Poster Discussion: Colorectal Cancer Posters 522-524

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Disclosure slide

- Honorarium
  - Merck Serono
  - Roche
  - Amgen Hellas
- Research Grand
  - Merck Serono
  - Amgen

Outline of the presentation

- Stage II and III colon cancer
- Molecular predictors
- DNA repair
- Critical Evaluation of posters 522-524
- Summary and conclusions

Adjuvant Chemotherapy for stage III Colon Cancer

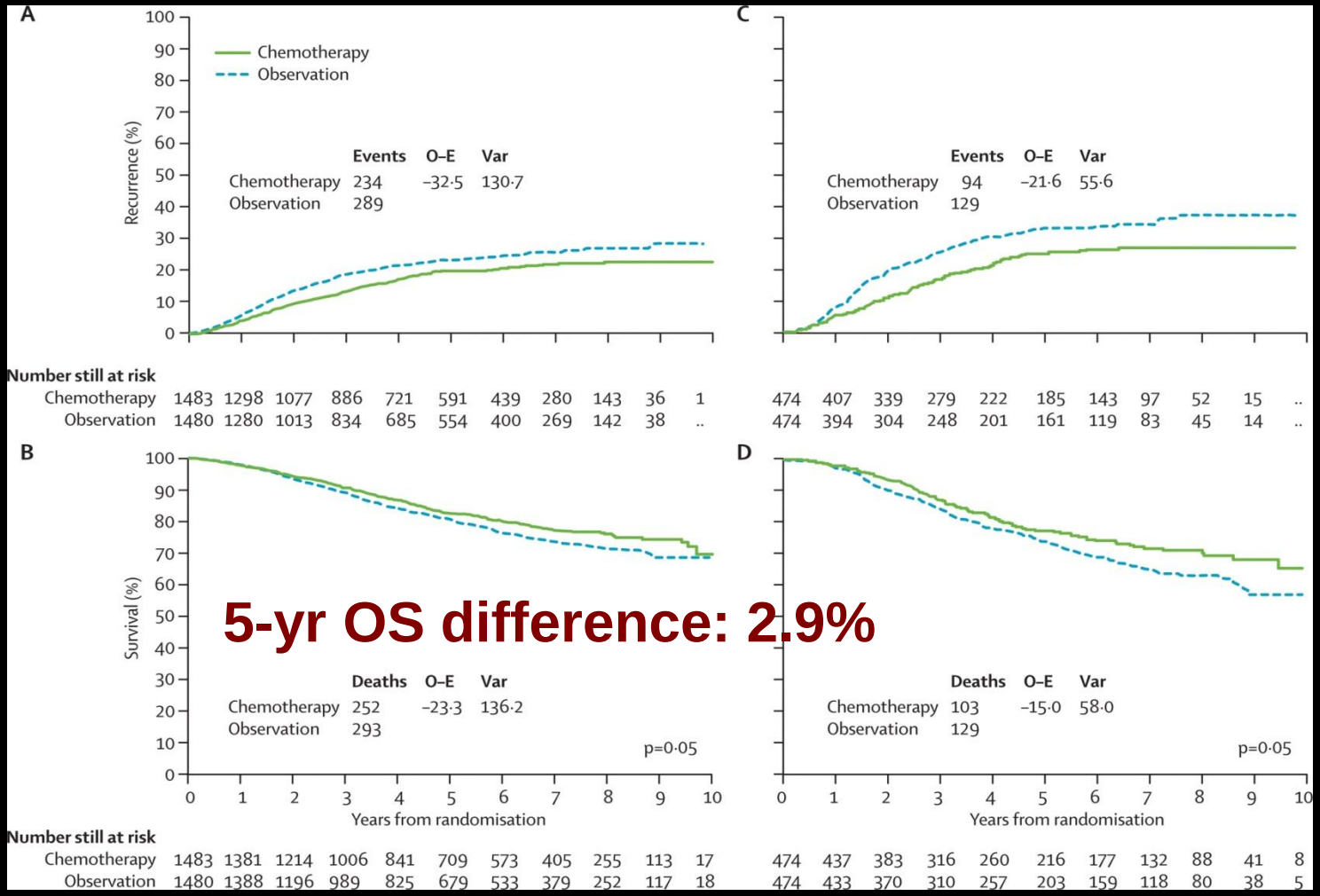
- 3 RCTs proved benefit for the addition of LOHP to 5FU/LV in 3 years DFS
  - MOSAIC HR: 0.77
  - NSABP C07 HR: 0.80
  - NO16986 HR: 0.80
- Selection should be based on individual characteristics and patient's preference

Adjuvant Chemotherapy for stage II Colon Cancer

- For stage II colon cancer the role of chemotherapy is still debated
- The proportional risk reduction is similar in Stages II and III[1]
- The benefit obtained by FU-based chemo may be attributed to subsets of patients:
  - Females
  - right-sided colon tumors

[1]Grill S et al *J Clin Oncol*; 2004
[2]Elsaleh H et al *Lancet*; 2000

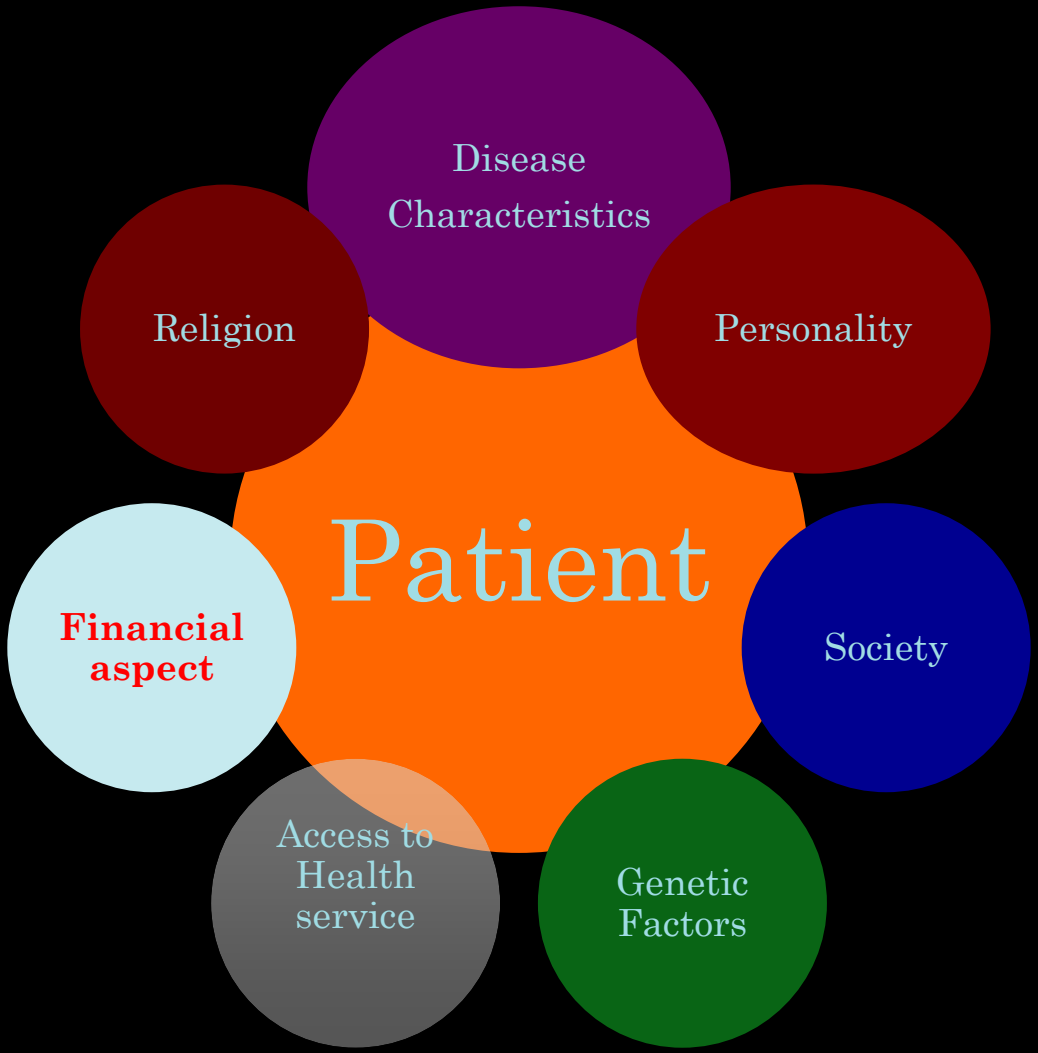
QUASAR RESULTS



Relative risk = 0.83 (95% CI, 0.71-0.97) *p* = .02

QUASAR collaborative group *Lancet* 2007; 370: 2002

Adjuvant treatment in stage II colon cancer



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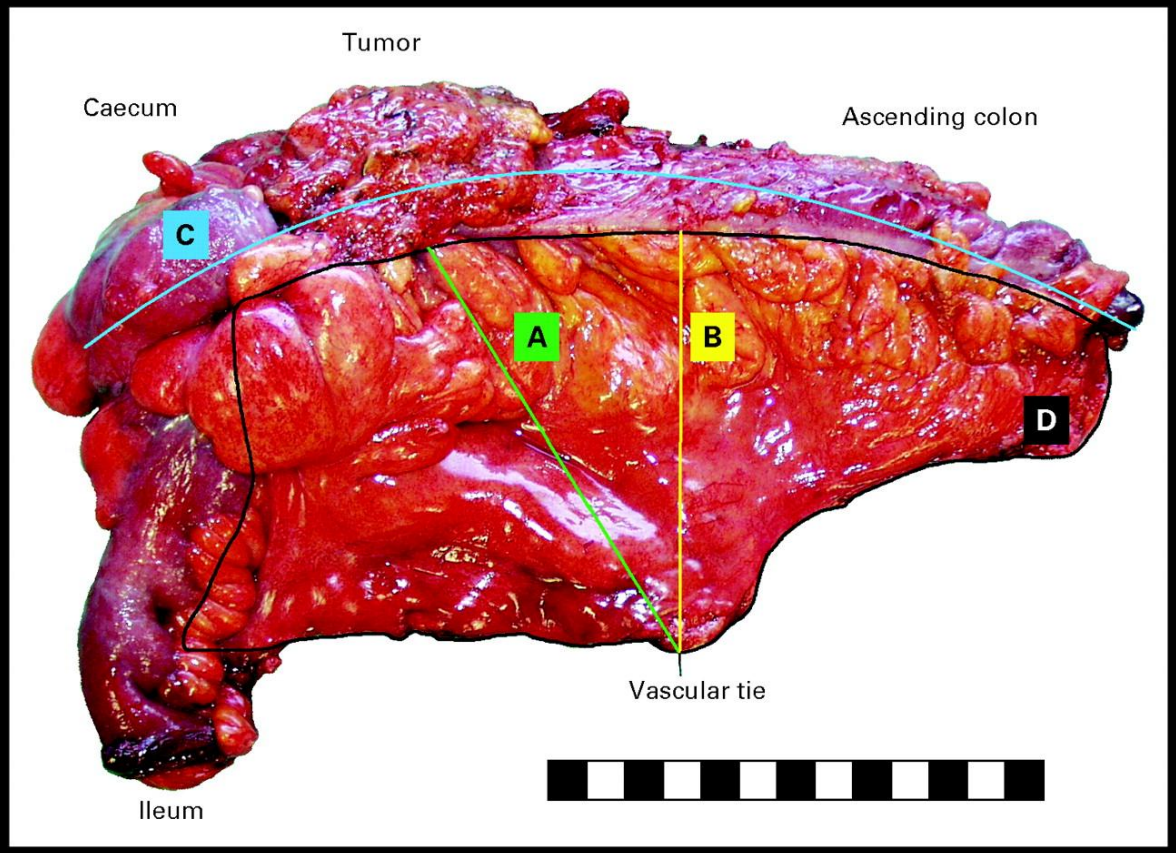
Prognostic factors early CRC

Established	Potential
T4	
Obstruction/Perforation	tumour budding
Rupture during surgery	tumour type
< 12 lymph nodes retrieved and ratio	low volume/ less experience
V1, L1, PN1	
Poor differentiation (G 3/4)	
MSI status	

None of these factors have been validated or tested prospectively

ESMO guidelines *Ann Oncol* 2012

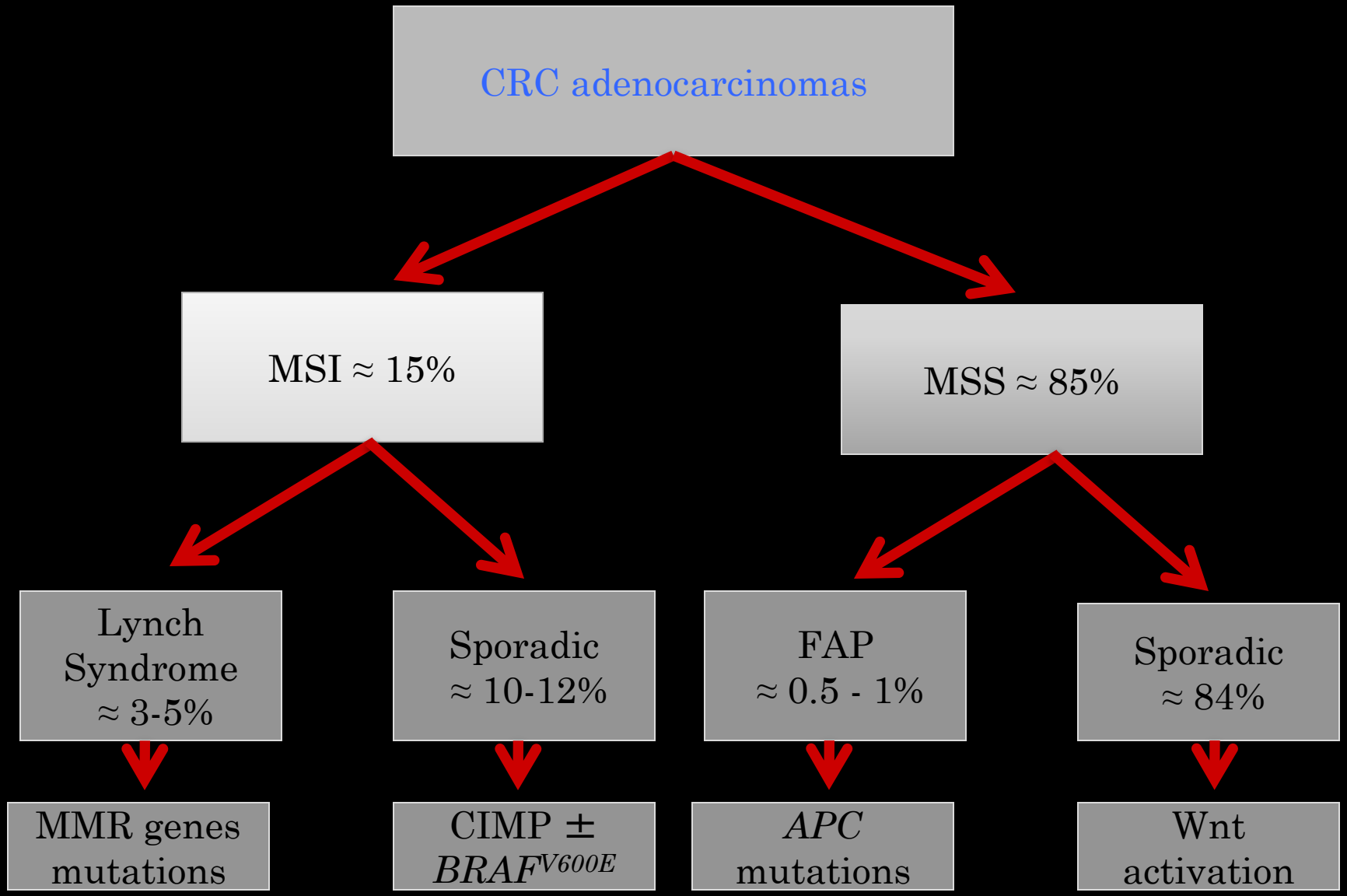
Adjuvant chemotherapy can not rescue patients from inadequate surgery



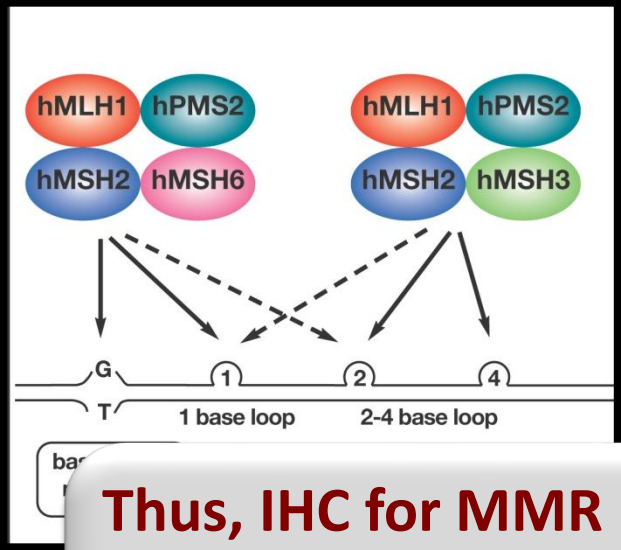
CME produced a 5-year survival rate > 89% in stage II-III

West, N. P. et al. J Clin Oncol; 28:272-278 2010

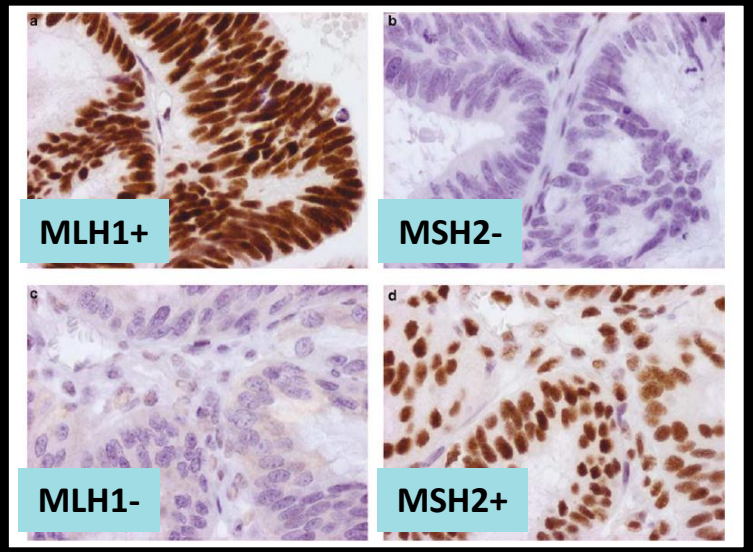
“Cancers” of the Colon

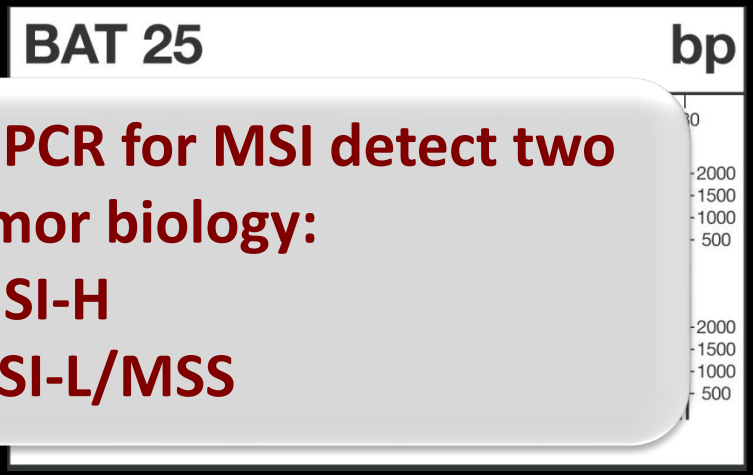


Mismatch Repair Deficiency (MMR-D):



IHC for MMR protein status





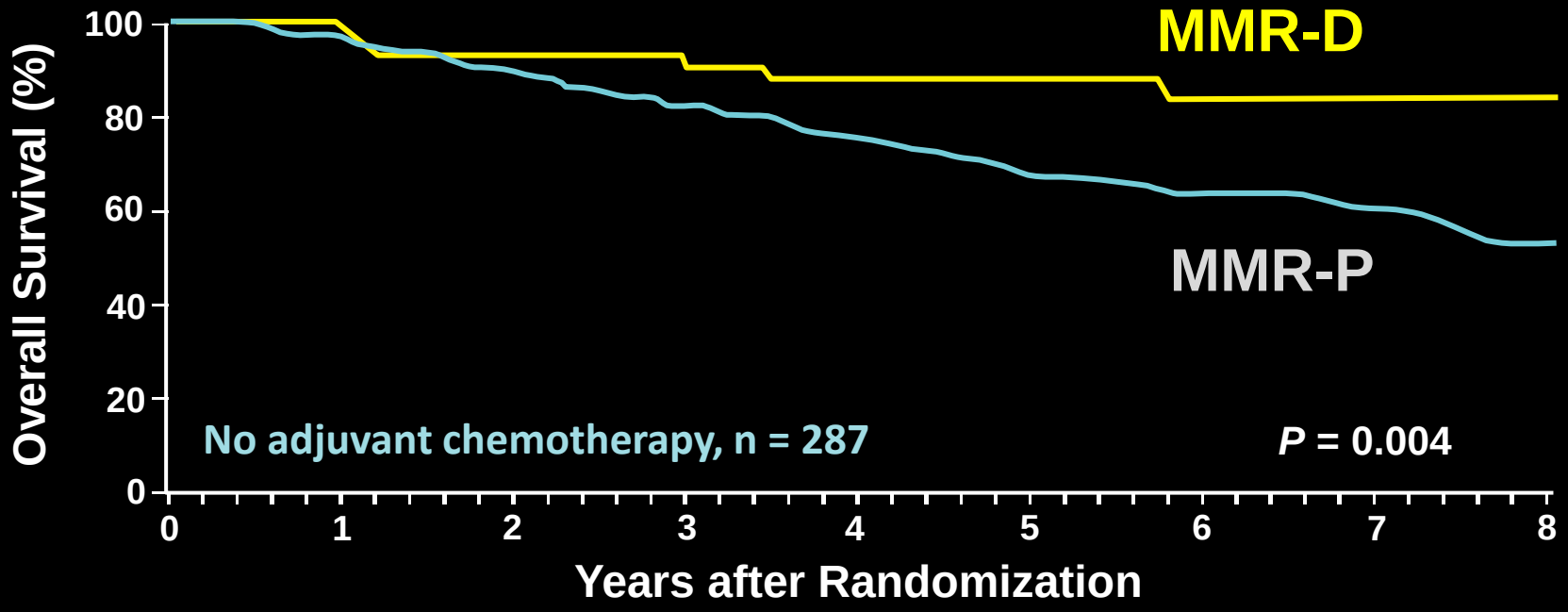
Thus, IHC for MMR proteins and PCR for MSI detect two manifestations of the same tumor biology:

- **MMR-D is synonymous with MSI-H**
- **MMR-P is synonymous with MSI-L/MSS**

Imai K, et al. *Carcinogenesis*. 2008;29:673-680.
Umetani N, et al. *Ann Surg Oncol*. 2000;7:276-280.
Rosen DG, et al. *Mod Pathol*. 2006;19:1414-1420.

MMR-D and Risk of Recurrence

Pooled Analysis of Stage II and III colon cancer patients (surgery alone)



Multiple studies have consistently demonstrated that the ~15% of colon cancer patients with MMR-D tumors have markedly lower recurrence risk, particularly for stage II colon cancer patient.

Ribic CM, et al. *N Engl J Med*. 2003;349:247-257.

Recommendations for MSI testing

ESMO guidelines Ann Oncol 2012

MSI-H/dMMR patients have a proven better prognosis in stage II and III than low frequency MSI (MSI-L) or microsatellite stable (MSS) patients

At this moment determination of any prognostic factor for therapeutic decisions is not recommended (except for MSI status for early stage colon cancer) [II, B].

Whole Genome Array

Training Set (stage I-IV) (n=188) [1]
Netherlands Cancer Institute, Leiden Medical Center, Slotervaart

Selection of Final 18-Gene Set & Algorithm

Development

Standardization of Analytical Methods

In-silico Validation Study (stage I-III)
public datasets (n=322)

Clinical Validation Study 1 (stage I-III)
Institute Catala d'Oncologia Barcelona *(J Clin Oncol. 2011;29:17-24)*

Clinical Validation Study 2 (stage II)
Munich Hospital Rechts der Isar *(J Clin Oncol 28:15s (abstract 3513)*

Clinical Validation Study 3 (stage II)
Vall d'Hebron, MedUni Vienna, University of Ferrara

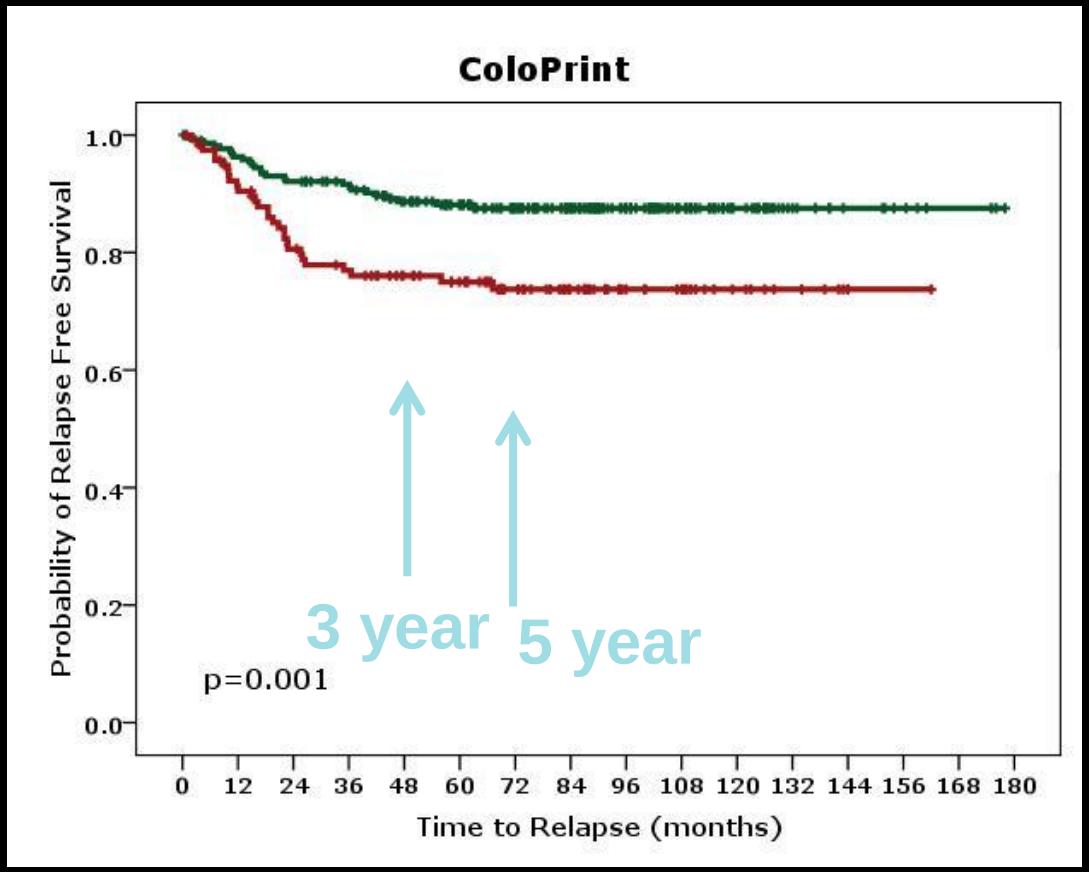
Pooled analysis

Clinical Validation Study 4 (stage II-III)
MD Anderson *(ongoing)*

PARSC Prospective Study (stage II + III) - *ongoing*
US, Asian, and European Center (N ~600 stage II)

Validation of ColoPrint

Local, Regional and Distant Relapse in stage II and IIIA patients

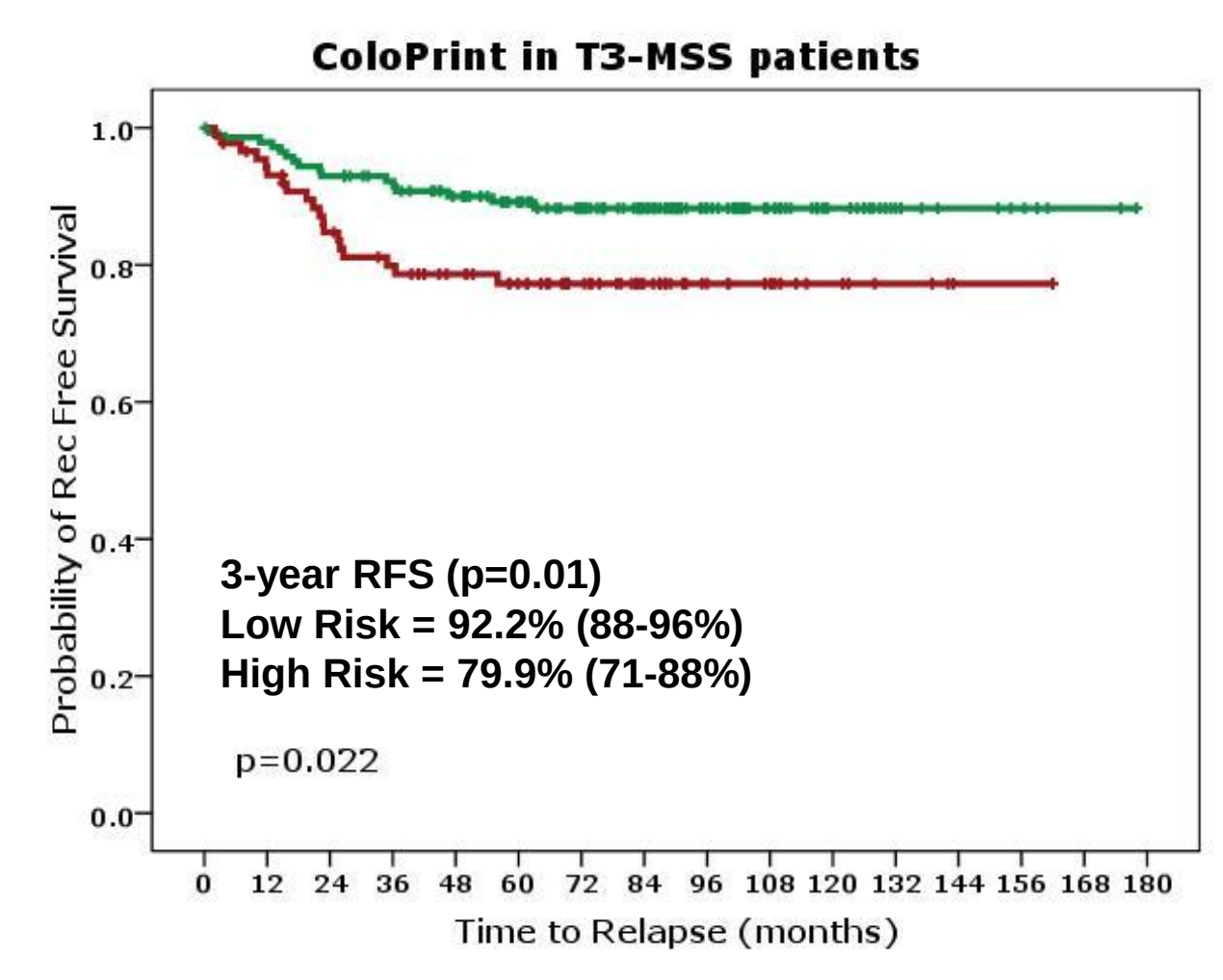


3-year RFS
Low Risk = 92% (88-95%)
High Risk = 77% (69-85%)

5-year RFS
Low Risk = 88% (84-92%)
High Risk = 75% (67-83%)

Bachleitner-Hofmann T et al ESMO 2012: abst # 522PD

ColoPrint in patients with T3/MSS



Bachleitner-Hofmann T et al ESMO 2012: abst # 522PD

Bachleitner-Hofmann T et al: abst # 522PD

- Technically well validated assay
- Reports prognostic significance for recurrence only
- No survival data
- Adjuvant treatment not reported
- Quality of Surgery?

The 12-Gene Oncotype DX® Colon Cancer Recurrence Score®

Recurrence Score

STROMAL
FAP
INHBA
BGN

CELL CYCLE
Ki-67
C-MYC
MYBL2

GADD45B

Reference Genes

ATP5E
GPX1
PGK1
UBB
VDAC2

Recurrence Score =
– 0.15 × Stromal Group
– 0.30 × Cell Cycle Group
+ 0.15 × GADD45B

O'Connell MJ, et al. *J Clin Oncol*. 2010;28:3937-3944.
Kerr D, et al. *J Clin Oncol*. 2009;27: abstract 4000.

Development and Validation of the 12-Gene Colon Cancer Recurrence Score Assay[8-10]

Colon Cancer Technical Feasibility

Development Studies (Surgery)
NSABP C-01/C-02 (n = 270)
Cleveland Clinic (n = 765)

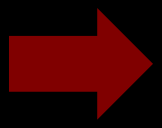
Development Studies (5FU/LV)
NSABP C-04 (n = 308)
NSABP C-06 (n = 508)

Selection of Final Gene List & Algorithm

Standardization and Validation of Analytical Methods

Clinical Validation Study – Stage II Colon Cancer
QUASAR (N = 1436)

Confirmation Study – Stage II Colon Cancer
CALGB 9581 (N = 690)



Clinical Validation Study – Stage II/III Colon Cancer
5FU vs 5FU+Oxaliplatin
NSABP C-07 (N = 892)

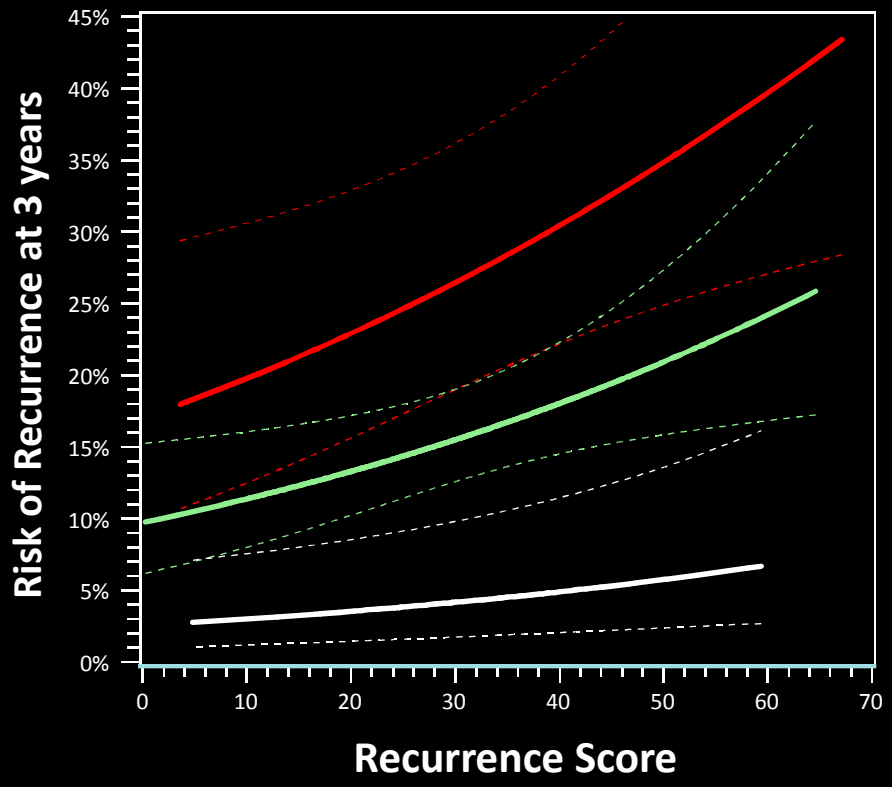
QUASAR Validation Study

- Significant association between recurrence score and risk of recurrence at 3 yrs following surgery in pts receiving surgery alone
  (n = 711; *P* = .004)
  - Comparison of recurrence risk in high vs low recurrence score risk groups also significant (HR: 1.47; *P* = .046)
  - Prespecified clinical and pathologic covariates also significant in multivariate analysis in pts receiving surgery alone (n = 605)

Clinical or Pathologic Variable	HR (95% CI)	*P* Value
MMR (deficient vs proficient)	0.32 (0.15-0.69)	< .001
Tumor stage (T4 vs T3)	1.83 (1.23-2.75)	.005
Tumor grade (high vs low)	0.62 (0.40-0.96)	.026
Number of nodes examined (< vs ≥ 12)	1.47 (1.01-2.14)	.040
LVI (present vs absent)	1.40 (0.88-2.23)	.175
Recurrence score (continuous, per 25 units)	1.61 (1.13-2.29)	.008

Kerr D, et al. ASCO 2009. Abstract 4000.

QUASAR Results: Recurrence Score, T Stage, andMMR Deficiency



T4 and MMR proficient (13%)

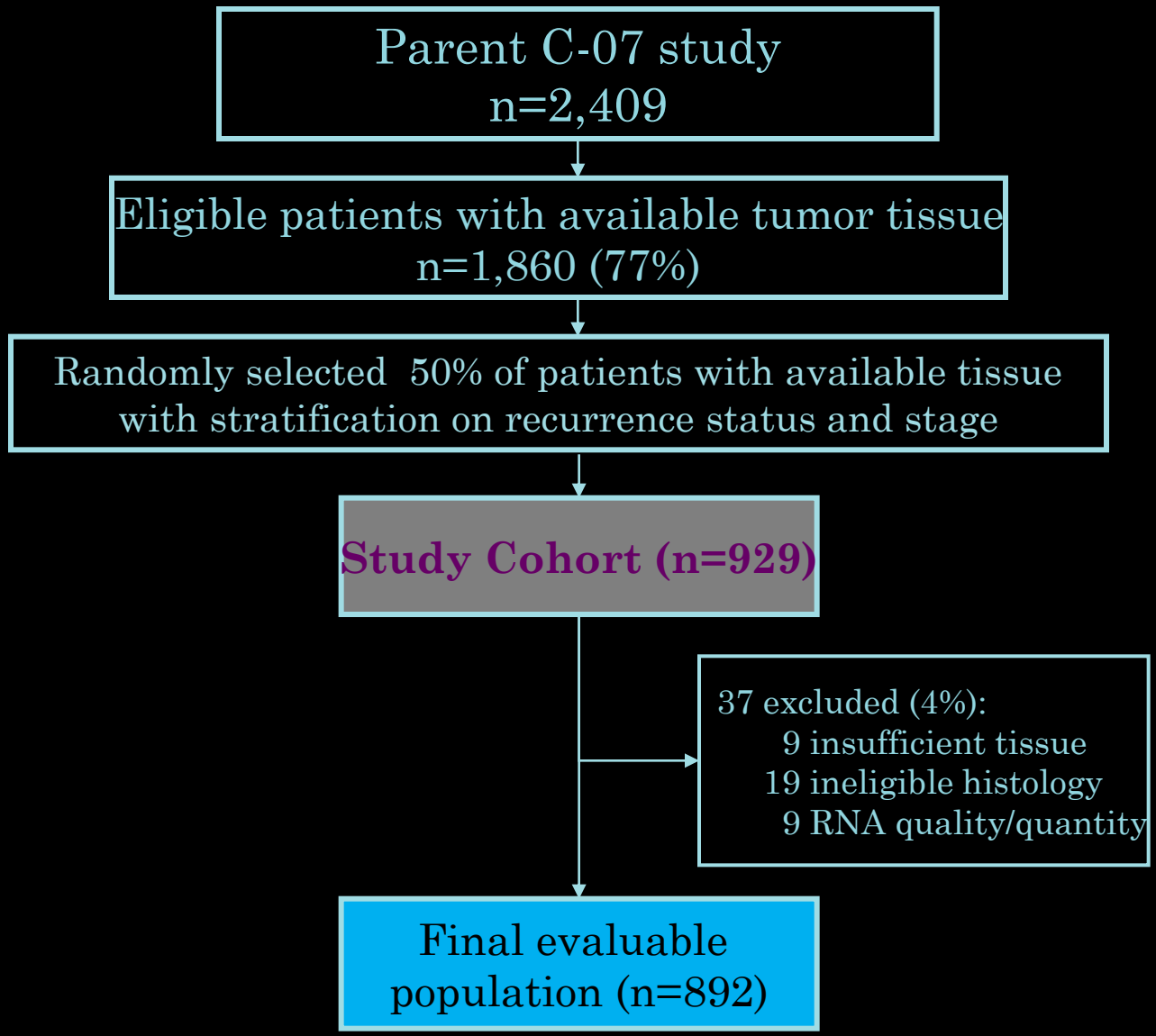
T3 and MMR proficient (74%)

T3 and MMR deficient (11%)

Rare patients (2% of all patients) with T4, MMR-D tumors had estimated recurrence risks that approximated (with large confidence intervals) those for patients with T3 stage, MMR-P tumors and were not included in this figure.

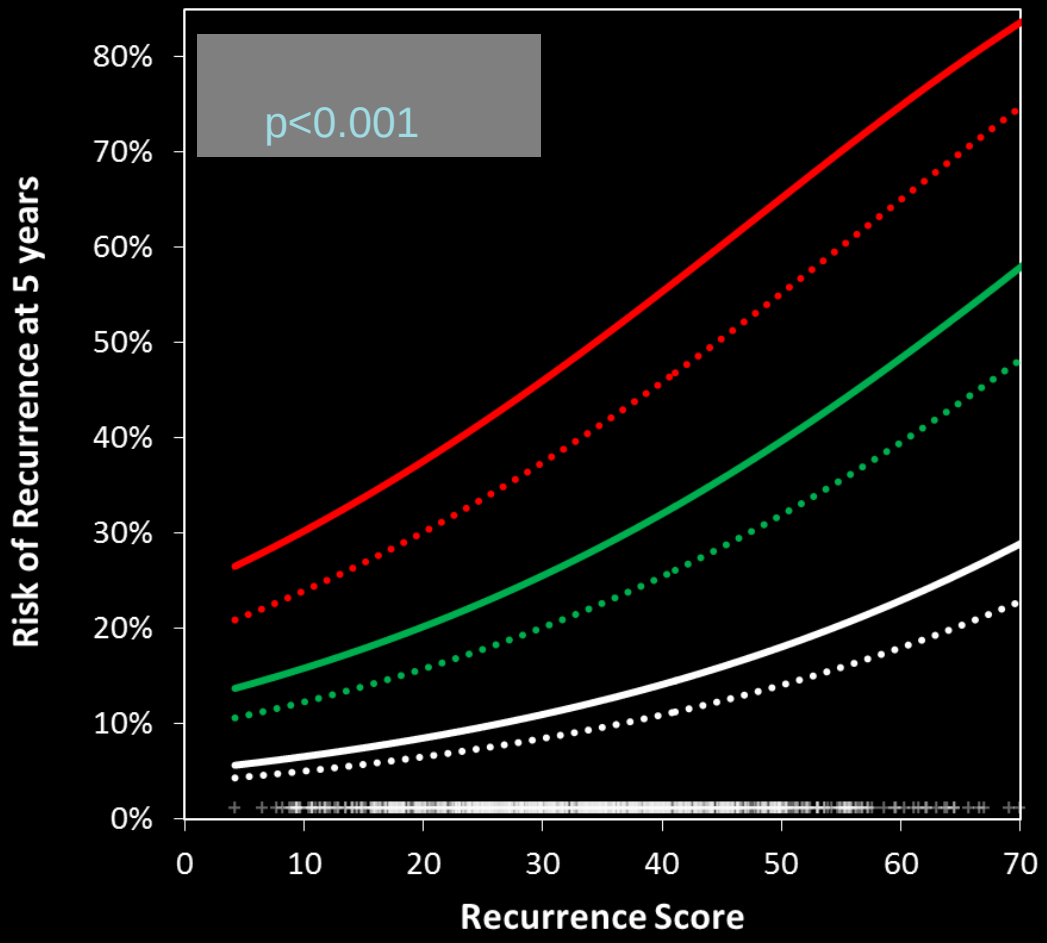
Kerr D, et al. *J Clin Oncol*. 2009;27: abstract 4000.
Gray R, et al. *J Clin Oncol*. In press.

Study Population: Validation of Recurrence Score



O'Connell MJ et al ESMO 2012: abst # 523PD

Recurrence Score in Stage II & III Colon Cancer Patients in NSABP C-07 (n=892)



Stage III C

Stage III A/B

Stage II

Solid: 5FU
Dashed: 5FU+Ox

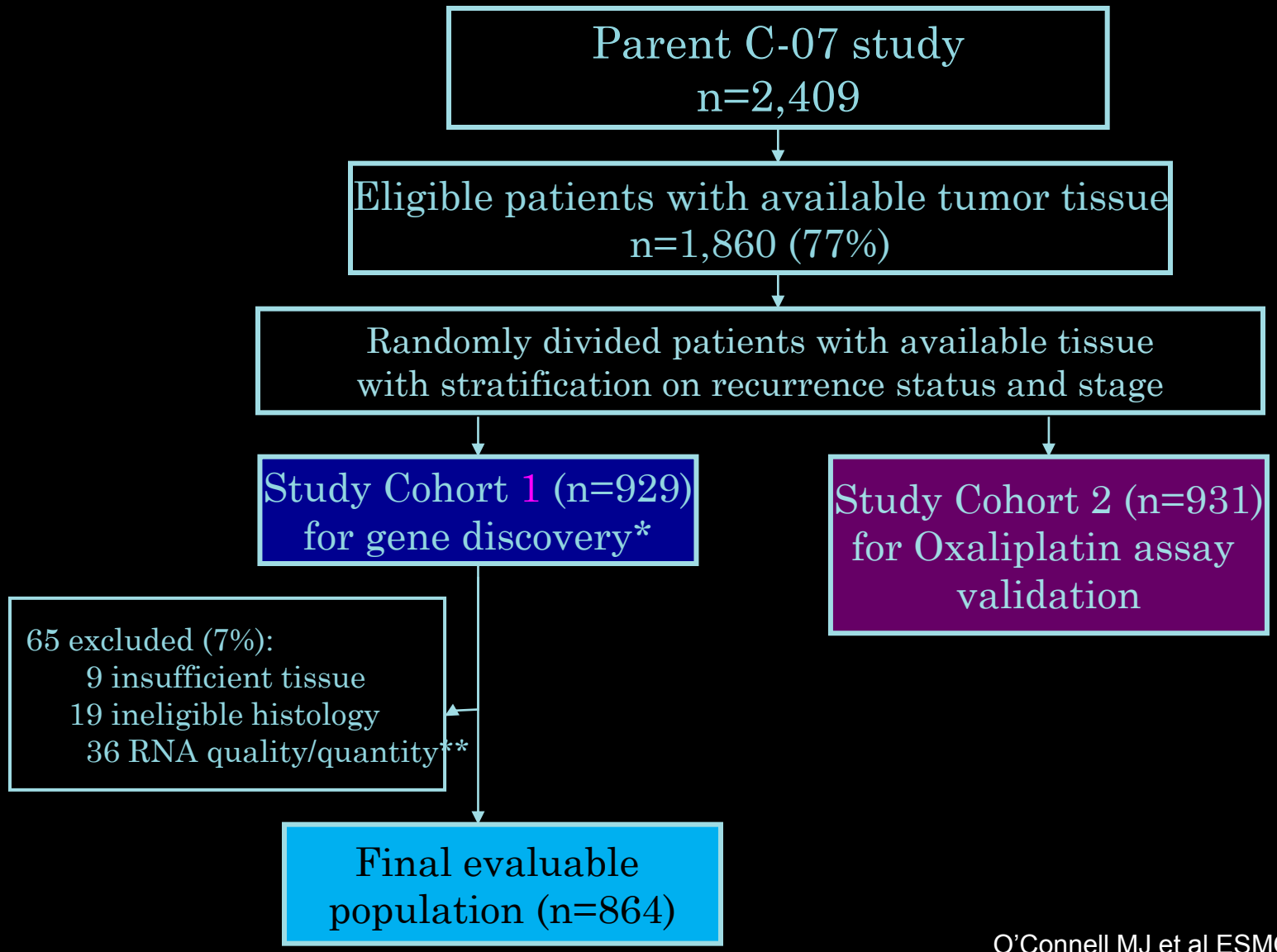
- With similar relative benefit of oxaliplatin added to adjuvant 5FU across the range of Recurrence Score results, absolute benefit of oxaliplatin increases with increasing Recurrence Score result, most apparently in stage II and stage IIIA/B patients

Recurrence Score Beyond Clinical and Pathologic Covariates
Pre-specified Multivariate Analysis (n=892)

Variable	Value	HR	HR 95% CI	P value
Stage (by nodal status)	 Stage III A/B vs II Stage III C vs II	 0.97 2.07	 (0.55,1.71) (1.16,3.68)	<0.001
Treatment	5FU+Ox vs 5FU	0.82	(0.64,1.06)	0.12
MMR	MMR-D vs MMR-P	0.27	(0.12,0.62)	<0.001
T-stage	T4 st II & T3-T4 st III vs T3 st II & T1-T2 st III	3.04	(1.84,5.02)	<0.001
Nodes examined	<12 vs ≥12	1.51	(1.17,1.95)	0.002
Tumor grade	High vs Low	1.36	(1.02,1.82)	0.041
RS	**per 25 units**	**1.57**	**(1.19,2.08)**	**0.001**

- The Recurrence Score value is significantly associated with risk of recurrence after controlling for effects of T and N stage, MMR status, number of nodes examined, grade and treatment.

Study Population: Discovery of Oxaliplatin Benefit Genes



O'Connell MJ et al ESMO 2012: abst # 523PD

* Same cohort as sampled for Recurrence Score validation study

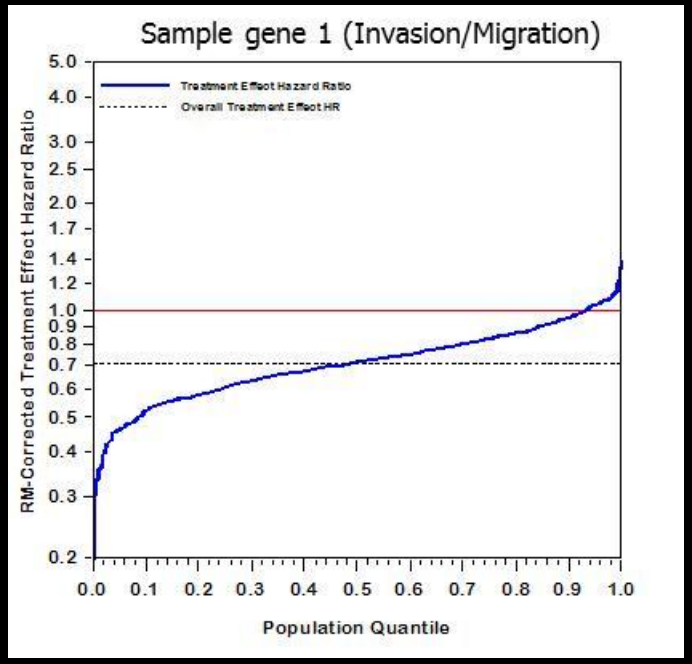
** RNA needed to assess >700 gene candidates

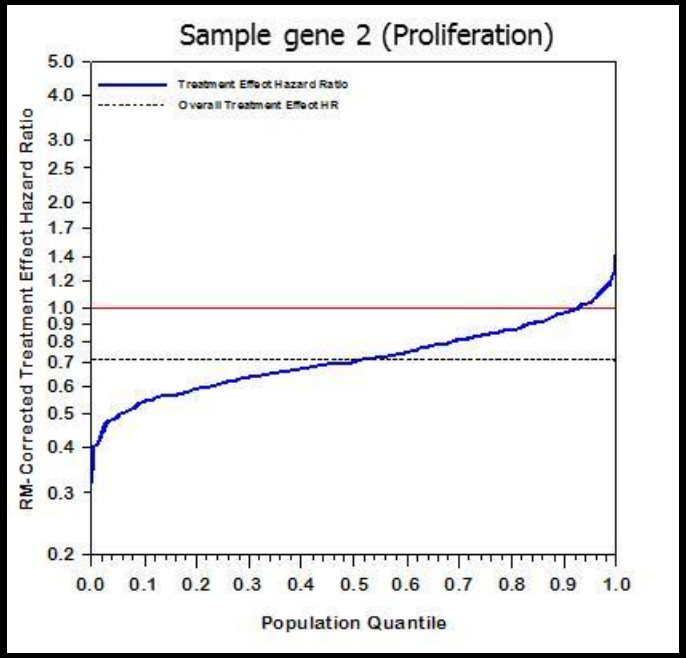
Results

- We identified 16 genes predictive of oxaliplatin benefit controlling false discovery rate at 20%
  - Consistent performance for prediction of oxaliplatin benefit across various endpoints including RFI, DFS and Colon Cancer Specific Survival
  - Multiple biological pathways are represented
    - DNA Damage Repair
    - Apoptosis
    - Cell Cycle
    - Drug Metabolism/Transporter/Resistance
  - Initial models based on multiple genes show promising improvement in performance compared to single-gene models

O'Connell MJ et al ESMO 2012: abst # 523PD

Treatment Effect Predictiveness Curves Corrected for Regression to the Mean



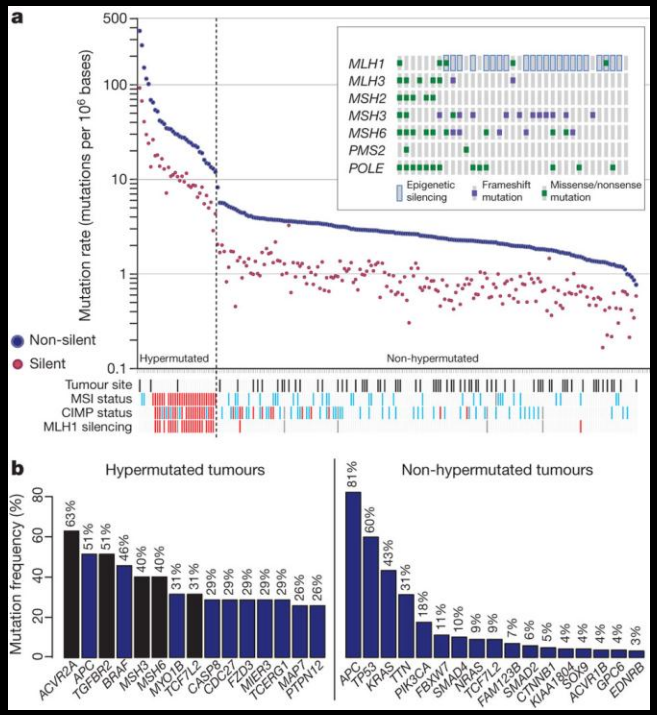


O'Connell MJ et al ESMO 2012: abst # 523PD

O'Connel MJ et al: abst # 523PD

- Technically and clinically well validated assay
- Reports prognostic significance for recurrence only
- Clinically important information only in MMR-D T3 tumors
- No survival data
- The predictive assay for Oxaliplatin is promising
- Quality of Surgery?

Complexity of genetic alterations in human CRC



The Cancer Genome Atlas Network *Nature* **487**, 330-337 (2012) doi:10.1038/nature11252

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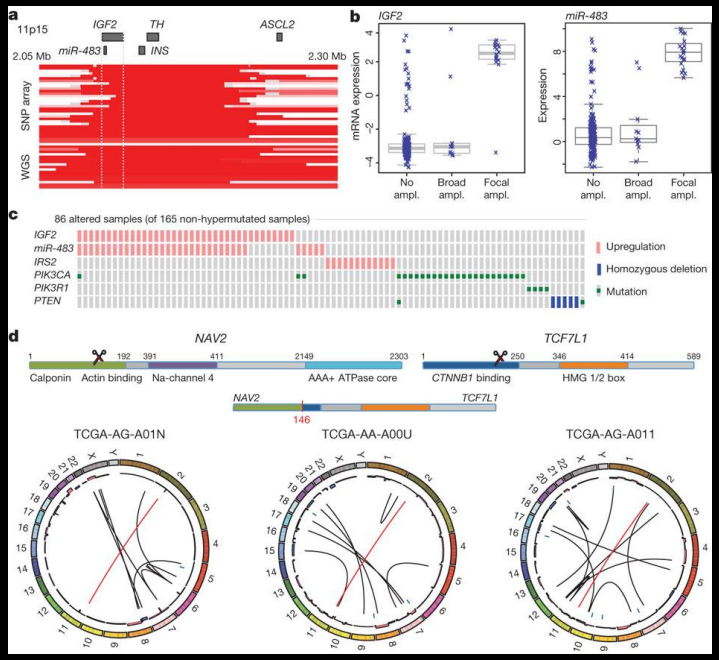
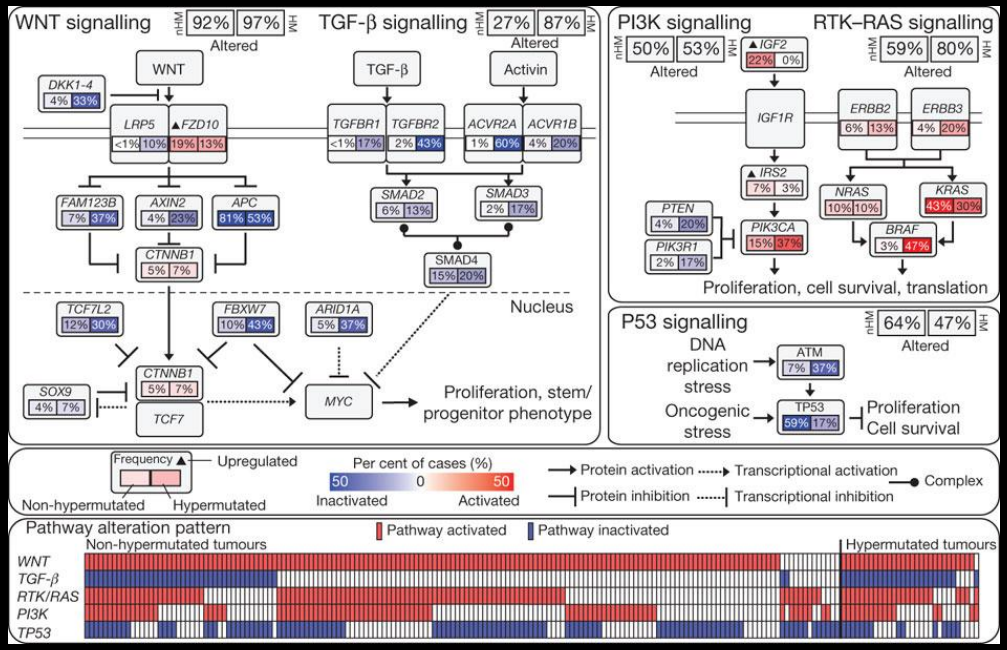
Copy-number changes and structural aberrations in CRC



The Cancer Genome Atlas Network *Nature* **487**, 330-337 (2012) doi:10.1038/nature11252

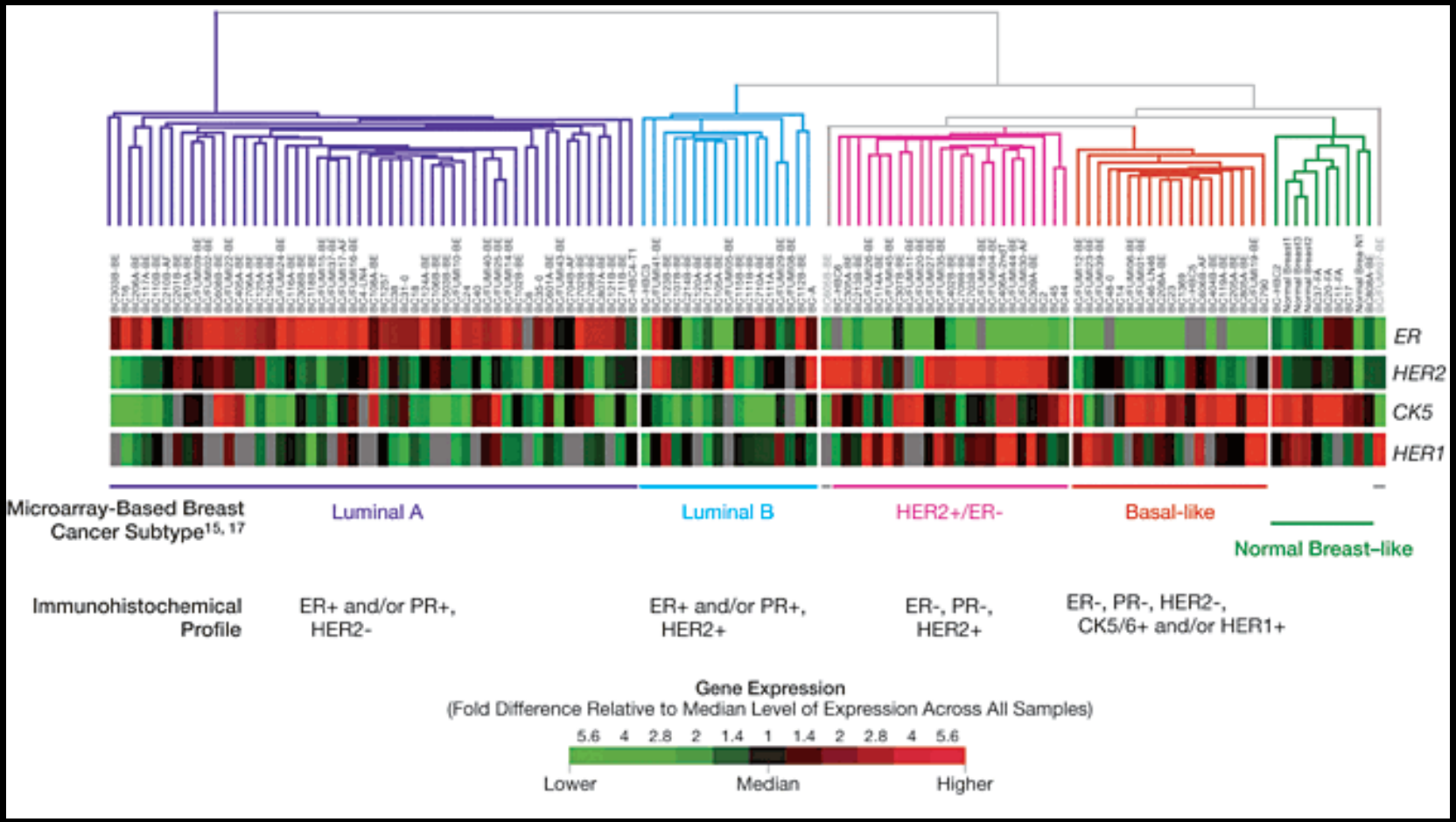
Diversity and frequency of genetic changes leading to deregulation of signalling pathways in CRC



The Cancer Genome Atlas Network *Nature* **487**, 330-337 (2012) doi:10.1038/nature11252

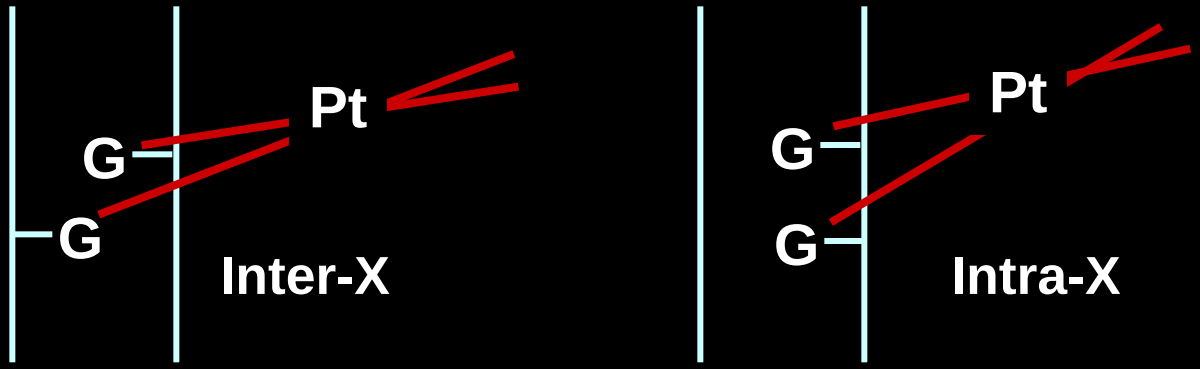
Selection of therapeutic strategy

upon tumor biology and clinical factors



Resistance to Platinum analogs: multifactorial

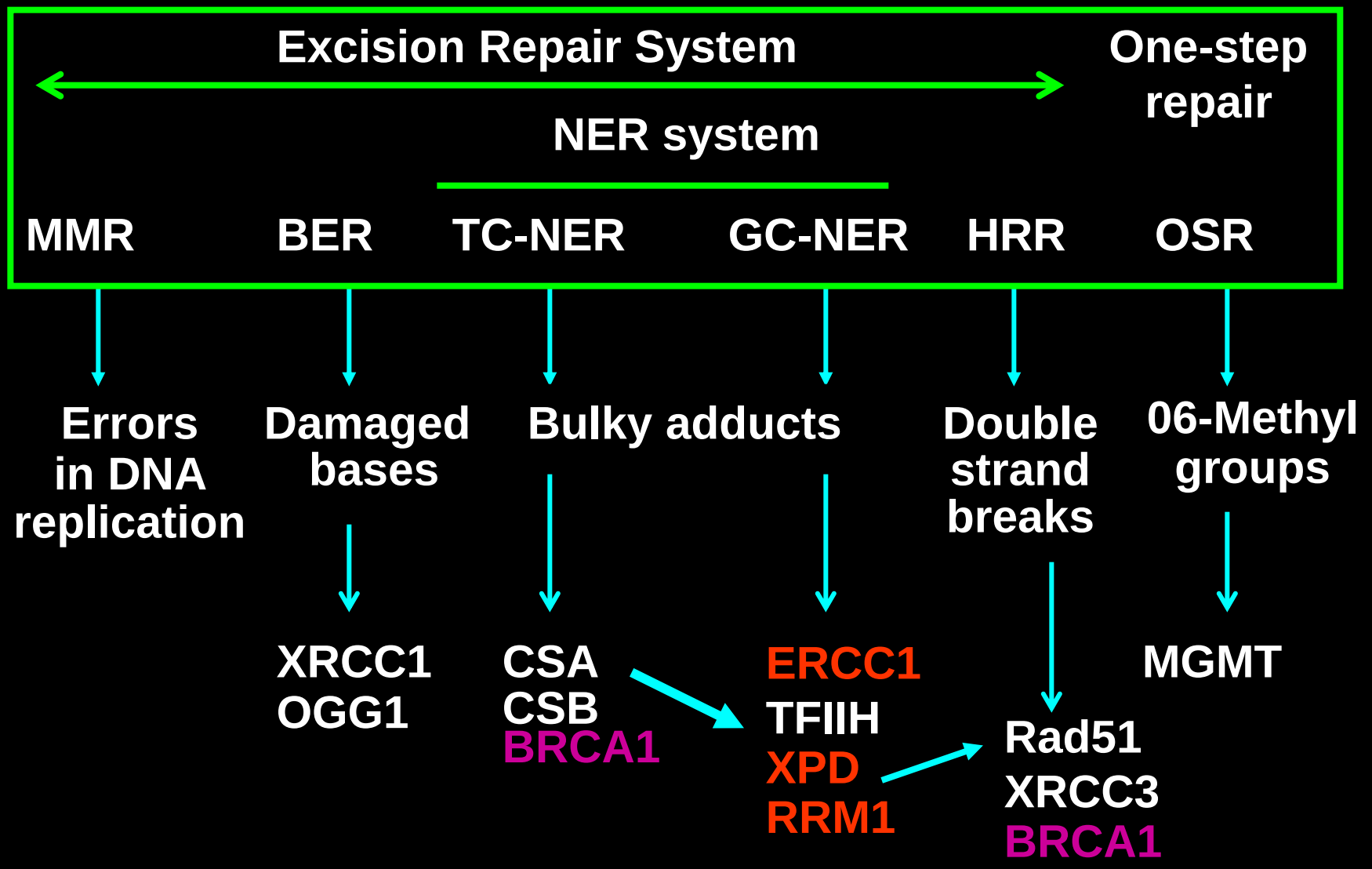
N7 position of purine bases



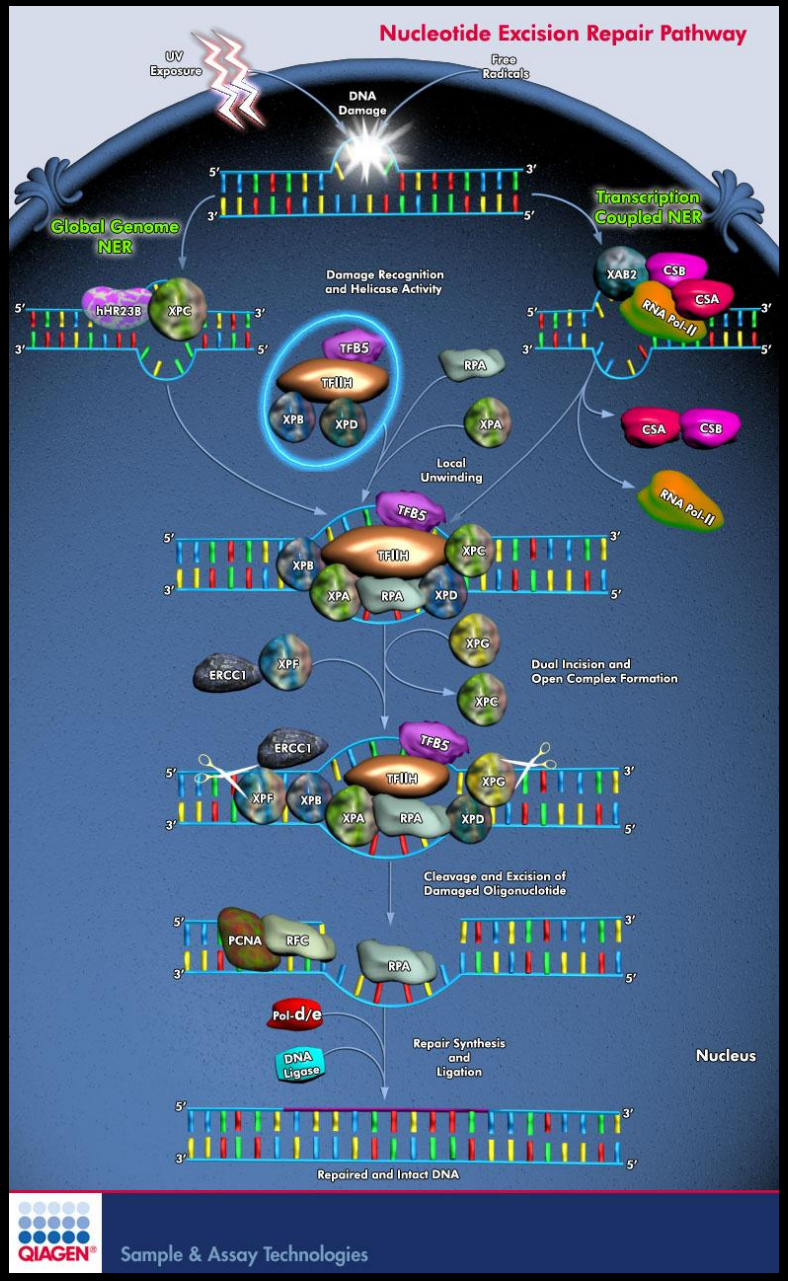
These agents react with DNA leading to the formation of inter- and intrastrand X-links that are the critical cytotoxic lesions.

- Reduced cisplatin uptake and decreased drug accumulation
- Elevated levels of metallothionines and glutathione
- Enhanced tolerance of platinum damage in DNA
- Altered expression of regulatory genes
- Increased levels of DNA repair activity to remove CDDP adducts

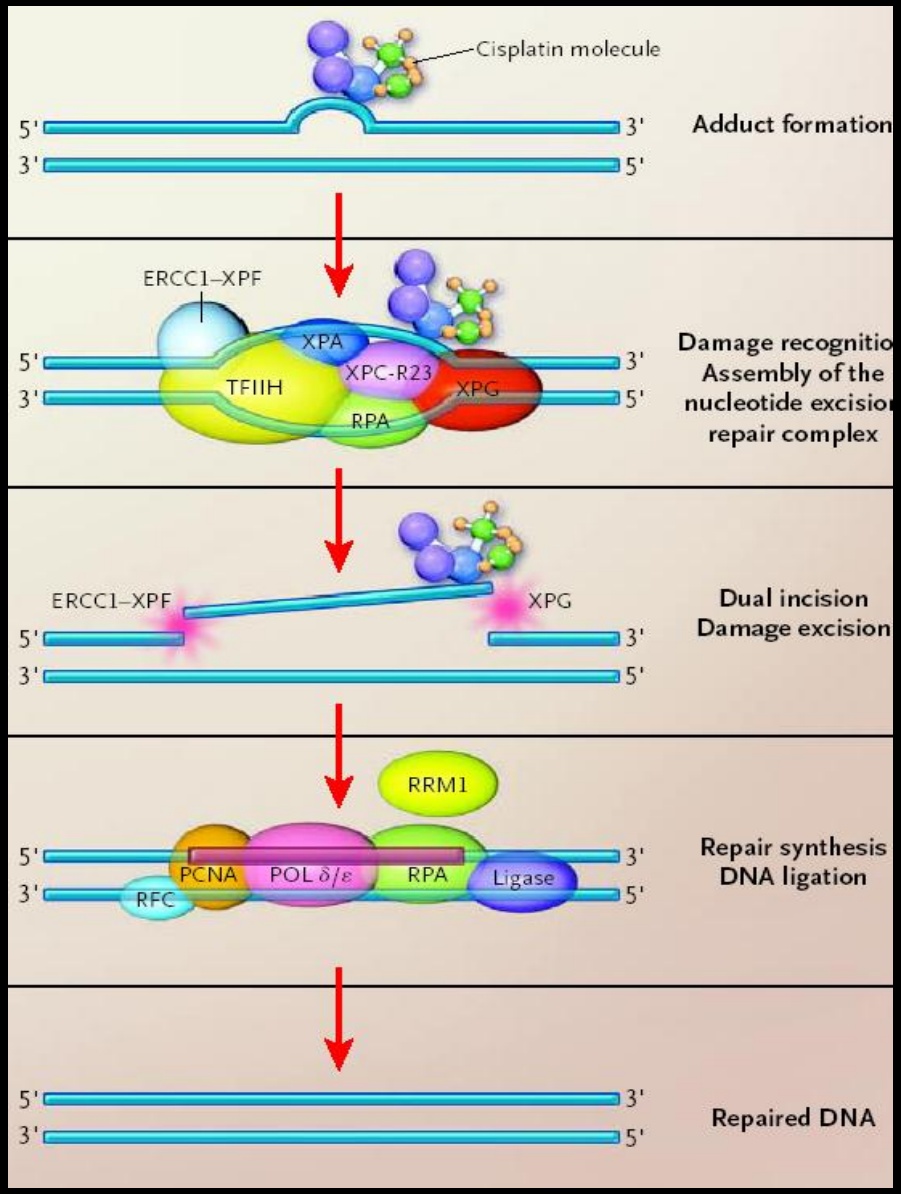
DNA Repair Systems



Rosell et al. Sem Oncol 2003


Nucleotide Excision Repair Pathway
UV Exposure
Free Radicals
DNA Damage
Global Genome NER
Transcription Coupled NER
Damage Recognition and Helicase Activity
hHR23B
XPC
TFB5
TFIIH
XPB
XPD
RPA
XPA
XAB2
CSB
CSA
RNA Pol-II
Local Unwinding
ERCC1
XPF
XPG
Dual Incision and Open Complex Formation
Cleavage and Excision of Damaged Oligonucleotide
PCNA
RFC
Pol-d/e
DNA Ligase
Repair Synthesis and Ligation
Nucleus
Repaired and Intact DNA
QIAGEN
Sample & Assay Technologies

NER: Nucleotide Excision Repair System



ERCC1:

1) recognizes cisplatin DNA damage;
2) ERCC1/XPF, makes the 5' incision of the DNA damage.

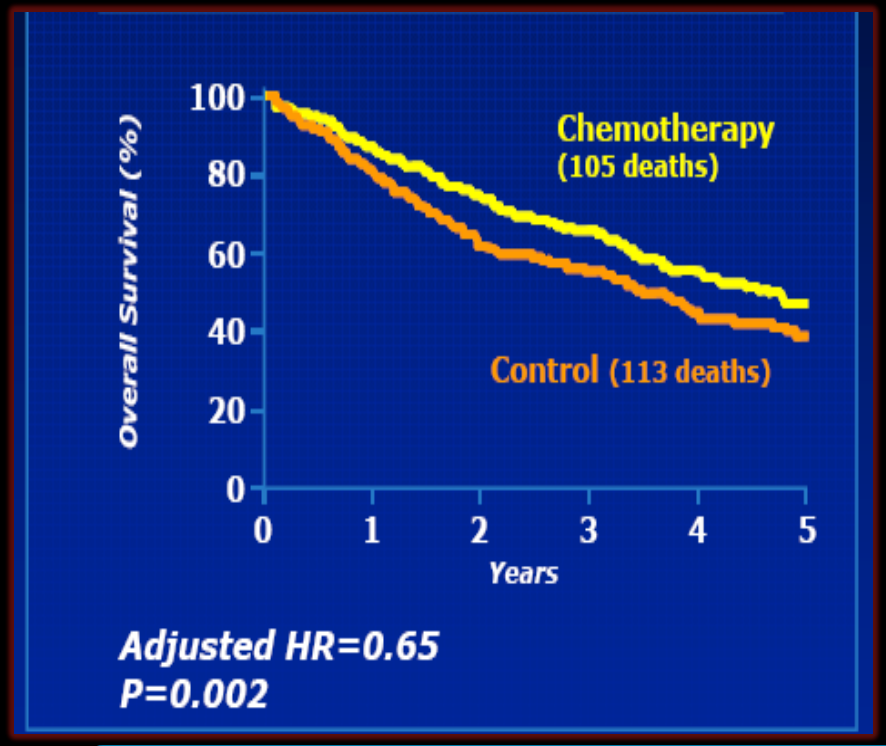
Gazdar NEJM 2007

Summary of findings for the Prognostic and Predictive value of *ERCC1* in NSCLC

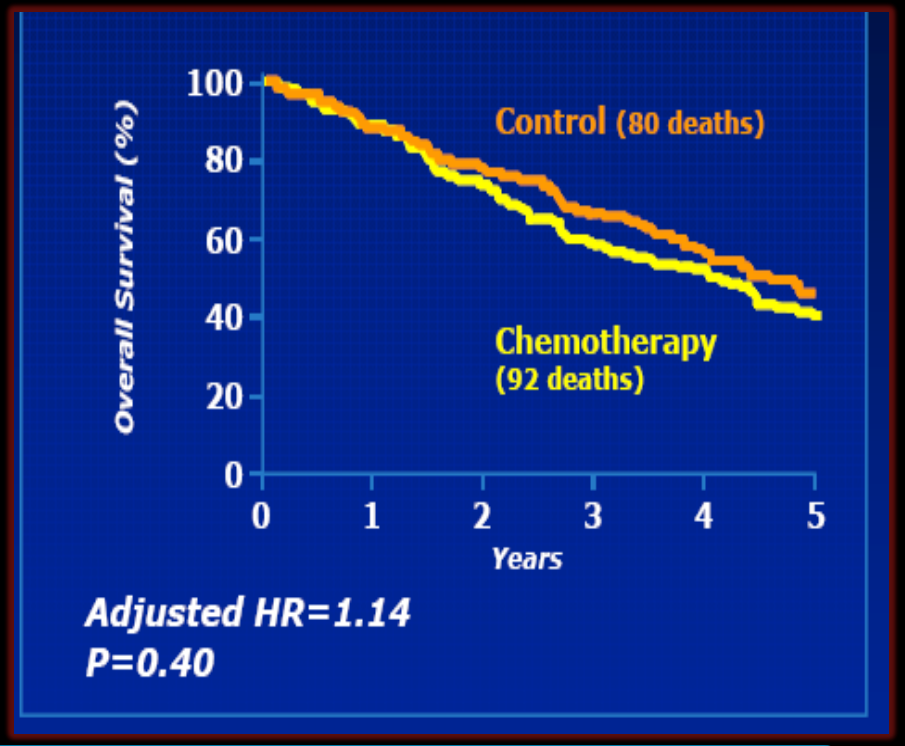
Reference	No of pts	pts Group-CT	Method	Findings
Simon, Chest 2005	51	Resected-Retrospective	RT-PCR	prognostic; high expression of ERCC1 correlated with improved survival (94,6m vs. .35,5m; p=0,01)
Olaussen, NEJM 2006	761	Adjuvant-Cisplatin Retrospective Analysis	ICH	predictive; ERCC1-negative tumors benefit from cisplatin (56 vs. 50m; p=0,002 vs..0,4)
Lord, CCR 2002	56	Advanced-Gem/CDDP Retrospective Analysis	RT-PCR	predictive; low ERCC1 mRNA levels correlated with improved survival(15m vs 5m; p=0,09)
Ceppi, An Onc 2006	70	Advanced-Gem/CDD Retrospective analysis	RT-PCR	low ERCC1 mRNA levels correlated with longer survival (23 vs 12,4m; p=0,0001)
Rosell, PLOSone 2007	126	Resected chemonaive Retrospective analysis	RT-PCR	with longer survival (23 vs 12,4m; p=0,0001)
Cobo, JCO 2007	225	Advanced-DC Prospective III trial	RT-PCR	ERCC1 expression is predictive marker of response (47 vs. 37%; p=0,03)

IALT-Bio Study

Patients with ERCC1 Negative Tumors



Patients with ERCC1 Positive Tumors



Patients with ERCC1-negative tumors benefit from adjuvant cisplatin-based CT but those with ERCC1 positive tumor do not

Interaction test *p*=0.009

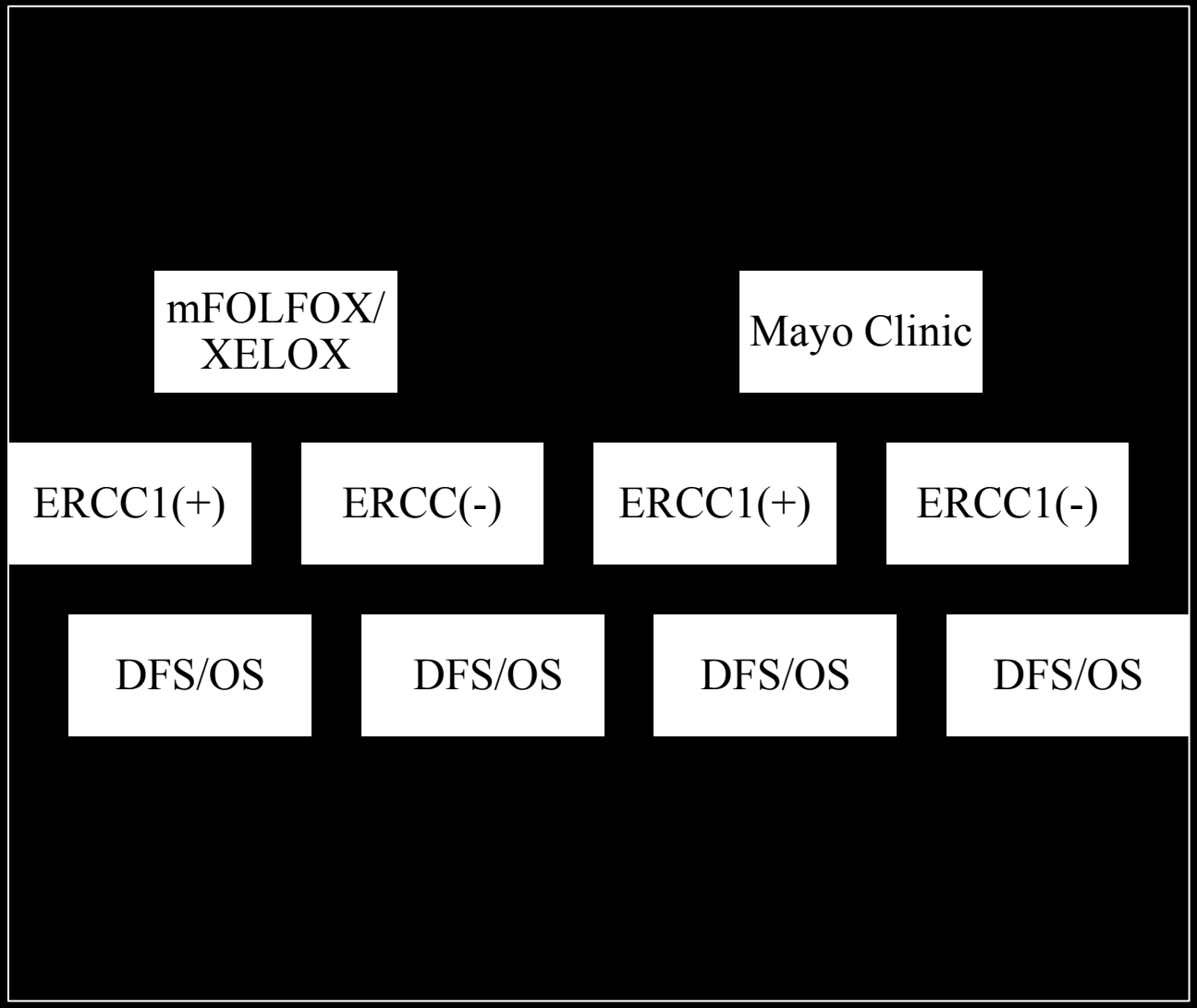
Olaussen K et al. N Engl J Med 2006;355:983-991

ERCC1 in NSCLC: A double-edged sword

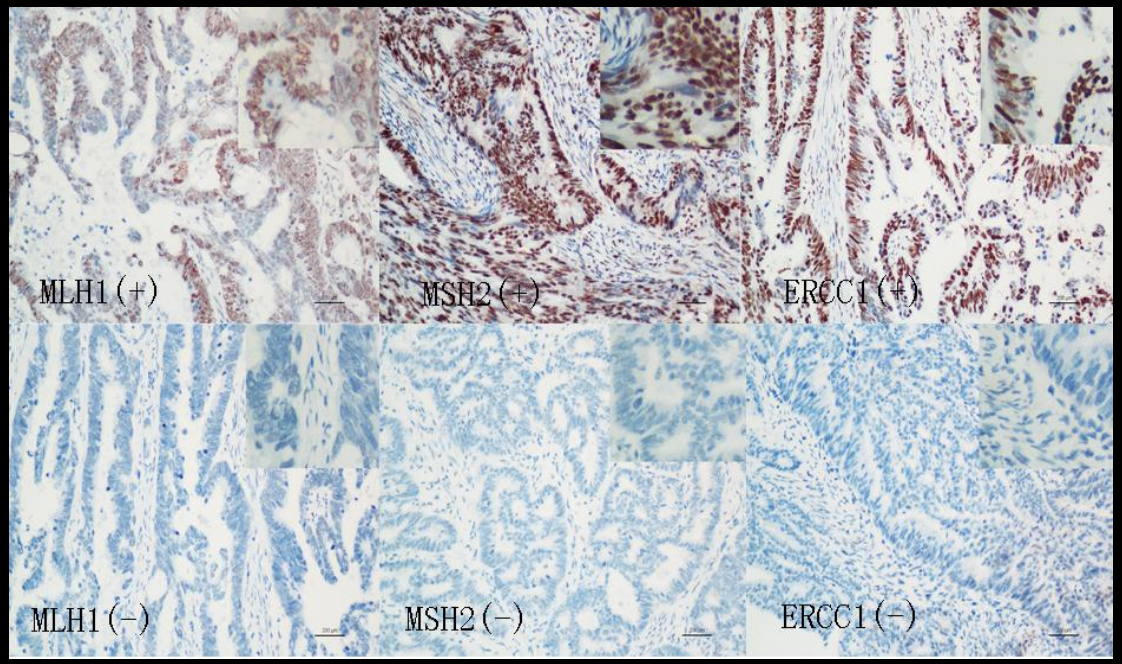
- *ERCC1* expression is clearly linked to platinum resistance
- It is, at the same time, a **favorable prognostic factor** in untreated patients with early NSCLC
  - Possible due to its role in cancer susceptibility

- Comparative studies of gene expression and IHC might be necessary

STUDY DESIGN



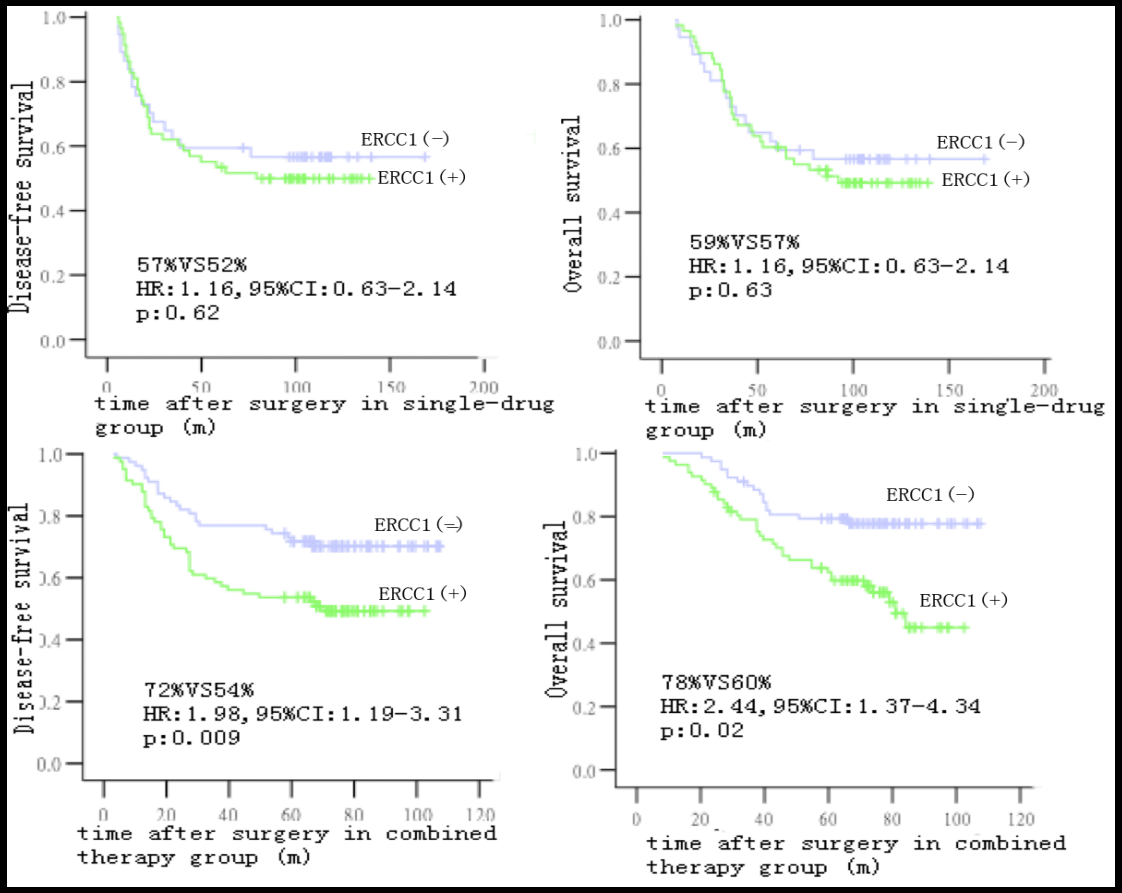
IHC RESULT



Pan L and Chen G ESMO 2012: abst # 524PD

Pan L and Chen G ESMO 2012: abst # 524PD

Survival analysis

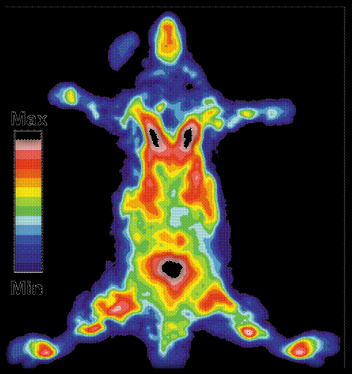


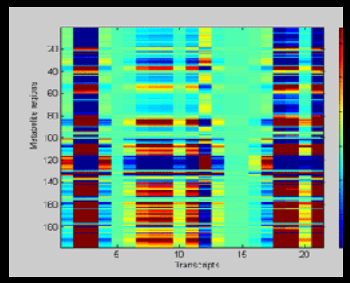
Pan L and Chen G ESMO 2012: abst # 524PD

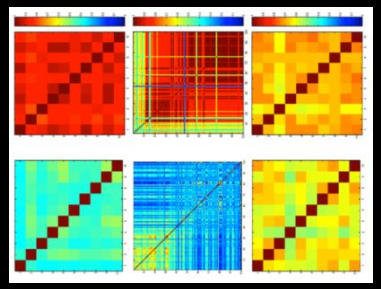
Summary

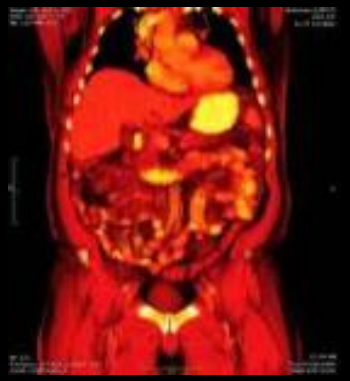
- Two studies (522-523PD) with expression profiles:
  - Well validated
  - The biological information is missing
  - Limited clinical application (Oncotype DX in selected patient)
- An exploratory analysis (524PD) in a small data set
  - Use of a qualitative and not generally accepted assay
  - Single biomarker study
  - Hypothesis generating study only

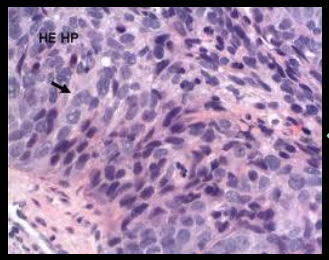
Re-defying RD in colon cancer



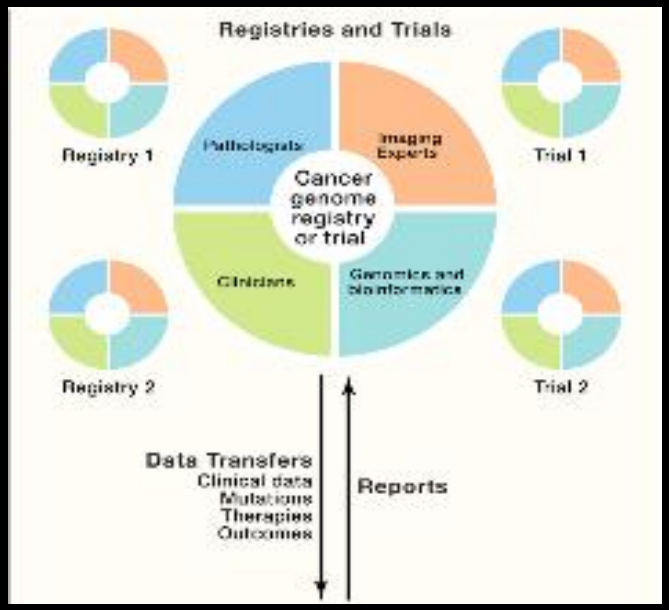


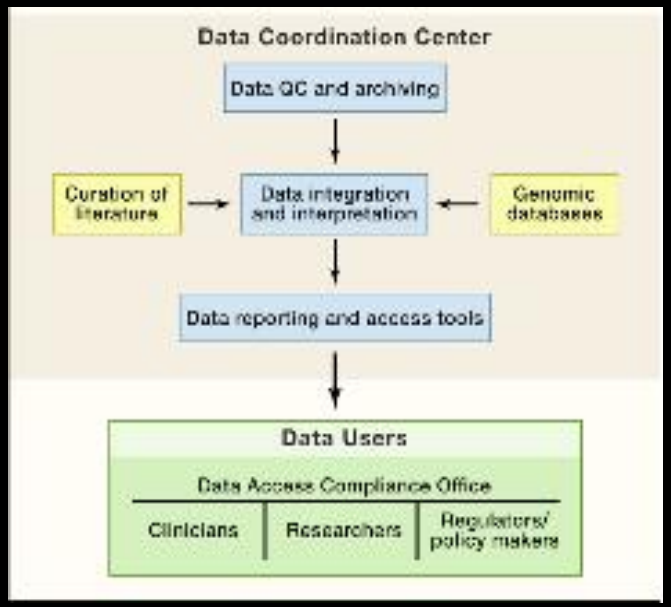






Novel Models for Sharing Cancer Biomarkers Datasheets





Dancey EJ et al *Cell* 2012

The way to move forward

4 P Cancer Medicine

- Predictive
  - information arising from personal genome sequences and longitudinal molecular, cellular and phenotypic measurements
- Personalized
  - large difference in individuals ultimately requires the use of the patient's own baseline healthy data
- Preventive
  - disease-perturbed molecular networks
- Participatory
  - Multidisciplinary collaboration-Patients partnership

Leroy Hood and Stephen H. Friend et al Nat Rev Clin Oncol 2011

You may say I am a dreamer

but I am not the only one

Nor will man miss it. For what man has sought for is, indeed, neither pain nor pleasure, but simply Life. Man has sought to live intensely, fully, perfectly. ….
It will be complete, and through it each man will attain to his perfection. The new Individualism is the new Hellenism.

Oscar Wilde The sole of Man 1891