ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ORGANIZATION AND ROLE OF THE MOLECULAR TUMOR BOARD

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(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

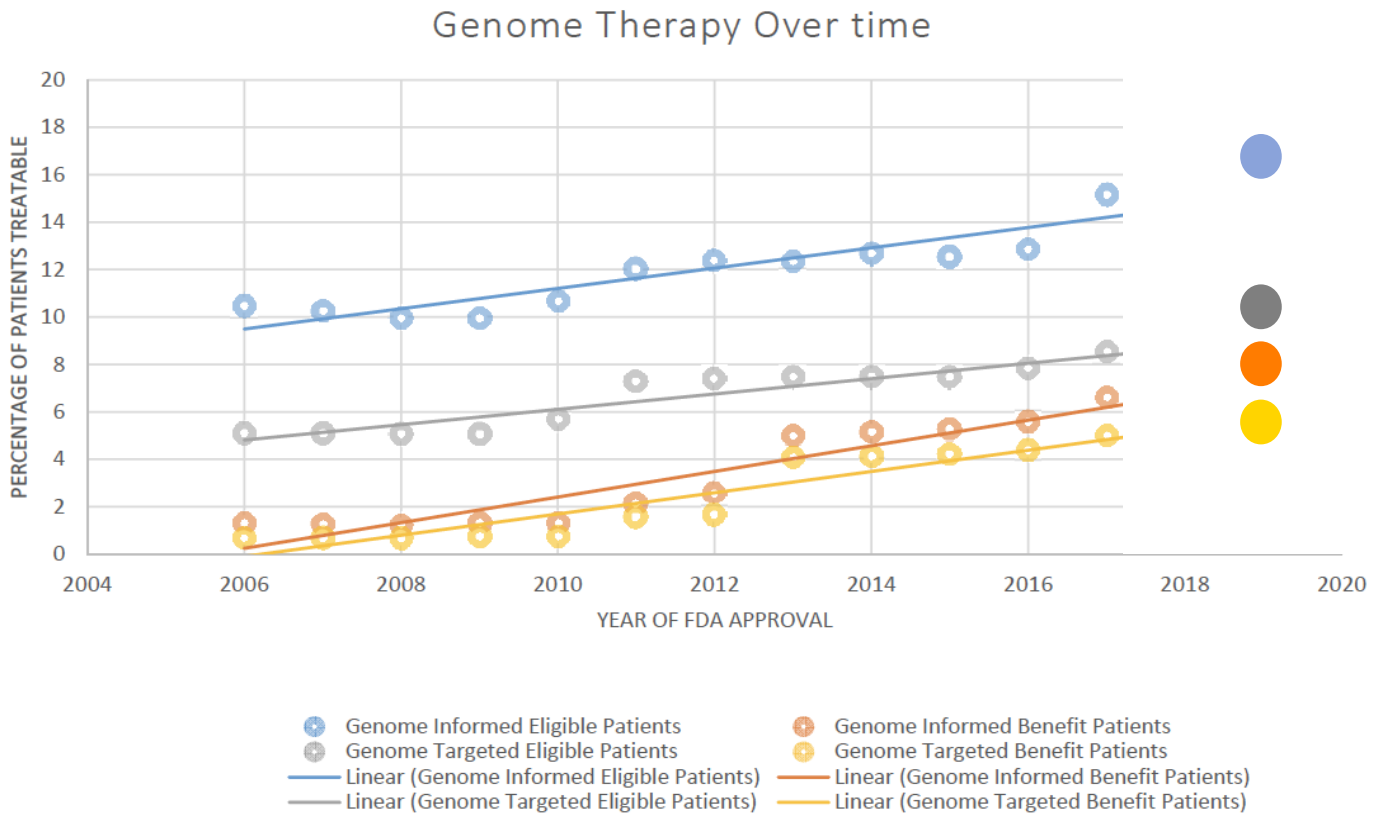
APPROVED (OR CLOSE TO) GENOMICS-GUIDED THERAPIES

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

EMERGING GENOMICS-GUIDED THERAPIES

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

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



~17% Genome-informed

~11% Genome-targeted

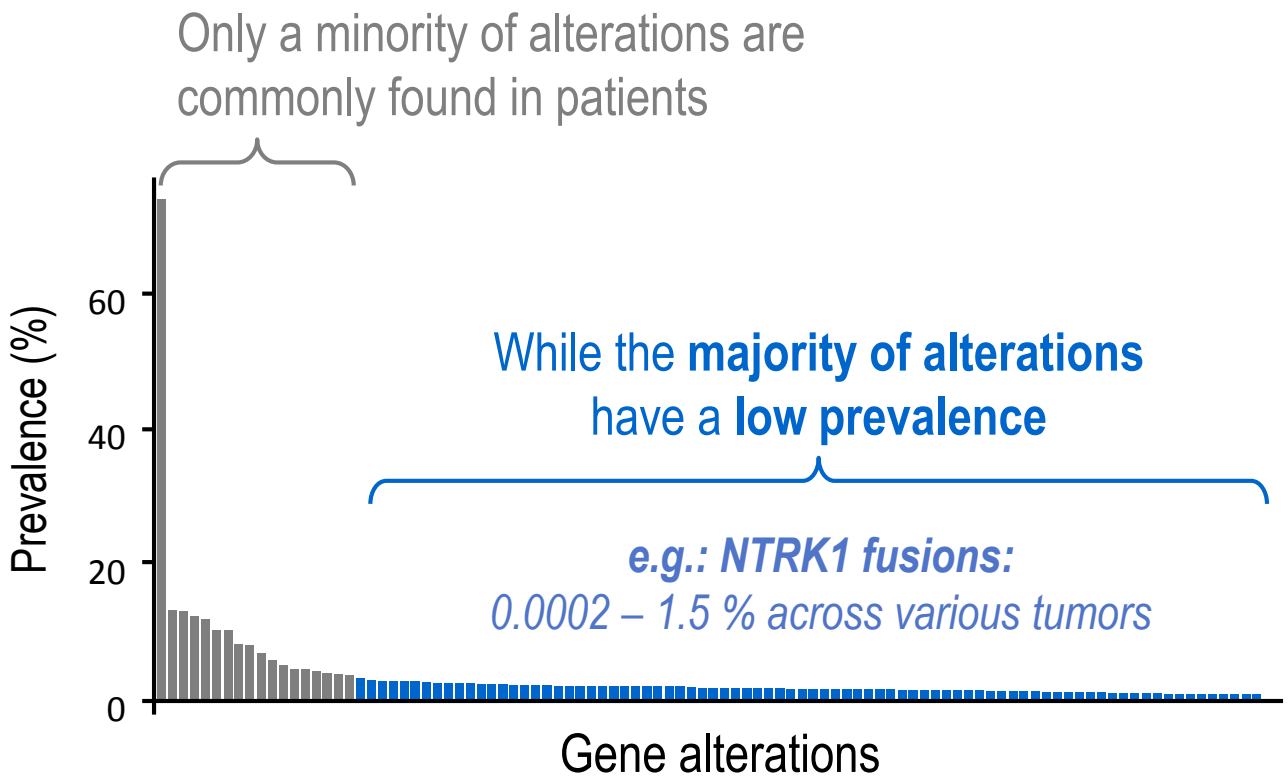
~8% Benefit genome-informed

~6% Benefit genome-targeted

~50% benefit

Adapted from Marquart et al, JAMA Oncol 2018

MANY TARGETS, SMALL POPULATIONS



Adapted from Gatalica et al, Mod Pathol 2019

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)

Adapted from Gatalica et al, Mod Pathol 2019

MEDICAL KNOWLEDGE IS CONSTANTLY INCREASING

Clinical studies presented at major congresses	Clinically relevant genomic alterations	Available targeted therapies	Therapies in development
328 abstracts from ASCO 2018 contained the keywords 'profiling' or 'targeted therapy' in combination with 'clinical study' or 'clinical trial'	**203** variants of genes are associated with cancer therapies • Approved by the FDA • Used as standard of care or • With demonstrated clinical evidence	**125** unique targeted therapies are approved across a range of cancers	At least **31** unique therapies are being assessed in pan-tumour basket trials

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

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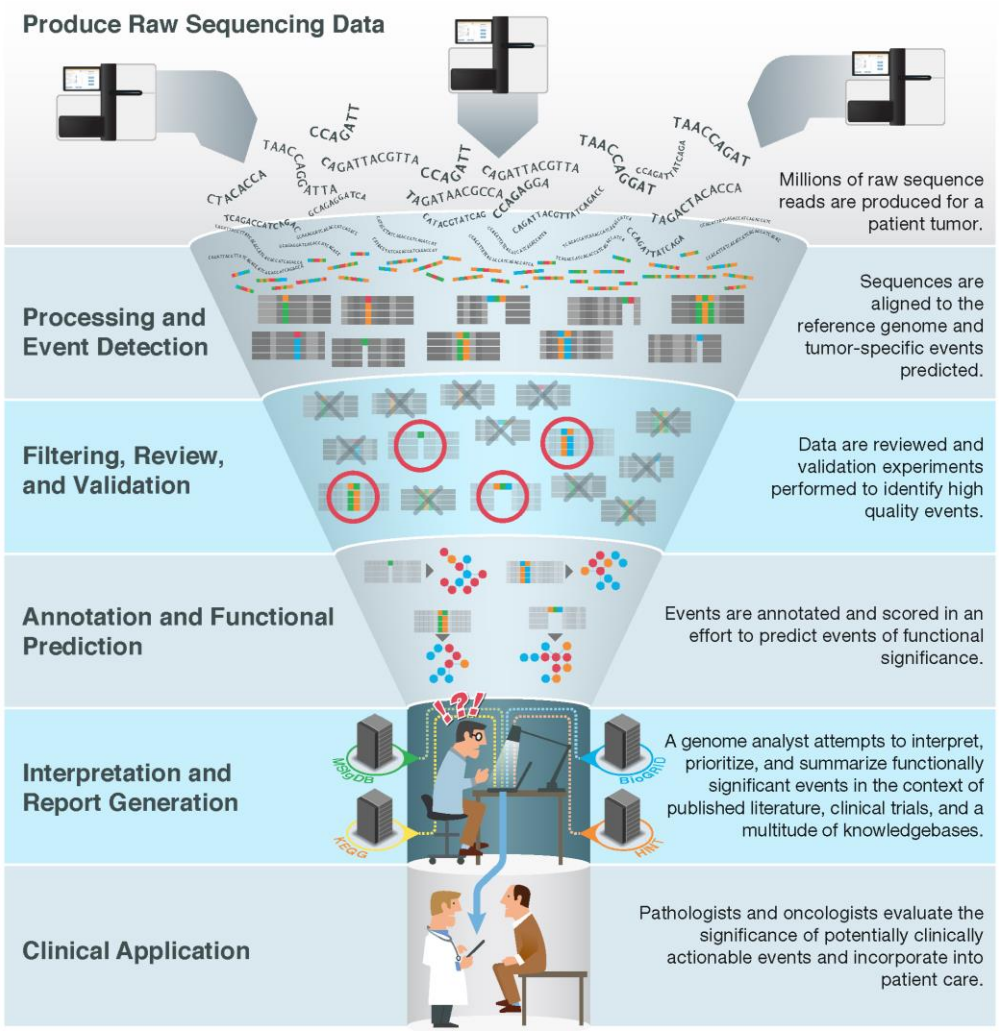
INTERPRETATION FUNNEL



Good et al, Genome Biol 2014

"MINIMAL" DATA IN GENOMICS REPORT (MY OPINION)

THERAPEUTIC

Functional variants (mutation, copy number, fusion)

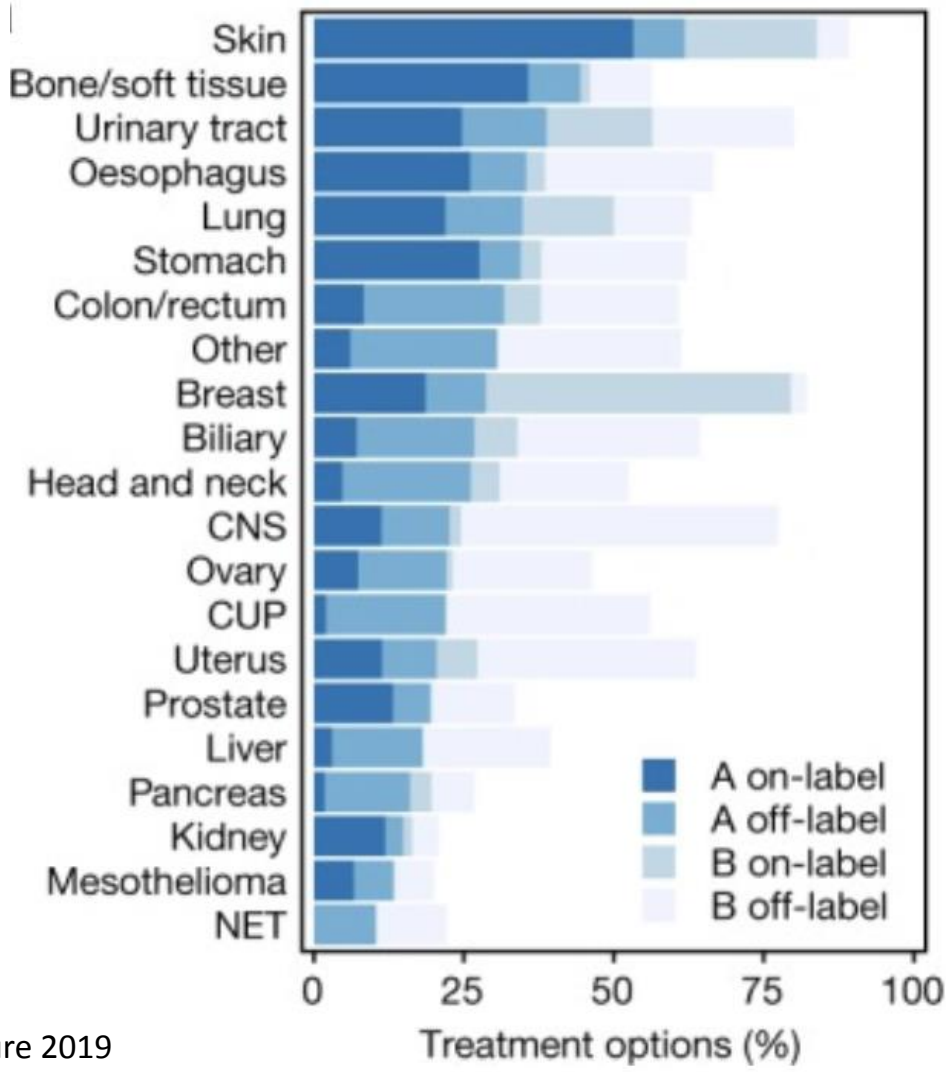
- Level of evidence for actionability — *On-label vs. Clinical trial/Off-label vs. Biological relevance*
- Resistance markers — *Upfront and/or acquired (co-existing alterations)*
- Mutant allele fraction — *Clonality vs. subclonality*

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

Priestley et al, Nature 2019

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/

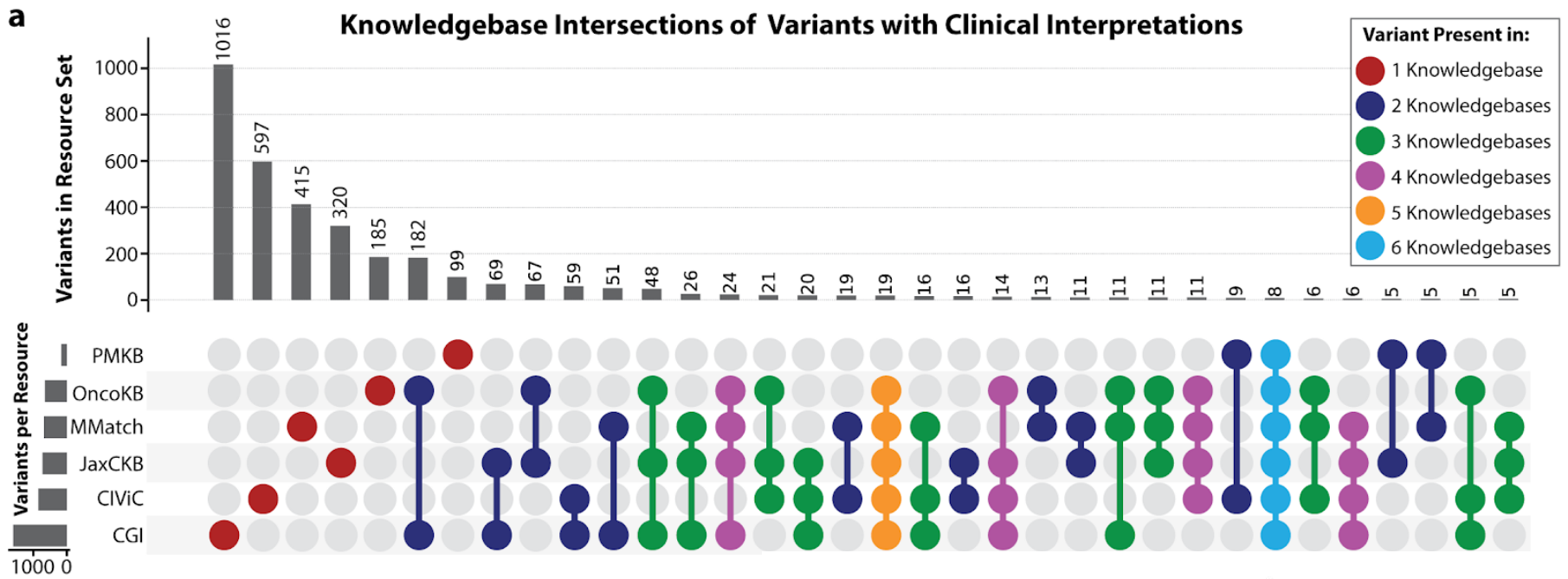
FUNCTIONAL AND/OR ACTIONABILITY

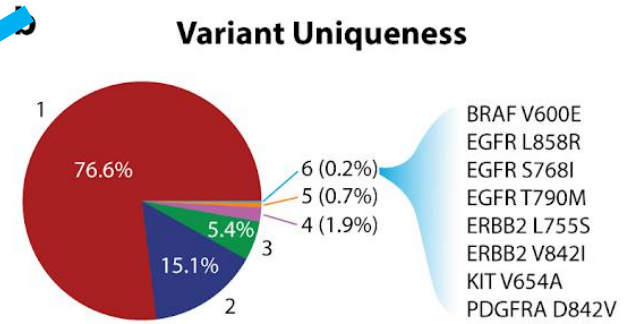
- cBioPortal - https://cbioportal.org/
- COSMIC (Sanger) - http://cancer.sanger.ac.uk/cosmic

MOLECULAR EPIDEMIOLOGY

- Clinical Trials - https://www.clinicaltrials.gov/

REDUNDANT EFFORTS
NON-OVERLAPPING INTERPRETATIONS



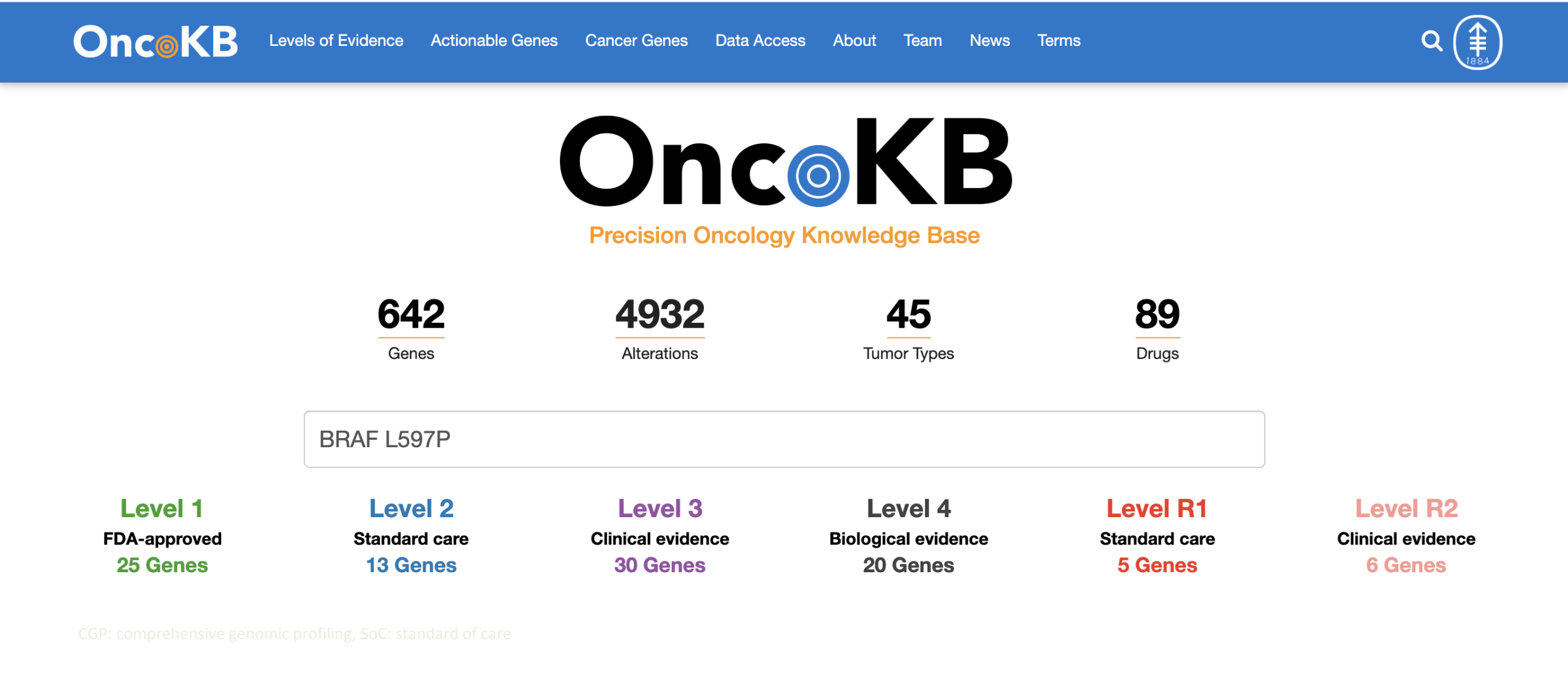


Only 8 gene variants across all databases

Wagner et al, Nat Genetics in press

OncoKB FOR TREATMENT DECISION MAKING

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



CGP: comprehensive genomic profiling, SoC: standard of care

OncoKB FOR TREATMENT DECISION MAKING

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

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

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

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

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Compelling biological evidence supports the biomarker as being predictive of response to a drug but neither biomarker and drug are standard of care

CGP: comprehensive genomic profiling, SoC: standard of care

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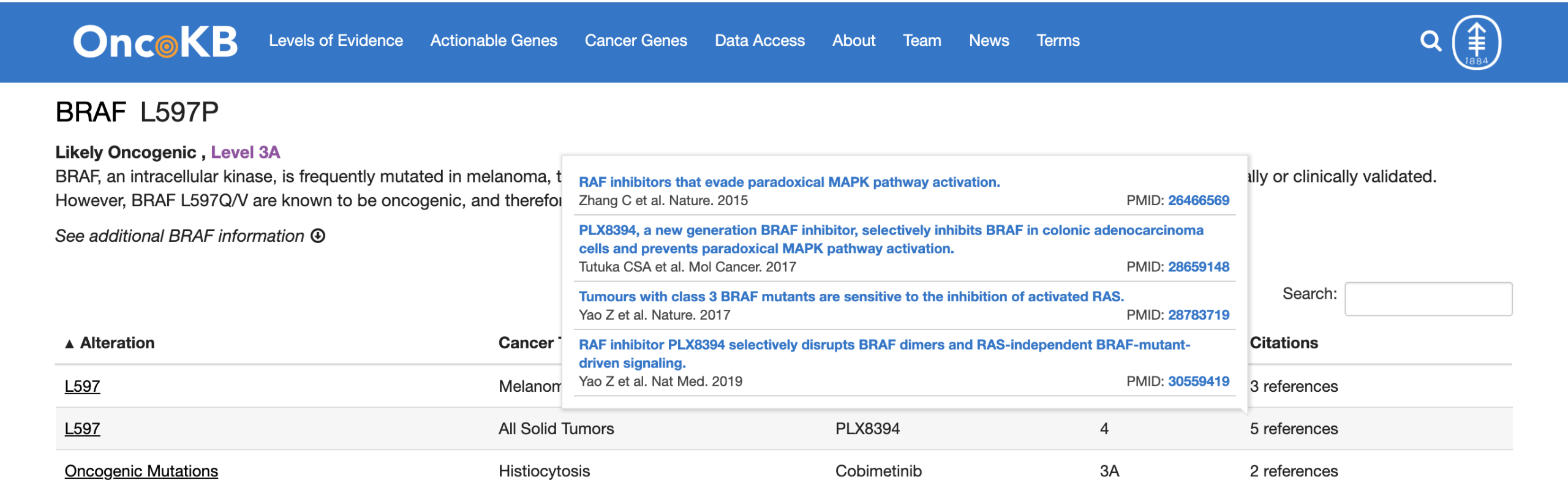

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OncoKB Levels of Evider

BRAF L597P

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BRAF, an intracellular kinase, is frequently

However, BRAF L597Q/V are known to be

See additional BRAF information

▲ Alteration
L597
L597
Oncogenic Mutations

NCBI Resources How To

PubMed.gov 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 Y[1], Su W[1], Yaeger R[2,3], Tao J[2], Na N[1], Zhang Y[4], Zhang C[4], Rymar A[4], Tao A[5], Timaul NM[1], Mcgriskin R[1], Outmezguine NA[1], Zhao H[1], Chang Q[1], Qeriqi B[1], Barbacid M[6], de Stanchina E[1], Hyman DM[2,3], Bollag G[4], Rosen N[7,8,9].

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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 monomers[1]. 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 dimer[1-3]. Moreover, acquired resistance to these drugs is usually due to molecular lesions that cause V600 mutants to dimerize[4-8]. We show here that PLX8394, a new RAF inhibitor[9], 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.

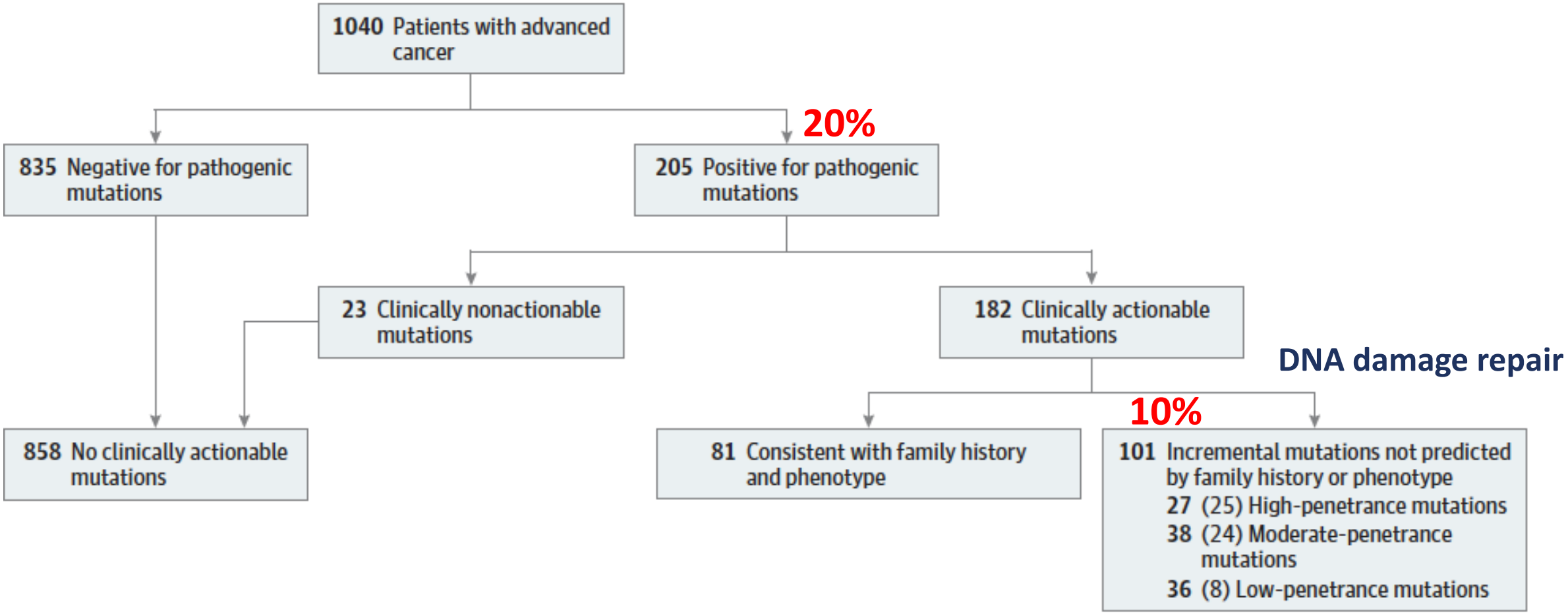
unctionally or clinically validated.

Search:

Citations
3 references
5 references
2 references

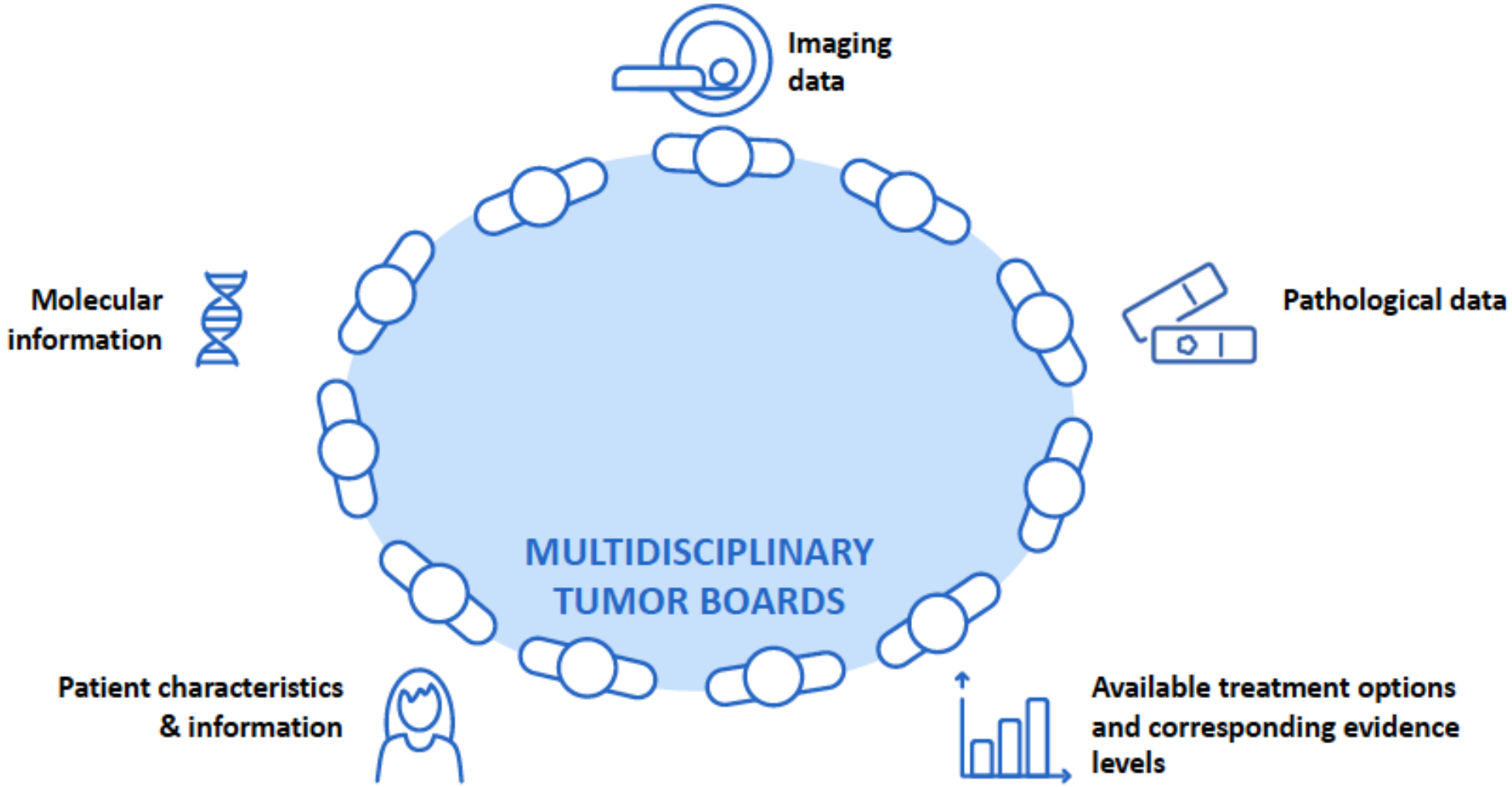
CGP: comprehensive genomic profiling, SoC: standard of care

UNSUSPECTED GERMLINE ACTIONABLE ALTERATIONS



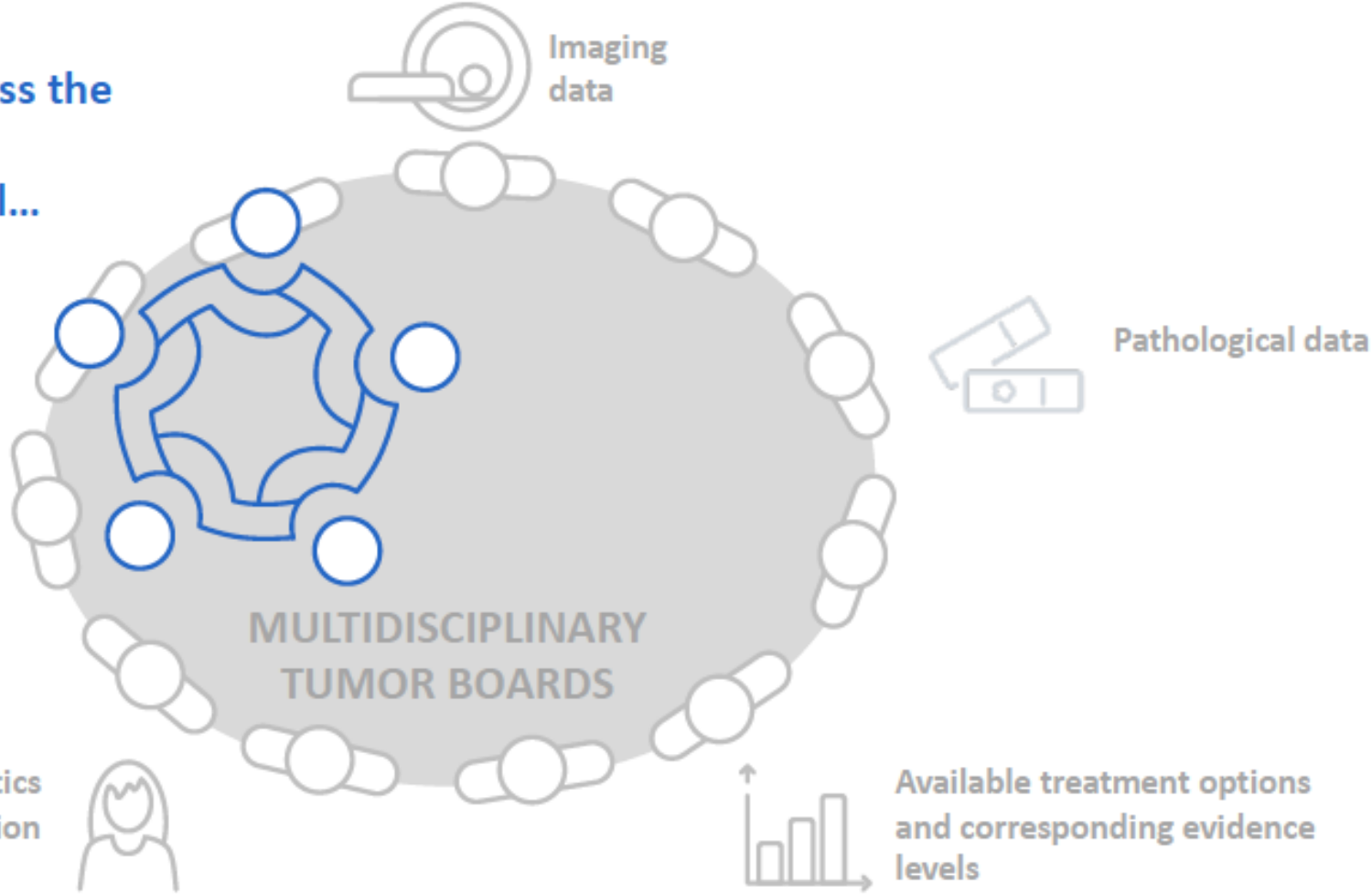
Mandelker et al, JAMA 2017

MULTIDISCIPLINARY DECISION MAKING

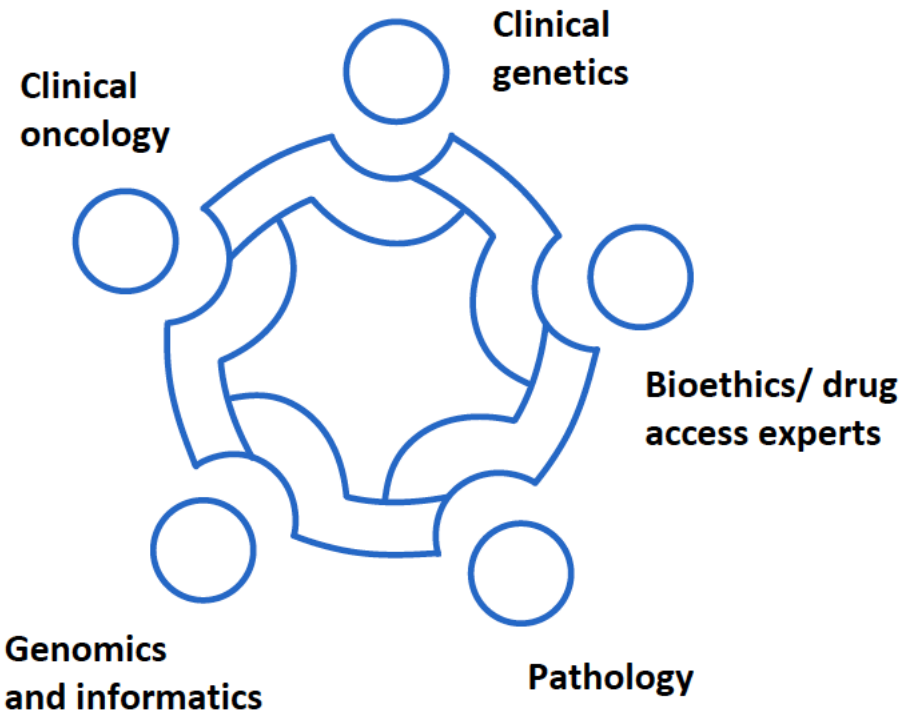


MULTIDISCIPLINARY DECISION MAKING

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



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

Rieke et al, JCO Precision Oncol 2018

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

- variant **pathogenicity**

ClinVar

BRCA EXCHANGE

- variant **oncogenicity**

OncoKB

CIViC

- biomarkers of disease diagnosis, prognosis and **drug response**

CANCER GENOME INTERPRETER

OncoKB

CIViC

- gene/variant **information in tumor samples**

COSMIC Cancer Gene Census

cBioPortal FOR CANCER GENOMICS

- gene/variant **information in healthy samples**

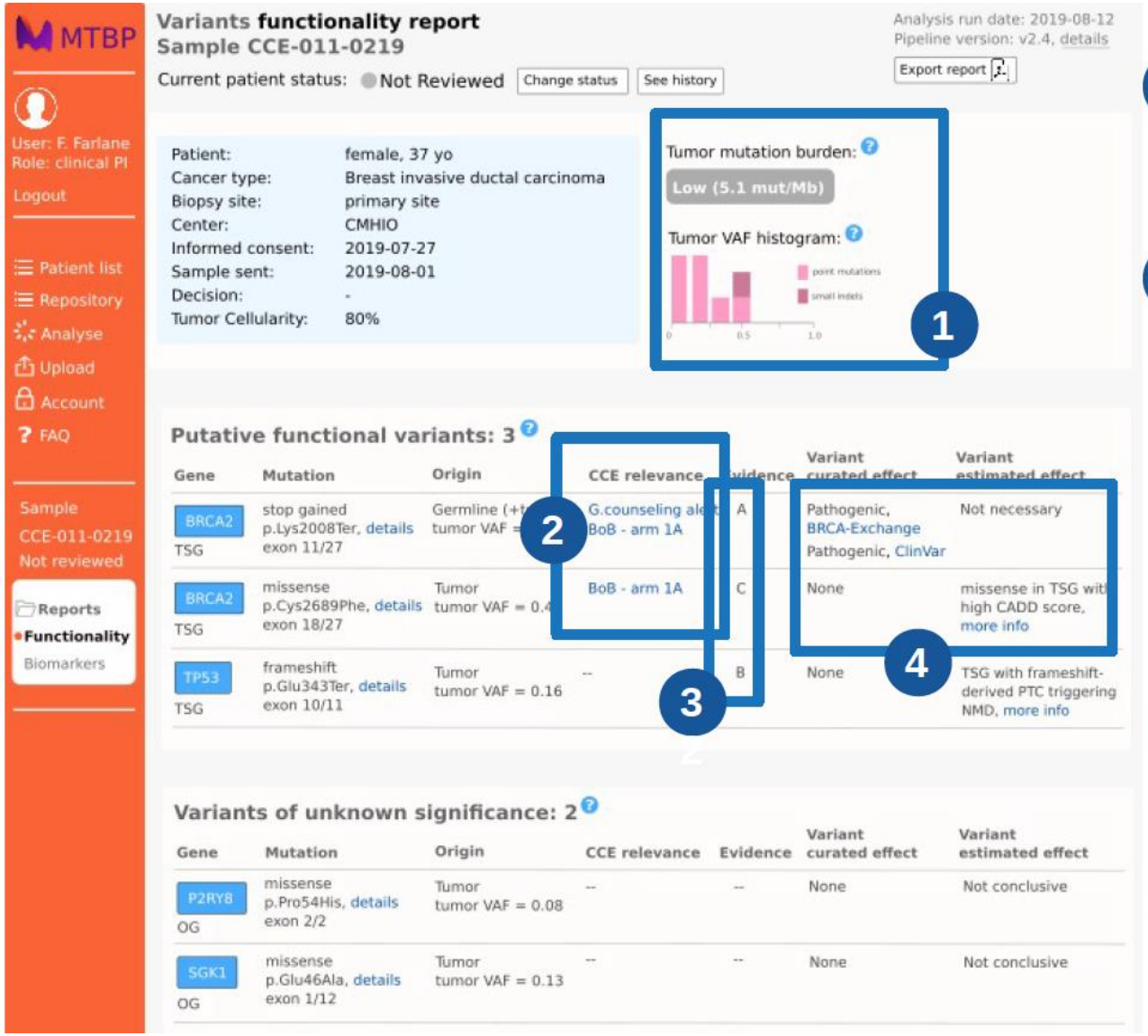
gnomAD

1000 Genomes

Cancer Core Europe

http://*www.mtbp.org*

INTERACTIVE MOLECULAR TUMOR BOARD PORTAL



1. Sample-wide calculations
   - e.g. the **tumor mutation burden**

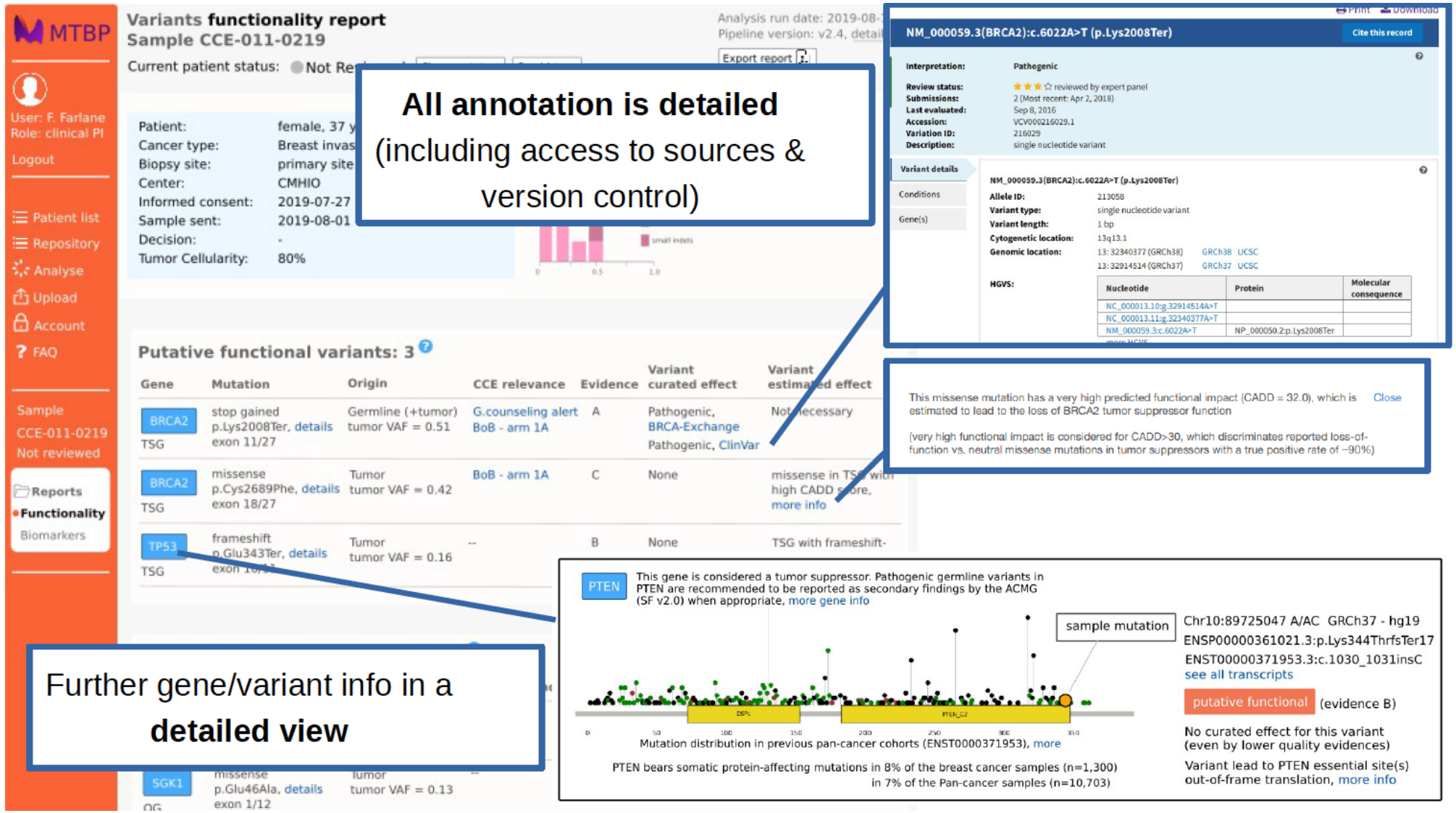
2. **Clinically relevant** flags
   - Pathogenic germline BRCA2 (***genetic counseling*** *alert)*
   - Second somatic BRCA2 hit (***clinical trial*** *for DNA damage repair deficient tumors)*

3. Level of the **supporting evidence**

   A – known
   B – similar effect
   C – predicted

4. Summary of the **data supporting** that classification

INTERACTIVE MOLECULAR TUMOR BOARD PORTAL



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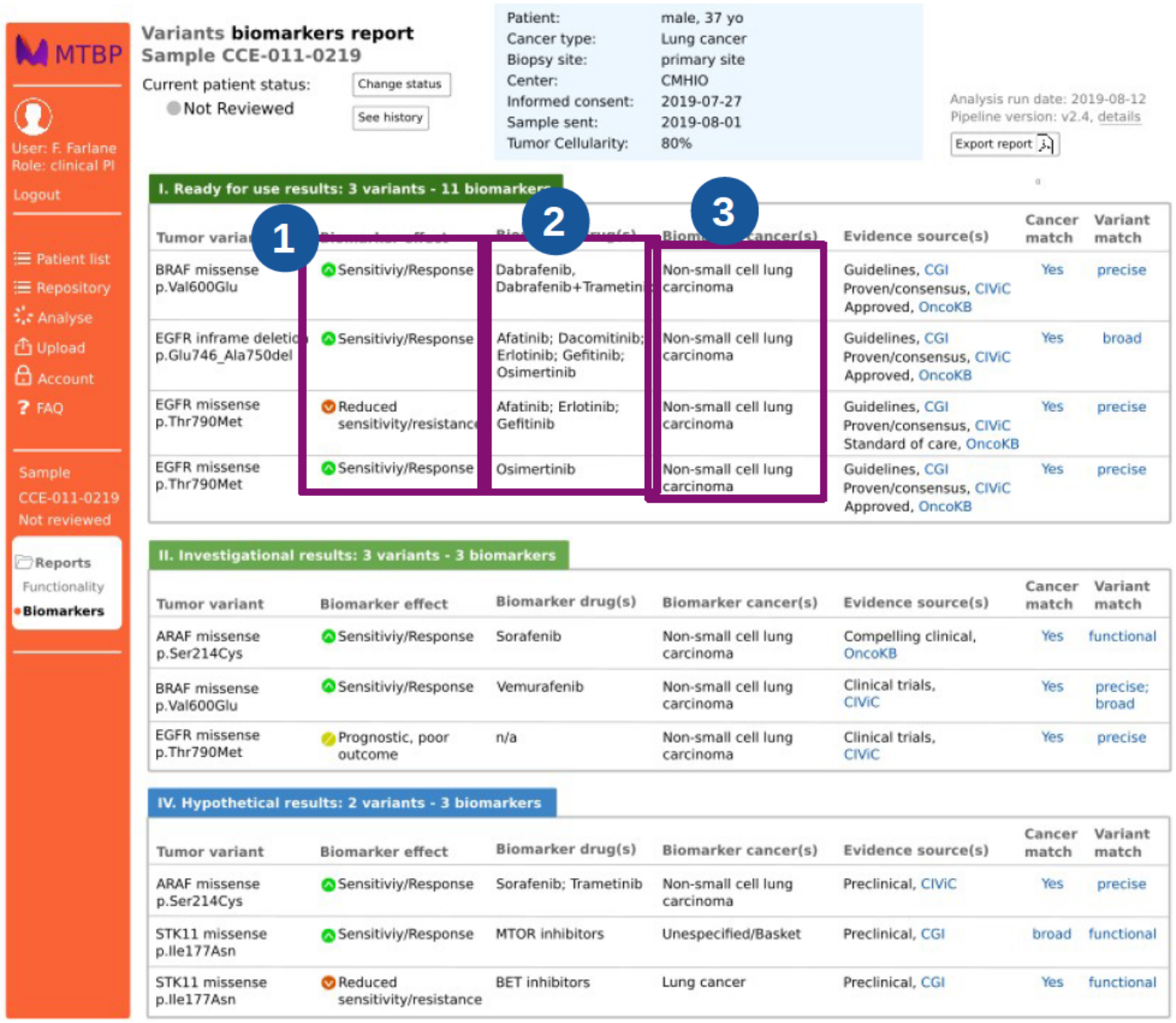
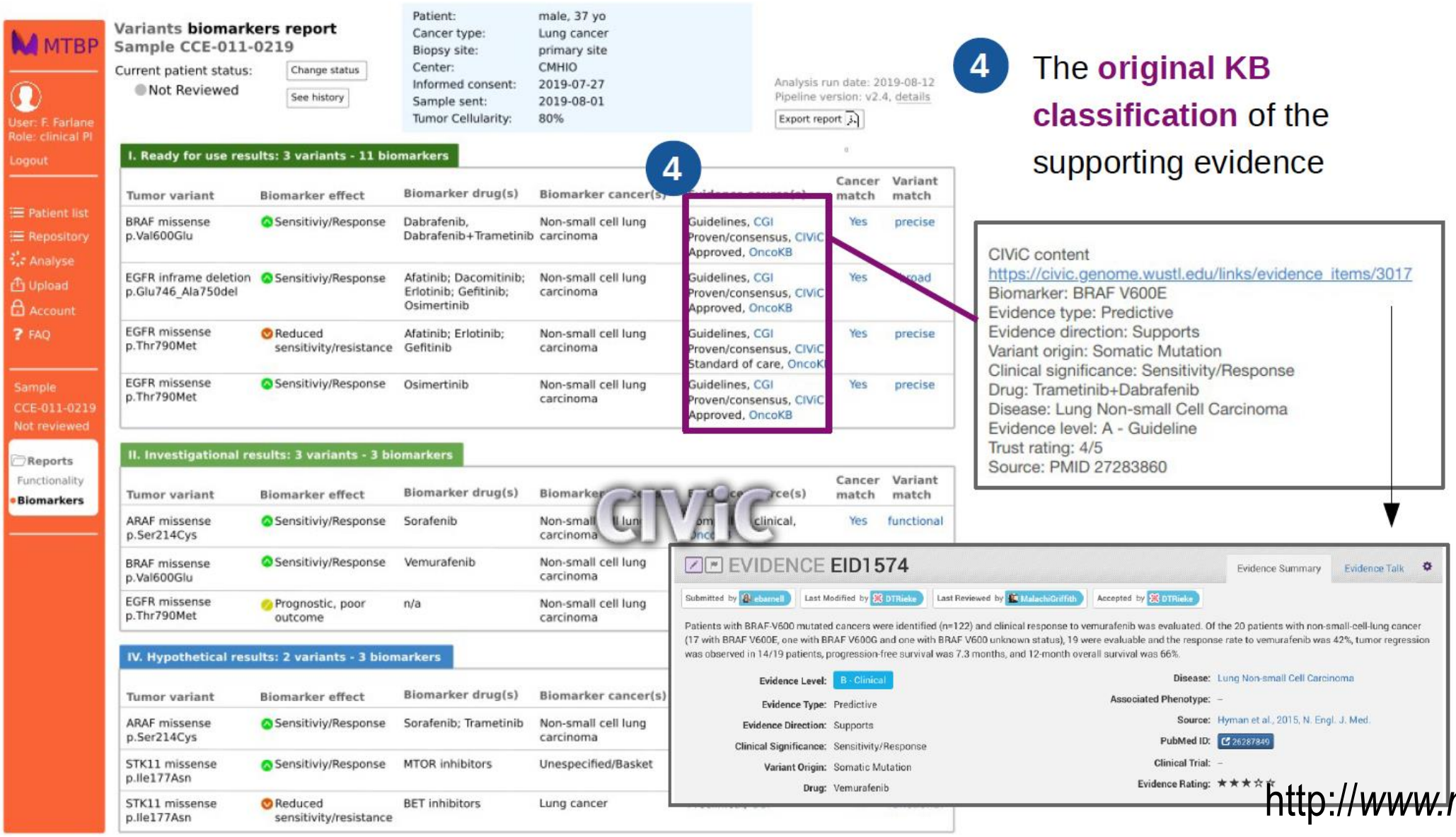


1. Biomarker **effect**
2. **Drug**(s) affected *(if applies)*
3. **Cancer type** in which the biomarker **is reported**

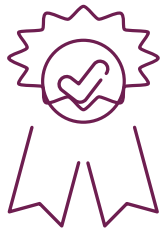
http://*www.mtbp.org*

INTERACTIVE MOLECULAR TUMOR BOARD PORTAL



http://www.mtbp.org

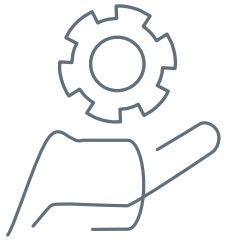
CLINICAL DECISION SUPPORT SYSTEMS (CDSS)



Informative

Guidelines and consensus

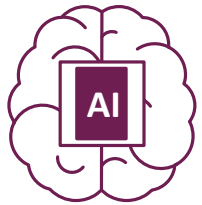
- NCCN guidelines
- ASCO / ESMO guidelines
- Hospital guidance



Interactive

Rule-based analysis

- Clinical pathways
- MTB



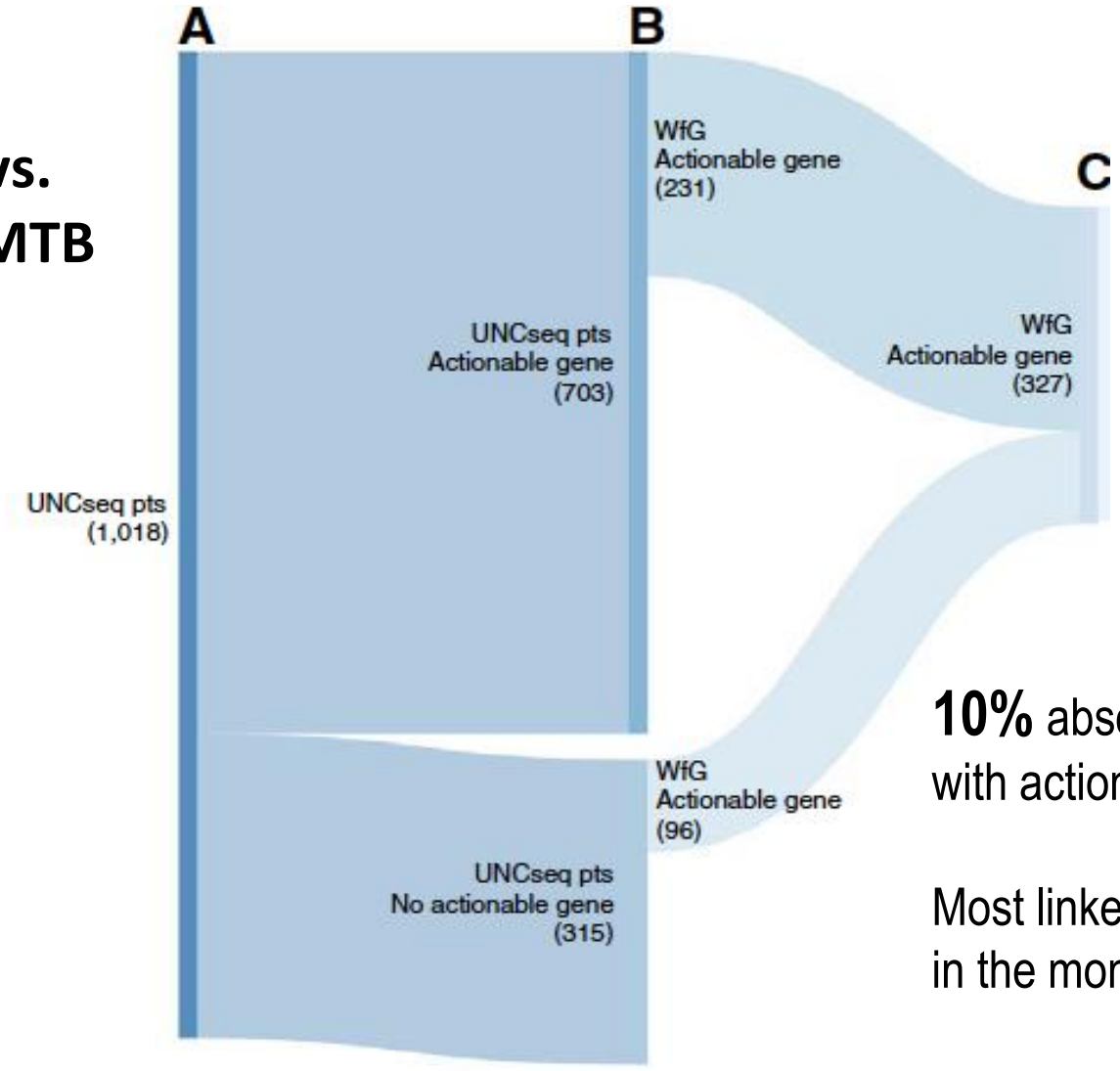
Predictive

Artificial intelligence

- Continuous learning that integrate all available data

COGNITIVE COMPUTING VS. MOLECULAR TUMOR BOARD

IBM Watson for Oncology vs. University North Caroline MTB

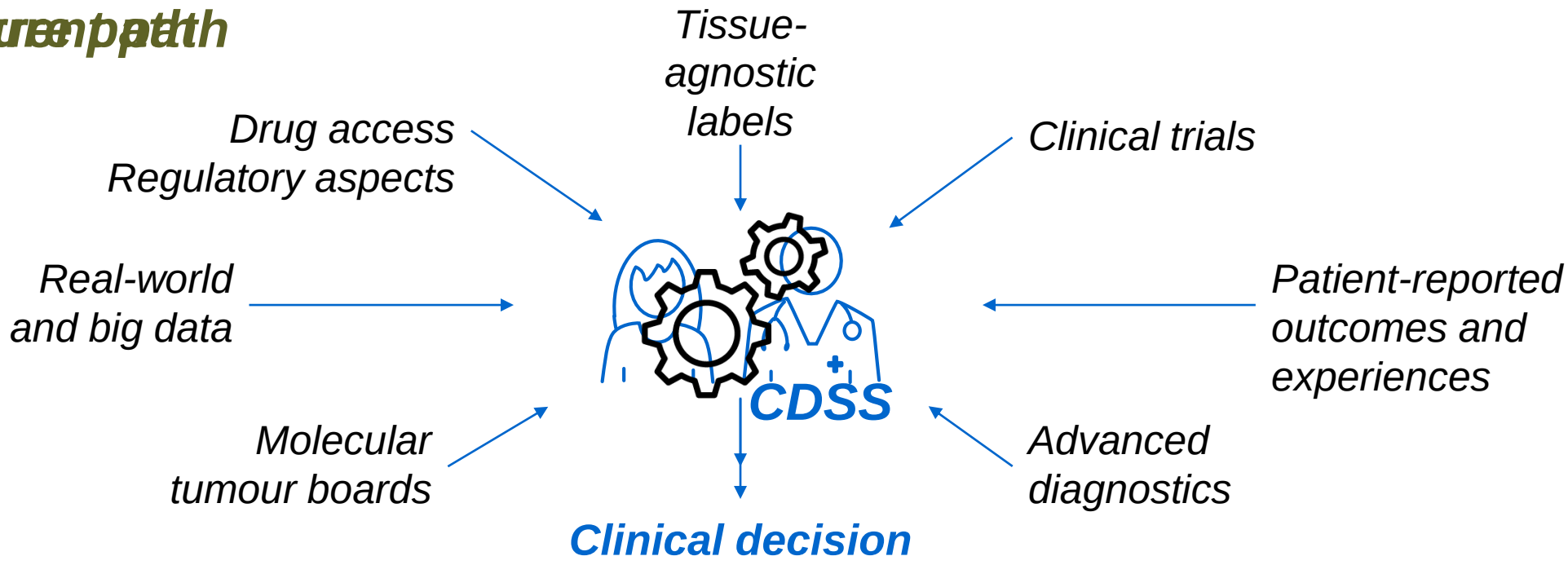


10% absolute increase in patients with actionable alterations

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

CLINICAL DECISION SUPPORT SYSTEMS (CDSS)

The future pathway



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PRECISION MEDICINE "TEST-DRIVE" SERIES

Scaling up genomics-guided therapies with clinical trials use

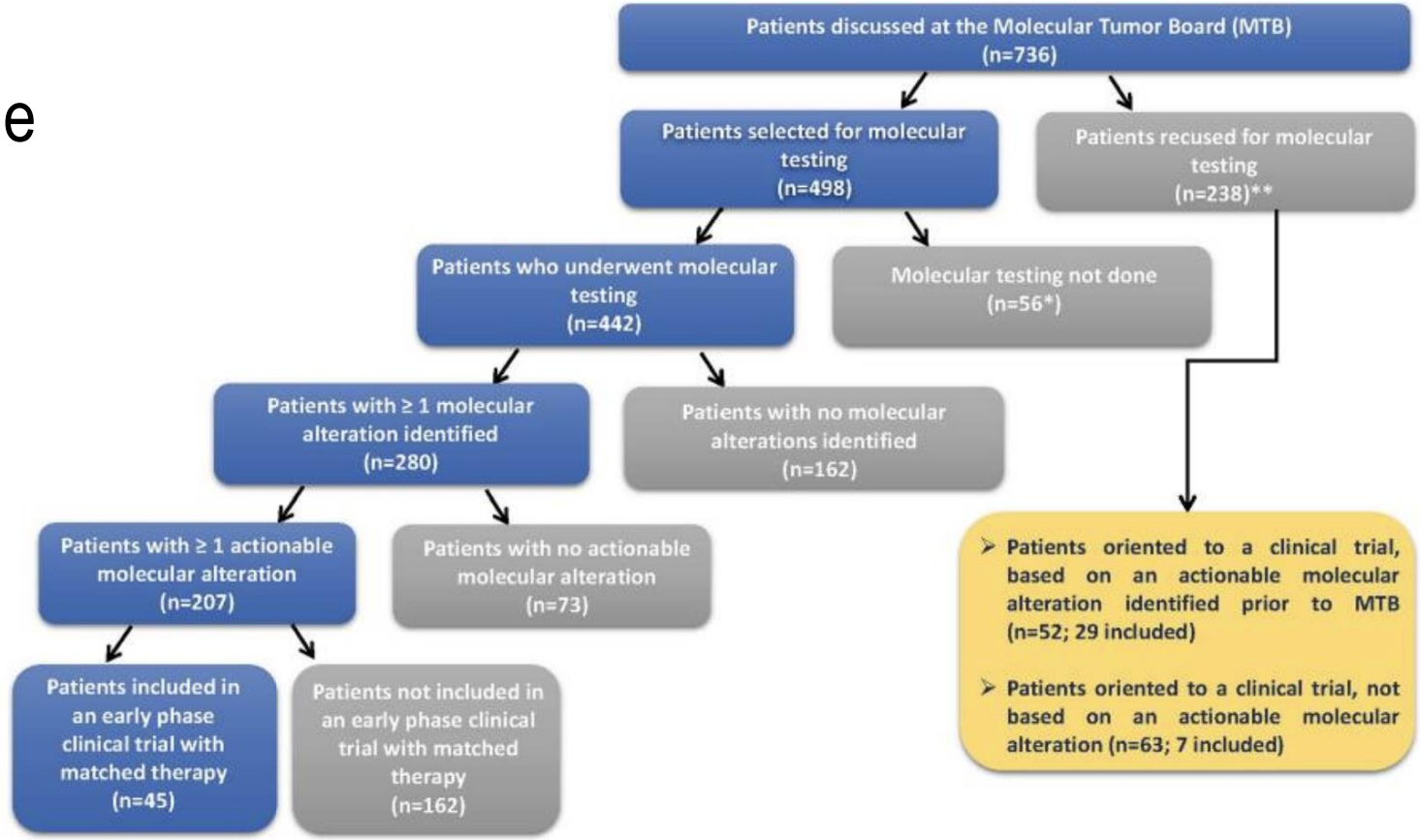
Serie	N	Molecular profile	Actionable alteration	Matched trials
MSK-IMPACT	10,945	91%	37%	11%
NCI MATCH	5,963	93%	18%	11%
VHIO	3,900	90%	38%	10%
PROFILER	2,676	73%	52%	7%
MDACC	2,601	77%	39%	5%
COMPACT	1,893	86%	50%	5%
MOSCATO	1,035	81%	40%	19%
RANGE (median)		**73%-91% (86%)**	**18%-52% (38%)**	**5%-19%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

Adapted from Remon & Dienstmann, ESMO Open 2018

PRECISION MEDICINE "TEST-DRIVE" SERIES

Scaling up genomics-guided therapies with clinical trials use

Institut Curie



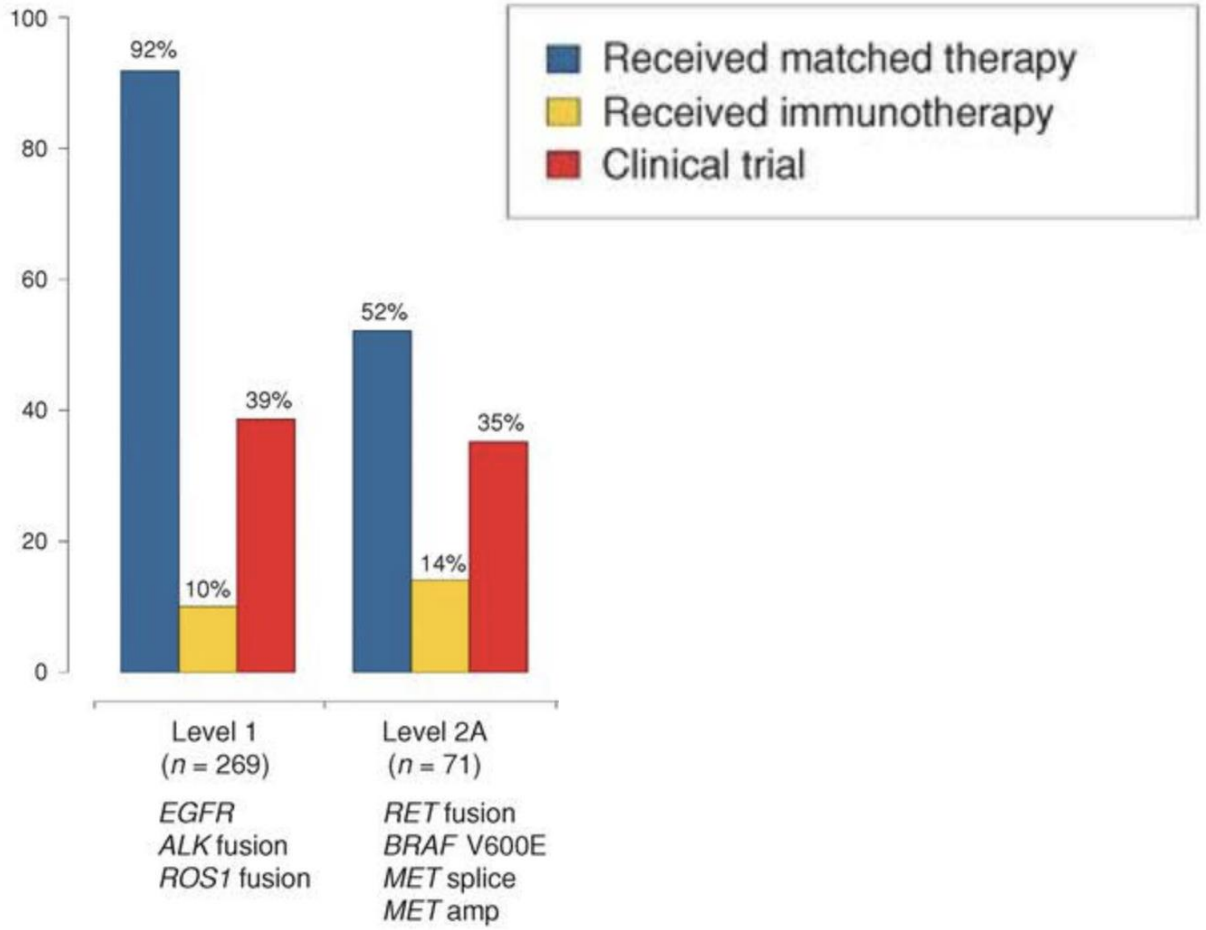
10%
(45/442)

Basse et al, ESMO Open 2018

PRECISION MEDICINE "TEST-DRIVE" SERIES

Scaling up genomics-guided therapies with clinical trials use

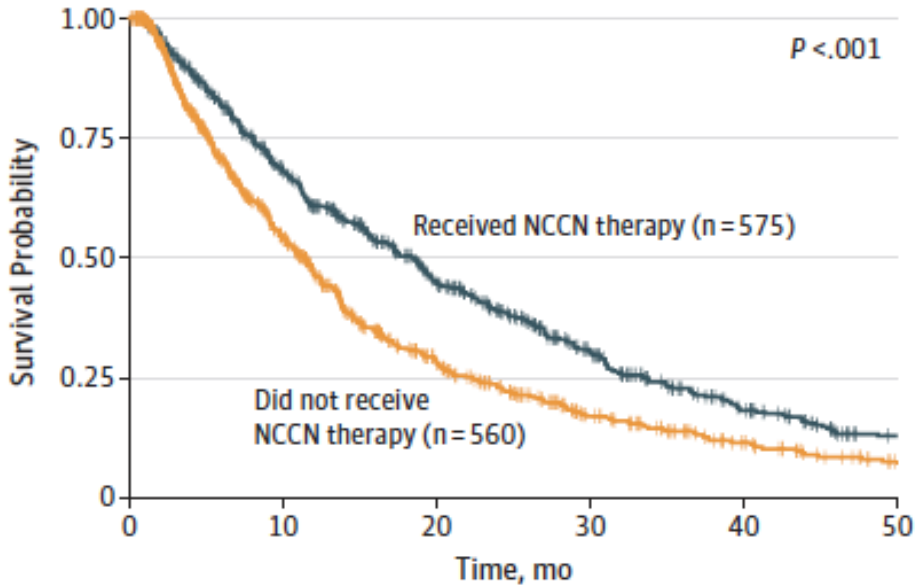
MSKCC – lung cancer



Jordan et al, Cancer Discov 2017

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

Singal et al, JAMA Oncol 2019

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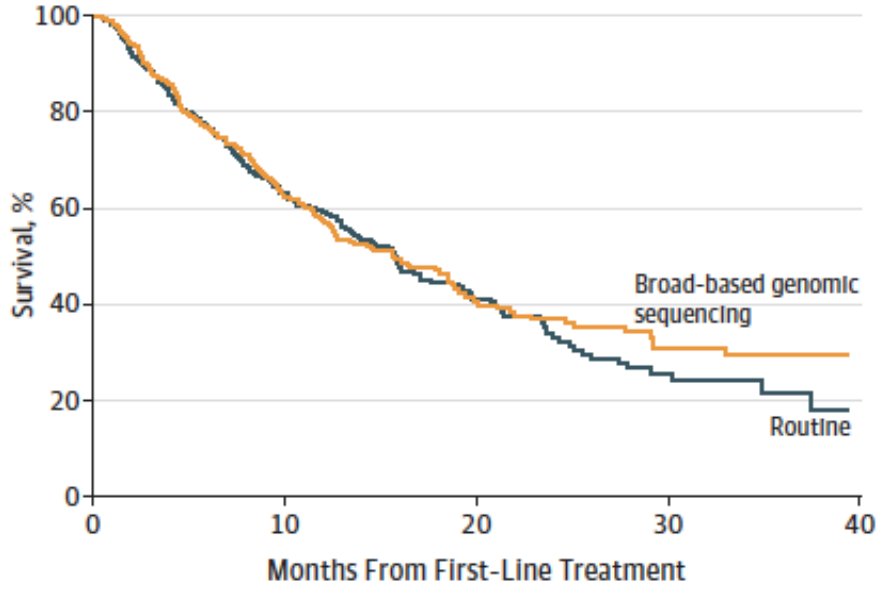
Routine testing vs. Broad-based Genomic Sequencing



No. at risk					
Testing method					
Broad-based genomic sequencing	515	195	64	23	8
Routine	513	192	66	18	<5

14% had actionable alterations
(on top of EGFR/ALK)
4.5% received BGS-guided therapies
(on top of EGFR/ALK)

Presley et al, JAMA Oncol 2018

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

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