



META-PRISM

A retrospective analysis of more than a 1,000 metastatic tumors.

21/02/2022 – IFSBM Big data



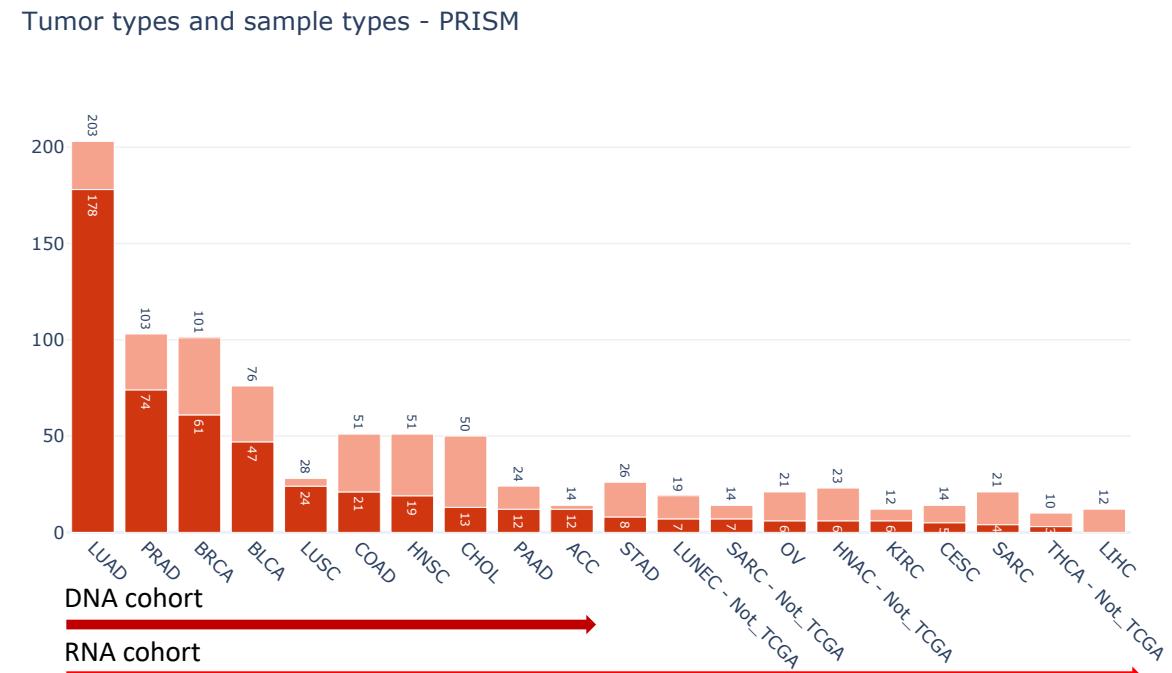
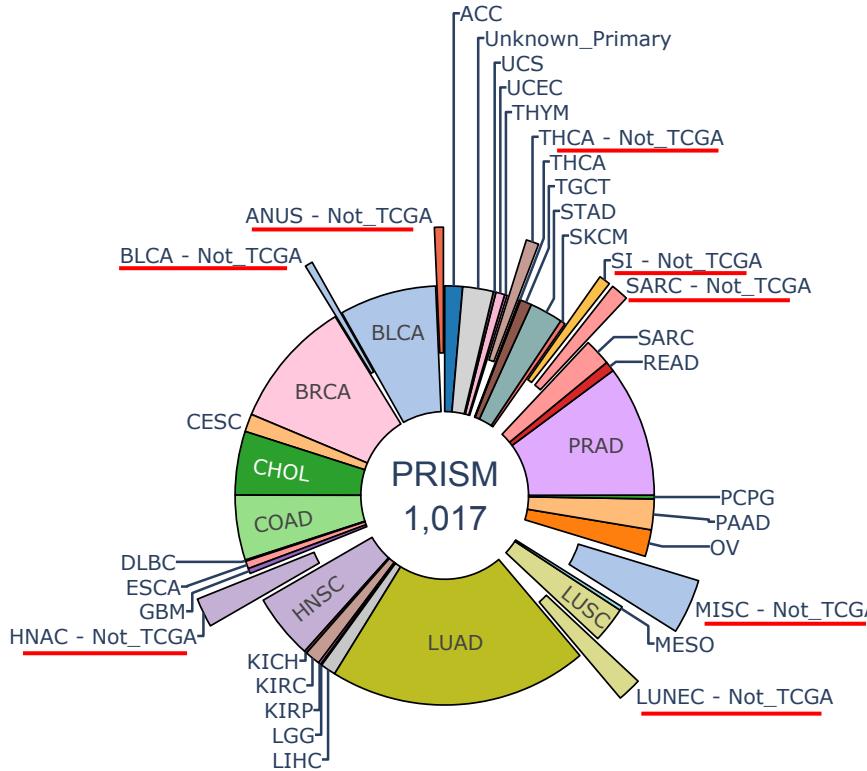
Yoann Pradat^{2,6}, Konstantin Gunbin³, Luigi Cerbone¹, Julien Viot¹, Guillaume Grisay¹, Ismael Padoleau³, Andrei Iurchenko³, Loic Verlingue¹, Rebecca Clodion¹, Stefan Michiels⁴, Marc Deloger⁵, Antoine Lainé⁷, Gerome Jules-Clément⁵, Yohann Loriot^{1,3}, Benjamin Besse^{1,3}, Fabrice Andre^{1,3}, Paul-Henry Cournede², Daniel Gautheret^{6,7,*}, Sergey Nikolaev^{3,*}

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Outline

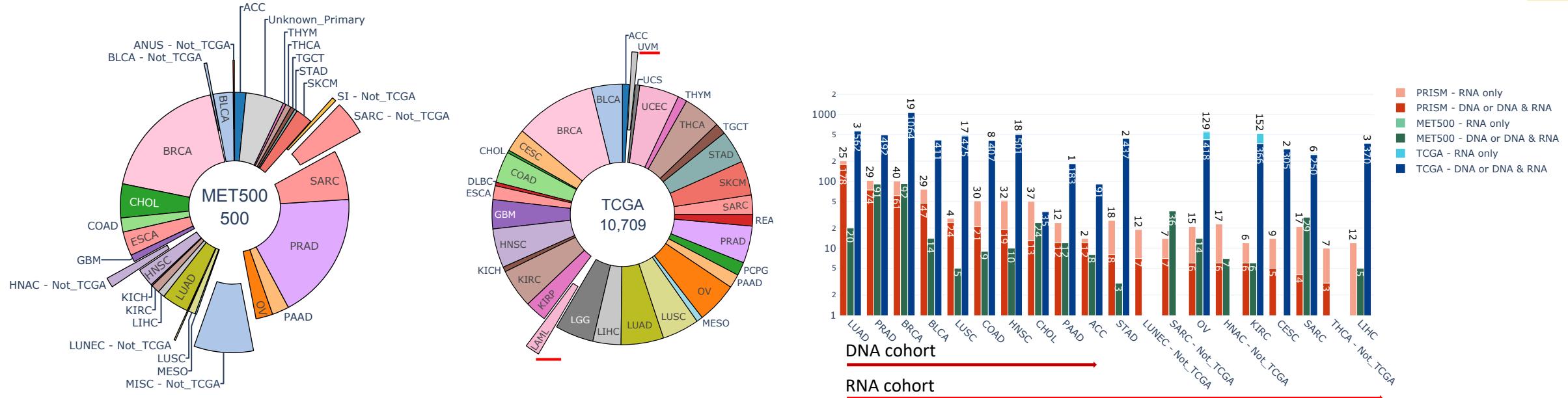
1. Data presentation
2. DNA-seq analysis
3. RNA-seq analysis
4. Ongoing research

1. Data presentation – The PRISM cohort



- 1,017 tumors **difficult-to-treat or refractory to conventional treatments**
- About 10% of rare tumor types
- DNA cohort: 10 tumor types
- RNA cohort: 20 tumor types

1. Data presentation – Validation/comparison cohorts

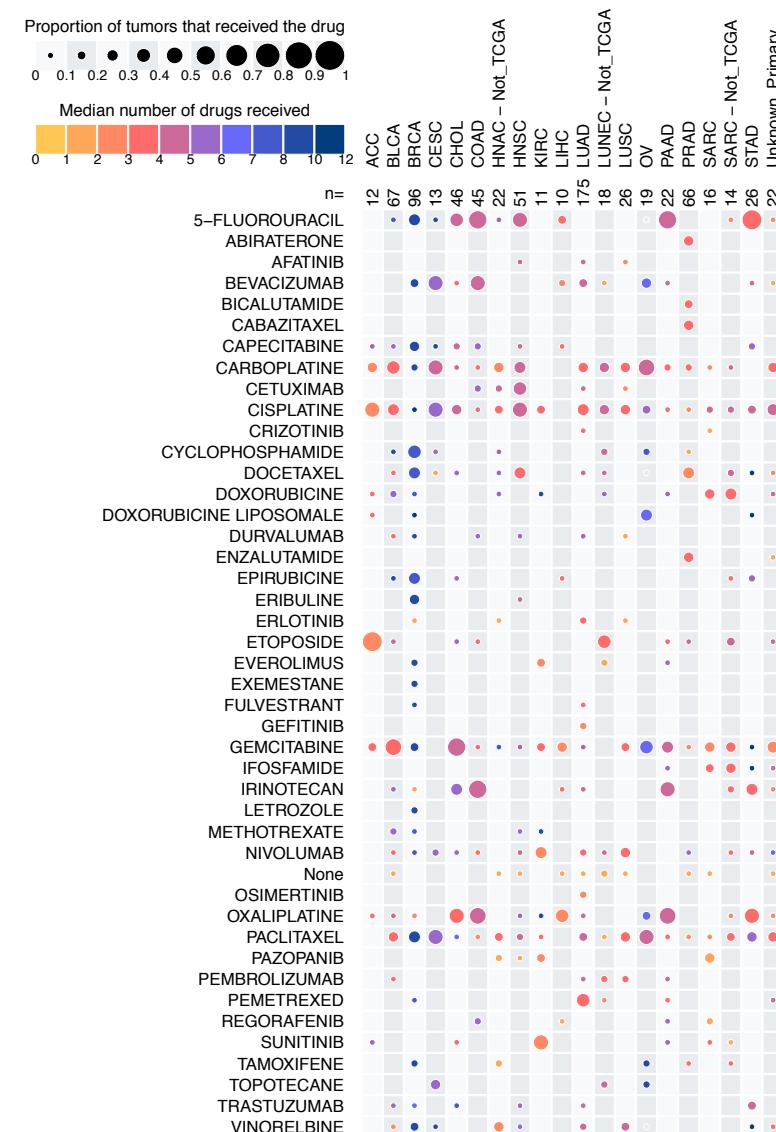
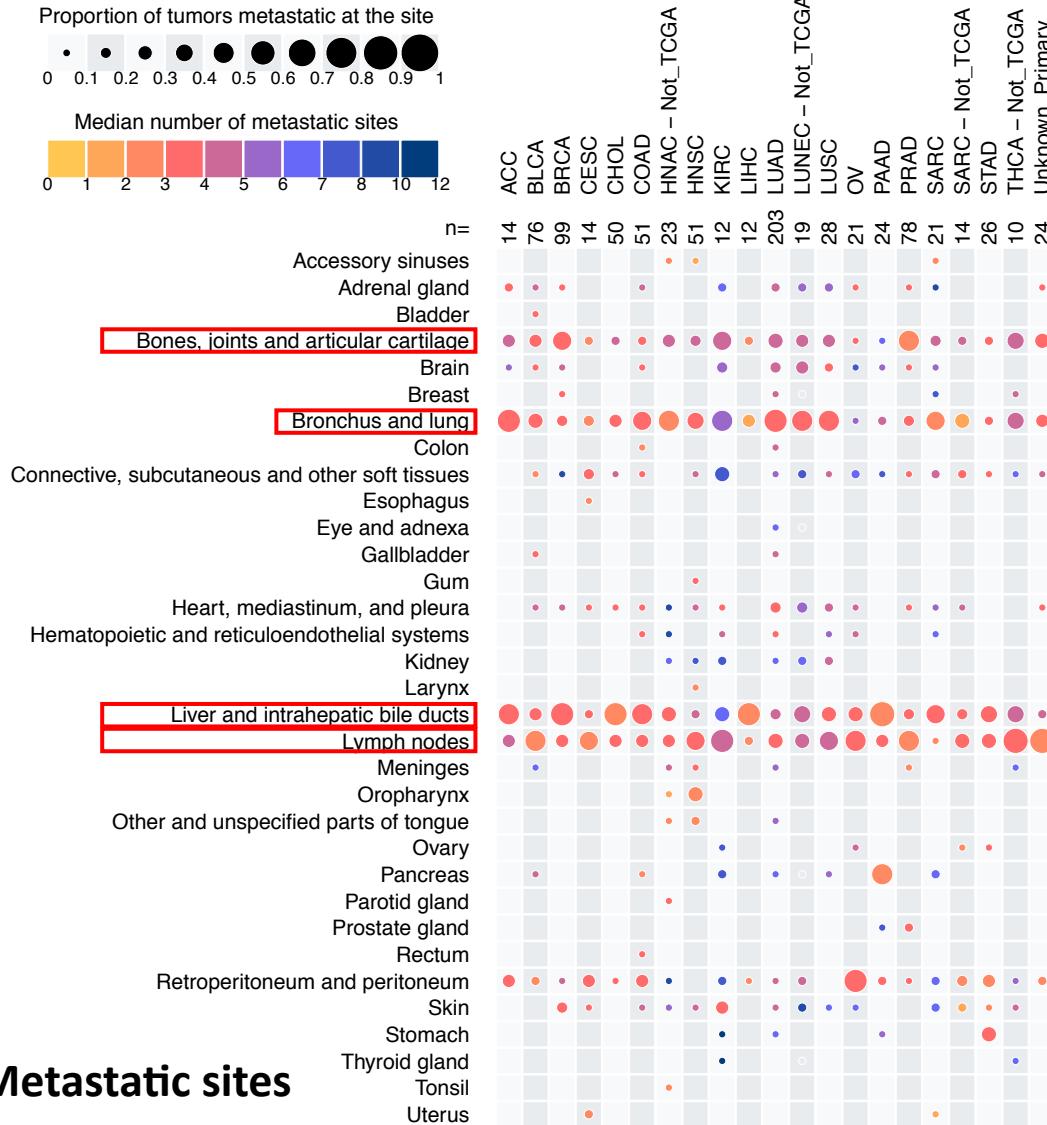


Priestley et al. 2019 Nature.

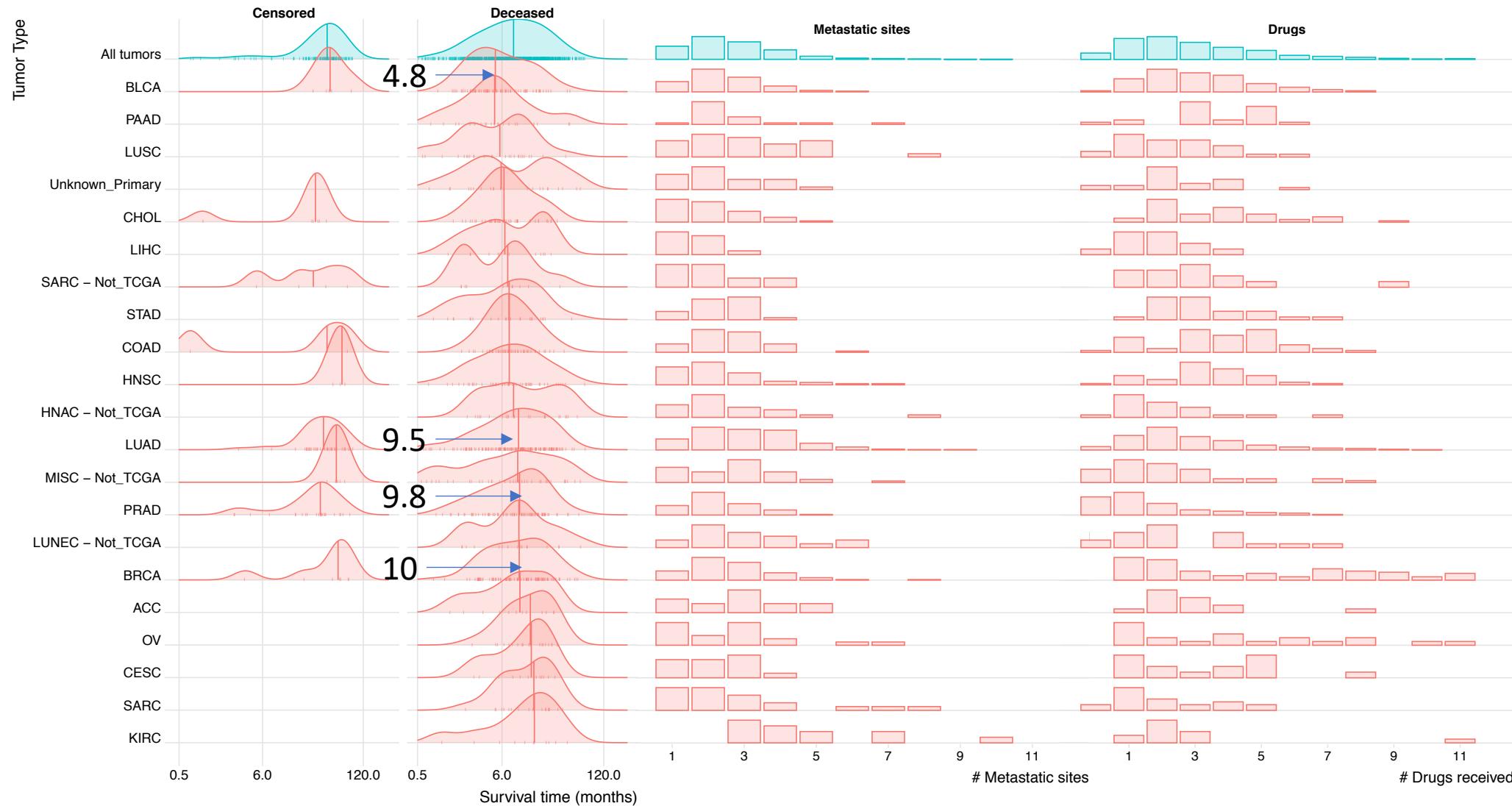
TCGA – 33 tumor types and 33 papers in Cell in 2018
<https://www.cell.com/consortium/pancanceratlas>

- DNA & RNA for all 500 samples of MET500
- 10x more samples in TCGA (early cancers)
- TCGA older => be aware of batch effects

1. Data presentation – Metastases & Treatments



1. Data presentation – Survival



Outline

1. Data presentation

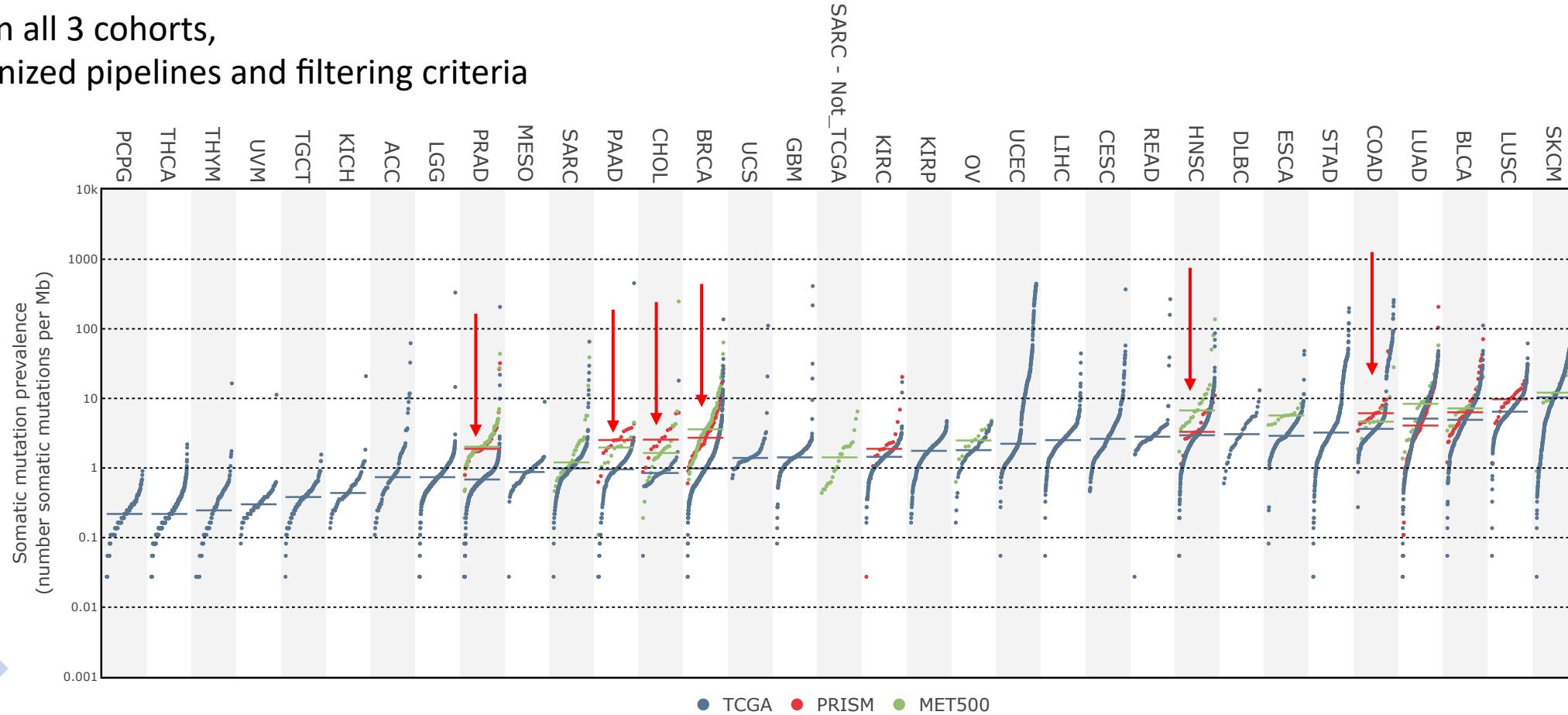
2. DNA-seq analysis

3. RNA-seq analysis

4. Ongoing research

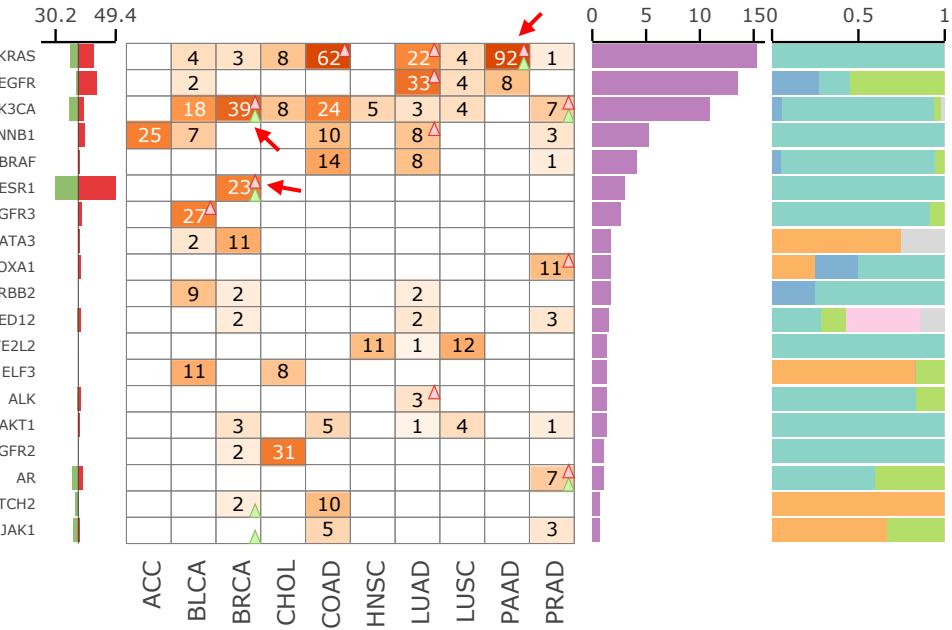
2. DNA-seq analysis – Mutational burden

WES on all 3 cohorts,
harmonized pipelines and filtering criteria



- Clear increase in the mutational burden in metastatic tumors, validated in MET500

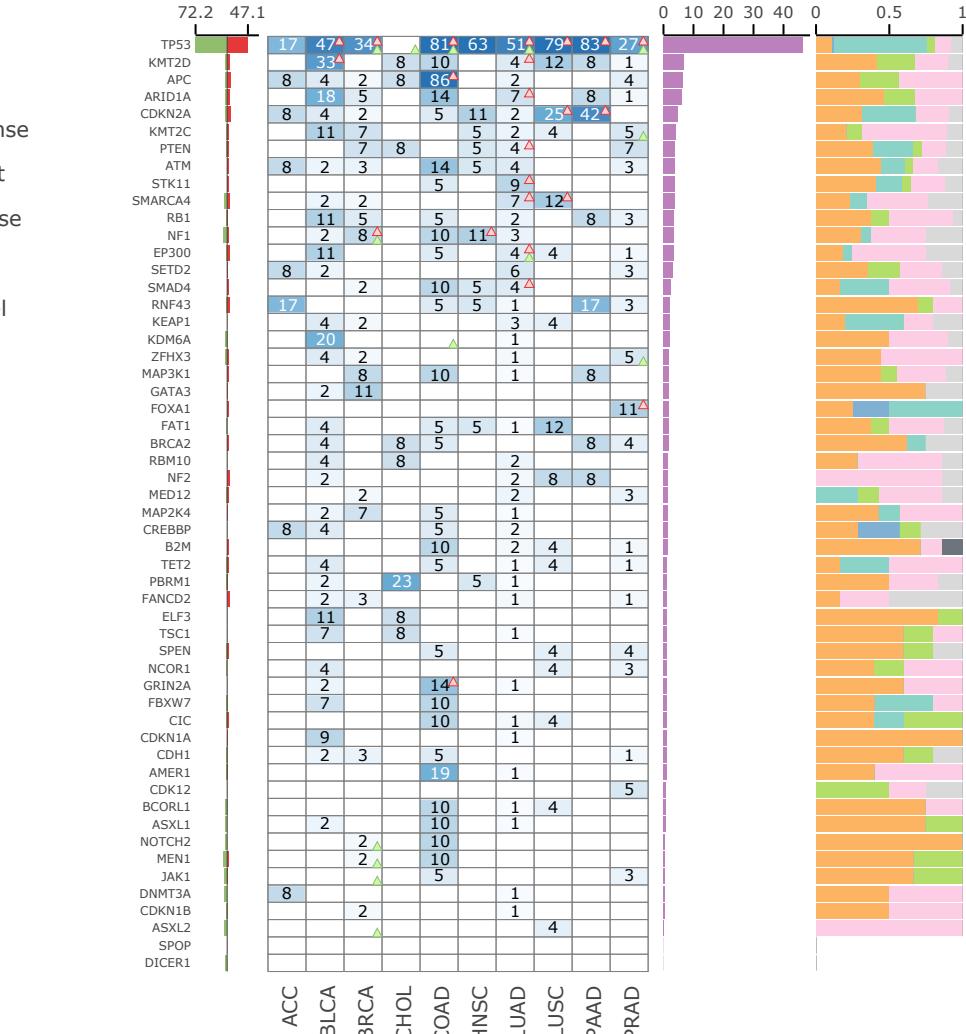
2. DNA-seq analysis – Annotated somatic mutations



Oncogenes

Annotated mutations

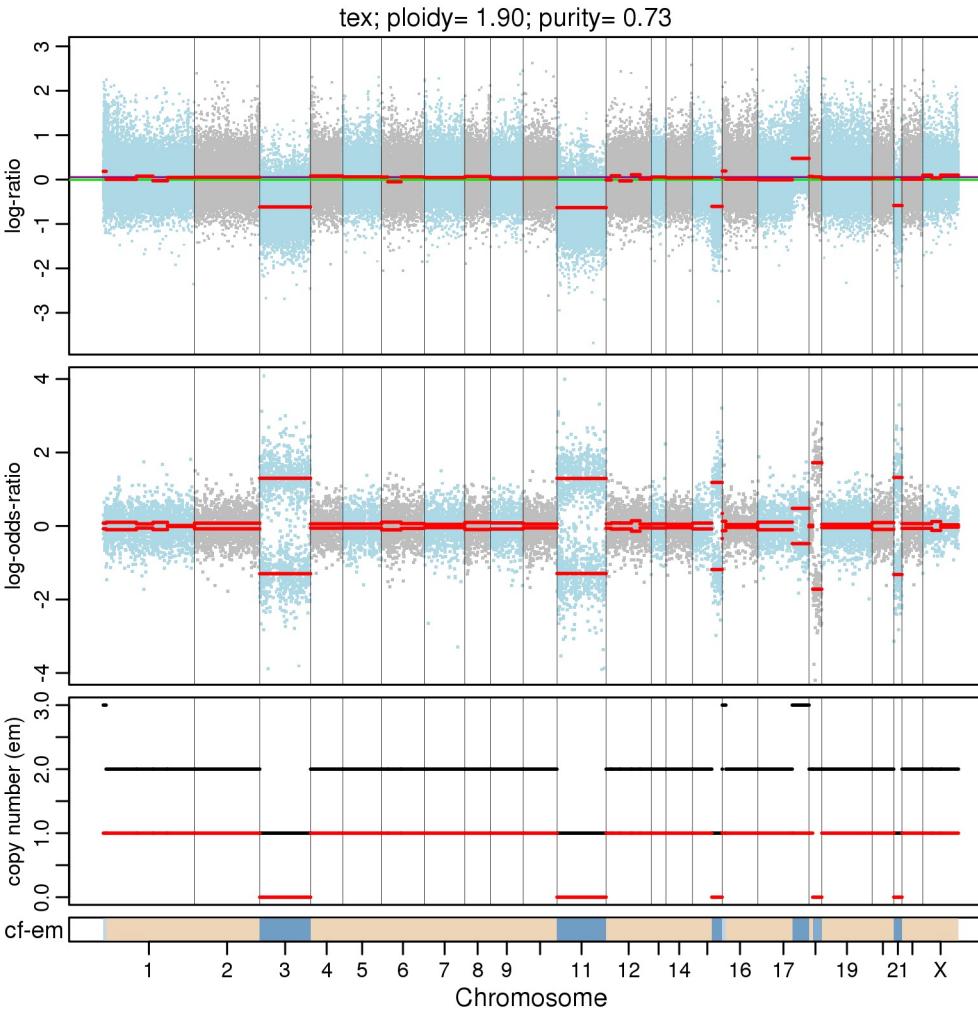
- Present in OncoKB
- Present in CIViC
- Present in CGI (not finished yet)



Tumorsuppressor genes

2. DNA-seq analysis – Copy number (FACETS)

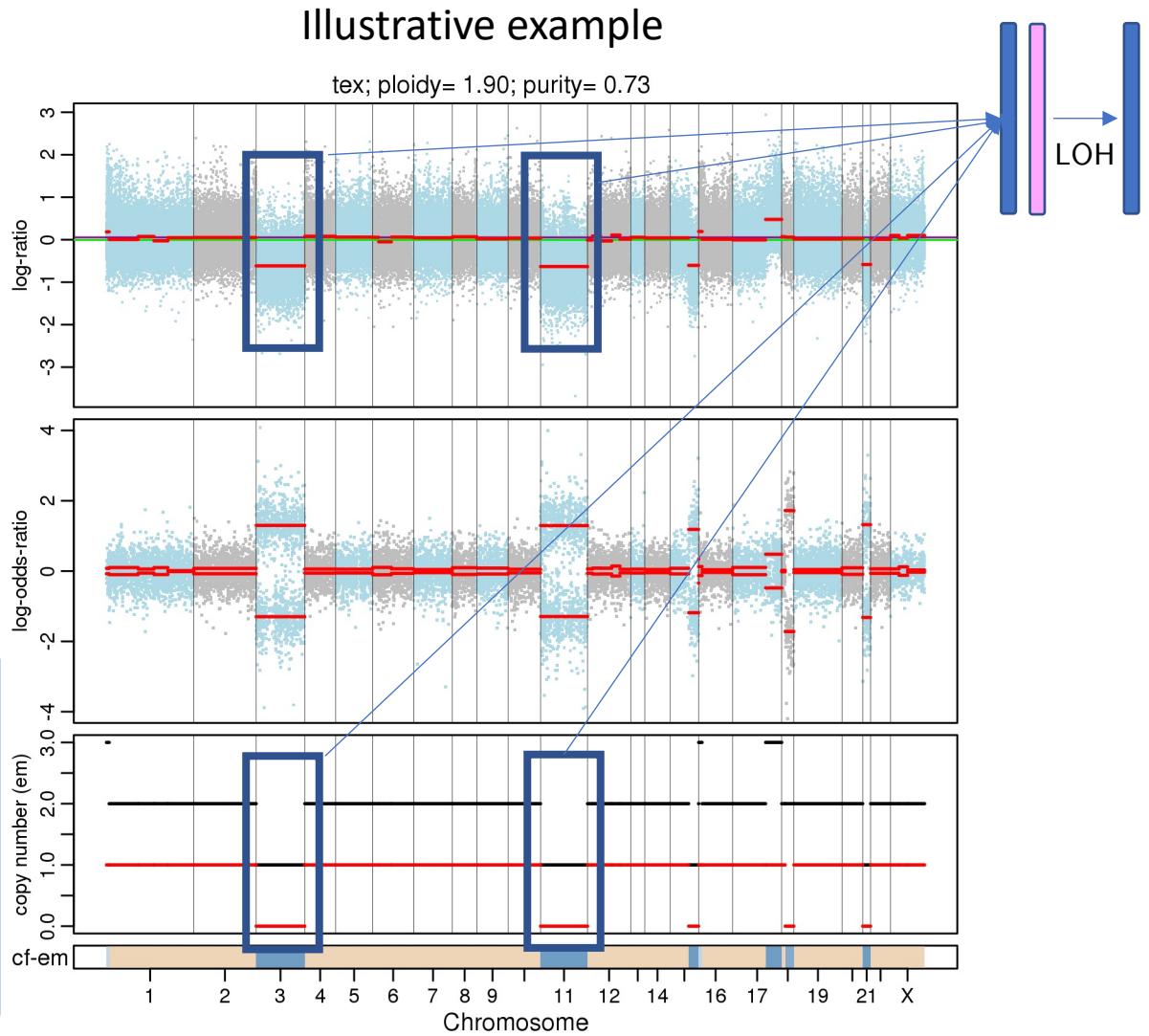
Illustrative example



2. DNA-seq analysis – Copy number (FACETS)

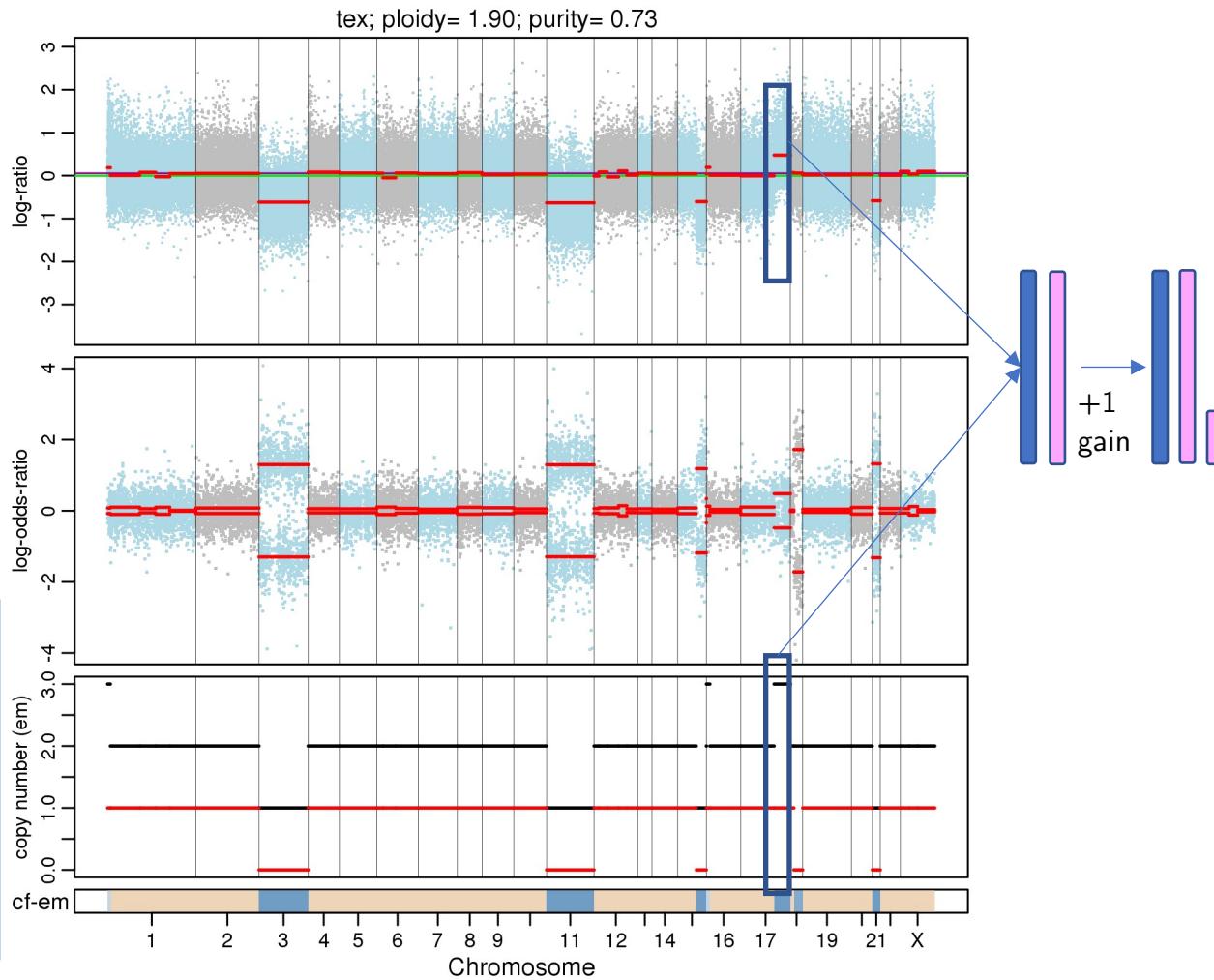
Illustrative example

tex; ploidy = 1.90; purity = 0.73



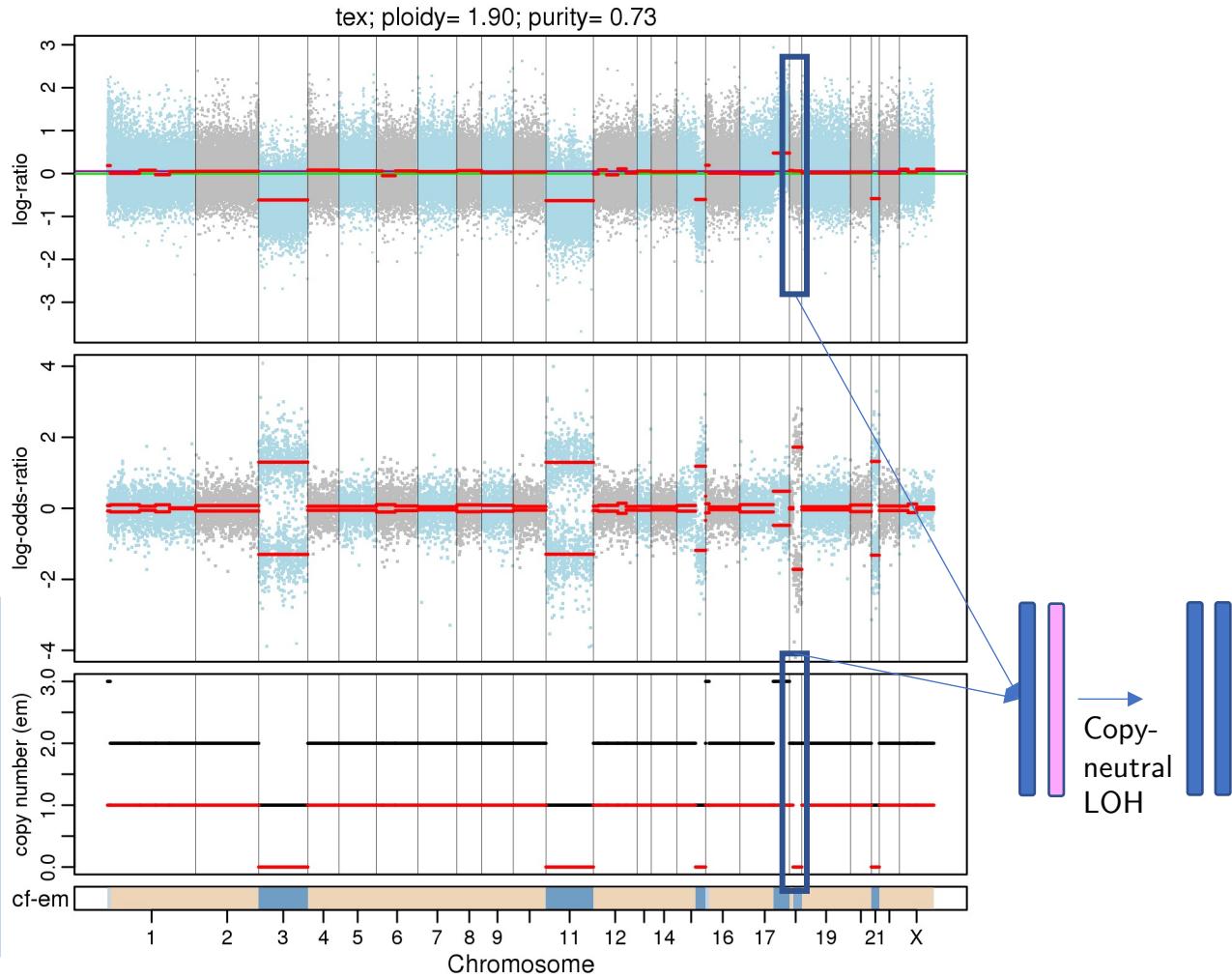
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Illustrative example



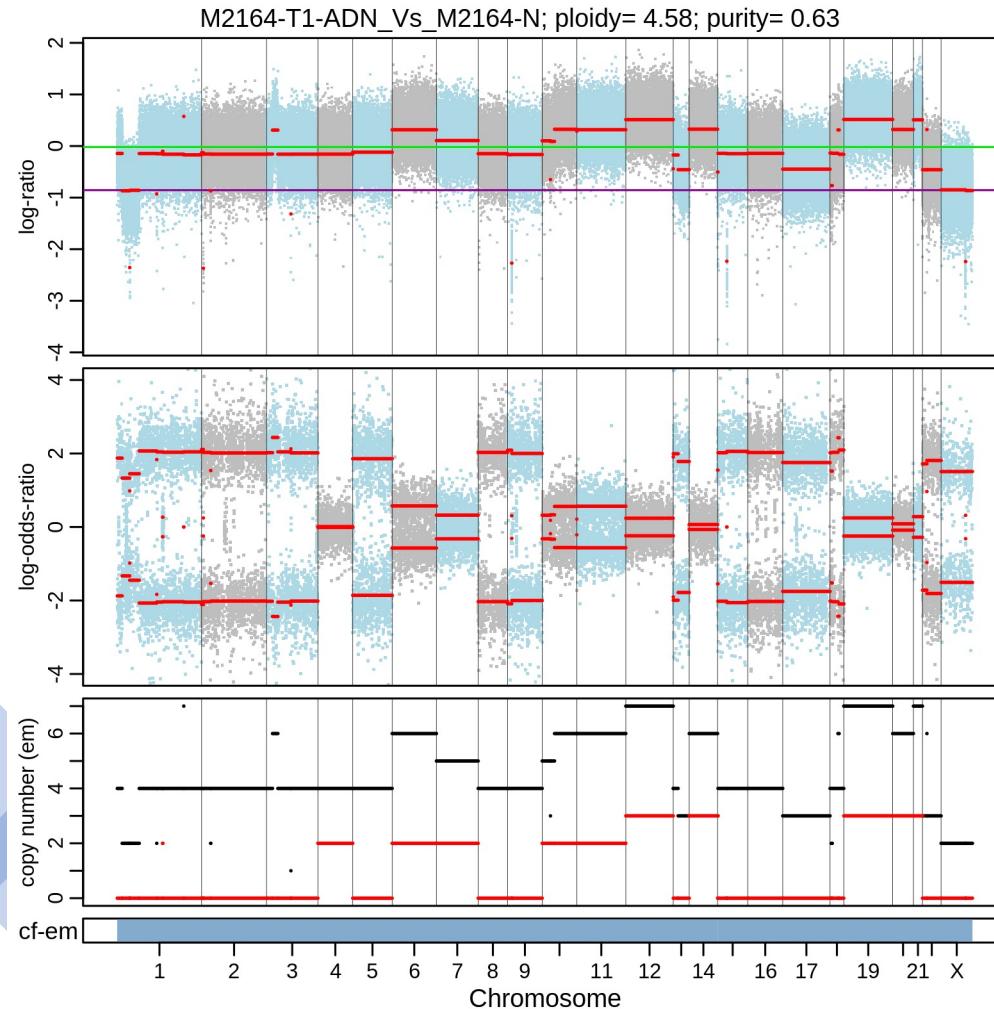
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Illustrative example

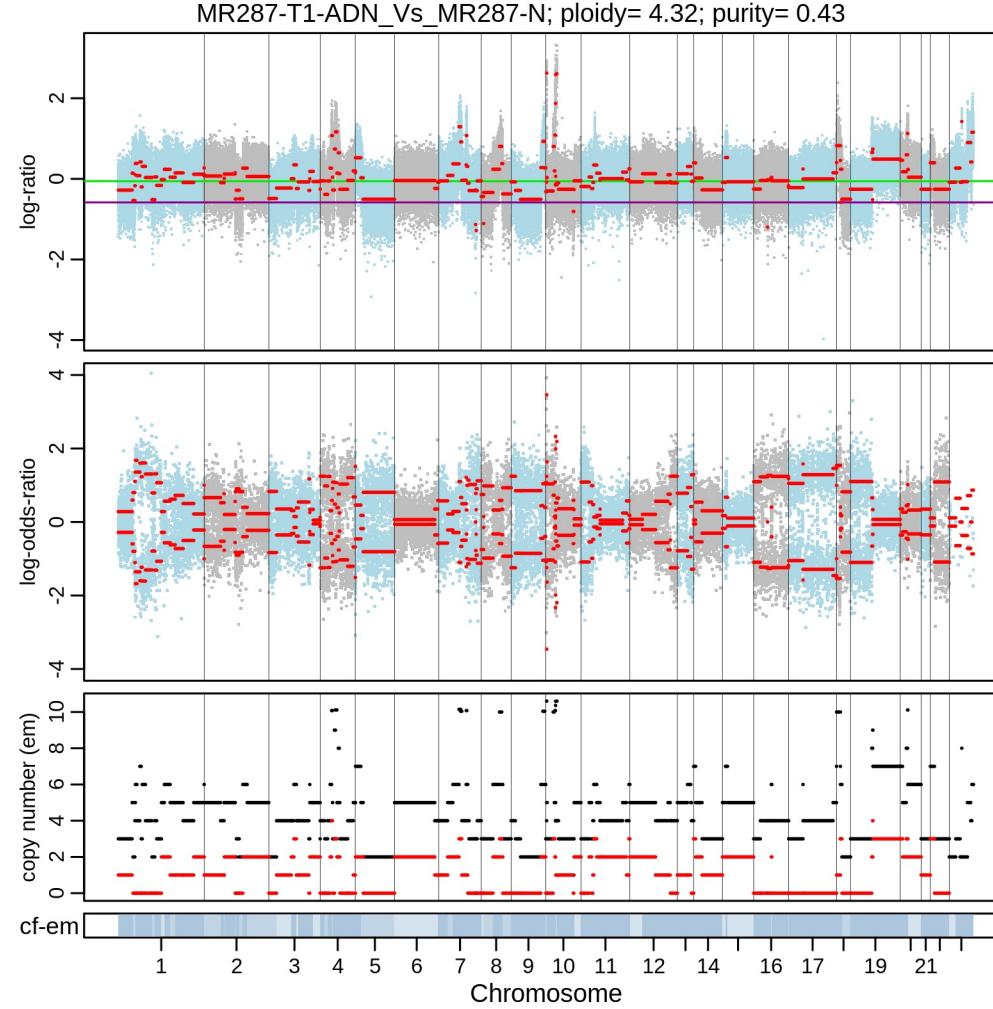


2. DNA-seq analysis – Copy number (FACETS)

PRISM example 1

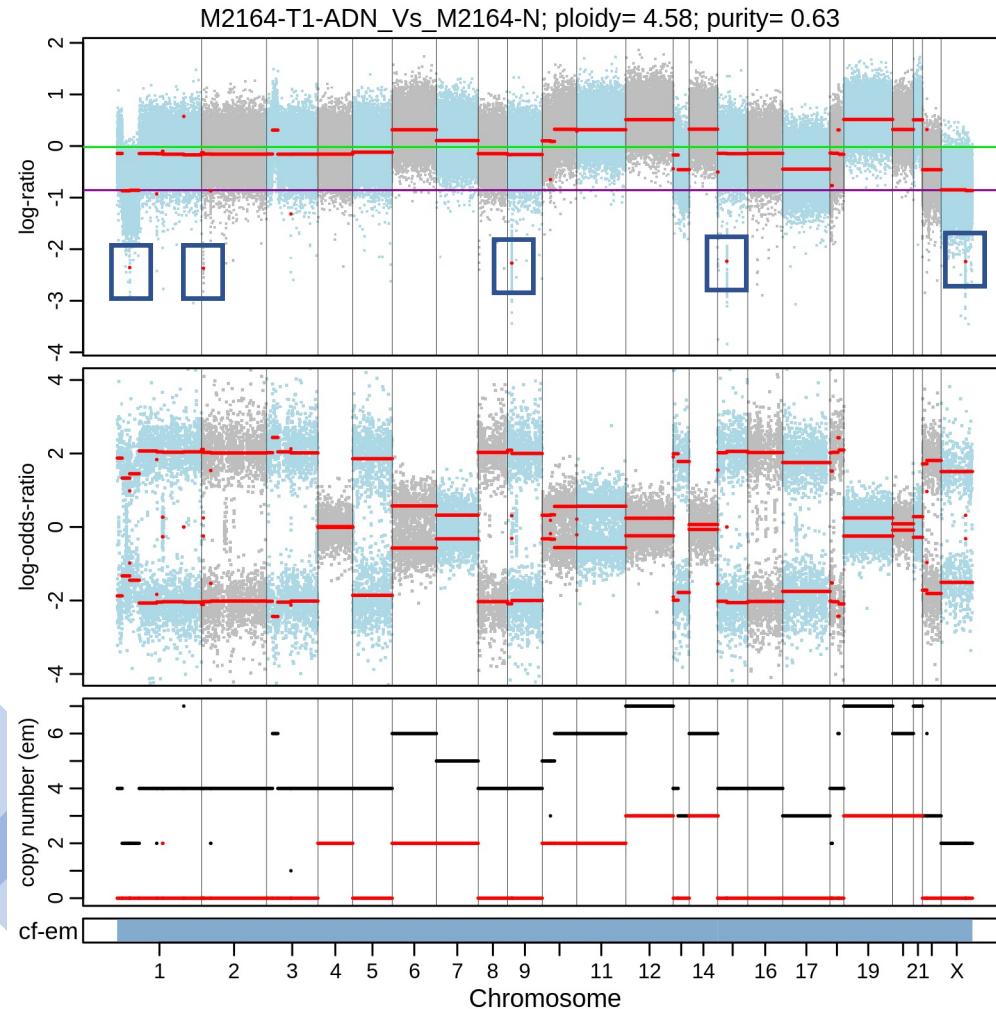


PRISM example 2

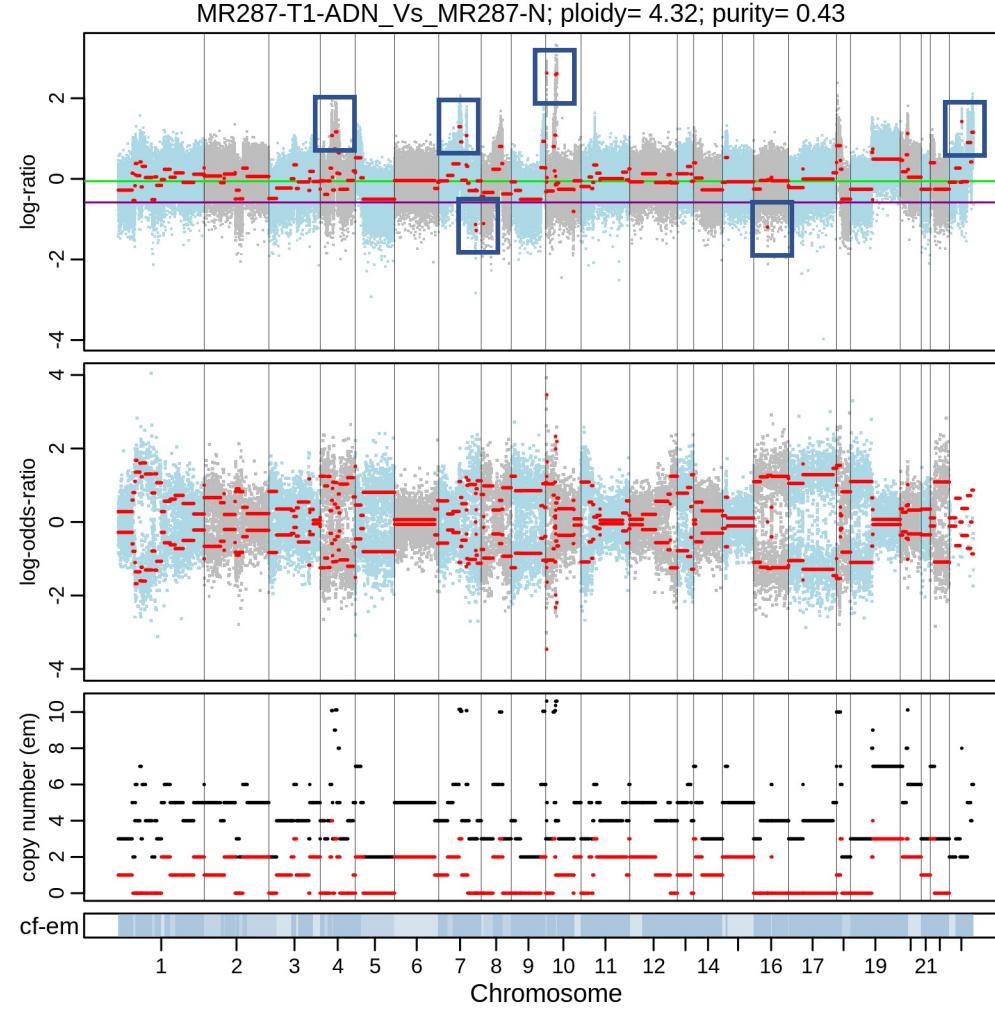


2. DNA-seq analysis – Copy number (FACETS)

PRISM example 1



PRISM example 2



Outline

1. Data presentation

2. DNA-seq analysis

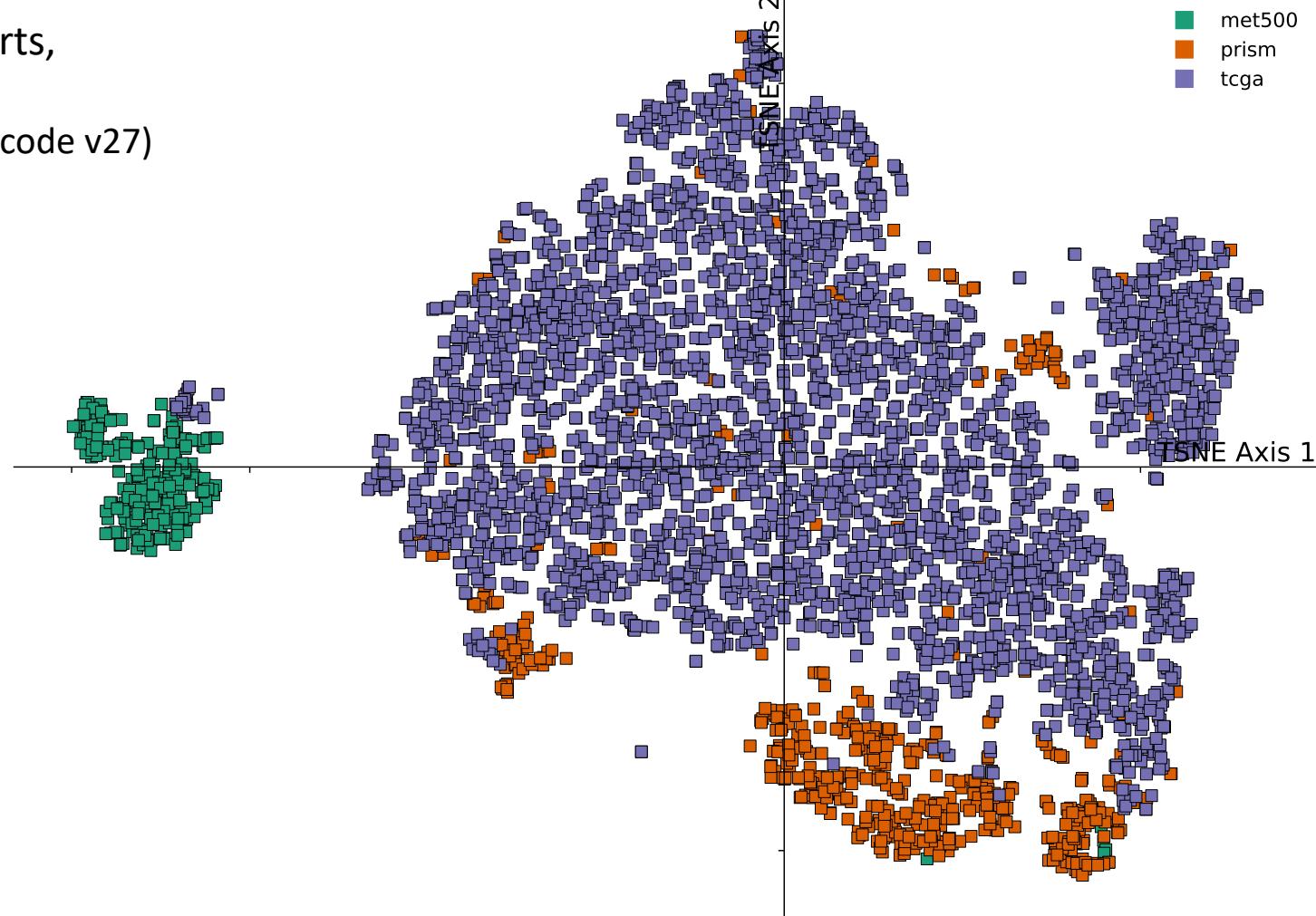
3. RNA-seq analysis

4. Ongoing research

3. RNA-seq analysis – Be aware of batch effects

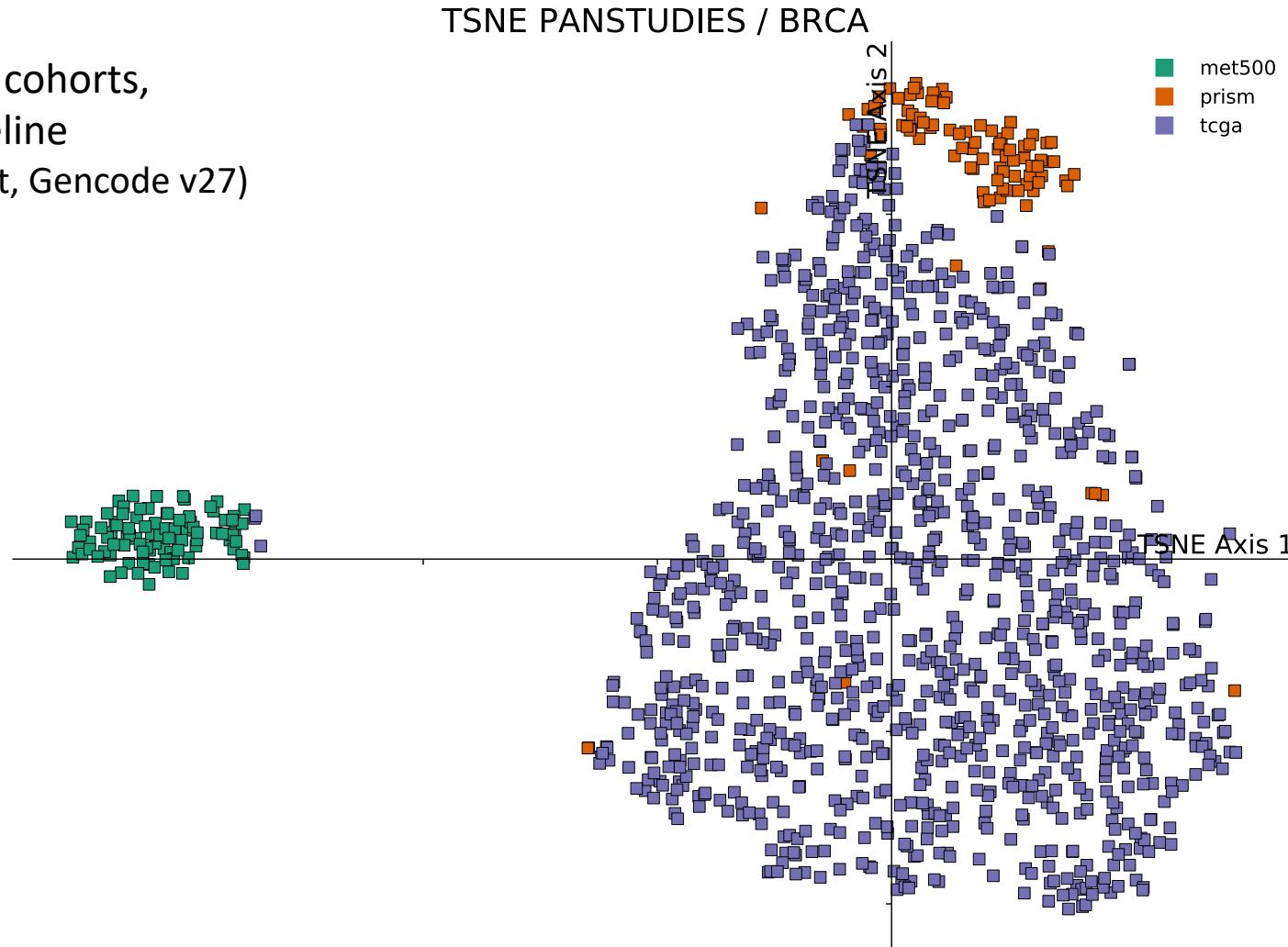
RNA-seq on all 3 cohorts,
Harmonized pipeline
(Kallisto & TxImport, Gencode v27)

TSNE PANSTUDIES / PANCANCER (6)

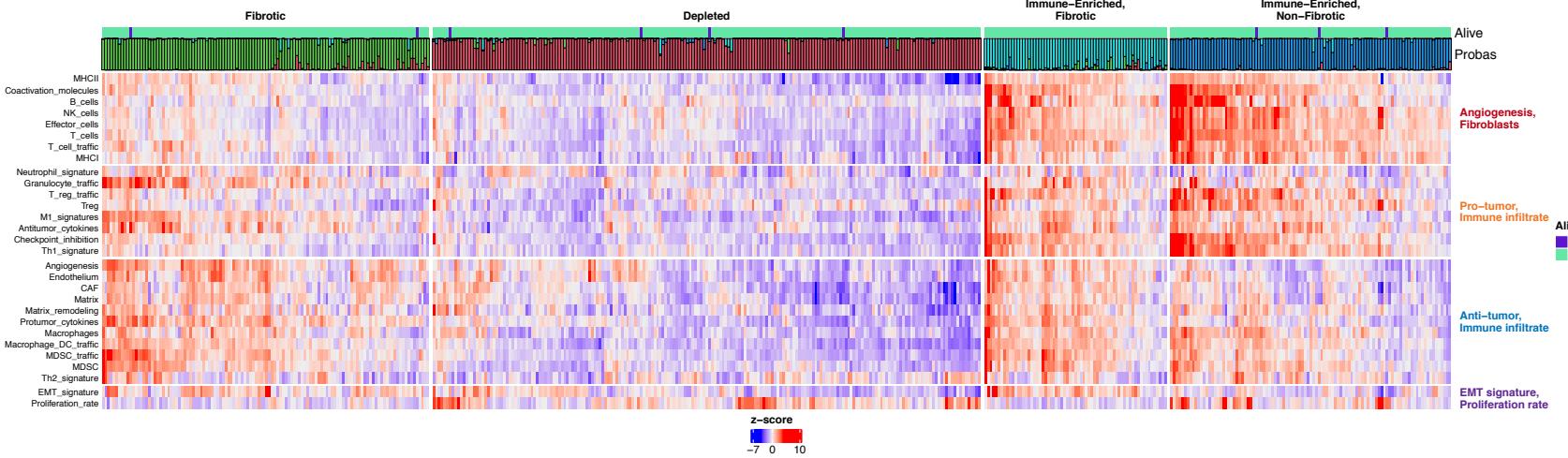


3. RNA-seq analysis – Be aware of batch effects

RNA-seq on all 3 cohorts,
Harmonized pipeline
(Kallisto & TxImport, Gencode v27)

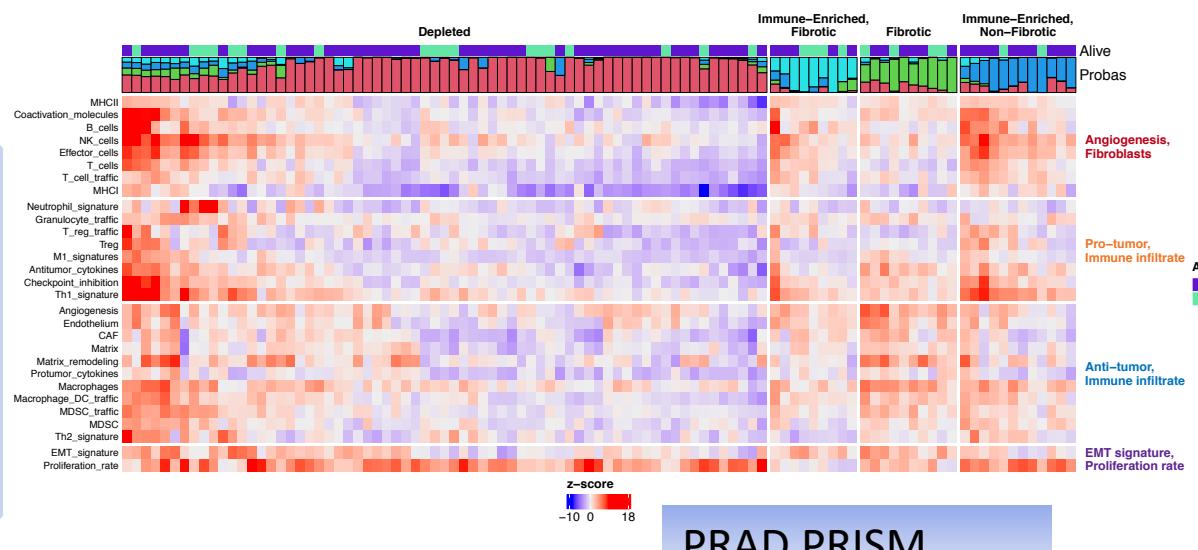


3. RNA-seq analysis – Tumor micro-environment

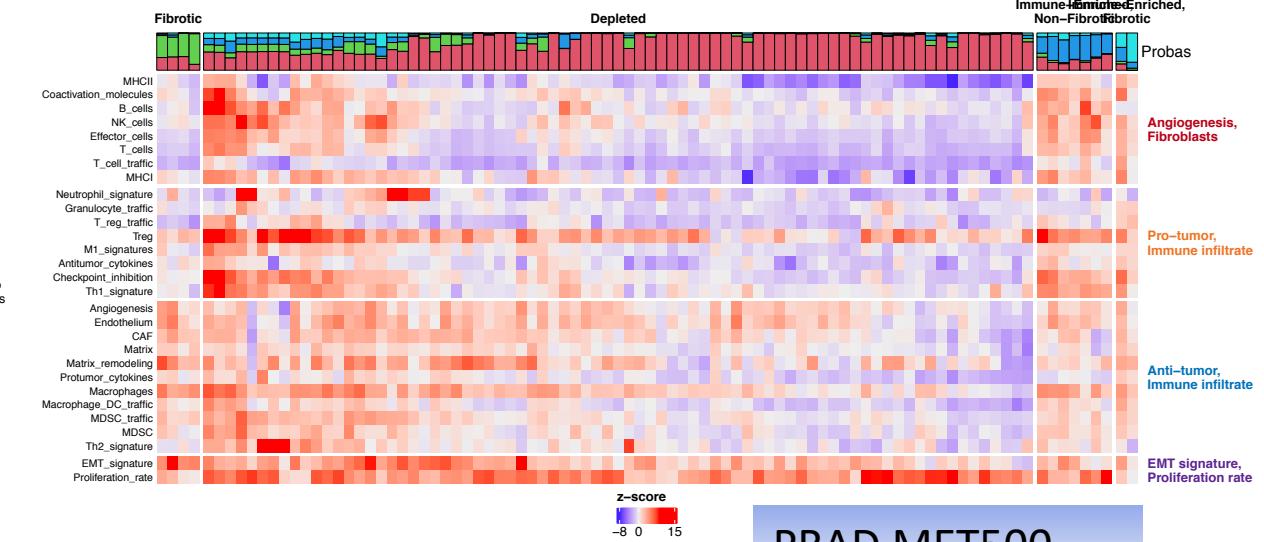


Bagaev et al. 2021 Cell.

PRAD TCGA

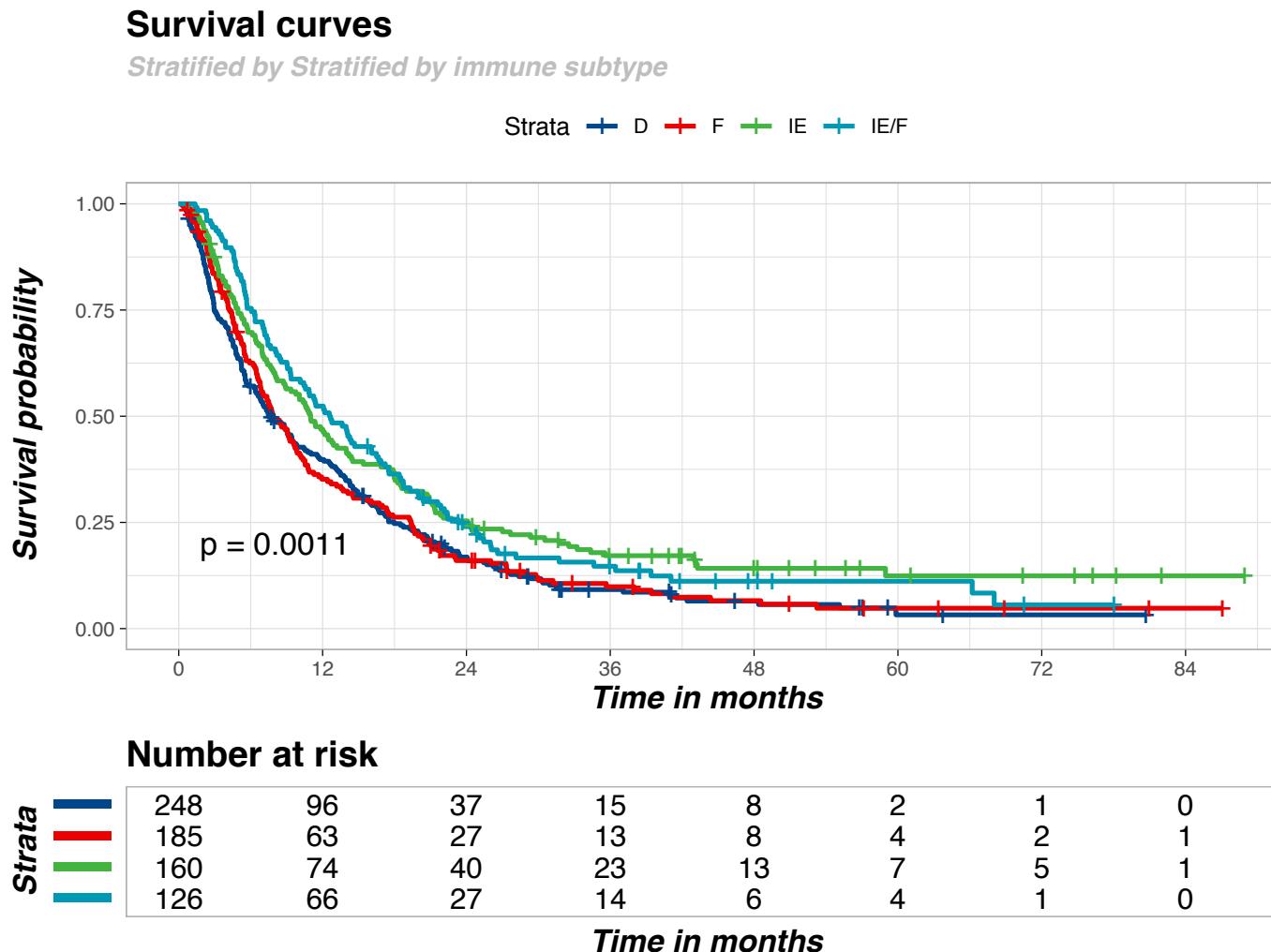


PRAD PRISM



PRAD MET500

3. RNA-seq analysis – Tumor micro-environment

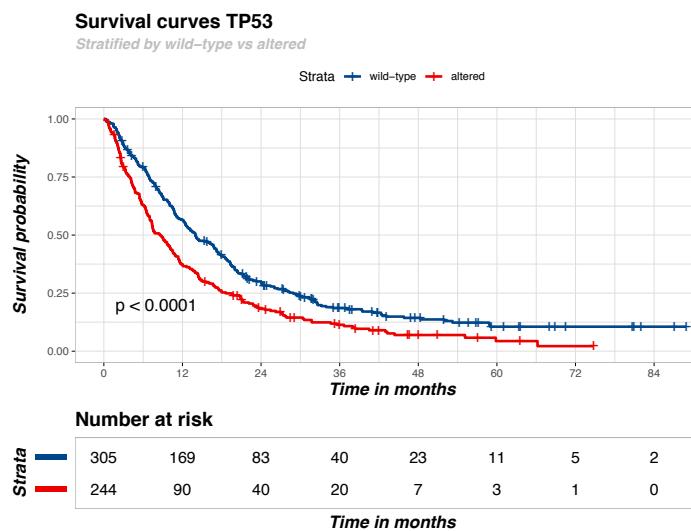
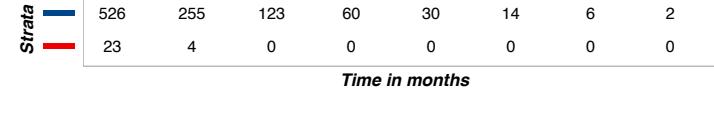
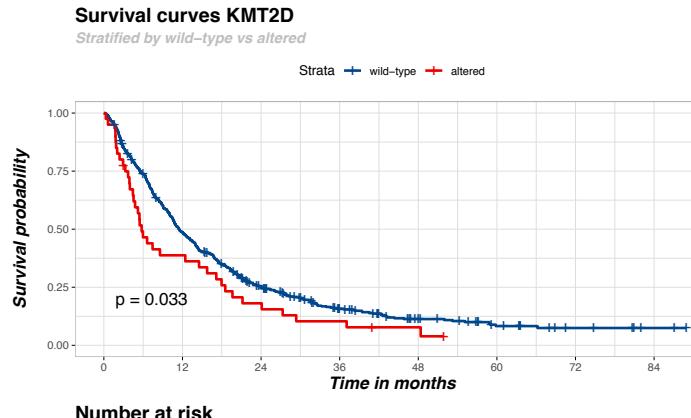
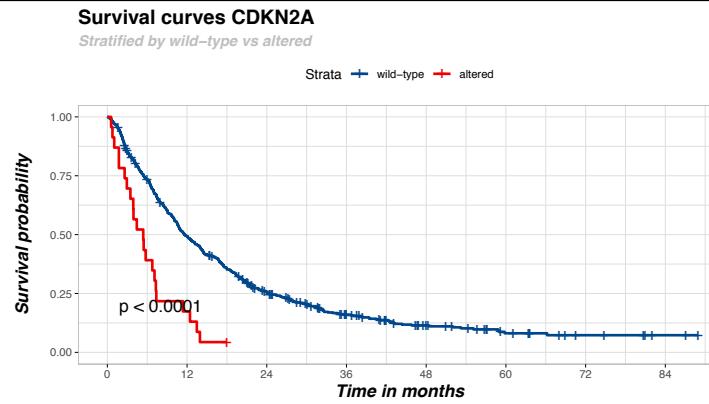


Bagaev et al. 2021 Cell.

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4. Ongoing research – Predict survival from genetics



Genes tested (at least 20 tumors with annotated mutations)

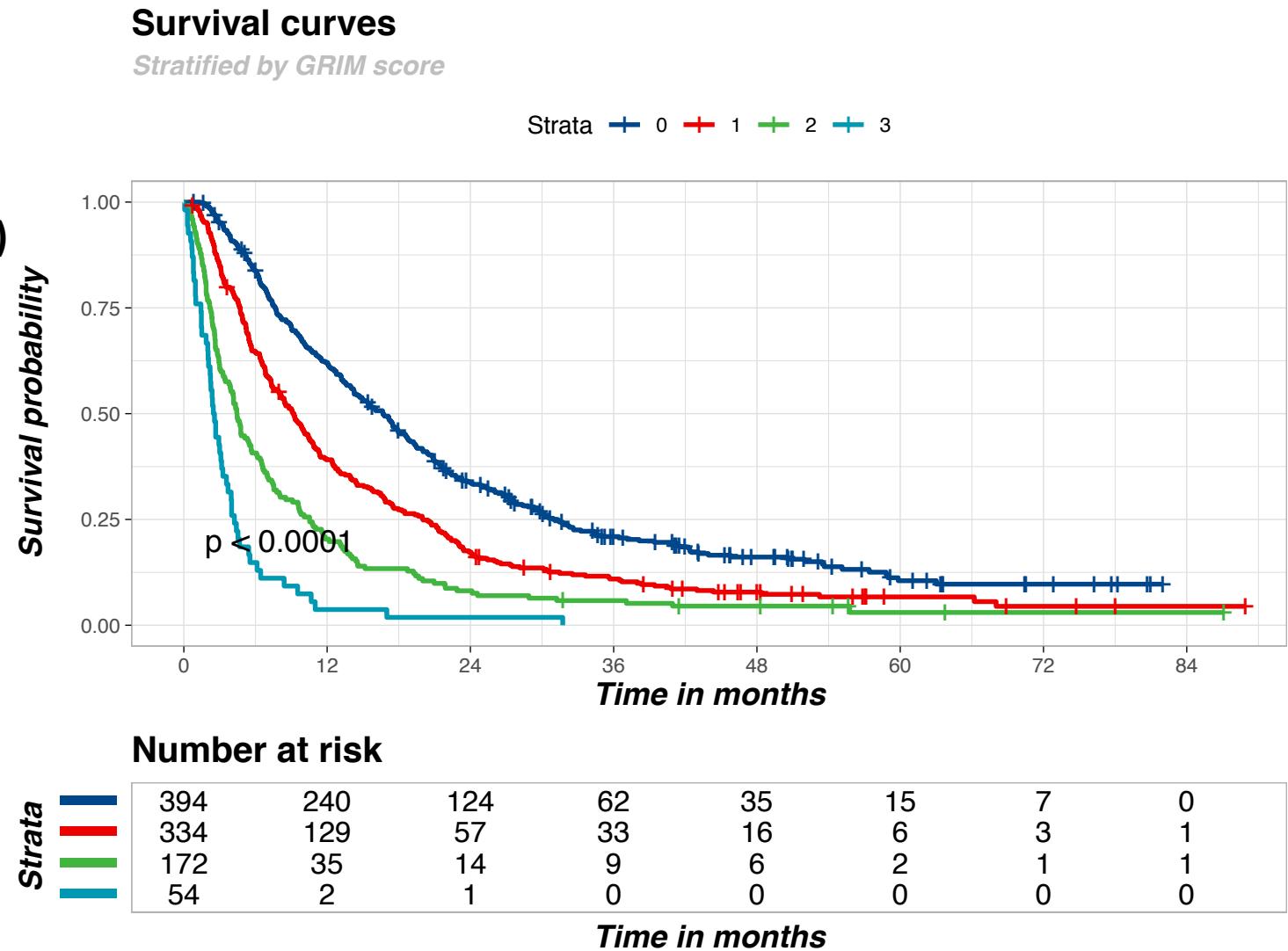
- ARID1A
- APC
- BRAF
- CDKN2A
- CTNNB1
- EGFR
- KMT2C
- KMT2D
- KRAS
- PIK3CA
- PTEN
- TP53

4. Ongoing research – Can we do better?

GRIM score (modification of RMH score)

Each of these contribute 1 point

- LDH(UI/L) > 247
- Albumine(g/L) < 35
- $\frac{\text{Neutrophils}(10^9/\text{L})}{\text{Lymphocytes}(10^9/\text{L})} > 6$



4. Ongoing research

1. Extract markers/scores for each omic modality and correlate these with phenotypes.
 - Mutational signatures (mutations)
 - Tumors immune micro-environment (mRNA)
 - Alterations scores per biological pathways (mutations, mRNA, CNA, fusions).
2. Correlate molecular profiles to survival. From snapshot at time t, can we establish a risk profile?
 - Cox multivariate models
3. Correlate molecular profiles to treatments resistances and metastates localizations.
 - Supervised classification models

Acknowledgements

**Department of Medical Oncology, Gustave Roussy,
Villejuif, France**

- Dr Julien Viot
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- Dr Luigi Cerbone
- Dr Rebecca Clodion
- Dr Loic Verlingue
- Pr Benjamin Besse
- Pr Yohann Loriot
- Pr Fabrice Andre

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CentraleSupélec

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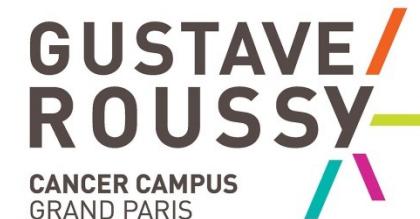
- Dr Konstantin Gunbin
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- Dr Andrei Iurchenko

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Oncostat U1018 INSERM, Univ. Paris-Saclay**

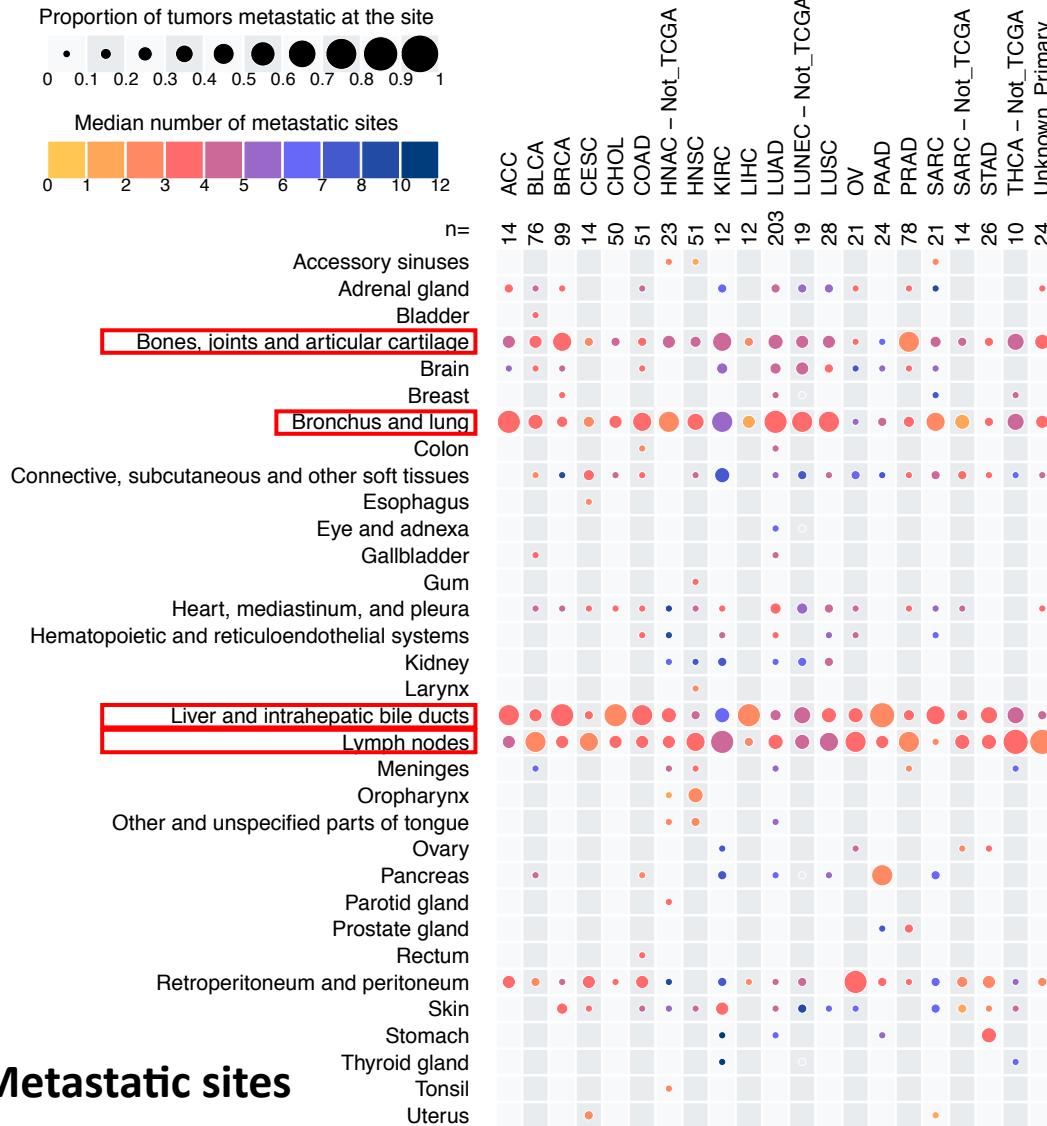
- Pr Stefan Michiels
- Dr Marc Deloger

**IHU PRISM, Gustave Roussy, Villejuif, France; I2BC, CNRS, CEA,
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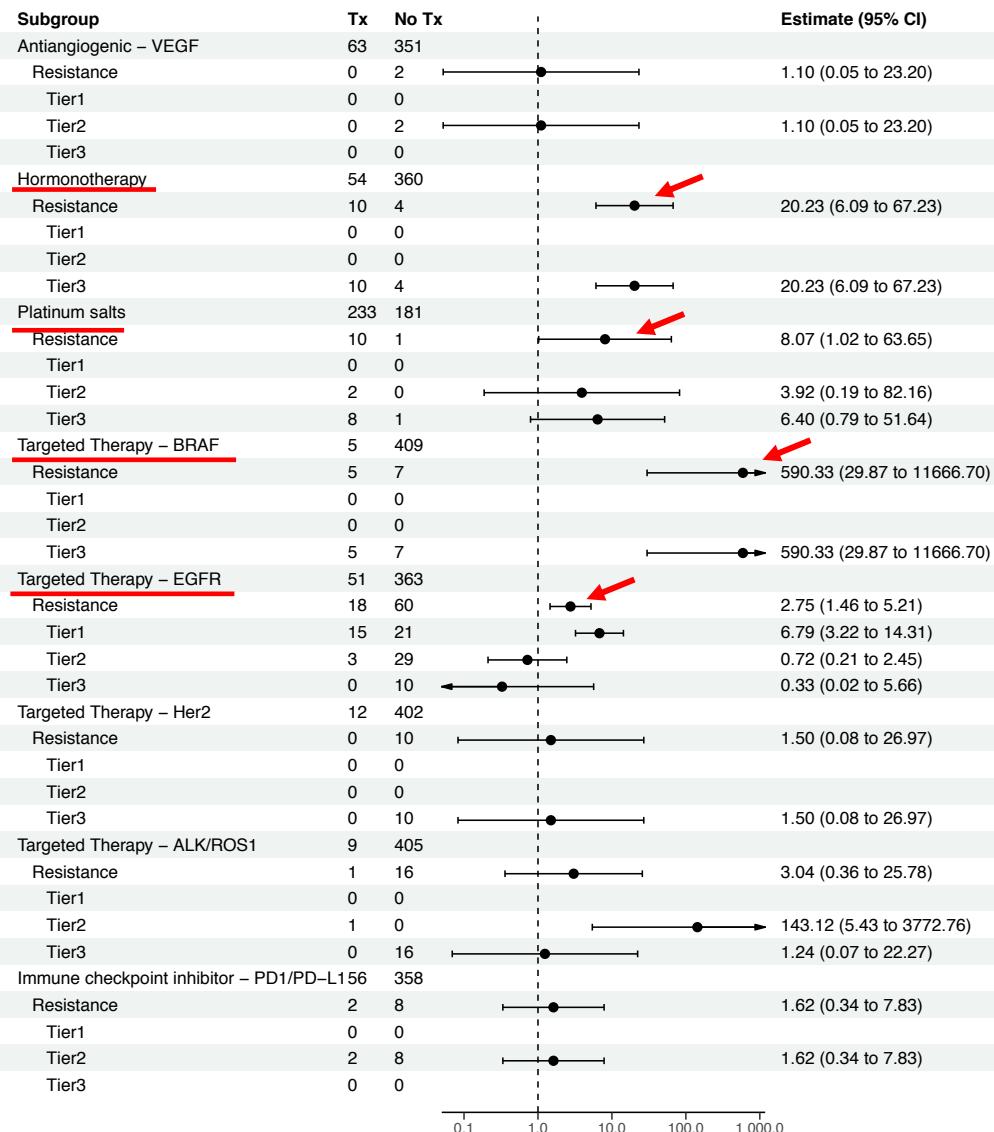
- Pr Daniel Gautheret
- Antoine Lainé



1. Data presentation – Metastases & Treatments



2. DNA-seq analysis – Annotated somatic mutations



ESCAT classification of resistance events

1. Tier1 SOC
 - OncoKb R1; CiViC A
2. Tier 2 Investigative
 - OncoKb R2; CiViC B
3. Tier 3 Preliminary
 - OncoKb R3; CiViC C,D,E

Treatments received correlate with presence of resistance alterations