RETOS DE LA MEDICINA DE PRECISIÓN

XXV ANIVERSARIO

Servicio de Oncología médica

Hospital de Basurto

Francisco Ayala de la Peña
Hospital G. Universitario Morales Meseguer
Universidad de Murcia

25 ONKOLOGIA MEDIKOAREN URTEURRENA
ANIVERSARIO ONCOLOGÍA MÉDICA

Etorkizunari begira
Mirando al futuro

DECLARACIÓN DE POTENCIALES CONFLICTOS DE INTERESES

Título de la presentación: Retos de la Medicina de Precisión
Autor: Francisco Ayala de la Peña

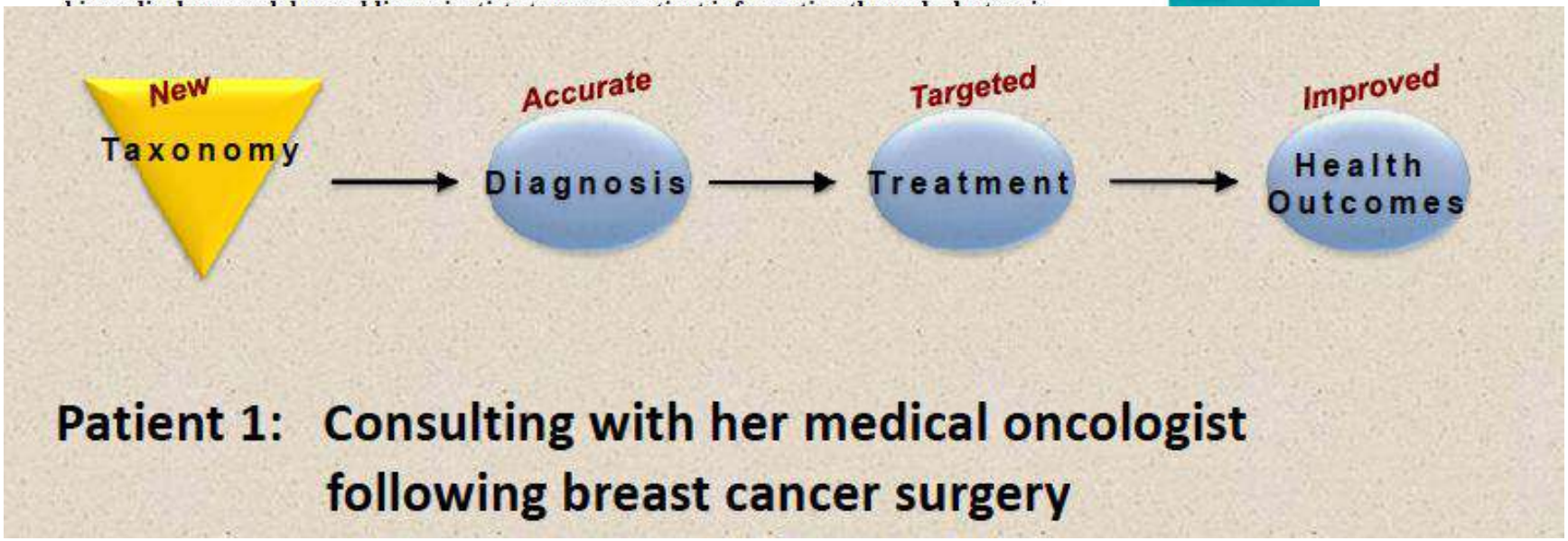
- Relativas a esta presentación existen las siguientes relaciones que podrían ser percibidas como potenciales conflictos de interés:
  - Advisory: Pfizer, Roche
  - Fondos para investigación: Celgene, Roche
  - Charlas en reuniones promovidas por industria: AstraZeneca, Celgene, Eisai, Novartis, Pfizer, Pierre Fabre, Roche
  - Congresos/Symposia: Celgene, Eisai, Pfizer, Pierre Fabre, MSD, Roche
  - Programas educacionales: MSD, Roche

NATIONAL ACADEMY OF SCIENCES
NATIONAL ACADEMY OF ENGINEERING
INSTITUTE OF MEDICINE
NATIONAL RESEARCH COUNCIL

REPORT IN BRIEF

Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease

A new data network that integrates emerging research on the molecular makeup of diseases with clinical data on individual patients could drive the development of a more accurate classification of disease and ultimately enhance diagnosis and treatment. Recent advances in biomedical research have caused an explosion of data, offering the potential to develop a "New Taxonomy" that defines disease based on underlying molecular and environmental causes, rather than on physical signs and symptoms. This report outlines how research and clinical data can be captured in a "Knowledge Network" that will be broadly accessible to researchers and clinicians. As well as improving health care, the new data network could also improve



Patient 1: Consulting with her medical oncologist following breast cancer surgery

http://dels.nas.edu/Materials/Presentations/Precision-Medicine?bname=bls

LAS “PROMESAS” DE LA MEDICINA DE PRECISIÓN

Conocimiento molecular de la enfermedad y estratificación pronóstica

Identificación de dianas terapéuticas y disponibilidad de biomarcadores predictivos

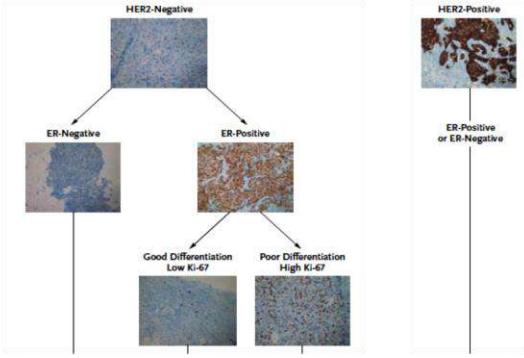
Conocimiento molecular de la evolución de la neoplasia y adaptación del tratamiento

Conocimiento de las características del huésped y personalización del tratamiento de acuerdo a la respuesta o toxicidad esperables

Precisión en el diagnóstico precoz

Mejora de los resultados del tratamiento

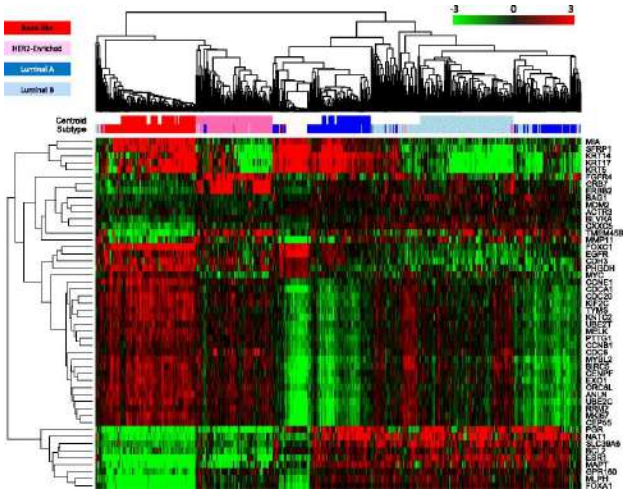
Clasificación molecular del cáncer de mama

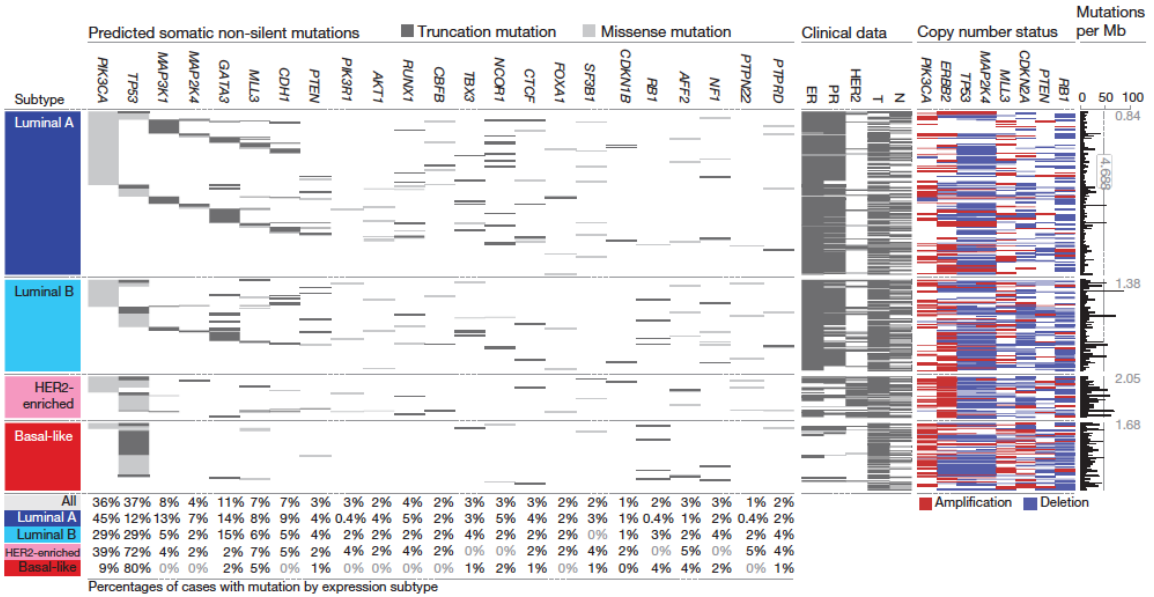


CM triple negativo
Her2-, RE-, RP-
(CK5/6, EGFR)

CM luminal u hormonosensible
RE+ o/y RP+
(Ki67: LumA/ LumB)

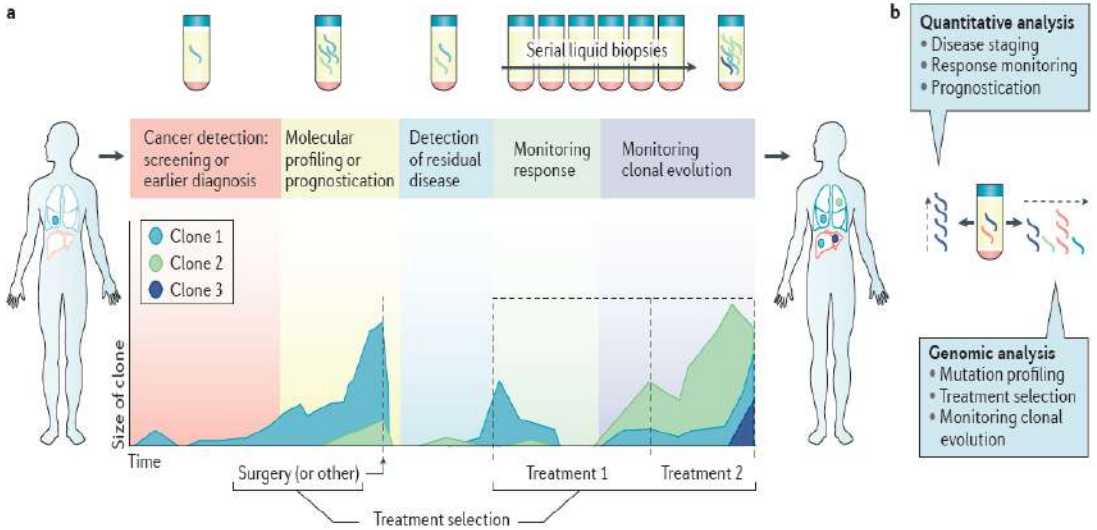
CM Her2+
Her2++
(RE/RP + o -)

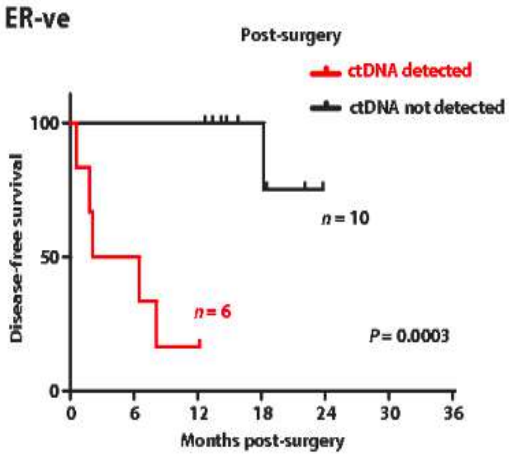


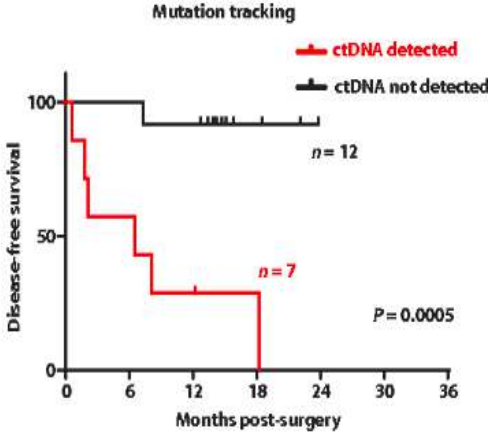


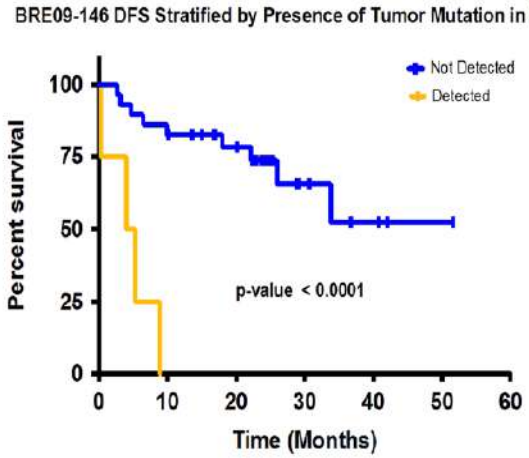
Perou, Nature 00; Prat, Nat Med 09; Coates, Ann Oncol 2015; TCGA, Nature 2012

Biomarcadores (ctDNA, CTC) para identificar grupos de mal pronóstico









Wan, Nat Rev Cancer 2017; Chan, NPJ Breast Cancer 2017; Garcia-Murillas, Sci Transl Medicine 2015

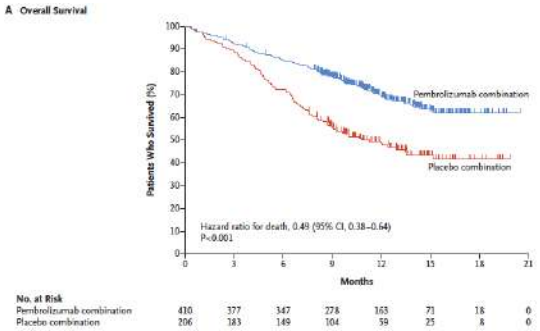
Identificación de nuevas dianas

LUNG CANCER IN 2018

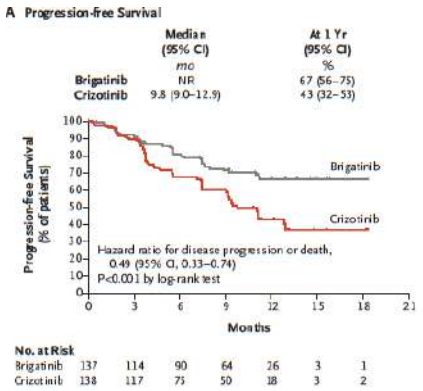
A banner year for immunotherapy and targeted therapy

Jennifer W. Carlisle and Suresh S. Ramalingam

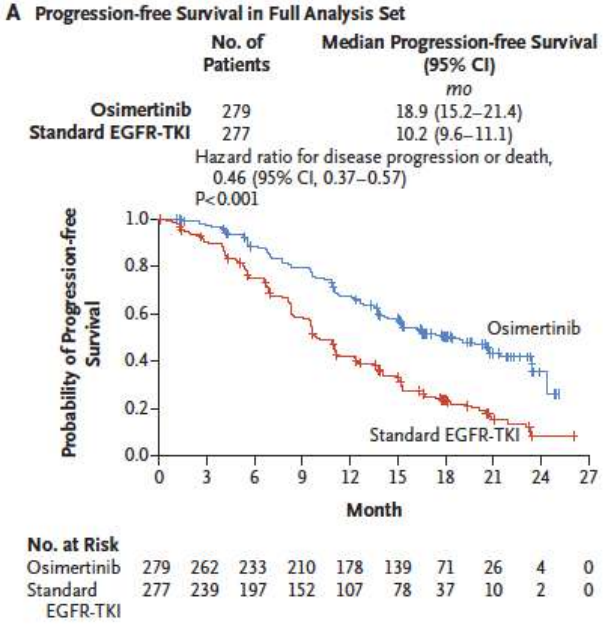
Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer



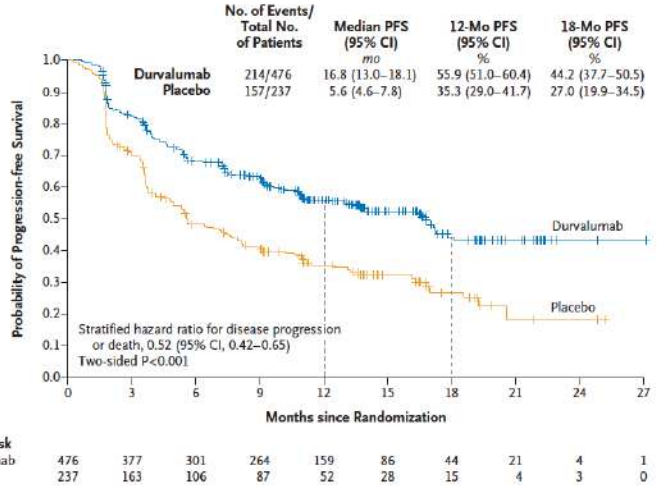
Brigatinib versus Crizotinib in *ALK*-Positive Non–Small-Cell Lung Cancer



Osimertinib in Untreated *EGFR*-Mutated Advanced Non–Small-Cell Lung Cancer



Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer



Carlisle&Ramalingam, Nat Rev Clin Oncol 2019; Camidge, N Engl J Med 2018; Antonia, N Engl J Med 2018; Soria, N Engl J Med 2018; Gandhi, N Engl J Med 2018

Identificación de nuevas dianas agnósticas (o casi agnósticas)

ARTICLE

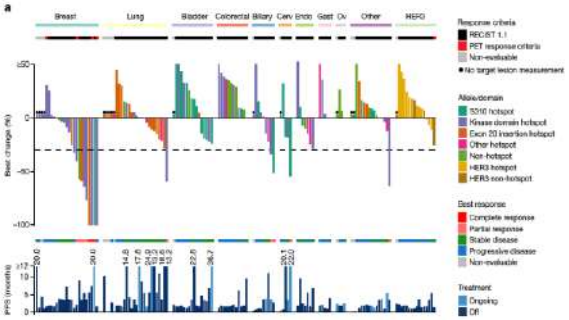
doi:10.1038/nature25475

HER kinase inhibition in patients with HER2- and HER3-mutant cancers

David M. Hyman[1], Sarina A. Piha-Paul[2], Helen Won[1], Jordi Rodon[2], Cristina Saura[3], Geoffrey I. Shapiro[4], Dejan Juric[5], David L. Quinn[6], Victor Moreno[7], Bernard Doger[7], Ingrid A. Mayer[8], Valentina Boni[9], Emiliano Calvo[9], Sherene Loi[10], Albert C. Lockhart[11], Joseph P. Erinjeri[3], Maurizio Scaltriti[1], Gary A. Ulaner[3], Juber Patel[3], Jiabin Tang[1], Hannah Beer[1], S. Duyga Selcuklu[1], Aphrothiti J. Hanrahan[1], Nancy Bouvier[1], Myra Melcer[1], Rajmohan Murali[1], Alison M. Schram[1], Lillian M. Smyth[1], Komal Jhaveri[1], Bob T. Li[1], Alexander Drilon[1], James J. Harding[1], Gopa Iyer[1], Barry S. Taylor[1], Michael F. Berger[1], Richard E. Cutler Jr[12], Feng Xu[12], Anna Butturini[12], Lisa D. Eli[12], Grace Mann[12], Cynthia Farrell[12], Alshad S. Lalani[12], Richard P. Bryce[12], Carlos L. Arteaga[8], Funda Meric-Bernstam[2], José Baselga[1] & David B. Solit[1]

Mutacion HER2-3

Neratinib

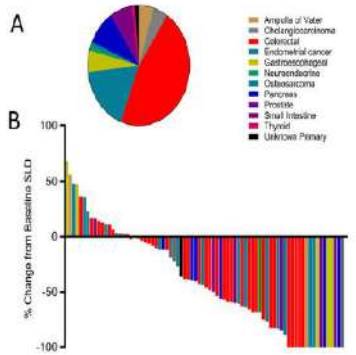


Published in final edited form as:
Science. 2017 July 28; 357(6349): 409–413. doi:10.1126/science.aan6733.

Mismatch-repair deficiency predicts response of solid tumors to PD-1 blockade

MSI-high

Pembrolizumab



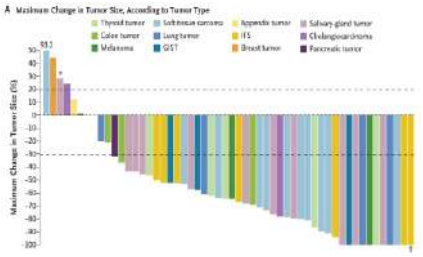
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy of Larotrectinib in *TRK* Fusion–Positive Cancers in Adults and Children

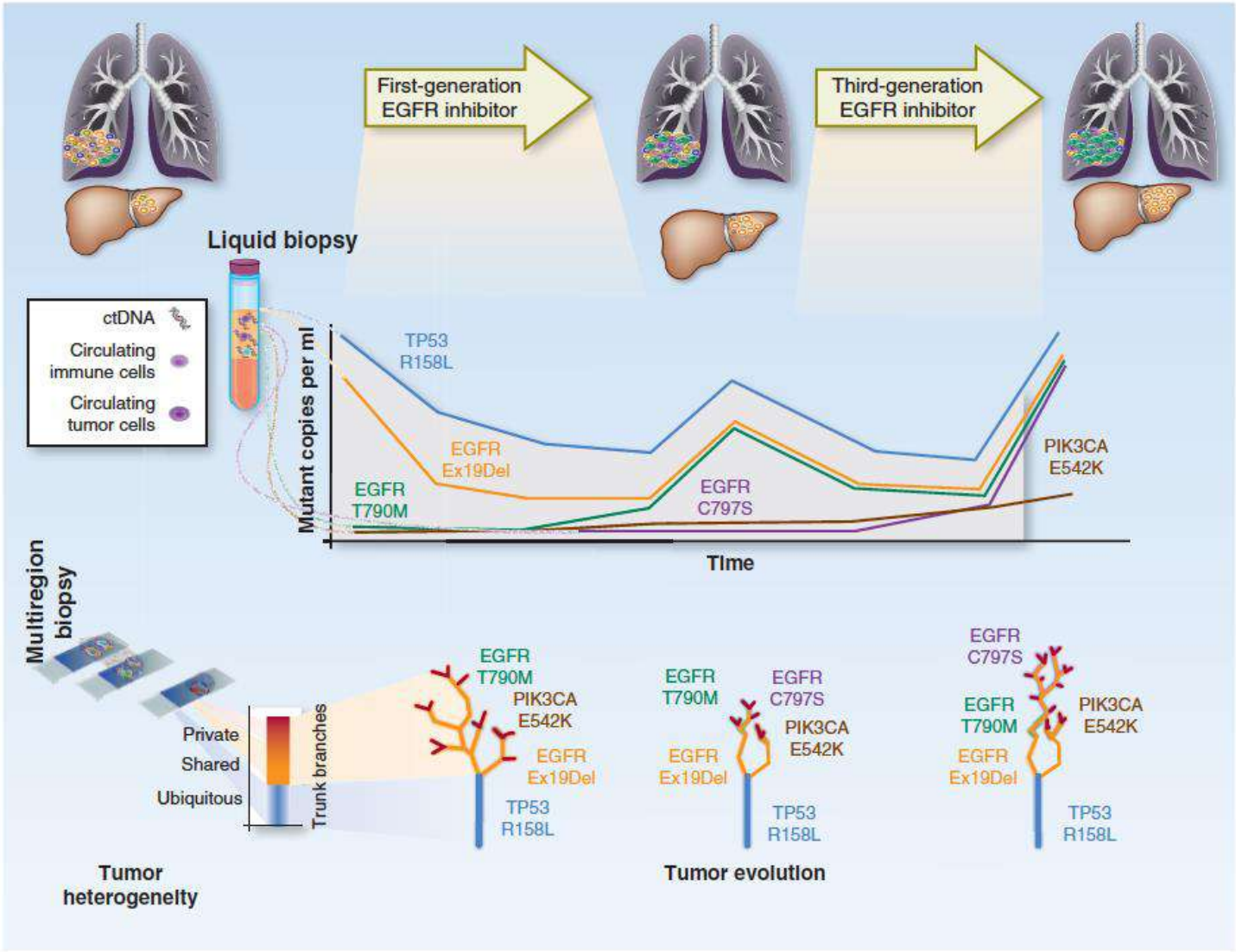
Fusión TRK

Larotrectinib



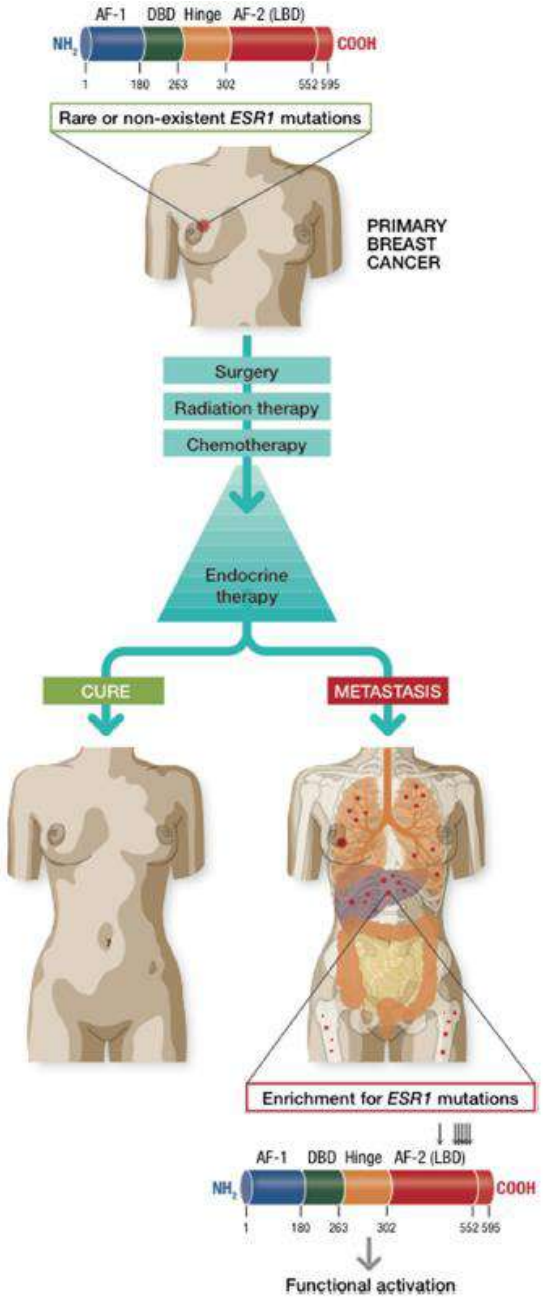
Hyman, Nature 2018; Le, Science 2017; Chen, N Engl J Med 2018

Resistencia al tratamiento: EGFR TKI

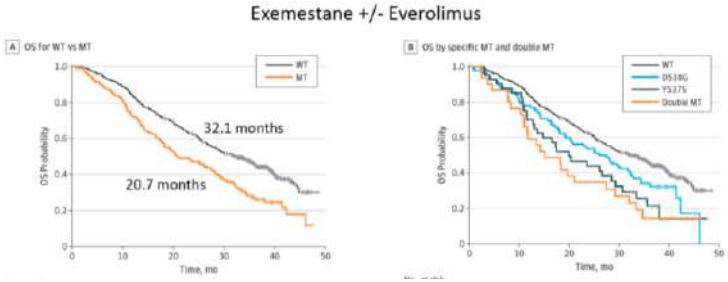


Amirouchene-Angelozzi, Cancer Discov 2017

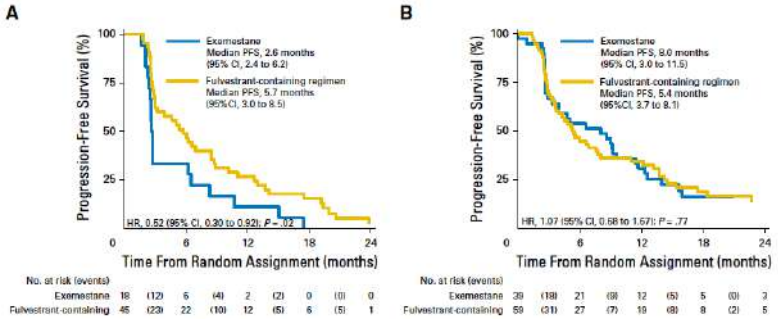
Resistencia a tratamiento: inhibidores de aromatasa



- **Valor pronóstico en CMM luminal (BOLERO-2)**



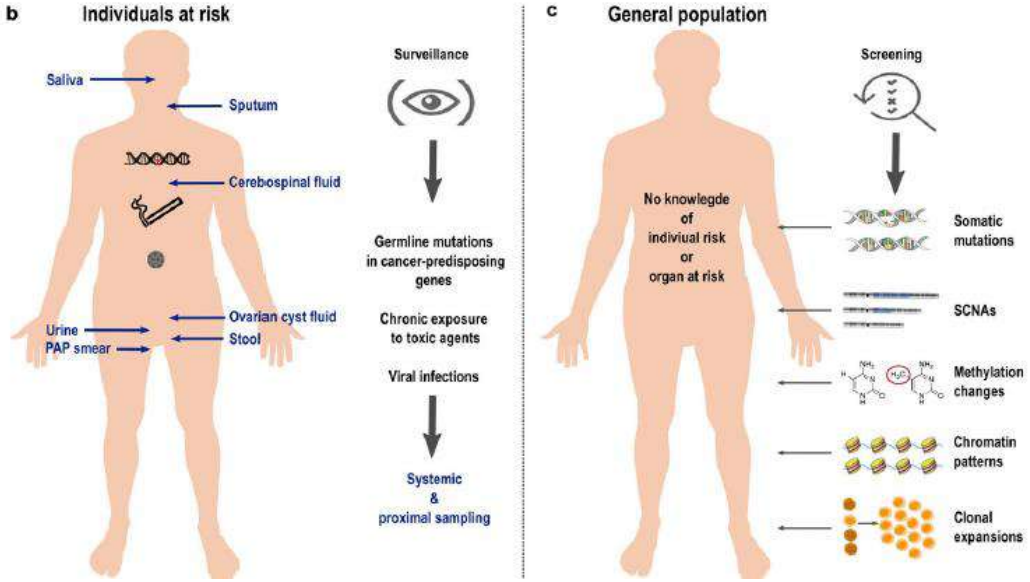
- **Valor predictivo de beneficio de fulvestrant (SG) superior a IA (SOFEA)**

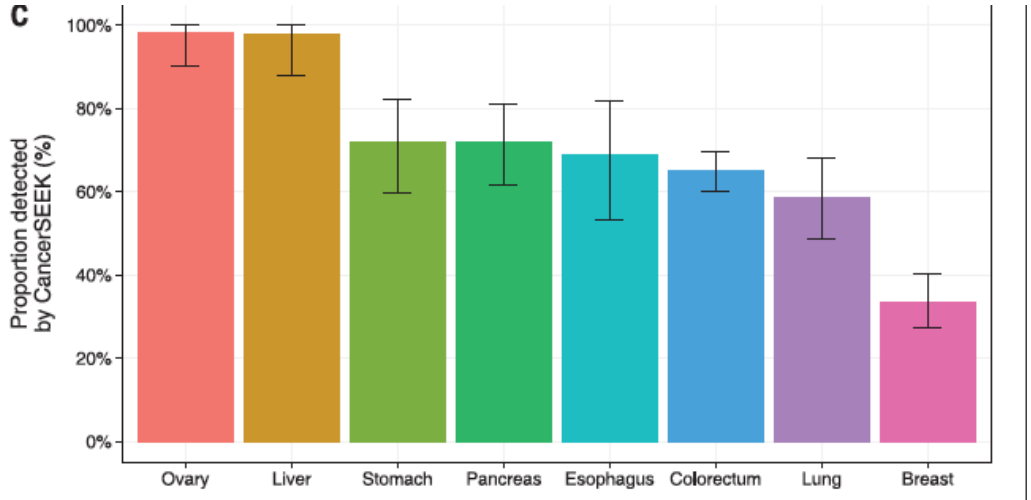


- **Relación con beneficio de everolimus (BOLERO-2) en mut Y537S**

Toy, Nat Gen 2013; Yamamoto-Isubiki, BMC Med 2015; Ma, Nat Rev Cancer 2015; Prat, IMPAKT 2017; Jeselsohn, Clin Cancer Res 2014; Chandarlapaty, JAMA Oncol 2016; Fribbens, J Clin Oncol 2016

Precisión en el diagnóstico precoz: ctDNA





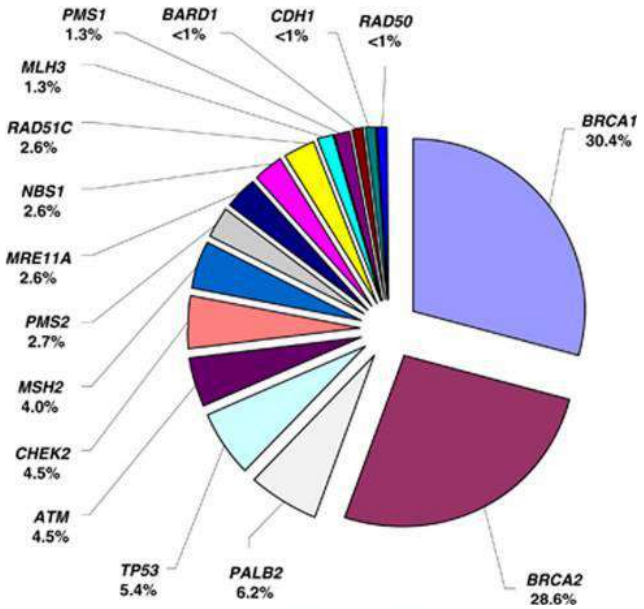
CANCER

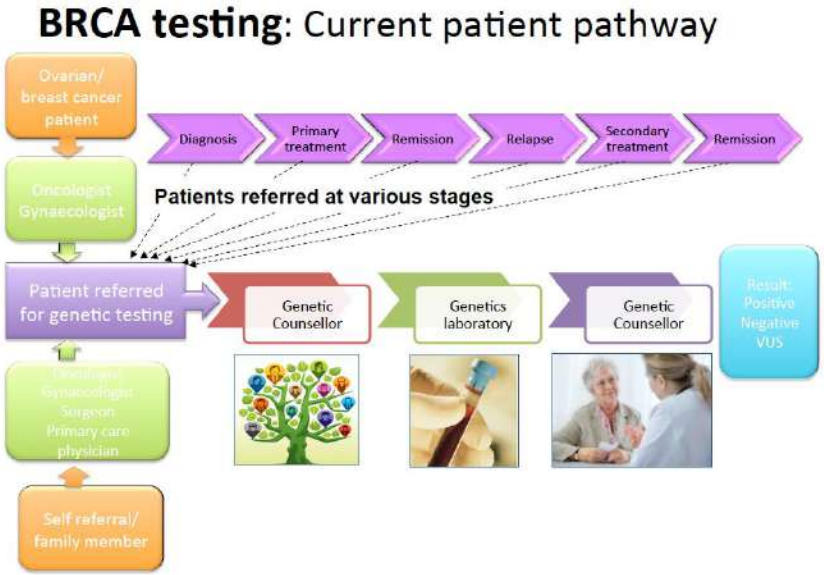
Detection and localization of surgically resectable cancers with a multi-analyte blood test

Joshua D. Cohen,[1,2,3,4,5] Lu Li,[6] Yuxuan Wang,[1,2,3,4] Christopher Thoburn,[3] Bahman Afsari,[7] Ludmila Danilova,[7] Christopher Douville,[1,2,3,4] Ammar A. Javed,[8] Fay Wong,[1,3,4] Austin Mattox,[1,2,3,4] Ralph. H. Hruban,[3,4,9] Christopher L. Wolfgang,[8] Michael G. Goggins,[3,4,9,10,11] Marco Dal Molin,[4] Tian-Li Wang,[3,9] Richard Roden,[3,9] Alison P. Klein,[3,4,12] Janine Ptak,[1,2,3,4] Lisa Dobbyn,[1,3,4] Joy Schaefer,[1,3,4] Natalie Silliman,[1,2,3,4] Maria Popoli,[1,3,4] Joshua T. Vogelstein,[13] James D. Browne,[14] Robert E. Schoen,[15,16] Randall E. Brand,[15] Jeanne Tie,[17,18,19,20] Peter Gibbs,[17,18,19,20] Hui-Li Wong,[17] Aaron S. Mansfield,[21] Jin Jen,[22] Samir M. Hanash,[23] Massimo Falconi,[24] Peter J. Allen,[25] Shibin Zhou,[1,3,4] Chetan Bettegowda,[1,3,4] Luis A. Diaz Jr.,[1,3,4*] Cristian Tomasetti,[3,6,7†] Kenneth W. Kinzler,[1,3,4†] Bert Vogelstein,[1,2,3,4†] Anne Marie Lennon,[3,4,8,10,11†] Nickolas Papadopoulos[1,3,4†]

Heitzer, Precision Oncology 2017; Cohen, Science 2018

Medicina de precisión: pacientes





The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Olaparib for Metastatic Breast Cancer in Patients with a Germline *BRCA* Mutation

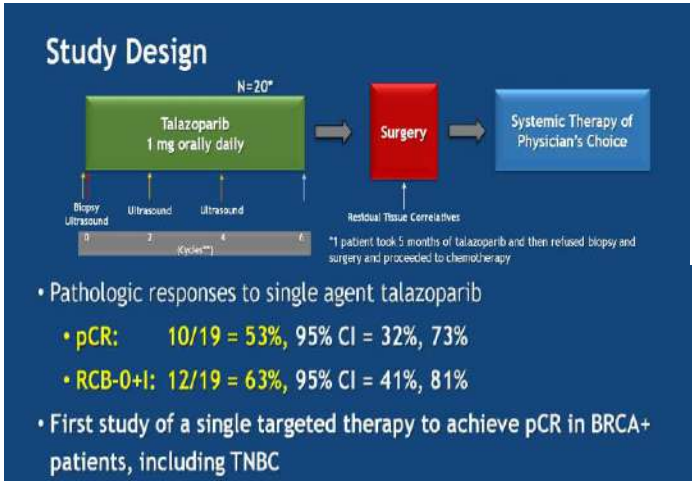
Mark Robson, M.D., Seock-Ah Im, M.D., Ph.D., Elzbieta Senkus, M.D., Ph.D., Binghe Xu, M.D., Ph.D., Susan M. Domchek, M.D., Norikazu Masuda, M.D., Ph.D., Suzette Delaloge, M.D., Wei Li, M.D., Nadine Tung, M.D., Anne Armstrong, M.D., Ph.D., Wenting Wu, Ph.D., Carsten Goessl, M.D., Sarah Runswick, Ph.D., and Pierfranco Conte, M.D.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

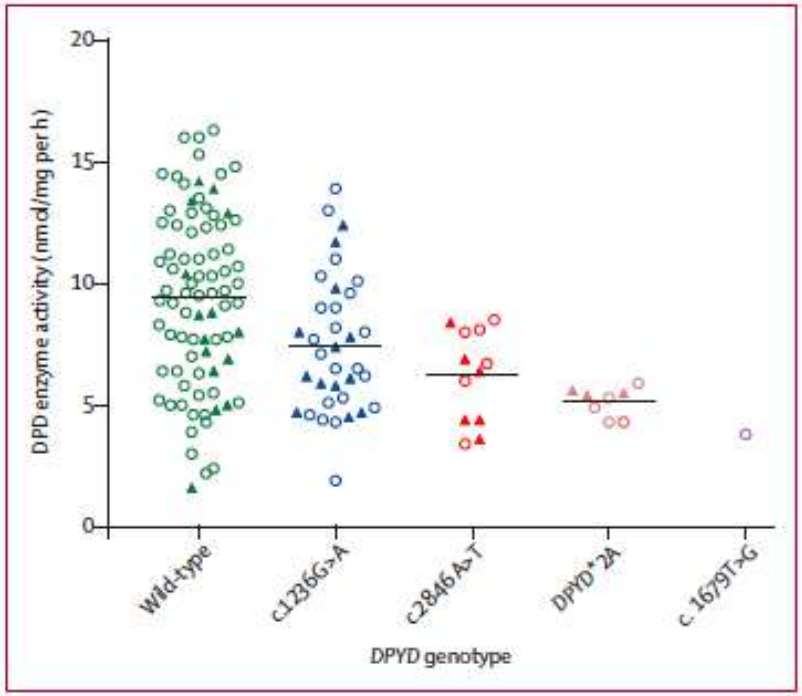
Talazoparib in Patients with Advanced Breast Cancer and a Germline *BRCA* Mutation

Jennifer K. Litton, M.D., Hope S. Rugo, M.D., Johannes Ettl, M.D., Sara A. Hurvitz, M.D., Anthony Gonçalves, M.D., Ph.D., Kyung-Hun Lee, M.D., Ph.D., Louis Fehrenbacher, M.D., Rinat Yerushalmi, M.D., Lida A. Mina, M.D., Miguel Martin, M.D., Ph.D., Henri Roché, M.D., Ph.D., Young-Hyuck Im, M.D., Ph.D., Ruben G.W. Quek, Ph.D., Denka Markova, Ph.D., Iulia C. Tudor, Ph.D., Alison L. Hannah, M.D., Wolfgang Eiermann, M.D., and Joanne L. Blum, M.D., Ph.D.



Castera, Eur J Hum Gen 2014; Hyman, AACR 2018; Robson, N Eng J Med 2017; Litton, ASCO 2018; Litton, N Engl J Med 2018

Medicina de precisión: pacientes



Toxicidad grado ≥ 3

	DPYD variant carriers treated with reduced dose (current study)*	DPYD variant carriers treated with full dose† (previous meta-analysis)
c.1236G>A	1·69 (1·18–2·42)	1·72 (1·22–2·42)
c.2846A>T	2·00 (1·19–3·34)	3·11 (2·25–4·28)
DPYD*2A	1·31 (0·63–2·73)	2·87 (2·14–3·86)
c.1679T>G	NA‡	4·30 (2·10–8·80)

DPYD genotype-guided dose individualisation of fluoropyrimidine therapy in patients with cancer: a prospective safety analysis

Linda M Henricks*, Carin A T C Lunenburg*, Femke M de Man*, Didier Meulendijks, Geert W J Frederix, Emma Kienhuis, Geert-Jan Creemers, Arnold Baars, Vincent O Dezentjé, Alexander L T Imholz, Frank J F Jansissen, Johanna E A Portielje, Rob L H Jansen, Paul Hamberg, Albert J ten Tije, Helga J Droogendijk, Miriam Koopman, Peter Nieboer, Marlène H W van de Poel, Caroline M P W Mandigers, Hilde Rosing, Jos H Beijnen, Erik van Werkhoven, André B P van Kuilenburg, Ron H N van Schaik, Ron H J Mathijssen, Jesse J Swen, Hans Gelderblom, Annemieke Cats, Henk-Jan Guchelaar, Jan H M Schellens

Summary

Background Fluoropyrimidine treatment can result in severe toxicity in up to 30% of patients and is often the result

Lancet Oncol 2018; 19:1459–67

European Journal of Cancer 107 (2019) 60–67

Available online at www.sciencedirect.com

ScienceDirect

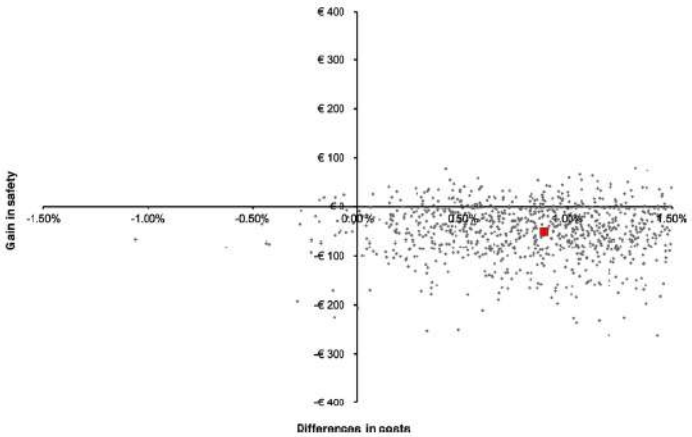
journal homepage: www.ejcancer.com

ELSEVIER

EJC

Original Research

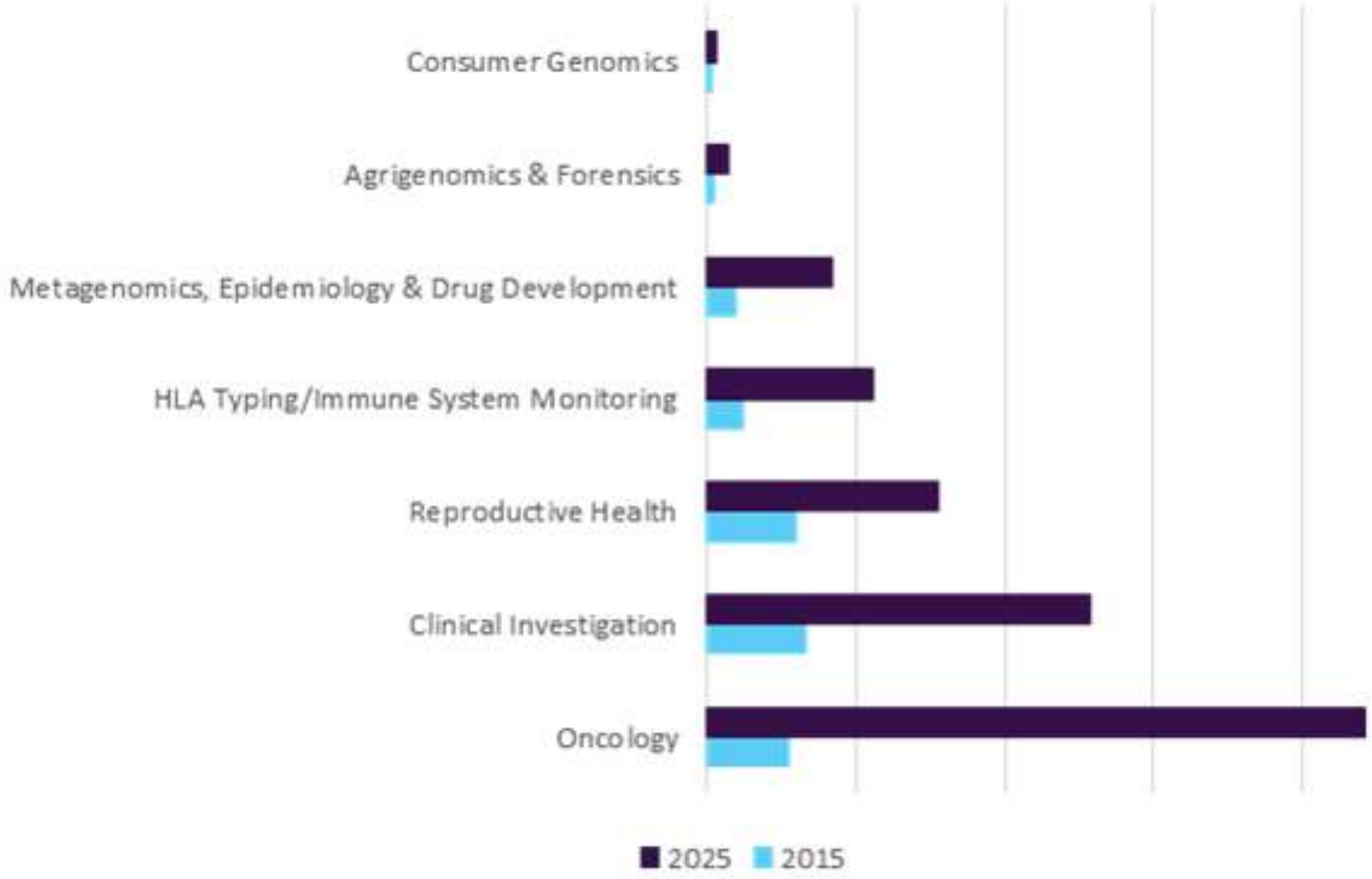
A cost analysis of upfront *DPYD* genotype–guided dose individualisation in fluoropyrimidine-based anticancer therapy



Henricks, Lancet Oncol 2018; Henricks, Eur J Cancer 2019; Meulendijks, Lancet Oncol 2015

ENTORNO RÁPIDAMENTE CAMBIANTE

NGS / BIOMARCADORES



https://www.genome.gov/sequencingcostsdata

MEDICINA DE PRECISIÓN: ¿HASTA DONDE?

Tratamientos dirigidos ≠ Tratamientos precisos

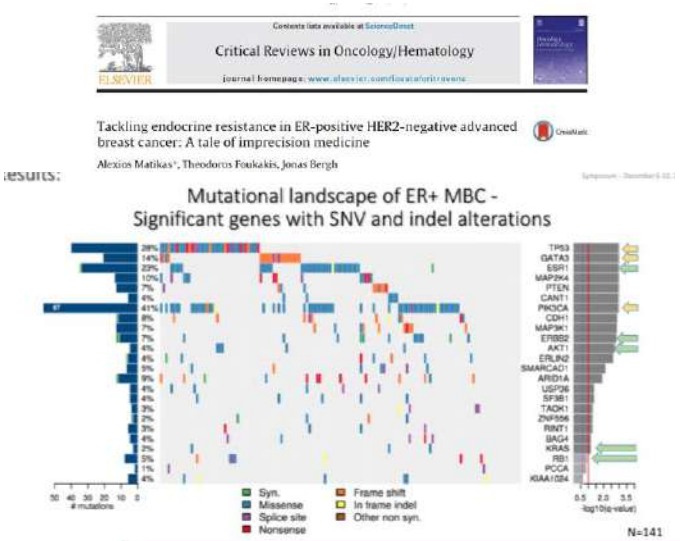
Biomarcadores predictivos imperfectos + heterogeneidad: combinaciones vs secuencia de tratamientos dirigida por resistencia

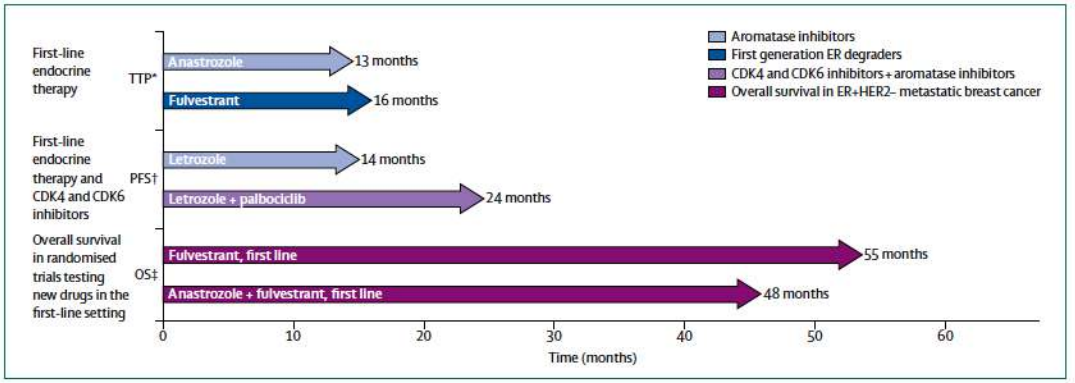
¿Mejora real de los resultados del tratamiento?

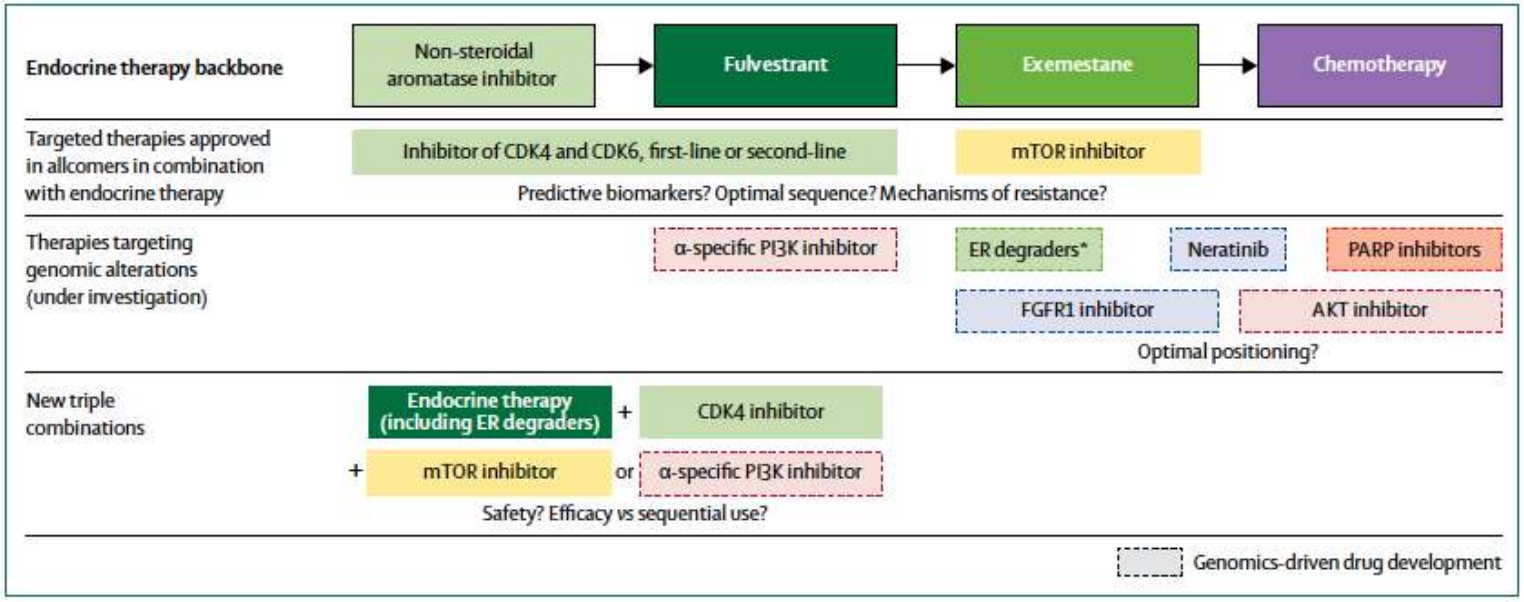
Rentabilidad diagnóstica frente a pérdidas de oportunidad: ¿NGS para todos los pacientes o selección por criterios clínicos? ¿En todos los tumores?

¿Predicción en los escenarios más comunes?

Dirigidos pero imprecisos



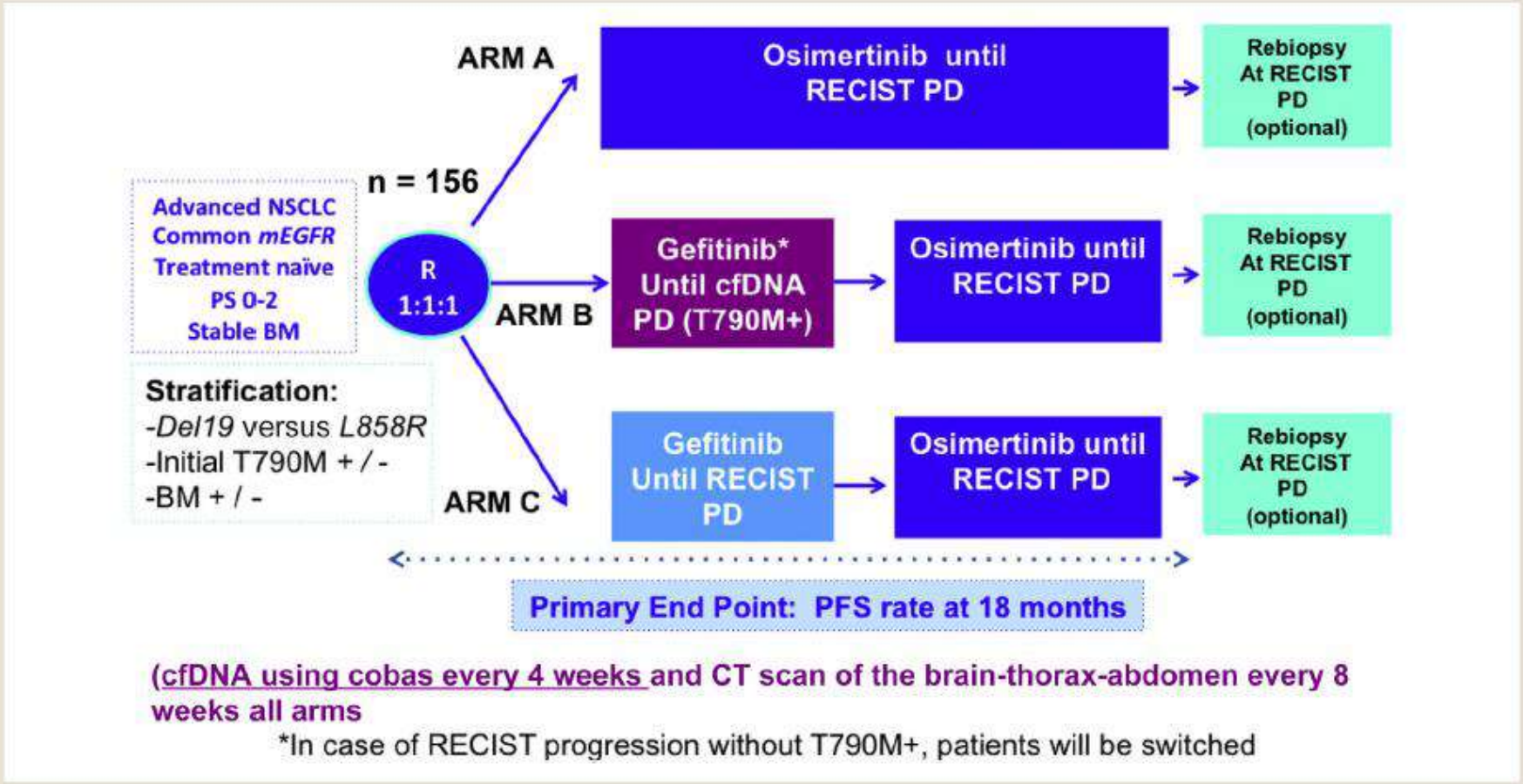




Matikas, Crit Rev Oncol/Hematol 2017; Turner, Lancet 2017; Turner, SABCS 2017

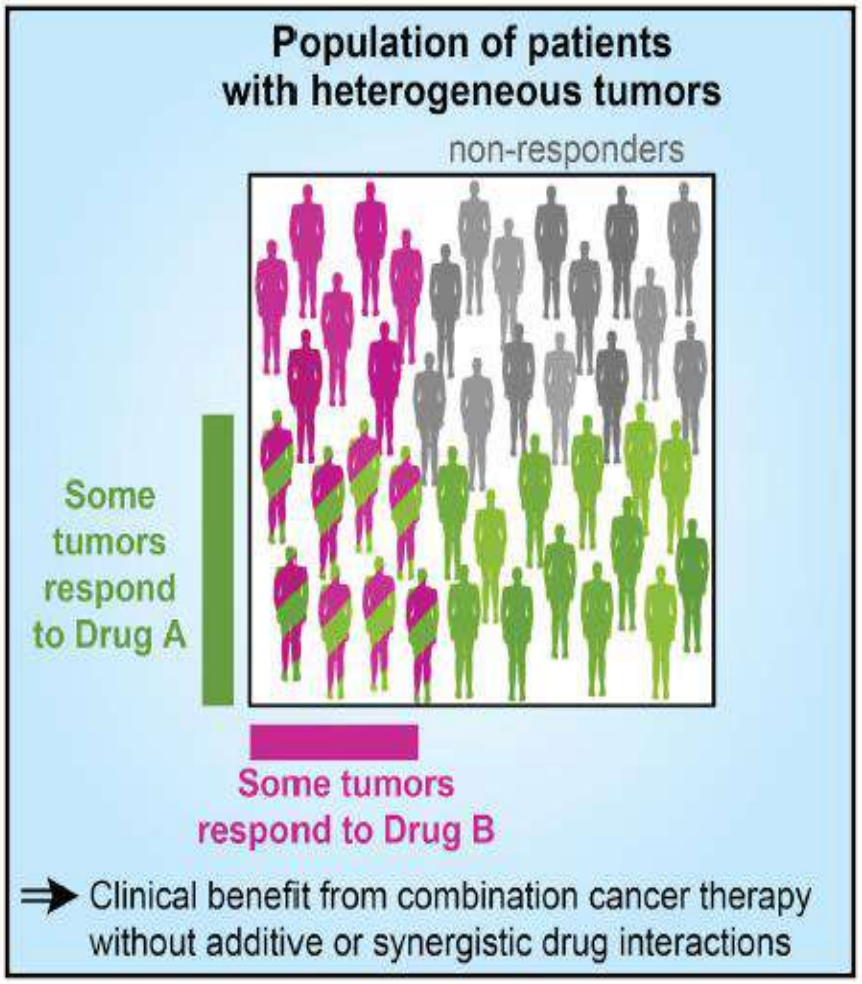
Biomarcadores imperfectos + heterogeneidad tumoral: "condenados" a la combinación

EORTC APPLE



Soria, NEJM 2018; Planchard, ELCC 2018; Remón, Clin Lung Cancer 2017

Biomarcadores imperfectos + heterogeneidad tumoral: "condenados" a la combinación



Neoplasias menos agresivas en las que la secuencia no suponga pérdida considerable de pacientes entre líneas

Neoplasias menos agresivas en las que seamos capaces de identificar claramente el desarrollo de resistencias con biomarcadores claros

Neoplasias en las que la presión menos nuevas vulnerabilidades (¡identificables!)

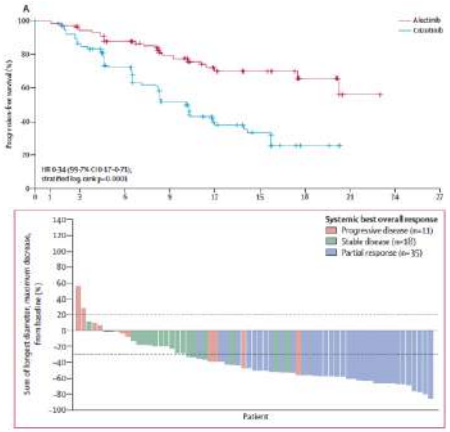
¿ A DONDE VAMOS?

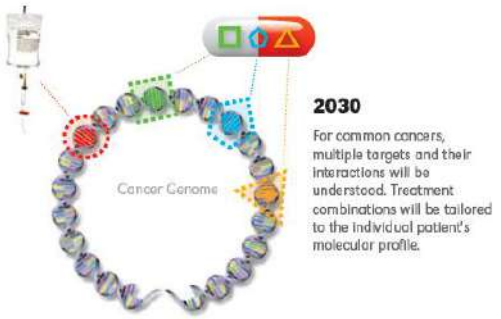
1ª generación

- ❑ Secuenciación regiones codificantes
- ❑ Estadios avanzados
- ❑ Éxitos en enfermedades con alteración clonal única

2ª generación

- ❑ Valoraciones moleculares completas y nuevos enfoques bioinformáticos
- ❑ Estadios más precoces
- ❑ Tratamientos de combinación frente a múltiples dianas



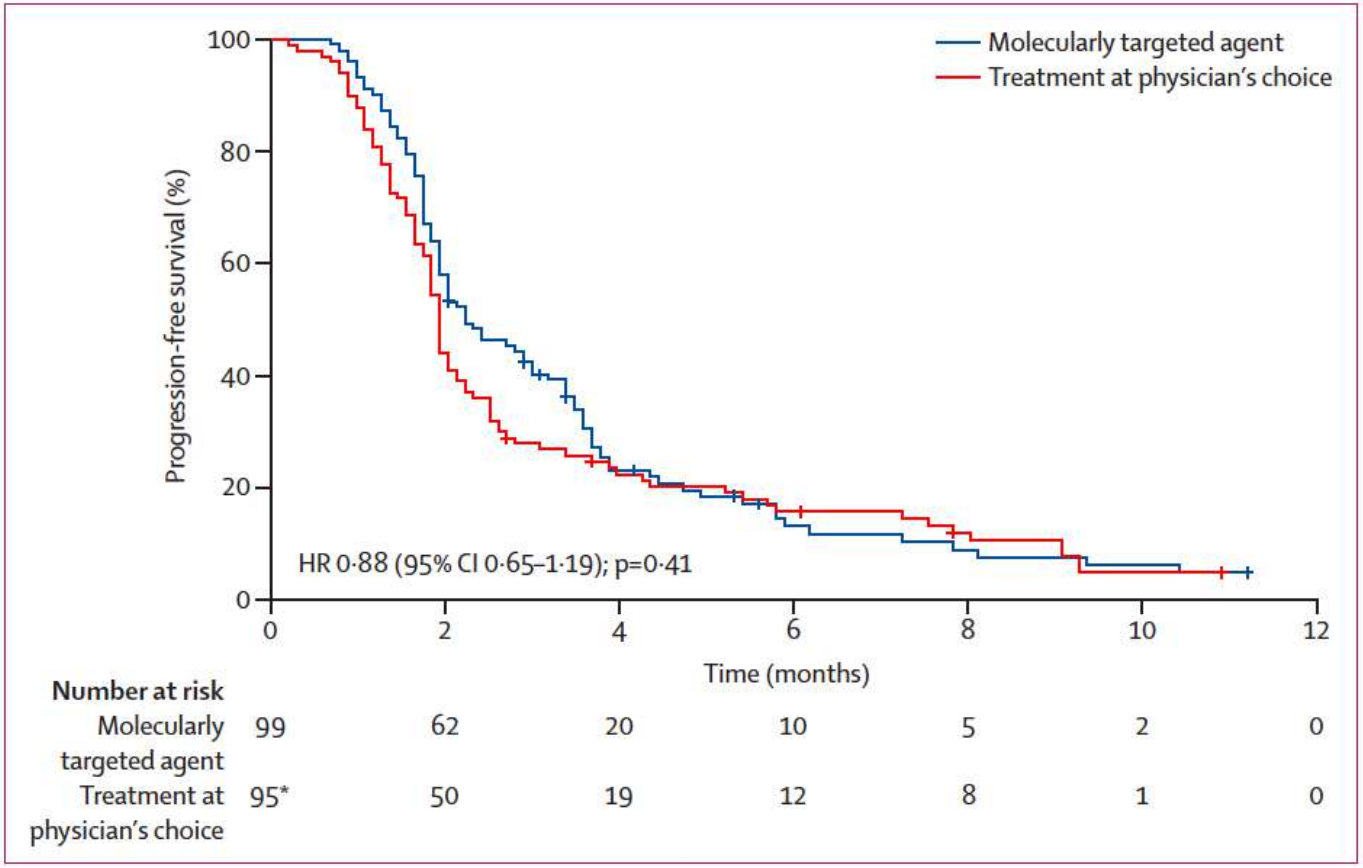


André, MAP 2018; Hida, Lancet 2017; Shaw, Lancet Oncol 2017; ASCO 2015

¿Utilidad clínica?

Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial

Christophe Le Tourneau, Jean-Pierre Delord, Anthony Gonçalves, Céline Gavoille, Coraline Dubot, Nicolas Isambert, Mario Campone, Olivier Trédan, Marie-Ange Massiani, Cécile Mauborgne, Sebastien Armenoult, Nicolas Servant, Ivan Bièche, Virginie Bernard, David Gentien, Pascal Jezequel, Valéry Attignon, Sandrine Boyault, Anne Vincent-Salomon, Vincent Servois, Marie-Paule Sablin, Maud Kamal, Xavier Paoletti, for the SHIVA investigators



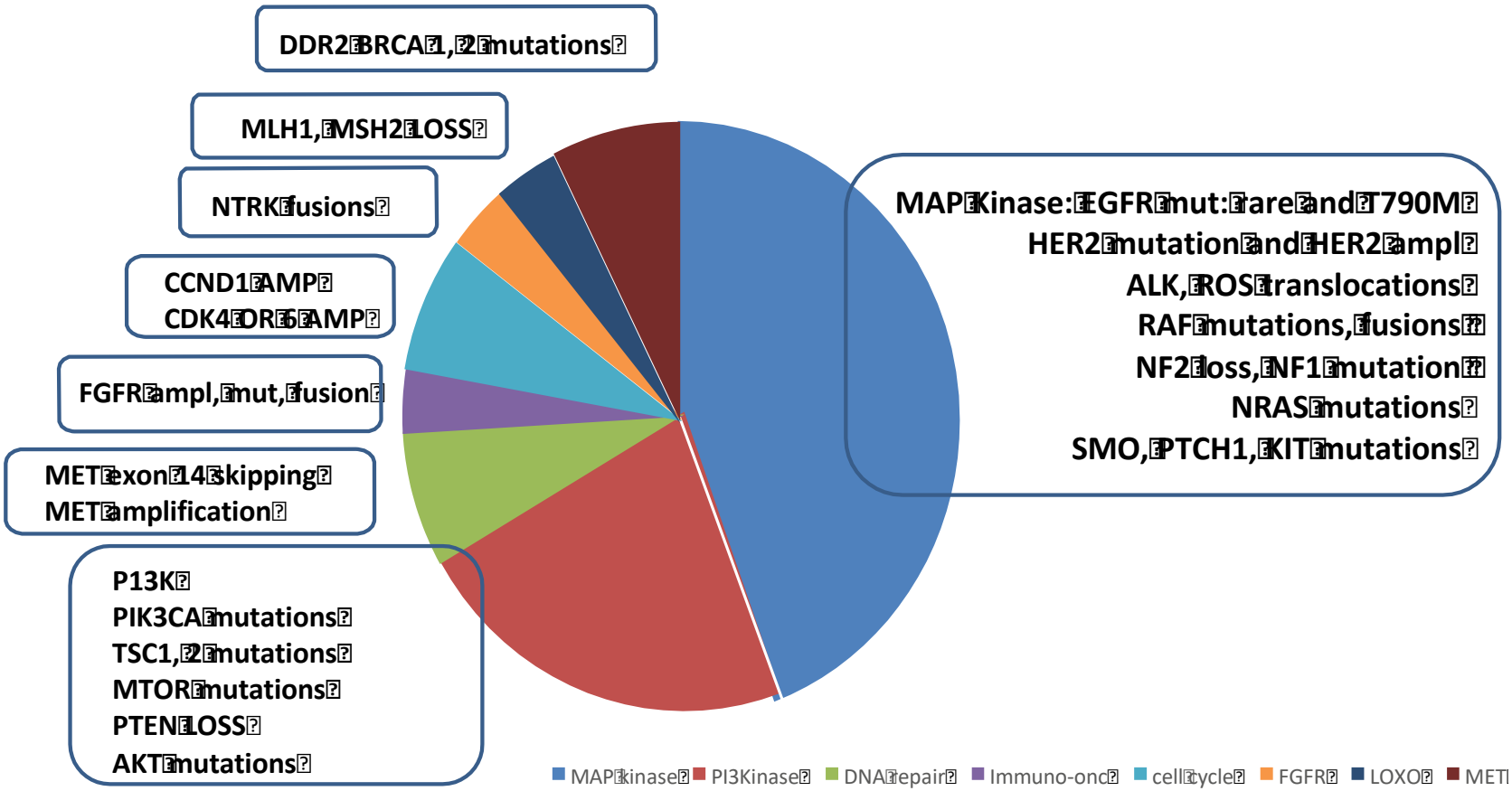
Le Tourneau, Lancet Oncol 2015

¿Utilidad clínica?

- Prevalencia alteraciones genéticas: 0-3.5%
- 35 brazos de tratamiento

NCI-Molecular Analysis for Therapy Choice (NCI-MATCH / EAY131)

Treatment Arms in NCI-MATCH by Molecular Pathway



Flaherty, ECOG-ACRIN NIH Feb-19

¿Utilidad clínica?

NCI-Molecular Analysis for Therapy Choice (NCI-MATCH / EAY131)

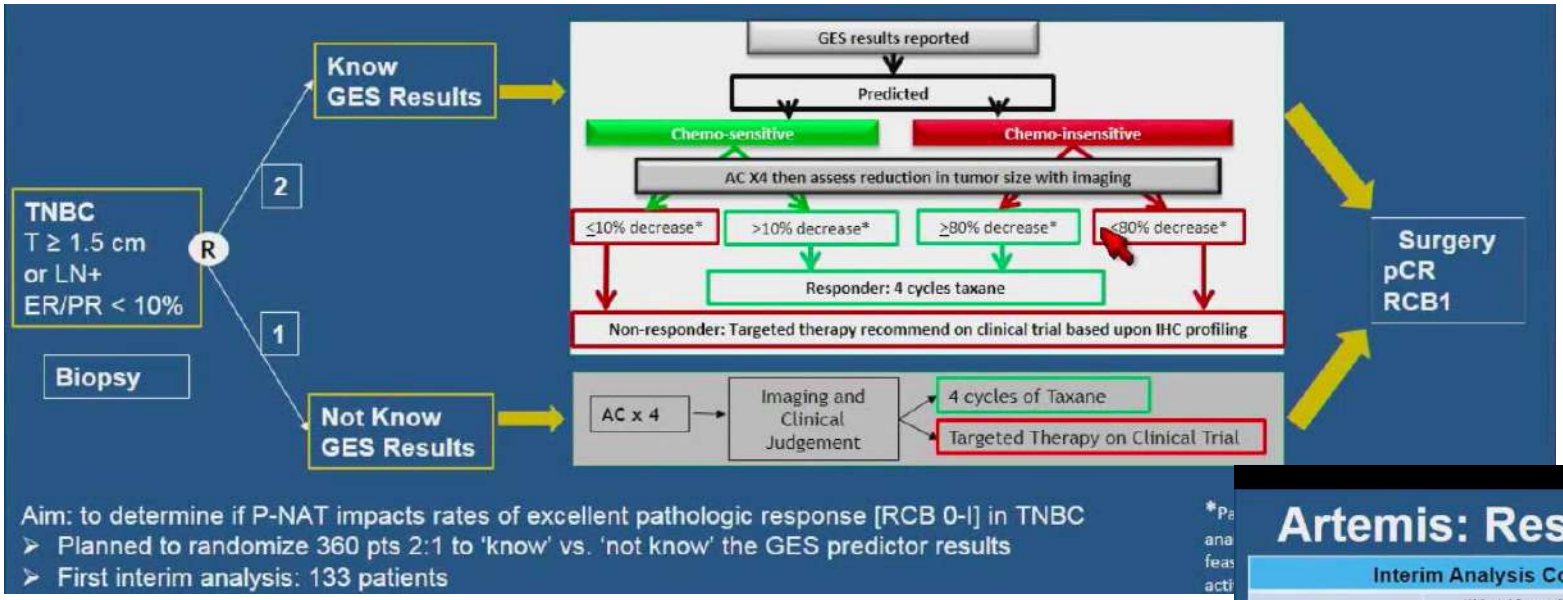
Drug	Drug/Variant	Arm	Primary Result (ORR Confirmed)	Publication/Presentation
Ado-trastuzumab emtansine	HER2 amplification	Q	8%	Jhaveri KL, ASCO 2018 (oral)
AZD4547	FGFR pathway aberrations	W	8%	Chae YK, ASCO 2018 (oral)
Taselisib	PIK3CA mutations	I	0%	Krop IE, ASCO 2018 (oral)
GSK2636771	PTEN expr or loss by IHC	N & P	5% arm N (mut/del) 0% arm P	Janku FM, ESMO 2018 (poster discussion)
Capivasertib	AKT mutations	Y	23%	Kalinsky KM, EORTC-NCI-AACR 2018 (oral plenary)
Nivolumab	dMMR status	Z1D	*Coming soon!*	
Afatinib	HER2 activating mutations	B		
Palbociclib	CCND1, 2, and 3 amplifications and Rb protein expression by IHC	Z1B		
ACD1775	BRCA1 or BRCA2 mutations	Z1I		

Flaherty, ECOG-ACRIN NIH Feb-19

¿Utilidad clínica?

Precision neoadjuvant therapy (P-NAT): a planned interim analysis of A Randomized, TNBC Enrolling trial to confirm Molecular profiling Improves Survival (ARTEMIS)

S Moulder, MD, MSCI; K Hess, PhD; R Candelaria, MD; GM Rauch, MD, PhD; L Santiago , MD; B Adrada, MD; WT Yang, MD,; M Gilcrease, MD, PhD; L Huo, MD, PhD; MC Stauder, MD; B Arun, MD; R Layman, MD; RK Murthy, MD; S Damodaran, MD; NT Ueno, MD, Ph D; AM Thompson, MD; B Lim, MD; E Mittendorf, MD, Ph D; J Litton, MD; WF Symmans, MD



Artemis: Results

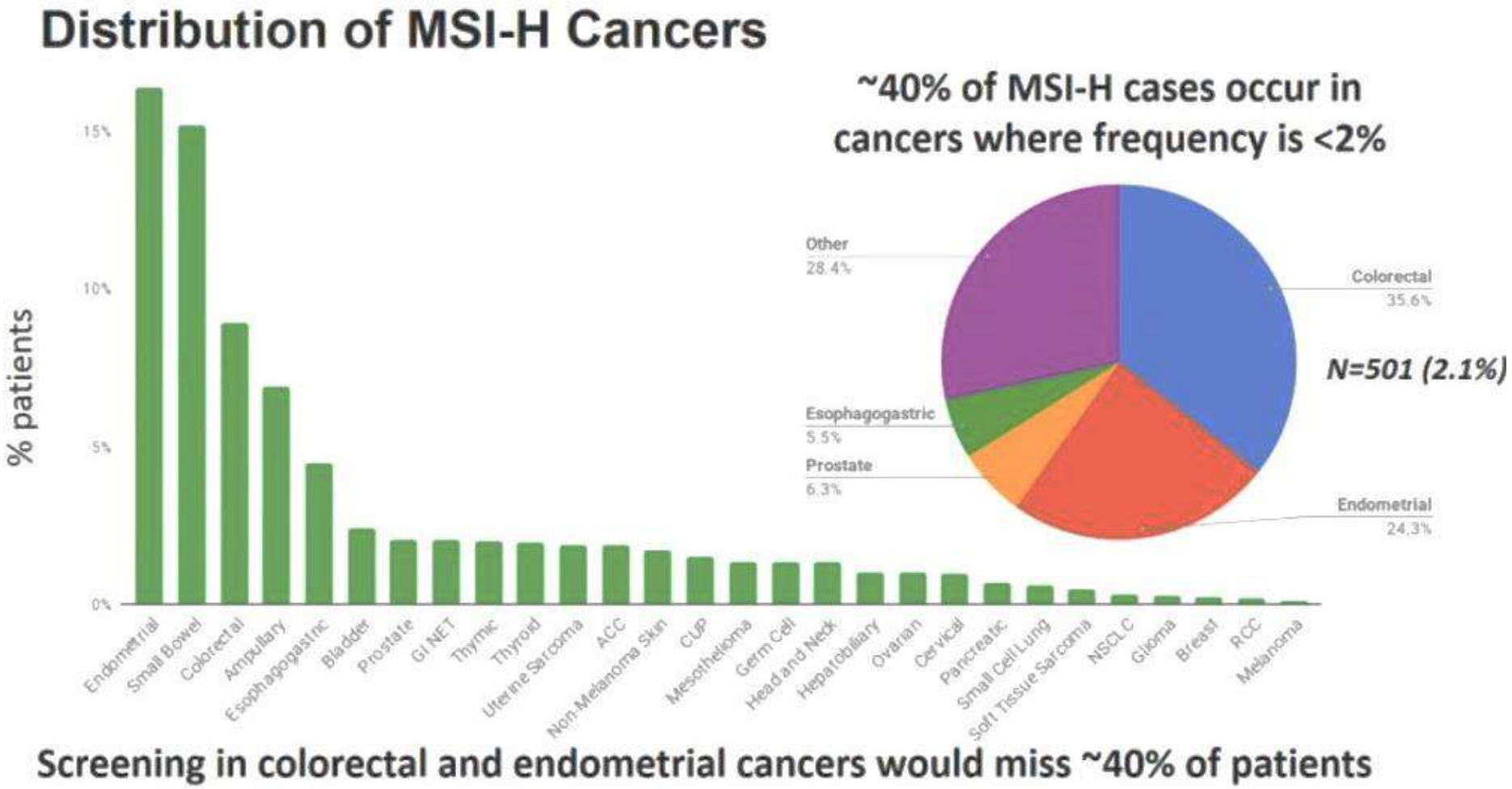
Interim Analysis Cohort (N=133)	"Not Know" GES results (n=42)	"Know" GES results (n=91)	p value
pCR			
Yes – n (%)	21 (50%)	39 (43%)	0.44
RCB Index			
pCR/RCB-I – n (%)	26 (62%)	51 (56%)	0.52
RCB-II/III – n (%)	16 (38%)	40 (44%)	

US Resistant Cohort (n=43)	Targeted Treatment (N=31)	SOC (N=12)	p value
pCR			
Yes – n (%)	5 (16%)	0 (0%)	0.3
RCB Index			
pCR/RCB I – n(%)	9 (29%)	2 (17%)	0.7
RCB-II/III – n (%)	22 (71%)	10 (83%)	

- Tratamiento basado en GES (VPP 65%, VPN 26%) no mejor que basado en radiología (RMN)/clínica
  - Interrupción de la aleatorización y continuación como brazo único con IHQ para identificar dianas en tumores sin respuesta
- Dificultades para demostrar utilidad clínica

Moulder, ASCO 2018

¿NGS sistemática ?



Hyman, AACR 2018

¿Paneles NGS de cáncer hereditario para todos los pacientes?

editorial

Advances in Genetic Testing in Pati
Breast Cancer, High-Quali
and Responsibl

Kara L. Ni

THE AMERICAN SOCIETY OF
Breast Surgeons

Consensus Guideline on Genetic Testing for Hereditary Breast Cancer

2. **Genetic testing should be made available to all patients with a personal history of breast cancer**. Recent data support that genetic testing should be offered to each patient with breast cancer (newly diagnosed or with a personal history). If genetic testing is performed, such testing should include BRCA1/BRCA2 and PALB2, with other genes as appropriate for the clinical scenario and family history. For patients with newly diagnosed breast cancer, identification of a mutation may impact local treatment recommendations (surgery and potentially radiation) and systemic therapy. Additionally, family members may subsequently be offered testing and tailored risk reduction strategies.

TABLE 2. Patie

Group	mes Panel (11 genes)	Large Cancer Panel (80 genes)
In guideline	2.51	6.26	9.39
Out of guideline	0.63	3.54	7.92

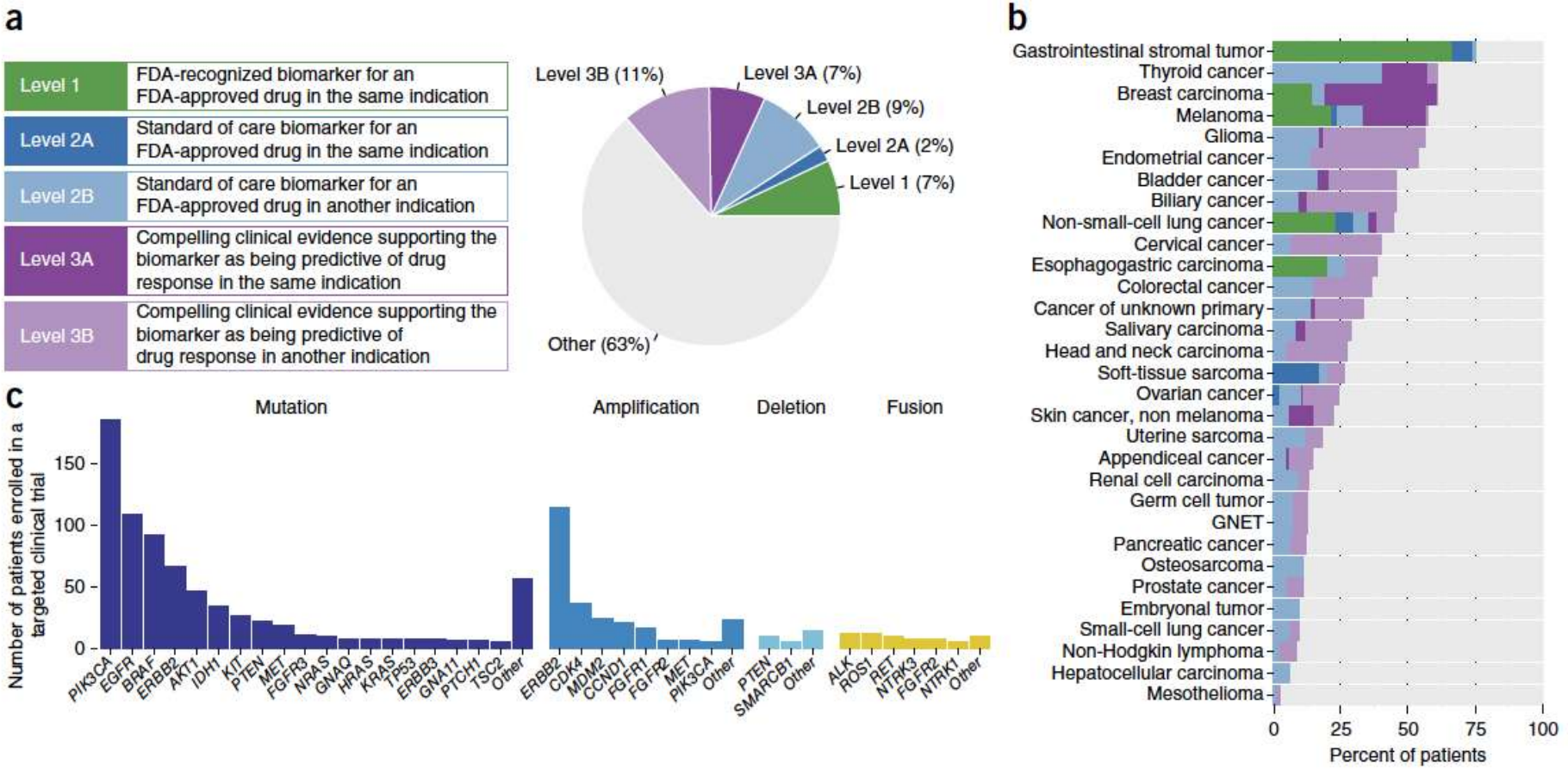
t Meet NCCN Criteria

6 7 8 9 10

PTEN
RAD50
RAD51C
RAD51D
RB1
RECQL4
RET
TP53
VHL
WRN

Beitsch, J Clin Oncol 2019; Milliron, J Clin Oncol 2019; https://www.breastsurgeons.org

¿NGS sistemática?



A Zehir, Nat Medicine 2017

UTILIDAD CLÍNICA: PONIENDO ORDEN

Table 2. The ESCAT

	ESCAT evidence tier	Required level of evidence	Clinical value class	Clinical implication
Ready for routine use	I: Alteration-drug match is associated with improved outcome in clinical trials	I-A: prospective, randomised clinical trials show the alteration-drug match in a specific tumour type results in a clinically meaningful improvement of a survival end point I-B: prospective, non-randomised clinical trials show that the alteration-drug match in a specific tumour type, results in clinically meaningful benefit as defined by ESMO MCBS 1.1 I-C: clinical trials across tumour types or basket clinical trials show clinical benefit associated with the alteration-drug match, with similar benefit observed across tumour types	Drug administered to patients with the specific molecular alteration has led to improved clinical outcome in prospective clinical trial(s)	Access to the treatment should be considered standard of care
Investigational	II: alteration-drug match is associated with antitumour activity, but magnitude of benefit is unknown	II-A: retrospective studies show patients with the specific alteration in a specific tumour type experience clinically meaningful benefit with matched drug compared with alteration-negative patients II-B: prospective clinical trial(s) show the alteration-drug match in a specific tumour type results in increased responsiveness when treated with a matched drug, however, no data currently available on survival end points	Drug administered to a molecularly defined patient population is likely to result in clinical benefit in a given tumour type, but additional data are needed	Treatment to be considered 'preferable' in the context of evidence collection either as a prospective registry or as a prospective clinical trial
Hypothetical target	III: alteration-drug match suspected to improve outcome based on clinical trial data in other tumour type(s) or with similar molecular alteration	III-A: clinical benefit demonstrated in patients with the specific alteration (as tiers I and II above) but in a different tumour type. Limited/absence of clinical evidence available for the patient-specific cancer type or broadly across cancer types III-B: an alteration that has a similar predicted functional impact as an already studied tier I abnormality in the same gene or pathway, but does not have associated supportive clinical data	Drug previously shown to benefit the molecularly defined subset in another tumour type (or with a different mutation in the same gene), efficacy therefore is anticipated for but not proved	Clinical trials to be discussed with patients
	IV: pre-clinical evidence of actionability	IV-A: evidence that the alteration or a functionally similar alteration influences drug sensitivity in preclinical *in vitro* or *in vivo* models IV-B: actionability predicted *in silico*	Actionability is predicted based on preclinical studies, no conclusive clinical data available	Treatment should 'only be considered' in the context of early clinical trials. Lack of clinical data should be stressed to patients
Combination development	V: alteration-drug match is associated with objective response, but without clinically meaningful benefit	Prospective studies show that targeted therapy is associated with objective responses, but this does not lead to improved outcome	Drug is active but does not prolong PFS or OS, probably in part due to mechanisms of adaptation	Clinical trials assessing drug combination strategies could be considered
	X: lack of evidence for actionability	No evidence that the genomic alteration is therapeutically actionable	There is no evidence, clinical or preclinical, that a genomic alteration is a potential therapeutic target	The finding should not be taken into account for clinical decision

ESMO

SPECIAL ARTICLE

A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT)

J. Mateo[1], D. Chakravarty[2], R. Dienstmann[3], S. Jezdic[4], A. Gonzalez-Perez[4], N. Lopez-Bigas[4,5], C. K. Y. Ng[6], P. L. Bedard[7], G. Tortora[8,9], J.-Y. Douillard[10], E. M. Van Allen[11], N. Schultz[2], C. Swanton[12], F. Andre[13,14] & L. Pusztai[15]

Amplificación de HER2

Mutaciones activadoras AKT1

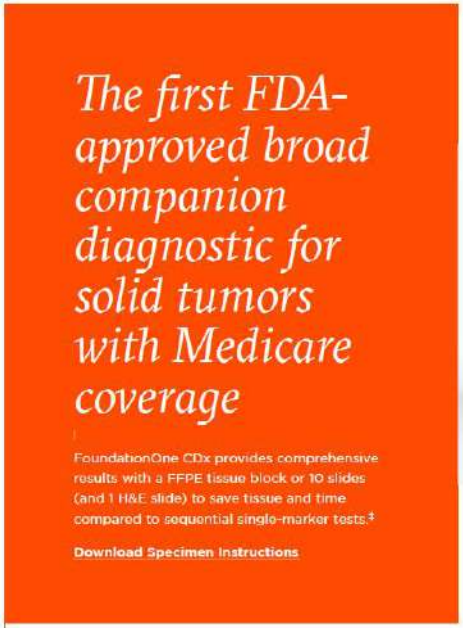
Mutaciones pérdida de función PALB2

Mutaciones activadoras de PI3KCA

Mutaciones activadoras de EGFR

Mateo, Ann Oncol 2018; Salgado, Eur J Cancer 2017; Hyman, J Clin Oncol 2017

¿NGS sistemática en enfermedad avanzada?



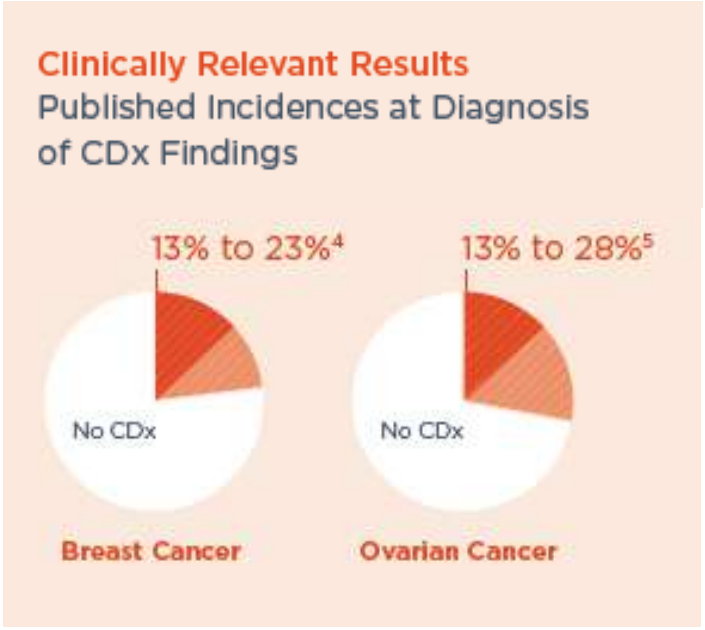


TABLE 2. Selected Genomic Alterations and Relevance for Clinical Trials With Novel Drug Therapies

Molecular Alteration	Subtype Considerations	Drug Class
***ERBB2* Mutation**	2%–4% HER2–negative	HER2 TKI
***PIK3CA* Mutation**	30%–40% ER+/HER2–, 20%–25% HER2+, 10%–15% TNBC	PI3-kinase inhibitor (α-isoform–specific/selective)
***AKT1* Mutation**	2%–5% breast cancer	AKT inhibitor mTOR inhibitor
***ESR1* Mutation**	30%–40% ER+/HER2– after AI	Oral selective estrogen receptor degrader
***NTRK* Fusion**	Enriched in secretory (TNBC)	TRK inhibitor
High Tumor Mutation Burden	1%–5% breast cancers	Immune checkpoint inhibitor
Mismatch Repair Deficiency Signature	< 5% breast cancers	Immune checkpoint inhibitor

Kratz, ASCO 2018

PRECISION MEDICINE OUTLOOK

PERSPECTIVE

The precision–oncology illusion

Precision oncology has not been shown to work, and perhaps it never will, says **Vinay Prasad**.

Original Investigation ONLINE FIRST

April 17, 2018

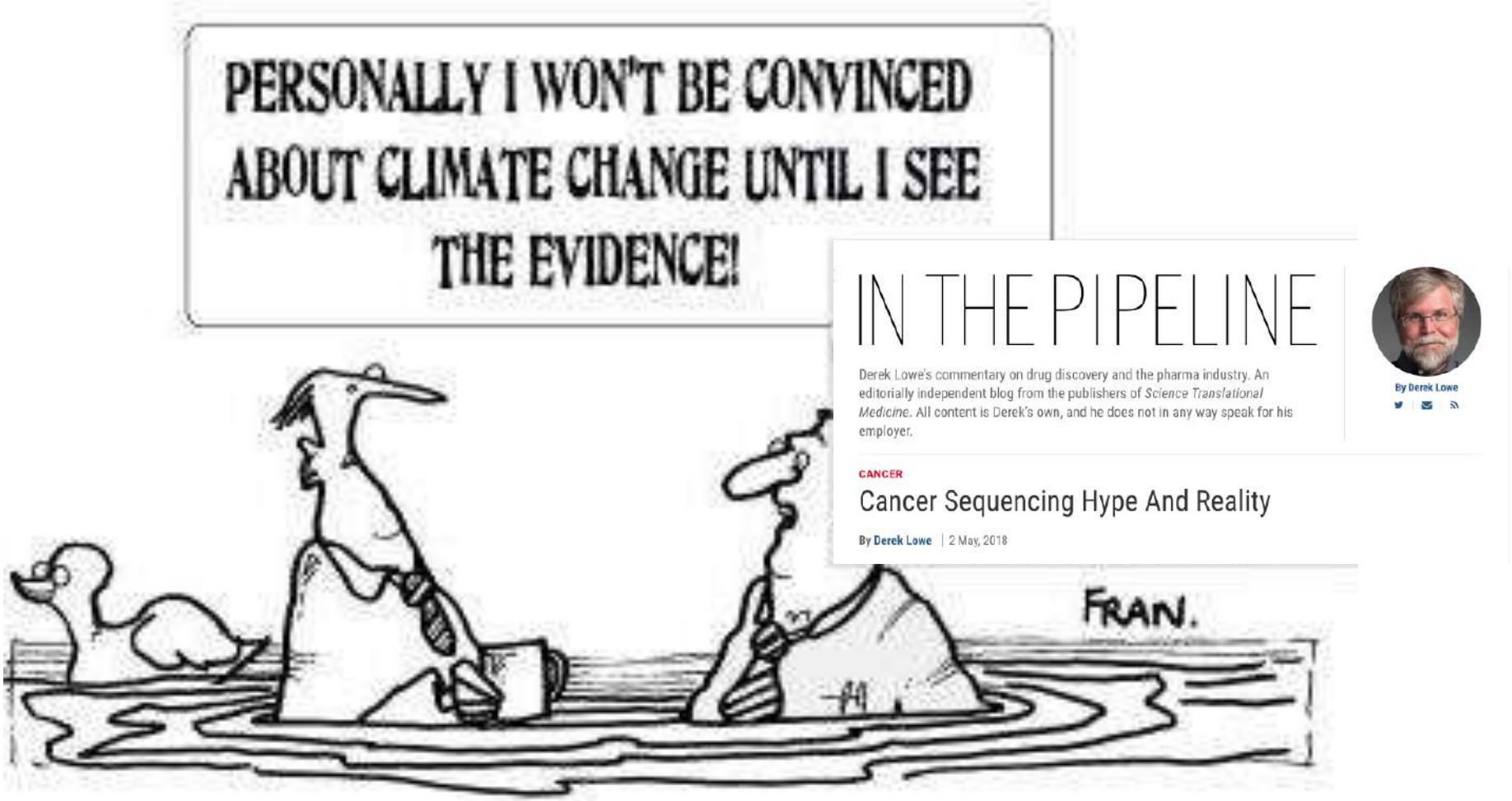
Estimation of The Percentage of US Patients With Cancer Who Benefit From Genome-Driven Oncology

John Marquart, BA[1]; Emerson Y. Chen, MD[2]; Vinay Prasad, MD, MPH[2,3,4]

» Author Affiliations

JAMA Oncol. Published online April 17, 2018. doi:10.1001/jamaoncol.2018.1660

Prasad, Nature 2016; Marquart, JAMA Oncol 2018; Le Tourneau, Lancet Oncol 2015; Oliveira, SABCS 2017; Kruse, SABCS 2017

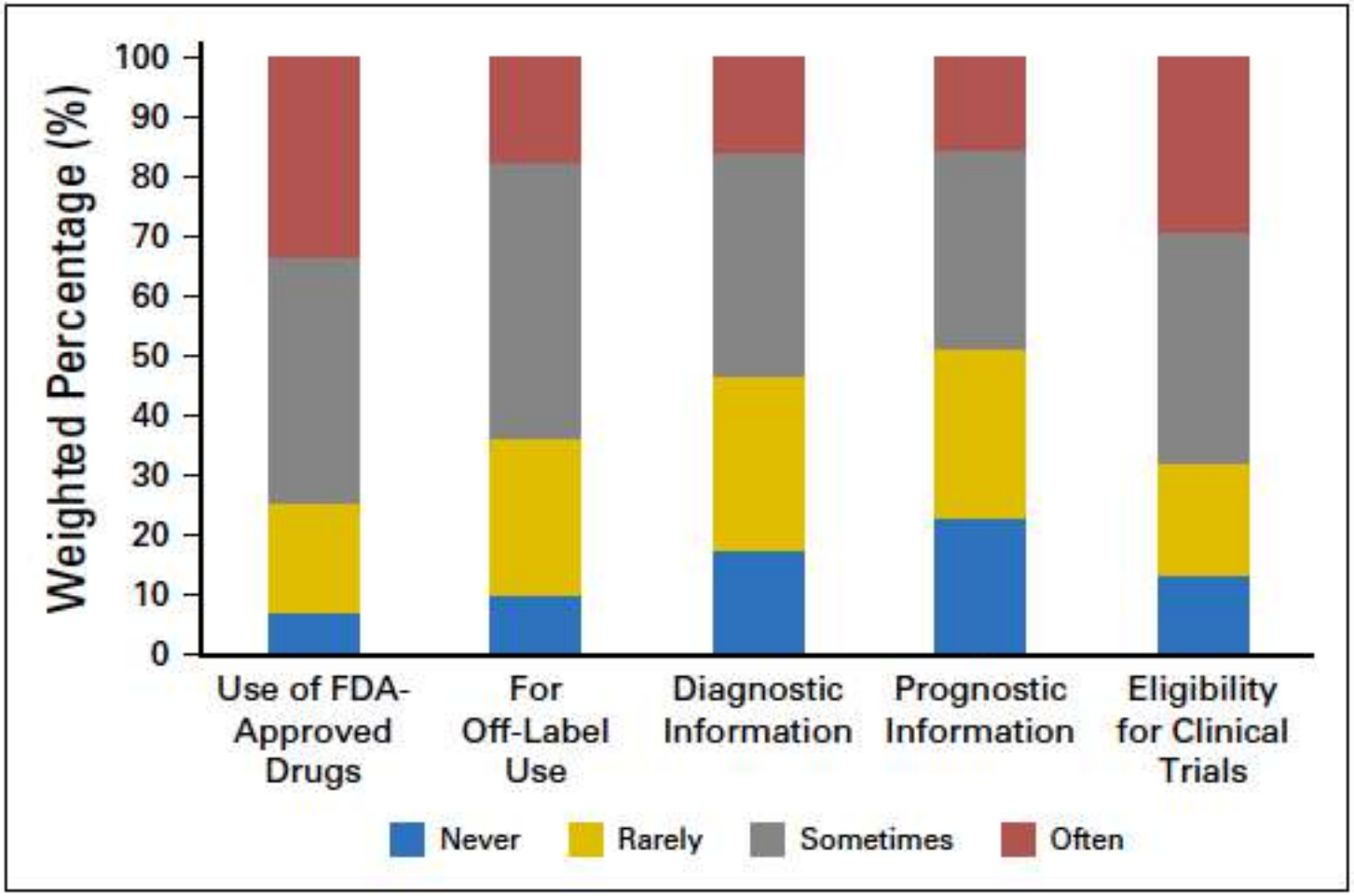


Lowe, Sci Transl Med 2018

Apocalípticos e integrados

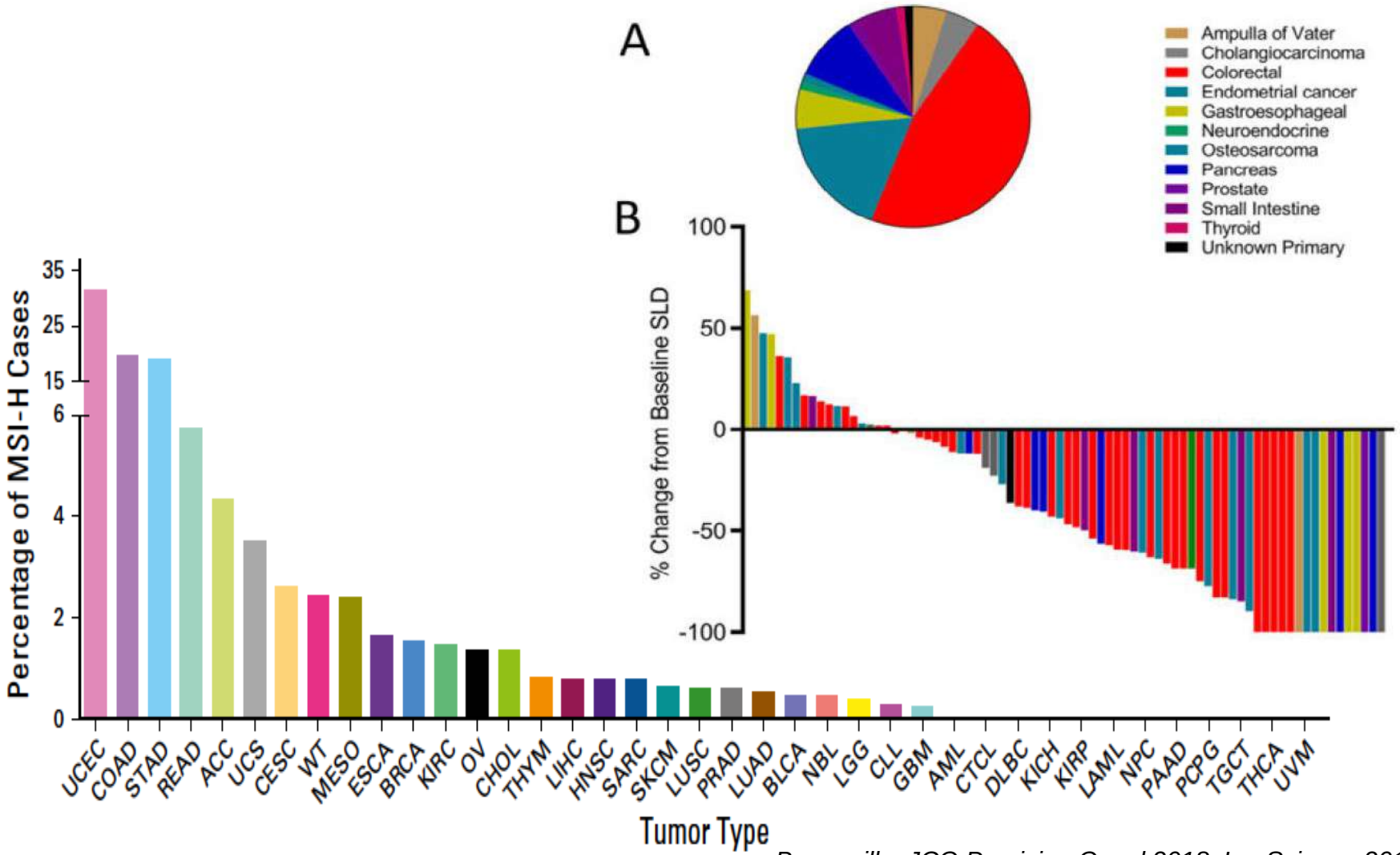
La realidad: uso creciente de NGS

75%



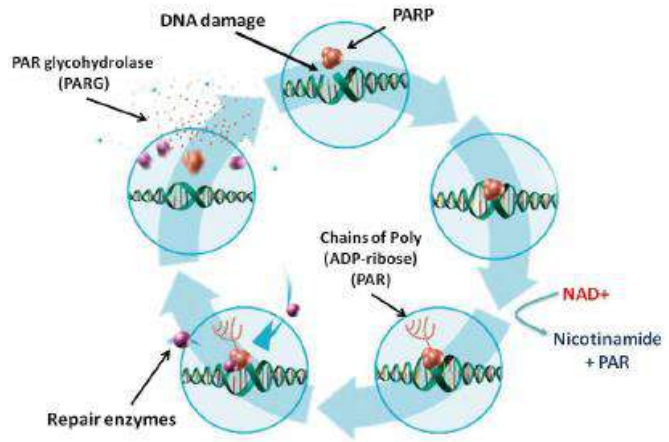
Freedman, JCO Precision Oncol 2018

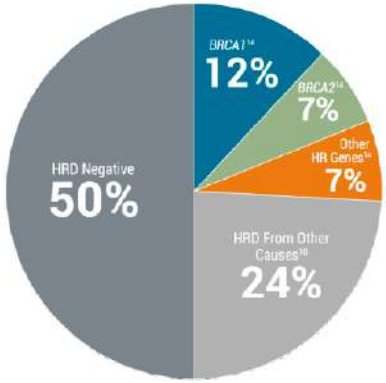
Oportunidades para la eficiencia / ineficiencia: MSI / Pembrolizumab



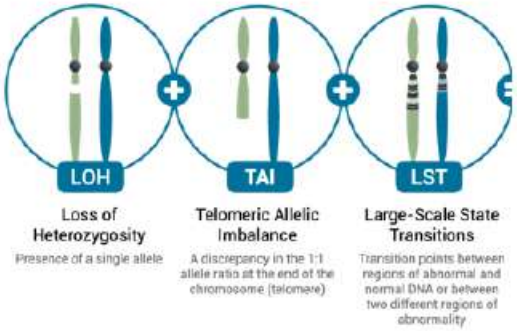
Bonneville, JCO Precision Oncol 2018; Le, Science 2017

Oportunidades para la eficiencia/ineficiencia: HRD / iPARP





MYRIAD myChoice® HRD



	OLAPARIB			NIRAPARIB			RUCAPARIB		
	2-3ªL P-Sen BRCA mut	2ª-3ªL P-s BRCA wt	1ªL P-s BRCA mut	2ª-3ªL P-s BRCA mut	2ª-3ªL P-s BRCA wt HRD +	2ª-3ªL P-s BRCA wt HRD -	2ª-3ªL P-s BRCA mut	2ª-3ªL P-s BRCA wt HRD +	2ª-3ªL P-s BRCA wt HRD -
SLP (HR)	0.18 (0.10-0.31)	0.54 (0.34-0.85)	0.30 (0.23-0.41)	0.27 (0.17-0.41)	0.38 (0.23-0.63)	0.58 (0.30-0.92)	0.23 (0.16-0.34)	0.44 (0.26-0.66)	0.58 (0.40-0.85)
Δ SLP	7 meses	2 meses	>36 meses	15 meses	5.6 meses	3.1 meses	11.2 meses	4.3 meses	1.3 meses
SLP control	4.3 meses	5.5 meses	13.8 meses	5.5 meses	3.7 meses	3.8 meses	5.4 meses	5.4 meses	5.4 meses
SG (HR)	0.62 (0.41-0.94)	0.83 (0.55-1.24)	-						
Δ SG	4.7 meses (signific.)	2 meses (NS)	-						
SG control	32 meses	26 meses	-						
Valor clínico ESMO	**4**	**3**	**3 (vs 4)**	**3**	**3**	**3**	**3**	**3**	**2**
Referencia	Ledermann, Lancet Oncol 2014 y Lancet Oncol 2016			Mirza, N Engl J Med 2016			Coleman, Lancet 2017		
Método HRD	--			Myriad My Choice (LOH, LST, TAI)			Foundation Medicine, T5 NGS (cut-off 16% LOH high)		

Toss, J Cancer Sci Ther 2013; Ledermann, Lancet Oncol 2014; Ledermann, Lancet Oncol 2016; Mirza, N Engl J Med 2016; Coleman, Lancet 2017

RETOS PARA EL FUTURO (INMEDIATO)

Prevención

Precisión también para el paciente

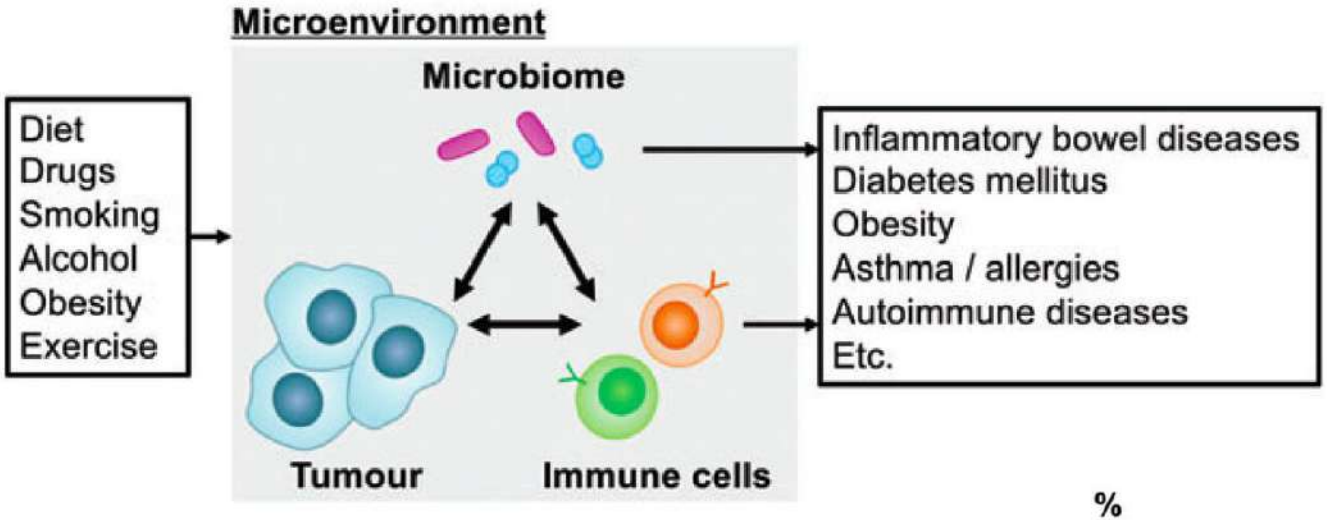
Acceso a biomarcadores y a ensayos clínicos

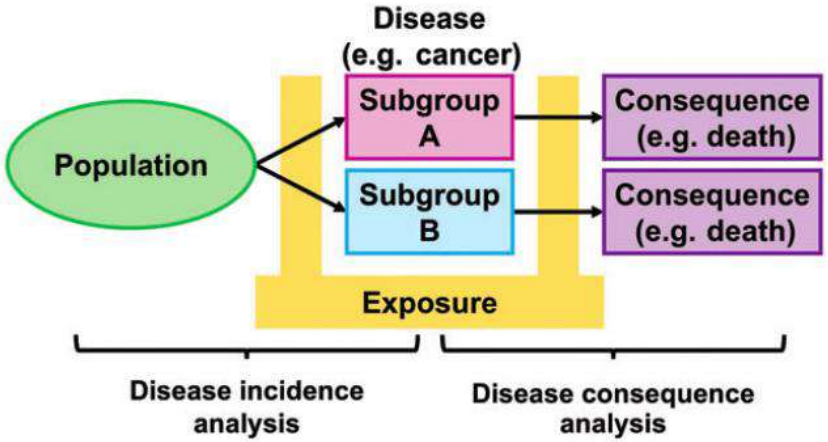
Calidad analítica

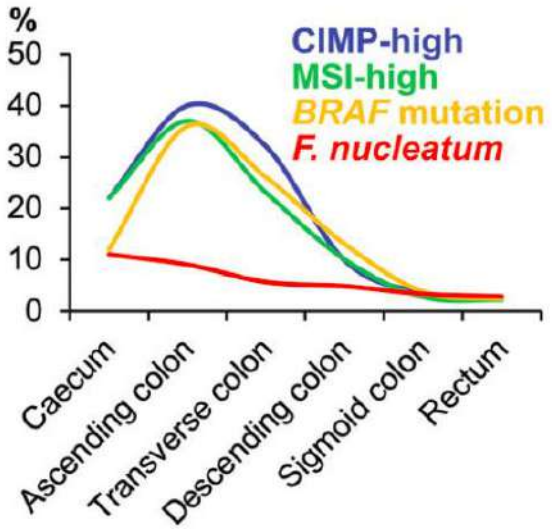
Entorno colaborativo de estudio y validación de dianas y biomarcadores

Gestión de la información: investigación y asistencia

Retos: no solo tratamiento, también prevención



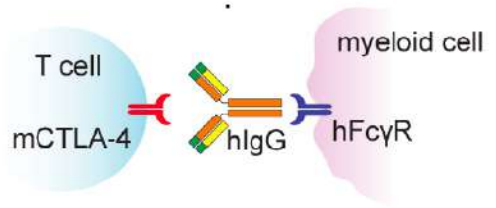


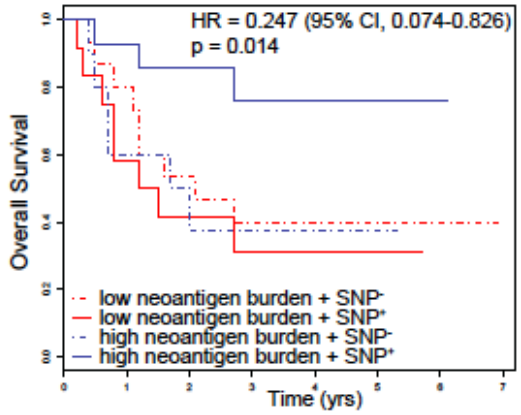


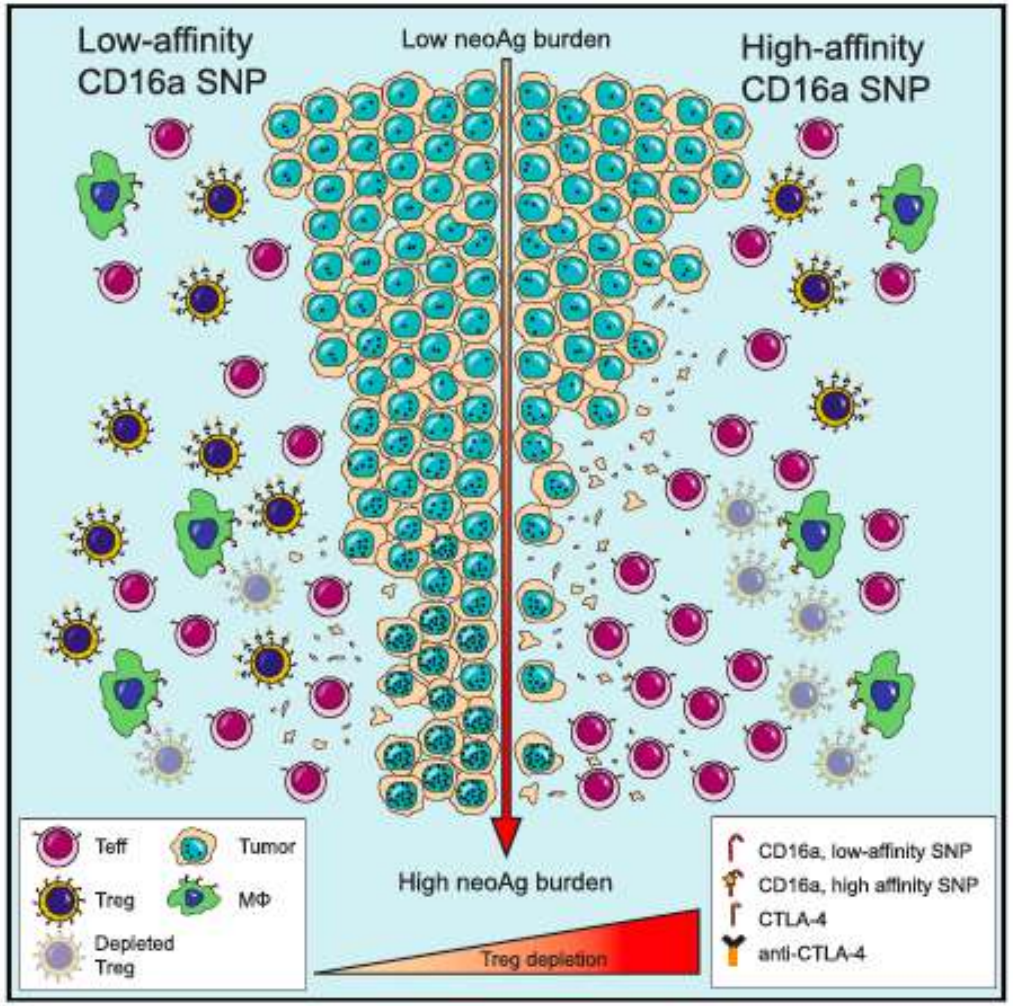
Hamada, J Pahtol 2019

Retos: ¿Algo más de precisión también en el paciente?

Variación genética hereditaria en respuesta inmune tumoral







Lim,PNAS 2019; Arce Vargas, Cancer Cell 2018

Retos: acceso a biomarcadores

Gestión Hospitalaria

La Sociedad Española de Oncología Médica está analizando el acceso a los biomarcadores

infosalus / **asistencia**

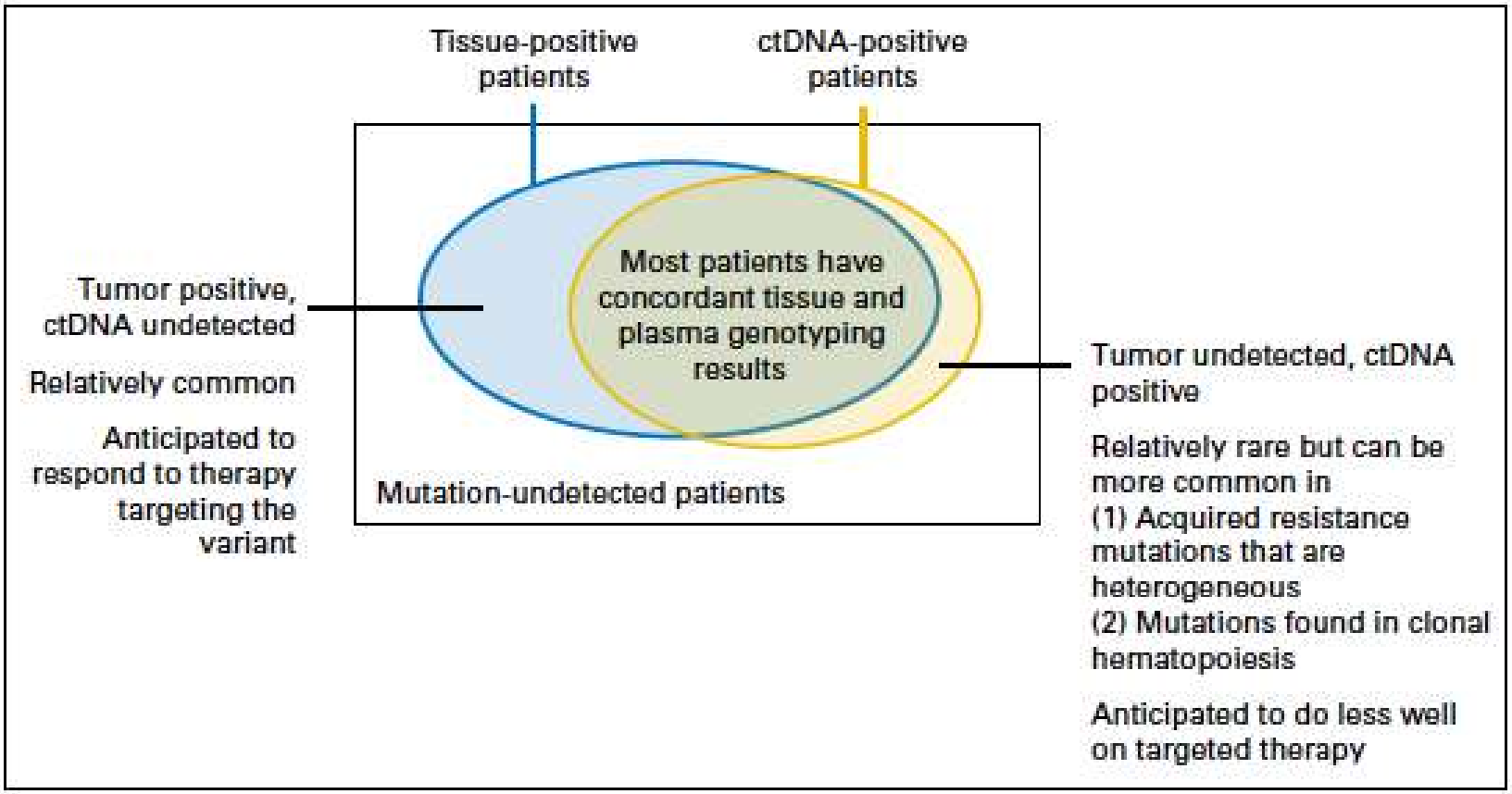
SEOM pide que la Estrategia de Medicina de Precisión esté "dotada de recursos, coordinada y mantenida en el tiempo"

Retos: calidad y metodología común

VOLUME 36 · NUMBER 16 · JUNE 1, 2018
JOURNAL OF CLINICAL ONCOLOGY ASCO SPECIAL ARTICLE

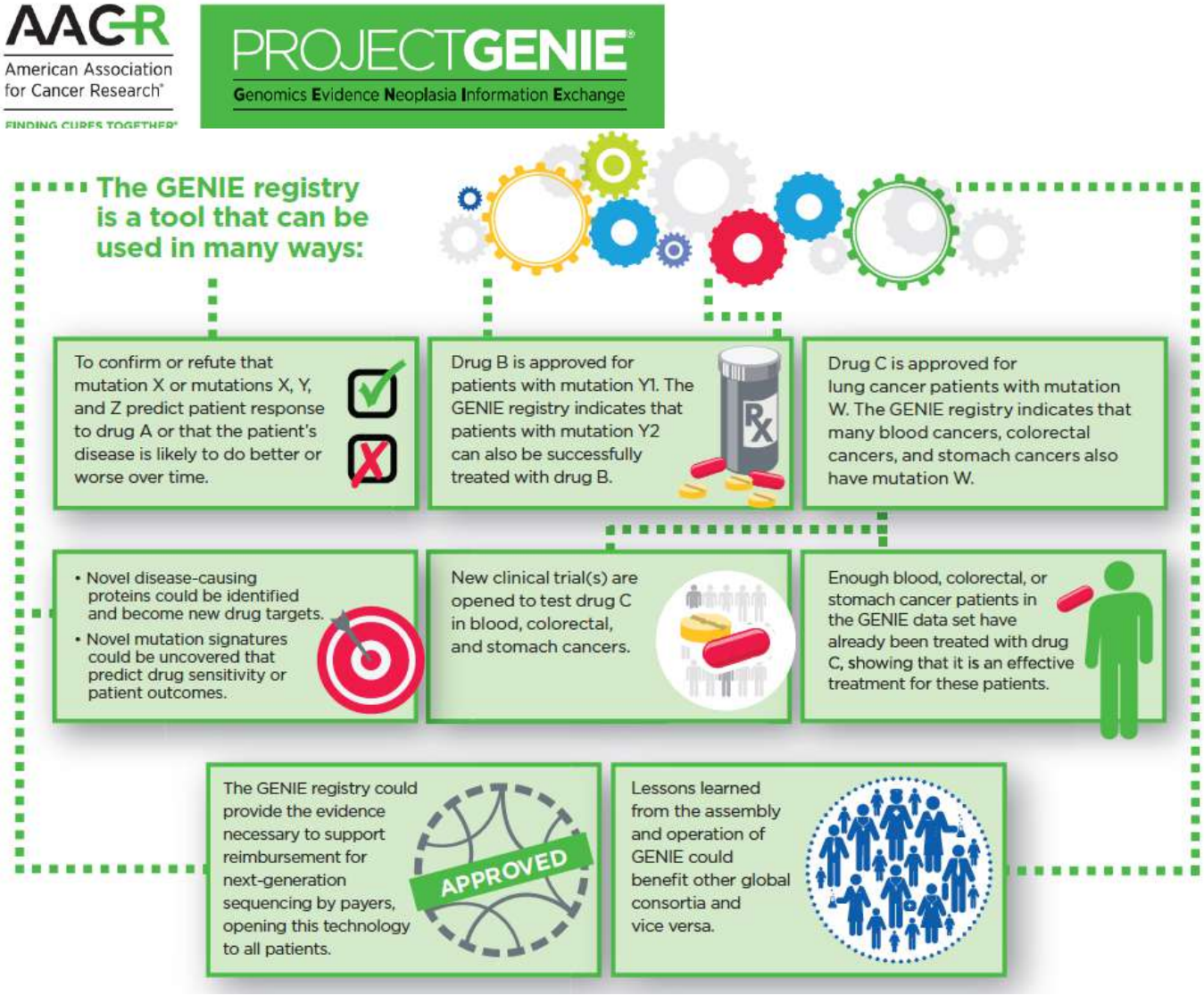
Circulating Tumor DNA Analysis in Patients With Cancer: American Society of Clinical Oncology and College of American Pathologists Joint Review

Jason D. Merker, Geoffrey R. Oxnard, Carolyn Compton, Maximilian Diehn, Patricia Hurley, Alexander J. Lazar, Neal Lindeman, Christina M. Lockwood, Alex J. Rai, Richard L. Schilsky, Apostolia M. Tsimberidou, Patricia Vasalos, Brooks L. Billman, Thomas K. Oliver, Suanna S. Bruinooge, Daniel F. Hayes, and Nicholas C. Turner



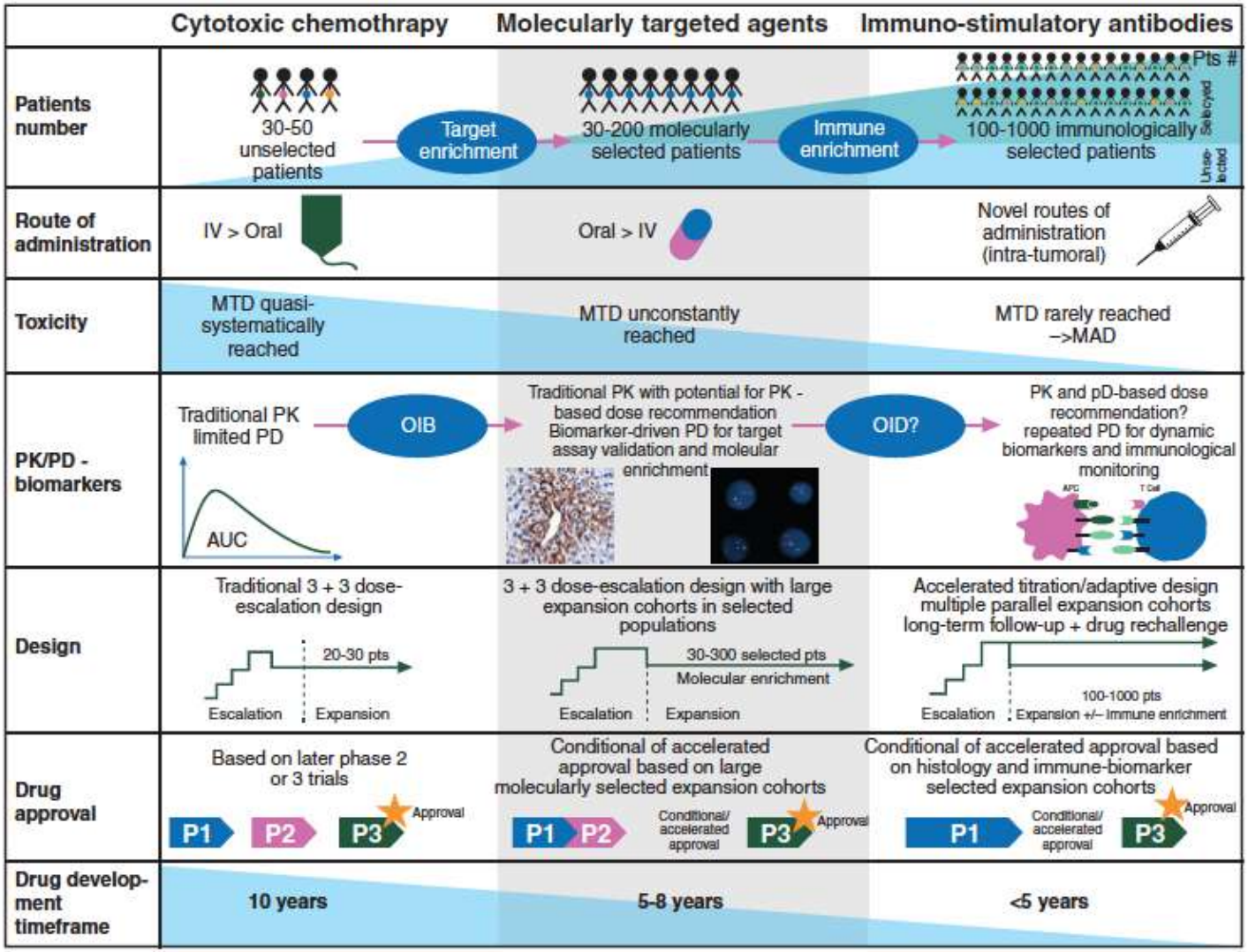
Marker, J Clin Oncol 2018

Retos: colaboración multicéntrica



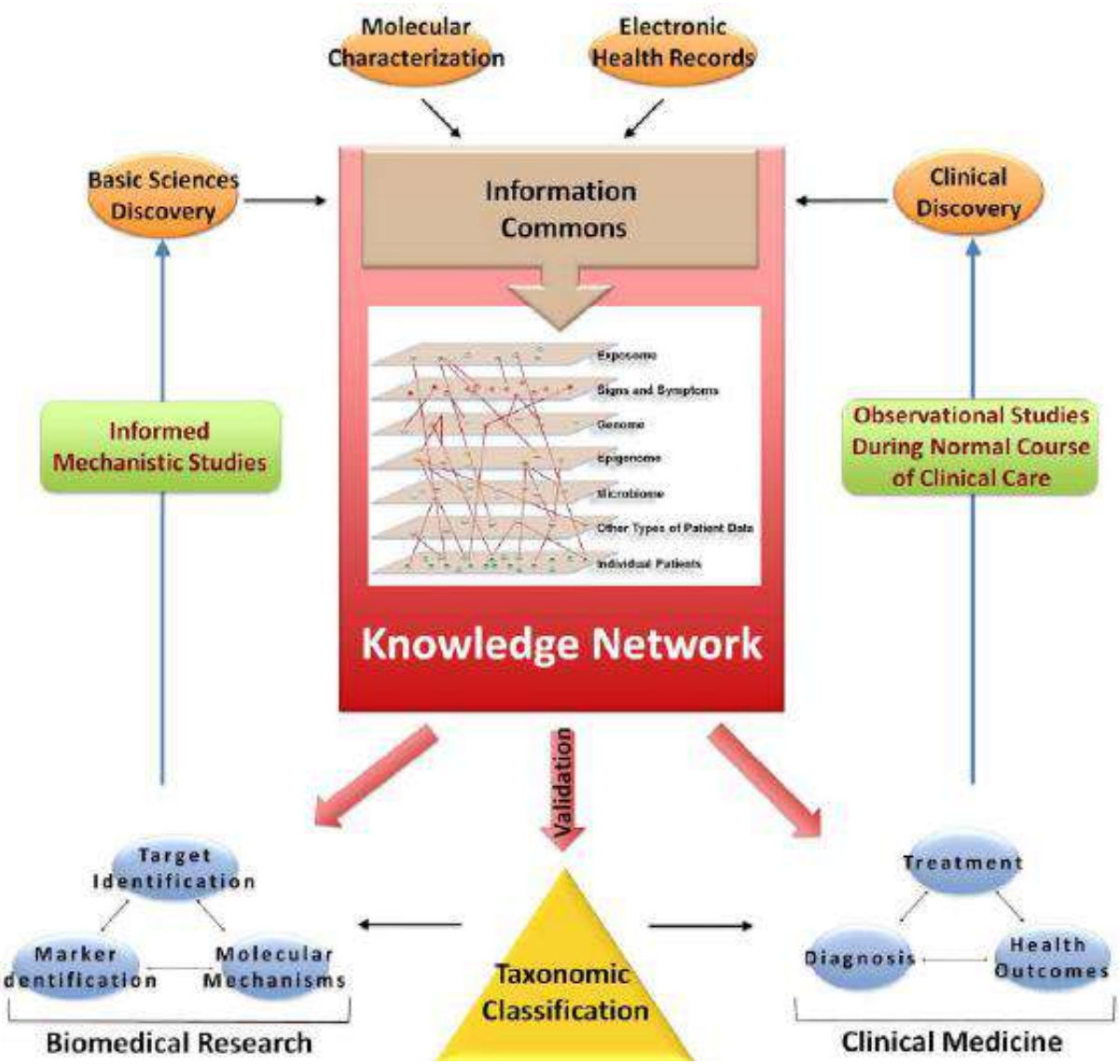
AACR Genie Consortium, Cancer Discov 2017

Retos: colaboración multicéntrica



Postel-Vinay, Ann Oncol 2016; Postel-Vinay, Eur J Cancer 2014; Dientsmann, MAP 2018; Aguilar, MAP 2018; Oliveira, SABCS 2017

Retos: la gestión de la información



http://dels.nas.edu/Materials/Presentations/Precision-Medicine?bname=bls

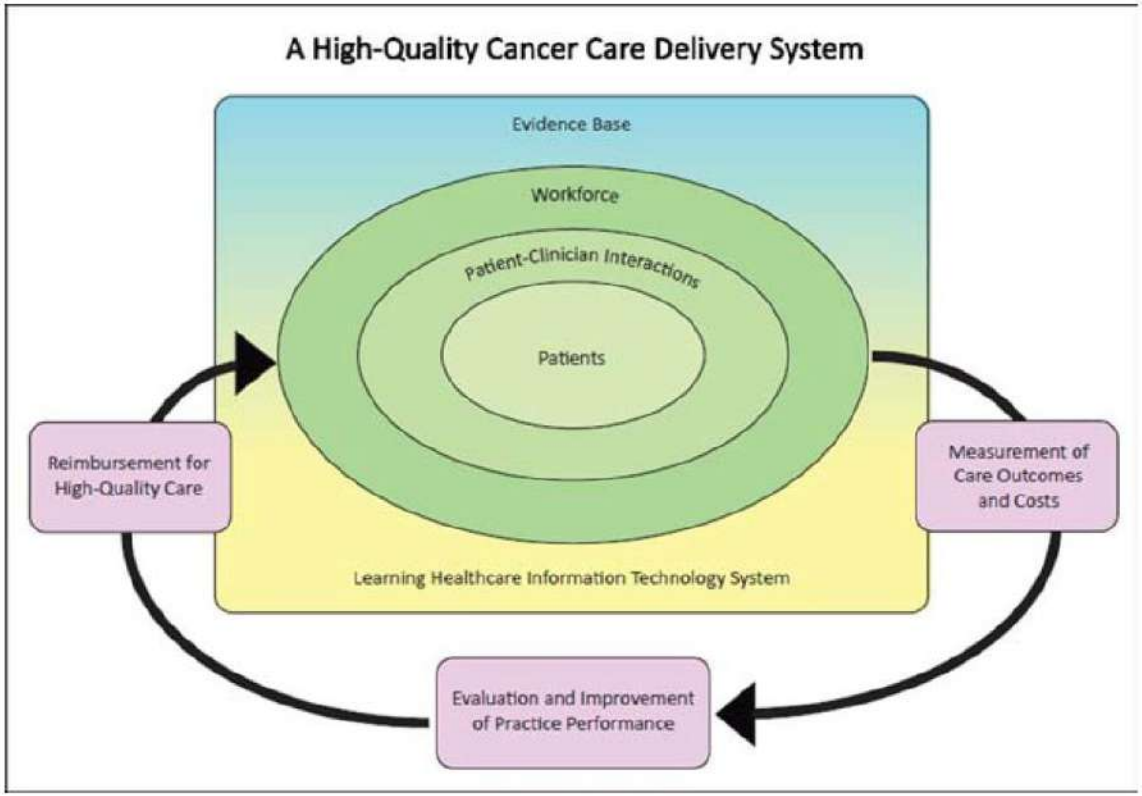
Perspective

Improving the quality of cancer care in America through health information technology

Thomas W Feeley,[1] George W Sledge,[2] Laura Levit,[3] Patricia A Ganz[4,5]

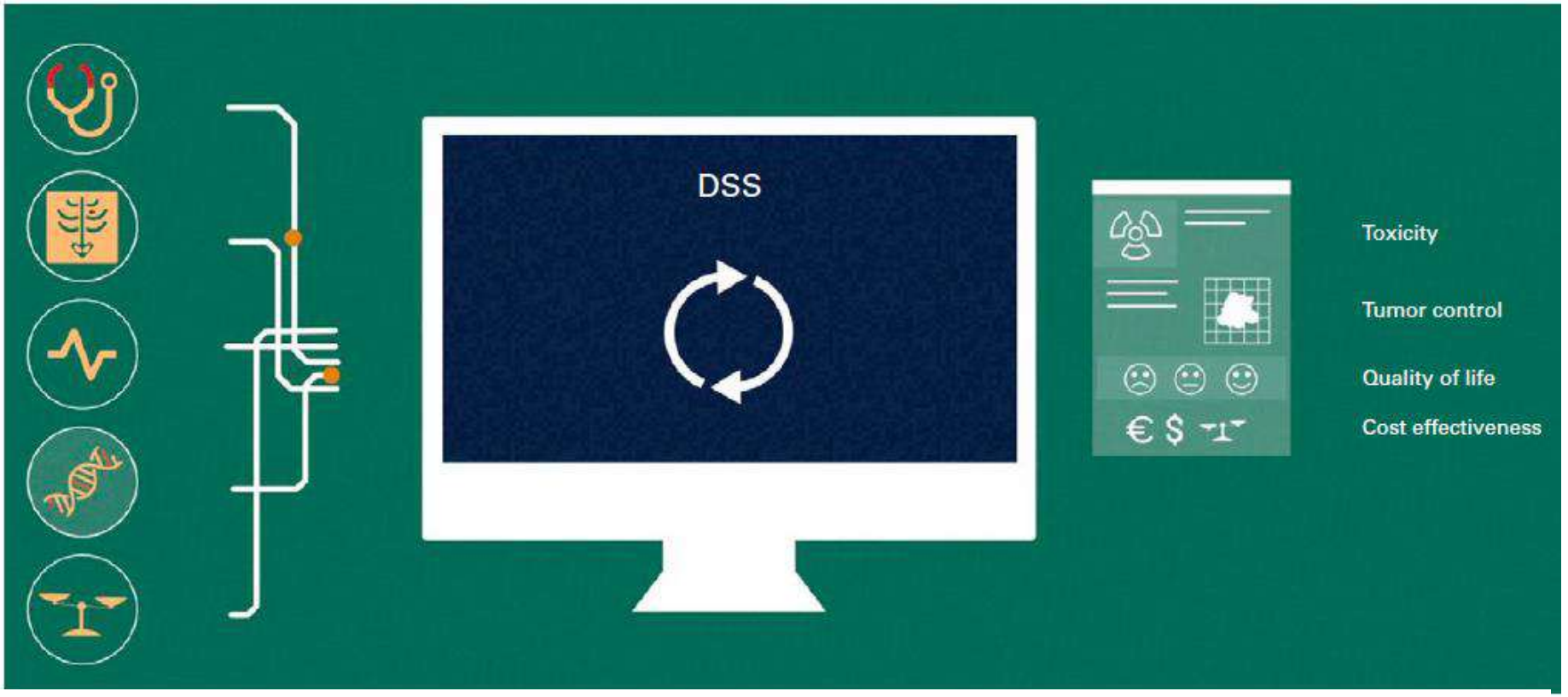
Box 1 Goals of the 10 recommendations to improve the quality of cancer care in America

1. Provide patients and their families with understandable information about cancer prognosis, treatment benefits and harms, palliative care, psychosocial support, and costs.
2. Provide patients with end-of-life care that meets their needs, values, and preferences.
3. Ensure coordinated and comprehensive patient-centered care.
4. Ensure that all individuals caring for cancer patents have appropriate core competencies.
5. Expand the breadth of data collected in cancer research for older adults and patients with multiple comorbid conditions.
6. Expand the depth of data collected in cancer research through a common set of data elements that capture patient-reported outcomes, relevant patient characteristics, and health behaviors.
7. Develop a learning healthcare information technology system for cancer that enables real-time analysis of data from cancer patients in a variety of care settings.
8. Develop a national quality reporting program for cancer care as a part of learning healthcare system.
9. Implement a national strategy to reduce disparities in access to cancer care for under-served populations by leveraging community interventions.
10. Improve the affordability of cancer care by leveraging existing efforts to reform payment and eliminate waste.



http://www.nap.edu/catalog.php?record_id=18359; *Feeley, J Am Med Inform Assoc 2014*

Retos: la gestión de la información



Sistemas de apoyo a la decisión multifactoriales

Freedman; JCO Precis Oncol 2018; Walsh, JCO Clin Cancer Informatics 2019

Nuevos retos: diagnóstico genético DTC

FDA Clears 23AndMe's DTC Breast Cancer Gene Test -- But 'Buyer Beware'

Arlene Weintraub, CONTRIBUTOR
I cover the science and business behind drug development and health
FULL BIO
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Anne Wojcicki, CEO of 23andMe Inc., believes consumers should have better access to BRCA

The direct-to-consumer genetic-test marketer 23andMe celebr
an historic first today, with the first FDA approval of its test fo
some BRCA1/BRCA2 mutations. The genes that the test cover
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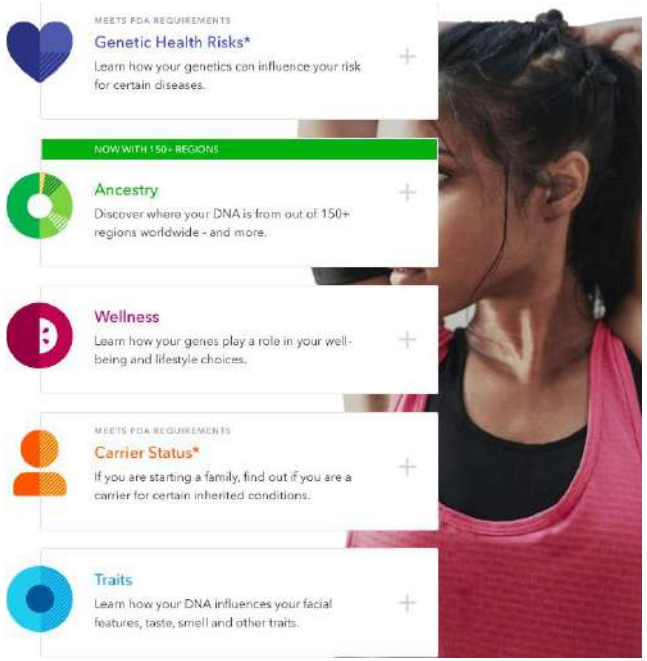

CONCLUSIONES

Cambio extremadamente rápido

Beneficios reales, pero no siempre y a veces escasos

Retos científicos y logísticos

España: acceso no equitativo y ausencia de planificación

Balance difícil: eficiencia marcador o fármaco / ineficiencia marcador o fármaco

Retos asistenciales