

# Association for Molecular Pathology

Comments to MEDCAC  
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*Expertise that advances patient care through education, innovation, and advocacy.*

[www.amp.org](http://www.amp.org)



# Financial Disclosure

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## Dr. Sam Caughron:

- Genetech – Speakers Bureau >\$10,000
- Pfizer – Speakers Bureau < \$10,000
- Biotheranostics – Consultant and Speakers Bureau <\$10,000
- Precision Medicine Network – Medical Advisory Board <\$10,000

## Association for Molecular Pathology (AMP)

- AMP presents no financial conflicts

# About the Association for Molecular Pathology

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The Association for Molecular Pathology (AMP) was founded in 1995 to provide structure and leadership to the emerging field of molecular diagnostics. AMP's 2,300+ members include individuals from academic and community medical centers, government, and industry; including pathologist and doctoral scientist laboratory directors, basic and translational scientists, medical technologists, and trainees. Through the efforts of its Board of Directors, Committees, Working Groups, and members, AMP is the primary resource for expertise, education, and collaboration on the fastest growing fields in healthcare. AMP members influence policy and regulation on the national and international levels, ultimately serving to advance innovation in the field and protect patient access to high quality, appropriate testing.

# Key Question 1

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**KQ 1. Overarching Question:** Is there direct evidence that the addition of the specified molecular pathology tests used alone or in combination with traditional prognostic factors changes physician decisionmaking and improves outcomes for adult patients with CRC, breast, lung, or bladder cancer compared with the use of traditional factors to predict risk of recurrence (RR) for adults with these cancers?

**AMP will address this question and focus specifically on the prognostic utility of CRC molecular markers**

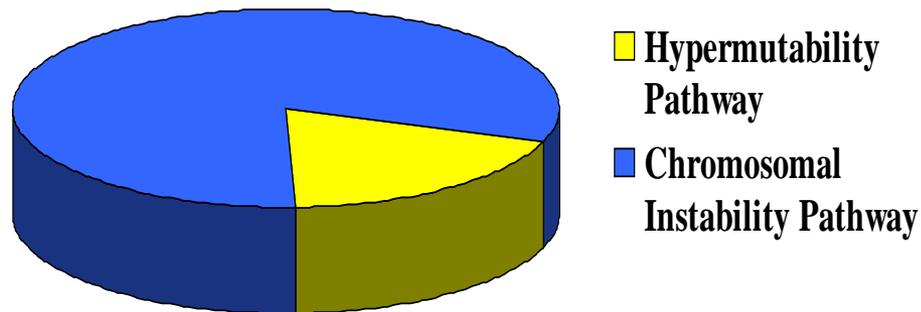
# AHRQ Technology Assessment Asserts Insufficient Evidence of Clinical Utility of CRC Markers

**Table B. Summary of findings and strength of evidence for impact on treatment decisions, clinical utility, and our overarching question (continued)**

Test: Cancer	Outcome	N studies; N subjects	Conclusions	Strength of Evidence
BRAF: CRC	RR	5; 4,106	All studies assessed clinical validity; no prognostic value; test is unlikely to improve outcomes	Low
	CSS	7; 5,409	All studies assessed clinical validity; no evidence that test use leads to improved CSS	Insufficient
	OS	10; 7,610	All studies assessed clinical validity; no evidence that test use leads to improved mortality	Insufficient
	Decisions about Rx	0; 0	NA	Insufficient
KRAS: CRC	RR	5; 4,085	All studies assessed clinical validity; no prognostic value; test is unlikely to improve outcomes	Low
	CSS	2; 1,174	All studies assessed clinical validity; no evidence that test use leads to improved outcomes	Insufficient
	OS	10; 5,328	All studies assessed clinical validity; no prognostic value; test is unlikely to improve mortality	Low
	Decisions about Rx	0; 0	NA	Insufficient
MSI: CRC	RR	10; 7,130	All studies assessed clinical validity; no evidence that test use leads to improved outcomes	Insufficient
	CSS	6; 3,439	All studies assessed clinical validity; no evidence that test use leads to improved CSS	Insufficient
	OS	12; 8,839	All studies assessed clinical validity; no evidence that test use leads to improved mortality	Insufficient
	Decisions about Rx	0; 0	NA	Insufficient

# Colorectal Cancer: Molecular Pathways

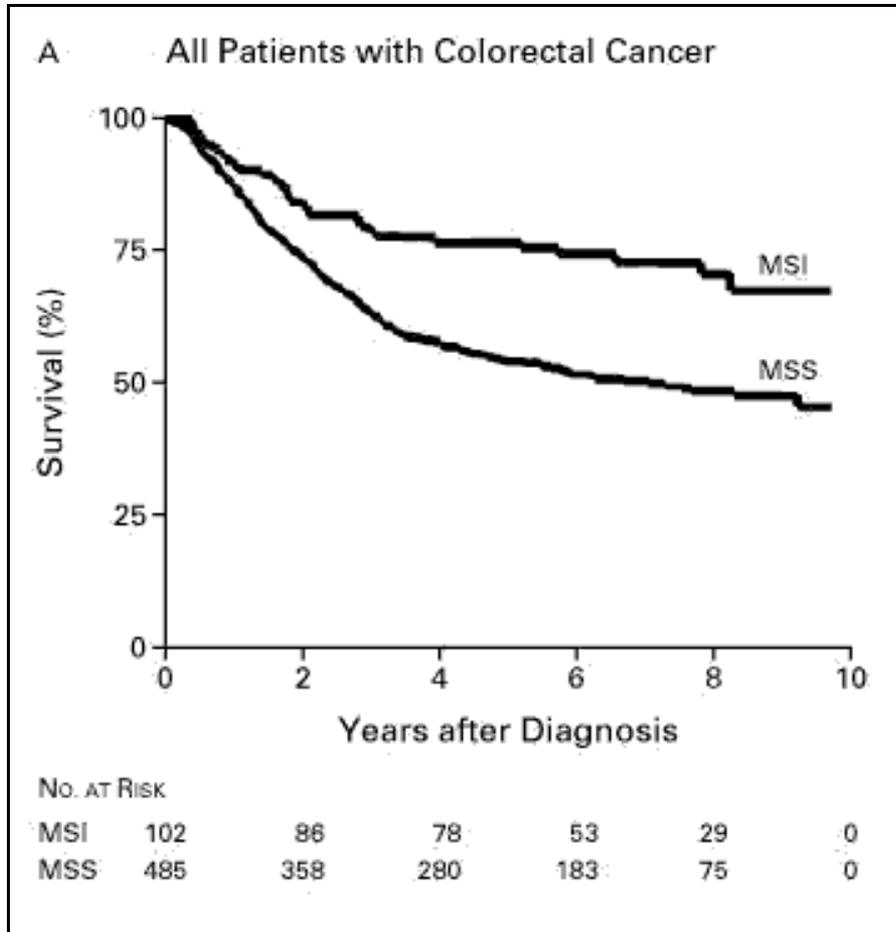
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Value:

1. Prognosis
2. Lynch Syndrome
3. Therapy selection

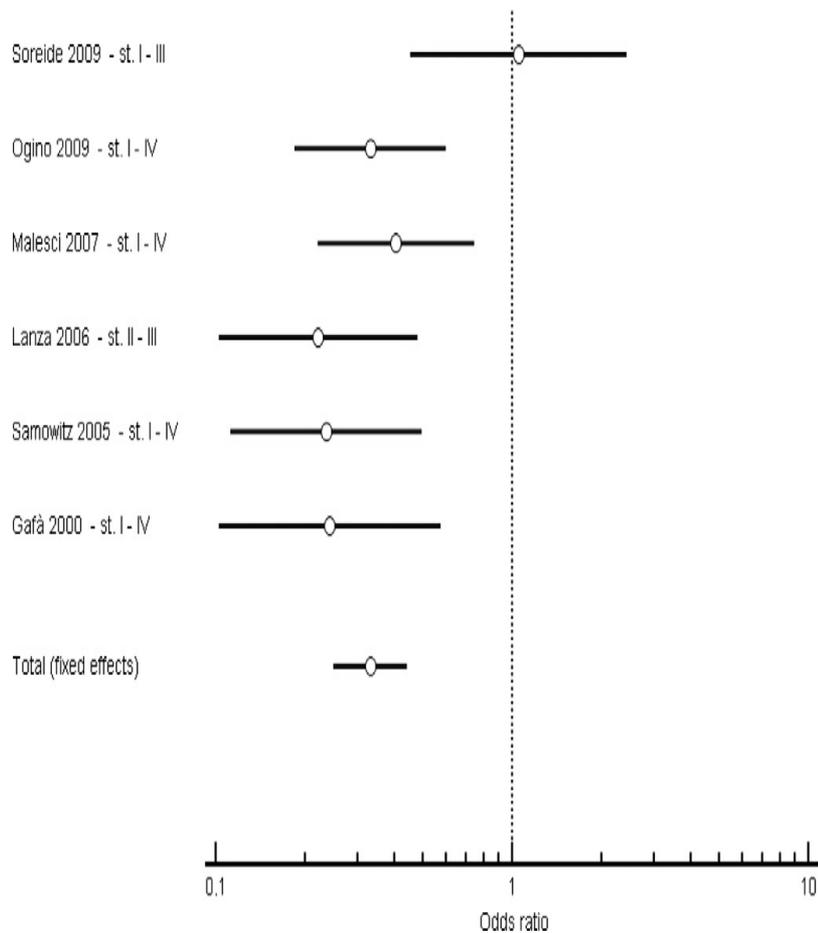
# Prognostic Significance of MSI-H in Sporadic CRC



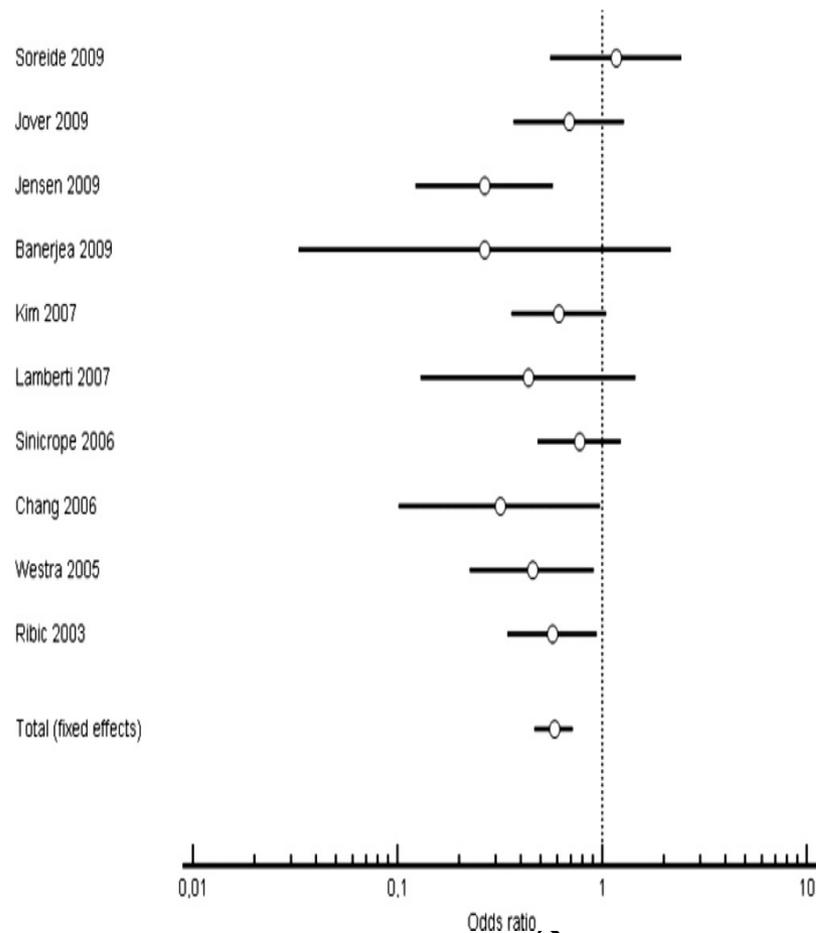
*Gryfe, R et al, NEJM 2000; 342:69-77*

# Microsatellite Instability as a Marker of Prognosis and Response to Therapy: A Meta-Analysis of CRC Survival Data

OR for DSS for MSI-H



OR for DFS for MSI-H



# MSI and Lynch Syndrome

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- HNPCC – Hereditary Non-Polyposis Colon Cancer
  - Lynch Syndrome I
  - Lynch Syndrome II
- Accounts for 3-4% of all colon cancers
- Accounts for 15-20% of MSI tumors
- Inherited *predisposition* to many different cancers, including colon cancer

# Clinical Significance of Recognizing Lynch Syndrome

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1. The patient is at risk for other cancers and needs appropriate surveillance.
2. Surgical decision making.
3. The patient's relatives will also be at increased risk if they carry the same mutation, and will need appropriate surveillance.
4. Relatives can be tested to determine their risk, and level of surveillance.

# EGAPP Recommendation Statement

*Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group*

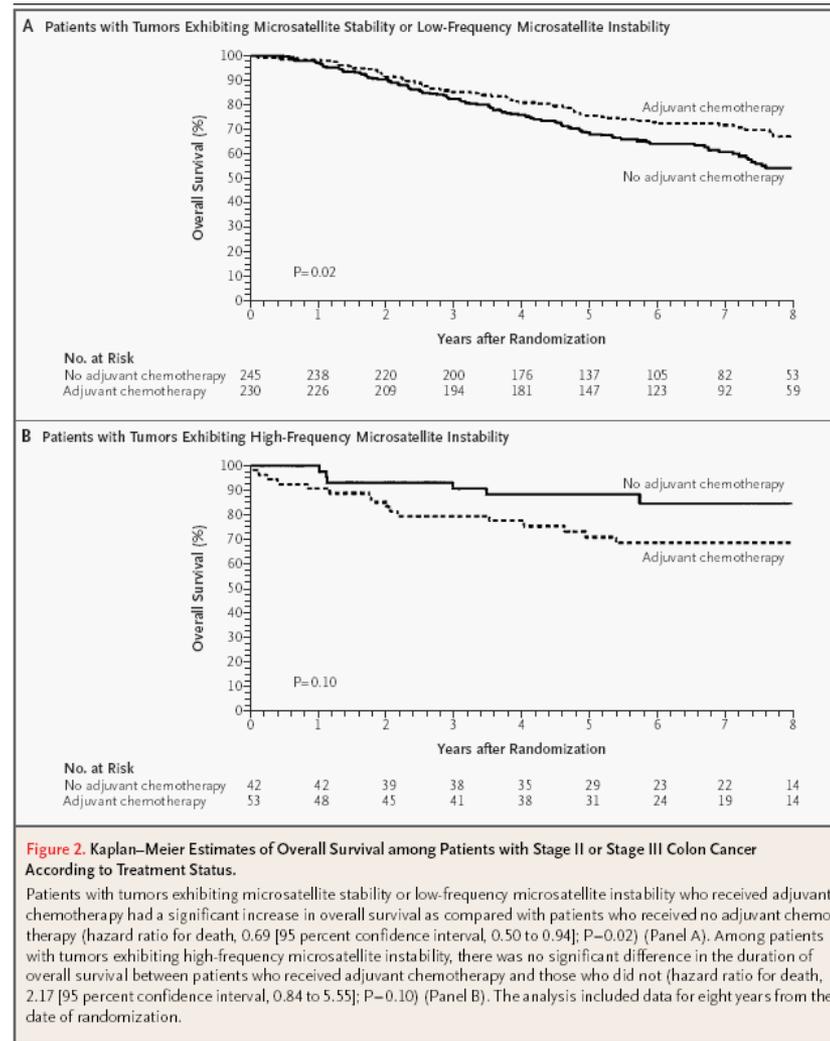
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“...found sufficient evidence to recommend offering genetic testing for Lynch syndrome to individuals with newly diagnosed colorectal cancer to reduce morbidity and mortality in relatives.”

**= universal testing of all new CRCs**

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

# Tumor Microsatellite-Instability Status as a Predictor of Benefit from Fluorouracil-Based Adjuvant Chemotherapy for Colon Cancer



MSS tumors

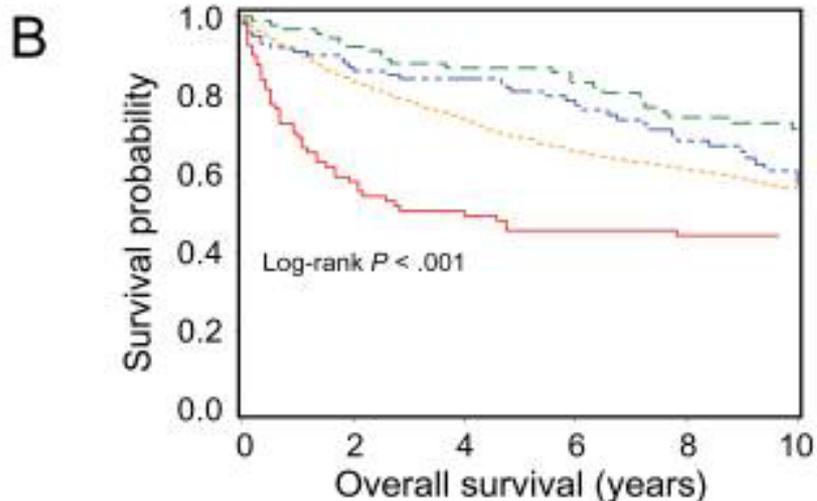
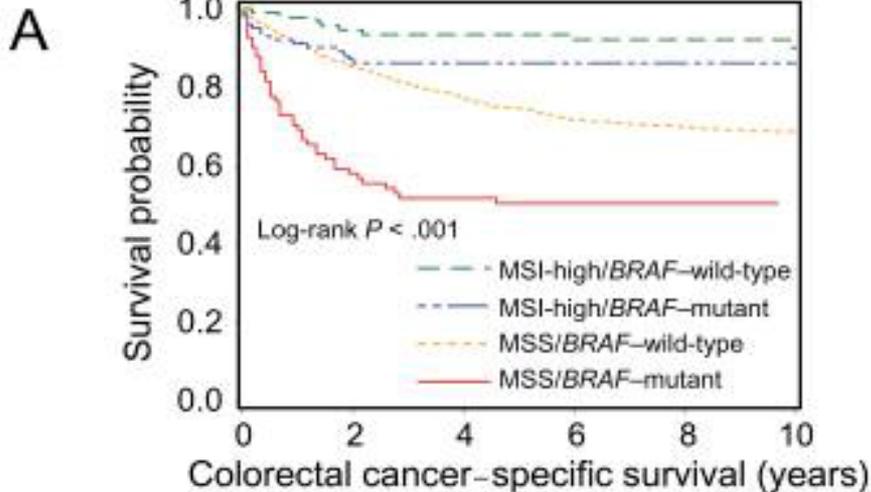
MSI-H tumors

# Prognostic Value of BRAF Status in CRC

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- Prognostic
  - Dependent on MSI status
- Informative for Lynch Syndrome

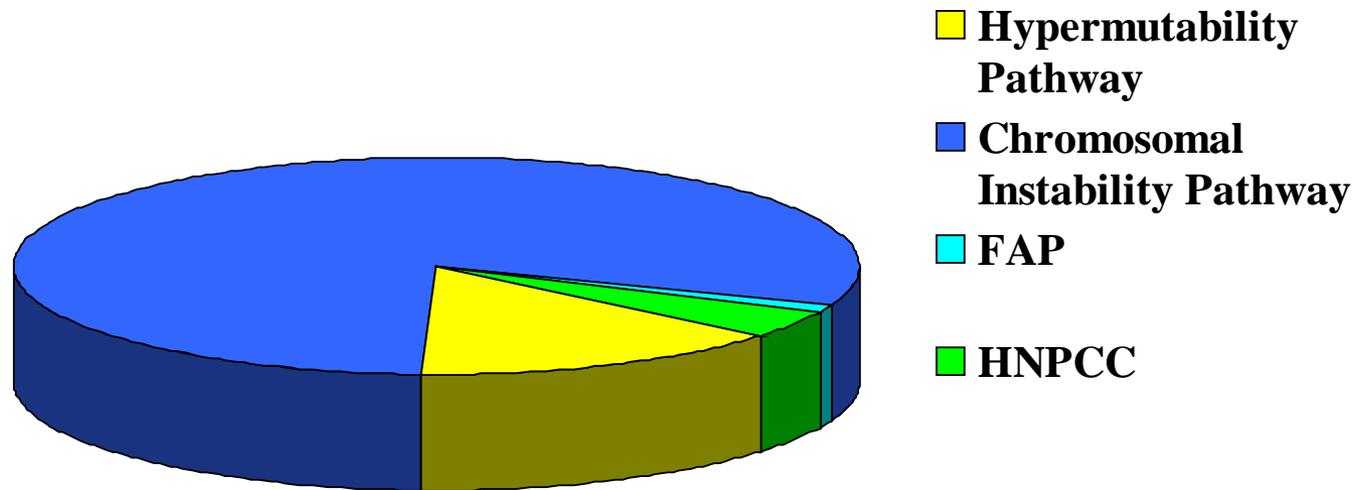
# Prognostic Significance of *BRAF* Mutation in CRC



Lochhead, Paul et al. "Microsatellite Instability and *BRAF* Mutation Testing in Colorectal Cancer Prognostication." *JNCI Journal of the National Cancer Institute* 105.15 (2013): 1151–1156.

# Inherited Syndromes of CRC Predisposition

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# Value of KRAS mutation Testing for CRC

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Mutations in KRAS (codons 12, 13, 62 etc) and NRAS (codons 12, 13 ,etc) are predictive of lack of response to EGFR targeted therapies

Relevant for patients eligible for anti EGFR therapy, i.e. Stages III and IV

# Molecular Markers Related to Colon Cancer Prognostic Significance

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## Microsatellite Instability (MSI)

Major prognostic indicator

Major indicator for Lynch Syndrome risk

Response to conventional therapies

## BRAF

Major predictive indicator (MSS)

Major indicator for Lynch Syndrome risk

## MLH1 Promoter hypermethylation

Major indicator for Lynch Syndrome

## KRAS

Primarily a predictive indicator for response to targeted therapy

Equivocal prognostic value