

**Role and Impact of Molecular Markers on treatment decisions in the adjuvant setting?**

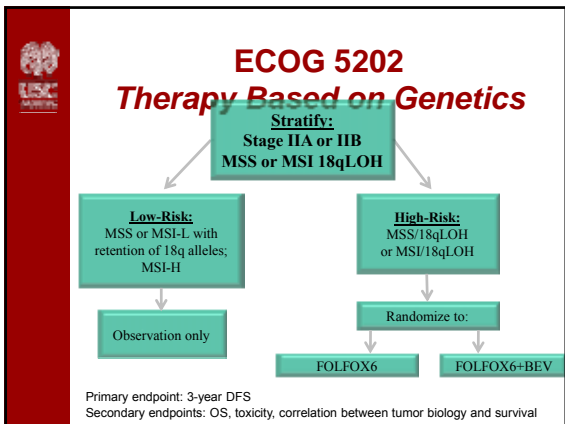
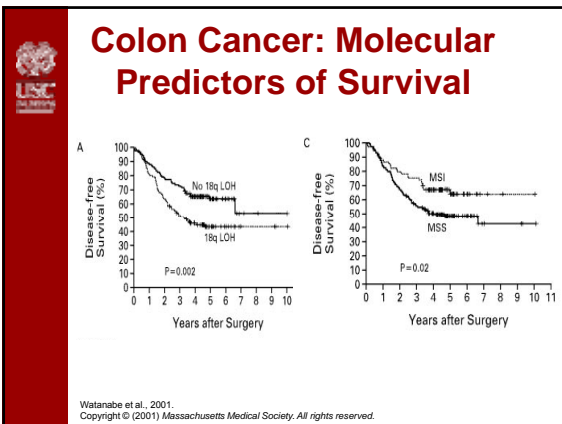
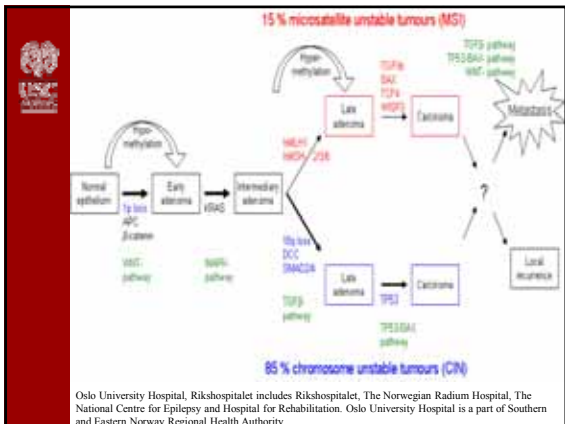
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Barcelona, June 27, 2009



**What Markers in the Adjuvant Setting**

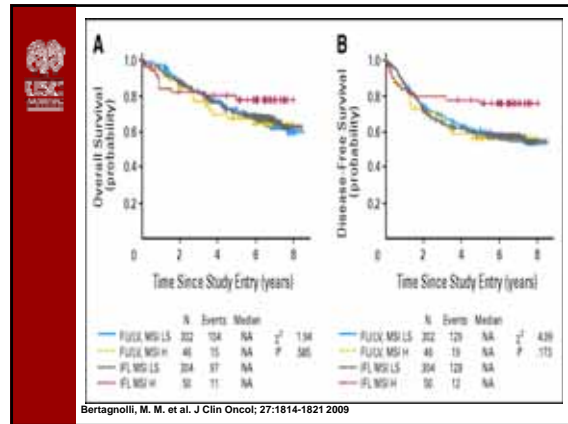
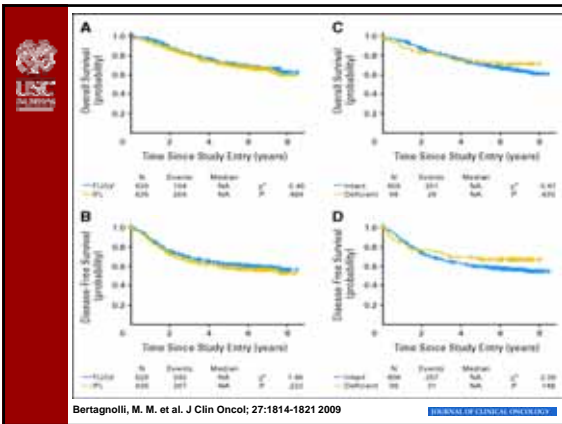
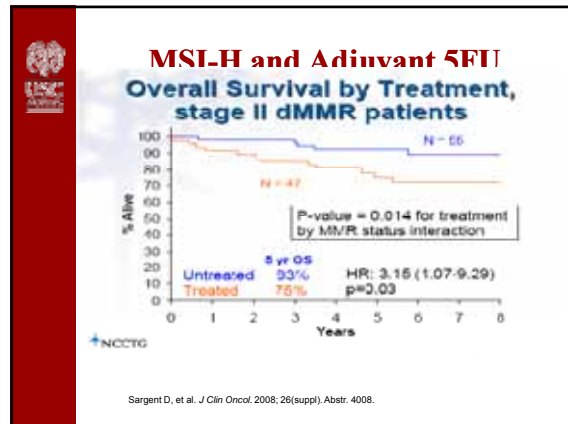
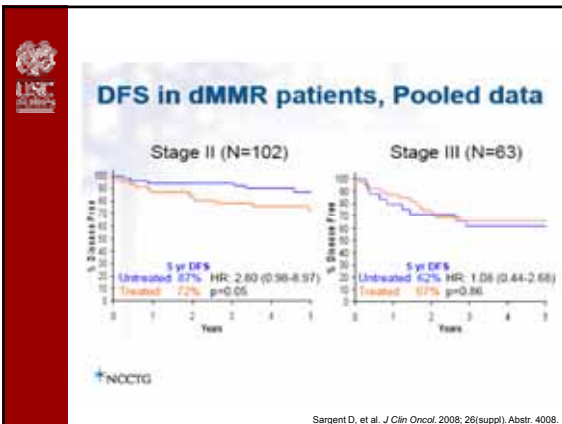
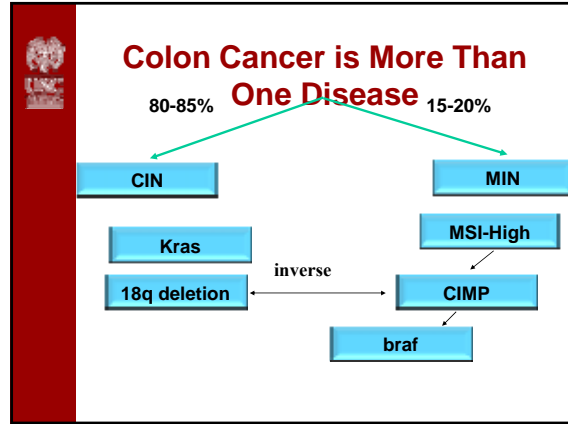
- MSI
- 18q deletion
- Stage II versus stage III disease
- Predictive versus Prognostic Markers (when and with what to treat)



## Defective MMR: Colon Cancer

- Characterized by presence of MSI and loss of MLH1, MSH2, MSH6 or PMS2 expression (MYH)
- Clinical correlations: Right-sided, female, early stage, better prognosis
- Tumors: Poorly differentiated, signet-ring cell, lymphocytic infiltration, near diploid

Carethers et al., 1999; Arnold et al., 2003



Population Stage III		Rate of 5-Year RFS	95% CI	N
All patients analyzed		62%	(0.59 - 0.66)	N=842
Prognostic analysis		61%	(0.57 - 0.64)	N= 702
Predictive analysis within treatment arm	All patients with MSI-H tumors	72%	(0.60-0.86)	N= 103
	All patients with MSS tumors	67%	(0.57-0.76)	N= 96
Predictive analysis within tumor subtype	All patients with MSI-H tumors	59%	(0.54-0.64)	N= 739
	All patients with MSS tumors	60%	(0.56-0.64)	N= 606
FU/LV /Irinotecan	All patients with MSI-H tumors	69%	(0.57-0.83)	N= 49
	All patients with MSS tumors	76%	(0.64-0.88)	N= 50
Predictive analysis within tumor subtype	All patients with MSI-H tumors	64%	(0.59-0.69)	N=372
	All patients with MSS tumors	59%	(0.53-0.64)	N= 304
FU/LV	All patients with MSI-H tumors	72%	(0.60-0.86)	N= 54
	All patients with MSS tumors	57%	(0.42-0.71)	N= 46
FU/LV /Irinotecan	All patients with MSI-H tumors	69%	(0.57-0.83)	N= 49
	All patients with MSS tumors	76%	(0.64-0.88)	N= 50

Purple and red (1) J Clin Oncol.27:1814-21, 2009

### Conclusions from PETACC3

- Microsatellite instability is a strong prognostic factor for RFS and OS in stage II
- The prognostic effect is weaker in stage III
  - conclusions are limited by sample size, the unbalance of MSI in the stages and multiple testing.
- Taken together this may suggest stage specific biological effects of MSI.
- Prognostic effect
  - retained for RFS and OS despite treatment with 5FU
- Predictive:
  - no evidence for an effect of the addition of irinotecan in MSI-H
- Discordances with previous studies
  - Biomarker studies may be confounded small size studies, retrospective studies, pooled analysis
  - Biology: Confounded by molecular heterogeneity

### Prognostic Value(Univariate analysis)

Marker	Stage II (n=420)		Stage III (n=984)		Interaction *
	HR <sup>§</sup>	p val**	HR <sup>§</sup>	p val**	
MSI (Hi vs Stable)	0.3	0.004	0.7	0.06	0.04
18qLOH	2.1	0.03	1	0.91	0.05
SMAD4 (any loss)	1.4	0.21	1.6	<0.0001	0.23
hTERT (High)	1.4	0.32	1.5	0.01	0.92
p53 (High)	1.0	0.98	1.3	0.03	0.37
TS (High)	0.5	0.03	0.7	0.02	0.30
KRAS (Mutated)	1.1	0.84	1.0	0.72	0.32
BRAF(Mutated)	0.9	0.90	1.2	0.28	0.38

\* p value from Likelihood ratio test to assess differences between the stages  
 \*\* p values from the Wald test in a univariate Cox regression  
 § HR = hazard ratio

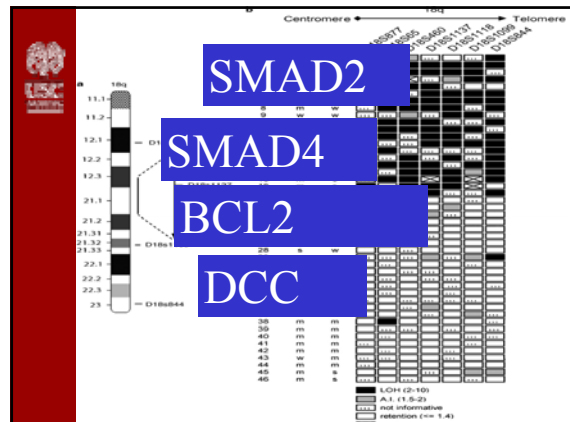
### Prognostic Value (RFS) Multivariate Analysis in whole population

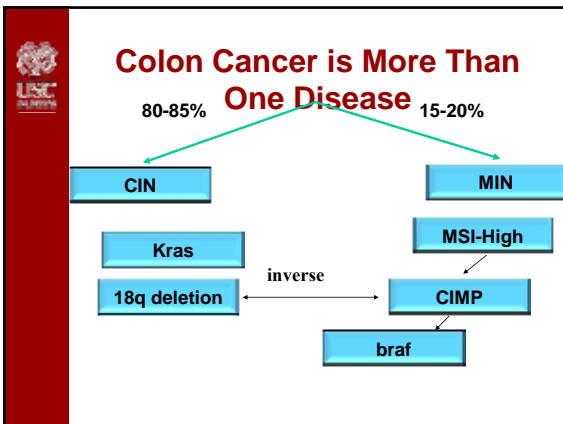
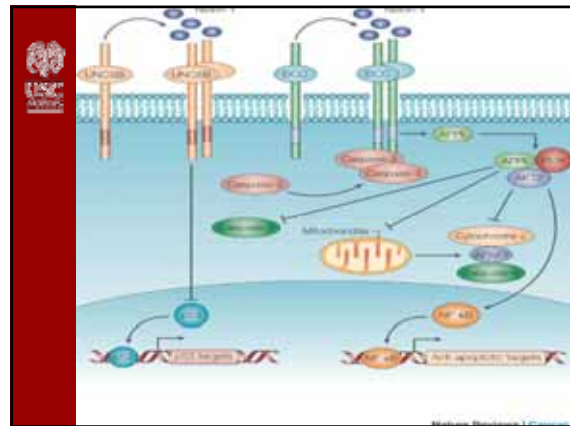
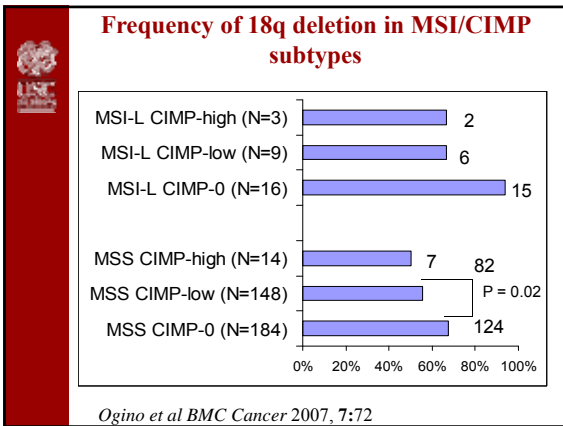
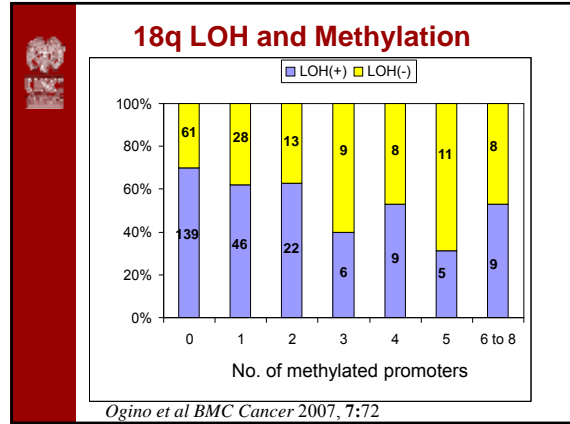
Markers	Stage II		Stage III	
	HR <sup>§</sup>	p value*	HR <sup>§</sup>	p value*
T Stage (T4 vs T3)	2.8	0.0001	1.6	0.0006
N Stage (N2 vs N1)	N/A	N/A	2.2	<0.0001
Histologic Grade (3-4 vs 1-2)	0.6	0.55	1.4	0.07
Age (>60 vs ≤60)	1.8	0.026	1.1	0.3
MSI (High vs Stable)	0.3	0.027	0.7	0.12
p53 (High)	0.7	0.27	1.3	0.015
SMAD4 (any loss)	1.0	0.9	1.6	0.0002

Treatment, Sex, Site, KRAS, BRAF, TS, 18qLOH (Stage II: HR 1.4, p=0.33), hTERT: not significant  
 \* p values from the Wald test in a multivariate Cox regression  
 § HR = hazard ratio

### MSI and 18qLOH in a minimal multivariate model in stage II disease

T4 v. T3	2.58 [1.56 - 4.28]	0.00024
MSI-H v. MSS	0.28 [0.10 - 0.72]	0.0089
18qLOH	1.37 [0.67 - 2.77]	0.38

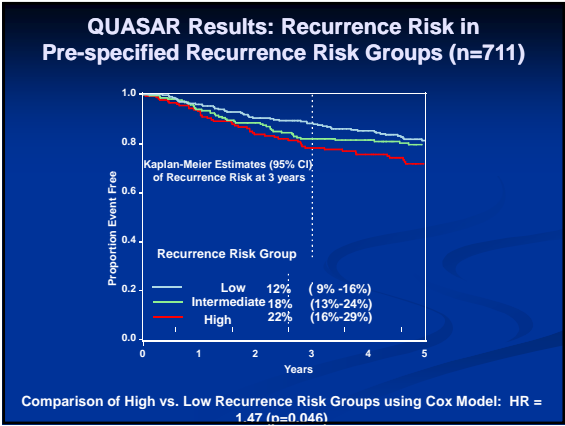




### QUASAR Results: Clinical/Pathological Covariates and Recurrence

Pre-specified Multivariate Analysis, Surgery Alone Patients (n=605)

Variable	Categories	HR	HR 95% CI	P value
Mismatch Repair (MMR)	13% Deficient vs. 87% Proficient	0.32	(0.15,0.69)	<0.001
T Stage	15% T4 vs. 85% T3	1.83	(1.23,2.75)	0.005
Tumor Grade	29% High vs. 71% Low	0.62	(0.40,0.96)	0.026
Number of Nodes Examined	62% <12 vs. 38% ≥12	1.47	(1.01,2.14)	0.040
Lympho-Vascular Invasion	13% Present vs. 87% Absent	1.40	(0.88,2.23)	0.175
Recurrence Score	continuous per 25 units	1.61	(1.13,2.29)	0.008

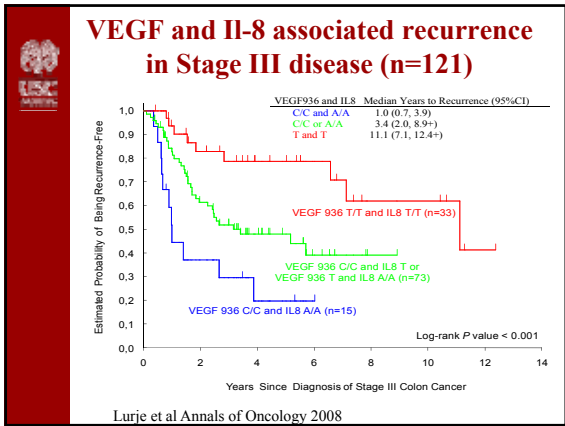
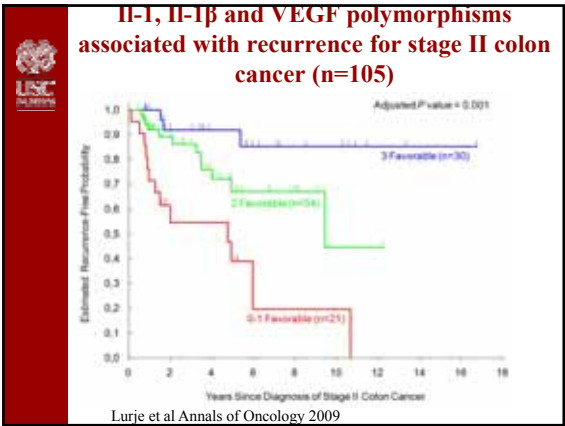


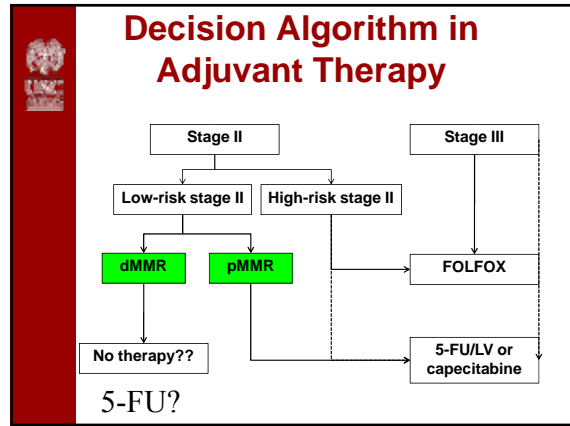
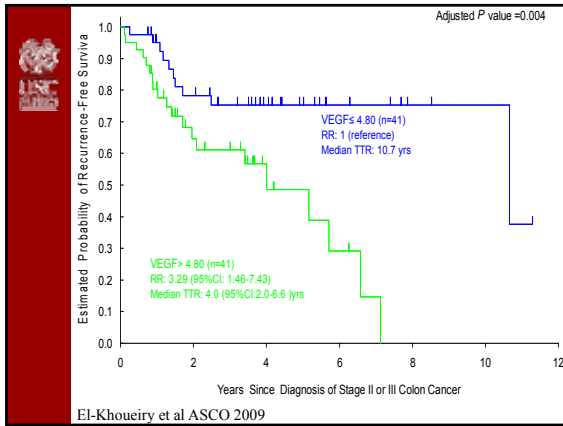
- Treatment Score by Treatment Interaction not significant when adjusted for prognostic covariates
- Treatment Score by Treatment Interaction not significant for DFS (interaction p=0.12) or OS (interaction p=0.15)



### Different Molecular Markers for Recurrence in Stage II and III

Stage III	Stage II
VEGF 936 C/T	VEGFR2 AC repeat
IL-8 -251 T/A	EGFR CA repeat
	AM CA repeat
	IL1β +3954 C/T





- ### Key Takeaways
- dMMR validated as a prognostic marker in stage II colon cancer
  - Controversy data on benefit of 5-FU and CPT-11 sensitivity in dMMR
  - 18q deletion not an independent factor in stage II? Does E5202 have the right design?
  - Stage II and III may be different diseases
  - Anti Angiogenesis negative in stage II/III: Different tumor biology between microscopic and macroscopic disease.
  - The answer is in molecular make up: when and with what to treat.

