Healthy Blue

Medical Policy

Subject:	Genetic Testing for Frontotemporal Dementia (FTD)		
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Description/Scope

This document addresses genetic testing for the screening, diagnosis and management of frontotemporal dementia (FTD). This document does not address genetic testing for Alzheimer's disease.

FTD is a degenerative condition characterized by focal atrophy of the frontal and anterior temporal lobes of the brain. It differs from other causes of dementia such as Alzheimer's, Lewy Body and Creutzfeldt Jakob's diseases. FTD was originally known as Pick's disease but over the course of time has been referred to by various terms including but not limited to, frontal lobe dementia, frontal lobe degeneration, frontotemporal lobar degeneration, and Pick complex.

Note: For additional information regarding related genetic topics, please see the following:

- CG-GENE-13 Genetic Testing for Inherited Diseases
- CG-MED-88 Preimplantation Genetic Diagnosis Testing
- GENE.00003 Genetic Testing and Biochemical Markers for the Diagnosis of Alzheimer's Disease

Position Statement

Investigational and Not Medically Necessary:

Genetic testing for frontotemporal dementia (FTD) is considered **investigational and not medically necessary** for all indications, including but not limited to the following:

- As a diagnostic or prognostic technique in individuals with symptoms suggestive of FTD; **or**
- As a screening technique in asymptomatic individuals with or without a family history of FTD; **or**
- Prenatal or preimplantation genetic testing to establish a diagnosis of FTD in the offspring of individuals with a genetic mutation known to cause FTD.

Rationale

FTD, formerly known as Pick's disease, represents a clinically, neuropathologically and genetically heterogeneous group of progressive non-Alzheimer dementias characterized by progressive atrophy of the frontal and anterior temporal lobes of the brain. These neurodegenerative changes result in behavioral and language disturbances in the presence of intact memory and visuospatial functions.

The fundamental features of FTD include an insidious onset with gradual progression of the disease, early impairment in personal conduct, early decline in social conduct, emotional blunting and loss of insight. Changes in behavior may include a decline in personal hygiene, distractibility and hyperorality. Changes in speech and language may include echolalia and altered speech output. Physical changes may include tremor, rigidity, incontinence and primitive reflexes (Williamson, 2004).

Common pathologic findings in FTD include atrophy and neuronal loss affecting the frontal and temporal lobes of the brain. There is histologic heterogeneity in individuals with FTD, but about 55% of these individuals have FTD with ubiquitin-positive inclusions and 45% have FTD with tau-positive inclusions. While there appears to be a direct relationship between the causative gene and histopathological changes, there is some overlap in the correspondence between causative gene and clinical presentation. In the absence of pathological data, there may be significant overlap in clinical presentation between Alzheimer's disease and FTD. Practitioners may not be able to predict the causative gene on the basis of phenotype alone (Cardarelli, 2010; Loy, 2014).

Although data are limited, approximately 20-50% of individuals younger than 65 years with dementia have FTD, a prevalence similar to that of Alzheimer disease in persons 45 to 64 years of age (15 per 100,000). The age of onset is typically between 45 and 65 years, although approximately 10% of affected individuals have an onset above the age of 70 years. Parkinsonian features are a common sign and support the diagnosis of FTD, but typically emerge in a later stage of the disease. Motor neuron disease (MND) develops in as much as 13% of the individuals with FTD. Because many individuals with FTD present with behavioral changes, it is suspected that estimates of incidence and prevalence are conservative, since a subset of these individuals is likely to be referred to psychiatric services. There is a wide range in the duration of disease (2-20 years) which may suggest different underlying pathologies. Mortality usually occurs within 6-8 years (Cardarelli, 2010; Cohn-Hokke, 2012; Mohandas, 2009; Neary, 1998; Seelaar, 2008).

There is no cure for FTD and no treatment to prevent or delay the development of the disease. Treatment is usually focused on managing the manifestations of the disorder. As an example, sedative or antipsychotic medications may be beneficial to help reduce roaming behavior, extreme restlessness, delusions, and hallucinations. Selective serotonin reuptake inhibitors may be utilized for depressive symptoms, repetitive behaviors and disinhibition. Extrapyramidal signs are usually only partially responsive or unresponsive to treatment with L-dopa. Psychological support for the individual, partners or other caregivers may also be provided.

A part of the diagnostic workup for suspected FTD includes the exclusion of other neurodegenerative conditions with similar presentations, including but not limited to Alzheimer disease. The diagnosis of FTD has historically been based primarily on clinical assessment. A detailed history including the onset of new or unusual behaviors as well as family history (other family members with dementia, age of onset and mode of inheritance) can provide valuable insight. Neuroimaging studies may exclude alternative pathologies and/or provide supporting findings. A neuropsychiatric assessment and neuropsychological testing may be completed. Laboratory tests may be performed to exclude potentially reversible contributors or causes of the cognitive impairment. The definitive diagnosis of FTD is made post-mortem via brain autopsy.

FTD is frequently divided into three clinical subtypes, dependent upon the leading features at presentation: behavioral variant FTD (bvFTD); semantic dementia (SD); and progressive non-fluent aphasia (PNFA). The most common type of FTD is bvFTD, which typically manifests by disinhibition, compulsive or perseverative behavior, and apathy with emotional bluntness. Individuals with PNFA exhibit reduced speech production, while SD is characterized by difficulties in recognizing objects and understanding words. FTD spectrum may also include apraxia of speech, corticobasal degeneration, progressive supranuclear palsy and MND (Cohn-Hokke, 2012; Johnson, 2005; Leyton, 2011; Loy, 2014; McKhann, 2001; Mohandas, 2009; Warren, 2013).

Several diagnostic criteria for FTD have been published. The Neary criteria (1998) remain a valuable description of the clinical subtypes of frontotemporal dementia. However, the more recently published criteria are likely to improve the sensitivity and specificity of clinical diagnosis (Boeve, 2003; Henry, 2011; McKhann, 2001; Mesulam, 2001; Rascovsky, 2011).

In 2010 the European Federation of Neurological Societies (EFNS) published a guideline on the Molecular Diagnosis of Channelopathies, Epilepsies, Migraine, Stroke and Dementias, which recommends the following:

> If the clinical diagnosis is that of a frontotemporal dementia, genetic testing for mutations in PGRN and MAPT is clearly indicated and useful for genetic counseling in patients with autosomal dominant FTLD … regardless of the presence or severity of extrapyramidal features.

This recommendation is based on evidence from retrospective studies that evaluated a specific mutation in a previously confirmed and clinically diagnosed group of individuals. Based on a review of case reports, the group also recommended that genetic testing be considered in familial and sporadic cases, although mutations are found only in less than 5% (Burgunder, 2010).

The American Psychiatric Association practice guideline for the treatment of patients with Alzheimer's disease and other dementias states that "individuals with a clinical picture suggestive of frontotemporal dementia and a family history suggesting autosomal dominant inheritance can be tested for certain mutations" (APA, 2007).

Genetic Mutations
Unlike Alzheimer's disease, FTD has a strong genetic basis and family history of FTD has been estimated to occur in 40-50% of cases. FTD is a genetically complex (multifactorial) disorder which is inherited in an autosomal dominant fashion with high penetrance in the majority of cases. Three causative genes account for more than 80% of cases of FTD in families with a strong autosomal dominant family history: (microtubule-associated-protein-tau (MAPT), progranulin (PGRN), and chromosome 9 open reading frame 72 (C9orf72). Other possible causes of FTD which are being investigated include, but are not necessarily limited to, the valosin-containing protein (VCP), TAR DNA binding protein (TDP-43), charged multivesicular body protein 2B (CHMP2B), fused in sarcoma protein (FUS), presenilin-1 (PSEN1) and leucine-rich repeat kinase (Lrrk2).

Diagnostic genetic testing is being explored as a means to identify symptomatic individuals with probable FTD as well as predictive genetic testing to identify FTD in asymptomatic individuals at risk for FTD. Preconceptional,

preimplantation and prenatal genetic testing are being investigated as a means to determine carrier status and/or guide reproductive decisions when an FTD gene mutation has been confirmed in a parent or other close relative. Requests for prenatal diagnosis of (typically) adult-onset diseases are uncommon (Cohn-Hokke, 2012; Goldman, 2012; Lindquist, 2009; Loy, 2014).

Genetic testing for FTD mutations is available from some CLIA approved laboratories. Specific testing methods vary depending on the laboratory used and may include, but are not necessarily limited to deletion/duplication analysis, sequence analysis of select exons and/or sequence analysis of the entire coding region.

MAPT Gene Mutation (Frontotemporal dementia with parkinsonism-17 [FTDP-17])
Familial FTD with parkinsonism (FTDP-17) has been associated with mutations in the MAPT gene on chromosome 17 encoding the protein tau. Mutations in the MAPT gene disrupt the normal structure and function of tau which leads to the development of tauopathies. According to a review by Benussi and colleagues, the frequency of MAPT gene mutations is extremely variable, ranging from 0–3% in sporadic cases to 5–20% in familial FTD. The clinical sensitivity of MAPT mutations in individuals with FTD and a positive family history for dementia ranges between 13% and 30%. The analytic sensitivity of genetic testing for MAPT mutations is 99%. MAPT, encoding the tau protein, is the only gene in which mutation is known to cause hereditary tauopathies (Benussi, 2015).

MAPT genetic mutations are inherited in an autosomal dominant manner with most cases reporting complete penetrance. MAPT mutation carrier phenotypes typically demonstrate behavioral changes, dementia and parkinsonism. Heterogeneous clinical phenotypes have been detected in individuals and families bearing the same MAPT gene mutation. The onset of disease is also extremely variable, ranging from 45 to 65 years of age, with a mean age of onset of 55 years. The average duration of the disease is approximately 7 years. The most common subtype associated with MAPT mutations is bvFTD which may manifest as behavioral inhibition, impaired social behavior, and obsessive–compulsive disorder. While MAPT gene mutations are most frequently found in individuals with typical FTDP-17, the identification of MAPT gene mutations in individuals with other conditions such as progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), mild late-onset parkinsonism and dementia with epilepsy suggests that FTDP-17 is part of a larger spectrum of tauopathies. Therefore, there is the possibility that some individuals who test positive for an MAPT mutation will have a disorder other than FTD-17 (Benussi, 2015; Kertesz, 2003).

Diagnostic, predictive, prenatal and/or preimplantation genetic testing for the MAPT gene mutation is available through some CLIA certified laboratories. The specific services offered and type of method used to carry out the test may vary from one laboratory to another.

GRN (GRN-related frontotemporal dementia)
The features of GRN-related FTD result from the gradual loss of neurons in regions near the frontal and temporal lobes of the brain. The frontal lobes are involved in problem-solving, reasoning, planning, and judgment, while the temporal lobes assist with processing hearing, speech, memory, and emotion. The death of neurons in these areas may result in the loss of critical brain functions. However, it is unclear why individuals with GRN-related FTD

experience the loss of neurons in the frontal and temporal lobes more often than other regions of the brain (Hsiung, 2013).

GRN-related frontotemporal dementia results from mutations in the GRN gene which provides instructions for making the protein granulin (also known as progranulin). Granulin, a glycoprotein active in many different tissues in the body, helps regulate the growth, division, and survival of cells. Most mutations in GRN are null mutations that lead to reduced expression of progranulin in cerebrospinal fluid, plasma, and serum in symptomatic and asymptomatic GRN mutation carriers. As a result, mutation carriers can be identified by measuring serum progranulin concentrations. While it is unclear how a shortage of this protein leads to the features of GRN-related FTD, studies have shown that the disorder is characterized by the buildup of the TAR DNA-binding protein (TDP-43) in certain brain cells. Researchers are investigating how mutations in the GRN gene, and the resulting loss of granulin, are related to a buildup of TDP-43 in the brain. Researchers have also found that some individuals with mutations in the GRN gene have ubiquitin-based histopathological abnormalities (Baker, 2006; Benussi, 2015; Cruts, 2006; Hsiung, 2013, Loy, 2014).

Mutations in GRN are the only known cause of FTD-GRN. The GRN gene is inherited in an autosomal dominant manner with reduced penetrance. The clinical presentation of individuals with GRN mutations is extremely variable; phenotypic heterogeneity may be demonstrated in the same family carrying an identical pathogenic mutation. The age of symptom onset ranges from 35 to 89 years, with an average of 65 years. Penetrance is 50% by the age of 60 and almost completely penetrant (90%) by age 70. Within families, there may be substantial variation in the age of onset, varying by as much as 20 years between consecutive generations. The most commonly reported initial clinical diagnosis in individuals carrying GRN mutations is bvFTD, with apathy and social withdrawal (Benussi, 2015).

With regards to the clinical validity of genetic testing, GRN mutations are present in approximately 5-10% percent of all FTD and in 17-23% of familial FTD cases. The analytical sensitivity has been reported at 99% when using polymerase chain reaction followed by sequencing all 12 exons (coding and splicing regions) of the GRN gene. Approximately 95% of individuals diagnosed with FTD-GRN have an affected parent. The proportion of cases caused by de novo mutations is unknown but has been estimated at 5% or less. Each offspring of an individual with FTD-GRN has a 50% chance of inheriting the gene mutation ((Benussi, 2015; Gass, 2006; Pickering-Brown, 2008).

The clinical manifestations of FTD significantly overlap with those of other inherited conditions including familial Parkinson disease and Alzheimer disease. This clinical overlap makes it difficult to determine which family has a genetic mutation associated with FTD by clinical presentation alone.

Historically, the diagnosis of FTD-GRN is based on clinical features, brain imaging studies and characteristic neuropathologic findings of TDP-43 inclusions. More recently, genetic testing has been proposed as a means to assist with the diagnosis of FTD-GRN. As mentioned above, several diagnostic criteria for FTD have been published (Hsiung, 2012).

Genetic testing for FTD-GRN mutations is offered via CLIA certified laboratories. At the time of this review, several laboratories were identified which offer diagnostic and mutation confirmation testing for individuals believed to have the FTD-GRN mutation. Laboratories offering genetic testing as a screening tool and predictive genetic testing in asymptomatic individuals were also identified. No laboratories that offer prenatal or preimplantation genetic testing for FTD-GRN mutations were identified. The genetic testing method identified included, but is not necessarily limited to sequencing analysis of the entire coding region. Since the GRN mutations impose a null allele and are thought to lead to an insufficiency of GRN protein, it has been speculated that in the future the results of genetic testing for GRN mutations could be used to identify which individuals with FTD may benefit from GRN protein replacement therapy.

Pottier and colleagues (2018) conducted a study to identify potential genetic modifiers of disease onset and disease risk in GRN mutation carriers. The study was carried out in three stages: a discovery stage, a replication stage, and a meta-analysis of the discovery and replication data. The statistical analyses in the discovery stage consisted of 382 unrelated symptomatic GRN mutation carriers and 1146 controls free of neurodegenerative diseases. The replication stage was comprised of 210 participants (67 symptomatic GRN mutation carriers and 143 individuals with FTLD without GRN mutations pathologically confirmed as FTLD-TDP type A) and 1798 controls free of neurodegenerative diseases. No genome-wide significant association with age at onset was identified in the discovery, meta-analysis or replication stages. However, in the case-control analysis, the researchers replicated the previously reported TMEM106B association (rs1990622 meta-analysis odds ratio [OR] 0.54, 95% CI, 0.46–0.63; $p=3.54 \times 10^{-16}$), and identified a new genome-wide significant locus at GFRA2 on chromosome 8p21.3 (rs36196656) that is associated with disease risk. Expression analyses demonstrated the risk-associated allele at rs36196656 decreased GFRA2 mRNA concentrations in cerebellar tissue (p=0.04). No effect of rs36196656 on plasma and CSF progranulin concentrations was identified by ELISA; however, co-immunoprecipitation experiments in HEK293T cells did allude to a direct binding of progranulin and GFRA2. The authors concluded that TMEM106B-related and GFRA2-related pathways might be used as future targets to treat FTLD, however, additional research is needed to understand the biological interaction between progranulin and these potential disease modifiers.

C9orf72 Gene Mutation (FTD-ALS or ALS-FTD)
Researchers have identified a genetic mutation in C9orf72 as one of the genetic causes of familial amyotrophic lateral sclerosis (ALS), familial FTD and ALS-FTD. The C9orf72 gene mutation belongs to a class of mutations called repeat expansion mutations. The chromosome 9-linked ALS-FTD mutation is a hexanucleotide repeat expansion in which a string of nucleotides coded GGGGCC is repeated many more times in individuals with ALS, FTD or ALS-FTD than in individuals unaffected by either or both of the two disorders. The maximum number of hexanucleotide repeats in individuals who are not affected by ALS appears to be approximately 20, with an average of around 3; the exact numbers of repeats in individuals with ALS, FTD or ALS-FTD has not yet been determined. While it appears that some cases of familial FTD and familial ALS are caused by the C9orf72 expansion, there are familial cases in which no expansion is found. In these cases, the lack of a mutation in other known FTD and ALS genes suggests that there are still other unidentified causal genes implicated in FTD and/or ALS (Fong, 2012).

Majounie and colleagues (2012) reported the frequency of a hexanucleotide repeat expansion in C9orf72 was 59 (6%) of 981 white Europeans with sporadic FTD and 99 (24%) of 400 white Europeans with familial FTD. The authors also reported that the hexanucleotide repeat expansion in C9orf72 in cases of ALS and FTD was non-penetrant in individuals younger than 35 years, 50% penetrant by age 58 but almost fully penetrant by age 80.

Cintra and colleagues (2018) investigated the presence of the G4C2 repeat expansion in C9orf72 amongst a group of individuals with MND and/or behavioral or cognitive impairment from three different geographic regions of Brazil. Of the 471 individuals from 463 unrelated families included in the study; 404 had ALS/MND, 67 FTD, and 63 were healthy controls. Although the C9orf72 mutation was identified in 5% of individuals with pure ALS/MND (11.8% of familial and 3.6% of sporadic cases) and in 7.1% of individuals with pure familial FTD, the highest frequencies of the C9orf72 mutation were present in the ALS-FTD group (50% of familial and 17.6% of sporadic cases). Among G4C2 repeat mutation carriers, 68.8% of the participants who developed dementia symptoms were females. This frequency was significantly higher than the percentage attained for men with the C9orf72 expansion who had this phenotype (p=0.047). No abnormal repeat expansion was identified in the control groups.

Perrone and colleagues (2018) conducted a pilot study to determine if gene panel testing could identify causal genes linked to neurodegenerative brain diseases in individuals suspected of having dementia, but who had not been assigned a precise clinical diagnosis. The authors used the DNA samples of 211unrelated individuals from a larger prospective study of dementia (Engelborghs, 2003), who had symptomatology of dementia at early age, but who had been excluded from research due to an unclear clinical diagnosis of a specific dementia subtype. In the cases that lacked age at onset data of the participants, the researchers used a cutoff age at inclusion of 70 years. In the study group, mean age of onset or inclusion age was 59.9 ± 8.2 years (range 33-70), and 27.4% (58/211) had at least 1 affected first-degree relative. In order to test for the genetic mutations, the researchers used a panel of 16 major genes linked to Alzheimer's disease, frontotemporal dementia, amyotrophic lateral sclerosis, Parkinson's disease, and prion diseases. Additionally, participants were tested for the presence of a pathogenic C9orf72 repeat expansion. Overall, the researchers identified 13 different rare variants in 15 subjects, including a carrier of variants in 2 different genes. A total of six individuals (2.84%), carried a mutation in a Mendelian causal gene, that is, APP, MAPT, SOD1, TBK1, and C9orf72. In the other 7 subjects, 7 variants were of uncertain significance, including a frameshift mutation in PSEN2, p.G359Lfs*74 in 2 individuals sharing a common haplotype, and in LRRK2, p.L2063fs*. Gene expression studies demonstrated reduced PSEN2 and a near complete loss of LRRK2 in lymphoblast cells or brain material of these individuals. The authors concluded that the study results underscore the relevance of genetic testing to identify causal genes in individuals who have symptoms of neurodegenerative dementia but lack a clear clinical diagnosis.

Studies investigating the clinical phenotype of C9orf72 mutation carriers are ongoing. The most common clinical presentation is bvFTD, which is frequently accompanied by motor neuron involvement. As many as 40% of expansion carriers with bvFTD demonstrated upper or lower motor neuron signs. While small subsets of individuals with nonfluent variant primary progressive aphasia (PPA) carry the expansion, semantic variant PPA, corticobasal syndrome, and progressive supranuclear palsy have not been associated with C9orf72 expansions. An interesting feature of the C9orf72 expansion is its association with delusions and hallucinations (Boeve, 2012; Fong, 2012).

The clinical phenotype of individuals with C9orf72 mutations is highly heterogeneous and variable even within families affected by the same mutation. The most common clinical presentations are FTD, ALS or a combination of both FTD and ALS. Approximately 50% of individuals with ALS have some degree of cognitive or behavioral impairment, while only approximately 15-25% of individuals meet the criteria for a clinical diagnosis of ALS-FTD. Both ALS and FTD are diseases without cures. ALS is characterized by motor neuron degeneration that eventually leads to respiratory failure with a median survival of 3 years after onset. While different mutations of various genes have been associated with different phenotypes of FTD, C9orf72 specifically has been linked to behavioral variant FTD. Pathological changes in FTD caused by the C9orf72 mutation may also include TDP-43 inclusion and ubiquitin-binding protein 62 (Benussi, 2015; Boeve, 2012; Friedland, 2012).

A clinical diagnosis of ALS is typically made by excluding other causes of progressive loss of upper and lower motor neuron function. ALS phenotypes include progressive muscular atrophy, primary lateral sclerosis and progressive bulbar palsy, each involving different bulbar or spinal segments at onset but with variable progression to widespread disease. Among individuals with a C9orf72 expansion, magnetic resonance imaging (MRI) has revealed bilateral, symmetrical frontal atrophy, with grey matter loss in orbitofrontal, medial, and dorsolateral regions, as well as atrophy in the anterior temporal region. In contrast to other bvFTD-associated gene mutations, cerebellar and thalamic atrophy appear to be uniquely associated with the expansion (Fong, 2012; Sha, 2012; Whitwell, 2012).

Genetic testing for C9orf72 mutations is offered via CLIA certified laboratories. At the time of this review, one laboratory was identified which offered genetic testing for C9orf72 mutations using polymerase chain reaction (PCR) as a means to detect repeat expansions in the CC9orf72 gene. One of the barriers to its widespread clinical utility is the unknown minimum number of repeats that confer a phenotype. At the time of this review no laboratories offering prenatal and preimplantation diagnostic testing were identified (Fong, 2012).

Summary
The definitive diagnosis of FTD is made upon autopsy. To further confirm the clinical validity of genetic testing for FTD, additional studies are needed in which individuals diagnosed with FTD by genetic testing are followed to death and autopsy is performed to provide clinicopathologic verification of the diagnosis. The clinical utility of diagnostic testing for genetic mutations related to FTD is uncertain. There is no clear difference in the management of an individual with suspected or genetically confirmed FTD. No studies were found that demonstrated that the results of genetic testing for a mutation in the MAPT, GRN or C9orf72 gene altered treatment or improved health outcomes of individuals suspected of having FTD. While genetic testing for FTD may predict the likelihood that an individual will develop the disease, it cannot predict when symptoms will appear or how fast the disease will progress. Also, while preconception and preimplantation genetic testing for FTD is available via some clinical laboratories, there are limited data which explore the impact of such testing on reproductive decisions.

Background/Overview

Frontotemporal degeneration (FTD) is one of the more common forms of dementia affecting individuals under the age of 65 years. Symptoms of FTD are caused by the gradual and continual loss of neurons in the frontal and temporal regions of the brain although, in some cases, other regions can be affected.

The frontal lobes of the brain are involved in several functions such as personality, behavior, planning, reasoning, judgment, motor function and impulse control. The temporal lobes of the brain are involved in functions such as language, speech and memory.

The clinical presentation of FTD varies from one individual to the next but may include changes in personality, loss of empathy, poor judgment and inappropriate social behavior. Changes in language may manifest as difficulty with word meaning. The affected individual may also experience alterations in movement such as tremors, difficulty walking or maintaining balance. An individual with FTD will experience symptoms worsening with the passage of time.

At the current time, there is no cure for FTD. Treatment may include medications which help to manage the symptoms of the disease.

Definitions

Akinesia: Slowing or absence of movements.

Apraxia: Loss of the ability to carry out learned purposeful movements.

Bradykinesia: Unusually slow movement.

Deletion/Duplication Analysis: Laboratory testing that identifies the absence of a segment of DNA (deletion) and/or the presence of an extra segment of DNA (duplication).

First-degree relative: Any relative who is a parent, sibling, or offspring to another.

Frontotemporal lobar degeneration (FTLD): A larger group of disorders which includes FTD as a subgroup.

Heterogenous: Made up of similar parts.

Myoclonus: Involuntary muscle spasms.

Nucleotides: The building blocks (or bases) of DNA.

Preimplantation genetic diagnosis (PGD): Refers to genetic testing of an early embryo resulting from in vitro fertilization (IVF). The testing is performed before implantation. PGD has been recently used as an alternative to

prenatal testing with amniocentesis or CVS techniques for detecting single gene disorders in embryos that have been identified as being at high risk for inheriting the gene disorder.

Progranulin: A glycoprotein with a variety of cellular regulatory functions.

Repeat expansion: A repeat is a string of nucleotides that occurs sequentially multiple times in a given stretch of DNA. A repeat expansion arises when an error causes the number of repeats to increase.

Sequence Analysis: The process by which the nucleotide sequence for a particular gene is determined for a segment of DNA.

Tau: A microtubule binding protein involved in the transport of cellular components. Mutations in MAPT can either disrupt tau protein structure or alter the availability of different tau isoforms.

Tauopathies: A group of diseases characterized by an abnormal buildup of tau in the brain.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement document. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Investigational and Not Medically Necessary:

CPT

81406	Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia) [when specified as the following]: • *GRN (granulin)* (eg, frontotemporal dementia), full gene sequence • *MAPT (microtubule-associated protein tau)* (eg, frontotemporal dementia), full gene sequence
81479	Unlisted molecular pathology procedure [when specified as C9orf72 PCR Fragment Analysis]

ICD-10 Diagnosis

F02.80	Dementia in other diseases classified elsewhere without behavioral disturbance [when specified as FTD]
F02.81	Dementia in other diseases classified elsewhere with behavioral disturbance [when specified as FTD]
G31.01	Pick's disease

G31.09	Other frontotemporal dementia

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The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Reviewed	11/05/2020	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated Rationale, References and Websites sections.
Reviewed	11/07/2019	MPTAC review. Updated review date, Websites and History sections.
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New	08/14/2014	MPTAC review.
New	08/08/2014	Behavioral Health Subcommittee review. Initial document development.