University of Michigan
Health System

Cascade Genetic Testing in Families with Lynch Syndrome

Elena M. Stoffel MD MPH
University of Michigan
January 26, 2016

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

Centers for Disease Control Genomics and Health Impact Blog

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 $\geq$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]

1. Ladabaum, U., et al., Ann Intern Med, 2011. **155**(2): p. 69-79.
2. Sharaf, R.N., et al., Clin Gastroenterol Hepatol, 2013. **11**(9): p. 1093-100.

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 (?)

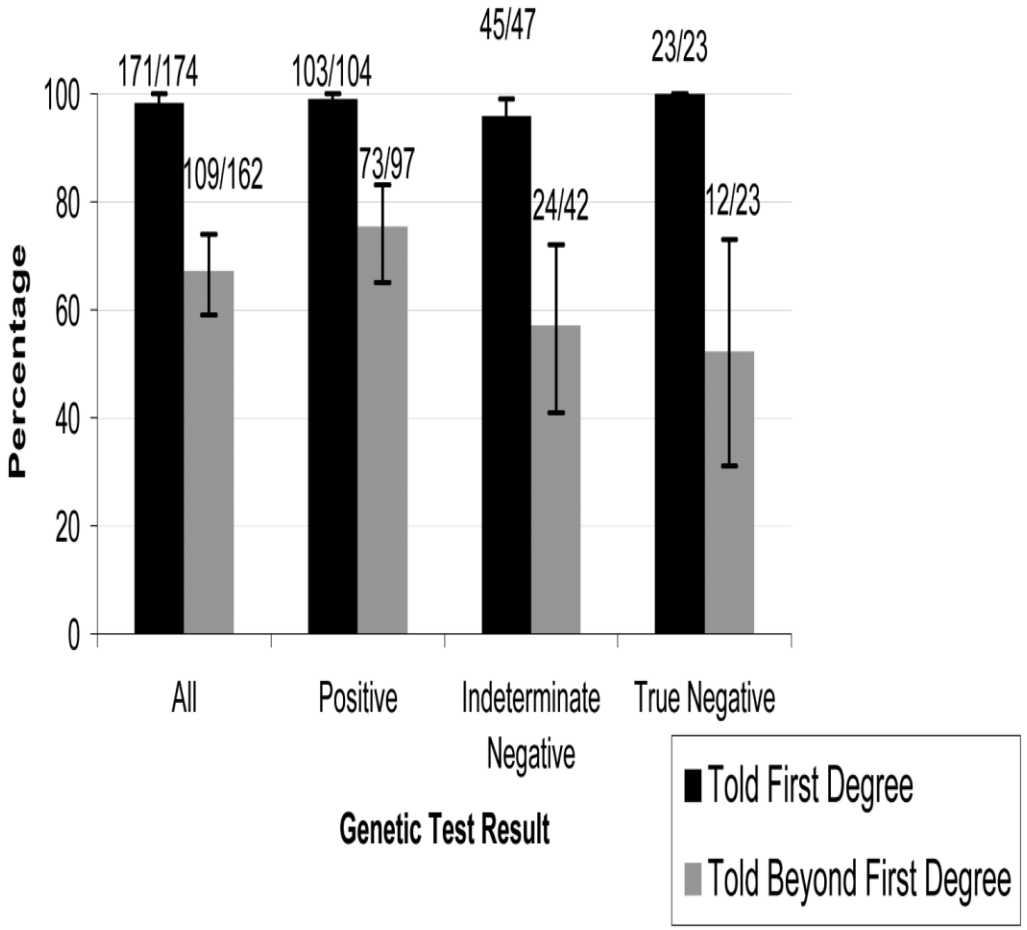
Duty to Warn (ACMG/ASHG)

- 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

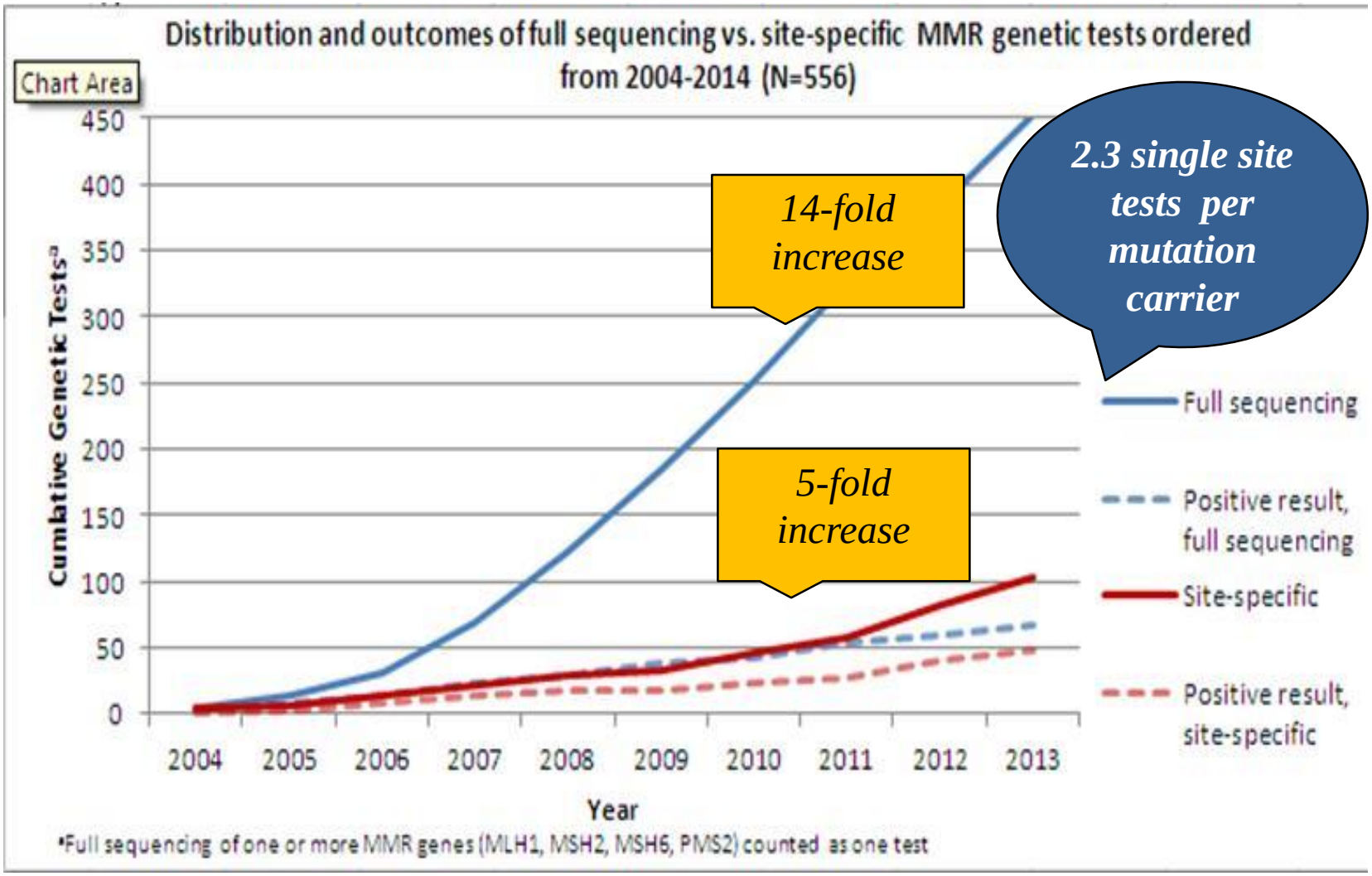
- >4,000 individuals referred for clinical genetic evaluation
- IRB-approved longitudinal research study
  - Pedigrees
  - Clinical data
  - Genetic test results

  - >200 Lynch syndrome families enrolled

Results: Review of LS Genetic Tests 2004-2014

- 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%)

Genetic Testing for MMR Gene mutations: 2004-2014



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

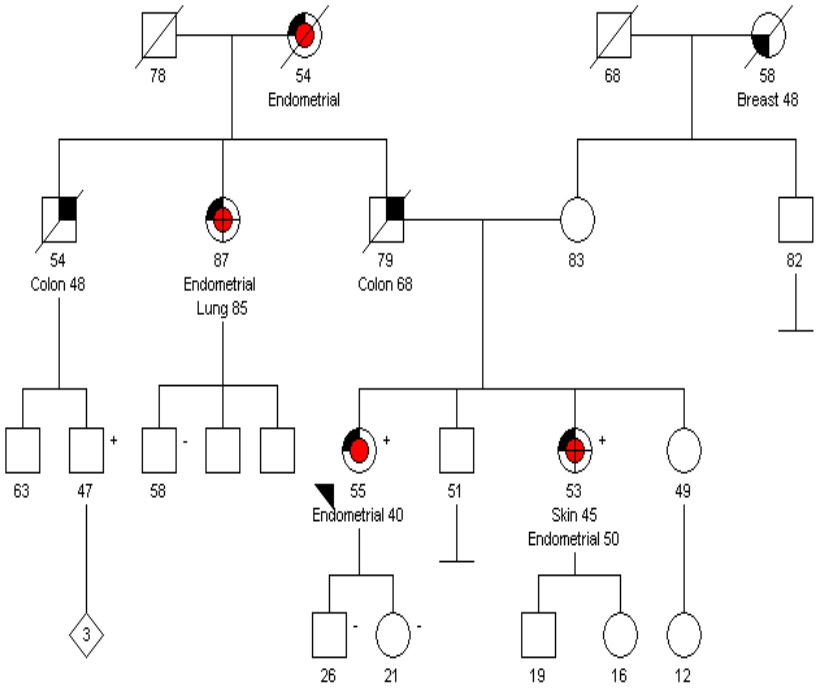
Endometrial cancer (40)

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

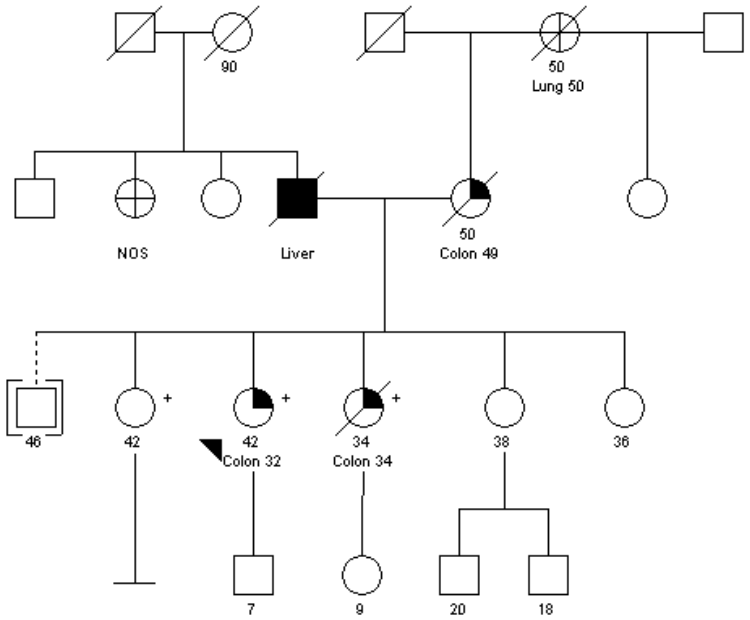
Colon and Rectal cancer (32)

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*

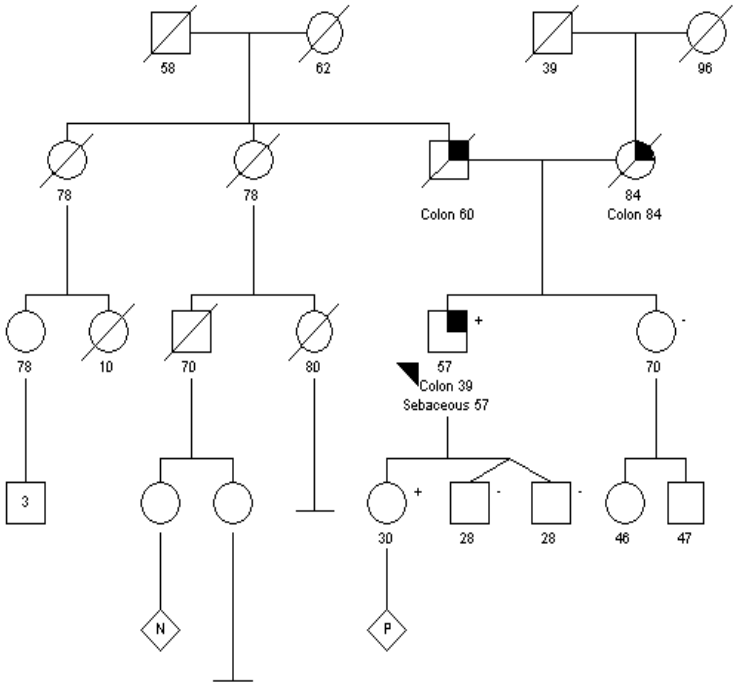
- *"Children, I have not told them because they are young; 10 and 8."*



Participant 5734-00, Male

Colon cancer (39), Rectal cancer (47)
Tested positive for MLH1 mutation at age 57

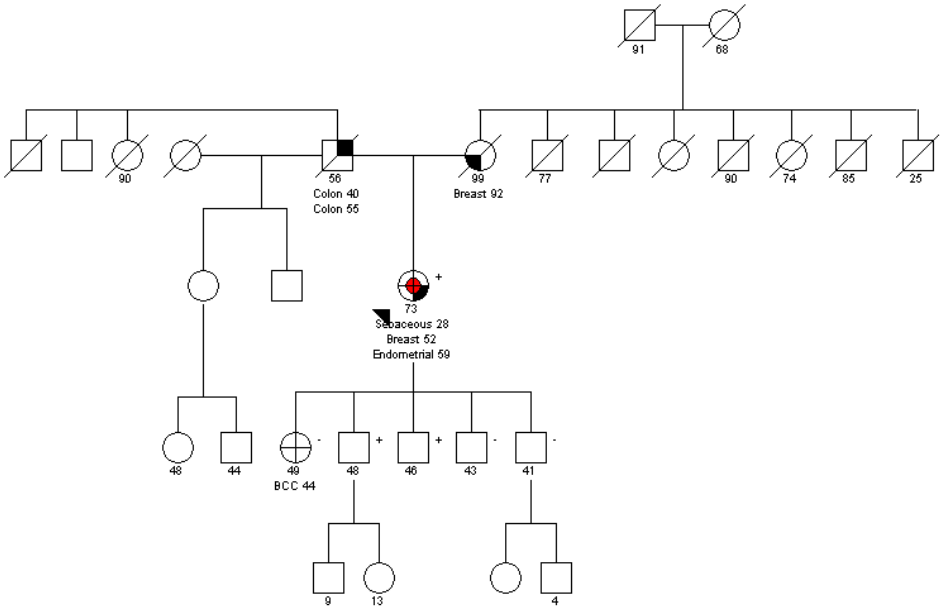
- 4/6 living at risk tested (1+, 3-)
  - participant reported 4/4 FDR, 0/2 SDR
- *He reported that he told children, siblings, and cousins, but not parents, or aunts/uncles*



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

Obstacles to Cascade Testing

Communication Barriers

- Patient level of understanding of the genetic condition
- "Closeness" to relatives
- Privacy concerns
- Fear of blame

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

MD Anderson

- 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

S. Peterson, P. Lynch at MD Anderson

Issues in Communication of Test Results

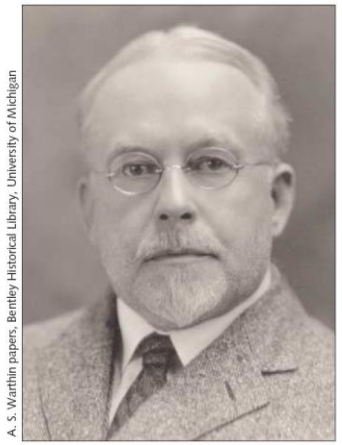
- Who initiates contact?
  - Proband/family member
  - Genetics team (?)
  - Public Health Department (?)
    - Model after “contacts” of STD cases
- Duty to warn—how far does it extend?
- Privacy and autonomy of relatives

A Recent Case

- 35 year old woman presents for genetic evaluation

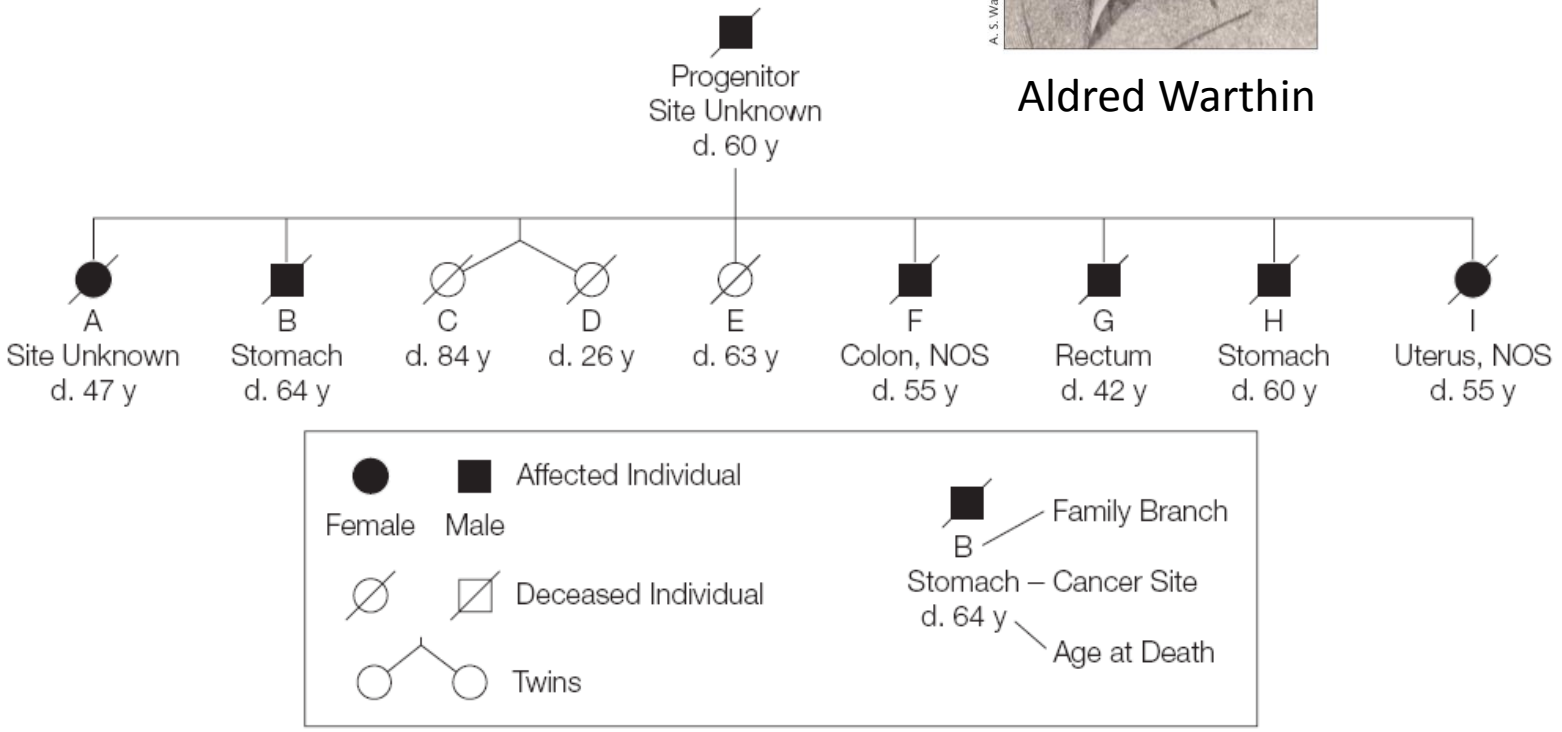
- Ancestry research revealed her great uncle was part of Family G

Family G (1914)



Aldred Warthin

MSH2 exon 4



NOS indicates not otherwise specified.

Douglas, JAMA, 2005.

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?