Bioinformatics In Biomarker Discovery

Dr Adrian Carr
Bioinformatics Team Leader

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.

fios GENOMICS

‘Omics Analysis

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

Biomarker ID

Patient Stratification

Personalised Medicine

Biologicals

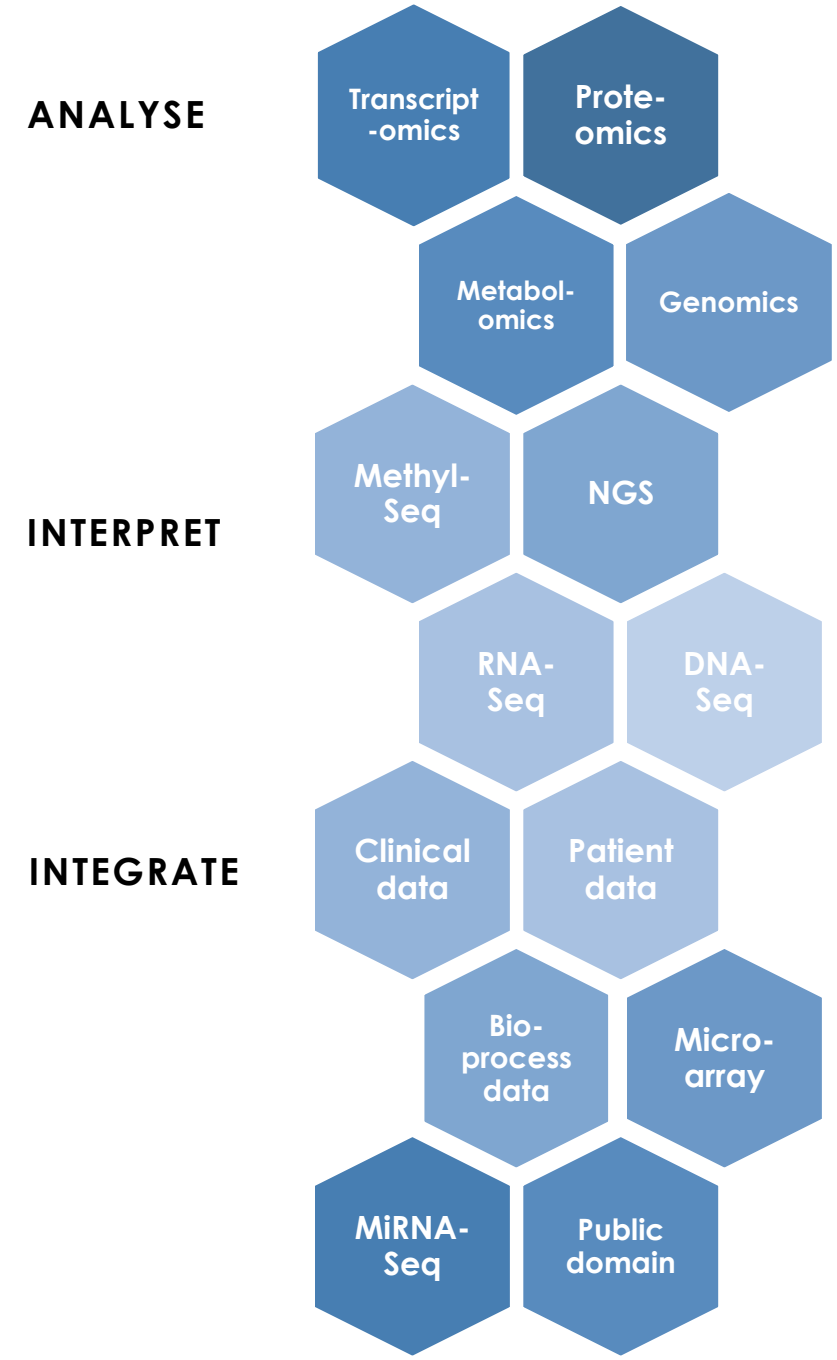
Issues:

- 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

fios GENOMICS

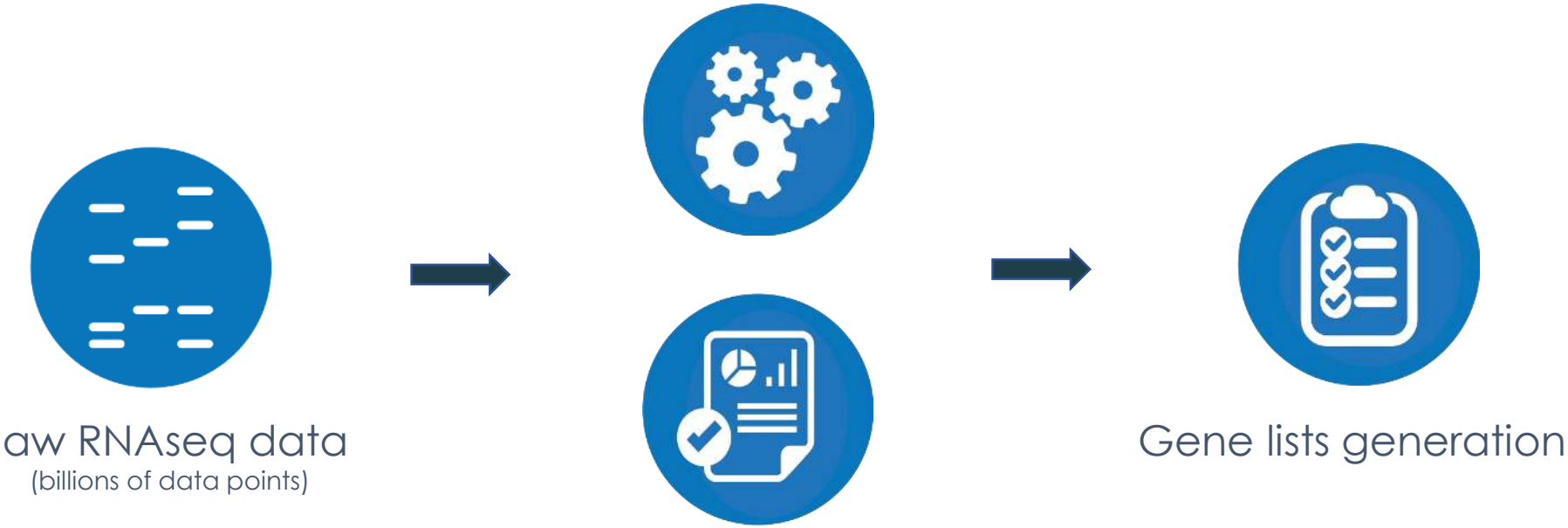
How Can Fios Help?

- 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.



fios GENOMICS

What we do

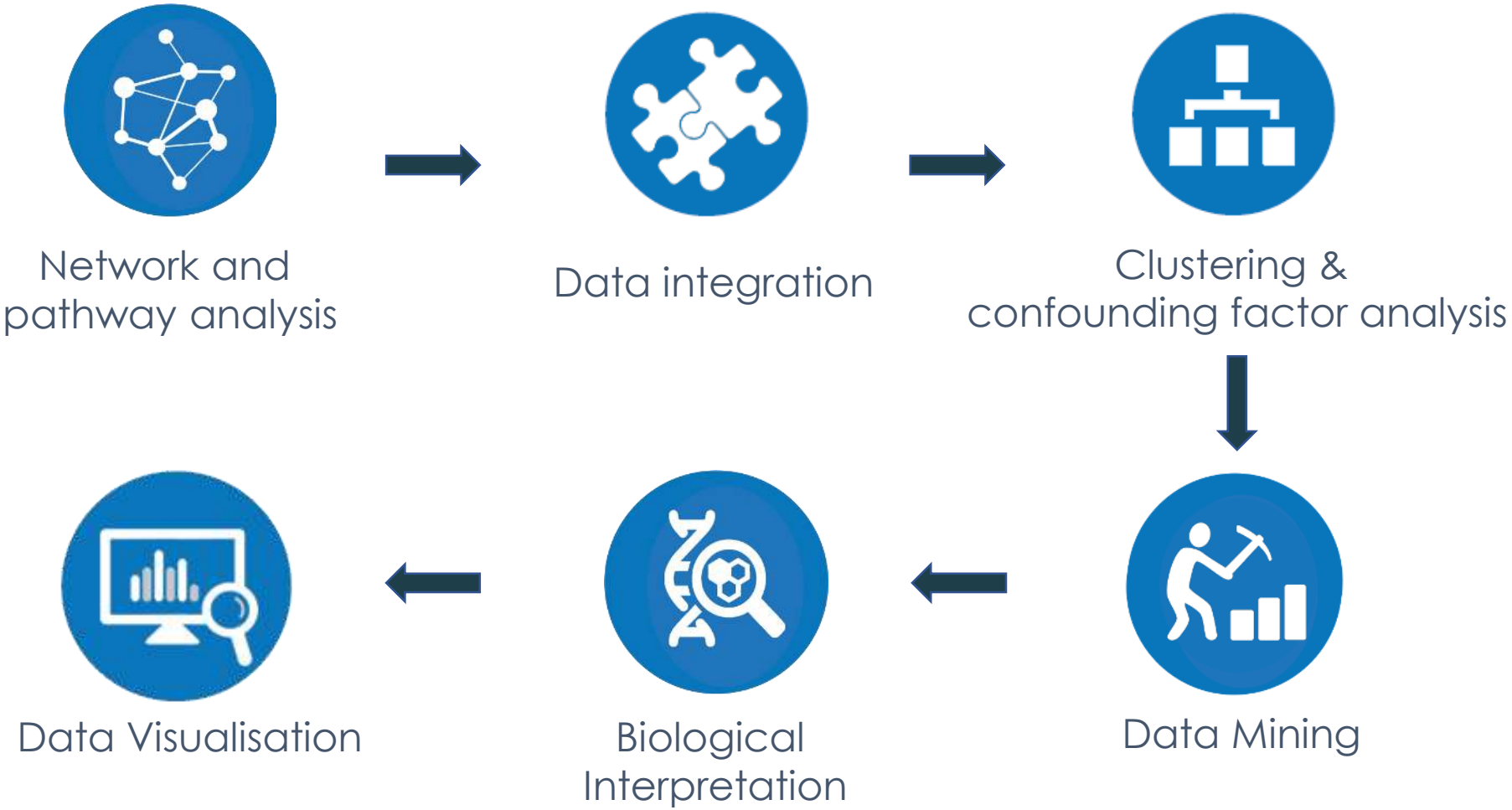


Raw RNAseq data
(billions of data points)

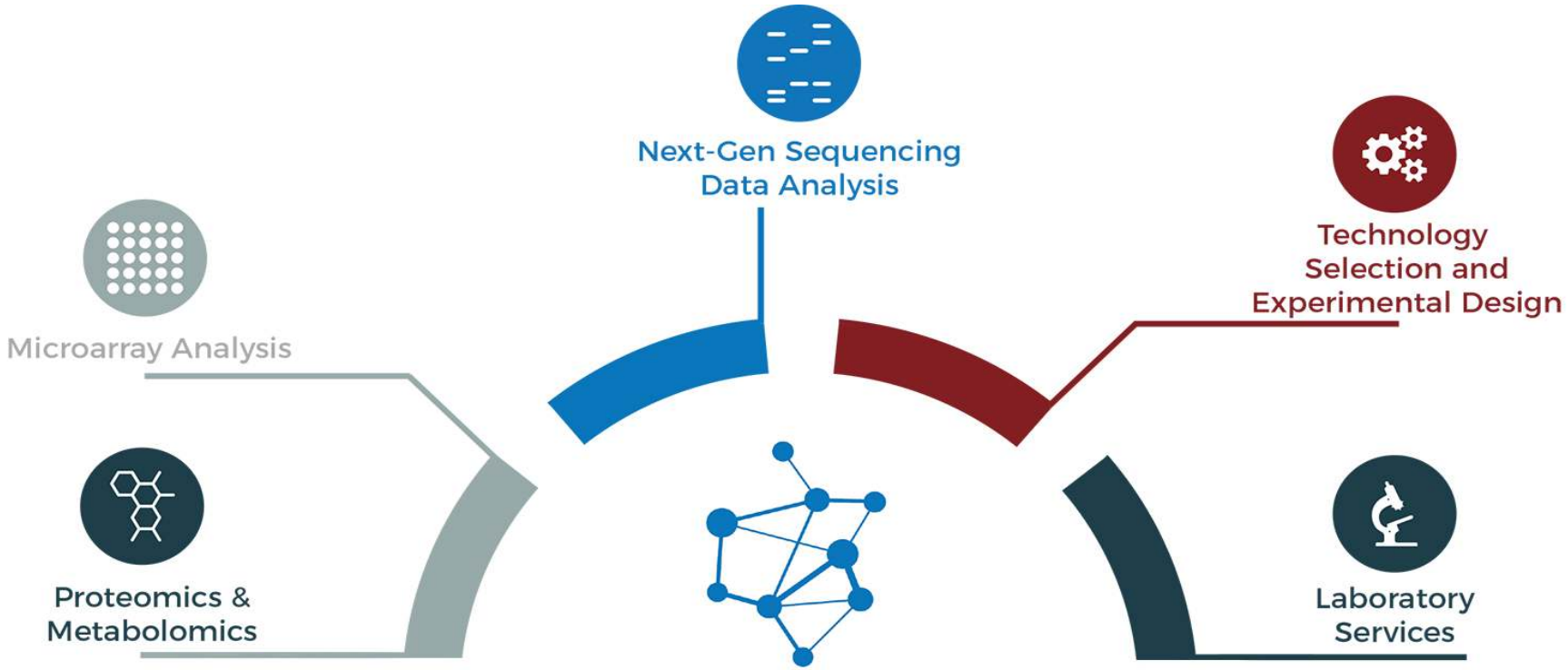
Data QC and normalisation

Gene lists generation

What we do


Network and pathway analysis
Data integration
Clustering & confounding factor analysis
Data Mining
Biological Interpretation
Data Visualisation

Case studies



fios GENOMICS

Example – Hutchinson *et al.*

CLINICAL CANCER RESEARCH | TRANSLATIONAL CANCER MECHANISMS AND THERAPY

Comprehensive Profiling of Poor-Risk Paired Primary and Recurrent Triple-Negative Breast Cancers Reveals Immune Phenotype Shifts

Katherine E. Hutchinson[1], Susan E. Yost[2], Ching-Wei Chang[3], Radia Marie Johnson[4], Adrian R. Carr[5], Paul R. McAdam[5], Daniel L. Halligan[5], Chun-Chieh Chang[3], Daniel Schmolze[6], Jackson Liang[1], and Yuan Yuan[2]

Example – Hutchinson *et al.*

Background and experimental design

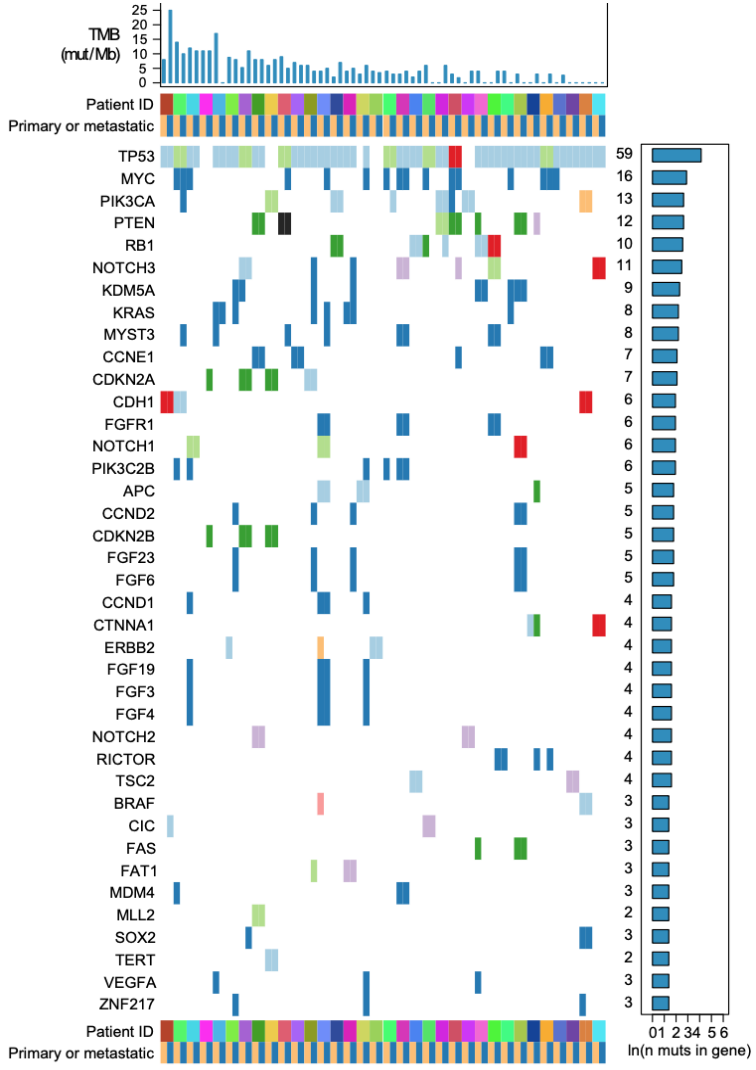
- Emerging data suggest immune checkpoint inhibitors have reduced efficacy in heavily pretreated triple-negative breast cancer (TNBC)
- Paired primary and metastatic samples collected from 43 patients with recurrent TNBC
- Targeted exome sequencing and whole transcriptome sequencing performed
- Somatic mutation profiles, tumor mutation burden (TMB), molecular subtypes, immune-related gene signatures, stromal TILs, recurrence-free survival (RFS) and overall survival (OS) analysed

fios GENOMICS

Example – Hutchinson *et al.*

Genomic landscape of recurrent TNBCs

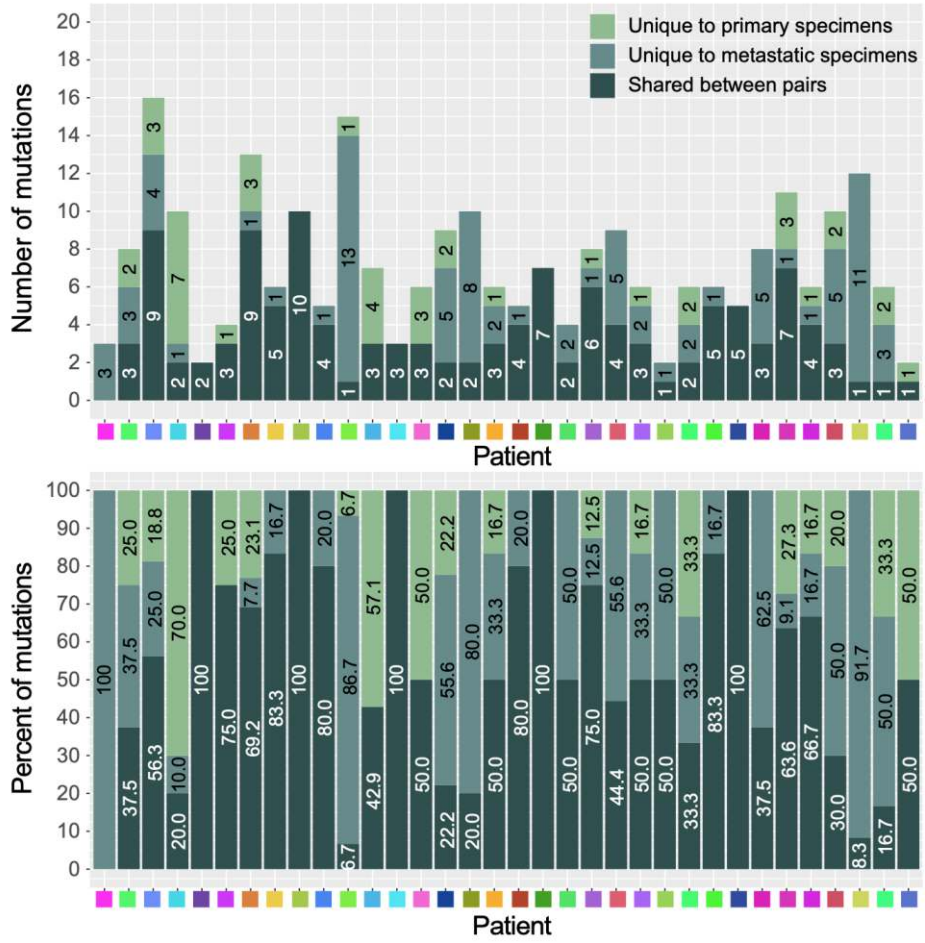
- 34 TNBC pairs (68 samples) were sequenced using FoundationOne targeted NGS assay
- The most common mutations were in: TP53, MYC, PIK3CA, PTEN and RB1
- On average, 50% of mutations were shared between pairs, 16% unique to primary samples and 34% unique to metastatic
- No consistent mutational shifts observed between primary and metastatic
- No significant copy number or tumor mutation burden (TMB) changes observed between primary and metastatic



fios GENOMICS

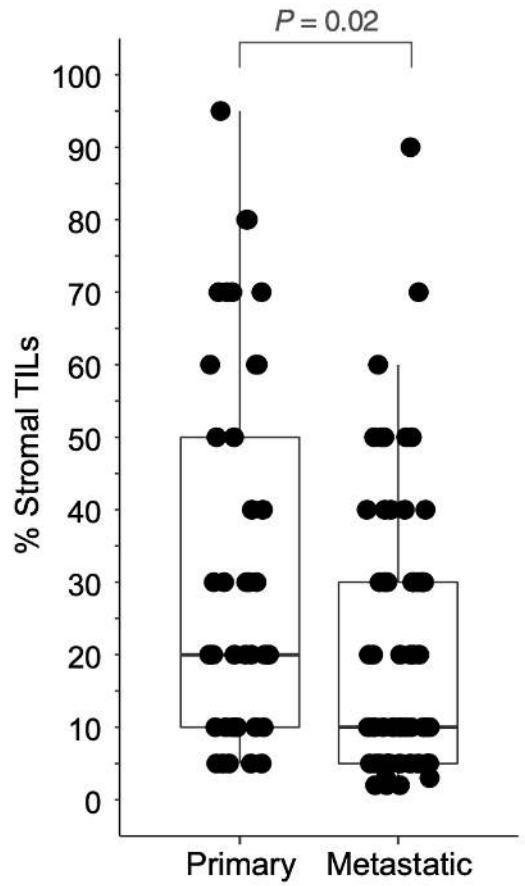
Example – Hutchinson *et al.*

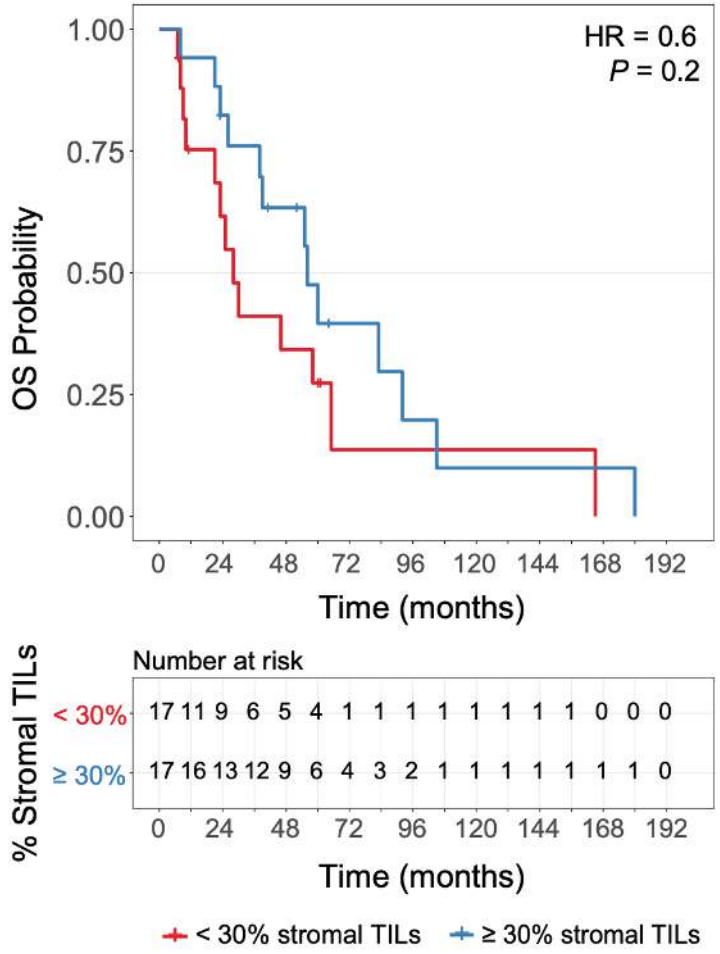
Concordance of oncogenic variants between primary and metastatic samples.



Example – Hutchinson *et al.*

Tumor infiltrating lymphocytes (TILs) and survival



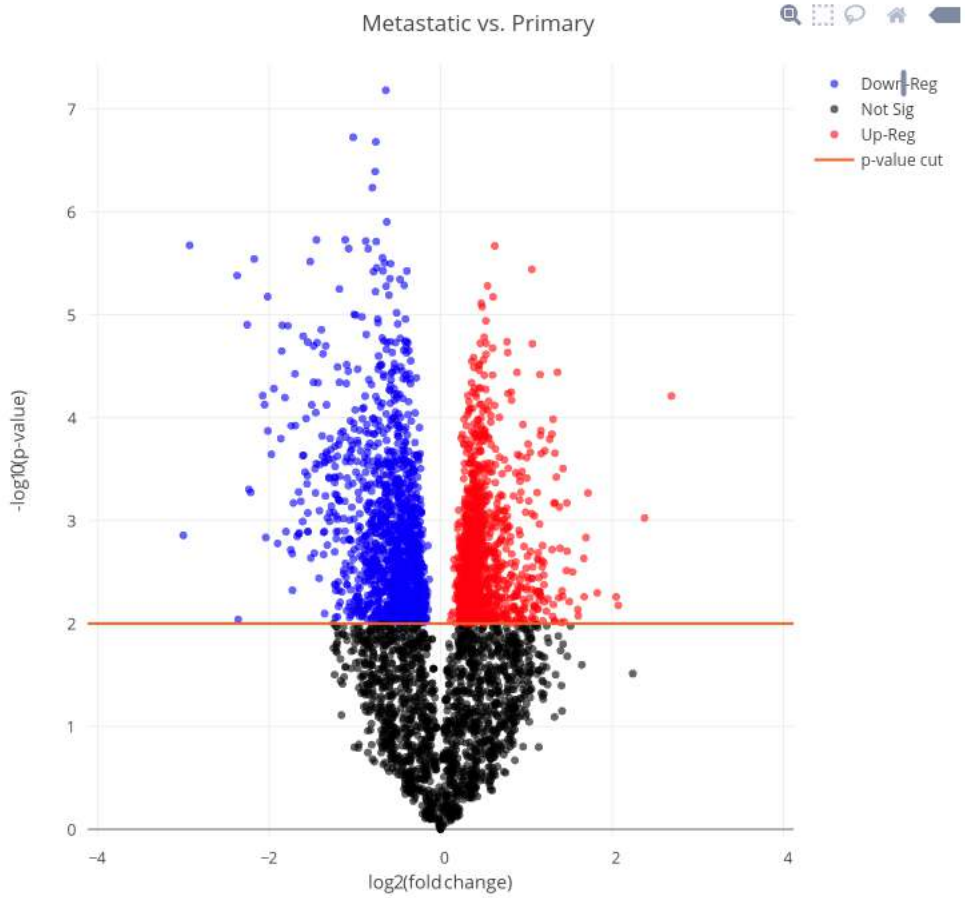


fios GENOMICS

Example – Hutchinson *et al.*

Differential Gene Expression Analysis

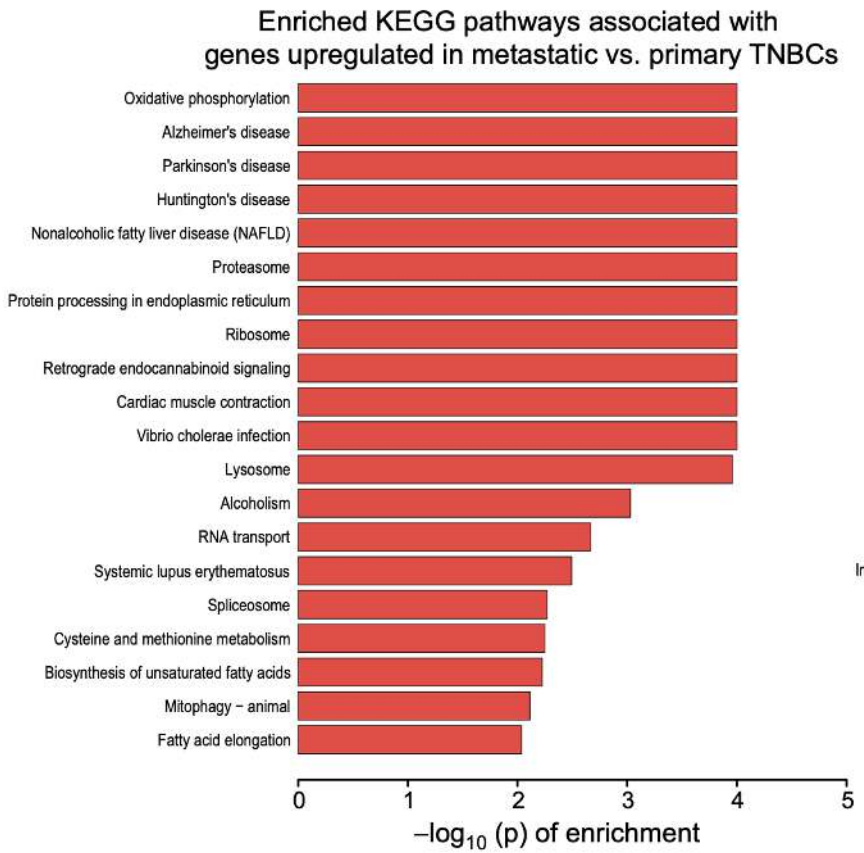
- RNA-seq performed on 35 P/M pairs of specimens
- Metastatic vs. Primary comparison identified 1,001 genes (FDR < 0.05)
- Immune-related KEGG pathways were enriched in genes that were down-regulated in metastatic

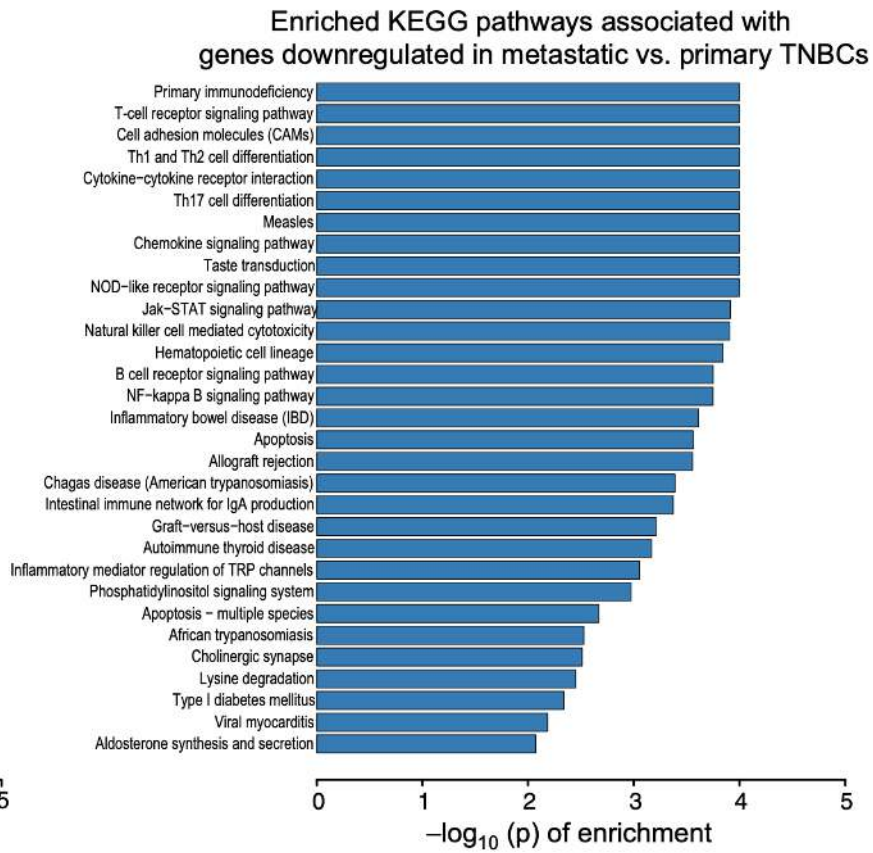


fios GENOMICS

Example – Hutchinson *et al.*

KEGG pathway enrichment in metastatic vs. primary TNBCs

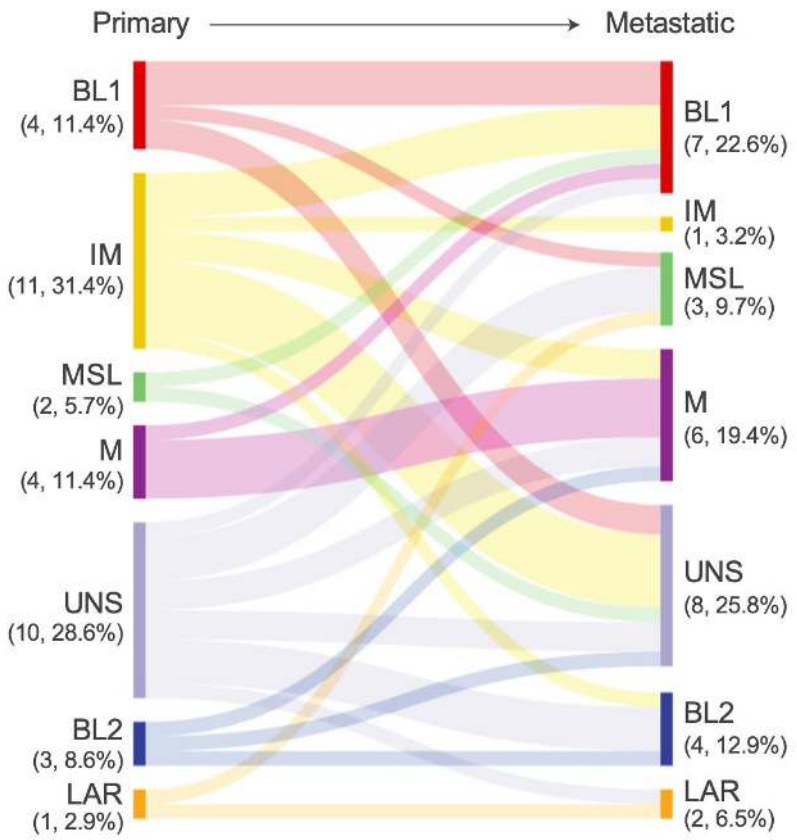




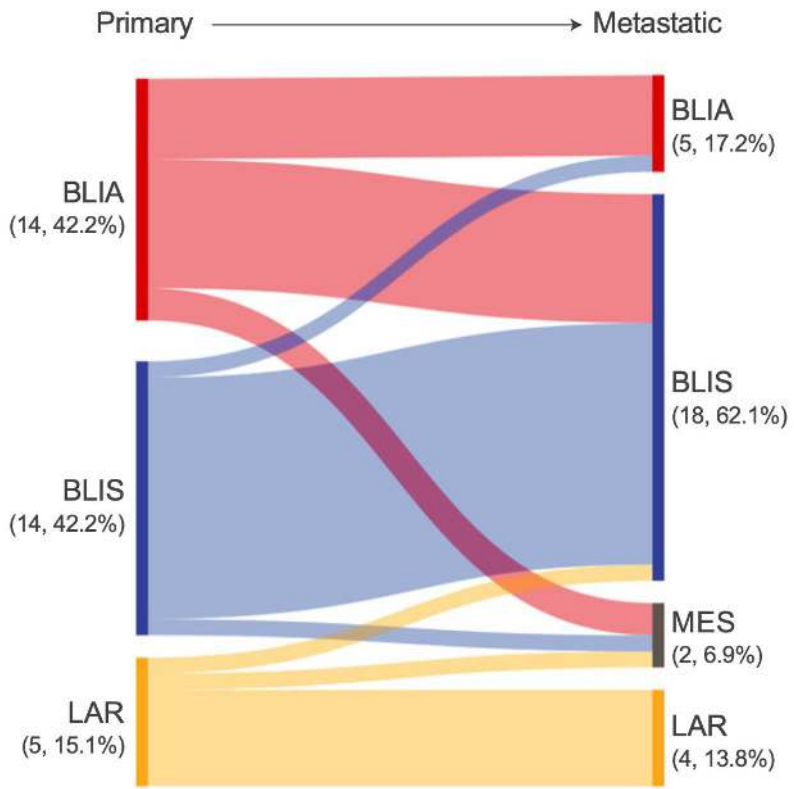
Example – Hutchinson *et al.*

Molecular subtypes shifts between primary and metastatic TNBC pairs

Lehmann-Pietenpol subtypes



Burstein subtypes

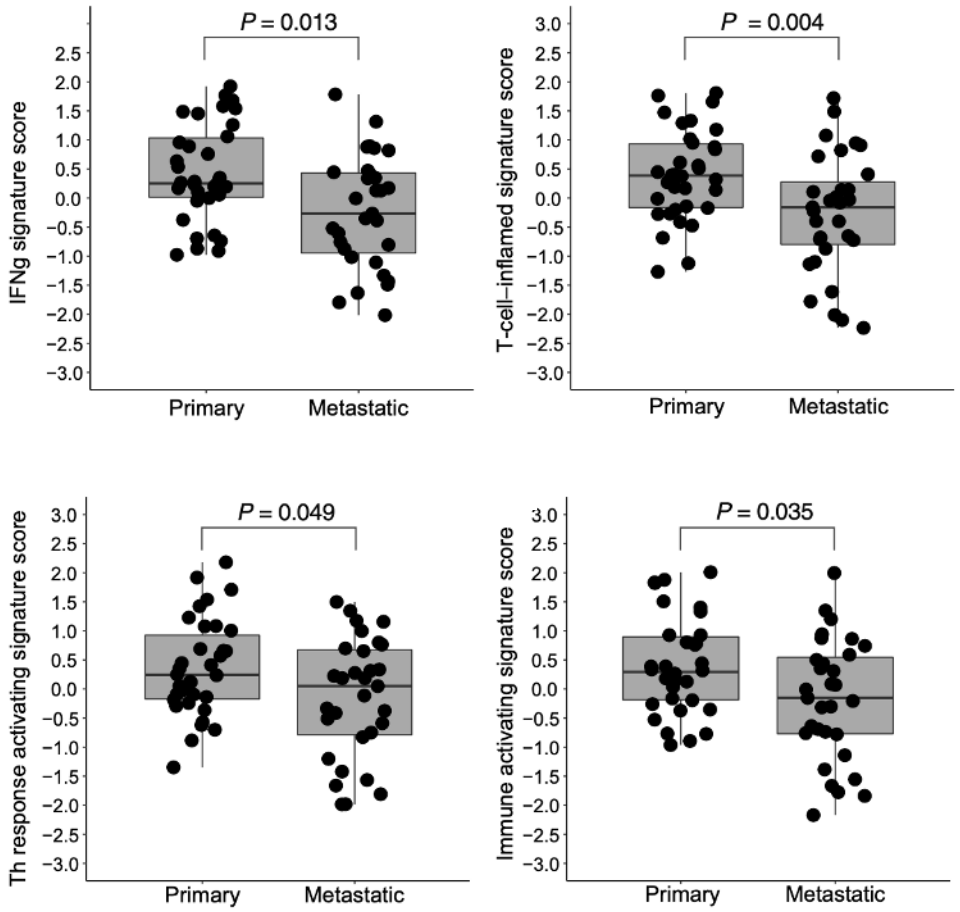


fios GENOMICS

Example – Hutchinson *et al.*

Immunomodulatory Gene Signatures

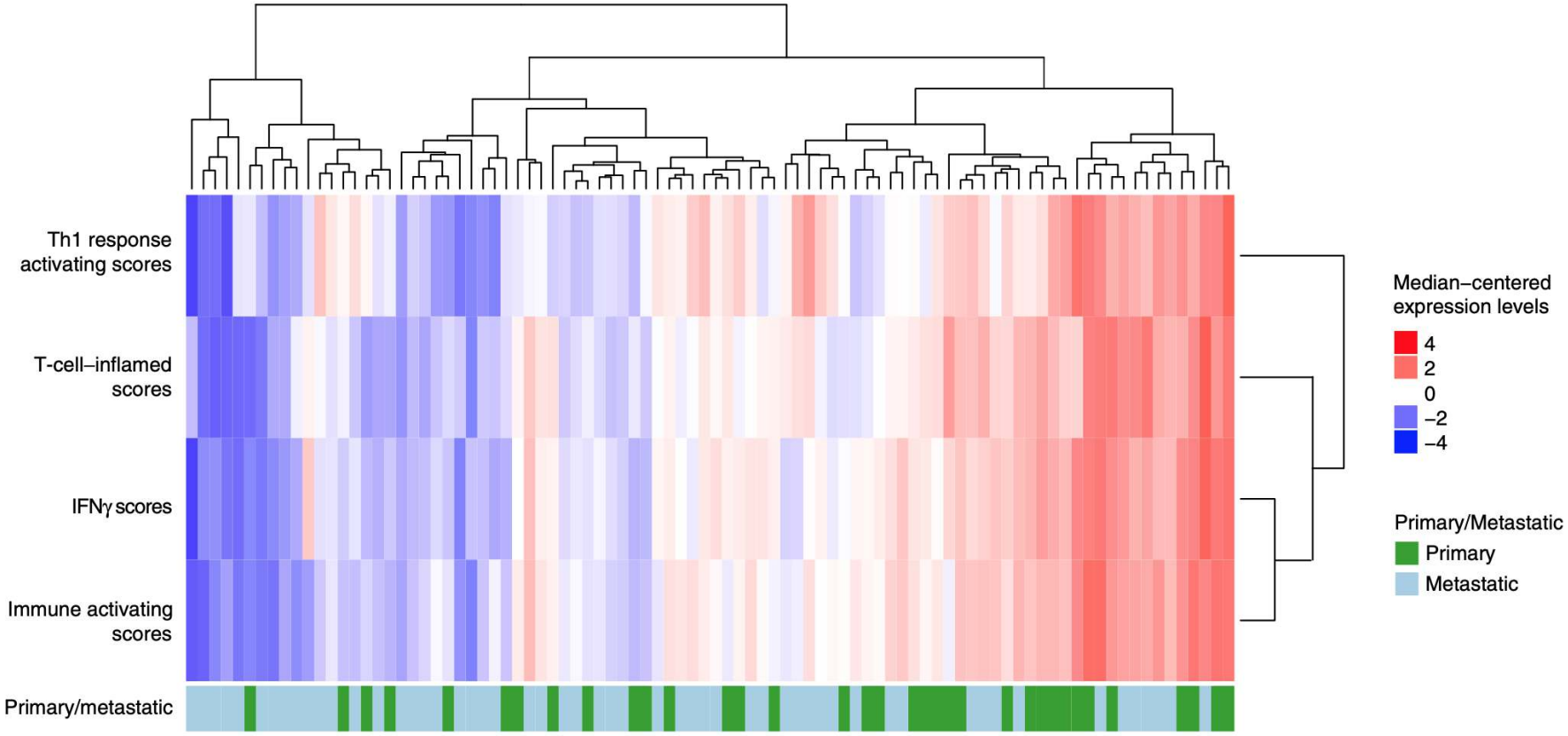
- Composite expression score calculated for 4 published immunological activity gene signatures
- IFNg, T-cell inflamed, Th1 response-activating and Immune-activating
- Composite scores compared: metastatic vs primary
- All four were significantly lower ($P < 0.05$) in metastatic tumors



fios GENOMICS

Example – Hutchinson *et al.*

Immunomodulatory Gene Signatures

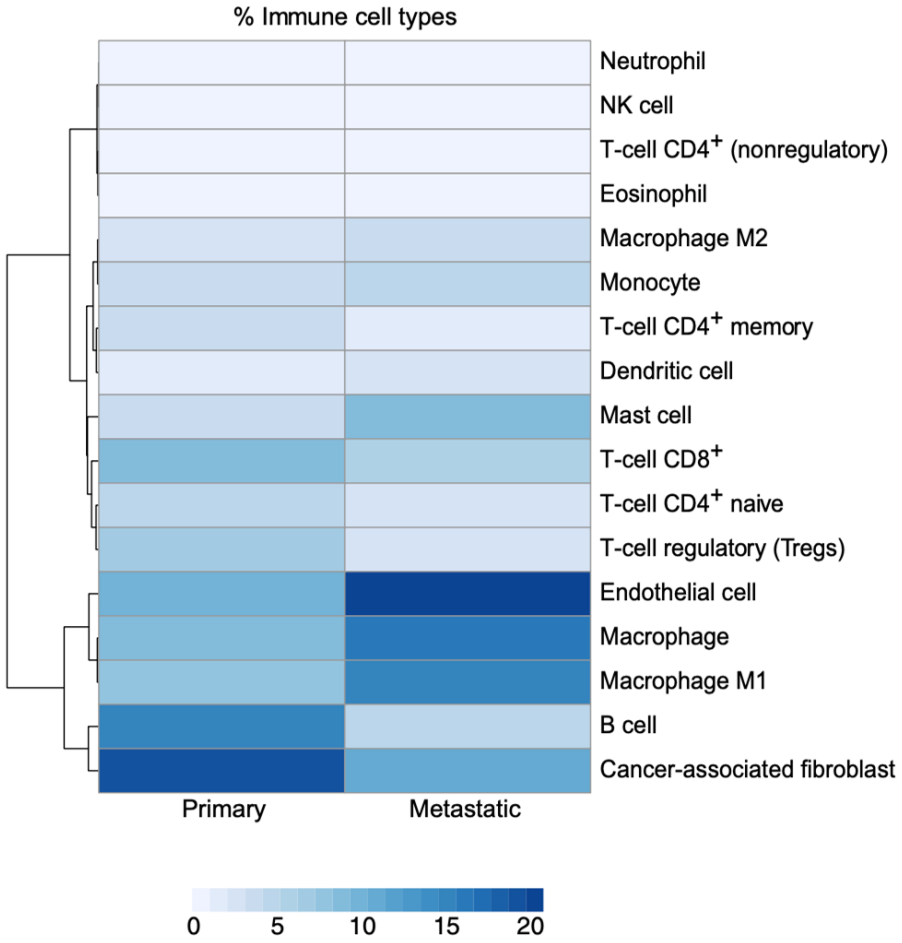


TIOS GENOMICS

Example – Hutchinson *et al.*

Cell Type Deconvolution Analysis

- Cell type proportions estimated from gene expression data
- Average cell type proportions compared: metastatic vs primary
- Significant decrease of B-cell, CD4+ naïve T-cell, CD8+ T-cell and cancer-associated fibroblast subtypes
- Significant increase of endothelial cell, macrophage, and M1 macrophage subtypes



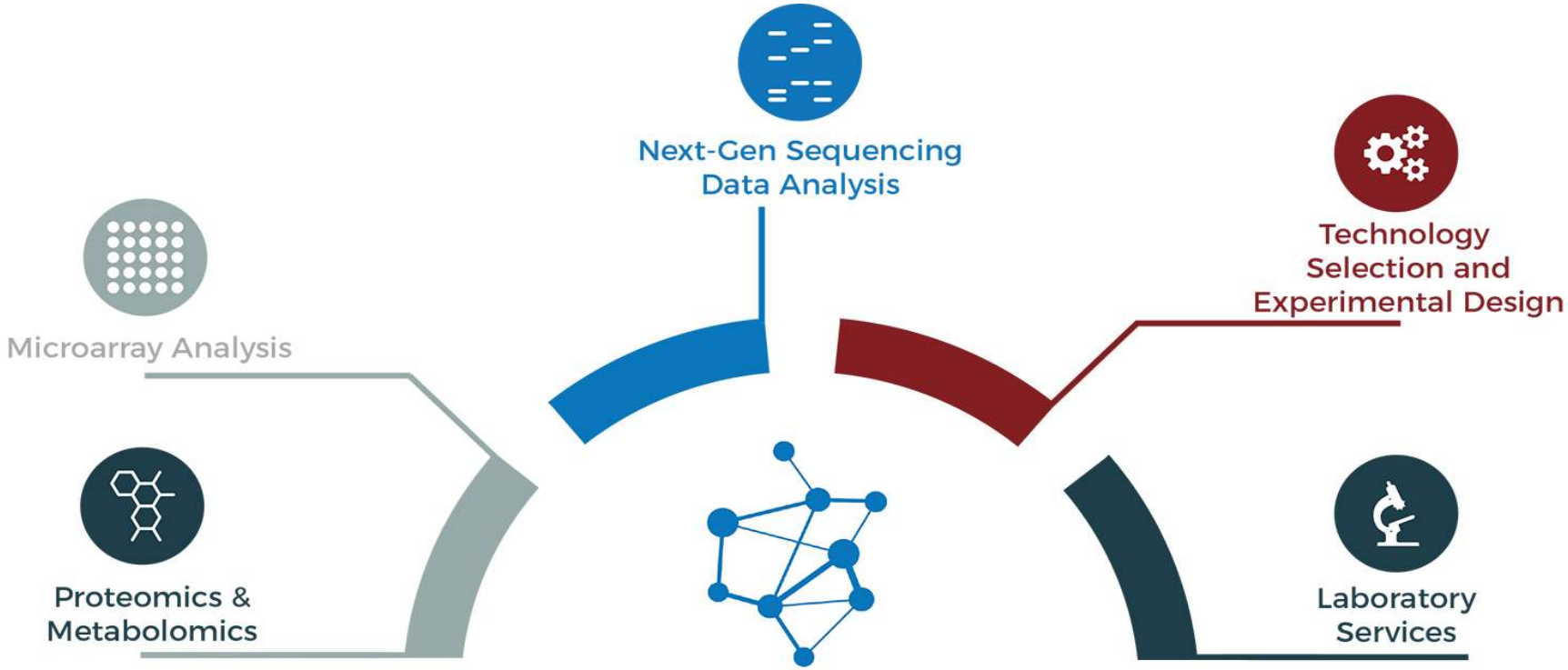
Example – Hutchinson *et al.*

Conclusions

- Few mutational shifts, but largely consistent transcriptomic shifts in longitudinally paired TNBCs.
- Stromal tumor infiltrating lymphocytes significantly decreased in metastatic samples
- Transcriptomic analysis revealed significantly reduced immune-activating gene expression signatures in recurrent TNBCs
- Data may explain the observed lack of efficacy of immune checkpoint inhibitors (ICI) in heavily pretreated TNBCs

fios GENOMICS

Other examples



fios GENOMICS

Example – Mariathasan *et al.*

TGFβ 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 Castiglioni[1], Kobe Yuen[1], Yulei Wang[1], Edward E. Kadel III[1], Hartmut Koeppen[1], Jillian L. Astarita[1], Rafael Cubas[1], Suchit Jhunjhunwala[1], Romain Banchereau[1], Yagai Yang[1], Yinghui Guan[1], Cecile Chalouni[1], James Ziai[1], Yasin Şenbabaoğlu[1], Stephen Santoro[1], Daniel Sheinson[1], Jeffrey Hung[1], Jennifer M. Giltnane[1], Andrew K. Pierce[1], Kathryn Mesh[1], Steve Lianoglou[1], Johannes Riegler[1], Richard A. D. Carano[1], Pontus Eriksson[2], Mattias Hoglund[2], Loan Somarriba[3], Daniel L. Halligan[3], Michiel van der Heijden[4], Yohann Loriot[5], Jonathan E. Rosenberg[6], Lawrence Fong[7], Ira Mellman[1], Daniel S. Chen[1], Marjorie Green[1], Christina Derleth[1], Gregg D. Fine[1], Priti S. Hegde[1], Richard Bourgon[1] & Thomas Powles[8]

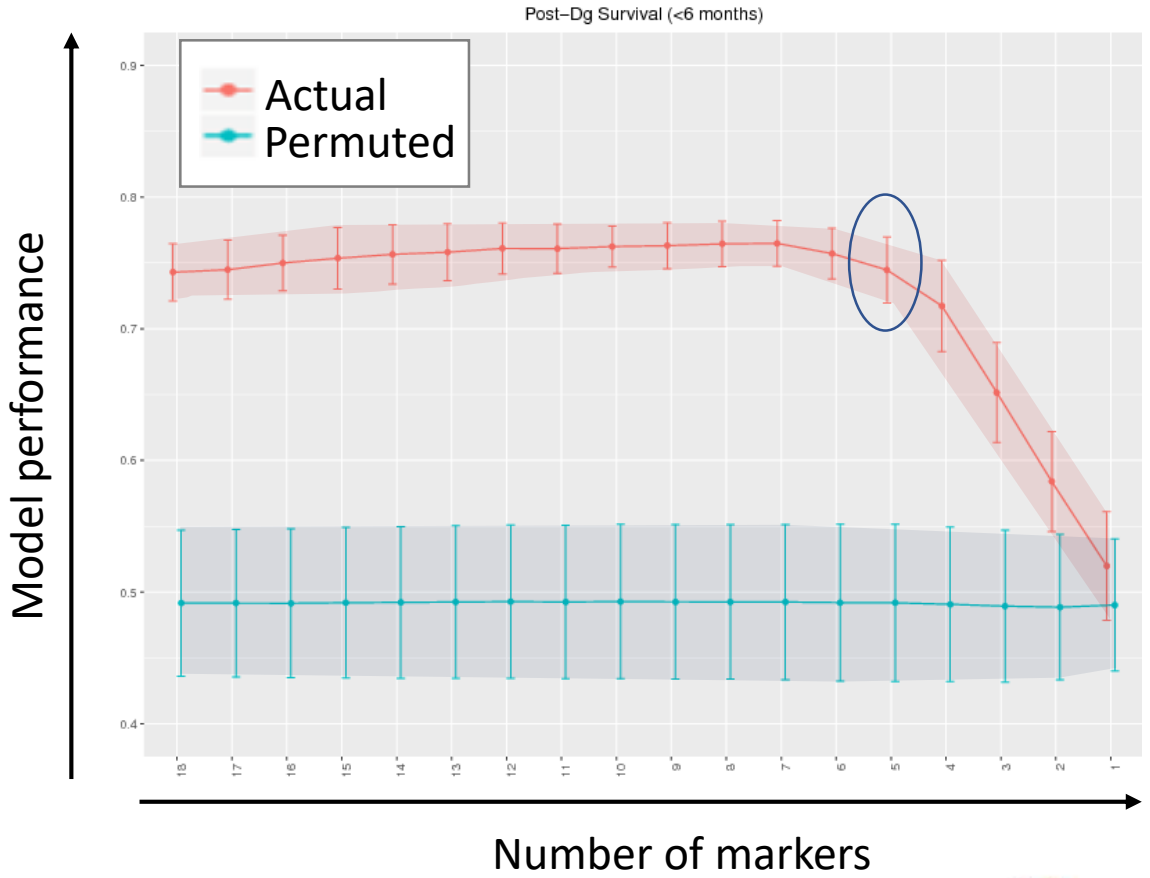
Nature **554**, 544–548 (22 February 2018)

fios GENOMICS

Other examples

Machine learning

- Survival prediction in mesothelioma using Lasso regression
- Identification of a composite signature (combination of features) that can predict OS



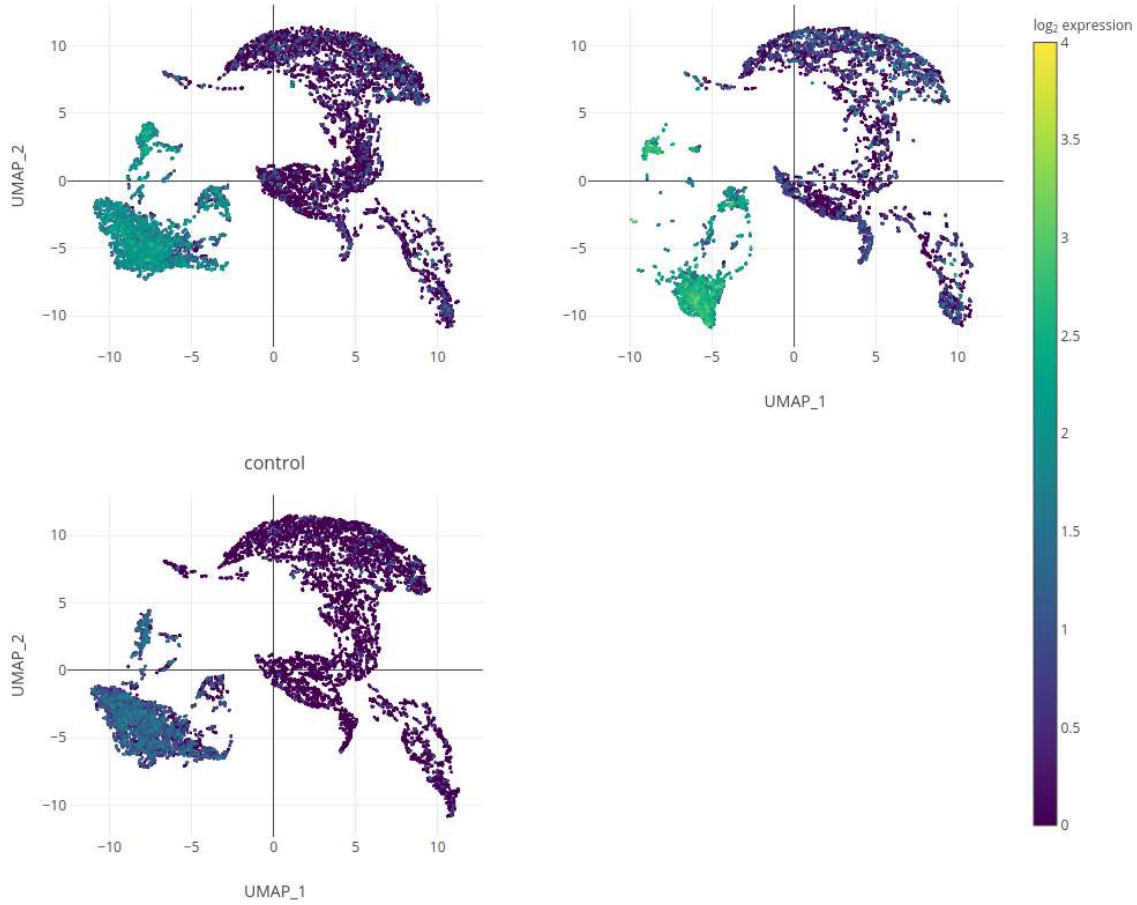
Kidd *et al.*, BMJ Open Respiratory Research, 2018

fios GENOMICS

Other examples

Single-cell RNAseq

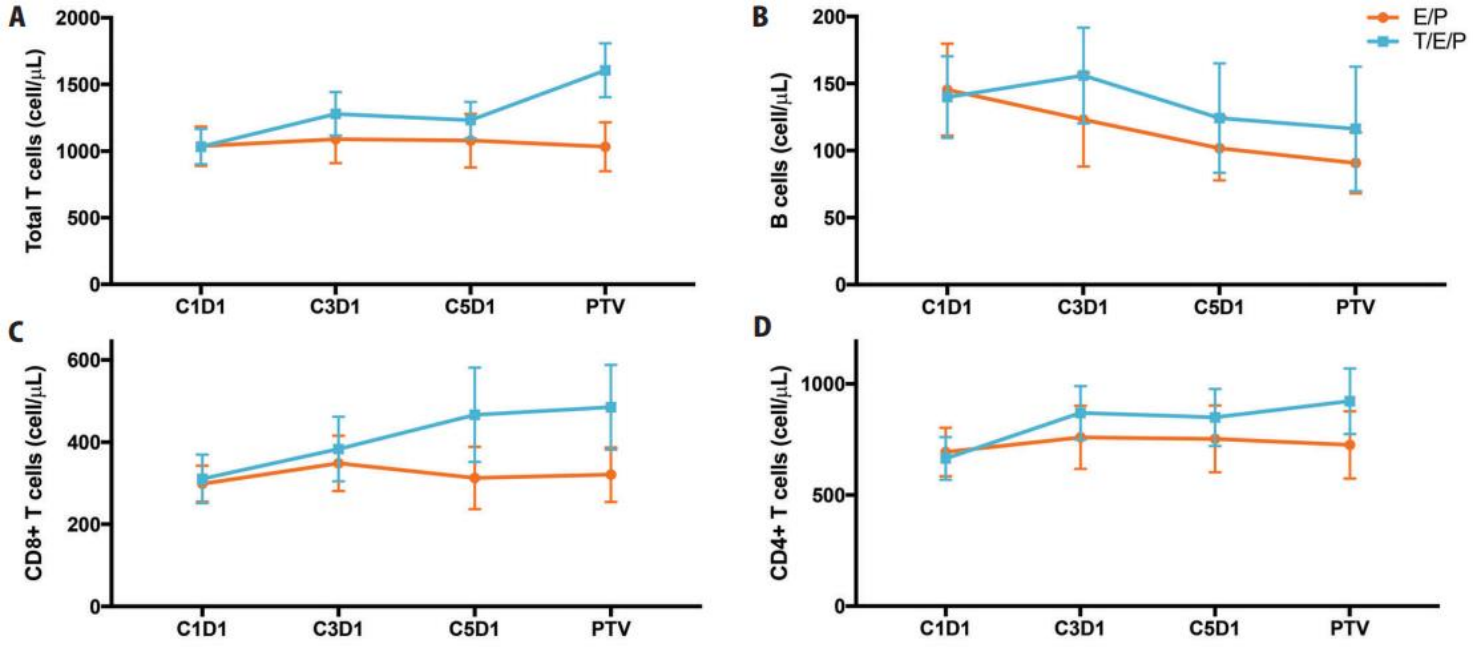
- Clustering and annotation of cell types in hematopoietic and tissues sample.
- Celltype specific treatment response



Other examples

Flow cytometry

- Longitudinal linear mixed-effect models of lymphocyte subpopulations across treatment groups
- Identifying cell subtypes that change over time & treatment

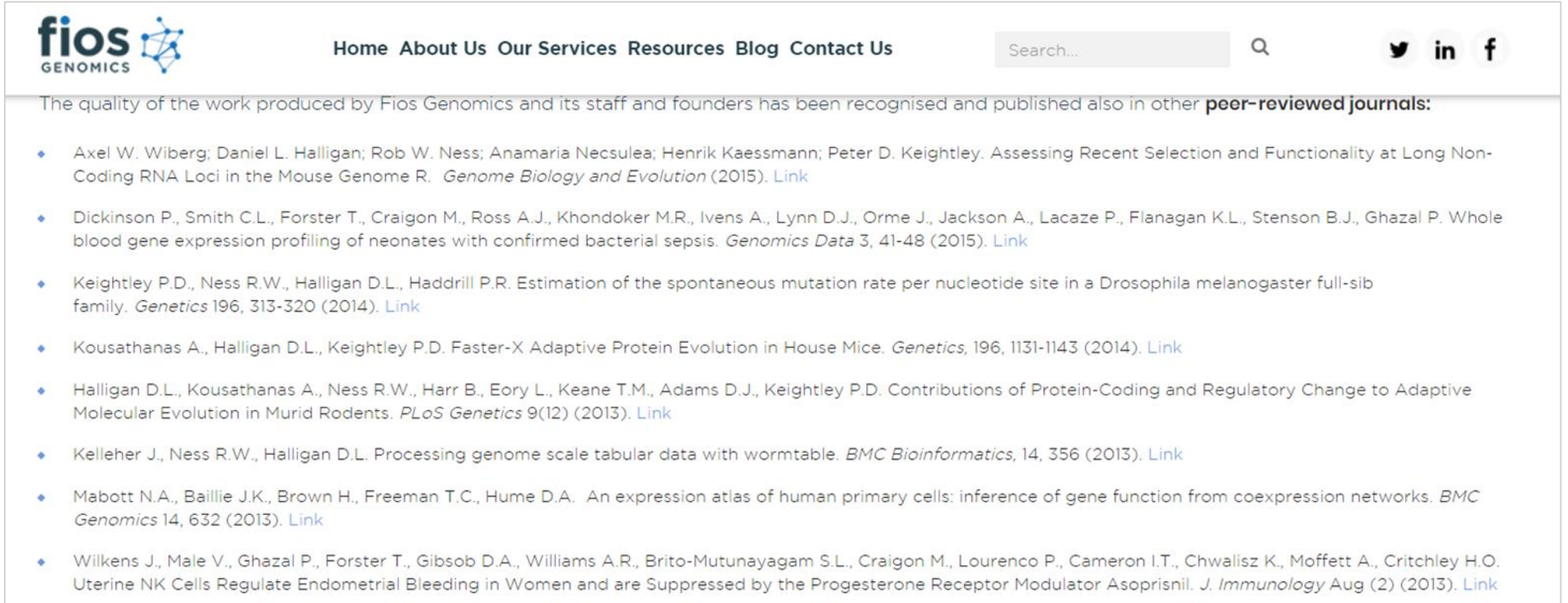


Sorrentino et al, #1671P, ESMO 2018.

fios GENOMICS

Publications

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



fios GENOMICS

Home About Us Our Services Resources Blog Contact Us

Search...

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:**

- 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., Gibsob 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

Thank you