Article:
Smith, CG, Fisher, D, Harris, R et al. (15 more authors) (2015) Analyses of 7,635 Patients with Colorectal Cancer Using Independent Training and Validation Cohorts Show That rs9929218 in CDH1 Is a Prognostic Marker of Survival. Clinical Cancer Research, 21 (15). pp. 3453-3461. ISSN 1078-0432

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Supplementary Information for: Analyses of 7,635 patients with colorectal cancer using independent training and validation cohorts show that rs9929218 in *CDH1* is a prognostic marker of survival.

Supplementary References

The Health Professionals Follow-up Study (1), the Nurses' Health Study (2-4), the Physicians' Health Study (5), the VITamins And Lifestyle Study (6), the Women's Health Initiative (7), and, the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (8,9). Protocols for assessing survival in these studies (1,4,6,10-12). A full listing of WHI investigators can be found at: https://www.whi.org/researchers/Documents%20%20Write%20a%20Paper/WHI%20Investigator%20Short%20List.pdf.

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Supplementary Tables

Supplementary Table S1 - Multivariate model of overall survival including known prognostic factors (training phase cohort)

Variable		HR (95% CI)	*P*-value
rs16892766	AC and CC vs. AA	1.29 (1.12-1.48)	$3.9x10^{-4}$
rs9929218	AA vs. AG and GG	1.33 (1.09-1.62)	$4.7x10^{-3}$
rs10795668	AA vs. AG and GG	0.65 (0.52-0.80)	$7.1x10^{-5}$
WHO PS	1 vs. 0	1.24 (1.10-1.40)	$4.1x10^{-4}$
	2 vs. 0	1.68 (1.35-2.10)	$5.2x10^{-6}$
No. of metastatic sites	≥2 vs. 0 or 1	1.26 (1.12-1.42)	$1.7x10^{-4}$
WBC	≥10000/µl vs. <10000/µl	1.52 (1.33-1.73)	$2.5x10^{-10}$
Alkaline phosphatase	≥300U/l vs. <300U/l	1.74 (1.49-2.03)	$2.8x10^{-12}$
KRAS status	Mutant vs. wild-type	1.36 (1.21-1.53)	$3.7x10^{-7}$
BRAF status	Mutant vs. wild-type	2.32 (1.90-2.83)	$1.4x10^{-16}$

Results from a single, multivariate, Cox model with the outcome of overall survival (n=1626 patients [1210 deaths]). PS - Performance Status, WBC - white blood cell count. The continuous variables WBC and alkaline phosphatase were grouped into two categories by use of defined cut-off points. Analyses were carried out with the best models that fitted the data.

Supplementary Table S2 - Univariate analyses of survival in our validation phase cohort

SNP	N genotyped	Alleles		N deaths	HR (95% CI)	*P*-value
rs16892766	5536	AA	4566	1767	1.01 (0.91-1.14)	0.81
		AC/CC	970	394		
rs9929218	5552	GG/GA	5069	1946	1.19 (1.02-1.38)	$2.5x10^{-2}$
		AA	483	201		
rs10795668	5542	GG/GA	4970	1921	1.07 (0.92-1.23)	0.39
		AA	572	221		

Survival analyses were carried out under the model that was found to best fit the training phase data: rs16892766 - dominant; rs9929218 and rs10795668 – recessive (*unadjusted*). Note - rs9929218 was directly genotyped in all of the studies. rs16892766 and rs10795668 were directly genotyped in some studies and imputed in others - so numbers represent the best calls.

Supplementary Table S3: Gene-dose effect for rs9929218

Analysis phase	Alleles	N genotyped[a]	N deaths	HR (95% CI)
Training phase	GG	1060	782	1.00 (ref)
	GA	853	634	1.01 (0.91-1.12)
	AA	163	139	1.44 (1.20-1.73)
Validation phase[b]	GG	1014	458	1.00 (ref)
	GA	789	361	0.98 (0.85-1.12)
	AA	154	79	1.26 (0.99-1.61)
Combined	GG	2074	1240	1.00 (ref)
	GA	1642	995	1.00 (0.92-1.09)
	AA	317	218	1.37 (1.19-1.59)

Data shown are hazard ratios (HRs) for GA vs GG and AA vs GG. HRs for the validation phase and the combined analysis are pooled effects using a one-stage fixed-effects meta-analysis. [a]Includes patients with data on age, sex and time of diagnosis; [b]Excludes patients from GECCO. ref – reference.

Supplementary Table S4 – Distribution of rs9929218 genotype by disease stage

Stage	Alleles	N genotyped	N expected[a]	*P*-value
1	GG	547	539.7	
	GA	440	454.6	
	AA	103	95.7	0.29
2	GG	243	237.3	
	GA	174	185.5	
	AA	42	36.2	0.18
3	GG	239	242.1	
	GA	185	178.9	
	AA	30	33.0	0.47
4	GG	1846	1847.9	
	GA	1465	1461.2	
	AA	287	288.9	0.88

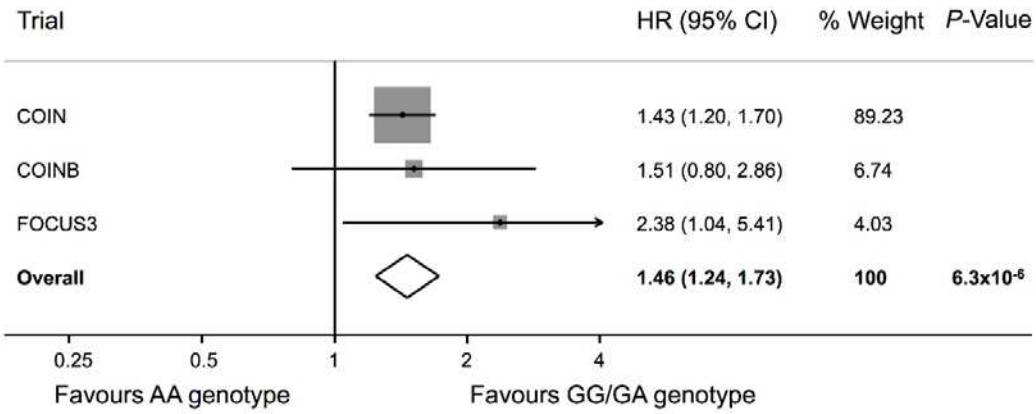
[a]Numbers expected from the Hardy-Weinberg Equilibrium together with *P*-values compared to those observed. Note – Some patients from GECCO were classified as stages 2/3 and were excluded from this analysis.

Supplementary Table S5 - Univariate analysis of rs9929218 on overall survival according to COIN trial arm

Treatment arm		N	HR (95% CI)	*P*-value
A	GG/GA	611	1.00	<0.001
	AA	61	1.76 (1.32-2.34)	
B	GG/GA	657	1.00	$4.8x10^{-2}$
	AA	52	1.37 (1.00-1.88)	
C	GG/GA	646	1.00	0.116
	AA	51	1.29 (0.94-1.77)	

Patients were randomised to receive continuous oxaliplatin and fluoropyrimidine chemotherapy (Arm A), continuous chemotherapy plus cetuximab (Arm B), or intermittent chemotherapy (Arm C). No significant heterogeneity was observed between treatment arms (χ^2=1.95, 2 df, *P*=0.38).

Supplementary Figure



The effect of rs9929218 on survival from the time of diagnosis to death in 2444 trial patients (from COIN, COINB and FOCUS3) for whom we had relevant clinical information, adjusted for age and sex. rs9929218 was highly associated with this alternative measure of survival (P=6.3x10^{-6}).