# Application of a semi-quantitative metric to assess medical actionability of genomic findings

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# Incidental/secondary findings

- The vast majority of genomic variants have no known clinical relevance and thus poor positive predictive value
- Therefore, it is imperative to maximize specificity and avoid reporting variants with no known clinical validity in the setting of an asymptomatic individual
  - Setting a “high bar” to ensure that variants reported to physicians/patients can be incorporated into clinical care in an evidence-based fashion, and ***ignore everything else*** until we know what to do with it

# Role of individual preferences

- Genome-scale sequencing, like any other complex medical test, can help, harm or confuse
  - Each individual will hold different views on the benefits and risks of genetic information
  - There is ***no standard of care for return of results*** from genome-scale sequencing
- We propose calibrating results by the potential benefits and risks of the incidental findings
  - Taking into account patient preferences when evidence of direct clinical benefit is lacking

# Framework for genomic analysis

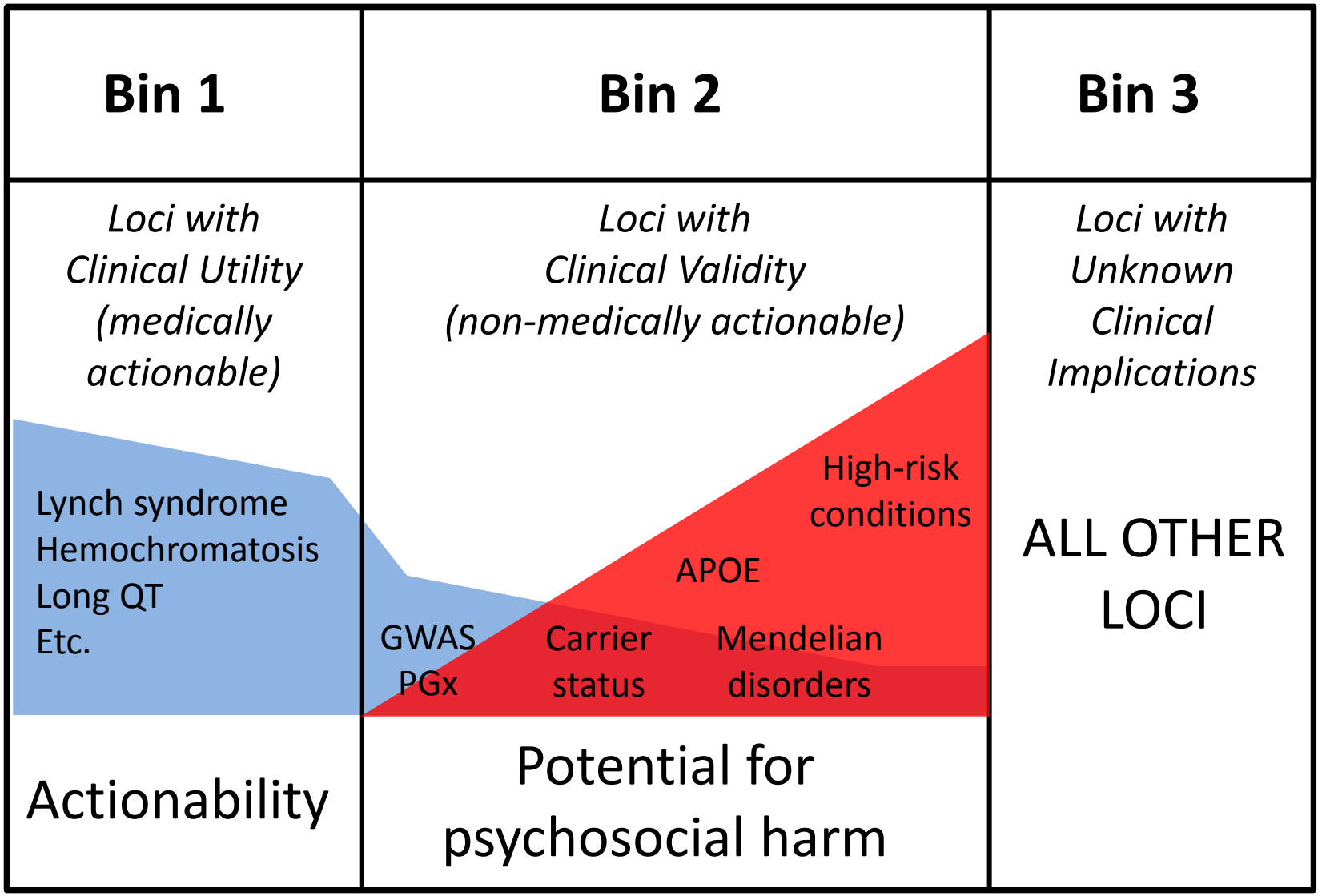
- An *a priori* structured framework for handling genomic findings
  - Avoiding “one-off” decisions that may not be consistent from one patient to the next
  - Organized around the concepts of clinical validity and clinical utility (“actionability”)
  - Intended to facilitate pre-test informed consent, analysis, and post-test return of results

# The “binning” process

- Step 1: Categorize **gene/phenotype pairs** into **“bins”** according to clinical actionability and risk for psychosocial harm
  - Assuming a pathogenic mutation and considering the most severe outcome
- Step 2: Define the types of variants that should be reported
  - **Known pathogenic**, likely pathogenic (?), ~~VUS~~, ~~likely benign~~, ~~benign~~ (setting a high threshold for return)
- Step 3: Sort the individual’s variants computationally into predetermined “bins”
  - Review/report only variants in binned genes, meeting defined criteria

# Clinical Actionability

- Requires technical and interpretive accuracy (analytic validity and clinical validity)
  - Findings with high specificity and thus high PPV
  - Hence the high threshold for reporting variants
- In the context of incidental findings or an asymptomatic individual, “actionability” implies that an intervention exists that can mitigate harm before a clinical diagnosis is made
  - And that such an intervention does not impose undue hazards to an individual


Bin 1
Bin 2
Bin 3
Loci with Clinical Utility (medically actionable)
Loci with Clinical Validity (non-medically actionable)
Loci with Unknown Clinical Implications
Lynch syndrome
Hemochromatosis
Long QT
Etc.
GWAS
PGx
Carrier status
APOE
Mendelian disorders
High-risk conditions
ALL OTHER LOCI
Actionability
Potential for psychosocial harm

# Locus-Variant Binning Committee

- Multidisciplinary team charged with defining the content of “Bin 1” for the NCGENES project
  - Medical geneticists (adult, pediatric)
  - Genetic counselors
  - Neurologist
  - Cardiologist
  - Generalist physician
  - Molecular lab
  - Bioethicist
  - IRB representative

# “Binning” by Consensus

- The challenge is determining which genes cross a threshold for “Bin 1”
  - Expert consensus-based methods inevitably result in a list that no one really likes
- Definitions of “actionability” will differ
- Specific decisions are sometimes inconsistent
- We saw a definite need for a transparent, reproducible, evidence-based method

# Elements of “actionability”

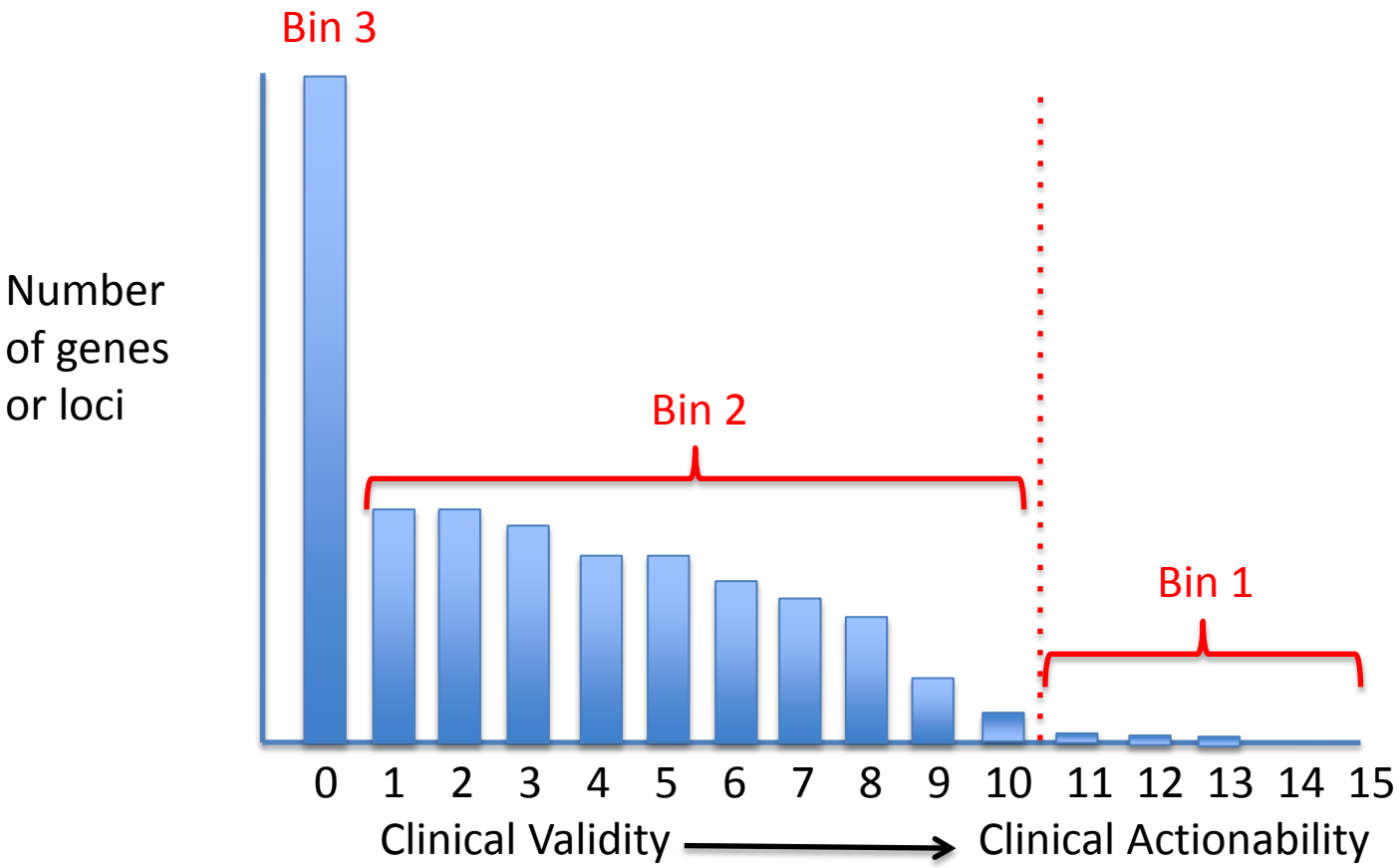
- Severity of disease
  - Typically the most severe possible outcome
- Likelihood of a severe outcome
  - Matched to the outcome of interest
- Effectiveness of intervention
  - To mitigate the severe outcome
- Acceptability of intervention
  - Encompassing the hazards of the intervention
- Knowledge-base
  - Including knowledge about the gene/phenotype association, disease manifestations, and interventions

# Semi-quantitative metric

| | |
|---|---|
| – Severity of disease | (0-3) |
| – Likelihood of a severe outcome | (0-3) |
| – Effectiveness of interventions | (0-3) |
| – Acceptability of interventions | (0-3) |
| – Knowledge base | (0-3) |
| | 0-15 |

These elements can be used to generate a semi-quantitative “clinical actionability” score for every gene-phenotype pair

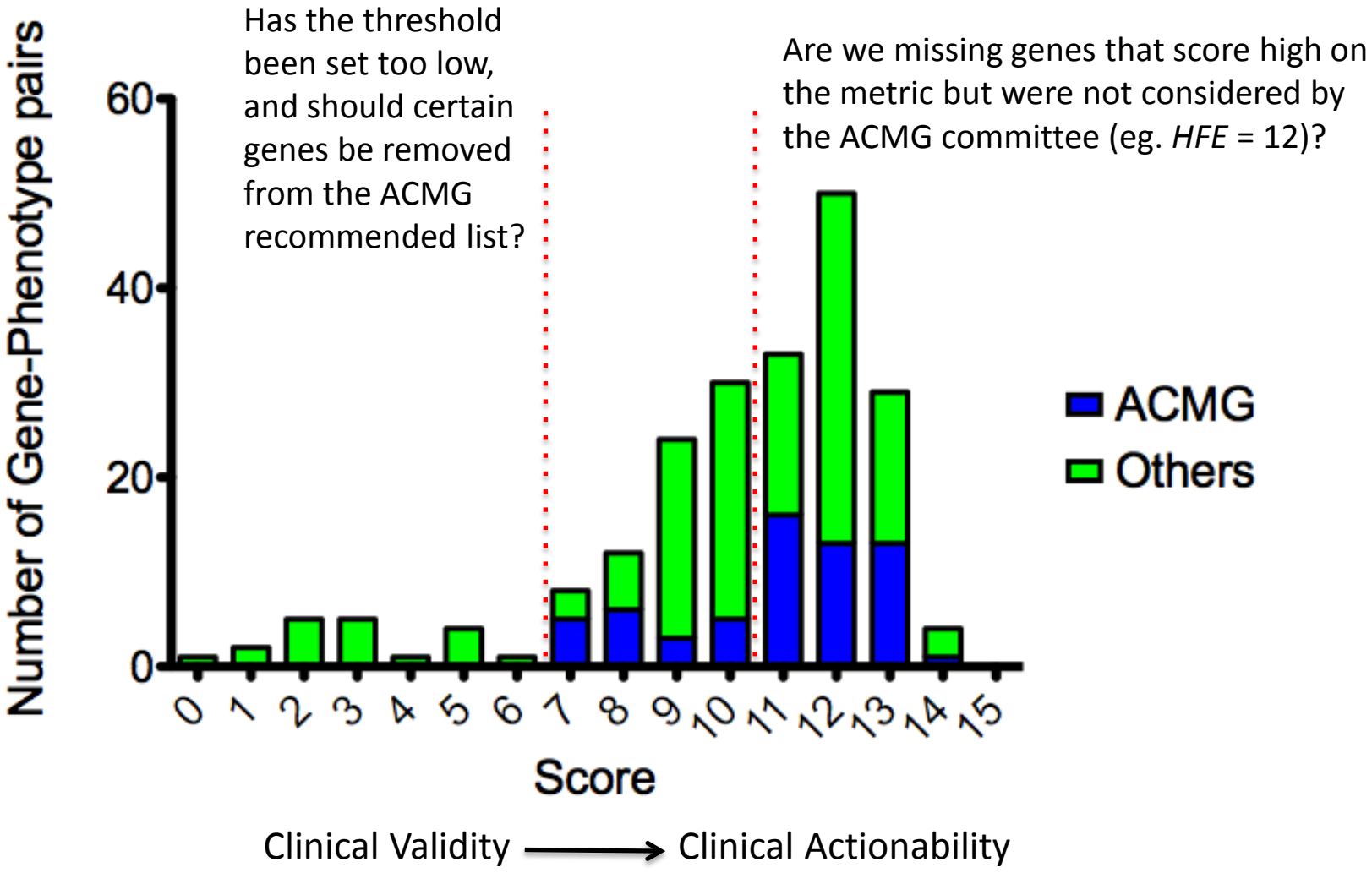
# Theoretical results



# Flexibility of a standardized score

- Setting thresholds = striking a balance
  - Benefit versus harm
  - Paternalism (duty to warn / do no harm) versus patient preference (right to know / not to know)
- Now being used in NC NEXUS, CEER, ClinGen
  - Could be useful in other efforts such as ACMG recommendations for return of incidental findings

# Application of the metric



# Advantages

- Transparent, less subjective than expert opinion
- Evidence base can be clearly defined
- Workload could be crowd-sourced (eg. ClinGen)
  - Analyze consistency/variability of scores
- Allows different end users to set thresholds
  - Can differentially weight parameters depending on the scenario (research, diagnostic testing, healthy adults, newborn screening, etc.)
- Scores can be revisited over time as new evidence accrues

# Acknowledgements


- Jim Evans
- NCGENES LVBC
  - Kate Foreman
  - Kristy Lee
  - Julianne O'Daniel
  - Cecile Skrzynia
  - Myra Roche
  - Dan Nelson
  - Brian Jensen
  - Cindy Powell
  - Karen Weck
  - Kirk Wilhelmsen

NHGRI

"NCGENES" CSER U01 HG006487-01

"NC NEXUS" NBS U19 HD077632-01

"ClinGen" CRVR U01 HG007437-01

"GeneScreen" CEER P50 HG004488-06

EGAPP Working Group