

Somatic variant calling and interpretation in the context of cancer

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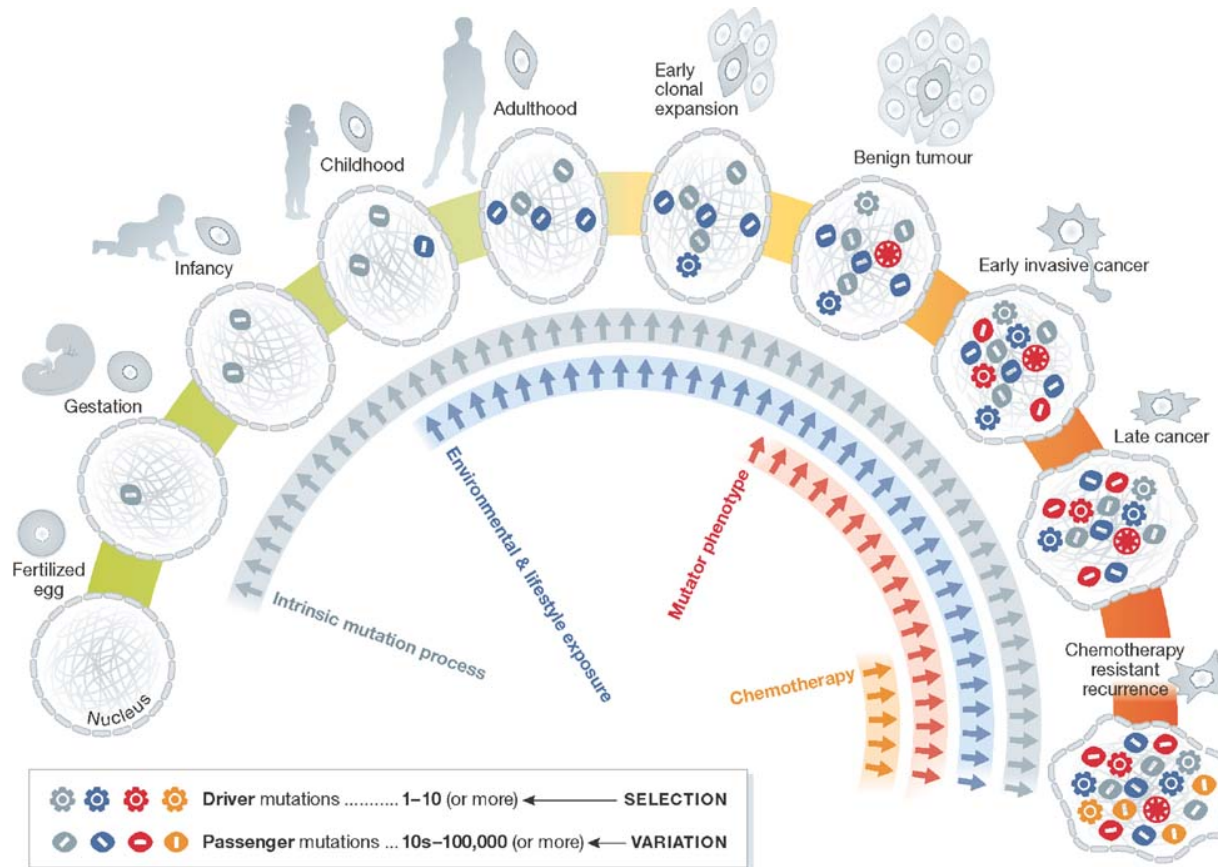
Department of Informatics

University of Oslo

IN-BIOS 5000/9000 – Fall 2022

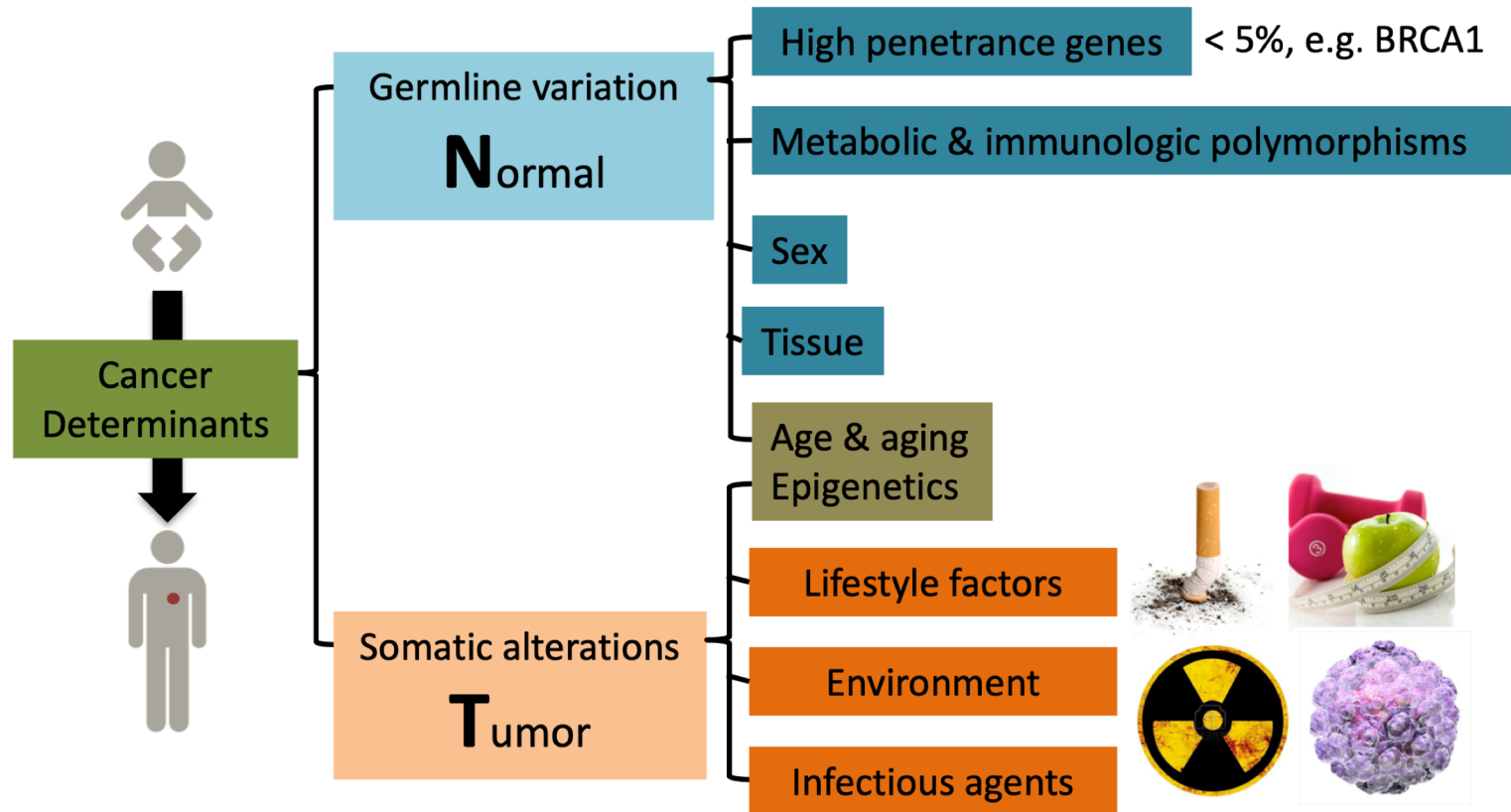
Why cancer?

Cancer – a disease of the genome



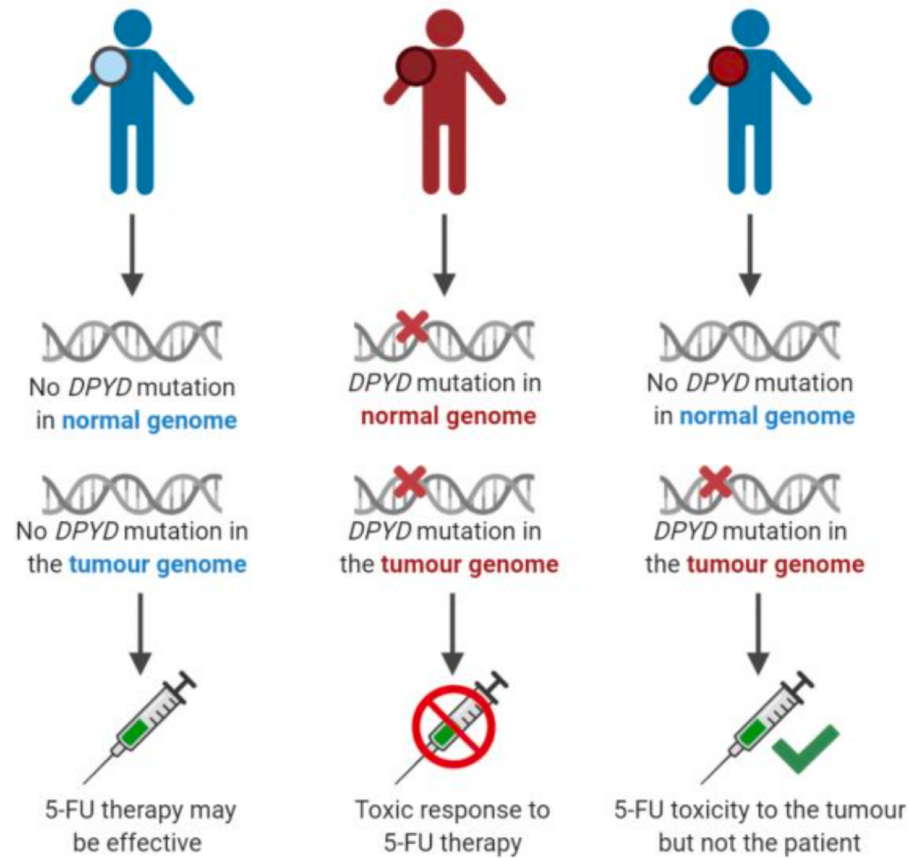
Stratton et al., EMBO Mol Med, 2013

Cancer – a disease of the genome



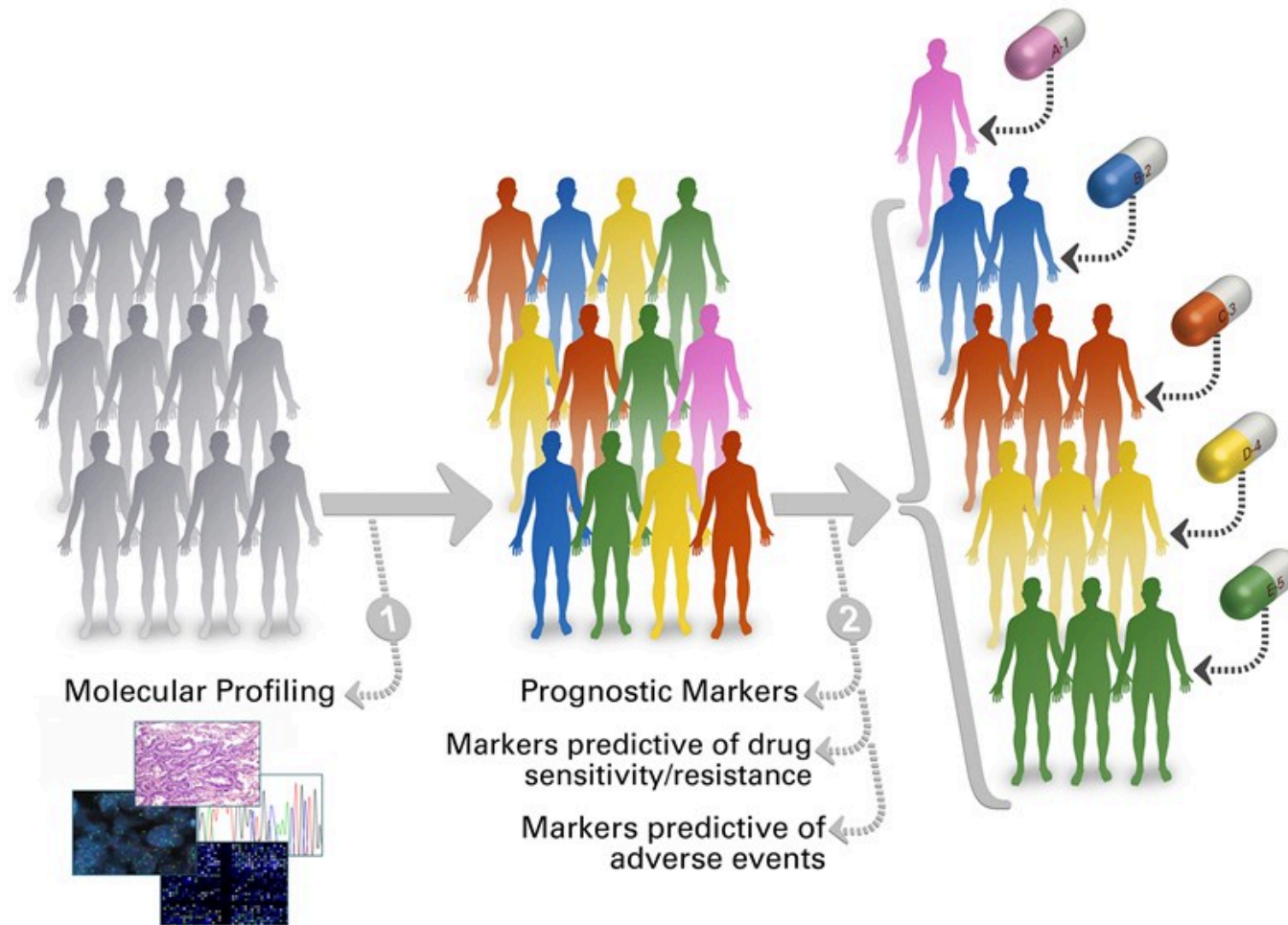
GATK: Introduction to Somatic Variant Discovery

Cancer sequencing informs on treatment options

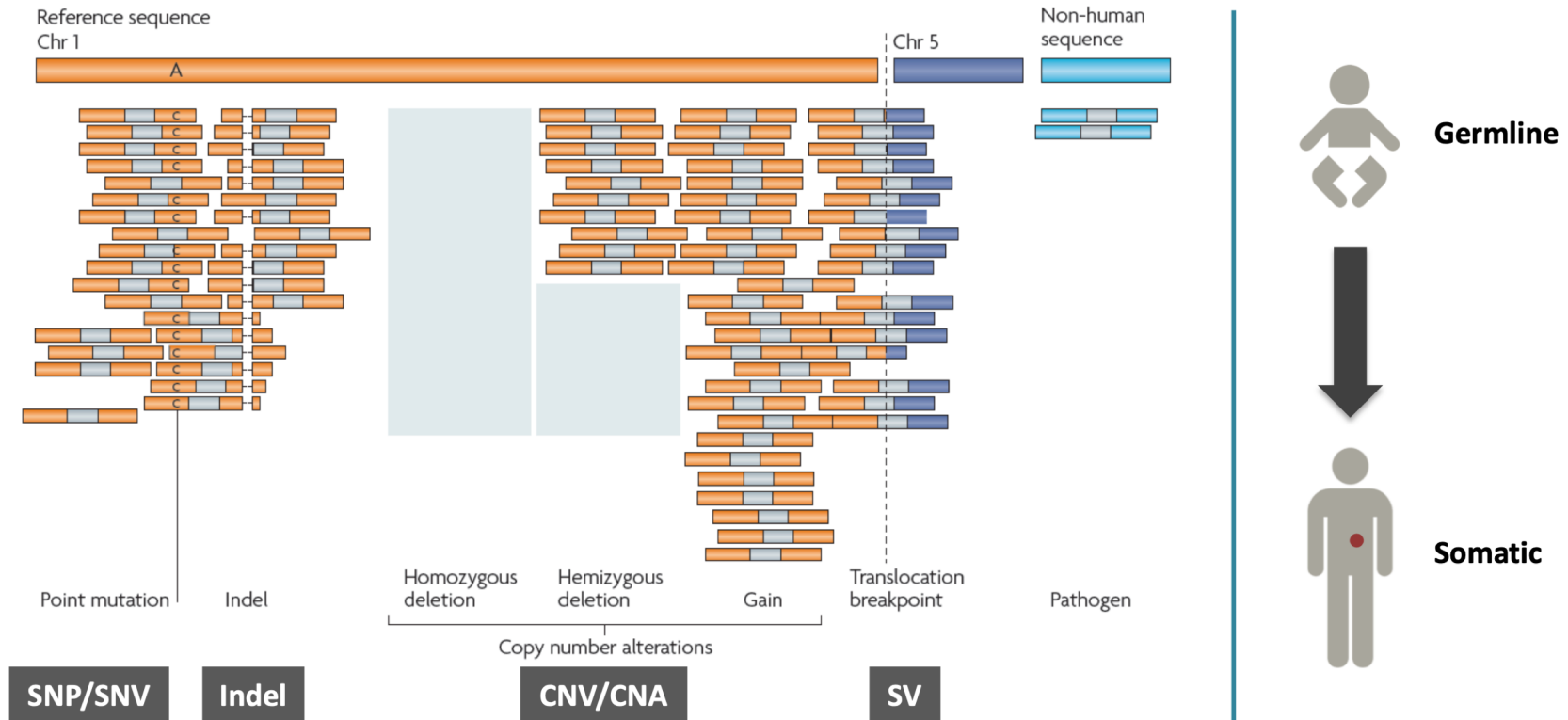


<https://www.bcgsc.ca/news/genome-sequencing-helps-prioritize-cancer-treatment-options>

Precision cancer medicine



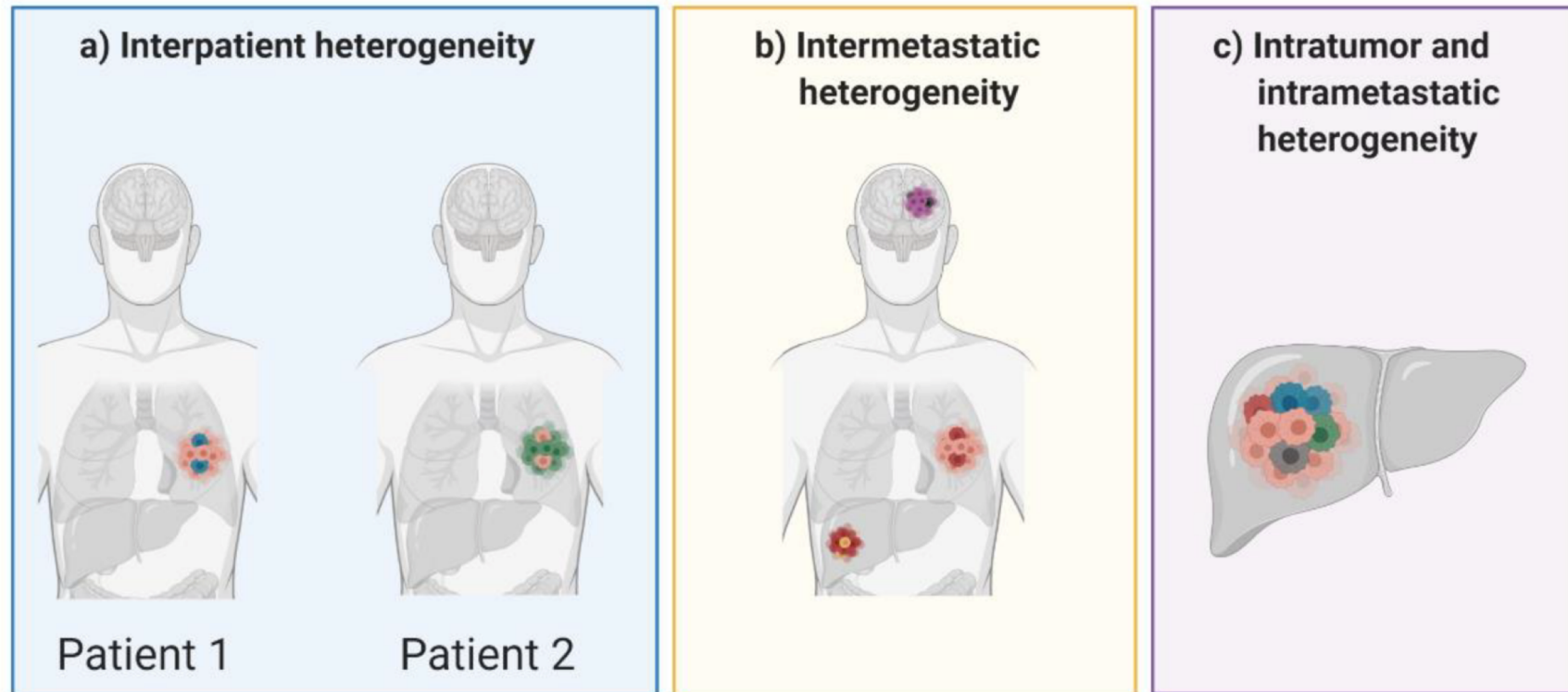
Cancer: multiple types of DNA aberrations



GATK: Introduction to Somatic Variant Discovery

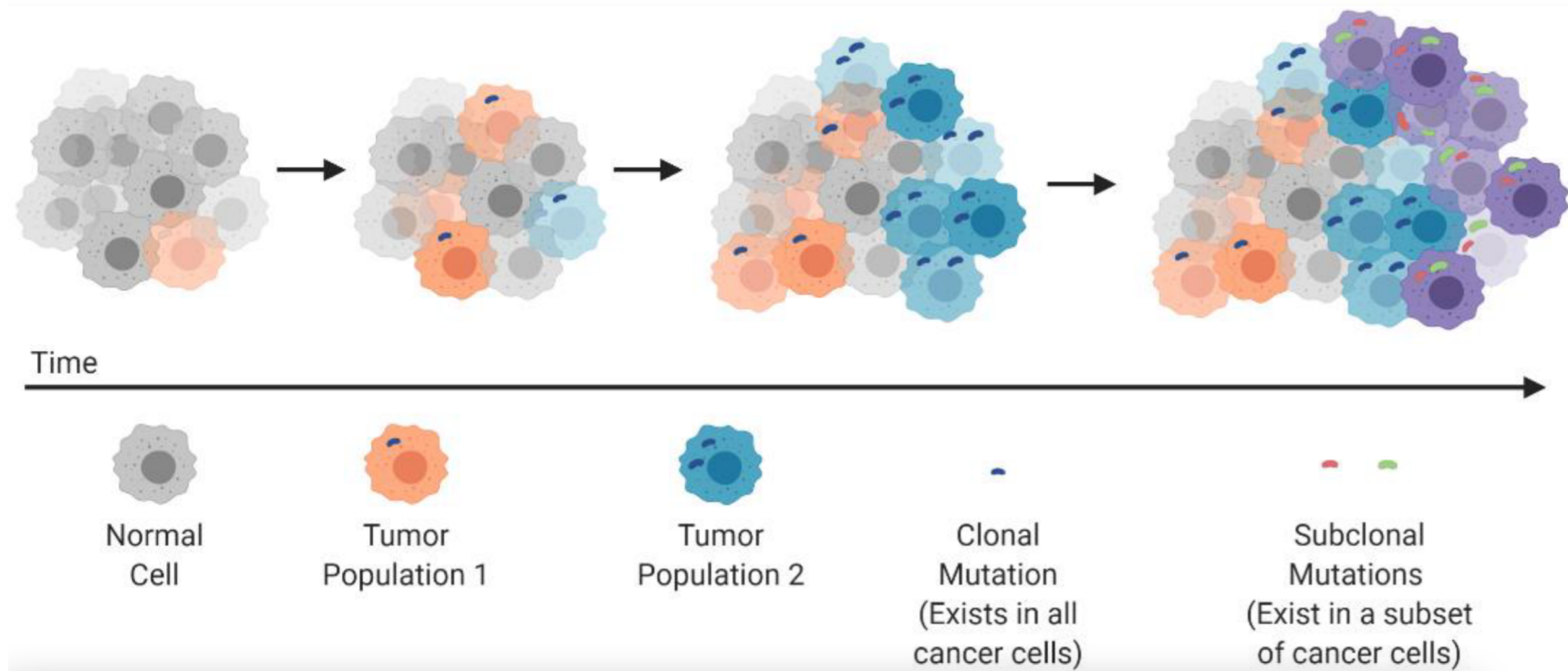
Why is somatic variant calling so challenging?

Cancer complexity



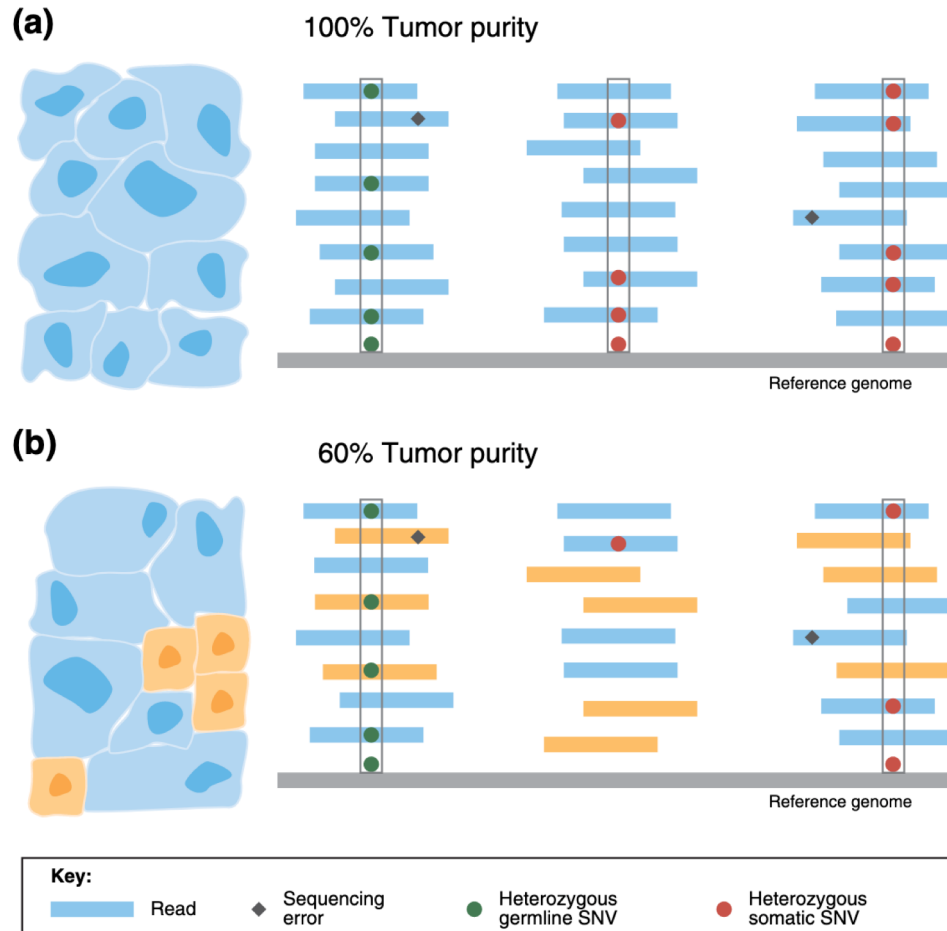
El-Sayes et al., Cancers, 2021

Tumor purity and heterogeneity (I)



El-Sayes et al., Cancers, 2021

Tumor purity and heterogeneity (II)

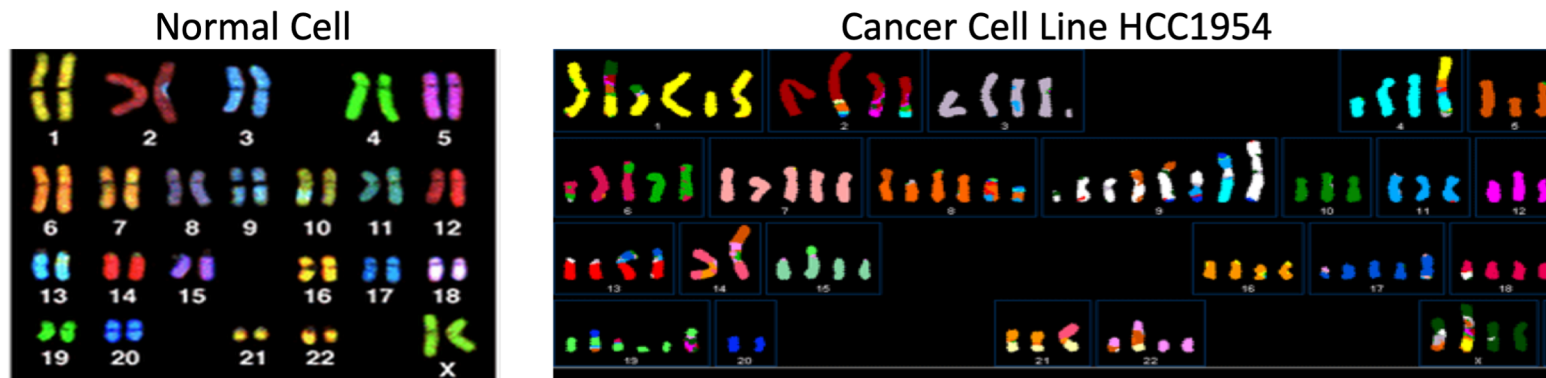


$$\text{Tumor purity} = \frac{\text{tumor cells}}{(\text{normal} + \text{tumor cells})}$$

- Deep sequencing
- Implications for targeted sequencing coverage
- Purity is traditionally assessed manually by pathologists, but can also be inferred computationally

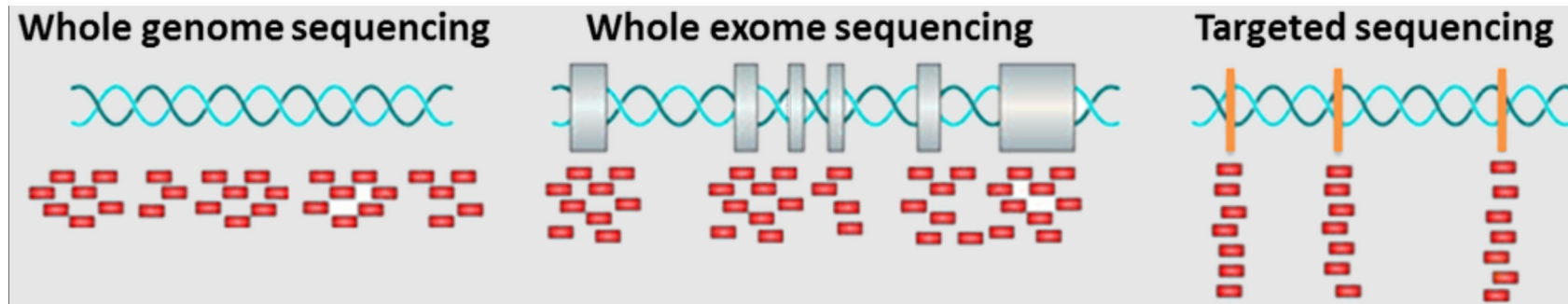
Raphael et al., *Genome Med*, 2014

Tumor ploidy



- Somatic variant calling: make no ploidy assumption!

Cancer sequencing: assay design



- Typically 30-40x coverage
- More even coverage than WES
- Covers coding and non-coding/regulatory variation
- All types of variants (reliable detection of SVs)

- Typically 80-100x coverage
- Coding regions only
- Cost-effective

- Typically > 300X coverage – captures subclonal variants at low allele frequencies
- Targets custom genes/regions – e.g. clinically actionable genes
- Most cost-effective

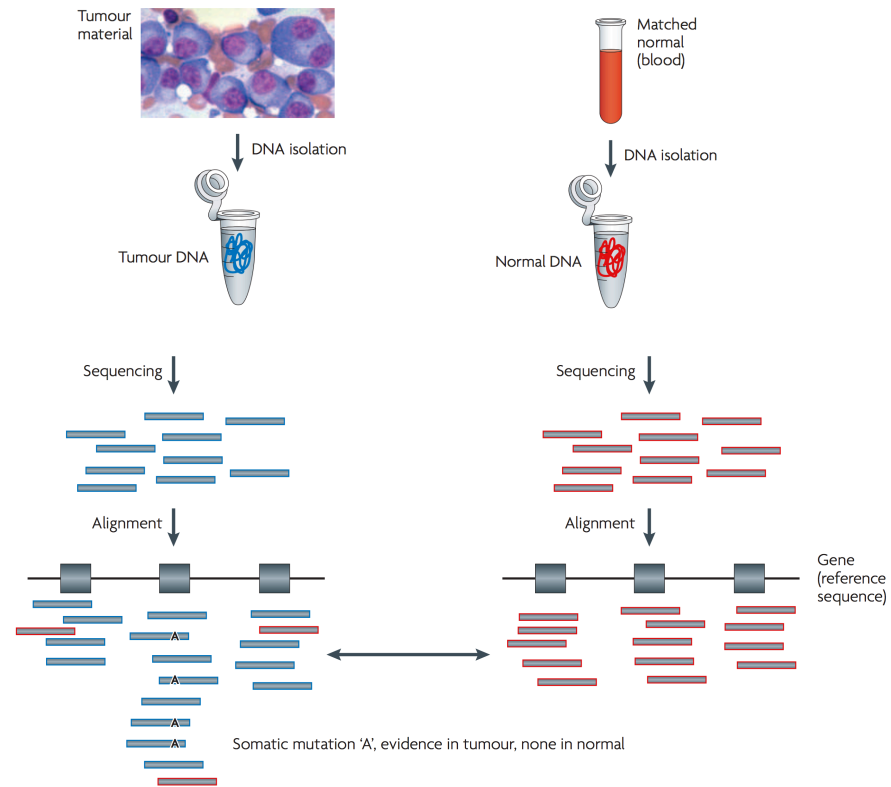
Research



Clinical applications

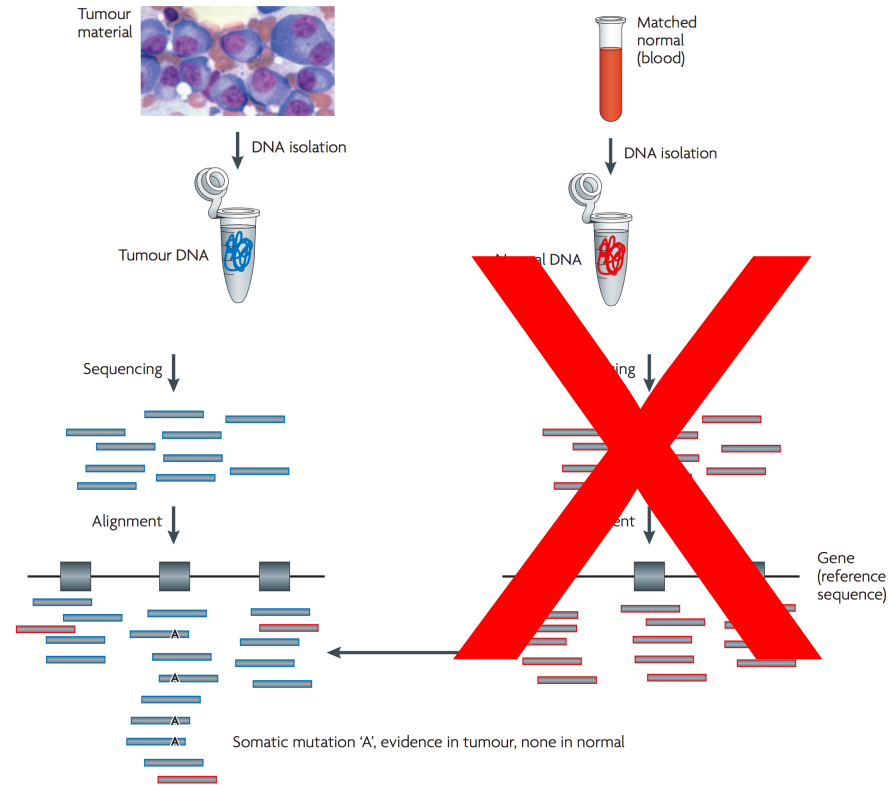
Cancer sequencing: calling design

- Two typical sequencing designs for detection of somatic variants
 - Tumor-control (T + N): most accurate

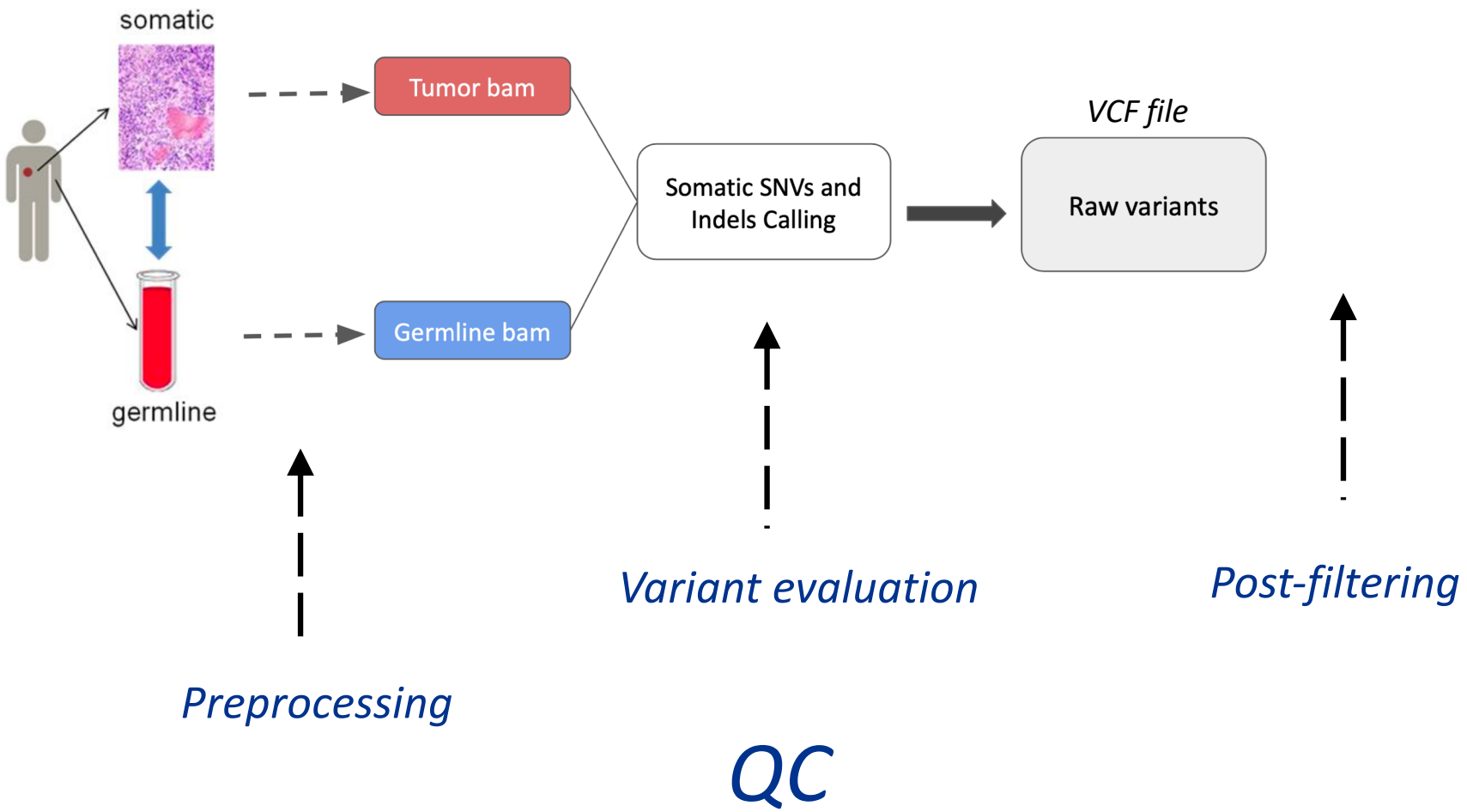


Cancer sequencing: calling design

- Two typical sequencing designs for detection of somatic variants
 - Tumor-control (T + N): most accurate
 - Tumor-only: most cost-effective



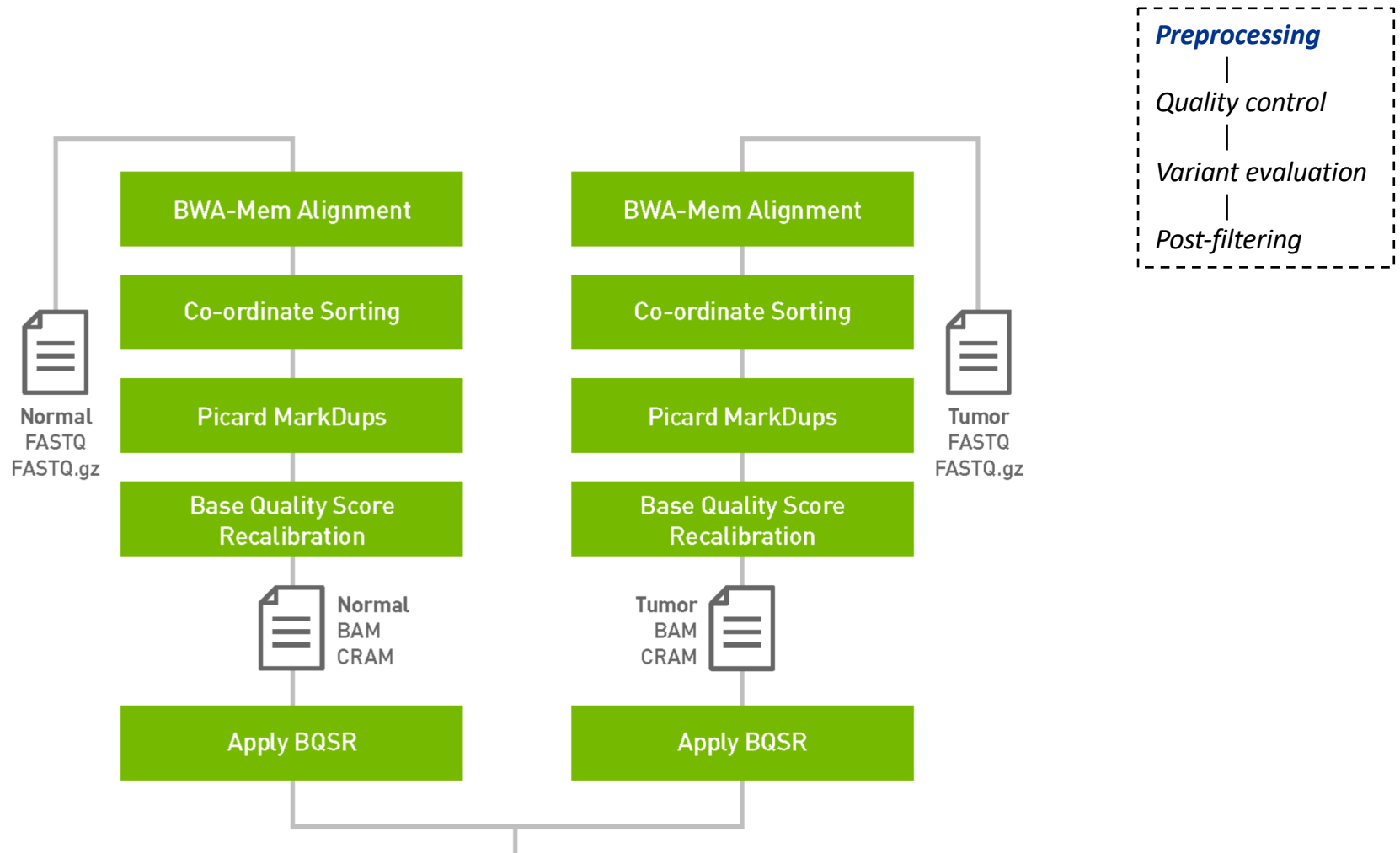
Somatic variant calling



GATK: Introduction to Somatic Variant Discovery

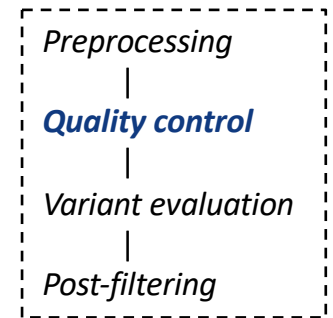


Somatic variant calling: pre-processing



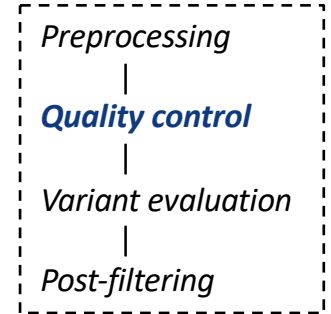
<https://docs.nvidia.com/clara/parabricks/v3.0/>

Quality control (I)

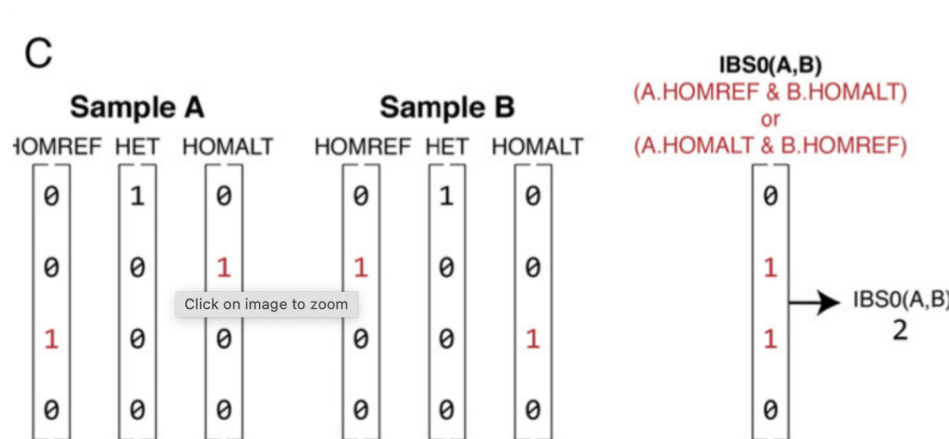


- Tumor samples subject to oxidative DNA damage during sample preparation could confound variant identification
 - Oxidation-induced C>A:G>T variants
- **Detection?**
 - Imbalance between complementary nucleotide substitutions
 - Tools: **GATK**

Quality control (II)

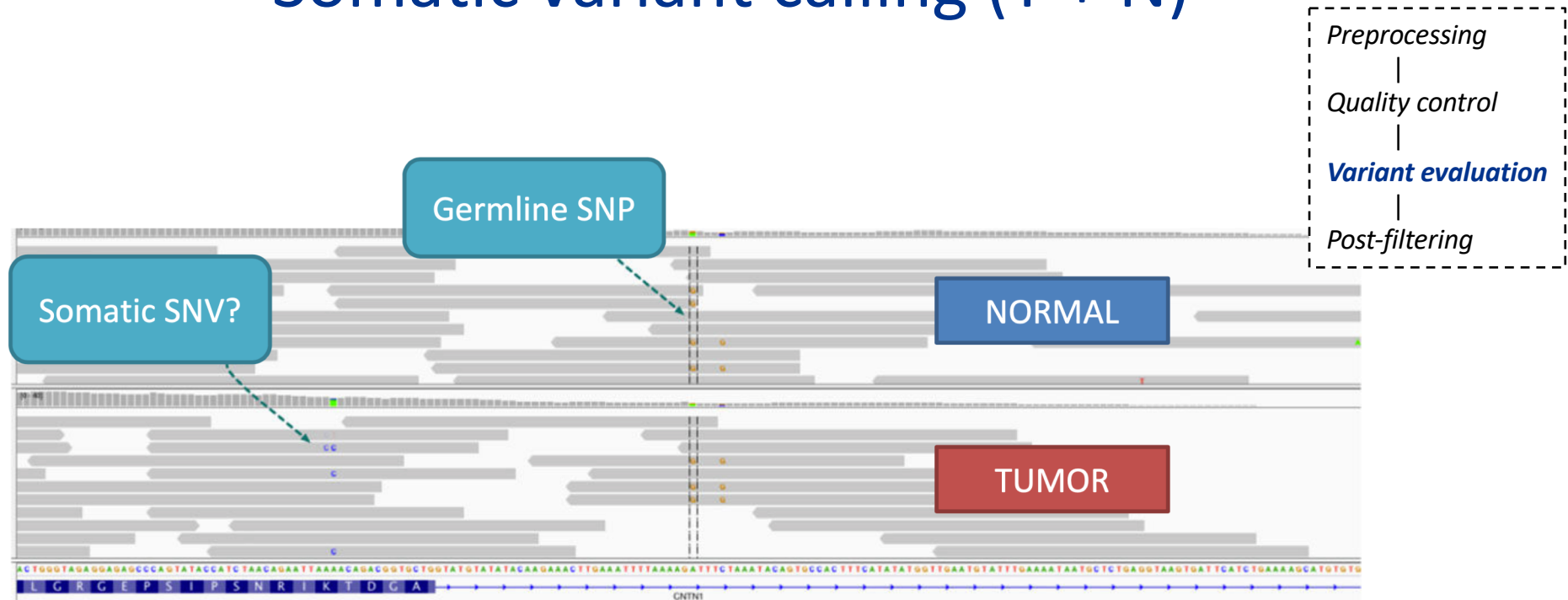


- Cross-sample contamination and sample relatedness
 - Different samples are frequently handled/sequenced together
 - Cross-individual contamination may occur, even small levels of contamination will have an impact on somatic variant detection
 - **T + N**: Check that tumor and normal sample come from the same individual!
 - Tools: **Conpair/Somalier**



Pedersen et al., Genome Med, 2020

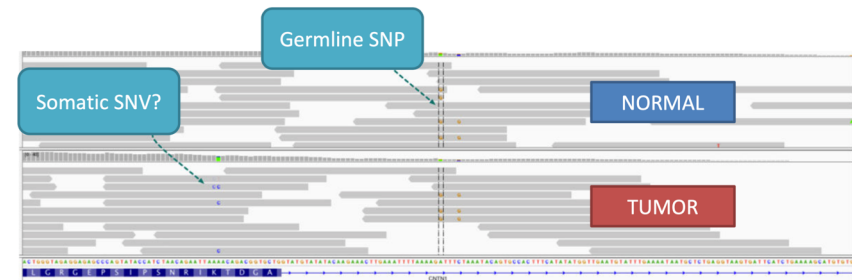
Somatic variant calling (T + N)



- Logic for somatic variant calling algorithms using tumor-normal design:
 ”subtract” the germline background
 - For a given candidate site, is the difference between tumor and normal significant?

Somatic variant calling (T + N)

- How to choose variant calling algorithm for a particular sequencing project?
 - Check out benchmarking results
 - A few benchmarking datasets are available – providing “gold sets” of somatic mutations
 - **Precision vs. recall**
 - Benchmarking results are often misleading
 - Which calling parameter values should be used?
 - Check whether the algorithm is designed for your assay and technology
 - E.g. has it shown good performance for detection of subclonal variants at low allele frequencies?

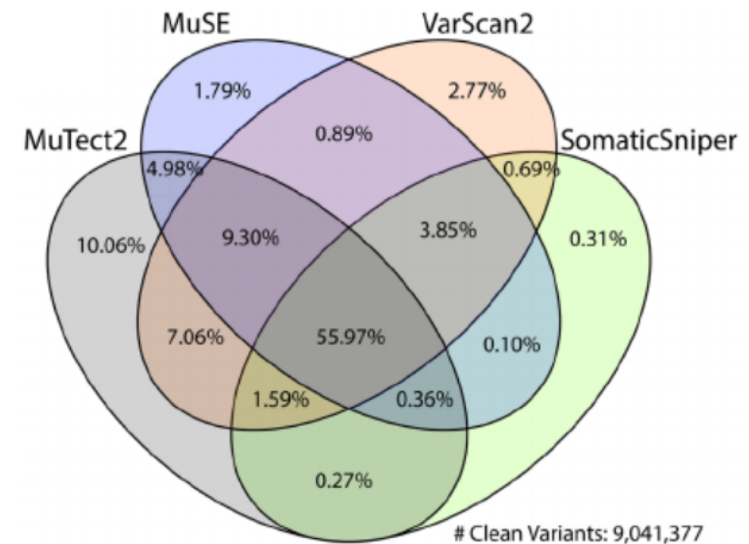


A comprehensive assessment of somatic mutation detection in cancer using whole-genome sequencing

Tyler S. Alloto, Ivo Buchhalter, Sophia Derdak, Barbara Hutter, Matthew D. Eldridge, Eivind Hovig, Lawrence E. Heisler, Timothy A. Beck, Jared T. Simpson, Laurie Tonon, Anne-Sophie Sertier, Ann-Marie Patch, Natalie Jäger, Philip Ginsbach, Ruben Drews, Nagarajan Paramasivam, Rolf Kabbe, Sasithorn Chotewutmontri, Nicole Diessi, Christopher Previti, Sabine Schmidt, Benedikt Brors, Lars Feuerbach, Michael Heindl, Susanne Gröbner, Andrey Korshunov, Patrick S. Tarpey, Adam P. Butler, Jonathan Hinton, David Jones, Andrew Menzies, Keiran Raine, Rebecca Shepherd, Lucy Stebbings, Jon W. Teague, Paolo Ribeca, Francesc Castro Giner, Sergi Beltran, Emanuele Raineri, Marc Dabad, Simon C. Heath, Marta Gut, Robert E. Denroche, Nicholas J. Harding, Takafumi N. Yamaguchi, Akihiro Fujimoto, Hidewaki Nakagawa, Victor Quesada, Rafael Valdés-Mas, Sigve Nakken, Daniel Vodák, Lawrence Bower, Andrew G. Lynch, Charlotte L. Anderson, Nicola Waddell, John V. Pearson, Sean M. Grimmond, Myron Peto, Paul Spellman, Minghui He, Cyriac Kandoth, Semin Lee, John Zhang, Louis Létourneau, Singer Ma, Sahil Seth, David Torrents, Liu Xi, David A. Wheeler, Carlos López-Otin, Elias Campo, Peter J. Campbell, Paul C. Boutros, Xose S. Puente, Daniela S. Gerhard, Stefan M. Pfister, John D. McPherson, Thomas J. Hudson, Matthias Schlesner, Peter Lichter, Roland Eils, David T. W. Jones & Ivo G. Gut - Show fewer authors

Somatic variant calling (T + N)

- How to choose variant calling algorithm for a particular sequencing project?
 - Each caller typically has some strengths and weaknesses
 - a common strategy is now to **apply multiple callers and combine the variant sets**
 - “The wisdom of crowds”
 - Consensus? Majority vote? Machine learning?
 - Combining information from VCF files/callers are frequently challenging in practice



Zhang et al., Nat Commun, 2021

Somatic variant calling: VCF

```
#CHROM POS ID REF ALT QUAL FILTER INFO FORMAT CPCT02080287R CPCT02080287T
```

```
1 854389 . G A 590 PASS
```

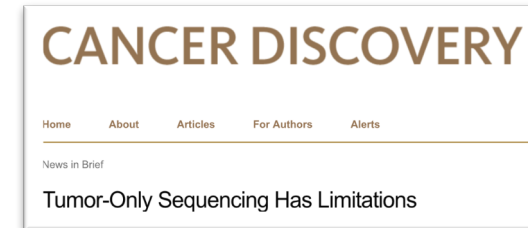
```
IMPACT=LINC02593,ENST00000609207,non_coding_transcript_exon_variant,NONE,  
E,false,n.2008C>T,,,NONE,1
```

```
GT:AD:AF:DP:RABQ:RAD:RC_CNT:RC_IPC:RC_JIT:RC_QUAL:RDP:SB 0/0:42,0:0:42:152  
8,0:42,0:0,0,0,0,0,42,42:0:0,0,0:0,0,0,0,0,1097,1097:42:0 0/1:43,20:0.317:63:1626,741:46,21:  
17,3,0,0,0,43,63:0:0,0,0:533,57,0,0,0,1318,1908:67:0.35
```

↑
*Allelic support – tumor
sample*

↑
*Allelic support – normal
sample*

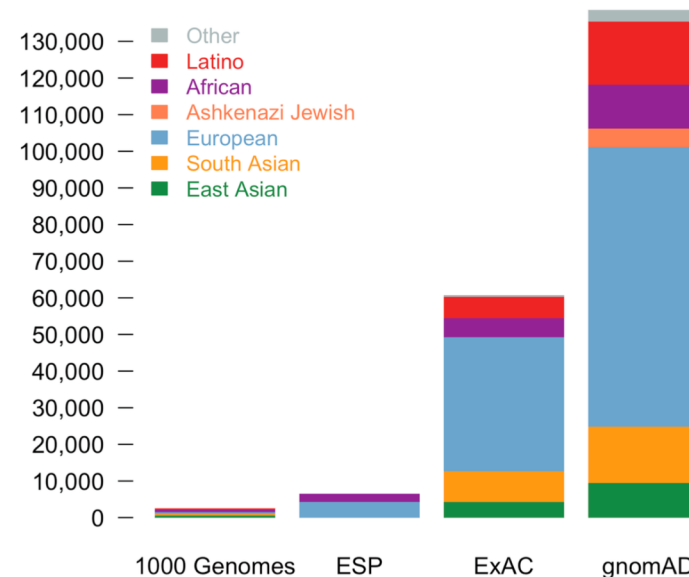
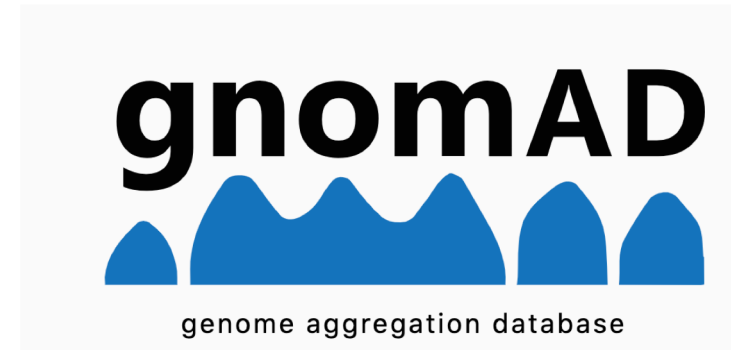
Somatic variant calling: Tumor-only



- Cost-effective strategy for identification of somatic variants – much used in the clinic
- Main challenge: robust subtraction of the germline background
 - Approach: use other sources of germline variation (databases)
 - Each individual is estimated to carry an extensive set of rare variants (i.e. *singletons*)
 - Ethnic subpopulations are under-represented in germline variant databases


Tumor-only variant filtering: gnomAD

- genome **A**ggregation **D**atabase
- **H**armonizes germline variant both exome and genome sequencing data from a wide variety of large-scale sequencing projects
- **F**reely available to the scientific community
- ~125,000 WES samples
- ~16,000 WGS samples



Tumor-only variant filtering: norgene

Norwegian Germline variants browser



Explore the Norwegian Germline variations database

Norwegian Cancer Genomics Consortiums database of normal variation in the Norwegian population. This database currently contains 1 547 121 individual variants coming from 1590 normal chromosomes of cancer patients. Genome build hg19/GRCCh37.

[Enter](#)

Based on vcf-miner from Mayo Clinic
The funding was provided by the [Center for Individualized Medicine](#) at Mayo Clinic.
[Terms and Conditions of Use](#)

norgene.no

Tumor-only variant filtering: **panel-of-normals**

- What is a «panel-of-normals (PON)»?
 - Variant calls made from a set of unrelated “normal” samples
- Purpose of PON?
 - Eliminate common/recurring technical artifacts
 - should use normals made using the same data generation techniques (e.g. same capture kit for exomes, same sequencing platform etc.)
 - Secondary purpose: also eliminates germline variants not called in the matched normal (or approximates the normal if none is available)

Somatic variant calling: summary

- The complexity of tumors pose challenges for variant identification – intratumor heterogeneity, tumor purity, ploidy
- WGS – WES – Targeted sequencing (research → clinic)
- Two fundamental sequencing designs: Tumor-control and tumor-only
- Multiple calling algorithms exist – each with strengths and weaknesses - a common strategy is to combine output from several callers
- Benchmarking results exist – can they be generalized?
- Understand the nature of your data/tumor and the priorities of the variant identification procedure when choosing a calling strategy

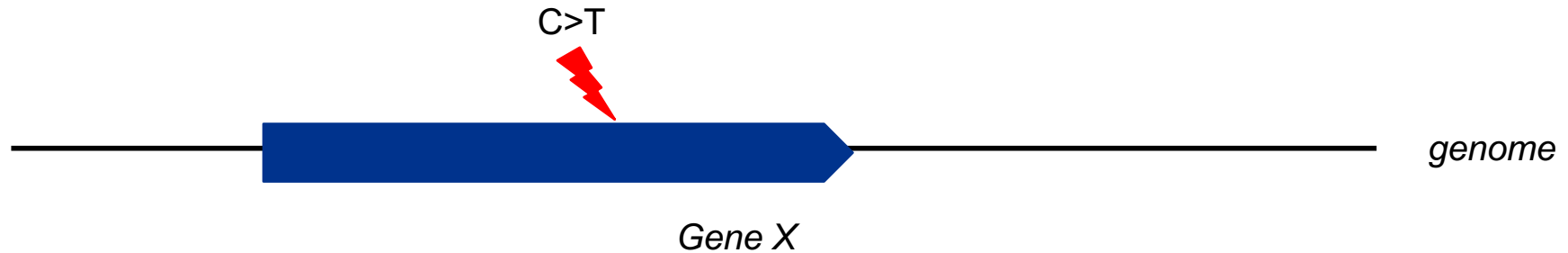
Variants have been found – now what?

ACTG**C**CTACGTCTCACCGTCGACTTCAAATCG**C**TTAACCCGTACTCCCATGCTACTGC
ATCTCGGGTAACTCGACGTTTT**T**CATGCATGTGTGCACCCCAATATATATGCA**A**CTT
TTGTGCACCTCTGTCACGCGGAGTTGGCACTGTGCCCCCTGTGTGCATGTGCACTGT
CTC**T**CGCTGCACTGCCTACGTCTCACCGTCGACTTCAAATCG**C**TTAACCCGTACTCCC
ATGCTACTGCATCTCGGGTAACTCGACGTTTT**G**CATGCATGTGTGCACCCCAATATA
TATGCA**A**CTTTTGTGCACCTCTGTCACGCGGAGTTGGCACTGTGCCCCCTGTGTGCA
TGTGCACTGTCTC**T**CGAGTTTT**G**CATGCATGTGTGCACTGTGCACCTCTGTTACGTCT



QUESTIONS/BREAK

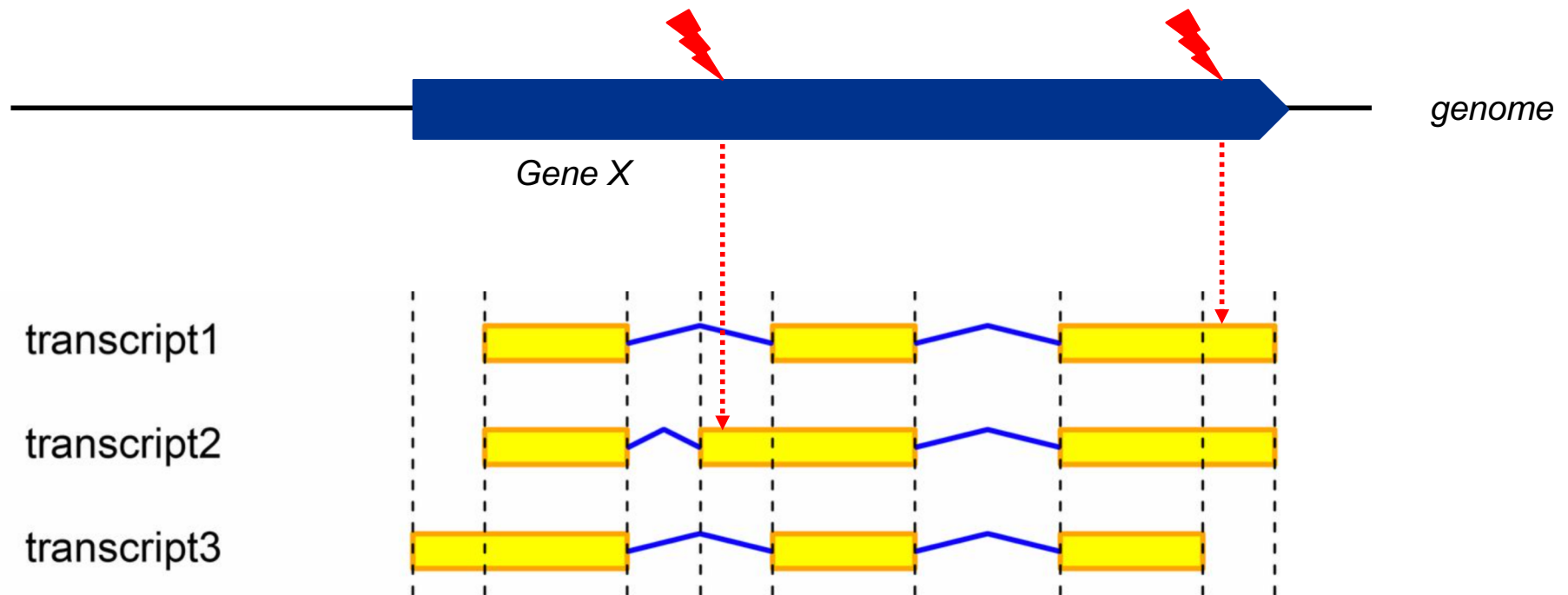
Variant interpretation - general



1. Which genes are affected by variants?
2. For a given gene variant, what is the consequence for the encoded protein?
 - Loss-of-function?

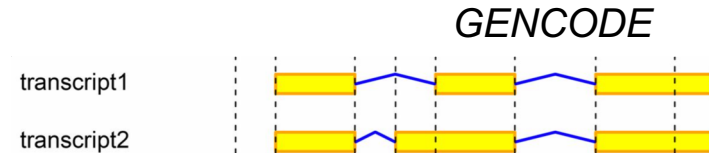
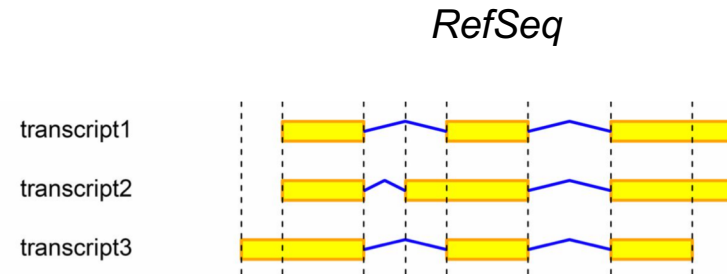
Variant interpretation - general

- A gene consists of multiple transcript isoforms



Variant interpretation – general (II)

- Several transcript databases
 - RefSeq
 - Ensembl
 - GENCODE
- Choice of transcript database impacts variant consequence/annotation
- Frequent strategy: Report variant consequence in most commonly expressed isoform (i.e. *principal* isoform)



Ve!P

Variant interpretation - cancer

- Variant interpretation for cancer precision medicine
 - Where are the mutations located (**which genes** are mutated, and which variants are most relevant)?
 - **Therapeutic markers** (diagnosis and prognosis)
 - Germline (predisposing) + somatic
 - **What types** of mutations are found?
 - **Mutational signatures**
 - Tumor etiology, therapeutic and diagnostic markers
 - **How many** mutations are found?
 - **Tumor mutational burden** - immunotherapy



Personal Cancer Genome Reporter

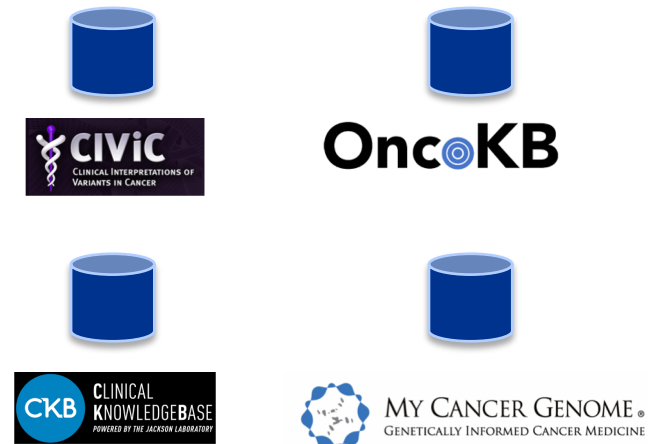


Cancer Predisposition Sequencing Reporter

Which genes are mutated? (I)

- Specific genetic aberrations indicate clinical actionability
 - **Drug sensitivity**
 - Prognosis / Diagnosis
 - Drug resistance
- Multiple initiatives curate clinical variant associations in cancer
 - **Variant X** in **phenotype Y** indicates sensitivity to **drug Z**
 - **Challenge:** harmonization of knowledge databases
 - VICC (Variant Interpretation for Cancer Consortium)

- *HER2 amplification – Trastuzumab – Breast Cancer*
- *BRAF V600E – Vemurafenib – Melanoma*
- *BRAF V600E – Trametinib + Dabrafenib – NSCLC*
- *IDH1/2 mutations – Ivosidenib – AML*
- ..
- ..



Which genes are mutated? (II)

- Which somatic aberrations are most relevant in my tumor sample (actionability)?

- Ranking and standardization frameworks - tiers
- Key: **Strength of evidence**
- Tumor type (**on-label** vs. **off-label**)

- **TIER 1** – strong evidence for clinical impact, same tumor type as query
- **TIER 2** – strong evidence for clinical impact in other tumor type or weak evidence for clinical impact in query tumor type
- **TIER 3** – uncertain clinical significance; coding variants in tumor suppressor genes/proto-oncogenes (mutation hotspots etc)
- **TIER 4** – other coding variants

SPECIAL ARTICLE | VOLUME 29, ISSUE 9, P1895-1902, SEPTEMBER 01, 2018

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

J. Mateo • D. Chakravarty • R. Dienstmann • S. Jezdic • A. Gonzalez-Perez • N. Lopez-Bigas • C.K.Y. Ng • P.L. Bedard • G. Tortora • J.-Y. Douillard • E.M. Van Allen • N. Schultz • C. Swanton • F. André • L. Pusztai • Show less

SPECIAL ARTICLE | VOLUME 19, ISSUE 1, P4-23, JANUARY 01, 2017

Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer

A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists

Marilyn M. Li • Michael Datto • Eric J. Duncavage • Shashikant Kulkarni • Neal I. Lindeman • Somak Roy • Apostolia M. Tsimberidou • Cindy L. Vnencak-Jones • Dayna J. Wolff • Anas Younes • Marina N. Nikiforova • Show less

How many mutations are found?

- **Tumor mutational burden (TMB)** - number of somatic mutations per megabase of interrogated genomic sequence
- A key driver in the generation of immunogenic neopeptides – influences **response to immune checkpoint inhibitors (ICIs)**

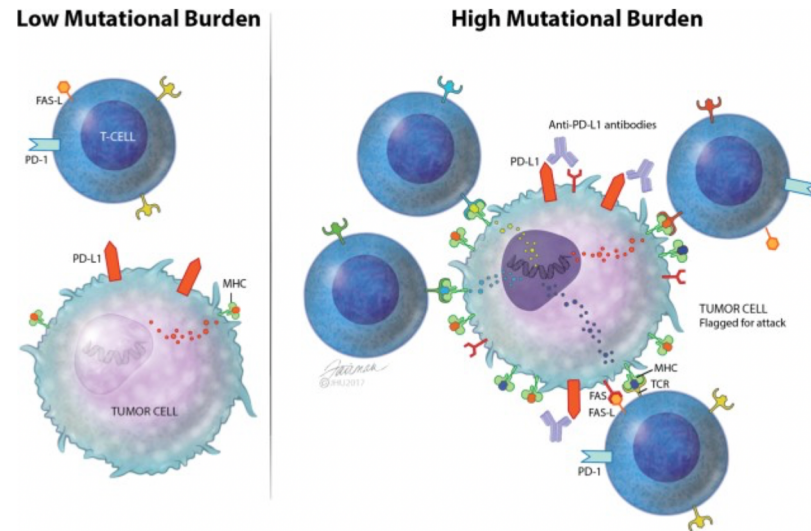


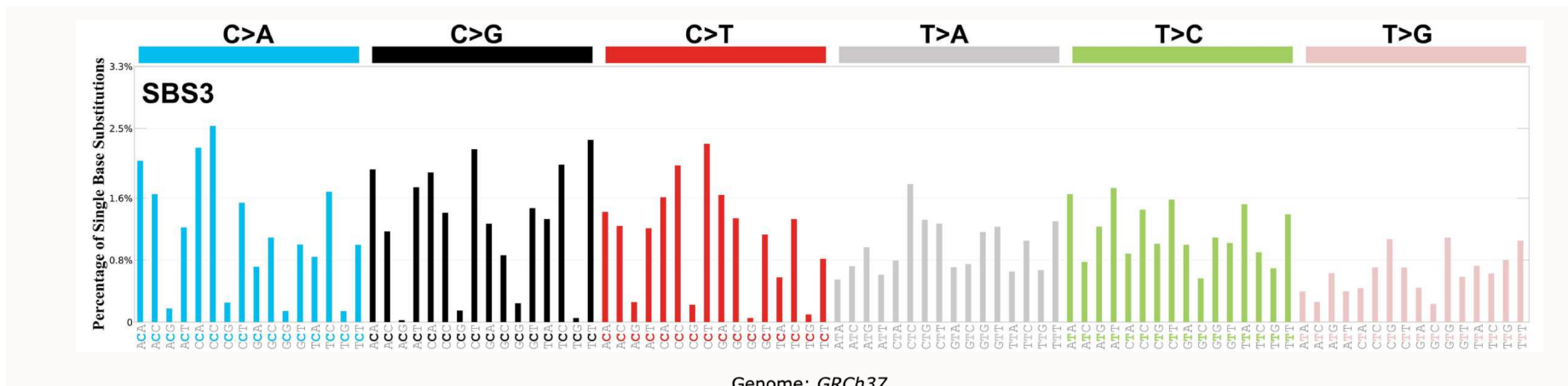
Illustration from Sharabi et al., The Oncologist (2017)

What types of mutations are found?

- **Mutational signatures:** characteristic mutation patterns (types and sequence context) that arise from a specific mutational process
- **Premise:** mutational processes are context-dependent (occur non-randomly in DNA)
- **Footprint:** The global set of mutations harvested from NGS **reveals a «historical footprint»** of the mutational processes that have shaped a given tumor
 - Environmental mutagens
 - Endogenous mutation processes (e.g. DNA repair defects)
 - Treatment effects
 - **Approximatly 50 established mutational signatures**

Mutational signatures (I)

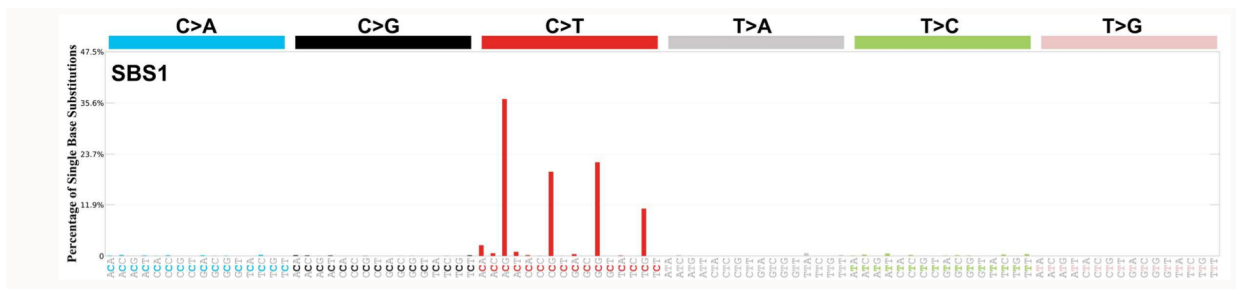
- Mutational signatures are most commonly presented through the **96-channel** approach (single base substitutions, SBS)
 - Mutation type + flanking bases



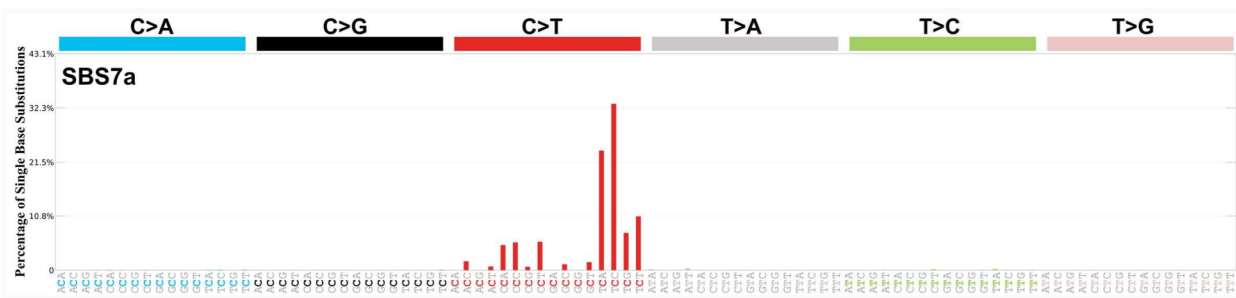
- A single signature (attributed to a given process) is thus characterized as the **relative frequency of 96 different channels**

Mutational signatures (II)

- Aging
 - spontaneous or enzymatic deamination of 5-methylcytosine to thymine (clock-like signature)

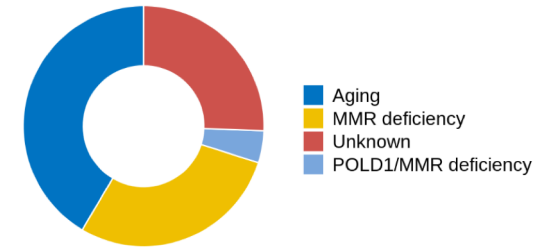


- Exposure to UV light
 - cyclobutane pyrimidine dimers or 6-4 photoproducts



Mutational signatures (III)

- Tools can «deconstruct» the profile of somatic mutations in a tumor towards contribution of known signatures
- Signatures are emerging as an important biomarker for drug response
- Often considered in combination with other markers
- Challenge: **confidence**



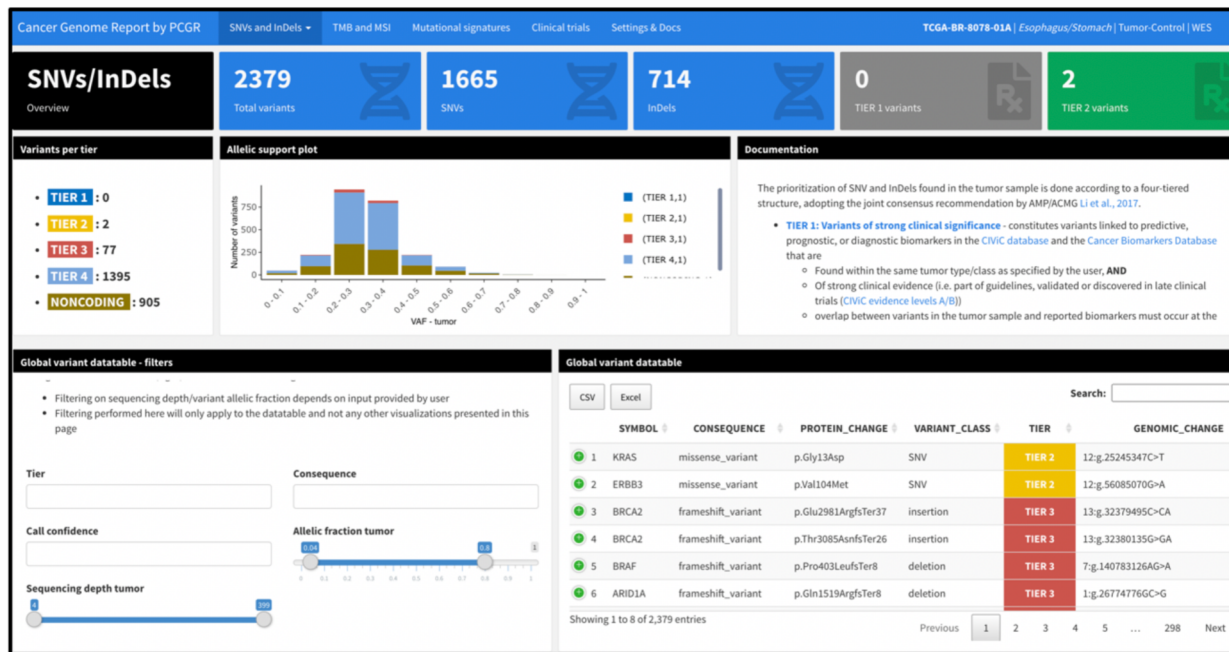
		CS-3	CS-8	Homologous Recombination Repair Deficiency	PARP inhibition ³²⁻³⁴ , Platinum-based chemotherapy ³⁵⁻³⁷
CS-6	CS-15	CS-20	CS-26	Mismatch Repair Deficiency	PD1-immunotherapy ^{48-49,52}
		CS-5	CS-8	Nucleotide Excision Repair Deficiency	Cisplatin ⁶³⁻⁶⁵
		CS-18	CS-30	Base excision Repair Deficiency	
			CS-10	Deficient DNA polymerase proofreading activity	PD1-immunotherapy ^{48-49,52}

Adopted and modified from Van Hoeck et al., BMC Cancer, 2019

Personal Cancer Genome Reporter (I)



- In brief: A reporting engine for clinical interpretation of tumor genomes (VCF → interactive report)



Nakken et al., Bioinformatics, 2017

<https://github.com/sigven/pcgr>



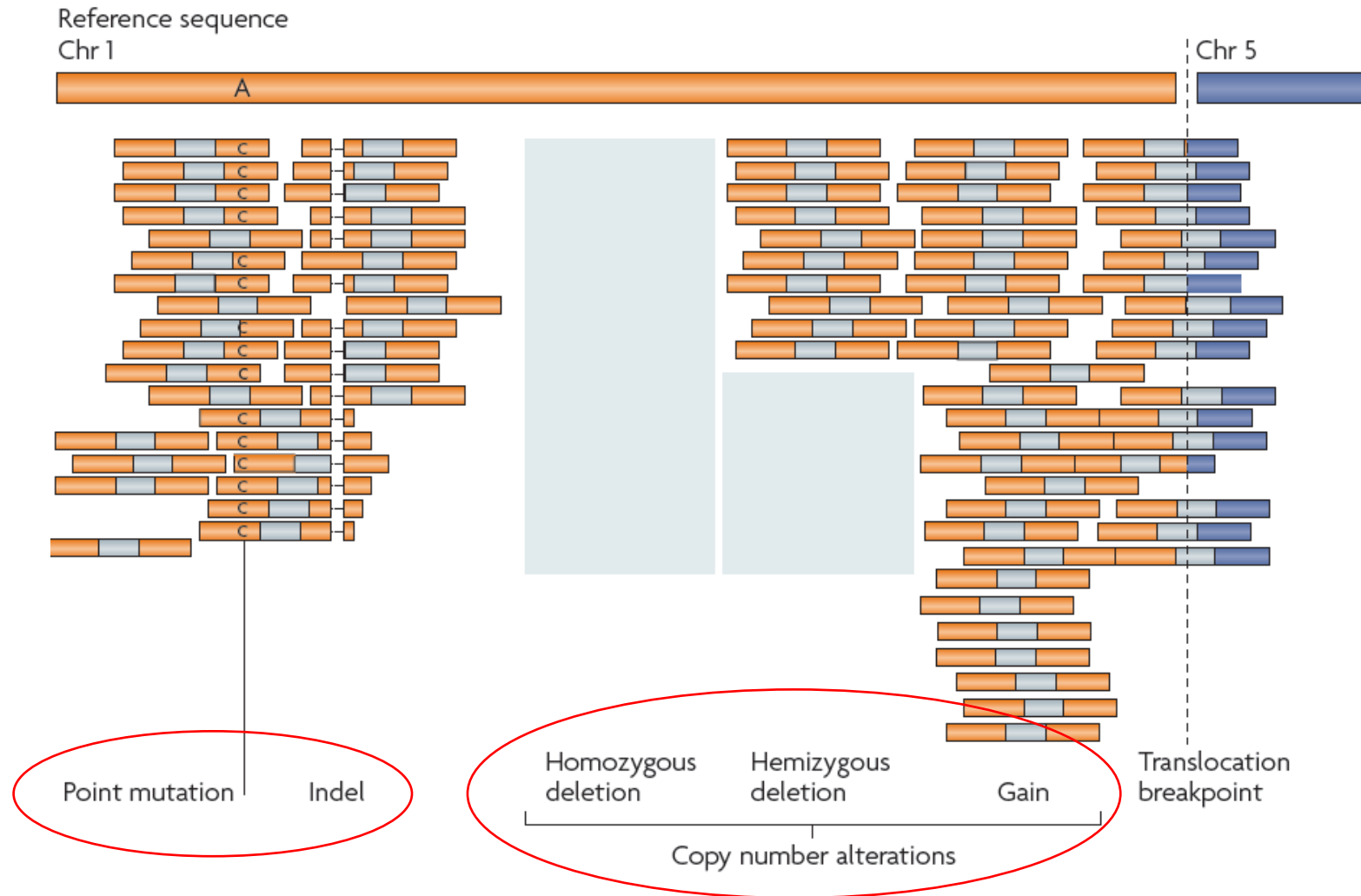
Personal Cancer Genome Reporter (II)



- PCGR captures current knowledge on cancer precision medicine through **data integration** of publicly available databases
 - Targeted cancer drugs
 - Known biomarkers for prognosis and diagnosis
 - Known biomarkers for drug sensitivity/resistance
 - Mutational hotspots in cancer
 - ++



Personal Cancer Genome Reporter (III)



Meyerson et al. Nat Rev Genet 2010

Personal Cancer Genome Reporter (IV)



Cancer Genome Report by PCGR | SNVs and InDels | sCNA | TMB and MSI | Mutational signatures | Clinical trials | Settings & Docs | TCGA-EW-A1J5-01A | Breast | Tumor-Control | WGS

TIER 2 SNVs and InDels | **1** Biomarker genes | **1** Biomarker variants | **0** Diagnostic evidence items | **1** Prognostic evidence items | **6** Predictive evidence items

Tier 2 variant evidence items - filters

Evidence items associated with variants in TIER 2 (right panel) can be interactively explored according to various criteria:

Cancer type **Consequence**

Clinical significance **Evidence type**

Evidence level

Rating

Biomarker mapping

Therapeutic context

NOTE: Reported biomarkers in CIVIC/CGI are mapped at different resolutions (i.e. filter **Biomarker mapping**). The accuracy of a match between variants in the tumor sample and the reported biomarkers will vary accordingly (highlighted by gene symbols with different color backgrounds):

- Biomarker match at the **exact variant/codon level**
- Biomarker match at the **exon/gene level**

Tier 2 - variant evidence items

CSV Excel Search:

	SYMBOL	PROTEIN_CHANGE	CANCER_TYPE	EVIDENCE_LEVEL	CLINICAL_SIGNIFICANCE	EVIDENCE_TYPE
1	PIK3CA	p.Glu545Lys	Lung Adenocarcinoma	B: Clinical evidence	Resistance	Predictive
3	PIK3CA	p.Glu545Lys	Her2-receptor Positive Breast Cancer	D: Preclinical evidence	Resistance	Predictive
5	PIK3CA	p.Glu545Lys	Her2-receptor Positive Breast Cancer	D: Preclinical evidence	Resistance	Predictive
7	PIK3CA	p.Glu545Lys	Her2-receptor Positive Breast Cancer	D: Preclinical evidence	Resistance	Predictive

Showing 1 to 4 of 4 entries (filtered from 7 total entries) Previous 1 Next



Personal Cancer Genome Reporter (IV)



Cancer Genome Report by PCGR
SNVs and InDels ▾
sCNA ▾
TMB and MSI
Mutational signatures
Clinical trials
Settings & Docs
TCGA-14-0866-01B | CNS/Brain | Tumor-Control | WES

SCNA

Overview

7

Copy number gains

50

Copy number losses

1

TIER 1 biomarkers

6

TIER 2 biomarkers

Copy number segments - filters

The following user-defined thresholds determine copy number aberrations shown here:

- Copy number amplifications** : Log(2) ratio ≥ 0.4
- Homozygous deletions** : Log(2) ratio ≤ -0.4

A total of **57** unfiltered aberration segments satisfied the above criteria.

- A total of **57** copy number segments satisfy the current filtering criteria.

Log-ratio

(range: -6.208 to 3.471)

Cytoband

Event type

Copy number segments

CSV
Excel
Search:

	SEGMENT	SEGMENT_LENGTH_MB	CYTOBAND	LOG_R	EVENT_TYPE
1	chr7:54942675-55577616	0.63494	chr7:p11.2	3.471	focal
2	chr7:24039878-24040383	0.0005	chr7:p15.3	2.207	focal
3	chr7:705284-24035127	23.32984	chr7:p22.3 - p15.3	0.476	broad
4	chr7:24126318-52647610	28.52129	chr7:p15.3 - p12.1	0.465	broad
5	chr7:82610187-158385118	75.77493	chr7:q21.11 - q36.3	0.462	broad
6	chr7:63112265-82605569	19.4933	chr7:q11.21 - q21.11	0.453	focal
7	chr20:455764-62219837	61.76407	chr20:p13 - q13.33	0.452	broad

Showing 1 to 10 of 57 entries

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Key findings

- Proto-oncogenes subject to amplifications: **28**
- Tumor suppressor genes subject to homozygous deletions: **19**
- Other drug targets subject to amplification: **18**

Documentation

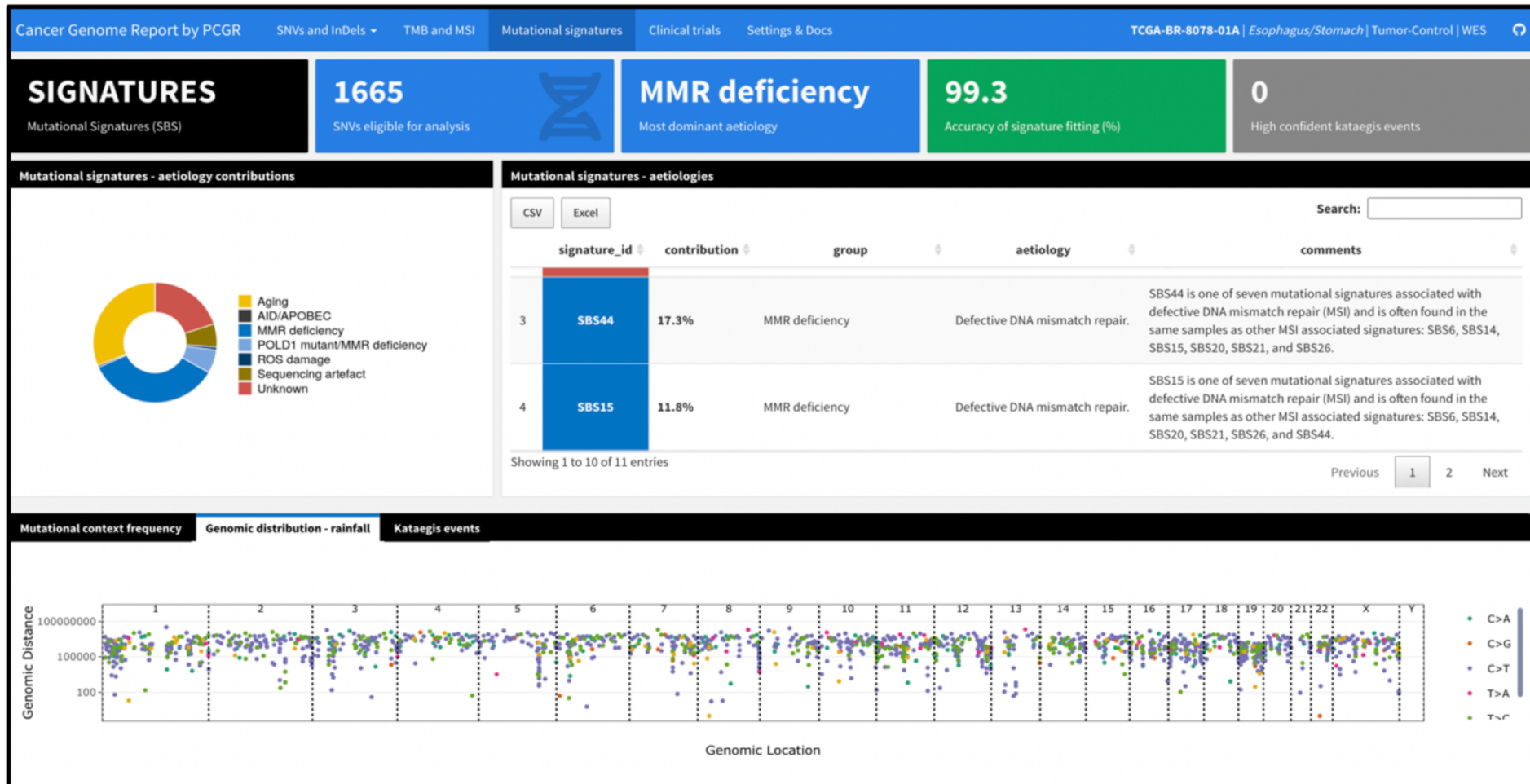
Somatic copy number aberrations identified in the tumor sample are classified into **two main tiers**:

- TIER 1: Aberrations of strong clinical significance** - constitutes amplified/lost genes linked to predictive, prognostic, or diagnostic biomarkers in the [CIVIC database](#) and the [Cancer Biomarkers Database](#) that are
 - Found within the same tumor type/class as specified by the user, **AND**
 - Of strong clinical evidence (i.e. part of guidelines, validated or discovered in late clinical trials ([CIVIC evidence levels A/B](#)))
- TIER 2: Aberrations of potential clinical significance** - constitutes amplified/lost genes linked to predictive, prognostic, or diagnostic biomarkers in the [CIVIC database](#) and the [Cancer Biomarkers Database](#) that are either
 - Of strong clinical evidence in other tumor types/classes than the one specified by the user, **OR**
 - Of weak clinical evidence (early trials, case reports etc. ([CIVIC evidence levels C/D/E](#)))) in the same tumor type/class as specified by the user

Included in the report is also a complete list of [all oncogenes subject to amplifications](#), [tumor suppressor genes subject to homozygous deletions](#), and [other drug](#)



Personal Cancer Genome Reporter (IV)



Personal Cancer Genome Reporter (IV)



Cancer Genome Report by PCGR SNVs and Indels ▾ sCNA ▾ TMB and MSI Mutational signatures Clinical trials Settings & Docs TCGA-BR-8078-01A | Esophagus/Stomach | Tumor-Control | WES

Clinical trials (Beta)

Molecularly targeted trials

116
Not yet recruiting

437
Recruiting

10
Enrolling by invitation

67
Active, not recruiting

1
Unknown status

Molecularly targeted trials - filters

(e.g. inclusion/exclusion criteria) attempts to highlight the presence of established molecular biomarkers in cancer and relevant therapeutic contexts.

Condition (cancer subtype)

Status

Drug(s)

Drug target(s)

Therapeutic context mentions (text-mined)

ER Positive, HER2 Negative, HR deficiency/PARPi, Immunotherapy, PR Positive, Radiotherapy

Biomarker mentions (text-mined)

Phase

Gender

All
 Female
 Male

Minimum age

Maximum age

Metastases mentions (text-mined)

Molecularly targeted trials

CSV Excel
Search:

NCT_ID	TITLE	OVERALL_STATUS	CONDITION	KEYWORD	INTERVENTION	PHASE	START_DATE
464	NCT02734004 A Phase I/II Study of MEDI4736 in Combination With Olaparib in Patients With Advanced Solid Tumors.	Active, not recruiting	Malignant Gastric Neoplasm	ER Positive, HER2 Negative, HR deficiency/PARPi, Immunotherapy, PR Positive, Radiotherapy	Bevacizumab , Durvalumab , Olaparib	1.5	2016-03-17

PRIMARY_COMPLETION_DATE 2022-08-05

CONDITION_RAW Malignant Gastric Neoplasm

INTERVENTION_RAW Bevacizumab, Durvalumab, Olaparib

INTERVENTION_TARGET CD274, PARP1, PARP2, PARP3, VEGFA

BIOMARKER_INDEX ATM mutation, BARD1 mutation, BRCA1 mutation, BRCA2 mutation, BRIP1 mutation, CDK12 mutation, CHEK1 mutation, HER2 gene mutation, HER2 mutation, HER2 negative

METASTASES_INDEX Bone Metastases|Brain Metastases

GENDER All

MINIMUM_AGE 18

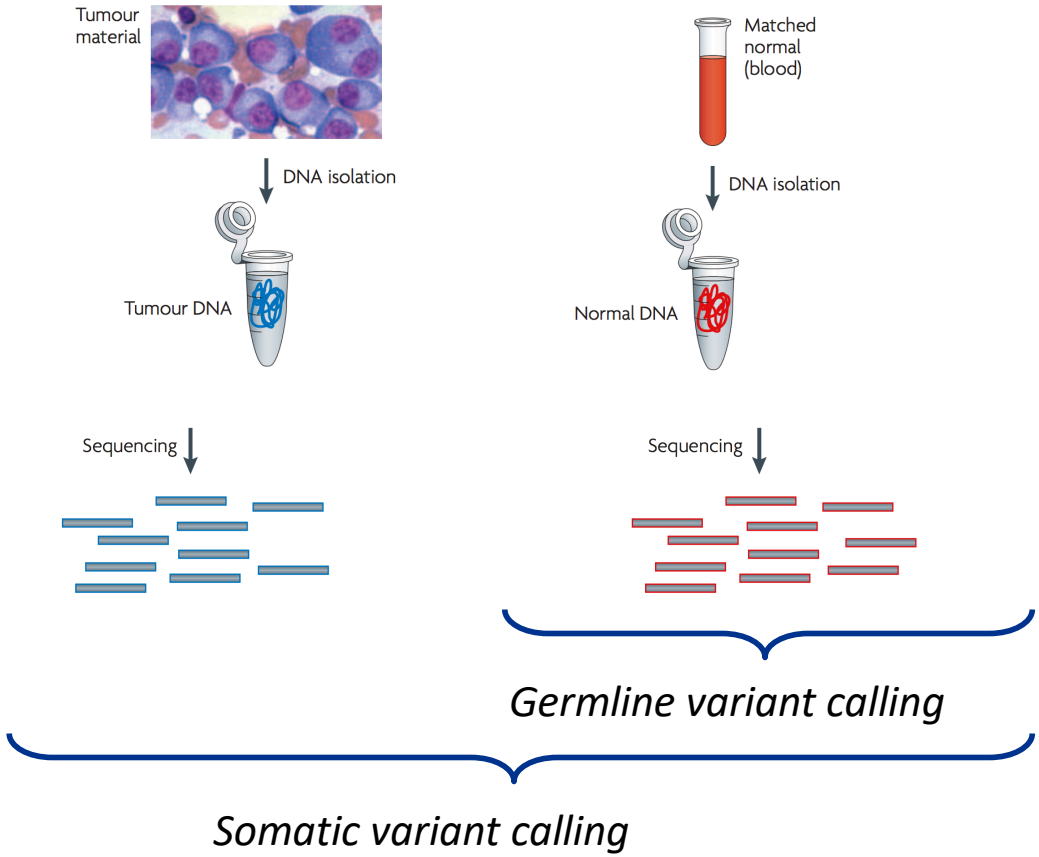
MAXIMUM_AGE 100

Showing 1 to 1 of 1 entries (filtered from 644 total entries)

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Cancer patients - germline background



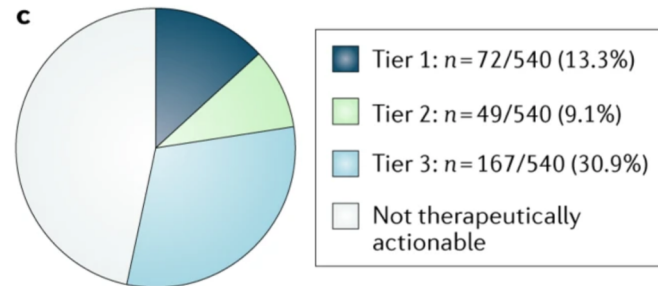
Cancer predisposition interpretation

- Goal: Identify pathogenic variants (germline) conferring increased risk of tumor development
- Why important?
 - Implement surveillance and risk-reducing interventions
 - May impact type of surgery (radical /conservative)
 - Targeted therapy implications
 - BRCA (PARP)



Review Article | Published: 19 February 2019

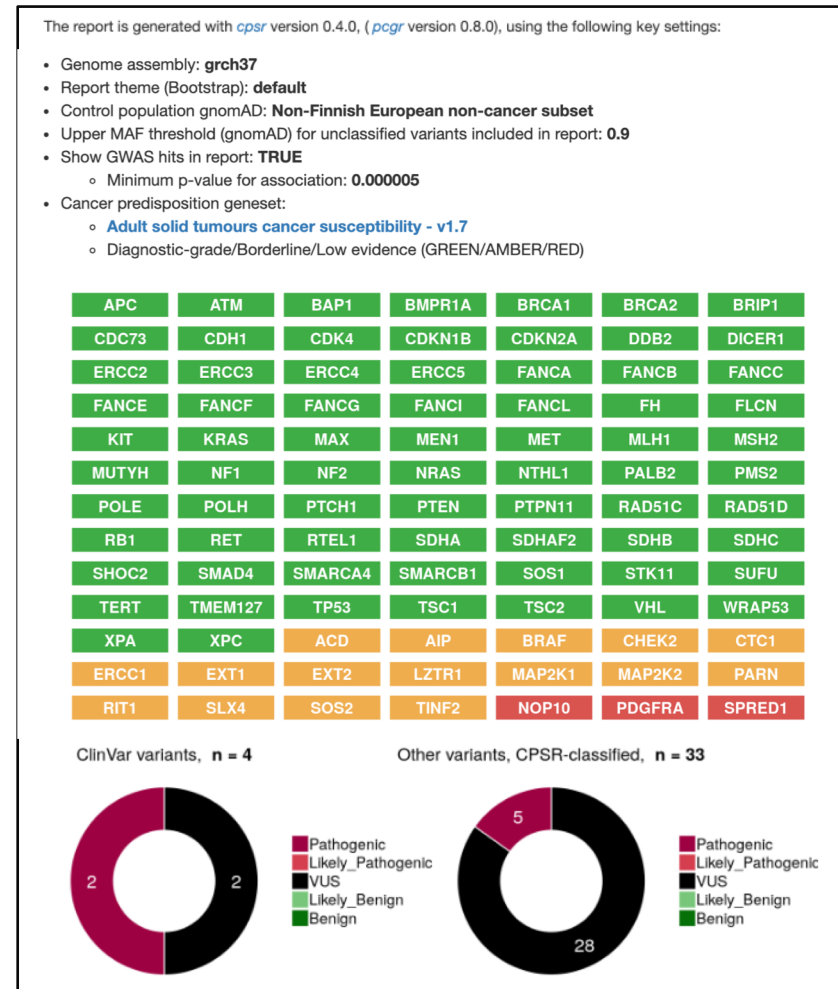
Therapeutic implications of germline genetic findings in cancer



Clinical actionability - TCGA

Cancer Predisposition Sequencing Reporter

- **CPSR:** Flexible reporting tool for interpretation of sequencing screens for cancer predisposition
- Which germline variants confer risk of tumor development? Tier structure
 - Pathogenic
 - Likely pathogenic
 - Unclassified variants
 - Likely Benign
 - Benign
- Automated pathogenicity classification
 - Predicted loss-of-function
 - population allele frequency
 - ++
- Incidental findings can also be reported



Cancer Predisposition Sequencing Reporter



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Class 5 - Pathogenic variants

- A total of n = 5 variants are registered with a *Pathogenic* clinical significance in ClinVar.
- A total of n = 4 *non-ClinVar* variants (i.e. not registered in ClinVar) are classified with a *Pathogenic* significance by CPSR (ACMG criteria - based on population frequency and variant effect).

ClinVar

Consequence

Genotype heterozygous

Gene

CPSR classification (ACMG criteria codes)

CPSR pathogenicity score

MAF gnomAD (Non-Finnish European non-cancer subset)

Search:

	SYMBOL	SOURCE	CONSEQUENCE	PROTEIN_CHANGE	GENOTYPE	GENE_NAME	
+	1	POLE	Other	frameshift_variant	p.Lys1170AsnfsTer49	heterozygous	DNA polymerase epsilon, catalytic subunit
+	4	POLD1	Other	frameshift_variant	p.Arg180GlyfsTer3	heterozygous	DNA polymerase delta 1, catalytic subunit

Showing 1 to 2 of 2 entries (filtered from 4 total entries) Previous Next

Nakken et al., Int J Cancer, 2021

<https://github.com/sigven/cpsr>



Cancer Predisposition Sequencing Reporter



- Flexible reporting tool for interpretation of sequencing screens for cancer predisposition
- Which germline variants confer risk of tumor development? Tier structure
 - Pathogenic
 - Likely pathogenic
 - Unclassified variants
 - Likely Benign
 - Benign
- Automated pathogenicity classification
 - Predicted loss-of-function
 - population allele frequency
 - ++
- Incidental findings can also be reported

Genomic biomarkers

- Variants (class 4/5) in the query sample that overlap with reported clinical biomarkers from the [database for clinical interpretations of variants in cancer, CIVIC](#) are considered. Note that several variants in the query can overlap the same existing biomarker, given that biomarkers are reported at different resolutions (variant/gene level). Total number of clinical evidence items that coincide with query variants:
 - Predisposing: 1 evidence items
 - Predictive: 2 evidence items
 - Prognostic: 0 evidence items
 - Diagnostic: 0 evidence items

Predisposing Predictive Prognostic Diagnostic

Cancer type

Gene

Clinical significance

Biomarker mapping

Evidence level

Therapeutic context

The table below lists all variant-evidence item associations:

CSV Excel Search:

	SYMBOL	GENE_NAME	CANCER_TYPE	CLINICAL_SIGNIFICANCE	EVIDENCE_LEVEL
1	NF1	neurofibromin 1	Plexiform Neurofibroma	Sensitivity/Response	B: Clinical evidence
2	POLE	DNA polymerase epsilon, catalytic subunit	Glioblastoma Multiforme	Sensitivity/Response	C: Case study

Showing 1 to 2 of 2 entries Previous 1 Next

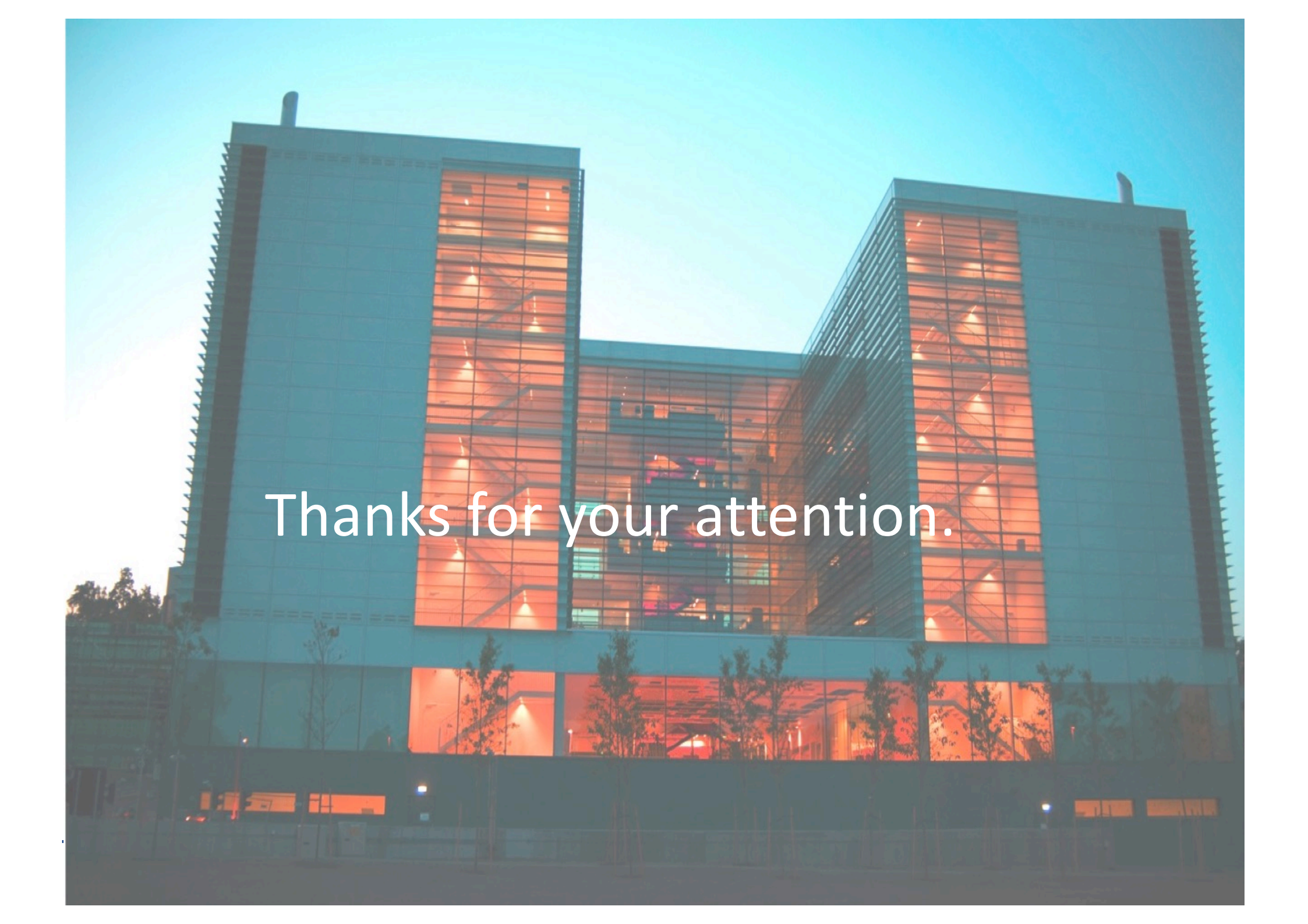
Nakken et al., Int J Cancer, 2021

<https://github.com/sigven/cpsr>



Variant interpretation in cancer: summary

- Comprehensive DNA variant interpretation is critical for implementation of precision cancer medicine
- Types of mutations, number of mutations, mutation locations – all may have therapeutic implications
- Variant consequences are transcript-specific
- A large number of resources have been erected to facilitate clinical interpretation of cancer genomes
- Variant prioritization: tier structure
- Interpretation of the germline background of cancer patients adds an additional dimension for clinical interpretation

A photograph of a modern, multi-story building at dusk. The building features a prominent glass facade that is illuminated from within, creating a warm, orange glow. The sky is a deep blue, and the overall scene is captured in a cinematic style. The text "Thanks for your attention." is overlaid in white, centered on the image.

Thanks for your attention.