

ClinGen Pediatric Actionability Working Group Training



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Training Steps for New PAWG Scorers

- ✓ Review the following materials:
 - PAWG 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

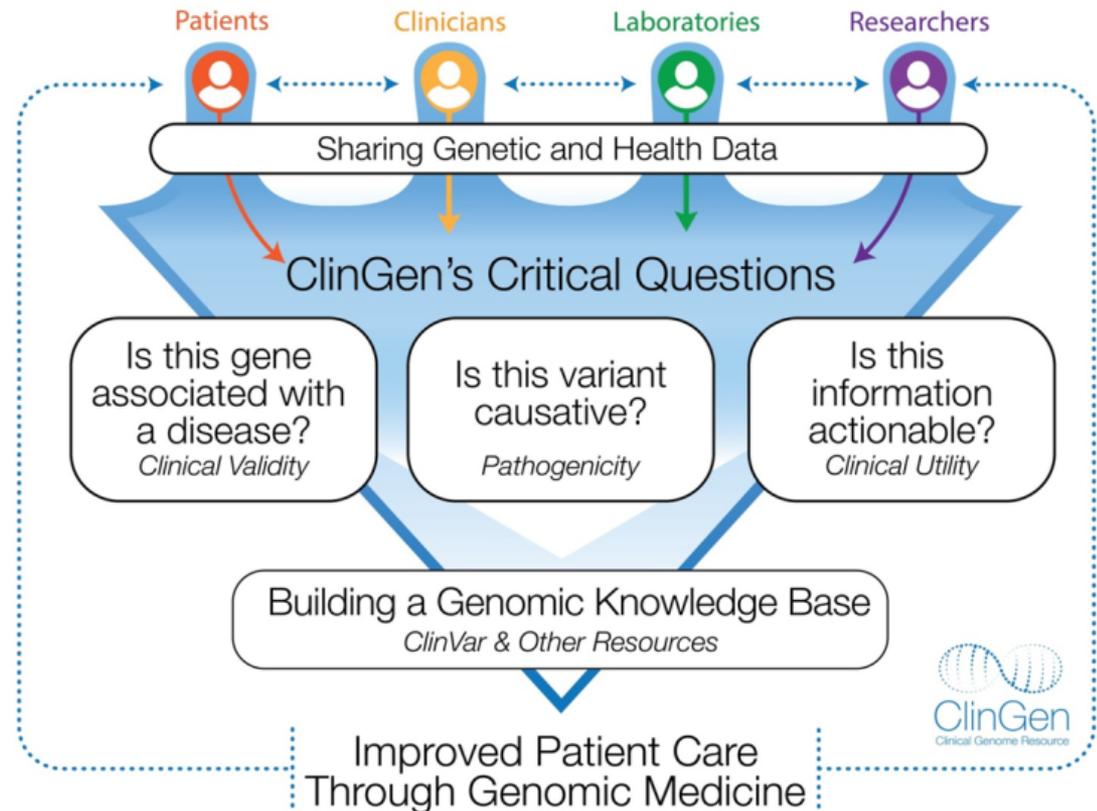
- Launched in 2013
- Co-funded by NHGRI, NICHD, and NCI
- Collaboration with NCBI's ClinVar
- >250 researchers and clinicians from >75 institutions

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





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.

Two AWGs



- AWG: Adult-focused clinical actionability
 - PAWG: Pediatric-focused clinical actionability
- Both AWGs will be supported by the Knowledge Synthesis Team (KST) to generate summary reports for scoring

Clinical Context



- There are many points during a person's life when genomic information may be acted upon
- For the purposes of the pediatric AWG (PAWG), the clinical context has been defined as:
 - A-pediatric patient (<18 years) with an incidental or secondary finding identified via genome-scale sequencing
 - This patient has not been previously diagnosed with the genetic disorder
 - However, this patient 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



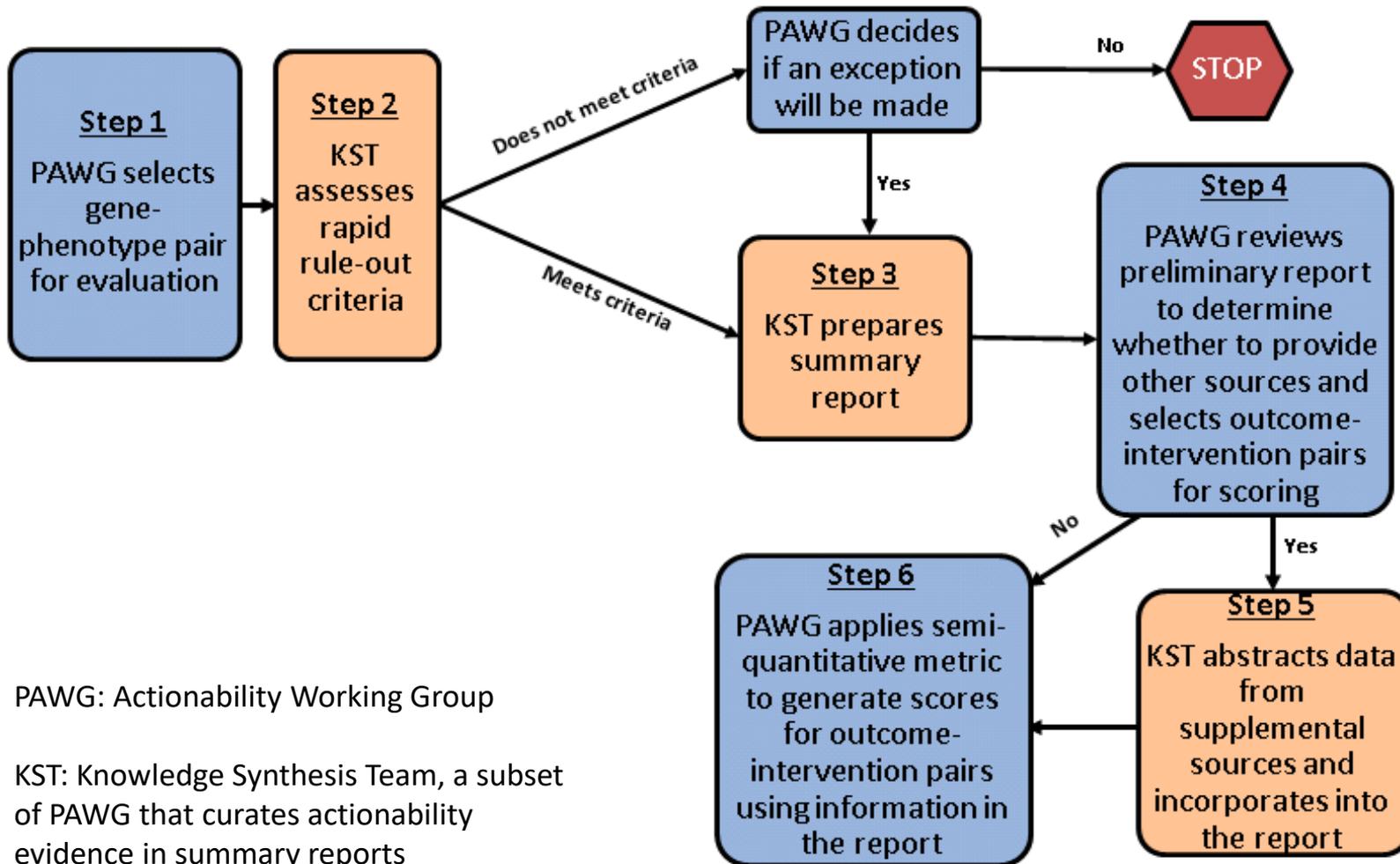
- There are many actions a person can receiving genetic risk information
- For the purposes of the PAWG, “clinical actionability” has been defined as:
 - Well-established, clinically prescribed interventions
 - Interventions that are specific to the genetic disorder under consideration (we do not consider general lifestyle and behavioral changes that are recommended to the general population, with the exception of special cases, such as smoking cessation in α 1-antitrypsin deficiency)
 - Lead to disease prevention or delayed onset, lowered clinical burden, or improved clinical outcomes
- Though important, we do not current consider factors such as personal utility, reproductive decision-making, and ending the diagnostic odyssey

Timing of Interventions



- The PAWG will consider interventions during the pediatric period that lead to disease prevention or delayed onset to improve downstream clinical outcomes
- This scope includes outcomes with pediatric onset
- This scope also includes outcomes which typically do not present until adulthood if there is evidence that an intervention during childhood or adolescence can optimize outcomes (e.g., use of statins in familial hypercholesterolemia)

Overview of the PAWG Workflow



PAWG: Actionability Working Group

KST: Knowledge Synthesis Team, a subset of PAWG 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., familial thoracic aortic aneurysm and dissection genes)
- The PAWG will start with topics already assessed by the adult AWG that have childhood onset, including genes that did not pass the early rule out stage for the adult AWG due to childhood onset
- Additional gene-disorder pairs assessed by the PAWG have been nominated by PAWG members and non-PAWG stakeholders

Step 2:

KST Performs a Rapid Rule-Out Assessment

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

- 1. Actionability:** Is there an 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. Penetrance:** Is there a pathogenic variant with at least moderate penetrance ($\geq 40\%$)? [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

GENE/GENE PANEL:

GENE↔DISORDER PAIRS: [e.g., F8 ↔306700; F9 ↔306900]

HGNC ID:

DISORDER:

OMIM 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	
<input type="checkbox"/>	<input type="checkbox"/>	Patient Management
<input type="checkbox"/>	<input type="checkbox"/>	Surveillance or Screening
<input type="checkbox"/>	<input type="checkbox"/>	Circumstances to Avoid

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), Penetrance (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 rapid rule-out, it moves automatically to the generation of a summary report
- If the gene-disorder pair does not pass the rapid rule-out criteria, the PAWG may decide that an exception should be made to proceed to the 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 does not meet the penetrance threshold, but the outcome may be considered severe enough that an exception could be 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 base 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, 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:

PAWG Reviews the Summary Report

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

- Assessment for accuracy
- Nomination of additional references
 - References nominated by PAWG 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 43-51 on how to access Confluence

Step 5:

The KST Revises the Summary Report

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

- Incorporate any suggested edits or nominated references from the PAWG
- Ensure there is sufficient evidence for the effectiveness of interventions selected for scoring, if available

Step 6:

The PAWG Applies the SQM to Generate Scores

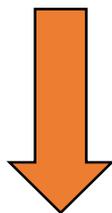
(Scoring is done in the PAWG interface, see slides 32-42 on how to access the scoring interface)

SEVERITY	What is the nature of threat to health to individual carrying a clearly deleterious allele in this gene?	
	3 = Sudden death (e.g., Long QT syndrome) 2 = Death or major morbidity (e.g., familial adenomatous polyposis) 1 = Modest morbidity 0 = Minimal or no morbidity	
LIKELIHOOD	What is the chance a serious outcome will materialize given a deleterious variant?	
	3 = > 40% chance 2 = 5-39% chance 1 = 1-4% chance 0 = < 1% chance	A = Substantial evidence (Tier 1) B = Moderate evidence (Tier 2) C = Minimal evidence (Tier 3 or 4) D = Poor evidence, or missing E = Expert contributions (Tier 5)
EFFECTIVENESS	How effective is intervention for preventing or significantly diminishing the risk of harm?	
	3 = Highly effective 2 = Moderately effective 1 = Minimally effective 0 = Controversial or unknown effectiveness IN = Ineffective*	A = Substantial evidence (Tier 1) B = Moderate evidence (Tier 2) C = Minimal evidence (Tier 3 or 4) D = Poor evidence, or missing E = Expert contributions (Tier 5)
NATURE OF INTERVENTION	How risky, medically burdensome or intensive is the intervention?	
	3 = Low risk, medically acceptable, and low intensity 2 = Moderate risk, moderately acceptable or intensive 1 = Greater risk, less acceptable and substantial 0 = High risk, poorly acceptable, or intensive	

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

Scoring Process

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



Each scorer provides a preliminary score

Score discussion on PAWG call

Each scorer provides a final score



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: *SCN5A* may be scored separately from *KCNQ1* and *KCNH2* due to varying effectiveness of interventions across long QT types
 - Sex: Hemophilia, an X-linked disorders, may be scored separately for males and females given the differences in severity
 - Zygosity: Heterozygotes and homozygotes may be 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 PAWG 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 thyroidectomy
 - **0 points:** Removal of an organ with very high associated morbidity such as 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

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

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, if the effectiveness score for aortic aneurysm surveillance for Marfan syndrome is 3B, we could extrapolate it to other aortic aneurysm disorders (e.g., Loeys-Dietz syndrome) but we would downgrade the evidence level to a “C” because we extrapolated the data
- ✓ 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 PAWG 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 echocardiography in Marfan syndrome, do not consider the ability of echocardiography to detect dilation of the aorta alone (proximal effectiveness), but also consider the effectiveness of echocardiography surveillance to allow for timely repair of the aorta to reduce morbidity and mortality from aortic aneurysm (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 be not be used to guide clinical care

Scoring in the Actionability Interface

The next set of slides will show you how to access the PAWG 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 Ronak Patel (Ronak.Patel@bcm.edu)

Step 1:

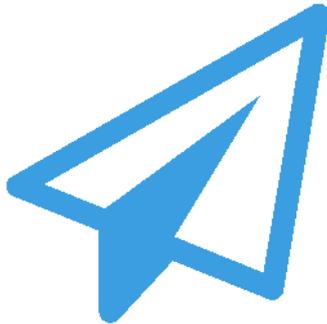
Go to <http://actionability.clinicalgenome.org/>, click 'LOGIN' and enter in your login information.



CLINICAL ACTIONABILITY



[LOGIN](#)



ClinGen Actionability Work-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 of ClinGen Actionability Work Group:

- 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
- Nominate genes and diseases to score for "clinical actionability"
- Produce evidence-based reports and semi-quantitative metric scores using a standardized method for nominated gene disease pairs
- Make these reports and actionability scores publicly available to aid broad efforts for prioritizing those human genes with the greatest relevance for clinical intervention.

Step 2:

Once logged in you should see the screen below, click the 'search' button to retrieve entry result(s).



ClinGen Actionability Report

Create New

Search

Search

Filter ▾

Sort By ▾

Sign Out

View Active Gene-Disease pairs

Showing 50 of 83 topics

Syndrome ▲	Genes	Last Updated	Status	
Acute Intermittent Porphyria	HMBS	Thu, 11 Jan 2018	Released	☰ 📄 ↻ ↗
Adrenoleukodystrophy	ABCD1	Thu, 11 Jan 2018	Released	☰ 📄 ↻ ↗
Adult-onset type II citrullinemia	SLC25A13	Thu, 11 Jan 2018	Released	☰ 📄 ↻ ↗
Alpha-1 Antitrypsin Deficiency	SERPINA1	Thu, 11 Jan 2018	Released	☰ 📄 ↻ ↗
Arrhythmogenic Right Ventricular Dysplasia	PKP2, DSP, DSC2, TMEM43, DSG2	Thu, 11 Jan 2018	Released	☰ 📄 ↻ ↗
Arterial tortuosity syndrome	SLC2A10	Wed, 14 Feb 2018	Entered	☰ 📄 ↻ ↗
Autosomal Dominant Polycystic Kidney Disease	PKD1, PKD2	Mon, 23 Oct 2017	Released	☰ 📄 ↻ ↗

Step 3:

Find the topic assigned for scoring using the search box at the top (use disorder name or gene).



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Create New

Search

Search

Filter

Sort By

Sign Out

View Active Gene-Disease pairs

Showing 50 of 83 topics

Syndrome	Genes	Last Updated	Status	
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Step 4:

When you find the topic, click on the edit button (the pencil and paper icon on the far right).



ClinGen Actionability Report

Create New

Search

Search

Sort By

Sign Out

View Active Gene-Disease pairs

Showing 50 of 83 topics



Syndrome ▲	Genes	Last Updated	Status	
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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.



Genes:
HMBS (OMIM: 609806)

Acute Intermittent Porphyria
OMIM: 176000
Aliases: Acute Intermittent Porphyria
Porphyrias are inherited defects in the biosynthesis of heme. Acute intermittent porphyria, the most common form of porphyria, is an autosomal dominant disorder characterized by recurrent attacks of abdominal pain, constipation, dysfunction, and...

Status: Released - Under Revision
Last edited by: Elizabeth Clarke

Score

- Severity of outcome
- Likelihood of outcome
- Effectiveness of intervention
- Nature of Intervention
- Summary
- Reset Scores
- Status: Complete

Severity

Prevalence of the Genetic Disorder: < 1-2 in 100000

The prevalence estimates for acute intermittent porphyria (AIP) across all European countries (excluding Sweden) range from 5.4-5.9/1,000,000. In Sweden, the incidence and prevalence of AIP are about 4 times higher than in Europe due to a founder effect.

References:
OrphaNet (2016) Prevalence of rare d ...
Elder G (2013) J Inherit Metab Dis
SD Whatley (2016) GeneReviews(R))

Clinical Features:

AIP results from half normal activity of the enzyme hydroxymethylbilane synthase (HMBS) involved in the biosynthesis of heme. The condition is characterized by intermittent and sometimes life-threatening acute neurovisceral attacks of severe abdominal pain without peritoneal signs. These attacks may be accompanied by nausea, vomiting, distention, constipation, diarrhea, tachycardia, hypertension, and hyponatremia. Neurologic findings may also occur including mental changes (e.g., insomnia, paranoia), convulsions, hallucinations, peripheral neuropathy (that may progress to respiratory paralysis), pain in extremities, paresis, weakness, and altered consciousness (from somnolence to coma). Attacks may be provoked by certain drugs, crash dieting, alcoholic beverages, smoking, endocrine factors, calorie restriction, stress, and infections or surgery which can increase the demand for hepatic heme. Attacks are usually due to the additive effects of several triggers, including some that are unknown.

References:
SD Whatley (2016) GeneReviews(R))
Anderson KE (2005) Ann Intern Med
PORPHYRIA, ACUTE INTERMITTENT; AIP (OMIM: 176000)
Acute intermittent porphyria, Disease (Orphanet)

Score Severity

Severity Help
Please enter a value for SEVERITY OF THE DISEASE:
0 = Minimal or No Morbidity
1 = Modest Morbidity
2 = Major Morbidity or Possible Death
3 = Sudden Death

Save

Outcome: Neurovisceral attacks

Not Scored 0 1 2 3

Enter notes here...

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.



Genes:
HMBS (OMIM: 609806)

Acute Intermittent Porphyria
OMIM: 176000
Aliases: Acute Intermittent Porphyria
Porphyrias are inherited defects in the biosynthesis of heme. Acute intermittent porphyria, the most common form of porphyria, is an autosomal dominant disorder characterized by recurrent attacks of abdominal pain, constipation, dysfunction, and...

Status: Released - Under Revision
Last edited by: Elizabeth Clarke

Score

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- Likelihood of outcome
- Effectiveness of intervention
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- Status: Complete

Severity

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References:
SD Whatley (2016) GeneReviews((R))
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Score Severity

Severity Help
Please enter a value for SEVERITY OF THE DISEASE:
0 = Minimal or No Morbidity
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2 = Major Morbidity or Possible Death
3 = Sudden Death

Save

Outcome: Neurovisceral attacks

Not Scored 0 1 2 3

Enter notes here...

Step 7:

Once you have completely scored each section, chose the “Summary” option in the left. Here you can review your scores.



Genes:
HMBS (OMIM: 609806)

Acute Intermittent Porphyria
OMIM: 176000
Aliases: Acute Intermittent Porphyria
Porphyrias are inherited defects in the biosynthesis of heme. Acute intermittent porphyria, the most common form of porphyria, is an autosomal dominant disorder characterized by recurrent attacks of abdominal pain, constipation, dysfunction, and...

Status: Released - Under Revision
Last edited by: Elizabeth Clarke

Score

- Severity of outcome
- Likelihood of outcome
- Effectiveness of intervention
- Nature of Intervention
- Summary
- Reset Scores
- Status: Complete

Severity

Prevalence of the Genetic Disorder: < 1-2 in 100000

The prevalence estimates for acute intermittent porphyria (AIP) across all European countries (excluding Sweden) range from 5.4-5.9/1,000,000. In Sweden, the incidence and prevalence of AIP are about 4 times higher than in Europe due to a founder effect.

References:
Orphanet (2016) Prevalence of rare d ...
Elder G (2013) J Inherit Metab Dis
SD Whatley (2016) GeneReviews((R))

Clinical Features:

AIP results from half normal activity of the enzyme hydroxymethylbilane synthase (HMBS) involved in the biosynthesis of heme. The condition is characterized by intermittent and sometimes life-threatening acute neurovisceral attacks of severe abdominal pain without peritoneal signs. These attacks may be accompanied by nausea, vomiting, distention, constipation, diarrhea, tachycardia, hypertension, and hyponatremia. Neurologic findings may also occur including mental changes (e.g., insomnia, paranoia), convulsions, hallucinations, peripheral neuropathy (that may progress to respiratory paralysis), pain in extremities, paresis, weakness, and altered consciousness (from somnolence to coma). Attacks may be provoked by certain drugs, crash dieting, alcoholic beverages, smoking, endocrine factors, caloric restriction, stress, and infections or surgery which can increase the demand for hepatic heme. Attacks are usually due to the additive effects of several triggers, including some that are unknown.

References:
SD Whatley (2016) GeneReviews((R))
Anderson KE (2005) Ann Intern Med
PORPHYRIA, ACUTE INTERMITTENT; AIP (OMIM: 176000)
Acute intermittent porphyria, Disease (Orphanet)

Score Severity

Severity Help
Please enter a value for SEVERITY OF THE DISEASE:
0 = Minimal or No Morbidity
1 = Modest Morbidity
2 = Major Morbidity or Possible Death
3 = Sudden Death

Save

Outcome: Neurovisceral attacks

Not Scored 0 1 2 3

Enter notes here...

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”.

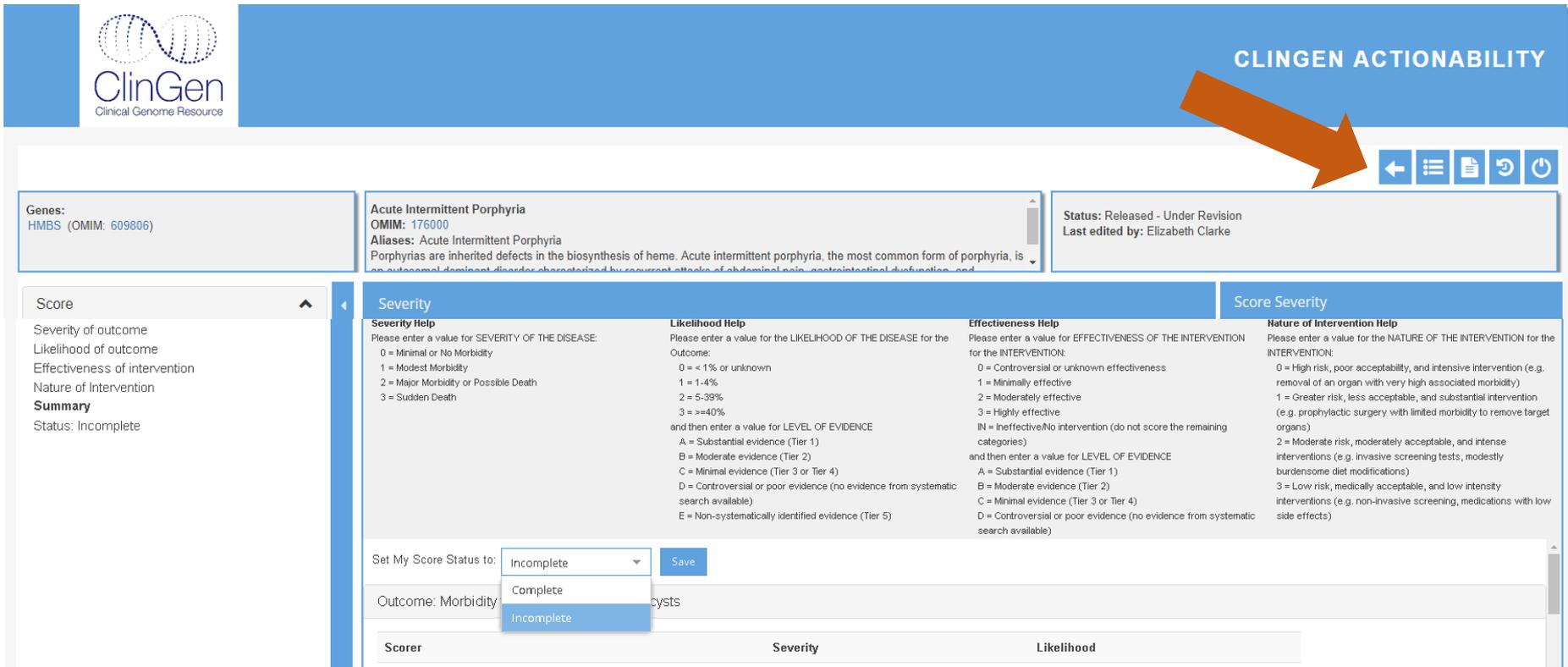
The screenshot displays the ClinGen Actionability tool interface. At the top left is the ClinGen logo (Clinical Genome Resource). The top right header reads "CLINGEN ACTIONABILITY". Below the header, there are navigation icons (back, list, document, refresh, power). The main content area is divided into several sections:

- Genes:** HMBS (OMIM: 609806)
- Acute Intermittent Porphyria** (OMIM: 176000). Aliases: Acute Intermittent Porphyria. Description: Porphyrias are inherited defects in the biosynthesis of heme. Acute intermittent porphyria, the most common form of porphyria, is an autosomal dominant disorder characterized by recurrent attacks of abdominal pain, neurovegetative dysfunction, and...
- Status:** Released - Under Revision. Last edited by: Elizabeth Clarke
- Score** (left sidebar): Severity of outcome, Likelihood of outcome, Effectiveness of intervention, Nature of Intervention, Summary. Status: Incomplete.
- Severity Help:** Please enter a value for SEVERITY OF THE DISEASE: 0 = Minimal or No Morbidity, 1 = Modest Morbidity, 2 = Major Morbidity or Possible Death, 3 = Sudden Death.
- Likelihood Help:** Please enter a value for the LIKELIHOOD OF THE DISEASE for the Outcome: 0 = < 1% or unknown, 1 = 1-4%, 2 = 5-39%, 3 = >=40%. and then enter a value for LEVEL OF EVIDENCE: A = Substantial evidence (Tier 1), B = Moderate evidence (Tier 2), C = Minimal evidence (Tier 3 or Tier 4), D = Controversial or poor evidence (no evidence from systematic search available), E = Non-systematically identified evidence (Tier 5).
- Effectiveness Help:** Please enter a value for EFFECTIVENESS OF THE INTERVENTION for the INTERVENTION: 0 = Controversial or unknown effectiveness, 1 = Minimally effective, 2 = Moderately effective, 3 = Highly effective. IN = Ineffective/No intervention (do not score the remaining categories). and then enter a value for LEVEL OF EVIDENCE: A = Substantial evidence (Tier 1), B = Moderate evidence (Tier 2), C = Minimal evidence (Tier 3 or Tier 4), D = Controversial or poor evidence (no evidence from systematic search available).
- Nature of Intervention Help:** Please enter a value for the NATURE OF THE INTERVENTION for the INTERVENTION: 0 = High risk, poor acceptability, and intensive intervention (e.g. removal of an organ with very high associated morbidity), 1 = Greater risk, less acceptable, and substantial intervention (e.g. prophylactic surgery with limited morbidity to remove target organs), 2 = Moderate risk, moderately acceptable, and intense interventions (e.g. invasive screening tests, modestly burdensome diet modifications), 3 = Low risk, medically acceptable, and low intensity interventions (e.g. non-invasive screening, medications with low side effects).

At the bottom, there is a "Set My Score Status" dropdown menu with options: Incomplete, Complete, Incomplete. A blue "Save" button is next to it. A large orange arrow points to the "Save" button. Below the dropdown, there is a table with columns: Scorer, Severity, Likelihood.

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.



The screenshot shows the ClinGen Actionability interface for Acute Intermittent Porphyria. The top navigation bar includes the ClinGen logo and the text "CLINGEN ACTIONABILITY". An orange arrow points to a navigation icon (a left-pointing arrow) in the top right corner. The main content area is divided into several sections:

- Genes:** HMBS (OMIM: 609806)
- Acute Intermittent Porphyria**
OMIM: 176000
Aliases: Acute Intermittent Porphyria
Porphyrias are inherited defects in the biosynthesis of heme. Acute intermittent porphyria, the most common form of porphyria, is an autosomal dominant disorder characterized by recurrent attacks of abdominal pain, neurovegetative dysfunction, and
- Status:** Released - Under Revision
Last edited by: Elizabeth Clarke
- Score**
 - Severity of outcome
 - Likelihood of outcome
 - Effectiveness of intervention
 - Nature of Intervention
 - Summary**
Status: Incomplete
- Severity**
 - Severity Help**
Please enter a value for SEVERITY OF THE DISEASE:
0 = Minimal or No Morbidity
1 = Modest Morbidity
2 = Major Morbidity or Possible Death
3 = Sudden Death
 - Likelihood Help**
Please enter a value for the LIKELIHOOD OF THE DISEASE for the Outcome:
0 = < 1% or unknown
1 = 1-4%
2 = 5-39%
3 = >=40%
and then enter a value for LEVEL OF EVIDENCE
A = Substantial evidence (Tier 1)
B = Moderate evidence (Tier 2)
C = Minimal evidence (Tier 3 or Tier 4)
D = Controversial or poor evidence (no evidence from systematic search available)
E = Non-systematically identified evidence (Tier 5)
 - Effectiveness Help**
Please enter a value for EFFECTIVENESS OF THE INTERVENTION for the INTERVENTION:
0 = Controversial or unknown effectiveness
1 = Minimally effective
2 = Moderately effective
3 = Highly effective
IN = Ineffective/No intervention (do not score the remaining categories)
and then enter a value for LEVEL OF EVIDENCE
A = Substantial evidence (Tier 1)
B = Moderate evidence (Tier 2)
C = Minimal evidence (Tier 3 or Tier 4)
D = Controversial or poor evidence (no evidence from systematic search available)
 - Nature of Intervention Help**
Please enter a value for the NATURE OF THE INTERVENTION for the INTERVENTION:
0 = High risk, poor acceptability, and intensive intervention (e.g. removal of an organ with very high associated morbidity)
1 = Greater risk, less acceptable, and substantial intervention (e.g. prophylactic surgery with limited morbidity to remove target organs)
2 = Moderate risk, moderately acceptable, and intense interventions (e.g. invasive screening tests, modestly burdensome diet modifications)
3 = Low risk, medically acceptable, and low intensity interventions (e.g. non-invasive screening, medications with low side effects)
- Score Severity**
 - Set My Score Status to: **Incomplete** (dropdown menu) **Save**
 - Outcome: Morbidity
 - Scorer: **Severity** Likelihood

Step 10:

When you are done, log out by using the “power” button on the far right.

ClinGen
Clinical Genome Resource

CLINGEN ACTIONABILITY

Genes:
HMBS (OMIM: 609806)

Acute Intermittent Porphyria
OMIM: 176000
Aliases: Acute Intermittent Porphyria
Porphyrias are inherited defects in the biosynthesis of heme. Acute intermittent porphyria, the most common form of porphyria, is an autosomal dominant disorder characterized by severe attacks of abdominal pain, constipation, dysfunction, and

Status: Released - Under Revision
Last edited by: Elizabeth Clarke

Score

- Severity of outcome
- Likelihood of outcome
- Effectiveness of intervention
- Nature of Intervention
- Summary**

Status: Incomplete

Severity	Likelihood	Effectiveness	Nature of Intervention
Severity Help Please enter a value for SEVERITY OF THE DISEASE: 0 = Minimal or No Morbidity 1 = Modest Morbidity 2 = Major Morbidity or Possible Death 3 = Sudden Death	Likelihood Help Please enter a value for the LIKELIHOOD OF THE DISEASE for the Outcome: 0 = < 1% or unknown 1 = 1-4% 2 = 5-39% 3 = >=40% and then enter a value for LEVEL OF EVIDENCE A = Substantial evidence (Tier 1) B = Moderate evidence (Tier 2) C = Minimal evidence (Tier 3 or Tier 4) D = Controversial or poor evidence (no evidence from systematic search available) E = Non-systematically identified evidence (Tier 5)	Effectiveness Help Please enter a value for EFFECTIVENESS OF THE INTERVENTION for the INTERVENTION: 0 = Controversial or unknown effectiveness 1 = Minimally effective 2 = Moderately effective 3 = Highly effective IN = Ineffective/No intervention (do not score the remaining categories) and then enter a value for LEVEL OF EVIDENCE A = Substantial evidence (Tier 1) B = Moderate evidence (Tier 2) C = Minimal evidence (Tier 3 or Tier 4) D = Controversial or poor evidence (no evidence from systematic search available)	Nature of Intervention Help Please enter a value for the NATURE OF THE INTERVENTION for the INTERVENTION: 0 = High risk, poor acceptability, and intensive intervention (e.g. removal of an organ with very high associated morbidity) 1 = Greater risk, less acceptable, and substantial intervention (e.g. prophylactic surgery with limited morbidity to remove target organs) 2 = Moderate risk, moderately acceptable, and intense interventions (e.g. invasive screening tests, modestly burdensome diet modifications) 3 = Low risk, medically acceptable, and low intensity interventions (e.g. non-invasive screening, medications with low side effects)

Set My Score Status to: **Incomplete** Save

Outcome: Morbidity cysts

Scorer	Severity	Likelihood

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/display/CLIN/Pediatric+Actionability>, enter in your login information, and click “Log in.”

Log in

Username

Password

Remember me



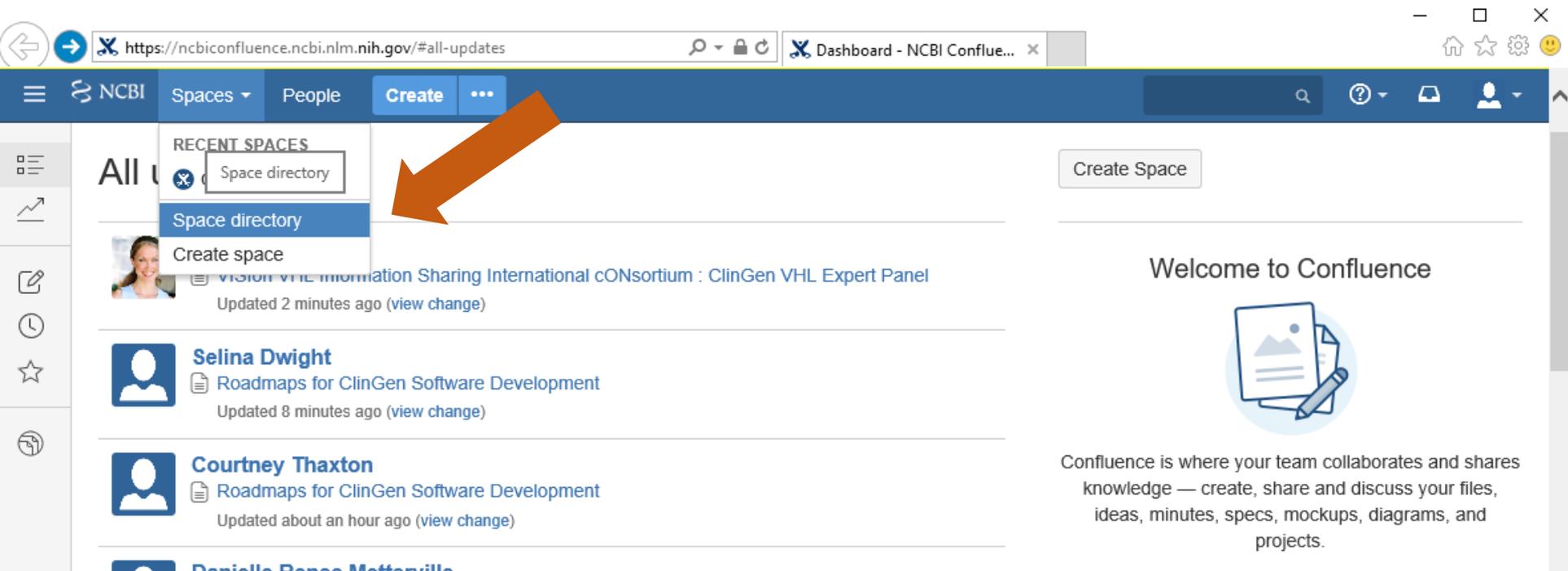
[Deutsch](#) · [English \(UK\)](#) · [English \(US\)](#) · [Español](#) · [Français](#) · [Português](#) · [Русский](#) · [中文](#) · [日本語](#) · [한국어](#)

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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.



The screenshot shows the NCBI Confluence dashboard. The browser address bar displays <https://ncbiconfluence.ncbi.nlm.nih.gov/#all-updates>. The navigation bar includes 'NCBI', 'Spaces', 'People', and 'Create'. A dropdown menu is open under 'Spaces', with 'Space directory' highlighted. A large orange arrow points to this option. Below the menu, a list of recent spaces is shown, including 'VISION VHL Information Sharing International cONsortium : ClinGen VHL Expert Panel' (updated 2 minutes ago) and 'Roadmaps for ClinGen Software Development' by Selina Dwight (updated 8 minutes ago) and Courtney Thaxton (updated about an hour ago). A 'Create Space' button is visible on the right. The main content area features a 'Welcome to Confluence' message with an icon of a document and pencil, and a brief description of the platform's purpose.

Step 3:

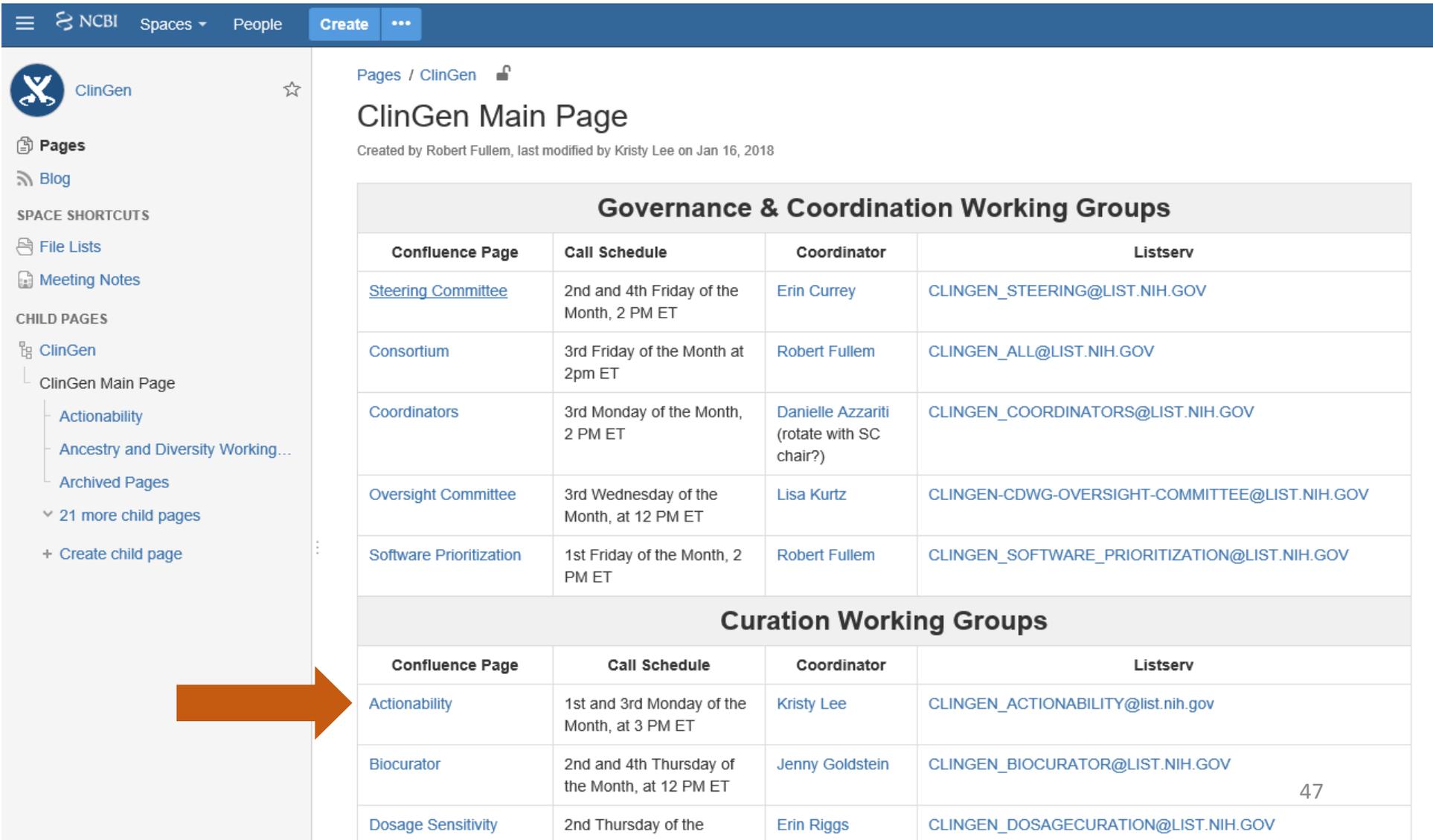
Under 'Site Spaces,' click 'ClinGen' which will take you to a page listing many entities including 'ClinGen;' click on 'ClinGen.'

The screenshot shows the NCBI Space Directory interface. The top navigation bar includes 'NCBI Spaces', 'People', 'Create', and a search bar. The main heading is 'Space Directory' with a 'Create Space' button. A left sidebar lists navigation options: 'All Spaces', 'Site Spaces', 'Personal Spaces', 'My Spaces', 'Archived Spaces', and 'CATEGORIES' (Documentation, Knowledge-bases, Teams). The main content area is titled 'Site Spaces' and features a table with columns for 'Space', 'Description', and 'Categories'. A 'Filter' input is located at the top right of the table. The table lists several spaces, with a red arrow pointing to the 'ClinGen' entry. The 'ClinGen' entry has a tooltip that says 'ClinGen' and 'oolkit'. The 'ClinGen' entry has a 'teams' category. Other entries include 'Clinical Variation', 'ClinVar-UniProtKB', 'EcoliK12', and 'Education'.

Space	Description	Categories
ClinGen toolkit		
ClinGen		teams
Clinical Variation		
ClinVar-UniProtKB		
EcoliK12		documentation
Education		teams

Step 4:

Under 'ClinGen Main Page,' click 'Actionability' which will take you to the AWG page.'



Pages / ClinGen

ClinGen Main Page

Created by Robert Fullem, last modified by Kristy Lee on Jan 16, 2018

Governance & Coordination Working Groups

Confluence Page	Call Schedule	Coordinator	Listserv
Steering Committee	2nd and 4th Friday of the Month, 2 PM ET	Erin Currey	CLINGEN_STEERING@LIST.NIH.GOV
Consortium	3rd Friday of the Month at 2pm ET	Robert Fullem	CLINGEN_ALL@LIST.NIH.GOV
Coordinators	3rd Monday of the Month, 2 PM ET	Danielle Azzariti (rotate with SC chair?)	CLINGEN_COORDINATORS@LIST.NIH.GOV
Oversight Committee	3rd Wednesday of the Month, at 12 PM ET	Lisa Kurtz	CLINGEN-CDWG-OVERSIGHT-COMMITTEE@LIST.NIH.GOV
Software Prioritization	1st Friday of the Month, 2 PM ET	Robert Fullem	CLINGEN_SOFTWARE_PRIORITIZATION@LIST.NIH.GOV

Curation Working Groups

Confluence Page	Call Schedule	Coordinator	Listserv
Actionability	1st and 3rd Monday of the Month, at 3 PM ET	Kristy Lee	CLINGEN_ACTIONABILITY@list.nih.gov
Biocurator	2nd and 4th Thursday of the Month, at 12 PM ET	Jenny Goldstein	CLINGEN_BIOCURATOR@LIST.NIH.GOV
Dosage Sensitivity	2nd Thursday of the	Erin Riggs	CLINGEN_DOSAGECURATION@LIST.NIH.GOV

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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.

NCBI Spaces People Create

ClinGen ☆

Pages Blog

SPACE SHORTCUTS

File Lists Meeting Notes

CHILD PAGES

ClinGen Main Page

Actionability

- AWG Goals, Deliverables, and...
- AWG Phenotype-Gene Nomina...
- AWG Summary Reports
- 4 more child pages
- Create child page

Working Documents

Include any documents, links, and other resources that the WG is currently discussing and working on.

Description	Preview ONLY (if available)	Date	Status	Download Original File
▼ Summary Reports for Review by date		> Select date to view minutes	PENDING	Go to Summary Report to download
January 22, 2018 Summary Report				
December 4, 2017 Summary Report				
November 27, 2017 Summary Report				
November 20, 2017 Summary Report				

actionability of gene/phenotype pairs

Email : CLINGEN_ACTIONABILITY@list.nih.gov

- > [Click here to see List-Serv Members](#)
- > [Click Here for Call-In Information](#)

Actionability Attendance

- > [2017 Actionability Attendance](#)
- > [2016 Actionability Attendance](#)
- > [2015 Actionability Attendance](#)
- > [2014 Actionability Attendance](#)

Step 6:

On the summary report page, clickable pdfs of the reports, report summaries and a comments section are available. Log out when done.

The screenshot shows a web interface for ClinGen. The top navigation bar includes 'NCBI Spaces', 'People', 'Create', and search icons. The left sidebar shows 'ClinGen' with a star icon, and a list of 'CHILD PAGES' including 'AWG Summary Reports' and 'January 22, 2018 Summary Report'. Two orange arrows point from the sidebar to the main content: one from 'Meeting Notes' to a PDF link, and another from 'January 22, 2018 Summary Report' to the main report text.

Pages / ... / AWG Summary Reports Edit Save for later Watch Share ...

January 22, 2018 Summary Report

Created by Mackenzie Trapp on Jan 09, 2018

[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 SDHB) 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.



Suggested Meetings

+ Get more add-in

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/Phechromocytomas) 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.

NCBI Spaces People Create

Actionability

Created by Preetha Nandi, 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.

[\[Goals \]](#) [\[Working Documents \]](#) [\[Archived Documents \]](#) [\[Presentations from previous calls \]](#) [\[Documents from previous calls \]](#)

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.

Most recent meeting

[2018-02-19 Actionability WG Meeting Minutes](#)

Actionability WG Overview

Chairs : Katrina Goddard (Katrina.AB.Goddard@kpchr.org) and Jim Evans (jpevans@med.unc.edu)

Coordinator: Kristy Lee (kristy_lee@med.unc.edu)

Call Schedule : Every 2nd and 4th Monday of every month, 3:00 PM ET/ 2:00 PM CT / 12:00 PM PT

Goals: To develop procedures for defining clinical actionability of gene/phenotype pairs, to curate clinical actionability of gene/phenotype pairs

Email : CLINGEN_ACTIONABILITY@list.nih.gov

[Click here to see List-Ser Members](#)

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 Ronak Patel (Ronak.Patel@bcm.edu).

Welcome to the ClinGen AWG!