Aetna considers putaminal magnetic resonance spectroscopy measurements of myo-inositol and N-acetylaspartate for the diagnosis of Huntington's disease experimental and investigational because the clinical value of this approach has not been established.

Aetna considers the use of sarco-endoplasmic reticulum-associated ATP2A2 calcium pump (SERCA2) and vascular endothelial growth factor (VEGF) mRNA as molecular biomarkers for monitoring onset and/or progression of Huntington's disease experimental and investigational because of insufficient evidence.

Aetna considers measurement of iron accumulation in the basal ganglia as a biomarker for Huntington's disease experimental and investigational because of insufficient evidence.

Aetna considers the following interventions (not an all-inclusive list) for the treatment of Huntington's disease experimental and investigational because their effectiveness for this indication has not been established:
Bupropion
Coenzyme Q10
Cysteamine
Deep brain stimulation
Donepezil Electro-convulsive therapy Ethyl
Eicosapentaenoic acid Fetal
striatal transplantation
Gene silencing (e.g., through RNA interference)
Latrepirdine
Minocycline
Music therapy
Neurotrophic factors (e.g., brain-derived neurotrophic factor, ciliary neurotrophic factor, glial cell line-derived neurotrophic factor)
Pallidotomy (for the treatment of dystonia associated with Huntington’s disease)
Pridopidine
Stem Cell Transplantation (e.g., fetal stem cell transplantation, mesenchymal stem cell transplantation, and neural stem cell transplantation)
Transcranial direct current stimulation
Transcranial magnetic stimulation
Triheptanoin

See also **CPB 0307 - Parkinson's Disease.**

**Background**

Huntington's disease (HD) is a progressive, fatal, autosomal dominant neuro-degenerative disease caused by increased CAG repeats in the huntington gene. It is characterized by chorea and imbalance as well as deterioration in cognitive and neuropsychiatric function. Primary pathological changes are found in the caudate-putamen (striatum), where gabaaminergic neurons undergo degenerative changes. There is also evidence that HD is a multi-system degeneration. A recent study reported that cortical degeneration is present in early stages of HD and may explain at least some of the clinical symptoms (Rosas et al, 2002).
Deep Brain Stimulation:

Gonzalez et al (2014) noted that experience of globus pallidus internus (GPI) deep brain stimulation (DBS) in the treatment of HD has been limited to a small number of case reports. These researchers analyzed long-term motor outcome of a cohort of HD patients treated with GPI DBS. A total of 7 patients with pharmacologically resistant chorea and functional impairment were included in a prospective open-label study from 2008 to 2011. The main outcome measure was the motor section of the Unified Huntington’s Disease Rating Scale (UHDRS). The primary end-point was reduction of chorea. Patients underwent magnetic resonance imaging (MRI)-guided bilateral GPI implantation. The median duration of follow-up was 3 years. A significant reduction of chorea was observed in all patients, with sustained therapeutic effect; the mean improvement on the chorea subscore was 58.34 % at the 12-month follow-up visit (p = 0.018) and 59.8 % at the 3-year visit (p = 0.040). Bradykinesia and dystonia showed a non-significant trend toward progressive worsening related to disease evolution and partly to DBS. The frequency of stimulation was 130 Hz for all patients. Deep brain stimulation-induced bradykinesia was managed by pulse-width reduction or bipolar settings. Levodopa mildly improved bradykinesia in 4 patients. Regular off-stimulation tests confirmed a persistent therapeutic effect of DBS on chorea. The authors concluded that GPI DBS may provide sustained chorea improvement in selected HD patients with pharmacologically resistant chorea, with transient benefit in physical aspects of quality of life before progression of behavioral and cognitive disorders. Moreover, DBS therapy did not improve dystonia or bradykinesia. They stated that further studies including quality of life (QoL) measures are needed to evaluate the impact of DBS in the long-term outcome of HD.

Gruber et al (2014) stated that recent case reports suggested beneficial effect of GPI-DBS in selected patients suffering from HD with marked disabling chorea. These investigators present a 41-year old man with genetically confirmed HD following quadruple GPI- and sub-thalamic nucleus (STN)-DBS. Motor function was assessed by Abnormal Involuntary Movement Scale (AIMS) and by UHDRS pre-surgery and post-surgery for up to 4 years. Furthermore, cognitive, neuropsychiatric state and QoL including life satisfaction (QLS) were annually evaluated. Chorea assessed
by AIMS and UHDRS subscores improved by 52 and 55 %, 45 and 60 %, 35 and 45 % and 55 to 66 % at 1 to 4 years, respectively, compared to pre-surgical state following GPI-STN-DBS. During these time periods bradykinesia did not increase following separate STN- and combined GPI-STN-DBS compared to pre-surgical state. Mood, QoL and QLS were ameliorated. However, dysexecutive symptoms increased at 4 years post-surgery. The present case report suggested that bilateral GPI- and STN-DBS may represent a new treatment avenue in selected HD patients. Clinically, GPI-DBS attenuated chorea and was associated with a larger effect-adverse effect window compared to STN-DBS. However, GPI-DBS-induced bradykinesia may emerge as one main limitation of GPI-DBS in HD. The authors concluded that quadruple GPI-STN-DBS may be indicated, if separate GPI-DBS does not result in sufficient control of motor symptoms. Moreover, they stated that future controlled studies are needed to confirm if the present anecdotal observation of additive beneficial effects of GPI- and STN-DBS in a HD patient with severe generalized chorea and relatively intact cognitive and affective functions indeed represents a new therapeutic option.

Donepezil:

Mestre and Ferreira (2012) noted that HD is a neuro-degenerative disease with diverse symptoms for which there is no curative or disease-modifying treatment available. Currently, tetrabenazine is the only drug approved for HD by a regulatory agency, and only for the treatment of chorea. These researchers presented updated results from recent clinical trials and ongoing clinical research efforts to find safe and effective treatments for HD motor, and neuropsychiatric and cognitive symptoms. They used a systematic review approach that included data from well-designed randomized controlled trials. The authors concluded that there is weak evidence to support most of the treatment decisions in HD and thus clinicians may be guided only by expert opinion-based therapeutic recommendations.

On behalf of the American Academy of Neurology, Armstrong and Miyasaki (2013) developed an evidence-based guideline assessing pharmacologic options for treating HD chorea. These
investigators evaluated available evidence from a structured literature review performed through February 2011. If HD chorea requires treatment, clinicians should prescribe tetrabenazine (up to 100 mg/day), amantadine (300 to 400 mg/day), or riluzole (200 mg/day) (Level B) for varying degrees of expected benefit. Occurrence of adverse events should be discussed and monitored, particularly depression/suicidality and parkinsonism with tetrabenazine and elevated liver enzymes with riluzole. Clinicians may also prescribe nabilone for modest decreases (1- to less than 2-point changes on the UHDRS chorea score) in HD chorea (Level C), but information is insufficient to recommend long-term use, particularly given abuse potential concerns (Level U). Clinicians should not prescribe riluzole 100 mg/day for moderate (2- to less than 3-point UHDRS chorea change) short-term benefits (Level B) or for any long-term (3-year) HD antichoreic goals (Level B). Clinicians may choose not to prescribe ethyl-EPA (Level B), minocycline (Level B), or creatine (Level C) for very important improvements (greater than 3-point UHDRS chorea change) in HD chorea. Clinicians may choose not to prescribe coenzyme Q10 (Level B) for moderate improvements in HD chorea. Data are insufficient to make recommendations regarding the use of neuroleptics or donepezil for HD chorea treatment (Level U).

Fetal Striatal Transplantation:

Fetal neural transplantation has been demonstrated to be a feasible treatment for patients with Parkinson’s disease (PD). Embryonic mesencephalic tissue containing dopaminergic cells is implanted into the patient’s striatum to modify motor disability of patients with advanced PD. However, the effectiveness of fetal neural transplantation for the treatment of PD has yet to be established.

Recently, fetal neural transplantation has also been performed as a potential treatment for HD. While it is clear that the techniques of neural transplantation is feasible for various neurodegenerative diseases, significant problems remain in the availability of suitable donor tissues and defining the optimal conditions for reliable survival of the implanted cells. There is
insufficient data on the "progress" of HD patients following fetal striatal transplantation. Furthermore, a recent study on the use of bilateral fetal striatal transplantation for the treatment of HD found that patients with moderately advanced HD are at risk for subdural hemorrhages following transplantation surgery (Hauser et al, 2002). Thus, the safety and effectiveness of fetal striatal transplantation for the treatment of HD has yet to be established.

In an article on the safety and tolerability of intrastriatal neural allografts in patients with HD, Bachoud-Levi and colleagues (2000) called for caution regarding the involvement of HD patients in experimental surgical protocols. In an editorial on fetal striatal transplantation for the treatment of HD published in the Neurology, Greenamyer and Shoulson (2002) stated that the benefits (of this procedure) -- even the theoretical benefits -- are unclear. Rosser and Dunnett (2003) noted that a small number of studies have demonstrated the feasibility and safety of transplantation in HD, but it will require several more years before the effectiveness of the procedure can be confidently established.

In a long-term follow-up study, Bachoud-Levi and colleagues (2006) stated that although they have shown in 3 out of 5 patients with HD that motor and cognitive improvements 2 years after intra-cerebral fetal neural grafts are correlated with recovery of brain metabolic activity in grafted striatal areas and connected regions of the cerebral cortex, neural grafts are not known to have protective effects on the host brain per se. These investigators undertook long-term follow-up of previously reported patients with the disease to ascertain the nature and extent of any secondary decline after grafting. Five patients with HD from the authors’ pilot study were assessed annually with the UHDRS, neuropsychological tests, and MRI, for up to 6 years after neural grafting. Resting cerebral activity was recorded at 2 and 6 years. Clinical improvement reached a plateau after 2 years and then faded off variably 4 to 6 years following surgery. Dystonia deteriorated consistently, whereas chorea did not. Cognitive performance remained stable on non-timed tests, whereas progression of motor disability was shown by deterioration on timed tests. Hypo-metabolism also affected the brain
heterogeneously, sparing the benefits in the frontal cortex and at the precise location of the grafts, but showing a progressive deterioration in other areas. Two patients who had no benefit from grafting at 2 years continued to decline in the same way as non-grafted patients. These researchers noted that neuronal transplantation in HD provides a period of several years of improvement and stability, but not a permanent cure for the disease. Improvement of the surgical procedure as well as in patient selection could improve the therapeutic value, but neuroprotective treatment seems to be unavoidable in the disease.

Keene et al (2007) reported the pathological findings in 2 patients with HD who died 74 and 79 months after transplantation. Neostriatum from both patients showed typical neuropathological changes of advanced HD. Surviving grafts were identified in both patients (6/6 sites and 7/8 sites, respectively) as well-demarcated nests within host neostriatum with associated needle tracts. Grafted neurons adopted either dominant calbindin/parvalbumin or calretinin immunoreactivity (IR). Few neurofilament, MAP-2, DARPP-32, tyrosine hydroxylase, or calbindin IR processes traversed the host parenchyma-graft interface despite minimal junctional gliosis. Immunohistochemistry for CD68 showed microgliosis that was more pronounced in host striatum than graft. Scattered CD45 and CD3 IR cells were present within grafts and host parenchyma. No ubiquitin IR neuronal intra-nuclear inclusions were identified in graft neurons, although these were prevalent in host cells. The authors concluded that these 2 autopsies confirm previous findings of neuronal differentiation and survival of transplanted fetal tissue from the ganglionic eminence and also demonstrate viability of neurons from fetal transplants in human neostriatum for more than 6 years. Despite prolonged survival, these grafts had poor integration with host striatum that is likely responsible for lack of clear clinical improvement in these patients.

In an editorial that accompanied the article by Keen et al, Frank and Biglan (2007) stated that "more work is needed in the design of trials, clinical and pathologic follow-up, and methods of
transplantation of various cells. There are cell-based therapies that are commercially available, mostly outside the United States. Rather than referring patients to centers that will infuse or implant cells, these procedures should only be done in the setting of a rigorous research trial using established criteria”.

Reuter et al (2008) reported the findings of 2 patients with moderate HD who received bilateral fetal striatal allografts. One patient demonstrated, for the first time, increased striatal D2 receptor binding, evident with 11C-raclopride positron emission tomography, and prolonged clinical improvement over 5 years, suggesting long-term survival and efficacy of the graft. The other patient did not improve clinically or radiologically. The authors stated that these results indicated that striatal transplantation in HD may be beneficial but further studies are needed to confirm this.

Gallina and colleagues (2010) reported the findings of 4 HD patients who underwent bilateral transplantation with human fetal striatal tissues (9 to 12 week gestation). Small blocks of whole ganglionic eminencies were processed to obtain cell suspension and then stereotactically grafted in the caudate head and in the putamen. Follow-up period ranged between 18 and 34 months (mean of 24.7 months). Surgery was uneventful. Starting from the 4th month after grafting, neo-generation of metabolically active tissue with striatal-like MRI features was observed in 6 out of 8 grafts. The increase in D2 receptor binding suggested striatal differentiation of the neo-generated tissue in 3 patients. New tissue, connecting the developing grafts with the frontal cortex and, in 1 case, with the ventral striatum, was also observed. The new tissue growth halted after the 9th month post-transplantation. All patients showed stabilization or improvement in some neurological indices. No clinical and imaging signs, suggestive of graft uncontrolled growth, were seen. This study provided the first evidence in humans that neuroblasts of a striatal primordium can develop and move into the brain following neurotransplantation. Primordium development resulted in the building of a new structure with the same imaging features as the corresponding mature structure, combined with short- and long-distance targeted migration of
neuroblasts. The results of this study support both the reconstructive potential of fetal tissue and the remarkably retained plasticity of adult brain. The authors stated that further studies are needed to evaluate the clinical effectiveness of human fetal striatal transplantation for the treatment of HD.

**Latrepirdine:**

In a multi-center, double-blind, randomized, placebo-controlled trial, Kieburtz K et al (2010) evaluated the safety and tolerability of latrepirdine in HD and explored its effects on cognition, behavior, and motor symptoms. A total of 91 patients with mild to moderate HD enrolled at 17 United States and United Kingdom centers from July 18, 2007, through July 16, 2008. Subjects received latrepirdine, 20 mg thrice-daily (n = 46), or matching placebo (n = 45) for a 90-day treatment period. The primary outcome variable was tolerability, defined as the ability to complete the study at the assigned drug dosage. Secondary outcome variables included score changes from baseline to day 90 on the UHDRS, the Mini-Mental State Examination (MMSE), and the Alzheimer Disease Assessment Scale-cognitive subscale (ADAS-cog). Latrepirdine was well-tolerated (87 % of the patients given latrepirdine completed the study versus 82 % in the placebo group), and adverse event rates were comparable in the 2 groups (70 % in the latrepirdine group and 80 % in the placebo group). Treatment with latrepirdine resulted in improved mean MMSE scores compared with stable performance in the placebo group (treatment effect, 0.97 points; 95 % confidence interval [CI]: 0.10 to 1.85; p = 0.03). No significant treatment effects were seen on the UHDRS or the ADAS-cog. The authors concluded that short-term administration of latrepirdine is well-tolerated in patients with HD and may have a beneficial effect on cognition. They stated that further investigation of latrepirdine is warranted in this population with HD.

**Magnetic Resonance Spectroscopy:**

Sturrock et al (2010) evaluated in-vivo brain metabolite differences in control subjects, individuals with pre-manifest HD (pre-HD), and individuals with early HD using ¹H magnetic
resonance spectroscopy (MRS) and assessed their relationship with motor performance. A total of 85 subjects (30 controls, 25 pre-HD, and 30 early HD) were recruited as part of the TRACK-HD study; 84 were scanned at 3T with single-voxel spectroscopy in the left putamen. Disease burden score was greater than 220 among pre-HD individuals. Subjects underwent TRACK-HD motor assessment including UHDRS motor scoring and a novel quantitative motor battery. Statistical analyses included linear regression and 1-way analysis of variance. Total N-acetylaspartate (tNAA), a neuronal integrity marker, was lower in early HD (approximately 15%) versus controls (p < 0.001).

N-acetylaspartate (NAA), a constituent of tNAA, was lower in pre-HD (approximately 8%) and early HD (approximately 17%) versus controls (p < 0.05). The glial cell marker, myo-inositol (mI), was 50% higher in early HD versus pre-HD (p < 0.01). In early HD, mI correlated with UHDRS motor score ($R^2 = 0.23$, p < 0.05). Across pre-HD and early HD, tNAA correlated with performance on a tongue pressure task ($R^2 = 0.30$, p < 0.0001) and with disease burden score ($R^2 = 0.17$, p < 0.005). The authors demonstrated that lower putaminal tNAA in early HD compared to controls in a cross-section of subjects. A novel biomarker role for mI in early HD was also identified. These findings resolve disagreement in the literature about the role of MRS as an HD biomarker. The authors concluded that putaminal MRS measurements of NAA and mI are promising potential biomarkers of HD onset and progression.

The American College of Radiology (ACR)’s Appropriateness Criteria on “Dementia and movement disorders” (Wippold et al, 2014) rendered a “3” rating regarding the use of MR spectroscopy of the head without contrast for individuals suspected of HD (Rating scale of 1, 2, or 3 denotes “usually not appropriate”).

Mesenchymal Stem Cells:

Clelland et al (2008) stated that a major impetus for research into the treatment of HD has centered on cell therapy strategies to protect vulnerable neuronal cell populations or to replace dysfunctional or dying cells. The work underlying 3 approaches to HD cell therapy includes (i) the potential for self-repair through
the manipulation of endogenous stem cells and/or neurogenesis, (ii) the use of fetal or stem cell transplantation as a cell replacement strategy, and (iii) the administration of neurotrophic factors to protect susceptible neuronal populations. These approaches have shown some promising results in animal models of HD. Although striatal transplantation of fetal-derived cells has undergone clinical assessment since the 1990s, many cell therapy strategies have yet to be applied in the clinic environment. A more thorough understanding of the pathophysiology underlying HD as well as the response of both endogenous and exogenous cells to the degenerating brain will inform their merit as potential therapeutic agents and enhance the framework by which the success of such therapies are ascertained.

Sadan et al (2012) stated that excitotoxicity and reduced availability of neurotrophic factors (NTFs) likely play roles in HD pathogenesis. These researchers developed a protocol that induces adult human bone marrow derived mesenchymal stem cells (MSCs) into becoming NTF secreting cells (NTF(+) cells). Striatal transplantation of such cells represents a promising autologous therapeutic approach whereby NTFs are delivered to damaged areas. These investigators examined the effectiveness of NTF(+) cells using the quinolinic acid (QA) rat model for excitotoxicity. They showed that NTF(+) cells transplanted into rat brains after QA injection survive transplantation (19 % after 6 weeks), maintain their NTF secreting phenotype and significantly reduce striatal volume changes associated with QA lesions. Moreover, QA-injected rats treated with NTF(+) cells exhibit improved behavior; namely, perform 80 % fewer apomorphine-induced rotations than phosphate-buffered saline (PBS)-treated QA-injected rats. More importantly, these researchers found that MSCs derived from HD patients can be induced to become NTF(+) cells and exert efficacious effects similarly to NTF(+) cells derived from healthy donors. To the authors' knowledge, this is the first study to take adult bone marrow derived MSCs from patients with an inherited disease, transplant them into an animal model and evidence therapeutic benefit. Using MRI the authors demonstrated in-vivo that PBS-treated QA-injected striatae exhibit increasing T(2) values over time in lesioned regions, whereas T(2) values decrease in equivalent regions of
QA-injected rats treated with NTF(+) cells. The authors concluded that NTF cellular treatment could serve as a novel therapy for managing HD.

**Neurotrophic Factors:**

Furthermore, an UpToDate review on “Huntington disease: Management” (Suchowersky, 2014) states that “Neurotrophic factors -- Increasing the presence of neurotrophic factors (e.g., brain-derived neurotrophic factor [BDNF], ciliary neurotrophic factor [CNTF], glial cell line-derived neurotrophic factor [GDNF]) in the striatum is a possible approach to prolong the survival of native neurons in patients with HD. A number of studies have shown benefit in animal models, but clinical evidence is limited. A preliminary human study used encapsulated CNTF-releasing cells in the ventricle of patients over two years with no clear benefit. The technical difficulties were significant and remain an obstacle to this technology”. In this review, neurotrophic factors are listed among several investigational therapies (including DBS) for HD. The review states that “The utility of deep brain stimulation in HD is unknown. Data are limited to case studies, which suggest some benefit in chorea”.

**Pridopidine:**

In a randomized, double-blind, placebo-controlled, 4-week trial, Lundin et al (2010) evaluated the safety and effectiveness of the dopaminergic stabilizer pridopidine (ACR16) in patients with HD. Subjects received pridopidine (50 mg/day, n = 28) or placebo (n = 30). The primary outcome measure was the change from baseline in weighted cognitive score, assessed by cognitive tests (Symbol Digit Modalities, verbal fluency, and Stroop tests). Secondary outcome measures included changes in the UHDRS, Hospital Anxiety and Depression Scale, Leeds Sleep Evaluation Questionnaire, Reitan Trail-Making Test A, and Clinical Global Impression of Change. Safety assessments were also performed. There was no significant difference between pridopidine and placebo in the change from baseline of the weighted cognitive score. However, secondary measures such as affective symptoms showed trends toward improvement, and there was significant
improvement in voluntary motor symptoms compared with placebo (p < 0.05). Pridopidine was well-tolerated, with a safety profile similar to placebo. The author concluded that pridopidine shows promise as a treatment for some of the symptoms of HD. In this small-scale study, the most notable effect was improvement in voluntary motor symptoms. The authors stated that larger, longer-term trials are needed.

*Sarco-Endoplasmic Reticulum-Associated ATP2A2 Calcium Pump (SERCA2) and Vascular Endothelial Growth Factor (VEGF) mRNS as Molecular Biomarkers:*

Cesca et al (2015) stated that abnormalities of intracellular calcium homeostasis and signaling as well as the down-regulation of neurotrophic factors in several areas of the central nervous system and in peripheral tissues are hallmarks of HD. As there is no therapy for this hereditary, neurodegenerative fatal disease, further effort should be made to slow the progression of neurodegeneration in patients through the definition of early therapeutic interventions. For this purpose, molecular biomarker(s) for monitoring disease onset and/or progression and response to treatment need to be identified. In the attempt to contribute to the research of peripheral candidate biomarkers in HD, these researchers adopted a multiplex real-time PCR approach to analyze the mRNA level of targeted genes involved in the control of cellular calcium homeostasis and in neuroprotection. For this purpose these investigators recruited a total of 110 subjects possessing the HD mutation at different clinical stages of the disease and 54 sex- and age-matched controls. This study provided evidence of reduced transcript levels of sarco-endoplasmic reticulum-associated ATP2A2 calcium pump (SERCA2) and vascular endothelial growth factor (VEGF) in peripheral blood mononuclear cells (PBMCs) of manifest and pre-manifest HD subjects. The authors concluded that these findings provided a potentially new candidate molecular biomarker for monitoring the progression of this disease and contribute to understanding some early events that might have a role in triggering cellular dysfunctions in HD.

*Measurement of Iron Accumulation in the Basal Ganglia:*
Domínguez and colleagues (2016) measured iron accumulation in the basal ganglia in HD using quantitative susceptibility mapping (QSM), and ascertained its relevance in terms of clinical and disease severity. In this cross-sectional investigation, weighted imaging was undertaken on 31 pre-manifest HD, 32 symptomatic HD and 30 control participants as part of the observational IMAGE-HD study. Group differences in iron accumulation were ascertained with QSM. Associations between susceptibility values and disease severity were also investigated. Compared with controls, both pre-manifest and symptomatic HD groups showed significantly greater iron content in pallidum, putamen and caudate. Additionally, iron accumulation in both putamen and caudate was significantly associated with disease severity. The authors concluded that these findings provided the first evidence that QSM is sensitive to iron deposition in subcortical target areas across pre-manifest and symptomatic stages of HD. They noted that such findings could open up new avenues for biomarker development and therapeutic intervention.

Other Interventions:

In an UpToDate review on “Huntington disease: Management” (Suchowersky, 2015) states that “Interventions for HD that have failed to show significant benefit in clinical trials include ethyl eicosapentaenoate (a fatty acid derivative and a component of HUFA) and minocycline .... Experimental surgery in HD has encompassed a number of possible interventions in symptom management. The utility of deep brain stimulation in HD is unknown. Data are limited to case studies, which suggest some benefit in chorea. Bilateral pallidotomy for dystonia in a patient with juvenile onset HD resulted in minimal benefit and worsening of spasticity”.

Gene Silencing:

Rollnik (2015) noted that HD is a progressive neurodegenerative disorder characterized by hyperkinetic movements, psychiatric (e.g., depression and psychosis) and cognitive symptoms (frontal lobe dementia. The author reviewed the clinical course, epidemiology, genetics, differential diagnoses, pathophysiology,
symptoms and causal therapeutic options. Publications on animal and human HD studies and trials and reviews available in Medline have been taken into account. Only genetic testing allows diagnostic certainty. The CAG repeat length influences age of onset, disease course and life expectancy. The mechanism by which mutant huntingtin protein (mHTT) causes HD is complex and poorly understood but led to cell death, in particular in striatal neurons. In clinical trials anti-oxidants (e.g., coenzyme Q10), selisistat, PBT2, cysteamine, N-methyl-D-aspartate (NMDA)-receptor antagonists and tyrosine kinase B receptor agonists have been studied in HD. The author concluded that no disease-modifying therapy is currently available for HD; however, gene silencing (e.g., through RNA interference) is a promising technique which could lead to effective therapies in the future.

Transcranial Magnetic Stimulation:

Ni and Chen (2015) noted that common neurodegenerative diseases include PD, AD, amyotrophic lateral sclerosis (ALS) and HD. Transcranial magnetic stimulation (TMS) is a non-invasive and painless method to stimulate the human brain. Single- and paired-pulse TMS paradigms are powerful ways to study the pathophysiological mechanisms of neurodegenerative diseases. Motor evoked potential studied with single-pulse TMS is increased in PD, AD and ALS, but is decreased in HD. Changes in motor cortical excitability in neurodegenerative diseases may be related to functional deficits in cortical circuits or to compensatory mechanisms. Reduction or even absence of short interval intra-cortical inhibition induced by paired-pulse TMS is common in neurodegenerative diseases, suggesting that there are functional impairments of inhibitory cortical circuits.

Decreased short latency afferent inhibition in AD, PD and HD may be related to the cortical cholinergic deficits in these conditions. Cortical plasticity tested by paired associative stimulation or theta burst stimulation is impaired in PD, AD and HD. Repetitive TMS (rTMS) refers to the application of trains of regularly repeating TMS pulses. High-frequency facilitatory rTMS may improve motor symptoms in PD patients whereas low-frequency inhibitory stimulation is a potential treatment for levodopa-induced dyskinesia; rTMS delivered both to the left and right
dorsolateral prefrontal cortex improves memory in AD patients. The authors concluded that supplementary motor cortical stimulation in low frequency may be useful for HD patients. However, the effects of treatment with multiple sessions of rTMS for neurodegenerative diseases need to be tested in large, sham-controlled studies in the future before they can be adopted for routine clinical practice.

**Triheptanoin:**

Adanyeguh et al (2015) stated that based on their previous work in HD showing improved energy metabolism in muscle by providing substrates to the Krebs cycle, these researchers wished to obtain a proof-of-concept of the therapeutic benefit of triheptanoin (a synthetic triglyceride compound) using a functional biomarker of brain energy metabolism validated in HD. These investigators performed an open-label study using (31)P brain MRS to measure the levels of phosphor-creatine (PCr) and inorganic phosphate (Pi) before (rest), during (activation), and after (recovery) a visual stimulus. They performed (31)P brain MRS in 10 patients at an early stage of HD and 13 controls. Patients with HD were then treated for 1 month with triheptanoin after which they returned for follow-up including (31)P brain MRS scan. At baseline, these researchers confirmed an increase in Pi/PCr ratio during brain activation in controls-reflecting increased adenosine triphosphate synthesis-followed by a return to baseline levels during recovery (p = 0.013). In patients with HD, these investigators validated the existence of an abnormal brain energy profile as previously reported. After 1 month, this profile remained abnormal in patients with HD who did not receive treatment. Conversely, the MRS profile was improved in patients with HD treated with triheptanoin for 1 month with the restoration of an increased Pi/PCr ratio during visual stimulation (p = 0.005). The authors concluded that the findings of this study suggested that triheptanoin is able to correct the bioenergetic profile in the brain of patients with HD at an early stage of the disease. This study provided Class III evidence that, for patients with HD, treatment with triheptanoin for 1 month restored an increased MRS Pi/PCr ratio during visual stimulation. The results of this proof-of-concept study need to be
validated by well-designed studies.

**Bupropion:**

In a phase IIb, multi-center, randomized, double-blind, placebo-controlled, prospective, cross-over trial, Gelderblom and associates (2017) assessed the safety and effectiveness of bupropion in the treatment of apathy in HD. Patients with HD and clinical signs of apathy according to the Structured Clinical Interview for Apathy-Dementia (SCIA-D), but not depression (n = 40) were randomized to receive either bupropion 150/300 mg or placebo daily for 10 weeks. The primary outcome parameter was a significant change of the Apathy Evaluation Scale (AES) score after 10 weeks of treatment as judged by an informant (AES-I) living in close proximity with the study participant. The secondary outcome parameters included changes of (i) AES scores determined by the patient (AES-S) or the clinical investigator (AES-C), (ii) psychiatric symptoms (NPI, HADS-SIS, UHDRS-Behavior), (iii) cognitive performance (SDMT, Stroop, VFT, MMSE), (iv) motor symptoms (UHDRS-Motor), (v) activities of daily function (TFC, UHDRS-Function), and (vi) caregiver distress (NPI-D). In addition, these researchers examined the effect of bupropion on brain structure as well as brain responses and functional connectivity during reward processing in a gambling task using MRI. At baseline, there were no significant treatment group differences in the clinical primary and secondary outcome parameters. At end-point, there was no statistically significant difference between treatment groups for all clinical primary and secondary outcome variables. Study participation, irrespective of the intervention, lessened symptoms of apathy according to the informant and the clinical investigator. The authors concluded that bupropion did not alleviate apathy in HD. However, study participation/placebo effects were observed, which documented the need for carefully controlled trials when investigating therapeutic interventions for the neuropsychiatric symptoms of HD.

**Coenzyme Q10:**

In a multi-center, randomized, double-blind, placebo-controlled
McGarry and colleagues (2017) tested the hypothesis that chronic treatment of early-stage HD with high-dose coenzyme Q10 (CoQ) will slow the progressive functional decline of HD. Patients with early-stage HD (n = 609) were enrolled at 48 sites in the U.S., Canada, and Australia from 2008 to 2012. Subjects were randomized to receive either CoQ 2,400 mg/day or matching placebo, then followed for 60 months. The primary outcome variable was the change from baseline to month 60 in Total Functional Capacity score (for patients who survived) combined with time to death (for patients who died) analyzed using a joint-rank analysis approach. An interim analysis for futility revealed a conditional power of less than 5 % for the primary analysis, prompting premature conclusion in July 2014. No statistically significant differences were seen between treatment groups for the primary or secondary outcome measures; CoQ was generally safe and well-tolerated throughout the study. The authors concluded that these findings do not justify use of CoQ as a treatment to slow functional decline in HD.

**Cysteamine:**

Verny and colleagues (2017) noted that cysteamine has been demonstrated as potentially effective in numerous animal models of HD. In a randomized, double-blind, placebo-controlled study, a total of 96 patients with early-stage HD were randomized to 1,200-mg delayed-release cysteamine bitartrate or placebo daily for 18 months. The primary end-point was the change from baseline in the UHDRS Total Motor Score. A linear mixed-effects model for repeated measures was used to assess treatment effect, expressed as the least-squares mean difference of cysteamine minus placebo, with negative values indicating less deterioration relative to placebo. At 18 months, the treatment effect was not statistically significant -- least-squares mean difference, -1.5 ± 1.71 (p = 0.385) -- although this did represent less mean deterioration from baseline for the treated group relative to placebo; treatment with cysteamine was safe and well-tolerated. The authors concluded that the effectiveness of cysteamine was not demonstrated in this study population of patients with HD; post-hoc analyses indicated the need for definitive future studies.
*Electro-Convulsive Therapy:*

Cusin and colleagues (2013) noted that many patients with HD develop psychiatric symptoms such as depression and psychosis. In a retrospective chart review, these investigators identified 7 patients with HD who received electro-convulsive therapy (ECT) at Massachusetts General Hospital in the past 20 years. In all cases, ECT was well-tolerated and produced improvement in psychiatric and behavioral symptoms. The authors concluded that the findings of this case-series study supported the hypothesis of a positive risk-benefit ratio for ECT in patients with HD and severe depression or psychosis. These preliminary findings need to be validated by well-designed studies.

*Music Therapy:*

In a randomized, controlled trial, van Bruggen-Rufi and co-workers (2017) examined the effectiveness of music therapy in comparison with recreational therapy in improving quality of life (QOL) of patients with advanced HD by means of improving communication. A total of 63 HD-patients with a Total Functional Capacity (TFC) score of less than or equal to 7, admitted to 4 long-term care facilities in the Netherlands, were randomized to receive either group music therapy or group recreational therapy in 16 weekly sessions. They were assessed at baseline, after 8, 16 and 28 weeks using the Behavior Observation Scale for Huntington (BOSH) and the Problem Behavior Assessment-short version (PBA-s). A linear mixed model with repeated measures was used to compare the scores between the 2 groups. Group music therapy offered once-weekly for 16 weeks to patients with HD had no additional beneficial effect on communication or behavior compared to group recreational therapy. The authors concluded that this was the first study to evaluate the effect of group music therapy on HD patients in the advanced stages of the disease. The beneficial effects of music therapy, recorded in many, mainly qualitative case reports and studies, could not be confirmed with the design (i.e., group therapy versus individual therapy) and outcome measures that have been used in the present study.
Precious and co-workers (2017) stated that HD is a neurodegenerative disease that offers an excellent paradigm for cell replacement therapy because of the associated relatively focal cell loss in the striatum. The predominant cells lost in this condition are striatal medium spiny neurons (MSNs).

Transplantation of developing MSNs taken from the fetal brain has provided proof of concept that donor MSNs can survive, integrate and bring about a degree of functional recovery in both pre-clinical studies and in a limited number of clinical trials. The scarcity of human fetal tissue, and the logistics of coordinating collection and dissection of tissue with neurosurgical procedures makes the use of fetal tissue for this purpose both complex and limiting. Alternative donor cell sources that are expandable in culture prior to transplantation are currently being sought. Two potential donor cell sources that have received most attention recently are embryonic stem (ES) cells and adult induced pluripotent stem (iPS) cells, both of which can be directed to MSN-like fates, although achieving a genuine MSN fate has proven to be difficult. All potential donor sources have challenges in terms of their clinical application for regenerative medicine, and thus it is important to continue exploring a wide variety of expandable cells. The authors discussed 2 less well-reported potential donor cell sources: (i) embryonic germ (EG) cells and (ii) fetal neural precursors (FNPs), both are fetal-derived and have some properties that could make them useful for regenerative medicine applications.

Tartaglione and colleagues (2017) noted that HD is an inherited neurodegenerative disorder, characterized by impairment in motor, cognitive and psychiatric domains. Currently, there is no specific therapy to act on the onset or progression of HD. The marked neuronal death observed in HD is a main argument in favor of stem cells (SCs) transplantation as a promising therapeutic perspective to replace the population of lost neurons and restore the functionality of the damaged circuitry. The availability of rodent models of HD encourages the investigation of the restorative potential of SCs transplantation longitudinally. However, the results of pre-clinical studies on SCs therapy in HD
are so far largely inconsistent; this hampers the individuation of
the more appropriate model and precludes the comparative
analysis of transplant efficacy on behavioral end-points. The
authors described the state of the art of in-vivo research on SCs
therapy in HD, analyzing in a translational perspective the
strengths and weaknesses of animal studies investigating the
therapeutic potential of stem cell transplantation on HD
progression.

Marsh and Blurton-Jones (2017) stated that neurodegenerative
disorders such as AD, PD, and HD currently affect millions of
people worldwide. Unfortunately, as the world's population ages,
the incidence of many of these diseases will continue to rise and
is expected to more than double by 2050. Despite significant
research and a growing understanding of disease pathogenesis,
only a handful of therapies are currently available and all of them
provide only transient benefits. Thus, there is an urgent need to
develop novel disease-modifying therapies to prevent the
development or slow the progression of these debilitating
disorders. A growing number of pre-clinical studies have
suggested that transplantation of neural stem cells (NSCs) could
offer a promising new therapeutic approach for
neurodegeneration. While much of the initial excitement about
this strategy focused on the use of NSCs to replace degenerating
neurons, more recent studies have implicated NSC-mediated
changes in neurotrophins as a major mechanism of therapeutic
efficacy. The authors discussed recent work that examined the
ability of NSCs to provide trophic support to disease-effected
neuronal populations and synapses in models of
neurodegeneration. They also discussed some of key challenges
that remain before NSC-based therapies for neurodegenerative
diseases can be translated toward potential clinical testing.

Transcranial Direct Current Stimulation:

Eddy and associates (2017) stated that transcranial direct current
stimulation (tDCS) combined with a cognitive task can enhance
targeted aspects of cognitive functioning in clinical populations.
Huntington's disease is associated with progressive cognitive
impairment. Deficits in working memory (WM) can be apparent
early in the disease and impact functional capacity. In a cross-over study, these researchers examined if tDCS combined with cognitive training could improve WM in patients with HD, and if baseline clinical or cognitive measures may predict effectiveness. A total of 20 patients with HD completed this trial, undergoing 1.5 mA anodal tDCS over left dorsolateral prefrontal cortex (pFC) and sham stimulation on separate visits. Subjects and evaluator were blinded to condition order, which was randomized across subjects. All participants completed baseline clinical and cognitive assessments. Pre- and post-stimulation tasks included digit reordering, computerized n-back tests and a Stroop task. During 15-min of tDCS/sham stimulation, participants practiced 1- and 2-back WM tasks. Participants exhibited an increase in WM span on the digit re-ordering span task from pre- to post-stimulation after tDCS, but not after sham stimulation. Gains in WM were positively related to motor symptom ratings and negatively associated with verbal fluency scores. Patients with more severe motor symptoms showed greatest improvement, suggesting that motor symptom ratings may help identify patients who are most likely to benefit from tDCS. The authors concluded that dorsolateral pFC tDCS appeared well-tolerated in HD and enhanced WM span compared to sham stimulation. They stated that these findings strongly encouraged further investigation of the extent to which tDCS combined with cognitive training could enhance everyday function in HD.

Talsma and colleagues (2017) noted that tDCS is a promising tool for neurocognitive enhancement. Several studies have shown that just 1 session of tDCS over the left dorsolateral pFC (IDLPFC) can improve the core cognitive function of WM in healthy adults. Yet, recent studies combining multiple sessions of anodal tDCS over IDLPFC with verbal WM training did not observe additional benefits of tDCS in subsequent stimulation sessions nor transfer of benefits to novel WM tasks post-training. Using an enhanced stimulation protocol as well as a design that included a baseline measure each day, the current study aimed to further examine the effects of multiple sessions of tDCS on WM. Specifically, these researchers examined the effects of 3 subsequent days of stimulation with anodal (20 minutes, 1 mA) versus sham tDCS (1 minute, 1 mA) over IDLPFC (with a right supraorbital reference)
paired with a challenging verbal WM task; WM performance was measured with a verbal WM updating task (the letter n-back) in the stimulation sessions and several WM transfer tasks (different letter set n-back, spatial n-back, operation span) before and 2 days after stimulation. Anodal tDCS over IDLPFC enhanced WM performance in the 1st stimulation session, an effect that remained visible 24 hours later. However, no further gains of anodal tDCS were observed in the 2nd and 3rd stimulation sessions, nor did benefits transfer to other WM tasks at the group level. Yet, post-hoc individual difference analyses revealed that in the anodal stimulation group the extent of change in WM performance on the 1st day of stimulation predicted pre- to post-changes on both the verbal and the spatial transfer task. Notably, this relationship was not observed in the sham group.

Performance of 2 individuals worsened during anodal stimulation and on the transfer tasks. The authors concluded that these findings suggested that repeated anodal tDCS over IDLPFC combined with a challenging WM task may be an effective method to enhance domain-independent WM functioning in some individuals, but not others, or can even impair WM. They called for a thorough investigation into individual differences in tDCS responses as well as further research into the design of multi-session tDCS protocols that may be optimal for boosting cognition across a wide range of individuals.

**CPT Codes / HCPCS Codes / ICD-10 Codes**

*Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":*

<table>
<thead>
<tr>
<th>CPT codes not covered for indications listed in the CPB:</th>
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<td>0310T</td>
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61863 - Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (e.g., thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), without use of intraoperative microelectrode recording

61864 - Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (e.g., thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), with use of intraoperative microelectrode recording

61867 - Revision or removal of intracranial neurostimulator electrodes

61870 - Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to a single electrode array or with connection to 2 or more electrode arrays

90867 - Therapeutic repetitive transcranial magnetic stimulation (TMS) treatment

90869 - Electronic analysis of implanted neurostimulator pulse generator system (e.g., rate, pulse amplitude, pulse duration, configuration of wave form, battery status, electrode selectability, output modulation, cycling, impedance and patient compliance measurements)

95970 - Electronic analysis of implanted neurostimulator pulse generator system (e.g., rate, pulse amplitude and duration, battery status, electrode selectability and polarity, impedance and patient compliance measurements), complex deep brain neurostimulator pulse generator/transmitter, with initial or subsequent programming

**HCPCS codes not covered for indications listed in the CPB:**

C1767 Generator, neurostimulator (implantable), nonrechargeable

C1778 Lead, neurostimulator (implantable)
C1816 _receiver and/or transmitter, neurostimulator (implantable)
C1883 _adaptor/extension, pacing lead or neurostimulator lead (implantable)
C1897_lead, neurostimulator test kit (implantable)
E0745_neuromuscular stimulator, electronic shock unit
L8680 - L8683, L8685 - L8689_neurostimulators and accessories
L8695_external recharging system for battery (external) for use with implantable neurostimulator, replacement only

There is no specific code for fetal striatal transplantation:

CPT codes not covered for indications listed in the CPB:

38230 Bone marrow harvesting for transplantation; allogeneic
38232 Bone marrow harvesting for transplantation; autologous
38240 Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
38241 autologous transplantation
61720 Creation of lesion by stereotactic method, including burr hole(s) and localizing and recording techniques, single or multiple stages; globus pallidus or thalamus
61798 Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 complex cranial lesion
61799 each additional cranial lesion, complex (List separately in addition to code for primary procedure)
76390 Magnetic resonance spectroscopy [putaminal MRS measurements of myoinositol and N-acetylaspartate]

HCPCS codes not covered for indications listed in the CPB:
Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including: pheresis and cell preparation/storage; marrow ablative therapy; drugs, supplies, hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre-and post-transplant.

Injection, minocycline HCl, 1 mg

There are no specific codes for SERCA2, VEGF mRNA, donepezil, ethyl eicosapent, latrepirdine or pridopidine or neurotrophic factors (e.g., brain-derived neurotrophic factor, ciliary neurotrophic factor, glial cell line-derived neurotrophic factor):

ICD-10 codes not covered for indications listed in the CPB:

Huntington's disease

The above policy is based on the following references:


18. Ramaswamy S, Shannon KM, Kordower JH. Huntington's


39. Domínguez D JF, Ng AC, Poudel G, et al. Iron accumulation in the basal ganglia in Huntington's disease: Cross-sectional...


48. Marsh SE, Blurton-Jones M. Neural stem cell therapy for neurodegenerative disorders: The role of neurotrophic support. Neurochem Int. 2017 Feb 20 [Epub ahead of
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