New Frontiers of Cancer Genetics and Personalized Medicine

Winter Refresher Course for Family Medicine Providers
2/1/18

Michael P. Mullane, MD
Medical Director, Hereditary Cancer Prevention and Management Center
Attending, Oncology Precision Medicine Clinic
Aurora Cancer Care

Genomic Medicine in Oncology

- Hereditary Cancer Syndromes
  - Risk Assessment
  - Cancer Risk Management
  - Cancer Treatment (new)
- Somatic Tumor Testing
  - Personalized Treatment of Advanced Cancer
Disclosures

• I have no financial conflicts of interest.

Educational Objectives

• At the completion of this seminar, participants will be able to:
  • Identify patients appropriate for genetic cancer risk assessment
  • Describe a new model for genetic cancer risk management
  • Differentiate germline genetic testing from somatic tumor testing
  • Define genetic variant based treatment of advanced cancer “Oncology Precision Medicine”
RISK FACTORS for CANCER

- AGING
- ENVIRONMENTAL EXPOSURES
- FAMILY HISTORY
  - FAMILIAL
  - HEREDITARY (10-15%)
- HORMONAL/HOST FACTORS
- INFECTIOUS AGENTS
  - HPV, HBV
  - H. pylori
- MODIFIABLE RISK FACTORS
  - ACTIVITY
  - DIET
  - ALCOHOL
  - TOBACCO

SUSPECT HEREDITARY CANCER

- YOUNG AGE
- BILATERAL CANCERS
- MULTIPLE PRIMARY CANCERS
- CANCERS in MULTIPLE CLOSE RELATIVES
- MULTIPLE RARE CANCERS
- MALE BREAST CANCER
- CANCER and ASSOCIATED FINDINGS THAT FIT a SYNDROME
- LIMITED FAMILY STRUCTURE
- ADOPTION or UNKNOWN FH
- de novo MUTATIONS

Key Educational Point!
HEREDITARY CANCER IDENTIFICATION and RISK MANAGEMENT

- The most common model of medical management for hereditary cancer families.

"At-risk" relatives may also be tested, but all return to separate referring providers and may receive differing levels of care. This model increases the potential for mismanagement of individuals at the highest risks for cancer.

All follow-up is expected from the referring provider, regardless of his or her specialty.

Some patients fail to receive multi-organ based care.

Recent Changes in GCRA

May 2013

October 2013
COST of DNA SEQUENCING;
EFFECT of MASSIVELY PARALLEL TECHNOLOGY

MacConaill, LE JCO 2013; 31: 1815-1824
**KNOWN CANCER GENES: PENETRANCE versus FREQUENCY**

![Graph showing the distribution of penetrance and frequency of cancer genes.]

**Mission Statement:**

The purpose of the Aurora Hereditary Cancer Prevention and Management Center (HCPMC) is to provide continuity and coordination of care for patients and at-risk relatives with hereditary cancer conditions.
Coordination of Care for the Family

The Aurora HCPMC will provide:

✓ Multi-organ based care, coordinated by one organizing multidisciplinary clinic;
✓ Consistent risk assessment, medical management, management recommendations, and/or genetic testing to at-risk relatives;
✓ A forum for implementing the most current and appropriate medical management strategies, and coordinating research opportunities for hereditary cancer families.

WELL ESTABLISHED CANCER PREDISPOSITION SYNDROMES

- SYNDROME
  - HBOC
  - Li Fraumeni
  - Lynch
  - Cowden
  - PC/PGL
  - Hereditary Melanoma
  - Birt Hogg Dube
  - FAP
  - von Hippel-Lindau
  - Multiple Endocrine Neoplasia

- ASSOCIATED GENE(S)
  - BRCA1 and BRCA2
  - TP53
  - MLH1, MSH2, MSH6, PMS2
  - EPCAM
  - PTEN
  - SDHx
  - CDKN2A
  - FLCN
  - APC
  - VHL
  - MEN1, RET

Educational Point! Germline Testing Used to Identify Hereditary Cancer Predisposition Syndromes
HCPMC: TARGET POPULATION

- Complex hereditary cancer syndromes
  - Li Fraumeni
  - Lynch
  - Cowdens
  - GI Polyposis Syndromes (Peutz-Jeghers, FAP, MUTYH)
  - MEN
- Suspected hereditary cancer without an identified pathogenic germline genetic variant

HCPMC: TARGET POPULATION

- Common hereditary cancer syndromes with rare additional cancers or new management options
  - HBOC and pancreas or prostate cancer
  - HBOC and fertility preservation
- Recently discovered genes/syndromes with no or evolving management options
  - CHEK2
  - PALB2
  - ATM
Diagnosis = Panc
Diagnosis = Pr

Diagnosis = CRC

Diagnosis = C.".

Diagnosis = pr

Diagnosis = pr

Diagnosis = pr

Diagnosis = pr

Diagnosis = pr

Diagnosis = pr

Diagnosis = pr

Diagnosis = pr

Diagnosis = pr

Diagnosis = pr

Diagnosis = pr

Diagnosis = pr

+ MSH2: 2397del4
Lynch Syndrome

LYNCH SYNDROME MANAGEMENT

<table>
<thead>
<tr>
<th>Cancer</th>
<th>General Population Risk</th>
<th>Mutation Carrier Risk</th>
<th>Mean Age at Diagnosis</th>
<th>Management Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal</td>
<td>5.5%</td>
<td>40-80%</td>
<td>44-61 yrs.</td>
<td>Colonoscopy, ASA/NSAIDs, Risk Reducing Surgery</td>
</tr>
<tr>
<td>Endometrial</td>
<td>2.7%</td>
<td>25-60%</td>
<td>48-62</td>
<td>Screening, Risk Reducing Surgery</td>
</tr>
<tr>
<td>Ovary</td>
<td>1.6%</td>
<td>4-24%</td>
<td>42</td>
<td>Screening, Risk Reducing Surgery</td>
</tr>
<tr>
<td>Gastric</td>
<td>&lt;1%</td>
<td>1-13%</td>
<td>56</td>
<td>Screening EGD</td>
</tr>
<tr>
<td>Small Bowel</td>
<td>&lt;1%</td>
<td>3-6%</td>
<td>47-49</td>
<td>Screening EGD</td>
</tr>
</tbody>
</table>

Adapted from NCCN Guidelines, version 2.2015, 10/7/15
**LYNCH SYNDROME MANAGEMENT**

<table>
<thead>
<tr>
<th>Cancer</th>
<th>General Population Risk</th>
<th>Mutation Carrier Risk</th>
<th>Mean Age at Diagnosis</th>
<th>Management Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepato-Biliary</td>
<td>&lt;1%</td>
<td>1-4%</td>
<td>50-57</td>
<td>? (CT or MR imaging)</td>
</tr>
<tr>
<td>Urothelial</td>
<td>&lt;1%</td>
<td>1-4%</td>
<td>54-60</td>
<td>Annual urine cytology</td>
</tr>
<tr>
<td>Brain/CNS</td>
<td>&lt;1%</td>
<td>1-3%</td>
<td>50</td>
<td>?</td>
</tr>
<tr>
<td>Pancreas</td>
<td>&lt;1%</td>
<td>1-6%</td>
<td>NR</td>
<td>? (EUS or MRI or alternate) CAPS criteria</td>
</tr>
</tbody>
</table>

Adapted from NCCN Guidelines, version 2.2015, 10/7/15

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**HCPMC MANAGEMENT OPTIONS**

- **HIGH RISK SCREENING-PRIMARY/SECONDARY**
- **TYPICALLY LESS INVASIVE**
- **USUALLY DOES NOT DECREASE RISK of CANCER**
- **EXAMPLES**
  - High risk breast cancer screening with PBE q. 6m, annual MRI, and annual mammogram (BRCA1, BRCA2, TP53, PTEN, CDH1, ATM, PALB2, CHEK2, STK11)
  - Colonoscopy q. 1-2 years (Lynch syndrome: MLH1, MSH2, MSH6, PMS2, EPCAM)
  - Biochemical screening and imaging (MEN1, RET, SDHx, MAX)
HCPMC MANAGEMENT OPTIONS

• HIGH RISK SCREENING-PRIMARY/SECONDARY
  • EXAMPLES
    • Renal Imaging-typically MRI (VHL, MET, FLCN, FH, SDHx, PTEN, TSC1/2)
    • Dermatologic exam (PTCH, CDKN2A, CDK4)
  • EXAMPLES of QUESTIONABLE EFFICACY
    • Pancreatic imaging (EUS, MRI or both)
    • Ovarian cancer screening

HCPMC MANAGEMENT OPTIONS

• RISK REDUCING SURGERY
  • REDUCES RISK of CANCER
  • SIGNIFICANT CLINICAL IMPACT
    • EXAMPLES
      • BILATERAL MASTECTOMY (BRCA1, BRCA2, PTEN, CDH1, TP53)
      • BILATERAL SALPINGOOIPHERECTOMY (BRCA1, BRCA2, Lynch syndrome)
      • COLECTOMY (Lynch syndrome, polyposis syndromes)
      • THYROIDECTOMY (MEN2 high risk RET mutations)
      • HystereCTOMY (Lynch syndrome)
      • GASTRECTOMY (CDH1)
HCPMC MANAGEMENT OPTIONS

• CHEMOPREVENTION
  • REDUCES RISK or DELAYS DEVELOPMENT of CANCER
  • EXAMPLES
    • Selective Estrogen Receptor Modulators or Aromatase Inhibitors to reduce risk of breast cancer
    • OCP to reduce risk of ovarian cancer
    • ASA/NSAID to reduce risk of CRC
HCPMC: GCR MANAGEMENT

- Multidisciplinary/multicancer risk management of patients and family members with established genetic cancer syndromes
- Develop and update management guidelines for newly described syndromes
- Develop and update management guidelines based on empiric risk estimates for families with an apparent genetic cancer syndrome without an identified mutation
- Adapt management guidelines to genotype-phenotype correlations, risk modifiers and patient specific factors

Precision Medicine-Oncology

Somatic Tumor Testing

- What is precision medicine
- NIH US precision medicine initiative
- Precision medicine-oncology
- Precision medicine-tumor testing
  - Hot spot (prognostic factor versus predictive factor)
  - Multi gene panel (Foundation One)
    - Druggable target
    - Candidate for immunotherapy
    - Germline implications
    - Pharmacogenomics
- Precision medicine in oncology-a clinic

Educational Point!-Somatic Tumor Testing
Used to Identify Targeted Treatment Options
Precision Medicine

- Using a patient’s individual genetic, epigenetic, lifestyle and environmental factors to:
  - Identify a predisposition to a health problem
  - Make a specific diagnosis
  - Individualized prognosis
  - Individualized treatment

Precision Medicine is not new in oncology

- Lifestyle
  - Tobacco, Diet/BMI, EtOH, IVDA/viral, sun exposure, exercise
- Environment
  - Occupation, pollution, hormonal
- Genetic
  - Hereditary cancer risk assessment
  - mutEGFR: lung and colon Ca
- Epigenetic
  - BRAF promoter methylation

Predisposition to disease
- Tobacco-> lung cancer
- Cirrhosis-> HCC
- Asbestos-> mesothelioma
- BRCA1/2-> HBOC

Specific diagnosis
- t(9;22) BCR-ABL=CML

Prognostic factors
- HPV and H&N Ca

Tailored treatment
- ER/PR, Her2, BRCA1/2
- EGFR/ALK/ROS1
- MSI-H-> Immunotherapy
- Imatinib (Gleevec) for CML
**OPM: Driver Mutation**

10/31/14

Pathology: Adenocarcinoma. EGFR mutational studies: positive for heterozygous in frame deletion in exon 19 (c.2236_2250del15)

1/22/15  Treatment with Erlotinib

**OPM: Clonal Evolution**

8/17/16  Progression on Erlotinib

10/17/16  Treatment with Osimertinib

Pathology: Adenocarcinoma. EGFR mutational studies positive for heterozygous in frame deletion in exon 19 (c.2236_2250del15) as originally identified and a second mutation (heterozygous point mutation) in exon 20 (p.T790M)
OPM: Somatic Tumor Testing - Treatment Options for Advanced Disease

- Level A
  - FDA approved targeted therapy
  - FDA approved histology-agnostic immunotherapy
- Level B
  - Histology specific targeted therapy based on RCT or consensus guidelines
- Level C
  - FDA approved targeted therapy in another tumor type
  - Candidate for variant based clinical trial
- Level D
  - Targeted therapy based on pre-clinical data or case reports

Educational Point! Variant based targeted therapy

OPM: Variant based Clinical Trial Design

- Histology Specific “Umbrella Design”
  - ALCHEMIST
  - LUNG-MAP
  - BEAT-AML
- Histology Agnostic “Basket Design”
  - TAPUR
  - MATCH
  - MPACT
  - Novartis Signature
Case: Stage IV Uterine LMS

- 46 year old female patient
  - Diagnosed August 2015
  - Multiple surgeries
  - 4 lines of chemotherapy
  - Palliative XRT
  - Precision Medicine: FoundationOne testing, MTB discussion and acquisition of rucaparib (PARP inhibitor) for BRCA2 loss

8/15/17 10/12/17

Thanks Pamela Vanderwall, MD for images
Case: Stage IV Uterine LMS

8/15/17

10/12/17

Thanks Pamela Vanderwall, MD for images

Somatic Tumor Testing-Germline Implications

Patient ID: [Redacted]

Tumor Type: Breast Carcinoma (HER2+)

Somatic Alterations:
- TP53
- PIK3CA

Germline Alterations:
- BRCA1
- BRCA2

Therapeutic Implications:

- Palbociclib (CDK4/6 inhibitor)
- Olaparib (PARP inhibitor)

Note: Germline alterations detected may be associated with family history of breast cancer, but also known to occur in patients with breast cancer of unknown origin. Identifiers are presented in order of potential clinical utility for the patient.
Somatic Tumor Testing-Germline Implications

Genomic Medicine in Oncology

Conclusions

- Hereditary Cancer Predisposition Syndromes
  - Molecularly defined by germline variants
  - Cascade testing to identify at-risk family members
  - Multi-cancer risk management
    - Primary/secondary screening for early detection of cancer
    - Risk reducing surgery
    - Prevention: chemoprevention and lifestyle
  - Family planning
  - Treatment of advanced disease
    - PARPi for HRD deficient cancers (BRCA1/2, PALB2, etc.)
    - Immunotherapy for MMR deficient cancers (Lynch syndrome)
Genomic Medicine in Oncology

Conclusions

• Oncology Precision Medicine/Molecular Tumor Board
  • Targeted treatment of advanced disease based on somatic tumor testing
• New clinical trial designs
  • Umbrella trials: Histology restricted variant based
  • Basket trials: Histology agnostic variant based
• Much hype but limited benefit thus far
• Germline implications

Aurora Health Care
Genomic and Precision Medicine Programs

• Manager
  • Deborah Wham, MS, CGC
• Genetic Counselors
  • Nicole Stiles Gill, MS, CGC
    • Melissa Sepko West, MS, CGC
    • Amy Mach Schoenbeck, MS, CGC
    • Kara Schoeffel, MS, CGC
    • Amanda Lasidhe, MS, CGC
    • Kate Strauer, MS, CGC
    • Eric Manthot, MS, CGC
    • Laura McFarlane, MS, CGC
    • Scott Weissman, MS, CGC
• Support staff
  • Angie Stadl, Admin Axt
  • Kim Jacques, Admin Axt

• Hereditary Cancer Prevention and Management Center
  • Deborah Wham, MS, CGC
  • Manager, Genomic Medicine
• Brenda Ramezyk, RN, BSN, OCN
  • Cancer Services Program Coordinator
• Kara Schoeffel, MS, CGC
  • Genetic Counselor
• Aurora Oncology Precision Medicine
  • Michael Thompson, MD, PhD
    • Co-Director
    • Jennifer Gorden, Pharm D
      • Co-Director
    • Antony Ruggeri, MD
      • Medical Oncologist
    • Michael Mulane, MD
      • Medical Oncologist
    • Amanda Wilson, MD
      • Pathologist
    • Brenda Ramezyk, RN, OCN
      • Cancer Services Program Coordinator
    • Deborah Wham, MS, CGC
      • Manager, Genomic Medicine
    • Scott Weissman, MS, CGC
      • Genetic Counselor
    • Angi Kraut, RN, BSN, OCN
      • Research Coordinator
    • James Weese, MD, FACS
      • Vice-President, Aurora Cancer Care