

Somatic variant calling and interpretation in the context of cancer

Sigve Nakken

Centre for Cancer Cell Reprogramming (CanCell)

Dept. of Tumor Biology

Institute for Cancer Research

Oslo University Hospital

Centre for Bioinformatics

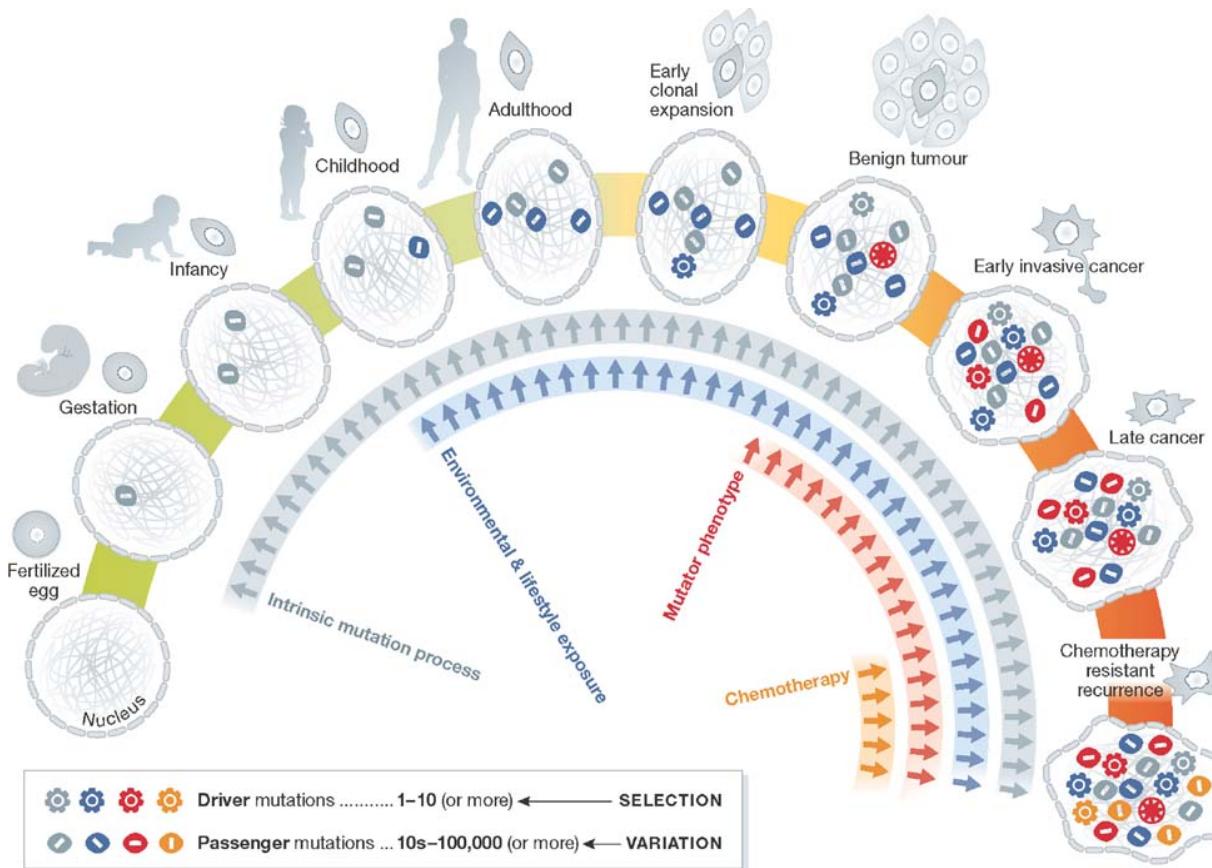
Department of Informatics

University of Oslo

IN-BIOS 5000/9000 – Fall 2022

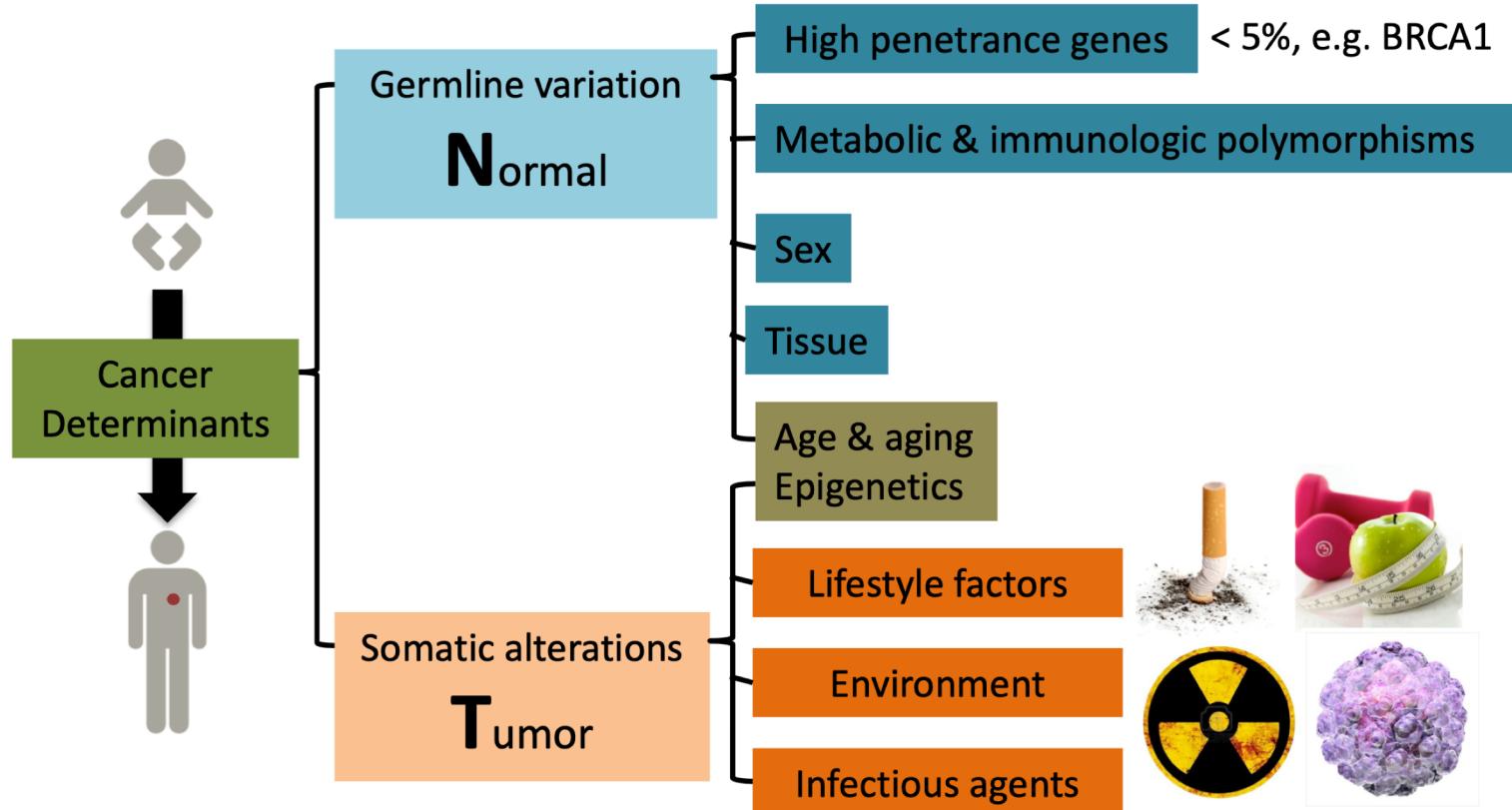
Why cancer?

Cancer – a disease of the genome



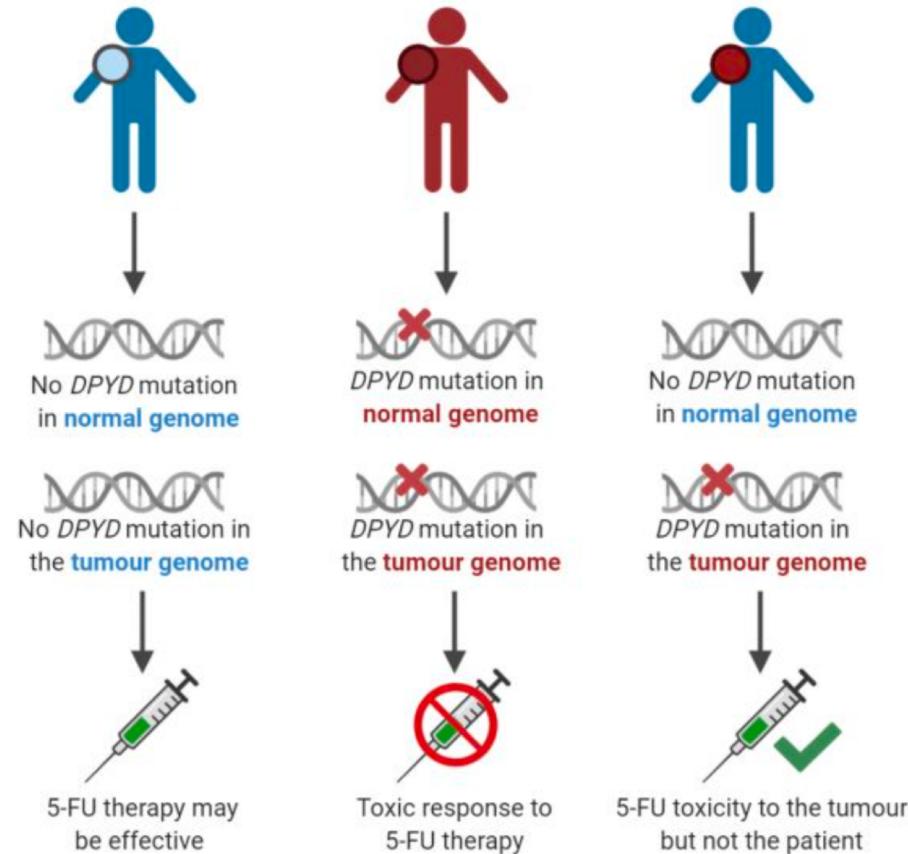
Stratton et al., EMBO Mol Med, 2013

Cancer – a disease of the genome



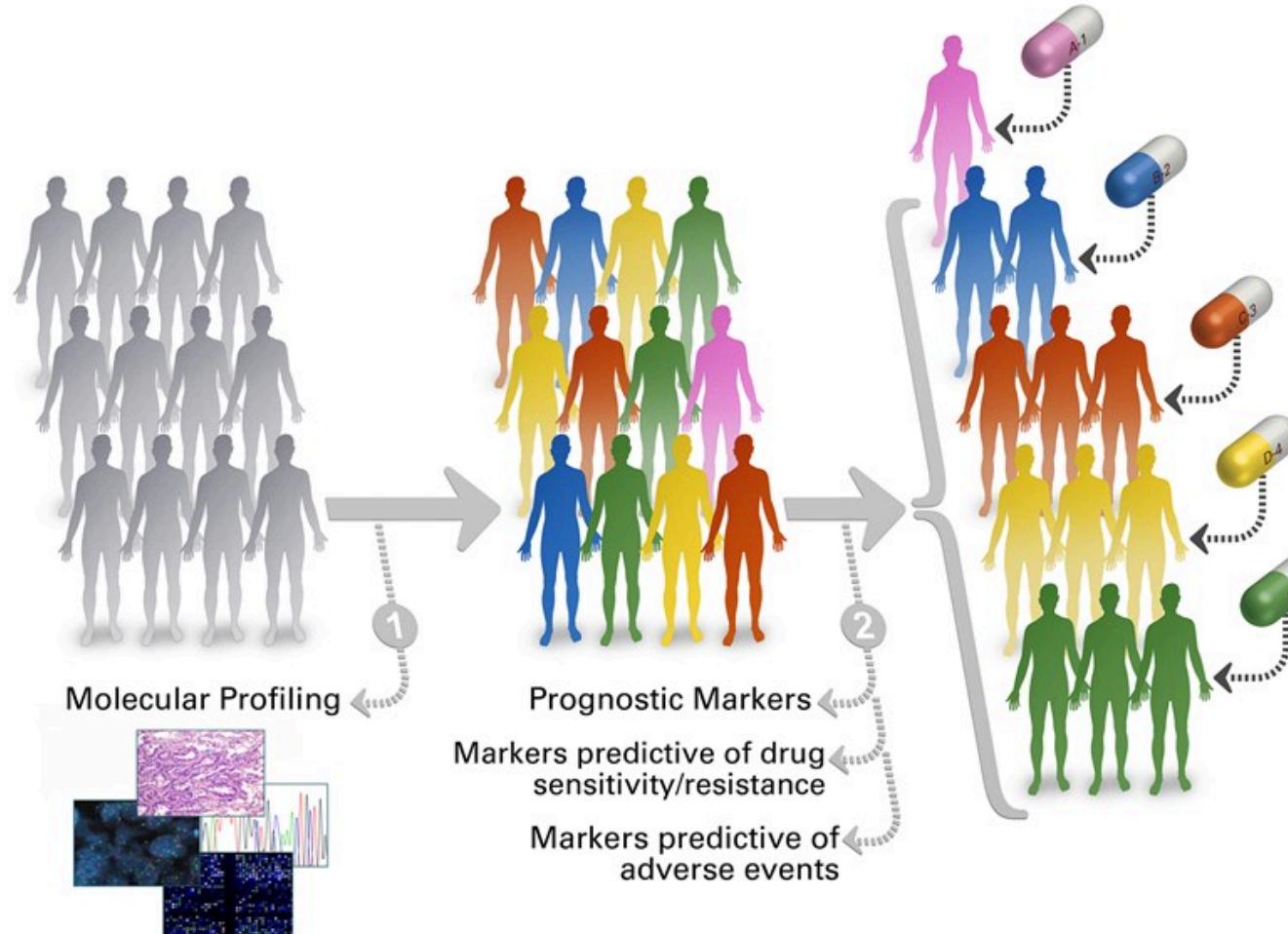
GATK: Introduction to Somatic Variant Discovery

Cancer sequencing informs on treatment options

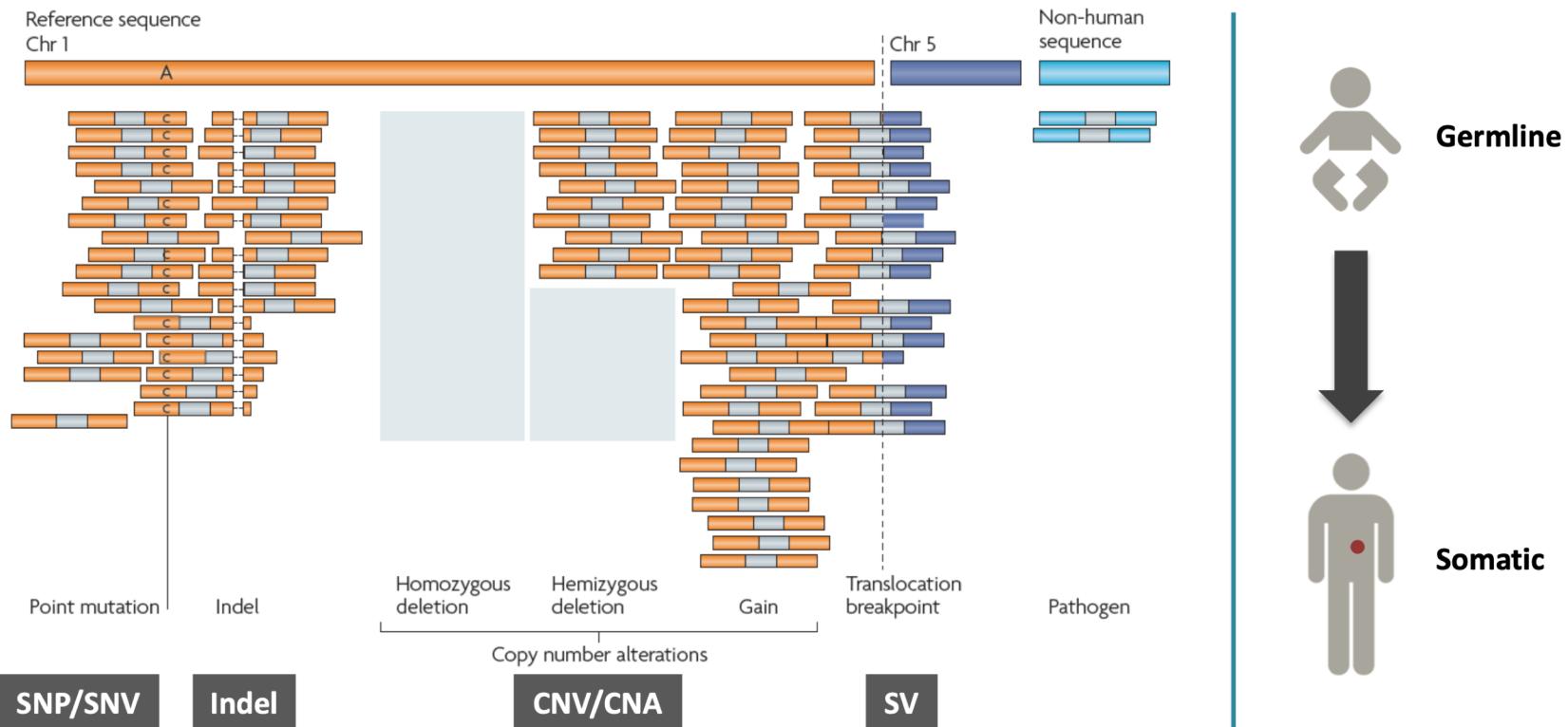


<https://www.bcgsc.ca/news/genome-sequencing-helps-prioritize-cancer-treatment-options>

Precision cancer medicine



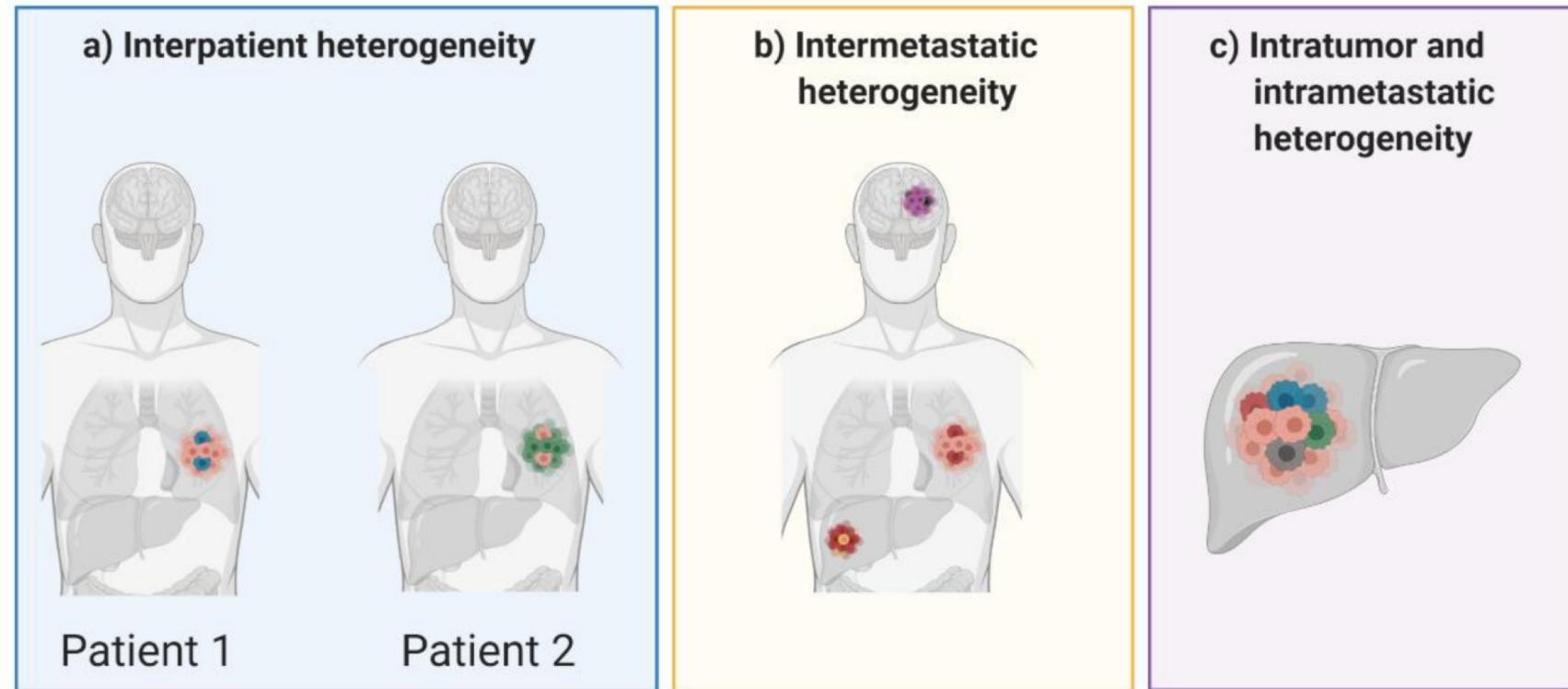
Cancer: multiple types of DNA aberrations



GATK: Introduction to Somatic Variant Discovery

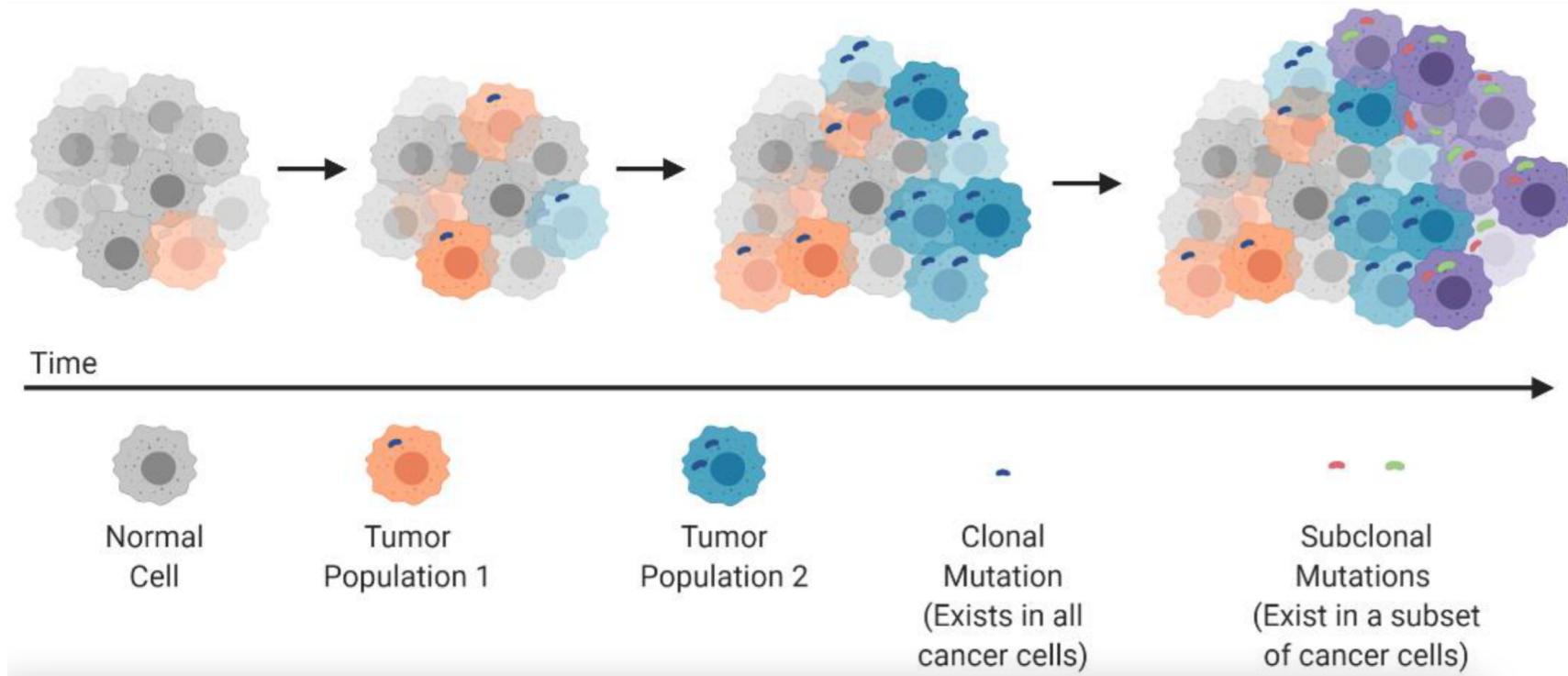
Why is somatic variant calling so challenging?

Cancer complexity



El-Sayes et al., Cancers, 2021

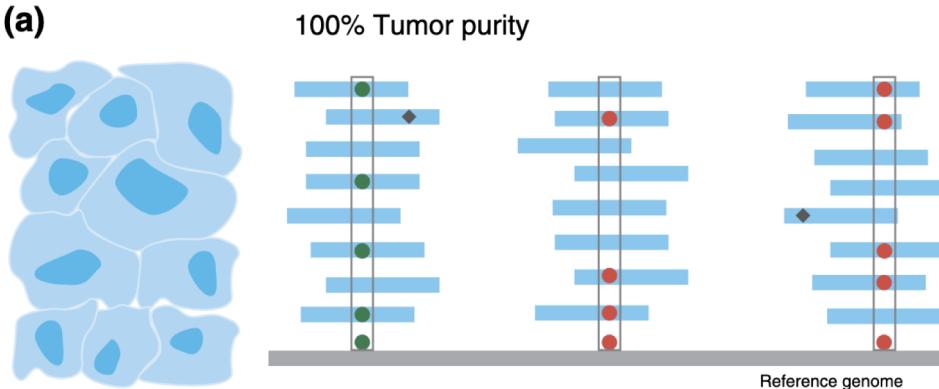
Tumor purity and heterogeneity (I)



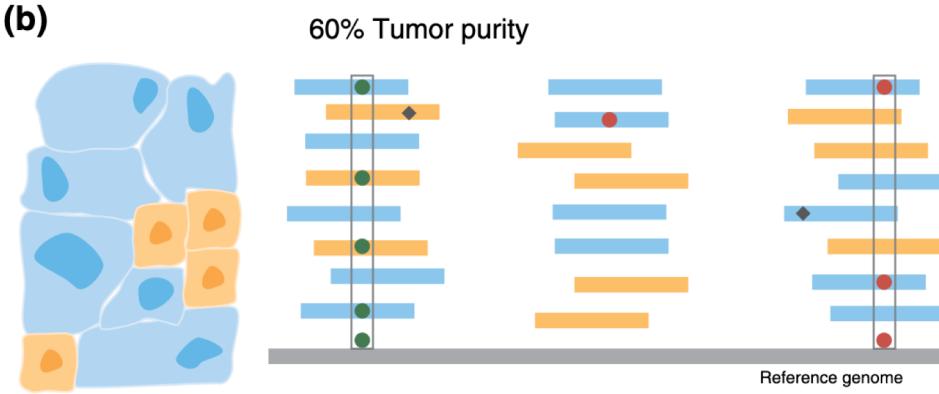
El-Sayes et al., Cancers, 2021

Tumor purity and heterogeneity (II)

(a)



(b)



Key:

Read

Sequencing
error

Heterozygous
germline SNV

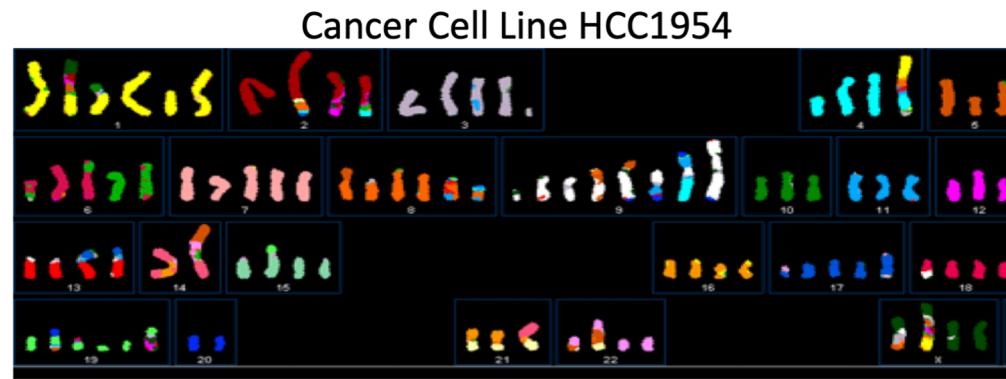
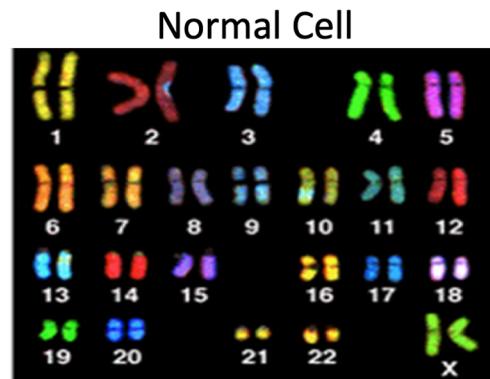
Heterozygous
somatic SNV

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

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

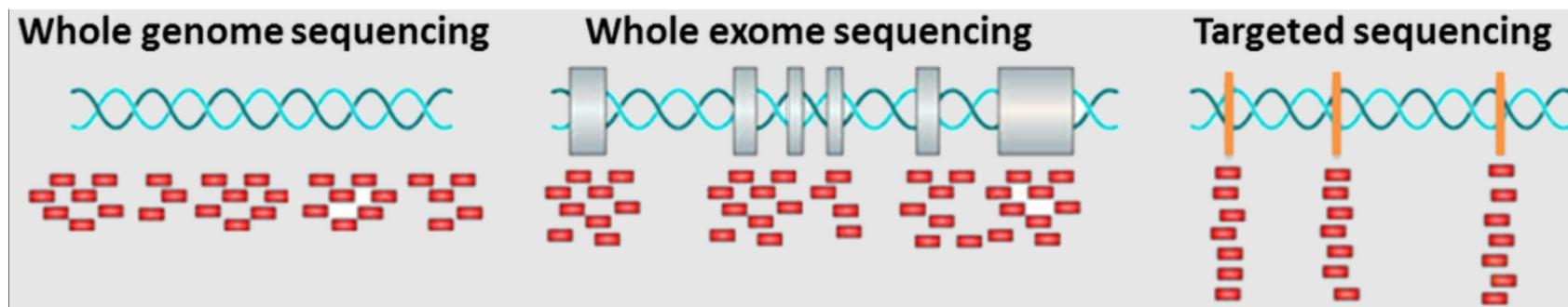
Raphael et al., Genome Med, 2014

Tumor ploidy



- Somatic variant calling: make no ploidy assumption!

Cancer sequencing: assay design

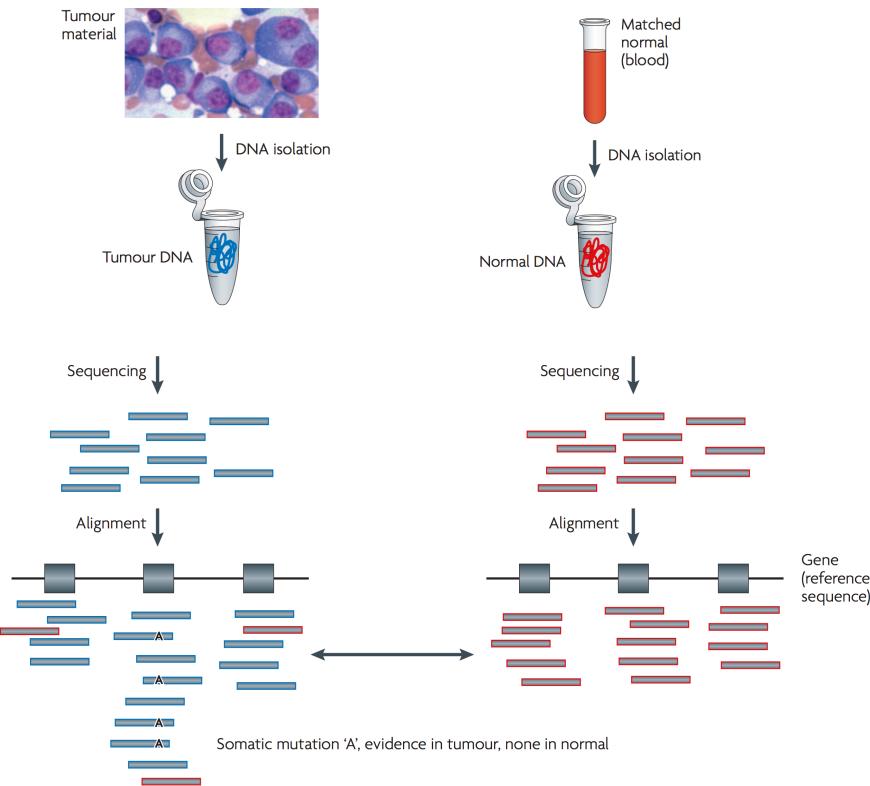


- Typically 30-40x coverage
- More even coverage than WES
- Covers coding and non-coding/regulatory variation
- All types of variants (reliable detection of SVs)
- Typically 80-100x coverage
- Coding regions only
- Cost-effective
- Typically > 300X coverage – captures subclonal variants at low allele frequencies
- Targets custom genes/regions – e.g. clinically actionable genes
- Most cost-effective

Research ← → *Clinical applications*

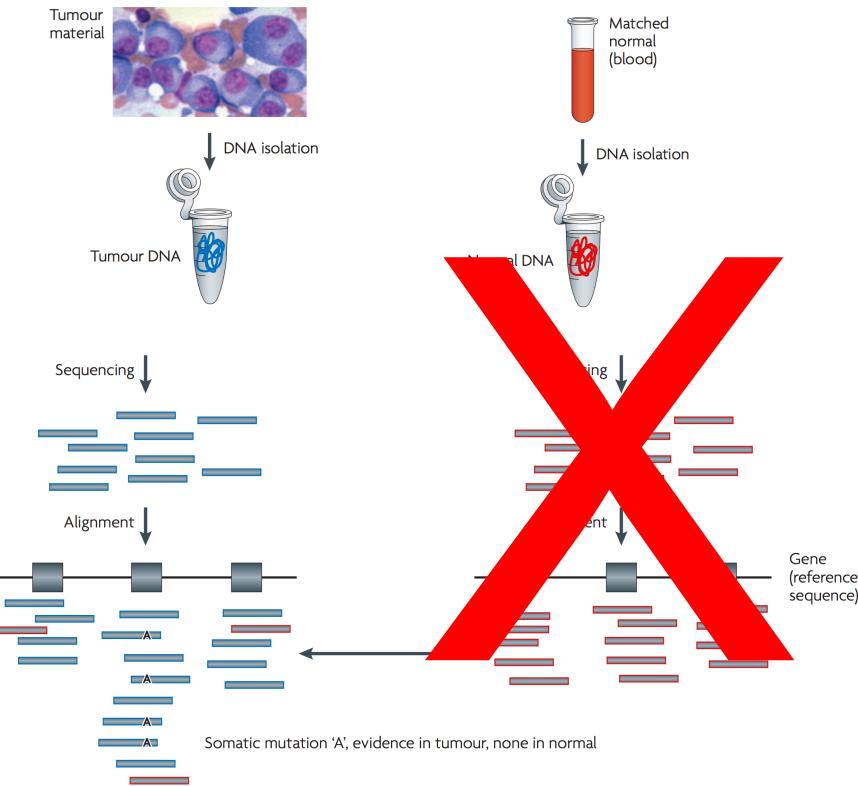
Cancer sequencing: calling design

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

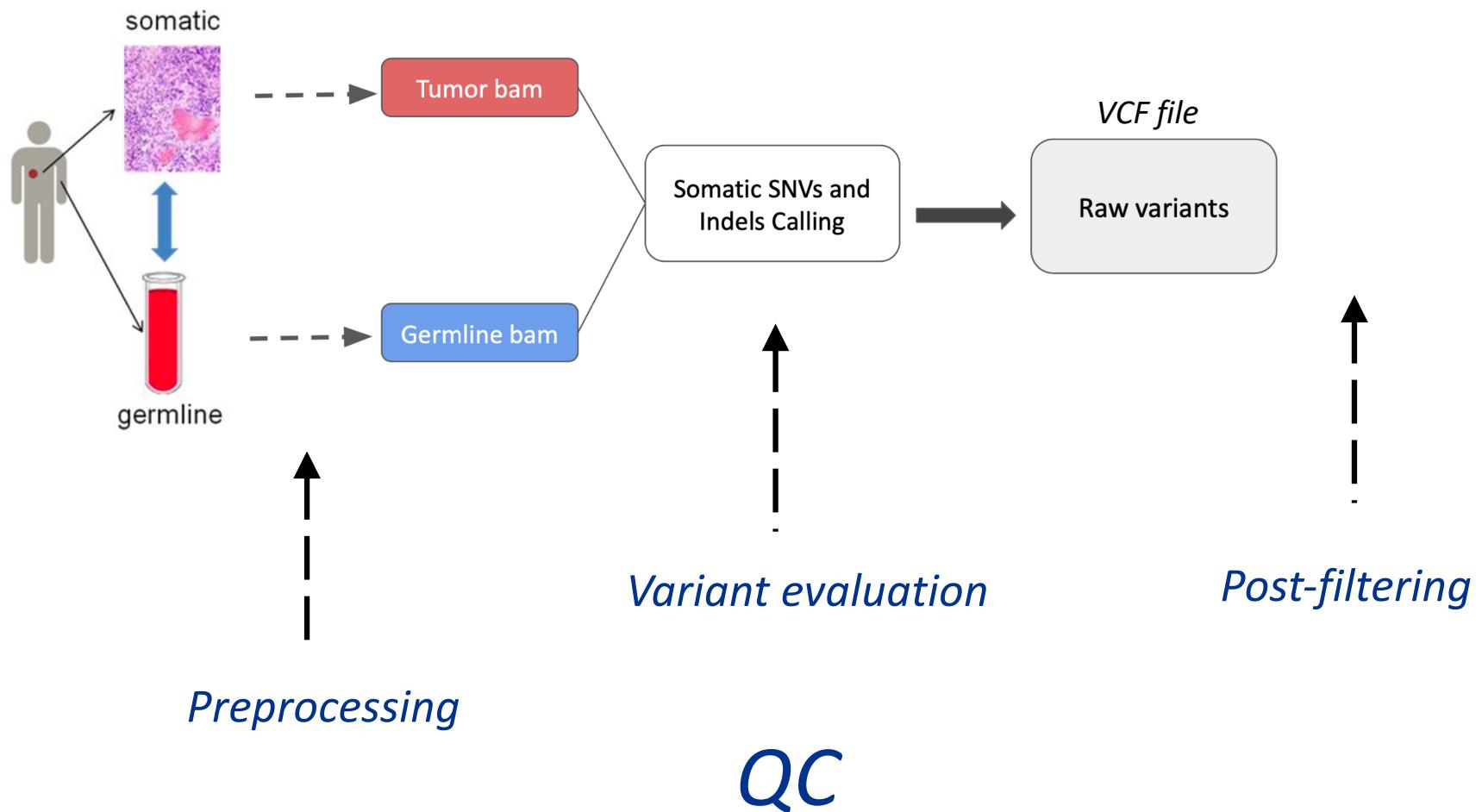


Cancer sequencing: calling design

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

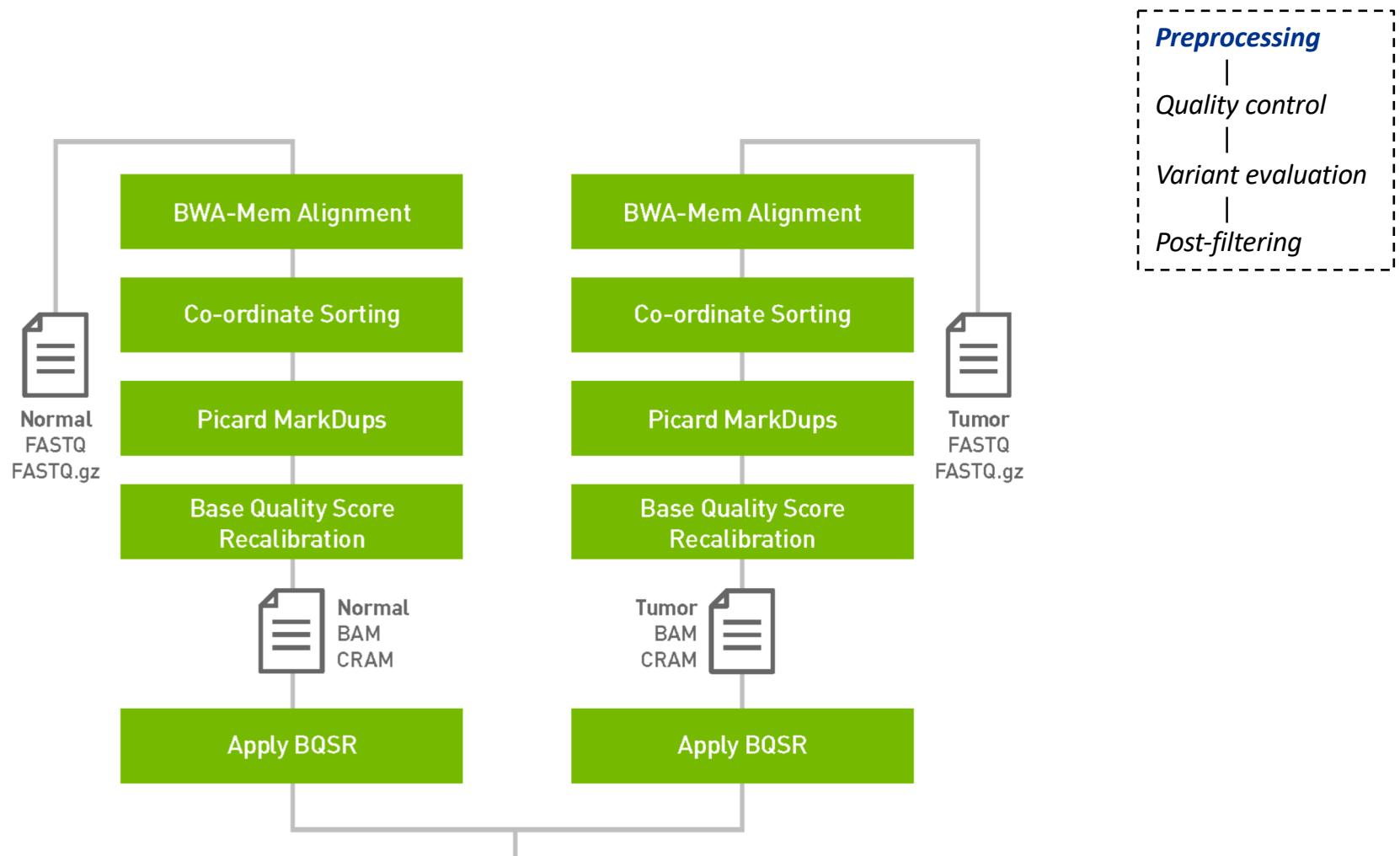


Somatic variant calling



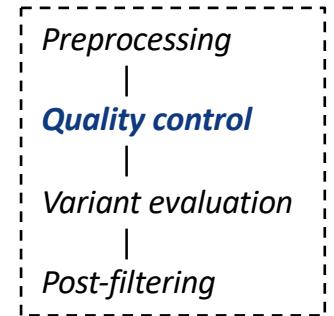
GATK: Introduction to Somatic Variant Discovery

Somatic variant calling: pre-processing



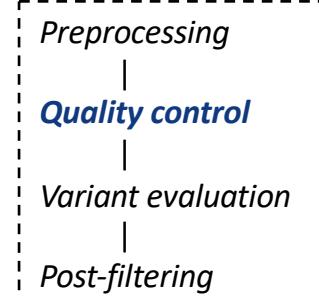
<https://docs.nvidia.com/clara/parabricks/v3.0/>

Quality control (I)

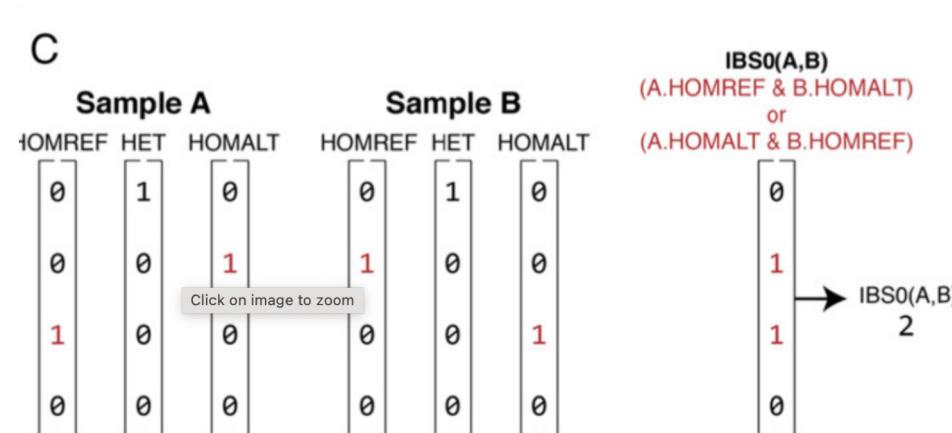


- Tumor samples subject to oxidative DNA damage during sample preparation could confound variant identification
 - Oxidation-induced C>A:G>T variants
- Detection?
 - Imbalance between complementary nucleotide substitutions
 - Tools: **GATK**

Quality control (II)

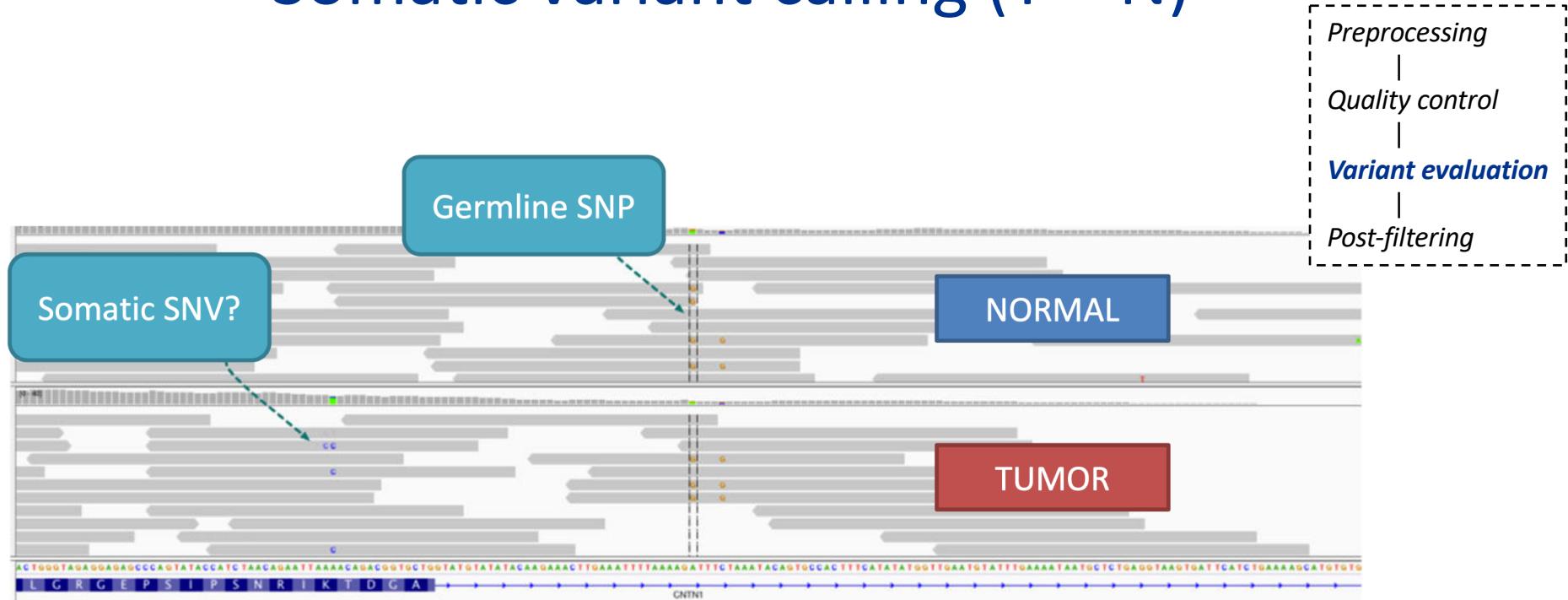


- Cross-sample contamination and sample relatedness
 - Different samples are frequently handled/sequenced together
 - Cross-individual contamination may occur, even small levels of contamination will have an impact on somatic variant detection
 - T + N: Check that tumor and normal sample come from the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



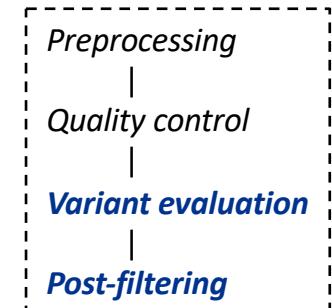
Pedersen et al., Genome Med, 2020

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)



- ***First generation***: call somatic candidates through heuristic rules/ad-hoc filters
 - Rule out sequencing artefacts by thresholds (number of supporting reads etc)
 - Statistical test of difference between tumor and normal
 - Callers: [VarScan2](#), [VarDict](#)
- ***Second generation***: probabilistic modeling of allele frequencies
 - What is the likelihood of non-reference base being somatic, and not sequencing noise (considering base quality, sequence context etc.)?
 - Callers: [MuTect2](#), [Strelka2](#)
- ***Post-filtering***: add additional quality control on call set (read support, minimum coverage, support on both strands etc.)

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?

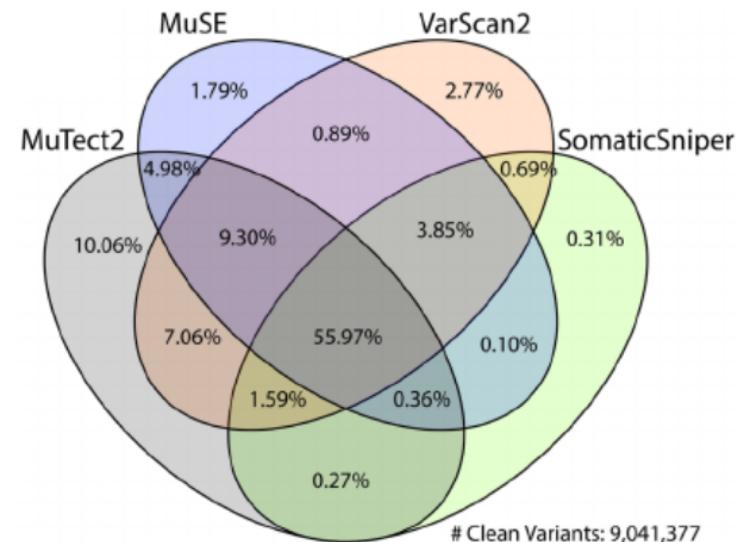


A comprehensive assessment of somatic mutation detection in cancer using whole-genome sequencing

Tyler S. Alioto, 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, Nicolle Diessl, Christopher Previt, Sabine Schmidt, Benedikt Brors, Lars Feuerbach, Michael Heinold, 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, Siege 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-Otín, 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,NON
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
8,0:42,0:0,0,0,0,0,42,42:0:0,0,0,0,0,0,0,1097,1097:42:0 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

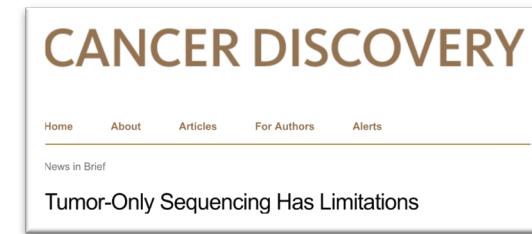
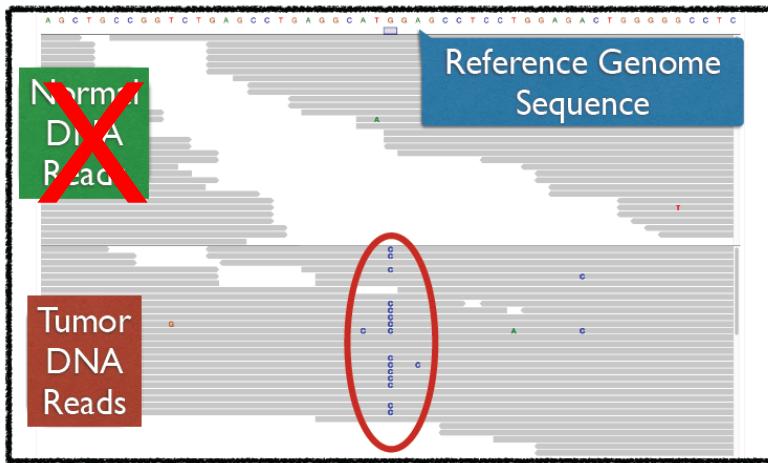


*Allelic support – tumor
sample*



*Allelic support – normal
sample*

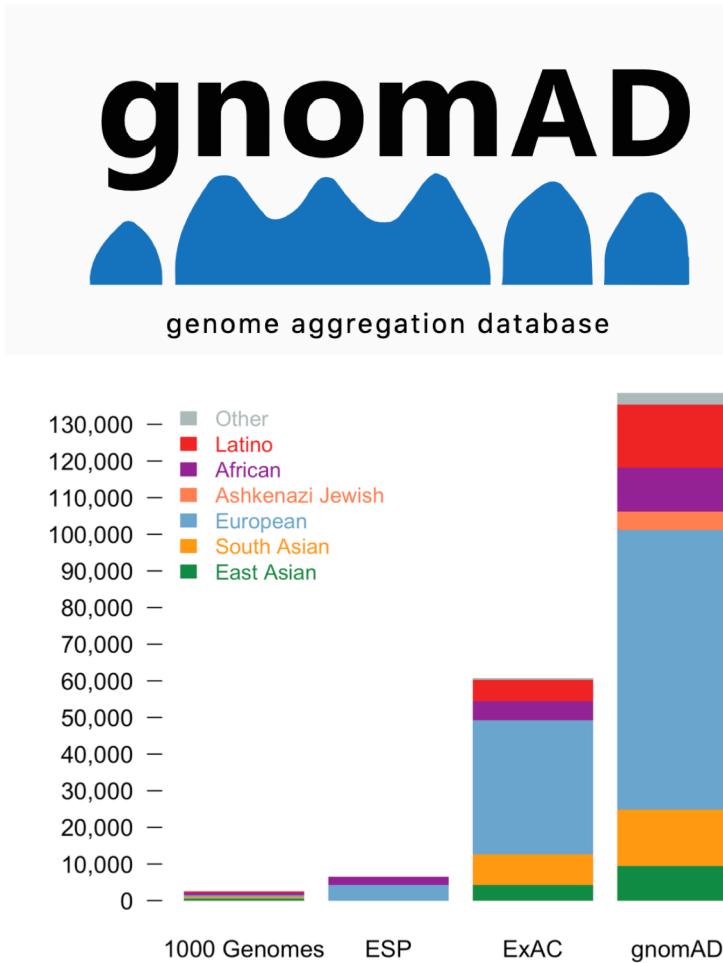
Somatic variant calling: Tumor-only



- 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 Aggregation Database
- **Harmonizes** germline variant both exome and genome sequencing data from a wide variety of large-scale sequencing projects
- **Freely 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 Consortium's 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/GRCh37.

[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)

GATK: Introduction to Somatic Variant Discovery

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

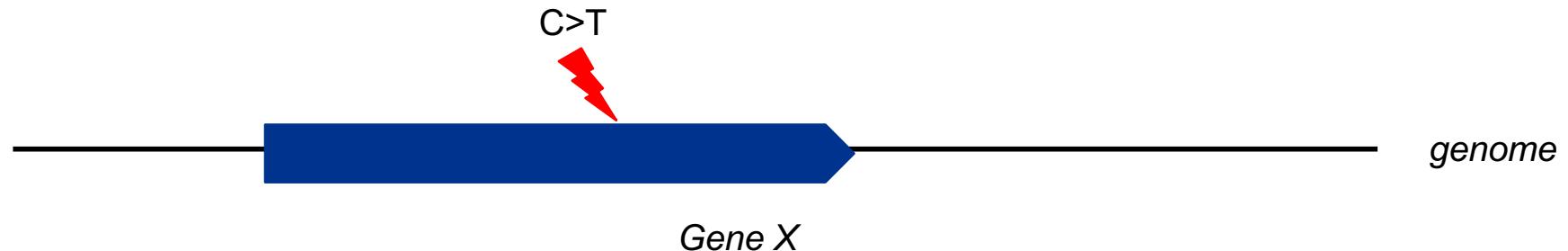
Variants have been found – now what?

ACTG**C**CTACGTCTACCGTCGACTTCAAATCG**C**TTAACCCGTACTCCCATTGCTACTGC
ATCTCGGGTTAACTCGACGTTT**T**CATGCATGTGTGCACCCCAATATATATGCA**A**CTT
TTGTGCACCTCTGTCA CGCGCGAGTTGGCACTGTCGCCCTGTGTGCATGTGCACTGT
CTC**T**CGCTGCACTGCCTACGTCTACCGTCGACTTCAAATCG**C**TTAACCCGTACTCCC
ATGCTACTGCATCTCGGGTTAACTCGACGTTT**G**CATGCATGTGTGCACCCCAATATA
TATGCA**A**CTTTGTGCACCTCTGTCA CGCGCGAGTTGGCACTGTCGCCCTGTGTGCA
TGTGCACTGTCTC**T**CGAGTTT**G**CATGCATGTGTGCACCTCTGTTACGTCT



QUESTIONS/BREAK

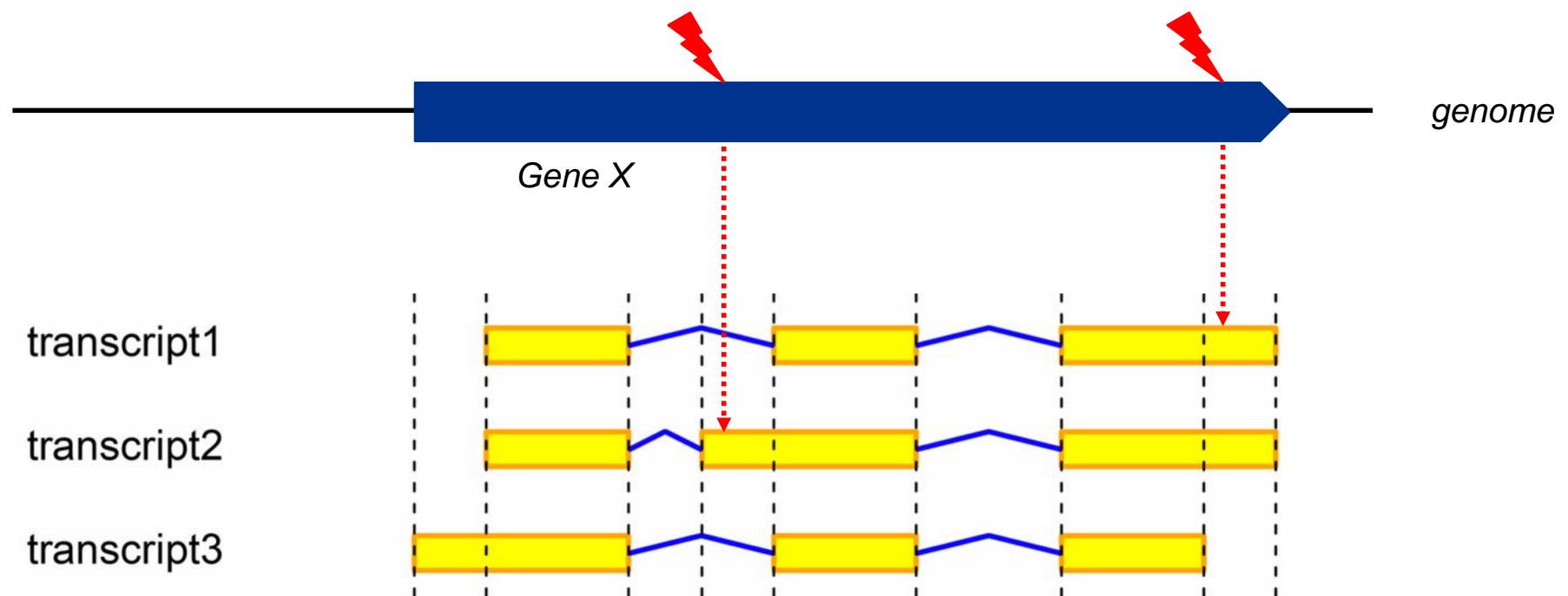
Variant interpretation - general



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

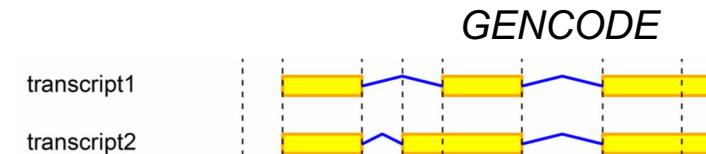
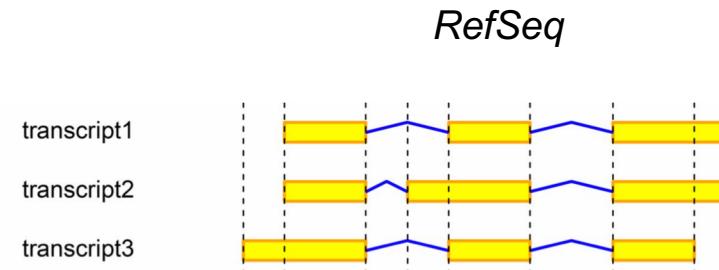
Variant interpretation - general

- 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)



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)
-
- The slide features four blue cylinder icons representing knowledge databases, arranged in a 2x2 grid. Below each icon is the logo for a specific database:
Top-left: CIViC logo (blue cylinder with 'CIViC' and 'CLINICAL INTERPRETATIONS OF VARIANTS IN CANCER')
Top-right: OncoKB logo (blue cylinder with 'OncoKB')
Bottom-left: CKB logo (blue cylinder with 'CKB CLINICAL KNOWLEDGEBASE POWERED BY THE JACKSON LABORATORY')
Bottom-right: My Cancer Genome logo (blue cylinder with 'MY CANCER GENOME GENETICALLY INFORMED CANCER MEDICINE')

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**)

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. Tsimeridou • Cindy L. Vnencak-Jones • Dayna J. Wolff • Anas Younes • Marina N. Nikiforova • Show less

- **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

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)**

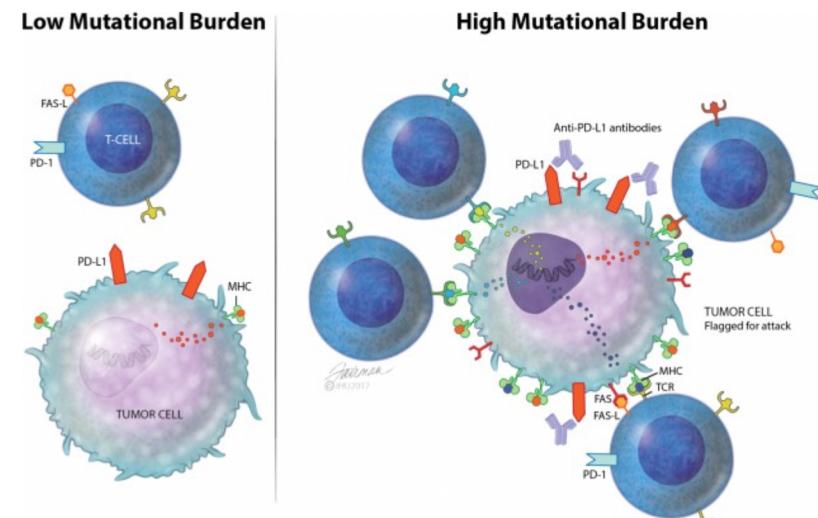


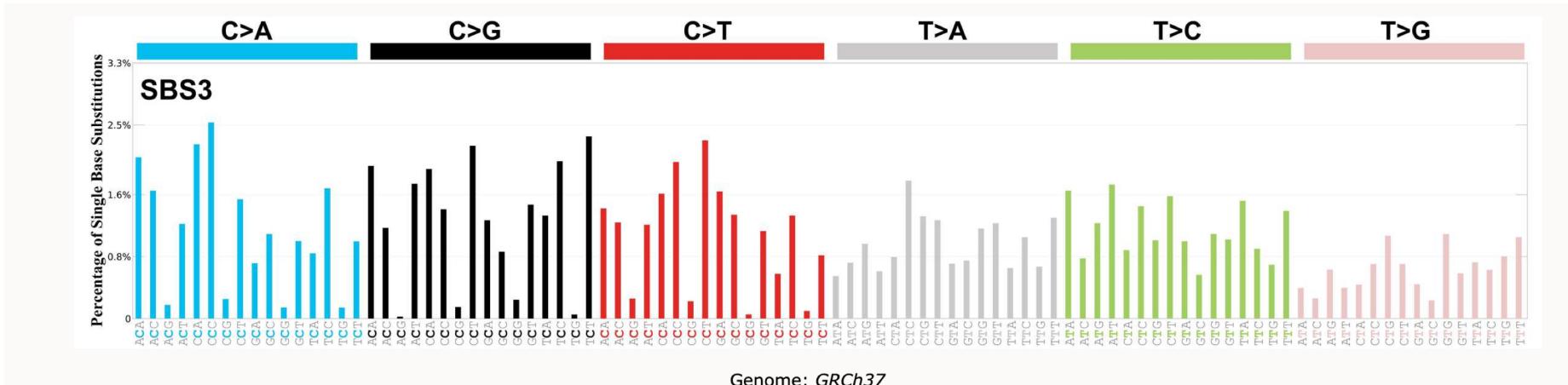
Illustration from Sharabi et al., *The Oncologist* (2017)

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
 - **Approximately 50 established mutational signatures**

Mutational signatures (I)

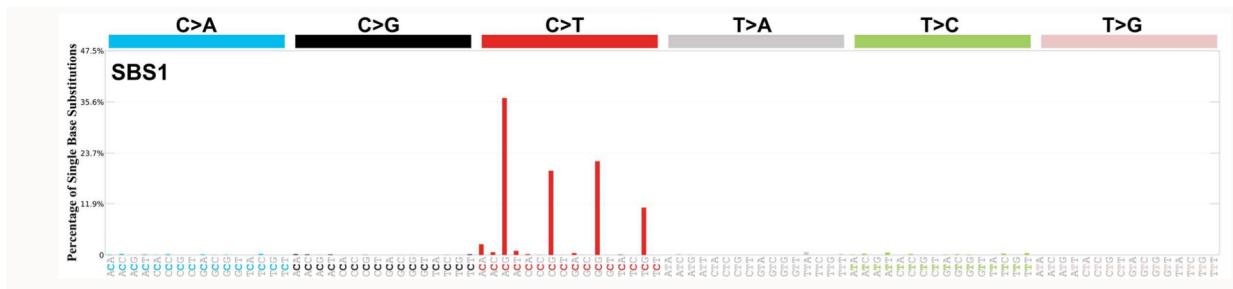
- Mutational signatures are most commonly presented through the **96-channel** approach (single base substitutions, SBS)
 - Mutation type + flanking bases



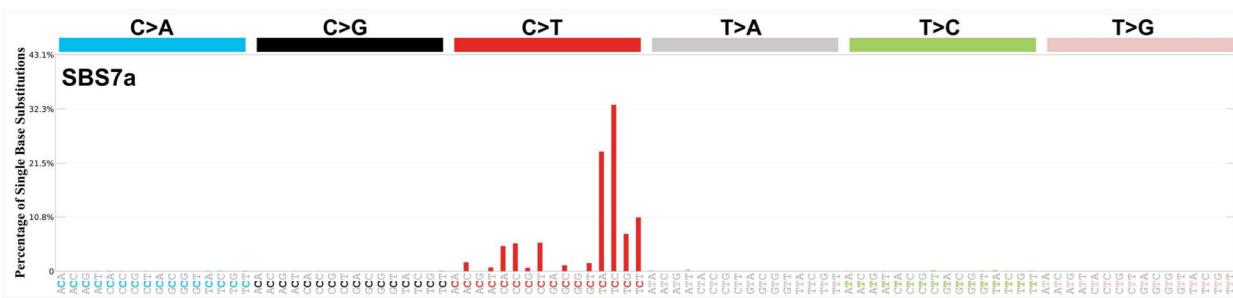
- A single signature (attributed to a given process) is thus characterized as the **relative frequency of 96 different channels**

Mutational signatures (II)

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

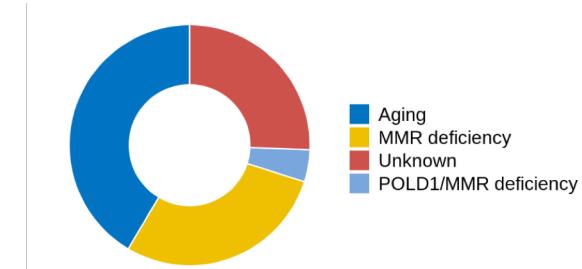


- Exposure to UV light
 - cyclobutane pyrimidine dimers or 6-4 photoproducts



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**

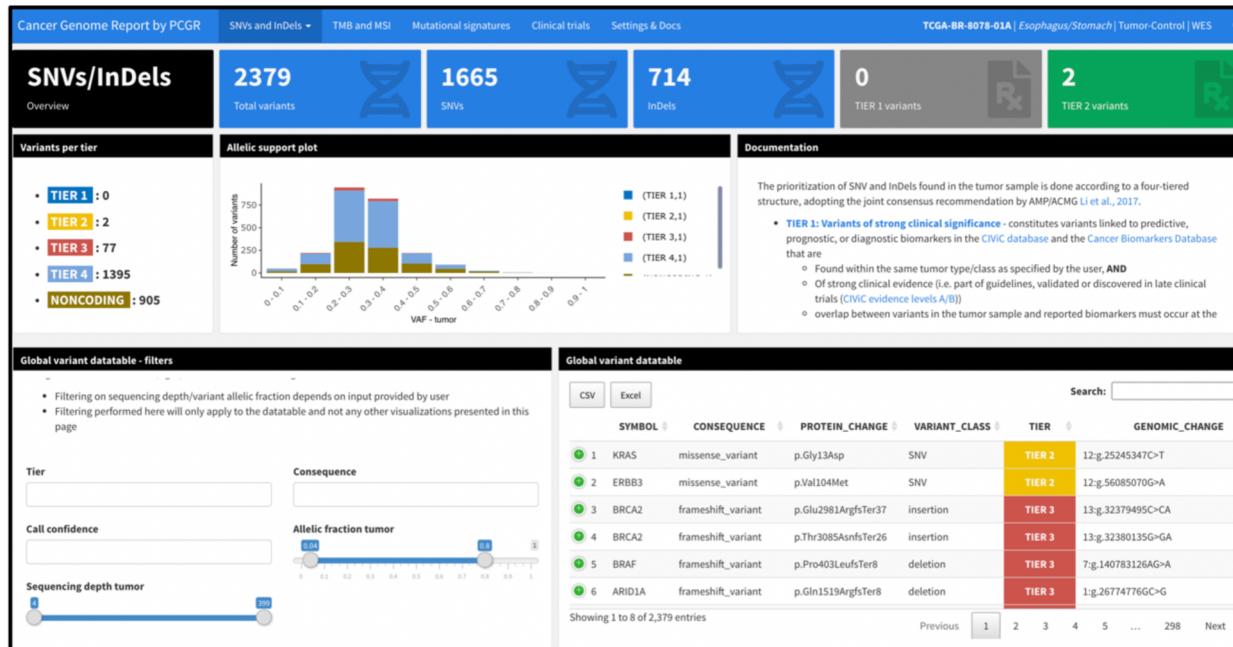
CS-6	CS-15	CS-3	CS-8	Homologous Recombination Repair Deficiency	PARP inhibition ³²⁻³⁴ , Platinum-based chemotherapy ³⁵⁻³⁷
		CS-20	CS-26	Mismatch Repair Deficiency	PD1-immunotherapy ^{48-49,52}
		CS-5	CS-8	Nucleotide Excision Repair Deficiency	Cisplatin ⁶³⁻⁶⁵
		CS-18	CS-30	Base excision Repair Deficiency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

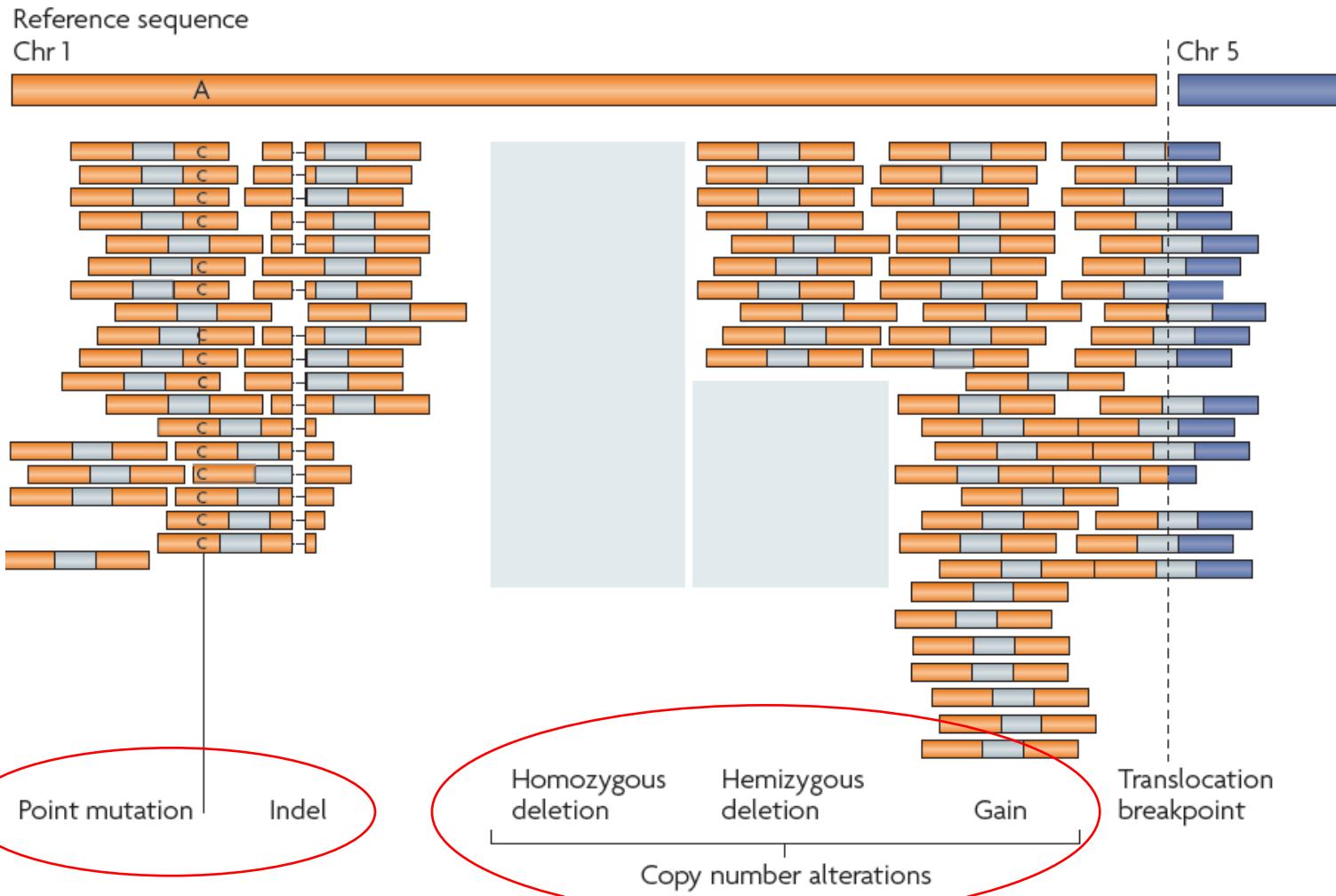


Personal Cancer Genome Reporter (II)

- 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 [Logout](#)

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
<input type="text"/>	<input type="text"/>
Clinical significance	Evidence type
<input type="text"/> Resistance	<input type="text"/> Predictive
Evidence level	Biomarker mapping
<input type="text"/>	<input type="text"/>
Rating	Therapeutic context
<input type="range" value="2"/>	<input type="text"/>

Tier 2 - variant evidence items

CSV Excel Search:

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

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**

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

Cytoband

Event type

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 targets subject to amplification](#).

Oslo
University Hospital
Norwegian Radium Hospital

UiO • University of Oslo



Personal Cancer Genome Reporter (IV)

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

SIGNATURES 1665 MMR deficiency 99.3 0

Mutational Signatures (SBS) SNVs eligible for analysis Most dominant aetiology Accuracy of signature fitting (%) High confident kataegis events

Mutational signatures - aetiology contributions

Legend:

- Aging
- AID/APOBEC
- MMR deficiency
- POLD1 mutant/MMR deficiency
- ROS damage
- Sequencing artefact
- Unknown

Mutational signatures - aetiologies

signature_id	contribution	group	aetiology	comments	
3	SBS44	17.3%	MMR deficiency	Defective DNA mismatch repair.	SBS44 is one of seven mutational signatures associated with defective DNA mismatch repair (MSI) and is often found in the same samples as other MSI associated signatures: SBS6, SBS14, SBS15, SBS20, SBS21, and SBS26.
4	SBS15	11.8%	MMR deficiency	Defective DNA mismatch repair.	SBS15 is one of seven mutational signatures associated with defective DNA mismatch repair (MSI) and is often found in the same samples as other MSI associated signatures: SBS6, SBS14, SBS20, SBS21, SBS26, and SBS44.

Showing 1 to 10 of 11 entries Previous 1 2 Next

Mutational context frequency **Genomic distribution - rainfall** **Kataegis events**

Genomic Distance Genomic Location

Legend:

- C>A
- C>G
- C>T
- T>A
- T>C



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) 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) Phase

Status Gender

Drug(s) All Female Male

Drug target(s)

Therapeutic context mentions (text-mined)

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

Minimum age 0 76

Maximum age 20 100

Metastases mentions (text-mined)

Biomarker 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

BIMARKER_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

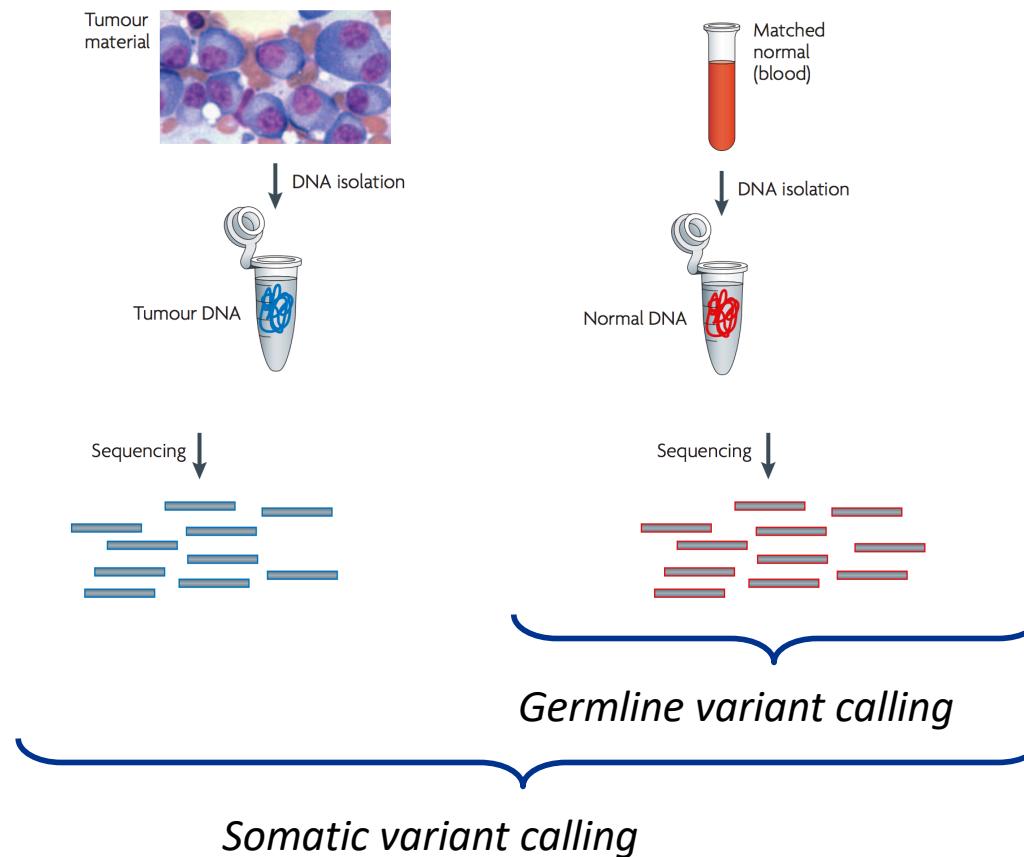
MINIMUM_AGE 18

MAXIMUM_AGE 100

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

Previous 1 Next

Cancer patients - germline background



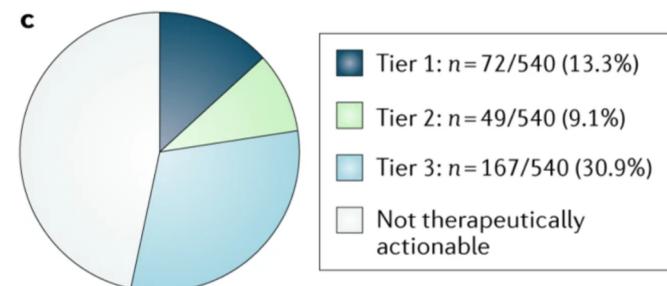
Cancer predisposition interpretation

- 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

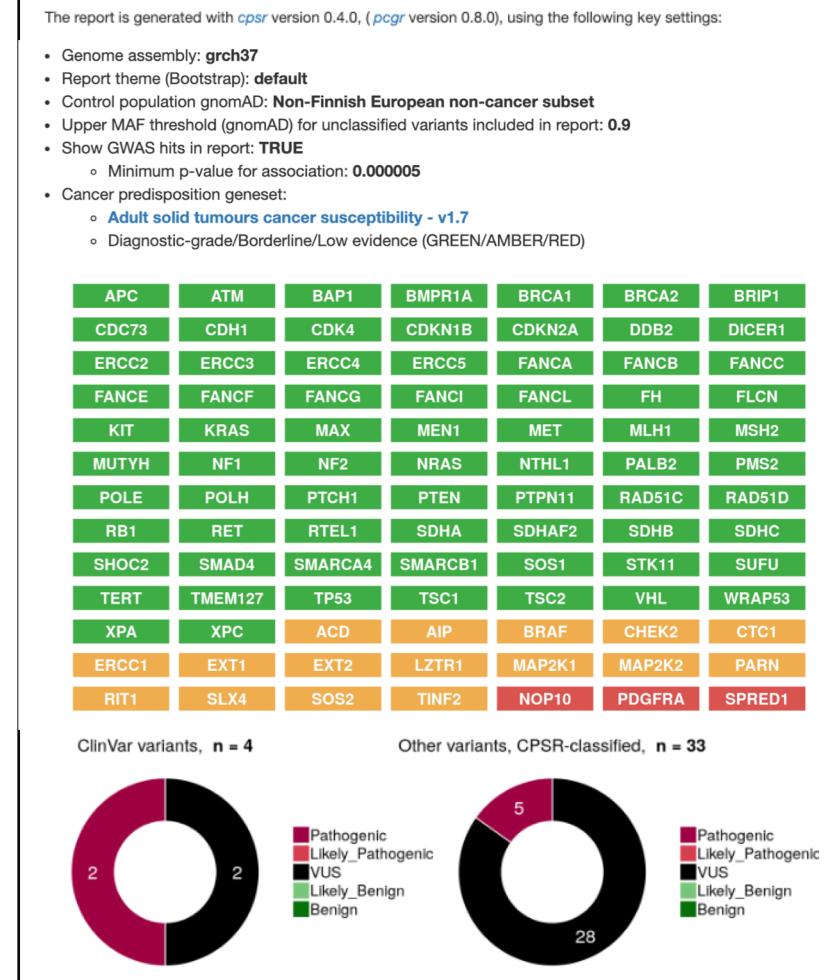
Therapeutic implications of germline genetic findings in cancer



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



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

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 Non-ClinVar

Consequence CPSR classification (ACMG criteria codes)

Genotype CPSR pathogenicity score

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

heterozygous

POLD1 | POLE

CSV Excel 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, CIVC](#) 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

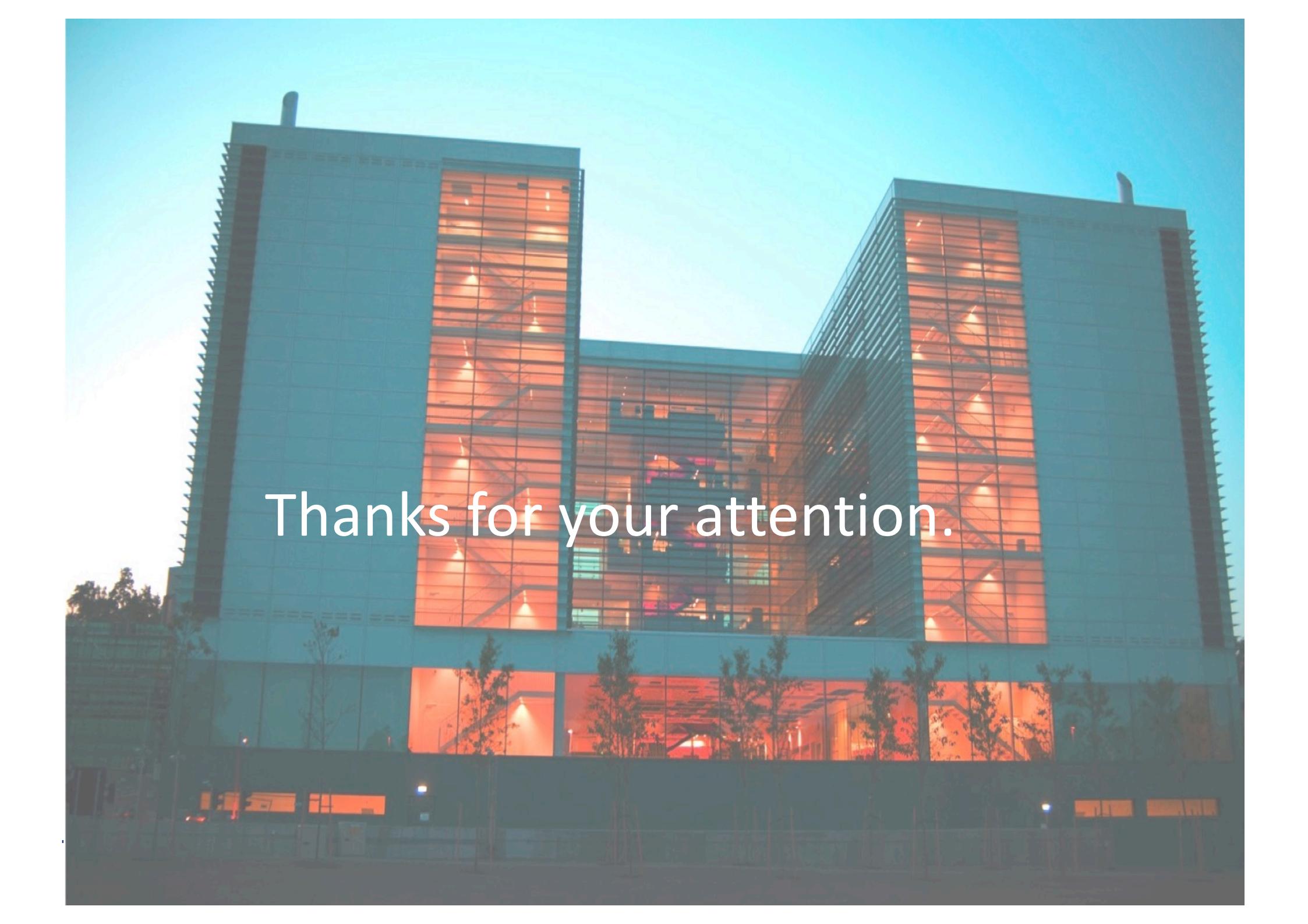
Showing 1 to 2 of 2 entries Previous Next

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 architectural complex at dusk or night. The building features a grid-like facade with large glass windows that are brightly lit from within, casting a warm orange glow. The sky is a clear, pale blue. In the foreground, there are some small trees and a dark, flat surface.

Thanks for your attention.