Precision Cardiovascular Medicine for **Multiethnic** Populations

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How can we make **rational** decisions with molecular data?
probabilities + utilities = rational decisions

... but we often stray
big data can help us compute missing probabilities and inform rational decisions across demographic groups that are underrepresented in past studies
Genetic Misdiagnoses and the Potential for Health Disparities

Arjun K. Manrai, Ph.D., Birgit H. Funke, Ph.D., Heidi L. Rehm, Ph.D., Morten S. Olesen, Ph.D., Bradley A. Maron, M.D., Peter Szolovits, Ph.D., David M. Margulies, M.D., Joseph Loscalzo, M.D., Ph.D., and Isaac S. Kohane, M.D., Ph.D.
Hypertrophic Cardiomyopathy (HCM)

- Heart failure
- Arrhythmias
- Obstructed blood flow
- Infective endocarditis
- Sudden cardiac death

Maron et al., Circulation 1995

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A Molecular Basis for Familial Hypertrophic Cardiomyopathy: A β Cardiac Myosin Heavy Chain Gene Missense Mutation

Anja A.T. Geisterfer-Lowrance★, Susan Kass†, Gary Tanigawa†, Hans-Peter Vosberg‡, William McKenna§, Christine E. Seidman★, J.G. Seidman†

Figure 1. Inheritance of FHC and the βD-425 Polymorphism in Family A

(A) The pedigree of family A is presented using standard nomenclature. Males (squares) and females (circles) are identified by generation and subject number. The disease status of each individual is indicated by shading: closed symbols, affected; open symbols, unaffected. Deceased individuals are represented by a slash. The genotype of each individual is shown. Allele 1 indicates a 425 bp fragment, and allele 2 represents a 385 bp fragment identified by βD-425.

(B) Southern blot of Ddel-digested DNAs from members of a small nuclear family from family A (dashed box in [A]) hybridized to the βD-425 probe (see Experimental Procedures).
MOLECULAR DIAGNOSTICS REPORT

Specimen Type: Blood, Peripheral
Received Date: 08/07/2008
Referring Physician: DR. SMITH
Referring Facility: UNIV OF AMERICA
Related Accession(s): OTHER CONTACTS, MS, CGC
Lab Control Number: 00-222-55555
Copies To: SENDOUT UNIVERSITY OF AMERICA
Family Number: F000000

TEST DESCRIPTION - HCM Panel (18 Genes)
Sequence Confirmation Test
Copy Number Variation Analysis

TEST PERFORMED - PCM-pltB; SeqConfirm; CNV-a

INDICATION FOR TEST - Clinical features of HCM

RESULTS

DNA VARIANTS:
Heterozygous c.1504C>T (p.Arg502Trp), Exon 17, MYBPC3, Pathogenic

INTERPRETATION:
Positive. DNA sequencing and copy number assessment of the coding regions and splice sites of ACTC1, ACTN2, CSRP3, GLA, LAMP2, MYBPC3, MYH7, MYL2, MYL3, MYOZ2, NEXN, PLN, PRKAG2, TNNC1, TNNI3, TNNT2, TPM1 and TTR identified the variant listed above.

SUMMARY (see below for variant interpretations): This individual carries a pathogenic variant in MYBPC3, which is consistent with the clinical diagnosis of HCM.

Cardiomyopathy due to pathogenic variants in the MYBPC3 gene is typically inherited in an autosomal dominant pattern. Each first-degree relative has a 50% (or 1 in 2) chance of inheriting a variant and its risk for cardiomyopathy. Disease penetrance and severity can vary due to modifier genes and/or environmental factors. The significance of a variant should therefore be
Current scale for reporting variants
Risk Stratification

KEY

- Affected male
- Unaffected male
- Unaffected female
- Affected female

Cardiac follow-up, lifestyle modifications

NO Cardiac follow-up

P? resolve ambiguous clinical presentation

ICD / lifestyle modifications..etc.
Challenge Question #1

What are the chances that a son inherits his father’s HCM pathogenic mutation in MYBPC3 (Chr. 11)?

(a) 100%
(b) 50%
(c) 25%
(d) 0.2% (general population prevalence)
When do variant classifications change?
"pathogenic/disease causing" mutations in 84 cardiomyopathy genes

measure genotype frequency

NHLBI ESP (4300 EAs, 2203 AAs)
HCM Prevalence = 1:500
HCM Inheritance = Autosomal Dominant
A

- **Remaining 89 mutations**: 26%
- **TNNT2 (K247R)**: 43%
- **JPH2 (G505S)**: 3%
- **MYBPC3 (G278E)**: 4%
- **TNNT13 (P82S)**: 4%
- **OBSCN (R4344Q)**: 20%
Classified as pathogenic 2005-2007

<table>
<thead>
<tr>
<th>Gene</th>
<th>European Americans</th>
<th>African Americans</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNNT2 (K247R)</td>
<td>2.88%</td>
<td>27.14%</td>
</tr>
<tr>
<td>O8SCN (R4344Q)</td>
<td>0.33%</td>
<td>15.27%</td>
</tr>
<tr>
<td>TNNI3 (P82S)</td>
<td>0.03%</td>
<td>4.07%</td>
</tr>
<tr>
<td>MYBPC3 (G278E)</td>
<td>0.02%</td>
<td>3.15%</td>
</tr>
<tr>
<td>JPH2 (G505S)</td>
<td>0.80%</td>
<td>2.92%</td>
</tr>
<tr>
<td>Remaining 89 mutations</td>
<td>6.67%</td>
<td>7.18%</td>
</tr>
</tbody>
</table>
All P/LP misclassifications in patients of African or unspecified ancestry

**Table 1. Clinical Findings for High-Frequency Variants Associated with Hypertrophic Cardiomyopathy.**

<table>
<thead>
<tr>
<th>Originally Reported Status of Variant*</th>
<th>Patient’s Age</th>
<th>Patient’s Ethnic Background</th>
<th>Report Year</th>
<th>Report Result</th>
<th>Variant</th>
<th>Most Significant Pathogenic Variant†</th>
<th>Indication for Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>46 yr</td>
<td>Unavailable</td>
<td>2005</td>
<td>Positive</td>
<td>TNNI3 (P82S)</td>
<td>Yes</td>
<td>Clinical diagnosis of hypertrophic cardiomyopathy</td>
</tr>
<tr>
<td>Pathogenic</td>
<td>75 yr</td>
<td>Unavailable</td>
<td>2005</td>
<td>Positive</td>
<td>TNNI3 (P82S)</td>
<td>Yes</td>
<td>Family history and clinical symptoms of hypertrophic cardiomyopathy</td>
</tr>
<tr>
<td>Presumed pathogenic</td>
<td>32 yr</td>
<td>African ancestry</td>
<td>2005</td>
<td>Positive</td>
<td>TNNI3 (P82S)</td>
<td>No</td>
<td>Clinical diagnosis of hypertrophic cardiomyopathy</td>
</tr>
<tr>
<td>Pathogenicity debated</td>
<td>34 yr</td>
<td>African ancestry</td>
<td>2005</td>
<td>Positive</td>
<td>TNNI3 (P82S)</td>
<td>No</td>
<td>Clinical diagnosis and family history of hypertrophic cardiomyopathy</td>
</tr>
<tr>
<td>Unknown significance</td>
<td>12 yr</td>
<td>African ancestry</td>
<td>2006</td>
<td>Inconclusive</td>
<td>TNNI3 (P82S)</td>
<td>Yes</td>
<td>Family history of hypertrophic cardiomyopathy</td>
</tr>
<tr>
<td>Unknown significance</td>
<td>40 yr</td>
<td>African ancestry</td>
<td>2007</td>
<td>Inconclusive</td>
<td>TNNI3 (P82S)</td>
<td>Yes</td>
<td>Clinical diagnosis of hypertrophic cardiomyopathy</td>
</tr>
<tr>
<td>Unknown significance</td>
<td>45 yr</td>
<td>African ancestry</td>
<td>2007</td>
<td>Inconclusive</td>
<td>TNNI3 (P82S)</td>
<td>Yes</td>
<td>Clinical features of hypertrophic cardiomyopathy</td>
</tr>
<tr>
<td>Unknown significance</td>
<td>16 yr</td>
<td>Asian ancestry</td>
<td>2008</td>
<td>Positive</td>
<td>TNNI3 (P82S)</td>
<td>No</td>
<td>Clinical diagnosis and family history of hypertrophic cardiomyopathy</td>
</tr>
<tr>
<td>Presumed pathogenic</td>
<td>59 yr</td>
<td>African ancestry</td>
<td>2006</td>
<td>Positive</td>
<td>MYBPC3 (G278E)</td>
<td>Yes</td>
<td>Clinical features of hypertrophic cardiomyopathy</td>
</tr>
<tr>
<td>Presumed pathogenic</td>
<td>15 yr</td>
<td>African ancestry</td>
<td>2007</td>
<td>Positive</td>
<td>MYBPC3 (G278E)</td>
<td>Yes</td>
<td>Clinical diagnosis of hypertrophic cardiomyopathy</td>
</tr>
<tr>
<td>Presumed pathogenic</td>
<td>16 yr</td>
<td>African ancestry</td>
<td>2007</td>
<td>Positive</td>
<td>MYBPC3 (G278E)</td>
<td>Yes</td>
<td>Clinical diagnosis of hypertrophic cardiomyopathy</td>
</tr>
<tr>
<td>Presumed pathogenic</td>
<td>22 yr</td>
<td>African ancestry</td>
<td>2007</td>
<td>Positive</td>
<td>MYBPC3 (G278E)</td>
<td>No</td>
<td>Clinical diagnosis and family history of hypertrophic cardiomyopathy</td>
</tr>
<tr>
<td>Unknown significance</td>
<td>48 yr</td>
<td>African ancestry</td>
<td>2008</td>
<td>Positive</td>
<td>MYBPC3 (G278E)</td>
<td>No</td>
<td>Clinical diagnosis of hypertrophic cardiomyopathy</td>
</tr>
</tbody>
</table>

* All variants subsequently have been reclassified as benign.
† Information in this column indicates whether the variant was unequivocally the most pathogenic variant in the original report that was provided to the patient.
<table>
<thead>
<tr>
<th>Gene (Variant)</th>
<th>Reference</th>
<th>Discovery Phase</th>
<th>No. of Cases</th>
<th>No. of Controls</th>
<th>Variant Assessment</th>
<th>Country</th>
<th>Included in LMM Clinical Panel</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TNNT2 (K247R)</strong></td>
<td>García-Castro et al.(^{21})</td>
<td>Targeted gene sequencing of unrelated cases and controls from Asturias</td>
<td>30</td>
<td>200</td>
<td>No No</td>
<td>Spain Yes</td>
<td></td>
</tr>
<tr>
<td><em><em>OBSCN</em> (R434Q)</em>*</td>
<td>Arimura et al.(^{22})</td>
<td>Targeted gene sequencing of unrelated Japanese cases and controls</td>
<td>144</td>
<td>288</td>
<td>Yes No</td>
<td>Japan No</td>
<td></td>
</tr>
<tr>
<td><strong>TNNI3 (P82S)</strong></td>
<td>Niimura et al.(^{23})</td>
<td>Targeted gene sequencing of unrelated cases and controls(^{†})</td>
<td>31</td>
<td>85</td>
<td>No No</td>
<td>United States Yes</td>
<td></td>
</tr>
<tr>
<td><strong>MYBPC3 (G278E)</strong></td>
<td>Richard et al.(^{24})</td>
<td>Targeted gene sequencing of unrelated cases and controls(^{‡})</td>
<td>197</td>
<td>100</td>
<td>No No</td>
<td>France Yes</td>
<td></td>
</tr>
<tr>
<td><em><em>JPH2</em> (G505S)</em>*</td>
<td>Matsushita et al.(^{25})</td>
<td>Targeted gene sequencing of Japanese cases and controls</td>
<td>195</td>
<td>236</td>
<td>Yes No</td>
<td>Japan No</td>
<td></td>
</tr>
</tbody>
</table>

* OBSCN and JPH2 have never been included in cardiomyopathy testing at the Laboratory for Molecular Medicine (LMM).

\(^{†}\) No specific ethnic background was provided, but “informed consent was obtained in accordance with human subject committee guidelines at Brigham and Women’s Hospital, St. George’s Hospital Medical School [U.K.], and Minneapolis Heart Institute Foundation.”\(^{23}\)

\(^{‡}\) “Patients were recruited in France, and most of them were of European origin.”\(^{24}\) The sample of patients included persons of African ancestry (Richard P: personal communication).
Studies took place around the world but not in Africa
**TNNT3, P82S**

No ethnicity information provided, but three separate populations

85 controls

Niimura et al. 2002

**MYBPC3, G278E**

"Patients were recruited in France, and most of them were of European origin."

100 controls

Richard et al. 2003
Including African American controls would have ruled out pathogenicity.
SNP: rs3730238
Ancestral Allele: T
Derived Allele: C

Manrai et al., New England Journal of Medicine, 2016
\[
P(D|G) = \frac{P(G|D)P(D)}{P(G|D)P(D) + P(G|\overline{D})P(\overline{D})}
\]
Table 3: Current Criteria Used to Determine Probability for Pathogenicity of an HCM Mutation.

<table>
<thead>
<tr>
<th>Pathogenicity Criterion</th>
<th>Description</th>
<th>Potential Limitations for Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cosegregation</td>
<td>Determine whether mutation is present in relatives with LVH and absent in those without LVH</td>
<td>Often impractical; Family size may be small; Relatives unavailable; Family compliance unpredictable; Requires resources for imaging/DNA studies in ≥3 relatives (other than proband) including ≥1 with HCM phenotype†</td>
</tr>
<tr>
<td>Prior evidence of pathogenicity</td>
<td>Documentation that mutation is HCM disease–causing in ≥1 patient in published literature, or in the individual experience of a testing laboratory</td>
<td>Absence of established comprehensive, curated, and cooperative database tabulating mutations‡; High rate of novel (de novo; “private”) mutations in 65% of probands; Interpretation of pathogenicity can be inconsistent among testing laboratories</td>
</tr>
<tr>
<td>Control population</td>
<td>Confidence for pathogenicity increased when mutation absent from large, ethnicity-matched ostensibly healthy population</td>
<td>Often insufficient size§; Control subjects should be unrelated, ethnicity-specific and free of the disease in question; Potentially pathogenic variants can occur in subjects judged clinically normal; Many rare benign (missense) variants in normals, termed “background noise”</td>
</tr>
<tr>
<td>Major disruption protein structure, and function</td>
<td>Mutant proteins are judged to have substantially altered physical properties</td>
<td>Inferred from evidence obtained from in nonhuman sources¶</td>
</tr>
</tbody>
</table>

†Requires imaging/DNA studies in ≥3 relatives other than proband
‡Stimulated database not currently available
§Sample size must be sufficiently large to account for expected frequency of mutation
¶Inferred from evidence obtained from nonhuman sources
Figure 5. Prognostic Pathways and Primary Treatment Strategies Within the Broad Clinical Spectrum of Hypertrophic Cardiomyopathy (HCM)

Most patients have an uncomplicated and benign course without major complications. However, individual patients can experience adverse disease progression along 1 or more of the complication pathways, each nevertheless associated with a potentially effective treatment strategy. AF indicates atrial fibrillation; ICD, implantable cardioverter-defibrillator; and RF, radiofrequency.
Genetic testing
The most definitive resolution of this important differential diagnosis can come from genetic testing. Indeed, a rapid genetic test is now available, analysing by direct DNA sequencing mutations in the eight most common HCM causing genes. While a positive test result in an athlete can resolve the diagnostic ambiguity between athlete’s heart and HCM, there is however significant potential for false negative test results in which a HCM diagnosis cannot be excluded.

Figure 1 Criteria used to distinguish hypertrophic cardiomyopathy (HCM) from athlete’s heart when the left ventricular (LV) wall thickness is within the shaded “grey zone” of overlap, consistent with both diagnoses. ↓ indicates decreased; LA, left atrial; LV, left ventricular hypertrophy. Reproduced from Maron et al., with permission of American Heart Association.
The initial estimate of the prevalence of hypertrophic cardiomyopathy (HCM) came largely from the CARDIA (Coronary Artery Risk Development in Young Adults) study, which relied on echocardiographic identification of probands. Among the factors contributing to the revised estimate of more common than 1 in 500 were the identification of gene carriers who are negative for the HCM phenotype; enhanced clinical identification of the HCM phenotype with advanced imaging; recognition that because of the autosomal-dominant inheritance pattern, multiple relatives of probands (and carriers) would be affected by HCM; and recognition that up to 0.6% of the population may carry HCM-causing sarcomere mutations. CMR = cardiac magnetic resonance.
Valsartan for Attenuating Disease Evolution In Early Sarcomeric HCM (VANISH)

This study is currently recruiting participants. (see Contacts and Locations)

Verified April 2016 by New England Research Institutes

Sponsor:
New England Research Institutes

Collaborator:
National Heart, Lung, and Blood Institute (NHLBI)

Information provided by (Responsible Party):
New England Research Institutes

ClinicalTrials.gov Identifier: NCT01912534

First received: June 5, 2013
Last updated: May 16, 2016
Last verified: April 2016

History of Changes
Eligibility Criteria

Inclusion Criteria:

1. All subjects must have a Pathogenic or Likely Pathogenic HCM Sarcomere Mutation
   a. The following categories of mutations are considered acceptable for subjects who have previously undergone clinical genetic testing. If results are ambiguous, they will be reviewed by the Clinical Coordinating Center to determine eligibility.

   - Laboratory for Molecular Medicine (Pathogenic, Likely Pathogenic)
   - Transgenomics/ PGXHealth (Class I)
   - GeneDx (Disease causing; Variant; likely disease-causing; Published, disease-causing mutation; Novel, likely disease-causing, mutation)
   - Correlagen (Associated; Probably Associated)
P defines meaningful G

G defines meaningful P???
Table 2. Comparison of LVH in African American and White Athletes

<table>
<thead>
<tr>
<th>Athlete Group</th>
<th>African American (n = 406)</th>
<th>White (n = 107)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum mean LVWT, mm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted (95% CI)</td>
<td>11.2 (11.1-11.3)</td>
<td>10.5 (10.3-10.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Adjusted (95% CI)</td>
<td>11.2 (11.1-11.4)</td>
<td>10.4 (10.2-10.6)</td>
<td></td>
</tr>
<tr>
<td>Mean LVMI, g/m²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted (95% CI)</td>
<td>106.3 (104.6-108.0)</td>
<td>102.2 (99.0-105.4)</td>
<td>.03</td>
</tr>
<tr>
<td>Adjusted (95% CI)</td>
<td>106.5 (104.8-108.2)</td>
<td>101.7 (98.4-105.0)</td>
<td></td>
</tr>
<tr>
<td>Mean RWT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted (95% CI)</td>
<td>0.39 (0.38-0.40)</td>
<td>0.35 (0.34-0.36)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Adjusted (95% CI)</td>
<td>0.39 (0.38-0.40)</td>
<td>0.35 (0.34-0.36)</td>
<td></td>
</tr>
<tr>
<td>LVH, No. (%)b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concentric nondilated</td>
<td>60 (53.1)</td>
<td>4 (19.0)</td>
<td>.004</td>
</tr>
<tr>
<td>Eccentric nondilated</td>
<td>7 (6.2)</td>
<td>0</td>
<td>.60</td>
</tr>
<tr>
<td>Concentric dilated</td>
<td>19 (16.8)</td>
<td>7 (33.3)</td>
<td>.13</td>
</tr>
<tr>
<td>Eccentric dilated</td>
<td>27 (23.9)</td>
<td>10 (47.6)</td>
<td>.03</td>
</tr>
</tbody>
</table>

Abbreviations: LVH, left ventricular (LV) hypertrophy; LVMI, LV mass index; LVWT, LV wall thickness; RWT, relative wall thickness.

a Linear regression was used to calculate adjusted means after adjustment for age, body surface area, and systolic and diastolic blood pressure.

b Pattern of hypertrophy is shown as percentages of African American and white athletes with subtypes of hypertrophy.
Challenge Question #2

Causes of left ventricular hypertrophy other than hypertrophic cardiomyopathy (HCM) include:

(a) Systemic hypertension
(b) Athletic conditioning
(c) Aortic valve stenosis
(d) a and b
(e) a, b, and c
P = G + E
HCM is one test of many
Challenge Question #3

If a test to detect a disease whose prevalence is 1/1000 has a false positive rate of 5 percent, what is the chance that a person found to have a positive result actually has the disease, assuming you know nothing about the person’s symptoms or signs?

(a) 100%
(b) 95%
(c) 50%
(d) 25%
(e) 2%
Formal approach: Bayes’ Rule

\[ P(D^+ | T^+) = \frac{P(D^+)P(T^+ | D^+)}{P(D^+)P(T^+ | D^+) + P(D^-)P(T^+ | D^-)} \]
Intuitive approach

1000 people
  999 healthy
    (prevalence = 1/1000)
  1 disease
    (false positive rate = 5%)
    ~949 true negatives
    ~50 false positives
    0 false negatives

PPV ≈ 1 in 51

1 true positive
Reconciling with Bayes

1000 people

999 healthy

1 disease

1 true positive

0 false negatives

~50 false positives

~949 true negatives

$$\frac{P(D^+)P(T^+ | D^+)}{P(D^+)P(T^+ | D^+) + P(D^-)P(T^+ | D^-)} = P(D^+ | T^+)$$

PPV ≈ 1 in 51
Figure. Distribution of Responses to Survey Question Provided in the Article Text

Most common answer: 95%
Correct answer: 2%

- Students (n = 10)
- House staff (n = 26)
- Attending physicians (n = 25)
Common Mistakes

“true positive rate” = 1 – “false positive rate”
Specificity = 1 – “false positive rate”
95% specificity is “very good”
Prevalence influences the quality of a test
Positive test makes the disease less likely (8 respondents)
Even a completely random positive test result will not decrease PPV below prevalence
INTERPRETATION BY PHYSICIANS OF CLINICAL LABORATORY RESULTS

WARD CASSCELLS, B.S., ARNO SCHOENBERGER, M.D.,
AND THOMAS B. GRABOYS, M.D.

As both the number and cost of clinical laboratory tests continue to increase at an accelerating rate, physicians are faced with the task of comprehending and acting on a rising flood tide of information. We conducted a small survey to obtain some idea of how physicians do, in fact, interpret a laboratory result.
Genomics for the world

Carlos D. Bustamante, Francisco M. De La Vega & Esteban G. Burchard

**SAMPLING BIAS**
Most genome-wide association studies have been of people of European descent.

96% European descent
4% Non-European descent

Genomics is failing on diversity

Alice B. Popejoy & Stephanie M. Fullerton

12 October 2016

An analysis by Alice B. Popejoy and Stephanie M. Fullerton indicates that some populations are still being left behind on the road to precision medicine.

Subject terms: Diseases • Genetics • Genomics • Health care
PERSISTENT BIAS

Over the past seven years, the proportion of participants in genome-wide association studies (GWAS) that are of Asian ancestry has increased. Groups of other ancestries continue to be very poorly represented.

2009
- 373 studies
- 1.7 million samples
- 96% European ancestry
- 4% Non-European ancestry

2016
- 2,511 studies
- 35 million samples
- 81% European ancestry
- 19% Non-European ancestry

BREAKDOWN
Proportion of non-European ancestry samples

Terms for ethnicity are those used in the GWAS Catalog. Some have changed between 2009 and 2016 as sampling has increased. Samples of European origin have the most specific descriptions of population ancestry.

Summary

• We identified common (benign) genetic variants misclassified (as pathogenic) exclusively in African Americans

• This creates the potential for healthcare disparities due to genomic misdiagnosis

• Variants vetted in diverse control populations can help prevent false positives

• Statistics over calculus for rational decision making
Acknowledgments

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Thank you