SYSTEMATIC ASSESSMENT OF CLINICAL ACTIONABILITY ASSOCIATED WITH GENOMIC VARIATION

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Kaiser Permanente Northwest
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ClinGen
Clinical Genome Resource

Acknowledgements

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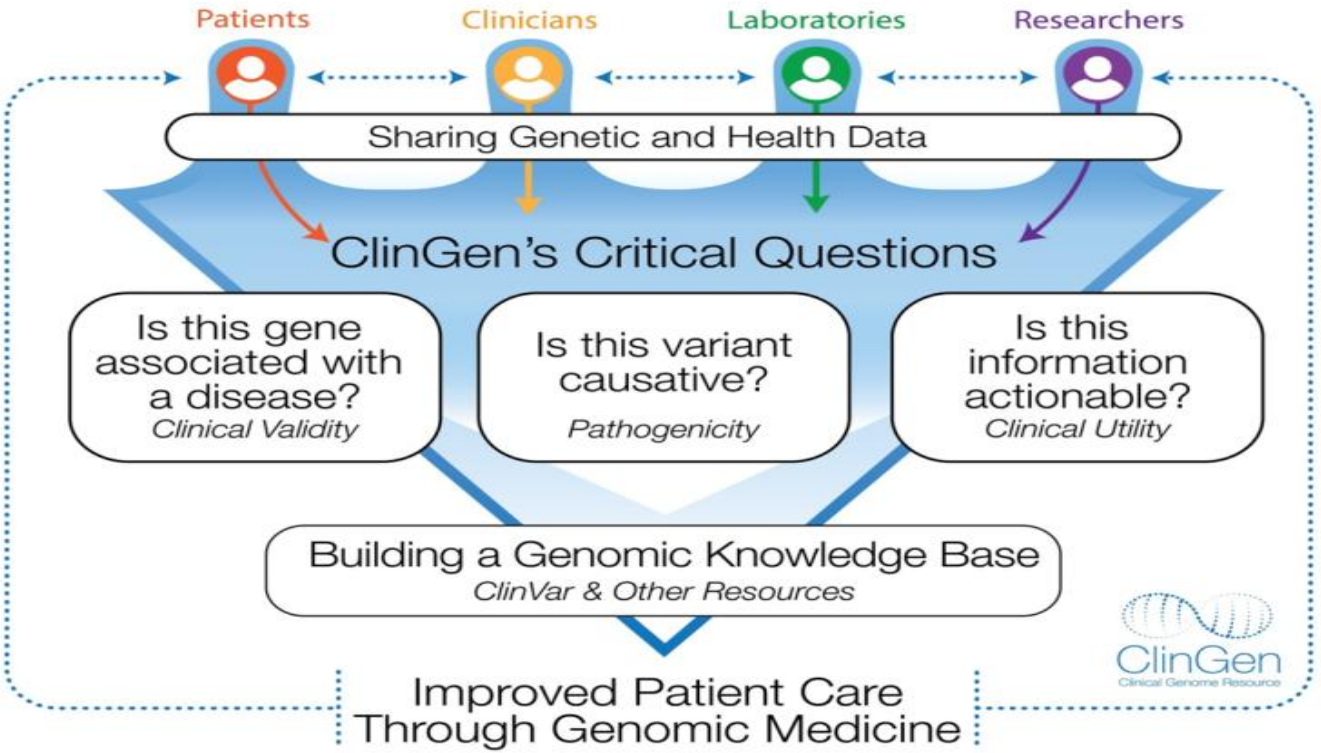
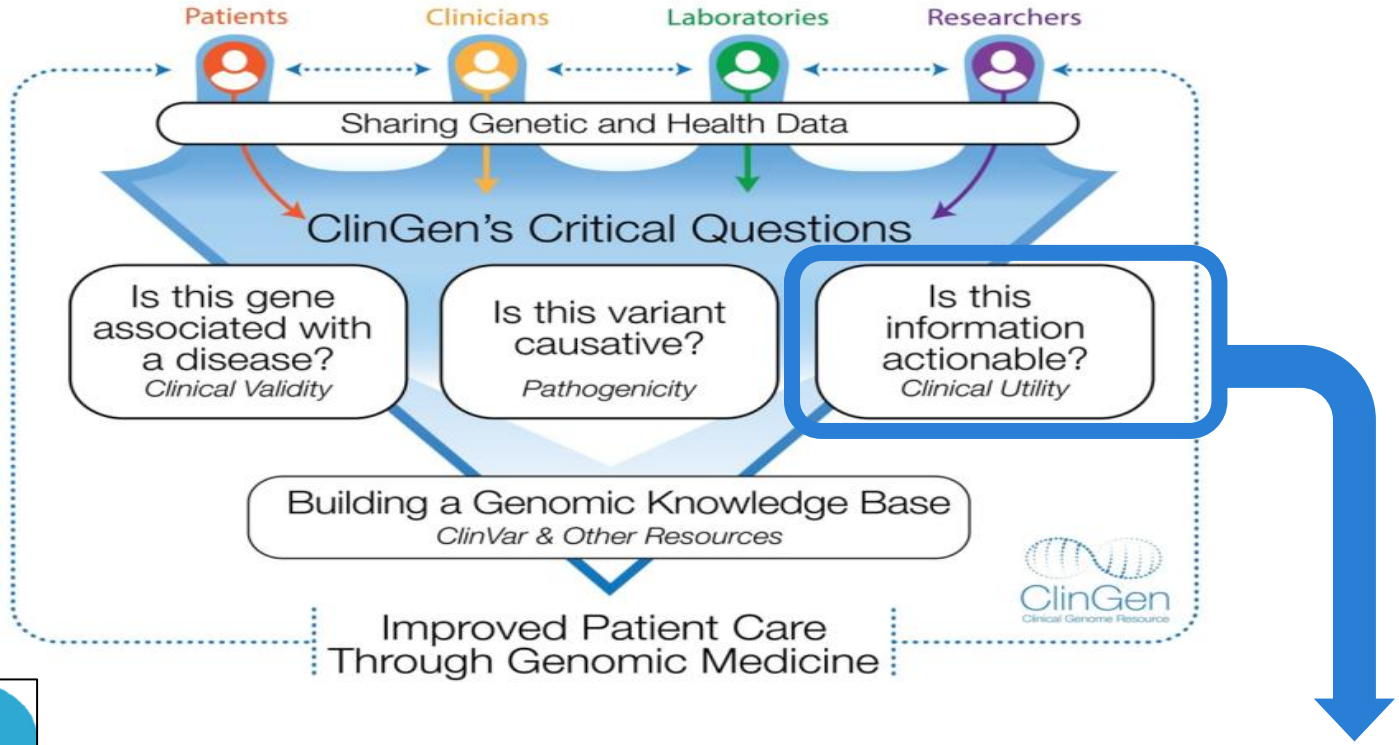
Clinical Genome Resource

Clinical Genome Resource (ClinGen)

- **NIH-funded program launched Sept. 2013**
  - Co-funding from the NHGRI, NICHD, and NCI
  - Collaboration with NCBI's ClinVar
  - > 250 researchers & clinicians from >75 institutions
- **Purpose:** Create authoritative central resource that defines the clinical relevance of genomic variants for use in precision medicine and research.

ClinGen
Clinical Genome Resource


Patients
Clinicians
Laboratories
Researchers
Sharing Genetic and Health Data
ClinGen's Critical Questions
Is this gene associated with a disease?
Clinical Validity
Is this variant causative?
Pathogenicity
Is this information actionable?
Clinical Utility
Building a Genomic Knowledge Base
ClinVar & Other Resources
ClinGen
Clinical Genome Resource
Improved Patient Care Through Genomic Medicine



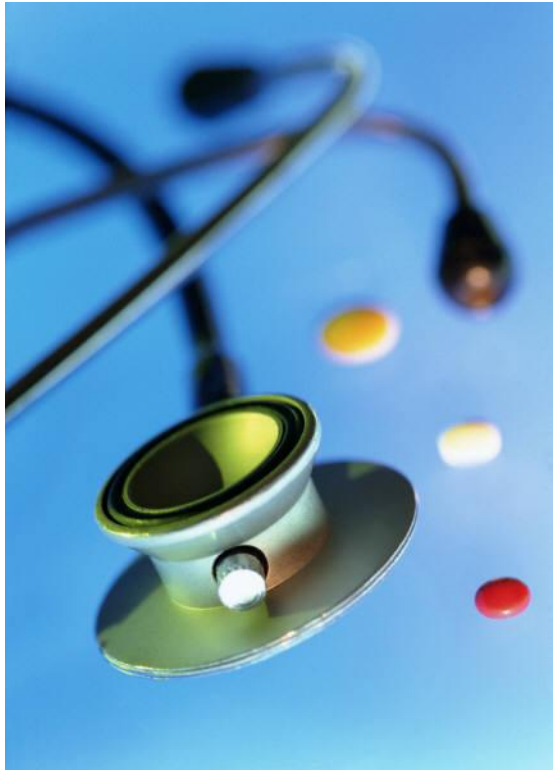
ClinGen Actionability Working Group:

Develop a framework to provide a transparent and systematic evidence base for prioritizing genes based on their clinical actionability.

Clinical Context

- Adult with an incidental or secondary finding via genome-scale sequencing
- Strong or definitive association with disease
- Not previously diagnosed with the genetic condition
- May have signs or symptoms of disease, but not diagnosed

Clinical Actionability

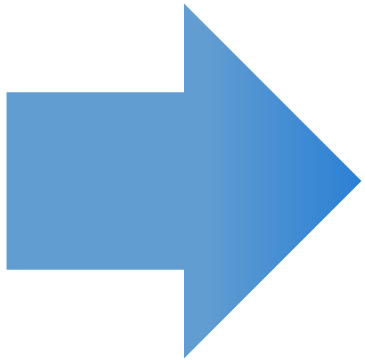


- Well established clinical interventions
- Specific to the genetic disorder under consideration
- Lead to disease prevention or delayed onset, lowered clinical burden, or improved clinical outcomes

Knowledge Synthesis Team

Qualitative Evidence Synthesis

- Standardized
- Reproducible
- Feasible



Actionability Working Group

Semi-Quantitative Metric

- Quantify
- Prioritize
- Compare

Knowledge Synthesis Team

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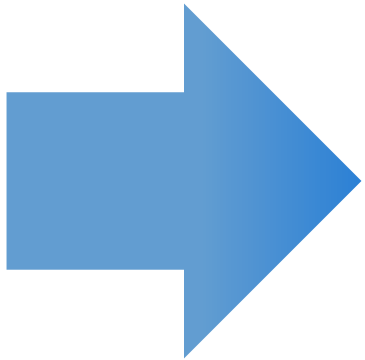

Actionability Working Group

Semi-Quantitative Metric

- Quantify
- Prioritize
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Stage II: Evidence Synthesis

Evidence Sources

Standardized search:

Systematic reviews, clinical practice guidelines, and meta-analyses

OMIM, GeneReview, and OrphaNet entries

Clinical Utility Gene Cards

EXCLUDED: Narrative reviews and primary literature excluded

Highest Tier of Evidence

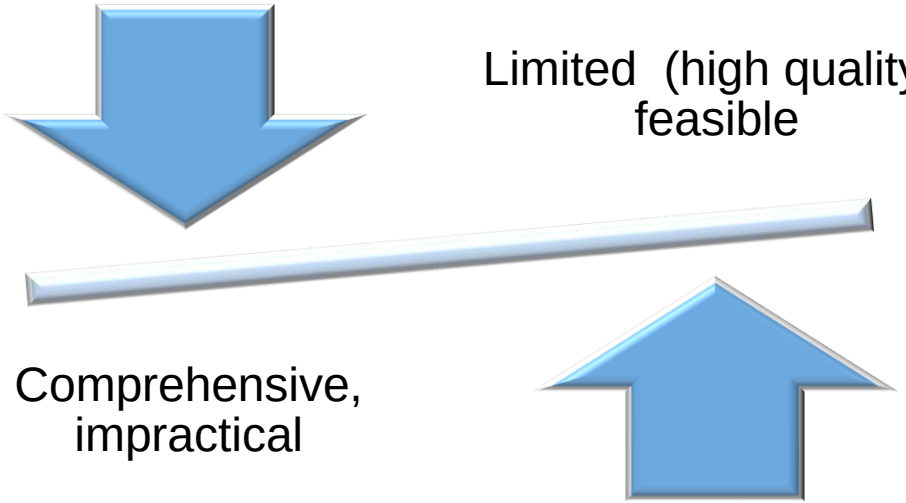
Tier 1: Systematic review, meta-analysis or practice guideline based on systematic review

Tier 2: Practice guideline or expert consensus

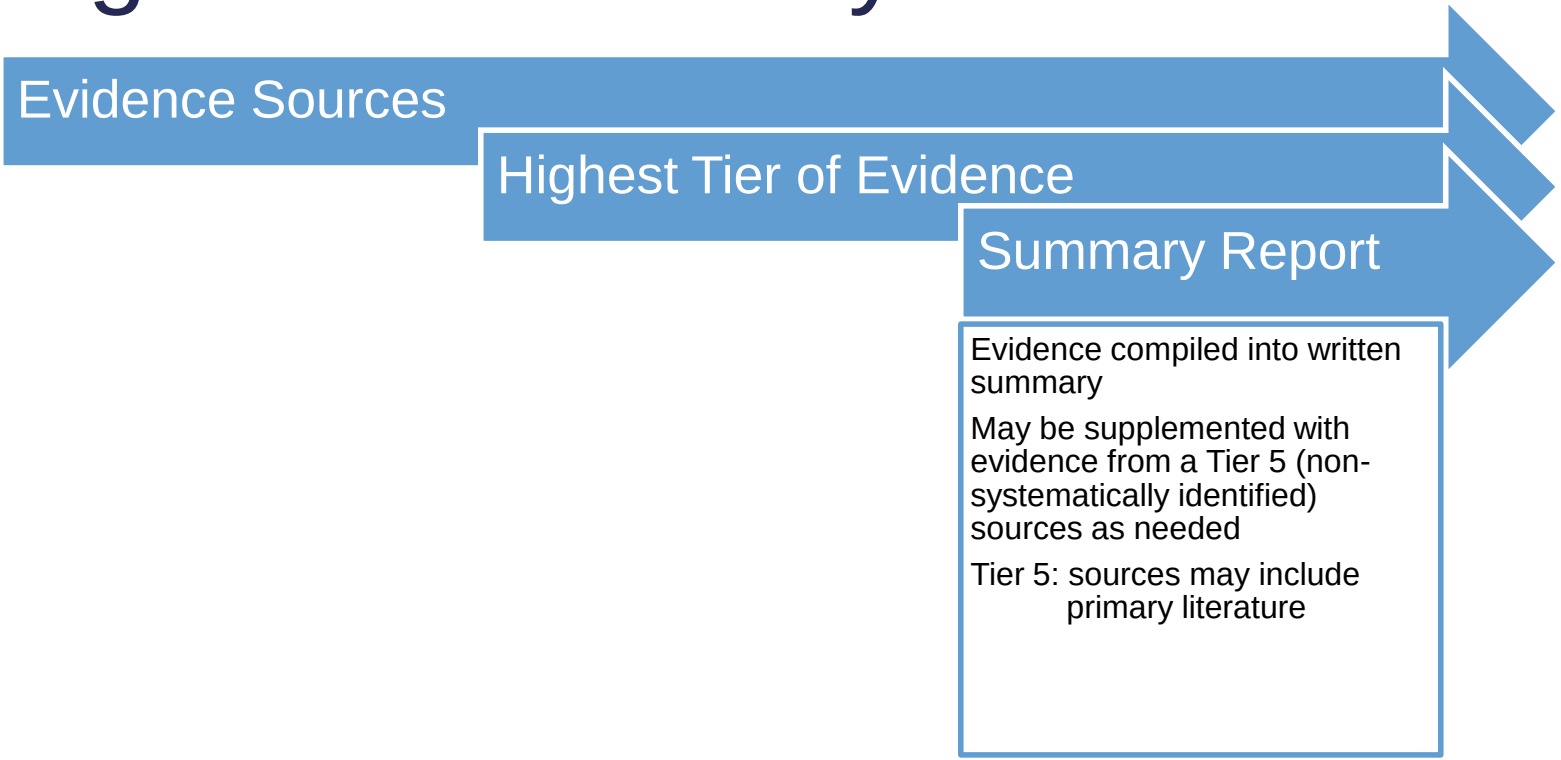
Tier 3: Non-systematic evidence review with citations (eg, GeneReview, OMIM)

Tier 4: Non-systematic evidence review with no citations (eg, OrphaNet)

Stage II: Evidence Synthesis



Stage II: Evidence Synthesis



Domains of Clinical Actionability

DOMAIN	
SEVERITY	What is the nature of the threat to health to individuals carrying a clearly deleterious allele?
LIKELIHOOD	
EFFECTIVENESS	
NATURE OF INTERVENTION	
CHANCE TO ESCAPE CLINICAL DETECTION	

Domains of Clinical Actionability

DOMAIN	
SEVERITY	What is the nature of the threat to health to individuals carrying a clearly deleterious allele?
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NATURE OF INTERVENTION	
CHANCE TO ESCAPE CLINICAL DETECTION	

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EFFECTIVENESS	How effective is intervention for preventing or significantly diminishing the risk of harm?
NATURE OF INTERVENTION	
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Domains of Clinical Actionability

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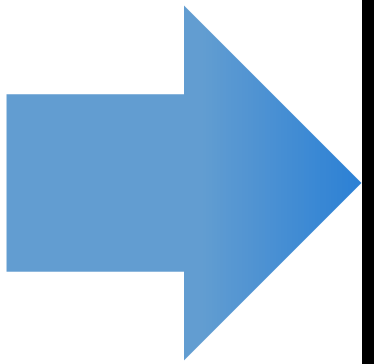
EFFECTIVENESS	How effective is intervention for preventing or significantly diminishing the risk of harm?
NATURE OF INTERVENTION	How risky, medically burdensome or intensive is the intervention?
CHANCE TO ESCAPE CLINICAL DETECTION	Would the underlying risk or condition escape detection prior to harm in the setting of recommended care?

Knowledge Synthesis Team

Qualitative Evidence Synthesis

- Standardized
- Reproducible
- Feasible



Actionability Working Group

Semi-Quantitative Metric

- Quantify
- Prioritize
- Compare

Domains of Clinical Actionability

DOMAIN		SCORING METRIC
SEVERITY	What is the nature of the threat to health to individuals carrying a clearly deleterious allele?	3 = Sudden death 2 = Death or major morbidity 1 = Modest morbidity 0 = Minimal or no morbidity
LIKELIHOOD	What is the chance a serious outcome will materialize given a deleterious variant?	
EFFECTIVENESS	How effective is intervention for preventing or significantly diminishing the risk of harm?	
NATURE OF INTERVENTION	How risky, medically burdensome or intensive is the intervention?	

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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
EFFECTIVENESS	How effective is intervention for preventing or significantly diminishing the risk of harm?	
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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/Unknown IN = Ineffective/No intervention
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Domains of Clinical Actionability

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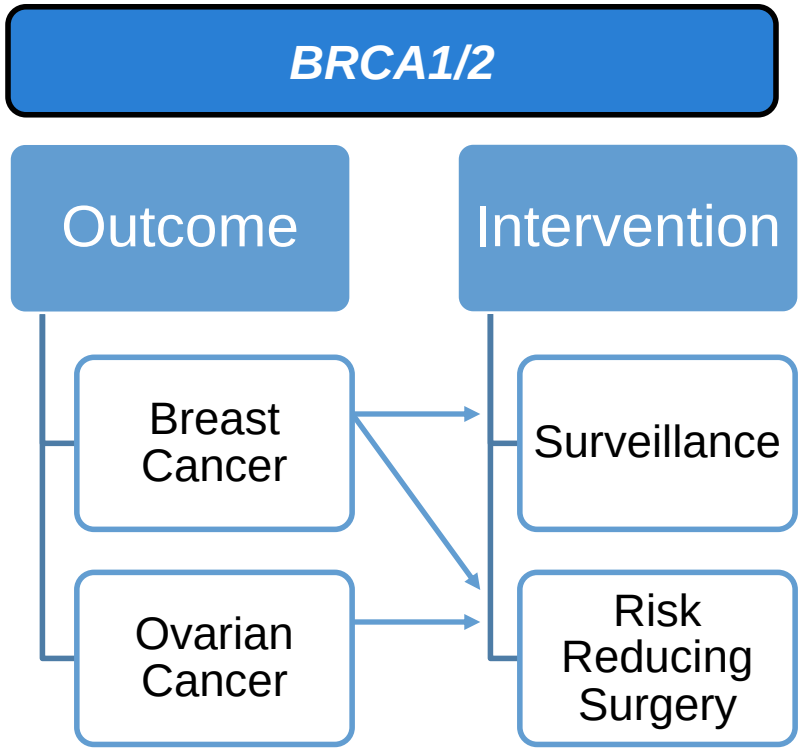
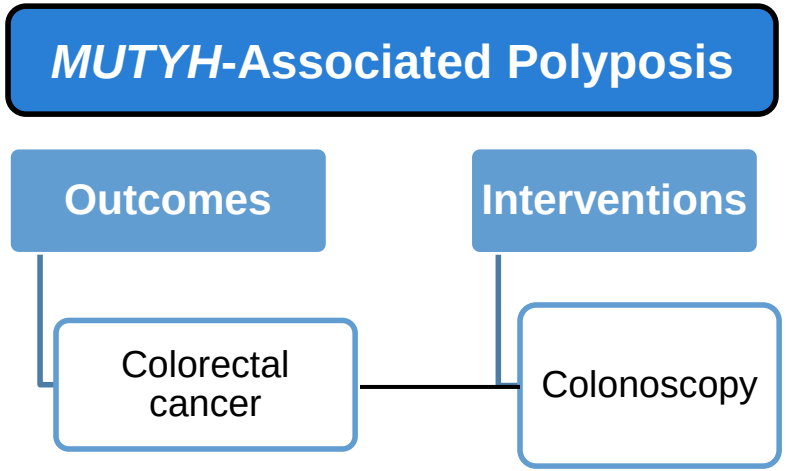
NATURE OF INTERVENTION	How risky, medically burdensome or intensive is the intervention?	3 = Low risk, medically acceptable, and low intensity 2 = Moderate risk, moderately acceptable or intensive 1 = Greater risk, less acceptable and substantial 0 = High risk, poorly acceptable, or intensive	

Scoring Outcome-Intervention Pairs



- Breast Cancer + Surveillance: **10AA**
- Breast Cancer + Mastectomy: **9AA**
  - ↑ Effectiveness
  - ↓ Nature of the intervention
- Ovarian Cancer + Oophorectomy: **8AA**
  - ↑ Effectiveness
  - ↓ Penetrance
  - ↓ Nature of the intervention

Scoring Outcome-Intervention Pairs



Scoring Process

Preliminary Score

Discussion

Final Score

Consensus Score

Actionability of the ACMG 56

Genetics inMedicine | ORIGINAL RESEARCH ARTICLE Official journal of the American College of Medical Genetics and Genomics

Open

A standardized, evidence-based protocol to assess clinical actionability of genetic disorders associated with genomic variation

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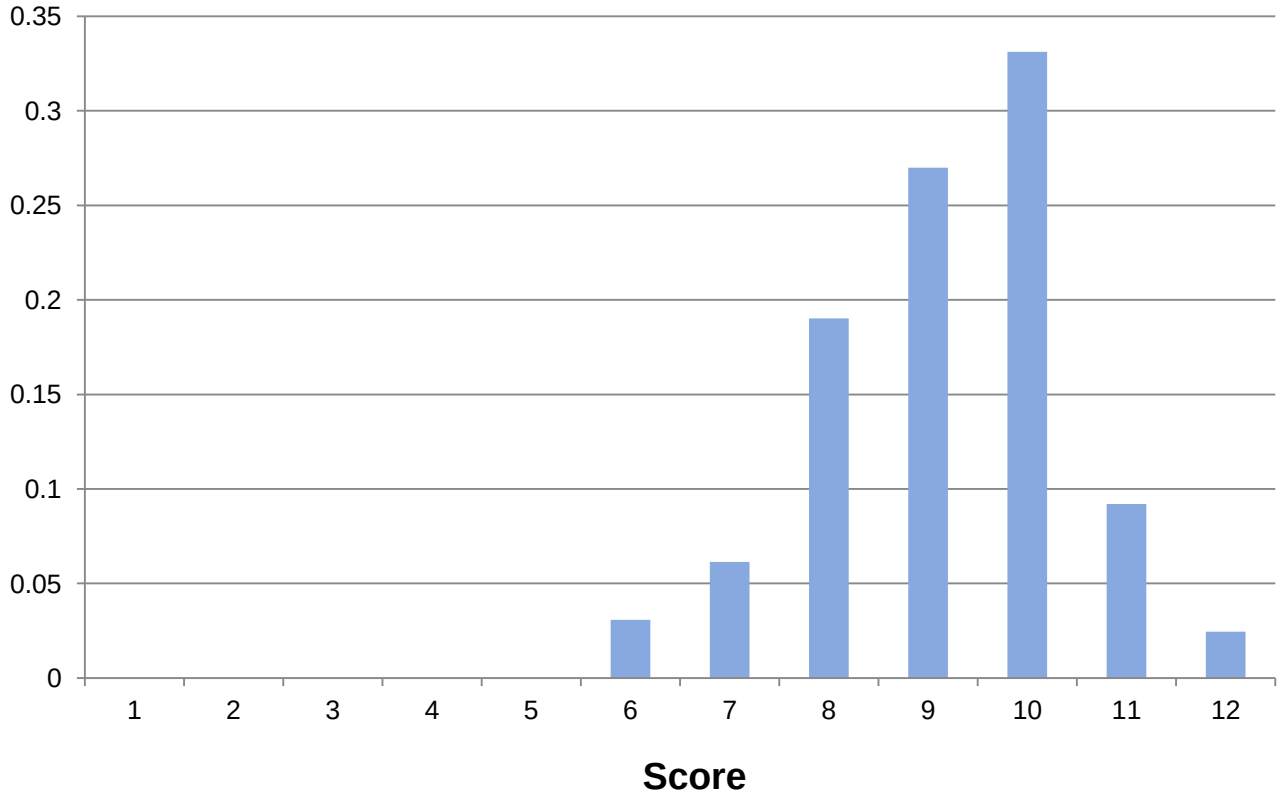
Genet Med. 2016 Dec 18(12): 1258-1268

Perfect 12s

- 4 pairs have received perfect scores
- All genes currently on ACMG list (*FBN1, TGFBR1, TGFBR2, SMAD3*)

- Loeys-Dietz syndrome 1 and Marfan syndrome
  - Beta-blockers for prevention of aortic dilation progression
  - Surveillance for aortic aneurysms

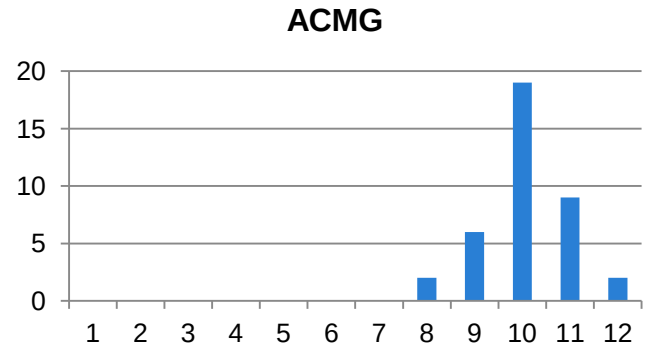
Distribution of scores for all Outcome-Intervention Pairs



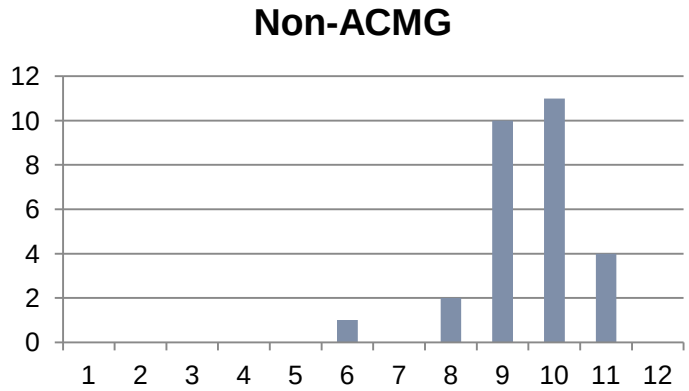
To date:
66 topics,
166 pairs scored

Average score: 9.3

ACMG and non-ACMG topics



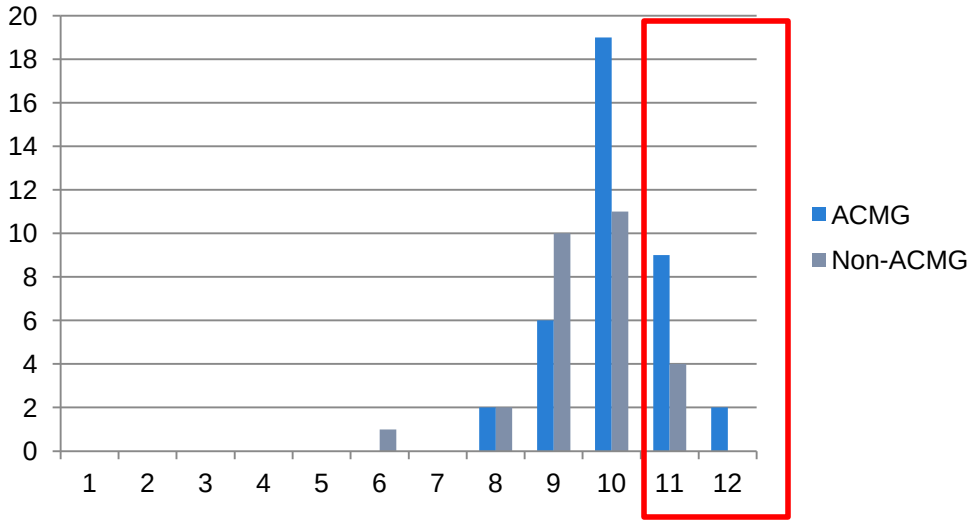
- ACMG: Average- 9.5
  - Range: 8-12
    - 8: *APC* (FAP)
      - Nature of the intervention scores low for colectomy



- Non-ACMG: Average- 8.8
  - Range: 6-11
    - 6: *MEFV* (Autosomal dominant familial Mediterranean fever)
      - No evidence on penetrance in AD form, less severe phenotype
      - Autosomal recessive form scores higher

High scores not on ACMG list

4 genes have scored 11



- *SERPINA1* (Alpha-1 Antitrypsin Deficiency)
  - Smoking cessation
  - Serum A1AT monitoring
- *BTD* (Biotinidase deficiency)
  - Biotin therapy
- *HNF1A* (Maturity Onset Diabetes of the Young, Type 3)
  - Sulfonylureas for diabetic control
- *ENG* (Hereditary Hemorrhagic Telangiectasia)
  - Echocardiography to detect pulmonary arteriovenous malformations

Extrapolation

- Lack of effectiveness data for some interventions specific to population
- Example: *LFS*

Familial Breast Cancer

NICE National Institute for Health and Care Excellence

Clinical guideline 164
Familial breast cancer, 2013 (Tier 1)

	Breast cancer risk category		
	Near population risk	**Moderate risk**	**High risk**[1]
Lifetime risk from age 20	Less than 17%	Greater than 17% but less than 30%	30% or greater
Risk between ages 40 and 50	Less than 3%	3–8%	Greater than 8%

[1]This group includes known *BRCA1*, *BRCA2* and *TP53* mutations and rare conditions that carry an increased risk of breast cancer such as Peutz-Jegher syndrome (*STK11*), Cowden (*PTEN*) and familial diffuse gastric cancer (E-Cadherin).

- Tier 1: Evidence-based
- BRCA1/BRCA2: HBOC
  TP53: LFS
- Breast cancer rec's by risk category:
  - Risk reducing surgery
  - Surveillance
- High risk rec's based on *BRCA* populations

Effectiveness of the Intervention Scores		Risk Reducing Surgery	Surveillance
	HBOC	3A	2A
	LFS	3B*	2B*

Wilson Disease

"Unknown" Penetrance

- No penetrance estimates in literature
- Segregation analysis → Autosomal recessive inheritance
- Penetrance of at least some clinical characteristics would need to be high

Penetrance = 3D
3 = High (>40%)
D = Poor evidence/Missing

Hemophilia A and B

Disorders with (mostly) Childhood Onset

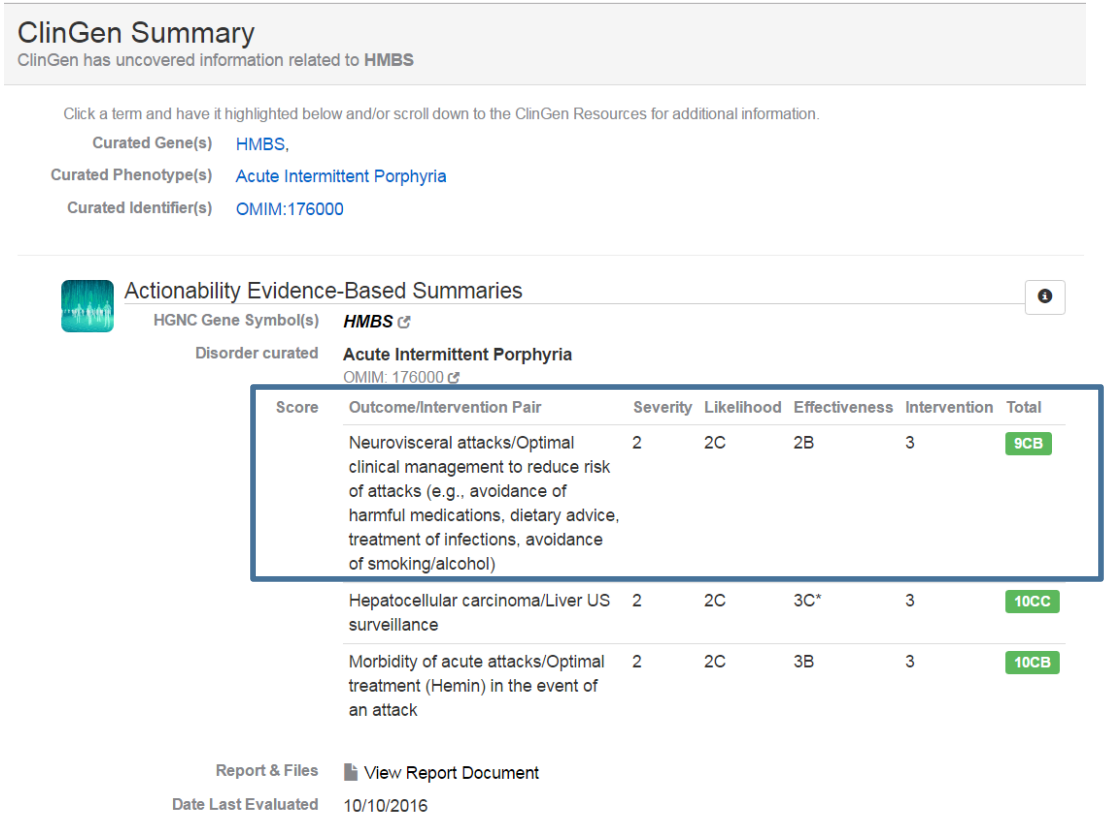
Severity	Factor Level	Age	Spontaneous Bleeding	Bleeding with trauma
Severe	<1%	<2 yrs	+++	+++
Moderate	1-5%	<5-6 yrs	+	++
Mild	6-40%	Later in life	-	+

	SEVERITY
Scorer 1	2
Scorer 2	2
Scorer 3	3
Scorer 4	2
Scorer 5	2
Scorer 6	3
CONSENSUS	**2**

SEVERITY
- 3 = Sudden death
- 2 = Death or major morbidity
- 1 = Modest morbidity
- 0 = Minimal or no morbidity

How to communicate scores

How do you interpret a 9CB?



ClinGen Summary

ClinGen has uncovered information related to **HMBS**

Click a term and have it highlighted below and/or scroll down to the ClinGen Resources for additional information.

Curated Gene(s) HMBS,

Curated Phenotype(s) Acute Intermittent Porphyria

Curated Identifier(s) OMIM:176000

Actionability Evidence-Based Summaries

HGNC Gene Symbol(s) ***HMBS***

Disorder curated **Acute Intermittent Porphyria**

OMIM: 176000

Score	Outcome/Intervention Pair	Severity	Likelihood	Effectiveness	Intervention	Total
	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	2B	3	9CB
	Hepatocellular carcinoma/Liver US surveillance	2	2C	3C*	3	10CC
	Morbidity of acute attacks/Optimal treatment (Hemin) in the event of an attack	2	2C	3B	3	10CB

Report & Files View Report Document

Date Last Evaluated 10/10/2016

Going Forward

- Evidence summaries and scores publically available:

  www.clinicalgenome.org
- Additional topics
- Expand protocol to address sequencing in children
- Visualization of scores

Questions?

Genes and Disorders Assessed ACMG 56

- Arrythmogenic right-ventricular cardiomyopathy
- Brugada syndrome*
- Catecholaminergic polymorphic ventricular tachycardia
- Dilated cardiomyopathy
- Ehlers Danlos syndrome, type 4
- Fabry disease
- Familial adenomatous polyposis
- Familial hypercholesterolemia
- Familial thoracic aortic aneurysms and dissections
- Hereditary breast and ovarian cancer
- Hereditary paraganglioma-pheochromocytoma syndrome
- Hypertrophic cardiomyopathy
- Li-Fraumeni syndrome
- Loeys-Dietz syndrome
- Lynch syndrome
- Malignant hyperthermia susceptibility
- Marfan syndrome
- Multiple endocrine neoplasia, type 1
- Multiple endocrine neoplasia, type 2A/Familial medullary thyroid cancer
- Multiple endocrine neoplasia, type 2B
- MUTYH-associated polyposis
- Neurofibromatosis, type 2
- Peutz Jeghers syndrome
- *PTEN* hamartoma tumor syndrome
- Retinoblastoma*
- Romano-Ward long QT syndrome
- Tuberous sclerosis complex
- Von Hippel-Lindau syndrome
- *WT1*-related Wilms tumor*

Hunter et al. 2016 Genetics in Medicine

*Did not pass Stage I

Genes and Disorders Assessed Beyond the ACMG 56

- Acute intermittent porphyria
- Alpha-1 antitrypsin deficiency
- Alzheimer disease*
- Basal cell nevus syndrome
- Biotinidase deficiency
- Birt-Hogg-Dube syndrome
- BRCA2-Pancreatic cancer*
- CADASIL
- Charcot-Marie-Tooth, type 1
- Congenital disorders of glycosylation, type Is*
- Cystic fibrosis*
- Factor V leiden
- Familial atrial fibrillation*
- Familial Mediterranean Fever
- Gaucher
- Gastrointestinal stromal tumor*
- Hemophilia A and B
- Hemochromatosis
- Hereditary diffuse gastric cancer
- Hereditary hemochromatosis, type 1
- Hereditary hemorrhagic telangiectasia
- Hereditary neuropathy with liability to pressure palsies
- Homocystinuria
- Juvenile polyposis syndrome
- Leiomyomatosis and renal cell cancer
- Maturity onset diabetes of the young, type 3
- Methylmalonic acidemia
- Ornithine transcarbamylase deficiency
- Parkinson disease*
- PALB2-Breast cancer
- Phenylketonuria
- Polycystic kidney disease
- Pompe disease
- Wilson disease

*Did not pass Stage I

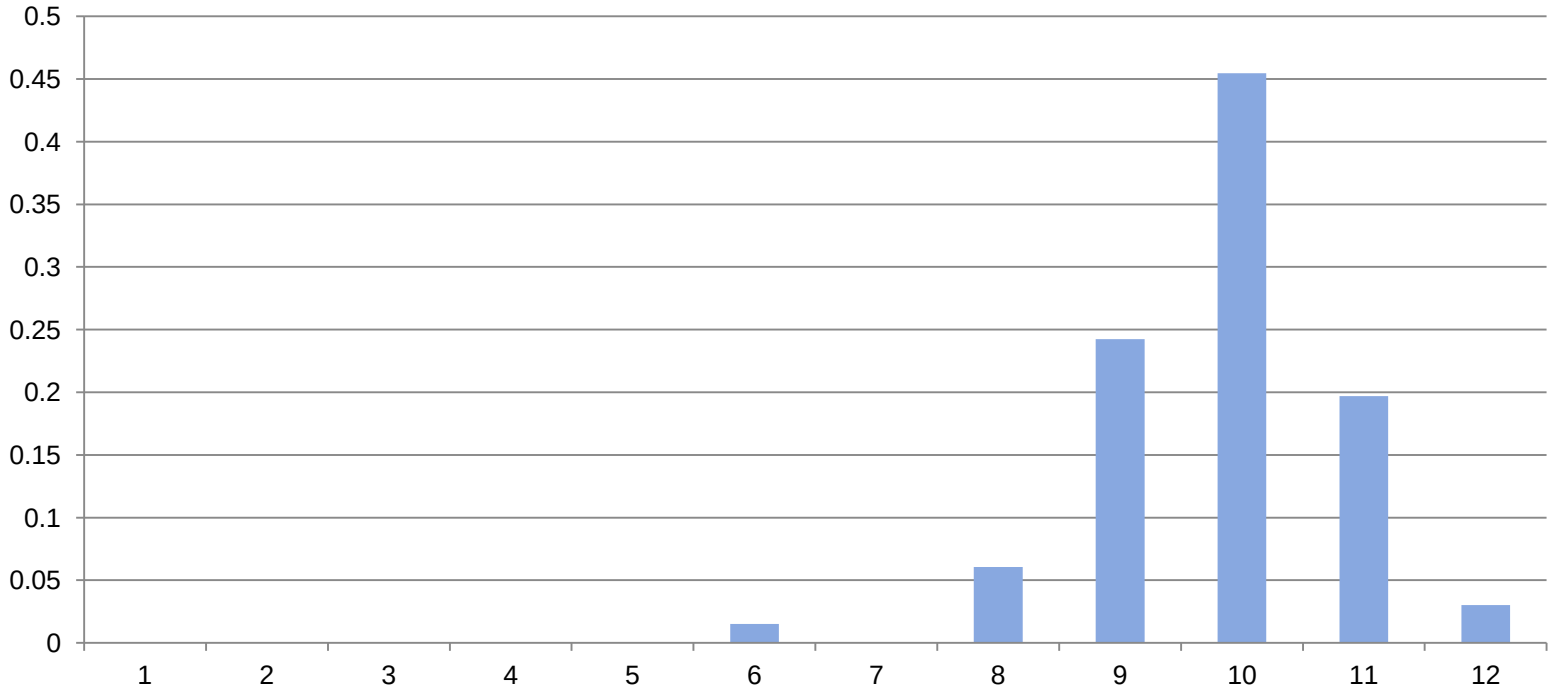
Stage I: Quick Rule-Out

ACTIONABILITY	• Is there a qualifying resource, such as a practice guideline or systematic review, for the genetic condition? • Does the practice guideline or systematic review indicate that the result is actionable? • Is the result actionable in an undiagnosed adult with the genetic condition?
PENETRANCE	• Is there at least one known pathogenic variant with at least moderate penetrance (≥40%) or moderate relative risk (≥2) in any population?
SIGNIFICANCE/ BURDEN OF DISEASE	• Is this an important health problem?

Examples of topics that did not pass Stage 1

- Childhood onset:
  - Retinoblastoma
  - *WT1*-related Wilms tumor
- Penetrance:
  - *Brugada syndrome: exception made*
- Lack of guidelines:
  - Cystic fibrosis
  - *KCNE2* (familial atrial fib)
  - *KIT/PDGFRA* (GISTs)

Highest Score for Each Topic



Familial Breast Cancer

Extrapolation of Evidence

- PALB2 Penetrance
  - 14% by age 50
  - 35% by age 70

	Breast cancer risk category		
	Near population risk	**Moderate risk**	**High risk**[1]
Lifetime risk from age 20	Less than 17%	Greater than 17% but less than 30%	30% or greater
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Effectiveness of the Intervention Scores		Risk Reducing Surgery	Surveillance
	HBOC	3A	2A
	LFS	3B*	2B*
	PALB2	3B*	2B*

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Extrapolation of Evidence

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  - 14% by age 50
  - 35% by age 70

While no breast cancer screening recommendations were identified for PALB2 mutation carriers, breast cancer screening guidelines agree that women at an increased risk level corresponding to the lifetime risk of a PALB2 mutation carrier should receive earlier breast cancer screening than the general population. However, recommendations for age to start, frequency, and the use of mammography versus MRI vary between guidelines.

Effectiveness of the Intervention Scores		Risk Reducing Surgery	Surveillance
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	PALB2	3B*	2B*