ClinGen Pediatric Actionability Workgroup Protocol: Generation of Summary Reports and Semi-Quantitative Metric Scoring

Introduction

As genome scale sequencing is increasingly performed for clinical reasons, there is the potential for genetic information to be derived from an individual that is not related to the original indication for testing. Determining those genes that, if sequenced in the course of broad genomic analysis, may warrant additional scrutiny as secondary findings to detect pathogenic variants and avert patient harm, led to the general conclusion that medical actionability should be defined in as rigorously of a fashion as possible. Medical actionability related to secondary findings represents a known ability to intervene with specific measures and thereby avert a poor outcome due to a previously unsuspected high risk of disease. The assessment of medical actionability of variants in human genes during childhood is important due to the great heterogeneity of the human genome and the varying clinical implications of pathogenic variants in different genes.

The assessment of medical actionability of genes in pediatric patients requires consideration of specific characteristics of testing in this setting. In particular, issues surrounding parental proxy consent, assent of older children and adolescents, and the principle of maintaining an open future affects genetic conditions that may not be considered actionable as secondary findings in children despite being actionable in adults. For instance, a pathogenic variant in *BRCA1* or *BRCA2* associated with hereditary breast and ovarian cancer would not be considered a medically actionable finding given the relevant cancers do not typically develop prior to age 18, and surveillance for people with such findings would be delayed until adulthood. More generally, assessment of medical actionability in the pediatric setting must include consideration of the timing of this return of results, and include assessment of age-related penetrance and the age at which the first medical intervention regarding a finding would take place.

The scope of this protocol is specifically targeted to determination of medical actionability of secondary findings in pediatric patients undergoing clinically indicated diagnostic testing. The criteria to determine actionability here may capture some elements that could be relevant for determination of which genetic findings to consider in a population-based screen. However, this protocol does not consider factors such as systems-based practice and availability of population-scale follow-up that would be necessary to evaluate genetic testing on a public-health scale. Because of this, actionability under this protocol is *not* a sufficient determinant for recommending screening in asymptomatic cohorts.

A rough ranking of genes by medical actionability will also help the broader medical and genetics community prioritize attention to those genes that are likely to have the most clinical impact when discovered to harbor pathogenic variants. Such a metric (with appropriate future modifications as deemed necessary by the community) should serve to inform a variety of contexts, especially as genomics is applied more broadly and in varying realms.

A semiquantitative metric (SQM) has been developed for this purpose by the ClinGen Pediatric Actionability Working Group (PAWG). This SQM is based on the work of many and is not meant to be

final or definitive. The necessarily subjective nature of medical actionability will preclude universal agreement. However, a standardized approach and framework should help ClinGen prioritize clinically important genes and facilitate progress in the field as it grapples with these issues. The metric developed by this group will certainly change with input from the broad community; the present metric should be seen simply as a starting point.

The SQM is based on the conclusion that four broad parameters are most relevant to the determination of medical actionability when an individual harbors a deleterious variant in a given gene: severity of outcome, likelihood of a severe outcome, efficacy of available interventions to avert that outcome, and the nature of the intervention with regards to factors such as risk and burden. The assessment of any given gene-disorder pair will be on a four-point scale for each parameter.

Finally, the assignment of an actionability score is meant to be a starting place, not an end. It will serve to highlight those genes that warrant further consideration and discussion. It is not meant to be a dispositive arbiter of medical actionability; a nuanced and context-dependent concept cannot be captured by a single score.

The anticipated use of the output of the PAWG is for a decision-making panel of experts to review the evidence and scores in the summary document and make decisions about clinically actionable secondary findings. Different decision- making bodies may come to different decisions on which secondary findings should be routinely reported. Panels are convened by various stakeholders, including professional organizations, payers, and governmental agencies, and may include disease/gene experts among other areas of expertise, depending on the goals of the decision-making panel.

Terminology

Important terms defined for the purposes of this protocol:

- **Genetic variant**: a change in the DNA sequence of an individual compared to a reference sequence, which could be pathogenic and could result in clinical manifestations
- **Genetic disorder**: a defect wholly or partly caused by a genetic variant
- **Clinical manifestation**: disease or other clinical signs or symptoms that results from the presence of a pathogenic variant
- **Asymptomatic**: the patient does not show symptoms of the clinical manifestation
- **Symptomatic**: the patient shows symptoms of the clinical manifestation
- **Undiagnosed**: the patient may or may not have symptoms of the genetic disorder, but has **not** previously been found to carry a genetic variant or been diagnosed with the associated genetic disorder
- **Penetrance**: the fraction of individuals with a genotype known to cause a disease who have any signs or symptoms of the disease
- **Age-related penetrance:** penetrance estimates expressed as the fraction of individuals with a genotype with signs or symptoms by a specific age
- **Neonate**: birth to 30 days

- **Important health problem**: a severe or serious health problem or clinical disorder that causes significant morbidity or mortality

Clinical Scenario

For the purpose of this protocol, we assume a **pediatric** patient (<18 years) has received genome or exome sequencing as part of clinical care **for a medical reason unrelated to the genetic disorder under consideration**. In addition, the patient is currently not diagnosed with the genetic disorder under consideration, but may or may not have signs or symptoms for the clinical manifestation(s) associated with the genetic disorder.

Examples:

- **Undiagnosed and without signs or symptoms:** A patient has never been diagnosed with colorectal cancer and is unaware that he/she carries a genetic variant that causes increased risk for familial adenomatous polyposis (FAP).
- **Undiagnosed but with signs or symptoms:** A patient may have dystonia and may be receiving treatment for it, but is unaware that he/she carries a genetic variant for Dopa-responsive dystonia.

Overview of Process
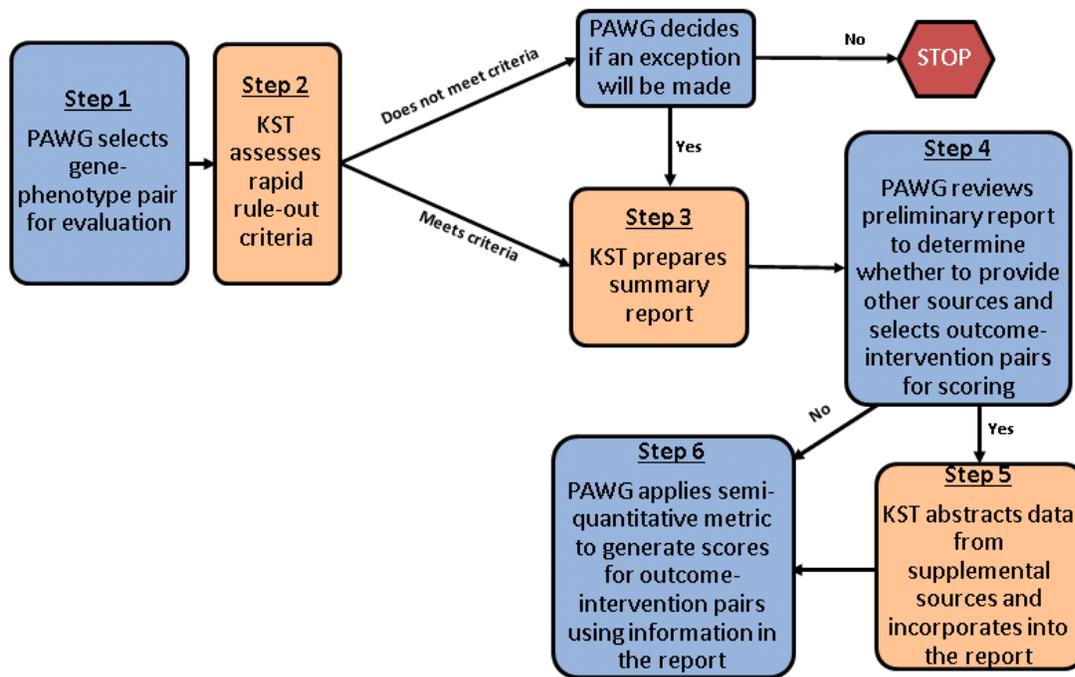
The workflow is composed of three distinct stages:

Early Rule-Out: Initial assessment of topic against rule out criteria and initial report by the
Knowledge Synthesis Team (KST)

Step 1: The Pediatric Actionability Work Group (PAWG) selects gene-disorder pair(s) for
qualitative synthesis and scoring.

Step 2: Early rule-out process to rapidly eliminate gene-disorder pairs that do not meet
a defined threshold.

Summary Report Generation: The KST synthesizes a summary report, which is finalized with
input from the PAWG.

Step 3: Gene-disorder pairs that pass this initial threshold are subjected to a more
resource-intensive search of the literature, with the relevant evidence synthesized into
a short summary report.

Step 4: PAWG reviews preliminary report and selects outcome-intervention pairs for
scoring.

Step 5: KST abstracts data from supplemental sources provided by PAWG and incorporates them into the report.

Step 6: PAWG applies SQM to generate scores for outcome-intervention pairs using information from summary report. Individual and combined scores for each category are finalized by consensus.

Decision Making: Stakeholders (e.g., policy makers, laboratory directors, payors) consider the summary report and consensus scores for final selection of secondary findings that are clinically actionable in the pediatric setting.

This protocol focuses on the steps needed to complete early rule-out and generation of the summary report.

Early Rule Out Process

Overview: Following selection of a gene-disorder pair by the PAWG, two KST members perform an assessment of early rule-out criteria independently to determine whether the initial criteria are met to move the topic on to the generation of the summary report and corroborate to resolve any discrepancies. If the early rule-out criteria are met, one KST member will complete the summary report protocol and document all identified sources. A second KST member will perform a secondary review of the summary report including the documented sources, the tier notation for each relevant source, and the accuracy of the report content.

Note: For specifics of documentation of sources and reports see Appendix A.

Step 1: Topic Selection

 Potential gene-disorder pair(s) are selected by the PAWG for qualitative synthesis and scoring.

- Define the precise gene-disorder pair(s) for report generation:
- Generally, this will be a single gene (e.g. *APC)* and a single disorder (e.g. colorectal cancer). If the genes involved have very similar outcomes (e.g. the familial thoracic aortic aneurysm and dissection genes) one could envision bundling the genes and looking at a particular outcome, like aortic aneurysm.
    - o For example, if hereditary hemorrhagic telangiectasia is to be assessed, designated which genes (e.g. *ENG, ACVRL1, SMAD4, GDF2*).

Step 2: Early Rule Out

The purpose of Step 2 is to eliminate from further consideration gene-disorder pairs that do not meet a minimal threshold for three criteria of clinical actionability at that time:

1. Available clinical intervention relevant in an undiagnosed pediatric patient based on a guideline [i.e., is there an intervention initiated during childhood (<18 years of age)?]

2. Moderate to high (≥40%) penetrance or penetrance unknown
3. Association with a significant health condition.

References used to address the criteria include existing guidelines, systematic reviews, or expert-derived guidance. The references are identified using a predefined method for searching existing databases for related materials. Only one reference is required to meet any given criteria for this step. Therefore, the search procedure is focused and not necessarily comprehensive. For each gene-disorder pair, it is most efficient to begin with an area suspected to not meet the criteria.

This step requires high sensitivity, so the gene-disorder pair should be retained when it is uncertain if the minimum threshold is met.

Available clinical intervention

Evidence- or consensus-based guidelines should be identified to determine actionability in an undiagnosed pediatric patient as it applies to interventions or treatments that might lead to disease prevention, lowered clinical burden, or improved clinical outcomes. To be considered actionable in a pediatric population, these interventions could address manifestations that appear in childhood or adulthood, but are recommended to be implemented during childhood:

- **Patient management:** For asymptomatic patients, effective interventions might prevent clinical manifestations, delay onset, or reduce clinical severity. For symptomatic patients, effective interventions or altered treatment might reduce the severity of clinical outcomes and improve recovery.
- **Surveillance or screening:** For asymptomatic patients, surveillance and screening might result in earlier diagnosis to increase the likelihood of a less burdensome disease.
- **Circumstances to avoid**: The avoidance of certain exposures or situations might improve clinical outcomes.

If no such guidance or review exists that indicates actionability in an **undiagnosed pediatric patient**, our process defines the gene-disorder pair as not actionable. If a guideline or systematic review is available but recommends care in a patient only once symptoms have manifested and does not recommend any altered care in a symptomatic patient, then the actionability criteria have not been met for an undiagnosed pediatric patient. Rarely, a disorder may be difficult and time-consuming to diagnose based on clinical manifestations, and the opportunity for effective early intervention, if available, may be lost. For example, the non-specific symptoms of Familial Mediterranean Fever (e.g., fever and rheumatic manifestations) may lead to a delayed diagnosis in those with a pathogenic variant in the *MEFV* gene. Actionability in such situations will be decided on a case by case basis. Lastly, if clinical signs and symptoms are generally recognized in adulthood and the scope of available guidelines and reviews only address manifestations and interventions in adulthood, then the actionability criteria have not been met for a pediatric patient. However, it is possible that manifestation may occur in adulthood but an intervention may be enacted in childhood to prevent or delay onset, lower clinical burden, or improve clinical outcomes (e.g., treatment of high cholesterol levels in an child with a pathogenic variant

associated with familial hypercholesterolemia); in this case, a condition may still qualify as actionable in the pediatric population.

Method for identifying guidelines or systematic reviews:

Note: Only include guidelines and reviews published in English.

Task 1: **Begin your search by identifying synonyms for the disease, name of involved gene(s), and the OMIM ID# using the OMIM and GeneReviews entries for the disorder.**

     a) OMIM: http://www.ncbi.nlm.nih.gov/omim/
     b) GeneReviews: http://www.ncbi.nlm.nih.gov/sites/GeneTests/review/

Task 2: **Review the following sources for evidence of actionability.**

     Note: If you don't find sufficient evidence for actionability in these sources, move on to Task 3. If you do find evidence that indicates actionability in an undiagnosed pediatric population, you may skip to Task 4.

     a) GeneReviews: http://www.ncbi.nlm.nih.gov/sites/GeneTests/review/
     b) OrphaNet: http://www.orpha.net/consor/cgi-bin/index.php
     c) Clinical Utility Gene Cards: http://www.nature.com/ejhg/archive/categ_genecard_012011.html

Task 3: **If you don't find sufficient evidence for actionability in Task 2, review the following sources to identify a treatment guideline or systematic review for the disease.**

     a) If a GeneReviews exists, search for a link to a treatment guideline within the text or reference list. This may be highlighted by a "Guideline" flag, but might also be listed among the references.
     b) Search OMIM for link to a treatment guideline.
     c) If an OrphaNet entry exists, look for a link to a treatment guideline at the bottom of the entry page.
     d) Search the CDC guideline database (https://phgkb.cdc.gov/PHGKB/tierStartPage.action) for disease name and any synonyms, as well as keywords from the disease name, listed in GeneReviews and/or OMIM.
     e) Search MedGen (http://www.ncbi.nlm.nih.gov/medgen) for all practice guidelines and systematic reviews for the condition and any synonyms.
     f) In PubMed:
         i. Select "MeSH" from the search pull-down menu.
         ii. Search for the disorder.
         iii. In the list of results select the one that is relevant.
         iv. On the right side select "Add to search builder" and then "Search PubMed".

> v. On the side under article types select "Consensus Development Conference," "Consensus Development Conference, NIH," "Meta-Analysis," "Practice Guidelines," and "Systematic Reviews".
> *Note:* If no relevant MeSH term is identified using the disorder name, determine whether MeSH terms exist for the synonyms, individual genes, or a larger category that the disease might fall under (e.g., inborn errors of metabolism). If the MeSH term identified is too specific (i.e., few sources are identified), consider using the MeSH term for the larger category of the disease. If no terms are identified or the term is too broad or too specific, search PubMed using the disorder or gene name as text words and limit article types to "Consensus Development Conference," "Consensus Development Conference, NIH," "Meta-Analysis," "Practice Guidelines," and "Systematic Reviews".
>
> g) If a relevant practice guideline published by a specific professional organization is identified, check the website of that organization to determine whether the guideline is still current. If a more recent version of that specific guideline or another guideline relevant to the genetic disorder has been published, use the most recent guideline.

Note: If no sources indicating actionability in an undiagnosed pediatric population are identified in tasks 1, 2, or 3, then stop here: no further tasks need to be completed.

Penetrance

At least one variant in the gene(s) under consideration should have high or moderate penetrance or risk in any population. We selected a threshold of either ≥ 40% penetrance or relative risk ≥2. Penetrance data from studies in affected individuals may be used if data from an unselected population are not available. Unless other data on penetrance are unavailable, data regarding penetrance or risk in founder populations should be avoided and interpreted with caution as this information is not reflective of the risk in persons with genetic backgrounds distinct from the founder population. **If no data regarding penetrance are available and all other criteria are met, the gene-disorder pair should advance to Step 3.**

Method for determining penetrance:

Task 4: **Check for penetrance and/or relative risk numbers in the GeneReviews, OrphaNet and Clinical Utility Gene Cards**. If data are not available or claims are made without citation (e.g., *VHL* genetic variants are highly penetrant) other sources will need to be reviewed.

> *Note:* Once you find the penetrance or relative risk, you may skip to task 5. If the criteria for penetrance are not met (i.e., penetrance is <40% and/or relative risk is <2) then stop here: no further tasks need to be completed.
>
> a) GeneReviews: http://www.ncbi.nlm.nih.gov/sites/GeneTests/review/
> b) OrphaNet: http://www.orpha.net/consor/cgi-bin/index.php

    c) Clinical Utility Gene Cards:
http://www.nature.com/ejhg/archive/categ_genecard_012011.html

4.1: Check for references and penetrance or relative risk numbers in OMIM

OMIM: http://www.ncbi.nlm.nih.gov/omim

4.2: Search PubMed: *disease OR gene name* **AND** *penetrance*

PubMed: http://www.ncbi.nlm.nih.gov/pubmed/

 4.3: Search PubMed: *gene name* **AND** *disease name* **AND** *relative risk*

PubMed: http://www.ncbi.nlm.nih.gov/pubmed/

Note: If no sources indicating penetrance are identified in Task 4, then stop here: no further tasks related to penetrance need to be completed. If the disorder passes all other requirements, it may proceed to Step 3 without further review by the AWG.

Burden of Disorder

The disorder should cause significant morbidity or mortality. The trait or disorder should be related to a severe or serious health or clinical disorder (e.g., not eye color, baldness, or the benign elevation of bilirubin seen in Gilbert's Syndrome). We do not address untreatable infertility alone or reproductive decision making as part of this approach, recognizing that these could be important in some settings.

Method for determining burden of disease:

Task 5:   **Review information from GeneReviews.** If a GeneReviews entry is not available or does not include citations, search for a relevant background publication in PubMed.

Review of Early Rule Out by PAWG: The early rule-out is intended for triaging topics. If any of the three criteria are not met, the gene-disorder pair does not automatically proceed to the generation of a summary report and is sent to the PAWG to determine if an exception should be made and the gene-disorder pair should proceed to the generation of a summary report. In particular, the PAWG may choose to make an exception to the criteria of >40% penetrance if the outcome of under consideration is considered particularly severe. If an exception is not made by the PAWG, the gene-disorder pair is excluded from further consideration.

Summary Report Generation

The purpose of this process is to document and summarize the readily available evidence related to key features of **actionability** to evaluate candidates for a clinically actionable incidental finding. Although a relatively high bar for clinical actionability must be met for a gene-disorder pair to qualify for routine reporting, we allow for a relatively low threshold for the type of evidence, including nonsystematic or expert-based references. This approach is both pragmatic and efficient because this represents the most

common available evidence for highly penetrant rare genetic disorders. The level of evidence is documented using a tiered system and quality rating that is included in the actionability report.

Step 3: Literature Search and Report Synthesis

In Step 3, we conduct a reproducible search of existing synthesized literature using the predefined method to create a summary report that provides information on five domains associated with the gene-disorder pair:

1. **Nature of the genetic disorder:** Prevalence, clinical features, natural history
2. **Actionability:** Patient management, surveillance, circumstances to avoid
3. **Likelihood:** Prevalence of the associated genetic variants, penetrance/relative risk, variable expressivity
4. **Nature of the intervention:** risk and burden
5. **Chance to escape clinical detection prior to harm in the clinical setting**

Identify all potential sources of information that will be considered:

Method for identifying guidelines, systematic reviews, or other eligible sources:

Task 1:   **Find all treatment guidelines/systematic reviews for the disease.**

Note: Use all sources listed below to conduct the search. Do not skip tasks.

Note: Only include guidelines and reviews published in English.

a) If a GeneReviews entry exists, search for a link to a treatment guideline within the text or reference list. This may be highlighted by a "Guideline" flag, but might also be listed among the references.
b) Search OMIM for any links to a treatment guideline.
c) Search the CDC guideline database (https://phgkb.cdc.gov/PHGKB/tierStartPage.action) for disease name and any synonyms listed in Gene Reviews and/or OMIM.
d) Search MedGen (http://www.ncbi.nlm.nih.gov/medgen) for all practice guidelines and systematic reviews for the condition and any synonyms.
e) In PubMed:
   i. Select "MeSH" from the search pull-down menu.
   ii. Search for the disorder.
   iii. In the list of results select the one that is relevant.
   iv. On the right side select "Add to search builder" and then "Search PubMed".
   v. On the side under article types select "Consensus Development Conference," "Consensus Development Conference, NIH," "Meta-Analysis," "Practice Guidelines," and "Systematic Reviews".
   Note: If no relevant MeSH term is identified using the disorder name, determine whether MeSH terms exist for the synonyms, individual genes, or a larger

category that the disease might fall under (e.g., inborn errors of metabolism). If the MeSH term identified is too specific (i.e., few sources are identified), consider using the MeSH term for the larger category of the disease. If no terms are identified or the term is too broad or too specific, search PubMed using the disorder or gene name as text words and limit article types to "Consensus Development Conference," "Consensus Development Conference, NIH," "Meta-Analysis," "Practice Guidelines," and "Systematic Reviews".

f)   If a relevant practice guideline published by a specific professional organization is identified, check the website of that organization to determine whether the guideline is still current. If a more recent version of that specific guideline or another guideline relevant to the genetic disorder has been published, use the most recent guideline.

g)   Guidelines may also be identified by going to the website of a professional organization known to specialize in a particular disorder (e.g. National Comprehensive Cancer Network and cancer disorders).

Task 2:   **Identify other sources that may be considered.**

a)   GeneReviews: http://www.ncbi.nlm.nih.gov/sites/GeneTests/review/
b)   OMIM: http://www.ncbi.nlm.nih.gov/omim/
c)   OrphaNet: http://www.orpha.net/consor/cgi-bin/index.php
d)   Clinical Utility Gene Cards: http://www.nature.com/ejhg/archive/categ_genecard_012011.html

Task 3:   **Identify relevant sources.** Once a full search for potentially relevant references is completed, examine these references to determine relevance. In the context of incidental findings, relevant references are those that provide information on the actionability in a pediatric patient who has not been diagnosed with the genetic disorder, though they may be symptomatic with clinical manifestations associated with the genetic disorder. Any references deemed irrelevant are excluded. For disorders with an abundance of available references, priority may be given to the most recent literature. For example, if literature from the past 10 years provides a sufficient amount of information to complete the summary report then older literature does not need to be considered.

Determine the Tier of Evidence for each source:

To assess the relative quality of the identified references, each relevant reference is placed into one of five tiers. This tier assignment will be based on the methods of the systematic review and/or meta-analysis and represents the highest tier level for the overall reference. The tiers are used to facilitate a hierarchical method for examining existing literature, starting with the most evidence based.

Method for determining the Tier of Source:

Task 4:   Determine Tier of Evidence for each Source.

a) Evidence from a systematic review, a meta-analysis clearly based on a systematic review, or a clinical practice guideline clearly based on a systematic review[1] (**Tier 1**)

b) Evidence from clinical practice guidelines or broad-based expert consensus with some level of evidence review, but using undescribed methods or using sources that were not systematically identified 1 (**Tier 2**)

c) Evidence from another source with non-systematic review of evidence (e.g., GeneReviews, OrphaNet, and Clinical Utility Gene Cards, or opinion of a single or few (<5) expert(s) that provides guidance) with primary literature cited (**Tier 3**)

d) Evidence from another source with non-systematic review of evidence (e.g., GeneReviews, OrphaNet, and Clinical Utility Gene Cards, or opinion of a single or few (<5) expert(s) that provides guidance) with no citations to primary data sources (**Tier 4**)

e) Evidence from a non-systematically identified source **(Tier 5)**

[1]Systematic review of evidence means that traditional systematic review methods are followed including: a) a clearly stated set of objectives, b) an explicit, reproducible methodology, c) systematic search that attempts to identify all studies that would meet the eligibility criteria, d) inclusion and exclusion criteria for studies are pre-defined, and e) an assessment of the validity of findings in the included studies, and f) a systematic presentation and synthesis of the characteristics and findings of the included studies. Please see Cochrane Handbook for Systematic Reviews of Interventions, Section 1.2.2. "What is a systematic review?" (https://handbook-5-1.cochrane.org/)

Abstraction of Key Data Elements onto Template:

A narrative summary is abstracted and documented for each gene-disorder pair. For each question, use the reference(s) with the highest available tier of evidence for data abstraction. All sources of that tier are referenced if they are in agreement. If not, the reviewer determines the best reference based on considerations including quality, methods (e.g., search strategy, inclusion criteria, analytic methods, funding source), and date of publication (e.g., more recent publications may be more relevant). If there is not a best reference, then abstract data from all relevant references. The tier of evidence is recorded for each abstracted data element.

Method for abstracting key data elements:

Task 5:   Identification of the Data Source and Abstraction of Each Key Data Element.

a) For each data element in the template, identify the source(s) in the highest available tier of evidence that can be used to abstract the data (i.e., that reports on the data element).

b) If there is more than one source for the data element in the same (highest) tier, determine if the sources are in agreement.

            i.   If the sources are in agreement, list all the sources from that tier in the
                    reference column.
            ii.   If the sources are not in agreement, record the discrepancy by abstracting
                    the conflicting data elements from all the relevant sources. Record the
                    source for each data element in the reference column.
    c) Abstract the data element from the selected source, and briefly summarize in the
        narrative description.
    d) Record the tier of evidence for the particular data element in the Narrative
        Description column.
            i.   The tier of evidence may differ from the overall tier of the source, which
                    represents the highest tier level for the overall reference.
            ii.   For actionability (Section 2 of the summary report), clinical
                    recommendations abstracted from the references are not allowed a
                    higher tier than the tier for the overall reference, but can be assigned a
                    lower tier using the tier guidelines on page 7. For example, a
                    recommendation from a Tier 1 reference can be assigned a Tier 2 if the
                    recommendation is formulated with some expert opinion, perhaps due to
                    a lack of evidence.
            iii.   For information on effectiveness of the actionability items, additional
                    citations can be identified from the original source in order to obtain
                    specific data to show effectiveness (e.g. odds ratios, improve survival
                    rates, etc.). These additional citations do not need to be referenced and
                    the information will be given the same tier as the original actionability
                    item.
            iv.   For the remaining items (Sections 3-5), each abstracted data element will
                    be given a tier based on the context within the reference. For example,
                    Tier 1 for a result of a meta-analysis or Tier 3 for background information
                    with citations. Thus, different tiers of evidence can be present in the same
                    document.
            v.   In the event that a clinical guideline uses guidelines from a previous clinical
                    guideline (and thus provides a citation), then tier and abstract
                    recommendations from the cited guideline; this may require pulling
                    additional sources, if they were not discovered in the original search(es).
    e) Repeat Task 5 for each data element in the Template.

Note: Particular attention should be paid to age-related penetrance in the creation of reports on
pediatric actionability. In addition, the age to start screening should be clearly noted for
recommendations. The natural history should, when possible, also clearly state the earliest age of
onset and typical age of onset of manifestations.

Task 6:   Supplementation of information.

a) To ensure that the summary report contains all relevant information required to assign a score based on the PAWG scoring metric, additional sources may be identified using a non-systematic method.
b) These sources may be identified and recommended by the KST or by the PAWG during the review period or during the scoring discussion of the summary reports.
c) These additional sources may include primary literature, references included in MedGen (http://www.ncbi.nlm.nih.gov/medgen), and websites of relevant major health organizations such as the CDC (www.cdc.gov), American Cancer Society (www.cancer.org), or other trusted website.
d) In the situation that these supplemental sources provide conflicting information, the KST and the PAWG will come to an "expert consensus" of which source to include in the summary report.
e) Any information from these supplementary sources included in the summary report will be assigned a Tier 5.

Secondary Review

A second KST member will perform a secondary review of the summary report with the main goals to:

a) Review the Endnote coding for relevance and inclusion for each reference
b) Review tiering for each included reference
c) Review the accuracy of the report content.

Bridge Searches

Two weeks before the summary report goes to the PAWG for review, a bridge search should be performed to ensure that the Summary Report is up-to-date if more than 3 months have passed since the last update of the report.

a) Create a new folder for the topic on the file server that will contain all new sources identified in the bridge search.
b) Repeat all searches performed in the original literature search for the topic. These should be documented in the source documentation file along with the primary search making sure to include the date of the bridge search.
c) Determine whether OMIM, GeneReviews, or OrphaNet entries have been updated since the last search.
    i) If updated, save the latest version and update entry in EndNote.
    ii) If relevant, abstract new information to the Summary Report.
d) Rerun searches in National Guideline Clearinghouse and PubMed using the same search terms.
    i) Document any new sources identified and import reference into EndNote.
    ii) Determine relevance for each source.
    iii) Download a copy of all relevant sources.

iv)   Abstract information to the Summary Report and edit EndNote entry as needed to reflect relevance and inclusion.

e)   For all professional guidelines included in the Summary Report, go to the relevant websites and determine whether a more recent version is available. Also look for additional relevant guidelines.

   i)   Document any new guideline versions, import into Endnote, and save a copy.

   ii)   Abstract information to the Summary Report and edit EndNote entry as needed to reflect relevance and inclusion.

f)   Bridge searches should be reviewed by the appropriate secondary reviewer.

Note: some previously included information may be deleted if a new source is identified with a higher tier or more recent information.

Step 4: ClinGen Pediatric AWG Review of Summary Report and Selection of Scoring Pairs

The PAWG is given time to review Summary Reports for accuracy and to nominate additional sources for reference. The KST protocol may not identify all information required in the report to be able to address all aspects of the scoring metric. In this case, the PAWG may recommend additional sources to be added to the summary report.

In addition, the PAWG designates the specific intervention(s) (e.g., periodic aortic imaging, beta-blockers) to be scored with the selected gene-disorder pair and the outcome to be assessed. The PAWG will determine whether any genes or specific populations (e.g., homozygous/heterozygous, male/female) will be scored separately.

Step 5: Updating of Summary Report with Additional Sources

As needed, the KST may edit the Summary Report based on the review of the PAWG. If additional sources are identified by the PAWG these will be designated as: Tier 5: Evidence from a non-systematically identified source.

Step 6: The SQM will then be applied to the final summary report generated by KST for the gene-disorder pair:

Defined gene-disorder pairs will be scored with an SQM for "medical actionability" with regard to a designated intervention by rating several parameters, since this concept hinges on various attributes of any given genetic condition and associated gene. Please follow these guidelines when generating scores for each category. Always assuming that one has found a maximally deleterious variant, an aggregate score for medical actionability will be generated by first scoring defined gene-disorder pairs in four categories:

1.   Severity: **What is the nature of the threat to health to an individual carrying a clearly deleterious allele in this gene?** When scoring this category, specify the specific outcome to be considered. This

may, for example, be the most penetrant and/or severe outcome for a gene-disorder pair with multiple outcomes (e.g. for *APC* – Familial Adenomatous Polyposis, score colorectal cancer). Be sure to define what aspect of the outcome is being scored. Assign:
- o 3 points for sudden death as a "reasonably possible" outcome (example would be Long QT)
- o 2 if diagnosis with this condition implies a reasonable possibility of death or major morbidity (examples of genes/conditions that would score a 2 would include APC/Familial Adenomatous Polyposis gene given the non-trivial risk of death when diagnosed with cancer)
- o 1 for expected modest morbidity
- o 0 for minimal or no morbidity

2. Likelihood of disease: **What is the chance that a serious outcome will materialize given a deleterious variant (akin to penetrance)?** For this category, one is scoring the likelihood of a serious outcome for a heterozygote or homozygote (please specify) in a population known to have this disease, for example, family members who have a known familial pathogenic variant. This is necessary given that almost all of our data about penetrance comes from such contexts (although it is recognized that penetrance is likely to be lower in the general population in the future).

Note: Gene-disorder pairs will be considered by the PAWG whenever there is an intervention that would be used during childhood (<18 years), even if the age at onset typically or always occurs in adults. For instance, in familial hypercholesterolemia, although cholesterol measures may be elevated during childhood, typically the manifestations of the condition do not occur until adulthood. Nevertheless, this condition may still be considered by the PAWG because of interventions that could begin during childhood to reduce cholesterol levels and potentially lower risk. There is no absolute threshold for the proportion of cases that could benefit from childhood intervention. This must be assessed on a case by case basis, taking into account other factors such as the effectiveness and nature of the intervention.
- o For conditions with age-related penetrance, define what age was considered (e.g. "penetrance by age 10")
- o Assign points as follows:
    - i. 3 points for > 40% chance
    - ii. 2 for 5-39% chance
    - iii. 1 for 1-4% chance
    - iv. 0 points for < 1% chance
- o If penetrance is unknown, expert consensus will be used to assign a value and the associated evidence score will reflect that (level E)

3. Efficacy of specific interventions: **How effective is the selected, specific intervention for preventing or significantly diminishing the risk of harm when initiated during childhood (< 18 years)?** To be clear, the harm in this situation may present in childhood or adulthood, while the effectiveness of the intervention is being assessed based on initiation during childhood only. The score for this category should directly reflect a specific intervention in the categories in the report of 1) patient management, 2) surveillance or screening, and 3) circumstances to avoid. Assume ideal adherence

and access to care. Only score specific interventions known to ameliorate risk for people with this condition AND that would be initiated during childhood (<18 years) (e.g. do not consider general "lifestyle" and behavioral changes that are generally recommended to individuals in many contexts). Factors including "personal utility", reproductive decision making, and ending the diagnostic odyssey should NOT be considered when scoring this category. A report will be generated only for gene-disorder pairs with at least one effective intervention unless the PAWG makes an exception based on a predefined methodology. One may score numerous interventions but for each exercise, specify the specific intervention being scored. For example, if one is scoring *APC* and colon cancer as the outcome of interest, efficacy of risk-reducing gastrectomy could be scored OR efficacy of heightened surveillance in diminishing death could be scored. An intervention would be given a score of IN if it would not be initiated during childhood. For instance, for hereditary breast and ovarian cancer (HBOC), there are effective interventions in adults (e.g., risk reducing surgery, surveillance), but these interventions are not recommended for children.

> Thus, it is critical to specifically define the gene, the outcome and the intervention being assessed. Assign:
> - o   3 points if highly effective
> - o   2 if moderately effective
> - o   1 if minimally effective
> - o   0 if controversial or have unknown effectiveness
> - o   IN* if the intervention is ineffective or if there is no intervention during childhood
>
> * If a score of IN is given, no scores are given for the other categories, such as severity, likelihood and nature of the intervention. The final composite score will be IN.

4. Nature of intervention: This category is designed to assign a score to how risky, medically burdensome or intensive a given intervention is. The group acknowledges that this is subjective and context-dependent. It also recognizes that a patient's perception of how burdensome or intensive a given intervention is may differ from that of his/her physician. Nonetheless, scoring in this category is necessary. This is because how risky, medically burdensome or intensive an intervention is an important part of the equation that must be balanced against any potential benefits of effective intervention, especially if one is deciding whether to engage in screening of asymptomatic individuals (opportunistic or otherwise). Assign:
    - o   3 points for low risk, or medically acceptable and low intensity interventions
      Examples: Non-invasive screening, ultrasonography, echocardiography, electrocardiography, 24-hour urine tests or spot blood tests, ophthalmological exams, thorough physical exams, medications with low side effects, simple dietary interventions such as avoiding a specific nutrient (such as galactose) or vitamin supplementation (such as biotin)
    - o   2 points for moderate risk, moderately acceptable or intensive interventions
      Examples: CT scans with contrast (risks of radiation and contrast), catheterization for imaging, medications with tolerable but irksome side effects, synthetic diets such as low protein, ophthalmologic exam under anesthesia.
    - o   1 point for greater risk, less acceptable and substantial interventions

Examples: Prophylactic surgery with limited morbidity to remove target organs, such as thyroidectomy, prophylactic bone marrow transplantation not requiring marrow ablation, repeated examinations requiring general anesthesia in children.
- o 0 points for high risk, poorly acceptable, or intensive interventions
Examples: removal of an organ with very high associated morbidity such as pancreatectomy and prophylactic bone marrow transplantation requiring marrow ablation.

Level of Evidence Reviewed: This category is separate from the four "actionability" criteria and measures the availability and tier of evidence for this gene-disorder pair with regard to likelihood of disease and efficacy of intervention based on the evidence report.

- o An individual score is reported for each component. For example, a gene-disorder pair could receive a score of Severity=2, Likelihood=3C, Effectiveness=1B, and Nature of Intervention=2, indicating a likelihood level of evidence of C and efficacy of intervention level of evidence of B.
- o Assign scores thusly:
    - i. A for substantial evidence
    - ii. B for moderate evidence
    - iii. C for minimal evidence
    - iv. D for poor evidence or conflicting evidence
    - v. E for non-systematically identified evidence

Rating	Label	Proposed Definition
A	Substantial evidence	- Evidence is available and provided in the report - Information in the report is based on high tier evidence (Tier 1)
B	Moderate evidence	- Evidence is available and provided in the report - Information in the report is based on moderate tier evidence (Tier 2)
C	Minimal evidence	- Evidence is available and provided in the report - Information in the report is based on lower tier evidence (Tier 3 or Tier 4)
D	Poor evidence or conflicting	- Evidence is conflicting are not available and unable to be provided in the report
N	Subjective evidence based on expert contributions	- Evidence that is not systematically identified. Only expert provided evidence is available (Tier 5). - Evidence is provided in the report.

Data on the effectiveness of a particular treatment or screening protocol can be extrapolated from the experience with other similar conditions when there is a lack of data specific to the topic being scored. When using extrapolated data, the number score will reflect its effectiveness, but the level of evidence should be downgraded by one letter. For instance, the score for the effectiveness of imaging for aortic aneurysm screening should theoretically be the same regardless of the causative gene. Therefore, we

can use the effectiveness score for aortic aneurysm surveillance for Marfan syndrome (3B), but we would downgrade the evidence level to a "C" when scoring other aortic aneurysm disorders, like Loeys-Dietz syndrome, because we extrapolated the data.

In addition, sometimes there is a lack of concordance between the judgment of the PAWG members on the level of evidence and the tier of evidence. The PAWG scorers can choose to override the actual available evidence giving it a higher or lower level of evidence score when appropriate based on their expert opinion. For example, a disorder may be given a score of 3A for likelihood based on expert opinion of the PAWG when the evidence level tier in the summary report indicates a 3C.

Both above scenarios will be indicated by a numbered footnote in the actionability curation interfaced (ACI).

If any additional sources are identified during the scoring discussion and incorporated into the scoring decision, the KST will add the source to the summary report following the discussion. The summary report will be subsequently re-reviewed by the Pediatric AWG to ensure that the addition reflects the use of the source as part of the discussion.

Decision Making

The purpose of this process is for a decision-making panel of experts to review the evidence in the summary document and make decisions about clinically actionable secondary findings. Different decision- making bodies may come to different decisions on which secondary findings should be routinely reported. Panels are convened by various stakeholders, including professional organizations, payers, and governmental agencies, and may include disease/gene experts among other areas of expertise, depending on the goals of the decision-making panel.

Appendix A: Process for Electronic Documentation

All steps of the methods should be documented electronically using the following steps:

- a. A separate folder should be created for each gene/disorder pair on the CRVR file server to hold the relevant files.
- b. All guidelines, systematic reviews, and other sources identified during the literature search above should be documented:
  - i. Perform literature search
  - ii. Save ALL identified references in Endnote
  - iii. For OMIM and GeneReviews entries, save as an 'Electronic Citation' and include the hyperlink to the article.
  - iv. For all guidelines, save to Endnote as the appropriate type of reference (e.g. report or journal article) and use the user defined fields to track search information:

Field	Information	Example
Custom 1	Source + Date Accessed (MM.DD.YYYY)	PubMed + 02.13.2014
Custom 2	Relevance and Inclusion*	YYN
Custom 3	Tier	Tier 2
Custom 4	Notes	Retired

  *This entry indicates whether the identified reference was relevant after title/abstract review (Y/N), relevant after review of full text (Y/N), and included in the final report (Y/N).

  - v. PubMed references can be exported into a text file and imported directly into Endnote.
  - vi. For guidelines identified on guidelines.gov, export the PDF summary of the guideline and import into Endnote. For any of these guidelines deemed relevant, import those separately into Endnote either by hand or via PubMed.
  - vii. For literature searches that require search terms (PubMed, Guidelines.gov) document the search terms used into the Documentation form. For multiple searches in the same database, track which search terms were used (Guidelines.gov 1, Guidelines.gov 2, etc.). Boolean terms can be used to simplify the search in PubMed but should be used with caution in Guidelines.gov due to their search algorithm.
  - viii. For any guideline identified during the literature search that has a more recent version available, save both versions in Endnote. For the outdated version, indicate 'Y' for relevance and 'Outdated' in notes. For the more recent version, indicate 'Y' for relevance and 'Updated' in notes. Other guidelines might be retired or retracted by the issuing committee or

association. In this event, indicate 'Y' for relevance and 'Retired' or 'Retracted' in notes.

c. Save a copy of the full text of all relevant articles.

d. The Rule-Out Dashboard and Summary Report will be completed and stored the ClinGen Interface (http://actionability.clinicalgenome.org/site/cg-actionability).