Test for the prediction of prognosis and response in colorectal cancer patients

Madrid, 2 de julio de 2014

GOBIERNO DE ESPAÑA MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD
MEDICAMENTOS INNOVADORES Plataforma Tecnológica Española
farmaindustria

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1. The Institutions
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   b) Innovative mechanisms of action
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   e) IPR protection
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3. Partnering Opportunities

S. ONCOLOGÍA MÉDICA

Grupo 32. Oncología Traslacional

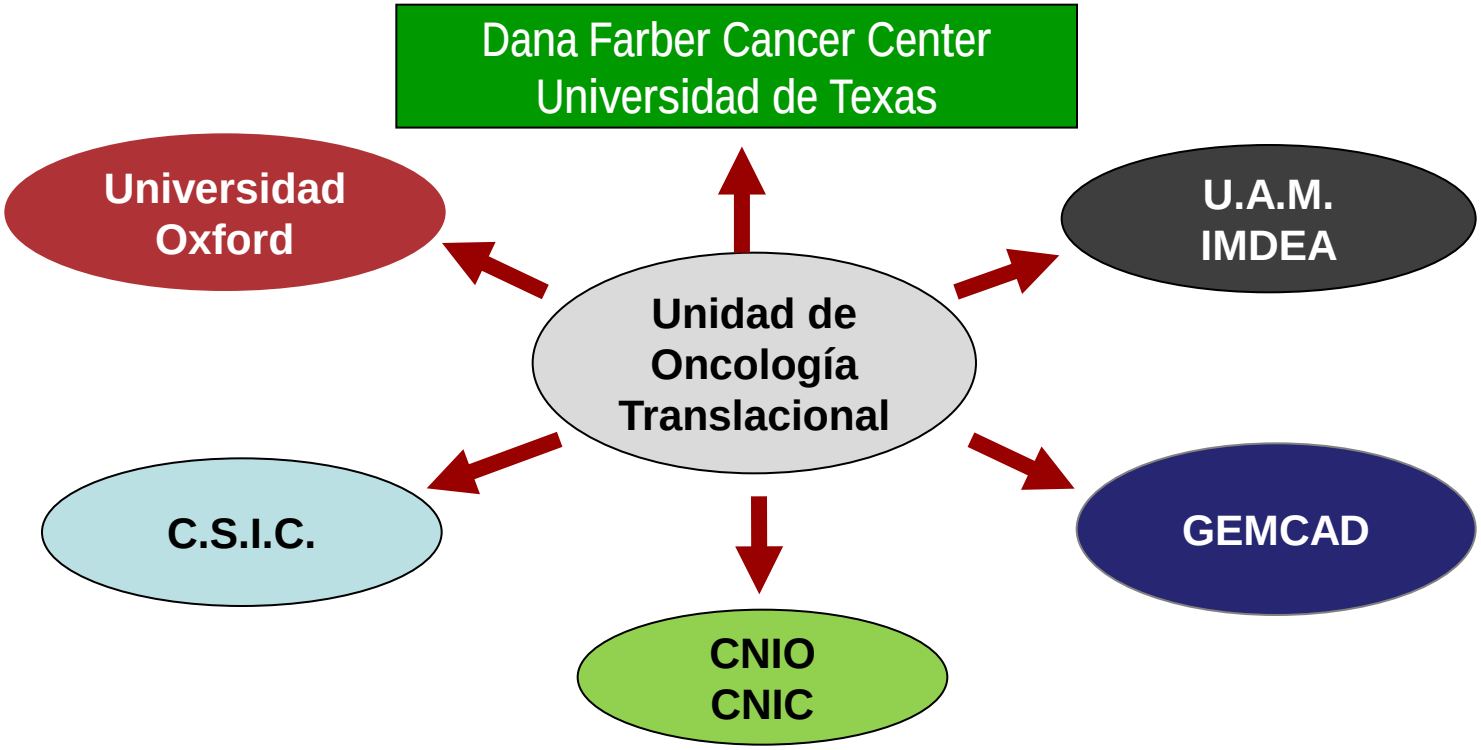
OBJETIVES

- Study of molecular biomarkers with prognostic and predictive value in the most prevalent tumors (colon, lung, breast, etc)
- Identification of the new therapeutics targets
- Application of biomarkers in drug development

Customize cancer treatment

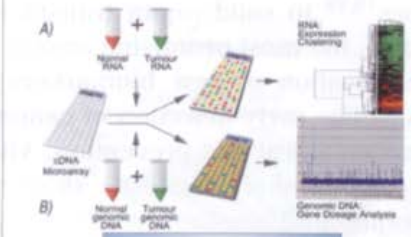
Content

1. **The Institutions:** We are a multidisciplinary research group dedicated to the identification of molecular markers predictive of treatment response and prognosis to the most prevalent cancer types.



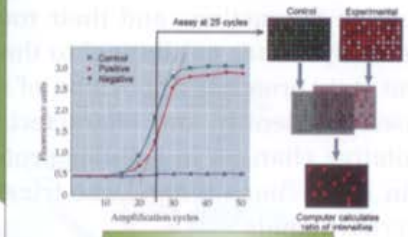
CANCER DIAGNOSTICS

GENOME



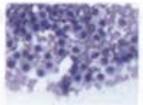
CGH, SNP
DNA Sequencing

TRANSCRIPTOME



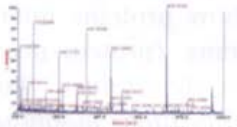
DNA micro-array
RT-PCR

VALIDATION ASSAYS

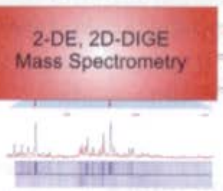


Immunohistochemistry
Immunoblotting
ELISA, TMA

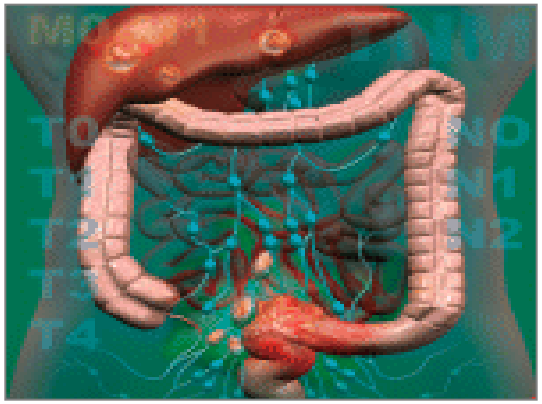
PROTEOME



2-DE, 2D-DIGE
Mass Spectrometry



IDENTIFICATION OF BIOMARKERS FOR PREDICTION AND PROGNOSTIC IN COLORECTAL CANCER PATIENTS



Importance

- Third neoplasia in developed countries
- First neoplasia considering together men and woman
- Third leading cause of cancer death

Content

2. The Products

Colorectal cancer research field:

a) P201130863: «Huella genómica para la predicción de la respuesta clínica a terapia antitumoral en cáncer colorrectal (IDIPAZ-UAM-H. I. Sofía)

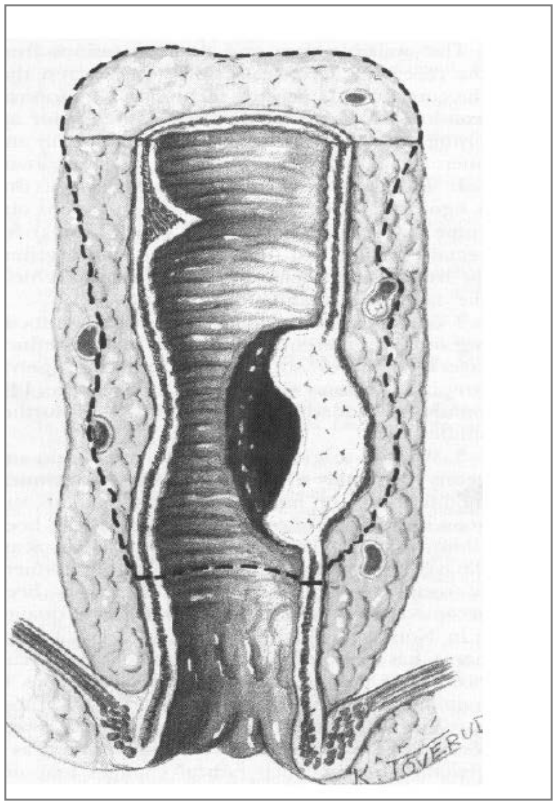
b) P201231918: «Métodos y kits para el pronóstico del cáncer colorrectal (IDIPAZ-IMDEA)

Ca. de Recto

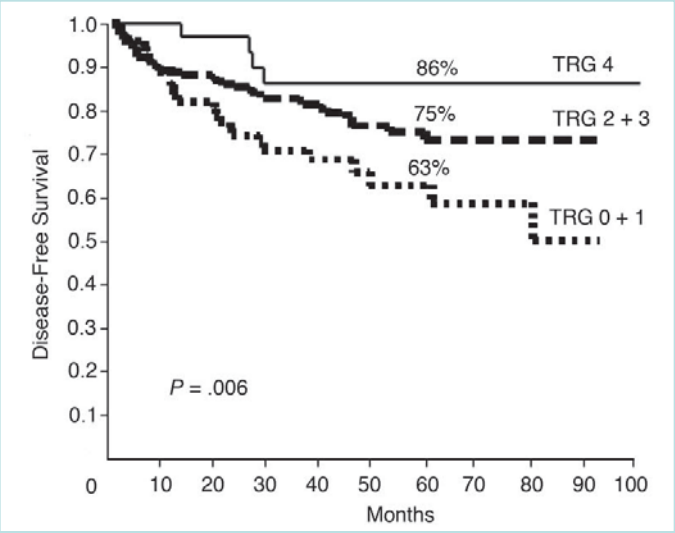
Estadios II/III

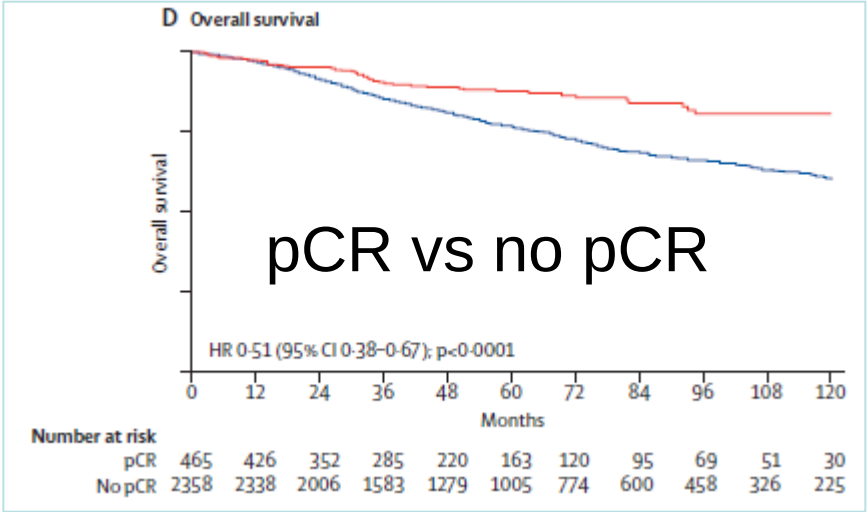
- Treatment: QT-RT → Surgery
  - 5-years survival (75%)

- Problems
  - Delays local treatment in non responders
  - Toxicity
  - Increase the complications of surgery



Predicting response to neoadjuvant QT-RT





More than half of the patients have a poor neoadjuvant treatment response (TRG0+1) which will delay the curative process (the surgical in several months increasing the risk for distal metastases.

(1) Rodel,C., et al..Prognostic significance of tumor regression after preoperative chemoradiotherapy for RC. 2005 J.Clin.Oncol., 23:8688-8696
(2) Maad et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. Lancet Oncol 2010. 11: 835.
(3) Fokas E. et al. Tumor regression grading after preoperative chemoradiotherapy for locally advanced rectal cancer. Updated results of the CAO/ARO/AIO-94 Trial. J. Clin Oncol 2014;32:1554-1562

2. The Product

a) P201130863: «Huella genómica para la predicción de la respuesta clínica a terapia antitumoral en cáncer colorrectal (IDIPAZ-UAM-H. I. Sofía)

Target Indications: Identification of rectal cancer patients reponders to neoadjuvant treatment.

Biopsy (colonoscopy)
Rectal cancer diagnosis

Treatment

(months)

Surgical removal of the tumor

RNA isolation for QPCR study of the predictor

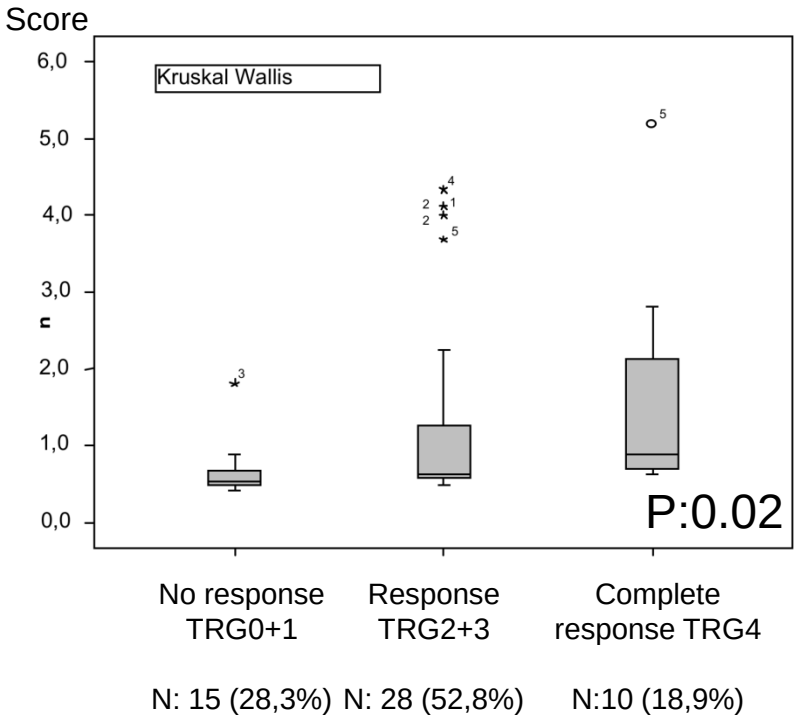
Tumoral regression analyzed by a pathologist

2. The Product

a) P201130863: «Huella genómica para la predicción de la respuesta clínica a terapia antitumoral en cáncer colorrectal (IDIPAZ-UAM-H. I. Sofía)

Target Indications: Identification of rectal cancer patients reponders to the neoadjuvant treatment.

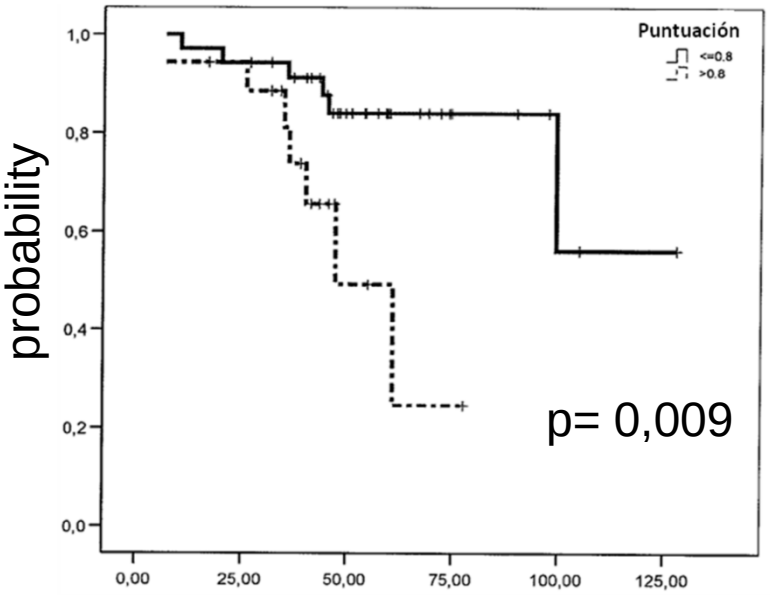
	Componente		
	1	2	3
Gen 1	,011	-,014	,997
Gen 2	,940	,186	,010
Gen 3	,930	,310	,042
Gen 4	,128	,937	-,054
Gen 5	,958	,064	-,033
Gen 6	,564	,577	,102



2. The Product

a) P201130863: «Huella genómica para la predicción de la respuesta clínica a terapia antitumoral en cáncer colorrectal (IDIPAZ-UAM-H. I. Sofía)

Target Indications: Identification of rectal cancer patients reponders to the neoadjuvant treatment. This tool has also prognostic value



2. The Product

a) P201130863: «Huella genómica para la predicción de la respuesta clínica a terapia antitumoral en cáncer colorrectal (IDIPAZ-UAM-H. I. Sofía)

Innovation and Differential features facing the market: It represent a innovation to what´s available for these patients

- There are no prognosis or response prediction factors to neoadjuvant treatment in rectal cancer

- This tool can help to personalyze rectal cancer therapy, improving the survival and reducing toxicities and unnecessary costs

2. The Product

a) P201130863: «Huella genómica para la predicción de la respuesta clínica a terapia antitumoral en cáncer colorrectal (IDIPAZ-UAM-H. I. Sofía)

Differential features facing the market:

There are no comercially available kits to predict neoadjuvant treatment response in rectal cancer.

2. The Product

a) P201130863: «Huella genómica para la predicción de la respuesta clínica a terapia antitumoral en cáncer colorrectal (IDIPAZ-UAM-H. I. Sofía)

Current state of validation: Validation stage.

We have collected pre-treatment rectal biopsies from 4 different clinical trials involving locally advanced rectal cancer patients from the cooperative group GEMCAD.

2. The Product

a) P201130863: «Huella genómica para la predicción de la respuesta clínica a terapia antitumoral en cáncer colorrectal (IDIPAZ-UAM-H. I. Sofía)

PAST:

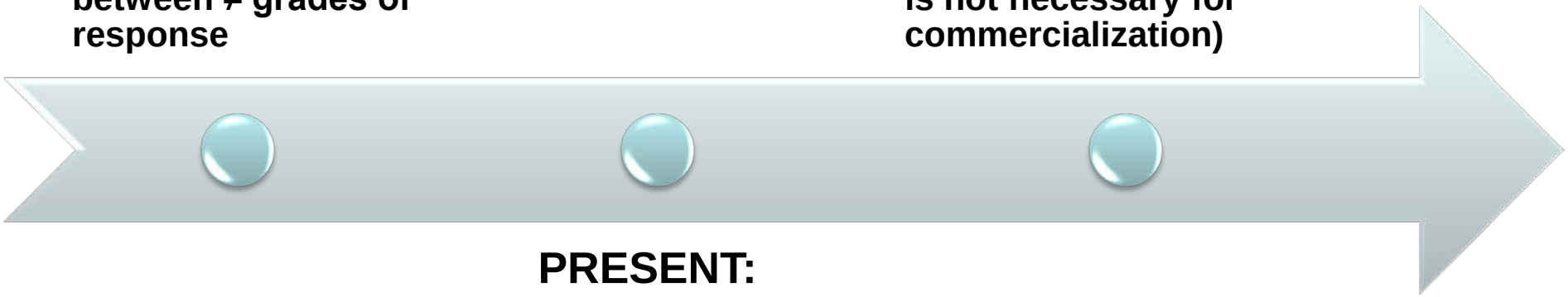
- ***In vitro*** **studies in +50 human samples**
- **Predictive value of response**
- **Discrimination between ≠ grades of response**

PRESENT:

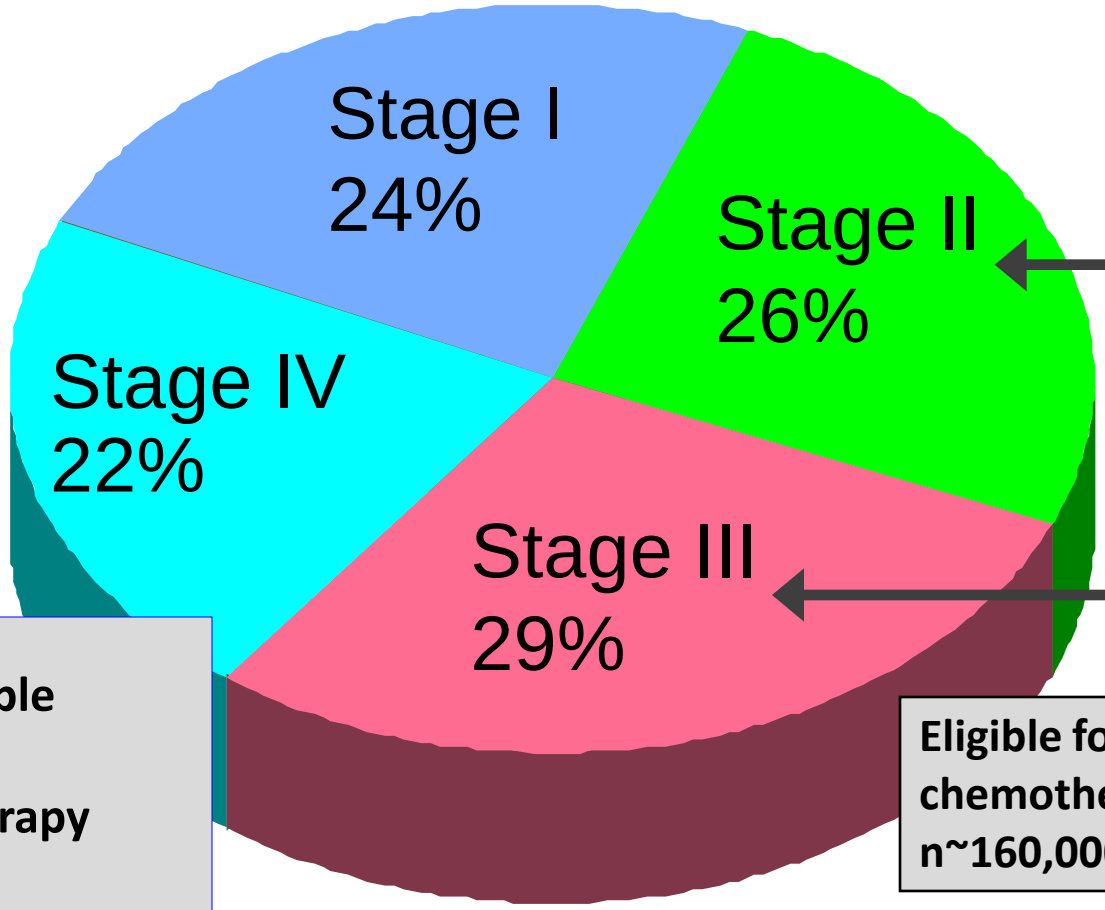
- **200 samples from clinical trials already available**

FUTURE:

- **1st: Validation**
- **2nd: Clinical trial (although it is not necessary for commercialization)**



Colon Cancer Incidence in USA and Europa 2003 (n=300.000)



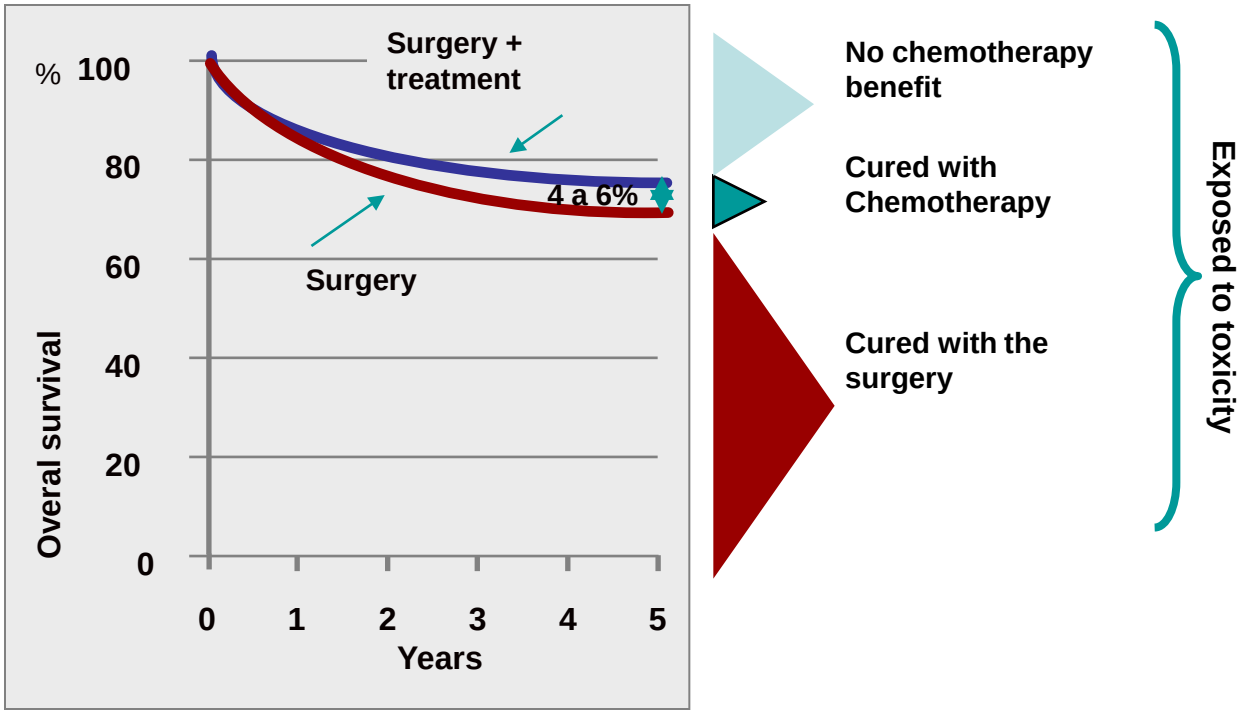
Initially eligible for systemic therapy n~60,000

Eligible for adjuvant chemotherapy n~160,000 (55%)

2. The Product

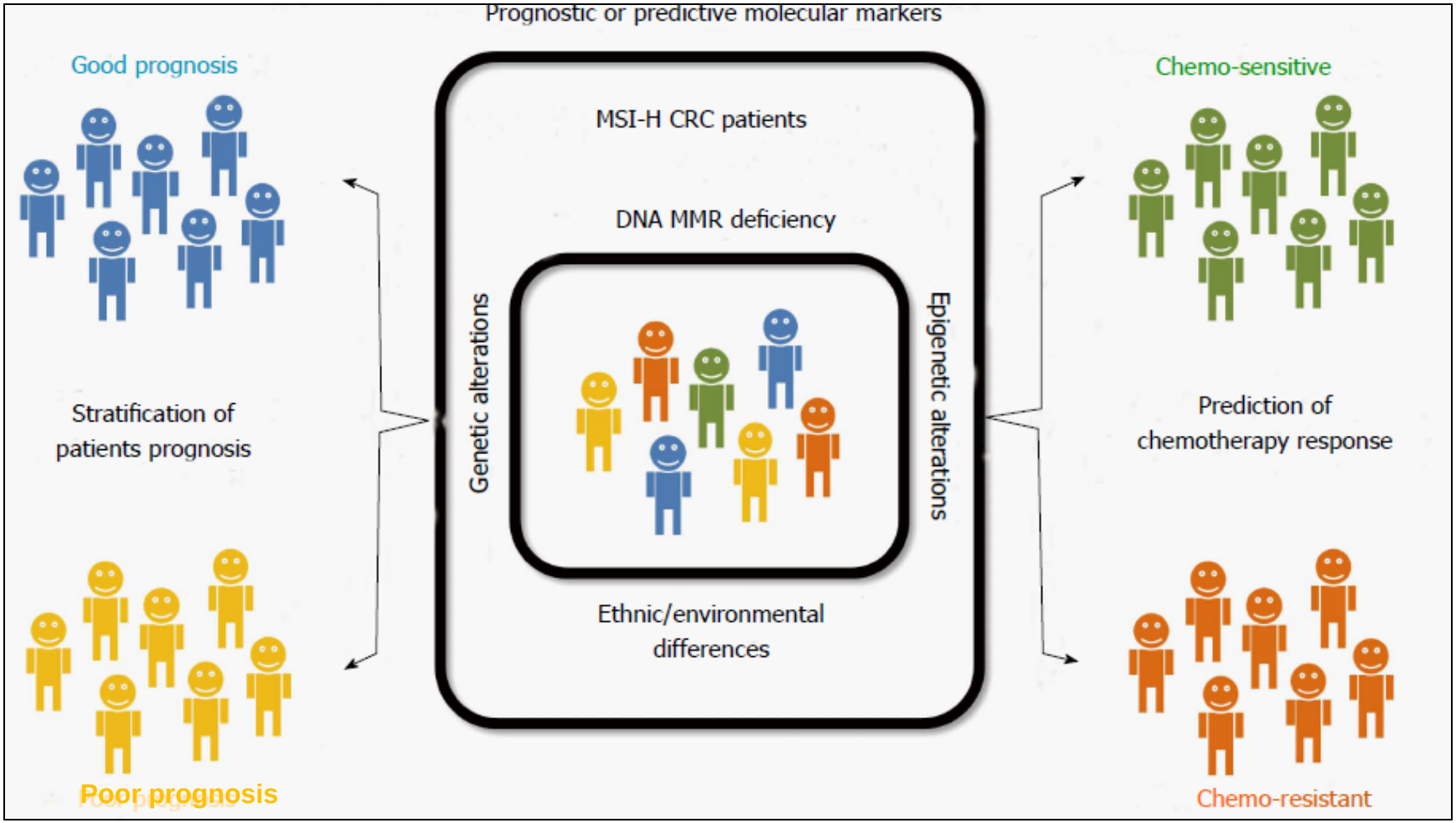
a) P201231918: «Métodos y kits para el pronóstico del cáncer colorrectal (IDIPAZ-IMDEA)

Target Indications: Identification patients diagnosed with stage II CRC that will have a terapeutical benefit to standard chemotherapy.



Adjuvance in CC Stage II…For who?

"We have to treat 100 stage II patients to cure 3 or 4, while accepting that up to 40 percent of those treated will suffer significant toxicity…."



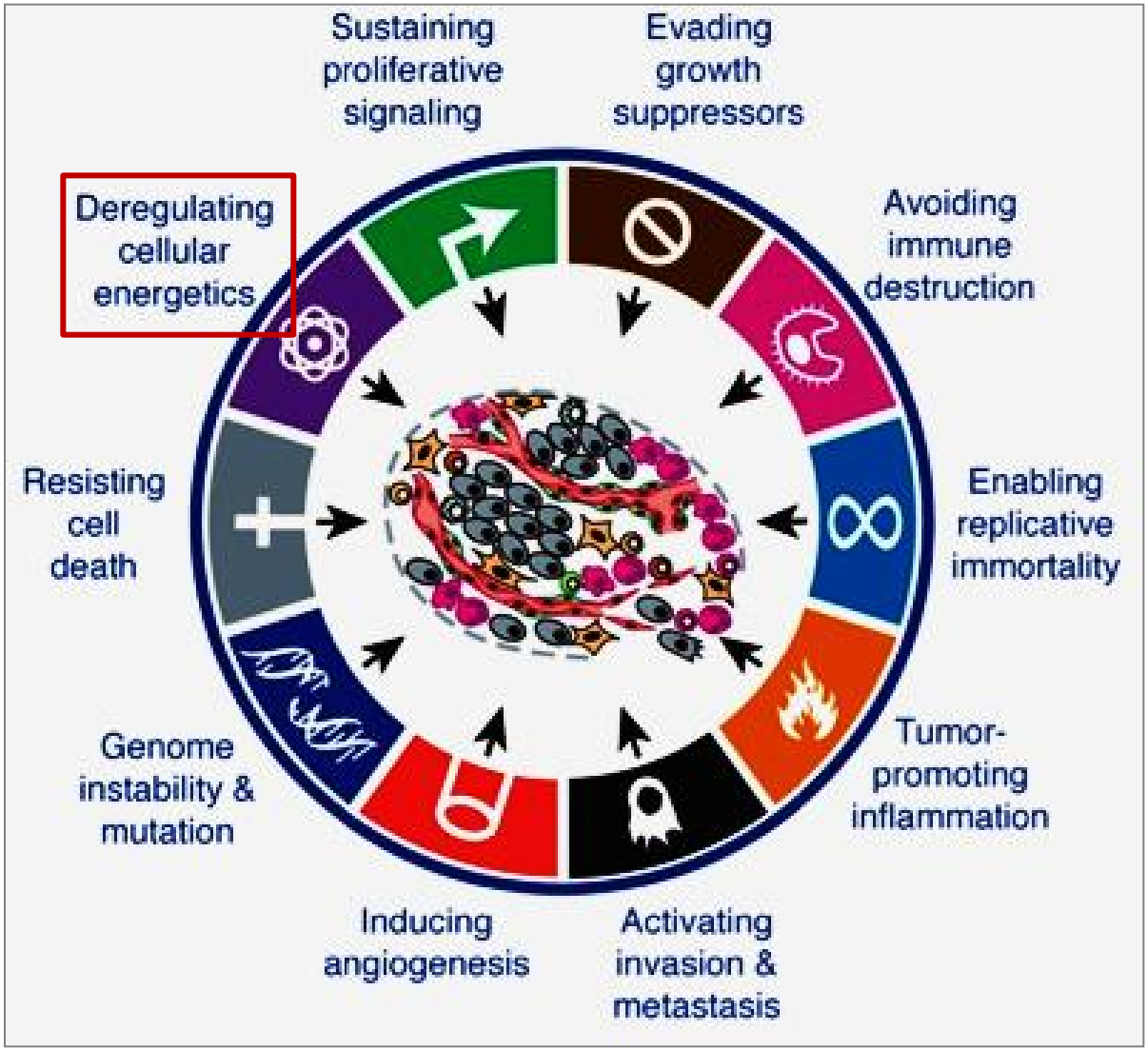
Ho Kim World J Gastroenterol 2014

Expert Recomendations

	ASCO (2004)	NCCN (2013)	ESMO (2012)
T4 primary tumor	+	+	+
Inadequately sampled nodes	+ (<13)	+ (<12)	+ (<12)
Poorly differentiated tumor	+	+	+
Perforation	+	+ (localized)	+
Obstruction		+	+
LVI		+	+
PNI		+	+
Close/indeterminate or positive margins		+	

Innovative mechanism of action

Cancer Hallmarks



Study Design

Design Phase

83 lipid metabolism related genes and genes related with cancer or metabolic disease (real time PCR)

77 patients with stage II (FFPE biopsies)

4 lipid-related gene

Validation Phase

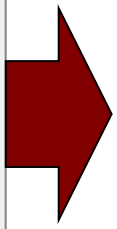
119 patients with stage II (H. La Paz)

120 patients with stage II (Barcelona and Valencia hospitals)

Phase Design

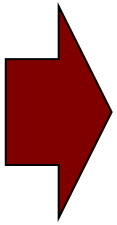
83 Genes related with:

- Adipocytokine signaling
- Bile and biosynthesis
- Endocytosis of specific ligands
- Fatty acid biosynthesis
- Lipid metabolism peroxisomes
- Phospholipids metabolism
- PPAR signaling
- Cholesterol transport
- Triacylglycerol metabolism
- Cancer
- Diabetes
- Hyperlipidemia



Univariable analisis

11 gene related with DFS



Multivariable analisis

4 gene related with DFS

Univariate Cox-Regression analysis for DFS

	Training group							
	Low Risk		High Risk		Unadjusted		Adjusted#	
Variable	R	N	R	N	HR(95% CI)	P	HR(95% CI)	P
Gen 1	7	43	15	34	3·08 (1·25-7·56)	0·010	3·76 (1·4-10·08)	0·006
Gen 2	10	51	12	26	2.93 (1.26-6.81)	0.013	2.34 (0.91-6.02)	0.082
Gen 3	8	51	14	26	4.31(1.8-10.32)	0.001	3.54 (1.39-9)	0.007
Gen 4	3	26	19	51	3·57 (1·06-12·08)	0·018	3·13 (0·9-10·93)	0·046
ASCO risk High vs Low risk	2	14	20	63	2·53 (0·59-10·81)	0·157		
ColoLipid Gene High vs Low Risk	9	55	13	22	4.65 (1.98-10.93)	<0·001	3.94 (1.54-10.11)	0·005

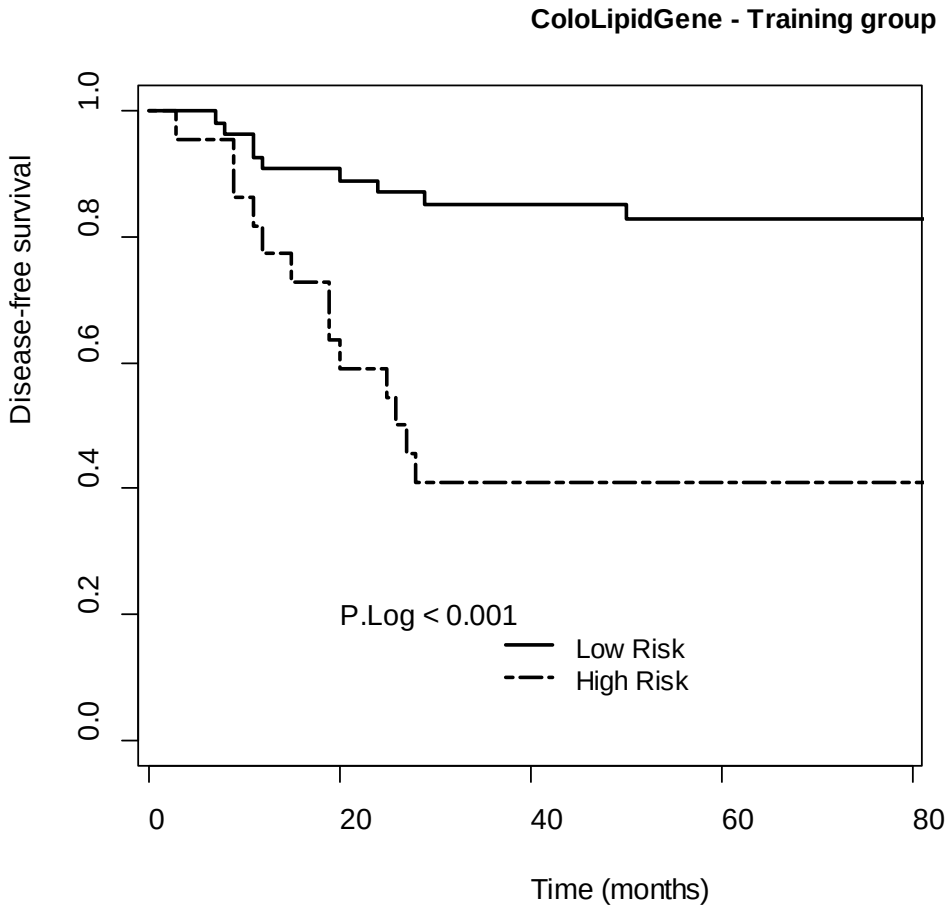
Univariate Cox-Regression analysis for DFS

Variable	Validation group I							
	Low Risk		High Risk		Unadjusted		Adjusted#	
	R	N	R	N	HR (95% CI)	P	HR (95% CI)	P
Gen 1	6	65	12	54	2.63 (0.99-7)	0.045	3.12 (1.1-8.82)	0.026
Gen 2	5	61	13	58	3.12 (1.11-8.76)	0.021	3.86 (1.16-12.79)	0.017
Gen 3	4	52	14	67	3.11 (1.02-9.47)	0.03	4.45 (1.31-15.11)	0.009
Gen 4	3	57	15	62	5.32 (1.54-18.38)	0.002	4.08 (1.12-14.9)	0.017
ASCO risk High vs Low risk	0	13	18	106	4·35 (0·6-554·13)	0·187		
ColoLipid Gene High vs Low Risk	4	72	14	47	6.57 (2.15-20.02)	<0·001	6.55 (2.06-20.75)	<0·001

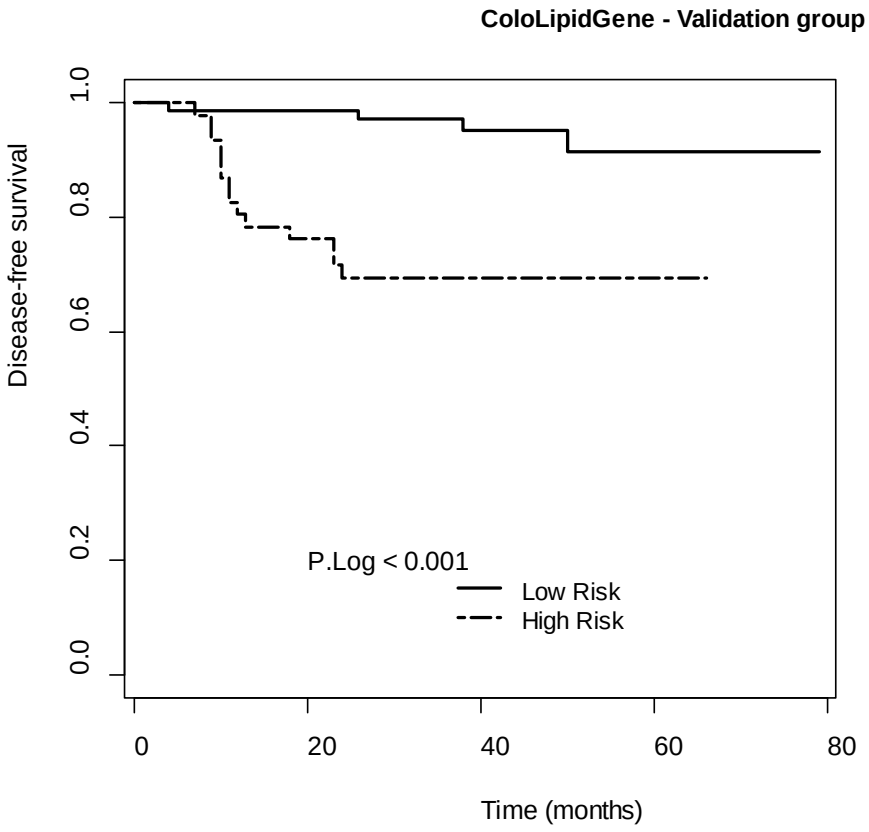
Univariate Cox-Regression analysis for DFS

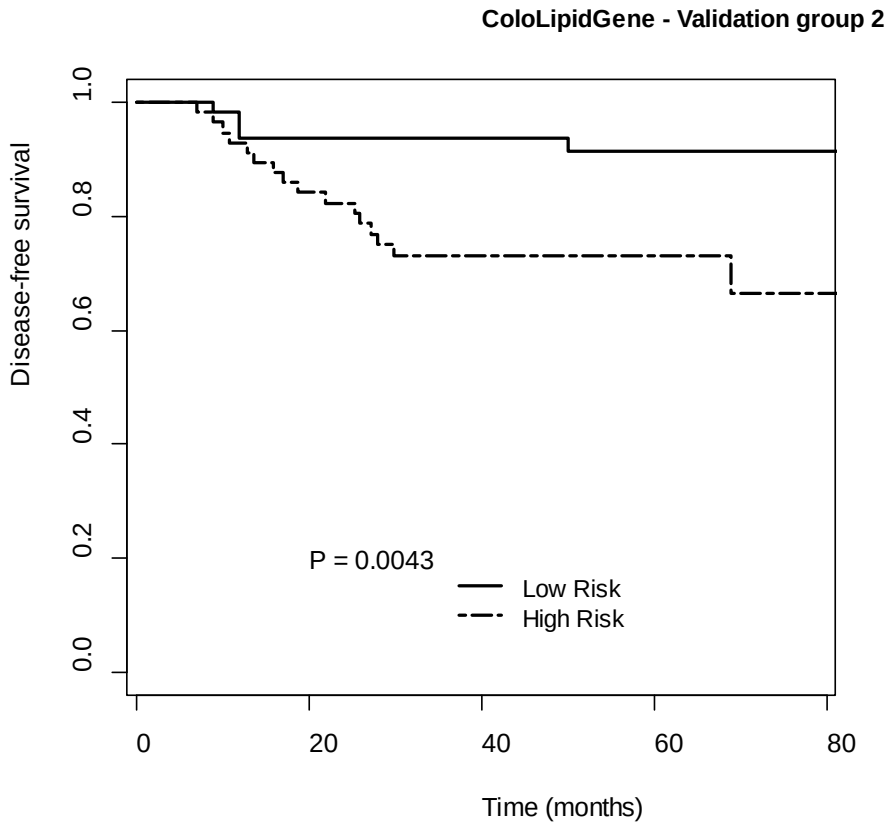
Variable	Validation group II							
	Low Risk		High Risk		Unadjusted		Adjusted#	
	R	N	R	N	HR(95% CI)	P	HR(95% CI)	P
Gen 1	3	47	18	73	4.21(1.24-14.32)	0.007	5.05 (1.44-17.65)	0.003
Gen 2	2	29	19	91	3.35 (0.78-14.4)	0.056	4.89 (1.04-22.97)	0.018
Gen 3	3	40	18	80	3.24 (0.95-11)	0.032	3.11(0.89-10.93)	0.049
Gen 4	12	83	9	37	1.76 (0.74-4.18)	0.208	2.17 (0.85-5.57)	0.113
ASCO risk High vs Low risk	2	40	19	80	5.52 (1.28-23.73)	0.004		
ColoLipid Gene High vs Low Risk	5	63	16	57	3.88 (1.42-10.59)	<0.005	6.89 (2.05-23.19)	<0.001

COLOLIPID test: RESULTS



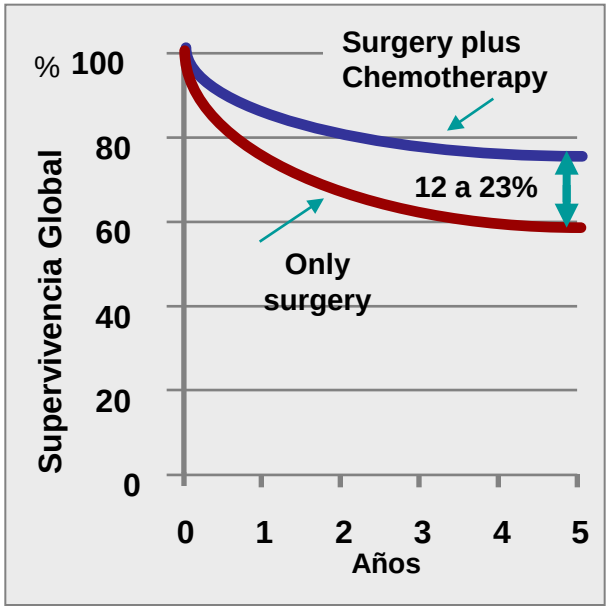
COLOLIPID test: VALIDATION SERIES



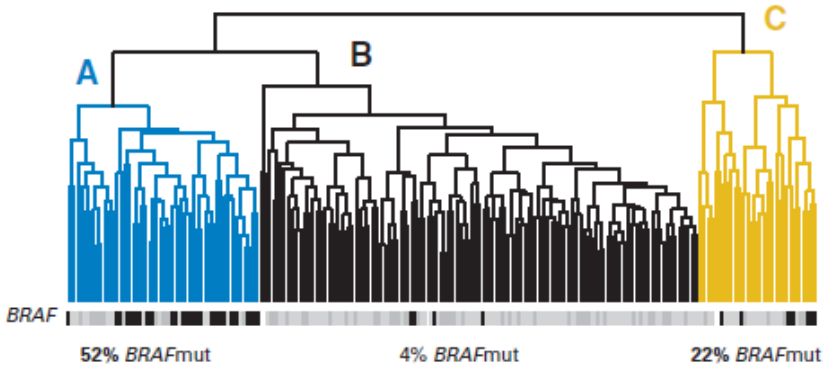


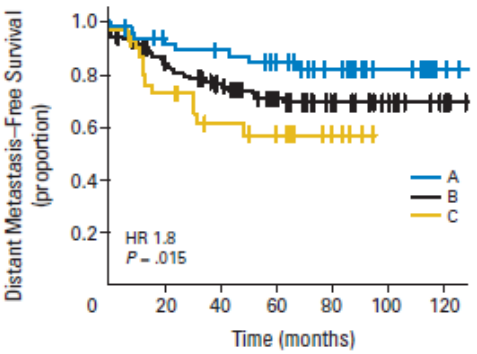
COLOLIPID test: Aplications

- Predicting the prognosis of patients with stage II CC
- Assist in decision making
  - Capacity for predicting response?
  - Stage III?
  - Can be applied to others tumors?



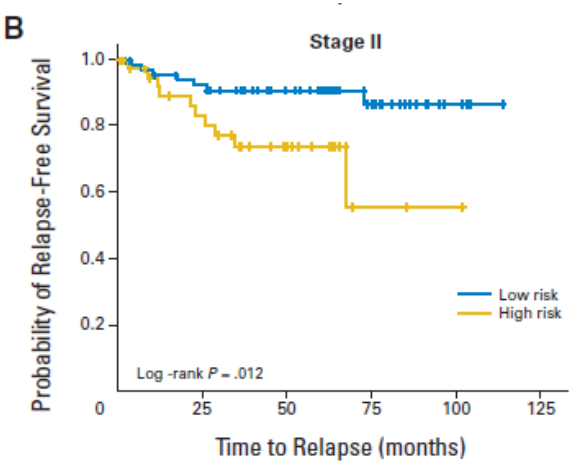
Differential features facing the market: **Gene Expression Signature: Coloprint:**





206 patients
Stage I, II, III
18 genes
Fresh tissue

Salazar JCO 2008



Differential features facing the market: Gene Expression Signature: Oncotype

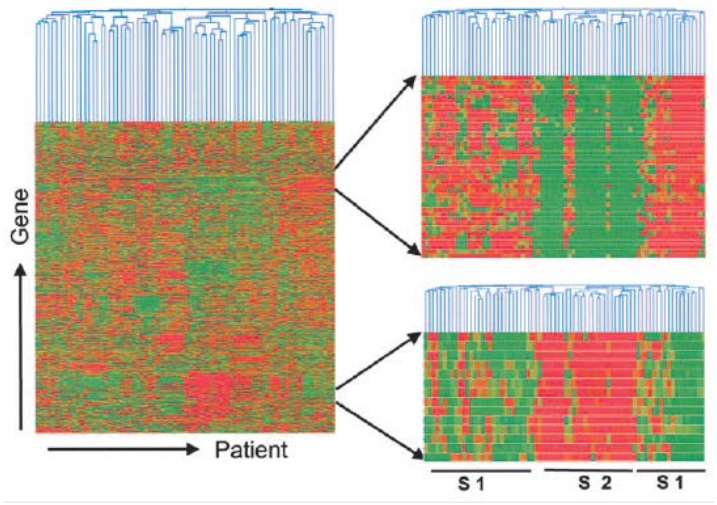


Table 1. Prediction of Recurrence Risk: Kaplan-Meier Estimates of Recurrence Risk at 3 Years and Associated 95% CIs from Bootstrap Analysis for Patients With Stage II Disease in Surgery-Alone Studies

Recurrence Risk Group	Patients (median %)	Risk of Recurrence at 3 Years (%)	95% CI
Low (RS < 30)	25	8	5 to 12
Intermediate (RS 31-40)	39	11	7 to 15
High (RS ≥ 41)	37	25	18 to 32

Abbreviation: RS, recurrence score.

Prognostic score genes: validated

Stromal	Cell cycle	Reference
BGN	*Ki-67*	*ATP5E*
FAP	*C-MYC*	*GPX1*
INHBA	*MYBL2*	*PGK1*
		UBB
		VDAC2
Early response		
GADD45B		

7 + 5 genes

Treatment score gene: not validated

Angiogenesis, migration, and cell-cell signaling	Apoptosis	Reference
EFNB2	*BIK*	*ATP5E*
		GPX1
Transcription factor	**Cell cycle**	*PGK1*
RUNX1	*MAD2L1*	*UBB*
		VDAC2
	Wnt pathway	
	AXIN2	
	Heat shock	
	HSPE1	

6 + 5 genes

O´Connel MJ et al. JCO 2010

Advantages over competitors

- Developed exclusively in patients with stage II CC
- Simplicity (only 4 genes)
- The 4 genes have prognostic value separately
  - Reinforce the reliability of the test
  - All are in the same biological process 'metabolic activation'. Useful for other tumor types?
- FFPE biopsies

Current Status of Development

- Retrospective Validation √
- Publication of the results √
- Prospective validation

Current Status of Development

PAST:

- **Diagnosis action shown in 77 patients**
- **1st validation (119 patients)**
- **2nd validation (additional 120 patients; ≠ hospitals; ≠ regions)**

FUTURE:

- **Option 1: Another validation**
- **Option 2: Clinical trial (Best option)**

PRESENT

Pitfalls & Risks to be considered

- Two major competitors
  - Coloprint
  - Oncotype
- Need validation in a prospective study?

IPR protection:

a) P201130863: «Huella genómica para la predicción de la respuesta clínica a terapia antitumoral en cáncer colorrectal (IDIPAZ-UAM-H. I. Sofía)

b) P201231918 «Métodos y kits para el pronóstico del cáncer colorrectal (IDIPAZ-IMDEA)–under prosecution and PCT/ES2013/070964 international patent application

Partnering Opportunities

- Investors to finance the subsequent phases of the research project
- Patent licenses
- Partners interested in getting involved in the subsequent phases of the research project, etc.