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Review Article

Lab to Point-of-Need Technology (LPoNT) Solves A^3 - Puzzle of *In-vitro* Diagnostics?

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Abstract

The role of medical diagnostics is morphing rapidly in the face of imminent challenges such as pandemic preparedness. Correspondingly, *in-vitro* diagnostics are evolving- growing beyond the traditional Centralized Diagnostic Laboratories (CDL) and now include Point-of-Care Diagnostic (PoCD) Devices and lab-on-wheels (mobile diagnostic labs) as well. However, even now, the triple challenge of simultaneously meeting Accessibility, Accuracy and Affordability still remains unaddressed by and large. This implies that all the current diagnostic paradigms either do not provide a sufficiently large range of assays, or do so at the expense of accuracy and/or affordability. This paper proposes a new diagnostic paradigm that has the potential to address this A^3 challenge. It highlights how the current, diffused efforts towards miniaturizing CDL and building more PoCD devices will not be able to address the specified challenges. It is proposed that these efforts be converged upon a modular, portable, open-platform technology that supports a wide variety of in-vitro diagnostic assays. A true Lab to Point-of-Need Technology requires the development of novel/innovative solutions that transcend the barriers imposed by the existing methods. These solutions need to target all the three primary steps of all *in-vitro* diagnostic procedure - sample preparation, processing and analysis. However, to achieve these lofty goals, different communities such as the research, medical, policy-making and industrial communities need to agree upon a common set of targets and work together. This article aims to initiate that process.

Keywords: Medical diagnostics; Point-of-care; *In-vitro* diagnostics

Introduction

The two current *in-vitro* diagnostic paradigms and the unmet need

In-vitro diagnostics have traditionally been carried out in well-equipped Centralized Diagnostic Labs (CDL) by thoroughly trained technicians. The open platform available in such central laboratories enables them to carry out just about any diagnostic test and they can manage a high throughput as well. However, such facilities are simply infeasible to be set up in large numbers (so as to reach most of the population) or at remote locations [1]. While the involved cost for such an effort would be prohibitive for most of the developing world, the requirement of well-trained personnel is also unlikely to be met. Therefore, currently, samples acquired from people in remote/rural areas are often shipped to the nearest city for analysis [2,3]. This not only costs time and money but also poses a risk of sample degradation leading to incorrect results. A relatively new niche of diagnostic devices aimed at the end-user has emerged in the last few decades [4]. This Point-of-Care Diagnostics (PoCD) technology market caters to people with known ailments looking to continuously monitor or periodically test a particular (or a small set of) medically relevant parameters, such as blood glucose levels. These devices aim to be very user-friendly such that anyone would be able to operate them without training, and they offer a low cost per test. But PoCD devices are not available for the vast majority of the important assays and thus cannot be used to carry out a sufficient breadth of tests for the general populace. Also, they are not generally sensitive enough for an accurate early diagnosis [5].

Both these diagnostic paradigms have their own importance and run parallelly, without noticeably affecting each other's market. However, a third paradigm is needed that services global needs currently not catered to by both, CDL and PoCD paradigms (Figure 1). This third paradigm should offer the required breadth of assay (like a full-fledged CDL) while still allowing enough mobility for on-demand field deployments (like a PoCD device). Such a Laboratory to Point-of-Need (LPoN) Technology would enable accurate, accessible, and affordable (A^3) service for multiple applications. These include serving resource-constrained settings such as remote areas and low-income urban areas, natural disaster affected areas, and niche areas of defense and space [7].

The spectrum of assays to be covered

The most important in-vitro medical diagnostic tests which should be covered by LPoN technology can be broadly classified into four categories: molecular biology techniques for pathogen detection & identification, protein detection (primarily based on immune-chemistry based methods), cell detection/cytology, and biochemical identification and quantification [8].

For all the assays, the basic process flow is the same: sample collection followed by preparation and processing (such as serum/plasma separation in case of blood, dilution); analysis (incubation with reagents); and finally read-out to generate the test report. However, depending on the assay type, the processing and analysis can be quite varied. For instance, Biochemical identification requires time-consuming sample incubation while Cytology doesn't need the same. However, Cytology is inherently resource (skill and infrastructure) intensive. Thus, a comprehensive solution to the automation and

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interoperability challenges is needed. An ideal LPoN technology should be able to solve these [9].

The Proposed Solution

LPoNT: A new paradigm

The unmet needs highlighted so far cannot be met merely *via* further miniaturization of existing laboratory methods or inventing more and more point-of-care devices for additional diseases. This is because such diffused efforts will (a) neither converge on a single field-usable device that can replace a lab, nor (b) address the larger issues of platform incompatibilities. Instead, such efforts would only culminate in protocols, assays, consumables and devices that are not interoperable and also require separate training sessions for the operators [10]. The only way to realize a truly versatile, cost-effective and open-platform (adaptable and future-ready) LPoNT paradigm is to work cohesively towards generating new (and integrating existing) assay workflows, including novel sample preparation and assay methods, into one unified platform. Such a paradigm could draw upon the way smart phones have revolutionized our life- they provide many of the commonly used services in everyday life in a single package (Figure 2) [11,12]. This is enabled by a completely different manner of providing such services- all of them are based on a generalized digital processing and communication platform, rather than their usual, completely different (hardware/firmware/software) technologies that are application specific. Although this required the development of new methods of performing the existing functionalities, the end result is a product that is much more than the sum of its parts. It not just allows a multitude of functionality in a hand-held device; it also enables functionality that did not exist earlier [13]. For instance, consider the evolution of retail financial transactions. While cash is accepted universally, debit/credit cards allow a lighter wallet and no concern about being stolen since they can be simply blocked. However, both these financial instruments still couldn't satisfy the demand for what has become one of the most popular uses of a smart phone - internet banking on the go. The underlying hardware and software of a smart phone allow financial transactions very conveniently, despite the unit not having the hardware to handle cash currency or credit cards as such. This is leading to 'cashless' economies where even a roadside vendor can accept digital payments, using only a smart phone [14].

Similarly, an integrated LPoN system needs new methods to perform the conventional biological assays, along with corresponding innovations in reagent storage, sample preparation, sample processing and analyte sensing. In this regard, the CDL paradigm is akin to the usage of cash currency while PoCD is similar to debit/credit cards with a card-reader. And a capable LPoN system would be analogous to smart phone based digital payment- offering uniquely new capability [15].

Just as a smart phone may run a variety of operating systems, an LPoN system could avail one or a combination of the many sensing/actuation methods currently in use as well as reported in, such as opto-fluidic and electrical sensing. Each of these has its utility and the research community may converge on a set that could satisfy all requirements for an LPoN system as outlined here. Also, a reagent storage pack for compact, refrigeration-free storage could be plugged in for carrying out a variety of assays, just as a smart phone would accept memory cards and other accessories for enhanced functionality. This could be built using a variety of methods including, but not limited to, droplet microfluidics [7], hydrogels [3] and sugar based dry storage cartridges [16].

The proposed LPoN system isn't intended to displace the existing CDL and PoCD methods, rather it is meant to fill in the gap that neither of them is serving currently. Again, an analogy can be drawn here to the way smart phones demonstrate this kind of utility. Just as a house would have individual utility items such as a clock, wired phone, etc.; yet, each home would also need a miniaturized version of these items such as wristwatches and (non-smart) mobile phones [18]. Similarly, the medical diagnostic scenario would need CDL as well as PoCD devices, while an LPoN system would serve the unmet needs (Figure 1).

Some use case scenarios

Consider the chronic case of Malaria infection in developing countries such as India. Eradicating the same would require screening the entire population as many people may carry the parasite without demonstrating the symptoms. However, the entire population cannot be expected to travel to health centers for this purpose; instead, healthcare workers would need to conduct door-to-door assays. In this case, dormant carriers may not be identified as the usual PoCD devices such as RDT (Rapid Diagnostic Test) would be unable to detect their low parasitemia level [5,11,14]. On the other hand, the conventional method of preparing a dry smear and manually examining it would be simply impractical in such a scenario. The only solution then would be an LPoN system that could be taken by healthcare workers to each home (or a set of homes) and conduct the assay in a short time, yet with sufficient sensitivity for a reliable screening. No such LPoN system exists yet [19].

A similar challenge is presented by the genetic hematological disorder, Sickle Cell Disease. It has been detected in large numbers and found to be heavily concentrated in a few geographical and ethnic clusters, including central and southern India [2,10,20]. However, the cases of the severe Sickle Cell Disease (SCD) still haven't been fully differentiated from the more prevalent but non-lethal Sickle Cell Trait (SCT). PoCD test such as the solubility test can only screen but not provide this sub- classification. It currently requires expensive and time consuming procedures such as HPLC, which aren't accessible in remote area, especially to financially constrained governments. This has important implications for the SCD patients as they are denied their due healthcare benefits which would otherwise be available had they been correctly identified as SCD positive. A low-cost, portable LPoN system would resolve this problem since it could be carried to these low-population density areas and deliver a quick disease sub-classification there itself, with only a prick of blood. No such LPoN system exists yet. Another example is the need to ascertain the cause of febrile diseases. This is especially important in sub-Saharan Africa and Southeast Asia where a plurality of pathogens may cause the fever and thus the detection methods for them may differ significantly. The causal diseases include malaria, dengue, chikungunya, influenza and other bacterial/viral infections. While some of them, such as Malaria, are diagnosed *via.* Cellular inspection (using microscopy), others need immunochemistry based tests (Dengue) or molecular biology based tests (Chikungunya). No PoCD device exists to cover this breadth of assay needs and mobile diagnostic labs would be unable to service the far-flung areas. The only solution would, again, be a portable LPoN system. The LPoN system must target an aggressive set of specifications that not only satisfy the major requirements of assay breadth and accuracy, but also fulfill other demands such as being low-cost and requiring minimal user training. Such specifications have been drafted in Table 1 (Figure 3).

Figure 1: Some scenarios unserved by both, CDL and PoCD. Clockwise from the bottom – Remotely located or sparsely populated rural areas (hard to reach hence inaccessible, need affordability also); Health kiosks only offering a small set of non-invasive tests (only a few tests accessible as of now); mobile medical units requiring thoroughly trained personnel (limited number of tests accessible, also need to be affordable); defense forces operating in remote locations including underwater without access to medical diagnostic facility (severe accessibility challenge); manned space stations (again, severe accessibility challenge) ; areas affected by natural disaster (need accessibility and accuracy); and pre-immigration health checks(needs wide variety of test . Such scenarios represent a point-of-need for a broad array of assay abilities not serviced by CDL and not supported by PoCD.

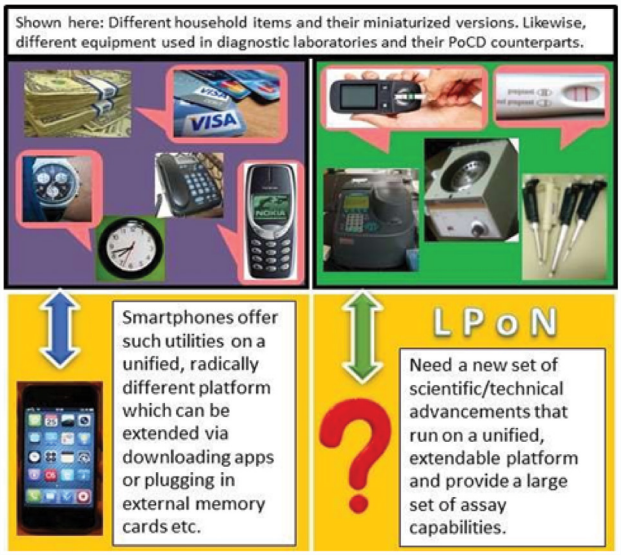

Figure 2: An analogy between the feature-rich, unified, extendible platform offered by a smart phone and the need for a similar set of innovations and subsequent integration to produce a truly useful LPoN Technology.

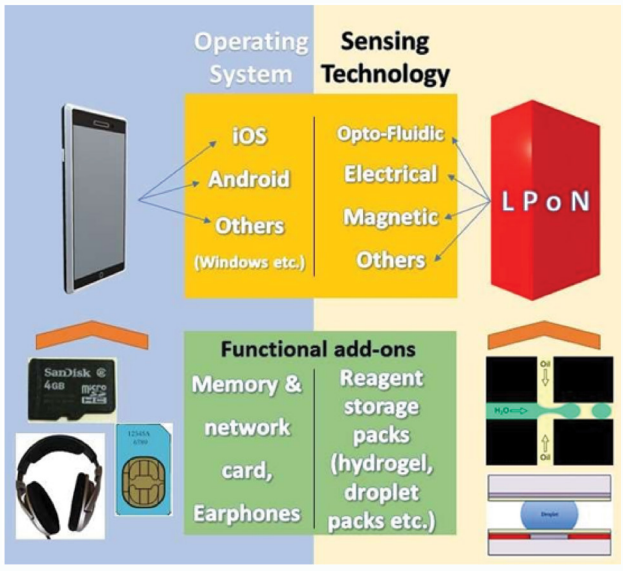

Figure 3: An LPoN system could be built with a variety of core technologies. Just as a smartphone may function with a variety of operating system, while still delivering the intended utility. Similarly, an LPoN system should support multiple add-ons for reagent storage and perhaps other functionality, just as a smart phone accepts different cards and plug-ins.

Available mobile diagnostic laboratories (lab-on-wheels) and the lack of a true LPoNT

There exist several mobile laboratory systems such as Lab-in-Bag, Lab-on-Bike, Lab-in-Bus, and others [1,15,18]. These can be broadly divided into three categories: (a) systems that repackage existing diagnostic laboratory infrastructure into mobile units, (b) systems that pack a set of point-of-care devices into a single container, and (c) systems with a hybrid approach of repackaging some laboratory equipment along with some PoCD devices. A majority of the systems belong to the first category. These have been quite useful in areas which are accessible but do not have CDL facilities such as mass eye and dental checkups in remote villages. However, they still require thoroughly trained personnel to perform the assays. The overall cost of such systems is significant since along with the cost of equipment, the cost of setting up a transport and human operators are also added up. Moreover, these lab-in-bus and other systems do not offer sufficient accessibility, which rules out large scale population screening which

Table 1: A comparison of available and desirable features of *in-vitro* diagnostic test paradigms.

	CDL	PoCD	Ideal LPoN Technology
Assay breadth	▪▪▪▪▪	▪	▪▪▪▪
Accuracy	▪▪▪▪▪	▪▪▪	▪▪▪▪▪
	Very sensitive, specific and quantitative assessment	Useful for screening or parameter monitoring. Often qualitative.	Should provide same level of performance as CDL.
Mobility	▪	▪▪▪▪▪	▪▪▪▪▪
Sensitivity	▪▪▪▪▪	▪▪	▪▪▪▪▪
Cost per test	▪▪▪▪▪	▪▪▪	▪▪▪▪
Equipment cost	▪	▪▪▪▪▪	▪▪▪
Sample volume	▪	▪▪▪▪▪	▪▪▪▪▪
	Large (few ml) volume such needed	Usually works with low (µl) volumes	Should work with micro volumes as finger-prick blood
Infrastructure required	▪	▪▪▪▪▪	▪▪▪▪▪
Operator skill required	▪	▪▪▪▪▪	▪▪▪▪▪
	Several years of training required to become an operator.	Usable by anyone after a brief reading of instructions.	Should be as easily usable as a PoCD device.
Turn Around	▪▪▪	▪▪▪▪▪	▪▪▪▪
Time (TAT)	▪▪▪▪▪	▪	▪▪▪
Throughput Assay novelty	▪▪▪▪▪	▪▪▪▪	▪▪▪▪▪
Target user	Hospitals, high-density population areas	End-user (patients with known ailments)	Urban populace with limited health- care access, rural areas, niche sectors (defense, space, natural disaster response, airport health screening etc.)

requires door-to-door testing. This requirement is best served by a compact system, say, no larger than the size of a backpack. But it can't be satisfied by the second approach of using PoCD devices alone either since they simply do not exist for most assays. Even if they did, carrying a large set of individual devices defeats the purpose of mobility itself. Also, they may not have sufficient sensitivity to detect diseases in the early stages. The third, hybrid approach only partly alleviates the problems faced by the earlier two approaches. It still does not incur significant expenses while not providing sufficient range of assays, nor does it provide significantly improved mobility [21].

Apart from medical diagnostics, mobile laboratories have also been built for soil, water, food adulteration and other diagnostic needs. Many of these are "lab-on-wheels", i.e., the setup can be carried in a box mounted on a two or four wheeler. These have been of special utility for farmers and environmental agencies. Their usage is quite different from medical diagnostic platforms, wherein mobile laboratories acquire a different dimension as the they solve the big for the same and hopes to ignite deliberations towards the technical/ product specifications needed. Even a broad set of such specifications would help in identifying the specific R&D needed, and thus, research teams across academia and industry could look for appropriate people. These teams could then work towards their individual projects targeted at a unified platform. Eventually, such projects could be integrated into a LPoNT that would be then benchmarked with gold standard methods. While the underlying platforms can be quite incompatible, the sensing and actuation methods from the domain of lab-on-chip could form the very basis of LPoN system. These include opto-fluidic methods for cell interrogation, Nucleic Acid Testing (NAT), analyte quantification etc. Another well reported set of diagnostic methods utilize electric fields for cell sorting, impedometric cytometry, NAT etc. Other methods include hydrodynamics, magnetic field based methods, acoustofluidics, centrifugal force based methods etc. The above mentioned methods can be used to build one or a set of underlying diagnostic mechanism for a fully functional, modular LPoN system. The eventual choice of technologies can be finalized by the research community and be subject to continuous revision as well.

A Proposed LPoNT Architecture

Architecture for the LPoNT is presented here, based on the discussions so far. It consists of a base unit (the "platform") which provides all the necessary support for the assay to be carried out. The assay itself will be conducted inside disposable cartridges, with the aid of reagent carriers (collectively called as the "consumables"). We first describe the constitution of the underlying platform and then delve into the consumables.

The platform is envisaged to be completely automated and thus a central Control and Processing Unit (CPU) should form the core of the hardware. Since fluids (samples/reagents) would be involved, a Fluid Handling Unit (FHU) is imperative. Physical motion will be required to move the assay components, including ejection of used consumables and thus a Translation Unit (TU) is necessary too. Sensors would form an integral part of the system, along with actuators which will produce the required assays conditions; thus, a sensors and actuators unit (S&AU) is needed. The CPU would control these fluid handling and translation units, based on feedback from the sensors and actuators unit. The whole system would interface to a display (the Human-Computer Interface or HCI) which could be present on the integrated platform or be connected wirelessly, such as over WiFi/ Bluetooth with the GUI on a tablet/phone. A Power Unit (PU) would consist of both, utility power and a back-up/battery power system. This architecture (and the corresponding workflow) is denoted in Figure 4. It must be pointed out here that the S&AU constitution will depend on the modality used- an optofluidic system would require a set of LEDs, photodiode and cameras while an impedance-based system would require resistive heating, coulter counter etc. Similarly, any other modality would require an appropriate design of the S&AU while the rest of the system need not be modified.

Once a sample is loaded and a cartridge is inserted into the platform, the sample preparation steps would be initiated by the CPU. The FHU along with the S&AU would perform steps such as sample dilution, analyte concentration, serum extraction (in case of blood), DNA elution (in case of NAT assay) and other tasks as needed. The

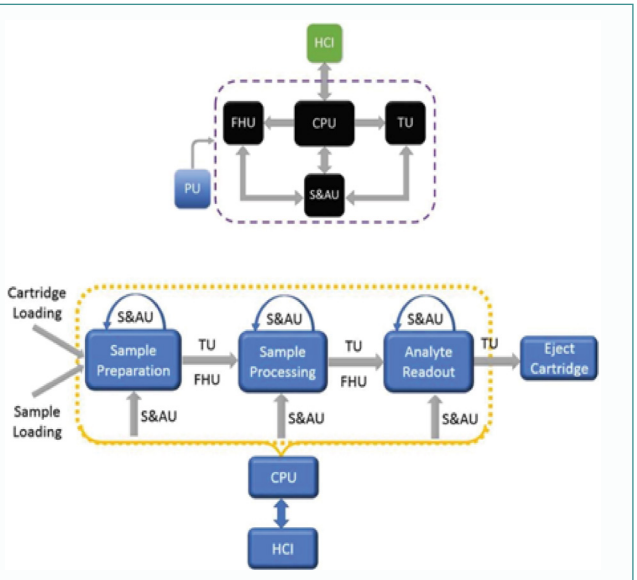

Figure 4: Proposed architecture and workflow of the LPoN system. Abbreviations- HCI: Human- Computer Interface; CPU: Control & Processing Unit; FHU: Fluid Handling Unit; TU: Translation Unit; S&AU: Sensors & Actuators Unit; PU: Power Unit. The HCI could be a stand-alone touch screen LCD or a mobile phone. This would provide the control to the end-user over the specific assay to be performed and the exact protocol to be followed. The CPU would execute this assay via the three functional units- TU for moving the assay cartridge; FHU to dispense and discard the sample and reagent fluids; and the S&AU to complete the sample preparation, processing and analyte sensing. While the HCI and PU could be externally pluggable units, the rest of the units have to be contained inside of the platform device.

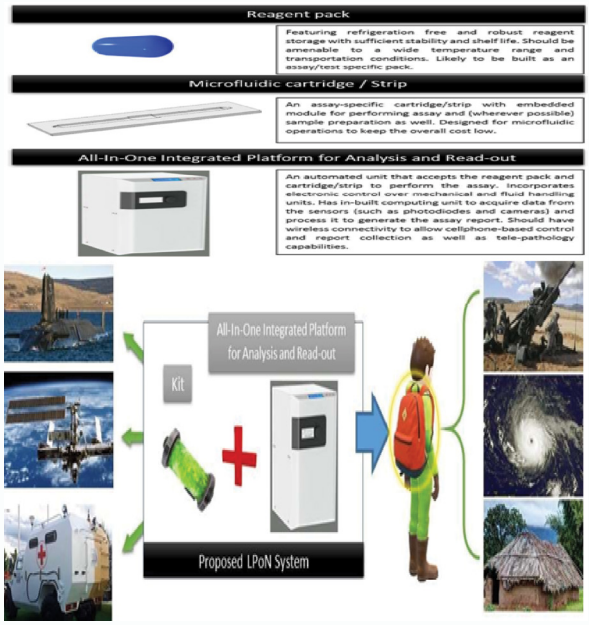

Figure 5: Top: A detailed description of the components of the proposed LPoN system. Bottom: use case scenarios for the proposed LPoN system. Clockwise from top right: Conducting tests on-site in remote areas and hence removing errors due to sample degradation during transportation. Conducting tests in areas affected by natural disaster and warzones, submarines and space stations where sample transport to a central lab is otherwise not possible. Utility in health kiosks which can be installed in urban areas for quick yet comprehensive health tests available at convenient locations.

TU would then move the cartridge to a sample processing stage where it would be subjected to thermal changes/optical imaging/impedance-based counting etc. as per the assay needs. Thereafter, the readout will be performed by the S&AU and the data will be interpreted into an assay report by the CPU. Finally, the used cartridge would be ejected out by the TU [16].

A Proposed opto-fluidic LPoN System

One of the modalities for an LPoN could be the use of microfluidics for sample preparation and opto-fluidics for sensing. An overview of such a system is presented in Figure 5. The LPoN platform would accept a specially designed microfluidic assay cartridge/strip and reagent pack, and these would be specific to the assay being performed. The pack would contain all the necessary reagents for performing the assay, with storage in dry/hydrogel/microdroplet states. It may only be a few centimeters in size but would contain sufficient reagents for conducting a few to several hundred tests. For some specific assays, a reagent may not be needed at all and thus the pack can be forgone. For instance, a cytology based test for cell count may not need a separate reagent dose and the processing on the cartridge itself could be enough for a successful assay. The use of microfluidics would cut down on sample volume requirement, enabling features such as blood based testing *via* only a finger prick. It would also cut the test cost by reducing the reagent volumes. Furthermore, for certain kinds of test, the assay time would be reduced due to lower processing volume and higher surface area to volume ratio. Such a system could be easily transported in a backpack. Another way of implementing this would be in health-ATMs and health kiosks, enabling them to perform a wide variety of diagnostic tests, such as quick blood-based tests for malaria, diabetic markers, kidney and liver health, etc. Since these kiosks could be easily linked to health insurance providers, the tests could be conducted in a cashless manner. This would also increase compliance towards regular health screening [14].

The Road Ahead

A true LPoN system will be much more than just a bunch of diagnostic devices put together; it'll be an open, new platform based development paradigm with next-generation LPoN technologies and scientific advancements. Efforts to keep on developing PoCD devices (miniaturization) and subsequent integration cannot be expected to automatically lead to an LPoNT at some point of time. Scientific and technical R&D efforts should be actively converged towards a new direction (apart from CDL and PoCD) to realize a true LPoN system. These require a long-term, planned teamwork. Thankfully, this is the right time to initiate such efforts as a relatively recent and continued thrust is seen on the advancement of most of the required fronts for LPoN system. These include the surge of the semiconductor industry driving nanofabrication science and the subsequent adoption of it to biosciences including bio-microfluidics. Also, newer techniques for molecular diagnostics, cost-effective programmable electronics, the falling cost of intensive computing and new manufacturing paradigms such as 3D printing will immensely aid in LPoN system development [19].

Much thought and efforts need to be invested to create a successful system and a thoroughly inter-disciplinary effort is required. While the platform itself can take shape quickly, scientific challenges need new, trans-disciplinary approaches. The major domains of scientific investigation will be fully automated sample preparation and rugged reagent storage. Also, the methods of performing assays themselves can be innovated upon (such as opto-thermal nucleic acid amplification

instead of the traditional electro-thermal method). Accordingly, the standard assay protocols can be modified, or novel assays can be developed which can be realized in an LPoN system. These modified protocols will need to be validated against gold standard techniques. Since refrigeration and other resource-intensive storage conditions may not be available, newer storage methods are needed for the assay reagents [15].

Finally, the cartridges are to be designed specifically for each assay. Much scope for automation and miniaturization resides here, especially *via.* the use of microfluidic techniques. The aim must be to automate as many sub-steps as possible on the cartridge itself, while still keeping the cost low. This is possible if the cartridge can be mass produced (preferably while using bio-compatible, and ideally, bio-degradable materials. It must be ensured that the overall quality (sensitivity, specificity and accuracy) of an LPoN assay should match or surpass that of a CDL assay.

The rewards, however, will be worth the effort. A true LPoN system will unlock a large, socio-economically important market (rural/remote areas) that has hitherto been unserviceable. The ability to rapidly extend its capability to any new assay implies that governments would cut the time (and hence the financial and human cost) needed to carry out accurate mass screening. These augers very well for pandemic preparedness. Also, LPoNT would help prevent and eradicate chronic infectious diseases that are currently hard to tackle. For instance, suffering due to sickle cell and Thalassemia can be prevented if the people carrying these traits refrain from having offspring. This would be possible *via* screening of the population in areas known to be affected- an obvious step which is hard to implement right now due to the limited diagnostic abilities of CDL and PoCD as highlighted here. Rapid, comprehensive assays could be performed by self-service kiosks, leading to early diagnosis and reduced financial burden on families. Medical service in battlefields and areas affected by natural and manmade disasters would be completely revamped, potentially saving innumerable lives. With open-platform architecture, innovators could come up with more, interesting uses of the system that can't be envisaged here. A common platform would also speed up development by focusing the otherwise diffused efforts of researchers working towards a myriad of devices on to than one, highly impactful one. To conclude, the LPoN paradigm has significant potential to make a lasting and widespread impact on people's lives, and it remains to be seen how the industry and research community harvest it.

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