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New Trends, Applications, and IVD Industry Analysis

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INSIDE THIS ISSUE

Top of the News: Multi-Cancer Screening Tests Are Getting Closer to Reality

The hope of developing a single blood test capable of detecting multiple types of early-stage cancer is getting closer to becoming a reality. Two hopeful players, GRAIL (Menlo Park, Calif.) and Thrive (Cambridge, Mass.), recently made big announcements to coincide with the American Society of Clinical Oncology's (ASCO's) annual meeting (May 31 to June 4; Chicago).

With a head start, GRAIL released new data at ASCO regarding its test's performance on the first 2,300 patients in ongoing clinical trials.

Data reported at ASCO are based on initial analysis of 2,301

Continued on page 2

Top of the News: Consumers Interested in Raw Genetic Data, Third Party Interpretation Tools

Consumers of direct-to-consumer (DTC) genetic testing download raw data at high rates and frequently use third-party interpretation (TPI) tools, according to a study published June 13 in the *American Journal of Human Genetics*. Given that individuals will have increasing routes to access their raw genetic data, the authors say it is important to understand how consumers use raw data given the expanding number of available TPI services.

"Rather than taking sides in a potential ensuing 'culture war' about raw data, the professional genetics community has an opportunity to proactively engage with users, understand the complexity of their motivations for pursing third-party analysis, and ultimately educate them about potential limitations," write the authors led by **Sarah Nelson**, from University of Washington in Seattle.

In the near future, it is likely that patients will have access to their raw genetic data from an increasing number of sources. There

Continued on page 10

Multi-Cancer Screening Tests Are Getting Closer to Reality, *from page 1*

participants from a sub-study of the Circulating Cell-free Genome Atlas (CCGA) study. Analysis included 1,422 participants with more than 20 cancer types across all stages plus 879 participants without diagnosed cancer. Analysis also broke out 12 pre-specified, deadly cancer types—anorectal, colorectal, esophageal, gastric, head and neck, hormone receptor negative breast, liver, lung, ovarian, and pancreatic, plus multiple myeloma and lymphoid neoplasms—which, together, account for approximately 63 percent of all cancer deaths in the United States, the company says.

The test showed a very high specificity of at least 99 percent. However, across all 20 cancer subtypes and stages, the overall detection was 55 percent, while the overall detection rate for the 12 pre-specified deadly cancer types across all stages was 76 percent. GRAIL's ability to correctly identify cancer type depended on both cancer stage and the tissue of origin. Stage 1 cancers were predictably the hardest to detect, with the test doing so only 34 percent of the time versus more than 90 percent of the time for metastatic, stage 4 cancers. For earlier cancers—stages 1 through 3—head and neck cancer was most easily detectable, while lung cancer was the hardest.

Additionally, the company announced it has narrowed its technological approach. Previously, the company pursued three different detect methods—targeted DNA sequencing, whole-genome sequencing, and methylation analysis. The company announced it will pursue the latter, methylation analysis, which covers 30 million sites across the genome. Additionally, the test uses a proprietary database and machine-learning algorithms to both detect the presence of cancer and identify the tumor's tissue of origin.

"Based on these positive data, we plan to advance development of our test toward commercialization," **Jennifer Cook**, the recently departed CEO at GRAIL, previously said in a statement.

The test was able to provide a tissue of origin result across more than 20 cancer types for 94 percent of all cancers, with the test correctly identifying the tissue of origin in 90 percent of these cases. The tissue of origin accuracy was consistent regardless of stage ranging.

GRAIL is using its capital for further, large-scale clinical trials.

- GRAIL is conducting three pre-planned, sub-studies within CCGA to further train and validate its test. The 15,000-person trial completed enrollment at 142 centers across the United States and Canada.
- The prospective STRIVE study completed enrollment of approximately 100,000 women at the time of their screening mammogram across 37 sites in the United States. STRIVE is designed for clinical validation of GRAIL's multi-cancer test in an intended use population with data reporting anticipated in 2020.
- The prospective SUMMIT study is enrolling 50,000 cancer-free men and women in the United Kingdom. Approximately half of the participants will be people at high risk of lung and other cancers due

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to a significant smoking history. This trial is designed for clinical validation of the multi-cancer test in a second intended use population and to evaluate clinical utility of the test in a high-risk population.

GRAIL Is Not the Only Player Seeking to Enter the Multi-Cancer Screening Space

On May 30, Thrive announced it closed $110 million in a series A round of financing to advance development and commercialization of its CancerSEEK liquid biopsy test.

CancerSEEK combines targeted DNA and protein analysis in a liquid biopsy test to detect multiple cancer types at earlier stages of disease. The Johns Hopkins University spinout says it will integrate real-world data and machine learning to continue to improve the test over time and to create a cost-effective, "comprehensive care solution" for primary care physicians.

The test assesses eight protein biomarkers and tumor-specific mutations in circulating DNA. Last February, test performance was reported in *Science*. In the study of 1,000 patients previously diagnosed with cancer and 850 healthy control individuals, CancerSEEK detected cancer with a sensitivity ranging from 69 percent to 98 percent for the detection of five cancer types (ovary, liver, stomach, pancreas, and esophagus) for which there are no screening tests available for average-risk individuals. Specificity was 99 percent. Additionally, CancerSEEK determined the anatomic location of the cancer in 83 percent of the patients.

Currently, CancerSEEK is being evaluated in DETECT, a study of 10,000 healthy women. The trial is being conducted in conjunction with Geisinger. Results will further inform test performance and provide insight into integration of test findings into clinical care. CancerSEEK previously received Breakthrough Device designation from the U.S. Food and Drug Administration for the detection of genetic mutations and proteins associated with pancreatic and ovarian cancers.

Two High-Profile Players

Both spun out of well-known entities—GRAIL from Illumina in 2016 and Thrive from Johns Hopkins University this year.

Both raised enormous amounts of money—GRAIL more than $1.5 billion over three years and Thrive $110 million in its first round.

Both have liquid biopsy tests with accurate screening performance — 99 percent specificity.

Both received U.S Food and Drug Administration's Breakthrough Device designation.

Takeaway: New evidence provides positive performance data for two blood tests capable of screening for multiple types of cancer. These well-funded companies continue large-scale clinical trials in the march toward commercialization.

EMERGING TESTS: HPV DNA from Oral Rinse Samples May Be Prognostic Marker for Head, Neck Cancer

Samples collected from a mouth rinse can detect human papillomavirus (HPV) DNA. These easily collected samples might provide important monitoring information for patients with certain head and neck cancers.

Two recently published studies shed light on both the feasibility of using oral gargle samples and the potential clinical utility of HPV viral load surveillance during and following primary treatment. Both studies show the viability of using oral gargle rinse samples. However, one study was able to show that detection of persistent HPV DNA in oral rinses following primary treatment was tied to poorer patient outcomes.

Most of the clinically relevant HPV genotypes found in oropharyngeal squamous cell carcinoma tumors can be detected using oral gargle samples, according to a study published March 28 in *JAMA Otolaryngology Head Neck Surgery*.

"Currently the preferred method of HPV status determination is p16 immunohistochemistry, which does not provide specific HPV genotype information," write the authors, led by **Laura Martin-Gomez**, M.D., Ph.D., from Moffitt Cancer Center, Tampa, Fla. "As development of HPV-targeted treatment approaches, such as genotype-specific therapeutic vaccines, moves forward, it may be important to adapt an HPV detection method that can determine the specific HPV genotypes for each patient."

Adult male patients with newly diagnosed squamous cell carcinoma of the oropharynx (stage I to IV; May 2014 through October 2017) were evaluated. Paired oral gargle and tumor specimen samples were available for 171 men. A highly sensitive in vitro reverse hybridization assay (DDL Diagnostic Laboratory) was used to detect HPV DNA in both sample types.

The researchers found that the detection rate of HPV genotypes was 93.0 percent in tumor specimens and 82.8 percent in oral gargle samples. Only one oral gargle sample failed DNA quality assessment. Of the 171 paired gargle and tumor specimens, there was 74 percent agreement for HPV 16 and 94 percent agreement or higher for all other HPV types, including the high-risk HPV 18 genotype. The oral gargle samples detected low-risk HPV genotypes that were not identified in tumors, but these low-risk genotypes were always a coinfection with high-risk genotypes. Multiple HPV types were present in 7.6 percent of the tumor specimens and 9.9 percent of the oral gargle samples.

"Oral gargle samples are reliable, noninvasive sources of HPV DNA in patients with known oropharyngeal squamous cell carcinomas," wrote **Ricardo Ramirez** and **Jose Zevallo**, both from Washington University in St. Louis, Mo., in an accompanying editorial. "Unfortunately, their study does not bring us any closer to defining practical, clinically relevant applications for this technology."

However, a second, independent study published May 2 in *JAMA Oncology* provides some evidence that HPV DNA samples derived from oral rinses hold promise as a marker for treatment response and risk of progression among patients with oral and oropharyngeal cancers. The study showed that the prevalence and viral load of tumor-type HPV DNA decreased rapidly with therapy, but that persistent HPV DNA detection was associated with increased risk of cancer recurrence and death.

"Our data suggest that persistent tumor-type oral HPV DNA identified a subset of HPV-positive patients with increased risk of recurrence and consequently inferior overall survival," write the authors led by **Carole Fakhry**, M.D., from Johns Hopkins University in Baltimore, Md. "Patients with persistent HPV DNA may benefit from close clinical surveillance or adjuvant therapy."

In the present study tumor samples were assessed for 37 HPV DNA types, while HPV load was measured in oral samples for 22 HPV types using type-specific real-time polymerase chain reaction. Samples were considered positive if HPV copy number was above the lower-limit of reproducibility (≥3). In total, 396 patients (217 had oropharyngeal cancer; 170, oral cavity cancer) with newly diagnosed oral cavity or oropharyngeal squamous cell carcinomas were evaluated at two locations from July 11, 2011, to May 7, 2016. Oral rinse samples (a 30-second rinse and gargle with saline) were prospectively collected at diagnosis and at completion of primary therapy, as well as weekly during radiotherapy.

The researchers found that just over half of patients overall (51 percent) had HPV-positive tumors, although a higher percentage of oropharyngeal cancer patients were HPV-positive (86.2 percent). For detection of any oral HPV DNA at diagnosis, oral rinse samples had a sensitivity of 84 percent, specificity of 88 percent, a positive predictive value of 88 percent, and a negative predictive value of 84 percent for a diagnosis of an HPV-positive tumor. Among the 202 patients with HPV-positive tumors, nearly 80 percent had the same HPV DNA type detected in the oral rinse sample and in the tumor at baseline.

The prevalence and load of tumor-type HPV decreased significantly during primary therapy (surgery and radiotherapy). For most patients, there was a 24 percent relative reduction in DNA load per radiotherapy visit. Yet, tumor-type HPV was detectable after treatment in14.3 percent of HPV-positive patients.

There was significantly lower two-year overall survival among the HPV-positive patients with persistent detection of tumor-type HPV after therapy versus patients without detectable tumor-type DNA after therapy (68 percent versus 95 percent). Similar results were seen for recurrence-free survival (55 percent versus 88 percent). Finally, among patients with detectable tumor-type DNA post-therapy, the cumulative incidence of recurrence by 2

Continued on page 6

HPV DNA from Oral Rinse Samples May Be Prognostic Marker for Head, Neck Cancer, *from page 5*

years was 45.3 percent versus 12.2 percent among those without detectable tumor-type HPV DNA post-treatment.

"The clinical utility may be constrained by a need to identify the tumor-type infection, a low-moderate positive predictive value for recurrence, and weak associations with risk of distant metastases," the authors caution. "Ongoing studies will evaluate whether multiplexed detection of plasma HPV DNA can improve these limitations."

Takeaway: HPV DNA is detectable in oral rinse samples and holds promise for ongoing monitoring and surveillance of treatment response in patients with certain head and neck cancers. While feasible, additional research will be needed to determine the full clinical utility of this sample collection method.

EMERGING TESTS: Researchers Find Marker That May Aid Diagnosis of Erectile Dysfunction

The neutrophil-lymphocyte ratio (NLR) may be a marker to aid in diagnosing erectile dysfunction (ED), according to a small study published in the *Journal of Urology*.

ED is common and its incidence increases with age, with estimates that it affects one in five men over the age of 20, but nearly three-quarters of men over the age of 75 years. Often though, diagnosis is made based on a man's medical history and a physical exam looking for underlying conditions known to be associated with ED, like obesity, diabetes, and hypertension.

Given the known link between ED and cardiovascular disease, the researchers assessed the relationship between ED and NLR, a nonspecific inflammatory marker. Ninety patients with ED and 94 healthy subjects (between 40 and 70 years of age) seen at internal medicine and urology clinics at Ordu University in Turkey (between September 2016 and July 2017) were included in this study. Laboratory tests included: total blood count, sedimentation, C-reactive protein, and blood chemistry.

The researchers found in univariate analysis that increased neutrophil and the NLR values, as well as the presence of diabetes and coronary artery disease were all associated with increased risk of ED. However, when controlling for other factors, only NLR was an independent predictor of ED. Using a cut-off value of 1.574, NLR predicted ED with 81.8 percent sensitivity and 67.0 percent specificity.

Takeaway: With further validation, NLR may provide clinicians with an objective marker to assist in the diagnosis of ED.

INSIDE THE DIAGNOSTICS INDUSTRY

Search Intensifies for Markers for Prosthetic Joint Infection

Nearly one million total hip arthroplasties and total knee arthroplasties are performed in the United States each year, a number that is expected to continue to increase for decades given the aging of the population and increases in body mass index.

Prosthetic joint infection (PJI) is one of the most dreaded complications following arthroplasty surgery and is the leading cause of implant failure and costly revision surgery, with PJI rates estimated at up to 1 percent for hip and shoulder replacements and up to 2 percent in knee replacements. Yet, there is no definitive test for PJI, as most laboratory tests are indirect measures of infection.

Painful joint history and physical exam remain the primary diagnostic tools. However, much research is currently happening, searching for specific markers of PJI. *DTET* examined recent studies of promising markers associated with PJI.

Protein Markers In Synovial Fluid May Diagnose, Provide Ongoing Monitoring of PJI

Interleukin (IL)-16, IL-18, and cysteine-rich with EGF-like domains 2 (CRELD2) are potential biomarkers for PJI diagnosis, according to a study published in the April issue of *Bone & Joint Research*. Tests of these markers in synovial fluid outperformed blood tests and may be useful for follow-up monitoring of PFJI to assess the success of debridement, the authors say.

Analysis included 48 patients (including 39 PJI and nine aseptic loosening case controls) who required knee or hip revision surgery between January 2016 and December 2017. Synovial fluid and blood samples were analyzed by protein microarray and enzyme-linked immunosorbent assay to compare protein expression patterns among patients with aseptic loosening and PJI. C-reactive protein level and leucocyte numbers were also assessed.

The researchers report that with cut-off values of 1,473 pg/ml, 359 pg/ml, and 8.45 pg/ml were established for IL-16, IL-18, and cysteine-rich with EGF-like domains 2 (CRELD2), respectively. Receiver operating characteristic curve analysis showed that these markers showed excellent accuracy as predictors of PJI, with an area of 1. Like plasma CRP concentration and blood leucocyte number, IL-16, IL-18, and CRELD2 levels returned to their respective baseline values following the completion of debridement, suggesting them as potential biomarkers for determining the timing of prosthesis reimplantation.

Continued on page 8

Search Intensifies for Markers for Prosthetic Joint Infection, *from page 7*

"Based on the findings of this study and future diagnostic trends, we believe that single-molecule-based diagnosis [for PJI] is inadequate," write the authors led by **M-F. Chen**, Ph.D., from Chang Gung Memorial Hospital in Taiwan. "A scoring system using multiple factors for PJI diagnosis would be optimal. Although the establishment of such a scoring system requires continued efforts to perform marker evaluation, the identification of IL-16, IL-18, and CRELD2 as diagnostic markers for PJI and successful debridement in this study represents a promising first step in the process."

Sequencing Can Speed Definitive Infection Diagnosis

Metagenomic sequencing can successfully identify the cause of PJI, according to presentation at the European Congress of Clinical Microbiology and Infectious Diseases (April 13-16; The Netherlands). The culture-free method uses DNA isolated directly from the clinical sample and can provide results in hours rather than the five to 10 days needed with current gold standard of cultures of periprosthetic tissue samples collected during surgery.

The researchers from University of Oxford in the United Kingdom sought to improve the microbiological diagnosis of infections associated with orthopedic devices using whole-genome sequencing technologies in order to achieve faster, more sensitive results, with the ultimate goal of improving antibiotic stewardship and patient outcomes.

The researchers report that they initially started using the Illumina MiSeq platform. Sequencing took approximately 2.5 days and required at least 1,150 reads for an individual species or at least 125 reads for an individual species if the at least 15 percent of the total bacterial reads belonged to same species. Species-level sensitivity and specificity was 88 percent. However, the researchers learned that human DNA was "problematic" with human DNA accounting for more than 90 percent of reads in 97 percent of samples. Further, the researchers determined more reads are needed in order to determine the organisms' antimicrobial sensitivity.

The researchers next adopted nanopore sequencing technology, which offered the benefits of being portable, having long read lengths, and providing real-time analysis. The so-called CRuMPIT (Clinical Real-time Metagenomics Pathogen Identification Test) relies upon a redesigned workflow that involves removing surgical removal of a prosthetic implant and then placing it in saline and sonicating it to obtain approximately 40 mL of sonication fluid, which is essentially the largest volume easily handled in the laboratory. This approach maximizes the number of cells DNA can be extract from. Following extraction,

the DNA is then cleaned, prepared into libraries, and sequenced. Findings show that the methodology enables sequencing of near-whole genomes and antimicrobial resistance can be determined within hours of surgery.

Diagnosis of Joint Infection in Patients With Inflammatory Disease

Alpha-defensin can accurately diagnose PJI even in patients with systemic inflammatory disease undergoing revision total hip or knee arthroplasty, according to a study published April 13 in the *Journal of Arthroplasty*.

Measuring alpha-defensin concentrations in synovial fluid is increasingly used to test for PJI in conjunction with other laboratory tests, however, the use of inflammatory markers (e.g., C-reactive protein, erythrocyte sedimentation rate, and white blood cell counts) has been questioned, particularly in patients with inflammatory diseases (e.g., rheumatoid arthritis, psoriatic arthritis, and sarcoidosis).

Researchers from the Cleveland Clinic (Ohio) retrospectively reviewed 1,374 cases who underwent revision total hip or knee arthroplasty at a single healthcare system from 2014 to 2017. Analysis included 41 cases with rheumatologist-diagnosed inflammatory diseases (17 with rheumatoid arthritis, seven with psoriatic arthritis, five with ulcerative colitis, six with polymyalgia rheumatica, three with sarcoidosis, one with polymyositis, one with systemic lupus erythematosus, and one with systemic sclerosis). All patients with available preoperative alpha-defensin results were included. The laboratory-based immunoassay for alpha-defensin (Synovasure; CD Diagnostics) was performed on synovial fluid. Three to five samples were taken from patients undergoing a one-stage revision arthroplasty, the first stage of two-stage revision arthroplasty, or irrigation and debridement and samples were cultured for seven to 14 days.

The alpha-defensin test demonstrated a sensitivity of 93 percent, a specificity of 100 percent, a positive predictive value of 100 percent, a negative predictive value of 96 percent, and an overall accuracy of 97 percent for diagnosing PJI. There was one false-negative result in a patient with polymyositis.

"As a relatively new marker for diagnosing PJI, alpha-defensin has been widely reported to have excellent diagnostic accuracy in diagnosing PJI," write the authors led by **Yushi Miyamae**, M.D., Ph.D. "To our knowledge, this was the first study to analyze the utility of laboratory-based alpha-defensin exclusively for patients with inflammatory diseases, and the results of our study confirmed the diagnostic accuracy for diagnosing PJI, even in patients with inflammatory diseases, with no false-positive result."

Continued on page 10

INSIDE THE DIAGNOSTICS INDUSTRY

Search Intensifies for Markers for Prosthetic Joint Infection, *from page 9*

Markers May Predict Which Patients Need Knee Replacement

CTX-I (C-telopeptide of crosslinked collagen type I), a marker of bone resorption, and CTX-II (C-telopeptide of crosslinked collagen type II), a potential marker of cartilage degradation, may predict joint failure among patients with osteoarthritis, according to a study published April 15 in a supplement to Osteoarthritis and Cartilage, highlighting abstracts resented at the 2019 Osteoarthritis Research Society International's World Congress on Osteoarthritis (May 2-5; Toronto). Specifically, serum CTX-I and urinary CTX-II levels at baseline were associated with increased risk of undergoing knee or hip replacement surgery over two years of follow-up.

Based on post-hoc analysis using data from two clinical trials investigating oral salmon calcitonin in osteoarthritis in more than 1,300 patients, 27 total joint replacements of the knee or hip were reported.

Researchers from University Health Network in Toronto, Canada found that at baseline, high CTX-II was statistically significantly associated with a 3.08 times higher risk of undergoing joint replacement during the study period, and 8.94 times higher risk of specifically knee arthroplasty. Similarly, high sCTX-I was statistically significantly associated 3.4 times higher risk of undergoing either knee or hip arthroplasty, but did not reach statistical significance for risk of knee arthroplasty alone.

Takeaway: Given the expected increase in the number of total joint replacements, and accompanying PJIs, there is great interest in discovering objective markers for diagnosis of PJI. These recent studies show promising candidates.

Consumers Interested in Raw Genetic Data, Third Party Interpretation Tools, *from page 1*

are indications that the the direct access right granted under the Health Insurance Portability and Accountability Act of 1996 includes sequencing data. Further, national-level bodies, like the National Academies of Sciences, Engineering, and Medicine, issued recommendations supporting returning "individual research results," while large-scale, research-based, sequencing efforts, like the National Institutes of Health's All of Us, indicated plans to make raw genetic data available to participants.

Genetic researchers wishing to better understand the implications of returning raw sequencing data can understand individuals' use of this information by studying DTC customers' behavior.

The researchers recruited 1,137 DTC customers (October and November 2017) through social media to take part in a survey assessing raw data access and third-party tool usage following DTC genetic testing. The

authors acknowledge that recruitment methods may have skewed results by identifying "likely highly motivated individuals" who were active in genetic online forums.

The researchers found that the vast majority of survey respondents (89 percent) reported downloading their raw data. Among raw data downloaders, 94 percent used at least one tool, most commonly GEDmatch (84 percent), Promethease (63 percent) or, and DNA.Land (53 percent). Most used multiple tools, with 76 percent (623 of 820) using two or more tools.

More than half of participants (56 percent) used both health-related and non-health-related tools (genealogy and ancestry).

"We found that individuals who are initially motivated to learn about ancestry and genealogy frequently end up engaging with health interpretations of their genetic data, too," said senior author **S. Malia Fullerton** in a statement. "This has implications for the regulation of such testing and interpretation practices."

Across all tools, respondents reported positive outcomes from using these tools, including increasing their understanding of genetics in general (76 percent) and, more specifically, for how DTC companies interpret genetic data (67 percent). Most were satisfied with the information received (88 percent). However, some reported feeling confused (35 percent) or upset (6 percent) after receiving information.

After receiving results, most participants reported sharing the results with a family member (85 percent) or non-family member friend or loved one (71 percent). More than half (55 percent) pursued additional analysis using another analysis tool, while 33 percent pursued more genetic testing and 35 percent participated in a genetic research study. Few respondents reported making changes to either health insurance (0.9 percent) or other types of insurance (e.g., life or long-term care; 1 percent).

Only 15 percent of respondents reported sharing results with a health care provider. When shared with a health care provider, results were most commonly shared with a general practitioner (79 percent), while 11 percent reported sharing results with a medical geneticist or genetic counselor. Results were also shared with other practitioners from non-genetics specialties (e.g., cardiologist, gastroenterologist, ophthalmologist), psychiatry/psychology, and alternative medicine practitioners).

"This will present challenges for primary care physicians, especially given that TPI reports are typically longer and harder to digest compared to DTC company reports," the authors write.

Takeaway: While the authors say future research should evaluate how individuals' interactions with their raw data compare across DTC testing, clinical sequencing, and return of results from research, there is preliminary evidence that consumers are interested in receiving raw data and using TPI tools to learn more health, ancestry, and genealogy.

Emergence of Hybrid Model Changes the Genetic Testing Landscape

While direct-to-consumer genetic testing garners headlines and the ire of the clinical laboratory industry, a new hybrid model for genetic testing emerged, relatively unnoticed, according to a Viewpoint published May 30 in the Journal of the American Medical Association.

The National Institutes of Health's genetic testing registry estimates that there are nearly 300 U.S. laboratories performing genetic testing, with the most falling into the traditional laboratory model. However, the emergence and growth of the hybrid model that combines features of direct-to-consumer testing and traditional laboratory models has significant implications for clinicians, consumers, policymakers, and payers.

The authors highlight Invitae (San Francisco, Calif.) as a high-profile example of the hybrid model. In SEC filings, the company, which has a stated goal of making "medical genetics affordable and accessible for everyone," reported year-to-year growth in volume and revenue of more than 100 percent from 2017 to 2018. Testing volume over the period grew from 145,000 to 292,000 with revenue increasing from $68.2 million to $147.7 million.

The hybrid model provides clinical-grade testing and relies on clinicians to order tests and communicate results. However, the hybrid model facilitates enhanced, consumer-driven access by facilitating connections to physicians in the laboratory's own network, rather than relying on the consumer's usual care physician.

While there are not published studies, comparing the three models, the authors, led by Kathryn A. Phillips, Ph.D., from University of California, San Francisco, say the hybrid model holds the potential for increasing access to testing, providing greater convenience to both patients and clinicians unburdened with prior authorizations for out-of-pocket testing, and potentially lowering costs. Concerns about the model include potential reductions in continuity of care, as well as potentially abbreviated counseling and unnecessary testing.