Next act in genomics: the consumer orders

Karen Titus

April 2019—For years, laboratories have chafed against testing being, literally and figuratively, an out-of-sight, out-of-mind transaction. Now a new, highly visible era in genetics may be pushing testing the other way, into the hands of consumers who value entertainment as well as medical information. Anyone who wants to write a book about this shift has a ready-made title: *From Basement to Big Top.*

It's not that clinical testing is becoming an actual circus. But ever since the first consumer genetic tests entered the market in 2007—in a nonphysician-ordered, SNP array technology way—labs, physicians, and regulatory agencies have had plenty to juggle. Today that includes relatively affordable sequencing, DNA ancestry searches, and patient empowerment. Throw in a little Silicon Valley verve, and we arrive at the present: presumably healthy consumers who want a peek at their own genetic profiles.

Some call this consumer-directed testing. Others prefer consumer-facing testing.

Jill Hagenkord, MD, adds a few more to the mix. Dr. Hagenkord, chief medical officer at Color Genomics, refers to direct-to-consumer and easy-access testing, placing them both in the category of consumer genomics.

Dr. Jill Hagenkord (right) with Wendy McKennon, vice pres-ident of product and user experience, at Color Genomics. "We're all part of this first group of clinical pathologists and laboratories that are actually doing real consumer genetics," Dr. Hagenkord says. (Photo courtesy of Cindy Charles)

Whatever the phrase, the shift is striking. Patient-centered care sounds almost quaint. With consumers pulling up their own chairs to the table—or rather, a digital screen—even the phrase "test menu" takes on a different tone. Menus aren't being handed only to clinicians who order for themselves and patients, like a well-heeled gentleman announcing "The lady will have. . . ." The lady can do her own ordering, thank you very much.

When she gives talks on the subject, Dr. Hagenkord makes a point of differentiating between nonclinically valid information—"ancestry, eye color, fun stuff"—and tests that are clinically valid. She notes that with their ability to sequence a genome or exome, consumer labs have the option of including "infotainment" genetic information as well as clinically valid information. The infotainment piece, she says, engages consumers and can increase their

genetic literacy, as well as drive family health discussions.

Matthew Ferber, PhD, agrees. He's the director of Mayo Clinic GeneGuide, a genetic testing experience that lets consumers initiate the test; Mayo's hook, so to speak, is education.

Mayo has partnered with PWN Health, a physician provider and genetic counseling network licensed in all 50 states, and Helix, which performs the actual sequencing. Dr. Ferber, a clinical molecular geneticist who is also co-director of Mayo's clinical genomics laboratory and founder of the institution's clinical genome sequencing center, uses the term near-consumer testing to describe the service.

GeneGuide launched at the end of last September, after a roughly two-year development period. "We felt there was an opportunity for Mayo to do it in a very responsible way," says Dr. Ferber.

It's crucial, he says, for consumers to know exactly what they will and won't get out of the experience (a word that pops up a lot in these conversations). GeneGuide is not aimed at people looking for a diagnosis, but rather at increasing genomic literacy; it does so by including topics such as autosomal recessive diseases, pharmacogenomics, and complex disease. "It's purely educational," Dr. Ferber says. The goal is to get people excited about learning, starting with their own DNA. This in turn should lead to deeper conversations about health with family members and physicians, he says.

Mayo advertises on social media and online radio stations but has taken steps to prevent a floodgates-have-opened scenario that many fear. When a consumer purchases a kit online ($199.99, plus $9.95 standard shipping), that triggers a qualification questionnaire that is reviewed by PWN Health. Just because a consumer orders a test doesn't mean it's appropriate—you can probably order sushi at a truck stop, too, but that doesn't make it right.

A pregnant woman can order the GeneGuide test, for example, but will need to acknowledge she understands that the test is not diagnostic and that comprehensive carrier screening is available elsewhere. If a consumer says they are affected by any of the conditions covered by GeneGuide (including as part of their family history), they can't order the test; instead, they are directed to see their personal physician and pursue diagnostic testing. Likewise, the test is not deemed appropriate for someone who has had a bone marrow transplant or a liver transplant.

Once they're collected, samples are sent directly to Helix for sequencing.

Mayo receives an alert when sequencing has been completed and will download the portion of data required to drive the GeneGuide interpretation engine. Dr. Ferber reviews the results and interpretations and signs out the reports. These results go first to PWN Health, which does its own review. PWN Health may reach out to patients and schedule a genetic counseling session in the event of a troubling finding—two cystic fibrosis alterations, say, or a positive malignant hyperthermia variant. Only after everyone is comfortable will Mayo release the data to the consumer on its app, says Dr. Ferber.

GeneGuide is not meant to compete with clinical diagnostics, Dr. Ferber says. Its limited menu is meant to whet the appetite of consumers. Testing is divided into four categories:

- *Carrier screening:* cystic fibrosis, *GJB2*-related hearing loss, MCAD deficiency, and sickle cell disease.
- *Medication response:* over-the-counter ibuprofen and omeprazole metabolism, and pseudocholinesterase deficiency and malignant hyperthermia susceptibility. The latter two were chosen after discussions with Mayo anesthesiologists. Says Dr. Ferber: "They felt like having that data was as good as having a piece of family history data in a pre-op visit. That level of information, coming from an educational experience like this,

would be of value to consumers as well."

- *Disease risk:* age-related macular degeneration, atrial fibrillation, coronary artery disease, and venous thrombo–embolism.
  All four entail genetic risk but are also influenced by environment, gender, and lifestyle, Dr. Ferber says. Mayo portrays individual risks using a beaker analogy that shows consumers the changing water levels as risks are added/reduced. In many cases, the genetic risks are relatively minor compared with other factors, he notes. With CAD, for example, "If you're a smoker, that's a bigger risk than the independent genetic factors that are included within the test. People need to know that." He and his fellow "nerds are quite happy with how we did this," he says with a laugh. "I'm eager to see post-market surveys to see if consumers are enjoying this as much as we did in the lab as we built it."
- *Health traits:* alcohol flush reaction, atopic dermatitis, and lactase persistence.

These are not Mayo's "sweet spots," Dr. Ferber concedes, but these common traits were included to potentially provide consumers with an a-ha! moment.

Once it completes the sequencing, Helix stores the data on its secure server. "This is important," says Dr. Ferber. Even though Helix is doing whole exome sequencing, Mayo Clinic GeneGuide has access only to the data being tested for in the GeneGuide kit.

Down the road, the additional data might prove important. And since the test started with the consumer, later follow-up might be easier when, say, a new variant is reclassified—the consumer can be reached directly and quickly. Or, as Dr. Ferber puts it, "The report isn't just for the physician anymore."

While waiting for results, users can peruse education modules that cover a range of topics, including genetic fundamentals, heredity, precision medicine, and common familial diseases. Clearly Mayo deems this information important, but Dr. Ferber admits the material continues to be tweaked—based on early returns, he says, consumers appear to be quite focused on their test results, and perhaps a little less so on education.

And for a dose of fun and learning (Dr. Ferber's words), GeneGuide also offers an interactive pedigree drawing tool, similar to what's used in professional medical settings, but in a simpler version. Consumers can fill out and edit an electronic survey; users can toggle between a consumer view and a physician view. Dr. Ferber sees several advantages to this flexible approach. First, it keeps the language consistent, without overwhelming patients or oversimplifying matters for professionals. It also helps with accuracy. His clinical colleagues, he says, tell him that patients often inadvertently provide inaccurate information during an office visit. It also encourages patients to include other relatives. "It's not just you and your doctor and maybe a significant other in the room, trying to recall all this stuff. This allows you to fill out this information while sitting on your couch, in the comfort of your own home." Ideally, he adds, it will be possible to link individual pedigrees to patients' EHRs, though this goal is a ways off. "It's a great idea, but a complex one," he says.

David Bick, MD, chief medical officer and a faculty investigator at HudsonAlpha, has been keeping a close watch on the field. He's a coauthor (as are Drs. Hagenkord and Ferber) of an article (Lu JT, et al. *J Mol Diagn.* 2019;21[1]:3–12) that looked at consumer genomics, including a framework for evaluating analytical and interpretive components of the tests. "The concept for the article was hatched maybe two years ago, when we all

realized that elective genomic testing"—Dr. Bick's preferred phrase—"was becoming extremely widespread. We were saying this is clearly happening—there's no doubt about that. Let's do it in a responsible way."

Adds Dr. Hagenkord: "We're all part of this first group of clinical pathologists and laboratories that are actually doing real consumer genetics. None of this is hypothetical to us. We run into expected and unexpected problems every day, and we're starting to amass enough of a knowledge base to help" with future guidelines. The authors noted, for example, that testing in elective settings, in a low-risk population, needs to control false-positive rates in a way that's different from the diagnostic setting.

Dr. Bick is also associate laboratory director of HudsonAlpha's Clinical Services Laboratory, which provides a fee-for-service whole genome sequencing and pharmacogenetics test called Insight. About three years ago the company started the Smith Family Clinic for Genomic Medicine (Dr. Bick is the medical director), which uses genomics in regular patient care for those with rare and undiagnosed diseases. When the standard practice of medicine didn't return an answer, Dr. Bick explains, the next step would entail using whole genome sequencing. Medical history, family history, physical exam results, and medical records from the patient's personal physician are all sent to the laboratory with the sample. "The laboratory has a lot of clinical information to help them look at the genome and personalize the results to the individual," he says, adding, "This is what patients/consumers want: a test result that reflects their personal medical situation."

When he gave talks about this approach, he says, he would invariably be approached by someone who expressed interest in having their own genome sequenced, even though they had no known genetic condition.

For a long time, says Dr. Bick, "We said no—that's not what we're focused on. But literally, we got so many requests for this, we said, 'Why are we telling people that they can't have their genome analyzed? Why is that? If they want to pay for their own testing, then it should be possible.'"

The ultimate goal, he says, is to identify risk in people who are ostensibly healthy. "What's happening over and over again," Dr. Bick says, "is the realization that restricting genetics to people who have some obvious, in-your-face problem leaves out a lot of people who could benefit."

Of the approximately 50 patients who've had their sequencing done, several have been found to have an unexpected variant that suggested a different approach to, say, colorectal cancer screening. Dr. Bick calls this a primary result, related to the individual's medical problem(s).

Sequencing also yields secondary results, which may lead to disease in the future. One patient was interested in a possible genetic clue to his Parkinson's disease; no link was found, but he did have a pathogenic variant in *BRCA2*, which prompted discussions with his sons and granddaughters about possible inheritance.

The clinic also offers carrier status testing. In this case, says Dr. Bick, consumers see the information as a gift of sorts for their children and grandchildren. (The self-pay approach tends to self-select older clients, he says.)

In the case of the pharmacogenetics testing, the clinic tests for 89 different drugs with pharmacogenetic variants. Patients may not currently be on any of the drugs, but having the information available may be useful if they're prescribed one, he says. "The time you need a pharmacogenetics test is the day before the doctor orders the drug for you." In one case, an individual who was on Plavix (clopidogrel) was found to have a DNA variant that interfered with his ability to convert the drug into its active form; he subsequently switched to a different platelet inhibitor.

At Color, Dr. Hagenkord says, the focus is on using genetics for population health management. Though consumers can purchase the test online ($208.95, including shipping and handling), the company's business model is broader—she calls it business-to-business-to-consumer, versus the business-to-consumer model used by companies such as 23andMe. Color partners with large institutions that are responsible for the health care of an entire population—a health care institution, say, or a large, self-insured employer—and offers whole genome sequencing as a health benefit.

Color has started by optimizing for a gene set based on a National Academy of Medicine paper (Murray MF, et al.

“A Proposed Approach for Implementing Genomics-Based Screening Programs for Healthy Adults.” Dec. 3, 2018). The physician-ordered test covers hereditary breast and ovarian cancer syndrome (*BRCA1, BRCA2*), Lynch syndrome (*MLH1, MSH2, MSH6, PMS2, EPCAM*), and familial hypercholesterolemia (*LDLR, APOB, PCSK9*). All three conditions have high penetrance and effective interventions for prevention or reducing risk, yet most people at risk are unaware of their status.

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The panel not only has the academy’s imprimatur, she says, but it’s the perfect size, at least for now. “People go too much, too far, too fast with genes,” she says. “It’s completely overwhelming to the primary care physician—really, to all physicians except geneticists. But starting with these three conditions makes it just a little bit easier of a starting base.” Consumer genomics needs to be a good experience for physicians as well as patients, she says.

“We also have to convince our buyers that our product is going to have beneficial health outcomes,” Dr. Hagenkord says. “So we can’t optimize it for junky ‘trinkets’ or fun stuff.” Once the health hurdle has been cleared, however, it makes sense to “use whatever other levers we can with genetics—because people find it so interesting—to create continued engagement around health actions you want them to take.”

“Genetics has been shown to be an activator,” she continues. “People have this health awareness moment when they get the genetics,” which, ideally, can be used to nudge them into the programs that would be most beneficial. Color also offers a collaborative health history and personal health history app, which Dr. Hagenkord characterizes as “a learning system that tracks its own effectiveness as we go along.” Participants can have the results sent to physician(s) of their choice; for health care clients, results are integrated into the EHR.

Says Dr. Hagenkord: “Patient-reported outcomes turns out to be pretty reliable for certain types of information.” She suggests that answering a survey while sitting on the couch—in the consumer genomics world, patients seem to enjoy filling out forms while sitting on their couches—is less stressful than sitting in a physician’s office “and being judged by the white coat.” The app allows family members to share family health history and build information “that’s much richer and more reliable than the health history you give in 60 seconds during your doctor’s visit,” she says. “You can actually ask your Uncle Mark in Green Bay, Wis., if he ever had a blood clot, or what kind of cancer he had, and how old was he? And then we can share that in a structured way with our health system partners.”

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Several studies have demonstrated this engagement also translates to compliance, she says. One study showed that patients who were prescribed a statin and received genetic information were up to 43 percent more compliant with their drug, up to 18 months out, than a group that received no such information at the time of prescription. Yet traditional medicine has never considered using genetics to motivate patients, she says.

Dr. Hagenkord doesn’t mince words when she peers into the future. Labs “will have to get on board eventually.”

Drawing on her years in Silicon Valley, Dr. Hagenkord says, “If you look at the way we do everything else in our lives right now, everything is app-based, convenient, frictionless. The only thing really left in our lives that is analog and not consumer-friendly, and very 20th century, is health care. Ten years from now, that’s going to be completely different,” she says. Case in point: 10 years ago, the roads were Uber-free and smartphones were a novelty. “You can see how that completely changed our expectations on how to live our daily lives. I think that’s going to happen in health care.”

In the relatively near future, Dr. Hagenkord predicts, sequencing will be within-rounding error-free and become a commodity. “So the value of genomic sequencing isn’t having the sequence itself; the value is in what you do with it.”

Different companies are placing different bets on what that value is. Color, obviously, is “making a population health play. Some of us are going to be more focused on health outcomes,” she says. “Some of us are going to be more focused on fun and delight. Some of us are going to be more focused on ancestry.” Trying to understand the field as it unfolds will be futile without understanding the underlying business models.

She worries, however, that the various models are making matters needlessly complicated. A test designed for research and ancestry, using older technologies, won’t detect pathogenic rare variants and novel variants. “It’s confusing the marketplace,” Dr. Hagenkord says, even with clear FDA labeling that indicates the limitations of such genetic testing. That in turn could sow doubt among physicians just when they need to become more involved.

Dr. Ferber says he himself was a skeptic early on. “I used to look at these consumer-focused genomics companies and quite honestly, I didn’t agree with the direction they were going. And some of them, I still don’t.” But done right, he says, everyone can benefit.

Even so, he says, “The vast majority of physicians aren’t comfortable talking about genetics.” So it wouldn’t surprise him, he says, if many of them dismissed consumer genomics tests out of hand. “I totally get it,” he says.

But the move toward digital and automation is inevitable, he says, echoing, Dr. Hagenkord. “So it’s going to be even more important, as this happens, to make sure that people know that consumer tests are for an otherwise well population,” Dr. Ferber says. “If somebody is sick, or suspects themselves of having a disease, that, to me, is off limits. That, to me, is a physician visit. We have to work hard to not confuse people. That’s not safe, and that’s not good for any of us.”

Companies that got an early start in consumer genetic testing have played their cards differently than clinical labs—a game of Go Fish versus contract bridge. By focusing on consumers, not the test per se, "They've always been a bit more Silicon Valley," Dr. Ferber says, "a little bit more, *Don't confuse people with the details—just keep them engaged, keep them excited.* But the details are important. How do you communicate—without losing them?" He's confident clinical labs will find the answer. "It may seem like we're behind, but this is a pretty long race to run. It's not too late."

Dr. Ferber also foresees a time when consumer genomics will become the norm. At a low enough price, he says, widespread genetic testing will be as valuable as newborn screening. "I see a time when everybody gets this. I don't know what the appropriate age would be. But there comes a time when healthy people should just know this type of stuff."

Using his own experience as a guide, Dr. Ferber would like physicians at least to start thinking and talking about it. "My knee-jerk reaction was, *This is bad*. And it's met with a lot of cautionary tales about the demands it will place on the health care system." Done correctly, however, the right people will receive the right tests, he insists, and labs will be educating an important group of patients about genetics much faster than they ever could before.

Dr. Bick thinks he sees an easier road. Many labs are already running clinical tests that could transfer to the elective realm. "That's an immediate way to get into offering elective testing without a huge financial commitment." He agrees physicians might push back—but not all of them. "Not to be too mean to the oldsters," he says (noting that he's in his 60s), "but younger physicians are more likely to look at regular diagnostic genetic testing as part of regular care—and by the same token, elective genetic testing."

Labs that do become involved can help head off the horror stories that emerge when people receive confusing results. "Having raw data doesn't help you; it could, in fact, confuse you," Dr. Bick says. A sophisticated laboratory can tell patients and physicians if the data are good, and what they mean. "Labs need to step up and be involved in doing this from the get-go. They're the experts. They're the ones who should be directing elective genomics. And they should be doing it tomorrow."

Some of the pushback Dr. Hagenkord has seen from physician colleagues is tied to outdated information. "Most people aren't up to date on how consumer genomics has evolved," she says. When polygenic risk scores came on the scene as part of the first wave of DTC genomic testing, "no one was talking about consumers. And the entire complaint by the entire medical professional community was almost exclusively on the fact that there was no established clinical validity for the polygenic risk scores that these companies were providing." That has changed, she says. Old technology was SNP-based, but virtually everyone has moved to clinical-quality sequencing and uses board-certified experts to interpret/report results, she says. Nevertheless, colleagues are still reciting the old mantra about lack of clinical validity.

The debate needs to change, she says. "It's not about, is this test accurate or not? It's the same test that you would get at any clinical lab," but cheaper and easier to get.

Since Color launched in 2015, Dr. Hagenkord has learned a few things about the consumer perspective. Chief among her findings: "People love to learn about themselves, and they love to talk about themselves." Combining the two leads to a "virtuous cycle, an exchange of information that both parties seem to benefit from."

Consumers want to know, among other things, their *APOE*-related Alzheimer's risk, she says. Even though they can't act on this information, "Consumers find it interesting and engaging. People are declaring what they find to have personal utility as opposed to this very strict clinical utility model that we have in the nonconsumer world."

Need more proof? Dr. Hagenkord recounts 23andMe's voluntary research efforts, which she says attracts a very high percentage of the test's buyers. As part of those efforts, the company asks its users what topics they're interested in. One example in particular makes Dr. Hagenkord laugh. "23andMe was able to, with a few clicks of a button, do the world's largest genomewide association study on stretch marks.

“Trust me: The NIH is never going to fund a $5 million, five-year stretch marks project.”

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