BACKGROUND: Genetic testing for families with hypertrophic cardiomyopathy (HCM) provides a significant opportunity to improve care. Recent trends to increase gene panel sizes often mean variants in genes with questionable association are reported to patients. Classification of HCM genes and variants is critical, as misclassification can lead to genetic misdiagnosis. We show the validity of previously reported HCM genes using an established method for evaluating gene-disease associations.

METHODS: A systematic approach was used to assess the validity of reported gene-disease associations, including associations with isolated HCM and syndromes including left ventricular hypertrophy. Genes were categorized as having definitive, strong, moderate, limited, or no evidence of disease causation. We also reviewed current variant classifications for HCM in ClinVar, a publicly available variant resource.

RESULTS: Fifty-seven genes were selected for curation based on their frequent inclusion in HCM testing and prior association reports. Of 33 HCM genes, only 8 (24%) were categorized as definitive (MYBPC3, MYH7, TNNT2, TNNT3, TPM1, ACTC1, MYL2, and MYL3); 3 had moderate evidence (CSRP3, TNNC1, and JPH2; 33%); and 22 (66%) had limited (n=16) or no evidence (n=6). There were 12 of 24 syndromic genes definitively associated with isolated left ventricular hypertrophy. Of 4191 HCM variants in ClinVar, 31% were in genes with limited or no evidence of disease association.

CONCLUSIONS: The majority of genes previously reported as causative of HCM and commonly included in diagnostic tests have limited or no evidence of disease association. Systematically curated HCM genes are essential to guide appropriate reporting of variants and ensure the best possible outcomes for HCM families.
Hypertrophic cardiomyopathy (HCM) is an inherited cardiomyopathy, characterized by left ventricular hypertrophy (LVH) in the absence of loading conditions such as hypertension.\textsuperscript{1,2} HCM affects \( \approx 1 \) in 500 in the general population\textsuperscript{3,4} with clinical features in patients ranging from asymptomatic to heart failure and sudden cardiac death. Since the first chromosomal location was mapped in 1989,\textsuperscript{5} variants in numerous genes have been reported to cause HCM. Clinical diagnostic genetic testing for HCM has become increasingly part of mainstream clinical management of patients\textsuperscript{6–8} with a key role in cascade testing of family members. Genotype positive relatives can be targeted for ongoing cardiac screening while genotype negative relatives can be released from life-long surveillance and worry.\textsuperscript{8} Although there is potential for HCM genetic testing to add significant value to family management, nonjudicious use has potential for harm including variant misclassification and genetic misdiagnosis.\textsuperscript{9}

The implementation of next-generation sequencing has led to a rapid expansion in the number of genes included in a typical diagnostic gene panel. Gene selection, in addition to increased stringency and expert classification of variants,\textsuperscript{8–11} is a crucial but often overlooked first step. Identification of variants in genes with limited gene-disease association has the potential to add uncertainty and misinterpretation of variants as causative.\textsuperscript{12–14} Here, we examine the evidence supporting 57 genes included on diagnostic HCM gene panels using the National Institutes of Health-funded Clinical Genome Resource (ClinGen) framework for evaluating gene-disease clinical validity.\textsuperscript{15,16} Although other recent studies have investigated specific aspects of HCM gene association such as gene burden, we bring together all available evidence in a systematic way. We evaluate the quantity and quality of clinical genetic and experimental data using a scoring matrix and give a final overall summary classification. In addition, we use the public repository ClinVar,\textsuperscript{17} to cross-reference HCM variant classifications and to examine the impact of including insufficiently supported genes in clinical testing.

METHODS
All data and materials have been made publicly available on the ClinGen website \url{https://www.clinicalgenome.org/working-groups/clinical-domain/cardiovascular-clinical-domain-working-group/hypertrophic-cardiomyopathy-gene-ep/} and can be accessed at URL in the Data Supplement. No institutional review board approval was required. The full Methods are available in the Data Supplement.

RESULTS
Selection of the Gene List
Of 328 gene panels identified in the National Center for Biotechnology Information Genetic Testing Registry, 24 were included (Table I in the Data Supplement; 20 panels identified as HCM panels and 4 cardiomyopathy panels). The mean (±SD) number of genes per panel was 33±25, including 8±0.3 sarcomere genes, 4±2 storage cardiomyopathy, and RASopathy genes (LAMP2, PRKAG2, TTR, GLA, PTPN11, RIT1, and RAF1) and 22±23 other genes (range, 0–75). There were 162 unique genes represented across all panels (Figure II in the Data Supplement; Table II in the Data Supplement). Only 23 (14%) genes were present on >50% of the panels. All panels included key sarcomere genes (MYBPC3, MYH7, TNNT2, TNNI3, TPM1, ACTC1, MYL2, and MYL3), except one that did not include MYH7. The final curation list included 57 genes (Tables III and IV in the Data Supplement); 33 were curated for HCM and 24 for syndromes or conditions including LVH (Figure III in the Data Supplement; Table V in the Data Supplement). Twenty-six of the 57 genes had prior reported association with HCM in Online Mendelian Inheritance in Man (http://www.omim.org; Tables VI and VII in the Data Supplement).

Classification of HCM Genes
Of the 33 genes classified for HCM, 8 (24.2%) were classified as definitive, 3 (9.1%) as moderate, 16 (48.5%) as limited, and 6 (18.2%) as no evidence (Figure 1). Those classified as definitive included well-known disease genes that have been included in diagnostic gene panels for over a decade (MYBPC3, MYH7, TNNT2, TNNI3, TPM1, ACTC1, MYL3, and MYL2). All definitive genes primarily reached this classification because of genetic evidence reflecting numerous reports from the literature of causative variants in cases with HCM. Furthermore, all genes had some variants with strong segregation data and an aggregate variant excess in cases compared with controls (Table 1).\textsuperscript{12} Moderate level gene classifications included TNNC1, JPH2, and CSRP3, with evidence typically including either segregation evidence or reported \textit{de novo} variants and some experimental evidence (Table 2). The majority \((n=22; 66.7\%)\) of genes had limited or no evidence of HCM association. Limited evidence genes typically included evidence from candidate gene studies, with observation of rare variants in cases, but without statistical evidence of an excess of rare variation in cases compared with background variation in controls, or segregation data, and minimal experimental evidence mostly from expression data. In some cases, limited evidence was available from animal models (KLF10, MYOZ2, and MYPN).

Impact of Including HCM Candidate Genes in Diagnostic Gene Panels
The American College of Medical Genetics and Genomics and the Association for Molecular Pathology variant...
Classification framework requires substantial evidence for a gene-disease association to assign a pathogenic or likely pathogenic classification to variants identified in any specific gene. The inclusion of insufficiently supported genes in diagnostic testing practice increases the likelihood of inconclusive results being provided to clinicians. Moreover, this effect can be pronounced when these genes have a high rate of population variation. To investigate this, we analyzed ClinVar variant entries for the HCM genes included in our curation effort. This resulted in 4191 assertions for variants in 50 genes (Table VIII in the Data Supplement). Of all assertions, 831 (20%) were classified as pathogenic, 584 (14%) were likely pathogenic, and 2776 (66%) were variants of uncertain significance (VUS) (Figure 2; Table IX in the Data Supplement). There were 65 (5%) variants in genes with limited or no evidence classified as likely pathogenic or pathogenic, with most (n=38) being truncating or splice variants in TTN, which are known to occur at high frequency (≈1%) in the general population. In total, 1252 VUS assertions were in HCM genes adjudicated as limited or no evidence and accounted for 30% of all assertions in ClinVar meeting analysis criteria for this study.

Classification of Syndromic Genes

Twenty-four genes were curated for syndromes involving LVH, with the specific syndrome the gene was curated for shown in Table 3. Two genes (ACTN2 and PLN) best fit an intrinsic (primary) cardiomyopathy phenotype given there were no extracardiac features reported. PLN reached a definitive classification, with the phenotype spectrum including HCM, arrhythmogenic right ventricular cardiomyopathy, and dilated cardiomyopathy. ACTN2 reached a moderate classification, with the reported phenotypes including HCM, left ventricular noncompaction, atrial arrhythmias, and idiopathic ventricular fibrillation. Dilated cardiomyopathy cases were carefully reviewed to exclude end-stage HCM.

Twelve genes were curated for syndromes that may present with isolated, or seemingly isolated, LVH. Of those, 11 were classified as having a definitive association with their respective syndromes. CACNA1C is associated with Timothy syndrome. Infants may present with severe biventricular hypertrophy, and 2 variants at a single amino acid position (p.Arg518Cys and p.Arg518His)
have been reported to occur in families with LVH, prolonged QT interval, and sudden cardiac death. Variants in *DE5* cause a desminopathy, often occur de novo and are associated with a range of features including progressive skeletal muscle weakness, cardiomyopathy, including LVH in some cases, and cardiac conduction disease. *FHL1* has been shown to cause Emery-Dreifuss muscular dystrophy, which can include LVH, even in the absence of significant muscle weakness. *FLNC* causes a myofibrillar myopathy, though families with isolated LVH are known. Four genes, all associated with metabolic storage phenotypes that can mimic HCM (*GLA*: Fabry disease, *LAMP2*: Danon disease, *PRKAG2*: PRKAG2 cardiomyopathy, and *TTR*: transthyretin amyloidosis), were classified as definitive. *PTPN11*, *RAF1*, and *RIT1* are associated with Noonan syndrome and were classified as definitive. Autosomal recessive loss-of-function variants in *ALPK3* cause a severe infant-onset cardiomyopathy and were classified as strong. Ten genes were curated for syndromes that may include LVH only in combination with overt extracardiac phenotypic features, therefore making variants in these genes of limited diagnostic value. A summary of all genes curated for HCM is provided in Table 2.

Table 2. Genetic, Experimental, and Overall Classifications for Genes Curated for HCM

| Gene   | Genetic Evidence | Experimental Evidence | Score | Classification | Presence on GTR Panels, n (%) | ClinVar LP/P HCM Submissions, n (%) | Inheritance Pattern | Variant Type* |
|--------|------------------|-----------------------|-------|----------------|-------------------------------|-------------------------------------|---------------------|---------------|
| MYL2   | 11.5             | 4.5                   | 18    | Definitive     | 24 (100)                      | 33 (2.3)                            | AD, Missense        |
| TNNT2  | 12               | 6                     | 18    | Definitive     | 24 (100)                      | 71 (5.0)                            | AD, Missense, splice|
| ACTC1  | 12               | 5.5                   | 17.5  | Definitive     | 22 (92)                       | 11 (0.8)                            | AD, Missense        |
| MYBPC3 | 11               | 6                     | 17    | Definitive     | 24 (100)                      | 628 (44.4)                          | AD, Missense, LOF  |
| MYH7   | 12               | 5                     | 17    | Definitive     | 23 (96)                       | 393 (27.8)                          | AD, Missense        |
| TPM1   | 11               | 6                     | 17    | Definitive     | 24 (100)                      | 26 (1.8)                            | AD, Missense        |
| TNNT3  | 10.5             | 6                     | 16.5  | Definitive     | 24 (100)                      | 64 (4.5)                            | AD, Missense        |
| MYL3   | 11.5             | 2.5                   | 14    | Definitive     | 24 (100)                      | 16 (1.1)                            | AD, Missense, splice|
| CSR13  | 8.4              | 2.5                   | 10.9  | Moderate       | 16 (67)                       | 8 (0.6)                             | AD, Missense, LOF  |
| TNX1   | 4                | 5                     | 9     | Moderate       | 22 (92)                       | 8 (0.6)                             | AD, Missense, LOF  |
| JPH2   | 4.2              | 4.5                   | 8.7   | Moderate       | 12 (50)                       | 4 (0.3)                             | AD, Missense        |
| TTN    | 1.5              | 4.5                   | 6     | Limited        | 10 (42)                       | 42 (3.0)                            | AD, Missense        |
| KLF10  | 1.25             | 4.5                   | 5.75  | Limited        | 1 (4)                         | 0 (0)                               | AD, Missense        |
| MYPHV  | 0.9              | 2.5                   | 3.4   | Limited        | 9 (38)                        | 2 (0.1)                             | AD, Missense, LOF  |
| ANKRD1 | 1.1              | 2                     | 3.1   | Limited        | 10 (42)                       | 1 (0.1)                             | AD, Missense        |
| MYLK2  | 0.1              | 3                     | 3.1   | Limited        | 10 (42)                       | 2 (0.1)                             | AD, Missense        |
| MYOZ2  | 1.5              | 1.5                   | 3     | Limited        | 15 (63)                       | 2 (0.1)                             | AD, Missense        |
| NEXN   | 0.5              | 1.5                   | 2     | Limited        | 15 (63)                       | 2 (0.1)                             | AD, Missense        |
| VCL    | 0.5              | 1                     | 1.5   | Limited        | 12 (50)                       | 3 (0.2)                             | AD, Missense        |
| TRIM63 | 0.4              | 1                     | 1.4   | Limited        | 2 (8)                         | 0 (0)                               | AD, Missense, LOF  |
| RYR2   | 0.9              | 0.5                   | 1.4   | Limited        | 5 (21)                        | 0 (0)                               | AD, Missense, LOF  |
| MYH6   | 0.3              | 1                     | 1.3   | Limited        | 15 (63)                       | 4 (0.3)                             | AD, Missense        |
| OBSCN  | 0.3              | 1                     | 1.3   | Limited        | 2 (8)                         | 0 (0)                               | AD, Missense, LOF  |
| PDUM3  | 0.3              | 0.5                   | 1     | Limited        | 2 (8)                         | 0 (0)                               | AD, Missense, LOF  |
| TCAP   | 0.2              | 1                     | 1.2   | Limited        | 12 (50)                       | 3 (0.2)                             | AD, Missense        |
| MYOM1  | 0.5              | 0.5                   | 1     | Limited        | 2 (8)                         | 1 (0.1)                             | AD, Missense        |
| CALR3  | 0.2              | 0                     | 0.2   | Limited        | 7 (29)                        | 1 (0.1)                             | AD, Missense        |
| ACTA1  | 0.2              | 0                     | 0     | No evidence    | 1 (4)                         | 0 (0)                               | ...                 |
| CASQ2  | 0.2              | 0                     | 0     | No evidence    | 1 (4)                         | 0 (0)                               | ...                 |
| CACNB2 | 0.2              | 0                     | 0     | No evidence    | 2 (8)                         | 0 (0)                               | ...                 |
| DSP    | 0.2              | 0                     | 0     | No evidence    | 5 (12)                        | 0 (0)                               | ...                 |
| KCNQ1  | 0.2              | 0                     | 0     | No evidence    | 2 (8)                         | 2 (0.1)                             | ...                 |
| TEMPO  | 0.2              | 0                     | 0     | No evidence    | 3 (13)                        | 0 (0)                               | ...                 |

AD, autosomal dominant inheritance; HCM, hypertrophic cardiomyopathy; GTR, genetic testing registry; LOF, loss of function; and LP/P, likely pathogenic and pathogenic.

*Type of variant for those counted in genetic evidence. Other variant types may have been reported but not included in score if maximum number already reached. LOF includes insertions and deletions leading to a frameshift, canonical splice, and nonsense variants.

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genes unlikely to be reasonably mistaken for typical HCM (Table 3).

DISCUSSION

We report a systematic classification of genes commonly included in HCM genetic testing or previously reported as HCM genes in the public domain, using the ClinGen gene curation clinical validity framework. Two-thirds of the curated genes had limited or no evidence of HCM association. We observed little consistency among currently offered diagnostic gene panels, likely influenced by the lack of widely accepted systematic curation efforts and absence of clear guidelines about the design of clinically valid gene panels. Reporting a VUS may cause confusion, especially to clinicians less sanguine in understanding their marginal utility for clinical care. As genetic testing enters mainstream medical practice, discontinuity between evidence in support of specific gene-disease associations and the interpretation and use of variant data can be minimized with robust systematic gene classification efforts.

Our findings have direct clinical implications for the genetic evaluation and care of HCM families. We show that in ClinVar, a large publicly accessible database, nearly 30% of assertions made for HCM in our curated gene list were VUS in genes with limited or no evidence of HCM association. This illustrates VUS inflation because of reporting of variants in these genes. Genetic test results are probabilistic and some degree of uncertainty is inherent, though efforts should be made to minimize this where possible in the clinical setting, focusing on results that are meaningful to the clinician, patient, and family. Given the uncertainty we face in understanding the significance of rare variation in numerous genes, the reporting of VUS in genes with tenuous HCM association is at best unnecessary and time-consuming, and at worst has potential to inflict harm to families who may be over-investigated or inappropriately treated, especially in the absence of specialized disease-specific expertise. As predictive testing
becomes mainstream, it will be increasingly important to consider the evidence supporting a disease association to avoid misclassification of uncertain variants that can lead to unnecessary medical action.

Clearly defined boundaries are needed for when candidate genes should be used for clinical testing. The current plethora of genes purported to be associated with HCM is the result of dedicated efforts to better elucidate its genetic architecture. A decade ago, the promise of identifying new genes to explain gene-negative HCM cases was the driver of numerous candidate gene studies. At that time a missense variant in a conserved region, absent in a small set of control alleles, and with some evidence of segregation, suggested a new HCM gene association. Such an approach is now widely recognized as insufficient\(^{10,29}\); however, published disease associations have led to inclusion of such genes on clinical test panels.

Diagnostic gene panels should include genes considered to have definitive or strong evidence of disease association to minimize the risk of inconclusive findings. Moderately associated genes should be considered more carefully, though variants may be considered causative if there is very clear supportive evidence of a functional or damaging effect for the variant. Inclusion of genes with limited or no evidence for a disease association can be useful when the availability of large pedigrees allows clarification of uncertain variants identified in the proband, or when multiple family member exome or genome testing is used for clinically challenging cases. However, these applications currently straddle the boundary between diagnostic and research

### Table 3. Genetic, Experimental, and Overall Classifications for Genes Curated for Syndromes Including LVH

| Intrinsic cardiomyopathy genes | Genetic Evidence | Experimental Evidence | Score | Classification | Phenotype Spectrum Curated | Isolated* LVH? | Presence on GTR HCM Panels, n (%) |
|--------------------------------|------------------|-----------------------|-------|----------------|---------------------------|---------------|-----------------------------------|
| ACTN2                          | 3.6              | 4.5                   | 8.1   | Moderate       | LVH, LVNC, DCM, and idiopathic VF | Yes           | 14 (58.3)                        |
| PLN                            | 8.75             | 6                     | 14.75 | Definitive     | HCM, DCM, and ARVC        | Yes           | 15 (62.5)                        |

| Syndromic genes, where isolated LVH may be seen | Genetic Evidence | Experimental Evidence | Score | Classification | Phenotype Spectrum Curated | Isolated* LVH? | Presence on GTR HCM Panels, n (%) |
|------------------------------------------------|------------------|-----------------------|-------|----------------|---------------------------|---------------|-----------------------------------|
| ALPK3                                         | 9                | 3.5                   | 12.5  | Strong         | Infant-onset HCM/DCM      | Yes           | 1 (4)                             |
| CACNA1C                                       | 10.85            | 6                     | 16.85 | Definitive     | Timothy syndrome          | Yes           | 2 (8.3)                           |
| DES                                           | 12               | 6                     | 18    | Definitive     | Desminopathy              | Yes           | 8 (33.3)                          |
| FHL1                                          | 12               | 6                     | 18    | Definitive     | Emery-Dreifuss MD         | Yes           | 5 (20.8)                          |
| FLNC                                          | 7.5              | 6                     | 13.5  | Definitive     | Myofibrillar myopathy     | Yes           | 2 (8.3)                           |
| GLA                                           | 12               | 5                     | 17    | Definitive     | Fabry disease             | Yes           | 19 (79.2)                         |
| LAMP2                                         | 12               | 3.5                   | 15.5  | Definitive     | Danon disease             | Yes           | 20 (83.3)                         |
| PRKAG2                                        | 12               | 6                     | 18    | Definitive     | PRKAG2 cardiomyopathy     | Yes           | 20 (83.3)                         |
| PTPN11                                        | 12               | 6                     | 18    | Definitive     | Noonan syndrome           | Yes           | 7 (29.2)                          |
| RAF1                                          | 12               | 6                     | 18    | Definitive     | Noonan syndrome           | Yes           | 7 (29.2)                          |
| RIT1                                          | 12               | 6                     | 18    | Definitive     | Noonan syndrome           | Yes           | 2 (8.3)                           |
| TTR                                           | 12               | 5.5                   | 17.5  | Definitive     | Transthyretin amyloidosis | Yes           | 17 (70.8)                         |

| Syndromic genes, where LVH is seen only with overt syndromic features | Genetic Evidence | Experimental Evidence | Score | Classification | Phenotype Spectrum Curated | Isolated* LVH? | Presence on GTR HCM Panels, n (%) |
|---------------------------------------------------------------------|------------------|-----------------------|-------|----------------|---------------------------|---------------|-----------------------------------|
| ABC9                                                               | 12               | 1                     | 13    | Definitive     | Cantu syndrome            | No            | 4 (16.7)                          |
| BAG3                                                               | 7                | 5                     | 12    | Definitive     | Myofibrillar myopathy     | No            | 6 (25.0)                          |
| CAV3                                                               | 8.5              | 6                     | 14.5  | Definitive     | Caveolinopathy            | No            | 15 (62.5)                         |
| COX15                                                              | 8                | 5                     | 13    | Strong         | Leigh syndrome            | No            | 4 (16.7)                          |
| CRYAB                                                              | 7                | 6                     | 13    | Definitive     | Alpha-B crystallinopathy  | No            | 5 (20.8)                          |
| FXN                                                                | 10               | 6                     | 16    | Definitive     | Friedreich ataxia         | No            | 3 (12.5)                          |
| GAA                                                                | 12               | 6                     | 18    | Definitive     | Pompe disease             | No            | 4 (16.7)                          |
| LDB3                                                               | 3.3              | 4.5                   | 7.8   | Moderate       | Myofibrillar myopathy     | No            | 9 (37.5)                          |
| MYO6                                                               | 12               | 3                     | 15    | Definitive     | Bilateral hearing loss, LVH† | No           | 0 (0)                             |
| SLC25A4                                                            | 7.5              | 6                     | 13.5  | Definitive     | Mitochondrial disease     | No            | 3 (12.5)                          |

ARVC indicates arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; GTR, genetic testing registry; HCM, hypertrophic cardiomyopathy; LVH, left ventricular hypertrophy; LVNC, left ventricular noncompaction; MD, muscular dystrophy; and VF, ventricular fibrillation.

*Includes seemingly isolated LVH.

†One family reported to have 4/10 affected relatives also having LVH.
CONCLUSIONS

HCM genetic testing has entered mainstream medical care. HCM genetic testing has important benefits for asymptomatic at-risk relatives and in the future may play a role in prognostic and therapeutic stratification of the proband. Our findings highlight that most re-directed panels are configured to evaluate several disorders with clinical and genetic overlap, however, this approach is likely to result in greater identification of VUS.

Study limitations include genes potentially not curated in this iteration. However, our systematic approach to selecting genes ensured that we included most with a published association with HCM and those commonly included on panels. The ClinGen gene curation framework assumes a Mendelian mode of inheritance; more complex models, should they be relevant, exceed this analysis paradigm. Gene classifications provided were based on available evidence at the time of curation; ongoing and updated reassessments of gene-disease associations are essential. Importantly, our framework relies on variant curation, and whereas the difficulties in determining variant pathogenicity have been well documented,12,13,30,31 we relied on variant curation best practices as foundational to this effort. The materials and framework to perform gene curation are publicly available. Summaries for the gene-disease evidence assessments are available online (https://search.clinical-genome.org/kb/gene-validity) and in Document II in the Data Supplement.

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