

ORGANIZATION AND ROLE OF THE MOLECULAR TUMOR BOARD

Rodrigo Dienstmann



(PERSONAL) CONFLICTS OF INTEREST

Advisory role: Roche, Foundation Medicine
Boehringer-Ingelheim

Speaker's fee: Roche
Amgen
Ipsen
Servier
Sanofi
MSD

Research grant: Merck
Pierre Fabre
BMS

WHY MOLECULAR TUMOR BOARDS?



Genomic testing



Genomic reporting



Genomic matching



APPROVED (OR CLOSE TO) GENOMICS-GUIDED THERAPIES



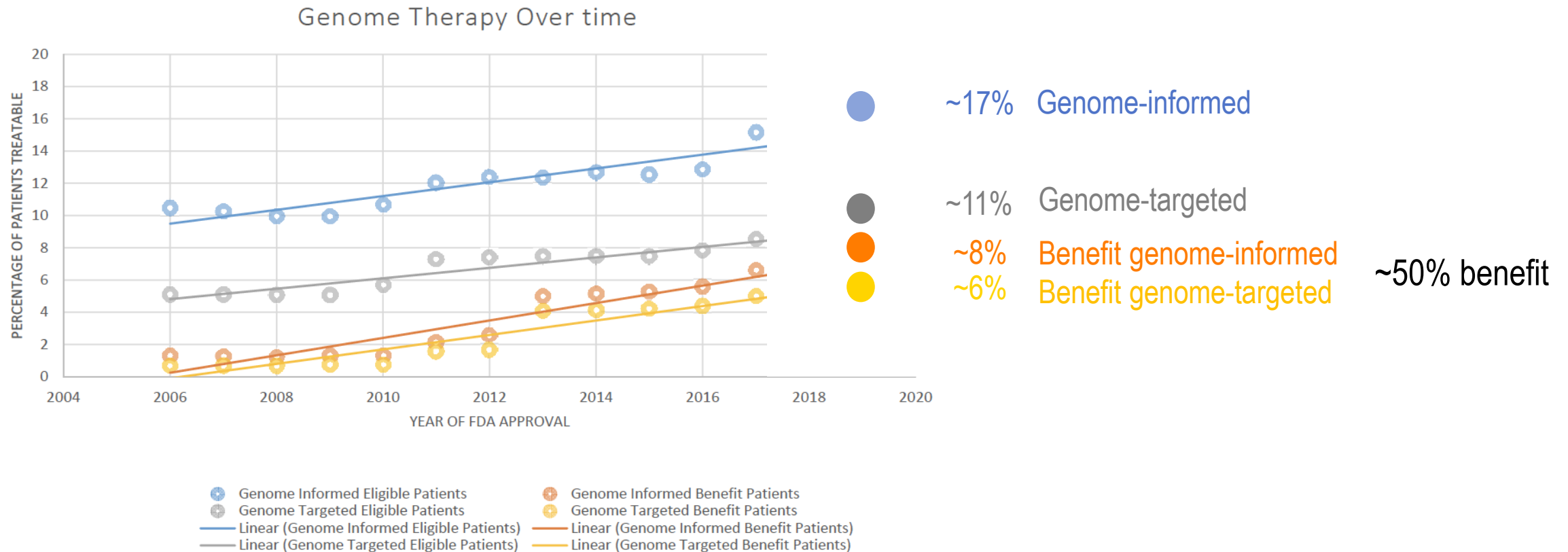
<i>ABL1</i> fusion/ mut	Leukemia	Imatinib, Dasatinib, Nilotinib, Bosutinib, Ponatinib
<i>ALK</i> fusion/ mut	Lung	Crizotinib, Ceritinib, Alectinib, Lorlatinib, Brigatinib
<i>BRAF</i> V600 mut	Melanoma, Lung, Thyroid, CRC	Vemurafenib, Dabrafenib, Encorafenib, Trametinib, Cobimetinib, Binimetinib
<i>BRCA1/2</i> mut	Ovary, Breast, Pancreas, Prostate	Olaparib, Niraparib, Rucaparib, Talazoparib
<i>EGFR</i> mut	Lung	Gefitinib, Erlotinib, Afatinib, Dacomitinib, Osimertinib
<i>ERBB2</i> ampl/mut	Breast, Gastric, CRC	Trastuzumab, Pertuzumab, T-DM1, Lapatinib, Neratinib
<i>FGFR2/3</i> fusions/ mut	Bladder	Erdafitinib
<i>FLT3</i> mut	Leukemia	Midostaurin, Gilteritinib
<i>IDH1/2</i> mut	Leukemia, Biliary tract	Ivosidenib, Enasidenib
<i>KIT</i> mut	GIST	Imatinib, Sunitinib, Regorafenib, Sorafenib
<i>KRAS</i> wt	CRC	Cetuximab, Panitumumab
<i>MET</i> ampl/ exon 14 skip	Lung, Renal	Crizotinib, Cabozantinib
<i>NRAS</i> wt	CRC	Cetuximab, Panitumumab
<i>NTRK1/2/3</i> fusion	All solid tumors	Larotrectinib, entrectinib
<i>PDGFB</i> fusion	Sarcoma	Imatinib
<i>PDGFRA/B</i> fus	Leukemia	Imatinib
<i>PIK3CA</i> mut	Breast	Alpelisib
<i>ROS1</i> fusion	Lung	Crizotinib
<i>TSC1/2</i> mut	Brain	Everolimus

EMERGING GENOMICS-GUIDED THERAPIES

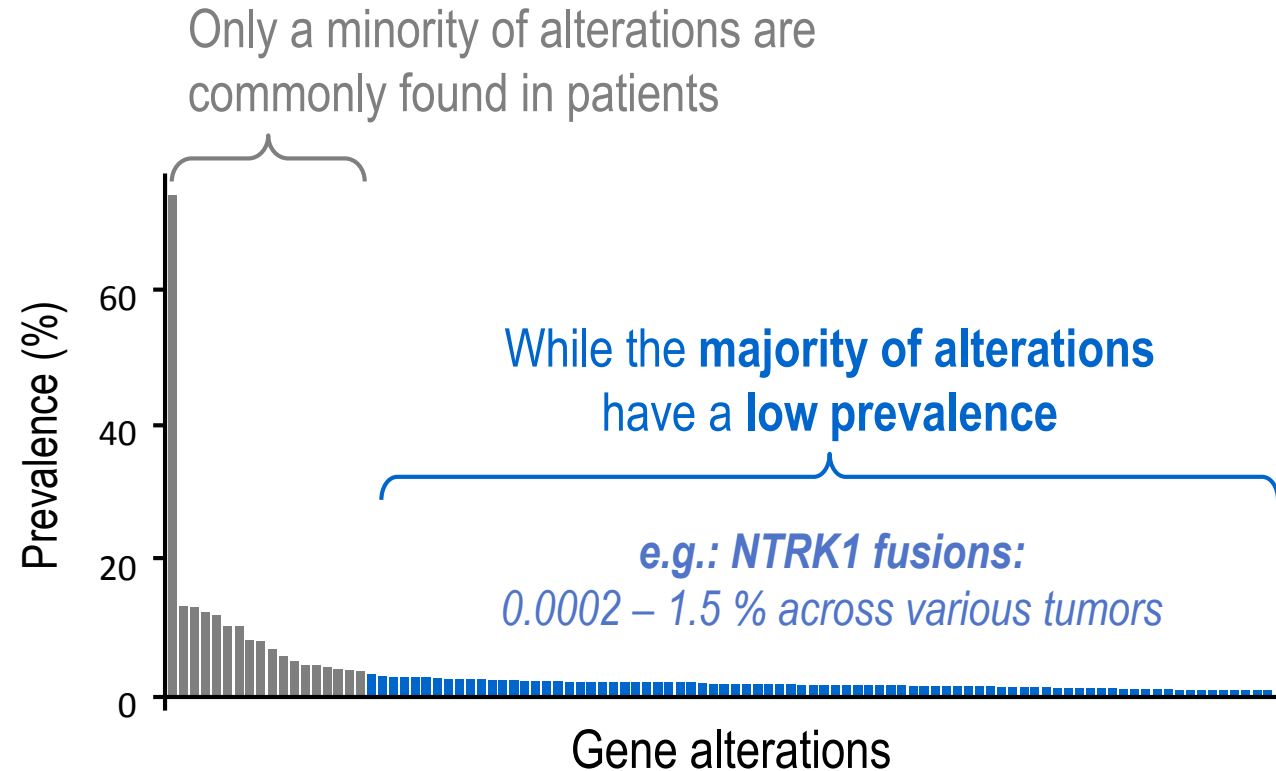


<i>ATM</i> mut	Prostate	Olaparib
<i>BRAF</i> L596/K601 mut	Melanoma	Trametinib
<i>CDK4</i> amp	Sarcomas	Abemaciclib, Palbociclib, Ribociclib
<i>ESR1</i> mut	Breast	Fulvestrant
<i>EZH2</i> mut	Lymphoma	Tazemetostat
<i>HRAS</i> mut	Head & Neck	Tipifarnib
<i>JAK2</i> fus	Leukemia	Ruxolitinib
<i>KRAS</i> G12C mut	Lung	AMG510
<i>MAP2K1</i> mut	Ovarian, Melanoma, Lung	Cobimetinib, Trametinib
<i>MTOR</i> mut	Renal, Bladder	Everolimus, Temsirolimus
<i>NRAS</i> mut	Melanoma	Cobimetinib, Binimetinib
<i>PALB2</i> mut	Pancreas, Prostate	Olaparib
<i>PTCH1</i> mut	Skin, Embryonal	Vismodegib, Sonidegib
<i>RET</i> fus/mut	Lung, Thyroid	Selpercatinib, pralsetinib

LINEAR INCREASE (0.5% - 1.0% ANNUAL) IN GENOMICS-GUIDED THERAPIES (USA, 2006-2018)



MANY TARGETS, SMALL POPULATIONS



INCREASED COMPLEXITY OF GENOMIC BIOMARKERS

Targeted inhibitors

+

Cancer immunotherapies

**Single-gene
biomarkers**

(e.g. *EGFR*, *ALK*,
ROS1, etc.)

**Multiple-gene
biomarkers**

(e.g. *BRCA1/2*,
PALB2, etc.)

Complex genomic signatures

(Homologous
Recombination
Deficiency)

(Microsatellite
instability)

(Tumour
mutational
burden)

**Decreasing utility of single
marker testing**

**Increasing need for
comprehensive genomic profiling**

MEDICAL KNOWLEDGE IS CONSTANTLY INCREASING

Clinical studies presented
at major congresses

328 abstracts from ASCO 2018 contained the keywords 'profiling' or 'targeted therapy' in combination with 'clinical study' or 'clinical trial'

Clinically relevant genomic
alterations

203 variants of genes are associated with cancer therapies

- Approved by the FDA
- Used as standard of care or
- With demonstrated clinical evidence

Available targeted
therapies

125 unique targeted therapies are approved across a range of cancers

Therapies in
development

At least **31** unique therapies are being assessed in pan-tumour basket trials

How to manage increasing available clinic-genomic data and knowledge?

WHY MOLECULAR TUMOR BOARDS?



Genomic testing



Genomic reporting



Genomic matching





“MINIMAL” DATA IN GENOMICS REPORT (MY OPINION)

THERAPEUTIC

Functional variants (mutation, copy number, fusion)

Level of evidence for actionability

*On-label vs. Clinical trial/Off-label
vs. Biological relevance*

Resistance markers

Upfront and/or acquired (co-existing alterations)

Mutant allele fraction

Clonality vs. subclonality

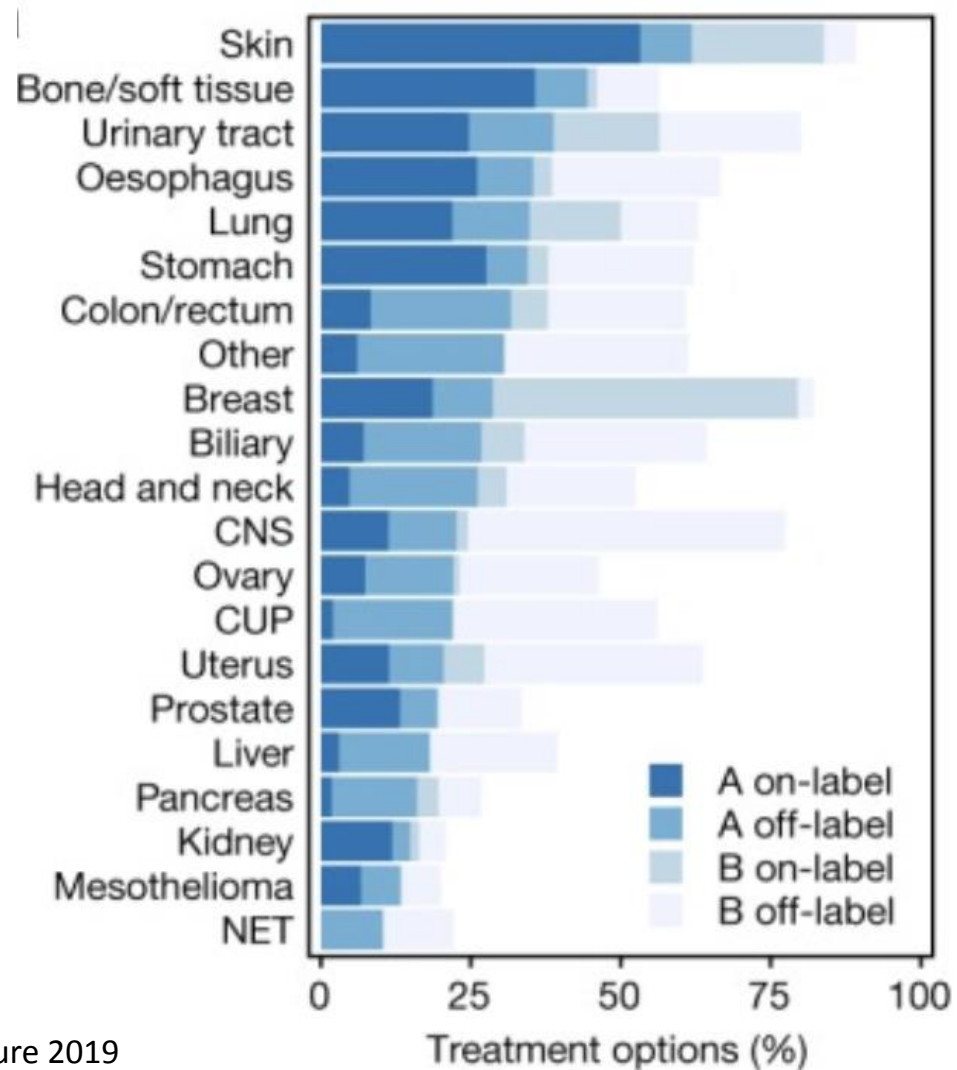
Variants of unknown significance

Other information

Mutation signatures: HRD, MSI, TMB, others

Germline testing recommendations

ACTIONABILITY PREVALENCE



Level A – approved or guidelines
Level B – clinical trial or hypothetical target

MULTIPLE PUBLIC KNOWLEDGEBASES

- ♦ OncoKB (MSKCC) - <http://oncokb.org/#/>
- ♦ MyCancerGenome (Vanderbilt) - <https://www.mycancergenome.org/>
- ♦ CGI (Barcelona) - <https://www.cancergenomeinterpreter.org/home>
- ♦ CIViC (WashU) - <https://civic.genome.wustl.edu/#/home>
- ♦ PMKB (Cornell) - <https://pmkb.weill.cornell.edu/>
- ♦ JAX-Clinical Knowledgebase (Jackson lab) - <https://ckb.jax.org/>
- ♦ PCT (MD Anderson) - <https://pct.mdanderson.org/>
- ♦ MTBP - <https://public-mtb.scilifelab.se/>

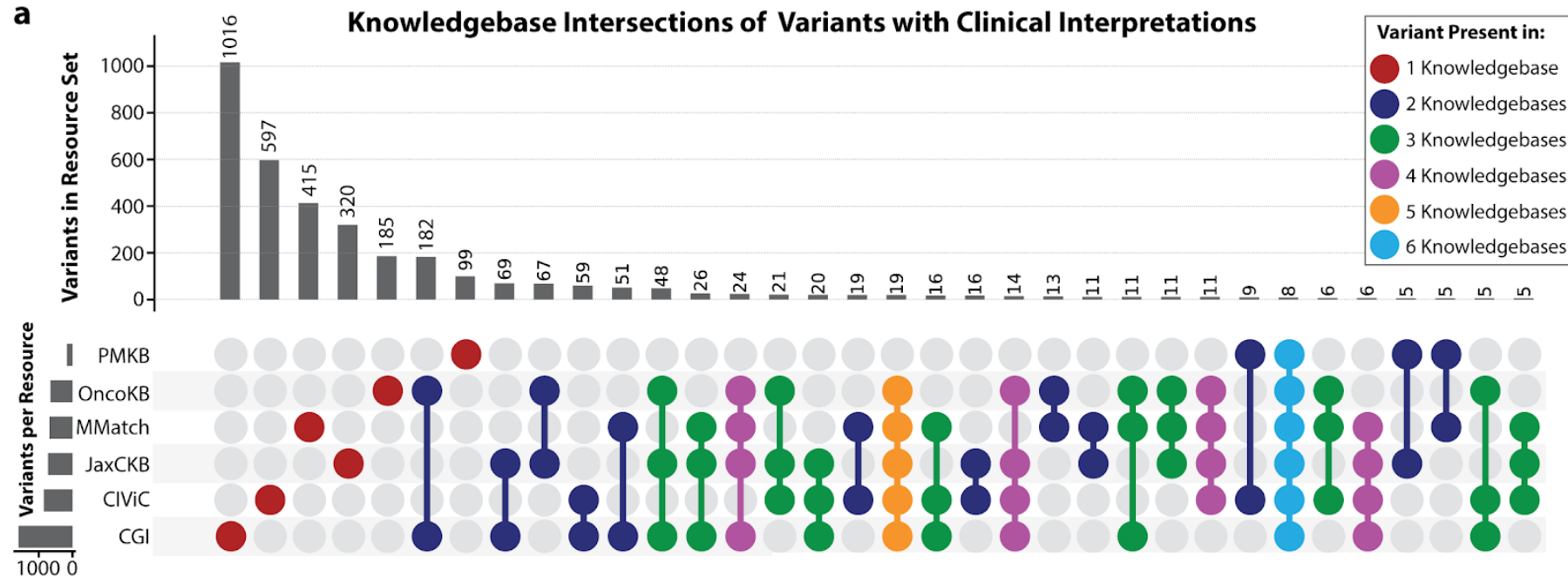
- ♦ cBioPortal - <https://cbioportal.org/>
- ♦ COSMIC (Sanger) - <http://cancer.sanger.ac.uk/cosmic>

- ♦ Clinical Trials - <https://www.clinicaltrials.gov/>

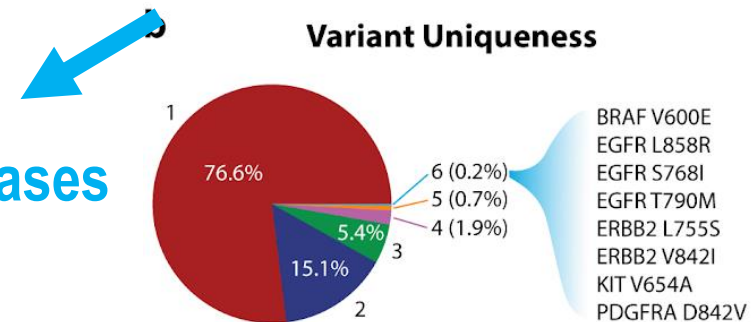
FUNCTIONAL
AND/OR
ACTIONABILITY

MOLECULAR
EPIDEMIOLOGY

REDUNDANT EFFORTS NON-OVERLAPPING INTERPRETATIONS



Only 8 gene variants across all databases



OncoKB FOR TREATMENT DECISION MAKING

Example: *Rectal cancer patient refractory to SoC therapy, CGP: BRAF L597P*

[Levels of Evidence](#)[Actionable Genes](#)[Cancer Genes](#)[Data Access](#)[About](#)[Team](#)[News](#)[Terms](#)

Precision Oncology Knowledge Base

642

Genes

4932

Alterations

45

Tumor Types

89

Drugs

BRAF L597P

Level 1

FDA-approved
25 Genes

Level 2

Standard care
13 Genes

Level 3

Clinical evidence
30 Genes

Level 4

Biological evidence
20 Genes

Level R1

Standard care
5 Genes

Level R2

Clinical evidence
6 Genes

OncoKB FOR TREATMENT DECISION MAKING

Example: Rectal cancer patient refractory to SoC therapy, CGP: BRAF L597P



BRAF L597P

Likely Oncogenic , Level 3A

BRAF, an intracellular kinase, is frequently mutated in melanoma, thyroid and lung cancers among others. The BRAF L597P mutation has not been functionally or clinically validated. However, BRAF L597Q/V are known to be oncogenic, and therefore BRAF L597P is considered likely oncogenic.

See additional BRAF information ⓘ

Search:

▲ Alteration	Cancer Type	Drug(s)	▼ Level	Citations
L597	Melanoma	Trametinib	3A	3 references
L597	All Solid Tumors	PLX8394	4	5 references
Oncogenic Mutations	Histiocytosis	Cobimetinib	3A	2 references

OncoKB FOR TREATMENT DECISION MAKING

Example: Rectal cancer patient refractory to SoC therapy, CGP: BRAF L597P



Levels of Evidence Actionable Genes Cancer Genes Data Access About Team News Terms



BRAF L597P

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Search:

▲ Alteration	Cancer Type		▼ Level	Citations
L597	Melanoma	Compelling biological evidence supports the biomarker as being predictive of response to a drug but neither biomarker and drug are standard of care	3A	3 references
L597	All Solid Tumors	PLX8394	4	5 references
Oncogenic Mutations	Histiocytosis	Cobimetinib	3A	2 references

OncoKB FOR TREATMENT DECISION MAKING

Example: Rectal cancer patient refractory to SoC therapy, CGP: BRAF L597P



Levels of Evidence Actionable Genes Cancer Genes Data Access About Team News Terms



BRAF L597P

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▲ Alteration	Cancer	Drug	Level	Citations
L597	Melanom			3 references
L597	All Solid Tumors	PLX8394	4	5 references
Oncogenic Mutations	Histiocytosis	Cobimetinib	3A	2 references

[RAF inhibitors that evade paradoxical MAPK pathway activation.](#)

Zhang C et al. Nature. 2015

PMID: [26466569](#)

[PLX8394, a new generation BRAF inhibitor, selectively inhibits BRAF in colonic adenocarcinoma cells and prevents paradoxical MAPK pathway activation.](#)

Tutuka CSA et al. Mol Cancer. 2017

PMID: [28659148](#)

[Tumours with class 3 BRAF mutants are sensitive to the inhibition of activated RAS.](#)

Yao Z et al. Nature. 2017

PMID: [28783719](#)

[RAF inhibitor PLX8394 selectively disrupts BRAF dimers and RAS-independent BRAF-mutant-driven signaling.](#)

Yao Z et al. Nat Med. 2019

PMID: [30559419](#)

Search:

ally or clinically validated.

OncoKB FOR TREATMENT DECISION MAKING

Example: Rectal cancer patient refractory to SoC therapy, CGP: BRAF L597P

OncoKB

Levels of Evidence

BRAF L597P

Likely Oncogenic , Level 3A

BRAF, an intracellular kinase, is frequently mutated in colorectal cancer. However, BRAF L597Q/V are known to be associated with resistance to anti-EGFR therapy.

See additional BRAF information ⓘ

▲ Alteration

L597

L597

Oncogenic Mutations

NCBI

Resources

How To

PubMed

US National Library of Medicine

National Institutes of Health

PubMed

Advanced

Format: Abstract

Send to

Nat Med. 2019 Feb;25(2):284-291. doi: 10.1038/s41591-018-0274-5. Epub 2018 Dec 17.

RAF inhibitor PLX8394 selectively disrupts BRAF dimers and RAS-independent BRAF-mutant-driven signaling.

Yao Z^{1,2}, Gao Y¹, Su W¹, Yaeger R^{2,3}, Tao J², Na N¹, Zhang Y⁴, Zhang C⁴, Rymar A⁴, Tao A⁵, Timaul NM¹, Mcgriskin R¹, Outmezguine NA¹, Zhao H¹, Chang Q¹, Qeriqi B¹, Barbacid M⁶, de Stanchina E¹, Hyman DM^{2,3}, Bollag G⁴, Rosen N^{7,8,9}.

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6 Molecular Oncology Programme, Centro Nacional de Investigaciones Oncológicas, Madrid, Spain.

7 Program in Molecular Pharmacology, Memorial Sloan Kettering Cancer Center, New York, NY, USA. rosen@mskcc.org.

8 Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA. rosen@mskcc.org.

9 Center for Mechanism-Based Therapeutics, Memorial Sloan Kettering Cancer Center, New York, NY, USA. rosen@mskcc.org.

Abstract

Activating BRAF mutants and fusions signal as RAS-independent constitutively active dimers with the exception of BRAF V600 mutant alleles which can function as active monomers¹. Current RAF inhibitors are monomer selective, they potently inhibit BRAF V600 monomers but their inhibition of RAF dimers is limited by induction of negative cooperativity when bound to one site in the dimer¹⁻³. Moreover, acquired resistance to these drugs is usually due to molecular lesions that cause V600 mutants to dimerize⁴⁻⁸. We show here that PLX8394, a new RAF inhibitor⁹, inhibits ERK signaling by specifically disrupting BRAF-containing dimers, including BRAF homodimers and BRAF-CRAF heterodimers, but not CRAF homodimers or ARAF-containing dimers. Differences in the amino acid residues in the amino (N)-terminal portion of the kinase domain of RAF isoforms are responsible for this differential vulnerability. As a BRAF-specific dimer breaker, PLX8394 selectively inhibits ERK signaling in tumors driven by dimeric BRAF mutants, including BRAF fusions and splice variants as well as BRAF V600 monomers, but spares RAF function in normal cells in which CRAF homodimers can drive signaling. Our work suggests that drugs with these properties will be safe and useful for treating tumors driven by activating BRAF mutants or fusions.

unctionally or clinically validated.

Search:

Citations

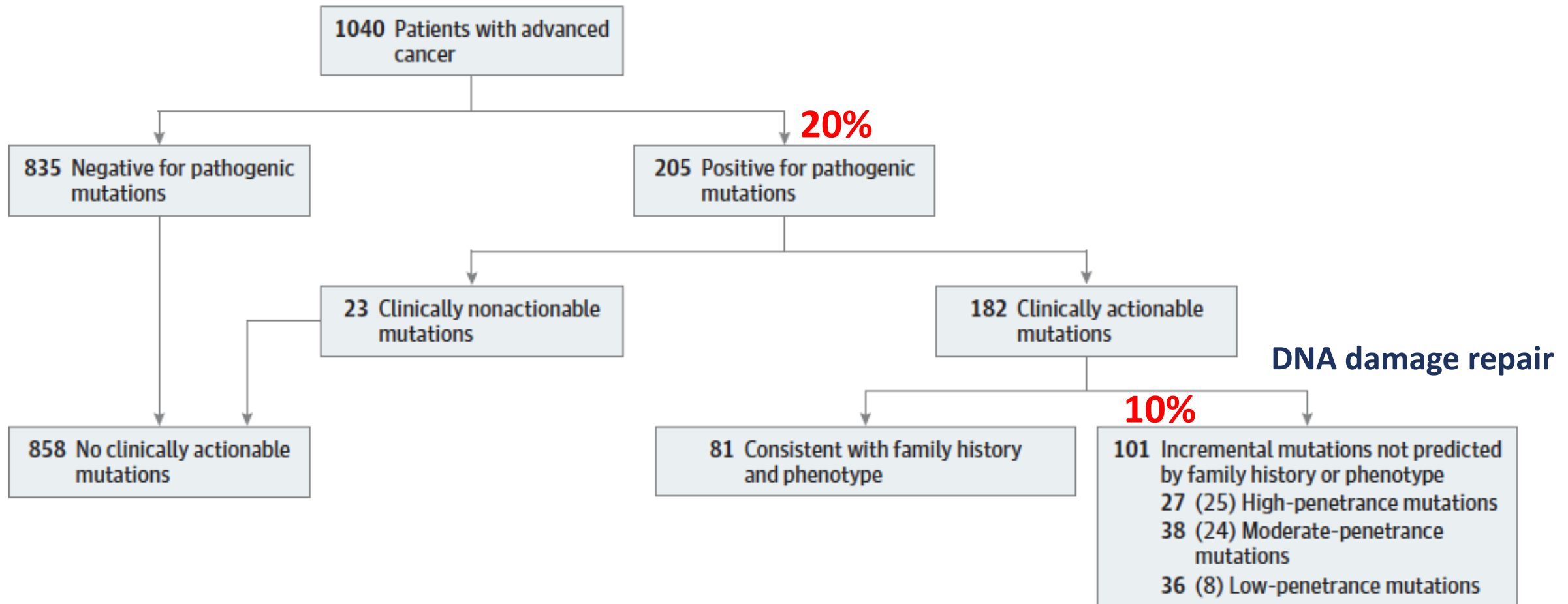
3 references

5 references

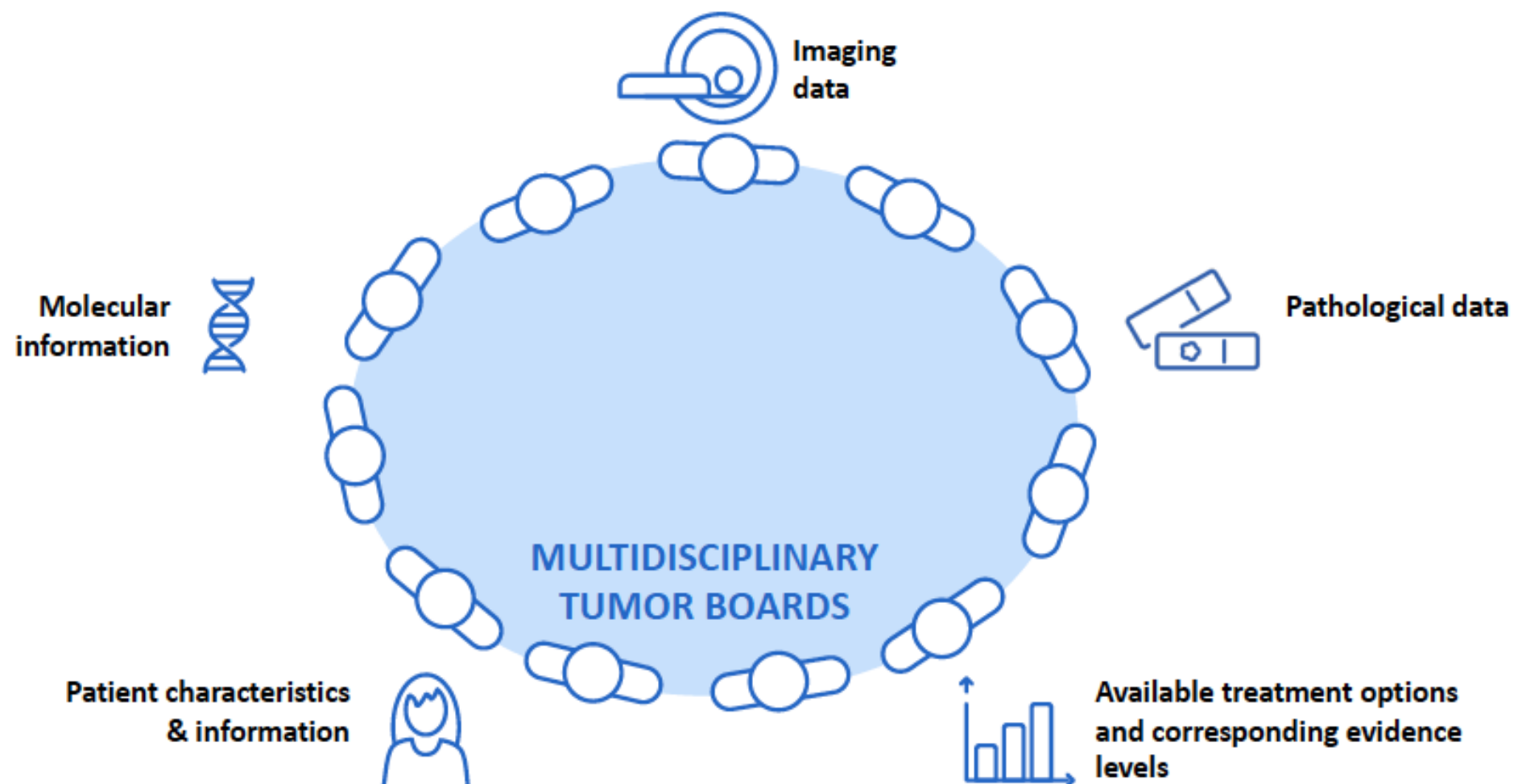
2 references

CGP: comprehensive genomic profiling, SoC: standard of care

UNSUSPECTED GERMLINE ACTIONABLE ALTERATIONS



MULTIDISCIPLINARY DECISION MAKING



MULTIDISCIPLINARY DECISION MAKING

Let's look at how to address the complexity of molecular information in more detail...

Molecular information



Imaging data



Pathological data



Patient characteristics & information

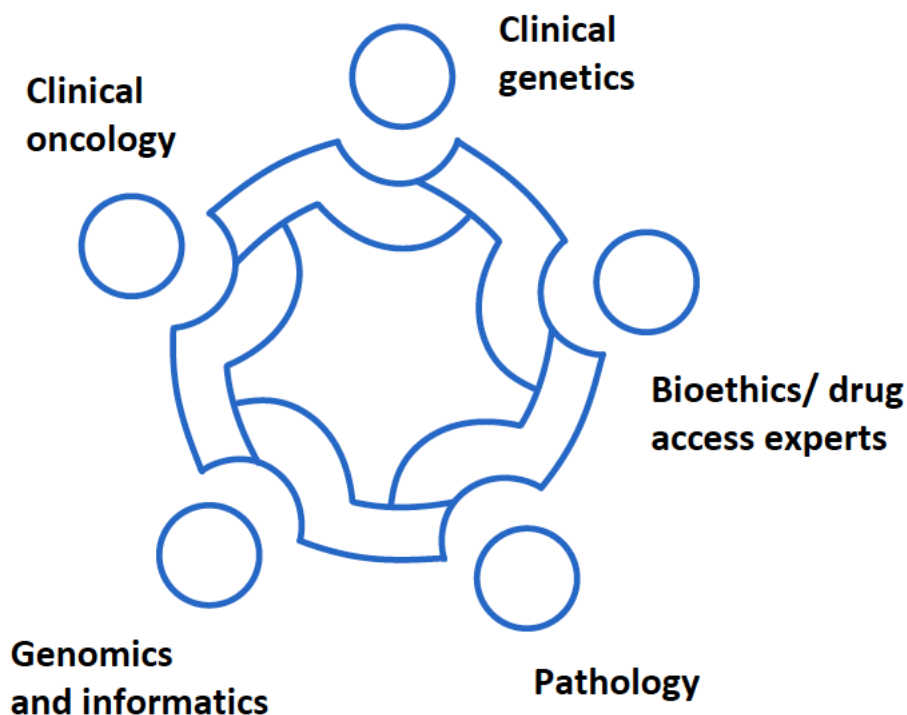


MULTIDISCIPLINARY
TUMOR BOARDS

Available treatment options
and corresponding evidence levels



MOLECULAR TUMOR BOARD



MTBs aim to improve patient outcomes by:

- > **Providing a platform** to discuss complex cases
- > Enabling multidisciplinary discussion for **integration of diverse patient information**
- > Providing **more precise, unified therapy** recommendations
- > **Identifying patients** eligible for clinical trials
- > **Aligning and optimising** testing and treatment **practices**
- > Continuous **medical education** on **emerging biomarkers**

MOLECULAR TUMOR BOARD DISCORDANCES












26 years-old, bladder cancer, chemotherapy-refractory

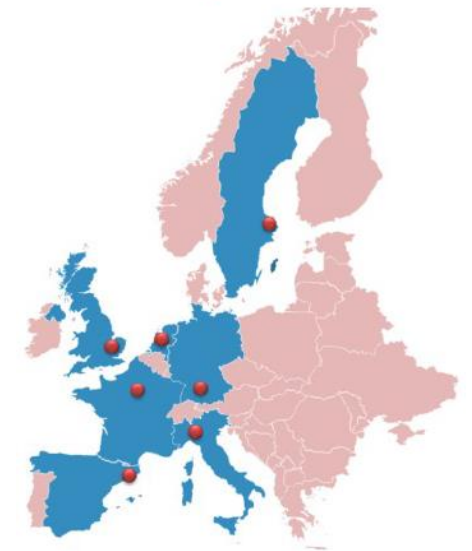
NGS: **KRAS G12V**, *TP53* H214fs, *CDKN2C* L65F, *CTNNA1* K577_L578 > TKL, *MAP3K1* T949-E950insT, *MYCN* E47fs*8 P365A, **JAK1 I597M**, *FANCL* T367fs*12 **PIK3CA ampl**, **MYC ampl**, *MYCL1* ampl, *SOX2* ampl, *MUTYH* amp (all > 6 copies)

Tumor Board	Recommendation	Provided Rationale	Additional Recommendation
1	<i>PIK3CA</i> , <i>AKT</i> , or mTOR	<i>PIK3CA</i> mutation	
2	<i>JAK1</i> allele frequency testing (infiltrating blood cells?) and if consistent with tumor: ruxolitinib	<i>JAK1</i> mutation (after considering allele frequency)	
3	Immunotherapy, atezolizumab	Independent of biomarker	Consider genetic counseling and potential germline testing (mutation burden, <i>TP53</i> mutation, patient age)
4	Phase I trial with bromodomain inhibitor	<i>MYC</i> amplification	Everolimus clinical trial (<i>PIK3CA</i> amplification), sorafenib (<i>KRAS</i> mutation)
5	<i>PIK3CA</i> or mTOR inhibitor	<i>PIK3CA</i> amplification (data from case study)	MEK inhibitor (<i>TP53</i> and <i>KRAS</i> mutation) or checkpoint inhibition (independent of biomarker, despite potential <i>JAK1</i> resistance)
6	N/A because of missing information		

INTERACTIVE MOLECULAR TUMOR BOARD PORTAL

The MTBP supports the Cancer Core Europe clinical decisions by classifying the **functional** and **predictive relevance** of the germline/somatic tumor variants

<ul style="list-style-type: none">- variant pathogenicity	 	<ul style="list-style-type: none">- gene/variant information in tumor samples
<ul style="list-style-type: none">- variant oncogenicity	 	 
<ul style="list-style-type: none">- biomarkers of disease diagnosis, prognosis and drug response	  	<ul style="list-style-type: none">- gene/variant information in healthy samples  



<http://www.mtbp.org>

INTERACTIVE MOLECULAR TUMOR BOARD PORTAL

User: F. Farlane
Role: clinical PI
Logout

- Patient list
- Repository
- Analyse
- Upload
- Account
- FAQ

Sample
CCE-011-0219
Not reviewed

Reports
Functionality
Biomarkers

Variants functionality report

Sample CCE-011-0219

Analysis run date: 2019-08-12
Pipeline version: v2.4, [details](#)

Current patient status: Not Reviewed [Change status](#) [See history](#) [Export report](#)

Patient: female, 37 yo
Cancer type: Breast invasive ductal carcinoma
Biopsy site: primary site
Center: CMHIO
Informed consent: 2019-07-27
Sample sent: 2019-08-01
Decision: -
Tumor Cellularity: 80%

Tumor mutation burden: [?](#)
Low (5.1 mut/Mb)

Tumor VAF histogram: [?](#)

Putative functional variants: 3 [?](#)

Gene	Mutation	Origin	CCE relevance	Evidence	Variant curated effect	Variant estimated effect
BRCA2	stop gained p.Lys2008Ter, details TSG exon 11/27	Germline (+tumor) tumor VAF = 0.4	G.counseling alert BoB - arm 1A	A	Pathogenic, BRCA-Exchange Pathogenic, ClinVar	Not necessary
BRCA2	missense p.Cys2689Phe, details TSG exon 18/27	Tumor tumor VAF = 0.4	BoB - arm 1A	C	None	missense in TSG with high CADD score, more info
TP53	frameshift p.Glu343Ter, details TSG exon 10/11	Tumor tumor VAF = 0.16	--	B	None	TSG with frameshift-derived PTC triggering NMD, more info

Variants of unknown significance: 2 [?](#)

Gene	Mutation	Origin	CCE relevance	Evidence	Variant curated effect	Variant estimated effect
P2RY8	missense p.Pro54His, details OG exon 2/2	Tumor tumor VAF = 0.08	--	--	None	Not conclusive
SGK1	missense p.Glu46Ala, details OG exon 1/12	Tumor tumor VAF = 0.13	--	--	None	Not conclusive

- Sample-wide calculations
 - e.g. the tumor mutation burden
- Clinically relevant flags
 - Pathogenic germline BRCA2 (*genetic counseling alert*)
 - Second somatic BRCA2 hit (*clinical trial for DNA damage repair deficient tumors*)
- Level of the supporting evidence
 - A – known
 - B – similar effect
 - C – predicted
- Summary of the data supporting that classification

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BRCA2	missense p.Cys2689Phe, details exon 18/27	Tumor tumor VAF = 0.42	BoB - arm 1A	C	None	missense in TSG with high CADD score, more info
TP53	frameshift p.Glu343Ter, details exon 10/13	Tumor tumor VAF = 0.16	--	B	None	TSG with frameshift-
SGK1	missense p.Glu46Ala, details exon 1/12	tumor tumor VAF = 0.13	--	--	--	--

All annotation is detailed
(including access to sources & version control)

NM_000059.3(BRCA2):c.6022A>T (p.Lys2008Ter)

Cite this record

Interpretation: Pathogenic

Review status: ★★☆☆ reviewed by expert panel

Submissions: 2 (Most recent: Apr 2, 2018)

Last evaluated: Sep 8, 2016

Accession: VCV000216029.1

Variation ID: 216029

Description: single nucleotide variant

Variant details

Conditions

Gene(s)

Allele ID: 213058

Variant type: single nucleotide variant

Variant length: 1 bp

Cytogenetic location: 13q13.1

Genomic location: 13:32340377 (GRCh38) GRCh38 UCSC
13:32914514 (GRCh37) GRCh37 UCSC

HGVs:

Nucleotide	Protein	Molecular consequence
NC_000013.10:g.32914514A>T		
NC_000013.11:g.32340377A>T		
NM_000059.3:c.6022A>T	NP_000050.2:p.Lys2008Ter	

This missense mutation has a very high predicted functional impact (CADD = 32.0), which is estimated to lead to the loss of BRCA2 tumor suppressor function

(very high functional impact is considered for CADD>30, which discriminates reported loss-of-function vs. neutral missense mutations in tumor suppressors with a true positive rate of ~90%)

Further gene/variant info in a detailed view

PTEN

This gene is considered a tumor suppressor. Pathogenic germline variants in PTEN are recommended to be reported as secondary findings by the ACMG (SF v2.0) when appropriate, more gene info

sample mutation

Chr10:89725047 A/AC GRCh37 - hg19
ENSP00000361021.3:p.Lys344ThrfsTer17
ENST00000371953.3:c.1030_1031insC
see all transcripts

putative functional (evidence B)

No curated effect for this variant (even by lower quality evidences)

Variant lead to PTEN essential site(s) out-of-frame translation, more info

Mutation distribution in previous pan-cancer cohorts (ENST00000371953), more

PTEN bears somatic protein-affecting mutations in 8% of the breast cancer samples (n=1,300) in 7% of the Pan-cancer samples (n=10,703)

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[Export report](#)

I. Ready for use results: 3 variants - 11 biomarkers

Tumor variant	Biomarker effect	Biomarker drug(s)	Biomarker cancer(s)	Evidence source(s)	Cancer match	Variant match
BRAF missense p.Val600Glu	1 Sensitivity/Response	2 Dabrafenib, Dabrafenib+Trametinib	3 Non-small cell lung carcinoma	Guidelines, CGI Proven/consensus, CIVIC Approved, OncoKB	Yes	precise
EGFR inframe deletion p.Glu746_Ala750del	Sensitivity/Response	Afatinib; Dacomitinib; Erlotinib; Gefitinib; Osimertinib	Non-small cell lung carcinoma	Guidelines, CGI Proven/consensus, CIVIC Approved, OncoKB	Yes	broad
EGFR missense p.Thr790Met	Reduced sensitivity/resistance	Afatinib; Erlotinib; Gefitinib	Non-small cell lung carcinoma	Guidelines, CGI Proven/consensus, CIVIC Standard of care, OncoKB	Yes	precise
EGFR missense p.Thr790Met	Sensitivity/Response	Osimertinib	Non-small cell lung carcinoma	Guidelines, CGI Proven/consensus, CIVIC Approved, OncoKB	Yes	precise

II. Investigational results: 3 variants - 3 biomarkers

Tumor variant	Biomarker effect	Biomarker drug(s)	Biomarker cancer(s)	Evidence source(s)	Cancer match	Variant match
ARAF missense p.Ser214Cys	Sensitivity/Response	Sorafenib	Non-small cell lung carcinoma	Compelling clinical, OncoKB	Yes	functional
BRAF missense p.Val600Glu	Sensitivity/Response	Vemurafenib	Non-small cell lung carcinoma	Clinical trials, CIVIC	Yes	precise; broad
EGFR missense p.Thr790Met	Prognostic, poor outcome	n/a	Non-small cell lung carcinoma	Clinical trials, CIVIC	Yes	precise

IV. Hypothetical results: 2 variants - 3 biomarkers

Tumor variant	Biomarker effect	Biomarker drug(s)	Biomarker cancer(s)	Evidence source(s)	Cancer match	Variant match
ARAF missense p.Ser214Cys	Sensitivity/Response	Sorafenib; Trametinib	Non-small cell lung carcinoma	Preclinical, CIVIC	Yes	precise
STK11 missense p.Ile177Asn	Sensitivity/Response	MTOR inhibitors	Unspecified/Basket	Preclinical, CGI	broad	functional
STK11 missense p.Ile177Asn	Reduced sensitivity/resistance	BET inhibitors	Lung cancer	Preclinical, CGI	Yes	functional

- 1 Biomarker **effect**
- 2 **Drug(s)** affected *(if applies)*
- 3 **Cancer type** in which the biomarker **is reported**

INTERACTIVE MOLECULAR TUMOR BOARD PORTAL



User: F. Farlane
Role: clinical PI

Logout

Patient list

Repository

Analyse

Upload

Account

FAQ

Sample
CCE-011-0219
Not reviewed

Reports

Functionality

Biomarkers

Variants biomarkers report Sample CCE-011-0219

Current patient status:

● Not Reviewed

Change status

See history

Patient: male, 37 yo
Cancer type: Lung cancer
Biopsy site: primary site
Center: CMHIO
Informed consent: 2019-07-27
Sample sent: 2019-08-01
Tumor Cellularity: 80%

Analysis run date: 2019-08-12
Pipeline version: v2.4, details

Export report

I. Ready for use results: 3 variants - 11 biomarkers

Tumor variant	Biomarker effect	Biomarker drug(s)	Biomarker cancer(s)	Evidence source(s)	Cancer match	Variant match
BRAF missense p.Val600Glu	↑ Sensitivity/Response	Dabrafenib, Dabrafenib+Trametinib	Non-small cell lung carcinoma	Guidelines, CGI Proven/consensus, CIVIC Approved, OncoKB	Yes	precise
EGFR inframe deletion p.Glu746_Ala750del	↑ Sensitivity/Response	Afatinib; Dacomitinib; Erlotinib; Gefitinib; Osimertinib	Non-small cell lung carcinoma	Guidelines, CGI Proven/consensus, CIVIC Approved, OncoKB	Yes	broad
EGFR missense p.Thr790Met	↓ Reduced sensitivity/resistance	Afatinib; Erlotinib; Gefitinib	Non-small cell lung carcinoma	Guidelines, CGI Proven/consensus, CIVIC Standard of care, OncoKB	Yes	precise
EGFR missense p.Thr790Met	↑ Sensitivity/Response	Osimertinib	Non-small cell lung carcinoma	Guidelines, CGI Proven/consensus, CIVIC Approved, OncoKB	Yes	precise

II. Investigational results: 3 variants - 3 biomarkers

Tumor variant	Biomarker effect	Biomarker drug(s)	Biomarker cancer(s)	Evidence source(s)	Cancer match	Variant match
ARAF missense p.Ser214Cys	↑ Sensitivity/Response	Sorafenib	Non-small cell lung carcinoma	Guidelines, CGI Proven/consensus, CIVIC Approved, OncoKB	Yes	functional
BRAF missense p.Val600Glu	↑ Sensitivity/Response	Vemurafenib	Non-small cell lung carcinoma	Guidelines, CGI Proven/consensus, CIVIC Approved, OncoKB	Yes	functional
EGFR missense p.Thr790Met	● Prognostic, poor outcome	n/a	Non-small cell lung carcinoma	Guidelines, CGI Proven/consensus, CIVIC Approved, OncoKB	Yes	functional

IV. Hypothetical results: 2 variants - 3 biomarkers

Tumor variant	Biomarker effect	Biomarker drug(s)	Biomarker cancer(s)
ARAF missense p.Ser214Cys	↑ Sensitivity/Response	Sorafenib; Trametinib	Non-small cell lung carcinoma
STK11 missense p.Ile177Asn	↑ Sensitivity/Response	MTOR inhibitors	Unspecified/Basket
STK11 missense p.Ile177Asn	↓ Reduced sensitivity/resistance	BET inhibitors	Lung cancer

4

The original KB classification of the supporting evidence

CIVIC content
https://civic.genome.wustl.edu/links/evidence_items/3017
Biomarker: BRAF V600E
Evidence type: Predictive
Evidence direction: Supports
Variant origin: Somatic Mutation
Clinical significance: Sensitivity/Response
Drug: Trametinib+Dabrafenib
Disease: Lung Non-small Cell Carcinoma
Evidence level: A - Guideline
Trust rating: 4/5
Source: PMID 27283860

CIVIC

EVIDENCE EID1574

Evidence Summary

Evidence Talk

Submitted by: ebernell Last Modified by: DTRieke Last Reviewed by: MalachiGriffith Accepted by: DTRieke

Patients with BRAF-V600 mutated cancers were identified (n=122) and clinical response to vemurafenib was evaluated. Of the 20 patients with non-small-cell-lung cancer (17 with BRAF V600E, one with BRAF V600G and one with BRAF V600 unknown status), 19 were evaluable and the response rate to vemurafenib was 42%, tumor regression was observed in 14/19 patients, progression-free survival was 7.3 months, and 12-month overall survival was 66%.

Evidence Level: B - Clinical

Disease: Lung Non-small Cell Carcinoma

Evidence Type: Predictive

Associated Phenotype: -

Evidence Direction: Supports

Source: Hyman et al., 2015, N. Engl. J. Med.

Clinical Significance: Sensitivity/Response

PubMed ID: 26287849

Variant Origin: Somatic Mutation

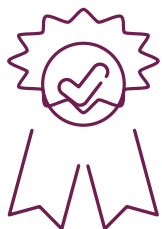
Clinical Trial: -

Drug: Vemurafenib

Evidence Rating: ★★★★★

<http://www.mtbp.org>

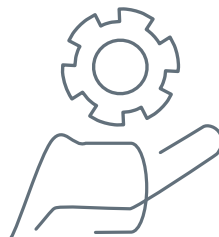
CLINICAL DECISION SUPPORT SYSTEMS (CDSS)



Informative

Guidelines and consensus

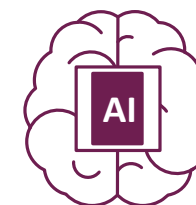
- NCCN guidelines
- ASCO / ESMO guidelines
- Hospital guidance



Interactive

Rule-based analysis

- Clinical pathways
- MTB



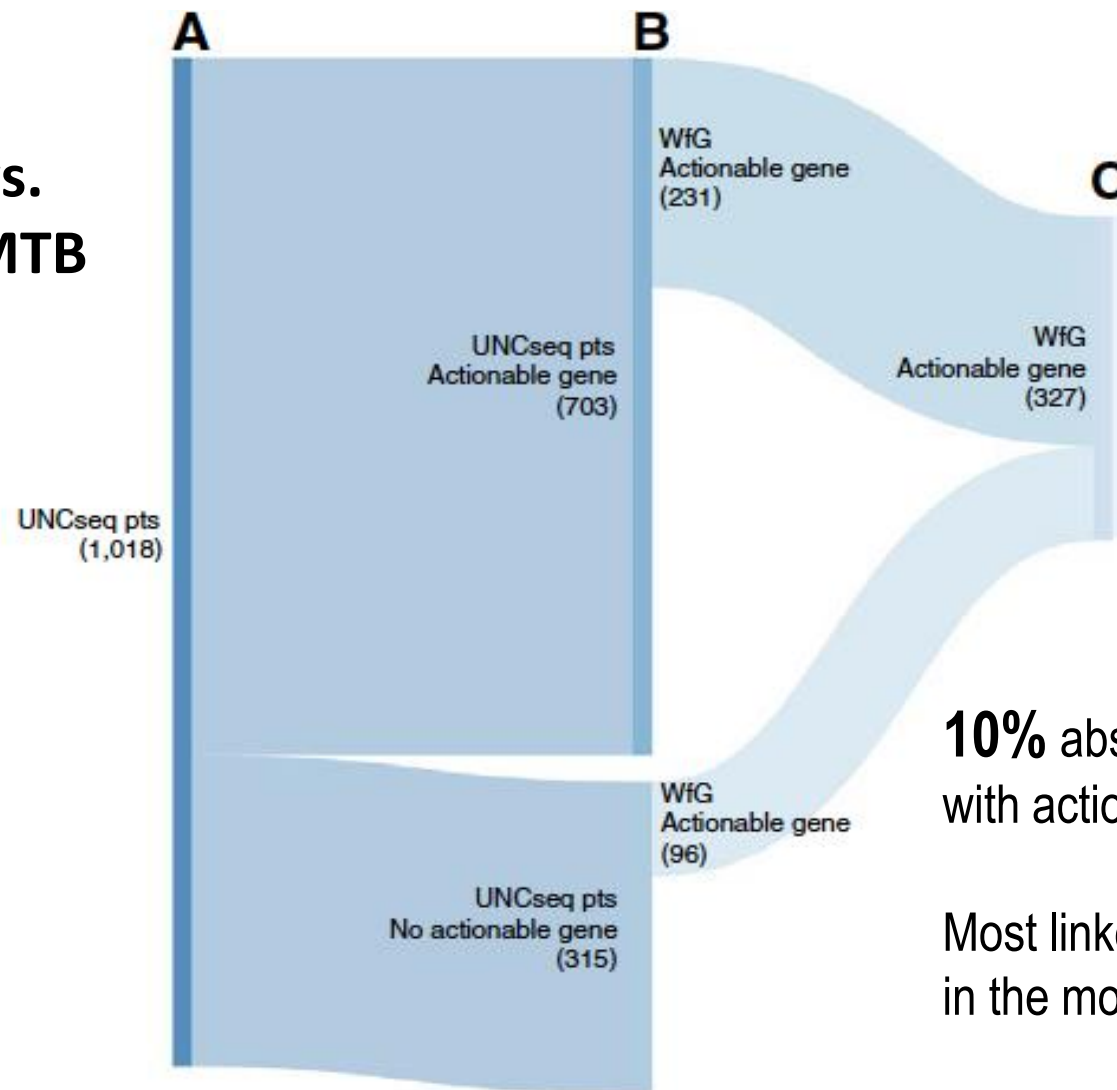
Predictive

Artificial intelligence

- Continuous learning that integrate all available data

COGNITIVE COMPUTING VS. MOLECULAR TUMOR BOARD

IBM Watson for Oncology vs. University North Carolina MTB

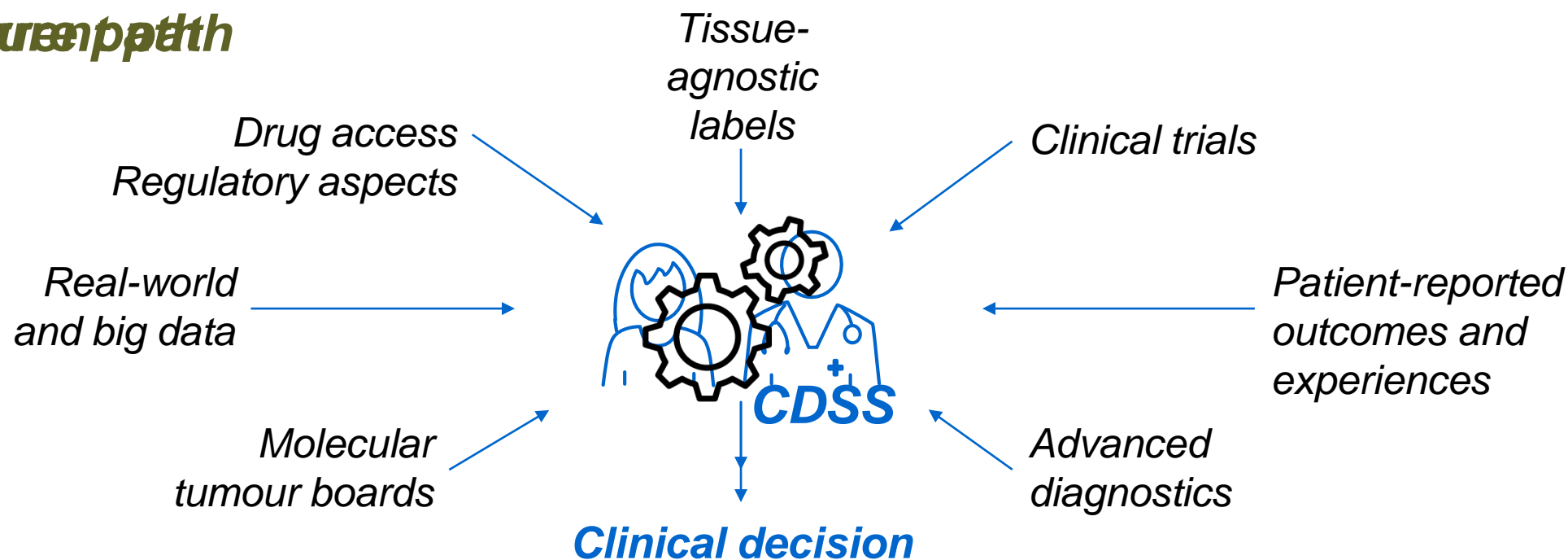


10% absolute increase in patients
with actionable alterations

Most linked to clinical trial opened
in the month before study.

CLINICAL DECISION SUPPORT SYSTEMS (CDSS)

The future path



WHY MOLECULAR TUMOR BOARDS?



Genomic testing



Genomic reporting



Genomic matching



PRECISION MEDICINE “TEST-DRIVE” SERIES

Scaling up genomics-guided therapies with clinical trials use



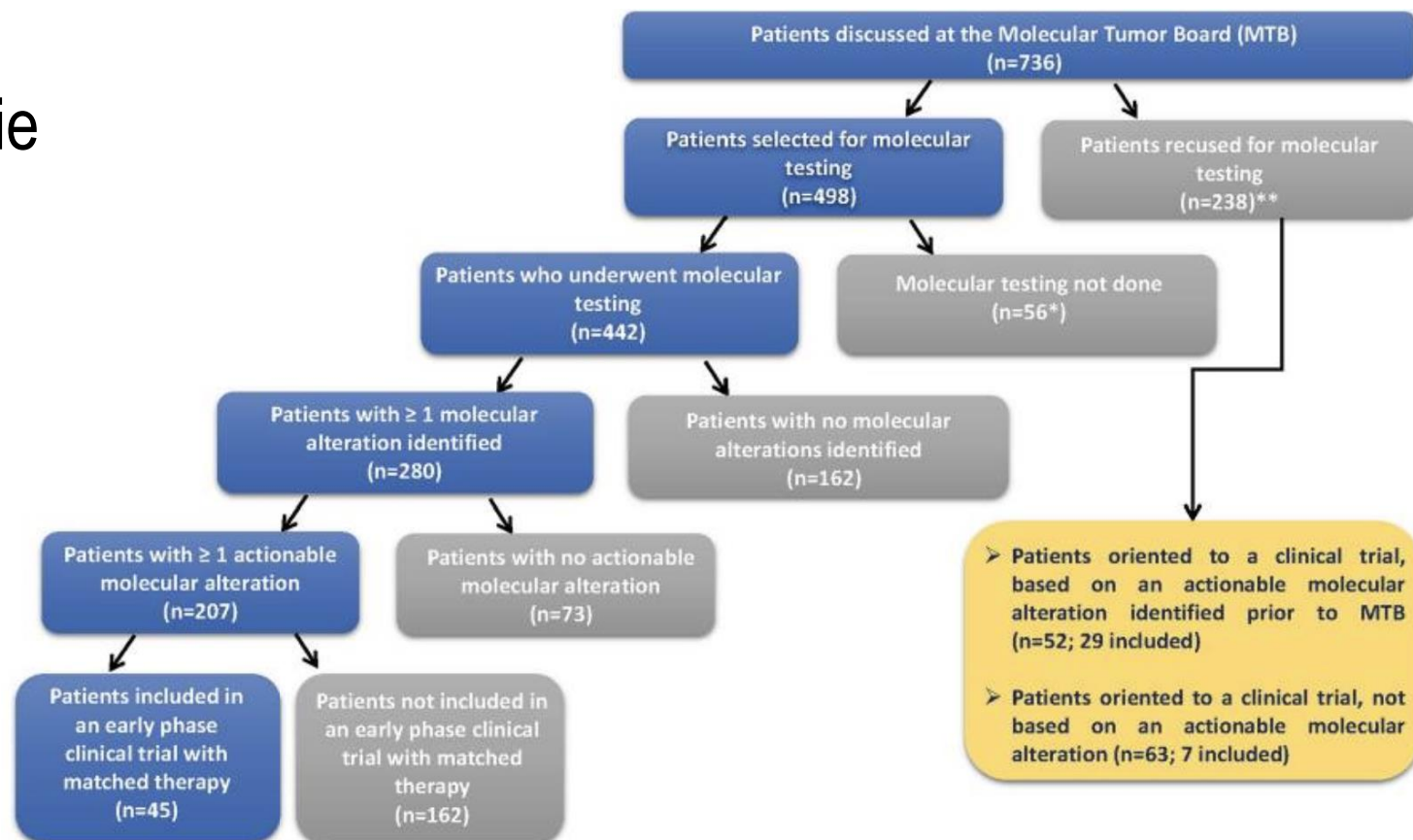
Serie	N	Molecular profile	Actionable alteration	Matched trials
MSK-IMPACT	10,945	91%	37%	11%
NCI MATCH	5,963	93%	18%	11%
VHIO	3,900	90%	38%	10%
PROFILER	2,676	73%	52%	7%
MDACC	2,601	77%	39%	5%
COMPACT	1,893	86%	50%	5%
MOSCATO	1,035	81%	40%	19%
RANGE (median)		73%-91% (86%)	18%-52% (38%)	5%-19% (10%)

PRECISION MEDICINE “TEST-DRIVE” SERIES

Scaling up genomics-guided therapies with clinical trials use

Institut Curie

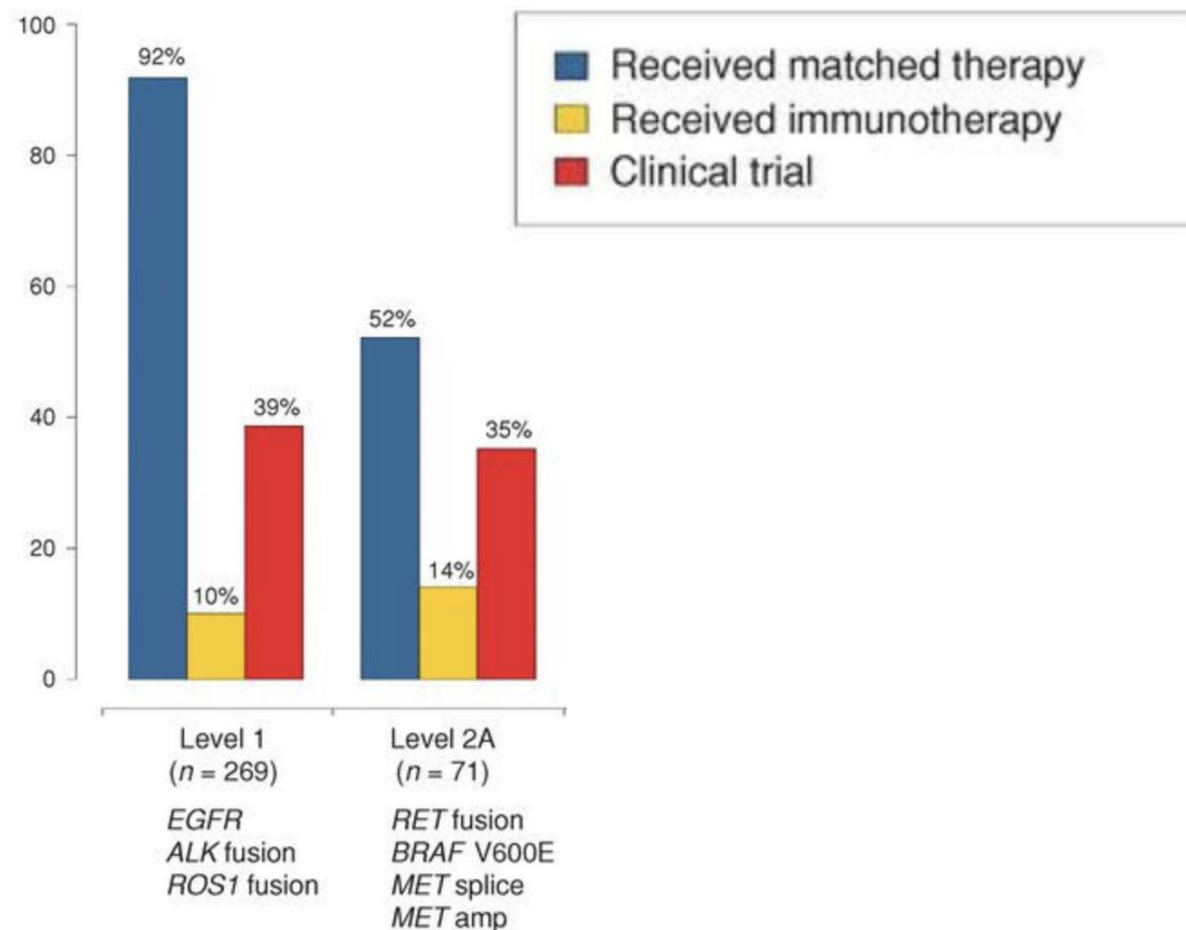
10%
(45/442)



PRECISION MEDICINE “TEST-DRIVE” SERIES

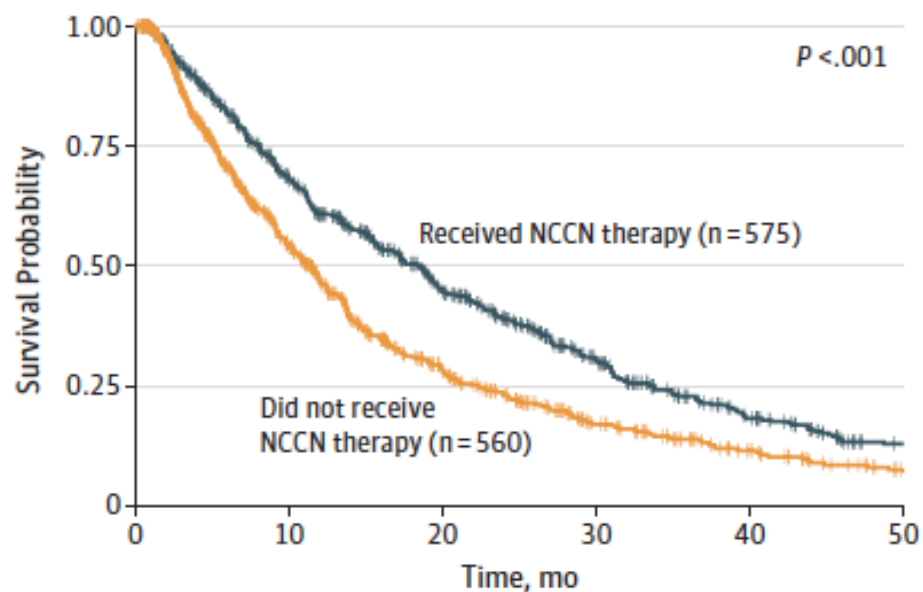
Scaling up genomics-guided therapies with clinical trials use

MSKCC – lung cancer



PRECISION MEDICINE “REAL WORLD” SERIES

Genomic-guided targeted therapy

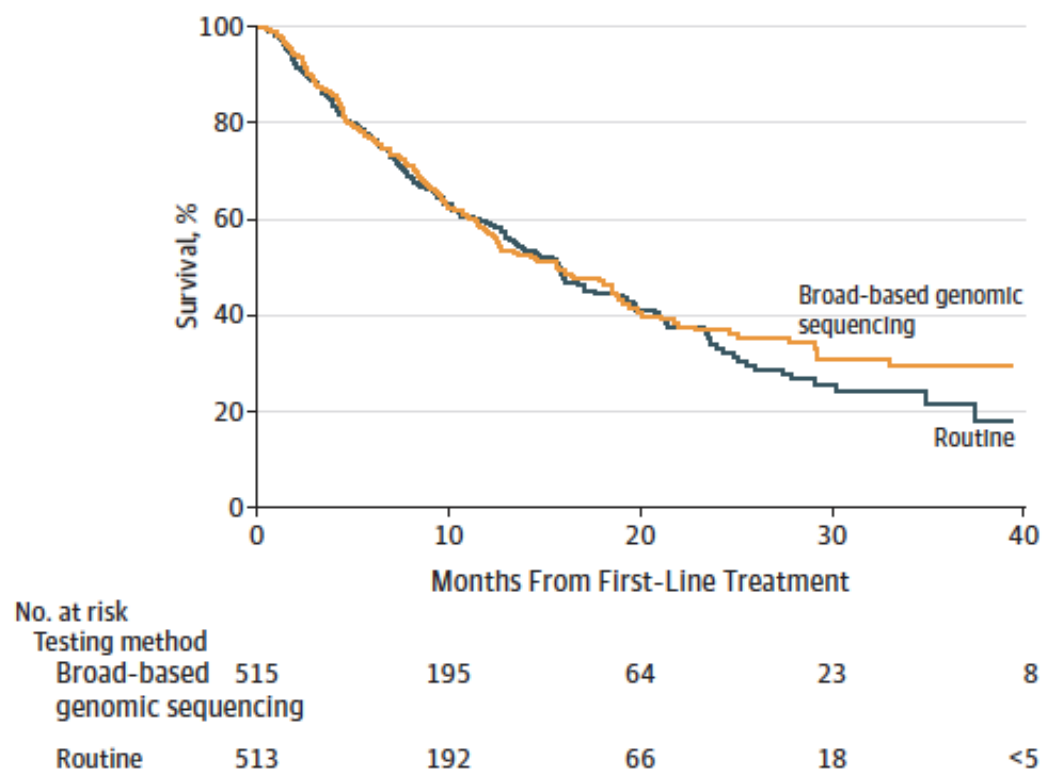


No. at risk						
Received NCCN therapy	2	168	142	91	59	32
Did not receive NCCN therapy	55	196	93	54	28	13

60-70% of *EGFR* mut or *ALK* fusion received targeted therapy
< 40% of other NCCN genomic alt. received targeted therapy

PRECISION MEDICINE “REAL WORLD” SERIES

Routine testing vs. Broad-based Genomic Sequencing



14% had actionable alterations

(on top of EGFR/ALK)

4.5% received BGS-guided therapies

(on top of EGFR/ALK)

CONCLUSIONS & RECOMMENDATIONS



- **There is no need to oversell genomics-guided therapies!**
 - Genomic testing for some diseases (e.g., lung) already passed the tipping point for broad utility based on efficiency in cost and tissue use.
- **Avoid dubious genomics-guided therapies off-label based on scant evidence.**
 - Always keep high standards for CLINICAL TRIAL matching and declaring success.
- **Molecular tumor boards facilitate knowledge spread on emerging biomarkers.**
 - Cross-disciplinary education is critical.
 - Interactive clinical decision support systems have huge potential.

MTBs are critical in providing objective evidence-based translation of observed molecular alterations into patient-centred clinical action

ACKNOWLEDGEMENTS



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 - ♦ Judith Balmaña Team Hereditary Cancer Unit
-
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