Biomarker screen makes case for MODY genetic testing

Anne Paxton

February 2020—Cost-effectiveness analysis of health care diagnosis and treatment, unfortunately connoting quotas and spartan budgets, may not have the best reputation among the general public. “A lot of people approach studies of cost-effectiveness with suspicion,” says Matthew S. GoodSmith, a medical student and researcher at the University of Chicago Pritzker School of Medicine. “When you say ‘cost-effectiveness,’ people think ‘death panels.’”

A new study using computer simulation models to demonstrate the cost-effectiveness of genetic testing for maturity-onset diabetes of the young (MODY) in a subpopulation of patients could help turn that impression around while making progress in treatment of this inherited disease. Surprisingly, it turns out that for MODY, not only is genetic testing of a patient cost-effective, but cascade testing of the patient’s relatives is cost-effective as well.

In the recently published study, “The Impact of Biomarker Screening and Cascade Genetic Testing on the Cost-Effectiveness of MODY Genetic Testing,” GoodSmith and colleagues at the University of Chicago report that a combined strategy of biomarker screening and genetic testing for MODY in the U.S. pediatric diabetes population is cost-saving compared with usual care, increasing average quality of life and decreasing costs by $191 per simulated patient over 30 years. The addition of cascade genetic testing boosts cost savings even further, to $735. “Widespread implementation of this strategy could improve the lives of patients with MODY while saving the health system money,” the authors conclude (GoodSmith MS, et al. *Diabetes Care.* 2019;42[12]:2247–2255).

The MODY study is a strong example of the promise of personalized medicine, says coauthor Elbert S. Huang, MD, MPH, professor of medicine, director of the Center for Chronic Disease Research and Policy, and associate director of the Chicago Center for Diabetes Translation Research, University of Chicago. “It shows that routine testing for genetic disorders can be tailored based on a simple clinical screen and it can improve the health of people while also not increasing costs to the health system.”

Although only about 0.8 to 2.5 percent of the diabetes population has MODY, the extent of misdiagnosis of MODY and the expense, discomfort, and potential harm of incorrect therapies make better testing strategies important. But genetic testing for MODY has often been delayed because of insurers’ reluctance to cover it, GoodSmith notes. “At the moment, genetic testing for MODY is often denied by payers. The goal of testing the cost-effectiveness of alternative strategies for genetic testing is to identify the strategies that benefit patients and make sense financially for payers and society.”

Payers may have had good reason to be wary of MODY genetic testing. As researchers at the same center found in the first cost-effectiveness analysis of MODY genetic testing conducted in the U.S., which compared Sanger sequencing for mutations in *HNF1A, HNF4A*, and *GCK* to no genetic testing, it would be “prohibitively expensive” to implement such genetic testing across the entire study population of (in this case) young adults with type two diabetes. The incremental cost-effectiveness ratio—that is, dollars per quality-adjusted life year—was $205,000, the authors found (Naylor RN, et al. *Diabetes Care.* 2014;37[1]:202–209). In other words, “If you just start genetic testing in the 95 percent of people who have type two diabetes, without any kind of clinical screening or attempt to narrow the testing population to people likely to have the genetic disorder, it turns out not to be cost-effective,” Dr. Huang says.

In this new study, the coauthors believed that appropriately winnowing down the screening population might justify the cost of genetic testing. They used the fact that the vast majority of MODY patients are negative for islet autoantibodies and positive for C-peptide to select biomarker screening of GAD65 and IA-2 autoantibodies and plasma fasting C-peptide. These tests were applied to the entire testing arm cohort of the study to identify patients with a high probability of having MODY. The biomarker screening restricted genetic testing to 23.9 percent of the total U.S. pediatric population with diabetes. These patients were modeled to undergo simultaneous genetic

testing for heterozygous mutations in G*CK, HNF1A*, and *HNF4A* at a set cost of $3,723.96 per individual, including an additional outpatient visit. About five percent of the patients who received the genetic tests were MODY positive.

Dr. Huang

Computer simulations are a powerful means of drawing actionable conclusions about diagnosis and treatment. “In the case of chronic conditions like diabetes, coronary artery disease, or hypertension,” Dr. Huang says, “we almost always rely on forecasting models or simulation models of complications. You’re making changes in treatment, and because of the long-term nature of those diseases, diabetes in particular—between diagnosis and the emergence of complications is a decade—typically to see the effects of therapy requires a simulation model.” Otherwise, he says, “For many of us, the trials would outlive us. We wouldn’t have any answers to make decisions today.”

Cost-effectiveness analysis in diabetes goes back to the late 1990s, when some of the first questions around the economic value of diabetes treatment emerged, Dr. Huang says. More recently, studies employing simulation models of distinct forms of diabetes to forecast the clinical and economic consequences of testing strategies have explored the cost-effectiveness of new technologies used particularly in type one diabetes, such as continuous glucose monitoring and insulin pumps. “In comparison to studies of new drugs and technologies, health economic research on genetic diagnosis of diabetes is still a relatively new field,” Dr. Huang says. The University of Chicago’s Center for Chronic Disease Research and Policy is one of the only groups that has repeatedly revisited the idea of genetic testing.

In Europe, cost-effectiveness analyses are more common. “That’s one of the ways that the U.K. government decides what it pays for,” GoodSmith says. “There, cost-effectiveness is much more entrenched in their decision-making process.”

The process does require assumptions to be made about future costs. “There is always the risk—and this has definitely happened—that costs of therapies will change in ways we didn’t expect,” GoodSmith says. “But if you need to make a decision today, we use the best information we have right now with what we know about the natural history of diseases. These models provide evidence to help answer a question now.”

“The traditional cutoff for cost-effectiveness and the one used in most studies is $50,000 per quality-adjusted life year,” he adds. “That’s kind of a convention that’s developed. Some studies say it might be closer to $70,000 or $80,000 per quality-adjusted life year, in terms of what payers would be willing to pay for.”

A testing strategy’s cost-effectiveness can be improved, however, by narrowing the population to be tested. The first U.S. cost-effectiveness study’s finding of an incremental cost-effectiveness ratio of $205,000 was far above the threshold, GoodSmith says. “But in their sensitivity analysis in that paper, they showed that if the MODY prevalence was increased among the testing population to six percent, that would make the testing intervention cost-effective.” A U.K. study from 2016 (Shepherd M, et al. *Diabetes Care.* 2016;39[11]:1879–1888) did accomplish that, using biomarker screening in six pediatric clinics to help narrow the genetic testing pool.

For the latest research, GoodSmith says, “we decided to conduct the study in a pediatric population where the prevalence of type one diabetes is higher. The average cost for a type one diabetes patient is generally higher due to increased insulin requirements and earlier development of many complications. With this in mind, we thought we could perhaps find a cost-effective strategy in genetic testing.”

MODY is an inherited disorder, a monogenic diabetes, causing symptoms that develop gradually. But MODY can be

confused with type one or type two diabetes. That was one reason the researchers chose to focus on MODY, GoodSmith says. “It’s frequently misdiagnosed, and there are easy treatment changes you can make for the patient to quickly change their outcomes.”

For HNF1A and HNF4A MODY patients, “switching to sulfonylureas is known to improve glucose control and reduce the number of adverse events,” he explains. “This medication works downstream of the genetic defect to allow for increased insulin release, so it improves HbA1c levels and general diabetes management relative to usual care. For GCK MODY, it’s known that no medication is required, outside of pregnancy. However, many doctors do not routinely think about GCK MODY in their clinical practice, and as a result, a lot of patients are prescribed insulin just because they were repeatedly tested and continued to be hyperglycemic. This unnecessary insulin use leads to negative effects.” Insulin is expensive relative to sulfonylureas, which is one of the older class of therapy, so removing it when it’s not necessary can produce cost savings, he adds. “These are things that make MODY a good candidate for this kind of study.”

The choice of a 30-year time frame was based in part on the pediatric population (age 10 to 20) under study. “It is a concrete period of time that people can grasp, and it adds immediacy to the study versus a lifetime model,” GoodSmith says. “And you can make more of an argument that this is something that will save costs to the health system sooner if you do it on a more contracted timescale than over a lifetime.” However, the researchers also ran lifetime numbers (included in a supplemental table) which reaffirmed the cost-effectiveness of the testing strategy. “It increased cost savings further and increased quality of life further.”

This study is a rare application of precision medicine, GoodSmith says. “In precision medicine, an individual’s genetics, environment, and lifestyle are explored to help develop new treatment strategies. This includes applying a specific genetic testing strategy to individual patients to improve their health. Normally that’s an expensive proposition because you’re applying expensive tests to a small number of people, which is hard to do on a populationwide scale, unless you do something like we did—an innovative, focused testing strategy that identifies the people most likely to benefit.”

He didn’t expect to see the impact of even a relatively conservative use of cascade genetic testing—testing of the patients’ relatives to further narrow the screening population. The MODY study shows that cost savings simply with biomarker screening and genetic testing can be achieved. But with cascade genetic testing, the cost savings increase considerably. “With the biomarker screening and genetic testing, the average cost savings is $191 per patient. That increases to $735 when you add the cascade testing. That’s quite a cost difference, and you also get a change in the quality-of-life benefits. So even though it is difficult to sample the relative and find relatives willing to undergo genetic testing, any one person you find through cascade testing increases cost-effectiveness drastically, because the chance of that one person having MODY is so high,” GoodSmith says.

The potential power of cascade testing has been relatively untapped, he believes. “We have never seen a cost-effectiveness analysis for genetic testing in MODY that included cascade testing, which we thought was surprising because its potential to increase cost-effectiveness is so great. But as you can imagine, at least in the current environment, one of the barriers to cascade testing is this: If insurance providers don’t approve the test to begin with for the proband, how would you expect them to approve the test for their relative?” The researchers still hope, however, that such expanded genetic testing will get a better hold on MODY, GoodSmith says.

The high cost of commercial genetic tests also continues to be a barrier. “We know from our prior work that 73 percent of patients found to have MODY were diagnosed as part of a research study rather than by commercial-based genetic testing. So that kind of shows the barriers to clinical implementation of genetic testing for MODY in the U.S. The findings from our paper provide more evidence that this barrier should be removed,” GoodSmith says.

“When you start one of these studies,” Dr. Huang says, “you don’t really know what side of the ledger some of these results will be on, whether they will be cost-effective or cost-saving, because few people have the genetic condition and you’re spending a lot of money to screen a pretty large population. So it was a bit surprising to find that the therapy saved money.” Despite introducing the cost of genetic testing, “you end up with kind of a neutral

economic picture."

The takeaway from this study and others, Dr. Huang says, is that personalized medicine is a better way of providing care. "What you're doing is shifting resources around in the population, and it's probably a better way of allocating resources. But it doesn't produce dramatic cost savings that would solve the major health care problem of rising health care costs."

Predicting testing costs, Dr. Huang says, is easier than predicting treatment costs. "Genetic testing costs have been steadily declining, while treatment costs are going in the opposite direction. So if we can generate a lot of value from diagnostic testing, that's a really smart way to go because it's something that's declining in cost."

Interestingly, the MODY study represents a switch from original cost-effectiveness analyses conducted two decades ago because it addresses quality of life, Dr. Huang points out. "Those earlier studies ignored quality-of-life issues around the daily experience of taking medications and how it affects people. We have done two large-scale studies of patient quality of life. And I think many clinicians would not be surprised at this, but the route of administration of a drug matters a lot to patients. The desire to avoid an injectable drug is powerful, and we've quantified what that means to patients. If you can allocate therapies to match what the patient needs and switch from injectables like insulin to oral agents, it is an additional benefit to patients' quality of life."

Insurance coverage remains a significant factor, Dr. Huang agrees. "Genetic testing is simply not systematically covered by insurance. I also think that the insurance plans don't have a clear understanding that these different forms of diabetes even exist. So patients and their doctors who are ordering these tests face many challenges in explaining what the test is for."

"Figuring out insurance coverage in the era of precision medicine is a bigger, broader problem," he continues. "This particular paper is talking about young adults, and most of the insurance plans that would be affected by this sort of cost-effectiveness analysis would probably be employer-sponsored insurance, rather than Medicare. In my experience, insurance plans have a lot of difficulty keeping up with changes in medicine, and explaining to somebody on the phone who doesn't know these genes or doesn't know what the consequences of testing are is going to be difficult." Cascade testing will be even more difficult to justify or explain, he adds.

To flesh out the cost-effectiveness questions, it would also be important to address the societal component. "We likely don't capture all the societal costs. There's a lot we don't know about the societal spillover effects of how having genetic information about people might affect their employment or their education attainment, for example." Whether a person is on insulin can affect whether he or she can have a job such as bus driver or airline pilot, jobs that historically have been barred to people with type one diabetes, Dr. Huang says. "But let's say you have a genetic form of diabetes that can be managed successfully with oral agents. That could change your outlook completely, above and beyond the health effects of the better regulation of the disease."

The most exciting implication of this cost-effectiveness study, GoodSmith says, is that it shows the benefits of the focused use of a personalized medicine tool. The implications of the study could go well beyond diabetes, in his view. "If you apply expensive tests in innovative ways, it can lead to cost savings. I imagine there are other diseases with other available biomarkers where this kind of analysis could be applied."

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