IS CLINICAL GENOMICS TESTING WORTH IT?

Cost-effectiveness studies yield answers to the complex question of whether clinical genomics testing has value.

Whole-genome testing has now reached the long-anticipated “$1,000 genome” level; and more targeted genetic panels cost even less. But the costs associated with genomic testing don’t end with sequencing. Additional expenditures—for follow-up testing or treatments—may far exceed the investment in sequencing itself.

“I hear people say, ‘of course it’s cheaper and better to just sequence people up front: More information is better,’” says Kathryn Phillips, PhD, professor of clinical pharmacy at the University of California, San Francisco. “In fact, it might be better in some situations but not others.” Phillips and others are trying to pinpoint the situations for which the health benefits of genomic testing outweigh the costs, using cost-effectiveness analyses.

It’s not a simple task: The inputs—such as the risks associated with a genetic variant and the possible benefits of testing—are uncertain. Sequencing also provides information about many different genes, and each variant will have a different cost-benefit ratio. “You can’t do a holistic view of the full benefit of these tests,” says Eman Biltaji, PhD, graduate research assistant at the University of Utah. “You can only do a study focusing on one piece of it and then another study focused on another piece of it.” Finally, patients’ preferences and behaviors complicate things. For example, if a patient who gets a negative genetic test decides to forego routine disease screening as a result, that could be a hidden cost of testing.

As payers (insurance companies and governmental insurers) weigh whether to cover the costs of testing or not, cost-effectiveness research may help provide some answers to the key question: how to deliver the right service to the right patient at the right time. Cost-effectiveness analyses are revealing valuable benefits for certain patients, in the areas of rare pediatric disease, cancer, and pharmacogenomics. But the jury is still out as to whether whole exome or whole genome sequencing (WES or WGS) for healthy patients is worth it.

Rare Diseases in Children: Test Early!

Children affected by rare monogenic conditions often undergo an extended diagnostic odyssey during which they are poked, prodded, tested and hospitalized at great expense to their families and the healthcare system. A study of 40 such patients published in *Genetics in Medicine* in January 2017 found that cost-effectiveness was maximized when patients were offered WES as soon as a problem was suspected. “If you find out what’s happening early in the diagnostic trajectory, it does allow you to influence management of the genetic disorder a lot more than if you’re provided with an answer a few years down the track,” says Zornitza Stark, MD, a clinical geneticist at Murdoch Children’s Research Institute in Melbourne, Australia, one of the lead researchers on the study.

Another similar study of 150 pediatric neurology patients in the Netherlands also found early use of WES to be cost-effective; and a Canadian study of 103 pediatric patients with suspected genetic disorders found that WGS provided a

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**Cost per Genome**

The cost of sequencing a human genome has dropped significantly since 2001 and has significantly outpaced Moore’s Law since 2008 with the advent of next-generation sequencing technology. Courtesy of NHGRI, https://www.genome.gov/sequencingcostsdata/
far higher diagnostic yield (41 percent) than a gene panel (24 percent) or WES (34 percent), suggesting that WGS may be cost-effective in this context as well.

Studies like these have an impact because they can convince payers that genomic testing is worth reimbursing, Stark says. “Our state government has recently announced big money—$8 million—for rare disease diagnosis so that

Stark and her colleagues compared the diagnostic trajectory and resulting diagnostic yield and costs per patient for 40 infants with monogenic disorders under four conditions including standard care (yield: 7 diagnoses) and three other models: (1) WES as a last resort after exhausting all standard investigations, including planned gene tests (yield: 13 diagnoses); (2) WES replacing some investigations, particularly gene sequencing tests, complex biochemical tests, and invasive tests, (yield: 25 diagnoses); and (3) WES replacing most investigations (yield: 25 total diagnoses). Model 3 was the most cost effective per diagnosis ($6003) while standard care was the least cost effective ($27,050). Reprinted by permission from Macmillan Publishers Ltd from Stark Z, Schofield D, et al., Prospective comparison of the cost-effectiveness of clinical whole-exome sequencing with that of usual care overwhelmingly supports early use and reimbursement, Genet Med 19: 867-874 (2017).

we can provide this type of testing.”

Stark is now interested in pushing for rapid testing in hopes of returning WES results in a few days rather than 4 to 6 months. “It costs a lot more but potentially allows better decisions in ICUs (intensive care units) which are expensive places anyway.” A day in the ICU costs about $4,500, she says, while rapid testing costs about the same. But the costs still need to be studied to determine whether testing actually makes a difference. “I think in the rare disease space, there’s been an assumption that it doesn’t really matter: These children are just considered incurable, untreatable. You’re just giving it a name,” she says. “That is sometimes true, but you’d be surprised by how much of an impact we’ve had on our patients. It has certainly exceeded our expectations.”

Cancer:
Testing the Right Genes at the Right Time

In the cancer arena, some gene panels assess patients’ risk of various cancers and others evaluate the genetic makeup of a specific tumor to determine the most effective treatment.

“Cost-effectiveness of Genomics Testing

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these treatments for the right patients.”

But is it best to do a single gene test for the RAS mutation or a gene panel that provides information about other genes implicated in treatment response as well? Another challenge: Testing a tumor’s gene expression once isn’t enough because the tumor evolves, Biltaji notes. If it is difficult to get new tumor biopsies—from the brain, for example—a patient might continue to be treated based on old, incorrect information. That would change the cost-effectiveness analysis.

Pharmacogenomics Panels: A Few Base Hits

Pharmacogenomic screening can reveal how a person’s genes affect his or her response to drugs, leading to safer prescribing and dosing. But the question remains whether routine pharmacogenomics screening is cost effective.

In a recent study of elderly patients taking three or more medications, Biltaji and her colleagues found that, compared with matched controls, screened patients had a lower rate of hospitalizations and ER visits—but higher outpatient visits—during the ensuing four-month period. Overall, there was a cost saving in the genetic testing arm—but the dollar amount was small—$218 net savings per patient, including the cost of the test.

“In the pharmacogenomics space, people have been looking for a home run example where we’ll be saving lives left and right and revolutionize medicine,” Veenstra says. “But it’s not about that; it’s about a bunch of base hits.” In order to justify pharmacogenomic screening of healthy people generally, he says, “Panel testing will need to be in the hundreds of dollars …. And I think that’s where we are going.”

Genome Testing of Healthy Folks: The Big Question Mark

Genetic panels and WES for people who are already ill is one thing. Whole genome sequencing or gene panels for otherwise healthy patients is another. “Usually tests are done for a particular reason,” Phillips says. “If you’re just fishing, then it’s a question of how to put a value on that.” There’s also the question of whether integrating genome tests into healthy patient treatment could lead to overuse—or possibly even underuse—of healthcare resources.

“How do people who are ‘negative’ for risk genes behave?” wonders Veenstra. “Are they less likely to get a mammogram even though a negative BRCA finding doesn’t mean they are at lower risk for breast cancer? You want people to follow recommendations but not pursue health care consumption behaviors that aren’t justified.”

There’s also the question of how to handle incidental findings—i.e., the discovery of genetic variants that were not the target of the genetic test’s original goal. For example, if a person is tested for colorectal cancer treatment purposes, but the test reveals variants with other medical implications, should the patient be informed of these results? This issue rose to the fore a few years ago when the American College of Medical Genetics and Genomics (ACMG) recommended that clinical laboratories performing genomic testing should routinely report any incidental findings relevant to 56 (at the time—now 59) genes considered actionable and having a high probability of causing disease. The recommendation was later revised to state that patients may opt out of receiving the findings.

Prior to making the recommendation, the ACMG had not evaluated whether returning incidental findings to patients would be cost-effective. In work published in Genetics in Medicine in 2014, Veenstra took on that challenge. He and his colleagues applied some clever strategies to determine that the return of incidental findings could prove cost effective for some patient populations. “Our work to date has shown that the reporting of incidental findings could be worth doing,” Veenstra says. “But we need better estimates of penetrance and how people behave when provided this information.”

A group at Brigham and Women’s Hospital in Boston is trying to find the answer to that very question. As part of a large research project called MedSeq, Kurt Christensen, PhD, instructor in genetics and medicine at Harvard Medical School, and his colleagues performed WGS on primary care patients at a cost of about $5,250 per patient. They then looked at whether the information gained led to higher healthcare expenditures in the ensuing six-month period. Compared with untested patients, those with WGS results incurring about $350 more in healthcare costs during that time (a difference that was not statistically significant), Christensen says. The MedSeq team will continue to follow these patients long term. “Six months out is too soon to see the kinds of cost-savings you might see as a result of correct dosing or avoiding adverse reactions to medicines, or detecting or preventing disease,” he says.

But there are methodological challenges to this kind of cost-effectiveness research. “What are the right methods for capturing services linked to the genetic information so that we can distinguish what was ordered in response to sequencing as opposed to other conditions that might arise?” he asks.

Knowing Enough to Make Good Decisions

Ultimately, the value of genomic sequencing lies in how it affects clinical practice. Veenstra predicts that in five to ten years, even run-of-the-mill healthcare systems will be considering screening untested populations for the ACMG and pharmacogenomic genes. And cancer gene testing is well underway in many healthcare settings. If the cost of WES and WGS continue to drop, perhaps they will become routine as well.

“The exciting part,” Veenstra says, “is that there’s a good chance these tests have good economic value.”