Update: Integrating Genetic and Genomic Medicine Processes for Systematic Identification of Heritable Neoplasias

Charis Eng, MD, PhD
On Behalf of the Cancer Team

NHGRI Genomic Medicine Colloquium, Dallas, TX, Jan. 28-29, 2013
Some Topics Considered by the Cancer Team (GM II & III)

• Universal MSI Analysis and Mismatch Repair Protein IHC for Lynch Syndrome Screening for All Resected Colorectal Cancers on Main Campus (Update from 1 Experienced and 1 Naïve Site)

• Implementation of MSI Analysis and Mismatch Repair Protein IHC for Lynch Syndrome Screening for All Endometrial Cancers on Main Campus

• Systematic Standardized Screening for Heritable Pheochromocytoma and Paraganglioma

• Somatic Genomics

3-Year Experience on Uptake of a Prototype Cancer Family History Tool
Update: Universal Screening of All Colorectal Cancers for Lynch Syndrome

Charis Eng, MD, PhD
Cleveland Clinic

Katherine L. Nathanson, MD
University of Pennsylvania
Quickie Reminder re Lynch Syndrome

• Most Common Adult-Onset Inherited Colorectal Cancer (CRC) Syndrome
  – Autosomal Dominant Inheritance
  – Caused by Germline Mutations in Mismatch Repair Genes (MMR)
  – High Risk of Colorectal, Endometrial and Other Cancers
  – Lynch Syndrome Diagnosed in 3-5% of all CRC Presentations

• Cellular Phenotype of Lynch-CRC
  – Microsatellite Instability (MSI)
  – MMR Protein Null (IHC detectable)

• Making Lynch Dx Changes Management for Patient and Mutation Positive Family Members

• Would Meet One of 2 Genomics Agenda Items of Healthy People 2020
Cleveland Clinic Clinical Workflow for Screening All CRC for Lynch Syndrome (2004.1-2007.7) = Approach 1

Colorectal Surgery and High Risk Gastroenterology

Resected Colorectal CA

Pathology Workflow

MSI-High or MMR-IHC Null?

Yes

MSI/IHC Status Noted in Pathology Report

Colorectal Surgeon Calls Patient to Refer to Genetics Clinics

Patient Comes to Genetics Clinic, Receives Counseling

No

Not HNPCC

Consider Not Using 5FU

Genomic Medicine Institute
Digestive Diseases Institute
Pathology/Lab Med Institute
1108 colorectal cancers

Approach 1

Abnormal MSI/IHC

52/237 (22%)

Presumed sporadic

21/38 (55%)

Referred for GC

12/38 (32%)

Underwent GC

10/38 (26%)

Pursued GT

3/38 (8%)

Positive GT

GC = Genetic Counseling
GT = Genetic Testing

Heald et al. *J Clin Oncol*, in press
Cleveland Clinic Clinical Workflow for Screening All CRC for Lynch Syndrome (2007.8-2008.7) = Approach 2

Colorectal Surgery and High Risk Gastroenterology

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Resected Colorectal CA

Pathology Workflow

MSI-High or MMR-IHC Null?

Not HNPCC

Consider Not Using 5FU

Yes

No

MSI/IHC Status Noted in Pathology Report

Patient Comes to Genetics Clinic, Receives Counseling

Colorectal Surgeon Calls Patient to Refer to Genetics Clinics

GC Notifies Colorectal Surgeon of MSI/IHC Results
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Approach 1

- Abnormal MSI/IHC: 52/237 (22%)
- Presumed sporadic: 14
  - Referred for GC: 21/38 (55%)
    - Underwent GC: 12/38 (32%)
      - Pursued GT: 10/38 (26%)
        - Positive GT: 3/38 (8%)

Approach 2

- Abnormal MSI/IHC: 17/87 (20%)
- Positive GT: 6
  - Underwent GC: 7/11 (64%)
    - Pursued GT: 5/11 (45%)
      - Presumed sporadic: 1/11 (9%)

GC = Genetic Counseling
GT = Genetic Testing

Heald et al. *J Clin Oncol*, in press
Cleveland Clinic Clinical Workflow for Screening All CRC for Lynch Syndrome (2008.7-onwards) = Approach 3

Colorectal Surgery and High Risk Gastroenterology

Resected Colorectal CA

Pathology Workflow

- **MSI-High or MMR-IHC Null?**
  - Yes
    - **MLH1-IHC Null?**
      - Yes
        - Consider Not Using 5FU
      - No
        - **BRAF Analysis**
          - Yes
            - **MLH1 Methylation**
              - Not Somatic Methylation
              - Germline Single Gene Testing
              - Patient Comes to Genetics Clinic, Receives Counseling
          - No
            - Not HNPCC
            - Genomic Med Inst Genetic Counselor (GC) Scans List
            - GC Calls Patient to Invite Patient in to Cancer Genetics Clinic
1108 colorectal cancers

**Approach 1**
- Abnormal MSI/IHC: 52/237 (22%)
  - Presumed sporadic: 21/38 (55%)
    - Referred for GC: 12/38 (32%)
      - Underwent GC: 10/38 (26%)
        - Pursued GT: 3/38 (8%)

**Approach 2**
- Positive GT: 17/87 (20%)
  - Presumed sporadic: 9/11 (82%)
    - Underwent GC: 7/11 (64%)
      - Consented GT: 5/11 (45%)

**Approach 3**
- Positive GT: 109/784 (14%)
  - Presumed sporadic: 109/784 (14%)
    - Underwent GC: 6 (6%)
      - Consented GT: 53 (71%)

**Approach 1**
- Abnormal MSI/IHC: 52/237 (22%)
  - Presumed sporadic: 21/38 (55%)
    - Referred for GC: 12/38 (32%)
      - Underwent GC: 10/38 (26%)
        - Pursued GT: 3/38 (8%)

**Approach 2**
- Positive GT: 17/87 (20%)
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- Positive GT: 109/784 (14%)
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**Heald et al. J Clin Oncol, in press**
GC = Genetic Counseling
GT = Genetic Testing
Penn Med Update (and Challenges) on Adopting Universal Lynch Screening

• [In Process ....]
Quickie Reminder re Importance of Spotting Heritable Pheochromocytoma & Paraganglioma

- PCC/PGL Uncommon Neuroendocrine Tumours (NET)
- Can be Malignant or Not
- Can be in Inconvenient (Organ-Threatening) Spots
- Hormonally Active Ones -> Sudden Death, Hypertension, Stroke, etc
- 30-40% of All Comers Germline Mutations in ~10 Known Genes
- Gene-Specific Risks and Management
- Genotype-Clinical Outcome Association
- Actionable
- No Practice Guidelines
Out of GMII and III Came:
“Systematic EMR-based ascertainment, genomic screening and clinical management of PC/PGL”

- **Four Primary Health Systems:**
  - Cleveland Clinic Health System
    - Charis Eng, MD, PhD
    - Clinical Cancer Geneticist and Medical Oncologist
    - Co-Leader, European-American PC/PGL Registry and Work Group
  - Medical College of Wisconsin
    - David Dimmock, MD
    - Clinical Geneticist
  - Northwestern University Health System
    - Peter Kopp, MD, PhD
    - Endocrinologist
  - University of Pennsylvania Health System
    - Katherine L. Nathanson, MD
    - Internist and Medical Geneticist
    - Director, PennNET
    - Co-Chair, TCGA PC/PGL Project
Objectives

• **Aim 1: To develop a systematic approach for ascertaining all PC and PGL patients for clinical genetics evaluation**
  – Construct and implement an EMR alert to remind clinicians that referral to genetics is indicated
  – Measure improvements in ascertainment/referral using EMR searches
  – Provide genetics education and clinical decision support for physicians involved in the care of PC and PGL patients
  – Query pathology and billing reports for PC/PGL on a regular basis for quality control

• **Aim 2: To determine the most impactful genetic testing strategy for the patient with an apparently non-syndromic high-risk PC/PGL**
  – Track yield (frequency of finding mutation) and costs for patients tested with traditional single-gene, tiered genetic testing versus whole exome sequencing
  – Compare effectiveness of single-gene tiered testing with panels
  – Offer whole exome sequencing to high-risk patients with negative testing
  – Track psychosocial impact between traditional testing versus exome approaches using MICRA
Objectives (Cont’d)

• **Aim 3:** To measure impact of gene testing process and recommended follow-up and surveillance for gene positive and familial patients
  – Track patient compliance with screening recommendations
  – Record incident new neoplasias and size during screening of mutation positive individuals
  – Model cost-effectiveness of traditional genetic testing process compared to exome approach
  – Define screening recommendations for Hereditary PC/PGL syndrome patients, so that we may use this study to create standard of care guidelines (ASCO, ACMG) for patients with Hereditary Paraganglioma-Pheochromocytoma Syndrome

• Submitted to U01 GM Pilot Demonstration Projects RFA
Three-Year Experience with Web-Based Patient-Entered Cancer Family History Prototype Tool

• Cancer Family History Prototype Tool (MyFHH)
• Cleveland Clinic Oncology-Focused Clinical Settings
• Scheduling Qualifying Appointment Triggers Invite to Patient to Complete MyFHH at Secure Portal
• MyFHH is a Cleveland Clinic Quality Improvement Initiative
  – To improve the efficacy of taking cancer family history assessment
  – Without introducing care disparity
• Analyzed Uptake of MyFHH by:
  – Personal diagnosis of neoplasm
  – Sex
  – Age
  – Socioeconomic status (SES)

Doerr and Eng, unpublished
Hypotheses

• Uptake of MyFHH Higher for Individuals with Personal Neoplasia History
• Uptake of MyFHH Higher for <65 y/o
• Uptake of MyFHH Higher for Higher SES
Sept 2009-Aug 2012: 1161 Patients Scheduled Qualifying Appointments with Invite to Enter MyFHH

- Personal History of Neoplasia: 877 (76%)
- Female: 1002 (84%)
- Age <65: 994 (87%)
- SES Estimated by Median Family Income by Zip Census Tabulation Area

Doerr and Eng, unpublished
Odds of Completing MyFHH (Univariate Analysis)

• NO Difference in Odds of Completing MyFHH:
  – Personal Diagnosis of Neoplasm
  – Sex (Trend for Men Not Completing)
  – SES

• Decreased Odds of Completing MyFHH for Those >65 yo
  – OR 0.47; 95%CI 0.31, 0.71; P<0.001
  – Multivariate Analysis (Adjusted for Personal Dx, Sex, SES) OR 0.48; 95%CI 0.32, 0.72; P<0.001

Doerr and Eng, unpublished
Next Steps

• Focus Group and Survey for Barriers of >65 YO Participants
• Focus Groups and Survey to Determine Shared Domains Across All Ages Correlating with Uptake
• MyFamily: Scalable Family Health History Tool:
  – Web-Based, Patient-Entered Family History and Clinical Decision Support Platform at the Point of Care
  – Automated Risk Assessment by Modules, examples include:
    • General Cancers
    • Hereditary Breast-Ovarian Cancer Syndrome
    • Lynch Syndrome
    • Abdominal Aortic Aneurysm
    • Diabetes Mellitus
    – EMR-Compatible
• MyFamily Currently Beta-Testing in 5 Diverse Clinical Settings Across Cleveland Clinic Health System (Sept., 2012 ff)
  – Beta Test Data to be Analyzed Q1-2, 2013
• Will Need to Beta-Test with Clinical Settings Distinct from Cleveland Clinic