At Risk for Huntington Disease

The PHAROS (Prospective Huntington At Risk Observational Study) Cohort Enrolled

The Huntington Study Group PHAROS Investigators*

**Objective:** To identify the emerging clinical precursors that indicate the early onset of Huntington disease (HD) in a reliable and gene-specific manner. This information is critical for the development of therapeutic trials aimed at postponing clinical onset in HD gene carriers.

**Methods:** Between July 1999 and January 2004, 1001 adults at 50-50 risk for HD agreed to provide longitudinal clinical data and a blood DNA sample under consent provisions that require their individual clinical and genetic information to never be revealed.

**Results:** The Prospective Huntington At Risk Observational Study (PHAROS) cohort is characterized by a 2:1 predominance of women to men, high educational attainment, and gainful employment. Despite the gender disparity, the demographic, hereditary, and clinical characteristics of the female and male participants were similar. Investigators, who are unaware of individual gene status, characterized the baseline cohort to be highly functional with minimal motor or cognitive impairment; 92.3% of participants were judged to have no or nonspecific motor abnormalities; 6.7%, to have possible or probable motor signs; and only 1.0%, to have unequivocal HD.

**Conclusion:** The baseline characteristics of the PHAROS cohort make it well suited to generate objective and prospective data about gene-specific clinical precursors that can be used as outcomes in controlled trials aimed at postponing the onset of HD.

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Huntington Disease (HD) is an adult-onset, progressively disabling, and fatal neurodegenerative disorder that is inherited in an autosomal dominant pattern, owing to an expanded trinucleotide repeat mutation of cytosine-adenine-guanine \((\text{CAG})_n\) in the 5’-translated region of the \(IT-15\) gene on chromosome 4p16.3.\(^{1,2}\) The extent of the \(\text{CAG}_n\) expansion is inversely correlated with the age when HD becomes clinically manifest and is estimated to account for at least half of the variance in determining age at clinical onset.\(^{2,3}\) Individuals who inherit the HD gene spend on average about two thirds of their shortened life in a healthy-appearing state before gradually emerging motor, cognitive, and behavioral signs and symptoms are recognized as manifest illness.\(^{4,5}\) Some 30 000 individuals in the United States and Canada have HD. Although an additional 150 000 are at 50-50 risk of having inherited the HD gene,\(^6\) only a small proportion of at-risk individuals have chosen to undergo presymptomatic predictive DNA testing to learn whether they have the HD gene.\(^7,8\) Important information has emerged about individuals who have been tested.\(^8\) In contrast, relatively little is known about the larger numbers of individuals at risk to develop HD who are unaware of or have chosen not to undergo predictive DNA testing. This group of individuals provides a unique research opportunity to define prospectively and objectively the earliest and most specific signs and symptoms of HD as a critical prelude to examining experimental treatments aimed at postponing the onset of illness.

The Prospective Huntington At Risk Observational Study (PHAROS) is a non-interventional, longitudinal investigation of the HD gene-specific features that are predictive of manifest disease, defined by prespecified criteria and using strict measures to conceal individual genetic data. Our major aim is to identify the clinical features that reliably indicate the
able genetic data. A confidentiality certificate from the
National Institutes of Health Office of Research Management11
provided an additional assurance that genetic or diagnostic
information is protected from legal action. A bar-code system
deidentified the samples, thereby preventing researchers from
gaining access to or linking identifiable genetic and clinical
data. In the event that PHAROS research participants decide to
undergo clinical DNA testing, they are referred to established
testing sites for comprehensive genetic counseling and asked
not to reveal their CAGn status to PHAROS researchers.

ASSESSMENT OF CLINICAL FEATURES

At the baseline evaluation, a site coordinator and site investi-
gator obtained a comprehensive medical history and per-
formed a physical examination, including the Unified Hun-
tington’s Disease Rating Scale (UHDRS), version 1999,12 and
the Beck Depression Inventory (BDI).13 An independent rater
at each site served strictly as a motor examiner, interacting with
research participants only to perform the motor component of
the UHDRS. Site coordinators, site investigators, and inde-
pendent raters underwent annual reliability training for the UHDRS
motor examination using videotapes of research participants
in the US-Venezuela HD Project.3,14 A key item on the motor
examination required the rater to assign a level of “diagnostic
confidence of HD” (Figure 1). The rating of a 4 (clinically de-
finite HD) has been found to have good reliability among inde-
pendent raters.13

GENOTYPE ASSESSMENT

Coded venous blood samples from research participants were
sent to the DNA laboratory of the Molecular Neurogenetics Unit
at Massachusetts General Hospital where CAGn analysis was
performed under the direction of Marcy MacDonald, PhD, using
previously described techniques.15

SAMPLE SIZE CONSIDERATIONS
AND STATISTICAL ANALYSIS

A sample size of 1000 PHAROS participants was estimated to
consist of about 400 individuals with expanded CAGn,4,5,16
Assuming 20% of participants with expanded CAGn develop
an HD gene–specific clinical sign, the projected sample of 400
HD gene–positive individuals and 600 gene-negative individu-
als provides 80% power, at a significance level of .05, to detect
a difference of 7% in the prevalence of a specific clinical pre-
cursor of HD among participants with and without the CAGn expansion.17 Based on data from Brinkman et al,18 we esti-
imated the annual incidence rate of manifesting HD to be 6%,
defined by the first diagnostic rating of “definite HD” (Figure 1). Thus, 400 individuals with expanded CAGn, fol-
lowed up for an average of 4 years, will yield approximately
(4) \times (0.06) \times (0.96) = 96 individuals who manifest HD. Allow-
ing for an annual withdrawal rate of 5%, about 77 research
participants are projected to manifest HD during an observa-
tion period of 4 years.

Using survivorship analysis and a proportional hazard
model for the risk of manifesting HD,17 we estimated that a
total of 77 individuals will provide 80% power to detect the
influence of a dichotomous risk factor corresponding to a haz-
ard ratio of 2.0, provided the prevalence of this risk factor in
the population of individuals with expanded CAGn lies
between 30% and 70%. To maintain the objectivity of ongoing
clinical assessments and the integrity of future phenotype-
genotype analyses, the protocol specified that the effect of

METHODS

STUDY ELIGIBILITY, CONSENT, AND CONFIDENTIALITY

Beginning in 1999, investigators at 43 research sites of the Hun-
tington Study Group (www.huntington-study-group.org) in the
United States and Canada participated in the screening, enroll-
ment, and evaluation of research participants. Institutional re-
view boards at all participating sites approved the research pro-
tocols and consent procedures.

The PHAROS participants included unaffected adults, aged
26 to 55 years, who were at nominal 50-50 risk for having
inherited the HD gene by virtue of having an affected parent
or sibling, who had chosen not to undergo predictive DNA
testing for the HD gene, and who wished to remain unaware
of their gene status. Subjects consented to participate in this
longitudinal research study with the provision that privacy
was maintained and individual clinical and genetic data would
never be disclosed. The eligibility of 26 to 55 years of age was
chosen because this age group has the highest actuarial risk
for developing HD during the planned period of prospective
evaluation.4,9

No experimental treatments were assigned in this observa-
tional study. Prescribed, over-the-counter, and natural rem-
edies were not restricted, except that neuroleptic or atypical
antipsychotic medication could not be taken within 6 months
of enrollment. Potential participants were excluded if they had
been previously diagnosed with HD or had clinical evidence
of psychosis or severe depression.

Consenting research participants agreed to be evaluated at
approximately 9-month intervals at their enrolling site for a mini-
imum of 4 years of observation. Our goal was to enroll indi-
viduals who were not clinically affected with HD while hon-
oring a condition of consent that participants would not be
informed of clinical status. Accordingly, protocol contingenc-
ies were also provided to enroll a small number of clinically
affected, otherwise eligible individuals without informing them
of their clinical status. We estimated that up to 5% of the base-
line cohort would represent such individuals.12 In the event that
participants request information about their clinical status, they
are referred to health care professionals and seen outside of for-
mal research visits.

A blood sample was obtained at baseline from each
research participant to measure CAGn of the HD gene under an
arrangement stipulating that no party, including research par-
ticipants and investigators, would ever be informed of identifi-

Figure 1. Confidence rating of Huntington disease (HD) motor abnormalities
(Item 17 of Unified Huntington’s Disease Rating Scale4,9 1999).

Table 1: Confidence ratings of Huntington disease (HD) motor abnormalities
(Item 17 of Unified Huntington’s Disease Rating Scale4,9 1999).

<table>
<thead>
<tr>
<th>Confidence Rating</th>
<th>Description</th>
<th>Probability Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal (no abnormalities)</td>
<td>100%</td>
</tr>
<tr>
<td>1</td>
<td>Nonspecific motor abnormalities (&lt;50% confidence)</td>
<td>50%</td>
</tr>
<tr>
<td>2</td>
<td>Motor abnormalities that may be signs of HD (50%-89% confidence)</td>
<td>80%</td>
</tr>
<tr>
<td>3</td>
<td>Motor abnormalities that are likely signs of HD (90%-99% confidence)</td>
<td>90%</td>
</tr>
<tr>
<td>4</td>
<td>Motor abnormalities that are unequivocal signs of HD (&gt;99% confidence)</td>
<td>99%</td>
</tr>
</tbody>
</table>
CAGn on study outcomes will not be determined until 77 participants are judged by the independent rater to have developed unequivocal motor signs of HD (Figure 1). Statistical analyses were performed on the baseline data, which included demographic variables, medical histories, UHDRS scores, and BDI scores. Baseline characteristics were compared for men and women, using either χ² test or t test as appropriate. The present results report accrued data for baseline characteristics as of January 31, 2004, and entered into the database as of July 13, 2004. Data pertaining to a detailed analysis of baseline UHDRS data and the prospective follow-up of the cohort will be reported separately.

### RESULTS

#### ACCRUAL

Between July 9, 1999, and January 31, 2004, 1001 research participants were enrolled at 43 research sites in the United States and Canada, with a mean ± SD of 23 ± 11.9 participants per site (range, 3-58). The pace of accrual was largely linear, but about a 2:1 ratio of enrolled women to men among all age groups persisted (Figure 2A). The disproportionate representation of women to men was not appreciably influenced by special recruitment efforts that began in 2001 to attract more female research participants.

#### BASELINE CHARACTERISTICS

Table 1 presents the baseline characteristics of the research participants. The mean ± SD age of research participants at enrollment was 41.8 ± 7.3 years. Racial distribution was 98% Caucasian, 1% African American, and 1% Asian or Native American. Ethnic representation included 2.5% Hispanic participants. Marital status was distributed as 70% married, 18% single, and 12% divorced, similar for men and women. Forty percent of the women and 29% of the men reported that they were naturally or surgically sterile.

Both female and male research participants were highly educated, with mean±SD 14.9 ± 2.6 years of formal education (range, 6-28 years); 45% reported at least 16 years of education (comparable with 4 years of college) and 96%, at least 12 years of education (comparable with 4 years of high school). Nearly all PHAROS participants (96%; 94% of women, 99% of men) were active in the labor force in roles self-reported as professional (45%; 44% of women, 48% of men), managerial (36%; 40% of women, 26% of men), service (8%; 8% of women, 8% of men), craftsperson (5%; 1% of women, 14% of men), or laborer (1%; 1% of women, 3% of men).

Only 6% of research participants reported symptoms that concerned them as possibly related to HD (44% motor, 32% cognitive, 23% psychiatric, 2% mixed). A self-reported history of psychiatric illness at baseline was common (29% depression, 9% suicidal ideation, 4% suicide attempt), significantly more so in women than men (depression, 33% vs 18%; suicidal ideation, 11% vs 6%; and suicide attempt, 5% vs 2%, respectively). However, the overall severity of the baseline BDI scores was modest; only 6.5% of participants had BDI scores considered to be in a depressed range. Distribution of BDI scores was similar for women and men.

Except for antidepressant medication, which 14% of participants reported taking at enrollment (16% women, 9% men), there was little reported use of medications commonly used to treat patients with HD. Only 2.7% of participants were taking coenzyme Q₁₀ at a mean±SD daily dosage of 100±59.4 mg, and no participants were taking a dosage exceeding 300 mg/d. Only 1.8% reported taking anxiolytics; 1%, fish oil supplements; 0.6%, minocycline; and 0.3%, creatine.

#### BASELINE UHDRS SCORES

The baseline UHDRS scores, including motor, cognitive, and behavioral component scores, are summarized in Table 2. The total motor UHDRS score of 2.8±4.3 units (mean ± SD) was near the floor of the 31-item scale.

### Table 1. Baseline Characteristics*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (N = 1001)</th>
<th>Women (n = 689)</th>
<th>Men (n = 312)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>41.8 ± 7.3</td>
<td>41.7 ± 7.2</td>
<td>42.0 ± 7.4</td>
</tr>
<tr>
<td>Height, cm</td>
<td>168.6 ± 9.7</td>
<td>164.2 ± 7.1</td>
<td>178.1 ± 7.3</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>78.8 ± 20.1</td>
<td>74.0 ± 18.9</td>
<td>89.6 ± 18.4</td>
</tr>
<tr>
<td>Education, y</td>
<td>14.9 ± 2.6</td>
<td>14.8 ± 2.5</td>
<td>15.1 ± 2.7</td>
</tr>
<tr>
<td>Mother affected, %</td>
<td>53.9</td>
<td>57.2</td>
<td>46.6</td>
</tr>
<tr>
<td>Father affected, %</td>
<td>46.1</td>
<td>42.8</td>
<td>53.4</td>
</tr>
<tr>
<td>Age mother affected, y</td>
<td>48.5 ± 11.1</td>
<td>48.5 ± 10.8</td>
<td>48.4 ± 11.8</td>
</tr>
<tr>
<td>Age father affected, y</td>
<td>48.6 ± 10.1</td>
<td>47.9 ± 10.1</td>
<td>49.8 ± 10.2</td>
</tr>
</tbody>
</table>

*Values are expressed as mean ± SD unless otherwise indicated. Height and weight differ significantly (P<.01) for men and women.
Overall cognitive performance was high; verbal fluency, symbol digit scores, and Stroop scores were within the reported scores for a normal age-appropriate population. Behavioral UHDRS assessment also showed minimal impairment; composite behavioral frequency (mean ± SD, 4.1 ± 4.3) and severity (mean ± SD, 4.2 ± 4.4) scores were at the floor of these 11-item scales that ranged from 0 to 44 units of severity. There were no significant gender differences in these baseline UHDRS characteristics.

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### Table 2. Baseline UHDRS Characteristics*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (N = 1001)</th>
<th>Women (n = 689)</th>
<th>Men (n = 312)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Motor assessments</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total UHDRS motor assessment score (range, 0-124)</td>
<td>2.8 ± 4.3</td>
<td>2.6 ± 3.9</td>
<td>3.3 ± 4.9</td>
</tr>
<tr>
<td>Total maximal chorea score (range, 0-28)</td>
<td>0.5 ± 1.5</td>
<td>0.4 ± 1.2</td>
<td>0.7 ± 1.9†</td>
</tr>
<tr>
<td>Total maximal dystonia score (range, 0-20)</td>
<td>0.1 ± 0.5</td>
<td>0.1 ± 0.3</td>
<td>0.1 ± 0.6</td>
</tr>
<tr>
<td>Composite bradykinesia + gait + tandem walk + retropulsion pull test score (range, 0-16)</td>
<td>0.3 ± 0.8</td>
<td>0.3 ± 0.8</td>
<td>0.3 ± 0.7</td>
</tr>
<tr>
<td>Composite finger taps + pronate/supinate hands score (range, 0-16)</td>
<td>0.5 ± 1.1</td>
<td>0.5 ± 1.0</td>
<td>0.5 ± 1.1</td>
</tr>
<tr>
<td>Composite saccade velocity + initiation score (range, 0-16)</td>
<td>0.6 ± 1.3</td>
<td>0.6 ± 1.3</td>
<td>0.6 ± 1.3</td>
</tr>
<tr>
<td>Luria score (range, 0-4)</td>
<td>0.3 ± 0.7</td>
<td>0.2 ± 0.6</td>
<td>0.4 ± 0.8</td>
</tr>
<tr>
<td>Dysarthria score (range, 0-4)</td>
<td>0 ± 0.1</td>
<td>0 ± 0.1</td>
<td>0 ± 0.1</td>
</tr>
<tr>
<td><strong>Cognitive assessments</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal fluency test score (observed range, 8-82)</td>
<td>38.6 ± 11.7</td>
<td>39.1 ± 11.5</td>
<td>37.4 ± 12.0</td>
</tr>
<tr>
<td>Symbol Digit Modalities Test score (observed range, 19-96)</td>
<td>52.9 ± 10.1</td>
<td>53.6 ± 10.2</td>
<td>51.4 ± 9.8‡</td>
</tr>
<tr>
<td>Stroop color naming score (observed range, 25-150)</td>
<td>79.9 ± 14.2</td>
<td>80.6 ± 13.9</td>
<td>78.5 ± 14.9</td>
</tr>
<tr>
<td>Stroop word reading score (observed range, 10-160)</td>
<td>95.0 ± 13.2</td>
<td>95.4 ± 12.8</td>
<td>94.0 ± 14.0</td>
</tr>
<tr>
<td>Stroop interference score (observed range, 11-120)</td>
<td>46.1 ± 11.8</td>
<td>46.2 ± 11.1</td>
<td>45.8 ± 13.2</td>
</tr>
<tr>
<td><strong>Behavioral assessments</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Behavioral assessment: frequency (range, 0-44)</td>
<td>4.1 ± 4.3</td>
<td>4.2 ± 4.2</td>
<td>3.9 ± 4.3</td>
</tr>
<tr>
<td>Behavioral assessment: severity (range, 0-44)</td>
<td>4.2 ± 4.4</td>
<td>4.3 ± 4.4</td>
<td>3.9 ± 4.4</td>
</tr>
</tbody>
</table>

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**Baseline Diagnostic Confidence**

The distribution of diagnostic confidence categories (Figure 1) at baseline, as reported by the site investigator, is illustrated in Figure 3. 92.3% of participants were judged to have ratings of 0 or 1; 6.7%, to have ratings of 2 or 3; and only 1.0% (3 women, 7 men), to have a rating of 4 (unequivocal HD). There were no major gender differences in the distribution of the diagnostic confidence categories for ratings 0, 1, 2, or 3.

Analysis of 6-month epochs during the 4.5-year accrual phase showed no change in the time-related distribution of unequivocal (rating 4) or likely (rating 3) signs of HD at baseline. However, there was a time-related trend for increased severity of diagnostic judgments for the categories of possible (rating 2) and nonspecific (rating 1) signs, paralleling the repeated annual training sessions that the investigators underwent during the 4.5 years of enrollment.

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**Comment**

The PHAROS cohort of 1001 adults at risk for HD, accrued over 4.5 years at 43 specialized research sites in the United States and Canada, consists of eligible research participants who are predominantly women, highly educated, and gainfully employed. While such individuals are more likely to participate in clinical trials, the disproportionate participation by women in this observational study is not indicative of the gender parity observed in interventional clinical trials involving research participants who have manifest signs of HD.
The reasons for the gender imbalance in PHAROS are not obvious. Although we attempted to enhance recruitment of men by emphasizing the importance of their participation, the 2:1 representation of women to men was steady throughout the period of accrual. This imbalance was foreshadowed by a planning survey to assess interest and feasibility in PHAROS that yielded 2:1 women to men respondents. In an earlier cross-sectional study of 585 individuals at risk for HD, 69% of the participants were women. Data from the National Institutes of Health–supported National Research Roster for Huntington Disease Patients and Families (NS 82396) indicate that 1295 (69.1%) of the 1873 respondents who were at 50-50 risk for HD were women (P. M. Conneally, PhD, oral communication, February 2002). Similarly, about 65% of adults worldwide who seek predictive DNA testing for HD are women.

These patterns suggest that unaffected women at risk for HD are twice as likely as their male counterparts to participate in observational clinical research as well as predictive DNA testing. We have not been able to identify aspects of PHAROS particularly aversive to men. Rather, it seems that women are more willing than men to contribute to observational clinical research that is unlikely to provide any direct benefits, a finding perhaps related to a greater interest by women in their reproductive fate. This gender disparity in observational studies of individuals at risk for HD should be considered in planning therapeutic trials where the availability of experimental treatments and potential direct benefits are expected to produce greater gender parity. The under-representation of minorities in PHAROS is similar to prior studies involving individuals with manifest HD but may be related to the nearly exclusive use of English-language materials and the geographic distribution of study sites with limited access to a broader sampling of ethnic and racial groups.

The demographic and clinical characteristics of the female and male participants in PHAROS were similar despite the gender disparity. The more common baseline reports by women of symptoms of depression are in keeping with reports of a higher incidence of self-reported depression in women than in men in general and may also reflect the greater willingness of women than men to participate in this observational study. Nonetheless, we remain vigilant to the risk of suicide because of the high occurrence of attempted and completed suicide among patients with HD and individuals at risk for HD.

Our enrolled research participants reported infrequent use of putative disease-modifying treatments such as coenzyme Q10, creatine, and minocycline. This finding seems surprising in view of the relative availability of these potential remedies and the generally well-educated background of this cohort. However, the uncertainty of benefits and dosage, the risks of long-term adverse effects, and the cost of taking these unproven treatments might also be viewed as consistent with educated and informed decision making.

Distribution of baseline diagnostic confidence levels was consistent with the research aims and design of PHAROS to enroll an unaffected cohort of adults at risk for HD. Despite our projection that we would enroll about 5% individuals already affected by HD, only about 1% of our cohort at baseline was judged to have unequivocal motor features of HD. This low level of manifest HD at baseline should enhance longitudinal detection of the early, specific features marking the onset of HD.

The low prevalence of unequivocal HD findings among PHAROS participants is in keeping with that found in previous studies of at-risk individuals. In a cross-sectional analysis of 637 subjects at risk for HD, 4.9% were diagnosed with manifest HD on initial examination, and subsequent genetic analyses showed that 3 of the 20 individuals clinically classified as having manifest HD did not have an expanded CAG repeat. Similarly, in a group of 124 subjects at risk for HD, 2.4% were diagnosed with manifest disease, and 3 subjects classified as having “equivocal” HD were found not to carry a CAG expansion. Whether these classifications are false-positive diagnoses or whether these subjects have other autosomal dominant choreic disorders would require more extensive follow-up evaluations. When prospective evaluation of the PHAROS cohort is completed and genetic data are analyzed, we will have a clearer estimate of the extent of false-positive clinical diagnosis for HD.

The PHAROS genotype data have not yet been analyzed because of concerns about biasing the ongoing and blinded longitudinal evaluations of phenotype. The planned prospective observation of at least 4 years and high participant retention will enhance identification of the early HD gene–specific precursors and more accurately estimate the rate of “phenoconversion.” In turn, this knowledge will help inform the sample size, power, and effect size for experimental treatments aimed at postponing the onset of HD (Figure 4). The PHAROS co-

![Figure 4](https://www.archneurol.com/article-figures/4315631208685.jpg)

**Figure 4.** Relationship between phenoconversion rate (p0) in the placebo group, the effect size or ratio of the phenoconversion rate between treatment and placebo groups (rr), and the total sample size requirements for a prospective randomized trial in preclinical Huntington disease, assuming a significance level=.05, power=.80, and 1:1 allocation of placebo and active treatments. For example, p0 of 0.2 for a given period of assessment requires a total sample size of 400 participants (point A). For the same p0, greater (point B) or smaller (point C) effects require correspondingly smaller or larger sample sizes. However, if p0 increases with longer duration of prospective evaluation, smaller effects can be detected (point D) with the same sample size (point A).
hort at enrollment, largely unaffected clinically and with a range of diagnostic confidence, is well suited to generate objective data, comparing participants who do and do not carry the CAG\textsubscript{n} expansion, as well as those who do and do not manifest HD.

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