ANCO/UCSF Presents

Precision Oncology Symposium

November 9, 2019

Marines Memorial Club & Hotel, San Francisco

ANCO

Educating and Empowering the
Northern California Cancer Community

UCSF

University of California
San Francisco

advancing health worldwide

The opinions expressed in this publication are those of the participating faculty and not necessarily those of the *Association of Northern California Oncologists* (ANCO) or *University of California, San Francisco* (UCSF), its members, or any supporters of this meeting.

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ANCO/UCSF

presents

Precision Oncology Symposium

Saturday, November 9, 2019; 8:00AM-3:20PM

Marines Memorial Club and Hotel, San Francisco

Agenda & Schedule

8:00 am	Registration and Continental Breakfast	
8:30 am	Welcome and Introduction	W. Michael Korn, MD
8:40 am	Milestone and Technology Update	W. Michael Korn, MD
9:10 am	Crossfire Session: Tissue vs. Liquid	James P. Grenert, MD, PhD David R. Gandara, MD
10:10 am	Coffee Break	
10:25 am	Germline Testing	James M. Ford, MD
10:45am	Biomarkers in Immuno-Oncology	David Spetzler, MS, MBA, PhD
11:45 am	Molecular Tumor Board	**Moderator:** David R. Gandara, MD **Panelists**: James M. Ford, MD James P. Grenert, MD, PhD Michael Zachary Koontz, MD W. Michael Korn, MD Philip C. Mack, PhD Pamela Munster, MD Sai-Hong Ignatius Ou, MD, PhD Sachdev Thomas, MD
12:30 pm	Lunch	
1:00 pm	Comprehensive Molecular Profiling: Clinical Utility	
	• EGFR, ALK, KRAS, HER2 with Tissue Specificity	Sachdev Thomas, MD
	• Biomarkers with Cross-Disease Relevance	Philip C. Mack, PhD,
	• Novel Targets: NTRK, FGFR, and Beyond	Sai-Hong Ignatius Ou, MD, PhD
2:30 pm	Clinical Trials in Precision Oncology: Current State and Future Perspectives	Pamela Munster, MD
3:00 pm	Patient Access To Molecular Testing	Michael Zachary Koontz, MD
3:20 pm	Adjourn	

Precision Oncology Symposium

Program Faculty

Chair
W. Michael Korn, MD
University of California, San Francisco

Faculty
James M. Ford, MD
Stanford University

David R. Gandara, MD
University of California, Davis

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University of California, San Francisco

Michael Zachary Koontz, MD
Pacific Cancer Care

Philip C. Mack, PhD
Mount Sinai, New York

Pamela Munster, MD
University of California, San Francisco

Sai-Hong Ignatius Ou, MD, PhD
University of California, Irvine

David Spetzler, MS, MBA, PhD
Caris Life Sciences

Sachdev Thomas, MD
The Permanente Medical Group

Precision Oncology Symposium

Disclosure of Relevant Financial Relationships

The *Faculty* members have disclosed the following actual or potential conflicts of interest in regard to this program:

James M. Ford, MD**,** disclosed that he does not have any relevant financial relationships with any commercial interests.

David R. Gandara, MD*,* disclosed that he has consulted for *AstraZeneca, Celgene, CellMax Life, Fujifilm, Roche-Genentech, Guardant Health, Inviata, IO Biotech, Lilly, Liquid Genomics, Merck, Samsung Bioepis, Pfizer.*

James P. Grenert, MD, PhD, disclosed that he does not have any relevant financial relationships with any commercial interests.

Michael Zachary Koontz, MD*,* disclosed that he does not have any relevant financial relationships with any commercial interests.

W. Michael Korn, MD, disclosed that he is the Chief Medical Officer of *Caris Life Sciences;* has consulted for *Merck;* and, owns stock at *Caris Life Sciences*.

Philip C. Mack, PhD, disclosed that he has received a speaking honorarium from *Guardant Health.*

Pamela Munster, MD*,* disclosed that she does not have any relevant financial relationships with any commercial interests.

Sai-Hong Ignatius Ou, MD, PhD, disclosed that he has received a speaking honorarium from *Merck and Pfizer.* He has also disclosed that he has consulted for and received a speaker honorarium from *AstraZeneca, Roche-Genentech, Takeda/ARIAD, and Turning Point Therapeutics.*

David Spetzler, MS, MBA, PhD, disclosed that he is the President and Chief Scientific Officer of *Caris Life Sciences*

Sachdev Thomas, MD, disclosed that he does not have any relevant financial relationships with any commercial interests.

Acknowledgement of Financial Support

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Caris Life Sciences

Coherus Biosciences

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Foundation Medicine

Genomic Health

Heron Therapeutics

Jazz Pharmaceuticals

Merck

Novartis Oncology

Pfizer Oncology

Pharmacyclics

Tempus Labs

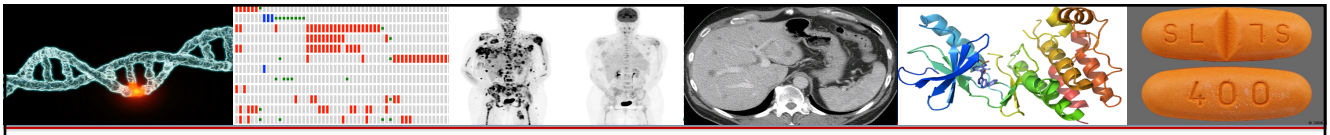
&

UC San Francisco Referral Liasion Services

Precision Oncology Symposium

Milestone and Technology Update

W. Michael Korn, MD



Milestones and Technology Update

W. Michael Korn, M.D. – Eric Collisson, M.D.

UCSF Division of Hematology/Oncology

UCSF University of California San Francisco

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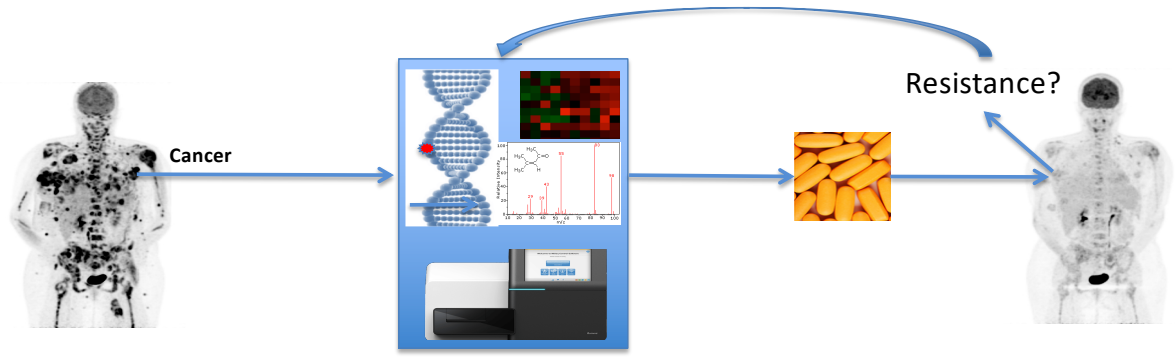
Precision Oncology: The Promise



Tailoring treatment to the Individual characteristics of each patient and their disease

More efficient treatments • Less Toxicity

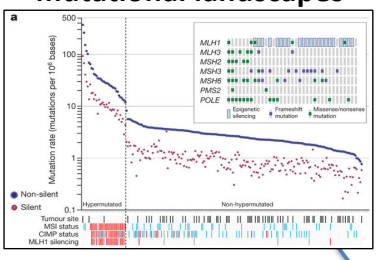
2

Precision Oncology: Growing Complexity

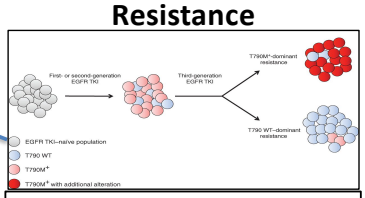
3

Precision Oncology: Challenges

Complex, disease-specific mutational landscapes



De-novo and acquired Resistance



Molecularly Driven Therapies

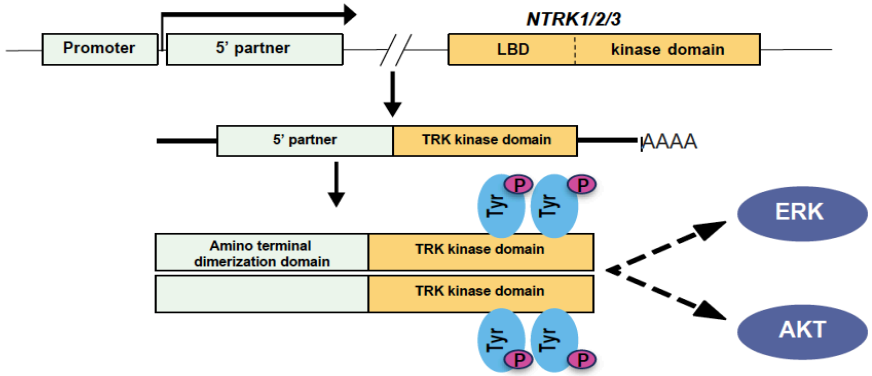
Tumor heterogeneity
Micro-environment
Microbiome

Drug development

4

Rare Fusion Genes with High Impact

NTRK gene fusions are rare but recurrent oncogenic drivers



- Larotrectinib is a highly potent small-molecule inhibitor of TRKA, TRKB, and TRKC (5–11 nM IC_{50} in cellular assays)

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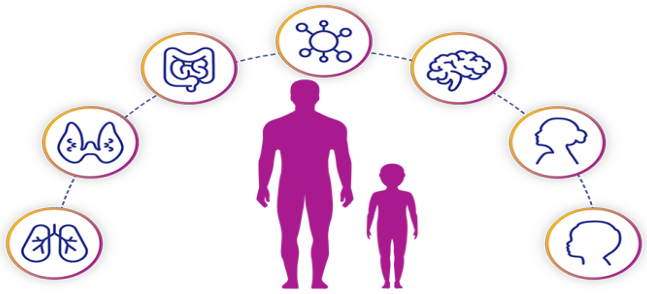
NTRK Fusions occur all over the body



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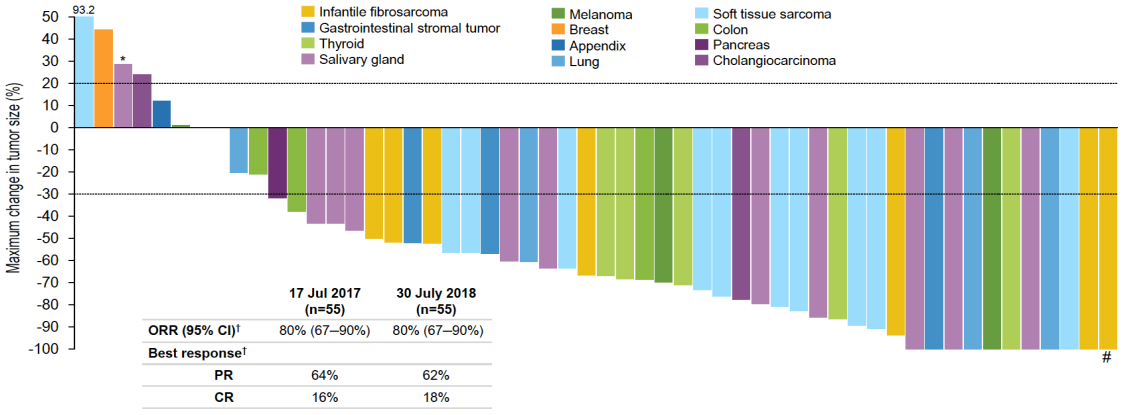
Responses to the TRK inhibitor Larotrectinib



	17 Jul 2017 (n=55)	30 July 2018 (n=55)
ORR (95% CI)†	80% (67–90%)	80% (67–90%)
Best response†		
PR	64%	62%
CR	16%	18%

Lassen et al., ESMO 2018

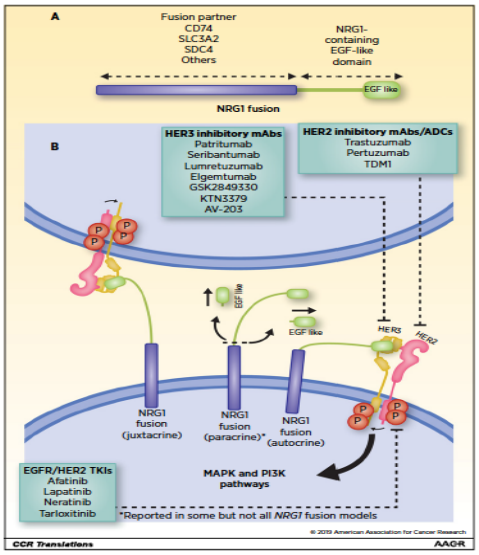
7

7

FDA Approval of Larotrectinib (Vitrakvi)

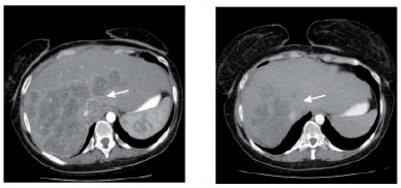
8

NRG1 Fusions: Constitutive Activation of HER3 Signaling



Dimou and Carmidge, Clin. Cancer Res., 2019

Fusions preserve EGF-like domain of NRG1 and transmembrane domain of fusion partner



Measurable response after 16 weeks of apatinib treatment in patient with NRG1-fusions positive cholangiocarcinoma and hepatic metastases

Jones et al., 2017

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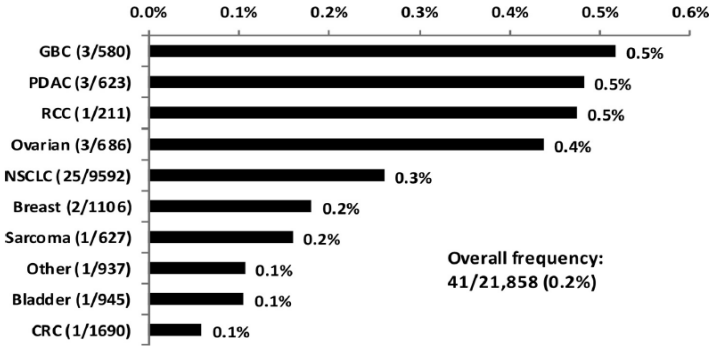
Precision Medicine and Imaging

Clinical Cancer Research

Detection of NRG1 Gene Fusions in Solid Tumors

Sushma Jonna[1], Rebecca A. Feldman[2], Jeffrey Swensen[2], Zoran Gatalica[2], Wolfgang M. Korn[2], Hossein Borghaei[3], Patrick C. Ma[4], Jorge J. Nieva[5], Alexander I. Spira[6], Ari M. Vanderwalde[7], Antoinette J. Wozniak[8], Edward S. Kim[9], and Stephen V. Liu[1]



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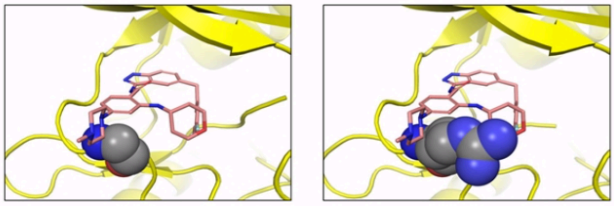
NTRK Resistance Mutations

IC_{50} (nM)	Ba/F3-ETV6-TRKC WT	Ba/F3-ETV6-TRKC-G623R
Entrectinib	2.0	507.0
LOXO-101	13.7	>1000
Crizotinib	88.0	>1000

IC_{50} (nM)	Ba/F3-TPM3-TRKA WT	Ba/F3-TPM3-TRKA-G595R
Entrectinib	5.9	>1000
LOXO-101	14.0	>1000
Crizotinib	133.8	>1000

Wildtype

Solvent front mutation
(TrkA G595R, TrkC G623R)

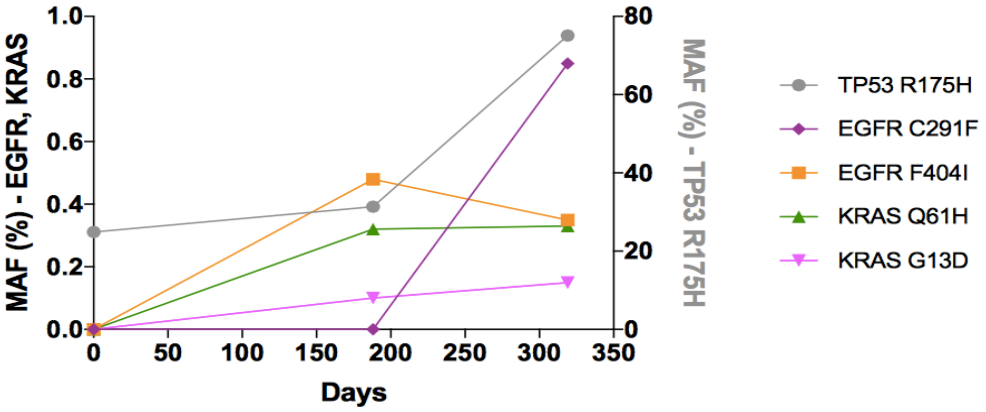


The patient was detected to have *NTRK3 G623R* in a post-progression biopsy

11

Detection of Clonal Dynamics by Cell-free DNA

63 y.o woman with metastatic sigmoid colon cancer, initially KRAS WT



Strickler et al., Cancer Discov., 2018

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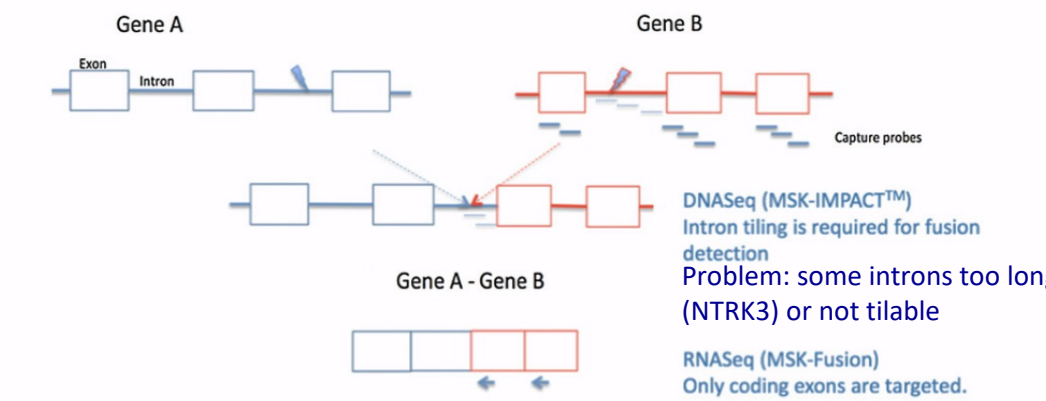
Gene Fusion Detection: RNA superior to DNA



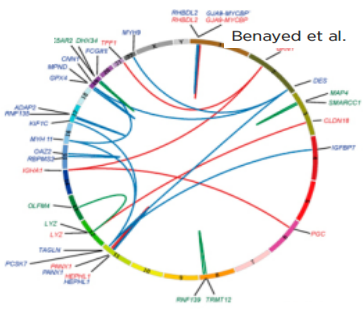
- 14% (36/254) fusions detected by RNAseq that were missed by MSK-IMPACT.
- 48% gene fusions identified exclusively by RNAseq would have been expected to be detected by the MSK-IMPACT panel based on its design.

Benayed. et al, Clin. Cancer Res., 2019

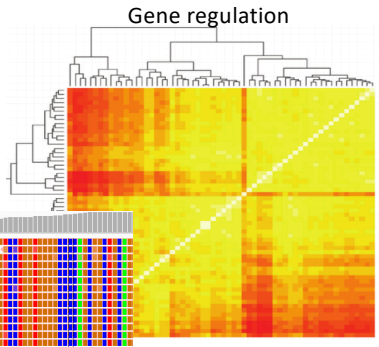
13

Whole Transcriptome RNA Sequencing Provides Diverse Analytical Insights

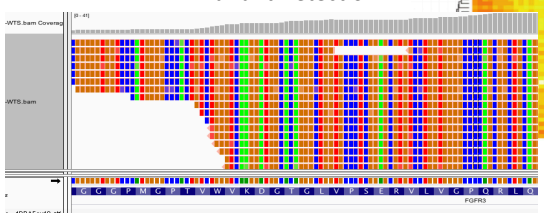
Fusion Detection



Gene regulation



mRNA Variant Detection



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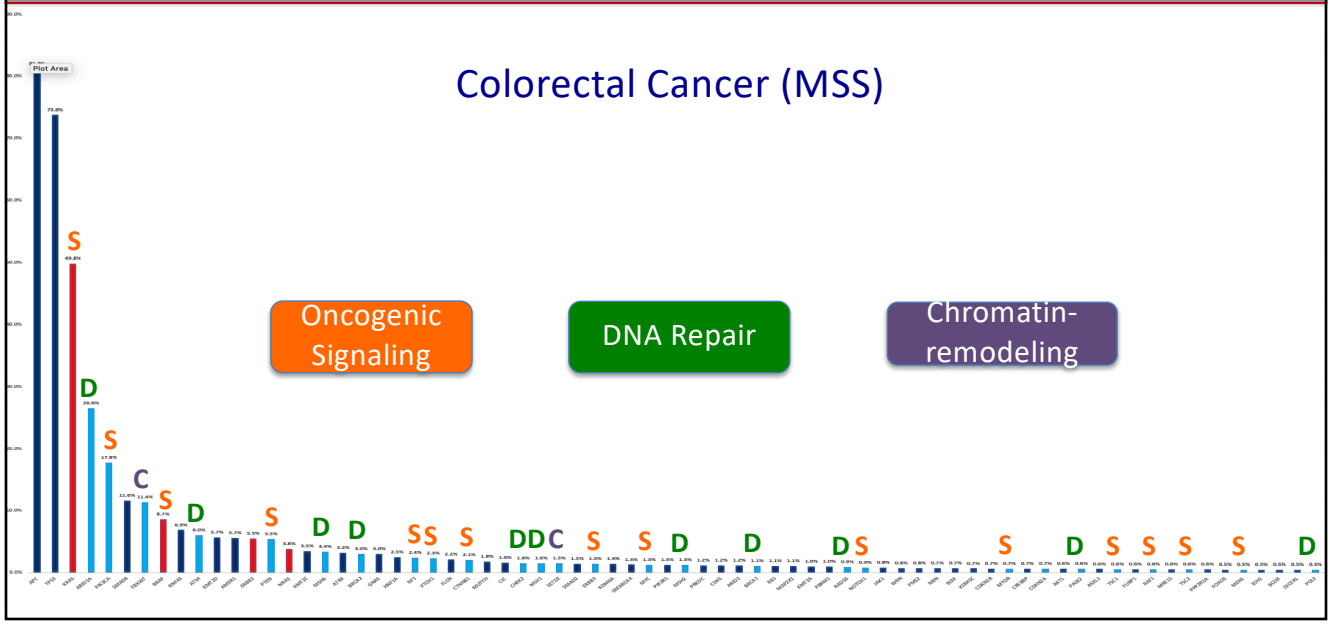
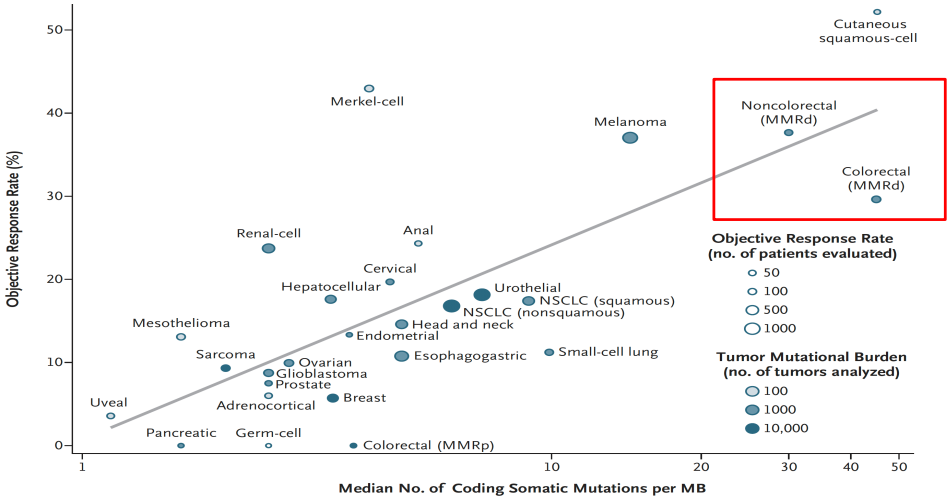
Low Frequency Mutations Share Common Themes



15

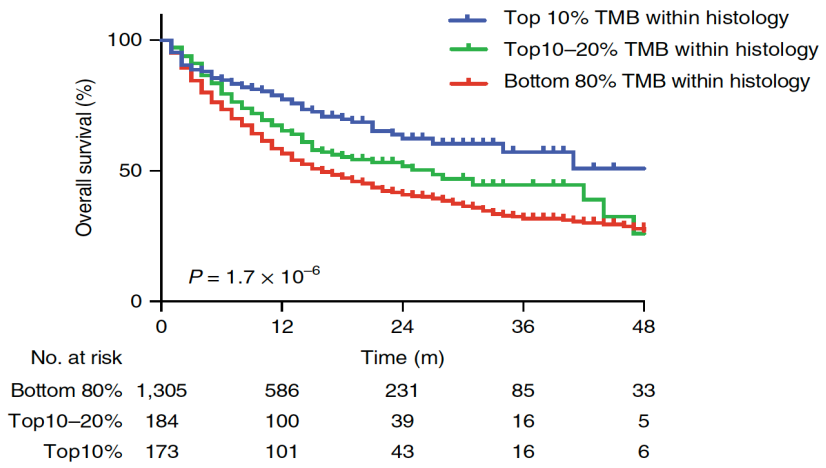
Tumor Mutational Burden explains 55% of variability in response to immune checkpoint inhibition



Yarchoan et al., NEJM 2017

16

Disease-Specific Distribution of TMB Predicts Sensitivity to Immune-checkpoint Inhibition

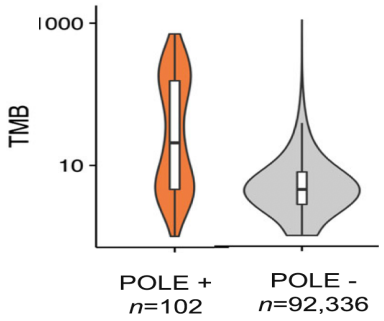


Samstein et al., 2019

17

PolE mutations: Taking TMB to the extreme

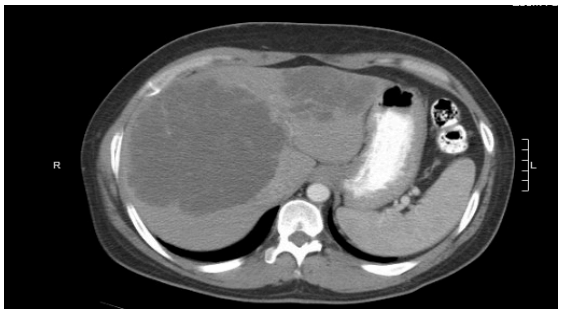
- A 39 y/o man presented to UCSF GI Oncology with extensively metastatic colon cancer and PD on conventional chemotherapy.
- Patient in poor performance status, referred to hospice.
- Next-generation DNA sequencing revealed a pathogenic **PolE P286R** mutation as well as a large number of additional mutations.



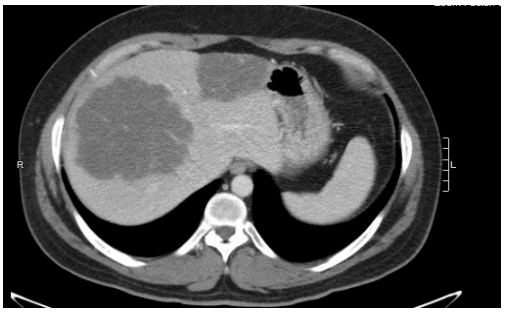
18

Prolonged response to immunotherapy

- Single agent anti-PD-L1 therapy with pembrolizumab was initiated in December 2016.



October 2016



July 2018

- Treatment ongoing, patient active and in good performance status.

Courtesy Dr. van Loon, UCSF

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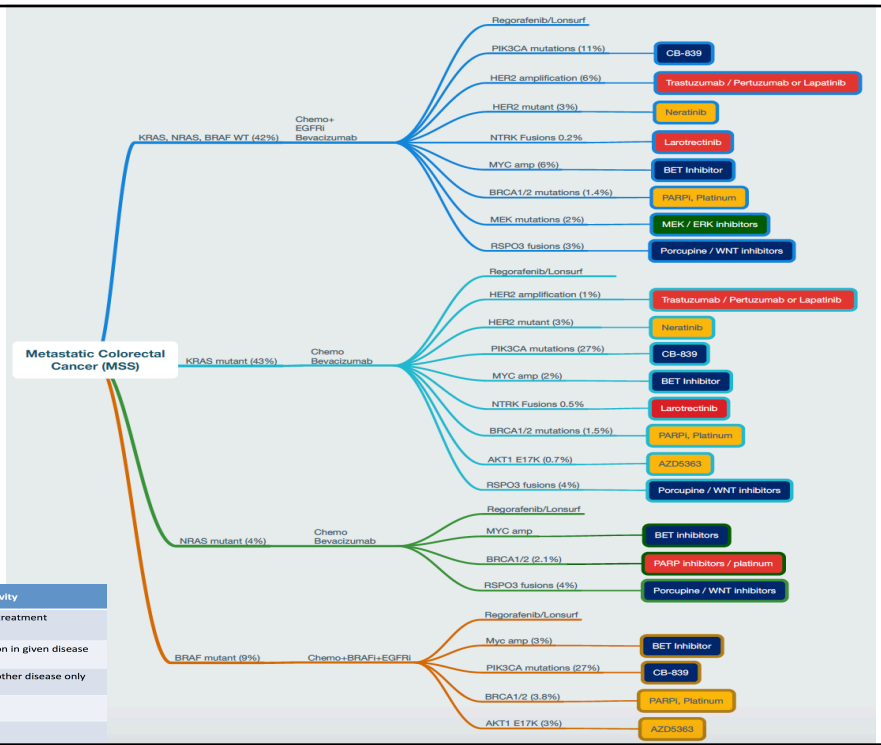
Colorectal Cancer: Precision Oncology Roadmap



Level of Evidence	Evidence for association of mutations and drug activity
High - 1	Relationship of molecular finding and efficient drug treatment established through clinical trials for a given disease
2	Limited evidence for association of drug and mutation in given disease
3	Evidence for association of drug and mutation in another disease only
4	Preclinical evidence
Low - 5	Inferential association

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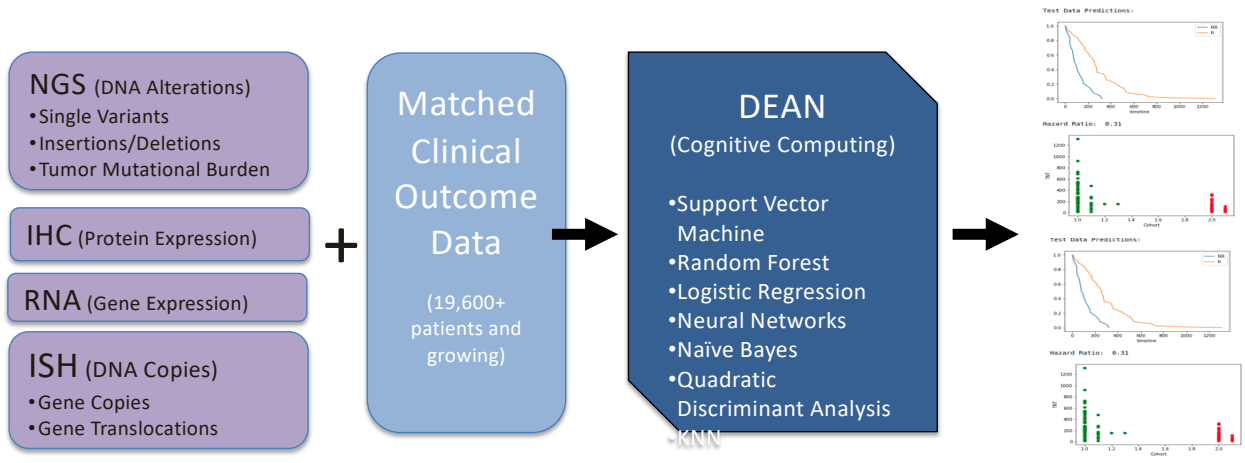
Next Generation Profiling (NGP): Discovery of Clinically Relevant Signatures through Machine Learning



Abraham et al., Caris Life Sciences, *unpublished*

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An Assembly of Mathematical Models Coupled With Neural Networks

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NGP FOLFOX Predictor

Patient Characteristics (Testing Dataset)

Characteristic	Benefit N=103 (%)	No Benefit N=61 (%)	p
Median Age	58	59	0.250
Female/Male	44/56	49/51	0.603
Colon/Rectal	93/7	77/23	0.003
Left/Right/unknown	35/42/23	51/38/11	0.069
Bevacizumab	100	100	1.000
Cetuximab	9	15	0.351

Abraham et al., Caris Life Sciences, *unpublished*

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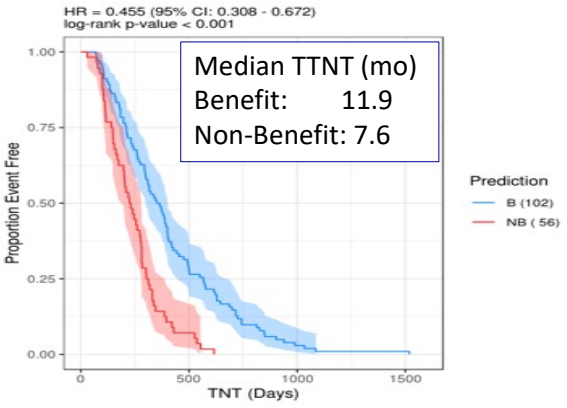
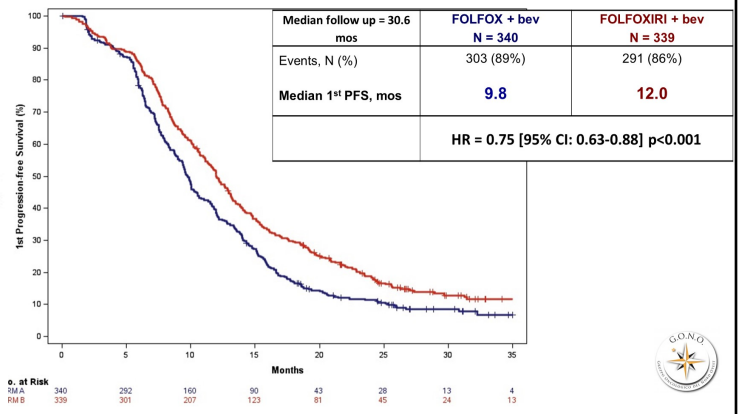
Clinical validation using an independent cohort of patients who received FOLFOX in 1st line

FOLFOX-NGP



TRIBE-2



Median follow up = 30.6 mos	FOLFOX + bev N = 340	FOLFOXIRI + bev N = 339
Events, N (%)	303 (89%)	291 (86%)
Median 1st PFS, mos	9.8	12.0
	HR = 0.75 [95% CI: 0.63-0.88] p<0.001	

Abraham et al., Caris Life Sciences, *unpublished*
Cremolini et al., ASCO 2019

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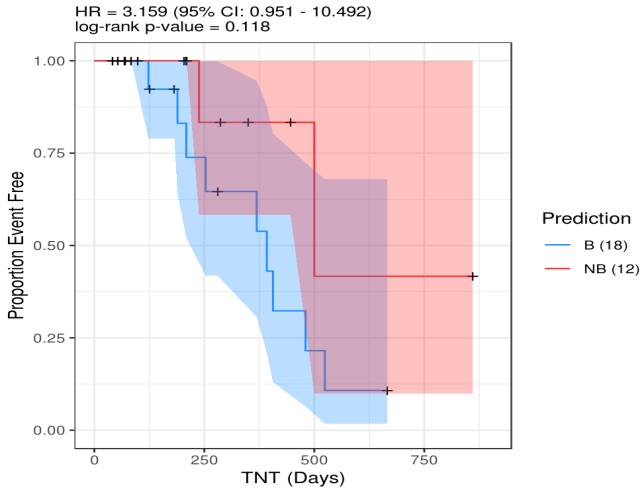
FOLFOX Predictor Not Predictive of Response to First-Line FOLFIRI



Abraham et al., Caris Life Sciences, *unpublished*

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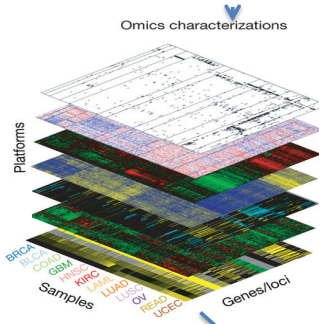
The Future of Precision Oncology

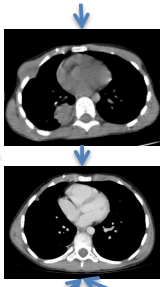
Improved Access to Molecular Profiling

Earlier Testing:
IO Predictors, Gene Fusions etc.

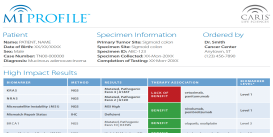


Next generation DNA sequencing
Copy Number
RNA expression / Gene fusion analysis
Proteomics
Liquid biopsy
Clinical Outcomes

Real-World Clinical Outcomes Data



Improved Outcomes



Machine Learning

Individualized Reporting

Basket Trials

Distributed Trials
(Just-in-Time)

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Acknowledgement

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University of Southern California
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CARIS LIFE SCIENCES

Medical Affairs
Todd Maney
Rebeca Feldman
Joanne Xiu

R & D
David Spetzler
James Abraham
Dan Magee
Mark Miglarese

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Chiara Cremolini

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Cortney Flookes
Jose L. Gonzales

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UCSF Helen Diller Family Comprehensive Cancer Center

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Thank You!

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Precision Oncology Symposium

Crossfire Session: Tissue vs. Liquid

James P. Grenert, MD, PhD and David R. Gandara, MD

Emerging Role of Liquid Biopsy in Precision Medicine: Non-Small Cell Lung Cancer as a Model

David R. Gandara, MD
University of California Davis
Comprehensive Cancer Center

1

Disclosures

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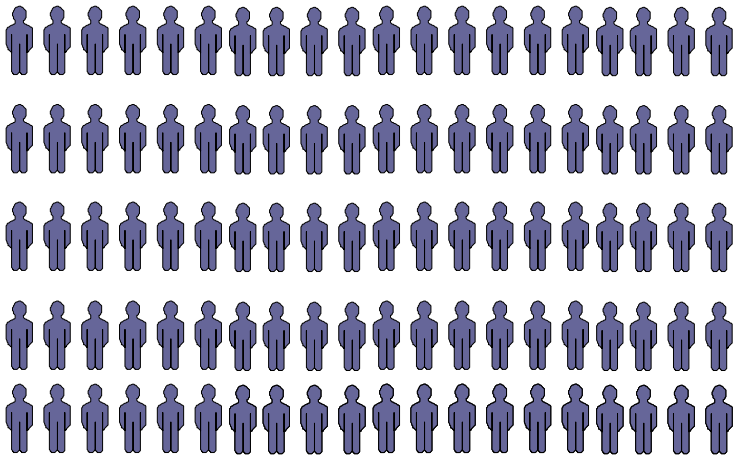
- Consultant/Advisory Board: AstraZeneca, Celgene, CellMax, FujiFilm, Roche-Genentech, Guardant Health, Inivata, IO Biotech, Lilly, Merck, Samsung Bioepis

2

100 patients with Advanced Stage Non-Small Cell Lung Cancer (NSCLC): They all look alike, but they are not



NSCLC

3

100 patients with Advanced Stage Non-Small Cell Lung Cancer (NSCLC): They all look alike, but they are not

In 2019 most Oncologist would agree that these are different malignancies.
In 2019 most Oncologists would agree that these patients need different therapies

4

Evolution & Expanding List of Guideline Recommendations for Genomic Testing in NSCLC

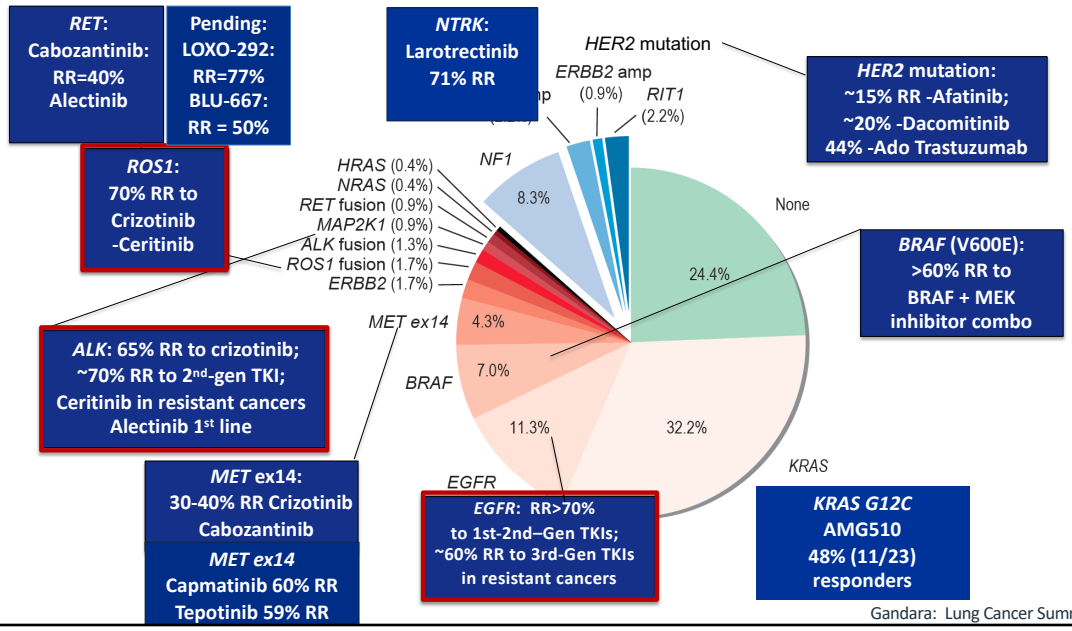
"The NCCN NSCLC Guidelines Panel strongly endorses **broader molecular profiling** with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials. **Broad molecular profiling** is a key component of the improvement of care of patients with NSCLC)."

Genomic Alteration (i.e. driver event)	Available targeted agents with activity against driver event in lung cancer*
EGFR mutations	osimertinib, erlotinib, gefitinib, afatinib, dacomitinib
ALK rearrangements	alectinib, brigatinib, ceritinib, crizotinib, lorlatinib
HER2 mutations	ado-trastuzumab emtansine, afatinib
BRAF V600E mutations	dabrafenib + trametinib, vemurafenib
MET amplification/mutation	crizotinib
ROS1 rearrangements	crizotinib, ceritinib
RET rearrangements	cabozantinib, vandetanib
NTRK rearrangements	entrectinib, larotrectinib

NCCN Clinical Practice Guidelines. NSCLC. v3.2019.

5

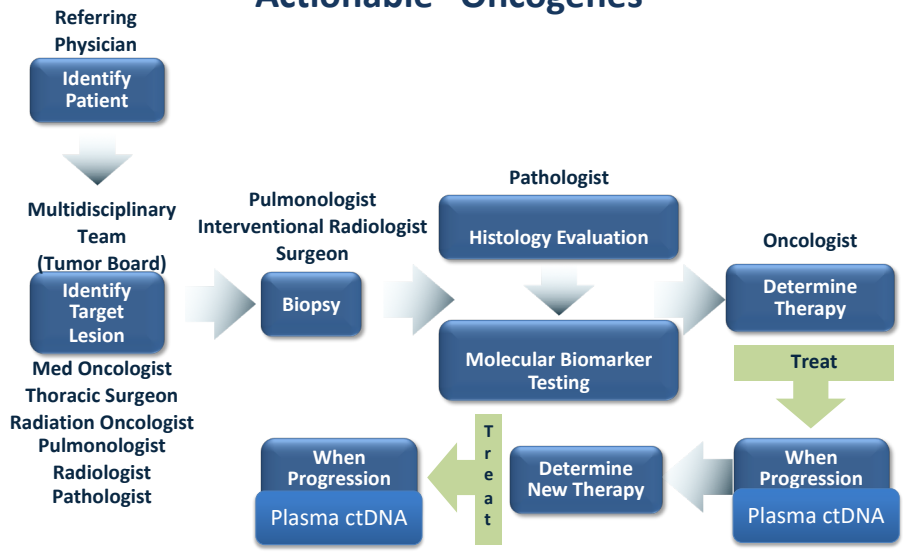
Growing Number of Oncogene-driven NSCLCs with Active Targeted Therapies



Gandara: Lung Cancer Summit. ESMO19

6

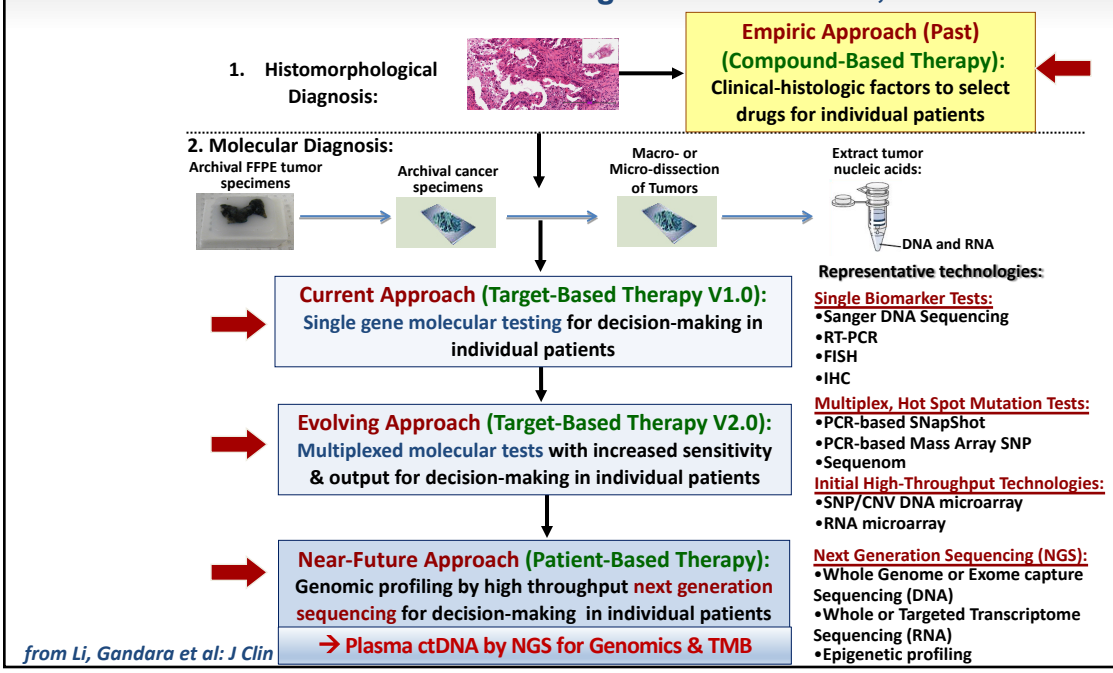
Schema for Multidisciplinary Integration of Biomarker Testing in Advanced Stage NSCLC: Looking for "Actionable" Oncogenes



Adapted from: Raez, Gandara et al Clin Lung Cancer 2016

7

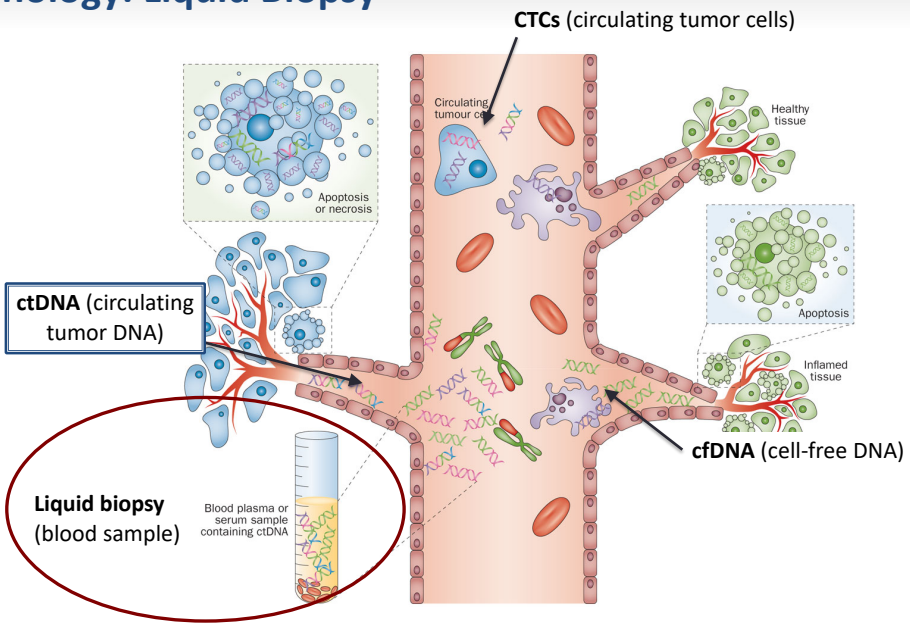
Evolution of Biomarker Testing in NSCLC: Past, Current & Future



from Li, Gandara et al: J Clin

8

Terminology: Liquid Biopsy



Crowley E, et al. Nat Rev Clin Oncol 2013;10:472–484.

9

REVIEW ARTICLE

IASLC

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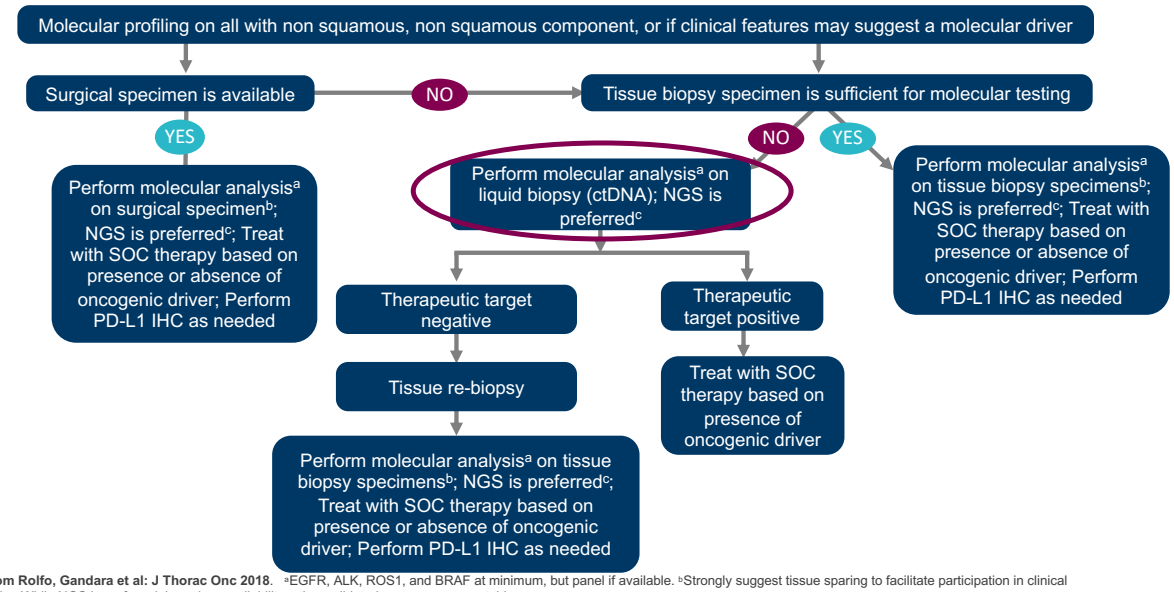
10

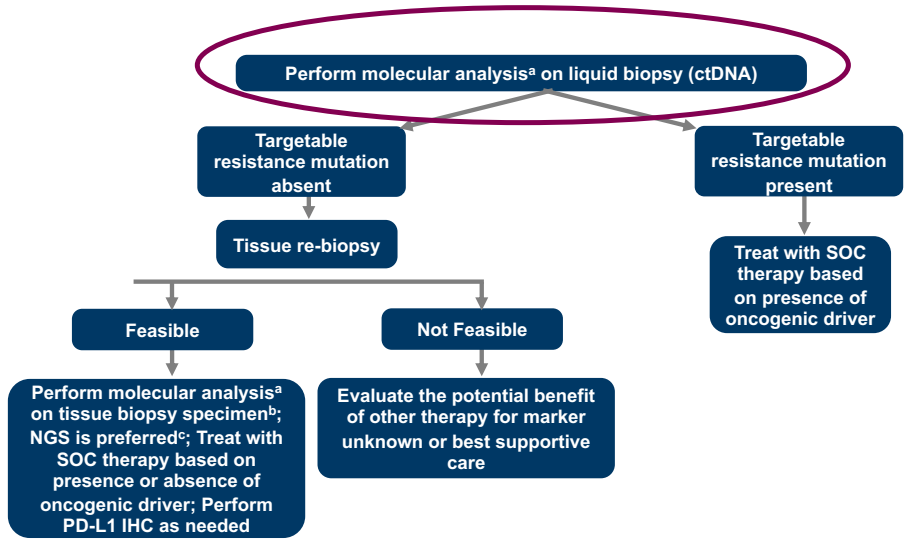
Patient with Advanced Treatment-naïve NSCLC



From Rolfo, Gandara et al: J Thorac Onc 2018. [a]EGFR, ALK, ROS1, and BRAF at minimum, but panel if available. [b]Strongly suggest tissue sparing to facilitate participation in clinical trials. [c]While NGS is preferred, based on availability, other validated assays are acceptable.

11

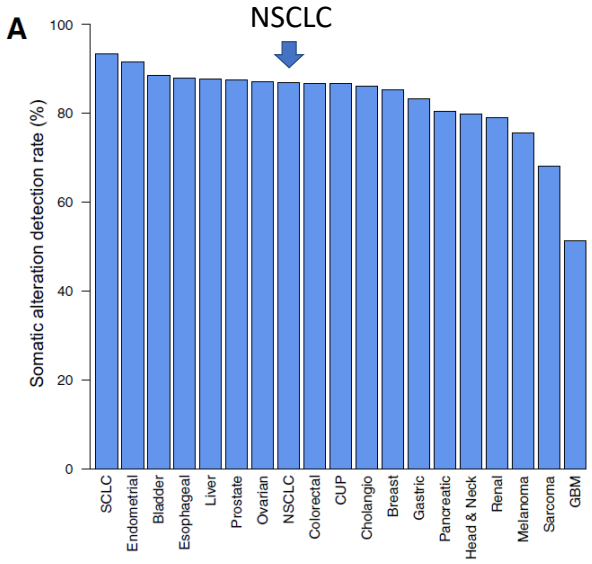
Patient with NSCLC progressive or recurrent disease during therapy



from Rolfo, Gandara, et al: J Thorac Onc 2018. [a]cobas/ddPCR for EGFR mutation NGS preferred for ALK and ROS1. [b]Strongly suggest tissue sparing to facilitate participation in clinical trials. [c]While NGS is preferred, based on availability, other validated assays are acceptable.

12

High Circulating Tumor (ct)DNA Detection Rate across Multiple Cancer Types (N=21,807)

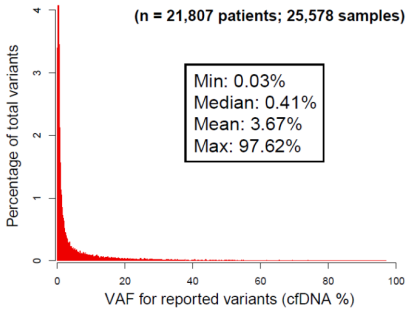


Guardant360 plasma NGS assay for detection of somatic alterations in 21,807 cancer patients

85% detection rate across all cancers

- **93% SCLC**
- **87% NSCLC**

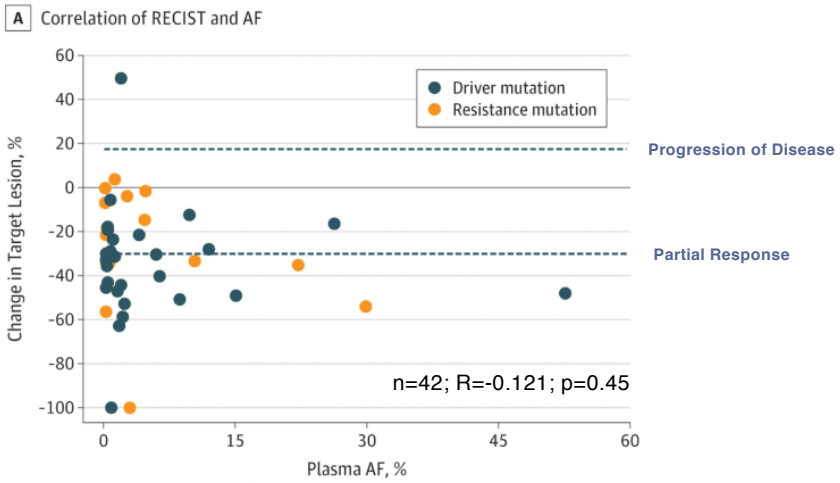
Median VAF: 0.41% (range 0.03-97.6)



Zill, Mack, Gandara, Landman et al, CCR 2018

13

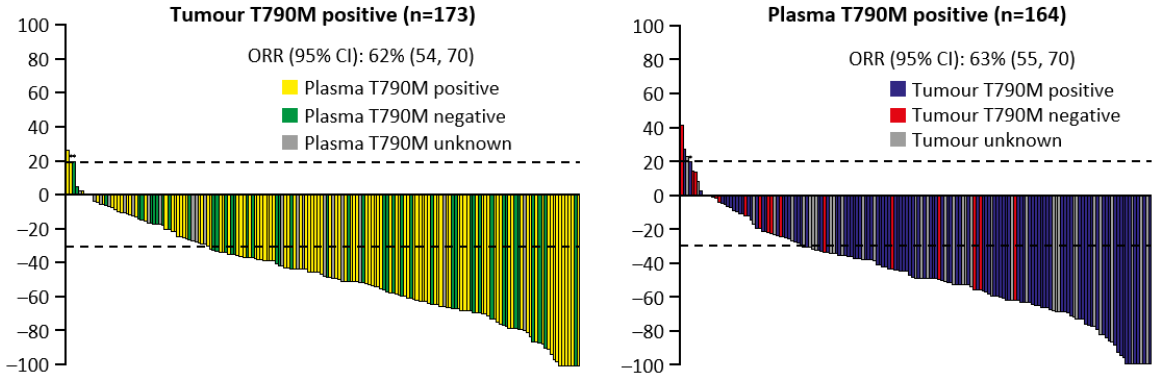
PENN2 Study: Response to Targeted Therapy is Independent of Plasma Mutation Allelic Fraction



Aggarwal et al: JAMA Oncol 2018

14

High ORR in Patients With Tumor- or Plasma-Detected, T790M-Positive NSCLC Treated With Osimertinib



Oxnard et al. *J Clin Oncol*. 2016;34:3375.

15

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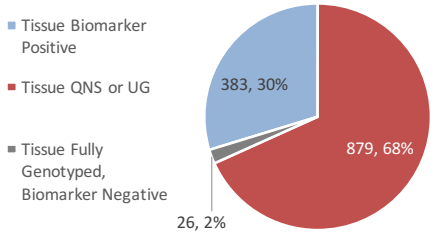
16

ctDNA Utility in Under-Genotyped/QNS Non-Squamous NSCLC

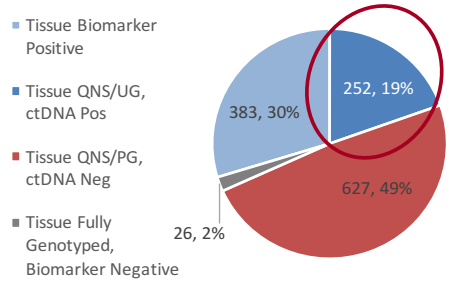


Biomarker	N in Tissue
EGFR	256
KRAS	61
ALK fusion	27
ROS1 fusion	9
RET fusion	4
BRAF V600E	10
MET amp	10
MET E14	4
HER2 mutation	1
FGFR3 fusion	1
TOTAL	**383**

Tissue Genotyping Status (N=1288)

383 of 1288 (30%) Biomarker Positive for Driver Oncogene

879 (68%) Quantity Insufficient (QNS) or Undergenotyped (UG)



Biomarker	N in ctDNA*
EGFR	42
KRAS	127
ALK fusion	3
ROS1 fusion	2
RET fusion	14
BRAF V600E	13
MET amp	23
MET E14	7
HER2 mutation	21
TOTAL	**252**

ctDNA NGS Increased Biomarker Yield

ctDNA analysis identified 252 *additional* actionable biomarkers (19% of 1288) (29% of 879) not previously detected in tissue QNS/UG cases

Adapted from Zill, Mack, Gandara, Landman et al, CCR 2018

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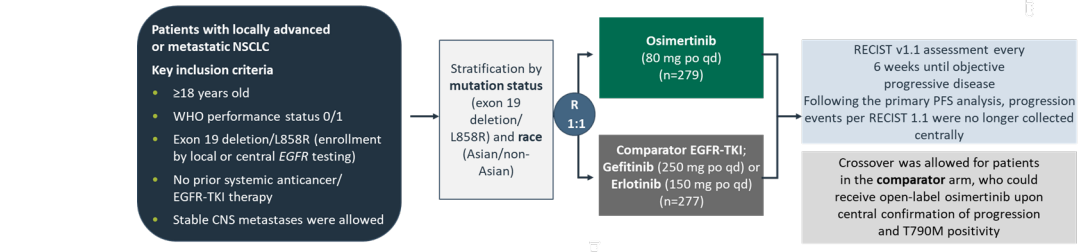
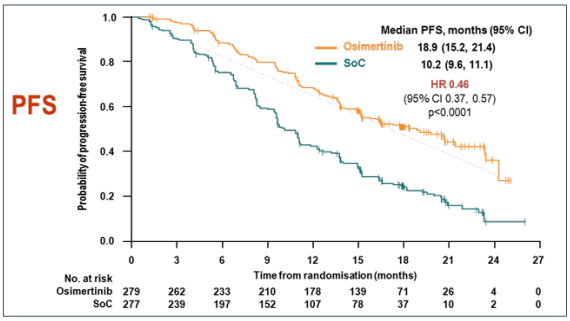
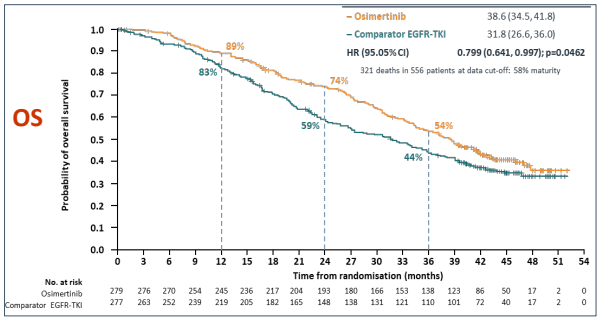
18

FLAURA: Osimertinib vs Gefitinib/Erlotinib in 1st line therapy of EGFR-mutated NSCLC





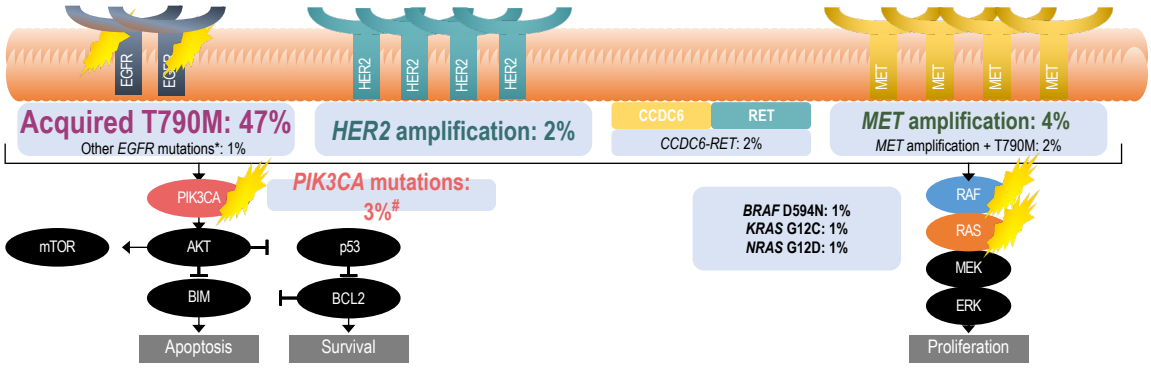


Soria et al: NEJM 2017 & Ramalingam et al: ESMO 2019

19

FLAURA: Acquired Resistance Mechanisms in Comparator EGFR TKIs (n=129)

The most common acquired resistance mechanisms were T790M mutation (47%), *MET* amplification and *HER2* amplification

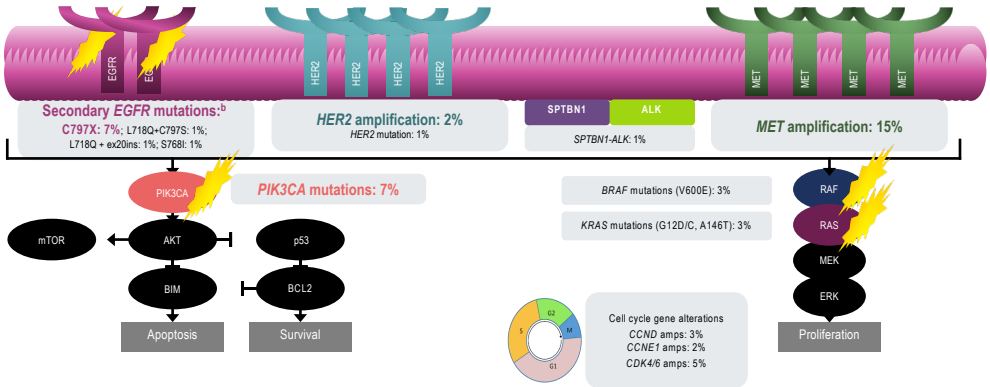


*Resistance mechanism reported may overlap with another; #Acquired T790M + C797S + L718Q: 1%; †PIK3CA + T790M (n=1), PIK3CA + T790M + C797S (n=1), and PIK3CA (n=1)

20

FLAURA: Acquired Resistance Mechanisms after Osimertinib first-line therapy (n=91)[a]

- No cases of acquired *EGFR* T790M
- The most common resistance mechanisms were *MET* amplification (15%) and *EGFR* C797X mutation (10%)
  - Other mechanisms included HER2 amplification/mutation (3%), *PIK3CA(7%), RAS/RAF* mutations and ALK transformation



[a]Resistance mechanism reported may overlap with another; [b]Two patients had de novo T790M mutations at baseline of whom one acquired C797S at progression

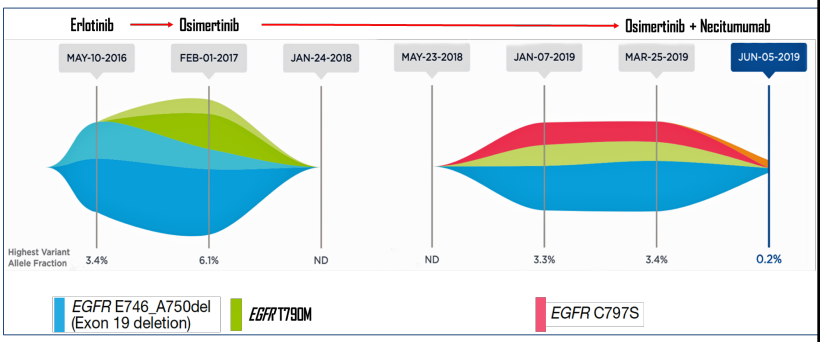
Ramalingam SS, et al. ESMO 2018. Abstract LBA50.

21

Case Example: Serial plasma ctDNA monitoring

52 yo female, never-smoker, with new Dx of stage IV lung adenocarcinoma, May 2016, lymphangitic spread-R. lung, bone mets

- EGFR Ex19del identified (May 2016). Initially treated with erlotinib → PR.
- Progressive disease in Feb 2017, found to be T790M+. Treated with osimertinib → PR.
- In Jan 2018 & May 2018, monitoring shows absence of Ex19del & T790M.

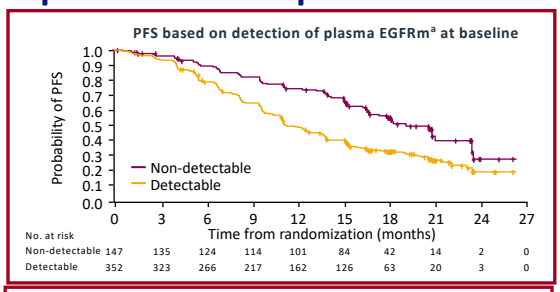


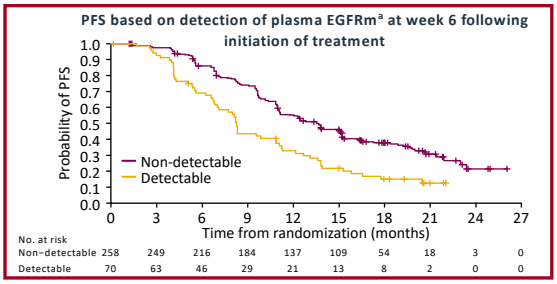
- In Jan 2019, new cough & SOB. CT scan read as "stable", but possible "pneumonia".
- Plasma ctDNA identifies EGFR C797S resistance mutation.
- Re-read of CT scan consistent with recurrent lymphangitic spread. Navigational bronchoscopy shows recurrent adenocarcinoma.
- Started on therapy designed for C797S+ disease.
- June 2019: CT scan shows major response. C797S= non-detectable

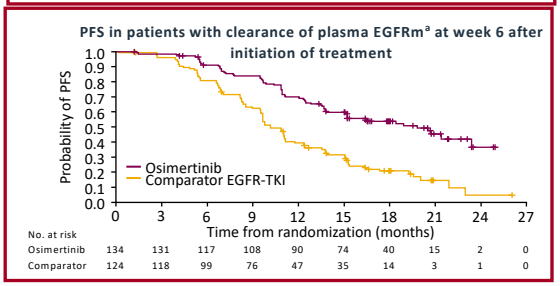
Case Report Courtesy of David Gandara MD, UC Davis

22

FLAURA: Early clearance of plasma EGFR mutations as a predictor of response to osimertinib and comparator EGFR-TKIs





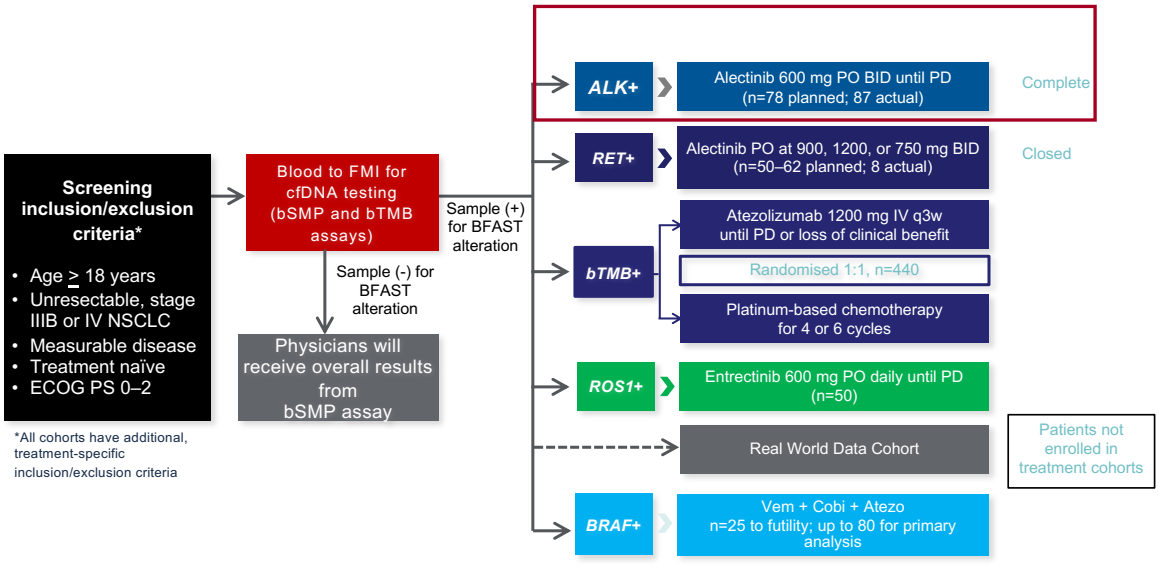


- This analysis of FLAURA confirms prior studies showing that presence of EGFR mutation in plasma ctDNA at baseline is a poor prognostic factor
- Patients with plasma EGFR mutation clearance have improved PFS
- Clearance of EGFR mutation from ctDNA favors osimertinib in PFS

[a]Presence of plasma EGFR mutations detected by ddPCR; ddPCR, droplet digital polymerase chain reaction

23

BFAST: Phase 2/3 screening trial in patients with treatment-naïve NSCLC: Initial results from the *ALK*+ cohort



Gadgeel S, et al. ESMO 2019. Abstract LBA81_PR.

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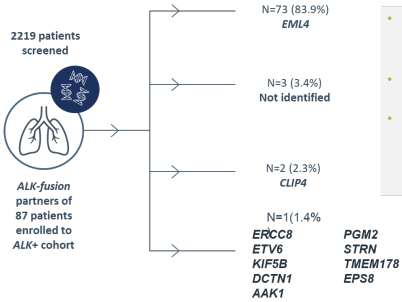
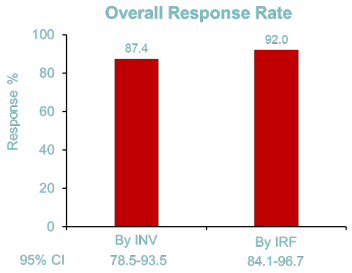
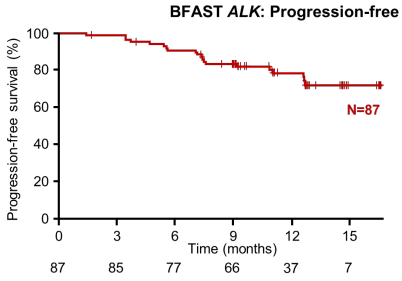
BFAST *ALK*: Results using ctDNA alone



- The 5.4% (119 of 2219) prevalence of *ALK* in the screening population is close to the expected rate of 5%[1]
- Overall, 38/87 (43.7%) patients had a *TP53* mutation
- **Median bTMB** at baseline was **two mutations** (range: 0 to 21)
  - 3/87 (3.4%) patients had bTMB ≥ 16 mutations





Patients with event, n (%)	20 (23)
Median PFS, months (95% CI)	NE (NE)
12-month PFS, % (95% CI)	78.38 (69.07–87.69)
ALEX[1]	N=152
12-month PFS, % (95% CI)	68.4 (61.0–75.9)

Gadgeel S, et al. ESMO 2019. Abstract LBA81_PR.

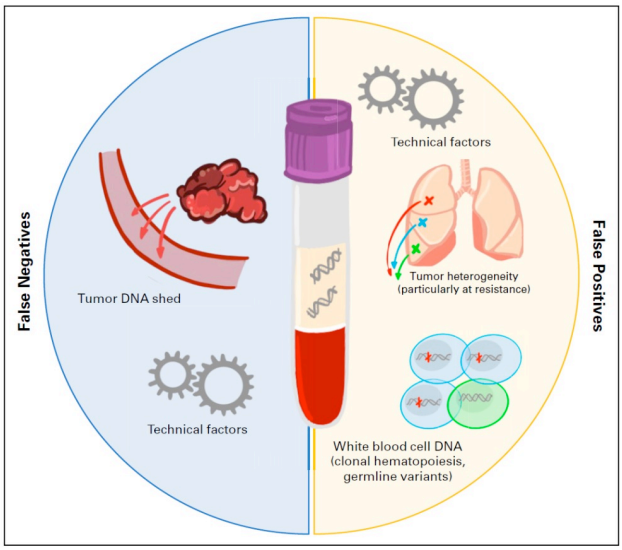
25

Causes of "False Negative" & "False Positive" Liquid Biopsy Results (assumes Tissue=Gold Standard)

"False Negatives" in Liquid Biopsy

Insufficient DNA shed into plasma: (low tumor volume, eliminated by therapy)

Technical Issues: Insufficient sensitivity in older assays



"False Positives" in Liquid Biopsy

Technical Factors: Sample differences (> 6 months from tissue to plasma sampling)

WBC contamination: Germline Variants Clonal Hematopoiesis

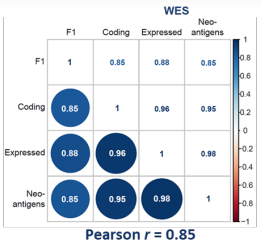
Tumor Heterogeneity: Positive Plasma & Negative Tissue (assumes tissue is "Gold standard")

Adapted from Oxnard et al: JCO 2019

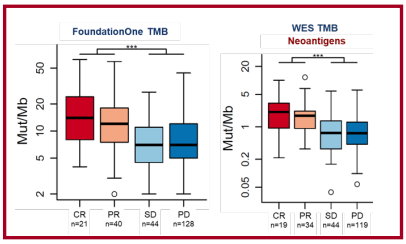
26

Tumor Mutational Burden (TMB) as a Candidate Predictive Biomarker for Cancer Immunotherapy

- **Somatic mutations in cancers are multifactorial** (including DNA repair defects, carcinogens & enzymatic alterations in DNA polymerases)
- These mutations produce **neoantigens** that induce anti-tumor immune responses
- **TMB is an emerging predictive biomarker** for cancer checkpoint immunotherapy (CIT)
- TMB can be estimated using whole-exome sequencing (WES) or comprehensive genomic profiling by NGS (e.g., FoundationOne & FACT in blood[bTMB]) . MSK-IMPACT. Guardant OMNI[1-8]
  - Studies show that TMB either by WES or CGP correlate with each other & with efficacy of CPI therapy in multiple cancer types[1-3]
- **Predicted neoantigen load (NAL),** a component of TMB most closely linked to immune response, correlates with F1 TMB[4,5,7]
- **TMB identifies a distinct patient population** not currently captured by PD-L1 IHC or other immune biomarkers[5,6]



Pearson *r* = 0.85



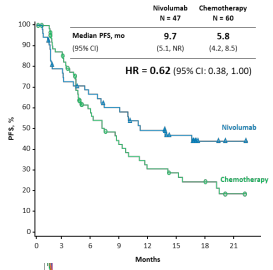
From Gandara, LeGrand et al: ASCO 2018

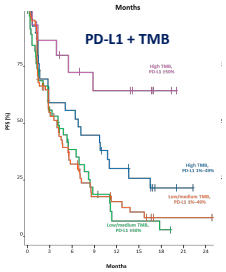
IHC, immunohistochemistry; PD-L1, programmed death-ligand 1; TMB, tumor mutational burden.
1. Yarchoan M, et al. *N Engl J Med.* 2017; 2. Chalmers ZR, et al. *Genome Med.* 2017; 3. Goodman AM, et al. *Mol Cancer Ther.* 2017; 4. Efremova M, et al. *Front Immunol.* 2017; 5. Topalian SL, et al. *Nat Rev Cancer.* 2016; 6. Kowanetz M, et al. WCLC 2017. 7. Mariathansan, et al. Nature 2018. 8. Rizvi et al: ESMO IO 2018.

27

High Tissue TMB is associated with increased efficacy of Checkpoint Inhibitor Monotherapy

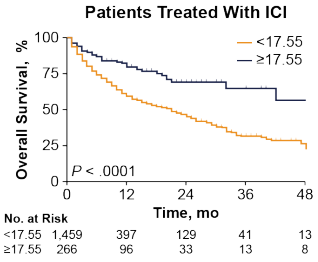
WES: CM-026 NSCLC (Nivo -high TMB)

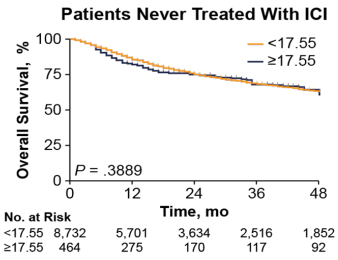




Carbone et al: NEJM 2017

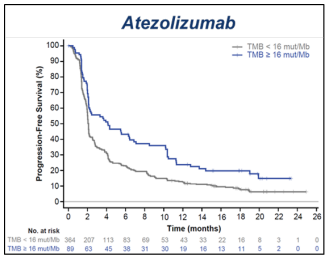
NGS -IMPACT: Multiple Tumor Types

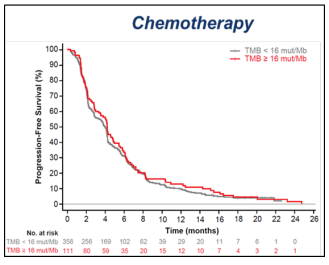




Samstein et al: NatGen 2019

NGS Foundation-One: Multiple Tumor Types





Gandara, Legrand et al: ASCO 2018

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Analytical & Clinical Validation of Tumor Mutational Burden in Blood (bTMB) in association with Atezolizumab efficacy in advanced NSCLC (POPLAR & OAK Trials)

bTMB Computational Methodology and Study Design

Blood collection, plasma isolation & cfDNA extraction

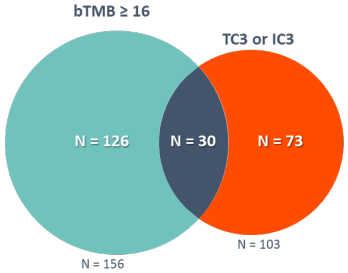
Sequencing

- 394 gene-based NGS assay
- All base substitutions with ≥0.5% allele frequency
- Remove germline polymorphisms & predicted driver mutations

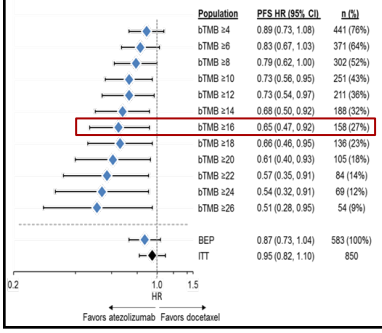
bTMB

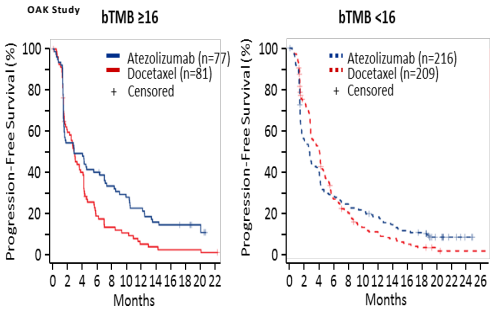
POPLAR (training) — 211/273 biomarker evaluable

OAK (validation) — 583/797 biomarker evaluable



Progression-Free Survival – OAK





BEP (N = 229)

	PFS HR (95% CI)	OS HR (95% CI)
bTMB ≥16	0.64 (0.46, 0.91)	0.64 (0.44, 0.93)
TC3 or IC3	0.62 (0.41, 0.93)	0.44 (0.27, 0.71)
bTMB ≥16 and TC3 or IC3	0.38 (0.17, 0.85)	0.23 (0.09, 0.58)

Gandara DR, et al. Nature Med 2018.

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B-F1RST: Proof of Principle trial for Blood Tumor Mutational Burden (bTMB) Selection of Atezolizumab Immunotherapy

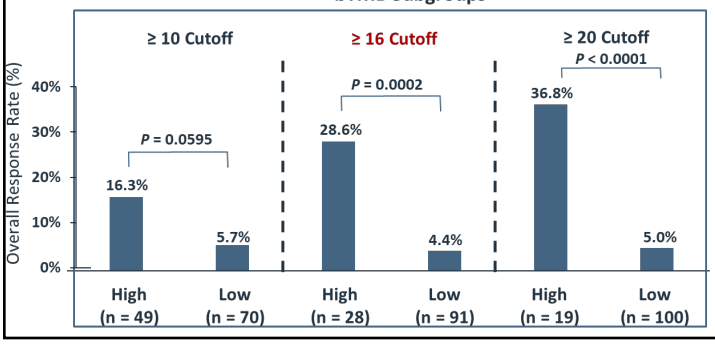
- Stage IIIB – IVB[a] advanced or metastatic NSCLC (any histology)
- Immunotherapy-naïve
- ECOG PS 0 or 1
- No EGFR/ALK+
- No active brain mets requiring treatment
- All comers (no Dx selection)
- Provision of blood[b]

→ Atezolizumab 1200 mg IV q3w N=150 → Until PD[c] or unacceptable toxicity

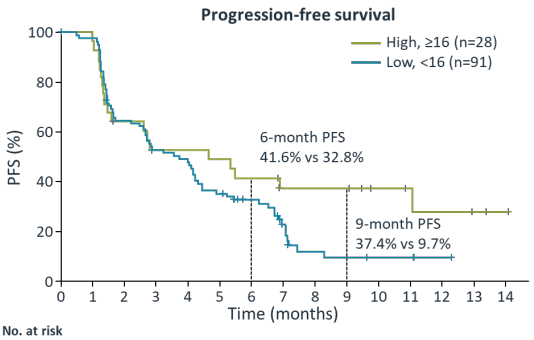
Prospectively evaluate TMB in blood by FoundationOne NGS (bTMB)

➢ **ORR & PFS in bTMB high (≥16) vs low**

bTMB Subgroups



Progression-free survival



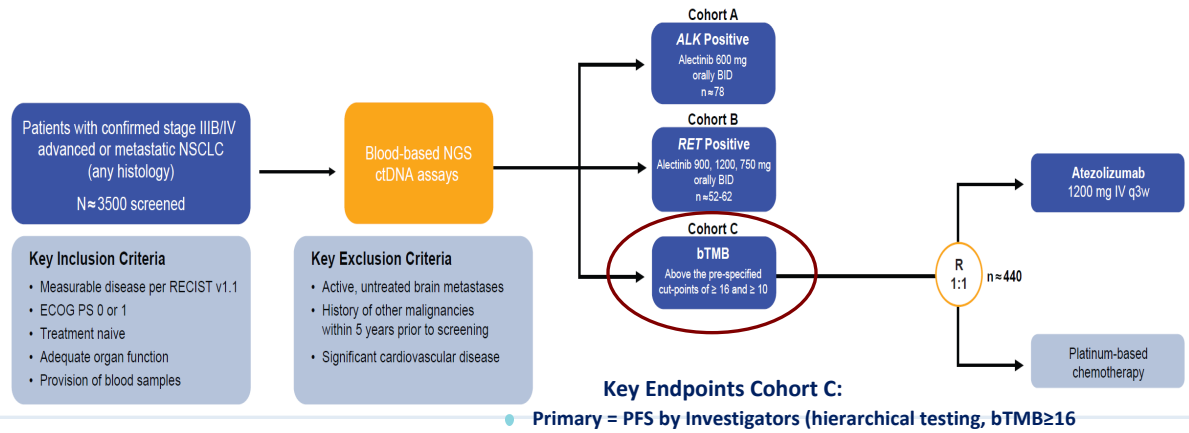
No. at risk

High (≥)	28	27	17	14	14	13	11	8	8	8	5	4	3	2	1
Low (<)	91	86	56	43	39	28	21	11	5	4	3	3	1		

Kim ES, et al. ESMO 2018. Abstract LBA55.

30

BFAST (Blood First Assay Screening Trial): Phase II/III in Advanced Treatment-naïve NSCLC



Key Endpoints Cohort C:

- **Primary = PFS by Investigators (hierarchical testing, bTMB≥16 first, then bTMB ≥10)**
- **Secondary = PFS by IRF, OS, ORR, PRO**

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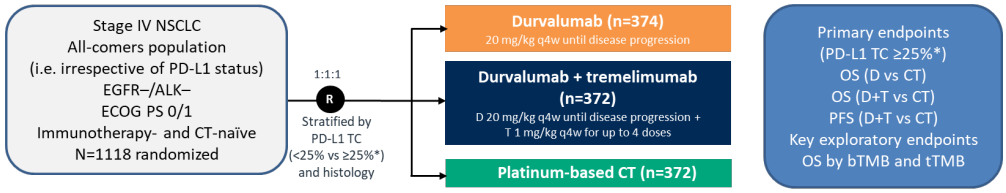
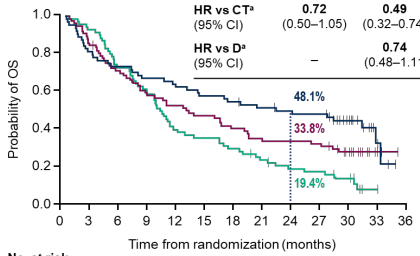
MYSTIC: 1L durvalumab ± tremelimumab vs chemotherapy in metastatic NSCLC – bTMB



ctDNA by Guardant OMNI

bTMB ≥20 mut/Mb

	D (n=77)	D+T (n=64)	CT (n=70)
mOS, months (95% CI)	12.6 (7.8–18.6)	21.9 (11.4–32.8)	10.0 (8.1–11.7)
HR vs CT[a] (95% CI)	0.72 (0.50–1.05)	0.49 (0.32–0.74)	–
HR vs D[a] (95% CI)	–	0.74 (0.48–1.11)	–

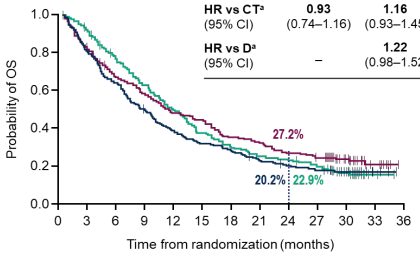


No. at risk

D	77	64	53	44	39	35	30	25	25	23	10	1	0
D+T	64	50	47	43	40	37	35	32	29	29	14	2	0
CT	70	65	51	41	27	25	21	16	12	11	6	0	0

bTMB <20 mut/Mb

	D (n=209)	D+T (n=204)	CT (n=185)
mOS, months (95% CI)	11.0 (8.9–14.9)	8.5 (6.7–9.8)	11.6 (9.6–13.1)
HR vs CT[a] (95% CI)	0.93 (0.74–1.16)	1.16 (0.93–1.45)	–
HR vs D[a] (95% CI)	–	1.22 (0.98–1.52)	–



D	209	167	134	114	98	86	72	63	55	49	21	8	0
D+T	204	161	129	98	75	65	55	45	39	35	18	4	0
CT	185	162	135	110	89	68	53	45	41	34	17	1	0

Rizvi NA, et al. ASCO 2019. Abstract 9016.

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REVIEW ARTICLE

IASLC

Liquid Biopsy for Advanced Non-Small Cell Lung Cancer (NSCLC): A Statement Paper from the IASLC

Christian Rolfo, MD, PhD, MBA,[a] Philip C. Mack, PhD,[b] Giorgio V. Scagliotti, MD, PhD,[c] Paul Baas, MD, PhD,[d] Fabrice Barlesi, MD, PhD,[e] Trever G. Bivona, MD, PhD,[f] Roy S. Herbst, MD, PhD,[g] Tony S. Mok, MD,[h] Nir Peled, MD, PhD,[i] Robert Pirker, MD,[j] Luis E. Raez, MD,[k] Martin Reck, MD, PhD,[l] Jonathan W. Riess, MD,[b] Lecia V. Sequist, MD, MPH,[m] Frances A. Shepherd, MD,[n] Lynette M. Sholl, MD,[o] Daniel S. W. Tan, MBBS, PhD,[p] Heather A. Wakelee, MD,[q] Ignacio I. Wistuba, MD,[r] Murry W. Wynes, PhD,[s] David P. Carbone, MD, PhD,[t] Fred R. Hirsch, MD, PhD,[u,*] David R. Gandara, MD[b]

What can Liquid Biopsy provide in November 2019 for NSCLC?
Tumor Genomics & blood-based Tumor Mutational Burden (investigational)

Advantages of plasma ctDNA over Tumor biopsy or re-biopsy:

- Indicated when tumor tissue not available or biopsy is high risk (or "plasma-first" situations)
- Reflects shed tumor DNA into plasma from all tumor sites, providing a "global perspective"
  - May abrogate the issue of tissue heterogeneity and under-genotyping due to small sample
- Can determine mechanism of resistance without biopsy, to guide subsequent therapy
- Can be repeated serially (longitudinal assessment) for response & early progressive disease
- Relatively non-invasive & high acceptance rate by patients
- Detection of Minimal Residual Disease (i.e. after surgical resection)

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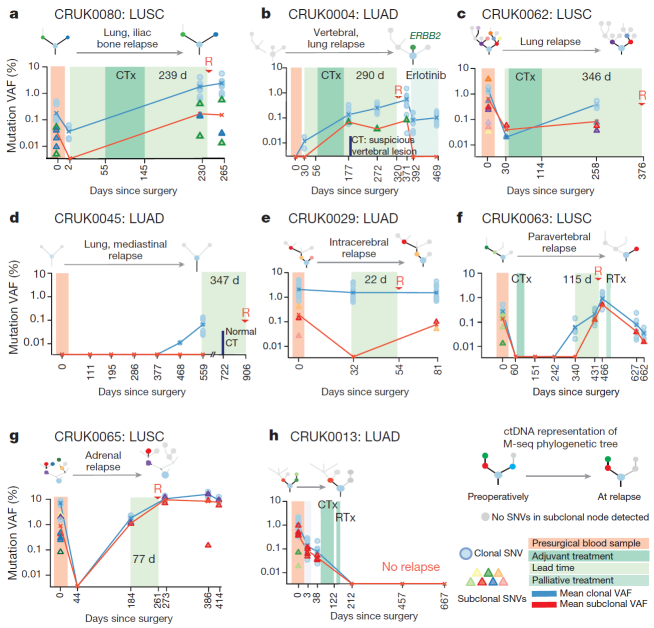
Prediction of Relapse after Surgery for Early Stage NSCLC by plasma ctDNA



Swanton et al: Nature 2017

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Precision Oncology Symposium

Germline Testing

James M. Ford, MD

STANFORD
CANCER INSTITUTE

Next-Generation Approaches to Assessing Hereditary Cancer Risk in the Genome Era

James M. Ford, MD, FASCO
Professor of Medicine/Oncology and Genetics
Director, Clinical Cancer Genomics
Stanford University School of Medicine

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Disclosures

- Clinical Trial Funding from:
  - *–Genentech*
  - *–AstraZeneca*
  - *–Pfizer*
  - *–Puma*
  - *–Myriad*

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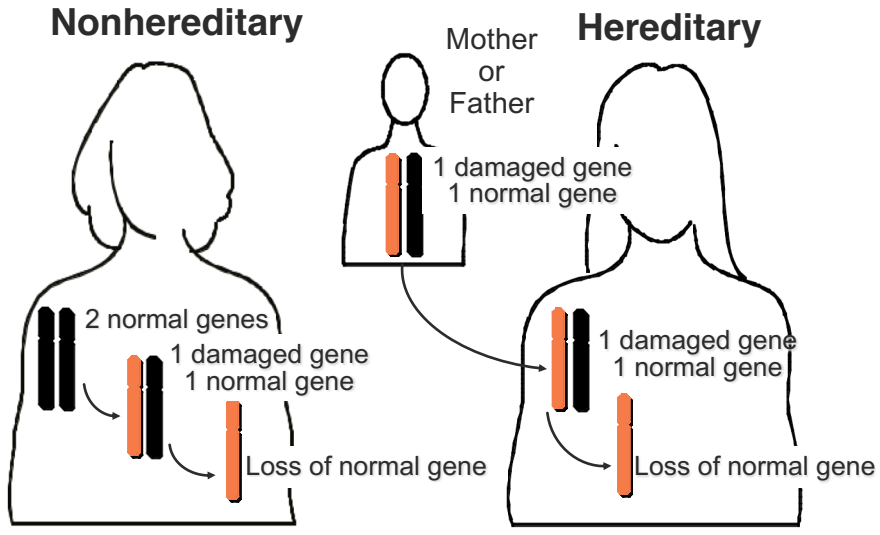
Precision Medicine in Cancer: Germline Genetic Risk Assessment

- Identification of germline and familial genetic alterations that increase **risk** of cancer
- Development of targeted **screening and early detection** techniques prevent development of advanced cancers
- Incorporation of moderate and low-penetrant, common genetic variants in risk prediction and screening modification
- Germline genetic testing and risk assessment based on **tumor genomic profiles**
- **Targeted therapies** based on germline mutations

3

The Development of Hereditary Cancer



4

Clinical Cancer Center

Stanford Cancer Genetics Clinic

Risk Assessment, Genetic Counseling And Interventions For Members Of Cancer Families

Autosomal Dominant Inherited Cancer Syndromes

• Breast and Ovarian Cancer *pancreatic, prostate*	BRCA1&2 *Chek2, ATM PALB2 . . .*
• Colon Cancer and Polyposis	
HNPCC (Lynch)	MMR
FAP	APC
Polyposis	MYH
Cowdens	PTEN
Peutz-Jehgers	STK11
Juvenile Polyposis	SMAD4
	BMPR1A
• Other GI Cancers	
Gastric	CDH1
Pancreas	p16
• MEN1	Menin
• MEN2/MTC	RET
• VHL	VHL
• Li-Fraumeni	p53

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Familial Syndromes including Breast Cancer

Syndrome	Gene	Frequency	Breast Ca Risk
HBOC	*BRCA 1 & 2*	1/40 – 1/400	40 – 80%
Li-Fraumeni	*p53*	1/5000 – 1/50K	90%+
Cowden's	*PTEN*	1/100,000	25 – 50%
HDGC	*CDH1*	Very rare	~60% (lobular)
Peutz Jeghers	*STK11/LKB1*		44 – 50%
Lynch Syndrome	*MMR*	1/440	1 - 5

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Genetics of Colorectal Cancer

Syndrome	Gene(s)
Lynch syndrome	*MLH1, MSH2, MSH6, PMS2, EPCAM*
Adenomatous polyposis	
Familial Adenomatous Polyposis(FAP)	*APC*
Attenuated FAP	*APC*
MYH-associated polyposis	*MYH (biallelic)*
Hamartomatous polyposis	
Peutz-Jeghers Syndrome	*STK11*
Juvenile Polyposis Syndrome	*SMAD4/BMPR1A*
Cowden Syndrome	*PTEN*

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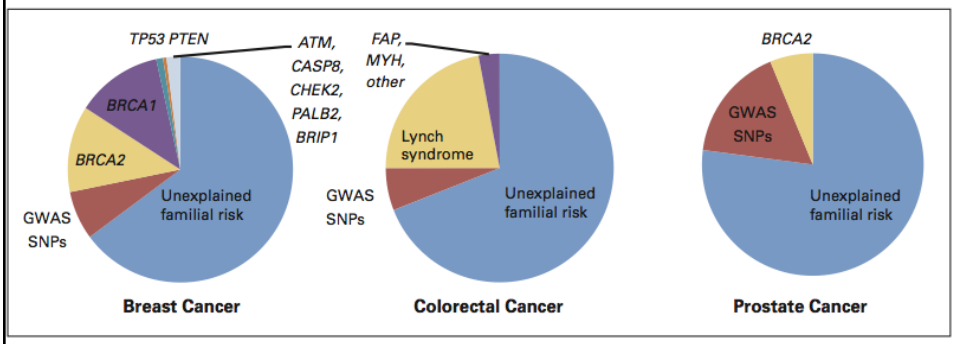
Familial Syndromes with Pancreatic Cancer

Syndrome	Gene	Frequency	PC Lifetime Risk
HBOC	*BRCA 1 & 2*	1/40 – 1/400	3 – 5%
FAMM	*CDKN2A (p16)*	rare	10 –19%
Peutz Jeghers	*STK11*		11 – 36%
Lynch Syndrome	*MMR*	1/440	4%

8

Identifying “heritable” causes of cancer



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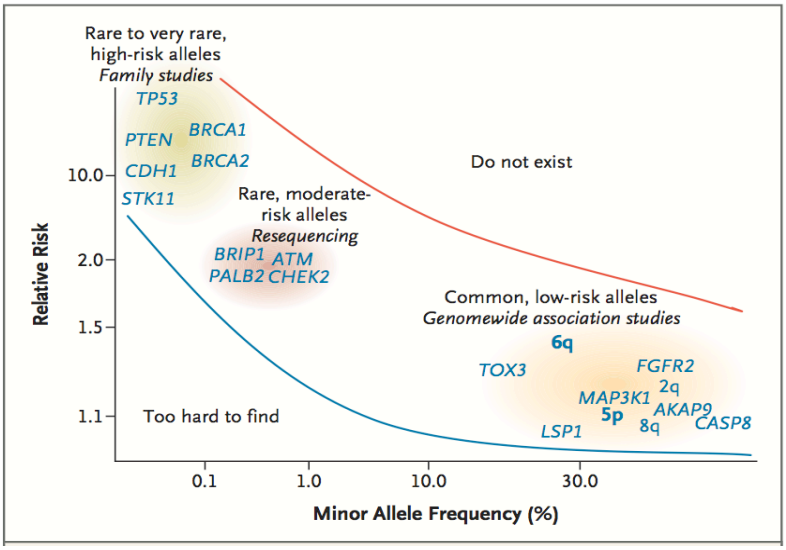
Breast Cancer Risk Genes



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Multigene Panel Study

Hypothesis: A Next-Gen Sequencing multiple cancer-gene panel provides actionable results

APC	*FANCE*	*PMS2*
ATM	*FANCF*	*PRSS1*
BLM	*FANCG*	*PTCH1*
BMPR1A	*FANCI*	*PTEN*
BRCA1	*FANCL*	*RAD51C*
BRCA2	*LIG4*	*RET*
BRIP1	*MEN1*	*SLX4*
CDH1	*MET*	*SMAD4*
CDK4	*MLH1*	*SPINK1*
CDKN2A	*MLH2*	*STK11*
EPCAM	*MSH6*	*TP53*
FANCA	*MUTYH*	*VHL*
FANCB	*NBN*	
FANCC	*PALB2*	
FANCD2	*PALLD*	

Kurian, Ford et al. Journal of Clinical Oncology 2014

11

Multiple-Gene Panel Testing

Study	N	Population	Race/Ethnicity	Gene Panel	Non-*BRCA* PVs	VUS
Kurian J Clin Oncol 2014	198	Met *BRCA1/2* guidelines	70% White, 20% Asian	42 genes (Invitae)	11%	88%
Tung Cancer 2014	2,158	Cancer genetics clinic sample	Mostly White	25 genes (Myriad)	4%	42%
Desmond JAMA Oncol 2015	1,046	Cancer genetics clinic sample	82% White	25 genes (Invitae)	4%	41%
LaDuca Genet Med 2014	2,079	Clinical testing lab database	72% White, 2-3% other	13-24 genes (Ambry)	10%	25%
Maxwell Genet Med 2014	278	Breast cancer, age <40	69% White, 24% Black	22 genes (Agilent)	11%	19%
Selkirk Fam Cancer 2014	63	Cancer genetics clinic sample	81% White	13-24 genes (Ambry)	7%	20%
Couch J Clin Oncol 2014	1,824	Triple-negative breast cancer	97% White	17 genes (Agilent)	4%	NR
Churpek BrCa Res Trt 2015	289	Cancer genetics clinic sample	100% Black	10 genes (BROCA)	5%	<1%
Thompson J Clin Oncol 2016	2,000	Cancer genetics clinic sample	Not reported (Australia)	18 genes	4%	NR
Tung J Clin Oncol 2016	488	Breast oncology clinic sample	89% White	25 genes (Myriad)	5%	33%
Norquist JAMA Oncol 2016	1,915	Ovarian cancer, unselected	89% White	20 genes (BROCA)	4%	NR
Slavin NPJ Breast Ca 2017	2,134	Cancer genetics clinic sample	81% White	26 genes	8%	NR
Shimelis JNCI 2018	10,901	Triple-negative breast cancer	Most White; >1K Black	17-21 genes (Ambry)	6%	NR
Idos/Kurian JCO Precis Oncol 2018	2,000	Prospective clinical sample	39% Hispanic, 12% Asian	25-28 genes (Myriad)	8%	34%

- Informative results (pathogenic variants) increased by ~ two-fold
- Uninformative results (VUS) increased by ten-fold

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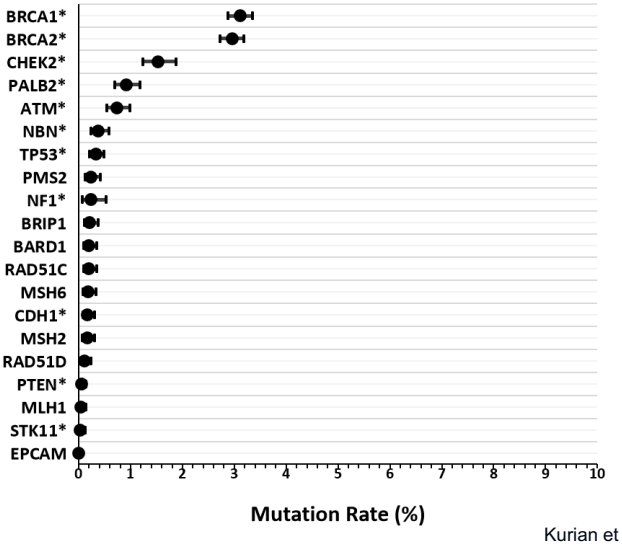
Mutation Prevalence Estimates, Breast

- 77,085 newly diagnosed breast cancer patients, 2013-2014 (statewide SEER, GA & CA)
- 18,500 (24%) had clinical genetic test results from ≥1 of 4 collaborating laboratories



Kurian et al, JCO 2019

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Multiple Gene Panels: Challenges

- New approach to Genetic Counseling
- Unexpected gene mutations in non-syndromic families (p53, CDH1)
- Variants of Uncertain Significance Common
- Genes with Low or Moderate CA Risk
- Clinical Utility and Impact on Care

14

What Could Possibly Go Wrong?

VOLUME 34 · NUMBER 34 · DECEMBER 1, 2016
JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Conflicting Interpretation of Genetic Variants and Cancer Risk by Commercial Laboratories as Assessed by the Prospective Registry of Multiplex Testing

Judith Balmaña, Laura Digiovanni, Pragna Gaddam, Michael F. Walsh, Vijai Joseph, Zsofia K. Stadler, Katherine L. Nathanson, Judy E. Garber, Fergus J. Couch, Kenneth Offit, Mark E. Robson, and Susan M. Domchek

© American College of Medical Genetics and Genomics

ORIGINAL RESEARCH ARTICLE | Genetics inMedicine

Open

False-positive results released by direct-to-consumer genetic tests highlight the importance of clinical confirmation testing for appropriate patient care

Stephany Tandy-Connor, MS, Jenna Guiltinan, MS, Kate Krempely, MS, Holly LaDuca, MS, Patrick Reineke, BS, Stephanie Gutierrez, BS, Phillip Gray, PhD and Brigette Tippin Davis, PhD, FACMG

PACIFIC NORTHWEST NEWS

Lawsuit: Woman had unnecessary mastectomy, hysterectomy based on mistaken diagnosis

Updated on October 24, 2017 at 11:35 AM
Posted on October 23, 2017 at 6:13 PM

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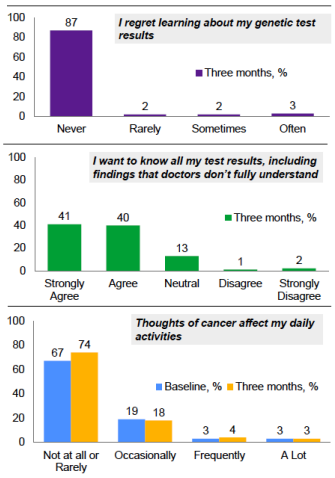
Prospective Clinical Trial of Multiplex Sequencing

- USC and Stanford; Myriad Genetics
- 25-gene NGS Panel
- Enrolled 2000 patients
- Diverse: 43% Hispanic, 33% high school only

- Test yield: 12% positive, 38% uncertain

- Patient understanding and reactions:
  - Preventive surgery was rare (0.4%-1%)
  - Positives > others urged relatives to test
  - Distress scores generally low

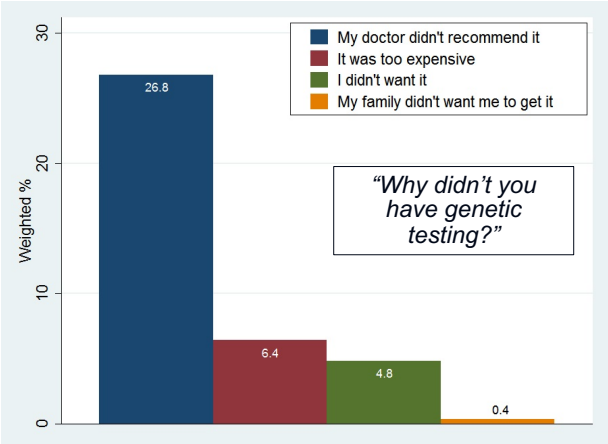


Idos, Kurian, Gruber, Ford et al. JCO PO 2019

16

Deficits in "Real World" Genetic Testing

- Population-based sample (SEER) of 2,529 newly diagnosed breast cancer patients
- 29% reported genetic testing for *BRCA1/2* and/or additional genes
- Of high-risk (met guidelines testing criteria), only 53% reported genetic testing:



Kurian et al, JAMA 2017

17

Genes with Screening or Risk Reduction Guidelines

ACS, ACOG, ASCO, ClinGen, and/or NCCN Recommendations	Genes (n=48)
Annual screening breast magnetic resonance imaging	*ATM, BARD1, BRCA1, BRCA2, CDH1, CHEK2, NBN, NF1, PALB2, PTEN, STK11, TP53*
Earlier and more frequent colonoscopy/endoscopy	*APC, AXIN2, BMPR1A, CHEK2, EPCAM, GREM1, MLH1, MSH2, MSH6, PMS2, MSH3 (homozygote, h.); MUTYH (h.), NTLH1 (h.), POLD1, POLE, PTEN, SMAD4, STK11, TP53*
Risk-reducing mastectomy	*BRCA1, BRCA2, PALB2, PTEN, STK11, TP53*
Risk-reducing salpingo-oophorectomy, +/- hysterectomy	*BRCA1, BRCA2, BRIP1, EPCAM, MLH1, MSH2, MSH6, PMS2, RAD51C, RAD51D*
Risk-reducing colectomy	*APC*
Risk-reducing gastrectomy	*CDH1*
Other targeted screening (e.g., RCC, pheochromocytoma)	*MEN1, NF2, RB1, RET, SDHAF2, SDHB, SDHC, SDHD, TSC1/2, VHL, TP53, WT1*

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Paired Tumor/Germline: New Challenges

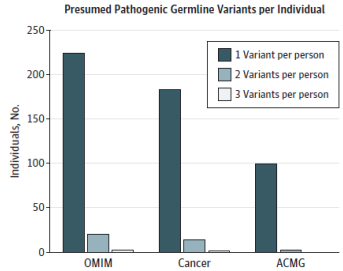
Research
JAMA Oncol. 2016;2(1):104-111. doi:10.1001/jamaoncol.2015.5208
Original Investigation

Germline Variants in Targeted Tumor Sequencing Using Matched Normal DNA

Kasmintan A. Schrader, MBBS, PhD, FRCPC, DABMG; Donavan T. Cheng, PhD; Vijai Joseph, PhD; Meera Prasad, MS; Michael Walsh, MD; Ahmet Zehir, PhD; Ai Ni, PhD; Tinu Thomas, MS; Ryma Benayed, PhD; Asad Ashraf, MS; Annie Lincoln, MS; Maria Arcila, MD; Zsofia Stadler, MD; David Solit, MD; David Hyman, MD; Liying Zhang, MD, PhD; David Klimstra, MD; Marc Ladanyi, MD; Kenneth Offit, MD; Michael Berger, PhD; Mark Robson, MD

- 16% had a presumed pathogenic germline variant
- 59% of these were not concordant with the patient's cancer type
- 100% had at least one VUS
- *How to address the clinical implications for patients and relatives?*

Figure 1. Individuals With at Least 1 Presumed Pathogenic Germline Variant in OMIM Genes, Including the Cancer and ACMG Subsets



	OMIM	Cancer	ACMG
1 Variant per person	224	183	99
2 Variants per person	20	14	2
3 Variants per person	2	1	

The number of genes in the entire Online Mendelian Inheritance in Man (OMIM) subset is 187 (http://omim.org), which includes the Cancer subset of 93 genes and the partially overlapping American College of Medical Genetics (ACMG) subset of 26 genes[8] (eTable 4 in the Supplement).

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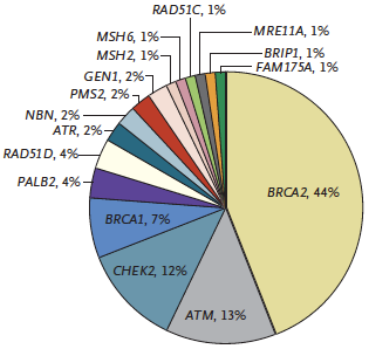
The NEW ENGLAND JOURNAL of MEDICINE

Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer

C.C. Pritchard, J. Mateo, M.F. Walsh, N. De Sarkar, W. Abida, H. Beltran, A. Garofalo, R. Gulati, S. Carreira, R. Eeles, O. Elemento, M.A. Rubin, D. Robinson, R. Lonigro, M. Hussain, A. Chinnaiyan, J. Vinson, J. Filipenko, L. Garraway, M.-E. Taplin, S. AlDubayan, G.C. Han, M. Beightol, C. Morrissey, B. Nghiem, H.H. Cheng, B. Montgomery, T. Walsh, S. Casadei, M. Berger, L. Zhang, A. Zehir, J. Vijai, H.I. Scher, C. Sawyers, N. Schultz, P.W. Kantoff, D. Solit, M. Robson, E.M. Van Allen, K. Offit, J. de Bono, and P.S. Nelson



This article was published on July 6, 2016, at NEJM.org.

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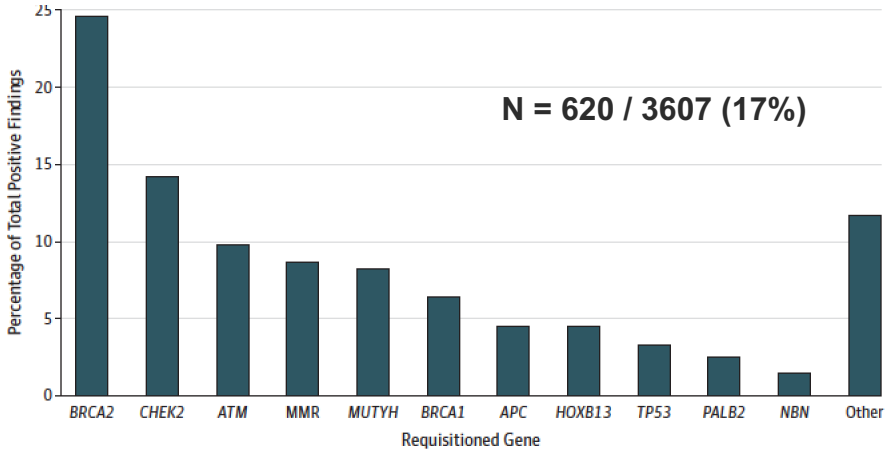
JAMA Oncology | Original Investigation 2019

Prevalence of Germline Variants in Prostate Cancer and Implications for Current Genetic Testing Guidelines

Piper Nicolosi, PhD; Elisa Ledet, PhD; Shan Yang, PhD; Scott Michalski, MS, LCGC; Brandy Freschi, MS, CGC; Erin O'Leary, MS, CGC; Edward D. Esplin, MD, PhD; Robert L. Nussbaum, MD; Oliver Sartor, MD



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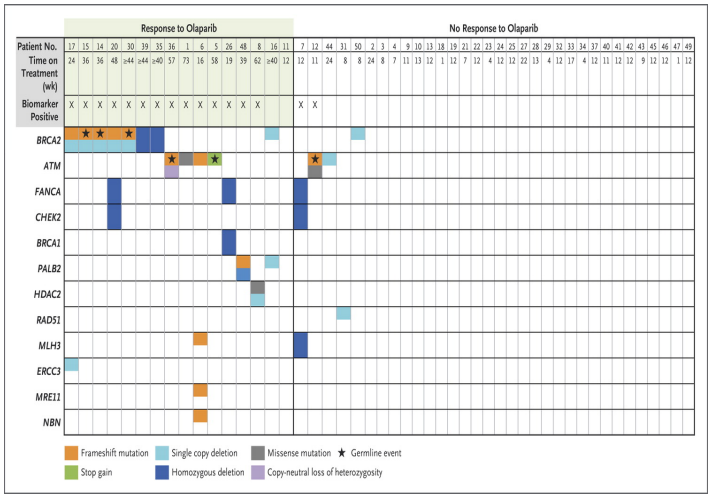
TOPARP-A trial: PARP inhibitor activity in metastatic prostate cancer with DNA repair gene mutation



Mateo et al NEJM 2015

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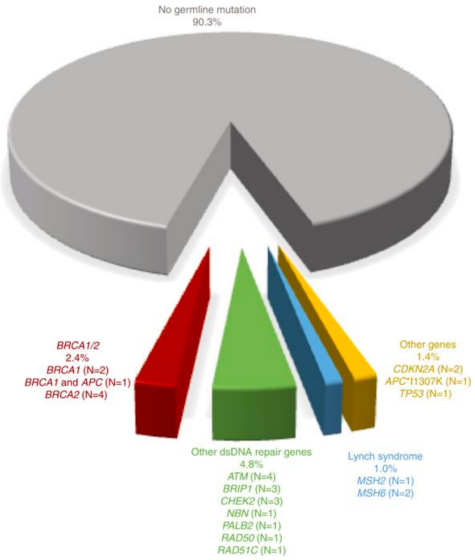
Germline Mutations in Pancreatic Cancer



N = 298

Yurgelun et al. GIM 2018

23

Germline Mutations in Pancreatic Cancer

Gene	Fold-Risk PC	Incidence in FPC
BRCA2	**3.5**	17 – 19%
BRCA1	**2**	2 – 3%
STK11	**132**	
PALB2		2 – 3%
ATM		2%
CDKN2A	**13 - 38**	10 – 17%
MMR	**0 - 8**	

Prevalence of gBRCA1/2 mutations in all PC: 4 - 7% (12% AJ)

Somatic BRCA1/2 mutations in 10% PC

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Maintenance Olaparib for Germline *BRCA*-Mutated Metastatic Pancreatic Cancer

Talia Golan, M.D., Pascal Hammel, M.D., Ph.D., Michele Reni, M.D., Eric Van Cutsem, M.D., Ph.D., Teresa Macarulla, M.D., Ph.D., Michael J. Hall, M.D., Joon-Oh Park, M.D., Ph.D., Daniel Hochhauser, M.D., Ph.D., Dirk Arnold, M.D., Ph.D., Do-Youn Oh, M.D., Ph.D., Anke Reinacher-Schick, M.D., Ph.D., Giampaolo Tortora, M.D., Ph.D., Hana Algül, M.D., Ph.D., M.P.H., Eileen M. O'Reilly, M.D., David McGuinness, M.Sc., Karen Y. Cui, M.D., Ph.D., Katia Schlienger, M.D., Ph.D., Gershon Y. Locker, M.D., and Hedy L. Kindler, M.D.

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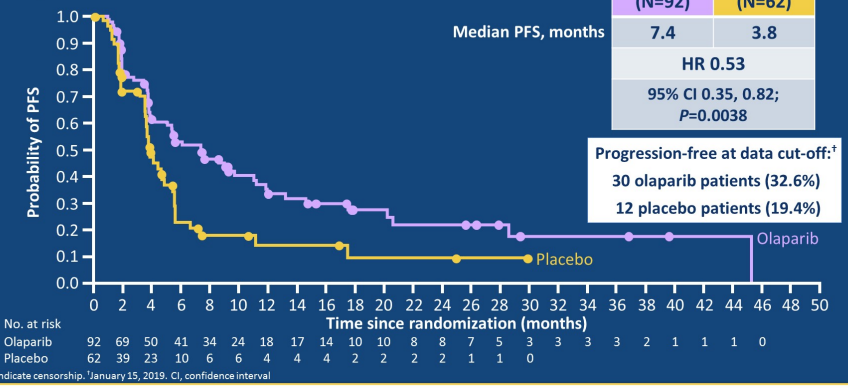
Primary endpoint: PFS by blinded independent central review*



	Olaparib (N=92)	Placebo (N=62)
Median PFS, months	7.4	3.8
HR 0.53		
95% CI 0.35, 0.82; *P*=0.0038		

Progression-free at data cut-off:†
30 olaparib patients (32.6%)
12 placebo patients (19.4%)

No. at risk																									
Olaparib	92	69	50	41	34	24	18	17	14	10	10	8	8	7	5	3	3	3	3	2	1	1	1	0
Placebo	62	39	23	10	6	6	4	4	4	2	2	2	2	1	1	0								

*Dots indicate censorship. †January 15, 2019. CI, confidence interval

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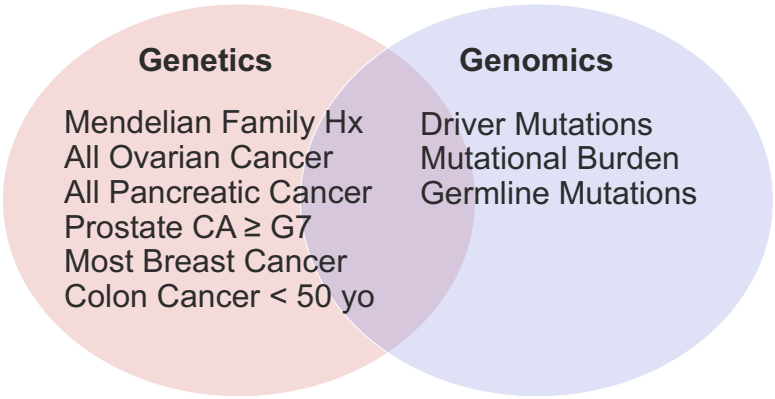
Testing Indications



Therapeutic Indications
- PARP inhibitors – BRCA1/2 . . .
- IO - MSH2, MLH1 . . .

Unexpected Familial Risk
Therapeutic Implications
- IO - MSI-H, TMB

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GERMLINE TESTING REFERRALS FOR PATIENTS WITH *BRCA1/2* MUTATIONS ON SOMATIC TUMOR TESTING AT STANFORD.

Kate Vlessis, BA

STANFORD UNIVERSITY

28

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines

- Genetic/Familial High-Risk Assessment: Breast and Ovarian
- Pathogenic somatic BRCA1/2 variants first published as meeting testing criteria September 19, 2016

> *"BRCA1/2 pathogenic/likely pathogenic variant detected by tumor profiling on **any tumor type** in the absence of germline pathogenic/likely pathogenic variant analysis."*

Pilarski et al. (2019)

29

Tumor Groupings (N=164)

Tumor grouping	Overall (n=164)
Gynecologic	64 (39.0)
Ovarian	49 (76.6)
Uterine	8 (12.5)
Peritoneal	4 (6.3)
Fallopian tube	3 (4.7)
Gastrointestinal	24 (14.6)
Colorectal	11 (45.8)
Pancreatic	10 (41.7)
Gastric	2 (16.7)
Esophageal	1 (4.2)
Genitourinary	16 (9.8)
Prostate	9 (56.3)
Bladder	6 (37.5)
Kidney	1 (6.3)

Tumor grouping	Overall (n=164)
Lung	15 (9.1)
Breast	15 (9.1)
Sarcoma	11 (6.7)
Skin	8 (4.9)
Squamous cell	5 (62.5)
Merkel cell	2 (25.0)
Melanoma	1 (12.5)
Head and Neck	5 (3.0)
CNS/PNS	5 (3.0)
Other†	1 (0.6)

† perivascular epithelioid cell tumor (PEComa)

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What influenced recommendations?

Variable	N	<-- Less likely More likely-->	Odds Ratio (95% CI)	P-value
Gender				
Male	53		Reference	
Female	107		1.73 (0.45, 7.03)	0.428
Ethnicity				
Caucasian or Northern European	80		Reference	
Asian	25		1.12 (0.23, 5.77)	0.886
Ashkenazi Jewish	20		5.15 (0.80, 44.49)	0.105
Hispanic	20		1.02 (0.18, 6.43)	0.985
Other	15		0.28 (0.04, 2.54)	0.239
Age of cancer onset	160		0.95 (0.90, 0.99)	0.029
Stage				
1	17		0.26 (0.04, 1.45)	0.132
2	22		2.32 (0.46, 14.33)	0.328
3	60		0.98 (0.27, 3.50)	0.975
4	61		Reference	
Tumor group				
Breast/Gynecologic	78		Reference	
Gastrointestinal	24		0.64 (0.09, 5.34)	0.660
Genitourinary	15		0.03 (0.00, 0.30)	0.003
Lung/Thoracic	15		0.04 (0.01, 0.21)	<0.001
Sarcoma	11		0.02 (0.00, 0.14)	<0.001
Other	9		0.01 (0.00, 0.12)	<0.001
Skin	8		0.01 (0.00, 0.16)	0.002
Variant allele frequency	160		1.01 (0.98, 1.03)	0.625
Tumor report date after NCCN guidelines				
No	55		Reference	
Yes	105		2.08 (0.66, 6.89)	0.215

Patients diagnosed with…

- Genitourinary
- Lung
- Skin
- Sarcoma
- 'Other'

…cancers were significantly **less likely** to be referred/ recommended germline testing in comparison to patients with breast/ gynecologic tumors

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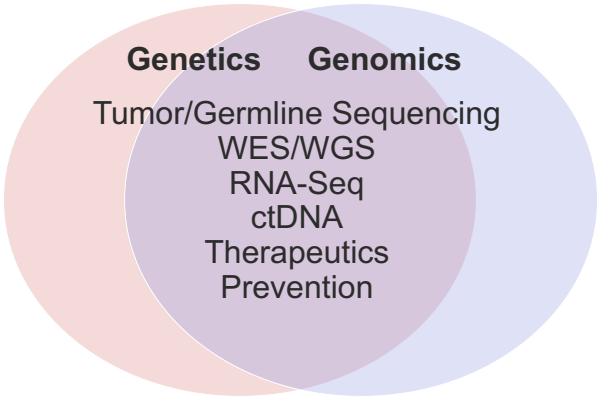
Future Approach



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Summary and Conclusions

- ~10% of most common cancers will have potentially targetable DNA repair defects associated with germline genetic mutations
- Germline > Somatic alone
- Poorly predicted by age, family history
- Consider screening high-risk individuals
- Prognostic and predictive value
- Role for checkpoint inhibitors, PARP inhibitors, others

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Stanford Cancer Genomics: Who

Molecular Tumor Board:

Jim Ford	Director
Christina Curtis	Co-Director
Ash Alizadeh	Med Oncology
Max Diehn	Rad Oncology
Jim Zehnder	Molecular Pathology
Carlos Suarez	Molecular Pathology
Henning Stehr	Moledular Pathology
Rochelle Reyes	Clinical Coordinator/APP
Meredith Mills	Research Coordinator
Alex Ooms	Research Assistant
Ivy Lau	Clinical Trials Coordinator
Meredith Gerhart	Genetic Counselor

Cancer Genetics Clinic:

Jim Ford	Director
Allison Kurian	Co-Director, Women's Cancers
Uri Ladabaum	Gastrointestinal Cancers
Kerry Kingham	Lead Genetic Counselor
Nicolette Chun	Genetic Counselor
Rachel Hodan	Genetic Counselor
Meredith Gerhart	Genetic Counselor
Madeline Graf	Genetic Counselor
Courtney Rowe-Teeter	Genetic Counselor
Rochelle Reyes	APP/PA
Alexandra Ooms	Research Assistant
Cindy Ma	Research Assistant

34

Precision Oncology Symposium

Biomarkers in Immuno-Oncology

David Spetzler, MS, MBA, PhD

Biomarkers in Immune-Oncology

November 9, 2019

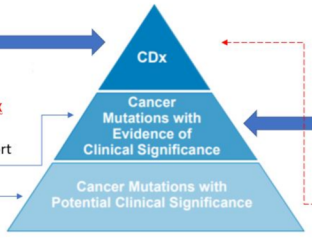
David Spetzler, MS,MBA, PhD
President and Chief Scientific Officer
Caris Life Sciences

1

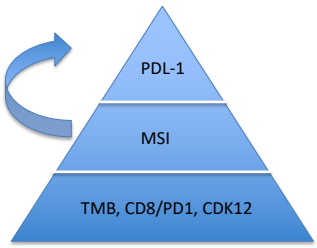
FDA Classification of Biomarkers

PMA
Gene panel
CDx genes must have one of these:
- Clinical study linking test to outcomes
- **OR** benchtop concordance to prior CDx

- Based on paper dossiers, test may also report
- "Mutations with clinical significance"
- And/or
- "Mutations with potential clinical significance"



510(k)
Gene panel
High analytical validity
Genes can be reported based on paper dossiers for:
- "Mutations with clinical significance"
- And/or
- "Mutations with potential clinical significance"
- But, under some conditions, clinical data can support 510(k) as a CDx; read: K173492.
- Hence, FDA and CMS now refers to "cleared or approved" CDx's



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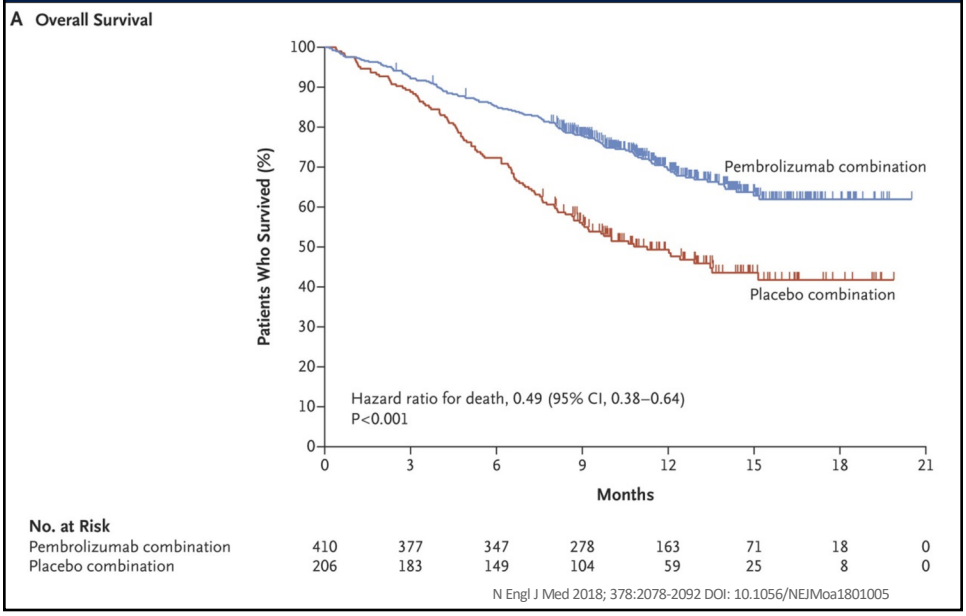
3

Complex State of PD-L1 Testing: Caris Uses the Right Assay for the Right Patient

PD-L1 antibody IO Therapy	SP142 (Ventana) Atezolizumab (Roche)	SP263 (Ventana) Durvalumab (Astrazeneca)	22c3 (Dako) Pembrolizumab (Merck)	28-8 (Dako) Nivolumab (BMS)	73-10 (Dako) Avelumab (Merck KGaA)
Non-small cell lung cancer (NSCLC)	***Complementary*** **Threshold: TC ≥50% or IC ≥10%**	-	***Companion*** **TPS ≥1**	*Complementary* Threshold: TC ≥1% (increasing benefit for 5% and 10%)	-
Bladder Cancer	***Companion*** **Threshold: IC ≥5% (IC2/3)**	*Complementary* Threshold(s): TC ≥25% (membranous), or ICP >1% and IC ≥25%, or ICP =1% and IC = 100%	***Companion*** **Threshold: CPS ≥10**	*Complementary* Threshold: TC ≥1%	Threshold: TC ≥5%
Melanoma	Threshold: ≥1%	-	-	Threshold: ≥1%	-
Head and neck squamous cell carcinoma (HNSCC)	-	-	***Companion*** **Threshold: CPS ≥1**	*Complementary* Threshold: TC ≥1%	-
Kidney Cancer	-	-	-	Threshold: TC ≥1%	-
Merkel Cell Carcinoma (MCC)	-	-	-	-	Threshold: TC ≥1%
Gastric and Gastroesophageal Junction (GE/GEJ)	-	-	***Companion*** **Threshold: CPS ≥1**	-	-
Esophageal (SCC)	-	-	***Companion*** **Threshold: CPS ≥10**	-	-
Cervical Cancer	-	-	***Companion*** **Threshold: CPS ≥1**	-	-
Hepatocellular Cancer (HCC)	-	-	-	Threshold: TC ≥1%	-
Breast (TNBC)	***Companion*** **IC ≥1% (IC1/2/3)**	-	-	-	-
Vulvar Cancer (SCC)	-	-	***NCCN-recommended*** **CPS ≥1**	-	-

3

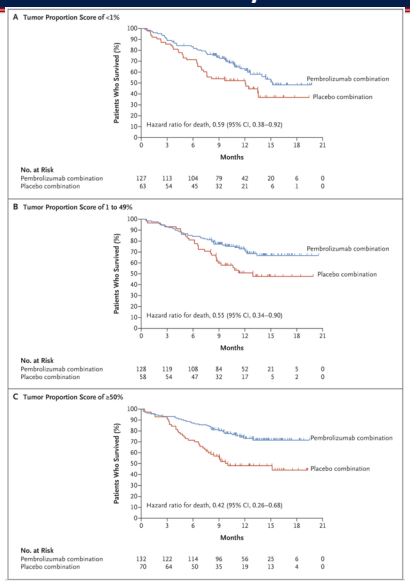
PDL-1 Positive NSCLC Patients response to IO



N Engl J Med 2018; 378:2078-2092 DOI: 10.1056/NEJMoa1801005

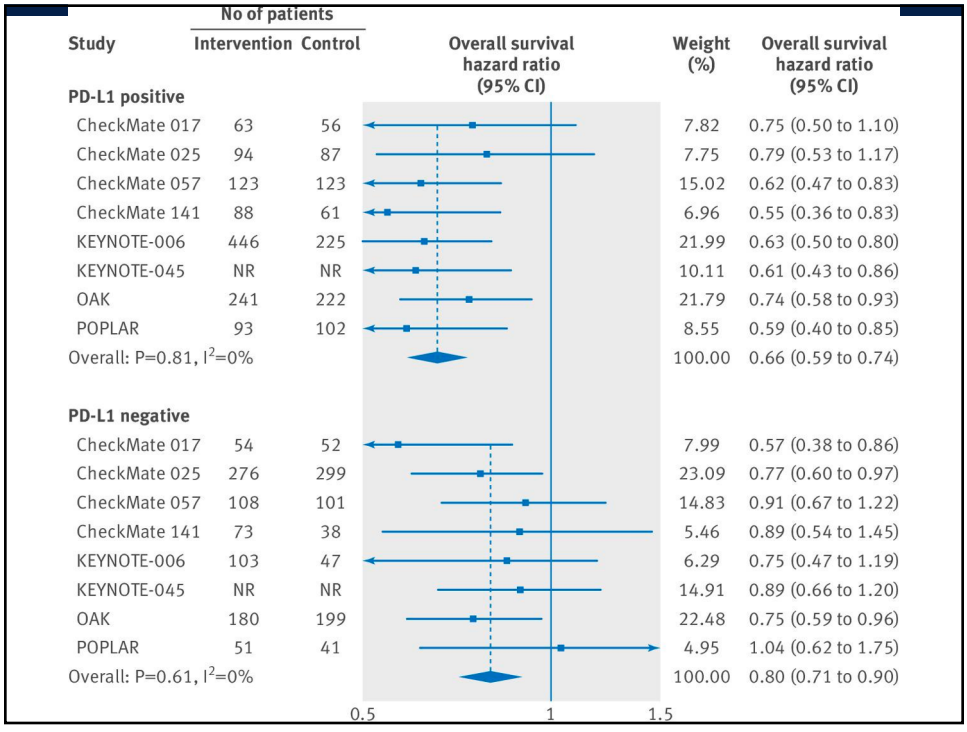
4

Responses are influenced by PDL-1 staining Percent



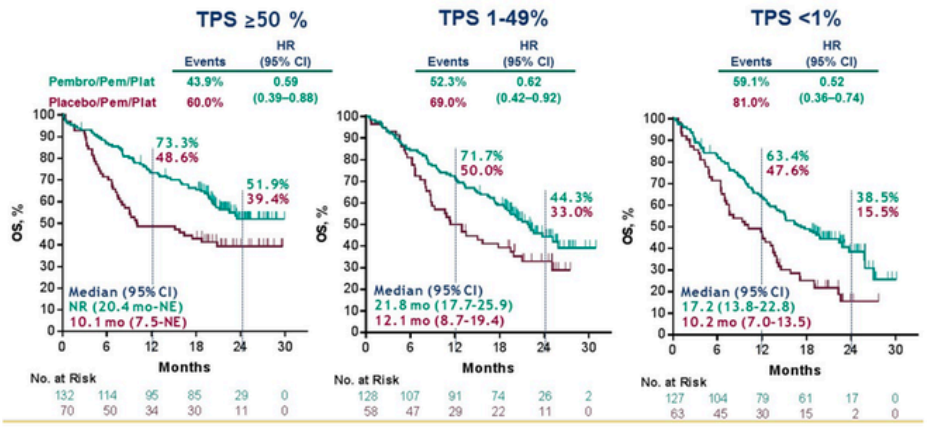
N Engl J Med 2018; 378:2078-2092 DOI: 10.1056/NEJMoa1801005

5



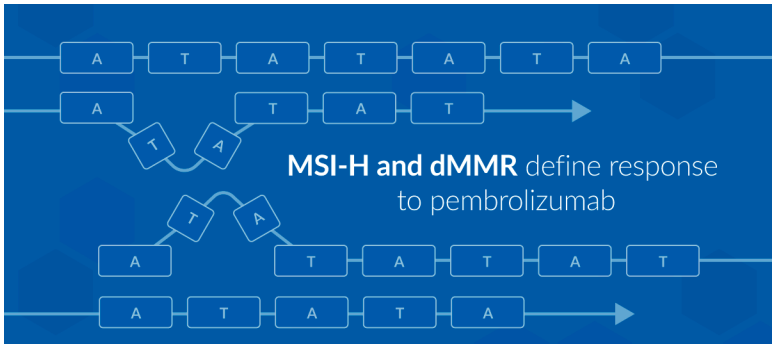
6

Figure 2. KEYNOTE-189: Updated OS Analysis by PD-L1 TPS[6]



7

The First Pan-Cancer FDA Drug Approval Based on a Molecular Marker: Microsatellite Instability



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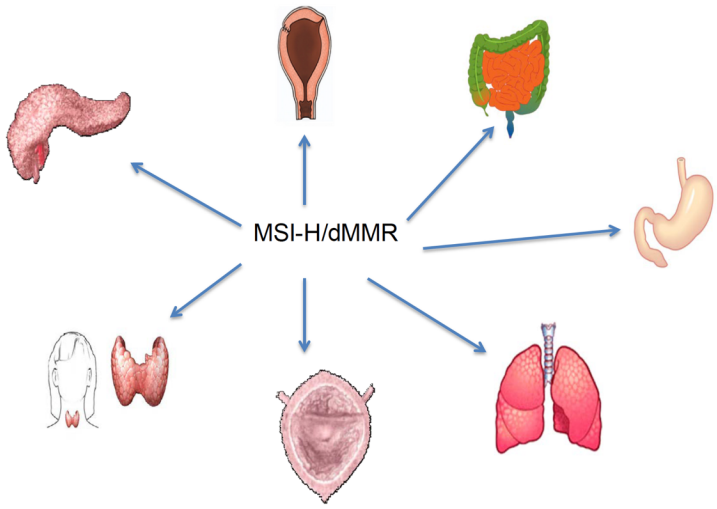
8

MSI-H/dMMR, not the organ, defines the indication



9

What is MSI-H/dMMR? •

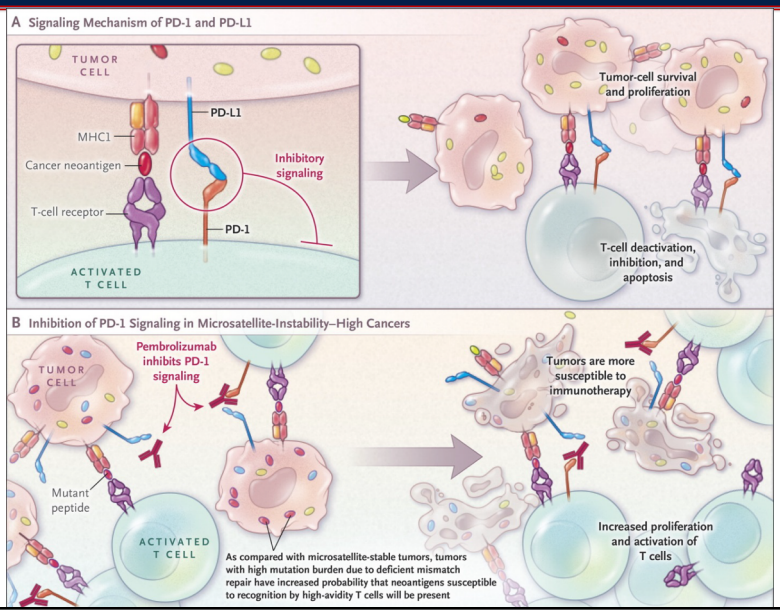
- MSI-H = microsatellite instability
- dMMR = deficient mismatch repair
- Causes of dMMR/MSI-H:
  - Mutation in DNA repair proteins
  - Can occur in Lynch syndrome –
  - Inactivation of DNA repair proteins

Why does this matter?

- Impairment in mismatch repair causes –
  - Greatly increased number of mutations in tumors
  - Some mutations (neo-antigens) may be targeted by immune system
  - Pembrolizumab can facilitate immune system attack in some MSI-H/dMMR cancers

10

Mechanism of Action



11

Data resulting in the FDA Approval

Pembrolizumab Response Rate by Tumor Type.*

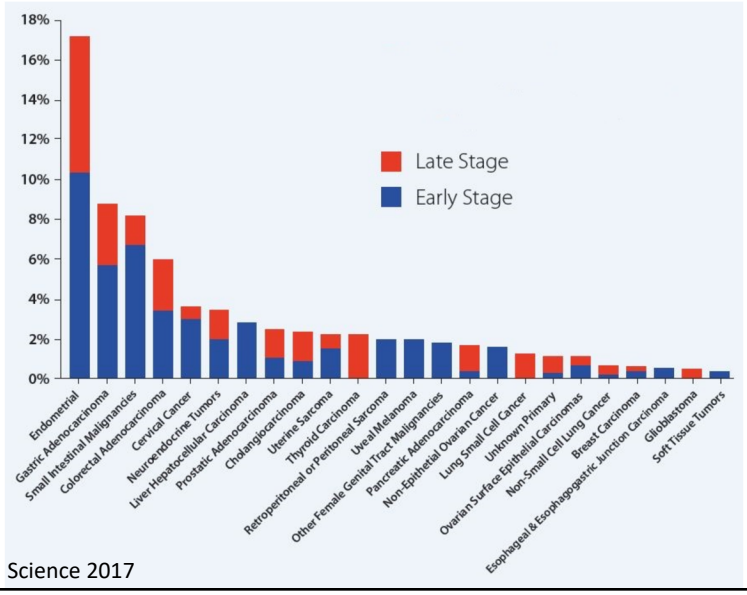
Tumor Type	No. of Tumors	Patients with a Response	Range of Response Duration
		no. (%)	*mo*
Colorectal cancer	90	32 (36)	1.6+ to 22.7+
Endometrial cancer	14	5 (36)	4.2+ to 17.3+
Biliary cancer	11	3 (27)	11.6+ to 19.6+
Gastric or gastroesophageal junction	9	5 (56)	5.8+ to 22.1+
Pancreatic cancer	6	5 (83)	2.6+ to 9.2+
Small-intestine cancer	8	3 (38)	1.9+ to 9.1+
Breast cancer	2	2 (100)	7.6 to 15.9
Prostate cancer	2	1 (50)	9.8+
Other cancers	7	3 (43)	7.5+ to 18.2+

* Response was as defined by RECIST. "Other cancers" includes one patient each with the following tumor types: bladder, esophageal, sarcoma, thyroid, retroperitoneal, small-cell lung cancer, and renal cell cancer (includes two patients who could not be evaluated and were considered not to have had a response). A + sign indicates that the response was ongoing at the time of data cutoff.

Lemery, NEJM, 2017

12

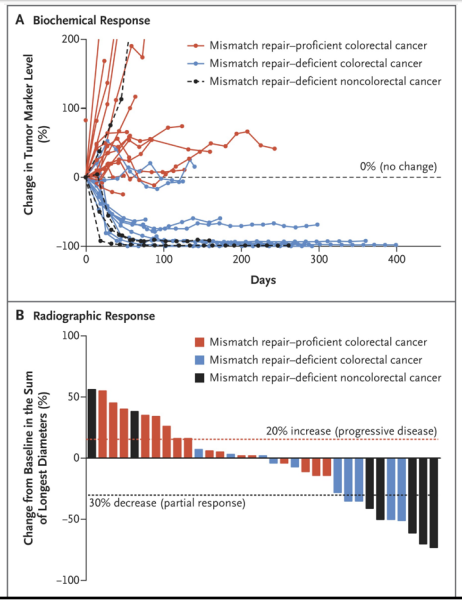
Distribution Across Cancer Types



Le et al. Science 2017

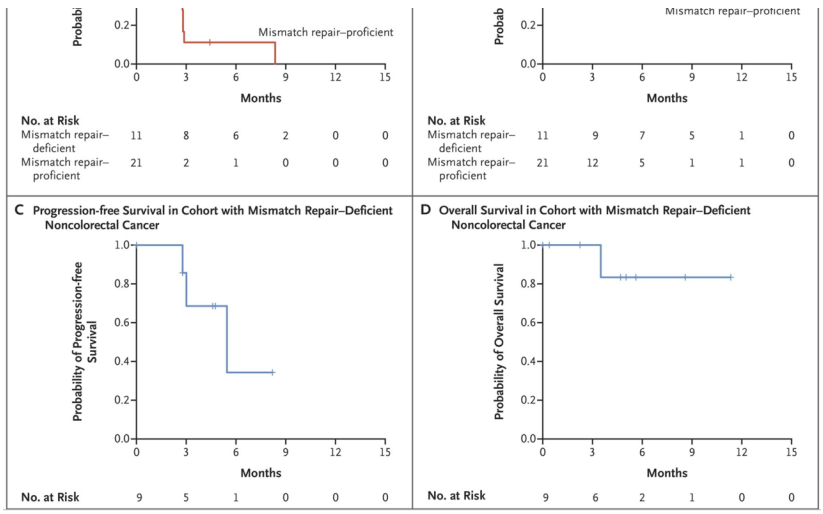
13

Strong response in MSI-H patients



N Engl J Med 2015; 372:2509-2520
DOI: 10.1056/NEJMoa1500596

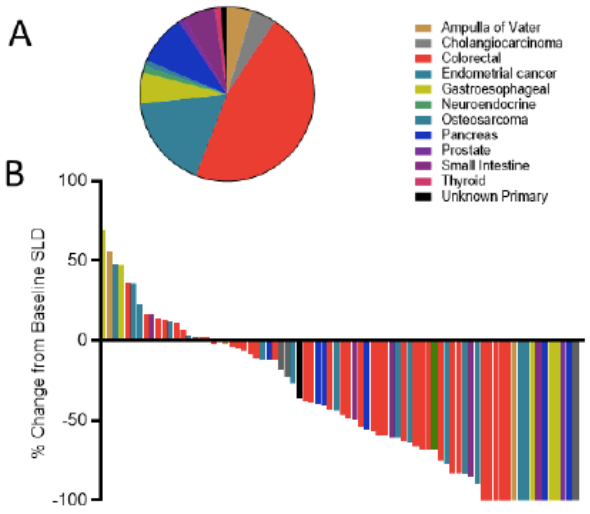
14



N Engl J Med 2015; 372:2509-2520 DOI: 10.1056/NEJMoa1500596

15

Sensitivity to PD-1 Inhibition in MSI-H Cancer

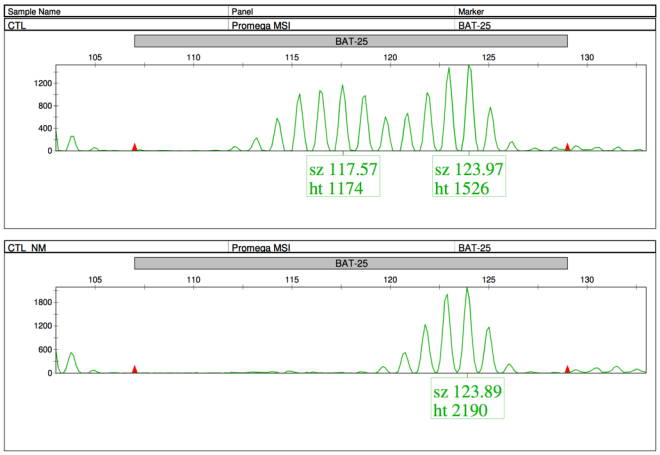


Le et al. Science 2017

16

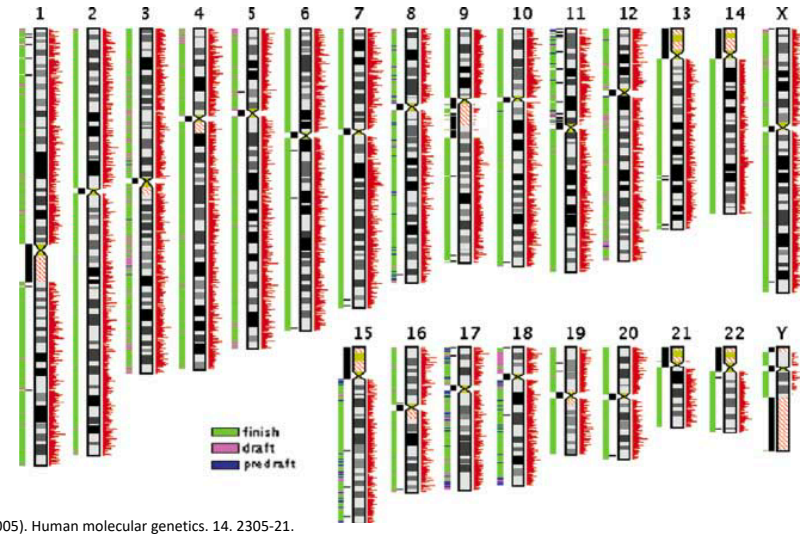
16

Traditional approach is to use PCR and compares tumor to normal across 5 loci



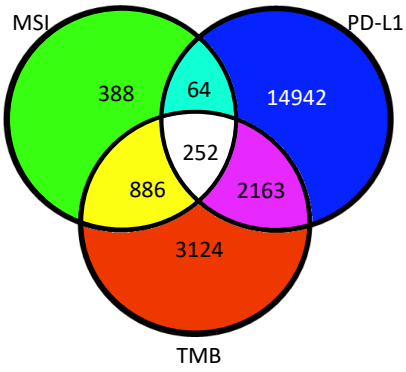
17

Distribution of 27 039 polymorphic microsatellite markers across the human

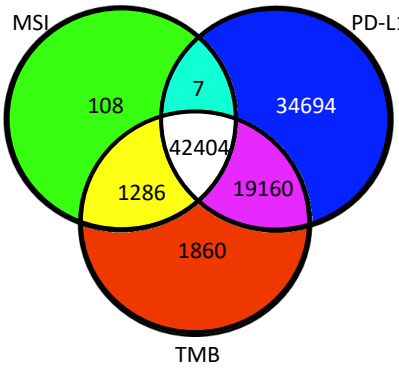


Tamiya (2005). Human molecular genetics. 14. 2305-21. 10.1093/hmg/ddi234.

18



TMB High and MSI High vs. PD-L1 positive cases



All TMB, MSI and PD-L1 tested cases

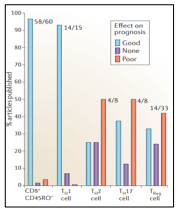
19

Prognostic and predictive IHC biomarkers in cancer and immunotherapy

20

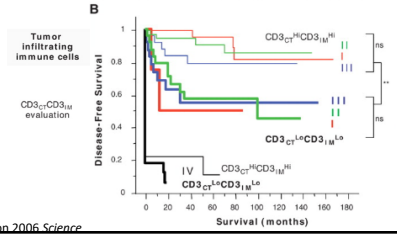
TILs – Assessing Hot vs Cold tumors – prognostic capacity

Cytotoxic and memory T cells associate with favorable prognosis



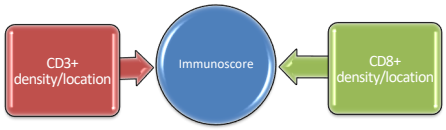
Fridman 2012 *Nature Reviews: Cancer*

Type, Density, and Location of Immune Cells Within Human Colorectal Tumors Predict Clinical Outcome

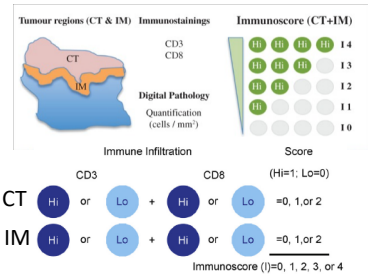


Galon 2006 *Science*

Immunoscore was proposed as a method of classifying tumors by quantifying in situ T cells and cytotoxic T cells



The densities of CD3+ and CD8+ T cells are determined in the tumor center and invasive margin regions



Galon 2012 *Journal of Translational Medicine*

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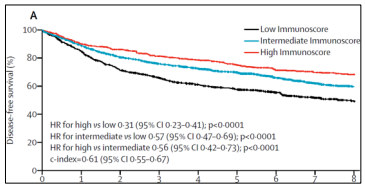
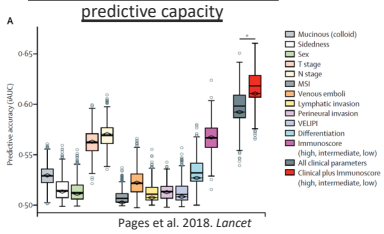
Immunoscore – A consortium of 14 centers in 13 countries assessed a predefined Immunoscore assay in patients with stage I–III colon cancer

Disease-free survival according to the Immunoscore in patients with stage I–III colon cancers.



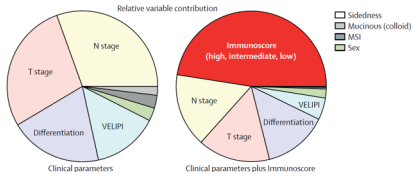
Pages et al. 2018. *Lancet*

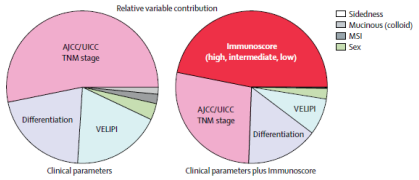
Immunoscore has high-degree of predictive capacity



Pages et al. 2018. *Lancet*

Immunoscore was stronger than all these clinical parameters at predicting survival and risk of recurrence





Pages et al. 2018. *Lancet*

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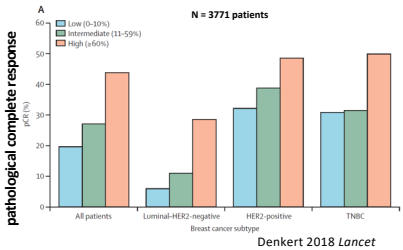
International Immunooncology Biomarkers Working Group:

TIL concentration and response to neoadjuvant combination chemotherapy

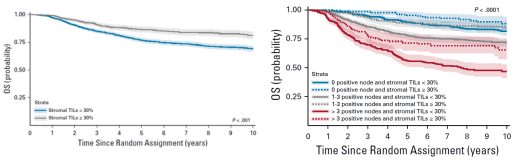
Stromal TILs were quantified on H&E sections of core biopsies obtained before the start of neoadjuvant chemotherapy.



Denkert 2018 *Lancet*

Strong prognostic role of stromal TILs in early-stage TNBC

Stromal TILs were quantified on H&E sections from patients with early stage TNBC treated with anthracycline-based chemotherapy with or without taxanes



Loi 2019 *Journal of Clinical Oncology*

Have expanded standardized scoring of TILs to:

- Melanoma
- Gastrointestinal tract carcinomas
- Non-small cell lung carcinoma and mesothelioma
- Endometrial and ovarian carcinomas
- Squamous cell carcinoma of the head and neck
- Genitourinary carcinomas
- Primary brain tumors

(Hendry 2017 *Adv Anat Pathol.*)

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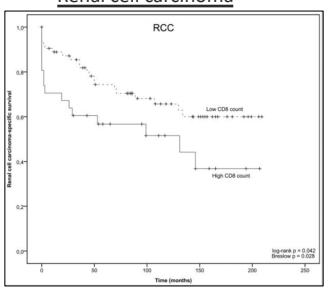
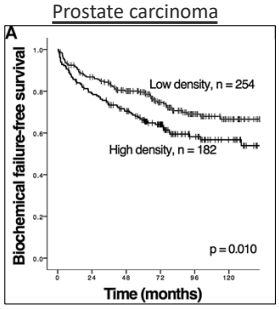
However: T cell infiltration does not always associate with better prognosis; i.e. RCC and Prostate C.

Renal cell carcinoma



Mella et al. 2015. *OncoImmunology*

Prostate carcinoma



Ness et al. 2014. *The Prostate*

Plausible explanations

- Immunosuppressive landscape that dampens T cell function (Tregs, M2 Macrophages, MDSCs, T_H2, T_H17)
- Increase in inhibitory molecules that downregulate T cell-mediated tumor-killing (checkpoint molecules, immunosuppressive cytokines)
- Low number of antigen-specific T cells (i.e. low TMB and subsequent low neoantigens)

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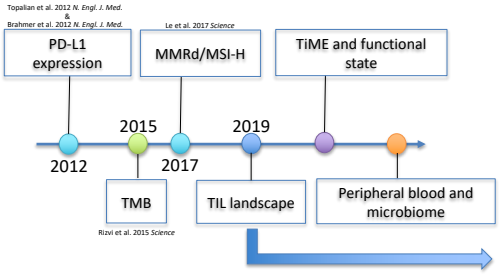
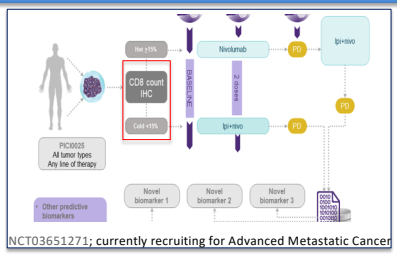
TILs – Assessing Hot vs Cold tumors – **predictive capacity**

Currently: only approximately 20%–40% of patients benefit from checkpoint inhibition - predictive biomarkers that maximize immunotherapy efficacy are needed

Predictive biomarkers for response to immunotherapy



First of its kind – treatment stratified by CD8+ T cell density



NCT03651271; currently recruiting for Advanced Metastatic Cancer

This study will shed light on 'hot' vs 'cold' tumors by evaluating:

- TiME and functional state by m-IHC
- Deep dive into the functional state of immune cells using CyTOF
- Underlying genetics by whole exome and RNA sequencing
- Whether the gut microbiome influences responsiveness to treatment

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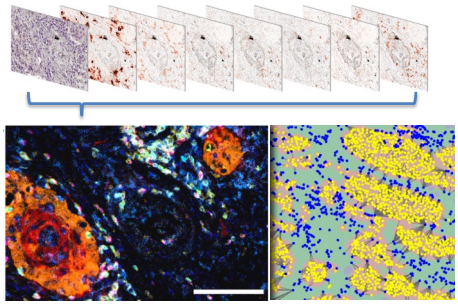
Bridging this gap – immunoprofiling for therapy prediction

Multiplex IHC – getting more from less

- Assessment of multiple parameters simultaneously on a single slide significantly decreases tissue requirement
- Simultaneous analysis of multiple immune cells (and their functional states) allows for a deeper understanding of the TME
  - Proximity between individual cells (i.e. spatial relationships)



Adapted from Tsujikawa et al. 2017. *Cell Reports*

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Biomarker panel – hot vs cold tumors

Landscape/functional multiplex IHC panel: 6-plex + Tumor marker + DAPI

Marker	Present on	TiME function
CD3	**Pan T lymphocytes** (effector, helper, cytotoxic, memory, regulatory, NK-T, γδ)	Cell-mediated immunity
CD8	$CD3^+CD8^+$ (**Cytotoxic T cells**) $CD3^+CD8^-$ (**Helper T cells**)	Cytotoxic - Tumor killing Helper – regulate immune response
CD163	**M2 Macrophages (TAMs)**	Direct and indirect suppression of T cell function and recruitment Hypoxia / fibrosis
FoxP3	**Regulatory T cells**	Maintain immune homeostasis Suppress anti-tumor immunity
PD-1	• Activated/exhausted T cells • B cells • APCs • NK cells	Inhibits T cell proliferation, survival, and effector function Decreases expression of survival molecules
PD-L1	T cells B cells DCs APCs MDSCs Tumor cells	Same as PD-1

Hot tumors
- High degree of T cell and cytotoxic T cell infiltration
- Checkpoint activation (PD-1, PD-L1)

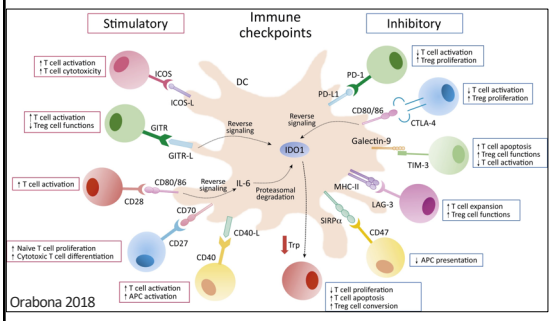
Cold tumors
- Absence of T cells within the tumor core and at the tumor margins

Altered-immunosuppressed tumors
- Poor T cell and cytotoxic T cell infiltration (or bordered at tumor margin)
- Presence of immune suppressive cells (M2 macrophages, regulatory T cells)
- Active T cell checkpoints (PD-1, PD-L1)

28 open clinical trials targeting TAMs in combination with anti-PD-1/PD-L1 therapy - as of 04/24/19

27

Immunomodulatory targets in active clinical trials



Orabona 2018

Active TIM-3 and LAG-3 clinical trials:

LAG-3
- IMP321 – soluble anti-LAG-3 mAB
- LAG525 – anti-LAG-3 mAB
- BMS986016 - anti-LAG-3 mAB
- REGN3767 – anti-LAG-3 mAB
- Sym022 – anti-LAG-3 mAB
- TSR-033 – anti-LAG-3 mAB
- MGD013 – bispecific anti-PD-1 and LAG-3 mAB
- FS118 - bispecific anti-PD-L1 and LAG-3 mAB
- EOC312 – soluble anti-LAG-3 mAB

TIM-3
- TSR-022 – anti-TIM-3 mAB
- LY3321367 – anti-TIM-3 mAB
- MBG453 – anti-TIM-3 mAB
- Sym023 – anti-TIM-3 mAB
- BGB-A425 – anti-TIM-3 mAB
- INCAGN02390 – anti-TIM-3 mAB
- RO7121661 – bispecific anti-PD-1 and TIM-3 mAB

T cell functional state multiplex IHC panel:

1. CD3 – landscape - Pan-T cells
2. CD8 – landscape – Cytotoxic T cells
3. PD-1 – function – T cell exhaustion
4. PD-L1 – function – T cell exhaustion
5. TIM-3 – function – T cell exhaustion
6. LAG-3 – function – T cell exhaustion

6-plex + Tumor marker + DAPI

NCT01968109 - anecdotal proof of principal

Patients with solid tumors that progressed on anti-PD-1/PD-L1 therapy were treated with Anti-LAG-3 (BMS-986016) + Nivo
- Interim results: ORR of 11.5% and disease control rate of 49%.
  - In 33 patients with LAG-3 expression ≥ 1% at baseline, the ORR was 18%; in the subgroup of these patients that also showed PD-L1 expression <1%, the ORR was 27%

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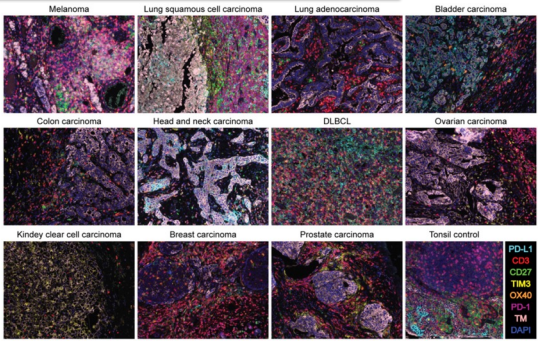
How would a clinician be able to use this data?

The effectiveness of immunomodulatory strategies is inherently dependent on the presence of tumor-associated (or circulating) immune components

Expanding mIHC approach for precision medicine

Bethmann 2018 *Current opinion in Immunology*

- Automated staining methods will improve reproducibility of multiplex staining and allow for CLIA standards, so that multiplex staining can be used to make clinical decisions.
- Ultimately, machine learning algorithms will aid to interpret data from tissue and lead to improved delivery of precision medicine.



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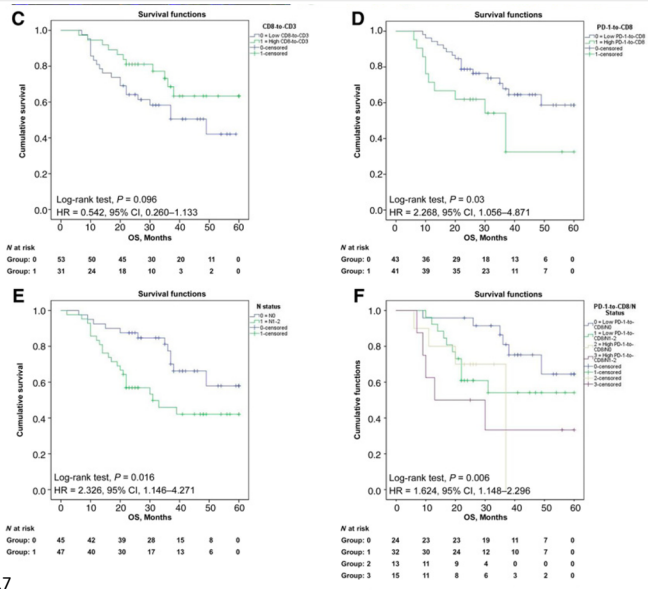
Predictive effect of PD-1 to CD8 in patients diagnosed with NSCLC treated with nivolumab (E: DFS and G: OS): low PD-1/CD8 ratio corresponds with response



Mazzaschi *et al*, 2017

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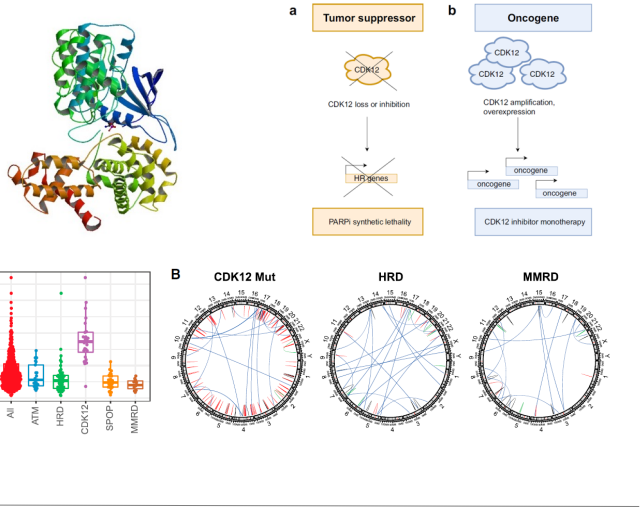
CDK12 – An emerging IO Biomarker



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CDK12 Gene Structure

Dixon-Clarke et al. 2015

- Located on chromosome 17q12
- 14 exons → 1490 amino acids → Molecular weight 164 kDa
- Arginine/serine-rich (RS) motifs: **involved in pre-mRNA processing** and NLS
- Proline-rich motifs (PRMs): binding sites for SH3 and WW domains
  - Suggests **potential protein interaction partners from a wide range of signaling pathways**

Liu et al. 2018 (review)

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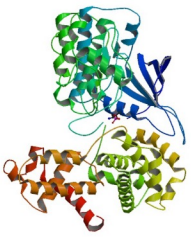
CDK12 Function

- CDK12 regulates gene transcription as a complex with cyclin K
  - Expression and alternative last exon (ALE) splicing of **genes with long transcripts and large numbers of exons**
- CDK12 knockdown leads to genomic instability
  - Alteration of 2.67% of tested genes (microarray)
    - Majority were downregulation of genes with large numbers of exons
  - Enrichment of genes involved in DNA replication, recombination and repair centered on the BRCA1 module. **Significantly lower levels of *BRCA1, ATR, FANCI* and *FANCD2***.
  - CDK12 required for optimal pre-mRNA processing of the *MYC* gene, with gene depletion reducing levels of polyadenylated *MYC* RNA
- CDK12 or cyclin K **knockdown sensitized cells to DNA-damaging agents**
  - Suggests CDK12/cyclin K is a **master regulator of proteins specifically involved in DNA damage repair (DDR) and response to DNA damage**



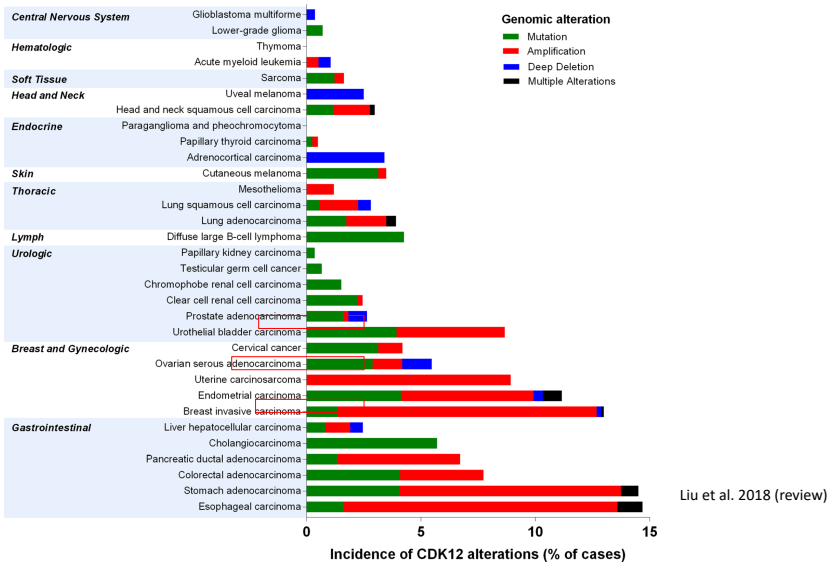
CDK12-cyclin K complex

Liu et al. 2018 (review)

33

34

Genomic alterations of the CDK12 gene across TCGA (as of May 2018)



Liu et al. 2018 (review)

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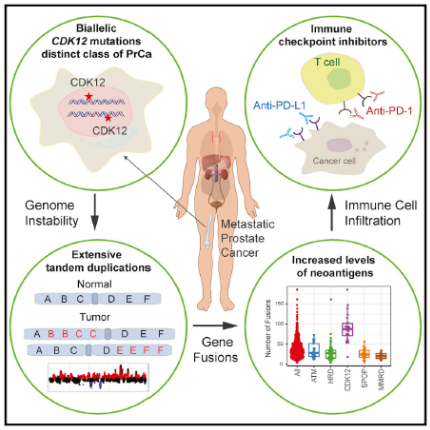
CDK12 alterations in Prostate Cancer

- Inactivating biallelic CDK12 mutations constitute a prostate cancer subtype
- CDK12 loss is associated with genomic instability and focal tandem duplications
- CDK12 loss leads to increased gene fusions, neoantigen burden, and T cell infiltration
- Patients with CDK12 mutant tumors may benefit from immune checkpoint inhibition



Wu et al. 2018

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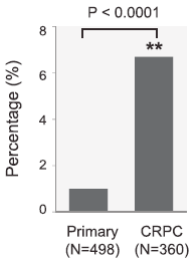
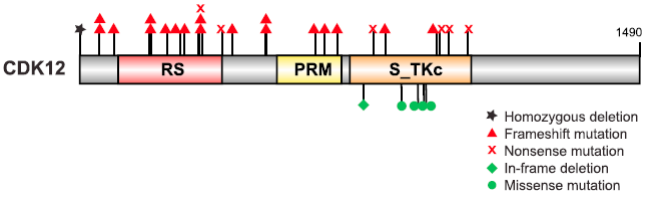
CDK12 alterations more frequent in metastatic CR-Prostate Cancer

- Detected aberrations of CDK12 in 25/360 of mCRPC patients (6.9%), significantly higher than in primary PCa, 6/498 patients (1.2%)
  - **Majority of CDK12 mutations (83%) were truncating and resulted in the loss of the kinase domain**
  - Missense mutations were clustered around conserved residues in the kinase domain





- CDK12 has very **low tolerability for germline loss-of-function variants**
  - No germline aberrations were detected

Wu et al. 2018

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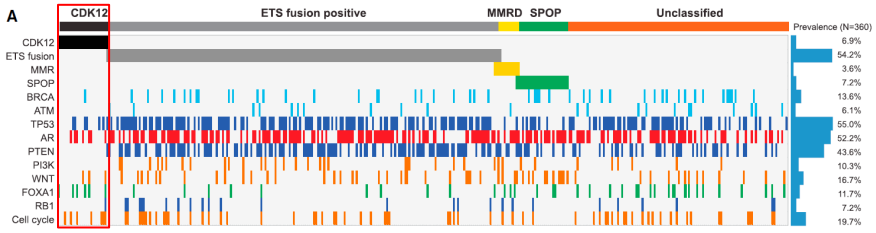
Mutual exclusivity of CDK12 mutation in mCRPC

- CDK12 loss was mutually exclusive with ETS fusions, mismatch repair deficiency (MMRD), SPOP mutations, and homologous recombination deficiency (HRD)



Wu et al. 2018

- "Biallelic BRCA2, CDK12, and ATM inactivating mutations were mutually exclusive"

Quigley et al. 2018

37

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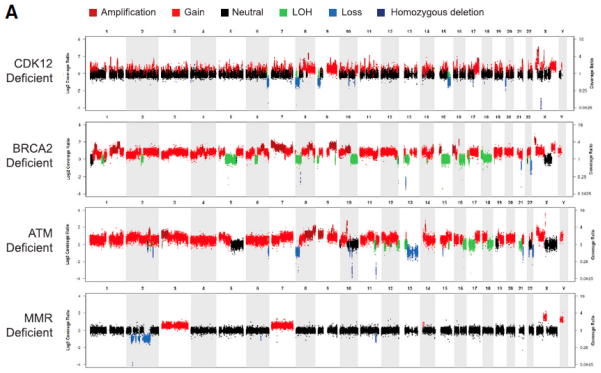
CDK12 loss results in a distinct pattern of Genome Instability

- CDK12 mutant tumors were baseline diploid, had few arm-level copy-number aberrations (except gain of 8q), and **hundreds of focal copy-number gains**



- CDK12 biallelic inactivation was strongly associated with this form of genomic instability

Wu et al. 2018

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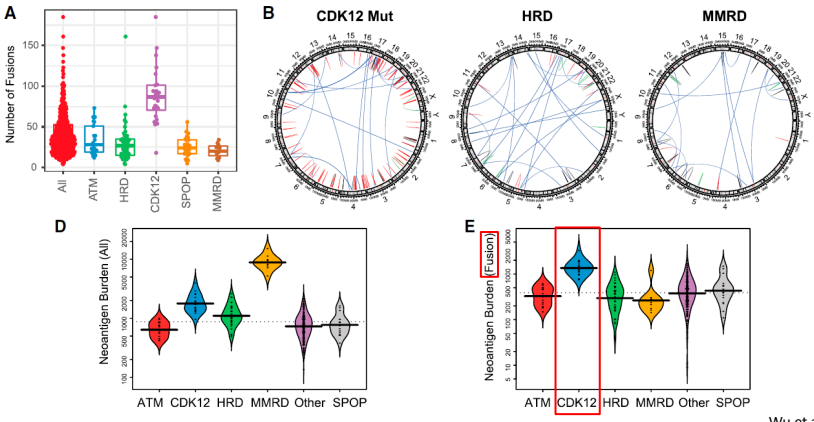
CDK12 loss results in distinct Structural Variation signature and Neoantigens

- CDK12 mutant has highest fusion burden, consistent with the large number of focal copy-number events generated by tandem duplications



- CDK12 mutant has highest Neoantigen Burden resulting from Fusions

Wu et al. 2018

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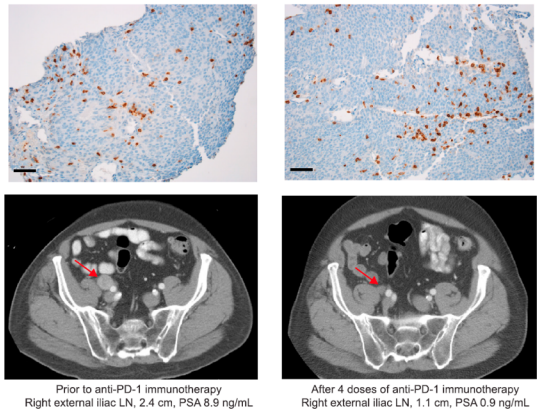
Response of CDK12 Mutant Patients to Anti-PD1 Checkpoint Inhibitor IO-therapy

- Metastatic lymph node biopsy shows robust CD3 staining
  - presence of T lymphocytes
- Marked decline in pelvic lymph node disease burden following anti-PD1 treatment
  - Suggests mCRPC patients who harbor biallelic CDK12 loss may have a higher likelihood of response to IO-therapy



Prior to anti-PD-1 immunotherapy
Right external iliac LN, 2.4 cm, PSA 8.9 ng/mL

After 4 doses of anti-PD-1 immunotherapy
Right external iliac LN, 1.1 cm, PSA 0.9 ng/mL

40

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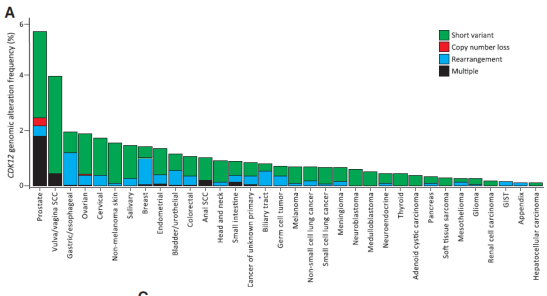
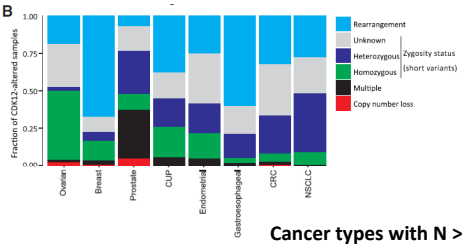
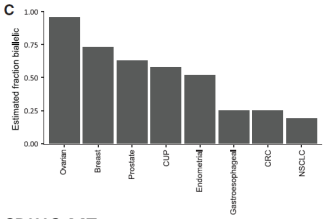
Prevalence of Biallelic CDK12 alteration across All Cancer Types

- Biallelic CDK12 alterations were defined as:
  a) mutations with loss of heterozygosity (LOH) at the wild-type allele, as determined by zygosity status
  b) copy number loss (homozygous deletion)
  c) ≥2 CDK12 GAs in a given sample







Cancer types with N > 50 CDK12-MT cases

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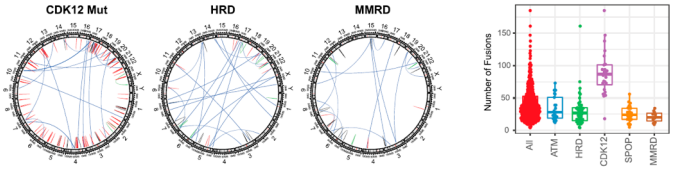
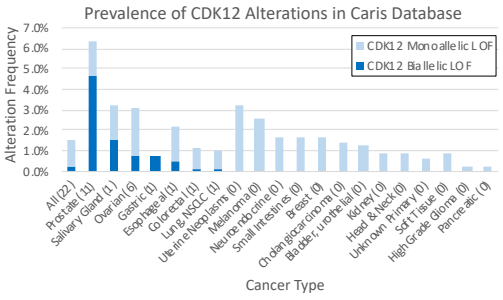
CDK12: an emerging biomarker of Response to IO therapy

- In prostate and ovarian cancer, biallelic inactivation of CDK12 is associated with a unique genomic structural variant phenotype characterized by focal tandem duplication events
  - These duplication events often result in gene fusions that increase neoantigen burden

(Adapted from Wu et al., 2018)



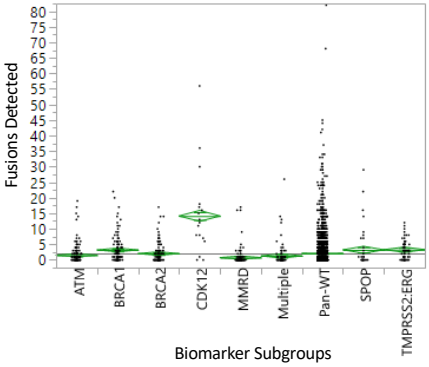
- With the incorporation of WTS to the Caris tumor profile, all gene fusion events can be detected and mapped back to the genome to assess the changes in genome structure
- Fusion sequences can also be examined for immune epitopes to identify antigenic peptides that may invoke an immune response
- We have identified cases with CDK12 alterations across multiple cancer types to evaluate the potential of CDK12 as pan-tumor biomarker of response to IO therapy



42

Fusion Rates associated with Biomarker Subgroups

- Cases stratified into subgroups based on biomarker analysis
  - CDK12 subgroup = CDK12-Biallellic LOF
  - Multiple subgroup = cases with various combination of biomarker alterations
  - Pan-WT subgroup: cases lacking alterations for each biomarker listed
- High fusion rate associated with CDK12 subgroup
- Several Pan-WT cases also show high fusion rates
  - Suggests additional driver mutations of high fusion rate remain to be discovered

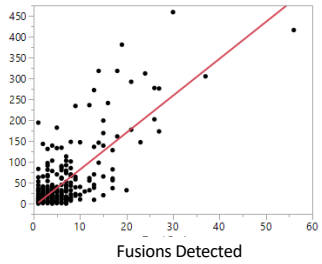


43

High neo-antigen burden correlates with increased fusion rate

- Immune Epitope Database (IEDB) MHC-I binding prediction:
  - Peptide libraries generated from fusion sequences for each fusion isoform detected by WTS
  - HLA genotyping performed to enable prediction of HLA allele-specific affinities for each peptide
  - Interpretation of peptide affinities based on guidelines reported by IEDB:
    - "Peptides with IC50 values <50 nM are considered **high affinity**, <500 nM **intermediate affinity** and <5000 nM **low affinity**. Most known epitopes have high or intermediate affinity. Some epitopes have low affinity, but no known T-cell epitope has an IC50 value greater than 5000"

High Affinity Peptides (IC50 < 50 nM)



44

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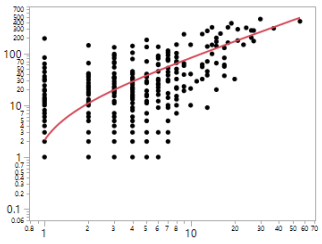

Fusions Detected

45

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Thank you!

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Precision Oncology Symposium

Molecular Tumor Board

Precision Oncology Symposium

Comprehensive Molecular Profiling: Clinical Utility

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Comprehensive Molecular Profiling: Clinical Utility

EGFR, ALK, KRAS, Her-2 with Tissue Specificity

Sachdev Thomas, MD
Hematology/Oncology
Genomic Oncology Lead- Kaiser Permanente Northern California.

November 5, 2019

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EGFR, ALK, HER-2 K-RAS : Tissue specificity

EGFR ALK	NON SMALL CELL CA LUNG
HER-2	BREAST CA, GASTRIC/GE JN
K-RAS	COLON CA

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EGFR, ALK, HER-2 K-RAS : Tissue specificity

EGFR	NON SMALL CELL CA LUNG
ALK	Neuroblastoma(pediatric), Anaplastic Large Cell Lymphoma
HER-2	BREAST CA, GASTRIC/GE JN, COLON, NON SMALL CELL LUNG, SALIVARY GLAND
K-RAS	COLON CA, NON SMALL CELL LUNG

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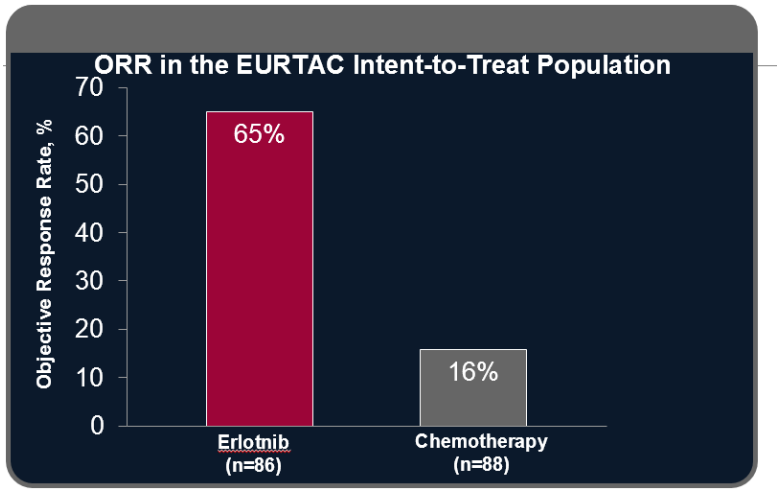
EGFR DIRECTED THERAPY IN EGFR MUTANT NSCLC



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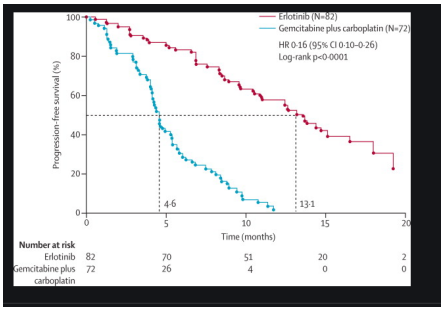
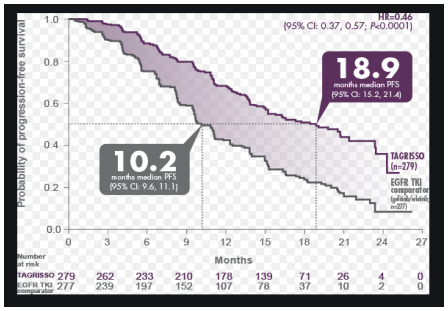
EGFR IN NON SMALL CELL CA LUNG





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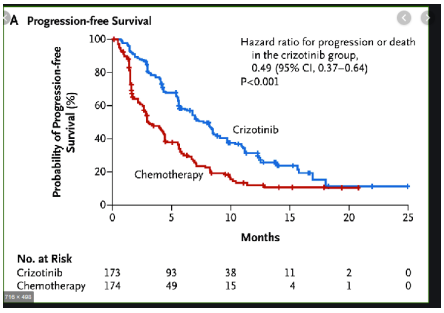
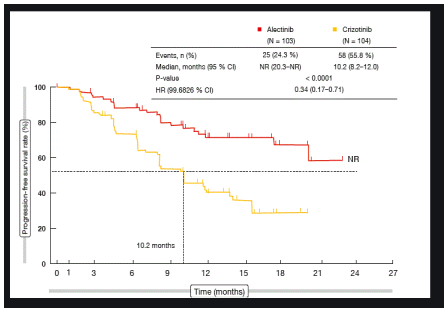
ALK in NON SMALL CELL LUNG CA





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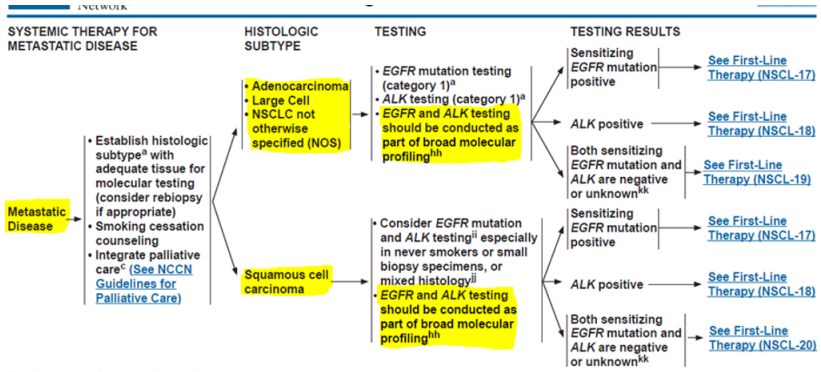
CAP /NCCN GUIDELINES 2016



[a] See Principles of Pathologic Review (NSCL-A).
[c] Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 2010;363:733-742.
[hh] The NCCN NSCLC Guidelines Panel strongly endorses broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials. Broad molecular profiling is a key component of the improvement of care of patients with NSCLC. See Emerging Targeted Agents for Patients With Genetic Alterations (NSCL-H).
[ii] In patients with squamous cell carcinoma, the observed incidence of *EGFR* mutations is 2.7% with a confidence that the true incidence of mutations is less than 3.6%. This frequency of *EGFR* mutations does not justify routine testing of all tumor specimens. Forbes SA, Bharma G, Bamford S, et al. The catalogue of somatic mutations in cancer (COSMIS). Curr Protoc Hum Genet 2008;chapter 10:unit 10.11.
[jj] Paik PK, Varghese AM, Sima CS, et al. Response to erlotinib in patients with *EGFR* mutant advanced non-small cell lung cancers with a squamous or squamous-like component. Mol Cancer Ther 2012;11:2535-2540.
[kk] Consider ROS1 testing; if positive, may treat with crizotinib. Shaw AT, Ou S-HI, Bang Y-J, et al. Crizotinib in ROS1-rearranged non-small cell lung cancer. N Engl J Med 2014;371:1963-1971.

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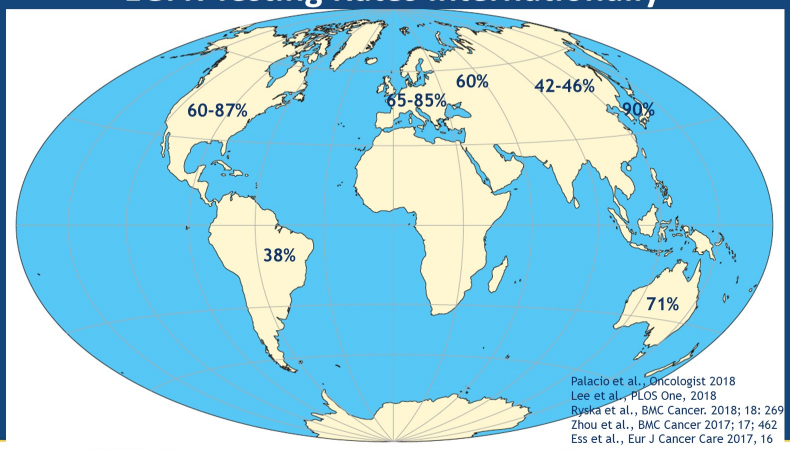
EGFR Testing Rates Internationally



Palacio et al., Oncologist 2018
Lee et al., PLOS One, 2018
Ryska et al., BMC Cancer. 2018; 18: 269
Zhou et al., BMC Cancer 2017; 17; 462
Ess et al., Eur J Cancer Care 2017, 16

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PRESENTED BY: Nathan Pennell Cleveland Clinic @drBpennell
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Presented By Nathan Pennell at 2019 ASCO Annual Meeting

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2916 NCCN GUIDELINES NSCLC

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2016
Non-Small Cell Lung Cancer

NCCN Guidelines Index
NSCL Table of Contents
Discussion

of the EGFR exon 19 deletion or exon 21 L858R mutation is predictive of treatment benefit from EGFR tyrosine kinase inhibitor (EGFR-TKI) therapy; therefore, these mutations are referred to as *sensitizing* EGFR mutations (see *EGFR Mutations* in this Discussion).[108,109] However, the presence of EGFR exon 19 deletions (LREA) or exon 21 L858R mutations does not appear to be prognostic of survival for patients with NSCLC, independent of therapy.[110] The ALK fusion oncogene (ie, ALK gene rearrangement) is a predictive biomarker that has been identified in a small subset of patients with NSCLC (see *ALK Gene Rearrangements* in this Discussion and *Principles of Pathologic Review* in the NCCN Guidelines for Non-Small Cell Lung Cancer). Other gene rearrangements (ie, gene fusions) have recently been identified (such as ROS1, RET) that are susceptible to targeted therapies.[111-116]

Testing for ALK gene rearrangements and EGFR mutations is recommended (category 1) in the NSCLC algorithm for patients with nonsquamous NSCLC or NSCLC not otherwise specified (NOS) so that patients with these genetic abnormalities can receive effective treatment with targeted agents such as erlotinib, gefitinib, afatinib, crizotinib, ceritinib, and alectinib (see *Targeted Therapies* in this Discussion and in the NCCN Guidelines for Non-Small Cell Lung Cancer).[117-121] Although rare, patients with ALK rearrangements or sensitizing EGFR mutations can have mixed squamous cell histology.[122,123] Therefore, testing for ALK rearrangements and EGFR mutations can be considered in patients with squamous cell histology if they are never smokers, small biopsy specimens were used for testing, or mixed histology was reported. EGFR, KRAS, and ALK genetic alterations do not usually overlap.[124,125]

Patients with NSCLC may have other genetic alterations (see *Emerging Targeted Agents for Patients with Genetic Alterations* in the NCCN Guidelines for Non-Small Cell Lung Cancer).[73,126,127] Mutation screening assays for detecting multiple biomarkers simultaneously (eg, Sequenom's MassARRAY® system, SNaPshot® Multiplex System) have been developed that can detect more than 50 point mutations, including EGFR.[128,129] However, these multiplex polymerase chain reaction (PCR) systems do not detect gene rearrangements, because they are not point mutations. ALK gene rearrangements can be detected using fluorescence in situ hybridization (FISH) (see *ALK Gene Rearrangements* in this Discussion). Broad molecular profiling systems, such as next-generation sequencing (NGS) (also known as massively parallel sequencing), can detect panels of mutations and gene rearrangements if the NGS platforms have been designed and validated to detect these genetic alterations.[130-137] It is important to recognize that NGS requires quality control as much as any other diagnostic technique; because it is primer dependent, the panel of genes and abnormalities detected with NGS will vary depending on the design of the NGS platform. For example, some NGS platforms can detect both mutations and gene rearrangements, as well as copy number variation, but they are not uniformly present in all NGS assays being conducted either commercially or in institutional laboratories.

Other driver mutations and gene rearrangements (ie, driver events) are being identified such as HER2 (also known as ERBB2) and BRAF V600E mutations, ROS1 and RET gene rearrangements, and high-level MET amplification or MET exon skipping mutation.[111,112,114,116,138-147] Targeted agents are available for patients with NSCLC who have these other genetic alterations, although they are FDA approved for other indications (see *Emerging Targeted Agents for Patients with Genetic Alterations* in the NCCN Guidelines for Non-Small Cell Lung Cancer).[131,148] Thus, the NCCN Panel strongly endorses broader molecular profiling (also known as precision medicine) to identify rare driver mutations to ensure that patients receive the most appropriate

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2016 NCCN GUIDELINES

NSCL-16
- Footnote "hh" added: "The NCCN NSCLC Guidelines Panel strongly endorses broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials. Broad molecular profiling is a key component of the improvement of care of patients with NSCLC. See Emerging Targeted Agents for Patients with Genetic Alterations (NSCL-H)."

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NCCN Guidelines Version 1.2015 Updates
Non-Small Cell Lung Cancer

NCCN Guidelines Index
NSCLC Table of Contents
Discussion

Updates in Version 1.2015 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 4.2014 include:

NSCL-16
- Footnote "hh" added: "The NCCN NSCLC Guidelines Panel strongly endorses broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials. Broad molecular profiling is a key component of the improvement of care of patients with NSCLC. See Emerging Targeted Agents for Patients with Genetic Alterations (NSCL-H)."
- Testing results added for squamous cell carcinoma with links to treatment recommendations.
- Testing results modified: "*Both* sensitizing EGFR mutation and ALK are negative or unknown."

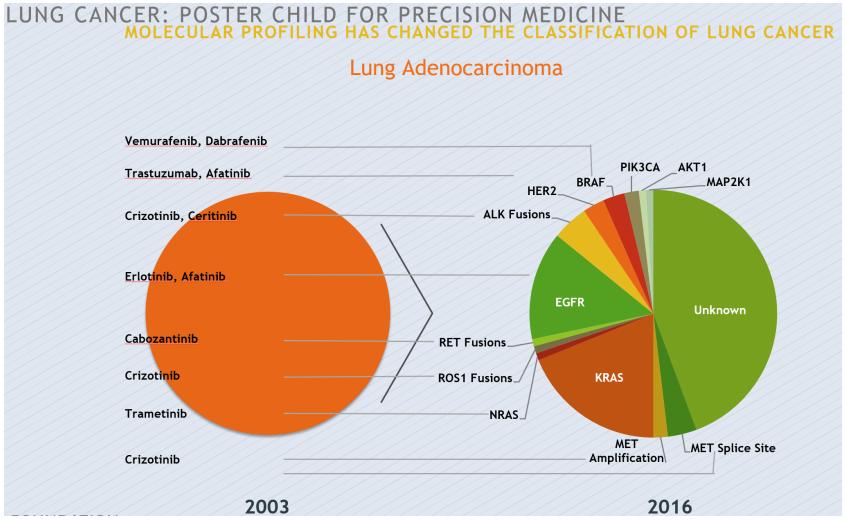
NSCL-17
- For progressive disease with multiple symptomatic systemic lesions, recommendation is for treatment with first-line therapy options as per NSCL-19 or NSCL-20.
- If there is second disease progression after subsequent therapy, recommendation is for treatment with first-line therapy options as per NSCL-19 or NSCL-20.
- Footnote "gg" modified: "Prior to changing therapy, a biopsy ~~on progression~~ is reasonable to determine mechanism of acquired resistance. ~~because proportion of patients will transform to SCLC at progression~~.

NSCL-18
- Crizotinib changed from a category 2A recommendation to a category 1 recommendation for patients with an ALK rearrangement discovered prior to first-line chemotherapy.
- For progressive disease with multiple symptomatic systemic lesions, recommendation is for treatment with first-line therapy options as per NSCL-19 or NSCL-20.
- If there is second disease progression after subsequent therapy, recommendation is for treatment with first-line therapy options as per NSCL-19 or NSCL-20.
- Footnote "ll" added: For performance status 0-4.
- Footnote removed: See third-line therapy (NSCL-21) for progressive disease with multiple symptomatic systemic lesions after treatment with crizotinib, ceritinib, and/or platinum doublet ± bevacizumab.

NSCL-19
- First-line therapy: the combination regimen cetuximab/vinorelbine/cisplatin was deleted. (also applies to NSCL-20)
- Maintenance therapy:
  - Continuation maintenance with cetuximab removed as a treatment option. (also applies to NSCL-20)
- Subsequent therapy: Ramucirumab + docetaxel added as a treatment option with a category 2B designation. (also applies to NSCL-20)
- Footnote "yy" added: "Chemotherapy preferred in this setting. Grassino M, Martelli O, Broggini M, et al. Erlotinib versus docetaxel as second lin-line treatment of patients with advanced NSCLC and wild type EGFR tumors (TAILOR): a randomized trial. Lancet Oncol 2013; 14:981-988." (also applies to NSCL-20)
- Footnote "zz" added: "Recommend proteomic testing for patients with NSCLC and wild-type EGFR or with unknown EGFR status. A patient with a 'poor' classification should not be offered erlotinib in the second-line setting. Gregorc V, Novello S, Lazzari C, et al. Predictive value of a proteomic signature in patients with non-small-cell lung cancer treated with second-line erlotinib or chemotherapy (PROSE): a biomarker stratified, randomised phase 3 trial. Lancet Oncol 2014; 15:713-21." (also applies to NSCL-20)

10

2016 Landscape NSCLC



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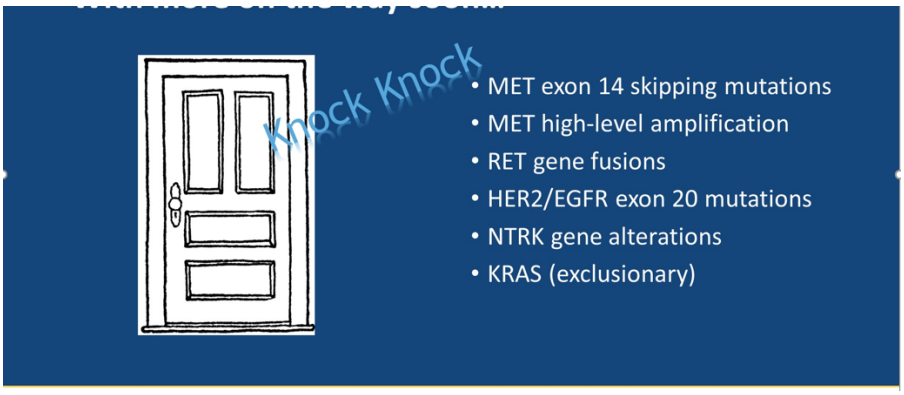
…and a few more.



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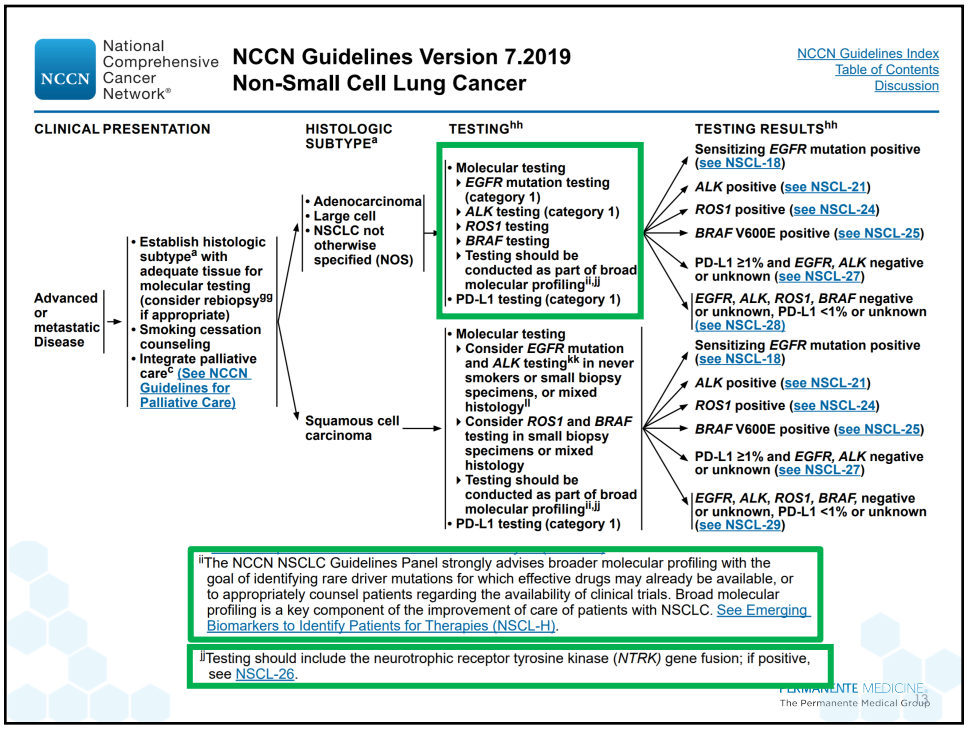

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NSCLC-NCCN Guidelines

EMERGING BIOMARKERS TO IDENTIFY NOVEL THERAPIES FOR PATIENTS WITH METASTATIC NSCLC

Genetic Alteration (ie, Driver event)	Available Targeted Agents with Activity Against Driver Event in Lung Cancer
High-level *MET* amplification or *MET* exon 14 skipping mutation	Crizotinib[1-5]
RET rearrangements	Cabozantinib[6,7] Vandetanib[8]
ERBB2 (HER2) mutations	Ado-trastuzumab emtansine[9]
Tumor mutational burden (TMB)*	Nivolumab + ipilimumab[10] Nivolumab[11]

*TMB is an evolving biomarker that may be helpful in selecting patients for immunotherapy. There is no consensus on how to measure TMB.

KRAS p.G12C and STK11 and or KEAP1 next likely biomarker to be added?

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Detection Methodologies

Test	Detects	Can Miss
IHC	Protein expression	Any alteration not known of ahead of time
FISH	Copy number alterations, Rearrangements	Indels, Substitutions
Hot Spot Panels	Substitutions	Indels, Copy number alterations, Rearrangements

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FACTORS INFLUENCING MOLECULAR TESTING IN NSCLC

CLINICS AND HOSPITALS OFTEN TEST ONE OR TWO ALTERATIONS AT A TIME USING

- IHC
- FISH
- PCR BASED METHODS, EITHER SEQUENTIALY OR IN A MULTIGENE PANEL

COSTS RANGE FROM $400 FOR SINGLE ALTERATION OR $3200 FOR MULTIGENE PANELS.

Foundation One CDx, an FDA-approved panel that detects mutations in 324 genes, has a list price of~ $5800.

Caris Molecular Intelligence costs~ $6500.

One analysis of claims data pegged the cost of a broad NGS panel at $2860 for commercial payers, while Medicare would pay $627.50.(Pennell NA, Mutebi A et al *JCO Precis Oncol*. 2019;3:1-9.)

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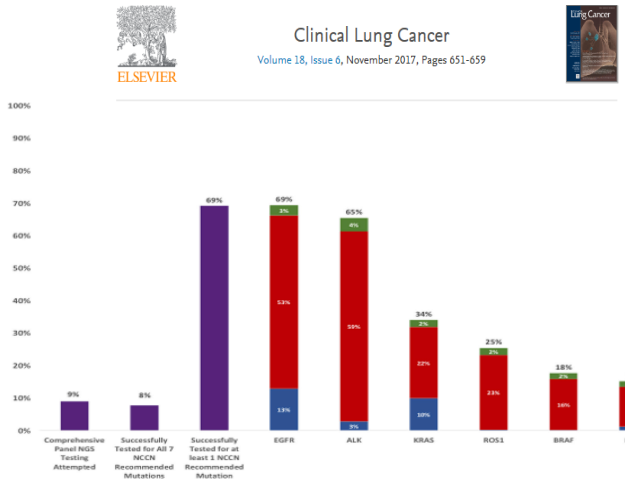
Testing Rates for NCCN Recommended Alterations : NSCLC



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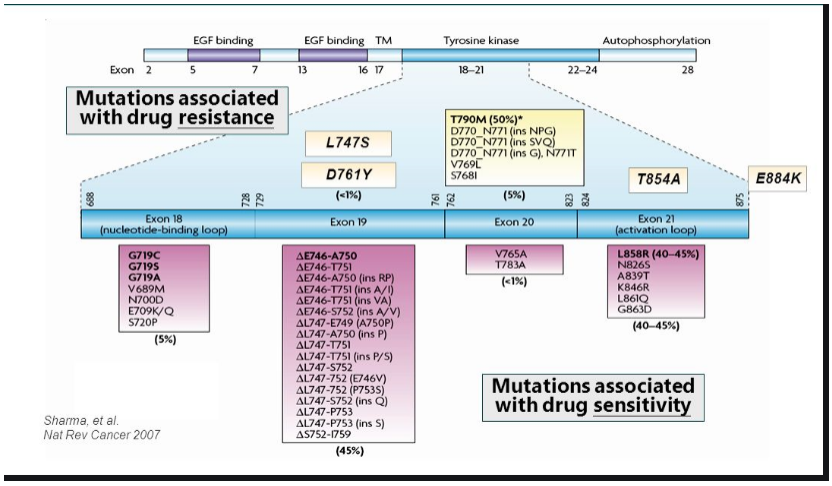
EGFR in NSCLC



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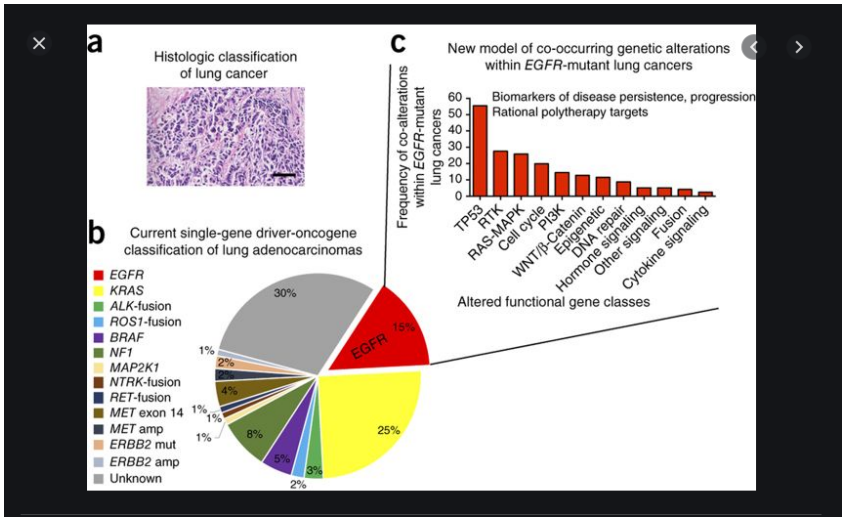
EGFR in NSCLC



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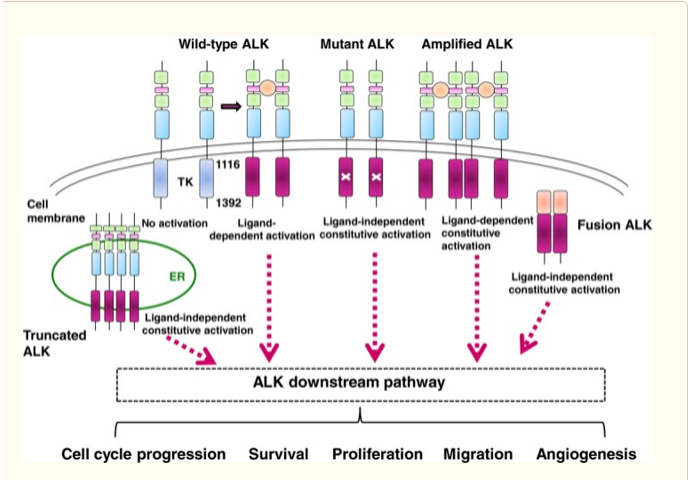
ALK ALTERATIONS



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NGS: Targeted sequencing with initial sequence enrichment. Hybrid capture/Amplicon(PCR)

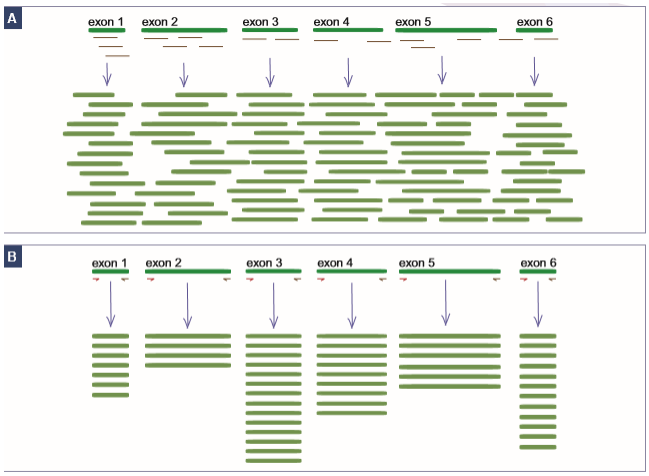

Figure 1: Schematic representations of amplicon and hybridisation enrichment approaches.

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WHAT IS THE BEST WAY TO TEST…?

SINGLE GENE TESTS

- Fast
- Require less material per test- maybe
- Reimbursed by Insurance
- Only viable for limited number of tests

NGS/BROAD PANEL

- Longer TAT than single gene
- Require more material
- Cost more than a single gene test
- Can cover all genes of interest both currently recommended and emerging targets

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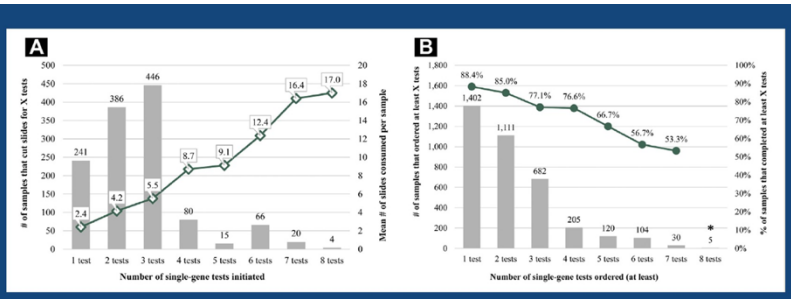
SINGLE GENE TESTS ARE NOT TISSUE SPARING



Yu et al., Clin Lung Cancer 2019;20(1):20-29.

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THE COST ISSUE

original report

Economic Impact of Next-Generation Sequencing Versus Single-Gene Testing to Detect Genomic Alterations in Metastatic Non–Small-Cell Lung Cancer Using a Decision Analytic Model

Nathan A. Pennell, MD, PhD[1]; Alex Mutebi, PhD[2]; Zheng-Yi Zhou, PhD[3]; Marie Louise Ricculli, MSc[3]; Wenxi Tang, MS[3]; Helen Wang[3]; Annie Guerin, MSc[4]; Tom Arnhart, PharmD, MS[2]; Anand Dalal, PhD[2]; Medha Sasane, PhD[2]; Kevin Y. Wu, MD[2]; Kenneth W. Culver, MD[2]; and Gregory A. Otterson, MD[5]

- Compared sequential or simultaneous testing of single gene tests for EGFR-ALK-ROS1-BRAF to up-front NGS.
- Used CMS and commercial payer reimbursement rates for testing in a hypothetical cohort of NSCLC patients.

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PRESENTED BY:

Pennell et al., JCO Prec Onc 2019 22

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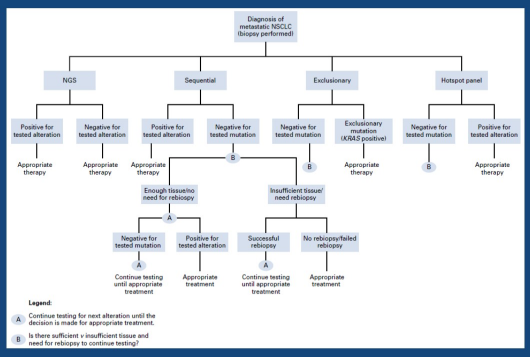
NGS versus Single Gene Results

- Up-front NGS saved between $127K and $1.5M compared to single gene testing
- Time to test results was fastest with NGS and more pts were successfully tested than with single-gene



PRESENTED AT: 2019 ASCO ANNUAL MEETING #ASCO19 Slides are the property of the author, permission required for reuse.

PRESENTED BY:

Pennell et al., JCO Prec Onc 2019

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Presented By Nathan Pennell at 2019 ASCO Annual Meeting

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REIMBURSEMENT

Three FDA-approved NGS tests for patients with NSCLC

1) Oncomine(limited genes)
2) MSK-IMPACT(Integrated Mutation Profiling of actionable Cancer Targets)
3) Foundation One CDx (F1CDx)

CMS approved coverage of NGS testing under the Parallel Review Program

Private payer coverage for NGS testing is variable.

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My Conclusion for Molecular testing EGFR, ALK in the context of NSCLC- Clinical Utility

A single test, Comprehensive Molecular Profiling (NGS) covering all markers is more tissue and cost efficient and will likely result in a higher rate of successful testing.

However…this is still a lab test.

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CASE 1.

Patient with Metastatic NSCLC- adenocarcinoma with Exon 19 del diagnosed in 2016.

Genomic Alterations Detected	Allele Frequency	FDA-Approved Therapies (in patient's tumor type)	FDA-Approved Therapies (in another tumor type)	Potential Clinical Trials
EGFR amplification, C797S, exon 19 deletion (E746_A750del), L792H, T790M	N/A, 0.62%, 82.3%, 1.2%, 17.9%	(-) Erlotinib ‡ (-) Gefitinib ‡ (-) Osimertinib ‡	Cetuximab Panitumumab	Yes, see clinical trials section
PIK3CA E545K	25.8%	None	Everolimus Temsirolimus	Yes, see clinical trials section

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CASE

Patient with Metastatic NSCLC with Exon 19 del. EGFR C797S

EGFR C797S

OncoKB

Oncogenic · Gain-of-function

EGFR, a receptor tyrosine kinase, is altered by amplification and/or mutation in lung and brain cancers among others. The EGFR C797S mutation is known to be oncogenic.

MY CANCER GENOME

Implications for Targeted Therapeutics	
Response to osimertinib	Confers decreased sensitivity
Response to anti-EGFR antibodies	Currently no role for *EGFR* mutation in predicting response in NSCLC

964	An EGFR resistance mu...	Non-small Cell Lung Ca...	Osimertinib
1396	Case report of a patient...	Lung Adenocarcinoma	Osimertinib
4837	Currently, there are no e...	Non-small Cell Lung Ca...	Brigatinib, Panitumuma...

CIViC Clinical Interpretations of Variants in Cancer

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VARIANT C797S

Variant Summary | Variant Talk

Last Modified by LynzeyK | Last Reviewed by kkrysiak | Last Commented On by kkrysiak

Aliases: CYS797SER and RS1057519861

Allele Registry ID: CA16602785

This Variant does not currently have a Summary.

Variant Type:
Missense Variant

HGVS Expressions:
ENST00000275493.2:c.2389T>A ,
NC_000007.13:g.55249091T>A ,
NM_005228.4:c.2389T>A , and
NP_005219.2:p.Cys797Ser

ClinVar ID:
376342

CIViC Variant Evidence Score:
17.5

Representative Variant Coordinates
Ref. Build: GRCh37 Ensembl Version: 75

Chr.	Start	Stop	Ref. s	Var. Bases
7	55249091	55249091	T	A

Transcript
ENST00000275493.2

ClinVar ID	ClinVar Clinical Significance
376342	not provided

COSMIC ID (v68)	dbSNP RSID	HGVS ID
--	rs1057519861	chr7:g.55249091T>A

SnpEff Effect	SnpEff Impact	gnomAD Adj. AF
missense variant	MODERATE	--

MyVariant.info

View MyVariant.info Details

Evidence for C797S 3 total items

Get Data | Help

EID	DIS	DRUGS	DESC...	EL	ET	ED	CS	VO	ER
964	Lung Non-small Cell Carcinoma	Osimertinib		B					3★
1396	Lung Adenocarcinoma	Osimertinib		C					1★
4837	Lung Non-small Cell Carcinoma	Brigatinib, Panitumumab, Cetuximab (Co...		D					4★

EVIDENCE EID4837

Evidence Summary | Evidence Talk

Submitted by MarioLamping | Last Modified by kkrysiak | Last Reviewed by arpaddanos | Last Commented On by arpaddanos

CAUTION: This Evidence Item has not been accepted as accurate or complete!

Currently, there are no effective therapeutic strategies to overcome the C797S/T790M/activating-mutation (triple-mutation)-mediated EGFR-TKI resistance to Osimertinib. In the present study, we identify brigatinib to be effective against triple-mutation-harbouring cells in vitro and in vivo. The efficacy of brigatinib is enhanced markedly by combination with anti-EGFR antibodies Ceutximab or Panitumumab because of the decrease of surface and total EGFR expression. Thus, the combination therapy of brigatinib with anti-EGFR antibody is a powerful candidate to overcome triple-mutant EGFR

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Genotype is not destiny, phenotype is…

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Case:

Pt with Met Lung CA:

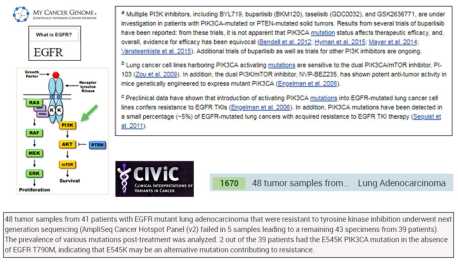
Pt had been treated with Erlotinib and responded.

Upon progression, original sample was sent for NGS

Genomic Alterations Detected	Allele Frequency	FDA-Approved Therapies (in patient's tumor type)	FDA-Approved Therapies (in another tumor type)	Potential Clinical Trials
EGFR amplification, C797S, exon 19 deletion (E746_A750del), L792H, T790M	N/A, 0.62%, 82.3%, 1.2%, 17.9%	(-) Erlotinib ‡ (-) Gefitinib ‡ (-) Osimertinib ‡	Cetuximab Panitumumab	Yes, see clinical trials section
PIK3CA E545K	25.8%	None	Everolimus Temsirolimus	Yes, see clinical trials section

PIK3CA c.1633G>A (E545K) Mutation in Non-Small Cell Lung Cancer

Properties	
Location of mutation	Helical domain; Exon 10 (coding exon 9)
Frequency of PIK3CA mutations in NSCLC	1–3% (COSMIC; Kawano et al. 2006; Samuels et al. 2004)
Frequency of E545K mutations in PIK3CA-mutated NSCLC	26.7% (COSMIC)
Implications for Targeted Therapeutics	
Response to PI3K inhibitors	Unknown at this time[a]
Response to dual PI3K/mTOR inhibitors	Unknown at this time[b]
Response to AKT inhibitors	Unknown at this time
Response to EGFR TKIs	Unknown at this time[c]
Response to anti-EGFR antibodies	Unknown at this time



[a] Multiple PI3K inhibitors, including BYL719, buparlisib (BKM120), taselisib (GDC0032), and GSK2636771, are under investigation in patients with PIK3CA-mutated or PTEN-mutated solid tumors. Results from several trials of buparlisib have been reported: from these trials, it is not apparent that PIK3CA mutation status affects therapeutic efficacy, and, overall, evidence for efficacy has been equivocal (Bendell et al. 2012; Hyman et al. 2015; Mayer et al. 2014; Vansteenkiste et al. 2015). Additional trials of buparlisib as well as trials for other PI3K inhibitors are ongoing.

[b] Lung cancer cell lines harboring PIK3CA activating mutations are sensitive to the dual PIK3CA/mTOR inhibitor, PI-103 (Zou et al. 2009). In addition, the dual PI3K/mTOR inhibitor, NVP-BEZ235, has shown potent anti-tumor activity in mice genetically engineered to express mutant PIK3CA (Engelman et al. 2006).

[c] Preclinical data have shown that introduction of activating PIK3CA mutations into EGFR-mutated lung cancer cell lines confers resistance to EGFR TKIs (Engelman et al. 2006). In addition, PIK3CA mutations have been detected in a small percentage (~5%) of EGFR-mutated lung cancers with acquired resistance to EGFR TKI therapy (Sequist et al. 2011).

48 tumor samples from 41 patients with EGFR mutant lung adenocarcinoma that were resistant to tyrosine kinase inhibition underwent next generation sequencing (AmpliSeq Cancer Hotspot Panel (v2) failed in 5 samples leading to a remaining 43 specimens from 39 patients). The prevalence of various mutations post-treatment was analyzed. 2 out of the 39 patients had the E545K PIK3CA mutation in the absence of EGFR T790M, indicating that E545K may be an alternative mutation contributing to resistance.

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Case:

Pt with Met Lung CA:

Pt had been treated with Erlotinib and responded.

Upon progression, original sample was sent for NGS

Genomic Alterations Detected	Allele Frequency	FDA-Approved Therapies (in patient's tumor type)	FDA-Approved Therapies (in another tumor type)	Potential Clinical Trials
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PIK3CA E545K	25.8%	None	Everolimus Temsirolimus	Yes, see clinical trials section

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Patient with progression after Erlotinib

Based on the NGS test results you would recommend

1. Trial of Everolimus.
2. Trial of Palbociclib
3. Trial of Abemaciclib approved for PIK3CA E545K alteration.
4. None of the above.

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Rates of Grade III/IV toxicities with m-TOR and CDK 4&6 inhibitors

EVROLIMUS.

5.2 Infections

AFINITOR/AFINITOR DISPERZ has immunosuppressive properties and may predispose patients to bacterial, fungal, viral, or protozoal infections, including infections with opportunistic pathogens *[see Adverse Reactions (6.1)]*. Localized and systemic infections, including pneumonia, mycobacterial infections, other bacterial infections, invasive fungal

infections (e.g., aspergillosis, candidiasis, or **PJP**) **and viral infections (e.g.,** reactivation of hepatitis B virus) have occurred. Some of these infections have **been severe (e.g., sepsis, septic shock, or resulting in multisystem organ failure)** or fatal. The incidence of **Grade 3 and 4 infections** was up to 10% and up to 3%, respectively. The incidence of serious infections was reported at a higher frequency in patients < 6 years of age *[see Use in Specific Populations (8.4)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Non-infectious Pneumonitis

Non-infectious pneumonitis is a class effect of rapamycin derivatives. Non-infectious pneumonitis was reported in up to 19% of patients treated with AFINITOR/AFINITOR DISPERZ in clinical trials, some cases were reported with pulmonary hypertension (including pulmonary arterial hypertension) as a secondary event. The incidence of Grade 3 and 4 non-infectious pneumonitis was up to 4% and up to 0.2%, respectively *[see Adverse Reactions (6.1)]*. Fatal outcomes have been observed.

Consider a diagnosis of non-infectious pneumonitis in patients presenting with non-specific respiratory signs and symptoms. Consider opportunistic infections such as pneumocystis jirovecii pneumonia (PJP) in the differential diagnosis. Advise patients to report promptly any new or worsening respiratory symptoms.

PALBOCICLIB

5.1 Neutropenia

Neutropenia was the most frequently reported adverse reaction in Study 1 (PALOMA-2) with an incidence of 80% and Study 2 (PALOMA-3) with an incidence of 85%. A Grade 3-4 decrease in neutrophil counts was reported in 66% of patients receiving IBRANCE plus letrozole in Study 1 and 66% of patients receiving IBRANCE plus fulvestrant in Study 2. In Study 1 and 2, the median time to first episode of any grade neutropenia was 15 days and the median duration of Grade 3-4 neutropenia was 7 days [see Adverse Reactions (6.1)].

Monitor complete blood counts prior to starting IBRANCE therapy and at the beginning of each cycle, as well as on Day 15 of the first 2 cycles, and as clinically indicated. Dose interruption, dose reduction, or delay in starting treatment cycle is recommended for patients who develop Grade 3 or 4 neutropenia [see Dosage and Administration (2.2)].

Febrile neutropenia has been reported in 1.9% of patients exposed to IBRANCE across Studies 1 and 2. One death due to neutropenic sepsis was observed in Study 2. Physicians should inform patients to promptly report any episodes of fever [see Patient Counseling Information (17)].

5.2 Interstitial Lung Disease (ILD)/Pneumonitis

Severe, life-threatening, or fatal interstitial lung disease (ILD) and/or pneumonitis can occur in patients treated with cyclin-dependent kinase 4/6 (CDK4/6) inhibitors, including IBRANCE when taken in combination with endocrine therapy.

Across clinical trials (PALOMA-1, PALOMA-2, PALOMA-3), 1.9% of IBRANCE-treated patients had ILD/pneumonitis of any grade, 0.1% had Grade 3 or 4 and no fatal cases were reported. Additional cases of ILD/pneumonitis have been observed in the postmarketing setting, with fatalities reported [see Adverse Reactions (6.2)].

Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis (e.g. dyspnea, cough, dyspnea). In patients who have new or worsening respiratory symptoms and are suspected to have developed pneumonitis, interrupt IBRANCE immediately and evaluate the patient. Permanently discontinue IBRANCE in patients with severe ILD or pneumonitis [see Dosage and Administration (2.2)].

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NSCLC: m-TOR inhibitors, PIK3CA inhibitors,

Table. Updated Results of Completed Lung-MAP Substudies

Substudy Closure Date	Final Accrual	Response: Patients (%)	PFS Median (95% CI)	OS Median (95% CI)
S1400A (non-match) 12/18/15	Total: 116 Durvalumab: 78 Docetaxel: 38	11 (16%)	2.9 (1.8, 4.1)	11.6 (10.1, 15.4)
S1400B PI3K 12/12/16	Total: 39 Taselisib: 31 Docetaxel: 8	1 (4%)	2.8 (1.7, 4.0)	5.9 (4.1, 11.5)
S1400C (CCGA+) 9/1/16	Total: 54 Palbociclib: 37 Docetaxel: 17	2 (6%)	1.8 (1.6, 2.9)	7.2 (4.0, 14.6)
S1400D (FGFR+) 10/31/16	Total: 45 AZD4547: 35 Docetaxel: 10	2 (7%)	2.7 (1.4, 4.5)	7.5 (3.6, 9.3)
S1400E (MET+) 11/26/14	Total: 9 Rilotumumab + Erlotinib: 4 Erlotinib only: 5	3 (5%)	2.7 (1.9, 2.9)	7.7 (6.7, 9.2)

Abbreviations: PFS, progression-free survival; OS, overall survival; CI, confidence interval; CCGA, cell cycle genetic alterations.

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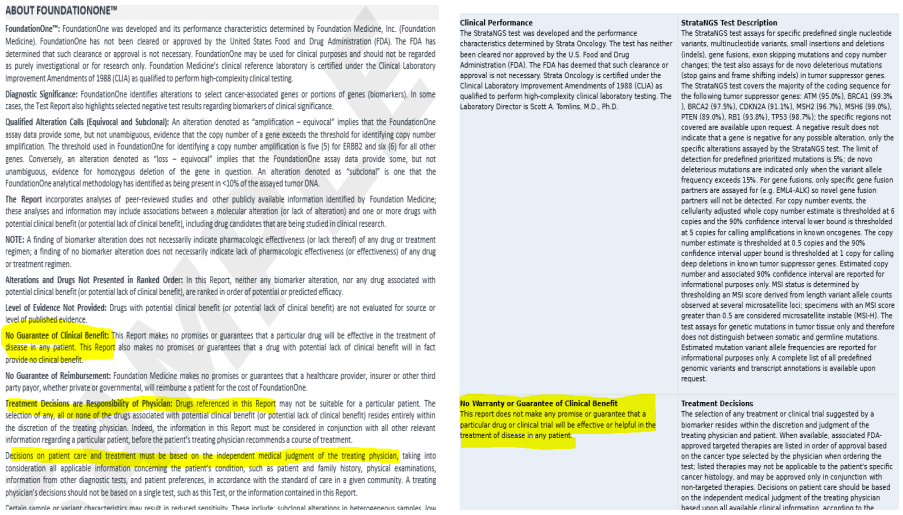
REPORTING OF NGS RESULTS



ABOUT FOUNDATIONONE™

FoundationOne™: FoundationOne was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). FoundationOne has not been cleared or approved by the United States Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary. FoundationOne may be used for clinical purposes and should not be regarded as purely investigational or for research only. Foundation Medicine's clinical reference laboratory is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing.

Diagnostic Significance: FoundationOne identifies alterations to select cancer-associated genes or portions of genes (biomarkers). In some cases, the Test Report also highlights selected negative test results regarding biomarkers of clinical significance.

Qualified Alteration Calls (Equivocal and Subclonal): An alteration denoted as "amplification – equivocal" implies that the FoundationOne assay data provide some, but not unambiguous, evidence that the copy number of a gene exceeds the threshold for identifying copy number amplification. The threshold used in FoundationOne for identifying a copy number amplification is five (5) for ERBB2 and six (6) for all other genes. Conversely, an alteration denoted as "loss – equivocal" implies that the FoundationOne assay data provide some, but not unambiguous, evidence for homozygous deletion of the gene in question. An alteration denoted as "subclonal" is one that the FoundationOne analytical methodology has identified as being present in <10% of the assayed tumor DNA.

The Report incorporates analyses of peer-reviewed studies and other publicly available information identified by Foundation Medicine; these analyses and information may include associations between a molecular alteration (or lack of alteration) and one or more drugs with potential clinical benefit (or potential lack of clinical benefit), including drug candidates that are being studied in clinical research.

NOTE: A finding of biomarker alteration does not necessarily indicate pharmacologic effectiveness (or lack thereof) of any drug or treatment regimen; a finding of no biomarker alteration does not necessarily indicate lack of pharmacologic effectiveness (or effectiveness) of any drug or treatment regimen.

Alterations and Drugs Not Presented in Ranked Order: In this Report, neither any biomarker alteration, nor any drug associated with potential clinical benefit (or potential lack of clinical benefit), are ranked in order of potential or predicted efficacy.

Level of Evidence Not Provided: Drugs with potential clinical benefit (or potential lack of clinical benefit) are not evaluated for source or level of published evidence.

No Guarantee of Clinical Benefit: This Report makes no promises or guarantees that a particular drug will be effective in the treatment of disease in any patient. This Report also makes no promises or guarantees that a drug with potential lack of clinical benefit will in fact provide no clinical benefit.

No Guarantee of Reimbursement: Foundation Medicine makes no promises or guarantees that a healthcare provider, insurer or other third party payor, whether private or governmental, will reimburse a patient for the cost of FoundationOne.

Treatment Decisions are Responsibility of Physician: Drugs referenced in this Report may not be suitable for a particular patient. The selection of any, all or none of the drugs associated with potential clinical benefit (or potential lack of clinical benefit) resides entirely within the discretion of the treating physician. Indeed, the information in this Report must be considered in conjunction with all other relevant information regarding a particular patient, before the patient's treating physician recommends a course of treatment.

Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking into consideration all applicable information concerning the patient's condition, such as patient and family history, physical examinations, information from other diagnostic tests, and patient preferences, in accordance with the standard of care in a given community. A treating physician's decisions should not be based on a single test, such as this Test, or the information contained in this Report.

Certain sample or variant characteristics may result in reduced sensitivity. These include: subclonal alterations in heterogeneous samples; low

Clinical Performance

The StrataNGS test was developed and the performance characteristics determined by Strata Oncology. The test has neither been cleared nor approved by the U.S. Food and Drug Administration (FDA). The FDA has deemed that such clearance or approval is not necessary. Strata Oncology is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical laboratory testing. The Laboratory Director is Scott A. Tomlins, M.D., Ph.D.

StrataNGS Test Description

The StrataNGS test assays for specific predefined single nucleotide variants, multinucleotide variants, small insertions and deletions (indels), gene fusions, exon skipping mutations and copy number changes; the test also assays for de novo deleterious mutations (stop gains and frame shifting indels) in tumor suppressor genes. The StrataNGS test covers the majority of the coding sequence for the following tumor suppressor genes: ATM (95.0%), BRCA1 (99.3%), BRCA2 (97.9%), CDKN2A (91.1%), MSH2 (96.7%), MSH6 (99.0%), PTEN (89.0%), RB1 (93.8%), TP53 (98.7%); the specific regions not covered are available upon request. A negative result does not indicate that a gene is negative for any possible alteration, only the specific alterations assayed by the StrataNGS test. The limit of detection for predefined prioritized mutations is 5%; de novo deleterious mutations are indicated only when the variant allele frequency exceeds 15%. For gene fusions, only specific gene fusion partners are assayed for (e.g. EML4-ALK) so novel gene fusion partners will not be detected. For copy number events, the cellularity adjusted whole copy number estimate is thresholded at 6 copies and the 90% confidence interval lower bound is thresholded at 5 copies for calling amplifications in known oncogenes. The copy number estimate is thresholded at 0.5 copies and the 90% confidence interval upper bound is thresholded at 1 copy for calling deep deletions in known tumor suppressor genes. Estimated copy number and associated 90% confidence interval are reported for informational purposes only. MSI status is determined by thresholding an MSI score derived from length variant allele counts observed at several microsatellite loci; specimens with an MSI score greater than 0.5 are considered microsatellite instable (MSI-H). The test assays for genetic mutations in tumor tissue only and therefore does not distinguish between somatic and germline mutations. Estimated mutation variant allele frequencies are reported for informational purposes only. A complete list of all predefined genomic variants and transcript annotations is available upon request.

No Warranty or Guarantee of Clinical Benefit

This report does not make any promise or guarantee that a particular drug or clinical trial will be effective or helpful in the treatment of disease in any patient.

Treatment Decisions

The selection of any treatment or clinical trial suggested by a biomarker resides within the discretion and judgment of the treating physician and patient. When available, associated FDA-approved targeted therapies are listed in order of approval based on the cancer type selected by the physician when ordering the test; listed therapies may not be applicable to the patient's specific cancer histology, and may be approved only in conjunction with non-targeted therapies. Decisions on patient care should be based on the independent medical judgment of the treating physician based upon all available clinical information, according to the

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Reporting

Most reports are designed to provide evidence that every tested patient may benefit from the test.

Actionability is one of the most abused words in precision oncology/.

Providing treatment recommendations without a full history is nearly impossible.

Transparency in details is critical

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Comprehensive Molecular Profiling: Clinical Utility.

HER-2

November 5, 2019

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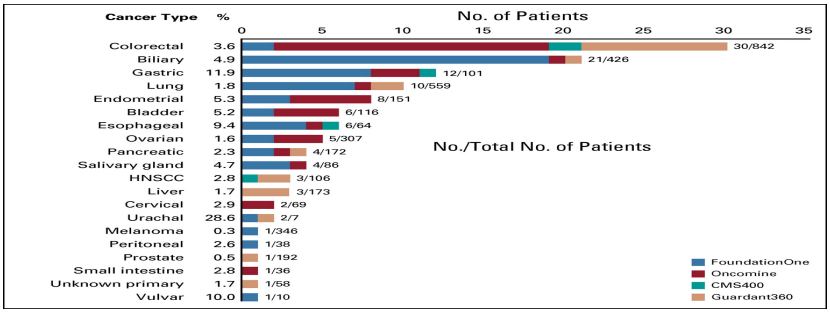
Comprehensive Molecular Profiling: Clinical Utility, Her-2 with Tissue Specificity

HER-2 — BREAST CA, GASTRIC/GE JN, COLON, NON SMALL CELL LUNG, SALIVARY GLAND.



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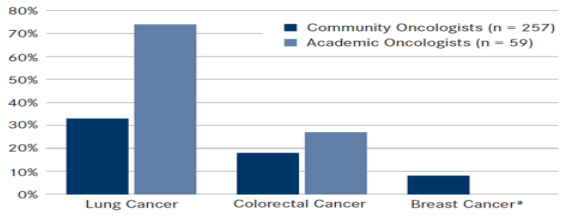
Comprehensive Molecular Profiling: Clinical Utility, Her-2 with Tissue Specificity

BREAST CANCER:

Most patients with newly diagnosed advanced/metastatic breast cancers are triaged on the basis of ER/PR, Her-2 status.

Until May 2019- No FDA-labelled indications based on somatic alterations in breast Ca.

Figure. Community Versus Academic Use of Molecular Profiling[5]



*None of the academic oncologists surveyed indicated use of molecular profiling for breast cancer.

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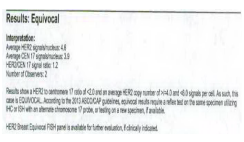
CASE 2.

37 yr. old female diagnosed with Invasive ductal multifocal Breast Ca, ER+, PR+, Her2 Equivocal by IHC and FISH, S/P MRM + ALND May 2016

After surgery treated with AC-TH followed by TAMOXIFEN.

Sacral Met July 2017. Biopsy confirmed. ER+, Her2 equivocal by IHC

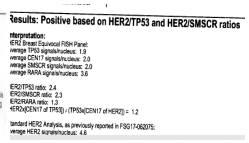
FISH Studies: X 2 :


Results: Equivocal

Interpretation:
Average HER2 signals/nucleus: 4.8
Average CEN 17 signals/nucleus: 2.0
HER2/CEN 17 signal ratio: 2.2
Number of Observers: 2

Results show a HER2 to centromere 17 ratio of <2.0 and an average HER2 copy number of >=4.0 and <6.0 signals per cell. As such, this case is EQUIVOCAL. According to the 2013 ASCO/CAP guidelines, equivocal results require a reflex test on the same specimen utilizing IHC or FISH with an alternate chromosome 17 probe, or testing on a new specimen, if available.

*HER2 Breast Equivocal FISH panel is available for further evaluation, if clinically indicated.


Results: Positive based on HER2/TP53 and HER2/SMSCR ratios

Interpretation:
IDENT Breast Equivocal FISH Panel:
average TP53 signals/nucleus: 1.9
average CEN17 signals/nucleus: 2.0
average SMSCR signals/nucleus: 2.0
average RARA signals/nucleus: 3.6

ER2/TP53 ratio: 2.4
ER2/SMSCR ratio: 2.3
ER2/RARA ratio: 1.3
HER2x2/(CEN17 of TP53) - (TP53x2/CEN17 of HER2) = 1.2

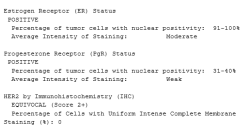
Standard HER2 Analysis, as previously reported in FISG17-002075:
average HER2 signals/nucleus: 4.8

Oophorectomy Nov 2017 + Palliative XRT

Palbociclib + Fulvestrant Dec 2017

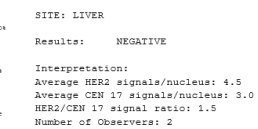
August 2018: Liver Lesion.

FNA consistent with **Met ductal breast Ca**.


Estrogen Receptor (ER) Status
POSITIVE
Percentage of tumor cells with nuclear positivity: 91-100%
Average Intensity of Staining: Moderate

Progesterone Receptor (PgR) Status
POSITIVE
Percentage of tumor cells with nuclear positivity: 31-60%
Average Intensity of Staining: Weak

HER2 by Immunohistochemistry (IHC)
EQUIVOCAL (Score 2+)
Percentage of Cells with Uniform Intense Complete Membrane Staining (%): 0


SITE: LIVER

Results: NEGATIVE

Interpretation:
Average HER2 signals/nucleus: 4.5
Average CEN 17 signals/nucleus: 3.0
HER2/CEN 17 signal ratio: 1.5
Number of Observers: 2

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NGS TEST RESULTS

Positive Test Results

The patient tested positive for the following genomic alteration(s):

- ERBB2 amplification
  Estimated copy number: 6, confidence interval: 5.7 - 7.1
  Associated FDA-approved targeted therapies in breast cancer: trastuzumab, lapatinib, ado-trastuzumab emtansine, pertuzumab, neratinib
- ESR1 p.Y537S
  NM_001122740.1:c.1610A>C
  Estimated variant allele frequency: 47%
- FGFR3 amplification
  Estimated copy number: 7, confidence interval: 5.3 - 8.7

Negative Test Results

The patient tested negative for all targeted genomic alterations in the following genes:

Hotspot mutation: AKT1, ALK, AR, ARAF, BRAF, CDK4, CTNNB1, EGFR, ERBB2, ERBB3, ERBB4, EZH2, FGFR2, FGFR3, GNA11, GNAQ, HRAS, IDH1, IDH2, JAK1, JAK2, JAK3, KIT, KRAS, MAP2K1, MAP2K2, MAP2K4, MAP2K7, MAPK1, MET, MTOR, MYD88, NRAS, NTRK1, PDGFRA, PIK3CA, POLE, RAF1, RET, RIT1, ROS1, SF3B1, SMO, SPOP, TERT

Hotspot mutation or deleterious mutation: ATM, BRCA1, BRCA2, CDKN2A, MSH2, MSH6, PTEN, RB1, TP53

Gene amplification: ALK, AR, BRAF, CCND1, CDK4, CDK6, EGFR, ESR1, FGFR1, FGFR2, FGFR4, IGF1R, KIT, KRAS, MDM2, MET, MYC, MYCN, PDGFRA, PIK3CA

Deep gene deletion: ATM, BRCA1, BRCA2, CDKN2A, MSH2, MSH6, PTEN, RB1, TP53

Gene fusion: AKT2, ALK, AR, AXL, BRAF, EGFR, ERBB2, ERBB4, ERG, ESR1, ETV1, ETV4, ETV5, FGFR1, FGFR2, FGFR3, FGR, FLT3, JAK2, KRAS, MET, MYB, MYBL1, NF1, NOTCH1, NOTCH4, NRG1, NTRK1, NTRK2, NTRK3, NUTM1, PDGFRA, PDGFRB, PIK3CA, PPARG, PRKACA, PRKACB, PTEN, RAD51B, RAF1, RELA, RET, ROS1, RSPO2, RSPO3, TERT

The patient tested negative for microsatellite instability.

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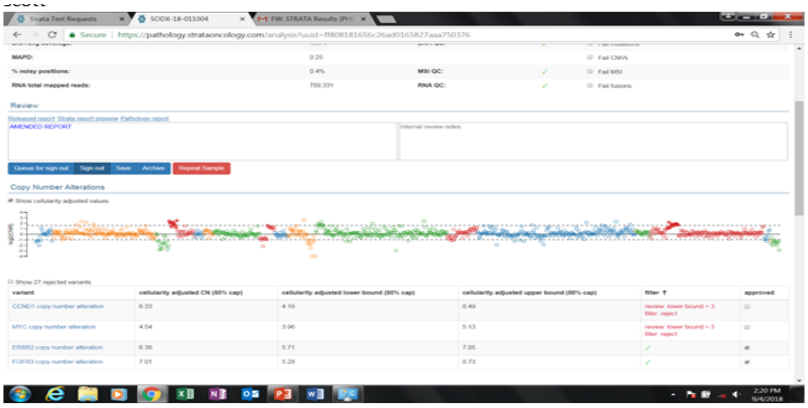
Is the ERBB2 a TRUE POSITIVE?

Yes. ERBB2 is the gene in solid red bubbles right above the up arrow in the filter column (towards the right).



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Clinical Trial Recommendation.

FGFR amplification (1.86% frequency) Drug: erdafitinib Exceptions: transitional cell carcinoma of the bladder and/or urothelial tract	K1	35 (31)	06/20/2018
FGFR mutations or fusions (1.00% frequency) Drug: erdafitinib Exceptions: transitional cell carcinoma of the bladder and/or urothelial tract	K2	35 (11)	06/20/2018

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HER-2

COLORECTAL CA

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Comprehensive Molecular Profiling: Clinical Utility, Her-2 with Tissue Specificity: Colon CA.

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NCCN Guidelines Version 3.2019
Colon Cancer

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SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE - CHEMOTHERAPY REGIMENS

Trastuzumab[§] + pertuzumab[33] (HER2-amplified and RAS WT)
Trastuzumab 8mg/kg IV loading dose on Day 1 of Cycle 1, then 6mg/kg IV every 21 days
Pertuzumab 840mg IV loading dose on Day 1 of Cycle 1, then 420mg IV every 21 days

Trastuzumab[§] + lapatinib[34] (HER2-amplified and RAS WT)
Trastuzumab 4mg/kg IV loading dose on Day 1 of Cycle 1, then 2mg/kg IV weekly
Lapatinib 1000mg PO daily

Irinotecan + cetuximab + vemurafenib[35]
(*BRAF* V600E mutation positive)
Irinotecan 180 mg/m² IV every 2 weeks
Cetuximab 500 mg/m² IV every 2 weeks
Vemurafenib 960 mg PO twice daily

Irinotecan + panitumumab + vemurafenib[35]
(*BRAF* V600E mutation positive)
Irinotecan 180 mg/m² IV every 2 weeks
Panitumumab 6 mg/kg IV over 60 minutes every 2 weeks
Vemurafenib 960 mg PO twice daily

Dabrafenib + trametinib + cetuximab[36]
(*BRAF* V600E mutation positive)
Dabrafenib 150 mg PO twice daily
Trametinib 2 mg PO daily
Cetuximab 400 mg/m² followed by 250 mg/m² weekly

Dabrafenib + trametinib + panitumumab[36]
(*BRAF* V600E mutation positive)
Dabrafenib 150 mg PO twice daily
Trametinib 2 mg PO daily
Panitumumab 6 mg/kg IV every 14 days

Encorafenib + binimetinib + cetuximab[37,38]
(*BRAF* V600E mutation positive)
Encorafenib 300 mg PO daily
Binimetinib 45 mg PO twice daily
Cetuximab 400 mg/m² followed by 250 mg/m² weekly

Encorafenib + binimetinib + panitumumab[37,38]
(*BRAF* V600E mutation positive)
Encorafenib 300 mg PO daily
Binimetinib 45 mg PO twice daily
Panitumumab 6 mg/kg IV every 14 days

Larotrectinib[39]
(*NTRK* gene fusion positive)
100 mg PO twice daily

Entrectinib[40]
(*NTRK* gene fusion positive)
600 mg PO once daily

[§] An FDA-approved biosimilar is an appropriate substitute for trastuzumab.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

References

COL-D
11 OF 13

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Comprehensive Molecular Profiling: Clinical Utility, Her-2 with Tissue Specificity: Stomach, Salivary,

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NCCN Guidelines Version 2.2019
Gastric Cancer

NCCN Guidelines Index
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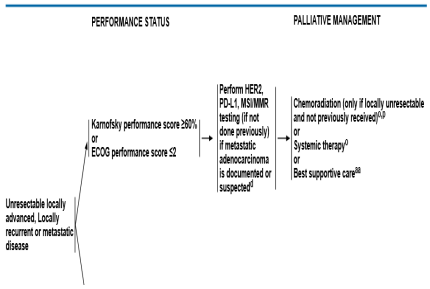

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NCCN Guidelines Version 3.2019
Salivary Gland Tumors

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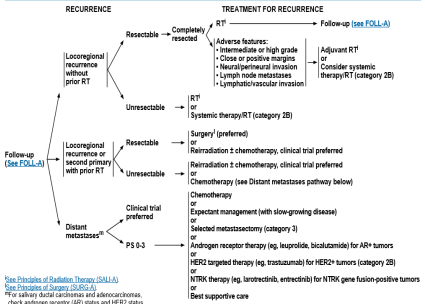

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Comprehensive Molecular Profiling: Clinical Utility, Her-2 with Tissue Specificity-

IT DEPENDS ON THE TISSUE…

The role of NGS/Comprehensive molecular profiling for a patient with newly diagnosed metastatic breast is CA and perhaps gastric /GE Jn is limited.

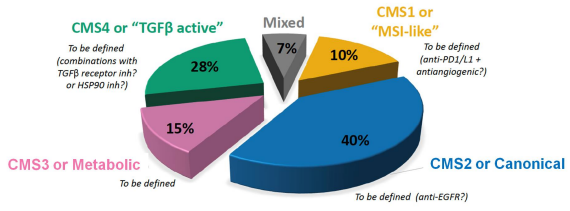
NGS has utility in 2nd line setting for metastatic breast CA

Comprehensive molecular profiling to screen for HER-2 amplification in RAS WT metastatic Colon Ca should be considered.

Testing can identify highly actionable alterations other than HER-2 amplification; BRAF V600E, NTRK and MSI

COLON CANCER MOLECULAR PROFILE

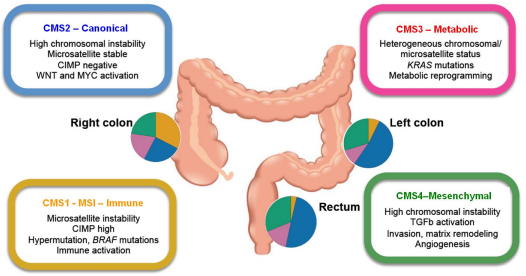
Consensus Molecular Subtype (CMS) groups



Modified from Guinney J, Dienstmann R et al. Nat Med 2015

Presented By Josep Tabernero at 2018 ASCO Annual Meeting

CMS subtypes – clinical and molecular correlates



Guinney J, Dienstmann R et al. Nat Med 2015

Presented By Josep Tabernero at 2018 ASCO Annual Meeting

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Comprehensive Molecular Profiling: Clinical Utility.

KRAS

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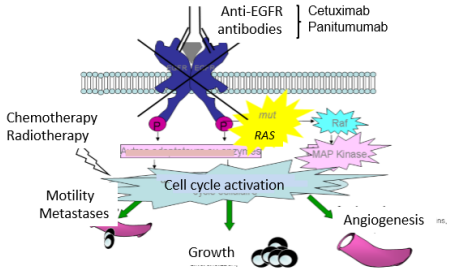
Comprehensive Molecular Profiling: Clinical Utility, KRAS with Tissue Specificity- COLON

Anti-EGFR targeted therapies

RAS mutations = marker of resistance



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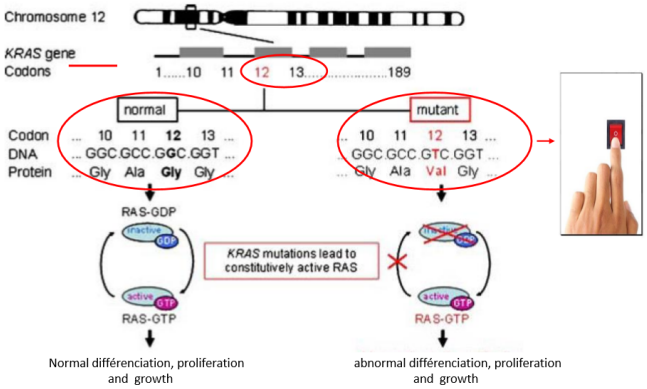
Comprehensive Molecular Profiling: Clinical Utility, KRAS with Tissue Specificity- COLON

Résistance: mutations *KRAS*



Adapté de Van Krieken et al. Virchows 2008;453:417-431

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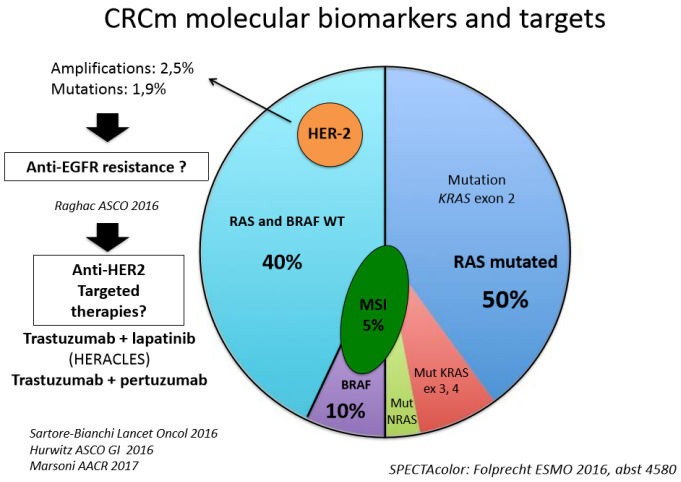
Comprehensive Molecular Profiling: Clinical Utility, KRAS with Tissue Specificity- COLON



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Comprehensive Molecular Profiling: Clinical Utility, KRAS with Tissue Specificity- COLON

KRAS testing in colon ca can be performed using single gene test.

In clinical practice MSI status is usually available via standard IHC methods

However, abnormal *HER2* gene function is found in 3% of mCRC cases;

Amplifications and mutations occur in approximately 6% to 8% of *RAS/RAF* wild-type CRC

The category, in turn, accounts for about 50% of the tumor type.

Comprehensive Molecular profiling has clinical utility for KRAS status as it can provide additional information : ERBB2 amplification, activating mutations and MSI status.

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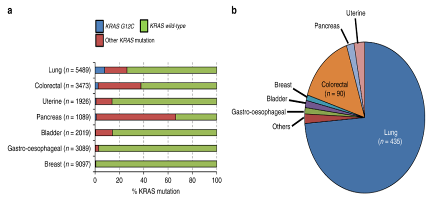
Comprehensive Molecular Profiling: Clinical Utility, KRAS with Tissue Specificity- NSCLC

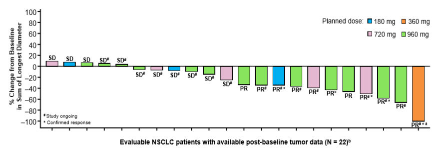


KRAS G12C mutation in cancer. **a** Proportions of G12C and non-G12C KRAS mutations in seven cancers with the most KRAS G12C cases. **b** Percentage contribution of each cancer type to KRAS G12C cancer

Phase 1 Study of AMG 510, a Novel KRAS[G12C] Inhibitor, in Advanced Solid Tumors With *KRAS p. G12C* Mutation: ESMO 2019

EFFICACY IN NSCLC

Change in Tumor Burden From Baseline



[a]Patient had complete response to the target lesion; [b]1 patient discontinued study due to PD prior to the 1st assessment without available post-baseline tumor burden data, and therefore is not shown on the graph. Evaluable patients: patients who have been followed up for at least 6 weeks; NSCLC = non-small-cell lung cancer; PD = progressive disease; PR = partial response; SD = stable disease

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Comprehensive Molecular Profiling: Clinical Utility.

NGS

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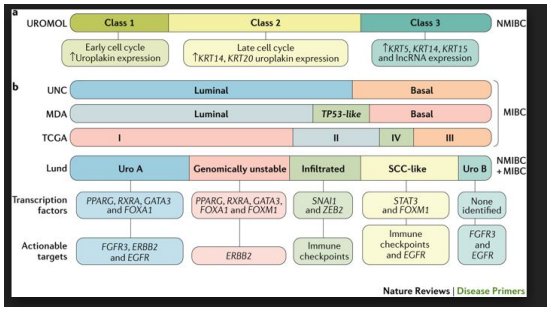
Bladder Cancer Molecular Profile



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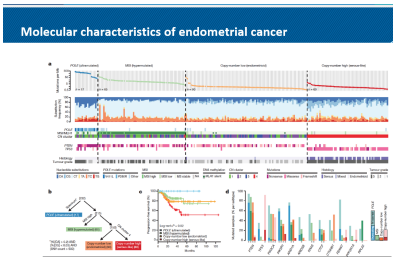
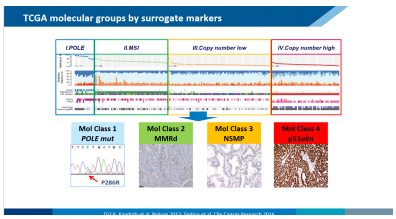
TGGA . Kandoth et al; Nature 2013





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Comprehensive Molecular Profiling: Clinical Utility- EGFR, ALK, KRAS, Her-2 with Tissue Specificity

CONCLUSIONS:

Utilization of a single test Comprehensive Molecular Profiling for EGFR, ALK, KRAS, HER-2 and other alterations in NSCLC is efficient and should be widely adopted in routine practice.

Comprehensive Molecular profiling in advanced breast cancer currently is most useful for enrolling patients to clinical trials

It is appropriate to utilize NGS testing for identification of therapeutic targets in advanced colorectal ca; however, additional test such as IHC/FISH for HER-2 amplification /expression may be needed.

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THANK YOU

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Precision Oncology Symposium

Biomarkers with Cross-Disease Relevance

Philip C. Mack, PhD

NOTES

Novel and Emerging targets: NTRK, FGFR, and beyond

Sai-Hong Ignatius Ou, MD PhD

ANCO-UCSF Precision Oncology Symposium

November 8, 2019

Health Science Clinical Professor
Chao Family Comprehensive Cancer Center
University of California Irvine School of Medicine
Orange, CA92868, USA

siou@uci.edu

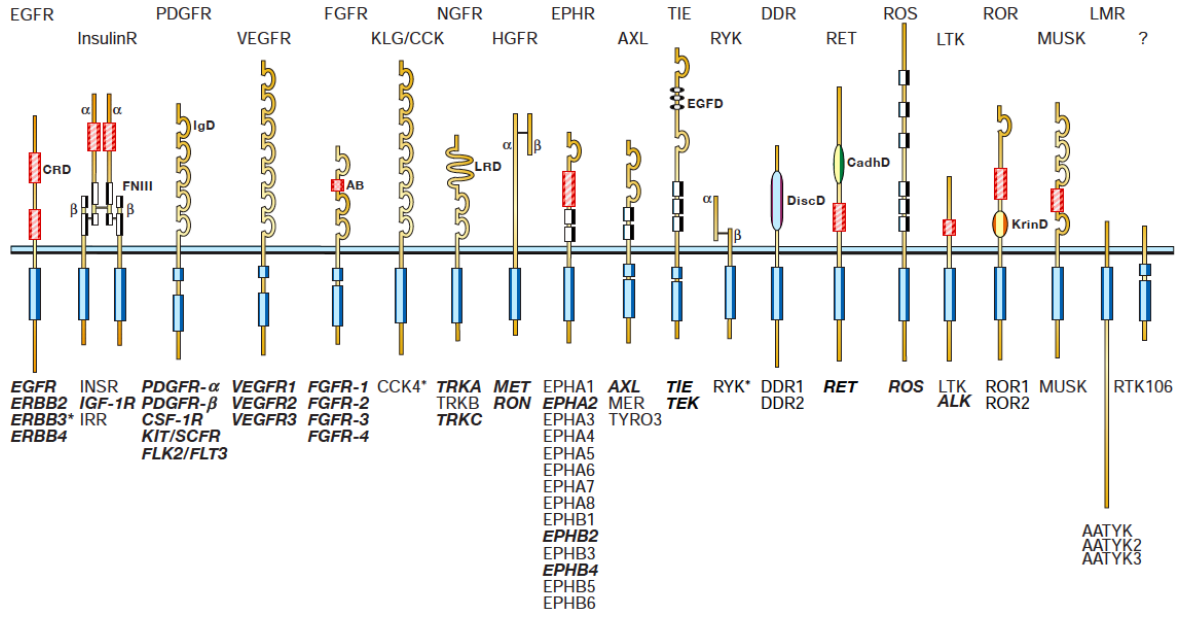
1

Disclosure

Stock Ownership	Turning Point Therapeutics (TPTX)
Scientific Advisory Board	Turning Point Therapeutics (former), AnHeart Therapeutics
Speaker Bureau	Pfizer, Astra Zeneca, Roche/Genentech, Takeda/ARIAD, Merck
Consultant	Pfizer, Roche/Genentech, Astra Zeneca, Takeda/ARIAD

2

Human Receptor Tyrosine Kinases (N = 58, divided into 20 sub-families)



Blume-Jensen P, Hunter T. *Nature* 2001: 411: 355-365

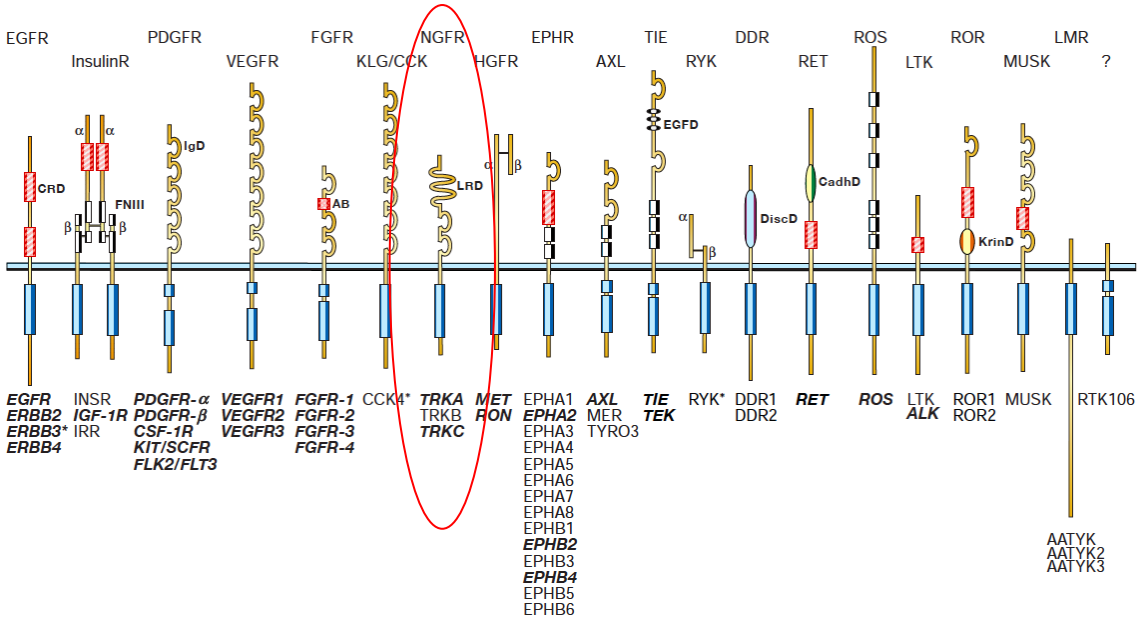
3

Approved drugs

- NTRK1-3 (TRK A-C) (RTK fusion)
  - Entrectinib, Larotrectinib
- FGFR (RTK fusion and RTK mutations)
  - FGFR fusion (FGFR2, FGFR3)
  - FGFR mutations
- NRG1 fusion (ligand fusion)
  - None

4

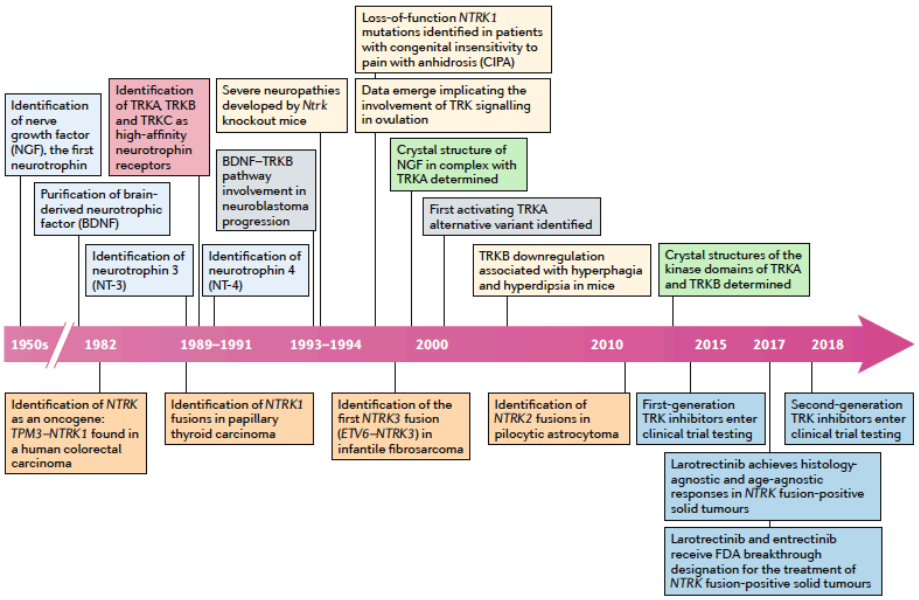
Human Receptor Tyrosine Kinases (N = 58)



Blume-Jensen P, Hunter T. *Nature* 2001: 411: 355-365

5

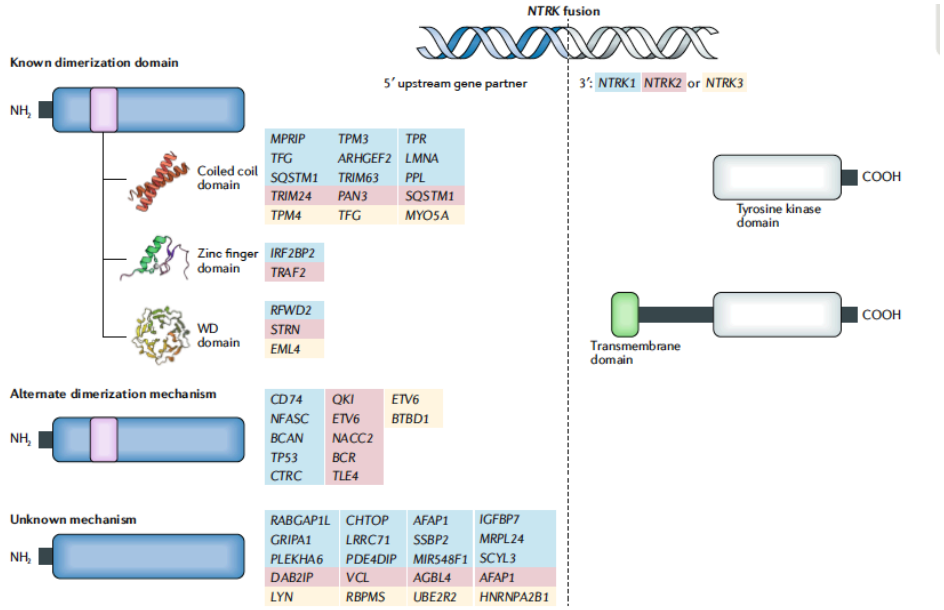
TNRK fusions were discovered years ago and only in recent years been "recognized" as a therapeutic target



Cocco, Nat Rev Clin Oncol 2018; 15: 731-747

6

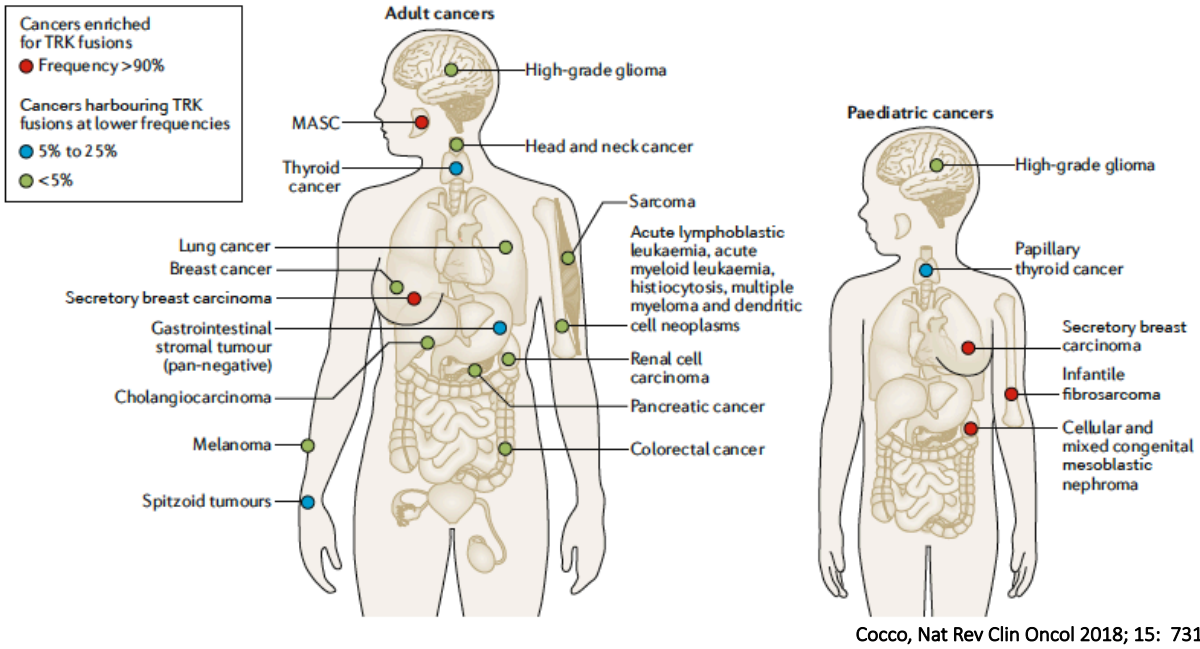
NTRK fusions involve multiple partners



Cocco, Nat Rev Clin Oncol 2018; 15: 731-747

7

NTRK fusions are oncogenic in multiple organs in adult and pediatric population



Cocco, Nat Rev Clin Oncol 2018; 15: 731-747

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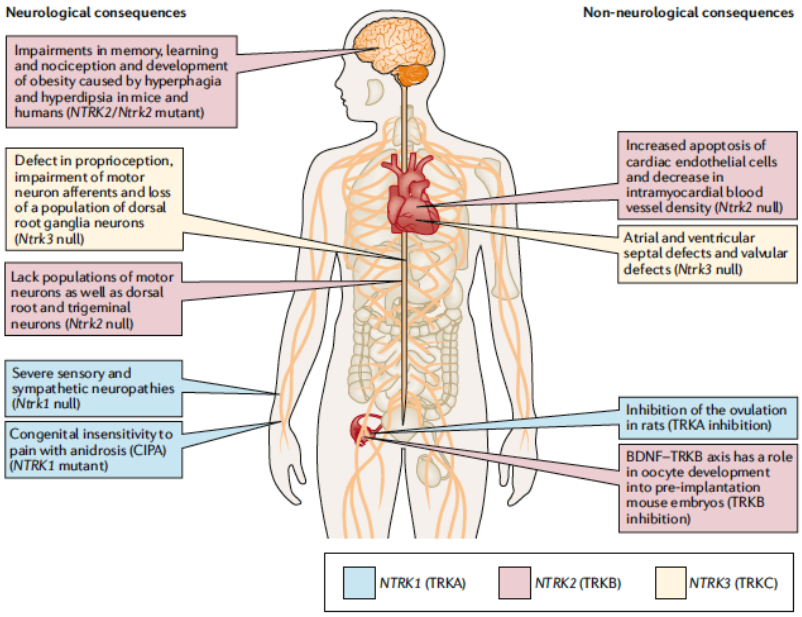
NTRK bloackade have a diverse and unique side effects



Cocco, Nat Rev Clin Oncol 2018; 15: 731-747

9

Two TRK TKIs have been approved by the FDA

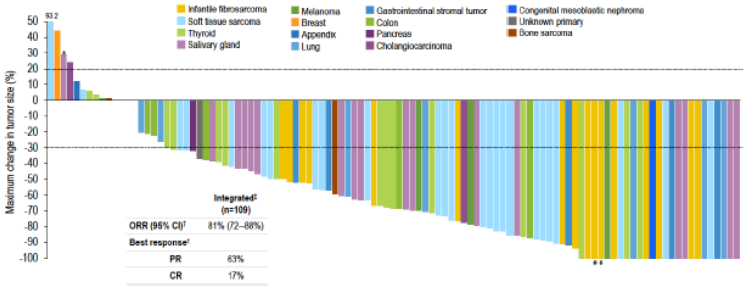
Larotrectinib

ORR 81%

(95% CI 72–88%, n=109)

Median DoR not reached

Median PFS not reached



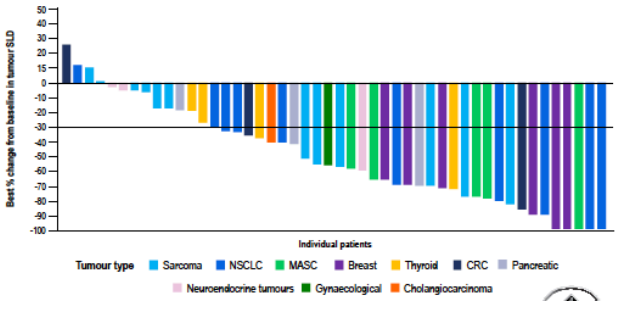
Entrectinib

ORR 57%

(95% CI 43–71%, n=54)

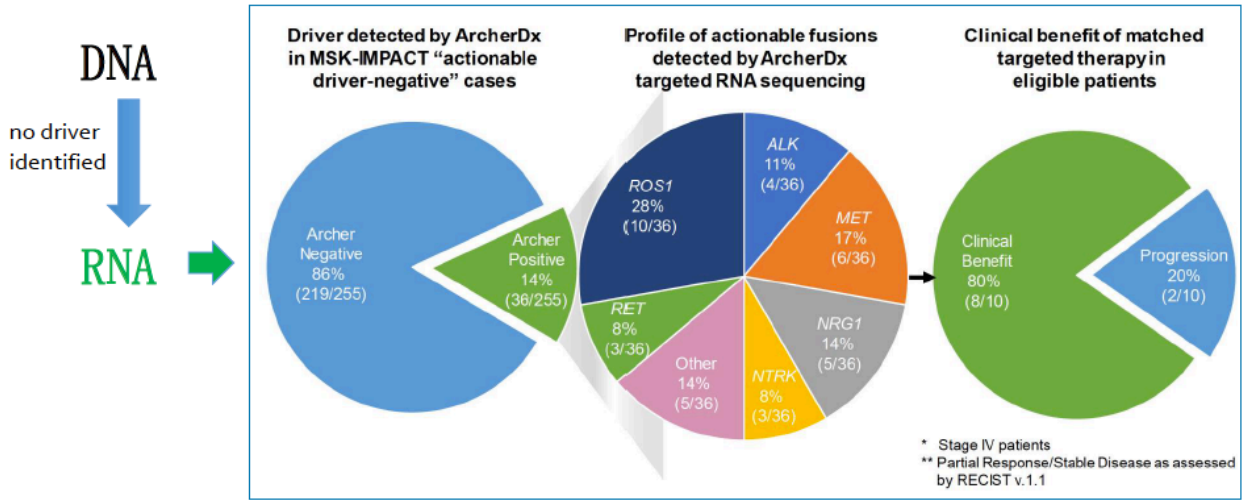
Median DoR 10 mos

Median PFS 11 mos



10

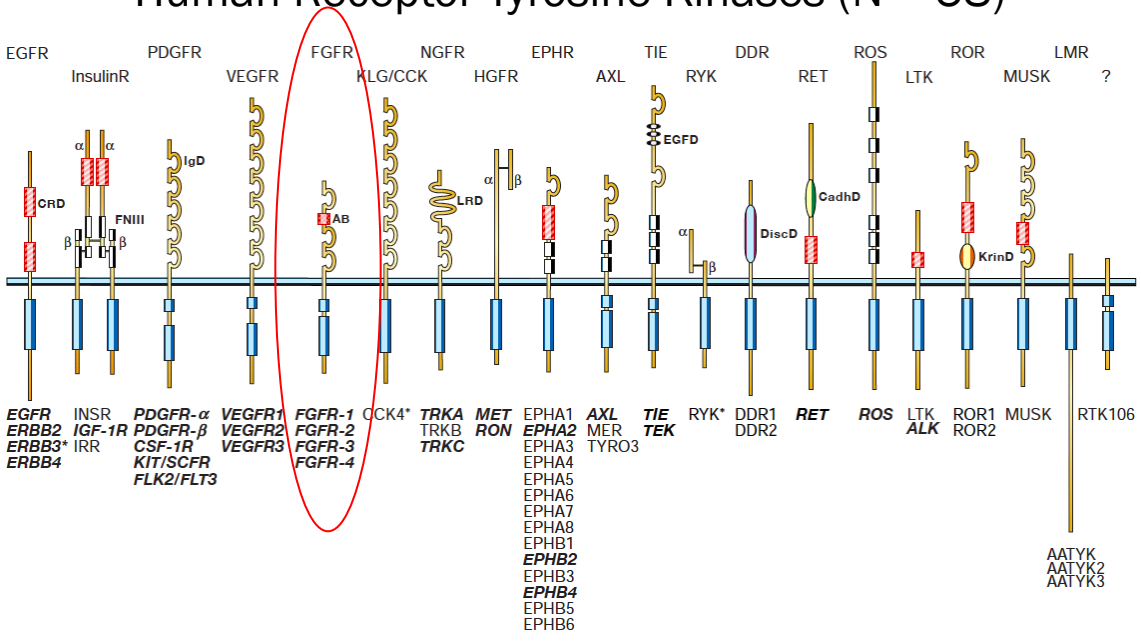
RNA sequencing increases the detection rate of actionable driver mutations especially RTK and Ligand fusions



Benayed et al, CCR 2019

11

Human Receptor Tyrosine Kinases (N = 58)



Blume-Jensen P, Hunter T. *Nature* 2001: 411: 355-365

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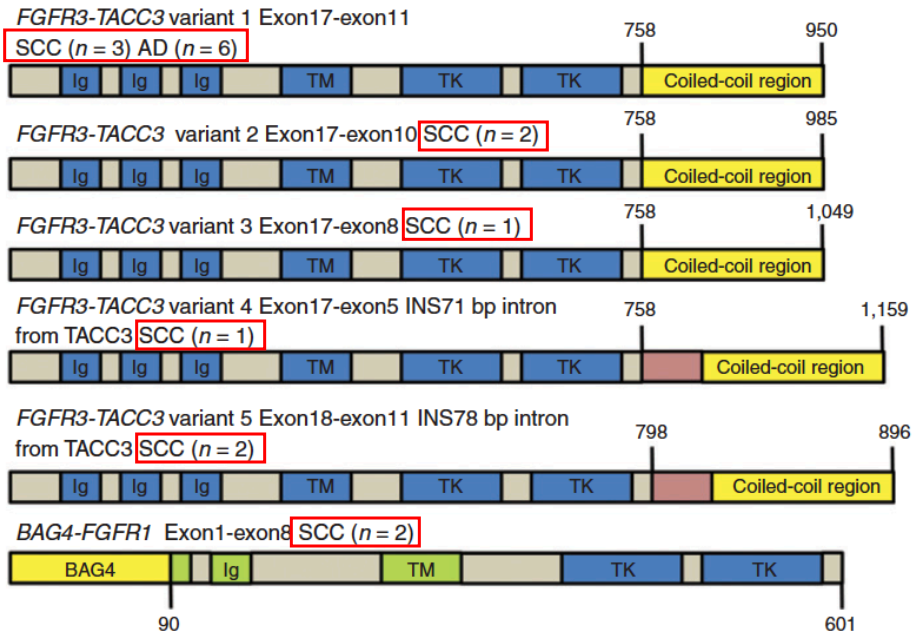
FGFR fusions in NSCLC



Wang et al, Clin Cancer Res 2014; 20; 4107-4114

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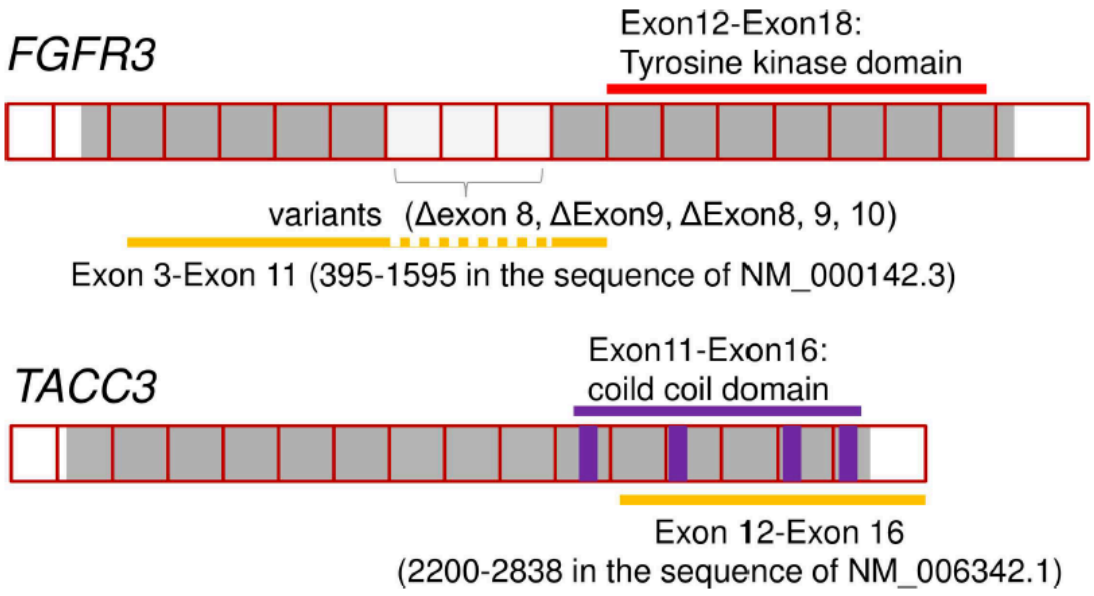
FGFR3 and TACC 3 exons



Kurobe et al, *PLosOne* 2016;11(12):e0165109

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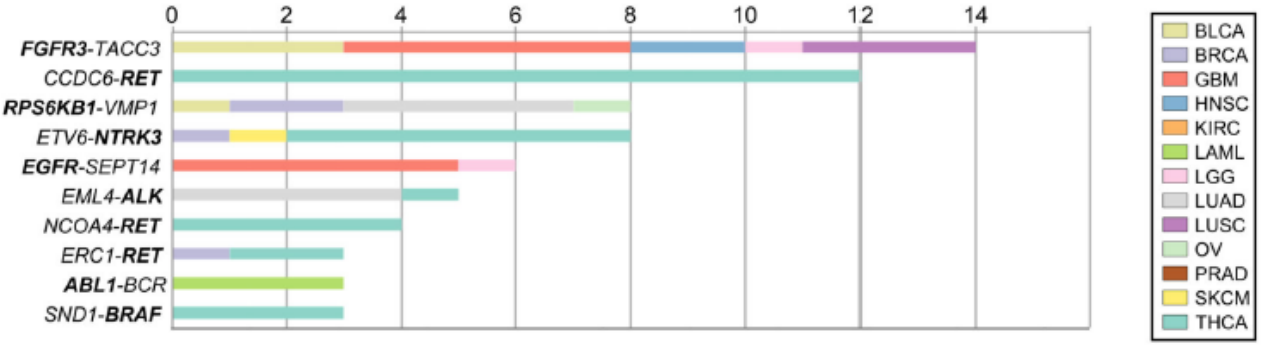
FGFR3-TACC3 is one of the most common RTK fusion variant in solid tumors



Yoshihara et al, *Oncogene* 2015;10: 4845-4854

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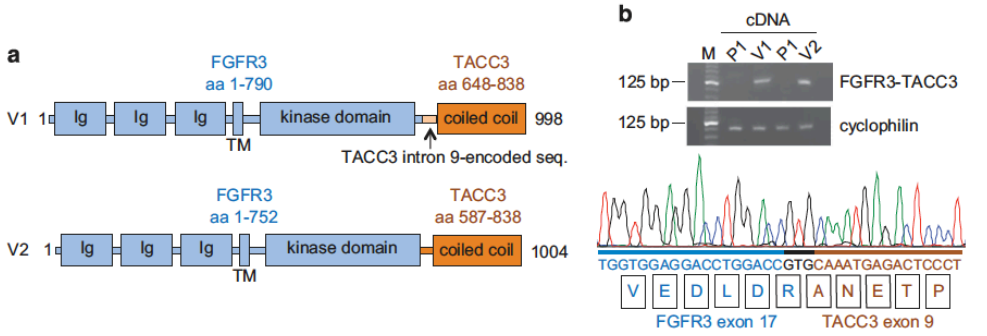
ORIGINAL ARTICLE

FGFR3-TACC3 fusion proteins act as naturally occurring drivers of tumor resistance by functionally substituting for EGFR/ERK signaling

C Daly, C Castanaro, W Zhang, Q Zhang[1], Y Wei, M Ni, TM Young, L Zhang, E Burova and G Thurston

Oncogene (2017) **36**, 471–481

www.nature.com/onc



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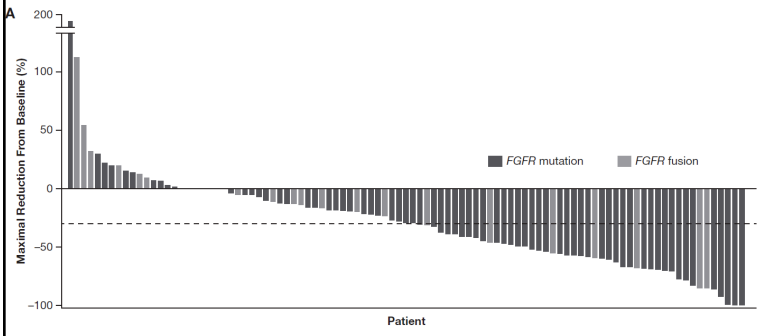
The NEW ENGLAND JOURNAL of MEDICINE

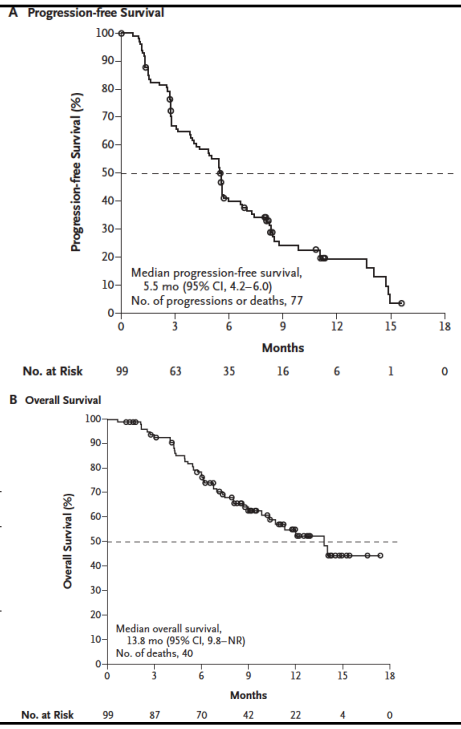
ORIGINAL ARTICLE

Erdafitinib in Locally Advanced or Metastatic Urothelial Carcinoma

Y. Loriot, A. Necchi, S.H. Park, J. Garcia-Donas, R. Huddart, E. Burgess, M. Fleming, A. Rezazadeh, B. Mellado, S. Varlamov, M. Joshi, I. Duran, S.T. Tagawa, Y. Zakharia, B. Zhong, K. Stuyckens, A. Santiago-Walker, P. De Porre, A. O'Hagan, A. Avadhani, and A.O. Siefker-Radtke, for the BLC2001 Study Group*

NEJM2019; 381: 338-348





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Trends in Cancer

CellPress REVIEWS

Review

Receptor Tyrosine Kinase Fusions as an Actionable Resistance Mechanism to EGFR TKIs in *EGFR*-Mutant Non-Small-Cell Lung Cancer

Viola W. Zhu,[1] Samuel J. Klempner,[2] and Sai-Hong Ignatius Ou[1,*]

Tumor resistance to EGFR tyrosine kinase inhibitors (TKIs) occurs invariably, and receptor tyrosine kinase (RTK) fusions have emerged as rare but actionable resistance mechanisms. In 2015, the detection of RTK fusions as acquired resistance (AR) in two cases was first reported. Subsequently, a survey of *FGFR3-TACC3* fusion and other RTK fusions from a large commercial genomic sequencing company database was published, followed by large-scale clinical trials of EGFR TKIs demonstrating the emergence of RTK fusions in AR. However, detailed examination of the AR RTK fusion landscape in non-small-cell lung cancer is lacking. Hence, we conducted a comprehensive review to categorize these fusion events by the generation of EGFR TKIs, the specific RTK fusions and their fusion partners, the founder *EGFR* mutations, and their methods of detection. To support the actionability and clinical significance of AR RTK fusions we present all available data demonstrating clinical benefit of concurrent dual blockade of the AR RTK fusion and the original *EGFR* mutation.

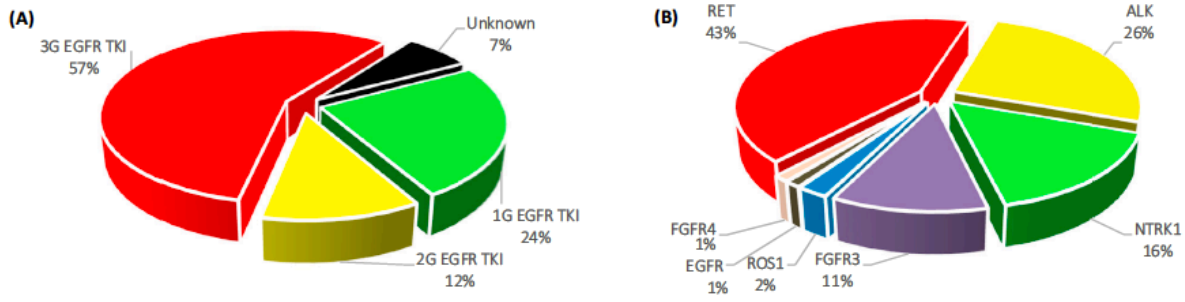
Highlights

A total of 86 AR RTK fusions have been identified from a literature review. These represent an emerging and validated mechanism of resistance against all three generations of EGFR TKIs.

The most common AR RTK fusions involve *RET* (43%), *ALK* (26%), *NTKR1* (16%), and *FGFR3* (11%).

Although *KIF5B–RET* fusion is the

Zhu, Klempner, Ou
Trends in Cancer 2019 online now



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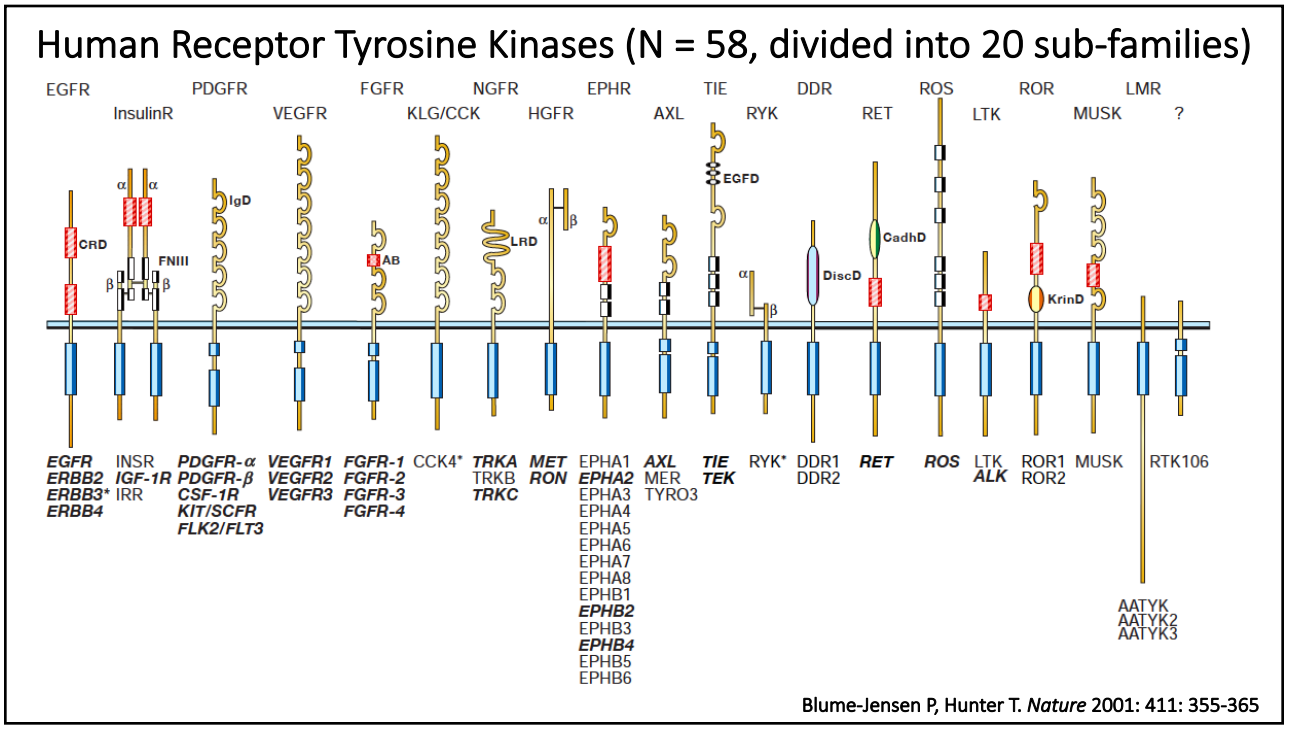
Human Receptor Tyrosine Kinases (N = 58, divided into 20 sub-families)
EGFR
InsulinR
PDGFR
VEGFR
FGFR
KLG/CCK
NGFR
HGFR
EPHR
AXL
TIE
RYK
DDR
RET
ROS
LTK
ROR
MUSK
LMR
?
CRD
FNIII
IgD
AB
LRD
EGFD
DiscD
CadhD
KrinD
EGFR ERBB2 ERBB3* ERBB4
INSR IGF-1R IRR
PDGFR-α PDGFR-β CSF-1R KIT/SCFR FLK2/FLT3
VEGFR1 VEGFR2 VEGFR3
FGFR-1 FGFR-2 FGFR-3 FGFR-4
CCK4*
TRKA TRKB TRKC
MET RON
EPHA1 EPHA2 EPHA3 EPHA4 EPHA5 EPHA6 EPHA7 EPHA8 EPHB1 EPHB2 EPHB3 EPHB4 EPHB5 EPHB6
AXL MER TYRO3
TIE TEK
RYK*
DDR1 DDR2
RET
ROS
LTK ALK
ROR1 ROR2
MUSK
RTK106
AATYK AATYK2 AATYK3
Blume-Jensen P, Hunter T. Nature 2001: 411: 355-365

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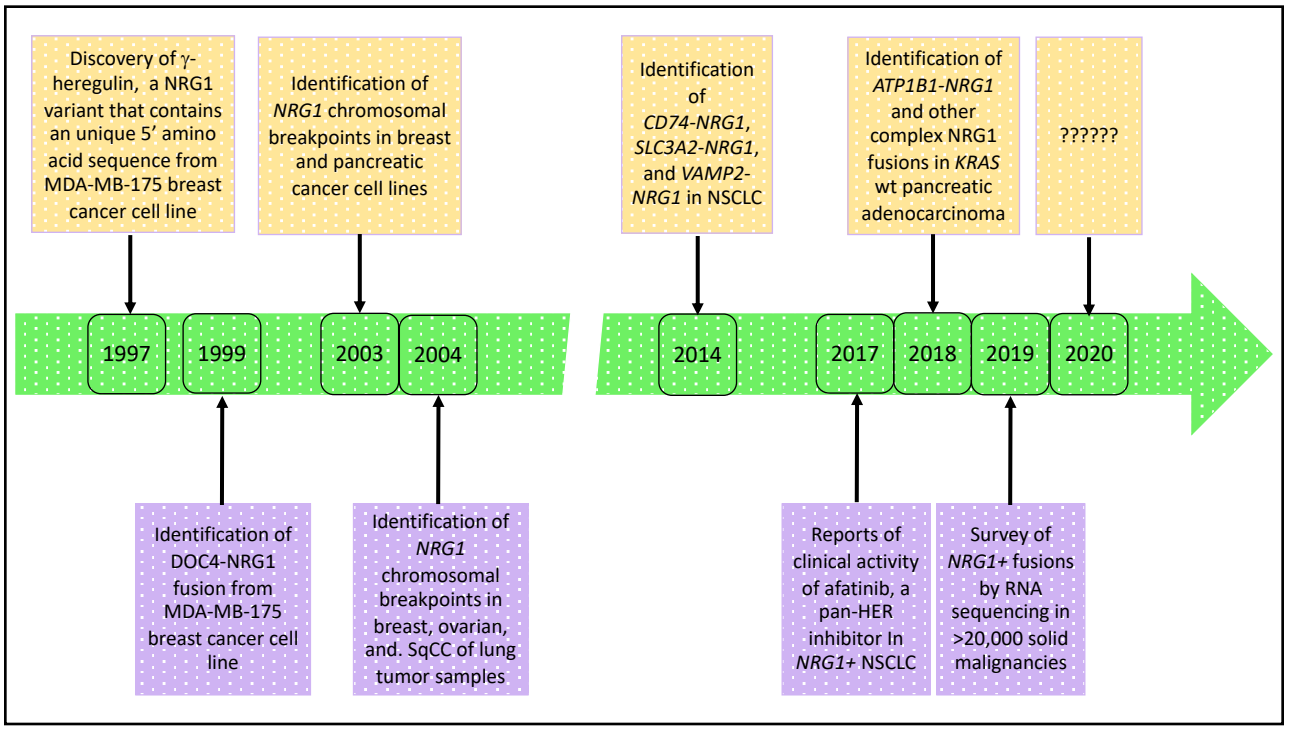
Discovery of γ-heregulin, a NRG1 variant that contains an unique 5' amino acid sequence from MDA-MB-175 breast cancer cell line
Identification of NRG1 chromosomal breakpoints in breast and pancreatic cancer cell lines
Identification of CD74-NRG1, SLC3A2-NRG1, and VAMP2-NRG1 in NSCLC
Identification of ATP1B1-NRG1 and other complex NRG1 fusions in KRAS wt pancreatic adenocarcinoma
??????
1997
1999
2003
2004
2014
2017
2018
2019
2020
Identification of DOC4-NRG1 fusion from MDA-MB-175 breast cancer cell line
Identification of NRG1 chromosomal breakpoints in breast, ovarian, and. SqCC of lung tumor samples
Reports of clinical activity of afatinib, a pan-HER inhibitor In NRG1+ NSCLC
Survey of NRG1+ fusions by RNA sequencing in >20,000 solid malignancies

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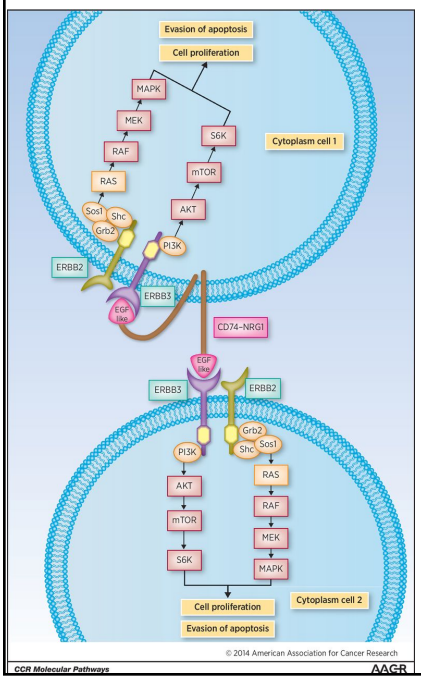
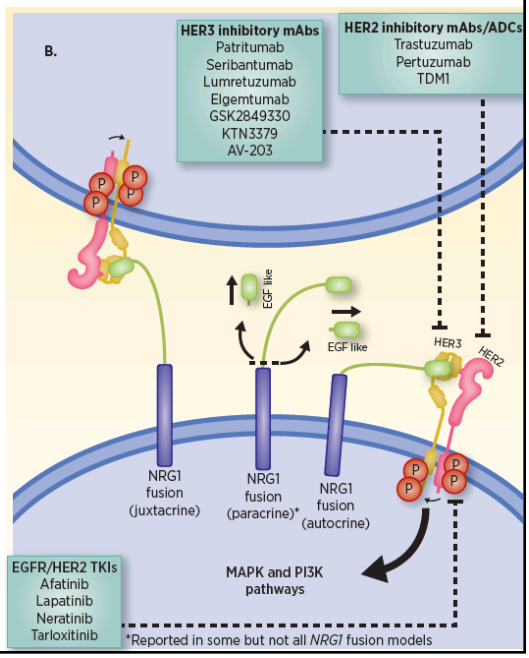
Neuregulin-1 (NRG1) Fusion



Fernandez-Cuesta & Thomas
Clin Cancer Res 2015; 21: 1989-1994



Dimou & Camidge 2019 CCR

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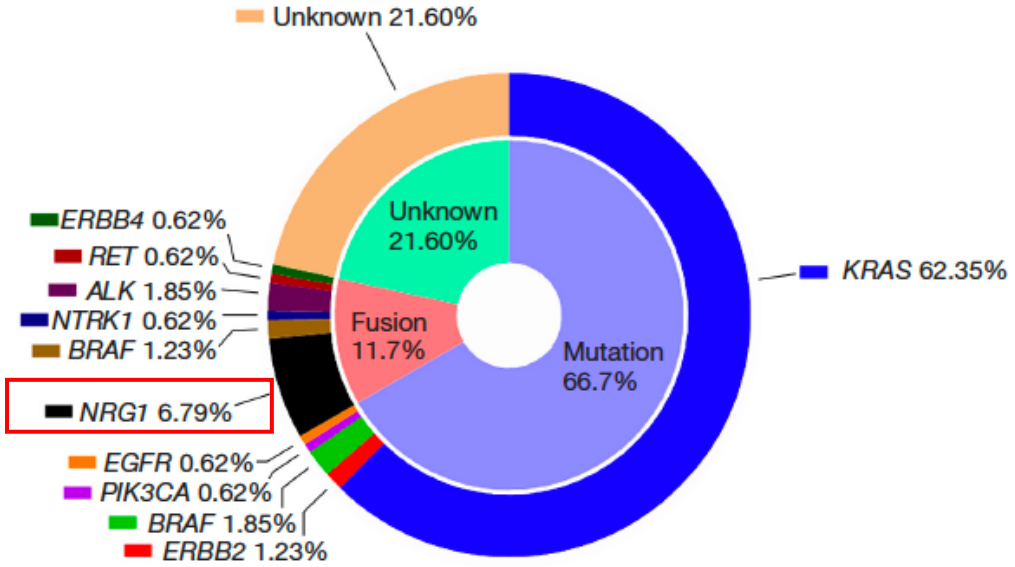
NRG1 fusions constitutes a minority of Invasive Mucinous Adenocarcinoma (IMA) (N = 162)



Cha & Shim, TLCR 2017; 6: 508-512

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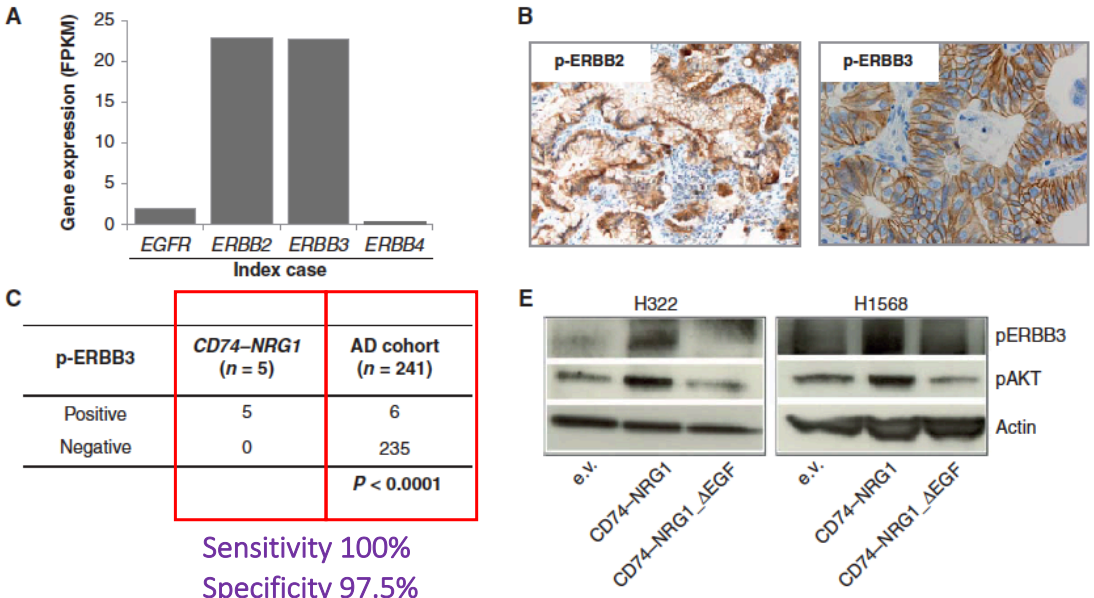
Potential using p-HER3 IHC as a screening strategy



p-ERBB3	*CD74–NRG1* (*n* = 5)	AD cohort (*n* = 241)
Positive	5	6
Negative	0	235
		P < 0.0001

Sensitivity 100%
Specificity 97.5%

Fernandez-Cuesta et al, Cancer Dis 2014; 4: 415-422

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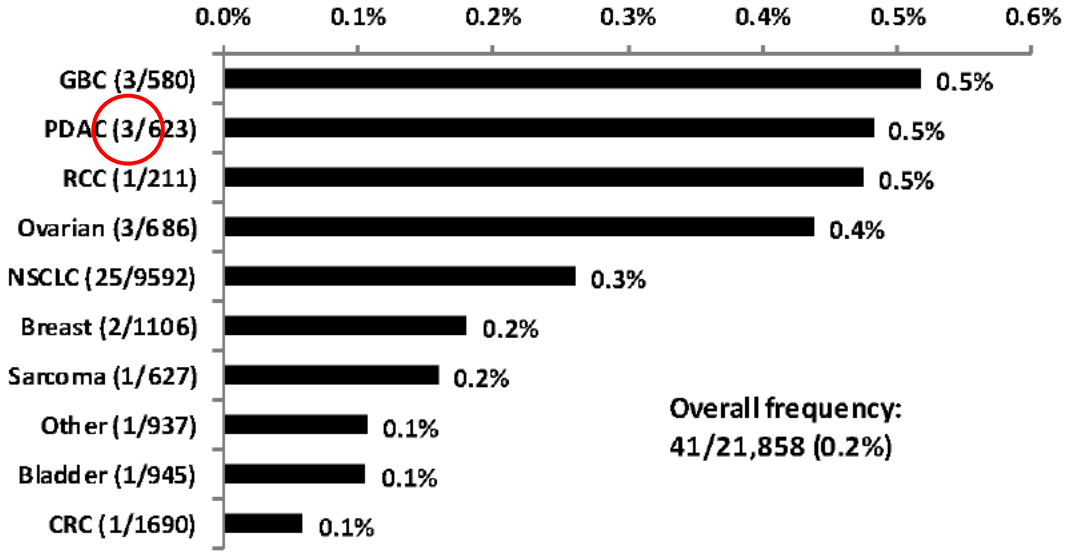
Frequency of NRG1 fusions in solid malignancies



Jonna et al, *Clin Cancer Res* 2019; 25: 4966-4972

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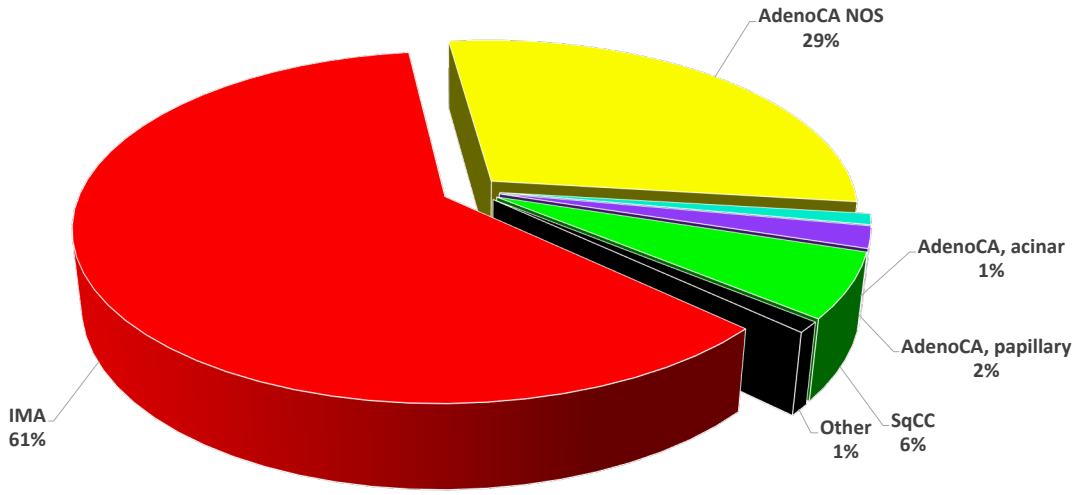
Distribution of histology of NRG1+ NSCLC



Nagasaka & Ou *J Thorac Oncol* 2019;14: 1354-1359

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NRG1 gene has many splice forms

- Type I-III (major)
- Type IV-VI (minor)
- EGF motif is located immediate 5' of the TMD of NRG1, and is proteolytically cleaved after the full-length neuregulin protein is translated
- EGF motif is located at exon 6
- NRG1 fusion is more complicated in Pancreatic Adenocarcinoma than in NSCLC

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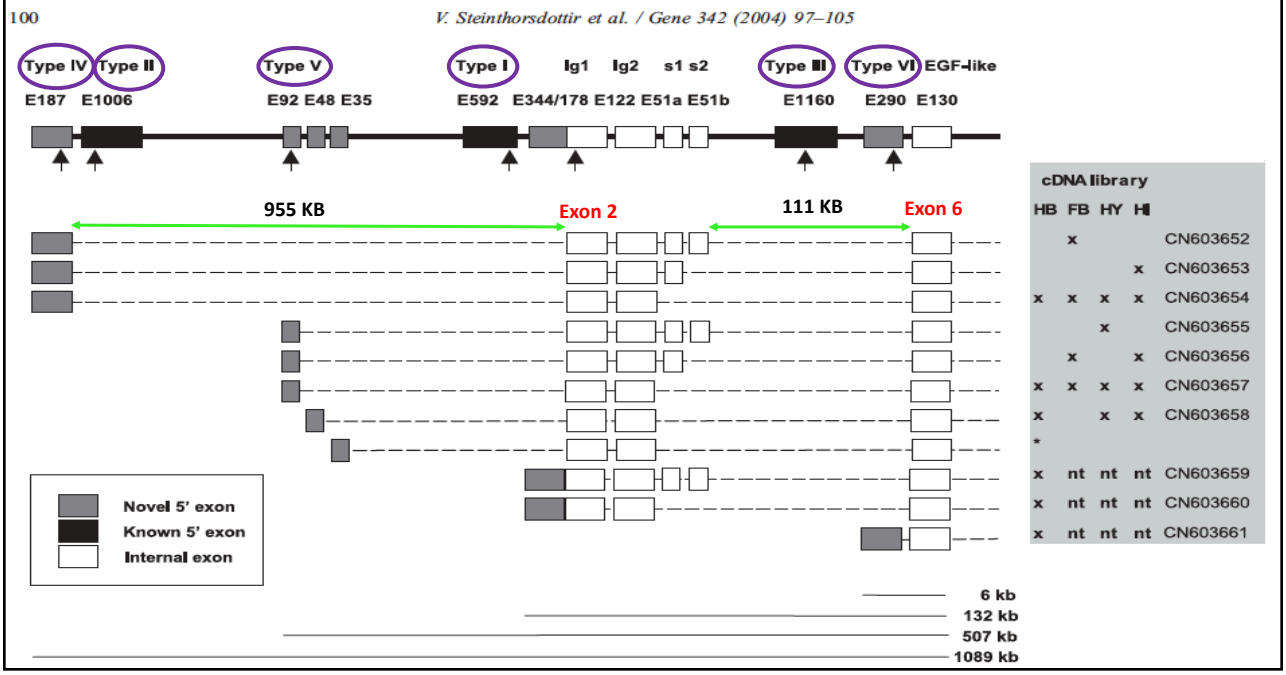
Multiple transcription start sites in *NRG1*



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Fusion partners identified in *NRG1+* NSCLC

Number	Fusion Partner	Fusion breakpoint	Reference
1	CD74	CD74-NRG1	Fernandez-Cuesta, Cancer Discovery, 2014
2	SLC3A2	SLC3A2-NRG1	Nakaoku, Clin Cancer Res, 2014
3	SDC4	SDC4-NRG1 (S4,N6)	Dhanasekaran, Nat Commu 2014
4	RBPMS	RBPMS-NRG1 (R6,N6)	Dhanasekaran, Nat Commu 2014
5.	WRN (SqCC)	WRN-NRG1	Dhanasekaran, Nat Commu 2014
6	VAMP2	VAMP2-NRG1	Jung, J Thorac Oncol, 2015; Shim, J Thorac Oncol 2015
7	KIFI3B	KIFI3B-NRG1	Xia, International J. Surgical Pathology, 2017
8	THAP7	THAP7-NRG1 (T6, N6)	Drilon, Cancer Discovery, 2018
9	SMAD4	SMAD4-NRG1	Drilon, Cancer Discovery, 2018
10	ATP1B1	ATP1B1-NRG1 (A2,N2)	Jonna, Clin Cancer Res 2019
11	TNC	TNC-NRG1 (T11, N6)	Jonna, Clin Cancer Res 2019
12	MDK	MDK-NRG1 (M5, N6)	Jonna, Clin Cancer Res 2019
13	MRPL13	MRPL13-NRG1 (M3,N2)	Jonna, Clin Cancer Res 2019
14	DIP2B	DIP2B-NRG1 (D2, N2)	Jonna, Clin Cancer Res 2019
15*	ROCK1	ROCK1-NRG1 (R1, N2)	Jonna, Clin Cancer Res 2019
16*	PARP8	PARP8-NRG1 (P2, N2)*	Jonna, Clin Cancer Res 2019
17*	DPYSL2	DPYSL2-NRG1 (D8, N2)*	Jonna, Clin Cancer Res 2019
18	ITGB1	ITGB1-NRG1 (I5, N2)	Pan, JTO 2019

*out of frame variant of unknown significance

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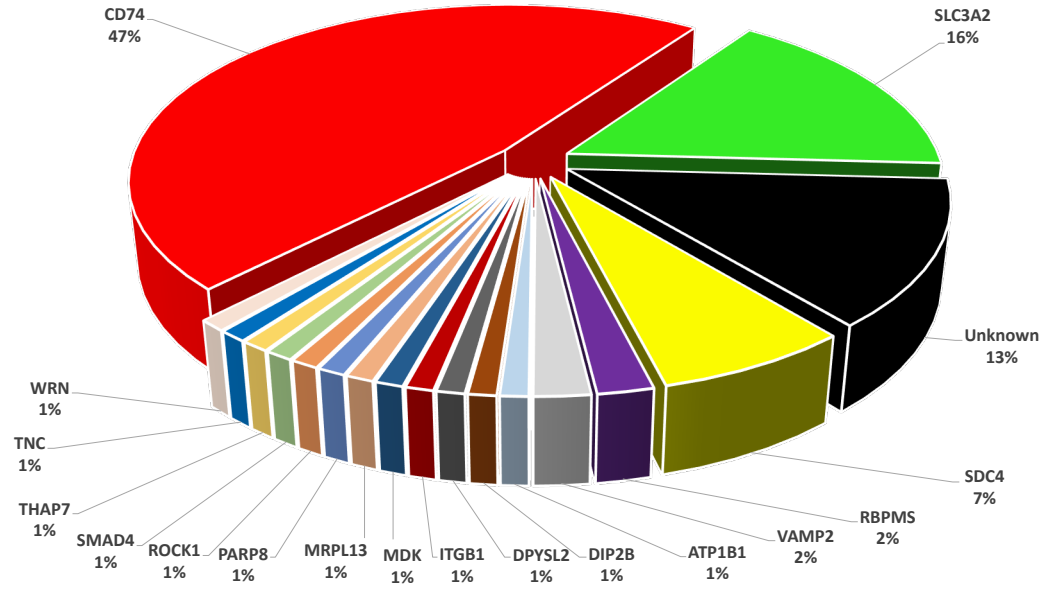
Distribution of 5'Fusion partners in *NRG1+* NSCLC (N = 99)



Modified from Nagasaka & Ou *J Thorac Oncol* 2019;14: 1354-1359

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Fusion partners identified in *NRG1+* Pancreatic Adenocarcinoma

Number	Fusion Partner	Fusion breakpoint	Reference
1	CD74	CD74-NRG1	Drilon 2018
2	ROCK1	ROCK1-NRG1	Drilon 2018
3	ATP1B1	ATP1B1-NRG1	Heining 2018, Jonna 2019
4	APP	APP-NRG1-APP	Heining 2018
5.	SARAF (5'), CHD6 (3')	SARAF-NRG1-CHD6	Heining 2018
6	CDH1	CDH1-NRG1	Jonna 2019
7	CVTCN1	VTCN1-NRG1	Jonna 2019

*out of frame variant of unknown significance

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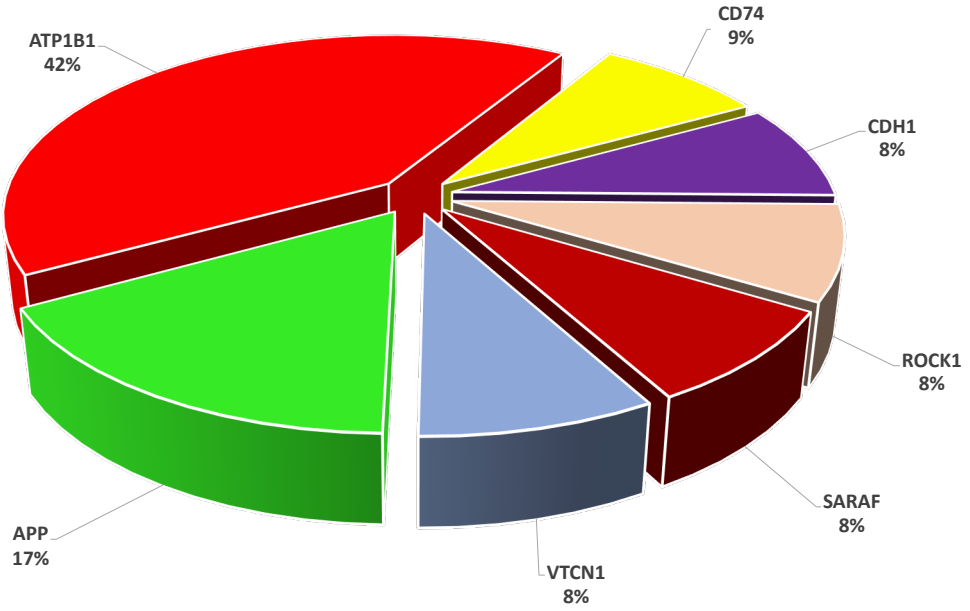
Distribution of 5'Fusion partners of *NRG1+* Pancreatic adenocarcinoma (N = 12)



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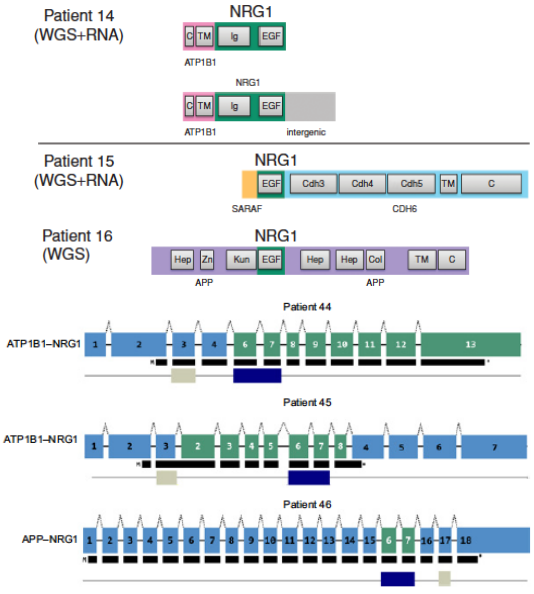
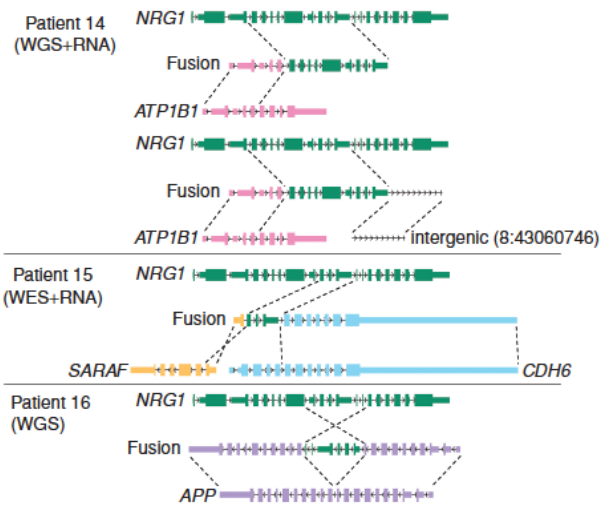
NRG1+ Pancreatic ADC has more complex re-arrangements



Jone et al, *Clin Cancer Res* 2019; 25: 4674-4681



Heining et al, *Cancer Disc* 2018; 8: 1087-1095

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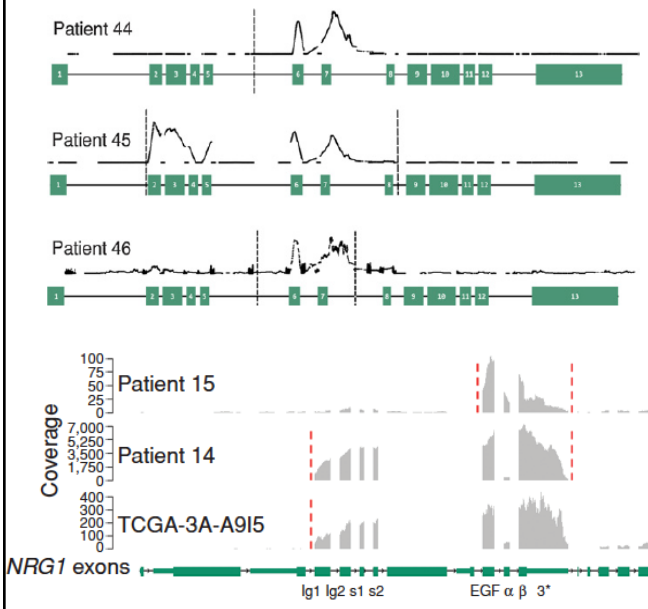
Nano-string (differential exon expression) approach



Jones et al, *Clin Cancer Res* 2019; 25: 4674-4681

Heining et al, *Cancer Disc* 2018; 8: 1087-1095

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List of fusion partners in other *NRG1+* solid malignancies

Solid tumor	NRG1 fusion	Reference
Breast	FOXA1-NRG1	Drilon 2019
	AKAP13-NRG1	Drilon 2019
	ADAM9-NRG1	Jonna 2019
	COX10-AS1-NRG1	Jonna 2019
Bladder cancer	GDF15-NRG1	Jonna 2019
Cholangiocarcinoma	ATP1B1-NRG1	Jones 2017, Jonna 2019
	NOTCH2-NRG1	Jonna 2019
Colorectal adenocarcinoma	POMK-NRG1	Jonna 2019
Head and Neck cancer	THBS1-NRG1	Drilon 2018
	PDE7A-NRG1	Drilon 2018
Ovarian adenocarcinoma	RAB3IL1-NRG1	Drilon 2018
	TSHZ2-NRG1	Jonna 2019
	SETD4-NRG1	Jonna 2019
	ZMYM2-NRG1	Jonna 2019
Prostate adenocarcinoma	NRG1-STMN2*	Drilon 2018
Renal cell carcinoma	PCM1-NRG1	Drilon 2018
	RBPMS-NRG1	Jonna 2019
Sarcoma	WHSC1L1-NRG1	Jonna 2019
Sinonasal teratocarcinosarcoma	HMBOX1-NRG1	Jonna 2019
Uterine	NRG1-PMEPA1*	Drilon 2019

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List of case reports of inhibiting HER2/3 in NRG1 fusions

Case	Age	Sex	NRG1 fusions variant	Solid malignancies	Treatment modality	Duration of Response	References
1	42	M	SLC3A2-NRG1	LUAC	Afatinib 40 mg qD	12 months	Gay
2	62	M	CD74-NRG1	LUAC (mucinous)	Afatinib 40 mg qD	10 months	Gay
3	43	F	SDC4-NRG1	LUAC	Afatinib 30 mg qD	12 months	Jones
4	38	F	ATP1B1-NRG1	Intrahepatic cholangiocarcinoma	Afatinib	8 months	Jones
5	62	F	CD74-NRG1	Lung IMA	Afatinib 40 mg qD	6.1 months (26 weeks)	Cheema
6	81	M	CD74-NRG1	Lung IMA	Afatinib 40 mg qD	Stable disease for 6 weeks	Drilon
7	56	F	SDC4-NRG1	Lung IMA	Afatinib 40 mg qD	Progression disease	Drilon
8	51	M	CD74-NRG1	Lung IMA	Afatinib 40 mg qD	Progressive disease	Drilon
9	86	M	CD74-NRG1	Lung IMA	GSK2849330* (anti-HER3 mab)	19 months**	Drilon
10	55	F	SLC3A2-NRG1	Lung IMA	Lumretuzumab*** + erlotinib	Stable disease for ~ 3.8 months	Kim
11	42	F	SLC3A2-NRG1	Lung IMA	Lumretuzumab + erlotinib	Stable disease for ~ 3.8 months	Kim

*inhibits NRG1 binding to HER3 and inhibits HER3 heterodimeriziation
** no response to afatinib after disease progression on GSK2849330
*** lumretuzumab is a antiHER3 monoclonal antibody
IMA: Invasive mucinous adenocarcinoma; M:Male; F:Female; LUAC: lung adenocarcinoma; mab:monoclonal antibody

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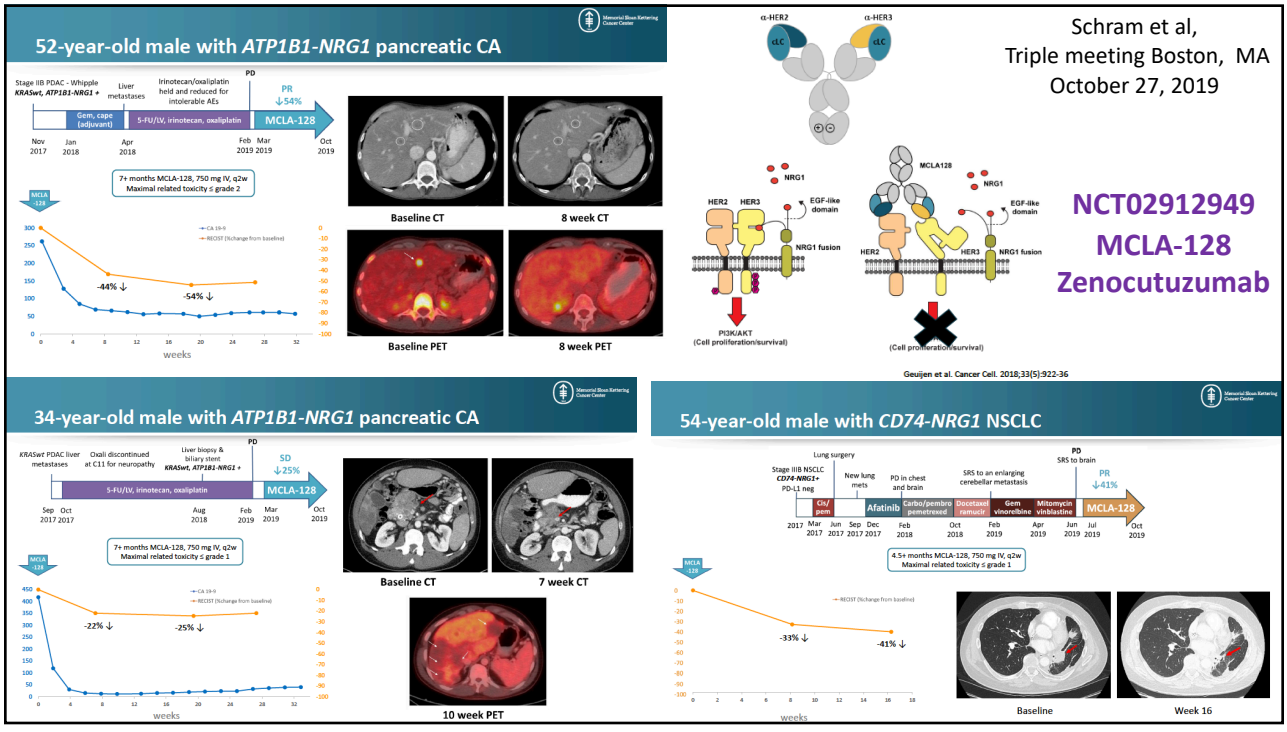

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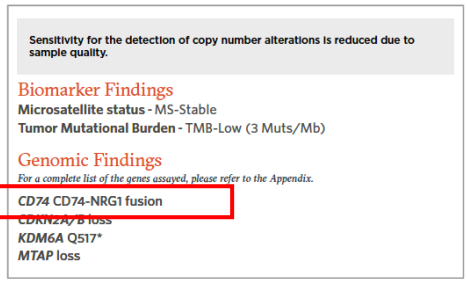
US commercial labs identification of *NRG1+* fusions (my two patients)



Sensitivity for the detection of copy number alterations is reduced due to sample quality.

Biomarker Findings

Microsatellite status - MS-Stable

Tumor Mutational Burden - TMB-Low (3 Muts/Mb)

Genomic Findings

For a complete list of the genes assayed, please refer to the Appendix.

CD74 **CD74-NRG1 fusion**

~~***CDKN2A/B*** **loss**~~

KDM6A **Q517***

MTAP **loss**

FMI Hybrid capture DNA NGS

Whole Transcriptome sequencing
Using Nova Seq 6000 system

Final Report CARIS LIFE SCIENCES

Gene Fusion and Transcript Variant Detection by RNA Sequencing

GENES TESTED WITH GENE FUSION OR TRANSCRIPT VARIANT DETECTED			
Biomarker	Fusion/Isoform	Splice Site	Transcript ID
NRG1	SLC3A2:NRG1	exon 5:exon 6	NM_001012662.2/NM_001159999.2

Interpretation: An SLC3A2-NRG1 fusion was detected in this tumor. This fusion has been reported in lung adenocarcinomas (Shin 2018 Dual Targeting of ERBB2/ERBB3 for the Treatment of SLC3A2-NRG1-Mediated Lung Cancer. Mol Cancer Ther 17:2024). Exon 5 of SLC3A2 (NM_001012662.2) is joined in-frame to exon 6 of NRG1 (NM_001159999.2).

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Summary

- NTRK and NRG1 fusions are very rare
- FGFR3-TACC3 fusions are an important driver mutations among FGFR1-4 fusions
  - One pan FGFR inhibitor has been approved by the US FDA
- RNA sequencing (targeted or whole transcriptome sequencing) increase the detection rate/frequency/incidence of actionable driver mutations and will be linchpin for identifying these rare TRK and NRG1 fusions

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Precision Oncology Symposium

Clinical Trials in Precision Oncology:
Current State and Future Perspectives

Pamela Munster, MD

Precision Oncology Symposium

Patient Access To Molecular Testing

Michael Zachary Koontz, MD

ANCO

Educating and Empowering the
Northern California Cancer Community

Pacific Cancer Care

Advanced Treatment. Personalized Care.

Precision Oncology: Patient Access

M. Zach Koontz, MD

Pacific Cancer Care

Monterey, CA

Disclosures

- No monetary or other affiliations with commercial entity of relevance
- No desire to promote/defame any company
- First exposure to NGS platform for patients while at Stanford, Foundation One 2012
- Where I work: Pacific Cancer Care

  6 Oncologists/hematologists and 4 RNPs
- I spend (like you) an unbearable amount of time on peer-to-peer calls, letters, reviews, appeals

When is Precision Oncology Relevant?

- When is it NOT?

Relevant Definitions

- Precision Oncology, broadly stated, is any test/ treatment that is highly specific to patient, disease, or tissue

- Here, specifically mean germline and somatic mutation panels

  NOT lung (EGFR, BRAF, ALK, ROS1), colorectal (RAS/RAF), breast (ER/PR, HER2), PDL1

- Current panels detect mutations, rearrangements, deletions/insertions, frame-shifts, over-expression, sometimes RNA, protein expression

Question 1:

- How many Genetic/NGS panels do you personally order per month?

1. 0-2
2. 3-5
3. 5-10
4. >10

Precision Oncology: Patient Access

- Necessary and sufficient for Access:

  Patient Need? →.

  Test Available? →.

  Provider Knowledge →.

  Test Covered *AND/OR* Reasonably Priced

California Cancer Statistics

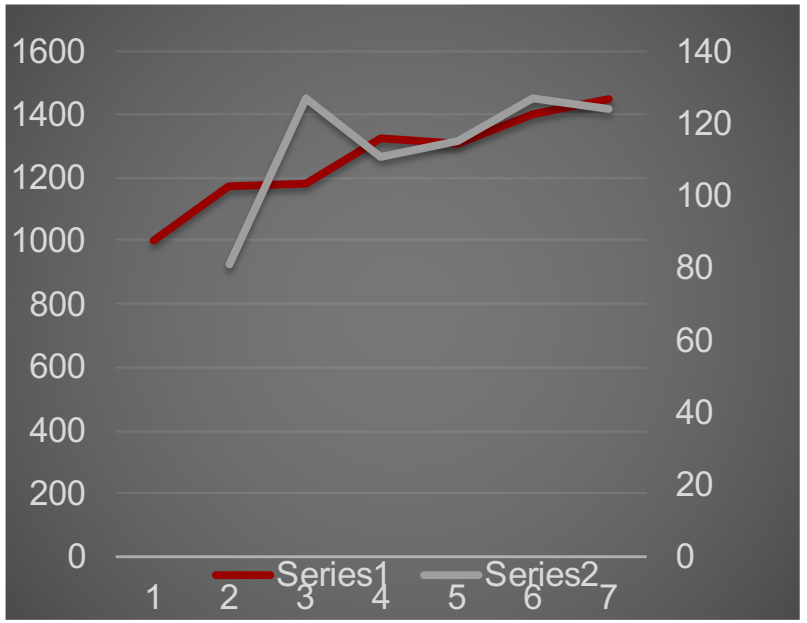
California

AT A GLANCE

Estimated new cases, 2019	Estimated deaths, 2019	Incidence rates, 2011-2015	Death rates, 2012-2016
186,920	**60,590**	**411.2** Average annual rate per 100,000, age adjusted to the 2000 US standard population.	**145.1** Average annual rate per 100,000, age adjusted to the 2000 US standard population. Rates for PR are for 2011-2015.

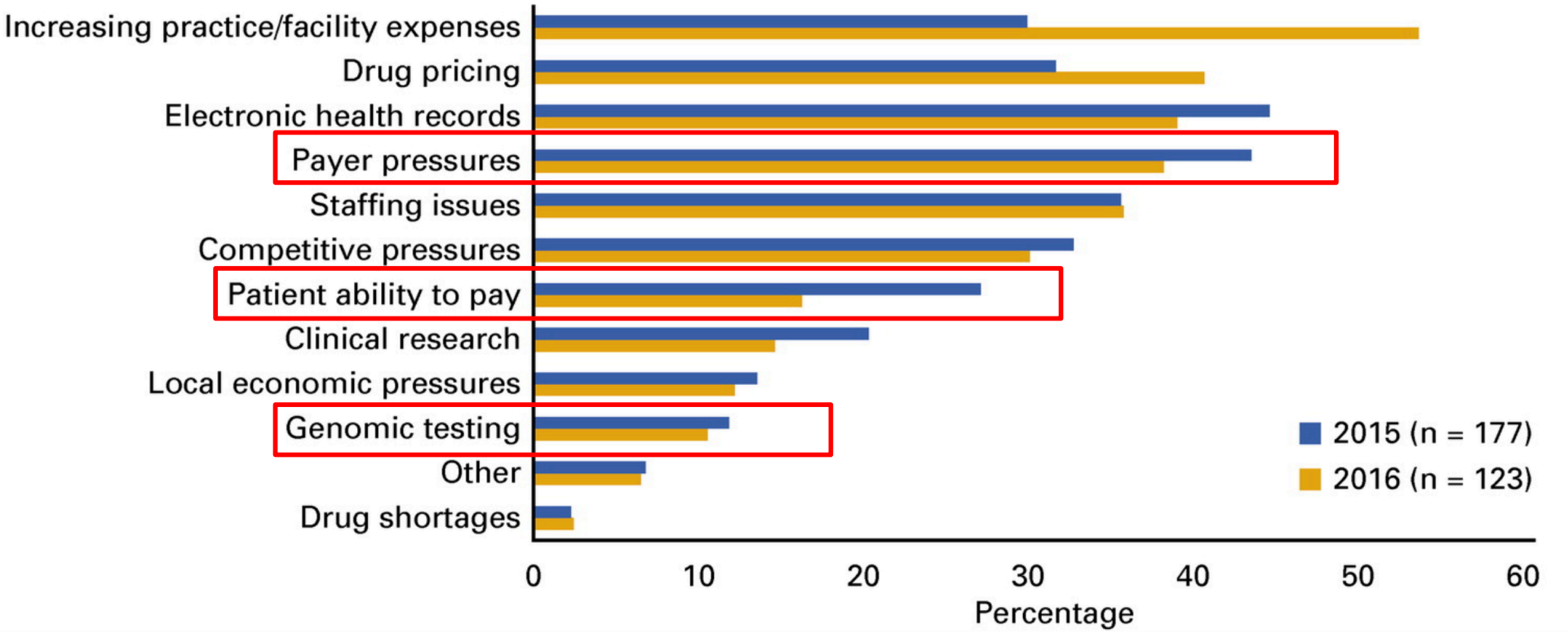
Precision Oncology in Community Practice

- Where are patients treated?
  - Community practices still treat > 50% of patients (COA, 2016)
- Cancer care growing complexity
  - Disease Breadth
  - Patient Volume
  - Aging population
  - Diagnostic Options
  - Treatment Decisions
  - Payers



Practice Pressures

ASCO State of Cancer, 2017



Need: Whom Should We Test?

- Somatic testing
  - When?
    - Upfront, or wait until burn through standard options?
  - Where?
    - Primary or metastatic sites
- Germline testing
  - Any ovarian cancer, or family history
  - Breast with risk factors*
  - Any pancreatic cancer
  - High risk prostate
  - Others ?????

Germline: NCCN HBOC

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2019
BRCA-Related Breast and/or Ovarian Cancer Syndrome

NCCN Guidelines Index
Table of Contents
Discussion

BRCA1/2 TESTING CRITERIA[a,b]

Meeting one or more of these criteria warrants further personalized risk assessment, genetic counseling, and often genetic testing and management.
Testing of an individual without a cancer diagnosis should only be considered when an appropriate affected family member is unavailable for testing.

- Individual from a family with a known *BRCA1/2* pathogenic/likely pathogenic variant, including such variants found on research testing[b]
- Personal history of breast cancer[c] + one or more of the following:
  - Diagnosed ≤45 y
  - Diagnosed 46-50 y with:
    - An additional breast cancer primary at any age[d]
    - ≥1 close blood relative[e] with breast cancer at any age
    - ≥1 close blood relative[e] with high-grade (Gleason score ≥7) prostate cancer
    - An unknown or limited family history[a]
  - Diagnosed ≤60 y with:
    - Triple-negative breast cancer
  - Diagnosed at any age with:
    - ≥1 close blood relative[e] with:
      - breast cancer diagnosed ≤50 y; or
      - ovarian carcinoma;[f] or
      - male breast cancer; or
      - metastatic prostate cancer;[g] or
      - pancreatic cancer
    - ≥2 additional diagnoses[d] of breast cancer at any age in patient and/or in close blood relatives
  - Ashkenazi Jewish ancestry[h]
- Personal history of ovarian carcinoma[f]
- Personal history of male breast cancer
- Personal history of pancreatic cancer[i]
- Personal history of metastatic prostate cancer[g]
- Personal history of high-grade prostate cancer (Gleason score ≥7) at any age with
  - ≥1 close blood relatives[e] with ovarian carcinoma, pancreatic cancer, or metastatic prostate cancer[g] at any age or breast cancer <50 y; or
  - ≥2 close blood relatives[e] with breast, or prostate cancer (any grade) at any age; or
  - Ashkenazi Jewish ancestry[h]
- *BRCA1/2* pathogenic/likely pathogenic variant detected by tumor profiling on any tumor type in the absence of germline pathogenic/likely pathogenic variant analysis
- Regardless of family history, some individuals with an *BRCA*-related cancer may benefit from genetic testing to determine eligibility for targeted treatment[j]
- An individual who does not meet the other criteria but with ≥1 first- or second-degree blood relative[k] meeting any of the above criteria. The significant limitations of interpreting test results for an unaffected individual should be discussed.

BRCA testing criteria met → See Follow-up (BRCA-2)

If *BRCA* testing criteria not met, consider testing for other hereditary syndromes → If criteria for other hereditary syndromes not met, then cancer screening as per NCCN Screening Guidelines

[a] For further details regarding the nuances of genetic counseling and testing, see BR/OV-A.
[b] Irrespective of degree of relatedness.
[c] For the purposes of these guidelines, invasive and ductal carcinoma in situ breast cancers should be included.
[d] Two breast cancer primaries includes bilateral (contralateral) disease or two or more clearly separate ipsilateral primary tumors diagnosed either synchronously or asynchronously.
[e] Close blood relatives include first-, second-, and third-degree relatives on same side of family. (See BR/OV-B)
[f] Includes fallopian tube and primary peritoneal cancers. *BRCA*-related ovarian cancers are associated with epithelial, non-mucinous histology. Lynch syndrome can be associated with both non-mucinous and mucinous epithelial tumors. Be attentive for clinical evidence of Lynch syndrome (see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal). Specific types of non-epithelial ovarian cancers and tumors can also be associated with other rare syndromes. Examples include an association between sex-cord tumors with annular tubules and Peutz-Jeghers syndrome or Sertoli-Leydig tumors and DICER1-related disorders.
[g] Metastatic prostate cancer is biopsy-proven and/or with radiographic evidence and includes distant metastasis and regional bed or nodes. It is not a biochemical recurrence.
[h] Testing for Ashkenazi Jewish founder-specific pathogenic/likely pathogenic variant(s), should be performed first. Comprehensive genetic testing may be considered if ancestry also includes non-Ashkenazi Jewish relatives or if other *BRCA*-related criteria are met. Founder pathogenic/likely pathogenic variants exist in other populations.
[i] Approximately 2%–5% of unselected cases of pancreatic adenocarcinoma will have a *BRCA1/2* pathogenic/likely pathogenic variant. However, the disease is highly lethal and the option to test the affected relative may not be available in the future. Thus, there may be significant benefit to family members in testing these patients near the time of diagnosis. In addition, increasing evidence suggests that identification of a *BRCA1/2* pathogenic/likely pathogenic variant may direct use of targeted therapies for patients with pancreatic cancer (See NCCN Guidelines for Pancreatic Adenocarcinoma). (Holter S, Borgida A, Dodd A, et al. J Clin Oncol 2015;33:3124-3129. Shindo K, Yu J, Suenaga M, et al. J Clin Oncol 2017;35:3382-3390.)
[j] Eg, PARP inhibitors for ovarian cancer and metastatic HER2-negative breast cancer; platinum therapy for prostate cancer. See the relevant NCCN treatment guidelines (eg, NCCN Guidelines for Breast Cancer; NCCN Guidelines for Prostate Cancer) for further details.
[k] This may be extended to an affected third-degree relative if related through two male relatives (eg, paternal grandfather's mother or sister).

Germline: NCCN Prostate Cancer

National Comprehensive Cancer Network®

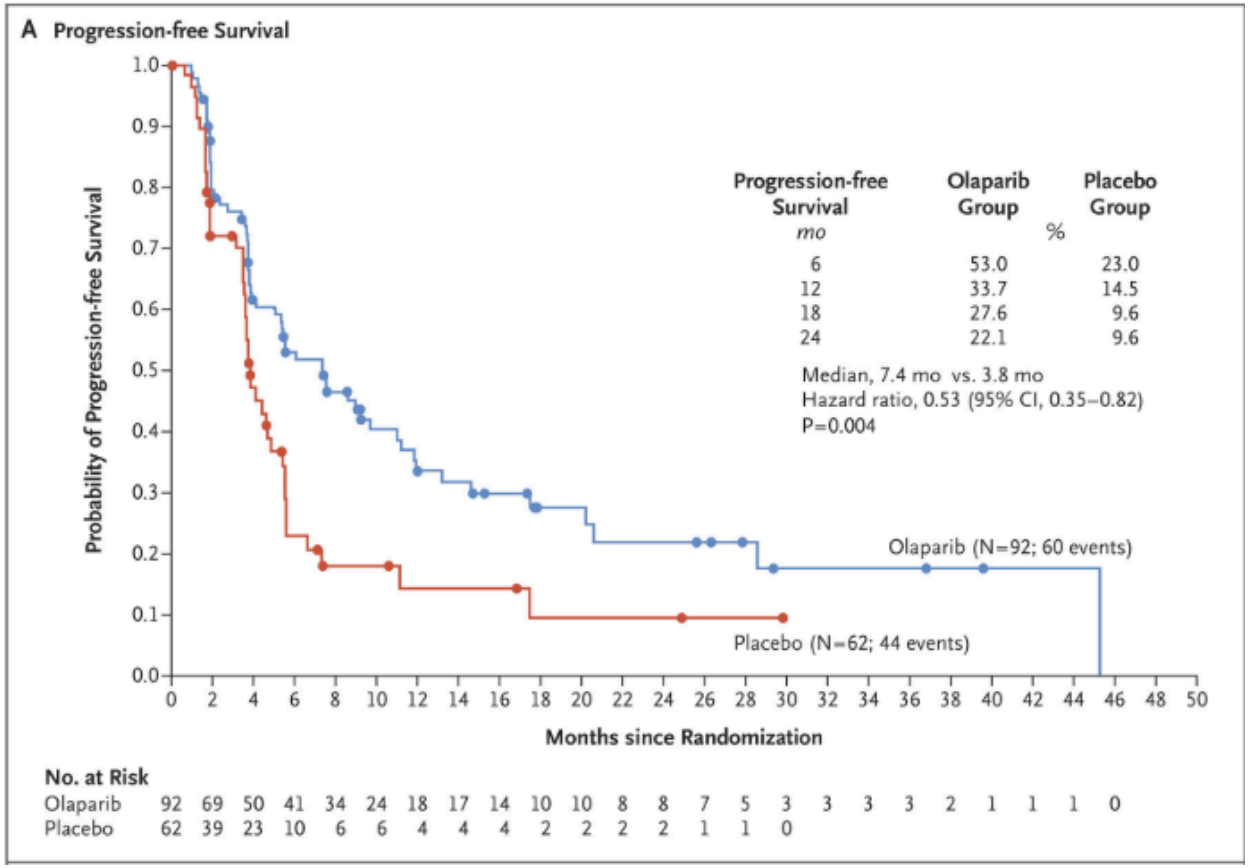
[d] Family history criteria and consideration to prompt genetic testing:

- A strong family history of prostate cancer consists of: brother or father or multiple family members who were diagnosed with prostate cancer (but not clinically localized Grade Group 1) at less than 60 years of age or who died from prostate cancer
- Ashkenazi Jewish ancestry
- ≥3 cancers on same side of family, especially diagnoses ≤50 years of age: bile duct, breast, colorectal, endometrial, gastric, kidney, melanoma, ovarian, pancreatic, prostate (but not clinically localized Grade Group 1), small bowel, or urothelial cancer

Pancreas: POLO Treatment Implications

ORIGINAL ARTICLE

Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer



N Engl J Med 2019; 381:317-327

Precision Oncology: Patient Access

- Necessary and sufficient for Access:

  Patient Need? →.

  Test Available? →.

  Provider Knowledge →.

  Test Covered *AND/OR* Reasonably Priced

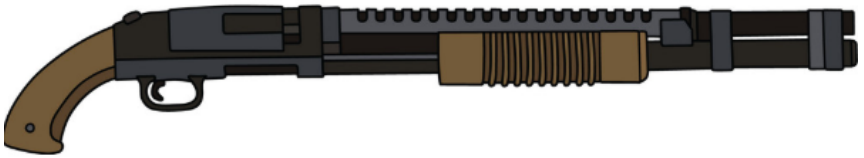
Available: Germline Testing Options

Ambry Genetics®
A Konica Minolta Company

INVITAE

OR

myriad®
WHEN DECISIONS MATTER



Available: Somatic Mutation Testing

Question 2

- How comfortable do you feel choosing somatic or germline testing in general?

1. I always know exactly what panel
2. I'm fairly comfortable ordering
3. I'm somewhat Uncomfortable ordering
4. Honestly, often I have no idea which one

Question 3

- Estimate the percent of your patients' care positively impacted (ie, improved OS or PFS) as a result of somatic tumor profiling.
- 1. <1%
- 2. 1-5%
- 3. 5-20%
- 4. 20-50%
- 5. all of them

Precision Oncology: Patient Access

- Necessary and sufficient for Access:

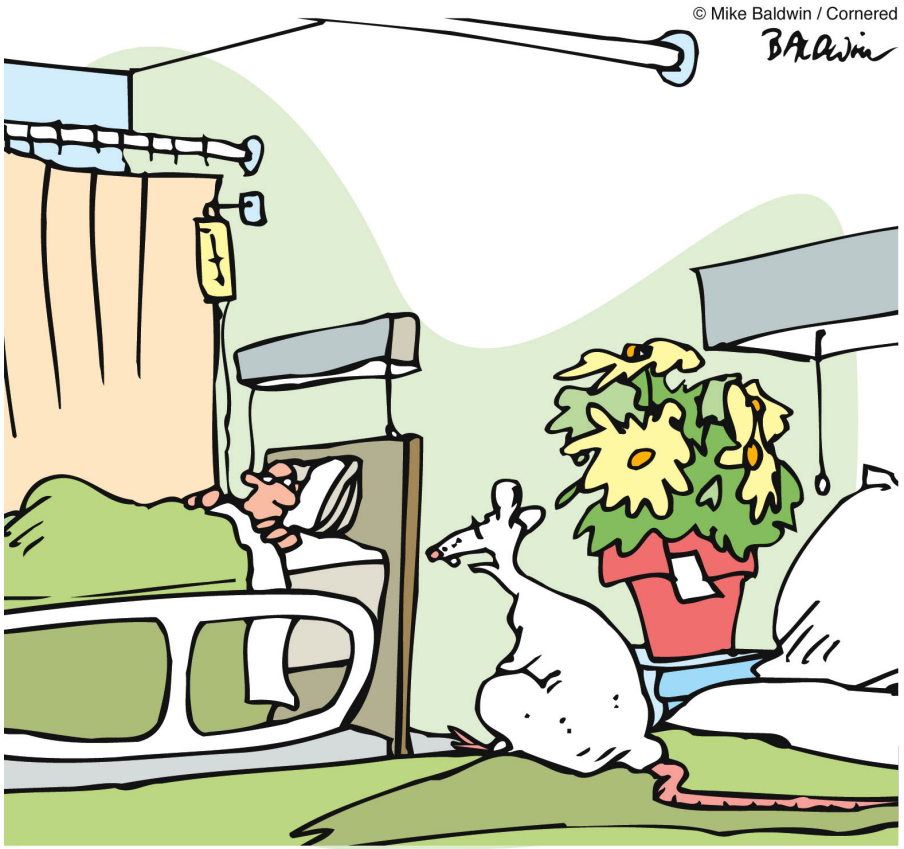
  Patient Need? →.

  Test Available? →.

  Provider Knowledge →.

  Test Covered *AND/OR* Reasonably Priced

Access to Drugs



"I go home today. They cured me using this new miracle drug. I'm afraid it'll be years before it's approved for humans."

Knowledge: Does it make a difference?

Journal of Clinical Oncology®
An American Society of Clinical Oncology Journal

DEVELOPMENTAL THERAPEUTICS AND TUMOR BIOLOGY (NONIMMUNO)

Utility of somatic mutation panel testing in patients with advanced cancer receiving treatment in an Irish teaching hospital.

Hadia Khan, Louise O' Callaghan, Gul Ahmed, Brian Richard Bird, Derbrenn O'Connor, Conleth G. Murphy

	Number	Percent
Total tests	74	100%
Mutation detected	39	53%
Potentially actionable	21	28%
Test-based treatment	9	12%

KYT Program

Clinical Cancer Research

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Personalized Medicine and Imaging

Molecular Profiling of Pancreatic Cancer Patients: Initial Results from the Know Your Tumor Initiative

Michael J. Pishvaian, Robert J Bender, David Halverson, Lola Rahib, Andrew E. Hendifar, Sameh Mikhail, Vincent Chung, Vincent J Picozzi, Davendra Sohal, Edik M Blais, Kimberly Mason, Emily E. Lyons, Lynn M Matrisian, Jonathan R. Brody, Subha Madhavan, and Emanuel F. Petricoin

DOI: 10.1158/1078-0432.CCR-18-0531 Check for updates

- 640 pancreatic cancer patients
- 172 (27%) with “highly actionable” mutations
- 17 (2.7%) treated with identified targeted drug
- PFS 4.1mo vs 1.9mo, OS non-sig improvement

Pacific Cancer Care/ My Practice

- Germline

  Consistent with guidelines, adherent to common sense

  72 in 2018 (3.5 med/onc)

- Somatic Panels

  Since 2013:

  > 150 ordered

  Foundation: 111 reports, 10 in process, 43 cancelled

  Practice 2018: 67

Question 4

Have you ever had a patient file bankruptcy because of cancer care?

1. Yes
2. No
3. I don't know
4. I'm too afraid to answer

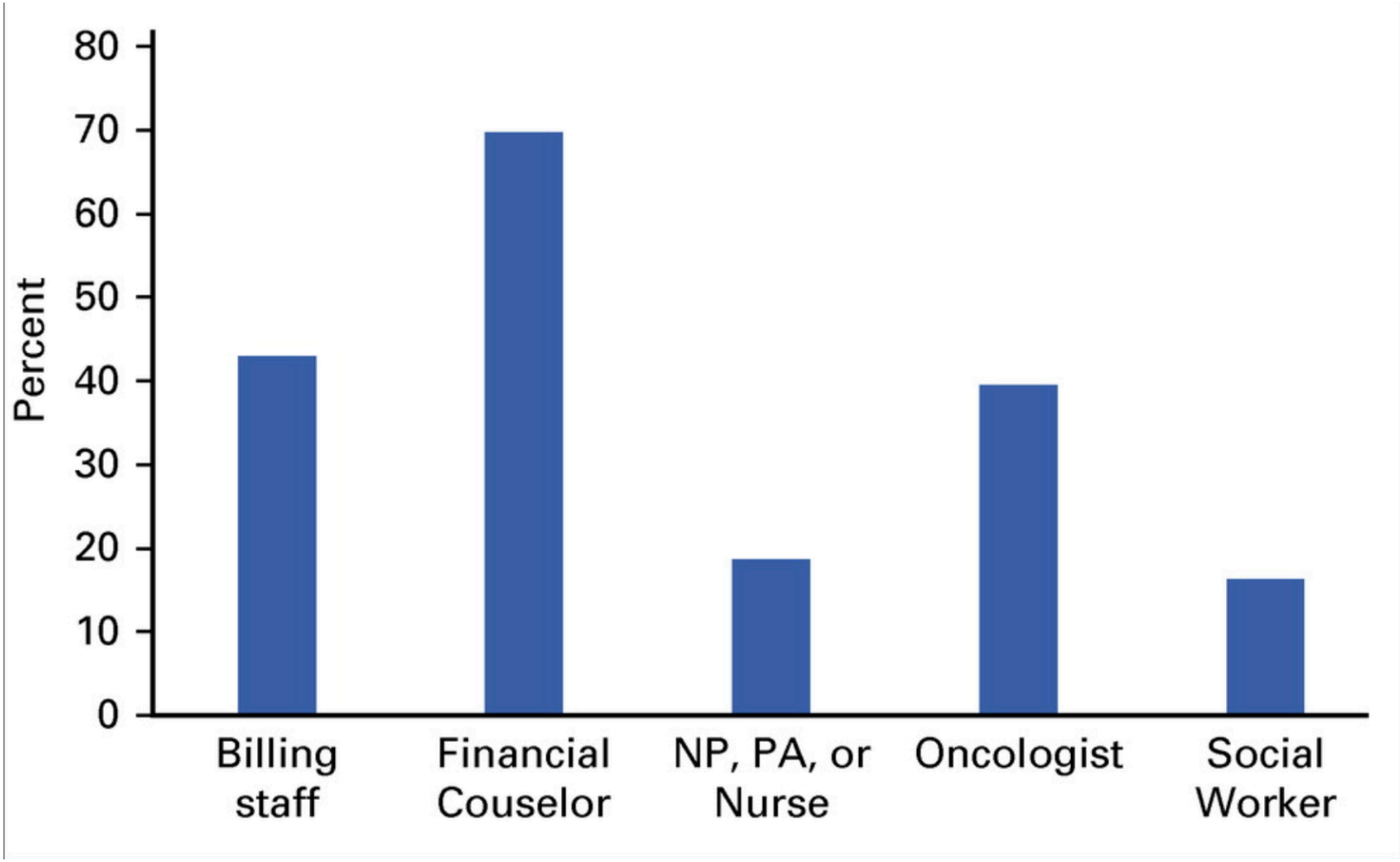
Cost of Care

- Survey 2012 LIVESTRONG
  - 1/3 working-age patients in debt after cancer
  - >50% more than $10k
  - 3% file bankruptcy
- Cost of cancer drugs can exceed $100k/year
- Imaging
- Hospitalization costs ($2-4k/day)
- Loss of work

Health Aff (Millwood). 2016 Jan;35(1):54-61.

Cost to Patients: ASCO State of Cancer 2017

Percentage of staff that discuss cost of care with patients



California Payers

Covered California Health Insurance Carriers

Find Health Insurance Companies Offered on the California Health Exchange

- We have >100 payers, different processes, contacts, payment rules, etc.
- 2013 study: 1/3 had some kind of policy, moderate consistency, half specifically excluded a genetic test

Personalized Medicine. 2013;10(3):235-243.

Cost/Coverage

"Most health insurance plans will cover the cost of genetic testing when recommended by a physician. However, all coverage and reimbursement is subject to Medicare, Medicaid, and third-party payer benefit plans. Therefore, ASCO strongly encourages you to verify with the patient's insurer to understand what type of services will be covered."
-ASCO 2019 website

https://www.asco.org/practice-guidelines/cancer-care-initiatives/genetics-toolkit/genetic-testing-coverage-reimbursement

Medicare, ACA

- Medicare: Tests performed in the absence of signs, symptoms, complaints, or personal histories of disease or injury are not covered unless explicitly authorized by statute..

  "…therefore, Medicare does not currently provide coverage for genetic testing in individuals without a personal history of cancer. [except]:

  [BRCA1/2 meeting criteria…]

  [CRC meeting criteria…]"

- ACA: esssential health benefits clause only covers BRCA1/2

Sample Germline Plan Policy

- Aetna considers genetic testing medically necessary to establish a molecular diagnosis of an inheritable disease when *all* of the following are met:

  →The member displays clinical features, or is at direct risk of inheriting the mutation in question (pre-symptomatic); *and*

  →The result of the test will directly impact the treatment being delivered to the member; *and*

  →After history, physical examination, pedigree analysis, genetic counseling, and completion of conventional diagnostic studies, a definitive diagnosis remains uncertain, and one of the following diagnoses is suspected (this list is not all-inclusive); *and*

  →Disease-specific criteria met.

Cost of genetic testing

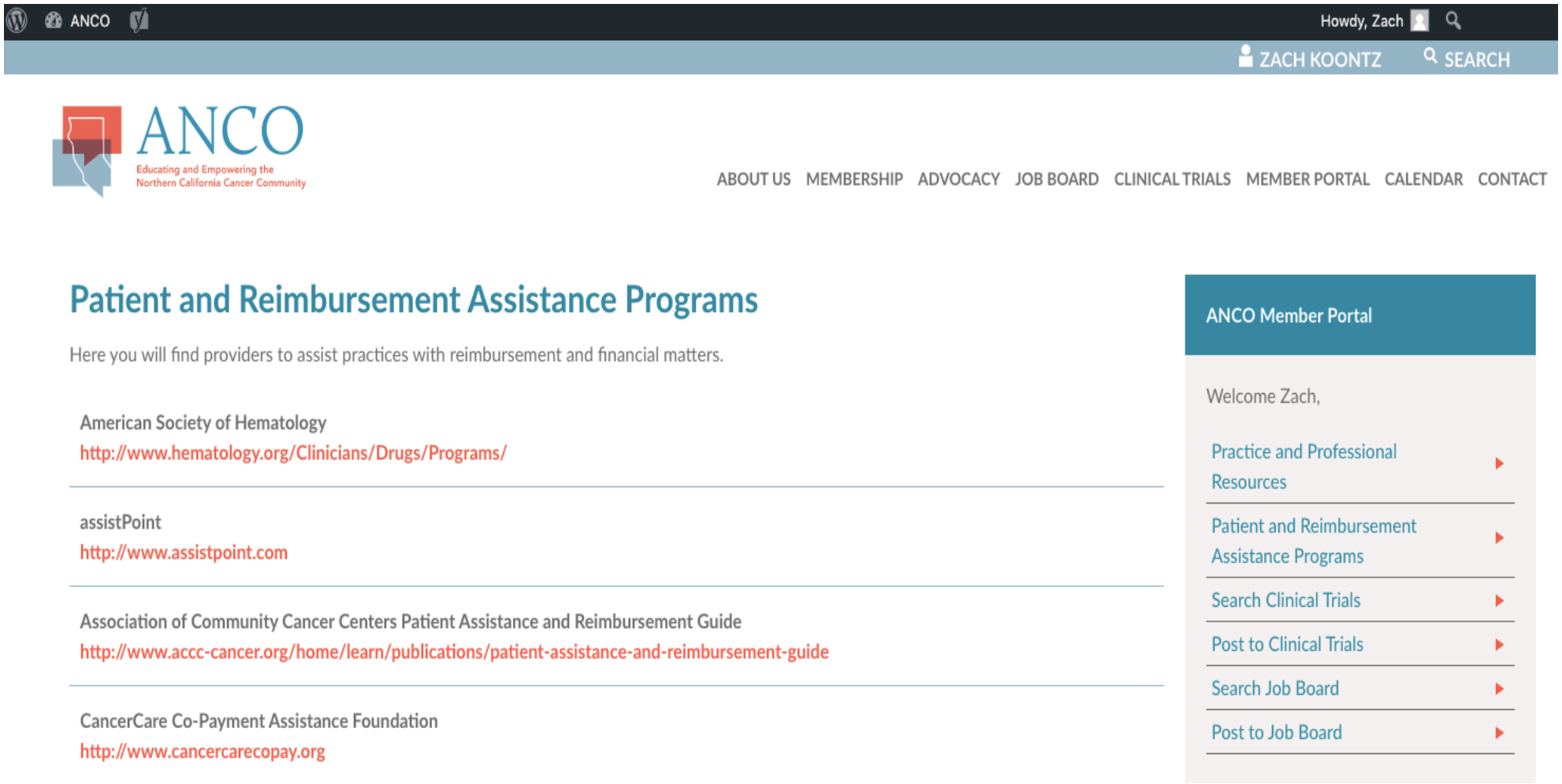
- $150 - $20,000
- Most range $500-$1500
- Overwhelmingly this has not been a barrier to testing

  ***with exceptions

The Industry is our Ally

- Invitae offers FREE genetic testing and counseling for patients diagnosed with
  - Pancreas adenocarcinoma
  - Pancreas NET
  - Prostate cancer stage II+
- Most (if not all) companies have policies to not go after patients and will work not only with them, but for them

Help is out there!



ANCO Advocacy

- Part of ANCO mission, to advocate for providers and patients, communicates concerns with DHS, Sacramento, private insurers
- Supports/Opposes relevant State and National Legislation with the help of *Noteware and Rosa Government Relations*
- AB1860 - $250 monthly cap oral medication legislation

Conclusion: Challenges/Gaps

- Identifying which patients to test evolving
- Date of Service Rule
- Duplicate testing
- Drug coverage once identified target?
- Interpreting tests and finding therapies

Conclusion: The Good News

- Supreme court says you can't own a gene
- NGS is getting cheaper, faster, more efficient, with higher genome coverage and fidelity
- More "options" exist
- Industry has been supportive thus far
- ASCO, ASH, ANCO and other organizations are advocating for our patients

Conclusion

- Necessary and sufficient for Access:

  Patient Need? → MOSTLY, YES

  Test Available? → YES

  Provider Knowledge → YES?

  Test Covered *AND/OR* Reasonably Priced

  SO FAR SO GOOD*


Thanks!
ANCO
Sponsors
Panel members