

ClinGen's Actionability Working Group



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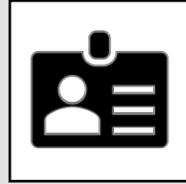
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Department of Translational and Applied
Genomics

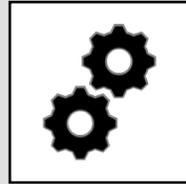
Center for Health Research

Kaiser Permanente Northwest

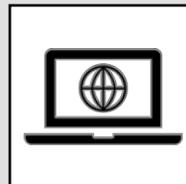
Talk Overview



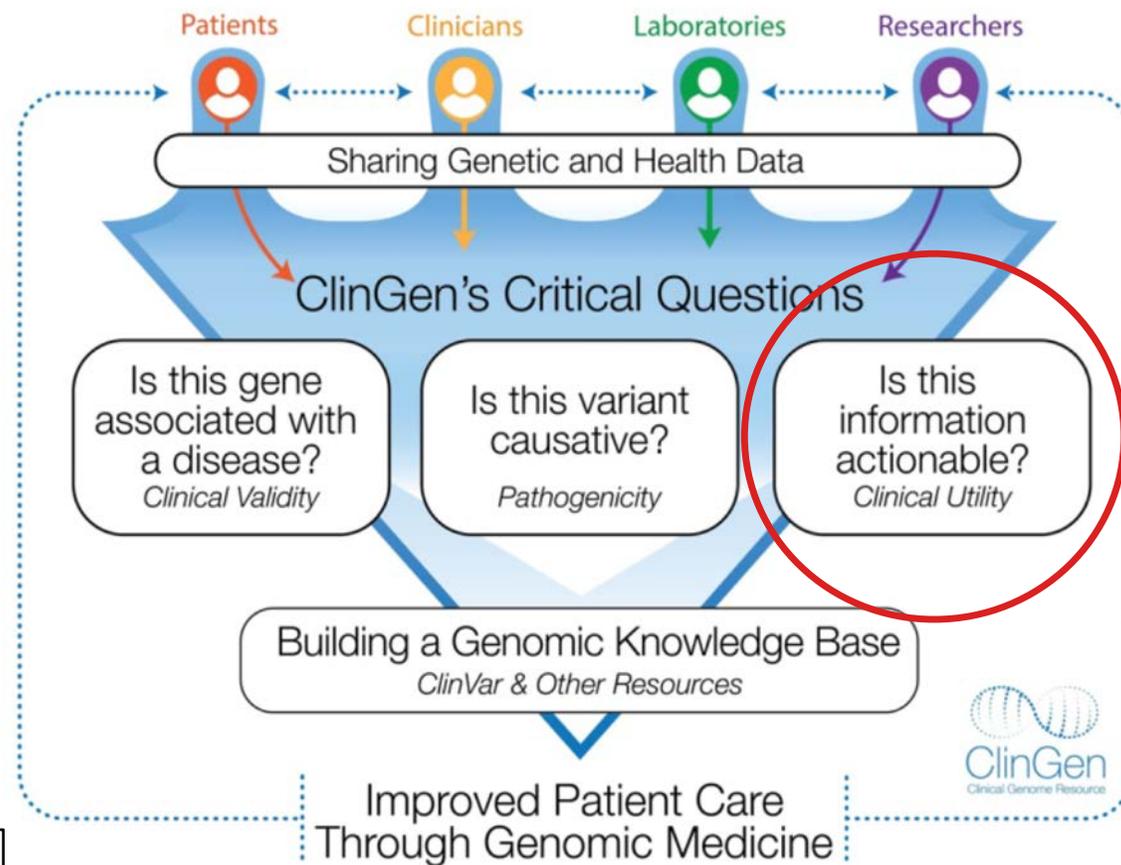
Description of the AWG and clinical actionability



Overview of the AWG actionability framework



Availability and review of AWG products



ClinGen Actionability Working Group:

Provide a transparent and systematic evidence base for prioritizing genes based on their clinical actionability.

AWG: Actionability Working Group

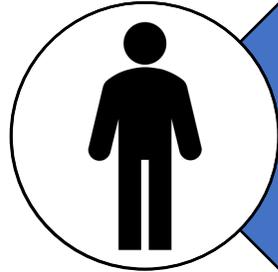
The overarching goal of the AWG is to identify those human genes that, when significantly altered, confer a high risk of serious disease that could be prevented or mitigated if the risk were known.

Goals:

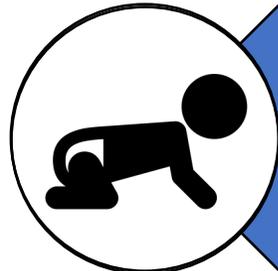
1. Develop rigorous and standardized procedures for categorically defining “clinical actionability”; a concept that includes a known ability to intervene and thereby avert a poor outcome due to a previously unsuspected high risk of disease.
2. Nominate genes and diseases to score for “clinical actionability.”
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.



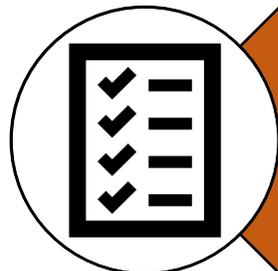
Structure of the AWG



Adult AWG: Adult-focused clinical actionability



Pediatric AWG: Pediatric-focused clinical actionability



Both AWGs are supported by the Knowledge Synthesis Team (KST) that generates actionability summary reports for scoring

Clinical Context

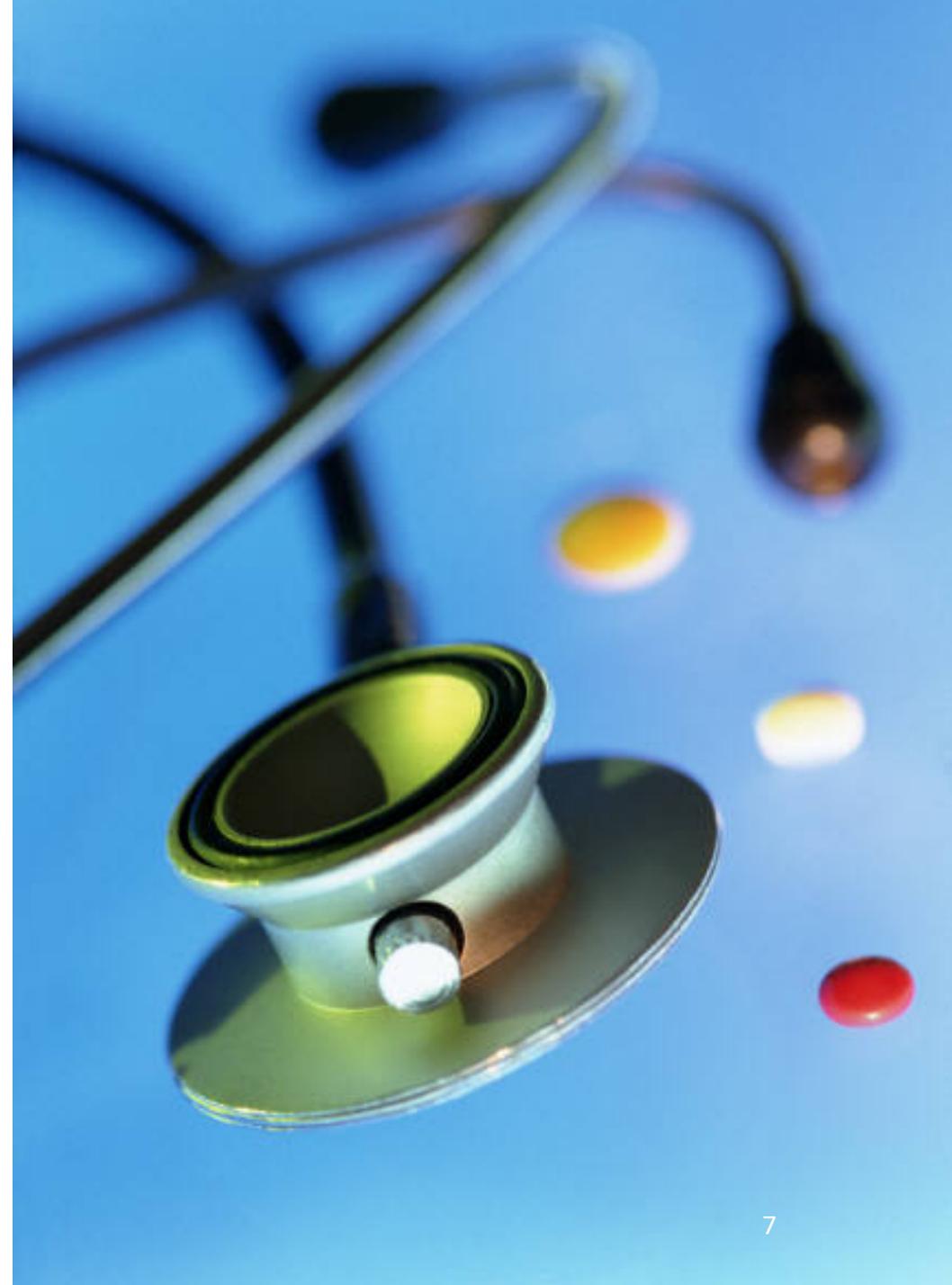


- A person with an incidental or secondary finding identified via genome-scale sequencing
 - Adults: Adult AWG
 - Children and adolescents: Pediatric AWG
- Not previously diagnosed with the genetic disorder
- May have signs or symptoms of the genetic condition

We do not currently consider the context of population-wide screening or the diagnostic setting.

Clinical Actionability

- Well-established, clinically prescribed interventions
- Interventions specific to the genetic disorder
- Lead to disease prevention or delayed onset, lowered clinical burden, or improved clinical outcomes
- Do not currently consider factors such as personal utility, reproductive decision-making, and ending the diagnostic odyssey



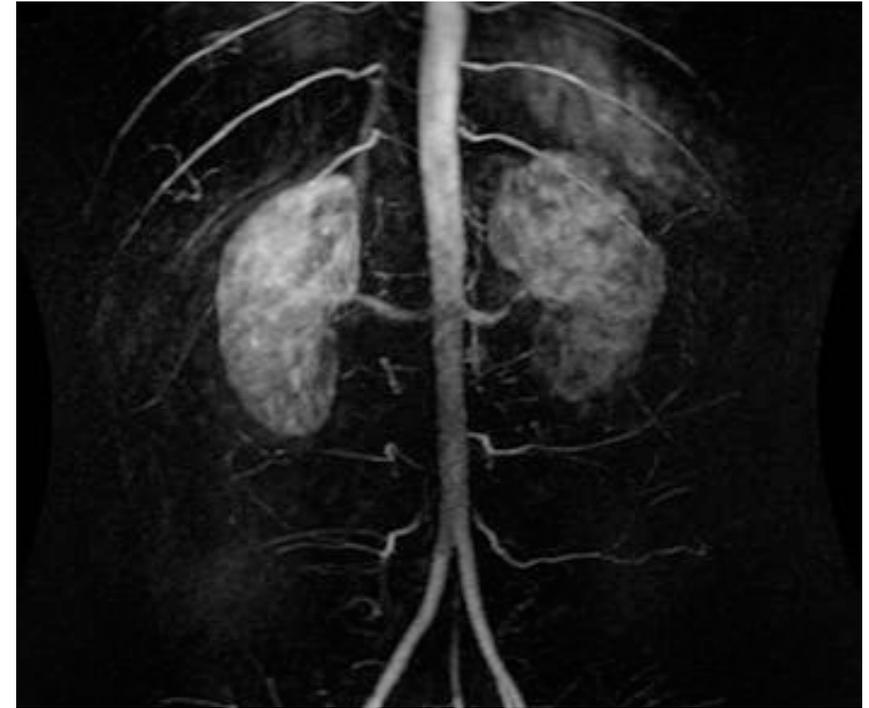
Clinical Actionability

- Patient management
- Surveillance
- Circumstances to avoid



Examples of Clinical Actionability

- Familial thoracic aortic aneurysms and dissections
 - Increased risk of dilation and/or dissection of the thoracic aorta
 - Recommendations:
 - Frequent aortic imaging to detect and track aortic enlargement to guide aortic repair
 - Beta blockers to slow aortic dilation
- Malignant hyperthermia susceptibility
 - Increased risk of uncontrolled skeletal muscle hypermetabolism after exposure to certain volatile anesthetics
 - Recommendation:
 - Avoidance of triggering anesthetics



Timing of Interventions in Pediatrics



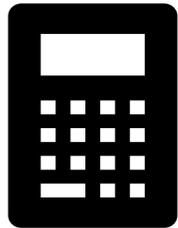
- Interventions recommended to be initiated during the pediatric period that may prevent outcomes during:
 - Infancy, childhood, or adolescence
 - Adulthood

AWG Actionability Framework



Step 1: Generate summary report

- 1a. Identify gene-condition pair
- 1b. Rapid rule-out process
- 1c. KST drafts report



Step 2: AWG generates scores using semi-quantitative metric



Step 3: AWG makes assertion of actionability

Step 1a: Select Gene- Disorder Pairs

- Pairs
 - Single gene and disorder (e.g., *APC* and familial adenomatous polyposis)
 - Bundles of genes associated with the same disorder (e.g., *MLH1*, *MSH2*, *MSH6*, and *PMS2* and Lynch syndrome)
- Started with genes recommended by ACMG for return as secondary findings (e.g., ACMG56 and ACMG v2.0 SF)
- Additional pairs have been nominated by AWG members and non-AWG stakeholders

Step 1b: Rapid Rule-Out Assessment

The rapid rule-out step quickly rules out 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 ($\geq 40\%$)?
- 3. Burden of disease:** Is this an important health problem?

Example: Brudaga Syndrome



Rule-Out Dashboard

Adult or Pediatric Secondary Findings

[Permalink](#) | [Current Version](#) | [Summary Report - Adult](#) | [Summary Report - Pediatric](#) | [Release History - Adult](#) | [Release History - Pediatric](#)

Status (Adult): Passed
Status (Pediatric): Passed

CONTEXT: Adult
DISORDER: Brugada Syndrome
GENE/GENE PANEL: SCN5A
GENE↔DISEASE PAIRS: SCN5A ↔601144

CONTEXT: Pediatric
DISORDER: Brugada Syndrome
GENE/GENE PANEL: SCN5A
GENE↔DISEASE PAIRS: SCN5A ↔601144

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
 Patient management
 Surveillance or Screening
 Circumstances to Avoid
 YES (≥ 1 of above) NO
3. Is it actionable in an undiagnosed adult with the condition?
 YES NO
4. Is there an intervention that is initiated during childhood (<18 years of age) in an undiagnosed child with the genetic condition?
 YES NO
5. Does the disease present outside of the neonatal period?
 YES NO

SIGNIFICANCE/BURDEN OF DISEASE

6. Is this condition an important health problem?
 YES NO
- #### PENETRANCE
7. 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

NEXT STEPS

8. ADULT - Are Actionability (Q1-3) and Significance (Q6) "YES", and Penetrance (Q7) "YES" or "UNKNOWN"?
 YES (Proceed to Summary Report for AAWG)
 NO (Consult AAWG)
 Exception granted, proceed to Summary Report
 Exception not granted, STOP
9. PEDIATRIC - Are Actionability (Q1, Q2, Q4, Q5) and Significance (Q6) "YES", and Penetrance (Q7) "YES" or "UNKNOWN"?
 YES (Proceed to Summary Report for PAWG)
 NO (Consult PAWG)
 Exception granted, proceed to Summary Report
 Exception not granted, STOP

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

Patient management

Surveillance or Screening

Circumstances to Avoid

YES (≥ 1 of above)

NO

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

YES

NO

4. Is there an intervention that is initiated during childhood (<18 years of age) in an undiagnosed child with the genetic condition?

YES

NO

5. Does the disease present outside of the neonatal period?

YES

NO

SIGNIFICANCE/BURDEN OF DISEASE

6. Is this condition an important health problem?

YES

NO

PENETRANCE

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

YES

NO

UNKNOWN

NEXT STEPS

8. ADULT - Are Actionability (Q1-3) and Significance (Q6) "YES", and Penetrance (Q7) "YES" or "UNKNOWN"?

YES (Proceed to Summary Report for AAWG)

NO (Consult AAWG)

Exception granted, proceed to Summary Report

Exception not granted, STOP

9. PEDIATRIC - Are Actionability (Q1, Q2, Q4, Q5) and Significance (Q6) "YES", and Penetrance (Q7) "YES" or "UNKNOWN"?

YES (Proceed to Summary Report for PAWG)

NO (Consult PAWG)

Exception granted, proceed to Summary Report

Exception not granted, STOP

Step 1c: KST Generates Summary Report

The summary report documents the available evidence related to actionability:

- Structured protocol to make search for evidence standardized and reproducible across curators
- Evidence search is limited in scope to make the process feasible:
 - Included: Clinical practice guidelines, systematic reviews, meta-analyses, OMIM, GeneReviews, OrphaNet, and Clinical Utility Gene Cards
 - Not included: Narrative reviews and primary literature

Step 1c: KST Generates Summary Report

All evidence is tiered base on quality:

Tier 1: Systematic review, meta-analysis, or practice guideline based on systematic review

Tier 2: Practice guideline or expert consensus

Tier 3: Non-systematic evidence review (e.g., GeneReview) with primary literature cited

Tier 4: Non-systematic review of evidence (e.g., GeneReview) with no citations

Tier 5: Non-systematically identified source

Step 1c: KST Generates Summary Report

Abstract 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 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 2:
AWG
Generate
Scores

SEVERITY		
LIKELIHOOD		
EFFECTIVENESS		
NATURE OF INTERVENTION		

Step 2: AWG Generate Scores

SEVERITY	3 = Sudden death 2 = Death or major morbidity 1 = Modest morbidity 0 = Minimal or no morbidity	
LIKELIHOOD		
EFFECTIVENESS		
NATURE OF INTERVENTION		

Step 2: AWG Generate Scores

SEVERITY	3 = Sudden death 2 = Death or major morbidity 1 = Modest morbidity 0 = Minimal or no morbidity	
LIKELIHOOD	3 = > 40% chance 2 = 5-39% chance 1 = 1-4% chance 0 = < 1% chance	
EFFECTIVENESS		
NATURE OF INTERVENTION		

Step 2: AWG Generate Scores

SEVERITY	<p>3 = Sudden death</p> <p>2 = Death or major morbidity</p> <p>1 = Modest morbidity</p> <p>0 = Minimal or no morbidity</p>
LIKELIHOOD	<p>3 = > 40% chance</p> <p>2 = 5-39% chance</p> <p>1 = 1-4% chance</p> <p>0 = < 1% chance</p>
EFFECTIVENESS	<p>3 = Highly effective</p> <p>2 = Moderately effective</p> <p>1 = Minimally effective</p> <p>0 = Controversial/unknown effectiveness</p> <p>IN = Ineffective*</p>
NATURE OF INTERVENTION	

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

Step 2: AWG Generate Scores

SEVERITY	3 = Sudden death 2 = Death or major morbidity 1 = Modest morbidity 0 = Minimal or no morbidity
LIKELIHOOD	3 = > 40% chance 2 = 5-39% chance 1 = 1-4% chance 0 = < 1% chance
EFFECTIVENESS	3 = Highly effective 2 = Moderately effective 1 = Minimally effective 0 = Controversial/unknown effectiveness IN = Ineffective*
NATURE OF 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

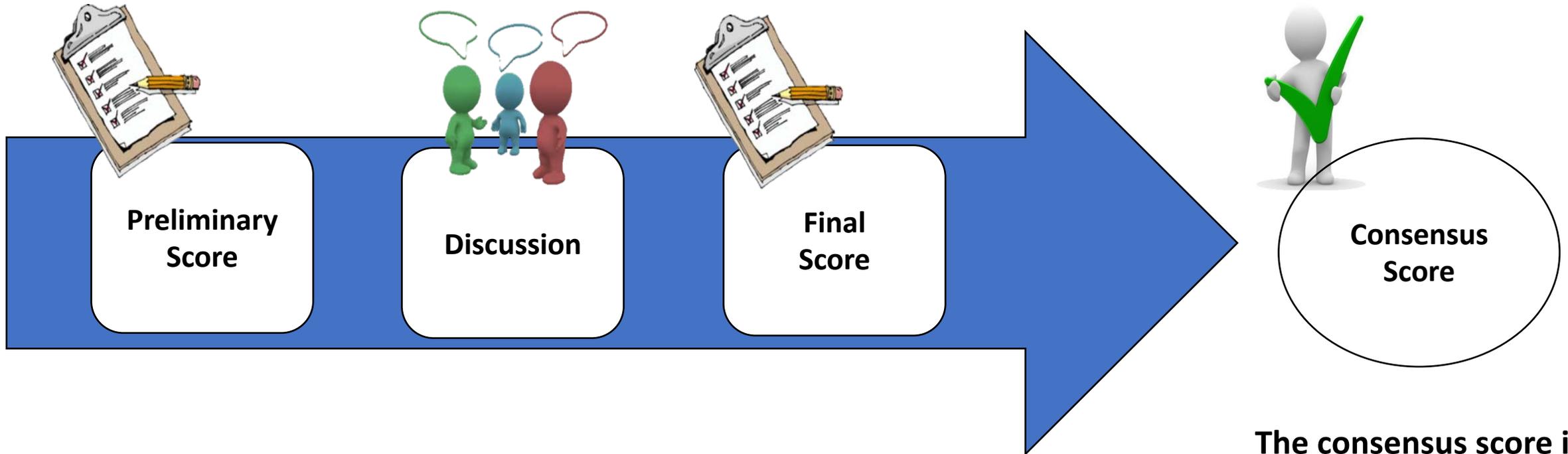
* If a score of IN is given, no scores are given for the other categories.

Step 2: AWG Generate Scores

SEVERITY	3 = Sudden death 2 = Death or major morbidity 1 = Modest morbidity 0 = Minimal or no morbidity	
LIKELIHOOD	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	3 = Highly effective 2 = Moderately effective 1 = Minimally effective 0 = Controversial/unknown effectiveness IN = Ineffective*	
NATURE OF 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



The consensus score is the majority, but the individual final scores don't have to agree

Things We Consider During Scoring

- ✓ Subgroups may be scored separately if they are known to differ across actionability domains, which may be defined by:
 - Gene: *BRCA1* and *BRCA2* scored separately due to varying penetrance
 - Sex: Hemophilia, an X-linked disorder, scored separately for males and females due to differences in severity
 - Zygosity: Heterozygosity and homozygosity were scored separately for familial hypercholesterolemia due to differences in interventions and severity

Things We Consider During Scoring

- ✓ Data on effectiveness of an intervention can be extrapolated from a similar condition when there is a lack of data for the condition being scored
 - The effectiveness score will reflect the intervention's effectiveness, but evidence score should be downgraded by a letter
 - Example:
 - Effectiveness of aortic surveillance in Marfan syndrome was scored as "3B" based on available evidence
 - No evidence for this intervention in Loeys-Dietz syndrome, so score was extrapolated from Marfan syndrome with the evidence score downgraded for a score of "3C"

Things We Consider During Scoring

- ✓ Scorers can choose to override the available evidence and give it a higher score based on their expert opinion
 - E.g., FAP was given a score of 3A for likelihood based on expert opinion of the AWG when the evidence level in the summary report indicated a score of 3C

Things We Consider During Scoring

- ✓ When scoring effectiveness of a surveillance intervention, the effectiveness considered is not based on the surveillance mechanism to detect the outcome, but for the timely implementation of downstream treatments to reduce morbidity and mortality
 - E.g., for mammography, effectiveness is not based on the ability of mammography to detect a tumor in the breast (proximal effectiveness), but the effectiveness of mammography programs to reduce morbidity and mortality by allowing for earlier detection and treatment of breast cancer (distal effectiveness)

Step 2:
AWG
Generates
Scores

- 4 scores
 - Severity: 0-3
 - Likelihood: 0-3
 - Effectiveness: 0-3
 - Nature of the intervention: 0-3
- Total scores: 0-12

Step 3: AWG Makes an Assertion

Assertion	Total Score	Other Rules
Strong actionability	10-12	Effectiveness score > 0
Moderate actionability	8-9	Effectiveness score > 0
Limited actionability	<8	Effectiveness score = 0

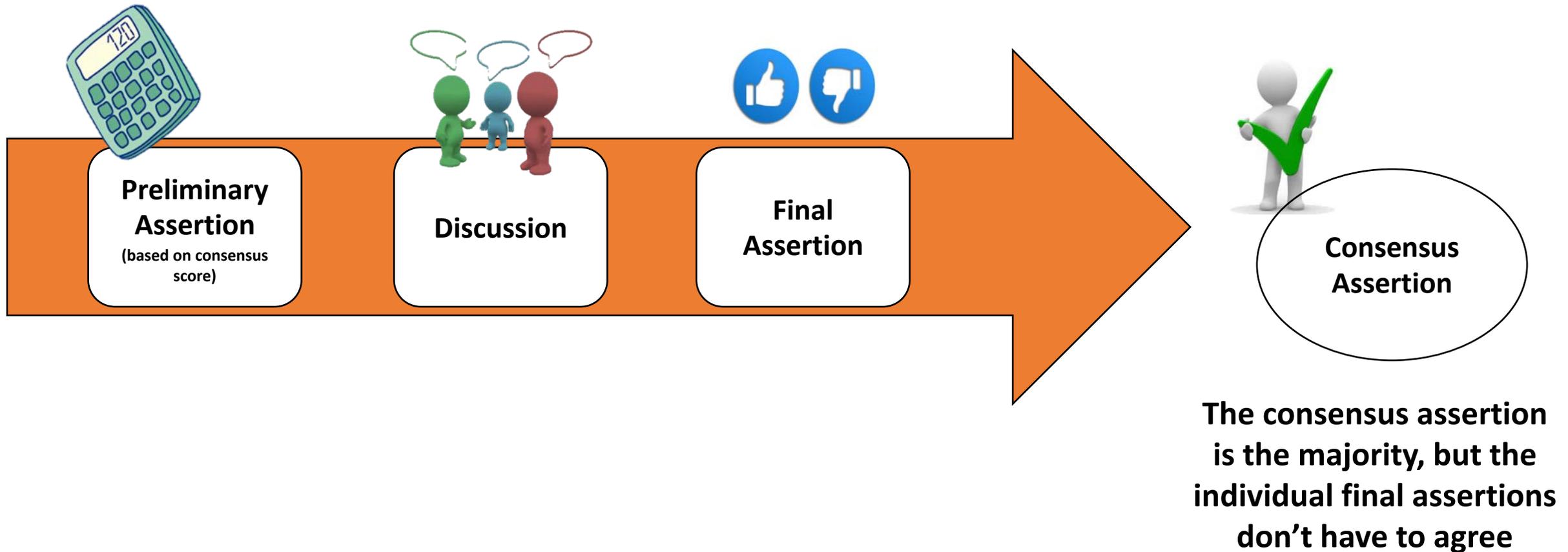
* Can change the final assertion based on consensus discussion

Step 3: AWG Makes an Assertion

Assertion	Total Score	Other Rules
Definitive actionability	10-12	<p>Penetrance evidence from unselected population</p> <p>Effectiveness evidence from exact population (i.e., not extrapolated)</p> <p>Effectiveness evidence is based on a direct impact of intervention on the outcome (i.e., no indirect “chain” of evidence)</p>
Strong actionability	10-12	Effectiveness score > 0
Moderate actionability	8-9	Effectiveness score > 0
Limited actionability	<8	Effectiveness score = 0

* Can change the final assertion based on consensus discussion

Assertion Process



Things We Consider When Making an Assertion

- ✓ The final assertion may be different than the original assertion due to:
 - Meets criteria for “Definitive Actionability”
 - Limited evidence or poor quality of the evidence for any part of the score
 - Intervention widely used in current clinical practice that has not been systematically evaluated
 - High quality evidence or larger studies are not forthcoming or would be unethical

Dissemination of AWG Reports, Scores, and Assertions

- Once a gene-disease topic is completed, the summary report, consensus scores, and assertions become publicly available on the ClinGen website
 - ~175 topics released to date
 - NOTE: Some website changes will be happening
- These products 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



Documents

Publications 6

Supporting Documents 1

Training Materials 2

Show All Documents

Expert and lay perspectives on burden, risk, tolerability, and acceptability of clinical interventions for genetic disorders

Tools & Resources



Clinical Actionability Tools

Clinical Actionability tools support the curation process 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.

Curations

interface

Actionability Working Group

Publications - November 1, 2018

Actionability

Harmonizing Outcomes for Genomic Medicine: Comparison of eMERGE Outcomes to ClinGen Outcome/Intervention Pairs

Expert and lay perspectives on burden, risk, tolerability, and acceptability of clinical interventions for genetic disorders

Publications - April 26, 2019

Actionability

Semi-quantitative Scoring Metric



Get Started | About Us | Curation Activities | Working Groups | Expert Panels | Documents & Announcements | Tools

Adult Actionability Working Group

Actionability Subgroup

Membership | Documents

Documents

Curation Activity Procedures 1 | Training Materials 1

- ClinGen Adult Actionability Working Group Protocol**
Curation Activity Procedures - August 6, 2020
Adult Actionability Working Group
- ClinGen Adult Actionability Working Group Slides**
Training Materials - April 22, 2020
Adult Actionability Working Group

Working Group Membership

Membership spans many fields, including genetics, medical, academia, and industry.

Chairs



Adam Buchanan, MS, MPH,
LGC



Katrina Goddard, PhD

Documents

Curation Activity Procedures 1 | Training Materials 1

- ClinGen Adult Actionability Working Group Protocol**
Curation Activity Procedures - August 6, 2020
Adult Actionability Working Group
- ClinGen Adult Actionability Working Group Slides**
Training Materials - April 22, 2020
Adult Actionability Working Group

Data Sharing Resources GenomeConnect Events Contact

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Clinical Genome Resources

Get Started About Us Curation Activities Working Groups Expert Panels Documents & Announcements Tools

Actionability

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.

Subgroups Documents Tools Membership



Chairs

Tools & Resources



Clinical Actionability Tools

Clinical Actionability tools support the curation process 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.

Curations  interface 

Documents

Publications 6 Supporting Documents 1 Training Materials 2 Show All Documents

Expert and lay perspectives on burden, risk, tolerability, and acceptability of clinical interventions for genetic disorders
Publications - April 26, 2019
Actionability

Semi-quantitative Scoring Metric



Browse Curations



List of all adult and pediatric actionability reports by topic

View and export all adult and pediatric actionability summary reports in a customizable, searchable interface.

Reports by topic



Browse scores in the adult context

View and export all Adult Actionability Working Group consensus scores for outcome-intervention pairs in a customizable, searchable interface.

Adult Consensus Scores



Browse scores in the pediatric context

View and export all Pediatric Actionability Working Group consensus scores for outcome-intervention pairs in a customizable, searchable interface.

Pediatric Consensus Scores



Semi-quantitative Scoring Metric

View the semi-quantitative scoring metric used to generate the consensus scores from the Actionability Working Groups

Scoring Metric

Display 25 topics

Search:

Filter by Context

Filter by Status

Export

API

Syndrome



Filter by Context

Filter by Status

Export

API

Gaucher Disease

Hereditary Diffuse Gastric Cancer

Hereditary Diffuse Gastric Cancer

CDH1

Adult

Tue, 04 Jun 2019

Released

1.1.1

Tue, 19 Jan 2021
(00:47:29)



Hereditary Diffuse Gastric Cancer

CDH1

Pediatric

Tue, 04 Jun 2019

Ent



Juvenile polyposis syndrome

Juvenile polyposis syndrome

BMPR1A, SMAD4

Adult

Fri, 18 Dec 2015

Rele

(00:42:20)



Juvenile polyposis syndrome

BMPR1A, SMAD4

Pediatric

(N/A)

E



Paragangliomas 1, 2, 3, 4, 5; Pheochromocytoma

Paragangliomas 1, 2, 3, 4, 5; Pheochromocytoma

MAX, SDHA, SDHAF2, SDHB, SDHC, SDHD, TMEM127

Adult

Tue, 31 Oct 2017

Re



Glanzmann thrombasthenia

Glanzmann thrombasthenia

ITGA2B, ITGB3

Adult

Thu, 12 Mar 2020

Released

1.0.0

Mon, 11 Jan 2021
(21:01:37)



(Under revision)

Rule out report
Report
Prior versions

Pediatric Summary Report

Secondary Findings in Pediatric Subjects

Non-diagnostic, excludes newborn screening & prenatal testing/screening

[Permalink](#) | [Current Version](#) | [Rule-Out Dashboard](#) | [Release History](#)

Status (Pediatric): Passed (Consensus scoring is Complete)

Curation Status (Pediatric): Released

GENE/GENE PANEL: ACADM

Condition: Medium-chain acyl coenzyme A dehydrogenase deficiency

Mode(s) of Inheritance: Autosomal Recessive

Actionability Assertion

Gene Disease Pairs(s)

ACADM⇔0008721 (acyl-coa dehydrogenase, medium-chain, deficiency of; acadmd)

Final Assertion

Strong Actionability

Final Consensus Scores^a

Outcome / Intervention Pair	Severity	Likelihood	Effectiveness	Nature of the Intervention	Total Score
Gene Disease Pairs: ACADM⇔0008721					
Morbidity associated with metabolic decompensation / Metabolic management (dietary management and illness protocols)	2	3N	3B	3	11NB
Morbidity associated with metabolic decompensation / Carnitine therapy when carnitine levels are insufficient	2	3N	0D	3	8ND
Mortality associated with metabolic decompensation / Metabolic management (dietary management and illness protocols)	3	2C	3B	3	11CB
Mortality associated with metabolic decompensation / Carnitine therapy when carnitine levels are insufficient	3	2C	0D	3	8CD

a. To see the scoring key, please go to : https://www.clinicalgenome.org/site/assets/files/2180/actionability_sq_metric.png

Pediatric Summary Report

Secondary Findings in Pediatric Subjects

Non-diagnostic, excludes newborn screening & prenatal testing/screening

[Permalink](#) | [Current Version](#) | [Rule-Out Dashboard](#) | [Curation History](#) | [Release History](#)

Status (Pediatric): Passed (Consensus scoring is Complete)

Curation Status (Pediatric): Collecting

Status (Adult): Passed (Consensus scoring is Complete)  

GENE/GENE PANEL: APC

Condition: Familial Adenomatous Polyposis

Mode(s) of Inheritance: Autosomal Dominant

Actionability Assertion

Gene Disease Pairs(s)

Final Assertion

APC⇔0021057 (familial adenomatous polyposis 1; fap1)

Definitive Actionability

Actionability Rationale

The evidence for effectiveness is from the exact population. The effectiveness of the intervention is supported by the fact that surveillance will lead to a more intensive intervention only if polyps are found. Penetrance evidence is from this population, although in adulthood. We have 2-3 decades of guidelines to start colonoscopy in the 2nd decade of life and follow up with colectomy in the early 3rd decade as appropriate.

Final Consensus Scores^a

Outcome / Intervention Pair

Severity

Likelihood

Effectiveness

Nature of the Intervention

Total Score

Gene Disease Pairs: APC⇔0021057

Morbidity and mortality due to colorectal cancer /
Colonoscopic surveillance to determine polyp burden
and guide (if appropriate) timing of (procto)
colectomy

2

3C

3A

2

10CA

a. To see the scoring key, please go to : https://www.clinicalgenome.org/site/assets/files/2180/actionability_sq_metric.png

Topic	Narrative Description of Evidence	Ref
1. What is the nature of the threat to health for an individual carrying a deleterious allele?		
Prevalence of the Genetic Disorder	Estimates of the prevalence of familial adenomatous polyposis (FAP) vary from 1:3,333 to 1:43,478 live births. Attenuated FAP (AFAP) is likely underdiagnosed given the lower number of polyps and lower risk for colorectal cancer (CRC) compared to FAP.	(1, 2, 3, 4, 5, 6, 7, 8)
Clinical Features (Signs / symptoms)	Classical FAP is characterized by the presence of ≥ 100 adenomatous polyps, with cases usually developing hundreds to thousands of adenomatous polyps, and extremely early onset and multifocal carcinogenesis. Most patients are asymptomatic for years until the adenomas are large and numerous, and cause rectal bleeding or even anemia, or cancer develops. Extracolonic manifestations are variably present and include polyps of the gastric fundus and duodenum, osteomas, dental anomalies, congenital hypertrophy of the retinal pigment epithelium (CHRPE), soft tissue tumors, desmoid tumors, epidermoid cysts, adrenal gland adenoma, hepatoblastoma (HPB), thyroid cancer, and brain tumors. AFAP is a milder phenotype of the disorder, which occurs in approximately 8% of cases and is characterized by fewer polyps (< 100), frequent right-sided distribution of polyps, cancers occurring at older ages, and more variable extraintestinal manifestations.	(1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15)
Natural History (Important subgroups & survival / recovery)	<p>The average age of classic FAP diagnosis in patients presenting with symptoms is 35.8 years (range: 4–72 years). Colorectal adenomatous polyps begin to appear, on average, by age 16 (range: 7–36 years). Approximately 75% of affected individuals will develop multiple polyps by the age of 20. By age 35, 95% of FAP patients have polyps. The mean age of CRC diagnosis in untreated individuals if has been reported between 34–50 years, with cancer developing nearly universally by age 50. Cancer occurs only rarely (estimates range from 0.2–1.3%) in patients with FAP who are younger than 20 years; however, these cases are usually associated with a severe polyposis phenotype. Although unusual, CRC has been reported as early as 6 years of age. Although rare, asymptomatic individuals in their 50s have been reported. Duodenal cancer and desmoid tumors are the most common causes of death in patients with FAP after CRC. Duodenal adenocarcinoma has been reported to occur between ages 17 and 81 years, with the mean age of diagnosis between 45 and 67 years. The incidence of desmoid tumors in FAP is highest in the second and third decades of life, with 80% occurring by age 40. Between 5–50% of individuals with FAP experience morbidity and/or mortality from desmoid tumors. The mean age of diagnosis of thyroid cancer is between 28 and 33 years, ranging from 12 to 62 years, with a female preponderance observed. The majority of HPBs occur prior to age five years, have a 25% mortality rate, and exhibit a male preponderance. Medulloblastoma accounts for most of the brain tumors found in patients with FAP, predominantly in females younger than age 20 years. CHRPE is most often multiple and bilateral.</p> <p>While the phenotype of AFAP is not well defined, widely used clinical criteria include the following: a delay in onset of adenomatous polyposis and colorectal cancer of 10–25 years compared with classical FAP; < 100 adenomatous polyps at 25 years of age or older; and/or a late onset of disease (≥ 45 years of age) irrespective of polyp number.</p>	(1, 2, 3, 4, 5, 6, 7, 9, 13, 14, 15, 16, 17)

2. How effective are interventions for preventing harm?

Information on the effectiveness of the recommendations below was not provided unless otherwise stated.

Patient Management	<p><i>No patient management recommendations have been provided for the Pediatric context.</i></p>	
	<p>The recommendations detailed below are largely applicable to classic and AFAP; however AFAP, with its milder course, may be manageable by colonoscopy and polypectomy and these patients may never require colectomy depending on polyp burden. However, the decision to forego colectomy should only be considered if high quality surveillance and robust recall systems are in place. (Tier 1)</p>	(4, 6)
	<p>Treatment for FAP should include coordinated, timely and high-quality care to reduce cancer risk and improve compliance with recommendations for management and surveillance. Patients should be followed in dedicated units (national registries, genetic counseling centers, or high-risk cancer centers) where surveillance recommendations are monitored and audited, in order to improve adherence and provide the highest quality of care. Patients should also have access to a full range of management options that minimize the risk of morbidity and mortality. (Tier 1)</p>	(4, 6)
	<p>A systematic review of studies comparing CRC incidence and mortality before and after registry commencement, found 8 studies (3101 individuals) examining CRC incidence and 6 studies examining CRC mortality. Odds ratios for CRC incidence following registration range from 0.09-0.44, with all but one study showing a statistically significant effect. Odds ratios for CRC-related mortality range from 0.11-0.22, all significant. (Tier 1)</p>	(11)
	<p>Surgery is necessary to prevent CRC in adulthood. Therefore, endoscopic management of colorectal adenomas alone is not recommended in individuals with classic FAP. For most patients, the choice of surgery will be between total colectomy with ileorectal anastomosis (IRA) and proctocolectomy and ileal pouch anal anastomosis (IPAA). Decisions regarding the timing and type of operation should be discussed at a specialist center in a multidisciplinary setting and take into account disease phenotype (colon and rectal polyp burden, extensiveness of rectal involvement, presence and size of high-grade dysplasia, increase in polyp burden between screenings, severity of symptoms); genotype; family planning; personal and family history of desmoid disease; social, personal, and educational factors; likelihood of compliance with follow-up; and the pros and cons of the surgical options. The age of prophylactic colectomy is not fixed and is a topic that should be discussed in adolescence. (Tier 1)</p>	(2, 4, 6)
	<p>There remains a risk of adenoma and CRC cancer after colectomy, and the extent of risk is influenced by the type of procedure chosen and type of tissue-sparing. Risk of developing adenomas at 10-year follow-up after IPAA is 51%. Registry studies indicate that 50-53% of patients undergo additional surgeries after their initial rectal-sparing procedure. The cumulative risk of</p>	(2, 4, 6)

3. What is the chance that this threat will materialize?

Mode of Inheritance	Autosomal Dominant	
Prevalence of Genetic Mutations	Pathogenic variants in APC can be identified in between 70-95% of FAP cases and 10% in cases of AFAP, meaning that the prevalence of APC pathogenic variants should be lower, although similar, to the prevalence of FAP. (Tier 3)	(2, 3, 4, 7, 10, 13)
Penetrance (Include any high risk racial or ethnic subgroups)	<p>The penetrance information presented here applies to classic FAP unless noted otherwise.</p> <p>The penetrance of colon cancer is estimated at 90-100% in untreated individuals, within AFAP the risk of cancer approaches 70% by age 80. (Tier 3)</p> <p>Jejunal and ileal polyps can be found in 20-70% of FAP patients. (Tier 3)</p> <p>The lifetime risk of duodenal polyposis approaches 100% in FAP. Adult studies have estimated the prevalence of duodenal adenomatoses in FAP to be approximately 65%. The lifetime risk of duodenal cancers has been estimated at 3-12%. (Tier 3)</p> <p>In a meta-analysis of 5 pediatric case series including 189 children, 41% were found to have duodenal adenoma. (Tier 1)</p> <p>While gastric polyps occur in 20-100% of patients. Gastric adenomatous polyps, which can lead to gastric cancer, represent 10% of the gastric polyps in these patients. The lifetime risk for gastric cancer in FAP in Western countries is estimated between 0.14-0.55%. (Tier 3)</p> <p>In meta-analyses of cohort studies of patients with FAP, the pooled prevalence was 2.6% (95% CI: 1.3-4.8%) for thyroid cancer, 48.8% (95% CI: 34-64%) for benign thyroid masses, and 6.9% (95% CI: 4.5-10%) for endocrinologic thyroid disorders. Among thyroid cancer, 95% were in females, 46% was bilateral, and 59% was multicentric. (Tier 1)</p> <p>A second meta-analysis estimated the incidence of thyroid cancer in FAP as 1.6% (range of 0.4-11.8% across studies), with a female-to-male odds ratio of 6.9:1. (Tier 1)</p> <p>The lifetime pancreatic cancer risk is estimated as 1-1.7%. (Tier 2)</p> <p>The absolute risk of HPB in FAP-affected children is 1-2%. (Tier 3)</p> <p>The absolute risk for CNS tumors is 1-2%. (Tier 3)</p> <p>In a meta-analysis of 10 studies (4625 patients), 559 (12%) developed desmoid tumor. (Tier 1)</p> <p>Adrenal masses occur in 7-13% of patients; however, most are asymptomatic incidental findings. (Tier 3)</p> <p>In a meta-analysis of observational studies in people with FAP estimated that osseous jaw lesions (including osteomas, dense bone islands, and hazy sclerosis) had an overall prevalence of 65% (95% CI: 47-82%) and dental anomalies (including odontomas, supernumerary teeth, and unerupted teeth) had an overall prevalence of 31% (95% CI: 19-43%). (Tier 1)</p>	<p>(3, 4, 5, 6, 7, 13, 17)</p> <p>(5, 20)</p> <p>(2, 3, 4, 5, 6, 7, 12, 13, 18)</p> <p>(18)</p> <p>(2, 4, 5, 6)</p> <p>(16)</p> <p>(9)</p> <p>(3, 5)</p> <p>(2, 3, 5, 7, 13)</p> <p>(5)</p> <p>(14)</p> <p>(3)</p> <p>(21)</p>

4. What is the Nature of the Intervention?		
Nature of Intervention	Endoscopic surveillance is burdensome for individuals. In children and young teenagers, most endoscopic procedures are performed under general anesthesia.	(1, 2)
	The morbidity and functional outcomes of colectomy can include poor sphincter function, changes in bowel movements, incontinence, sexual dysfunction, pelvic dissection and dietary restrictions and are partially dependent on the type of procedure chosen and whether the rectum is retained. In addition, an increased risk of desmoid tumors have been noted among individuals with FAP who have undergone abdominal surgery. There is some risk of loss of fertility in women following proctocolectomy, with some evidence estimating up to a 54% decrease, which is more common among women who had their first surgical procedure at a younger age.	(2, 4, 12)
	Mental health related quality of life scores are reported to be significantly lower in FAP patients under the age of 18 compared to adults, warranting psychological support for these patients. Psychological compliance of pediatric patients regarding colectomy surgery is also of concern due to the associated major functional and anatomical sequelae.	(5, 17)
5. Would the underlying risk or condition escape detection prior to harm in the setting of recommended care?		
Chance to Escape Clinical Detection	Most patients are asymptomatic for years until the adenomas are large and numerous, and cause rectal bleeding or even anemia, or cancer develops. (Tier 4)	(8)
	Due to the high proportion of de novo FAP cases (up to 40% of FAP patients), there is a 25% incidence of CRC in newly diagnosed FAP cases. Because of this presentation and the early onset of CRC in FAP patients (prior to population screening age), there is a high chance for FAP patients to escape clinical detection. (Tier 3)	(5, 10, 17)



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Pediatric Consensus Scores



Semi-quantitative Scoring Metric

View the semi-quantitative scoring metric used to generate the consensus scores from the Actionability Working Groups

Scoring Metric

Adult Actionability Reports - Summary of Overall Scores from Released Reports

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Doc Id	Latest Search Date	Gene	Disease	Status-overall	Outcome	Intervention					
Aceruloplasminemia											
AC157	Thu, 03 Jan 2019	CP	Aceruloplasminemia	Released	Morbidity due to iron accumulation	Iron chelation and avoidance of iron supplementation	2	3C	3	2D	10CD
Acute Intermittent Porphyria											
AC095	Wed, 14 Sep 2016	HMBS	Acute Intermittent Porphyria	Released	Neurovisceral attacks	Optimal clinical management to reduce risk of attacks (e.g., avoidance of harmful medications, dietary advice, treatment of infections, avoidance of smoking/alcohol)	2	2C	3	2B	9CB
AC095	Wed, 14 Sep 2016	HMBS	Acute Intermittent Porphyria	Released	Hepatocellular carcinoma	Liver US surveillance	2	2C	3	3C	10CC
AC095	Wed, 14 Sep 2016	HMBS	Acute Intermittent Porphyria	Released	Morbidity of acute attacks	Optimal treatment (Hemin) in the event of an attack	2	2C	3	3B	10CB
Adrenoleukodystrophy											
AC117	Wed, 16 Nov 2016	ABCD1	Adrenoleukodystrophy	Released	Neurological/Cognitive decline	Neurological surveillance to plan initiation of HCT	2	3C	3	3C	11CC
AC117	Wed, 16 Nov 2016	ABCD1	Adrenoleukodystrophy	Released	Adrenal insufficiency (males only)	Monitoring adrenal hormones with replacement as needed	1	2C	3	3C	9CC
Adult-onset type II citrullinemia											
AC118	Tue, 13 Dec 2016	SLC25A13	Adult-onset type II citrullinemia	Released	Hepatic encephalopathy	Dietary modification with arginine and sodium pyruvate supplementation	2	0D	3	1N	6DN
AC118	Tue, 13 Dec 2016	SLC25A13	Adult-onset type II citrullinemia	Released	Liver failure	Liver transplantation	2	0D	0	3C	5DC
Alkaptonuria											

Column Visibility Export API

Final Notes



- Regularly update reports
- Assertions process is recent, not available for all gene-disease pairs yet
- Plans for the AWG going forward
 - Continue to curate and update curations for gene-disease pairs
 - Adapt actionability framework for new clinical contexts
 - Population screening
 - Polygenic risk scores



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