Perspectiva de Género en Cáncer de Pulmón: Aspectos Biológicos

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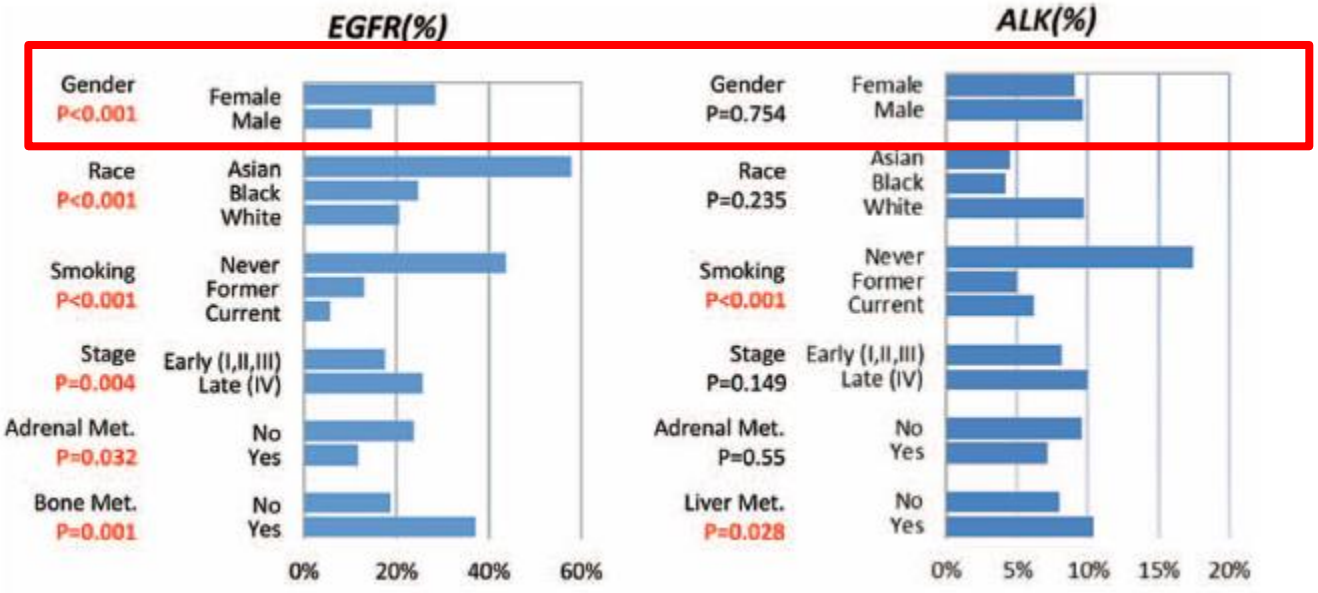
- Estudios individuales: *ROS1, RET, HER2*
- Reflexiones clínicas y metodológicas
- Conclusiones

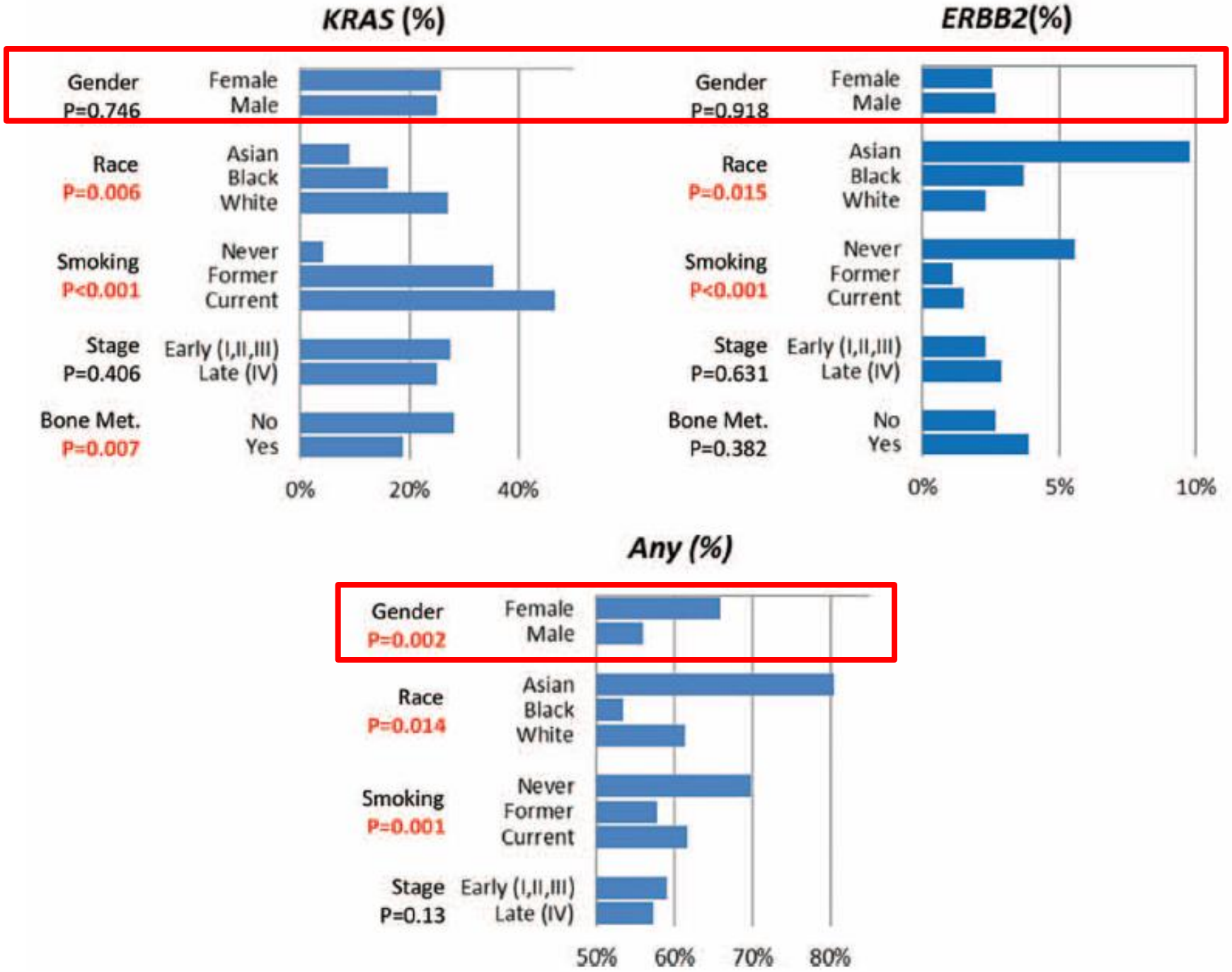
Multi-institutional Oncogenic Driver Mutation Analysis in Lung Adenocarcinoma

The Lung Cancer Mutation Consortium Experience

Lynette M. Sholl, MD, Dara L. Aisner, MD, PhD,† Marileila Varella-Garcia, PhD,†‡ Lynne D. Berry, PhD,§ Dora Dias-Santagata, PhD,‖ Ignacio I. Wistuba, MD,¶ Heidi Chen, PhD,§ Junya Fujimoto, MD, PhD,¶ Kelly Kugler, BA,‡ Wilbur A. Franklin, MD,† A. John Iafrate, MD, PhD,‖ Marc Ladanyi, MD,# Mark G. Kris, MD,# Bruce E. Johnson, MD,** Paul A. Bunn, MD,‡††, John D. Minna, MD,‡‡, and David J. Kwiatkowski MD, PhD,** On behalf of the LCMC Investigators*



J Thorac Oncol 2015


KRAS (%)
Gender
P=0.746
Female
Male
Race
P=0.006
Asian
Black
White
Smoking
P<0.001
Never
Former
Current
Stage
P=0.406
Early (I,II,III)
Late (IV)
Bone Met.
P=0.007
No
Yes
0%
20%
40%
ERBB2(%)
Gender
P=0.918
Female
Male
Race
P=0.015
Asian
Black
White
Smoking
P<0.001
Never
Former
Current
Stage
P=0.631
Early (I,II,III)
Late (IV)
Bone Met.
P=0.382
No
Yes
0%
5%
10%
Any (%)
Gender
P=0.002
Female
Male
Race
P=0.014
Asian
Black
White
Smoking
P=0.001
Never
Former
Current
Stage
P=0.13
Early (I,II,III)
Late (IV)
50%
60%
70%
80%

Routine molecular profiling of patients with advanced non-small-cell lung cancer: results of a 1-year nationwide programme of the French Cooperative Thoracic Intergroup (IFCT)

*Fabrice Barlesi, Julien Mazieres, Jean-Philippe Merlio, Didier Debieuvre, Jean Mosser, Hervé Lena, L'Houcine Ouafik, Benjamin Besse, Isabelle Rouquette, Virginie Westeel, Fabienne Escande, Isabelle Monnet, Antoinette Lemoine, Rémi Veillon, Hélène Blons, Clarisse Audigier-Valette, Pierre-Paul Bringuier, Régine Lamy, Michèle Beau-Faller, Jean-Louis Pujol, Jean-Christophe Sabourin, Frédérique Penault-Llorca, Marc G Denis, Sylvie Lantuejoul, Franck Morin, Quân Tran, Pascale Missy, Alexandra Langlais, Bernard Milleron, Jacques Cadranel, Jean-Charles Soria, Gérard Zalcman, for the Biomarkers France contributors**

Lancet Oncol 2016

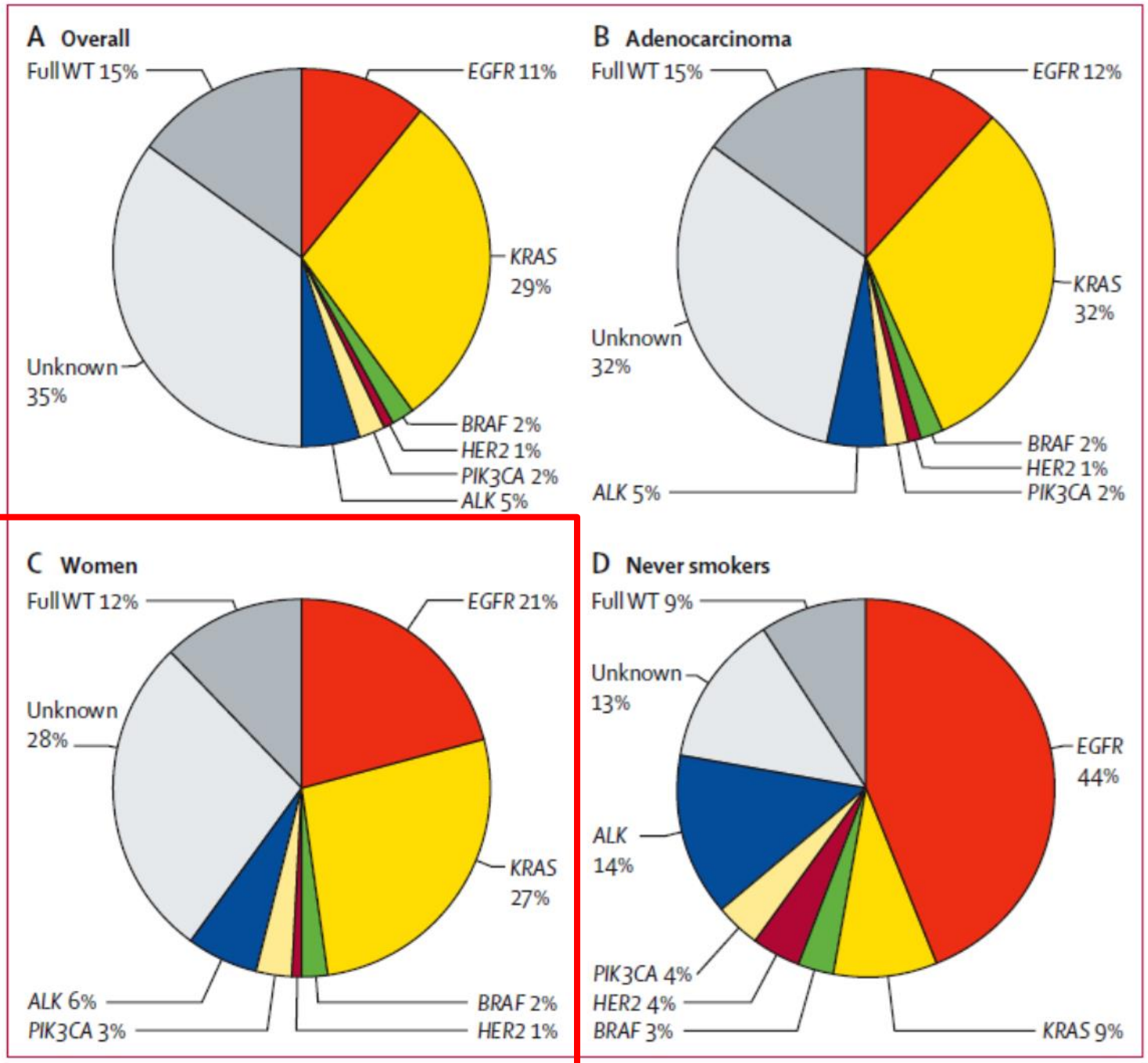


Figure 2: Frequency of genetic alterations

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ROS1 expression and translocations in non-small-cell lung cancer: clinicopathological analysis of 1478 cases

Arne Warth,[1] Thomas Muley,[2,3] Hendrik Dienemann,[3,4] Benjamin Goeppert,[1] Albrecht Stenzinger,[1] Philipp A Schnabel,[1,3] Peter Schirmacher,[1] Roland Penzel[1] & Wilko Weichert[1]

ROS1 EXPRESSION IS ASSOCIATED WITH FEMALE SEX, LOWER T STAGE, ADENOCARCINOMA HISTOMORPHOLOGY, AND DIAGNOSTIC IMMUNOMARKERS

Age was not related to either ROS1 immunohistochemistry or FISH status. However, ROS1 IHC positivity was significantly ($P < 0.001$) more likely in females (35/446, 7.8%) than in males (33/1032, 3.2%). Correspondingly, we observed a significantly higher rate of *ROS1* translocations in females (6/446, 1.3%) than in males (3/1032, 0.3%).

Histopathology 2014

ROS1 copy number alterations are frequent in non-small cell lung cancer

Sergi Clavé[1,2], Javier Gimeno[3], Ana M. Muñoz-Mármol[4], Joana Vidal[5], Noemí Reguart[6], Enric Carcereny[7], Lara Pijuan[3], Sílvia Menéndez[2,3], Álvaro Taus[5], José Luís Mate[4], Sergio Serrano[3], Joan Albanell[2,5], Blanca Espinet[1,2], Edurne Arriola[2,8] and Marta Salido[1,2]

Table 1: Clinicopathological features of the 314 *ROS1*-screened NSCLC patients

Feature	Global population	*ROS1* positive ($n = 5$)	p-value
	n (%)		
Median Age: y (range) ($n = 307$)	64 (25-91)	59 (42-74)	0.503
Sex ($n = 309$)			
Male	212 (69)	1 (20)	0.039
Female	97 (31)	4 (80)	

ROS1 rearrangements in lung adenocarcinoma: prognostic impact, therapeutic options and genetic variability

Matthias Scheffler[1,2,*], Anne Schultheis[1,3,*], Cristina Teixido[4], Sebastian Michels[1,2], Daniela Morales-Espinosa[5], Santiago Viteri[6], Wolfgang Hartmann[7], Sabine Merkelbach-Bruse[1,3], Rieke Fischer[1,2], Hans-Ulrich Schildhaus[8], Jana Fassunke[1,3], Martin Sebastian[9], Monika Serke[10], Britta Kaminsky[11], Winfried Randerath[11], Ulrich Gerigk[12], Yon-Dschun Ko[13], Stefan Krüger[14], Roland Schnell[15], Achim Rothe[16], Cornelia Kropf-Sanchen[17], Lukas Heukamp[1,3], Rafael Rosell[6,18,19], Reinhard Büttner[1,3,*], Jürgen Wolf[1,2,*]

Table 1: Clinical characteristics of patients with ROS1-rearrangement ($n = 19$)

Characteristics	Number of patients	Years	%
Age at diagnosis *Mean* *Standard deviation* *Median* *Range*	19	 58.6 14.8 60 26–82	100
Gender *Women* *Men*	 9 10		 47.4 52.6
Smoking *Never* *Former* *Current*	 13 3 3		 68.4 15.8 15.8

Clinicopathological Characteristics of *RET* Rearranged Lung Cancer in European Patients

Sebastian Michels, MD,[a,b,c] Andreas Hans Scheel, MD,[c,d] Matthias Scheffler, MD,[a,b,c]

Results: Rearrangements of *RET* were identified in 22 patients, with a prevalence of 2.2% in the *KRAS/EGFR/ALK* wildtype subgroup. Co-occurring genetic aberrations were detected in 10 patients, and the majority had mutations in *TP53*. The median age at diagnosis was 62 years (range, 39–80 years; mean ± SD, 61 ± 11.7 years) with a higher proportion of men (59% versus 41%). There was only a slight predominance of nonsmokers (54.5%) compared to current or former smokers (45.5%).

J Thorac Oncol 2016

Lung cancer patients with *HER2* mutations treated with chemotherapy and *HER2*-targeted drugs: results from the European EUHER2 cohort

J. Mazières[1*], F. Barlesi[2], T. Filleron[3], B. Besse[4], I. Monnet[5], M. Beau-Faller[6], S. Peters[7], E. Dansin[8], M. Früh[9], M. Pless[10], R. Rosell[11], M. Wislez[12], P. Fournel[13], V. Westeel[14], F. Cappuzzo[15], A. Cortot[16], D. Moro-Sibilot[17], J. Milia[1] & O. Gautschi[18]

Table 1. Clinical and biological characteristics of patients with an *HER2* mutation ($n = 101$)

	Number	Value
Age at initial diagnosis, years ($n = 101$)		
Median		61
Range		30–87 years
Gender		
Male	38	37.6%
Female	63	62.4%

Ann Oncol 2016

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Original Investigation

Association Between Younger Age and Targetable Genomic Alterations and Prognosis in Non–Small-Cell Lung Cancer

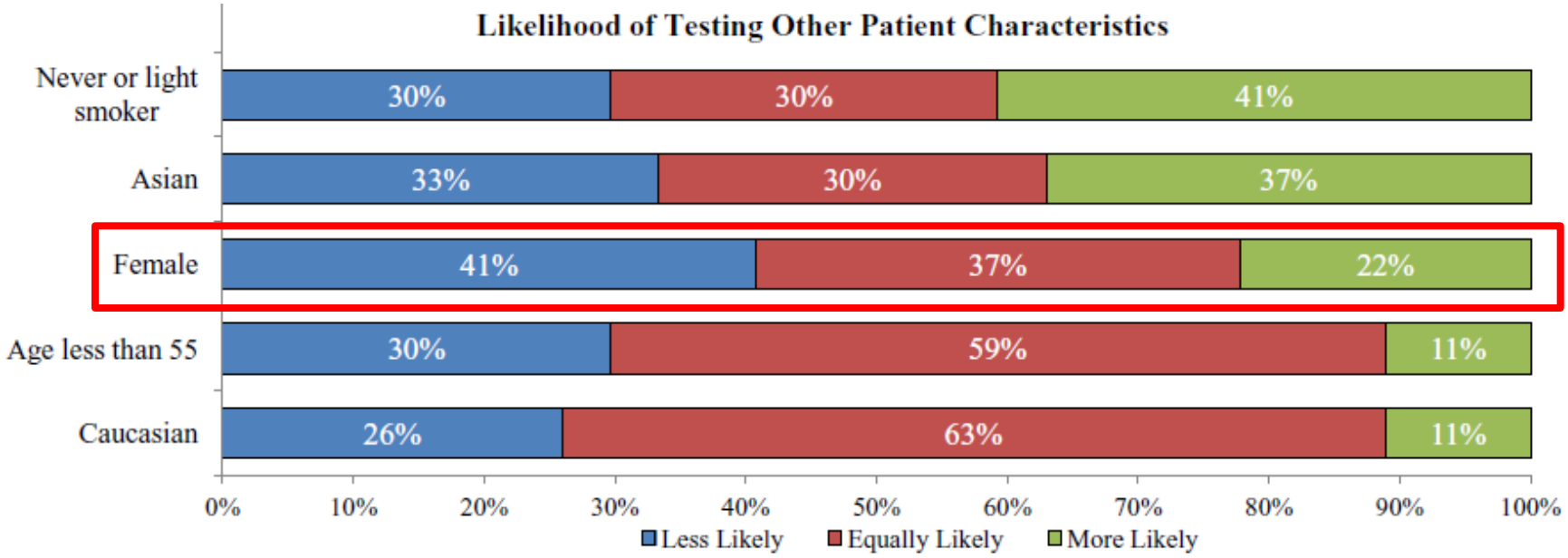
Adrian G. Sacher, MD; Suzanne E. Dahlberg, PhD; Jennifer Heng, BS; Stacy Mach, BA; Pasi A. Jänne, MD, PhD; Geoffrey R. Oxnard, MD

expected, smoking status ($P < .001$), female sex ($P = .02$), and Asian race ($P = .03$) were significantly associated with presence of a targetable genotype. Controlling for these factors, we found that this model maintained a significant association between age and the presence of a targetable genotype ($P = .006$) (eTable 1 in the Supplement). Examining the individual targe-

tient. We are not suggesting substandard genotyping in older patients but rather advocating more aggressive efforts to routinely search for rare and even potentially novel targetable alterations in young patients. Because not all patients have ac-

ALK rearrangement testing and treatment patterns for patients with *ALK*-positive non-small cell lung cancer

Annie Guérin [a,*], Medha Sasane [b], Jie Zhang [b], Alexander R. Macalalad [c], Philip Galebach [c], John Jarvis [c], Andrew Kageleiry [c], Kenneth Culver [b], Eric Q. Wu [c], Heather Wakelee [d]



Cancer Epidemiology 2015

Published OnlineFirst January 7, 2015; DOI: 10.1158/1078-0432.CCR-14-2683

Personalized Medicine and Imaging

Clinical Cancer Research

Broad, Hybrid Capture–Based Next-Generation Sequencing Identifies Actionable Genomic Alterations in Lung Adenocarcinomas Otherwise Negative for Such Alterations by Other Genomic Testing Approaches

Alexander Drilon[1], Lu Wang[1], Maria E. Arcila[1], Sohail Balasubramanian[2], Joel R. Greenbowe[2], Jeffrey S. Ross[2], Phil Stephens[2], Doron Lipson[2], Vincent A. Miller[2], Mark G. Kris[1], Marc Ladanyi[1], and Naiyer A. Rizvi[1]

Genomic alteration uncovered by NGS that prior non-NGS testing was poised to detect	
Alteration	**Potential reason not detected by non-NGS testing**
None	N/A
None	N/A
SOCS5-ALK	*ALK* FISH clearly negative, possible complex rearrangement
CCDC6-RET	*RET* FISH failure, after fusion detected by NGS, alternate FISH protocol performed and *RET* fusion was confirmed
None	N/A
KRAS Q61H	Potentially secondary to lower sensitivity of Sequenom
None	N/A
None	N/A
EGFR exon20 ins V769_D770 insGGTR	Potentially secondary to lower sensitivity of *EGFR* sizing assay
None	Note: *EGFR* L747P was a double mutation (c.2239_2240TT>CC) that was not interrogated by Sequenom
None	N/A
None	N/A
None	N/A
CD74-ROS1	Negative via *ROS1* FISH, poor hybridization noted in some areas
None	N/A
BRAF V600E	Potentially secondary to lower sensitivity of Sequenom: a low frequency of the alteration was detected via NGS
KIF5B-RET	Negative via *RET* FISH at MSK and outside institution, initially identified as complex *RET* fusion by NGS and later determined to be *KIF5B-RET* after RNAseq testing

Drilon *et al*. Clin Cancer Res 2015

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Conclusiones

- “Grasp all, lose all”
- Protocolizar los pacientes pan-negativos
- Teoría: con cada marcador negativo aumenta probabilidad de encontrar una diana
- Práctica: redundancia molecular

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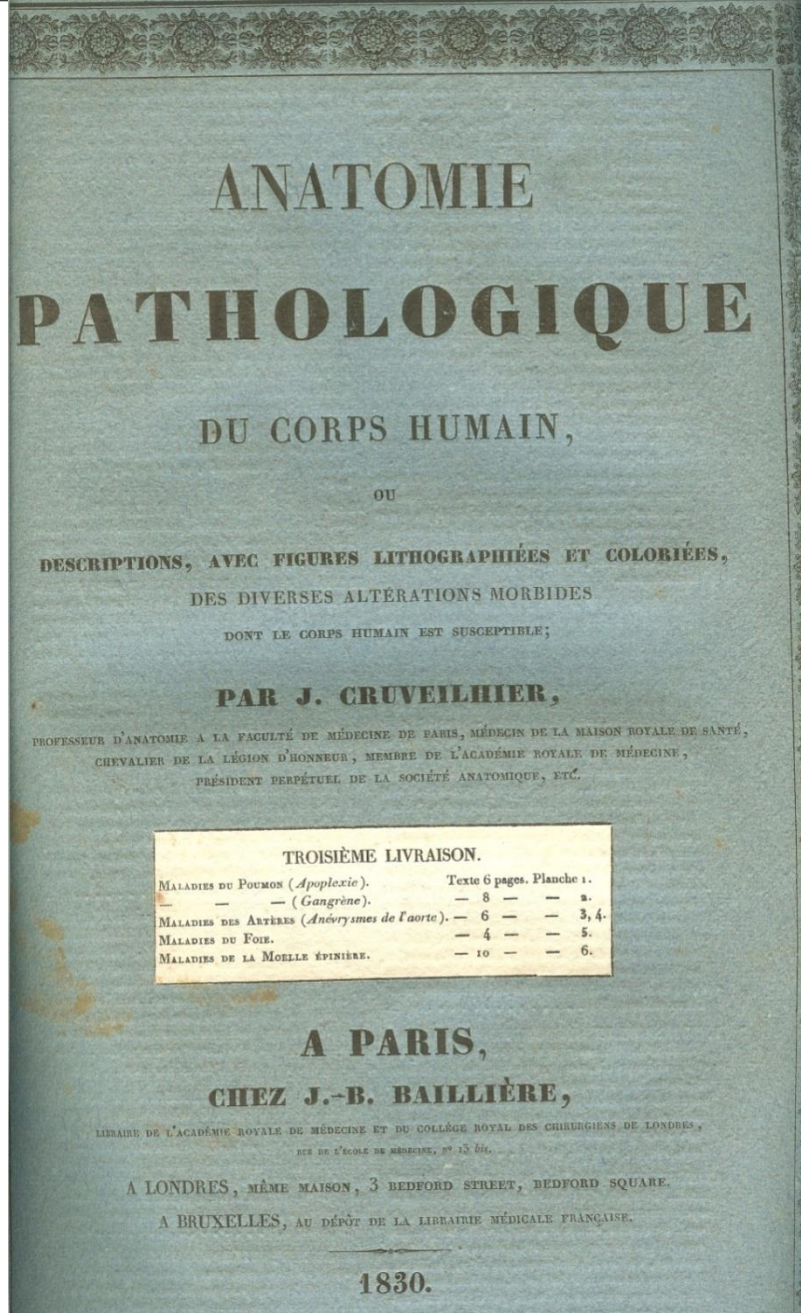

ANATOMIE

PATHOLOGIQUE

DU CORPS HUMAIN,

OU

DESCRIPTIONS, AVEC FIGURES LITHOGRAPHIÉES ET COLORIÉES,

DES DIVERSES ALTÉRATIONS MORBIDES

DONT LE CORPS HUMAIN EST SUSCEPTIBLE;

PAR J. CRUVEILHIER,

PROFESSEUR D'ANATOMIE A LA FACULTÉ DE MÉDECINE DE PARIS, MÉDECIN DE LA MAISON ROYALE DE SANTÉ, CHEVALIER DE LA LÉGION D'HONNEUR, MEMBRE DE L'ACADÉMIE ROYALE DE MÉDECINE, PRÉSIDENT PERPÉTUEL DE LA SOCIÉTÉ ANATOMIQUE, ETC.

TROISIÈME LIVRAISON.

Maladies du Poumon (*Apoplexie*).	Texte 6 pages.	Planche 1.
— — — (*Gangrène*).	— 8 —	— 2.
Maladies des Artères (*Anévrysmes de l'aorte*).	— 6 —	— 3, 4.
Maladies du Foie.	— 4 —	— 5.
Maladies de la Moelle épinière.	— 10 —	— 6.

A PARIS,

CHEZ J.-B. BAILLIÈRE,

LIBRAIRE DE L'ACADÉMIE ROYALE DE MÉDECINE ET DU COLLÉGE ROYAL DES CHIRURGIENS DE LONDRES, RUE DE L'ÉCOLE DE MÉDECINE, N° 13 bis.

A LONDRES, MÊME MAISON, 3 BEDFORD STREET, BEDFORD SQUARE.

A BRUXELLES, AU DÉPÔT DE LA LIBRAIRIE MÉDICALE FRANÇAISE.

1830.