



Bioinformatics solutions to biomarker discovery

Fios Genomics

- University of Edinburgh spin-out
- Formed in 2008
- Based in Edinburgh's BioQuarter
- Provides bioinformatic data analysis services to pharma, biotech, CROs and academia
- Over 500 contracts completed.



'Omics Analysis

Advances in sequencing & array technologies has opened several new avenues for drug development/process improvement



Biomarker ID



Patient Stratification



Personalised
Medicine



Biologicals

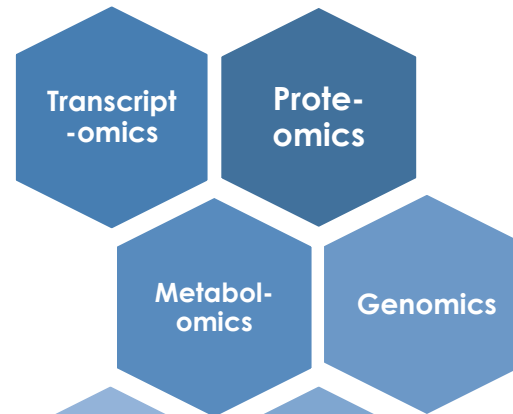
Issues:

- Volume of data
- Complexity of outputs
- Diverse and large number of data/knowledge base systems
- Current "gold standard" for genomics analysis
- What technology to use where?
- Interpretation issues

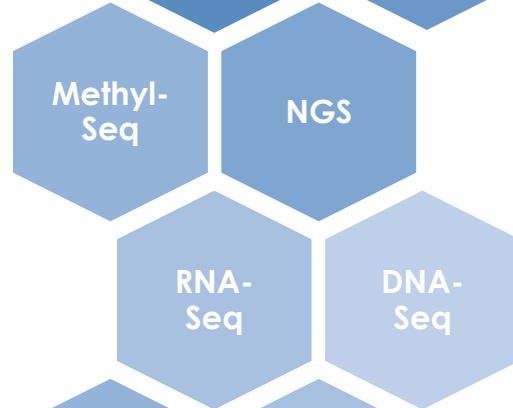
How Can Fios Help?

- Experimental design
- Technology/platform selection
- Data analysis platform independent
- Integration of 'omics data with virtually any other quantitative outputs
- Use of proprietary modular work flows to simplify complex projects.

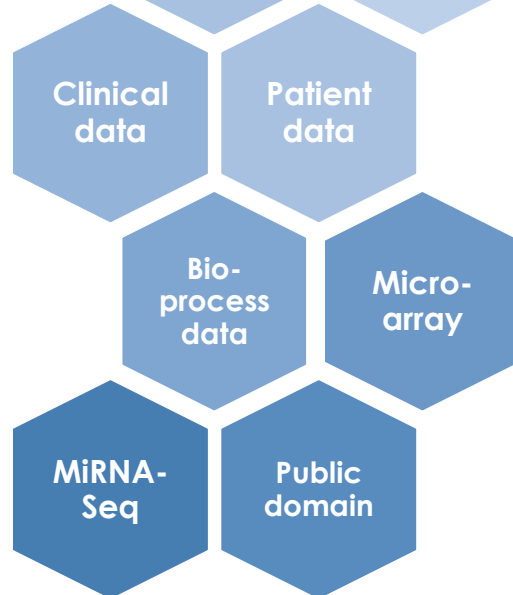
ANALYSE



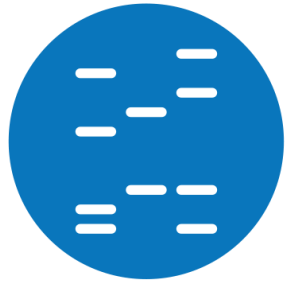
INTERPRET



INTEGRATE



What we do



Raw RNAseq data
(billions of data points)

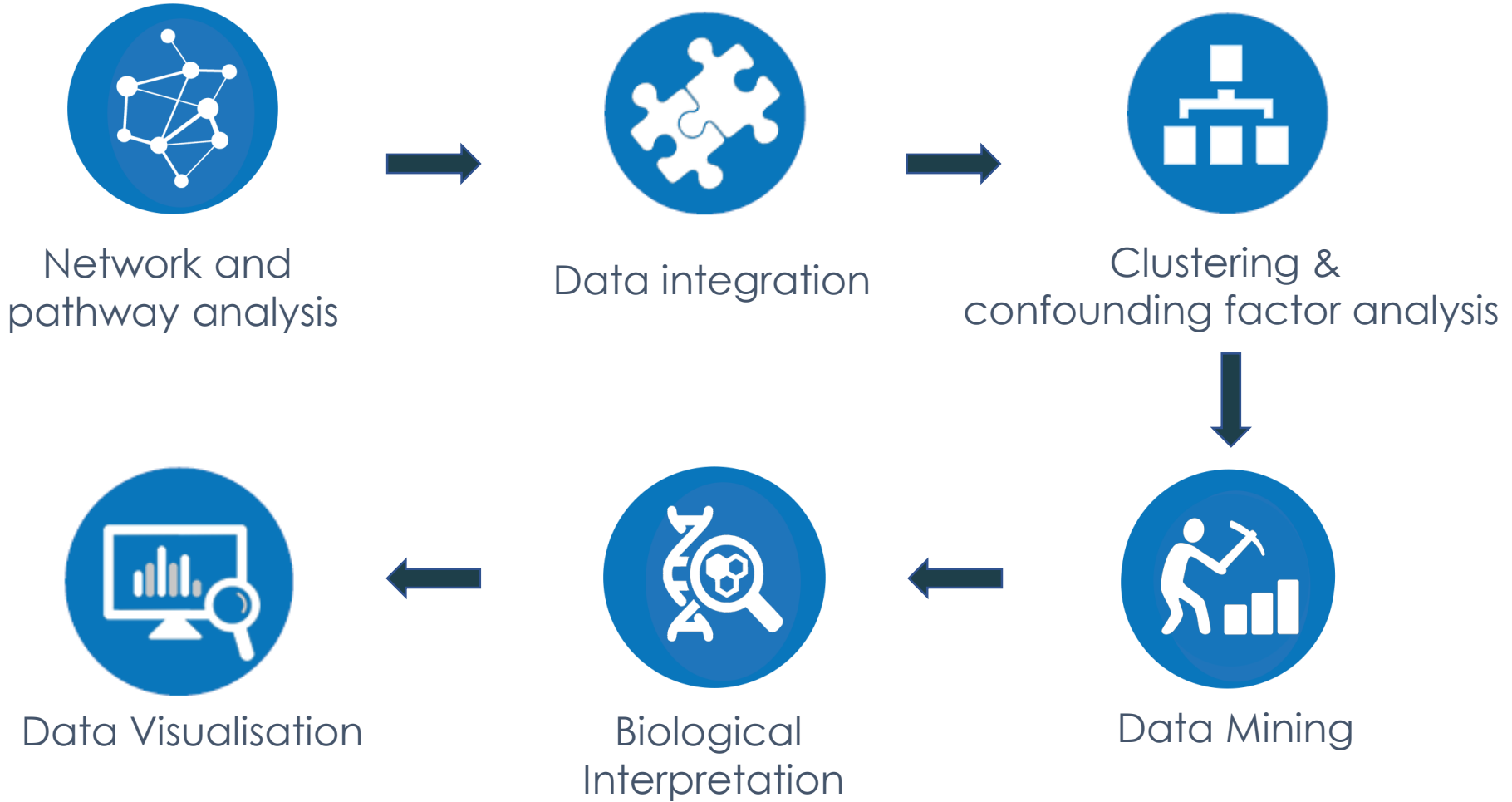


Data QC and normalisation

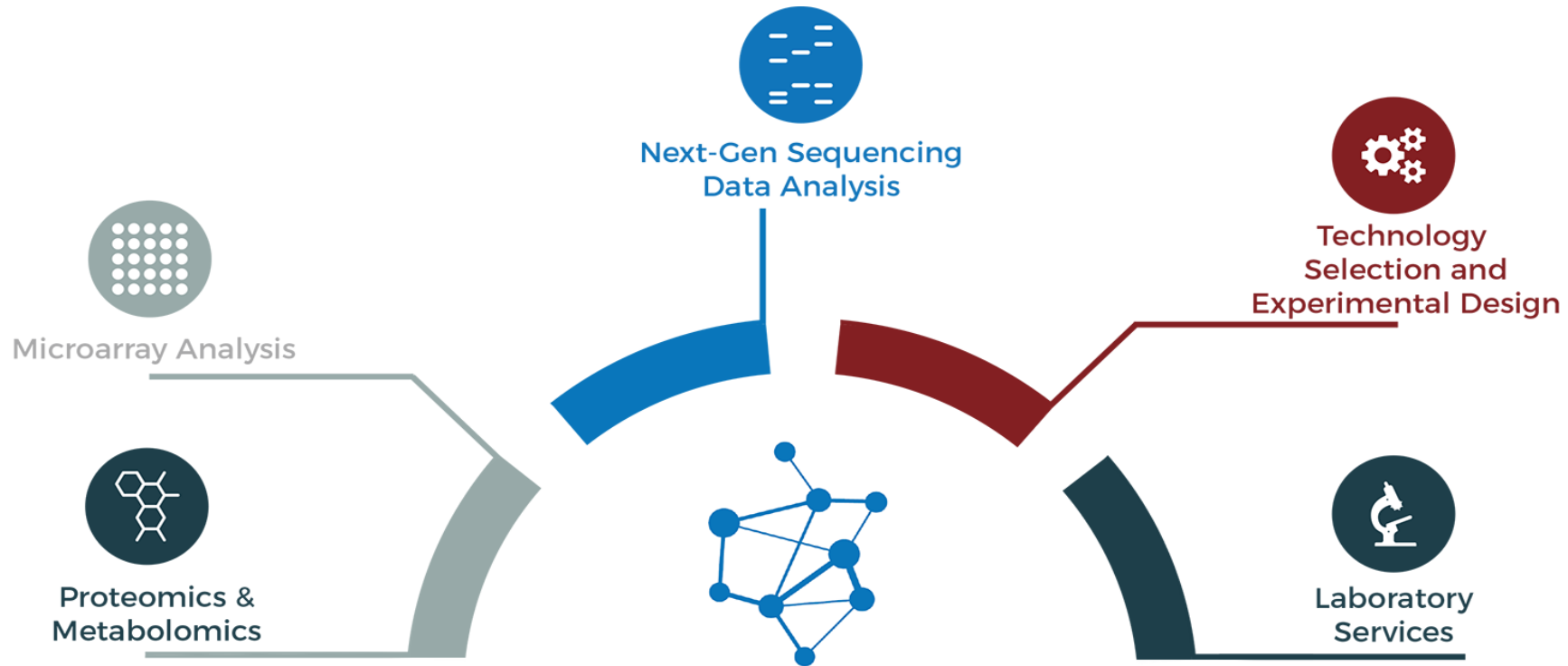


Gene lists generation

What we do



Examples



Example – Mariathasan *et al.*

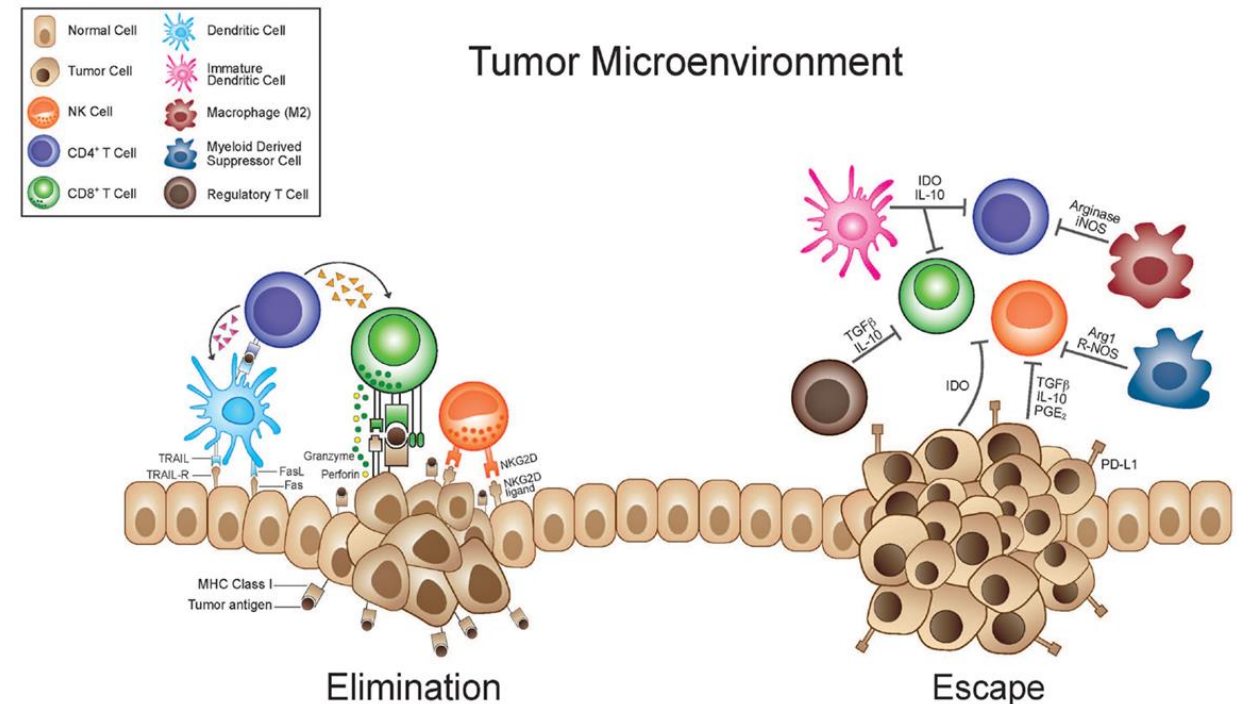
TGF β attenuates tumour response to PD-L1 blockade by contributing to exclusion of T cells

Sanjeev Mariathasan^{1*}, Shannon J. Turley^{1*}, Dorothee Nickles^{1*}, Alessandra Castiglioni¹, Kobe Yuen¹, Yulei Wang¹, Edward E. Kadel III¹, Hartmut Koeppen¹, Jillian L. Astarita¹, Rafael Cubas¹, Suchit Jhunjhunwala¹, Romain Banchereau¹, Yagai Yang¹, Yinghui Guan¹, Cecile Chalouni¹, James Ziai¹, Yasin Şenbabaoglu¹, Stephen Santoro¹, Daniel Sheinson¹, Jeffrey Hung¹, Jennifer M. Giltmane¹, Andrew K. Pierce¹, Kathryn Mesh¹, Steve Lianoglou¹, Johannes Riegler¹, Richard A. D. Carano¹, Pontus Eriksson², Mattias Hoglund², Loan Somarriba³, Daniel L. Halligan³, Michiel van der Heijden⁴, Yohann Lorient⁵, Jonathan E. Rosenberg⁶, Lawrence Fong⁷, Ira Mellman¹, Daniel S. Chen¹, Marjorie Green¹, Christina Derleth¹, Gregg D. Fine¹, Priti S. Hegde¹, Richard Bourgon¹ & Thomas Powles⁸

Nature **554**, 544–548 (22 February 2018)

Example – Mariathasan *et al.*

- Programmed death ligand-1 (PD-L1) is a regulatory molecule expressed in immune cells that can dampen the immune response
- Some diseases (e.g. cancer) take advantage of this immune checkpoint pathway by expressing PD-L1 on their cell surfaces to evade the immune response



Example – Mariathasan *et al.*

- Therapeutic antibodies that block the PD-L1 pathway are able to produce anti-tumourigenic effects in a variety of cancers
- However only a subset of patients respond to anti-PD-L1 treatment
- Robust biomarkers required to accurately stratify patients who will respond from those who will not



Example – Mariathasan *et al.*

- IMvigor210: A single-arm phase-II trial investigating the effects of atezolizumab in metastatic urothelial carcinoma (mUCs) (NCT02108652)
- Atezolizumab is an monoclonal antibody against PD-L1
- Evaluation to identify predictors of outcome linked to overall survival (OS)
- Multi-omics data integration
 - Clinical/demographical data
 - RNASeq
 - FMI



Example – Mariathasan *et al.*

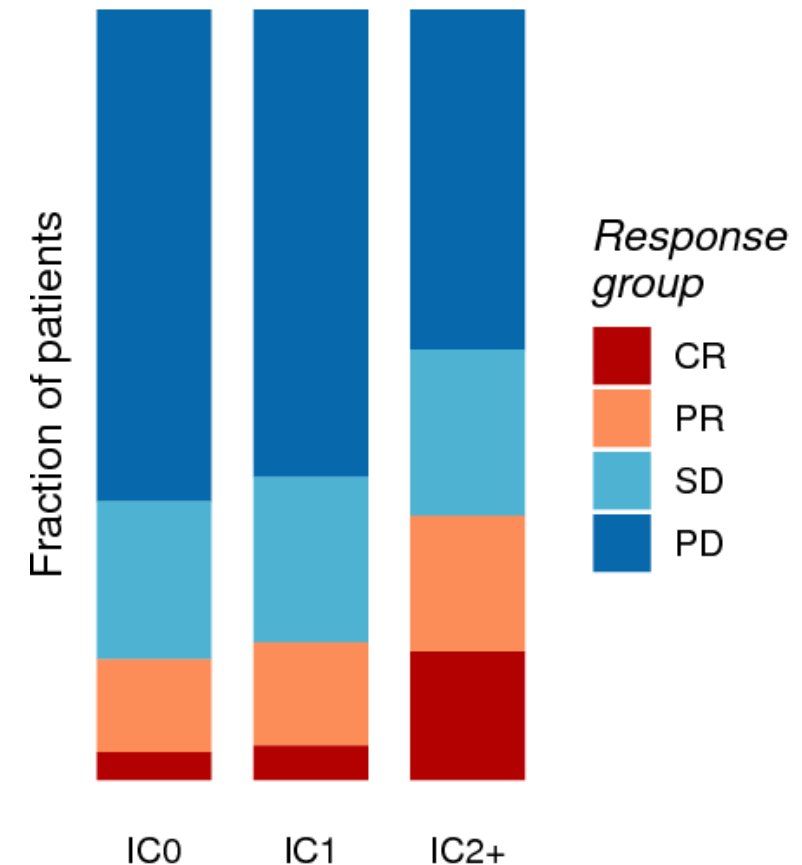
- **Is treatment response linked to presence of PD-L1?**
 - PD-L1 levels in immune cells (IC) assessed by IHC and scored as
 - **IC0** (< 1%)
 - **IC1** ($\geq 1\%$ and < 5%), or
 - **IC2+** ($\geq 5\%$)
 - Response to treatment defined as (RECIST v1.1)
 - Complete response (CR)
 - Progressive disease (PD)
 - Stable disease (SD)
 - Partial response (PR)

Example – Mariathasan *et al.*

- Is treatment response linked to presence of PD-L1?

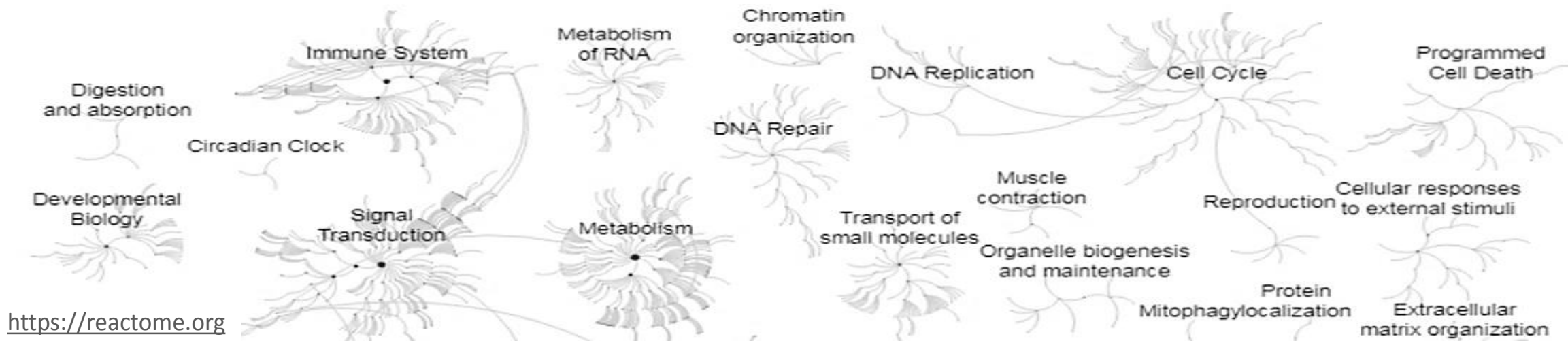
	CR+PR	SD+PD	Total
IC0	13	70	83
IC1	20	92	112
IC2+	35	67	102
Total	68	229	297

$p = 0.0038$, two-sided Fisher's exact test



Example – Mariathasan *et al.*

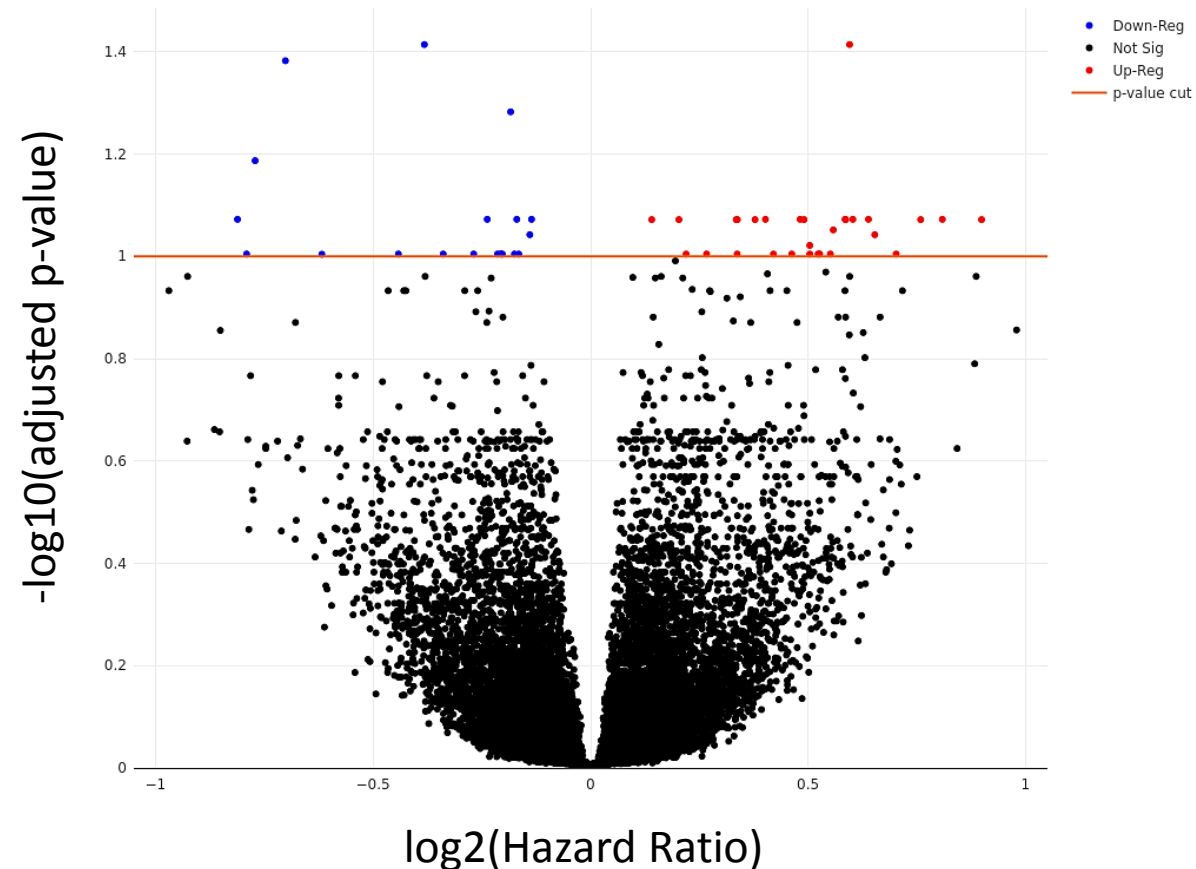
- **What genes & pathways are associated with survival outcomes?**
 - Identification of gene expression levels significantly associated with OS (Cox PH)
 - Pathway analysis of significant genes



Example – Mariathasan *et al.*

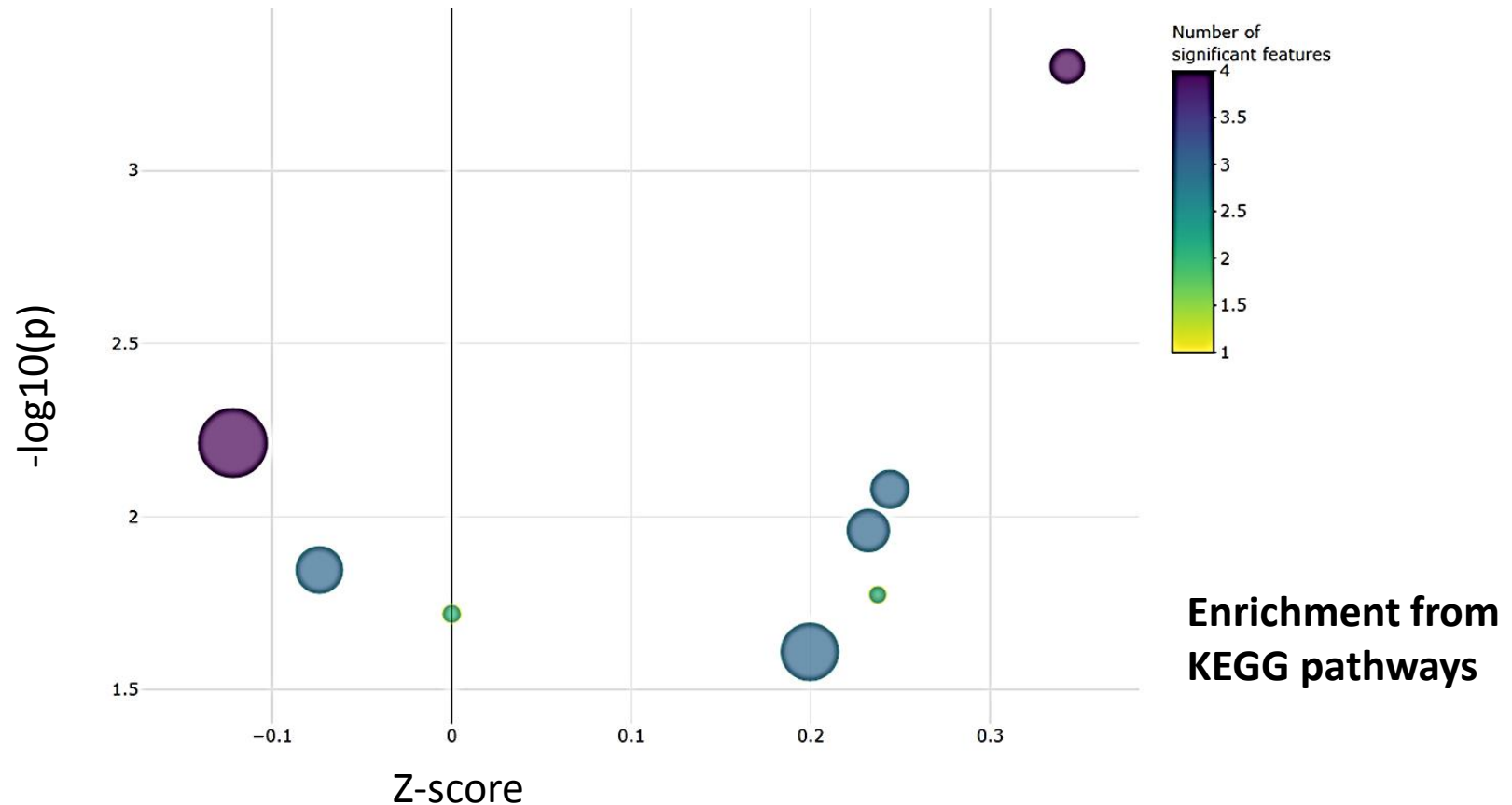
- **What genes & pathways are associated with survival outcomes?**

- 48 genes were associated with overall survival at an FDR adjusted threshold of $p < 0.1$
- Of these 48-genes, 19 were associated with improved overall survival, and 29 with worsening survival at higher expression levels



Example – Mariathasan *et al.*

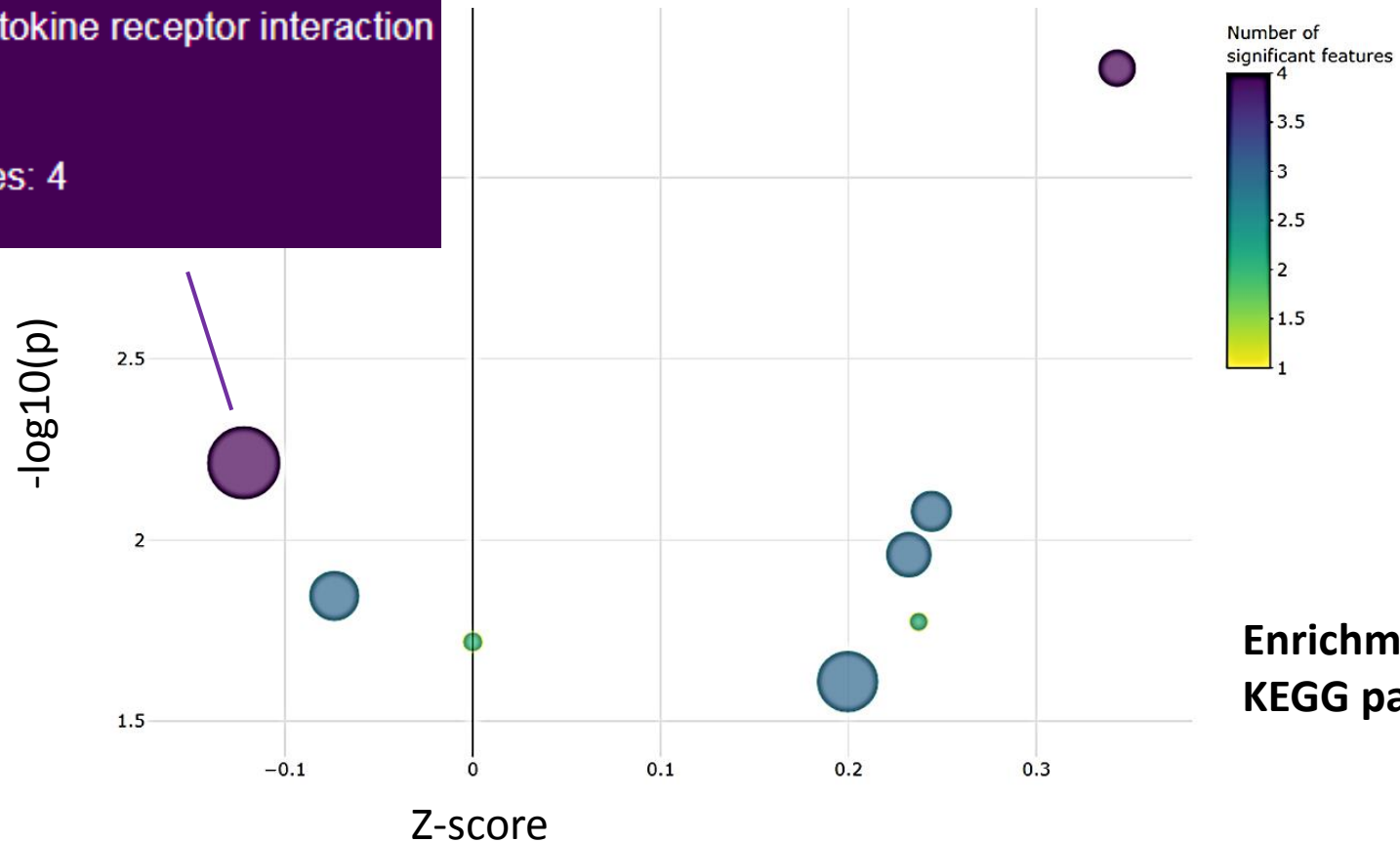
- What genes & pathways are associated with survival outcomes?



Example – Mariathasan *et al.*

- What genes & pathways are associated with survival outcomes?

Pathway: Cytokine-cytokine receptor interaction
Z-score: -0.12194
-log₁₀(P): 2.213
No. Significant features: 4
Pathway size: 269

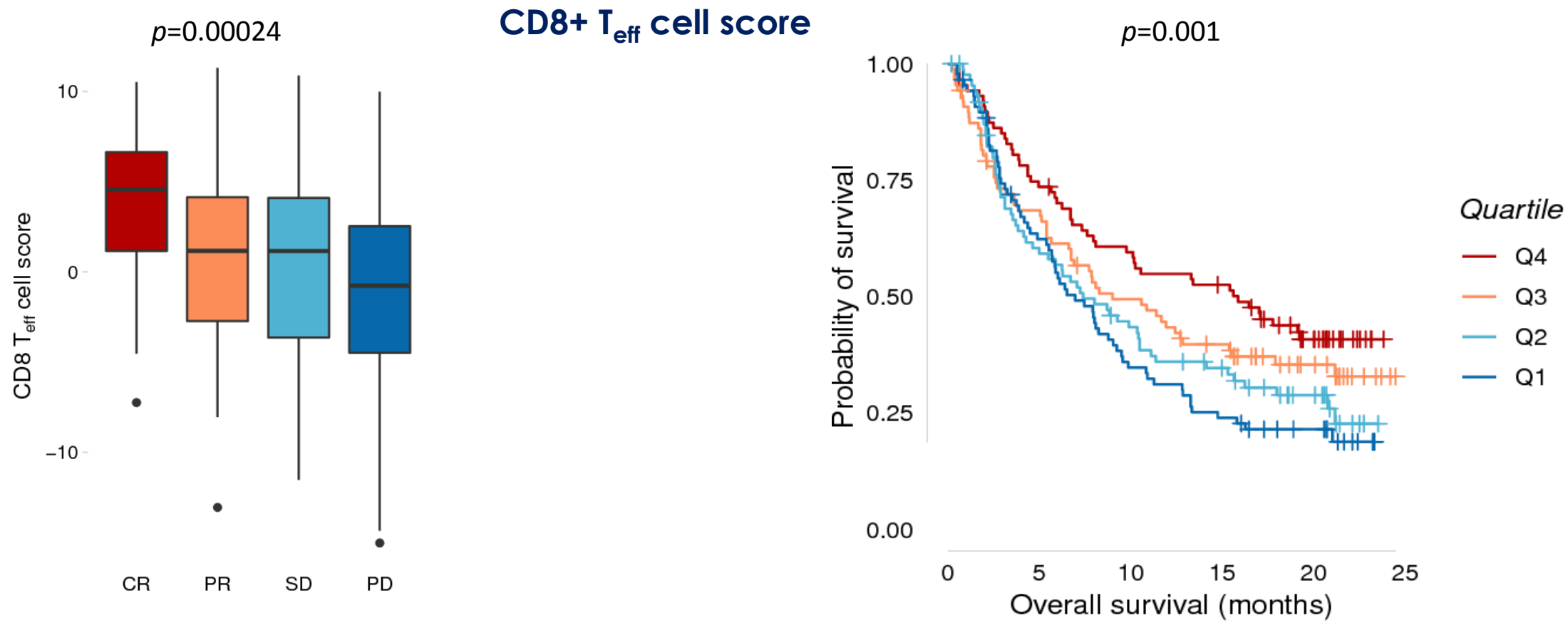


Example – Mariathasan *et al.*

- **Do genomic markers explain response and survival rates?**
 - CD8+ T_{eff} cell score:
 - Signature score derived from gene expression levels of CD8A, GZMA, GZMB, PRF1, INFG, and TBX21 (Balar *et al.*, *Lancet*, 2017)
 - Tumour mutational burden:
 - Estimated from the Foundation Medicine One (FMI) platform
 - TGFβ1 expression
 - From RNASeq expression levels

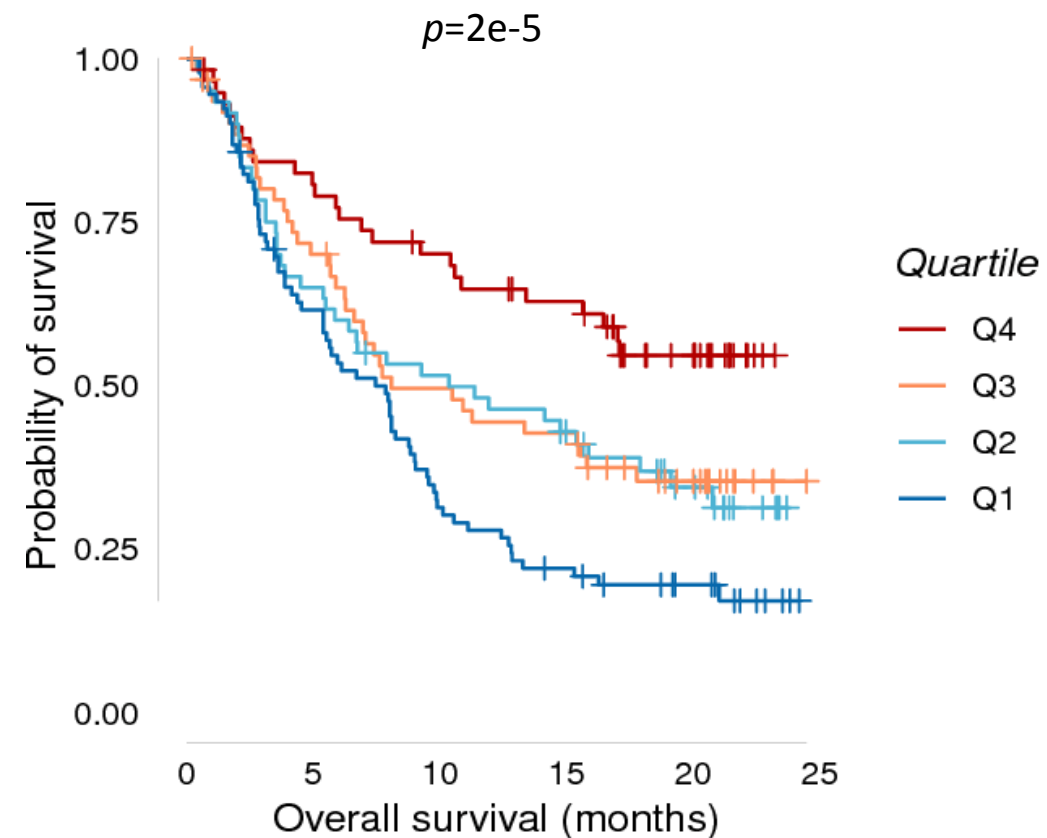
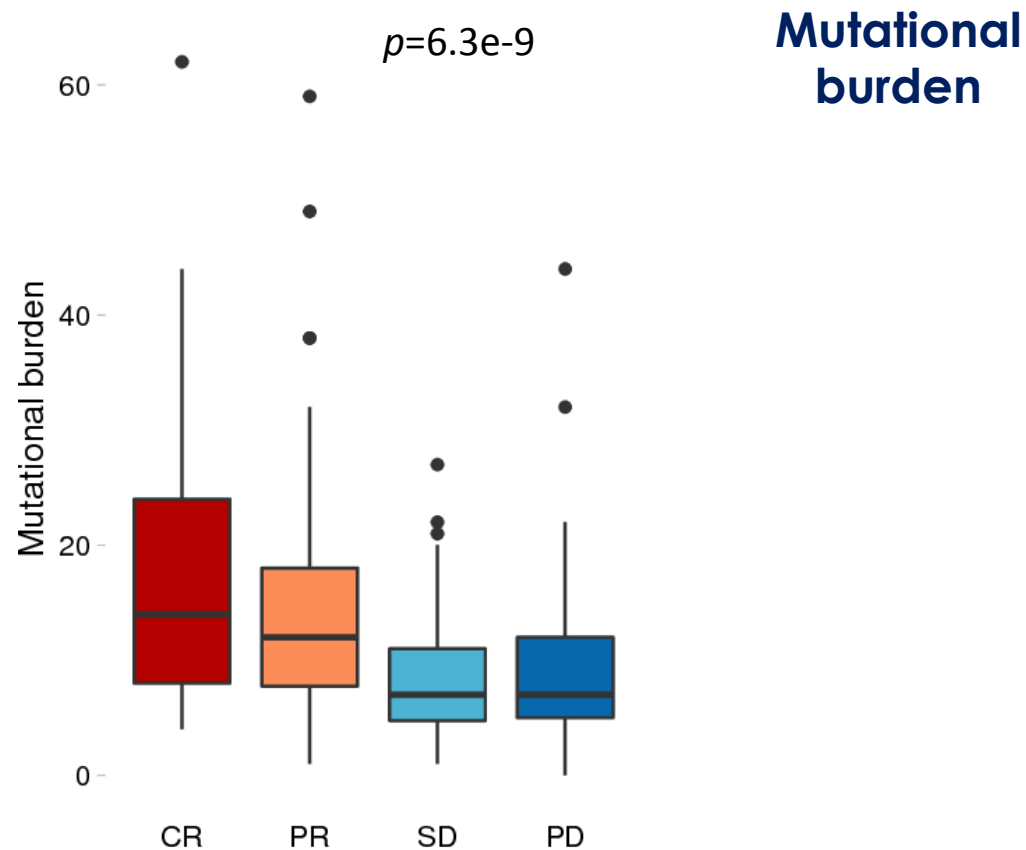
Example – Mariathasan *et al.*

- Do genomic markers explain response and survival rates?



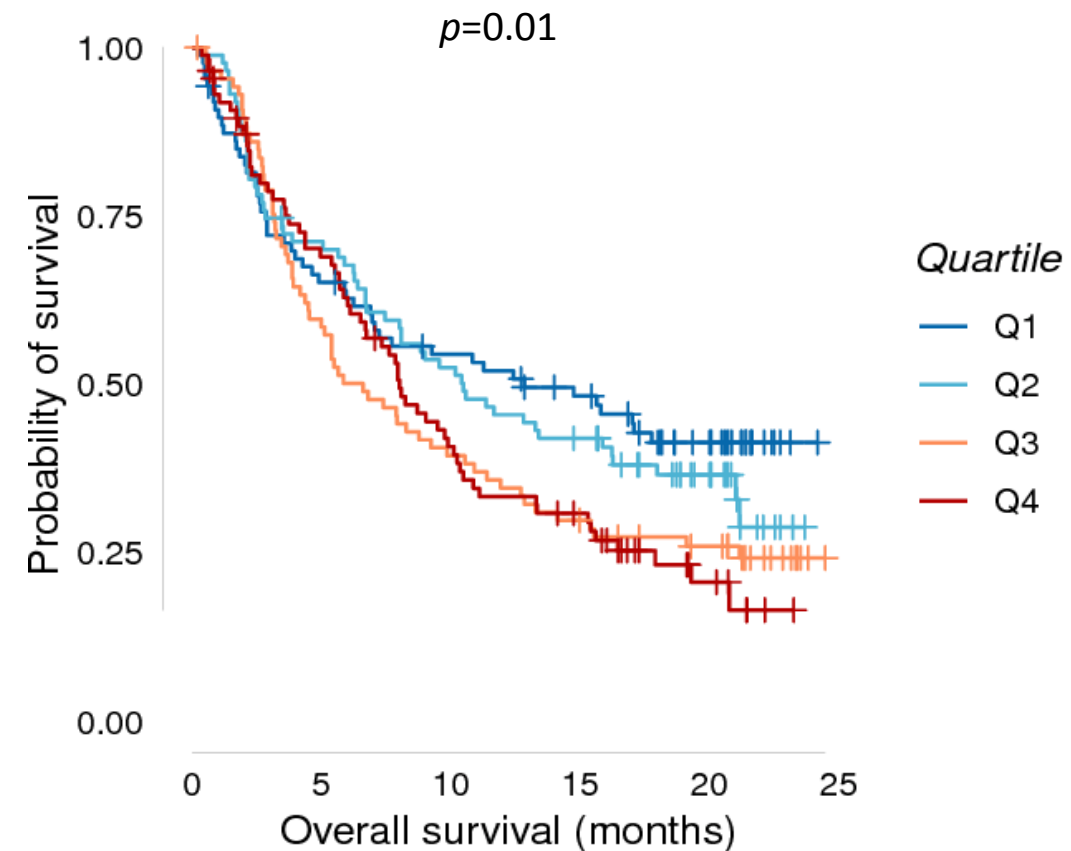
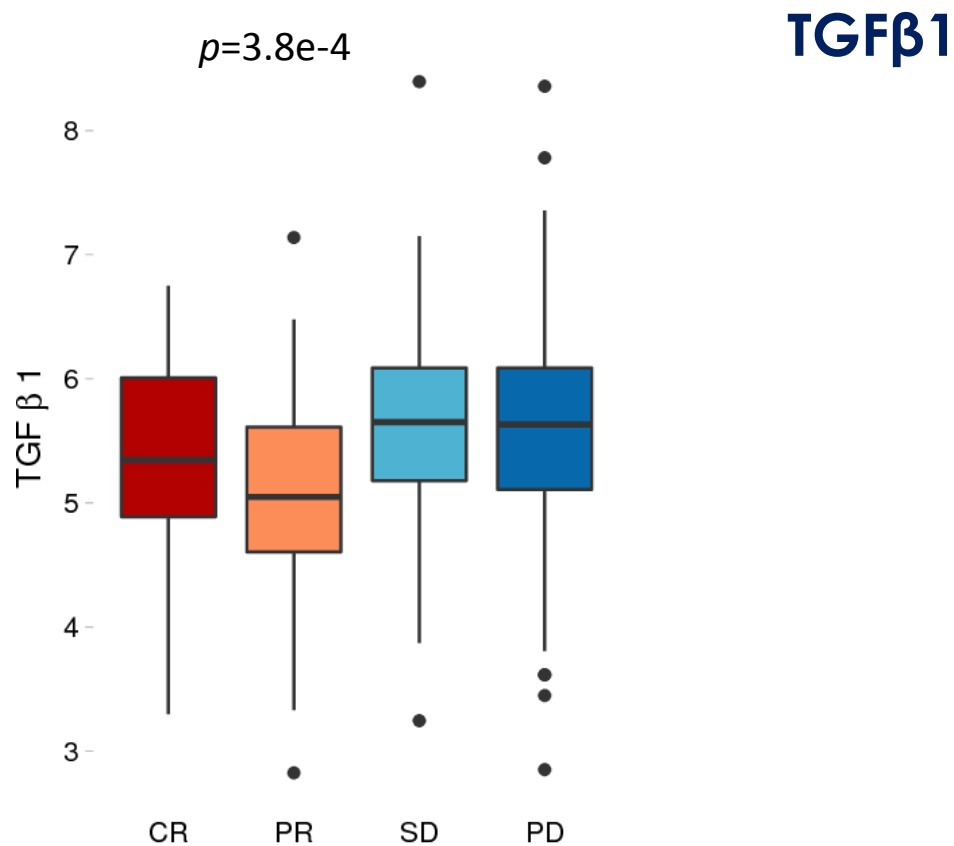
Example – Mariathasan *et al.*

- Do genomic markers explain response and survival rates?



Example – Mariathasan *et al.*

- Do genomic markers explain response and survival rates?

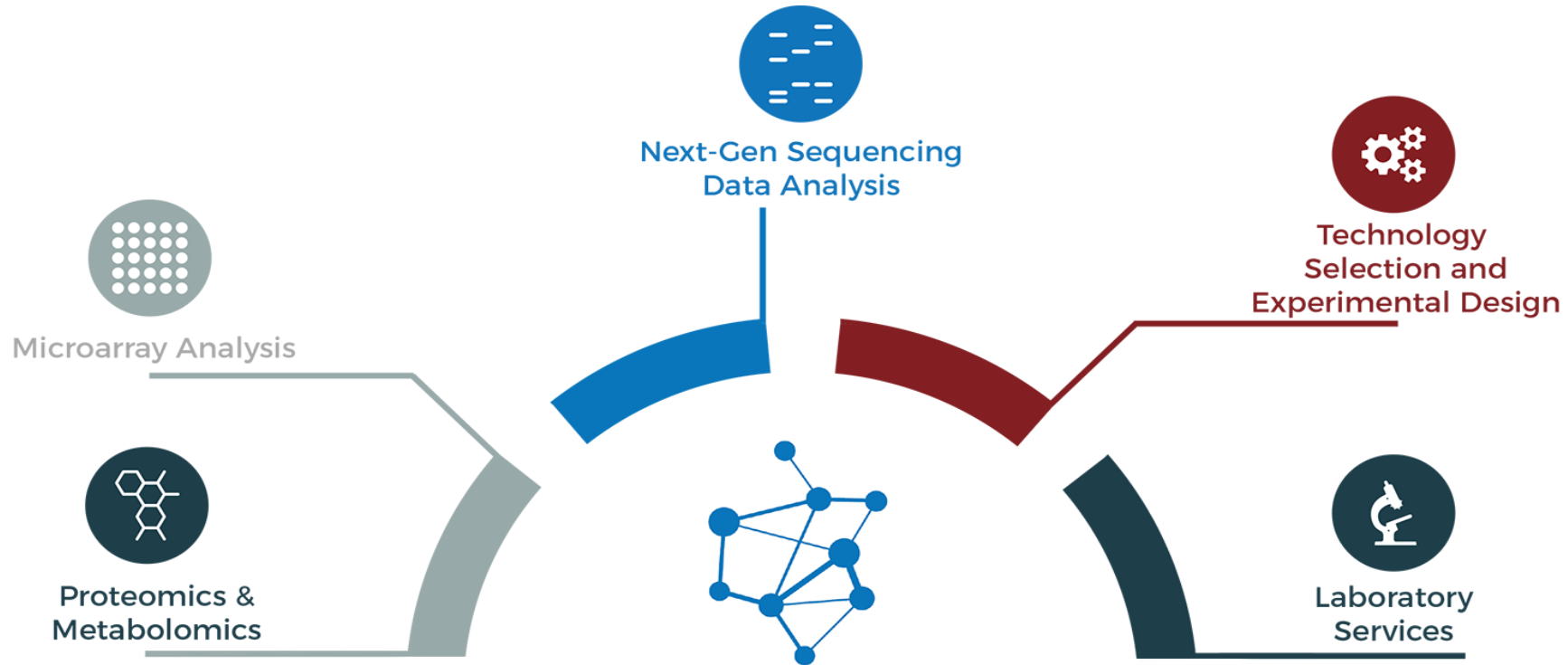


Example – Mariathasan *et al.*

- **Conclusions**

- Response to treatment was associated with a CD8+ T-effector cell phenotype and increased tumour mutation burden
- Lack of response was primarily associated with a signature of transforming growth factor β (TGF β) signalling

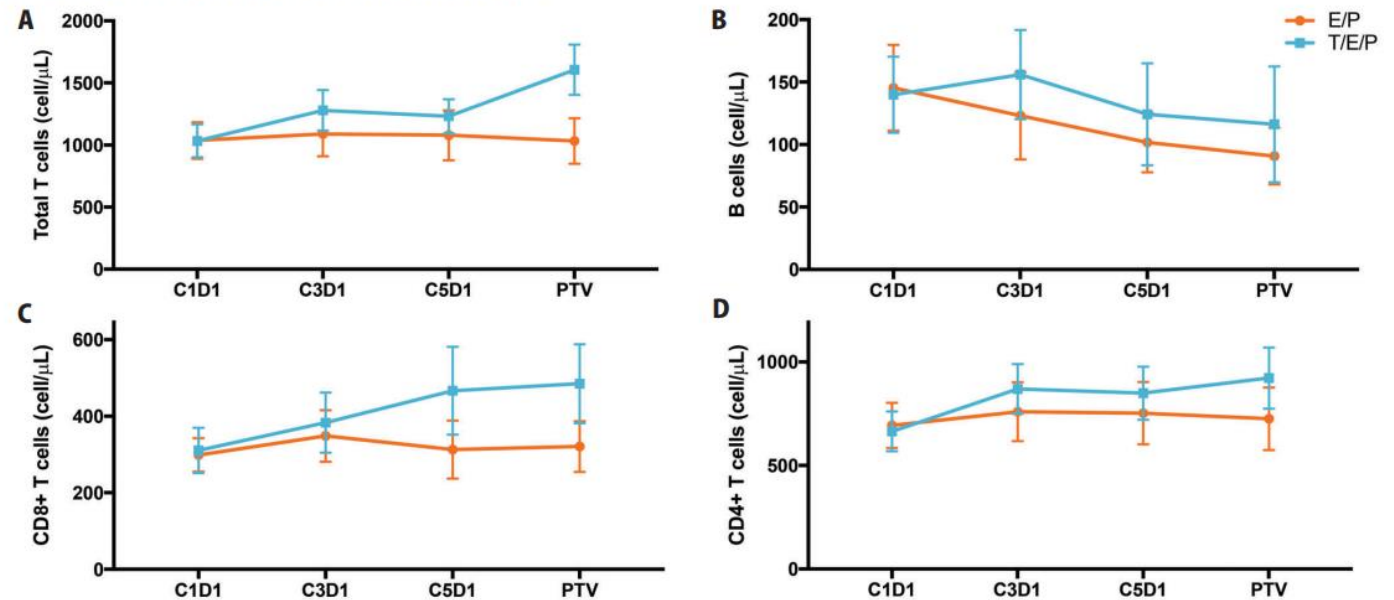
Other examples



Other examples

- **Flow cytometry**
 - Longitudinal mixed linear models of lymphocyte subpopulations across treatment groups

FIGURE 3. LYMPHOCYTE SUBPOPULATIONS

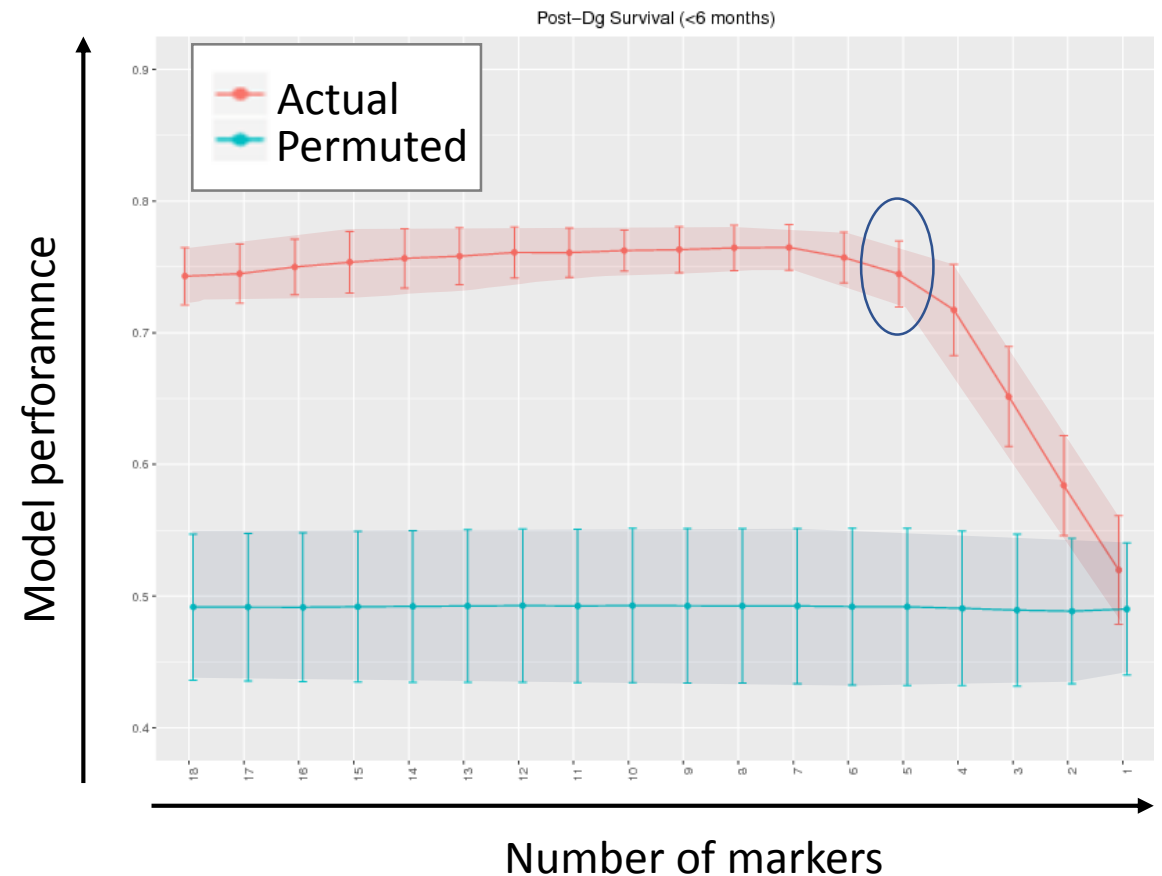


Sorrentino et al, #1671P, ESMO 2018.

Other examples

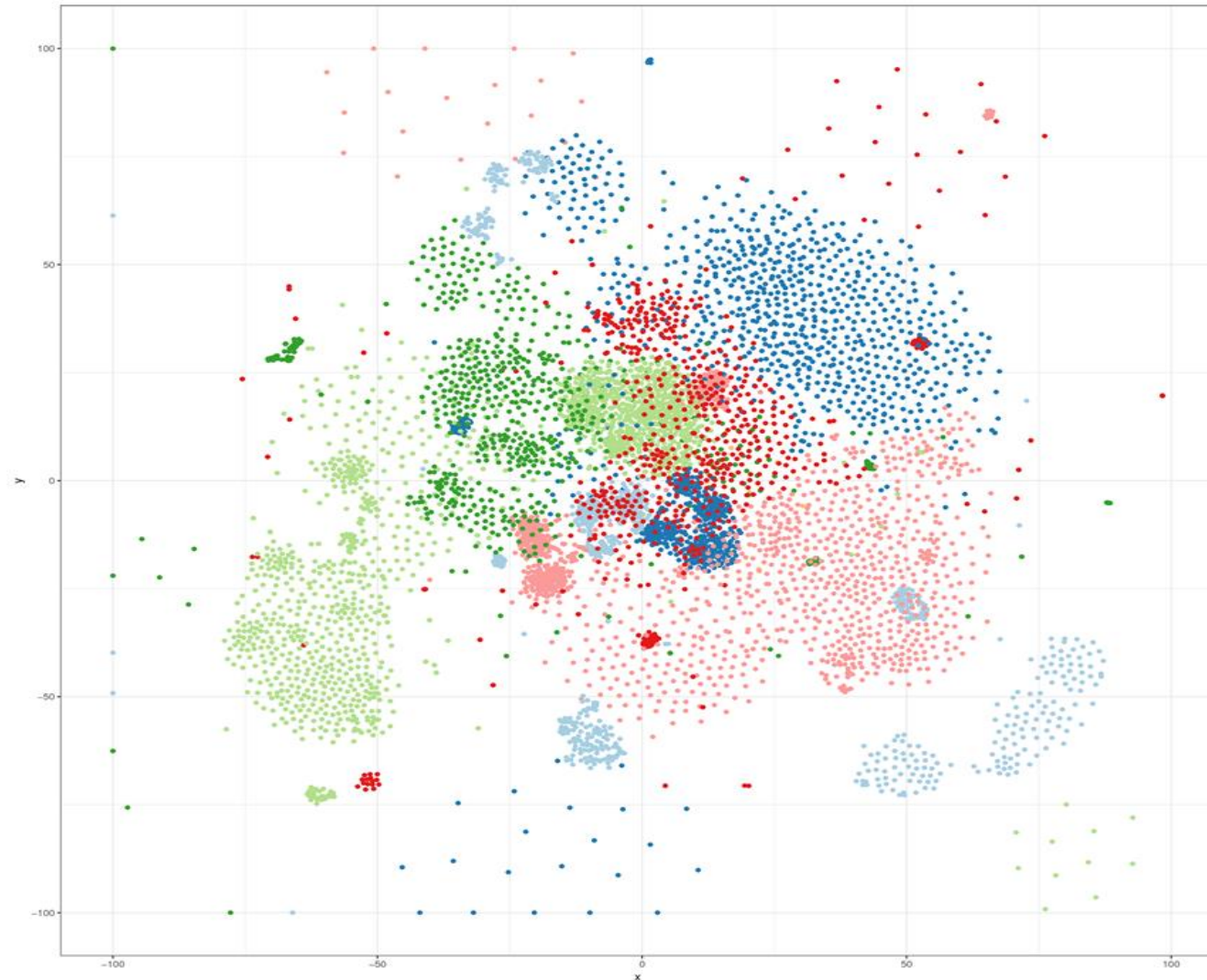
- **Machine learning**

- Survival prediction in mesothelioma using Lasso regression



Other examples

- **Single-cell RNASeq**
 - Clustering of immune cell types



Publications

- Full list of publications at <https://www.fiosgenomics.com/publications/>



The screenshot shows the Fios Genomics website. At the top left is the logo for Fios Genomics, which consists of the word "fios" in a bold, lowercase font and "GENOMICS" in a smaller, uppercase font below it, with a stylized network diagram to the right. To the right of the logo is a navigation menu with links for "Home", "About Us", "Our Services", "Resources", "Blog", and "Contact Us". Further right is a search bar with the placeholder text "Search..." and a magnifying glass icon. To the right of the search bar are three social media icons for Twitter, LinkedIn, and Facebook.

The main content area of the page features a heading: "The quality of the work produced by Fios Genomics and its staff and founders has been recognised and published also in other **peer-reviewed journals**:". Below this heading is a list of seven publications, each preceded by a blue diamond bullet point. The publications are:

- ♦ Axel W. Wiberg; Daniel L. Halligan; Rob W. Ness; Anamaria Necsulea; Henrik Kaessmann; Peter D. Keightley. Assessing Recent Selection and Functionality at Long Non-Coding RNA Loci in the Mouse Genome R. *Genome Biology and Evolution* (2015). [Link](#)
- ♦ Dickinson P., Smith C.L., Forster T., Craigon M., Ross A.J., Khondoker M.R., Ivens A., Lynn D.J., Orme J., Jackson A., Lacaze P., Flanagan K.L., Stenson B.J., Ghazal P. Whole blood gene expression profiling of neonates with confirmed bacterial sepsis. *Genomics Data* 3, 41-48 (2015). [Link](#)
- ♦ Keightley P.D., Ness R.W., Halligan D.L., Haddrill P.R. Estimation of the spontaneous mutation rate per nucleotide site in a *Drosophila melanogaster* full-sib family. *Genetics* 196, 313-320 (2014). [Link](#)
- ♦ Kousathanas A., Halligan D.L., Keightley P.D. Faster-X Adaptive Protein Evolution in House Mice. *Genetics*, 196, 1131-1143 (2014). [Link](#)
- ♦ Halligan D.L., Kousathanas A., Ness R.W., Harr B., Eory L., Keane T.M., Adams D.J., Keightley P.D. Contributions of Protein-Coding and Regulatory Change to Adaptive Molecular Evolution in Murid Rodents. *PLoS Genetics* 9(12) (2013). [Link](#)
- ♦ Kelleher J., Ness R.W., Halligan D.L. Processing genome scale tabular data with wormtable. *BMC Bioinformatics*, 14, 356 (2013). [Link](#)
- ♦ Mabott N.A., Baillie J.K., Brown H., Freeman T.C., Hume D.A. An expression atlas of human primary cells: inference of gene function from coexpression networks. *BMC Genomics* 14, 632 (2013). [Link](#)
- ♦ Wilkens J., Male V., Ghazal P., Forster T., Gibbs D.A., Williams A.R., Brito-Mutunayagam S.L., Craigon M., Lourenco P., Cameron I.T., Chwalisz K., Moffett A., Critchley H.O. Uterine NK Cells Regulate Endometrial Bleeding in Women and are Suppressed by the Progesterone Receptor Modulator Asoprisnil. *J. Immunology* Aug (2) (2013). [Link](#)

In summary...

- Fios Genomics can help get the most out of 'omics experiments:
 - Deeper analysis
 - Faster turnaround
- Flexible and bespoke service.
- Help with technology selection/study design through to result interpretation.



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Thank you