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Challenges and opportunities for translating medical microdevices: insights from the programmable bio-nano-chip

This perspective highlights the major challenges for the bioanalytical community, in particular the area of lab-on-a-chip sensors, as they relate to point-of-care diagnostics. There is a strong need for general-purpose and universal biosensing platforms that can perform multiplexed and multiclass assays on real-world clinical samples. However, the adoption of novel lab-on-a-chip/microfluidic devices has been slow as several key challenges remain for the translation of these new devices to clinical practice. A pipeline of promising medical microdevice technologies will be made possible by addressing the challenges of integration, failure to compete with cost and performance of existing technologies, requisite for new content, and regulatory approval and clinical adoption.

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In 1971, a team at Intel led by Ted Hoff introduced the first microprocessor, the 4004 'micro-programmable computer on a chip,' launching a new industry and beginning a new era of integrated electronics [1]. When asked by one of Intel's customers to develop several custom chips for a variety of calculators, Hoff reasoned that it would be easier to manufacture a single general-purpose chip that could be reprogrammed through software to perform various tasks. Computers that once occupied entire rooms and required expert operators were now replaced by these tiny devices as they found their way into everyday items such as household appliances, automobiles, games, office equipment, etc. The success of the microprocessor is attributed to its small, integrated form factor, ability to simultaneously reduce manufacturing cost and improve performance over existing computers, and value added through new capabilities to a host of commercial products. As a result, the microprocessor not only revo-

lutionized commercial products, but it also profoundly changed the fabric of society by the way we communicate, use information, and interact with our environment.

Lab-on-a-chip (LOC) devices have the potential to transform medicine just as the microprocessor transformed the computer industry. Inspired by the principles of scalability and microfabrication of microelectronics [2,3], the prospect of performing a wide variety of chem- and bio-assays on programmable MEMS-based sensors is enticing to a broad audience including medicine, food safety, military, veterinary and consumer wellness. Unlike the computer industry, however, the LOC field requires expertise across a wide variety of disciplines – chemical, electrical, mechanical and bioengineering, materials science, optics, clinical laboratory science and medicine to name a few. As a result of its multidisciplinary and complex nature, LOC technology development requires substantial initial investments in specialized equipment

Michael P McRae¹,
Glennon Simmons²
& John T McDevitt^{*1,2,3}

¹Department of Bioengineering,
Rice University, Houston, TX, USA

²Department of Biomaterials, New York
University, New York, NY, USA

³Department of Chemistry,
Rice University, Houston, TX, USA

*Author for correspondence:
mcdevitt@nyu.edu

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and human resources. This high barrier to entry has been attributed to LOC technology's slow uptake since the first significant papers were published in the early 1990s [4,5].

In the 20th century, breakthroughs in medical and bioanalytical sciences were facilitated by large, government-funded, 'top-down' infrastructures. Much like the early days of computing when a single computer occupied an entire room and required expert users to operate, the majority of bioanalytical data today are acquired in similar central and remote laboratories by trained clinical specialists. While these clinical analyzers are well-suited for high volume, high-throughput and expertly staffed laboratories, this 20th century solution is ill-equipped to solve 21st century problems such as a growing population's inaccessibility to affordable healthcare, the ever-increasing demand for quality diagnostic information, and the absence of reliable medical infrastructure in developing countries. The idea that healthcare can be personalized by the introduction of miniature medical devices is tantalizing; as such, one of the most attractive uses for LOC devices is for point-of-care (POC) diagnostics. Smaller reagent volumes, faster analysis times, lower power requirements, and higher level of integration are just a few of the numerous advantages POC platforms have over central and remote laboratories [6]. Furthermore, POC devices are both inexpensive and portable, making them accessible to a broader audience than laboratory facilities [7]. The area of POC diagnostics, made possible through LOC technology, embody a 21st century 'bottom-up' approach to healthcare where small, easy-to-use, and inexpensive devices are deployed globally to address unmet clinical needs on an individual or small community basis.

The terms LOC/microfluidic are described in the classical μ TAS definition [4] as a device intended to analyze a given sample. Lateral flow or immunochromatographic test strips are relatively simple paper-based microfluidic products which have been around for 30–40 years in the form of home pregnancy or glucose test kits and are often considered to be the most successful application of microfluidics. Recent innovations in paper-based microfluidics have resulted in a variety of low-cost, portable, and relatively simple devices for POC applications [8], for example, the works of the Whitesides group [9–12]. In the early 2000s, DNA microarrays were widely popular and experienced relatively successful translation, for example, the Affymetrix GeneChip® [13]. In the area of multiplexed protein immunoassays, suspension arrays, such as the Luminex xMap® [14], have seen successful penetration in the clinical laboratory market. While there has been much speculation about the 'killer application' for LOC/microfluidics, the POC diagnostics industry

is often cited as the most promising application with high-end cancer and molecular diagnostic instruments paving the way for other cost-sensitive devices [15]. In the POC market, the i-Stat® (Abbott) [16] and the Triage® cardiac panels (Biosite) [17] are commercially available and approved for routine clinical use. However, despite the enormous potential of these devices to contribute to society, only a few of these systems have been US FDA-approved and successfully translated from academia and industry to the clinic [18].

The problems of translation for novel LOC systems have been covered extensively in the literature [19,20]; for instance, the relatively slow uptake of these devices has been attributed to inadequate understanding of economies of scale in mass manufacturing, lack of standardization and integration, and failing to create the 'killer app' [21]. While academics often neglect the challenge of technology transfer and deflect this responsibility to their industrial counterparts [22], these practical issues need to be directly addressed early in the design phase. Importantly, researchers developing new LOC technologies must ensure that their device adds substantial value to the target application to maximize clinical utility. We have identified four key challenges for the translation of LOC systems to clinical practice [23]:

- Integration: Integrating LOC systems into POC structures that completely replicate the full functionality provided in laboratory settings.
- Failure to compete: Current LOC systems fail to compete with central and remote laboratories in terms of cost and performance.
- Need for new content: LOC systems need to develop new content that adds substantial value to the target application and is currently unavailable at central and remote labs.
- Regulatory approval and clinical adoption: Technology developers need to develop strategies for streamlining regulatory approval *en route* to clinical adoption.

In this perspective, we address these four key challenges related to the broad scale release and scaling of LOC systems, highlight opportunities for success, and provide solutions in the context of the programmable bio-nano-chip (p-BNC) system [24–32]. As such, this article is not meant to serve as a general review of the challenges and successes to date in the translation of these mini microdevices (for excellent reviews and focus papers in this area, see works by the Sia group [20], Becker [2,15,21,22,33], Whitesides [3], Yager [6] and others [8,19,34,35]); rather, we provide specific insights from our experiences developing the p-BNC system.

Integration

The translation of LOC devices from research laboratories to clinical practice remains largely underwhelming, primarily due to a lack of integration between the chip and its peripheral interfaces. This challenge of integration has been documented extensively, giving rise to the pun repeated *ad nauseum* that most LOC devices are merely ‘chips-in-a-lab’ [19,20], a common reality in which tiny chips rely on cumbersome external equipment and complex interfaces, rendering the chip unusable outside of the academic lab. The following topics pose significant integration challenges to the LOC community and are covered in detail here: world-to-chip interface, fluid delivery, device programmability, and automation.

World-to-chip interface

A device’s ‘world-to-chip’ interface (i.e., the methods through which fluids such as the sample, capture and/or detection reagents, buffers, and waste are maneuvered in the device) is one of the most important design considerations of a maturing LOC concept. For LOC devices to be considered fully integrated, provisions must be made to reduce the number of fluid handling steps performed by the user. For example, devices that perform ‘on-chip’ preprocessing of the biospecimen are desired over less integrated chips requiring extensive sample manipulation.

The p-BNC system streamlines this sample introduction process. First, the sample is deposited into the designated sample loading port, where surface properties of the cartridge’s laminate layers allow the sample to passively fill the device via capillary flow. Automatic sample metering (~100 µl, 2 drops) governed by a passive valve ensures precise and accurate sample volumes. Once loaded, the user closes the sample loading port with an easy-peel adhesive cap. Finally, in-line filters facilitate ‘on-chip’ processing of serum and saliva. All of these design features were implemented to maximize ease-of-use so that nonexpert users can obtain highly reproducible assay conditions.

Another major consideration for simplifying the world-to-chip interface is the introduction of buffers and reagents to the device. Most immunoassays require a sterile aqueous solution for performing various assay steps. LOC devices often utilize external syringe pumps for introducing fluids to the chip; however, these devices are not practical for clinical use due to size and weight constraints. An elegant solution to these constraints is to embed all the necessary fluids and reagents in the device itself. The challenge is to protect and encapsulate this sterile fluid source within the LOC device in a way that reduces complicated backend manufacturing steps.

The p-BNC solves this issue by introducing two blister packs filled with phosphate-buffered saline (PBS) mounted directly on the cartridge (these are further described in the ‘Fluid Delivery’ subsection below). Briefly, the foil blister packs serve as the on-board fluid source for the immunoassay and are externally compressed by an automated fluid delivery system for accurate and repeatable flow rates. These foil packs are simple to manufacture in high volumes and are easily attached to the cartridge with double-sided adhesive. Using a dual blister approach, the p-BNC serves both the antigen delivery (right blister) and detecting antibody reagents (left blister) without the use of active valves that would otherwise complicate the design. While the blister pack approach is attractive for its high level of integration and scalability, device makers transitioning from syringe pumps to this more integrated fluid delivery system should consider the implications of smaller available volumes and slower flow rates on assay performance, particularly during wash steps where high volumes and fast flow rates contribute to better S/Ns by more thoroughly washing away unbound reagents.

A final world-to-chip consideration is how contaminated devices and potentially biohazardous contents are disposed. There is a sustained interest in the LOC community in inexpensive, single-use disposable devices [7], and while it is impractical for some devices which use relatively large liquid volumes, an attractive solution is to implement reservoirs that contain the waste fluids directly on the LOC device. The p-BNC cartridge has two such chambers for collecting waste fluids. Once the assay is completed, the entire cartridge can be safely ejected from the instrument and disposed in a biohazardous waste container.

Fluid delivery

Fluid motivation is one of the most important features of microfluidic systems. While fluids may be manipulated in numerous ways (e.g., pressure, electric, magnetic, capillary, centrifugal, acoustic), in the case of bead-based p-BNC devices, pressure-driven flow plays a critical role on analyte capture [25]. These porous beads exhibit a multikinetic effect in which the exterior is reaction-limited and the interior is transport-limited; thus, the flow rate conditions directly affect capture efficiency. Although capture efficiency is a primary concern for the fluid motivation system, other considerations such as volume limitations and time constraints could impact the flow conditions. Therefore, it is important to develop flexible instrumentation that can cover a range of accurate and repeatable flow rates.

The p-BNC platform features an automated fluid delivery system in which PBS-containing blister packs

are mounted directly on the cartridge. These foil structures not only hermetically seal the buffers to prevent contamination and evaporation, but also provide a means to induce fluid flow. Upon actuation via stepper motor actuators, force sensors detect when the actuator makes contact with the blisters and when the blister bursts releasing its contents into the cartridge. In addition, a model of the blister's dome-like geometry informs the velocity of the actuator in order to produce constant, highly accurate, and reproducible flow rates [31].

Programmability

Most commercially available LOC devices are relatively simple in design and function, and their target analytes are usually limited to a subset of biomarkers for a particular disease application. Collectively, these devices form a complicated and cumbersome ecosystem targeting single application verticals [34]. There is a lack of broadly responsive bioassay systems with the ability to agilely adopt new disease applications.

The p-BNC, a universal platform to digitize biology, consists of two sensing modalities (bead-based sensors for soluble chemistries and membrane-based chips for cytology measurements) which collectively represent one of the largest portfolios of analyte targets to date [25]. In the bead-based configuration, multiplexed measurements are made possible through spatially programmed bead sensors. The p-BNC's cell capture membrane is capable of supporting various cytology assays. A reagent pad inside the p-BNC cartridge allows for assays to be easily reconfigured with detecting reagents. In addition to the bio- and chem-programming capabilities of the p-BNC system, the portable analyzer software allows for highly customizable flow protocols and analysis routines.

Automation

Another major challenge for integration of LOC devices is creating an automated workflow that is compatible for inexperienced users with limited to no human intervention required between sample introduction and data presentation [36]. Automation is necessary not only to eliminate the need for technical training, but also to reduce the variability between tests and across test sites, allowing for quality standard measurements with a high degree of reproducibility and repeatability.

The p-BNC system automates several key assay procedures. The p-BNC analyzer performs fluid handling that would otherwise have been supervised by a trained lab technician. Further, the analyzer automatically acquires optical measurements, performs data analysis on the acquired images, converts the image into usable data (i.e., biomarker concentrations) and relays the

results to disease-specific machine learning algorithms for diagnosis or prognosis.

Co-evolution of chip & analyzer

In the field of LOC, it is common to see significant time and resources devoted to developing and optimizing the chip or biosensing elements before any progress on integration is completed. Consequently, the first integrated reader is developed long after major design features of the device have already been established, resulting in overly complicated and awkward instrumentation [20].

A co-evolution approach was used to develop the p-BNC system (Figure 1). Early prototypes of the p-BNC were for all intents and purposes 'chips in a lab.' This 'macroscale' system consisted of reusable silicon chips with flow-through bead microcontainers attached to external syringe pumps, and measurements were collected with a research-grade fluorescence microscope. Although not translatable, this early system defined the specifications for a more integrated laminate labcard made via xurography. This multilayer prototype featured microfluidic channels for routing fluids, sample metering, semipermeable vent membranes, herringbone mixers, blister packs, self-contained waste chambers, and a flow-through bead microchip fabricated with UV-curable epoxy [37]. A 'micro-scale' instrumentation platform consisting of a blister actuator module was developed to automate the fluid delivery, and the same research-grade microscopes were used. The laminate labcard fabrication process was ideal for rapid design iterations; however, the manual process was labor intensive and not scalable. More recently, an injection molded plastic cartridge [30] and an integrated analyzer prototype were developed [31]. These fully functional and integrated p-BNC prototypes are capable of producing quality clinical measurements at the POC and will define bulk manufacturing and production runs for the commercial-ready platform.

Failure to compete

Another major barrier to clinical translation for LOC devices is the failure to compete with central and remote laboratories in terms of cost and performance. In general, POC devices are both more expensive and yield performance inferior to the laboratory setting [24,25,38]. To reach their full potential, it is necessary for these new LOC devices to simultaneously achieve reduced cost and enhanced performance relative to established laboratory methods.

Cost

The microelectronics industry serves as a role model for the diagnostics industry. In particular, the scal-

Figure 1. Co-evolution of the cartridge and analyzer for the programmable bio-nano-chip system. This process shows how the programmable bio-nano-chip system evolved from ‘chip in a lab’ prototypes to point-of-care-ready lab-on-a-chip devices with each new generation of the cartridge (A–D) and instrumentation (E–H) achieving higher degrees of integration.

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(G) Adapted with permission from [31] © Royal Society of Chemistry (2015).

ability of microelectronics was made possible through the development of novel microfabrication techniques, allowing for massive replication and parallel fabrication of features on the order of microns and smaller. While these techniques inspired the field of microfluidics/LOC early on, there are now many alternative ways to fabricate these devices, both for small quantity production and for mass manufacture. Despite having the requisite technical capabilities to mass produce them, many LOC devices fail to reach clinical utilization simply because manufacturing costs are too high [33]. Further, the expectation of many academic groups is that once a functional prototype is built, industry partners are responsible for the design for manufacture (DFM)

process, in other words, the design phase dealing with various issues relating to cost-effective manufacturability and scalability such as reducing the number of parts, increasing robustness, minimizing assembly steps, and specifying appropriate tolerances [22,33,35,39]. This expectation is far from reality if there is any hope that the device will reach clinical realization, and academic groups proposing new LOC devices must play a more active role in the DFM process. This process involves working directly with commercial partners to simplify the design to the least amount of parts possible, modifying features to be more easily manufactured, preparing product requirements and specifications documents, etc. Further, the DFM mentality should begin in the

prototype stage (or as early as possible), such that new device concepts are compatible with highly scalable and repeatable manufacturing processes.

Originally inspired by highly scalable and repeatable manufacturing processes, the first p-BNC chip prototypes were comprised of anisotropically etched silicon 100 wafer bead microcontainers. After completing the necessary proof-of-concept experiments and moving towards single-use disposables, the same chip patterns were fabricated in modest quantities with a casting method using UV-curable epoxy and a micromachined aluminum mold, and these hand-fabricated chips were embedded in a laminate microfluidic labcard made using xurography techniques. More recently, these prototype devices were replaced with scalable injection molded plastic. Our group has established strong relationships with industry partners to accomplish the goal of providing cost-effective devices to multiple clinical audiences. Through these joint efforts, we greatly simplified the designs to bring down the cost in several ways. For example, the laminate prototype's seven layers were reduced to three layers containing only one injection molded fluidic layer and two capping layers. Components such as semipermeable vent membranes for releasing trapped air in the cartridge were removed or relocated to reduce complexity and the number of parts. Likewise, the number of manufacturing steps and backend processes were minimized to simplify the fabrication process.

Performance

In addition to cost, another stumbling block for LOC technology is performance. Generally speaking, microfluidic/LOC devices represent novel solutions to an already existing market where cost and performance for a given analysis are well established [33]. Thus, in order for widespread clinical uptake, these new systems must substantially outperform existing technologies in terms of faster analysis times, increased sensitivity, decreased sample volume, better multiplexing capabilities, lower cost, etc. For example, a new device that provides the same results, but much more rapidly, may be attractive for clinical applications where timely diagnosis is important, such as cardiac biomarker detection in the emergency department. Similarly, new devices offering increased sensitivity and lower LODs are attractive for assays which the increase in sensitivity improves diagnostic performance. Automated POC devices that are substantially easier to use than their central and remote laboratory counterparts may also find opportunities in consumer markets, home monitoring, and resource-limited settings.

The p-BNC system is capable of high-fidelity biomarker detection at the POC with performance that

rivals remote laboratory instrumentation [25]. **Table 1** shows the analytical performance (range and LOD) of the p-BNC for a multitude of biomarkers as acquired with the 'macroscale' version of the p-BNC platform. The method for determining the LOD is described as 'practical' or 'theoretical.' In the practical method, LOD was determined as the lowest antigen concentration providing an average bead signal three standard deviations above (for two-type immunometric assays) or below (for competitive assays) the mean value of a zero analyte calibrator bead. For the theoretical method, a 4- or 5-parameter logistic curve was fit to an experimental dose response curve, and the LOD was calculated from the mean fluorescence intensity three standard deviations above the mean of three 'blank' runs. In each area, the p-BNC is capable of quantifying the pathophysiological ranges for healthy and diseased statuses. This analytical performance is made possible in part by the high surface-to-volume ratios of the p-BNC's porous bead sensors. These 3D agarose bead matrices support layering of signal 1000- to 20,000-times larger than planar microarrays (i.e., an ELISA plate) [27]. Compared to other bead-based clinical analyzers, the p-BNC system has relatively short analysis times. For instance, Luminex xMap® technology implements a suspension array of magnetic microspheres for the simultaneous detection of multiple analytes. However, long incubation times ranging from 2 h to overnight render this technology unsuitable for some POC applications. The p-BNC system, on the other hand, uses pressure-driven flow and a dual diffusive/convective transport regime to speed up analysis times to about 20 min [25] with assays completed in as fast as 7 min [31].

New content

Over the past few decades, biomarker measurements have become ubiquitous to the practice of medicine and play a critical role in clinical decision making. Biomarkers are like keys that unlock valuable information pertaining to patient health that would otherwise be inaccessible. The availability and rapid access to biomarker data are increasingly important for the diagnosis and prognosis of a variety of diseases; however, major inadequacies have resulted in a disappointing rate of biomarker translation to clinical practice over the years. To illustrate this point, from 1995 to 2005 over 26,000 papers were published for cancer and cardiac disease combined, yet only about one protein biomarker per year received US FDA approval (**Figure 2**) [40]. While this statistic highlights a major gap in biomarker translation from academic and industrial labs into clinical practice, it also illustrates major opportunities for new technologies that will greatly enhance bench-to-bedside translation.

Table 1. Summary of bead-based programmable bio-nano-chip performance.				
Biomarker	Clinical use	Range (ng/ml)	LOD (ng/ml)	Method
CRP	Cardiac – risk	0.1–10,000	0.1	Theoretical
sCD40L	Cardiac – risk	0.1–1000	0.1	Practical
MCP-1	Cardiac – risk	0.001–20	0.001	Practical
MPO	Cardiac – risk	0.05–500	0.05	Practical
MPO (multiplexed)	Cardiac – risk	1.2–500	1.2	Theoretical
IL-1 β	Cardiac – risk	0.001–1	0.001	Practical
IL-6	Cardiac – risk	0.001–1	0.001	Practical
TNF- α	Cardiac – risk	0.01–10	0.01	Practical
Human serum albumin	Cardiac – risk	1–1000	1	Practical
cTnI	Cardiac – AMI	0.05–50	0.05	Theoretical
Myoglobin	Cardiac – AMI	0.1–1000	0.1	Theoretical
CK-MB	Cardiac – AMI	1.7–50	1.7	Theoretical
ApoA-I	Cardiac – recurrence	1–1000	1	Practical
ApoB	Cardiac – recurrence	1–1000	1	Practical
BNP	Cardiac – HF	0.05–10	0.05	Theoretical
NT-proBNP	Cardiac – HF	0.1–500	0.1	Theoretical
CEA	Ovarian cancer	0.1–100	0.02	Theoretical
CA-125	Ovarian cancer	1–400 [†]	1 [†]	Theoretical
HER2/neu	Ovarian cancer	0–60	0.27	Theoretical
PSA	Prostate cancer	0.1–100	0.1	Theoretical
Free PSA	Prostate cancer	0.1–100	0.1	Theoretical
Complexed PSA	Prostate cancer	0.63–100	0.63	Theoretical
Cocaine	Drugs of abuse	1.3–10,000	1.3	Practical
Diazepam	Drugs of abuse	0.14–1000	0.14	Practical
Tetrahydrocannabinol	Drugs of abuse	0.22–10,000	0.22	Practical
D-amphetamine	Drugs of abuse	0.22–1000	0.22	Practical
Methamphetamine	Drugs of abuse	10–8000	1	Practical
Oxazepam	Drugs of abuse	1.6–100,000	1.6	Theoretical
Nordiazepam	Drugs of abuse	0.72–100,000	0.72	Theoretical
Temazepam	Drugs of abuse	1.1–100,000	1.1	Theoretical
Morphine	Drugs of abuse	0.46–1000	0.46	Theoretical
Methadone	Drugs of abuse	1.02–10,000	1.02	Theoretical
MDA	Drugs of abuse	7.1–1000	7.1	Theoretical
MDMA	Drugs of abuse	0.41–1000	0.41	Theoretical

[†]Units are expressed as U/ml.
 This list summarizes the biomarker assays developed on the bead-based programmable bio-nano-chip platform, their targeted use, and device performance characteristics. All assays listed here were developed on the programmable bio-nano-chip 'macro-scale' configuration. Adapted with permission from [25].

For a clinical community to adopt new technology requires the device to add substantial value over pre-existing methods. Typically, added value of a device is measured based on performance compared with a predicate device for the same application. While sub-

stantial improvements in design may overcome existing methods in performance, these improvements may not be enough to convince ultimate clinical adoption. Rather, LOC developers should also focus on adding new content to maximize clinical appeal.

Figure 2. The biomarker bottleneck. Despite key scientific advancements that have unlocked insights into disease pathophysiology and promising new therapies, the approval rate of protein biomarkers for clinical use remains dismal.

Multivariate index assays

The combination of machine learning algorithms and diagnostic devices is poised to revolutionize the way we quantify health. Implemented correctly, *in vitro* diagnostic multivariate index assays (IVD-MIA) could outperform existing methods for diagnosis and prognosis of a variety of diseases [41]. The FDA defines an IVD-MIA as a device that ‘combines the values of multiple variables in an interpretation function to yield a single, patient-specific result (e.g., a classification, score, or index) that is intended for use in the diagnosis, treatment, or prevention of a disease’ and that ‘provides a result whose derivation is nontransparent and cannot be independently derived by the end user’ [42]. The basic idea is that aggregate information in the form of multiplexed biomarker measurements will outperform any individual biomarkers. Further, the formation of new classifications, scores, or indices from multivariate machine learning models provides substantial added value over biomarker concentration values in their interpretation alone.

The McDevitt laboratory is developing multivariate index assays for cardiac disease and oral cancer applications. Cardiac disease is the number one killer in the US and on a global basis [43], and staggering direct and indirect costs make cardiac disease a major contributor to the already enormous healthcare burden in the US economy [44]. Toward the goals of saving lives and driving down healthcare costs, we are developing the Cardiac ScoreCard – a series of machine learning algorithms that quantify risk for a spectrum of cardiovascular diseases using multiplexed biomarker measurements, symptoms,

medical history, and demographics [45]. Through frequent monitoring, prevention, and early detection of cardiac disease, these new tools have the potential to promote wellness and prevention in populations globally. Similarly problematic, oral cancer ranks in the top three most common cancers in India, the world’s second most populous country [46]. Although oral cancer is less prevalent in the US [47], the disease is one of the most deadly and expensive cancers to treat [48]. We are in the process of developing novel computer vision cytology methods and machine learning algorithms for the differential diagnosis of suspicious lesions so that healthcare providers can identify the disease at an early stage when the survivability rate is high. Through these efforts we hope to establish ‘killer applications’ that will propel the p-BNC technology beyond the academic lab bench to clinical communities around the world.

Mobile health

Mobile health, or mHealth, is the practice of using devices such as smartphones, tablets, and laptop computers to acquire, manage, and provide medical and public health information, and it is a rising technology trend with the potential to fulfill unmet needs of healthcare systems in developed and developing nations, alike. More specifically, mHealth is emerging as a solution to problems relating to high disease burden, limited resources, and inaccessibility to adequate healthcare. Recently, mobile technologies have continued to spread at an exponential rate, particularly in low- and middle-income countries [49], offering a promising new channel for the cost-effective dissemination of healthcare informa-

tion [50]. Leveraging the ubiquity of mobile devices in consumer markets, wellness-oriented apps that record, monitor, or track a user's health information could add substantial value over existing platforms with less connectivity and consumer appeal.

The McDevitt lab is in the process of developing the p-BNC ecosystem (Figure 3) comprising a portable cartridge/analyzer assay system, automated data analysis and machine learning software, and intuitive mHealth interfaces. Together, these components serve as a platform to digitize biology, in other words, a general-purpose platform that can complete multiplex testing over a broad range of clinical application areas. In each application, bio-signatures are recorded via a video chip in a process driven by microfluidic chips with the ultimate signal recorded in the form of a digital image; the p-BNC literally digitizes biology through this universal interface. Automated image analysis and computer vision methods isolate pixel regions of interest, extract signal, and convert it to biomarker concentrations. With the collection of a broad range of clinical data for various health conditions and bridging this information to artificial intelligence, it has been possible recently to create a sensor system that learns. The McDevitt lab is in the process of developing a mobile application for the Cardiac ScoreCard. This ScoreCard app offers users an intuitive interface to display and interpret their cardiovascular wellness, and it allows users to view trends by tracking their cardiac scores over time. By making the end user experience a priority, intuitive interfaces such as the Cardiac ScoreCard app may lessen the psychological reluctance to adopt new technologies over tried-and-true methods and ultimately appeal to broader clinical and commercial audiences.

Regulatory approval & clinical adoption

Despite large investments in translational research programs, most bioscience research efforts remain largely decoupled from real-world clinical practice. As a result, regulatory approval of groundbreaking medical technologies is at an all-time low [51]. Device development – whether in academia, national labs, or industry – is usually a complicated and lengthy process that occurs in a linear, suboptimal manner consuming precious time and resources from venture capital and public funding sources. Before embarking on the path to device approval, a number of assumptions are too often made in the absence of evidence that supports the use of the candidate technology for an intended diagnostic target. Such missing information may include invalidity of the intended target itself, absence of a market for its use, or improbability of its adoption as part of clinical practice.

A typical device development pathway is shown in Figure 4 and starts with some consideration for the profile for the new product. Next, consideration is given to choices for the intended diagnostic targets (i.e., the biomarkers) as well as the mode of detection (i.e., the platform) for these diagnostic targets. The output from the 'omics' disciplines are too often decoupled from the mode of detection in the final clinical setting and are thus excluded completely from the next stages of development. Once the biomarker and detection modes are selected, efforts are directed to develop the candidate product prototype. This transition stage involving proof of principle, lab- and field-testing, and usage models for real-world clinical implementation is critically important to success, yet it remains the major bottleneck for diagnostic device translational efforts to date inheriting the term 'Valley of Death' – the development phase of a startup company marked by inconsistent and uncertain cash flows to perform tasks such as research, prototype design, and preclinical testing. Here, highly controlled clinical samples relevant to the final clinical usage model, standard operating protocols, electronic data capture system, user needs and specifications, and detailed information related to the regulatory pathway need to be made available to promising new medical microdevice developers in an effort to propel these activities into real-world clinical practice.

An example of the dismal translation rate of medical tests into clinical practice was presented by Schully *et al.* [52]. Publications and funded research grants were reviewed and categorized as follows: T0 for discovery research, T1 for research to develop a candidate device or therapy, T2 for research that evaluates a candidate and develops evidence-based recommendations, T3 for research that explores how to integrate the evidence-based recommendation in clinical practice, and T4 for research that evaluates health outcomes and population-level impact. According to their results, 1.8% of the grants and 0.6% of the publications were characterized as T2 research and above. Importantly, the lack of translation is further complicated by the mixture of disparate disciplines that exist in the LOC/medical microdevice communities. Here it is necessary to bridge between the disciplines of bioscience and microfabrication – two areas that in the past have remained largely separate.

Technologies for advanced screening, diagnosing, and monitoring that are simple to use, rapid, noninvasive, accurate, sensitive, and accessible to the patients in a variety of settings, such as physicians and dentists offices, pharmacies, and at home, are now being developed and promise to overcome

Figure 3. The programmable bio-nano-chip mHealth ecosystem. The mHealth ecosystem comprises a (A) cartridge/analyzer assay system, (B) data analysis and machine learning software, and (C) intuitive user interfaces.

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major past limitations for POC technologies, such as cost and lack of sensitivity [53]. However, there is a strong tendency for commercial devices based on microfluidics that originate from academic research to suffer from the gap that separates academia and industry. The realities of academic research in terms of pressure to get funding tend to lead researchers

onto paths that deviate from a sharp focus on practicality. Differences here include the type of materials and fabrication methods used to build the devices, the type, origin, and volumes of bodily fluids used as clinical samples, as well as the lack of a strict analytical process with appropriate metrics and statistical rigor of the type that governs FDA approval. Fur-

Figure 4. Typical development pathway for new medical devices from inception to clinical adoption.

thermore, whether for applications in developed or developing countries, devices created in isolation in both academia and industry result in large discrepancies between the engineered product and the unmet clinical need [54].

Consequently, the major obstacles in the product development pipeline include a lack of standardization across platforms of samples and reagents used in the clinical studies needed to evaluate devices, a poorly defined and understood path to commercialization, and a frequent lack of understanding on the part of the technology developers for the clinical unmet needs and the targeted market. Collectively, these shortcomings are frequent causes for product implementation failure and an overall dismal translation rate of such devices from academic and start-up companies to clinical use.

A pipeline of promising medical microdevice technologies will be made possible through the establishment of unmet clinical needs, the formation of world-class clinical collaborations, the generation of standard testing protocols and operating procedures, definition of rigorous user requirements, and the creation of potent commercialization relationships. Clinical and user needs must be established early on in the development process, and efforts to define the competitive landscape and regulatory pathways for these new test modalities is essential. Technology developers must also leverage multi-disciplinary expertise through close clinical collaborations to address barriers to regulatory approval, commercialization and clinical implementation. Device developers should participate in generating standardized testing protocols, securing access to critically important clinical samples, and information sharing related to user requirements for new diagnostic tests areas in nontraditional healthcare settings. Close teaming relationships with established commercialization partners is necessary to generate

background specifications and initial performance data that are needed for these commercial partners to remove risk associated with their investment in new technologies. These key steps will serve to help prototype developers to bridge the ‘Valley of Death’ that so often results in promising academic efforts ‘dying on the vine.’

The medical microdevice revolution will rely on the coordination of key technologies and information content, similar to the establishment of the information highway. The information highway, which emerged initially from electrical and computer engineering efforts, has been made widely distributable via scalable electronics and intuitive software interfaces. The healthcare industry will follow an analogous pathway via the ‘biomarker highway,’ leveraging well-established hardware and software industry standards along with a new goal of increasing the translation rate of biomarker tests per time (i.e., Moore’s law applied to medicine) [24].

The McDevitt laboratory has sustained efforts for the development, testing, and clinical implementation of technologies that serve as standard tools for biomarker measurements. Our group has established a large number of collaborative projects, launched three centers in medical microdevices, founded a number of diagnostic companies in this space, and now manages six major clinical trials involving over 5000 patients at ten clinical sites (Table 2). In the area of cardiac heart disease, we are aiming to validate 15 cardiac biomarkers in serum and saliva for the screening of acute myocardial infarction in chest pain patients presenting to the emergency room [45]. For oral cancer, two major clinical studies have been initiated, resulting in one of the largest cytology databases related to oral cancer ever created. Through these efforts, over 10 million single cell cytology measurements have been recorded tar-

Table 2. The Programmable Bio-Nano-Chip system is involved in six clinical studies targeting major disease applications through the validation of biomarkers.

Study	Sponsor	Area	Subjects	Biomarkers
Development of A Lab-on-a-Chip System for Saliva-Based Diagnostics	National Institute of Dental and Craniofacial Research (NIDCR)	Cardiac disease	1050 patients	15 proteins
Monitoring of Oral Cancer Patients Using Novel Lab-on-a-Chip Ensembles	National Institute of Dental and Craniofacial Research (NIDCR)	Oral cancer	950 patients	7 cellular markers
Texas Cancer Diagnostics Pipeline Consortium: Oral Cancer	Cancer Prevention Research Institute of Texas (CPRIT)	Oral cancer	2200 patients	7 cellular markers
Texas Cancer Diagnostics Pipeline Consortium: Ovarian Cancer	Cancer Prevention Research Institute of Texas (CPRIT)	Ovarian cancer	1250 patients	4 proteins
Texas Cancer Diagnostics Pipeline Consortium: Prostate Cancer	Cancer Prevention Research Institute of Texas (CPRIT)	Prostate cancer	400 patients	3 proteins
Advanced Bio-nano-chips for Saliva Based Drug Tests at the Point of Arrest	UK: Home Office	Drugs of abuse	240 participants	12 drugs

getting six cellular markers and over 100 image-based parameters [55]. In the area of ovarian cancer, we are in the process of validating four protein biomarkers for the early diagnosis of ovarian cancer [26]. Likewise, in the area of prostate cancer we are developing an early detection method featuring a 3-plex panel of total, free, and complexed PSA in order to improve treatment options and outcomes and reduce costs associated with treating advanced stages of the disease. Lastly, through our saliva-based drug tests we are validating the measurement of 12 drugs of abuse [30]. These p-BNC roadside drug tests are projected to save time and simplify the enforcement procedure by avoiding the need to take the suspected drugged drivers to a police station or healthcare facility for testing. The current and past activities represent novel infrastructure and a unique education, networking-, and training-rich environment that aims to help move these new tools from multiple developers into broad-scale practice using shared resources, standards, and protocols.

Future perspective

Despite the many challenges facing LOC/microfluidics technology developers today, there is a great opportunity to advance the field through the creation of ‘killer apps.’ In this perspective, we laid out the most pressing challenges and offered unique solutions to bridge the gap between academia and clinical adoption. Further, these strategies have the potential to empower device developers with a set of tools and knowledge that will allow them to have a measurable impact in healthcare toward the goal of bending the healthcare cost curve through the application and broad-scale release of new medical microdevices that are developed with Moore’s law-like ambitions.

Looking to the future, we believe that the LOC/microfluidic bioanalysis community will increasingly rely on the generation of large datasets and successful implementation of machine learning algorithms for unprecedented performance in disease diagnosis and prognosis. While the race to acquire massive amounts of health information is in its infancy (e.g., initiated by large pharmaceutical/medical corporations, insurance companies, or governments), the applications of these high quality and high-dimensional clinical datasets will play a large role in medicine in the years to come as direct to consumer testing becomes more prominent. Thus, it is important for device developers to establish strong clinical collaborations to identify disease targets, oversee the generation of standardized testing protocols, and address unmet clinical needs such that the new LOC technology has the largest possible social and economic impact.

Disclaimer

The content is solely the responsibility of the authors and does not necessarily represent or reflect views of the NIH or the Federal Government.

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Executive summary

- There is an unmet need for universal lab-on-the-chip (LOC) platforms that can be easily 'reprogrammed' to perform a variety of analyses at the point-of-care (POC). However, the adoption of novel LOC devices has been slow due to inadequate understanding of economies of scale in mass manufacturing, lack of standardization and integration, and failing to create the 'killer app.'
- Several key challenges remain for the translation of new LOC devices to clinical practice.
 - Integration: Integrating LOC systems into POC structures that completely replicate the full functionality provided in laboratory settings requires significant technological innovations. In particular, developers should carefully consider the world-to-chip interface, fluid delivery, device programmability, and automation.
 - Failure to compete: Current LOC systems fail to compete with central and remote laboratories both in terms of cost and performance. To reach their full potential, it is necessary for these new LOC devices to simultaneously achieve reduced cost and enhanced performance relative to established laboratory methods. Academic groups must play an active role in the design for manufacture process and work closely with commercial partners to reduce manufacturing costs. At the same time, these devices must outperform existing technologies in terms of faster analysis times, increased sensitivity, decreased sample volume, multiplexing capabilities, and/or lower cost to convince widespread clinical adoption.
 - Need for new content: LOC systems need to develop new content that adds substantial value to the target application and is currently unavailable at central and remote labs. Multivariate index assays that aggregate multiple measurements into a single-valued score add value both in terms of ease of interpretation and increased diagnostic accuracy. Intuitive mHealth interfaces lessen the psychological reluctance to adopt new technologies and ultimately appeal to broader clinical and commercial audiences.
 - Regulatory approval and clinical adoption: Device makers need to develop strategies for streamlining regulatory approval *en route* to clinical adoption. A pipeline of promising medical microdevice technologies will be made possible through the establishment of unmet clinical needs, the formation of world-class clinical collaborations, the generation of standard testing protocols and operating procedures, definition of rigorous user requirements, and the creation of potent commercialization relationships.
- While there has been much speculation about the 'killer application' for LOC/microfluidics, the direct to consumer POC clinical testing that focuses on wellness profiles and early disease detection may indeed be the most promising applications that pave the way for other scalable and cost-sensitive devices with potential to increase quality of life and reduction in overall healthcare costs.

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