Meta-analysis of crowdsourced data compendia suggests pan-disease transcriptional signatures of autoimmunity [version 1; referees: 2 approved]

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Abstract

**Background**: The proliferation of publicly accessible large-scale biological data together with increasing availability of bioinformatics tools have the potential to transform biomedical research. Here we report a crowdsourcing Jamboree that explored whether a team of volunteer biologists without formal bioinformatics training could use OMiCC, a crowdsourcing web platform that facilitates the reuse and (meta-) analysis of public gene expression data, to compile and annotate gene expression data, and design comparisons between disease and control sample groups.

**Methods**: The Jamboree focused on several common human autoimmune diseases, including systemic lupus erythematosus (SLE), multiple sclerosis (MS), type I diabetes (DM1), and rheumatoid arthritis (RA), and the corresponding mouse models. Meta-analyses were performed in OMiCC using comparisons constructed by the participants to identify 1) gene expression signatures for each disease (disease versus healthy controls at the gene expression and biological pathway levels), 2) conserved signatures across all diseases within each species (pan-disease signatures), and 3) conserved signatures between species for each disease and across all diseases (cross-species signatures).

**Results**: A large number of differentially expressed genes were identified for each disease based on meta-analysis, with observed overlap among diseases both within and across species. Gene set/pathway enrichment of upregulated genes suggested conserved signatures (e.g., interferon) across all human and mouse conditions.

**Conclusions**: Our Jamboree exercise provides evidence that when enabled by appropriate tools, a "crowd" of biologists can work together to accelerate the pace by which the increasingly large amounts of public data can be reused and
meta-analyzed for generating and testing hypotheses. Our encouraging experience suggests that a similar crowdsourcing approach can be used to explore other biological questions.

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Introduction
The volume of large-scale biological data in the public domain is increasing at an unprecedented rate; as a result, data reuse is becoming an increasingly viable means to generate and test hypotheses (Figure 1). The reusability of public data, however, depends on the quality and availability of the associated metadata and annotations. Given a research goal, for example, to generate gene expression signatures for a biological phenotype, one has to first identify and annotate relevant public data, followed by the construction of comparison group pairs (or CGP - see Figure 1 - e.g., a group of samples corresponding to the phenotype of interest versus a group of control samples) and subsequent bioinformatics analyses. Bench scientists are uniquely empowered with biological knowledge to identify and annotate relevant public data and form proper comparisons. Recently, there have also been a variety of crowdsourcing efforts, including hackathons, datathons and open challenges, in which diverse groups of individuals work together to accelerate the pace of pursuing common goals. Thus, we were interested in assessing what could be accomplished by harnessing the collective biological knowledge of a group of biologists to explore, identify, and annotate public datasets when empowered with a user-friendly web platform and a shared scientific goal; would this approach accelerate the pace by which useful biological comparison groups could be constructed and utilized? What would be the specific strengths and hurdles, from both a social and scientific perspective? Towards addressing these questions, we conducted a crowdsourcing “Jamboree” exercise within the NIH immunological community to test the hypothesis that the use of OMiCC (https://omicc.niaid.nih.gov), an open, programming-free web platform that enables a crowdsourcing approach to public gene expression data reuse, can facilitate the rapid assembly of a large data compendium followed by bioinformatics analyses to generate biological hypotheses. Select aspects of this exercise, particularly on how it provides evidence that a tool such as OMiCC can enable biologists without bioinformatics training to directly explore public data, have been highlighted elsewhere and for which this work serves as a companion (also see supplemental website to ref. 5 - https://omicc.niaid.nih.gov/2016-nih-jamboree-analysis/report.html); here we focus on the post-Jamboree data quality control, analysis, and observations, as well as discussing the utility and caveats of this approach.

Figure 1. New research paradigm incorporating exploration and reuse of public data. Increasing availability of public data opens new opportunities for biologists to generate hypotheses. The NIH OMiCC Jamboree was a social experiment to assess whether a group of biologists without computational experience can identify and annotate public datasets and construct CGPs using the OMiCC tool. This paper describes the data analysis, including meta-analysis and gene set enrichment analysis, to derive gene expression signatures across human and mouse.
For this crowdsourcing experiment, we focused on assessing the gene expression patterns of and shared signatures among several common human autoimmune and inflammatory diseases and the corresponding mouse models. Mouse models of human diseases can be informative for studying disease mechanisms, but may not accurately reflect the underlying biology in humans. We were particularly interested in determining whether we could detect shared gene expression signatures among diseases (pan-disease signatures), including type I diabetes (DM1), multiple sclerosis (MS), rheumatoid arthritis (RA), sarcoidosis (sarcoid), Sjögren’s syndrome (SS), and systemic lupus erythematosus (SLE), as well as among their mouse models. We chose these diseases because they have reasonably well-established mouse models and both human and mouse gene expression data are available publicly. A prior study has also evaluated pan-disease transcriptional signatures and found conserved signals across RA, SLE and SS. Here we are including more diseases and are additionally interested in assessing whether human and mouse have shared pan-disease signatures. Given that data from mouse are often generated from non-blood tissues while those from humans usually come from blood, such cross-species comparisons could also point to potential links between blood and non-blood tissues. Cross-species comparisons of gene expression signatures have been performed previously in sepsis, for example, where both conserved and divergent signals have been detected. While our analyses are motivated by these questions, our primary goal here is not to validate previous findings or to generate new biological knowledge per se, but to use this exercise as a proof-of-concept to illustrate the potential utility of data reuse with crowdsourcing.

Methods
Crowdsourcing: team composition and responsibilities
The Jamboree was advertised on the NIH Immunology Listserv, which is primarily subscribed by local researchers to disseminate and share immunology-focused information. No inclusion or exclusion criteria were applied to the identification of the participants. The Jamboree involved a half-day group training session using the OMicc platform followed by a day-long Jamboree, during which 29 volunteer biologists were separated into ten 2- or 3-member teams to search OMicc for public gene expression datasets of DM1, MS, RA, sarcoid, and SLE (Figure 2). The assignments of teams and topics were based on the participants’ self-declared research backgrounds; additionally, each group had at least one participant who felt proficient using OMicc after the half-day orientation. Half of the groups were assigned to focus on humans with one group per disease and similarly, the other half of the groups were assigned to the corresponding mouse models. The participants were asked to use OMicc (https://omicc.niaid.nih.gov) to annotate sample groups and create CGPs between disease and control samples in the studies they identified. They were also encouraged to consult the primary publications describing the studies to help ensure the accuracy of their annotations. Although Sjögren’s syndrome was not originally assigned to any group, the sarcoidosis groups were not able to find sufficient studies from which to construct CGPs and thus was subsequently assigned to focus on Sjögren’s syndrome. Compendia of CGPs created by the teams can be accessed and reused within OMicc (see Data and Software Availability).

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Figure 2. NIH OMicc Jamboree workflow/timeline. Workflow of the NIH Jamboree detailing steps taken prior to, during, and after the actual Jamboree event.
Data curation and quality control (QC) for downstream analyses

A total of 86 human CGPs were collected from the Jamboree, spreading across the six diseases. Participants were instructed to identify public microarray datasets in OMiCC that contained data derived from whole blood (WB) or peripheral blood mononuclear cells (PBMCs) of both healthy controls and affected patients; they were asked to avoid studies of stimulated cells. Post-Jamboree CGP QC was required in order to correct misplaced annotations or to standardize annotations created with free text. Only 54 of the 86 CGPs were created with samples annotated as PBMC or WB. We removed an additional 15 CGPs for the following reasons: 1) incorrect sample annotations; 2) the CGP did not contain sample groups from both cases and controls; and 3) the samples in the CGP significantly overlapped with those in another CGP (Jaccard index > 66%). As a result, 39 human CGPs representing five diseases (note that no WB or PBMC samples passed QC for Sjögren’s syndrome) were included in the downstream analyses (Table 1).

In addition to the individual disease datasets (i.e., a collection of CGPs), all the CGPs for each species were combined to create a pan-disease compendium—one for human and one for mouse.

Meta-analysis

Meta-analysis was conducted in OMiCC to derive differential expression signatures for each dataset (note that OMiCC uses a rank-based meta-analysis R package called RankProd\(^1\), version 2.36.0). The results were reported at the gene level, based on internal OMiCC mappings between platform-specific probe identifiers and standard HUGO gene names. For each gene, this method reports the false prediction rate (PFP - similar to false discovery rate (FDR)) for both increased and decreased expression (herein referred to as the UP and DOWN genes, or differentially expressed (DE) genes when they are combined). Using PFP <= 0.05 as a threshold, we identified UP and DOWN genes for each disease (meta-analysis per species) and for each species (meta-analysis across all CGPs within a species to derive pan-disease gene signatures). Genes with conflicting indications (which is possible with the RankProd method used

| Dataset       | CGPs | Unique Cases | Unique Controls | Common Genes | UP Genes | DOWN Genes |
|---------------|------|--------------|-----------------|--------------|----------|------------|
| human_dm1     | 3    | 168          | 146             | 10681        | 762      | 766        |
| human_ms      | 9    | 171          | 99              | 7909         | 971      | 1106       |
| human_pan-disease | 39  | 1101         | 795             | 7808         | 1021     | 976        |
| human_ra      | 15   | 335          | 188             | 11254        | 1316     | 1550       |
| human_sarcoid | 4    | 141          | 160             | 16012        | 2513     | 2381       |
| human_sle     | 8    | 286          | 202             | 10689        | 1183     | 500        |
| mouse_dm1     | 13   | 62           | 26              | 5753         | 739      | 670        |
| mouse_ms      | 4    | 17           | 14              | 7009         | 326      | 403        |
| mouse_pan-disease | 34 | 141          | 84              | 5644         | 849      | 682        |
| mouse_ra      | 9    | 32           | 20              | 12801        | 1123     | 662        |
| mouse_sle     | 8    | 30           | 24              | 13040        | 626      | 524        |
by OMiCC), i.e. those suggested to have increased and decreased expression for the same disease, were removed. The resulting gene lists and meta-analysis output were exported as text files for further processing. Prior to any downstream analyses, mouse genes were mapped to human genes using NCBI’s homology maps (ftp://ftp.ncbi.nlm.nih.gov/pub/homology_maps/human/; version 12/27/15) and those with either no or non-unique mappings were discarded. The robustness of the RankProd (rank based) results was evaluated using another effect-size metric called Cohen’s $d$, which was calculated in R as

$$
d = t \frac{n_0 + n_c}{n_D n_C} \left( \frac{n_0 + n_c}{n_D + n_C - 2} \right),
$$

where $t$ is the $t$ statistic reported by OMiCC, and $n_0$ and $n_c$ are the number of samples in the disease and control groups, respectively.

**Gene set enrichment analysis**

Gene set based enrichment (or over-representation) analyses were carried out separately for the UP and DOWN genes from each of the four diseases in human and mouse (i.e., DM1, MS, RA, and SLE) against terms in KEGG (http://www.genome.jp/kegg/) or Reactome (http://www.reactome.org/) containing 3 to 500 genes, using the R clusterProfiler$^{12}$ (version 3.0.5) and ReactomePA$^{13}$ (version 1.16.2) packages, respectively. In addition, to illustrate how similar analyses can be performed without any programming, enrichment analyses were also carried out using the web-based Toppgene tool$^{14}$ (https://toppgene.cchmc.org/enrichment.jsp; using default settings and discarding any input gene that mapped to multiple entries). Pan-disease signatures were generated by meta-analyzing each of the two pan-disease compendia (one for human and one for mouse)—a pan-disease compendium contains the CGPs from all diseases within a species. The method implemented by the above software determines enrichment by evaluating the statistical significance of the overlap between the input DE gene list and target gene sets using the hypergeometric test, and we considered gene sets and pathways with an adjusted p-value of <=0.05 to be significantly enriched. Conserved signatures between human and mouse were determined simply by finding the gene sets and pathways that were significantly enriched in both human and mouse.

**Ethics**

This work did not require ethics approval, as per NIH guidelines.

**Results**

**Dataset 1. R data file**

http://dx.doi.org/10.5256/f1000research.10465.d146994

Contains: 1) detailed information about the CGPs included in our analyses; 2) gene-by-compendium matrices of FFP values (can be interpreted as FDR) outputted by OMiCC (one matrix for UP genes; another for DOWN genes)—starting with this data matrix the user can elect to use any FFP cutoff to define DE genes (note that we have one compendium per disease per species, and a pan-disease compendium per species); and 3) gene-set over-representation analysis results generated in R.

**Dataset 2. R markdown script to generate the data analysis report**

http://dx.doi.org/10.5256/f1000research.10465.d146995

The script can be used with Dataset 1 as the data source to generate the main data figures and associated descriptions.

**Dataset 3. Meta-analysis output files exported from OMiCC**

http://dx.doi.org/10.5256/f1000research.10465.d146996

**Dataset 4. Results of Toppgene analyses against KEGG, Reactome, and Gene Ontology (GO) Biological Process terms using the DE genes listed in Table S1 as input**

http://dx.doi.org/10.5256/f1000research.10465.d146997

**Disease gene signatures**

Using the 39 human and 34 mouse CGPs created by the Jambo-ree participants (after QC), for each disease we ran meta-analysis across the CGPs in each disease within OMiCC. The number of DE genes varies substantially across diseases, possibly driven in part by differences in sample sizes and in the number of common genes shared among profiling platforms in each disease/CGP collection (Table 1 and Figure 3A; a list of DE genes for each disease is in Table S1). Comparison of the DE gene sets among diseases, separately for UP and DOWN genes, reveals strong signature overlaps among some diseases. Figures 3B–C show the odds ratios (OR) between pairs of diseases and those with OR > 1 have higher than the expected number of overlapping genes. Interestingly, there tended to be stronger overlap between pairs of diseases within a species than that between the same disease across human and mouse.

**Effect size comparison**

Given that meta-analysis results can be method dependent$^{15}$, next assessed the robustness of the rank-based meta-analysis method used by OMiCC by an independent analysis using a standardized effect-size metric known as Cohen’s $d$, which is the mean difference of expression values between the case and control groups normalized by the joint standard deviation. For each CGP, we ranked the genes according to their Cohen’s $d$ value. Then for each collection of CGPs by which an OMiCC meta-analysis was performed (e.g., RA in humans), we calculated the median rank of each gene among the CGPs. The genes with large effect sizes according to Cohen’s $d$ should be enriched for those identified as having increased expression by the rank-based method in OMiCC, and conversely for the decreased expression genes. The comparison indicates that for most diseases, the OMiCC rank-based results are largely consistent with the effect-size approach, although there were a number of genes discordant between the two methods (Figure S1).
**Figure 3.** Comparison of differentially expressed genes across diseases in human and mouse. (A) Number of differentially expressed genes and (B–C) the proportion of genes that overlap (i.e., Jaccard index) between UP and DOWN genes (PFP ≤ 0.05) for pairs of diseases, as indicated by the size and color intensity of the circles. The number in each cell denotes the odds ratio, which is a measure of statistical association between the two groups based on the degree of gene overlap. An odds ratio of 1 suggests no association. Hs = human; Mm = Mouse.

**Enriched biological processes/pathways**

To gain higher level insights (e.g., pathway and biological processes) into the gene signatures identified, we assessed whether the UP and DOWN genes identified in the previous steps (Figure S2 and Table S2) are enriched for gene sets and pathways annotated in KEGG and Reactome. The analyses were conducted in R (version 3.3.1) and also with Toppgene (a web-based tool). Note that the differences between the R and Toppgene analyses can be partially explained by the fact that Toppgene assumes that all genes in the genome have been measured (i.e., the “background” set), which is not true in this analysis because we only assessed genes common among gene-expression profiling platforms used to generate the data in the compendium (Table 1).

To generate pan-disease signatures, we next attempted to extract common enriched pathways across all diseases within each species. One simple approach is to identify overlapping signatures from the significantly enriched pathways of individual diseases, but its statistical power could be limited. Indeed, using this strategy the only globally enriched pathway is the Reactome term “Chemokine receptors bind chemokines” from the UP genes of the mouse datasets. Thus, we also tested an alternative approach where all
CGPs from each species across diseases were pooled together to form a single OMiCC compendium for meta-analysis (i.e., “human_pan-disease” and “mouse_pan-disease”; Figure 4). In this manner, the large number of samples increased the statistical power of the meta-analysis, thus resulting in the larger number of pan-disease enrichment signatures, including those reflecting broad immune activation and the well-appreciated interferon signature in human⁸ (Figure 4). However, this approach can potentially be confounded by variation in sample sizes across diseases, e.g., diseases with larger numbers of samples may dominate the signal.

Conserved signatures between human and mouse
We next used a conservative approach to assess shared gene set/pathway signatures between human and mouse by requiring that enriched terms be statistically significant in both human and mouse (after multiple-testing correction). Interestingly, using this criterion, all pan-disease enrichments conserved between human and mouse were derived from the UP genes (Figure 5), which may partially reflect that increases in immune cell frequencies (e.g., increases in monocytes in blood and/or tissues) were potential underlying drivers of these species-conserved, pan-disease signatures.

Figure 4. Pan-disease enrichment signatures. Over-representation analyses of the (A) UP genes and (B) DOWN genes (PFP <= 0.05) identified by using all CGPs from each species in the meta-analysis. The analyses were performed in both R and ToppGene; the top 20 enriched terms identified in R are shown. Terms found also in ToppGene are indicated by an asterisk (*). P-values are adjusted by Benjamini and Hochberg (BH) FDR correction (shown as ‘adj.p’). Counts (indicated by circle size) and gene ratios (x-axis) respectively denote the number and proportion of genes in the UP or DOWN signature that also appear in the target gene set.
Figure 5. Pan-species, pan-disease signatures: Overlap of enriched biological processes between human and mouse. Over-representation analyses of the (A) UP genes and (B) DOWN genes (PFP <= 0.05) identified within OMiCC were carried out against KEGG and Reactome terms (see also Figures 4 and Figure S2 and Table S2). For each individual CGP compendium (disease or pan-disease), gene sets or terms with adjusted p-value <= 0.05, as defined by the hypergeometric test after adjustment by the Benjamini and Hochberg (BH) FDR procedure, in both human and mouse are listed. These overlapping terms highlight signatures conserved between human and mouse. Gene ratios (x-axis) denote the fraction of genes in the respective signature (human and mouse as denote by blue and red, respectively) that are in the target gene set (y-axis).
Discussion

Our crowdsourcing exercise illustrates that a group of biologists without formal bioinformatics training can use OMiCC, a programming-free web-based platform, to generate a sizable number of CGPs during a day-long group exercise with a shared scientific goal. This is encouraging because CGP construction can be time consuming, requires biological expertise, and is often required for public data reuse and meta-analysis. Our observation suggests that other groups should be able to replicate our experience in their own institutions to pursue other scientific questions. However, there are some caveats: substantial QC was required to remove improperly constructed CGPs, such as those created from data obtained using stimulated cells (which was an exclusion criteria we specified, but nonetheless, compliance was less than perfect). Additionally, CGPs were more difficult to construct for the biologically more complex mouse models, and thus more were removed in the QC process. It is likely that early participant feedback on CGP quality during the Jamboree would help ensure higher quality CGPs, thereby reducing some of the required post-Jamboree QC. This also suggests that extending the Jamboree to two days, for example, with another day to review and QC the CGPs by the participants, could be valuable.

Following QC, meta-analysis performed within OMiCC led to several interesting observations: firstly, evaluation of DE genes showed substantial signature overlaps among diseases within species, and to a lesser extent, between the two species. Secondly, these findings were largely consistent when evaluated using an effect-size based approach. However, caution needs to be exercised in interpreting the results as the identification of DE genes can be influenced by a number of variables that cannot be controlled in this type of analysis. For example, as more CGPs from independent studies using different platforms are included in the analysis, the number of common genes among the platforms typically decreases, thus reducing the number of genes for which differential expression can be evaluated. Meta-analysis of CGPs containing overlapping samples can also give a false sense of robustness because the true PFP (or FDR) can be higher than what is reported. Other potential confounding factors include unequal distributions of age and race (or strain for mice) between sample groups within CGPs. However, these can also increase the heterogeneity across CGPs, so any conserved signals that emerge from the meta-analyses of the CGPs are likely relatively robust\(^4\). Barring differences in meta-analysis methodologies, our analysis identified a larger number of pan-disease DE genes in human compared to an earlier, similar meta-analysis effort\(^4\) (1021 versus 210 UP and 976 versus 202 DOWN genes), likely in part because our analysis included a larger number of CGPs/studies curated by the Jamboree participants. This highlights the potential benefit of using crowdsourcing to amass a large multi-study dataset within a relative short amount of time.

Using tools outside of OMiCC, gene set/pathway enrichment analysis revealed that, as expected, a higher level of conservation across diseases than that at the gene level. Some of the enriched KEGG and Reactome terms were consistent with previous reports, e.g., “cytokine signaling” was enriched in genes with increased expression in human SLE. It is well-established that SLE patients exhibit increased expression of IFN-inducible genes in blood compared to healthy controls\(^13,15\). The term “cytokine signaling” was also enriched (albeit to a lesser magnitude) in RA, as well as in the human and mouse pan-disease signatures, and it was furthermore conserved between human and mouse; these results are again consistent with previous reports\(^13,15\). Our pathway enrichment analysis also identified some less well-established, but potentially biologically interesting associations. For example, the KEGG term “Malaria” is enriched in the UP genes in RA due to genes such as CR1, GYPA, ICAM1, PECAM1, and TLR4. It is not clear whether this is related to the fact that anti-malarial drugs, such as hydroxychloroquine, have been used as a secondary treatment for RA for many years\(^2\), and it has been suggested that hydroxychloroquine interferes with Toll-like receptor signaling\(^25\) to reduce immune cell activation and proliferation, although its exact mechanism of action in ameliorating RA is still not well understood. Another potentially interesting observation is the enrichment of platelet-related pathways in a number of signatures. The involvement of platelets has been implicated in various autoimmune diseases\(^24\), particularly in RA\(^2\), and has been proposed as a potential therapeutic target for some of the autoimmune diseases assessed here\(^26\).

In reflection, there are several ways in which our Jamboree could have been improved, such as offering more extensive training using OMiCC prior to data exploration, providing early feedback on the construction of CGPs, and creating independent discovery and validation cohorts to strengthen the robustness of our preliminary observations. Despite some of the caveats associated with our analyses and results, overall we provided evidence that user-friendly crowdsourcing and analysis platforms, such as OMiCC, can potentially accelerate the pace by which public data can be utilized to generate and test hypotheses.

Data and software availability

Gene expression and sample group data

The comparison group pairs (CGPs, e.g., RA versus healthy) created by the Jamboree participants and used in the post-Jamboree analyses have been made public in OMiCC at: https://omicc.niaid.nih.gov/. They are collected in compendia whose names have the format 2016-NIH-Jamboree-Species-Disease (species can either be Human or Mouse while diseases include DM1, MS, RA, SLE, and Sarcoid). These compendia can be retrieved in OMiCC by using the compendia search function (on OMiCC homepage: Search > On Compendia) and searching for the keyword ‘2016-NIH-Jamboree’. This information can also be retrieved from Dataset 1 listed below.

To retrieve the raw microarray data, a user can construct new compendia using selected CGPs from the Jamboree compendia collection (see the Community and Sharing Features section of the OMiCC Tutorial) and export the gene expression data from the web site.

Meta-analyses and gene enrichment analyses data

F1000Research: Dataset 1. R data file, 10.5256/f1000research.10465.d146994\(^27\)

F1000Research: Dataset 2. R markdown script to generate the data analysis report, 10.5256/f1000research.10465.d146995\(^28\)
**Author contributions**

WWL helped design the Jamboree, performed post-Jamboree data curation, designed and performed post-Jamboree data analysis, and wrote the manuscript; RS designed and organized the Jamboree, performed post-Jamboree data curation, and wrote the manuscript; OJWG participated in the Jamboree; JST conceived and guided the project, designed and helped organize the Jamboree, helped design post-Jamboree data analysis plan, helped post-Jamboree data curation, and wrote the manuscript.

**Competing interests**

No competing interests were disclosed.

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Supplementary material
Figure S1. Meta-analysis results are largely consistent between the rank-based and effect-size-based meta-analysis methods. For each dataset, bar-code plots are used to illustrate the positions of the (A) UP and (B) DOWN genes identified by the rank-based meta-analysis method in the gene list sorted by the median rank (across CGPs) of the effect size indicated by the Cohen’s d statistic in each CGP. The gene lists are sorted in ascending order with higher statistics indicating larger effect sizes. The red and blue areas represent genes with positive and negative median Cohen’s d values, respectively.

Click here to access the data.

Figure S2. Top 20 enriched biological processes for individual diseases. Over-representation analyses of the (A) UP and (B) DOWN genes (PFP <= 0.05) identified by a rank-based meta-analysis method (RankProd within OMiCC) were carried out for each disease individually from human and mouse against KEGG and Reactome terms. The analyses were performed in both R and ToppGene; the top 20 enriched terms identified in R are shown. Terms found also in ToppGene are indicated by an asterisk (*). P-values are adjusted by Benjamini and Hochberg (BH) FDR correction. Counts (indicated by circle size) and gene ratios (x-axis) respectively denote the number and proportion of genes in the UP signature that also appear in the target gene set.

Click here to access the data.

Table S1. Differentially expressed genes in each dataset. A spreadsheet listing all of the genes identified by RankProd (in OMiCC) to exhibit increased (UP) and decreased (DOWN) expression (PFP <= 0.05) in disease versus control comparisons in each of the datasets.

Click here to access the data.

Table S2. Enriched pathways for the differentially expressed genes in each dataset. A spreadsheet listing all of the enriched KEGG and Reactome terms (p.adj <= 0.05; adjusted by Benjamini and Hochberg correction) in disease versus control comparisons in each of the datasets.

Click here to access the data.

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This paper describes a thorough case study using the author’s recently published OMiCC web service. This service provides re-processed expression data and allows the curation and selection of datasets by disease experts without requiring bioinformatic expertise. Performing gene expression meta-analyses is challenging and time consuming for precisely the reasons this tool addresses and tools like OMiCC are therefore a welcome addition to the field.

The paper is clearly written and both design and implementation are in general solid.

A shortcoming of the design is that the curation teams were all assigned different tasks. It would have been interesting to see the overlap of curations obtained by independent teams.

In addition, I have a few minor comments and optional suggestions regarding the analyses:
1. A brief literature review of existing solutions (for example InsilicoDB) appears to be missing in both this manuscript and the main paper.
2. A challenge of comparing array data from different platforms is that some genes might be captured with varying quality across platforms. It is unclear what was done to identify problematic probe sets or genes. Various R packages (e.g. metaArray) for example calculate Integrative Correlation scores. These scores identify probe sets which behave differently across platforms in terms of co-expressed genes.
3. Another challenge is the extensive reuse of specimens and data in public datasets. The authors write that duplicates were identified and removed. As a completely optional suggestion, we recently published the doppelgangR package that automates the identification of duplicates.
4. It is unclear if the software can generate more classical meta-analysis visualizations like forest plots.
5. The number of different platforms included in the meta-analysis and whether platform was a significant source of heterogeneity could be made clearer.
6. I probably would have performed the gene set analysis using expression data collapsed to pathways, for example by GSVA, ssGSEA or related newer methods. These methods turn a gene-by-sample matrix into a pathway-by-sample matrix; the same gene-centric methods can be
then applied to pathways. I am not aware of any existing literature comparing pathway meta-analysis methods and this is thus another optional comment. This might however be a cleaner approach than pooling the mouse and human datasets.

7. Axis and legend labels sometimes use R variable names (such as "gene.ratio") instead of proper annotation (using xlab(), scale_fill_discrete() etc.)

8. fRMA is in theory better for meta-analyses compared to standard RMA since then all datasets use the same reference pool for normalization. I am however again not aware of a systematic comparison and the impact on meta-analyses.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

**Competing Interests:** No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Hans Lehrach ¹, Hans-Jörg Warnatz ², Thomas Risch ²

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Lau and colleagues describe an interesting effort of a group of biologists without formal bioinformatics training to use a programming-free web-based platform to generate a sizable number of comparison group pairs (CGPs) during a day-long group exercise, using gene expression data from humans and mouse models. The subsequent gene and gene set enrichment analyses – performed after quality control of the generated CGPs – yield reasonable results for a number of autoimmune diseases, resulting in
plausible enrichments identified for genes and gene sets associated with inflammation and immune processes.

The described effort is a potentially scalable method for analysis of very large data sets using the combined manpower of a large number of individuals. To produce pore quantifiable data of this process, it would however be interesting to compare the results of duplicates (do individual groups working in isolation on the same question come up with the same or different results. How does the result of such a 1 day Jamboree compare with the results of a single expert working for a month? If you would rerun the exercise, how different would you expect the results to be?

It might also be interesting to systematically eliminate one dataset at a time to quantitate its influence on the final result.

One major aspect of the study worth more detailed reporting is the way quality controls are carried out on the CGPs collected by the crowd. This aspect will become even more important when a large crowd is used, and more CGPs are collected, and constitutes one of the main pillars of all subsequent analyses. Therefore, I would suggest that the authors report in more detail their strategies and the conduction of the quality controls, along also with more details on potential caveats and pitfalls.

Other comments:

**Methods**

Major comment:
- “we considered gene sets and pathways with an adjusted p-value of <=0.05 to be significantly enriched”
  Here it is not clear if p-values were adjusted for multiple testing, e.g. using Benjamini-Hochberg correction.

- A more detailed description should be given for the ToppGene analysis

Minor comment:
- Toppgene is actually spelled “ToppGene”

**Competing Interests:** No competing interests were disclosed.

*We have read this submission. We believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.*