# The Tiresias complex: Huntington's disease as a paradigm of testing for late-onset disorders

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ABSTRACT **Huntington's disease represents the first disorder for which positional cloning techniques successfully localized an autosomal gene—in 1983. Events since that time have proved the gene recalcitrant to identification and characterization. Since 1986, presymptomatic and prenatal testing for Huntington's disease has been available internationally, although on a limited basis. Testing for Huntington's disease provides an excellent model for designing service programs for genetic testing for late-onset, fatal disorders, particularly when the gene is not yet in hand and no therapeutic intervention is possible. Special training and precautions must be in place before presymptomatic genetic testing should be offered. —Wexler, N. S. The Tiresias complex: Huntington's disease as a paradigm of testing for late-onset disorders. *FASEB J.* 6: 2820–2825; 1992.**

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THE BLIND SEER TIRESIAS CONFRONTED Oedipus with the quintessential dilemma of modern genetics: "It is but sorrow to be wise when wisdom profits not" (1). Do you want to know how and when you are going to die, especially if you have no power to change the outcome? Should such knowledge be made freely available? How does a person choose to learn this momentous information? How does one cope with the answer?

Ball and Harper (2) cogently describe some of the arenas in which we, as professionals, families that are involved, and society in general confront challenges with respect to testing for Huntington's disease, a fatal, autosomal dominant, neurodegenerative disorder of mid-life onset. They conclude by saying that testing for Huntington's disease is a harbinger of things to come, such as we are already witnessing in testing for familial Alzheimer's disease and other disorders. Ball and Harper (2) also observe that the gene causing Huntington's disease will soon be cloned and a direct test for the gene will be made available.

Ball and Harper (2) comment on the ethical issues involved in providing testing services. If one construes the provision of good service as an ethical requirement and any deviation as an ethical breach, the conversation remains on ethical territory. But I believe some of the most perplexing, demanding, and absorbing dilemmas and frictions surround varying definitions of adequate care and delivery of services. Much of the stress associated with the test and many of the most vexing questions are not necessarily ethical, but clinical.

Almost all of these issues will be exacerbated when the Huntington's disease gene (HD gene) is cloned and a direct test using oligonucleotides for the gene is at hand. We are still unprepared and ill-equipped for the limited amount of testing we are currently offering. When a direct test exists, demand for the test may well increase. The linkage test as it now exists is onerous to take, because it requires that many relatives of a person requesting to be tested give blood for DNA analysis and undergo neurological examinations. Some people at risk have stated that these necessities dissuade them from being tested. Also, all those who have insufficiently genetically informative families will be eligible for testing once we can test for the gene itself. If demand for the test increases, we will be in a worse position: lacking trained personnel to provide counseling and other services, absent monitoring and follow-up, and in danger of making grave mistakes.

## WHAT INFORMATION IS LEARNED—NOW AND IN THE FUTURE?

The College of Physicians and Surgeons of Columbia University has provided presymptomatic and prenatal testing for Huntington's disease as a pilot research project since 1986. As director of this program and primary counselor, I have had the opportunity to speak with more than 100 individuals at risk and their family members regarding testing. I have also had the benefit of conversations with my colleagues in the U.S., Canada, and Europe who provide testing, and many of the points made here reflect our common experience. (The few published articles on testing for Huntington's disease have focused on laboratory more than clinical aspects; the wealth of clinical information collected at testing centers has yet to be published.) The following observations are distillations of several years of research at Columbia University and input from my colleagues. Data are from in-depth interviews. Although anecdotal in nature, they are meant to guide us toward additional areas of research and policy development with respect to test development and monitoring.

Presymptomatic testing for Huntington's disease makes use of closely linked markers for the gene to determine whether a person has a very high likelihood of either escaping or developing the disease (3, 4). In a genetically informative family, there is a small (between 2% and 4%) chance that a recombination event separates the markers from the gene and the information being provided in the test does not reflect the actual genetic reality (5–10). The fact that one only changes one's odds and does not get definitive information dissuades some, perhaps many, from taking the test. They feel it is futile to suffer needlessly if the test cannot provide definitive information with respect to the presence or absence of the gene.

The ambiguity in the position of the gene makes it difficult to specify recombination fractions precisely, even with the newest markers being used. Many testing programs consider a family genetically uninformative if the newly calculated



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risk is not at least 96% in either direction, increased or decreased risk; in this instance a client is told that the test is noninformative.

Once the test is completely informative, barring laboratory error, these people may believe that their "excuse" is now gone and feel compelled to take a test about which they are highly ambivalent. Against the prevailing ethos of our society that knowledge is power and that both are good, a rational, scientific reason for demurring from the test is the only one that counts. Once these "pseudo-legitimate" reservations are removed, what remains is only the preference not to know—an unpopular point of view since the age of reason.

The existence of the recombination fraction, the percentage chance that the information given was not correct, may mean vastly different things to those who have been tested, depending on their resultant genotypes. Those with a high likelihood of escaping the disease virtually ignore the possibility that a recombination event might have occurred. Compared to a previous high risk, a new low risk is perceived as certainty of escaping the disease. The recombination fraction becomes merely an intellectual construct with no meaning.

To those with a heightened risk, however, that fraction can swell to take over the field: since someone has to be a recombinant, why not them? Jason Brandt, head of the John Hopkins University testing program, reported that in follow-up visits after an initial result of increased risk, subjects rated their risk as once again approaching 50%, notwithstanding a realization that their risk was reported to them to be 96% or higher. When asked to explain this discrepancy they replied, "The test was in error." "I am a recombinant." "God—or science—will save me" (J. Brandt, personal communication).

Denial and hope are the twin mainstays of survival in impossible circumstances. To some extent, denial and hope must be present in order to take a presymptomatic test: denial that the disease is present and hope for a good outcome. In the Columbia University testing program people requested the test to know the truth, to end uncertainty, and to plan for the future—and all hoped to learn that the disease was not present. If the test reveals that the gene is most likely to be found, denial and hope must be remobilized as even more necessary defenses. Many deny that the disease will start any time soon—even while in the same breath saying that they notice symptoms in themselves—and hope, *passionately*, for a cure in the interim.

Once a molecular test for the gene itself is available, the possibility of taking comfort from the recombination fraction will be removed and realities of the information will be made more stark.

## PRENATAL TESTING

There are two types of prenatal tests being offered as part of presymptomatic testing programs (11–13). In full-disclosure prenatal testing, the fetus is treated as an at-risk individual and the genotype of the fetus is determined fully.

The prenatal testing most frequently requested is "nondisclosing," or exclusion testing. An expectant couple is only told if the fetus has inherited the short arm of chromosome 4, known to be the locus for the HD gene, from the affected or unaffected grandparent (1, 10). This test is particularly valuable in two circumstances: *1)* when at-risk parents do not have sufficiently genetically informative families to determine their genotypes definitely and *2)* when at-risk parents prefer not to know their genotypes. Prenatal information about the fetus's genotype can still be given, but the probabilities for the fetus are either the same as for the at-risk parent, usually 50% depending on the age of the parent, or a 1% or 2% risk, approximately one-half the risk of recombination.

Most people who choose exclusion testing do not have sufficiently genetically informative families to be tested themselves. Exclusion testing is their only chance to ensure that offspring will not have the HD gene. If the outcome is good, parents can revel in the knowledge that their children and grandchildren will be forever free from suffering the disease, even if their own parenting may be compromised or cut short by the onset of Huntington's disease.

If parents are unlucky, they are faced with the choice of aborting a fetus with a 50% risk of developing the disease. To some, this is tantamount to aborting themselves, as they share the identical risk. It is absolutely essential to determine a couple's motivations for requesting prenatal testing before beginning the process. There is no medical justification for performing prenatal testing for Huntington's disease if termination is not the intention. If a couple decides to continue the pregnancy and the at-risk parent subsequently develops Huntington's disease, it is obvious that the child will follow in its parent's footsteps. The right of privacy for a minor is violated if the child's genotype is revealed through its parents. Obviously individuals always are entitled to change their minds. But careful counseling can help clarify misunderstandings about the test and work through possible alternative outcomes before a couple is committed to a path of action (see ref 2 for discussion of testing minors).

In-depth and detailed counseling must accompany both disclosing and nondisclosing prenatal testing. Ball and Harper (2) emphasize this point and I strongly concur. Because of the delicate and complex issues surrounding any kind of testing in which detection of increased risk of Huntington's disease may occur, when prenatal services are offered they should be incorporated into a specialized Huntington's disease testing program rather than be part of routine prenatal testing services. Not every presymptomatic testing program is required to have a prenatal testing component. Even more important, every general service genetic counseling program should not provide prenatal testing for Huntington's disease without some special training.

Once a probe for the gene is available in the future, prenatal testing that is fully disclosing may more often be sought by couples who right now cannot or do not wish to know the at-risk parent's genotype. Some parents may opt to test the fetus without testing themselves. If the fetus has a normal genotype, the at-risk parent is spared knowing his or her genotype. But if the fetus tests positive for the HD gene, a double tragedy occurs when parent and child are diagnosed simultaneously. Some people who themselves are diagnosed presymptomatically struggle with choices about whether or not to test future pregnancies or bear children at all. (N. S. Wexler and M. R. Hayden, personal communications with persons in testing programs). Counseling must help individuals choose their best psychological options.

## WHO COMES FOR TESTING AND WHY?

There are several categories of people coming for counseling, each group with slightly different motivations (14–18). Those coming for family planning purposes have already been discussed.

### The newly at risk

Most people whose parents have just been diagnosed find themselves intensely uncomfortable with their new situation of ambiguity. Anything seems better than uncertainty. And yet these people are frequently unfamiliar with Huntington's disease, particularly in its last stages, and cannot really make an informed choice as to whether or not they wish to know if this is to be their fate. Ensuring that clients know the face of the disease is difficult for counselors, particularly when at the same time they must shoal up the defenses of people who have just learned of their own risk. Videotapes and literature can provide graphic means of rapid education but can also be traumatic for the unprepared. The wife of a newly diagnosed young man saw a television program on Huntington's disease and said she "cried for a year afterwards."

### The altruistic at risk

Most older at-risk individuals have made decisions regarding marriage, children, and careers and have usually had many years to come to terms with their risk, although they are by no means complacent about being out of danger. But they know that time is on their side; their odds have declined and they hope for the best. Some feel—correctly—that their decreased odds make it more likely for them to have a good outcome on a presymptomatic test; but others do not want to dash their conviction, still tenuous, that they have escaped.

The "altruistic testee" usually has children who are old enough to date, or even marry and have children. If the older at-risk parent is tested and is clear, so too is the next generation. In some instances, at-risk parents have not yet informed their children that they and their children are at risk. Parents gamble that if the news is good they will never have to face this calamitous prospect. Altruistic testees would not be tested if it were not for the benefit of others, and many prefer not to be tested. Helping these parents cope with a bad outcome is difficult, as they did not wish to know for their own sakes, and the newly increased risk for their children brings dramatic repercussions for the entire family.

If an altruistic parent is tested who genuinely prefers not to be, any resulting depression or even suicide after a gene-positive diagnosis can be as harmful or more to the family than living in doubt and hope. An important role for the counselor is to legitimize not taking the test as well as taking it.

Often younger parents will ask to be tested in order to clarify the risk for their young children. If the counselor suggests that these parents bank DNA for security and wait a few years to see the outcome of research (if nothing else is pressing them to be tested), these parents are immensely relieved and grateful. Many express the feeling that they thought one should be tested in order to be a good parent. Especially if parents feel guilty about having children and exposing them to any risk, being tested themselves against their own desires is a way of atoning.

Making sure that parents bank DNA is the most important factor. There may be variants of the HD gene that necessitate knowing which allele predominates in a family.

### Young adults

The majority of people requesting testing are young adults: some just starting out in life and facing critical decisions; others who have already chosen a marriage or career and even children. The majority of these people say they want to be tested to end the uncertainty. Some may be contemplating a career change or an additional child if the outcome is good. Most are young enough so that a positive diagnosis does not mean that the disease is imminent, but they are old enough to imagine symptoms in themselves and watch themselves for every physical or psychological misstep.

Counseling with this group is the most complicated and perilous. Their genetic risk is highest. They may be showing minute neurological abnormalities that might mean nothing and might mean everything. Telling them about these concerns may convince them that the disease has already begun, and the counselor or neurologist could easily be wrong. And yet these signs might presage a positive result on the diagnostic test. One must weigh how catastrophic this outcome might be to each individual.

People who come for testing are usually well aware of the benefits of presymptomatic testing; it is this knowledge that propels them toward the test. The test is their only opportunity to end the uncertainty of their situation and plan unambiguously for the future. Many would like to resolve this central, pervasive mystery in their lives once and for all. But even though people have thought intensely about what it means to be at risk and about the test itself, they often have not actually thought through just how this new diagnostic information will be integrated into their lives. They are very specific about what they will do if the disease is not present, but less certain about what they would do if the outcome indicates that the HD gene is most likely there. The counseling process should focus on helping people choose whether or not they wish to be tested and understanding the impact of the test results.

At the Columbia University testing program we found that many people at risk feel paralyzed to some degree by their risk situation, unable to move in any direction. Some believe that a gene-negative outcome will free them to do the things they are now impeded from pursuing and a gene-positive outcome will galvanize them to use whatever time they have left constructively. A major component of our counseling revolves around this paralysis. Why has the paralysis thwarted them until now and will it continue to do so regardless of the test outcome? Often the obstacles people put in the way of action are illusory but have become ingrained as character structure. A test result can act like dynamite to get people moving, but counseling or therapy can also have the same effect, perhaps in a more lasting fashion.

Individuals coming for testing will frequently state that they want to be tested to determine whether to continue in school, change jobs, get married, sign up in advance for a nursing home with a long waiting list, or take a vacation. If one presses whether these choices are really dependent on having diagnostic information, it usually turns out they are not.

People can be encouraged to pursue fulfilling plans regardless of Huntington's disease. As a first step in the counseling process we try to help people clarify what, to them, is a satisfying life, rather than organizing their lives around the specter of Huntington's disease. The second step is to explore the potential impact of positive or negative test results on their current situation and on future plans. If people decide to make changes on the basis of their own preference, we try to help them predict the impact of a diagnosis of Huntington's disease on these new life plans. Would it or should it impede them? For example, a person at risk sometimes requests testing in order to inform a fiance of what might lie ahead. The fiance, however, does not always want to know because he or she does not intend to break the engagement regardless of the outcome and wants the wedding to be a happy occasion.

Anecdotal evidence from testing centers around the world suggests that those receiving a gene-negative outcome felt freer to make changes in their lives. Those with a gene-positive result tended not to make the changes they had claimed before testing that they wished to make. By and large, both groups did not change as much as they had anticipated before testing. It has been our experience that it helps in coping with the test and its outcome when people understand their motivations as clearly as possible. This, in turn, enables them to make the most appropriate decisions.

One of the main reasons people request presymptomatic testing is to end uncertainty. Some individuals also claim that they despise being at risk and cannot bear the endless anxiety of watching themselves for symptoms. They feel that this state of chronic anxiety is as bad as the disease itself, or is in fact prodromal to the disease and they are already affected. They are convinced of the worst and want to end the anxiety and dread of waiting for the diagnosis.

The irony of this stance is that some people who most detest the uncertainty of being at risk also hate and fear every aspect of the disease itself. It is mostly their conviction that the disease is already there that makes them want to proceed with the test. Yet hope still persists that they are wrong, or they would not be so tortured by uncertainty. If people are so disturbed by the *possibility* of having Huntington's disease because they see the disorder as so unbearable, why do they expect the *reality* of it to be any better? If they cannot accommodate to the idea of having this disease when they have a 1 in 2 chance of escaping it, why do they assume they will adjust better when they know the disease will soon be present? And they might be equally tormented by anxiety, wondering when the illness will begin. Good news will relieve them of this prison, but what will bad news bring? Counselors must carefully review with them before the test how they relieve the anxiety of worrying about Huntington's disease when they are at risk; for example, do they persuade themselves that their symptoms are merely imaginary? What means of reassurance will they use, knowing that the disease gene is, in fact, at hand?

## COUNSELING ISSUES

Everyone who takes a presymptomatic or prenatal test for Huntington's disease gambles. People do not want to learn that the disease is present, but are willing to risk finding out in the hope of learning something better or changing a state of uncertainty. They gamble that the outcome will be worth the risk.

Kahneman and Tversky (19, 20) have shown that most people are not adverse to taking risks, only to taking losses. When they perceive themselves to be in a "win" situation, they will be more conservative in order to preserve the win. If they believe that they are already in a "lose" situation, they will be more willing to gamble to escape the loss, even if they risk greater losses in so doing.

Genetic counseling should help people delineate the gains and losses before them. What could be gained by the information and what could be lost? Is the joy of hearing good news worth risking the turmoil of hearing bad news? Is the satisfaction of ending the agony of uncertainty worth risking knowing the certitude of a prolonged and early death? What can people do after tomorrow's news that they cannot do today? Some people who feel most impeded by their risk situation, whether it is not knowing their own fate, not being able to plan, wishing to have children, or feeling responsible for the fate of others, feel themselves to be already in a loss situation and so are most willing to gamble. If they perceived their lives differently, would it change what risks they take?

## FUTURE PROGNOSTICATIONS

### Gene positive

Even for the best prepared, it is almost inconceivable to imagine hearing that one is going to die of a progressively fatal disease that robs one of intellectual prowess while retaining the capacity to comprehend the loss—a disease that leaves the body in a constant tumult of roiling motion, saps speech, and leaves one dependent for many years.

To date, the response to this information has been measured. A few have attempted suicide or have required brief hospitalizations. But the majority seem not to have had major and detectable cataclysms in their lives. There may be fewer than 100 people worldwide who have tested positive for the gene (21), and we have yet to follow this group for very long—certainly not until they become diagnosed symptomatically, which will be another critical phase. Also, for the most part people have received testing at centers specializing in Huntington's disease with extensive pre- and post-test counseling given by experts in the field. This is now changing as the test becomes more widely available.

In addition to the visible and noisy upheavals caused by diagnostic information, we must be acutely atuned to the subterranean disturbances. What effect does the news that one is gene-positive have on day-to-day life, on buying new clothes or investing in a house or car, on family relations, on the incessant internal conversations that were once cluttered with thoughts of being at risk? It is not in the big events, people say, but in the daily routine and fantasies of the future that the news strikes home.

### Gene-negative

It is almost as inconceivable for people to learn that they are not in harm's way. Identities have been built around being "at risk": commitments abandoned, lives led in the fast lane. Some people who learn that they are free of the long-dreaded gene are stunned and unprepared. Suddenly they are ordinary; vulnerable now to other diseases, responsible for their lives as never before. Friends and relatives who had sacrificed for them in the past may feel cheated and vengeful or disturbed to find themselves deprived of their role of tending to an invalid. Some people describe "survivor guilt," especially if they have a sibling or close relative who tested positive for the gene (N. S. Wexler and M. R. Hayden, personal communications). These people and their families also need help—preferably *before* test results are given, because their dilemmas are foreseeable—and long-term follow-up afterward.

### The need for counseling

My conviction, stemming from my experience directing the presymptomatic testing program for Huntington's disease at Columbia University and talking with colleagues in other programs, is that many people who come for presymptomatic testing would benefit from intensive counseling, sometimes in lieu of the test itself. Most people who come for the test have never had any counseling or therapy. They usually know the rudimentary genetics of the disease, taught them by their parents, and have not interacted with genetic counselors. They also do not consider themselves "psychologically ill." If they do consider seeking help, many cannot afford

therapy (which is rarely reimbursed by insurance coverage) or they complain that the therapists know less about the illness than they do and are not helpful.

Being at risk has had a profound effect on most people's lives. They have had an ill parent, with whom they may or may not have had contact, and perhaps other relatives, including siblings, who have suffered from Huntington's disease. Most have made an excellent adaption to their circumstances, but almost all welcome the opportunity to talk to someone knowledgeable about their experiences.

For people at risk, daily life can be like living in a city in a state of siege—never knowing if or where the next bomb will drop. People do a superb job of coping, but the reality is that they have a 1 in 2 chance of dying of a degenerative disease of the brain. No matter how adaptive their coping mechanisms may be, this reality never changes. The genetic test gives people a crystal ball to see the future: will the city be free of bombs from now on or will a bomb crash into their home, killing them and jeopardizing their children?

The current linkage test for Huntington's disease provides some built-in brakes on the testing process while tissue samples are being collected and relatives are being neurologically examined. Also, parents and other relatives usually know that a person is being tested, as their samples are being used to conduct the test. This gives others the opportunity to make their feelings known about the test, and in some instances even stop the test from proceeding if they are sufficiently opposed—a power that causes internecine warfare in some families.

Once a direct test for the gene is possible, testing can be done with much greater privacy. This has advantages and disadvantages. Fewer people in the family are disrupted by having to be neurologically examined, but there is also less opportunity for family members to intervene. There is even the danger of surreptitiously testing a sample from some unsuspecting person who has not given permission: for example, a spouse might want the other spouse tested in order to decide about children. A test should never be conducted without fully informed consent, but it will be technically feasible to do so in the future, whereas now it is not. Some family members have already expressed interest in the possibility of surreptitiously testing spouses or children.

The biggest danger of direct testing for the Huntington's disease allele will be to speed up the testing process and short-circuit counseling. There is already a trend toward fewer counseling sessions. Often counselors in genetic testing programs are not trained for psychotherapy or in-depth counseling and cannot see the need for proceeding beyond the cursory establishment that a person wants this test, like any other test. Counseling can be uncomfortable, even painful at times, when people are forced to consider the possibilities before them. But it is better to consider them before testing than afterward. Frequently people at risk have built up layers of protection to cope with their risk situation. These must be peeled back enough to explore the potential impact of the test information. And each client must be understood individually.

### Quality assurance

Another problem is that even when there are good protocols for providing testing, as there are for presymptomatic testing for Huntington's disease (22, 23), there is no mechanism for enforcing the protocols or for supervising compliance. A testing protocol has been developed under the auspices of the Huntington's Disease Society of America. This protocol should be used by all who provide presymptomatic and prenatal testing for Huntington's disease. With no monitoring or oversight, one is relegated to relying on the goodwill of colleagues and the fear of public pressure. These are not adequate safeguards in such a critical realm. There have already been egregious errors when protocols have not been followed. Government regulations should cover laboratory proficiency testing, including genetic linkage analysis. And professional organizations or some other regulatory body should supervise and enforce the more complex areas of counseling, genetic and psychological, which are essential. It is particularly difficult to obtain reimbursement for the long-term counseling critical to helping someone cope with a positive diagnosis.

## LESSONS FOR THE FUTURE

The lessons of the Huntington's disease experience for other testing programs are numerous. Perhaps Huntington's disease testing emphasizes most of all that each individual is unique and the correct solution for that person must be sought. The test for the HD gene raises critical issues with respect to the right of people to know genetic information, their right not to know, and the right of privacy for minors. These rights hold true in testing for any disease, even when intervention is possible.

Genetic testing programs must be designed to take into account the specific attributes of the disease for which testing is being offered. Testing programs should increasingly be coupled with therapy programs, for example, for familial polyposis. The testing of minors is advantageous when early intervention is the most effective prevention or treatment; careful attention must be given to designing appropriate informed consent permissions for minors.

Genetic counseling should also include a discussion of the potential economic and social ramifications of learning diagnostic information. People who are identified to have a high risk for developing certain disorders may be also at high risk for losing health and life insurance. In certain circumstances, just being at risk for the disorder (such as for Huntington's disease) is sufficient to make someone uninsurable; there may be nothing to lose. If individuals are presymptomatically diagnosed with breast or colon cancer, for example, they may be in serious financial trouble if they are deprived of the very insurance they need to carry out preventive monitoring, surgery, or treatment. Issues of potential job discrimination and social stigmatization must be part of the counseling.

In all cases, truly informed consent, including a full psychological appreciation of the ramifications of the information, must be the principle upon which testing programs are designed. Information should not be foisted on someone without permission. And if it is requested, it must be phrased in such a way as to be maximally useful.

Widespread genetic testing for cystic fibrosis will likely begin soon, and genetic testing for other disorders, including cancers caused by mutations in the P53 gene, breast and colon cancers, fibrocystic kidney disease, and many more, is in the offing. We have a tremendous amount to learn about people's responses to genetic tests and how they use the information provided. We also have a dismaying dearth of providers: there are fewer than 2,000 medical geneticists and genetic counselors in the U.S. (24). At current rates of training, this number will not double for 10 years (24).

Testing should be provided in a setting that is maximally conducive to learning, both for those undergoing testing and those concerned with providing the best services. The psychology and psychological reactions of people seeking and

receiving genetic information are complex, manifold, and not to be assumed without research. Pilot projects should be supported and follow-up studies conducted to study how information is utilized and what psychological and medical impact it has on those receiving it.

Above all, we do not wish to compound the difficulties families coping with genetic disease are already enduring. All must be served, veterans and novices to genetic information alike, in a way that allows each to take full advantage of the potential benefits of such information and protects them from harm. FJ

## REFERENCES


1. Sophocles, Oedipus the King. (1957) In *Eight Great Tragedies* pp. 65-66, Mentor Books, New York.
2. Ball, D. M., and Harper, P. S. (1992) Presymptomatic testing for late-onset genetic disorders: lessons from Huntington's disease. *FASEB J.* **6**,
3. Gusella, J. F., Wexler, N. S., Conneally, P. M., Naylor, S. L., Anderson, M. A., Tanzi, R. E., Watkins, P. C., Ottina, K., Wallace, M. R., Sakaguchi, A. Y., Young, A. B., Shoulson, I., Bonilla, E., and Martin, J. B. (1983) A polymorphic DNA marker genetically linked to Huntington's disease. *Nature (London)* **306**, 234-238
4. Wexler, N. S., Conneally, P. M., Housman, D., and Gusella, J. F. (1985) A DNA polymorphism for Huntington's disease marks the future. *Arch. Neurol.* **42**, 20-24
5. Conneally, P. M., Gusella, J. F., and Wexler, N. S. (1985) Huntington's disease: linkage with G8 on chromosome 4 and its consequences. *Prog. Clin. Biol. Res.* **77**, 53-60
6. Conneally, P. M., Gusella, J. F., and Wexler, N. S. (1988) Huntington's disease: genetics, presymptomatic and prenatal diagnosis. *Nucleic Acid Probes and Diagnosis of Human Genetic Diseases* (Willey, A. M., ed) pp. 137-152, Alan Liss, New York
7. Gilliam, T. C., Tanzi, R. E., Haines, J. L., Bonner, T. I., Faryniarz, A. G., Hobbs, W. J., MacDonald, M. E., Cheng, S. E., Folstein, S. E., Conneally, P. M., Wexler, N. S., and Gusella, J. F. (1987) Localization of the Huntington's disease gene to a small segment of chromosome 4 flanked by D4S10 and the telomers. *Cell* **50**, 565-571
8. Hayden, M. R., Robbins, C., Allard, D., Haines, J., Fox, S., Wasmuth, J., Fahy, M., and Bloch, M. (1988) Improved predictive testing for Huntington's disease by using three linked DNA markers. *Am. J. Hum. Genet.* **43**, 689-694
9. MacDonald, M. E., Cheng, S. V., Zimmer, M., Haines, J. L., Poustka, A., Allito, B., Smith, B., Whaley, W. L., Romano, D. M., and Jagadeesh, J. (1989) Clustering of multi-allele DNA markers near the Huntington's disease gene. *J. Clin. Invest.* **84**, 1013-1016
10. MacDonald, M. E., Haines, J. L., and Zimmer, J. (1989) Recombination events suggest potential sites for the Huntington's disease gene. *Neuron* **3**, 183-190
11. Quarrell, O. W. J., Meredith, A. L., Tyler, A., Youngman, S., Upadhyaya, M., and Harper, P. S. (1987) Exclusion testing for Huntington's disease in pregnancy with a closely linked DNA marker. *Lancet* **1**, 1281-1283
12. Hayden, M. R., Hewitt, J., Kastelein, J. J. P., Langlois, S., Wilson, R. D., Fox, S., Hilbert, C., and Bloch, M. (1987) First trimester prenatal diagnosis for Huntington's disease with DNA probes. *Lancet* **1**, 1284-1285
13. Tyler, A., Quarrell, O. W. J., Lazarou, L., Meredith, A. L., and Harper, P. S. (1990) Exclusion testing in pregnancy for Huntington's disease. *J. Med. Gen.* **27**, 488-495
14. Meissen, J., Mastromauro, C. A., Kiely, D. K., McNamamra, D. S., and Myers, R. H. (1991) Understanding the decision to take the predictive test for Huntington's disease. *Am. J. Med. Genet.* **39**, 404-410
15. Quaid, K. A., Brandt, J., Faden, R. R., and Folstein, S. E. (1989) Knowledge, attitude, and the decision to be tested for Huntington's disease. *Clin. Genet.* **36**, 431-438
16. Huggins, M., Bloch, M., Kanani, S., Quarrell, O. W. J., Thellman, J., Hedrick, A., Dickens, B., Lynch, A., and Hayden, M. (1990) Ethical and legal dilemmas arising during predictive testing for adult-onset disease: the experience of Huntington's disease. *Am. J. Hum. Genet.* **47**, 4-12
17. Wexler, N. S. (1991) Presymptomatic testing for Huntington's disease: harbinger for the new genetics. (Bankowski, Z., and Caprons, A. M., eds) In *Genetics, Ethics and Human Values* (Proceedings of the XXIVth CIOMS Conference held July 22-27, 1990, Tokyo and Inuyama City, Japan) Council for International Organizations of Medical Sciences, Geneva, Switzerland
18. Wexler, N. S. (1992) Clairvoyance and caution: repercussions from the human genome initiative. *The Code of Codes: Scientific and Social Issues in the Human Genome Project* (Kevles, D. J., and Hood, L., eds) pp. 211-244, Harvard University Press, Cambridge, Massachusetts
19. Kahneman, D., and Tversky, A. (1982) The psychology of preference. *Sci. Am.* **246**, 161-171
20. Tversky, A., and Kahneman, D. (1981) The framing of decisions and the psychology of choice. *Science* **211**, 453-458
21. Harper, P. S. (1991) Predictive testing for Huntington's disease. A worldwide perspective (abstr.) Proceedings of the 8th International Congress of Human Genetics. *Am. J. Hum. Genet.* **49**, (Suppl. 62)
22. World Federation of Neurology Research Group on Huntington's disease. (1989) Ethical issues policy statement on Huntington's disease molecular genetics predictive test. *J. Neurol. Sci.* **94**, 327-332
23. World Federation of Neurology Research Group on Huntington's disease. (1990) Ethical issues policy statement on Huntington's disease molecular genetics predictive test. *J. Med. Gen.* **27**, 34-38
24. Holtzman, N. A. (1989) *Proceed with Caution*, Vol. 157, Johns Hopkins University Press, Baltimore, Maryland.