Supplementary Material

Eligibility criteria

We considered research papers in English that were published in 2015 and afterwards, including pre-prints. We excluded reviews, opinion pieces, conference proceedings, non-indexed publications, and publications that did not use ML to integrate multi-omics data.

Information sources

We used the Google Scholar database, covering the years 2015 to present. The date we last accessed it was 4 July 2022. The year 2015 marked a new era in ML research, since the release of software libraries like TensorFlow (Abadi 2016) and Keras (Chollet et al., 2015 available at https://github.com/fchollet/keras) in 2015 and Pytorch (Paszke 2019) in 2016 allowed for easier application of ML models on GPUs. Following this, the application of ML methods has rapidly gained popularity.

Search

Our full search strategy for the Google Scholar database was as follows:

1) Set a custom time range to 2015-present.
2) Search for "machine learning AND multi-omics AND integration".
3) Order results by the Google Scholar "relevance" algorithm, which seems to be heavily influenced by citation count (Beel 2009)[1] . In our experience, it seems to also prioritise more recent papers.

[1] While this may exclude some newer papers which have not had as much time to gather citations, we argue that it is a worthy trade-off for finding the most influential papers in the field.

4) Open each result, check if it fits our eligibility criteria.
5) Obtain answers to our review questions.
6) Stop when we reach 100 eligible publications.

Synthesis of results

Publications were individually assessed by the researchers and data was collected per research question. These were then manually collated. Following this, we went through the collated results to extract patterns/ trends/ clusters of paper types, using plots when applicable. All processed data and plotting scripts are available in the project's Gitlab repository. gitlab.com/polavieja_lab/ml_multi-omics_review , or in Zenodo doi.org/10.5281/zenodo.7361807

Data charting process

For each research question we created a spreadsheet. In the leftmost column we entered the names of our 100 papers. In the next column we entered the answer we had found for the research question after reading the paper. We categorised each of the papers sequentially by entering a '1' in the relevant column to the right. As we went through the papers, we added further category columns as necessary. After completing this process, we used python libraries, primarily pandas and seaborn (Pandas dev. team 2020, Waskom 2021), to structure the data and create the plots for this report.

Data items/ characteristics of sources of evidence

For each paper, we gathered answers to our research questions, namely:

Research question	**Data gathered**
What was the goal of the ML application?	Which broad ML goal did the study fit under, out of: ● Classification ● Regression ● Dimensionality reduction ● Network inference ● Other
Which ML techniques were used?	Which type of technique was used, without using categories we simply noted each machine learning technique used in each paper.
Was a specific dataset used?	We noted which dataset was used and whether this was: ● The Cancer Genome Atlas (TCGA) ● Other

Which omics types were used?	We categorised the omics types into: ● Transcriptomics, including: ● RNA-Seq ● MiRNA-Seq ● Long non-coding RNA ● Whole transcriptome ● Epigenomics, including: ● Hi-C ● Chip-Seq ● DNA methylation ● Gene methylation ● CpG ● Chromatin accessibility ● Open chromatin regions ● Genomics, including: ● Copy number variation ● Copy burden ● Copy aberration ● Copy alteration ● Whole genome, SNPs ● Mutation ● Transcription factor binding sites ● Metabolomics

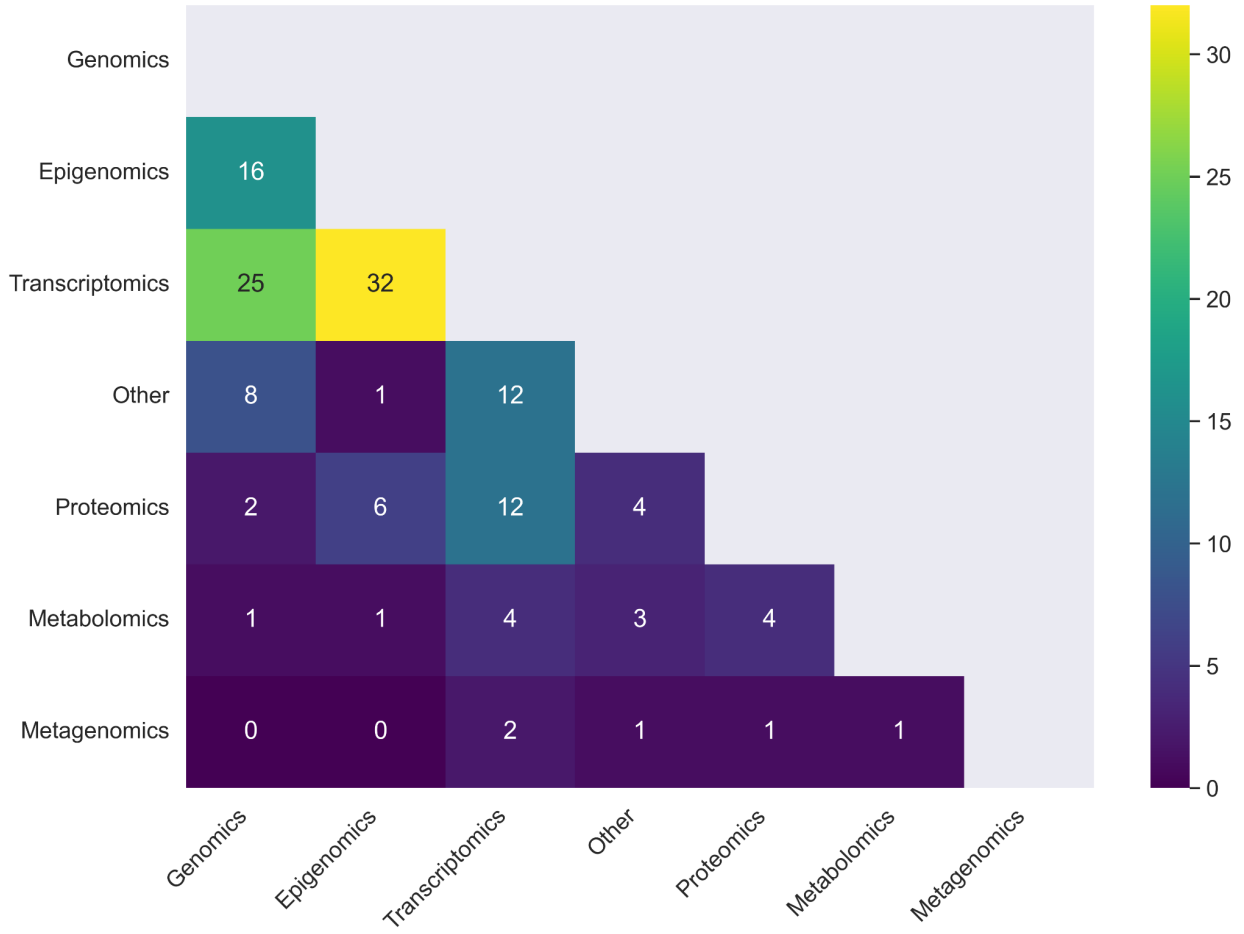
	● Proteomics
	  ● Protein expression
	  ● Reverse phase protein array
	● Metagenomics, e.g. 16s
	● Other, including:
	  ● Fluxome
	  ● QTX
	  ● Histopathological features
	  ● Microarray
	  ● Clinical
	  ● Flow cytometry
	  ● Imaging

What was the shape of the data?	Where multiple studies were performed within a paper, we took the maximum.

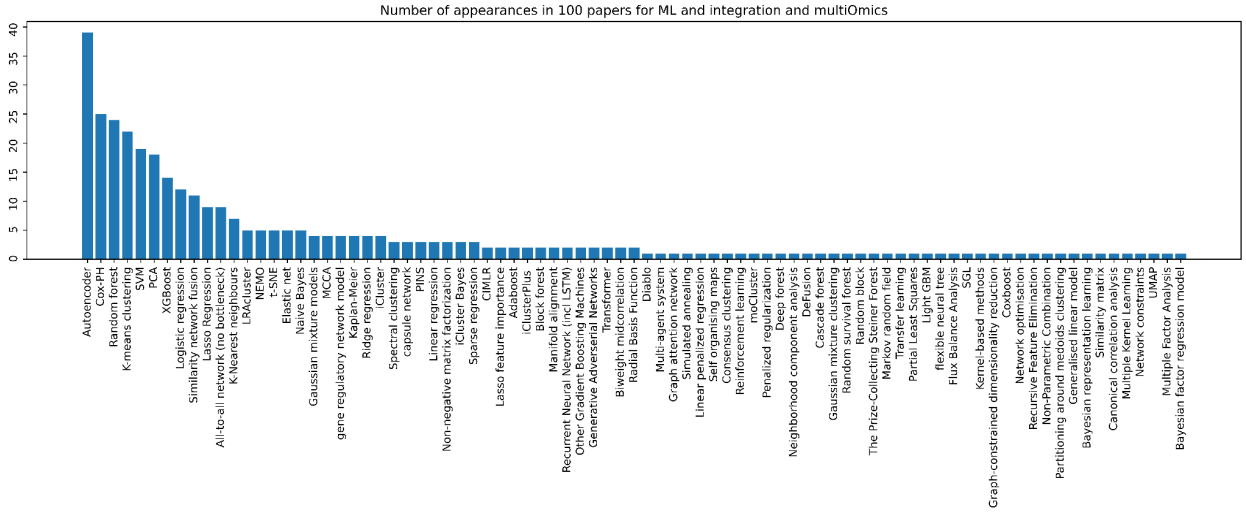
What labels were used?	We categorised the type of label used into: ● Survival prediction ● Disease subtype ● Patient/ organism subtype ● Predict response to interventions ● Individual omic level ● None ● Disease progression ● Clustering to find survival subtypes ● Known association of omic to disease ● Case vs control ● Disease A vs disease B

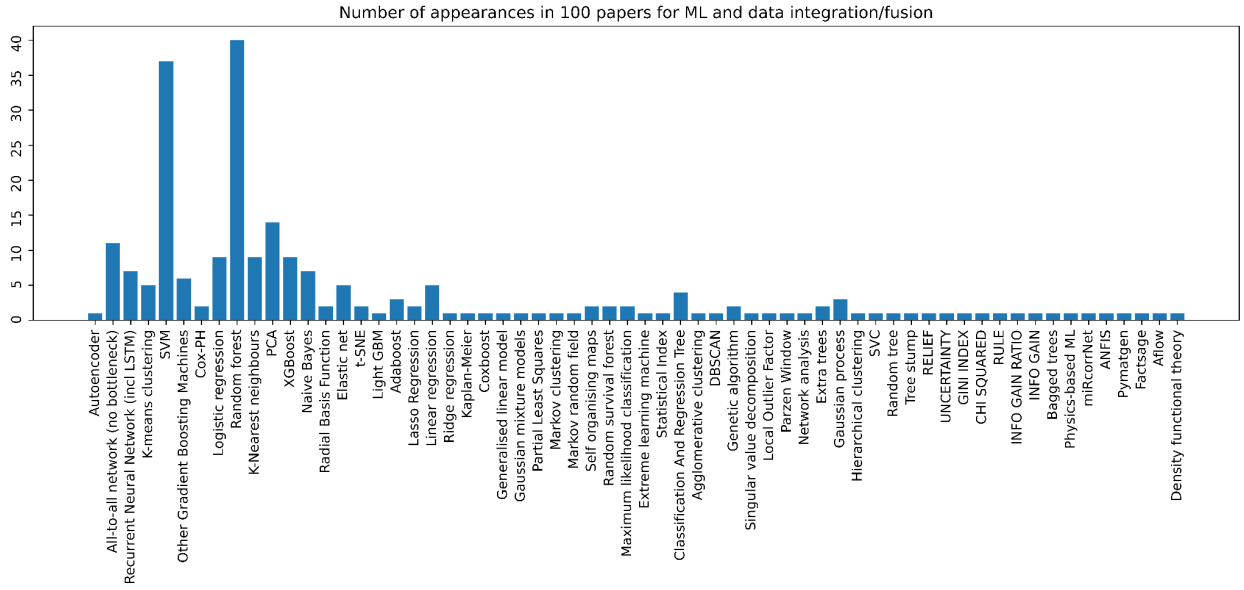
Selection and results of sources of evidence

The full list of the publications included in this review can be found in the references. All tables with specific responses to the research question for each are included in the GitLab repository: https://gitlab.com/polavieja_lab/ml_multi-omics_review/

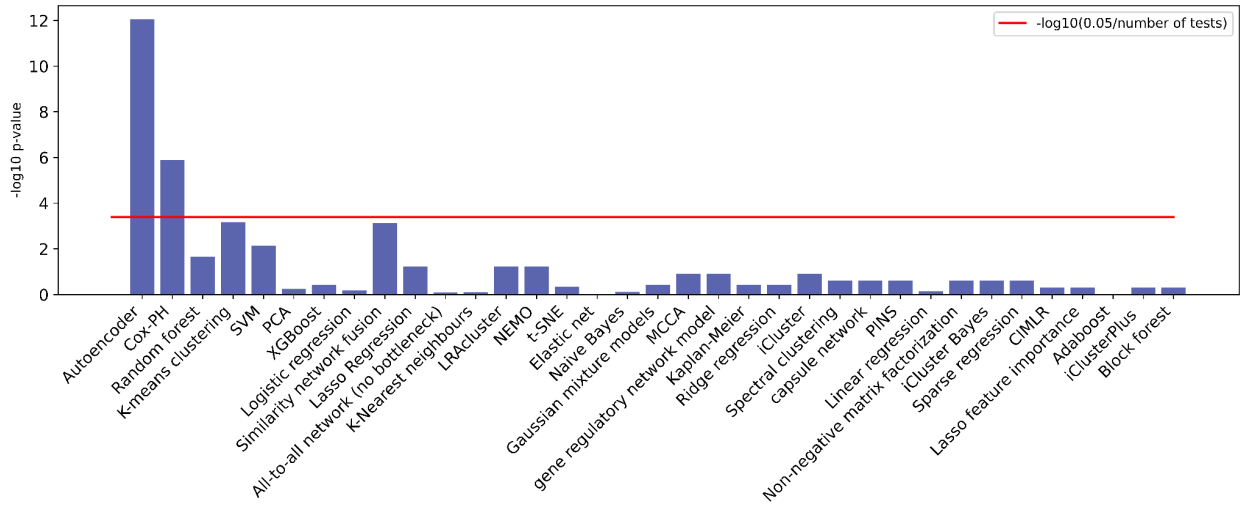


Supplementary Figure 1. Distribution of the number of -omics type combinations used across papers, excluding TCGA.





Supplementary figure 2. Top: all ML AND Integration AND multi-omics techniques, bottom: all ML AND Integration techniques.



Supplementary figure 3. Fisher's exact test showing which techniques are used significantly more often in "ML AND Integration AND multi-omics" versus in "ML AND Integration techniques"

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Lists of the reviewed papers

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