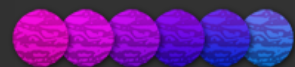


Reporting intermediate and advanced stage colorectal cancer: what is new and what is important.

Phil Quirke

Leeds University, UK

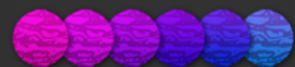


Whats new?



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- Intermediate stage
 - Definitions
 - Planes
 - Deficient mismatch repair
 - High risk features
 - Response to therapy
 - Molecular tests
- Advanced cancers
 - Metastatic
 - Molecular stratification



Intermediate stage



- Key decisions
 - Extent and quality of resection
 - Further therapy

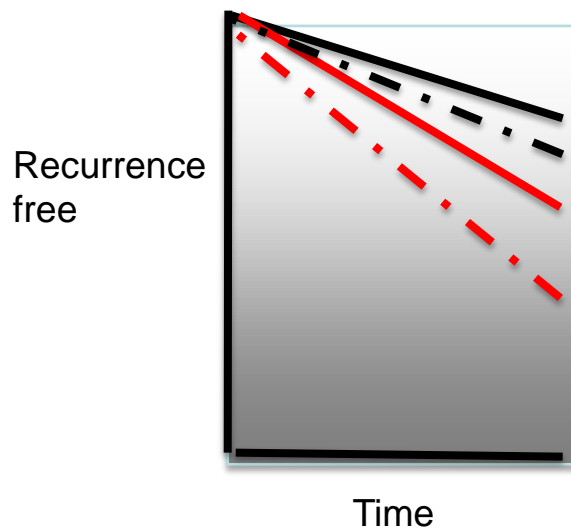
Future decision ?

- Preoperative therapy
- Neutrophil/lymphocyte ratio

➤ Feasibility of preoperative chemotherapy for locally advanced, operable colon cancer: the pilot phase of a randomised controlled trial

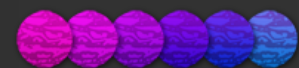
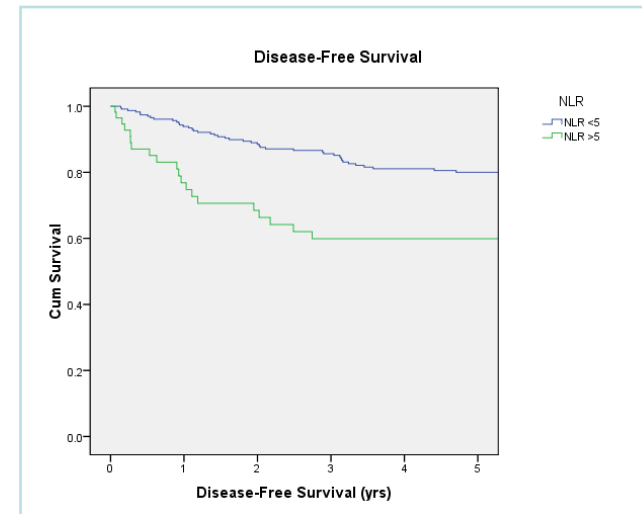
FOxTROT Collaborative Group*

Adjuvant therapy



II 3% chemo benefit

III 8-12% chemo benefit

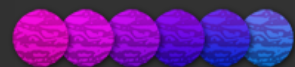
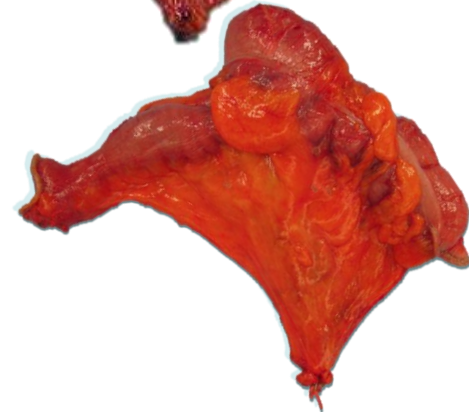
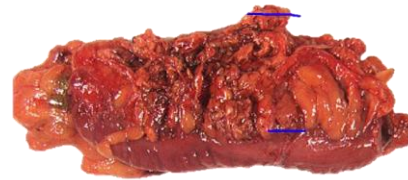
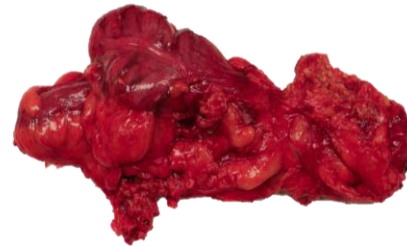


Extent and quality of resection



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- Differs between clinicians
 - Quality and type of surgery
 - Should be captured

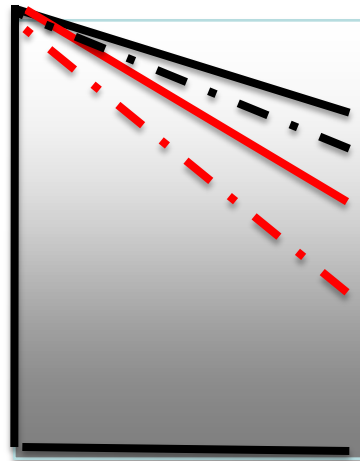


Risk of recurrence and adjuvant treatment



UNIVERSITY OF LEEDS

- Currently stage I and II vs high risk stage II or III
- Why not **absolute risk of recurrence** and potential level of reduction of recurrence, physical status and co-morbidity



II 3% chemo benefit

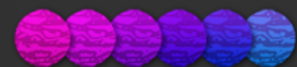
III 8-12% chemo benefit



Absolute risk of recurrence and degree of benefit of chemotherapy

vs

physical status and co-morbidity



What is intermediate stage II vs III



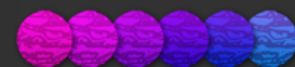
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- Dukes' B
- TNM stage II
 - v4,v5,v6,v7
 - Tumour deposits



	TNM4	TNM5	TNM6	TNM7	TNM4	TNM5	TNM6	TNM7	TNM4	TNM5	TNM6	TNM7
TNM stage	1992	1997	2003	2009	1992	1997	2003	2009	1992	1997	2003	2009
I												
II												
III												
			Lymph node metastasis				Smooth tumour deposit (2mm)				Irregular tumour deposit (5mm)	

- Stage II - Heterogeneous stage T3 1mm – Perforated tumour, peritoneal invasion and invading other organs with EMVI
- Stage III v5 lymph node positive and nodules > 3 mm
- Towards individual risk rather than II/III?



Adjuvant therapy in stage II Which patients? - Pathology



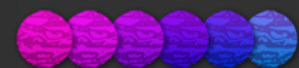
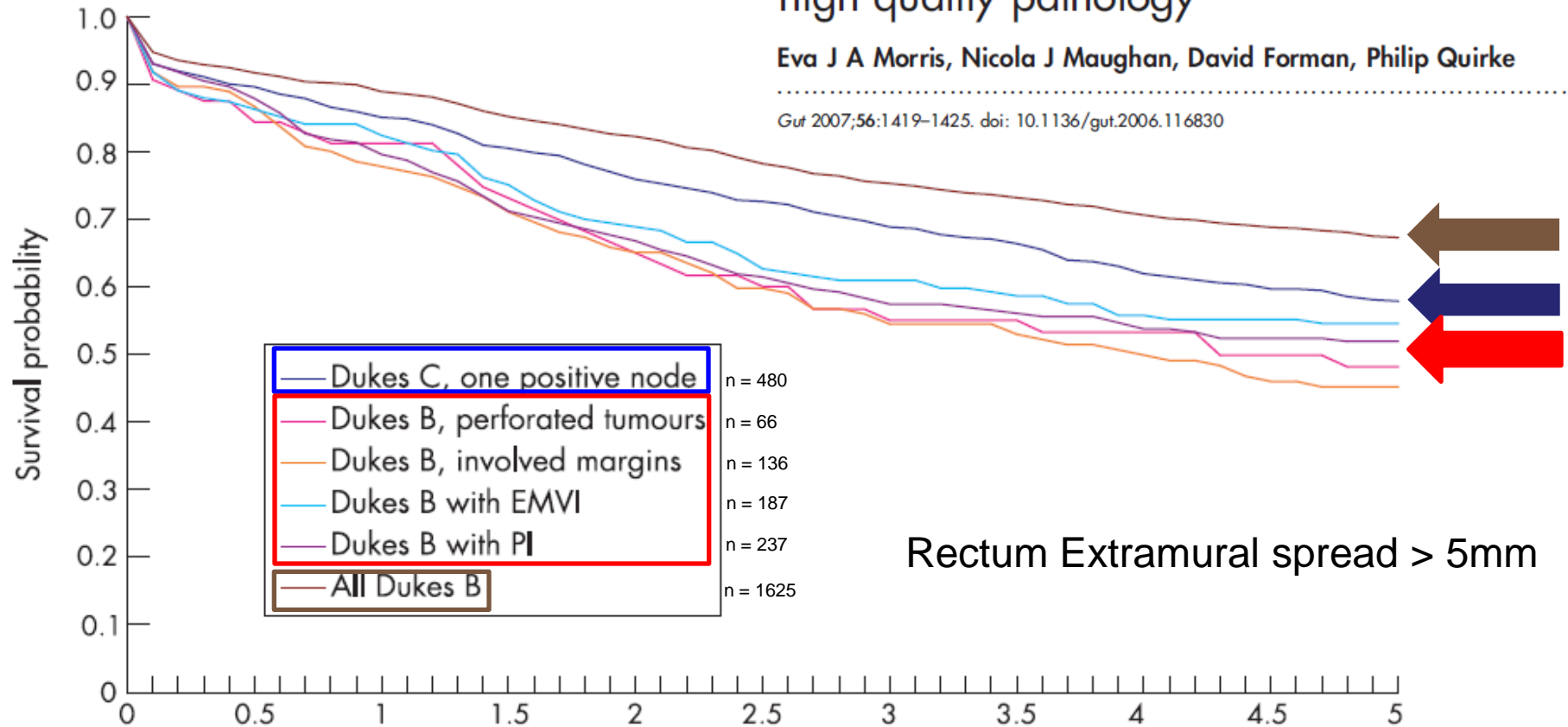
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N=1625 stage II Yorkshire Region
1995-2000

Who to treat with adjuvant therapy in Dukes B/stage II colorectal cancer? The need for high quality pathology

Eva J A Morris, Nicola J Maughan, David Forman, Philip Quirke

Gut 2007;56:1419-1425. doi: 10.1136/gut.2006.116830

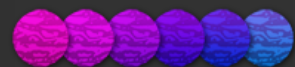
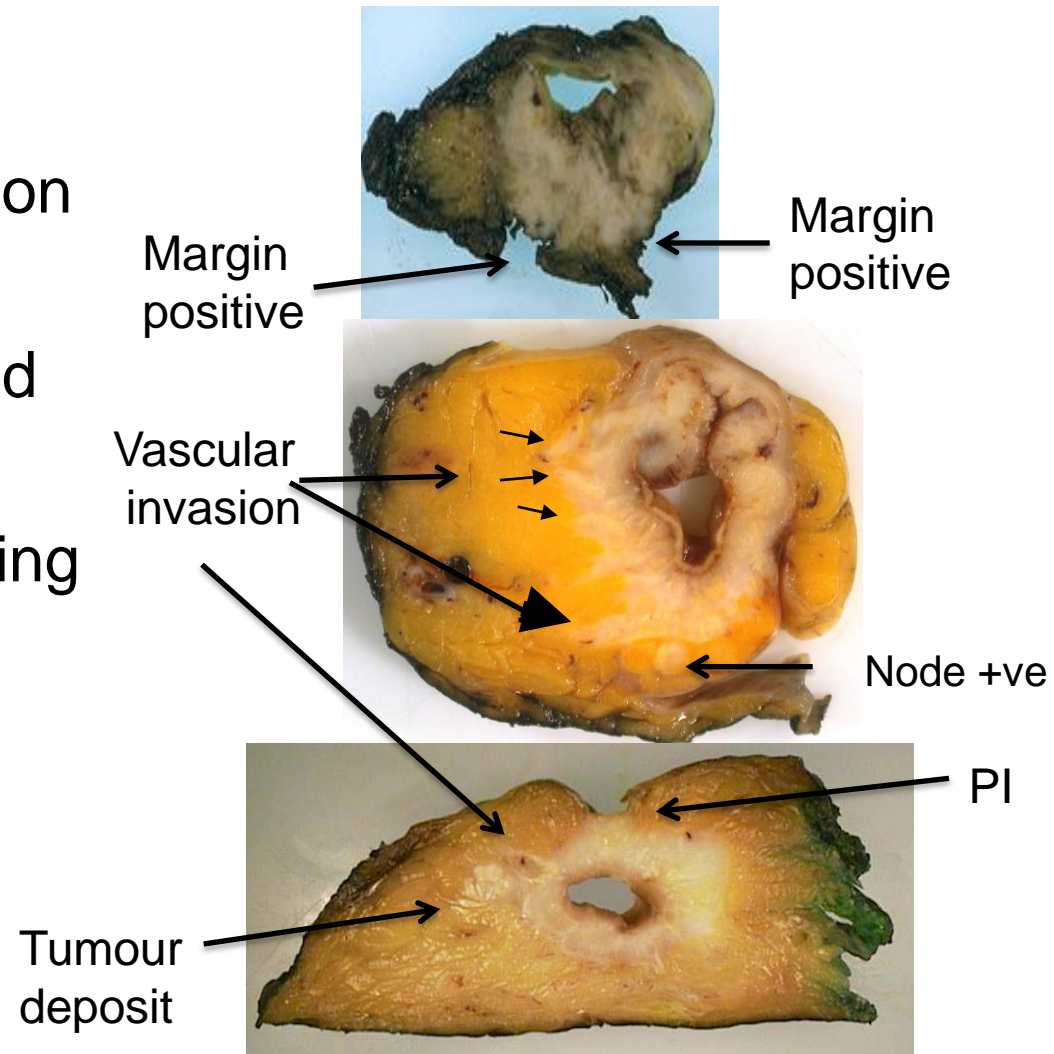


Careful macroscopic examination



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- Circumferential margin
- Extramural vascular invasion
- Peritoneal involvement
- Distance extramural spread
- Perforations
- Protocol sampling for staging and complete response
- Proforma reporting

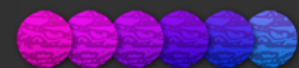
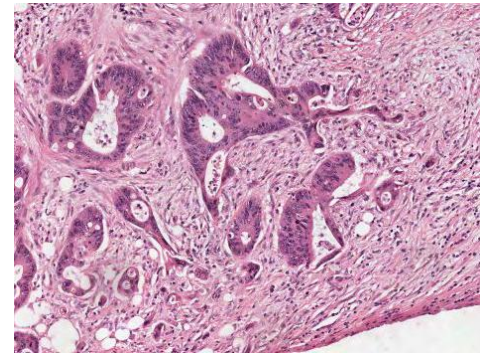
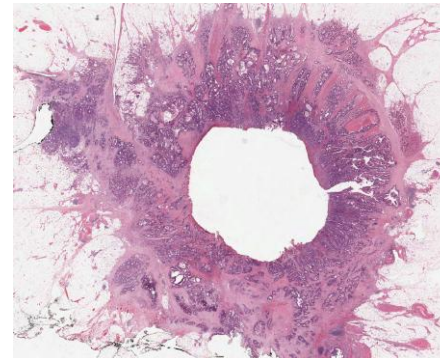
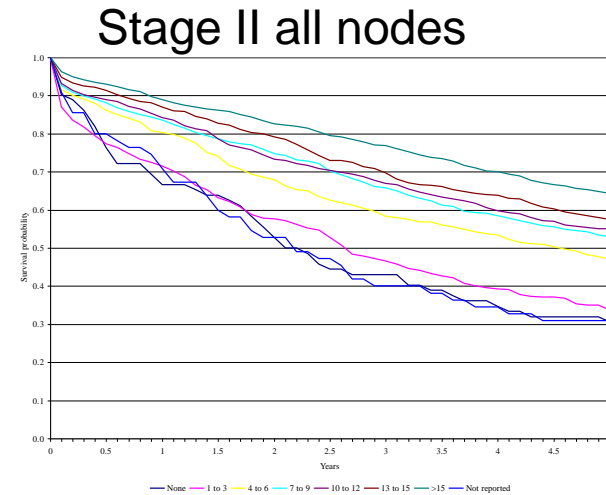


Other poor prognosis markers

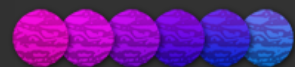


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- Low number of lymph nodes
- No lymphocytic reaction
- Infiltrating border
- High stroma
- Neural invasion
- Budding
 - Which system ?
- How do we capture these risks
- Collection of the Proforma!

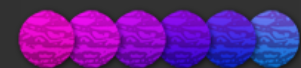
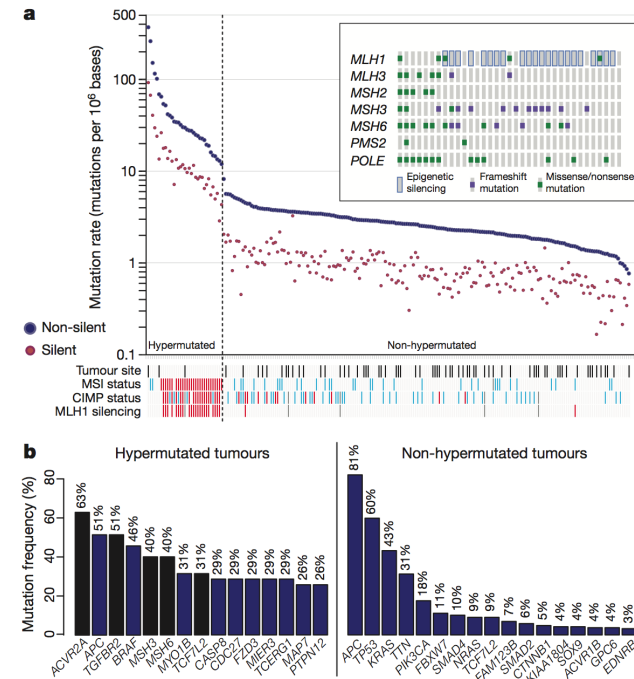
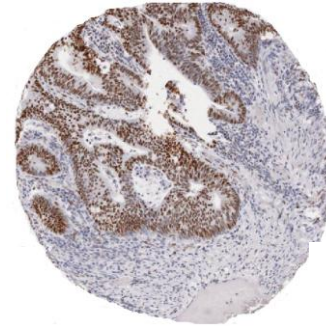


- We should move away from crude Stage II vs III
- Better estimates of recurrence risk are required
 - Includes the clinical issues
 - Informed of effectiveness of drugs from trials
 - Informed of the level of individual risk from pathology
 - Identifies the level of risk in your own system
 - Quality of treatment you provide – radiology, SURGERY, pathology etc ...
- What else can we do?
 - Molecular
 - Predictive



Molecular markers - Prognostic

- Proven prognostic
 - Deficient mismatch repair
- For discussion
 - Kirsten ras mutations
 - Braf
 - Oncotype Dx
 - Coloprint
 - ColoGuideEx

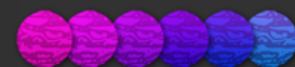
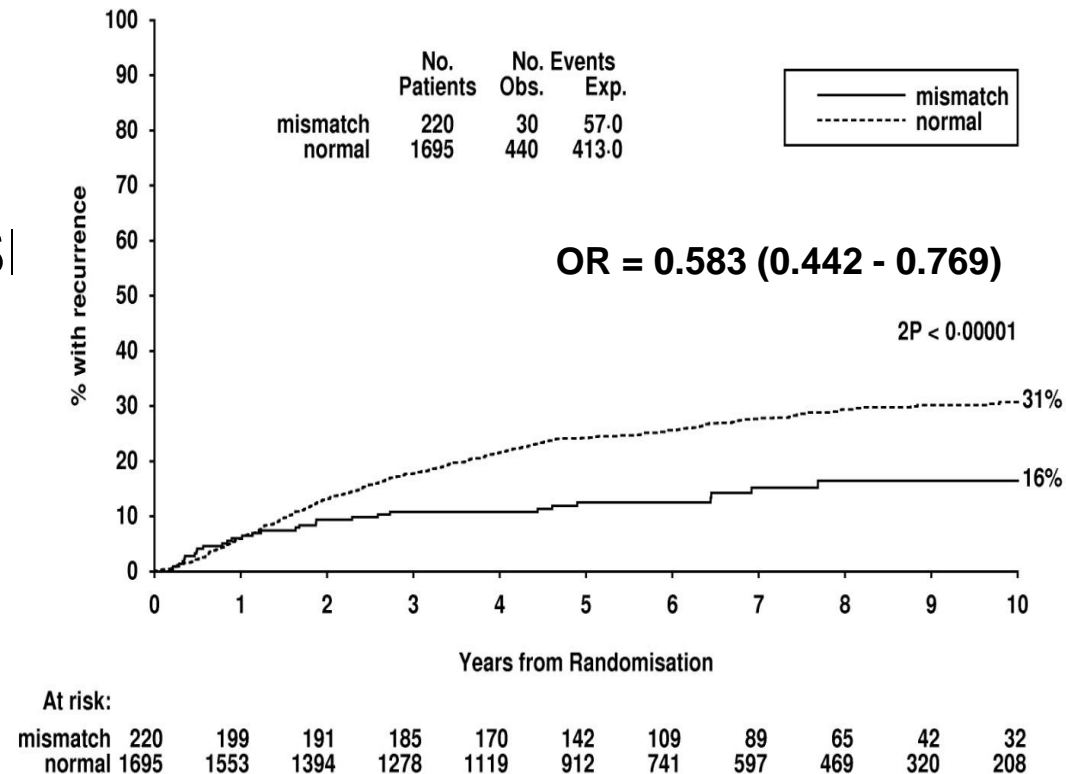


dMMR: Time to any recurrence Quasar Stage II / III (n=1915)



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- Substantial evidence
 - NHPCC
 - Reduced recurrence rate
 - Increased second cancers
- Immunohistochemistry/MSI
 - Many studies
 - Level 1 evidence
 - Quasar trial
 - Petacc – 3 trial

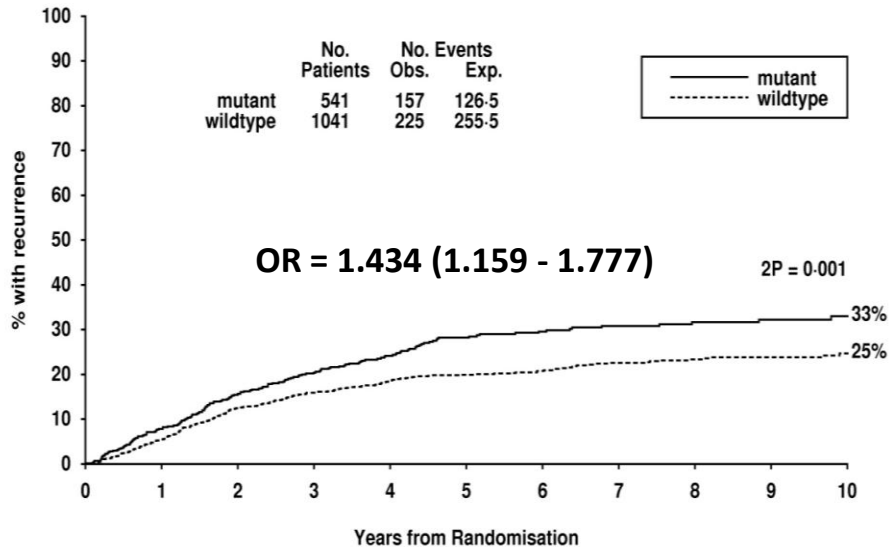


Quasar KiRAS and B-RAF Recurrence (n=1582)



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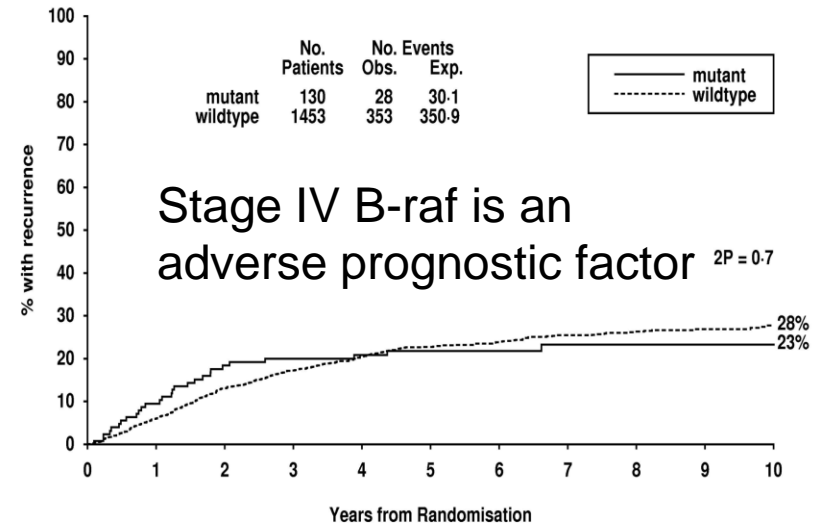
Recurrence – by KIRAS 12,13,61



At risk:

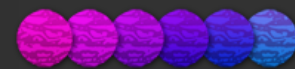
mutant	541	489	432	397	350	281	238	206	152	113	81
wildtype	1041	959	866	816	739	638	515	421	346	244	161

Recurrence – by BRAF Status



At risk:

mutant	130	113	101	97	91	77	60	48	41	29	17
wildtype	1453	1336	1198	1117	999	844	696	582	459	330	227



Prognostic Role of *KRAS* and *BRAF* in Stage II and III Resected Colon Cancer: Results of the Translational Study on the PETACC-3, EORTC 40993, SAKK 60-00 Trial

Arnaud D. Roth, Sabine Tejpar, Mauro Delorenzi, Pu Yan, Roberto Fiocca, Dirk Klingbiel, Daniel Dietrich, Bart Biesmans, György Bodoky, Carlo Barone, Enrique Aranda, Bernard Nordlinger, Laura Cisar, Roberto Labianca, David Cunningham, Eric Van Cutsem, and Fred Bosman

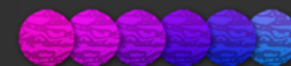
VOLUME 28 · NUMBER 3 · JANUARY 20 2010

JOURNAL OF CLINICAL ONCOLOGY

Table 5. Multivariable Survival Analysis With Proportional Hazard Regression in the Whole Population and Patients With MS-L/S Tumors

Prognostic Markers	Stage II + III (n = 1,217)			Stage II (n = 388)			Stage III (n = 829)		
	Hazard Ratio	95% CI	P	Hazard Ratio	95% CI	P	Hazard Ratio	95% CI	P
RFS in whole patient population									
MSI-H v MS-L/S	0.50	0.34 to 0.74	.00059	0.27	0.10 to 0.72	.0094	0.59	0.38 to 0.91	.016
<i>KRAS</i> mutation	1.20	0.96 to 1.49	.11	1.26	0.75 to 2.13	.38	1.21	0.95 to 1.54	.12
<i>BRAF</i> mutation	1.30	0.87 to 1.95	.21	1.93	0.67 to 5.60	.23	1.23	0.79 to 1.92	.35
OS in whole patient population									
MSI-H v MS-L/S	0.39	0.24 to 0.65	.00023	0.14	0.03 to 0.64	.011	0.48	0.28 to 0.81	.0063
<i>KRAS</i> mutation	1.29	0.99 to 1.67	.060	1.51	0.79 to 2.90	.21	1.28	0.97 to 1.71	.086
<i>BRAF</i> mutation	1.78	1.15 to 2.76	.010	3.83	1.09 to 13.5	.036	1.67	1.04 to 2.68	.035

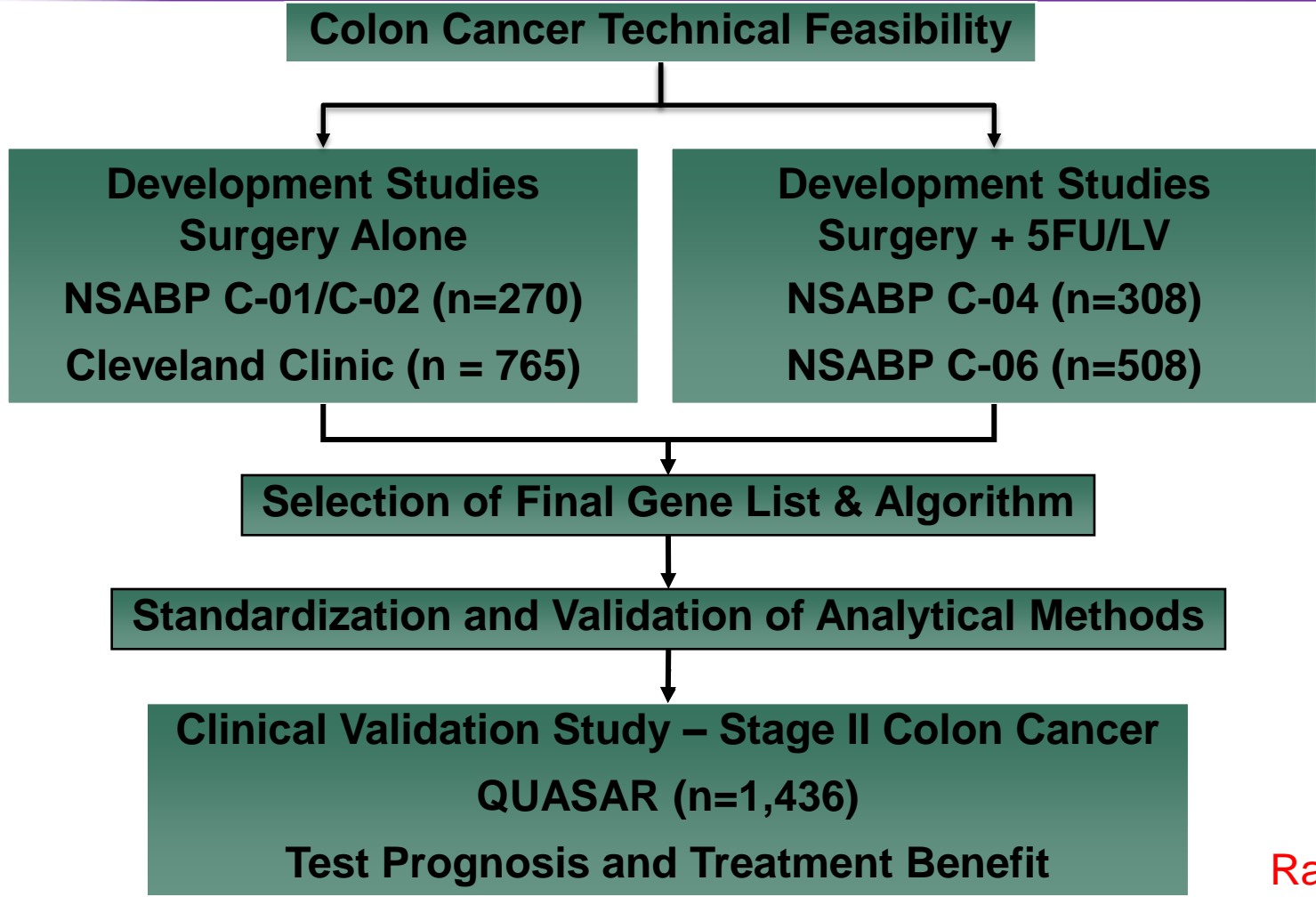
N = 1321



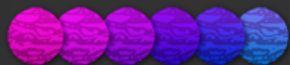
Validation of a Multi-Gene RT-PCR Colon Cancer Assay – Oncotype Dx colon in Quasar



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Raised \$100M



QUASAR: Pre-Specified Primary Endpoint: Recurrence Risk



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- 757 genes tested in 308 patients on a second cohort
- 142 genes validated in second series
- 7 genes chosen for prognosis
- 6 genes for treatment

RECURRENCE SCORE Calculated from Tumor Gene Expression

STROMAL

FAP
INHBA
BGN

CELL CYCLE

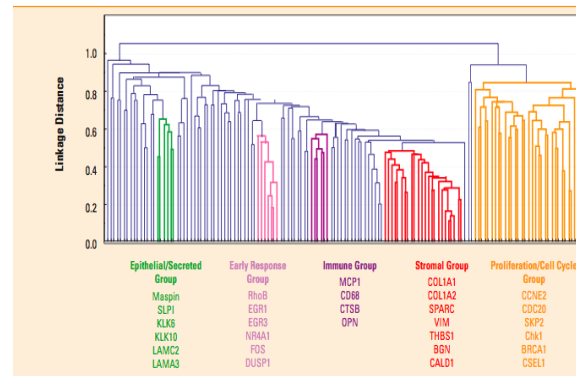
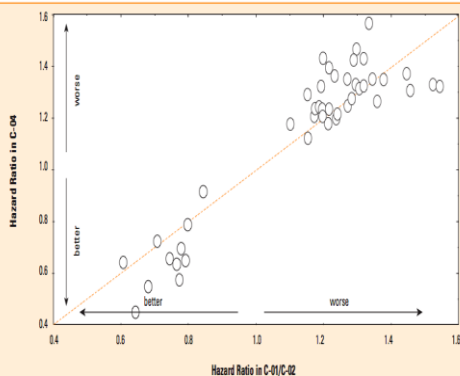
Ki-67
C-MYC
MYBL2

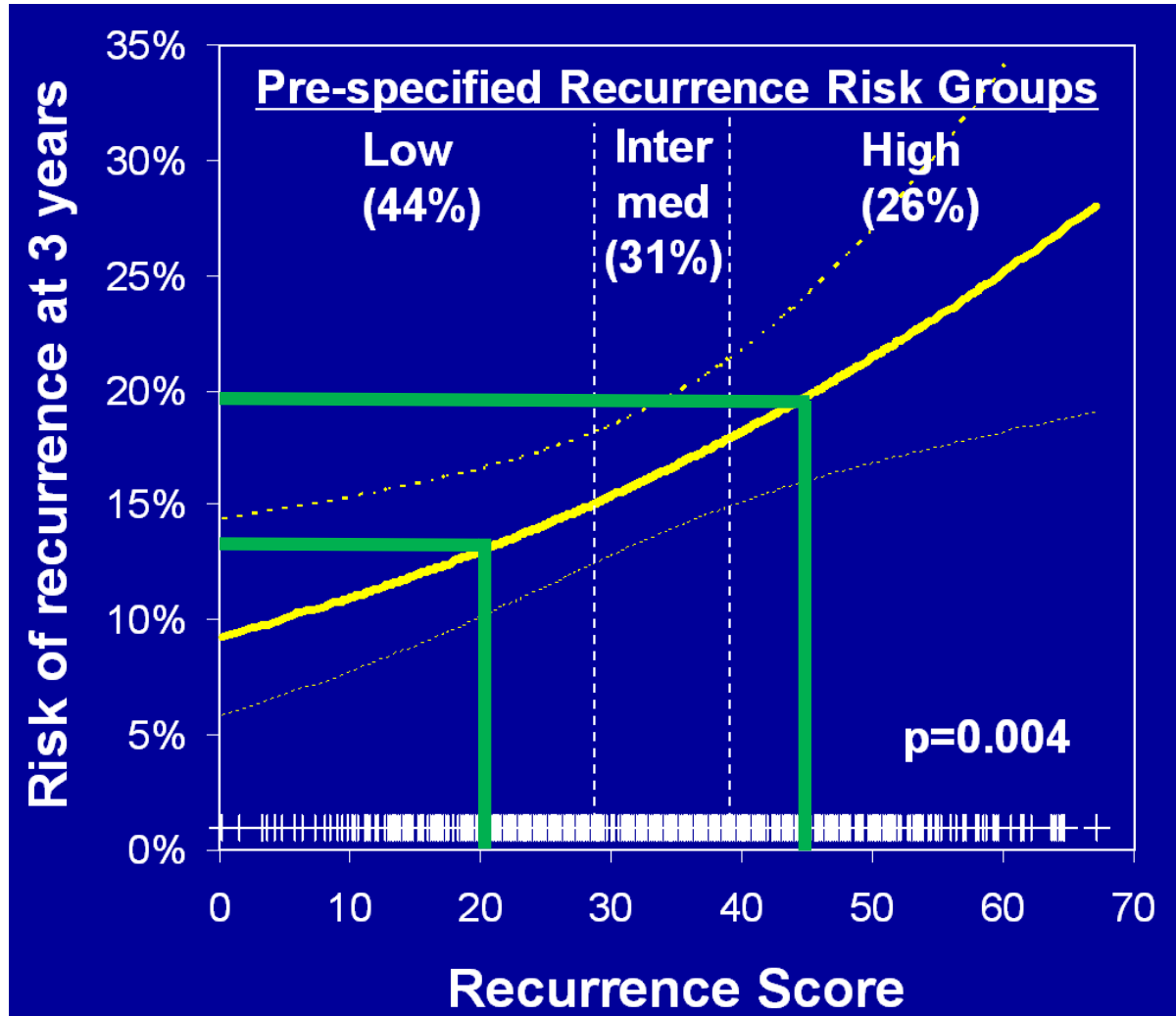
GADD45B

REFERENCE

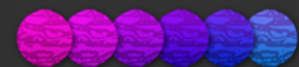
ATP5E
GPX1
PGK1
UBB
VDAC2

Figure 8. Relationship of C-04 Results to C-01/C-02 Results





HR 1.4



Others Coloprint and ColoGuideEx



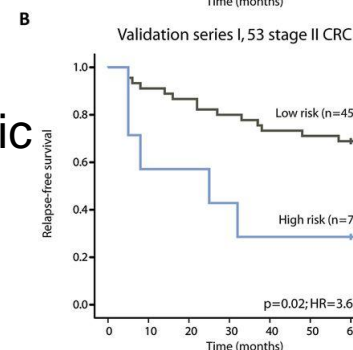
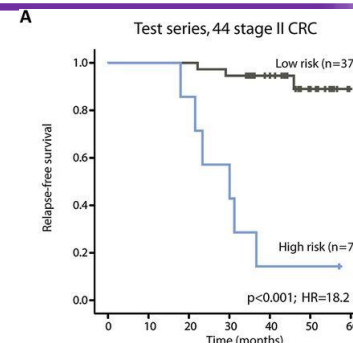
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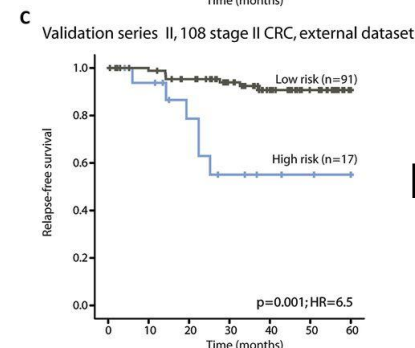
ColoGuideEx
 13 genes
 series 1 44
 Series 2 52
 Series 3 108
 No pathology
 variable prognostic



P<0.001



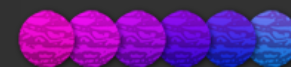
P=0.02



P=0.001

Ågesen T H et al. Gut 2012;61:1560-1567

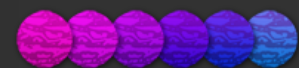
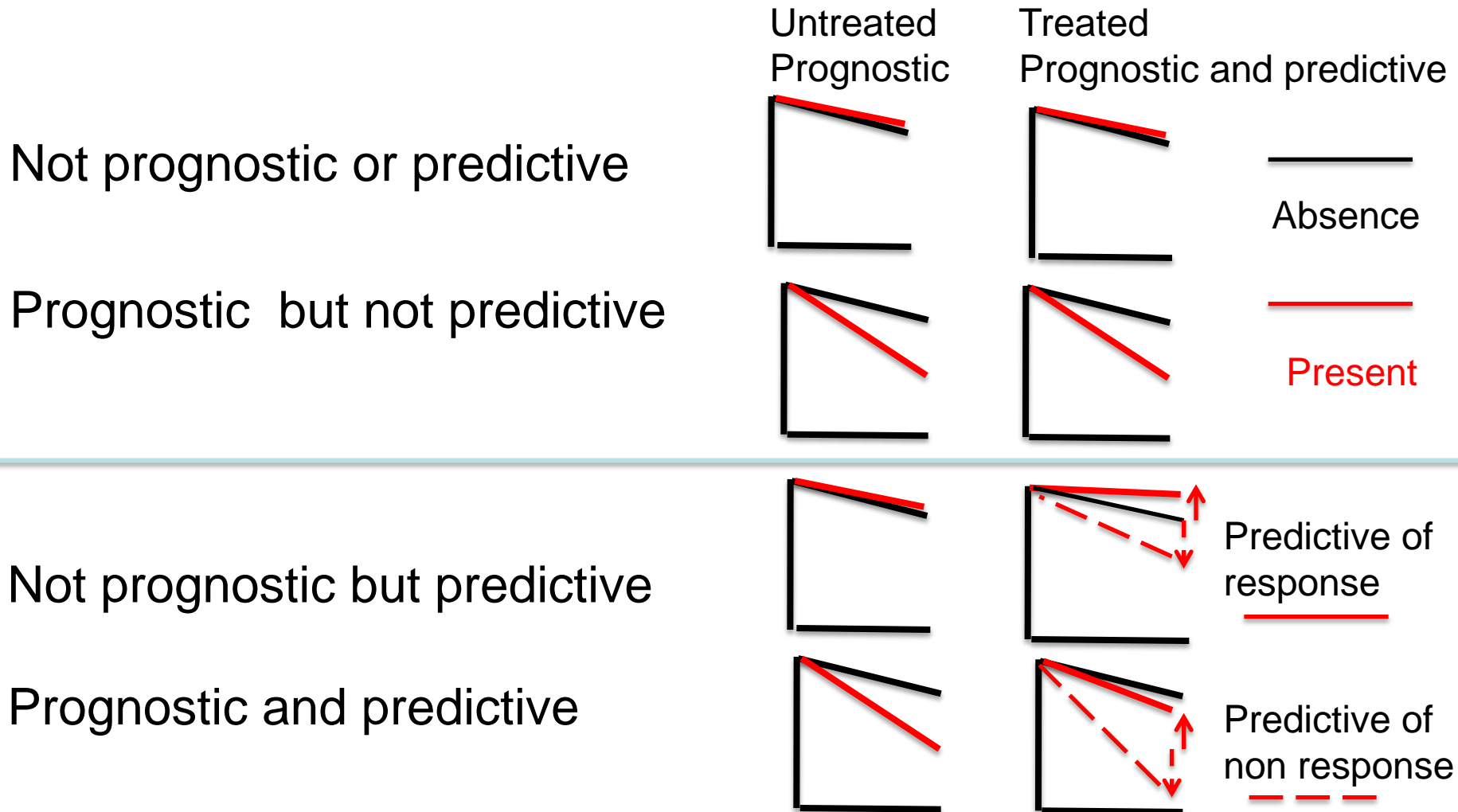
ColoPrint
 Agilent expression arrays
 Rosenberg
 135 and 206 cases with 18 gene assay
 Fresh tissue
 73% low risk 95% metastasis free survival
 27% high risk 80% metastasis free survival
 Tabanero
 320 cases HR 2.74
 Pathological features not prognostic on multivariate
Agendia raised 65M\$



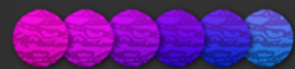
Prognostic vs predictive – marker X absent / present



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- Deficient Mismatch Repair
 - Suggested non response to 5FU
- Oncotype Dx colon cancer
 - Validation study of previous predictive studies
 - Panel RT-PCR
 - Funded by Genomic Health via a research grant



Adjuvant chemotherapy in dMMR patients prediction of response to 5FU



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VOLUME 28 NUMBER 20 JULY 10 2010

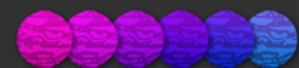
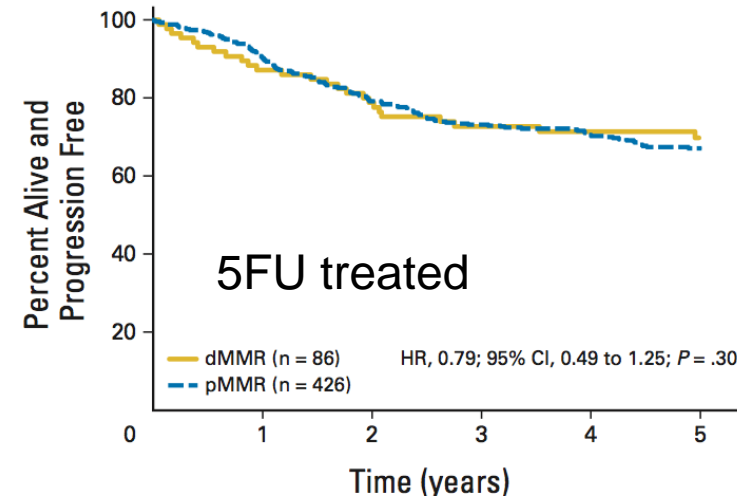
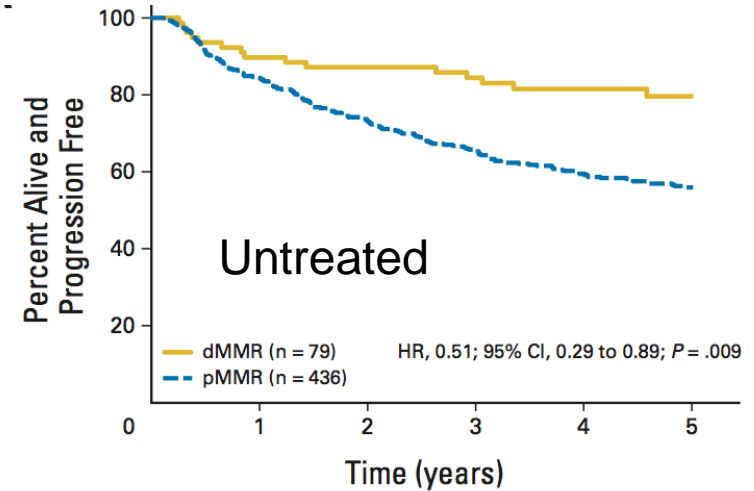
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Defective Mismatch Repair As a Predictive Marker for Lack of Efficacy of Fluorouracil-Based Adjuvant Therapy in Colon Cancer

David J. Sargent, Silvia Mariani, Genetiana Murgu, Stephen N. Thibodeau, Robert Ladman, Stanley A. Hanelen, Amy J. French, Brian Kralj, Andrew B. Fisher, Yuhai Tang, Christine Zlob, Axel Grothey, Malcolm Moore, Alberto Zanetti, Juan Francisco Sells, Frank Sirocchi, and Steve Gallinger
See accompanying editorial on page 3207 and 3210

- JCO 2010 Dan Sargent
 - Pooled analysis 5 small studies
 - n=1027 n= 165 dMMR
 - Mixture MSI and IHC
 - Stage II / III patients dMMR / MSI
- dMMR no benefit from chemotherapy
- Test hypothesis in QUASAR
- Twice the sample size



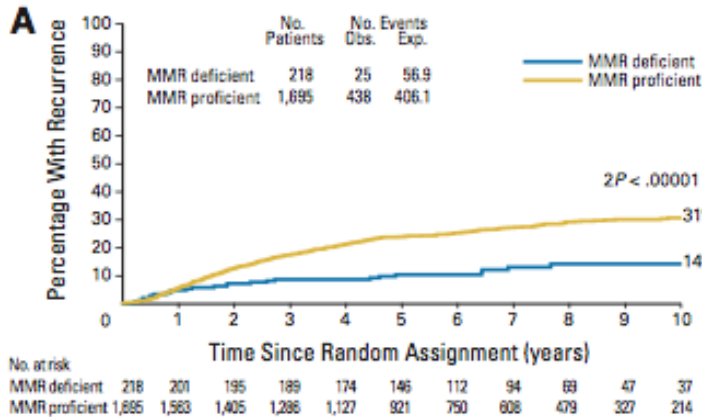
dMMR: prognosis and prediction



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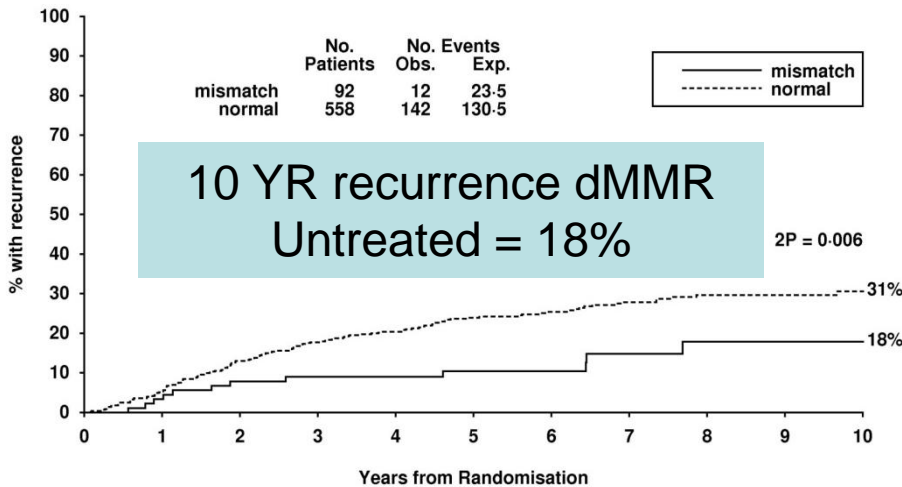
10 YR recurrence
dMMR 16% vs pMMR 31%

OR = 0.583 (0.442 - 0.769)



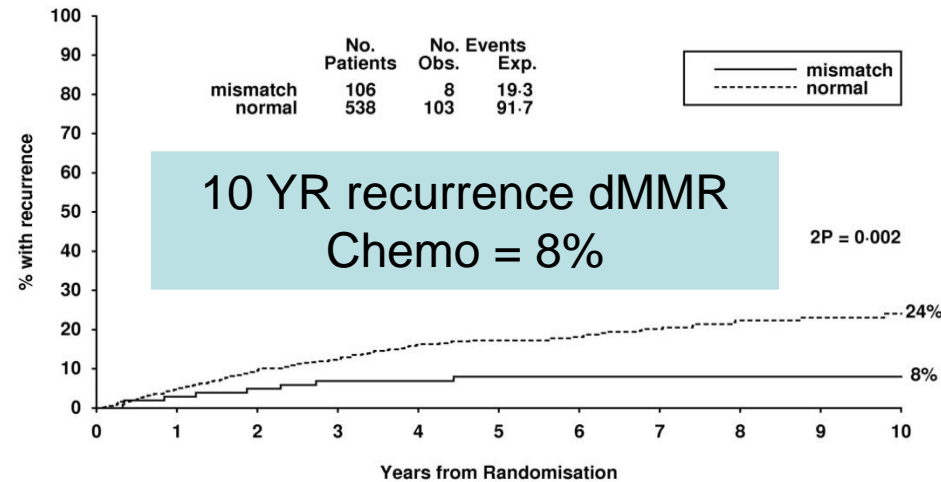
n=198 with dMMR

Recurrence – csII no chemo patients by MMR Status

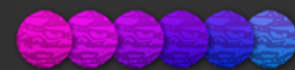


10 YR recurrence dMMR
Untreated = 18%

Recurrence – csII chemo patients by MMR Status



10 YR recurrence dMMR
Chemo = 8%

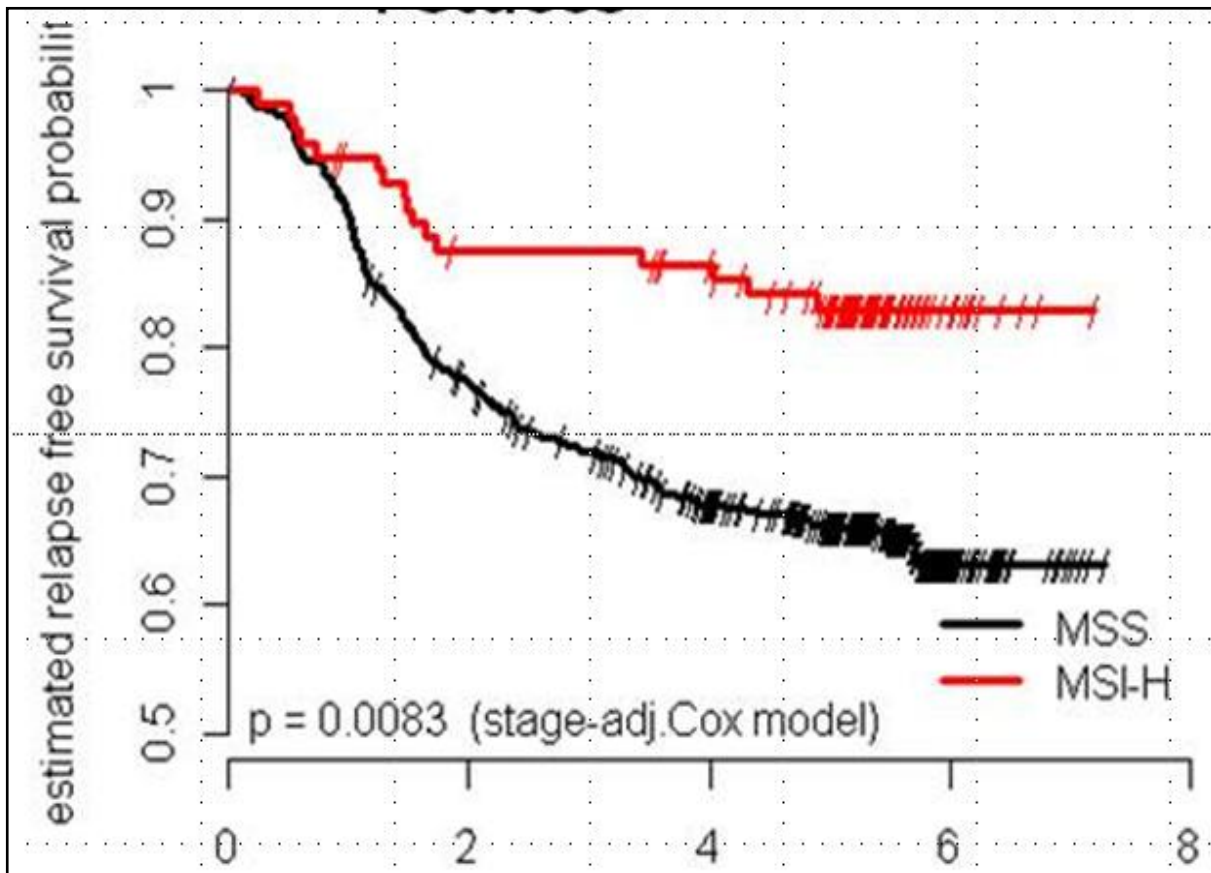


Petacc 3



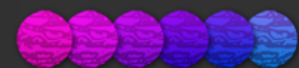
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5-FU/LV vs. 5-FU/LV + Irinotecan No untreated arm no effect of irinotecan



1235 patients
188 MSI high

Cannot substantiate
the USA claim



QUASAR results: Oncotype Dx prediction in all patients (n=1436)



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Treatment Score Genes	Accession Number
AXIN2	NM_004655
BIK	NM_001197
EFNB2	NM_004093
HSPE1	NM_002157
MAD2L1	NM_002358
RUNX1	NM_001754

Others predicting adjuvant therapy

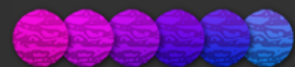
Kiras, Braf, PIK3CA no value

Anti EGFr therapy no value

Bevacizumab no value

- No significant difference in benefit of chemotherapy at low RS vs high RS
- Was also prognostic

Genomic Health raised 100M\$
Prior to these results



In vivo prediction advanced stage II/III



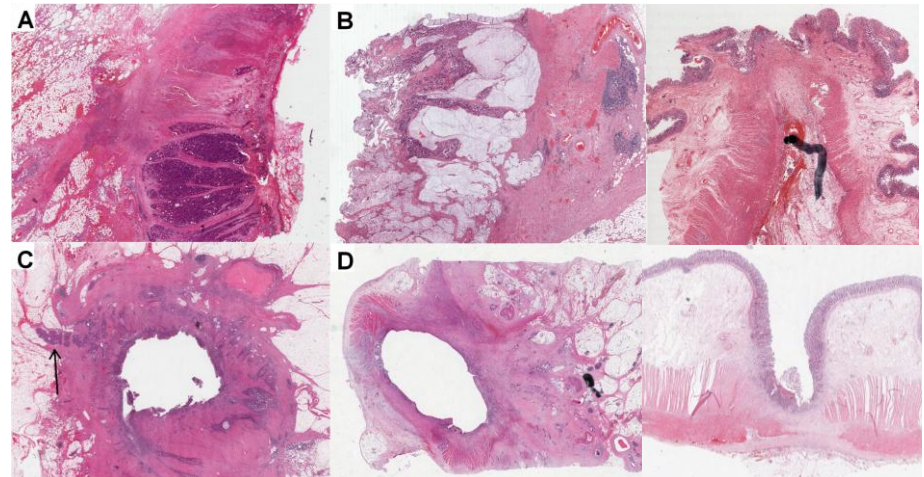
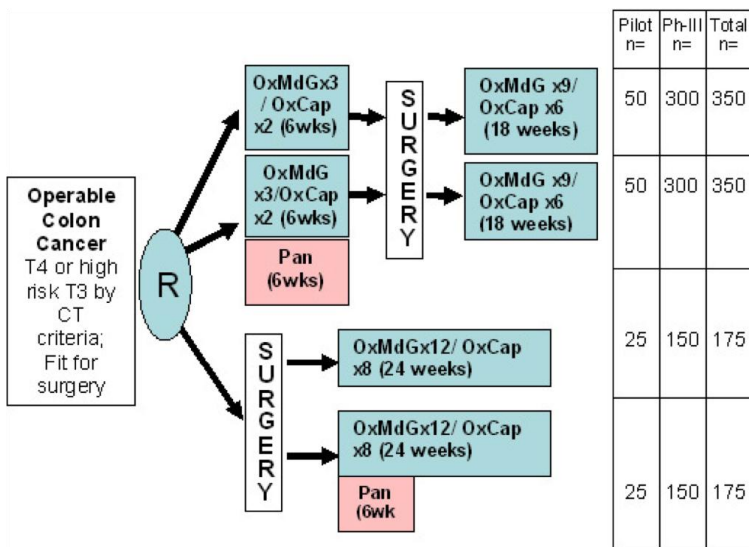
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- In vivo
 - Pathology – Foxtrot

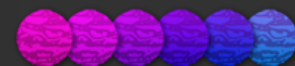
➔ Feasibility of preoperative chemotherapy for locally advanced, operable colon cancer: the pilot phase of a randomised controlled trial

FOxTROT Collaborative Group*

Lancet Oncol 2012; 13: 1152-60



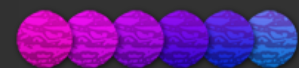
Implications for further treatment – non response change adjuvant treatment ?



Downstaging



	Preoperative and post-operative chemotherapy group (n=99)	Postoperative chemotherapy only group (n=50)*	p value
Resection margins			
R0-complete	95 (96%)	40 (80%)	0.002
R1-incomplete/R2	4 (4%)	10 (20%)	..
Mean distance to nearer margin (mm)	68.4 (56.6); n=97	70.9 (59.9); n=46	0.81
Maximum tumour thickness (mm)	18.5 (12.1); n=61	24.4 (16.7); n=33	0.08
Maximum tumour diameter (mm)	49.6 (45.4); n=93	62.2 (28.0); n=46	0.05
Distance to retroperitoneal margin (mm)	20.7 (16.1); n=65	19.7 (25.6); n=32	0.85
Maximum spread beyond muscularis propria (mm)	6.9 (6.4); n=89	8.7 (7.4); n=43	0.14
Apical nodes positive	1/98	10/50	<0.0001
Extramural vascular invasion	34/97	24/48	0.085
Tumour regression grading			
Complete response	2	0	MH=0.0004;
Marked regression	2	0	..
Moderate regression	25	1	..
Little/no regression	65	45	..

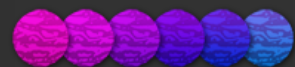


Advanced stage - trials, mutations and therapy



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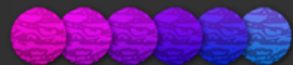
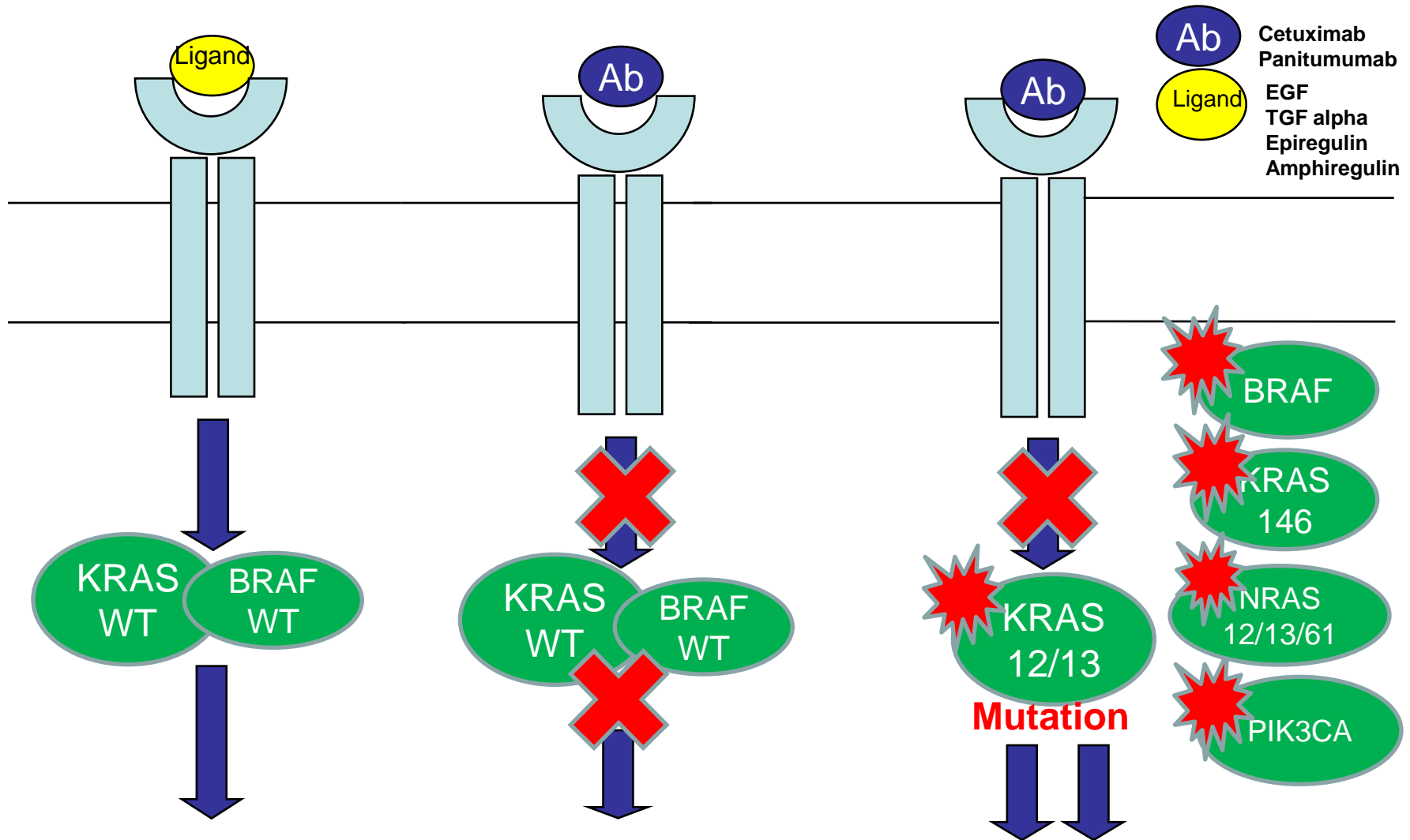
- Current chemotherapy agents
 - 5FU/folinic acid
 - Capecitabine
 - Oxaliplatin
 - Irinotecan
- } No predictors of response
- Current targeted therapies
 - Anti EGFR – mutations in ras/raf pathway
 - Anti VEGF – no predictors of response
 - Anti HER2 – HER 2 amplification



Effect of mutations on EGFr ab's in stage IV

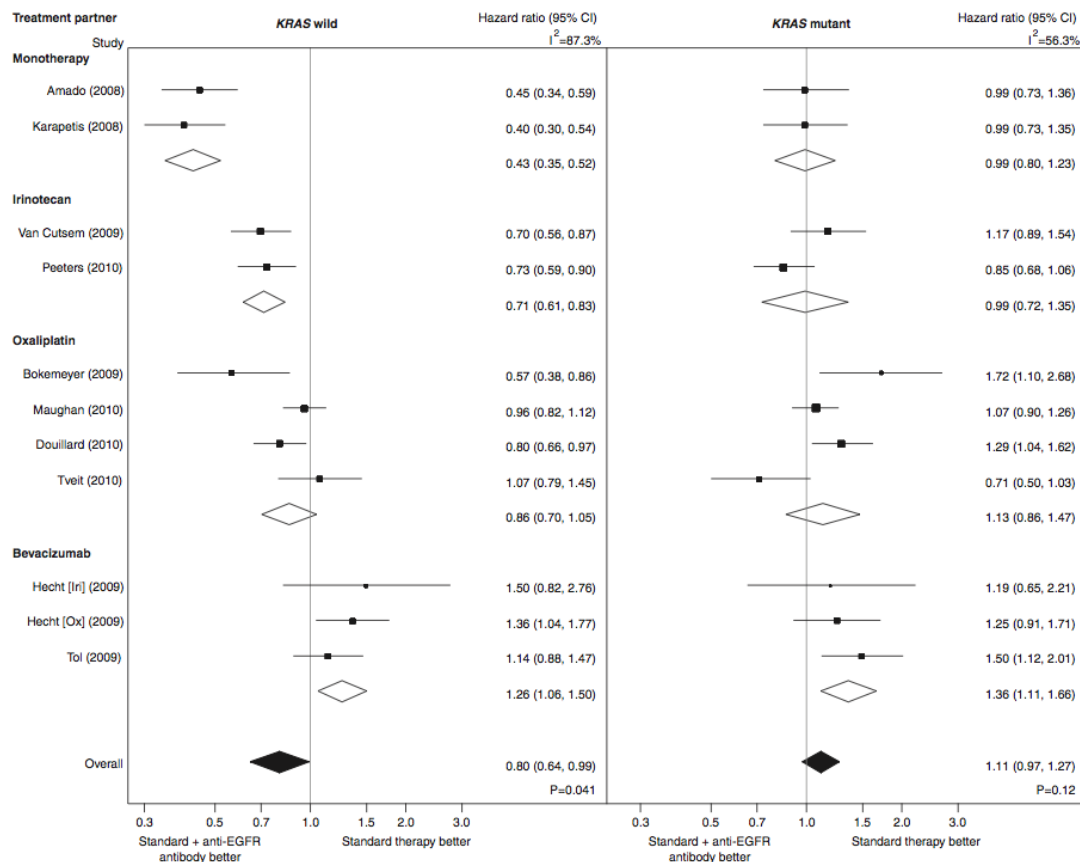


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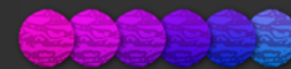




Meta-analysis of anti-EGFr antibodies and ras mutations



Progression free survival



- Retrospective analysis
- 11 centers 7 countries
- Cetuximab
- N=448 WT Ki ras
- Prospective trial
- Second line of WT Ki Ras

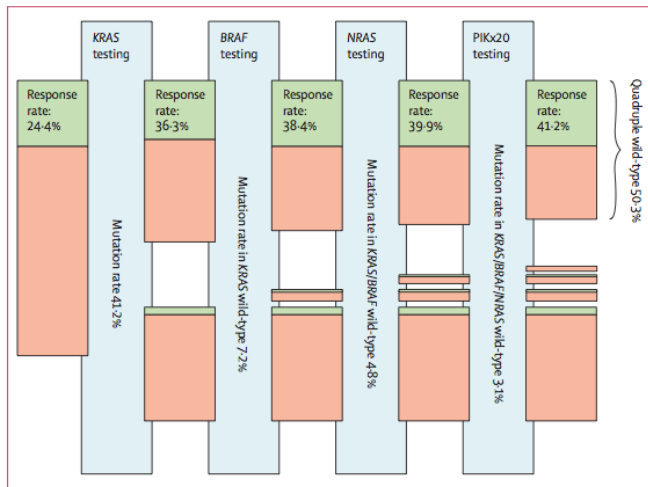
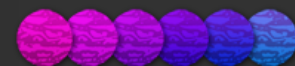
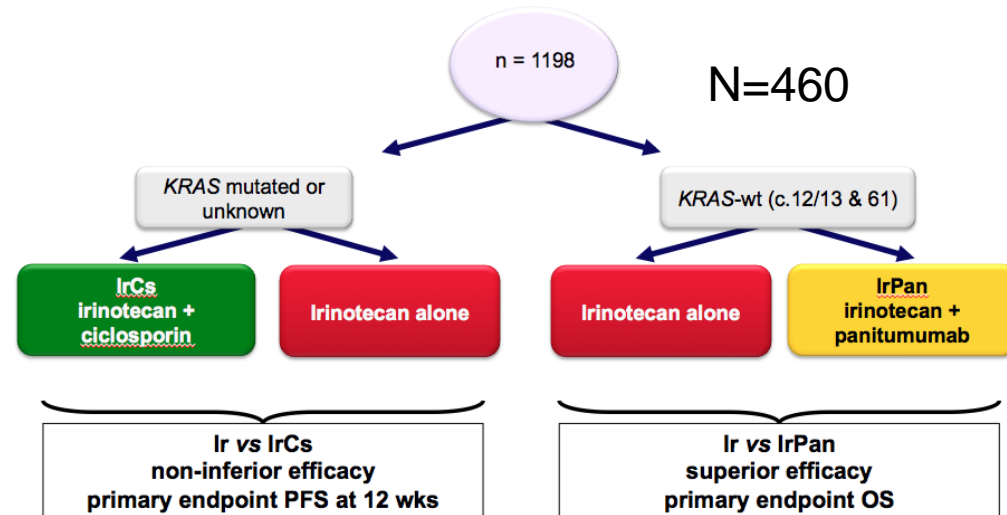


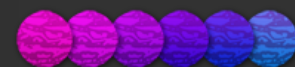
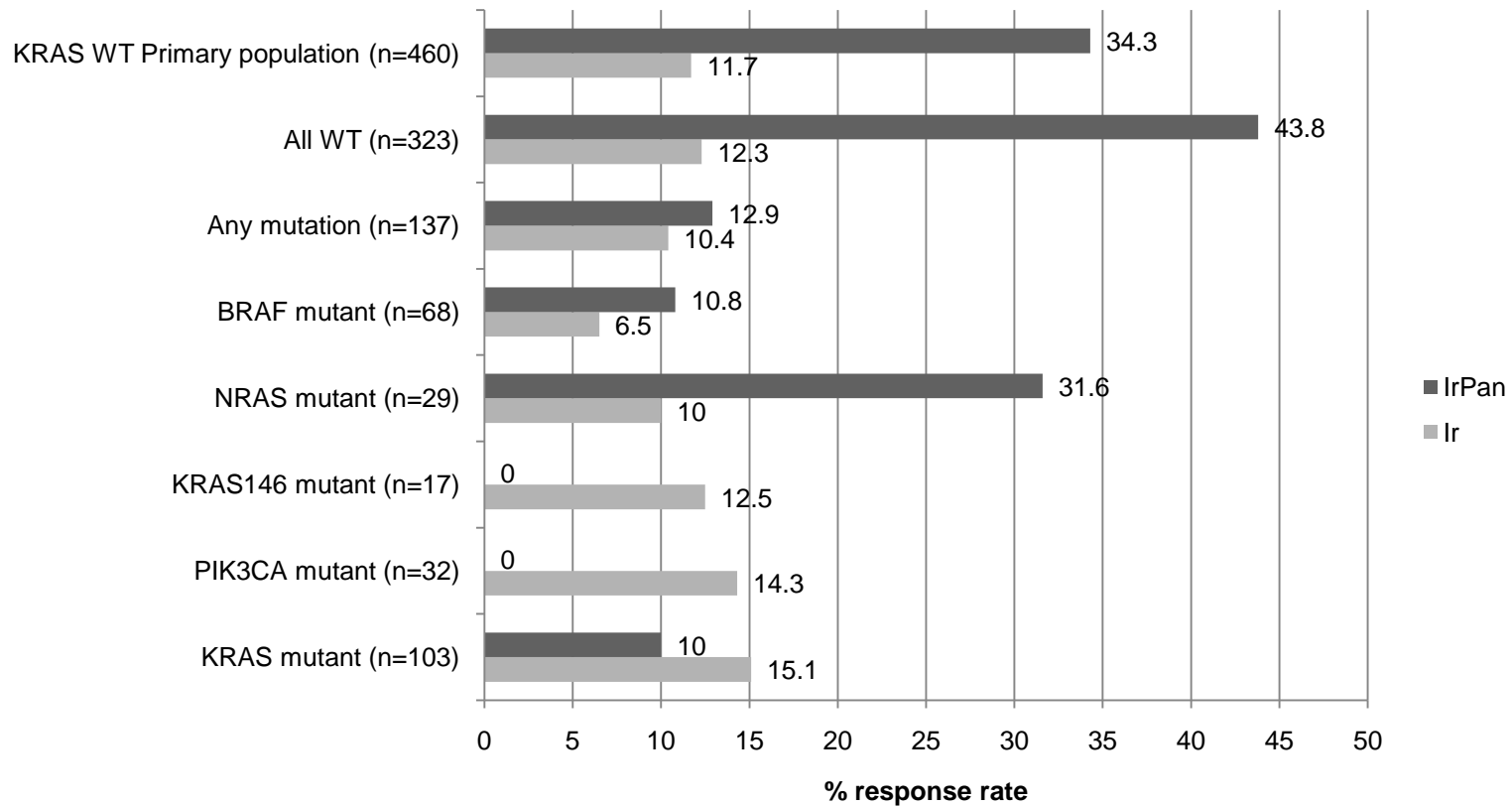
Figure 3: The improvement in response prediction gained by assessing the mutation status of each gene. Patients with missing data for any of the markers studied in this analysis were omitted from the start. The green bars represent responders; the orange bars non-responders. Bottom bars represent mutant tumours; upper bars wild-type tumours. The size of the bars is in agreement with the corresponding percentages. PIK3CA=PIK3CA exon 20.



What effect can we see with other mutations?



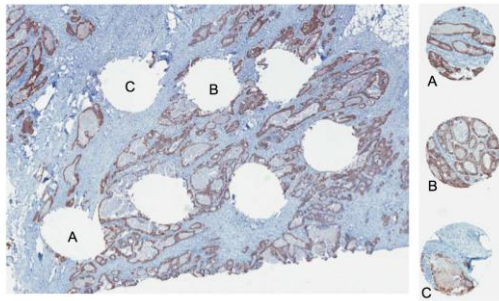
Molecular Subgroup Analyses: Response Rate



Her2 overexpression and KRAS/BRAF mutation status in MRC Focus



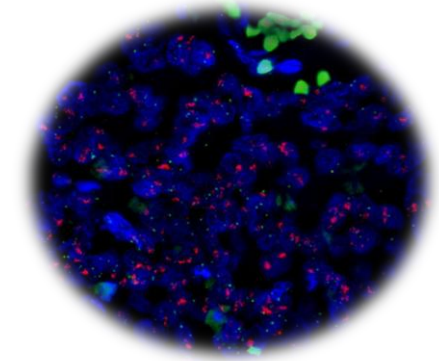
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895 tumours



542
KRAS/BRAF
data



258 (47.6%)
KRAS/BRAF-WT



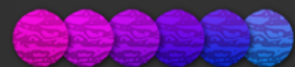
14/258 (5.4%)
Her2 overexpression

284 (52.4%)
KRAS/BRAF-mutant

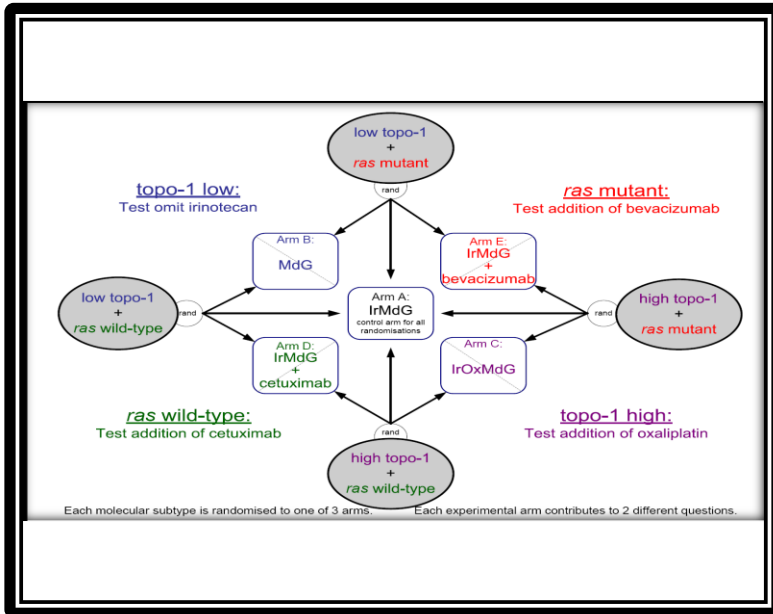


4/284 (1.4%)
Her2 overexpression

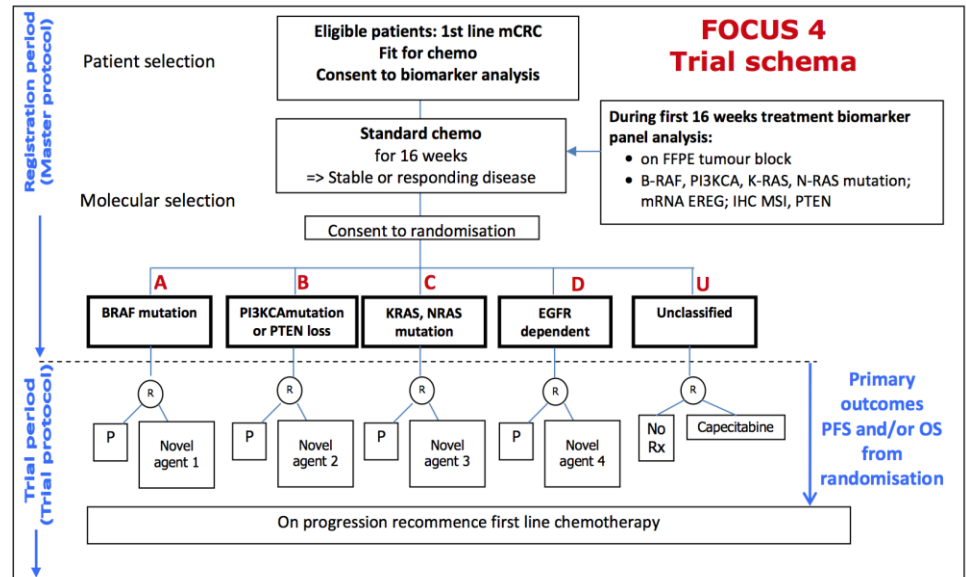
(Fisher's exact test $p=0.02$)



MRC FOCUS 3



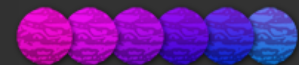
EME Focus 4



Turned around KiRas/Braf/Topo1

332 patients Biomarker results were provided to oncologists:
 within 10 working days (wd) in 71% patients
 within 15 working days in 91% patients
 within 20 working days in 99%. patients

Starts 2013

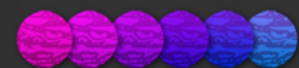


Thanks to



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- NCRI Quasar trials group
 - Gordon Hutchins, Katie Southward, Jens Stahlschmidt, Richard Gray, Kelly Handley
- Genomic Health
 - Mark Lee, Rick Baehner
- NCRI Piccolo trial group
 - Matt Seymour, Susan Richman
- MRC Focus trials group
 - Matt Seymour, Susan Richman, Mike Braun, Philip Chambers
- Funding: Yorkshire Cancer Research, NCRI (UK), CRUK, Genomic Health

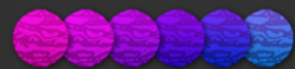


What is important



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- FOBT Screening – 16% reduction in mortality – screened population
- Better primary surgery – 10-20% reduction in mortality in operated cases
- Liver resection – 60% reduction in mortality from liver metastases
- Stage III chemotherapy 8-12% reduction
- Stage II 3% reduction
- Short course radiotherapy no mortality reduction
- Preoperative chemoradiotherapy?
- Preoperative chemotherapy?



ARTICLE

doi:10.1038/nature11252

Comprehensive molecular characterization of human colon and rectal cancer

The Cancer Genome Atlas Network*

3 3 0 | N A T U R E | V O L 4 8 7 | 1 9 J U L Y 2 0 1 2

N= 224

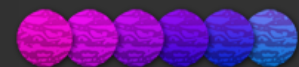
Exome sequence, DNA copy number, promoter methylation, mRNA and miRNA,

N = 97

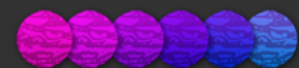
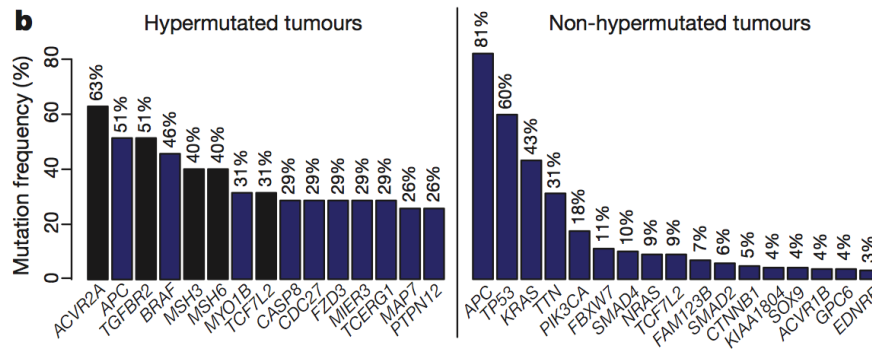
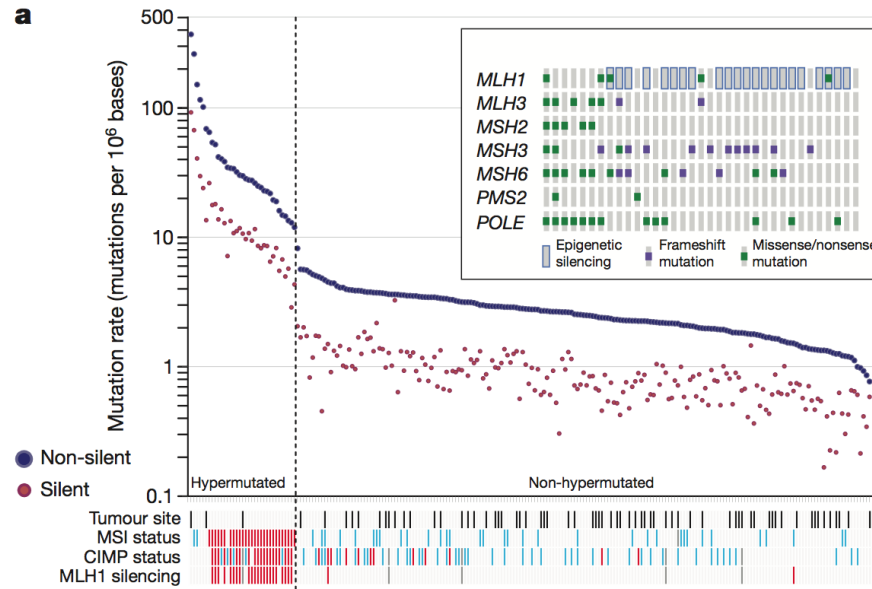
low depth whole genome sequencing

Hyper mutated cancers and non hyper mutated

Otherwise colon and rectum same mutational patterns



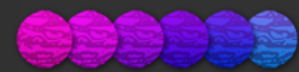
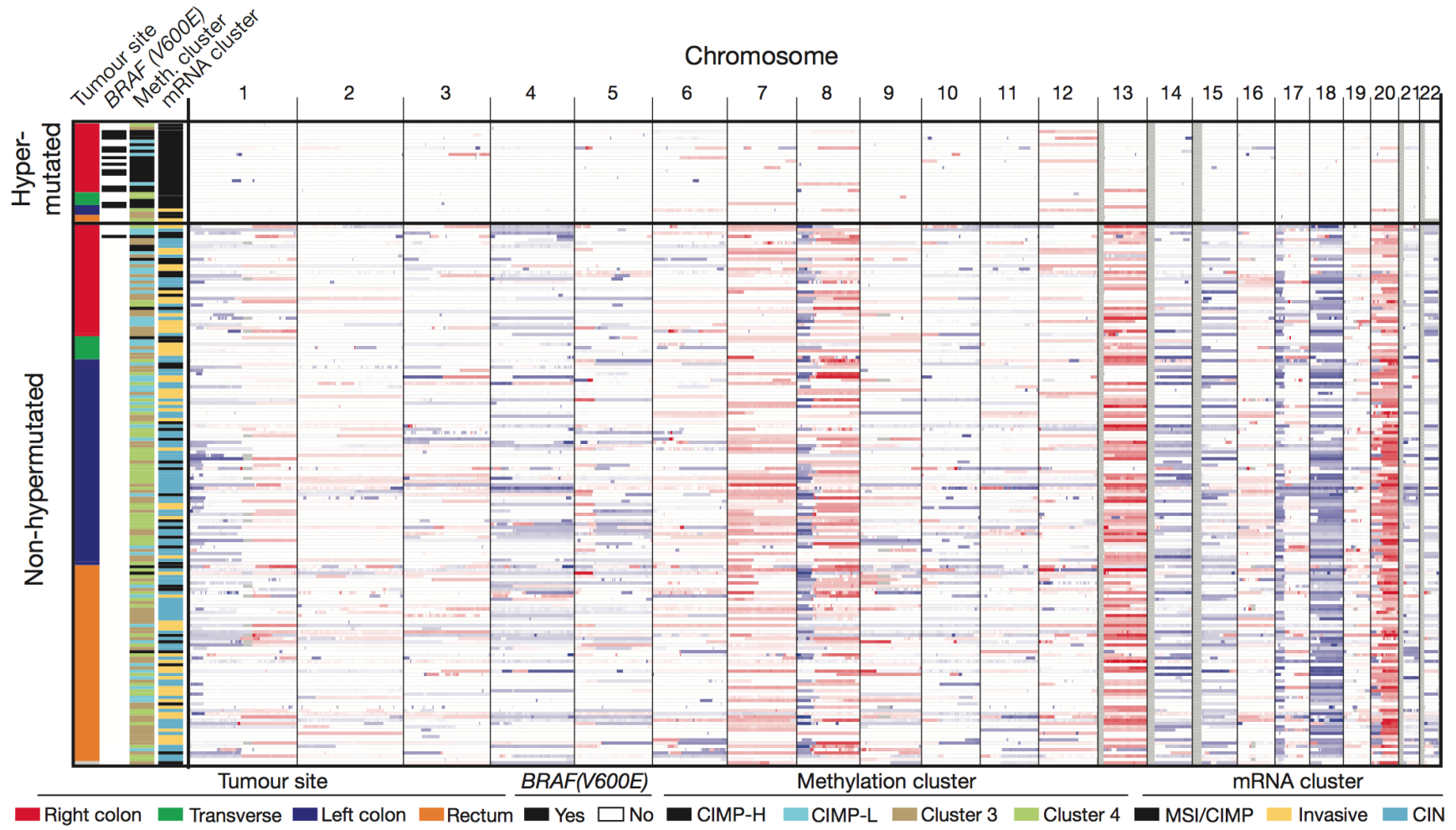
Mutations



Copy number variation



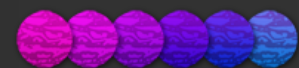
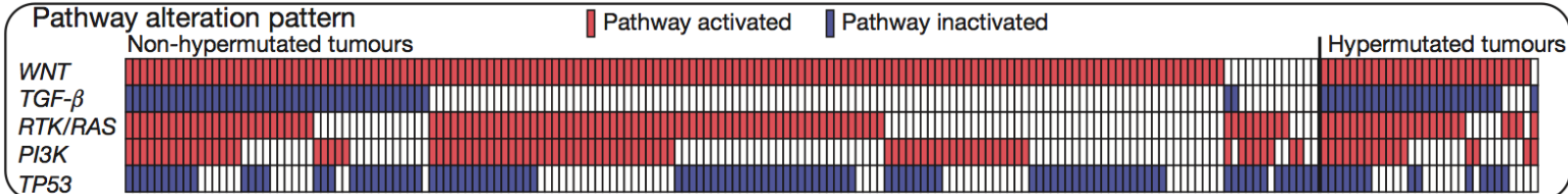
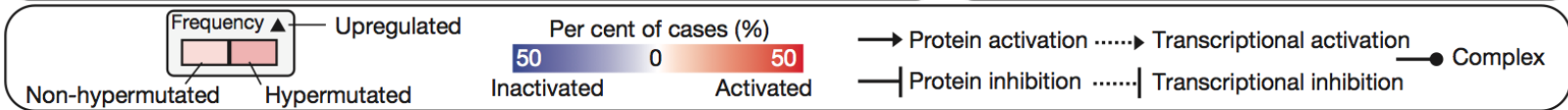
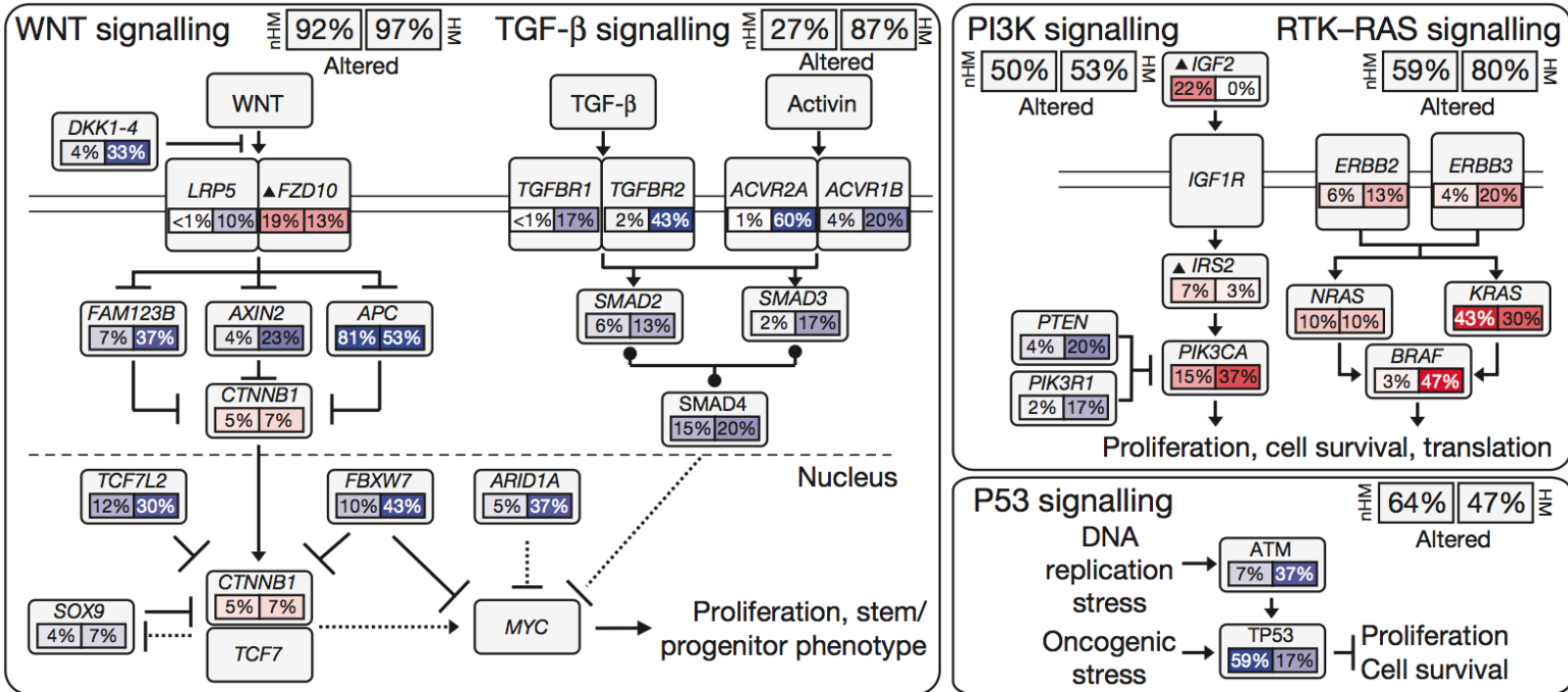
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Pathways in CRC



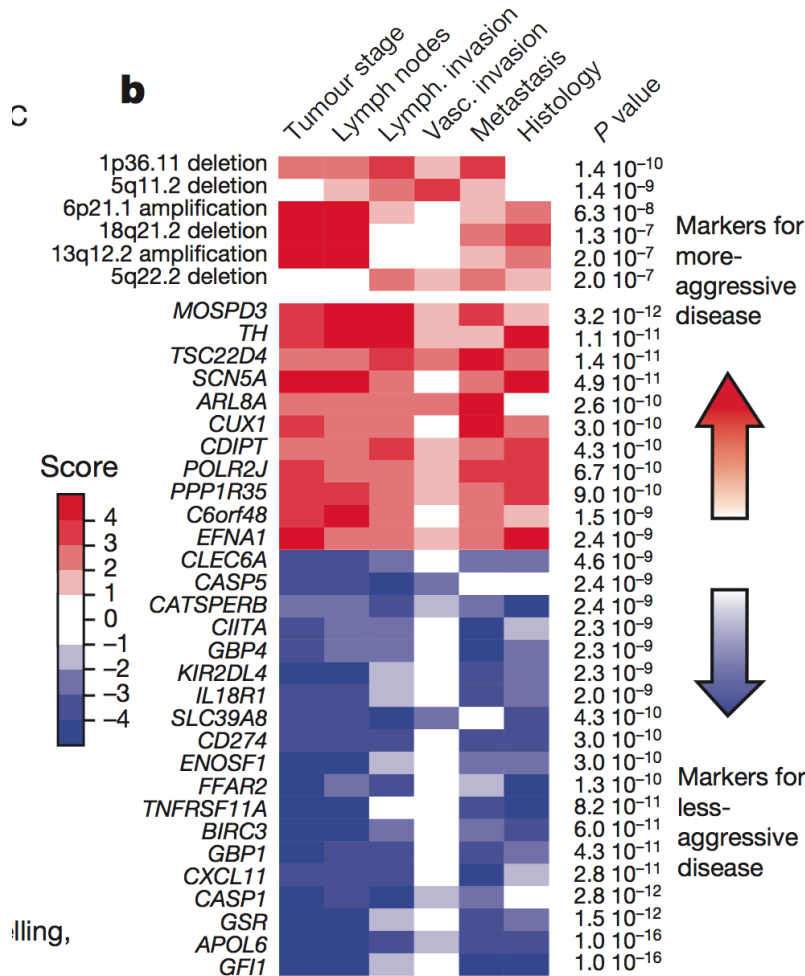
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Association with aggressive biology

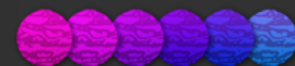


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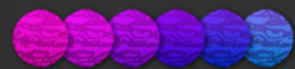


FBXW7 and metastasis never occurred
 20q13.12 HNF4A
 22q 12.13

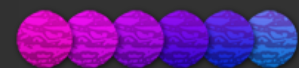
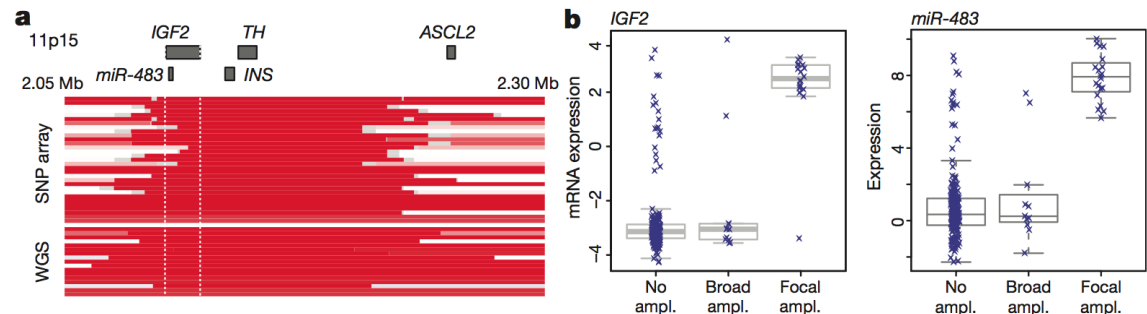
17q21.1 7 genes including ERBB2



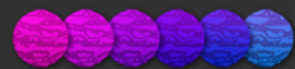
- Inactivated in 93%
 - Biallelic inactivation of APC
 - Activation of CTNNB1
 - Mutations SOX9
 - Mutations and deletions in TCF7L2, AXIN, FBXw7, ARIDIA, FAM123B
 - FXD10 overexpressed
 - NAV2-TCF7L1 fusions



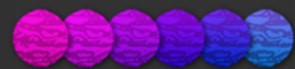
- Alterations in RAS-MAPK
 - KRAS, NRAS or BRAF (55%)
- Alterations in PI3K
 - IGF2 and IRS2 overexpression
 - PIK3R1 (2%) and PIK3CA(15%) mutations
 - Deletions in PTEN (4%)
 - Inversely associated with IGF2 amplification (7%) and overexpression (15%) and miR-483



- TGF β pathway
 - TGFBR1, TGFBR2, ACVR2A, ACVR1B, SMAD2, SMAD3 and SMAD4
 - 27% non hyper mutated vs 87% hyper mutated
- P53 pathway
 - TP53 (59%) and ATM (7%) inverse
- MYC pathway always abnormal



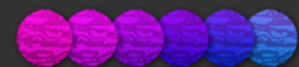
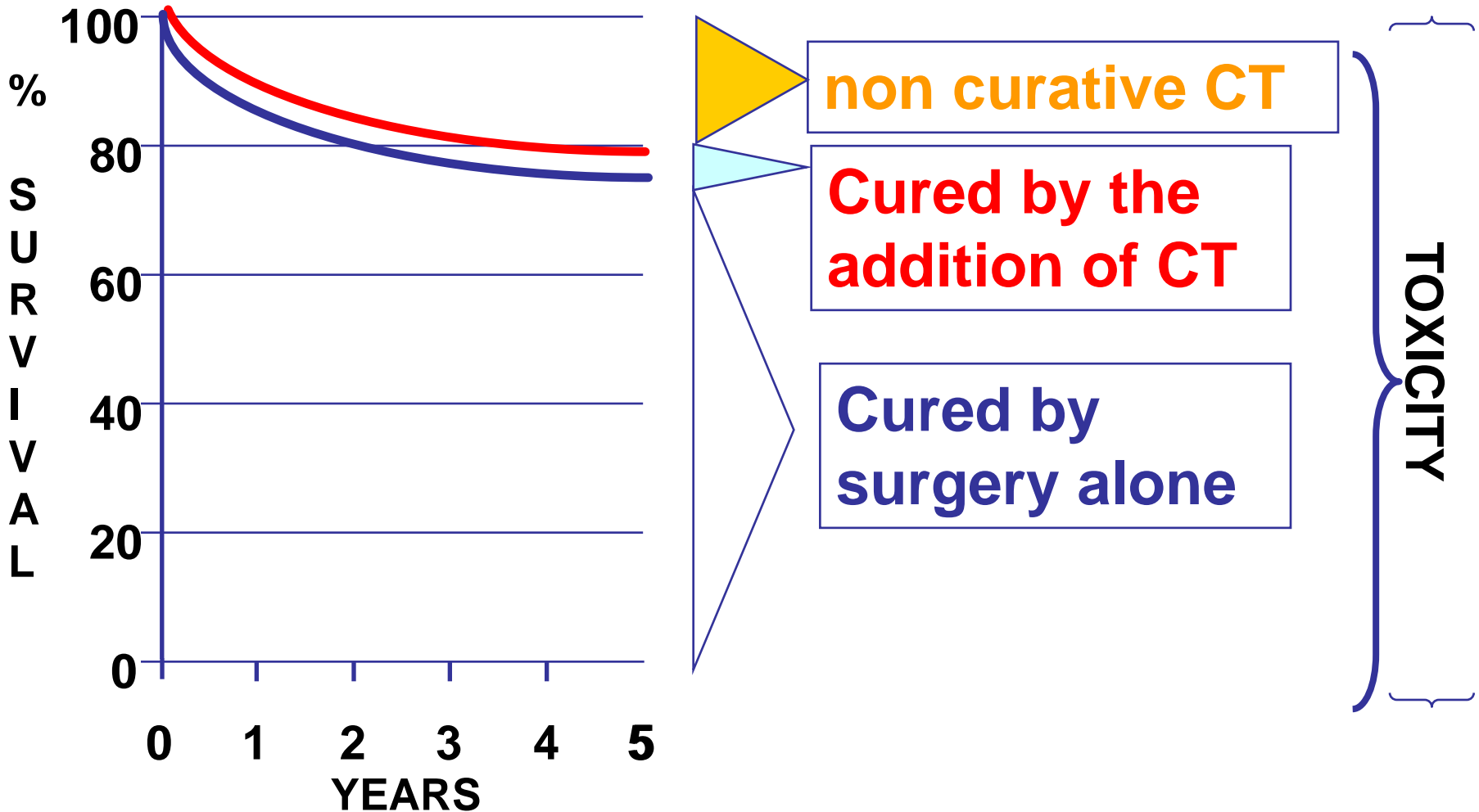
- Chemotherapy has limited effect in stage II
- Multiple factors affect risk of recurrence
- Decisions based upon individual risk rather than stage II
- Quality of pathology can help stratify prognosis
- Deficient Mismatch repair is prognostic and not predictive
- No predictive factors for therapy
- RNA tests uncertain value, costly and beware the marketing
- Value of *in vivo* chemosensitivity



Value of adjuvant chemotherapy in stage II bowel cancer



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Value of adjuvant chemotherapy in stage III bowel cancer



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