Cascade Genetic Testing in Families with Lynch Syndrome

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Cascade Genetic Screening

• “An active process to find relatives of patients affected with certain genetic disorders for which interventions exist which can save lives”

• Examples of “actionable” diseases (Tier1):
  – Familial hypercholesterolemia, Hereditary Breast Ovarian Cancer, and Lynch Syndrome
    • 2 million people in the US are affected with one of these conditions
Screening for LS

• Diagnosis of germline mutations in DNA mismatch repair (MMR) genes can impact clinical management

• Cost-effectiveness of screening for LS is influenced by
  – Cost of genetic testing
  – Number of cancers prevented

• Screening of CRCs for LS is cost-effective if $>3$ additional relatives (for each affected proband) undergo genetic testing.\(^1\)

• U.S. studies which have examined uptake of genetic testing among relatives in families with Lynch syndrome have been limited by small sample sizes\(^2\)

International Experience Cascade Testing for LS

• Europe
  – National cancer registries used to ID LS families and coordinate surveillance (Norway)

• Australia
  – Public health regional coordinators track IHC results, arrange genetic testing, contact relatives of MMR carriers, and schedule surveillance exams

• US (?)
Duty to Warn (ACMG/ASHG)

• Clinician has the duty to inform his/her patient of risks to other family members

• May offer to assist in disclosure

• Clinician does not have a duty to notify at-risk relatives
Family Communication of Genetic Test Results (2006-2008)

• Survey of 174 probands who underwent genetic testing for LS
  – Boston, Dana-Farber Cancer Institute

• 98% disclosed results to first degree relatives

• 67% disclosed results to more distant relatives

Ford, B Clinical Gastro and Hepatology 2008
Obstacles to Cascade Testing

Communication Barriers

• Patient level of understanding of the genetic condition

• “Closeness” to relatives

• Privacy concerns

• Fear of blame
Aim: Estimate the uptake of genetic testing among relatives in LS Families

Approach:

1. Examine trends in clinical genetic testing for MMR genes ordered over a 10 year period*  
   Full gene sequencing vs site-specific tests

2. Survey probands from LS families regarding communication of results and uptake of genetic testing among relatives

*University of Michigan Cancer Genetics Clinic 2004-2014
University of Michigan Cancer Genetics Registry

• >4,000 individuals referred for clinical genetic evaluation
• IRB-approved longitudinal research study
  – Pedigrees
  – Clinical data
  – Genetic test results

  – >200 Lynch syndrome families enrolled

• N=556 tests for germline sequencing of MMR genes ordered

  – 453 (81.5%) requested full gene sequencing
    • Mutation identified in 68/453 (15%)

  – 103 (18.5%) Site-Specific
    • Mutation identified in 48/103 (47%)

- 5-fold increase
- 14-fold increase
- 2.3 single site tests per mutation carrier
Patient Surveys

- Individuals who underwent genetic evaluation for Lynch Syndrome (LS) were mailed surveys at least one year following their evaluation.

- Subjects were asked whether they shared their genetic test result with family members and whether any of their relatives underwent genetic testing.

- Participant report of family testing was validated against family history stored in the participant and family members’ medical records.
Survey Results

• 122/296 (41%) individuals completed surveys

• 21 from families with a known LS germline mutation
  – All reported disclosing their test result to ≥1 first degree relative (FDR)
    76% disclosed to ≥1 second degree (SDR) or third-degree relative (TDR)

• 74 additional family members (beyond the proband) reportedly had genetic testing
  – 57 (77%) were FDR of the proband

• The average number of relatives tested per proband
  – 2.7 FDRs (range 0-7)
  – 0.7 SDR (range 0-4)
Summary

• All respondents disclosed their genetic test result to at least one FDR and 3/4 told at least one SDR or TDR.

• Reasons reported for not communicating results to family members were:
  – Family members were “too young/old” for the genetic test to be actionable
  – Relatives were deceased
Participant 7086-00, Female
Endometrial cancer (40)
Tested positive for MSH2 mutation at age 51

• 6/14 living at risk tested (4+, 2-)
  • participant reported 3/5 FDR, 0/4 SDR, 3/5 TDR

• She reported that she told children, siblings, and cousins, but not parents or aunts/uncles

“I got the gene from my father. He died before I had the test. His sister had uterine cancer and is likely Lynch (+). She has 3 sons, who I’ve told. Because she is 87Y, we have agreed not to tell her.”
Participant 103-00, Female
Colon and Rectal cancer (32)
Tested positive for MLH1 mutation at age 35

• 2/9 living at risk tested (2+, 0-)
  • participant reported 1/6 FDR, 0/3 SDR

• *She reported that she told siblings, but not parents, aunts/uncles, cousins, or children*

• *“Children, I have not told them because they are young; 10 and 8.”*
Participant 5734-00, Male
Colon cancer (39), Rectal cancer (47)
Tested positive for MLH1 mutation at age 57

- 4/6 living at risk tested (1+, 3-)
  - participant reported 4/4 FDR, 0/2 SDR

- He reported that he told children, siblings, and cousins, but not parents, or aunts/uncles

Participant 4634-00, Female
Breast cancer (51), Endometrial cancer (59), Sebaceous (72)
Tested positive for MLH1 mutation at age 73

- 5/8 living at risk tested (2+, 3-)
  - 5/5 FDR, 0/3 SDR

- She reported that she told children, siblings, and cousins, but not parents, or aunts/uncles
Results

• Females were more likely than males to communicate test results to extended family members (81% vs 40%, p=0.11)

• Subjects who communicated their genetic test results to SDRs also reported a higher uptake of genetic testing in SDRs
Limitations

• Validity of patient reports:
  – Comparison of survey responses with existing clinic records revealed that **one-third** (7/21) of probands did not report >1 FDR or SDR who **we know** had undergone genetic testing
Conclusions

• Data from genetic test orders and patient surveys suggest that for each MMR mutation carrier identified, 2-3 at-risk relatives undergo predictive genetic testing.

• Variability in uptake of genetic testing among at-risk relatives in families with LS suggests a need for interventions to facilitate communication of genetic information in LS families.
  • Especially to SDR and TDR.
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Barriers to Genetic Testing

• Physician level of understanding
• Insurance
  – eg. Degree relatedness
Strategies for Minimizing Communication Barriers

• Family letters

• Newer technologies
  – Social media
Kintalk
(UCSF)

• Web-based platform to help patients share genetic test results with relatives
  – Upload test results
  – Invite relatives to view
    – Kintalk.org

  – Also has genetics resources, news updates, links to publications

J. Terdiman, M. Myers, P. Conrad at UCSF
• Aim: Develop and evaluate a prototype of a web-based intervention that will facilitate the communication of relevant health and health history information among family members affected by Lynch syndrome, a hereditary colorectal cancer syndrome
Issues in Communication of Test Results

• Who initiates contact?
  – Proband/family member
  – Genetics team (?)
  – Public Health Department (?)
    • Model after “contacts” of STD cases

• Duty to warn—how far does it extend?

• Privacy and autonomy of relatives
A Recent Case

• 35 year old woman presents for genetic evaluation

• Ancestry research revealed her great uncle was part of Family G
Family G (1914)

**MSH2 exon 4**

Aldred Warthin

Family G--Updates

• Family reunion hosted by University of Michigan Genetics in 2000

• 27 family members attended
  – only 17 agreed to be tested for the familial mutation
  – Based on this 97 relatives could be excluded as mutation carriers
Questions

• Can we reliably trace whether her branch of the family carries the mutation?

• Will insurance cover her genetic testing?
Summary

• MMR germline mutations are relatively common
  – 1 in 350 (general population)
  – 3 in 100 CRC patients
• Universal screening of CRCs has increased ID of cancer-unaffected MMR mutation carriers (*success*)
• Streamlining communication of test results (letters *vs* social media) is key to success of cascade screening
• What more can clinicians/public health personnel do to help?