Lab on a Chip

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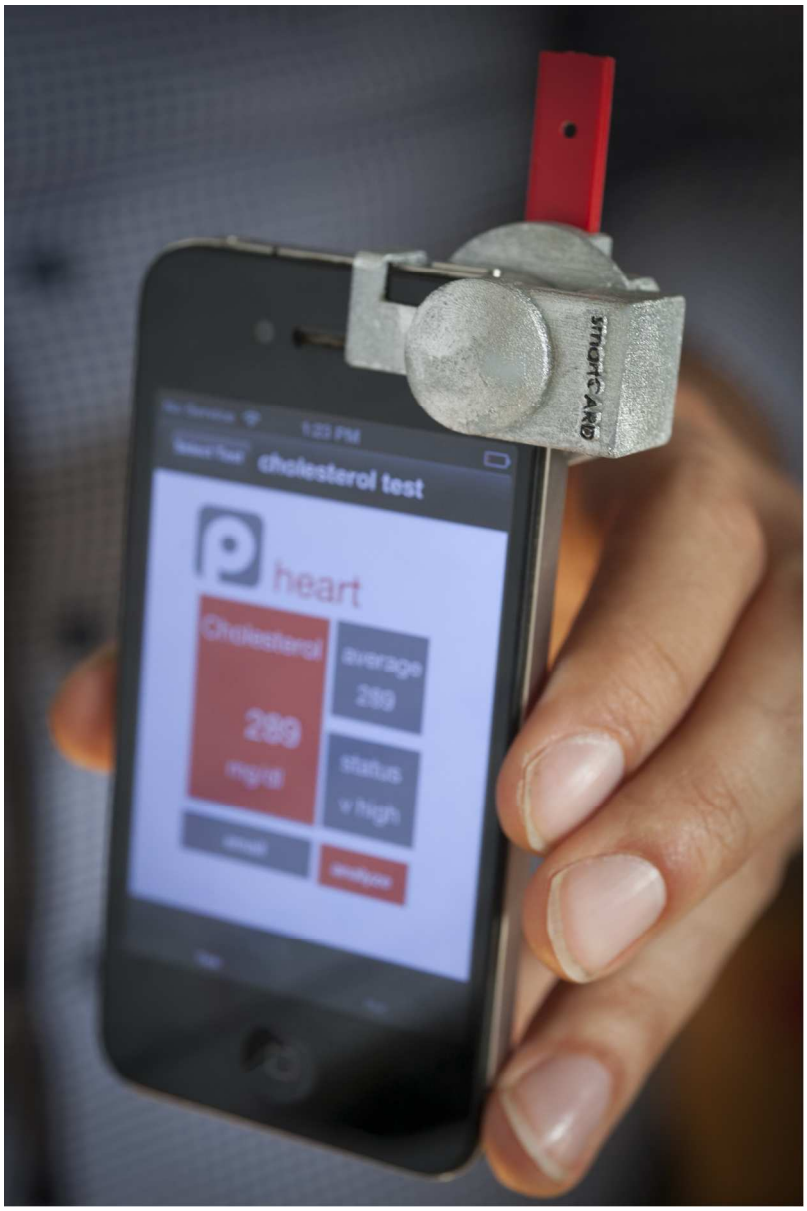

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Smartphone technology can be transformative to the deployment of lab-on-chip diagnostics

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Abstract

The rapid expansion of mobile technology is transforming the biomedical landscape. By 2016 there will be 260M active smartphones in the US and millions of health accessories and software "apps" running off them. In parallel with this have come major technical achievements in lab-on-a-chip technology leading to incredible new biochemical sensors and molecular diagnostic devices. Despite these advancements, the uptake of lab-on-a-chip technologies at the consumer level has been somewhat limited. We believe that the widespread availability of smartphone technology and the capabilities they offer in terms of computation, communication, social networking, and imaging will be transformative to the deployment of lab-on-a-chip type technology both in the developed and developing world. In this paper we outline why we believe this is the case, the new business models that may emerge, and detail some specific application areas in which this synergy will have long term impact, namely: nutrition monitoring and disease diagnostics in limited resource settings.

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Introduction

The concept of lab-on-a-chip based diagnostics originated more than 20 years ago (see an early review by Manz *et al.* [1]). One of the key envisioned benefits of the technology at that time was that it would enable the deployment of easy to use, disposable, and informative molecular diagnostic tests directly to the consumer allowing them to take better control of their own health. The technical vision usually comprised of a two part system: a consumable chip that contains microfluidics and a sensor for detecting the analyte of interest, and an instrument-type reader that interprets the signal from the chip and provides results to the user. Since this vision was first put forward, the technology has advanced at an incredible rate to the point where we now have: devices that can operate huge numbers of microfluidic valves in parallel [2], fully integrated sample-in-answer-out chips for genetic analysis [3], nanosensors that can detect a handful of molecules [4], and many other systems.

There have been numerous commercial successes using technology that can trace its roots back to these early visions. Most of these accomplishments however have been in developing what has been referred to as "chips-in-a-lab" or microfluidic technology that is used to enhance the: throughput, parallelity, sensitivity/specificity, or other analytical metrics for biochemical assays conducted within research or centralized lab facilities. Far fewer commercial successes have come from lab-on-chip technology that has transitioned to the consumer diagnostics market. While there are numerous successful biomedical consumer products that contain microscale channels or similar features (*e.g.* inhalers for asthmatics), most of these are at least conceptually different from the traditional vision of a LOC device.

There are, of course, numerous reasons for this, however it seems unlikely that the major roadblocks are technological in nature. Rather it seems to at least partially result from two reasons. The first is the difficulty in obtaining quantitative results with a simple one-off test. The majority of commercially available tests for the consumer market are Rapid Diagnostic Tests (RDTs) based on the lateral flow

principle (*e.g.* [5]). Such products are popular because the user only needs to insert the sample and the fluid transport, sample processing, and detection reaction all occur autonomously. Unfortunately, these types of tests are typically only able to provide non-quantitative information and thus are only useful when the desired result is binary (*e.g.* pregnant/not-pregnant). Obtaining a quantitative result requires a more complex sensor system and sample handling technique, which typically must be interpreted and displayed by a reusable and often research grade instrument. While some simple visual feedback systems have been developed, as with colorimetric tests, these tend to rely on higher initial target number than are found in most applications and are subject to user interpretation error.

A second challenge is that most of the analytes a typical consumer wants to be tested for (*e.g.* vitamin D) do not require frequent testing. In the consumer market the reader and consumable model has proven most successful where the user must make numerous measurements over the course of a day or week, as is done with blood glucose monitoring. In such a case the consumer is willing to spend a little more to purchase a reader since it will be used so frequently, or conversely the company may be willing to sell the reader at a loss in order to increase consumable sales. For cases where measurements are made sporadically or with much lower frequency, the cost of purchasing a personal reader system can be prohibitively high, particularly for the casual user, representing a high bar to market entry.

A role for smartphone based lab-on-chip diagnostics

We believe the extreme societal penetration of the smartphone and its ubiquity, familiarity, and functionality, can fundamentally alter this predicament. Almost 46% of American adults have a smartphone today and this number is expected to keep increasing with an anticipated 250 million smartphones in use in the US by the year 2016 [6]. This means that nearly every person in the US (and by extension most

developed countries) is either carrying a smartphone with them or has near immediate access to one. Not only do these devices contain state-of-the-art imaging, data analysis, communications, and social networking capabilities, they are an extremely easy to use and familiar to almost all age groups. It is common to see everyone from the elderly to pre-school children using them. This familiarity can dramatically reduce required training requirements and potentially user errors during testing. As we and others have demonstrated, the majority of the functionality required to make and interpret a quantitative *in-vitro* measurement is already embedded in smartphones. Figure 1 shows a few examples of recently demonstrated system for colorimetric test strip analysis [7], microscopy [8], genetic testing [9], and electrochemical detection [10]. As can be seen, a typical system comprises of an accessory, which is either fitted to the smartphone and interacts with the on-board camera or the communications port, and a test "chip" (or similar) which is inserted into the accessory. The key of such systems is that the vast majority of the cost and complexity is embedded in the smartphone, which the user can be expected to have and therefore need not be engineered separately into the system. This is transformative for lab-on-chip technology because now it can be relied upon that most consumers will already own a test reader/instrument in the form of a smartphone and business models can be constructed around selling the test strips at high margins with a significantly lower barrier to entry. The opportunity is even more apparent in lower and middle income countries where the relatively low infrastructure requirements associated with establishing high-quality cellular (or mobile) networks makes smartphones one of the few widely deployed technologies.

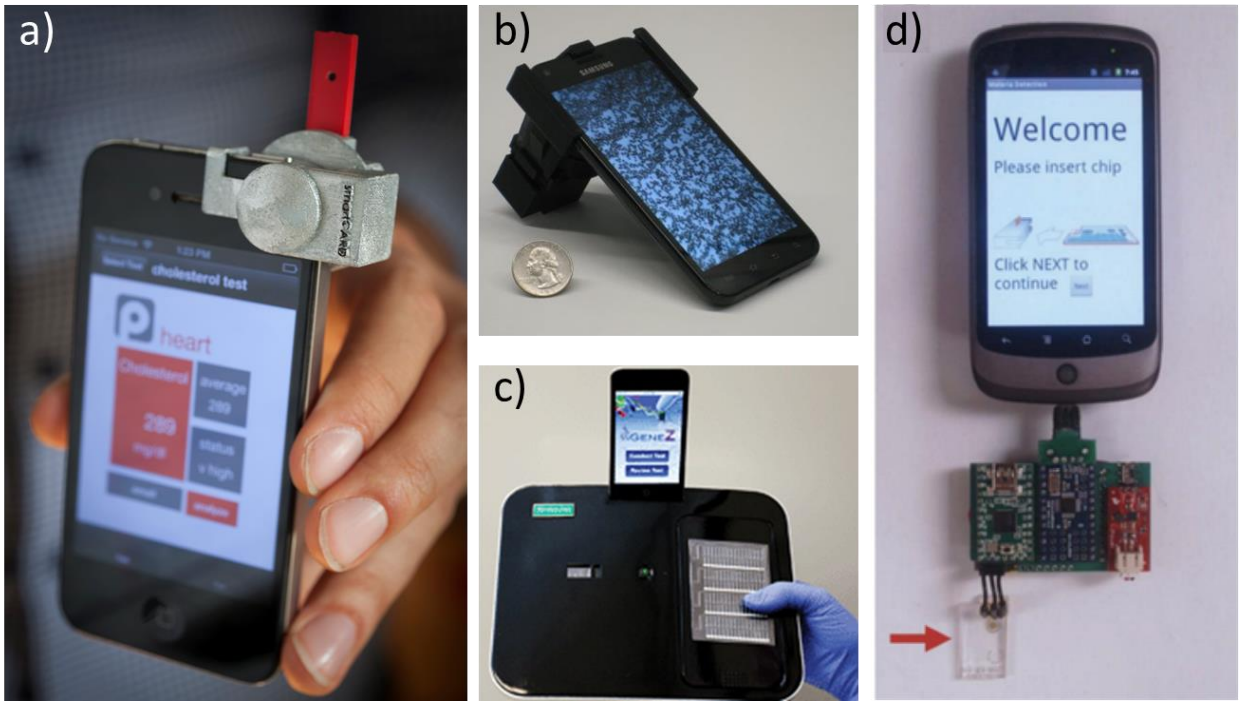

Figure 1: Smartphone based microfluidic and lab-on-chip technology (a) colorimetric analysis for serum cholesterol detection [7] (b) smartphone microscopy [8] (c) genetic testing [9] and (d) electrochemistry analysis [10]. Images (b), (c), and (d) Reproduced from [8], [9], and [10] respectively with permission from The Royal Society of Chemistry

Classifying the state-of-the-art and the path forward.

Recognizing the potential for smartphone-based health monitoring, a number of health-related systems have recently been developed. The field is advancing rapidly, though as of the writing of this article the commercial state-of-the-art in the area includes fitness applications and smartphone accessories that record basic healthcare information such as blood pressure and Body Mass Index. Examples of these include: exercise and fitness monitoring applications, heart-rate and blood-pressure monitoring, vaccine logs, sleep monitoring applications, diagnosis decision support apps, and applications that can be used to image and diagnose skin cancer. Large efforts [11, 12] have been formed to try to integrate many of these technologies into a single platform, encouraged by such programs as the TriCorder X-prize [13]. In 2011, smartphone

based healthcare was worth $1.3 billion, up nearly twice its 2010 value, with the majority of the revenue coming from accessory sales [14].

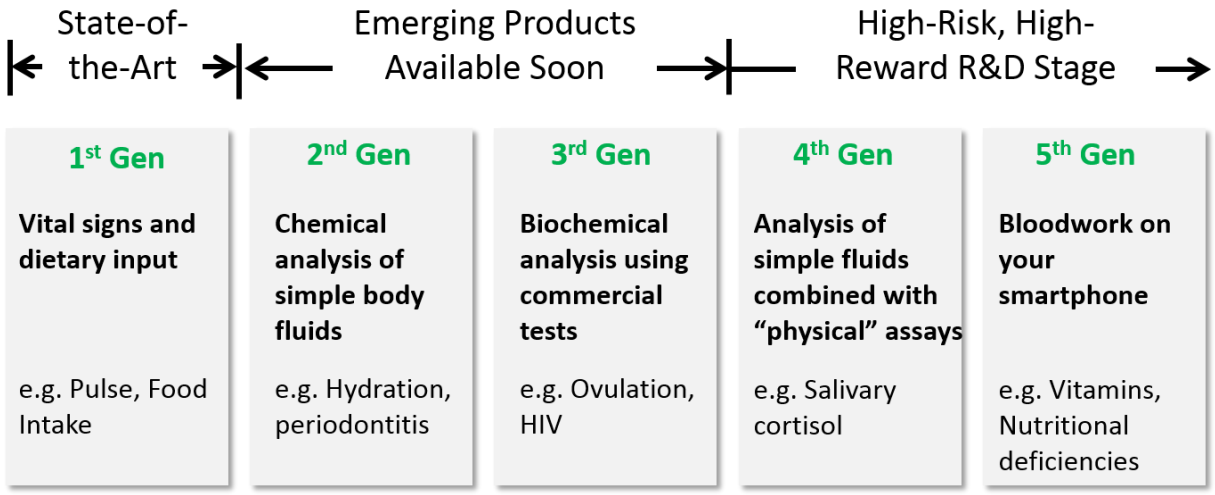

Figure 2: Smartphone based Lab-on-Chip Technology Roadmap. Image illustrates the possible technological progression of smartphone based lab-on-chip technology from the existing product state to likely areas of high-reward R&D.

Most of these broadly available existing commercial systems rely on user input or physical measurements that are generally non-specific to a particular pathology but easy to obtain. As outlined on our technology development roadmap, Figure 2, these can be classified as "1st generation" systems. Expansion beyond these coarse measurements requires molecular analysis of bodily fluids like sweat, saliva, urine and blood, all of which contain a much deeper wealth of physiological information. Given that handling and analyzing these fluids represents the core technological strength of lab-on-chip devices, the opportunities for synergies are apparent. Towards this end a number of start-up and larger companies will be the first to offer 2nd and 3rd generation products. These are labeled in Figure 2 as "Emerging Products Available Soon". The first of these are likely to be products related to "healthy living", wellness, fitness and sports, which are attractive both in terms of the premium the target customer is able/willing to pay and the potential for a lower regulatory barrier. An example of this is a recent device by our group that monitors sweat and salivary pH for hydration analysis and oral health, respectively [15]. Others works include the development of apps and accessories that will interpret the urine test strips commonly used in doctors' offices or existing rapid

diagnostic test strips. For conflict of interest reasons we will not list any of these companies herein. Though the overall market size may be relatively small for any one of these given diagnostics, applications which take advantage of existing test-strip are appealing points of entry from a commercial point of view as they represent existing well-established markets and require limited development time. As of the writing of this article regulatory agencies are still deciding how such systems will be regulated, however it is likely that the barrier to approval will be lower than that required for the development of entirely new diagnostics (see Yetisen *et al.* [16]).

Referring back to Figure 2, what we have delineated as the 4th and 5th generation systems are those that are perhaps the most interesting as they are likely to have the longest term impact. 4th generation systems that combine chemical and physical assays are likely to have greater sensitivity and specificity than either technique individually. For example one can imagine a long term stress testing system that combines salivary cortisol (a typical chemical marker for increased stress but subject to a number of confounders) with physical assays that look at vocal changes [17]. As for 5th generation systems, there are already a few smartphone based systems that have demonstrated blood analysis [18]. Generally speaking however the wealth of information available from blood analysis (ranging from general markers of infectious disease, to cancer diagnostics, to vitamin and micronutrient deficiencies) is so incredible that further research will certainly lead to more exciting applications.

For those interested in the area, there are a number of different application entry-points, some of which we have outlined above. Prior to concluding this paper we expand on two case studies: nutrition and micronutrient monitoring and limited resource setting disease diagnostics. As with the previous parts of this paper, the purpose of these sections is not to provide a detailed review of the work done in the field, but rather outline what we see as the major advantages of smartphone based lab-on-a-chip technology

applied to these areas and some of the challenges with deployment. These overall advantages are summarized in Figure 3.

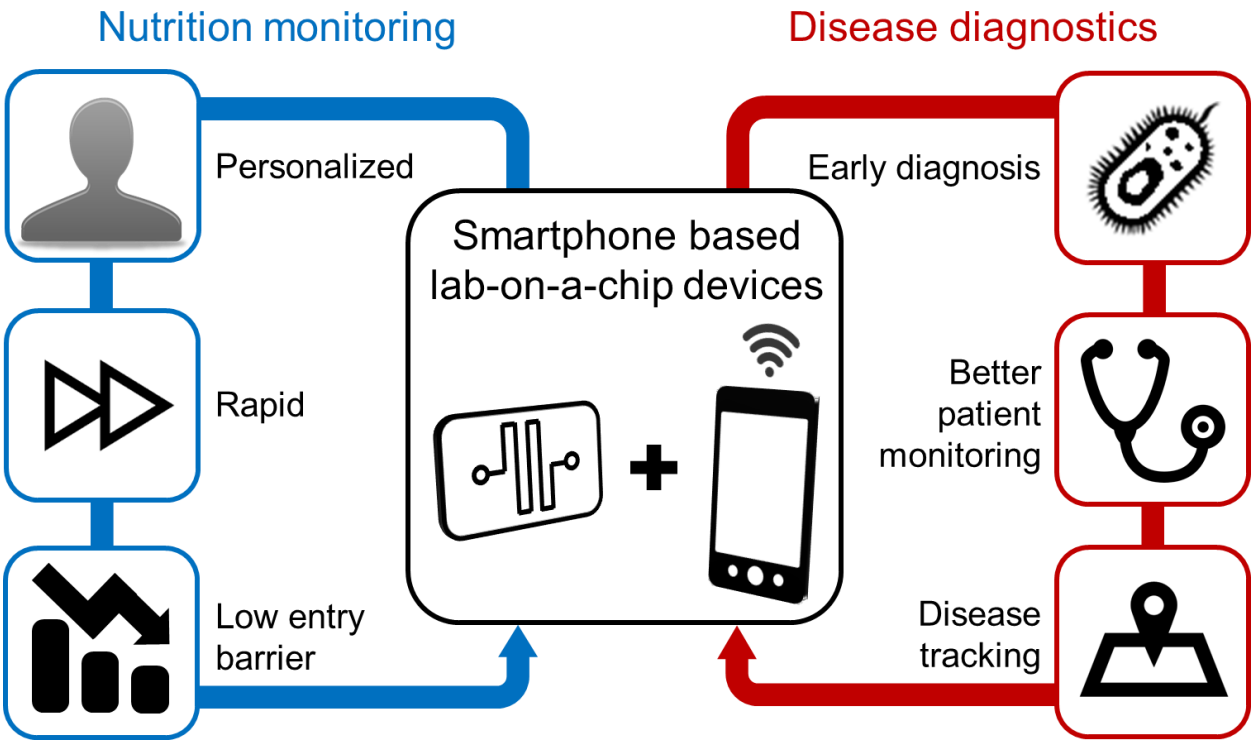

Figure 3: Smartphone based LOC technology could provide a number of important advantages for health monitoring and diagnostics. Key benefits for nutrition monitoring include personalized and rapid care with a low barrier to entry while for disease diagnostics it offers early diagnosis, better patient monitoring, and spatiotemporal tracking capability.

Example application area 1: Nutrition and micronutrient monitoring

2.6M people died from the consequences of high cholesterol in 2004 [19] and nearly 30% of all cancers in the US have been estimated to be a result of poor diet [20]. A third of the world's population is estimated to suffer from micronutrient deficiencies, with vitamin A and zinc deficiencies alone thought to be responsible for more than 1M deaths each year worldwide [21]. While the chronic social, political, and environmental challenges that are responsible for suboptimal nutrition in many parts of the world are

unlikely to be solved through the development of the technologies described herein, there are some areas where they can be impactful.

The near term impact that smartphone based monitoring can have is in enabling more rapid personalized, or at least localized, awareness of deficiencies or suboptimal nutrition through direct physiological feedback. Many nutrition problems can be controlled through changes in diet by taking supplements or other therapeutics (*e.g.* statins for cholesterol) or behavior modification. In the absence of a simple feedback mechanism it is difficult for an individual to judge how well any of these interventions are working. One relatively simple example is micronutrient deficiencies, which the Copenhagen Consensus has identified as the most cost-effective intervention to further global development and progress [22]. Domestically, the Institute of Medicine recently concluded that as many as half of older adults in the United States who had hip fractures were vitamin D deficient [23]. The problem with diagnosing micronutrient deficiencies is that they are often not clinically obvious. At present feedback is usually obtained via the cumbersome and centralized procedures that lab-on-a-chip technology was originally envisioned to disrupt (in the US this typically involves drawing blood at a phlebotomist visit, sending the sample to a centralized lab for analysis, and receiving the results weeks later at a physician's visit). Determining if interventions (*i.e.* supplements or changes in diet) have made any difference has to wait until the next visit to a physician. This feedback cycle can be expensive, slow, and lead to lower compliance.

Addressing this problem fits well into the advantages of smartphone based lab-on-chip diagnostics for a number of reasons. Firstly, the healthy ranges of most markers (*e.g.* cholesterol) are typically well defined and broadly accepted. This is useful because it simplifies the system's ability to provide direct feedback. Secondly, while deficient/non-deficient or low/good/high type non-quantitative feedback is useful, precise quantification of levels is clearly more valuable in terms of tracking outcomes. Thirdly, while the current feedback loop may be too long, it is rare that a given nutrition marker will require anything beyond periodic monitoring. This latter point is particularly important as it means that users may be willing to pay a higher

premium for the test if they do not also have to purchase a separate reader, thus reducing the barrier to entry into the market for the test. In limited resource setting environments or where access to proper nutrition may be limited, this type of technology can also be useful in helping to analyze populations quickly and help governments or NGOs provide better target nutritional interventions.

Example application area 2: Disease diagnostics in limited resource settings

Significant opportunity also exists in the development of smartphone-based lab-on-chip diagnostics for communicable (*e.g.* the flu) and non-communicable (*e.g.* certain cancers) disease diagnostics in limited resource settings. The relatively low level of infrastructure required for mobile phone networks combined with low cost mass manufacturing of handsets and relatively flexible licensing terms for some operating systems (*e.g.* Andoid) has led to relatively broad access to smartphone technology in these settings [24]. We note that while the terms "limited resource settings" and "low income countries" are often conflated, they clearly mean very different things. Both developed and less developed countries are likely to have regions that have limited access to what might be considered routine healthcare or diagnostic services elsewhere in the country. This has important consequences because it means that there are significant co-development opportunities in which technologies can be developed for limited resource settings in countries that hold the economic capacity to pay for the required research and development, while the resulting products can ultimately be deployed globally.

We see three key advantages that smartphone based lab-on-chip diagnostics can offer in limited resource settings: (1) facilitating early-stage accurate diagnosis, (2) maintaining better communication and monitoring of patients, and (3) enabling better tracking of disease outbreaks. One of the key advantages of lab-on-chip and biosensor technology is that they can produce diagnostic sensitivities and specificities that are comparable to those obtained with centralized testing without, in principle, having to go to a centralized facility. Though certainly not always true, generally speaking these higher sensitivities and specificities

can lead to early stage detection of certain diseases and, again general speaking, early detection is relatively well correlated with better mortality and morbidity outcomes. The accuracy of any molecular diagnostic procedure however is reliant on the test steps, timing, and device being used correctly. At least some of the procedural errors can be reduced simply through the incorporation of smartphones since users are likely to already be familiar with the interface and that interface has already been highly tuned to be intuitive and easy to use. Other errors can be addressed through a combination of proper training (particularly in the case which a healthcare worker is deployed to perform the test), careful device engineering, and taking advantage of the imaging, computation, and voice features of the device to determine if a test has been done correctly and troubleshoot problems. With regards to the second point, a key problem with all diagnostics that require a patient to provide a sample (e.g. blood or biopsy) which then must be assessed by a specialist at a centralized facility is in getting back in touch with the original patient after the results are available. By linking the diagnostic test to a smartphones, even if the test itself cannot be interpreted immediately and must be verified by a remote specialist, it should be easier to get back in touch with the patient to relay the results and provide instructions for further treatment. Thirdly, aggregation and spatiotemporal tagging of test results can greatly facilitate real-time tracking of disease vectors and mapping of outbreaks. Combining efforts that track indirect measures of sickness, such as social media chatter [25], with direct biomedical data could help better target interventions.

Summary

The worldwide update in smartphone-type technology represents a potentially transformative opportunity for the deployment of lab-on-chip technology. The fact that most individuals in the world carry around, or at least have access to, a robust, intuitive to use, and incredibly powerful: imaging, computation, communication, and social networking device should be accounted for in the development of future lab-on-chip devices. In this paper we have outlined why we think it will be transformative and what new

business models will result as well as outlined a couple of application areas where we believe will be impactful in the short term.

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