Although the majority of all clinical testing is performed in a central laboratory environment within the hospital or reference laboratory, there is a growing trend to provide laboratory results in near-patient or point-of-care testing environments. In addition, there is growing evidence of testing being performed outside of a healthcare facility, with sample collection and/or testing being performed by the patient in an at-home setting. For waived, low-complexity testing, this approach may be appropriate; however, direct-to-consumer (DTC) marketing has also made highly complex testing available to the consumer via self-collection of a buccal (cheek) swab and routine mailing to specialized laboratories for genetic testing and risk assessment. We asked 5 professionals representing academic clinical laboratories, medical genetics subspecialties, and DTC laboratories to comment on this growing trend.

(A) Are there distinct advantages to direct-to-consumer genotyping (DTCG) that are not available through traditional clinical laboratories?

Lew Bender: One of the goals of personalized healthcare is to prevent disease through proactive understanding of our health risks, setting goals to become healthier, and ultimately giving consumers the tools they need to make more informed decisions to manage their health. DTC testing enables individuals to hone in on a particular condition they’re interested in, learn more about it from their test kit and online support, and take a simple cheek swab in the privacy of their own home. There are significant advantages to this type of testing, provided DTC genetic tests have analytic and clinical validity, are clinically useful, and at the same time provide actionable, personalized guidance that consumers can then follow to minimize their genetic risks.

Lawrence M. Silverman: Accessibility of esoteric testing is a mixed blessing. On one hand, the consumer is able to choose which laboratory and what tests are being performed, which is often difficult when third-party payers control the choice of laboratories. However, removing healthcare professionals from the process makes quality and laboratory performance difficult to assess. Most importantly, without adequate preanalytical control, appropriate pretest education and potential sampling issues are usually absent or of minimal value. Finally, interpretation of results, particularly those associated with risk assessment, presymptomatic disorders, and right-to-know issues with at-risk family members, can be problematic.

Mary Beth Dinulos: There are potential advantages of DTCG. Certainly from the standpoint of a clinical geneticist, one benefit is the greater awareness of genetics in the general population and the increased accessibility to genetic testing. DTCG enables consumers to become proactive in making their own healthcare decisions. DTCG is empowering
to the consumer because it provides a means of gaining medical information without utilizing the traditional medical system. Consumers have a greater sense of autonomy with this type of genetic testing. An additional benefit is the ability to preserve anonymity with DTCG. Ordering tests and receiving results directly over the Internet bypasses the medical record and allows for increased privacy of the information obtained.

Jim Nickel: Yes, there are several major advantages including: (1) Much lower cost—patient savings from lower testing fees, no doctor visit needed, and no expenses for gas, child care, parking, etc. (2) Easier test ordering—done online at home with no waiting and no appointments needed. (3) Simpler specimen collection—no blood draw at the lab; DTCG uses a small saliva sample collected at home in a lab-provided container that is mailed back in a postage-paid envelope. (4) Greater privacy—the privacy of the patient’s own home plus the use of stringent privacy and security technology by DTCG laboratories. (5) Patient-oriented laboratory reports—more comprehensive, written by genotyping experts in language understandable to patients, and e-mailed to patients. (6) Better online support—more information about genotyping, genetic diseases, ancestry, genetic counseling, doctor referrals, and relevant links.

Wayne Grody: The purported advantages include convenience, ready access, and confidentiality, especially appealing for those who have no relationship with a clinical genetics professional or who have privacy or discrimination concerns. However, it is unfortunate that they do not realize that these same concerns can be addressed with appropriate safeguards within the more traditional clinic-based genetics setting. I also believe that one of the most appealing aspects of online services such as 23andMe is the feeling of personal, individualized attention they convey to the user, something these people apparently feel is lacking in their encounters with regular clinics and physicians. This is ironic, since the feedback from these Web sites is almost entirely autogenerated, with little if any input from a real human being (let alone an expert in genetics) on the other end.

(B) What are some of the most common hurdles to overcome if DTCG is to be successful?

Lew Bender: It is important for consumers of these services to understand the benefits and limitations of these technologies. DTCG provides specific information that requires action to become useful. At present, the information and utility must be carefully and well defined. In recent years, our knowledge on the genetics of risk for common chronic diseases or conditions has increased significantly. Our understanding of how to apply this information in a useful manner to improve health is evolving. It is important to approach genetic testing with the understanding that it is not intended to be complete and fixed. As the science of genomics evolves and more information is learned, improvements and better products will become available, provided the genetic tests have clinical evidence supporting them. DTCG must be accompanied by extensive guidance and support tools to help the consumer understand what to do with the information and how to have the proper perspective.

Lawrence M. Silverman: Regulation regarding services provided by these laboratories is the major hurdle. Some laboratories are claiming that CLIA accreditation should not be needed since these tests are not traditional laboratory tests (i.e., 23andMe in California). Without mechanisms to assess laboratory performance and with the concerns mentioned in item A (above), these services are of questionable quality and value.

Mary Beth Dinulos: In order for DTCG to be successful, several major issues must be addressed. First of all, the clinical validity of each individual test must be established before its entry into the market. Ideally, the clinical utility of each test should also be established: A statistically significant association between a particular genome variant and a disease does not necessarily mean that the presence of that variant in a given indi-
individual is clinically meaningful. Second, the quality of the tests and the laboratories performing these tests must be rigorously controlled. Lastly, and in my opinion most importantly, it is imperative to involve a healthcare professional in the testing process—to provide pre- and posttest counseling, interpretation of test results, and guidance in posttest decision-making.

**Jim Nickel:** Some of these hurdles include: (1) Need for more research—much of the genotyping information currently obtainable lacks scientific evidence for interpretation and usability. (2) Slow acceptance by the medical community—medical providers have been slow to implement genotyping results in patient care, partly because of concerns about the validity and clinical utility of genotyping; increased physician education is also needed in the area of genetics. (3) Obsolete regulations—current regulations are not designed to enable across-state-line testing, Internet medical care, or DTC testing and reporting. (4) Concerns over potential harm that could be caused by knowledge of genetic information—as with all medical tests, procedures, and treatments, the potential harm must be weighed against the potential benefit. (5) Concerns over the privacy of genetic information—this hurdle is lessening due to protections afforded by many recent laws and regulations. (6) Nonreimbursement for testing—third-party payers generally do not pay for DTCG.

**Wayne Grody:** I feel the landscape of DTCG has already been fouled by some disreputable or bogus providers in the field, such as those offering genotyping tests purported to predict athletic ability, risk of various diseases for which little is understood about the genetic factors, and “nutrigenomics.” The field also suffers from a lack of regulatory oversight, absence of peer review, and in many cases a paucity of legitimate scientific underpinning for the tests being offered.

**(C) From a patient-management perspective, there is the potential for several drawbacks to this type of testing. How and when would you know if this is the right thing for the right patient at the right time?**

**Lew Bender:** How and when these technologies are used depends on the question that the patient and physician are asking. There is a multitude of beneficial genetic tests that are physician-ordered and can enable important healthcare decisions, especially for monogenic disease. When you look at DTC tests and how they might be used between health providers and their patients, there must be a level of education that happens among providers to develop understanding of the utility and limitations of a particular test so that they can make informed decisions about whether or not it would be beneficial for their patient.

**Lawrence M. Silverman:** Professional organizations need to take leadership roles (and many have). See: “ASHG Statement on Direct-to-Consumer Genetic Testing in the United States” (Obstet Gynecol 110:1392–5).

**Mary Beth Dinulos:** It is important for the patient and healthcare provider to realize that DTCG is essentially a screening test. Results are typically reported as “average,” “above average,” or “below average” risk for each condition. This information, combined with family history, may be helpful in guiding preventative health maintenance. However, the clinical utility of these tests is uncertain at best, and thus the family history should remain a more sensitive indicator of disease in the family. DTCG should not be used to diagnose specific medical conditions, such as breast cancer. Specific genetic testing should be used in those circumstances.

**Jim Nickel:** Many health risks can be mitigated by making appropriate changes in lifestyle or medical treatment. Knowledge of a person’s genetic makeup can assist patients and their doctors in making such decisions. Medical indications and instances when DTCG might be appropriate include: (1) Childbearing concerns—prospective parents might wish to know if they are genetic carriers for potential medical problems that could affect their child. (2) Drug treatment information—some people are genetically predisposed to react more or less positively to treatment with a certain drug. (3) Cancer susceptibility—certain cancers are known to have a familial or genetic predisposition. (4) Obesity—knowledge of a genetic predisposition to obesity or obesity-related diseases can motivate patients to change dietary and exercise behaviors. (5) Risk assessment—certain diseases such as diabetes, heart disease, and Alzheimer’s are known to have a genetic component associated with increased risk of developing the disease. (6) Patients’ desires to understand their own genetic makeup to prioritize and personalize their lifestyle choices and healthcare.

**Wayne Grody:** The vast majority of the genomic markers tested and reported by these companies are drawn from raw research data, usually in the form of genome-wide association studies, and have never been clinically validated. The disease risks imparted, usually in the form of odds ratios that are of little clinical consequence but commonly overinterpreted by those on the receiving end, can easily lead to anxiety, depression, stigmatization, unnecessary physician visits, and clinical interventions that at best place an undue economic
strain on an already overburdened healthcare system and at worst may lead to physical or psychological harm that then has to be managed by the bona fide medical establishment. Already, for example, our UCLA Medical Genetics Clinic is starting to be contacted by otherwise healthy individuals who have taken the 23andMe test, become anxious or confused about the results, and now expect us to explain it all to them—despite the fact that we would never have ordered these unvalidated tests on our own patients in the first place.

(D) In the current healthcare environment, do you think DTCG is the future of genetic testing for risk assessment and other applications?

Lew Bender: Yes. Lifestyle and medical management of an individual can be greatly assisted by DTCG. There’s significant interest and utility for providing meaningful health and wellness tests for consumers. Individuals who would like to know if they have increased risk of an early heart attack can take the Interleukin Genetics Heart Health test and identify whether they have a significant increase in risk for a heart attack due to chronic inflammation. Such information can be a strong motivator for individuals to do more to reduce their risk. However, there are other exciting applications for DTCG for physicians to work with patients. For instance, Interleukin Genetics recently published a study with NYU and Duke University medical centers that showed variations in a particular gene (interleukin-1 receptor antagonist) strongly and significantly influenced whether a person is likely to go on to develop severe knee osteoarthritis. Despite at least 1 in 10 Americans being diagnosed with the disease, there is no drug on the market to alter its progression. This observation for the first time shows that variations of the gene may identify who will likely progress with the disease and require surgery. This finding can help in the clinical management of patients.

Lawrence M. Silverman: No. I have little confidence in these laboratories but am even more concerned about the dubious quality of the postanalytical interpretation and follow-up.

Mary Beth Dinulos: In its present state, I do not believe that DTCG is the future of genetic testing for risk assessment. Consumers receive test results for a number of common conditions, such as obesity or hypertension, which include their risk compared with someone of the same age, or gender, in the general population. These results have the potential of being quite misleading, as the estimated risks might be accurate on average, but very inaccurate for that particular individual.

Jim Nickel: Yes, I think DTCG is the future of genetic testing for risk assessment because it addresses several major issues in the current healthcare environment, such as: (1) Cost and utilization concerns—DTCG lowers the cost per test. It could potentially increase utilization, but this will be less of a concern as the usefulness of the information increases. (2) Patient empowerment—DTCG testing gives patients more knowledge about and control over their own health. (3) Widespread availability of medical information via the Internet and other sources—demand for DTCG testing will increase as patients learn more about health issues. (4) Environmental concerns—DTCG testing benefits the environment by eliminating the need for travel to obtain medical care. (5) Increased emphasis on preventive care—preventive care is the wave of the future, and knowledge of a patient’s genotype will be of paramount importance in personalizing their preventive care plan. (6) Electronic medical records—DTCG companies are healthcare industry leaders on this issue. (7) Privacy concerns—DTCG companies are highly sensitive to this issue.

Wayne Grody: I would be disappointed if that were to be the case, at least based on the offerings and methods of these companies thus far. These DTC genetic-testing companies try to implant in the minds of a naive public that simply because DNA is easily collected and unique to each individual, doing all manner of genotypic testing on it should be deemed an entertaining free-for-all, open to any and all who are interested and willing to pay for it, even for frivolous reasons. However, the information provided from these test results is claimed to have potentially serious medical implications, entailing future risk for Parkinson disease, breast cancer, Crohn disease, and many other conditions. In most cases the activity is conducted in the absence of any pre- or post-test genetic counseling, the client/patient interacting only with automated software on a distant Web site.

(E) Are adequate protective measures in place to ensure privacy of genetic information and accuracy of result interpretation?

Lew Bender: We believe there are strong laws and technologies in place to ensure privacy of genetic information and accuracy of result interpretation. Interleukin Genetics, Inc., adheres to strict privacy standards to ensure samples are in our possession at all times until they are destroyed after processing in 10 days from arrival. In addition, we established a number of safeguards so that we are in fact exceeding all relevant regulatory standards. User information is always stored separately from genetic information so that
genetic information remains anonymous to laboratory personnel.

Our fully certified CLIA laboratory where we process samples is located on site at Interleukin Genetics and is capable of handling a substantial volume of DNA samples with precision. Our laboratory includes a clean room and the latest robotics and instrumentation to ensure the highest accuracy in sample analysis. The Genetic Information Nondiscrimination Act of 2008 has also provided a strong protection against abuses by insurance companies and employers against misuse of genetic information.

**Lawrence M. Silverman:** No. This is also a concern regarding traditional reference and clinical laboratories. The current trend toward electronic medical records may exacerbate the privacy issues.

**Mary Beth Dinulos:** In DTCG, privacy of genetic information may be compromised. It is unclear who has access to the genetic information, both personal history and biological sample, that is provided by the consumer to the company over the Internet. Each company is unique in its testing and reporting, and there is no governing body overseeing this type of genetic testing in the United States. The accuracy of result interpretation by these laboratories is based upon the clinical validity and clinical utility of the testing, which at best is marginal.

**Jim Nickel:** Absolutely! Many laws and regulations now exist regarding both privacy and quality of genetic information, and more are coming, as this area is of great concern to the public and to regulators and legislators. All DTCG laboratories must be CLIA certified and meet stringent standards for quality. The Health Insurance Portability and Accountability Act (HIPAA) laws are strong and protect patient privacy. Some DTCG companies, such as Pathway Genomics, have a chief privacy officer and complex computer systems with state-of-the-art privacy protection, as well as computer programs that are frequently updated with the latest interpretations of testing results.

**Wayne Grody:** I do not think this important aspect has been seriously addressed as of yet. We all know that nothing sent over the Internet can ever be considered completely private, and it further concerns me that 23andMe uses the informatics infrastructure of its business partner, Google, giving it tremendous power to collect, manipulate, disseminate, or otherwise use for its own business purposes all of the genomic data it is collecting on millions of customers who think they are doing this solely for their own personal genetic assessment.

I maintain that DNA is a clinical laboratory analyte just like any other and should be subject to exactly the same oversight, regulation, quality-assurance, and practice guidelines as all other activities in the clinical laboratory. Indeed, DNA is arguably the most complex of all clinical analytes and, if anything, requires far more care and expertise in its analysis. If DNA is considered suitable for DTC analysis, without any regulatory or quality-assurance oversight, should we then declare open season on self-ordering of all clinical laboratory tests? Should individuals be free to request, from the privacy of their own homes and without any involvement of a healthcare professional, their own thyroid hormone levels, liver enzymes, prostate-specific antigen, and even serum troponin to determine if they have recently experienced a heart attack?

**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 of Potential Conflicts of Interest:** Upon manuscript submission, all authors completed the Disclosures of Potential Conflict of Interest form. Potential conflicts of interest:

- **Employment or Leadership:** L. Bender, C.E.O., Interleukin Genetics; J. Nickel, Laboratory Director, Pathway Genomics.
- **Consultant or Advisory Role:** J. Nickel, Pathway Genomics; W.W. Grody, Roche Molecular Diagnostics.
- **Stock Ownership:** L. Bender, Interleukin Genetics; J. Nickel, Pathway Genomics.
- **Honoraria:** None declared.
- **Research Funding:** None declared.
- **Expert Testimony:** None declared.

**Role of Sponsor:** The funding organizations played no role in the design of study, choice of enrolled patients, review and interpretation of data, or preparation or approval of manuscript.

Previously published online at DOI: 10.1373/clinchem.2009.138743