

The Genetic Science Behind Hereditary Colorectal Cancer

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Disclosure

Speaker Bureau – Myriad Genetics

Relatively Common Hereditary Cancer Syndromes

- **Hereditary Breast/Ovary Syndrome (BRCA genes)**
 - Breast, ovary, others
- **Lynch Syndrome (Mismatch Repair genes)**
 - Colon, uterus, ovary, stomach, others
- **Colon polyposis syndromes (APC, MUTYH genes)**
 - Colon, upper GI, others

Hallmarks of Hereditary Cancer

- **Family clustering** of specific types of cancer among siblings or across multiple generations
- **Younger age** at diagnosis compared to non-hereditary cases of the same cancer
- **Multiple cancers** in the same person
- **Typical phenotypes** in some cancers

“FAMP” and Hereditary Cancer

Family

Age

Multiplicity

Phenotype

Take-Home Messages For Today

- Hereditary CRC is much more common than previously realized
- Historically, doctors do a rather poor job of recognizing these patients/families before it is too late
- Many of the resulting cancers could have been prevented, or at least found in an earlier, more curable stage
- The syndromes involve high risk for cancers other than CRC, and providers must be familiar with this spectrum of cancers

Why should we care?

Hereditary Cancer Syndromes

The Prevention Strategy

- These are relatively common cancers
- Many patients have cancer because of an inherited genetic defect, and are at risk to develop a future second cancer
- It is possible to identify these patients, as well as their family members who have the same defect but no cancer yet
- Once identified, we can actually **prevent** many of the cancers that were destined to occur
- Opportunity to identify the non-carriers within a cancer family, and to modify their risk management accordingly

Preventable Hereditary Cancers

Type of Cancer	Percent Hereditary	Percent Preventable	Effective Surveillance?*
Breast	5-10%	Nearly 100%	Yes
Ovary	13-16%	>95%	No
Uterus	3-5%	100%	+/-
Colorectal	5%	70-90%	Yes
Melanoma	5-10%	Unknown	Yes
Pancreas	5-10%?	Unproved	Evolving

* “Effective surveillance” implies that there is a high-risk surveillance strategy available that reliably leads to earlier diagnosis of the cancer at a more curable stage.

Hereditary Cancer Syndromes

Management Implications

- Some hereditary cancers may be **biologically distinct** from their sporadic counterparts, and this may have a significant effect on:
 - Overall prognosis
 - Surgical decision-making
 - Chemotherapy alternatives

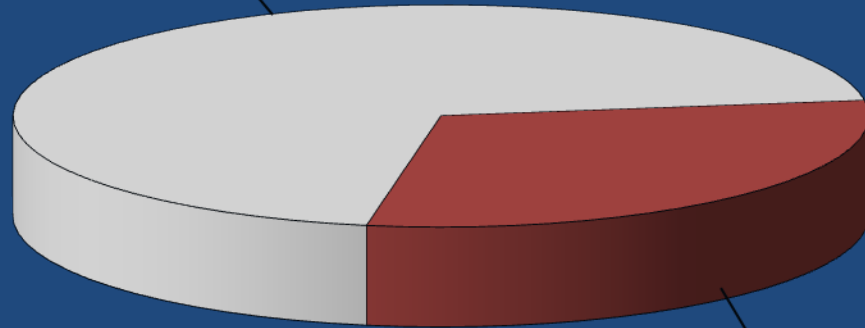
Hereditary Colorectal Cancer Management Implications

- Lynch CRC has a better prognosis than sporadic
- Consideration of total colectomy in Lynch or FAP pts
- Consideration of prophylactic hysterectomy in Lynch patients undergoing colon resection for CRC
- 5FU not effective as the dominant drug in Lynch CRC

Epidemiology of Colorectal Cancer

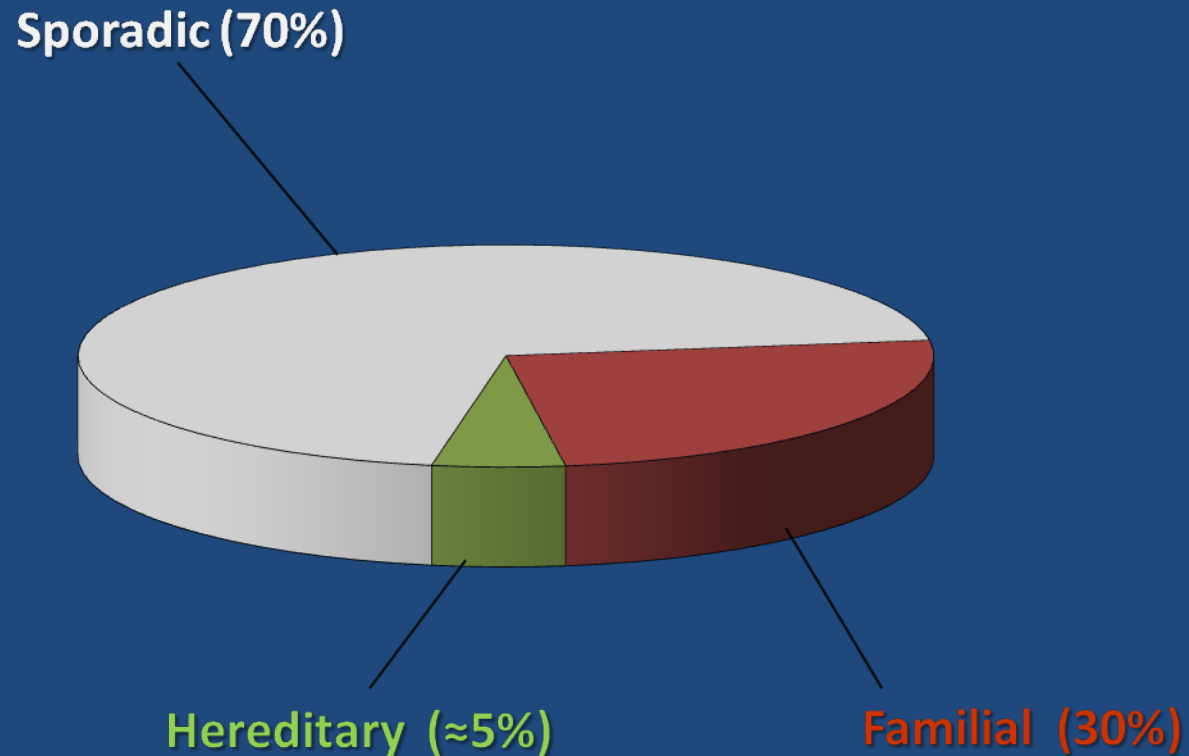
145,000 new U.S. cases/year

Sporadic (70%)



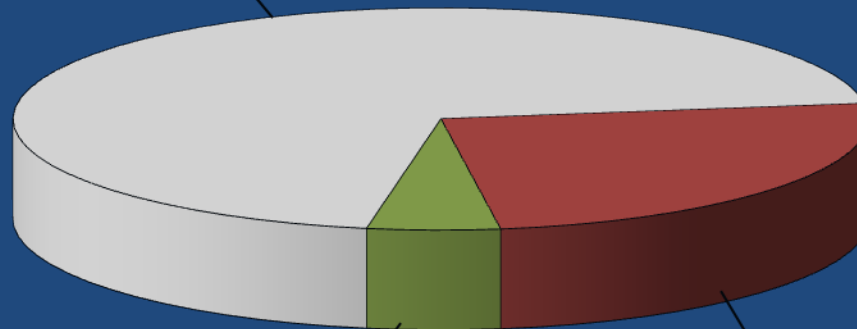
Familial (30%)

Epidemiology of Colorectal Cancer



Epidemiology of Colorectal Cancer

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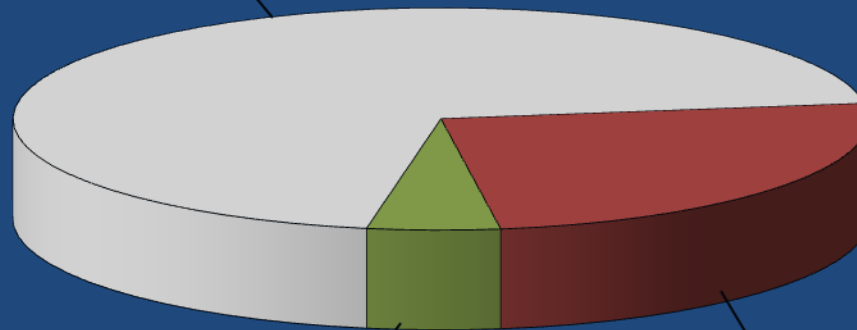
Familial (30%)

Hereditary ($\approx 5\%$)

Lynch (3%)
FAP ($\leq 1\%$)
MAP ($\leq 1\%$)
Others (?? %)

Epidemiology of Colorectal Cancer

Sporadic (70%)



Lynch (3%)
FAP ($\leq 1\%$)
MAP ($\leq 1\%$)
Others (? %)

Hereditary ($\approx 5\%$)

Familial (30%)

≈ 8000 New Cases/Year

Hereditary Colorectal Cancer: Common Syndromes

POLYPOSIS (many colon polyps):

Familial Adenomatous Polyposis (Classic FAP)

Attenuated FAP (AFAP)

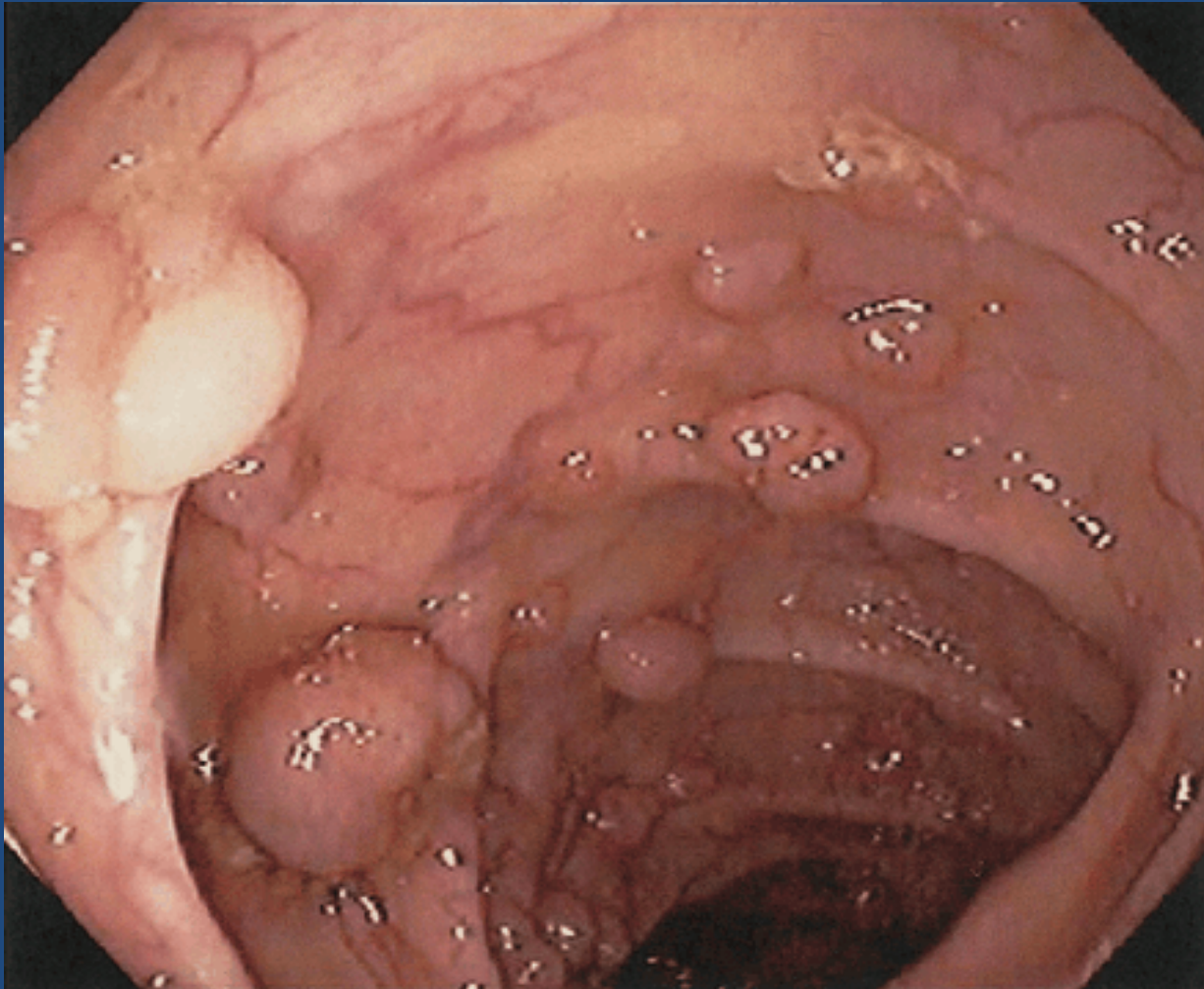
MUTYH-Associated Polyposis (MAP)

Serrated, juvenile, Peutz-Jeghers, Cowden,
other rare non-adenomatous syndromes

NON-POLYPOSIS (relatively few polyps):

Lynch Syndrome (formerly “HNPCC”)

Familial Adenomatous Polyposis



Familial Adenomatous Polyposis (Classic FAP)

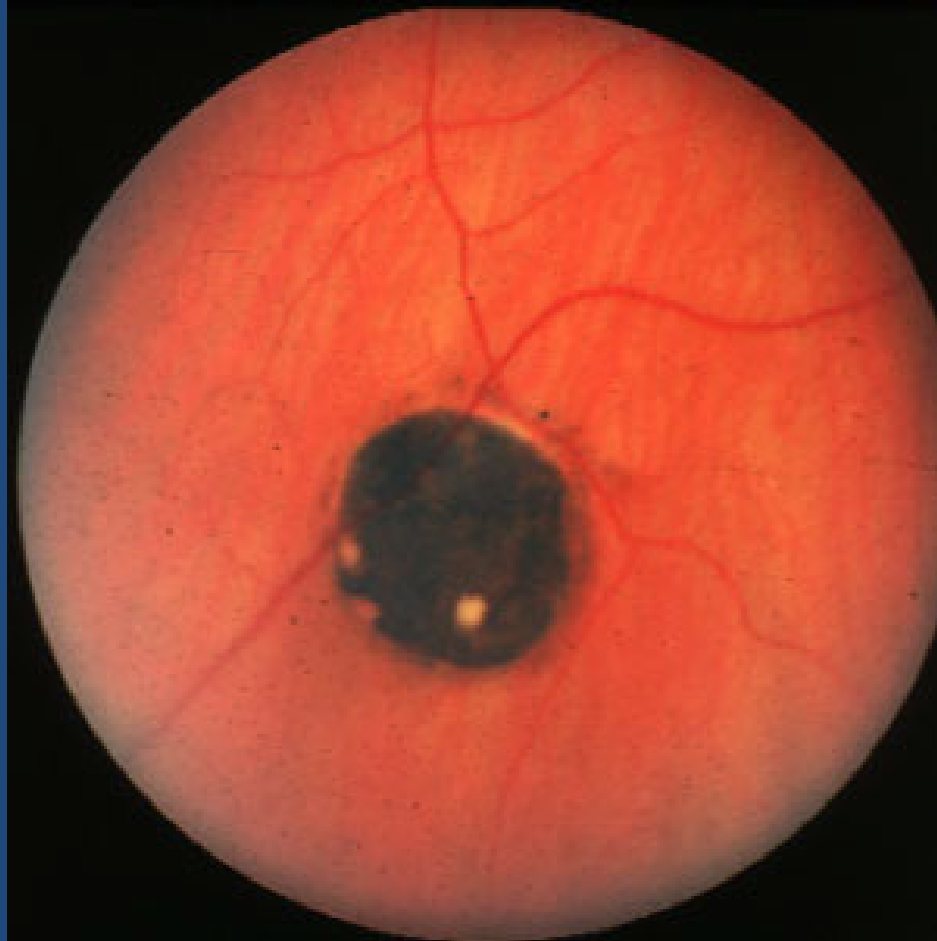
- Hundreds to thousands of polyps
- Early age of onset, frequently in teen years
- Mutation in the **APC gene**
- Autosomal dominant

- **30% of affected individuals represent de novo rather than inherited mutations, and therefore may have no family history of polyps or cancer**

Familial Adenomatous Polyposis (Classic FAP)

- Virtually 100% chance of developing colorectal cancer unless preventive total colectomy is performed
- Average age for colon cancer approximately 35-40 yrs
 - 7% occur by age 21, 90% by age 50
- **Gastric cancer in 2-5% (may be higher in Asians)**
- **Duodenal, periampullary cancer 4-12%**
- **Thyroid cancer 4-6%**
- Variety of other extraintestinal manifestations:
 - Osteomas, desmoid tumors (Gardner syndrome)
 - CNS medulloblastoma (Turcot syndrome)
 - CHRPE

Congenital Hypertrophy of the Retinal Pigment Epithelium



Attenuated FAP (AFAP)

- **“FAP Lite”**
- Typically less severe but highly variable degree of polyposis
- Often involves the right side of the colon more than the left
- Later age of onset, often 30’s or older

- Lower penetrance for colorectal cancer, estimated 80%
- Patients with relatively low polyp density can be managed with annual surveillance colonoscopy
- Some will still eventually require preventive surgery

Attenuated FAP (AFAP)

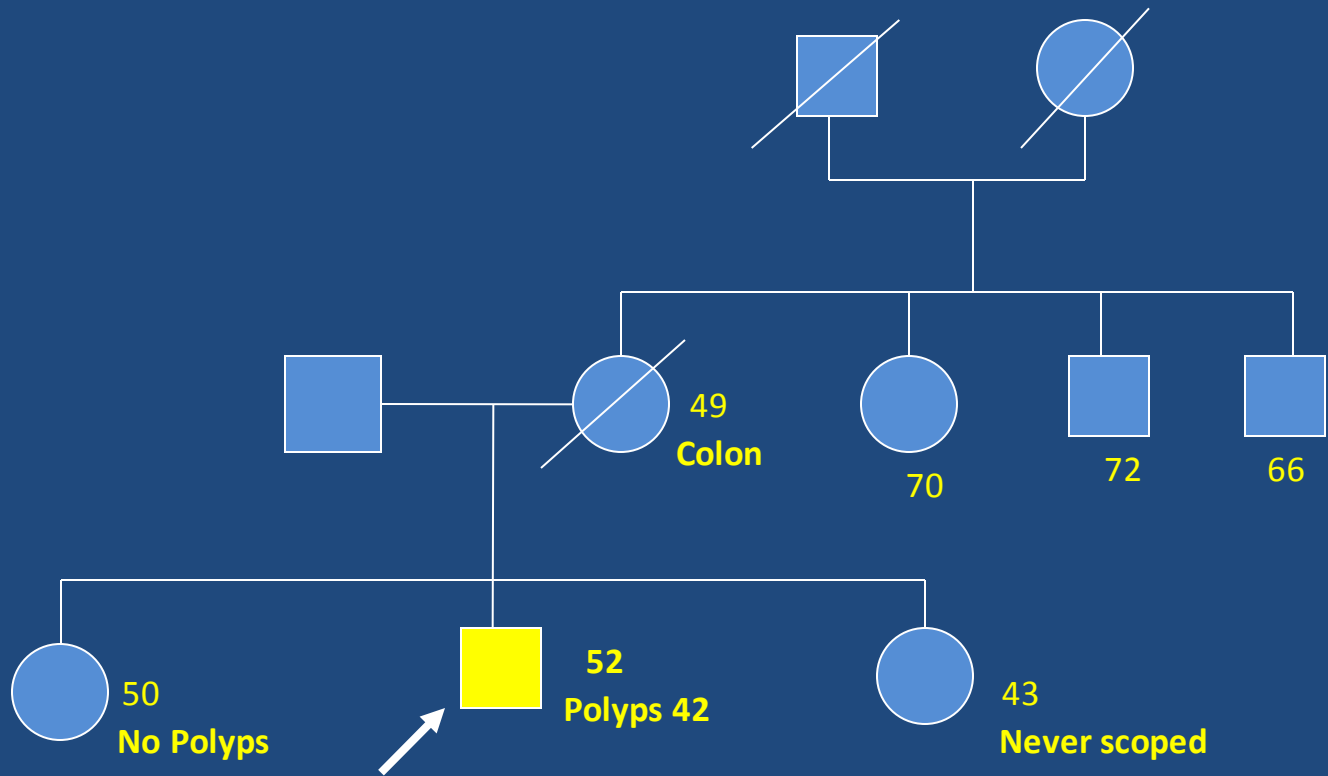
- Same gene as classic FAP, with same rate of de novo mutations
- **The upper GI cancer risks are not attenuated**
- Extracolonic manifestations similar to classic FAP, although CHRPE and desmoid tumors are not seen as commonly
- These patients are much harder to diagnose than classic FAP
- **Critically important to track the cumulative number of adenomatous polyps removed over time**
- **Ten** is the consensus number to trigger genetic evaluation
- Desmoid tumors should also lead to genetic testing

Case Study FM

- 52 y/o male who has been under high-risk surveillance for colon cancer since age 42
- At 42 he was found to have 2 sigmoid adenomas on his first screening colonoscopy
- Repeat scope q 2-3 yrs, with 1-3 polyps each time
- Scope at 52 shows 8 adenomas, mostly ascending and transverse. One is a villous adenoma with dysplasia.

- Mother died from colon cancer at 49
- No other history of CRC or polyps known in the family

Case Study FM



Case Study FM

- What is the key question to be asked for this patient?

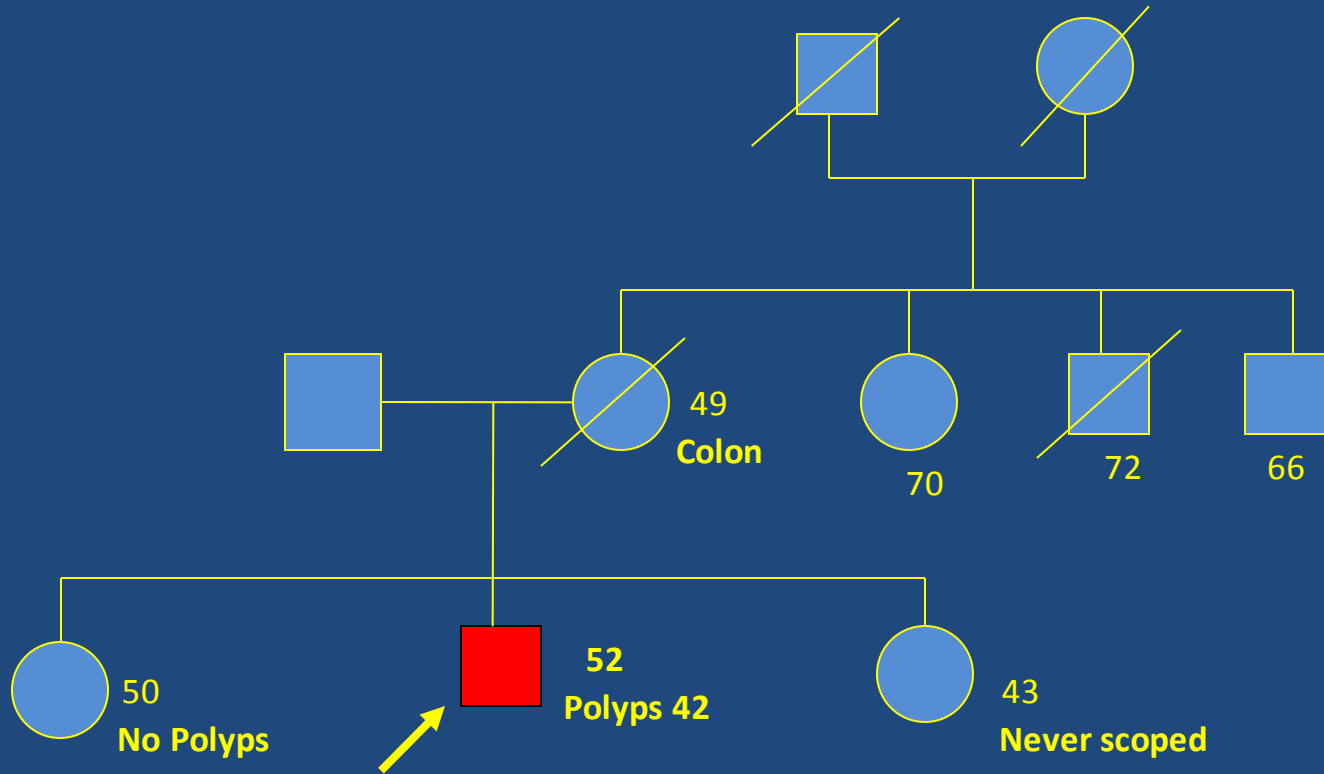
Case Study FM

- What is the key question to be asked for this patient?
- Cumulative number of adenomas is now **23** (two years earlier the number had been 15)

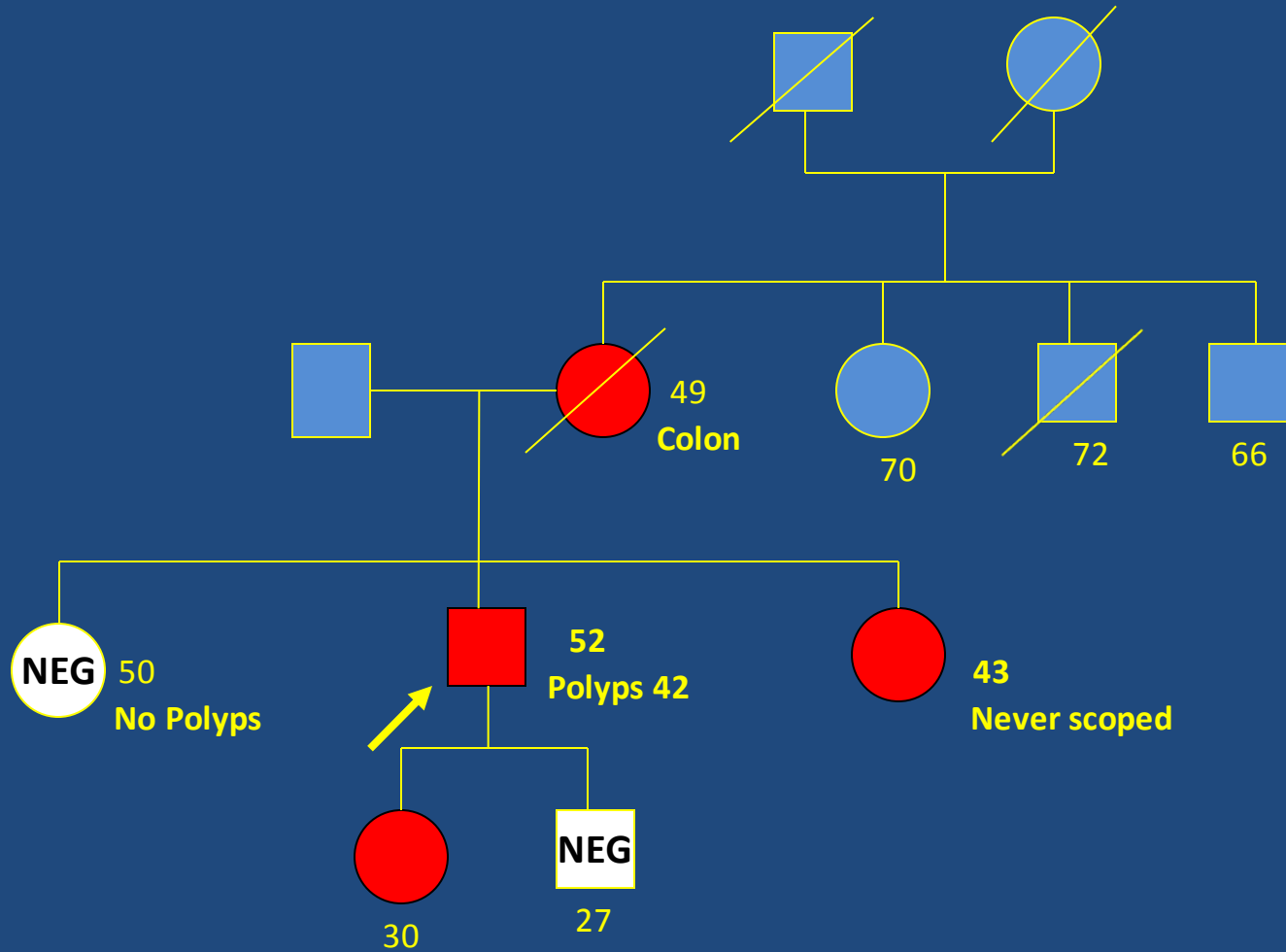
Case Study FM

- What is the key question to be asked for this patient?
- Cumulative number of adenomas is now **23** (two years earlier the number had been 15)
- Genetic consultation leads to germline testing, and he is found to carry a mutation in the **APC gene**

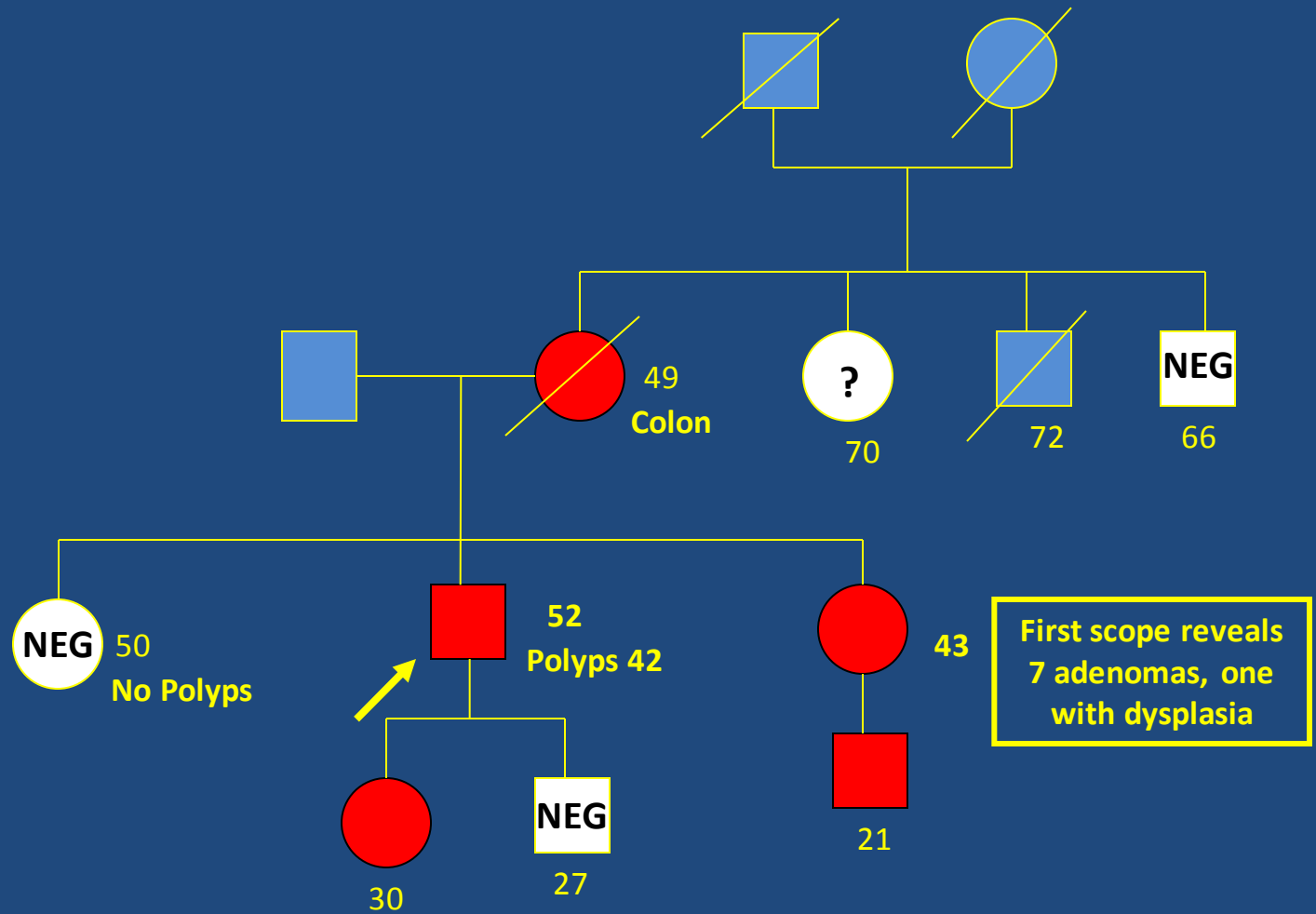
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Case Study FM



Case Study FM

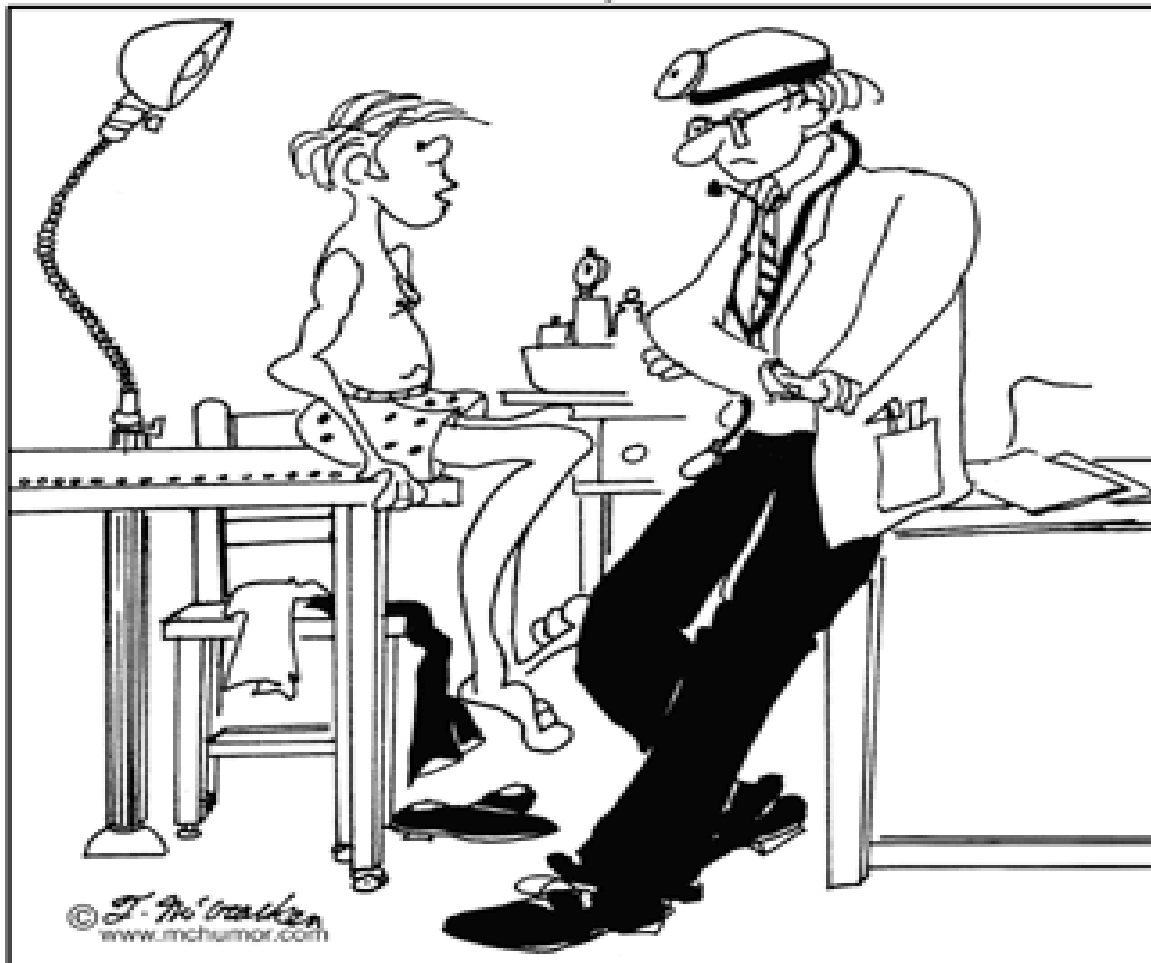


MUTYH-Associated Polyposis (MAP)

- MUTYH gene aka MYH
- **Recessive** trait rather than dominant
- 1-2% of Americans carry an MYH mutation, esp Europeans
- Patients who are doubly heterozygous typically have a **phenotype similar to attenuated FAP**, with highly variable degree of polyposis and age of onset, and increased incidence of duodenal polyps
- Other potential cancers include thyroid, ovary, breast, uterus, bladder, and skin – risks are not yet well characterized

MUTYH-Associated Polyposis (MAP)

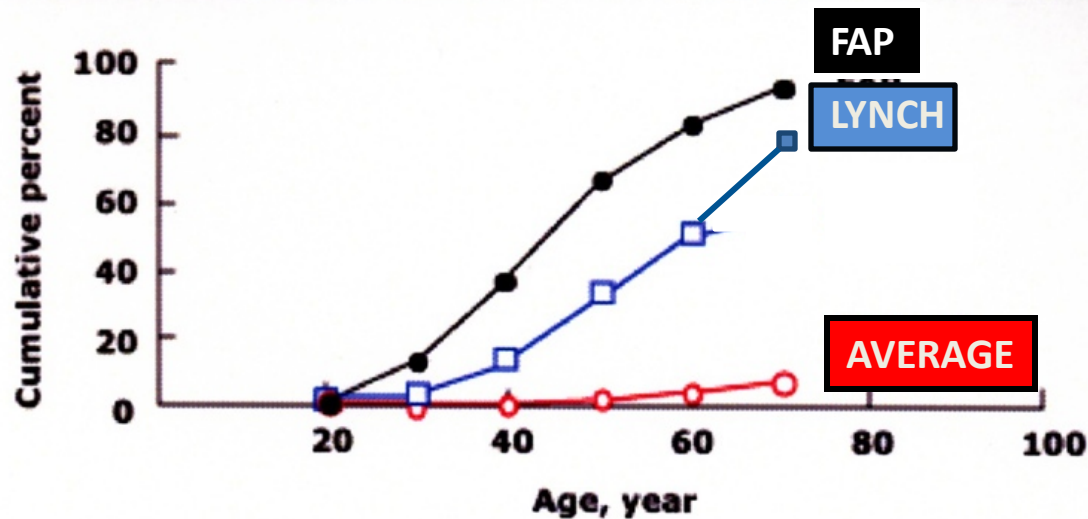
- “Average” patient has onset of polyps in 40’s, and cumulative number of ten by age 50
- Some patients never reach ten polyps, but start earlier in life
- Some have developed CRC, including at young age, without ever demonstrating “polyposis” per se
- The spectrum of MAP remains poorly defined, and the syndrome is likely to be highly underdiagnosed



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www.mchumor.com

“Gee. I had hoped to make it to the adult table at Thanksgiving before you recommended I have my first colonoscopy.”

Cumulative incidence of colorectal cancer by age in subjects with genetic syndromes compared with the general public



Data from Winawer, SW, Fletcher, RH, Mille, L, et al. AGA guidelines: Colorectal cancer screening: Clinical guidelines and rationale. Gastroenterology 1997; 112: 594.

Lynch Syndrome

Lifetime Risk of Cancers (vs Normal)

- Colorectal 80% (5-6)
- Endometrial 40-60% (2.5)
- Ovary 8-12% (1.5)
- Stomach 8-10% (<1)
- Urothelial 4-5% (<1)
- Biliary/Pancreas 2-4% (<1)
- Small intestine 1-2% (<1)
- CNS (GBM) 1-3% (<1)
- Breast? Prostate?

Prevalence of Hereditary Cancer: BRCA vs Lynch Syndrome

Which ratio most closely approximates the number of U.S. patients affected with BRCA mutations compared to the number affected by Lynch syndrome?

- A) 20 to 1
- B) 10 to 1
- C) 5 to 1
- D) 1 to 1

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- C) 5 to 1
- D) **1 to 1**

Prevalence of Hereditary Cancer: BRCA vs Lynch Syndrome

- Prevalence of BRCA mutations in U.S. \approx **1 in 400**
 - Prevalence of BRCA in American Jews \approx **1 in 40**
- Prevalence of Lynch syndrome in U.S. \approx **1 in 450**

Prevalence of Hereditary Cancer: BRCA vs Lynch Syndrome

- Prevalence of BRCA mutations in U.S. **≈ 1 in 400**
 - Prevalence of BRCA in American Jews **≈ 1 in 40**
- Prevalence of Lynch syndrome in U.S. **≈ 1 in 450**
- **Fewer than 10% of all BRCA carriers in U.S. have been identified, and fewer than 2% of Lynch patients have been found**

Colorectal Cancer Phenotype

Sporadic

- Avg age 60-65
- 2/3 left-sided
- Variable histology
- Slow evolution from polyp to cancer
- MSI 10-15%

Lynch

- Avg age 45-55
- **2/3 right-sided**
- **Mucinous, signet ring**
- **Rapid evolution from polyp to cancer**
- MSI 90%

Genetics of Lynch Syndrome

- Caused by an inherited defect in any one of several **“mismatch repair” genes (MMR)**. Five genes are currently available for clinical testing:
 - MLH1 (most common gene involved)
 - MSH2 (second most common, freq assoc with MTS)
 - MSH6 (excess of uterine cancers)
 - PMS2 (new, prevalence and features are uncertain)
 - EPCAM (not MMR, but adjacent to MSH2)
- Prior to 2011, clinical testing of the last two genes was not available, ie, suspicious patients who were previously “negative” may need to be retested

Genetics of Lynch Syndrome

- These mismatch repair genes normally function as part of the **“spell-check”** system to correct DNA mismatch mutations that occur naturally during the DNA replication phase of cell division
- Failure of the system leads to more rapid accumulation of these mutations – **“Genomic Instability”**
- Cancer occurs when a sufficient number of these mutations occur in critical genes – it’s just a matter of time

Lynch Syndrome

Accelerated Timeline For CRC

- Genomic instability in Lynch syndrome greatly accelerates the timeline from colon polyp to CRC
- Instead of the usual 7-10 years, it may be only 1-3 years
- Beware of the colon cancer that seemed to come out of nowhere, within 2-3 years of a normal colonoscopy
- This is not only the basis for the annual colonoscopy recommendation, but also an important clue to underlying Lynch syndrome

How do we find the people with Lynch syndrome?

- Traditional clinical criteria:
 - Amsterdam criteria
 - Bethesda criteria
- Rigorous application of “red flags” to newly diagnosed patients with colon or endometrial cancer
- Systematic review of cancer survivors
- Universal pathology screening of CRC and endometrial ca
- Computer prediction models (PREMM, MMRPro, etc)

Traditional Clinical Criteria For Lynch Syndrome

- **Amsterdam (1994)** – “3-2-1” analysis of family
 - **3** members with CRC, **2** of whom are 1st degree relatives of the 3rd, and **1** had to be under 50 at dx
 - Only colorectal cancer taken into account
 - Only 30% of Lynch families meet these criteria
- **Amsterdam II (2001)** – Included all Lynch cancers
 - Sensitivity improved to 50%
- **Revised Bethesda Guidelines (2004)** – Phenotypic
 - Age, location, histology
 - Simplified family history criteria
 - Still only captures 60-70% of Lynch families

“Red Flags” For Lynch Syndrome

- ANY pt diagnosed with CRC or uterine cancer by age 50
- ANY pt with multiple Lynch cancers, regardless of age
- Any patient with a Lynch cancer and a suspicious family history of other Lynch cancers **(3 cancers within 3 degrees)**
- Any colon or uterine cancer with typical Lynch phenotype:
 - Right-sided CRC (proximal to splenic flexure)
 - Lynch histology features (any one)
 - Loss of expression of a mismatch repair protein by IHC

“Pink Flags” For Lynch Syndrome

- Cancer of the ureter or renal pelvis
- Cancer of the small intestine
- Development of colorectal cancer less than three years out from a clean colonoscopy
- Sebaceous tumors (adenomas, carcinomas)
 - Muir-Torre syndrome (MTS)

Computer Models For Assessing Likelihood of Lynch Syndrome

- Several different models to determine the statistical likelihood that a given patient has Lynch syndrome
- Variables taken into account include:
 - Type and age of cancer in the patient
 - Multiplicity of cancers
 - Weighted family pattern for cancers in first and second degree relatives
- PREMM, MMRPro, others
- NCCN 2014: Patients with $> 5\%$ likelihood are appropriate for DNA testing

Diagnostic Tools For Lynch Syndrome

Tumor Testing:

- Microsatellite Instability (MSI)
- Immunohistochemistry (IHC) for MMR proteins
 - Useful for **automatic screening** of all CRC patients at the pathology level

Germline DNA Testing:

- Direct DNA analysis of one or more of the five genes
- **This is the only way to diagnose LS**, and the only way to track the mutation through the family

Microsatellite Instability (MSI)

- PCR-based test performed on the actual cancer, as well as normal tissue from the same patient
- **Detects the failure of mismatch repair** in the malignant clone compared to the normal tissue
- Confusing nomenclature: abnl test reported as “MSI-High”
- 12-15% of all CRC is MSI-high
- **This test is NOT DIAGNOSTIC of Lynch syndrome, and is only 20% specific (ie, 80% have a different underlying cause which is somatic, not hereditary)**
- 90% sensitive for LS

Immunohistochemistry (IHC)

- Performed on the cancer tissue, looking for the presence or absence of the four mismatch repair proteins in the tumor
- Theoretically, the defective gene will not produce the corresponding MMR protein
- **An abnormal test is NOT DIAGNOSTIC of Lynch syndrome, particularly if the missing protein is MLH1**
- Similar to MSI, IHC is 20% specific and 90% sensitive for LS, but the 10% it misses is not the same 10% that MSI misses – **together the tests are about 98% sensitive**
- Useful for screening population groups with colon and endometrial cancer

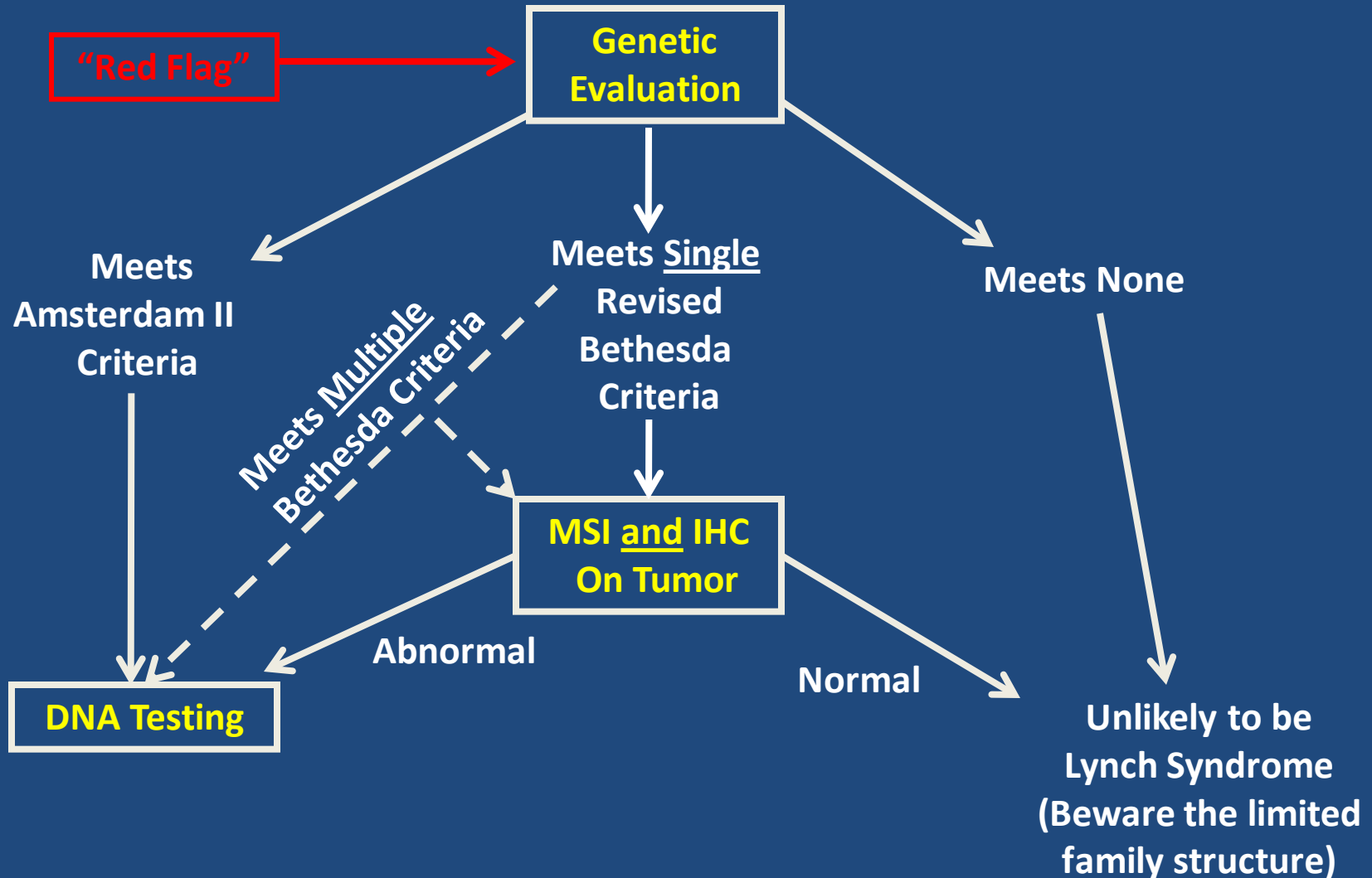
Germline DNA Testing

- Performed on blood or saliva
- Testing for mutations in any of the five Lynch genes that would render that gene defective, and therefore unable to produce the corresponding MMR protein
- **This is the only way to confirm the diagnosis of LS, and the only way to track a mutation through the family**

How Many CRC Patients Should Be Tested For Lynch Syndrome?

- NCCN guidelines and other consensus recommendations are set to trigger testing when the likelihood of being positive is approximately 10% or higher
- When guidelines are applied to large groups of patients, at least **20-25%** of patients with breast cancer or colorectal cancer appear to be appropriate for testing

Traditional Lynch Syndrome Algorithm



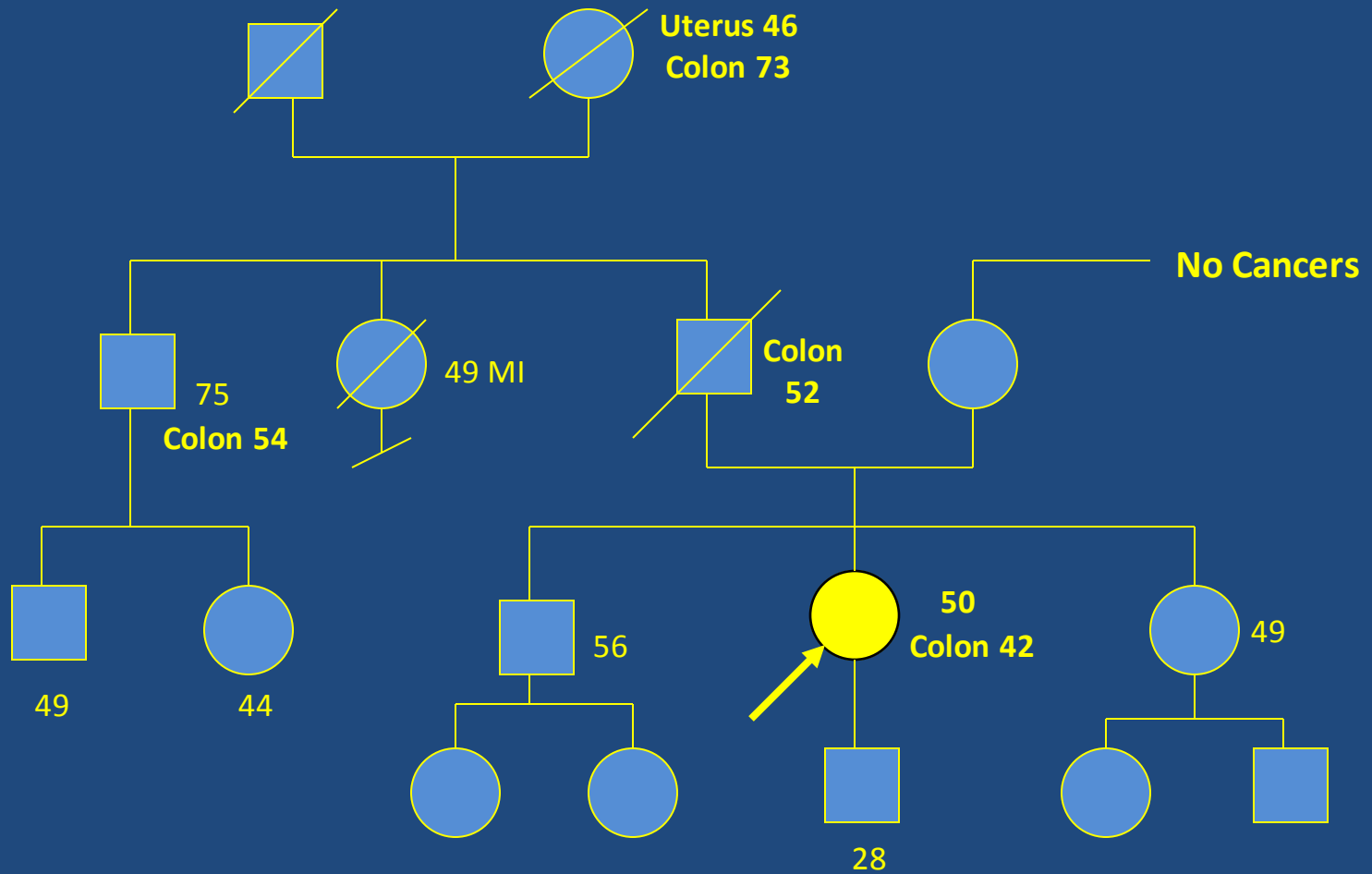
Case Study AC

- 50 y/o female who was diagnosed with ascending colon cancer at 42 (2000), at the time of her first screening colonoscopy
- Right hemicolectomy, adjuvant chemotherapy
- Father had colon cancer at 52, died at 54
- Paternal uncle had colon cancer at 54
- Paternal grandmother had uterine cancer at 46, then colon cancer at 73

Case Study AC – “Red Flags”

- 50 y/o female who was diagnosed with **ascending** colon cancer at **42**, at the time of her first screening colonoscopy
- Right hemicolectomy, adjuvant chemotherapy
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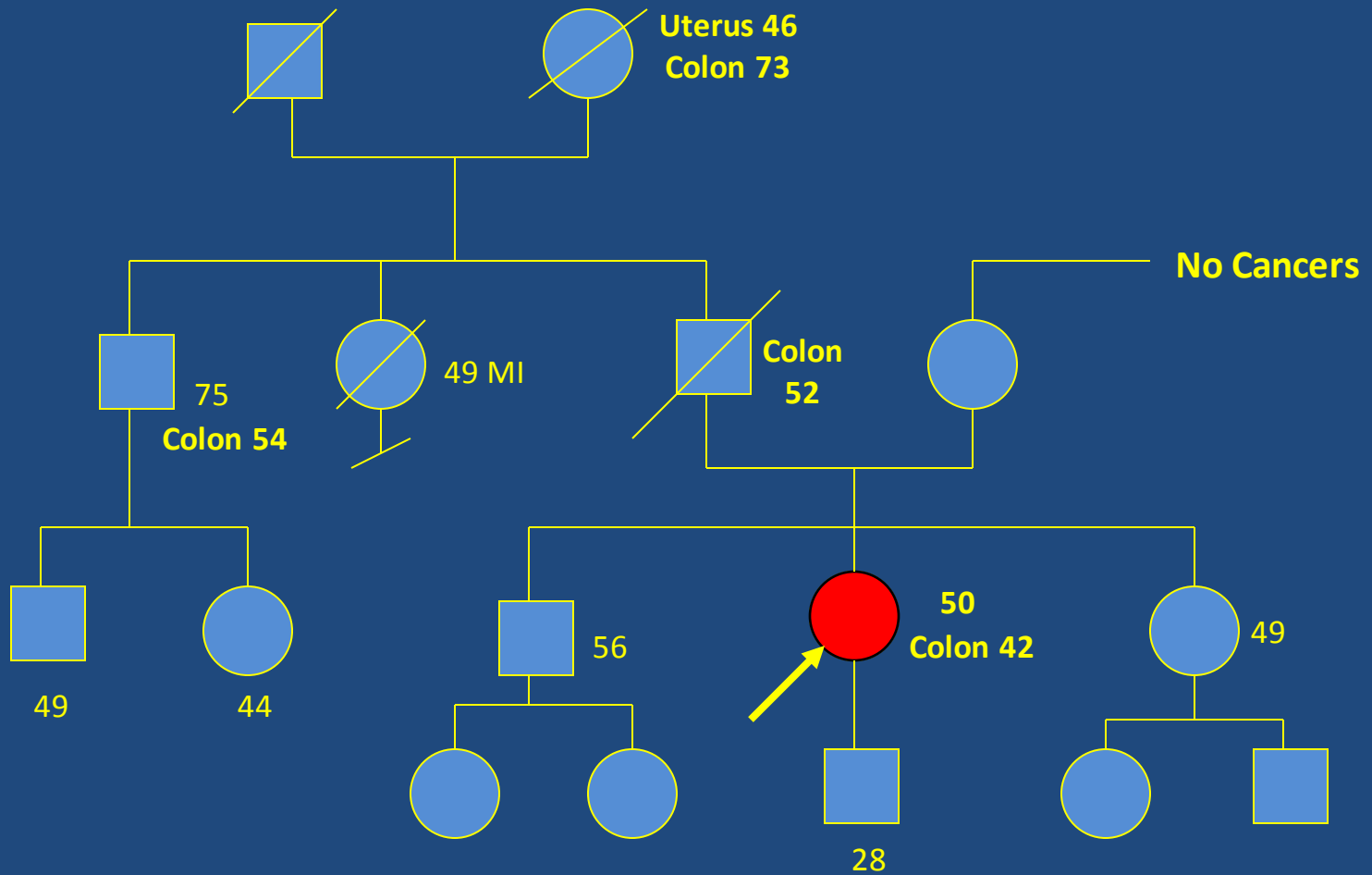
Case Study AC - FAMP



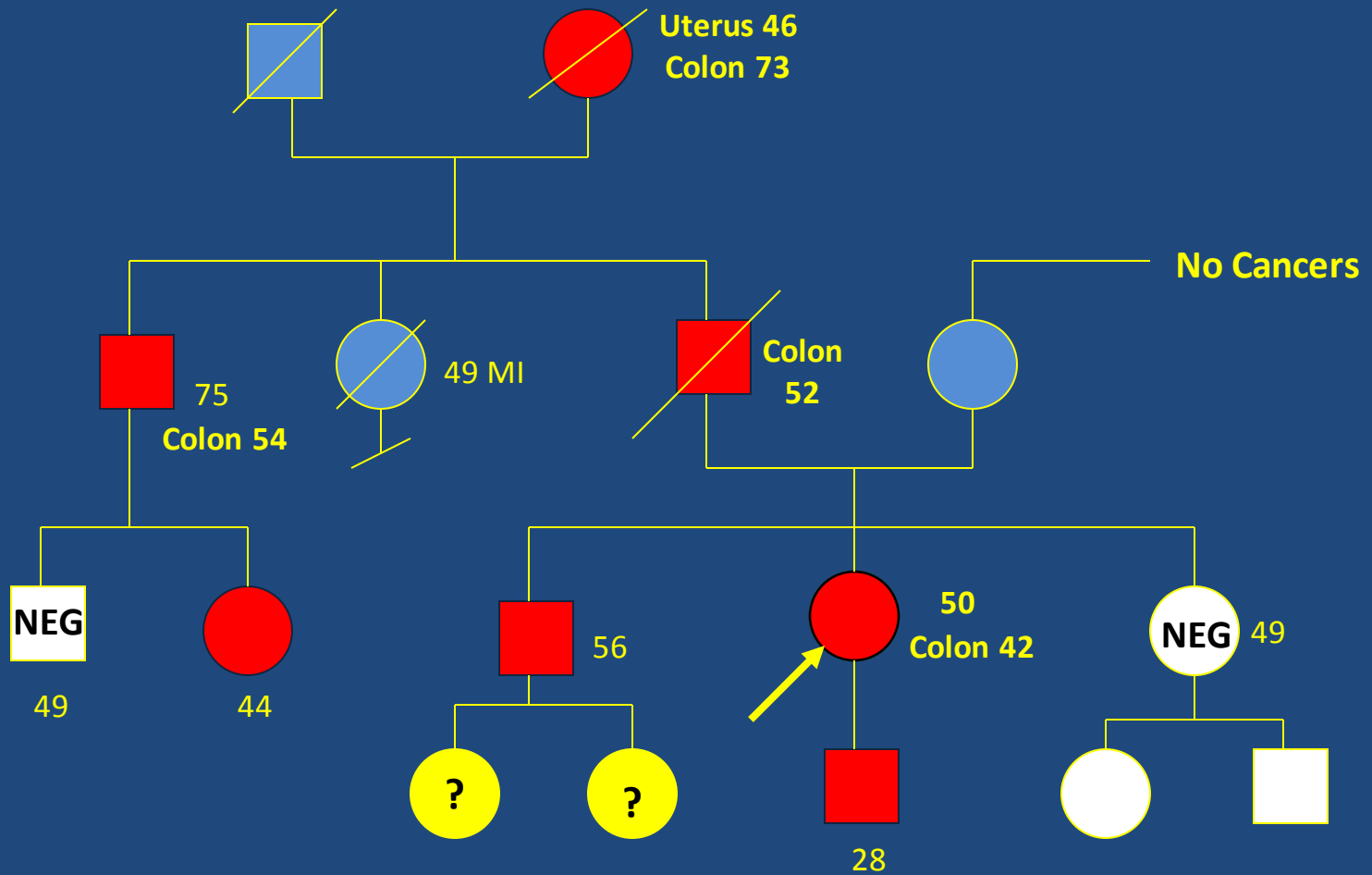
Case Study AC

- This patient and her family were missed at the time of her diagnosis at 42, and at every follow-up visit with multiple physicians over the next 7 years
- She was identified by systematically applying the “red flags” to our CRC survivor population
- She was found to carry a mutation in the **MSH2** gene

Case Study AC



Case Study AC



Lifetime Risk of Lynch-Related Cancers (vs Normal)

- Colorectal 80% (5-6)
- Endometrial 40-60% (2.5)
- Ovary 8-12% (1.5)
- Stomach 8-10% (<1)
- Urothelial 4-5% (<1)
- Biliary/Pancreas 2-4% (<1)
- Small intestine 1-2% (<1)
- CNS (GBM) 1-3% (<1)
- Breast?, Bladder?

Case Study AC

- She was found to carry a mutation in the **MSH2** gene
- She went on to have a prophylactic complete hysterectomy/oophorectomy
- This procedure could have been done as part of her hemicolectomy if her Lynch diagnosis had been timely

**How do we actually
manage cancer risk in
patients with Lynch syndrome?**

Lynch-Related Cancers With Effective Risk-Reducing Strategies

- **Colorectal 80% (5-6)**
- **Endometrial 40-60% (2.5)**
- **Ovary 8-12% (1.5)**
- **Stomach 8-10% (<1)**
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Cancer Risk Management In Lynch Syndrome

- Screening colonoscopy starting at 25*, annual after age 30
- Transvaginal sono and CA-125 starting at 30*, then annually
- Complete hysterectomy after child-bearing is complete (35-40)
- EGD starting at 30, then q 3 yrs unless gastric cancer in the family, or gastric polyps identified
- Annual U/A +/- urine cytology starting at 30
- ? Evolving role for EUS in screening for pancreas

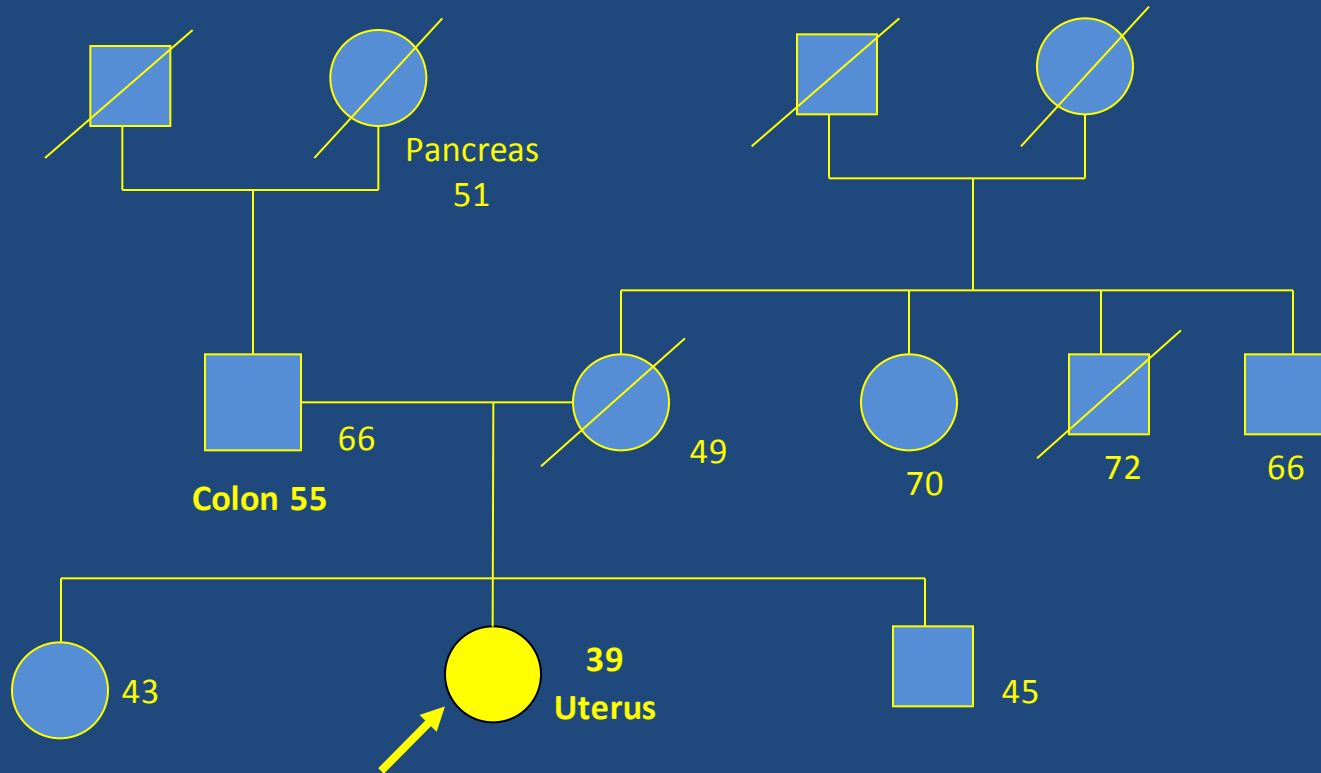
- *Age to start screening may need to be modified in families with cancers occurring at very young age

Case Study ME

- 39-year-old moderately obese female with menorrhagia
- Endometrial bx shows carcinoma
- Hysterectomy reveals Stage IA endometrioid carcinoma

- Family history reveals no other GYN malignancies
- Father had colon cancer at 55
- Paternal grandmother had pancreas cancer at 51

Case Study ME - FAMP



Case Study ME

- 39-year-old moderately obese female with Stage IA endometrial carcinoma
- At 44 she underwent her first screening colonoscopy (10-year rule), and was found to have a tubulovillous adenoma in the ascending colon

Case Study ME

- 39-year-old moderately obese female with Stage IA endometrial carcinoma
- At 44 she underwent her first screening colonoscopy (10-year rule), and was found to have a tubulovillous adenoma in the ascending colon
- Repeat colonoscopy one year later was normal
- When would you scope her again?

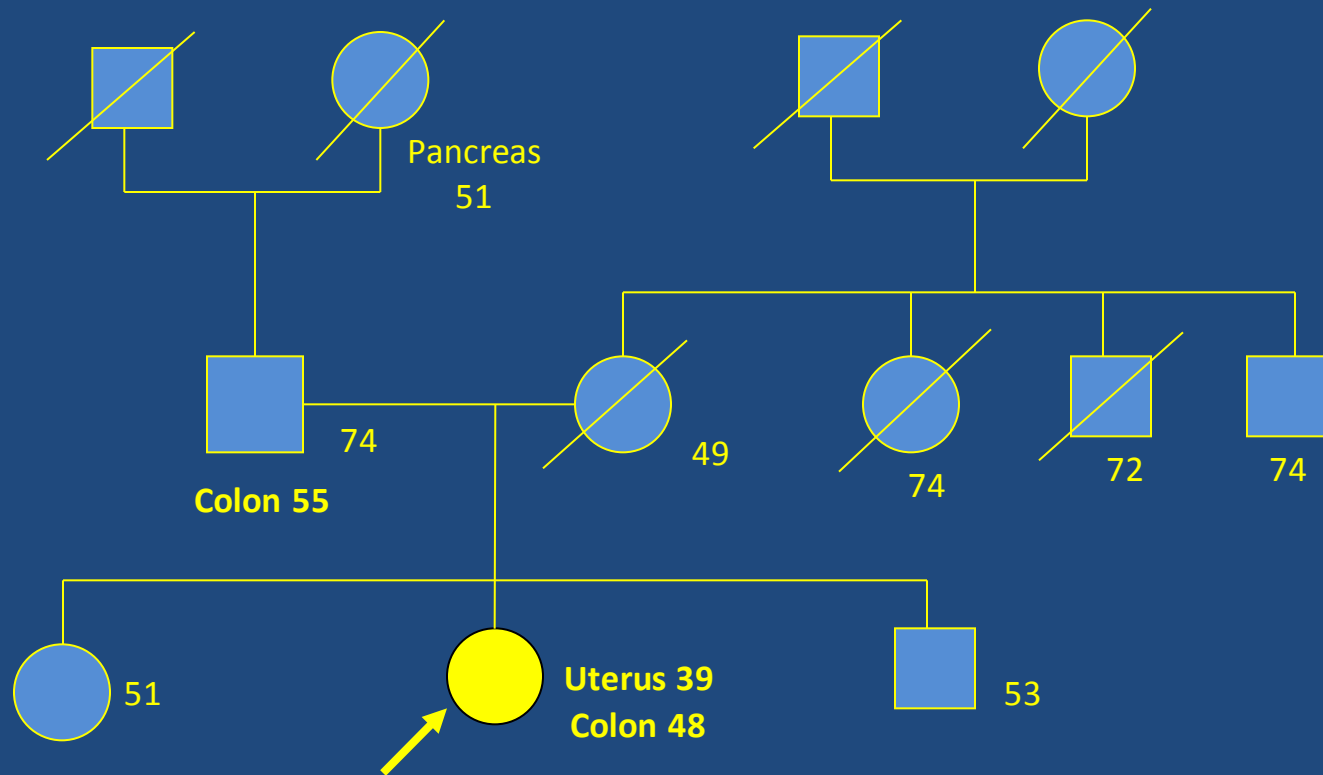
Case Study ME

- 39-year-old moderately obese female with Stage IA endometrial carcinoma
- At 44 she underwent her first screening colonoscopy (10-year rule), and was found to have a tubulovillous adenoma in the ascending colon
- She was advised to return for follow-up colonoscopy in 3 yrs

Case Study ME

- 39-year-old moderately obese female with Stage IA endometrial carcinoma
- At 44 she underwent her first screening colonoscopy (10-year rule), and was found to have a tubulovillous adenoma in the ascending colon
- She was advised to return for follow-up colonoscopy in 3 yrs
- At 48, she was found to have adenocarcinoma in the cecum
- Right hemicolectomy for Stage III-A cancer

Case Study ME -FAMP



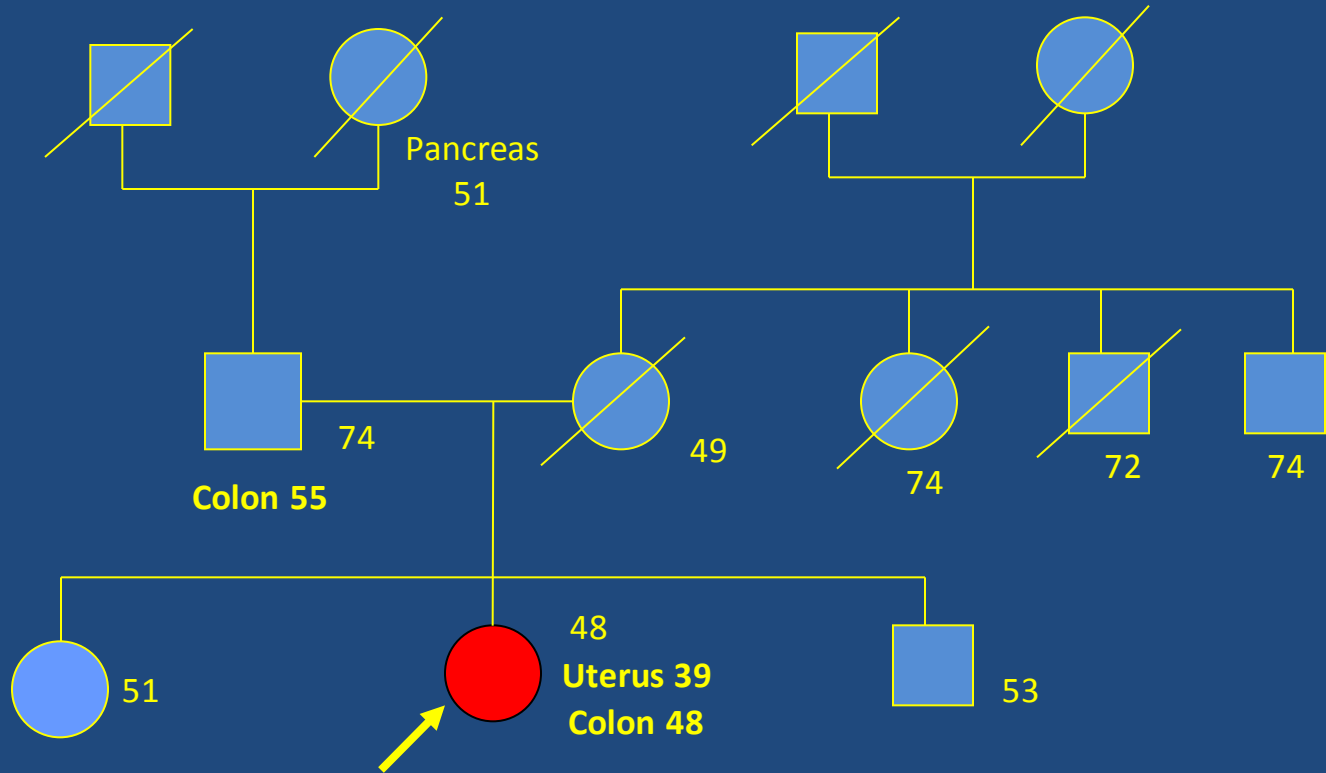
Case Study ME – “Red Flags”

- **39**-year-old moderately obese female with Stage IA **endometrial** carcinoma
- Right hemicolectomy at **48** for Stage II **cecal** cancer
- **Father had colon cancer** at 55
- **Paternal grandmother had pancreas cancer** at 51

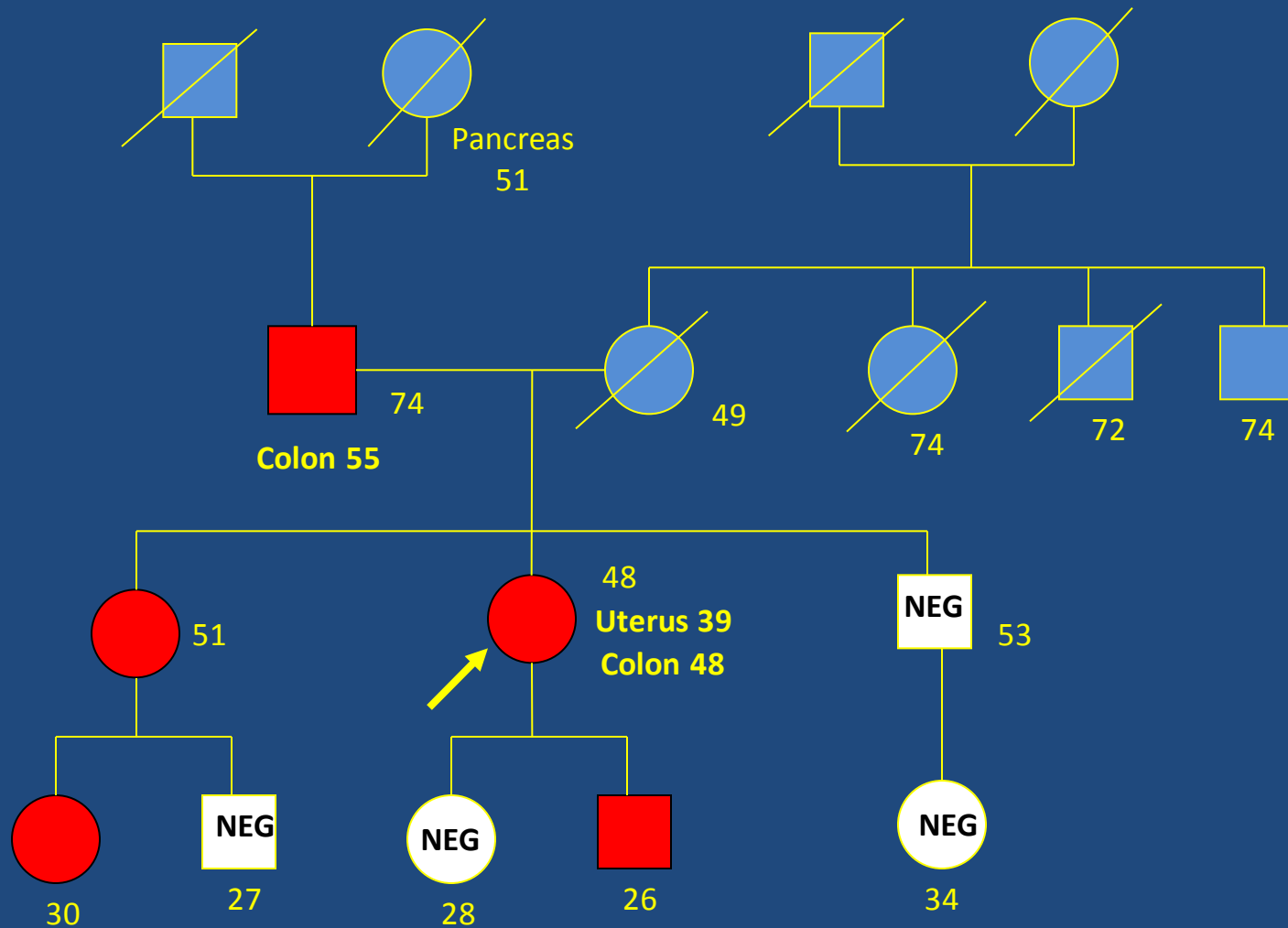
Case Study ME – “Red Flags”

- **39**-year-old moderately obese female with Stage IA **endometrial** carcinoma
- Right hemicolectomy at **48** for Stage II **cecal** cancer
- **Father had colon cancer** at 55
- **Paternal grandmother had pancreas cancer** at 51
- DNA testing revealed a mutation in **MSH6**

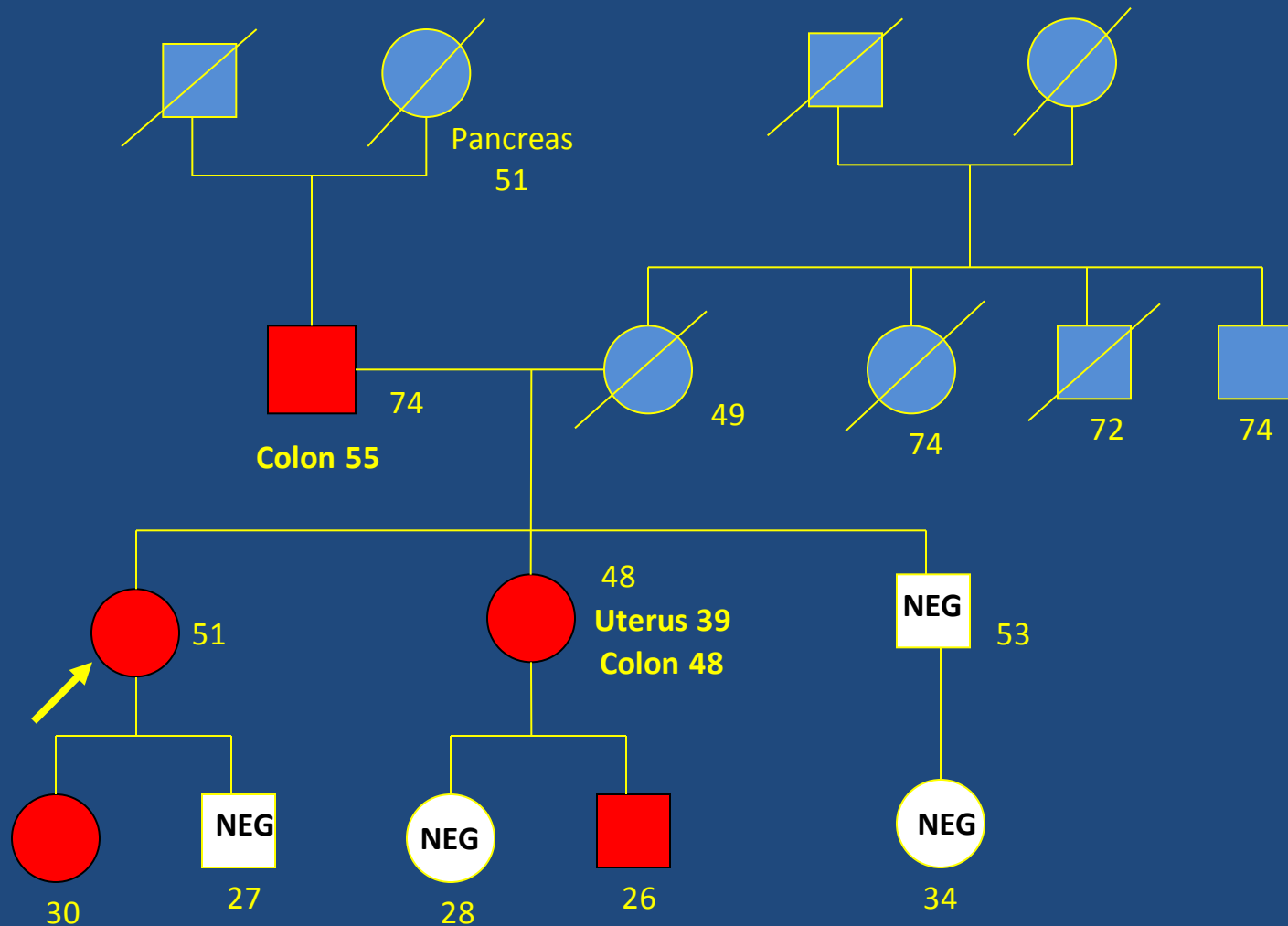
Case Study ME



Case Study ME



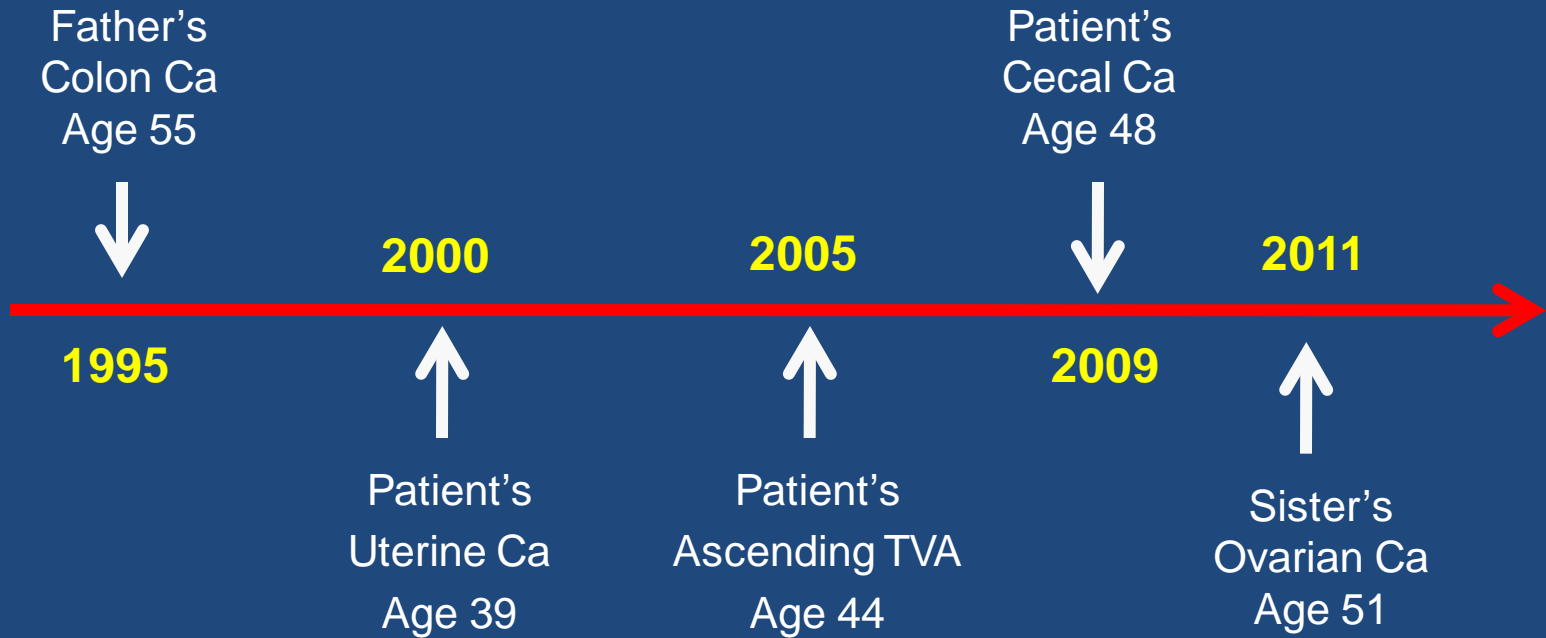
Case Study ME – The Sister



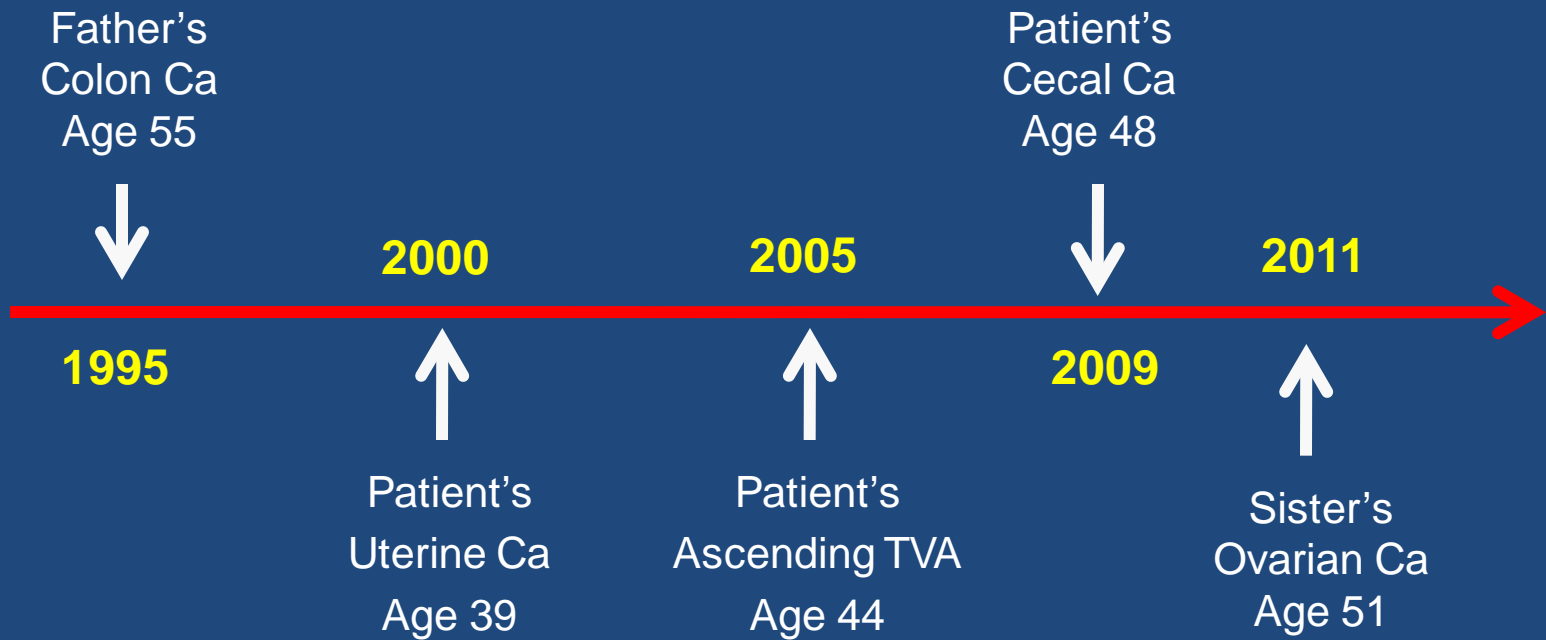
Case Study ME – The Sister

- Sister had normal colonoscopy and EGD
- Transvaginal sonogram showed a left adnexal mass, and CA-125 level was 580
- Mucinous cystadenocarcinoma of the ovary, Stage IIIC

Case Study ME Time-Line

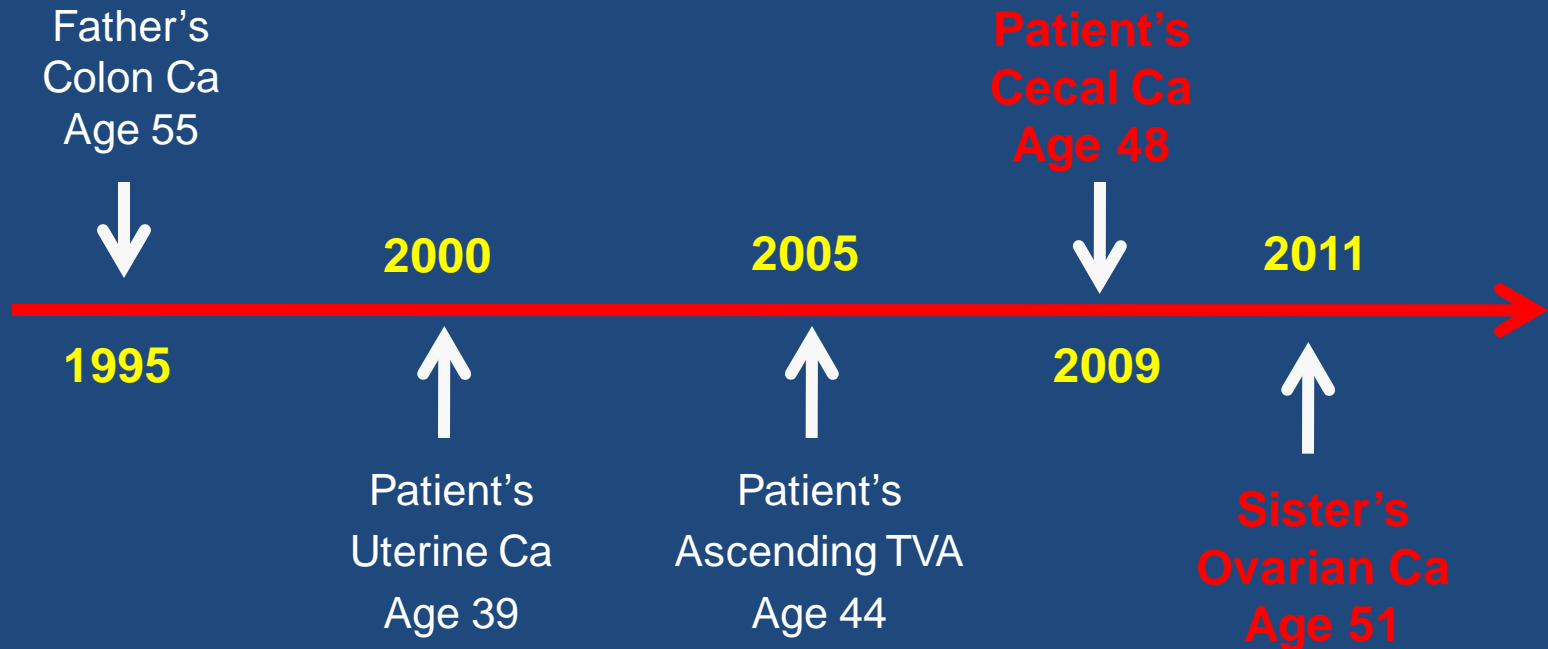


Case Study ME Time-Line



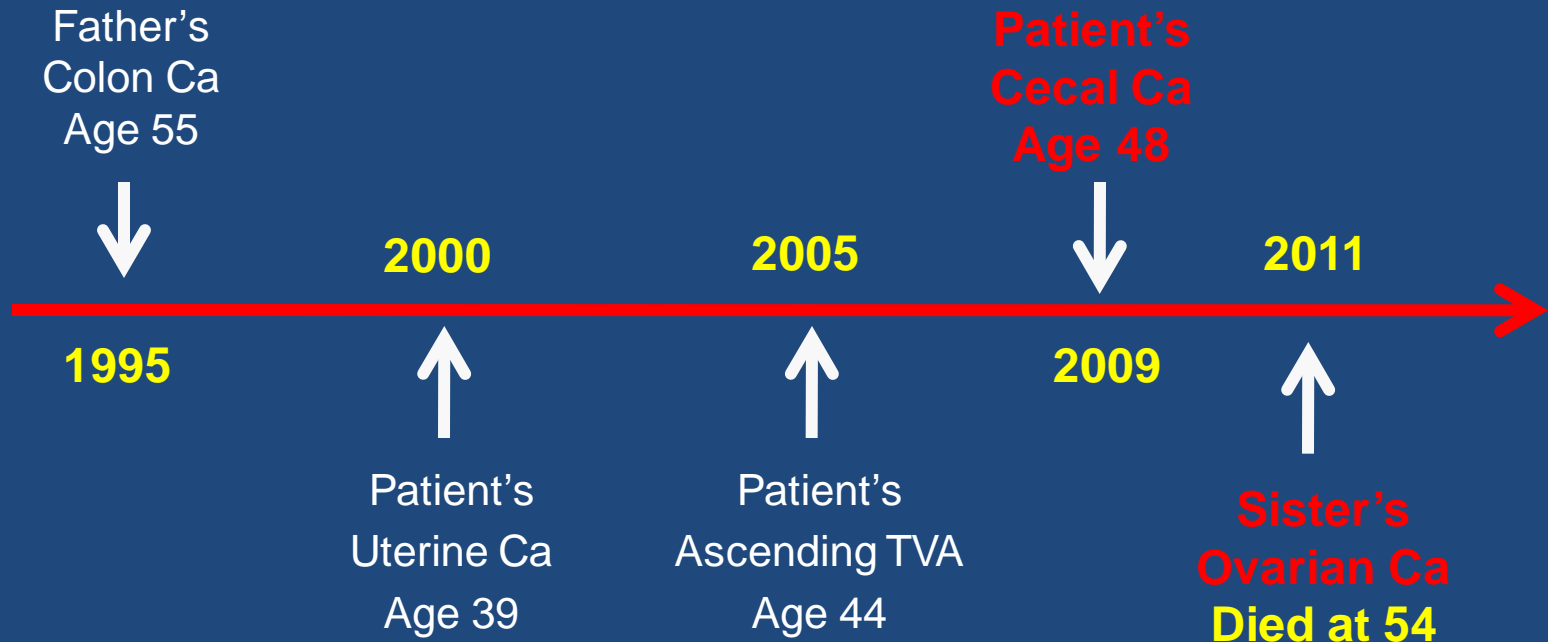
When should this family have been diagnosed?

Case Study ME Time-Line



At least 2 of these cancers could have been prevented

Case Study ME Time-Line



**At least 2 of these cancers could have been prevented
.....and 1 death**

Case Study RT

- 51 y/o woman with Stage II-B cancer of the cecum
- Presented with abdominal cramping only 18 months out from a normal screening colonoscopy
- First colonoscopy at age 25, and q 3 yrs since then
- Brother diagnosed with Stage IV colon ca at age 23
- Right hemicolectomy performed

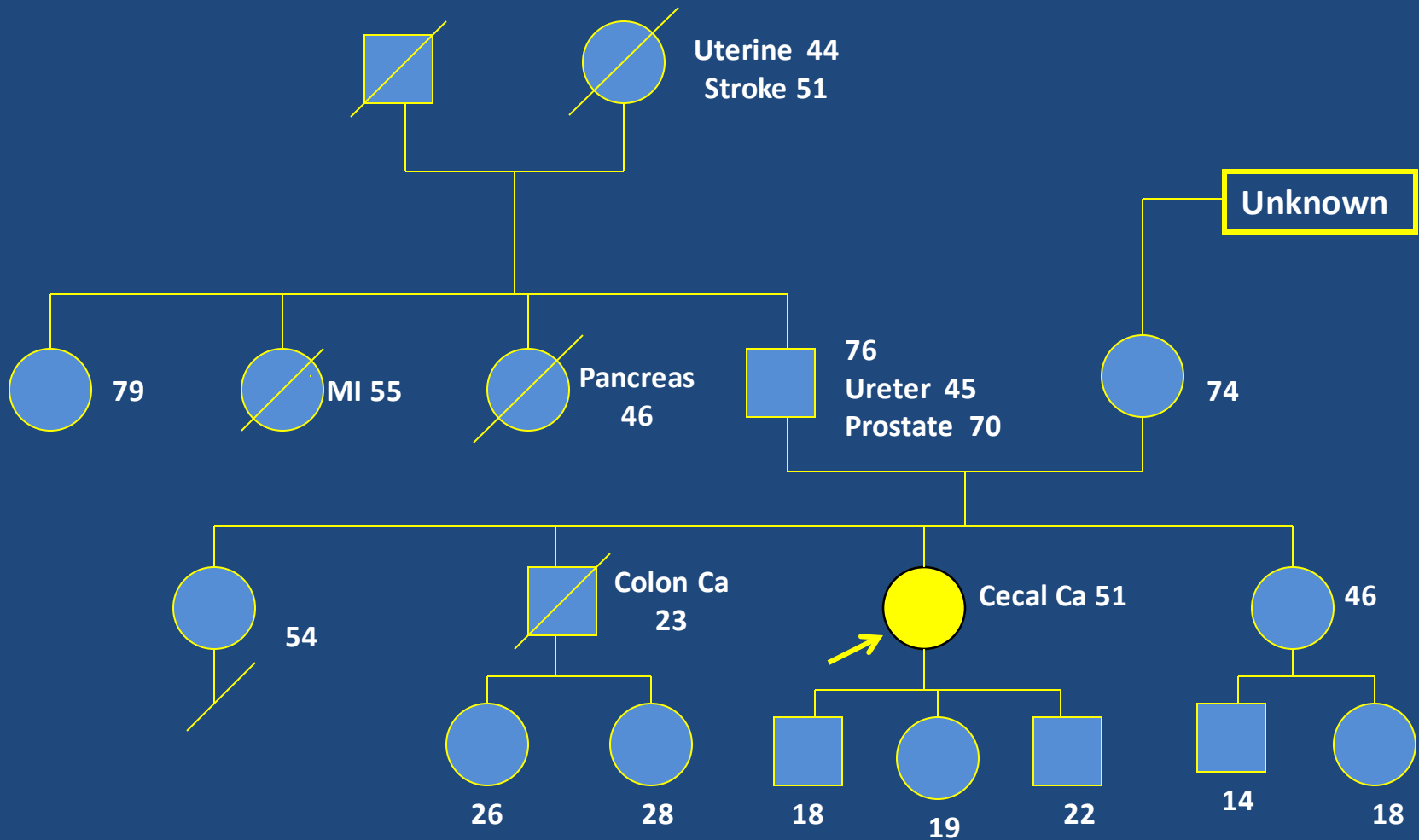
Case Study RT

- Brother died of colon cancer at 23
- No colon polyps in either sister with q3yr surveillance
- Father had ureteral ca at 45, then prostate ca at 70
- Paternal aunt died of pancreas ca at 46
- Paternal GM had uterine ca at 44

Case Study RT – “Red Flags”

- 51 y/o woman with Stage II-B cancer of the **cecum**, diagnosed **only 18 months after a normal colonoscopy**
- Brother diagnosed with Stage IV colon ca at age 23
- Father had **ureteral ca** at 45, then prostate ca at 70
- Paternal aunt died of **pancreas** ca at 46
- Paternal GM had **uterine ca at 44**

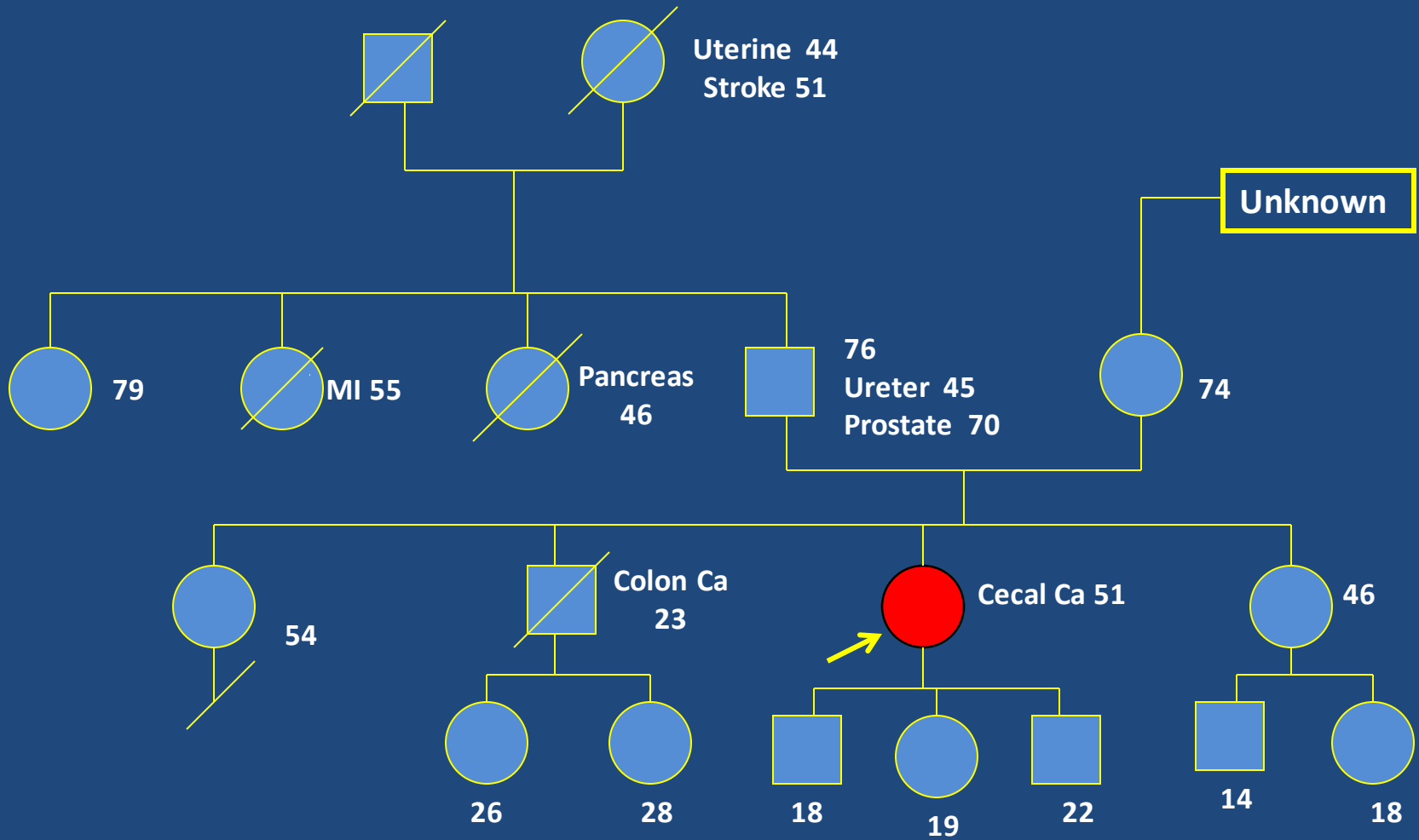
Case Study RT - FAMP



Case Study RT

- Genetic evaluation revealed a mutation in **MLH1**

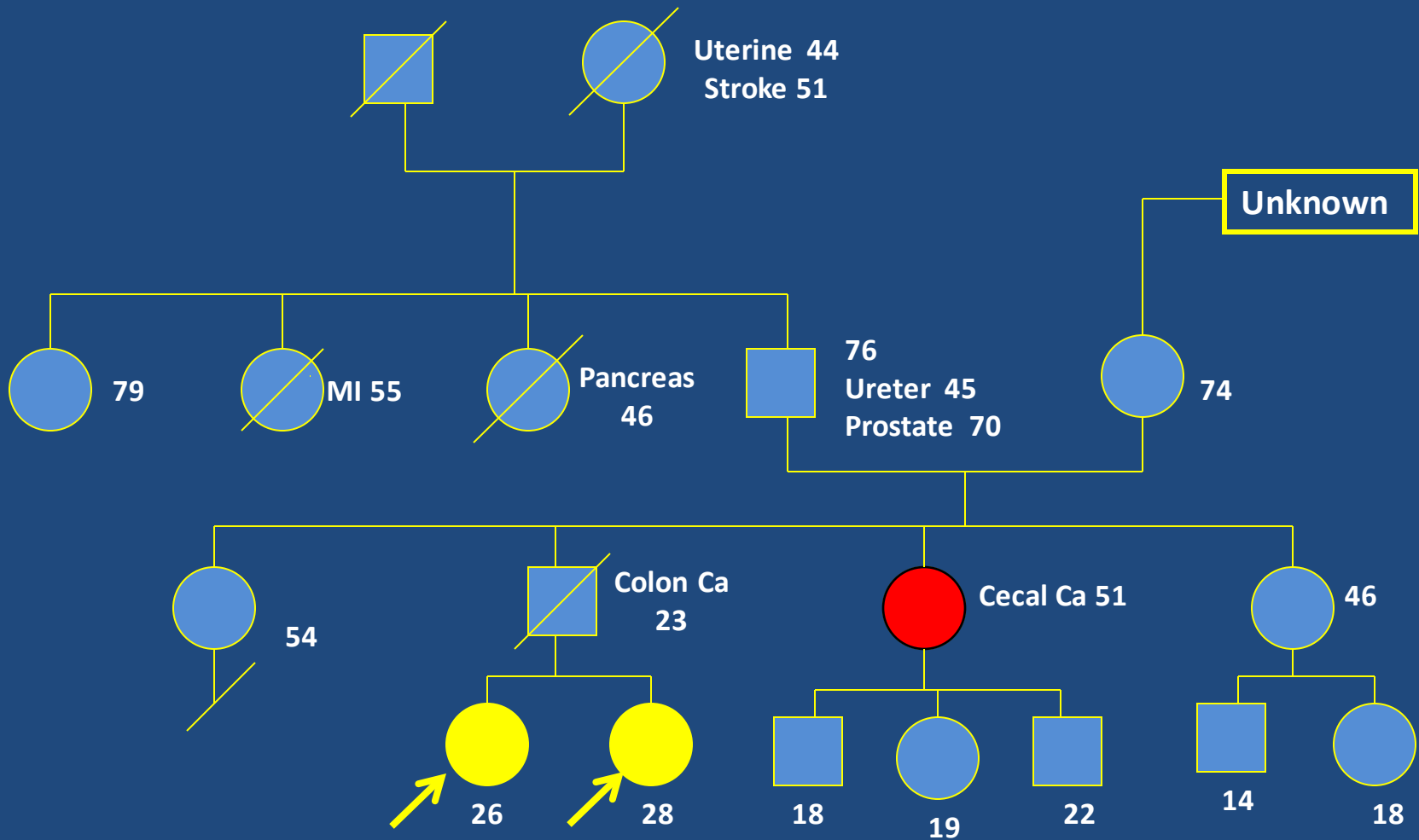
Case Study RT



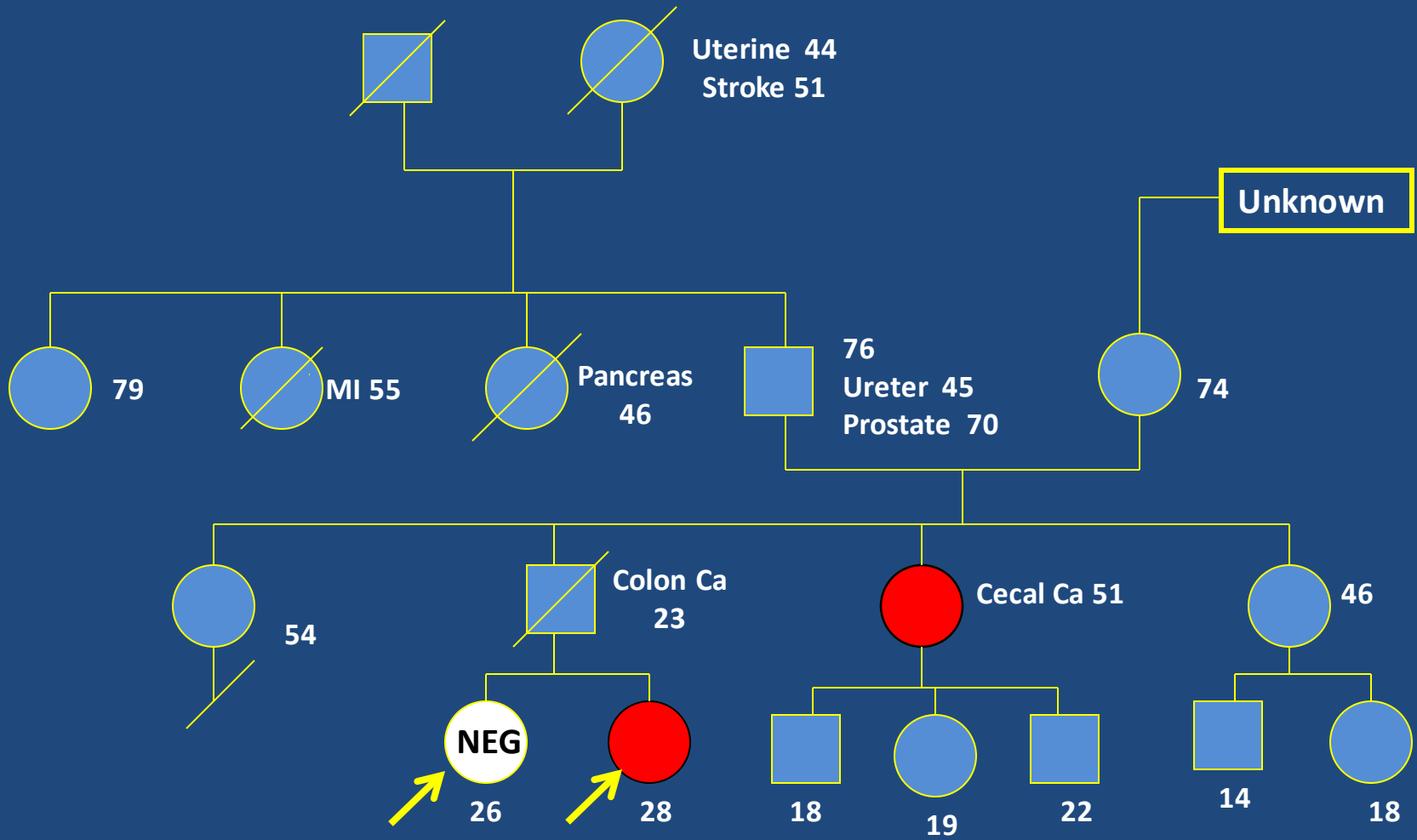
Case Study RT

- Genetic evaluation revealed mutation in **MLH1**
- Patient needed a second operation to remove her uterus and ovaries

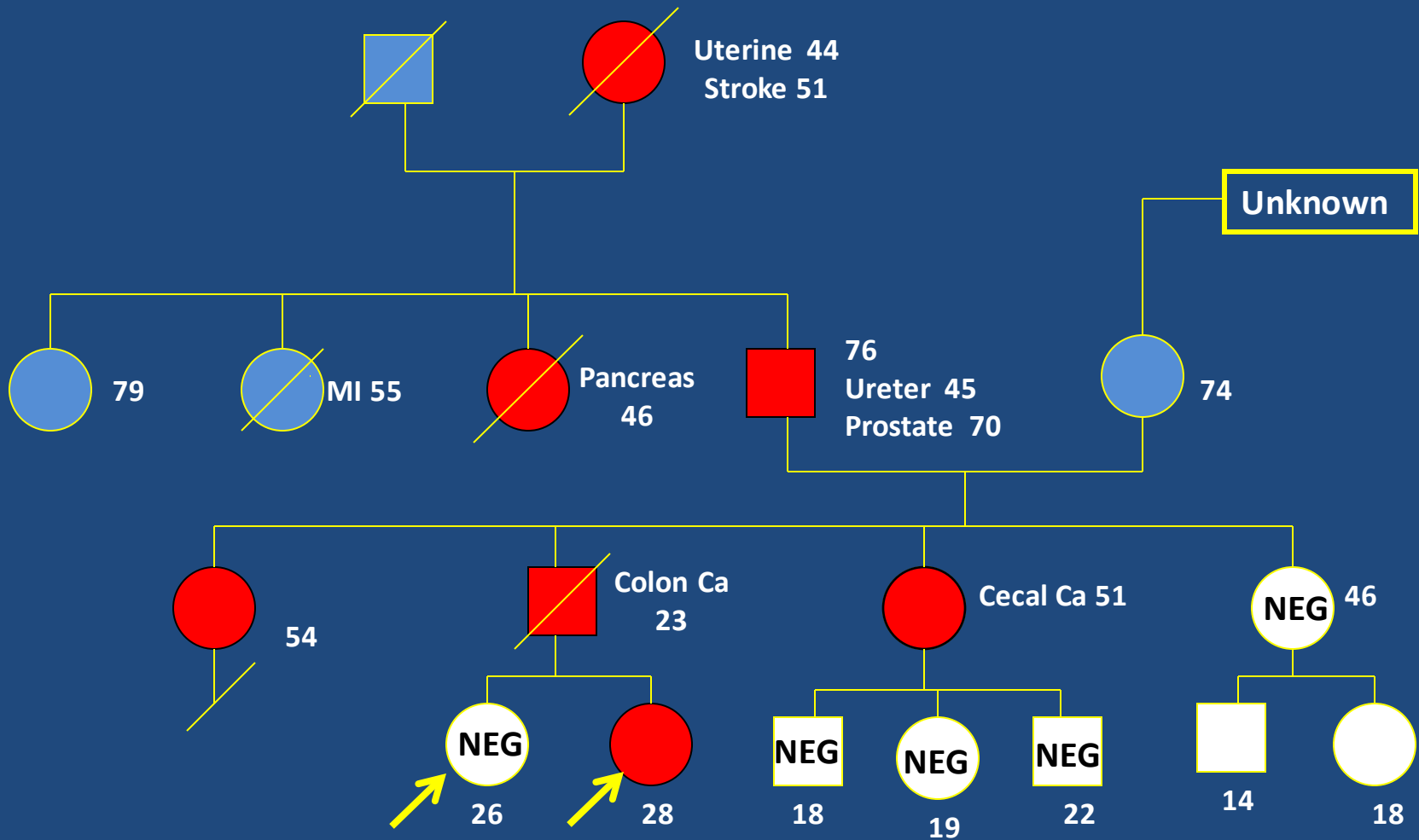
Case Study RT – The Nieces



Case Study RT – The Nieces



Case Study RT



Lynch Syndrome: How Are We Doing?

- Fewer than 2% of all patients affected with Lynch syndrome have yet been identified
- **Approximately 20-25% of all colorectal and endometrial cancer patients are suitable for focused genetic evaluation**

Screening For Lynch Syndrome: The Traditional Approach

- Traditional dependence on providers to identify these patients has been largely ineffective:
 - Wide spectrum of cancers and physicians
 - Providers underestimate the prevalence of these syndromes, and the associated cancer risks
 - Too much reliance on the “slam dunk” family history
 - Too little attention to the phenotype that is typical for Lynch colon cancer
- Families get missed, cancers continue to occur

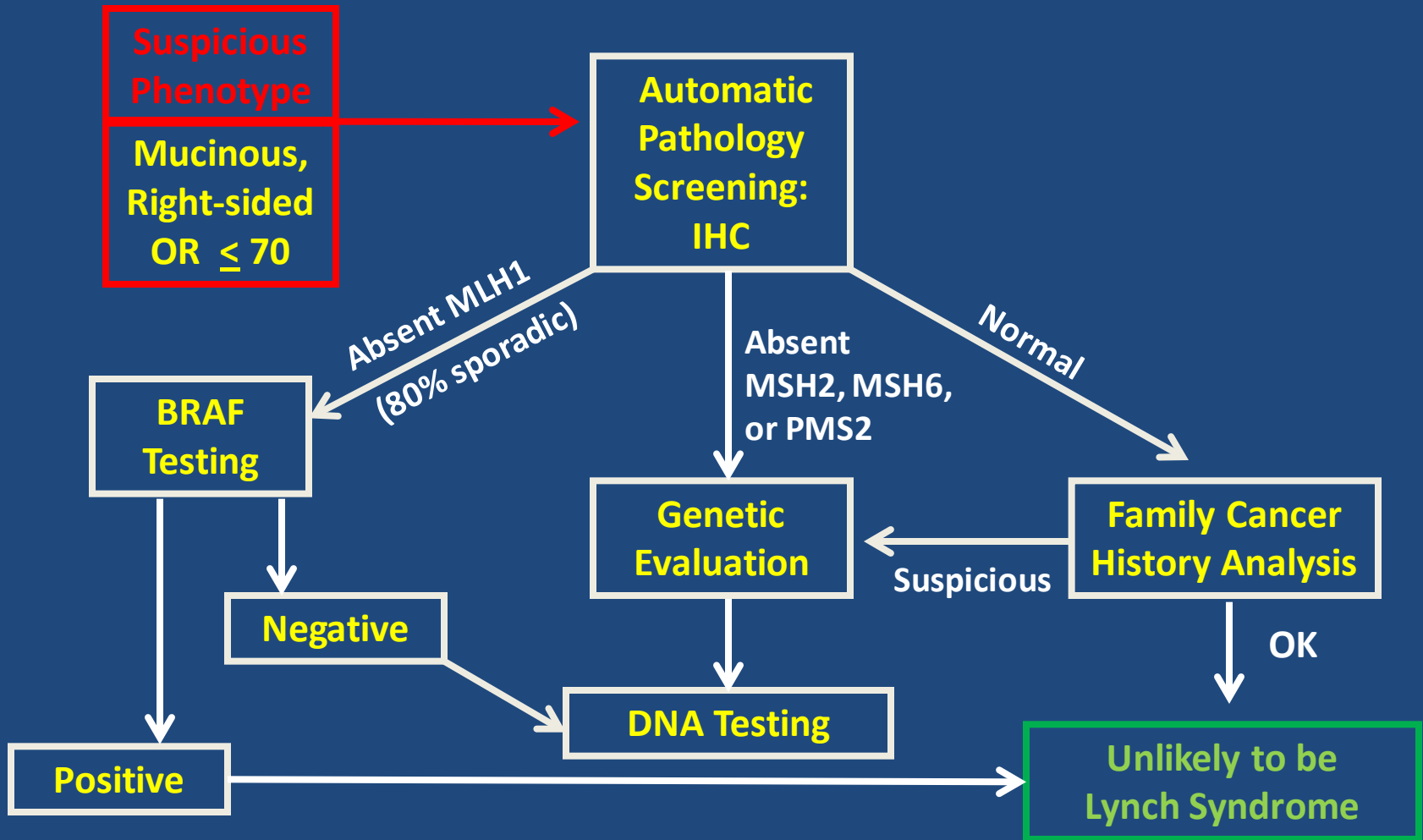
Screening For Lynch Syndrome: The Pathology Approach

- **Automatic screening** of colon or endometrial cancers at the pathology level using MSI or IHC testing
- 15% of all colon cancers will exhibit MSI or abnormal IHC , and 90% of the Lynch colon cancers will be within this group
- **Finding the 3% that are Lynch syndrome within this 15% is much easier than finding the 3% within the 100%**

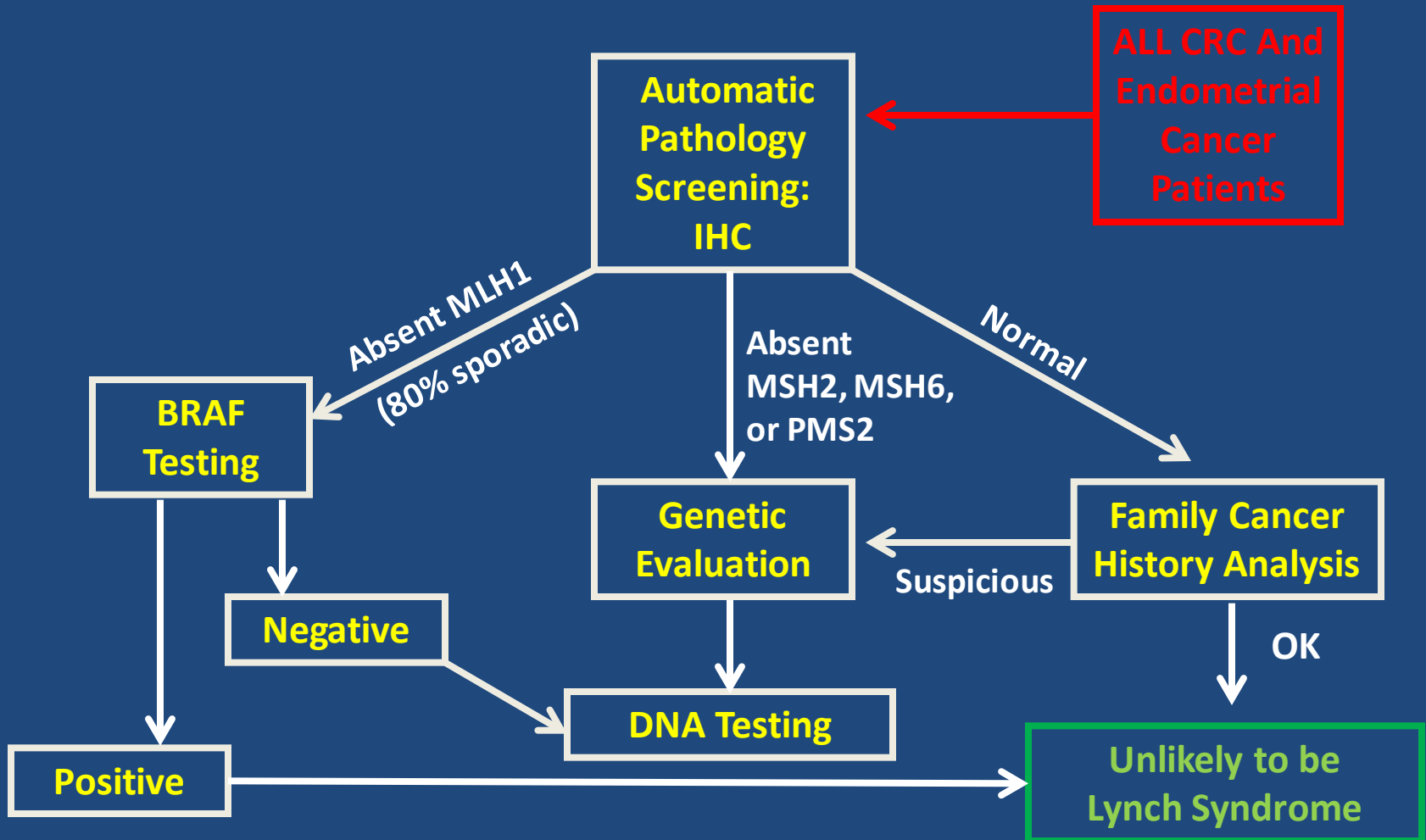
Screening For Lynch Syndrome: The Pathology Approach

- If MSI or IHC is abnormal, a genetic evaluation and appropriate DNA testing is triggered
- Most labs favor IHC over MSI screening:
 - Faster, cheaper, more readily available
 - Can be performed on biopsy material
 - May provide insight as to which of the MMR genes is defective

Lynch Syndrome Algorithm: The CRC Pathology Approach



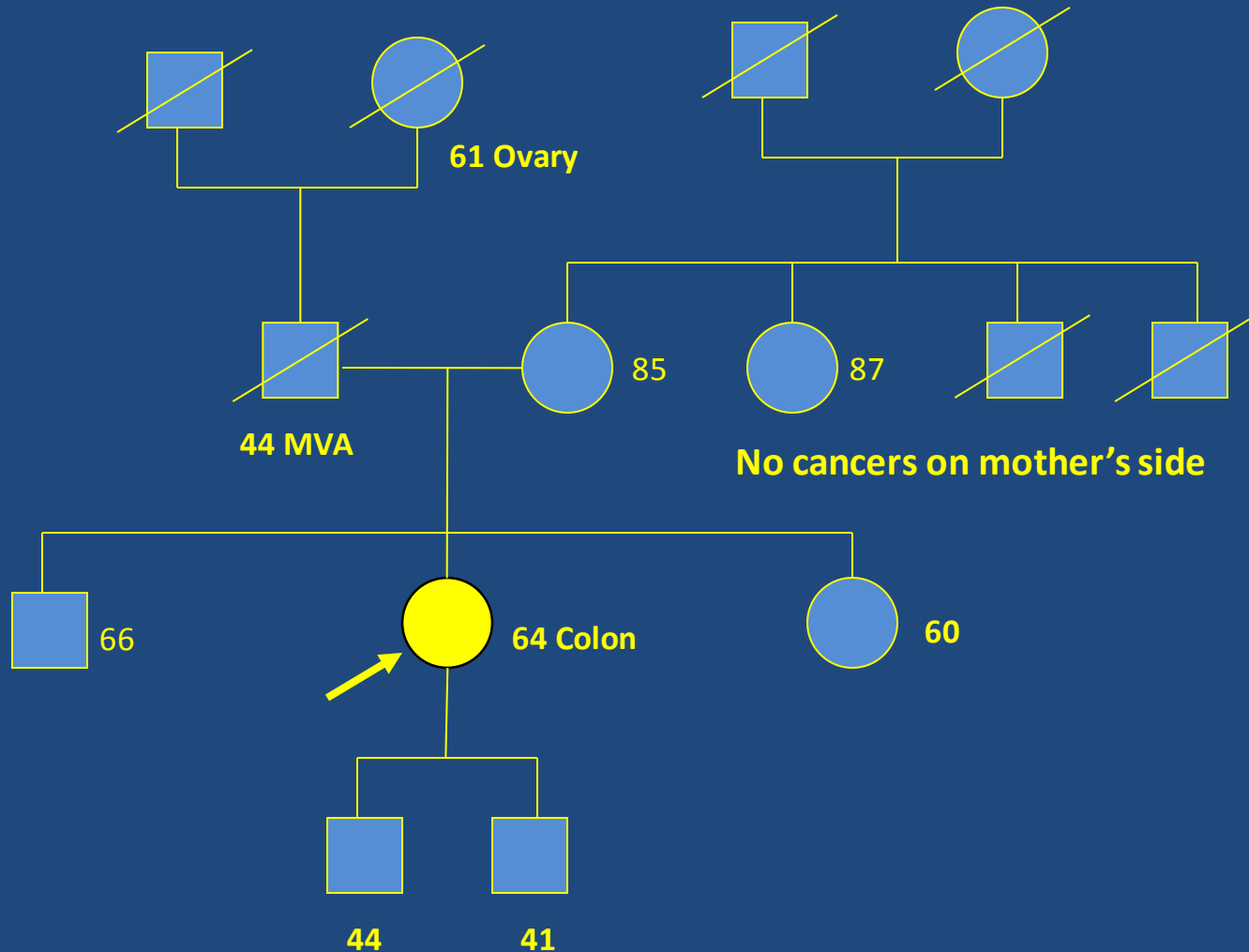
Lynch Syndrome Algorithm: The Universal Pathology Approach



Case Study PS

- 64 y/o woman found to have cancer in the descending colon on routine colonoscopy
- Left hemicolectomy, Stage II-A
- Previous TAH at 49 for fibroids
- Paternal grandmother had ovarian cancer at 61

Case Study PS



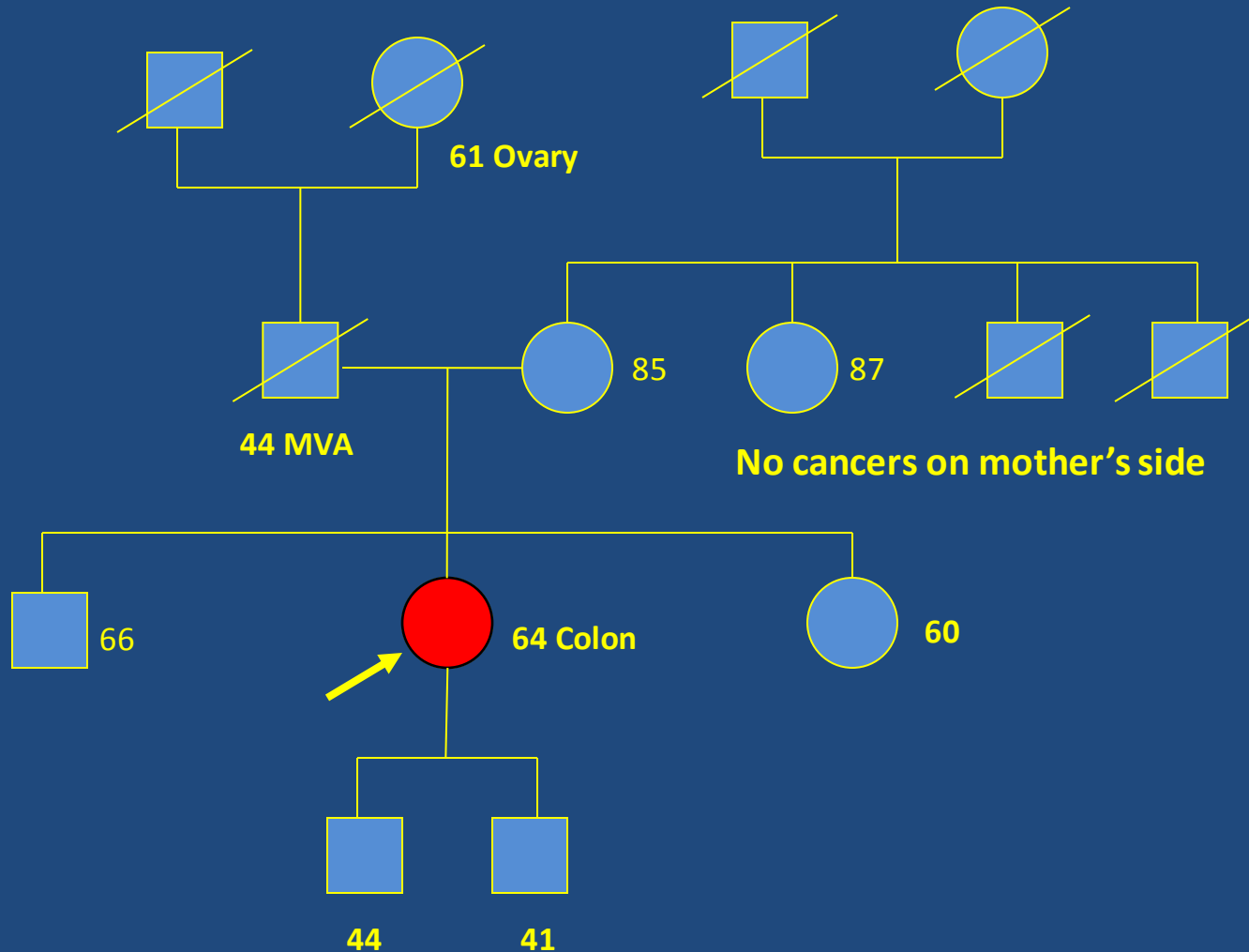
Case Study PS - No Red Flags

- 64 y/o woman found to have cancer in the descending colon on routine colonoscopy
- Left hemicolectomy, Stage II-A
- Previous TAH at 49 for fibroids
- Paternal grandmother had ovarian cancer at 61

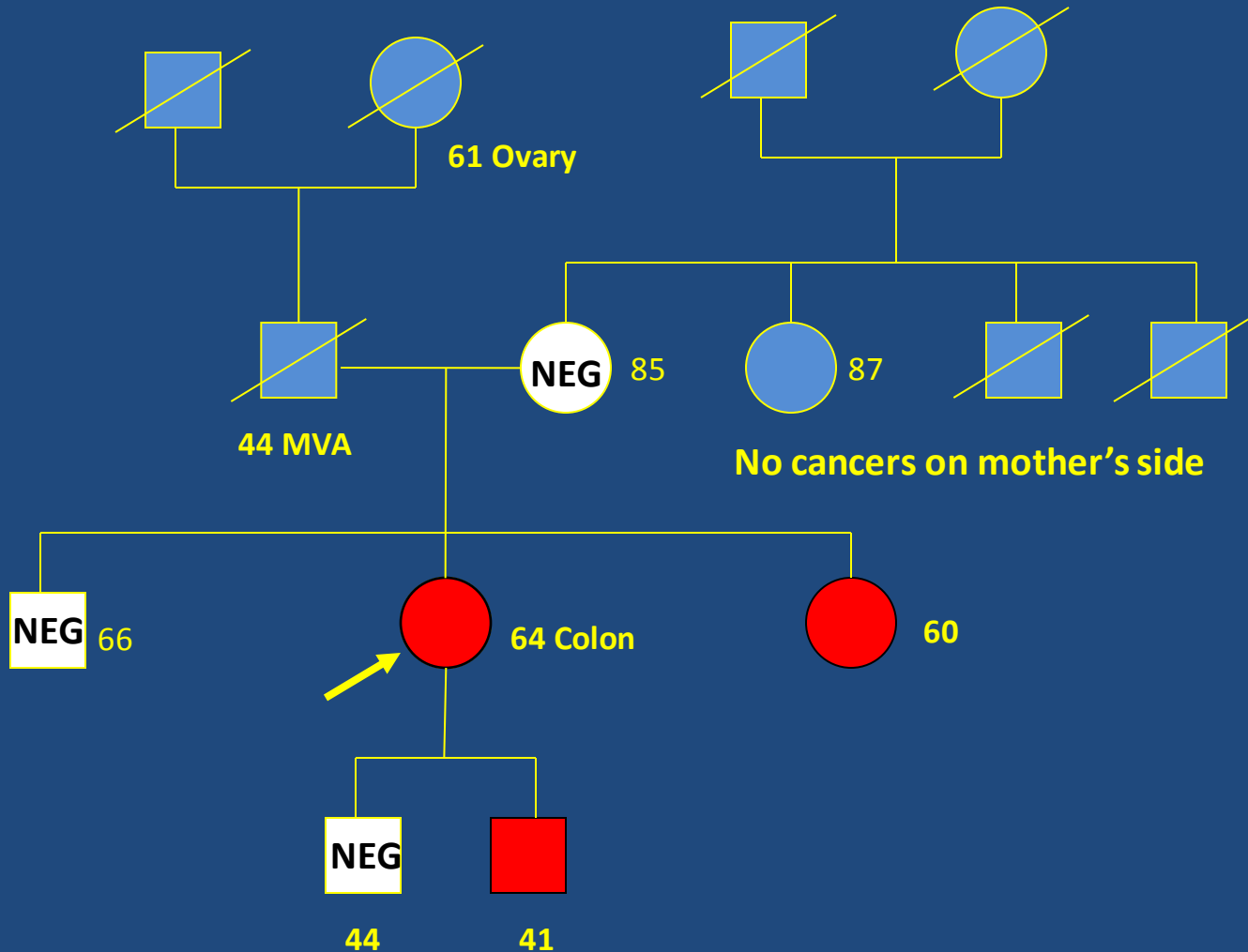
Case Study PS

- 64 y/o woman found to have cancer in the descending colon on routine colonoscopy
- Left hemicolectomy, Stage II-A
- Previous TAH at 49 for fibroids
- **Automatic pathology screening with IHC shows that the MSH6 protein is not expressed in the cancer**
- DNA testing confirms a mutation in the **MSH6** gene

Case Study PS



Case Study PS



Screening For Lynch Syndrome: Limitations of The Pathology Approach

- It will still miss the 10% of Lynch CRC and endometrial cancer who have normal tumor testing with IHC
- Still need proper attention to the family history, requiring providers to know the spectrum of Lynch cancers
- This strategy will not help to identify the many Lynch patients who are among the cancer survivors, or the carriers who have not yet had cancer

Summary and Call To Action

- These syndromes are more common than you may realize, and they are easily missed
- The potential impact on both cancer prevention and cancer management can be huge
- The cumulative number of colon adenomas needs to be systematically tracked in all patients with polyps

Summary and Call To Action

- Pay attention to family history of cancers other than CRC
 - Uterus, ovary, gastric, pancreas, urothelial
 - Update every time patient returns
- Universal IHC screening for MMR proteins should be performed on all CRC and endometrial cancer patients
- Consider doing it on biopsy material so that genetic results can be known before definitive surgery

Summary and Call To Action

- Rigorous application of the “red flags” will capture the majority of families in newly diagnosed patients
- Testing should be considered soon after diagnosis in appropriate patients
- A systematic process is required for providers to find the affected patients among their survivor populations

Summary and Call To Action

- Cancer genetics is now a critical element in providing high quality comprehensive cancer care
- Every physician and nurse has a role to play in identifying these patients and their families
- We can prevent many cancers that were destined to occur