Integration of Genomics in Cancer Care

Erika Maria Monteiro Santos, PhD, MS, RN
Quanetta T Edwards, PhD, FNPC, WHPc, FAANP
Milena Floria-Santos, PhD, MS, RN
Silvia Regina Rogatto, PhD
Maria Isabel Waddington Achatz, MD, PhD
Deborah J MacDonald, PhD, MS, RN, APNG
Purpose

- To introduce how genetics and genomics are integrated into cancer care from prevention to treatment
Topics

* Etiology of Cancer
* Cancer Risk Assessment
* Tumor Profiling
* Pharmacogenomics
* Targeted Cancer Therapy
Case Study

* Mr. J – 41 yrs of age, white, Northern European ancestry

* Biopsy: right-sided colon cancer; plus two adenomatous polyps

* No prior cancer history

* Medical history otherwise unremarkable
Case Study – Mr. J

Figure 1. Four-generation pedigree with significant family history of colon and uterine cancers, in the paternal lineage; suspect for Lynch syndrome (fictitious case).
Etiology of Cancer

- Hereditary
- Infection
- Chemical
- Radiation
Etiology of Cancer

Risk factors

- Radiation
  - UVB
  - Ionizing

- Chemical
  - Tobacco
  - Aflatoxin

- Biological
  - EBV
  - HPV

- Genetic Susceptibility
Etiology of Cancer

Classification of Tumors Due to Family History (FH)

- Hereditary
- Familial
- Sporadic
Etiology of Cancer

Classification of Tumors Due to Family History

75% of all cancers
Age of onset typically that expected for the type of cancer
Somatic (acquired) mutations in a specific tissue (e.g., breast, colon)
Etiology of Cancer

Classification of Tumors Due to Family History

Familial

10%-15% of all cancers
Same cancer type occurring at expected age in more than one close relative
Shared environmental + genomic influences
Hereditary Etiology of Cancer

5%-10 of all cancers
Earlier age at onset than usual
May or may not have FH of same cancer or other cancers associated with a cancer syndrome
Single gene mutation in the germline (egg or sperm)
Etiology of Cancer

Somatic mutations
- Occur in non-germline tissues
- Are not heritable

Germline mutations
- Present in egg or sperm
- Are heritable
- Cause cancer family syndromes

Somatic mutation (e.g., breast) → Non-heritable

Mutation in egg or sperm → All cells affected in offspring
Etiology of Cancer

How important is to recognize the difference among acquired and heritable genetic mutations?

Key to appropriate referral for further evaluation
Cancer Risk Assessment (CRA)

Objectives of CRA

- Define cancer risk
- Asses psychosocial and cultural implications of risk assessment
- Provide risk-based cancer screening and risk reduction strategies
- Identity individuals who may benefit from genetic testing
- Provide education, counseling to facilitate informed decision making

Objectives of CRA

Aiello-Laws, 2011; Weitzel et al. 2011
Cancer Risk Assessment

How to recognize individuals for CRA?

- Earlier age of cancer onset than expected
- Same type of cancer in two or more close relatives
- Two or more primary cancers in the same person
- Constelation of cancers characteristic of a hereditary syndrome
- Male breast cancer, ovarian cancer or medullary thyroid cancer cancer, at any age
- Previously identified cancer-associated mutation in the family
Figure 1. Four-generation pedigree with significant family history of colon and uterine cancers, in the paternal lineage; suspect for Lynch syndrome (fictitious case).
Evaluation of genomic, proteomic and epigenomic expression factors for cancer diagnosis, prognosis and therapeutics
Case Study – Mr. J

Immunochemistry – test for protein expression of 4 genes associated with colorectal cancer
Result: absence of MLH1 expression
Case Study – Mr. J

Other evidence of germline mutation: MSI testing
Result: MSI-H (MSI-High)

<table>
<thead>
<tr>
<th>Marker</th>
<th>N</th>
<th>T</th>
</tr>
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<tbody>
<tr>
<td>BAT26</td>
<td></td>
<td></td>
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<tr>
<td>BAT40</td>
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<td>BAT25</td>
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<td>BAT34c4</td>
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<td>D5S346</td>
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<td>T</td>
</tr>
<tr>
<td>MYCL</td>
<td></td>
<td>T</td>
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</tbody>
</table>

Symbols: N (Normal), T (Tumor)
Case Study – Mr. J

Construct modified nuclear pedigree: Invoke Amsterdam I/II or Bethesda Criteria
Include all maternal and paternal 1st and 2nd degree relatives.
Record all cancer occurrences.
Invoke cardinal principles of Lynch syndrome.
Must consider adoption, incomplete FH, denial/poor cooperation,
false paternity, low penetrance, Lynch syndrome-like (atypical) family.

Genetic counseling

MSI/IHC testing on CRC tissue block

MSI positive or loss of expression of IHC

MMR gene testing for MLH1, MSH2, MSH6

MMR positive

Genetic counseling and testing of consenting 1st and 2nd degree relatives

MMR positive relatives

Initiate high-risk screening program (See Part B)

MMR negative relatives

( cautionary )

Revert to general population screening

MSI negative

MSH6 excepted, a negative is a true negative

MMR testing negative or inconclusive → consider PMS2

Genetic counseling; retesting, research investigation for novel mechanisms

Lynch et al. (2006)
Case Study – Mr. J

Stop codon – exon 17 (c.1975C>T; p.Arg659*)
Tumor Profiling - Microarray

Normal cell

Isolate mRNAs

Make red and green fluorescent cDNAs

Add to DNA microarray

Cancer cell

Both red and green match

Only green matches

No matches

Only red matches

Scanned microarray
Figure 2  Forest plot of effect size and direction for the four SNPs associated with CRC. (a) rs961253. (b) rs4444235. (c) rs10411210. (d) rs9929218. Boxes denote allelic OR point estimates, their areas being proportional to the inverse variance weight of the estimate. Horizontal lines represent 95% CIs. The diamond (and broken line) represents the summary OR computed under a fixed-effects model, with the 95% CI given by its width. The unbroken vertical line is at the null value (OR = 1.0).
SNPs and Pharmacogenomics

Check
*P450 CYP2D6* gene

Patient A Treatment Plan
Targeted Therapy - Trastuzumab

Breast cancer patient

Growth factor

Herceptin blocks receptor

Growth slows
### Targeted Therapy

**Table 1. Selected Genetic Markers and Their Application in Cancer Treatment**

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Genetic marker</th>
<th>Description-application</th>
<th>Drug-implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>HER2 amplification</td>
<td>HER2-positive tumors indicates need for additional therapy.</td>
<td>Trastuzumab, lapatinib</td>
</tr>
<tr>
<td>Breast</td>
<td>OncotypeDx®</td>
<td>Microarray analysis of 21 genetic markers. Identifies if patients with early stage ER-positive, lymph node negative, Her2-negative tumors may benefit from adjuvant chemotherapy.</td>
<td>Chemotherapy evaluation</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>OncotypeDx®</td>
<td>Microarray analysis of 12 genetic markers. Identifies if patients with stage II disease may benefit from adjuvant chemotherapy.</td>
<td>Chemotherapy evaluation</td>
</tr>
<tr>
<td></td>
<td>KRAS mutation</td>
<td>Tumors with a KRAS mutation do not respond to treatment with EGFR monoclonal antibodies. KRAS status should be evaluated prior to treatment.</td>
<td>Cetuximab, panitumumab contraindicated</td>
</tr>
<tr>
<td></td>
<td>UGT1A1*28</td>
<td>Patients with a germline UGT1A1 variant are at risk for higher toxicity (especially neutropenia, diarrhea).</td>
<td>Irinotecan; consider dosage adjustment or alternate drug</td>
</tr>
<tr>
<td>Leukemia</td>
<td>BCR-ABL</td>
<td>Ph + CML; Ph + ALL. Presence of a BCR-ABL gene mutation indicates response to tyrosine kinase inhibitor therapy.</td>
<td>Imatinib, dasatinib, nilotinib</td>
</tr>
<tr>
<td>Non-small-cell lung cancer</td>
<td>EGFR mutation</td>
<td>EGFR mutation is associated with a better response to an EGFR-tyrosine-kinase inhibitor.</td>
<td>Erlotinib, gefitinib</td>
</tr>
<tr>
<td>Breast, ovarian</td>
<td>BRCA1/BRCA2 mutation</td>
<td>Patients with a germline BRCA gene mutation who have disease progression following initial therapy may respond to treatment with PARP inhibitors.</td>
<td>Olaparib, for example</td>
</tr>
<tr>
<td>Melanoma</td>
<td>BRAF V600E mutation</td>
<td>Tumors with this BRAF mutation are sensitive to a kinase inhibitor.</td>
<td>Vemurafenib indicated</td>
</tr>
</tbody>
</table>

*Note. ER = estrogen receptor; EGFR = epidermal growth factor receptor; Ph = Philadelphia chromosome; CML = chronic myelogenous leukemia; ALL = acute lymphoblastic leukemia; PARP = poly ADP ribose polymerase.*
Figure 1. Four-generation pedigree with significant family history of colon and uterine cancers, in the paternal lineage; suspect for Lynch syndrome (fictitious case).
Case Study – Mr. J

- MSI – Important to guiding treatment decision-making in early stage colon cancer
- IHC – Important to guiding genetic testing strategy
- Mutation detection – Important to guiding genetic counseling/testing for at-risk family members
Closing Remarks

* Genomic care is now central to the care of patients with cancer

* Nurses must be aware of developments in genomics and its impact in the cancer care continuum to help educate patients and support informed decision-making