Critical Reviews in Clinical Laboratory Sciences

ISSN: 1040-8363 (Print) 1549-781X (Online) Journal homepage: http://www.tandfonline.com/loi/ilab20

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To cite this article: Michelle Li & Eleftherios P. Diamandis (2016) Technology-driven diagnostics: From smart doctor to smartphone, Critical Reviews in Clinical Laboratory Sciences, 53:4, 268-276, DOI: 10.3109/10408363.2016.1149689

To link to this article: http://dx.doi.org/10.3109/10408363.2016.1149689

Accepted author version posted online: 08 Feb 2016.
Published online: 07 Mar 2016.

Critical Reviews in Clinical Laboratory Sciences

http://informahealthcare.com/lab
ISSN: 1040-8363 (print), 1549-781X (electronic)

Crit Rev Clin Lab Sci, 2016; 53(4): 268–276
 DOI: 10.3109/10408363.2016.1149689

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REVIEW ARTICLE

Technology-driven diagnostics: From smart doctor to smartphone

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Abstract

This review explores recent innovations in four seemingly unrelated areas of medical diagnostics, which, when used concurrently, promise to revolutionize the future of medicine. Novel microfluidics and microelectronics, combined with smartphones, allow individuals to test themselves at anytime and anywhere, thus providing instant health information. An emerging development is the availability of genomic testing directly to consumers for assessing disease predisposition. Some organizations have opened diagnostic laboratories in pharmacies and other public outlets, are encouraging consumers to test themselves, and claim that by doing so consumers will be empowered to diagnose the early disease that could be effectively treated or prevented. Another recent development is the initiation of large studies that aim to better understand wellness and disease processes, through the frequent and sometimes continuous monitoring of hundreds or thousands of parameters. These are then analyzed by health coaches who advise participants on follow-up steps to correct the abnormalities and return to wellness. A number of these approaches have now entered the health market and the services can be purchased. It is highly likely that further technological innovations will contribute to the popularity of these approaches among millions of health-conscious consumers. However, the evidence for the effectiveness of these strategies to prevent or detect early disease, or to promote wellness, does not yet exist. We here analyze the perceived benefits and (neglected) harms of these approaches, in an effort to balance the optimism about their utility, until the evidence for their benefit is clearly demonstrated.

Abbreviations: POCT: point-of-care testing; **LOC**: lab-on-a-chip; **PCR**: polymerase chain reaction; **SpO_2**: peripheral capillary oxygen saturation; **WGS**: whole genome sequencing; **SNV**: single nucleotide variation; **PSA**: prostate-specific antigen

Keywords

Diagnostics, point-of-care testing, genome sequencing, direct-to-consumer services, wellness initiatives, self-testing, Theranos

History

Received 29 October 2015
Revised 12 January 2016
Accepted 30 January 2016
Published online 7 March 2016

Introduction

Biotechnological advancements in the past decade have paved the way for a revolutionary wave of novel diagnostic developments. Ranging from clinical point-of-care testing (POCT) to commercialized genome sequencing, to large-scale wellness pilot studies and to self-testing services, unparalleled advancements promise to create the industry of patient medicine. Revolutionizing both physician and public consumer care, these products bring more than the obvious benefits of versatility and resource-efficiency. It is crucial to be critical of the practical implementation of the technologies that are described below. The purpose of this paper is to shine a spotlight on the potential advantages and harms of these developments. Behind the publicizing and marketing for upcoming technologies and services that are posed to change the industry, it remains essential to analyze the unseen costs (including harms) that attend the perceived benefits.

New technological advances in testing

Recent improvements in biotechnology have created numerous novel diagnostic devices. Improvements in microfluidics, microelectronics, assay testing and resource efficiency have helped to advance clinical care. Decades ago, the i-STAT handheld (Abbott Point of Care, Abbott Park, IL) was a revolutionary device that measured levels of electrolytes, other markers and blood gases in the whole blood. It stood out from competing devices because it was capable of performing a wide variety of tests on 2–3 drops (approximately ~150 μl)[1]

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of blood. Samples drawn from the patient are inserted into single-use cartridges in which the assays are carried out, and then the results are read by the handheld device. Each cartridge can measure one or more analytes. The detection methods are based on potentiometric, amperometric or conductance measurements. The combined effects of portable, handheld efficiency and reduced waste were a significant advance in clinical microelectronics. Instead of sending samples to a central laboratory, patients can have their sample drawn and analyzed at the beside within 30 min. The i-STAT handheld was quickly integrated into hospital settings, satellite laboratories and doctor's offices. The extended operating capacity of the i-STAT helped to minimize costs and processing time. However, since then, bioengineering developments have assisted in setting new quality standards.

Currently, numerous devices have improved on the technology used to construct the i-STAT. A key advance in microfluidics has further lowered the sample volume requirement so that a finger prick will suffice. The Theranos system (Theranos, Palo Alto, CA) claims that it is capable of using only 25 µl of blood drawn directly with special fingerstick as opposed to a venipuncture, making the test less painful and more accessible to children[2,3]; even with a venous draw, only a small quantity of blood is needed, enough to fill their ''nanotainers.'' This reduces sample waste and increases the test per microliter ratio. Although recent diagnostic systems still use similar microelectronics platforms, advancements in lab-on-a-chip (LOC) technology have resulted in increased efficiency and lower costs (Table 1).

The flexibility of test options has also increased; the EncompassMDx system (Rheonix, Ithaca, NY) can run a fully automated polymerase chain reaction (PCR) assay using a cartridge that holds 24 samples[4]. The i-STAT, on the other hand, is capable of testing only one blood sample at a time. The rHEALTH (DNA Medical Institute, Cambridge, MA), developed for research, clinical and consumer use, can run hundreds of tests on a single drop of blood[5]. Regardless whether testing is for an electrolyte, a marker, or blood gases, the rHEALTH's nanostrip fluorescence technology can perform them all on one sample. In comparison, each of the i-STAT's cartridges can perform only specific tests so multiple blood samples have to be drawn for separate testing if the desired markers are on different cartridge types; about half of the current i-STAT cartridges are capable of testing for only a single marker[1].

The i-STAT is capable of quantifying markers only in blood samples; evolution in testing adaptability has integrated multimedia sample testing capabilities into devices, allowing an even wider range of tests to be performed. The previously mentioned EncompassMDx PCR can run tests on tissues, urine, serum, saliva and blood[4]. Another novel diagnostic system, the AgPlus (AgPlus Diagnostics, Sharnbrook, Bedfordshire, England), captures recent advancements in assay flexibility within a clinically practical environment. AgPlus is capable of accepting different sample types, ranging from blood to urine to saliva for testing, due to the compatibility of its silver nanoparticle testing system[6]. The menu offered by AgPlus is described in the link (www.agplusdiagnostics.com/technology/assay-chemistry).

Perhaps the biggest improvement made on the i-STAT and similar device is the simplification of testing steps and data delivery. This allows for crossover outside of physician-administered care to a new level of POCT. A physical sampler is electronically linked to the consumer's smartphone and results are delivered instantly via a mobile app. Easy-to-use, convenient, and efficient, smartphone testing is increasingly popular with consumers who wish to constantly monitor their health without the hassle of visiting a clinic each time. A recent prototype of a dongle, engineered by Sam Sia of Columbia University, offers highly efficient HIV and syphilis tests linked directly to a smartphone[7]. Sia has designed a cartridge that draws power via audio signals from the audio jack of a mobile phone; these waves trigger an ELISA performed within an LOC platform and results are sent back to the phone using frequency-shift keying. The assay can run in 15 min (compared to the traditional 1 h requirement for such assays) on 1 µl of blood and is relatively cheaper than laboratory methods.

Other mobile-linked systems such as Scanadu (Scanadu, Moffett Field, CA) or Cue (Cue, San Diego, CA) are capable

Table 1. Comparison of perceived benefits and harms of self-testing based on the Theranos model.

Perceived benefits	Perceived harms
Convenience: Customers can walk in at any time during pharmacy operating hours without a doctor's note for the test. The flexibility of the system promotes a patient-empowered health care.	Data interpretation: Despite access to internet sources, patients are often unable to correctly judge the significance of their marker levels. Self-interpretation of results in the absence of trained professional leads to three outcomes – trends are potentially reflective of a disease, unnecessary anxiety and expensive follow-up testing for confirmation when the disease does not exist, and false reassurance that the patient is healthy when he or she is actually at risk.
Accessibility: Being an available service at virtually any pharmacy encourages more of the public to take the test.	False positives/negatives: If the public is encouraged to monitor their health via pharmacy testing on a daily basis, even when testing is unnecessary for the asymptomatic, the number of false positives and false negatives produced by a system that only identifies the presence of a certain marker is projected to increase.
Cost: Relatively cheaper in comparison to the tests taken at larger test institutions and hospitals.	Patient–doctor relationship: In cases where the patient is convinced he/she has a disease according to results but the doctor's stance differs, conflicts of interest may arise.
Information flow: The quantified data are sent directly to the consumer. The current model has a mobile app that receives the information and can be forwarded to the family physician.	Incidental findings: If clinical professional orders a test, there are some ''packaged deals'' that allow patients to test additional multiple parameters. This promotes incidental abnormal findings (overdiagnosis).

Table 2. Comparison of perceived benefits and harms of self-testing via smartphone technology such as that of cue and scanadu.

Perceived benefits	Perceived harms
Portable convenience: The smartphone and testing apparatus can be used wherever the user is. This promotes health monitoring at any time of day.	Unreliable results: If the user is untrained in proper handling or sampling methods or is incorrectly using the system, he/she is likely to produce wrong results.
Result speed: With the computations at fingertips, the analyzed data are usually delivered to the user in minutes. The minimal timeframe testing allows it to be fitted into most daily schedules.	Mechanical malfunctions: Current smartphone testing devices are not of the same grade as professional machines and tampered with mechanical malfunctions. Some systems require visual identification (Scanadu) which is a less reliant technology.
	Data leak: Personal health testing information is generally kept private but this privacy can be breached if the data are not kept secure on a mobile platform.

of performing tests on such samples as urine or blood/saliva/nasal swab samples, respectively (Table 2). The tests are performed on microchips and the results are transferred to the user's mobile device. The data are then made readable by an interface application and can be interpreted by the user or the doctor[8,9]. The previously mentioned rHEALTH provides a similar invention – a physical patch that the consumer sticks onto their body to constantly measure physiological changes throughout the day — eliminates the need for constant resampling; the data are sent wirelessly to a smartphone[10]. Today, smartphones even have built-in heart rate sensors and peripheral capillary oxygen saturation (SpO_2) readers[11]. Consumers are motivated to keep track of their physiological condition so they can detect irregular trends and potentially, early disease when they are still in the asymptomatic stage. The issues with consumer data interpretation will be discussed later in conjunction with self-testing services provided by companies such as Theranos.

A rapidly evolving sector in POCT is the focus on improving diagnostic testing in third world countries and in diseases-stricken areas. In light of recent Ebola and MERS outbreaks and the long-time devastating effects of HIV in Africa, devices have been designed to detect specific markers, which, when present or at high levels, signify disease. The qualifications for such inventions include ease of use, low cost and portability to maximize accessibility and usability in these areas. BioFire system (BioFire Diagnostics, Salt Lake City, UT) has designed a Biothreat-E assay to detect Ebola in whole blood, plasma or serum samples[12]. The test runs on the BioFire Film Array, a PCR system to detect biological warfare agents with a specific purpose of guiding individual patient treatment in military situations[13]. The Film Array requires minimal manual set up for a fully automated 1-h process. An RT-PCR assay has also been designed for the detection of genes corresponding to the MERS-CoV infection[14]. QuantuMDx (QuantuMDx, Chattanooga, TN) is already developing tests for malaria, tuberculosis and other diseases that can run in under 10 min[15]. All these projects are funded by health organizations and charities advocating for medical equality in third world countries. Recent technological advancements over the i-STAT handheld are summarized in Figure 1.

Direct-to-consumer testing

New methodologies are also broadening our understanding of disease pathology and origins. Whole genome sequencing (WGS) can determine an organism's entire DNA sequence from a small biological sample. In recent years, the Human Genome Project has accomplished the feat of recording over 99% of the genome (3 billion base pairs). The main motivation behind creating a map of the human genome is to be able to identify underlying factors that contribute to genetic conditions. When a sample is compared to the complete reference genome sequence, mutations and inborn patterns associated with predisposed diseases can be detected. Now, we are able to better identify cancer mutations between generations, link diseases to mutations and create individualized treatment plans based on a patient's genome[16].

Technical difficulties with sequencing include false-positive single nucleotide variations (SNV) read by the machine. Despite having a relatively low error read rate of 1 SNV per 500 kbp, WGS must sequence 3 billion base pairs per human sample, which results in 12 000 false-positive SNVs overall. The difficulty lies in verifying false-positive SNVs, which requires additional testing. Furthermore, WGS variations between platforms is also responsible for differences in SNVs[17]. These misreads severely impact the interpretation of genes and mutations; the difference of a single nucleotide could result in interpreting a normal variant as a pathogenic one, and vice versa. This leads to patient anxiety and further costs for verification tests[15]. These shortcomings will be addressed later.

Such technologies as deep RNA sequencing and proteomics have also evolved with similar premises, although these methods are less comprehensive because RNA and protein levels are not completely reflective of physiological conditions; nevertheless, they give patients an idea of their wellbeing[18,19]. A key step that has revolutionized the way in which the public perceives these technologies is the commercialization of such testing. The advancement in sequencing efficiency means that companies can offer the same services, usually performed for scientific reasons, to the public for a relatively small sum of money.

In recent years, corporations such as 23andMe (23andMe, Mountain View, CA) and Gene by Gene (Gene by Gene, Houston, TX) have nurtured a new market of consumers who are eager to understand their genetic composition. This audience's main motivation is to test for mutations that may signal an increased risk for a specific disease[20,21]. Yet, in many circumstances, treatment cannot or should not be started, because either the treatment does not exist or it poses a bigger health risk to treat than to not treat. 23andMe analyzes samples provided by the patients in order to

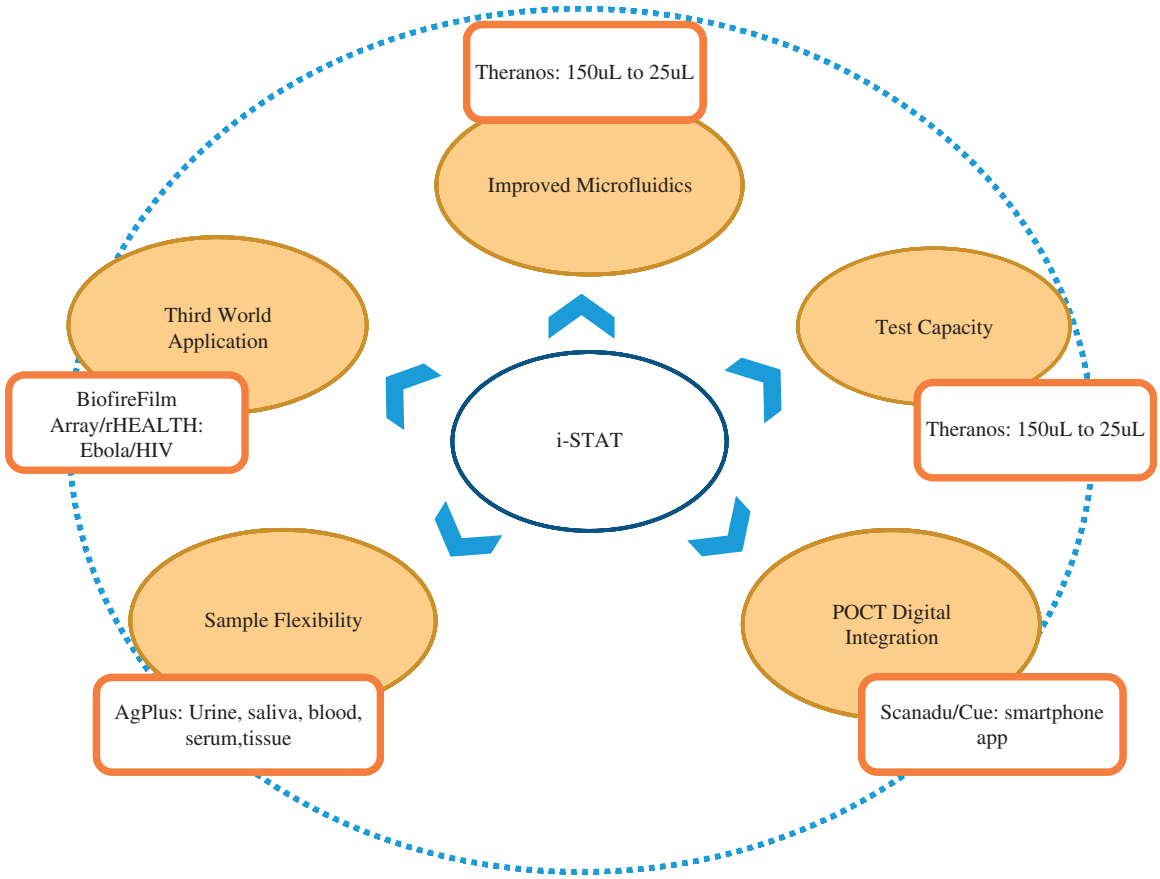

Figure 1. Advancements in point-of-care testing since Abbott's i-STAT. Developments in various areas of technology have driven the market to give birth to increasingly versatile and function-specific products. Microfluidics, test capacity, digital integration, sample media and application have been improved upon, to deliver more targeted care.

determine genetic, ancestral or other disease-related information. The samples are collected in kits that are shipped from and back to the company, allowing these sequencing technologies to be widely accessible to a large population[22]. Available tests include reports on inherited conditions such as cystic fibrosis and tyrosinemia, and potential genetic risks for hemochromatosis, celiac disease and more. By identifying an increased likelihood of these diseases, consumers hope that early action will either prevent the disease or help prepare them for the future. 23andMe also analyzes gene sequences to determine a consumer's response to drugs such as clopidogrel, a platelet aggregation inhibitor used to thin blood; if the patient is a poor metabolizer, the amount of drug administered would be adjusted to provide a therapeutic level.

Finally, heritable traits such as pain sensitivity and caffeine metabolism can be traced; such information is geared to customize lifestyles so that consumers are more aware of physiological factors when they make everyday decisions.

Gene by Gene offers a similar product – WGS with Illumina HiSeq for hundreds of genes that correspond to genetic conditions or diseases[23]. A consultant interprets the results before determining the risk for a condition. Gene by Gene also offers exome sequencing and mitochondrial DNA sequencing with next-generation sequencing to identify an even wider class of variants. The motivation for a deeper understanding of one's genes drives the market for these direct-to-consumer services. As the cost of sequencing continues to fall, more members of the public are being encouraged to sequence their genome so they are aware of potential factors. As described by Lu et al., the consumer sequencing campaign can lead to revolutionary changes in the future as the cost to sequence the genome dips below a doctor's examination; this has the potential to replace visits to physician's offices[24]. However, with this relatively novel technology, several obstacles are yet to be resolved[25].

Sequencing, like other analytical technologies, has many methodological and technical issues. As mentioned before, error sequencing rates and platform variability heavily impact our interpretations based on a limited knowledge base. Despite having sequenced all 3 billion base pairs of the human genome, we understand only a fraction of what we detect. Besides identifying a mutation variant, we have limited knowledge as to whether the mutation is pathogenic or non-pathogenic[26]. It is estimated that only 25 000 protein-coding genes have been found whereas the number of gene-regulated transcripts is 10- to 20-fold this number[27]. Our ability to interpret such data are slowly growing but still severely lacking. Furthermore, a genetic mutation may not be an indicator of the phenotype. A large portion of gene expression is controlled by environmental factors, making genome sequencing highly unpredictive of real-time conditions[28,29]. We have difficulty in telling how and if the gene will be expressed at all, and thus, a mutation finding may not affect the patient at all. We also risk unintentionally finding mutations for other diseases when sequencing for a particular gene. There is controversy surrounding whether incidental

findings should be revealed to minors; the lack of regulation around information disclosure undermines the moral ethics of sequencing[30]. Overall, the underdeveloped protocols for sequencing services and the uncertainty of the significance of sequenced information results in the delivery of much less useful information than customers expected based on the promotional material that they saw.

Wellness initiatives

Wellness initiatives and long-term health projects that use a similar approach to the consumer gene sequencing described above are an unprecedented trend that has emerged in the last decade. Headed by teams of researchers and wellness experts, these endeavors aim to study test populations of subjects in their natural environments so as to identify the course of development of certain diseases. These conditions are often ''nurture''-oriented or are heavily impacted by lifestyle choices made by these volunteers; by closely monitoring their actions and choices, researchers hope to pinpoint the underlying causes of common maladies such as diabetes and obesity (Table 3).

The 100K Wellness Project, an initiative of the Institute for Systems Biology (Institute for Systems Biology, Seattle, WA), which is recruiting 100 000 healthy participants, is examining them and their genome, proteome, phenotype and epigenome at 3-month intervals, and will monitored them over a 20- to 30-year period[31]. Parameters such as the brain, heart and colon activity are monitored using wrist sensors and blood and stool samples. Other lifestyle aspects such as sleep cycles, nutrition intake and activity levels are also recorded. After some time, the data on subjects that remain healthy and those who progress to worse health will be analyzed separately. This long-term study aims to provide researchers with an extensive database of information to detect trends and habits as sources of disease as well as promoters of wellness. Potentially, early markers and disease mechanisms can be identified along the way. This information, extracted from a diverse group of volunteers, may potentially benefit the public and researchers who can build upon these studies. Dr. Leroy Hood, the founder of the 100K project, says that recent data and developments from this project are fueling discoveries about wellness lifestyle maintenance but he remains vague as to what the findings are. He claims that the pilot stage of this project has uncovered useful information about microbiome impacts and living factors[32].

Dr. Hood has recently created a new longitudinal service called Arivale (Arivale, Seattle, WA). The company offers not only genome examination and interpretation, like 23andMe, but also analyzes a wide range of metrics, from gut microbiome to lifestyle, in order to provide optimal suggestions to achieve ''wellness''[33]. The company also provides a personal coach that monitors the consumer's health and gives customized feedback. Those who use these wellness services like to feel in control of their lives by knowing details of their physiology and making improvements to live a healthier life.

A similar endeavor titled the Lake Nona Life project (Lake Nona Life Project, Orlando, FL) takes place within a closed community where participants can choose to live or work. Researchers perform similar tests and surveys in the onsite laboratory, where they examine lifestyle choices[34]. The project aims to test the effects of a health-oriented setting and help the participants to improve their longevity and wellness. Specific risk targets include the impact of sleep deprivation, missed breakfasts and excessive alcohol consumption on the participants. The motivation behind this long-term, the large-scale experiment is to provide individuals (current participants, and in the future, the public) with customized treatment plans based on their lifestyle and other factors that may otherwise not be detected using current medical standards. The study tries to account for hard-to-predict environmental factors that have as strong an impact as current drugs.

Many wellness initiatives with similar goals, each with a different subject group and range of prospective tests, have started in the past decade. The National Institutes of Health (NIH) are planning to launch the Million-person Precision Medicine Initiative Cohort, a volunteer-based research project that aims to involve a large participant base[35]. NIH researchers agree that a million-personal national study would reflect the population diversity and would greatly benefit their projects. A large sample platform would also

Table 3. Comparison of perceived benefits and harms of a customized health coach such as vida offers.

Perceived benefits	Perceived harms
Customized: Multiple professionals specializing in different fields are able to construct a plan catered to an individual's lifestyle.	Insufficient information: Very little can be concluded by testing the heart rate, SpO_2, or other parameters within the capacity of a smartwatch or directly from a phone (non-invasive). Consumers and professionals communicating over a screen may put too much emphasis on these numbers or trends.
Communication: Daily reminders and weekly video meetings aim to keep the user on track to their goals.	Variability in tests: Depending on the time of day, activity level and a variety of different environmental factors, tested parameters vary greatly and may cause unneeded anxiety in unfamiliar patients.
	Recording consistency: The majority of smartwatches and phone models require the user to manually initiate the test. If the user forgets to input data at regular intervals, the information available to the smartphone application or health coach for interpretation may be a misrepresentation of real conditions.
	Uneasy stress: Users may feel anxiety when they are not meeting their goals because their data are constantly recorded and sent to specialists. They may also feel stress if a text message or video call is initiated to notify them of abnormal trends.

assist in identifying patients with a variety of diseases. Although a leading research question has yet to be identified, the National Heart, Lung, and Blood Institute expressed great interest as well as proposed to focus on drug treatment responses, risk and prospective disease factors and clinical care implementation. The scientific value of such an endeavor, potentially to include child volunteers, would be immense in the research community.

Google's Baseline Study (Google, Mountain View, CA), run by the research-oriented arm, Google X, of the technology mogul, is planning in a similar way to use their resources and sample thousands of anonymous people on an international basis[36]. With the incorporation of technology, Google X aims to collect data in a more sophisticated way. For example, it is speculated that users may wear special contact lenses that constantly measure glucose levels. Other technology companies have also jumped on the bandwagon: Samsung introduced the SimBand prototype (Samsung Strategy and Innovation Center, Menlo Park, CA), a wearable wrist screen that tracks blood flow, hydration and other parameters that inform the user of daily trends[37]. The increased convenience and apparent benefit of mass data accumulation has motivated the public to embrace the birth of population wellness initiatives. Yet, evolving technology that constantly monitors an individual's systems raises the question of privacy and security. At any time of the day, information is being transmitted from these devices to a database that is analyzing body trends. The storage of mass biodata by large corporations the risk of data leaks into the hands of institutions such as insurance companies where the collected information could be used against the test subjects.

If people feel uncomfortable having a robot monitor them, the smartphone market provides a more humane alternative. Health apps such as Vida (Vida, San Francisco, CA) act as a ''24/7 health coach'' by transferring data to dieticians, nurses, personal trainers and physicians[38]. These specialists will analyze your data and reply via text messages and video check-ins. Services include analyzing sleep routines, activity and nutrition intake to customize a daily plan. Customers can use Vida to maintain low cholesterol levels, lose weight, prevent diabetes or reduce stress. As yet, the notion of regular data monitoring is simply an idea; customers have not yet experienced data cloud software that tracks their every move. Such invasion of privacy may be a fear for many users.

Testing for the masses

Another addition to social diagnostics is the self-testing model advocated by new patient-empowered care companies such as Theranos. The CEO and founder of this multibillion-dollar company, Elizabeth Holmes, claims that her technology could revolutionize public access to diagnostic tests[3]. Her patented systems aim to perform a wide menu of tests on a small sample of blood taken using a specialized finger prick device. Appointments can be booked directly from an application and results are delivered electronically to an application on the patient's smartphone[39]. The primary selling point of her service is the digital fluidity and physical flexibility of the tests. Consumers can walk into a pharmacy and test for a marker for a relatively low cost; the results come back privately to the patient in a few hours. The smartphone app helps to track trends and abnormalities with the tested values and is supposed to detect early signs of disease progression. By foregoing a doctor's requisition and a physical visit, patients are empowered to administer these tests outside the clinical setting and at their own discretion.

Similar technologies have been envisioned by IMEC (Imec, Leuven, Belgium), a world leader in nanotechnology, which predicts that advancements in LOC integration into POCT will propagate miniature chip testers that can be purchased at drug stores[40]. These testers would accept a finger prick blood sample and sort through 2 million cells per second. The technology is based on scatter patterns created by cells and measured by a sensor. Results are conveniently transferred digitally to a mobile app that can forward them to the family physician. This creates a wall between the patient and the doctor; patients can access their test results and the reference ranges on the internet and may develop preconceptions that prevent their doctors from carrying out their responsibilities. The patient can interpret their own data before the doctor sees it; the benefits of this empowerment are disputable and later discussed in the overdiagnosis section. This may enable self-diagnostic technology to permeate an even larger fraction of the public, increasing not only the demand for this service but also the need to constantly track one's physiological condition. A video describing IMEC's approach can be found at the link: https://vimeo.com/108889853.

Testing for the masses becomes problematic when the data are not passed through a professional *en route* to the patient. Tests performed at pharmacies are left to the individual's discretion to interpret; this new-found form of independence may cause numerous issues to arise. Despite having access to Google and online medical consulting sources, it is difficult for a lay person to correctly interpret whether he/she is at risk for a disease. First, the reference range is not an absolute measurement for confirming the presence or absence of the disease; since the ''healthy'' physiology of individuals varies, marker quantification is only a portion of the larger diagnostic picture. However, the lay person may put great emphasis on this number[3]. Second, prior to diagnosing disease, clinical professionals consider the trend of results and external factors that may affect readings. Depending on the time of day, activity level, nutrition intake and other environmental parameters, the marker reading may vary greatly. Without considering the impact of such factors (e.g. testing at a time that is convenient for the patient rather than at the optimal time), patients may interpret the trends of multiple results incorrectly. If their marker levels are outside the ''healthy range'' found on the internet or if an abnormal variation is observed over a period of time, this will cause patient anxiety. Neither the exact level nor the rise and fall in a marker level may be entirely representative of a condition, yet this can easily be interpreted to be so without physician-facilitated testing. A fictional but potentially likely scenario of self-testing and self-interpretation is illustrated in Figure 2.

The diagnosis of a disease requires a trained physician to accurately gauge and assess signs and symptoms, and testing data in context; the numbers themselves may not be entirely representative due to the nature of the tests, and to low

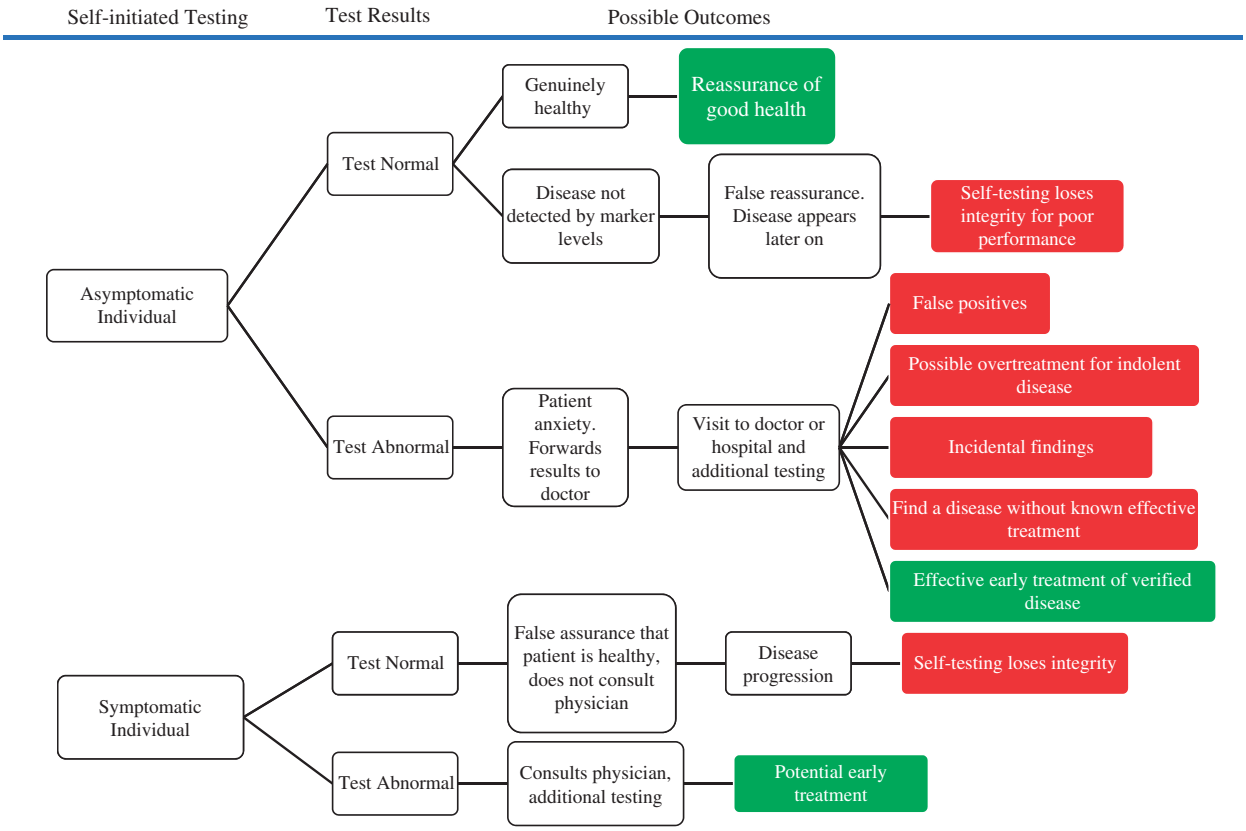

Figure 2. The hypothetical scenario of a patient who performs self-testing following the Theranos or similar models. A predicted system of response to results of self-testing leads to various favorable and unfavorable outcomes, colored green (light gray in print edition) and red (dark gray in print edition), respectively.

positive and negative predictive values of diagnostic tests in this setting. Thus, interpretation of results solely by the patient may lead to unneeded stress, doctor visits, additional testing, and health care expenses.

Overdiagnosis and incidental findings

Other critical components brought on by the wave of consumer-empowered testing are the harms of overdiagnosis and overtreatment[41]. The increase in available diagnostic tests that bypass clinical oversight encourages members of the public, especially asymptomatic individuals, to test themselves. As discussed before, this may result in abnormal but harmless findings. For a worried patient, excessive tests at the doctor's office or in other settings often reveal incidental conditions (termed incidentalomas) that may never affect a patient in their lifetime. Despite the absence of health risk posed by such findings, doctors or patients will be tempted to treat, sometimes with significant side-effects. For example, the level of serum prostate-specific antigen, a commonly-used marker for prostate cancer, correlates with tumor stage. A trial done by the Center for Chronic Disease Outcomes discovered that radical prostatectomy did not significantly increase the chances of survival compared to observation without surgery[42]. This implies that some indolent cancers will not pose a threat within the patient's lifetime, and unnecessary treatment is stressful and financially costly.

Furthermore, not all incidentalomas must be surgically excised. Adrenal masses are commonly discovered during imaging; the discovery of these incidentalomas is correlated with the frequency of radiographic imaging[43]. Frequently, the mass is identified as an adrenal cortical adenoma, which are considered benign and do not have malignancy potential. Another extremely rare diagnosis is that of adrenal cortical carcinoma, a malignant cancer that occurs with an incidence rate of 1 in 1.7 million in Americans[44]. Treating an adrenal adenoma as an adrenal carcinoma and surgically removing the benign mass has proven to be extremely harmful because this may cause the patient to develop severe adrenal deficiency. Most adenomas remain asymptomatic but, for the 20% responsible for Cushing syndrome, cortisol-inhibiting drugs can be used without tumor excision.

Despite the recent hype surrounding detecting diseases early, it is important to keep in mind that some diagnostic tests are ineffective and expensive and do more harm than good[39,43,44]. Furthermore, the patient age at which medically directed screening is performed is set to maximize efficiency. Early and persistent screening may result in the discovery of incidentalomas or produce harmful effects (e.g. radiation, bleeding)[39]. Late screening is ineffective because the benefits of treatment are outweighed by the costs in the short lifespan left[45,46]. Sometimes, less screening and treatment produces a better patient outcome, which is the optimal goal of healthcare.

Another form of harm from overdiagnosis exists when the doctor uses a treatment that has not been proven to be effective, has minimal beneficial effects, or, in extreme cases, has been shown to have negative effects. For example, over 40% of US adults have hypertension but more than half of those may have minimal risk[47]. However, a large majority

Table 4. Summary of companies and projects representative of novel diagnostics, direct-to-consumer services and wellness projects.

Name of company/project		Description of purpose
Technology diagnostics	i-STAT	Well-established diagnostic care in hospital and other clinical settings. Capable of measuring electrolytes, other markers and gas levels with a specialized cartridge. Results are returned in minutes by a handheld reader.
	Theranos	Fingerstick and nanotube aim to fluidify self-testing process in pharmacies. Model hopes to increase diagnostic accessibility to the public. Hundreds of markers in test menu for one drop of blood.
	rHEALTH	Hundreds of tests from the diverse menu can be run on a single drop of blood without cartridge swap between tests. Attachable patch that monitors vitals on the patient.
	Scanadu	Urinary pads produce quantitative results scannable by smartphone. Mobile and portable convenience for the consumer.
	Cue	Sample collector can accept different sample types; tests easily performed without blood draw, results linked to the mobile phone. Limited tests available.
Direct-to-consumer providers	23andMe	Genome SNV and sequencing services; internationally accessible. Genetic information provided concerning inherited conditions, drug response and phenotypic traits.
	Gene by Gene	Hundreds of genes available for sequencing. Exome and mitochondrial genome sequencing available.
	Arivale	Package includes wide-ranging testing; personal coach gives advice based on levels; optimize wellness.
Ongoing wellness projects	100K Wellness	Large selection of participants is closely monitored over long time periods; sleep activity, exercise, diets, microbiome and genetic information is recorded frequently. Trends that lead to healthy or diseased outcomes may reveal important keys to living well.
	Lake Nona Life Project	Volunteers either work or live in the Lake Nona community and are closely monitored. Surveys and data measurements are performed regularly.
	Google Baseline Study	Potentially to involve participants from an international stage using monitoring technology such as glucose-reading contact lenses to mass collect data.

receive overtreatment through the prescription of a common and unneeded blood pressure-lowering drugs, even though the success rates and prevented death rates have yet to be determined. This unnecessary practice alone is estimated to cost the US healthcare system $32 billion. Such overtreatment is often fueled by stereotypes surrounding diseases severity and the extent to which treatment should be initiated.

Conclusion and future predictions

The technological developments described above, combined with other advances in the field of clinical diagnostics and public testing services, are part of an unprecedented revolution that will depart from the traditional structural system and bring a new focus on cost efficacy and patient convenience. Increasingly specialized and effective POCT models are built on the diagnostic foundations laid out by the i-STAT handheld; services to customize treatments by delivering information on a personally-sequenced genome, mass pilot studies to map the influence of external factors on health, and wide-spread, patient-oriented, self-testing centers bring a new era of change for professionals and the public. In the future, perhaps, there will be advancements in the industry that help us to seamlessly integrate these innovations into everyday life; undoubtedly, at present, there is already a niche to explore and enlarge. Yet, it is important to remain cautious about technological advancements that open up new information that may negatively harm the user. Potential detriments presented in this review focus on critical shortcomings if and when the technology is fully implemented. With an optimistic outlook, we hope that these dangers will be acknowledged and addressed in full. The future is open. The best advances will contribute significantly to our healthcare; it is up to us to create, choose and present the optimal solutions.

Declaration of interest

The authors declare no conflicts.

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