www.stvincent.org

Universal Screening for Lynch Syndrome

St. Vincent/Ameripath protocol proposal

Lynch syndrome (HNPCC)

- 1/35 individuals with colorectal cancer has Lynch syndrome
- Over half individuals are >50 at time of first dxs CRC
- Autosomal dominant
- Associated with mutation in one of 4 mismatch repair genes
  - Results in microsatellite instability

Lynch syndrome

Lifetime cancer risks:

- Colorectal 50-80%
- Endometrial 20-60%
- Gastric 13-19%
- Ovarian 9-12%
- Urinary tract 12%
- Pancreas 4%
- Small bowel 1-4%
- Biliary tract 2%
- Brain/CNS 1-3%

Features of Colon Cancer Associated with Lynch Syndrome

- Right-sided
- Proximal
- Mucinous, signet ring cell
- Microsatellite instability present
- Accelerated time between adenomas and tumor
- Increased survival

IHC screening

- Antibodies stain for presence or absence of MLH1, MSH2, MSH6 and PMS2 proteins
- Indicates which gene likely to be mutated
- Quick, inexpensive
- Available in-house
- Can be performed on biopsy specimen
- Correlates well with Lynch syndrome
  - ~97% Lynch will have abnormal IHC

Why determine which CRC cases have Lynch syndrome (LS)?

- All MSI-H CRC patients have a better prognosis
- MSI-H CRC patients MAY need different treatment in future
- LS patients at high risk for second primary cancers (CRC and others)
- LS patients have at-risk relatives who could benefit from genetic testing

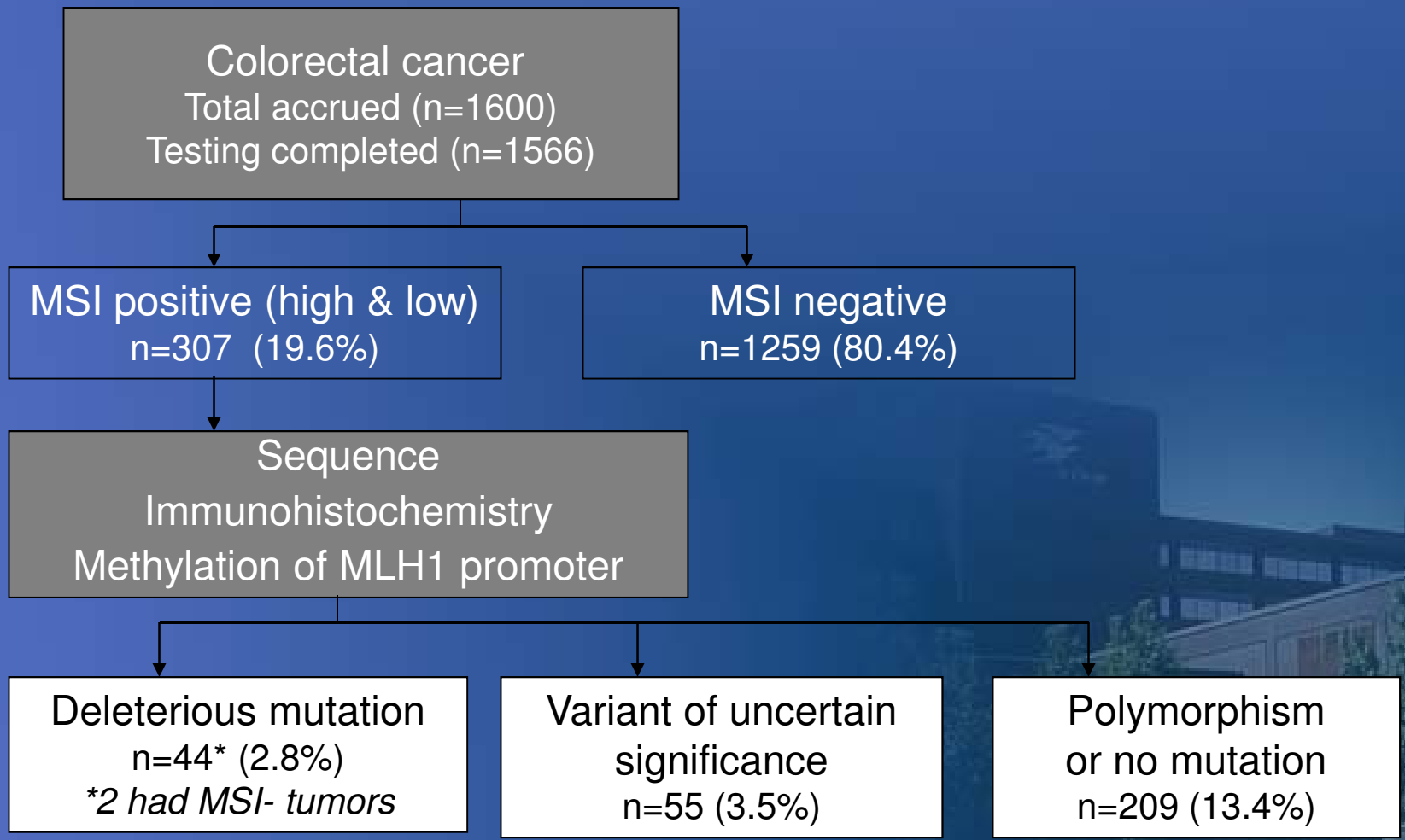
Lynch Syndrome Implications for Patient

- 16-30% chance of second primary CRC in the 10 years after their first diagnosis
- NCCN guidelines differ for CRC patients with LS and without LS
  - With LS, colonoscopy every 1-2 years for life
  - Without LS, colonoscopy 1 yr after dx, repeat in 2-3 yrs, then every 3-5 years based on findings
- Management also changes due to the risk for other cancers

Lynch Syndrome Implications for Family

- 6 relatives tested on average per proband identified with LS
- 50% with LS need increased cancer surveillance
  - Compliance with surveillance is good (96% for CRC and 97% for Gyn)
  - Cancer risk ratio of relatives with LS compared to relatives without LS is 5.8
  - No significant difference in cancer mortality (RR, 2.28) or overall death rates (RR, 1.26)
- 50% without LS can follow the ACS guidelines

Columbus-area HNPCC study (1999-2005)



Hampel et al. *New Engl J Med* 2005; 352:1851-60
Hampel et al. *J Clin Oncol* 2008; 26:5783-88

OSU Universal screening experience:

44 CRC probands with deleterious mutations:

- Age at diagnosis – 51.4 (range 23-87)
- 50% diagnosed over age 50
- 25% did not meet either Amsterdam or Bethesda criteria

Hampel et al. NEJM 2005;352:1851-60.

EGAPP

(Evaluation of Genomic Applications in Practice and Prevention)

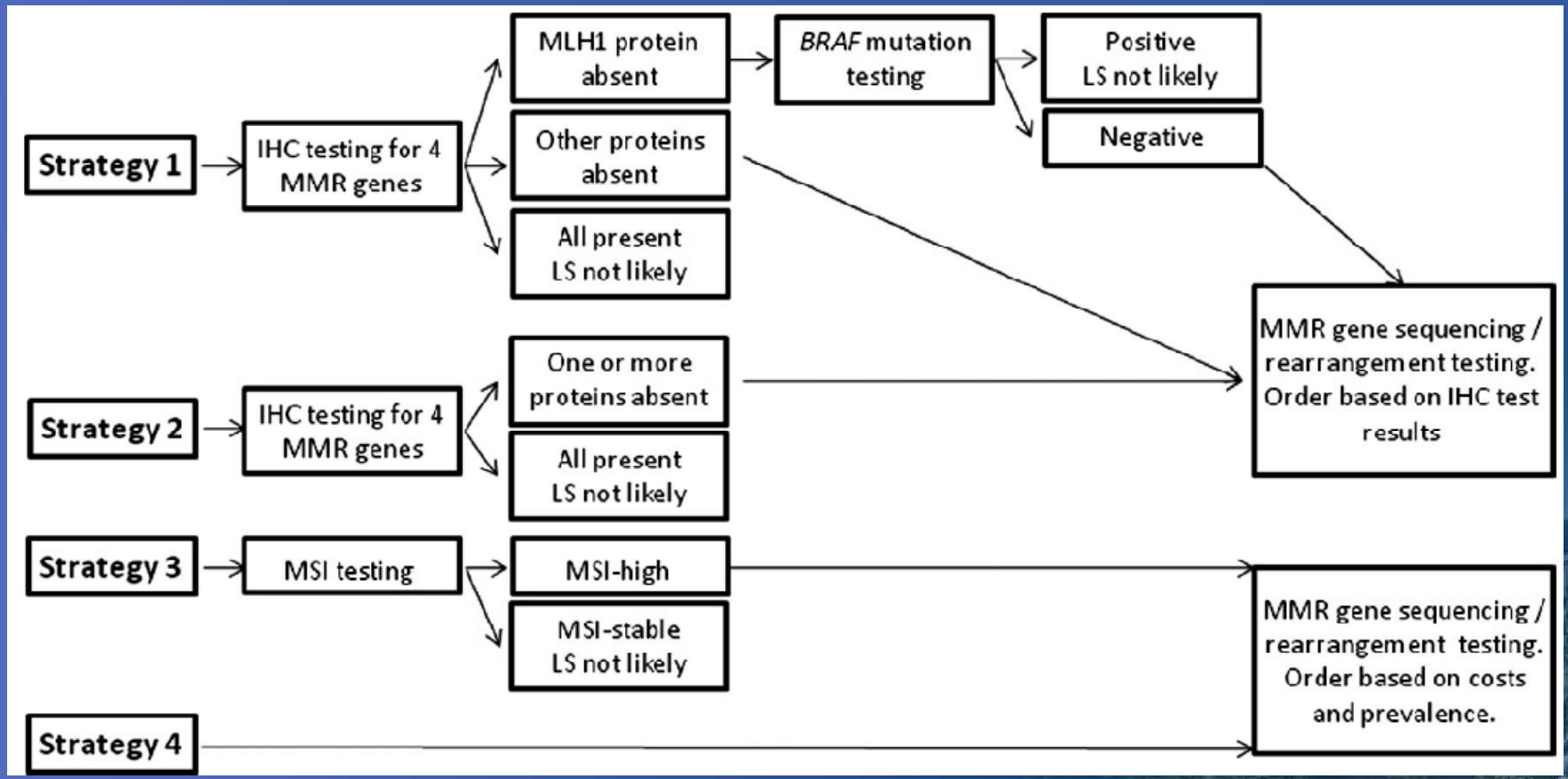
- Established in 2005 to assess evidence regarding the validity & utility of rapidly emerging genetic tests for clinical practice.
- Independent, multidisciplinary panel prioritizes and selects tests, reviews CDC-commissioned evidence reports, finds gaps, and provides guidance.

EGAPP Recommendations

- Moderate certainty that testing patients with CRC for LS and then testing their relatives would provide moderate population benefit.
- Adequate evidence to conclude that the analytic sensitivity and specificity of the preliminary and diagnostic tests were high.
- Adequate evidence to describe the clinical sensitivity and specificity of three preliminary tests and four testing strategies.
- Adequate evidence for testing uptake, compliance with surveillance, relatives approachable, harms associated with f/u and effectiveness of routine cx supporting the use of genetic testing strategies to reduce morbidity and mortality in relatives with LS.
- No one test strategy was clearly superior.
- Inadequate evidence that screening for LS will reduce EC morbidity or mortality

EGAPP Genet Med 2009;11:35-41; Palomaki G, Genet Med 2010;11:42-65.

Cost effectiveness study



Cost-effectiveness Results

Table 1 Outcomes and costs associated with Lynch syndrome testing strategies among newly diagnosed patients with colorectal cancer (CRC) and testing and surveillance for CRC among their first degree relatives

	Strategy for detecting Lynch syndrome in newly diagnosed patients with colorectal cancer[a]			
Universal offer of testing of all newly diagnosed patients with CRC	IHC, *BRAF* testing and then sequencing (Strategy 1)	IHC testing and then sequencing (Strategy 2)	MSI testing and then sequencing (Strategy 3)	Genetic sequencing for all four genes (Strategy 4)
No. of newly diagnosed patients with CRC with Lynch syndrome detected	2,469	2,477	2,540	2,982
No. of relatives approached	9,895	9,930	10,225	12,788
No. of relatives tested for Lynch syndrome	4,888	4,905	5,051	6,317
No. of relatives with Lynch syndrome detected	2,197	2,205	2,261	2,654
Life-years saved among relatives	2,346	2,353	2,413	2,833
Costs of detecting Lynch syndrome in newly diagnosed patients with CRC[b]	$43,492	$45,442	$90,493	$391,479
Costs of detecting Lynch syndrome in relatives[b]	$3,014	$3,024	$3,114	$3,895
Costs of surveillance and treatment for CRC[b]	$36,112	$36,233	$37,209	$44,597
Total costs[b,c]	$82,617	$84,699	$130,817	$439,971

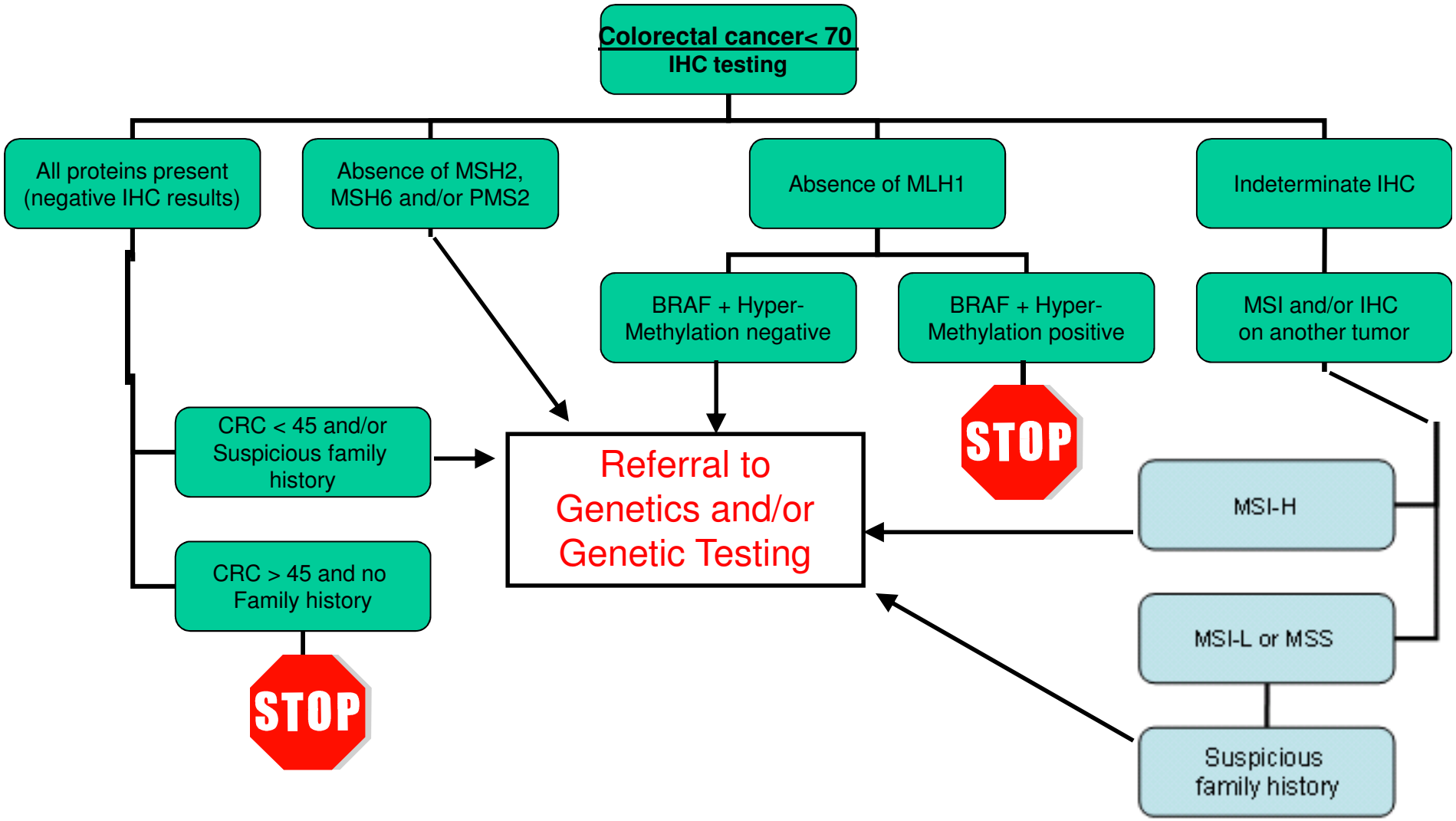
Incremental Cost-Effectiveness Ratios per LYS compared to no testing at all

Strategy	Medicare rates	List prices from labs	12 relatives
IHC, BRAF testing & sequencing	$22,552	$30,331	$12,332
IHC testing & sequencing	$23,321	$30,740	$12,663
MSI testing & sequencing	$41,511	$49,272	$20,470
Genetic sequencing for 4 genes	$142,289	$200,037	$63,773

Cost-Effectiveness Evaluation

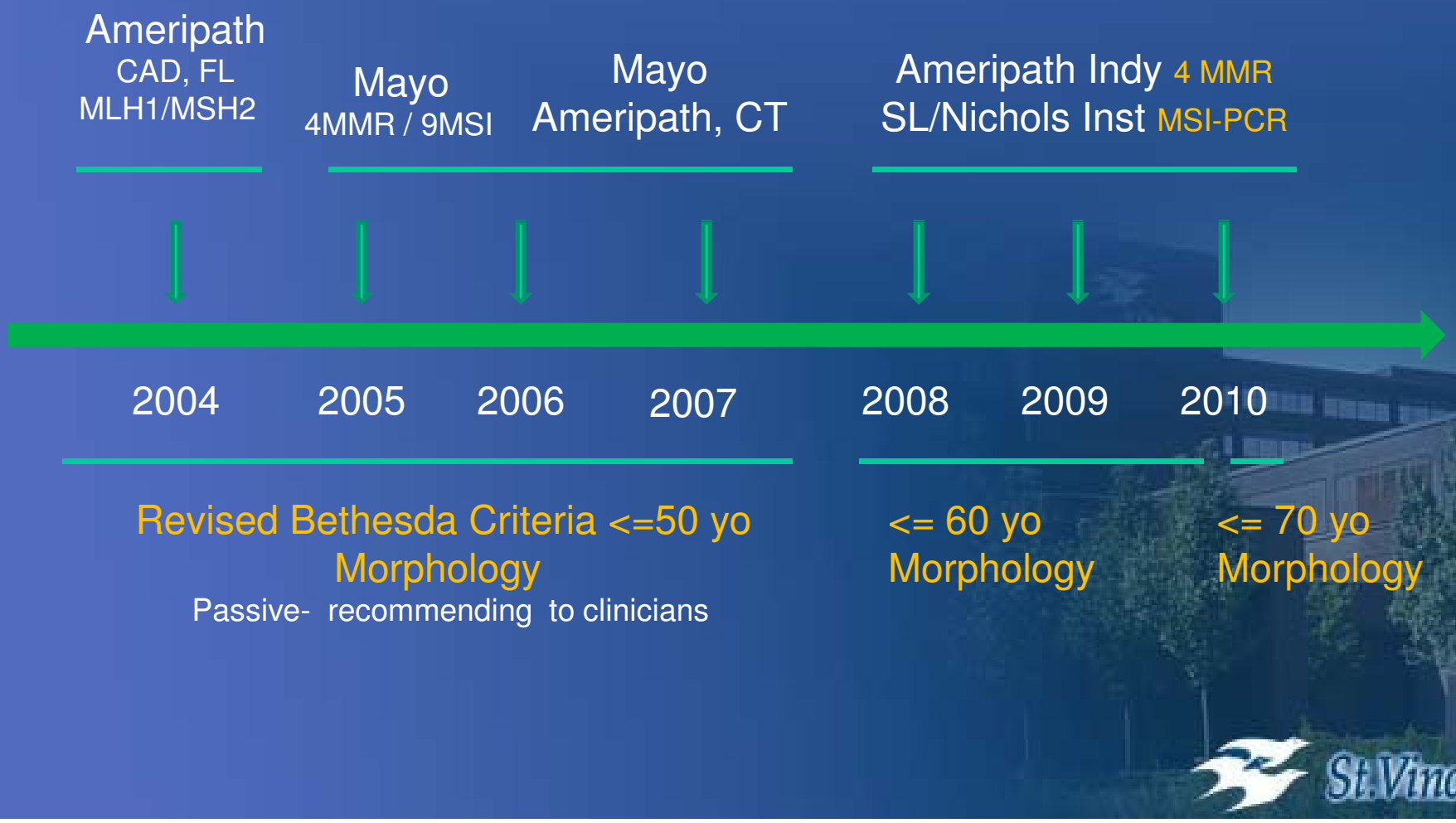
- Universal screening detects nearly twice as many cases of LS as targeting younger patients
- Strategy 1 is the most cost effective strategy
- Cost-effectiveness ratio of universal screening is ≤ $25,000 per life-year saved relative to no testing
- ICER comparable with other preventive services (colonoscopy every 10 years has ICER of $25,000)

Screening protocol at Ameripath Indiana



www.stvincent.org

Timeline of Ameripath Indiana Screening for Lynch Syndrome



St.Vincent

Ameripath Indiana Screening For Lynch Syndrome

	2008	2009	2010	total
Screened	40 (11%)	68 (20%)	54 (22%)	**162**
Total cases	350	333	245	**928**

MMR intact	145
MSH2/6 def	6
MLH1/PMS2 def	26
PMS2 def	2
MMR+MSI-H	1
21% abnormal	34 cases

→

76 M
62 M
60 F
54 M
47 F
40 F

Cancer Genetics Program

2008	2009	2010	Total cases
14	7	6	27

- At least 12 of these had not had IHC performed prior to appointment
- Most referred by oncology
- Missing at least 44% abnormal IHCs identified on screening

Proposal

- Abnormal IHC result gets faxed to Cancer Genetics Risk Assessment program
- GC will review case and request additional testing (hypermethylation/BRAF or MSI, eg) directly from pathology as needed
- In appropriate cases, GCs will fax referral form to ordering MD
- If MD agrees with referral, then will sign and fax back for us to contact patient for appointment
  - MD will need to alert patient as to need for appointment

www.stvincent.org

Medical education

Distance learning

Lynch symposium

http://www.stvincent.org/secure/distancelearning/default.aspx?category=Lynch+Syndrome+Symposium