Multiple Paths to Genetic Counseling/Testing

- Family history triggers referral
- Cancer Diagnosis
  - Colon – Mismatch repair
  - Tumor sequencing/germline sequencing
- Pre-natal testing
- Direct-to-consumer
Estimated Cumulative Risks of Breast and Ovarian Cancer in Mutation Carriers

Kaplan-Meier estimates of cumulative risks of breast and ovarian cancers. In the breast cancer analysis, women were censored at risk-reducing bilateral mastectomy. In the ovarian cancer analysis, women were censored for risk-reducing salpingo-oophorectomy. Number at risk indicates the number of women who remained at risk at the end of the 10-year age category (e.g., in panel A, there were 138 women with BRCA1 mutations still at risk of breast cancer at the end of the age 50-60 years period). The earliest follow-up started at age 18 years.
# Cancer Risks in Individuals with Lynch Syndrome Age ≤70 Years Compared to the General Population

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>General Population Risk</th>
<th>Lynch Syndrome (MLH1 and MSH2 heterozygotes)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Risk</td>
</tr>
<tr>
<td>Colon</td>
<td>4.8%</td>
<td>52%-82%</td>
</tr>
<tr>
<td>Endometrium</td>
<td>2.7%</td>
<td>25%-60%</td>
</tr>
<tr>
<td>Stomach</td>
<td>&lt;1%</td>
<td>6%-13%</td>
</tr>
<tr>
<td>Ovary</td>
<td>1.4%</td>
<td>4%-12%</td>
</tr>
<tr>
<td>Hepatobiliary tract</td>
<td>&lt;1%</td>
<td>1.4%-4%</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>&lt;1%</td>
<td>1%-4%</td>
</tr>
<tr>
<td>Small bowel</td>
<td>&lt;1%</td>
<td>3%-6%</td>
</tr>
<tr>
<td>Brain/central nervous system</td>
<td>&lt;1%</td>
<td>1%-3%</td>
</tr>
<tr>
<td>Sebaceous neoplasms</td>
<td>&lt;1%</td>
<td>1%-9%</td>
</tr>
</tbody>
</table>

[https://www.ncbi.nlm.nih.gov/books/NBK1211/]
Test Results

Variant of Uncertain Significance (VUS)

Negative
- Likely Benign
- Unknown Significance

Positive
- Likely Pathogenic
RESULT: NEGATIVE - NO CLINICALLY SIGNIFICANT MUTATION IDENTIFIED

Note: “CLINICALLY SIGNIFICANT,” as defined in this report, is a genetic change that is associated with the potential to alter medical intervention.

<table>
<thead>
<tr>
<th>GENE</th>
<th>VARIANT(S) OF UNCERTAIN SIGNIFICANCE</th>
<th>INTERPRETATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLH1</td>
<td>c.xxxxy (p.xxxx) (aka xxyy)</td>
<td>UNCERTAIN CLINICAL SIGNIFICANCE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>There are currently insufficient data to determine if these variants cause increased cancer risk.</td>
</tr>
<tr>
<td>MSH2</td>
<td>c.xxxx (p.xxxx)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(aka xxxx)</td>
<td></td>
</tr>
</tbody>
</table>

Details About Non-Clinically Significant Variants: All individuals carry DNA changes (i.e., variants), and most variants do not increase an individual’s risk of cancer or other diseases. When identified, variants of uncertain significance (VUS) are reported. Likely benign variants (Favor Polymorphisms) and benign variants (Polymorphisms) are not reported and available data indicate that these variants most likely do not cause increased cancer risk. Present evidence does not suggest that non-clinically significant variant findings be used to modify patient medical management beyond what is indicated by the personal and family history and any other clinically significant findings.

Variant Classification: Myriad’s myVision™ Variant Classification Program performs ongoing evaluations of variant classifications. In certain cases, healthcare providers may be contacted for more clinical information or to arrange family testing to aid in variant classification. When new evidence about a variant is identified and determined to result in clinical significance and management change, that information will automatically be made available to the healthcare provider through an amended report.
Genomic Sequencing/Multi-Gene Panels

Variants of Uncertain Significance

Number of genes in panel
Results and Interpretation

- Informative – risk clarified
  - True negative – known familial mutation not inherited
  - True positive - known pathogenic/deleterious mutation – variable penetrance

- Uninformative – risk not clarified
  - Possibility of hereditary cancer cannot be ruled out
    - negative (unaffected and no known familial mutation; family consistent with hereditary cancer syndrome)
  - variants of uncertain clinical significance (VUS)
Sources of Uncertainty

- Incomplete Penetrance
  - Susceptibility (risk) ≠ Disease
- Variations in Penetrance
  - Modifier factors (genes/environment)
- Variants of Uncertain Significance
- Uninformative tests
The VUS Challenge

- Lacks adequacy of information to classify as disease-causing or normal variation
- Association with disease risk is unknown
- Limited clinical utility
- No evidence-based guidelines
- Patients and providers may over-interpret the meaning of result
NCCN Guidelines Version 2.2017
BRCA-Related Breast and/or Ovarian Cancer Syndrome

BRCA-RELATED FOLLOW-UP
BRCA testing criteria met

FAMILY STATUS
Deleterious familial BRCA1/BRCA2 mutation known
No known familial BRCA1/BRCA2 mutation

GENETIC TESTINGa
Recommend BRCA1/BRCA2 testing for specific familial mutation
Consider comprehensive BRCA1/BRCA2 testing of patient or if unaffected, test family member with highest likelihood of a mutation
Consider multi-gene testing, if appropriate

TEST OUTCOMEa
Positive for familial BRCA1/BRCA2 mutation
BRCA1/BRCA2 testing not performed
Negative for familial BRCA1/BRCA2 mutation
Mutation found
Not tested
No mutation found
Variant of unknown significance found (uninformative)

SCREENING RECOMMENDATION
See BRCA-Related Mutation-Positive Management (BRCA-A)
Cancer screening as per NCCN Screening Guidelines
See BRCA-Related Mutation-Positive Management (BRCA-A)
Offer research and individualized recommendations according to personal and family history

Note:
- a: Genetic testing includes both BRCA1 and BRCA2 testing.
- Mutations in BRCA1 and BRCA2 are associated with an increased risk of breast and ovarian cancer.
- BRCA1/BRCA2 testing is recommended for individuals with a family history of these cancers.

Resources:
Association between BRCA VUS Results and Surgical Decisions

• University of Washington Seattle: BRCA
  • 10.3% (11 of 107) of women with a BRCA VUS had risk-reducing mastectomy
  • 20.6% (22 of 107) had risk-reducing bilateral salpingo-oophorectomy

• City of Hope compared BRCA VUS results (n=71) with Uninformative results (n=714)
  • Similar risk reducing mastectomy (7%)
  • Risk-reducing oophorectomy 5%; 3%
  • More distress among those with VUS

Murray et al Genetic in Medicine 2011; 13:998-105
Culver et al Cin Genet 2013; 84:464-472
Lynch Syndrome: Patient Understanding of VUS

- Qualitative study of 28 individuals with a Lynch Syndrome VUS
  - “I’m just a waiting ticking time bomb for the cancers…”
  - “I would rather believe this is a positive interpretation so that way I could have a follow-up plan.”
  - “And getting my ovaries out – that was a hard decision….I want to live. Definitely safe vs sorry, absolutely.” (37 yo)
  - Pts expressed that ongoing or future contact from their providers would be appreciated, even if no new info
  - Emphasized the benefit from having a plan of action to reduce cancer risk in the face of uncertainty

Solomon et al J. Genet Counsel (2017) 26:866-877
Integrating into Clinical Practice

Toward clinical genomics in everyday medicine: perspectives and recommendations

Sarah Bowdin, MD,1,2, Adel Gilbert, MS3, Emma Bedoukian, MS3,4, Christopher Carew, MBA1, Margaret P. Adam, MD1, John Belmont, MD, PhD1,2, Barbara Bernhardt, MS1, Leslie Bieseker, MD1, Hans T. Bjornson, MD, PhD1,2,3, Miriam Blitzer, PhD1,2, Lisa C.A. D’Alessandro, MD4, Matthew A. Deardorf, MD, PhD1,2,3,4, Laurie Demmer, MD5, Alison Elliott, PhD6,7, Gerald L. Feldman, MD1,8, Ian A. Glass, MBChB8, MD8, Gail Herman, MD, PhD1,9, Lucia Hindorff, PhD1,9, Fuki Hisama, MD10,11, Louanne Hudgens, MD10,11, A. Michell Innes, MD10,11, Laird Jackson, MD10, Gail Jarvik, MD, PhD12, Raymond Kim, MD, PhD12, Bruce Kort, MD, PhD13, David H. Ledbetter, PhD13,3, Mindy Li, MD13, Eriksay Liston, MS13, Christian Marshall, PhD13, Livlja Medne, MS13, M. Stephen Meyn, MD, PhD14,2,3, Nasim Monfared, MSC2,3, Cynthia Morton, PhD15, John J. Mulvihill, MD16, Sharon E. Plon, MD, PhD17, Heidi Rehm, PhD18, Amy Roberts, MD18, Cheryl Shuman, MS19, Nancy B. Spinner, PhD19, D. James Stavropoulos, PhD19, Kathleen Valverde, MS20, Darrel J. Waggoner, MD20, Alisha Wilkens, MS20, Ronald D. Cohn, MD20,21, Ian D. Krantz, MD20,21,22.

Recommendations for the integration of genomics into clinical practice

The impact of whole-genome sequencing on the primary care and outcomes of healthy adult patients

The Geisinger MyCode Community Health Initiative: an electronic health record-linked biobank for Precision Medicine research

David J. Carey1, Samantha N. Fettersolf, F. Daniel Davis, William A. Fauccett, H. Lester Kirchner, Uyenlinh Mrshahi, Michael F. Murray, Diane T. Smelser, Glenn S. Gerhard, and David H. Ledbetter

Geisinger Health System, 100 N. Academy Avenue, Danville, PA 17822
Integral Role of Primary Care

- Ascertainment/counsel/refer – clinical utility
- Interpretation of results
- Communication (patient/family)
- Follow-up care
- Family care
- Helping patients coping with uncertainty
- Reclassification updates of VUS