CREATING A MEDICALLY ACTIONABLE GENETIC SCREENING PANEL FOR HEALTHY INDIVIDUALS

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Disclosure statement: All authors are employees and stockholders of Invitae Corporation
The emerging area of preventive genetics

- Rapidly growing interest in broad access to genetic information
  - Decreasing DNA sequencing costs make genetic information more accessible and push it further into mainstream healthcare
  - Healthy adults proactively seeking information to inform long term healthcare
  - Medically relevant information requested

- Expansion of medically relevant genetic tests to a broader audience should continue to involve healthcare providers
  - Genetic counselors are important stakeholders
  - Evaluation, education, and expectations
Genetic testing in healthy individuals

• Since the 2013 ACMG guidance, clinical WES and WGS have reported incidental findings in healthy individuals
  – Healthy parents from diagnostic trio analysis
  – Healthy WES/WGS available from some labs

• 1 in 20 to 1 in 50 of these individuals with no indication receive a medically important result
  – ACMG56
Access to genetic testing is increasing

- The cost of genetic testing is continuing to decrease
  - Lower cost increases access
  - WES, WGS, NGS-based gene panels

- How do you ensure that genetic information is provided in a medically responsible way?

- Does a 2-5% clinical yield justify offering testing broadly?
Developing a medically actionable panel

- A medically responsible test, provided with appropriate support
  - Provider-ordered test (not direct-to-consumer)
  - Critical to include genetic counseling
  - Educational materials for patients and HCPs

- Access to information that could potentially impact healthcare
  - Individuals interested in comprehensive healthcare, including genomics
  - Patients who actively engage with their HCP to guide their healthcare
  - Unknown or limited family history
Benefit of a panel-based approach

• Most of the data generated from WES/WGS is not interpretable or applicable for healthy individuals
  – Difficult to integrate meaningfully into routine healthcare
  – Focus should be on medically actionable findings

• Panel-based approach allows:
  – Diagnostic-grade evaluation of genes (no gaps, full coverage, del/dups)
  – Patient education for genes/conditions evaluated
  – Set expectations and counsel on possible results
Reporting of results in preventive testing

• Rigorous evaluation of detected variants following most recent ACMG guidelines

• Only return results that could have medical implications (no VUS)
  – In a healthy context, VUS are not reported because they are not actionable
  – Recommended by 2013 ACMG guidance on incidental findings

• Findings:
  – Positive results described in terms of increased risk for a disorder
  – Negative results are put into context of baseline population-level risk
Creating a medically actionable panel

- Team of clinical and medical geneticists, GCs, and PhD scientists

- Sources evaluated:
  - Gene lists published by multiple groups since ACMG 2013 guidance
  - Broader expansion of already represented clinical conditions
  - A few additional conditions

- Similar criteria for inclusion:
  - Penetrance, inheritance, management recommendations
Creating a medically actionable panel

- 124 genes, with the ACMG56 as the foundation

<table>
<thead>
<tr>
<th>Clinical area</th>
<th># of genes</th>
<th>Added genes</th>
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<tbody>
<tr>
<td>Cancer</td>
<td>24</td>
<td>ATM, BAP1, BMPR1A, BRIP1, CDC73, CDH1, CDK4, CDKN2A, CHEK2, DICER1, EPCAM, FH, FLCN, KIT, PDGFRA, MAX, MET, SDHA, TMEM127, PALB2, PRKAR1A, PTCH1, SMAD4, SMARCB1</td>
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<tr>
<td>Cardiovascular</td>
<td>38</td>
<td>ACTN2, ACVRL1, BAG3, BMPR2, CACNA1C, CACNB2, CASQ2, CAV1, CAV3, CRYAB, CSRP3, DES, DMD, ENG, EMD, F2, F5, F9, FHL1, GPD1L, HCN4, JUP, KCNE1, KCNE2, KCNJ2, LDLRAP1, PRKG1, PLN, PROC, PROS1, RBM20, SERPINC1, SGCD, SMAD4, TCAP, TGFB2, TGFB3, TNNC1, VCL,</td>
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<tr>
<td>Other</td>
<td>6</td>
<td>HAMP, HFE, HFE2, SLC40A1, SERPINA1, TFR2</td>
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New models in genetic counseling

- Transition from counseling on incidental findings to primary findings in healthy individuals
- Real and predicted increase in patient-driven requests for genetic information
  - Feel empowered to participate in their healthcare
  - Proactive, healthy patients focused on preventive care
- Shifting paradigm for genetic counseling and care
New models in genetic counseling

• Shifting paradigm will necessitate new and creative ways to approach genetic counseling

• Opportunities for genetic counseling
  – Education
    • Limitations and benefits of preventive genetic testing to determine risk for Mendelian disorders
    • Implications for healthy family members
  – Discussion of appropriate next steps for positive findings
    • Long term management for optimal health
Challenges of preventive genetic testing

• Identifying individuals appropriate for diagnostic versus preventive testing
  – Important to perform a family and personal history evaluation
  – Referrals from HCPs who have traditionally not utilized genetic testing

• Incomplete understanding of the penetrance of conditions in a healthy context
  – Clinical next steps with a positive finding need to be carefully considered
  – Guidelines and recommendations are based on literature from affected individuals and their families

• Testing of additional family members for a medically important variant identified
  – Family members with no manifestations, or subclinical phenotype
Thank you!

- Robert Nussbaum, MD
- Ed Esplin, MD, FACMG, FAAP
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- Britt Johnson, PhD, FACMG
- Stephanie Gandomi, MS, LCGC*
- Sienna Aguilar, MS, CGC
- Kate Lynch, MS, LCGC
- April Lynch

- Looking for GC interest to participate in an Advisory Board on Preventive Genetics
- Please see Eden

* Now at Blue Shield of CA