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Huntington's Disease Clinical Trials Corner: January 2019

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Abstract. In this edition of the Huntington's Disease Clinical Trials Corner we expand on the GENERATION-HD1 and PACE-HD trials, and we list all currently registered and ongoing clinical trials in Huntington's disease.

Keywords: Huntington disease, clinical trials

INTRODUCTION

The Huntington's Disease Clinical Trials Corner is a regular section devoted to highlighting ongoing and recently completed clinical trials in Huntington's disease (HD). Clinical trials previously reviewed by the Huntington's Disease Clinical Trials Corner are listed in Table 1.

In this edition, we highlight the GENERATION-HD1 trial (NCT03761849) [1], and the PACE-HD trial (NCT03344601) [2], and briefly summarise the trial evidence around physiotherapy and exercise interventions in HD. Finally, we tabulate all currently registered and ongoing clinical trials in Tables 2 to 4. For further details on the methodology used, please refer to the first edition of Huntington's Disease Clinical Trials Corner [3].

If you would like to draw attention to specific trials, please feel free to email us at: f.rodrigues@ucl.ac.uk and e.wild@ucl.ac.uk.

In addition to the above, the published report of the PRIDE-HD trial (NCT02006472) is worthy of mention. The paper reports that "*the study did not meet its primary of secondary endpoints at 26 weeks*" [4], confirming the results of previous trials [5–7] and suggests that pridopidine is unlikely have an effect on the motor symptoms of HD as assessed with the Unified Huntington's Disease Rating Scale (UHDRS) Total Motor Score (TMS).

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ONGOING CLINICAL TRIALS

A list of all ongoing clinical trials is given in Tables 2–4.

GENERATION-HD1 (NCT03761849)

Study title

A Randomized, Multicenter, Double-Blind, Placebo-Controlled, Phase III Clinical Study to Evaluate the Efficacy and Safety of Intrathecally Administered RO7234292 (RG6042) in Patients With Manifest Huntington's Disease [1].

Intervention

RG6042 (120 mg) – formerly known as IONIS-HTT_{Rx} / ISIS443139 – an antisense oligonucleotide that targets the *HTT* transcript allele-nonspecifically with the aim of lowering the production of mutant huntingtin protein [8].

Table 1
Clinical trials previously reviewed by the Huntington's Disease Clinical Trials Corner

	Trial name	Intervention	Edition
NCT02519036	IONIS-HTTRx	IONIS-HTT_{Rx}*	September 2017(3)
NCT02215616	LEGATO-HD	Laquinimod	
NCT02197130	Amaryllis	PF-02545920	
NCT02006472	PRIDE-HD	Pridopidine	
NCT03225833	PRECISION-HD1	WVE-120101	February 2018(33)
NCT03225846	PRECISION-HD2	WVE-120102	
NCT01795859	FIRST-HD	Deutetrabenazine	
NCT02481674	SIGNAL	VX15/2503	August 2018(34)
NCT00712426	CREST-E	Creatine	
NCT03761849	GENERATION-HD1	RG6042*	January 2018
NCT03344601	PACE-HD	Physical activity	

*IONIS-HTT_{Rx} and RG6042 refer to the same molecule.

Description

The GENERATION-HD1 trial, sponsored by Hoffmann-La Roche, aims to evaluate the efficacy, safety, and biomarker effects of monthly and bimonthly (i.e. every other month) 120 mg of intrathecal RG6042 in adults (25 to 65 years of age) with manifest HD (i.e. a UHDRS Diagnostic Confidence Level of 4, a UHDRS Independence Score [IS] above or equal to 70, and a CAG-age Product equal or greater than 400) and intact functional independence at baseline to maintain self-care and core activities of daily living, comparing with intrathecal placebo, for disease modification.

This trial is a phase 3, international, multi-centre, randomized, placebo controlled, double-blind, parallel study. It will have 3 study arms: monthly intrathecal injections of 120 mg RG6042; monthly intrathecal injections alternating between 120 mg RG6042 and placebo; and monthly intrathecal placebo. The intervention will be administered for 25 months, and participants will be followed for 29 months. All participants are expected to be invited to an optional open-label extension (OLE) involving monthly or bimonthly (i.e. every other month) drug administration after the end of the blinded phase of the study, assuming the program is continuing.

The trial had not started recruitment at the time of writing, but has a recruitment target of 660 participants, over around 15 countries and 80 to 90 study sites, and it is planned to start enrolment by early 2019. It is currently public that recruitment will happen in the United States of America and Canada, where expected clinical sites were announced in December [9]. Details about further countries and sites will be released in the future.

This pivotal trial will have two primary clinical outcomes for regulatory purposes, the UHDRS Total Functional Capacity (TFC) for the FDA, and the composite UHDRS (cUHDRS) [10] for the EMA [11]. Secondary outcomes will involve other components of the UHDRS, clinical global impression, adverse events, the Montreal Cognitive Assessment (MoCA), the Columbia-Suicide Severity Rating Scale (C-SSRS), pharmacokinetic markers, cerebrospinal fluid mutant huntingtin and neurofilament light chain, and MRI brain volumes.

Sponsors/funders: Hoffmann-La Roche

Comments

This trial is the first to test huntingtin-lowering in a pivotal phase 3 trial, and is part of a development plan that includes the completed first-in-man phase 1b/2a IONIS-HTT_{RX} (NCT02519036) trial [12], its ongoing OLE (NCT03342053) [13], the now-recruiting HD Natural History Study (NCT03664804) [14], and the imminent GENERATION-HD1 (NCT03761849) trial [1]. The phase 1b/2a involved 46 people with early stage HD and showed RG6042 to be safe and well-tolerated, and to reduce cerebrospinal fluid mutant huntingtin concentrations in a dose-dependent manner [15]. Results are currently being prepared for peer-reviewed publication [11]. After completion, all participants were invited to an OLE study aimed at studying long-term safety, tolerability, pharmacokinetics and pharmacodynamics of RG6042 over 15 months; this is currently ongoing. Participants entering the OLE were randomly allocated to monthly or bimonthly intrathecal doses of 120 mg RG6042.

The HD Natural History Study is a prospective longitudinal observational study that aims to recruit 100 people with early stage HD, matched individually to the participants of the open label extension study [16]. It aims to measure clinical and biomarkers (i.e.

Table 2
Ongoing pharmacological clinical trials registered at the World Health Organization (WHO) International Clinical Trials Research Platform (ICTRP) for people with Huntington's disease (HD)

Registration ID	Trial name	Intervention	Mechanism of Action	Population	Comparison	Main outcome	Study design	Estimated Enrolment	Sponsor	Location
NCT03761849*	GENERATION-HD1	RG6042	Allele-nonselective antisense oligonucleotide	HD	Placebo	Clinical efficacy at 101 weeks	Randomized, double-blind, placebo-controlled, parallel trial	660	Hoffmann-La Roche	USA, Canada, Europe (multi centre)
NCT03787758*	–	SAGE-718	NMDA positive allosteric modulator	HD	Placebo	Safety at 21 days	Randomized, double-blind, placebo-controlled, multiple ascending dose trial	10	Sage Therapeutics	N/S
NCT03575676*	–	SOM3355	VMAT2 inhibitor and β1 antagonist	Early and moderate HD with chorea	Placebo	Chorea at 6 months	Randomized, double-blind, placebo-controlled, cross-over trial	30	SOM Biotech SL	Spain (multi centre)
NCT03515213*	–	Fenofibrate	PPARα agonist	HD	Placebo	Pharmacodynamics at 6 months	Randomized, double-blind, placebo-controlled, parallel trial	20	University of California, Irvine	USA (single centre)
NCT03764215*	Tasigna HD	Nilotinib	Selective Bcr-Abl tyrosine kinase inihbitor	HD	None	Safety, tolerability and pharmacody-namics at 3 months	Open label, multiple ascending dose	20	Georgetown University	USA (single centre)
NCT03342053	IONIS-HTT_{RX} OLE	ISIS 443139	Allele-nonselective antisense oligonucleotide	HD	None	Safety and tolerability at 74 weeks	Open label extension	46	Ionis Pharmaceuticals Inc.	Canada, Germany and UK (multi-centre)

(*Continued*)

Table 2
(*Continued*)

Registration ID	Trial name	Intervention	Mechanism of Action	Population	Comparison	Main outcome	Study design	Estimated Enrolment	Sponsor	Location
NCT03225833	PRECISION-HD1	WVE-120102	Allele-selective antisense oligonucleotide	HD	Placebo	Safety and tolerability at 1 and 120 days	Randomized, double-blind, placebo-controlled, combined single ascending dose/multiple ascending dose trial	48	Wave Life Sciences Ltd.	Canada and Poland (multi-centre)
NCT03225846	PRECISION-HD2	WVE-120102	Allele-selective antisense oligonucleotide	HD	Placebo	Safety and tolerability at 1 and 120 days	Randomized, double-blind, placebo-controlled, combined single ascending dose/multiple ascending dose trial	48	Wave Life Sciences Ltd.	Canada and Poland (multi-centre)
NCT02453061	TRIHEP 3	Triheptanoin	Anaplerotic therapy	HD	Placebo	Pharmacodynamic efficacy at 6 months	Randomized, double-blind, placebo-controlled, parallel trial	100	Institut National de la Santé Et de la Recherche Médicale, Ultragenyx Pharmaceutical Inc	France, Netherlands (multi centre)
NCT02509793	–	Tetrabenazine	VMAT2 inhibitor	HD with impulsivity	None	Cognitive and behavioural effects at 8 weeks	Single group, open-label trial	20	University of Texas Health Science Center, and H. Lundbeck A/S	USA (single centre)
NCT02507284	STAIR	SRX246	Vasopressin 1a Receptor Antagonist	Early and moderate HD with irritability	Placebo	Feasibility at 12 weeks	Randomized, double-blind, placebo-controlled, parallel trials	108	Azevan Pharmaceuticals, National Institute of Neurological Disorders and Stroke (NINDS), and NeuroNEXT Network	USA (multi centre)

(*Continued*)

Table 2
(*Continued*)

Registration ID	Trial name	Intervention	Mechanism of Action	Population	Comparison	Main outcome	Study design	Estimated Enrolment	Sponsor	Location
NCT02481674	SIGNAL	VX15/2503	Anti-semaphorin 4D monoclonal antibody	Late premanifest or early HD	Placebo	Safety and tolerability at 15 and 21 months	Randomized, double-blind, placebo-controlled, parallel trial	240	Vaccinex Inc., Huntington Study Group	USA (multi centre)
NCT02336633	REVHD	Resveratrol	Dietary supplement	HD	Placebo	Neuroimaging biomarkers at 1 year	Randomized, double-blind, placebo-controlled, parallel trial	102	Assistance Publique - Hôpitaux de Paris	France (multi centre)
EUCTR2013-002545-10-SE	OSU6162 Open1309	(–)-OSU616	Monoaminergic stabilizer	HD, PD, brain trauma, stroke, myalgic encephalomyelitis and narcolepsy	None	Safety at 3, 6 and 12 months	Single group, open-label trial	240	A. Carlsson Research AB	Sweden (multi centre)
NCT00514774	UDCA-HD	Ursodiol	Bile acid	HD	Placebo	Safety, tolerability and pharmacokinetics at 35 days	Randomized, double-blind, placebo-controlled, parallel trial	21	Oregon Health and Science University, Huntington Study Group, Huntington Society of Canada	N/S
ACTRN126-16001611415	VCAS-HD	Varenicline	Nicotinic acid receptor partial agonist	HD	Placebo	Efficacy at 10 weeks	Randomized, double-blind, placebo-controlled, parallel trial	40	University of Auckland	New Zealand (single centre)

N/S, not specified; PD, Parkinson's disease; VMAT2, Vesicular Monoamine Transporter 2. Note: IONIS-HTT$_{Rx}$, ISIS 443139 and RG6042 refer to the same molecule. New trials since the last Clinical Trials Corner are indicated by *.

Table 3
Ongoing invasive non-pharmacological clinical trials registered at the World Health Organization (WHO) International Clinical Trials Research Platform (ICTRP) for people with Huntington's disease (HD)

Registration ID	Trial name	Intervention	Mechanism of Action	Population	Comparison	Main outcome	Study design	Esimated Enrolment	Sponsor	Location
ISRCTN52651778*	TRIDENT	Foetal stem cell transplant	Stem cell therapy	Early stage HD	Usal care	Safety at 4 weeks	Randomized, open label, controlled, parallel trial	30	Cardiff University	UK (single centre)
NCT02728115*	SAVE-DH	Cellavita	Stem cell therapy	HD	None	Safety at 5 years	Non-randomized, open label, uncontrolled, parallel trial	6	Azidus Brasil	Brazil (single centre)
NCT03252535	ADORE-HD	Cellavita	Stem cell therapy	HD	Placebo	Efficacy at 120 days	Randomized, double-blind, placebo-controlled, parallel trial	35	Azidus Brasil	Brazil (single centre)
NCT03297177	–	Autologous stem/stromal cells	Autologous stem/stromal cell injection	HD, AD, PD, CBD, MS	None	Safety at 5 years	Single group, open-label trial	300	Healeon Medical Inc, Global Alliance for Regenerative Medicine, Regeneris Medical	USA and Honduras (multi-centre)
NCT02535884	HD-DBS	GP DBS	Deep brain stimulation	Moderate HD with chorea	Sham intervention	Efficacy at 12 months	Randomized, double-blind, sham-controlled, parallel trial	50	Heinrich-Heine University, KKS Netzwerk, Medtronic, The George Institute, EHDN, CHDI Foundation, Inc.	Austria, Germany, Switzerland (multi centre)
NCT01834053	BMACHC	Bone Marrow Derived MNC transplant	Bone marrow transplant	HD with chorea	None	Cognitive and behavioural effects at 6 months	Single group, open-label trial	50	Chaitanya Hospital, Pune	India (single centre)
NCT02263430	–	GP DBS	Deep brain stimulation	HD with chorea	Sham stimulation	Efficacy at 12 months	Randomized, double-blind, placebo-controlled, parallel trial	8	Beijing Pins Medical Co., Ltd, Beijing Tiantan Hospital	China (single centre)
NCT02252380	–	Magnetic Resonance Guided Focused Ultrasound	Extracranial stereotactic radioablation	HD, ET, HT, PD, WD, dystonia, TD, or orofacial dyskinesias	None	Adverse events after the procedure	Single group, open-label trial	10	InSightec	Canada (single centre)

AD, Alzheimer's disease, CBD; Corticobasal Degeneration; DBS, deep brain stimulation; ET, Essential Tremor; GP, Globus pallidus; HT, Holmes Tremor; MNC, mononuclear cells; MS, Multiple Sclerosis; PD, Parkinson's disease; TD, Tardive dyskinesia; WD, Wilson's disease. New trials since the last Clinical Trials Corner are indicated by *.

Table 4
Ongoing non-invasive non-pharmacological clinical trials registered at the World Health Organization (WHO) International Clinical Trials Research Platform (ICTRP) for people with Huntington's disease (HD)

Registration ID	Trial name	Intervention	Mechanism of Action	Population	Comparison	Main outcome	Study design	Esimated Enrolment	Sponsor	Location
ACTRN12618001717246*	–	Multidisciplinary therapy program	Exercise, cognitive training, lifestyle guidance and social activities	PremanifestHD	Standard of care	Feasability and safety	Clustered, non-randomized, open label, parallel trial	40	Edith Cowan University, Deakin University and Lotterywest	Australia (two centres)
NCT03417583*	–	Neuropsychiatric treatment protocol	Multidisciplinary intervention	HD with neuropsychiatric symptoms	Standard of care	Change in quality of life at 18 months	Non-randomized, assessor-blinded, parallel trial	100	Vanderbilt University Medical Center and Teva Pharmaceuticals USA	USA (single centre)
CTRI/2018/01/011359	–	Repetitive transcranial magnetic stimulation	Transcranial magnetic stimulation	Early to moderate HD and PD	Sham stimulation	Efficacy at 5 days	Randomized, single-blind, placebo-controlled, parallel trial	40	Vinay Goyal	India (single centre)
NCT03344601	PACE-HD	Supported structured aerobic exercise training program	Physiotherapy	HD	Activity as usual	Data completeness, recruitment, retention, safety, adherence, fidelity and acceptability at 12 months	Nested open-label, randomized controlled parallel trial	120	Cardiff University and CHDI Foundation, Inc	Germany, Spain and USA (multi centre)

(*Continued*)

Table 4
(*Continued*)

Registration ID	Trial name	Intervention	Mechanism of Action	Population	Comparison	Main outcome	Study design	Esimated Enrolment	Sponsor	Location
NCT03306888	–	Physical Activity Coaching Intervention	Physiotherapy	Premanifest and early HD	None	Change in physical activity at 4 months	Single group, open-label trial	14	Columbia University	USA (single centre)
ACTRN1261700 1269325	–	Swallowing skill training	Speech and language therapy	HD and ALS	None	Swallowing function and quality of life at 2 weeks	Single group, open-label trial	54	University of Canterbury	New Zealand (single centre)
NCT02990676	CogTrainHD	Computerised Cognitive Training	Cognitive training	HD	No intervention	Feasibility at 4 years	Open-label, controlled, parallel trial	50	Cardiff University	UK (single centre)
NCT02464293	–	Mindfulness-based Cognitive Therapy	Cognitive therapy	Premanifest and early HD with behavioural symptoms	None	Behavioural effect at 2 weeks, 3 months and 1 year	Single group, open-label trial	16	Lancaster University, Central Manchester University Hospitals NHS Foundation Trust	UK (single centre)
NCT02216474	–	tDCS	Transcranial magnetic stimulation	HD or Tourette Syndrome	Sham stimulation	Efficacy at 2 weeks	Randomized, double-blind, placebo-controlled, cross-over trial	100	Birmingham and Solihull Mental Health NHS Foundation Trust, University of Birmingham	UK (single centre)

AD, Alzheimer's disease; ALS, Amyotrophic Lateral Sclerosis; ET, Essential Tremor; HT, Holmes Tremor; MS, Multiple Sclerosis; PD, Parkinson's disease; TD, Tardive dyskinesia. New trials since the last Clinical Trials Corner are indicated by *.

cerebrospinal fluid neurofilament light chain, mutant huntingtin and tau, brain MRI volumes, and digital biomarkers) over a 15-month period in a sample comparable to the phase 1b/2a and open label extension studies. Participants are being recruited in United States of America, Canada, Germany and United Kingdom. Participants will be offered continued open-label access to RG6042 after study termination.

Notably, for the pivotal phase 3 trial, GENERATION-HD1, Roche has opted for an enrichment strategy based on the inclusion criterion "CAG-age Product superior to 400". The CAG-age product (CAP score) is an estimate of lifetime exposure to mHTT toxicity [17], given by:

[*HTT* CAG repeat length – 33.66] × age

Together with the remaining inclusion criteria, namely the UHDRS Diagnostic Confidence Level of 4, a UHDRS IS above or equal to 70, and functional independence at baseline, the use of a CAP score cutoff aims to produce a relatively homogeneous sample of early stage participants, whose expected progression during trial follow-up is greater and less variable [17]. This should improve the statistical power of the sample. It produces rigid minimum age cutoffs for each *HTT* CAG repeat length, as shown in Table 5.

Table 5
Minimum age at which individuals with each *HTT* CAG count will have a CAP score of ≥400, permitting them to meet this inclusion criterion for Generation-HD1 and related trials

CAG	Minimum age
36	Ineligible
37	Ineligible
38	Ineligible
39	Ineligible
40	63.09
41	54.50
42	47.96
43	42.83
44	38.68
45	35.27
46	32.41
47	29.99
48	27.89
49	26.08
50 or over	25

Note that those with CAG counts of 36–39 will never meet this criterion while they still meet the maximum age inclusion criterion of 65, while those with repeats of 50 or over all meet the CAP score cutoff, but would need to additionally meet the minimum age inclusion criterion of 25.

This criterion will doubtless be a point of focus in discussions with potential volunteers.

PACE-HD (NCT03344601)

Study title

A Longitudinal Cohort Study With Nested Randomised Pragmatic Controlled Trial to Evaluate Physical Activity and Exercise Related Outcomes in People With Huntington's Disease (PACE-HD) [2].

Intervention

Supported structured aerobic exercise training program (18 face-to-face coaching sessions of ∼1 hour).

Description

The PACE-HD trial, sponsored by Cardiff University and CHDI Foundation, Inc., aims to evaluate the feasibility, tolerability, and safety of supported structured aerobic exercise training program in adults (≥18 years of age) with genetically confirmed early manifest HD, compared with activity as usual.

PACE-HD is an international, multi-centre, observation study with a nested randomized, controlled, open label, parallel study. It will involve 120 participants, 60 of whom will take part on a longitudinal observational evaluation of physical fitness and physical activity over a period of 12 months, while the remaining 60 will be randomized to a supported structured aerobic exercise training program, or exercise as usual over a period of 12 months. Recruitment is currently open at various sites in the United States of America, Germany, and Spain.

The primary outcomes are data completeness, recruitment, retention, safety, adherence, fidelity, and acceptability. Secondary outcomes include exercise tests, walk endurance measures, the HD Pro-Triad, the Brunel Lifestyle Physical Activity Questionnaire, and digital biomarkers.

Sponsors/funders: Cardiff University and CHDI Foundation, Inc.

Comments

With multiple trials of agents intended to engage with the core pathobiology of HD underway, and more planned, the relevance of clinical interventions such as rehabilitation therapies, as both stand-alone and adjunctive therapies, has never been more significant. Similar to current management guidelines for Parkinson's disease [18] and multiple sclerosis [19], rehabilitation therapies - including physiotherapy,

occupation therapy, exercise and physical activity - could be used alongside disease-modifying interventions with the potential to maximize patient outcomes.

Animal models of HD have provided pre-clinical evidence that exercise has the potential to modify disease progression. In R6/1 mice, sustained wheel running was shown to improve gait and motor coordination, as well as reduce striatal neuron loss [20]. More recent work with the longer life-span CAG140 mouse model demonstrated that 6 months of treadmill training resulted in increased striatal dopamine D2 receptor expression and dopamine neurotransmitter levels, reduction in HTT aggregate formation, as well as improved behavioural and cognitive symptoms [21]. These pre-clinical findings have set the stage for several clinical feasibility studies in people with early and moderate HD [22–25], as well as in several multi-disciplinary rehabilitation trials [26–30].

Combined pre-clinical and clinical data provide support for the evaluation of exercise as a therapeutic intervention strategy in HD. A recent systematic review reported on findings from 20 studies and found preliminary support for the benefits of exercise and physical activity in terms of motor function, gait speed, and balance [31, 32]. The review also reported a range of physical and social benefits identified through patient-reported outcomes. Interventions incorporating aerobic and strengthening exercises were most prevalent across studies, and several studies noted improvement or maintenance of motor function over 9 months or longer.

In order for rehabilitation interventions to be considered an important adjunctive therapy alongside pharmacological interventions, high-quality studies using innovative statistical methods and trials designs are needed. PACE-HD is a pragmatic study that includes both a longitudinal observational study and a nested (i.e. within-cohort) randomized controlled trial of a 12-month physical therapy and exercise intervention. The intervention incorporates the use of wearable physical activity monitors to measure both outcomes and activity levels throughout the trial. The study is conducted alongside Enroll-HD, which minimizes subject burden and will provide a basis for comparative analysis on disease progression measures. Results of this study are due in the summer of 2020.

A formal Clinical Guideline for Exercise in HD is currently in development. This will provide evidence-based recommendations for healthcare providers and persons with HD, and is planned to be available later in 2019.

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CONFLICTS OF INTEREST

FBR and EJW were sub-investigators on LEGATO-HD (NCT02215616) and IONIS HTT_{Rx} (NCT02519036), and are sub-investigators on the IONIS HTT_{Rx} OLE (NCT03342053) and Roche Natural History Study (NCT03664804) trials, and EJW was a sub-investigator on the Amaryllis study (NCT02197130). The authors did not make use of confidential or privileged information: all materials included in this manuscript were collected from publicly available sources. EJW has participated in scientific advisory boards with Hoffmann-La Roche Ltd, Ionis, Shire, GSK, Wave Life Sciences, PTC Therapeutics and Mitoconix. All honoraria were paid through UCL Consultants Ltd, a wholly owned subsidiary of UCL. Their Host Institution, University College London Hospitals NHS Foundation Trust, has received funds as compensation for conducting clinical trials for Ionis Pharmaceuticals, Pfizer and Teva Pharmaceuticals. Hoffman La Roche Ltd has supported UCL with research funding for EJW. LQ received honoraria from the Huntington Study Group and royalties from Elsevier Publishing.

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