Huntington's Disease

Number: 0614

Policy

*A Please see amendment for Pennsylvania Medicaid at the end of this CPB.*

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.

Policy History

Last Review 07/14/2016
Effective: 05/14/2002
Next Review: 07/13/2017

Review History

Definitions
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:

- Deep brain stimulation
- Donepezil
- Ethyl eicosapentaenoate
- Fetal striatal transplantation
- Gene silencing (e.g., through RNA interference)
- Latrepirdine
- Mesenchymal stem cell transplantation
- Minocycline
- 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
- Transcranial magnetic stimulation
- Triheptanoin

See also [CPB 0307 - Parkinson's Disease (../300_399/0307.html)](../300_399/0307.html).

**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 gabaminergic 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 UHDRS. The primary end-point was reduction of chorea. Patients underwent 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.

Donpezil:

Mestre and Ferreira (2012) noted that HD is a neurodegenerative 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 anti-choreic 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 $^1$H 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 Unified Huntington's Disease Rating Scale (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) mRNAs 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.

### 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 "+":

**ICD-10 codes will become effective as of October 1, 2015:**

Deep Brain Stimulation:

CPT codes not covered for indications listed in the CPB:
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>61863 - 61864</td>
<td>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</td>
</tr>
<tr>
<td>61867 - 61868</td>
<td>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</td>
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<td>61880</td>
<td>Revision or removal of intracranial neurostimulator electrodes</td>
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<tr>
<td>61885 - 61886</td>
<td>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</td>
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<tr>
<td>90867 - 90869</td>
<td>Therapeutic repetitive transcranial magnetic stimulation (TMS) treatment</td>
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<tr>
<td>95970 - 95971</td>
<td>Electronic analysis of implanted neurostimulator pulse generator system (eg, rate, pulse amplitude, pulse duration, configuration of wave form, battery status, electrode selectability, output modulation, cycling, impedance and patient compliance measurements)</td>
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<tr>
<td>95974 - 95975</td>
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<tr>
<td>95978 - 95979</td>
<td>Electronic analysis of implanted neurostimulator pulse generator system (eg, 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</td>
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**HCPCS codes not covered for indications listed in the CPB:**

- C1767 Generator, neurostimulator (implantable), nonrechargeable
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>C1778</td>
<td>Lead, neurostimulator (implantable)</td>
</tr>
<tr>
<td>C1816</td>
<td>Receiver and/or transmitter, neurostimulator (implantable)</td>
</tr>
<tr>
<td>C1883</td>
<td>Adaptor/extension, pacing lead or neurostimulator lead (implantable)</td>
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<td>C1897</td>
<td>Lead, neurostimulator test kit (implantable)</td>
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<td>Neuromuscular stimulator, electronic shock unit</td>
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<td></td>
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<tr>
<td>L8689</td>
<td></td>
</tr>
<tr>
<td>L8695</td>
<td>External recharging system for battery (external) for use with implantable neurostimulator, replacement only</td>
</tr>
</tbody>
</table>

*There is no specific code for fetal striatal transplantation:*

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

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

**HCPCS codes not covered for indications listed in the CPB:**
S2150 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.

J2265 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:

G10 Huntington's disease

The above policy is based on the following references:


17. Frank S, Biglan K. Long-term fetal cell transplant in
28. Armstrong MJ, Miyasaki JM; American Academy of


37. Ni Z, Chen R. Transcranial magnetic stimulation to understand pathophysiology and as potential treatment...


AETNA BETTER HEALTH® OF PENNSYLVANIA

Amendment to
Aetna Clinical Policy Bulletin Number: 0614
Huntington's Disease

There are no amendments for Pennsylvania Medicaid.

www.aetnabetterhealth.com/pennsylvania
Updated 02/2017