The Problem

Lynch syndrome is under-recognized

The Solution

Collaboration between Surgeon, Pathologist and Genetic Counselor

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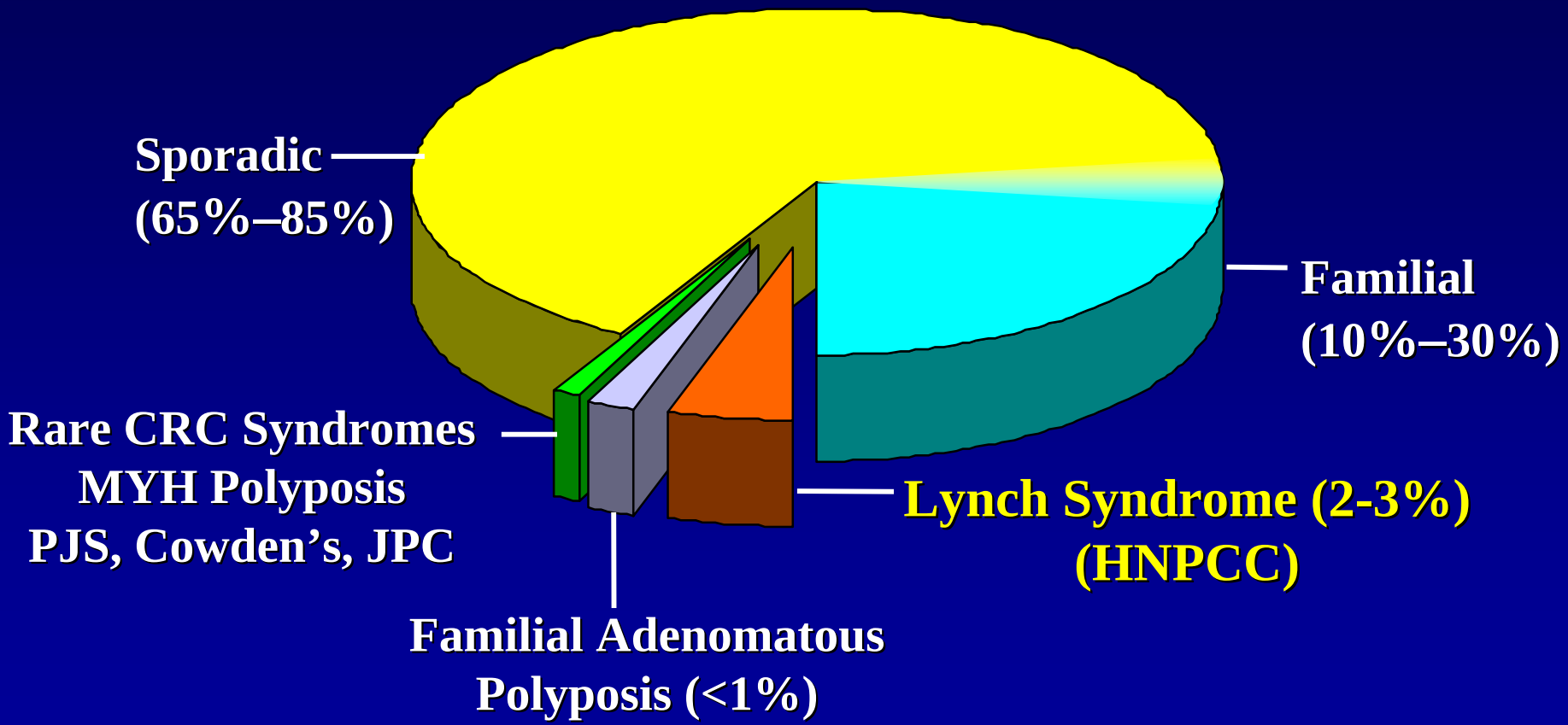
Learning Objectives

- Recognize that Lynch Syndrome is an important clinical problem
- Understand why Lynch Syndrome is under-recognized
- Discuss proposal for molecular analysis of all CRCs

Hereditary Colon Cancer Syndromes



Adapted from Burt RW et al. *Prevention and Early Detection of CRC*, 1996

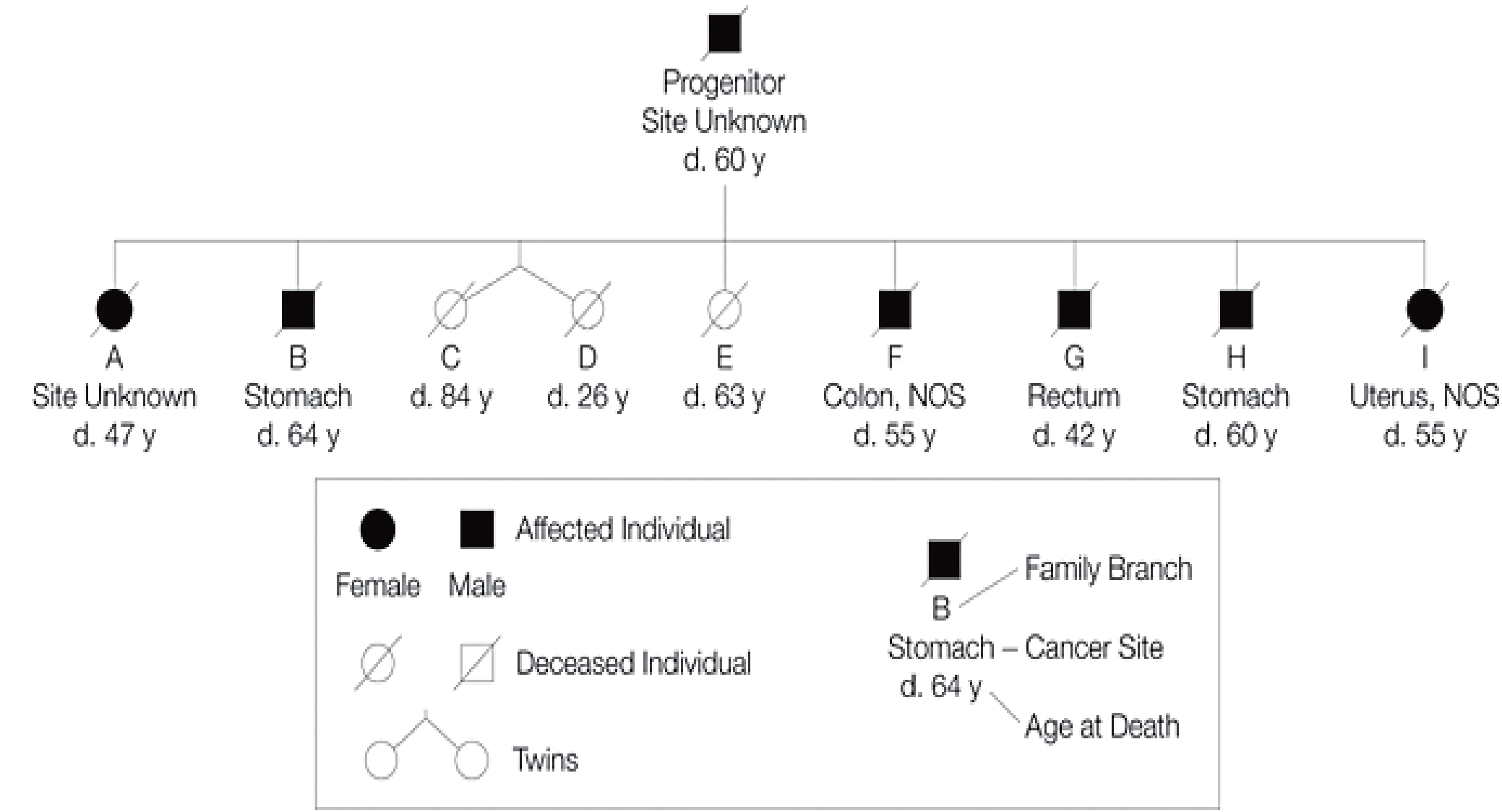
Warthin Syndrome?

- Aldred Scott Warthin MD PhD
- University of Michigan, Dept of Pathology 1895-1931

A little field, well tilled
Sir William Osler

- Seamstress' story
- Family G

Warthin- Family G

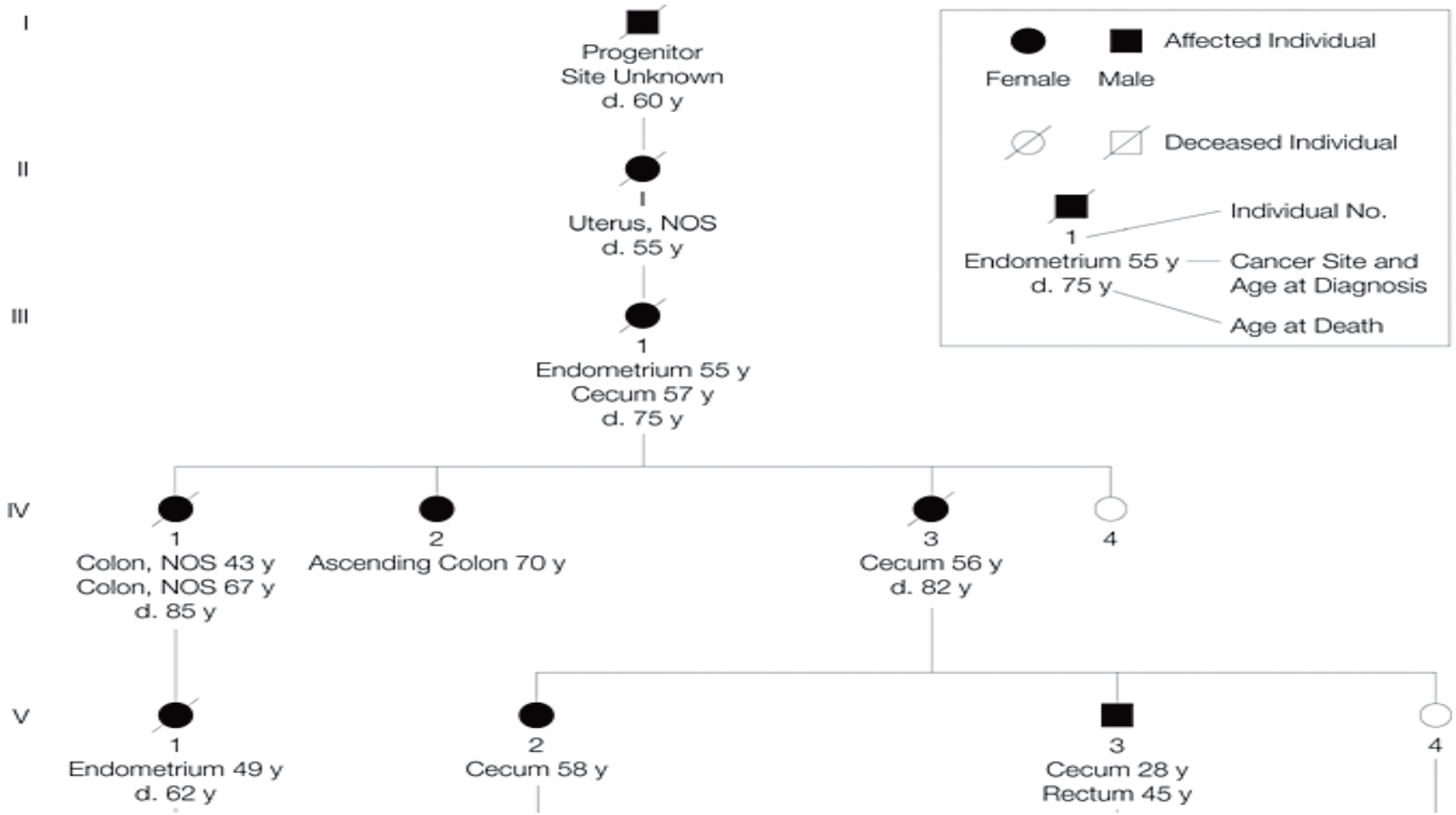


Lynch Syndrome

- Updated Family G
- Described other families
- Popularized recognition of Hereditary Colon Cancer Syndromes

Henry T. Lynch, M.D.
Professor of Medicine and Prev Medicine
Creighton University School of Medicine

Lynch- Family G, Branch I



What's in a name?

Cancer Fraternities

Cancer Family Syndrome

Hereditary Site Specific Colorectal Cancer

Lynch Syndrome

- Lynch Syndrome I- colon only families
- Lynch Syndrome II- colon, uterus, others

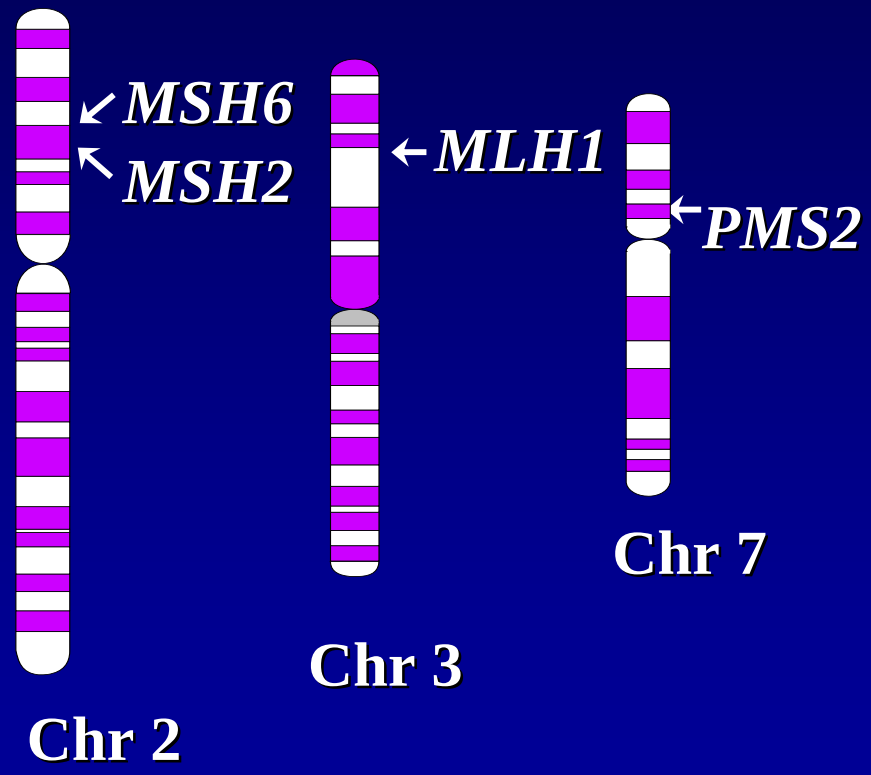
Hereditary Nonpolyposis Colorectal Cancer (HNPCC)

Muir-Torre Syndrome (with skin manifestations)

Turcot Syndrome (with brain tumors)

Genetic Features of Lynch Syndrome

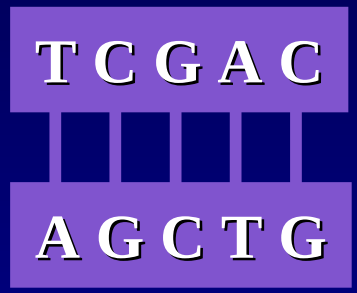
- Familial Clustering of CRC
- Autosomal Dominant
  - Vertical Transmission
  - 50% risk in siblings/children
- Due to germline mutation in one of 4 DNA mismatch repair genes



Lynch Syndrome Results From Failure of Mismatch Repair (MMR) Genes

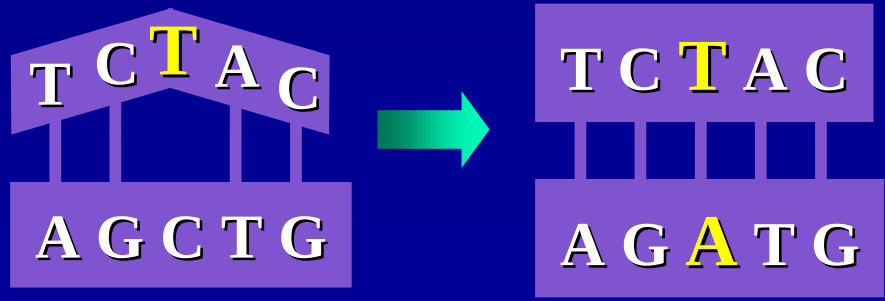
Base pair mismatch

Normal DNA repair

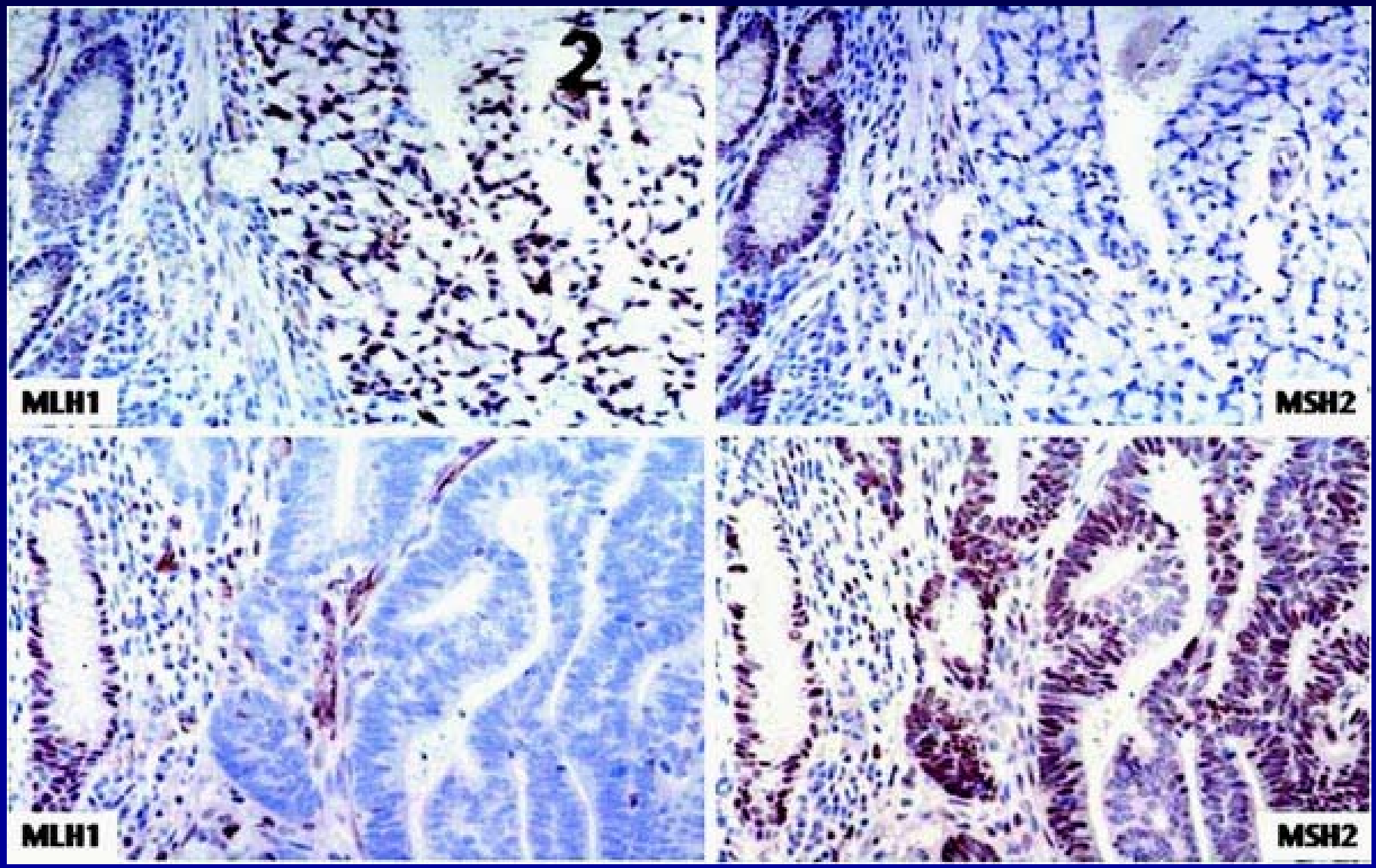


Molecular Diagnosis of Lynch CRCs
Loss of MMR proteins by IHC
or MSI by PCR

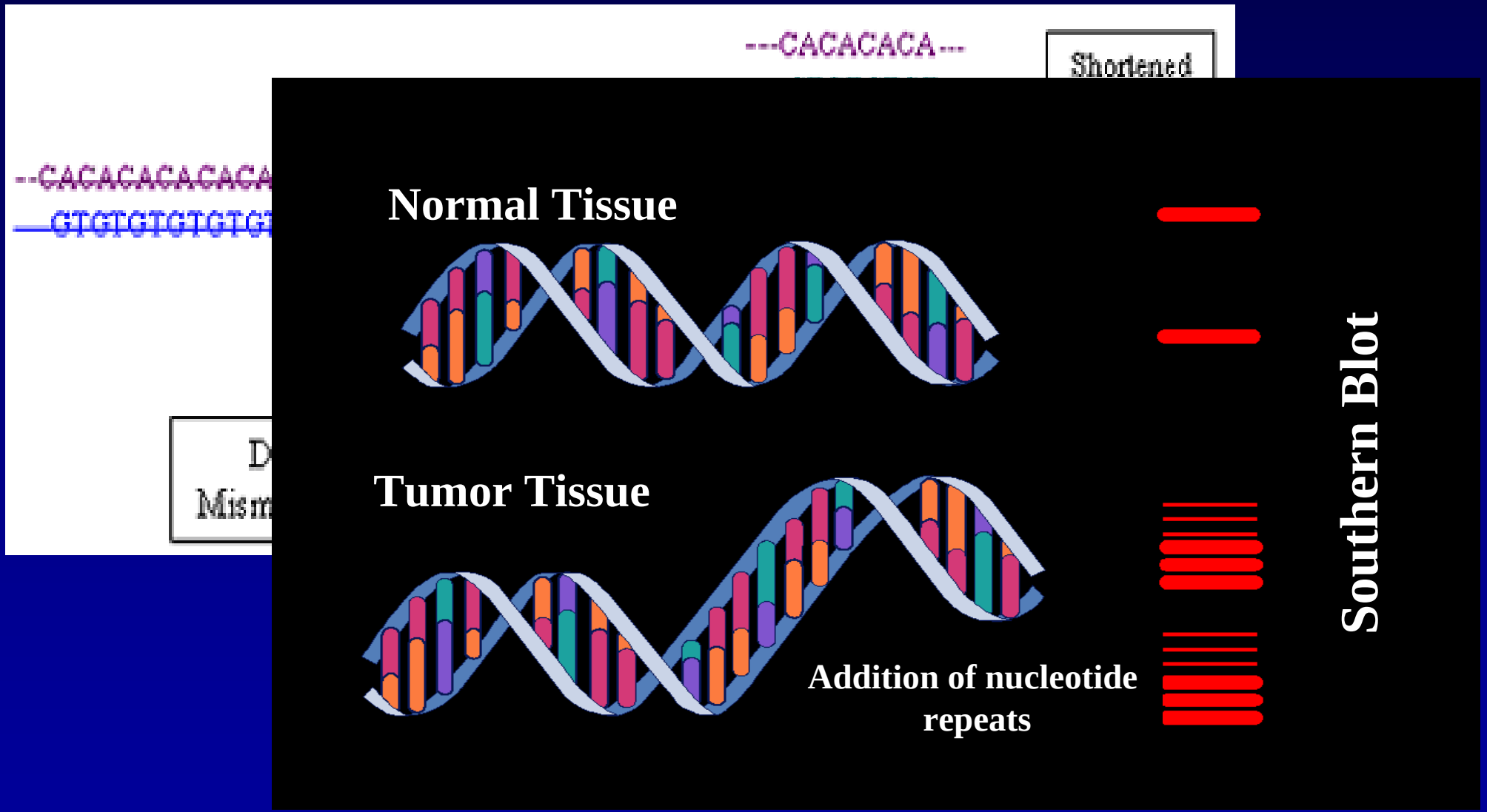
Defective DNA repair (MMR+)



IHC for MMR Proteins

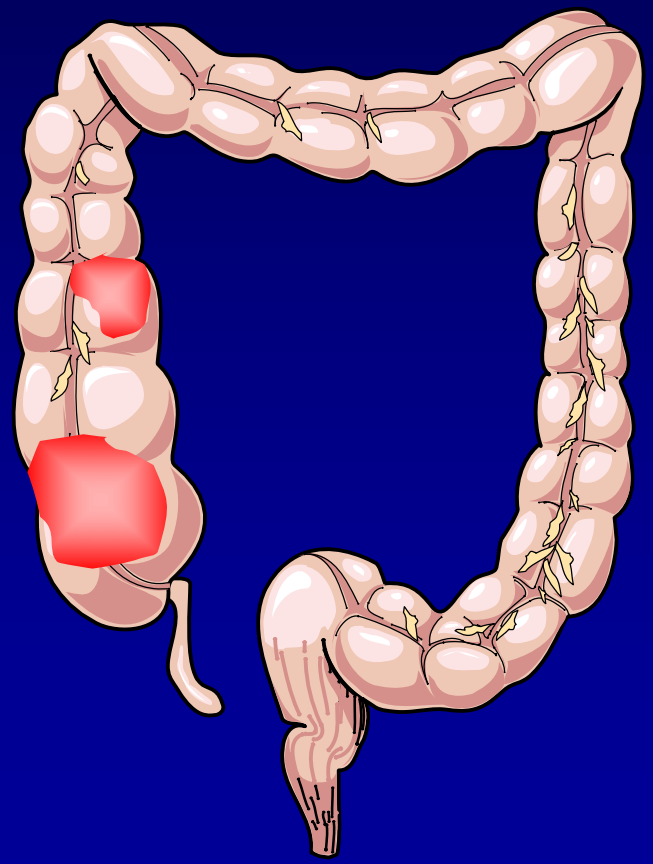


MMR System Repairs Replication Looping

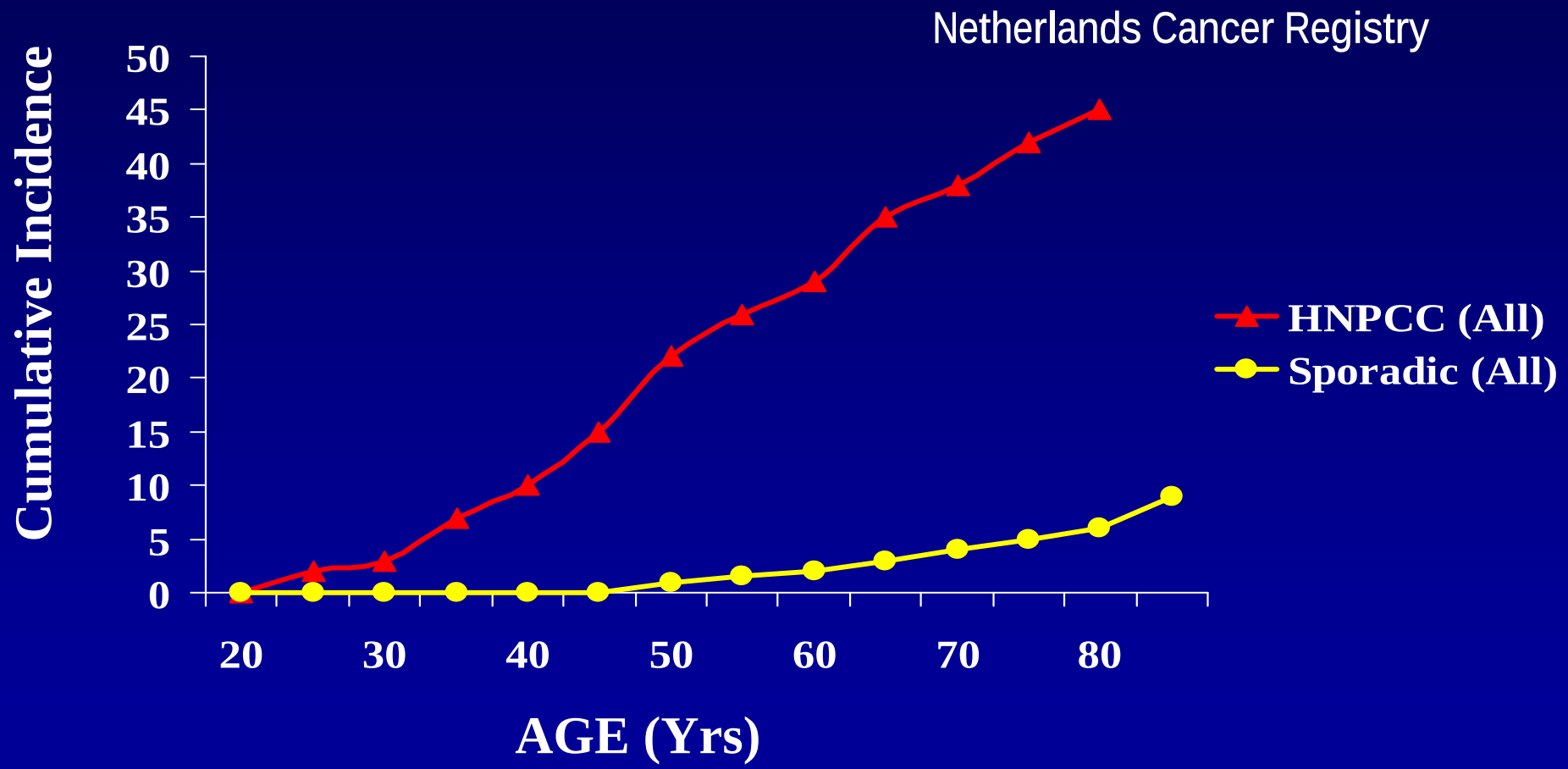


Clinical Features of Lynch Syndrome

- High CRC risk- up to 80%
- Few adenomas with high cancer propensity
- Early onset- 44 yrs
- Proximal location- 65%
- Synchronous/Metachronous CRC- 20%
- Other cancers

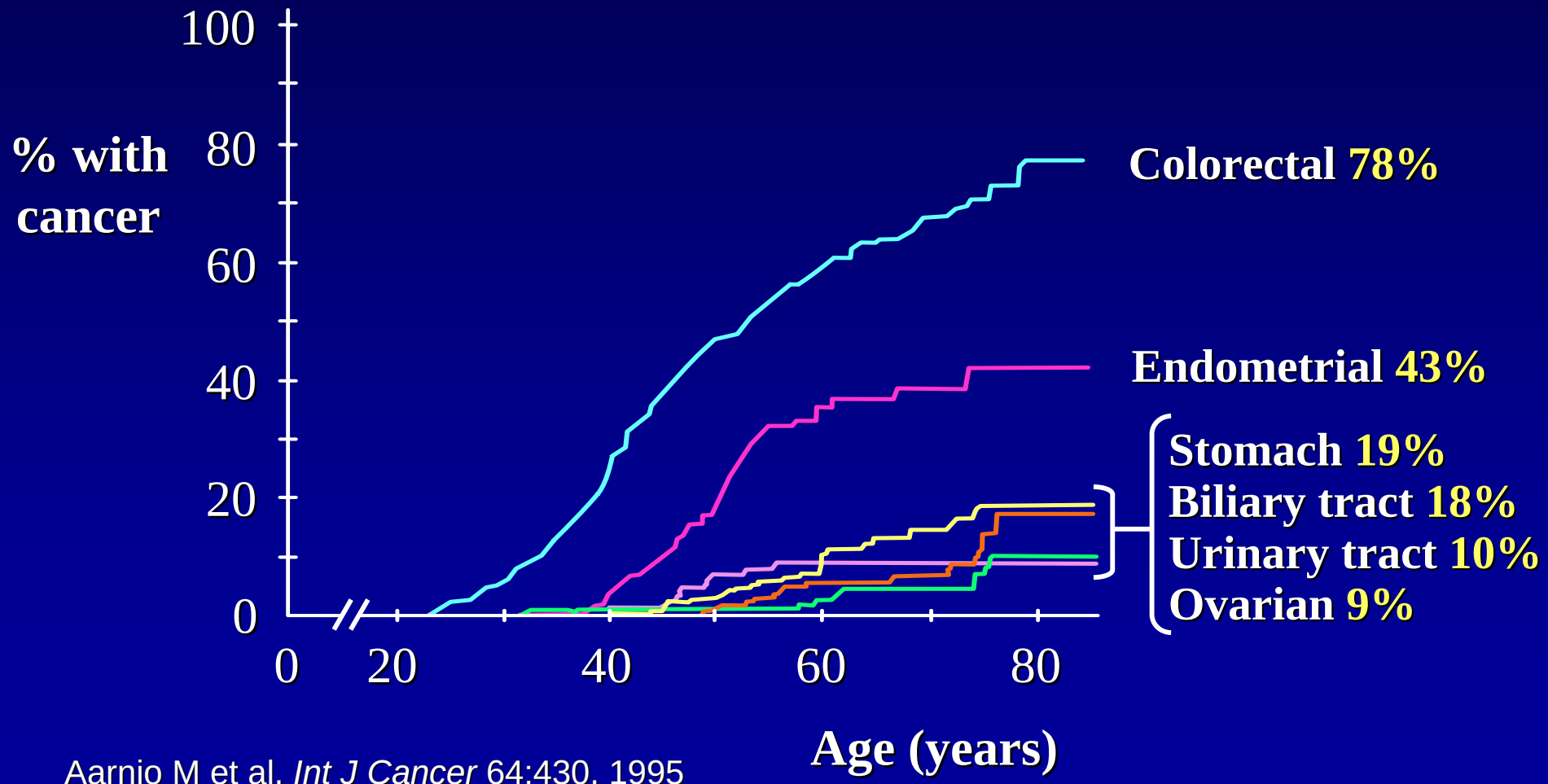


Incidence of CRC in Lynch Syndrome vs Sporadic



Voskuil, Int. J. Cancer, 1997

Cancer Risks in Lynch Syndrome

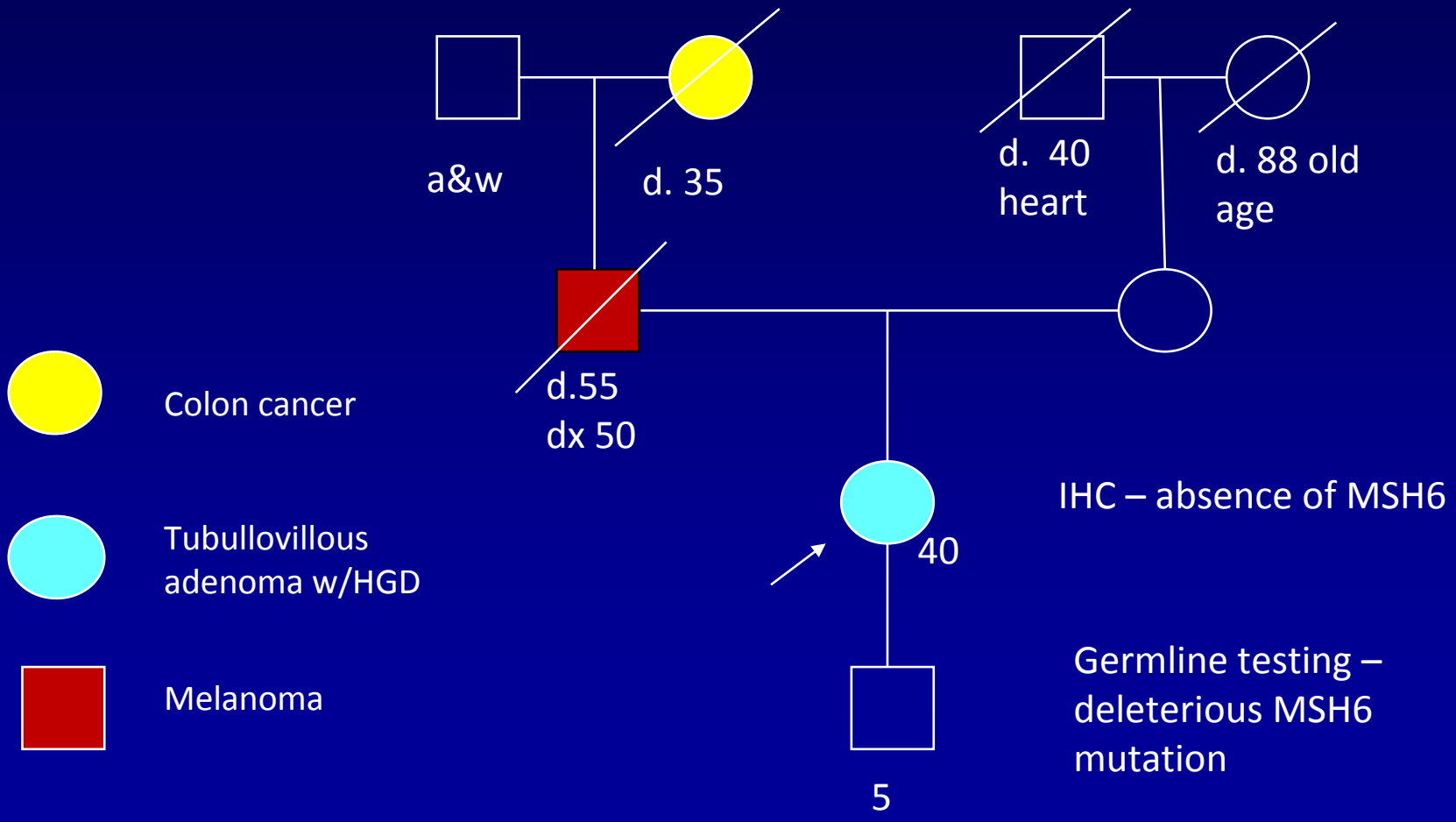


Aarnio M et al. *Int J Cancer* 64:430, 1995

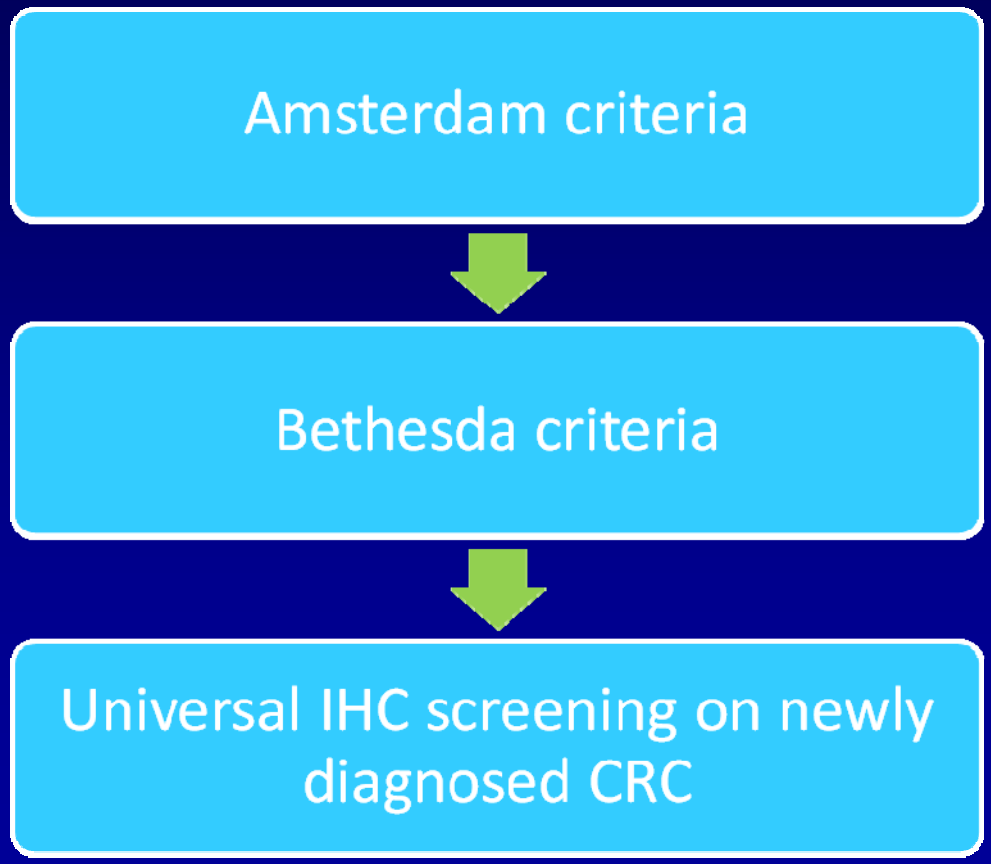
Clinical Management of Lynch Syndrome Gene Carriers or At Risk Family Members

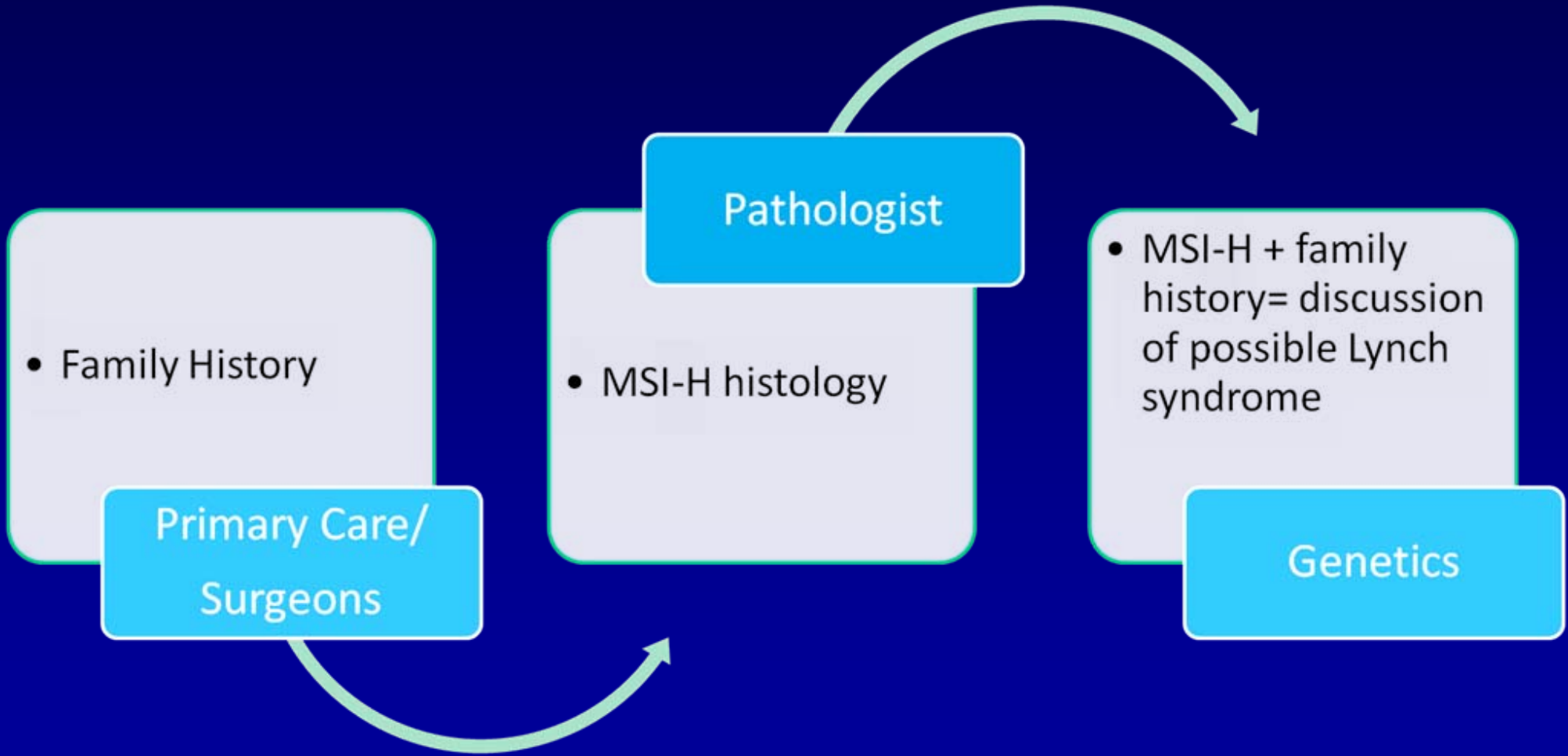
- Colonoscopy, age 25 years, or 10 years younger than earliest diagnosis, repeat annually
- Colectomy for CRC or high risk adenoma
  - Type? Subtotal colectomy with IRA vs segmental resection
  - IHC of biopsy useful in pts < 50 yrs to tailor initial resection
- Other tumor screening
  - Endometrial, ovarian, gastric, small bowel, urinary tract
  - Prophylactic hysterectomy/oophorectomy

CASE STUDY: 40 YEAR OLD FEMALE PRESENTS FOR COLONOSCOPY



Evolution of identification of Lynch syndrome




• Family History
Primary Care/ Surgeons
Pathologist
• MSI-H histology
• MSI-H + family history= discussion of possible Lynch syndrome
Genetics

Lynch syndrome estimates

- Estimated population incidence of Lynch syndrome is 1 in 370.

  (Based on the 2.8% incidence of Lynch syndrome in newly diagnosed colon cancers and the penetrance of Lynch syndrome being about 50%)

- That equals 829,800 out of 307,006,550 Americans
- Estimate that no more than 1.2% (10,000/829,800) of individuals with Lynch syndrome are aware of their diagnosis

Cancer Prevention Research, 4(1):1-5; 2011

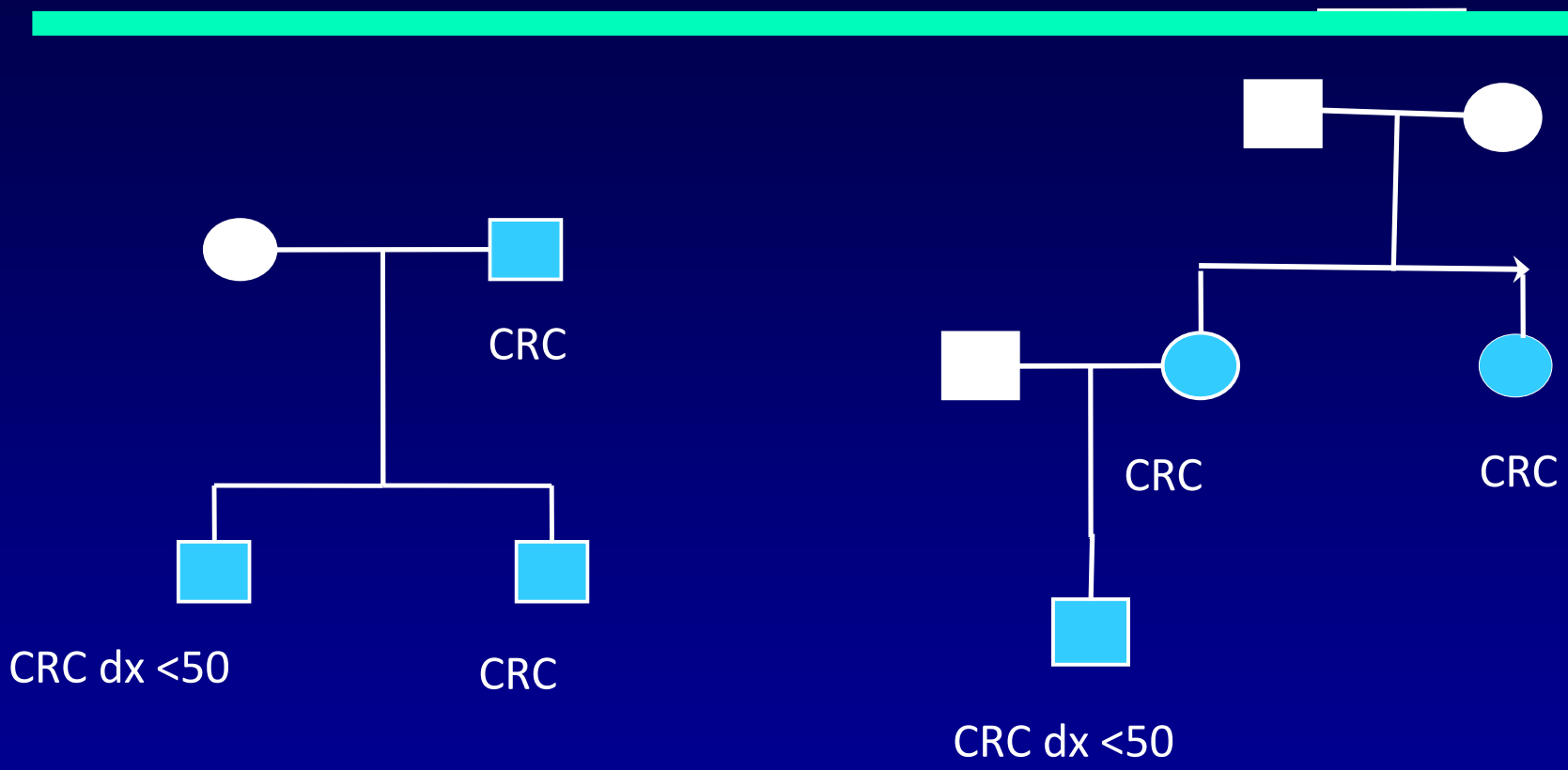
Identification of Lynch Syndrome Makes a Difference

- Significant data indicate that an early diagnosis of Lynch syndrome followed by intense cancer surveillance and/or prophylactic surgery can prevent morbidity and mortality from LS cancers
  - 62% reduction in colon cancer risk in individuals with LS undergoing surveillance
  - 30% of women with LS who did not have risk reducing surgery had developed endometrial cancer and 5.5% developed ovarian cancer over a 10 year period

Genetics in Med 35-41, 2009

Amsterdam criteria

Amsterdam Criteria



- **3 first-degree relatives with CRC**
- **2 or more generations**
- **1 CRC by age 50**

Amsterdam Criteria II

Other cancers, may be substituted for colon cancer in making the diagnosis

- endometrial cancer
- ovarian cancer
- gastric cancer
- hepatobiliary
- small bowel
- transitional cell ca of renal pelvis or ureter

Limitations of Amsterdam criteria

Amsterdam criteria

- requires careful assessment of family history
- Gathering:
  - 3 generation family history
  - Age of cancer diagnosis
  - Individuals tend to know the first degree history well but 2nd and 3rd degree less
- Family history inconsistently recorded by clinicians
- Inherited pattern may not be evident due to different types of cancer

Limitations of Amsterdam criteria

- <50% of Lynch syndrome families meet Amsterdam clinical diagnostic criteria

AND

- 50% of families meeting Amsterdam don't have Lynch syndrome. They likely represent Familial Colorectal Cancer Syndrome X involving only risk for colon cancer

Bethesda criteria

Revised Bethesda criteria

- Perform MSI and/or IHC
  - CRC diagnosed in patient under age 50, OR
  - Synchronous/metachronous LS tumors, regardless of age, OR
  - CRC with MSI-H histology diagnosed in patient under age 60, OR
  - CRC in patient with ≥1 first-degree relative with LS cancer, one cancer diagnosed < age 50, OR
  - CRC in patient with ≥2 first- or second-degree relatives with LS cancer, regardless of age

MSI-H Histology

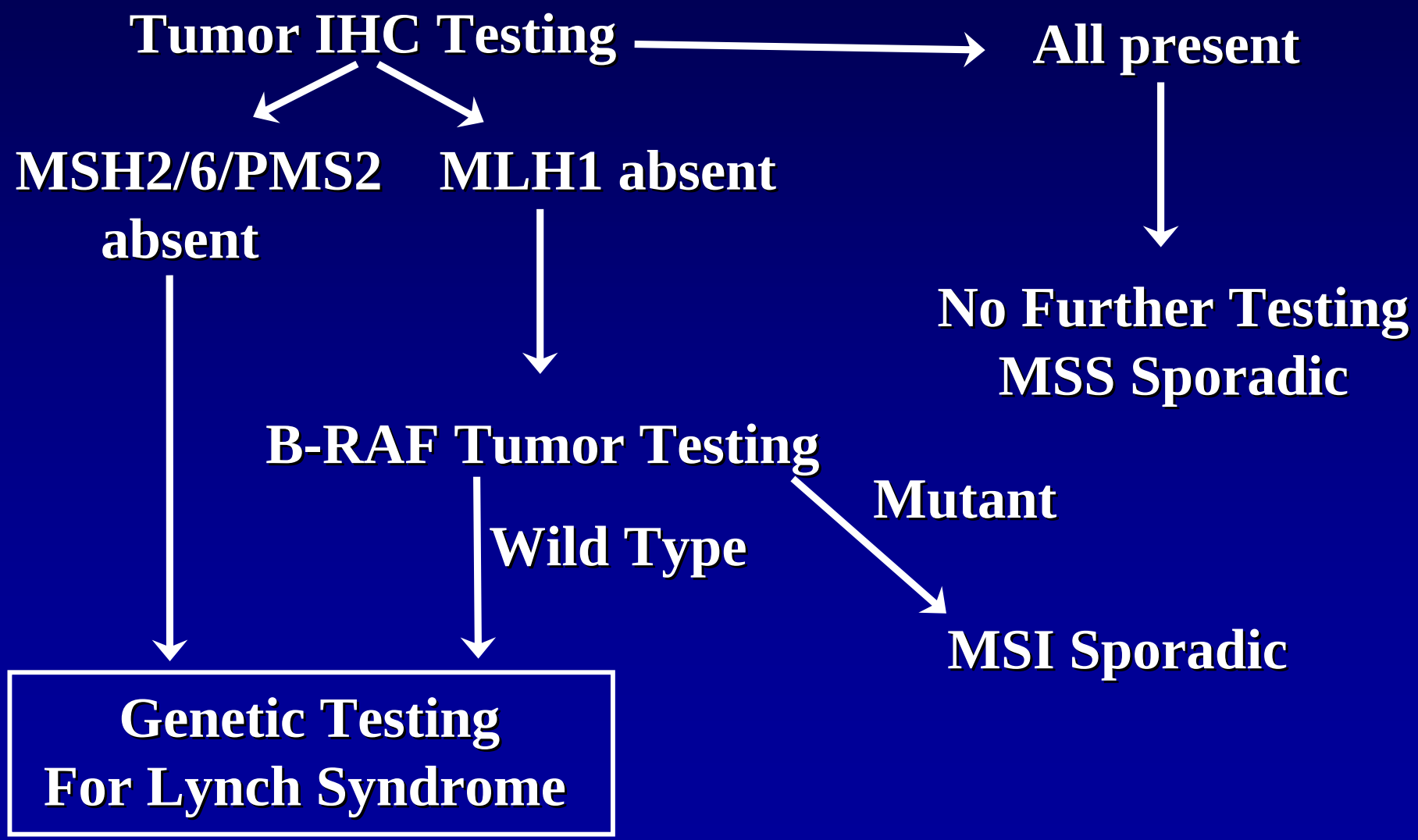
- Tumor infiltrating lymphocytes, OR
- Crohn's-like lymphocytic reaction, OR
- Mucinous/signet-ring differentiation, OR
- Medullary growth pattern

Microsatellite Instability

- 12-20% of all CRC exhibit MSI and abnormal IHC[1-5]
  - 75% of these do not have LS but rather acquired hypermethylation of the *MLH1* promoter which silences gene expression [6-7]
  - Associated with somatic mutation V600E in the BRAF gene
    - Correlates with better prognosis (versus those with MSS CRC)
    - May benefit less from 5-FU-based chemotherapy
- Almost all LS-related CRCs exhibit MSI and/or abnormal IHC
- MSI and IHC analysis show >94% concordance[8]

[1]J Clin Oncol 2008;26:5783-5788.
[2]N Engl J Med 2005;352:1851-1860.
[3]N Engl J Med 1998;338:1481-1487.
[4]J Clin Oncol 2000;18:2193-2200.
[5]Gastroenterology 2001;121:830-838.
[6]Cancer Res 1998;58:3455-3460.
[7]Cancer Res 1997;57:808-811.
[8]Fam Cancer 2005;4:255-265.

Genetic Testing for Lynch Syndrome Using IHC on Tumor Tissue



But…

- 25% of patients with LS did NOT meet Bethesda guidelines
- 56% of patients with LS were diagnosed ≥50
- 35% of patients with LS did not have the characteristic histologic features

[1]J Clin Oncol 2008;26:5783-5788.
[2]N Engl J Med 2005;352:1851-1860.

Universal IHC/MSI testing

National Comprehensive Cancer Network (www.nccn.org)

- *"Recently, IHC and/or MSI screening of all colorectal cancer and endometrial cancer regardless of age at diagnosis or family history, has been implemented at some centers to identify individuals at risk for Lynch syndrome."*
- **Currently done at:**
  - University of Colorado Hospital
  - Ohio State
  - Huntsman Cancer Institute
  - Cleveland Clinic
  - Etc…

- Mandated to start at VA nationwide within 18 months

Genet Med 2009:11(1):35-41.
Genet Med 2010;12(2):93-104.

EVALUATION OF GENOMIC APPLICATIONS IN PRACTICE AND PREVENTION (EGAPP) Working Group Recommendations

- Offer screening for Lynch syndrome to all individuals at time of CRC diagnosis
- Focus on improved outcome in unaffected relatives who can then be tested
- MSI sensitivity 89%, IHC sensitivity 83%

Genet Med 2009:11(1):35-41.

Support for EGAPP Recommendations

- Universal testing:
  - Detects nearly twice as many cases of Lynch syndrome vs. targeting those diagnosed < age 50
  - Has cost-effectiveness ratio comparable with other preventive services (less than $25,000 per LY saved – same as colonoscopy every 10 years in adults ≥50 yrs)
- Findings support EGAPP recommendations
- Testing strategies using IHC have the most favorable cost-effectiveness ratios

Genet Med 2010;12(2):93-104.

Response to Screening

- MSI/IHC considered a screening test
- Screening well received by both patients/family members and medical professionals
- 90% of individuals screened through a research study proceeded with genetic counseling but a substantial decrease in follow-up was seen in a clinical setting
- Individuals may or may not choose to proceed with genetic testing following discussion

NEJM 1851-1860: 2005, Genetic in Med 812-817, 2009

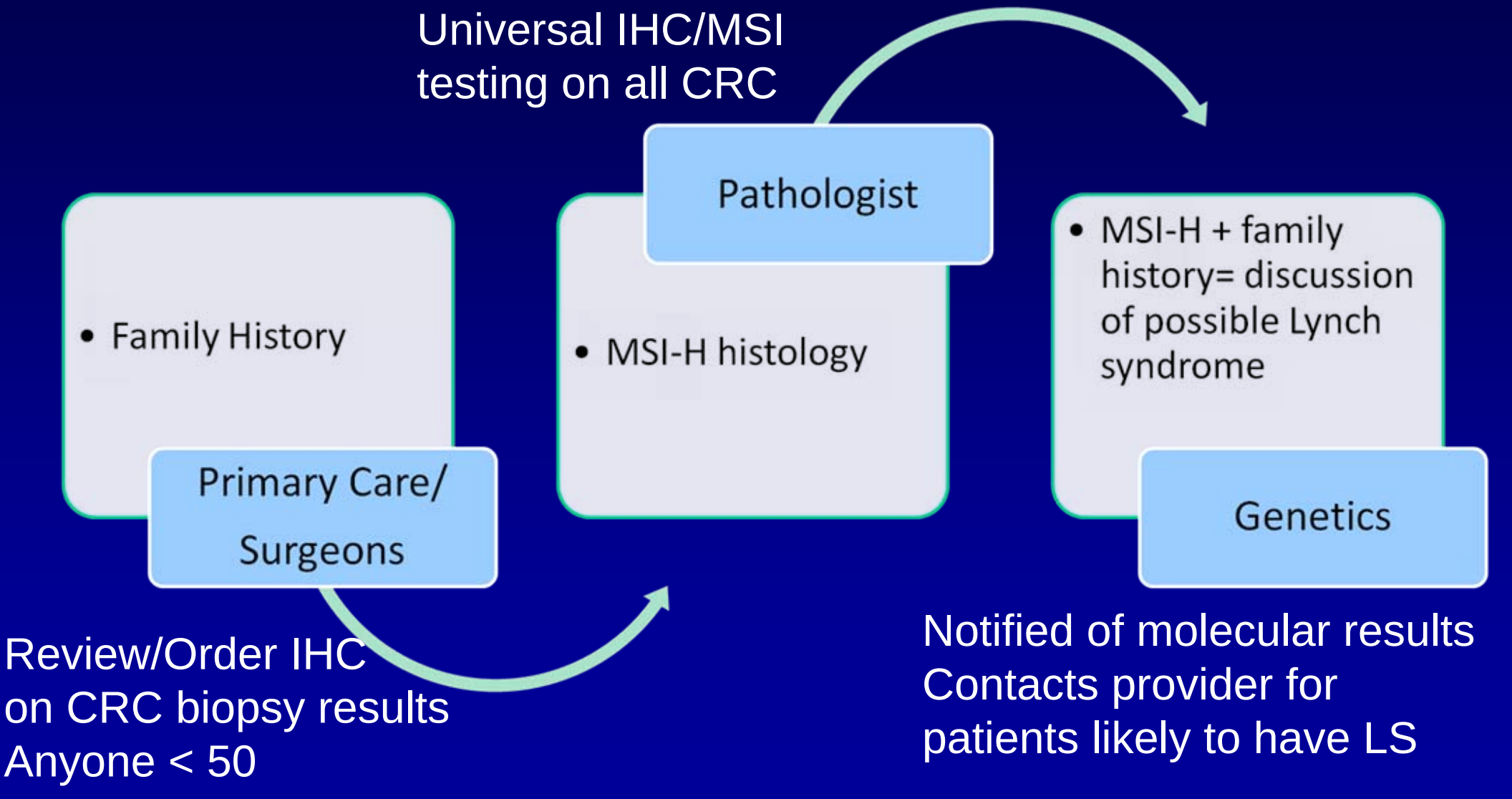
Pitfalls

- Exclusions
  - Any tumor exposed to XRT should not have MSI since there is contraction and expansion of MSI due to XRT
- Loss to follow-up
- Identifying low risk patients?

Informed Consent

- There is a general consensus that informed consent is not required for MSI/IHC analysis of biopsied or resected tumor samples.
  - Patient already has diagnosis of CRC
  - MSI or IHC not definitive for genetic diagnosis
  - Directed by patient care decisions
  - Have option to get genetic testing
- Some institutions include a fact sheet with pre-surgery packet

Solution:


Universal IHC/MSI testing on all CRC
Pathologist
• MSI-H histology
• Family History
Primary Care/ Surgeons
• MSI-H + family history= discussion of possible Lynch syndrome
Genetics
Review/Order IHC on CRC biopsy results Anyone < 50
Notified of molecular results Contacts provider for patients likely to have LS