ClinGen Actionability Working Group Training
# Table of Contents

- Training Steps for New Scorers  
  - Slide 3
- ClinGen Overview  
  - Slide 4
- Actionability Working Group (AWG) Overview  
  - Slide 7
- General AWG Methods  
  - Slide 10
- Generation of a Summary Report  
  - Slide 15
- Scoring a Topic  
  - Slide 21
- Scoring Process  
  - Slide 22
- Dissemination of AWG Reports and Scores  
  - Slide 30
- Using the AWG Interface  
  - Slide 31
- How to Access Confluence  
  - Slide 41
- Additional Resources  
  - Slide 50
Training Steps for New AWG Scorers

- Review the following materials:
  - ClinGen Project Summary Report Protocol
  - AWG Scoring Protocol
  - Manuscript on AWG methods development and scoring of the ACMG56

- Review these training slides

- Orientation call with Kristy Lee

- Listen in on a couple of AWG calls and practice scoring without entering scores into interface
**ClinGen: Clinical Genome Resource**

- Launched in 2013
- Co-funded by NHGRI, NICHD, and NCI
- Collaboration with NCBI’s ClinVar
- >250 researchers and clinicians from >75 institutions

**Purpose:** To build an authoritative central resource that defines the clinical relevance of genes and variants for use in precision medicine and research.
ClinGen Overview

Key Goals

• Share genomic and phenotypic data provided by clinicians, researchers, and patients through centralized databases for clinical and research use
• Standardize clinical annotation and interpretation of genomic variants
• Implement evidence-based expert consensus for curating genes and variants
• Improve understanding of variation in diverse populations to realize interpretation of genetic testing on a global scale
• Develop machine-learning algorithms to improve the throughput of variant interpretation
• Assess the “medical actionability” of genes and variants
• Structure and provide access to genomic knowledge for use in EHR ecosystems
• Disseminate the collective knowledge and resources for unrestricted use in the community

ClinGen Website: https://www.clinicalgenome.org/
Gene-Disease Validity

*Can variation in this gene cause disease?*

- By reviewing genetic and experimental data in the scientific literature, ClinGen is working to identify genes in which pathogenic variants clearly cause disease.
- The gene-disease validity curation process includes 6 classification categories (below) describing the level of evidence supporting a given gene-disease relationship.
- Use this information when deciding which genes to include in clinical testing panels, and which genes require more research studies.

- Definitive
- Strong
- Moderate
- Limited
- Disputed
- Refuted

Dosage Sensitivity

*Does loss or gain of a copy of this gene or genomic region result in disease?*

- The dosage sensitivity curation process collects evidence supporting or refuting haploinsufficiency (loss) and triplosensitivity (gain) as mechanisms for disease for genes and larger genomic regions.
- Evidence is scored according to the amount of evidence available (categories below).
- Use this information when interpreting the clinical significance of variants involving loss or gain of genomic material, such as those identified by chromosomal microarray (CMA).

- Sufficient Evidence
- Emerging Evidence
- Limited Evidence
- No Evidence
- Dosage Sensitivity Unlikely

Variant Pathogenicity

*Which changes in the gene cause disease?*

- The variant curation process combines clinical, genetic, population, and functional evidence with expert review to classify variants into 1 of 5 categories (below) according to ACMG guidelines.
- The results of these analyses are deposited in ClinVar for community access.
- Use ClinGen’s variant curation tools to evaluate evidence for a variant that has not yet undergone expert review, or for classification discrepancy resolution.

- Pathogenic
- Likely Pathogenic
- Uncertain
- Likely Benign
- Benign

Clinical Actionability

*Are there actions that could be taken to improve outcomes for patients with this genetic risk?*

- Certain genetic conditions have medical interventions that can delay symptoms, prevent disease, result in earlier detection, etc. Such conditions are considered “actionable”.
- The actionability curation process evaluates availability of effective medical interventions, accounting for the chance the outcome will happen, the severity of the condition to be avoided, and the risks associated with the intervention.
- Use this information to decide which secondary finding results to report back to patients. The actionability report is not intended to inform the treatment of individual patients.

- Severity and Likelihood of Disease
- Efficacy and Nature of Intervention
AWG: Actionability Working Group

The overarching goal of the AWG is to identify those human genes that, when significantly altered, confer a high risk of serious disease that could be prevented or mitigated if the risk were known.

Goals:

1. Develop rigorous and standardized procedures for categorically defining “clinical actionability”; a concept that includes a known ability to intervene and thereby avert a poor outcome due to a previously unsuspected high risk of disease.
2. Nominate genes and diseases to score for “clinical actionability”.
3. Produce evidence-based reports and semi-quantitative metric scores using a standardized method for nominated gene disease pairs.
4. Make these reports and actionability scores publicly available to aid broad efforts for prioritizing those human genes with the greatest relevance for clinical intervention.
Clinical Context

- There are many points during a person’s life when genomic information may be acted upon.
- For the purposes of the AWG, the clinical context has been defined as:
  - An adult with an incidental or secondary finding identified via genome-scale sequencing.
  - This person has not been previously diagnosed with the genetic disorder.
  - However, this person may have signs or symptoms of the genetic condition (e.g., the person may have high cholesterol and may be undergoing treatment for it, but does not know that they have familial hypercholesterolemia).
Clinical Actionability

• There are many actions a person can take after receiving genetic risk information
• For the purposes of the AWG, “clinical actionability” has been defined as:
  • Well-established, clinically prescribed interventions
  • Interventions that are specific to the genetic disorder under consideration (we do not consider general lifestyle and behavioral changes that are recommended to the general population, with the exception of special cases, such as smoking cessation in α1-antitrypsin deficiency)
  • Lead to disease prevention or delayed onset, lowered clinical burden, or improved clinical outcomes
• Though important, we do not currently consider factors such as personal utility, reproductive decision-making, and ending the diagnostic odyssey
Overview of the AWG Workflow

**Step 1**
AWG selects gene-phenotype pair for evaluation

**Step 2**
KST assesses rapid rule-out criteria

**Step 3**
KST prepares summary report

**Step 4**
AWG reviews preliminary report to determine whether to provide other sources and selects outcome-intervention pairs for scoring

**Step 5**
KST abstracts data from supplemental sources and incorporates into the report

**Step 6**
AWG applies semi-quantitative metric to generate scores for outcome-intervention pairs using information in the report

AWG: Actionability Working Group

KST: Knowledge Synthesis Team, a subset of AWG that curates actionability evidence in summary reports
Step 1:
Selecting Gene-Disorder Pairs

• The pairings can include a single gene (e.g., APC and familial adenomatous polyposis) or bundles of genes that are associated with the same disorder (e.g., MLH1, MSH2, MSH6, and PMS2 and Lynch syndrome)

• The AWG started with the list of genes recommended by the American College of Medical Genetics and Genomics (ACMG) for return as secondary findings (e.g., ACMG56 and ACMG 2.0 SF)

• Additional gene-disorder pairs assessed by the AWG have been nominated by AWG members and non-AWG stakeholders
Step 2: KST Performs a Rapid Rule-Out Assessment

The purpose of the rapid rule-out step is to quickly rule-out from further consideration any gene-disorder pair that does not meet 3 criteria:

1. **Actionability:** Is the result actionable in an undiagnosed adult?

2. **Penetrance:** Is there a pathogenic variant with at least moderate penetrance (≥40%)? [Penetrance is allowed to be “unknown.”]

3. **Burden of disease:** Is this an important health problem?
## Rapid Rule-Out Dashboard
### Secondary Findings in Adults/Pediatrics

<table>
<thead>
<tr>
<th>GENE/GENE PANEL:</th>
<th>DISORDER:</th>
</tr>
</thead>
<tbody>
<tr>
<td>GENE&lt;&lt;DISORDER PAIRS: [e.g., FB&lt;&lt;306700; F9&lt;&lt;306500]</td>
<td>OMIM ID:</td>
</tr>
</tbody>
</table>

### HGNC ID:

### Actionability

1. Is there a qualifying resource, such as a practice guideline or systematic review, for the genetic condition?

   - [ ] YES
   - [ ] NO

2. Does the practice guideline or systematic review indicate that the result is actionable in one or more of the following ways?

   - [ ] Yes
   - [ ] No

<table>
<thead>
<tr>
<th>Patient Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surveillance or Screening</td>
</tr>
<tr>
<td>Circumstances to Avoid</td>
</tr>
</tbody>
</table>

   - [ ] YES (≥ 1 of above)
   - [ ] NO

3. Is the result actionable in an undiagnosed adult with the genetic condition?

   - [ ] YES
   - [ ] NO

### Penetrance

4. Is there at least one known pathogenic variant with at least moderate penetrance (≥40%) or moderate relative risk (≥2) in any population?

   - [ ] YES
   - [ ] NO
   - [ ] UNKNOWN

### Significance/Burden of Disease

5. Is this condition an important health problem?

   - [ ] YES
   - [ ] NO

### Next Steps

6. Are Actionability (Q2-3), Penetration (Q4), and Significance (Q5) all "YES"?

   - [ ] YES (Proceed to Summary Report)
   - [ ] NO (Consult Actionability Working Group)

   - [ ] Exception granted, proceed to Summary Report
   - [ ] Exception not granted, STOP
Step 2:
KST Performs a Rapid Rule-Out Assessment

• If the gene-disorder pair passes the rule-out criteria, it moves automatically to generation of a summary report

• If the gene-disorder pair does not pass the rule-out criteria, the AWG may decide that an exception should be made to proceed to generation of a summary report
  • An example may be if the penetrance is known to be low and is below the penetrance threshold, yet there are compelling reasons to consider it for scoring (e.g., Brugada syndrome did not meet the penetrance threshold, but the outcome was considered severe enough that an exception was made)

• If an exception is not made, the gene-disorder pair is not considered further at that time, but may be reassessed at a later time when additional evidence comes available
Step 3: KST Generates the Summary Report

The purpose of the summary report is to document and summarize the available evidence related to key features of actionability.

- KST evidence sources:
  - The KST uses a detailed protocol to systematically identify relevant literature to make the process standardized and reproducible across curators.
  - The protocol to identify evidence is limited in scope to make the process feasible:
    - Evidence included: Clinical practice guidelines, systematic reviews, meta-analyses, OMIM, GeneReviews, OrphaNet, and Clinical Utility Gene Cards.
    - Evidence not included: Narrative reviews and primary literature.
Step 3:
KST Generates the Summary Report

All evidence identified by the KST for a gene-disorder pair is tiered based on quality:

**Tier 1:** Evidence from a systematic review, meta-analysis, or practice guideline based on a systematic review

**Tier 2:** Evidence from a practice guideline or expert consensus with some level of evidence review

**Tier 3:** Evidence from a non-systematic evidence review (e.g., GeneReview or OMIM entry) with primary literature cited

**Tier 4:** Evidence from a non-systematic review of evidence (e.g., GeneReview or OMIM entry) with no citations to primary data sources

**Tier 5:** Evidence from a non-systematically identified source (see slides 18 and 19)
Step 3:
KST Generates the Summary Report

The KST abstracts data from the highest tiered sources available for 5 domains associated with clinical actionability:

1. **Nature of the genetic disorder**: Prevalence, clinical features, natural history

2. **Actionability**: Patient management, surveillance, family management, and 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
Step 3:
KST Generates the Summary Report

To ensure that the summary report contains all relevant information required to assign a score based on the SQM, additional sources may be identified by the KST to supplement the report using a non-systematic method:

- These sources may include such sources as primary literature, references cited in MedGen, and websites of relevant major health organizations such as the CDC, American Cancer Society, or other trusted website

- Any information from these supplementary sources included in the summary report will be assigned a Tier 5 (i.e., evidence not identified by the systematic evidence search)
Step 4:
AWG Reviews the Summary Report

Once the KST generates a preliminary report, it is posted on Confluence for AWG review and comment with the goals of:

• Assessment for accuracy
• Nomination of additional references
  • References nominated by AWG members to incorporate into the report are designated as Tier 5
• Suggest specific outcomes and associated interventions to be scored for actionability
  • All topics are scored for specific outcome-intervention pairs, rather than the condition as a whole (e.g., colorectal cancer and colonoscopy for Lynch syndrome)

See slides 39-47 on how to access Confluence
Step 5:  
The KST Revises the Summary Report

After the AWG review, the KST revises the report to:

• Incorporate any suggested edits or nominated references from the AWG

• Ensure there is sufficient evidence for the effectiveness of interventions selected for scoring, if available
### Step 6:
The AWG Applies the SQM to Generate Scores
(Scoring is done in the AWG interface, see slides 28-38 on how to access the scoring interface)

<table>
<thead>
<tr>
<th>SEVERITY</th>
<th>What is the nature of threat to health to individual carrying a clearly deleterious allele in this gene?</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Sudden death (e.g., Long QT syndrome)</td>
</tr>
<tr>
<td>2</td>
<td>Death or major morbidity (e.g., Lynch syndrome)</td>
</tr>
<tr>
<td>1</td>
<td>Modest morbidity</td>
</tr>
<tr>
<td>0</td>
<td>Minimal or no morbidity</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LIKELIHOOD</th>
<th>What is the chance a serious outcome will materialize given a deleterious variant?</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>&gt; 40% chance</td>
<td>A = Substantial evidence (Tier 1)</td>
</tr>
<tr>
<td>2</td>
<td>5-39% chance</td>
<td>B = Moderate evidence (Tier 2)</td>
</tr>
<tr>
<td>1</td>
<td>1-4% chance</td>
<td>C = Minimal evidence (Tier 3 or 4)</td>
</tr>
<tr>
<td>0</td>
<td>&lt; 1% chance</td>
<td>D = Poor evidence, or missing</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EFFECTIVENESS</th>
<th>How effective is intervention for preventing or significantly diminishing the risk of harm?</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Highly effective</td>
<td>A = Substantial evidence (Tier 1)</td>
</tr>
<tr>
<td>2</td>
<td>Moderately effective</td>
<td>B = Moderate evidence (Tier 2)</td>
</tr>
<tr>
<td>1</td>
<td>Minimally effective</td>
<td>C = Minimal evidence (Tier 3 or 4)</td>
</tr>
<tr>
<td>0</td>
<td>Controversial or unknown effectiveness</td>
<td>D = Poor evidence, or missing</td>
</tr>
<tr>
<td>IN</td>
<td>Ineffective*</td>
<td>E = Expert contributions (Tier 5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NATURE OF INTERVENTION</th>
<th>How risky, medically burdensome or intensive is the intervention?</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Low risk, medically acceptable, and low intensity</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Moderate risk, moderately acceptable or intensive</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Greater risk, less acceptable and substantial</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>High risk, poorly acceptable, or intensive</td>
<td></td>
</tr>
</tbody>
</table>

* If a score of IN is given, no scores are given for the other categories.*
Scoring Process

Each scorer provides a preliminary score
Score discussion on AWG call
Each scorer provides a final score

Scorers are allowed to change their score after discussion with the rest of the AWG scorers

Consensus Score

The consensus score is the majority, but the individual final scores don’t have to agree
Points to Consider While Scoring

✓ The 4 domains of actionability are scored for each outcome-intervention pair for the gene-disorder

✓ Subgroups within the gene-disorder may be scored separately if they are known to differ across domains considered for actionability. Subgroups may be defined by such variables as:

   • Gene: BRCA1 and BRCA2 were scored separately due to varying penetrance for ovarian cancer
   • Sex: Hemophilia, an X-linked disorder, was scored separately for males and females given the differences in severity
   • Zygosity: Heterozygotes and homozygotes were scored separately for familial hypercholesterolemia due to differences in interventions and severity
Points to Consider While Scoring

Always assume a maximally deleterious variant has been identified

When scoring effectiveness of an intervention, assume ideal adherence and access to care

A score of ‘IN’ is given to an intervention where there is evidence provided that the intervention is NOT effective, whereas a score of ‘0’ is given where there is unclear or controversial evidence that an intervention is effective
Points to Consider While Scoring

✓ The Nature of the Intervention domain assigns a score to how risky, burdensome, or intensive an intervention is. This domain is particularly subjective and context-dependent, and perspectives of the AWG may differ from perspectives of a patient.

✓ Some examples for each Nature of the Intervention category are:

  • **3 points**: Non-invasive screening (e.g., ultrasonography, mammography), medications with low side effects, simple dietary interventions
  • **2 points**: 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
  • **1 points**: Prophylactic surgery with limited morbidity to remove target organs, such as prophylactic mastectomy or oophorectomy
  • **0 points**: Removal of an organ with very high associated morbidity such as gastrectomy or pancreatectomy
Points to Consider While Scoring

✓ All 4 domains are assigned a numerical score, while Likelihood and Effectiveness are also assigned a letter score based on the tier of evidence

<table>
<thead>
<tr>
<th>Rating</th>
<th>Label</th>
<th>Proposed Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Substantial evidence</td>
<td>Evidence is provided in the report and is based on high tier evidence (Tier 1)</td>
</tr>
<tr>
<td>B</td>
<td>Moderate evidence</td>
<td>Evidence is provided in the report and is based on moderate tier evidence (Tier 2)</td>
</tr>
<tr>
<td>C</td>
<td>Minimal evidence</td>
<td>Evidence is provided in the report and is based on lower tier evidence (Tier 3 or 4)</td>
</tr>
<tr>
<td>D</td>
<td>Poor evidence or conflicting</td>
<td>Evidence is conflicting or not available and unable to be provided in the report</td>
</tr>
<tr>
<td>E</td>
<td>Subjective evidence based on expert contributions</td>
<td>Evidence that was not systematically identified, and only expert provided evidence is available in the report (Tier 5)</td>
</tr>
</tbody>
</table>
Points to Consider While Scoring

✔ Data on the effectiveness of a particular intervention can be extrapolated from experience with a similar condition 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 evidence score should be downgraded by a letter
  • For example, the effectiveness of aortic aneurysm surveillance in Marfan syndrome was scored as “3B” based on available evidence; however, there was no evidence for this intervention in Loeys-Dietz syndrome, so the effectiveness score was extrapolated from Marfan syndrome with the evidence score downgraded for a score of “3C”

✔ In addition, scorers can choose to override the available evidence and give it a higher evidence score based on their expert opinion
  • For example, a disorder may be given a score of 3A for likelihood based on expert opinion of the AWG when the evidence level in the summary report indicates a score of 3C
Points to Consider While Scoring

✓ When scoring the effectiveness of a surveillance intervention, the effectiveness of the intervention considered is not limited to the effectiveness of the surveillance mechanism to detect the outcome, but to allow for the timely implementation of downstream treatments to reduce morbidity and mortality

  • For example, for the effectiveness of mammography, do not consider the ability of mammography to detect a tumor in the breast alone (proximal effectiveness), but also consider the effectiveness of mammography programs to reduce morbidity and mortality to allow for earlier detection and treatment for breast cancer (distal effectiveness)
Dissemination of AWG Reports and Scores

• Once a topic has been completed, the summary report and consensus scores become publicly available on the ClinGen website:

  https://www.clinicalgenome.org/working-groups/actionability/projects-initiatives/actionability-evidence-based-summaries/

• These reports and consensus scores can be used by stakeholders to guide decision-making regarding the return of secondary findings based on actionability

• The reports are not comprehensive and should not be used to guide clinical care
Scoring in the Actionability Interface

The next set of slides will show you how to access the AWG scoring interface to score gene-disorder pairs.

If you need login information or have trouble logging in, you may contact Jessica Hunter (Jessica.E.Hunter@kpchr.org) or Sai Subramanian (SaiLakshmi.Subramanian@bcm.edu)
Step 1:
Step 2:
Once logged in you should see the screen below, click the ‘search’ button to retrieve entry result(s).
**Step 3:**
Find the topic assigned for scoring using the search box at the top (use disorder name or gene).

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Genes</th>
<th>Last Updated</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Intermittent Porphyria</td>
<td>HMBS</td>
<td>Thu, 11 Jan 2018</td>
<td>Released</td>
</tr>
<tr>
<td>Adrenoleukodystrophy</td>
<td>ABCD1</td>
<td>Thu, 11 Jan 2018</td>
<td>Released</td>
</tr>
<tr>
<td>Adult-onset type II citrullinemia</td>
<td>SLC25A13</td>
<td>Thu, 11 Jan 2018</td>
<td>Released</td>
</tr>
<tr>
<td>Alpha-1 Antitrypsin Deficiency</td>
<td>SERPINA1</td>
<td>Thu, 11 Jan 2018</td>
<td>Released</td>
</tr>
<tr>
<td>Arrhythmogenic Right Ventricular Dysplasia</td>
<td>PKP2, DSP, DSC2, TMEM43, DSG2</td>
<td>Thu, 11 Jan 2018</td>
<td>Released</td>
</tr>
<tr>
<td>Arterial tortuosity syndrome</td>
<td>SLC2A10</td>
<td>Wed, 14 Feb 2018</td>
<td>Entered</td>
</tr>
<tr>
<td>Autosomal Dominant Polycystic Kidney Disease</td>
<td>PKD1, PKD2</td>
<td>Mon, 23 Oct 2017</td>
<td>Released</td>
</tr>
</tbody>
</table>
Step 4:
When you find the topic, click on the edit button (the pencil and paper icon on the far right).
Step 5:
Now you are at the first scoring page (Severity). Information from the summary report is shown in the middle of the screen. You will enter your scores on the right-hand side. Make sure you scroll down (grey bar at right) and score all outcomes. Hit “Save” when you have completed this section.
Step 6:
To go to the next section for scoring, go to the menu on the left side and select “Likelihood of outcome.” Make sure you scroll all the way down on the right side to ensure you have scored all outcomes. Save your scores when you are done.
Step 7:
Once you have completely scored each section, chose the “Summary” option in the left. Here you can review your scores.
**Step 8:**
You may return to any section at this time to edit or enter additional scores (be sure to save if you change your scores). Once you are happy with your scores, return to the summary page, change the “Set My Score Status” to “Complete”, and click “Save”.

![ClinGen Clinical Genome Resource EVIDENCE ACTIONABILITY](image-url)
Step 9:
To move on to the next topic, click on the icon highlighted below on the upper right-hand side (by the orange arrow) to go back to the topics page (shown in Step 2) and repeat.
Step 10:
When you are done, log out by using the “power” button on the far right.
Confluence

The next set of slides will show you how to access the Confluence interface to read and comment on the reports.

If you need login information or have trouble logging in, you may contact Melissa (landrum@ncbi.nlm.nih.gov)
Step 1:
Go to https://ncbiconfluence.ncbi.nlm.nih.gov/, enter in your login information, and click “Log in.”
Step 2:
Under ‘Spaces,’ click ‘Space directory’ which will take you to a page listing many entities including ‘ClinGen.’ If ‘ClinGen’ is already listed under ‘Spaces,’ click ‘ClinGen’ and proceed to slide 42.
Step 3:
Under ‘Site Spaces,’ click ‘ClinGen’ which will take you to a page listing many entities including ‘ClinGen;’ click on ‘ClinGen.’
Step 4: Under ‘ClinGen Main Page,’ click ‘Actionability’ which will take you to the AWG page.
Step 5:
Scroll down to ‘Working Documents,’ click ‘Summary Reports for Review by date’ which will display a clickable list of reports. Click on the report of interest.
Step 6:
On the summary report page, clickable pdfs of the reports, report summaries and a comments section are available. Log out when done.

**January 22, 2018 Summary Report**

Created by Mackenzie Trapp on Jan 09, 2019

F5_Deficiency_Binning_Template_20170108.pdf
HPPS_Update_SummaryReport_01052018.pdf
LFS_Update_SummaryReport_01052017.pdf

For the updated HPPS report: Last time we scored, we scored the 4 genes (SDHD, SDHAF2, SDHC, and SDHE) separately. All genes scored the same for all domains except for likelihood (penetrance estimates were missing for SDHAF2 and SDHC and thus scored lower). In the new report, we have added 3 additional genes (SDHA, MAX, and TMEM127) as well as new penetrance data that indicates that all genes are associated with high rates of penetrance (with the exception of SDHA which has a penetrance estimate of 39%, all other genes have penetrance estimates >39%). So we propose lumping of genes for this round of scoring.

2 Comments

**Anne Slavotinek**
For Factor V, we could score 1) avoidance of aspirin 2) pregnancy management on frequency of severe bleeding episodes, but it is unlikely there will be much data.

*Reply • Like • Jan 12, 2018*

**Adam Buchanan**
For factor V deficiency, could also consider something like: Blood products replacement : severe bleeding events.

*Reply • Like • Jan 18, 2018*

Write a comment...
Alternate:
When it is time to review reports, Kristy Lee sends out emails with links directly to the reports. Click on the link, log in, and it will directly right to the report to review.

Hi All,

Hope you had a nice holiday season! Just a reminder that we moved the Jan. 15th call to Jan. 22nd due to the Martin Luther King Holiday. Therefore, your summary report reviews are requested by COB on Friday Jan. 19th. You may click here to review the reports. There are three reports for review: 2 updates (Li-Fraumeni syndrome and Paragangliomas/Pheochromocytomas) and one new report (factor V deficiency).

Thanks!

Kristy

Kristy Lee, MS, CGC
Genetic Counselor
Associate Professor
Department of Genetics
UNC Chapel Hill
P: 919-843-3158
F: 919-966-4151
kristy.lee@med.unc.edu
Also on Confluence:
There are a variety of AWG-related documents stored on the Actionability page, including the current scoring metric, protocols, and meeting minutes.

Actionability
Created by Preetha Nandl last modified by Mackenzie Trapp on Jan 22, 2018

The Actionability Working Group aims to identify those human genes that, when significantly altered, confer a high risk of serious disease that could be prevented or mitigated if the risk were known.

Goals
1. Develop rigorous and standardized procedures for categorically defining “clinical actionability”; a concept that includes a known ability to intervene and thereby avert a poor outcome due to a previously unsuspected high risk of disease.
2. Nominate genes and diseases to score for “clinical actionability”.
3. Produce evidence-based reports and semi-quantitative metric scores using a standardized method for nominated gene disease pairs.
4. Make these reports and actionability scores publicly available to aid broad efforts for prioritizing those human genes with the greatest relevance for clinical intervention.

Working Documents
Include any documents, links, and other resources that the WG is currently discussing and working on.
Additional Resources for the ClinGen AWG

- **ClinGen AWG webpage** with list of members and link to publicly available summary reports and scores
- **ClinGen AWG manuscript** with method development and scores for ACMG56
- **Manuscript for EGAPP methods** used as a basis for AWG evidence synthesis
- **Manuscript for NCGENES methods** used as a basis for the AWG SQM
- Detailed **ClinGen AWG summary report protocol**
- Detailed **ClinGen AWG scoring protocol**
Have suggestions for improvement or clarification of the information within these slides? Please send them to Jessica Hunter (Jessica.E.Hunter@kpchr.org).

Having technical difficulties with the Actionability Interface? Contact Sai Subramanian (SaiLakshmi.Subramanian@bcm.edu).

Welcome to the ClinGen AWG!