Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 5/1/22**
(See policy history boxes for previous effective dates)

Title: Genetic Testing for Huntington Disease

Description/Background

Huntington Chorea/Disease (HD)

HD is an autosomal dominant neurodegenerative disease with an estimated prevalence of 1 in 10,000 in Caucasian populations. Clinical symptoms typically begin with psychiatric changes in adults aged 35-45 progressing to movement disorder and dementia with survival of approximately 15 to 18 years after diagnosis. Expansion of a cytosine-adenine-guanine (CAG) trinucleotide repeat in exon 1 in the huntingtin (*HTT*) gene is responsible for HD. Full penetrance is expected among those with ≥ 40 CAG repeats, although variability in age at onset is observed. Reduced penetrance is observed among those with 36 to 39 CAG repeats and while normal phenotype is observed among those with 27 to 35 CAG repeats, there is still risk of transmission of the disorder to offspring as these alleles can be unstable during meiosis.

Treatment

Currently there is no cure and treatment is limited to management of some symptoms. Because manifestation of HD phenotype requires inheriting only one penetrant allele, positive results have serious health implications for biologically related close family members. Due to the impact of positive results on the family, complicated ethical issues arise with differences in opinions towards genetic testing. Thus, genetic counseling is especially important for individuals and all closely related at-risk family members.

Genetic Testing

Various manufacturers provide direct detection of the CAG repeat expansion responsible for HD from DNA extracted from peripheral blood samples. Polymerase chain reaction (PCR) and fragment analysis by capillary electrophoresis are typically used for the CAG repeat determination. Genetic testing for HD is used for diagnostic, predictive, and prenatal or preimplantation genetic diagnosis purposes. Symptomatic patients with or without a family history may benefit from diagnostic testing for HD. Asymptomatic individuals with a family

history may undergo predictive testing to define personal risk or risk of transmission. Prenatal testing for HD may be indicated for asymptomatic couples with a family history of HD. Preimplantation testing to deselect embryos with HD allele(s) may be indicated for couples carrying penetrant HD alleles.

Regulatory Status

No approvals for genetic testing for HD alleles were found on the FDA website. Genetic tests are regulated under the Clinical Laboratory Improvement Amendments (CLIA) Act of 1988. ARUP Laboratories, Athena Diagnostics, CompGene, and Quest Diagnostics all have current CLIA certifications.

Medical Policy Statement

The safety and effectiveness of genetic testing have been established. It may be considered a useful diagnostic option when indicated.

Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

Inclusions:

- Genetic testing for HD to confirm the diagnosis of HD when clinical signs, symptoms and imaging results are consistent with HD.

Table 1. Symptoms of HD*

Neurologic	Psychiatric	Cognitive
Chorea	Apathy	Poor judgment
Dystonia	Irritability	Inflexibility of thought
Eye movement slowing	Depression	Loss of insight
Hyperreflexia	Delusions	Decreased concentration
Gait abnormality	Aggression	Memory loss
Myoclonus (rare)	Anxiety	Subcortical dementia
Parkinsonism (late stages)	Disinhibition	
	Paranoia	

*Suchowersky, O. Huntington disease: clinical features and diagnosis. UpToDate. November 2019.

- Testing in asymptomatic first or second degree relatives of a person with a genetically confirmed diagnosis of HD.
- Prenatal testing in fetuses from families in which there is a history of HD.

*Neuroimaging: axial MRI images through the lateral ventricles demonstrate caudate atrophy, defined by the loss of the normal protrusion of the caudate head into the lateral ventricle in late-stage HD. Caudate atrophy, quantified by simple analysis of linear caudate measurements, correlates with change in cognitive function. Functional imaging using

positron-emission tomography (PET) and MRI also show abnormal metabolic changes in the caudate.

Exclusions:
- Genetic testing for HD for routine screening.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

81401 81271 81274

Other codes (investigational, not medically necessary, etc.):

N/A

Note: Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.

Rationale

Analytical Validity
Kalman et al (2007) conducted diagnostic and predictive testing for HD requiring an accurate measurement of CAG repeats in the HD (IT15) gene.[1] However, precise repeat sizing can be technically challenging, and is complicated by the lack of quality control and reference materials (RM). The aim of this study was to characterize genomic DNA from 14 Huntington cell lines available from the National Institute of General Medical Sciences Human Genetic Cell Repository at the Coriell Cell Repositories for use as reference materials for CAG repeat sizing. Fourteen Huntington cell lines were selected for study. The alleles in these materials represent a large range of sizes that include important diagnostic cutoffs and allele combinations. The allele measurement study was conducted by ten volunteer laboratories using a variety of polymerase chain reaction-based in-house developed methods and by DNA sequence analysis. The Huntington alleles in the 14 genomic DNA samples range in size from 15 to 100 CAG repeats. There was good agreement among the ten laboratories, and thus, the 95% confidence interval was small for each measurement. The allele size determined by DNA sequence analysis agreed with the laboratory developed tests. The authors concluded that these DNA materials would facilitate accurate and reliable Huntington genetic testing.

Clinical Validity
The following studies report incidence of HD and testing uptake over periods of several years to over a decade of HD testing implementation.

Creighton et al (2003) investigated the uptake, utilization, and outcome of predictive, pre-natal and diagnostic testing in Canada from 1987 to April 1, 2000.[2] A retrospective design was used; all Canadian medical genetics centers and their affiliated laboratories offering genetic testing

for HD were invited to participate. A total of 15 of 22 centers (68.2%), currently offering or ever having offered genetic testing for HD, responded, providing data on test results, demographics, and clinical history. A total of 1061 predictive tests, 15 pre-natal tests, and 626 diagnostic tests were performed. The uptake for predictive testing was approximately 18% of the estimated at-risk Canadian population, ranging from 12.5% in the Maritimes to 20.7% in British Columbia. There appears to have been a decline in the rate of testing in recent years. Of the predictive tests, 45.0% of individuals were found to have an increased risk, and a preponderance of females (60.2%) sought testing. A greater proportion of those at < or = 25% risk sought predictive testing once direct CAG mutation analysis had become available (10.9% after mutation analysis vs. 4.7% before mutation analysis, p = 0.0077). Very few pre-natal tests were requested. Of the 15 pre-natal tests, 12 had an increased risk, resulting in termination of pregnancy in all but one. Diagnostic testing identified 68.5% of individuals to be positive by mutation analysis, while 31.5% of those with HD-like symptoms were not found to have the HD mutation. The positive diagnostic tests included 24.5% of individuals with no known prior family history of HD.

Harper et al (2000) conducted a prospective assessment of asymptomatic HD testing over a 10-year period from 1987 to 1997.[3] For this 10-year period, 2502 individuals underwent direct CAG length testing and 41% (1016/2502) were HD allele-positive. Linkage analysis was performed for 426 individuals and 42% (180/426) were at increased risk. For those tested by either method, 58% (1702/2928) were female and 93% (2722/2928) were at 50% prior risk.

Using Australia's publicly funded predictive testing services, Tassicker and colleagues (2006) conducted a retrospective assessment of predictive and prenatal HD testing over a 10-year period from 1994 to 2003.[4] Results are summarized below separately for predictive and prenatal testing:

- For predictive HD testing, 2036 direct CAG length tests were performed and 38% (776/2036) were positive for ≥ 40 CAG repeats (full penetrance) while 6% (120/2036) had 27 to 39 CAG repeats (normal to expandable to reduced penetrance). Prior genetic risks were 50% for 94% (1908/2036) and 25% for 6% (128/2036) of those that underwent predictive HD testing. The authors also note that a small number of individuals who underwent predictive HD testing had a prior genetic risk of ≤ 5%. Among those with prior genetic risk of 25%, 27% (34/128) tested positive for ≥ 40 CAG repeats.
- For prenatal HD testing, 44 direct CAG length and 19 linkage analysis tests were performed for a total of 63. Of the 44 direct CAG length prenatal tests, 50% (22/44) were positive for ≥ 40 CAG repeats. Of the 19 prenatal tests by linkage analysis, 42% (8/19) were high risk for full penetrance.

Ramond et al (2019) analyzed data from the files of all individuals seeking predictive testing for HD in Lyon, France, from 1994-2017.[5] Four hundred forty-eight out of 567 participants had exploitable data. Age at consultation dichotomized over 24 years toward an eightfold increase in individuals aged >55 (2/94 vs. 30/183; 2% to 16%; $p < .0001$) and twice as many individuals aged 18–20 (3/94 vs. 12/183; 3%–7%; $p < .05$). Motives for testing remained stable. The rate of withdrawal doubled over 24 years (9/94 vs. 38/183; 9%–21%; $p < .02$). Independently of the time period, less withdrawal was observed for married, accompanied, at 50% risk, and symptomatic individuals, and in those able to explicit the motives for testing or taking the test to inform their children. We also assessed the consistency between the presence of subtle symptoms compatible with HD found before the test by the team's neurologist, and the positivity of the molecular test. The concordance was 100% (17/17) for associated motor and

cognitive signs, 87% (27/31) for isolated motor signs, and 70% (7/10) for isolated cognitive signs. Furthermore, 91% (20/22) of individuals who requested testing because they thought they had symptoms, were indeed found carriers. This over-24 years study underlines an increasing withdrawal from protocol and a dichotomization of participants' age. There also appears a strong concordance between symptoms perceived by the neurologist or by the patient, and the subsequent positivity of the predictive molecular test.

Clinical Utility

In a European study focusing on the utility of testing for reproductive decisions, Evers-Kiebooms et al (2002) retrospectively surveyed 7 genetic centers to compare reproductive decision-making and reproduction between 180 and 270 eligible carriers and noncarriers of HD alleles, respectively.[6] Individuals who were 45 years of age at the time of receiving predictive test results were considered at reproductive age and were eligible for inclusion in the comparison. A questionnaire was developed specifically for this study and information was gathered from patient files of individual genetic centers. Patient files were updated by the respective genetic center when feasible for eligible individuals. Data was collected on test result, socio-demographic data, pretest reasons for testing, information on last contact with genetic center, pregnancies and pregnancy status at time of receiving test result, adoptions, perception on family completeness, and intentions for preimplantation diagnosis. Overall, the mean age was 31.5 years at the time of receiving predictive test results. One or more pregnancies prior to receiving predictive test results were reported for 47% and 51% of HD allele carriers and noncarriers, respectively. Overall, one or more pregnancies after receiving predictive test results were observed for 14% (26/180) and 28% (77/271) of carriers and noncarriers, respectively. Of the subgroup that originally expressed family planning as a motive for predictive testing, post-test pregnancies were smaller in number for HD allele carriers (32% = 18/57) compared with noncarriers (56% = 64/114) with statistical significance (P<0.01).

Summary of Evidence

Direct testing to determine CAG repeat size has been available since 1993, and recommended guidelines for laboratory practices for HD genetic testing were published in 1994 (International) and 1998 (U.S.). However, standard reference material has only recently been developed including 14 genomic DNA samples with CAG repeat lengths from 15 to 100.

The American College of Medical Genetics/American Society of Human Genetics (ACMG/ASHG) recommends confirmation of homozygous alleles by Southern blot for U.S. laboratory practices in genetic testing for HD. Kalman and colleagues reported that between PCR-based sizing assays and DNA sequencing for size determination, discrepancies were found for 3 of the 28 total alleles tested, although these were in agreement with the clinically relevant size category of > 40 repeats. A large amount of data exists for several years of genetic testing for HD for non-U.S. populations, especially of Caucasian populations. Review of large studies shows the need for standardization of reported results as most report *positive* for HD alleles for different categories of CAG repeat lengths such as ≥ 36 repeats ≥ 39 repeats, and ≥ 40 repeats. Research supports that the correlation between CAG length and age at onset is not linear, and may depend on other genetic factors and environment.

Currently, predictive testing for the purpose of making reproductive decisions may hold the greatest benefit for prevention of HD. In a European collaboration, Evers-Kiebooms and colleagues show that of those who specifically underwent predictive testing for HD for this purpose, the number of post-test pregnancies were significantly lower among carriers

(32%) of HD alleles as compared with noncarriers (56%) (*P*<0.01).

Government Regulations

National:

No NCD available for this testing.

Local:

No LCD available for this testing.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Genetic Testing and Counseling
- Genetic Testing—Carrier Screening for Genetic Diseases
- Genetic Testing—Preimplantation

References

1. Kalman L, Johnson MA, Beck J, et al. Development of genomic reference materials for Huntington disease genetic testing. Genet Med. Oct 2007;9(10):719-723.
2. Creighton S, Almqvist EW, MacGregor D, et al. Predictive, pre-natal and diagnostic genetic testing for Huntington's disease: the experience in Canada from 1987-2000. Clin Genet. Jun 2003;63(6):462-475.
3. Harper PS, Lim C, Craufurd D. Ten years of presymptomatic testing for Huntington's disease: the experience of the UK Huntington's disease prediction consortium. J Med Genet. 2000;37:567-571.
4. Tassicker RJ, Marshall PK, Liebeck TA, et al. Predictive and pre-natal testing for Huntington disease in Australia: results and challenges encountered during a 10-year period (1994-2003). Clin Genet. Dec 2006;70(6):480-489.
5. Ramond F, Quadrio I, Vavasseur LL, et al. Predictive testing for Huntington disease over 24 years: evolution of the profile of the participants and analysis of symptoms. Mol Genet Gen Med. Mar 2019. 7Le881.
6. Evers-Kiebooms, G, Nys K, Harper P, et al. Predictive DNA-testing for Huntington's disease and reproductive decision making: a European collaborative study. Eur J Hum Genetics. 2002;10:167-176.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through January 2022, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
5/1/20	2/18/20		Joint policy established
5/1/21	2/16/21		Routine policy maintenance, no change in policy status.
5/1/22	2/15/22		Routine policy maintenance, no change in policy status.

Next Review Date: 1st Qtr. 2023

Pre-Consolidation Medical Policy History

Original Policy Date	Comments
BCN:	Revised:
BCBSM:	Revised:

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENETIC TESTING FOR HUNTINGTON DISEASE

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	See policy guidelines
BCNA (Medicare Advantage)	See government section
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.