

# Identifying Patient-specific Neopeptides for Cell-based and Vaccine Immunotherapy Targets in Breast Cancer Patients by HLA Typing and Predicting MHC Presentation from Whole Genome and RNA Sequencing Data

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## Background

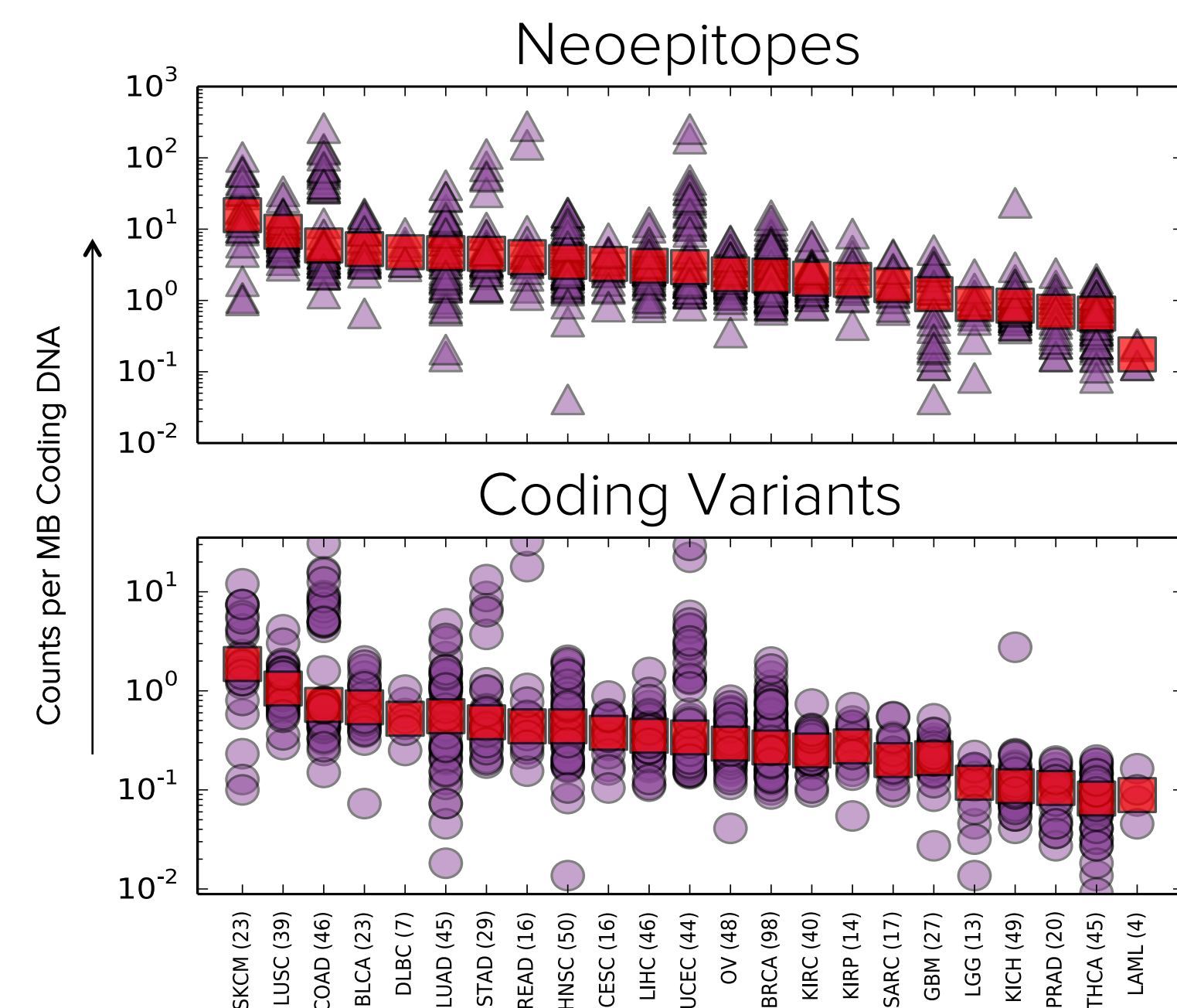
- Immunotherapies such as checkpoint inhibitors, CAR T cells, NK cells, and therapeutic vaccines are revolutionizing cancer medicine with remarkable responses in some patients.
- Current clinical immunotherapy strategies include targeting tumor associated antigens (TAAs) such as HER2 (trastuzumab) or targeting immune cell checkpoints (ipilimumab, nivolumab).
- Many patients fail to have responses with these drugs suggesting a lack of specific immune cells or insufficient amounts of the TAAs.
- We analyzed whole genome sequencing (WGS) and RNA sequencing (RNAseq) data from The Cancer Genome Atlas (TCGA) to identify neopeptides (tumor-specific antigens derived from mutations from cancer) that could be exploited to develop next-generation, patient-specific cancer immunotherapies.

## Methods

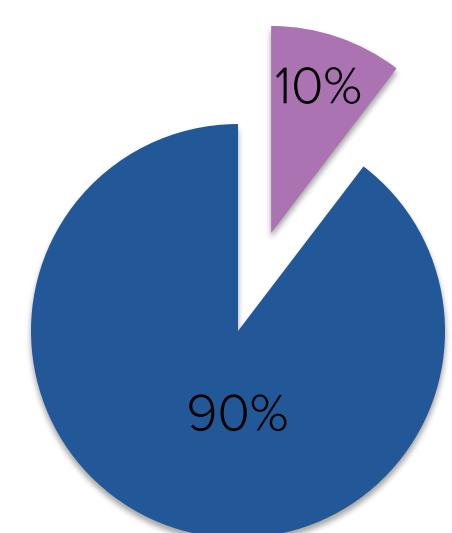
- TCGA WGS and RNAseq data were obtained from the University of California, Santa Cruz (UCSC) Cancer Genomics Hub (<https://cghub.ucsc.edu/>).
- Neopeptides were identified by creating all possible permutations of either 9-mer or 15-mer amino acid strings derived from single nucleotide variants (SNVs) or insertions/deletions (indels).
- All neopeptides were filtered against all possible 9-mer and 15-mer sequences from every known human gene along with dbSNP (<http://www.ncbi.nlm.nih.gov/SNP>) sites to include all possible variations.
- In-silico HLA typing was performed using WGS and RNAseq data along with alignments to the IMGT/HLA database. Typing results were obtained for HLA-A, HLA-B, HLA-C, and HLA-DRB1.
- NetMHC 3.4 (<http://www.cbs.dtu.dk/services/NetMHC-3.4/>) was used to predict MHC to neopeptide binding affinities.

## Results

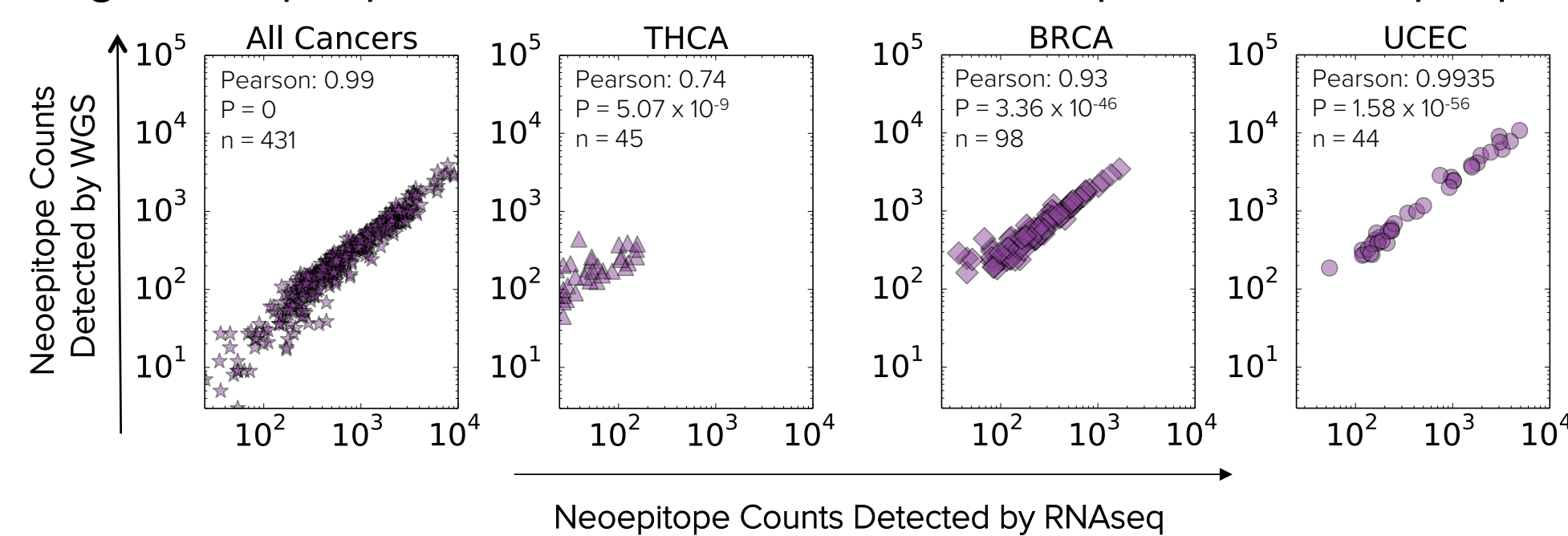
### Cancer Neopeptide Loads Across TCGA Dataset



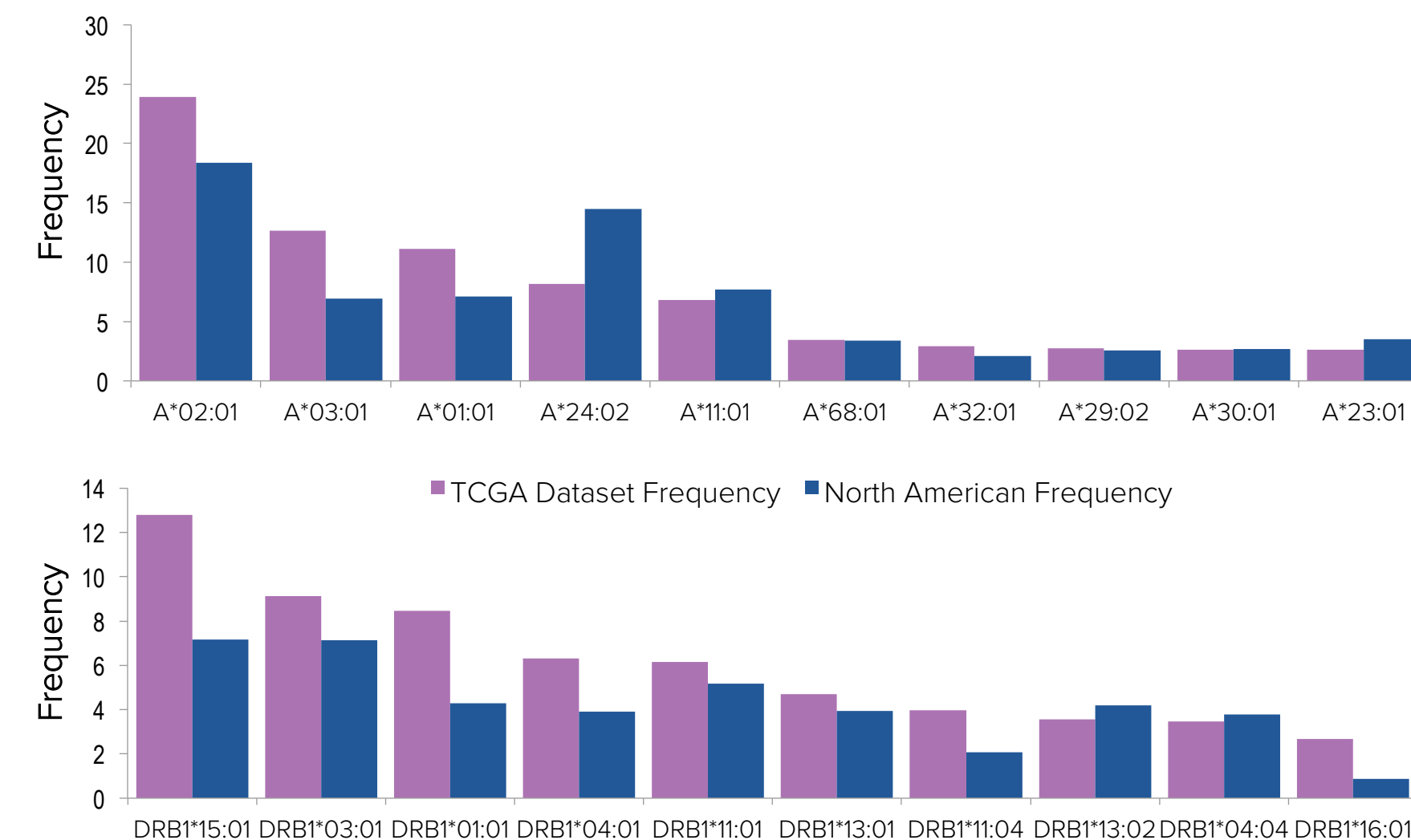
■ Normal Epitope  
 ■ Neopeptide



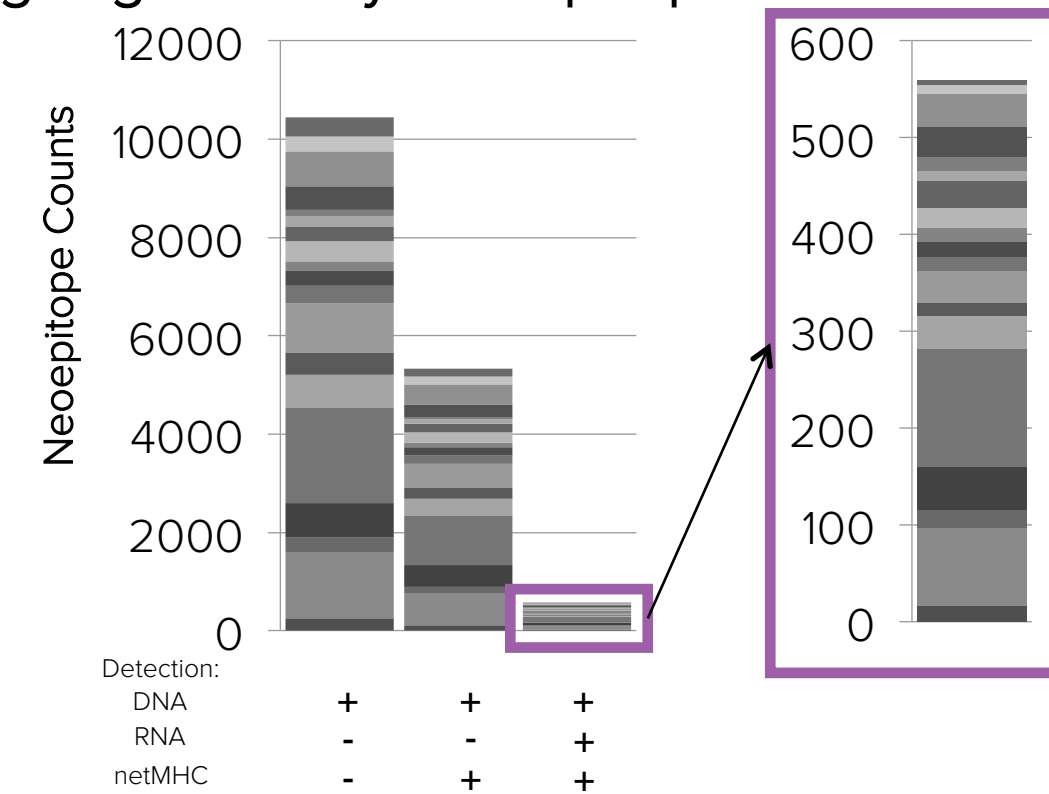
### High Neopeptide Burden Gives Rise to More Expressed Neopeptides



### HLA Distribution Within the TCGA Dataset



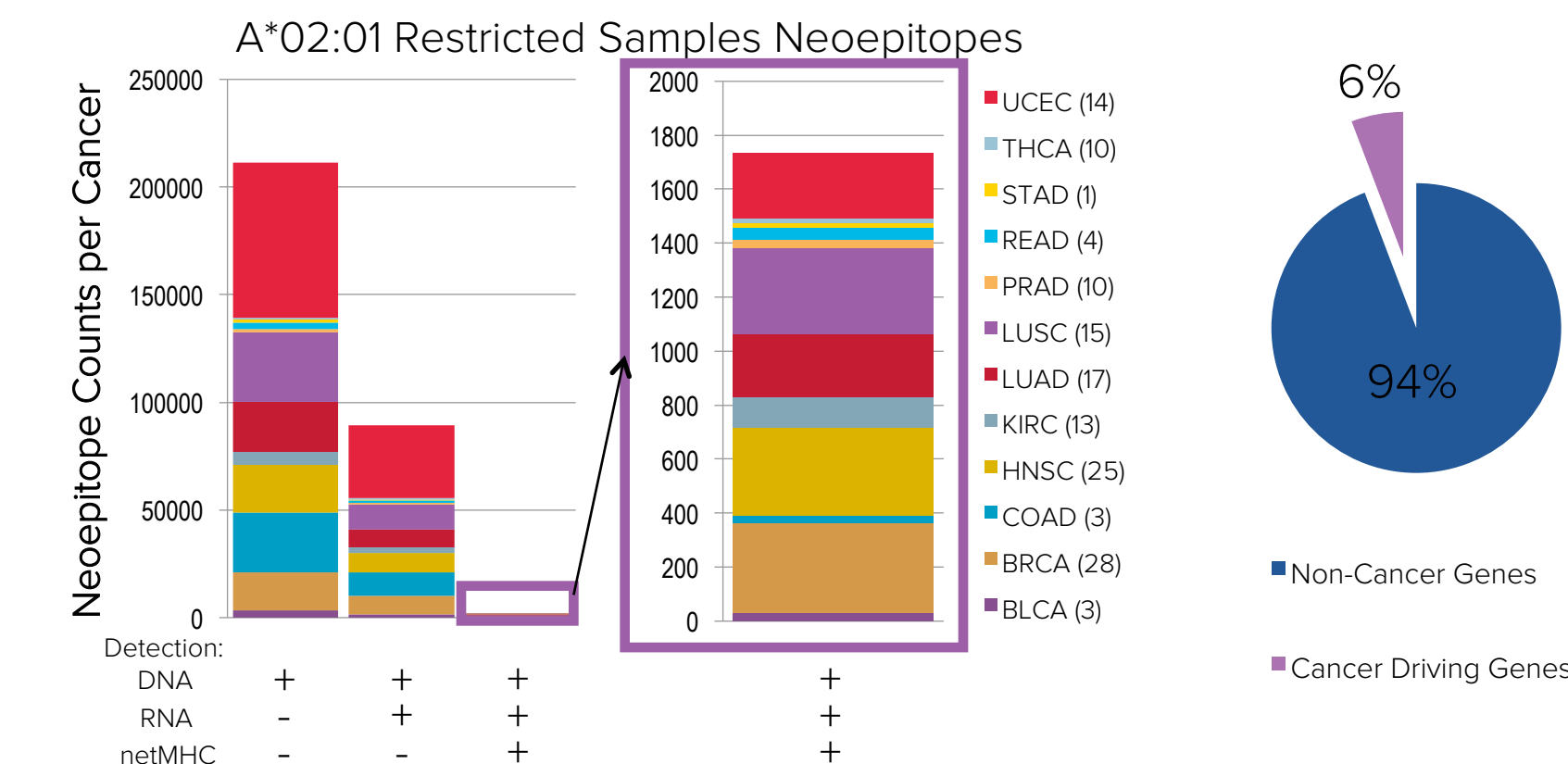
### Filtering High-Quality Neopeptides in HER2+ BRCA



### A Single Recurrent Neopeptide in TCGA HER2+ BRCA

TCGA Barcode	UCSC id	HUGO Gene Name	TPM	Neopeptide	Protein Change	Normal	Bound Allele	Bind Strength
TCGA-BH-A18R	uc003ean.2	FANCD2	21.39	FAKDGGLVT	P714L	FAKDGGPVT	C*03:03	131nM
TCGA-AO-AOJM			14.12				C*05:01	851nM

### Filtering High-Quality Neopeptides Across Cancers



### Shared Neopeptides Across Cancers

TCGA Barcode	UCSC id	HUGO Gene Name	Neopeptide	Protein Change	Normal	Cancers
TCGA-E2-A109, TCGA-CR-5249, TCGA-BA-6872, TCGA-CN-6989	uc001wxt.2	SOS2	YIHTHTFYV	p.T390I	YTHHTFYV	(3) HNSC, BRCA
TCGA-EW-A1J5, TCGA-21-1082, TCGA-GD-A2C5, TCGA-75-5147	uc001zyl.4	USP8	SQIWNLPV	p.R763W	SQIRNLNPV	LUAD, BLSA, LUSC, BRCA

## Conclusions

- Most identified neopeptides are patient-specific.
- Neopeptide-MHC interactions restrict more commonly shared mutations.
- Development of personalized immunotherapies is dependent on accurate DNA and RNA sequencing.

## Acknowledgement

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