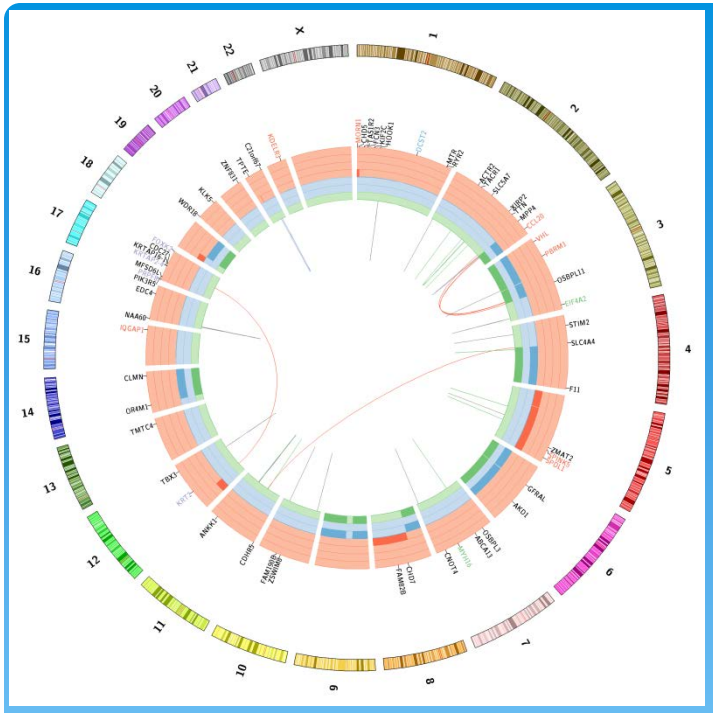


KIRC TCGA
Clinical TCGA Consortium (cTCGA)

Ari Hakimi, M.D.

Department of Urology

Memorial Sloan Kettering

James Hsieh Lab

cTCGA – Why it Matters

* Clinical information collected at time of TCGA limited
* Data often not reviewed in advance by disease experts
* Cancer specific outcomes often not collected
* Risk factors, post surgery treatment information, detailed metastatic information

Contribution by Center

Center	Key Contributors	Cases	Cases with Mutation Data
UNC	Kim Rathmell Eric Wallen	29	21
DFCI	Toni Choueiri Sabina Signoretti	40	37
MDACC	Pheroze Tamboli Nizar Tannir	71	67
UPMC	Leonard Appleman Jodi Maranchie Anil Parwani	107	93
MSKCC	Ari Hakimi James Hsieh Victor Reuter Paul Russo Robert Motzer Martin Voss Chris Sander Anders Jacobsen	142	124
Total:		389	342*

*Represents 82% of TCGA

Acquired Data – Patient Features

* History
  * Prior Cancer Hx
  * Family Hx
* Co-morbidities
  * DM, HTN, Hyperchol, BMI, Smoking
* Lab Values
  * Hg, WBC, Platelets, Ca, *LDH*, *ESR*
* Symptoms at presentation

Acquired Data – Tumor Features

* Metastatic Disease
  * Presence at Surgery
  * Location of metastatic Sites
* Longer F/U and Recurrence Info
* Systemic Therapy
  * Timing
  * Indication

Population Characteristics

Gender (%)	
Male	223 (65)
Female	119 (35)
Median age years (range)	61 (34-90)
Mean BMI	26.9 ± 11
Race (%)	
White	322 (94)
African American	10 (3)
Asian	7 (2)
Unknown	3 (1)
Prior tumor (%)	
Yes	42 (12)
No	300 (88)
Presentation (%)	
Incidental	175 (51)
Local	102 (30)
Systemic	34 (10)
Unknown	31 (9)

Metastatic disease at presentation (%)	
Yes	74 (22)
No	261 (76)
Unkown	7 (2)
Laterality (%)	
Right	180 (53)
Left	162 (47)
Smoking status (%)	
Current	41 (12)
Former	122 (36)
Never	164 (48)
Unknown	15 (4)
Systemic treatment (%)	
Neoadjuvant	5 (1.5)
Immediate	47 (13.7)
Adjuvant	5 (1.5)
Recurrence	29 (8.5)
None	241 (70.5)
Unknown	15 (4.4)

Utilizing Genomic Insights from TCGA into Epidemiologic Phenomena

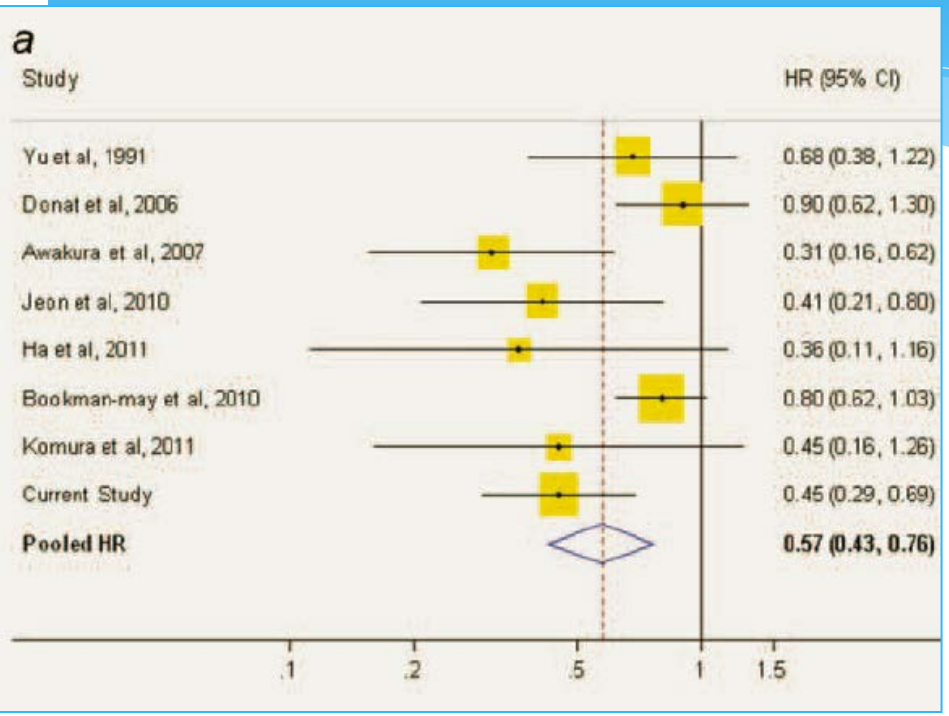
Background – Known Risk Factors for ccRCC

Risk factors	Association with RCC	Comment
*Established**		
Cigarette smoking	Positive	Dose–response association with pack-years Smoking cessation reduces risk
Excess body weight	Positive	Dose–response association with usual adult BMI Effect of weight change on risk unclear
Hypertension	Positive	Dose–response association with blood pressure Control of hypertension might reduce RCC risk Effect independent of body weight
Familial cancer syndromes	Positive	Inherited RCC in affected families
Suspected‡		
Diabetes mellitus	Positive	Effect independent of obesity and hypertension not yet established
End-stage renal disease	Positive	Increased subsequent RCC risk
Parity in women	Positive	Dose–response association with number of births Possible inverse association with age at first birth
Physical activity	Inverse	Dose–response association with activity level
Alcohol consumption	Inverse	Dose–response association with quantity consumed
Trichloroethylene exposure	Positive	Dose–response association with exposure level
Genetic predisposition	Positive	Positive association with a family history of kidney cancer Increased risk of sporadic RCC in genetically susceptible individuals

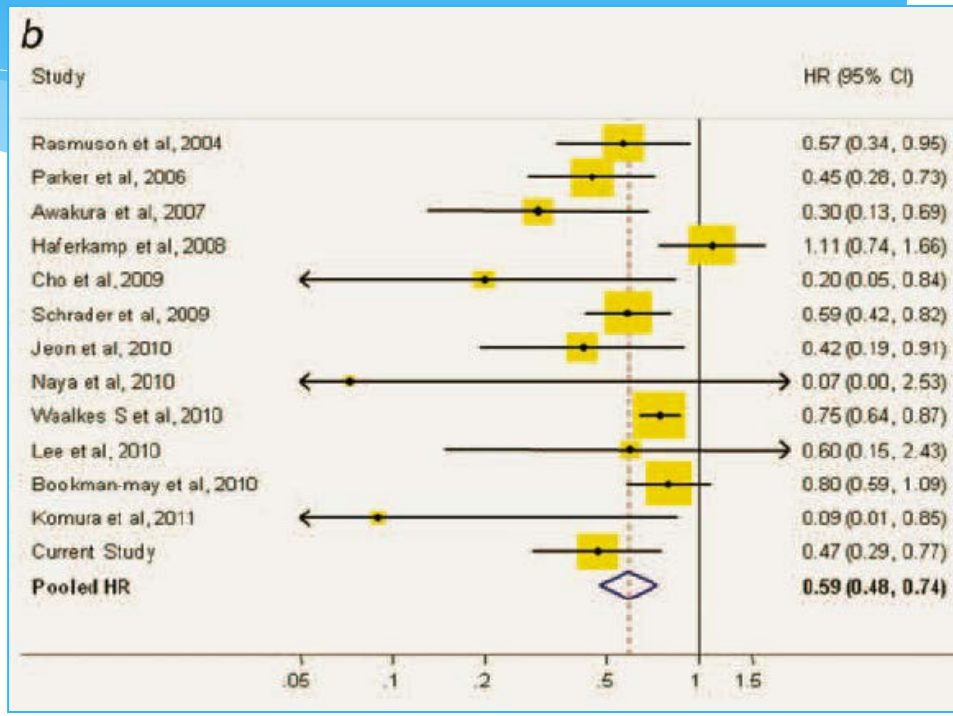
*Observed in nearly all studies; exposure precedes RCC; dose–response relationship; risk reduction with removal of exposure. ‡Observed in numerous studies, but results conflicting; exposure precedes RCC; dose–response relationship; effect independent of known risk factors not established; small number of exposed RCC cases; confounding by heightened clinical surveillance possible; exposure assessment incomplete. Abbreviation: RCC, renal cell carcinoma.

Chow et al Nature Reviews Urology 2010

BMI protective – Meta-analysis



Overall Survival



Cancer Specific Survival

Choi et al *IJC* 2012

Study Design

* 2,119 ccRCC patients who underwent renal mass surgery at MSKCC between 1995 and 2012.
* Logistic regression models produced associations between BMI and advanced disease overall, and in subgroups defined by co-morbidities, presentation, and albumin level.
* Multivariable competing risks regression models estimated associations between BMI and CSM.
* Somatic mutation, copy number, methylation, and expression data were examined by BMI among a subset of 126 patients who participated in TCGA for ccRCC.

Table 1. Characteristics of 2119 ccRCC patients by BMI category.

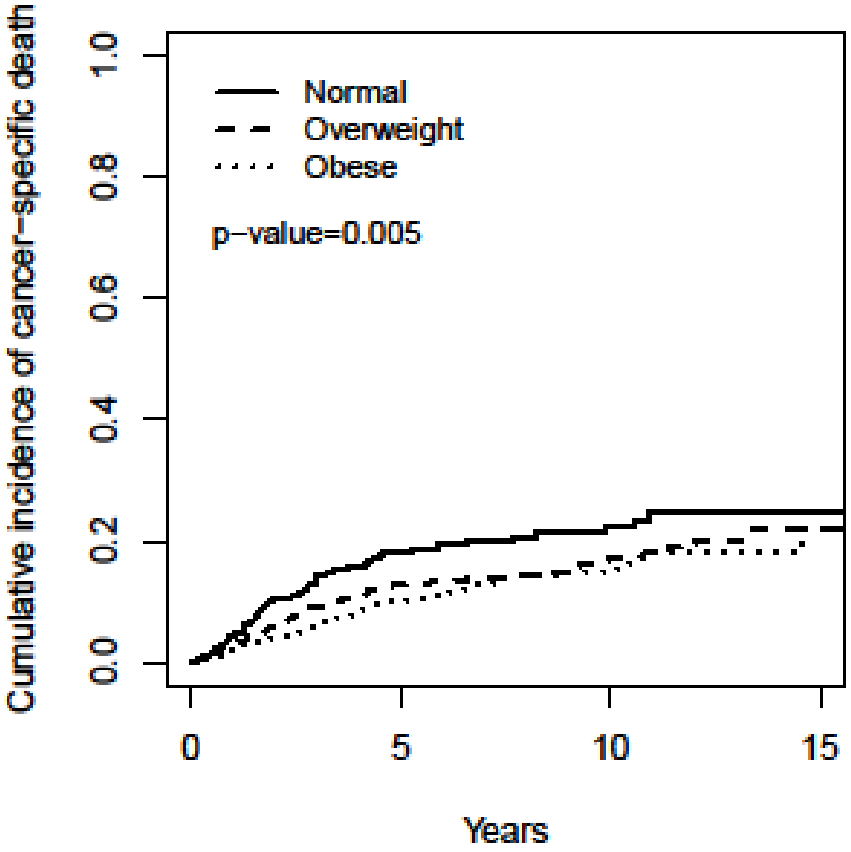
		BMI category			
	Overall n (%)	Normal (n=420;20%)	Overweight (n=806;38%)	Obese (n=893;42%)	p-value[1]
Age (years) Median (IQR)	60.8 (52.1,69.6)	61.4 (51.9, 71.2)	61.5 (53.4, 70.4)	59.8 (51.5, 67.7)	<.001
Sex					<.001
Male	1408 (66.4)	245 (58.3)	587 (72.8)	576 (64.5)	
Female	711 (33.6)	175 (41.7)	219 (27.2)	317 (35.5)	
Race					0.001
White	1935 (91.3)	368 (87.6)	736 (91.3)	831 (93.1)	
Other	164 (7.7)	50 (11.9)	58 (7.2)	56 (6.3)	
Missing	20 (0.9)	2 (0.5)	12 (1.5)	6 (0.7)	
Hypertension					<.001
Yes	1145 (54.0)	164 (39.0)	423 (52.5)	558 (62.5)	
No	974 (46.0)	256 (61.0)	383 (47.5)	335 (37.5)	
Diabetes					<.001
Yes	323 (15.2)	30 (7.1)	119 (14.8)	174 (19.5)	
No	1796 (84.8)	390 (92.9)	687 (85.2)	719 (80.5)	
Hypercholesterolemia					<.001
Yes	616 (29.1)	75 (17.9)	251 (31.1)	290 (32.5)	
No	1503 (70.9)	345 (82.1)	555 (68.9)	603 (67.5)	
CKD stage					0.036
1	300 (14.2)	75 (17.9)	96 (11.9)	129 (14.4)	
2	1149 (54.2)	235 (56.0)	457 (56.7)	457 (51.2)	
3	642 (30.3)	105 (25.0)	245 (30.4)	292 (32.7)	
4	19 (0.9)	3 (0.7)	6 (0.7)	10 (1.1)	
5	3 (0.1)	1 (0.2)	1 (0.1)	1 (0.1)	
Missing	6 (0.3)	1 (0.2)	1 (0.1)	4 (0.4)	
AJCC stage					<.001
1	1325 (62.5)	228 (54.3)	518 (64.3)	579 (64.8)	
2	98 (4.6)	22 (5.2)	35 (4.3)	41 (4.6)	
3	506 (23.9)	114 (27.1)	178 (22.1)	214 (24.0)	
4	188 (8.9)	56 (13.3)	75 (9.3)	57 (6.4)	
Missing	2 (0.1)	0 (0.0)	0 (0.0)	2 (0.2)	
Grade					0.008
1	98 (4.6)	18 (4.3)	35 (4.3)	45 (5.0)	
2	1095 (51.7)	202 (48.1)	426 (52.9)	467 (52.3)	
3	738 (34.8)	144 (34.3)	268 (33.3)	326 (36.5)	
4	170 (8.0)	50 (11.9)	69 (8.6)	51 (5.7)	
Missing	18 (0.8)	6 (1.4)	8 (1.0)	4 (0.4)	

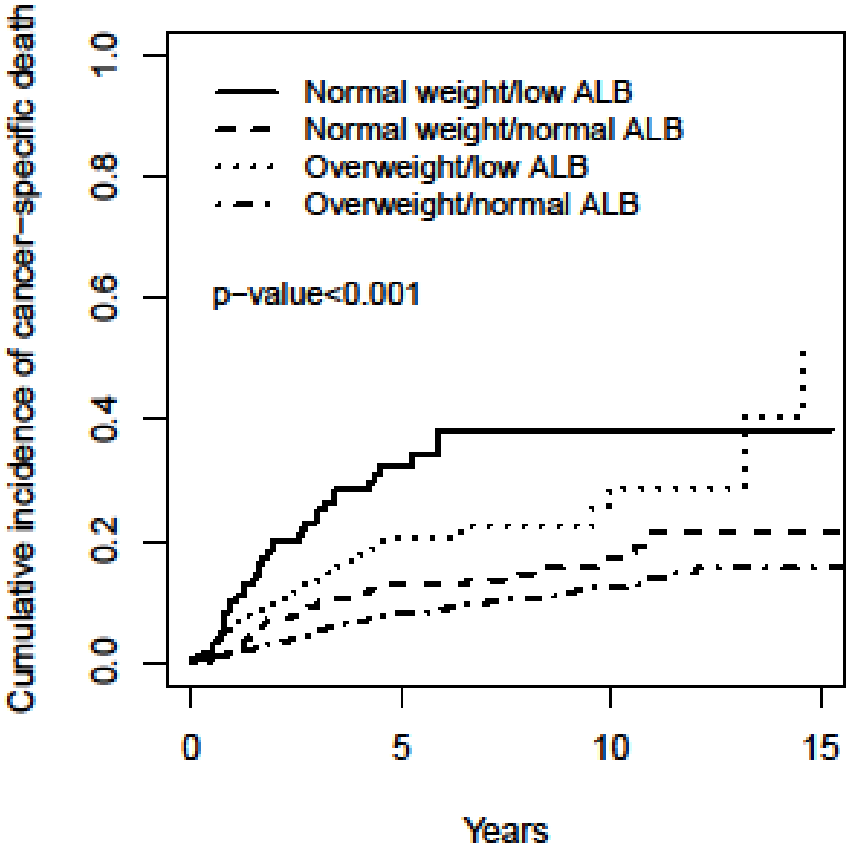
Table 3. Multivariable competing risks regression for the association between BMI and cancer-specific death.

	Before adjustment for stage and grade		After adjustment for stage and grade	
	HR (95% CI)[1]	**p-value**	**HR (95% CI)[1]**	**p-value**
BMI		0.011		0.130
Normal	1.0 (reference)		1.0 (reference)	
Overweight	0.73 (0.53 - 1.02)		1.02 (0.72 - 1.46)	0.910
Obese	0.59 (0.42 - 0.83)		0.75 (0.53 - 1.07)	0.120
Age at surgery	1.01 (1.00 - 1.02)	0.026	1.00 (0.99 - 1.01)	0.930
Sex		0.002		0.940
Male	1.0 (reference)		1.0 (reference)	
Female	0.61 (0.45 - 0.83)		1.01 (0.74 - 1.39)	
Race		0.120		0.063
White	1.0 (reference)		1.0 (reference)	
Other	0.61 (0.32 - 1.15)		0.53 (0.28 - 1.04)	
AJCC stage				<.001
1-2	---	---	1.0 (reference)	
3-4	---	---	7.47 (5.2 - 10.73)	
Grade				<.001
1-2	---	---	1.0 (reference)	
3-4	---	---	3.70 (2.62 - 5.23)	
Hypertension		0.053		0.014
Yes	0.75 (0.56 - 1.00)		0.69 (0.51 - 0.93)	
No	1.0 (reference)		1.0 (reference)	
Hypercholesterolemia		0.120		0.056
Yes	0.76 (0.54 - 1.08)		0.71 (0.50 - 1.01)	
No	1.0 (reference)		1.0 (reference)	
Albumin		<.001		0.011
<4 g/dL	2.71 (2.07 - 3.54)		1.45 (1.09 - 1.94)	
≥4 g/dL	1.0 (reference)		1.0 (reference)	

[1] Hazard ratio (HR) and 95% confidence interval (CI)

Protective Effect of BMI is Maintained Even in Poor Nutritional States





BMI – Epidemiologic Conclusions

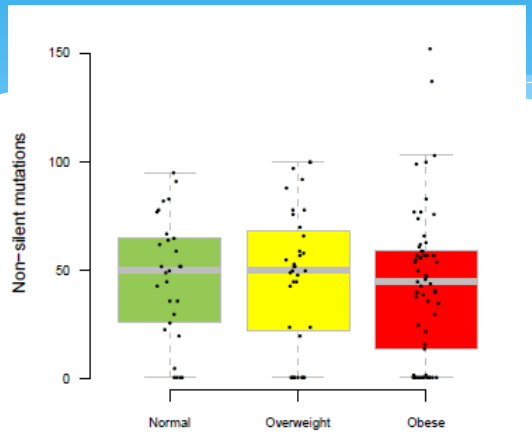
* Independent predictor of lower stage and possibly lower grade disease
* Univariately predicts betters survival independent of other confounding factors such as screening, or symptoms, but is related to nutritional status (alb)
* Suggests independent protective biological effect

Genomic Interrogation

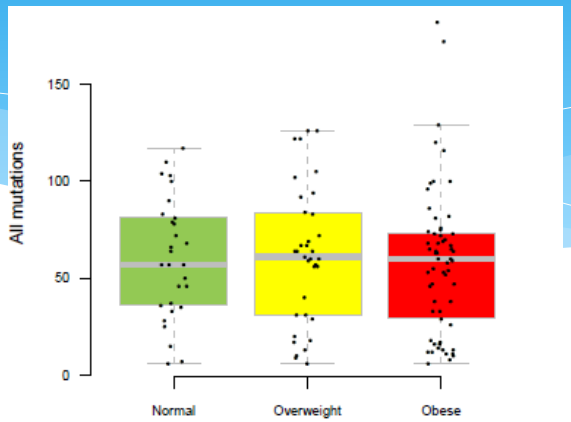
* Utilized 126 patients from the same cohort that were analyzed as part of TCGA
* Assessed impact of BMI classes on:
  * Mutations (global, and recurrent)
  * Copy number events (global and focal)
  * DNA promoter methylation
  * mRNA expression
* Performed pathway analysis of genes differentially expressed in the obese vs normal weight cohorts

Mutations

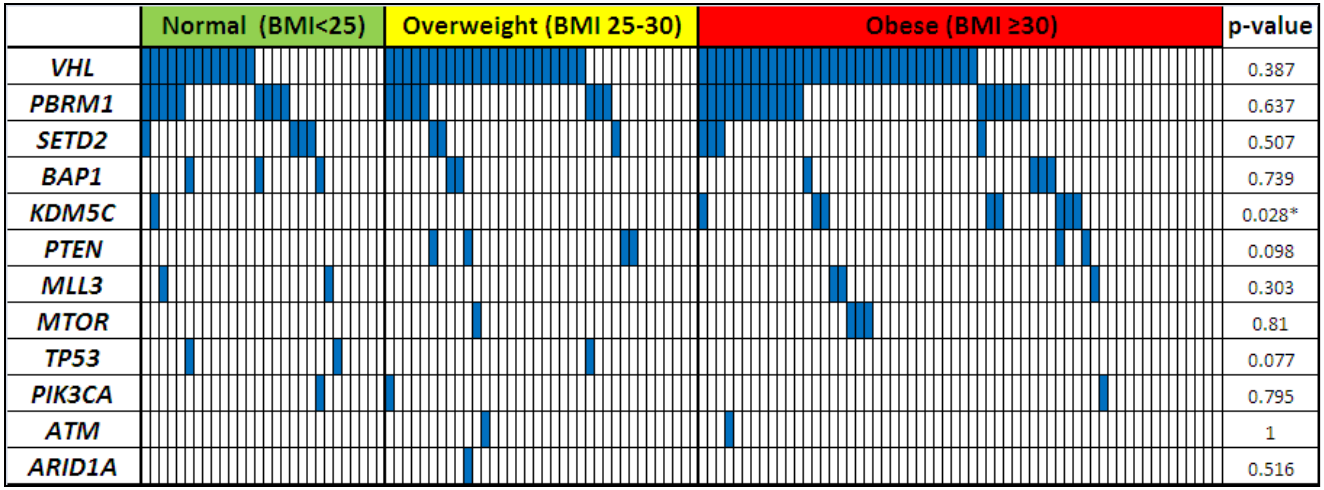
Non-Silent Mutations



All Mutations

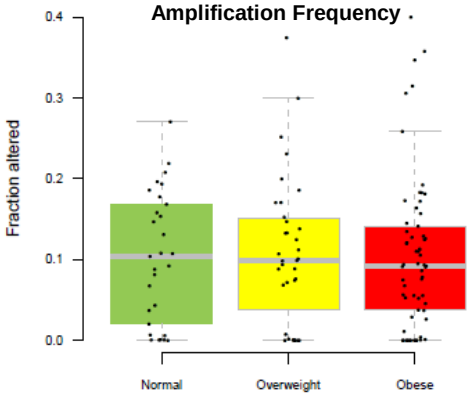


Recurrent Mutations



Hakimi et al JNCI 2013

Copy Number Alterations



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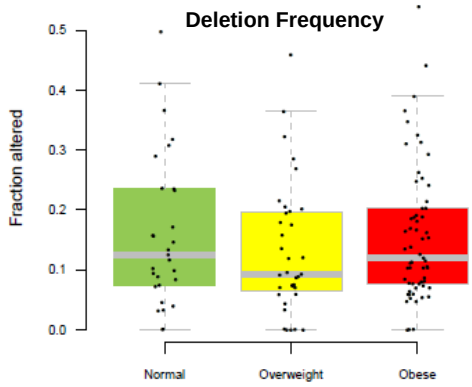


p=0.520

Rank	Chromosomal Region	Type	p-value	q-value	Enriched Set	Normal Wt [29]	Overweight [36]	Obese [61]	Sum
1	chr6:101061826-101437413	LOSS	0.06643211	0.23699619	Normal Wt	11	10	11	32
2	chr14:77938161-79403317	LOSS	0.07899873	0.23699619	Normal Wt	16	12	25	53
3	chr14:66040780-66719847	LOSS	0.07899873	0.23699619	Normal Wt	16	12	25	53
4	chr6:161687527-163072553	LOSS	0.12497824	0.26271668	Normal Wt	11	9	15	35
5	chr9:21953430-21986996	LOSS	0.1479589	0.26271668	Overweight	12	15	15	42
6	chr9:8302601-10625939	LOSS	0.17514446	0.26271668	Normal Wt	12	14	15	41
7	chr3:59707051-61212438	LOSS	0.30645927	0.36648218	Overweight	23	28	51	102
8	chr3:124266643-124363799	LOSS	0.32576194	0.36648218	Normal Wt	9	6	18	33
9	chr3:10157562-10170674	LOSS	0.44701889	0.44701889	Normal Wt	27	31	56	114

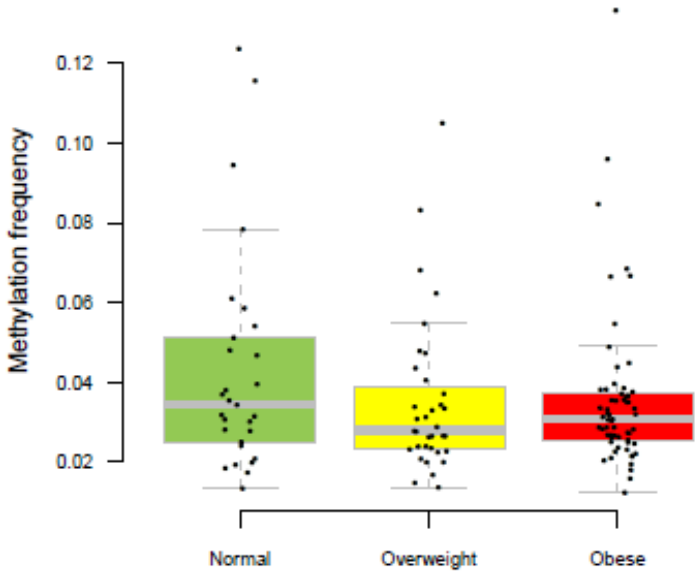
Rank	Chromosomal Region	Type	p-value	q-value	Enriched Set	Normal Wt [29]	Overweight [36]	Obese [61]	Sum
1	chr7:68848460-155095928	GAIN	0.0159947	0.03198939	Normal Wt	17	13	20	50
2	chr5:180465596-180539171	GAIN	0.46834879	0.46834879	Overweight	18	25	42	85

Rank	Chromosomal Region	Type	p-value	q-value	Enriched Set	Normal Wt [29]	Overweight [36]	Obese [61]	Sum
1	chr5:180465596-180539171	AMP	0.21507666	0.49142857	Obese	1	2	6	9
2	chr3:179603177-179637729	AMP	0.4087619	0.49142857	Normal Wt	1	0	1	2
3	chr2:163524241-212418042	AMP	0.49142857	0.49142857	Overweight	0	1	1	2

Rank	Chromosomal Region	Type	p-value	q-value	Enriched Set	Normal Wt [29]	Overweight [36]	Obese [61]	Sum
1	chr3:59707051-61212438	DEL	0.19612903	0.39225806	Overweight	0	2	1	3
2	chr3:10157562-10170674	DEL	0.49142857	0.49142857	Overweight	0	1	1	2

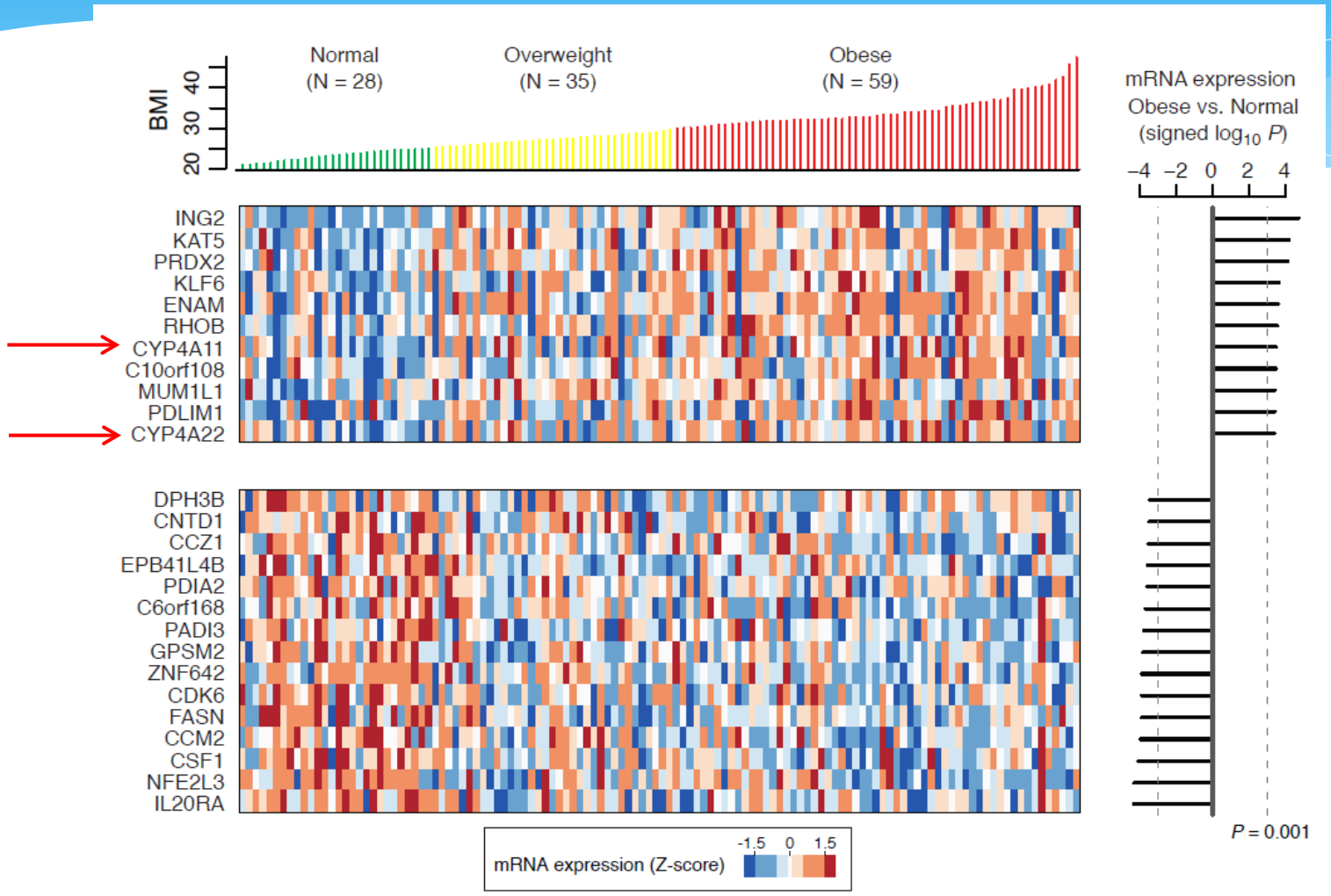
Global DNA Methylation

Hypermethylation Frequency

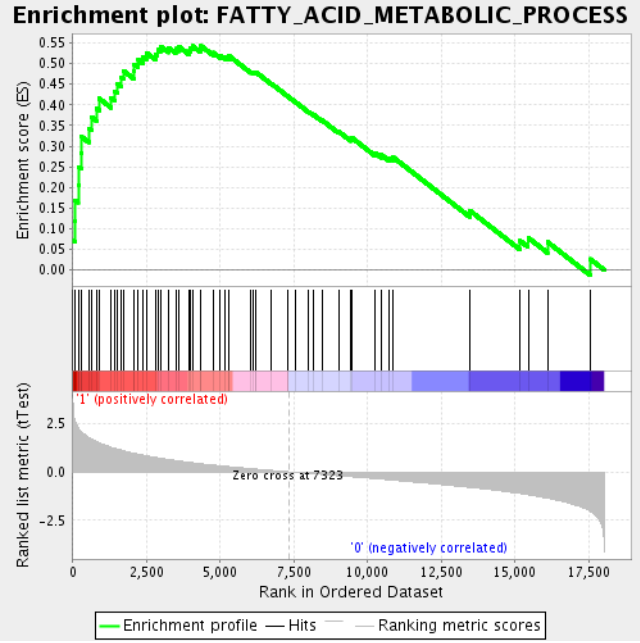


p=0.391

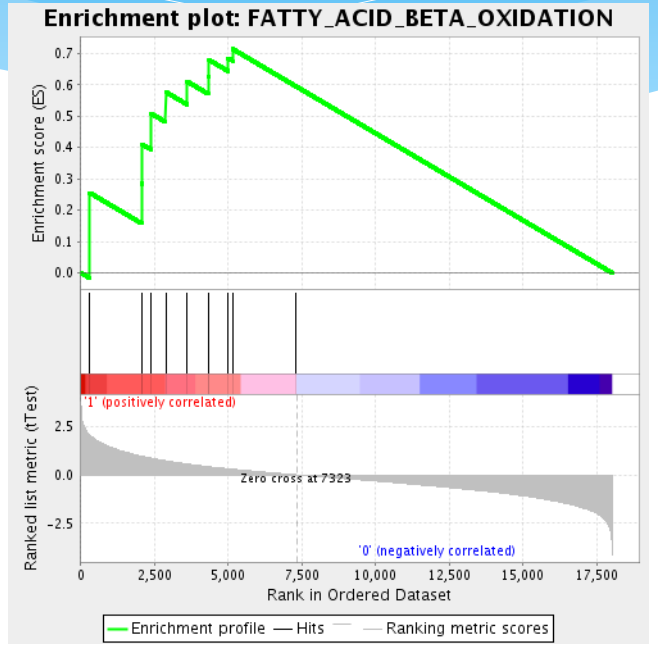
mRNA expression



Fatty Acid Metabolism and Beta-Oxidation Enriched in Obese

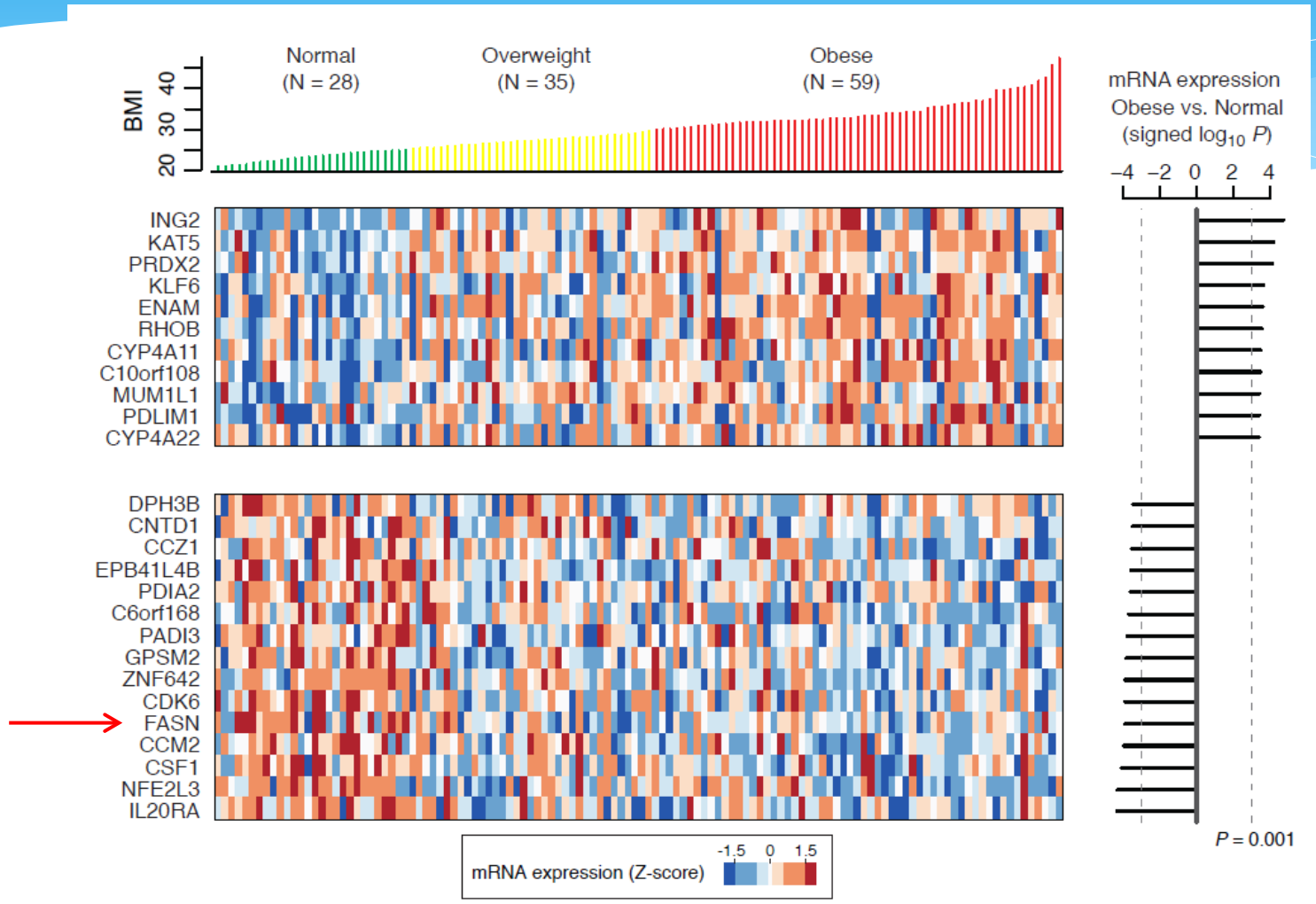


Ranked 8 out of 5,332 gene sets



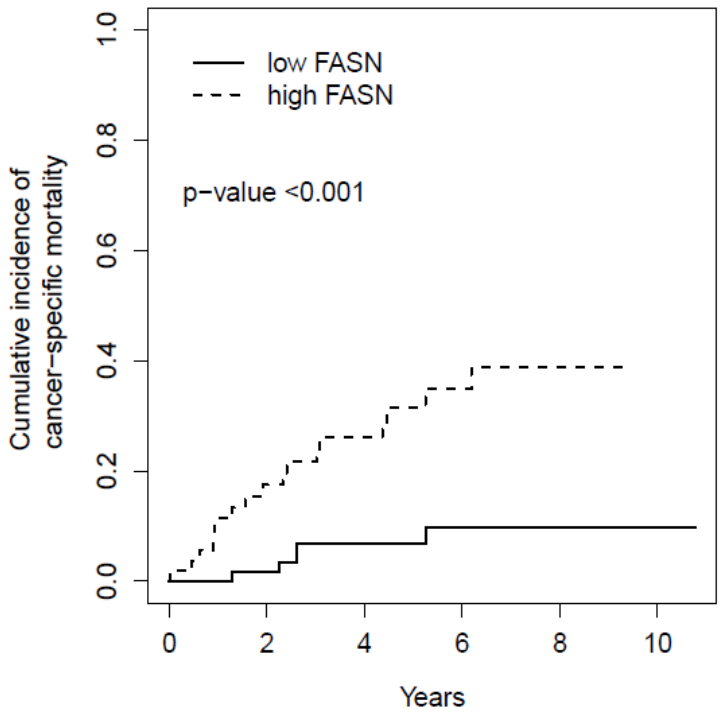
Ranked 12 out of 5,332 gene sets

FASN Downregulated in Obese

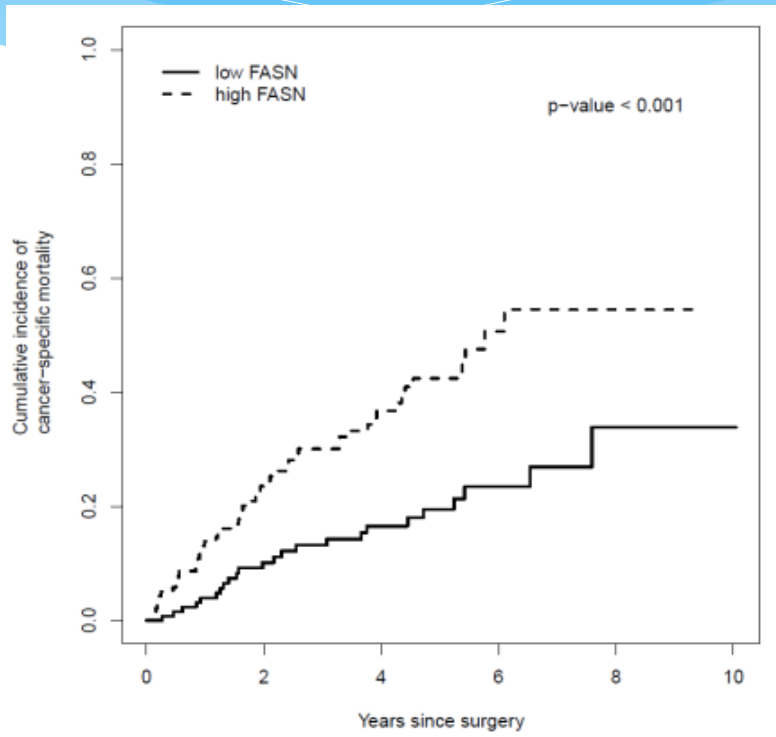


FASN Upregulation = Poor Prognosis

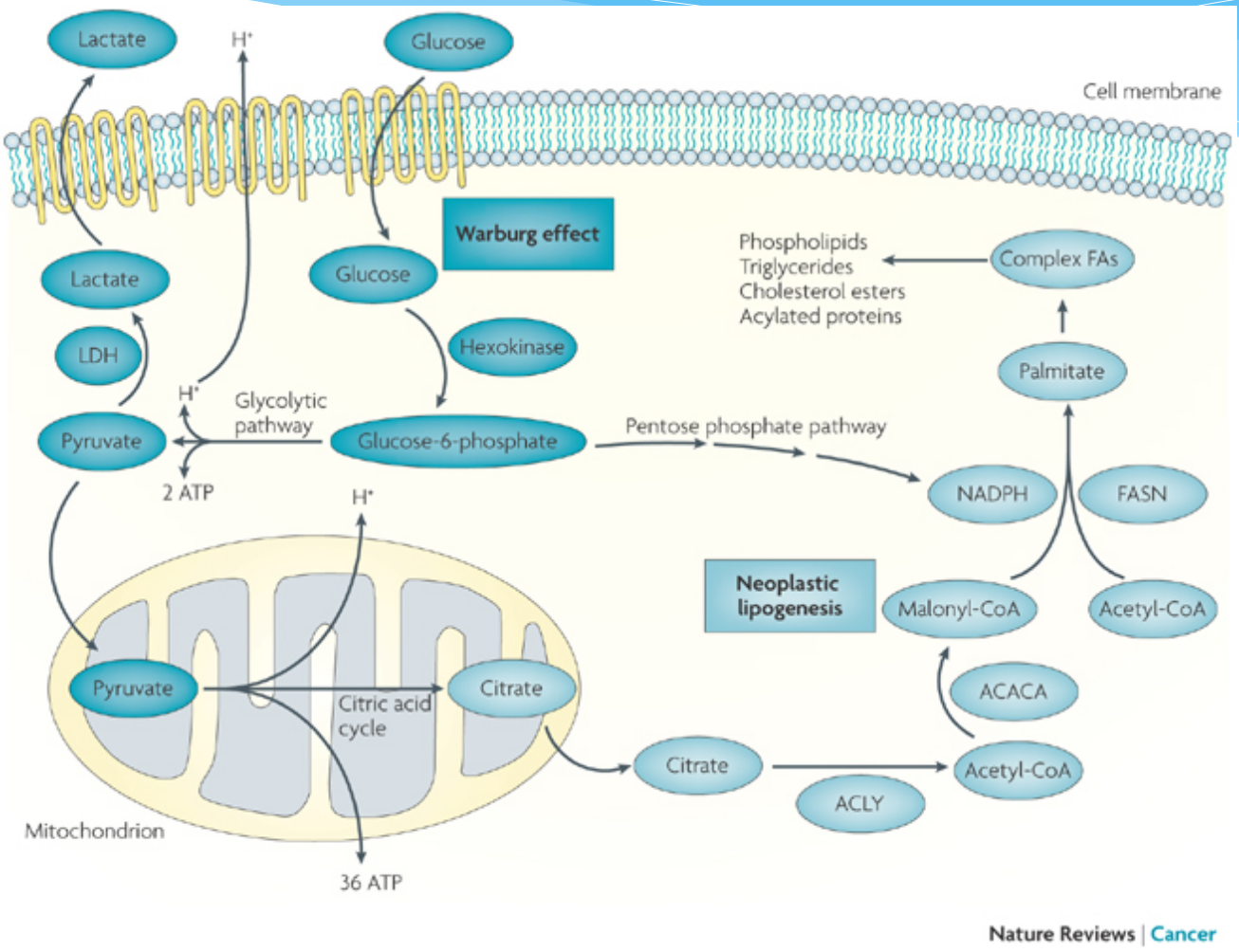
MSK TCGA Cohort (n=122)



Remaining TCGA Cohort (n=275)



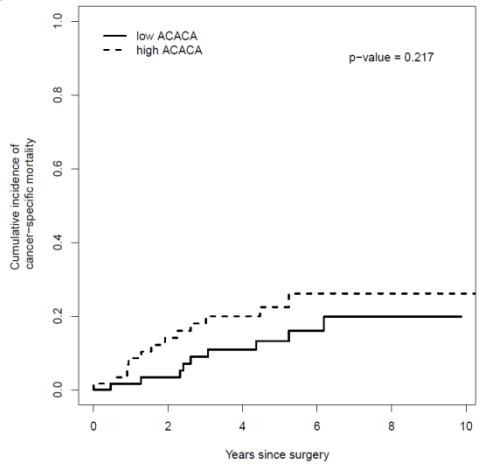
FASN's Role in Neoplastic Lipogenesis

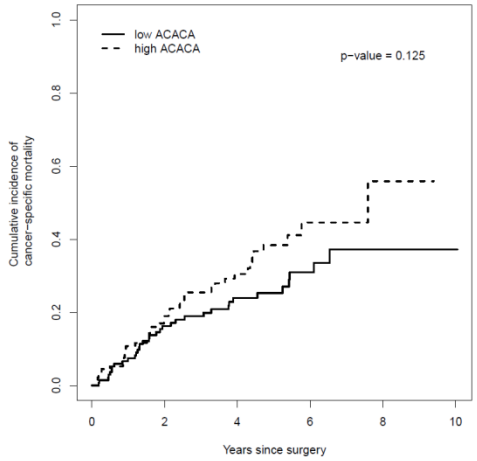


FASN Upregulation in Cancer

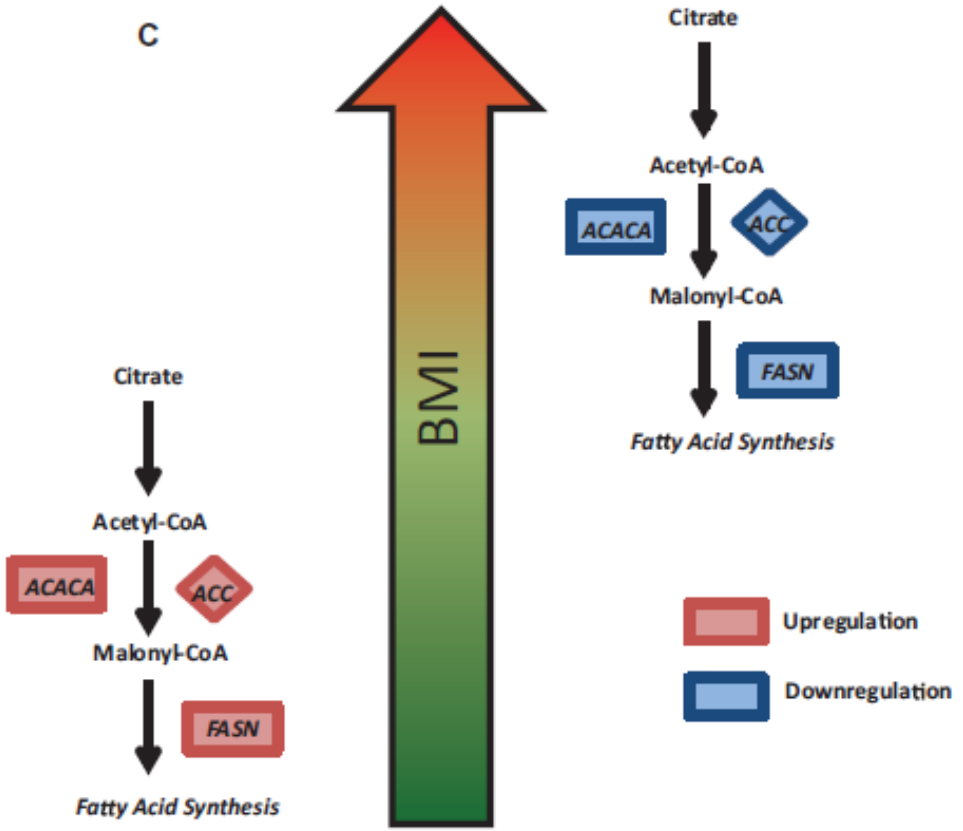
* *FASN* overexpression assessed by IHC associated with aggressive RCC and shorter cancer-specific survival, and that pharmacological inhibition of *FASN* can reduce RCC tumor growth in vitro (J Urol 2008).
* Lower expression of *FASN* among obese colorectal cancer patients from the Nurses' Health Study (JNCI 2012)
* Other studies among colorectal and prostate cancer patients suggest that the adverse impact of *FASN* overexpression is limited to obese patients (JCO 2008, 2010)

ACACA and *FASN*: Interaction with BMI and Survival





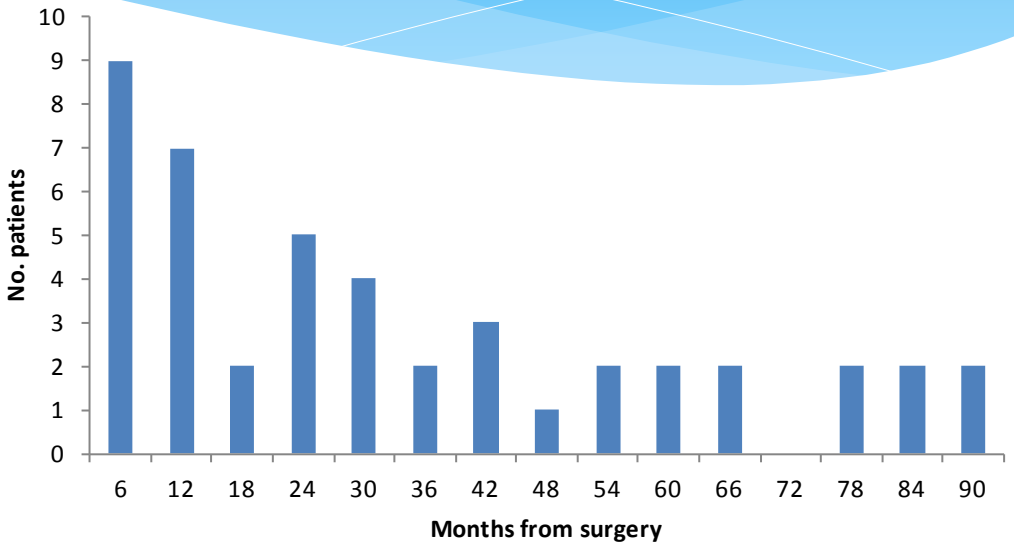
Better Survival



Insights into Metastatic Disease

Number and Timing

Table 1 - Number and Timing of Metastatic Cases		
Metastatic Disease	Yes	123
	No	219
Time Categories	Presentation	75
	During FU < 1 year	17
	During FU > 1 year	31
Multiple Metatstic Sites at Presentation	Yes	30
	No	45
Multiple Metatstic Sites Overall	Yes	78
	No	45

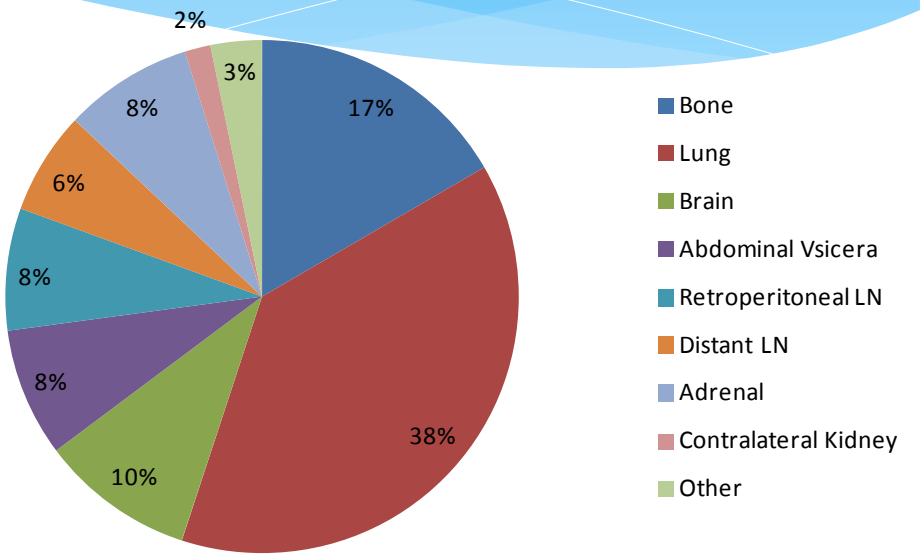


Location

Table 2 - Location of Metastatic Disease

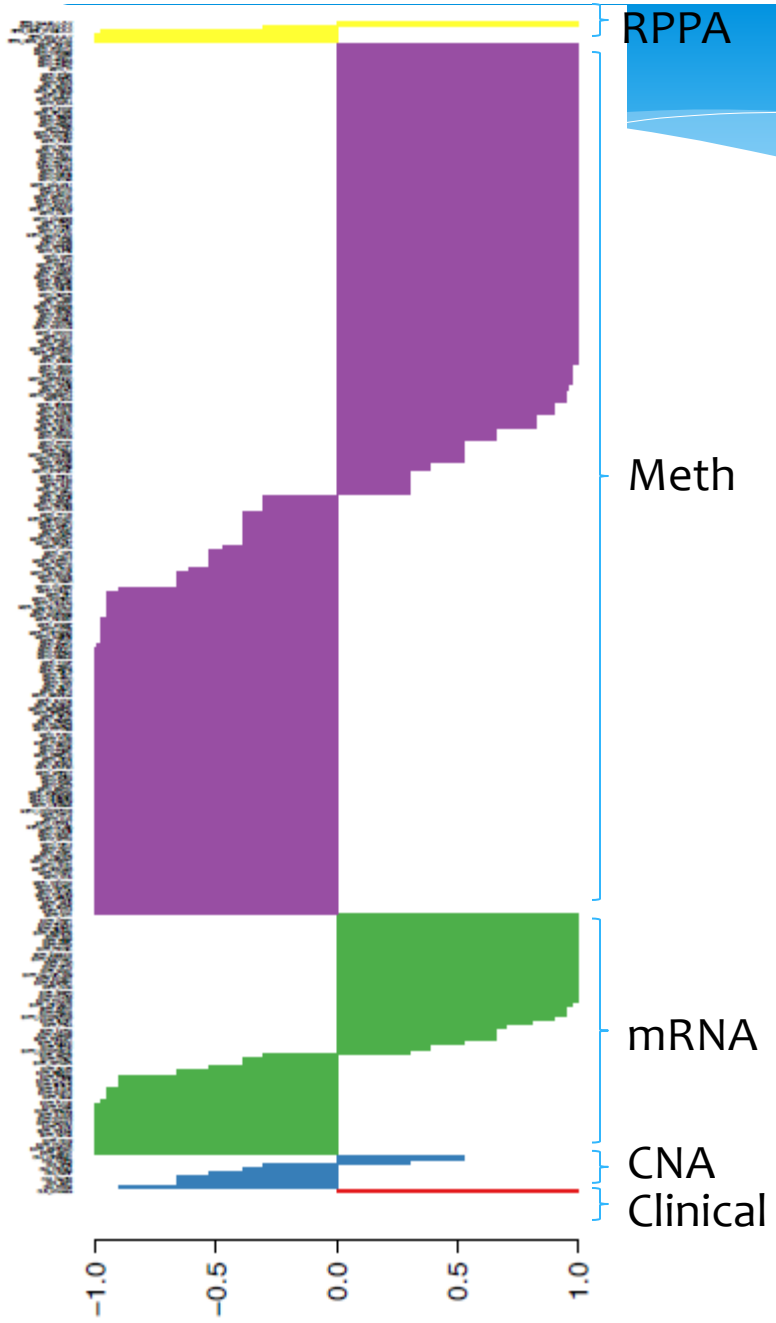
	At presentation	**Overall**
Bone	22	41
Lung	52	95
Brain	6	24
Abdominal Vsicera	8	20
Retroperitoneal LN	5	19
Distant LN	9	16
Adrenal	9	20
Contralateral Kidney	1	4
Other	4	8

Figure 2 - Overall percent of patients with metastatic disease according to location

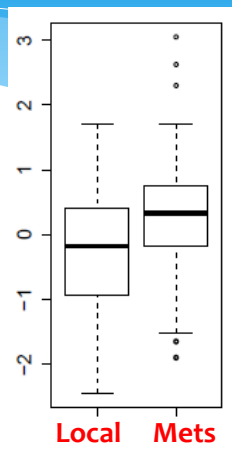


Treatment Information

Dana Farber Cancer Institute							
Pt	**TCGA pt ID #**	**1st line**	**2nd line**	**3rd line**	**4th line**	**5th line**	**6th line**
1	TCGA-CZ-4858	Sunitinib					
2	TCGA-CZ-4860	Sorafenib	Sunitinib				
3	TCGA-CZ-4861	Sorafenib					
4	TCGA-CZ-5454	Sunitinib	Sorafenib	Temsirolimus	Bevacizumab	Sunitinib	
5	TCGA-CZ-5455	Sunitinib					
6	TCGA-CZ-5456	Pazopanib	Sorafenib				
7	TCGA-CZ-5458	Sut/soraf					
8	TCGA-CZ-5461	Sunitinib	Temsirolimus				
9	TCGA-CZ-5462	Sunitinib					
10	TCGA-CZ-5464	Sunitinib	IMC-1121B	Temsirolimus	Sorafenib	Everolimus	Pazopanib
11	TCGA-CZ-5469	Sunitinib	Tem + bev	Pazopanib	Sorafenib		
12	TCGA-CZ-5987	Sunitinib					
Memorial Sloan-Kettering Cancer Center							
Pt	**TCGA pt ID #**	**1st line**	**2nd line**	**3rd line**	**4th line**	**5th line**	**6th line**
1	TCGA-BP-4354	Sunitinib+geftinib	Sunitinib	Sorafenib	Temsirolimus		
2	TCGA-BP-4169	Axitinib					
3	TCGA-BP-4338	Sunitinib	Sorafenib	Everolimus			
4	TCGA-BP-4985	Sunitinib					
5	TCGA-BP-4165	Sunitinib	Bevacizumab	Sorafenib			
6	TCGA-BP-4329	Temsirolimus					
7	TCGA-BP-4804	Sunitinib					
8	TCGA-BP-4352	Sunitinib					
9	TCGA-BP-4974	Sunitinib	Sorafenib				
10	TCGA-BP-4787	Sunitinib	Sorafenib	Temsirolimus			
11	TCGA-BP-5009	Sunitinib	Everolimus	RAD/bev(OSH)	pazo(OSH)		
12	TCGA-BP-5189	Temsirolimus	Bevacizumab				
University of North Carolina							
Pt	**TCGA pt ID #**	**1st line**	**2nd line**	**3rd line**	**4th line**	**5th line**	**6th line**
1	TCGA-B8-4153	Pazopanib	N/A				
2	TCGA-B8-5162	Sunitinib	N/A				



Cav1 RPPA



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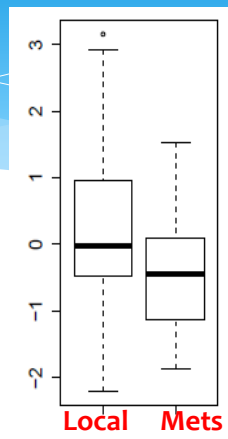
HER2 RPPA



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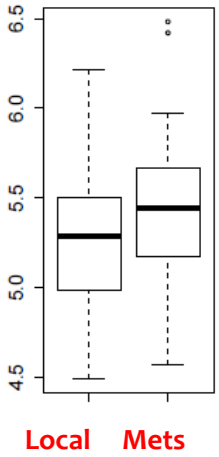

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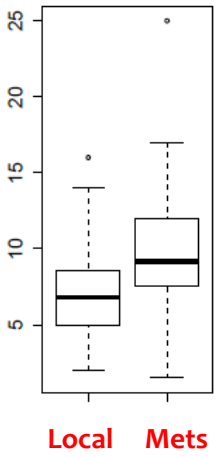
Tumor Size



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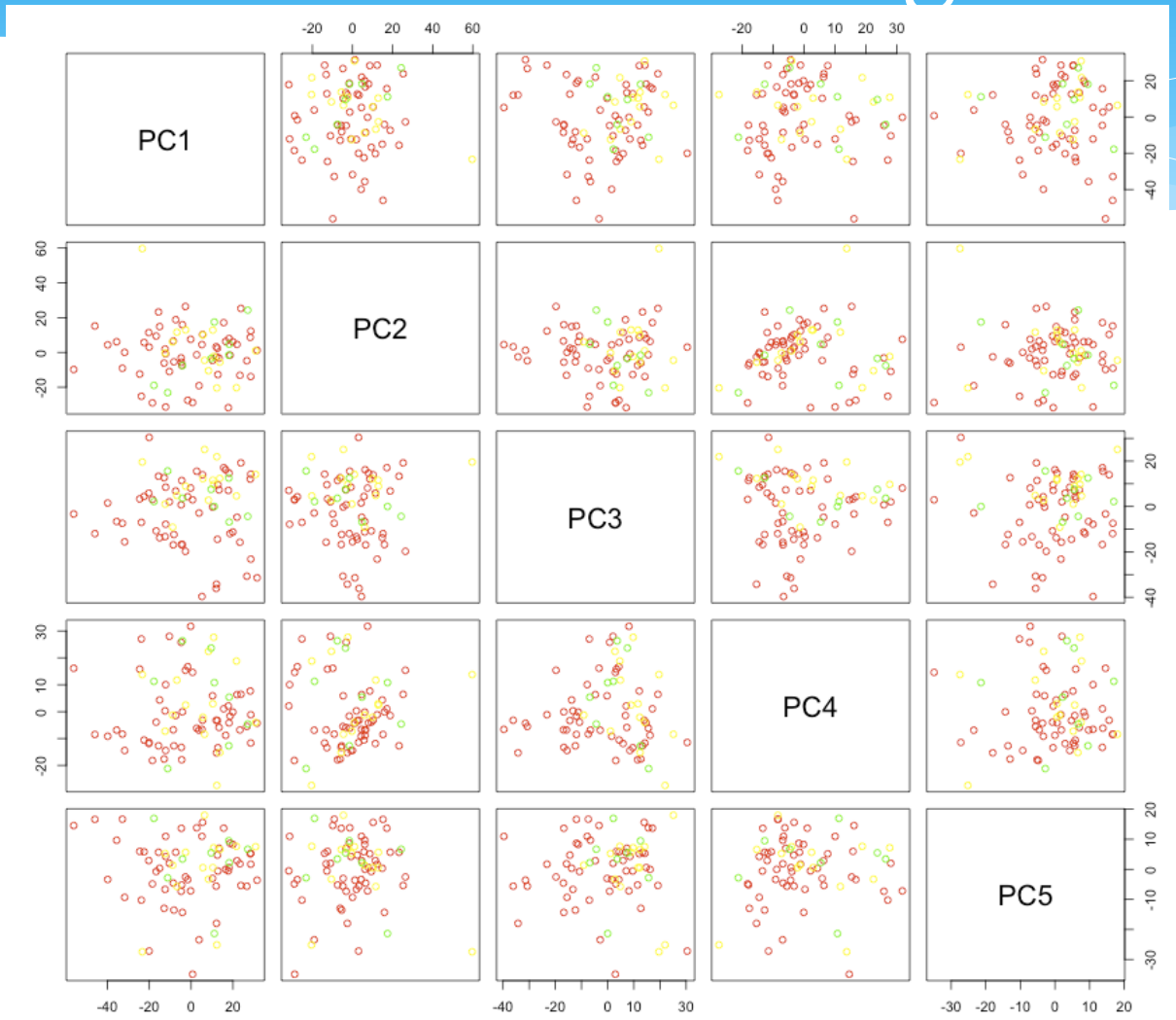
Methylation Groups by Metastatic Timing



Computational Algorithms

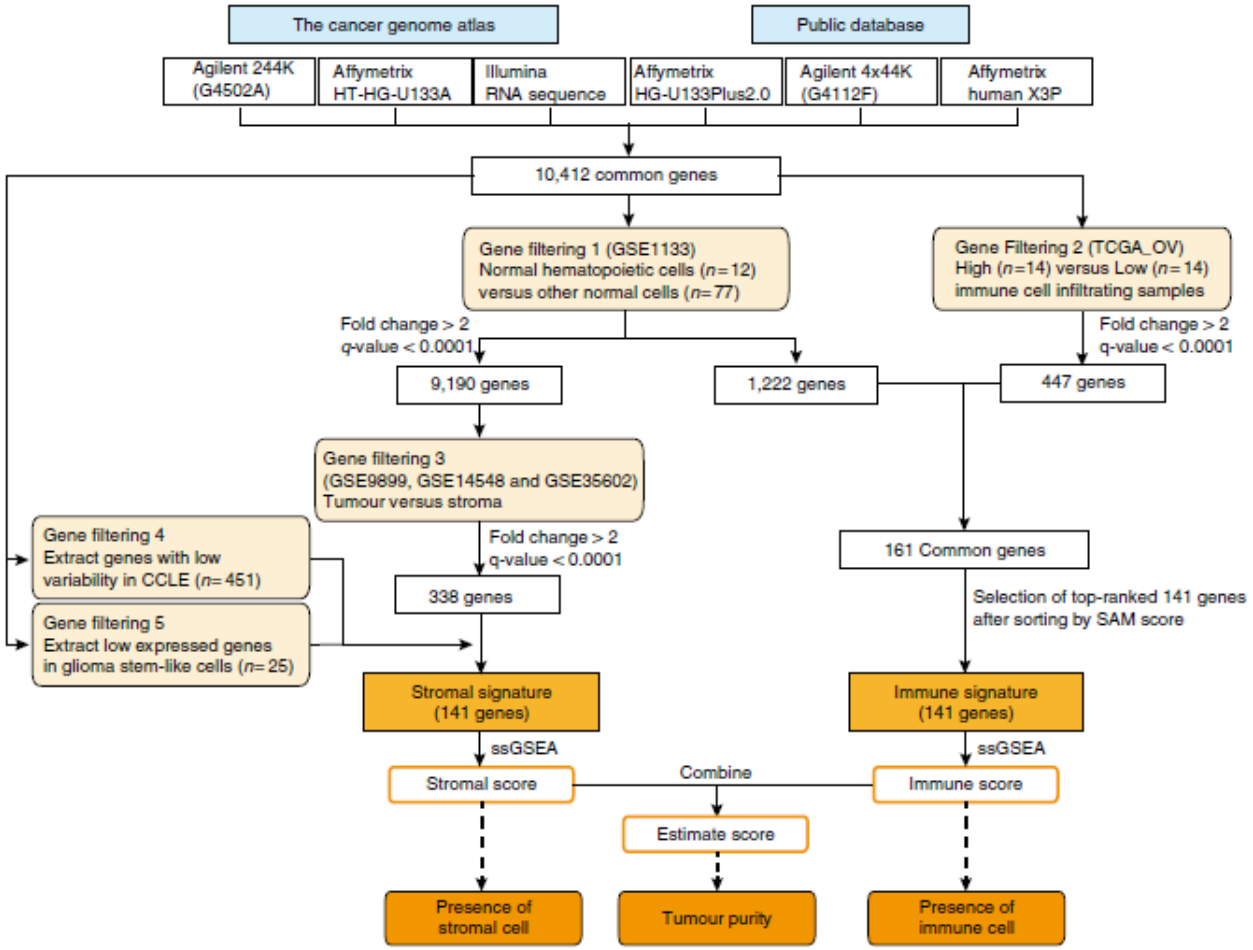


Figure 1 | An overview of the ESTIMATE algorithm. The ESTIMATE algorithm uses gene expression data to output the estimated levels of infiltrating stromal and immune cells and estimated tumour purity. Infiltrating stromal- and immune cell-related genes were identified by five gene filterings.

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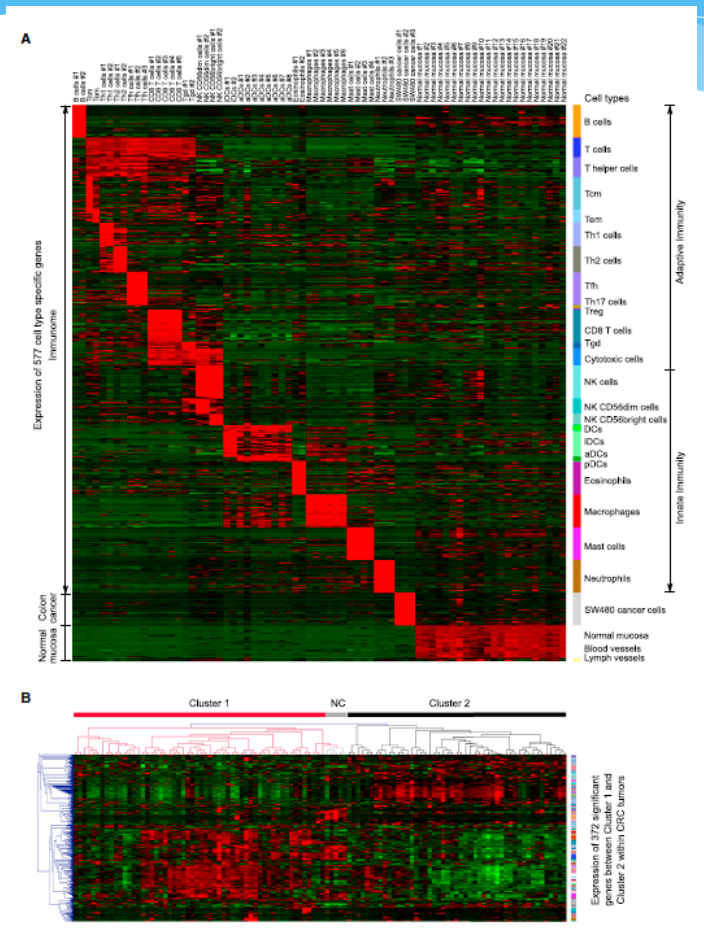

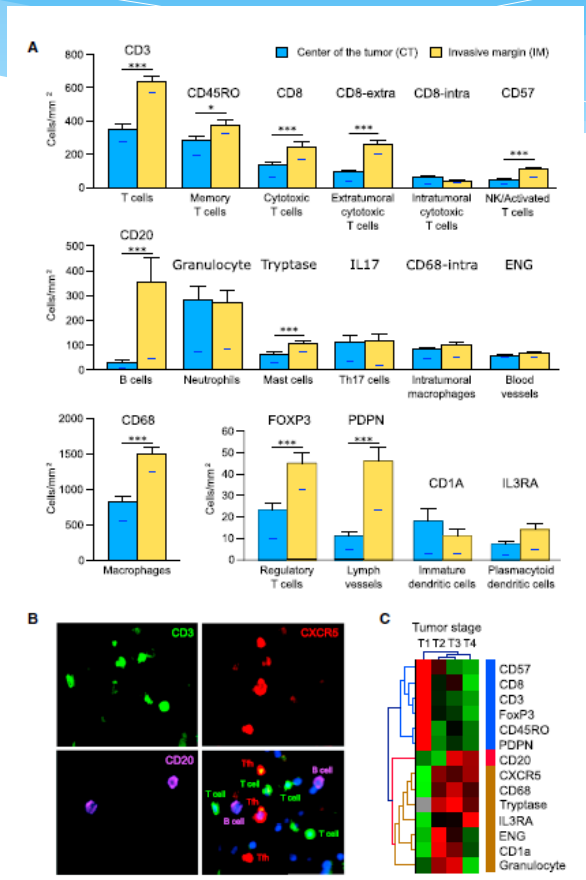

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cTCGA - Conclusions

* cTCGA Consortiums can provide powerful insights into clinical and epidemiologic phenomena
* The rich genomic information can serve as discovery sets for targeted validation in larger clinical cohorts
* Collaborative infrastructures are critical to make significant advances