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DATA SCIENCE (CLINDA)

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MUTATIONAL SIGNATURES USING NEURAL NETWORKS FOR ROBUST STRATIFICATION OF CANCER PATIENTS

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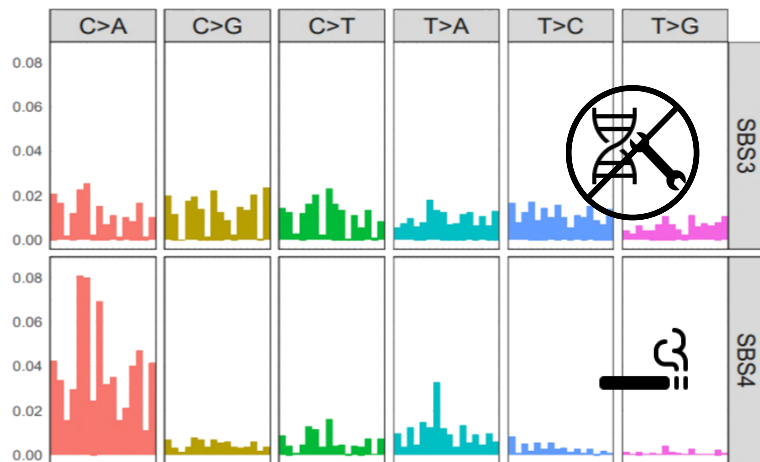
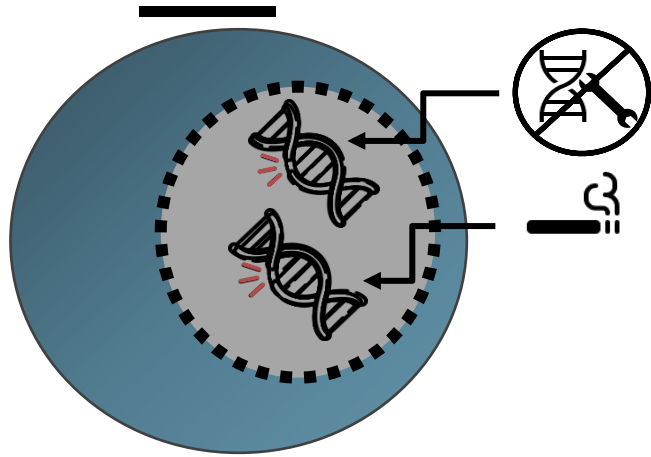
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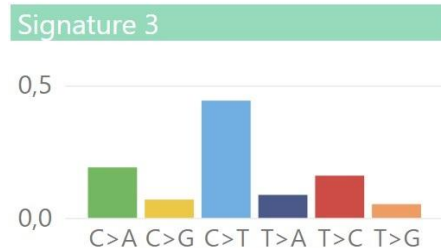
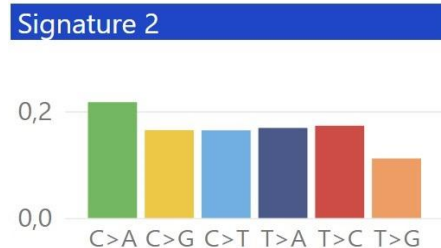
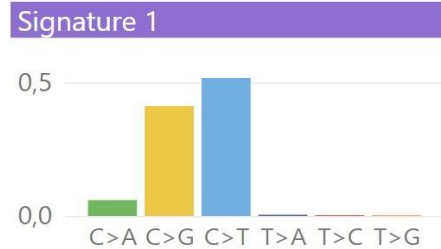
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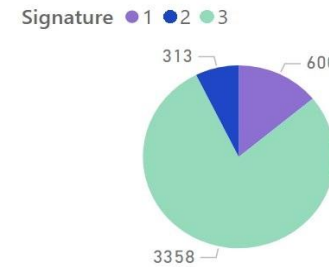
MUTATIONAL SIGNATURES - IDENTIFYING THE UNDERLYING PROCESSES BEHIND CANCER



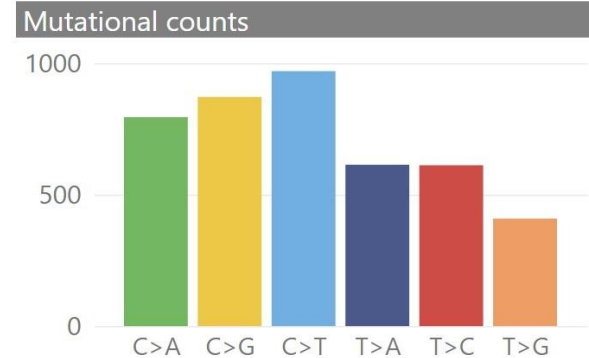
[COSMIC v. 3.4]



Signatures of mutational processes



Number of mutations provided by each signature



Mutational counts inferred by exposure to mutational processes

[Egendal 2021] inspired by
[Alexandrov et al. 2013]



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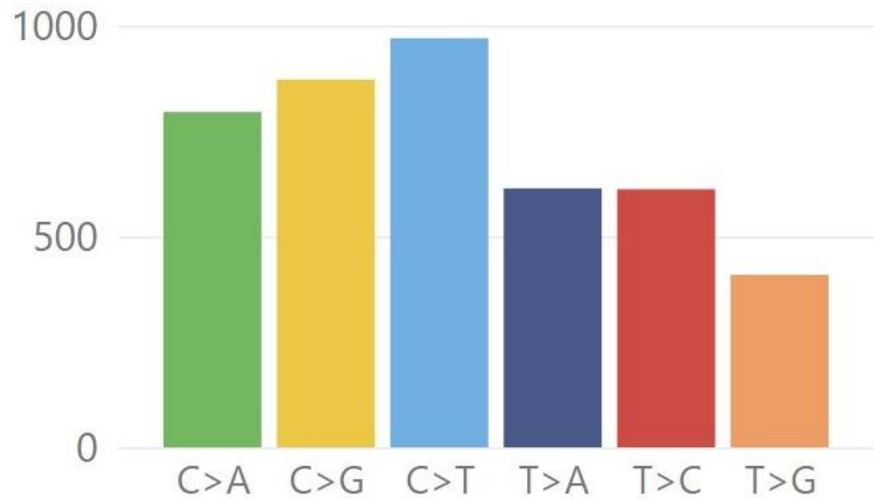
NON-NEGATIVE MATRIX FACTORIZATION

$$V \approx WH$$

$n \times m$ $n \times k$ $k \times m$

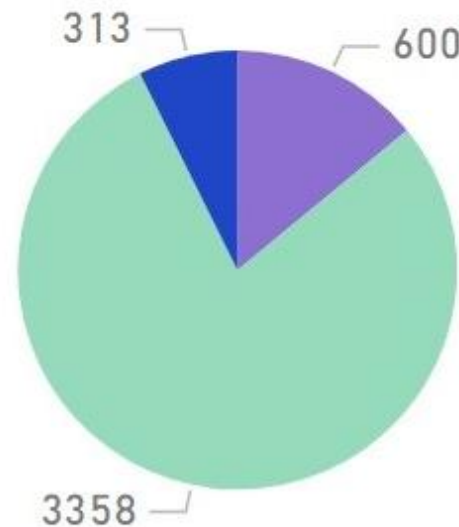
m features

Mutational counts



≈

Signature 1 2 3



Signature 1



Signature 2

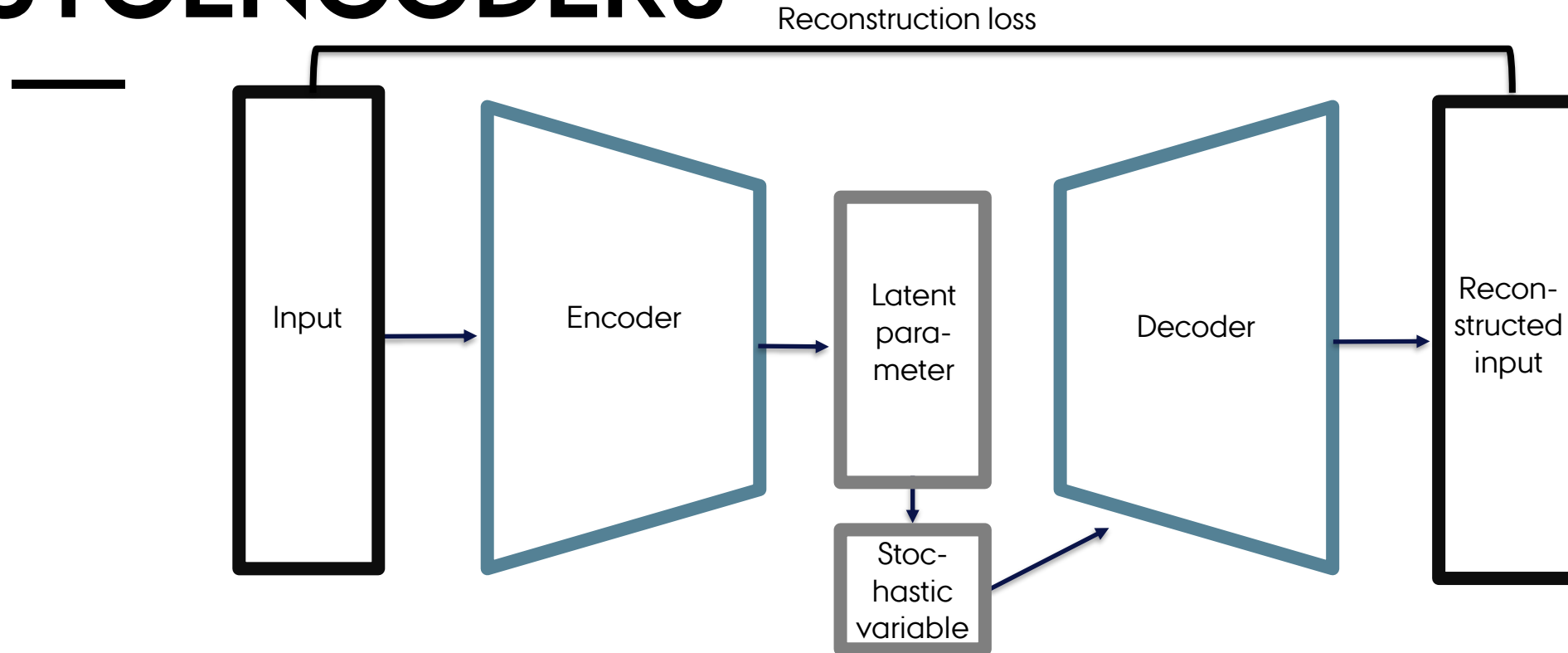


Signature 3



Signatures of mutational processes

VARIATIONAL AUTOENCODERS



Compresses data into a *stochastic* latent space

Latent space regularized by prior

Maximize the ‘evidence lower bound’ (ELBO), a lower bound of the marginal log-likelihood

$$\mathcal{L}_{ELBO}(v, w) = \log p_{\theta}(v) - \mathcal{D}_{KL}(q_{\phi}(w|v) || p_{\theta}(w|v))$$

VAE-MS: AN ASYMMETRIC VARIATIONAL AUTOENCODER FOR MUTATIONAL SIGNATURE EXTRACTION

Ida Egendal, Rasmus Froberg Brøndum,
Dan J Woodcock, Christopher Yau, and
Martin Bøgsted

In preperation

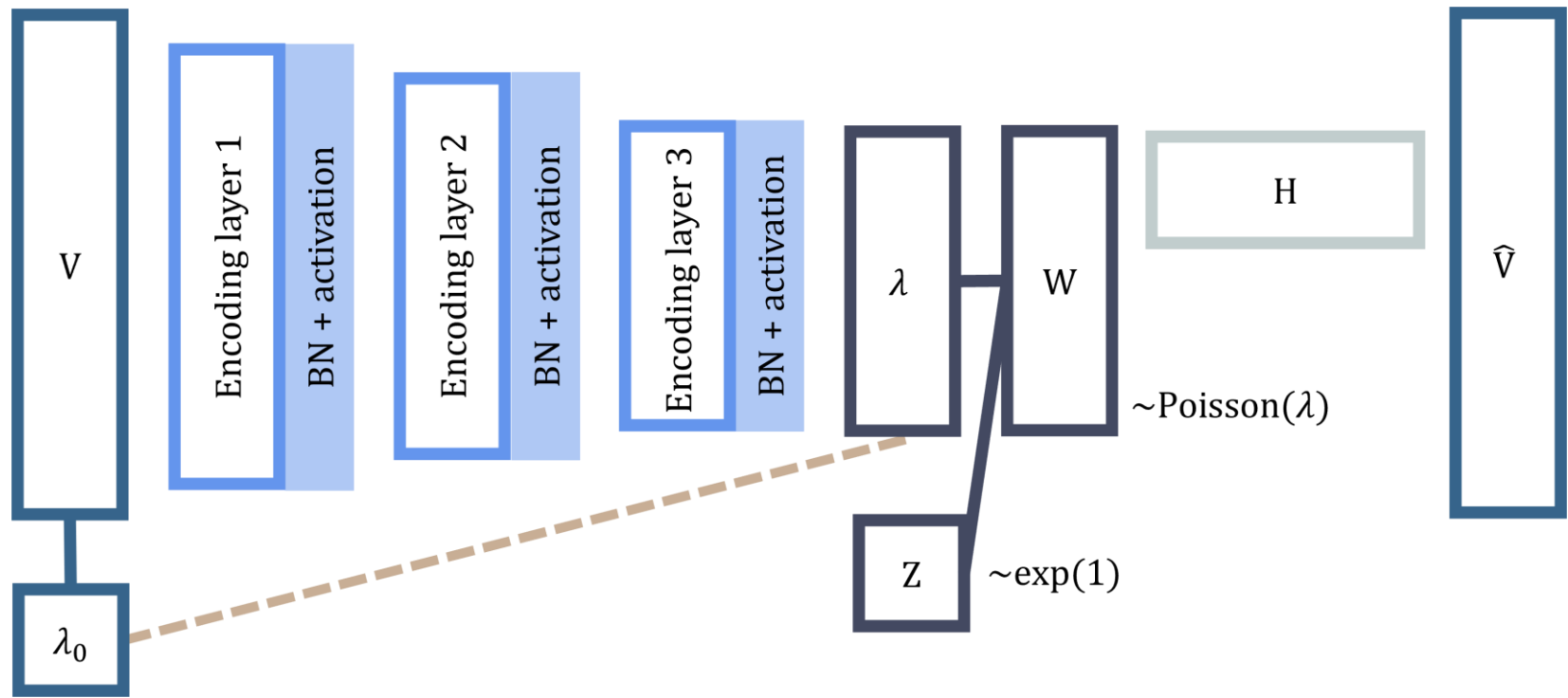
Develop an asymmetric Poisson
variational autoencoder for mutational
signature extraction

Evaluate against state-of-the-art models
in simulated data and a large,
heterogenous cohort of cancer patients



BACKGROUND

[Egendal et al., In Preparation]



Cohorts

Simulated Scenario 8 (n = 1000)
Simulated Scenario 14 (n = 2700)
PCAWG (n = 2780)

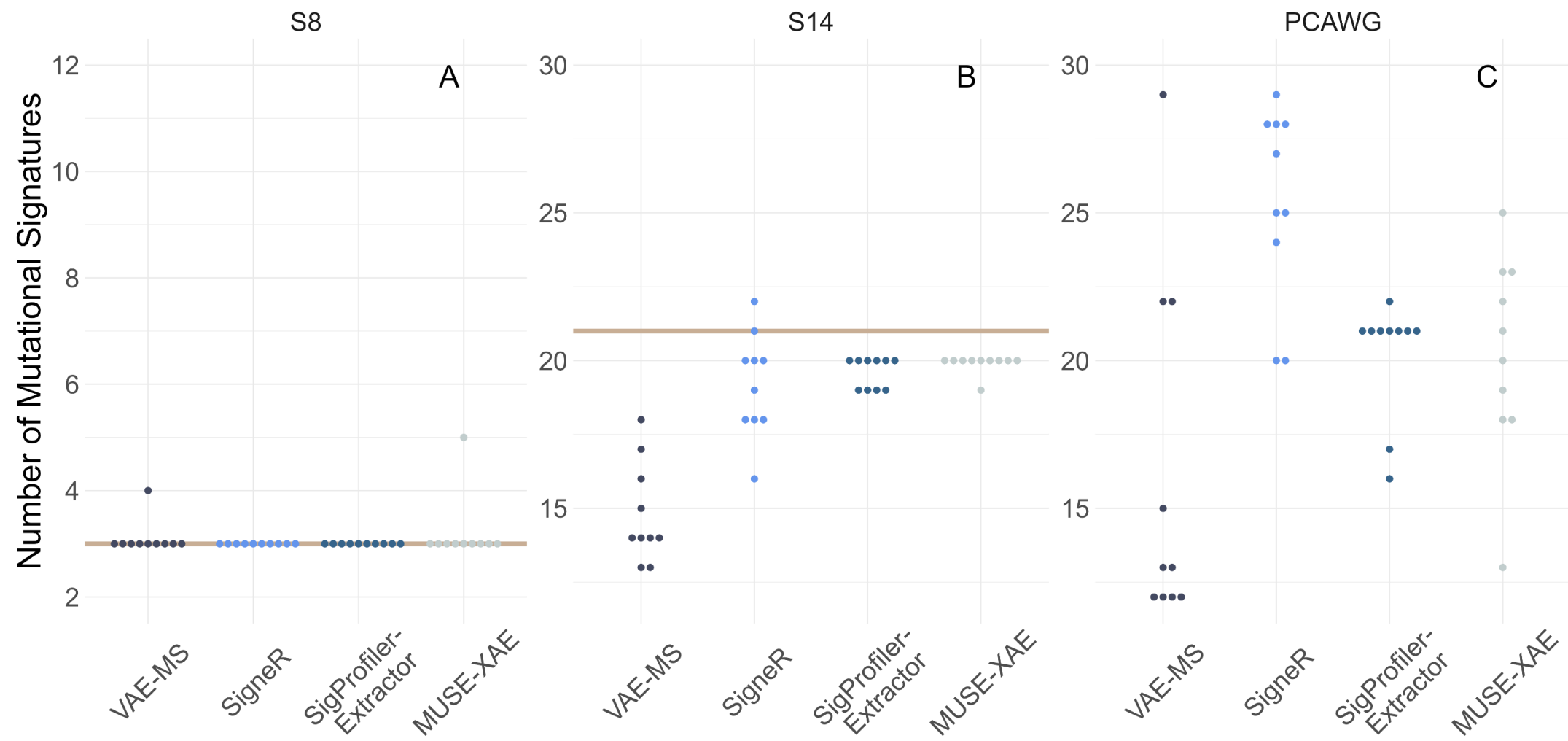


Method	Core Model	Reference
VAE-MS	Variational Autoencoder	Egendal et al. in preparation
MUSE-XAE	Autoencoder	Pancotti et al. 2024
Signer	Bayesian NMF	Rosales et al. 2017
SigProfilerExtractor	NMF	Islam et al. 2022



RESULTS

[Egendal et al., In Preparation]



RESULTS

	Model	$\mathcal{D}_{\text{KL}}$		$\mathcal{D}_{\text{MSE}}$		PACS
		Train	Test	Train	Test	
S8	VAE-MS	11.7	4.9	255	255	0.99
	SigneR	7.9	3.1	2	5	0.99
	SigProfilerExtractor	3.1	3.2	0.12	12	0.99
	MUSE-XAE	3.1	3.1	3.6	1.6	0.99
S14	VAE-MS	4.7	4.5	1817	1861	0.96
	SigneR	3.1	3.2	215	407	0.97
	SigProfilerExtractor	3.2	28.8	319	728112	0.99
	MUSE-XAE	4.5	4.4	7204	2169	0.96
PCAWG	VAE-MS	5.5	5.2	1876	1718	0.94
	SigneR	4.2	5.3	5713	53014	0.93
	SigProfilerExtractor	10.8	19.4	166035	464576	0.99
	MUSE-XAE	11.4	10.7	282514	216085	0.99

[Egendal et al., In Preparation]

CONCLUSIONS

VAE-MS is the first variational autoencoder for mutational signature extraction.

VAE-MS outperforms multiple state-of-the-art methods on real data.

VAE-MS displays inconsistent signature assignment and stability



MUTATIONAL SIGNATURES FOR PROGNOSTIC STRATIFICATION IN OVARIAN CANCER

Ida Egendal, Lasse Ringsted Mark, Anne Krejbjerg Motavaf, Inge Søkilde Pedersen, Karen Dybkær, Rasmus Froberg Brøndum, and Martin Bøgsted

In preparation

Apply VAE-MS in a clinical setting

Evaluate six state-of-the-art mutational signature extraction tools

Use mutational signature-derived biomarkers to **stratify survival** when subjected to platinum-based chemotherapy





A diagnosis



A well studied genomic disorder



A treatment targeting the genomic disorder



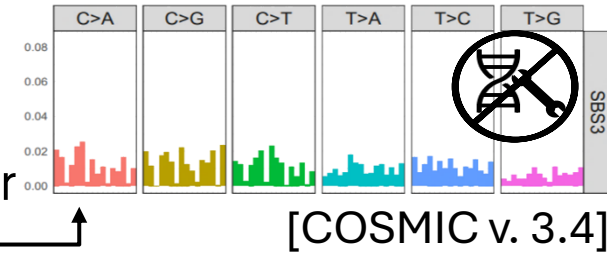
Ovarian cancer



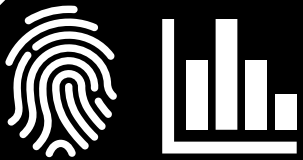
Homologous recombination deficiency



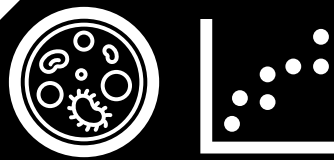
Platinum-based chemotherapy



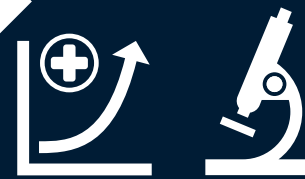
Extraction
of signatures



Biological or
statistical
association



Biomarker



Decision
support tool



RESULTS

[Egendal et al., In Preparation]



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VAE-MS derived HRD High
patients experienced the
longest progression-free
survival

[Egendal et al., In Preparation]



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RESULTS

[Egendal et al., In Preparation]



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RESULTS



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[Egendal et al., In Preparation]



CONCLUSIONS

HRD status from mutational signatures predicts platinum response beyond BRCA mutations.

VAE-MS identifies clinically relevant HRD status using fewer, more compact signatures.



THANK YOU

Martin Bøgsted

Rasmus Brøndum

Inge Søkilde Pedersen

Karen Dybkær

Cristopher Yau and the Yau Group

Dan Woodcock

Asger Hobolth

Marta Pelizzola

CLINDA

REPAIR KUBEN

DDSA

To you for listening



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