Integrating Clinical Genomics and Cancer Care

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Objectives

1) Recognize indications for cancer genetic assessment and resources for genetic counseling/testing.

2) Enable providers to incorporate cancer genetics into Survivorship Care Plans.

3) Discuss the role of genomic testing/tumor genomic profiling in cancer care and risk assessment.
Healthy People 2020: Cancer Genomics

Goal #1: Increase the proportion of women with a family history of breast and/or ovarian cancer who receive genetic counseling.

Goal #2: Increase the proportion of persons with newly diagnosed colorectal cancer who receive genetic testing to identify Lynch syndrome.
Cancer Genetics Program

1. Standard of Care:
   - COC Standard 2.3 Genetic Counseling and Risk Assessment
   - COC Standard 3.3 Survivorship Care Plan

2. Complete Package of Services:
   - National Accreditation Program for Breast Centers
   - Hereditary GI cancer clinics

3. **Volume:** while only 10-15% of cancer patients are estimated to have an underlying gene mutation, in aggregate, this is a lot of cancer prevention and risk assessment.
Cancer risk assessment, genetic counseling, and testing services are provided to patients either on-site or by referral, by a qualified genetics professional.*

http://www.facs.org/cancer
Referral and Cancer Risk Assessment Guidelines

- ACOG (Obstet Gynecol) – 2009
- ASBS – 2006
- NCCN (www.nccn.org) – yearly
- NSGC/ACMG (J Genet Counsel) – 2014
- SGO (Gyne Oncol) – 2014
- USPSTF (Ann Intern Med) – 2014 (2nd update)

The guidelines are recognized in the Affordable Care Act and pts who meet these guidelines should qualify for cancer risk assessment and genetic testing (BRCA1/2) at no cost.
Genetic Testing: Key elements for a Cancer Family History

• First-degree relatives: siblings, parents, children
• Second-degree relatives: grandparents, aunts, uncles, grandchildren, nieces, nephews, half-siblings
• Both maternal and paternal sides
• Record ancestry/ethnicity
• For each cancer case in the family, establish:
  – Age at cancer diagnosis
  – Type of primary cancer (Distinguish primary vs. metastatic)
  – Age and cause of death, or current age if survivor.
• Results of any cancer predisposition testing in any relative.

Case illustration #1: Diagnostic Conundrum

- 30y/o woman with recent diagnosis of invasive ductal carcinoma of the R breast
- ER+, PR+, Her2-
- Detailed family history reveals no other individuals with breast cancer, however one maternal aunt with endometrial cancer in her 40s
- Could this be HBOC, Li-Fraumeni, or Cowden?

BRCA1/2  
p53  
PTEN
Significant clinical overlap for many Hereditary Cancer Syndromes

Endometrial cancer

Pancreatic cancer

Breast cancer

Lynch & colorectal cancer

Ovarian cancer

Gastric cancer
BRCA1/2 TESTING CRITERIA<sup>a,b</sup>
Meeting one or more of these criteria warrants further personalized risk assessment, genetic counseling, and often genetic testing and management. Testing of an individual without a cancer diagnosis should only be considered when an appropriate affected family member is unavailable for testing.

- Individual from a family with a known deleterious BRCA1/BRCA2 gene mutation
- Personal history of breast cancer<sup>b</sup> + one or more of the following:
  - Diagnosed ≤45 y
  - Diagnosed ≤50 y with:
    - An additional breast cancer primary<sup>c</sup>
    - ≥1 close blood relative with breast cancer at any age
    - ≥1 close relative with pancreatic cancer
    - ≥1 relative with prostate cancer (Gleason score ≥7)
    - An unknown or limited family history<sup>a</sup>
  - Diagnosed ≤60 y with:
    - Triple negative breast cancer
    - Diagnosed at any age with:
      - ≥2 close blood relatives with breast cancer, pancreatic cancer, or prostate cancer (Gleason score ≥7) at any age
      - ≥1 close blood relative with breast cancer diagnosed ≤50 y
      - ≥1 close blood relative with ovarian<sup>e</sup> carcinoma
      - A close male blood relative with breast cancer
    - For an individual of ethnicity associated with higher mutation frequency (e.g., Ashkenazi Jewish) no additional family history may be required<sup>f</sup>
- Personal history of ovarian<sup>e</sup> carcinoma
- Personal history of male breast cancer

- Personal history of prostate cancer (Gleason score ≥7) at any age with ≥1 close blood relative<sup>d</sup> with ovarian carcinoma at any age or breast cancer ≤50 y or two relatives with breast, pancreatic, or prostate cancer (Gleason score ≥7) at any age
- Personal history of pancreatic cancer at any age with ≥1 close blood relative<sup>d</sup> with ovarian carcinoma at any age or breast cancer ≤50 y or two relatives with breast, pancreatic cancer, or prostate cancer (Gleason score ≥7) at any age
- Personal history of pancreatic cancer and Ashkenazi Jewish ancestry
- BRCA1/2 mutation detected by tumor profiling in the absence of germline mutation analysis
- Family history only (significant limitations of interpreting test results for an unaffected individual should be discussed):
  - First- or second-degree blood relative<sup>d</sup> relative meeting any of the above criteria
  - Third-degree blood<sup>d</sup> relative who has breast cancer<sup>d</sup> and/or ovarian<sup>e</sup> carcinoma and who has ≥2 close blood relatives<sup>d</sup> with breast cancer (at least one with breast cancer ≤50 y) and/or ovarian<sup>d</sup> carcinoma

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BRCA testing criteria met

See Follow-up (BRCA-2)

If BRCA testing criteria not met, consider testing for other hereditary syndromes

If criteria for other hereditary syndromes not met, then cancer screening as per NCCN Screening Guidelines
Multigene Panel Testing

### Table 1: Multi-Gene Testing Definitions

<table>
<thead>
<tr>
<th>TERM</th>
<th>DEFINITION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multi-gene panel</td>
<td>Laboratory test that includes testing for mutations of more than one gene.</td>
</tr>
<tr>
<td>Syndrome-specific test</td>
<td>Panel that only tests for one syndrome (e.g., Lynch syndrome, polyposis).</td>
</tr>
<tr>
<td>Cancer-specific panel</td>
<td>Panel that tests for more than one gene associated with a specific type of cancer.</td>
</tr>
<tr>
<td>“Comprehensive” cancer panel</td>
<td>Panel that tests for more than one gene associated with multiple cancers or multiple cancer syndromes.</td>
</tr>
<tr>
<td>Actionable mutation</td>
<td>Mutation that results in a recommendation for a change in clinical management.</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Genetic test result indicating a sequence variant in a gene that is of uncertain significance. Variants are generally not clinically actionable, and most (but not all) are ultimately re-classified as benign.</td>
</tr>
</tbody>
</table>

### Table 2: Pros and Cons of Multi-Gene Testing for Hereditary Colorectal Syndromes

<table>
<thead>
<tr>
<th>PROS</th>
<th>CONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• More efficient testing when more than one gene may explain presentation and family history.</td>
<td>• Higher chance of identifying pathogenic mutations for which clinical management is uncertain. Estimates suggest that 3%–4% (Gastroenterology. 2015 Sep;149:604-13.e20; Clin Genet 2014: 86: 510–520) of mutations identified are not clearly clinically actionable, such as finding a mutation in a moderate-risk gene for which management is unclear.</td>
</tr>
<tr>
<td>• Higher chance of providing proband with possible explanation for cause of cancer.</td>
<td>• Higher chance of identifying variants of uncertain significance that are not actionable; reported rates of finding variants of uncertain significance range from 17%–38%.</td>
</tr>
<tr>
<td>• Competitive cost relative to sequentially testing single genes.</td>
<td>• Higher chance that patient will mistakenly receive overtreatment and overscreening if variants of uncertain significance or mutations for which clinical management is uncertain are incorrectly interpreted.</td>
</tr>
</tbody>
</table>
Case illustration: Panel Testing

- 30y/o woman with recent diagnosis of invasive ductal carcinoma of the R breast:
  - ER+, PR+, Her2
- Detailed family history reveals no other individuals with breast cancer, however one maternal aunt with endometrial cancer in her 40s

Test results:

<table>
<thead>
<tr>
<th>GENES TESTED (28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>APC, ATM, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, GREM1, MLH1, MSH2, MSH6, MUTYH, PALB2, PMS2, POLD1, POLE, PTEN, RAD51C, RAD51D, RET, SMAD4, STK11, TP53, VHL</td>
</tr>
</tbody>
</table>

RESULTS SUMMARY

**POSITIVE: INDIVIDUAL AT RISK FOR DISEASE**
BRCA1-related Hereditary Breast and/or Ovarian Cancer Syndrome
Inheritance: Autosomal Dominant

No known or potential disease-causing mutations were detected in any other gene tested. A complete list of all conditions tested can be found on page 6.

**NEXT STEPS**
Genetic counseling is recommended and testing is appropriate for at-risk family members.
Case illustration #2

- 47 y/o G1P1 female presents with complaints of pelvic pain, intermenstrual bleeding and a family history of ovarian cancer.
- She is worried about risk of BRCA mutation.
- Patient’s sister died of PE/DVT at age 39. Found at autopsy to have occult ovarian ca.
- Patient’s mother recently diagnoses with breast cancer at age 78.
- Endometrial Biopsy shows high-grade dysplasia
Case illustration #2

Society of Gynecologic Oncology

SGO recommends that all women diagnosed with epithelial ovarian, Fallopian tube, and peritoneal cancers should receive genetic counseling and consider genetic testing, even in the absence of a family history of cancer.

Adapted from SGO Clinical Practice Statement, October 2014

SGO recommends that women diagnosed with endometrial cancer should be assessed for Lynch syndrome. In addition, women with a family history of endometrial and colon cancer should pursue genetic counseling, regardless of whether they have been diagnosed with cancer.

Adapted from SGO Clinical Practice Statement, March 2014

RESULT: POSITIVE - 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>MUTATION</th>
<th>INTERPRETATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>PMS2</td>
<td>c.2500_2501delinsG (p. Met834Glyfs*17) Heterozygous</td>
<td>High Cancer Risk This patient has Lynch syndrome/Hereditary Non-Polyposis Colorectal Cancer (HNPCC).</td>
</tr>
</tbody>
</table>
NextGen Testing: What to test??

“Cast the net widely, test nearly anyone”

Pros
— No sure approach for excluding anyone
— Find more mutation carriers

Cons
— Difficult to interpret and develop management recommendations

“Test Selectively:”

Pros
— Higher penetrance families
— Easier to interpret and recommend management

Cons
— Missed mutations

Standard: test the relative with the highest mutation probability in the family → Reduces non-informative negative results
Variant of uncertain significance: Result Interpretation

- **No Mutation (Negative)**
  - Medical management based on personal and family history. Uncertain results do not influence recommendations for care.

- **VUS-Likely Benign**
  - Uncertain Significance (VUS)

- **VUS-Likely Pathogenic**
  - Medical management based on cancer risks linked with gene where mutation found.

- **Pathogenic (Positive)**
Clinical Illustration #3: Who to Test?

*If a mutation is found in an affected person, testing will be more informative for other family members.*

<table>
<thead>
<tr>
<th>Test Performed</th>
<th>Result</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>MLH1</em> sequencing, comprehensive rearrangement</td>
<td>No Mutation Detected</td>
<td>No Mutation Detected</td>
</tr>
<tr>
<td><em>MSH2</em> sequencing, comprehensive rearrangement</td>
<td>No Mutation Detected del exons 1-6</td>
<td>No Mutation Detected Deleterious</td>
</tr>
</tbody>
</table>

**Test Results and Interpretation**

**POSITIVE FOR A DELETERIOUS MUTATION**

**NO MUTATION DETECTED**

<table>
<thead>
<tr>
<th>Test Performed</th>
<th>Result</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>del exons 1-6 <em>MSH2</em></td>
<td>No Mutation Detected</td>
<td>No Mutation Detected</td>
</tr>
</tbody>
</table>
Multigene Panel Testing: Special Considerations

Insurance criteria and limitations
- NCCN Guidelines vs. Insurance Criteria (e.g. Medicare)
- Panel testing may not be covered (e.g. BCBS Federal, Cigna)
- Genetic counseling may be required (e.g. Cigna, United)
- Specific forms/documentation may be required (e.g. Aetna, Cigna)
- Modified medical management may be required (e.g. Aetna, United)
- Many labs perform preauthorization and appeals (*if submitted for insurance billing*)

Bottom Line: The field of cancer genetics and management guidelines for mutation carriers are continually evolving. NCCN guidelines are updated annually and in 2017, they have provided additional guidance for genes included on the panels.
Objectives

1) Be able to identify patients that need cancer genetic assessment and resources to enable counseling/testing.

2) Enable providers to incorporate cancer genetics into Survivorship Care Plans

3) Discuss role of genomic testing/tumor genomic profiling in cancer care and risk assessment.
COC Standard 3.3 Survivorship Care Plan

• The cancer committee develops and implements a process to disseminate a treatment summary and follow-up plan to patients who have completed cancer treatment.

• The process is monitored and evaluated annually by the cancer committee.
Survivorship Care Program

NCCN Guidelines Version 2.2017
Survivorship

SCREENING FOR SECOND CANCERS

- Subsequent malignant neoplasms may occur in survivors, due to genetic susceptibilities (e.g., cancer syndromes), shared etiologic exposures (e.g., smoking, environmental exposures), and mutagenic effects of cancer treatment.
- The overall cancer rate in survivors is higher than in the general population.
- Treatment-related secondary primary cancers vary with the type and intensity of anticancer treatment and are associated in particular with radiation and specific chemotherapeutic agents.
- Screening for second primary cancers should be a shared responsibility between primary and oncology care physicians (See the NCCN Guidelines for Detection, Prevention, and Risk Reduction Table of Contents).
- Evidence suggests that excess radiation exposure from CT imaging may be associated with an increased risk of developing a radiation-associated cancer. Use of radiologic studies to screen for recurrent cancer should be based on diagnosis and evidence that early detection of recurrence will improve cancer-related outcomes.
- Regular updating of family cancer history is recommended to reassess hereditary risk, based on recent family diagnoses and on any new evidence in the field of cancer genetics that expands the basis for assessing inherited risk.
- Referral to genetic risk assessment and/or testing should be considered for appropriate survivors to identify those with a potential increased risk for second malignancies based on genetic profile. Appropriate candidates include survivors with a cancer diagnosis at a young age or with multiple primary cancers.
- Management recommendations for patients with known germline mutations linked to an increased risk for cancer can be found in the following NCCN Guidelines:
  - NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian
  - NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal
  - NCCN Guidelines for Gastric Cancer

Sleep Disorder: "Are you having problems falling asleep, staying asleep, or waking up too early?"

Healthy Lifestyle: "Do you engage in regular physical activity or exercise, such as brisk walking, jogging, weight/resistance training, bicycling, swimming, etc.?”
Cancer in Adolescents and Young Adults (AYA)

- Survival rates continue to increase
- Challenges of AYA survivorship:
  - “Late effects”
  - Oncofertility
  - Secondary prevention of LT morbidity/mortality
  - Transitional care

1. ASCO recommends that cancer family history information be gathered and reassessed periodically in survivors.

2. Genetic services will play an important role in facilitating this process.

3. What are the barriers and is this realistic to implement in the oncology clinic?
Case Illustration: survivorship care

Test Results and Interpretation

NO MUTATION DETECTED

Test Performed
BRCA1 sequencing
5-site rearrangement panel
BRCA2 sequencing

Result
No Mutation Detected
No Mutation Detected
No Mutation Detected

Interpretation
No Mutation Detected
No Mutation Detected
No Mutation Detected

RESULT: POSITIVE - 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.

GENE
CHEK2

MUTATION
c.1100del (p.Thr367Metfs*15) Heterozygous

INTERPRETATION
High Cancer Risk
This patient has CHEK2-associated Cancer Risk.

DETAILS ABOUT: CHEK2 c.1100del (p.Thr367Metfs*15): NM_007194.3

Functional Significance: Deleterious - Abnormal Protein Production and/or Function
The heterozygous germline CHEK2 mutation c.1100del is predicted to result in the premature truncation of the CHEK2 protein at amino acid position 381 (p.Thr367Metfs*15).

Clinical Significance: High Cancer Risk
This mutation is associated with increased cancer risk and should be regarded as clinically significant.
Benefits of Updated Germline Genetic Testing

\[ BRCA1/2 \rightarrow \text{Colon cancer} \]

7% of patients tested for \textit{BRCA1/2} meet NCCN guidelines for hereditary colon cancer

\[ \text{Colon cancer} \rightarrow BRCA1/2 \]

30% of patients tested for hereditary colon cancer meet guidelines for \textit{BRCA1/2}

Survivorship Care and Genetic testing: The Process

- Work closely with Nurse Navigators in tumor boards
- Hereditary cancer registry
- Utilize standardized template from ASCO
- Document in EPIC/EHR workflow in the oncology clinic → generates reports of SCP’s for Cancer Committee review and accreditation
Barriers to Genetic Testing: Survivorship Care Plans

**Barriers**

1. Logistic concerns (i.e. insurance coverage of cost)
2. Emotional concerns and distress.
3. Time – competing life concerns (i.e. caregiving responsibilities for children or other family members)
4. Lack of Provider recommendation

**Resolution**

1. More affordable and many insurances do cover.
2. Genetic counseling services/GINA
3. Genetic services alternatives: by nurses or telehealth can provide testing/evaluation efficiently.
4. Be mindful & systematic.
Objectives

1) Be able to identify patients that need cancer genetic assessment and resources to enable counseling/testing.

2) Enable providers to incorporate cancer genetics into Survivorship Care Plans.

3) Discuss role of genomic testing/tumor genomic profiling in cancer care and risk assessment.
Precision Oncology: Tumor Profiling
# Genomic Tumor Profiling: The Clinical Impact

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatanib</td>
<td>BCR-ABL and C-KIT</td>
<td>CML, GIST, PH+/−ALL</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>ERBB2/HER2/neu</td>
<td>Breast cancer, gastric or GEJ junction cancers</td>
</tr>
<tr>
<td>Crizotinib</td>
<td>EML4-ALK ALK missense mutation</td>
<td>NSCLC</td>
</tr>
<tr>
<td>Vermurafinib</td>
<td>BRAF V600E</td>
<td>Melanoma</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>EGFR missense</td>
<td>Lung cancer</td>
</tr>
<tr>
<td>Vandetanib</td>
<td>RET missense</td>
<td>Medullary Thyroid Cancer</td>
</tr>
<tr>
<td><strong>Germline status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Everolimus</td>
<td>TSC1/TSC2 mutation</td>
<td>Subependymal giant cell astrocytoma; Angiomyolipoma</td>
</tr>
<tr>
<td>Olaparib</td>
<td>BRCA1/2 germline mutation</td>
<td>Ovarian Cancer (PARP inhibitor) Metastatic breast cancer</td>
</tr>
</tbody>
</table>

**Baylor Scott & White Health**

Page 30
Clinical illustration: 52 y/o male with colorectal cancer:

Genomic Tumor Profiling: The Process

- Fragmentation of genomic DNA
- Isolation of exons and addition of adaptors
- Target enrichment on chips by hybridization
- Sequencing

Cell Proliferation, 47, 391–395

Hovelson et al, Neoplasia Vol. 17, No. 4, 2015
Precision Oncology: Growing the Evidence-Base

• ALCHEMIST: Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trials
  – Lung Cancer Master Protocol (Lung-MAP)

• TAPUR Study: Targeted Agent and Profiling Utilization Registry
  – Sponsored by ASCO
  – Prospective trial that aims to evaluate the safety and efficacy of genomics targeted therapy.

• NCI-MPACT: Molecular Profiling-based Assignment of Cancer Therapy

• NCI-MATCH: Molecular Analysis for Therapy Choice

Credit: National Cancer Institute
Tumor Profiling Options:

**Tumor/ Normal Paired**

- Tumor sample is submitted with a constitutional sample
- Somatic and germline results can be distinguished
- Consenting for multiple types of results
- Increased cost and TAT

**Tumor Only**

- Tumor sample is submitted independently
- Somatic and germline results not distinguished
- Limited informed consent
- Decreased cost and TAT
Using Tumor Profiling Results to Identify High-Risk patients

Benefits

• Independent of family history
• Identification of specific mutation
• Broad range of genes

Limitations

• Majority of mutations are not germline
• Limited utility of allele frequency
• Necessary to confirm all mutations with germline sequencing
• Confusing for patients/families
Approach to Tumor Profiling results:

Review
- Tumor type
- Age at diagnosis
- Deleterious mutations & VUSs identified

Filter
- Deleterious mutation in hereditary gene based on tumor type
- Hyper-mutated result
- Founder mutation (CHEK2 c.1100del)

Follow-Up
- High-risk patients -> refer for genetic counseling
- Low-risk patients -> review fhx -> no fhx no additional follow-up
Where to find Cancer Genetic Services in Texas
Thank you!

Questions

Baylor Scott & White Health
Division of Genetics

Maria.Blazo@BSWHealth.org

Acknowledgments:
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Stephanie Thompson MS CGC
Kim Russette, RN

References:
http://www.nih.gov/precisionmedicine.gov
www.nsgc.org
http://www.cdc.gov/genomics

HealthyPeople.gov

American College of Surgeons
Inspiring Quality: Highest Standards, Better Outcomes
Variant Allele Frequency

• Traditional model of allele frequency assumes two copies of the genome
  – Definition differs from population genetics

• Tumor profiling uses ASCN
  – Allele-specific copy number (ASCN)
  – The copy number is based on the allele frequency percentage within a sample

Problems with VAF

- Tumor heterogeneity
- Pseudo genes (e.g. CHEK2, PMS2)
- Driver mutations
- Copy number variations (CNVs)

Moderate Risk Breast Cancer Genes

ATM
• autosomal recessive (2 mutations) condition = Ataxia Telangiectasia
• carriers (i.e., single mutation) 2-4 fold increase risk for breast cancer
• data indicating a genotype/phenotype correlation
• other cancers: colon, gastric, pancreatic

CHEK2
• ~2-3 fold increase risk for breast cancer (23-48% LTR)
• other cancers: male breast, colon, likely others

PALB2
• ~ 40-60% risk of breast cancer depending on age and family history (high risk?)
  – Antoniou et al. NEJM 371(6):497-506; 2014
• other cancers: likely ovarian, possibly others