

Put to the Test

As genetic screening gets cheaper and easier, it's raising questions that health-care providers aren't prepared to answer.

BY HAROLD POLLACK

When my children were born in the mid-1990s, new parents could already see that prenatal genetic testing was altering the terrain of pregnancy and childbirth. Growing numbers of educated women were having children at older ages, with resulting difficulties and risks. More and more parents faced challenging, deeply personal decisions about whether to engage in genetic testing and what to do if they received unfavorable results.

I remember my own anxieties when my wife, Veronica, took a blood test that searched for elevated alpha-fetoproteins, which are associated with diverse ailments ranging from spina bifida to anencephaly. The mere prospect of these rare conditions—and even the choice to undergo the tests—was surprisingly painful. At least genetic counselors and other professionals were available to help guide us.

By that point, amniocentesis had been in wide use for more than two decades. As researchers identified the genetic markers associated with a growing list of important conditions, educated, secular, and affluent communities began to embrace genetic testing. A small but lucrative market in assisted reproductive technologies quickly emerged, which provided parents with greater control over the genetic characteristics of their offspring. In some parts of America, new diagnostic technologies provoked unease regarding their eugenic potential.

In retrospect, these innovations were incredibly tame. Technological limits, cost, intrusiveness, and risk constrained the scope of screening efforts. Roughly one in every 200 amniocenteses resulted in miscarriage, which made the procedure too risky to justify screening the full population of pregnant women. The human genome had yet to be sequenced. Newborn screening was routinely used to identify a handful of important metabolic disorders, but it was a very expensive process. There was a certain clarity, too. The most common use of amniocentesis was (and remains) to detect conditions associated with very serious physical or intellectual disabilities. When such conditions were detected, most parents chose to terminate the pregnancy.

Fast forward to 2010. Prospective parents can now be tested before pregnancy, and those found to be carriers for serious conditions have the option of in-vitro fertilization, whereby embryos can be pre-tested for genetic markers associated with Alzheimer's disease, hemophilia, muscular dystrophy,

Tay-Sachs disease, and more. Many of these same markers can also be detected by do-it-yourself genetic-testing kits, which are beginning to appear on the Internet and on drugstore shelves. Walgreens may soon sell a cheap home test that covers 37 genetic conditions. (Sales are postponed pending approval by the Federal Drug Administration.) You will soon be able to buy a test kit online, mail a finger-stick blood sample or a saliva swab to a lab, and receive an e-mail containing your detailed DNA workup a few days later. In the not-too-distant future, researchers note, you will be able to purchase your complete genetic sequence encoded onto a chip for \$1,000, or maybe even as little as \$100.

If you've recently had a child, you might be surprised by the number of rare conditions for which she was screened in the hospital nursery. All 50 states test newborns for sickle-cell disease and for cystic fibrosis. The emergence of a single technology, tandem mass spectrometry, now allows newborn-screening programs to simultaneously test for dozens of traits for roughly \$10 per blood sample. This dramatically expanded the scope of newborn screening. In 1995, the average state mandated newborn screening for five conditions. By 2005, this number had increased to 24. The American College of Medical Genetics now recommends that babies be screened for more than 50 primary and secondary disorders.

Yet knowledge of genetic markers does not always bring clinical benefits. Many optimistic accounts of the future of genetics fail to consider the full costs and implications of widespread screening: How will these technologies be regulated? How should public-health authorities and health-care providers—not to mention patients and their families—respond when unsettling results are found? Will patients and their families even understand the complex options available to them? Research suggests that patients often make poor decisions based on genetic information and that doctors don't do much better. We face an embarrassing mismatch between our lofty aspirations of personalized genomic medicine and the everyday capacities of our medical-care system. As Hank Greely, director of Stanford's Center for Law and the Biosciences, told *The Washington Post*, "Information is powerful, but misunderstood information can be powerfully bad."

As we identify new genetic markers associated with disease, and the immediate costs of screening drop precipitously,

Greely's warning is increasingly relevant. It's often unclear why we should screen millions of newborns for genetic traits. Are we helping parents with their reproductive planning or just allaying their anxieties about a baby who somehow appears different? Are we helping children through early diagnosis and treatment or are we stigmatizing them and thus doing harm?

At least in the short term, genetic testing is raising more questions than it's answering.

ALMOST 50 YEARS AGO, THE WORLD HEALTH Organization commissioned James Maxwell Glover Wilson, a British public-health leader, and Gunner Jungner, a Swedish clinical chemist, to develop a framework to address the issues surrounding early disease-detection efforts. In 1968, Wilson and Jungner published 10 principles to govern public-health screening, which remain essential guideposts in America and around the world. These principles require that screening specifically benefits the screened population and that the costs (including counseling and treatment) are reasonable. Informed consent and confidentiality also play an important role. When the Wilson-Jungner criteria are not met—for example, in testing people who display no symptoms to find out if they are carriers of genetic disorders—ethicists generally oppose mandatory universal screening.

The Wilson-Jungner criteria raise complex issues even when applied to familiar conditions such as Down syndrome. These issues become even more difficult—ethically, organizationally, and medically—when one considers more complicated genetic disorders such as fragile X. Though you've probably never heard of it, fragile X is the most common heritable form of intellectual disability. In 1943, J. Purdon Martin and Julia Bell identified the disorder's X chromosome-linked genetic footprint by tracing inheritance patterns in one family that included 11 disabled males. Although a chromosomal test has been available since 1969, fragile X's specific genetic mechanisms were not discovered until 1991—a breakthrough that Nobel Prize winner James Watson called “the first major human triumph of the human genome project.”

Fragile-X syndrome arises from a particular repeated sequence of amino acids on a gene of the X chromosome—the more repeats, the more severe the mutation is likely to be. If the repeated sequence is long enough, our cellular quality-control system suppresses production of a critical protein. People with more than 200 repeats are defined as having the full mutation, though there is no firm threshold for disability. An estimated one in 3,800 males exhibits the full mutation, and about 90 percent of those with the full mutation will display low IQ, characteristic physical features such as an elongated face and macroorchidism (grossly enlarged testes), and behaviors such as hand-flapping and palm-biting. People with fragile-X syndrome are often very shy with attention deficits, hyperactivity, and sensory issues. About one-fourth of boys with fragile-X syndrome also satisfy diagnostic criteria for autism. Girls and women affected by fragile X experience more varied symptoms, because their other X chromosome provides some protection. An estimated one in 2,400 females

carries the full mutation, and, according to one widely-cited estimate, about 25 percent of females with the full mutation have IQ scores below 70, the usual threshold used to define intellectual disability.

To further complicate things, perhaps 90 percent of people who would be identified by current fragile-X screening tests are “premutation carriers.” Like those with the full mutation, premutation carriers have an abnormal number of repeats, yet fewer than are typically required to cause fragile-X syndrome. For premutation carriers (and for a minority of those with the full mutation who display few symptoms), screening is beneficial mainly for reproductive planning. Because the number of repeats tends to grow over generations, carriers may have children with the full mutation. Premutation carriers themselves also face distinctive medical risks. Men may display Parkinson's-like syndromes later in life. Women face elevated risks of premature ovarian failure. Both genders face potential learning disabilities, attention problems, anxiety, and depression, with symptoms being more severe among men.

Fragile X can be difficult to diagnose. Two people with the same number of repeats can display very different symptoms, sometimes no apparent symptoms at all. The loose association between genetic markers and disease—what clinicians call the genotype-phenotype mismatch—complicates both treatment and policy. Of course, diagnostic delays could be avoided if the entire newborn population were screened. But pediatricians, geneticists, and medical ethicists disagree about whether and when newborn fragile-X screening actually satisfies the Wilson-Jungner criteria. Nearly everyone agrees that our medical and public-health systems are unprepared to do this screening well.

Moreover, the challenges and ambiguities associated with fragile-X screening will arise with many other conditions in coming years: Is it cost-effective to screen millions of newborns to identify perhaps just 1,000 per year who might be helped? What should we tell the parents of premutation carriers? Could screening stigmatize newborns for whom genetic information may provide no immediately useful information for treatment or services? Would parents provide informed consent before their newborns were screened? If so, how would this process work? What can we do to help families in the event of unfavorable test results? And, perhaps most crucially, what is our game plan for actually providing this help?

OUR PUBLIC-HEALTH SYSTEM IS MOBILIZED to do one kind of screening efficiently on a mass scale: newborn screening. If one wants to reach every American, this is the way we generally do it. For example, public-health authorities screen nearly every American infant for phenylketonuria (PKU), a devastating but readily treatable condition. Early PKU treatment has prevented permanent and profound intellectual disability among many thousands of children.

With these benefits of early diagnosis in mind, Donald Bailey of the Research Triangle Institute recently spearheaded one of the largest epidemiological studies of fragile X ever



performed. More than 1,000 parents of children diagnosed between 2001 and 2007 were surveyed regarding their experiences. These parents reported that they first became concerned when their sons were about 12 months old. Yet on average, these children did not receive a proper genetic diagnosis for another two years, and the delay was even longer for girls. Parents often spend thousands of dollars chasing false leads, in what is sometimes labeled the “diagnostic odyssey.” They also have other children before the correct diagnosis is made. In this same study of children with fragile-X syndrome, 27 percent of boys and 39 percent of girls had a younger sibling with the full mutation before they themselves were diagnosed.

Many families are treated cruelly or incompetently in the absence of proper diagnosis. “I knew something was [amiss] right after I gave birth to Josh,” wrote one mother, Eileen, on a fragile-X listserv operated by Emory University. “I went to numerous doctors because he was failing to reach his developmental milestones. I begged one doc to prescribe some early intervention therapy, and he laughed at me. My sister’s son was diagnosed with fragile X, and I went searching for answers.” Eileen eventually ordered a fragile-X test, which revealed the full mutation. For obvious reasons, many parents who endure such experiences are strong advocates for newborn screening.

As Eileen puts it, “It was because of me not giving up that my cousins learned why their siblings have odd behaviors and how they can be treated.” (Genetic information has its downsides, too. “It always makes us nervous when we hear people say, ‘I want to be tested because I want to find out if it came from *her*,’” says Dr. Darrel Waggoner, director of human genetics at the University of Chicago Medical Center, who has counseled hundreds of families.)

Genetic screening can help physicians make the diagnosis and link families with knowledgeable experts. That’s one good argument for clinical guidelines to recommend testing children with specific symptoms and difficulties. Given the sheer number of rare genetic conditions, it is unsurprising and, to some extent, unavoidable that health-care providers will be ignorant about some of them. When I spoke with 10 parents about their experiences with fragile X, every one of them indicated that their child’s general pediatrician didn’t know basic facts about the condition and was therefore ill-equipped to provide skilled treatment or (in some cases) to properly explain the results of genetic tests. Such ignorance renders newborn screening both more essential and less effective than it should be.

When Donald Bailey initially decided to study newborn screening, he was surprised, he says, to get “a lot of pushback. The more I talked to people about it, the more I realized that the issues were much more complicated than I realized.” For conditions like fragile X, many people who are screened will find out they have the disorder but will derive no immediate benefit from this information. Premutation carriers have strong reasons to know their genetic status for future reproductive planning, yet it’s not clear whether these carriers otherwise benefit from being diagnosed as newborns. Similar questions arise for the minority of individuals with the full mutation who appear only mildly affected or who display no apparent symptoms.

Some clinicians believe early diagnosis is still valuable for this group, especially to address prevalent concerns such as anxiety and depression that might otherwise be overlooked. One clinician commented, “I’ve actually never seen someone with a full mutation who is completely normal.” Others regard this as overstated and worry about stigmatizing people who lack tangible fragile-X symptoms. As one parent told me: “The worst thing was being told by the genetic counselor that I was ‘extremely high functioning for the number of repeats’ that I had. ... I have a master’s and bachelor’s degree.”

Promising treatments are now on the horizon for fragile-X syndrome. These are not cures, but they may modestly improve

social functioning. As better treatments become available, they will strengthen the case for newborn screening, at least for the full mutation. The development of effective drugs to address the specific mechanisms behind fragile-X syndrome would create “a whole different game,” says University of Chicago pediatrician and ethicist Lainie Friedman Ross. “But, right now, first of all, we would tell you that if you had a [son with the full mutation], he needs occupational, physical therapy, speech therapy. What do you tell a mother who has a girl with fragile X? When one-third won’t need those services ever and another one-third may or may not and only one-third definitely need it?”

Even if doctors can pinpoint the best treatment, they are likely to struggle in explaining it to families. Our health-care system is ill-prepared to help patients understand and respond to complicated genetic diagnoses. Most parents aren’t familiar with basic genetic concepts, let alone with complex disorders such as fragile X—and bringing them up to speed is a costly and difficult process. Current newborn-screening programs are cheap precisely because parents play no active role unless a diagnosis is made. PKU screening prevents profound disability in less than one out of every 10,000 U.S. newborns. Although PKU is rare, screening is still very cost-effective. The lab test costs only a few dollars, and the process imposes little burden on patients, their families, or the medical system. When PKU is found, early treatment prevents profound, permanent impairment.

If, in contrast, newborn screening were to require informed consent, parents would need real time and attention from skilled professionals. Even if the lab tests themselves were free, this would pose an economic challenge, especially in screening for rare conditions. Suppose that parents require a \$50 counseling session to provide genuine informed consent and that about 3,000 newborns were screened for each identified case of fragile-X syndrome. Although early diagnosis and treatment are surely valuable, the benefits are far less dramatic than those associated with, say, early PKU treatment. That same \$150,000 could provide a fragile-X patient with years of extensive services. When you consider that many conditions subject to newborn genetic screening are rarer than fragile X, the economic and logistic challenges become even more daunting.

“We see a lot of families who are now coming to see us because of a documented genetic condition, not screening,” Waggoner says. “Our job is to counsel them about what that means, and what the genetics is, and its implications. We work real hard at it, and try real hard, and spend hours with them. ... If you were to go interview those people two hours after their visits with us, the amount of information that they could accurately now give back to you ... is probably really limited.”

In most cases, it’s relatively uninformed generalists—not experts on genetic disorders like Ross and Waggoner—who provide diagnostic workups for children with developmental

difficulties. As Ross notes, genetics remains outside most providers’ training and daily routine. In the case of fragile X, a general pediatrician who treats 10,000 children over her career might encounter three patients with the full mutation, and perhaps 40 premutation carriers, many of whom would presumably go undetected. That’s a poor experience base to provide effective diagnosis and care. In one recent survey, 47 percent of pediatricians didn’t know that females could be affected by fragile-X syndrome. Only 28 percent knew that carriers can have adult health problems. Even if doctors are knowledgeable, genetic counseling competes for time with other important tasks that must be accomplished in a 15-minute pediatric visit. Ross describes the tradeoff: “I can either sit here and explain to you about the fact that your daughter has reproductive risks 25 years from now ... or I can make sure that your breastfeeding is going OK.”

In the United States, there are an estimated 2,500 genetic counselors who are trained to conduct these complicated conversations. That’s about one counselor for every 1,600 newborns each year. And medical students aren’t exactly clamoring to make genetics their specialty: According to one report, 58 percent of graduate medical education slots in clinical genetics went unfilled. Given these realities, general pediatricians and internists will remain patients’ main information source.

Researchers are exploring how to do newborn fragile-X screening better, thanks to a large pilot study funded by the National Institutes of Health. At three leading centers of fragile-X care, researchers are exploring which families agree to have their newborns tested, whether parents of carriers regret participating in the screening program, and the impact of such diagnoses on parental well-being and bonding. Such methodical research will take time, but we already know several important things.

First and most obvious, from an economic perspective, we are overly focused on the declining direct costs of laboratory tests when we should be worried about the overall cost of newborn screening, especially if informed parental consent is required. Second, our society places a great burden on prenatal and newborn screening to address issues that prospective parents should tackle long before that point. And third, much needs to be done to educate health-care providers and otherwise improve the care provided to people affected by genetic conditions.

These basic issues must be confronted before personalized genomic medicine becomes a useful everyday reality for millions of people. We continue to pump money into research and advanced treatments for conditions influenced by detectable genetic traits. That’s good. We must support the everyday patient and provider experiences of genetic screening and care with equal vigor. **TAP**

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