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## **Genetic Testing's Growing Ability To Predict Disease Makes It Vital To Soften The Shock Of Seeing The Future**

Dr. Jason Brandt of John Hopkins.

Suppose you are at risk of a genetic disease that threatens to render you recognizable to yourself. Physically, you realize, the disease will slowly erode your body to an incontinent mass of uncontrollable jerks and twitches. Mentally, it will eat away at your brain cells, impeding your ability to remember, pay attention, reason. And emotionally, it will blacken your days with irritability and all-consuming depression. Worst of all, you know the disease cannot be prevented or stalled, arrested or cured. To learn you have the offending gene is to receive a virtual death sentence that leaves only two questions unanswered: When will the nightmare begin? And how long will your suffering last?

Do you really want to know if you have the disease. Are you sure you want to know now, if the symptoms may not appear for decades? Are you prepared to handle the potential consequences of that knowledge?

Such thorny human concerns are at the heart of a pioneering research effort that is bent on clinically identifying the long-term emotional and social effects of early genetic testing. Directed by neuropsychologist Jason Brandt of the Johns Hopkins University School of Medicine, the project enlists the talents of psychiatrists, psychologists, social workers, nurses, geneticists and ethicists to track the consequences of testing for the genetic mutation that cause deadly Huntington's disease. The program, says Brandt, "is seeking to determine how best to offer this test."

Though HD afflicts just 25,000 Americans, with 125,000 more at risk, it illustrates the growing urgency to develop sound genetic-testing practices. As medical researchers race toward completing a map of the human genome, with its estimated 50,000 to 100,000 genes, they are discovering new genes, their role in specific diseases, and new diagnostic tests -- all at a breathtaking pace. Within 30 years, researchers expect to be able to produce a genetic "fingerprint" of an individual's potential future health that will enable doctors to wage pre-emptive battle. Already, testing before any symptoms appear makes possible the early treatment of some breast and colon cancers. Further down the line is the prospect of gene therapy, in which modified genes are introduced into existing cells to prevent or cure numerous diseases.

But for now, when a disease is non treatable, the burden of knowing can overwhelm the benefits. Nation wide, only 1,500 genetic counselors, most of the drawing on guidelines derived from Brandt's research, been trained to help people assess such risks. "The protocol developed by Brandt is a paradigm for other late onset, incurable diseases," says Nancy Wexler, president of the Hereditary Disease Foundation and a leading HD researcher. "It's very responsive to individual needs".

This summer a 44-year-old Baltimore native Jack was waiting to have the first of at least three test counseling sessions, spaced over a two month period. Jack had already cleared the neurological that, if it had turned up HD symptoms, would have made testing redundant. Though Jack is healthy, he was well versed in the disease: his grandmother and mother died from it, and he knows there is a fifty-fifty chance that he has inherited the time-bomb gene.

Two siblings have tested negative, two others positive. One sister is battling symptoms, including a depression that landed her in a psychiatric ward. "Until now," Jack says "I haven't cared to know my destiny because I didn't want it to change how I face my day-to-day life.

"But Jack's life has undergone some seismic shifts 'the past 18 months. His marriage of 12 years collapsed, and he was fired from a job in his wife's family's business, leaving him to search for new career options. "It became evident to me that I didn't have control over my life," he said a few days before the counseling session. "This is one small piece where I can get some control." Jack thought that a negative test result -- one that showed no abnormality in the gene IT-15 on chromosome 4 -- would inspire him to consider moving to another part of the county. And if the news was bad? "Maybe I would be less of a Type A and not work as hard." he said.

Jack had some firm ideas. If the news was good, he would not tell his two siblings who tested positive "I wouldn't tell them that I'm lucky and reconfirm that they're unlucky." he said He was certain that he neither wanted nor needed counseling that he had not yet picked the "confidant" who the program stipulates must accompany him to future sessions. "After what I've been through the last 18 months," he said, "I can handle anything."

Enter Brandt. 43, intelligent but unintimidating Long fascinated by the physiological aspects of memory disorder, Brandt started delving into amnesia, Alzheimer's and dementia while a graduate student at Boston University. Upon joining the Johns Hopkins faculty in 1981, he began focusing on HD, a disease that he says provides "an almost unique opportunity to study how a deterioration of systems in the brain could result in cognitive, emotional and movement problems."

After an hour long private session with Brandt, Jack admits, "I'm glad there's counseling involved Some stories he told gave me some insight." But, given the turmoil in Jack's life, is this an appropriate time for him to undergo a potentially devastating test? "I see our job as ruling out only people who clearly have psychological disorders that make them vulnerable to the stress and put them at risk for catastrophic outcomes," Brandt answers. "Then my job is raising issues. helping people reason it through, rather than being the gatekeeper " It is Brandt's experience that people rarely make a major life overhaul as a result of the test. It now seems clear that Jack will proceed to DNA analysis.

Since the program began in 1986 at Johns Hopkins, only five people have been denied testing, with an invitation to return later. "We've been accused of being paternalistic," says Brandt, "but nothing compels my team to do the test. 'We have to be ethically responsible " One turned away: an unemployed woman. newly relocated to Baltimore, who had a history of self-destructive behavior, eating disorders and possible alcohol abuse. Told that her testing would be postponed, she became so distraught that Brandt feared she would smash a glass table in his office. A year later, after settling into a home and a job, she was accepted for testing. But when the news was bad. says Brandt. "she took it very well and thanked us for making her wait. She said 'I couldn't have accepted it before as well as I can now.'" She is currently studying for the ministry.

Such time-elapse vignettes buttress Brandt's conviction that rigorous procedures are essential for effective testing. His program requires participants, who must be over age 18, to undergo a battery of psychological exams. During counseling it is stressed that the test is elective and the result confidential (a key concern for people who worry about health insurance). Misconceptions are dispelled: a positive result does not mean you are currently afflicted. And

the strenuous post-test requirements -- a visit every three months the first year and every six months the following two years -- are made clear. To date, 183 have been tested; almost twice that number have not kept appointments or have dropped out. "That's their way of telling us they don't really want the test." says Brandt. "We think of that as a success."

"Brandt's painstaking preparation is showing promising results. Of the 63 participants who tested positive, only two have required psychiatric hospitalization, in both cases after the onset of symptoms. Still, not all the others who now show symptoms are having an easy time. A team social worker occasionally has had to bail a patient out of jail "People make bad decisions." says Brandt, "especially in the early part of the disease.

"The team had hoped to be able to predict accurately both how people would test and how they would cope on receiving the results. "So far." says Brandt, "it's been a bust." The only predictor of test results remains age; since HD typically hits between ages 30 and 50, the older the person, the higher the chance of a negative result. As for predicting people's reactions, most preliminary hypotheses have been replaced by new ones. Contrary to expectations, for instance, married people have a harder time coping with bad news than singles (perhaps they worry about becoming a burden to their spouse), parents weather bad news better than childless adults (maybe the childless are newly disturbed by thoughts of never having a child).

The team's newest findings are among the most unexpected Often people who seek out the test say they are trying to decide whether to have children. Yet there have been 10 births among the 63 who test-ed positive. "Part of it is life affirming," says Brandt. "They say having children gives a sense of normalcy to their lives. " As for their children's health prospects, he says, "they're confident of a cure." The data also show 10 new marriages among those who found they have the gene. The spouse is often the person who served as confidant during the sessions.

Buried in those numbers are unexpected stories Ruth. 37, was among the first to be tested, in 1986, back when scientists knew only the approximate location of the gene and the test had only 95% accuracy. At the time. Ruth had a solid marriage, one son, another on the way, and no doubts about wanting to know whether she would get the disease that had driven her ailing mother to make three suicide attempts. "I believe that if you know you're at risk but don't know if you have the gene, you'll live your life like you have the disease," says Ruth Her plan if she tested positive: to find a good housekeeper for her husband and sons, then disappear "I wanted to spare my Family," she explains.

Ruth was less prepared for a happy outcome. Within a year of testing negative, she separated from her husband. "I didn't know what I wanted anymore." she says. "A lot of decisions I made didn't make sense. I just wanted to be free " After the discovery of the Huntington's gene in 1993 and the development of a virtually error-free test, Ruth was retested Again. negative. She has since remarried, had a third son and trained as a physical therapist. Often she works with H D patients.

Such tales of human resilience sustain Brandt as he watches some of the program's participants progress from risk to clinical manifestation to full-blown illness to death "You can't help being impressed by the human drama of it," he says. Indeed, the sharing of stories, both happy and dire. is often his best tool for compelling people to weigh seriously the pros and cons of testing. "Most people," he says, "resonate more to the stories than to the psychological tests and statistical results.

"And the clients resonate to Brandt. "He gave me perspective," says Ruth. Before testing, she was afraid that she would become "mean" like her mother. "He said to me, Your mother's personality is very different, so if you think the manifestations will be the same for you, you're wrong." I'll never forget that." The most moving testimony, though, came from John, a married man who deeply desired a child but feared passing on the Huntington's gene. In a recent letter to Brandt's team, John thanked them for providing the "strength and courage" to take the test, which turned out negative. Enclosed was tangible evidence of their impact: a snapshot of his three-month-old daughter.