CREATING A MEDICALLY ACTIONABLE GENETIC SCREENING PANEL FOR HEALTHY INDIVIDUALS

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The emerging area of preventive genetics

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- 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

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- 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

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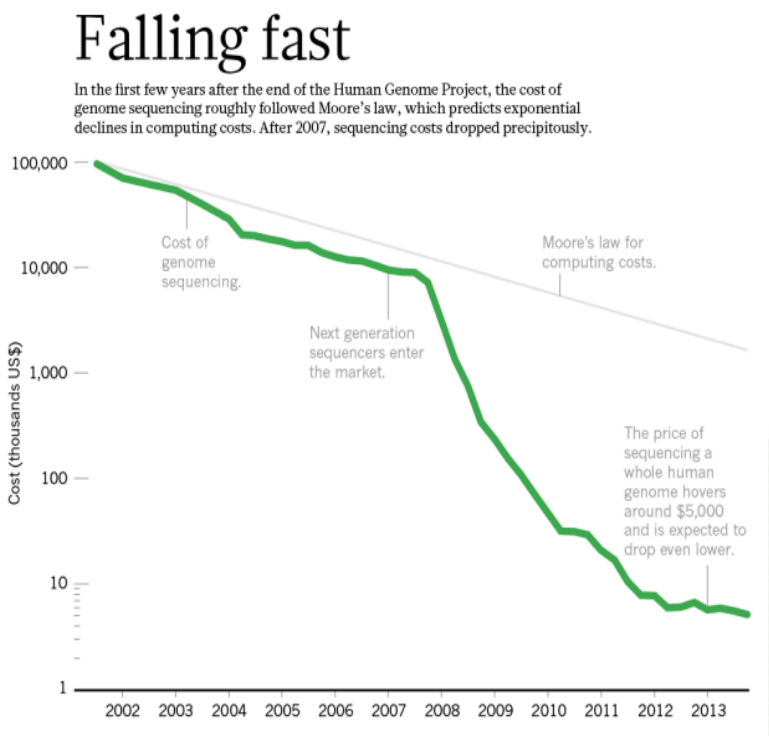
- The cost of genetic testing is continuing to decrease
  - Lower cost increases access
  - WES, WGS, NGS-based gene panels
- How do you ensure that genetic information is provided in a medically responsible way?
- Does a 2-5% clinical yield justify offering testing broadly?



Nature, March 2014

Developing a medically actionable panel

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- 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

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- 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

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- 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

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- 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

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- 124 genes, with the ACMG56 as the foundation

Clinical area	# of genes	Added genes
Cancer	24	ATM, BAP1, BMPR1A, BRIP1, CDC73, CDH1, CDK4, CDKN2A, CHEK2, DICER1, EPCAM, FH, FLCN, KIT, PDGFRA, MAX, MET, SDHA, TMEM127, PALB2, PRKAR1A, PTCH1, SMAD4, SMARCB1
Cardiovascular	38	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,
Other	6	HAMP, HFE, HFE2, SLC40A1, SERPINA1, TFR2

New models in genetic counseling

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- 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

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- 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

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- 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!

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- Robert Nussbaum, MD
- Ed Esplin, MD, FACMG, FAAP
- Swaroop Aradhya, PhD, FACMG
- 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

Thank you!

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