Princess Margaret Cancer Centre's Experiences with Blood-based and Breath-based Analyses of Mesotheliomas

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Princess Margaret Cancer Centre UHN

Disclosures

Honoraria, Advisory Boards

- Pfizer
- Novartis
- Takeda
- Roche
- Abbvie
- Merck
- Bristol Myers Squibb
- AstraZeneca
- Bayer

Speaking Engagements

- EMD Serono
- AstraZeneca

Research Grants

- CIHR
- CCSRI
- NCI (US) and NIDCR (US)
- AstraZeneca
- Takeda

Inpatients

My lab

Outpatients

Radiation

Recruit-ment

- Identification
- Approaching
- Consenting
- Logging

Data collection

- Demographics
- Patient-Repoted Questionnaire
- Preferences
- Data abstraction

Samples

- Blood Collection, processing, storage
- Tumour and Nomal tissu
- Xenografting

Outcomes

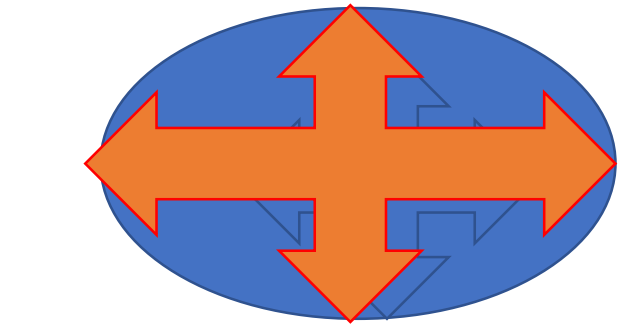
- Cancer Registry
- Physician Contact
- Chart Review
- Patient/Family contact

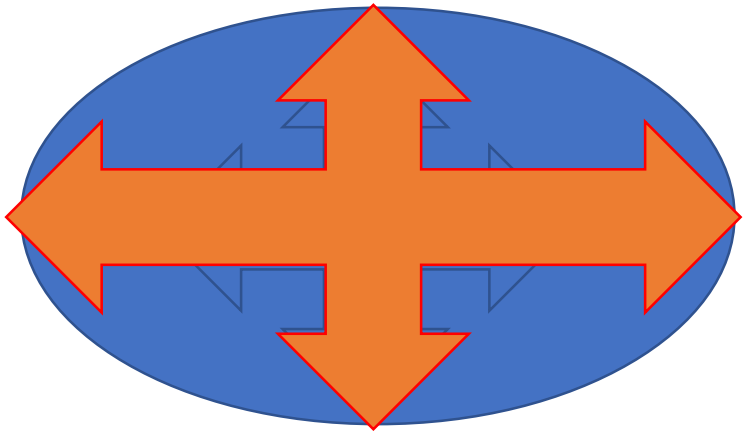
Biomarker Studies

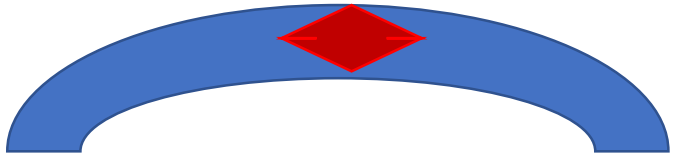
- Surrogate seromarker of bulk of disease (monitoring)
- Diagnostic seromarker
- Prognostic seromarker
- Etiological serobiomarker
- New and emerging breath biomarkers

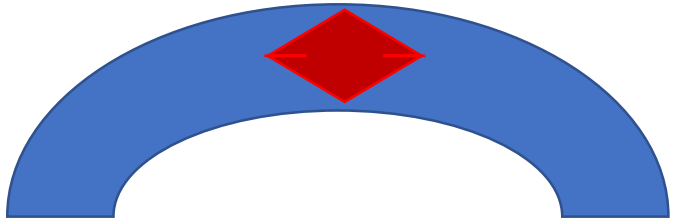
- Serial plasma/serum/whole blood collection for ~150 mesothelioma patients
- Pre-treatment blood sampling for ~50 more mesotheliomas
- One time collection (any time point) for ~80 more mesotheliomas
- One time or serial sampling for ~500 asbestos exposed individuals with negative CT scans for mesothelioma (screened participants)

Rationale: Mesothelioma growth patterns



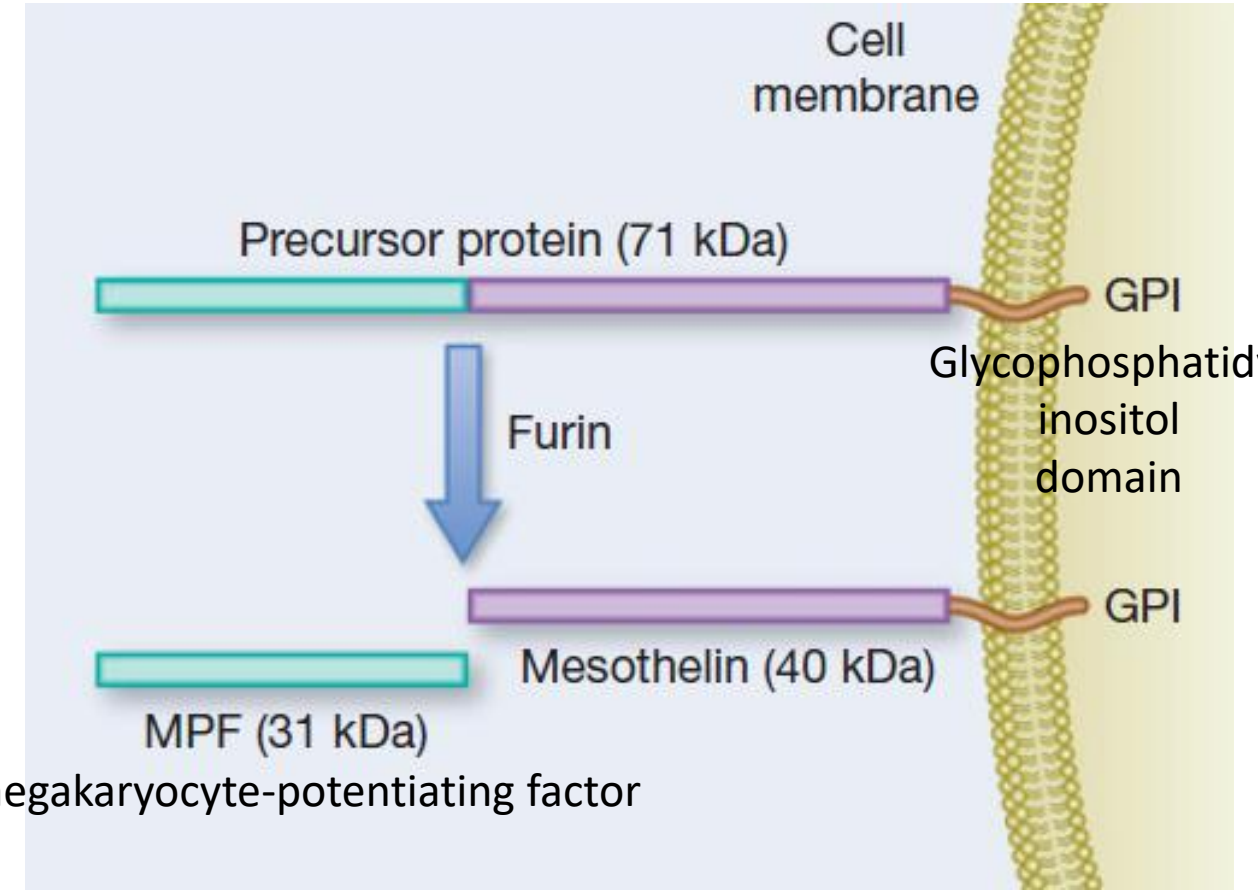






Mesothelin

- tumour differentiation antigen
- normally present on the mesothelial cells
- highly expressed in several human cancers including malignant mesothelioma, pancreatic, ovarian and lung adenocarcinoma.



Mesothelin as a surrogate of bulk disease

Soluble Mesothelin-Related Peptide and Osteopontin As Markers of Response in Malignant Mesothelioma

Paul Wheatley-Price, Boming Yang, Demetris Patsios, Devalben Patel, Clement Ma, Wei Xu, Natasha Leighl, Ronald Feld, B.C. John Cho, Brenda O'Sullivan, Heidi Roberts, Ming Sound Tsao, Martin Tammemagi, Masaki Anraku, Zhuo Chen, Marc de Perrot, and Geoffrey Liu

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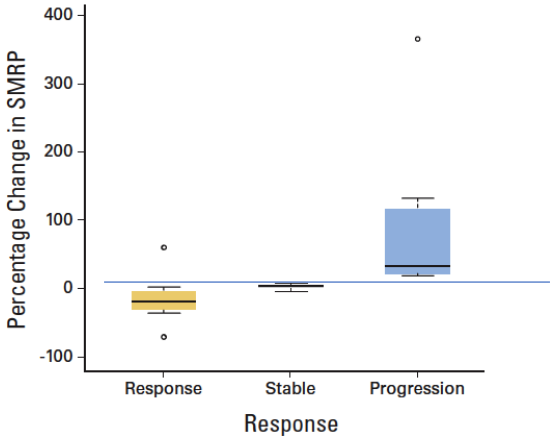
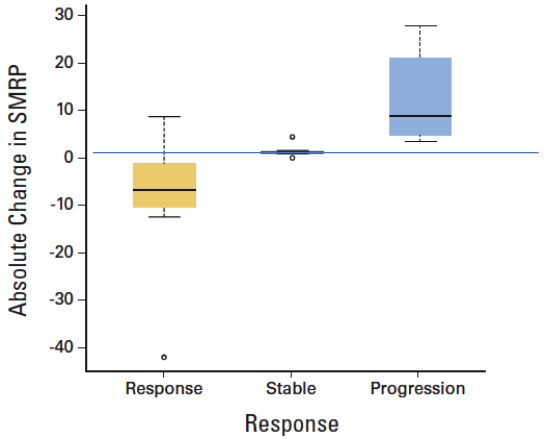
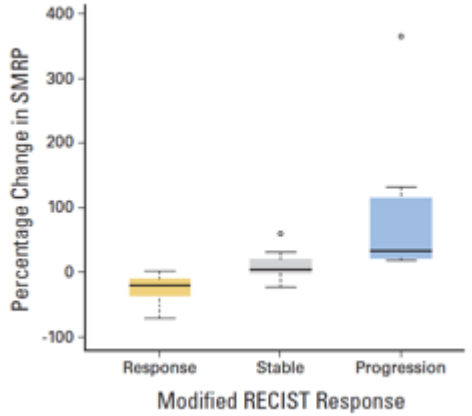
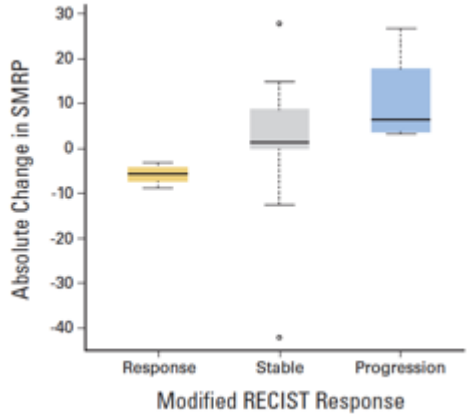
Correlations between sMRP and blinded descriptive assessment



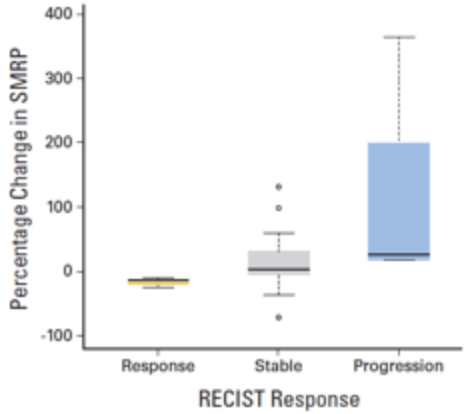


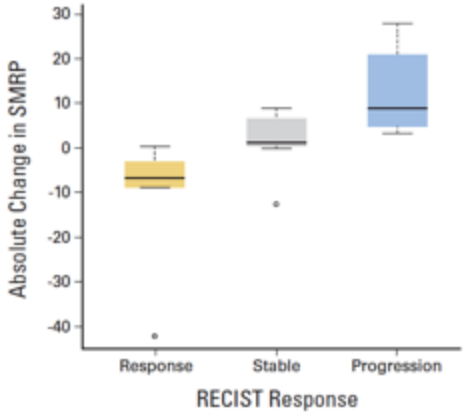
Correlations between sMRP and modified RECIST response criteria

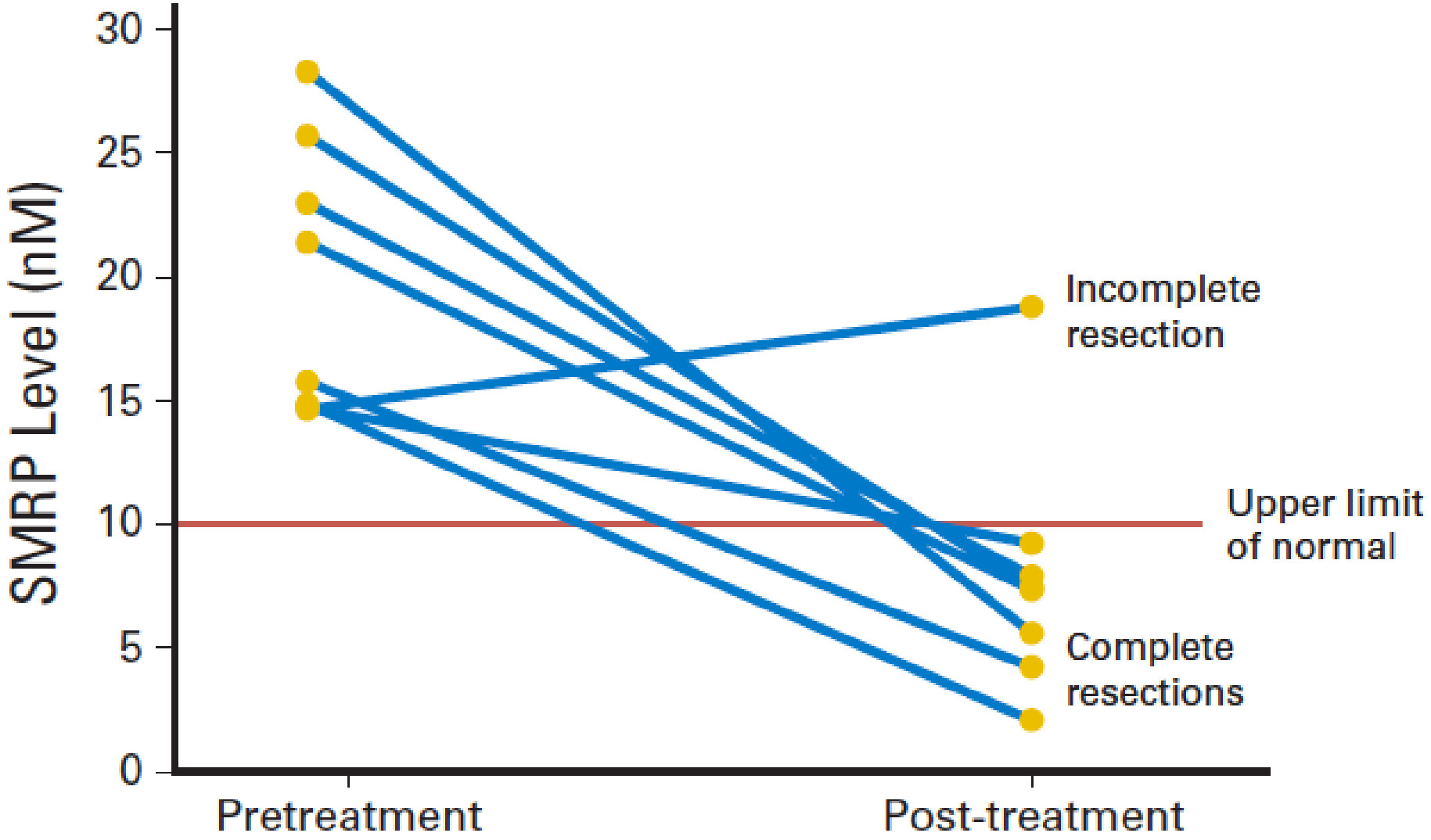




Correlations between sMRP and standard RECIST response criteria

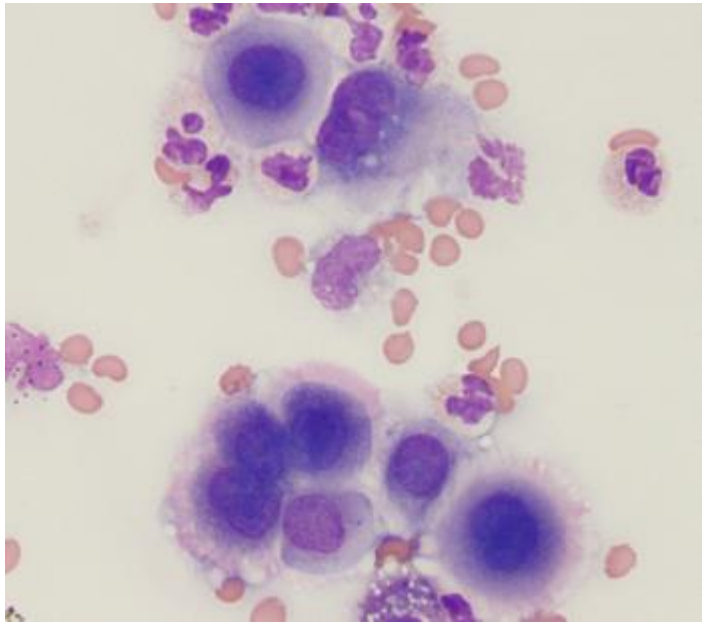




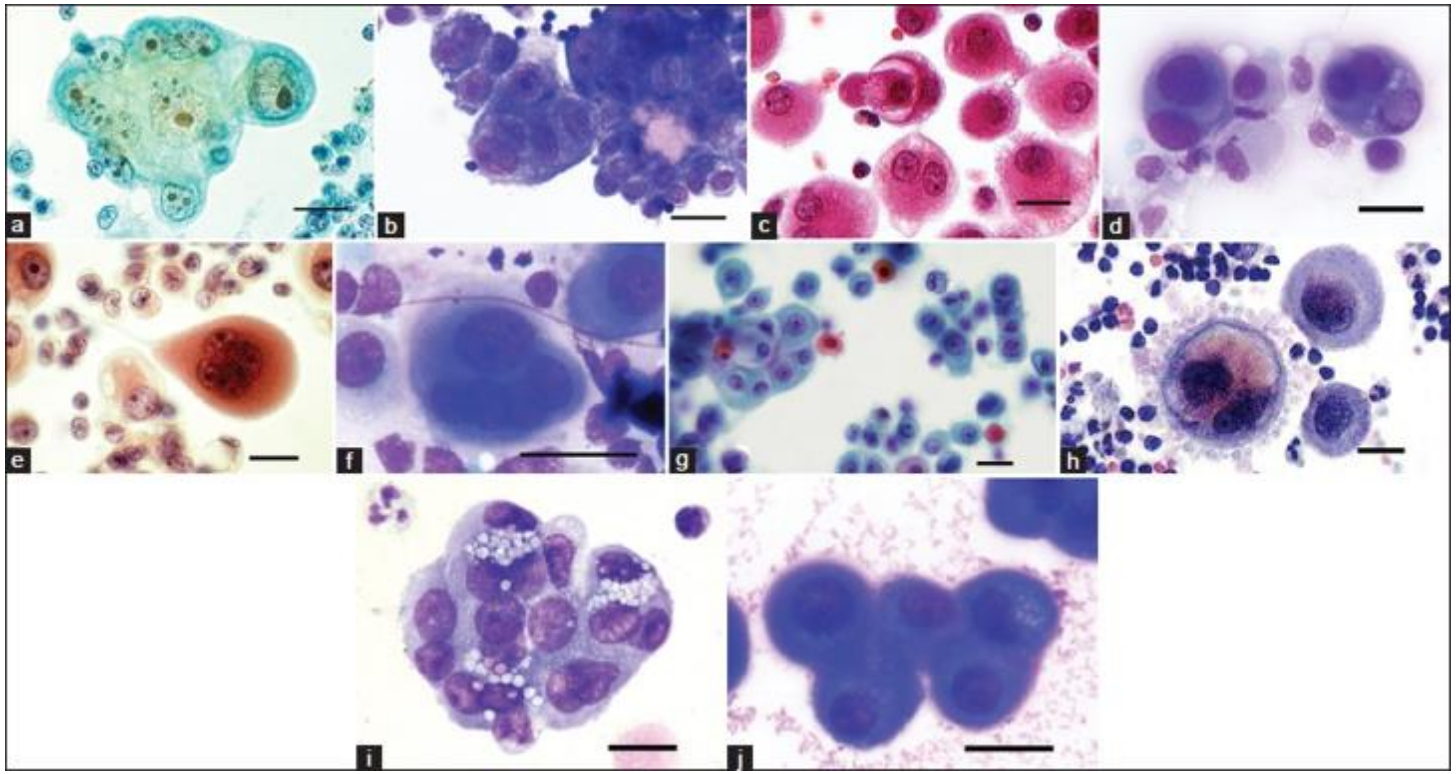

SMRP Level (nM)
30
25
20
15
10
5
0
Pretreatment
Post-treatment
Incomplete resection
Upper limit of normal
Complete resections

Diagnostic Biomarkers can be helpful

Benign

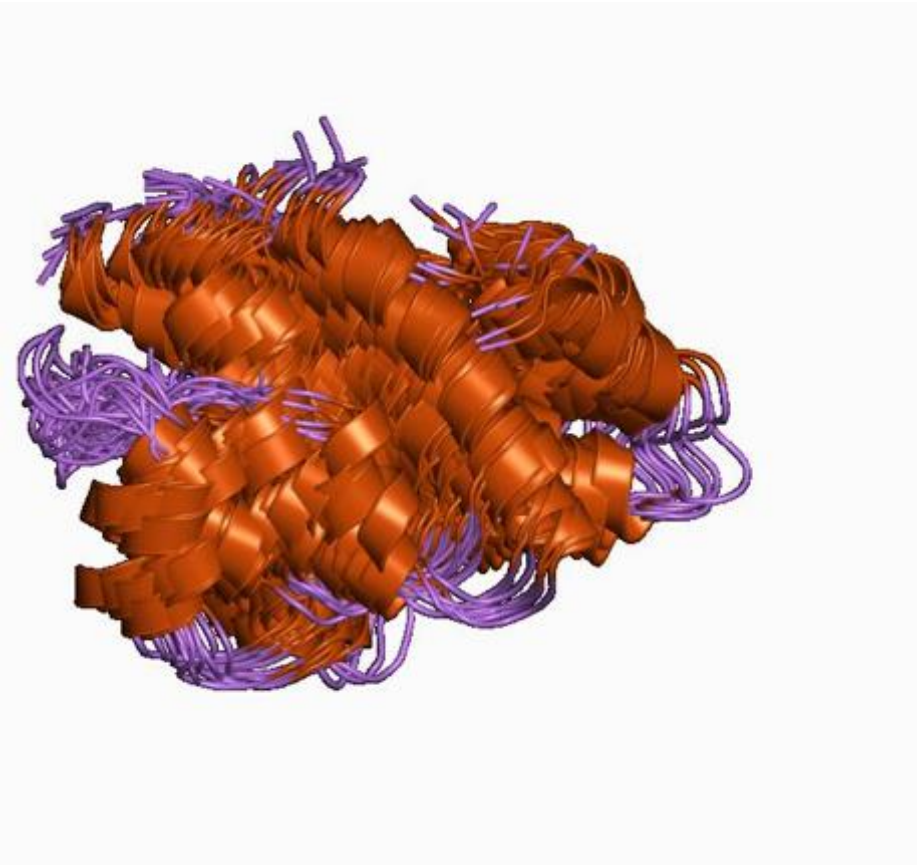


Malignant



Fibulin-3

- secreted glycoprotein, one of a family
- AKA: EGF-containing fibulin-like extracellular matrix protein 1, EFEMP1
- elongated structure with many calcium-binding sites (tandem arrays of epidermal growth factor-like domains)
- overlapping binding sites for several basement-membrane proteins, tropoelastin, fibrillin, fibronectin and proteoglycans.

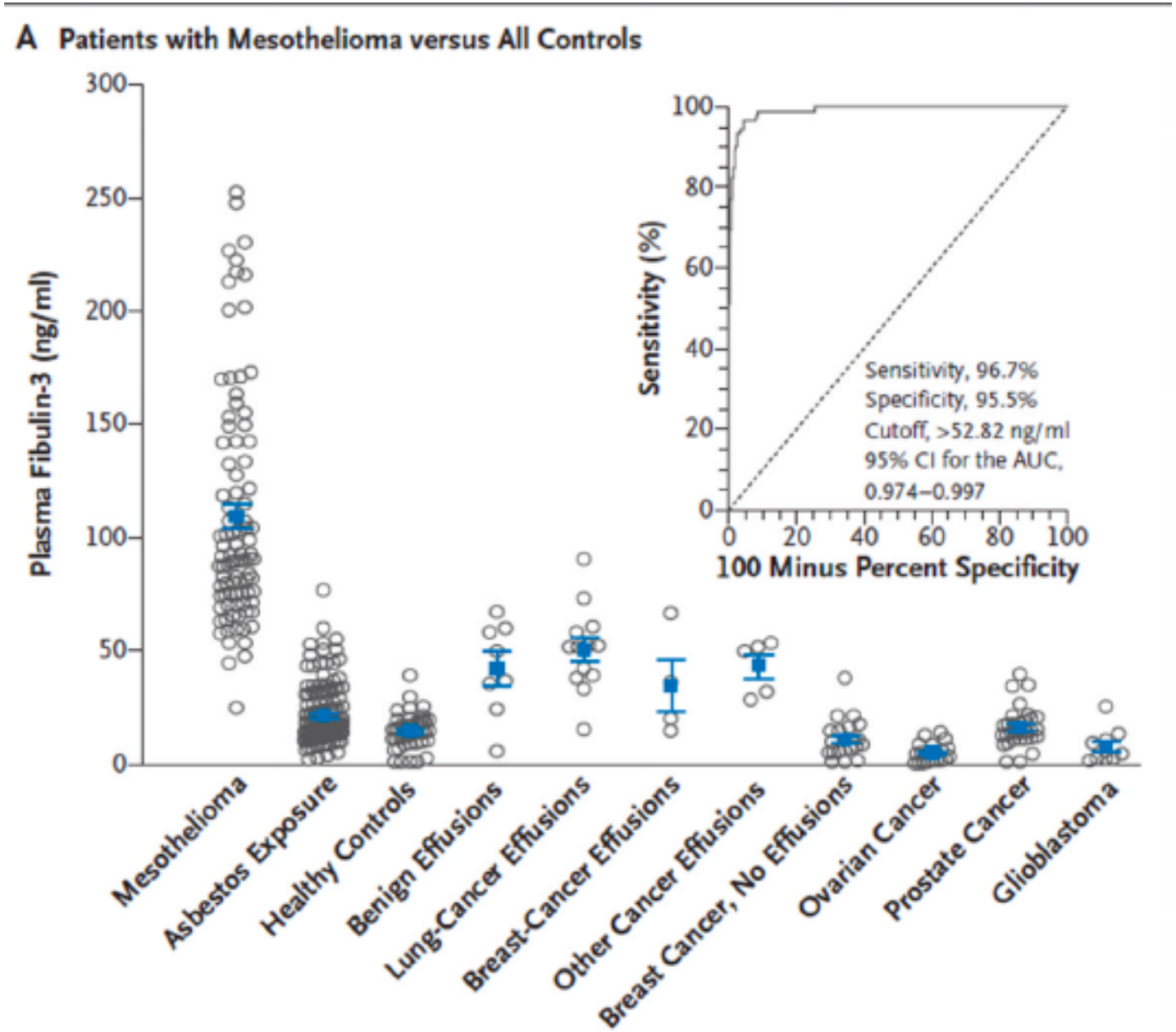


N Engl J Med. 2012 October 11; 367(15): 1417–1427. doi:10.1056/NEJMoa1115050.

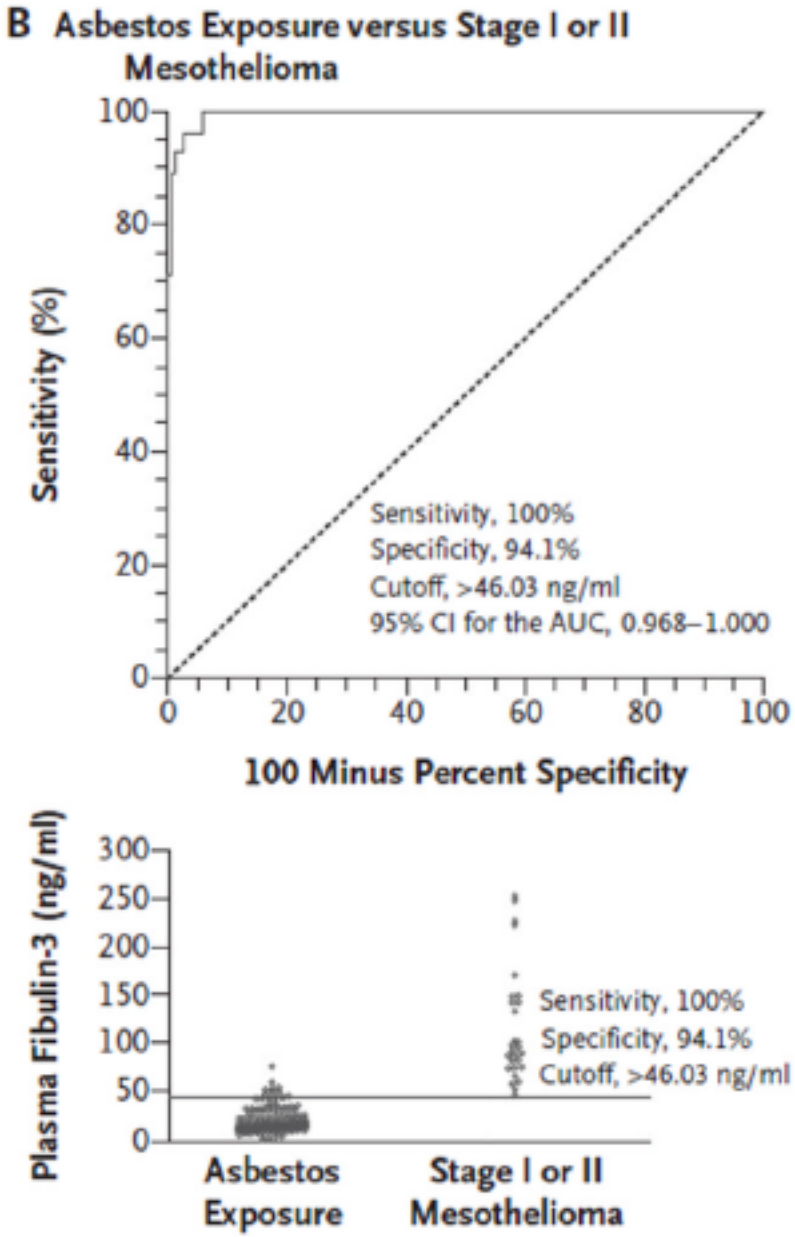
Fibulin-3 as a Blood and Effusion Biomarker for Pleural Mesothelioma

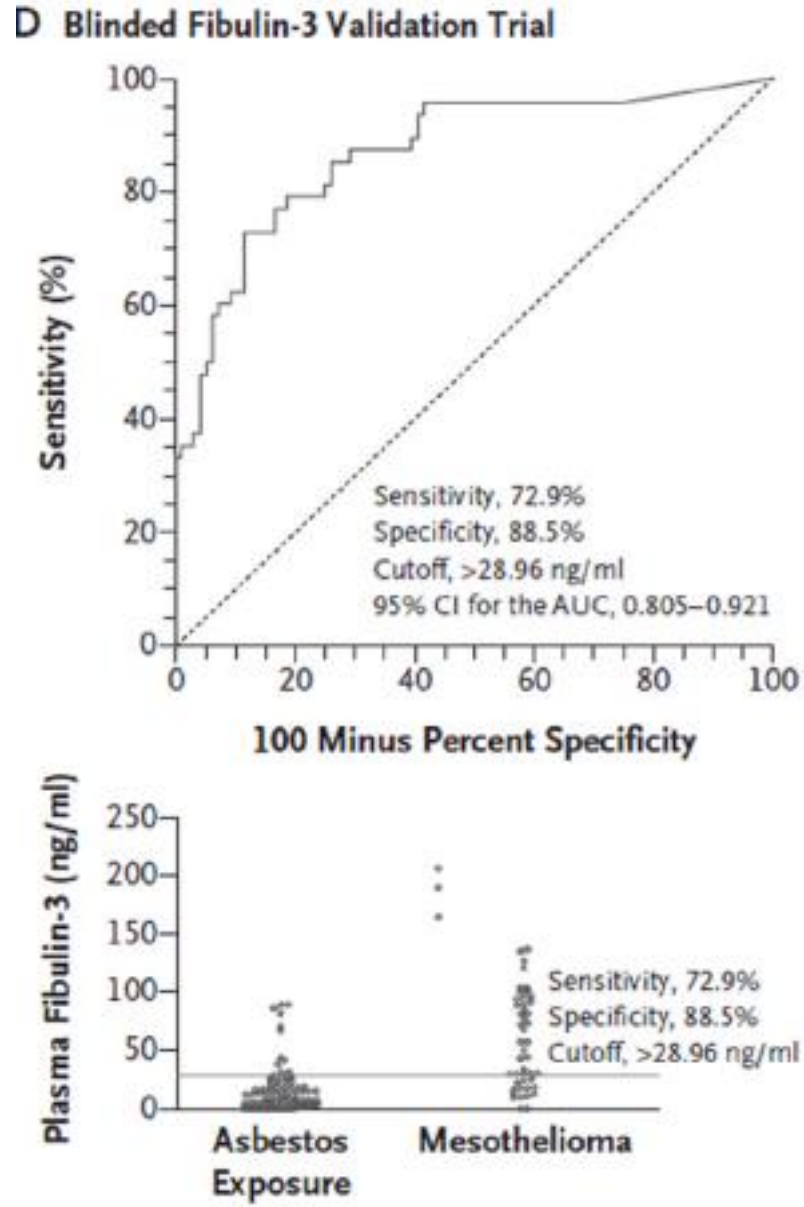
Harvey I. Pass, M.D., **Stephen M. Levin, M.D.**, **Michael R. Harbut, M.D.**, **Jonathan Melamed, M.D.**, **Luis Chiriboga, Ph.D.**, **Jessica Donington, M.D.**, **Margaret Huflejt, Ph.D.**, **Michele Carbone, M.D., Ph.D.**, **David Chia, Ph.D.**, **Lee Goodglick, Ph.D.**, **Gary E. Goodman, M.D.**, **Mark D. Thornquist, Ph.D.**, **Geoffrey Liu, M.D.**, **Marc de Perrot, M.D.**, **Ming-Sound Tsao, M.D.**, and **Chandra Goparaju, Ph.D.**

Departments of Cardiothoracic Surgery (H.I.P., J.D., M.H., C.G.) and Pathology (J.M., L.C.), New York University Langone Medical Center, and the Department of Preventive Medicine, Mount Sinai School of Medicine (S.M.L.) — both in New York; the National Center for Vermiculite and Asbestos-Related Cancers, Karmanos Cancer Institute, Detroit (M.R.H.); University of Hawaii Cancer Center, Honolulu (M.C.); the Department of Pathology and Laboratory Medicine, University of California, Los Angeles, Los Angeles (D.C., L.G.); Swedish Cancer Institute (G.E.G.) and Fred Hutchinson Cancer Research Center (M.D.T.) — both in Seattle; and Princess Margaret Hospital, University Health Network and University of Toronto, Toronto (G.L., M.P., M.-S.T.)

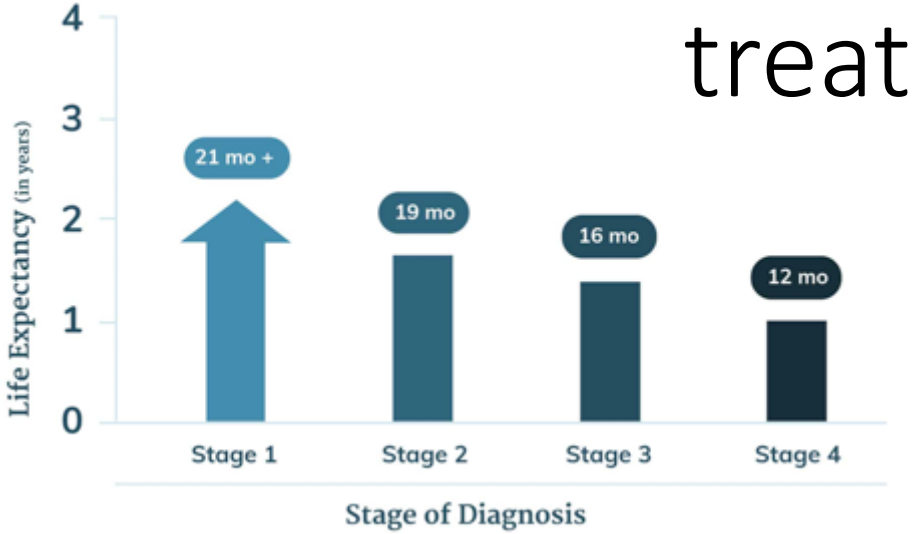

A Patients with Mesothelioma versus All Controls
Plasma Fibulin-3 (ng/ml)
300
250
200
150
100
50
0
Sensitivity (%)
100
80
60
40
20
0
0
20
40
60
80
100
100 Minus Percent Specificity
Sensitivity, 96.7%
Specificity, 95.5%
Cutoff, >52.82 ng/ml
95% CI for the AUC,
0.974–0.997
Mesothelioma
Asbestos Exposure
Healthy Controls
Benign Effusions
Lung-Cancer Effusions
Breast-Cancer Effusions
Other Cancer Effusions
Breast Cancer, No Effusions
Ovarian Cancer
Prostate Cancer
Glioblastoma

Princess Margaret data





Mesothelioma has variable prognosis dependent on tumour, stage, clinical, and treatment characteristics



Cancer Cell Type	Mesothelioma Location: Pleural (Lungs)	Mesothelioma Location: Peritoneal (Abdomen)
Epithelioid	19 Months	54 Months
Biphasic	13 Months	4.6 Months
Sarcomatoid	8 Months	Not enough data

MOA	Agent	Phase of Study	Number of Patients and Indication	Overall Response Rate (%)	Progression-Free Survival (months)	Overall Survival (months)
Immuno-oncology						
	Monotherapy PD-(L)1 (Pembrolizumab, nivolumab, avelumab)[3-8,11]	II	Total >150 MPM, > 1 line	9-26	2.6-5.4	10.7-18.0
	PD-(L)1 plus CTLA-4 (Nivolumab ± ipilimumab, durvalumab + tremelimumab)[13-15]	II	Total 221 MPM, > 1 line	25-38	4.3 - 6.1	11.8 – not reached
	Monotherapy CTLA-4 (Tremelimumab vs. BSC) 12	II/III	571, MPM, > 1 line	Trem, 4.5; BSC, 1.1	Trem, 2.8; BSC 2.7, (n.s.)	Trem, 7.7 BSC, 7.3 (n.s.)
Arginine depletion						
	ADI-PEG20 vs. BSC[16]	II	68, MPM, ASS1-deficient	A, 0; BSC, 0	A, 3.2; BSC, 2.0 (p = 0.03)	A, 11.5; BSC 11.1
Angiogenesis inhibition						
	Pemetrexed/cisplatin + nintedanib or placebo[3]	III, c	458 MPM, first line	NR	Nin, 6.8; placebo, 7.0 ; p = 0.91	Nin,14.4; placebo, 16.1 , p = 0.54
	Pemetrexed/cisplatin + bevacizumab or placebo[2]	III	448 MPM, first line	NR	Beva 9.2; placebo 7.3; p = 0.0001	Beva 18.8; placebo 16.1; p = 0.02
Mesothelin						
	Amatuximab[18]	II	89 first line	40	6.1	14.8
	Anetumab ravtansine vs. vinorelbine[17]	II	166 MPM, > 1 line, mesothelin positive	AR: 8.4, vin,: 6.1	AR: 4.3; vin, 4.5s; p = 0.859	AR: 10.1; vin, 11.6 months; p = 0.721

Mesothelioma.com

J Thorac Oncol. 2016 June ; 11(6): 900–909. doi:10.1016/j.jtho.2016.02.006.

Plasma Biomarker Enrichment of Clinical Prognostic Indices in Malignant Pleural Mesothelioma

Harvey I. Pass, MD[*,#], **Chandra Goparaju, PhD**[*], **Osvaldo Espin-Garcia, MMath**[+], **Jessica Donington, MD**[*], **Michele Carbone, MD**[@], **Devalben Patel, BSc**[+], **Zhuo Chen, PhD**[+], **Ronald Feld, MD**[+], **John Cho, MD**[+], **Shirish Gadgeel, MD**[^], **Antoinette Wozniak, MD**[^], **Abraham Chachoua, MD**[*], **Natasha Leighl, MD**[+], **Ming-Sound Tsao, MD**[+], **Marc de Perrot, MD**[+], **Wei Xu, PhD**[+], and **Geoffrey Liu, M.D**[+]

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Discovery (NYU/KCI) Cohort		
Prognostic variables	**EORTC CPI**	**CALGB CPI**
CPI alone (for log-osteopontin analysis)[1], c-index (95% CI)	0.649 (0.59–0.70)	0.641 (0.59–0.69)
CPI alone (for log-mesothelin analysis)[1], c-index (95% CI)	0.645 (0.59–0.70)	0.640 (0.59–0.69)
CPI + log-osteopontin, c-index (95% CI)	0.767 (0.71–0.82)	0.763 (0.71–0.81)
CPI + log-mesothelin, c-index (95% CI)	0.692 (0.63–0.76)	0.724 (0.66–0.79)
Improvement in Harrell's c-indices when adding log-osteopontin[2]	0.118 (0.10–0.18)	0.122 (0.11–0.18)
Improvement in Harrell's c-indices when adding log-mesothelin[2]	0.045 (0.03–0.11)	0.084 (0.06–0.13)

Validation (PMCC) Cohort		
Prognostic variables	**EORTC CPI**	**CALGB CPI**
CPI alone, c-index (95% CI)	0.596 (0.55–0.64)	0.602 (0.54–0.66)
CPI + log-osteopontin, c-index (95% CI)	0.811 (0.76–0.86)	0.781 (0.73–0.83)
CPI + log-mesothelin, c-index (95% CI)	0.650 (0.58–0.72)	0.649 (0.58–0.71)
Improvement in Harrell's c-indices when adding log-osteopontin[2]	0.216 (0.20–0.26)	0.179 (0.16–0.23)
Improvement in Harrell's c-indices when adding log-mesothelin[2]	0.054 (0.03–0.12)	0.047 (0.03–0.10)

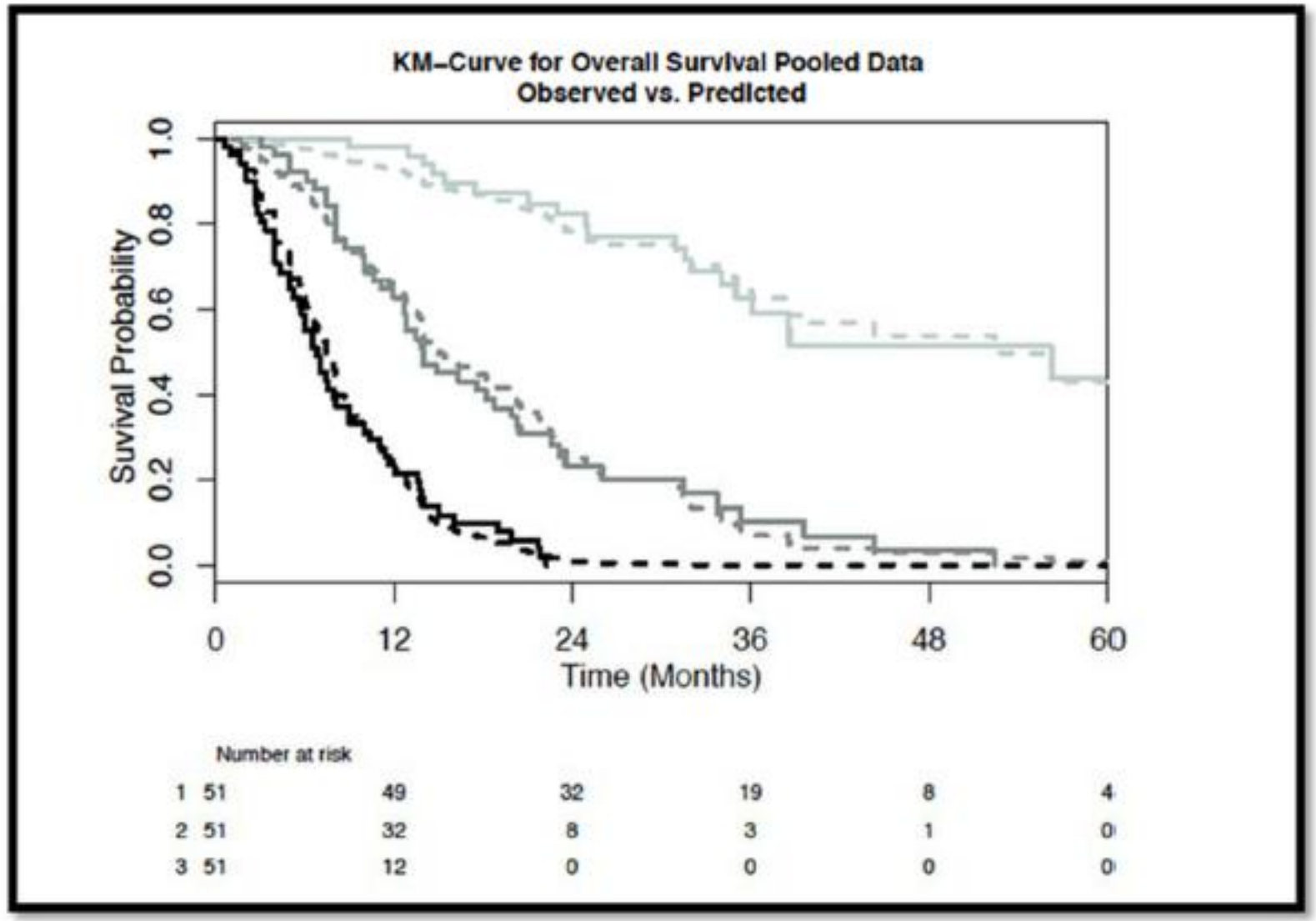


Figure 1. Visual inspection of model fit curves evaluating tertiles of the risk score generated from the pooled prognostic model

Germline Biomarker: SMARCA2/BRM functional polymorphisms

Molecular Carcinogenesis

RESEARCH ARTICLE

Association of two *BRM* promoter polymorphisms and smoking status with malignant pleural mesothelioma risk and prognosis

Min Joon Lee, Nathan Kuehne, Katrina Hueniken, Shermi Liang, Sudhir Rai, Hadas Sorotsky, Michael Herman, Daniel Shepshelovich, Jeffrey Bruce, Mindy Liang, Devalben Patel, Dangxiao Cheng, Zhuo Chen, Lawson Eng, M. Catherine Brown, John Cho, Natasha B. Leighl, Marc de Perrot, David Reisman, Wei Xu, Penelope A. Bradbury, Geoffrey Liu ... See fewer authors

First published: 29 July 2019 | https://doi.org/10.1002/mc.23088

SMARCA2/BRM is the ATP-engine of the SWI/SNF complex that drives chromatin remodeling; Loss of its function is associated with worse outcomes, as SMARCA controls many oncogenesis functions

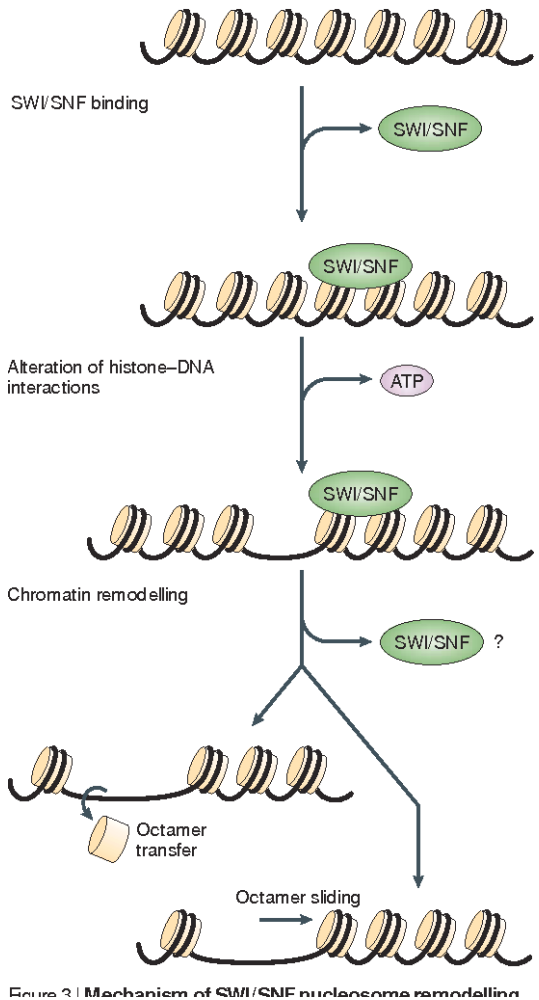
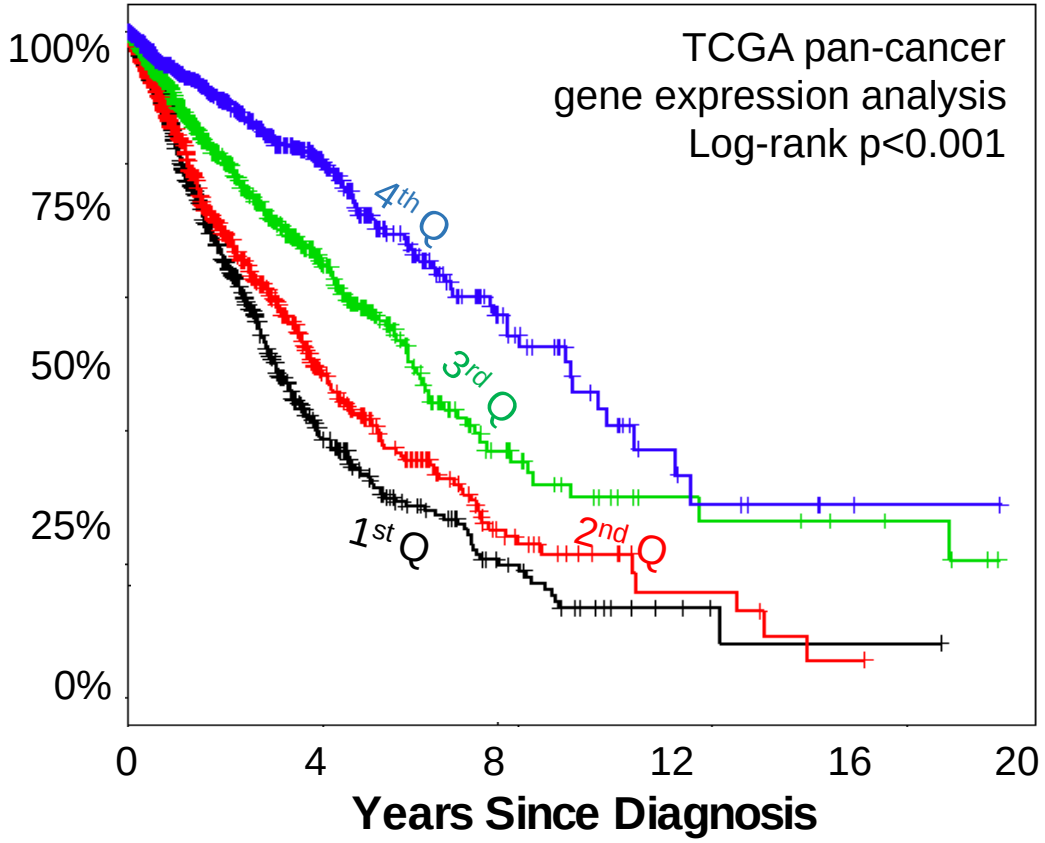
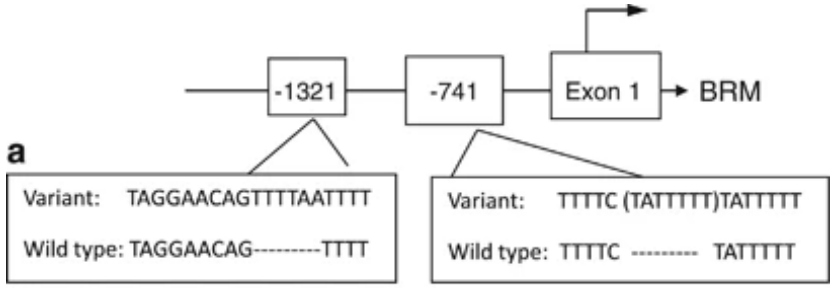


Figure 3 | Mechanism of SWI/SNF nucleosome remodelling



Liu et al, CCR, 2017

Two functional promoter SMARCA2/BRM polymorphisms are functional by altering binding of a MEF2D-HDAC complex that represses SMARCA2 gene expression



a

Variant: TAGGAACAGTTTTAATTTT
Wild type: TAGGAACAG---------TTTT

Variant: TTTTC (TATTTTT)TATTTTT
Wild type: TTTTC --------- TATTTTT

b

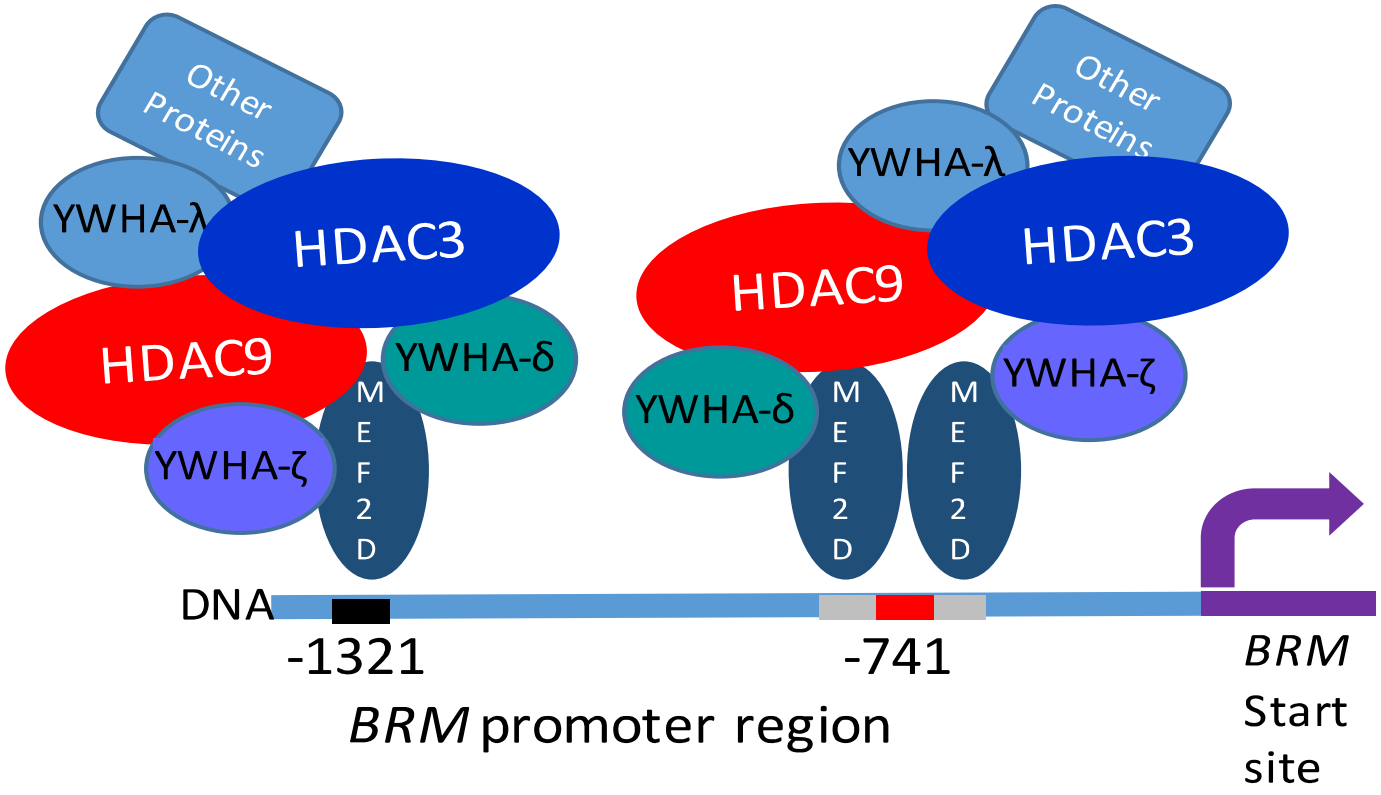
GCCTCCCTTTC (TATTTTT) TATTTTTTATT
TTTATTT TATTT
MEF2 BINDING MOTIF IS IN BOLD *BRM -741* polymorphism in parentheses

c

ACTGCATAGGAACAG (TTTTAA) TTTTAAGAGTCTTATTTATA
TTTTAT TTTTAA
MEF2 BINDING MOTIF IS IN BOLD *BRM -1321* polymorphism in parentheses

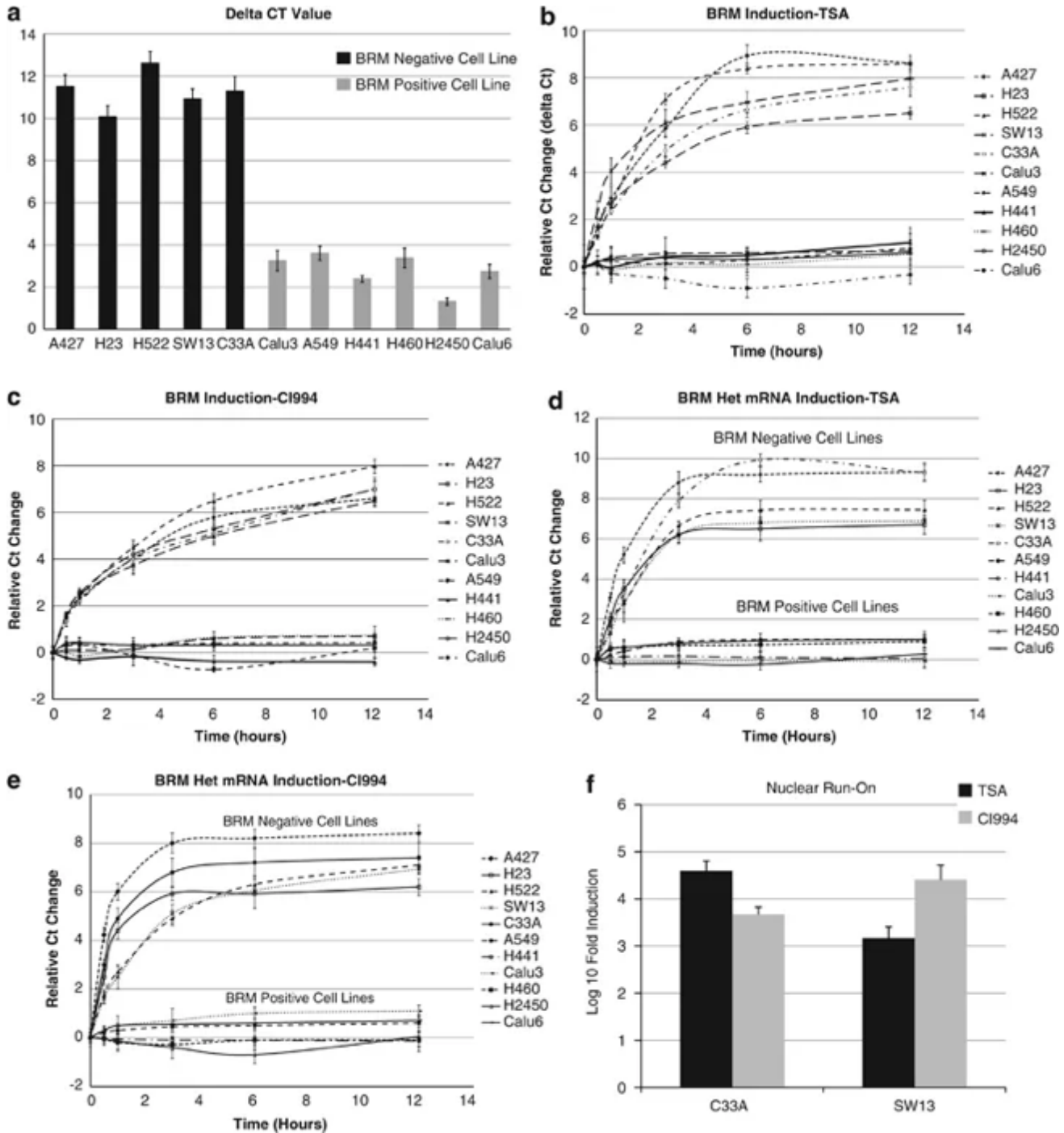
d

Polymorphism	BRM -1321			BRM -741		
Minor Allele Frequency	45%			45%		
Genotype Frequency	Wt	Hetero	Homo	Wt	Hetero	Homo
	29%	52%	19%	30%	48%	21%



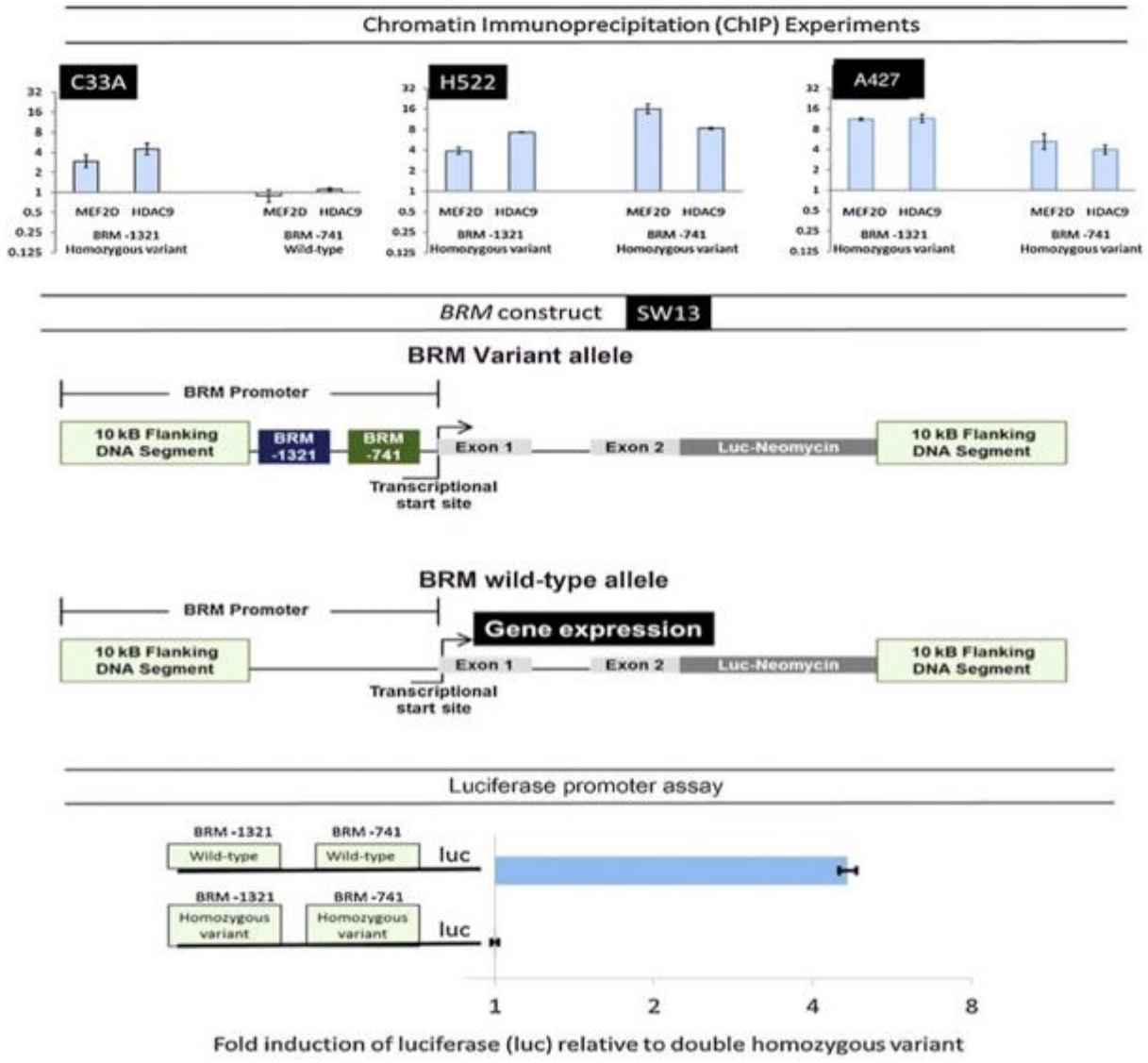
Liu et al, Oncogene, 2011

These two SMARCA2 promoter polymorphisms regulate SMARCA gene expression, which alters cellular proliferation through multiple mechanisms



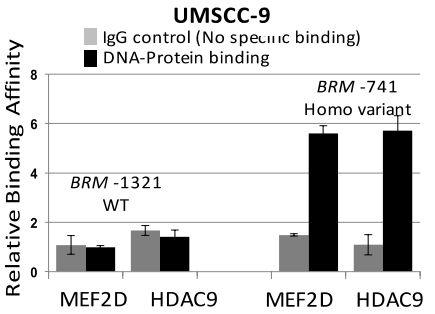
Liu et al, Oncogene, 2011

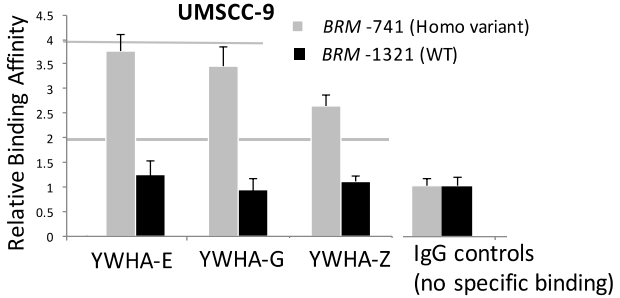
Chromatin Immunprecipitation and Luciferase promoter swap experiments across multiple cell lines supports MEF2/HDAC/skeletal binding and control of gene expression BRM polymorphisms

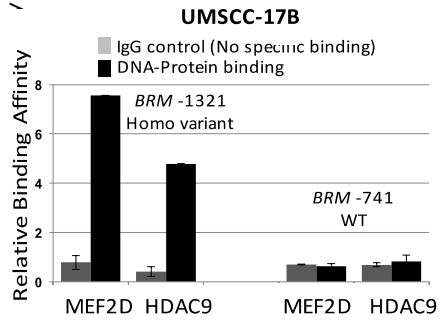


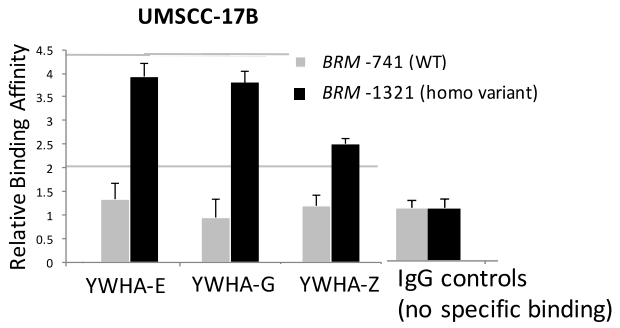
Left panels:
MEF2D, HDAC9

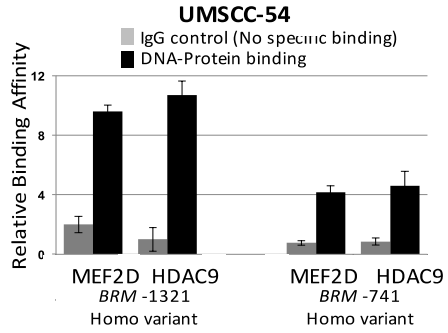
Right panels:
YWHA-E, YWHA-G, YWHA-Z

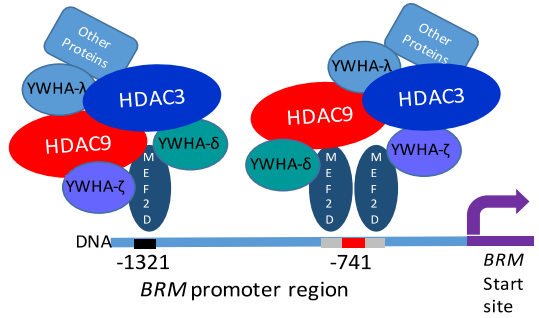












Lee et al, Mol Carcinogenesis, 2019; Liu et al, CCR, 2017

EMSA and DAPA analyses support the differential binding of the two SMARCA polymorphisms to MEF2/HDAC9 and scaffolding proteins

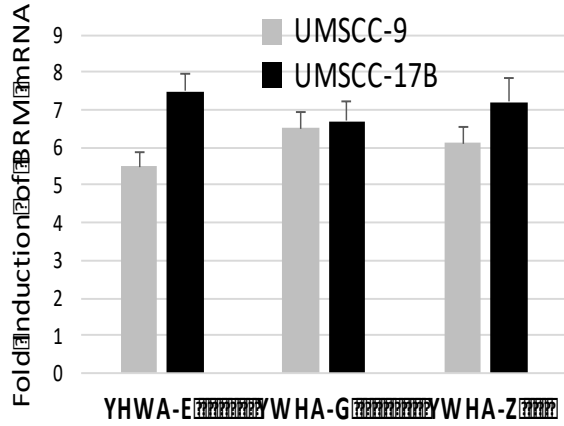
Lee et al, Mol Carcinogenesis, 2019

A. Oligonucleotide probes for *BRM* -1321

Probe Description	Abbreviation	Probe Sequence and Percent Homology to MEF2 binding site
Wildtype	W	5′-CTCGATAGGA**ACAG**TTTTAAGAGTCAAGCATA-3′ 70% homology
Variant	V	5′-CTCGATAGGAACAGTT**TTAATTTTAA**GAGTCAAGCATA-3′ 100% homology
Variant left tandem sequence replaced	V5R	5′-CTCGATAGGAACAGCG**CGCGTTTTAA**GAGTCAAGCATA-3′ 60% homology
Variant right tandem sequence replaced	V3R	5′-CTCGATAG**GAACAGTTTTA**ACGCGCGGAGTCAAGCATA-3′ 60% homology

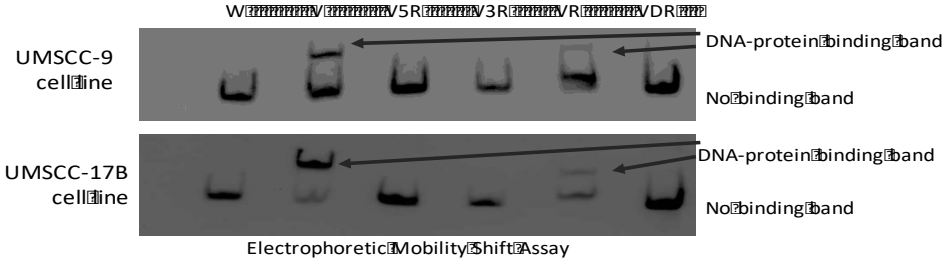
C. DNA affinity precipitation analysis (DAPA) in the UMSCC-9 cell line

D. BRM mRNA (by qPCR) fold changes during knockdown of YWHAs by anti-YWHA shRNAi

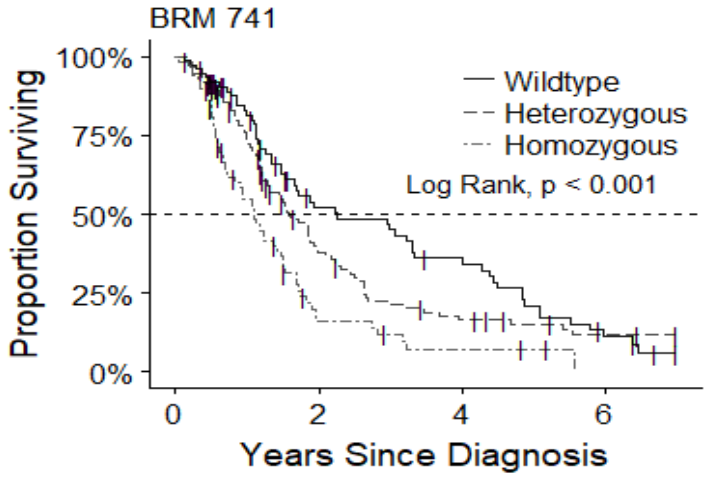


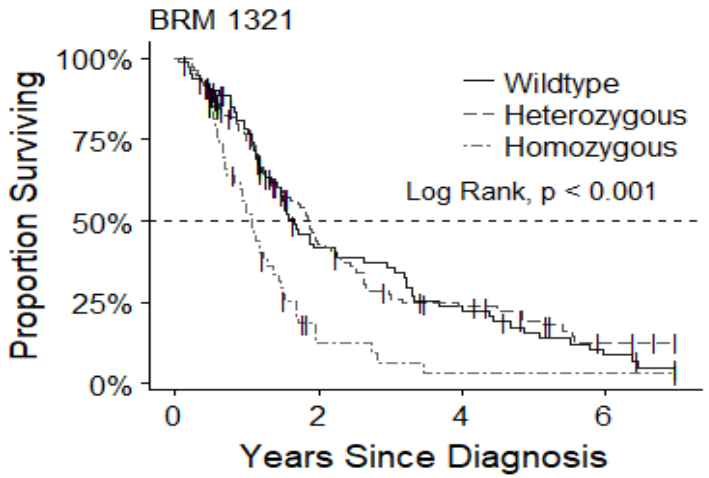
B. Oligonucleotide probes for *BRM* -741

Probe Description	Abbreviation	Probe Sequence and Percent Homology to MEF2 binding site
Wildtype	W	5′-CCCTTTT**CTATTTTTTA**TTTTTTTACCTGGAAT-3′ 90% homology
Variant	V	5′-CCCTTTT**CTATTTTTTA**TTTT**TTATTTTTTT**ACCTGGAAT-3′ 90% homology 80% homology
Variant left tandem sequence replaced	V5R	5′-CCCTTTTCGCGCGCTATTTT**TTATTTTTTT**ACCTGGAAT-3′ 80% homology
Variant right tandem sequence replaced	V3R	5′-CCCTTTT**CTATTTTTTA**TTTTTCGCGCGCTTACCTGGAAT-3′ 90% homology
Variant middle tandem sequence replaced	VR	5′-CCCTTTT**CTATTTTTCG**CGCGC**CTATTTTTTT**ACCTGGAAT-3′ 80% homology 90% homology
Variant middle sequence replaced, double length	VDR	5′-CCCTTTT**CTATTTTTCG**CGCGCGCGCGC**GTATTTTTTT**ACCTGGAAT-3 80% homology 80% homology



SMARCA2 Polymorphisms are associated with mesothelioma prognosis





BRM Polymorphisms and MPM Overall Survival

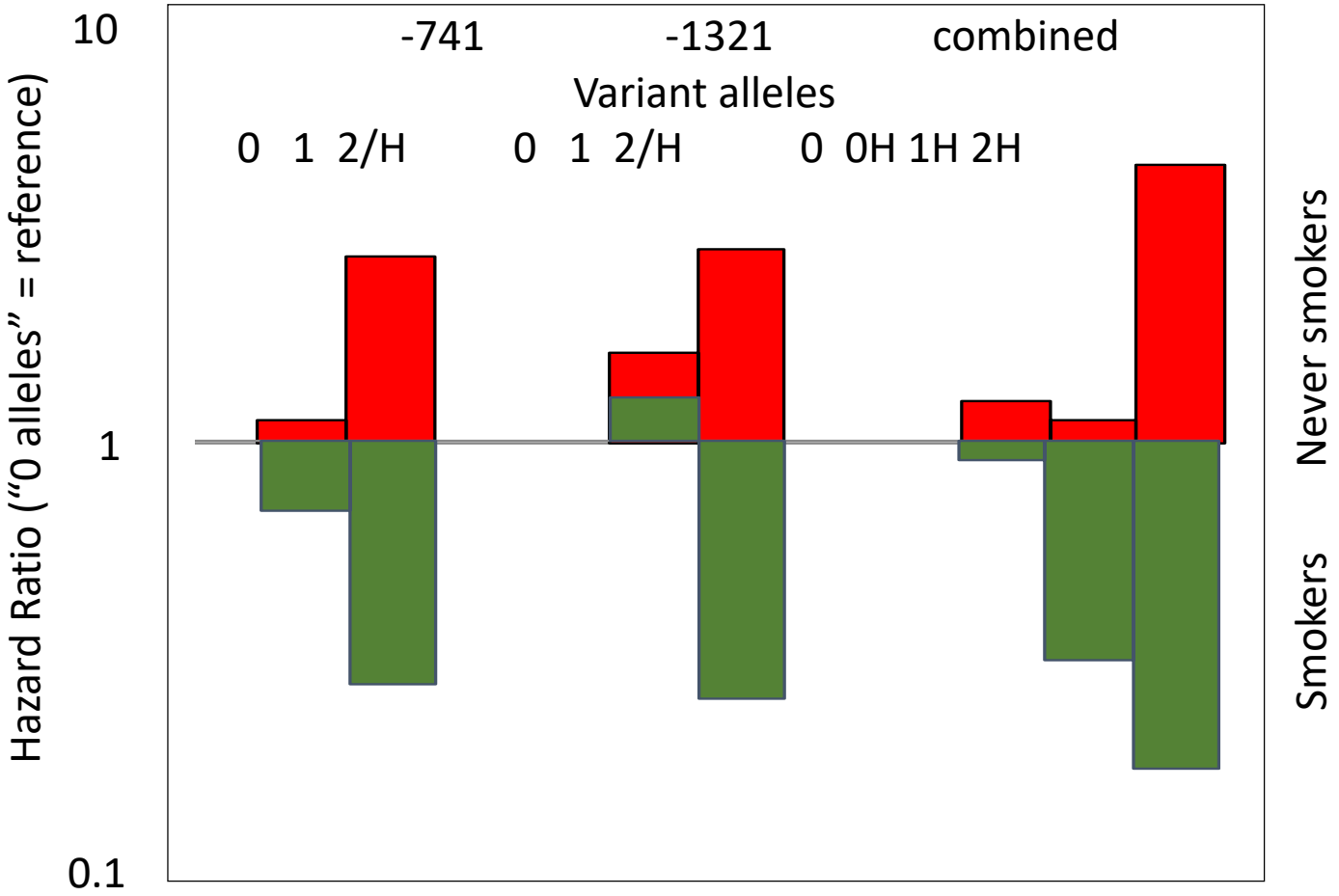
Polymorphism	Total N Univariable (Multivariable)	Genotype	%	Univariable HR (95% CI)	*p-value*	Multivariable[2] aHR (95% CI)	*p-value*
BRM-741	258 (253)	Wild type	29%	Reference		Reference	
		Heterozygote	45%	1.26 (0.9-1.8)	0.18	1.47 (1.0-2.1)	**0.04**
		Homozygote	26%	2.21 (1.5-3.2)	**<0.001**	2.71 (1.8-4.0)	**<0.001**
BRM-1321	256 (251)	Wild type	31%	Reference		Reference	
		Heterozygote	48%	0.93 (0.7-1.3)	0.68	1.19 (0.8-1.7)	0.32
		Homozygote	21%	2.02 (1.4-3.0)	**<0.001**	2.69 (1.8-4.1)	**<0.001**
Both *BRM-741* and *BRM-1321*	256 (251)	Double Wild type (DWt)	19%	Reference		Reference	
		No homozygotes but not DWt	50%	0.83 (0.6-1.2)	0.33	1.04 (0.7-1.5)	0.86
		One homozygous variant	16%	1.18 (0.8-1.9)	0.477	1.64 (1.0-2.7)	**0.04**
		Double homozygous variants	16%	2.46 (1.6-3.9)	**<0.001**	3.18 (2.0-5.1)	**<0.001**

SMARCA2 polymorphisms and differential risk by smoking status a new risk factor for never-smokers with mesothelioma? A protective factor in smokers?

BRM Polymorphisms and MPM Risk

	Variable	Ever-Smokers N (%)	Ever-Smokers adjusted OR[1] (95% CI)	Ever-Smokers *p-value*	Never-Smokers N (%)	Never-Smokers adjusted OR[1] (95% CI)	Never-Smokers *p-value*
BRM-741	Total N=1054	730 (100%)			324 (100%)		
	Wild type	191 (26%)	Reference		86 (27%)	Reference	
	Heterozygote	356 (49%)	0.69 (0.4-1.1)	0.11	139 (43%)	1.13 (0.6-2.3)	0.73
	Homozygote	183 (25%)	0.28 (0.2-0.5)	**<0.001**	99 (31%)	2.70 (1.3-5.6)	**0.007**
BRM-1321	Total N=1046	725 (100%)			321 (100%)		
	Wild type	263 (36%)	Reference		100 (31%)	Reference	
	Heterozygote	338 (47%)	1.26 (0.8-2.0)	0.29	135 (42%)	1.61 (0.8-3.2)	0.17
	Homozygote	124 (17%)	0.26 (0.1-0.6)	**0.002**	86 (27%)	2.80 (1.3-5.9)	**0.006**
Both *BRM-741/BRM-1321*	Total N=1040	721 (100%)			319 (100%)		
	Double Wild type (DWt)	131 (18%)	Reference		53 (17%)	Reference	
	No homozygotes but not DWt	360 (50%)	0.90 (0.5-1.5)	0.69	138 (43%)	1.25 (0.5-2.9)	0.60
	One homozygous variant	156 (22%)	0.32 (0.2-0.7)	**0.002**	72 (23%)	1.13 (0.4-2.9)	0.81
	Double homozygous variants	74 (10%)	0.18 (0.1-0.6)	**0.004**	56 (18%)	4.40 (1.7-11)	**0.002**

SMARCA2 polymorphisms and differential risk by smoking status a new risk factor for never-smokers with mesothelioma? A protective factor in smokers?



Blood-based biomarkers

- Risk factors and biology: BRM
- Diagnosis and diagnostic supplement: Fibulin-3
- Prognosis: Osteopontin and BRM germline genetics
- Monitoring: Mesothelin
- Future: BAP1 through liquid biopsies?

Now onto something new: Breathomics

“Fetor Oris”

- From ancient times
- Potential sign of abscess
- Dental care
- DDx by Pliny

- Pseudomonas aeriginosa
- Grape-like smell

Journal of Biotechnology
Volume 267, 10 February 2018, Pages 45-49

Short communication

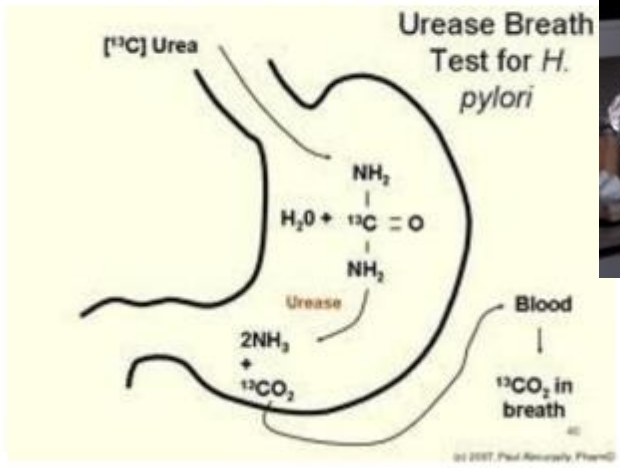
Smelling *Pseudomonas aeruginosa* infections using a whole-cell biosensor – An alternative for the gold-standard culturing assay

Igor Kviatkovski [a], Sagit Shushan [b, c], Yahav Oron [c, d], Idan Frumin [b], Daniel Amir [b], Lavi Secundo [b], Eitan Livne [b], Aharon Weissbrod [b], Noam Sobel [b], Yael Helman [a]

Show more

https://doi.org/10.1016/j.jbiotec.2017.12.023

Get rights and content



“Direct release” hypothesis

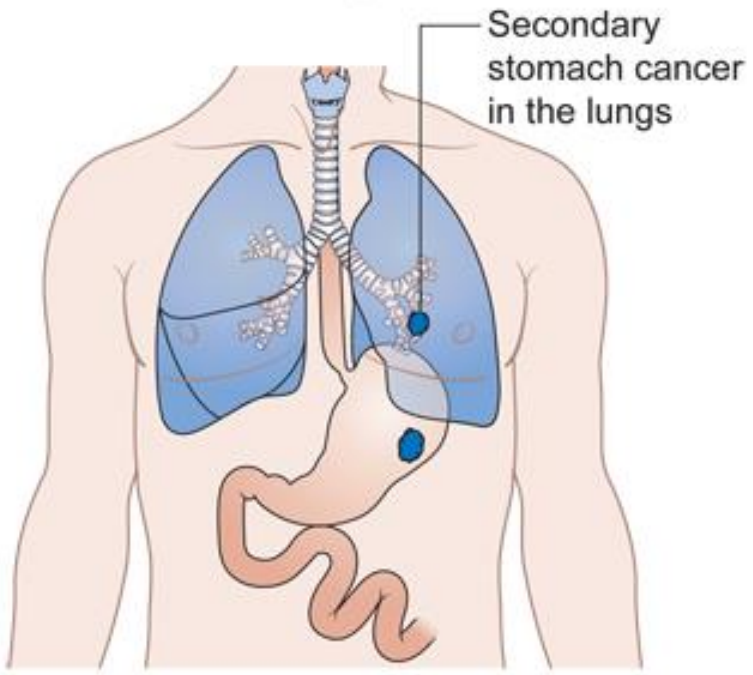
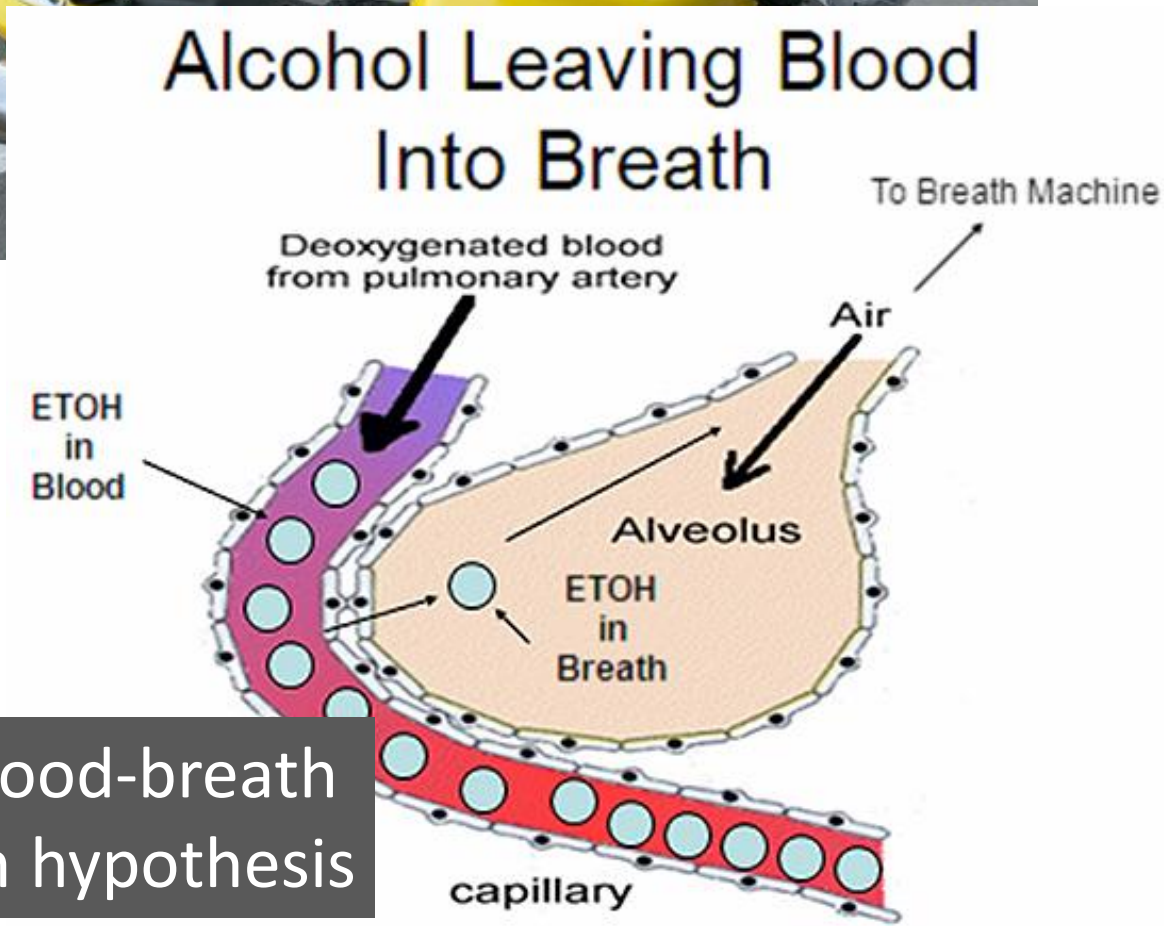


Diagram showing secondary stomach cancer in the lungs
Copyright © CancerHelp UK

Detecting Cancer from HN, Esoph, Stomach, Lung



Blood-breath equilibrium hypothesis

Dogs as Proof-of-Principle

HEALTHY LIVING 09/07/2015 11:13 EDT

'Groundbreaking' Trial Will Test Cancer-Sniffing Dogs

"We should not be turning our backs on these highly sensitive bio-detectors just because they have furry coats."

By Dominique Mosbergen, HuffPost US

- lung cancer
- melanoma
- breast cancer
- bladder cancer
- prostate cancer
- Colorectal cancer

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Quality control

Scale up issues

Proof-of-Principle

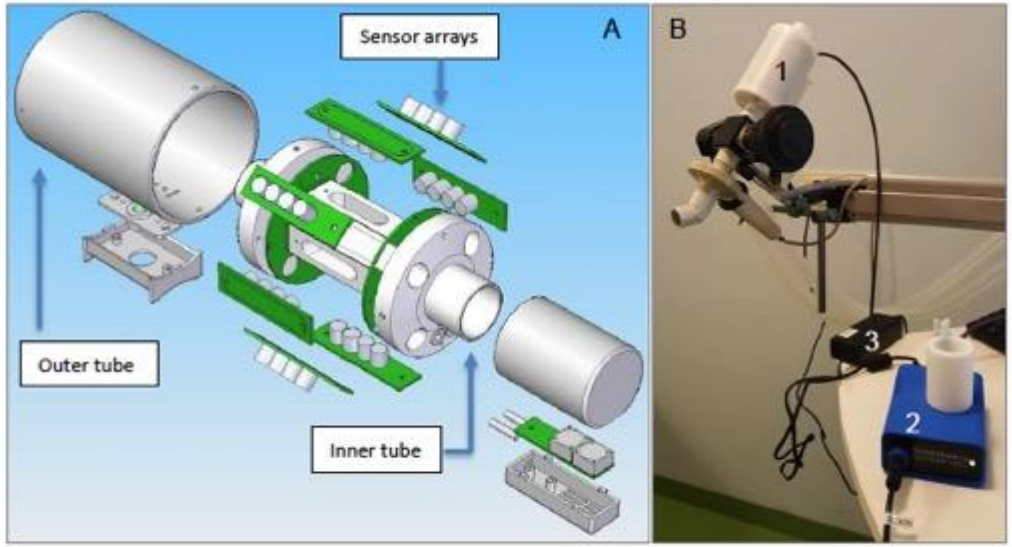
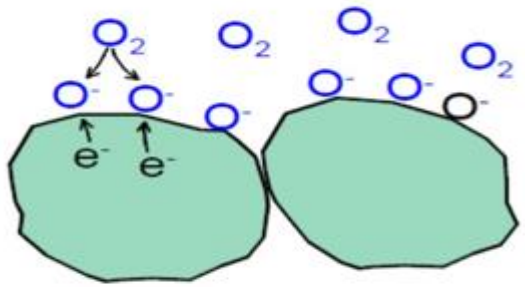


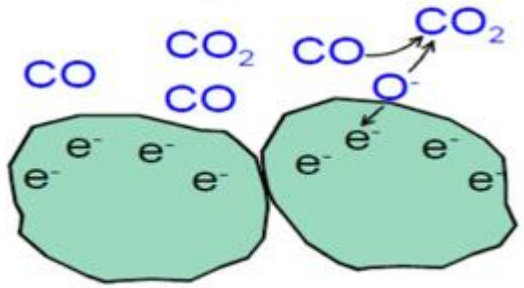
Figure 7. (A) Blown up version of the SpiroNose 2.0. (B) SpiroNose (1), Communication Unit (2) and power adaptor (3).

oxidising ambient

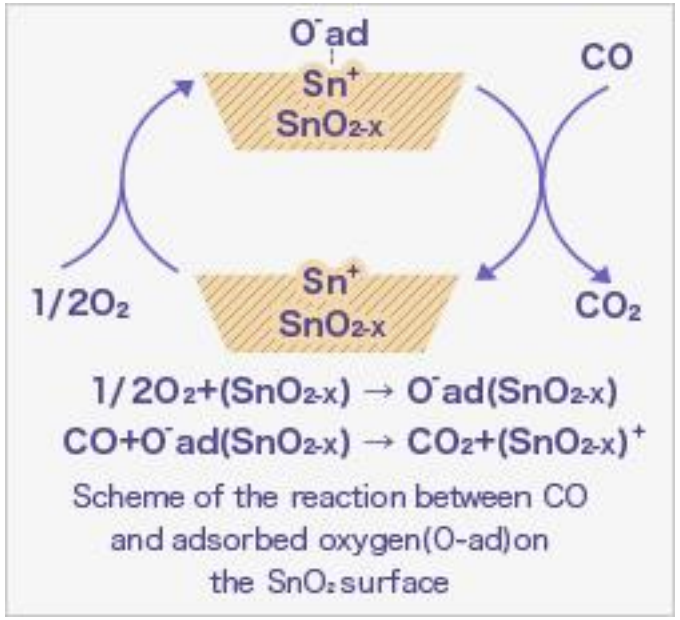


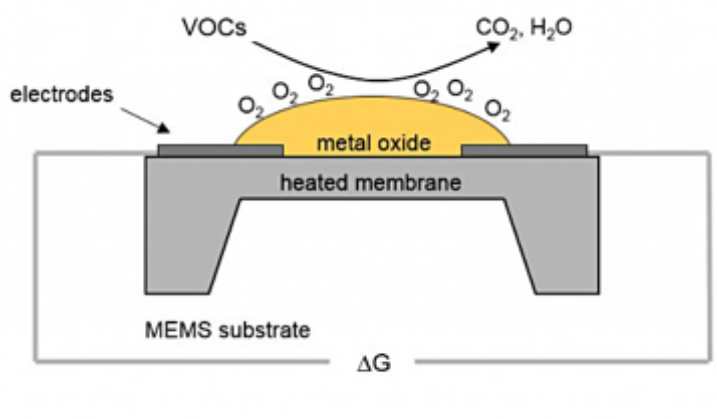
electron depletion
at surface and
grain boundaries
⇓
high resistance

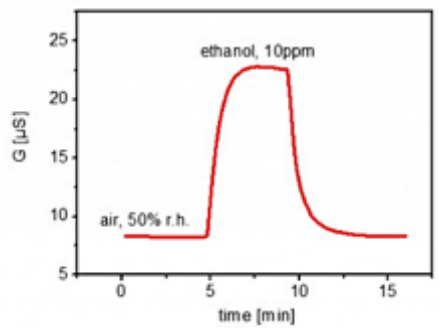
reducing ambient



electron rich surface
and grain boundaries
⇓
low resistance







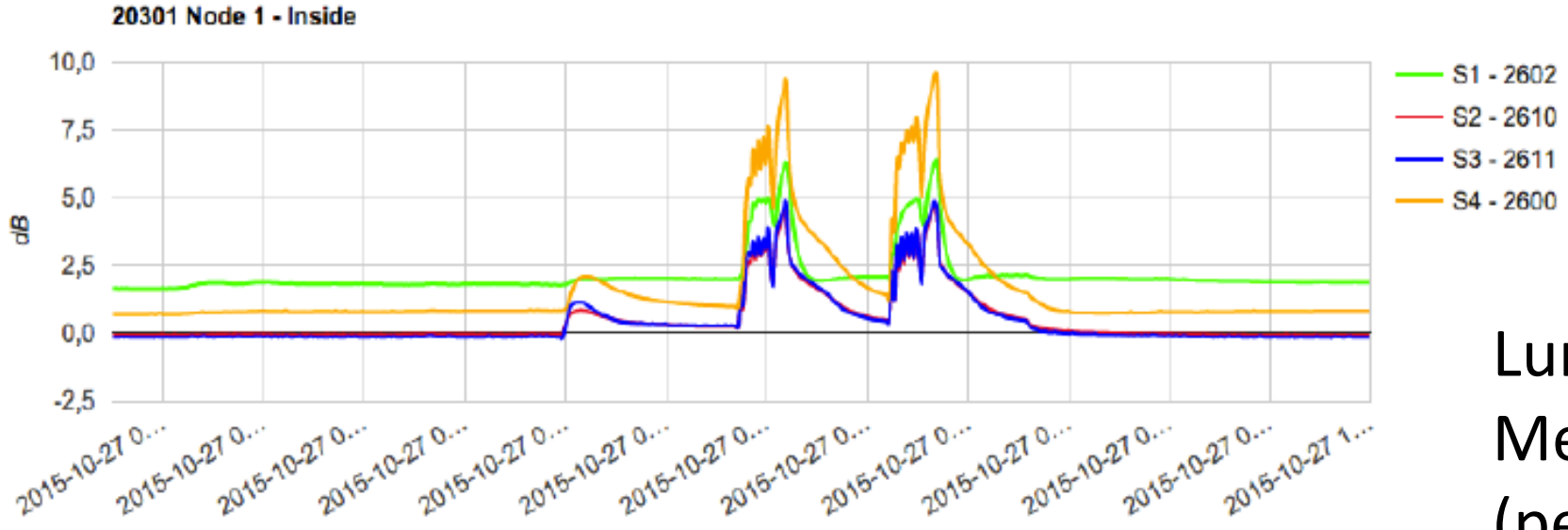
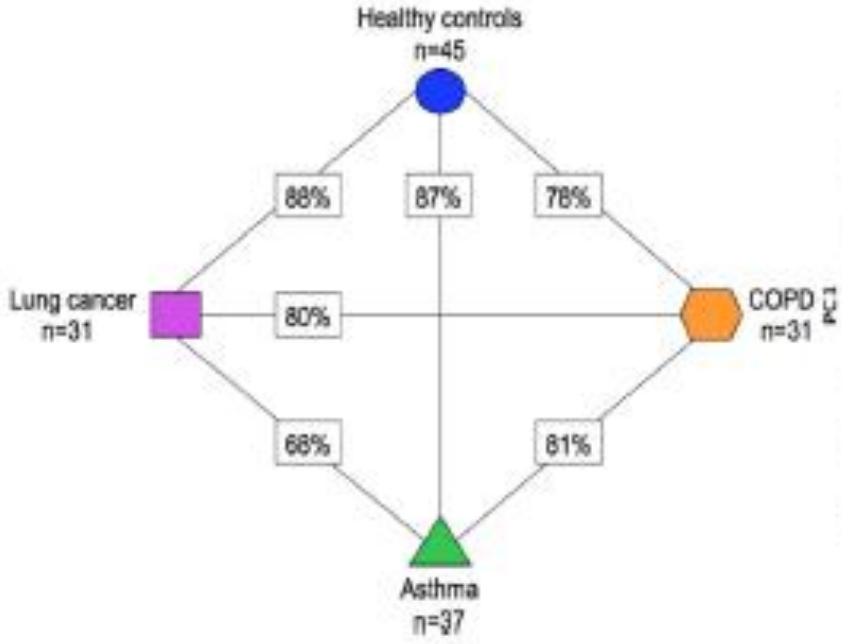
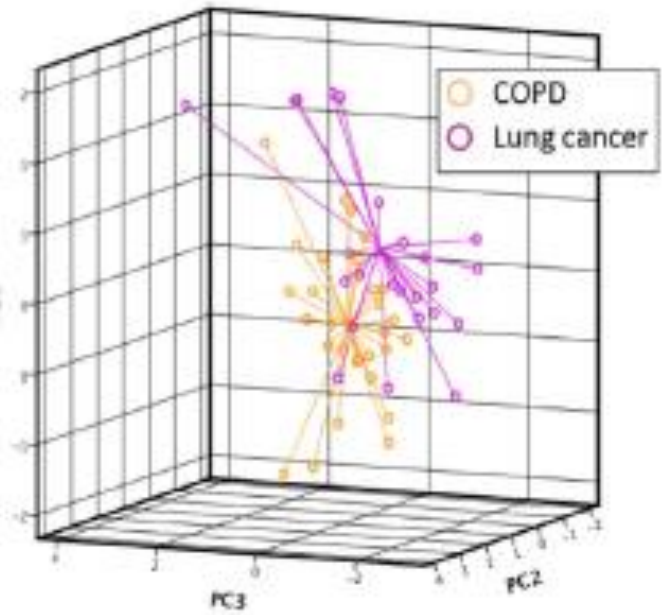
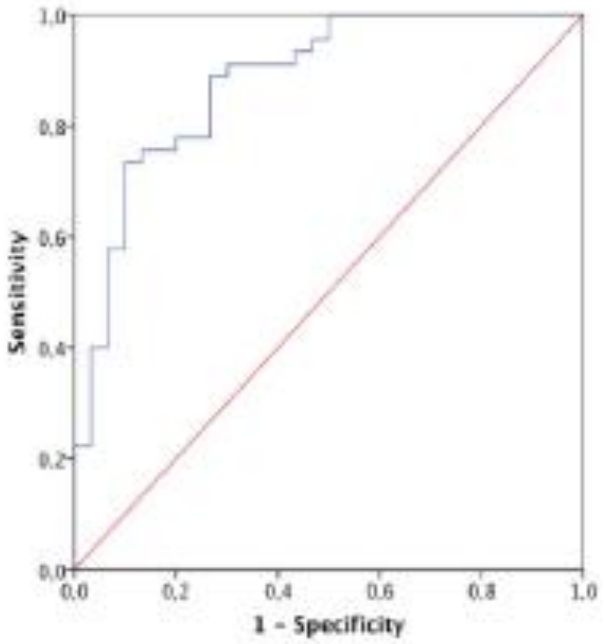


Figure 3: Sensor deflections of obtained by the SpiroNose during two successive exhaled breath measurements.

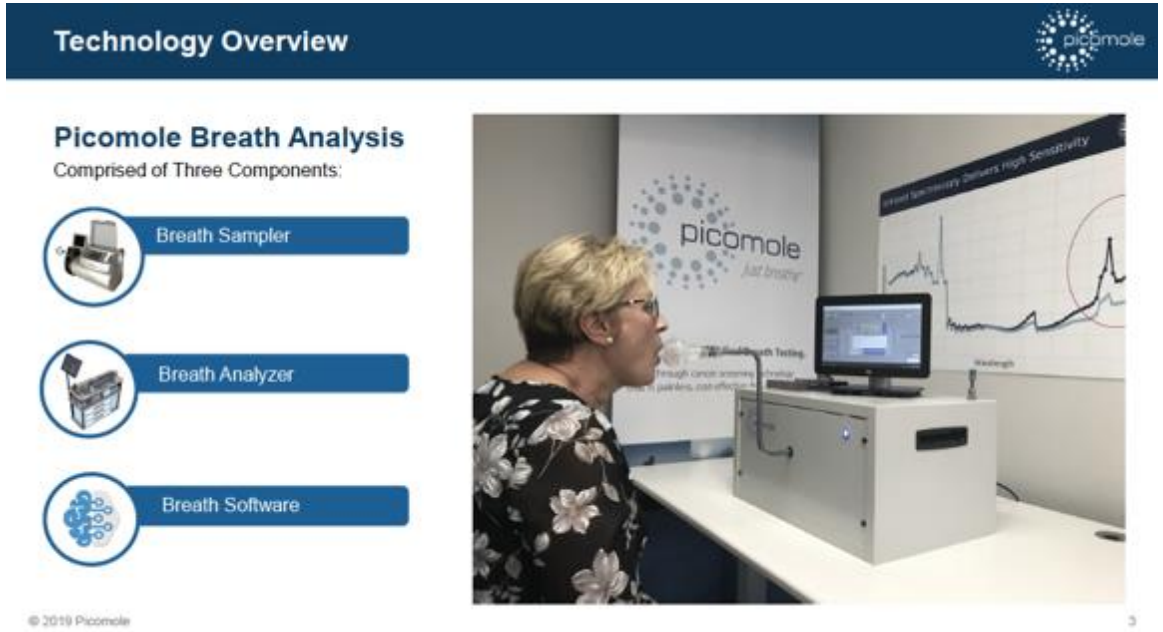
Lung cancer pilot
Mesothelioma
(pending funding)???

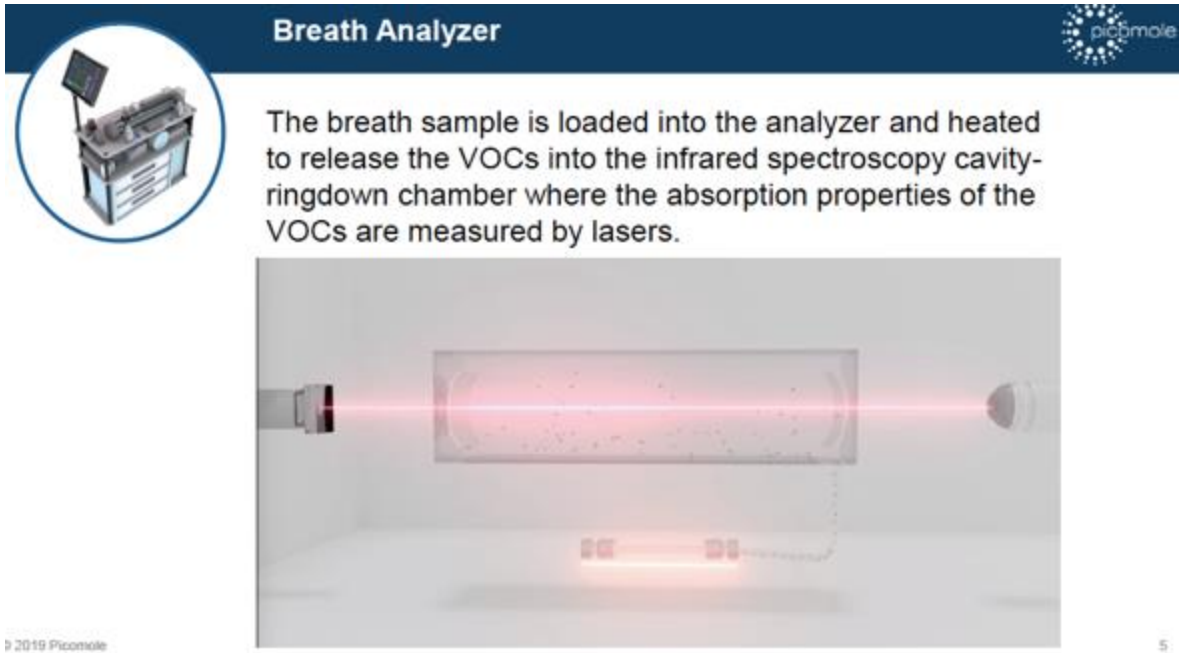


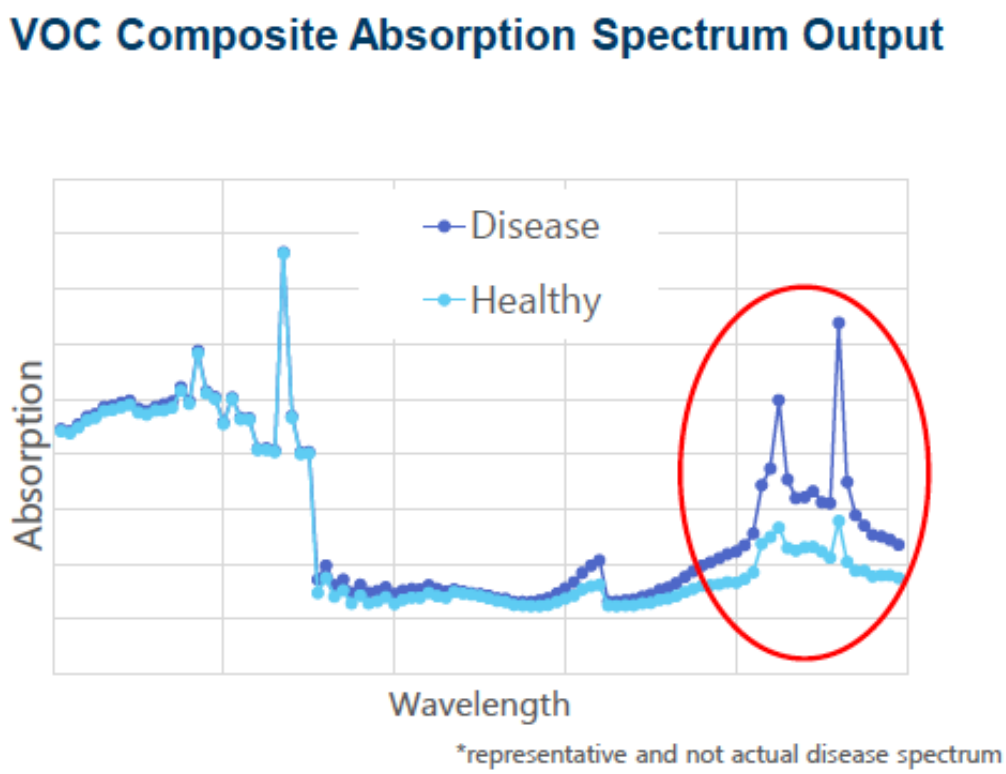




Other technologies: Picomole







Biomarker research can provide new information about biology and ALSO help with all aspects of mesothelioma care

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- I.U.O.E. Local 793
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- Motley Rice LLC
- Ontario Pipe Trades Council
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- United Association of Plumbing and Pipe Fitting Local 46
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