cultures, swab of suspected wound or respiratory tract/gynaecological swabs, chest radiograph. [15, Rank 5]

Some of these can be tested immediately to provide results (at the patient's bedside), others require sampling of bodily substances/fluids which can either be taken to a local analyser or sent to laboratories (these may be onsite or require further delivery to more specialist laboratories elsewhere offsite). Results may be published to patient's electronic records as soon as possible. Some of

the requested tests may be marked urgent or routine, as necessary. Bedside glucose tests, vital signs temperature probe, pulse oximetry or electronic blood pressure cuffs will often provide immediate results. Arterial or venous blood gas samples can be difficult to acquire if there is difficulty with gaining vessel access (sometimes alternative sampling techniques including femoral stab, or ultrasound-guided sampling is necessary). The local availability of analysers can, however, lead to results within minutes, including true oxygen and carbon dioxide saturations, pH, lactate and Electrolyte levels. [18, Rank 3]

Similarly urine samples may be tested with a dipstick for common abnormalities (protein, leukocytes, blood, glucose, nitrates), or urine test for pregnancy, prior to being sent for full investigation in the laboratory. Blood or swab cultures taken will require 5–10 days incubation; growth of any organisms and their sensitivities/resistance to various antibiotics will guide management and assist in identifying appropriate treatment(s). Currently, certain patients found to be positive with or exposed to certain microorganisms ('superbugs') may need more treatments by nursing staff to improve sanitation or nursing in isolation; examples include patients positive for Methicillin-resistant Staphylococcus aureus (MRSA), Vancomycin-resistant Enterococci (VRE), and Carbapenemase-producing Enterobacteriaceae (CPE), among others. [6, Rank 2]

Sexually Transmitted Diseases

Sexually transmitted infections (STIs) are among the most common acute conditions worldwide. In 2012, there were 357.4 million new global cases of four common curable STIs: chlamydia; gonorrhoea; syphilis and trichomoniasis. Although STIs are not normally fatal they do represent a significant burden of diseases and they can lead to complications such as pelvic inflammatory disease, ectopic pregnancy and infertility. STIs can increase infectiousness of a susceptibility to HIV and in pregnancy they can cause fetal or neonatal death. Chlamydia is globally the most common bacterial STI and causes reproductive complications in women. The LMICs and LDCs have the majority of global incidents of STIs, but the health systems are less well resourced to manage these. POCT could play an important role in supporting the management of conditions for individual patients and also provide wider control of STIs within developed countries, LMICs and LDCs. [20, Rank 3]

According to the Centers for Disease Control and Prevention (CDC), in the United States alone drug-resistant bacteria cause at least 23,000 deaths and 2 million infections

every year. This is therefore a public health problem, requiring innovative POCT approaches that can contribute to helping characterise the development and spread of resistant bacteria. This can have a transformative role in the treatments administered, constituting one step further in the path of personalised medicine. By allowing the rapid detection of infectious pathogens and resistance factors, practitioners can for example reduce unnecessary administration of antibiotics, contributing to alleviate the problem of antibiotic resistance.

Respiratory Tract Infections (RTI)

Respiratory tract infections (RTIs) are one of the problems that can be caused by a variety of bacterial and viral pathogens. Worldwide, they are the second greatest cause of morbidity and mortality. RTIs are the most common infections for those that are immuno-compromised. There is now also concerns about the number of infections caused by antimicrobial resistant (AMR) bacteria as well as community and hospital acquired infections, for example pneumonia. New lethal viruses and bacteria causing RTIs with epidemic potential have emerged over the last decade. These include severe acute respiratory syndrome coronavirus (SARS-CoV), swine-origin influenza A, multi-drug resistance tuberculosis and multi-drug resistance gram negative bacteria, for which there are very few effective therapy options. [25, Rank 5]

The key challenge for effective treatment of RTIs in a variety of different healthcare settings is for fast, sensitive and specific identification of pathogens and antibiotic resistance profiles. Also, it would be beneficial to determine whether a pneumonia was Community-acquired or Hospital-acquired (there are cases where this is still unclear). This differentiation can have a large impact on treatment regimen. If the infection is hospital-acquired, then treatment with intravenous antibiotics initially will be more beneficial. RTIs are the most common infections encountered within primary care and there is evidence that people presenting with acute uncomplicated RTIs will commonly receive antibiotics despite most RTIs being viral. There is therefore, a clear need for POCT that can differentiate RTIs within primary care and reduce unnecessary antibiotic prescribing as part of AMR stewardship. [16, Rank 2]

Non-Communicable Diseases

Non-communicable diseases with the highest health burdens include cardiovascular diseases, cancer and diabetes. The number of POCT that are commercially available

for non-communicable diseases is limited and reflects the challenge of measuring low concentrations of protein biomarkers in a variety of different biological samples, including blood, serum, urine and saliva. PSA is the most common tumour marker for prostate cancer. IL-6, an interleukin, is overexpressed in several different cancers including prostate cancer, as well as head and neck squamous cell carcinoma. The interleukins are part of the cytokine family and more generally play an important role in the inflammatory response of diseases such as rheumatoid arthritis, cardiovascular diseases (CVD), diabetes and Alzheimer's disease. The MMP family are part of the zinc-dependent endopeptidases, where MMP-2 is key in tumour growth, invasion and metastasis and MMP-3 is used to diagnose and monitor diseases such as head and neck squamous cell carcinoma and adrenal tumours. The alpha-fetoprotein, an oncofetal glycoprotein, is an important liver cancer tumour marker. CEA, a glycoprotein, is raised with inflammation or tumours in any endodermal tissue, including the gastrointestinal tract, respiratory tract, pancreas and breast, and can be used for diagnosis of lung cancer, ovarian carcinoma and breast cancer. The cancer antigen 125 (CA-125) is used for monitoring ovarian, breast and uterine cancer. [7, Rank 3]

"The cancer antigen 125 (CA-125) is used for monitoring ovarian, breast and uterine cancer"

These CLIA regulations led clinical practices to outsource many of their diagnostic tests to core laboratories - either regional centers like those operated by LabCorp or local centers within the hospital. This workflow is well-suited for tests where the results are not needed immediately, as the delivery of care would not be changed even if the information was immediate. However, there is a fairly recent push to perform certain tests at the POC. Because POC tests are portable, they allow for an expedited workflow and potentially shorter turnaround times. As a result, they carry the promise of providing the care giver with information at time points that can provide improved delivery of care and reduce the cost. However, to meet regulations, these tests must either be CLIA-waived or users of the devices must meet the associated standards in an attempt to prevent errors [9, Rank 4]

One example of a CLIA-waived, POC test is the blood glucose meter. With just a drop of blood from a finger-stick, these devices

can inform the user of their current blood glucose levels and enable them to better self-regulate their blood glucose values (As shown in fig.10).

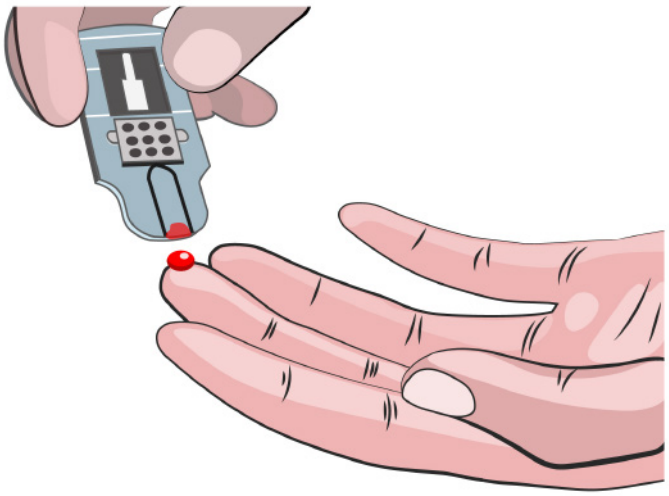

Figure 10: Blood glucometer: An example of CLIA waived POCT

This self-regulation would not be possible if a blood glucose meter for use at the point-of-care did not exist. As the demand for home-health information continues to grow, additional devices are being developed for home use. The ability to create cost-effective, disposable test cartridges that can store reagents, direct the flow of solutions with passive microfluidics, and automatically read the generated signal leads to POC technologies becoming more user-friendly. [4, Rank 4]

Development Towards Portable Diagnostics

Diagnosis of disease is commonly carried out by the quantification of DNA, RNA and proteins or other biomarkers using a variety of biochemical assays in a centralised laboratory setting and this remains powerful in accurately detecting diseases. The drawback of using large highly automated floor standing analysers in a centralized laboratory setting is that the instrumentation used is expensive and it requires operation by staff with specialized technical skills. Moreover, it can take a considerable amount of time for the assay to be performed, particularly if there is a requirement for batches of samples to be gathered before measurements can be made. More recent developments are focused toward automating and miniaturizing the traditional biochemical assays, (As shown in fig.11) such as enzyme linked immuno-sorbent assay (ELISA) and polymerase chain reaction (PCR) to increase their applicability and accessibility.

Microtiter plate assays are the gold standard for immuno-assays and are performed in an array of wells of varying density and volume as part of a microplate. The 96-well plate (well volume 530 µL) is fairly ubiquitous and the 384-well plate (well volume 149 µ L) is common. There is a trend towards higher-density, lower-volume well plates

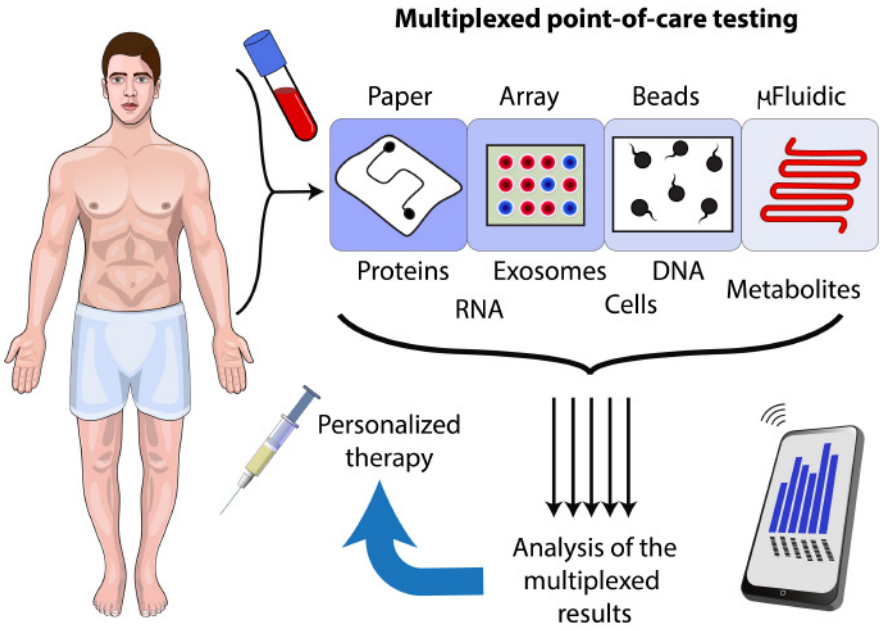

Figure 11: Most recent development in POCT and it's advantage

(with the 1536 well plates having a volume of 10 µL). The smaller volumes are crucial because they allow a lower volume of sample, solvents and reagents which greatly reduces the cost of the assay. The most commonly used immuno-assay format is the ELISA, which typically captures an analyte (antigen) between two antibodies and upon which, one antibody is labelled with an enzyme. The enzyme enables a signal enhancement by a factor of 100,000 by converting a substrate into a detectable signal. [14, Rank 3]

For signal generation, the substrate can be converted either into an absorbing dye (detected by absorption of transmitted light), into a fluorescent dye (detected via a fluorescence reader) or into a light emitting reaction (detected as luminescence). Fluorescence and luminescence are more sensitive as compared with absorbance but are also more expensive and can involve more complex protocols. The choice of approach for signal generation and detection is therefore generally dependent on the sensitivity and cost requirements.

Microtitre plate assays and ELISA are widely used for clinical analysis but they can typically take several hours and the complex assay protocol involves skilled personnel, as well as generally expensive automated analysers. The demand for portable diagnostics is, however, that they should be fast, reproducible and are able to be operated by untrained users. Lateral flow assays are widely used as a robust, simple and low cost analytical assay. There is now greater effort in the development of quantitative lateral flow assays. Lateral flow assays typically use antibody coated microparticles, which bind the analyte directly from the sample and are then enriched via binding against a second antibody in a target zone. This obviates the need for complex and costly enzymatic signal enhancement used within microplate ELISA. [19, Rank 5]

Impact of Quantification Tests in POCT

After the lateral-flow assays, simple electrochemical enzymatic assays are the most commonly used for quantification of small molecules, which can be detected quantitatively in redox-reactions. The most widely used application for these has been blood glucose monitoring for diabetes with a glucose oxidase enzyme acting as a catalyst for the conversion of a glucose substrate to a gluconolactone product and with amperometric detection. More recently, there has been increasing interest in the use of impedimetric sensing as a label-free approach for monitoring ligand receptor binding. [29, Rank 3]

Impedimetric sensing is also attractive since micro and nanofabrication techniques would allow development of the miniaturised transducers in a convenient manner. The potential of fabricating an impedimetric array in a polymer microfluidic cartridge has been demonstrated as a potential aid for diagnosis of Deep Vein Thrombosis/Pulmonary Embolism (DVT/PE) and towards low cost point-of-care diagnostics. An impedimetric array within a microfluidic cartridge could allow multiple measurements of a single biomarker or alternatively measurements of multiple biomarkers within the same microfluidic cartridge. [5, Rank 2]

For detection of pregnancy or drug-abuse, a simple Yes/No answer using "visual" read-out is sufficient, but the majority of clinical assays require quantification with defined handling for the applied volumes, incubation time and analysis of the generated signal. In recent years, there has been great interest in the use of "Lab-on-a-chip" or "microfluidic" systems which can allow fine control of fluidic operations with control elements, different detection elements and integrated bioreagents for internal standards and for assay. These have been developed for a variety of applications including diagnostics, bioprocessing and cytotoxicity testing as part of drug discovery.

The Lab-on-a-chip term is typically used when the device is performing a specific application whereas microfluidics is a more general term which applies for miniaturised fluidic volumes either as passive—within a container—or active so that the fluidics might be driven. Microfluidic devices can potentially fill the technological gap between simple "lateral flow" POC tests and sophisticated laboratory-based analysers. [18, Rank 4]

Specifically, microfluidics offer advantages of controlled microenvironment with automated and highly reproducible operations, reduced energy consumption as well as

reduced amount of reagents and shorter assay times. Microfluidics offer the potential for the development of devices as simple "sample in—answer out" with a minimum of handling steps, ease of use and a high level of robustness and reliability. There are considerable challenges in the widespread use and practical utility of microfluidic devices including: a reduction in the chip costs, which remain high; reducing the cost and size of optical readout systems; ease of fluidic control; and on-chip storage of reagents. [10, Rank 4]

New Age Portable Diagnostics

New progress in portable diagnostics is focused on lowering the cost, simplifying the instrumentation and, thus increasing the accessibility of diagnostic tools to the wider population. 3D printing technology has been used to significantly lower the cost and time of developing novel diagnostics devices compared with conventional manufacturing approaches. 3D printing technology has been used for incorporation of integrated valves as well as for point-of-care colorimetric analysis

Novel Photonic Systems

Cavity Enhanced Absorption Spectrometry (CEAS)

CEAS has been shown to have higher sensitivity than conventional single pass absorption detection. In CEAS, high sensitivity is achieved through increasing the pathlength by locating the sample between two highly reflective dielectric mirrors. The light reflects between the two mirrors to form an optical cavity which magnifies the optical absorption effect. A very small amount of light exits from the mirror and this is measured to give the CEAS signal. ***The CEAS technique has the potential to approach the sensitivity of fluorescence based detection but with the advantages of lower reader cost, due to fewer optical elements—and being label-free.*** Overall, CEAS offers the potential for higher sensitivity; wider applicability; less complex assay protocols with the associated lower assay costs(As shown in fig.12) [22, Rank 2].

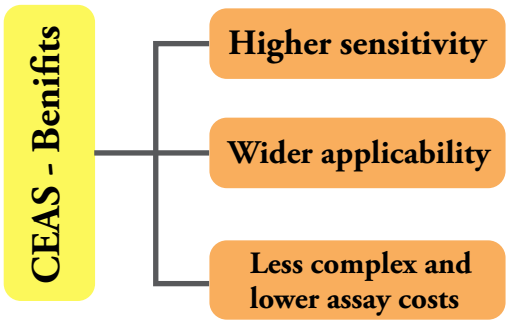

Figure 12 : Benefits of Cavity Enhanced Absorption Spectrometry (CEAS) technique

Plasmonics

Recent sensor developments using immuno-assays continue to yield higher sensitivity. Unlike conventional ELISA, plasmonic ELISA uses the aggregation of gold nanoparticles as the reporter when the biomarker is present that exhibits shifted extinction characteristics, thus a change in observable colors. Photonic crystal gratings are proposed as a new sensor for biosensing applications. Combining the photonic crystal grating with an immunoassay, C-reactive protein, which is produced in the presence of inflammation, can be detected at a detection limit of 12.24 pg/mL. Multiplexed sensors can diagnose more than one infectious disease by detecting various biomarkers. An electrophotonic sensor was able to profile biomarkers by combining electrochemical and photonic characterization. Using the selective chemical functionalization, the electrophotonic sensor array can identify different binding events. [15, Rank 5]

Digital Microarrays

Disease diagnostics have been evolving through the synergistic collaboration of medicine with engineering and science. With the advent of the measurement/sensing technologies that provided the ability of detecting trace substances in bodily fluids such as blood, urine, and cerebrospinal fluid in vitro Diagnostics (IVD) have become a cornerstone of clinical practice. Solid phase immuno-assays such as ELISA have long been established and are used extensively for diagnosis. The vast majority of sensing technologies used for molecular diagnostics are ensemble measurements, in other words they are analog. These immuno-assays have sensitivities in the picomolar (10 -12) range. However, the serum concentrations of most protein biomarkers in the early stages of infection are in the femtomolar (10 -15) range.

To achieve the desired 3-order-of-magnitude improvement, a new class of biological sensing technologies have emerged relying on single molecule counting or digital detection. Digital detection is a technology that can provide the necessary improvement in sensitivity. Furthermore, it is much easier to measure the presence or absence of signal than to detect the absolute amount of signal. Digital detection may lead to the most advanced disease diagnostic tools to become available at a low cost and at the point-of-need. [1, Rank 5]

Most of the digital detection techniques are based on particle confinement in an isolated microenvironment, allowing for the necessary signal-to-noise ratio. Among these sample compartmentalization techniques, the most notable one is digital PCR. Solid phase and microarray-based techniques

have the promise of low-cost and point-of-need operation. Their sensitivity, however, is often insufficient as a reliable diagnostic tool. This practical limit is not imposed by the microarray format itself, but rather the sensitivity of conventional methods involving fluorophores as labels and fluorescence readers.

Regulatory Issues

Point-of-care testing kits and equipment are considered "medical devices" and must be evaluated and approved by government agencies in most countries before the results can be considered for clinical decision-making. In the United States, commercial clinical laboratory tests are regulated by the Food and Drug Administration (FDA) to ensure they meet safety and effectiveness standards. A product is considered safe when its clinical benefit to the patient is judged to exceed the potential risk associated with using the technology, and effectiveness is established when clinically significant results can be obtained. Medical devices are categorized into classes based on the degree of risk posed to the patient: class I devices pose low risk, class II devices pose moderate risk, and class III devices pose the greatest risk. Some countries may accept the FDA decision, have comparable agencies responsible for approving the use of clinical laboratory tests, or simply allow the use of such kits without approval. [4, Rank 5]

In the United States, the Centers for Medicare & Medicaid Services (CMS) regulate all laboratory testing performed on humans according to the Clinical Laboratory Improvement Amendments (CLIA). There are three regulatory categories under CLIA, based on the potential risk to public health associated with the test of interest. Tests can fall into the waived category, or into a moderate or high complexity category. For a test to be considered CLIA-waived, it must employ sufficiently simple and accurate methodologies so the risk of erroneous results is negligible, or there is no significant risk of harm to the patient if the test is performed incorrectly. There are more than 120 waived tests, and these are the types of tests making their way into pharmacy practice because of their minimal regulatory oversight.

Significant research into POC assays for traumatic brain injury has been driven mainly by military research funding because of the critical need to assess concussive injury in military personnel. Most POC methods have been focused on developing rapid and sensitive assays for specific biomarkers in serum or cerebrospinal fluid. However, there is still debate about which biomarkers, or groups of biomarkers, con-

tain the highest diagnostic value. Continued research will shed new light on the role that each play in diagnosing traumatic brain injury. Furthermore, it is likely that assessment of traumatic brain injury at the point-of-care will include a psychological assessment in addition to the quantification of biomarkers. [8, Rank 2]

POCT Challenges

Point-of-care testing ordered by a clinician or obtained by a patient through publicly available kits have their own challenges. Furthermore, how the results are used in these situations may differ. Ideally, the pharmacist should act in collaboration with the patient and other health-care professionals to optimize the use of the data obtained and, consequently, the clinical outcomes.

Physician- and pharmacist-ordered POCT involves an expanding number of tests. Clinician-managed POCT has a significant level of control in terms of validity, interpretation, how the results are used, and incorporation of the results into the patient's record. However, it is the patient-obtained POCT that raises the most concerns such as determining whether such kits are accurate and which kits can be used by individual patients, where data from unsanctioned kits would go, what happens if patients make decisions based on a faulty understanding of the significance of the results, and how to handle data obtained from monitoring devices such as smart watches. Answers to these and other questions will be key to the broader and effective use of POCT. [9, Rank 5]

"Clinician-managed POCT has a significant level of control in terms of validity, interpretation, how the results are used, and incorporation of the results into the patient's record"

Probably the greatest concern with POCT is reliability. The CLIA-waived category guarantees simplicity and that problems adversely affecting patient care pose minimal risk, but not reliability. Simplicity is deceptive, however, and there are many ways a result can be wrong. Importantly, POCT results may not be comparable to those from a central laboratory. While the results should be comparable within the same test system, POCT may use different technology than that in central laboratories. Differences in the quality of the specimen, its potential storage before use, and other

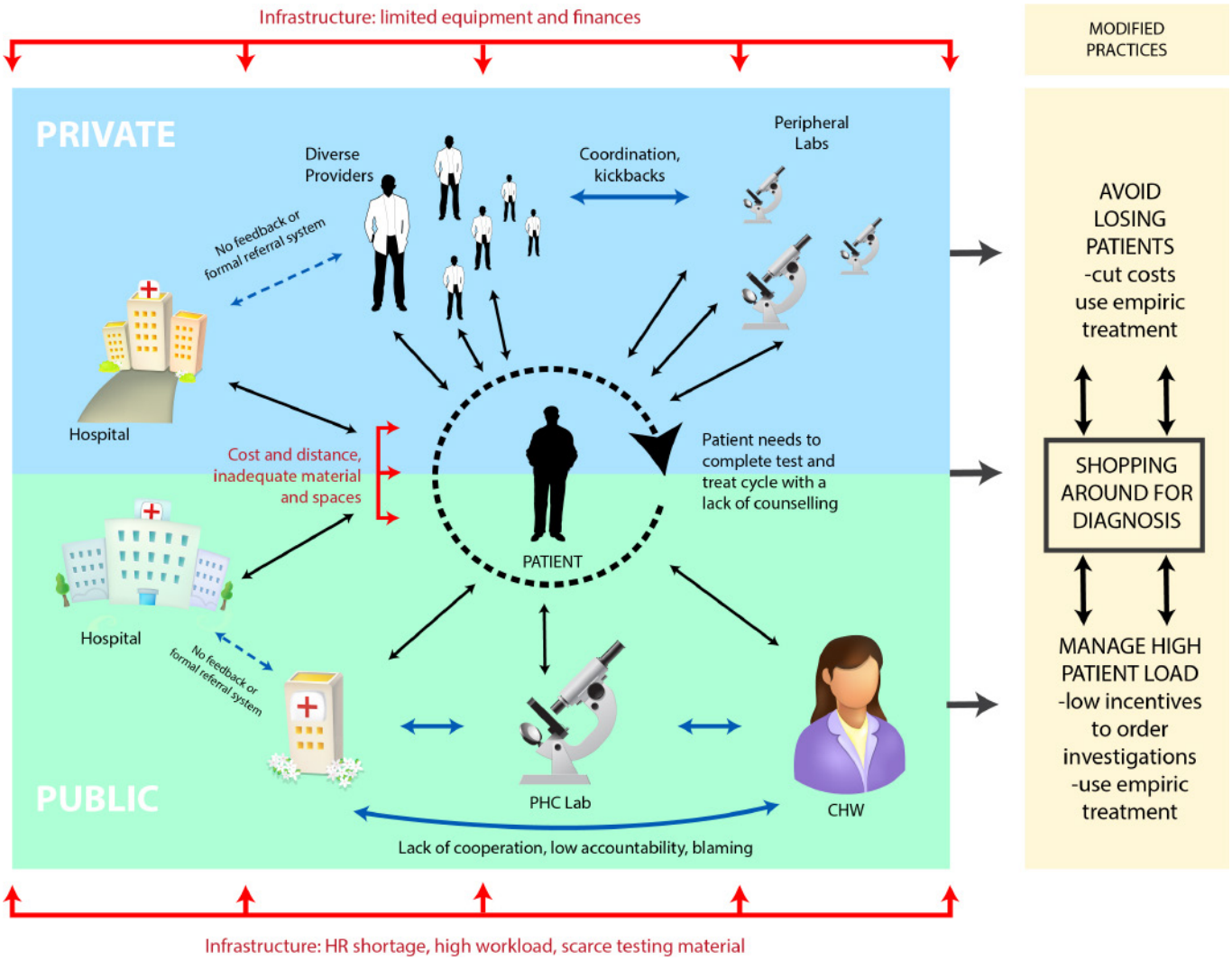

Figure 13. Major challenges for Point of care testing in clinical practice

technical factors may also affect the results. As POCT becomes more widely used, pharmacists are positioned to investigate this critical reliability concern through collaborative research projects.

Another major challenge with patient-initiated POCT is interpreting results. Although "normal" parameters can be established for all tests, what constitutes normal can vary and be affected by age, gender, diet, medications, co-morbidities, etc. Thus, while a nonspecialist (including the patient) may perform the test, who determines what action may need to be taken in response to the results is unclear. Traditionally, physicians order, review, interpret, and make clinical decisions based on test results. However, as POCT expands, physicians will not have the capacity to view all test results. An alternative may be pharmacists, the most accessible health-care professionals, who serve as first point of contact in terms of providing the test kits and doing an initial interpretation of the results leading to a care plan or patient referrals to appropriate follow-up care. [10, Rank 2]

A third significant challenge is taking action on test results. When a pharmacist does POCT, the patient history and a physical assessment should take place before determining whether testing is appropriate. However, once determined appropriate, it is essential that action be taken on both normal and abnormal results. This can involve a direct patient care intervention (ie, starting, changing, or stopping drug therapy) by the pharmacist, if within their scope of practice, including advanced prescribing authority and collaborative arrangement or referral to an appropriate health care provider. One example studied for actionability is POCT results for infectious diseases. Such testing could benefit patients and represents an opportunity to expand services in community pharmacies. Interestingly, about 75% of adults who visit a physician for pharyngitis receive a prescription for an antibiotic even though less than 5% of such problems involve bacteria (most pharyngitis is viral). Thus, pharmacists treating only those cases of pharyngitis accompanied by a positive strep test would provide more appropriate therapy.

Although the results of POCT ordered by a clinician, including pharmacists, should be incorporated into the patient's record, connecting POCT devices to an electronic medical record, or uploading numerical results from tests performed at home or other noninstitutional locations, requires a compatible computer interface and must overcome security and privacy issues. [1, Rank 1]

Currently, no electronic record systems are designed to accept data from a range of health-care providers and certainly not from patients themselves. However, with advances in wireless communication, the way in which patients are monitored and the data managed will change dramatically. Already, numerous consumer devices exist to monitor exercise, heart rate, and other physiologic parameters. These devices are creating more personalized health care,4 something POCT will further and assist with as it tailors interventions to individual patients. Inevitably, the role patients take in their own health care will increase, and it is possible that relevant data from these sources may become part of a patient's record.

Increasing the role of patients in their own care is appropriate and should be encouraged. However, POCT done by nonprofessionals should be limited to simple and largely error-proof tests . But even these types of tests will yield useful data, and problems associated with data interpretation, appropriate action in response to the results, and communication of results to the patient's physician or other relevant health care professionals must be addressed. Critical future needs include resources to assist

patients in understanding test results (a role pharmacists ideally fill) and data management systems that can handle the POCT results. Until such systems are in place (which may be a long time), it is likely that patient-initiated POCT results will remain informational, though will hopefully stimulate patients to take more formal actions. (As shown in fig.13)[9, Rank 4]

Major Upcoming Advancements in POCT

A major opportunity for POCT connectivity relates to infectious disease diagnosis and disease management. Smartphone-connected diagnostic tests with geo-referencing information could help prevent the spread of epidemics and transform the approach to global health. POCT could facilitate rapid diagnosis from simple blood pin-pricks or non-invasive swabs. Technologies currently under development aim for an operator without specialized training to safely collect and test a sample in the field within minutes. In brief, this provides faster confirmations without the necessity to send many samples to reference labs such as the CDC Atlanta, avoiding a process that can take days or even weeks before results are reported (delaying the response to outbreaks). While we highlight recent advances in POCT for infectious diseases below, we note that given the increase of non-communicable diseases within LMICs and LDCs—cardiovascular diseases and cancer have been the two highest causes of mortality—there is also very significant potential for use of POCT within these disease areas.

Advances in portable diagnostic technology have enabled multiple methods of pathogen detection that can be employed at (or close to) the point-of-care. Rapidly deployable, mobile labs and handheld sensor units can provide rapid pathogen identification and confirmation. Connecting results from a wide array of these tests with geospatial information could enable more rapid outbreak detection and a more effective public health response. Such a network of sensors could complement developing national biosurveillance systems and provide a platform for coordinated international response to emerging biothreats. [12, Rank 3]
Miniaturised sensing systems that use or connect to a smartphone are of particular interest, as they may be widely deployed and be more broadly integrated into disease-monitoring networks. Analytical techniques that may be integrated with a smartphone analyzer include nucleotide-based detection strategies (PCR, LAMP) and antibody-based detection (lateral flow, acoustic wave, or other immuno-

assay approaches). While these approaches generally require prior knowledge of the pathogen of interest, assay multiplexing is becoming increasingly feasible. Additionally, portable mass spectrometry and miniaturized sequencing strategies may soon enable portable, novel pathogen detection. In addition to providing pathogen identification or confirmation, portable analytical strategies have recently been combined with rapid incubation or culture methods to provide antibiotic resistance information in as few as 30 min. Rapid detection of developing antibiotic resistance though networked sensors could help ensure proper initial treatment and containment in an epidemic. [19, Rank 2]

Open Data Platforms for Infectious Diseases

Several open data platforms for infectious diseases have been deployed in developed or medium income countries, and may serve as a model for broader open platforms in resource limited areas. Real-time geo-tracking resources utilize user feedback, news outlets, and official reports to track outbreaks in real time. In fact, the US federal government has created several open access databases under the umbrella of the National Institute of Health's Bioinformatics Resource Centers (BRCs) for Infectious Diseases, to assist researchers studying infectious diseases. These efforts are happening globally, at a broader level, showing the relevance of the topic and how political commitment is changing the paradigm in different nations.

Rapid Gene Sequencing Technologies

Rapid gene sequencing technologies aid quick response to disease outbreaks, by identifying the virulence factor and the path of disease transmission. While this technique has generally been applied within centralized or regional laboratories, POC implementations are increasingly possible. Nanopore recording of DNA/RNA translocation is a promising technology in low-cost, rapid sequencing with sampling rates over 10k Samples. With a fast sequencing rate, the nanopore-based sequencing has a potential to reduce the detection time, and provide information about sub-strains and therapeutic resistance during an outbreak. [26, Rank 5]

Integrated complementary metal–oxide–semiconductor (CMOS) bioelectronic systems have also been developed, which incorporate the nanopore directly on the CMOS surface to reduce the noise source

and maximize the sampling rate. Using the high-density integration of CMOS integrated circuits, many nanopores can potentially record DNA translocations in parallel, yielding a much higher sequencing rate.. Recently, a genome sequencing system was used to support a rapid outbreak response by characterizing the infectious agent in Guinea with the ongoing epidemic

Antimicrobial Resistance

POCT could play an important role in supporting the management of conditions for individual patients and also provide wider control of STIs within developed countries. Novel and more effective screening techniques for Antimicrobial resistance (AMR) are particularly relevant in LMICs and LDCs. These countries have the majority of global incidents of STIs, but the health systems are not well-resourced to manage them. As an example, gonorrhoea is a significant public health concern with AMR in Neisseria gonorrhoea and so there is an urgent need for new antimicrobials and action for control. [28, Rank 4]

Multiple efforts are being developed around the topic of antimicrobial susceptibility. The technique provides an array of micro-channels to monitor microbial growth in broth microdilutions, by detecting and measuring the mass of individual microbes. Results have shown that a rapid antimicrobial susceptibility testing (AST) produces correct and repeatable outputs in both lyophilized and freshly prepared liquid antibiotic panels in under three hours.

The applicability of POCT can be greatly enhanced if the testing procedures are made available in a portable fashion. Aligned with such goal, the researchers propose a method for hand-held molecular diagnostics. In their proposed approach, an electronic module based on polymerase chain reaction is reportedly able to use a reagent to detect the presence of a target amplicon within an input sample. [27, Rank 5]

Reflecting the urgent need for countermeasures to the potential development and rapid global spread of infectious diseases, the United States' National Health Institute (NIH) and Biomedical Advanced Research and Development Authority (BARDA) jointly held a $20 million contest challenging groups to develop rapid POC diagnostic tests for antimicrobial resistant bacteria. The approaches that are adopted are likely to include advances in transduction mechanisms, microfluidics and use of machine learning to distinguish between viral and microbial infections, as well as the development of assay capable of identifying drug resistant bacteria.

Future Directions

The biggest challenge in getting portable diagnostic tests into the veterinary market is not convincing veterinarians to use them. Once a test is proven to provide a reliable basis on which a veterinarian can make a clinical decision, the hurdles of cost, ease of use, and storage stability are still critical. The cost of the technologies included in portable tests is going down fast. Tests that use glucose meters or cell phones to analyze milk samples are in the research phase. Fabrication technologies, including cloned reagents, especially synthetic antibodies, ink jet printing of biologics and optoelectronic circuits, organic optics, and roll-to-roll fabrication and assembly of devices will bring the cost down and enable the production of more robust and disposable tests. [21, Rank 4]

Conclusion

All countries face a gap between the funding that is needed to support healthcare infrastructure and the amount of funding that is actually available to meet these needs. This gap can in part be addressed through the use of connected POCT devices with AI/machine learning for enhanced sensing. This offers the huge possibility for earlier identification of disease where treatment is likely to be more effective as compared to a patient with symptomatic disease at a late stage. It also offers the urgently needed possibility of delivering care in a decentralised way within primary and tertiary care settings. Realisation of this vision will require considerable inter-disciplinary effort including in: chemistry, materials, biology, electronics, mechanics, micro and nanotechnologies, photonics, biotechnology, and particularly AI/machine learning. There are likely to be continued innovation in microfluidics, transducers, chemistry/biology, and AI/machine learning, which will help to unlock the full potential of POCT to transform testing and improve human health.

***Important information for post-test are highlighted in red letters, boxes and diagrams.**

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