Doctoral Thesis

<Lung Precancer Analysis>

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Abstract

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I Introduction

1.1 Lung Cancer

Lung cancer is the most common form of cancer as 12.3 % of all cancers (Minna, Roth, & Gazdar, 2002).

1.2 Non-small Cell lung cancer

Lung Adenocarcinoma (LUAD)

Lung Squamous Cell Carcinoma (LUSC)

LUSC vs. LUAD

1.3 Lung Precancer

1.4 Study Objectives

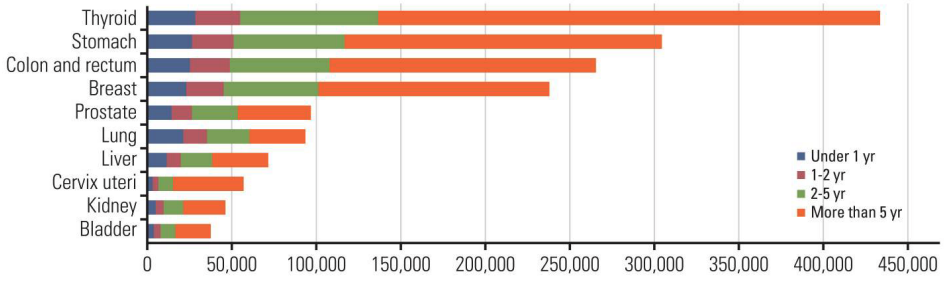


Figure 1: Common cancer survival rates (Hong et al., 2021)

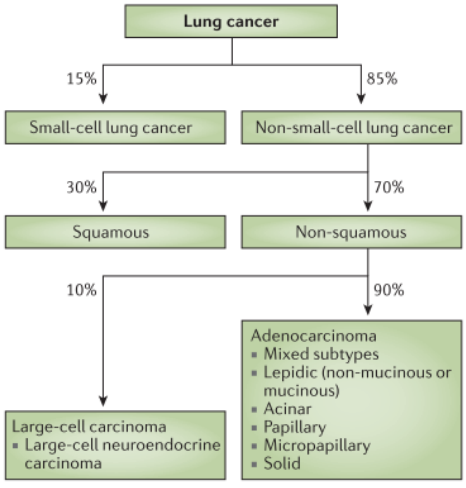


Figure 2: Lung cancer classification (Gridelli et al., 2015)

II Materials

2.1 List of IPNs

Carcinoma *in situ*

Carcinoma *in situ* (CIS)

Adenocarcinoma *in situ*

Adenocarcinoma *in situ* (AIS)

Atypical Adenomatous Hyperplasia

Atypical adenomatous hyperplasia (AAH)

Dysplasia

Minimally Invasive Adenocarcinoma

Minimally invasive adenocarcinoma (MIA)

2.2 Data Composition

Table 1: WES Data Composition

Cancer Subtype	Stage	Number of Samples
LUSC	Normal	77
	Dysplasia	5
	AAH	8
	CIS+AIS	73
	Primary	77
	Total	240
LUAD	Normal	18
	AAH	15
	CIS+AIS	9
	MIA	1
	Primary	18
	Total	61

Table 2: WTS Data Composition

Cancer Subtype	Stage	Number of Samples
LUSC	Normal	17
	Dysplasia	2
	CIS+AIS	34
	Primary	36
	Total	89
LUAD	Normal	13
	AAH	1
	CIS+AIS	5
	Primary	6
	Total	25

III Methods

3.1 Workflows

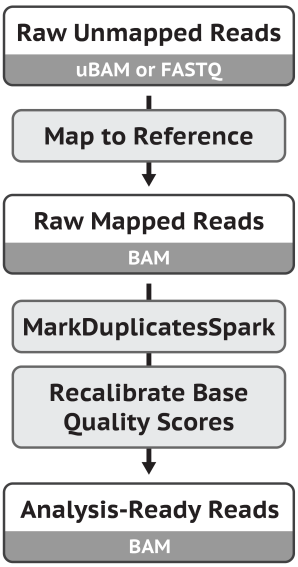


Figure 3: Workflow for data pre-processing for variant discovery (Van der Auwera et al., 2013; DePristo et al., 2011)

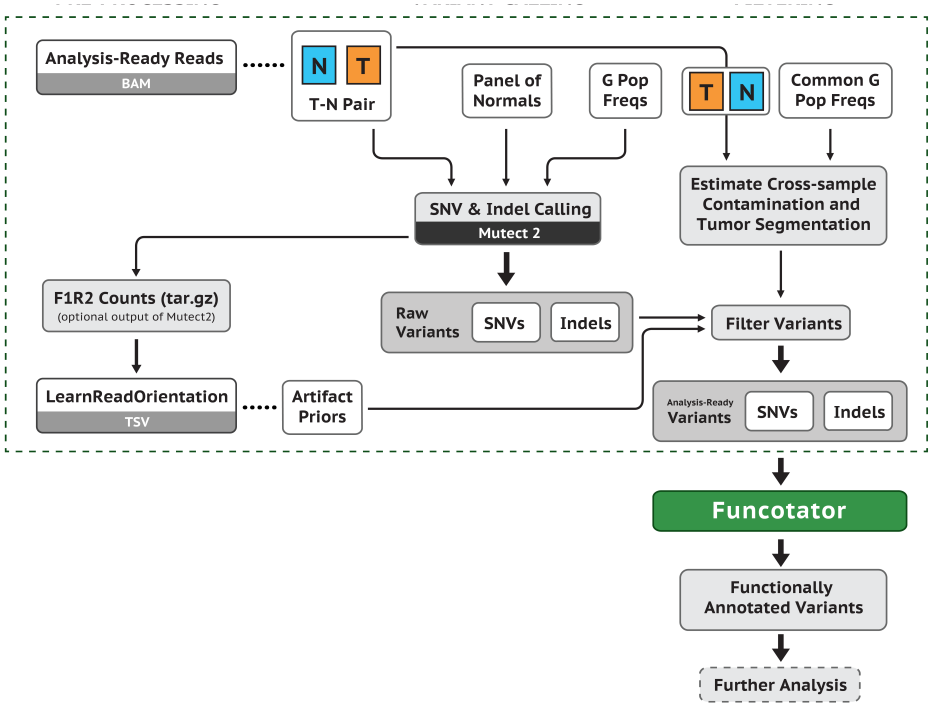


Figure 4: Somatic short variant discovery workflow (Van der Auwera et al., 2013; DePristo et al., 2011)

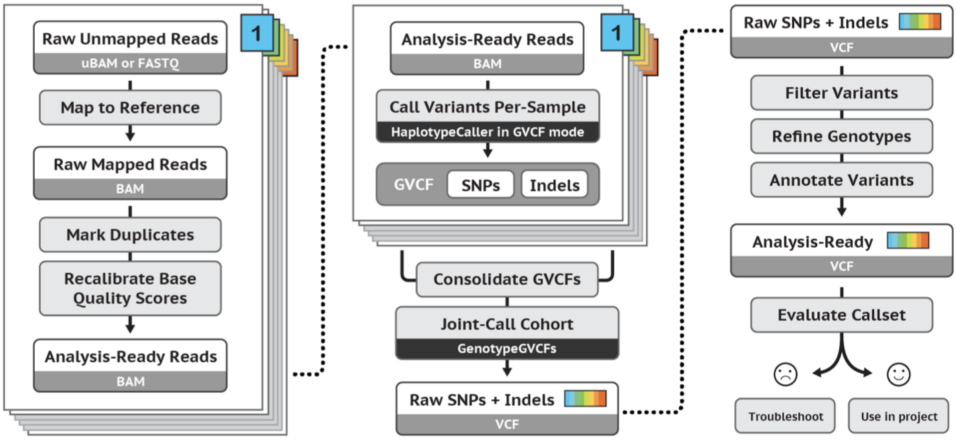


Figure 5: Germline short variant discovery workflow (Van der Auwera et al., 2013; DePristo et al., 2011)

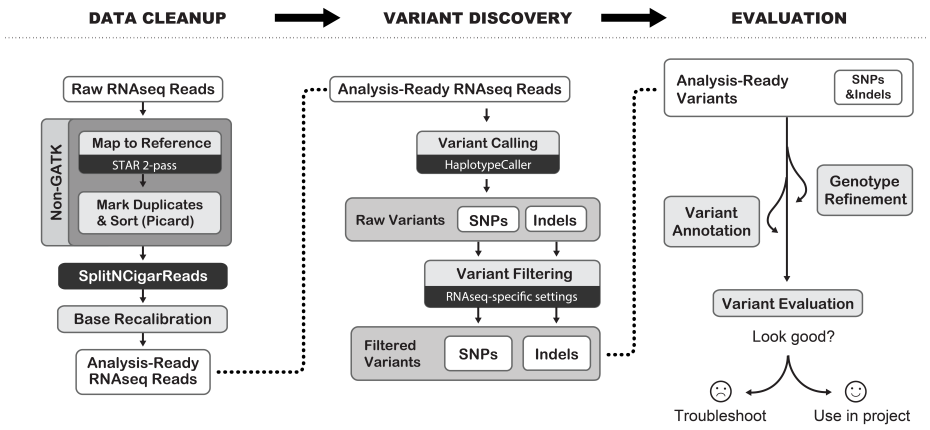


Figure 6: RNA-seq short variant discovery workflow (Van der Auwera et al., 2013; DePristo et al., 2011)

IV Results

4.1 Quality Checks

Quality Checks with FastQC

Quality Checks with Depths

Quality Checks with Picard

Findings in Quality Checks

4.2 Copy Number Variation Analyses

Purity and Ploidy

Copy Number Variation Analyses

Copy Number Variation Analyses with Recurrence

Copy Number Variation Analyses with Smoking History

Gistic Analyses

Gistic Analyses with Recurrence

Gistic Analyses with Smoking History

Findings in Copy Number Variation Analyses

4.3 Single Nucleotide Variation Analyses

Somatic Short Variation Analyses with Mutect2

Somatic Short Variant with Clinical Data

Findings in Somatic Short Variation Analyses

4.4 Variant Allele Frequency Analyses

Findings in Variant Allele Frequency Analyses

4.5 Bulk Cell Deconvolution Analyses

Single-cell Reference Data

GSE131907 as Reference

GSE162498 as Reference

GSE179994 as Reference

Findings in Bulk Cell Deconvolution Analyses

4.6 Mutational Signature Analyses

Single Base Substitutions

Double Base Substitutions

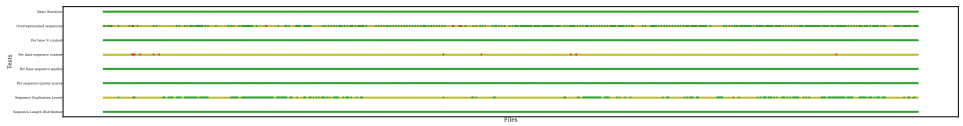


Figure 7: FastQC results with WES data

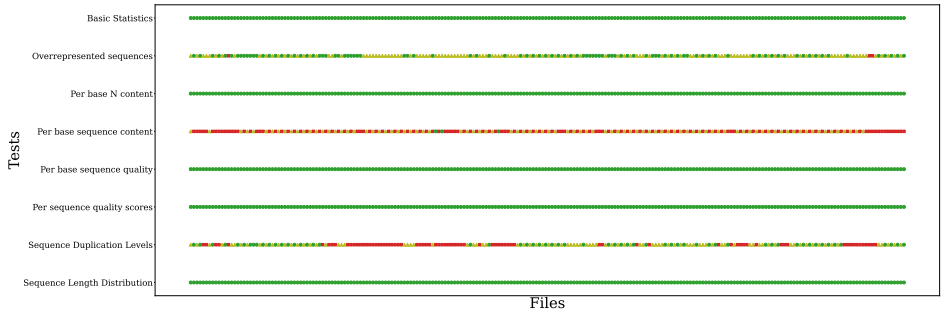
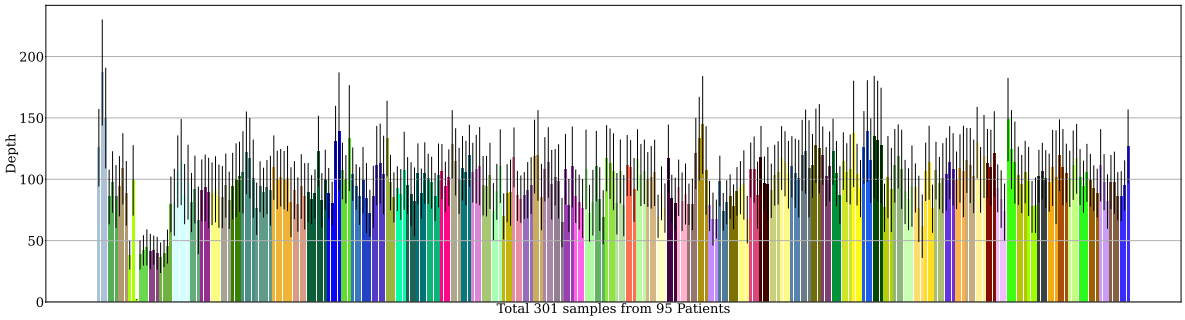
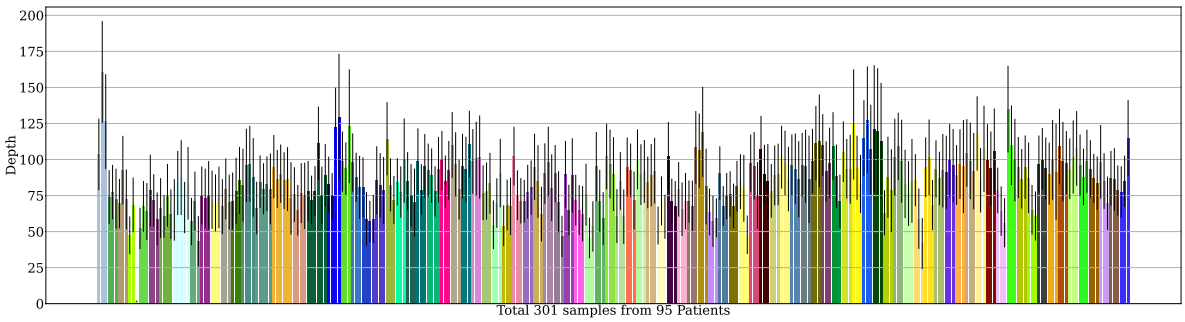


Figure 8: FastQC results with WTS data

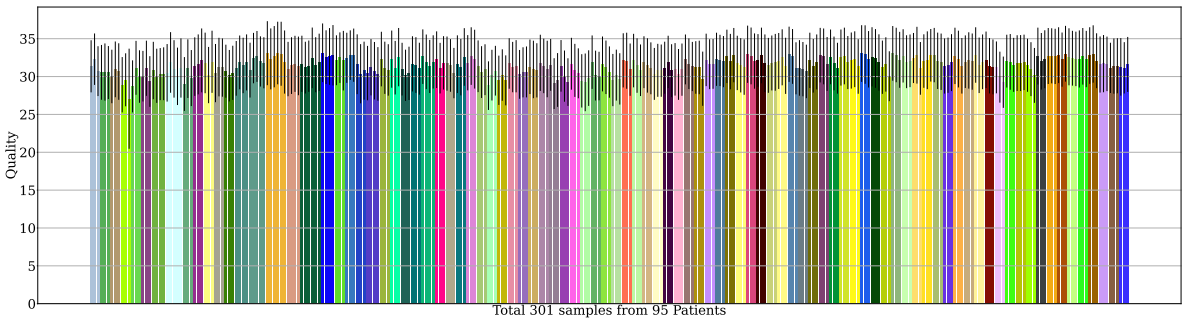


(a) BWA

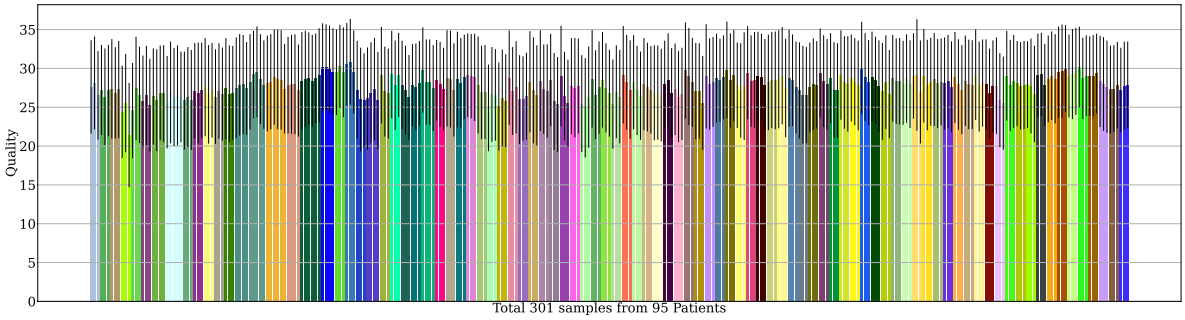


(b) Bowtie2

Figure 9: Depths plot with WES data

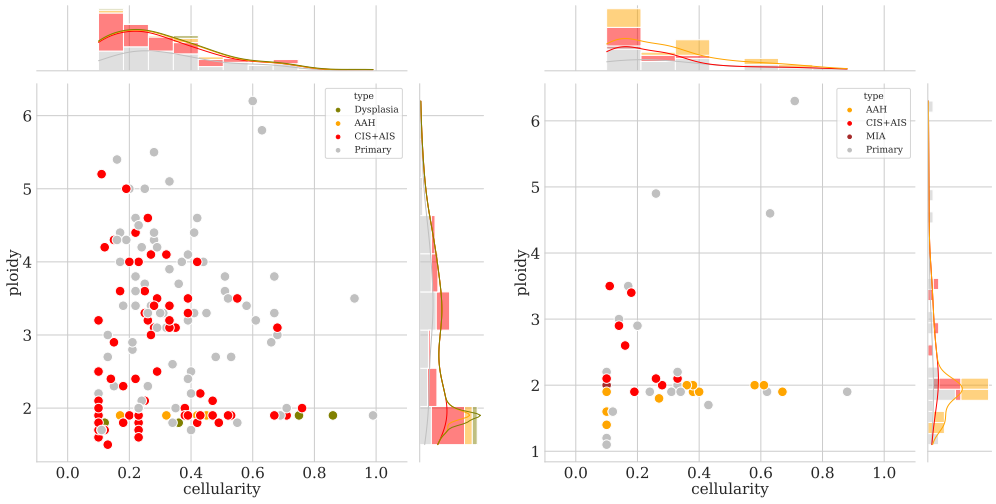


(a) BWA



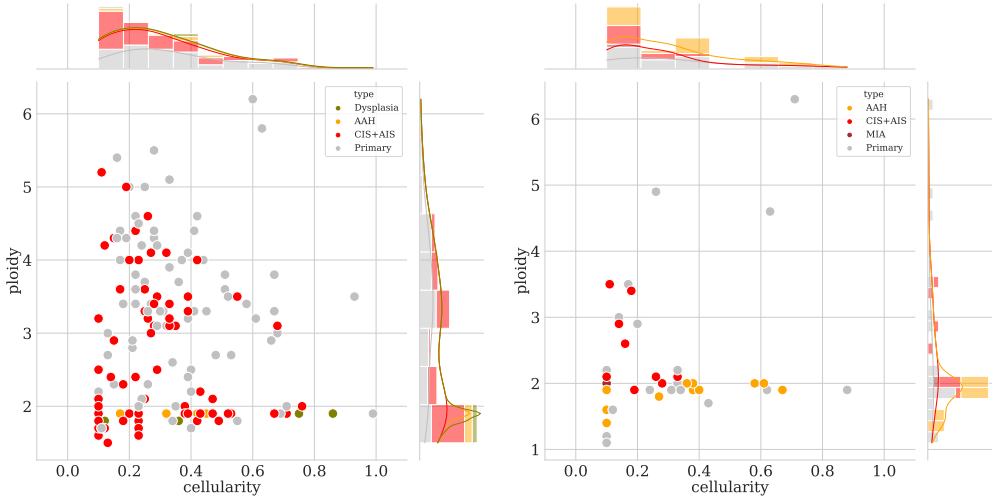
(b) Bowtie2

Figure 10: Quality Distribution by Samples



(a) Sequenza-BWA-LUSC

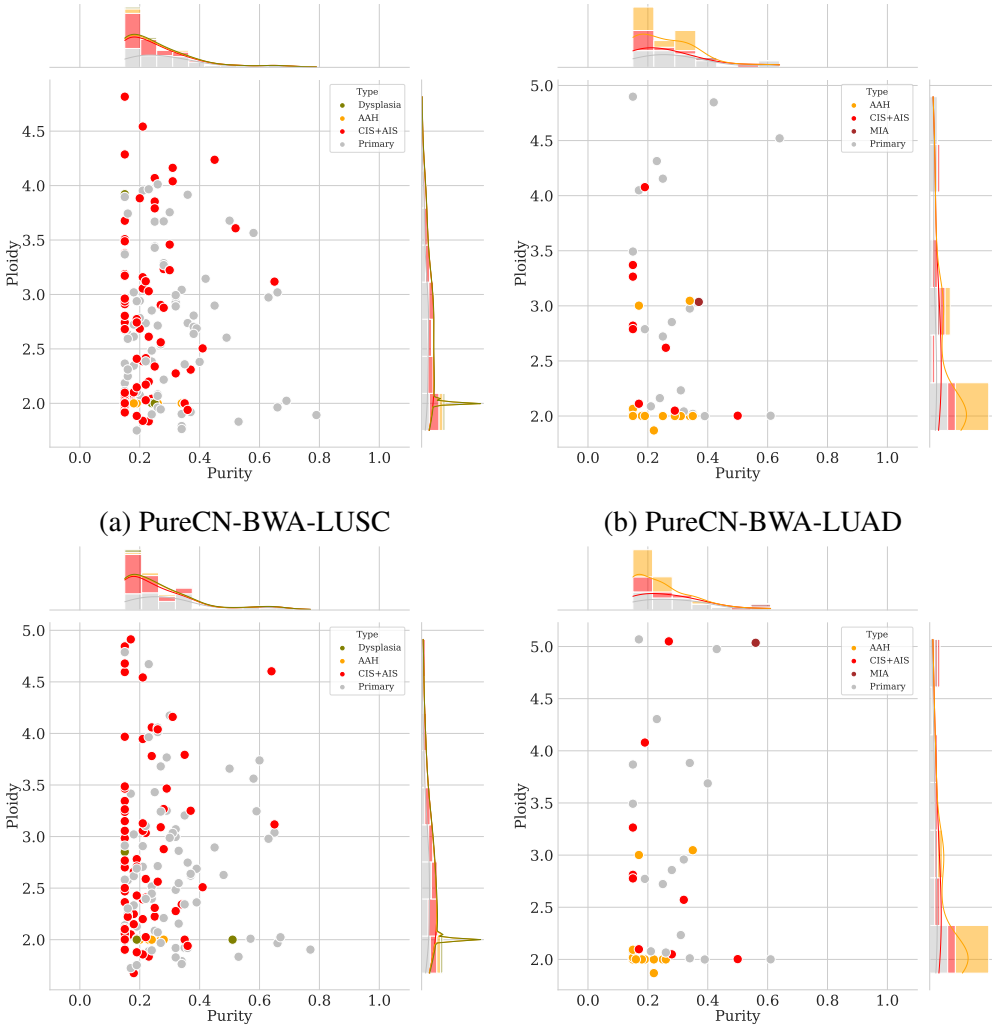
(b) Sequenza-BWA-LUAD



(c) Sequenza-Bowtie2-LUSC

(d) Sequenza-Bowtie2-LUAD

Figure 11: Sequenza Cellularity and Ploidy Plots



(a) PureCN-BWA-LUSC

(b) PureCN-BWA-LUAD

(c) PureCN-Bowtie2-LUSC

(d) PureCN-Bowtie2-LUAD

Figure 12: PureCN Purity and Ploidy Plots

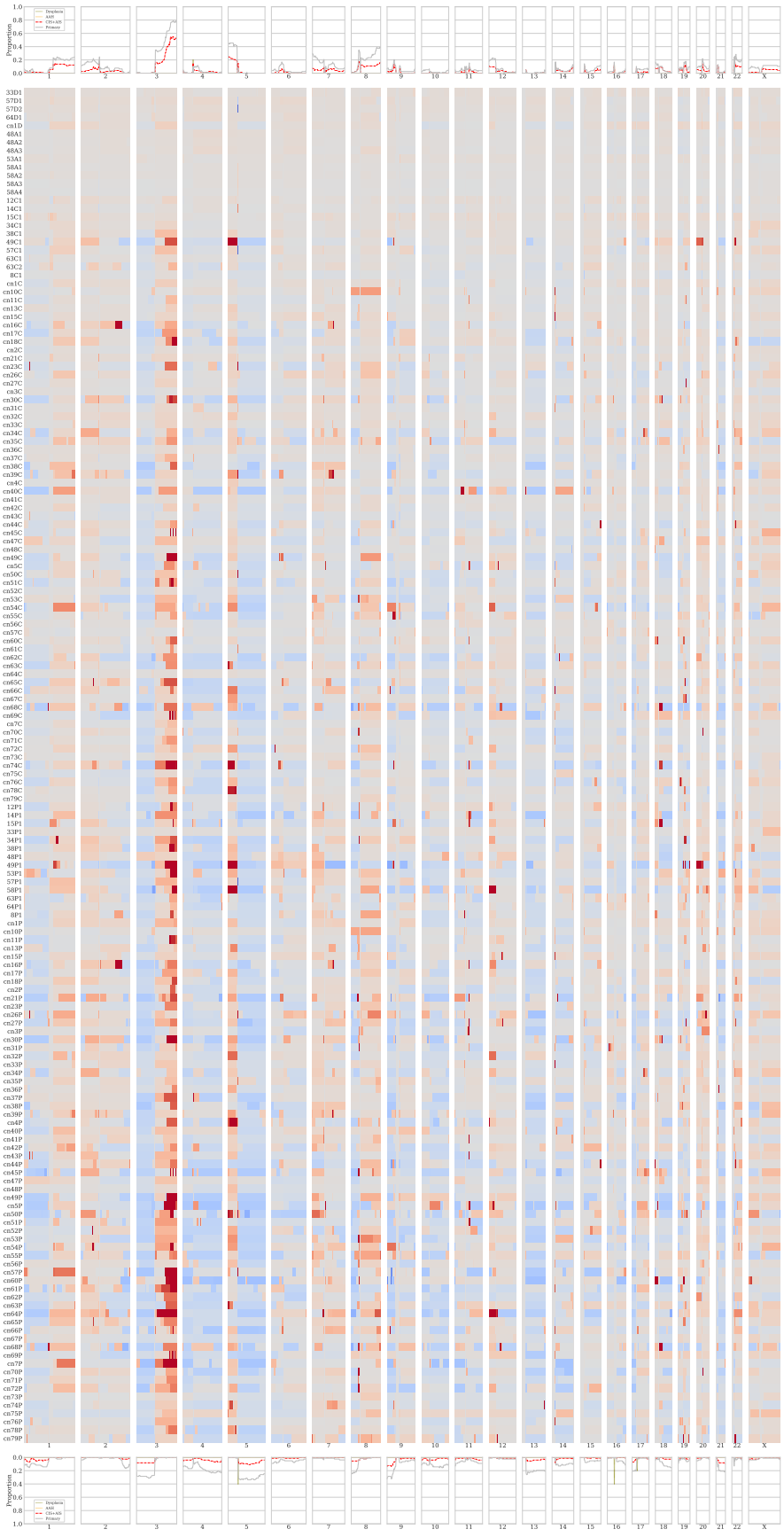


Figure 13: Sequenza LUSC Genome View Plot

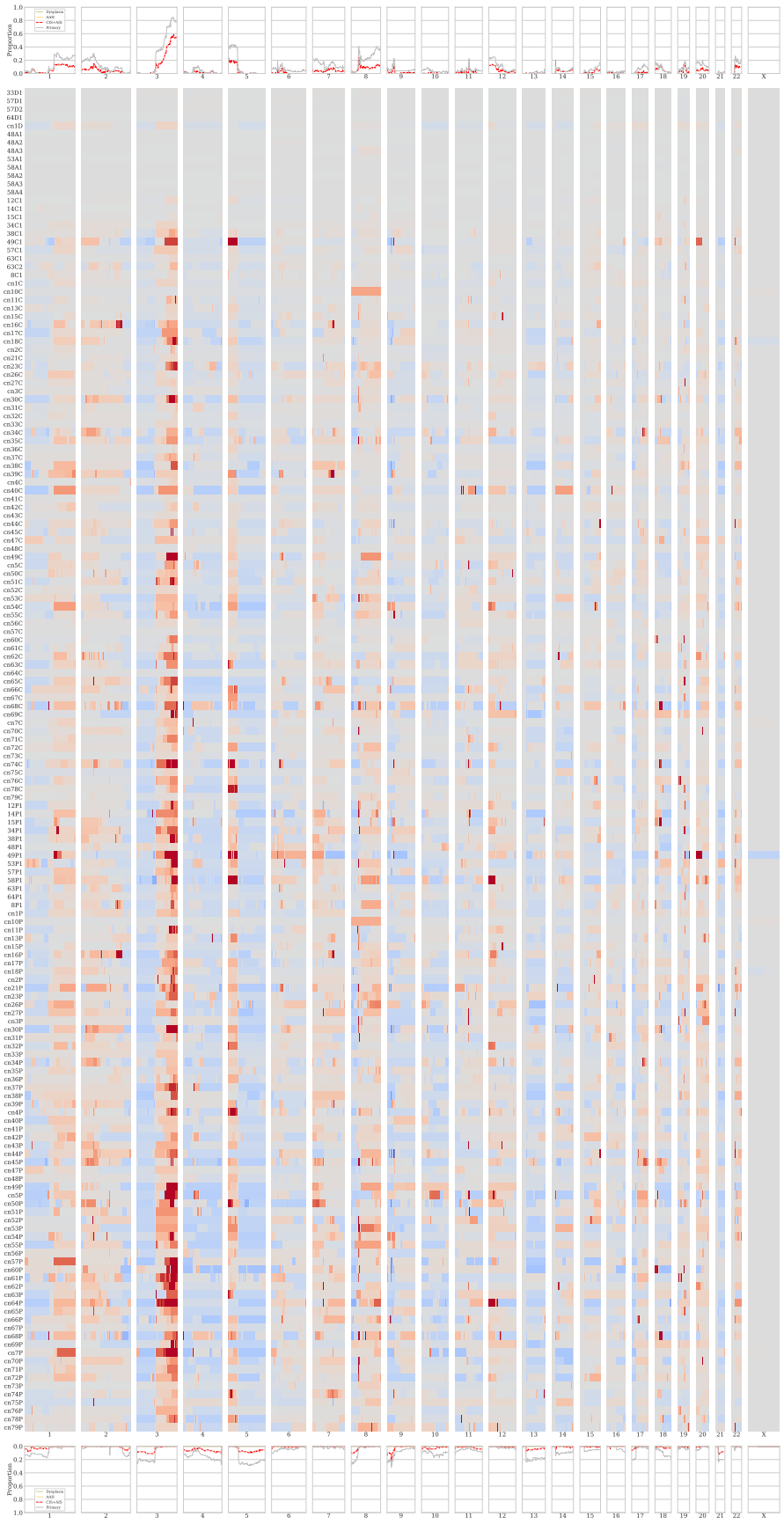


Figure 14: PureCN LUSC Genome View Plot

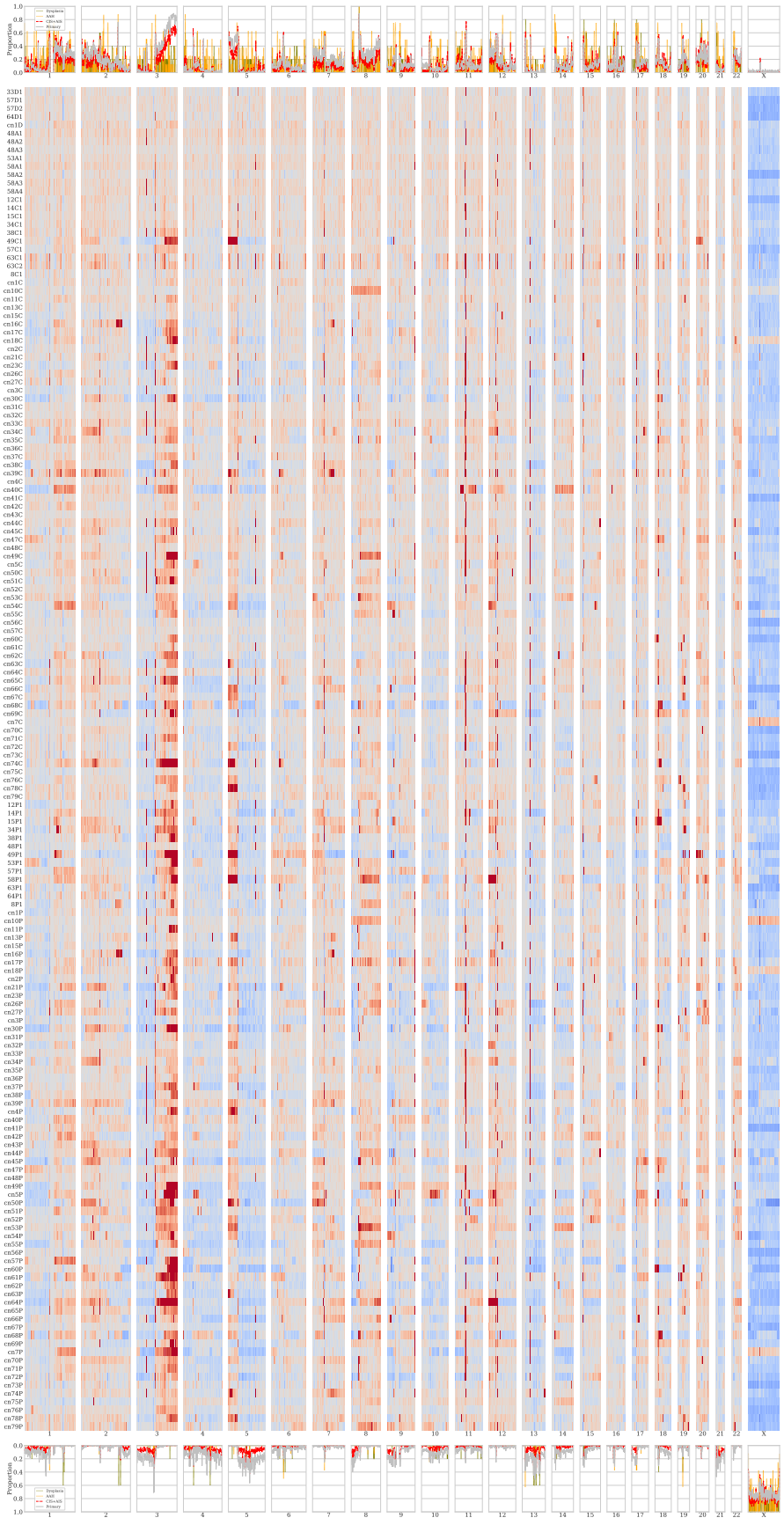


Figure 15: CNVkit LUSC Genome View Plot

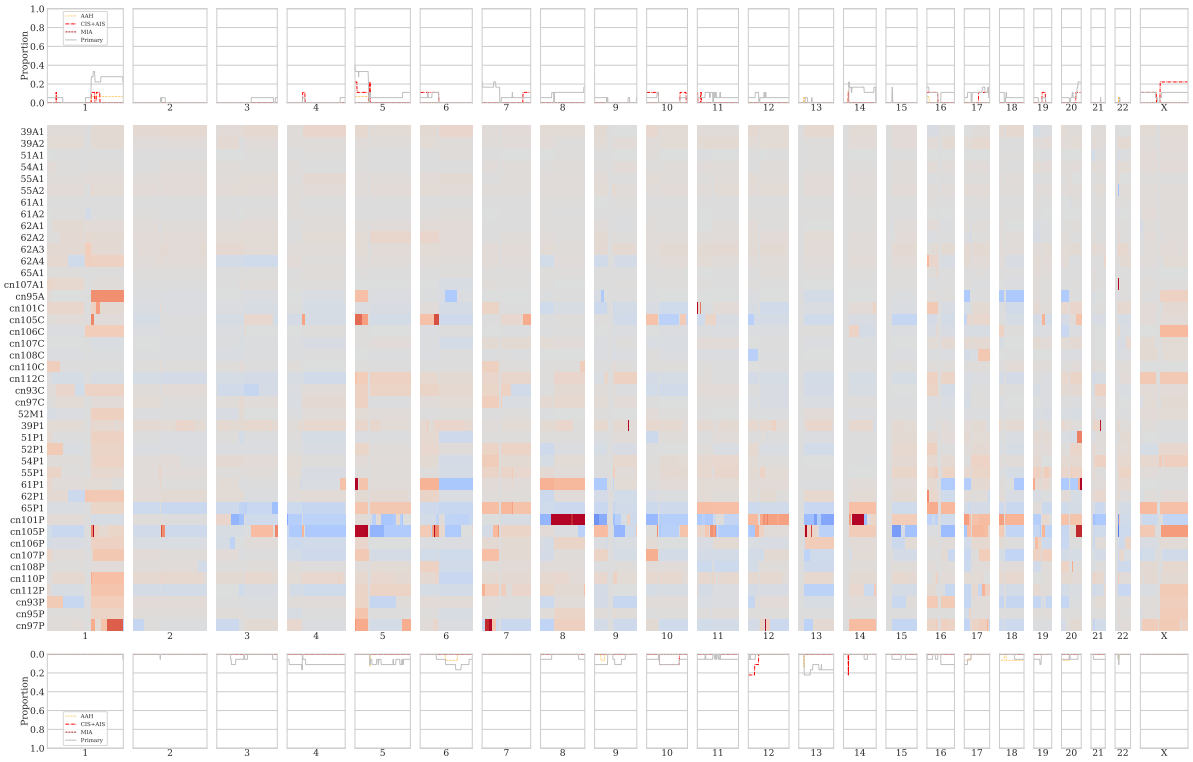


Figure 16: Sequenza LUAD Genome View Plot

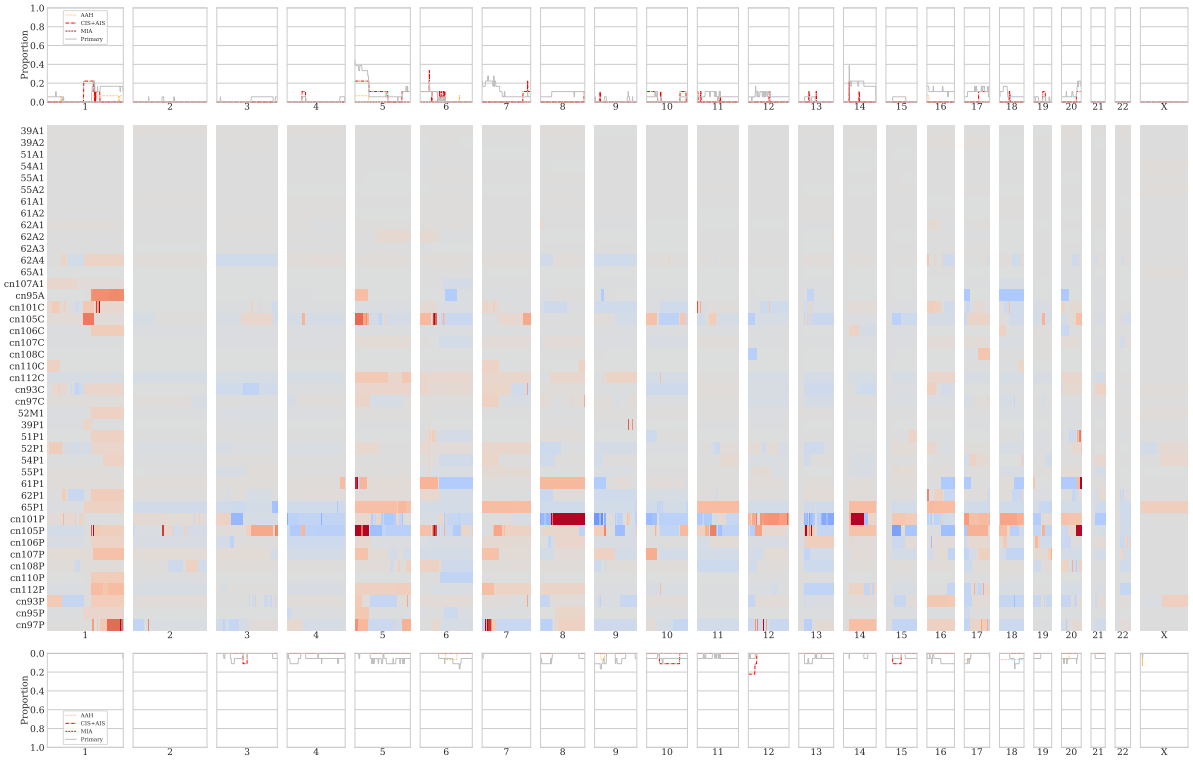


Figure 17: PureCN LUAD Genome View Plot

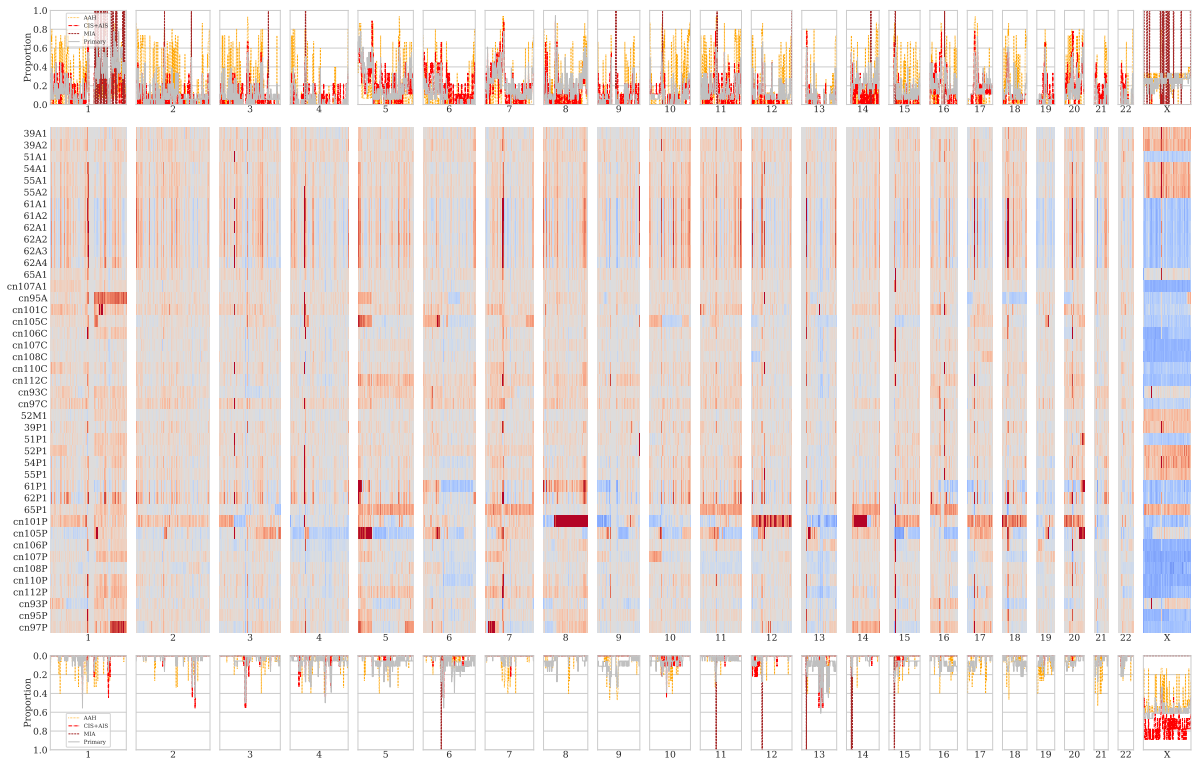


Figure 18: CNVkit LUAD Genome View Plot

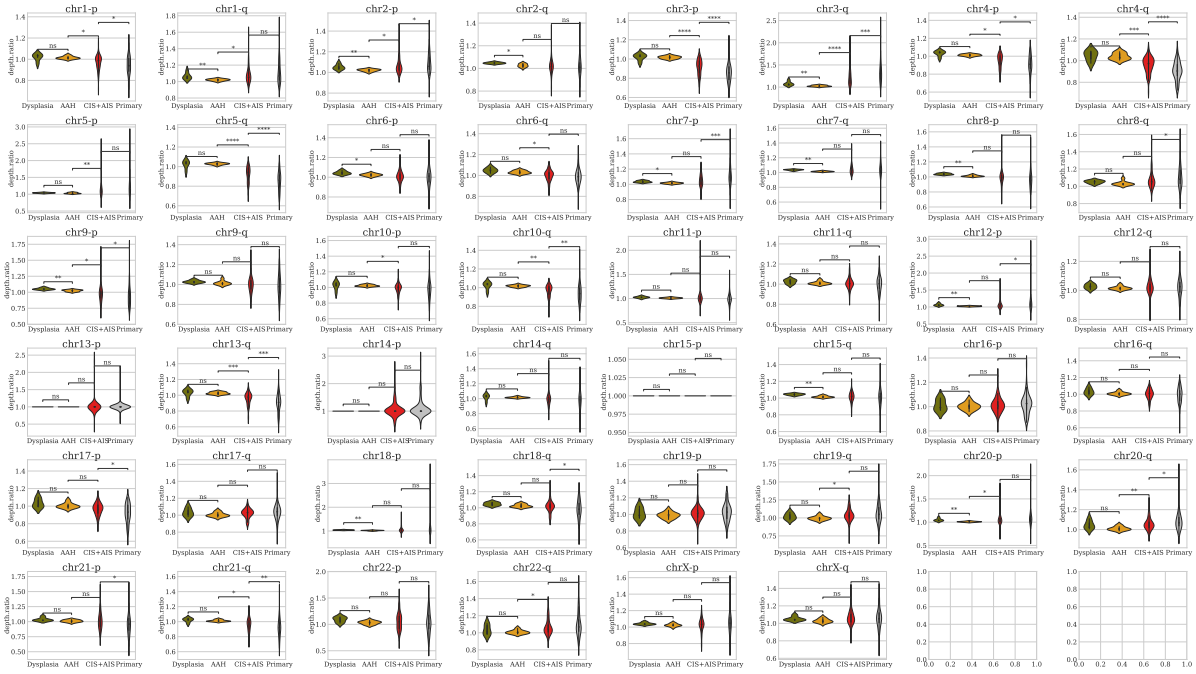


Figure 19: Sequenza LUSC Violin Plots

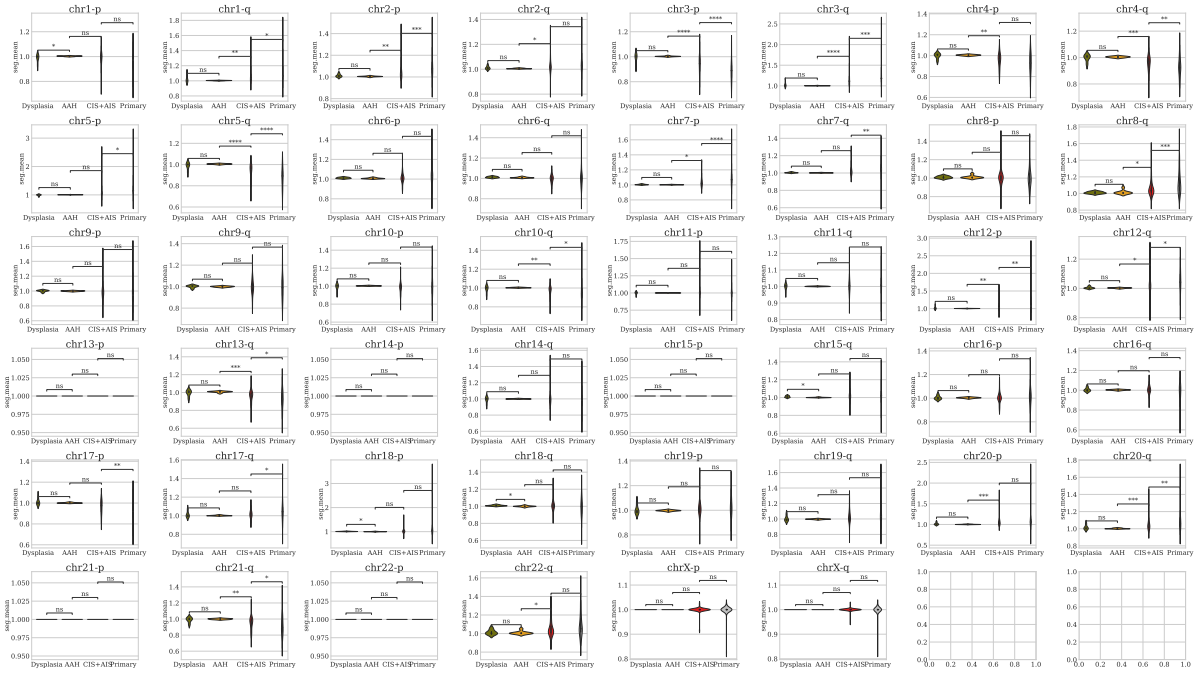


Figure 20: PureCN LUSC Violin Plots

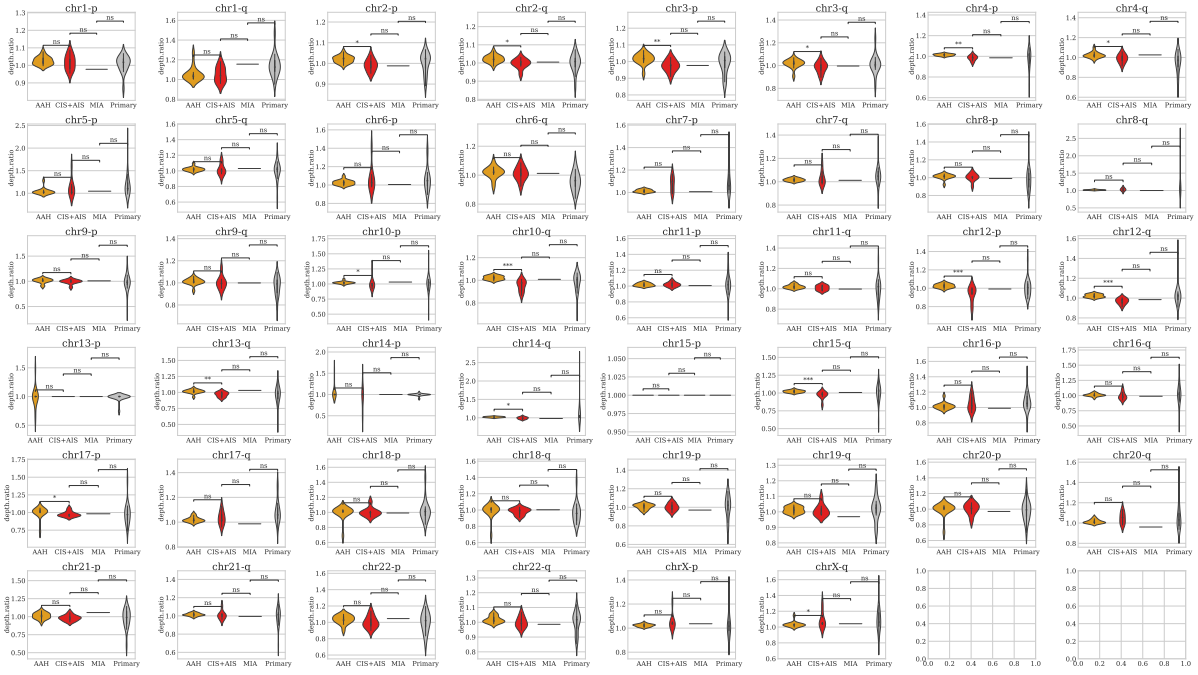


Figure 21: Sequenza LUAD Violin Plots

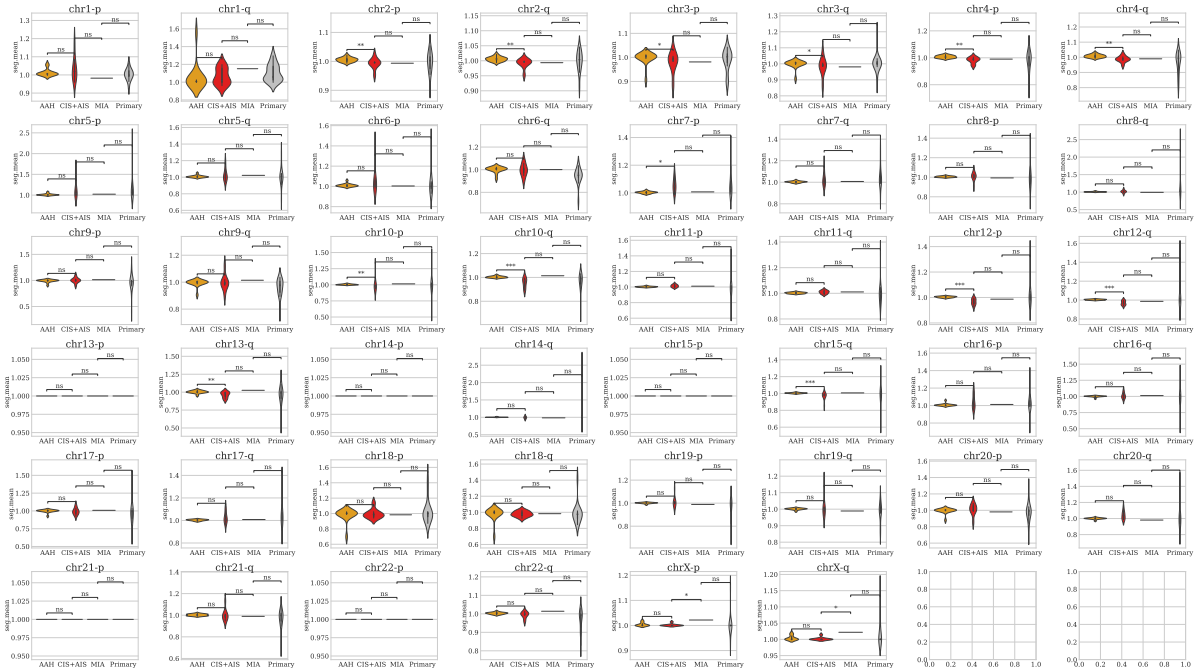
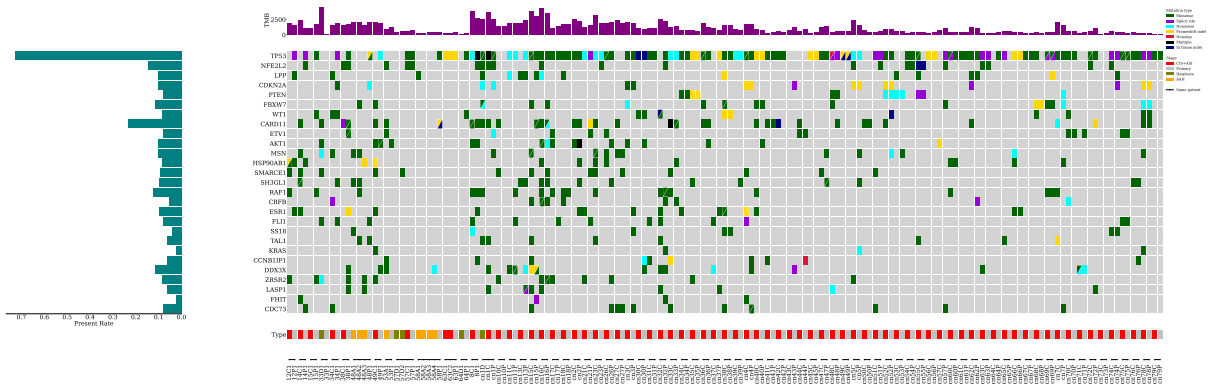
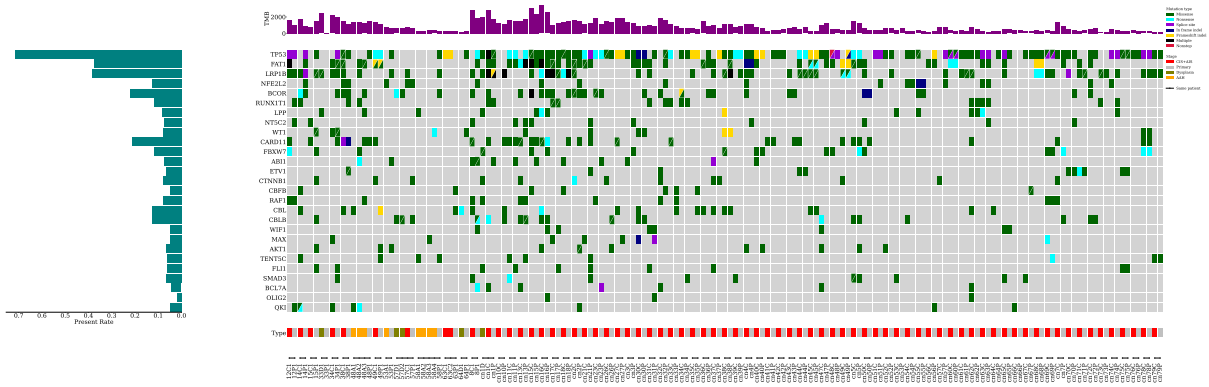


Figure 22: PureCN LUAD Violin Plots

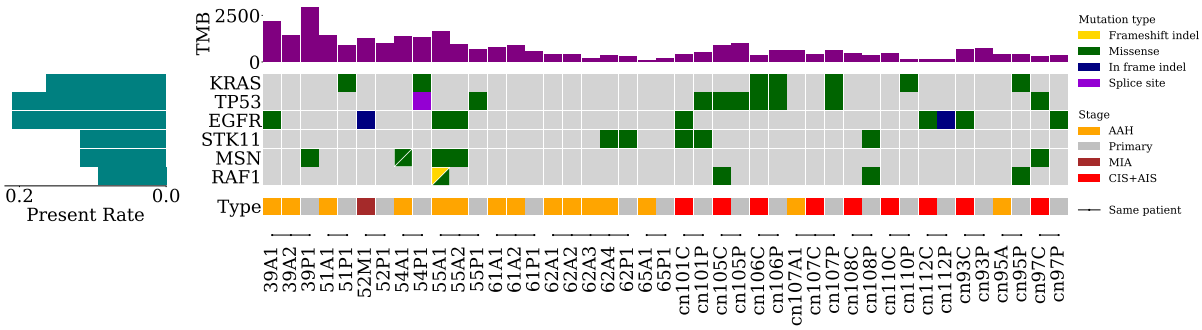


(a) BWA

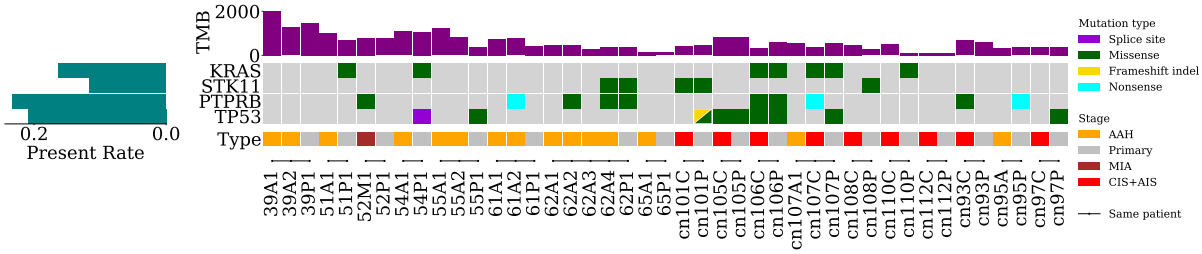


(b) Bowtie2

Figure 23: Comut Plot by LUSC

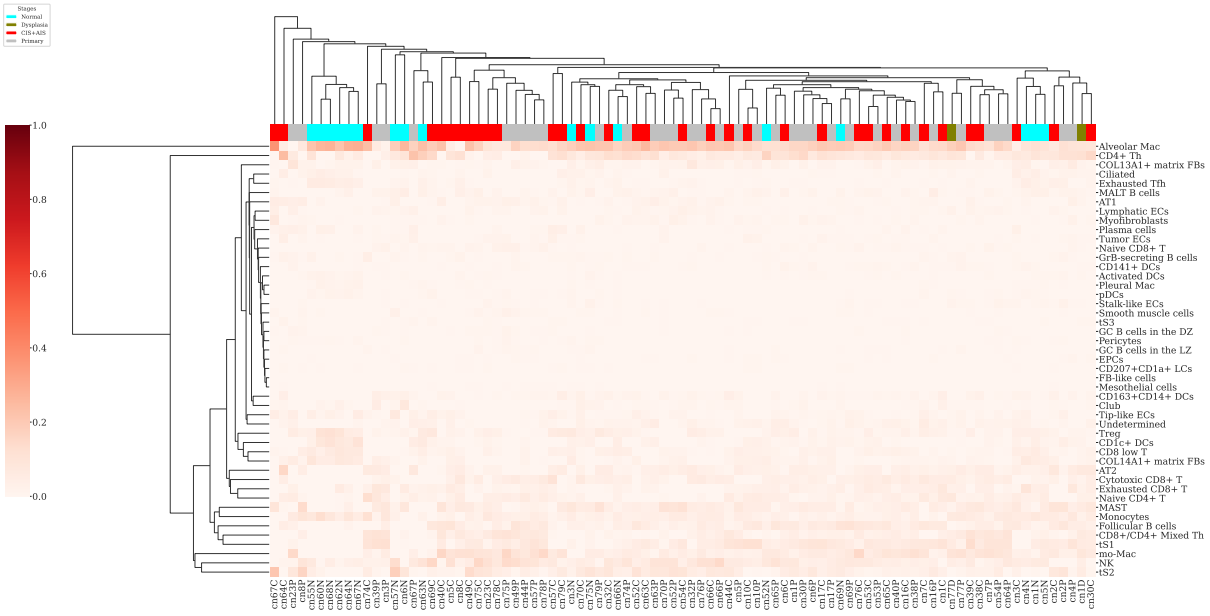


(a) BWA

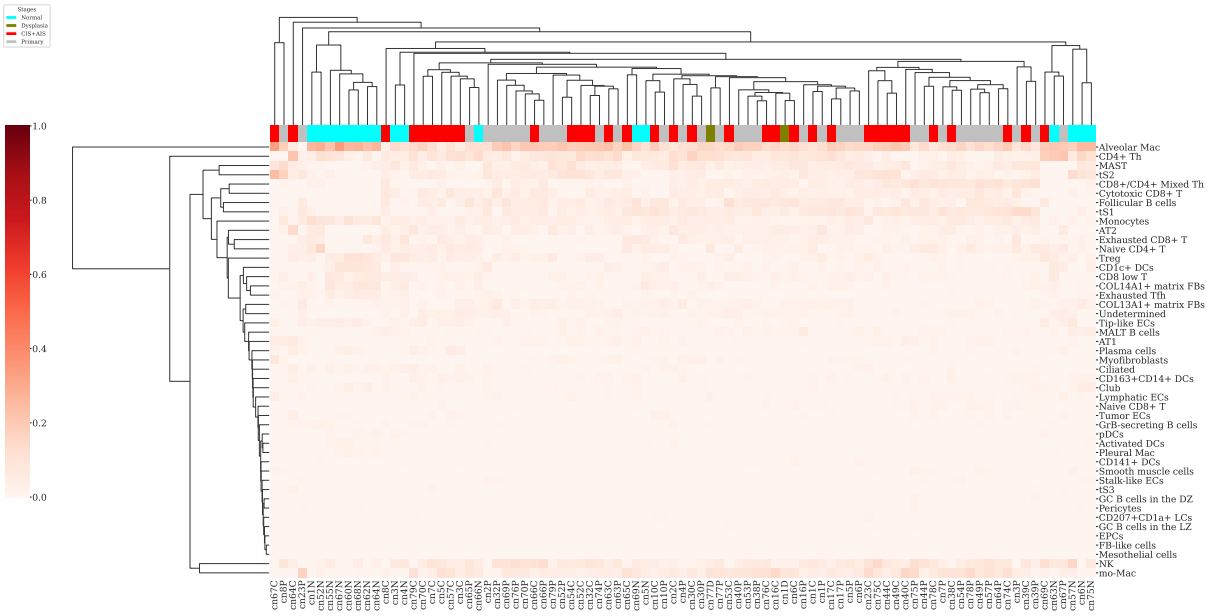


(b) Bowtie2

Figure 24: Comut Plot by LUAD

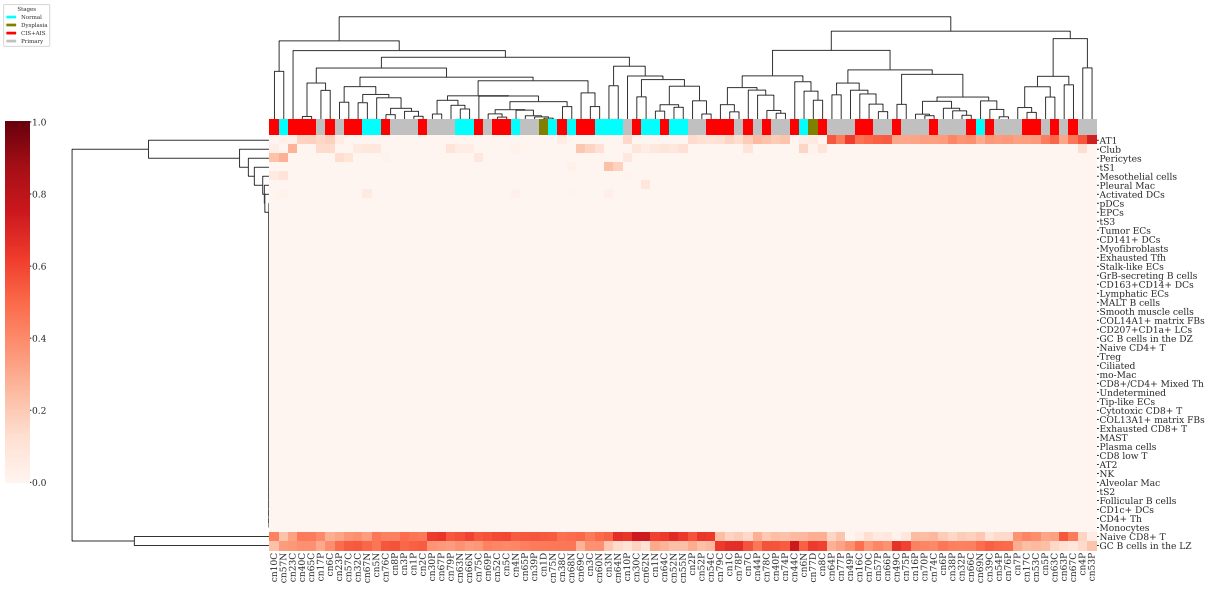


(a) STAR

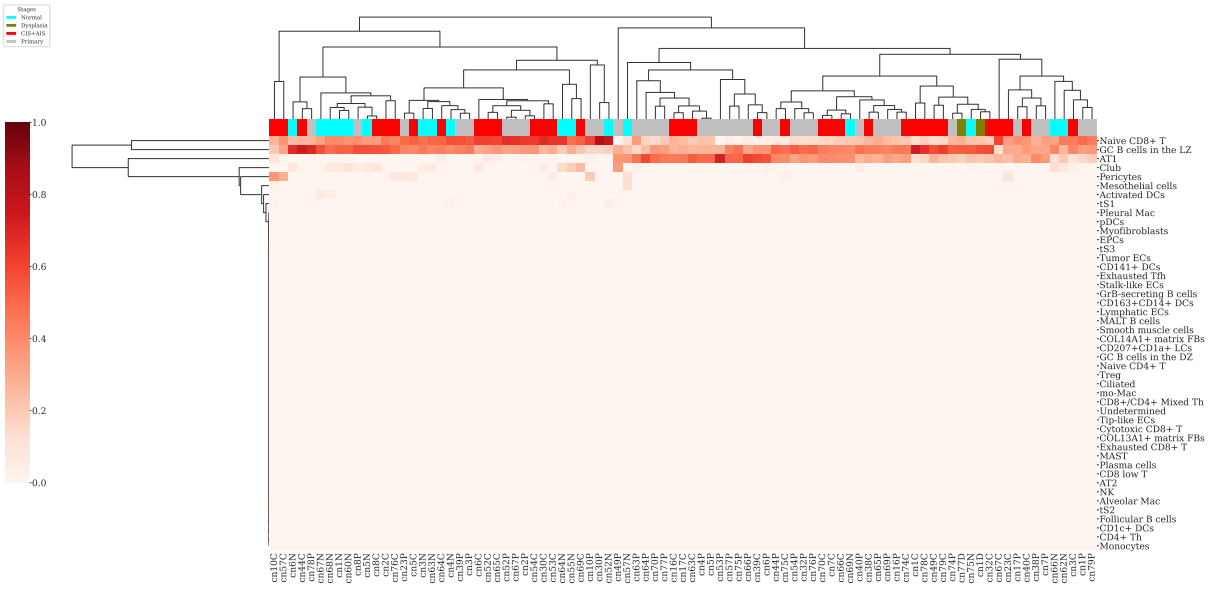


(b) Bowtie2

Figure 25: BisqueRNA clustermap plot with LUSC samples upon GSE131907

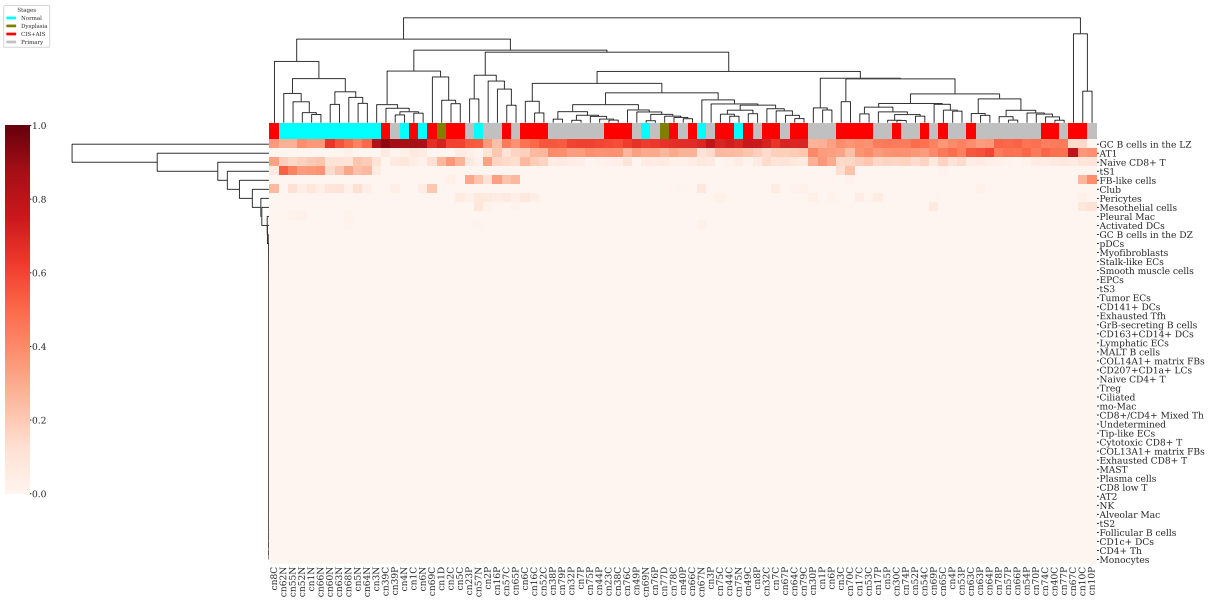


(a) STAR

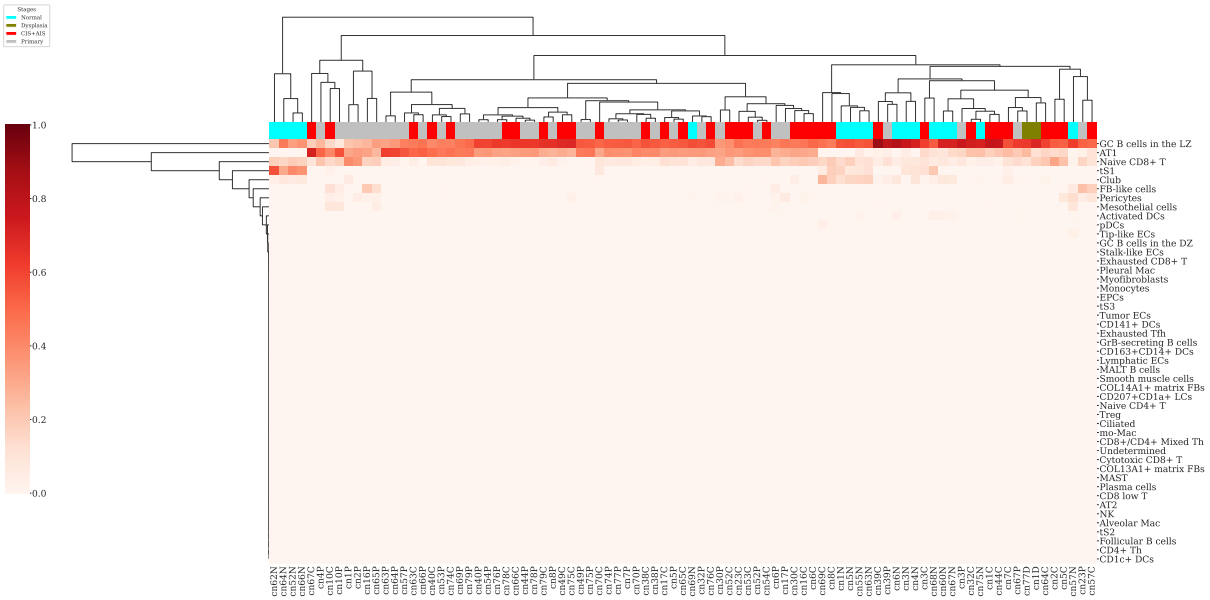


(b) Bowtie2

Figure 26: MuSiC clustermap plot with LUSC samples upon GSE131907

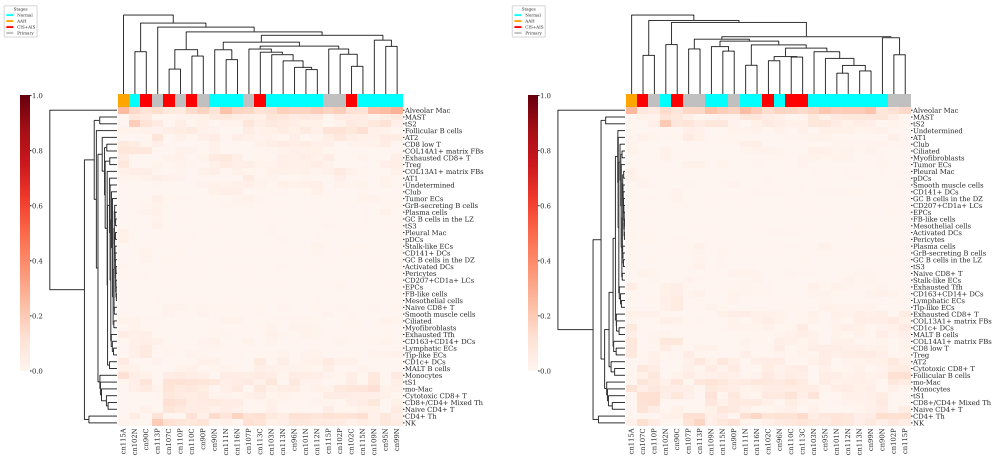


(a) STAR



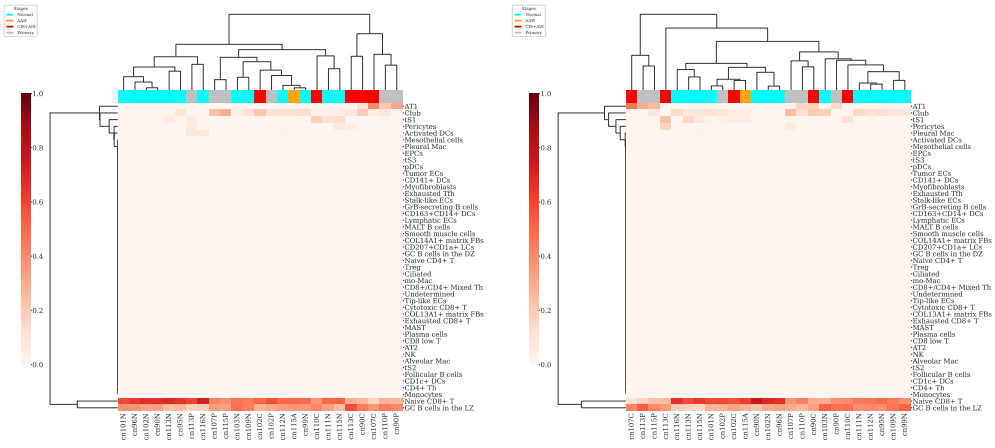
(b) Bowtie2

Figure 27: SCDC clustermap plot with LUSC samples upon GSE131907



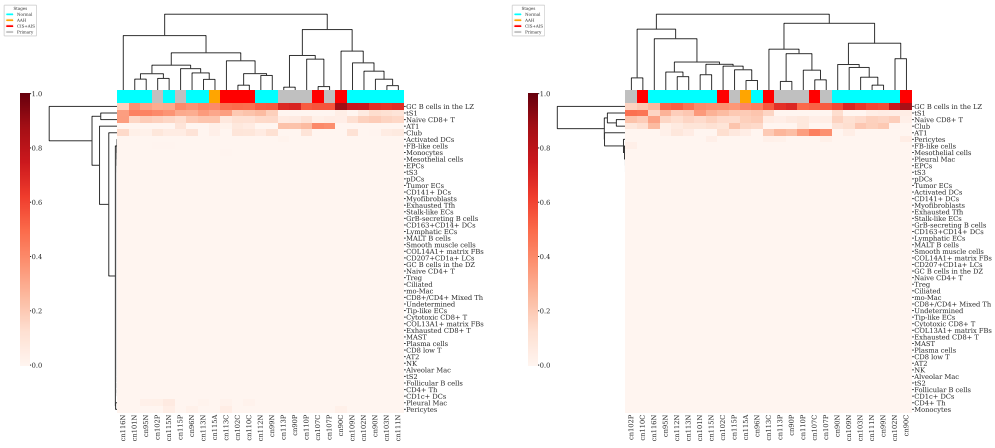
(a) STAR (b) Bowtie2

Figure 28: BisqueRNA clustermap plot with LUAD samples upon GSE131907



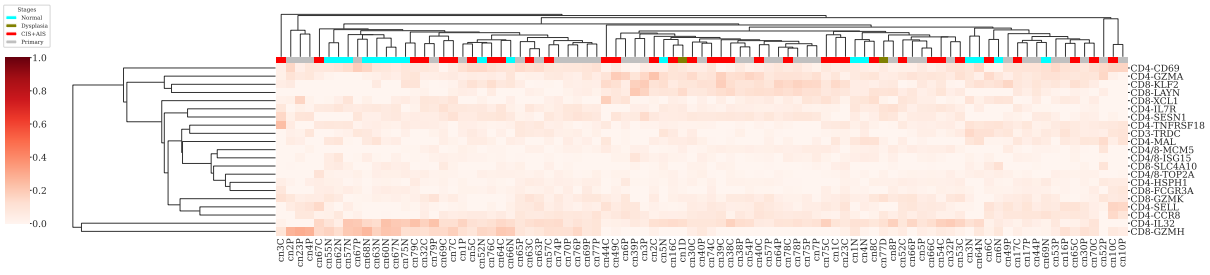
(a) STAR (b) Bowtie2

Figure 29: MuSiC clustermap plot with LUAD samples upon GSE131907

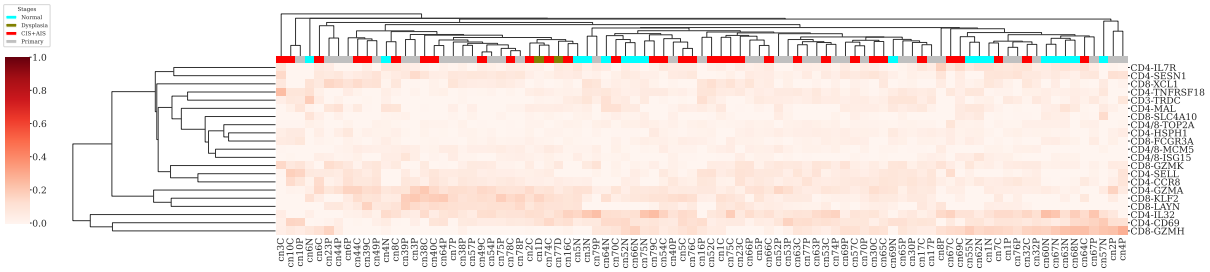


(a) STAR (b) Bowtie2

Figure 30: SCDCSiC clustermap plot with LUAD samples upon GSE131907

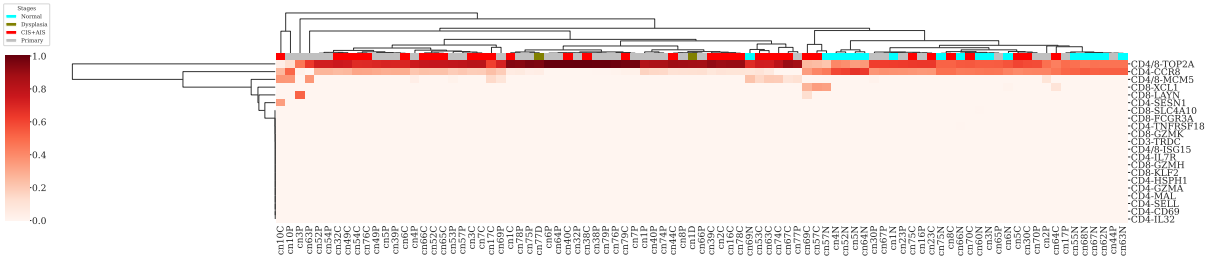


(a) STAR

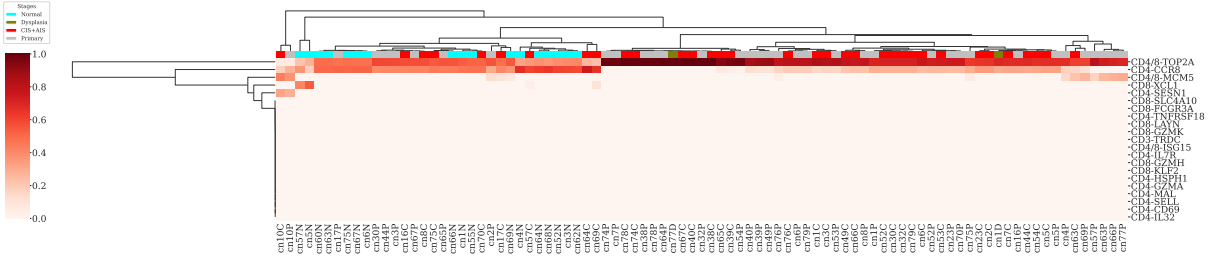


(b) Bowtie2

Figure 31: BisqueRNA clustermap plot with LUSC samples upon GSE162498

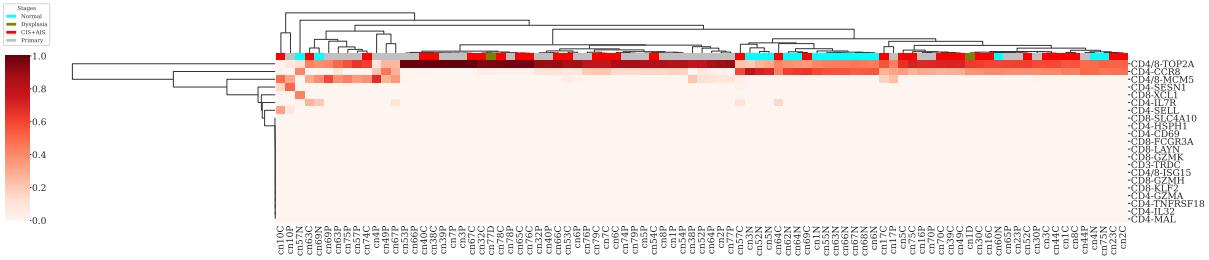


(a) STAR

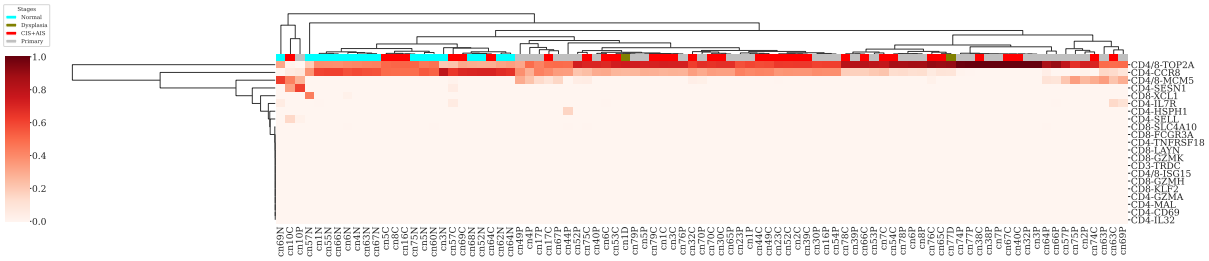


(b) Bowtie2

Figure 32: MuSiC clustermap plot with LUSC samples upon GSE162498

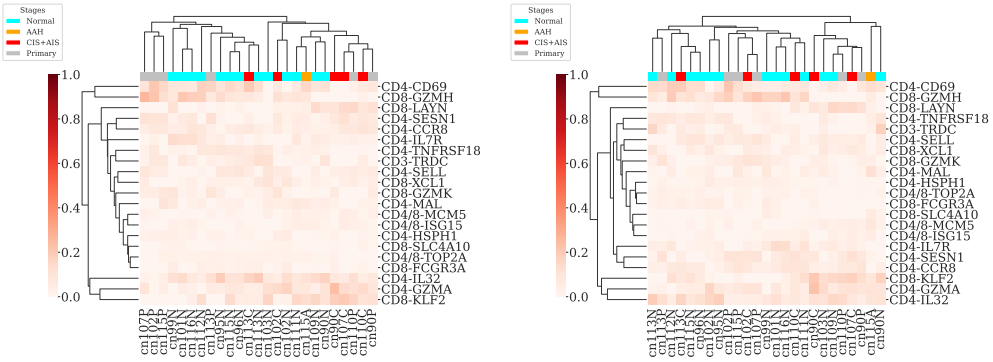


(a) STAR



(b) Bowtie2

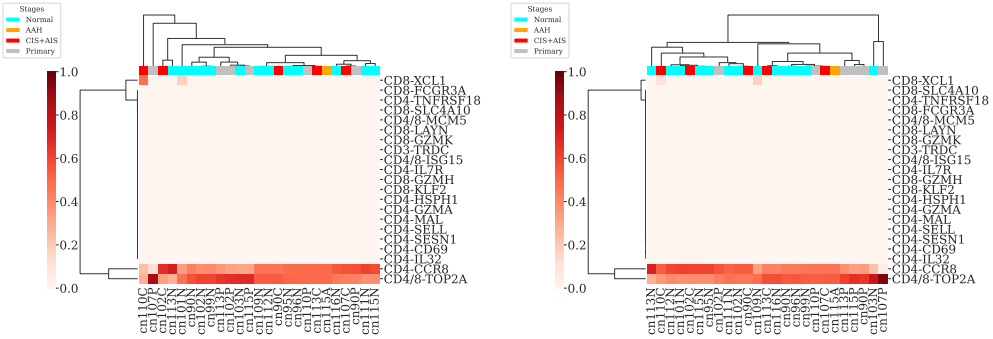
Figure 33: SCDC clustermap plot with LUSC samples upon GSE162498



(a) STAR

(b) Bowtie2

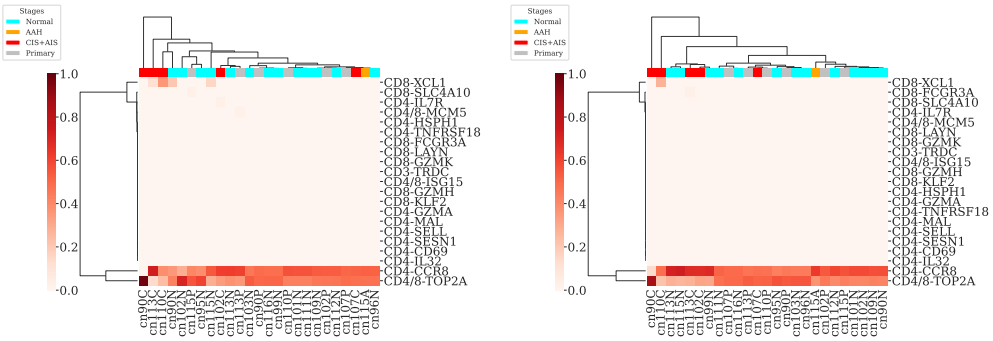
Figure 34: BisqueRNA clustermap plot with LUAD samples upon GSE162498



(a) STAR

(b) Bowtie2

Figure 35: MuSiC clustermap plot with LUAD samples upon GSE162498



(a) STAR (b) Bowtie2

Figure 36: SCDC clustermap plot with LUAD samples upon GSE162498

V Discussion

5.1 General Conclusions

5.2 Plan for Future

5.3 Future Perspective

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