CANCER GENOMICS CLINICAL INTERPRETATION

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From cohorts to individual tumors

Now we are not analysing **large cohorts** of profiled tumors to generate “biological” knowledge, but we want to use this **knowledge** to guide (clinical) decision making in a **single cancer patient**

PRECISION CANCER MEDICINE

PCM is based on **targeting** the molecular mechanism(s) that are **driving** the patient's tumor AND it is **addicted** to

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a) inhibiting the activity of **an oncogene** driving the tumor phenotypes

e.g. vemurafenib for tumors with BRAF mutations believed to be ***fundamental for sustaining their growth***

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PCM is based on **targeting** the molecular mechanism(s) that are **driving** the patient's tumor AND it is **addicted** to

b) targeting the **loss of activity of a tumor suppressor** driving the tumor phenotypes

> *restablishing its activity (?)*

> *targeting **synthetic lethality** vulnerabilities*

e.g. cells with BRCA-deficiency can not handle inhibition of the PARP-pathway (healthy cells do)

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c) "boosting" the patient **immune system** to target the cancer

> *farming **TILs***

> *targeting immune-suppressive mechanism used by the tumor*

e.g. PD1/PDL1 inhibitors for tumor cells that 'hijack' the PDL1 signaling to evade cytotoxic immune activity

OUTCOME OF *OMICS* GUIDED THERAPIES

→ A number of *omics*-guided therapies **are approved for standard-of-care**

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	Olaparib, Niraparib, Rucaparib, Talazoparib
EGFR mut	Lung	Gefitinib, Erlotinib, Afatinib, Dacomitinib, Osimetrinib
ERBB2 ampl	Breast, Gastric, CRC	Trastuzumab, Pertuzumab, T-DM1, Lapatinib, Neratinib
FGFR2/3 fusions/ mut	Bladder	Erdafitinib
FLT3 mut	Leukemia	Midostaurin, Gilteritinib
IDH1/2 mut	Leukemia	Ivosidenib, Enasidenib
KIT mut	GIST	Imatinib, Sunitinib, Regorafenib, Sorafenib
KRAS/NRAS wt	CRC	Cetuximab, Panitumumab
MET ampl/ exo14 skip	Lung, Renal	Crizotinib, Cabozantinib
NTRK1/2/3 fusion	All solid tumors	Larotrectinib, entrectinib
PDGFRA/PDGFB fusion	Leukemia, Sarcoma	Imatinib, Dasatinib
PIK3CA mut	Breast	Alpelisib
ROS1 fusion	Lung	Crizotinib
TSC1/2 mut	Brain	Everolimus

(Updated ~2020)

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NGS is frequently used also in patients w/o standard options in order to find **investigational treatment opportunities** *(off-label, clinical trials etc)*

(Updated ~2020)

CLINICAL INTERPRETATION OF NGS RESULTS

GERMLINE AND SOMATIC GENE ALTERATIONS

→ **Germline** variants are inherited (or acquired *de novo* during germ cells maturation/fertilization)

→ All the body cells share the same **germline** variants (including gametes, and thus may be passed to the offspring)

→ **Somatic variants** occur only to a certain number of body cells during their lifetime, due to intrinsic+extrinsic mutational processes)

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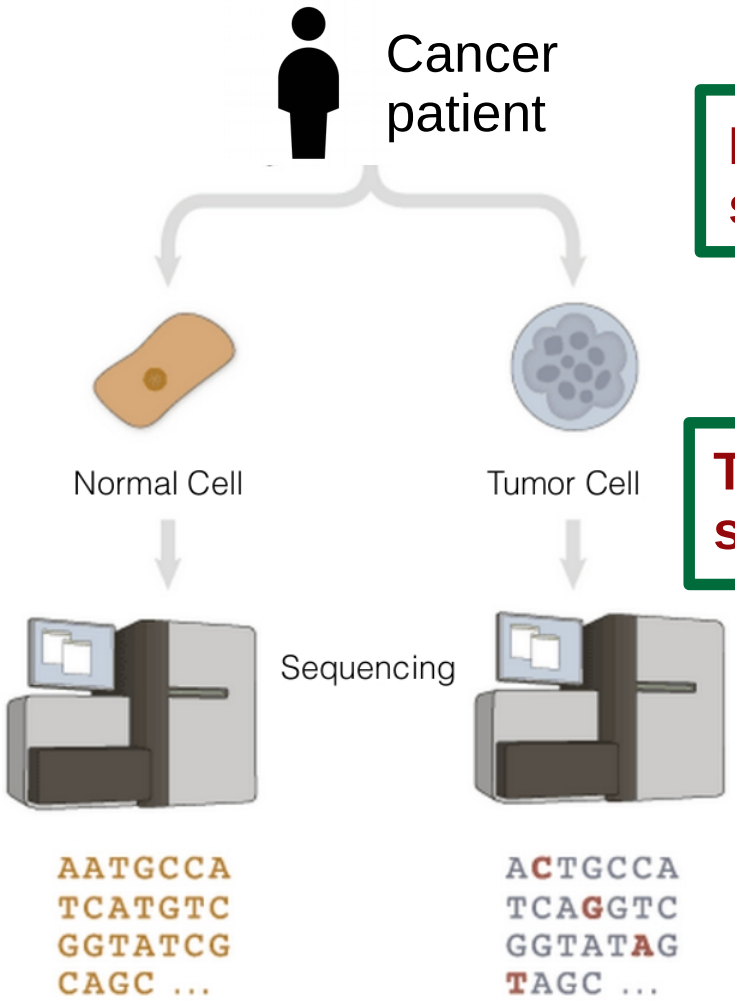
→ In **cancer**, some germline variants may **predispose** to certain cancer types

> *e.g. a germline variant in BRCA1 disrupts the WT function of the affected allele (and thus is 'easier' to lose the BRCA1 function due to a somatic event in the 2nd allele)*

→ **Somatic alterations** accumulate to drive onset and progression of cancer according to the selective pressures *(including drug treatments)*



Healthy sample = proxy tissue to sequence the "normal" germline variants in the patient cells *(e.g. blood)*

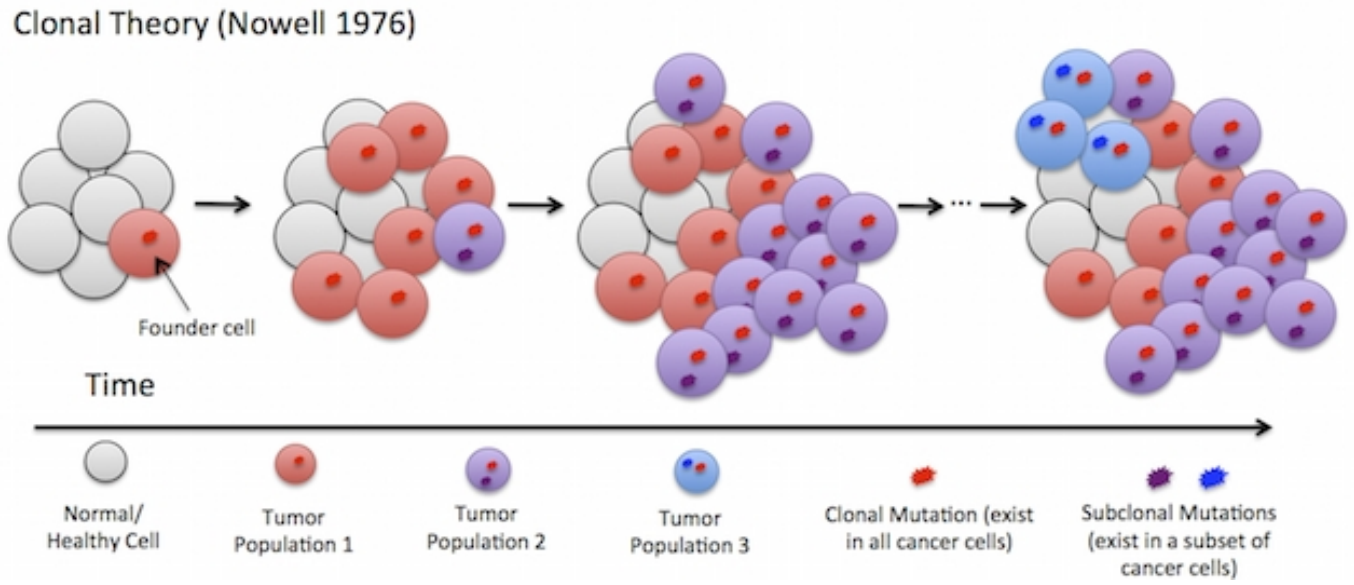
Tumor sample = germline variants plus those accumulated during tumor cells' development

> *Ideally, both normal and tumor tissues are sequenced, so you can "subtract" the germline variants from those observed in the tumor (and thus distinguish germline vs somatic)*

CLINICAL INTERPRETATION OF NGS RESULTS

TUMOR CLONAL HETEROGENEITY

> Tumors are **heterogeneous** populations of cells each of them composed by a **distinct set of mutations** *(aka tumor clones)*



> "Founder" mutations *(aka **clonal mutations**)* are present in all the tumor cells

> Mutations that appear later can be present in only a subset of the tumor cells *(aka **sub-clonal mutations**)*

> Subclonal mutations follow selective pressures

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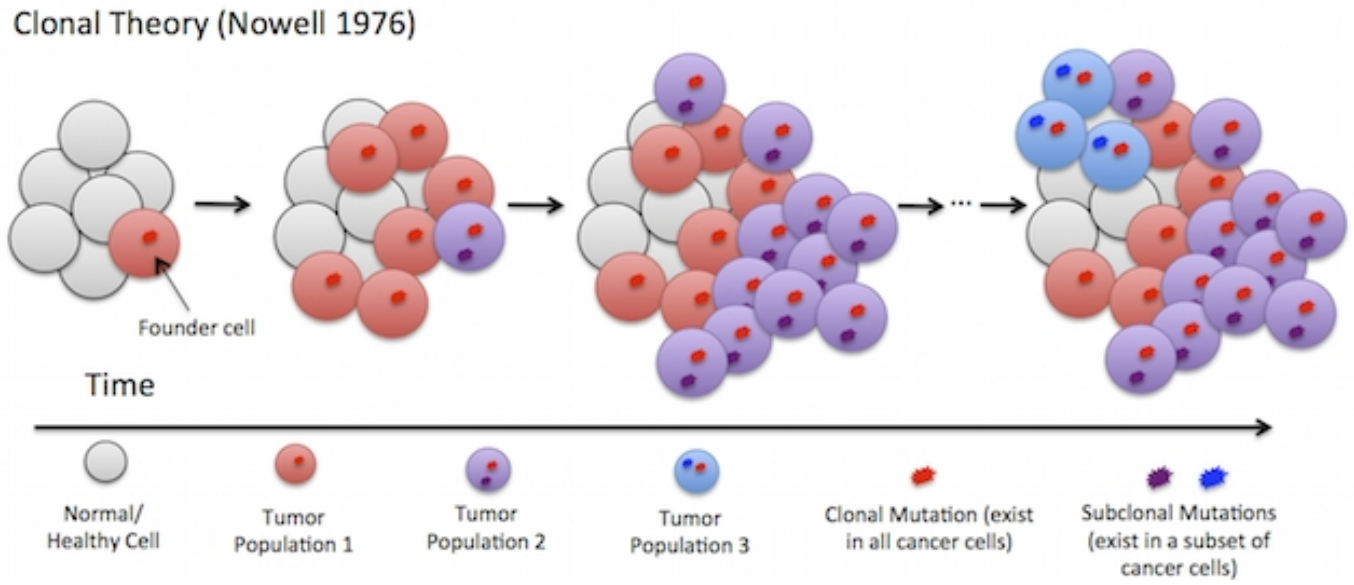

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> Subclonal mutations follow selective pressures

e.g. passenger mutations may be unevenly distributed across tumor cells

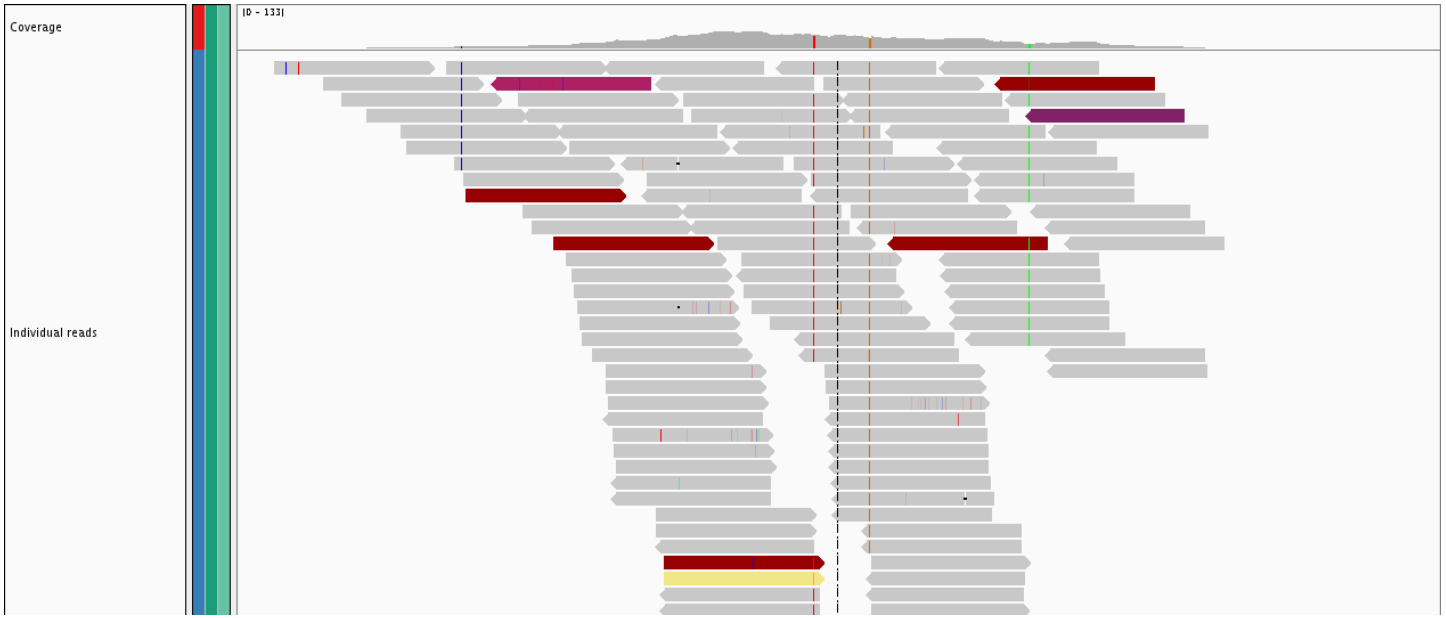
e.g. driver mutations can arise as subclonal but eventually take over the bulk

e.g. subclonal (driver) mutations can establish complex dynamics between them

Consequences for the NGS results

> What we sequence in a bulk sample is a mixture of mutations with different clonality

> Clonality can be inferred from the **variant allele frequency** (VAF), which is the proportion of **NGS reads** in which that variant is observed

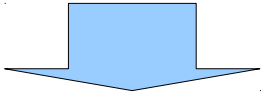


The larger is the proportion of reads sequenced in your tumor sample that bear the variant, the more clonal is that variant in the tumor cells population

Consequences for the NGS results

> Note that somatic variants affect only one **allele** of the gene

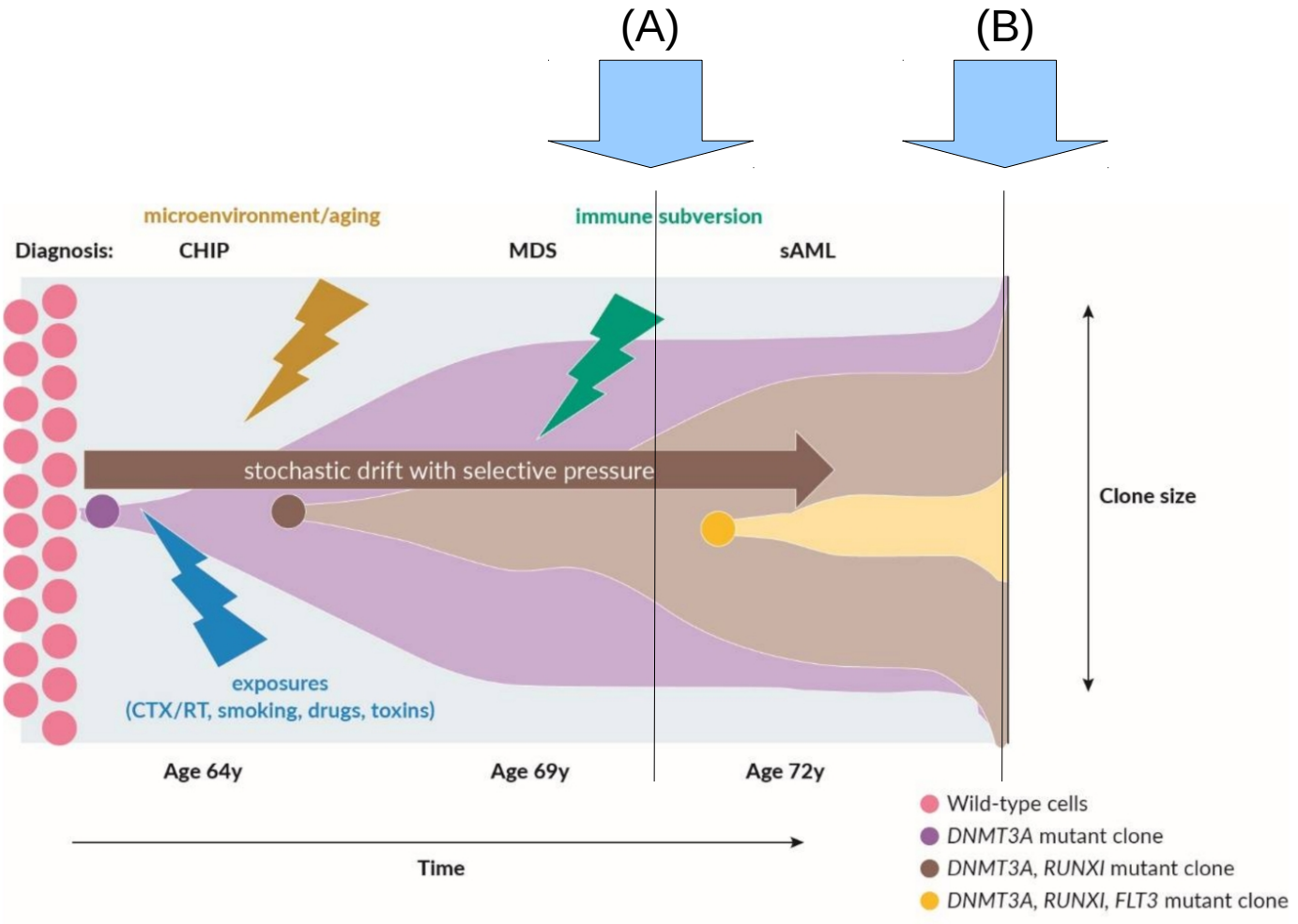
> Unless there is a copy number alteration*, you re sequencing the DNA of the two gene alleles (the mutated and the WT)



So a mutation present in all cells, aka clonal, is present in one out of two of the alleles of all the cells, meaning half of the reads, i.e. a VAF ~ 50%

**(e.g. if the WT allele is deleted by a somatic LoH, all the existing alleles would bear the mutation, and thus a clonal mutation would appear in all the reads, i.e. a VAF~100%)*

Consequences for the NGS results



If you sequence* in (A)
DNMT3A VAF=50%
RUNX1 VAF=30%

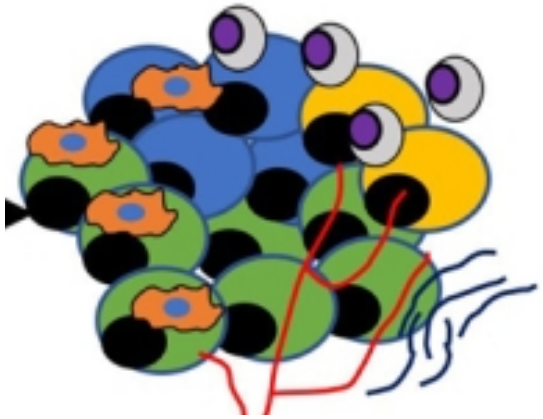
If you sequence* in (B)
DNMT3A VAF=50%
RUNX1 VAF=48%
FLT3 VAF=10%

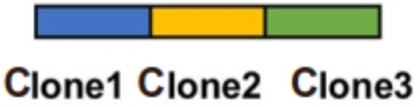
** assuming all genes are diploid*

Consequences for the NGS results

> Note that in tumor **bulk** samples, we often also have **non-tumor infiltrating cells**

Tumor bulk sample





The proportion of tumor cells in the tumor (bulk) sample is named "**tumor purity**"

Non-tumor cells in the tumor sample "dilutes" the VAF of the tumor mutations

e.g. if only half of the cells are tumor cells, a clonal tumor mutation (in diploid gene) shows VAF~ 25% instead of 50%

Consequences for the NGS results

> Note that in tumor **bulk** samples, we often also have **non-tumor infiltrating cells**

> The mutations we sequence is an “average” of the tumor clones and the non-tumor cells in the bulk* sample

> Variant allele frequency is a result of the clonality of the mutation, the ploidy of the region and the purity of the sample

** as opposite to single-cell sequencing*

mutation (in diploid gene) shows VAF~ 25% instead of 50%

CLINICAL INTERPRETATION OF NGS RESULTS

INTERPRETATION OF THE RELEVANCE OF TUMOR VARIANTS

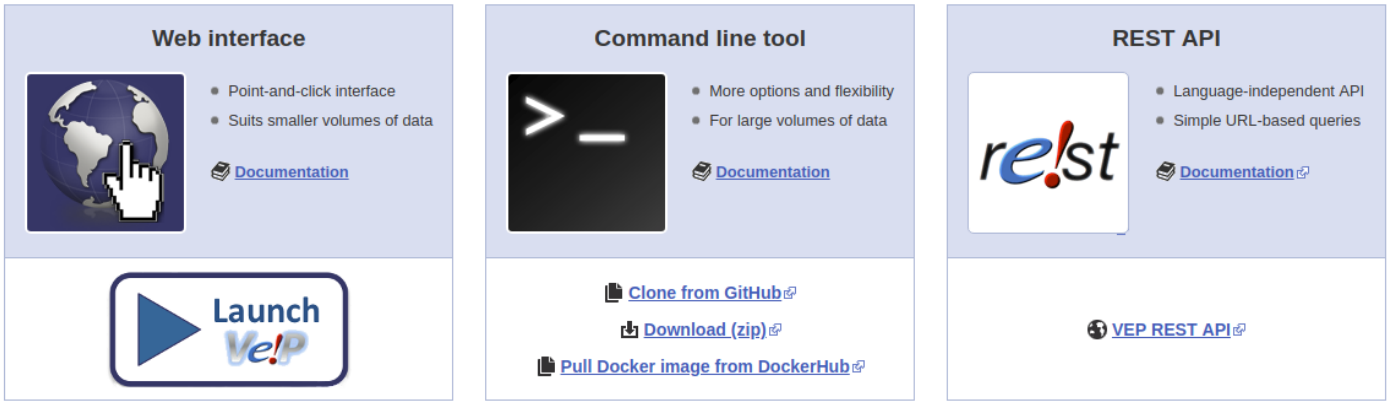
(1) Map the genomic variant for its consequence

> Given a **genomic variant***, first step is to map which gene (if any) is being affected and the corresponding consequence per transcript

* e.g. chr7 140453136 A>T (GRCh37)

> Different **bioinformatic tools** can be used for that

https://www.ensembl.org/info/docs/tools/vep/index.html



Variant Effect Predictor

New job

Species: Homo_sapiens

Assembly: GRCh37.p13

VEP for non-human species is now only available on this site for Human (GRCh37). For other species, please visit our main site.

Name for this job (optional):

```
7 140453136 . A T . . .
```

Examples: Ensembl default, VCF, Variant identifiers, HGVS notations — Run instant VEP for current line ›

Or upload file: Choose File — No file chosen

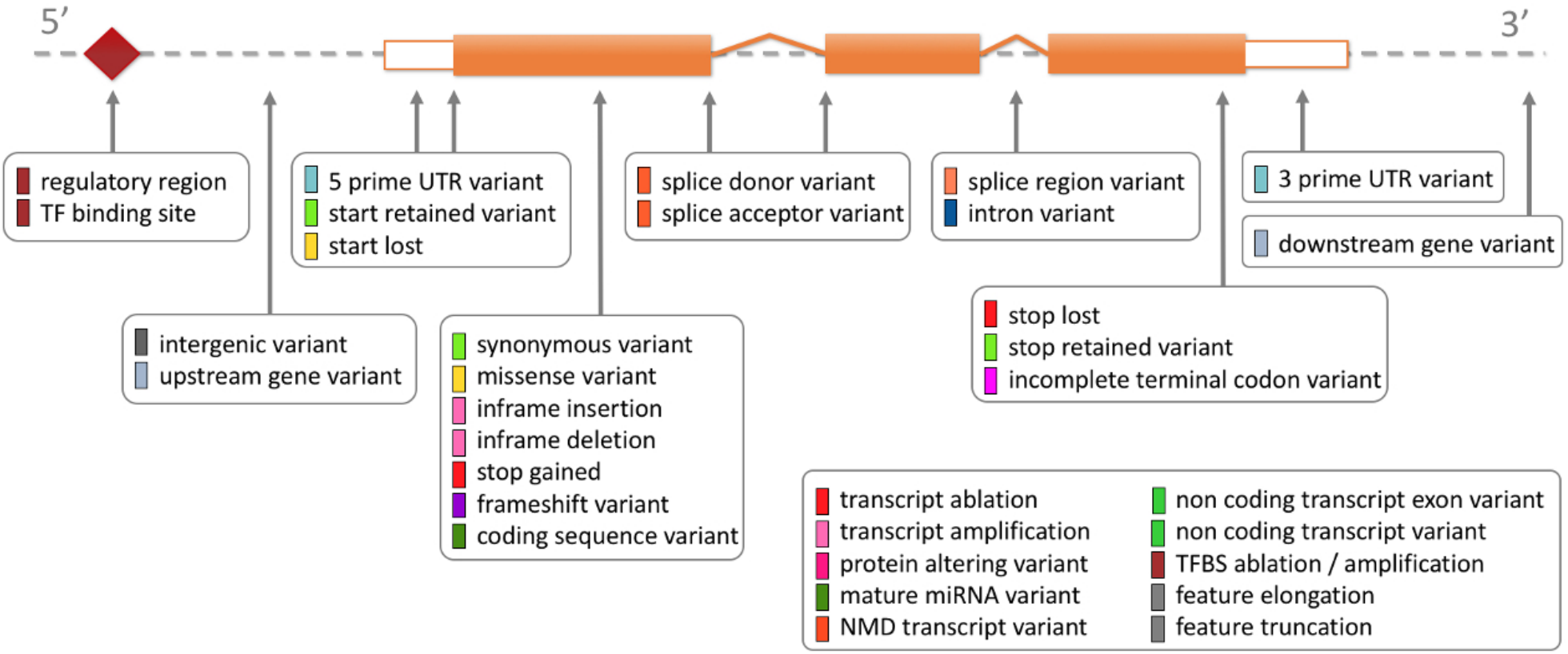
Or provide file URL:

Transcript database to use:

- (•) Ensembl/GENCODE transcripts
- ( ) Ensembl/GENCODE basic transcripts
- ( ) RefSeq transcripts
- ( ) Ensembl/GENCODE and RefSeq transcripts

Uploaded variant	Location	Allele	Consequence	Symbol	Gene	Feature type	Feature	Biotype	Exon	cDNA position	CDS position	Protein position	Amino acids	Codons	Ex va
.	7:140453136-140453136	T	missense_variant	BRAF	ENSG00000157764	Transcript	ENST00000288602.6	protein_coding	15/18	1860	1799	600	V/E	GTG/GAG	rs C C C C
.	7:140453136-140453136	T	missense_variant, NMD_transcript_variant	BRAF	ENSG00000157764	Transcript	ENST00000479537.1	nonsense_mediated_decay	2/6	83	83	28	V/E	GTG/GAG	rs C C C C
.	7:140453136-140453136	T	missense_variant	BRAF	ENSG00000157764	Transcript	ENST00000496384.2	protein_coding	6/10	622	623	208	V/E	GTG/GAG	rs C C C C
.	7:140453136-140453136	T	3_prime_UTR_variant, NMD_transcript_variant	BRAF	ENSG00000157764	Transcript	ENST00000497784.1	nonsense_mediated_decay	16/19	1834	-	-	-	-	rs C C C C

> Mutations in cancer genes can have very different consequences

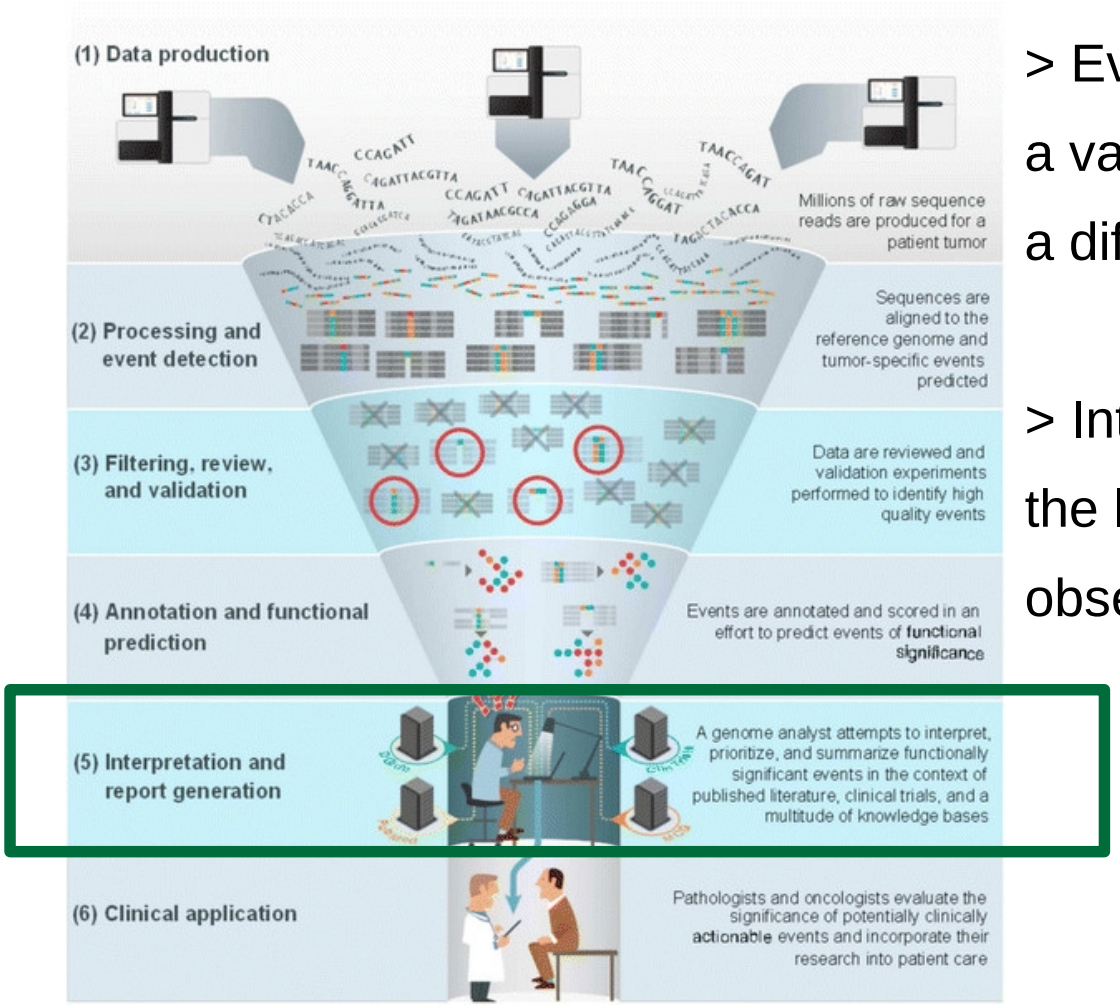


> Coding vs (splice) vs non-coding regions

> Variant affecting the protein sequence or not

> Missense versus disrupting mutations (i.e. nonsense & frameshifts)

(2) Interpret the relevance of that variant in that gene for cancer



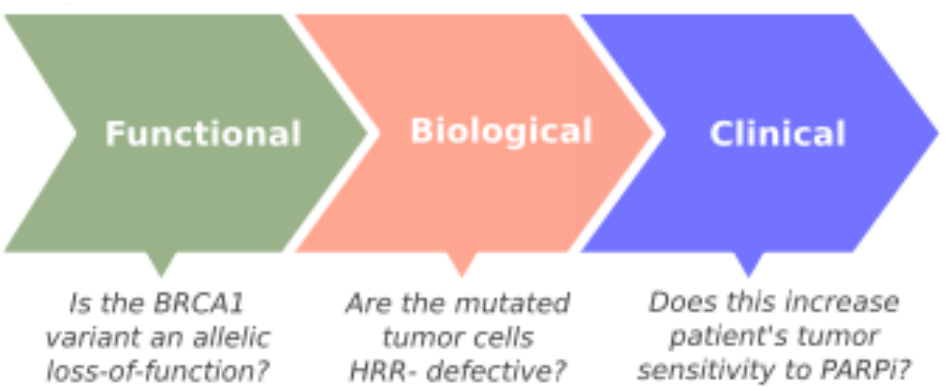
> Even with the same consequence type, a variant in a cancer gene can have a different importance for the disease

> Interpretation of the data is made at the level of each individual variant observed in the patient's tumor

Good et al. Genome Biology 2014

(2) Interpret the relevance of that variant in that gene for cancer

Clinical interpretation of cancer gene alterations:



(1) is the variant relevant for oncogenesis ?

Not all the mutations that occur in tumor cells, even in well known cancer genes, are functionally relevant for the oncogenesis

Only a subset of variants are driver mutations, while the rest are passengers

(2) given a functional alteration with a given biological consequence, is it clinically relevant?

Is it a biomarker of prognosis, diagnosis or drug response?

KNOWLEDGEBASES OF GENOMIC VARIANT EFFECTS

Knowledge about the effect of **cancer gene mutations** is accumulated via pre-clinical and clinical studies

Examples:

> *A given functional assay studying variants impairing TP53 binding sites*

> *“Epidemiological” study looking for BRCA germline variants and cancer risk*

> *A clinical trial associating RAS somatic mutations with MEK-inhibitors response*

This knowledge is gathered in different **knowledgebases** driven by several international initiatives

KNOWLEDGEBASES OF GENOMIC VARIANT EFFECTS

Focused on germline variants (pathogenicity), but also contains cancer related info (specially cancer predisposing variants)

Focused on germline BRCA1/2 variants in the context of cancer predisposing phenotypes

Focused on genomic alterations, specially somatic, reported to be biomarkers of disease diagnosis, prognosis and drug response

Focused on variants, specially somatic, reported to be oncogenic; also biomarkers of drug response

Contains also an in-house database of biomarkers of drug response

KNOWLEDGEBASES OF GENOMIC VARIANT EFFECTS

Note that these knowledgebases have different **scopes**, **data models and SOPs** to consolidate the available information that they curate

Also, some knowledgebases publish assertions that are not necessarily supported by “strong quality” data, which should be taken into account for (clinically) actionable genes

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BRCA EXCHANGE

Focused on germline BRCA1/2 variants in the context of cancer predisposing phenotypes

CIViC
CLINICAL INTERPRETATION

Focused on genomic alterations, specially somatic, reported to be biomarkers of disease diagnosis, prognosis and drug response

OncoKB

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CANCER GENOME INTERPRETER

Contains also an in-house database of biomarkers of drug response

enomic variation as it relates to human health

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FEEDBACK

NM_000546.5(TP53):c.994-1G>A

Cite this record

Interpretation: Pathogenic

Review status: ★★☆☆ criteria provided, multiple submitters, no conflicts
Submissions: 4 (Most recent: Sep 1, 2021)
Last evaluated: May 28, 2020
Accession: VCV000142161.9
Variation ID: 142161
Description: single nucleotide variant

Variant details

Conditions

Gene(s)

NM_000546.5(TP53):c.994-1G>A

Allele ID: 151875
Variant type: single nucleotide variant
Variant length: 1 bp
Cytogenetic location: 17p13.1
Genomic location: 17: 7670716 (GRCh38) GRCh38 UCSC
17: 7574034 (GRCh37) GRCh37 UCSC

HGVS:

Nucleotide	Protein	Molecular consequence
LRG_321t4:c.*13-1G>A		
LRG_321t3:c.*101-1G>A		
LRG_321t5:c.598-1G>A		

more HGVS

ClinVar
Clinically relevant variation

enomic variation as it relates to human health

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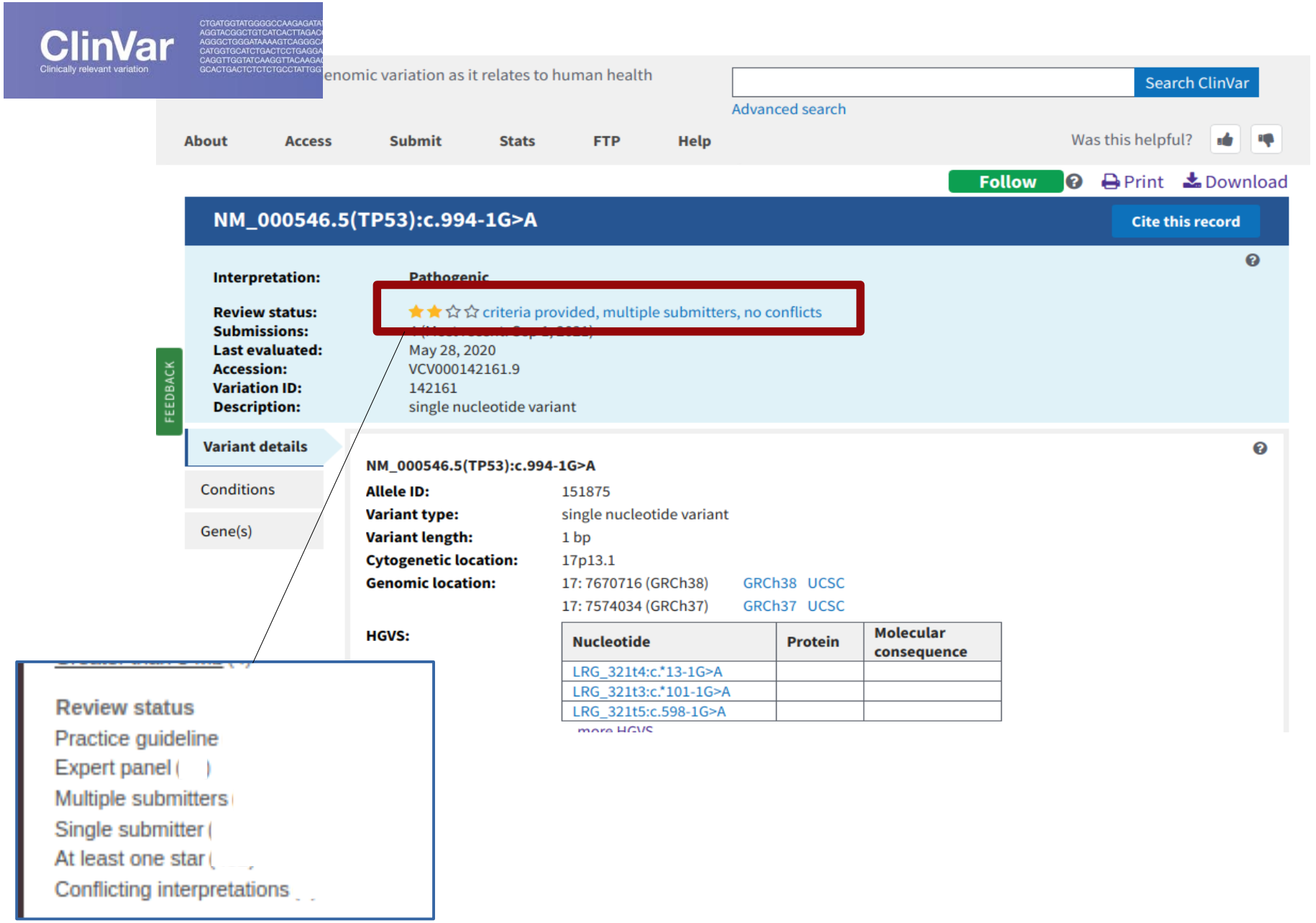
Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology

Sue Richards PhD, Nazneen Aziz PhD, Sherri Bale PhD, David Bick MD, Soma Das PhD, Julie Gastier-Foster PhD, Wayne W. Grody MD, PhD, Madhuri Hegde PhD, Elaine Lyon PhD, Elaine Spector PhD, Karl Voelkerding MD & Heidi L. Rehm PhD on behalf of ; on behalf of the ACMG Laboratory Quality

Interpretation (Last evaluated)	Review status (Assertion criteria)	Condition (Inheritance)	Submitter	Supporting information (See all)
Pathogenic (Oct 25, 2018)	criteria provided, single submitter (Ambry Autosomal Dominant and X-Linked criteria (3/2017)) Method: clinical testing	Hereditary cancer-predisposing syndrome Allele origin: germline	Ambry Genetics Accession: SCV000186055.6 Submitted: (Nov 30, 2020)	Evidence details Publications PubMed (1) Comment: The c.994-1G>A intronic pathogenic mutation results from a G to A substitution one nucleotide upstream from coding exon 9 of the TP53 gene This aleration … (more)
Pathogenic (May 28, 2020)	criteria provided, single submitter (Invitae Variant Classification Sherloc (09022015)) Method: clinical testing	Li-Fraumeni syndrome Allele origin: germline	Invitae Accession: SCV001578012.1 Submitted: (Jan 07, 2021)	Evidence details Publications PubMed (5) Comment: This sequence change affects an acceptor splice site in intron 9 of the TP53 gene. It is expected to disrupt RNA splicing and likely results … (more)
Pathogenic (Dec 13, 2019)	criteria provided, single submitter (GeneDx Variant Classification Process June 2021) Method: clinical testing	Not Provided Allele origin: germline	GeneDx Accession: SCV001816973.1 Submitted: (Sep 01, 2021)	Evidence details Comment: Canonical splice site variant in a gene for which loss-of-function is a known mechanism of disease; Observed in individuals with history consistent with pathogenic variants … (more)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enomic variation as it relates to human health
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NM_000546.5(TP53):c.994-1G>A
Cite this record
Interpretation:
Pathogenic
Review status:
criteria provided, multiple submitters, no conflicts
Submissions:
Last evaluated:
May 28, 2020
Accession:
VCV000142161.9
Variation ID:
142161
Description:
single nucleotide variant
FEEDBACK
Variant details
Conditions
Gene(s)
NM_000546.5(TP53):c.994-1G>A
Allele ID:
151875
Variant type:
single nucleotide variant
Variant length:
1 bp
Cytogenetic location:
17p13.1
Genomic location:
17: 7670716 (GRCh38)
GRCh38
UCSC
17: 7574034 (GRCh37)
GRCh37
UCSC
HGVS:
Nucleotide
Protein
Molecular consequence
LRG_321t4:c.*13-1G>A
LRG_321t3:c.*101-1G>A
LRG_321t5:c.598-1G>A
Review status
Practice guideline
Expert panel
Multiple submitters
Single submitter
At least one star
Conflicting interpretations

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GENE FLT3

FLT3 is an important cytokine receptor involved in normal hematopoiesis. Mutations in this gene are common in acute myeloid leukemia (AML) and screening for mutations in this gene has been recommended by the World Health Organization in patients with AML, particularly in cases of cytogenetically normal AML (CN-AML). FLT3 mutations commonly co-occur with mutations such as NPM1 that are associated with CN-AML and likely modulate prognostic impact. While FLT3-ITD mutations have been associated with poorer prognosis in AML, the prognostic impact of FLT3-TKD mutations are still up for debate.

Sources:

Stirewalt et al., 2003, Nat. Rev. Cancer
Vardiman et al., 2009, Blood

DGIdb Details
ProteinPaint Details

VARIANT D835E

Evidence Summary | Evidence Talk

Submitted by IlluminaBioInfo

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

In a retrospective study of 15 acute myeloid leukemia patients, the patients with FLT3 D835 mutation (n=2) were associated with improved response to sunitinib treatment (2/2 vs. 2/7) compared to FLT3 wild-type patients. The FLT3 D835 mutation positive patients were treated with sunitinib after failure of standard chemotherapy. After 4wk of sunitinib therapy, one patient showed morphological response and the other patient showed partial response to sunitinib therapy.

Evidence Level: C - Case Study
Evidence Type: Predictive
Evidence Direction: Supports
Clinical Significance: Sensitivity/Response
Variant Origin: Somatic
Drug: Sunitinib

Disease: Acute Myeloid Leukemia
Associated Phenotype: --
Source: Fiedler et al., 2005, Blood
PubMed ID: 15459012
Clinical Trial: --
Evidence Rating: ☆ ☆ ☆ ☆ ☆

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DGIc
ProteinI

Level	Name	Definition	Example and further comments
A	Validated association	Proven/consensus association in human medicine.	*"AML with mutated NPM1" is a provisional entity in WHO classification of acute myeloid leukemia (AML). This mutation should be tested for in clinical trials and is recommended for testing in patients with cytogenetically normal AML.* Validated associations are often in routine clinical practice already or are the subject of major clinical trial efforts.
B	Clinical evidence	Clinical trial or other primary patient data supports association.	*BRAF V600E is correlated with poor prognosis in papillary thyroid cancer in a study of 187 patients with PTC and other thyroid diseases.* The evidence should be supported by observations in multiple patients. Additional support from functional data is desirable but not required.
C	Case study	Individual case reports from clinical journals.	*A single patient with FLT3 over-expression responded to the FLT3 inhibitor sunitinib.* The study may have involved a large number of patients, but the statement was supported by only a single patient. In some cases, observations from just a handful of patients (e.g. 2-3) or a single family may also be considered a case study/report.
D	Preclinical evidence	In vivo or in vitro models support association.	*Experiments showed that AG1296 is effective in triggering apoptosis in cells with the FLT3 internal tandem duplication.* The study may have involved some patient data, but support for this statement was limited to in vivo or in vitro models (e.g. mouse studies, cell lines, molecular assays, etc.).
E	Inferential association	Indirect evidence.	*CD33 and CD123 expression were significantly increased in patients with NPM1 mutation with FLT3-ITD, indicating these patients may respond to combined anti-CD33 and anti-CD123 therapy.* The assertion is at least one step removed from a direct association between a variant and clinical relevance.

VARIANT D835E

Submitted by IlluminaBioInfo

CAUTION: This Evidence Item has n

In a retrospective study of 15 acute myeloid leukemia patients, the patients with FL
(2/2 vs. 2/7) compared to FLT3 wild-type patients. The FLT3 D835 mutation positive
sunitinib therapy, one patient showed morphological response and the other patient showed partial response to sunitinib therapy.

Evidence Level: C - Case Study
Evidence Type: Predictive
Evidence Direction: Supports
Clinical Significance: Sensitivity/Response
Variant Origin: Somatic
Drug: Sunitinib

Disease: Acute Myeloid Leukemia
Associated Phenotype: --
Source: Fiedler et al., 2005, Blood
PubMed ID: 15459012
Clinical Trial: --
Evidence Rating: ☆☆☆☆☆

KNOWLEDGEBASES OF GENOMIC VARIANT EFFECTS

Focused on germline variants (pathogenicity), but also contains cancer related info (specially cancer predisposing variants)

Focused on germline BRCA1/2 variants in the context of cancer predisposing phenotypes

Focused on genomic alterations, specially somatic, reported to be biomarkers of disease diagnosis, prognosis and drug response

Focused on variants, specially somatic, reported to be oncogenic; also biomarkers of drug response

Contains also an in-house database of biomarkers of drug response

FGFR3 R248C

Oncogenic · Gain-of-function · Level 1 · FDA Level 2

FGFR3, a receptor tyrosine kinase, is altered by mutation, chromosomal rearrangement or amplification in various cancers, most frequently in bladder cancer.

The FGFR3 R248C mutation is known to be oncogenic.

Select a cancer type

Therapeutic | **FDA-Recognized Content**

Level	Alterations	Level-associated cancer types	Drugs	Citations
1	S249C, Y373C, G370C, R248C	Bladder Cancer	Erdafitinib	2
4	Oncogenic Mutations	All Solid Tumors	Debio1347, Infigratinib, AZD4547, Erdafitinib	12

OncoKB

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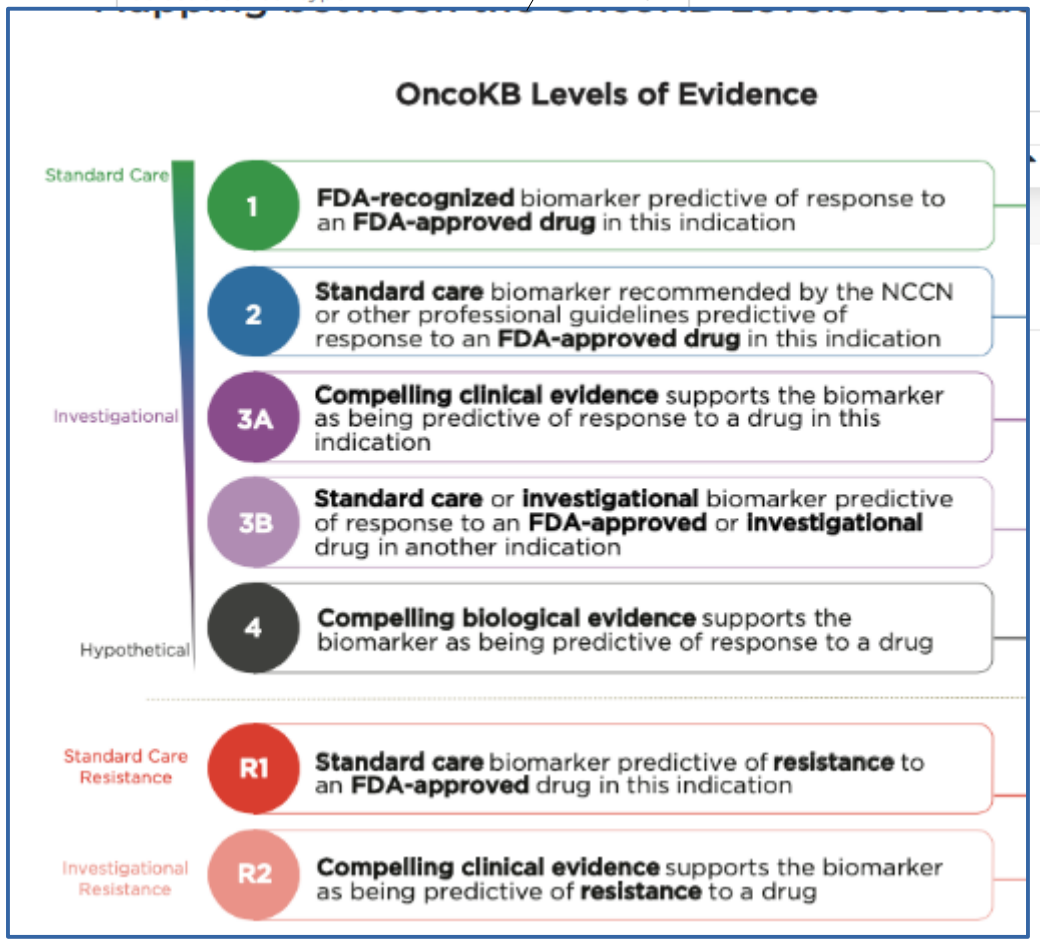

OncoKB

KNOWLEDGEBASES OF GENOMIC VARIANT EFFECTS

Ideally, a **comprehensive** variant annotation requires querying multiple knowledgebases, each with its own data model caveats

However, **most of the variants observed in cancer genes are still not well characterized** by current knowledge

For those, other **computational tools and other knowledge sources** can be used to interpret their effect

All together, data interpretation is a **very complex process**

Clinical interpretation is still mostly performed by manual processes

This is a significant burden for medical teams, as the process is:

> **Time consuming**

> Prone to **inaccuracies/errors***

> Difficult to keep pace with **current knowledge****

** note e.g. disparate formats for genomic data exchange*

*** note the tsunami of clinical and preclinical studies that are continuously generated in the community*

Use of clinical decision support systems (CDSS) can help addressing these complexities

- A CDSS can implement **efficient** processes to **annotate** and **report** NGS results with the specific aim of informing clinical decision-making

- **Automated**
- **Comprehensive**
- **Systematic**

Expert-driven !!!

(the framework executed by the CDSS is as good as the expertise behind its design)