C-GUIDE™

Clinician-reported Genetic testing Utility InDEx

An instrument to assess the post-test clinical utility of indication-based genetic testing from the clinician perspective

Manual & Interpretation Guide

The C-GUIDE™ Manual & Interpretation Guide: Hayeems, 2022.

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Preface

This manual describes the Clinician-reported Genetic testing Utility InDEx (C-GUIDE™). C-GUIDE™ measures the clinical utility of diagnostic, predictive, or pharmacogenomic germline genetic testing from the perspective of clinicians. It can be used for comparative studies to generate policy-relevant evidence pertaining to the clinical utility of genetic testing across a range of settings.

The C-GUIDE™ Manual & Interpretation Guide contains information about the rationale for, and development and validation of C-GUIDE™, as well as basic information about the administration and scoring of the index.

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Chapter 1: Introduction & Background

1.1 What is Clinical Utility?

The concept of clinical utility is often used to describe a range of benefits associated with genetic testing but specific definitions vary.[1-4] The American College of Medical Genetics and Genomics (ACMG) defines clinical utility broadly, as a genetic test's effect on diagnostic or therapeutic management, implications for prognosis, health and psychological benefits to patients and their relatives, and economic impacts on health-care systems.[5]

1.2 Importance of Measuring Clinical Utility

While a range of frameworks have helped to characterize this concept since the early 2000s[6,7] and evidence is accruing to support its individual components,[8] a single validated measure that quantifies clinical utility is not available. This empiric gap exists alongside policymakers' and payers' requests for evidence that reflects on the value of genetic testing to make funding and policy decisions.[3,7,9-12] To address this critical gap, we developed and validated a clinician-reported measure of clinical utility for genetic testing. While a wide range of -omic tests are emerging, the Clinician-reported Genetic testing Utility InDEx (C-GUIDE™) is designed to assess the post-test utility of indication-based genetic testing. Conceptually, our work draws upon Fryback and Thornbury's hierarchical model of efficacy.[13-15] While this framework includes a spectrum of value domains, C-GUIDE™ focuses on the domains of diagnostic thinking and management decision-making. For example, genetic testing may alter a clinician's thinking about differential diagnosis, strengthen an existing hypothesis, or reassure a clinician and patient that a speculated diagnosis has or has not been confirmed. Beyond this, a genetic test may have decisional impact associated with an alteration to the patient's care plan. When a diagnostic, predictive, or pharmacogenomic variant has been identified, for example, care plans may be tailored to suit prognoses that are better defined by the test result (e.g., subspecialist referrals, surveillance plans, medication implications, family member testing, reproductive planning). When no variant or a variant of uncertain significance has been identified, care plans may be tailored toward more extensive diagnostic investigations (e.g., muscle biopsies, additional genetic analyses) and monitoring. Since clinicians are well-placed to adjudicate the utility of a genetic test characterized in these ways, we developed C-GUIDE™ as an index of items to operationalize these components of value for diagnostic genetic testing.

Chapter 2: Development of C-GUIDE™

2.1 Initial Development of C-GUIDE™

To read in detail about the development of C-GUIDE™, please consult our open access publication: The development of the Clinician-reported Genetic testing Utility InDEx (C-GUIDE): a novel strategy for measuring the clinical utility of genetic testing.[15]

Briefly, preliminary item selection for C-GUIDE™ was informed by a scoping review of 194 publications.[8] Item reduction and refinement was guided by qualitative feedback from 35 semi-structured interviews with clinicians and quantitative feedback generated by a cross-sectional survey of 113 genetics and non-genetics professionals who routinely use genetic testing. Item selection, index scoring, and structure was guided by feedback from an expert panel of 11 genetics professionals who informed the content and wording of C-GUIDE™ Version 1.0.

2.2 Validity & Reliability of C-GUIDE™

Our approach to validity and reliability testing for C-GUIDE™ is described below. This content is also provided in our publication: The Clinician-reported Genetic testing Utility InDEx (C-GUIDE): Preliminary evidence of validity and reliability.[16]

Methods

Study 1: Construct validity

Construct validity was assessed through a prospective study based at The Hospital for Sick Children (SickKids) in Toronto, Canada, where genetics professionals provided C-GUIDE™ ratings on test results disclosed to predominantly pediatric patients or their family members. This study received ethics approval from the SickKids Research Ethics Board. Participants reviewed a consent document which indicated that survey completion constituted consent.

Construct validity, defined as the degree to which a test measures what it claims to measure,[17] was assessed by examining the association between C-GUIDE™ total scores and global item scores along with other clinically important variables. The global item is a single question that asks raters to select whether the test "did", "may" or "did not" change care provided to the patient or his/her family.

Sample and Recruitment

All genetics professionals within the Division of Clinical and Metabolic Genetics were eligible to participate. This included clinical geneticists, medical genetics resident physicians and fellows, and genetic counselors who routinely order (or arrange) diagnostic genetic testing. Eligible cases included patients for whom: (i) genetic testing of any type was ordered as part of a diagnostic work up and (ii) clinically validated positive or negative primary, secondary,[18] and/or pharmacogenomic results[19] were reported directly to the patient or family by a genetics professional. Ineligible cases included family members of probands who received cascade testing results (e.g. carrier/predisposition) and cases for whom genetic testing was reported in the prenatal period. To achieve at least a moderate correlation ($\geq$0.5) between C-GUIDE™ scores and global item scores, 200 C-GUIDE™ ratings were required, enabling 96% power to detect a correlation significantly different from zero.[20]

To achieve balance in our sample of rated cases across result type (i.e. diagnostic, partially/possibly diagnostic, non-diagnostic) and test type (i.e. targeted, non-targeted), a stratified recruitment approach was informed by testing patterns in the clinic at the time of study design. For result type, we aimed to achieve equal proportions of diagnostic and non-diagnostic results (n=75, respectively) and a smaller

proportion of partially/possibly diagnostic results (n=50). For test type, we aimed to achieve equal proportions of targeted (i.e. hypothesis-driven; n=100 single gene, gene panel, or targeted variant analysis) and non-targeted tests (i.e. hypothesis-free; n=100 microarray, karyotype, or exome/genome sequencing). We monitored responses and once the enrollment target was reached for a particular test or result type stratum, recruitment into that stratum was closed.

Data Collection

We pilot tested C-GUIDE™ Version 1.0[15] with two clinician raters to gather feedback on the clarity of the instructions and tool structure. In addition to minor edits to C-GUIDE™ instructions, we made minor wording changes to improve clarity in items 2, 6, 11, 13, 14, and the global item. As such, C-GUIDE™ Version 1.1 (Appendix 1) was used for this study.

To gather rater characteristics, clinicians completed a one-time Clinical Practice Survey. For each rated case, clinicians completed a Case Description Survey (Appendix 2) and C-GUIDE™. Surveys could be completed on paper or online via REDCap.[21] Raters were able to start, stop, and resume the surveys at their convenience. For each eligible case, clinicians were asked to rely on their knowledge of the case to complete the Case Description Survey and C-GUIDE™ within one week of reporting result(s) to the patient/family. The Case Description Survey included five items related to the index case: age, sex, primary indication for testing, number of prior genetic tests, and test urgency and five items related to the test itself: test type, result interpretation, disclosure modality, turnaround time, and time elapsed between result disclosure and C-GUIDE™ completion. Result interpretations were defined as follows: *diagnostic* is a pathogenic/likely pathogenic variant that provides a complete explanation of phenotype; *partially/possibly diagnostic* is a variant of unknown significance that could provide a complete explanation of phenotype OR is a pathogenic/likely pathogenic variant in a recessive gene without a second hit OR is a pathogenic/likely pathogenic variant that provides a partial explanation of phenotype; and *non-diagnostic* was defined as a test result that provides no explanation of phenotype.

C-GUIDE™ includes three sections to capture the utility of test results related to the primary indication for testing, secondary variants, and pharmacogenomic variants and two sections to capture global item ratings and rater feedback (Figure 1). Informed by the literature, current practice patterns in Ontario, and study design considerations, we hypothesized that C-GUIDE™ scores would rank as follows: A) diagnostic results > potentially/possibly diagnostic results > non-diagnostic results; B) targeted tests > non-targeted tests; C) prior genetic testing > no prior genetic testing; D); urgent tests > non-urgent tests; E) younger patients > older patients; F) patients with neurodevelopmental/CNS features > patients without neurodevelopmental/CNS features.

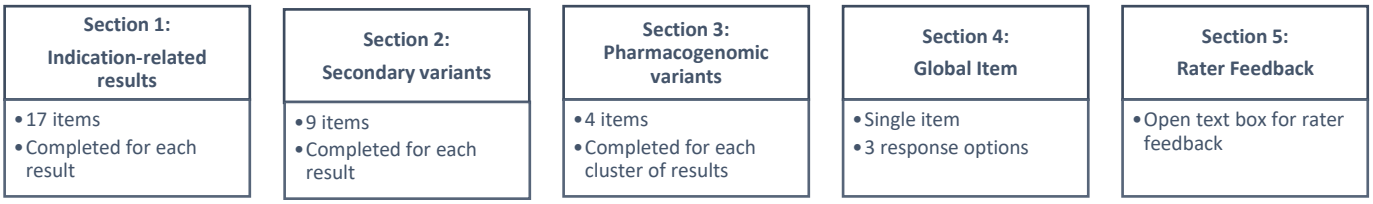

Figure 1. C-GUIDE™ Structure (Items and response options are provided in Appendix 1) Sections 1 and 4 were completed for all cases. Sections 2 and 3 were completed only when medically actionable secondary variants and/or pharmacogenomic variants are identified.[18,19] Section 5 was completed at the rater's discretion.

Analysis

Analysis of construct validity included four steps: (i) summarizing the case characteristics, (ii) calculating C-GUIDE™ scores for clinically important variables, (iii) testing hypotheses about the associations between C-GUIDE™ scores and clinically important variables, and (iv) verifying relationships between C-GUIDE™ scores and global item scores along with clinically important variables using a regression model.

We summarized case and test characteristics with descriptive statistics. Since clinical indication for testing was entered as free text, we developed a categorization scheme for organizing these data. Category 1 indications included neurodevelopmental and/or central nervous system (CNS) involvement. Within Category 1, cases were further classified according to the presence of any symptoms related to: (a) autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), learning disability (LD), intellectual disability (ID), or developmental delay (DD), (b) hearing or vision concerns, (c) hypotonia, d) seizures, or e) other. Cases were assigned to these sub-categories hierarchically based on the proportion of cases in the sample that manifested these symptoms. For example, since cases with ASD/ADHD/LD/ID/DD were most common, cases with any of these features were assigned to Category 1a even if other symptoms were present. For instance, a case with ASD and hearing loss was assigned to Category 1a whereas a case with only hearing loss was assigned to 1b. Category 2 indications included symptoms unrelated to neurodevelopment or CNS involvement. Within Category 2, all cases were assigned according to the presence of: (a) cardiovascular features, (b) dermatological features, (c) dysmorphic facial features, (d) growth concerns, (e) cancer, or (f) other. Category 2 assignments followed the same logic as Category 1. For example, a case with a heart defect and dysmorphic facial features was assigned to Category 2a whereas a case with only dysmorphic facial features was assigned to 2c.

C-GUIDE™ ratings were scored. Individual item scores ranged from -1 to 2. An item score >0 indicates positive utility, item scores <0 indicate the presence of negative utility ("disutility"), and item scores of 0 indicate no utility. For each case, a total C-GUIDE™ score was calculated for each result of each test disclosed to the family. As is commonplace for ordinal scales for which item weighting is not indicated, item scores were summed to calculate the total score.[15,20] Mean scores associated with relevant case characteristics were calculated. We also calculated the mean and range of C-GUIDE™ scores for the cases associated with each global item response option. Only complete survey entries were included in the analysis.

Construct validity was assessed. Given the absence of a normal distribution (i.e. data were right skewed, Kolmogorov-Smironov and Shapiro-Wilk tests were significant at $p<0.001$ and $p<0.001$ respectively), non-parametric tests were used to examine the relationship between clinically important variables (i.e. case characteristics) and C-GUIDE™ scores. Mann-Whitney/Kruskal-Wallis tests were used to compare C-GUIDE™ scores across diagnostic result categories, test types, presence vs absence of prior genetic testing, urgent vs non-urgent status, age categories, and clinical indications. Descriptive statistics, scoring, and non-parametric analyses were completed in SPSS version 27.[22] To account for the correlation of ratings among individual raters, we used a generalized estimating equation (GEE) to determine the association between C GUIDE™ scores and global item scores along with other potentially explanatory variables (i.e. age, clinical indication, number of prior genetic tests, test urgency, test type, and result type). The geepack package in R was used for modelling the GEE by using the function geeglm.[23] Finally, we reviewed free text responses to the rater feedback question to assist with interpretation of C-GUIDE™ scores and refine tool structure.

Results

Characteristics of clinician raters

Fifteen genetics professionals completed C-GUIDE™ ratings for a total of 210 cases. Of the 15 raters, 13 were female. The number of cases rated by each clinician ranged from 1 to 36. All clinician raters chose to complete C-GUIDE™ ratings online via REDCap.[21] Clinician characteristics are provided in Appendix 3.

Characteristics of cases and test results rated by C-GUIDE

The 210 rated cases were almost evenly split between male and female patients and the mean age was 9.14 (SD = 13.6) years. The clinical indication for testing included neurodevelopmental and/or CNS involvement for 59.5%, and most genetic tests were ordered non-urgently (85.2%). Of the primary test results that were rated for the full sample, 41.4% were diagnostic, 22.9% were potentially or partially diagnostic, and 35.7% were non-diagnostic. Test types were almost evenly split between targeted tests (48.6%) and non-targeted tests (51.4%). In half of the cases, results were reported to the family within four months of test ordering. In 75.7% of cases, raters completed C-GUIDE™ within one week of reporting results to the family and the greatest proportion of results were reported by video-conference (49.7%; Appendix 4).

C-GUIDE™ scores and clinical characteristics

Construct validity was assessed for results relevant to the primary indication for testing since 90% (188/210) of cases lacked secondary and/or pharmacogenomic results. The C-GUIDE™ scores for indication-related results in 210 cases ranged from -1 to 26; the mean score was 8.3 (SD = 7.5). Appendix 5 presents mean C-GUIDE™ scores according to case and test characteristics. Mean scores were higher among cases for whom diagnostic results were received compared to partially/potentially diagnostic results (15.8 vs. 4.4; $p<0.001$) and non-diagnostic results (15.8 vs. 2.1; $p<0.001$) and higher among cases for whom partially/potentially diagnostic results were received compared to non-diagnostic results (4.4 vs. 2.1; $p=0.003$). Mean scores were also higher among females compared to males (9.6 vs. 7.0; $p = 0.03$). Mean C-GUIDE™ scores did not differ statistically by patient age, clinical indication for testing, number of prior tests, test type, or test urgency.

C-GUIDE™ as a function of clinical characteristics

Using a GEE model to account for the presence of correlation among raters, we measured the association between C GUIDE™ scores and global item scores along with potentially explanatory clinical variables (Appendix 6). On average, a one-point increase in the global item score was associated with an increase of 3.0 in the C-GUIDE™ score ($p < 0.001$). Compared to diagnostic results, partially/potentially diagnostic and non-diagnostic results were associated with a decrease in the C-GUIDE™ score of 9.5 ($p < 0.001$) and 10.2 ($p < 0.001$), respectively. Age, sex, number of prior tests, clinical indication for testing, test type, and test urgency were not independently associated with unit changes in C-GUIDE™ scores (Appendix 6).

Incorporating secondary and pharmacogenomic findings

Over and above the primary variant results, there were 12 cases (among the 210) for whom two results related to the indication for testing were rated and three cases for whom three indication-related results were rated. In addition, there were 10 cases for whom secondary results were rated and two cases for whom pharmacogenomic results were rated. A summary of C-GUIDE™ scores that included ratings of more than one test result is presented in Appendix 7. The results indicate that a greater number of results generated by a particular genetic test may not be associated with a higher C-GUIDE™ score. For example, where two primary variants were identified in our cohort, the mean C-GUIDE™ score was

higher (14.3; SD=7.4) than for the cases for which three primary variants were identified (10.0; SD=7.2). A greater proportion of the variants in the former example were diagnostic (41.7% vs 11.1%). Similarly, where secondary and pharmacogenomic variants were rated, utility scores were not necessarily higher than for cases where only indication-related results were rated.

The global item score reflected the utility of all results rated per case. Overall, where global item ratings indicated that test results prompted better care (n=67), the mean C-GUIDE™ score was 15.6 (range: 1.0 to 26.0). Where global item ratings indicated that test results may prompt better care (n=66), the mean C-GUIDE™ score was 7.9 (range: 0 to 19.0) and where global item ratings indicated that test results did not prompt better care (n=77), the mean C-GUIDE™ score was 2.3 (range: -1.0 to 17.0).

Study 2: Inter-rater reliability

Inter-rater reliability, defined as the degree of agreement among raters,[24] was assessed using a vignette-based survey administered to an 11-member expert panel of genetics professionals.[15]

This study received ethics approval from the SickKids Research Ethics Board. Participants reviewed a consent document which indicated that survey completion constituted consent.

Sample Size

To determine the number of vignettes required for our fixed number of raters (n=11), we followed power contours provided by Donner and Eliasziw.[24] We determined that 19 unique vignettes provided 80% power to rule out inter-rater reliability lower than 0.6 assuming that the true value was 0.8. Each expert was required to rate 10 vignettes and each of the 19 vignettes required a rating from at least six experts.

Data Collection

We developed 19 unique patient vignettes (Appendix 8) to mimic the clinical scenarios for which C-GUIDE™ was designed. A geneticist worked with the study team to draft the vignettes; some were also informed by case reports in the literature.[25-29] All vignettes provided explicit details about the diagnostic, prognostic, management, reproductive, or psychosocial impact of genetic test results to enable raters to respond to all C-GUIDE™ items (Version 1.1). The vignettes were reviewed for face validity by three clinical geneticists. Vignettes were administered to the experts through an online REDCap survey. Raters were able to start, stop, and resume the survey at their convenience.

Each expert's survey included a core set of instructions and a customized set of 10 or 11 vignettes that had been randomly assigned. Where two or more raters received some of the same vignettes, they were presented in numeric (i.e. non-random) order. The instructions asked the expert raters to read each vignette and complete C-GUIDE™ as it related to the genetic test results reported in the vignette. As above, they were prompted to complete up to five C-GUIDE™ sections (Figure 1). Experts were asked to use only the information provided in the vignette to respond to each item, not their knowledge related to the clinical indication or test result. Experts were asked to complete a Clinical Practice Survey that was similar to the survey used in the validation study.

Krippendorff's alpha[30,31] was used to measure inter-rater reliability as it can be applied to any number of raters, cases, or levels of measurement. The Krippendorff's alpha summary statistic ranges from 1 when there is no disagreement (i.e. there is perfect agreement) to 0 when the observed disagreement is no different than that expected by chance. While alpha ≥ 0.80 is recommended, alpha ≥ 0.67 is considered to be an acceptable reliability threshold.[30,31] Krippendorff's alpha and confidence intervals for all items, including the global item, were calculated for all vignettes, using the *'irr'* package in R statistical software.[32]

Results

Of the 11 clinician raters, more than half had at least 16 years of clinical experience, worked in academic settings, provided all or some pediatric care, and ordered genetic testing ≥1 time per week. Seven were clinical geneticists and four were genetic counselors. Eight practiced in Canada and one practiced in each of Australia, the UK, and the US. All clinician raters chose to complete the survey online via REDCap. Across all 19 vignettes, Krippendorff's α was 0.675 (95% CI 0.63, 0.72), providing evidence of acceptable inter-rater reliability.

C-GUIDE™ Refinement

In response to raters' feedback, we made two item wording changes, updating the tool to Version 1.2 (items 2 and 7, Appendix 9). For item 2, we reverted back to the wording that stated, "Reduced the likelihood of other potential diagnoses in my differential." For item 7, we included study types beyond clinical trials (e,g. functional or natural history studies). In addition, we clarified seven items to assist raters' interpretation of the applicability of items in specific scenarios (e.g. deceased patients). Finally, raters highlighted that clinical utility, as defined by C-GUIDE, depends on the timepoint in a patient's journey during which it is assessed. For example, clinicians indicated that when parental cascade test results were pending, clinical utility ratings were not inclusive of the implications of those results. Also, they suggested that while implications related to surgical management may not have been relevant when they disclosed results (and provided C-GUIDE™ ratings), this aspect of clinical utility could change over time.

2.3 Limitations of C-GUIDE™

Our assessment of inter-rater reliability demonstrated that C-GUIDE™ raters achieved acceptable levels of agreement on vignette-based ratings. However, a vignette-based approach is limited by lack of authenticity, over-simplification of cases, and the potential for raters to interpret the wording used to describe each case differently. To address these limitations, a prospective study in which two clinician raters are independently completing C-GUIDE™ ratings on a shared set of clinical cases, is underway. In effort to achieve higher inter-rater reliability in this study, we made minor modifications to C-GUIDE™ instructions and developed decision rules to assist raters in their interpretation of response options. Ultimately, this work will provide a more rigorous assessment of inter-rater reliability.

We acknowledge additional limitations related to our assessment of construct validity. First, our cohort reflected a single Canadian site with a predominantly English-speaking patient population. Moreover, the majority of clinician raters were female. Second, we enrolled small numbers of cases for some recruitment strata for which we had pre-specified hypotheses that could not be tested. For example, the low rate of urgent cases (i.e. 15%) may have precluded our ability to assess the hypothesis that greater clinical utility would be achieved for urgent testing compared to non-urgent testing. Third, while 28% of rated cases and four of 19 vignettes reflected the clinical utility of genetic testing for adults, further validation in adult settings is warranted. Fourth, while C-GUIDE™ enables utility ratings for secondary and pharmacogenomic variants, these types of results were not generated in sufficient quantity to enable the inclusion of these ratings in our validity assessment.

Further testing of C-GUIDE™ and its scoring algorithm is required before it can be applied to a wider array of clinical settings. Using C-GUIDE™ in other settings may warrant further refinement and performance assessment. For example, its application to cancer, prenatal, or pre-symptomatic testing may warrant the removal of existing or inclusion of additional items. In its current form, prospective C-GUIDE™ studies are underway, aiming to understand the utility of genetic testing from the perspective of non-genetics sub-specialists, how the utility of genetic testing changes over time, how C-GUIDE™ related utility correlates with other measures of utility like diagnostic yield and change in medical management, and what C-GUIDE™ scores mean from a clinical perspective. Additionally, we recognize

this tool measures utility from the perspective of the healthcare professional; work is also underway to understand utility of genetic testing from the patient and parent perspective.

Chapter 3: Using C-GUIDE™

3.1 Administration of C-GUIDE™ **(Version 1.2 recommended for use, see Appendix 9)**

What does C-GUIDE™ measure?

C-GUIDE™ measures the post-test clinical utility of indication-based genetic testing from the clinician perspective. It measures the favourable and unfavourable informational impact of genetic testing.

Who is C-GUIDE™ designed for?

C-GUIDE™ was designed to measure the clinical utility of genetic testing from the perspective of clinicians who order genetic testing and disclose genetic test results as a routine part of clinical practice. The C-GUIDE™ has been validated for use by geneticists and genetic counsellors.

How is C-GUIDE™ administered?

C-GUIDE™ is intended to be self-administered. Clinicians complete C-GUIDE™ on an eligible case as soon as possible following result disclosure to the index case/family. An eligible case is one where the clinician (physician, genetic counsellor, or other qualified health care provider) is involved in disclosing any type of genetic test result (primary, secondary and/or pharmacogenomic). C-GUIDE™ can be used for all result types: positive results, negative results, and variants of uncertain significance. The clinician does not have to have ordered the test but does have to have been involved in the result disclosure. Completing C-GUIDE™ involves completing a 17-item section related to primary variants, and if applicable, a 9-item section related to secondary variants and a 4-item section related to pharmacogenomic variants. For the purpose of ongoing validation studies, C-GUIDE also includes a global item of utility, a single question that asks raters to select whether the test "did", "may" or "did not" change care provided to the patient or his/her family. The index takes approximately 5 minutes to complete and can be administered via REDCap. The data dictionary and a REDCap demonstration are available upon request. The patient is not involved in completing C-GUIDE™. Please see the Frequently Asked Questions section for further administration details and screenshots of selected C-GUIDE sections in REDCap (Appendix 10).

Rules for Item Interpretation

To provide further guidance for raters and to ensure consistent interpretation, some C-GUIDE™ items include rules for item interpretation. These rules are noted in Version 1.2 (Appendix 9) as "Guidance for raters."

3.2 Scoring C-GUIDE™

Basic Scoring Procedure

C-GUIDE™ is scored as follows:
Individual item scores range from -1 to 2. An item score >0 indicates positive utility, item scores <0 indicate the presence of negative utility ("disutility"), and item scores of 0 indicate no utility. For each case, a total C-GUIDE™ score is calculated for each result of each test disclosed to the family. As is commonplace for ordinal scales for which item weighting is not indicated, item scores are summed to calculate the total score.[15,20]

Missing Values

If any value is missing from an item that item is removed from the analysis completely. It is not treated as zero.

3.3 Interpretation of C-GUIDE™ Scores

Appendix 5 (C-GUIDE™ scores and clinical characteristics) is provided to give users a general idea of C-GUIDE™ and global item scores (means and standard deviations) that can be expected. Work is ongoing to guide the interpretation of C-GUIDE scores.

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Glossary

Clinical utility:

A genetic test's effect on diagnosis, therapeutic management, and prognosis, as well as health and psychological well-being for patients and their relatives, and economic impacts on health-care systems.[5]

Genetic testing:

Genetic testing is the use of a laboratory test to look for genetic variations associated with a disease. The results of a genetic test can be used to confirm or rule out a suspected genetic disease or to determine the likelihood of a person passing on a mutation to their offspring. Genetic testing may be performed prenatally or after birth. Ideally, a person who undergoes a genetic test will discuss the meaning of the test and its results with a genetic counselor.

Genomic testing:

Genomic testing refers to the process of analysing an entire genome. Genomic testing is different from genetic testing because it looks at all of a person's genes, rather than focusing on a specific gene, or set of genes. Genomic testing looks broadly for gene alterations, or harmful changes, anywhere in the genetic code.

Secondary variants:

Secondary findings are genetic test results that provide information about changes (variants) in a gene unrelated to the primary indication for testing.

Pharmacogenomics variants:

Pharmacogenomics is a branch of pharmacology concerned with using DNA and amino acid sequence data to inform drug development and testing. An important application of pharmacogenomics is correlating individual genetic variation with drug responses.

Construct validity:

The degree to which a test or instrument is capable of measuring a concept, trait, or other theoretical entity.

Inter-rater reliability:

The degree to which independent evaluators produce similar ratings in judging the same abilities or characteristics in the same target person or object. It often is expressed as a correlation coefficient.

Neurodevelopmental disorder:

Behavioural and cognitive disorders that arise during the developmental period that involve significant difficulties in the acquisition and execution of specific intellectual, motor, language, or social functions.

Diagnostic result:

A pathogenic/likely pathogenic variant that provides a complete explanation of phenotype.

Partially/possibly diagnostic result:

A variant of unknown significance that could provide a complete explanation of phenotype OR is a pathogenic/likely pathogenic variant in a recessive gene without a second hit OR is a pathogenic/likely pathogenic variant that provides a partial explanation of phenotype.

Non-diagnostic result:

A negative test result means that the laboratory did not find a change in the gene, chromosome, or protein under consideration. This result can indicate that a person is not affected by a particular disorder, is not a carrier of a specific genetic mutation, or does not have an increased risk of developing a certain disease. It is possible, however, that the test missed a disease-causing genetic alteration because many tests cannot detect all genetic changes that can cause a particular disorder. Further testing may be required to confirm a negative result.

Some definitions have been adapted from:

- American College of Medical Genetics[5]
- NIH: National Human Genome Research Institute[33]
- NIH: U.S. National Library of Medicine, Medline Plus[34]
- Dana Farber Cancer Institute[35]
- World Health Organization[36]
- American Psychological Association[37]

Frequently Asked Questions (FAQs)

What types of cases are appropriate for C-GUIDE™?

It is appropriate to complete C-GUIDE™ for cases where you were the physician, genetic counsellor, or other qualified health care provider involved in disclosing any type of genetic test result (primary, secondary and/or pharmacogenomic). C-GUIDE™ can be completed for positive results, negative results, and variants of uncertain significance.

Can C-GUIDE™ be completed for prenatal cases?

C-GUIDE™ is not meant to be used for prenatal cases, however if a prenatal genetic test result was returned following the birth of the baby, the case can be included. A modification of C-GUIDE™ for use in prenatal care settings is underway.

Can C-GUIDE™ be completed for deceased patients?

Yes, C-GUIDE can be completed for deceased patients. Items that are not be applicable (i.e. can be left blank) are indicated in Version 1.2.

I would like to make some changes to C-GUIDE™ to fit my clinical environment. Am I able to modify C-GUIDE™?

Please do not modify C-GUIDE™. If item wording is changed or if items are removed/added in the absence of validation, the integrity of the tool and the legitimacy of the findings generated from its use are compromised. For further inquiries regarding modifications, or if you would like to validate C-GUIDE™ for a different clinical population, please contact Dr. Robin Hayeems (robin.hayeems@sickkids.ca)

I did not order the genetic test or the genetic test was ordered from an outside institution. Can I still complete C-GUIDE™?

Yes. You do not need to have been the ordering clinician for the test being rated but you must have disclosed or been involved in the disclosure of the result to the index case/family.

I disclosed results related to DNA analyzed for my patient's parents or other family members. Can I complete C-GUIDE™ for these cases as well?

No. Please only complete C-GUIDE™ for the index case. If there are two index cases in the family (i.e., two affected siblings), you can complete C-GUIDE™ twice (one for each index case). If a parent or other family member has had carrier testing, please do not complete C-GUIDE™ for these individuals as it is not designed for this scenario. If the result of an indication-based test for a proband is carrier status, then this case is eligible for rating.

My patient's genetic test identified multiple variants (e.g. pathogenic variant, likely pathogenic variant). How do I complete C-GUIDE™?

Please rate each genetic test result (or variant) individually. For ease of survey completion, C-GUIDE™ can be programmed electronically so that multiple results from the same genetic test can be rated individually within a single survey entry. You can program C-GUIDE™ to accommodate multiple primary and secondary genetic test results. If you are completing C-GUIDE™ as a hard copy, you can print multiple copies of the primary and secondary results sections.

I disclosed results from more than one genetic test (e.g. chromosome microarray and a single gene test). How do I complete C-GUIDE™?

Please rate each genetic test individually. For ease of survey completion, C-GUIDE™ can be programmed electronically so that multiple tests for the same patient can be rated individually within a single survey entry. If you are completing C-GUIDE™ as a hard copy, you can print a new copy for each test.

Does my patient have to consent for me to complete C-GUIDE™?

No, the patient does not need to consent to this study. They are not involved in the C-GUIDE™ procedures.

I often disclose results over the phone or virtually (eg on Zoom). Can I still complete C-GUIDE™ for these cases?

Yes, you can complete C-GUIDE™ for phone or virtual disclosures.

I disclosed results with my colleague. Who should complete C-GUIDE™?

It's up to you! You can take turns or complete it together. If you complete it together, input your responses one time only.

How long will it take me to complete C-GUIDE™?

Once you become comfortable with the C-GUIDE™, it will take you approximately 5 minutes to complete.

Conditions of Use & Registration

The Clinician-reported Genetic testing Utility InDEx (C-GUIDE™) and all its versions are protected by copyright with all rights reserved to the C-GUIDE™ team. Users of the C-GUIDE™ shall not modify, abridge, or alter in any way shape or form the C-GUIDE™, including but not limited to minor or major changes in content or format without the prior written agreement of the C-GUIDE™ team. Researchers interested in using the C-GUIDE™ shall not translate the questionnaire without the prior written agreement of the C-GUIDE™ team. Users shall not reproduce the C-GUIDE™ except for use in registered research investigations and shall in no event distribute copies of the questionnaire or the Manual to third parties by sale, rental, lease, lending, or any other means.

If you are interested in using C-GUIDE™ please send us a request by mail or e-mail. A license agreement and user profile form must be completed.

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Acknowledgements & Funding

The development of C-GUIDE™ and manual has been supported by research grant awards from the Canadian Institutes of Health Research (CIHR) and the PhRMA Foundation Challenge Award, as well as funding from the Starbucks Clinical Genetics/Genomics Research Studentship Award through The Hospital for Sick Children. Special thanks to Ayushi Bhatt for her efforts with the various aspects of the C-GUIDE™ project to date.

Appendix 1: C-GUIDE™ Version 1.1 (not recommended for future use)

C-GUIDE Section 1: Results related to primary indication for testing

Item	Response Options
The genetic testing that my patient had…	
1. Provided a genetic explanation for my patient's health condition	□ Provided a COMPLETE genetic explanation □ Provided a PARTIAL genetic explanation □ Provided a POSSIBLE genetic explanation □ Provided NO genetic explanation
2. Reduced the likelihood of other differential diagnoses	□ COMPLETELY REDUCED the likelihood of other differential diagnoses □ PARTIALLY REDUCED the likelihood of other differential diagnoses □ DID NOT REDUCE the likelihood of other differential diagnoses
3. Provided information about the natural history of or medical issues associated with my patient's condition	□ Provided SIGNIFICANT information about the natural history of or medical issues associated with my patient's condition □ Provided SOME information about the natural history of or medical issues associated with my patient's condition □ Provided NO information about the natural history of or medical issues associated with my patient's condition
4. Indicated that further testing to identify a genetic diagnosis can be avoided	□ Indicated that further testing to identify a genetic diagnosis CAN BE AVOIDED □ Indicated that further testing to identify a genetic diagnosis MAY STILL BE REQUIRED, now or in the future
5. Indicated that previous surveillance or monitoring related to my patient's condition can be discontinued or avoided	□ Indicated that previous surveillance/monitoring can be DISCONTINUED OR AVOIDED □ Indicated that previous surveillance/monitoring is STILL REQUIRED □ Previous surveillance/monitoring is NOT RELEVANT to this case
6. Facilitated my patient's access to or continuation of a community or educational service (e.g. learning, rehabilitation resources) that would not have been available without the testing	□ FACILITATED access to or continuation of a community or educational service □ DID NOT FACILITATE access to or continuation of a community or educational service
7. Enabled me to identify and access a clinical trial that I	□ ENABLED me to IDENTIFY and ACCESS a clinical trial □ ENABLED me to IDENTIFY a clinical trial

wouldn't have been able to access without the testing	□ DID NOT ENABLE me to identify or access a clinical trial
8. Enabled me to identify a support group for my patient or his/her family that I wouldn't have considered without the testing	□ ENABLED me to identify a support group □ DID NOT ENABLE me to identify a support group
9. Prompted a referral or investigation for the purpose of surveillance or monitoring that would not have been prompted on clinical grounds	□ PROMPTED a referral or investigation for surveillance/monitoring □ PROMPTED a referral or investigation for surveillance/monitoring that MAY NOT BE NECESSARY (e.g. variant of uncertain significance) □ DID NOT PROMPT a referral/investigation for surveillance/monitoring
10. Provided information to guide medication management	□ GUIDED current medication management □ MAY GUIDE medication management in the future □ DID NOT PROVIDE information that would guide medication management, now or in the future
11. Provided information about surgical management	□ ENABLED a discussion or offer of a surgical option □ AVOIDED a discussion or offer of a surgical option □ A surgical option is NOT RELEVANT at this time or NOT RELATED to the genetic test results
12. Provided information about a contraindicated behaviour (e.g. competitive sports)	□ ENABLED me to provide information about a contraindicated behaviour □ Information about a contraindicated behaviour is NOT RELEVANT at this time
13. Provided recurrence risk information for my <u>patient</u>	□ Provided recurrence risk information that is RELEVANT to my patient at this time □ Provided recurrence risk information that MAY BE RELEVANT to my patient in the future □ Cannot be determined (e.g. variant of uncertain significance, did not provide information)
14. Provided recurrence risk information for my <u>patient's family</u>	□ Provided recurrence risk information that is RELEVANT to my patient's family at this time □ Provided recurrence risk information that MAY BE RELEVANT to my patient's family in the future □ Cannot be determined (e.g. variant of uncertain significance, family member(s) did not receive testing or unknown if tested)
15. Clarified potential health risks for my <u>patient's family</u>	□ CLARIFIED potential health risks for my patient's family □ DID NOT CLARIFY health risks for my patient's family □ Cannot be determined (e.g. variant of uncertain significance, family member(s) did not receive testing or unknown if tested)
16. Generated psychosocial benefit for my patient <u>or</u> his/her family	□ SIGNIFICANT psychosocial benefit was experienced □ MODERATE psychosocial benefit was experienced □ NO psychosocial benefit was experienced

	☐ Cannot be determined
17. Generated psychosocial concern for my patient or his/her family	☐ SIGNIFICANT psychosocial concern was experienced ☐ MODERATE psychosocial concern was experienced ☐ NO psychosocial concern was experienced ☐ Cannot be determined

C-GUIDE Section 2: Secondary Variants

Did you disclose SECONDARY variant results?

- ☐ Yes
- ☐ No

N.B. For the purpose of this index, secondary variants include medically actionable variants unrelated to the indication for testing.

Item	Response Options
The genetic testing that my patient had…	
1. Prompted a referral or investigation for the purpose of surveillance or monitoring that would not have been prompted on clinical grounds	☐ PROMPTED a referral or investigation for surveillance/monitoring ☐ PROMPTED a referral or investigation for surveillance/monitoring that MAY NOT BE NECESSARY (e.g. variant of uncertain significance) ☐ DID NOT PROMPT a referral/investigation for surveillance/monitoring
2. Provided information to guide medication management	☐ GUIDED current medication management ☐ MAY GUIDE medication management in the future ☐ DID NOT PROVIDE information that would guide medication management, now or in the future
3. Provided information about surgical management	☐ ENABLED a discussion or offer of a surgical option ☐ AVOIDED a discussion or offer of a surgical option ☐ A surgical option is NOT RELEVANT at this time or NOT RELATED to the genetic test results
4. Provided information about a contraindicated behaviour (e.g. competitive sports)	☐ ENABLED me to provide information about a contraindicated behaviour ☐ Information about a contraindicated behaviour is NOT RELEVANT at this time
5. Provided recurrence risk information for my patient	☐ Provided recurrence risk information that is RELEVANT to my patient at this time ☐ Provided recurrence risk information that MAY BE RELEVANT to my patient in the future ☐ Cannot be determined (e.g. variant of uncertain significance, did not provide information)
6. Provided recurrence risk information for my patient's family	☐ Provided recurrence risk information that is RELEVANT to my patient's family at this time ☐ Provided recurrence risk information that MAY BE RELEVANT to my patient's family in the future ☐ Cannot be determined (e.g. variant of uncertain significance, family member(s) did not receive testing or unknown if tested)
7. Clarified potential health risks for my patient's family	☐ CLARIFIED potential health risks for my patient's family

	☐ DID NOT CLARIFY health risks for my patient's family ☐ Cannot be determined (e.g. variant of uncertain significance, family member(s) did not receive testing or unknown if tested)
8. Generated psychosocial benefit for my patient or his/her family	☐ SIGNIFICANT psychosocial benefit was experienced ☐ MODERATE psychosocial benefit was experienced ☐ NO psychosocial benefit was experienced ☐ Cannot be determined
9. Generated psychosocial concern for my patient or his/her family	☐ SIGNIFICANT psychosocial concern was experienced ☐ MODERATE psychosocial concern was experienced ☐ NO psychosocial concern was experienced ☐ Cannot be determined

C-GUIDE Section 3: Pharmacogenomic Variants

Did you disclose PHARMACOGENOMIC results?

- ☐ Yes
- ☐ No

N.B. For the purpose of this index, pharmacogenomic results include those that are identified through a targeted pharmacogenomic analysis and could be relevant to medication management now or in the future.

If yes, please complete C-GUIDE once for the pharmacogenomic result(s) disclosed. For the purpose of this study, pharmacogenomic results are typically disclosed as a 'cluster' of variants to the patient or family.

Item	**Response options**
The genetic testing that my patient had…	
1. Provided information to guide medication management for my patient	☐ GUIDED current medication management ☐ MAY GUIDE medication management in the future ☐ DID NOT PROVIDE information that would guide medication management, now or in the future
2. Provided information to guide medication management for my patient's family	☐ GUIDED current medication management for my patient's family ☐ MAY GUIDE medication management for my patient's family in the future ☐ DID NOT PROVIDE medication management information for my patient's family, now or in the future ☐ Cannot be determined (e.g. variant of uncertain significance, family member(s) did not receive testing or unknown if tested)
3. Generated psychosocial benefit for my patient or his/her family	☐ SIGNIFICANT psychosocial benefit was experienced ☐ MODERATE psychosocial benefit was experienced ☐ NO psychosocial benefit was experienced ☐ Cannot be determined
4. Generated psychosocial concern for my patient or his/her family	☐ SIGNIFICANT psychosocial concern was experienced ☐ MODERATE psychosocial concern was experienced ☐ NO psychosocial concern was experienced ☐ Cannot be determined

C-GUIDE Section 4: Global item

Taking into account all of the results you have just rated for this test, the genetic testing that my patient had	☐ Prompted better care for my patient or his/her family ☐ May prompt better care for my patient or his/her family in the future ☐ Did not change the care provided to my patient or his/her family

Appendix 2: Case Description Survey

This is an example of a Case Description Survey. We recommend that users tailor the ascertainment of case characteristics to their study objectives, design, setting, and patient population.

Item	Response Options
1. Please indicate your role. If you are completing C-GUIDE™ with other providers, check all that apply	☐ Medical Geneticist ☐ Genetic Counsellor ☐ Fellow/Trainee (please specify) ☐ Other (please specify) If trainee, please specify: ☐ MD ☐ GC If other, please specify: _____
2. Age of proband • In years (for patients 2 and older) • In months (for children between 1 month and 23 months) • In days (for infants less than 1 month)	_____ years _____ months _____ days
3. Sex of proband	☐ Male ☐ Female
4. Primary clinical indication for testing (list up to 3 features)	_____
5. Before the test(s) you are rating today, how many genetic test results has the proband received to date?	☐ 0 ☐ 1 ☐ 2 ☐ >2 ☐ Don't know
6. Time elapsed between reporting test results to the patient/family and completing C-GUIDE	☐ Same day ☐ 1 to 3 days ☐ 4 to < 7 days ☐ 1 to < 2 weeks ☐ 2 to < 4 weeks ☐ > 4 weeks
7. How did you disclose results?	☐ In person ☐ By phone ☐ Virtually (eg Zoom) ☐ Other (please specify): _____

8. Type of genetic test rated being rated on C-GUIDE™ (check one)	☐ Microarray (please specify): _____
	☐ Single gene (please specify): _____
	☐ Gene panel (please specify): _____
	☐ Whole exome sequencing
	  ☐ Singleton
	  ☐ Duo
	  ☐ Trio
	☐ Whole genome sequencing
	  ☐ Singleton
	  ☐ Duo
	  ☐ Trio
	☐ Other (please specify): _____

9. Interpretation of result #1 related to PRIMARY indication	☐ **Diagnostic** (ie: pathogenic/likely pathogenic test result that provides a complete explanation of phenotype) ☐ **Possibly diagnostic** (ie: variant of unknown significance that could provide a complete explanation of phenotype OR a pathogenic/likely pathogenic variant in a recessive gene without a second hit) ☐ **Partially diagnostic** (ie: pathogenic/likely pathogenic test result that provides partial explanation of phenotype) ☐ **Non-diagnostic** (ie: test result provides no explanation for phenotype) ☐ Other (please specify): _____

10. Setting in which test ordered	☐ Outpatient
	  ☐ Urgent
	  ☐ Non-urgent
	☐ Inpatient
	  ☐ Urgent
	  ☐ Non-urgent
	☐ Inpatient – Intensive Care
	  ☐ Urgent
	  ☐ Non-urgent
	☐ Other (please specify): _____
	  ☐ Urgent
	  ☐ Non-urgent

11. Time elapsed between ordering this test and reporting test results to patient/family	☐ < 1 month ☐ 1 to < 2 months ☐ 2 to < 4 months ☐ 4 to < 6 months ☐ 6 to < 12 months ☐ 12 to < 24 months ☐ > 24 months

Appendix 3: Characteristics of clinician raters in construct validity sample (n=15)

Characteristic	Frequency (%)
Years of clinical experience	
≤ 15 years	7 (46.7%)
> 15 years	8 (53.3%)
Sex	
Male	2 (13.3%)
Female	13 (86.7%)
Ordering frequency	
Periodically (several times per month)	3 (20.0%)
Often (several times per week)	12 (80.0%)
Tests ordered	
Chromosome microarray	7 (46.7%)
Single gene test	5 (33.3%)
Multi-gene panel	1 (6.7%)
Exome sequencing	1 (6.7%)
Genome sequencing	1 (6.7%)
Number of cases rated[a]	
Genetic counselor	102 (48.3%)
Trainee (resident physician or fellow)	70 (33.2%)
Staff geneticist	39 (18.5%)

[a] The total is 211 because in one instance there were two respondents (a geneticist and a trainee completed C-GUIDE together).

Appendix 4: Characteristics of cases (n=210)

Clinical indication for testing	
Neurodevelopmental and/or central nervous system involvement	125 (59.5)
ASD/ADHD/LD/ID/DD[a]	67 (53.6)
Hearing loss or vision concerns	31 (24.8)
Hypotonia	6 (4.8)
Seizures	6 (4.8)
Encephalopathy	4 (3.2)
Other (e.g., psychiatric, developmental regression, brain/MRI differences)	11 (8.8)
Non-neurodevelopmental or CNS involvement	85 (40.5)
Cardiac abnormalities (e.g. arrhythmia, structural defect)	23 (27.1)
Dermatological abnormalities (e.g. cafe au lait macules)	15 (17.6)
Dysmorphic facial features	15 (17.6)
Anomalous growth	7 (8.2)
Cancer	7 (8.2)
Other (e.g., fhx genetic condition, post-natal f/u of prenatal testing)	18 (21.2)
Test turnaround time (TAT; date test ordered to date result disclosed to family)[b]	
< 4 months	106 (50.5)
≥ 4 months	104 (49.5)
C-GUIDE reporting interval (date result disclosed to family to date C-GUIDE completed)	
Same day	52 (24.8)
1-3 days	68 (32.4)
4 days – 1 week	39 (18.6)
>1 week	51 (24.3)
Disclosure modality (n = 185)[c]	
In person[d]	40 (21.6)
By phone	53 (28.6)
Virtually (i.e. video-conference)	92 (49.7)

[a] ASD = Autism Spectrum Disorder; ADHD = Attention Deficient Hyperactivity Disorder; LD = Learning Disability; ID = Intellectual Disability; DD = Developmental Delay

[b] TAT was correlated with test type; longer TAT associated with WES/WGS compared to conventional testing due to sample batching, out-of-country approval process, and out-of-country lab turnaround time. TAT was also longer where results were first disclosed by a general physician and then re-interpreted by a clinical genetics professional.

[c] The total is 185 because this question was added after data collection had already begun to capture the shift to virtual care during COVID-19.

[d] In 1 case, geneticist was on the phone and trainee was in person.

Appendix 5: C-GUIDE™ scores and clinical characteristics

n=210	Mean C-GUIDE Score (PV1)[a] (SD)	Mean Global score (SD)
Global score		
0	2.29 (4.01)	-
1	7.89 (5.38)	-
2	15.64 (5.60)	-
Patient age		
0 – 2 years	8.4 (7.0)	0.97 (0.81)
3 – 10 years	7.1 (7.2)	0.83 (0.82)
11 – 18 years	8.8 (7.8)	1.06 (0.86)
19+ years	10.0 (8.8)	1.00 (0.88)
Patient sex		
Male	7.0 (6.8)[b]	0.88 (0.82)
Female	9.6 (7.9)	1.03 (0.83)
Clinical indication for testing		
Neurodevelopmental and/or central nervous system involvement	7.7 (7.2)	0.92 (0.84)
Non-neurodevelopmental or CNS involvement	9.2 (7.7)	1.00 (0.82)
Number of prior genetic tests		
0	7.6 (7.1)	0.79 (0.84)[g]
1	9.8 (7.5)	1.17 (0.79)[h]
2	7.7 (7.5)	1.03 (0.80)
>2	7.3 (8.1)	0.88 (0.85)
Unknown[c]	17.0 (1.4)	1.50 (0.71)
Test urgency		
Urgent	9.9 (7.6)	1.13 (0.85)
Non-urgent	8.0 (7.4)	0.92 (0.82)
Test type		
Targeted (Single gene, targeted variant analysis, FISH/MLPA, gene panel)	8.9 (7.5)	0.96 (0.84)
Non-targeted (Microarray, karyotype, WES/WGS)	7.8 (7.4)	0.94 (0.82)
Result type		
Diagnostic	15.8 (4.0)[d]	1.52 (0.65)[i]
Potentially or partially diagnostic	4.4 (2.6)[e]	0.96 (0.62)[j]
Non-diagnostic	2.1 (4.4)[f]	0.29 (0.63)[k]

[a] PV1 = Primary variant 1 related to primary indication for testing. [b] Statistically significant difference as determined by Mann-Whitney test, p = 0.031. [c] For the 2 cases for which prior testing was unknown, the test rated by C-GUIDE was WES. [d/e/f] Statistically significant difference as determined by Kruskal-Wallis, p <0.001 between variable levels d and e, and d and f, p = 0.003 between variables e and f. [g/h] Statistically significant difference as determined by Kruskal-Wallis, p =0.043, between variable levels g and h, p = 0.036. [i/j/k] Statistically significant difference as determined by Kruskal-Wallis, p <0.001, between variable levels i & j, p =0.001, and variables i and k, and j and k, p <0.001.

Appendix 6: Associations between C-GUIDE score, global item score and clinical characteristics[a]

Variable	Estimate	Standard Error
Global item score	2.975[b]	0.498
Clinical Characteristics		
Age	0.818	0.042
Sex		
Female	0.527	0.439
Male (ref)	-	-
Result type		
Partially/potentially diagnostic	-9.517[b]	0.590
Non-diagnostic	-10.168[b]	0.968
Diagnostic (ref)	-	-
Test type		
Targeted	0.147	0.470
Non-targeted (ref)	-	-
Prior genetic tests		
>2	0.942	0.729
2	0.424	0.592
1	0.455	0.477
0 (ref)	-	-
Clinical indication		
Neurodevelopmental and/or central nervous system involvement	-0.724	0.523
Non-neurodevelopmental or CNS involvement (ref)	-	-
Test urgency		
Urgent	-0.398	0.705
Non-urgent (ref)	-	-

[a] A generalized estimating equation (GEE) was used to generate adjusted estimates to assess the association between potentially explanatory clinical characteristics and C-GUIDE scores. [b] $p<0.001$

Appendix 7: Mean C-GUIDE scores for cases with multiple variant ratings and frequencies of primary variant classifications among these cases

	Primary Variant Score (Variants related to primary indication; PV)			**Secondary Variant Score** (SV)		**Pharmacogenomic Variant Score** (PGx)
	PV1[a] (n = 210)	**PV1 & PV2**[b] (n = 12)	**PV1 & PV2 & PV3**[c] (n = 3)	**PV1 & SV**[d] (n = 9)	**PV1 & PV2 & SV**[e] (n=1)	**PV1 & SV & PGx**[f] (n =2)
C-GUIDE Mean (SD)	8.3 (7.5)	14.3 (7.4)	10.0 (7.2)	5.8 (4.8)	8.0 (0)	5.5 (0.7)
Primary variant classification	Frequency of Primary Variant Classifications (%)					
	n=210	n=24	n=9	n=9	n=2	n=2
Diagnostic	87 (41.4%)	10 (41.7%)	1 (11.1%)	1 (11.1%)	0 (0.0%)	0 (0.0%)
Potentially or partially diagnostic	48 (22.9%)	7 (29.2%)	5 (55.6%)	5 (55.6%)	2 (100.0%)	1 (50.0%)
Non-diagnostic	75 (35.7%)	7 (29.2%)	3 (33.3%)	3 (33.3%)	0 (0.0%)	1 (50.0%)

[a] Construct validity assessed for this group only. [b] 12 cases each had 2 primary variant results. [c] 3 cases each had 3 primary variant results. [d] 9 cases each had one primary variant result and one secondary variant result. [e] 1 case had 2 primary variant results and 1 secondary variant result. [f] 2 cases each had 1 primary variant result, 1 secondary variant result, and 1 pharmacogenomic result.

Appendix 8: Vignettes used for inter-rater reliability study

Vignette #1: A 10 month-old male with strabismus and hypertelorism was referred to an ophthalmologist. A general exam revealed low-set, irregularly shaped ears, a high arched-palate and micrognathia. The patient was born prematurely (36 weeks) and suffered from respiratory distress syndrome and intracranial hemorrhage. He also had undescended testicles, pulmonary stenosis and hypotonia. The patient was suspected to have a rasopathy and was referred to a geneticist. A rasopathy panel was performed and yielded a positive result for Noonan syndrome (de novo mutation in *PTPN11*) which fit the clinical diagnosis that the geneticist suspected. When informed of the diagnosis, the patient's parents were visibly upset. The patient was then referred to a cardiologist to assess heart function and develop a surveillance protocol. The patient was also referred for corrective surgery for his undescended testicles to reduce the chances of future infertility. The diagnosis suggested surveillance for leukemia and that the patient be monitored for potential intellectual disabilities. The parents were offered genetic testing and both tested negative for their son's variant. The parents were given information about a support group for Noonan syndrome. Once school-aged, the child will be eligible for additional support in the classroom if needed. Genetic counselling regarding reproductive risk will be available to the child in the future, if necessary.

Vignette #2: A 10 month-old male with strabismus and hypertelorism was referred to an ophthalmologist. A general exam revealed low-set, irregularly shaped ears, a high arched-palate and micrognathia. The patient was born prematurely (36 weeks) and suffered from respiratory distress syndrome and intracranial hemorrhage. He also had undescended testicles, pulmonary stenosis and hypotonia. The patient was suspected to have a rasopathy and was referred to a geneticist. The geneticist ordered a series of investigations, including a rasopathy panel, a microarray, an abdominal ultrasound, and a repeat brain MRI. All of these investigations were normal. When informed of these results, the patient's parents expressed a mix of relief and frustration. A follow-up with Genetics was scheduled for one year's time to review possible new testing options. The patient was also referred for corrective surgery for his undescended testicles to reduce the chances of future infertility.

Vignette #3: A 9 year-old male presented to the clinic with difficulty walking, repeated falls, inability to climb stairs, and muscle fatigue. He had no history of muscular pain and had a normal IQ. A general exam revealed that he had difficulty standing and walking, calf hypertrophy, hamstring muscle contracture, positive Gower's sign and an obese appearance. There was no muscle thinning or muscle twitching and cranial nerve examination was normal. Serological analysis found elevated creatine kinase, lactate dehydrogenase and alanine transaminase levels. Based on clinical findings, muscular dystrophy was suspected and complete sequencing of the dystrophin gene was ordered. Test results revealed a frameshift mutation due to deletions of exons 45-50. The patient was diagnosed with Duchenne Muscular Dystrophy (DMD) and a confirmatory muscle biopsy was deemed unnecessary. Based on these results, other diagnoses in the differential were deemed unlikely. He was started on corticosteroid therapy, referred for physiotherapy and for further cardiac and respiratory evaluation. Prophylactic limb and spine surgeries were discussed with the patient's parents. The patient was informed of his potential future reproductive risks. The patient's siblings were referred to Genetics for evaluation. As a result of receiving a diagnosis, the medical team and the parents had a better understanding of the child's prognosis. The child's parents expressed appreciation to have received an answer for their child's health issues. They also expressed interest in meeting with a DMD support network that you had suggested to them. With this diagnosis, the child was able to gain approval for an educational assistant at school.

Vignette #4: A 9 year-old female presented at a pediatric cardiology clinic with exertional dyspnea and generalized fatigue. An ECG showed evidence of atrial hypertrophy, right axial deviation, right bundle branch block and T-wave inversion in inferior leads. Chest x-rays showed cardiomegaly and echocardiography showed symmetric hypertrophy of the ventricles with dilation of the atria. Left ventricular systolic function was normal but she had mild diastolic dysfunction. No left ventricular outflow obstruction was found. A diagnosis of hypertrophic cardiomyopathy (HCM) was made and she was started on propranolol. She was tested for sarcomere related HCM; the panel included ACTC, *GLA, LAMP2, MYBPC3, MYH7, MYL2, MYL3, PRKAG2, TNNI3, TNNT* and *TPM1*. Only one heterozygous variant c.5786C>T (p.Thr1929Met)) was found in the MYH7 gene. This was the only candidate variant among all of the genes explored. This variant was listed in ClinVar as a variant of uncertain significance. The same variant was identified in the patient's mother and the mother's cardiac evaluation was normal. The patient's teenage sibling tested negative for the MYH7 variant and has had normal cardiac evaluations to date. As per clinical guidelines, the patient and her first-degree relatives continue to be followed by the cardiology clinic. To be on the safe side, the combination of the phenotype and the variant of uncertain significance led the clinician to advise the patient against competitive sports. Overall, the family was pleased to have additional information but were frustrated by its uncertain nature. At the end of their latest clinic appointment, the family met with a research assistant from the Genetics department recruiting for a cardiomyopathy clinical trial.

Vignette #5: A 9 year-old female presented at a pediatric cardiology clinic with exertional dyspnea and generalized fatigue. An ECG showed evidence of atrial hypertrophy, right axial deviation, right bundle branch block and T-wave inversion in inferior leads. Chest x-rays showed cardiomegaly and echocardiography showed symmetric hypertrophy of the ventricles with dilation of the atria. Left ventricular systolic function was normal but she had mild diastolic dysfunction. No left ventricular outflow obstruction was found. A diagnosis of hypertrophic cardiomyopathy (HCM) was made and she was started on propranolol. She was tested for sarcomere related HCM; the panel included ACTC, *GLA, LAMP2, MYBPC3, MYH7, MYL2, MYL3, PRKAG2, TNNI3, TNNT* and *TPM1*. The panel did not reveal any variants of interest. The patient's parents and teenage sibling have had normal cardiac evaluations to date. As per clinical guidelines, the patient and her first-degree relatives continue to be followed by the cardiology clinic. The patient's parents were pleased to learn their daughter's cardiomyopathy is less likely to be genetic in etiology as they expressed interest in having another child.

Vignette #6: An 8 year-old female visited a pediatric clinic with an abnormal gait due to decreased joint mobility. The symptoms were first noted when she was a toddler, when she presented with monoarthritis of her ankle. Septic arthritis was considered at the time, and she underwent painful joint aspirations. Further investigations at age 8 revealed destruction of carpal bones on both hands and olecranon bursitis. She also had a marfanoid habitus, cachexia, cutis laxia, micrognathia, a triangular face and bulging eyes. Her cognition was normal. Morphological abnormalities were absent in her parents. An x-ray showed osteolysis of the carpal and tarsal bones with dislocation of the first metatarsophalangeal joints and cyst-like structures on the right femoral epiphysis. She also had significant right kidney hypoplasia and a large left-kidney. Clinical trio whole exome sequencing revealed a de novo c.188C>T (p.Pro63Leu) variant in the *MAFB* gene. This variant is not found in ClinVar, but it occurs in a hotspot region of the *MAFB* gene. *In silico* analysis suggests that this variant is likely pathogenic and likely to be diagnostic of multicentric carpotarsal osteolysis syndrome. Based on this result, no further diagnostic testing was indicated. An infectious process was deemed unlikely, and joint aspirations were discontinued. Her renal function continued to be monitored. The family was grateful for the information but disappointed that other families with this variant could not be located. As a full-time educational assistant was already supporting the child's physical needs, there was no impact on educational services. The exome analysis also revealed

that the child and her mother carried a medically actionable secondary variant in the PCSK9 gene, associated with familial hypercholesterolemia. This prompted additional referrals for the family along with concern related to new health risks.

Vignette #7: An 8 year-old female visited a pediatric clinic with an abnormal gait due to decreased joint mobility. The symptoms were first noted when she was a toddler, when she presented with monoarthritis of her ankle. Septic arthritis was considered and she underwent painful joint aspirations. Further investigations at the age of 8 years revealed destruction of carpal bones on both hands & olecranon bursitis. She also had a marfanoid habitus, cachexia, cutis laxia, micrognathia, a triangular face and bulging eyes. Her cognition was normal. Morphological abnormalities were absent in her parents. An x-ray showed osteolysis of the carpal and tarsal bones with dislocation of the first metatarsophalangeal joints and cyst-like structures on the right femoral epiphysis. She also had significant right kidney hypoplasia and a large left-kidney. Clinical trio whole exome sequencing was negative; continued monitoring and treatment for her joints was recommended. During the disclosure appointment, the patient's father expressed disappointment the testing did not yield any findings to explain his daughter's symptoms. A plan was set to re-analyze trio data one year later. The exome analysis also revealed that the child and her mother carried a medically actionable secondary variant in the PCSK9 gene, associated with familial hypercholesterolemia. This prompted additional referrals for the family along with concern related to new health risks.

Vignette #8: Upon birth, a female was noted to have dysmorphic features and atrial tachycardia, for which she was transferred to the NICU. She was found to have an atrial septal defect and patent foramen ovale. She was started on propranolol and digoxin which helped stabilize her heart rhythm. She was discharged at one month, but was repeatedly hospitalized for failure to thrive and global developmental delay. By age 10 months, she had developed hydrocephalus (but had no signs of increased intracranial pressure), positional plagiocephaly, strabismus, pelviectasis, nephrocalcinosis, and GERD. She had no liver, bleeding or clotting issues. She had difficulties feeding and was reliant on an NG tube to meet her nutritional needs but kept pulling the NG tube out. A microarray conducted at 3 months was normal. Whole exome sequencing of the patient and both parents revealed a pathogenic de novo mutation (c.770A>Gp.gln257Arg) in the BRAF gene. She was subsequently diagnosed with cardiofaciocutaneous syndrome (CFC). No further diagnostic tests were conducted as other diagnoses were unlikely. She was also referred to cardiology, dermatology and orthopaedics for follow-up. At this time, the patient's prognosis remained unclear. This lack of information was upsetting to the child's parents. Genetic counselling regarding reproductive risk will be available to the child in the future, if necessary. A referral was sent to a pediatric community treatment and rehabilitation centre. Finally, pharmacogenomics analysis performed on the sequencing data identified a variant in the SLC01B1 gene that may be associated with an increased risk of developing simvastatin-related muscle toxicity. If statin therapy is needed in the future, a lower simvastatin dose or an alternative statin may be indicated.

Vignette #9: Upon birth, a female was noted to have dysmorphic features and atrial tachycardia, for which she was transferred to the NICU. She was found to have an atrial septal defect and patent foramen ovale. She was started on propranolol and digoxin which helped stabilize her heart rhythm. She was discharged at one month, but was repeatedly hospitalized for failure to thrive and global developmental delay. By age 10 months, she had developed hydrocephalus (but had no signs of increased intracranial pressure), positional plagiocephaly, strabismus, pelviectasis, nephrocalcinosis, and GERD. She had no liver, bleeding or clotting issues. She had difficulties feeding and was reliant on an NG tube to meet her nutritional needs, but kept pulling the NG tube out. A microarray conducted at 3 months was normal.

Whole exome sequencing of the patient and both parents was negative. The lack of information was upsetting to the child's parents. A referral was sent to a pediatric community treatment and rehabilitation centre. Finally, pharmacogenomics analysis performed on WGS identified a variant in the SLC01B1 gene that may be associated with an increased risk of developing simvastatin-related muscle toxicity. If statin therapy is needed in the future, a lower simvastatin dose or an alternative statin may be indicated.

Vignette #10: A pediatrician ordered a microarray for a 2 year-old boy with global developmental delay. It revealed a de novo 2p21p16.3 deletion that was 4.581Mb in size. The deletion contained 11 OMIM genes, (EPAS1, CRIPT, MCFD2, TTC7A, CALM2, EPCAM, MSH2, MSH6, LHCGR, FSHR, NRXN1). Given that NRXN1 was included in the deletion, it is likely the cause of the boy's delays and was reported as likely pathogenic. The deletion also contained 3 genes known to cause Lynch syndrome. As such, the boy was also diagnosed with Lynch syndrome and anticipatory information was given to the parents on the surveillance available to him in adulthood. The deletion was determined to be de novo in the child so the parents were reassured that they do not need to be concerned about their own cancer risks.

Vignette #11: A pediatrician ordered a microarray for a 2 year-old boy with global developmental delay. A de novo 2p21p16.3 deletion was found. This deletion did not explain the cause of the boy's delays but did contain one gene known to cause Lynch syndrome. As such, the boy was diagnosed with Lynch syndrome and anticipatory information was given to the parents on the surveillance available to him in adulthood. The deletion was determined to be de novo in the child so the parents were reassured that they do not need to be concerned about their own cancer risks. The patient was referred to Genetics to discuss further testing options.

Vignette #12: A 10 year-old male came to the cardiac clinic for routine follow-up. He had been a patient of the clinic since age 3 when his pediatrician noticed a murmur and subsequently referred him to the clinic for evaluation. It was determined that he was born with coarctation of the aortic valve and a bicuspid aortic valve. Balloon catherization was used to widen his aortic coarctation. He had 2-3 toe syndactyly but no other noteworthy phenotypic features. Parents were distantly related (5^{th} or 6^{th} cousins) and both had normal echocardiograms. The patient had younger twin brothers with cone and rod disease. The family was offered trio-based whole genome sequencing (WGS) through a research study. Results from WGS found a maternally-inherited TBX3 missense mutation (variant of uncertain significance; VUS). The VUS was in a gene associated with ulnar-mammary syndrome (congenital heart disease, growth delay, hypodontia, hypoplasia of structures of the chest/breast, upper limb hypoplasia and other congenital anomalies). Because of the uncertain pathogenicity, this result was not clinically validated. Based on the WGS, no changes to clinical management were indicated. The sequencing data were also interrogated for pharmacogenomic variants and determined that the proband may be warfarin sensitive (CYP2C9 *1/*3 and VKORC1 *1/*2) and require a lower than normal dosage if this medication is indicated in the future. Based on their potential clinical relevance, clinical validation of the pharmacogenomic variant was ordered and the variant was confirmed.

Vignette #13: A 10 year-old male came to the cardiac clinic for routine follow-up. He had been a patient of the clinic since age 3 when his pediatrician noticed a murmur and subsequently referred him to the clinic for evaluation. It was determined that he was born with coarctation of the aortic valve and a bicuspid aortic valve. Balloon catherization was used to widen his aortic coarctation. He had 2-3 toe syndactyly but no other noteworthy phenotypic features. His parents were distantly related (5^{th} or 6^{th} cousins) and both had normal echocardiograms. The patient had younger twin brothers with cone and rod

disease. The family was offered trio-based whole genome sequencing (WGS) through a research study. No pathogenic or likely pathogenic primary findings were found and no changes to clinical management were indicated. Reanalysis of the trio data were planned for one year later. Pharmacogenomic analyses determined that the proband may be warfarin sensitive (CYP2C9 *1/*3 and VKORC1 *1/*2) and require a lower than normal dosage if this medication is indicated in the future. Based on their potential clinical relevance, clinical validation of the pharmacogenomic variants was ordered.

Vignette #14: A healthy 43 year-old woman with no past medical history presented with concern about her risk for ovarian cancer. Her mother was diagnosed with breast cancer at age 63. The patient had three healthy maternal uncles and a maternal aunt who was diagnosed with breast cancer at age 64. Her maternal aunt has a daughter who was diagnosed with thyroid cancer at age 43. The patient's maternal grandmother died from a lung infection at age 27 and her maternal grandmother's sister died of ovarian cancer at age 40. The patient had no information about her father's family. The patient was eligible for provincial coverage and was offered a multi-gene panel test. Her mother and maternal aunt declined testing. The panel identified a variant of uncertain significance in *BRIP1*, a gene associated with a moderately increased risk of breast and ovarian cancer. It is unknown whether this gene was transmitted from the patient's maternal or paternal lineage. The panel test results triggered a discussion about the potential benefits and risks of preventive screening strategies and risk reducing surgeries. The patient felt frustrated by the uncertainty associated with the information she received. Should she develop breast cancer, she expressed interest in participating in a clinical trial that is recruiting patients with variants of uncertain significance in the *BRIP1* gene. Following the clinic appointment, the woman planned to discuss these results with her sister and provide her with the clinic's contact information if she wanted to follow up.

Vignette #15: A healthy 43 year-old woman with no past medical history presented with concern about her risk for ovarian cancer. Her mother was diagnosed with breast cancer at age 63. The patient had three healthy maternal uncles and a maternal aunt who was diagnosed with breast cancer at age 64. Her maternal aunt has a daughter who was diagnosed with thyroid cancer at age 43. The patient's maternal grandmother died from a lung infection at age 27 and her maternal grandmother's sister died of ovarian cancer at age 40. The patient had no information about her father's family. The patient was eligible for provincial coverage and was offered a multi-gene panel test. The panel identified a pathogenic mutation in the *BRCA1* gene, known to be associated with an increased risk of breast and ovarian cancer. The test results triggered a discussion about the potential benefits of preventive screening and risk reducing surgeries. She opted to proceed with a referral to discuss her surgical options in more detail. Following the clinic appointment, the woman discussed these results with her sister, mother, and maternal aunt. All three decided to proceed with genetic testing to determine their risk status. Upon learning that her sister also carried the *BRCA1* mutation, her sister proceeded to learn about her prophylactic surgical options.

Vignette #16: A 26 year-old male came to the emergency unit because of a carpopedal spasm that lasted four hours. He also reported muscle cramps in both legs and numbness at the perioral area. His birth and development history were normal and had no history of recurrent infections or cardiac disease. He had attended six years of elementary school and was working as an unskilled labourer. He did not drink alcohol or use illicit drugs. There was an unremarkable family history. Cardiac, chest and abdominal examinations were unremarkable. Lab investigations showed hypocalcaemia, hyperphosphataemia, and elevated serum PTH levels. Mild facial abnormalities were detected and mild intellectual disability was confirmed. The combination of these characteristics led to the suspicion of 22q11.2 deletion syndrome. Further investigations including echocardiography and renal ultrasound were normal. The patient was diagnosed with 22q11.2 deletion syndrome (confirmed by FISH) and discharged with elemental calcium as calcium carbonate and alfacalcidiol medications. The patient was visibly upset about the genetic test

results. Because of this and the associated psychiatric risks associated with 22q11.2, the patient was referred to psychiatry. Serum calcium level was maintained in lower than normal range to prevent hypercalciuria. The patient was informed that genetic counselling would be available to him if he was considering starting a family and recurrence risks were discussed. The patient's sister was unaffected and the recurrence risk for any future children for her was deemed to be low. The patient was referred to a social worker who conducted a thorough assessment of his home and work needs. With a clear diagnosis and other investigations completed, his prognosis was better understood. Despite his concerns about receiving this diagnosis, he appreciated the information he received.

Vignette #17: A 35 year-old Caucasian male presented to a respirology clinic with a persistent cough and recurring bronchitis. He was a music professor who had no difficulties playing wind instruments and apart from tonsillectomy, his childhood history was unremarkable. He had no problems gaining weight. Liver and renal function and blood glucose were normal. Pulmonary examination revealed resonance to percussion and symmetric breathing sounds with no wheezing. Spirometry showed a mild obstructive defect and chest X-rays showed significant hyperinflation and increased linear marking in the right lower lungs. Sweat chloride levels were found to be 79 and 86 mmol/L. He produced approximately 1 tablespoon of sputum per day and these cultures frequently grew *P.aeruginosa* and other bacteria. A CF panel was performed and the patient was found to have a single copy of the F508del mutation and a copy of the novel A457P mutation in exon 10 of the CFTR gene. This mutation appeared to be disease causing in the patient, and he was diagnosed with mild CF. At the disclosure appointment, the patient was visibly distressed after hearing the news. Soon after, he relaxed and said that he was very grateful to have an explanation for his symptoms and information for his family members. He was given brochures with information about a CF support group. He was subsequently put on a course of antibiotics and was referred to a urologist to address concerns about infertility. He also met with a research coordinator to discuss participation in CF clinical trial.

Vignette #18: A 21 month-old came to the Genetics Clinic with her parents to understand the genetic basis of her hearing loss. She presented as a newborn, with a failed newborn hearing screen. She was later confirmed to have bilateral profound sensorineural hearing loss. She was referred to ENT and underwent cochlear implantation at 8 months of age. At 21 months, aside from speech delay, her development was on track. She had no other major medical issues and physical exam was normal, including a normal skin exam, no heterochromia or stigmata of Waardenberg syndrome. All investigations, including a brain MRI and ophthalmologic examinations, were normal. There was no family history of hearing loss, and both parents had normal hearing. The hereditary hearing loss panel, which contains 80 genes related to syndromic and non-syndromic hearing loss showed two variants of uncertain significance (VUS) in the following genes: MITF, which can cause autosomal dominant Waardenberg syndrome and GJB6, which can cause both autosomal dominant and autosomal recessive deafness. However, the particular variant found in this child`s GJB6 gene has a frequency in population databases that is too high to be consistent with autosomal dominant inheritance and thus was interpreted in the context of an autosomal recessive trait. Since her second GJB6 gene copy did not have a pathogenic variant and dosage was normal, this single VUS in GJB6 was thought not sufficient to explain her hearing loss. Parental testing was offered for the other variant in MITF, which was found to be inherited from her father, who had normal hearing. At the end of the day, the genetic basis for the child`s hearing loss was not found. The family felt frustrated by this lack of explanation. They were asked to return to Genetics in 1-2 years to see if there was a new interpretation of these variants. Accurate recurrence risk information could not be provided.

Vignette #19: A baby was born with IUGR, hydrops and thrombocytopenia. He was later found to be CMV positive. He was followed in the Infectious Disease clinic and treated with IV Gancyclovir. Despite this, the child developed seizures. He also had microcephaly, profound sensorineural hearing loss, and was significantly delayed in his development. The family had always suspected a genetic cause in addition to his congenital CMV, and as such the child was eventually enrolled in a whole genome sequencing study. This test did not reveal a diagnosis, making both the treating team and the family more comfortable with the notion that the child's findings were consistent with his congenital infection. They felt reassured that this was not a genetic condition running in their family, after years of thinking a genetic cause was likely. However, the test did reveal a secondary finding in the DSC2 gene (c.1122_1123insAA, p.R375fs), a likely pathogenic mutation associated with arrhythmogenic right ventricular cardiomyopathy (ARVC). This prompted a new set of concerns for the parents as well as a referral to cardiology for the child for ongoing surveillance.

Appendix 9: C-GUIDE™ Version 1.2 (recommended for future use)

The Clinician-reported Genetic testing Utility InDEx (C-GUIDE)™ aims to capture the clinical utility of genetic testing once results are disclosed to patients/families, from the perspective of the ordering clinician.

C-GUIDE™ includes (i) 17 items related to results received for the primary indication for testing, and if applicable, (ii) 4-9 items related to secondary or pharmacogenomic variant results received.

Thinking about the result(s) you just disclosed related to the primary indication for testing, please complete the following:

N.B. If you disclosed multiple results from the same test, please complete the C-GUIDE™ once for each result disclosed. You will be prompted to do this after you complete C-GUIDE™ for the first result. If you disclosed secondary or pharmacogenomic results from this test, you will be asked about those specific results later.

C-GUIDE™ Section 1: Results related to primary indication for testing

Item	Response Options
The genetic testing that my patient had…	
1. Provided a genetic explanation for my patient's health condition	□ Provided a COMPLETE genetic explanation **[2]** □ Provided a PARTIAL genetic explanation **[1]** □ Provided a POSSIBLE genetic explanation **[1]** □ Provided NO genetic explanation **[0]**
2. Reduced the likelihood of other potential diagnoses in my differential	□ COMPLETELY REDUCED the likelihood of other potential diagnoses in my differential **[2]** □ PARTIALLY REDUCED the likelihood of other potential diagnoses in my differential **[1]** □ DID NOT REDUCE the likelihood of other potential diagnoses in my differential **[0]** □ Not applicable **[0]**
3. Provided information about the natural history of or medical issues associated with my patient's condition	□ Provided SIGNIFICANT information about the natural history of or medical issues associated with my patient's condition **[2]** □ Provided SOME information about the natural history of or medical issues associated with my patient's condition **[1]** □ Provided NO information about the natural history of or medical issues associated with my patient's condition **[0]**
4. Indicated that further testing to identify a genetic diagnosis can be avoided	□ Indicated that further testing to identify a genetic diagnosis CAN BE AVOIDED **[2]** □ Indicated that further testing to identify a genetic diagnosis MAY STILL BE REQUIRED, now or in the future **[0]**
5. Indicated that previous surveillance or monitoring related to my patient's	□ Indicated that previous surveillance/monitoring can be DISCONTINUED OR AVOIDED **[2]**

condition can be discontinued or avoided	□ Indicated that previous surveillance/monitoring is STILL REQUIRED **[0]** □ Previous surveillance/monitoring is NOT RELEVANT to this case **[0]**
6. Facilitated my patient's access to or continuation of a community or educational service (e.g. learning, rehabilitation resources) that would not have been available without the testing	□ FACILITATED access to or continuation of a community or educational service **[2]** □ DID NOT FACILITATE access to or continuation of a community or educational service **[0]**
7. Enabled me to identify and access a research study that I wouldn't have been able to access without the testing	□ ENABLED me to IDENTIFY and ACCESS a clinical trial **[2]** □ ENABLED me to IDENTIFY a clinical trial **[1]** □ Enabled me to IDENTIFY and/or ACCESS a natural history or functional study to assist with result interpretation **[1]** □ DID NOT ENABLE me to IDENTIFY or ACCESS a clinical trial, natural history or functional study **[0]**
8. Enabled me to identify a support group for my patient or his/her family that I wouldn't have considered without the testing	□ ENABLED me to identify a support group **[2]** □ DID NOT ENABLE me to identify a support group **[0]**
9. Prompted a referral or investigation for the purpose of surveillance or monitoring that would not have been prompted on clinical grounds	□ PROMPTED a referral or investigation for surveillance/monitoring **[2]** □ PROMPTED a referral or investigation for surveillance/monitoring that MAY NOT BE NECESSARY (e.g. variant of uncertain significance) **[1]** □ DID NOT PROMPT a referral/investigation for surveillance/monitoring **[0]**
10. Provided information to guide medication management	□ GUIDED current medication management **[2]** □ MAY GUIDE medication management in the future **[1]** □ DID NOT PROVIDE information that would guide medication management, now or in the future **[0]**
11. Provided information about surgical management	□ ENABLED a discussion or offer of a surgical option **[2]** □ AVOIDED a discussion or offer of a surgical option **[1]** □ A surgical option is NOT RELEVANT at this time or NOT RELATED to the genetic test results **[0]**
12. Provided information about a contraindicated behaviour (e.g. competitive sports)	□ ENABLED me to provide information about a contraindicated behaviour **[2]** □ Information about a contraindicated behaviour is NOT RELEVANT at this time **[0]**
13. Provided recurrence risk information for my <u>patient</u>	□ Provided recurrence risk information that is RELEVANT to my patient at this time **[2]**

	☐ Provided recurrence risk information that MAY BE RELEVANT to my patient in the future **[1]** ☐ Cannot be determined (e.g. variant of uncertain significance, did not provide information) **[0]**
14. Provided recurrence risk information for my patient's family	☐ Provided recurrence risk information that is RELEVANT to my patient's family at this time **[2]** ☐ Provided recurrence risk information that MAY BE RELEVANT to my patient's family in the future **[1]** ☐ Cannot be determined (e.g. variant of uncertain significance, family member(s) did not receive testing or unknown if tested) **[0]**
15. Clarified potential health risks for my patient's family	☐ CLARIFIED potential health risks for my patient's family **[2]** ☐ DID NOT CLARIFY health risks for my patient's family **[0]** ☐ Cannot be determined (e.g. variant of uncertain significance, family member(s) did not receive testing or unknown if tested) **[0]**
16. Generated psychosocial benefit for my patient or his/her family	☐ SIGNIFICANT psychosocial benefit was experienced **[2]** ☐ MODERATE psychosocial benefit was experienced **[1]** ☐ NO psychosocial benefit was experienced **[0]** ☐ Cannot be determined **[0]**
17. Generated psychosocial concern for my patient or his/her family	☐ SIGNIFICANT psychosocial concern was experienced **[-2]** ☐ MODERATE psychosocial concern was experienced **[-1]** ☐ NO psychosocial concern was experienced **[0]** ☐ Cannot be determined **[0]**

Guidance for Raters:

Item 3: This includes gaining insight about natural history by way of reverse phenotyping that may be prompted by genetic test results. Reverse phenotyping refers to the identification of clinical features based on genotype.

Item 6: This refers to whether genetic testing results theoretically facilitated access to services, not if results actually facilitated access to services. Due to school district specific policies, the final outcome may be unclear.

Item 11: This refers to whether genetic testing results provided information about surgical management, specifically. It does not refer to a situation where surgery was considered for diagnostic reasons (e.g. muscle biopsy).

Item 14: Family includes parents, siblings and extended family.

Item 15: Reduction of risk counts. For example, if there was a question that other family members could have the same condition, but the primary finding was de novo, there would be a reduction of risk for a family member.

Items 16/17: If you do not have a clear memory of the session or did not record psychological response in clinic notes, choose the 'cannot be determined' response option.

Items 5-7, 9-13: Not applicable when the proband is deceased. In this case, item should be left blank.

C-GUIDE™ Section 2: Secondary Variants

Did you disclose SECONDARY variant results?

- ☐ Yes
- ☐ No

N.B. For the purpose of this index, secondary variants include medically actionable variants unrelated to the indication for testing.

If yes, please complete a C-GUIDE™ once for each secondary result disclosed to the patient or family.

Item	Response options
The genetic testing that my patient had…	
1. Prompted a referral or investigation for the purpose of surveillance or monitoring that would not have been prompted on clinical grounds	☐ PROMPTED a referral or investigation for surveillance/monitoring **[2]** ☐ PROMPTED a referral or investigation for surveillance/monitoring that MAY NOT BE NECESSARY (e.g. variant of uncertain significance) **[1]** ☐ DID NOT PROMPT a referral/investigation for surveillance/monitoring **[0]**
2. Provided information to guide medication management	☐ GUIDED current medication management **[2]** ☐ MAY GUIDE medication management in the future **[1]** ☐ DID NOT PROVIDE information that would guide medication management, now or in the future **[0]**
3. Provided information about surgical management	☐ ENABLED a discussion or offer of a surgical option **[2]** ☐ AVOIDED a discussion or offer of a surgical option **[1]** ☐ A surgical option is NOT RELEVANT at this time or NOT RELATED to the genetic test results **[0]**
4. Provided information about a contraindicated behaviour (e.g. competitive sports)	☐ ENABLED me to provide information about a contraindicated behaviour **[2]** ☐ Information about a contraindicated behaviour is NOT RELEVANT at this time **[0]**
5. Provided recurrence risk information for my patient	☐ Provided recurrence risk information that is RELEVANT to my patient at this time **[2]** ☐ Provided recurrence risk information that MAY BE RELEVANT to my patient in the future **[1]** ☐ Cannot be determined (e.g. variant of uncertain significance, did not provide information) **[0]**
6. Provided recurrence risk information for my patient's family	☐ Provided recurrence risk information that is RELEVANT to my patient's family at this time **[2]** ☐ Provided recurrence risk information that MAY BE RELEVANT to my patient's family in the future **[1]** ☐ Cannot be determined (e.g. variant of uncertain significance, family member(s) did not receive testing or unknown if tested) **[0]**
7. Clarified potential health risks for my patient's family	☐ CLARIFIED potential health risks for my patient's family **[2]** ☐ DID NOT CLARIFY health risks for my patient's family **[0]**

	☐ Cannot be determined (e.g. variant of uncertain significance, family member(s) did not receive testing or unknown if tested) **[0]**
8. Generated psychosocial benefit for my patient <u>or</u> his/her family	☐ SIGNIFICANT psychosocial benefit was experienced **[2]** ☐ MODERATE psychosocial benefit was experienced **[1]** ☐ NO psychosocial benefit was experienced **[0]** ☐ Cannot be determined **[0]**
9. Generated psychosocial concern for my patient <u>or</u> his/her family	☐ SIGNIFICANT psychosocial concern was experienced **[-2]** ☐ MODERATE psychosocial concern was experienced **[-1]** ☐ NO psychosocial concern was experienced **[0]** ☐ Cannot be determined **[0]**

Items 1-4: Not applicable when the proband is deceased. In this case, item should be left blank.
Item 5: Not applicable when the proband is deceased. In this case, item should be left blank.
Item 6: Family includes parents, siblings and extended family.
Item 7: Reduction of risk counts. For example, if there was a question that other family members could have the same condition, but the primary finding was de novo, there would be a reduction of risk for a family member.
Items 8/9: If you do not have a clear memory of the session or did not record psychological response in clinic notes, choose the 'cannot be determined' response option.

C-GUIDE™ Section 3: Pharmacogenomic Variants

Did you disclose PHARMACOGENOMIC results?

- ☐ Yes
- ☐ No

N.B. For the purpose of this index, pharmacogenomic results include those that are identified through a targeted pharmacogenomic analysis and could be relevant to medication management now or in the future.

If yes, please complete C-GUIDE™ once for the pharmacogenomic result(s) disclosed. For the purpose of this study, pharmacogenomic results are typically disclosed as a 'cluster' of variants to the patient or family.

Item	Response options
The genetic testing that my patient had…	
1. Provided information to guide medication management for my <u>patient</u>	☐ GUIDED current medication management **[2]** ☐ MAY GUIDE medication management in the future **[1]** ☐ DID NOT PROVIDE information that would guide medication management, now or in the future **[0]**
2. Provided information to guide medication management for my <u>patient's family</u>	☐ GUIDED current medication management for my patient's family **[2]** ☐ MAY GUIDE medication management for my patient's family in the future **[1]** ☐ DID NOT PROVIDE medication management information for my patient's family, now or in the future **[0]** ☐ Cannot be determined (e.g. variant of uncertain significance, family member(s) did not receive testing or unknown if tested) **[0]**
3. Generated psychosocial benefit for my patient <u>or</u> his/her family	☐ SIGNIFICANT psychosocial benefit was experienced **[2]** ☐ MODERATE psychosocial benefit was experienced **[1]** ☐ NO psychosocial benefit was experienced **[0]** ☐ Cannot be determined **[0]**
4. Generated psychosocial concern for my patient <u>or</u> his/her family	☐ SIGNIFICANT psychosocial concern was experienced **[-2]** ☐ MODERATE psychosocial concern was experienced **[-1]** ☐ NO psychosocial concern was experienced **[0]** ☐ Cannot be determined **[0]**

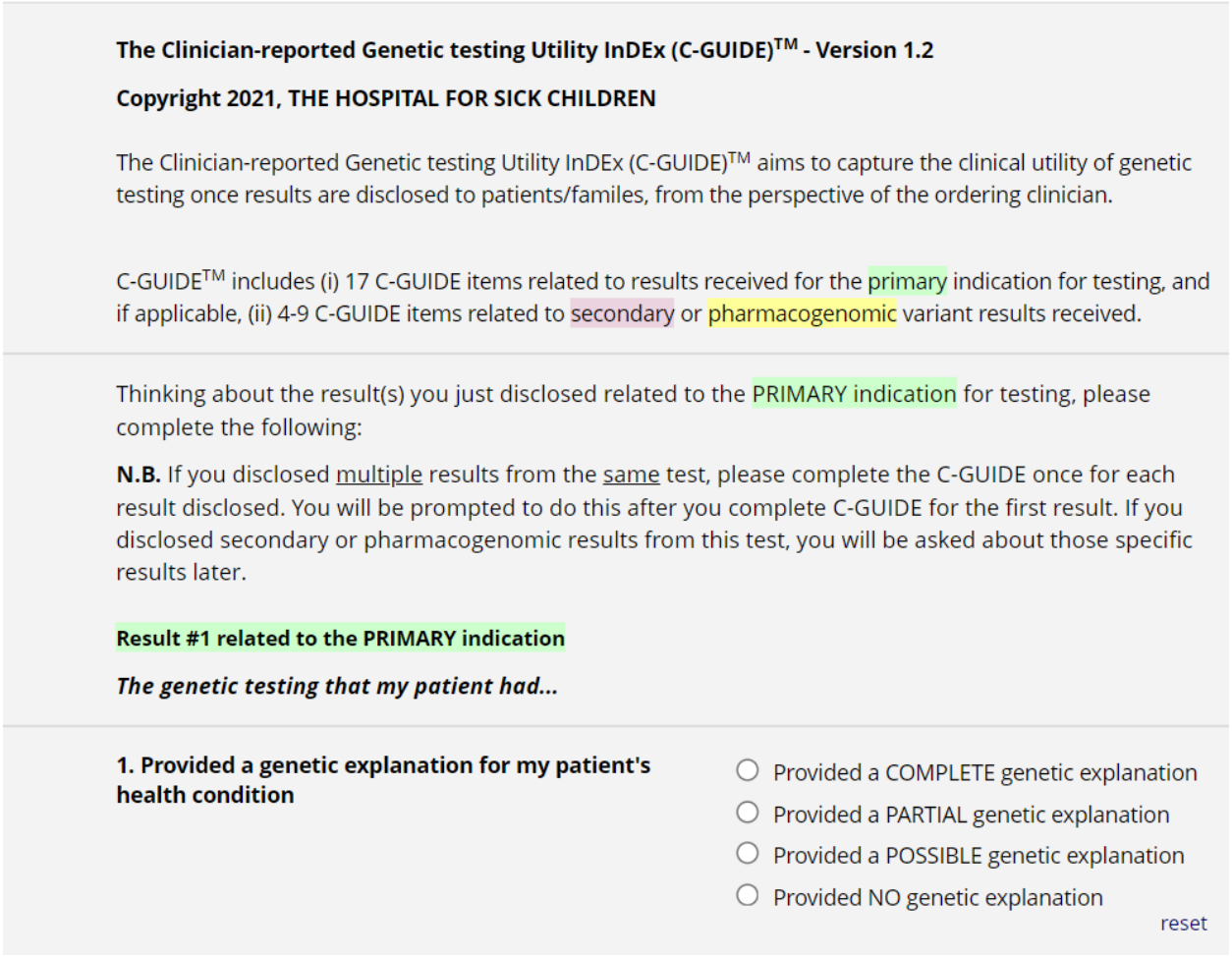
Item 1: Not applicable when the proband is deceased. In this case, item should be left blank.
Item 2: Family includes siblings and extended family.
Items 3/4: If you do not have a clear memory of the session or did not record psychological response in clinic notes, choose the 'cannot be determined' response option.

C-GUIDE™ Section 4: Global item

Taking into account all of the results you have just rated for this test, the genetic testing that my patient had	☐ Prompted better care for my patient or his/her family **[2]** ☐ May prompt better care for my patient or his/her family in the future **[1]** ☐ Did not change the care provided to my patient or his/her family **[0]**

Appendix 10: C-GUIDE™ Administration via REDCap - Example Images

Example image of the instructions and primary indication section:



The Clinician-reported Genetic testing Utility InDEx (C-GUIDE)™ - Version 1.2

The Clinician-reported Genetic testing Utility InDEx (C-GUIDE)™ aims to capture the clinical utility of genetic testing once results are disclosed to patients/familes, from the perspective of the ordering clinician.

C-GUIDE™ includes (i) 17 C-GUIDE items related to results received for the primary indication for testing, and if applicable, (ii) 4-9 C-GUIDE items related to secondary or pharmacogenomic variant results received.

Thinking about the result(s) you just disclosed related to the PRIMARY indication for testing, please complete the following:

N.B. If you disclosed multiple results from the same test, please complete the C-GUIDE once for each result disclosed. You will be prompted to do this after you complete C-GUIDE for the first result. If you disclosed secondary or pharmacogenomic results from this test, you will be asked about those specific results later.

Result #1 related to the PRIMARY indication

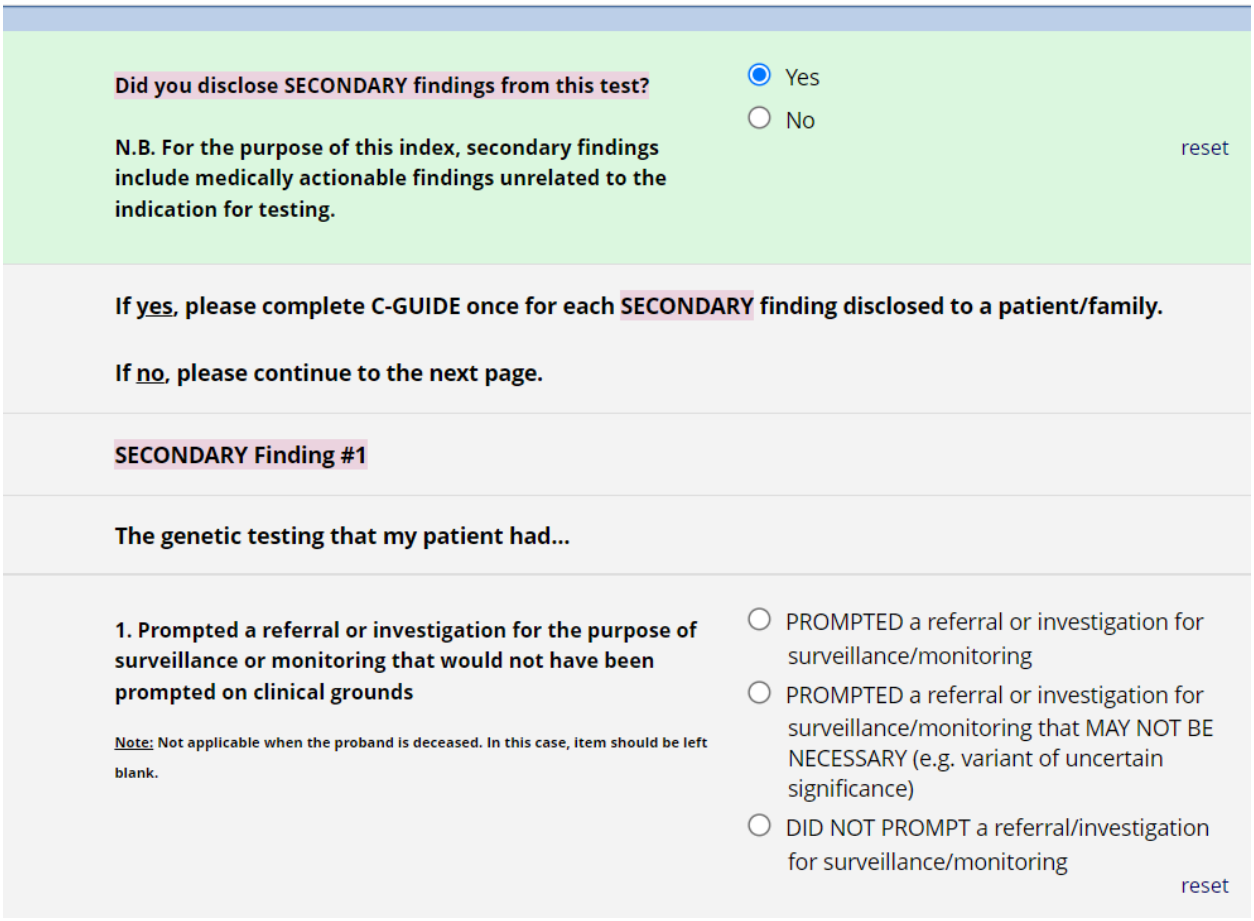
The genetic testing that my patient had...

1. Provided a genetic explanation for my patient's health condition

- ○ Provided a COMPLETE genetic explanation
- ○ Provided a PARTIAL genetic explanation
- ○ Provided a POSSIBLE genetic explanation
- ○ Provided NO genetic explanation

reset

Example image of the secondary findings section:



Example image of the pharmacogenomic section: