Inherited Cancer Genomics and Prevention:

How much cancer risk is inherited? Clinical utility of germline genetic testing in precision prevention and targeted therapy

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No conflicts to declare
The Heritability of Human Cancers As Measured By Unique Resources: the Scandinavian Twin Registry

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Heritable Fraction*</th>
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<tbody>
<tr>
<td></td>
<td>203,691 twin pairs</td>
</tr>
<tr>
<td>Stomach</td>
<td>0.22 (0-55)</td>
</tr>
<tr>
<td>Colon</td>
<td>0.15 (0-0.45)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>-</td>
</tr>
<tr>
<td>Lung</td>
<td>0.18 (0-0.42)</td>
</tr>
<tr>
<td>Breast</td>
<td>0.31 (0.11-0.51)</td>
</tr>
<tr>
<td>Cervix</td>
<td>-</td>
</tr>
<tr>
<td>Uterus</td>
<td>0.27 (0.11-0.43)</td>
</tr>
<tr>
<td>Ovary</td>
<td>0.39 (0.23-0.55)</td>
</tr>
<tr>
<td>Prostate</td>
<td>0.57 (0.51-0.53)</td>
</tr>
<tr>
<td>Bladder</td>
<td>0.30 (0-67)</td>
</tr>
<tr>
<td>Leukemia</td>
<td>0.57 (0-100)</td>
</tr>
</tbody>
</table>

*Heritable Fraction= proportion of cancers due to hereditary causes comparing monozygous and dizygous twins
Cancer Susceptibility Alleles 2018

- **BRCA1**
- **BRCA2**
- **MLH1**
- **MSH2**
- **CDH1**
- **CYP1A1**
- **CHEK2**
- **PALB2**
- **APC (I1307K)**
- **ATM**
- **CDKN2A**
- **JAK2**
- **STK11**
- **BLM (BLM^sh)**
- **BRIP1**
- **GSTM1**
- **KITLG**

**Population Frequency**

- **High Penetrance, Rare Cancer Predisposition Genes (Relative risk ≥ 5)**
  - **Very Rare (0.1%)**
  - **Common (40%)**

- **Low Penetrance, Common Risk Alleles* Single Nucleotide Polymorphisms (SNPs) (Relative risk < 1.5)**
  - Breast Cancer: 185 SNPs
  - Colon Cancer: 45+SNPs
  - Prostate Cancer: 170 SNPs
  - CLL: 41 SNPs

**Phenotypic Effect Size**

- **High-penetrance**
- **Low-penetrance**

*Low Penetrance, Common Risk Alleles*
Example of clinical Actionability:

Management of an Inherited Predisposition to Breast Cancer

Mark Robson, M.D., and Kenneth Offit, M.D., M.P.H.

Positive BRCA1 or BRCA2 test result

Identify at-risk adult relatives; offer genetic counseling/testing

Surgery

Increased surveillance

Chemo-prevention

Treatment PARP inhib

Mortality 70% (*)
Some Interventions for Hereditary Cancers Now Standard Of Care

<table>
<thead>
<tr>
<th>Tumor site (gene)</th>
<th>Intervention (surgery; drug)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GIST tumor (KIT)</td>
<td>imatinib</td>
</tr>
<tr>
<td>Thyroid (RET)</td>
<td>Thyroidectomy; vandetanib and cabozantinib</td>
</tr>
<tr>
<td>Colon (APC)</td>
<td>Colectomy (COX2 investigational)</td>
</tr>
<tr>
<td>Stomach (CDH1)</td>
<td>Gastrectomy</td>
</tr>
<tr>
<td>Kidney (STK11, VHL)</td>
<td>Screening; everolimus (mTOR)</td>
</tr>
<tr>
<td>Basal Cell (PTCH)</td>
<td>Screening vismodegib (Hedgehog)</td>
</tr>
<tr>
<td>Colon (MSH2)</td>
<td>Screening, Colectomy (PD-1 blockade, ASA)</td>
</tr>
<tr>
<td>Breast/Ovary (BRCA1/2)</td>
<td>Screening, Mastectomy, Hysterectomy (PARPi)</td>
</tr>
</tbody>
</table>
Targeting Prevention and Therapy in Lynch Syndrome

Lynch Syndrome

- CRC dx 45
- CRC dx 50s
- CRC dx 61
- CRC dx 75
- Ovarian Ca, dx 64
- CRC dx 42
- CRC dx 48
- CRC dx 52
- Endometrial Ca, dx 59
- 45
- CRC dx 42

Colonoscopy Start age 25

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

Stadler et al in press JCO

Distribution of MSI scores across tumor types

FDA News Release

FDA approves first cancer treatment for any solid tumor with a specific genetic feature

For Immediate Release: May 23, 2017

20% increase (progressive disease)

20% decrease (partial response)
Clinical actionability in newly discovered cancer susceptibility: reproductive and therapeutic aspects
SCREENING advanced cancer patients: 17.5% Actionable Germline Mutations

- 17.5% of patients have a clinically actionable mutation conferring cancer susceptibility
- 30-55% of these would not have been detected by clinical guidelines-directed testing, depending on case mix, ancestry and stage
- Results cascade to family

Mandelker et al., JAMA 2017;318(9):825-835; Lowery et al., JNCI, 2018 doi: 10.1093/jnci/djy024; Carlo et al., JAMA Oncol 2018 Sep 1;4(9):1228-1235
SCREENING at-risk populations: the BRCA Founder OutReach Study (BFOR):

- 3.5 M Ashkenazi Jews in U.S. >age 25 in U.S
- 90% not tested
- Pilot studies of AJ in London, Israel, Toronto
- Provide as medical test and involve MDs
- Pilot study 4,000 in NY, Phil, Boston, LA; half done
- Internet based, digital health platform: academic-commercial partnership; BFORstudy.com

Beth Karlan, Cedars Sinai; Judy Garber, DFCI; Nadine Tung, Beth Israel; Susan Domchek and Kate Nathanson, U.Penn, Ken Offit and Mark Robson, MSKCC
Direct to consumer genomics

• Is inherited cancer genomics like recreational genomics, or like recreational drug use?

• Empowerment vs exploitation?
  • Increasing access vs. commercial profiteering?

• De-medicalization and risk
  • false results
  • false reassurance
  • uncertain variants (“VUS”)
  • privacy

• Important role of federal government
  • NCI, NHGRI: ClinVar, ClinGEN
  • FDA

• Role of professional societies

• Role of the academy

Inherited Cancer Genomics and Prevention

- The burden of hereditary cancer is larger than initially thought, and depends on type, stage, and ancestry

- Hereditary cancers offer the opportunity for precision prevention as well as targeted therapy

- As such, testing for hereditary cancer is a medical and not a recreational endeavor

“As if we didn’t already know too much about ourselves, we’re having our DNA done.”