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Review Article

Huntington disease: A quarter century of progress since the gene discovery

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ABSTRACT

Huntington disease (HD) is an autosomal dominant neurodegenerative disorder characterized by motor, behavioral, and cognitive manifestations. It is caused by an expansion of a trinucleotide repeat in the *huntingtin* gene (*HTT*) on chromosome 4. Although disease onset is currently clinically defined by motor signs, the presence of non-motor symptoms prior to motor diagnosis is increasingly recognized. Complex multimodal symptoms adversely affect quality of life and longevity of patients. Thoughtful interdisciplinary symptomatic care can make a major positive impact for patients and families. A variety of symptomatic treatments are currently available, and new symptomatic and potentially disease modifying therapies are being actively developed. Functional and quality of life outcome measures can be used to assess efficacy of clinical interventions. These outcomes along with clinical data and novel longitudinal biomarkers are increasingly utilized in clinical trials, particularly those testing disease-modifying therapeutics. Recent advances in novel therapeutic strategies, including targeting mutant huntingtin (HTT) and the *HTT* gene, promise another wave of disease-modifying trials in the near future. Better appreciation of heterogeneous clinical phenomenology and immediate tractable treatment goals coupled with advances in new therapeutics heralds a golden age of HD treatment that will positively impact quality of life and longevity of HD patients and inform advances in other inherited and neurodegenerative neurological disorders.

1. Introduction

Discovery of the genetic cause for Huntington disease (HD) has had far-reaching impact not only on HD but on other heredodegenerative disorders. The localization of a genetic marker near the tip of the short arm of chromosome 4 in 1983 by Gusella and colleagues [1] was an important milestone in HD research. It took another ten years for the landmark announcement of the HD causal mutation in the novel gene *HTT* [2]. This was the first report of a human genetic variant localized by linkage analysis using restriction fragment length polymorphisms. This discovery a quarter century ago, the result of a decades-long effort by a multinational research team together with thousands of volunteers living with or at risk of developing HD, opened the "gene hunter" era [3]. The *HTT* mutation was also one of the first reported disease-causing trinucleotide repeat expansions [2,4].

HD is a highly penetrant, autosomal dominant, progressive neurodegenerative movement and neurobehavioral disorder associated with a variety of motor signs plus psychiatric symptoms and cognitive decline that progresses to dementia. Knowledge of the HD causal mutation allows recognition of an ever-widening range of HD phenotypes and phenocopies. Mean age at onset is approximately 40 years, with a reported range of 2 to 79+ years [5–8].

The current clinical onset definition is based on motor signs (for example, appearance of chorea), although it is well recognized that mood changes, cognitive decline and other non-motor symptoms can precede motor symptoms or signs by many years. HD, caused by an

Abbreviations: BDNF, brain-derived neurotrophic factor; BMI, body mass index; CGIC, clinician global impression of change; COHORT, Cooperative Huntington's Observational Research Trial; DBS, Deep brain stimulation; DCL, diagnostic confidence level; EGCG, (2)-epigallocatechin-3-gallate; GPi, internal globus pallidus; HD, Huntington disease; HTT, huntingtin protein; *HTT*, gene, also termed *huntingtin* and *IT15*, encodes huntingtin protein; IA, intermediate allele; JHD, juvenile Huntington disease; MCI, mild cognitive impairment; OT, occupational therapy; PDE10, phosphodiesterase 10 (PDE10); PGIC, patient global impression of change; PHAROS, Prospective Huntington Disease At-Risk Observational Study; PT, physical therapy; SI, suicidal ideation; SLP, speech language pathology; SNP, single nucleotide polymorphisms; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; TFC, total functional capacity; UHDRS, Unified Huntington Disease Rating Scale; VMAT2, type 2 vesicular monoamine transporter

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easily testable monogenic mutation, has served as a model for studying and potentially treating disease mechanisms long before onset of any observable symptoms or signs. Leveraging this advantage requires thoughtful scientific and ethical consideration.

2. Classification

Although HD is mainly conceptualized as a movement disorder with a wide range of motor signs in pediatric, adult, and geriatric clinical populations, the associated progressive cognitive decline and behavioral symptoms also place it within neurodegenerative dementias and neuropsychiatric disorders.

The etiologic classification of HD is an autosomal dominant monogenic disorder. The specific genetic classification is within trinucleotide repeat disorders. The CAG repeat expansion in exon one of the *HTT* gene is translated into an expanded polyglutamine repeat in an abnormal huntingtin protein (HTT). The key pathologic classification of HD is a neurodegenerative disorder, with disease-specific cortical and subcortical neuronal populations relatively vulnerable to damage and loss.

3. Pathogenesis

The pathogenic steps connecting the HD causal mutation and expression of an expanded polyglutamine-containing HTT protein to progressive neurodegeneration remain poorly understood. Functions of the normal HTT protein and potential neuropathological pathways related to mutated HTT are both areas of intense study [9–12]. Most work centers on toxic gain of function effects. In addition, possible HTT neurodevelopmental roles suggest loss of function mutation impacts, and potential protective effects of normal HTT against the mutated protein [13]. This section focuses on the impact of the two defining HD etiologic and pathogenic concepts on disease expression.

3.1. The CAG trinucleotide repeat mutation: how much information is in a number?

HD is a highly penetrant, autosomal dominant disorder caused by abnormal expansion of CAG repeats in the *HTT* gene. Concepts central to the CAG repeat expansion mutation are relevant to other trinucleotide repeat expansion disorders, a category founded in part by HD [2,4]. These include variability in age of onset across carriers of the same sized expansion; impact of the mutation type on heritability of the disorders; and grey zones between non-disease causing and fully disease causing repeat expansion lengths. The current normal, definitively non-disease causing CAG repeat length range is below 27, with cutoffs of 27 to 35 for intermediate alleles (discussed below), and 36 to 39 for reduced penetrance HD causal mutations.

The HD causal mutation is fully penetrant at *HTT* CAG repeat lengths of 40 and above. Similar to other trinucleotide repeat disorders, there is a clear inverse relationship between the number of CAG repeats and age at motor onset at the population level [14]. This is especially true when the CAG repeat expansion is very large (> 60) [5,6,15]. However, for the most common variants, 40-55 CAGs, repeat length has been reported to account for 56% of age of motor onset variability, with a 40+ year range in age at motor diagnosis among individuals with the same CAG repeat length [15]. Similarly, decline in cognitive ability in mutation carriers most closely correlates with CAG repeat number [16], as does weight loss [17]. Homozygotes do not clearly differ in phenotype from heterozygotes, and the normal allele size does not appear to influence onset age of motor signs [6,15]. The immediate genetic background or *HTT* haplotype does not appear to influence age at motor signs onset or disease progression [9,15,18]. New genome wide association studies are yielding loci associated with delay or hastening of HD motor onset, but no specific disease progression modifying genetic variants outside *HTT* have been confirmed [19,20]. New data may provide more individualized prognosis information and disease modifying therapeutic targets.

CAG repeat lengths are unstable between generations. This is the biological basis for anticipation, wherein observed age at disease onset decreases from one generation to subsequent generations [21]. Analysis of Venezuelan HD cohort parent/offspring pairs observed intergenerational CAG repeat length changes from maternal to child of -5 to +10 and paternal to child of -7 to +41 [22]. In the *HTT* CAG repeat, marked expansion occurs in spermatogenesis, with larger constitutive CAG lengths more likely to expand further [22,23]. Nonsymptomatic individuals including those carrying a reduced penetrance or intermediate allele (IA) may have offspring with a more expanded CAG repeat and clinical HD.

While there are currently no known specific genetic modifiers of individual disease onset or progression beyond the CAG mutation itself, there are direct genetic influences on CAG repeat instability. Male offspring are more likely to have CAG repeat expansions, and sibling sets have tighter CAG repeat length ranges than predicted from population data, implicating genetic modifiers in CAG length instability [22]. In addition, specific genetic haplotypes, sets of genetic markers on chromosome 4 that are inherited together along with the *HTT* gene itself, are associated with higher rates of intergenerational CAG repeat instability and expansion [18,24,25].

The CAG repeat range of 36 to 39 has reduced penetrance. These repeat lengths are relatively rare: 0.25% is one recent population estimate [26]. Due to the relative scarcity of the reduced penetrance CAG repeat length alleles, it is unknown if these patients clearly differ in age of motor signs onset or in symptom progression compared to patients with low but fully penetrant CAG repeat expansion sizes.

In contrast, *HTT* CAG repeats of 27 to 35 have a relatively high population frequency, estimated at 6.2% [26]. These “intermediate alleles” (IAs) have generally been considered non-pathogenic; however, there is growing evidence of associated clinical phenotypes [27–29]. Kenney and colleagues initially reported a 65-year-old man with 29 CAG repeats exhibiting symptoms of HD who had autopsy findings consistent with HD [28]. An analysis of European Huntington’s Disease Network Registry data from 76 intermediate allele and 581 $<$ 27 CAG repeat allele carriers found no significant differences in Unified Huntington Disease Rating Scale (UHDRS) (http://huntingtonstudygroup.org/tools-resources/uhdrs/) motor, behavioral, cognitive or total functional capacity (TFC) scores (see Diagnosis section below re: UHDRS subscales), or quality of life assessments, although the IA group had mildly but significantly greater cognitive decline after one year, and IA carriers age 60 and older had higher UHDRS chorea scores compared to similarly aged controls [30]. IA carriers in the Prospective Huntington Disease At-Risk Observational Study (PHAROS) had similar motor, cognitive and functional outcomes but worse suicidal ideation (SI) and apathy measures compared to individuals with normal CAG repeat lengths, and worse behavioral scores compared to normal allele and nonmanifest (no clear signs or symptoms) fully penetrant CAG expansion carriers [31]. Individuals with IAs in the Cooperative Huntington’s Observational Research Trial (COHORT) study exhibited mild motor and behavioral abnormalities [32]. Overall, observational cohort data suggesting IAs contribute to more subtle clinical phenotypes contrast with the growing case reports of IA-associated frank HD motor signs and neuropathology [27,33]. Potentially IA associated clinical syndromes may only be recognized after other family members are diagnosed with HD. Severe caudate glucose hypometabolism was demonstrated in a patient with 33 CAG repeats and subtle motor and cognitive findings; the patient’s son inherited a 48 CAG repeat expansion and developed HD [29]. Similarly, a patient with dementia was found to have a 33 CAG repeat allele after her daughter, carrying 48 CAG repeats, was diagnosed with HD [34]. The pathogenic significance of IAs may lie in somatic mosaicism, as suggested in some animal models and in patients with striatal neurons carrying CAG repeats longer than in other tissues in the same individual [35,36]. It is possible

that some neuronal populations in striatum express alleles of increased size due to somatic instability, thus increasing their susceptibility to degeneration [37]. IA cases thus provide opportunities to understand genetic modifiers of HD neuropathology.

The relatively high population frequency of IAs gives these *HTT* alleles an outsize role in determining HD population prevalence [26,38]. The highest HD prevalence estimates are reported in European ancestry populations, with some exceptions [15,39–41]. A new study reports a similar distribution of IA population frequencies, with IAs most common in Northern European and Hispanic American populations of the fifteen groups studied [38]. The most common *HTT*-containing haplotypes in European populations are associated with increased CAG repeat instability [18,24,25]. In general, populations with higher HD prevalence also have higher frequencies of specific higher expansion risk *HTT* haplotypes, mainly A1 and A2; low HD prevalence populations have rarer independent CAG expansions on a mix of other *HTT* haplotypes [9,15]. IA CAG lengths are observed preferentially with *HTT* haplotypes that are associated with increased CAG repeat instability [24,42]. The *HTT* haplotype background may therefore help create more IAs through increased CAG repeat length instability, plus help drive IAs to expand into more classically disease-causing CAG lengths. In one study HD prevalence correlated with IA population frequency, and with the proportion of IAs expressed on the A1 *HTT* haplotype background [38].

Overall, the combined impact of general CAG repeat instability that worsens as CAG repeat size increases, higher CAG instability on particular *HTT* haplotype backgrounds, and rates of abnormal CAG repeats particularly IAs on high expansion risk *HTT* haplotypes appears to drive differences in HD prevalence and new HD mutation rates across groups with different genetic backgrounds [38]. These observations directly impact the reach of new gene silencing allele-specific therapeutic approaches; for example, agents using haplotypes to target the mutant *HTT* allele would address most but far from all HD cases (see New and Experimental Therapeutics below) [9].

3.2. Huntington disease is a neurodegenerative disorder

Striatal neurodegeneration, particularly involving the medium spiny neurons, has long been considered the pathological hallmark of HD [43–46]. Contrary to the traditional view of caudate as the site of the brunt of pathology in HD, postmortem and imaging gross examinations of the brain of patients with HD show predominant putamen atrophy [47,48]. This is typically accompanied by cortical atrophy and multisystem degeneration [48,49]. Although the mutated and normal HTT proteins are ubiquitously expressed, specific neuronal populations are uniquely vulnerable to gradual progressive neurodegeneration. The prominent striatal neurodegeneration is likely linked to chorea, a classic component of the HD movement disorder [50], but entire brain weight is decreased, and well documented neuronal loss in other areas may contribute to both the movement disorder and other classic features of HD [51]. The widespread laminar cortical degeneration is probably clinically expressed as cognitive decline and various behavioral abnormalities [52]. Early loss of white matter may contribute to early clinical signs, such as abnormal (increased, hung up and pendular) reflexes [53]. Loss of specific hypothalamic neuronal populations may drive dysautonomic symptoms, sleep disturbances, and weight loss [54,55]. Cerebellar degeneration, classically associated with ataxia, is most typically encountered in juvenile onset HD (JHD). Recent postmortem and imaging studies in adult onset HD cases report evidence for cerebellar degeneration and grey matter changes, albeit in small cohorts [56,57].

Multiple imaging markers of neurodegeneration are under active investigation as potential biomarkers for disease progression in prodromal (minimal signs and/or minimally symptomatic) or nonmanifest (asymptomatic) populations [47,58] (see “Preclinical Stages” below). Various volumetric imaging studies have found good correlation between striatal atrophy and disease duration and CAG repeat length. Longitudinal studies of nonmanifest, at-risk individuals found that cortical thinning occurs early in disease and proceeds from posterior to anterior brain areas. Observations of smaller intracranial volume, found by volumetric imaging studies in prodromal HD, have led to the suggestion that HD is a neurodevelopmental disorder [59]. Even white matter atrophy may be initially observed up to 12-15 years before predicted motor onset [60]. Using 11C-(R)-PK11195 positron emission tomography (PET), microglial activation was found in nonmanifest mutation carriers and represents one of the earliest pathogenic processes associated with subclinical progression of disease [61]. Microglial activation also correlates with striatal neuronal dysfunction. Connectivity within the putamen whole-brain resting state networks has been found to negatively correlate with CAG repeat length on functional MRI studies [48]. For imaging biomarkers to be useful on an individual predictive level, multivariate analysis of volumetric and other measures may be required, rather than focusing on single measures [62]. These and other imaging and pathological studies continue to provide insights into pathogenic mechanisms of abnormal brain function in HD.

4. Diagnosis

4.1. HD as a clinical diagnosis

Motor manifest diagnosis, currently considered clinical disease onset, is based on the UHDRS diagnostic confidence level indicating 99% confidence that motor exam signs represent HD. The UHDRS motor section includes chorea, dystonia, bradykinesia, rigidity, ocular pursuits and saccades, dysarthria, motor impersistence, motor Luria testing, voluntary fine motor control tasks, gait, tandem gait, and postural reflexes. There are no specific cut-offs in terms of motor UHDRS item scores or total scores, nor are there mandated motor signs for diagnosis. The discovery of the *HTT* mutation allowed easier recognition of non-choreic HD phenotypes; for example, rigid, parkinsonian and/or dystonic phenotypes, common in JHD, may present in adult onset HD. Tics and Tourettism are another atypical presentation of adult-onset HD [63].

Although behavioral and cognitive changes may long precede motor signs in adult and juvenile onset [64–68], purely non-motor or mixed motor and non-motor diagnoses remain under debate. None of the other UHDRS sections are formally used in clinical diagnosis; however, their pragmatic use has been studied in specific research cohorts. The UHDRS Behavioral subscale covers frequency and severity of depressed mood, apathy, low self-esteem and guilt, suicidal thoughts, anxiety, irritability, aggression, obsessive thinking, compulsions, delusions and hallucinations. The UHDRS Cognitive section comprises verbal fluency, symbol digit modalities test, and Stroop interference tests. The UHDRS TFC addresses core functional areas of work, financial tasks, household tasks, activities of daily living, and living situation (home, chronic care) with a maximum score of 13. The TFC has been used to create disease stage categories, track progression in observational studies, and as an inclusion/exclusion clinical trial criterion. Other UHDRS subscales address impact of disease on function with more detailed, individual items within these broad categories. Neuropsychiatric aspects and functional impact of HD beyond the UHDRS are discussed further in the Clinical Features section.

The PREDICT-HD study observed mutation carriers, nonmanifest at enrollment, over several years. Investigators were asked to assess motor diagnosis, and to also make a separate diagnostic call based on all available information including all UHDRS areas and interactions with the participant and any caregivers. Of 186 participants who phenoconverted during the course of the study, 37% were first diagnosed with clinical HD via the multimodal approach, prior to their motor manifest

diagnosis [69]. Cluster analysis delineated three phenotype categories: primarily cognitively impaired; behaviorally impaired; and cognitively preserved [69]. Entirely non-motor diagnoses are currently considered the most difficult to implement: neuropsychiatric symptoms such as depression are too non-specific to provide diagnostic confidence, and normal cognitive baselines are highly individual. In PHAROS, in which both HD at risk participants and investigators were blinded to mutation status, cluster analysis of 345 participants with ≥37 CAG repeat expansions and 638 participants with < 37 CAG repeats found the mutation carrier group was at baseline more impaired in motor, behavioral, and most cognitive measures with no differences in functional measures [70]. Over time, the ≥37 CAGs group worsened and diverged from the < 37 group in all categories except behavioral, where both groups worsened [70]. Behavioral measures were the most nonspecific, with the possible exception of irritability observed more commonly in the ≥37 CAGs group. This suggests that specific cognitive or functional measures may be useful in future non-motor diagnosis criteria. The use of purely motor versus multidimensional clinical diagnoses will likely change as more is understood about HD signs and symptoms, and new therapies target non-motor features.

The combination of a 99% UHDRS diagnostic confidence level (DCL) and an expanded *HTT* CAG repeat length on genetic testing is considered the diagnostic gold standard. Given current barriers to confirmatory genetic testing, particularly in the US, a classic motor presentation plus a clear family history of HD is often pragmatically accepted for HD clinical diagnosis especially with known genetic testing results in another affected family member. However, in late onset adult HD cohorts 30% or more may have no HD family history [8]; in one cohort 68% were the initial diagnosis for the family [71]. There are many reasons for a negative family history in HD cases, ranging from adoption to non-paternity to death of mutation carriers at young ages from unrelated causes. New mutations are possible with intergenerational repeat expansions, as noted above for IA carrier parents and causal mutation expansion in their offspring. In addition, JHD and very late onset HD may represent the first known HD presentation in the family [7,8,71]. Parents of JHD patients, even parents with a causal HD mutation, may be nonmanifest when their child starts showing symptoms. Late onset patients' initial signs may be motor (e.g. chorea) with more gait unsteadiness than earlier onset age phenotypes; dementia is often of mixed pathology in some cohorts which can confound clinical diagnosis [8]. The availability of confirmatory genetic testing allows recognition of various phenotypic variants and facilitates appropriate genetic counseling [72]. While genetic testing can confirm a clinical diagnosis, the level of variability in outcomes for each CAG length blunts the individual prognostic value of the CAG length itself.

Genetic testing including IA results may play a bigger role in the diagnosis of very late onset HD diagnosis compared to midlife onset HD. While the impact of IAs is still an active area of investigation, their relatively high estimated population frequencies make them relevant to diagnosis of late onset chorea or even unexplained HD-like dementia. Consideration of mixed dementia diagnoses particularly in older cases will become more important when pathologic protein and/or mutation-specific disease modifying therapeutics come on line [73].

Individuals with an HD-like phenotype but negative *HTT* genetic test results are considered HD phenocopies (Table 1). A wide range of potentially reversible non-genetic causes are in this differential, including infectious, cerebrovascular, metabolic, medication-induced, and even functional (psychogenic) etiologies [74–76]. In children, the most common cause of chorea is the post-infectious entity Syndenham chorea. Genetic causes of non-HD phenocopies are individually rare but collectively relatively common [74,75,77,78]; in one cohort they made up 12.4% of cases seeking confirmatory HD genetic testing [79]. The current most common cause of an HD-like phenocopy in adults is the recently described *C9ORF72* expanded intronic hexanucleotide repeat mutation [80,81], thought to account for nearly 2% of all HD-like cases [74,75].

4.1.1. Juvenile onset Huntington disease

Juvenile onset HD (JHD), also referred to as the Westphal variant after the German psychiatrist who drew attention to this form of HD, has long been recognized as a unique phenotype. Juvenile onset (less than 21 years) constitutes about 5.4% of HD overall, up to 10% in some populations [7,82]. Most JHD cases have large expansions of 60 to 100 CAGs. As large CAG repeat expansions are more common but not exclusive to paternal transmission, most (70-90%) inherit HD from a mutation-carrying father. Juvenile cases can present with prominent ataxia, parkinsonism or rigidity-dystonia and little or no chorea [64,83]. Myoclonus is more common than chorea [7], and motor tics are much more prevalent than in the adult onset population [84]. Dominant JHD nonmotor features also differ from adult onset HD (see below). Seizures, not thought to be associated with adult onset HD, are a feature in roughly 40% of JHD cases, particularly very young onset patients [83].

Given the prominence of cognitive decline and behavioral changes as JHD presenting features [7,64,83] and the potential harm in long delayed JHD diagnoses, alternative JHD diagnosis criteria such as cognitive decline, seizures, or even severe persistent psychiatric disease especially in the setting of a high CAG repeat mutation is advocated by some in the field [7,64]. Advocates emphasize the diagnostic nature of such genetic testing for specific issues like loss of milestones. However, a relatively low HD causal expansion is difficult to interpret in JHD diagnosis with atypical features or mild nonspecific non-motor symptoms.

4.1.2. Preclinical stages

Multiple longitudinal observational studies report symptoms, mild motor signs, and brain imaging changes well before motor diagnosis [9,67]. The availability of HD genetic testing provides an opportunity to identify and potentially treat mutation carriers long before outward symptoms. Consensus terms for preclinical (nonmanifest and prodromal) HD states remain under development [85]. This review uses nonmanifest for outwardly asymptomatic stages, prodromal for minimally outwardly symptomatic and/or with mild exam signs not at the level of a clinical diagnosis, and manifest or motor symptomatic.

Mild motor signs such as increased motor restlessness that is not frank chorea, oculomotor defects, and slowed or dysrhythmic repetitive movements may precede motor diagnosis by several years (86-91). Prominent mood, thought, or personality disorders or mild cognitive impairment (MCI) can also present years prior to definitive motor signs (67, 92). This is also the case in JHD (7). Comorbid depression may contribute to poor cognitive performance (93). Serotonergic antidepressants use is higher in mutation carriers compared with controls, particularly as HD mutation carriers approach their motor clinical diagnosis (94). The earliest cognitive indicator of adult onset HD is emotional recognition, sometimes detected > 15 years prior to predicted motor diagnosis (65, 95). Mild changes in processing speed and other impairments may be fairly common in the decade or more prior to motor diagnosis: one study estimated MCI in almost 40% of HD mutations carriers (96). Changes in motor planning/speed and sensory-perceptual processing may predict time to motor diagnosis (97). Cognitive changes and MCI appear at higher rates in populations closer to predicted motor diagnosis (96). One study observed significantly worse performance scores than controls on nearly all cognitive tests for HD mutation carriers estimated to be less than 9 years from motor clinical diagnosis, whereas HD mutation carriers estimated 9 to 15 years to motor clinical diagnosis had worse than controls performance on about half the cognitive tests (98).

The fluid, gradually progressive nature of HD in preclinical stages combined with the potential burden of cognitive and psychiatric features complicates the timing of clinical diagnosis and genetic testing. Predictive genetic testing, as discussed below, may provide an opportunity for mutation carriers and their families to best understand and grapple with evolving symptoms years prior to frank motor signs, deal

Table 1
Huntington disease phenocopies [71–78]. Nomenclature from the 2016 International Parkinson and Movement Disorder Society Task Force for Nomenclature of Genetic Movement Disorders consensus recommendations [74].

Monogenetic disorders	
Autosomal dominant	
Repeat expansion mutations	
C9ORF72 associated movement disorders	Wide phenotype range includes motor neuron disease, frontotemporal dementia, other movement disorders
HDL2 / CHOR-*JPH3*	Families with African ancestry
Spinocerebellar ataxias (SCAs):	Choreic and bradykinetic-rigid forms
SCA1 / SCA-*ATXN1*	
SCA2 / SCA-*ATXN2*	
SCA3 / Machado-Joseph disease/SCA-*ATXN3*	Most common of this group
SCA17 / HDL4 / SCA-*TBP*	
DRPLA / SCA-*ATN1*	More common with Japanese ancestry
Large insertion	
HDL1 familial prion disease/CHOR-*PRNP*	Extremely rare
Other mutation types	
Neuroferritinopathy / NBIA3/NBIA/CHOR-*FTL*	
ADC5Y associated movement disorder / CHOR/DYT-*ADC5Y*	
PDE10 associated autosomal dominant pediatric onset chorea	
GNAO1 associated movement disorders	Phenotypes also include epilepsies
FOXG1 associated disorders	Pediatric onset; most de novo mutations
Fahr's disease/iBGC	Highly heterogeneous mixed movement disorders
GLUT1 deficiency / PxMD-*SLC2A1*	Phenotypes include paroxysmal disorder
Isolated benign familial chorea/CHOR-*NKX2*-1	Pediatric onset; More common phenotypes Brain-lung-thyroid syndrome, Brain and thyroid disease
Autosomal recessive	
Homozygous repeat expansion	
Friedreich's ataxia	Pediatric > adult onset
Other mutation types	
Other autosomal recessive ataxias:	
Ataxia-telangiectasia	Pediatric > adult onset
AOA1, AOA2	Pediatric onset
ChAc / Neuroacanthocytosis/CHOR-*VPS13A*	
PDE10 associated autosomal recessive pediatric onset chorea	
GPR88 associated pediatric onset movement disorders with developmental delay	
Brain iron accumulation related disorders:	
Aceruloplasminemia/NBIA/DYT/PARK-*CP*	
PKAN/NBIA/DYT-*PANK2*	
NBIA/DYT-*DCAF17*	
Autosomal recessive dystonias:	Pediatric onset, inborn errors of metabolism, may be part of infant screening panels
Glutaric aciduria type 1/DYT/CHOR-*GCDH*	
Methylmalonic aciduria/DYT/CHOR-*MUT*	
Propionic aciduria/DYT/CHOR-*PCCA/PCCB*	
Mitochondrial acetoacetyl-CoA thiolase deficiency / DYT/CHOR-*ACAT1*	
Methylglutaconic aciduria 3 / Costeff syndrome	Pediatric onset, Iraqi-Jewish descent
Phenylketonuria	Treatable with strict diet, chorea unusual; pediatric onset, in US part of newborn screening
Wilson disease/DYT-*ATP7B*	Treatable, chorea unusual; pediatric or adult onset
X-linked disorders	
McLeod neuroacanthocytosis syndrome / CHOR-*XK*	
Lesch-Nyhan syndrome / DYT/CHOR-*HPRT*	
Mitochondrial disorders	
Leigh's syndrome	
Sporadic disorders	
Stroke/cerebrovascular (hemichorea), Cerebral palsy, Static encephalopathy	
Functional (psychogenic) movement disorders	
Infectious or post-infectious	
Sydenham chorea - Most common pediatric Huntington disease phenocopy	
Sporadic CJD and new variant CJD	
HIV / AIDS	
Autoimmune	
Polycythemia vera (may be highly asymmetric)	
Celiac disease, Systemic lupus erythematosus, Sjögren's syndrome	
Antiphospholipid antibody syndrome	
Paraneoplastic disorders / encephalitis	
Metabolic disorders	
Nonketotic hyperglycemia (often hemichorea)	
Hypoglycemia, Hyperthyroidism, Renal failure, Hepatolenticular degeneration	
Iatrogenic/treatment related	
Ketogenic diet, Tardive syndromes	

AOAn ataxia with oculomotor apraxia type n; ChAc Chorea-acanthocytosis; CJD Creutzfeldt-Jakob disease; DRPLA Dentatorubropallidoluysian atrophy; GLUT1 glucose transporter type 1; HDL Huntington disease-like; iBGC idiopathic basal ganglia calcification; NBIA neurodegeneration with brain iron accumulation; PKAN Pantothenate kinase-associated neurodegeneration iron accumulation; SCA spinocerebellar ataxia

with changes in "at risk" status, and consider early clinical trial participation. Conversely, individuals and larger cultures may be more accepting of delaying genetic status information for an incurable disorder, even if subtle suggestive features are starting to accumulate [99].

4.1.3. Predictive genetic testing

Nonmanifest individuals or people with possible or mild signs and symptoms can obtain predictive genetic testing after appropriated genetic counseling [72,100]. The term "at risk" is used in the HD community to indicate a person with unknown genetic status and an affected relative. The risk level depends on the family relationship; for example, grandchildren of an HD patient are each at 25% at risk of inheriting the HD causal mutation. "At risk" can also indicate risk to develop disease rather than risk to inherit a mutation: for HTT CAG repeats over 39, the lifetime HD risk level is 100%, for reduced penetrance CAG repeat lengths the risk level is lower. This discussion matches current common usage of at risk as unknown genetic status. Similarly, "presymptomatic" and "predictive" are both used to describe genetic testing in nonmanifest or prodromal individuals, with "predictive" more common in genetic testing protocols. Predictive genetic testing of juveniles under age 18 is not recommended except in rare circumstances [100].

Reasons for predictive testing are highly individual [101]. In a 2007 study, worldwide uptake of predictive genetic testing averaged about 10-20% of at-risk individuals [102]. Many at risk individuals only consider testing once symptomatic [101]. This is likely to change as more potential disease modifying interventions are tested in clinical trials or become available. In one study cohort, women who were at risk to inherit an HD mutation from a mother were the most likely to undergo testing [103]. Subsequent studies observe a higher uptake of predictive genetic testing in women versus men, and in offspring of affected mothers versus fathers, but the underlying reasons for these differences in predictive genetic testing rates remain unclear [104].

Predictive genetic testing for the HD causal mutation is a complex procedure with medical, psychological, ethical, and financial implications for the person tested, their partner, and relatives. Social attitudes towards genetic disorders and genetic information shift over time, and legal protections against genetic discrimination also change. Referral to an experienced genetic counselor is strongly recommended before formal testing. In some cohorts reducing uncertainty is more frequently cited than reproductive decision making as the main reason for undergoing predictive genetic testing [103,105]. Ascertaining individual goals for testing and discussing whether or not learning HTT CAG repeat lengths will address those goals is critical. Pre-test discussion of the full range of potential genetic results and their known implications, including reduced penetrance and intermediate alleles, is warranted. International guidelines are available (e.g. from hdsainfo@hdsa.org), and are very helpful in structuring individualized approaches [102]. In person post-test results discussion, regardless of the result, is strongly recommended. Mutation negative individuals can have poor and even serious post-test reactions, emphasizing the importance of in-person results disclosure for all patients [103,106]. The HD predictive testing approach provides maximum actionable information to at risk people, and multiple points for decision changes. One prospective study tracked one year plus outcomes in people undergoing at least one step in an HD predictive testing protocol [104]. Initially 79% of participants expressed clear interest in genetic testing, but only 61% went forward with testing; one patient never returned for genetic testing results during a 4-year followup period [104]. Telehealth options may eventually decrease travel burden for the "in person" visits; currently there are very few data on positive or negative impacts of converting pre- or post-test visits to telehealth platforms. The HD predictive testing approach has been adopted in other adult-onset disorders [107].

sons for these differences in predictive genetic testing rates remain unclear [104]. Predictive genetic testing for the HD causal mutation is a complex procedure with medical, psychological, ethical, and financial implications for the person tested, their partner, and relatives. Social attitudes towards genetic disorders and genetic information shift over time, and legal protections against genetic discrimination also change. Referral to an experienced genetic counselor is strongly recommendedcial media, widespread genetic testing for other disorders, and gene modifying therapeutics. Still, longitudinal studies provide insights into potential predictors of adverse reactions to predictive genetic testing. Hopelessness and depressive symptoms were more commorning *HTT* CAG repeat lengths will address those goals is critical. Pre-test discussion of the full range of potential genetic results and their known implications, including reduced penetrance and intermediate alleles, is warranted. International guidelines are available (e.g. from hdsainfo@hdsa.org), and are very helpful in structuring individualized approaches [102]. In person post-test results discussion, regardless of the result, is strongly recommended. Mutation negative individuals can have poor and even serious post-test reactions, emphasizing the importance of in-person results disclosure for all patients [103,106]. The HD predictive testing approach provides maximum actionable information to at risk people, and multiple points for decision changes. One prospective study tracked one year plus outcomes in people undergoing at least one step in an HD predictive testing protocol [104]. Initially 79% of participants expressed clear interest in genetic testing, but only 61% went forward with testing; one patient never returned for genetic testing results during a 4-year followup period [104]. Telehealth options may eventually decrease travel burden for the "in person" visits; currently there are very few data on positive or negative impacts of converting pre- or post-test visits to telehealth platforms. The HD predictive testing approach has been adopted in other adult-onset disorders [107].

Use of this cautious individualized approach is associated with few adverse events [103,105,106,108]. However, in one study mutation carriers who had more intrusive thoughts, avoidance reactions, low self esteem and worse sense of well-being at the pre-test visit were more likely to be lost to follow-up after receiving predictive testing results, implying a possible systematic underestimation of adverse events [108]. This and most other similar studies were conducted well before the age of social media, widespread genetic testing for other disorders, and gene modifying therapeutics. Still, longitudinal studies provide insights into potential predictors of adverse reactions to predictive genetic testing. Hopelessness and depressive symptoms were more common up to 5 years post-test in mutation carriers with no children, married at time of genetic testing, and who were close to their estimated age of motor onset [108,109]. Feelings of hopelessness decreased after an initial spike, but then rose again 7 to 10 years post test [108]. In another study, major depression prevalence one year after predictive testing was 6% in mutation carriers versus 3% in mutation negative individuals [110]. Just as all mutation negative individuals do not have a uniformly rosy reaction to testing results, mutation carriers have a wide mix of individual outcomes. In one cohort knowledge of predictive genetic testing results played both motivating and obstructive roles in decisions regarding further education, career, or personal health five years after testing [111].

5. Clinical features

5.1. Motor signs and symptoms

HD was originally termed "Huntington's chorea" highlighting the most typical motor sign, but the term Huntington disease is more appropriate as it acknowledges other motor and non-motor features as well as non-choreic presentations [3]. Although chorea, derived from the Greek word meaning "to dance", is the most characteristic involuntary movement in HD, other hyperkinetic movements particularly dystonia as well as myoclonus and tics may be present, along with other motor manifestations including bradykinesia, incoordination, alterations in oculomotor function, and gait impairment, all of which

contribute to progressive physical disability [87,112]. Motor impersistence, manifested for example by inability to maintain tongue protrusion or a hand grip, may be a manifestation of chorea and frontal cortical dysfunction. In adult onset cases, generally chorea and dystonia co-occur with and may mask underlying bradykinesia and other motor signs [113]. Over time as the disease advances, chorea tends to lessen and be replaced by more dystonia and rigidity. Some adult onset patients have a purely bradykinetic rigid phenotype (Westphal variant), more commonly observed in JHD.

5.2. Non-motor features: cognition and neuropsychiatric symptoms

Along with motor signs, cognitive and neuropsychiatric features form the core HD phenotype triad. Cognitive and behavioral features may generate the greatest burden on families and are most strongly associated with functional decline [64,65,95]. During the natural course of the disease these non-motor features may precede or occur after the emergence of motor symptoms and signs, and can interact with each other to increase overall symptomatic disease burden.

Cognitive symptoms are progressive, generally impacting executive functions, attention, visuospatial and cognitive processing speed, over time invariably leading to dementia. Impaired problem solving, poor organizational skills, cognitive slowing, apathy, and construction deficits all impact day to day functioning. Language and memory are impacted, but, in contrast to Alzheimer disease, these areas are relatively preserved and usually decline more slowly than other domains [114,115]. The latest American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders (DSM-5) refers to "dementia" as "major neurocognitive disorder" [116]. In HD as in other disorders the terms are interchangeable. "Major cognitive disorder" in HD may help with acceptance of the condition in younger patients, and dispel confusion for example when there is dementia but relatively good memory. The DSM-5 details six cognitive domains: decline in one or more must be impacted enough to interfere with independence in daily life [116,117]. In contrast "mild cognitive disorder" describes cognitive decline that may impact effort level or ways of completing tasks but do not impact independence [116,117]. In HD, a neurodegenerative disorder, mild cognitive disorder progresses over time to major cognitive disorder i.e. dementia. Predicting individual cognitive symptom areas, onset, and progression rate in HD is very difficult. A primarily choreic rather than bradykinetic-rigid motor phenotype picture may be associated with better cognitive functioning [70,118]. In prodromal and early motor manifest HD, variable executive dysfunction, sensory-perceptual processing, motor planning, memory and concentration changes are well reported [97,119,120].

The combination of frontal and subcortical dysfunction in HD has been implicated in disinhibition, impulsivity, and apathy [65]. Apathy and executive dysfunction are particularly common in HD, and may occur very early [67]. In the European Registry cohort study, apathy was the most common UHDRS Behavioral Scale neuropsychiatric symptom, and had the strongest inverse correlation with the UHDRS TFC score [121]. Cognitive and psychiatric symptoms frequently interact. For example, cognition in HD can be impacted by comorbid depression [93]. A key area of interaction is between frontal and subcortical dysfunction and psychiatric symptoms, increasing risk of suicidality.

Suicidality prevalence is as high as 20% in both preclinical and motor manifest mutation carriers [122]. Depression, anxiety, irritability, alcohol and drug abuse may all be predictors of suicidal ideation (SI) [123]. In one study of 801 subjects at risk for HD (unknown mutation status), 40 expressed SI, comprising 6.3% of those with and 4.3% of those without a CAG expansion mutation. The SI group, including both mutation and non-mutation carriers, had significantly increased depression, hopelessness, irritability, aggression, and anxiety and an elevated motor score [124]. In addition, impulsivity, assessed in a subgroup of subjects, was significantly associated with SI. In another study of 4,171 individuals, SI in at-risk persons increased from 9.1% in those with normal UHDRS motor exams to 19.8% in those with non-specific signs and 23.5% in those with possible HD (DCL 2, or 50-80% confidence) [125]. In patients with diagnosed HD, the risk of SI initially decreased to 16.7% at stage 1 (early), then increased to 21.6% at stage 2 and 19.5% in stage 3, decreasing thereafter to 14.1%, and 9.8% in stages 4 and 5, respectively [125]. Thus the most critical period of suicide risk in at risk persons is immediately before receiving a formal HD diagnosis, with potential alleviation of SI post diagnosis. The next key SI risk period is in manifest HD when independence level decreases. This highlights the importance of assessing for and treating SI in all HD related populations (see Treatment and Clinical Care below).

Psychiatric disorders include depression, anxiety, labile mood, irritability and/or anger outbursts, obsessive behavior, rigidity of thought, and delusions [121]. There is high inter- and intra-patient variability of psychiatric symptoms in HD. In a Registry study, lifetime behavioral symptoms were common, with severe psychiatric symptoms in about 20% of individuals [126]; however, a subsequent analysis of the same cohort found 27% of 1,993 mutation carriers had no neuropsychiatric symptoms in the prior month [121]. Psychosis, while serious, is less common than other psychiatric conditions in adult onset HD [121,126]; one JHD caregiver survey reported a 39% prevalence of psychosis [84]. Irritability may occur very early [67], while other common symptoms such as obsessions and compulsions may be biased to motor manifest HD stages [127]. Irritability may be associated with depression, a very common issue in HD; however irritability, agitation, and vegetative symptoms impacting sleep and appetite appear to be poor discriminators for depression in HD [128]. Depression may be a key determinant of health-related quality of life [129] and caregiver burden in HD [130].

5.3. Non-motor features: sleep, dysautonomia, metabolic changes

Changes in sleep and circadian rhythms are also common in HD [84,131]. Sleep disturbances can be associated with mood disturbances and impaired cognition [132,133], although in one study subjective sleep complaints did not correlate with cognitive measures [133]. Restless sleep, frequent and too-early awakening, and insomnia are all reported. Increased motor activity in non-rapid eye movement sleep stages has been observed [134].

In addition to central nervous system based motor and non-motor features there is growing appreciation for symptoms related to the peripheral and autonomic nervous systems as well as widespread metabolic effects, given the expression of HTT throughout the body [135–137]. Autonomic dysfunction is reported in adult onset HD as well as in JHD [138]. Male sexual dysfunction may be under-recognized and progressive [139]. Profuse sweating and heat intolerance can be prominent particularly in younger onset groups. Impaired gluconeogenesis [140] and impaired cholesterol homeostasis [141] have been described in HD.

Progressive weight loss is nearly universal in HD patients [136]. Weight loss in HD was initially thought to be driven by hyperkinetic movements and dysphagia. This perspective changed with the availability of genetic testing. Mutation carriers may generate increased caloric requirements even in very early prodromal or nonmanifest stages, suggesting increased energy expenditure [142,143]. Weight loss in HD is now considered a multifactorial problem driven in part by a hypermetabolic state intrinsic to HD [17]. In one study high baseline body mass index (BMI) was associated with a significantly slower rate of functional, motor, and cognitive deterioration, independent of mutant *HTT* CAG repeat size [136]. In another study growth charts of JHD children indicated normal height but significantly decreased weight and BMI well prior to HD motor signs [144]. Differences in growth, and lower weight, BMI, and head circumference are reported in children with expanded CAG repeats and no motor signs versus controls [144].

5.4. Impact on functional outcomes

Core HD features interact to create common and disabling functional changes that impact quality of life. A prospective study of mutation carriers observed that accustomed work and financial capacity were the earliest functional outcomes to decline [145]. Addressing patient centered symptomatic concerns often requires a multifaceted approach targeting several symptomatic contributors. Dysphagia may be a primarily motor symptom, primarily cognitive behavioral with impulsive rapid intake or distractibility, or a functional consequence of multiple impairments. Driving can be affected by several areas: impaired oculomotor control (poor tracking of other vehicles), motor impersistence (difficulty keeping foot on the brake or accelerator at a fixed position), impaired visuospatial processing (clipping fixed objects), and executive dysfunction (difficultly planning a route or adjusting to detours) are some examples. Cognitive performance appears to be strongly associated with driving status [146].

Falls are common: up to 50% of HD patients fall more than twice a year [147,148]. Postural motor deficits in HD patients compared with controls correlate with UHDRS Total Motor Score, UHDRS TFC, UHDRS Functional Assessment Score, and the disease burden score [149]. The intrinsic HD gait disorder [150,151], which may be detected up to 5 years before predicted motor diagnosis [152], is one of several factors contributing to falls. In one HD study, falls occurred more commonly in patients with higher levels of chorea, bradykinesia, and aggression, and lower cognitive scores [153]. In addition, fallers had increased stride length variability and a significantly greater mediolateral trunk sway. Motor-cognitive dual task measures may be particularly useful in predicting fall rates and tracking HD progression [148], emphasizing the multifactorial nature of falls in HD.

6. Treatment and Clinical Care

There is currently no known intervention or drug therapy with demonstrated disease-modifying effects in HD. While exercise has been reported to beneficial for both motor-based and cognitive symptoms in neurodegenerative disorders, there is paucity of evidence-based data to support any neuroprotective effects in HD or HD animal models. A study of Dance Dance Revolution video game play found this intervention to be motivating, and observed improvements in walking balance [154]. Endurance training in a small open-label study stabilized HD motor deficits and observed significantly increased peak oxygen intake in HD and control groups [155]. Similarly, non-medication cognitive interventions may have measurable impact on both symptoms and brain structure in non-HD neurodegenerative disorders [156], and may also delay cognitive decline in HD [157]. For nonmanifest individuals, general positive “brain health” tactics such as exercise, stress management, adequate quality sleep, Mediterranean or similar diet, and social engagement can be productive if non-specific care areas.

Lifestyle modification recommendations in both nonmanifest and manifest HD populations remain non-specific as there are so far no clear known environmental risk modifiers for HD onset or progression. There are some data on HD onset risks from the PHAROS cohort, all at-risk individuals blind to their own HD mutation status and nonmanifest at enrollment. One study reported no clear impact of Mediterranean diet on timing of motor-based HD clinical diagnosis, although increased dairy and increased overall caloric intake were associated with increased risk to convert to motor manifest clinical diagnosis [158]. A recent analysis of PHAROS data on lifelong use of caffeine, tobacco products, alcohol, and common medications including nonsteroidal anti-inflammatory drugs observed an association between high caffeinated soda use and increased risk (hazard ratio) of HD motor clinical diagnosis [159]. This association was not observed with other caffeinated beverages; it is not clear if the observation is related to caffeine or something else, or if it will hold up in other cohort analyses [159].

Multiple clinical trials designed to evaluate potential disease-modifying interventions such as CoQ10 (2CARE) [160] and creatine (CREST-E) [161] in manifest HD were terminated for lack of benefit based on interim analyses. These are discussed under the next section. For current clinical care, there are no data to support continued over the counter use of vitamins or supplements such as CoQ10 in any HD stage.

General preventive care is essential to maximize quality of the many years of both preclinical and manifest HD: primary care and dental providers are therefore key care team members. Acute and poorly controlled chronic medical issues can have an outsized impact on HD clinical status, worsening cognition, mood, involuntary movement control, and balance. Conversely, abrupt changes in clinical status are often indications of unrelated medical issues, mandating thorough medical assessments. Given the progressive neurodegenerative nature of HD, an individuals’ symptoms and even symptom categories will shift over time, mandating regular review and adjustment of individually tailored treatment plans.

6.1. The interdisciplinary approach

Remarkable progress is being made in HD symptomatic treatment, which can have a significant positive impact for patients and families. Interventions targeted at one area may have positive impacts in other domains, general functional level, and quality of life. An interdisciplinary approach, including ancillary services, (physical therapy (PT), occupational therapy (OT), speech language pathology (SLP)), nutrition services, pharmacy, medical assist device experts as well as neurology, psychiatry, and psychology is invaluable in HD care [9]. Interdisciplinary evaluations targeting key functional, life quality, and safety concerns are relevant across all HD stages. OT and neuropsychology evaluations can help map out paths to continued work independence, and decision making around shifting types of work or considering disability. OT driving assessments can identify potential areas of safe driving and help plan ahead of change to maintain control of transportation decisions. SLP input on both communication and dysphagia treatment is strongly recommended during the full HD symptom severity range. Further examples of this approach are given throughout this section.

While the importance of the interdisciplinary care team is widely recognized, data on specific uses and impact of these modalities are scarce. HD patients are able to participate in PT based interventions: in a randomized controlled feasibility trial 82% of participants met minimum adherence criteria in the physical activity coaching intervention arm compared to 100% in the social interaction arm [162]. Both arms had excellent retention rates, highlighting the possibility of HD patient self-management of physical activity and tractable PT intervention study designs.

The vast majority of HD patients receive care outside of specialized HD centers. The idealized team-based care emphasized here is often not directly available, even at specialized centers: a survey of 121 Enroll-HD site clinics found less than half with ancillary services or a dietician [163]. A goal of this review is to widen the range of interventions considered by providers regardless of specialty or clinic size. Many HD specialty centers are happy to communicate with other clinics to help design feasible care strategies. Free on-line materials can be helpful to community providers without prior HD experience or nearby colleagues (e.g.https://huntingtonstudygroup.org/care-education-videos/). Non-profit community organizations continue to grow free databases of care resources (e.g.https://www.hdgem.org/).

6.2. Treatment of motor symptoms

Chorea is a motor sign with highly variable symptomatic impact. Different patients may experience very similar levels of chorea as a noticeable bothersome symptom, or as something they are mostly unaware of themselves, whether or not it is significantly impacting

function. Symptomatic treatment of chorea is an important consideration in HD, from both functional and quality of life perspectives [153,164–166], although this must be balanced against risk of potential side effects, likelihood of benefit, and other symptoms and comorbidities [74]. Traditionally, dopamine receptor blockers such as haloperidol and risperidone have been used to treat chorea but these neuroleptics have a variety of serious side effects including weight gain, metabolic syndrome, drowsiness, parkinsonism and tardive dyskinesia [167]. They still have a role particularly when psychotic symptoms are also present. Data on actual efficacy are very scarce [168]. In a study of six HD patients, aripiprazole was comparably effective and better tolerated than tetrabenazine for chorea [169]. High dose olanzapine was associated with improved motor scores in a prospective open-label study [170].

The first drug approved by the FDA for an HD-specific indication, the type 2 vesicular monoamine transporter (VMAT2) inhibitor tetrabenazine, is for chorea [171]. This VMAT2 inhibitor has the advantage over the dopamine blocking drugs in that it does not cause tardive dyskinesia [167,172,173]. In the pivotal clinical trial, TETRA-HD, tetrabenazine effectively lessened chorea as measured by the UHDRS total maximal chorea score, which was reduced by 5 points in the tetrabenazine arm and by 1.5 points in the placebo arm, a -3.5 unit difference ($p < 0.0001$) [171]. The clinical global improvement scores showed 45% of participants in active treatment were much or very much improved as compared to only 7% in the placebo group. Adverse events included sedation, insomnia, fatigue, depression, and restlessness. One patient in the tetrabenazine arm committed suicide, prompting a black box warning about suicidality. A recent analysis of Enroll-HD observational study data HD patients did not observe an increased rate of depression or suicidality in over 3500 patients using tetrabenazine compared to over 500 not taking this medication [174]. Tetrabenazine use was actually associated with a lower incidence of depression and suicidal ideation in patients with a history of prior depression [174]. The findings suggest tetrabenazine and other VMAT2 inhibitors can be used successfully in HD without worsening suicidality risk. All HD patients should be regularly assessed for depression and suicidality as discussed below.

Another VMAT2 inhibitor, deutetrabenazine, has recently been approved by the FDA for treatment of chorea in HD [167,172]. This novel compound contains deuterium instead of hydrogen at key points in the tetrabenazine molecule, strengthening those carbon-deuterium bonds compared to carbon-hydrogen, thus creating longer plasma half-life and lower risk of side effects, particularly sedation. In the pivotal study, First-HD, deutetrabenazine effectively lessened chorea with a -2.5 unit difference between deutetrabenazine and placebo groups ($p < 0.001$) [175]. There was also a significant beneficial effect on both patient global impression of change (PGIC) and clinician global impression of change (CGIC) measured as those reporting much or very much improved in overall HD (see below). Deutetrabenazine also has an FDA indication for tardive dyskinesia. Valbenazine, also approved for the treatment of tardive dyskinesia, is a prodrug of the tetrabenazine (+)-alpha isomer and has the longest half-life among current VMAT2 inhibitors, but is not under current consideration for FDA approval in HD treatment. Cautious dose titration of all of these VMAT2 inhibitors regardless of *CYP2D6* allelic status is recommended, which may obviate the clinical need for costly genetic testing [176,177].

American Academy of Neurology evidence-based guidelines recommended tetrabenazine, amantadine, or riluzole (Level B) for varying degrees of expected benefit on HD chorea [164]. However, these guidelines are based on arbitrarily chosen UHDRS anchors of unclear clinical relevance, and are not fully consistent with expert clinical opinion and experience [168,176]. The use of riluzole is particularly controversial, as is amantadine as a “first-line” agent [178]. In a randomized trial, amantadine had no significant effect on the mean chorea score compared to placebo, although most patients felt subjectively better [179]. In a multicenter, placebo-controlled trial, riluzole decreased the intensity of chorea without improving functional capacity, and caused reversible liver transaminase abnormalities that require long-term monitoring [180]. Another randomized controlled trial did not demonstrate a change in UHDRS chorea scores after 3 years of riluzole treatment [181]. Conversely, many clinicians continue to use non-VMAT2 inhibitors such as antipsychotics for chorea control, despite very limited published data (168). Based on Cochrane analysis of 22 controlled trials (1,254 subjects), duration of treatment ranging from 2 to 80 weeks, only tetrabenazine showed a clear efficacy for the control of chorea [182], yet use of antipsychotics in particular persists [168], in part due to the enormous differences in cost between VMAT2 inhibitors and antipsychotics in many regions. Overall, in the absence of strong clinical data, expert opinion-based recommendations may provide more practical guidance than strict evidence-based reviews [74,167].

Dystonia and rigidity may impact function, become uncomfortable or in later stages interfere with hygiene and general care. Tetrabenazine may positively impact dynamic forms of dystonia [175]. In addition to systemic medications such as baclofen or benzodiazepines, focal dystonia can be treated with local injections of botulinum toxin. Compounded topical medications including baclofen, lidocaine, and nonsteroidal anti-inflammatories may also be helpful. Levodopa may be used to relieve bradykinesia and rigidity, particularly when these are predominant motor features. PT and OT interventions such as modified seating, weighted assist devices, and environmental modifications can promote both safety and comfort in the context of significant abnormal movements, and prevention of contractures in significant rigidity and dystonia.

Addressing and preventing falls ideally begins well before any falls occur. The Tinetti Mobility Test and the Four Square Step Test may be useful balance and fall risk assessment tools in ambulatory motor manifest HD patients [183]. Improvement in gait after PT has been reported [184]. HD patients may be able to adjust trunk position using auditory cues, enabling compensation when seated or walking [185].

6.3. Treatment of cognitive and neuropsychiatric symptoms

Formal neuropsychology evaluation is recommended prior to initiating therapies if feasible. Neuropsychologists can generate specific treatment recommendations and interact with other care team members such as psychiatry and OT to coordinate care. Cognitive symptom progression can be tracked with screening tools and validated tests particularly Symbol Digit, Circle Tracing direct and indirect, and Stroop word reading [186,187], and an HD specific cognitive battery [68]. Although HD-specific data are scarce, the available symptomatic treatment of cognitive and behavioral symptoms associated with other neurological disorders such as Alzheimer’s disease may have utility in HD-related symptoms [188–190].

Cognitive and psychiatric symptoms can impact acceptance and implementation of plans of care across symptomatic domains. Anosognosia, the unawareness of clinical deficits, can have a particular negative impact as the patient cannot see a purpose to intervening on an issue they themselves do not recognize, even as it causes significant functional deficits and distress or even danger to others [173,191]. This lack of acceptance can extend to the clinical diagnosis of HD itself [99]. Anosognosia also impacts clinicians’ ability to assess the breadth and impact of symptoms, especially when caregiver input is unavailable. An analysis of PREDICT-HD participant and companion reported data observed significant longitudinal increases in 19 of 24 psychiatric measures from baseline in mutation carriers compared to controls, with the greatest differences in caregiver provided symptom reports [192]. The relatively greater caregiver reporting was magnified when participants were closest to time of motor clinical diagnosis [192]. This common feature of HD may be rooted in executive dysfunction, with further psychological contributions from strategies used to cope with progressive symptoms and gradually decreasing independence [191].

Clinical interview and patient-centered outcome approaches that focus on the general consequences of clinical signs and symptoms may help overcome anosognosia [191]. For example, despite the well-known frequency of unawareness of involuntary movements, in the deutetrabenazine anti-chorea pivotal trial discussed above the patient-reported PGIC reflected a greater beneficial impact than the clinician-reported CGIC: PGIC was much or very much improved in 51% of the deutetrabenazine group versus 20% of placebo, while CGIC was much or very much improved in 42% of the deutetrabenazine group versus 13% of placebo.

Psychiatric symptoms are often both disabling and treatable. Early identification and treatment are becoming increasingly important in both manifest, at risk, and mutation carrier populations. Specifically querying especially for classically underreported symptoms is a necessary first step in care. For example, irritability and emotional dyscontrol are often underreported but especially corrosive to home and social environments. Irritability and aggression may be predictors of SI [123]. Screening tools such as the depression subscale of the Hospital Anxiety and Depression Scale and the Depression Intensity Scale Circles may be helpful in HD [193] but suicidality can be present without clear signals on screeners [171]. Thus effectively querying for suicidality even in the absence of classic depressive symptoms is important. One study found two critical periods for increased suicide risk in HD: just before receiving a formal diagnosis, and when independence decreases [125].

Although HD specific data are scarce, the relative wealth of available symptomatic interventions makes this a key area of opportunity for clinical care [188]. Standard medication classes, such as selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants (TCAs) for depressive symptoms, are all applicable. Obsessive ideation, a common issue, may respond to SSRIs or clomipramine. Mood stabilizers such as lamotrigine, valproate, or carbamazepine are used in HD treatment. Medications as varied as valproate, aripiprazole, and antidepressants may be effective for irritability and aggression in HD. Psychotic symptoms often respond to neuroleptics, although isolated fixed delusions may be especially intractable. Behavioral modification, counseling, and other non-medication interventions can be effective, particularly for early manifest and prodromal populations. Caregiver behavioral modification and environmental adjustments can help ease symptoms such as anxiety or apathy that may have a cognitive component. Electroconvulsive therapy can be useful for intractable depression; impact on psychotic symptoms varies in case reports [194,195].

Consideration of psychiatric treatment impact on movement systems is necessary. Neuroleptics also decrease chorea, but potentially at the expense of overall functional level. Low doses of neuroleptics are often well-tolerated, whereas high doses of any but clozapine may impair significantly impair motor as well as cognitive function. Valproate, an excellent mood stabilizer, and most neuroleptics can cause parkinsonism, and thus may worsen bradykinesia and voluntary movement impairments. Benzodiazepines may negatively impact balance.

All neuroactive medications, particularly benzodiazepines, neuroleptics, and medications with some anticholinergic impact (example: TCAs) can have outsized cognitive impact and should be started at a very low dose, titrated up gradually, and tapered off when no longer necessary.

Given its impact on cognitive and psychiatric symptoms, recognition and modification of disrupted sleep is important in overall HD care. Identification and treatment of non-HD entities such as obstructive sleep apnea is recommended. Basic good sleep hygiene practices can make a positive impact in both nonmanifest and manifest populations. Melatonin is recommended before prescription sleep aides to reduce side effect burden and potential dependency. Use of sedating antidepressants such as trazodone, mirtazapine or TCAs can help modify sleep disturbances and treat mood symptoms. Bedtime medications to reduce chorea can improve insomnia secondary to the chorea itself and anxiety or agitation from movement. Prevention or mitigation of falls out of bed or on trips to the bathroom may require treating excessive involuntary movements or parkinsonism, addressing impulsivity, pharmacy review to reduce medication load, and utilizing PT and OT input for bed and environmental modifications.

6.4. Weight loss

Nutritional interventions including weight loss prevention can help improve motor-based symptoms and maximize functional status [196]. Increases in total caloric intake in both manifest and prodromal stages may be required to maintain weight, in addition to interventions addressing dysphagia and motor incoordination in manifest HD. Cognitive changes and psychiatric symptoms may impact food preferences and enjoyment as well as basic food intake functions [197]. SLP and OT assessments can help identify motor and non-motor contributors to feeding and swallowing difficulties. Maximizing food intake independence as well as preventing aspiration are treatment goals across the spectrum of manifest HD severity. In end stage patients, SLP driven interventions such as changing cup shapes and stabilizing posture may reduce chance of aspiration [198]. Advanced dysphagia can be treated with enteral nutrition, based on patient and family preferences [196].

6.5. Late stage care

Advanced stage HD is rarely addressed in clinical research. For example, both tetrabenazine and deutetrabenazine clinical trials were limited to ambulatory HD patients. A recent trial in 63 patients with UHDRS TFC $<=$ 7 (roughly speaking, not fully independent in any functional domain) randomized to weekly group music therapy versus group recreational therapy showed no gain of the former compared to the latter in behavioral control or communication [199]. Despite not separating out benefits of one therapy over another, this study usefully demonstrates the feasibility of work in late stage HD. Palliative care is an understudied yet crucial symptomatic intervention area [200]. Early and ongoing open discussions with patients, current or potential caregivers, and care team members throughout the spectrum disease state help avoid crises, capture changes in needs and preferences, and implement patient centered plans. New quality of life measures aimed at prodromal and motor manifest HD patient concerns are a start towards improving end of life care and much needed research in this area [201].

7. New and experimental therapeutics

This is an exciting era for new therapeutics in HD. The shift from symptomatic treatments to potentially disease modifying approaches, mechanistic targets of novel therapeutics, and clinical trial design challenges are relevant for many other neurodegenerative disorders. Manifest HD remains a clinical diagnosis based on the subjective DCL, itself based on a clinician scored exam scale; research diagnoses may allow use of non-motor potential HD features, or rely on functional scales such as TFC. Clinical scale scoring, DCL, and interpretation of research diagnostic criteria can thus vary between clinical trial sites. Many new studies focus on prodromal or early motor manifest stages with high functional levels and/or relatively high cognitive performance. This biases participation towards a particular HD phenotype, one with clear motor signs and limited neuropsychiatric or cognitive features, potentially excluding a high percentage of people at the same motor stage (see discussions in Diagnosis and Clinical Features above) [69,97,119,120]. Work in late stage HD is rare. These clinical trial participant population biases inhibit interpretation of benefits and risks observed in trial contexts, and may slow use of novel therapeutics in the full HD population. With these challenges in mind, the HD research and patient communities continue pushing the pace of new therapeutics development.

Table 2
Ongoing clinical trials in Huntington disease.

Agent	Target/mechanism	Development stage
Symptomatic: novel compounds or procedures		
SRX246 Azevan Pharmaceuticals	Irritability Vasopressin 1a receptor antagonist	Phase 1/2 RDB-PC Enrolling NCT02507284
ACTIVA® PC neurostimulator Heinrich-Heine University, Duesseldorf	Motor symptoms DBS of GPi	Phase 2 RDB parallel-group, sham controlled Enrolling NCT02535884
ExAblate InSightec	Motor symptoms Transcranial MRgFUS of unilateral GPi	Single site open label feasibility study, multiple movement disorders including HD Enrolling NCT02252380
Neuroprotection: investigational medical foods or supplements		
Resveratrol Hôpitaux de Paris	Oxidative stress Plant-based phenol	Phase 3 RDB-PC Single site Enrolling NCT02336633
Triheptanoin oil Institut National de la Santé Et de la Recherche Médicale Ultragenyx Pharmaceuticals	Brain energics Anaplerotic diet therapy	Phase 2 RBD-PC Two sites Enrolling NCT02453061
Disease modifying: novel compounds		
Laquinimod Teva Pharmaceuticals	Neuroinflammation Quinoline-3-carboxamide derivate, small molecule	Phase 2b RDB-PC Enrollment closed NCT02215616
VX15/2503 Vaccinex	Neuroinflammation mAb to semaphorin 4D	Phase 2b RDB-PC Second cohort enrolling in adaptive design NCT02481674

DBS deep brain stimulation; GPi globus pallidus interna; HD huntington disease; mAb humanized monoclonal antibody; MRgFUS MRI guided focused ultrasound thermal ablation; RDB-PC randomized double blind placebo controlled trial
Sources: clinicaltrials.gov, company websites, http://huntingtonstudygroup.org/hd-insights/category/vol-18/.

7.1. New symptomatic treatment approaches

While the newest FDA-approved compounds focus on chorea, novel therapeutics are also being tested against more general motor signs and symptom outcomes [202]. Pridopidine belongs to a novel class of dopaminergic stabilizers, which act primarily at dopamine type 2 receptors. Phase 3 studies to date have failed to meet pre-specified motor outcomes [203–205] (see also clinicaltrials.gov NCT02494778). For HD neuropsychiatric symptoms, there is an ongoing phase II placebo-controlled trial of SRX246, a vasopressin 1a receptor antagonist, targeting irritability in HD (NCT02507284) (Table 2). A phase 2 study of the green tea polyphenon (2)-epigallocatechin-3-gallate (EGCG) testing cognitive outcome measures was completed in 2015; results are not yet available (NCT01357681). PBT2, an 8-hydroxyquinoline transition metal ligand, is thought to reduce mutant HTT aggregation. A phase II randomized double-blind placebo-controlled study in HD observed overall good safety, with a trend towards improvement in one measure of executive function in the highest dose group [206]. A study of bupropion for apathy in HD failed, but all participants did better than predicted implying intensive non-medication interventions may be successful in neurocognitive symptom management [207].

This type of multistep non-medication approach to cognitive symptoms is gradually being specifically studied. Trials in other neurodegenerative disorders demonstrate measurable impacts on symptoms and brain structure from non-medication cognitive interventions such as mindfulness training [156], motivating study of the same techniques in HD. Cognitive intervention may delay HD cognitive decline; these types of therapies may therefore also be disease modifying [157].

Deep brain stimulation (DBS) of bilateral internal globus pallidus (GPi) may improve HD chorea without worsening bradykinesia, whereas cognitive functions might benefit from stimulation of the external part of the pallidum [208]. However, data particularly on long-term follow-up and prediction of immediate benefit are scarce, case series reports are very small (2-3 cases), and relative benefit may be outweighed by potential adverse effects and functional decline [209]. Despite these obstacles, attempts to prove efficacy and improve safety of GPi DBS for HD are ongoing (NCT02535884, NCT02263430). Novel DBS applications for HD cognitive symptoms are under investigation [210,211].

7.2. Neuroprotective and disease modifying therapeutics

How expression of an expanded polyglutamine containing HTT protein results in neurodegeneration is an intense area of study [9–12], but the normal role(s) of HTT and consequences of the mutation remain poorly to not understood. Current active new therapeutic development utilizes two main strategies: leveraging knowledge of potential neurodegeneration pathways (Table 2); and lowering levels of HTT protein (Table 3) [202,212,213]. Experimental work increasingly engages preclinical HD populations. The ability to predict an individuals age at motor onset or clinical diagnosis from CAG repeat length alone is poor, but some trials use combinations of CAG repeat length, current age, functional status, and UHDRS diagnostic confidence levels to either estimate time to motor clinical diagnosis or create prodromal and early symptomatic groups.

Recently completed work, including negative trials of CoQ10 [160] and creatine [161] mentioned in the previous section, targeted oxidative stress and mitochondrial dysfunction. Currently, a single site phase III study of the plant-based phenol resveratrol (NCT02336633) is ongoing. In a similar vein, an ongoing phase 2 study is investigating a form of medical food, triheptanoin oil, an anaplerotic diet therapy used to treat inherited metabolic disorders (NCT02453061). A proof of concept study observed improved brain bioenergetics, as measured by magnetic resonance spectroscopy, in HD patients treated with triheptanoin oil versus placebo [214].

Investigation of phosphodiesterase 10 (PDE10) inhibitors, based in part on enrichment of PDE10 in striatum, reported negative results for PF-02545920 (clinicaltrials.gov NCT02197130); studies on OMS824 (NCT02074410) were suspended in 2014 due to preclinical safety data concerns.

Intracerebral human fetal cell transplantation remains experimental and controversial, with ongoing studies in Europe [215]. Immunohistochemical and immunofluorescent stainings performed on grafted tissue of two HD patients who came to autopsy 9 and 12 years post-transplantation showed the presence of hyperphosphorylated tau, suggesting that transplants may have acquired tau pathology from the host brain [216]. A single site (Brazil) intravenous stem cell therapy safety trial is not yet enrolling (NCT02728115).

The most active current general neurodegeneration trial area involves compounds aimed at reducing neuroinflammation. Ongoing large multicenter late phase II efforts include the immunomodulator laquinimod (NCT02215616) [217], and the humanized IgG4 monoclonal antibody VX15/2503 binding to the semaphorin 4D antigen (NCT02481674) which may also influence oligodendrocyte differentiation [218]. (Table 2) Both trials focus on prodromal and early motor manifest patients.

Laquinimod may also upregulate brain-derived neurotrophic factor (BDNF) levels [217]. A phase 2/3 trial of cysteamine, which is thought

Table 3
Gene targeting huntingtin lowering agents in phase 1 or active preclinical development in Huntington disease.

Agent	Target/ mechanism	Development stage
Pre-mRNA targeted agents: repeated intrathecal or similar delivery required		
IONIS-HTT$_{Rx}$ Ionis Pharmaceuticals Roche	ASO non-allele specific	Phase 1/2a RDB-PC completed: 46 early manifest HD No safety concerns Lower mHTT in CSF in active drug group NCT02519036
WVE-120101 WVE-120102 WAVE Life Sciences	SNP targeted ASO allele specific	Phase 1/2a, RDB-PC recruiting: 48 early manifest HD each NCT03225833 NCT03225846
mRNA targeted agents: intracranial likely intraparenchymal delivery, may be single lifetime dose multiple sites, irreversible		
AMT-130 uniQure	AAV5 vector with microRNA non-allele specific	Pre-clinical IND enabling studies; IND and first in human planned 2018
VY-HTT01 Voyager Therapeutics Genzyme	AAV capsid carrying RNAi transgene non-allele specific	Pre-clinical, lead candidate selected 2017, IND planned 2018
Investigational compound Spark Therapeutics	AAV2 vector with shRNA non-allele specific	Pre-clinical

AAV adeno-associated virus; ASO: antisense oligonucleotide; IND investigational new drug application to FDA; IT intrathecal administration; mHTT mutant huntingtin protein; RDB-PC randomized double blind placebo controlled trial; RNAi RNA interference; shRNA short hairpin RNA; SNP single nucleotide polymorphism
Sources: clinicaltrials.gov, company websites, http://huntingtonstudygroup.org/hd-insights/category/vol-18/

to increase BDNF availability, failed to show benefit in in early motor manifest HD [219]. A July 2018 press release states the laquinimod trial failed to meet its primary endpoint of change in UHDRS total motor score 12 months after baseline, but a secondary endpoint of reduction in caudate volume loss was met. There was no information on other secondary endpoints. A full, reviewed analysis is not yet available.

One of the critical unmet needs in HD experimental therapeutics, particularly in nonmanifest and early symptomatic populations, is development of robust surrogate biomarker measures [9]. Several recent and ongoing phase 2 trials built in investigation of potential biomarker outcomes. A unique approach is being used in development of gene-modified BDNF-producing mesenchymal stem cells for direct intrastriatal implantation. An ongoing prospective longitudinal observational study of early symptomatic HD patients, PRE-CELL (NCT01937923), tracks multiple potential biomarkers in individuals who intend to enroll in the interventional HD-CELL trial of intrastriatal delivery of mesenchymal stem cell derived BDNF. PRE-CELL individual rates of change will anchor post-treatment HD-CELL analyses [220].

A major current therapeutic development focus is impacting the level of mutant HTT [212,221]. Gene silencing techniques are furthest along in trial development. The first phase I tests of antisense oligonucleotides against *HTT* mRNA in humans with early (motor) symptomatic HD launched in 2015, with positive top line safety results and lowered mutant HTT protein in cerebrospinal fluid announced in late 2017 (NCT02519036). Antisense oligonucleotides are designed to bind to target mRNA, resulting in increased RNAse H mRNA breakdown and/or blocked protein translation and reduced mRNA and protein expression. A variety of viral vector delivered and other RNA interference approaches are under preclinical development [221,222], with some publicly considering first in human studies (Table 3). Allele-nonspecific approaches could potentially benefit all HD mutation carriers, regardless of their genetic haplotypes. However, the risk of lowering both mutant and wildtype HTT levels is unknown. While most HD pathogenesis theories focus on toxic gain of function mechanisms, there are also likely loss of normal HTT function effects in HD, especially in neurodevelopment and potentially in protection against mutated HTT [9,10,12,13]. Transgenic model HTT knockouts are embryonic lethal [223]. Thus, while significantly lowering or eliminating mutant HTT is a well-accepted therapeutic goal, it is unclear how much normal HTT can be safely lowered, even in adults. Haplotype specific gene silencing approaches are in development [25]. These avoid lowering wildtype HTT but may require separate therapeutic development for each haplotype and/or limit access to people with mutations on the most common haplotype backgrounds (see Pathogenesis section above). A key example is antisense oligonucleotides targeting single nucleotide polymorphisms (SNPs) on mutated *HTT*; phase 1 studies of this allele-specific approach recently launched (NCT03225833, NCT03225846) (Table 3). Each trial utilizes an agent targeting a distinct SNP. Using CRISPR-Cas9 technology to genetically edit HD human induced pluripotent stem cells is a novel experimental approach that may eventually have therapeutic utility [224–226]. Future combinations of allele (haplotype) specific and non-specific techniques [227], or of partial HTT lowering techniques with a general neurodegenerative pathway agent may allow safe deployment of HD managing rather than HD curative disease modifying cocktails.

In contrast to other neurodegenerative diseases, HD provides an opportunity to explore how disease-modifying therapy can be implemented effectively and ethically in nonmanifest populations. The PREQUEL study evaluated safety of CoQ10 in 90 nonmanifest *HTT* mutation carriers, providing the first evidence that clinical trials could be safely and successfully carried out in this population [228]. PRECREST observed slowing of cortical and striatal atrophy neuroimaging biomarker measures in nonmanifest individuals compared to mutation negative controls with creatine, in contrast to the negative CREST-E trial outcome [229]. This suggest some disease modifying interventions may be more effective in preclinical populations. The PRECREST trial demonstrated feasibility of clinical trial participation for individuals who do not wish to know their mutation status. Nineteen known mutation carriers and 45 at risk individuals (17 mutation negative) were included; the biostatistician was the only team member aware of participant genetic status [229]. The mutation negative group data were used for internal biomarker control comparisons. These important efforts provide information on the feasibility and scientific importance of exposing at risk mutation negative, nonmanifest, and prodromal patients to research risks; however, work with these populations still carries unique ethical and scientific considerations. For example, creatine is not benign: 15 subjects (2 placebo) dropped out of PRECREST [229]. Work with novel compounds arguably creates much larger potential unnecessary medical and research risk burdens. Work with available compounds may widen risk exposure: at risk individuals outside PRECREST used high dose creatine in the hopes of positive benefit, despite its potential impact on renal function. Use of historical longitudinal observational data from studies such as PHAROS, COHORT, Registry, and Enroll-HD, could reduce the need to expose non-expanded CAG carriers to risk, reduce the number of mutation carriers exposed to novel therapeutics of unknown benefit and risk, and potentially accelerate the pace of novel therapeutic testing.

8. Conclusions

Twenty-five years after the groundbreaking *HTT* CAG repeat mutation identification, an HD “cure” remains elusive. Much has been learned about trinucleotide repeat mutations, contributions of motor and non-motor areas to HD phenotypes, and caring for and collaborating with HD mutation carriers and with at-risk individuals at all life

stages. Motor and non-motor features can interact to create functional deficits, key targets for symptomatic care. While focus remains on symptoms due to central nervous system pathology, there is increasing exploration of the symptomatic impact of mutant huntingtin outside the brain. Clinical trials are increasingly addressing the impact of experimental therapeutic intervention on functional and quality of life measures. Continued research has advanced our understanding of mechanisms behind clinical signs and symptoms and disease progression, and pathogenesis-targeted therapies have now entered clinical phase.

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