Comprehensive Genomic Profiling with FMI – bringing value to patients

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Medical lead Molecular Information

Region Europe

25 th October 2016

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Why should physicians consider profiling?

CGP from Foundation Medicine – ***understanding the difference***

Foundation Medicine's experience – ***translating into clinical benefit***

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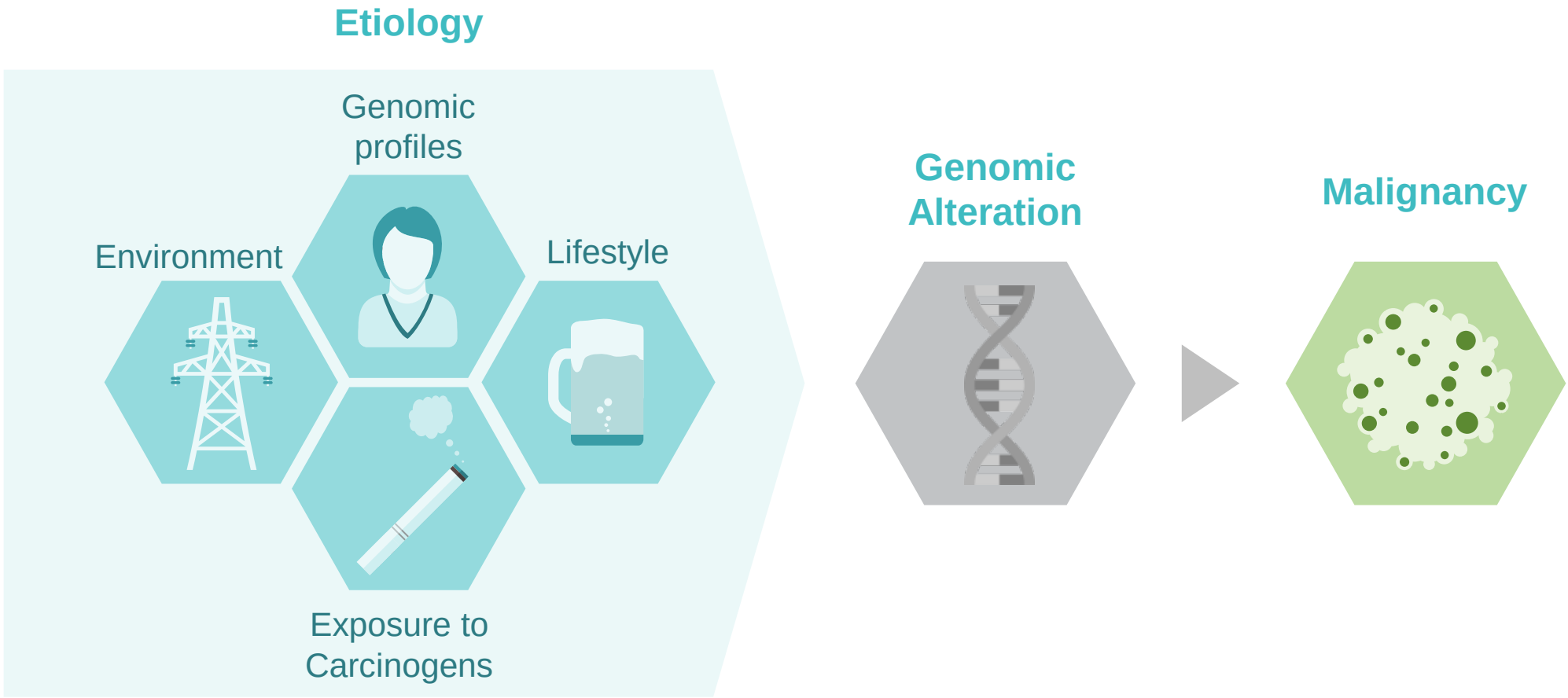
Cancer is a disease of the genome

Our understanding of cancer has been evolving



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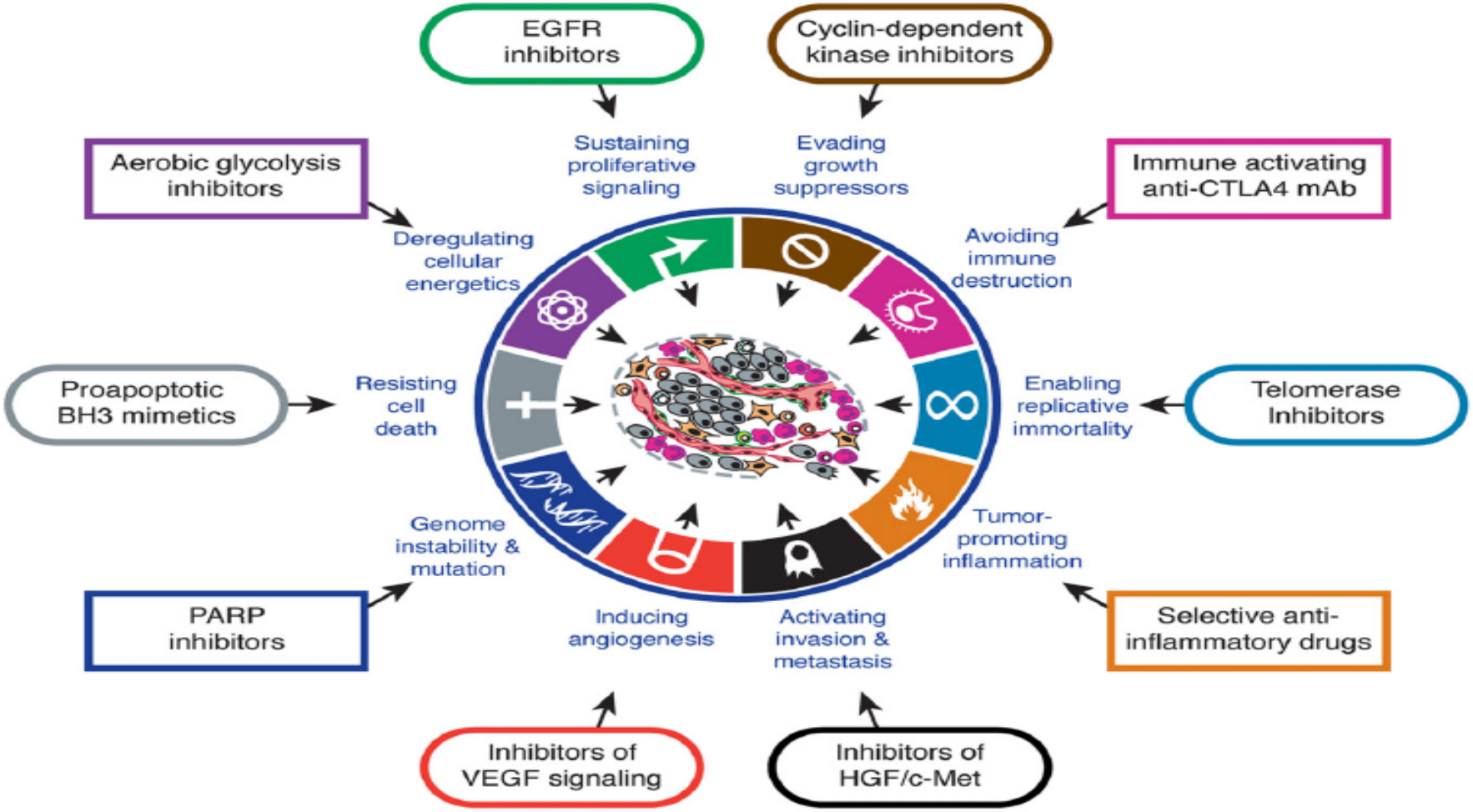
Many genetically driven characteristics–
many therapeutic options



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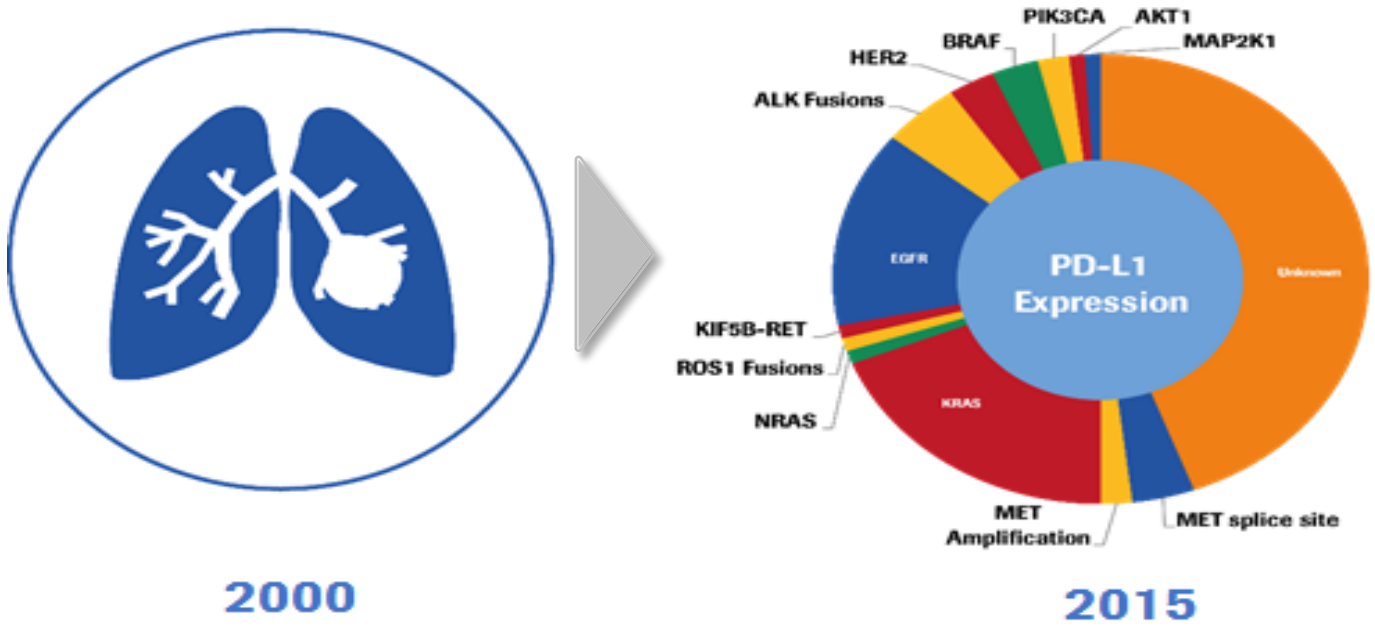
D. Hanahan & R. Weinberg 2011, Cell

Lung Adenocarcinoma:

Moving from one disease to multiple disease types by molecular alterations that require distinct tx plans



2015 NSCLC NCCN guidelines recommend broad molecular profiling for the following biomarker/drug associations:

Biomarker	Drugs
EGFR mutations	erlotinib, gefitinib, afatinib
ALK rearrangements	crizotinib
BRAF V600E	vemurafenib*, dafrafenib*
MET amplifications	crizotinib
ROS1 rearrangements	crizotinib
HER2 mutations	trastuzumab*, afatinib
RET rearrangements	cabozantinib*

** Drugs not approved for lung cancer*

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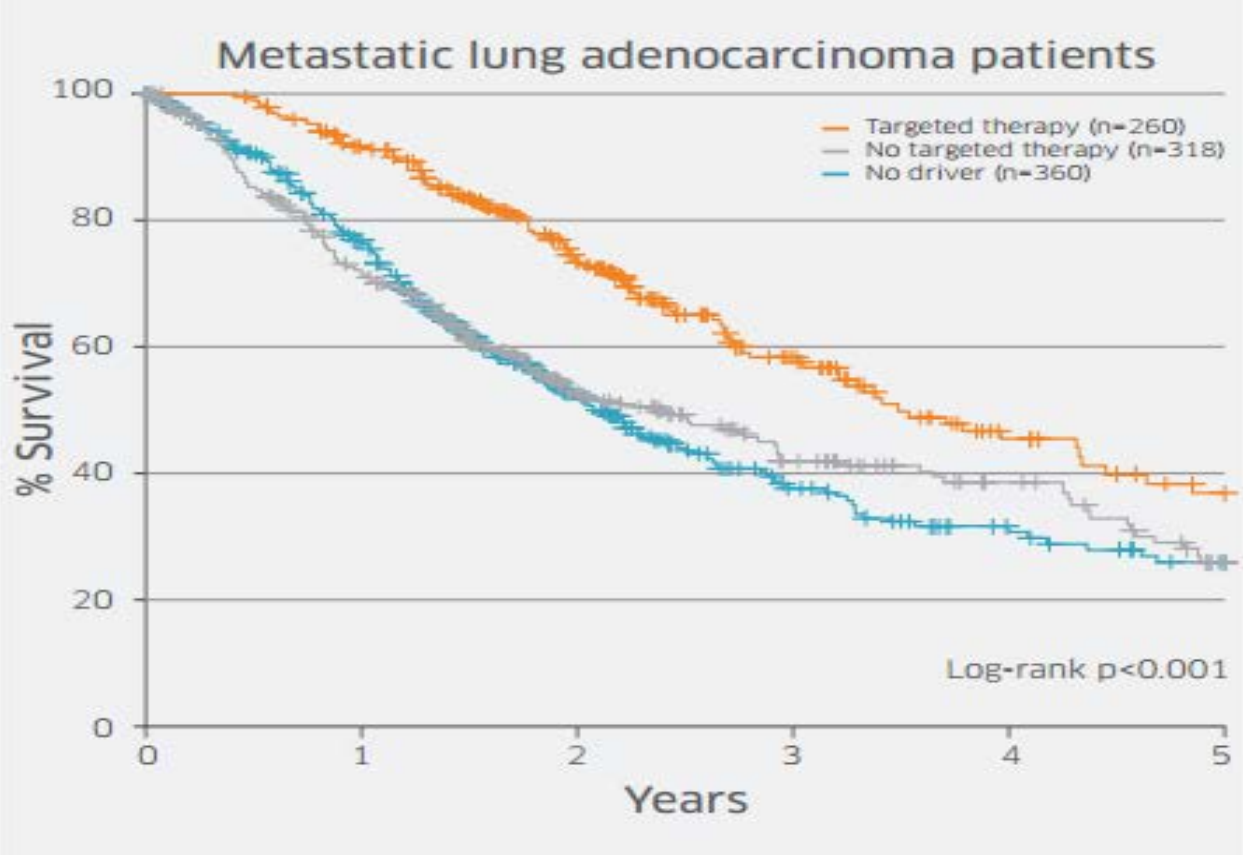
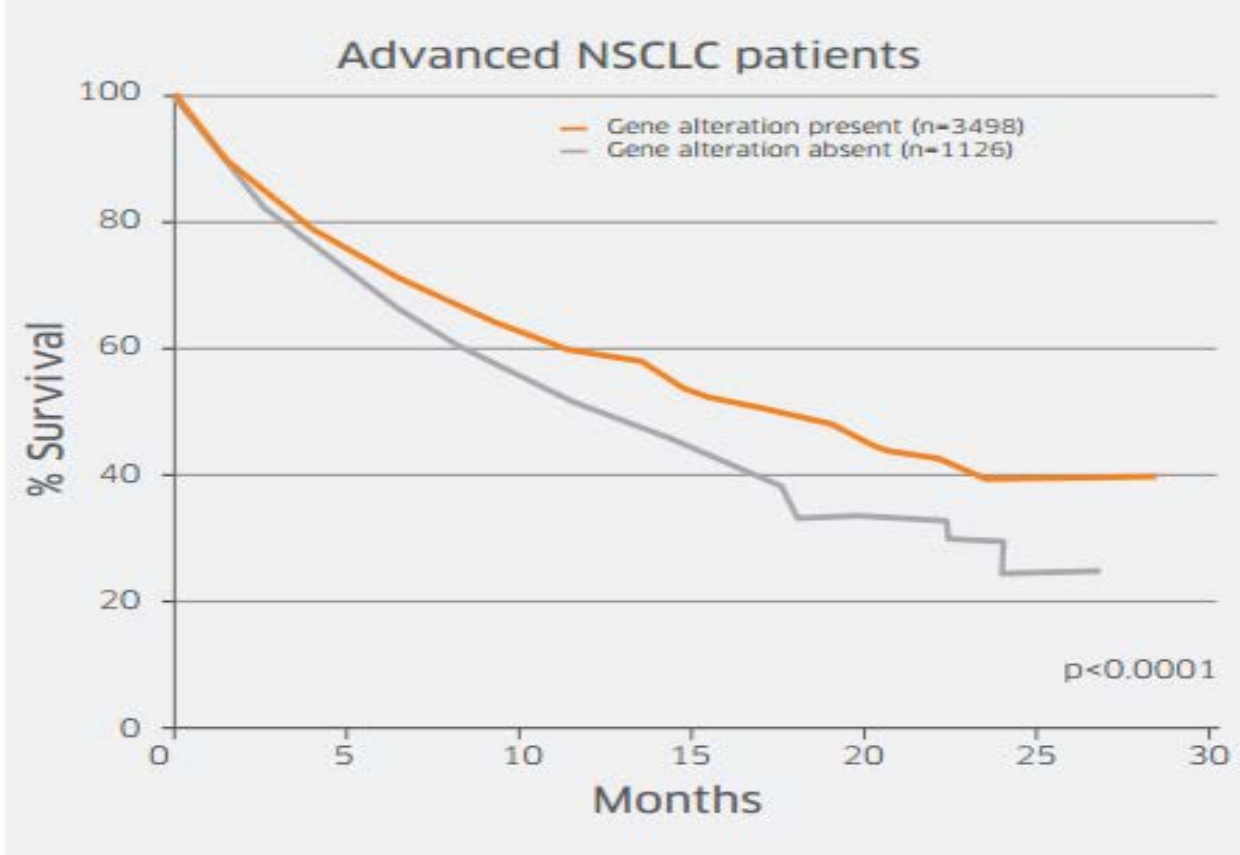
Treating Lung Cancer patients based on their tumour profiling results improves outcomes





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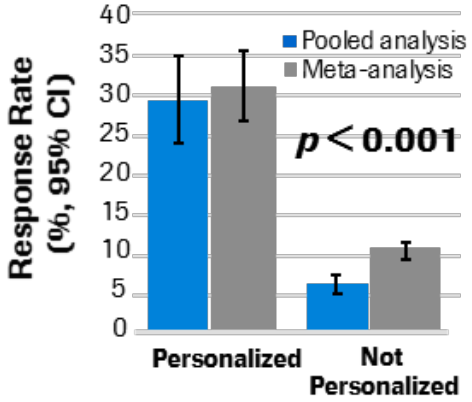
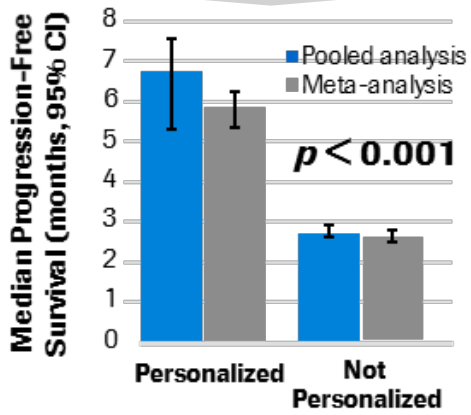
Kris MG et al(2014); JAMA 311 (19)
Barlesi R et al (2016); Lancet So140-6736

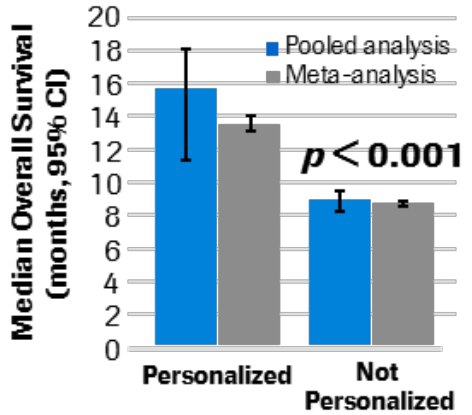
Meta-analysis of Phase II studies – 32 149 patients

Meta-analysis of **570 Phase II**, single-agent studies (including total of **32,149 patients**) studying the impact of personalized and targeted treatment strategies in diverse cancer types

RR, PFS and OS from pooled meta-analyses







Arms included (pooled and meta-analyes):
RR: Personalized n = 112 not personalized n = 526
PFS: Personalized n = 86 Not personalized n = 444
OS: Personalized n = 49 Not personalized n = 392

Personalized treatment strategies, across malignancies, were **independent predictors of better outcomes** and **fewer deaths** from treatment toxicity than non-personalized therapies

"Matched therapy using genomic markers offers better outcomes than using protein biomarkers"

"Matched therapies are associated with better outcomes than non-matched therapies"

Schwaederle, M., et al. (2015), J Clin Oncol 33(32):3817-25.

OS: Overall survival; PFS: Progression-free survival; RR: Response rate; CI: Confidence interval

Profiling guidelines

NCCN Guidelines® now recommend "broad molecular profiling" for advanced NSCLC patients

Genomic Alterations (i.e. driver event)	Available targeted agents with activity against driver event in lung cancer
EGFR mutations	erlotinib, gefitinib, afatinib
ALK rearrangements	crizotinib, ceritinib
HER2 mutations	trastuzumab, afatinib
BRAF V600E mutations	vemurafenib, dabrafenib
MET amplification	crizotinib
ROS1 rearrangements	crizotinib
RET rearrangements	cabozantinib

now recommends "broad molecular profiling" for advanced NSCLC patients

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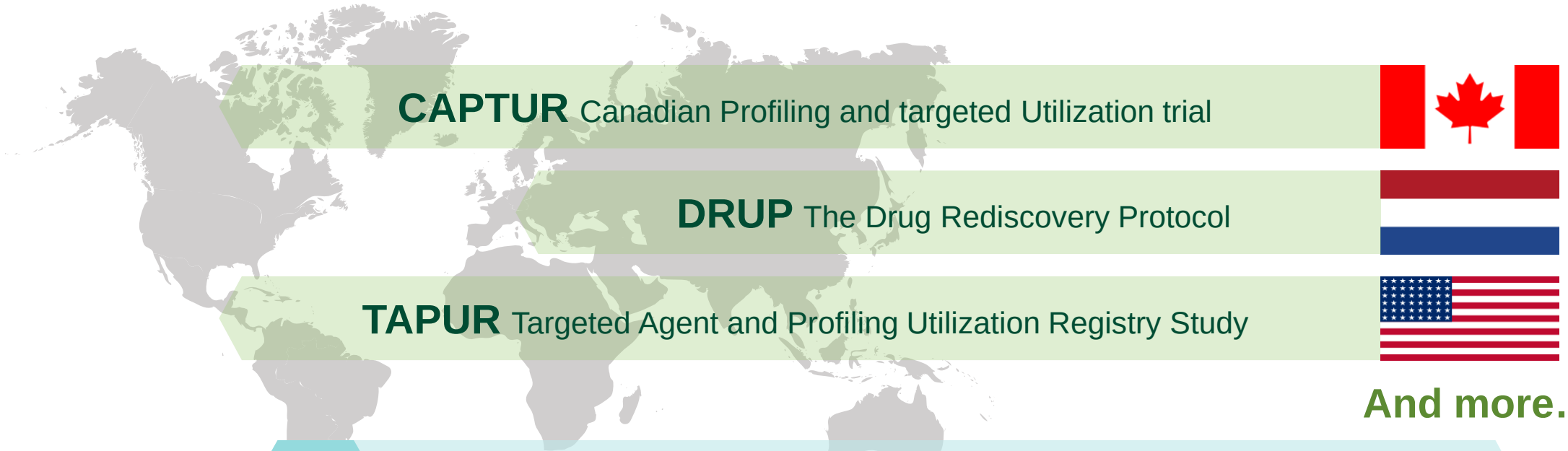
Profiling initiatives

Investigating the potential to match treatments to genomic alterations across tumor types



CAPTUR Canadian Profiling and targeted Utilization trial

DRUP The Drug Rediscovery Protocol

TAPUR Targeted Agent and Profiling Utilization Registry Study

And more…

Initiatives to decipher which patients respond to which therapies, irrespective of in which tumor type the therapies are approved in

http://www.nature.com/nm/journal/v22/n5/fig_tab/nm.4089_T1.html

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Why should physicians consider profiling?

Comprehensive genomic profiling from Foundation Medicine

How to benefit from Foundation Medicine’s experience

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Foundation Medicine

Pioneer and leader in molecular information

- Founded 2010 in Cambridge, MA, USA
- Proprietary molecular information platform
- First to market comprehensive genomic profiling solutions for cancer
- 90,000+ clinical cases profiled
- 30+ pharmaceutical clinical trial partners
- Roche collaboration for R&D and commercialization outside USA

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Foundation Medicine offers two solutions

FoundationOne® and FoundationOne® Heme

Comprehensive: Detect all classes of genomic alterations

FOUNDATIONONE™

- Coding regions of 315 genes
- Introns of 28 genes
- Known as drivers of solid tumors

Frampton G, et al. Nature Biotech, 2013, 31, 1023-34

FOUNDATIONONE™ Heme

- DNA sequences of 405 genes
- RNA sequences (cDNA) of 265 genes
- Commonly altered in hematologic malignancies(leukemia, lymphoma and myeloma) and

Jie H et al. Blood 2016

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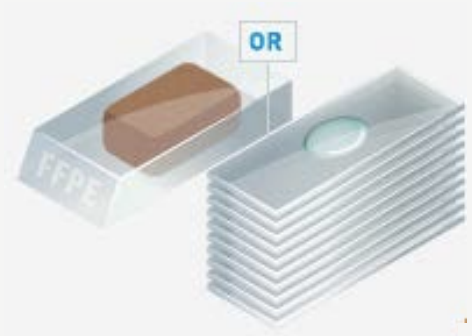
How does FoundationOne work?

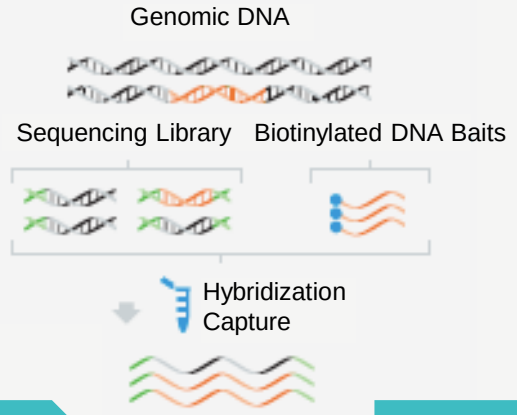
A process that follows standard operating processes

Pre-Analytic Process (Pre-Sequencing)



DNA extraction

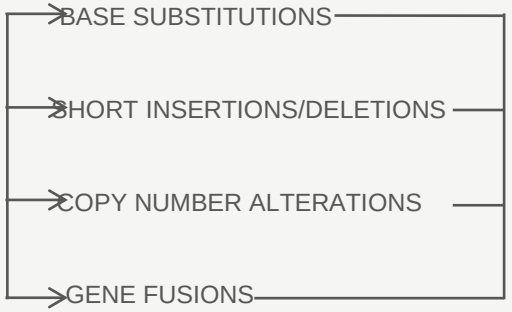
1) DNA/RNA extraction
Extensive optimization



Sequencing

2) LC, Hybrid Capture
Extensive optimization

Post-Analytic Process (Post-Sequencing)



Analysis & Interpretation

3) Analysis pipeline
Advanced computational biology

4) Clinical report
Resource intensive

Powered by 20+ bioinformaticians and genomic scientists who optimize state-of-the art algorithms to report the most clinically relevant information for a patient

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Types of genomic alterations driving tumor growth

Limitations of traditional and hotspot testing

BRAF V600E (BRAF inhibitor)

Base Substitutions

EGFR Exon 19 deletion (EGFR inhibitor)

Insertions and Deletions

HER2 amplification (HER2 inhibitor)

Copy Number Alterations

ALK fusion (ALK inhibitor)

Rearrangements

Test	Detects	Can Miss
IHC	Protein expression	Any alteration not known of ahead of time
FISH	Copy number alterations, Rearrangements	Insertions & deletions, Substitutions
Hot Spot NGS*	Substitutions	Insertions & deletions, Copy number alterations, Rearrangements

**Suh J et al. (2016) Oncologist. http://dx.doi.org/10.1634/theoncologist.2016–0030.*

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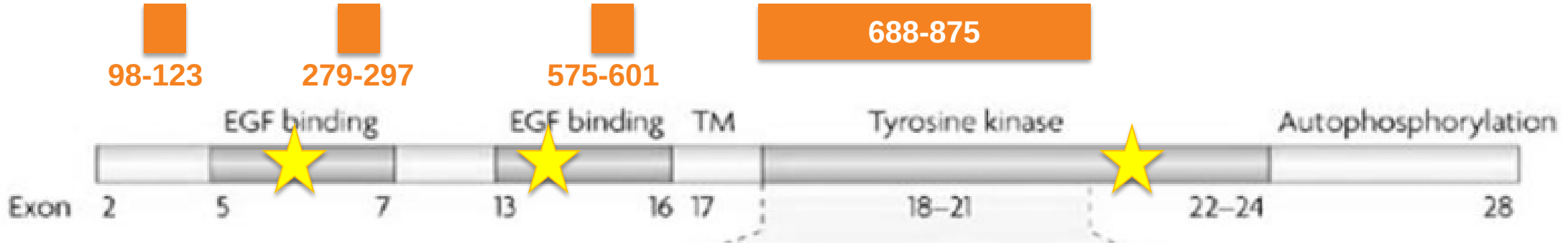
Foundation Medicine finds more targets

Completely sequencing genes enables detection of novel alterations missed by hot spot testing

Example: EGFR gene

Hot spot tests detect selective alterations in selective parts of the EGFR gene*

….When there is an insertion/deletion or rearrangement that removes one of the primer sites, hot spot tests will not amplify the region or detect the alteration



FoundationOne detects all genomic alterations across the entire EGFR gene

= Mutations not detected by hot spot

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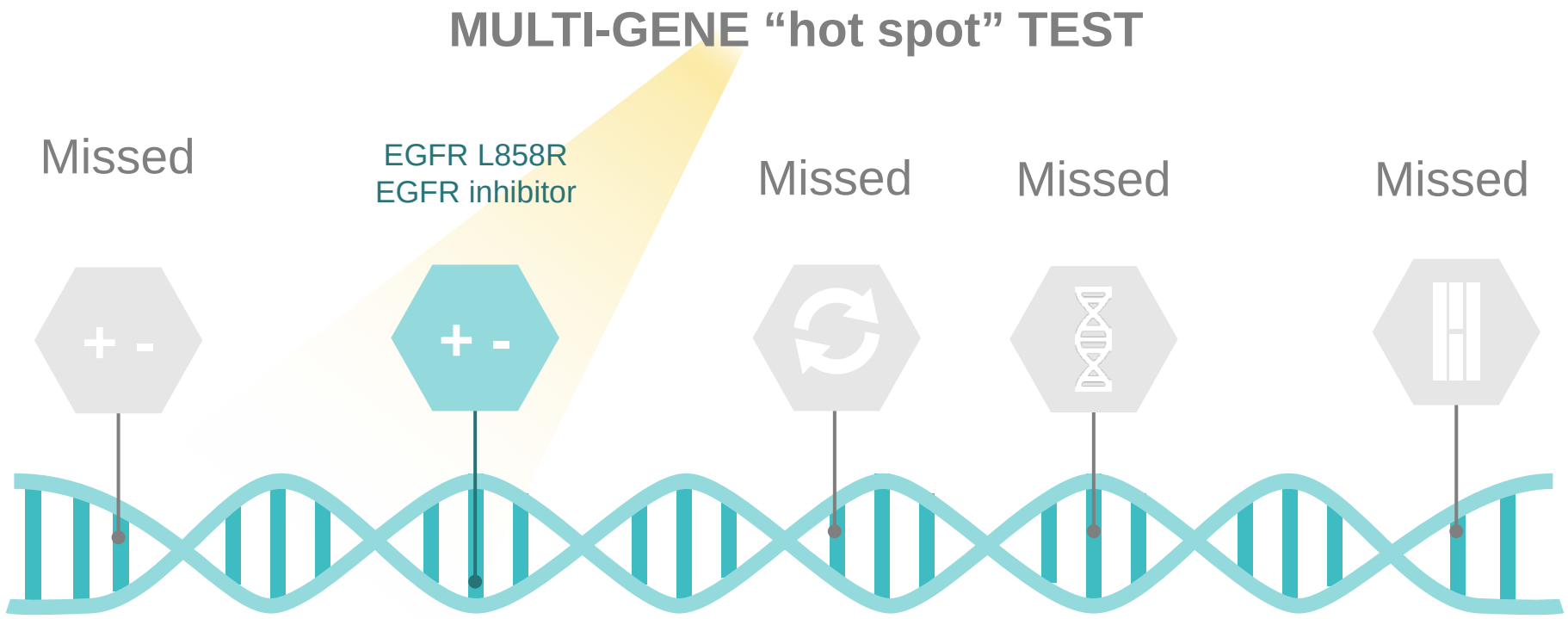
* Meric-Bernstam F et al. (2015) J Clin Oncol 33:2753-2762

Foundation Medicine finds more targets

While hot spot tests can miss alterations…



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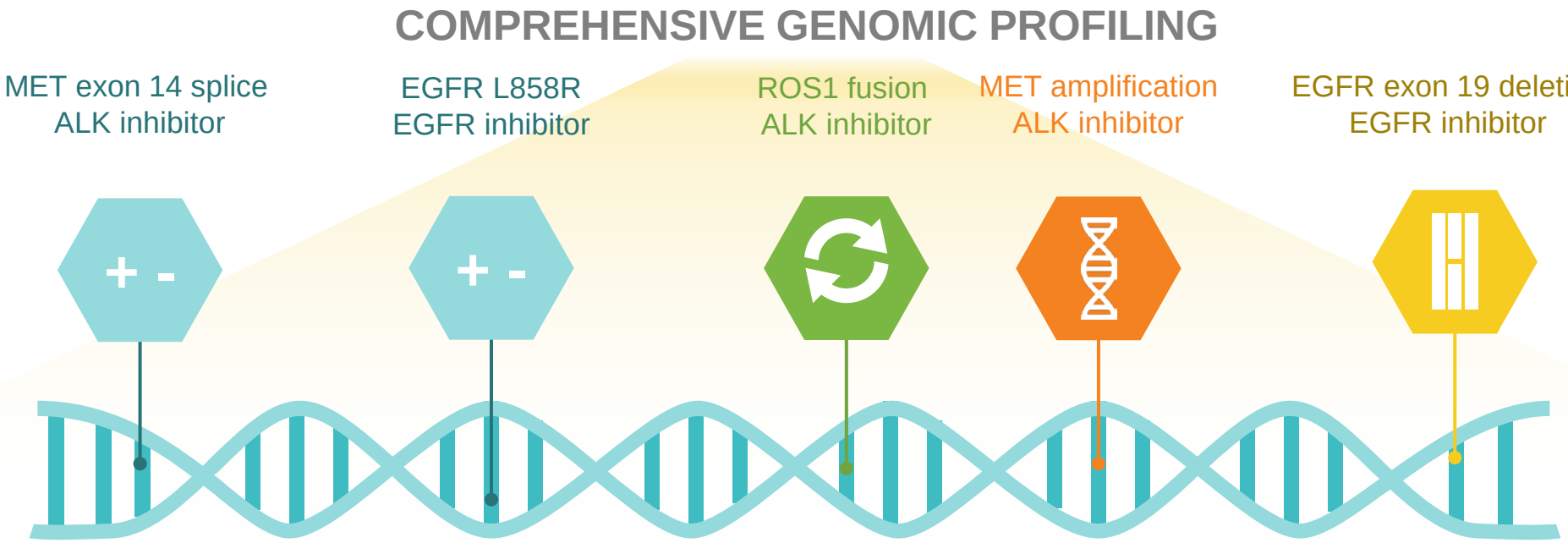
Foundation Medicine finds more targets

…Comprehensive Genomic Profiling identifies all four classes of alterations with validated performance



Validated performance published in peer-reviewed journal*

Base substitutions:
Sensitivity: >99%
PPV: >99%

Rearrangements:
Sensitivity: ≥90%
PPV: >99%

Copy number alterations:
Sensitivity: >95%
PPV: >99%

Insertions/deletions:
Sensitivity: >97%
PPV: >99%

** Frampton G et al. (2013) Nature Biotech 31, 1023-34*

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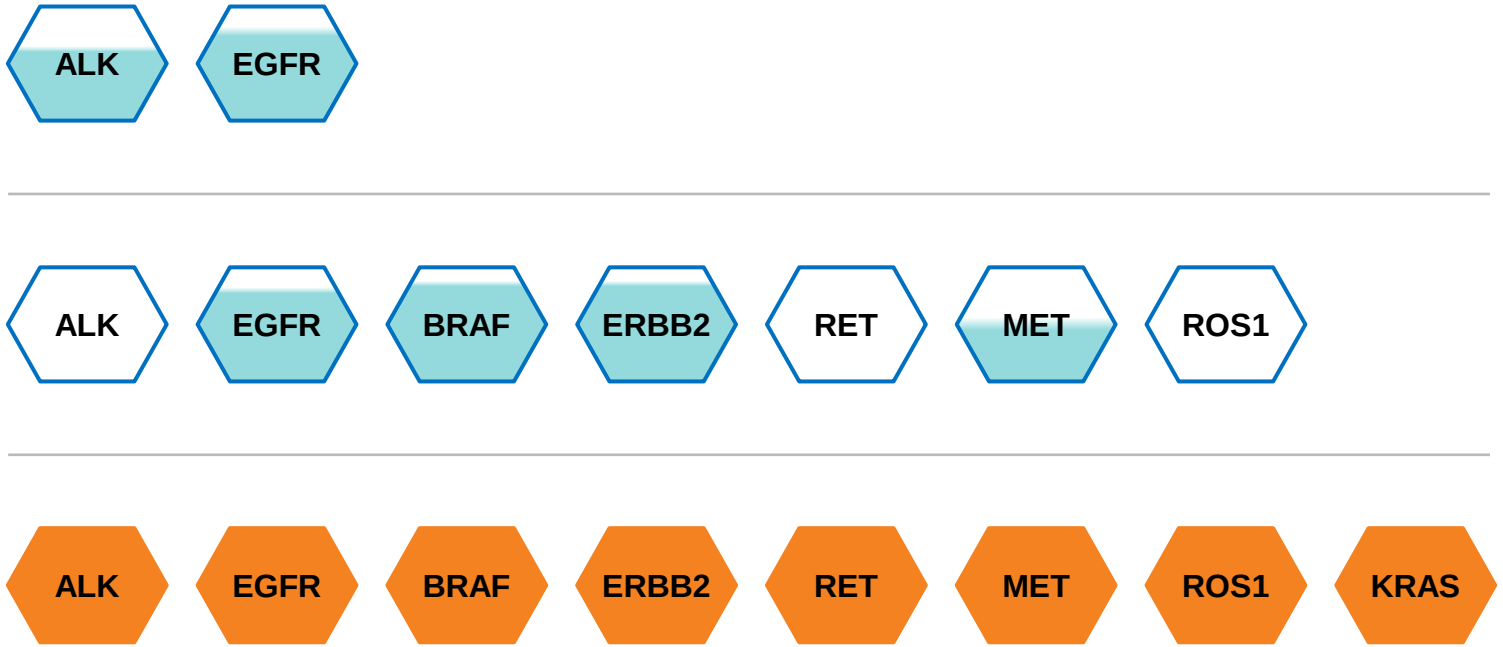
Improve profiling of NSCLC patients

FoundationOne finds more alterations associated with NCCN guidelines than single gene or hot spot NGS

SINGLE GENE TESTING
misses up to 35% of ALK rearrangements by FISH[1] and 17% of EGFR alterations by hot spot test[2]

Hot spot NGS
Up to 50% of targetable alterations can be missed without supplemental FISH[3]

FOUNDATIONONE®
detects all four classes of NSCLC clinically relevant alterations[3] and genetic biomarkers[4] included in the NCCN Guidelines®



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1. Ali S et al. (2016) Oncologist. doi:10.1634/theoncologist.2015–0497.
2 Schrock AB et al. (2016) Clin Cancer Res. Mar 1. pii: clincanres.1668.2015.
3 Suh J et al. (2016) Oncologist. http://dx.doi.org/10.1634/theoncologist.2016–0030
4. NCCN Guidelines® Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung

Clinical utility of finding more alterations with FoundationOne

NSCLC patients can benefit from targeted therapies

17% of EGFR exon 19 deletions missed by hotspot tests[1]

75% of NSCLC patients with EGFR exon 19 deletions can respond to EGFR tyrosine kinase inhibitors, with median OS > 1 year[2]

35% of ALK-rearranged cases missed by FISH[3]

80% of ALK-rearranged patients identified by FoundationOne respond to ALK inhibitor crizotinib[3]

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1. Schrock AB et al. (2016) Clin Cancer Res. Mar 1.
2. Sequist LV et al. (2007) J Clin Oncol. 25:587–95.
3. Ali AM et al. (2016) The Oncologist

Patient case: EGFR/ALK negative

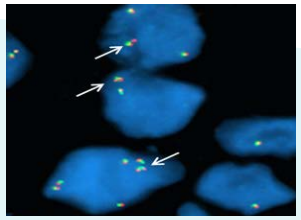
Identification of complex fusion led to treatment/response

Patient Information

- 43-year-old male
- Never-smoker

At Presentation

- Pericardial tamponade
- No detection of *EGFR* mutation; atypical FISH staining for *ALK*



Atypical pattern of double 3'ALK signals (red) fused with 5'ALK signal (green)

Diagnosis

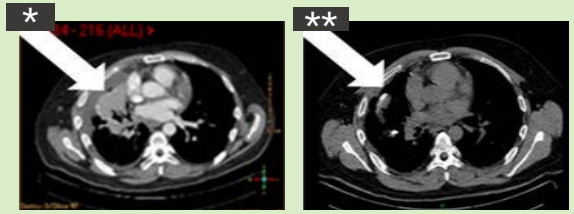
- **Metastatic NSCLC** with a pericardial tamponade

Treatment status

- Disease **progression** despite 4 cycles of cisplatin/pemetrexed

FoundationOne® analysis and subsequent treatment

- Identification of complex EML4-ALK fusion separated by genomic shards
- Initiation of treatment with crizotinib



Chest PET-CT before (*) and after 4 months (**) crizotinib treatment showing a significant shrinkage of the primary lesion

Patient had a rapid response to crizotinib treatment; **75% shrinkage** of primary lesion (RECIST) after 4 months of treatment

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Peled N et al. (2012) J Thorac Oncol. 7(9):e14-6.

FoundationOne may lead to improved outcomes

Studies show potential in other tumor types, ability to impact physician decisions

Triple-negative breast cancers

Targeted therapy based on tumor genomic alterations

Improved response (33% vs. 8%, p=0.018) & **longer progression-free survival**[1] (6.4 vs. 1.9 months; p=0.001)

Rare/refractory gynecological cancers

Targeted therapy based on tumor genomic alterations

Radiologic response or stability in 64% of patients[2]

Breast cancer

Targeted therapy based on tumor genomic alterations

41% of treatment decisions influenced by FoundationOne[3]

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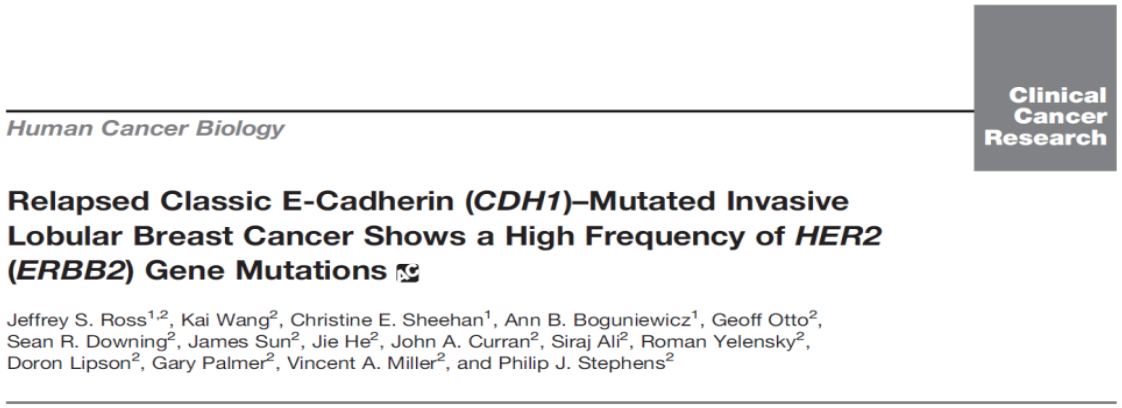
1. *Ganesan P et al. (2014) Mol Cancer Ther; 13(12); 3175–84.*
2. *Rodriguez-Rodriguez L et al. (2016) Gynecologic Oncology 141: 2–9*
3. *Reinbolt RE et al. (2016) Ohio State University, ASCO poster*

Targeting *ERBB2* Mutations in Metastatic Breast Cancer



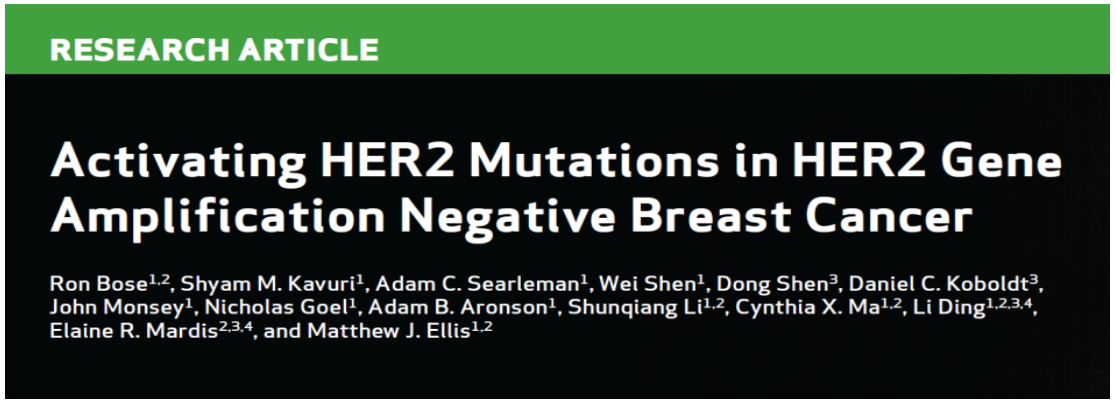
Clinical Cancer Research

Human Cancer Biology

Relapsed Classic E-Cadherin (*CDH1*)–Mutated Invasive Lobular Breast Cancer Shows a High Frequency of *HER2* (*ERBB2*) Gene Mutations

Jeffrey S. Ross[1,2], Kai Wang[2], Christine E. Sheehan[1], Ann B. Boguniewicz[1], Geoff Otto[2], Sean R. Downing[2], James Sun[2], Jie He[2], John A. Curran[2], Siraj Ali[2], Roman Yelensky[2], Doron Lipson[2], Gary Palmer[2], Vincent A. Miller[2], and Philip J. Stephens[2]

- Responses reported with both antibody therapeutics and kinase inhibitors
- 38% response rate in *ERBB2* mutated BC to kinase inhibitor at SABCS
- High frequency (> 30%) of *ERBB2* mutations in *CDH1* mutated relapsed ILC



RESEARCH ARTICLE

Activating HER2 Mutations in HER2 Gene Amplification Negative Breast Cancer

Ron Bose[1,2], Shyam M. Kavuri[1], Adam C. Searleman[1], Wei Shen[1], Dong Shen[3], Daniel C. Koboldt[3], John Monsey[1], Nicholas Goel[1], Adam B. Aronson[1], Shunqiang Li[1,2], Cynthia X. Ma[1,2], Li Ding[1,2,3,4], Elaine R. Mardis[2,3,4], and Matthew J. Ellis[1,2]

JNCCN The official journal of the NCCN

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***HER2*-Mutated Breast Cancer Responds to Treatment With Single-Agent Neratinib, a Second-Generation HER2/EGFR Tyrosine Kinase Inhibitor**

Noa Efrat Ben-Baruch, MD[a], Ron Bose, MD, PhD[b,c], Shyam M. Kavuri, PhD[b,c,d], Cynthia X. Ma, MD, PhD[b,c] and Matthew J. Ellis, MB, BChir, PhD, FRCP[b,c,d]

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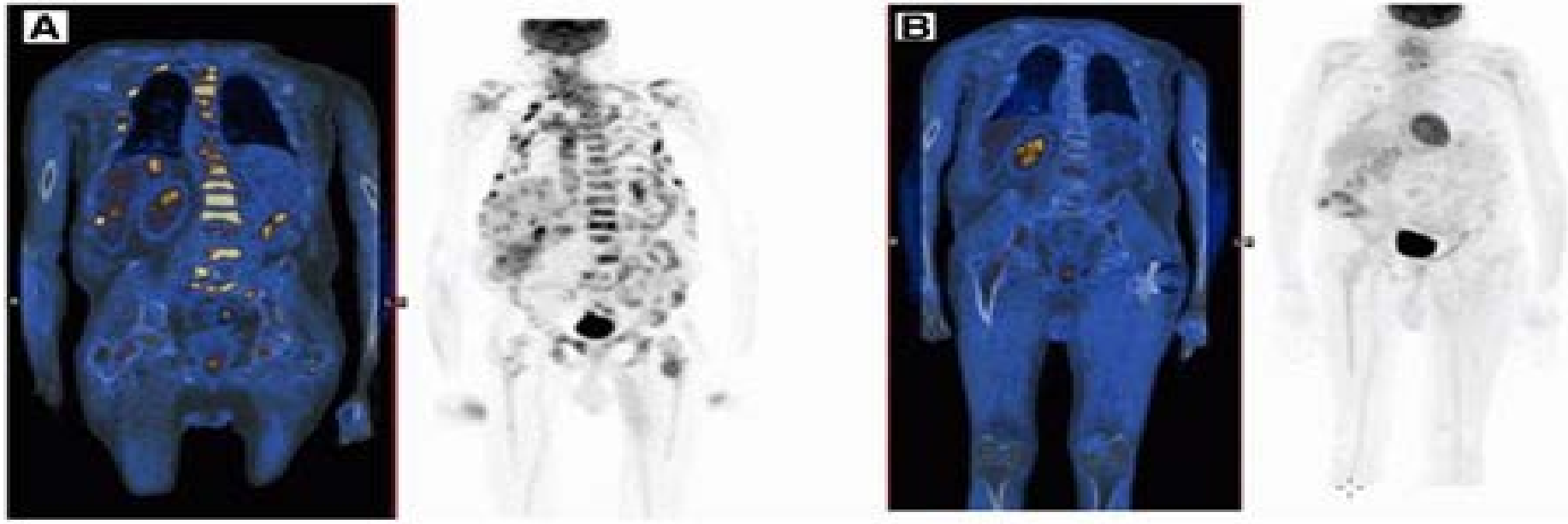
Washington University in St. Louis School of Medicine

Non-Amplification *ERBB2* Genomic Alterations in 5,605 Cases of Refractory and Metastatic Breast Cancer: an Emerging Opportunity for anti-HER2 Targeted Therapies

Ross JS [1, 2], Wang K[1], Ali SM[1], Chumsri S[3], Elvin JA[1], Bose R[3], Vergilio J[1], Suh J[1], Yelensky R[1], Lipson D[1], Chmielecki J[1], Miller, VA[1], Stephens PJ[1]

[1]Foundation Medicine, Inc., Cambridge, MA, [2]Albany Medical College Albany, NY, [3]Washington University School of Medicine

Response of a HER2 FISH/IHC Negative Cutaneous Adnexal Carcinoma with an *ERBB2* S310f Mutation to anti-HER2 Targeted Therapy



Vornicova O et al. The Oncologist 2014;19:1006-1007

The Oncologist

Why consider profiling with Foundation Medicine?

- **Profiling has been shown to improve outcomes for patients** with lung cancer or considering clinical trials, while evidence is evolving in additional indications[1-3]
- **Foundation Medicine's** profiling services are designed to **capture all four types of genomic alterations** which single gene and hotspot NGS testing can miss
- **Proprietary bioinformatics** have been optimized over 90,000 cases to call alterations
- These alterations are delivered in a **comprehensive report** which describes potential therapies, trials, and the latest clinical literature to inform physician's decisions
- Evidence has shown **FoundationOne detects alterations in patients that are pan-negative with single gene panels[4-6], and in some indications can improve outcomes[8-4, 7-8]**

Profiling with FoundationOne finds more clinically-relevant alterations and can lead to better patient outcomes

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1. Kris MG et al. (2014). JAMA 311(19):1998-2006; 2. Barlesi F et al. (2016). Lancet S0140-6736(16); 3. Ganesan P et al. (2014) Mol Cancer Ther; 13(12); 3175–84; 4. Ali S et al. (2016) Oncologist. 5 Schrock AB et al. (2016) Clin Cancer Res. Mar 1. pii: clincanres.1668.2015; 6 Suh J et al. (2016) Oncologist; 7. Drilon A et al. (2015) Clin Cancer Res 21(16):3631-9; 8. Rodriguez-Rodriguez L et al. (2016) Gynecologic Oncology 141: 2–9

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Doing now what patients need next

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