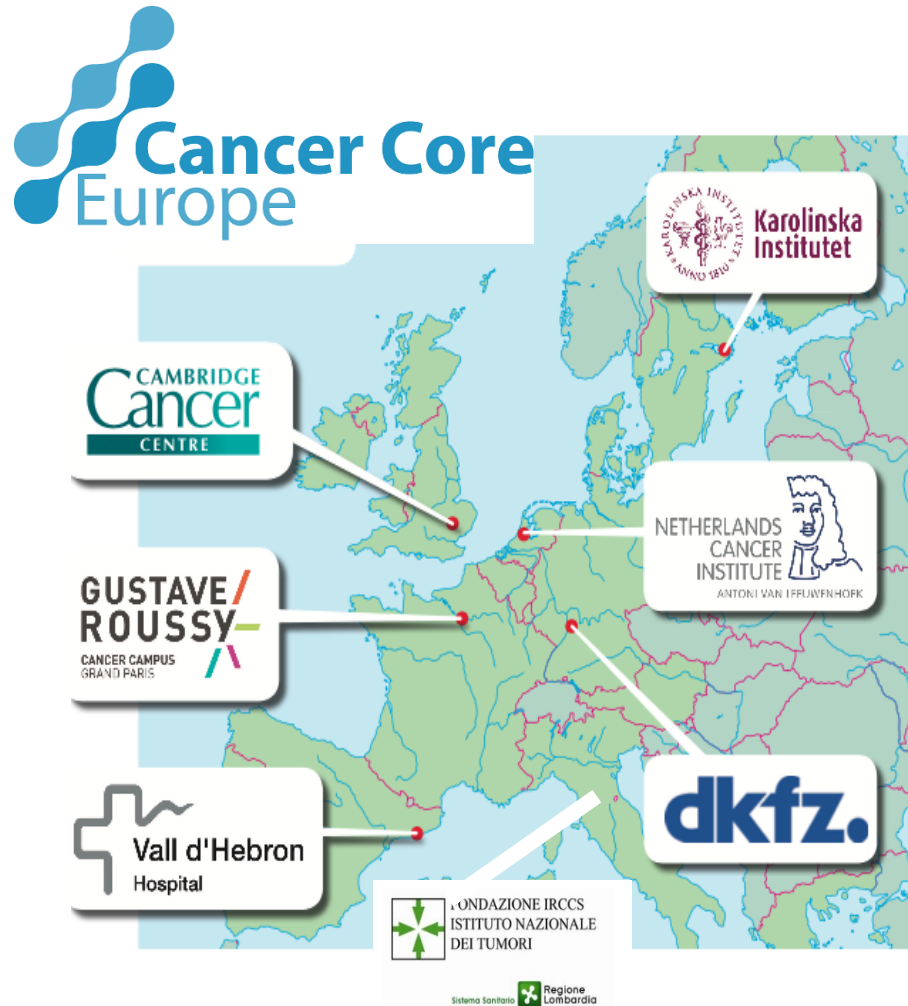


# INTERPRETATION FRAMEWORK OF THE MOLECULAR TUMOR BOARD PORTAL

# The Molecular Tumor Board Portal (MTBP) is a CDSS developed by the Cancer Core Europe



- CCE was established to **co-develop** new precision oncology **trials** across European cancer centers under an **unified framework**
- The MTBP is the CDSS for these initiatives and also supports this 'virtual hospital' model pursued by CCE  
*(as it creates a **single technological, scientific and legal infrastructure** shared between centers)*

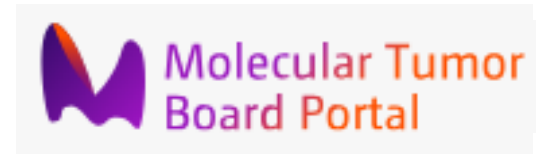
# The MTBP automates data transfer, interpretation and reporting across CCE centers

- > **Retrieval** from **clinical**, **pathology** & **molecular data** files from CCE and external labs

- > Data **integrity** & **harmonization** processes

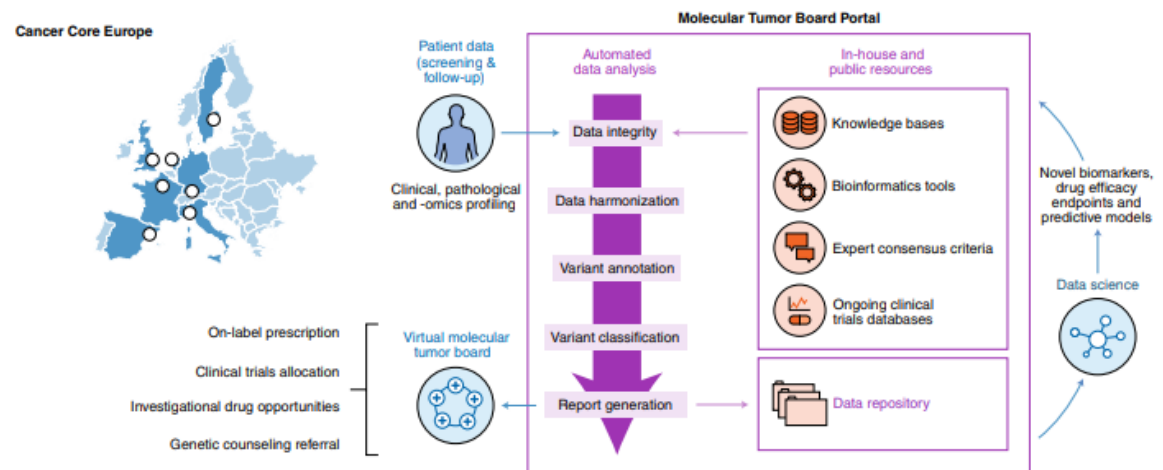
- > Variant annotation following a workflow **pre-agreed** among CCE **experts**

- > **Report generation** & **sharing** with clinical investigators



correspondence

Support systems to guide clinical decision-making in precision oncology: The Cancer Core Europe Molecular Tumor Board Portal



Tamborero et al. **Nature Medicine** 2020

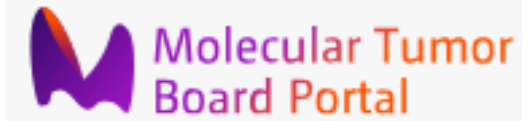
# The MTBP automates data transfer, interpretation and reporting across CCE centers

> **Retrieval** from **clinical**, **pathology** & **molecular data** files from CCE and external labs

> Data **integrity** & **harmonization** processes

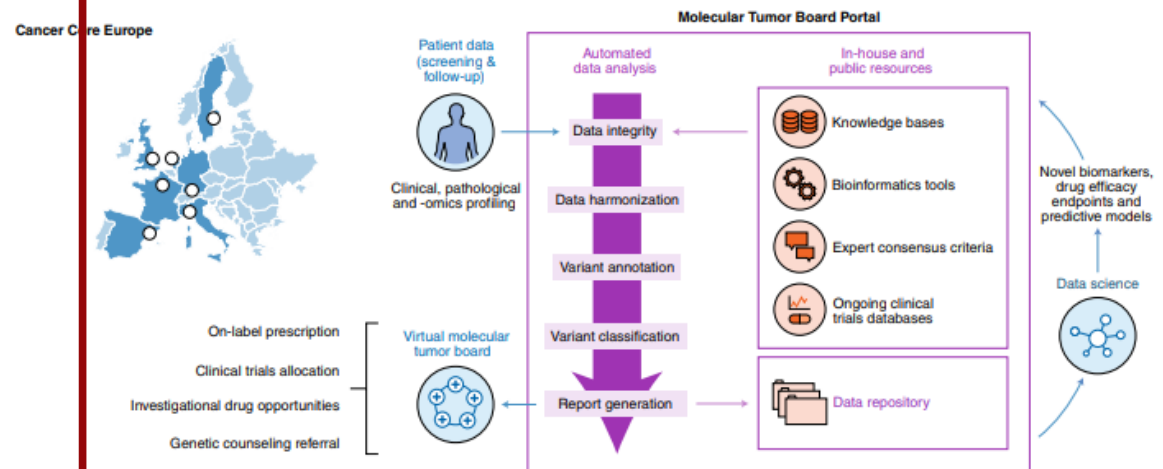
> Variant annotation following a workflow **pre-agreed** among CCE **experts**

> **Report generation** & **sharing** with clinical investigators



correspondence

Support systems to guide clinical decision-making in precision oncology: The Cancer Core Europe Molecular Tumor Board Portal



Tamborero et al. **Nature Medicine** 2020

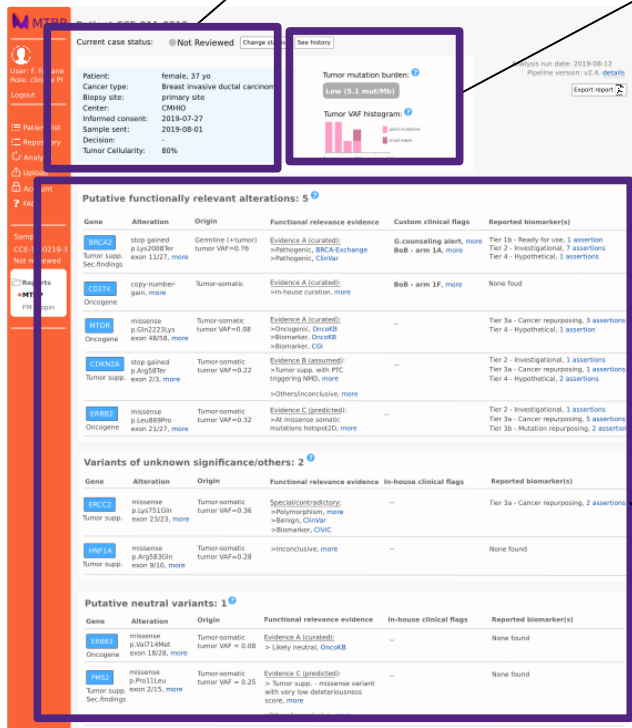
*Fully **automated** process !  
(time, accuracy and systematic advantages)*

# The MTBP reports are accessed via an online platform and discussed during (virtual) meetings

## Interactive reports

dashboard with patient's clinical & pathology data

'broad' genomic signatures



Variants classified according to their predictive **relevance**



Representatives from each CCE center connect via an online platform to discuss clinical recommendations

# The report classifies the individual variants for their functional and predictive relevance

Gene	Alteration	Origin	Functional relevance evidence	Custom clinical flags	Reported biomarker(s)
<b>BRCA2</b> Tumor supp. Sec.findings	stop gained p.Lys2008Ter exon 11/27, <a href="#">more</a>	Germline (+tumor) tumor VAF=0.76	<u>Evidence A (curated):</u> >Pathogenic, <a href="#">BRCA-Exchange</a> >Pathogenic, <a href="#">ClinVar</a>	<b>G.counseling alert</b> , <a href="#">more</a> <b>HRR- arm1</b> , <a href="#">more</a>	Tier 1 - Ready for use, <a href="#">1 assertion</a> Tier 2 - Investigational, <a href="#">7 assertions</a> Tier 4 - Hypothetical, <a href="#">1 assertions</a>
<b>CD274</b> Oncogene	copy-number- gain, <a href="#">more</a>	Tumor-somatic	<u>Evidence A (curated):</u> >In-house curation, <a href="#">more</a>	<b>BoB - arm 1F</b> , <a href="#">more</a>	None foud
<b>MTOR</b> Oncogene	missense p.Gln2223Lys exon 48/58, <a href="#">more</a>	Tumor-somatic tumor VAF=0.08	<u>Evidence A (curated):</u> >Oncogenic, <a href="#">OncoKB</a> >Biomarker, <a href="#">OncoKB</a> >Biomarker, <a href="#">CGI</a>	--	Tier 3a - Cancer repurposing, <a href="#">3 assertions</a> Tier 4 - Hypothetical, <a href="#">1 assertion</a>
<b>CDKN2A</b> Tumor supp.	stop gained p.Arg58Ter exon 2/3, <a href="#">more</a>	Tumor-somatic tumor VAF=0.22	<u>Evidence B (assumed):</u> >Tumor supp. with PTC triggering NMD, <a href="#">more</a>  >Others/inconclusive, <a href="#">more</a>	--	Tier 2 - Investigational, <a href="#">1 assertions</a> Tier 3a - Cancer repurposing, <a href="#">1 assertions</a> Tier 4 - Hypothetical, <a href="#">2 assertions</a>
<b>ERBB2</b> Oncogene	missense p.Leu869Pro exon 21/27, <a href="#">more</a>	Tumor-somatic tumor VAF=0.32	<u>Evidence C (predicted):</u> >At missense somatic mutations hotspot2D, <a href="#">more</a>	--	Tier 2 - Investigational, <a href="#">1 assertions</a> Tier 3a - Cancer repurposing, <a href="#">5 assertions</a> Tier 3b - Mutation repurposing, <a href="#">2 assertions</a>

*Female, 42y, ovarian cancer*

*Disease progression after initially successful PARP-inhibitor treatment*

# The report classifies the individual variants for their functional and predictive relevance

Gene	Alteration	Origin	Functional relevance evidence	Custom clinical flags	Reported biomarker(s)
<b>BRCA2</b> Tumor supp. Sec.findings	stop gained p.Lys2008Ter exon 11/27, <a href="#">more</a>	Germline (+tumor) tumor VAF=0.76	<u>Evidence A (curated):</u> >Pathogenic, <a href="#">BRCA-Exchange</a> >Pathogenic, <a href="#">ClinVar</a>	<b>G.counseling alert</b> , <a href="#">more</a> <b>HRR- arm1</b> , <a href="#">more</a>	Tier 1 - Ready for use, <a href="#">1 assertion</a> Tier 2 - Investigational, <a href="#">7 assertions</a> Tier 4 - Hypothetical, <a href="#">1 assertions</a>
<b>CD274</b> Oncogene	copy-number- gain, <a href="#">more</a>	Tumor-somatic	<u>Evidence A (curated):</u> >In-house curation, <a href="#">more</a>	<b>BoB - arm 1F</b> , <a href="#">more</a>	None foud
<b>MTOR</b> Oncogene	missense p.Gln2223Lys exon 48/58, <a href="#">more</a>	Tumor-somatic tumor VAF=0.08	<u>Evidence A (curated):</u> >Oncogenic, <a href="#">OncoKB</a> >Biomarker, <a href="#">OncoKB</a> >Biomarker, <a href="#">CGI</a>	--	Tier 3a - Cancer repurposing, <a href="#">3 assertions</a> Tier 4 - Hypothetical, <a href="#">1 assertion</a>
<b>CDKN2A</b> Tumor supp.	stop gained p.Arg58Ter exon 2/3, <a href="#">more</a>	Tumor-somatic tumor VAF=0.22	<u>Evidence B (assumed):</u> >Tumor supp. with PTC triggering NMD, <a href="#">more</a>  >Others/inconclusive, <a href="#">more</a>	--	Tier 2 - Investigational, <a href="#">1 assertions</a> Tier 3a - Cancer repurposing, <a href="#">1 assertions</a> Tier 4 - Hypothetical, <a href="#">2 assertions</a>
<b>ERBB2</b> Oncogene	missense p.Leu869Pro exon 21/27, <a href="#">more</a>	Tumor-somatic tumor VAF=0.32	<u>Evidence C (predicted):</u> >At missense somatic mutations hotspot2D, <a href="#">more</a>	--	Tier 2 - Investigational, <a href="#">1 assertions</a> Tier 3a - Cancer repurposing, <a href="#">5 assertions</a> Tier 3b - Mutation repurposing, <a href="#">2 assertions</a>

Descriptives of the gene and the variant

(*MTBP variant mapping via Ensembl-VEP*)



# The first step is to classify the variants that are functionally relevant for the tumor phenotypes

Gene	Alteration	Origin	Functional relevance evidence	
<b>BRCA2</b> Tumor supp. Sec.findings	stop gained p.Lys2008Ter exon 11/27, <a href="#">more</a>	Germline (+tumor) tumor VAF=0.76	<u>Evidence A (curated):</u> >Pathogenic, <a href="#">BRCA-Exchange</a> >Pathogenic, <a href="#">ClinVar</a>	>There are 3 sources of evidence supporting the functional classification: BoB - arm 1A, <a href="#">more</a> Tier 2 - Investigational, 7 assertions Tier 4 - Hypothetical, 1 assertions
<b>CD274</b> Oncogene	copy-number-gain, <a href="#">more</a>	Tumor-somatic	<u>Evidence A (curated):</u> >In-house curation, <a href="#">more</a>	A) as curated from clinical/ experimental data BoB - arm 1A, <a href="#">more</a>
<b>MTOR</b> Oncogene	missense p.Gln2223Lys exon 48/58, <a href="#">more</a>	Tumor-somatic tumor VAF=0.08	<u>Evidence A (curated):</u> >Oncogenic, <a href="#">OncoKB</a> >Biomarker, <a href="#">OncoKB</a> >Biomarker, <a href="#">CGI</a>	B) bona fide biological assumption Tier 3a - Cancer repurposing, 3 assertions
<b>CDKN2A</b> Tumor supp.	stop gained p.Arg58Ter exon 2/3, <a href="#">more</a>	Tumor-somatic tumor VAF=0.22	<u>Evidence B (assumed):</u> >Tumor supp. with PTC triggering NMD, <a href="#">more</a>  >Others/inconclusive, <a href="#">more</a>	C) bioinformatics prediction Tier 2 - Investigational, 1 assertions Tier 3a - Cancer repurposing, 1 assertions
<b>ERBB2</b> Oncogene	missense p.Leu869Pro exon 21/27, <a href="#">more</a>	Tumor-somatic tumor VAF=0.32	<u>Evidence C (predicted):</u> >At missense somatic mutations hotspot2D, <a href="#">more</a>	Tier 2 - Investigational, 1 assertions Tier 3a - Cancer repurposing, 5 assertions Tier 3b - Mutation repurposing, 2 assertions

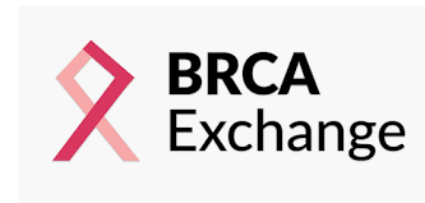
>It is a clinical decision which evidence you require to pursue an action in the variant !



# Functional relevance call based on known variant effects

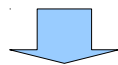
- > Any reported effect compatible with the variant being functional regardless of the “context”\*

*(pathogenicity, experimental assays, clinical data, biomarkers,...)*



\* *example: a BRCA1 variant can be considered loss-of-function if already:*

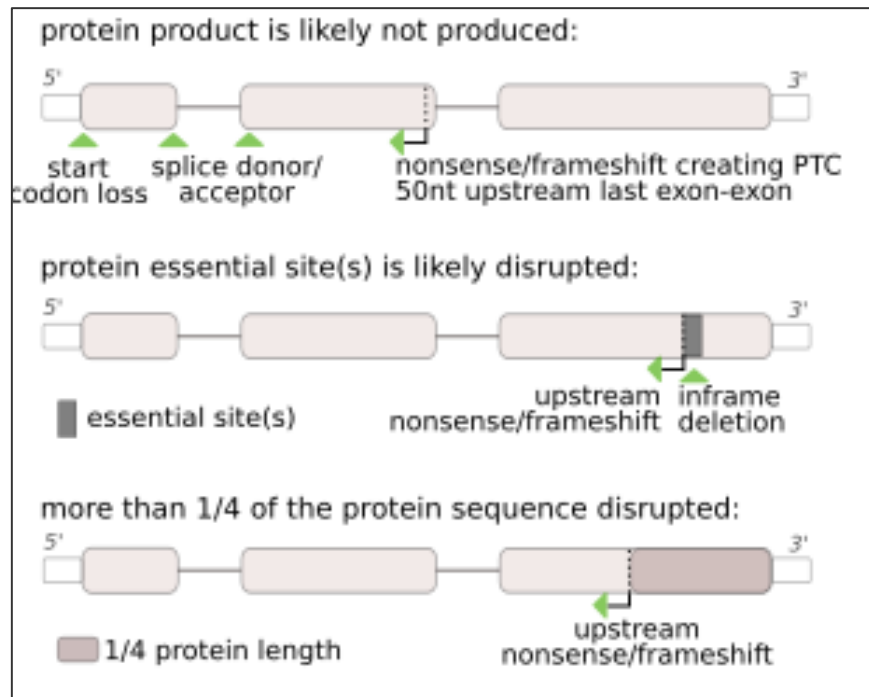
- > *described as pathogenic in germline genetic studies*
- > *found to disrupt WT protein in functional assays*
- > *reported as biomarker of PARP<sup>inh</sup> in a particular cancer type(s)*



*The context (origin, clonality, cancer type, co-occurring alterations..) is considered when evaluating the clinical relevance of such loss-of-function*

# Functional relevance call based on assumed effects

- > These are largely based on **sedimented** criteria established to identify loss-of-function events in Mendelian disease genes (99% PPV)

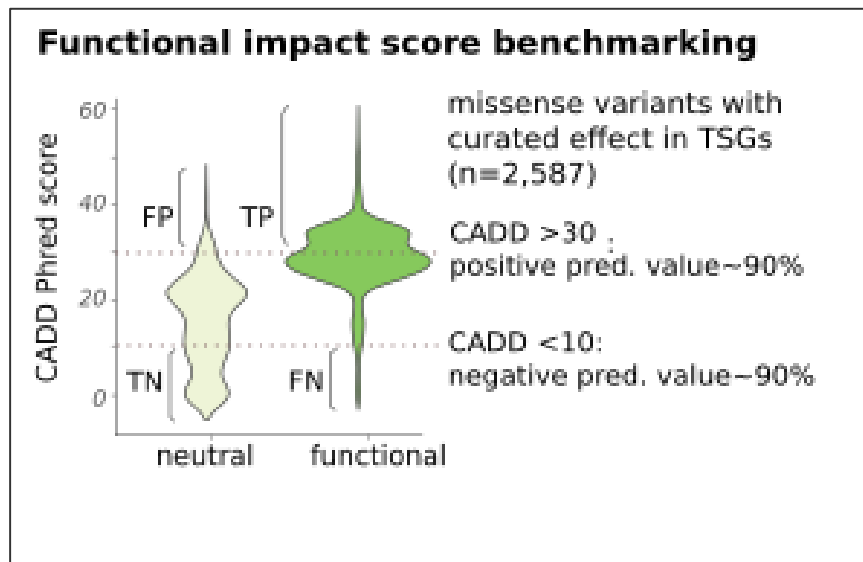


e.g. > when a PTC leads to NMD?

> when an essential protein region is disrupted?

# Functional relevance call based on bioinformatic predictions

- > Important: use those providing robust results (prioritizing PPV)
- > Mutation **hotspots**: use statistical methods that consider genomic background mutational processes to call an observed accumulation as significant
- > **Functional impact** scores: use a method benchmarked for you specific Analytical question and with thresholds adapted to the required PPV



# Tumor variants are then matched with cancer biomarkers reported at present

Gene	Alteration	Origin	Functional relevance evidence	Custom clinical flags	Reported biomarker(s)
<b>BRCA2</b> Tumor supp. Sec.findings	stop gained p.Lys2008Ter exon 11/27, <a href="#">more</a>	Germline (+tumor) tumor VAF=0.76	Evidence A (curated): >Pathogenic, <a href="#">BRCA-Exchange</a> >Pathogenic, <a href="#">ClinVar</a>	<b>G.counseling alert</b> <a href="#">more</a> <b>HRR- arm1</b> , <a href="#">more</a>	Tier 1 - Ready for use, <a href="#">1 assertion</a> Tier 2 - Investigational, <a href="#">7 assertions</a> Tier 4 - Hypothetical, <a href="#">1 assertions</a>
<b>CD274</b> Oncogene	copy-number- gain, <a href="#">more</a>	Tumor-somatic	Evidence A (curated): >In-house curation, <a href="#">more</a>	<b>BoB - arm 1F</b> , <a href="#">more</a>	None foud
<b>MTOR</b> Oncogene	missense p.Gln2223Lys exon 48/58, <a href="#">more</a>	Tumor-somatic tumor VAF=0.08	Evidence A (curated): >Oncogenic, <a href="#">OncoKB</a> >Biomarker, <a href="#">OncoKB</a> >Biomarker, <a href="#">CGI</a>	--	Tier 3a - Cancer repurposing, <a href="#">3 assertions</a> Tier 4 - Hypothetical, <a href="#">1 assertion</a>
<b>CDKN2A</b> Tumor supp.	stop gained p.Arg58Ter exon 2/3, <a href="#">more</a>	Tumor-somatic tumor VAF=0.22	Evidence B (assumed): >Tumor supp. with PTC triggering NMD, <a href="#">more</a>  >Others/inconclusive, <a href="#">more</a>	--	Tier 2 - Investigational, <a href="#">1 assertions</a> Tier 3a - Cancer repurposing, <a href="#">1 assertions</a> Tier 4 - Hypothetical, <a href="#">2 assertions</a>
<b>ERBB2</b> Oncogene	missense p.Leu869Pro exon 21/27, <a href="#">more</a>	Tumor-somatic tumor VAF=0.32	Evidence C (predicted): >At missense somatic mutations hotspot2D, <a href="#">more</a>	--	Tier 2 - Investigational, <a href="#">1 assertions</a> Tier 3a - Cancer repurposing, <a href="#">5 assertions</a> Tier 3b - Mutation repurposing, <a href="#">2 assertions</a>

>Cancer biomarkers means that the variant is functional \*AND\* shapes diagnosis, prognosis or drug response

# Actionability must be tiered for clinical utility

Gene	Alteration	Origin	Functional relevance evidence	Custom clinical flags	Reported biomarker(s)
BRCA2 Tumor supp. Sec.findings	stop gained p.Lys2008Ter exon 11/27, <a href="#">more</a>	Germline (+tumor) tumor VAF=0.76	Evidence A (curated): >Pathogenic, <a href="#">BRCA-Exchange</a> >Pathogenic, <a href="#">ClinVar</a>	G.counseling alert, <a href="#">more</a> HRR- arm1 , <a href="#">more</a>	Tier 1 - Ready for use, <a href="#">1 assertion</a> Tier 2 - Investigational, <a href="#">7 assertions</a> Tier 4 - Hypothetical, <a href="#">1 assertions</a>
CD274 Oncogene	copy-number- gain, <a href="#">more</a>	Tumor-somatic	Evidence A (curated): >In-house curation, <a href="#">more</a>	BoB - arm 1F, <a href="#">more</a>	None foud
MTOR Oncogene	missense p.Gln2223Lys exon 48/58, <a href="#">more</a>	Tumor-somatic tumor VAF=0.08	Evidence A (curated): <a href="#">OncoKB</a> >Biomarker, <a href="#">OncoKB</a> >Biomarker, <a href="#">CGI</a>	--	Tier 3a - Cancer repurposing, <a href="#">3 assertions</a> Tier 4 - Hypothetical, <a href="#">1 assertion</a>
CDKN2A Tumor supp.	stop gained p.Arg58Ter exon 2/3, <a href="#">more</a>	Tumor-somatic tumor VAF=0.22	Evidence B (assumed): >Tumor supp. with PTC triggering NMD, <a href="#">more</a>	--	Tier 2 - Investigational, <a href="#">1 assertions</a> Tier 3a - Cancer repurposing, <a href="#">1 assertions</a> Tier 4 - Hypothetical, <a href="#">2 assertions</a>
ERBB2 Oncogene	missense p.Leu585Val exon 21/27, <a href="#">more</a>	Tumor-somatic	Evidence C (predicted): mutations hotspot2D, <a href="#">more</a>	--	Tier 2 - Investigational, <a href="#">1 assertions</a> Tier 3a - Cancer repurposing, <a href="#">5 assertions</a> Tier 3b - Mutation repurposing, <a href="#">2 assertions</a>

>Biomarker info can be used to state functional relevance

*>if a mutation increase targeted drug sensitivity, is indeed functional!*

>Biomarker actionability must factor in **additional considerations** beyond the variant matching (aka, the “context”)

*> co-occurring alterations, cancer type match, biomarker clinical evidence, etc*

# Guidelines to tier biomarker actionability



*Annals of Oncology* 29: 1895–1902, 2018  
doi:10.1093/annonc/mdy263  
Published online 21 August 2018

## SPECIAL ARTICLE

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

# For non-standard therapies, we prioritize allocation to clinical trials (recruiting across CCE centers)

Gene	Alteration	Origin	Functional relevance evidence	Custom clinical flags	Reported biomarker(s)
<b>BRCA2</b> Tumor supp. Sec.findings	stop gained p.Lys2008Ter exon 11/27, <a href="#">more</a>	Germline (+tumor) tumor VAF=0.76	Evidence A (curated): >Pathogenic, <a href="#">BRCA-Exchange</a> >Pathogenic, <a href="#">ClinVar</a>	<b>G.counseling alert, <a href="#">more</a></b> <b>HRR- arm1 , <a href="#">more</a></b>	Tier 1 - Ready for use, <a href="#">1 assertion</a> Tier 2 - Investigational, <a href="#">7 assertions</a> Tier 4 - Hypothetical, <a href="#">1 assertions</a>
<b>CD274</b> Oncogene	copy-number- gain, <a href="#">more</a>	Tumor-somatic	Evidence A (curated): >In-house curation, <a href="#">more</a>	<b>BoB - arm 1F, <a href="#">more</a></b>	None foud
<b>MTOR</b> Oncogene	missense p.Gln2223Lys exon 48/58, <a href="#">more</a>	Tumor-somatic tumor VAF=0.08	Evidence A (curated): >Oncogenic, <a href="#">OncoKB</a> >Biomarker, <a href="#">OncoKB</a> >Biomarker, <a href="#">CGI</a>	--	Tier 3a - Cancer repurposing, <a href="#">3 assertions</a> Tier 4 - Hypothetical, <a href="#">1 assertion</a>
<b>CDKN2A</b> Tumor supp.	stop gained p.Arg58Ter exon 2/3, <a href="#">more</a>	Tumor-somatic tumor VAF=0.22	Evidence B (assumed): >Tumor supp. with PTC triggering NMD, <a href="#">more</a>  >Others/inconclusive, <a href="#">more</a>	--	Tier 2 - Investigational, <a href="#">1 assertions</a> Tier 3a - Cancer repurposing, <a href="#">1 assertions</a> Tier 4 - Hypothetical, <a href="#">2 assertions</a>
<b>ERBB2</b> Oncogene	missense p.Leu869Pro exon 21/27, <a href="#">more</a>	Tumor-somatic tumor VAF=0.32	Evidence C (predicted): >At missense somatic mutations hotspot2D, <a href="#">more</a>	--	Tier 3a - Cancer repurposing, <a href="#">5 assertions</a> Tier 3b - Mutation repurposing, <a href="#">2 assertions</a>

> Variants matching **trial eligibility** are flagged & prioritized in the MTBP reports

(**clinical, pathological and molecular** criteria passed via 'custom actionability' files)



# MTBP reports are HTML documents: use of interactive elements

Gene	Alteration	Origin
<a href="#">BRCA2</a>	stop gained p.Lys2008Ter exon 11/27, <a href="#">more</a>	Germli tumor
<a href="#">CD274</a>	copy-number- gain, <a href="#">more</a>	Tumor
<a href="#">MTOR</a>	missense p.Gln2223Lys exon 48/58, <a href="#">more</a>	Tumor
<a href="#">CDKN2A</a>	stop gained p.Arg58Ter exon 2/3, <a href="#">more</a>	Tumor
<a href="#">FBXW7</a>	missense p.Arg484Met exon 10/12, <a href="#">more</a>	Tumor

## BRCA2

This gene is considered a tumor suppressor. Pathogenic variants in BRCA2 are recommended to be reported as secondary findings by the ACMG (SF v2.0) when appropriate, due to -at least- its involvement with: Breast-ovarian cancer, familial 2 (MIM 612555), [more gene info](#)

### Gene mutations in previous pan-cancer cohorts ?

pan-cancer mutation count

aminoacid position in BRCA2-ENST00000380152

Pan-cancer predominant mutation type:  
● disrupting  
● inframe  
● missense

Mutations found in the sample:  
X AA #2008 (none observed in pan-cancer)

BRCA2 bears somatic protein-affecting mutations in 1.6% of the all Biliary Tract samples (n=245)  
BRCA2 bears somatic protein-affecting mutations in 4.6% of the Pan-cancer samples (n=10703)

very high predicted delet. score, [more](#)

# MTBP reports are HTML documents: use of interactive elements

The screenshot displays an MTBP report interface with several interactive elements and pop-up windows.

**Pop-up Window 1 (Top Left):**

- BRCA2 p.Lys2008Ter is annotated by ClinVar (records supported by stronger evidence)
- Effect: Pathogenic
- Allele origin: Germline
- Reviewed by expert panel
- <https://www.ncbi.nlm.nih.gov/clinvar/variation/216029/>

**Pop-up Window 2 (Top Right):**

- CD274 amplif. matches inclusion criteria for BoB-arm 1E
- > Matched trial alteration: PDL1 amplification
- > Matched trial cancer type: Any solid cancer
- Basket of Baskets information:
- BoB Module 1: use of PDL-1 inhibitor (atezolizumab) in advanced tumors with selected molecular alterations. Primary end point is the overall 12-weeks response rate by RECIST 1.1
- Contact: [jrodon@vhio.net](mailto:jrodon@vhio.net), [ibrana@vhio.net](mailto:ibrana@vhio.net)

**Main Report Content:**

Gene	Variant	Effect	Origin	Evidence	BoB - arm
CD274	copy-number-gain, more	Tumor-somatic		Evidence A (curated): >In-house curation, more	BoB - arm 1F, more
MTOR	missense p.Gln2223Lys exon 48/58, more	Tumor-somatic tumor VAF=0.2			
CDKN2A	stop gained p.Arg58Ter exon 2/3, more	Tumor-somatic tumor VAF=0.2			
FBXW7	missense p.Arg484Met exon 10/12, more	Tumor-somatic tumor VAF=0.3			

**Pop-up Window 3 (Bottom Center):**

- Tier 4 includes biomarkers described for this variant and matched cancer type according to pre-clinical evidence
- >Reported sensitivity/response: Sirolimus
- >Reported resistance/reduced sensitivity: Tubulin inhibitors
- <https://civic.genome.wustl.edu/links/variants/637>
- Biomarker: FBXW7 LOSS-OF-FUNCTION
- Variant origin: Somatic
- Clinical significance: Sensitivity/Response
- Drug: Sirolimus, Disease: Any cancer type
- Evidence level: D - Preclinical
- Trust rating: 4/5, Source: [PMID 18787170](https://pubmed.ncbi.nlm.nih.gov/18787170/)
- <https://www.cancergenomeinterpreter.org/biomarkers>
- Biomarker: FBXW7 oncogenic mutation
- Association: Resistant
- Drug: Tubulin inhibitors
- Disease: Any cancer type
- Evidence: Preclinical
- Source: [PMID:21368834](https://pubmed.ncbi.nlm.nih.gov/21368834/)

**Pop-up Window 4 (Bottom Right):**

- Tier 3a - Cancer repurposing, 3 assertions
- Tier 4 - Hypothetical, 1 assertion
- Tier 2 - Investigational, 1 assertions
- Tier 3a - Cancer repurposing, 1 assertions
- Tier 4 - Hypothetical, 2 assertions
- Tier 4 - Hypothetical, 2 assertions

# MTBP reports are HTML documents: use of interactive elements

BRCA2 p.Lys2008Ter is annotated by ClinVar  
(records supported by stronger evidence)

Effect: Pathogenic  
Allele origin: Germline  
Reviewed by expert panel  
<https://www.ncbi.nlm.nih.gov/clinvar/variation/216029/>

CD274	copy-number-gain, <a href="#">more</a>	Tumor-somatic	Evidence A (curated) >In-house curation, <a href="#">more</a>
MTOR	missense p.Gln2223Lys exon 48/58, <a href="#">more</a>	Tumor-somatic tumor VAF=0.28	Evidence A (curated) >Oncogenic, <a href="#">OncoKB</a> >Biomarker, <a href="#">OncoKB</a> >Biomarker, <a href="#">CGI</a>
CDKN2A	stop gained p.Arg58Ter exon 2/3, <a href="#">more</a>	Tumor-somatic tumor VAF=0.22	Evidence B (assumed) >Tumor supp. with PT triggering NMD, <a href="#">more</a> >Others/inconclusive,
FBXW7	missense p.Arg484Met exon 10/12, <a href="#">more</a>	Tumor-somatic tumor VAF=0.32	Evidence C (predicted) >Tumor supp. with mi very high predicted de

NM\_000059.3(BRCA2):c.6022A>T (p.Lys2008Ter) [Cite this record](#)

Interpretation: Pathogenic  
Review status: ★★☆☆ reviewed by expert panel  
Submissions: 2 (Most recent: Jan 7, 2021)  
Last evaluated: Sep 8, 2016  
Accession: VCV000216029.3  
Variation ID: 216029  
Description: single nucleotide variant

Variant details

Conditions

Gene(s)

NM\_000059.3(BRCA2):c.6022A>T (p.Lys2008Ter)  
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	nonsense

  
... more HGVS  
Protein change: K2008\*  
Other names: -  
Canonical SPDI: [NC\\_000013.11:32340376:A:T](#)  
Functional consequence: -  
Global minor allele frequency (GMAF): -  
Allele frequency: -  
Links: [ClinGen: CA335857](#)  
[dbSNP: rs863224467](#)  
[Varsome](#)

Submitted interpretations and evidence

Interpretation (Last evaluated)	Review status (Assertion criteria)	Condition (Inheritance)	Submitter	Supporting information (See all)
Pathogenic (Sep 08, 2016)	reviewed by expert panel (ENIGMA BRCA1/2 Classification Criteria (2015)) Method: curation	Breast-ovarian cancer, familial 2 Allele origin: germline	Evidence-based Network for the Interpretation of Germline Mutant Alleles (ENIGMA) Accession: SCV000300968.2 Submitted: (Sep 13, 2016)	Evidence details Comment: Variant allele predicted to encode a truncated non-functional protein.
Pathogenic (Dec 16, 2019)	criteria provided	Hereditary breast and ovarian cancer	Invitae Accession: SCV000253753.5	Evidence details Publications

# CLINICAL INTERPRETATION OF NGS RESULTS

## EXAMPLES

# CASE 1

> 49 years woman, advanced **ovarian cancer** with a **known** cancer family history

> **Panel sequencing results** – breast tumor biopsy (sample purity ~90%)  
+ paired germline control

MTBP Patient CCE-011-0219

Current case status: @ Not Reviewed Change status See history

Report report Analysis run date: 2024-02-12  
Pipeline version: v1.0.0, default

Patient: female, 37 yo  
Cancer type: Breast invasive ductal carcinoma  
Biopsy site: primary site  
Center: CHMO  
Informed consent: 2019-03-27  
Sample sent: 2019-08-01  
Section:  
Tumor Cellularity: 80%

Tumor mutation burden: 1.00 (1.00, 1.00)  
Tumor VAF histogram: 1.00 (1.00, 1.00)

Gene	Alteration	Origin	Functional relevance evidence	Custom clinical flags	Reported biomarker(s)
BRCA2	stop gained p.Lys285Phe Tumor supp even 11.07, more	Germline (x-tumor) Tumor VAF = 0.26	Evidence A (curated): >Pathogenic, BRCA Exchange >Pathogenic, Clinvar	G counseling alert, more Red - arm 1A, more	Tier 1a - Ready for use, 1 assertion Tier 2 - Investigational, 2 assertions Tier 4 - Hypothetical, 1 assertion
CCNE1	copy number gain, more	Tumor somatic	Evidence A (curated): >in-house curation, more	Red - arm 1F, more	None found
ESR1	missense p.Gln223Lys even 48.08, more	Tumor somatic Tumor VAF = 0.26	Evidence A (curated): >Oncogenic, Clinvar >Oncogenic, Clinvar >Oncogenic, COS	—	Tier 3a - Cancer repurposing, 3 assertions Tier 4 - Hypothetical, 1 assertion
ESR2	stop gained p.Arg85Gly Tumor supp even 27.5, more	Tumor somatic Tumor VAF = 0.22	Evidence B (curated): >Tumor supp. with TTC triggering NMD, more >Oncogenic, Clinvar, more	—	Tier 2 - Investigational, 1 assertion Tier 3a - Cancer repurposing, 1 assertion Tier 4 - Hypothetical, 2 assertions
ESR3	missense p.Arg85Gly Tumor supp even 27.5, more	Tumor somatic Tumor VAF = 0.22	Evidence C (curated): >Tumor supp. with missense of ESR2, more, more	—	Tier 4 - Hypothetical, 2 assertions

Variants of unknown significance/others: 2

Gene	Alteration	Origin	Functional relevance evidence	In-house clinical flags	Reported biomarker(s)
ESR1	missense p.Lys751Gln even 29.23, more	Tumor somatic Tumor VAF = 0.26	Splicing/contradictory: >Oncogenic, Clinvar >Oncogenic, Clinvar >Oncogenic, COS	—	Tier 3a - Cancer repurposing, 2 assertions
ESR2	missense p.Arg85Gly even 27.5, more	Tumor somatic Tumor VAF = 0.22	inconclusive, more	—	None found

Putative neutral variants: 1

Gene	Alteration	Origin	Functional relevance evidence	In-house clinical flags	Reported biomarker(s)
ESR1	missense p.Val751Gln even 29.23, more	Tumor somatic Tumor VAF = 0.26	Evidence A (curated): > Likely neutral, Clinvar	—	None found
ESR2	missense p.Pro123Gln Tumor supp even 27.5, more Sec findings	Tumor somatic Tumor VAF = 0.25	Evidence C (curated): > Tumor supp. - missense variant with very low disorder/burden score, more >Oncogenic, Clinvar, more	—	None found

5 genomic alterations classified as functionally relevant

## Zoom-in in the MTBP report: **Putative Functional Variants table**

Gene	Alteration	Origin	Functional relevance evidence	Custom clinical flags	Reported biomarker(s)
<b>BRCA2</b> Tumor supp. Sec.findings	stop gained p.Lys2008Ter exon 11/27, <a href="#">more</a>	Germline (+tumor) tumor VAF=0.86	<u>Evidence A (curated):</u> >Pathogenic, <a href="#">BRCA-Exchange</a> >Pathogenic, <a href="#">ClinVar</a>	<b>G.counseling alert</b> , <a href="#">more</a> <b>BoB - arm 1A</b> , <a href="#">more</a>	Tier 1 - Ready for use, <a href="#">2 assertions</a> Tier 2 - Investigational, <a href="#">7 assertions</a> Tier 4 - Hypothetical, <a href="#">1 assertions</a>
<b>CD274</b> Oncogene	copy-number-gain, <a href="#">more</a>	Tumor-somatic	<u>Evidence A (curated):</u> >In-house curation, <a href="#">more</a>	<b>BoB - arm 1F</b> , <a href="#">more</a>	None foud
<b>MTOR</b> Oncogene	missense p.Gln2223Lys exon 48/58, <a href="#">more</a>	Tumor-somatic tumor VAF=0.28	<u>Evidence A (curated):</u> >Oncogenic, <a href="#">OncoKB</a> >Biomarker, <a href="#">CGI</a>	--	Tier 3a - Cancer repurposing, <a href="#">3 assertions</a> Tier 4 - Hypothetical, <a href="#">1 assertion</a>
<b>CDKN2A</b> Tumor supp.	stop gained p.Arg58Ter exon 2/3, <a href="#">more</a>	Tumor-somatic tumor VAF=0.22	<u>Evidence B (assumed):</u> >Tumor supp. with PTC triggering NMD, <a href="#">more</a>  >Others/inconclusive, <a href="#">more</a>	--	Tier 2 - Investigational, <a href="#">1 assertions</a> Tier 3a - Cancer repurposing, <a href="#">1 assertions</a> Tier 4 - Hypothetical, <a href="#">2 assertions</a>
<b>FBXW7</b> Tumor supp.	missense p.Arg484Met exon 10/12, <a href="#">more</a>	Tumor-somatic tumor VAF=0.32	<u>Evidence C (predicted):</u> >Tumor supp. with missense of very high predicted delet. score, <a href="#">more</a>	--	Tier 4 - Hypothetical, <a href="#">2 assertions</a>



- > **BRCA2** nonsense, germline origin;
- > tumor VAF compatible with LoH
- > already reported as pathogenic

BRCA2 p.Lys2008Ter



<https://www.ncbi.nlm.nih.gov/clinvar/variation/216029>

Effect: Pathogenic

Allele origin: germline

Review status: reviewed by expert panel

Gene	Alteration	Origin	Functional relevance evidence	Custom clinical flags	Reported biomarker(s)
<b>BRCA2</b> Tumor supp. See findings	stop gained p.Lys2008Ter exon 11/27, <a href="#">more</a>	Germline (+tumor) tumor VAF=0.86	<u>Evidence A (curated):</u> >Pathogenic, <a href="#">BRCA-Exchange</a> >Pathogenic, <a href="#">ClinVar</a>	<b>G.counseling alert, <a href="#">more</a></b> <b>BoB - arm 1A, <a href="#">more</a></b>	Tier 1 - Ready for use, <a href="#">2 assertions</a> Tier 2 - Investigational, <a href="#">7 assertions</a> Tier 4 - Hypothetical, <a href="#">1 assertions</a>
<b>CD274</b> Oncogene	copy-number- gain, <a href="#">more</a>	Tumor-somatic	<u>Evidence A (curated):</u> >In-house curation, <a href="#">more</a>	<b>BoB - arm 1F, <a href="#">more</a></b>	None found
<b>MTOR</b> Oncogene	missense p.Gln2223Lys exon 48/58, <a href="#">more</a>	Tumor-somatic tumor VAF=0.28	<u>Evidence A (curated):</u> >Oncogenic, <a href="#">OncoKB</a> >Biomarker, <a href="#">CGI</a>	--	Tier 3a - Cancer repurposing, <a href="#">3 assertions</a> Tier 4 - Hypothetical, <a href="#">1 assertion</a>
<b>CDKN2A</b> Tumor supp.	stop gained p.Arg58Ter exon 2/3, <a href="#">more</a>	Tumor-somatic tumor VAF=0.22	<u>Evidence B (assumed):</u> >Tumor supp. with PTC triggering NMD, <a href="#">more</a>  >Others/inconclusive, <a href="#">more</a>	--	Tier 2 - Investigational, <a href="#">1 assertions</a> Tier 3a - Cancer repurposing, <a href="#">1 assertions</a> Tier 4 - Hypothetical, <a href="#">2 assertions</a>
<b>FBXW7</b> Tumor supp.	missense p.Arg484Met exon 10/12, <a href="#">more</a>	Tumor-somatic tumor VAF=0.32	<u>Evidence C (predicted):</u> >Tumor supp. with missense of very high predicted delet. score, <a href="#">more</a>	--	Tier 4 - Hypothetical, <a href="#">2 assertions</a>

Gene	Alteration	Origin	Functional relevance evidence	Custom clinical flags	Reported biomarker(s)
<b>BRCA2</b> Tumor supp. Sec.findings	stop gained p.Lys2008Ter exon 11/27, <a href="#">more</a>	Germline (+tumor) tumor VAF=0.86	<u>Evidence A (curated):</u> >Pathogenic, <a href="#">BRCA-Exchange</a> >Pathogenic, <a href="#">ClinVar</a>	<b>G.counseling alert</b> , <a href="#">more</a> <b>BoB - arm 1A</b> , <a href="#">more</a>	Tier 1 - Ready for use, <a href="#">2 assertions</a> Tier 2 - Investigational, <a href="#">7 assertions</a> Tier 4 - Hypothetical, <a href="#">1 assertions</a>
<b>CD274</b> Oncogene	copy-number- gain, <a href="#">more</a>	Tumor-somatic	<u>Evidence A (curated):</u> >In-house curation, <a href="#">more</a>	<b>BoB - arm 1F</b> , <a href="#">more</a>	None found
<b>MTOR</b> Oncogene	missense p.Gln2223Lys exon 48/58, <a href="#">more</a>	Tumor-somatic tumor VAF=0.28	<u>Evidence A (curated):</u> >Oncogenic, <a href="#">OncoKB</a> >Biomarker, <a href="#">CGI</a>	--	Tier 3a - Cancer repurposing, <a href="#">3 assertions</a> Tier 4 - Hypothetical, <a href="#">1 assertion</a>
<b>CDKN2A</b> Tumor supp.	stop gained p.Arg58Ter exon 2/3, <a href="#">more</a>	Tumor-somatic tumor VAF=0.22	<u>Evidence B (assumed):</u> >Tumor supp. with PTC triggering NMD, <a href="#">more</a> >Others/inconclusive, <a href="#">more</a>	--	Tier 2 - Investigational, <a href="#">1 assertions</a> Tier 3a - Cancer repurposing, <a href="#">1 assertions</a> Tier 4 - Hypothetical, <a href="#">2 assertions</a>
<b>FBXW7</b> Tumor supp.	missense p.Arg484Met exon 10/12, <a href="#">more</a>	Tumor-somatic tumor VAF=0.32	<u>Evidence C (predicted):</u> >Tumor supp. with missense of very high predicted delet. score, <a href="#">more</a>	--	Tier 4 - Hypothetical, <a href="#">2 assertions</a>

- > **CD274** amplification (estimated DNA material gain >6 copies)
- > **MTOR** somatic missense variant known to be oncogenic (evidence A - curated)
- > **CDKN2A** somatic nonsense “fair” to assume that is LoF (evidence B - assumed)
- > **FBXW7** somatic missense \*\*predicted\*\* to be LoF (evidence C - predicted)

Gene	Alteration	Origin	Effect	Clinical flags	Reported biomarker(s)
<b>BRCA2</b> Tumor supp. Sec.findings	stop gained p.Lys2008Ter exon 11/27, <a href="#">more</a>	Germ tumor	Biomarker: BRCA2 Oncogenic Mutations Effect: drug Responsive Level of evidence: LEVEL_2 Drug: Olaparib Disease: Breast Cancer Publications: 28578601 Abstracts: Dhawan, MS et al. JCO. Abstract# 2527  <a href="http://oncokb.org/#/gene/BRCA2/alteration/Oncogenic%20Mutations">http://oncokb.org/#/gene/BRCA2/alteration/Oncogenic Mutations</a> Biomarker: BRCA2 Oncogenic Mutations Effect: drug Responsive Level of evidence: LEVEL_2 Drug: Talazoparib Disease: Breast Cancer Publications: 30110579, 30563931 Abstracts: n/a	ing alert, <a href="#">more</a> 1A, <a href="#">more</a>	Tier 1 - Ready for use, <a href="#">2 assertions</a> Tier 2 - Investigational, <a href="#">7 assertions</a> Tier 4 - Hypothetical, <a href="#">1 assertions</a>
<b>CD274</b> Oncogene	copy-number-gain, <a href="#">more</a>	Tumor	Tumor VAF = 0.28 >Oncogenic, <a href="#">Oncokb</a> >Biomarker, <a href="#">CGI</a>	1F, <a href="#">more</a>	None foud
<b>MTOR</b> Oncogene	missense p.Gln2223Lys exon 48/58, <a href="#">more</a>	Tumor			Tier 3a - Cancer repurposing, <a href="#">3 assertions</a> Tier 4 - Hypothetical, <a href="#">1 assertion</a>
<b>CDKN2A</b> Tumor supp.	stop gained p.Arg58Ter exon 2/3, <a href="#">more</a>		Tier 3 includes variants described as drug/prognostic biomarkers according to established/compelling clinical evidence (tiers 1-2) for other cancer types (cancer type repurposing)  Please check the <a href="#">original assertions</a> provided by each knowledgebase listed below  >Reported sensitivity/response: Everolimus, Pazopanib  <a href="https://civic.genome.wustl.edu/links/variants/277">https://civic.genome.wustl.edu/links/variants/277</a> Biomarker: MTOR MUTATION Evidence type: Predictive Evidence direction: Supports Variant origin: Somatic Clinical significance: Sensitivity/Response Drug: Pazopanib, Everolimus Disease: bladder carcinoma Evidence level: C - Case study Trust rating: 3/5 Source: PMID 24625776  <a href="http://oncokb.org/#/gene/MTOR/alteration/Q2223K">http://oncokb.org/#/gene/MTOR/alteration/Q2223K</a> Biomarker: MTOR Q2223K Effect: drug Responsive Level of evidence: LEVEL_3A Drug: Everolimus Disease: Renal Cell Carcinoma Publications: 24622468 Abstracts: n/a  <a href="https://www.cancergenomeinterpreter.org/biomarkers">https://www.cancergenomeinterpreter.org/biomarkers</a> Biomarker: MTOR:Q2223K Association: Responsive Drug: Everolimus (MTOR inhibitor) Disease: renal Evidence: Case report Source: PMID:24622468	Off-label	Tier 2 - Investigational, <a href="#">1 assertions</a> Tier 3a - Cancer repurposing, <a href="#">1 assertions</a> Tier 4 - Hypothetical, <a href="#">2 assertions</a>
<b>FBXW7</b> Tumor supp.	missense p.Arg484Met exon 10/12, <a href="#">more</a>				Tier 4 - Hypothetical, <a href="#">2 assertions</a>

Ready-to-use biomarker

Off-label

- > **Genetic counseling alert** (not necessary for this case)
- > **BRCA2** pathogenic qualifies for **BoB** (arm 1A)
- > **PDL1** amplification qualifies for **BoB** (arm 1F)

Gene	Alteration	Origin	Functional relevance evidence	Custom clinical flags	Reported biomarker(s)
<b>BRCA2</b> Tumor supp. Sec.findings	stop gained p.Lys2008Ter exon 11/27, <a href="#">more</a>	Germline (+tumor) tumor VAF=0.86	Evidence A (curated): >Pathogenic, <a href="#">BRCA-Exchange</a> >Pathogenic, <a href="#">ClinVar</a>	<b>G.counseling alert, <a href="#">more</a></b> <b>BoB - arm 1A, <a href="#">more</a></b>	Tier 1 - Ready for use, <a href="#">2 assertions</a> Tier 2 - Investigational, <a href="#">7 assertions</a> Tier 4 - Hypothetical, <a href="#">1 assertions</a>
<b>CD274</b> Oncogene	copy-number- gain, <a href="#">more</a>	Tumor-somatic	Evidence A (curated): >In-house curation, <a href="#">more</a>	<b>BoB - arm 1F, <a href="#">more</a></b>	None found
<b>MTOR</b> Oncogene	missense p.Gln2223Lys exon 48/58, <a href="#">more</a>	Tumor			Tier 3a - Cancer repurposing, <a href="#">3 assertions</a> Tier 4 - Hypothetical, <a href="#">1 assertion</a>
<b>CDKN2A</b> Tumor supp.	stop gained p.Arg58Ter exon 2/3, <a href="#">more</a>	Tumor			Tier 2 - Investigational, <a href="#">1 assertions</a> Tier 3a - Cancer repurposing, <a href="#">1 assertions</a> Tier 4 - Hypothetical, <a href="#">2 assertions</a>
<b>FBXW7</b> Tumor supp.	missense p.Arg484Met exon 10/12, <a href="#">more</a>	Tumor			Tier 4 - Hypothetical, <a href="#">2 assertions</a>

The variant matches inclusion criteria for **BoB-arm 1F**

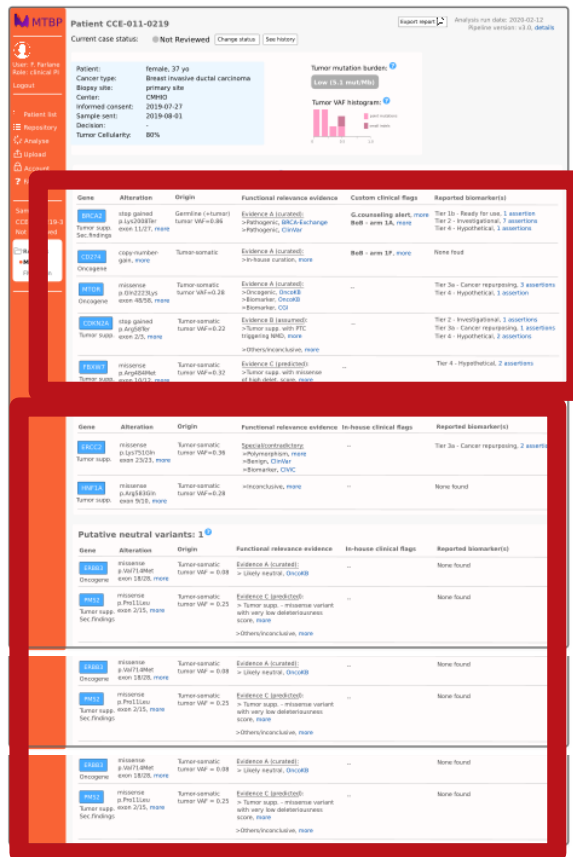
> Matched trial alteration: CD274:AMP  
> Matched trial cancer type: CANCER

**Basket of Baskets** info:  
Use of PDL-1 inhibitor (atezolizumab, module 1) or FGFR-inhibitor (module 2) in advanced tumors with selected molecular alterations. Primary end point is the overall 12-weeks response rate by RECIST 1.1  
Contact: jrodon@vhio.net, ibrana@vhio.net

# CASE 2

> 43 years man, advanced **colorectal adenocarcinoma**, known BRAF V600mut

> Panel sequencing results – primary tumor biopsy (sample purity ~80%) + paired germline control



6 genomic alterations classified as functionally relevant

Multiple mutations classified as VUS/likely neutral

## Zoom-in in the MTBP report: Putative Functional Variants table

Tumor Mutation Burden: **High (37.83 mut/Mb)** ?

Gene	Alteration	Origin	Functional relevance evidence	Custom clinical flags	Reported biomarker(s)
<b>MLH1</b> Tumor supp. Sec.findings	frameshift p.Arg497Glyfs*11 exon 13/19, <a href="#">more</a>	Germline (+tumor) tumor VAF=0.48	<u>Evidence A (curated):</u> >Pathogenic, <a href="#">ClinVar</a>	<b>G.counseling alert</b> , <a href="#">more</a> <b>BoB - arm 1A</b> , <a href="#">more</a>	None found
<b>BRAF</b> Oncogene	missense, p.Val600Glu exon 15/18, <a href="#">more</a>	Tumor-somatic tumor VAF=0.36	<u>Evidence A (curated):</u> >Oncogenic, <a href="#">OncoKB</a> >Biomarker, <a href="#">CGI</a> >Pathogenic, <a href="#">ClinVar</a> >Biomarker, <a href="#">CIVIC</a>	--	Tier 1 - Ready for use, 2 <a href="#">assertions</a> Tier 2 - Investigational, 27 <a href="#">assertions</a> Tier 3a - Cancer repurposing, 90 <a href="#">assertions</a> Tier 4 - Hypothetical, 1 <a href="#">assertions</a>
<b>MEN1</b> Tumor supp. Sec.findings	frameshift p.Arg521Profs*15 exon 10/10, <a href="#">more</a>	Tumor-somatic tumor VAF=0.35	<u>Evidence A (curated):</u> >Pathogenic, <a href="#">ClinVar</a>	--	None found
<b>MAP2K4</b> Ambiguous	missense p.Pro326Leu exon 9/11, <a href="#">more</a>	Tumor-somatic tumor VAF=0.28	<u>Evidence A (curated):</u> >Likely Oncogenic, <a href="#">OncoKB</a>	--	None found
<b>TP53</b> Tumor supp. Sec.findings	frameshift p.Ser90Profs*33 exon 4/11, <a href="#">more</a>	Tumor-somatic tumor VAF=0.35	<u>Evidence B (assumed):</u> >Tumor supp. with PTC triggering NMD, <a href="#">more</a>	--	Tier 3 - Cancer repurposing, 6 <a href="#">assertions</a>
<b>RNF43</b> Tumor supp.	frameshift p.Gly659Valfs+41 exon 9/10, <a href="#">more</a>	Tumor-somatic tumor VAF=0.32	<u>Evidence B (assumed):</u> >Tumor supp. with PTC triggering NMD, <a href="#">more</a>	--	None found



> Germline **MLH1** frameshift variant, reported as pathogenic; not previously known for this patient

Tumor Mutation Burden: **High (37.83 mut/Mb)** ?

Gene	Alteration	Origin	Functional relevance evidence	Custom clinical flags	Reported biomarker(s)
<b>MLH1</b> Tumor supp. Sec.findings	frameshift p.Arg497Glyfs*11 exon 13/19, <a href="#">more</a>	Germline (+tumor) tumor VAF=0.48	<u>Evidence A (curated):</u> >Pathogenic, <a href="#">ClinVar</a>	<b>G.counseling alert</b> , <a href="#">more</a> <b>BoB - arm 1A</b> , <a href="#">more</a>	None found
<b>BRAF</b> Oncogene	missense, p.Val600Glu exon 15/18, <a href="#">more</a>	Tumor-somatic tumor VAF=0.36	<u>Evidence A (curated):</u> >Oncogenic, <a href="#">OncoKB</a> >Biomarker, <a href="#">CGI</a> >Pathogenic, <a href="#">ClinVar</a> >Biomarker, <a href="#">CIVIC</a>	--	Tier 1 - Ready for use, 2 <a href="#">assertions</a> Tier 2 - Investigational, 27 <a href="#">assertions</a> Tier 3a - Cancer repurposing, 90 <a href="#">assertions</a> Tier 4 - Hypothetical, 1 <a href="#">assertions</a>
<b>MEN1</b> Tumor supp. Sec.findings	frameshift p.Arg521Profs*15 exon 10/10, <a href="#">more</a>	Tumor-somatic tumor VAF=0.35	<u>Evidence A (curated):</u> >Pathogenic, <a href="#">ClinVar</a>	--	None found
<b>MAP2K4</b> Ambiguous	missense p.Pro326Leu exon 9/11, <a href="#">more</a>	Tumor-somatic tumor VAF=0.28	<u>Evidence A (curated):</u> >Likely Oncogenic, <a href="#">OncoKB</a>	--	None found
<b>TP53</b> Tumor supp. Sec.findings	frameshift p.Ser90Profs*33 exon 4/11, <a href="#">more</a>	Tumor-somatic tumor VAF=0.35	<u>Evidence B (assumed):</u> >Tumor supp. with PTC triggering NMD, <a href="#">more</a>	--	Tier 3 - Cancer repurposing, 6 <a href="#">assertions</a>
<b>RNF43</b> Tumor supp.	frameshift p.Gly659Valfs+41 exon 9/10, <a href="#">more</a>	Tumor-somatic tumor VAF=0.32	<u>Evidence B (assumed):</u> >Tumor supp. with PTC triggering NMD, <a href="#">more</a>	--	None found

- > Also, a MEN1 mutation described as pathogenic
- > Reported in several individuals with multiple endocrine neoplasia type 1
- > However, not found in the germline sample in this patient, and tVAF=35% → somatic event, no genetic counseling referral flag in the report

NM\_001370259.2(MEN1):c.1546dup (p.Arg516fs)

Cite this record

Interpretation: Pathogenic

Review status: ★★☆☆ criteria provided, multiple submitters, no conflicts  
 Submissions: 8 (Most recent: Jul 4, 2021)  
 Last evaluated: Oct 12, 2020  
 Accession: VCV000279852.15  
 Variation ID: 279852  
 Description: 1bp duplication

Comment:  
 This duplication of one nucleotide in MEN1 is denoted c.1546dupC at the cDNA level and p.Arg516ProfsX15 (R516PfsX15) at the protein level. The normal sequence, with the base that is duplicated in brackets, is ACCCCCCC(dupC)GGAA. Using alternate nomenclature, this variant would be defined as MEN1 1561dupC, 1650insC, 1656dupC, 1657insC, 7766insC, or 7773insC. The duplication causes a frameshift which changes an Arginine to a Proline at codon 516, and creates a premature stop codon at position 15 of the new reading frame. Even though this frameshift occurs in the last exon of the gene, and nonsense-mediated decay is not expected to occur, it is significant since the last 95 amino acids are no longer translated correctly, and are replaced by 14 incorrect amino acids. This variant is predicted to cause loss of normal protein function through protein truncation. MEN1 c.1546dupC has been reported in at least one individual with familial isolated hyperparathyroidism and in many individuals with multiple endocrine neoplasia type 1 (Agarwal 1997, Bergman 2000, Warner 2004, Cardinal 2005, Pieterman 2012). This variant was reported to segregate with disease through five generations of a large Finnish MEN1 family (Kytola 2001). MEN1 c.1546dupC has been reported at a high frequency in patients with MEN1 in multiple populations and likely occurs as a result of a mutational hotspot (Giraud 1998, Kytola 2001, Ebeling 2004). In addition, in vitro functional studies show that this variant impairs nuclear localization of protein compared to wild-type (Ikeo 1999). Based on the currently available evidence, we consider this variant to be pathogenic. (less)

0 assertions  
ins

<b>MEN1</b> Tumor supp. Sec.findings	frameshift p.Arg521Profs*15 exon 10/10, <a href="#">more</a>	Tumor-somatic tumor VAF=0.35	<u>Evidence A (curated):</u> >Pathogenic, <a href="#">ClinVar</a>	--	None found
<b>MAP2K4</b> Ambiguous	missense p.Pro326Leu exon 9/11, <a href="#">more</a>	Tumor-somatic tumor VAF=0.28	<u>Evidence A (curated):</u> >Likely Oncogenic, <a href="#">OncoKB</a>	--	None found
<b>TP53</b> Tumor supp. Sec.findings	frameshift p.Ser90Profs*33 exon 4/11, <a href="#">more</a>	Tumor-somatic tumor VAF=0.35	<u>Evidence B (assumed):</u> >Tumor supp. with PTC triggering NMD, <a href="#">more</a>	--	Tier 3 - Cancer repurposing, <b>6 assertions</b>
<b>RNF43</b> Tumor supp.	frameshift p.Gly659Valfs+41 exon 9/10, <a href="#">more</a>	Tumor-somatic tumor VAF=0.32	<u>Evidence B (assumed):</u> >Tumor supp. with PTC triggering NMD, <a href="#">more</a>	--	None found

Tumor Mutation Burden: **High (37.83 mut/Mb)** ?

Gene	Alteration	Origin	Functional relevance evidence	Custom clinical flags	Reported biomarker(s)
<b>MLH1</b> Tumor supp. Sec.findings	frameshift p.Arg497Glyfs*11 exon 13/19, <a href="#">more</a>	Germline (+tumor) tumor VAF=0.48	<u>Evidence A (curated):</u> >Pathogenic, <a href="#">ClinVar</a>	<b>G.counseling alert</b> , <a href="#">more</a> <b>BoB - arm 1A</b> , <a href="#">more</a>	None found
<b>BRAF</b> Oncogene	missense, p.Val600Glu exon 15/18, <a href="#">more</a>	Tumor-somatic tumor VAF=0.36	<u>Evidence A (curated):</u> >Oncogenic, <a href="#">OncoKB</a> >Biomarker, <a href="#">CGI</a> >Pathogenic, <a href="#">ClinVar</a> >Biomarker, <a href="#">CIVIC</a>	--	Tier 1 - Ready for use, <a href="#">2 assertions</a> Tier 2 - Investigational, <a href="#">27 assertions</a> Tier 3a - Cancer repurposing, <a href="#">90 assertions</a> Tier 4 - Hypothetical, <a href="#">1 assertions</a>
<b>MEN1</b> Tumor supp. Sec.findings	frameshift p.Arg521Profs*15 exon 10/10, <a href="#">more</a>	Tumor-somatic tumor VAF=0.35	<u>Evidence A (curated):</u> >Pathogenic, <a href="#">ClinVar</a>		
<b>MAP2K4</b> Ambiguous	missense p.Pro326Leu exon 9/11, <a href="#">more</a>	Tumor-somatic tumor VAF=0.28	<u>Evidence A (curated):</u> >Likely Oncogenic, <a href="#">OncoKB</a>		
<b>TP53</b> Tumor supp. Sec.findings	frameshift p.Ser90Profs*33 exon 4/11, <a href="#">more</a>	Tumor-somatic tumor VAF=0.35	<u>Evidence B (assumed):</u> >Tumor supp. with PTC triggering NMD, <a href="#">more</a>		
<b>RNF43</b> Tumor supp.	frameshift p.Gly659Valfs+41 exon 9/10, <a href="#">more</a>	Tumor-somatic tumor VAF=0.32	<u>Evidence B (assumed):</u> >Tumor supp. with PTC triggering NMD, <a href="#">more</a>		

Tier 1 includes variants described as drug/prognostic biomarkers for this cancer type supported by the highest level of clinical evidence, i.e. approved/recommended by professional guidelines

Please check the original assertions provided by each knowledgebase listed below

>Reported sensitivity/response: Cetuximab, Encorafenib, Panitumumab

<http://oncokb.org/#/gene/BRAF/alteration/V600E>

Biomarker: BRAF V600E

Effect: drug Responsive

Level of evidence: LEVEL\_1

Drug: Encorafenib, Cetuximab

Disease: Colorectal Cancer

Publications: 31566309

Abstracts: n/a

<http://oncokb.org/#/gene/BRAF/alteration/V600E>

Biomarker: BRAF V600E

Effect: drug Responsive

Level of evidence: LEVEL\_2

Drug: Encorafenib, Panitumumab

Disease: Colorectal Cancer

Publications: 29431699, 31566309

Abstracts: n/a

EGFRi + RAFi

(KRAS  
wild-type)

Tumor Mutation Burden:

**High (37.83 mut/Mb)** ?

**genetic counseling alert;  
BoB arm 1A**

Gene	Alteration	Origin	Functional relevance evidence	Custom clinical flags	Reported biomarker(s)
<b>MLH1</b> Tumor supp. Sec.findings	frameshift p.Arg497Glyfs*11 exon 13/19, <a href="#">more</a>	Germline (+tumor) tumor VAF=0.48	<u>Evidence A (curated):</u> >Pathogenic, <a href="#">ClinVar</a>	<b>G.counseling alert, <a href="#">more</a></b> <b>BoB - arm 1A, <a href="#">more</a></b>	None found
<b>BRAF</b> Oncogene	missense, p.Val600Glu exon 15/18, <a href="#">more</a>	Tumor-somatic tumor VAF=0.36	<u>Evidence A (curated):</u> >Oncogenic, <a href="#">OncoKB</a> >Biomarker, <a href="#">CGI</a> >Pathogenic, <a href="#">ClinVar</a> >Biomarker, <a href="#">CIVIC</a>	--	Tier 1 - Ready for use, 2 <a href="#">assertions</a> Tier 2 - Investigational, 27 <a href="#">assertions</a> Tier 3a - Cancer repurposing, 90 <a href="#">assertions</a> Tier 4 - Hypothetical, 1 <a href="#">assertions</a>
<b>MEN1</b> Tumor supp. Sec.findings	frameshift p.Arg521Profs*15 exon 10/10, <a href="#">more</a>	Tumor-somatic tumor VAF=0.35	<u>Evidence A (curated):</u> >Pathogenic, <a href="#">ClinVar</a>	--	None found
<b>MAP2K4</b> Ambiguous	missense p.Pro326Leu exon 9/11, <a href="#">more</a>	Tumor-somatic tumor VAF=0.28	<u>Evidence A (curated):</u> >Likely Oncogenic, <a href="#">OncoKB</a>	--	None found
<b>TP53</b> Tumor supp. Sec.findings	frameshift p.Ser90Profs*33 exon 4/11, <a href="#">more</a>	Tumor-somatic tumor VAF=0.35	<u>Evidence B (assumed):</u> >Tumor supp. with PTC triggering NMD, <a href="#">more</a>	--	Tier 3 - Cancer repurposing, 6 <a href="#">assertions</a>
<b>RNF43</b> Tumor supp.	frameshift p.Gly659Valfs+41 exon 9/10, <a href="#">more</a>	Tumor-somatic tumor VAF=0.32	<u>Evidence B (assumed):</u> >Tumor supp. with PTC triggering NMD, <a href="#">more</a>	--	None found

# CASE 3

## Putative functionally relevant variants: 8

Gene	Alteration	Origin	Functional relevance evidence	Custom clinical flags	Other reported biomarker(s)
<b>MSH2</b> Tumor supp. Sec. findings	stop gained p.Arg383Ter exon 7/16, <a href="#">more</a>	Tumor Tumor VAF: FMI:n/d, CCE:n/d	Evidence A (curated): >Pathogenic, ClinVar >Likely Oncogenic, OncoKB	BoB-arm 1B, <a href="#">more</a>	None found
<b>PTEN</b> Tumor supp.	frameshift p.Asn329Lys/Trp14 exon 8/9, <a href="#">more</a>	Tumor Tumor VAF: FMI:n/d, CCE:n/d	Evidence A (curated): >Pathogenic, ClinVar	--	Tier 2-Investigational, 2 assertions Tier 3-Cancer repurposing, 5 assertions Tier 4-Hypothetical, 3 assertions
<b>KRAS</b> Oncogene	missense p.Gly12Val exon 2/5, <a href="#">more</a>	Tumor Tumor VAF: FMI:n/d, CCE:n/d	Evidence A (curated): >Pathogenic, ClinVar >Oncogenic, OncoKB >Biomarker, CIVIC >Biomarker, CGI Others/Inconclusive, <a href="#">more</a>	--	Tier 1-Ready for use, 6 assertions Tier 2-Investigational, 2 assertions Tier 2b-Investig. (case reports), 1 assertions Tier 3-Cancer repurposing, 20 assertions Tier 4-Hypothetical, 12 assertions Others - Diagnostic, 3 assertions
<b>RNF43</b> Tumor supp.	stop gained p.Arg132Ter exon 4/10, <a href="#">more</a>	Tumor Tumor VAF: FMI:n/d, CCE:n/d	Evidence A (curated): >Likely Oncogenic, OncoKB Others/Inconclusive, <a href="#">more</a>	--	Tier 2b-Investig. (case reports), 1 assertions
<b>TP53</b> Tumor supp. Sec. findings	missense p.Arg248Gly exon 7/11, <a href="#">more</a>	Tumor Tumor VAF: FMI:n/d, CCE:n/d	Evidence A (curated): >Likely Oncogenic, OncoKB Others/Inconclusive, <a href="#">more</a>	--	Tier 3-Cancer repurposing, 6 assertions
<b>SMO</b> Oncogene	missense p.Pro641Ala exon 11/12, <a href="#">more</a>	Tumor Tumor VAF: FMI:n/d, CCE:n/d	Evidence A (curated): >Biomarker, CGI Others/Inconclusive, <a href="#">more</a>	--	Tier 3-Cancer repurposing, 1 assertions
<b>FBXW7</b> Tumor supp.	frameshift p.Gly419Aaph/Trp11 exon 9/12, <a href="#">more</a>	Tumor Tumor VAF: FMI:n/d, CCE:n/d	Evidence B (assumed): >Tumor supp. with frameshift- derived PTC triggering NMD, <a href="#">more</a>	--	Tier 3-Cancer repurposing, 1 assertions Tier 4-Hypothetical, 2 assertions Others - Diagnostic, 1 assertions
<b>APC</b> Tumor supp. Sec. findings	frameshift p.Asp434Arg/Trp21 exon 10/16, <a href="#">more</a>	Tumor Tumor VAF: FMI:n/d, CCE:n/d	Evidence B (assumed): >Tumor supp. with frameshift- derived PTC triggering NMD, <a href="#">more</a>	--	Tier 4-Hypothetical, 3 assertions

## Variants of unknown/contradictory functional significance: 22

Gene	Alteration	Origin	Functional relevance evidence	Custom clinical flags	Other reported biomarker(s)
<b>PCOLCE</b> Tumor supp. (essential)	missense p.Ala188Thr exon 41/49, <a href="#">more</a>	Tumor Tumor VAF: FMI:n/d, CCE:n/d	>Others/Inconclusive, <a href="#">more</a>	<< if variant is reclassified >> BoB-arm 1C, <a href="#">more</a>	None found
<b>KDR</b> Oncogene	missense p.Cys482Arg exon 11/30, <a href="#">more</a>	Tumor Tumor VAF: FMI:n/d, CCE:n/d	Special/contradictory, <a href="#">info</a> >Likely Oncogenic, OncoKB >Polymorphism, <a href="#">more</a>	--	None found
<b>TEF1</b> ambiguous	missense p.Ser1796Leu exon 11/12, <a href="#">more</a>	Tumor Tumor VAF: FMI:n/d, CCE:n/d	>Others/Inconclusive, <a href="#">more</a>	--	None found
<b>FLT3</b> Oncogene	missense p.Val643Ile exon 15/24, <a href="#">more</a>	Tumor Tumor VAF: FMI:n/d, CCE:n/d	>Others/Inconclusive, <a href="#">more</a>	--	None found
<b>FLY1</b> --	missense p.Pro1201Leu exon 27/30, <a href="#">more</a>	Tumor Tumor VAF: FMI:n/d, CCE:n/d	>Others/Inconclusive, <a href="#">more</a>	--	None found
<b>CD276</b> --	missense p.Ala449Val exon 6/10, <a href="#">more</a>	Tumor Tumor VAF: FMI:n/d, CCE:n/d	>Others/Inconclusive, <a href="#">more</a>	--	None found
<b>IGF1R</b> --	missense p.Arg511Gln exon 7/21, <a href="#">more</a>	Tumor Tumor VAF: FMI:n/d, CCE:n/d	>Others/Inconclusive, <a href="#">more</a>	--	None found

> 52 years man, advanced  
**colorectal adenocarcinoma**

>Known KRAS G12C mut  
(also observed here, VAF compatible with  
clonal event)

### Putative functionally relevant variants: 8

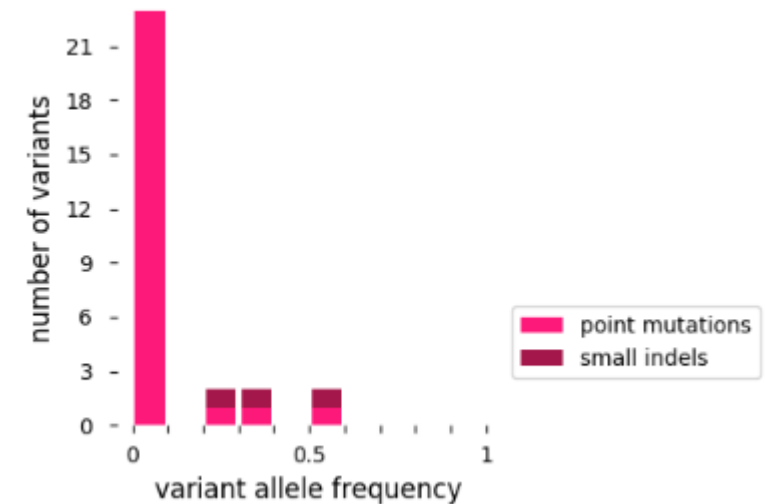
Gene	Alteration	Origin	Functional relevance evidence	Custom clinical flags	Other reported biomarker(s)
<b>MSH2</b> Tumor supp. Sec. findings	stop gained p.Arg383Ter exon 7/16, <a href="#">more</a>	Tumor Tumor VAF: FMI:n/d, CCE:n/d	Evidence A (curated): >Pathogenic, ClinVar >Likely Oncogenic, OncoKB	BoB-arm 1B, <a href="#">more</a>	None found
<b>PSTG</b> Tumor supp. Sec. findings	frameshift p.Aac329LysaTer14 exon 8/9, <a href="#">more</a>	Tumor Tumor VAF: FMI:n/d, CCE:n/d	Evidence A (curated): >Pathogenic, ClinVar	--	Tier 2-Investigational, 2 assertions Tier 3-Cancer repurposing, 5 assertions Tier 4-Hypothetical, 3 assertions Others - Diagnostic, 1 assertions
<b>KRAS</b> Oncogene	missense p.Gly12Val exon 2/5, <a href="#">more</a>	Tumor Tumor VAF: FMI:n/d, CCE:n/d	Evidence A (curated): >Pathogenic, ClinVar >Oncogenic, OncoKB >Biomarker, CIVIC >Biomarker, CGI Others/Inconclusive, <a href="#">more</a>	--	Tier 1-Ready for use, 6 assertions Tier 2-Investigational, 2 assertions Tier 2b-Investig. (case reports), 1 assertions Tier 3-Cancer repurposing, 20 assertions Tier 4-Hypothetical, 12 assertions Others - Diagnostic, 3 assertions
<b>RNF43</b> Tumor supp.	stop gained p.Arg132Ter exon 4/10, <a href="#">more</a>	Tumor Tumor VAF: FMI:n/d, CCE:n/d	Evidence A (curated): >Likely Oncogenic, OncoKB Others/Inconclusive, <a href="#">more</a>	--	Tier 2b-Investig. (case reports), 1 assertions
<b>TP53</b> Tumor supp. Sec. findings	missense p.Arg248Gly exon 7/11, <a href="#">more</a>	Tumor Tumor VAF: FMI:n/d, CCE:n/d	Evidence A (curated): >Likely Oncogenic, OncoKB Others/Inconclusive, <a href="#">more</a>	--	Tier 3-Cancer repurposing, 6 assertions
<b>SMD</b> Oncogene	missense p.Pro641Ala exon 11/12, <a href="#">more</a>	Tumor Tumor VAF: FMI:n/d, CCE:n/d	Evidence A (curated): >Biomarker, CGI Others/Inconclusive, <a href="#">more</a>	--	Tier 3-Cancer repurposing, 1 assertions
<b>FBXW7</b> Tumor supp.	frameshift p.Gly419AaphTer11 exon 9/12, <a href="#">more</a>	Tumor Tumor VAF: FMI:n/d, CCE:n/d	Evidence B (assumed): >Tumor supp. with frameshift- derived PTC triggering NMD, <a href="#">more</a>	--	Tier 3-Cancer repurposing, 1 assertions Tier 4-Hypothetical, 2 assertions Others - Diagnostic, 1 assertions
<b>APC</b> Tumor supp. Sec. findings	frameshift p.Asp434ArgaTer21 exon 10/16, <a href="#">more</a>	Tumor Tumor VAF: FMI:n/d, CCE:n/d	Evidence B (assumed): >Tumor supp. with frameshift- derived PTC triggering NMD, <a href="#">more</a>	--	Tier 4-Hypothetical, 3 assertions

### Variants of unknown/contradictory functional significance: 22

Gene	Alteration	Origin	Functional relevance evidence	Custom clinical flags	Other reported biomarker(s)
<b>POLE</b> Tumor supp. (essential)	missense p.Ala1885Thr exon 41/49, <a href="#">more</a>	Tumor Tumor VAF: FMI:n/d, CCE:n/d	>Others/Inconclusive, <a href="#">more</a>	<< if variant is reclassified >> BoB-arm 1C, <a href="#">more</a>	None found
<b>KDR</b> Oncogene	missense p.Cys482Arg exon 11/30, <a href="#">more</a>	Tumor Tumor VAF: FMI:n/d, CCE:n/d	Special/contradictory, <a href="#">info</a> >Likely Oncogenic, OncoKB >Polymorphism, <a href="#">more</a>	--	None found
<b>TEF1</b> ambiguous	missense p.Ser1796Leu exon 11/12, <a href="#">more</a>	Tumor Tumor VAF: FMI:n/d, CCE:n/d	>Others/Inconclusive, <a href="#">more</a>	--	None found
<b>FLT3</b> Oncogene	missense p.Val643Ile exon 15/24, <a href="#">more</a>	Tumor Tumor VAF: FMI:n/d, CCE:n/d	>Others/Inconclusive, <a href="#">more</a>	--	None found
<b>FLY1</b> --	missense p.Pro1201Leu exon 27/30, <a href="#">more</a>	Tumor Tumor VAF: FMI:n/d, CCE:n/d	>Others/Inconclusive, <a href="#">more</a>	--	None found
<b>CD276</b> --	missense p.Ala449Val exon 6/10, <a href="#">more</a>	Tumor Tumor VAF: FMI:n/d, CCE:n/d	>Others/Inconclusive, <a href="#">more</a>	--	None found
<b>IGF1R</b> --	missense p.Arg511Gln exon 7/21, <a href="#">more</a>	Tumor Tumor VAF: FMI:n/d, CCE:n/d	>Others/Inconclusive, <a href="#">more</a>	--	None found

>High number of mutations in the report  
(a small proportion being functional, the remaining being VUS or neutral)

>However, most of these mutations are subclonal



Many of these are C>T or T>C,  
which is the signature  
of mismatch DNA repair deficiency



## Putative functionally relevant variants: 8

Gene	Alteration	Origin	Functional relevance evidence	Custom clinical flags	Other reported biomarker(s)
<b>MSH2</b> Tumor supp. Sec. findings	stop gained p.Arg353Ter exon 7/16, <a href="#">more</a>	Tumor Tumor VAF: FMI:n/d, CCE:n/d	Evidence A (curated): >Pathogenic, ClinVar >Likely Oncogenic, OncoKB	BoB-am 1B, <a href="#">more</a>	None found
<b>PTEN</b> Tumor supp. Sec. findings	frameshift p.Asn325Lys/Trp14 exon 8/9, <a href="#">more</a>	Tumor Tumor VAF: FMI:n/d, CCE:n/d	Evidence A (curated): >Pathogenic, ClinVar	--	Tier 2-Investigational, 2 assertions Tier 3-Cancer repurposing, 5 assertions Tier 4-Hypothetical, 3 assertions Others - Diagnostic, 1 assertions
<b>KRAS</b> Oncogene	missense p.Gly12Val exon 2/5, <a href="#">more</a>	Tumor Tumor VAF: FMI:n/d, CCE:n/d	Evidence A (curated): >Pathogenic, ClinVar >Oncogenic, OncoKB >Biomarker, CIVIC >Biomarker, CGI Others/Inconclusive, <a href="#">more</a>	--	Tier 1-Ready for use, 6 assertions Tier 2-Investigational, 2 assertions Tier 2b-Investig. (case reports), 1 assertions Tier 3-Cancer repurposing, 20 assertions Tier 4-Hypothetical, 12 assertions Others - Diagnostic, 3 assertions
<b>RNF43</b> Tumor supp.	stop gained p.Arg132Ter exon 4/10, <a href="#">more</a>	Tumor Tumor VAF: FMI:n/d, CCE:n/d	Evidence A (curated): >Likely Oncogenic, OncoKB Others/Inconclusive, <a href="#">more</a>	--	Tier 2b-Investig. (case reports), 1 assertions
<b>TP53</b> Tumor supp. Sec. findings	missense p.Arg248Gly exon 7/11, <a href="#">more</a>	Tumor Tumor VAF: FMI:n/d, CCE:n/d	Evidence A (curated): >Likely Oncogenic, OncoKB Others/Inconclusive, <a href="#">more</a>	--	Tier 3-Cancer repurposing, 6 assertions
<b>SMO</b> Oncogene	missense p.Pro641Ala exon 11/12, <a href="#">more</a>	Tumor Tumor VAF: FMI:n/d, CCE:n/d	Evidence A (curated): >Biomarker, CGI Others/Inconclusive, <a href="#">more</a>	--	Tier 3-Cancer repurposing, 1 assertions
<b>FBXW7</b> Tumor supp.	frameshift p.Gly419Aaph/Trp11 exon 9/12, <a href="#">more</a>	Tumor Tumor VAF: FMI:n/d, CCE:n/d	Evidence B (assumed): >Tumor supp. with frameshift- derived PTC triggering NMD, <a href="#">more</a>	--	Tier 3-Cancer repurposing, 1 assertions Tier 4-Hypothetical, 2 assertions Others - Diagnostic, 1 assertions
<b>APC</b> Tumor supp. Sec. findings	frameshift p.Asp434Arg/Trp21 exon 10/16, <a href="#">more</a>	Tumor Tumor VAF: FMI:n/d, CCE:n/d	Evidence B (assumed): >Tumor supp. with frameshift- derived PTC triggering NMD, <a href="#">more</a>	--	Tier 4-Hypothetical, 3 assertions

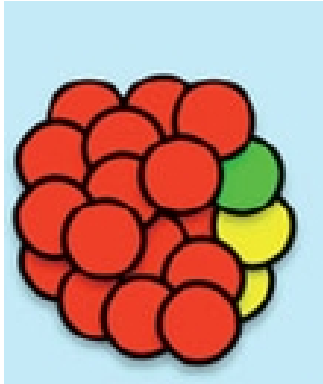
## Variants of unknown/contradictory functional significance: 22

Gene	Alteration	Origin	Functional relevance evidence	Custom clinical flags	Other reported biomarker(s)
<b>PCOLCE</b> Tumor supp. (essential)	missense p.Ala188Thr exon 41/49, <a href="#">more</a>	Tumor Tumor VAF: FMI:n/d, CCE:n/d	>Others/Inconclusive, <a href="#">more</a>	<< if variant is reclassified >> BoB-am 1C, <a href="#">more</a>	None found
<b>KDR</b> Oncogene	missense p.Cys482Arg exon 11/30, <a href="#">more</a>	Tumor Tumor VAF: FMI:n/d, CCE:n/d	Special/contradictory, <a href="#">info</a> >Likely Oncogenic, OncoKB >Polymorphism, <a href="#">more</a>	--	None found
<b>TEF1</b> ambiguous	missense p.Ser1796Leu exon 11/12, <a href="#">more</a>	Tumor Tumor VAF: FMI:n/d, CCE:n/d	>Others/Inconclusive, <a href="#">more</a>	--	None found
<b>FLT3</b> Oncogene	missense p.Val643Ile exon 15/24, <a href="#">more</a>	Tumor Tumor VAF: FMI:n/d, CCE:n/d	>Others/Inconclusive, <a href="#">more</a>	--	None found
<b>FLY1</b> --	missense p.Pro1201Leu exon 27/30, <a href="#">more</a>	Tumor Tumor VAF: FMI:n/d, CCE:n/d	>Others/Inconclusive, <a href="#">more</a>	--	None found
<b>CD276</b> --	missense p.Ala449Val exon 6/10, <a href="#">more</a>	Tumor Tumor VAF: FMI:n/d, CCE:n/d	>Others/Inconclusive, <a href="#">more</a>	--	None found
<b>IGF1R</b> --	missense p.Arg511Gln exon 7/21, <a href="#">more</a>	Tumor Tumor VAF: FMI:n/d, CCE:n/d	>Others/Inconclusive, <a href="#">more</a>	--	None found

> This can be explained by a **MSH2 nonsense mutation**, already reported as **pathogenic** and related to DNA mismatch repair deficiency

> This is not a germline event! (by age and tumor, this patient could have Lynch syndrome!)

> The mutation is a \*tumor somatic\* event, identified as subclonal (VAF~5%)



> A minority of the cells in the tumor have developed a \*somatic\* mismatch repair deficiency

> Of note, this phenotype is actionable by immune-checkpoint inhibitors

(high load of somatic mutations → high neoantigen burden → tumor sensitive to immune-recognition)

Should we use a targeted therapy for a mechanism that is not present in all the tumor cells?

# CONCLUSIONS

- > Clinical interpretation of NGS data (n=1) is aimed to use **current knowledge** to support the decision-making
- > Variant effects are supported by **distinct levels of evidence**, which may be used differently depending on the context
- > The use of **CDSS** implements **efficient, accurate and comprehensive** analyses based on predefined (expert) criteria

**-----Exercise with MTBP---**

# Public version of the MTBP

<https://www.mtbp.org/>

The screenshot shows the homepage of the Molecular Tumor Board Portal (MTBP). At the top left is the logo with the text "Molecular Tumor Board Portal". At the top right are "Login" and "Register" buttons. Below the header, a red banner reads: "New update of the cancer genes mechanism of action (January 22nd, 2021), read [more](#)". The main content area has a central box titled "The Portal interprets cancer genomic variants" with a description: "The public version of the MTB portal provides a general framework to interpret the [functional](#) and [predictive](#) relevance of a given list of gene variants in interactive [reports](#)". Below this are two buttons: "> Analyse your variants" and "> See examples". Below these are two side-by-side boxes. The left box, titled "The Portal uses distinct levels of supporting evidence" (with a checkmark icon), states: "Variants are annotated by a comprehensive set of [knowledgebases](#), bona fide biological [assumptions](#) and [computational estimations](#)" and includes a "Read more" link. The right box, titled "The portal follows clinical expert consensus" (with a speech bubble icon), states: "The portal is developed under the [Cancer Core Europe](#) umbrella following [expert consensus](#) and according to up-to-date [knowledge](#)" and includes an "About us" link. At the bottom, a small "Disclaimer and terms of use" section states: "This is an open access version of the Cancer Core Europe portal that provides a general interpretation of a given list of cancer gene variants. This platform is not intended as a substitute for professional medical help, judgment or advice, and a qualified health provider should always be consulted before any clinical intervention. The portal uses a number of computational tools and databases that are referenced (and linked when appropriate) in the results provided here. Please note that some of these resources are not fully open except for their use for academic research, and thus the use of the portal must be limited to that purpose. By analysing your data you confirm and warrant these terms of use. When using the MTB portal, please cite: [Tamborero D, Dienstmann R et al. Nature Medicine 2020](#)".

> Is a **lightweight** version as compared to the 'production' tool

*(generic analysis from a generic input, so clonality, origin, trials matching etc is not performed)*

> But you can upload your variants and obtain a report with their functional and predictive relevance