Report from Population Screening Working Group

Genomics & Population Health Action Collaborative Leadership Meeting
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Which Genes?

• Adhered to the principle of parsimony in medical/public health efforts that study real-world, generalizable implementation (i.e., don’t collect more information than you understand in this setting)

• Targeting optimal genes for population screening efforts conforms to basic principles of public health and clinical medicine
  • Pathogenic variants should confer risk of serious morbidity and/or mortality
  • Clinical penetrance should be high and well understood
    • Though penetrance in the setting of population screening is not well established for any genes outside of specific populations and (founder) mutations
  • Well-established, efficacious, specific, and acceptable interventions should be available for substantially mitigating risk
  • Established knowledge base regarding the gene and the condition(s) associated with P and LP variants in the gene

• Few genes meet these rigorous criteria
## Tier 1 and Tier 2 Genes

- Since criteria are qualitative, a degree of heterogeneity will prevail in different efforts to compile such lists.
- We pursued classification of “Tier 1/2” to allow for such heterogeneity.

### TIER 1
- Lynch syndrome-associated genes (e.g., \textit{MLH1, MSH2, MSH6, PMS2, EPCAM})
- Hereditary Breast & Ovarian Cancer-associated genes (\textit{BRCA1/2})
- Familial hypercholesterolemia (FH)-associated genes

### TIER 2
- Genes with unknown, variable or lower penetrance
- Highly efficacious interventions available
- Follow-up confirmatory tests available
- Examples may include: \textit{PALB2}, hereditary hemochromatosis, malignant hyperthermia, hypertrophic cardiomyopathy, Long QT syndrome, pharmacogenomic variants)

- In all cases, but especially for efforts involving Tier 2 genes, appropriate f/u should be pursued (e.g. clinical outcomes, efforts to assess actual penetrance)
- Access by those screened to professional advice/guidance is necessary
Specific Exclusions

- GWAS identified variants and risk-SNPs
  - Generally marginal RR
- Non-medical traits
  - Not within the purview of public health efforts
- Conditions associated with no, highly limited or non-specific interventions
  - Early onset Mendelian Alzheimer Disease, Huntington Disease, etc.
- Assessment of carrier status for AR disease
  - Although value for a subgroup (i.e. prospective parents) doesn’t have broad population-wide application
Reporting Variants

• Variants must be adjudicated by an experienced team with appropriate expertise, using the systematic process described by the ACMG document by Richards et al.

• Known Pathogenic and Likely Pathogenic variants were deemed most appropriate for return in screening efforts

• The WG advised against reporting VUS given the low prior probability of disease in the screened population (distinct from clinical/diagnostic settings)
Appropriate Settings for Screening Programs

- Not likely to be taken up by state NBS programs due to logistics, feasibility, resources, lack of consent, etc.
- May occur in the health-care delivery sector when evidence of utility is demonstrated
  - Cholesterol, BP, mammography, cervical cancer, CRC, etc.
- Integrated health systems
  - F/u “baked in” to the process
- University-affiliated healthcare/Research hospitals
  - Fragmentation of care is a challenge
- Self-insured employers
  - Interested in improving health of their employees
  - A “perk” for employees
- Military
  - A “captive” cohort
  - Not covered by GINA
- Interested public health agencies could play an important role
- We encourage all those pursuing such efforts to engage in ongoing assessment of outcomes, e.g.
  - Is screening ameliorating the impact of the screened conditions?
  - General public understanding & uptake
  - Unintended consequences of screening
  - Inclusion of diverse populations
Ethical Considerations

• Notions of “actionablity” vary
• Who should decide?
• Access to screening – and f/u care – varies widely, especially in the US
  • Determining high risk and need for intervention that is not accessible by the individual is highly problematic
• How to implement informing family and cascade testing?
• What gets returned?
  • It may not be appropriate or legal to withhold data from screening participants
    • Release of such data with poor ability to interpret its meaning could be highly problematic
    • A further argument for limited scope of analysis (targeting of selected genes)
Cost Effectiveness

• Exploring types of economic evaluations from different stakeholder perspectives (e.g., companies, health systems, government)
  • Budget impact analysis
  • Cost effectiveness analysis
  • Cost utility analysis

• What economic and health outcomes are important to measure? And over what time period?

• Where can economic data be stored and accessed?

• How can modeling help determine if a genomic screening program is cost effective?
Priorities for Next Phase

• Complete the paper; post to GPHAC website
• Short, executive summary style piece for peer-reviewed literature (?)
• Could take the form of well developed materials to assist implementation efforts, e.g.:
  • Sample consent
    • Likely online
  • Concretized “best practices” for such things as:
    • Collecting appropriate personal and Family Medical History at time of screening
      • Vital for proper interpretation of the ~98% of results that will be negative
      • Important for proper interpretation of positive results
        • Development/adaptation of tools to obtain necessary information
  • Exploration of ways of reaching diverse populations
• Continue priority of encouraging investigation of the penetrance of P/LP Variants in the public health setting
• Continue discussing pros and cons of targeted vs. genome scale sequencing for screening