Clinical Chemistry 63:3
635–641 (2017)

Direct-to-Consumer Testing

Moderators: Michelle Li[1] and Eleftherios P. Diamandis[1,2,3*]
Experts: David Grenache,[4] Michael J. Joyner,[5] Daniel T. Holmes,[6] and Rodger Seccombe[7]

Due to technological advancements, self-testing has become widely accessible to the public. Individuals can opt to have their genome sequenced or their blood tested for markers at a relatively cheap price. These direct-to-consumer services are essentially a commercialization of technologies being marketed to the general masses.

Some genomic giants in the industry include 23andMe and Gene by Gene. Their test kits can be delivered internationally and sampling is performed by the user and sent back for laboratory analysis, thus establishing an accessible and flexible service model. Users can opt to test for specific genes that correspond to a potential disease or learn about disease predisposition, drug responses, or genetic characteristics.

Other companies offer to quantify a range of biomarkers that can potentially predict the early onset of a disease or condition. Their kiosks and laboratories are situated within pharmacies and the blood tests can be performed without a physician's consent. The results are then electronically delivered to a physician or directly to the consumer, and are subject to self-interpretation.

The underlying notion is that such testing may uncover abnormalities that could potentially serve as an early marker of disease. By identifying this pathogenic link at an early, asymptomatic stage, the consumer can possibly take steps to prevent disease later on. However, it is important to keep in mind that due to epigenetics, environmental and other factors a gene sequence is not always reflective of a phenotype. The sequencing only provides minimal information about a possible genetic foundation, yet ambiguous gene expression deems results inconclusive. Likewise, testing for biomarker concentrations in the blood is not necessarily a reflection of a patient's condition. Due to the large variability in individual physiology, there can be ambiguity with self-interpretation. Despite having access to reference ranges/intervals from online sources, many patients are in a poor position to judge their own health. Factors such as lifestyle, time of day, eating patterns, and ethnicity heavily affect results; for these reasons, a physician may be best positioned to analyze results.

Here, we ask 4 individuals about their opinions on various aspects of direct-to-consumer testing.

Do you think whole genome sequencing in 2016 is beneficial in some shape or form to the majority of consumers?

David Grenache: It depends on what one considers beneficial. For some individuals, simply having access to their unique genetic information is itself the benefit, regardless of whether or not it is actionable. For others it's the knowledge of ancestry that accompanies direct-to-consumer genetic testing services that's of value. As with any service or product, the consumer makes the determination regarding value. Why should genetic information, or any laboratory test for that matter, be any different? That said, consumers of sequencing tests must be fully aware of the limitations of whole genome sequencing results and need to be educated about what these data can and cannot reveal about health and health risks.

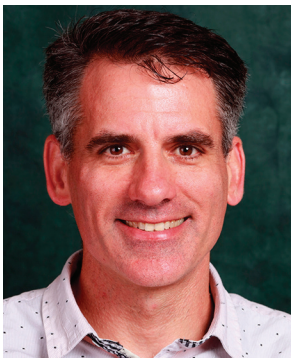
Michael J. Joyner: No, I believe this is a niche technology best used for research purposes and to investigate rare diseases that are difficult to diagnose or that are "one-offs." To do the latter it will need to be part of a comprehensive rare diseases or clinical genetics evaluation. This sort of testing is already providing causal insights in some but not all cases. Un-

[1] Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON, Canada; [2] Department of Clinical Biochemistry, University Health Network, Toronto, ON, Canada; [3] Department of Pathology and Laboratory Medicine, Mount Sinai Hospital, Toronto, ON, Canada; [4] Professor, Department of Pathology, University of Utah, Salt Lake City, Utah; [5] Caywood Professor of Anesthesiology, Distinguished Mayo Investigator, Mayo Clinic, Rochester, MN; [6] Division Head, Clinical Chemistry, St. Paul's Hospital Department of Pathology and Laboratory Medicine, Vancouver, BC, Canada; [7] Co-Founder and CEO, HealthTab Inc., Vancouver, BC, Canada.

* Address correspondence to this author at: Clin Biochem Section, 60 Murray St., 6th Floor Toronto, On, Canada, M5G 1X5. Fax 416-586-8628; e-mail Eleftherios.diamandis@sinaihealthsystem.ca.

Received May 3, 2016; accepted June 30, 2016.

fortunately, in many cases it does not lead to a beneficial therapeutic intervention but can help families think about future reproductive options and testing. In cases like channelopathies and sudden death in the young, a sort of "genetic purgatory" has emerged where an apparently causal DNA variant in the case is also seen in healthy relatives. Then the question is literally about who does or does not get an implantable defibrillator based on what criteria. For most issues in this area there are no easy answers and the potential for less than ideal unintended consequences and ambiguity is substantial.



Daniel T. Holmes: I think the key phrase in this question is "to the majority of consumers." My position is that presently it is generally not medically beneficial to the majority of consumers but may be useful in specific contexts. Consumers can receive various products from these companies. For example, they can purchase a single nucleotide polymorphism analysis but the clinical inferences one can make from single nucleotide polymorphisms are frequently of little value. How should a consumer respond to, "You have a 7.3% increased risk of disease X"? Accordingly, this type of report has been subject to regulatory limitation in North America due to the ambiguity of available evidence. Consumers can also receive ancestry reports, primarily for personal interest and carrier-status and drug-sensitivity reports, which may have utility in select circumstances. Finally, they can receive reports about certain well defined but medically banal Mendelian traits such as whether their earwax is crusty or slimy (no, I am not kidding).

Rodger Seccombe: While there remains a substantial gap between our current ability to complete vs effectively interpret a whole human genome sequence, we are already seeing the benefits of whole genome sequencing as a tool to help diagnose and treat rare diseases in symptomatic individuals, such as in England's 100 000 Genomes Project. The average curious consumer might also benefit in some ways. However, for most individuals, the insights gained would not justify the expense of completing a whole sequence.

Given the limitations of our current genomic knowledge base, the majority of whole genome sequencing consumers would not receive much "actionable" information beyond the basic pharmacogenomic and carrier status reporting that can be obtained from less costly genotyping services. That said, however, new discoveries are being made by comparing entire genomes. So on some level we are all benefiting from those individuals who are completing and agreeing to share their whole genome sequences for research.

How reflective of a patient's health are sequencing and blood testing results?

David Grenache: It depends on the gene associated with the sequence or the particular analyte being evaluated in the blood test. It's well known that many DNA polymorphisms have no effect on one's health while others are very predictive of disease. The result of any blood test represents a small snapshot in time captured at the moment of phlebotomy. No single test is capable of being reflective of "health" any more than a single word can reflect the plot story of a novel.

Michael J. Joyner: For the average person the results are likely to be of marginal or no benefit and difficult to put into context. A large issue here is the so-called incidentalome, which would reveal the presence of "pathologic" variants in individuals who are phenotypically normal.

Daniel T. Holmes: With respect to sequencing, in certain contexts, for example where there is a yet undiagnosed or subclinical monogenic disorder, the data could be very useful and reflective of the patient's current or future health. But this scenario would certainly represent the exception and not the rule.

The same is true of blood testing. Untargeted use of blood tests is more likely to lead to confusion and waste because of the Bayesian principle that as the disease prevalence approaches 0, the positive predictive value of the test approaches 0. This means that performing a nonindicated test leads to diagnostic confusion, further testing, and referrals.

If we factor in the principle that most reference intervals are based on the central 95%, then the probability that at least one test falls outside its reference interval by chance alone is $1-0.95^n$, when n tests are performed. This probability exceeds 50% for 14 or more tests.

There is also an implicit assumption that results inside the reference interval imply health and results outside the reference interval imply pathology. However, results outside the reference interval don't always imply pathology and there can be "inappropriately normal" results that are highly pathological, e.g., a TSH (thyroid-stimulating hormone) of 2.5 mIU/L that looks ostensibly

normal would be indicative of secondary hypothyroidism if the free thyroxine were 0.60 ng/dL (6.4 pmol/L).

Rodger Seccombe: We know that for certain disease states, some genetic mutations and serum biomarkers (particularly once confirmed) can be highly reflective of a patient's current health or even diagnostic in and of themselves. This is possible, in part, due to extensive research and standardization of laboratory testing for certain analytes, such as hemoglobin A_{1c}, creatinine/eGFR (estimated glomerular filtration rate), and lipids. Other results and genetic findings are not as well known, standardized, or uniquely predictive. However, they can still be important indicators when evaluated as a group and in the context of a patient's history and symptoms.

As technology enables more health- and lifestyle-related data points to be made accessible and analyzed in aggregate over time, the current and likely future state of a patient's health will become more certain. Until then, genomic sequencing and blood test results will reveal only part of the story.

What is your opinion on commercializing genome/exome sequencing to the masses? Is the motivation mainly for profit?

David Grenache: What motivates any individual to launch a company or provide a service? In an economic system based on capitalism, profiting from the sale of a product is necessary but that doesn't mean it's the main motivator. One could ask the same question of hospitals and healthcare delivery systems that often make huge profits from laboratory services because their charges are marked-up greatly, vary widely, and are not transparent. I believe we are at the threshold of a new era in medicine, one in which patients are growing much more engaged in how decisions are made regarding their care and are demanding access to information that, until recently, has not been easily available to them. Now that information is becoming increasingly available and at prices that are simultaneously transparent and affordable.

Michael J. Joyner: I believe some of the motivation is for profit. I also believe that this is a bit of a Trojan horse effort to get health information and DNA from a large sample in an effort to generate "big data" and look for rare variants that might give insights into potentially "druggable" or therapeutic targets. The goal at some level is to find the next proprotein convertase subtilisin/kexin type 9–like target.

Daniel T. Holmes: This appears a profit-motivated business directed at the well heeled, worried, and curious well. If this were about the good of humankind, we would expect philanthropic organizations working to bring these services to the underprivileged of the world, which they are not doing.

Rodger Seccombe: For-profit companies have been making significant investments to provide genomic services to the public, ultimately to create and return value to their shareholders. While there's a clear profit motive, these efforts also help fuel advancements in the underlying technology and enable new scientific discoveries.

As demand grows for these services, we will need to ensure the necessary safeguards are in place to protect the public's genetic information. For example, enacting new legislation, such as proposed Bill S-201 in Canada, to prohibit and prevent discrimination from insurance companies, employers, or others based on genetic characteristics.

What are the pros and cons of making self-testing accessible at pharmacies without a physician's oversight?

David Grenache: I see several benefits. Patients are becoming active consumers of medical information and are becoming more educated about their health. As such, they rightfully demand more control and access to personal health information. There are known benefits of patient self-testing, particularly when it comes to the management of chronic diseases like diabetes. Cost is always a concern, even more so for patients without health insurance or for those with high deductible insurance plans. Direct-to-consumer laboratory testing companies have price transparency and offer their services at a cost that is usually considerably lower than what would be charged in a hospital or reference clinical laboratory. One disadvantage is that easy and affordable access to laboratory tests could prompt some patients to over indulge, with the unintended consequence of initiating a cascade of events due to the inevitable false positive result. The disadvantage I hear voiced most frequently is that patients won't understand the results or will misinterpret them. I don't completely disagree with this but I do think that patient's who are engaged enough to use these services are motivated to learn what tests to consider and understand what test results mean. There is a great opportunity here for clinical laboratory professionals to be leaders in this patient education, which would have the added advantage of raising public awareness of the role we play in healthcare delivery.

Michael J. Joyner: I see no pros. I see only issues related to a reduction in quality and things being interpreted out of context.

Daniel T. Holmes: Are there pros? I suppose if someone checked their lipids or fasting blood glucose and obtained

increased results, this might spur them to see their physician. But they could get this self-same testing (essentially) free-of-charge though the medical system in Canada and through their usual insured care in the United States.

I see a number of cons, the first being device performance. Neither pharmacists nor consumers have a means to scientifically or clinically validate the performance of any analytical device, point-of-care or otherwise. The device's performance is evaluated not on accuracy and imprecision, but on its usability. The consequence is that a device can be underperforming without consumer or pharmacist's knowledge—even for an extended period—as illustrated by the regulatory and media reports on Theranos and its Edison device. When physicians are part of the equation, in both the laboratory and clinical care contexts, they can vet the data both scientifically and clinically, ensuring the consumers' safety and cost value.

Local to my university, HealthTab is offering direct-to-patient testing for some tests on the Piccolo Xpress device. We have one of these instruments at our hospital. While some analytes compare reasonably to core analyzers, others have very problematic bias and/or correlation problems.

The second con relates to regulatory and quality issues. Are direct-to-consumer laboratories required to conform to accreditation standards? Are they required to submit to an external quality assessment program?

Other quality-related issues exist. What do direct-to-consumer laboratories do with critical values? Who is medically and legally responsible if an abnormal result goes unaddressed and there are medical consequences?

The third con relates to economics. If the patient gets an abnormal result by chance alone and then self-refers to their physician, who bears the cost of the inappropriate referral? At present, it is the insurer.

Rodger Seccombe: The most important benefit we have seen with HealthTab is the ability to better engage individuals in their own healthcare, particularly in the case of chronic disease prevention and management. Pharmacists are often more accessible than physicians and can support patients to reach the targets laid out by their doctor or flag potential risks sooner. Direct testing can also provide an "educational moment" where pharmacists can reinforce the importance of a healthy living and/or medication adherence at a time when patients are more receptive.

On the con side, people often cite "creating the worried well." But studies show that most of us overestimate just how healthy we actually are. So for every person who is needlessly concerned by a test result, there are far more who are in fact unaware of their health risks and should be following-up with their doctors and/or taking preventive action.

Can direct-to-consumer services destabilize a patient-physician relationship?

David Grenache: I would hope not. Direct to consumer testing has been around in some form or another for decades (e.g., home glucose monitoring, pregnancy testing) and I don't see that it has had destabilizing effects. What's happened more recently is simply that the test menu available to patients has expanded beyond that provided by over-the-counter tests. It's easy to see how a patient could come to a doctor appointment with a laboratory report of results from tests they had performed and ask questions about what the result might mean. If that destabilizes their relationship then it's time to find another, more secure, physician. This issue is not going to go away and, with time, there will be more, increasingly mobile, ways in which patients will engage in self-testing. Medicine has a long and strong tendency towards paternalism and clinicians who are resistant toward empowered and knowledgeable patients are going to find they have a hard road ahead of them.

Michael J. Joyner: Not in a major way, there are many forms of information that are already changing this relationship and this is just one piece of technology that can be misapplied or misinterpreted.

Daniel T. Holmes: Good patient care is ongoing relationship-based patient care. Sometimes in laboratory medicine, we are so focused on numbers that we almost forget we are caring for people, not specimens. Laboratory testing happens to be something that can be commoditized but consumer-driven laboratory testing does not look at the patient's overall appearance and check their vital signs. It does not ask about family history, or the reason for the visit. It does not palpate the submandibular lymph nodes or the thyroid. It does not listen for a murmur. It does not feel for abdominal or breast masses. Most importantly it does not ask, "How are things going with your work?" or "Last time you were sad about your mom's passing. How are you coping with that?" And, of course, it does not order and interpret the tests in a clinically appropriate manner.

Rodger Seccombe: Technology is turning the patient–physician relationship on its head. This has been happening since the dawn of the Internet. Most patients these days (particularly the younger generation) will search the web first before seeing their doctor. So the physician is no longer the 'gate keeper' of health information but rather an expert advisor.

Direct access testing is really just an extension of this trend towards providing patients with more information and insights about their own bodies and health. Though not without challenges, this is ultimately positive because

it means patients are more informed and engaged when they visit their doctors or any other heath professional for that matter. It becomes more of a partnership.

Do you believe that the smart phone will become the repository of our health information for direct-to-consumer testing? How could a smartphone become a patient-operated medical device?

David Grenache: Absolutely! In fact, I'd argue that it's well on its way to becoming just that. We already save an incredible amount of personal and professional data on mobile devices, and in the Cloud health information is just one more piece. The smartphone is at the center of digital health wheel and patients are already generating and/or uploading their personal health data onto them, which can then be analyzed and graphically displayed on it. Equally important is the connectivity and data-sharing aspects that the smartphone enables. Combining small microfluidic devices with the processing power and display features of the smartphone makes smartphones as patient-operated medical devices a future certainty. Indeed, several private and public companies are already developing such applications.

Michael J. Joyner: Too soon to tell, and at least so far many wearables and apps have fallen short. The wearables have been plagued by imprecision and inaccuracy and the so-called Quitbit effect. Like gene testing, it is unclear just how motivating they are in the long run to get people to change behaviors. By contrast, text messages as reminders to take drugs, eat less, walk more might be useful. But this is a very low concept use of technology.

Daniel T. Holmes: I think it is feasible that we would all carry our medical record on a smart phone/watch in the future but I don't see this as an idea that would garner too much interest in the near term except possibly as a pilot project for a cohort of early technology-adopters. However, the smartphone is in essence a portable computer with ports for attachment of peripheral devices. This makes the smartphone an optimal tool to which one could attach a detection device of any sort—optical, audio, thermal, ultrasound, or biochemical. The computing power of a smart phone far exceeds what is required for data reduction for blood testing and this is an area of active engineering development. Naturally, there are technical challenges associated with the use of whole blood and a small sample volume that would need to be overcome, but I imagine that this kind of technology is inevitable and could be extremely beneficial in developing countries.

Rodger Seccombe: Absolutely. The smart phone along with connected medical and health tracking peripherals will be the most effective solution for securely collecting, storing and sharing data. Using the patient-owned smart phone as the hub will also solve the many challenges around consent and integration across disparate electronic medical and patient health record systems, leading to better continuity of care.

As we learn more from data mining genetic, health, and lifestyle information, there will be new advanced algorithms developed to enable earlier diagnosing, as well as personalized treatment and prevention strategies available directly from the smart phone. Advancements in point-of-care technology should also allow more data to be collected and analyzed in real time without the need to visit a laboratory, particularly for less complex tests such as glucose or lipids.

Will consumer testing become a privilege of rich people?

David Grenache: I don't believe so. Consumer testing has been available for many years and, over time, not only have technologies improved but costs have come down. One only needs to look at the test menus of the many laboratories that currently offer direct-to-consumer testing to see that the costs are not out of reach for most and are certainly not affordable only by the wealthy.

Michael J. Joyner: It will become a curse of the well off. They will get the extra testing, get hard to interpret risk data, demand extra interventions, and suffer the iatrogenic consequences of over testing. This is of course a great irony.

Daniel T. Holmes: I think consumer-based testing is already targeting the wealthy. In Canada, despite the fact that medically necessary healthcare is ubiquitously covered by the government-run system, private user-pay wellness clinics offering ancillary services have sprung up along with laboratories catering to this same clientele. At present, this is the face of Canadian consumer-oriented testing and its advertising is clearly geared to appeal to the financially privileged.

However, the business principle of the smart phone industry is to create relatively inexpensive apps peripherals that offer health metrics—most notably those measuring movement as a surrogate for caloric expenditure. The addition of an inexpensive biochemical sensor to the smartphone does not seem a far-fetched notion and this for-the-masses mentality may democratize the consumer-testing industry and prevent it from becoming a privilege of the elite.

Rodger Seccombe: There's no doubt that the early adopters of new consumer testing technologies will end up paying the most. Fortunately, with the help of

Moore's law we've seen how quickly prices can fall for the underlying technology, ultimately making these once extravagant products and services accessible to the masses. For example, one of the first direct-to-consumer whole genome sequencing services was priced at $350 000 in 2007. Today's price: approximately $2500, and likely less than $100 by 2020.

In certain cases, a direct-to-consumer testing model could result in significant healthcare savings and should be considered as the new "standard" approach. For example, providing point-of-care lipid testing in pharmacies for individuals diagnosed or at risk for heart disease or diabetes. By involving the pharmacist and engaging the patient, we know that we can enhance compliance to treatment, trigger lifestyle modifications and reduce unnecessary physician office visits.

In 10–15 years from now, what do you see coming in terms of technology targeted to self-diagnostics or totally noninvasive diagnostics?

David Grenache: Several technologies are coming together to permit a paradigm shift in self-diagnostics. The capabilities of the smartphone, as a conduit of health information, will continue to improve in ways that allow patients to diagnose disease. Things like virtual health assistant apps that permit users to type or speak symptoms and/or upload physical metrics and images will then be queried against vast databases to provide likely diagnoses. Additionally, the application of wearable and connected sensors (often referred to as the Internet of Things) to collect and share health data can be used not only to manage chronic disease but perhaps diagnose illness in early stages. Advancements in microfluidics will allow the production of small, self-contained laboratories that will interface with a smartphone to analyze and interpret results. This isn't science fiction; it's happening now. If you haven't started paying attention to the Qualcomm Tricorder XPRIZE, a 10 million dollar inducement prize contest offered to the team that can produce an automatic noninvasive health diagnostics device weighing <5 pounds that can diagnose patients better or equal to a physician, you should.

Michael J. Joyner: The Holy Grail is noninvasive blood glucose monitoring, tracking and adjustment of insulin administration rates. This has been the Holy Grail since before I started in medical school in 1982. It will be interesting to see if they get there.

Daniel T. Holmes: I think there will be a proliferation of machine learning ("deep learning") or crowd-based online tools designed for the submission of symptoms and clinical/biochemical/radiological data that will provide a differential diagnosis. Online tools like this currently exist and the big technology and information players, Apple, IBM, Google, and Microsoft, are all interested in deep-learning applications to medical diagnostics. All of these tools greatly appeal to an individual for whom travel to see a physician is undesired, inconvenient or impractical. This kind of tool could also represent a decision-support device to paramedical personnel. But algorithms lack the discernment and judgment so critical to medical decision-making. I find the investor-enthusiasm misplaced at the present time.

Although limited to cortisol in my part of the world, salivary diagnostics is an extremely active area of research in the arenas of genomics, transcriptomics, proteomics, metabolomics, and the microbiota using every imaginable detection technique. This will be interesting to watch unfold and will present many regulatory challenges.

In terms of near-term noninvasive in vivo biosensors, a number of companies are working to monitor glucose in tears as part of the management of diabetes mellitus, but biosensors of this type have been extended to lactate monitoring and should see other applications. Similar mouthguard-style biosensors have been made for salivary glucose, lactate, phosphate and other targets.

Rodger Seccombe: I think point-of-care technology will become increasingly sophisticated and advances in microfluidics will bring lab-on-a-chip technology closer to the consumer, where it would ultimately be integrated with smart phones. We'll likely also see the next generation of wearable devices capable of measuring and tracking much more biometric data, such as electrolytes, sodium, lactate, proteins, and other markers through sweat analysis. Eventually, we'll see even tighter integrations with health tracking technology, such as Google's smart contact lens or implantable continuous glucose monitoring systems.

The most powerful advancements, however, will come from improved decisions and diagnostics being made with the help of big data analytics and artificial intelligence. For example, IBM's Watson is already being used to make personalized cancer care decisions in US and Canadian hospitals. Eventually this type of intelligence will become readily accessible and help everyone become better educated and engaged in their own health.

Author Contributions: *All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.*

Authors' Disclosures or Potential Conflicts of Interest: *Upon manuscript submission, all authors completed the author disclosure form. Disclosures and/or potential conflicts of interest:*

Employment or Leadership: E.P. Diamandis, *Clinical Chemistry*, AACC; R. Seccombe, HealthTab Inc.
Consultant or Advisory Role: E.P. Diamandis, Sanis Biomedical, Abbott Diagnostics, Berg Diagnostics, and bioMerieux.
Stock Ownership: R. Seccombe, HealthTab Inc.
Honoraria: None declared.
Research Funding: None declared.
Expert Testimony: None declared.
Patents: None declared.

Previously published online at DOI: 10.1373/clinchem.2016.260349