Genetic testing is important for diagnosis and prediction of many diseases. The development of a clinical genetic test can be rapid for common disorders, but for rare genetic disorders this process can take years, if it occurs at all. We review the path from gene discovery to development of a clinical genetic test, using frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17) as an example of a complex, rare genetic condition. An Institutional Review Board-approved multidisciplinary research program was developed to identify patients with familial frontotemporal dementia. Genetic counseling is provided and DNA obtained to identify mutations associated with FTDP-17. In some cases it may be appropriate for individuals to be given the opportunity to learn information from the research study to prevent unnecessary diagnostic studies or the utilization of inappropriate therapies, and to make predictive testing possible. Mutations identified in a research laboratory must be confirmed in a clinical laboratory to be used clinically. To facilitate the development of clinical genetic testing for a rare disorder, it is useful for a research laboratory to partner with a clinical laboratory. Most clinical molecular assays are developed in research laboratories and must be properly validated. We conclude that the transition of genetic testing for rare diseases from the research laboratory to the clinical laboratory requires a validation process that maintains the quality-control elements necessary for genetic testing but is flexible enough to permit testing to be developed for the benefit of patients and families.

© 2003 American Association for Clinical Chemistry

The path to disease gene discovery frequently begins with the study of a familial disease and the recruitment of large families in an effort to identify genomic loci that segregate with disease. To this end, the information made available as a result of the Human Genome Project has facilitated the discovery of many disease genes (1, 2). Once a gene has been linked to a disease, further study may lead to the elucidation of disease-associated mutations. This discovery can then lead to new avenues of investigation that provide insight into the pathophysiology of the disease process and clinical variability. The ultimate goal of such research is the development of therapeutics that can either prevent the onset or slow and potentially halt the progression of disease (3). Another possible outcome of the identification of disease-associated mutations is the development of clinical genetic tests for the purpose of diagnosis, identification of carriers (for recessive disorders), prenatal or preimplantation genetic testing, and for predictive testing in late-onset disorders. The progression from gene discovery to development of clinical tests can be rapid for common disorders, but for rare genetic disorders (such as those affecting fewer than 200,000 people in the US) this process can take years, if it occurs at all. The process for development of a clinically available genetic test, irrespective of whether it is for a common or rare disorder, is influenced by clinical utility as well as many regulatory, financial, and organizational issues (4, 5). Here we review the path from gene discovery to development of a clinical genetic test using frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17)\(^1\) as an example of a complex, rare genetic condition.

\(^1\) Nonstandard abbreviations: FTDP-17, frontotemporal dementia with parkinsonism linked to chromosome 17; FTD, frontotemporal dementia; AD, Alzheimer disease; IRB, Institutional Review Board; and RFLP, restriction fragment length polymorphism.
Genetics of Frontotemporal Dementia

Frontotemporal dementia (FTD) is characterized clinically by a gradual onset of changes in personality, social behavior, and language dysfunction and is often associated with parkinsonian symptoms or motor neuron disease (6). As the name indicates, FTD generally affects the frontal and/or temporal areas of the brain with the clinical symptoms reflecting the regional brain involvement. FTD is largely considered to be a presenile dementia because it typically affects patients between the ages of 35 and 75 (6-8). The clinical presentation of FTD is heterogeneous, and for this reason, in part, FTDs are frequently mistaken for Alzheimer disease (AD) or a primary psychiatric disorder. The frequency of FTD has been difficult to ascertain, but it is most likely between ~5% and 15% of all dementias (8-15). In contrast, FTDs represent ~17-20% of presenile dementias, which also include early-onset AD (11-13, 15-19). Although the exact prevalence of FTD is not known, it was reported to be 15 per 100 000 presenile individuals in a study that looked at individuals under the age of 65 in the United Kingdom (20). This is comparable to a population studied in The Netherlands, where the prevalence was found to be 9.4 per 100 000 at ages 60-69, which is approximately twice as high as previously reported in the same population (10, 21, 22). The difficulty in the ascertainment of population data on FTD is attributable in part to the low prevalence, but it may also result from the different diagnostic criteria that are applied (10). Although FTDs display considerable heterogeneity both clinically and neuropathologically, consensus criteria for the diagnosis of FTD have been published (23, 24).

FTD is a complex disorder that can present either sporadically or as a familial disorder. In ~30-50% of individuals, a family history of loosely defined dementia is present, some of these displaying an autosomal dominant pattern of inheritance (7, 16, 22, 25-27). In 1994, linkage to chromosome 17 was first established in a pedigree with a form of FTD designated disinhibition-dementia-parkinsonism-amyotrophy complex (28). This linkage gave rise to the name frontotemporal dementia with parkinsonism linked to chromosome 17, or FTDP-17. The tau gene on chromosome 17 was a primary candidate gene because of the neuropathologic examination of brains in familial cases of FTD, which showed neuronal and glial intracytoplasmic tau inclusions. Tau is a microtubule-associated protein that promotes microtubule assembly and stability and is also involved in axonal transport. Abnormal tau accumulations are associated with the onset or progression of many neurodegenerative diseases. Diseases with widespread but varied tau pathology include AD, Pick disease, progressive supranuclear palsy, corticobasal degeneration, and FTD. In the late 1990s mutations in the tau gene were identified in many FTDP-17 cases, which provided direct evidence that tau protein dysfunction can lead to neurodegeneration (26, 29-36).

Since then, more than 25 different mutations, including missense mutations, splice-site mutations, and deletions, have been identified in more than 50 families (37). The frequency of tau mutations in sporadic cases of FTD, i.e., individuals without a family history of dementia, is extremely rare (16). In contrast, the tau mutation frequency for affected individuals having a family history of a similar disorder is between 9.4% and 40.5% depending on the study and population examined (16, 38, 39). Furthermore, a mutation frequency of 33% was obtained in a study looking at deceased individuals with a positive family history (at least one first-degree relative displaying dementia) and a pathologically confirmed diagnosis of FTD showing clear evidence of robust tau inclusions (38).

The existence of many cases of familial FTD that have neither tau mutations nor tau pathology is strong evidence that additional genes for familial FTD are likely to be discovered (40). Genetic heterogeneity in familial FTD is also supported by the fact that genetic linkage to chromosomes 3 and 9 has been found for clinical FTD variants (41-43).

The identification of tau mutations in FTDP-17 families has led to extensive and continuing research aimed at understanding how these mutations cause disease. The human tau gene contains 15 exons, of which 11 are expressed in the adult central nervous system (37). Exons 2, 3, and 10 are alternatively spliced to yield six tau protein isoforms. These isoforms are characterized by containing zero, one, or two amino-terminal inserts, which may have an important role in neuritic development and are thought to modulate interaction of microtubules with the plasma membrane (44), and three or four carboxy-terminal microtubule-binding repeats (45). Mutations in the tau gene have been identified in exons 1, 9, 10, 11, 12, and 13 as well as in intron 10 near the 3’ splice junction of exon 10 (45). Of these, the majority are found within exon 10 and in the adjacent intron 10 (Fig. 1). Tau mutations can alter tau splicing, disrupt tau protein function, or both. When abnormal tau is produced by either hyperphosphorylation (such as in AD) or as a result of a mutation, this may lead to the aggregation of tau or the disruption of microtubules, which are critical for supporting the intraneuronal transport system. It is theorized that a shift away from the normal one-to-one ratio of three to four repeat tau could lead to a reduction in available microtubule binding sites and therefore an excess of free tau. This could then lead to tau protein aggregation and filament formation, which is the pathologic hallmark of FTDP-17 (46).

FTDP-17 is generally pathologically characterized by filamentous tau deposits in both neurons and glia accompanied by nerve cell loss and gliosis; however, it has been well documented that different tau mutations can also produce distinct pathologic findings (47). The location of the mutation within the tau gene to some extent drives the cellular localization of tau pathology and the tau filament morphology. The mutations in the 5’ end of intron 10
occur in a region of the tau gene involved in splice regulation, and these mutations exert their effects either by disrupting a putative stem-loop structure or by altering the binding site of a regulatory protein. This generally leads to the overproduction of four-repeat tau. In addition to the pathologic heterogeneity of FTD, extensive clinical heterogeneity is observed in FTDP-17 patients with the same mutation and in some cases even within the same family (48). This is particularly true of the P301L mutation, first described in 1998 (33, 49–55). Thus, although a tau mutation may lead to neurodegeneration, there are environmental and/or other genetic factors yet to be elucidated that play a role in the clinical presentation of the disease (56).

Research Genetic Testing

After a disease gene has been identified, the discovery of novel mutations can be very helpful to the study of disease pathophysiology and clinical variability. Therefore, it is not surprising that within the research community investigations continue beyond the identification of the gene. Much emphasis is placed on the identification of more families with the condition in the hope of finding new mutations or novel gene associations. This can be accomplished by institution of a rigorous research genetic testing program. Thus, research genetic testing is performed to advance scientific knowledge about the genetic contribution to a disease and to learn more about the clinical phenotype and penetrance of gene mutations. Generally, persons interested in participating in genetic research studies are highly motivated individuals who are symptomatic or have one or more family members with an inherited disease (57). They are interested in helping researchers learn more about the disease, search for new therapies, and develop clinical genetic tests to help diagnose the condition regardless of whether they themselves or their family will directly benefit from the research. Human research, including genetic studies, in the US must be approved by an Institutional Review Board (IRB). Regulations specify that research results cannot be reported for clinical use because the laboratories in which such tests are performed are usually not licensed or certified for clinical testing and proper quality-control mechanisms may not be in place (58).

Genetic Research Study of tau Mutations

An IRB-approved research program to study the genetics of FTD was initiated in the Center for Neurodegenerative Disease Research at the University of Pennsylvania. This program is multidisciplinary in its approach to the identification of families with hereditary FTD, involving neurology, neuropathology, biochemistry, molecular pathology, and genetic counseling. FTD patients with a family history of a similar disorder seeing one of the neurologists in the program are offered the opportunity to enroll into the research study for molecular analysis of FTD. They are then referred to a genetic counselor who obtains a detailed family history and reviews the clinical information. Because the success of genetic research is dependent on the involvement of patients and families, it is important to consider issues related to the protection of humans in research (59). Separate informed consent forms for participation are used for affected individuals and unaffected family members, and as part of the informed consent process, the benefits and limitations of the research study are reviewed with all participants. Although participants in genetic research studies are generally willing to help advance the understanding of a disease with little or no personal benefit, it is important to recognize that some patients and their family members may be quite eager to learn the results of the research to benefit from potential genetic testing. Because most research studies do not guarantee the ability to share results with participants, such expectations need to be explored and discussed at the outset. Participants also need to be instructed regarding the differences between participating in research genetic testing studies and having a clinical genetic test performed. It can be most helpful for research participants to discuss the issues of genetic testing with a genetic counselor. For this reason, genetic counseling is a crucial component of genetic research studies.

Once informed consent and a blood sample are ob-
tained, DNA is extracted and either stored for later analysis or tested immediately. Because the tau mutations identified to date are located throughout the tau gene, it is important to use an appropriate mutation detection method. Although the armamentarium for mutation detection is expanding rapidly, DNA sequencing remains the gold standard for the identification of mutations found in several locations throughout a gene. This is primarily because of its specificity and ability to detect many different mutations in a single amplified PCR product. Alternatively, one way to decrease the cost and increase throughput is to utilize a screening or scanning method for the identification of variations in a target DNA sequence. Sequencing is then used only on those samples that demonstrate the presence of a heterozygous nucleotide change. The most commonly used screening methods are conformation-based techniques that are based on the fact that mutant molecules have aberrant electrophoretic migration under certain conditions (60). These methods include single-strand conformation polymorphism analysis, conformation sensitive gel electrophoresis, denaturing gradient gel electrophoresis, heteroduplex analysis, and denaturing HPLC (61). The advantage of a screening method is the relative ease with which many samples can be screened for the presence of a nucleotide variation. A disadvantage of screening methods is that conditions for analysis must be optimized individually for each target sequence, which can be time-consuming. In addition, these methods can only indicate that there is a difference between two sequences; they do not specify whether the difference is a polymorphism or a mutation, nor the exact location of the sequence variation. Therefore, conformation-sensitive methods are not useful in DNA fragments with many polymorphic sites as they will frequently be positive, leading to a high rate of confirmatory sequencing.

For the FTD genetics study in the Center for Neurodegenerative Disease Research, it was decided to use direct DNA sequencing of the tau coding region. All coding exons of the tau gene expressed in the adult central nervous system are PCR amplified along with adjacent intronic sequences and then sequenced using a Beckman-Coulter CEQ8000, as shown in Fig. 2. The identification of a known tau mutation provides the researchers with information that can be used to correlate clinical presentation and family history with the mutation and eventually, on the patient’s death, with pathology. The identification of novel coding or intronic nucleotide changes may or may not be associated with disease. Although mutations that affect the reading frame, cause a missense or nonsense mutation, or alter a splice site have a high likelihood of being pathogenic, definitive assessment of disease association requires in vitro expression and analysis of the variant gene product in conjunction with additional family studies to determine whether the variant segregates with disease (60).

The primary objectives of research genetic studies are to advance the understanding of disease pathophysiology and to further the therapeutic development process. These are accomplished through identifying mutations in a candidate gene, tau in this case; studying new mutations; and banking DNA samples for future studies of additional genes.

**Clinical Utility of Genetic Testing Results**

Until a gene’s disease association is well established, testing usually remains research-based. However, when disease association and penetrance are well understood, genetic testing results can have a substantial impact for the patient and family. For example, if a known FTDP-17 mutation is identified, then this information can prevent unnecessary diagnostic studies as well as prevent the utilization of inappropriate therapies. It is important to differentiate patients with FTD from those with AD because the clinical course and management of these neurodegenerative disorders are different, although there is no effective therapy for either. Thus, as research genetic studies progress it may be very appropriate, with IRB approval, for individuals to be given the opportunity to learn information from the research study. It is also of vital importance that when genetic research results are disclosed, genetic counseling is provided (59).

In the case of inherited FTD and other genetic conditions with late or adult onset, there are also asymptomatic family members at risk. Conditions with autosomal dominant inheritance, such as FTDP-17, pose a 50% risk to all offspring of an affected individual. In addition, in the majority of cases, siblings and parents of an affected individual are also at 50% risk. At-risk individuals have expressed an interest in genetic testing so that they can learn if they “inherited the gene”, and predictive genetic testing is not a new concept for families coping with
hereditary neurodegenerative conditions. Such testing has been offered to individuals at risk for Huntington disease, familial AD, and other conditions, and despite the lack of therapeutic intervention available, at-risk individuals often consider predictive testing informative and helpful. Individuals at risk for hereditary FTD and early-onset familial AD have considered predictive testing to assist with family- and life-planning decisions, to seek relief from anxiety, to address concerns about early symptoms of dementia, and to further basic research (62, 63).

There is no doubt that the results of research studies can in some cases be clinically useful, for example, by the detection of a disease-associated mutation in an affected individual and the correlation of that mutation with a known clinical phenotype. In these cases, research laboratories can, with appropriate IRB approval, issue a “For Research Use Only” report. However, to be used clinically, the result must be confirmed in a certified laboratory.

Research vs Clinical Genetic Testing

Whereas research testing is performed to advance scientific knowledge, clinical genetic testing is performed generally for the direct benefit or clinical care of patients. Clinical genetic testing is performed in a certified laboratory for a fee, at the request of a physician and often in consultation with a genetic counselor. Laboratories performing testing on human specimens must be certified under CLIA ’88. CLIA ’88 was enacted by Congress to establish quality standards for clinical laboratories with requirements for regular on-site inspections and proficiency testing (4, 5, 64). The Center for Medicare and Medicaid Services, formerly the Health Care Finance Administration, is responsible for implementing CLIA regulations. CLIA certification can be obtained from an organization or state with deemed status under CLIA, such as the College of American Pathologists or New York State. To become certified by CLIA, laboratories must be inspected regularly and follow strict guidelines for test validation and ongoing quality control, including proficiency testing.

From Research to Clinical Testing

Although clinical genetic tests are available for many genetic disorders, including some less common disorders, this is not the case for extremely rare or “orphan” genetic diseases. The high cost and time involved in the development of a clinical molecular test in a CLIA-certified laboratory generally limits development to assays or analytes that will have a high enough volume to offset costs. For this reason, genetic testing for rare diseases such as hereditary FTD remain in the research realm for a long time, and development of a clinical molecular test lags far behind gene discovery. This is particularly true for genes for which there are many disease-causing mutations spread throughout the gene. This is attributable to the difficulty associated with developing a cost-effective test with sufficient sensitivity to be of use clinically. In addition, if a clinical laboratory were to perform mutation screening and identify a novel mutation of unknown significance, this would have the effect of blurring the division between research and clinical testing because of the need for further research to assess the functional effects of the mutation. For disorders such as FTDP-17, the development of a clinical test is important for confirmation of mutations initially identified in the research laboratory and to provide predictive testing of family members of affected individuals with known mutations. Thus, a research laboratory can partner with a CLIA-certified laboratory to facilitate the development and validation of the testing. Some clinical laboratories may be willing to confirm any mutation identified in the research laboratory, whereas others may offer only limited testing for common mutations. The test development process is different in both scenarios. In the case of FTDP-17, genetic testing for select tau mutations is available in a few laboratories.

Molecular pathology laboratories must take many factors into account before deciding whether to offer a molecular genetic test. A test development process begins with a review of the clinical needs and value of the test, an evaluation of anticipated volume, feasibility of the required testing methodology for the laboratory, and a cost/benefits analysis of the test (4, 65). Volume and cost are usually not major factors in the decision to develop tests for rare genetic diseases. Once the decision is made to offer a clinical genetic test, an assay procedure must be developed with known positive and negative controls and using an appropriate mutation detection method. Although there are some Food and Drug Administration-cleared assays for molecular testing (primarily for infectious disease and HLA testing), the majority of molecular diagnostic tests are developed in individual laboratories as so-called “home-brew” assays (5). As required for clinical testing under CLIA, these assays must be validated to ensure that the correct results are obtained and that the performance characteristics are reproducible (5). The challenge is to simplify the test development process for rare diseases but maintain the regulatory and quality-control elements necessary for high-quality testing in a clinical laboratory.

The first step of the laboratory development phase is selection of a method. The clinical laboratory may elect to use the same method as the research laboratory, e.g., DNA sequencing, or to develop a mutation-specific method such as PCR amplification combined with restriction fragment length polymorphism (PCR-RFLP) analysis. The latter is relatively easy to develop if the mutation to be confirmed leads to the gain or loss of a restriction enzyme site, as shown in Fig. 3. In either case, the chosen test must be analytically validated. Analytic validity refers to the accuracy with which a particular genetic characteristic, e.g., a mutation, can be identified by a given laboratory test. Ideally, each analyte or mutation
should be analytically validated individually; however, for heterogeneous mutations, such as in tau, this is not feasible. Alternatively, it has been proposed that for methods that involve PCR amplification of a target sequence followed by a mutation detection method, the clinical laboratory can simply confirm that the primer sequences are correct and that the PCR products generated are of the expected sizes and/or DNA sequences compared with the research protocol. The initial analytic validation can be performed on available positive and negative controls obtained from the research laboratory. The wild-type sequence can serve as a subsequent control for DNA sequencing. This expedited validation permits reporting of any known mutation detected within the amplified sequence as long as the size of the original PCR product is verified. The use of PCR-RFLP analysis would require that the laboratory have a positive control and confirm that the expected pattern is produced (Fig. 3).

Regardless of disease prevalence, a genetic test can be used in clinical practice only once its clinical validity has been established (66). Clinical validity reflects both the sensitivity of the test, i.e., the proportion of affected people with a positive test (positive predictive value), and the penetrance of the mutations identified by the test. Penetrance refers to the proportion of people with the mutation who will manifest the disease. This is especially important if an assay is being used for predictive testing. In the case of FTDP-17 mutations, the penetrance is reported to be very high by the sixth decade of life (7).

Each laboratory is currently not required under CLIA to individually establish clinical validity for a genetic test; it is considered acceptable to rely on external validation reported in peer-reviewed literature (67). However, there have been some initiatives to increase regulation of genetic tests, which could increase the burden on the laboratory for documenting clinical validity (66). It must be recognized that for rare disorders this will not be possible. There must be a compromise that strikes a balance between making a potentially useful test available and preventing inappropriate genetic testing.

Aside from analytical and clinical validity, a laboratory must also verify the performance characteristics of the test (5, 67). The performance characteristics include a determination of accuracy and precision. Accuracy is the ability of a test to return a correct result compared with an external standard, and precision is the consistency with which an assay produces the same result on repeat testing. The accuracy can be assessed by either parallel testing with alternative technologies, e.g., DNA sequencing and PCR-RFLP analysis as shown in Fig. 3, or by testing previously tested patients or research samples. When a clinical laboratory is performing confirmatory testing for research results, a measure of accuracy is automatically present because the previous research report is available for comparison. If the laboratory is performing predictive testing on an individual, it is advisable to test an affected family member with a known

![Fig. 3. Methods for mutation analysis in FTDP-17.](image-url)

(A), DNA sequencing was performed on a patient with hereditary FTD, and an R406W mutation was identified in exon 13. This missense mutation results from a C-to-T conversion as seen by the heterozygous peak in the lower electropherogram. This mutation leads to the creation of an NcoI restriction site. (B), PCR product of exon 13 from wild-type (lane 2) and the patient’s (lane 1) DNA digested with NcoI. The wild-type sequence remains uncut, whereas the heterozygous R406W sample is digested, producing three bands [at 597, 456, and 141 (faint) bp]. Base-pair markers (lane M) are indicated.
Obtain informed consent.

Present alternatives to testing

Discuss motives of testing, anticipated result, psychosocial

Discuss the benefits, limitations, and risks of testing. Discuss

Review natural history and inheritance of condition, as well as

Obtain family history and confirm diagnoses.

Table 1. Key elements of pre- and posttest predictive genetic counseling.

<table>
<thead>
<tr>
<th>Pretest</th>
<th>Posttest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obtain family history and confirm diagnoses.</td>
<td>Disclosure of result must be a face-to-face encounter. A knowledgeable support person should be present.</td>
</tr>
<tr>
<td>Review natural history and inheritance of condition, as well as a priori risk.</td>
<td>Offer follow-up contact and support, including referral to medical and psychologic specialists as needed.</td>
</tr>
<tr>
<td>Discuss the benefits, limitations, and risks of testing. Discuss confidentiality of test results.</td>
<td></td>
</tr>
<tr>
<td>Discuss motives of testing, anticipated result, psychosocial preparedness, and support system.</td>
<td></td>
</tr>
<tr>
<td>Present alternatives to testing—testing must be voluntary.</td>
<td></td>
</tr>
<tr>
<td>Obtain informed consent.</td>
<td></td>
</tr>
</tbody>
</table>

Finally, to implement a newly developed molecular genetic test, the clinical laboratory must prepare a procedure manual and report templates that conform to laboratory certification guidelines. Testing done for confirmation of a research result also requires that a new blood specimen and informed consent form be obtained from the individual being tested. In addition, proficiency testing must be performed at least twice a year and could be done by sample exchange with the research laboratory or by an alternative method, such as clinical correlation (68).

Predictive Genetic Testing

Once clinical genetic testing is available, predictive genetic testing can be considered. An individual who has predictive genetic testing may learn that he or she is destined to have a progressive, debilitating disease. A multidisciplinary approach to predictive testing that offers a knowledgeable healthcare team (e.g., psychiatrist, neurologist, social worker, and genetic counselor) to address the complex nature of disease and issues associated with testing is therefore crucial (69). Genetic counselors are important members of this team because pre- and posttest education and counseling are essential. Many clinical centers and laboratories require that the individual go through a formal predictive testing protocol that has critical pre- and posttest components (Table 1). This offers the individual an opportunity to discuss his or her motives for testing, explore the possible result outcomes, anticipate his or her reaction and coping strategies, develop a support system, and discuss the risks associated with receiving a diagnosis (such as adverse psychologic outcome and insurance or employment discrimination) (70). In addition, it is necessary to have the specific genetic abnormality or mutation in an affected family member documented to confirm the diagnosis before testing at-risk individuals. If a genetic mutation is not known in the affected family member, testing in other relatives is likely to have a lower predictive value.

Most studies that have examined the impact of the availability of predictive testing have been aimed at Huntington disease. However, one study looked at the effect of DNA testing for FTDP-17 and early-onset familial AD in at-risk individuals. Interestingly, of 251 at-risk individuals to whom DNA testing was offered, only a small number, ~8%, requested genetic testing (62). This low interest is similar to that observed for individuals at risk for Huntington disease. In the FTD and familial AD study, the reasons given for requesting testing were concern about early symptoms of dementia, financial or family planning, and relief from anxiety. Afterward, the majority of asymptomatic individuals who underwent testing felt that it was beneficial, although a few experienced moderate anxiety or depression. Interestingly, although individuals with negative test results may have reported being happier overall, even they were faced with ongoing anxiety and depression. Therefore, DNA testing for adult onset conditions such as FTDP-17 can be of benefit in asymptomatic individuals, but it must be done only in the context of formal genetic counseling with ongoing follow-up and management.

Of note, genetic testing for untreatable conditions is not recommended in children, defined as under the age of 18. Children are not able to understand the implications of such testing and are incapable of providing informed consent. In addition, having a predictive diagnosis may give a child a “label” that may do great harm for his or her future, increasing the risk for insurance and employment discrimination, as well as psychologic damage (71).

Conclusions

New disease genes and associated mutations are constantly being discovered. In fact, there are ~10 000 genetic loci identified to date according to the Online Mendelian Inheritance in Man website (http://www.ncbi.nlm.nih.gov/omim/). Knowledge of these genes and their associated mutations aids scientists in understanding disease pathogenesis and can lead to the development of disease-specific tests and therapies (72). Diagnostic molecular genetic tests can be extremely useful to physicians to prevent unnecessary tests and inappropriate therapy. However, for these results to be used clinically they must be performed in CLIA-certified laboratories. The website GeneTests (www.genetests.org) serves as a genetic testing resource for the identification of genetic clinics and genetic testing laboratories offering both clinical and research genetic tests (73). As of May 2003, the GeneTests website data indicated that genetic tests are available for 962 diseases in either a clinical or research form and that,
of the 962, close to 400 are available only as research tests. For molecular testing for rare diseases to transition from basic research to clinical laboratories, there needs to be a validation process that maintains quality-control elements necessary in genetic testing but is flexible enough to permit testing to be developed for the benefit of patients and families (74).

We would like to acknowledge support for this work from NIH-National Institute on Aging Grants AG-10124 and AG-17586 and NIH-National Institute of Neurological Disorders and Stroke Grant K08 NS41408-03.

References
41. Miyamoto K, Kowalska A, Hasegawa M, Tabira T, Takahashi K, Araki W, et al. Familial frontotemporal dementia and parkinsonism...


