Harmonizing the Collection of Clinical Data on Genetic Testing Requisition Forms to Enhance Variant Interpretation in Hypertrophic Cardiomyopathy (HCM)

A Study from the ClinGen Cardiomyopathy Variant Curation Expert Panel

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Diagnostic laboratories gather phenotypic data through requisition forms, but there is no consensus as to which data are essential for variant interpretation. The ClinGen Cardiomyopathy Variant Curation Expert Panel defined a phenotypic data set for hypertrophic cardiomyopathy (HCM) variant interpretation, with the goal of standardizing requisition forms. Phenotypic data elements listed on requisition forms from nine leading cardiomyopathy testing laboratories were compiled to assess divergence in data collection. A pilot of 50 HCM cases was implemented to determine the feasibility of harmonizing data collection. Laboratory directors were surveyed to gauge potential for adoption of a minimal data set. Wide divergence was observed in the phenotypic data fields in requisition forms. The 50-case pilot showed that although demographics and assertion of a clinical diagnosis of HCM had 86% to 98% completion, specific phenotypic features, such as degree of left ventricular hypertrophy, ejection fraction, and suspected syndromic disease, were completed only 24% to 44% of the time. Nine data elements were deemed essential for variant classification by the expert panel. Participating laboratories unanimously expressed a willingness to adopt these data elements in their requisition forms. This study demonstrates the value of comparing and sharing best practices through an expert group, such as the ClinGen Program, to enhance variant interpretation, providing a foundation for leveraging cumulative case-level data in public databases and ultimately improving patient care. (J Mol Diagn 2021, 23: 589–598; https://doi.org/10.1016/j.jmoldx.2021.01.014)
interpreting genetic testing results has not been documented in the literature. Led by ClinGen’s Cardiomyopathy Variant Curation Expert Panel, herein referred to as the ClinGen Expert Panel, this study was set out to determine the minimum phenotypic data elements required to assign affected status for a case during variant classification and enhance the ability to interpret complex cases during variant classification for HCM.

**Materials and Methods**

**Development of the Expert Panel Cardiovascular Phenotypic Data Elements List**

Members of the expert panel developed a list of cardiovascular data elements typically documented in cardiology clinic notes and included in requisition forms. The list, which was generated to define the data collection approach for this study, was drafted by a cardiovascular genetic counselor (A.M.), and revisions were made by cardiologists (R.E.H., C.S., and J.W.) to ensure that the list was representative of the standard clinical diagnostic criteria of HCM. This comprehensive list was based on existing requisition forms and input from expert HCM clinicians. However, the list was not intended to replace or redefine the clinical diagnostic criteria for HCM, which should be determined only by physician expertise. It was rather intended to identify individuals to be counted as bona fide cases, consistent with the PS4 and PP1 evidence from the 2015 American College of Medical Genetics and Genomics/Association for Molecular Pathology guidelines.

**Review of Existing Laboratory Requisition Forms**

To characterize the extent of discrepancy across laboratory requisition forms used in the community, review of the Genetic Testing Registry database (https://www.ncbi.nlm.nih.gov/gtr, last accessed August 10, 2016) was performed.

| Expert panel cardiovascular data elements list | Information provided (LMM pilot study) | Participating laboratories reported frequency of obtaining data, % | Final consensus |
|-----------------------------------------------|----------------------------------------|---------------------------------------------------------------|-----------------|
| Sex                                           | 48/50                                  | Very frequently and frequently: 100; Sometimes: 0; Very infrequently and infrequently: 0 | Y               |
| Race and ethnicity                             | 43/50                                  | 50; 25; 25                                                    | Y               |
| Current age                                    | 50/50                                  | 100; 0; 0                                                     | Y               |
| Family history                                 | 45/50                                  | 62.5; 25; 12.5                                                | Y               |
| Clinical diagnosis of HCM                     | 49/50                                  | 62.5; 37.5; 0                                                 | Y               |
| Age at diagnosis                               | 25/50                                  | 12.5; 62.5; 25                                                | Y               |
| Left ventricular hypertrophy                  | 22/50                                  | 25; 75; 0                                                    | Y               |
| Left ventricular hypertrophy measurement      | 15/50                                  | 25; 25; 50                                                   | Y               |
| Left ventricular outflow tract obstruction     | 0/50                                   | 0; 71.43; 28.58                                              | N               |
| Reduced ejection fraction percentage           | 12/50                                  | 0; 62.5; 37.5                                                | N               |
| Ejection fraction percentage                  | 2/50                                   | 12.5; 25; 62.5                                               | N               |
| History of hypertension                        | 16/50                                  | 0; 50; 50                                                   | Y               |
| Blood pressure on treatment                   | 0/50                                   | 14.29; 14.29; 71.43                                          | Y               |
| Suspected syndromic HCM/other cause           | 15/50                                  | 0; 0; 100                                                    | Y               |
| ECG with left ventricular hypertrophy or atrial fibrillation | 22/50 | 0; 25; 75 | N               |
| History of syncope                             | 0/50                                   | 14.29; 57.14; 28.57                                          | N               |
| Nonsustained ventricular tachycardia on Holter| 3/50                                   | 0; 12.5; 87.5                                                | N               |
| Late gadolinium enhancement on cardiac MRI     | 0/50                                   | 0; 0; 100                                                    | N               |

ECG, electrocardiogram; HCM, hypertrophic cardiomyopathy; LMM, Laboratory for Molecular Medicine; MRI, magnetic resonance imaging; N, no; Y, yes.
### Table 2: Data Collection on Requisition Forms in Selected Laboratories

| Variable                                      | Laboratory 1 | Laboratory 2 | Laboratory 3 | Laboratory 4 | Laboratory 5 | Laboratory 6 | Laboratory 7 | Laboratory 8 | Laboratory 9 |
|------------------------------------------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|
| Demographics                                  | X            | X            | X            | X            | X            | X            | X            | X            |              |
| Ethnicity/ancestry                            | X            | X            | X            | X            | X            | X            | X            | X            |              |
| Family history                                |              |              |              |              |              |              |              |              |              |
| Syncope                                       |              |              |              | X            |              |              |              |              |              |
| Episodes                                      |              |              |              | X            |              |              |              |              |              |
| Cardiac arrest/sudden cardiac death           |              | X            |              | X            | X            | X            |              |              |              |
| HCM                                           | X            | X            |              |              |              |              |              |              |              |
| Congestive cardiac failure                    |              |              |              |              |              | X            |              |              |              |
| Stroke                                        |              |              |              |              |              |              |              |              | X            |
| Other cardiomyopathy                          | X            |              |              |              |              |              |              |              |              |
| Family genetic testing                        |              |              |              |              |              |              |              |              | X            |
| Free text (for family history only)           | X            | X            | X            | X            | X            | X            | X            | X            | X            |
| Proband history (risk factors)                | X            | X            |              |              | X            |              |              | X            |              |
| Sudden cardiac arrest history Y/N             |              |              |              |              |              |              |              |              |              |
| If SCD, number of episodes                    |              |              |              |              |              |              |              |              |              |
| If SCD, age at first episode                  |              |              |              |              |              |              |              |              | X            |
| Hypertension                                  |              |              |              |              |              |              |              |              | X            |
| History of syncope Y/N                       | X            | X            |              |              |              |              |              |              |              |
| Other symptoms                                | X            | X            |              |              |              |              |              |              | X            |
| Proband history (named diagnoses)             | X            | X            | X            | X            | X            | X            | X            | X            | X            |
| Free text (summary field for all clinical information) | X            |              |              |              | X            | X            | X            | X            | X            |
| Unknown diagnosis                             |              |              |              |              | X            |              |              |              |              |
| Unaffected                                    |              |              |              |              |              | X            |              |              | X            |
| Age at diagnosis                              | X            | X            | X            |              |              | X            |              |              |              |
| Cardiomyopathy                                | X            | X            | X            |              |              | X            |              |              | X            |
| Diagnosis Y/N                                 | X            | X            | X            | X            | X            | X            |              |              |              |
| HCM                                           | X            | X            | X            | X            | X            | X            |              |              |              |
| Conventional diagnostic criteria for HCM      |              |              |              |              |              |              |              |              | X            |
| Other cardiomyopathy                          | X            | X            | X            |              | X            | X            |              |              |              |
| Arrhythmia diagnosis Y/N                      | X            | X            | X            |              | X            | X            |              |              | X            |
| Atrial fibrillation                           | X            | X            | X            |              | X            | X            |              |              | X            |
| Ventricular                                   | X            | X            | X            |              | X            | X            |              |              | X            |
| tachycardia                                   |              |              |              |              |              |              |              |              |              |
| WPW                                           |              | X            |              |              |              |              |              |              | X            |
| Other arrhythmia types                        | X            | X            | X            |              | X            |              |              |              | X            |
| Features of Danon                             |              |              |              |              |              |              |              |              | X            |
| Features of Fabry                             |              |              |              |              |              |              |              |              | X            |
| Other genetic conditions                      | X            |              |              |              |              |              |              |              |              |
| Previous genetic testing                      | X            | X            |              |              |              |              |              |              |              |
| Cardiac procedure questions                   |              |              |              |              |              |              |              |              | X            |

*(table continues)*
for laboratories offering DNA-based testing for HCM. The requisition forms were downloaded from their respective websites, and each field was documented. Data were aggregated to identify fields that were common across laboratories. If fields requesting similar data but using different descriptors were identified, one term was chosen.

Retrospective Case Requisition Review

A pilot study was designed to examine provider compliance in providing data on requisition forms and to determine the feasibility of harmonizing laboratory requisition forms based on the expert panel—derived phenotypic data elements. The pilot study consisted of 50 consecutive cases sent for HCM testing to the Laboratory for Molecular Medicine (LMM; a representative laboratory) between June 2015 and June 2016. The requisition fields on the LMM form were matched to the proposed expert panel data elements list. If a field was completed by the ordering provider, it was counted as completed, independently of the answer.

Laboratory Director Survey Development

Using insights gained from the retrospective case requisition review, a Laboratory Director Survey was developed by the study principals (A.M., A.I., and M.V.) and conducted in...
the spring of 2018 to determine whether the proposed criteria were essential and sufficient for variant classification (Supplemental Appendix S1).

Laboratory Director Survey: Participant Recruitment

Survey participants were recruited from laboratories offering cardiomyopathy genetic testing that also used expert panel members or associates. An introductory e-mail was sent, inviting all laboratory directors to participate and to provide one response per laboratory. Confidentiality was assured, and participants were informed that only aggregate data would be reported. The senior author (M.V.), a clinical molecular geneticist acting as a laboratory director signing out cardiovascular genetic reports, designated an alternate to complete the survey.

Expert Panel Conflict of Interest Management

Before this study, and as part of their initial recruitment to the expert panel, participants were required to declare conflicts of interest. Financial conflict of interest was defined as having a financial relationship with a commercial entity that provides genetic testing services or where there could be a vested interest in a particular gene and variant classification. Individuals may be perceived to have an academic conflict of interest when they have participated in scientific discoveries or the general body of knowledge regarding a particular gene or variant.

Consensus Building

The consensus building phase consisted of surveys and telephone calls. On the basis of the results of the Laboratory Director Survey, a second survey was designed by study principals (ClinGen Expert Panel Survey). It contained five questions, including one question in which endorsement of the proposed criteria was assessed (Supplemental Appendix S2) and was sent to members of the ClinGen Expert Panel on December 19, 2018, and closed on January 18, 2019. The members invited to participate were informed that lack of a response was interpreted as acceptance of the proposal. Majority approval was defined as obtaining support from at least three-fourths of the members. Survey results were discussed during ClinGen Expert Panel follow-up calls, at which time consensus was reached.

Results

Review of Existing Laboratory Requisition Forms

A total of 63 data elements were represented across requisition forms from nine laboratories (Table 2). Comparison of structured fields showed that the criteria on the expert panel—derived list were not consistently identified across laboratories. Furthermore, there were substantial differences in the types of phenotypic data requested by laboratories.

Most broad categories, such as demographics and family history, were present on most laboratories’ requisition forms. The specificity of the family history field, however, varied among laboratories. For example, some laboratories asked specific cardiomyopathy questions, including cardiomyopathy type or symptoms in the family, whereas others only asked a general question for the ordering provider to complete in free text form. Similarly, six laboratories requested information specifically regarding the patient’s cardiomyopathy, although no specific phenotype features were consistently identified as a data element field across all nine forms (e.g., diagnosis of cardiomyopathy, Y/N? or left ventricular measurement).

Retrospective Case Requisition Review

Review of the LMM requisition form used for the pilot study of 50 HCM cases revealed that, with the exception of left ventricular outflow tract obstruction, blood pressure on treatment, history of syncope, and late gadolinium enhancement on cardiac magnetic resonance imaging, all of the initial elements on the expert panel phenotypic data list were represented by a stand-alone unique field (Table 1). Common demographics and basic phenotype fields were completed most of the time for the 50 cases, including sex (48/50; 96%), race and ethnicity (43/50; 86%), clinical diagnosis of HCM (49/50; 98%), and family history of HCM (45/50; 90%). However, specific phenotype features were completed less frequently, including LVH (22/50; 44%), reduced ejection fraction (12/50; 24%), and suspected syndromic HCM/other cause (15/50; 30%). Of note, two of the evaluated cases were specifically suspected to have a syndromic cause of HCM, suggesting that some of the cases with a reported clinical diagnosis of HCM may instead have had LVH due to a multisystem genetic etiology, and genetic testing was ordered to confirm the diagnosis. Data from this pilot support that most phenotypic data fields on requisition forms are not completed, and ordering providers generally list only limited phenotype information.

Laboratory Director Survey and Refinement of Essential Phenotypic Data Elements

Ten laboratories were invited, of which eight completed the survey. Participants included five US laboratories (Laboratory for Molecular Medicine; Ambry Genetics; GeneDx; Invitae; and Mayo Clinic) and three international laboratories (Children’s Hospital of Eastern Ontario, Canada; Oxford Molecular Genetics Laboratory, UK; and PathWest Laboratory Medicine, Australia). One response per laboratory was allowed. The participating laboratories are not necessarily the same laboratories represented in Table 2.

Participants were asked to evaluate the frequency of expert panel—derived phenotypic data elements received via clinical testing requisition forms. Similar to the 50-case pilot using LMM cases, demographic information (sex, race and ethnicity, and family history) and indication of a clinical
diagnosis of HCM were received very frequently or frequently, whereas the age of diagnosis and presence of LVH or hypertension were noted sometimes, and nuanced clinical information, such as LVH measurement or imaging, was infrequently or very infrequently provided. The remainder of the data elements were only infrequently or very infrequently obtained.

The survey data did not explicitly identify criteria in order of importance; however, on the basis of participants’ judgment, presence of left ventricular outflow tract obstruction, reduced ejection fraction (and percentage), electrocardiogram with LVH or atrial fibrillation, history of syncope, nonsustained ventricular tachycardia on Holter monitoring, and late gadolinium enhancement on cardiac magnetic resonance imaging were deemed nonessential for variant interpretation, considering that these data may not be sufficient to establish a case of HCM that could be added to the evidence base of a given variant. The survey resulted in 11 criteria, representing the minimum key clinical data elements recommended by laboratory directors for standard inclusion in requisition forms for HCM variant interpretation (Table 1).

### Considerations on Practicality and Feasibility of Implementation

All eight laboratory director participants agreed with standardizing the phenotypic data elements and future implementation. They also raised questions about practical feasibility and whether all proposed elements were essential components in their variant classification workflows. Five laboratories (63%) expressed willingness to implement these fields into their laboratory requisition forms, and the remaining 34% qualified their response, because the decision would be subject to review by a clinical expert, information technology team, and/or corporate approval.

### ClinGen Expert Panel Survey and Final Consensus

Of 19 entities represented in the expert panel, 14 participated. The consensus group, formed by laboratory directors, cardiologists, and genetic counselors, representing commercial and academic institutions in the United States and abroad, provided full endorsement of the following recommendations: i) there should be consensus on which data

### Table 3 Laboratory Requisition Module for HCM

| Essential elements                                      | Field type       | Format or options                                                                 |
|--------------------------------------------------------|------------------|----------------------------------------------------------------------------------|
| Birth sex                                              | Selection        | Male, female, other, or unknown                                                  |
| Race and ethnicity*                                    | Selection        | American Indian or Alaska Native, Asian, Black or African, Native Hawaiian or other Pacific Islander, White, or Hispanic |
| Current age                                            | Free text        | Years, or months if <1 year old                                                  |
| Family history                                         | Selection and free text | None, unknown, HCM, left ventricular hypertrophy, cardiomyopathy, sudden cardiac death, or other (free text) |
| Clinical diagnosis of HCM, **1** HPO, **1** HP:0001639, or MONDO:0005045**1** | Selection | Yes, no, or unknown                                                              |
| Age at diagnosis                                       | Free text        | Years, or months if <1 year old                                                  |
| Left ventricular hypertrophy (HPO HP:0001712)          | Selection        | Yes, no, or unknown                                                              |
| Maximum left ventricular wall thickness                | Free text        | Centimeters or millimeters                                                       |
| Suspected syndromic HCM/other cause                    | Selection and free text | Fabry disease, Danon disease, skeletal muscle weakness, or other (free text) |
| Nonessential elements                                  | Selection        | Yes, no, or unknown                                                              |
| Left ventricular outflow tract obstruction             | Selection        | Yes, no, or unknown                                                              |
| Reduced ejection fraction (HPO HP:0012664)             | Selection        | Yes, no, or unknown                                                              |
| Left ventricular ejection fraction (in %)              | Free text        | Percentage                                                                      |
| History of hypertension (HPO HP:0000822)              | Selection        | Yes, no, or unknown                                                              |
| Blood pressure on treatment                           | Free text        | Systolic/diastolic blood pressure                                                |
| ECG with left ventricular hypertrophy (HPO HP:0001712) or atrial fibrillation (HPO HP:0005110) | Selection | Yes (if yes: specify), no, or unknown                                           |
| History of syncope (HPO HP:0001279)                   | Selection        | Yes, no, or unknown                                                              |
| Nonsustained ventricular tachycardia on Holter         | Selection        | Yes, no, or unknown                                                              |
| Late gadolinium enhancement on cardiac MRI             | Selection        | Yes, no, or unknown                                                              |

* Racial and Ethnic Categories and Definitions for NIH Diversity Programs and for Other Reporting Purposes ([https://grants.nih.gov/grants/guide/notice-files/not-od-15-089.html](https://grants.nih.gov/grants/guide/notice-files/not-od-15-089.html), last accessed October 22, 2020).

** Filling criteria for the clinical diagnosis of HCM, per ordering clinician’s assessment.

**1** HPO, ([hpo.hax.org](https://hpo.hax.org), last accessed November 4, 2020).

**1** MONDO, ([monarchinitiative.org](https://monarchinitiative.org), last accessed November 4, 2020).

ECG, electrocardiogram; HCM, hypertrophic cardiomyopathy; HPO, Human Phenotype Ontology; MONDO, Mondo Disease Ontology; MRI, magnetic resonance imaging.
elements should be standard fields on requisition forms; ii) the expert panel considers the minimal phenotypic data elements as critical; iii) these data should be provided by clinicians when ordering genetic testing. Consistent with previous observations in the LMM pilot study and Laboratory Director Survey, some participants shared that blood pressure data would be difficult to obtain and thus also recommended against these data being part of the essential criteria for variant classification. The expert panel survey further reduced the list to nine data elements that were deemed essential for HCM variant classification. The results of this survey were presented during a conference call with the expert panel, during which the group affirmed consensus.

This consensus process resulted in a Laboratory Requisition Module that could be implemented to optimize collection of phenotypic data for HCM on requisition forms (Table 3). This module uses a tiered approach, with the nine data elements deemed critical for counting and characterizing cases for variant classification presented first, followed by those representing the phenotypic data elements that were considered nonessential by the expert panel. Because these data are critical for accurate case counts during variant interpretation, the ClinGen Expert Panel proposes that ordering providers routinely provide these essential data elements and that laboratories reach out to providers to obtain these data.

Discussion

This article presents a minimum set of clinical data elements that should be used for variant classification in the context of genetic testing for HCM. Support and acceptance of this nine-element data set across participating laboratories were high, with few modifications to the original expert panel proposed criteria. This harmonization effort was intended to aid interpretation and simplify requisition forms to improve ordering provider compliance. The successful implementation of this effort will produce a substantial amount of aggregate data that should, in turn, be standardized with data collection efforts from public databases, such as ClinVar. The implementation of acquiring this lean data set for each patient resides with the clinical testing laboratories; however, its success relies on the ordering clinicians’ willingness to provide the minimum phenotypic data set. Moreover, provider collaboration is more likely with wide adoption of this data set among laboratories. In fact, although receiving results with variants classified as variants of uncertain significance remains a major reason for frustration for health care providers, many tests are ordered without providing even the limited information requested by the laboratories. Having a minimal data set, such as the one proposed in this study, could ensure a subject meets criteria for the aforementioned American College of Medical Genetics and Genomics/Association for Molecular Pathology guidelines, potentially leading to a clinically significant variant reclassification that could incentivize ordering providers to submit relevant clinical information.

The chance of success in obtaining key data for variant interpretation could be improved by reinforcing efforts using a three-pronged approach, addressing gaps in clinic, education, and research. Cardiologists can benefit from increased collaboration with genetics providers to enhance and improve clinical care with genotype-informed management. Empirical observation suggests that genetics providers are more likely to include relevant clinical data in requisition forms that could enable efficient collaboration with clinical laboratories in this area. Ordering providers can also benefit from practical education on variant interpretation to illustrate the utility of appropriate case data when evaluating evidence for a given variant. Finally, studies that could shed light on the barriers impeding clinical data sharing and that show the value of this work are necessary. Ultimately, providers will be incentivized to provide relevant data when the process is simplified and made relevant by reducing uncertain variant classifications.

Evaluation of Phenotypic Data Elements

Several of the proposed phenotypic data elements (eg, sex and race and ethnicity) of the proposed HCM phenotypic data set are commonly included on laboratory requisition forms and routinely provided to the laboratory by the ordering clinicians in current practice, affirming their importance. Age of onset and LVH measurement are also critical data elements that are less frequently collected; however, they were deemed essential for variant interpretation. Although data from the LMM pilot support that most of the phenotypic data elements on requisition forms are not routinely completed by ordering providers, it is possible that a sole entry of a clinical diagnosis of HCM, which was determined to be present in 98% of the evaluated cases, may have resulted in exclusion of some of the other critical data elements. This practice of providing limited phenotypic data is at the core of this work, as excluding the other data elements, some of which are essential for identifying a countable case, would preclude a laboratory from classifying an otherwise rare and poorly understood variant.

Collecting additional information carries the potential for improved characterization of genotype-phenotype relationships, as exemplified by variants in the thin-filament genes TNNT2, TNNI3, TPM1, and ACTC1, which can be associated with milder and atypically distributed LVH. In addition, phenotypic data not typically associated with primary HCM are important in helping to determine whether LVH may be secondary to a different process. For example, a diagnosis of HCM in the context of an extensive history of athletic training or severe, uncontrolled hypertension requires special consideration when assessing the pathogenicity of a variant. Other phenotypic data elements that were deemed not essential for variant interpretation (left
ventricular outflow tract obstruction, reduced ejection fraction and percentage, electrocardiogram with LVH or atrial fibrillation, history of syncope, nonsustained ventricular tachycardia on Holter monitoring, and late gadolinium enhancement on cardiac magnetic resonance imaging) may be less frequently obtained owing to an absence of fields for these data on requisition forms. However, during review of the proposed minimal phenotypic data elements, all study participants (including the laboratories that currently collect this information) were in favor of not categorizing these as essential as they were not anticipated to provide useful data.

Practical Considerations and Acceptance of Recommendations

It is expected that these criteria will be implemented by the participating laboratories and provide further impetus for additional guidelines and refinement of phenotypic data elements. The ultimate power of standardizing data collection across laboratories lies in the ability to harness aggregate data, provided that all laboratories share their data into public databases that are structured to accommodate such standardized data. This illustrates a timely intersection between clinical genetic testing and academic consortium research efforts, providing fertile ground for collaboration. With its mission of building a genomic knowledge base to improve patient care and its guidance of expert variant curation, ClinGen is ideally situated to fulfill this role. Following recognition by the Food and Drug Administration, ClinGen has tasked variant curation expert panels with reassessing variant classifications in ClinVar. The data collected from harmonized laboratory requisitions could serve as a foundation for this process, particularly if ClinVar supports the collection of phenotypic data elements essential for variant classification along with an algorithm that aggregates proband counts across laboratories.

This study has some limitations. First, because of the small number of laboratories participating in the survey, there remains a possibility of ascertainment bias. These laboratories were recruited because they offer cardiomyopathy genetic testing and used expert panel members or associates. At the same time, although it is acknowledged that the participating laboratories are a highly selected group, they represent the vast majority of the cardiovascular cardiomyopathy genetic testing volume in the United States. Second, the Laboratory Directors Survey asked participants to select the frequency in which the data elements were provided by ordering providers to later inform the decision of whether a data element would be excluded from the final consensus list. As the participants were not asked to run a formal case review to provide a percentage of completion of each data element, their selection (very frequently/frequently/sometimes/very infrequently/infrequently) may have involved a degree of subjectivity in defining the various categories. Notwithstanding, this assessment was vetted by practicing cardiologists who are members of the expert panel who agreed that some of these items are not universally obtained for every patient with HCM. For example, not every patient with HCM will present with left ventricular outflow tract obstruction or have cardiac magnetic resonance imaging for late gadolinium enhancement assessment.

It should be recognized that the essential data elements are a limited list that can nonetheless serve as a starting point for laboratories to develop additional fields to capture other additional data as needed. Similarly, as a proof of concept, HCM was chosen for this study, but the application of standardizing the minimum data elements essential for variant classification should not be limited to HCM. Future directions include a follow-up study consisting of case evaluations before and after consensus to demonstrate the utility of laboratory requisition form harmonization by, for example, showing a reduction in variant of uncertain significance classifications. In addition, similar processes expanding the minimum phenotypic data set for case-level data in other cardiovascular phenotypes and in rare diseases, where the availability of detailed phenotype data has enabled new diagnoses, would be important contributions to the field. The results of future studies like these could be integrated into guidelines providing disease and gene specifications for variant classification.

Beyond application and implementation of additional guidelines, data sharing remains a powerful tool for genetic analysis and variant resolution. A proposed future application of the recommendations presented herein is to increase the granularity of laboratory submissions to ClinVar. ClinVar provides an opportunity to improve the accuracy of classified variants by capturing phenotypic data elements across the referral base for genetic testing. Cohesion between ClinVar, laboratories, and ordering providers is a highly desired strategic goal for harmonization of gene and sequence variant classifications.

Conclusion

The fields intended to collect phenotypic data on requisition forms for HCM genetic testing are widely divergent across laboratories, and the data elements important for variant classification are not uniformly collected. This study attempts to close this gap by defining the minimum data elements that are both useful and critical for counting and characterizing cases during variant classification for HCM. Endorsement of these phenotypic data elements can aid when counting cases for variant classification but does not substitute for HCM clinical diagnostic criteria or signify that clinical testing should be delayed or prevented in the absence of these data. This process could be replicated for use in other genetic conditions and could be leveraged to
enhance the utility of ClinVar. Ultimately, fulfilling the potential of this concept requires a collaborative relationship between the laboratories and ordering providers, one marked by a commitment to data sharing and high-quality care.

### Supplemental Data

Supplemental material for this article can be found at http://doi.org/10.1016/j.jmoldx.2021.01.014.

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