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Huntington Disease: A Case Study Describing the Complexities and Nuances of Predictive Testing of Monozygotic Twins

Audrey Helmler[1,3] and Andrea Zanko[2]

When a candidate for predictive testing for the Huntington disease gene is a monozygotic twin, confidentiality of the co-twin's diagnosis and autonomy of participation are among the critical genetic counseling issues. Predictive testing can proceed when twins voluntarily and simultaneously request counseling and evaluation in an HD testing program. This case describes a young man referred for predictive testing to an HD testing site on the East Coast of the United States. Family history revealed a twin brother of unknown zygosity who resided on the West Coast of the United States. The genetic counselors on opposite coasts collaborated to provide genetic counseling and evaluation for voluntary, informed predictive testing of the twins, protecting their rights while observing national protocol guidelines.

KEY WORDS: Huntington disease; predictive testing; twins; confidentiality; autonomy.

INTRODUCTION

Predictive testing for the Huntington disease gene was requested by a young man on the East Coast of the United States. The family history revealed that he had a twin brother of unknown zygosity, raising the issues of confidentiality and autonomy, if they were monozygous. The collabora-

[1]Huntington Disease Program, Department of Psychiatry, University of Connecticut Health Center, Farmington, Connecticut.
[2]Division of Genetics, University of California Medical Center, San Francisco, California.
[3]Correspondence should be directed to Audrey Helmler, Huntington Disease Program, Department of Psychiatry, University of Connecticut Health Center, Farmington, Connecticut 06032-1806.

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tion of two genetic counselors on opposite coasts of the United States sought a creative and successful resolution.

While this case highlights the novelty of bi-coastal collaboration, it is tangential to ethical and moral dilemmas integral to the predictive testing process, amplified by the introduction in 1993 of a direct predictive HD test when >99% of affected individuals were found to have an expanded CAG repeat within a novel gene (IT15) on chromosome 4 (4p16.3) (Huntington's Disease Collaborative Research Group, 1993). Prior to March, 1993, predictive testing was available only by linkage analysis based on a polymorphic DNA marker linked to HD reported in 1983 (Gusella *et al.*, 1983). Linkage analysis required blood samples from several relevant family members, in addition to the proband. Individuals were barred from testing if such samples were unobtainable. With direct testing, individuals at 50% or 25% risk for HD, based on a positive family history, can be tested without involvement of other family members.

The guidelines for HD predictive testing recommended by the Huntington Disease Society of America (HDSA) clearly include the supportive components of counseling, neurological evaluation, psychological assessment, and follow up. Early detection of HD symptoms changes the nature of testing from prediction to confirmation. The psychological interactions are critical for determination of the proband's voluntary and informed desire for testing, emotional stability, support network, and personal readiness.

The counselors were committed to insuring privacy and autonomy in their unique situation of bi-coastal counseling of twins. Both testing centers utilized established predictive testing protocols, however, the East Coast protocol required multiple counseling visits prior to laboratory analysis. The West Coast protocol relied on extended telephone contact prior to the initial visit for counseling, neurological and psychological evaluations and laboratory analysis, a model utilized by other centers serving a broad geographic area. (Benjamin *et al.*, 1994) Both programs rely on confidence in clinical judgment and effective multidisciplinary teams.

PROBAND, TWIN A

Twin A (III-9, Fig. 1) was a 32 year old married man with no children when he was referred for predictive testing in 1989 by the Huntington Disease Society of American (HDSA). A brief family history obtained during a telephone conversation with his wife, revealed the proband's father and several relatives had HD as shown in Fig. 1. When the wife stated that the couple preferred to defer scheduling an appointment, DNA banking was

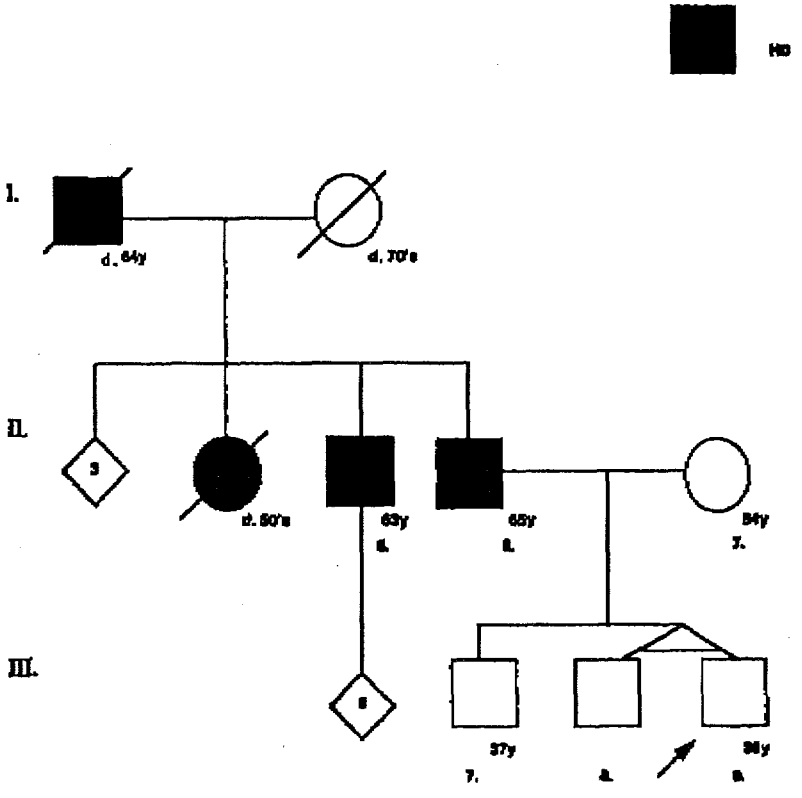

Fig. 1.

recommended for relatives whose participation would be required for linkage analysis.

Over 2 years went by, in which time Twin A's wife called twice with concerns about confidentiality and the deteriorating health of her father-in-law. She was reassured that her husband's records would be maintained as confidential, particularly as the couple was not submitting claims for third party coverage. She was further encouraged to bank the father-in-law's DNA without delay. A counseling appointment was scheduled for March, 1992, when Twin A requested testing as soon as possible because of a pending career decision.

When the couple was first seen for genetic counseling in March, Twin A was observed to be a Caucasian man, reportedly in excellent health. As the interview proceeded, he was noted to be composed, self-confident, am-

bitious, goal-oriented, and accustomed to success. Although he exhibited a sense of humor, his manner was cool, manipulative, and unemotional. His thinking was concrete. His future was already planned including alternatives that depended on clarification of his at-risk status. His wife was a professional with an MBA working as a consultant. She was expressive of her feelings and supportive of her husband. The couple stated they did not plan to have children. He planned on an early retirement in order to travel, and she planned to concentrate on career goals.

Blood samples from Twin A's parents (II-6 & 7) and paternal uncle (II-5) had been sent to the DNA bank at Indiana University. Medical records were obtained to confirm the diagnosis of HD in the twin's father and uncle. A detailed family history was obtained which revealed that the patient had a twin brother (Twin B) and an older singleton brother, both residing on the West Coast of the United States. Twin A was certain his twin was fraternal based on prior information from their mother. Basic information about HD and the predictive testing protocol was discussed.

Twin A was informed that it would be necessary first to determine zygosity. As a monozygotic twin, Twin A's test result would reveal the diagnosis of his co-twin, presenting an ethical dilemma. Therefore, if monozygotic (MZ), documentation of Twin B's informed consent and involvement in an authorized HD testing protocol would be required. The genetic counselor with whom Twin B would consult would be responsible for determining his readiness to clarify his HD status and for discerning the autonomy of his decision. Finally, Twin B would need to be informed of his test result to coincide with disclosure to Twin A. Based on his wish to expedite testing without involving family members, Twin A urged acceptance of dizygosity. His request was denied, referral information was provided for Twin B on the West Coast, and instructions for zygosity testing were outlined.

Twin A had been offered a position at another firm that would represent career advancement. If he were to test positive, he planned to remain in his present company to avoid jeopardizing his security and benefits. He was annoyed to learn that counseling and evaluation generally required several months, in compliance with the East Coast protocol.

Twin A was further dismayed to learn that informed consent and blood samples for linkage analysis would be required from his mother, father, paternal uncle, and twin brother, thereby eliminating his intent to avoid their anxiety by pursuing testing without their knowledge. Twin A described his twin brother as emotionally strong, and like himself, a goal-oriented, ambitious professional. He was more concerned about his older brother (III-7) who at 36 years of age, led an alternative lifestyle with little personal or professional commitment.

Twin A was seen again with his wife 3 weeks later. The twins had not arranged for blood typing, but the family had been informed of their plans, and Twin B had indicated his intent to proceed with the protocol for predictive testing.

During the counseling with Twin A, consideration of a number of post-test scenarios revealed the couple's expectations and preparation for positive or negative results. In spite of challenges which often provoke emotional responses, Twin A only discussed practical issues relating to financial and family planning matters.

Four months later, when the twins were determined to match for blood type, blood samples for DNA zygosity testing were received at the laboratory. Ten days later the laboratory reported that while monozygosity appeared likely, DNA from the twins' parents could confirm the zygosity. The relevant blood samples were obtained for this purpose.

In September, Twin A was stunned to learn that monozygosity had been established with better than 99% accuracy based on multiple markers on four chromosomes. To protect confidentiality, care was taken to omit the name of the co-twin on the laboratory reports and other documents placed in the medical chart.

Twin A remained well-protected psychologically. He admitted that he would be upset if he tested positive, but believed he would accept the result as a fact to be used as "a tool to plan his life." He was a man accustomed to control who now placed himself at the mercy of heredity and technology.

Blood samples were requested from the twins, their parents and affected uncle to establish informativeness for linkage analysis. By February, all blood samples had arrived at the East Coast testing laboratory.

Laboratory results indicated that the family was fully informative. There were six informative markers, three of which would be used to determine gene carrier status for the twins. Twin A was notified, and advised to proceed with psychiatric and neurological evaluations. In April, Twin A stated his wish to defer result disclosure until late summer due to his vacation and work schedule. This delay had implications for Twin B who would then also need to delay result disclosure.

Twin A's neurological and psychiatric evaluations had been completed and reported to be within normal limits. The HD Program counselor, neurologist and psychologist agreed to proceed with testing in late July, and permission was obtained to send medical records to the West Coast Genetic Counselor.

On the day of the test, the voluntary nature of the study was reiterated, and Twin A was reminded of the follow-up counseling protocol. He replied that he respected the expertise and experience documenting the efficacy of follow-up, but doubted that he would require it. Twin A was told that

while he could not be forced to comply, he might be ill-advised to assume that he would not experience emotions common to others who have completed testing.

Given the different time zones in which the twins resided, their appointments for result disclosure were scheduled 3 hours apart to coincide. Twin B was asked to telephone his genetic counselor to verify departure for his appointment with sufficient time to cancel his co-twin's appointment, if necessary. The West Coast Genetic Counselor was to notify the East Coast Genetic Counselor to proceed. Twin A was also advised of this plan.

Twin A arrived 45 minutes late, an unusual occurrence among individuals anticipating result disclosure. He also arrived alone, despite protocol advisement that his wife accompany him. Happily, he was informed that he was predicted not to be a carrier of the HD gene with 0.99537 accuracy. Twin A was tearful, and he volunteered that this was an unexpected and uncharacteristic display of emotion. Believing he had prepared himself for bad news, he expected to handle his results with his usual self-control. When told that underlying emotion and ambivalence had been apparent all along, he was puzzled until he was reminded of his oversights and delays regarding fulfillment of several terms of the protocol, behavior contrary to his efficient professional conduct. He was amused and seemingly enlightened. Before leaving, however, he refused to schedule a follow-up appointment at the recommended 2-week interval, stating that he would telephone after his return from vacation.

When Twin A did not call, he was contacted by telephone. He refused to schedule a follow-up appointment, claiming to be happy, busy, and no longer preoccupied with HD. In fact, he and his wife were planning a pregnancy. The written psychological tests usually completed at the first post-test follow-up appointment were mailed to him, but never returned.

PROBAND, TWIN B

Twin B (III-8) contacted the West Coast Genetic Counselor on December 14, 1992. By that time, monozygosity had been established, and much of the groundwork for linkage analysis had been requested and/or accomplished by the East Coast Genetic Counselor.

Twin B was 35 years old, in excellent general health, with a well-groomed, confident demeanor. He was self-described as professionally-driven, and remarkably similar to Twin A in his goal-orientation and pursuit of professional excellence. However, dissimilarly, Twin B was single, not involved in a relationship, and worked in academia rather than in the corporate arena.

Through December and January, five telephone consultations determined Twin B's valid pursuit of predictive testing, establishing to West Coast counselor the genuineness of his request and the absence of coercion for testing to satisfy the needs of Twin A. Both counselors agreed that honoring the twin's right not to know, was a valued principle, but one that relied on subjective evidence derived from Twin B's self-reported position. Considerable discussion challenged Twin B's understanding of the testing process and the possible implications for his professional and personal life. He was provoked with possible scenarios in order to examine his practical, behavioral, and emotional responses.

Upon first meeting Twin B in February 1993, he was in good spirits with minimal observable apprehension about formally beginning the testing process. Like Twin A, he expressed primary concern for financial preparedness, and had taken out a significant Long Term Disability plan for himself in the event of a positive test outcome. With that in place, Twin B described a sense of well-being, since the thought of becoming a financial burden was intolerable. When asked about emotional support, he tongue-in-cheek responded that by the time it would be needed, it probably would not matter. This attitude, however, could not mask his struggle with the possible loss of independence. His conflict between self-reliance and accepting/requiring the assistance of others was explored, and Twin B admitted financial preparation was his only strategy.

Twin B proceeded with his neurological consultation and psychologic assessment, both of which were unremarkable, within normal limits, and supportive of his readiness for testing. Twin B's laboratory sample was shipped to the testing facility.

In early April, Twin B was notified that the testing laboratory confirmed that the family was fully informative, and results could be available 3–5 weeks thereafter. However on April 13, 1993, East Coast Genetic Counselor informed West Coast Genetic Counselor that Twin A wished to delay result disclosure until August because of his employment pressures and travel schedule. West Coast Genetic Counselor contacted Twin B to discuss this change of plans, and Twin B remarked that his brother had already contacted him and explained his situation. Twin B stated that he was initially disgruntled by the extended wait, but understood the needs of his brother and would certainly comply. Upon reflection, he commented that he wished to do some traveling over the summer, and perhaps it would be better, after all, to vacation without the possible burden of the test result.

In July, East Coast Genetic Counselor contacted West Coast Genetic Counselor and a date was agreed upon for result disclosure, with scheduling 3 hours apart to allow for the time zone differences.

Twin B arrived for his result disclosure appointment alone, despite repeated reminders to be accompanied by an appropriate support individual. He simply stated he was more comfortable keeping the appointment alone. Twin B was shown the laboratory test results, and read the detailed interpretation and comments generated by the laboratory director. He was clearly moved and relieved by his good fortune, as he was predicted not to be an HD gene carrier with a 99% accuracy. Twin B expressed the pleasure of no longer being at risk, but reiterated his continued concerns for his older brother and for his parents. Twin B said he would welcome future contact in compliance with our protocol.

Follow-up discussions were by telephone, at 3- and 5-month intervals following results. Twin B's career was advancing, he was in the market for a new home, and was involved in a new relationship. He still maintained significant long term disability insurance, as he was not yet ready to reduce his coverage. Twin B welcomed our communications and volunteered continued involvement.

DISCUSSION

MZ twins share a 50% risk. In accordance with widely recognized standards for predictive testing, Twin A was denied testing unless Twin B voluntarily requested testing. (Harper, 1991) While the principle of autonomy implied that Twin A had the right to know whether he carried the HD gene, Twin B had not expressed an interest in learning his status. Testing Twin A meant that Twin B would be simultaneously tested. Thus, the issue of beneficence required consideration. Twin B could be at risk for psychological harm if information about his risk to develop HD was revealed without evaluation, counseling, and informed consent. The decision rested on the conclusion that even if Twin A never told his twin the test result, knowledge of his twin's status would be a violation of Twin B's right not to know. While there is no legally compelling basis for a decision to permit testing of one MZ twin without the other, ethical and moral factors weigh heavily in favor of providing testing only when both twins voluntarily give informed consent in compliance with other requirements of the predictive testing protocol (Huggins *et al.*, 1990).

The case described in this paper was complicated by the need to counsel, evaluate, and test the twins at two testing sites. The required simultaneous testing was easily resolved by the voluntary compliance of Twin B after his brother had taken the testing initiative. It is feasible, however, for a MZ twin to be unable to comply with the requirement to be tested as a pair because the twins are estranged or one twin is unwilling to undergo predictive testing. When twins are clients in the same testing program, the genetic counselor or psychologist can invite the twins to be counseled together to facilitate their assuming an active role in considering the moral, ethical, and personal dilemmas relevant to the test decision. Support can then also be provided to each twin regarding the eventual decision for or against joint testing.

Issues inherent to this case have broad application to other predictive testing situations. Consider the case of MZ twins who are never tested because one is unwilling. Several years hence, the adult child of one of the untested twin parents requests testing. The child is at 25% risk, but his or her result will reveal the status of the aunt or uncle who still does not want to know. Should the autonomy of the aunt or uncle take precedence over the young adult who is currently requesting testing?

A married MZ twin might request predictive testing to facilitate family planning. The co-twin, when questioned about simultaneous testing, might maintain that he or she feels incapable to cope with knowing. If the test is denied, the twin requesting testing will have only the option of prenatal diagnosis by exclusion and possible abortion(s) for normal fetuses. Is the autonomy of the twin who declines testing still compelling against testing the twin who wants to know?

The availability of direct testing allows the bypassing of relatives who are not available or not interested in testing. Therefore, an individual at 25% risk whose at-risk parent declines testing or is absent can be studied for the gene mutation. Similarly, technology allows prenatal diagnosis of a fetus at 25% risk whose at-risk parent declines study or is unavailable.

One may argue that the merits of these situations are quite different. The policy at one testing center might permit testing for the first scenario because the adult child is estranged from the parent, had the right to know, and was believed to be entitled to pursue the information. When nondisclosing exclusion is impossible or unacceptable, the policy at the same center might rule against allowing prenatal diagnosis because the at-risk parent is present and entitled not to know. Since the outcome of these deliberations affects more than one family member, it is advisable, whenever possible, to include the parent at 50% risk in the counseling. If these individuals refuse or are unavailable for counseling, then the rights of the individual at 25% and of the parent requesting diagnostic or exclusionary prenatal diagnosis on behalf of a fetus at 25% risk must be considered. (Chapman, 1990; World Federation of Neurology: Research Committee. Research Group on Huntington's Chorea, 1990).

The issue of autonomy is pivotal when parents request predictive testing for minor children. Parents may feel a need to resolve uncertainty about the future health of their at-risk children. When counseled, however, they usually appreciate that parenting may be influenced by the knowledge that a child will develop HD. The situation could be exacerbated by dissimilar results in two or more offspring. Other factors that mitigate parents' desire to have their children tested include the unavailability of medical intervention to alter the age of onset or progression of HD, the potential to stigmatize the child, and perhaps most importantly, the issue of autonomy. A minor child who has been predictively diagnosed has been deprived of the opportunity to make an informed decision as an adult (Block and Hayden, 1990).

Should decisions on these complex situations depend on the judgment of clinicians on a case by case basis or by policy consensus among professionals in appropriate disciplines providing services to patients seeking predictive testing? The HDSA has developed Guidelines for Predictive Testing (see Appendix). Most HD Predictive Testing Programs have developed protocols for genetic counseling and evaluation that conform with these guidelines (Craufurd and Tyler, 1992; Quaid, 1992; Bennett *et al.*, 1993; Benjamin *et al.*, 1994). However, there is still considerable diversity of opinions among testing centers worldwide regarding some issues relevant to criteria for predictive testing, such as the testing of individuals at 25% risk.

Even with the best of intentions, genetic counselors, laboratories, and others involved in predictive testing, will be at the mercy of their patients and referral sources to honestly provide medical and family history information. The strategy described in managing the MZ twin situation depended on two factors (1) an accurate family history (Twin A stated that he had two siblings, one of whom was his twin), and (2) the referral was made to HD Testing Programs where the ethical issues and methodology of testing twins were understood and presented as conditions to testing. As the public becomes more sophisticated about protocol and counseling prerequisites, it is possible that some individuals may withhold or alter information about family members whose autonomy could subsequently be violated.

It is encouraging to note that results of a 1 year post-test prospective study of 135 well-educated and middle-aged individuals who had requested predictive testing by linkage analysis, with counseling and psychological support throughout the pre-test and post-test periods, suggest an improvement in psychological well-being and quality of life when positive or negative test results relieved uncertainty about their at-risk genetic status. Forty of these participants who declined testing or whose results were inconclusive had higher scores for depression over the same 12-month study period. While one might have predicted less difficulty adjusting to negative test results, 10% suffered serious difficulties accepting their test result, reinforcing the advantage of post-test psychological support to all tested individuals (Wiggins *et al.*, 1992).

Research now planned or in progress at several centers will eventually provide similar data regarding individuals experiencing diagnosis by the direct test, without the required participation of family members. It would also be interesting to compare the psychological consequences of testing with and without compliance to accepted HD testing protocol. Another rich area of research and therapeutic interest would be the psychological impact on family members tangentially affected by direct testing of an adult child, sibling (including a twin), grandchild, or spouse.

Experience with HD has been the pioneering effort to develop prototypes for predictive testing and research protocols for late-onset genetic diseases, particularly with regard to the genetic counseling component (Babul *et al.*, 1993; Benjamin *et al.*, 1994). Criteria and protocol for predictive testing would be quite different for treatable late-onset genetic diseases. Professionals providing access to predictive testing for HD should be aware that there is rationale for supporting the establishment of standards of care for the psychological, medical, social, and moral well-being of their patients while providing examples for protocols and therapeutic approaches to other genetic diagnoses. The molecular diagnostic frontier calls for caution and wisdom, guided by such principles as autonomy, justice, and beneficence, with the awareness of nonmaleficience, wherein some actions that intend good may also have negative consequences. The hope is to clearly err on the side of accomplishing a greater good with the least possible harm.

SUMMARY

This case illustrates case management coordination for HD predictive testing of MZ twins residing 3000 miles apart by two genetic counselors on opposite coasts of the United States. Ethical, clinical, and practical issues that required resolve and collaboration included protection of privacy and autonomy, consideration for the emotional and logistic consequences of one twin's decisions and actions on the other, confidentiality, informed consent for zygosity and predictive testing, variation in protocol designs of testing centers, and coordination of result disclosure.

APPENDIX. THIS IS A SUMMARY OF RECOMMENDATIONS FOR GENETIC TESTING PREPARED BY THE HUNTINGTON DISEASE SOCIETY OF AMERICA, INC. THESE GUIDELINES ARE RECOMMENDED PROCEDURES, NOT REGULATIONS[a]

It is strongly recommended that pre and post-test counseling be incorporated in any presymptomatic testing program. While the HD gene discovery alters some aspects of the test, the personal, family, and ethical issues remain unchanged (from those related to linkage analysis studies) and the importance of counseling is therefore undiminished.

The decision to take the presymptomatic test should always be an informed, carefully considered, and freely chosen personal decision. Under no circumstances should an individual be coerced into testing.

The testing program should include the following components:
1. initial phone contact/prescreen interview;
2. three pre-test, in-person sessions, to include genetic counseling, neurological evaluation, and psychological evaluation;
3. a fourth session for disclosure of the results;
4. post-test counseling over a 2 year period.

The participant should be accompanied to all testing sessions by a companion (spouse or close friend, not a sibling).

The testing participant should identify a counselor close to home to be available for emotional support and/or counseling should the need arise.

Excluding prenatal nondisclosing testing or exceptional circumstances, there should be at least one month's interval between the pre-test sessions and the final decision to take the test.

Minors should not be tested unless there is a medically compelling reason for doing so.

Test results should not be divulged to anyone other than the participant without his /her written consent.

Test results should be given in person; results should never be given over the telephone or by mail.

Confirmatory testing may be offered to an individual with clear symptoms of HD and a documented family history. However, a clinical neurological examination remains the definitive means of diagnosis.

Laboratories are advised not to accept anonymous DNA samples for testing.

Individuals or couples considering prenatal testing should seek genetic counseling prior to conception.

[a]Huntington Disease Society of America (1994) Genetic Testing: Summary of Recommendations. *The Marker* Fall/Winter, p 5.

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inner strength to overcome whatever weakness or infirmity he/she may have.

Deborah DeLeon
Columbia University
Neurological Institute
710 W. 168th St
New York, New York 10032

Letters to the Editor

Testing for HD in Twins

To the Editor:

I read with some concern "Huntington Disease: A Case Study Describing the Complexities and Nuances of Predictive Testing of Monozygotic Twins" co-authored by Heimler and Zanko (1995). I appreciate that there may be special issues faced by a genetic counselor when a patient is a twin. As the authors state, there have been cases in the literature in which the patient was a twin and zygosity testing was carried out before genetic testing was undertaken. It was on the basis of these recommendations that the authors required zygosity testing. I do not believe that following this protocol is necessarily in the best interest of the patient nor, in this instance, do I think it was completely respectful of patient autonomy.

I agree with the authors that the patient should be apprised of the implications for himself and for his brother in each scenario, that is, he should understand that the issues depend on whether he and his brother are monozygotic or dizygotic. Just as the East Coast counselor did, I would strongly recommend that the patient talk with his twin and suggest that his twin see a genetic counselor to discuss the issues. A dilemma for the counselors was avoided when Twin B agreed to undergo testing, but an alternative outcome might have been that Twin B could have elected to forego testing and/or refused to speak with a genetic counselor. What if Twin A had flatly refused to discuss the testing with his twin? The inference of the article was that unless the uncertainty of the twins' zygosity was resolved, Twin A would have been refused testing. Is his right to know his "at risk" status to be denied because of the accidental circumstance of his conception, i.e., that he shared the womb with a twin? Should the right of Twin B not to know take precedence over the right of Twin A to know? I believe in this situation the autonomy of Twin A was compromised.

Another consideration is the issue of coercion. Are we completely certain that there was no coercion? If Twin B knew that his brother would be refused testing if he did not cooperate, might that not constitute coercion,

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