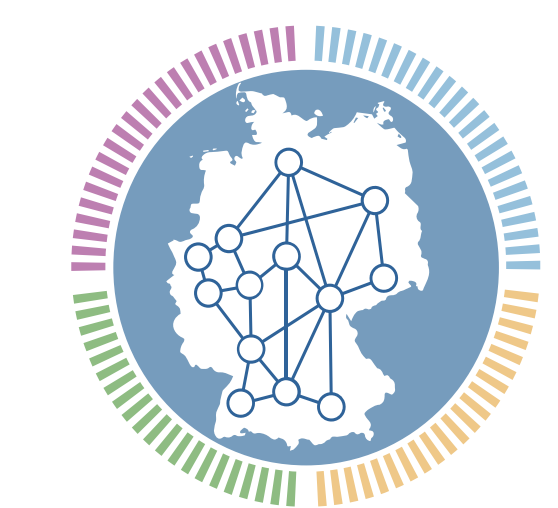




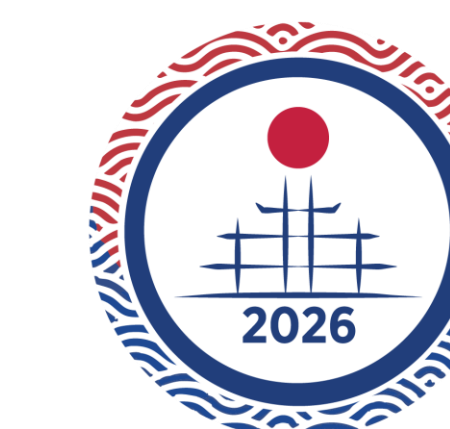
nNGM

Nationales Netzwerk
Genomische Medizin
Lungenkrebs

Genomic Profiling of a High-Risk Non-Small Cell Lung Cancer Cohort by the National Network Genomic Medicine in Germany

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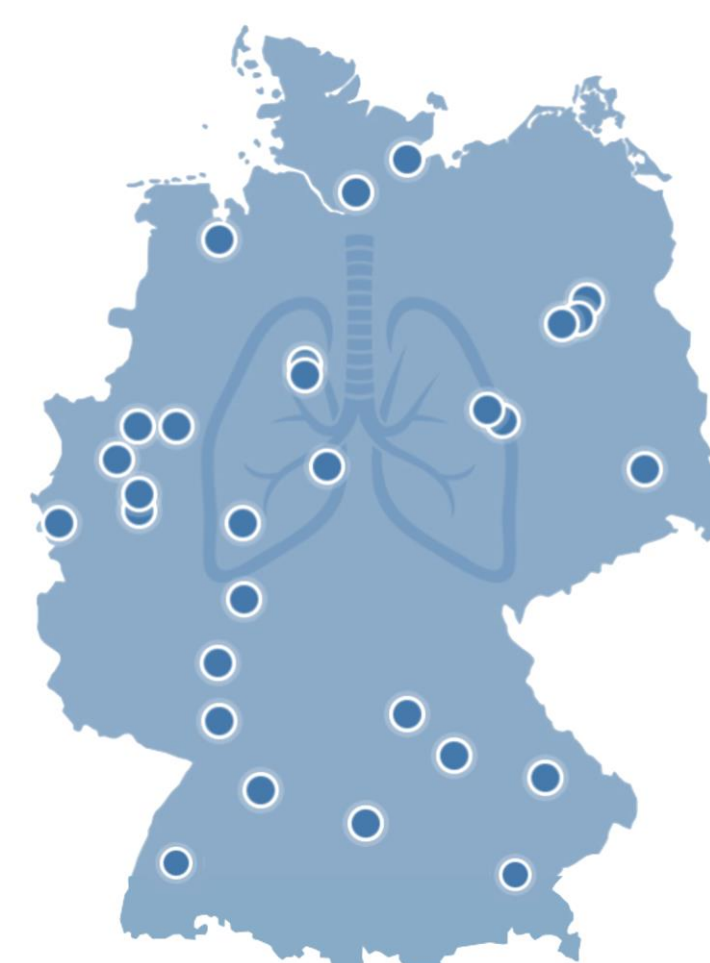
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Background

While **NSCLC** is predominantly driven by **well-characterized somatic alterations**, the contribution of **germline susceptibility** remains poorly defined. To address this, the **"Genetic Tumor Risk"** Task Force of the **national Network Genomic Medicine Lung Cancer (nNGM)** investigates the **somatic mutational landscape** in a cohort enriched for patients with a **family history of cancer**, **multiple primary tumors**, and **never-smokers**. The project is a multi-site effort across university hospitals across Germany, whereby **different library chemistries** and **sequencing data types** are implemented. **Encrypted data** is securely transferred between sites for computational analysis, reporting, and central storage. **Paired WGS of blood-derived DNA** and **WES of FFPE tumor tissue** was performed to assess whether **clinical enrichment for cancer predisposition translates into a distinct molecular profile**.

The network's sites in Germany



Patient enrollment criteria

- NSCLC and < 50 years old or
- NSCLC and ≥ 50 years old and at least one of the following criteria:
 - one or more additional tumor diseases
 - at least one first-degree relative with cancer
 - at least two second-degree relatives with cancer
 - previous tumor sequencing suggests pathogenic germline variant
 - rare tumor diagnosis (<6/100,000 per year)

The cohort at a glance

686
Germline
sequenced

270
Somatic
evaluated

71.3%
Family history of
cancer

47.1%
Multiple primary
tumors

22%
Never-
smokers

9.1%
Pathogenic germline
carriers

WGS meets WES: containerized pipeline for variant calling

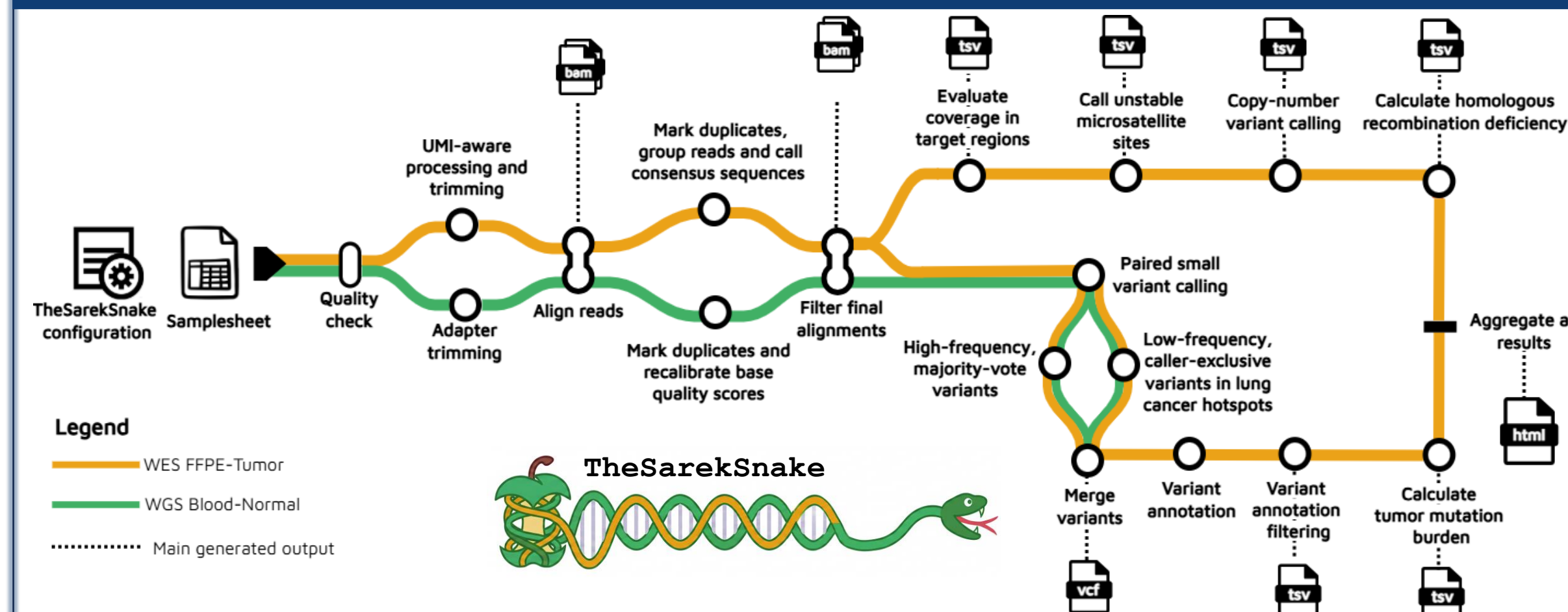


Fig. 1: TheSarekSnake pipeline overview. Containerized somatic variant-calling pipeline for paired WGS (blood-derived normal) and WES (FFPE tumor) data. Built in Snakemake, the workflow hands over to nf-core/sarek v3.2.2 (Nextflow) for mapping and multi-tool, short variant-calling steps. It is reproducible, portable, and customizable, adding variant annotation, complex-alteration analysis (steps outside of the nf-core/sarek scope – TMB, MSI, SCNA, LOH, and HRD), and quality control across 966 cancer-associated genes. Different analytical processes are triggered depending on tumor cell content (TCC): short variants require ≥ 20%, while complex alterations require ≥ 40%. Exception to this: somatic LOH at the inherited pathogenic locus is always reported. Line colors denote the two data streams; green for WGS blood-derived data and orange for WES FFPE tumor data.

Somatic mutation profile of the full cohort

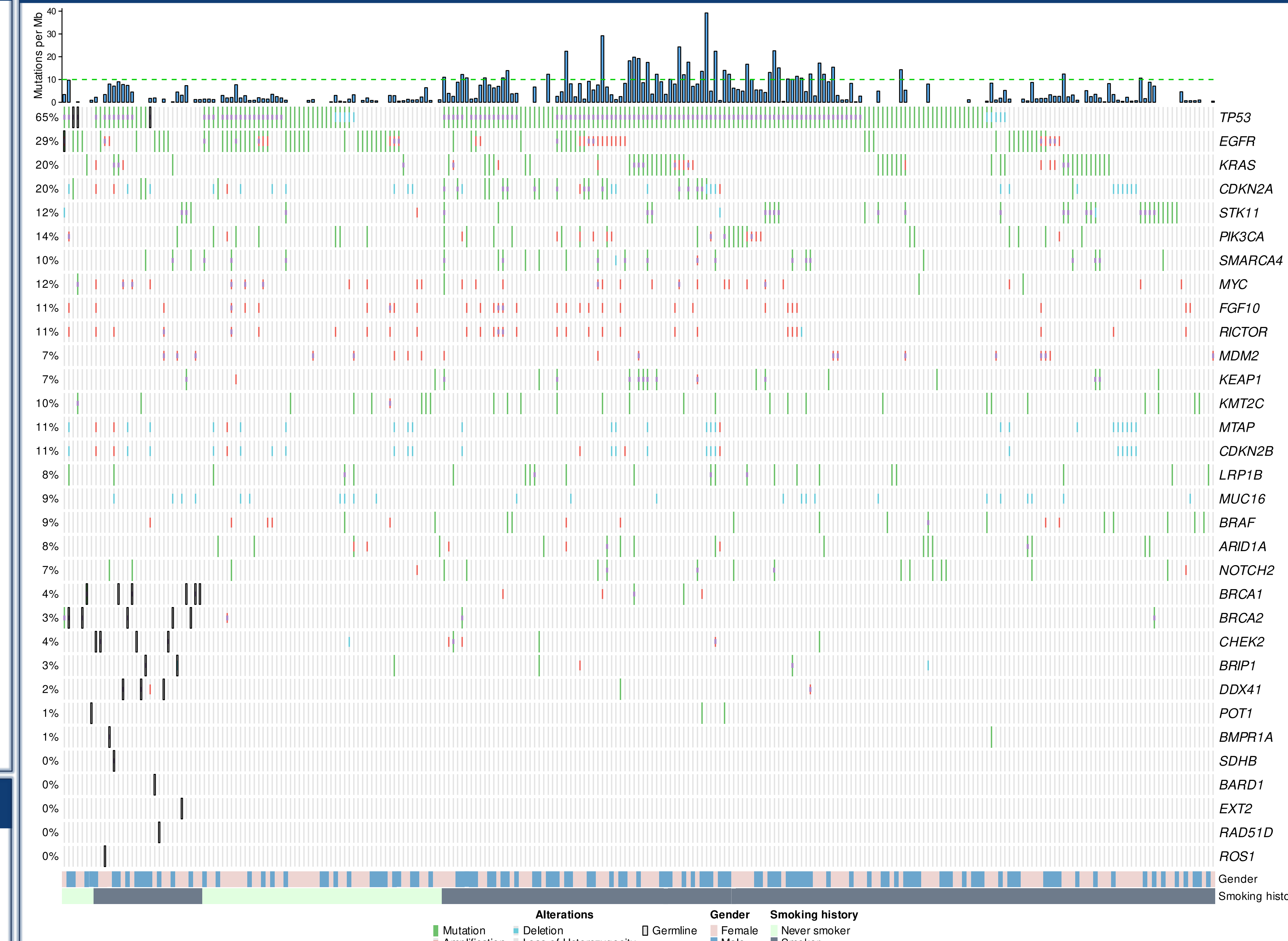


Fig. 2: Mutation profiles of the nNGM cohort (n=270) for 966 cancer-associated genes with predicted change of protein function, somatic copy number amplification, deletion, and loss of heterozygosity. Inherited (likely) pathogenic variants are indicated by outlined boxes overlaid on the corresponding gene. Columns represent tumors and rows represent genes. The percentage of samples harboring alterations is shown on the left for each gene. Tumor mutation burden (number of mutations per Mb) for each patient is shown at the top; the dashed green line indicates the common TMB-H threshold. Complex genomic alterations – including somatic copy number and genome-wide loss of heterozygosity – are only displayed for tumors with a tumor cell content ≥ 40%; samples below this threshold may still accumulate complex changes but cannot be reliably assessed for SCNAs or TMB. Samples are ordered by germline variant carrier status and smoking status.

Somatic mutation profile of pathogenic germline variant carriers

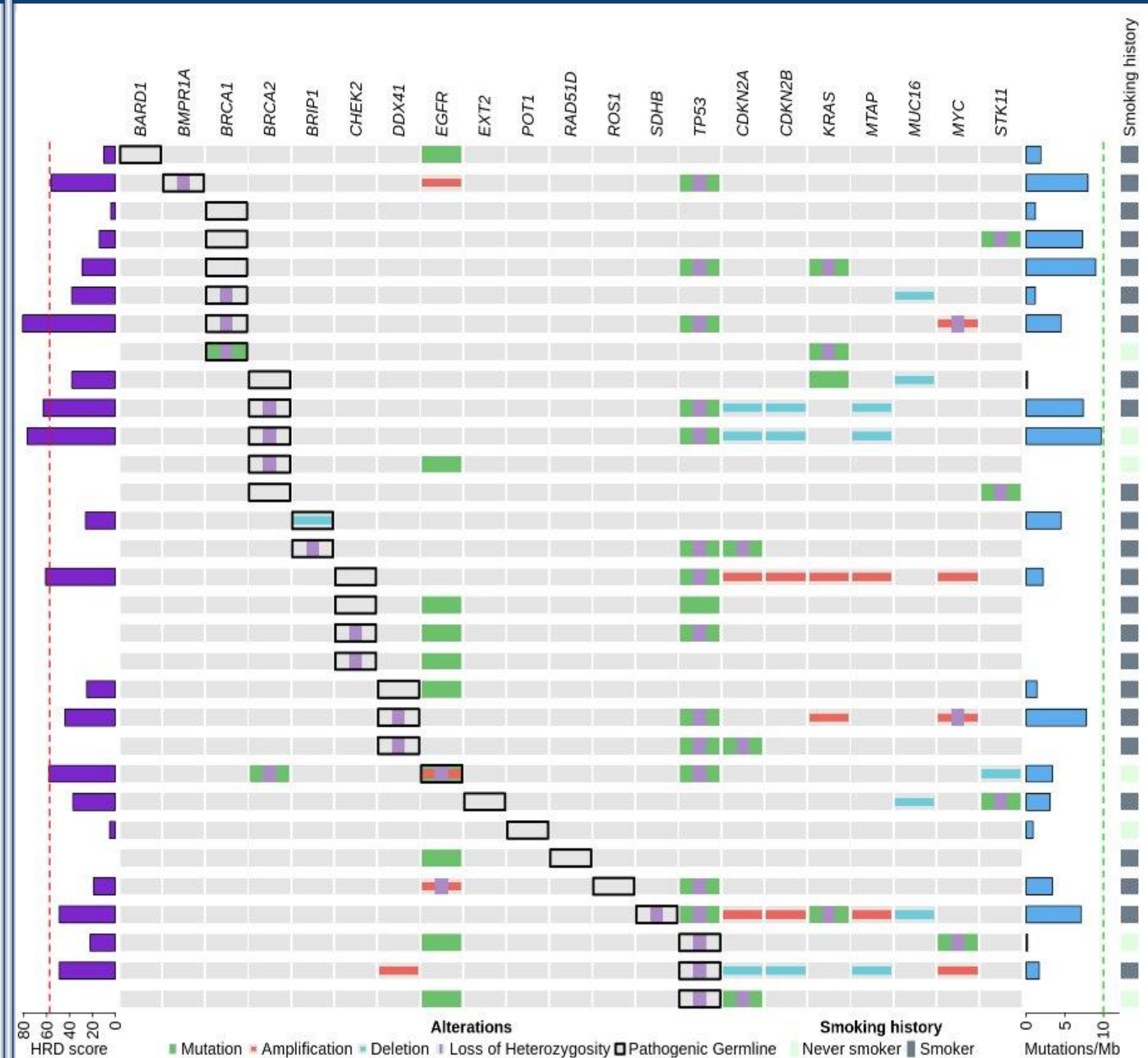


Fig. 3: Mutation profiles of germline variant carriers (n=31) for 966 cancer-associated genes with predicted change of protein function, somatic copy number amplification, deletion, and loss of heterozygosity. Inherited (likely) pathogenic variants are indicated by outlined boxes overlaid on the corresponding gene. Rows represent tumors and columns represent genes. Only tumor samples with at least 40% TCC are evaluated for complex genomic alterations, i.e. SCNAs, TMB status and HRD score. HRD score (left) and TMB (right) are blank for tumors below this TCC threshold and amplified/copy-number-loss genes are likewise not called. The dashed red line marks the 90th percentile of cohort HRD scores; the dashed green line marks the common TMB-H threshold. Samples are ordered alphabetically by the germline carrier gene.

HRD score by HRR pathway disruption tier

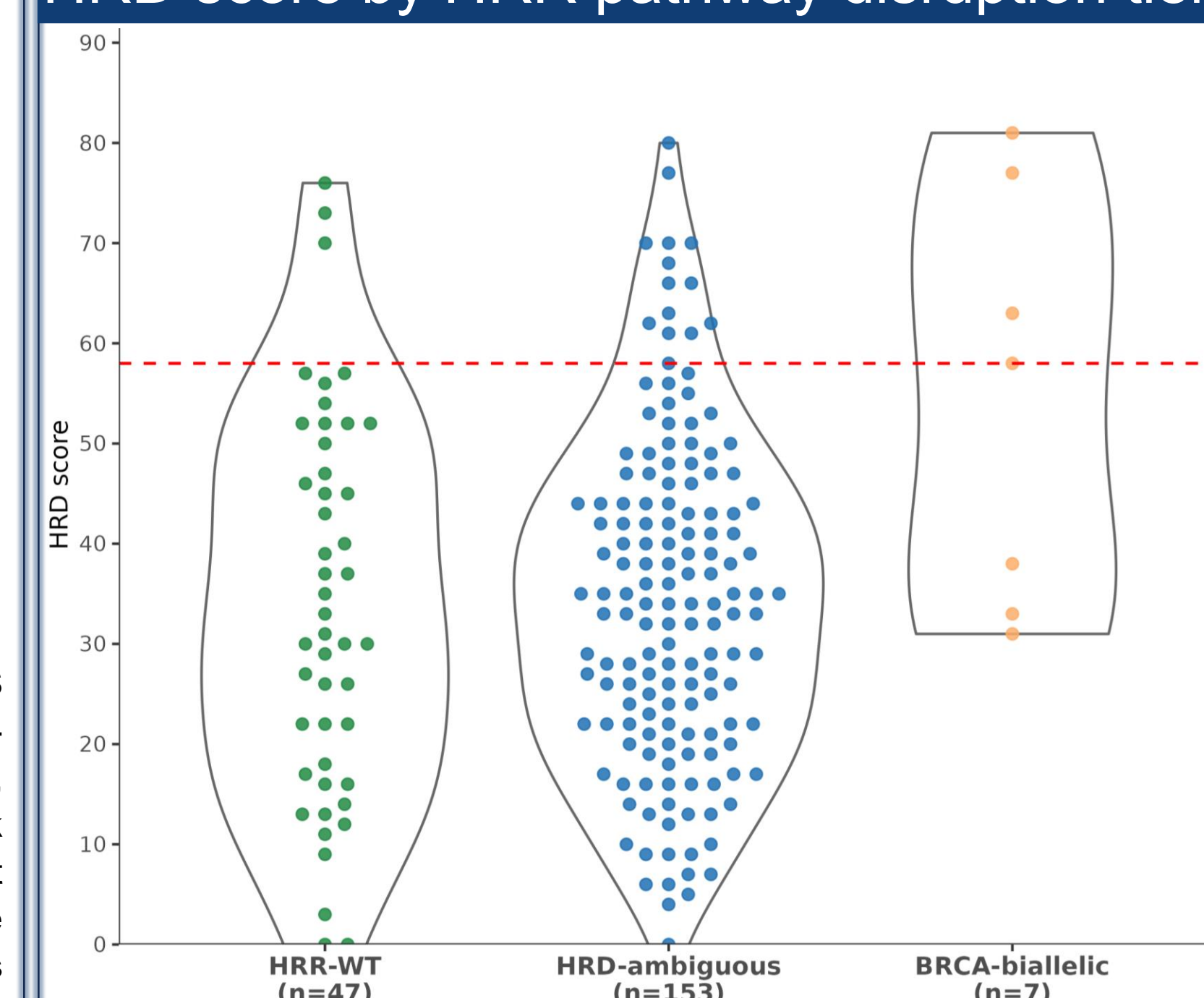


Fig. 4: Homologous recombination deficiency (HRD) scores by status of disruption in genes involved in the homologous recombination repair (HRR) pathway. Only tumor samples with at least 40% TCC are evaluated for HRD. BRCA-biallelic (homozygous deletion or germline with somatic LOH/somatic loss-of-function); HRR-WT (wild-type); HRD-ambiguous (monoallelic BRCA or other HR gene hits). The dashed red line marks the 90th percentile of cohort HRD scores.

Germline carriers and somatic LOH

Gene	Carriers	Class	LOH
BRCA1	6	HRR	3/6
BRCA2	5	HRR	3/5
CHEK2	4	HRR	2/4
BRIP1	2	HRR	1/2
BARD1	1	HRR	0/1
RAD51D	1	HRR	0/1
DDX41	3	Other	2/3
TP53	3	Other	3/3
EGFR	1	Other	1/1
EXT2	1	Other	0/1
POT1	1	Other	0/1
BMPR1A	1	Other	1/1
ROS1	1	Other	0/1
SDHB	1	Other	1/1

Key somatic findings

1. **Short mutations** in **EGFR** were enriched in **never-smokers** while mutations in **KRAS** were associated with **tobacco use** (FDR < 0.1)
2. **Somatic copy number alterations** showed **no association** with the **smoking history** of a patient (FDR > 0.1)
3. **Tobacco use** was **strongly associated** with the **accumulation of somatic mutations** ($p=2.3 \times 10^{-9}$)
4. **Two** out of the **38 TMB-H** tumors, all of which are from patient with a history of smoking, were also **MSI-H**
5. **Although ~11%** of patients evaluated for somatic alterations harbored pathogenic germline variants, **global somatic alterations were not significantly associated with them** (FDR > 0.1)
6. **HRD scores** were **broadly distributed** irrespective of mutation status in HRR genes, though **LOH in germline HRR pathogenic carriers** tended to track with **above median HRD scores**
7. **Highest HRD scores** were found in patients mutated in **BRCA2** (BRCA-biallelic – germline + somatic LOH/LOF – or HRD-ambiguous – only somatic LOH or LOF) and **PALB2** (HRD-ambiguous only – somatic only)

Conclusion

In this high-risk NSCLC cohort, **established diagnostic biomarkers predominate irrespective of germline status**. However, recurrent **biallelic inactivation through somatic LOH in HRR carriers** points to a **biologically distinct subgroup**. **HRD scores** themselves were **broadly distributed irrespective of germline status**, likely reflecting the **high baseline genomic instability** characteristic of NSCLC rather than HRR deficiency alone. Moreover, **integrative profiling of blood-derived DNA WGS and formalin-fixed tumor DNA WES** is feasible in clinical settings, with ongoing analyses to refine molecular stratification and actionable vulnerabilities.



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